JOC Article

A Reassessment of the Transition-Metal Free Suzuki-Type Coupling Methodology

Riina K. Arvela,† Nicholas E. Leadbeater,*,† Michael S. Sangi,† Victoria A. Williams,†
Patricia Granados,‡ and Robert D. Singer‡

*Department of Chemistry, University of Connecticut, Unit 3060, 55 North Eagleville Road,
Storrs, Connecticut 06269-3060, and Department of Chemistry, Saint Mary's University,
Halifax, Nova Scotia B3H 3C3, Canada*

nicholas.leadbeater@uconn.edu

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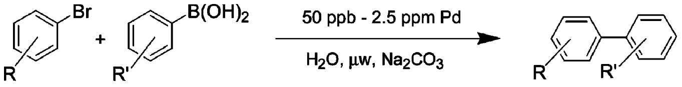

We present here a reassessment of our transition-metal free Suzuki-type coupling protocol. We believe that, although the reaction can be run without the need for addition of a metal catalyst, palladium contaminants down to a level of 50 ppb found in commercially available sodium carbonate are responsible for the generation of the biaryl rather than, as previously suggested, an alternative non-palladium-mediated pathway. We present a revised methodology for Suzuki couplings using ultralow palladium concentrations for use with aryl and vinyl boronic acids and discuss the effects of the purity of the boronic acid on the reaction.

Introduction

The Suzuki reaction (palladium-catalyzed cross-coupling of aryl halides with boronic acids) is one of the most versatile and utilized reactions for the selective construction of carbon−carbon bonds, in particular for the formation of biaryls.[1] As the biaryl motif is found in a range of pharmaceuticals, herbicides, and natural products as well as in conducting polymers and liquid crystalline materials, development of improved conditions for the Suzuki reaction has received much recent attention. A wide range of metal complexes have been used as catalysts in these coupling reactions, attention particularly being focused on palladium. There have been a number of recent reports of the use of so-called "ligandless" palladium catalysis of the Suzuki coupling. In 2002, we showed that, when using $Pd(OAc)_2$, the Suzuki coupling of a wide range of aryl bromides and aryl boronic acids can be performed using water as a solvent with the addition of TBAB as a phase-transfer agent. The coupling works equally well using either microwave or conventional heating. Similar observations have been made by other groups using palladium salts either in water,[2−5] ionic salts,[6,7] or pyridine without the need for addition of ligands.[8]

In 2003, we reported that, using the appropriate conditions, it is possible to perform Suzuki-type couplings *without the need for addition of a transition-metal catalyst*.[9−11] We have termed this "transition-metal free Suzuki-type coupling" since the levels of palladium found in reaction mixtures were below the level of detection of our apparatus (0.1 ppm). We also analyzed reaction mixtures for the presence of a wide range of other elements. Possible catalyst candidates include nickel,[12]

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† University of Connecticut.

‡ Saint Mary's University.

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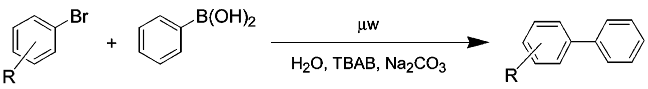
platinum,[13] copper,[14,15] and ruthenium[14] since all of these metals have been shown to act as catalysts for the Suzuki reaction either individually or together. However, none of these metals were present in the product mixture in concentrations above 1 ppm.

There have been a number of reports that have recently appeared in the literature that suggest that C−C coupling reactions can be catalyzed by trace quantities of palladium complexes. De Vries and co-workers have shown that the Heck reaction can be run with the addition of what they term "homeopathic" quantities of palladium catalysts, but find that when using very low metal concentrations the rate of reaction is too slow to be practical.[16,17] Choudary[18] and co-workers have obtained very high turnover numbers in Heck couplings with aryl chlorides when using layered double hydroxide supported nanopalladium catalysts. They suggest that the reaction occurs at the surface of the nanoparticles. Köhler and co-workers have recently studied the Heck reaction using a range of solid catalysts.[19] Their results suggest that there is in situ generation of highly active dissolved palladium species and thus that the catalysis is in effect homogeneous with palladium dissolution and reprecipitation being crucial and inherent parts of the catalytic cycle. Very high turnover numbers have also been reported for Suzuki coupling reactions, mostly involving the use of ligated palladium complexes such as those bearing N-heterocyclic carbene ligands,[20] bulky phosphines,[2] or else using palladacycles.[21] As with the Heck reaction, Suzuki couplings have been performed using solid catalysts.[18,22,23] Again, the in situ generation of small quantities of highly active dissolved palladium species is suggested.

