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Transition-Metal-Free Suzuki-Type Coupling Reactions: Scope and Limitations of the Methodology

Nicholas E. Leadbeater* and Maria Marco

Department of Chemistry, King's College London, Srand, London WC2R 2LS, United Kingdom

nicholas.leadbeater@kcl.ac.uk

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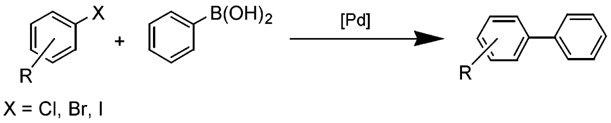
The scope and limitations of the transition-metal-free Suzuki-type coupling of aryl halides and arylboronic acids to form biaryls are presented. Confirmation that the reaction is indeed metal-free is presented. The effects of changing base, solvent, reaction temperature, phase-transfer catalyst, and substrate are shown and the implications of these results discussed in terms of their impact on the synthetic versatility of the methodology. The main findings are that the reaction works well for aryl bromides, water is necessary as a solvent for the reaction, the optimum temperature for the reaction is 150 °C, the reaction is best performed by using microwave promotion with the exception of an electron-poor aryl bromide example where conventional heating may be used, only limited boronic acids can be used as coupling partners, sodium carbonate is the best base for the reaction, tetrabutylammonium bromide proves to be the best phase-transfer catalyst for the reaction, the reaction is limited to couplings between aryl halides and aryl boronic acids with sp^2-sp^3 couplings proving ineffective, and $NaBPh_4$ can be used in the place of phenylboronic acid as a phenylating agent.

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. Indeed, in the last 10 years, there have been over 700 publications on the area of aryl−aryl bond formation. A wide range of metal complexes have been used as catalysts in these coupling reactions, attention particularly being focused on palladium. Suzuki couplings are used daily not only in research laboratories but also on industrial scales.[2]



In addition to a range of organic solvents, there has been considerable recent interest in the use of water as a reaction medium. Over the last 5−10 years, the concept of efficient and selective synthesis in water has been exemplified as the rates, yields, and selectivities observed for many reactions in water have begun to match or, in many cases, surpass those in organic solvents.[3] Water also offers practical advantages over organic solvents. It is cheap, readily available, nontoxic, and nonflammable. The use of water as a solvent for metal-mediated synthesis has attracted considerable research interest.[4] Suzuki couplings of water-soluble aryl iodides have been performed in water by using simple palladium salts[5,6] or amphiphilic polymer-supported palladium catalysts.[7] 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.[8] They report that when using water as a solvent the addition of 1 equiv of tetrabutylammonium bromide (TBAB) to the reaction mixture greatly facilitates 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 of the ammonium salts is

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* Corresponding author.

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(4) For an introduction to the use of organometallic catalysts in aqueous-phase catalysis see: *Aqueous-Phase Organometallic Catalysis, Concepts and Applications*; Cornils, B., Herrmann, W. A., Eds; Wiley-VCH: Weinheim, Germany, 1998.

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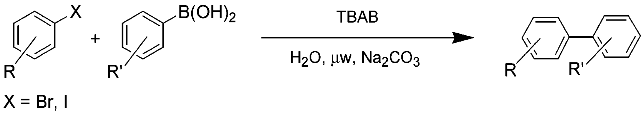
thought to be 2-fold. First they facilitate solvation of the organic substrates in the solvent medium. Second they are thought to enhance the rate of the coupling reaction by activating the boronic acid to reaction by formation of a boronate complex $[ArB(OH)_3]^{-}[R_4N]^{+}$. TBAB has been used recently in conjunction with a palladium oxime catalyst for the Suzuki coupling of aryl chlorides with phenylboronic acid in water[9] and as a promoter in the $Pd(PPh_3)_4$-catalyzed Suzuki coupling reaction of 4-bromobenzonitrile and phenylboronic acid in organic solvents.[10]

