

Ligand-Free Palladium Catalysis of the Suzuki Reaction in Water Using Microwave Heating

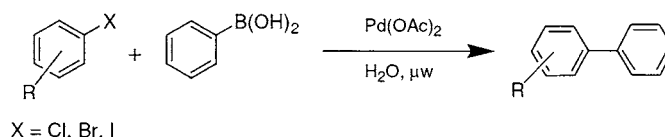
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ABSTRACT



We report the ligand-free palladium catalysis of the Suzuki reaction in water using microwave heating. Our methodology uses low palladium loadings (0.4 mol %), is fast (5–10 min reaction time), and is useful for couplings involving boronic acids and aryl iodides, bromides, and chlorides.

Water is a cheap, readily available nontoxic solvent for use in chemistry.¹ As well as for organic chemistry, water has also been used for metal-mediated organic synthesis.² There are, however, problems with the use of water, such as solubility of substrates and stability of the metal catalysts in water, but these problems have to some extent been overcome by the use of phase-transfer catalysts and water-soluble phosphine ligands or the design of novel heterogeneous catalysts.³ With its high dielectric constant, water is also potentially a very useful solvent for microwave-mediated synthesis.^{4,5} As well as benefiting from the rate enhancement effects found when using microwave heating, when water is heated well above its boiling point in sealed vessels, organic substrates can become more soluble.⁶

(1) For an introduction to the use of water as a solvent in organic synthesis see: (a) *Organic Synthesis in Water*; Greico, P. A., Ed.; Blackie Academic & Professional: London, 1998. (b) Li, C.-J.; Chen, T.-H. *Organic Reactions in Aqueous Media*; Kluwer Academic Publishers: Dordrecht, 1997.

(2) 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, 1998.

(3) For recent examples, see: (a) Gulyas, H.; Szollosy, A.; Hanson, B. E.; Bakos, J. *Tetrahedron Lett.* **2002**, *43*, 2543. (b) Brauer, D. J.; Hingst, M.; Kottsieper, K. W.; Like, C.; Nickel, T.; Tepper, M.; Stelzer, O.; Sheldrick, W. S. *J. Organomet. Chem.* **2002**, *645*, 14.

(4) See, for example: (a) Baudel, V.; Cazier, F.; Woisel, P.; Surpateanu, G. *Eur. Polymer J.* **2002**, *38*, 615. (b) An, J. Y.; Bagnell, L.; Cablewski, T.; Strauss, C. R.; Trainor, R. W. *J. Org. Chem.* **1997**, *62*, 2505.

The Suzuki reaction (palladium-catalyzed cross coupling of aryl halides or triflates 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.⁷ There have been a number of reports of the palladium-mediated Suzuki reaction being performed using water as a solvent,^{8,9} which relate to the coupling of aryl boronic acids with aryl iodides or activated bromides, with only one recent exception. This reports the coupling of aryl chlorides but involves the use of an oxime-carbapalladacycle as the catalyst.¹⁰ There have also been a number of reports of the use of water as a cosolvent for the reaction,

(5) For recent reviews on the use of microwaves in organic synthesis see: (a) Larhed, M.; Moberg, C.; Hallberg, A. *Acc. Chem. Res.* **2002**, in press. (b) Lew, A.; Krutzik, P. O.; Hart, M. E.; Chamberlin, A. R. *J. Comb. Chem.* **2002**, *4*, 95. (c) Lindström, P.; Tierney, J.; Wathey B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225. (d) Perreux L.; Loupy, A. *Tetrahedron* **2001**, *57*, 9199. (e) S. Deshayes, S.; Liagre, M.; Loupy, A.; Luche, J.-L.; Petit, A. *Tetrahedron* **1999**, *55*, 10851.

(6) Katritzky, A. R.; Siskin, M. *Chem. Rev.* **2001**, *101*, 837.

(7) For recent reviews, see: (a) Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359. (b) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147. Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.

(8) For a review of palladium-catalyzed reactions in water, see: Genêt, J.-P.; Savignac, M. *J. Organomet. Chem.* **1999**, *576*, 305.

(9) (a) Sakurai, H.; Tsukuda, T.; Hirao, T. *J. Org. Chem.* **2002**, *67*, 2721. (b) Badone, D.; Baroni, M.; Cardamone, R.; Ielmini, A.; Guzzi, U. *J. Org. Chem.* **1997**, *62*, 7170. (c) Bumagin, N. A.; Bykov, V. V. *Tetrahedron* **1997**, *53*, 14437.