These bodies of work made us critically reassess our transition-metal free protocol. We present our findings here. We believe that, although the reaction can be run without the need for addition of a metal catalyst, palladium contaminants down to a level of 50 ppb found in commercially available sodium carbonate are responsible for the generation of the biaryl rather than, as previously suggested, an alternative non-palladium-mediated pathway.

SCHEME 1



R	*Yield %*
H	90
4-COMe	98
4-Me	82
4-OMe	53

Results and Discussion

In our reports of 2003, we presented a general method for microwave-promoted transition-metal free Suzuki-type couplings of aryl bromides and aryl boronic acids in water using sodium carbonate as a base and TBAB as an additive. Central to the success of the methodology are the criteria that the reaction must be performed in water at 150 °C in a sealed vessel using microwave heating. **Caution**.[24] We found that while a wide range of functional groups on the aryl halide component are tolerated in the reaction, only the coupling with phenylboronic acid worked well (Scheme 1). Representative aryl iodides were also screened in the coupling reaction using our methodology but product yields were lower than their bromo counterparts. Aryl chlorides could not be coupled.

Our first objective in reassessing the methodology was to determine why the boronic acid scope was so limited. We found that the success of the reaction is dependent on the purity of the boronic acid used. Impurities in the boronic acid, even in very small amounts, can effectively shut down the reaction. We wanted to revisit the reaction to look more thoroughly at the scope of the boronic acid component since we felt that it may be the case that our previous screening of the boronic acids may have led to "false negatives". Therefore we embarked upon the purification of a range of boronic acids. We used three methods to achieve this. The boronic acids can be purified by column chromatography using hexane/ethyl acetate or, in certain cases, hexane/methanol as eluent. We start by eluting with pure hexane and then gradually increase the ratio of the more polar solvent. Any inorganic impurities will remain on the silica and traces of aryl chloride and other organic impurities can be removed before the polar boronic acid elutes from the column. An alternative strategy is to adsorb the boronic acid on to silica (7.5 g silica for each 1 g boronic acid) and then wash the silica with hexane followed by elution with pure ethyl acetate or methanol to obtain the purified boronic acid. This has the advantage of being procedurally easier and also, in some cases, leads to a greater recovery of the boronic acid then when using column chromatography. Boronic acids can be recrystallized from water[25] to give pure samples although we find that this can lead to significant material loss and does not always remove all the impurities effectively.

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(24) **Caution:** The water is heated well above its boiling point so all necessary precautions should be taken when performing such experiments. Vessels designed to withhold elevated pressures must be used. The microwave apparatus used here incorporates a protective cage around the microwave vessel in case of explosion. After completion of an experiment, the vessel must be allowed to cool to a temperature below the boiling point of the solvent before removal from the microwave cavity and opening to the atmosphere.

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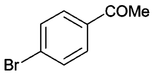
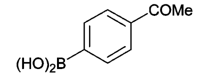
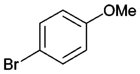
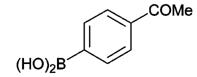
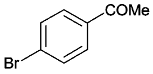
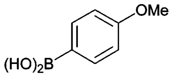
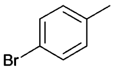
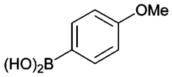
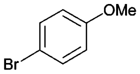
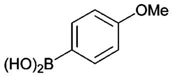
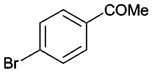
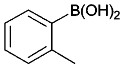
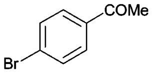
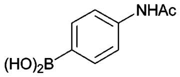
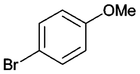
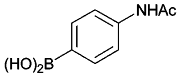
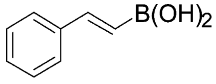
TABLE 1. Suzuki-Type Coupling of Aryl Bromides and Aryl Boronic Acids[a]

entry	aryl halide	boronic acid	Yield %
1			94
2			40
3			91
4			99
5			0
6			99
7			63
8			22

[a] Reactions run on 1 mmol scale with no added palladium. Microwave irradiation of 150 W used. Temperature ramped from rt to 150 °C and held for 5 min.