With its high dielectric constant water is also potentially a very useful solvent for microwave-mediated synthesis. The use of microwave ovens as tools for synthetic chemistry is a fast growth area.[11,12] Since the first reports of microwave-assisted synthesis in 1986,[13,14] the technique has been accepted as a method for reducing reaction times often by orders of magnitude and for increasing yields of product compared to conventional methods.[15,16] Much of the work in the field to date has been conducted with use of modified domestic microwave ovens. There are, however, problems associated with this, in particular poor reproducibility of reactions and the fact that it is hard to control the reaction precisely. In the last year or so, with the advent of scientific focused microwave systems, many of these problems can be overcome. By using these scientific microwaves it is possible to control the temperature, pressure, microwave power, and reaction times very easily and with a high degree of reproducibility. As a result, this has opened up the possibility of optimizing new reactions in a very short time. We have recently reported that it is possible to couple a range of aryl halides, including chlorides, with phenylboronic acid in neat water using microwave heating with palladium acetate as the catalyst and TBAB as an additive.[17] The total reaction time is between 5 and 10 min and low palladium loadings are used. The reactions can be performed on small (1 mmol) scales, using sealed tubes, or larger scales (20 mmol), using open reaction vessels. We have found subsequently that it is possible to perform the coupling reactions using aryl bromides and iodides equally well and in similar short times with conventional heating.[18] However, the reaction does not work for aryl chloride substrates. In our studies to understand further the role of the water and the TBAB, we have found that, using the appropriate conditions, it is possible to perform Suzuki-type couplings *without the need for a transition-metal catalyst*.[19] Since the use of metals leads to the generation of waste and can have a number of problems associated with it, the eradication of the catalyst from the Suzuki reaction offers significant advantages. This runs true even with today's highly active[20] or recyclable[21] metal catalysts for the reaction. The preparation of these catalysts, their extraction, and product purification can be time-consuming and costly. This is of particular importance when considering the synthesis of fine chemicals such as pharmaceuticals where contamination of the product with heavy metals is highly undesirable. In this paper we discuss the scope and limitations of this transition-metal-free methodology.



Results and Discussion

In our initial communication, we reported 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. (**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.) A wide range of functional groups are tolerated in the reaction and sterically demanding aryl bromides can be coupled with phenylboronic acid to give good yields of product (Table 1, entries 1−15). Representative aryl iodides were also screened in the coupling reaction by using our methodology, but product yields were lower than their bromo counterparts (Table 1, entries 16−18). Aryl chlorides could not be coupled. Reactions are run with a 1:1.3 molar ratio of aryl halide to boronic acid and take 5 min; the only organic materials found at the end of the reaction are the biaryl product, unreacted aryl halide, and traces of benzene. This highlights one of the problems with working at elevated temperatures, namely that there is competitive protodeboronation of the boronic acid to produce benzene (most of which is removed in the

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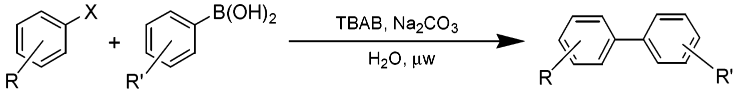
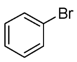
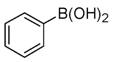
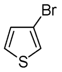
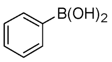
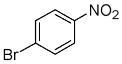
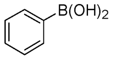
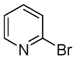
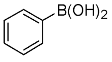
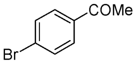
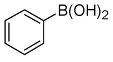
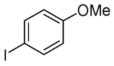
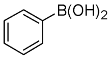
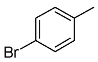
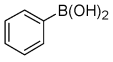
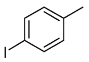
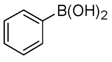
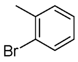
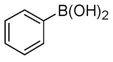
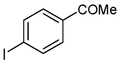
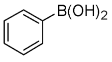
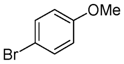
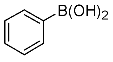
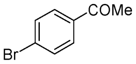
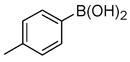
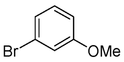
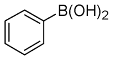
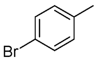
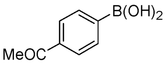
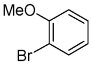
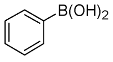
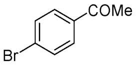
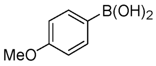
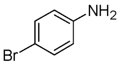
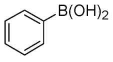
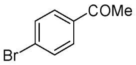
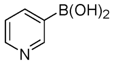
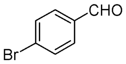
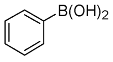
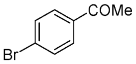
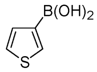
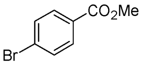
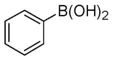
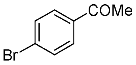
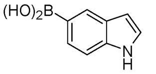
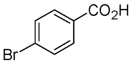
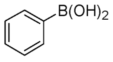
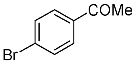
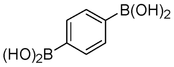
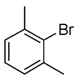
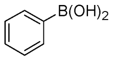
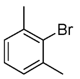
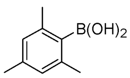
TABLE 1. Suzuki-Type Coupling of Aryl Halides and Boronic Acids in Water[a]