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again focusing on the use of aryl iodides or activated bromides,¹¹ and one recent report¹² of the use of aryl chlorides in a 20:1 DMA/water mix. The first reports of microwave-mediated Suzuki reactions came in 1996, using Pd(PPh₃)₄ as a catalyst both for homogeneous¹³ and solid-phase¹⁴ biaryl synthesis. More recently, microwave heating has been used to facilitate the coupling in water of aryl boronic acids with the poly(ethylene glycol) esters of an aryl iodide, triflate, and a bromothiophene.¹⁵ In the same report, 4-iodobenzoic acid methyl ester was also coupled with a range of boronic acids in water/poly(ethylene glycol) mixtures. Sodium tetraphenylborate has recently been used as a phenylation reagent for microwave-mediated aqueous-phase biaryl synthesis.¹⁶

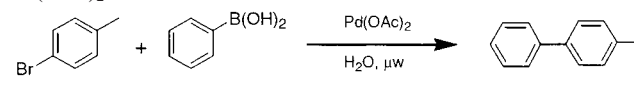
A range of palladium catalysts have been used in these studies, and in many cases it is possible to perform the reaction ligand-free using varying amounts of palladium salts⁹ or palladium on charcoal.^{9a,12} Although much attention has been focused on water-soluble aryl halides, non-water-soluble halides have also been coupled, but in the presence of a phase-transfer catalyst.^{9b,10}

In this Letter we present the results from our investigations into the ligand-free palladium catalysis of the Suzuki reaction in pure water using microwave heating. The methodology we report here uses low palladium loadings (0.4 mol %), is fast (5–10 min reaction time), and is useful for Suzuki coupling reactions involving a range of aryl iodides and bromides. In addition, we report that aryl chlorides can also be coupled, although in slightly lower yields than their bromo-counterparts.

As a starting point for the development of our microwave-mediated methodology, we chose to study the coupling of phenylboronic acid with 4-iodobenzoic acid. We found that using 5 mol % Pd(OAc)₂, Na₂CO₃ as base, and 1 mL water, it was possible to obtain an isolated yield of 95% of 4-phenylbenzoic acid after 10 min of microwave irradiation.¹⁷ Using a microwave power of 60 W we ramped the temperature from room temperature to 200 °C, which took 30–40 s, and then held it at this temperature for 5 min.¹⁸ Our

attention then turned to the coupling of phenylboronic acid with the non-water-soluble substrate 4-bromotoluene as this would act as a sharpening stone for optimizing reaction conditions (Table 1). Using the same conditions as for

Table 1. Microwave-Mediated Suzuki Coupling of 4-bromotoluene and Phenylboronic Acid in Water Using Pd(OAc)₂^a



entry	reaction conditions ^b	product yield % ^c
1	5 mol % Pd(OAc) ₂ , T = 200 °C, hold time 5 min	32
2	5 mol % PdCl ₂ , T = 200 °C, hold time 5 min	16
3	0.4 mol % Pd(OAc) ₂ , T = 200 °C, hold time 5 min	40
4	0.2 mol % Pd(OAc) ₂ , T = 200 °C, hold time 5 min	14
5	0.4 mol % Pd(OAc) ₂ , T = 150 °C, hold time 5 min	40
6	0.4 mol % Pd(OAc) ₂ , T = 150 °C, hold time 5 min, 0.5 equiv TBAB	87
7	0.4 mol % Pd(OAc) ₂ , T = 150 °C, hold time 5 min, 1 equiv TBAB	96
8	0.4 mol % Pd(OAc) ₂ , T = 150 °C, hold time 10 min, 1 equiv TBAB	92

^a 1 mmol of aryl halide, 1 mmol of PhB(OH)₂, 3 mmol of Na₂CO₃, 2 mL of water. Microwave irradiation = 60 W; temperature ramped to that stated and held there for the allotted time. ^b Conditions changed from entry 1 are highlighted in bold. ^c Determined by ¹H NMR.

4-iodobenzoic acid, we obtained a yield of 4-phenyltoluene of 32% (Table 1, entry 1). Our first thought was that the low yield was attributed to the poor solubility of 4-bromotoluene in water, even at these high temperatures. In working up this reaction, we found that all of the boronic acid had been consumed. Further investigation showed that at the temperatures we were using there was competitive protodeboronation of the boronic acid to produce benzene. This indicates that the low yield of Suzuki product obtained in the reaction is not solely due to poor substrate solubility. Changing the palladium complex from Pd(OAc)₂ to PdCl₂ had deleterious results, a lower yield of product being obtained (Table 1, entry 2). To overcome the problems of deboronation, we studied the effects of temperature and Pd(OAc)₂ loading on the reaction (Table 1, entries 3–5).

(18) **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 metal 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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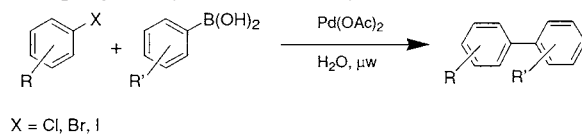
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(17) Microwave reactions were conducted using a CEM Discover Synthesis Unit (CEM Corp., Matthews, NC). The machine consists of a continuous focused microwave power delivery system with operator-selectable power output from 0 to 300 W. Reactions were 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. All experiments were performed using a stirring option whereby the contents of the vessel are stirred by means of a rotating magnetic plate located below the floor of the microwave cavity and a Teflon-coated magnetic stir bar in the vessel.