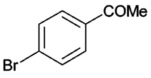
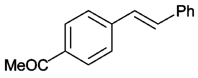
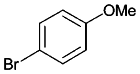
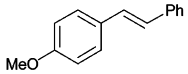
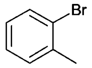
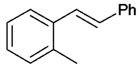
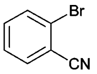
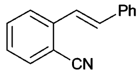
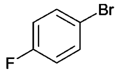
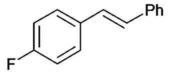
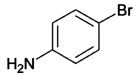
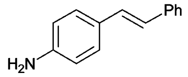
With a representative range of purified arylboronic acids in hand, we have screened them in the coupling protocol. The results are shown in Table 1. Using bromoacetophenone as the aryl halide substrate, we find that it is possible to couple this with pure boronic acids bearing electron-withdrawing or electron-donating groups. The presence of an *o*-methyl functionality on the boronic acid does not lead to a lowering in product yield (Table 1, entry 6). We have investigated the coupling of 4-methoxybenzeneboronic acid with 4-bromoacetophenone, 4-bromotoluene, and 4-bromoanisole (Table 1, entries 3–5). We find that in the case of the latter, no product is obtained as compared to high yields with the other examples where excellent yields of the desired biaryl are observed.

In an attempt to develop the methodology further, we wanted to investigate the coupling of alkenyl boronic acids with aryl halides and alkenyl halides with aryl boronic acids, the product in both cases being substituted alkenes. Suzuki couplings of these types of substrates are known using Pd catalysts. We first screened the reaction between *trans*-2-phenylvinylboronic acid (**1**) and 4-bromoacetophenone and 4-bromoanisole. We find that in both cases, the desired disubstituted alkene product is formed. We observe only the trans isomer of the stilbene products.



1

TABLE 2. Suzuki-Type Coupling of Aryl Bromides with 1[a]

entry	aryl halide	product	Yield %
1			99
2			46
3			26[b]
4			15[b,c]
5			17[c]
6			27

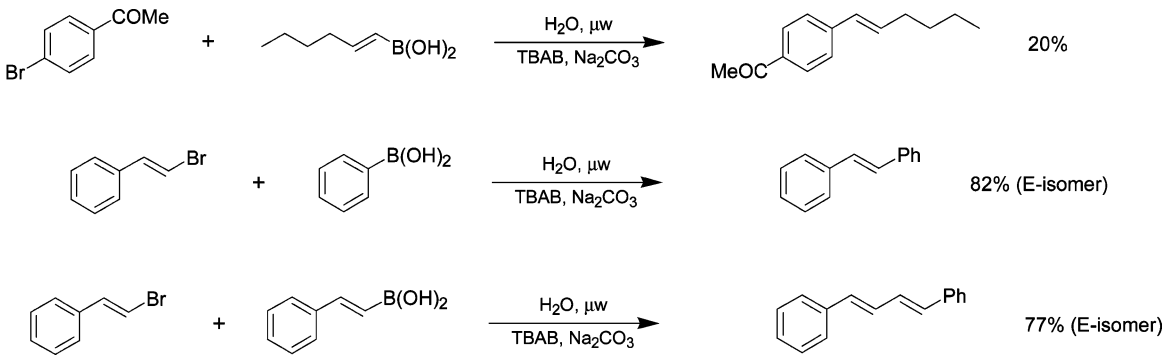
[a] Reactions run on 1 mmol scale with no added palladium. Microwave irradiation of 150 W used. Temperature ramped from rt to 150 °C and held for 5 min. [b] Significant quantities of styrene observed. [c] Decomposition observed.

To build on this, we then screened the coupling of **1** with a wider range of aryl bromides, the results being shown in Table 2. Yields vary depending on the nature and position of the substituents. When an ortho-substituted aryl halide is used, yields tend to be lower than with the para-substituted analogue due to competitive deboronation of **1** (Table 2, entries 3 and 4). A problem of the methodology seems to be the stability of the products in the hot basic aqueous media, with significant decomposition being observed in a number of cases.

To probe the coupling further, we screened the reaction of 4-bromoacetophenone with the less reactive 1-hexenylboronic acid and found that only a 20% yield of product is obtained (Scheme 2). The reaction between β-bromostyrene and purified phenylboronic acid yields stilbene in 82% yield (Scheme 2), this showing that coupling of an alkenyl bromide with an aryl boronic acid is possible without the need for addition of a catalyst. It is also possible to couple β-bromostyrene with **1** to yield a diene product.