X = Br, I

Entry	Aryl halide	Boronic acid	Yield %	Entry	Aryl halide	Boronic acid	Yield %
1			90[b]	14			0
2			99[b]	15			76[c]
3			98[b]	16			3[c]
4			82[b]	17			79[c]
5			61[b]	18			25[c]
6			53[c]	19			99
7			73[b]	20			78
8			55[b]	21			4[c]
9			82[c]	22			0
10			96[c]	23			0
11			71[c]	24			0
12			99[b]	25			0
13			50[b]	26			0

[a] 1 mmol of aryl halide, 1.3 mmol of boronic acid, 3.8 mmol of Na_2CO_3, 1.0 mmol of TBAB, 2 mL of water. Yields quoted are for microwave promotion, using a microwave power of 100 W. The temperature is ramped to 150 °C and held for 5 min. [b] Isolated yield. [c] Determined by ^{1}H NMR.

workup procedure and hence only traces are observed).[22] We find that addition of additional equivalents of boronic acid to the reaction mixture does not have an appreciable effect on the overall product yield. Of interest is that no homocoupling of either the aryl halide or boronic acid is observed during the course of any of the reactions.

We were keen next to explore the range of boronic acids that can be used in the coupling protocol and so we screened a number of substrates bearing different functional groups (Table 1, entries 19−26). However, we find

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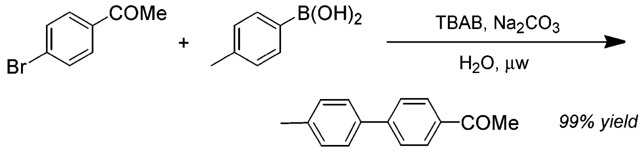
(22) This competitive deboronation of boronic acids in basic aqueous media has been reported on a number of occasions. For a study of the reaction see: (a) Kuvila, H. G.; Reuwer, J. F.; Mangravite, J. A. *J. Am. Chem. Soc.* **1964**, *86*, 2666. (b) Kuvila, H. G.; Nahabedian, K. V. *J. Am. Chem. Soc.* **1961**, *83*, 2159.

that the methodology is limited to electron-poor or electron-neutral boronic acids; electron-rich or heterocyclic examples not reacting with our conditions. This shows one of the limitations of the current methodology but we believe that after further optimization it may be possible to expand the scope of boronic acids that can be used in the transition-metal-free protocol. However, like with phenylboronic acid, in those cases where coupling does occur the reaction is very clean, no homocoupling of either the aryl halide or boronic acid being observed. These studies also allowed us to probe the regioselectivity of the reaction. Looking at the coupling of 4-bromoacetophenone with 4-methylboronic acid (Table 1, entry 19), we obtain pure 4-acetyl-4′-methylbiphenyl in 99% isolated yield with no evidence for formation of any other regioisomers. This illustrates that the reaction is totally regioselective.



Analysis of the Reaction Mixture. To show that the reaction is indeed transition-metal free, we used new glassware, apparatus, reagents (not only were new bottles of reagents used but also a range of suppliers' reagents were screened in the reaction and all found to lead to the same yields of biaryl formation),[1] and spatula and analyzed the entire crude product mixture from a reaction for palladium content. We found that there was no palladium in the mixture down to the level of detection of the analytical apparatus (less than 0.1 ppm). This, and the fact that the reaction is reproducible argues against catalytic contaminants. But to show that other metals that could possibly catalyze the reaction are present in too small amounts we have subsequently analyzed reaction mixtures for the presence of a wide range of elements. The results are shown in the Supporting Information. Possible catalyst candidates include nickel,[23] platinum,[24] copper,[25,26] and ruthenium[25] 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. We perform the reactions in 10-mL glass tubes sealed with a Teflon septum and the pressure of the reaction mixture is measured by a load cell connected to the vessel via an SiO_2-coated steel needle that penetrates just below the septum surface. A further postulate was that the reaction could be catalyzed by any metal exposed on the needle. To show that this was not the case, we performed the reaction in a vessel with a noninvasive pressure monitor and found that we still obtained the desired biaryl product.