Building on our results with the boronic acids, we wanted to probe the effects of purity of the other reagents on the coupling reaction. In light of the reports of "homeopathic" palladium catalysis of the Heck reaction,[17] we in particular wanted to reanalyze reagents and whole product mixtures for sub-ppm concentrations of palladium using ICP-MS analysis to enable us to measure lower concentrations than previously possible. One source of palladium could be the water used in the reaction. Since starting our program, we have been using ultrapure water, purified to a specific resistance of >16 mΩ·cm on every occasion. We analyzed this for palladium and found levels in the region of 0.24 ppb which we believe to be too low to be catalytically active. The organic reagents used in the reactions are all purified prior to use and we believe them to be palladium free. The only reagent we cannot easily purify is the sodium carbonate.

SCHEME 2[a]



[a] Reactions run on 1 mmol scale with no added palladium. Microwave irradiation of 150 W used. Temperature ramped from rt to 150 °C and held for 5 min.

Analysis of solutions of so-termed "ultrapure" sodium carbonate in ultrapure water at a concentration equal to half that used in the reaction showed a palladium concentration of between 10 and 24 ppb. Therefore the expected palladium concentration in our reaction vessels would be from 20 to 50 ppb. Study has shown that these levels of palladium are found in many commercially available sources of sodium carbonate but not potassium carbonate. Analysis of aqueous solutions of "ultrapure" potassium carbonate showed levels of palladium corresponding to 0.09 ppb in the concentrations used in our experiments. We therefore wanted to investigate in more detail why, as reported in our earlier papers, when the coupling methodology is performed using sodium carbonate as a base the reaction works well, but with the potassium analogue it does not. We wanted to see if the ppb levels of palladium in the Na_2CO_3 proved sufficient to catalyze the coupling reaction.

To probe this we performed the reaction of 4-bromoacetophenone and phenylboronic acid in the presence of 100 ppb palladium acetate (corresponding to approximately 50 ppb Pd). The reaction was performed on a 1 mmol scale, using potassium carbonate as the base, 2 mL of water as the solvent, and TBAB as a phase-transfer agent. The reaction mixture was heated in a sealed vessel to 150 °C in a scientific microwave and held at this temperature for 5 min. We obtained a 75% yield of product, this comparing to $<5\%$ product formation with potassium carbonate in the absence of the added palladium. This corresponds to a palladium loading of 0.0000008 mol % and a turnover number of 1 250 000. We then performed the same no-added palladium reaction using our sodium carbonate and obtained a 95% yield of the desired biaryl. This leads us to believe that, although the reaction occurs without the direct addition of a transition-metal complex, it is catalyzed by ppb levels of palladium originating from the commercially available sodium carbonate. The fact that the reaction is reproducible with a wide range of sources of commercially available sodium carbonate confirms our initial observation that palladium is a very low level contaminant found in this material.

To probe more thoroughly whether the reaction was Pd-mediated or not we revisited some earlier experiments we had performed using EDTA to scavenge ppb levels of palladium from the reaction mixture. In our initial studies we found that running the reaction of 4-bromoacetophenone and phenylboronic acid in the presence of a 1 000 000-fold excess of EDTA had no effect on the product yield. This added credence to our hypothesis that the reaction was taking place via a metal-free mechanism. However, we now find that running the same reaction using potassium carbonate as base leads to product formation but only when 100 ppb palladium is added to the reaction mixture. This indicates that EDTA does not efficiently sequester Pd from the reaction mixture at elevated temperatures or that the complex formed between the palladium acetate and the EDTA is, itself, catalytically active. We managed to obtain a sample of sodium carbonate containing only 0.21 ppb Pd and found that, when using this as the base in the reaction of 4-bromoacetophenone and phenylboronic acid, no product was obtained. Addition of 100 ppb palladium acetate to an identical reaction mixture leads to a 90% yield of the desired biaryl. This acts as definitive proof that the reaction is catalyzed by the ppb levels of Pd found in commercially available sodium carbonate.