Effects of Temperature on the Reaction. Having shown that the reaction is not transition-metal mediated we were next interested in looking at the components in the reaction mixture individually together with the reaction conditions. We looked first at the temperature at which the reaction is performed. In our initial experiments we used a reaction temperature of 150 °C, using a microwave power of 100 W. The reaction mixture takes approximately 50 s: 1 min to reach the target temperature that is then held for 5 min. To assess the effects of temperature on the reaction we have performed the coupling of 4-bromotoluene and phenylboronic acid at a range of different temperatures. We find that decreasing the temperature to 130 °C has the effect of stopping the reaction, no biaryl being formed. Increasing the temperature to 170 °C does not lead to an improvement in reaction yields and indeed is slightly deleterious. As already mentioned, one of the problems with working at elevated temperatures is that there is competitive protodeboronation of the boronic acid to produce benzene. However, running the reaction at 150 °C seems to have the effect of facilitating the coupling reaction while limiting the protodeboronation. Indeed at this temperature the coupling reaction must be significantly faster than the competing deboronation.

These results impact on the possibility of performing the reaction with conventional heating. We find that placing a sealed tube into an oil bath at 150 °C offers an easy way to perform the coupling reaction of phenylboronic acid with 4-bromoacetophenone, a 91% yield of product being obtained after heating for 2 h. (**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 being opened to the atmosphere.) However, with electron-rich and electron-neutral aryl bromide substrates it is not possible to perform the reaction so efficiently with conventional heating. With 4-bromotoluene a conversion of only 29% is obtained after heating for 16 h, while with 4-bromoanisole, no product is obtained after a similar reaction time. By inserting a thermal probe into the reaction mixtures we found that the solutions were not reaching more than 130 °C which, as we knew from our microwave studies, was not sufficient to promote biaryl formation. However, we find that increasing the temperature of the oil bath from 150 to 185 °C offers improvements in product yield for bromotoluene, a 100% conversion being obtained after 16 h of heating at this higher temperature. However, with 4-bromoanisole there was still no reaction. Since the start of the field of microwave-assisted synthesis, far shorter times for reactions as compared to those with "conventional" heating have been reported and this has sparked debate into the nature of the microwave heating.[27] 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 and our results show that this is the case with our coupling reactions.

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[23] (a) Zim, D.; Monteiro, A. L. *Tetrahedron Lett.* **2002**, *43*, 4009. (b) Griffiths, C.; Leadbeater, N. E. *Tetrahedron Lett.* **2000**, *41*, 2487. (c) Lipshutz, B. H.; Sclafani, J. A.; Blomgren, P. A. *Tetrahedron* **2000**, *56*, 2139. (d) Leadbeater, N. E.; Resouly, S. M. *Tetrahedron* **1999**, *55*, 11889.

[24] Bedford, R. B.; Hazelwood, S. L.; Albisson, D. A. *Organometallics* **2002**, *21*, 2599.

[25] Thathagar, M. B.; Beckers, J.; Rothenberg, G. *J. Am. Chem. Soc.* **2002**, *124*, 2159.

[26] (a) Liu, X. X.; Deng, M. Z. *Chem. Commun.* **2002**, 622. (b) Savarin, C.; Liebeskind, L. S. *Org. Lett.* **2001**, *3*, 2149.

[27] For a review see: Perreux, L.; Loupy, A. *Tetrahedron* **2001**, *57*, 9199.

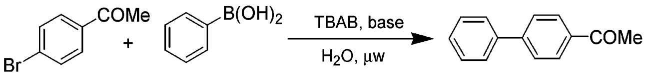
The microwave methodology offers a facile and very efficient method for holding the reaction mixture at a high temperature constantly thereby promoting the reaction.

We also investigated the possibility of activating aryl chlorides in the microwave-promoted methodology by using elevated temperatures. In our Pd-mediated Suzuki coupling protocol we find that aryl chlorides can be used as substrates only when the temperature is increased from 150 °C up to 175 °C.[17] We screened the reaction of 4-chlorotoluene with phenylboronic acid at temperatures up to 175 °C but no product was obtained indicating that, with the metal-free coupling protocol, simply increasing the temperature does not allow us to increase the substrate scope of the methodology.