A further interesting observation we made was that the coupling of 4-bromoacetophenone and phenylboronic acid was higher yielding when the reaction mixture was not stirred. In the absence of stirring, the reaction mixture forms two distinct phases: a lower aqueous layer containing the base and an upper organic layer containing the organic substrates. We believe that the TBAB sits in both the organic and aqueous phases. This made us probe the role of the water and TBAB. Running the reaction in the absence of water does not yield product, even with the addition of higher loadings of palladium. We believe that one of the key roles of the water is simply to dissolve the base and that the reaction takes place at the aqueous/organic interface. Badone and co-workers have investigated the effects of solvent, including water, on the rate of the ligandless palladium acetate catalyzed Suzuki reaction of a range of aryl bromides, iodides, and triflates.[26] They report that when using water as a solvent the addition of 1 equiv of tetrabutylammonium bromide (TBAB) to the reaction mixture greatly accelerates the reaction. They find that activated aryl bromides can be coupled with phenylboronic acid to yield biaryls fairly rapidly (1 h) and in good yields whereas with aryl iodides the reaction does not reach completion. The role

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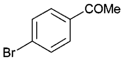
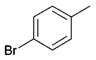
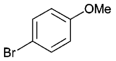
[26] Badone, D.; Baroni, M.; Cardamone, R.; Ielmini, A.; Guzzi, U. *J. Org. Chem.* **1997**, *62*, 7170.

TABLE 3. Suzuki Coupling of Aryl Bromides with Phenylboronic Acid

entry	reaction conditions			product yield %		
	Pd loading	base	heating method			
1	100 ppb	Na_2CO_3	μw[a]	56	3	3
2	250 ppb	Na_2CO_3	μw[a]	94	41	60
3	2.5 ppm	Na_2CO_3	μw[a]	99	92	81
4	100 ppb	Na_2CO_3	conventional[b]	8	0	0
5	250 ppb	Na_2CO_3	conventional[b]	70	60	0
6	2.5 ppm	Na_2CO_3	conventional[b]	81	70	64
7	100 ppb	K_2CO_3	μw[a]	5	4	2
8	250 ppb	K_2CO_3	μw[a]	57	14	36
9	2.5 ppm	K_2CO_3	μw[a]	89	81	79
10	2.5 ppm	K_2CO_3	conventional[b]	95	50	75

[a] Reactions run on 1 mmol scale. $Pd(NO_3)_2$ used as catalyst. Microwave irradiation of 150 W used. Temperature ramped from rt to 150 °C and held for 5 min. [b] Reactions run on 1 mmol scale. $Pd(OAc)_2$ used as catalyst. Reaction mixture placed into an oil bath preheated to 150 °C and held there for 7 min before being removed.

of the ammonium salts is thought to be 2-fold. First, they facilitate solvation of the organic substrates in the solvent medium. Second, they are thought to enhance the rate of the coupling reaction by activating the boronic acid to reaction by formation of a boronate complex $[ArB(OH)_3]^-[R_4N]^+$. TBAB has been used recently in conjunction with a palladium oxime catalyst for the Suzuki coupling of aryl chlorides with phenylboronic acid in water.[27] We wanted to explore whether it was the fact that we were using TBAB as an additive in our reactions that made the coupling so efficient at the very low palladium loadings. To test this, we needed to find an alternative phase-transfer agent to TBAB. In our initial research, we had screened a range of organic solvent/water mixtures as media for the coupling without the addition of TBAB or a metal catalyst and found that either the reaction was inhibited or else considerably lower yields of the desired biaryl were formed. We rescreened mixtures of water and, respectively, NMP, DMF, and methanol using the 100 ppb palladium acetate solution but no TBAB and found the same results as previously. We then focused on mixtures of water and alcohols and found that although methanol/water and butanol/water mixtures inhibited the reaction, a 1:1 ethanol/water mixture was an excellent solvent mixture giving comparable yields to when water alone is used in the presence of TBAB. This shows that the TBAB is not essential to the success of the coupling reaction.

A problem with using ultralow concentrations of palladium acetate in water for the reactions is the confidence that can be put on the exact metal concentration of the solution. Palladium acetate is only sparingly soluble in water, even when using high dilution. Working with sub-ppm quantities of metal complex, even small amounts of undissolved material will have a profound effect on the bulk concentration. For this reason, and also because the palladium contaminant in sodium carbonate is not likely to be $Pd(OAc)_2$, we wanted to turn our attention to a water-soluble simple Pd salt. Our attention has focused on palladium nitrate since this is readily soluble in water and hence solutions of exact and reliable concentration can be prepared. We wanted to develop a general methodology using ultralow levels of palladium and, initially, TBAB as phase-transfer agent and then using water/ethanol as the reaction medium. We decided to screen selected reactions of 4-bromoacetophenone, 4-bromotoluene, and 4-bromoanisole with phenylboronic acid. We used both sodium and potassium carbonate and worked at three palladium concentrations, namely 100, 250, and 2.5 ppm. These correspond to catalyst loadings of 0.0000016, 0.000004, and 0.00004 mol %, respectively. The reactions were run using a microwave power of 150 W we ramped the temperature from rt to 150 °C, this taking around 1−2 min and then held at this temperature for 5 min. Product yields are shown in Tables 3 and 4. Not surprisingly, product yields increase with increasing palladium concentration. We find that reactions run using water and ethanol are higher yielding than those using water and TBAB, especially at low palladium concentrations. Product yields obtained using K_2CO_3 are generally lower than those observed with Na_2CO_3.

We repeated the coupling between 4-bromoacetophenone and phenylboronic acid for different reaction times using water/TBAB and find that the reaction reaches completion within a total microwave irradiation time of 90 s. This corresponds to turnover frequencies of

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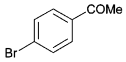
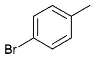
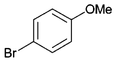
[27] Botella, L.; Nájera, C. *Angew. Chem., Int. Ed.* **2002**, *41*, 179.

TABLE 4. Suzuki Coupling of Aryl Bromides with Phenylboronic Acid Using Water/Ethanol as Solvent

entry	reaction conditions			product yield %		
	Pd loading	base	heating method			
1	100 ppb	Na_2CO_3	μw[a]	83	6	5
2	250 ppb	Na_2CO_3	μw[a]	99	60	19
3	2.5 ppm	Na_2CO_3	μw[a]	99	99	99
4	100 ppb	Na_2CO_3	conventional[b]	5	0	0
5	250 ppb	Na_2CO_3	conventional[b]	78	75	0
6	2.5 ppm	Na_2CO_3	conventional[b]	95	94	85
7	100 ppb	K_2CO_3	μw[a]	13	10	3
8	250 ppb	K_2CO_3	μw[a]	83	21	14
9	2.5 ppm	K_2CO_3	μw[a]	80	75	71
12	2.5 ppm	K_2CO_3	conventional[b]	95	71	75

[a] Reactions run on 1 mmol scale. $Pd(NO_3)_2$ used as catalyst. Microwave irradiation of 150 W used. Temperature ramped from rt to 150 °C and held for 5 min. [b] Reactions run on 1 mmol scale. $Pd(OAc)_2$ used as catalyst. Reaction mixture placed into an oil bath preheated to 150 °C and held there for 7 min before being removed.

28 000 000, 47 000 000, and 50 000 000 for palladium loadings of 100, 250, and 2.5 ppm, respectively.

Having undertaken a range of experiments using microwave heating, we wanted to compare our data with that obtained using conventional heating. Since the start of the field of microwave-assisted synthesis, far shorter times for reactions as compared to those using "conventional" heating have been reported, and this has sparked debate into the nature of the microwave heating.[28] The acceleration of reactions could simply be an effect of the thermal energy generated by the microwaves interacting with the substrates or could be an effect specific to microwave heating. In most cases, the observed differences between microwave and conventional heating can be attributed to simple thermal effects. We were interested in trying to ascertain whether the rates of the reactions we were observing in our Suzuki reaction were simply due to efficient thermal heating. In their report of cross couplings of boronic acids and poly(ethylene glycol) supported aryl iodides in water using $Pd(OAc)_2$ as catalyst, Schotten and co-workers do not comment specifically on whether their conditions for conventional heating are optimized or what temperature their microwave reactions reach but do report that reaction times for the microwave-assisted reactions are a matter of 2−4 min as compared to 2 h for the conventional thermal reactions. We performed the coupling of 4-bromoacetophenone and phenylboronic acid in water/TBAB with addition of 100 ppb Pd using conventional heating. We kept the quantities of reagents and solvent exactly the same as in the microwave-promoted protocol and performed the reaction in a sealed 10 mL microwave tube. We dipped the tube into an oil bath preheated to 150 °C and chose a reaction time of 7 min since this equated to the microwave heating conditions (2 min heat up and 5 min hold). **Caution**.[29] Using water and TBAB as reaction medium, a yield of 4-acetylbiphenyl of 8% was obtained. This compares to a yield of 56% when using microwave heating. We then screened other reaction conditions and reagents, looking primarily at the effects of changing the aryl halide substrate and palladium concentration. Product yields are shown in Tables 3 and 4 for water/TBAB and water/ethanol reaction mixtures, respectively. At low palladium concentrations, product yields obtained using conventional heating are significantly lower than those observed when using microwave heating. However at a palladium concentration of 2.5 ppm yields are much closer, particularly when a water and ethanol mixture is used as the reaction medium.