Effects of Solvent Variation on the Reaction. In our initial experiments we ran all the reactions using water as solvent. In contrast to many other solvents, water not only provides a medium for solution chemistry but often participates in elementary chemical events on a molecular scale. To explore the solvent scope of the reaction, we screened a number of other solvents in the coupling of 4-bromoacetophenone with phenylboronic acid. We find that running the reaction using dimethylformamide or methanol as solvent leads to significantly less coupling product (6% and 42% conversions, respectively). If a 1:1 mixture of water and DMF is used, no biaryl product is formed. The same is true if a 1:1 mixture of water and methanol is used. This clearly demonstrates that the use of water as a solvent is central to the success of the reaction. Running the reaction in D_2O leads to similar yields of coupling product as with H_2O although all of the protons of the methyl group of the methyl ketone functionality are exchanged for deuterium.

Effects of Base on the Reaction. In the absence of any base, the reaction does not proceed, indicating that it is essential to the procedure although its role is not currently fully understood. In our initial experiments we used Na_2CO_3 as base, finding that optimal product yields were obtained by using 3.7 equiv with respect to the aryl halide. Use of less than this results in a significant reduction in product yield. Using 4-bromoacetophenone and phenylboronic acid as substrates, we have screened a range of other metal carbonates in the reaction together with $(NH_4)_2CO_3$. The results are shown in Table 2. We find that, of the group 1 metal carbonates, Na_2CO_3 and Cs_2CO_3 are the only two that result in acceptable yields of product (Table 2, entries 2 and 4), Li_2CO_3 and K_2CO_3 proving inactive (Table 2, entries 1 and 3). Group 2 metal carbonates are not effective bases for the reaction, nor is $(NH_4)_2CO_3$ (Table 2, entries 5, 6, and 7). As all the metal carbonates screened have similar basicity, the results suggest that there may be a cation effect in the reaction, sodium being particularly good. To see if this was indeed the case we screened a number of other sodium-containing bases and found that anion is also important: NaOH proving inactive, $NaHCO_3$ and NaOAc leading to some product formation but only small quantities (Table 2, entries 8, 9, and 10). We also screened potassium phosphate and potassium fluoride as both of these are well-known bases in coupling reactions. We obtained a moderate yield with K_3PO_4, while KF was inactive (Table 2, entries 11 and 12).

TABLE 2. Effects of the Base on the Microwave-Promoted Suzuki-Type Coupling of 4-Bromoacetophenone and Phenylboronic Acid in Water[a]



entry	base	product conversion (%)[b]
1	Li_2CO_3	0
2	Na_2CO_3	100
3	K_2CO_3	17
4	Cs_2CO_3	89
5	Mg_2CO_3	11
6	$CaCO_3$	9
7	$(NH_4)_2CO_3$	0[c]
8	NaOH	0
9	$NaHCO_3$	33
10	NaOAc	4
11	K_3PO_4	47
12	KF	0

[a] 1 mmol of 4-bromoacetophenone, 1.3 mmol of phenylboronic acid, 1 mmol of TBAB, 3.7 mmol of base, 2 mL of water. Temperature ramped to 150 °C and held there for 5 min. [b] Determined by ^1H NMR. [c] No TBAB used.

Effects of Phase-Transfer Catalyst on the Reaction. We have assessed a number of phase-transfer catalysts in the reaction and attempted to probe their role in the reaction. The results are summarized in Table 3. The addition of phase-transfer catalysts such as tetraalkylammonium salts has been shown to improve yields of Suzuki reactions in both water[8,9] and polar organic solvents.[28] The role 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 $[ArB(OH)_3]^-[R_4N]^+$. We felt that both of these factors would help reduce the extent of hydrodeboronation in our experiments since increased solubility of the organic substrates in the water would mean increased concentration of reactive species and the formation of a complex between the boronic acid and the ammonium salt would favor Suzuki-type couplings over hydrodeboronation. Using 4-bromoacetophenone and phenylboronic acid as substrates, we find that optimal product yields are obtained when using a stoichiometric ratio of aryl bromide to TBAB of 1:1. Use of less TBAB results in a significant decrease in product yield (Table 3, entries 1, 2, and 3). To determine whether the TBAB was playing an integral role in the reaction mechanism we attempted to couple a more water soluble aryl bromide with a more water soluble arylboronic acid. We find that the reaction between 4-bromobenzoic acid and 4-carboxybenzeneboronic acid can be effected in the absence of TBAB giving a conversion of 27% (Table 3, entries 3 and 4). Although this is low, it is comparable to that obtained when using TBAB (Table 3, entry 5). It therefore does show that the reaction can occur without TBAB. This is further confirmed by the observation that, using 4-bromoacetophenone and phenylboronic acid as substrates, replacement of TBAB by poly(ethylene glycol) (PEG) as a phase-transfer catalyst results only in a slight decrease in product yield (Table 3, entry 6). To determine whether