We re-screened the coupling of **1** with representative aryl bromides using 2.5 ppm $Pd(OAc)_2$, the results being shown in Table 2. As with the no-catalyst added studies, yields vary depending on the nature of the substituents. However, not unexpectedly, the product yields were higher when using the 2.5 ppm $Pd(OAc)_2$ solution. We find that yields obtained when using TBAB as phase-transfer agent (Table 5, entries 1−5) are higher than those when using a mixture of water and ethanol as reaction medium (Table 5, entry 6). A combination of water, ethanol, and TBAB as a reaction medium gives very similar results as with water and TBAB (Table 5, entries 7−9). This would suggest that TBAB plays a more

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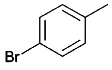
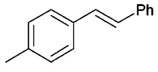
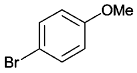
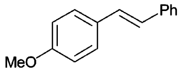
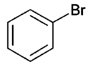
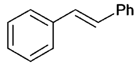
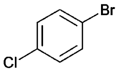
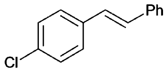
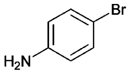
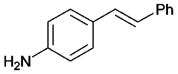
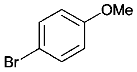
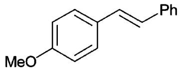
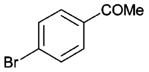
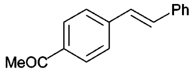
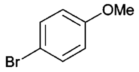
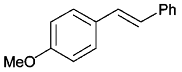
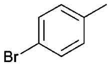
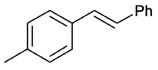
(28) For a review see: Perreux, L.; Loupy, A. *Tetrahedron* **2001**, *57*, 9199.

(29) **Caution:** A blast shield should be in place and vessels designed to withhold elevated pressures must be used. After completion of an experiment, the vessel must be allowed to cool before opening to the atmosphere.

TABLE 5. Suzuki Coupling of Aryl Bromides with 1[a]

entry	reaction medium	aryl halide	product	Yield %
1	H_20 / TBAB			99
2	H_20 / TBAB			81^b
3	H_20 / TBAB			91^b
4	H_20 / TBAB			56^b
5	H_20 / TBAB			56^b
6	H_20 / EtOH			26
7	H_20 / EtOH / TBAB			99
8	H_20 / EtOH / TBAB			82^b
9	H_20 / EtOH / TBAB			91

[a] Reactions run on 1 mmol scale. $Pd(OAc)_2$ used as catalyst. Microwave irradiation of 150 W used. Temperature ramped from rt to 150 °C and held for 5 min. [b] Decomposition observed.

TABLE 6. Effects of Palladium Concentration on the Coupling of 4-bromoacetophenone and Un-purified Phenylboronic Acid[a]

entry	Pd concentration	product yield (%)
1	50 ppb	18
2	100 ppb	48
3	1 ppm	93
4	2.5 ppm	94

[a] Reactions run on 1 mmol scale. $Pd(OAc)_2$ used as catalyst. Microwave irradiation of 150 W used. Temperature ramped from rt to 150 °C and held for 5 min.

important role in the reaction of aryl bromides with **1** as compared with arylboronic acids.

We finally wanted to return to the issue of the purity of the boronic acid. All our experiments above had been run using purified phenylboronic acid. As discussed earlier, impurities in the boronic acid, even in very small amounts, can effectively shut down the coupling reaction when no palladium catalyst is added. We wanted to see what level of palladium was required to effect the coupling in good yield when an impure batch of boronic acid was used. To do this, we took a sample of phenylboronic acid that we knew did not work in the no-added catalyst methodology and ran a series of experiments where we varied the palladium concentration and monitored the product yield in the coupling reaction with 4-bromoacetophenone. The results are shown in Table 6. We found that at a 50 ppb concentration we obtained only an 18% conversion. Increasing the palladium concentration to 1 ppm leads to a product conversion of 93%. These results show that the contaminants in boronic acids must either form a catalytically inactive complex with the palladium or else inhibit the reaction by some other pathway.