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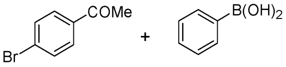
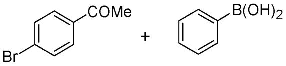
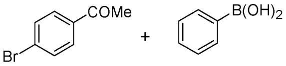
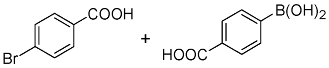
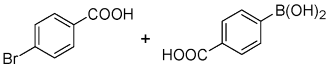
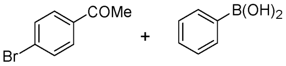
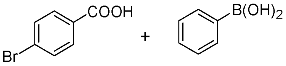
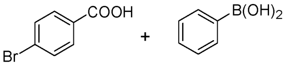
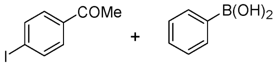
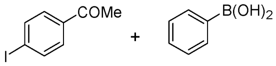
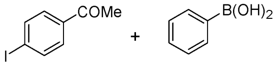
(28) Zim, D.; Monteiro, A. L.; Dupont, J. *Tetrahedron Lett.* **2000**, *41*, 8199.

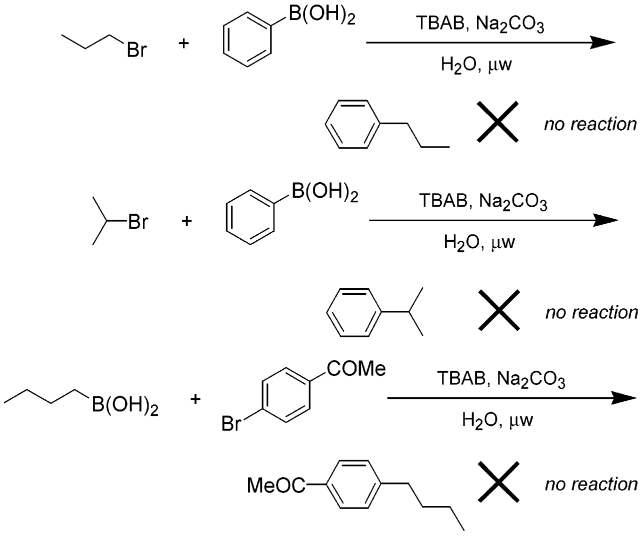
TABLE 3. Effects of the Phase-Transfer Catalyst on the Microwave-Promoted Suzuki-Type Coupling of Aryl Halides and Boronic Acids in Water[a]

entry	reactants	phase-transfer catalyst	product conversion (%)[b]
1		TBAB, 1 equiv.	100
2		TBAB, 0.5 equiv.	58
3		none	0
4		none	27
5		TBAB, 1 equiv.	34
6		PEG, 1 equiv.	87
7		TBACl, 1 equiv.	0
8		TBAB, 1 equiv.	82
9		TBAI, 1 equiv.	37
10		none[c]	78
11		none	59
12		TBACl, 1 equiv.	15
13		TBAB, 1 equiv.	25
14		TBAI, 1 equiv.	9

[a] 1 mmol of aryl halide, 1.3 mmol of boronic acid, phase-transfer catalyst, 3.7 mmol of Na_2CO_3, 2 mL of water. Temperature ramped to 150 °C and held there for 5 min. [b] Determined by ^1H NMR. [c] 1 equiv of NaBr added.

the bromide anion in the TBAB is important in the reaction we screened the chloro and iodo analogues, TBACl and TBAI, in the reaction and found that the use of either of these results in a decrease in product yield (Table 3, entries 7, 8, and 9). This clearly shows that not only does the bromide ion in the TBAB play a role in the reaction but the use of TBACl or TBAI actually has a deleterious effect. The role of bromide ion was further illustrated in the reaction of 4-bromobenzoic acid and phenylboronic acid with NaBr as an additive. A conversion of 78% is obtained, this being higher than when NaBr is omitted (Table 3, entries 10 and 11). This led us to investigate the possibility of increasing the scope of the reaction to aryl iodides and chlorides by selection of appropriate phase-transfer catalysts. We screened the reaction of 4-iodoacetophenone with benzeneboronic acid using TBACl, TBAB, and TBAI as phase transfer catalysts (Table 3, entries 12, 13, and 14). We find that, again, the use of TBAB leads to the highest conversion to the desired biaryl product.

Expansion of the Substrate Scope of the Reaction to Incorporate Alkyl Halides and Alkylboronic Acids. We have already shown that, when using aryl bromides, a wide range of functional groups are tolerated in the reaction and sterically demanding aryl bromides can be coupled with phenylboronic acid to give good yields of product. We wanted to determine whether, using our optimal reaction conditions, it was possible to perform sp^2-sp^3 coupling reactions of either alkylboronic acids with aryl halides or arylboronic acids with alkyl halides. These reactions have proven the focus of much recent research activity within the transition-metal mediated catalysis community because of the challenge associated with this but also the potential use of this methodology in the synthetic chemist's portfolio.[29,30] We screened the reaction of 1-bromopropane and with phenylboronic acid but no product was obtained. Similar observations were made when using the secondary alkyl halide 2-bromopropane. We next screened the reaction of butaneboronic acid with 4-bromoacetophenone again with no success. This suggests that the methodology in its current form is limited to use only with aryl−aryl coupling reactions.



Expansion of the Substrate Scope of the Reaction to Incorporate Tetratarylborates. We next wanted to explore the possibility of varying the boron-containing component, using group 1 metal tetraaryl borates in place of boronic acids. These would be less prone to hydrodeboronation and also would increase the scope of reagents that can be used in the coupling reaction. Borates such as $NaBPh_4$ have been used in the palladium-mediated Suzuki reaction previously, working well in water and transferring all four aryl rings.[5] Sodium tetraphenylborate has been used as a phenylation reagent for microwave-mediated aqueous-phase biaryl synthesis.[31] Our interest comes about from their solubility in neat water and thus opening up the possibility of performing our coupling reaction in the absence of a phase-transfer catalyst. We find that it is possible to couple 4-bromoacetophenone and $NaBPh_4$ in 58% yield, using a stoichiometric ratio of the two reagents of 4:1, respectively (Table 4, entry 1). The reaction is performed under the same conditions as for the couplings of aryl halides with boronic acids except that no TBAB is used. We have extended the methodology to encompass aryl bromides ranging from electron rich to electron poor, good yields of the desired biaryl being formed in each case (Table 4, entries 2, 3, and 4). We find that the product yields obtained when using $NaBPh_4$ are all lower than in the corresponding examples when using boronic acids. We attribute this to the poor solubility of the aryl bromides in the water. However, it is not possible to improve product yields by adding TBAB to the reaction mixture since this reacts with the borate in situ to form $[Bu_4N]^+[BPh_4]^-$ and NaBr, the former of which precipitates out of solution and is inactive in the coupling reaction (Table 4, entry 5). We have used $KBPh_4$ in place of $NaBPh_4$ but find that this results in a significant decrease in product yield (Table 4, entry 6).

Conclusions

We have presented in detail here our methodology for transition-metal-free coupling of aryl bromides with boronic acids using water as a solvent and in the presence of a base and a phase-transfer catalyst. We have discussed the scope and limitations of the methodology. In summary, the key observations are the following: the methodology is indeed transition-metal free as shown by analysis of the reaction mixtures by ICP-AA; the reaction works well for a range of aryl bromides; water is necessary as a solvent for the reaction, the use of other media such as organic solvents resulting in no product being formed; the optimum temperature for the reaction is 150 °C above which protodeboronation is observed and below which no coupling reaction occurs; the reaction is best performed by using microwave promotion with the exception of an electron-poor aryl bromide example where conventional heating may be used; only limited boronic acids can be used as coupling partners; Na_2CO_3 proves to be the best base for the reaction, other metal carbonates together with NaOH, $NaHCO_3$, and NaOAc being less active; tetrabutylammonium bromide is shown to be the best phase-transfer catalyst for the reaction, presumably due to the fact that it also interacts with the boronic acid present, but other phase-transfer catalysts can be