In summary, we have shown that when the Suzuki reaction is performed without the addition of a transition-metal catalyst but using sodium carbonate as a base, palladium contaminants down to a level of 50 ppb found in the commercially available base are responsible for the generation of the biaryl rather than, as previously suggested, an alternative non-palladium-mediated pathway. In light of this, we have presented here a revised methodology for Suzuki couplings using ultralow palladium concentrations for use with aryl and vinyl boronic acids. The methodology can be summarized as follows: The reaction is run using commercially avaliable aryl halides and boronic acids. Water is used as a solvent. Either ethanol or TBAB is used as a phase-transfer agent. For arylboronic acids both ethanol and TBAB are effective while for vinylboronic acids TBAB is the phase-transfer agent of choice. A palladium catalyst loading of 1 ppm Pd is recommended for optimal yields. The reaction is run for 7 min using microwave heating (2 min heating to temperature and 5 min at temperature). When using conventional heating, increasing the catalyst loading to 2.5 ppm is recommended for good yields of product after the 7 min reaction time. Regardless of the heating method, a reaction temperature of 150 °C is optimal.

Experimental Section

General Experimental Procedures. All reactions were carried out in air. Microwave reactions were conducted using a focused microwave unit. The machine consists of a continuous focused microwave power delivery system with operator selectable power output from 0 to 300 W. Reactions were performed in glass vessels (capacity 10 mL) sealed with a septum. The pressure is controlled by a load cell connected to the vessel via a 14-gauge needle which penetrates just below the septum surface. The temperature of the contents of the vessel was monitored using a calibrated infrared temperature control mounted under the reaction vessel. ^1H and ^{13}C NMR spectra were recorded at 293 K on a 400 MHz spectrometer. Mass spectroscopy was performed at Notre Dame University, IN.

General Procedure for the No-Catalyst-Added Coupling Reactions. In a 10 mL glass tube were placed aryl halide (1.0 mmol), arylboronic acid (1.3 mmol), Na_2CO_3 (392 mg, 3.7 mmol), tetrabutylammonium bromide (322 mg, 1.0 mmol), 2 mL of water, and a magnetic stir bar (optional). The vessel was sealed with a septum, shaken vigorously (essential), and placed into the microwave cavity. Microwave irradiation of 150 W was used, the temperature being ramped from rt to 150 °C. Once this temperature was reached, the reaction mixture was held at this temperature for 5 min. After allowing the mixture to cool to room temperature, the reaction vessel was opened and the contents poured into a separating funnel. Water (30 mL) and ethyl acetate (30 mL) were added, and the organic material was extracted and removed. After further extraction of the aqueous layer with ether, combining the organic washings and drying them over $MgSO_4$, the ethyl acetate was removed in vacuo leaving the crude product. The product was purified and isolated by chromatography using hexane/ethyl acetate as eluent.

General Procedure for the Palladium-Added Coupling Reactions Using TBAB as Phase-Transfer Agent. The protocol was as with the no-catalyst-added methodology but instead of adding 2 mL of water, aliquots of either a 10 or 1 ppm solution of $Pd(OAc)_2$ or $Pd(NO_3)_2$ were added, and the volume was made up to 2 mL with ultrapure water to give the desired metal concentration.

General Procedure for the Palladium-Added Coupling Reactions Using Ethanol as a Cosolvent. The protocol was as with the no-catalyst-added methodology but instead of adding 2 mL of water and 1 mmol of TBAB, 1 mL of EtOH was added, aliquots of either a 10 or 1 ppm solution of $Pd(OAc)_2$ or $Pd(NO_3)_2$ were added, and the volume was made up to 2 mL with ultrapure water to give the desired metal concentration.

General Procedure for the Conventional Heating Experiments. The reaction mixtures were prepared as in the case of the microwave heating experiments. After the tube was sealed with a septum it was placed into an oil bath preheated to 150 °C and held there for 7 min before being removed and allowed to cool, and then the product extracted and purified in a manner identical to that in the microwave protocol.

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Supporting Information Available: Spectral data for the cross-coupling products. This material is available free of charge via the Internet at http://pubs.acs.org.

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