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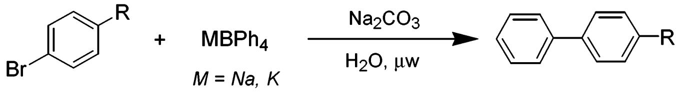
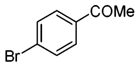
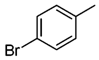
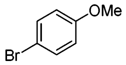
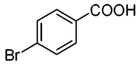
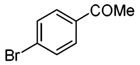
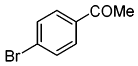
(29) For a review see: Luh, T. Y.; Leung, M. K.; Wong, K. T. *Chem. Rev.* **2000**, *100*, 3187.

(30) (a) Kirchhoff, J. H.; Netherton, M. R.; Hills, I. D.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 13662. (b) Netherton, M. R.; Fu, G. C. *Angew. Chem., Int. Ed. Engl.* **2002**, *41*, 3910. (c) Kirchhoff, J. H.; Dai, C. Y.; Fu, G. C. *Angew. Chem., Int. Ed. Engl.* **2002**, *41*, 1945. (d) Soderquist, J. A.; Leon, G.; Colberg, J. C.; Martinez, I. *Tetrahedron Lett.* **1995**, *36*, 3119.

(31) Villemin, D.; Gómez-Escalonilla M. J.; Saint-Clair, J.-F. *Tetrahedron Lett.* **1996**, *37*, 8219.

TABLE 4. Microwave-Promoted Suzuki-Type Coupling of Aryl Halides and Tetraphenylborates in Water[a]



entry	reactants	product yield (%)[b]
1	 + $NaBPh_4$	58
2	 + $NaBPh_4$	22
3	 + $NaBPh_4$	57[c]
4	 + $NaBPh_4$	79[c]
5	 + $NaBPh_4$	0[d]
6	 + $KBPh_4$	11[c]

[a] 1 mmol of aryl halide, 0.25 mmol of tetraphenylborate, 3.7 mmol of Na_2CO_3, 2 mL of water. Temperature ramped to 150 °C and held there for 5 min. [b] Conversion determined by ^{1}H NMR. [c] Isolated yield. [d] 1 equiv of TBAB added.

used with slight decreases in product yield observed; the reaction is limited in the scope of the boronic acids that can be used and is limited to couplings between aryl halides and arylboronic acids, sp^2-sp^3 couplings proving ineffective; and $NaBPh_4$ can be used in place of phenylboronic acid as an phenylating agent.

In terms of scope and conditions used, this transition-metal-free coupling procedure compares favorably with many of the palladium-mediated methodologies found in the literature. It of course has the major advantage that no metal catalyst is needed. Work is now underway to determine the mechanism of the coupling reaction and to apply the methodology to other reactions that are traditionally palladium mediated.

Experimental Details

General Procedure for the Microwave-Assisted Reactions. In a 10-mL glass tube was placed aryl halide (1.0 mmol), arylboronic acid (1.3 mmol), Na_2CO_3 (400 mg, 3.8 mmol), tetrabutylammonium bromide (322 mg, 1.0 mmol), 2 mL of water, and a magnetic stir bar. The vessel was sealed with a septum and placed into the microwave cavity. Microwave irradiation of 100 W was used, the temperature being ramped from rt to the desired temperature. Once this was reached, the reaction mixture was held at that 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 and diethyl ether (30 mL of each) were added and the organic material extracted and removed. After further extraction of the aqueous layer with ether, combining the organic washings and drying them over $MgSO_4$, the ether was removed in vacuo leaving the crude product. The product was purified and isolated by chromatography after, in the cases where the starting aryl halide was a liquid, first removing unreacted aryl halide by heating the crude residue while under a vacuum on a Schlenk line.

General Procedure for Conventionally Heated Reactions. The method was as for the microwave-assisted procedure except that after the tube was sealed with a septum it was placed into an oil bath preheated to the desired temperature rather than into the microwave cavity. The reaction mixture was held in the oil for the specified time before being removed, the vessel and contents were allowed to cool, and then the product was extracted and purified in an identical manner to that in the microwave protocol.

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Supporting Information Available: Elemental analysis data. This material is available free of charge via the Internet at http://pubs.acs.org.

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