Table 2. Microwave-Mediated Suzuki Coupling of Aryl Halides and Aryl Boronic Acids in Water Using Pd(OAc)₂^a

entry	aryl halide	boronic acid	isolated yield %	entry	aryl halide	boronic acid	isolated yield %
1			84	14			91 ^c
2			92	15			70
3			91	16			96
4			79	17			82 ^b
5			91	18			78 ^b
6			73	19			76 ^d
7			86	20			80
8			83	21			89 ^c
9			76 ^b	22			87 ^c
10			82	23			45 ^e
11			90	24			62 ^{b,e}
12			68	25			50 ^e
13			87 ^c				

^a 1 mmol of aryl halide, 1 mmol of boronic acid, 3 mmol of Na₂CO₃, 0.4 mol % Pd(OAc)₂, 1.0 mmol of TBAB, 2 mL of water. Microwave irradiation = 60 W; temperature ramped to 150 °C (taking 30–40 s) and held for 5 min. ^b Determined by ¹H NMR. ^c Without TBAB. ^d On a 3 mmol scale. ^e Microwave irradiation = 60 W; temperature ramped to 175 °C (taking 30–40 s) and held for 5 min.

Our thoughts were that by lowering the temperature and the catalyst loading, it would be possible to favor the Suzuki coupling reaction. This was borne out in our results. We found that reduction of the catalyst loading from 5 to 0.4 mol % improved the yield of the Suzuki product, as did decreasing the temperature from 200 to 150 °C, with both of these modifications producing a yield of 40% of 4-phenyltoluene.

We next addressed the issue of substrate solubility. Previous reports have shown the addition of phase-transfer catalysts, such as tetraalkylammonium salts, can greatly improve yields of Suzuki reactions in both water^{9b,10,19} and polar organic solvents.²⁰ The role of ammonium salts is thought to be two-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 $[\text{ArB}(\text{OH})_3]^-[\text{R}_4\text{N}]^+$.^{9b} We felt that both of these factors would help to reduce the extent of hydrodeboration in our experiments since increased solubility of organic substrates in 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 hydrodeboration. We found that addition of 0.5 equiv of tetrabutylammonium bromide (TBAB) increases the yield of product in the coupling of phenylboronic acid and 4-bromo toluene from 40% to 87% (Table 1, entry 6). Use of 1 equiv of TBAB instead of 0.5 equiv takes this yield to 94% (Table 1, entry 7). We find that increasing the hold time from 5 to 10 min has a marginal effect on product yields (Table 1, entry 8).

With our optimized reaction conditions in hand, we screened a range of aryl bromides together with some aryl iodides and chlorides in the Suzuki reaction.²¹ All reactions have been performed using 1:1 stoichiometric ratio of aryl halide and boronic acid, as compared to the 1:1.2 or 1:1.5 ratios often used in aqueous Suzuki coupling reactions.^{9–11} In addition, the reactions were performed in air and without degassing the water prior to use. The results are shown in Table 2.

The methodology is applicable to a wide range of aryl bromide substrates (Table 2, entries 1–19) with good yields

being obtained in the reaction with phenylboronic acid. A wide range of functional groups are tolerated in the reaction and not affected by the high temperature and aqueous conditions used. In addition, sterically demanding aryl bromides can be coupled with phenylboronic acid to give good yields of product (Table 2, entries 5, 6, and 9).

To show that the reaction can be scaled up without compromising the yield, the reaction of 4-bromotoluene and phenylboronic acid was repeated on a 3 mmol scale (Table 2, entry 19).²² The isolated yield of product is 76%, almost identical to that when the reaction is performed on a 1 mmol scale (79%).

Representative aryl iodides were also screened in the coupling reaction using our methodology (Table 2, entries 20–22). The good results obtained are noteworthy. When using conventional heating, it is often the case that non-water-soluble aryl iodides give incomplete conversion when reactions are performed in aqueous media, even in the presence of tetraalkylammonium salts.^{9b}

It is possible to couple some aryl chlorides with phenylboronic acid using our methodology (Table 2, entries 23–25), but we find that this is best achieved by raising the reaction temperature from 150 to 175 °C. Even the electron-rich aryl chloride 4-chloroanisole can be coupled in acceptable yield. Our results with chloro substrates are certainly as good as those in the literature to date,^{10,12} and in the case of 4-chloroanisole, they are better.

In conclusion, we have developed a methodology for the ligand-free microwave-mediated Suzuki coupling of boronic acids and aryl halides in water and have shown the application of this to the synthesis of a number of biaryls starting from a range of aryl halides. The methodology has the advantage of low catalyst loadings, rapid reaction times, ease of reaction (no need for anaerobic conditions), and use of a nontoxic, nonflammable solvent. The methodology is currently being used in other C–C coupling reactions, and we anticipate that further enhancements in reactivity will be possible.

Acknowledgment. The Royal Society is thanked for a University Research Fellowship (N.E.L.) and King's College London for a Ph.D. studentship (M.M.). Funding from Hoffmann La Roche and King's College London is acknowledged.

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(21) **General Procedure.** In a 10-mL glass tube were placed aryl halide (1.0 mmol), phenylboronic acid (122 mg, 1.0 mmol), Na_2CO_3 (315 mg, 3 mmol), $\text{Pd}(\text{OAc})_2$ (1 mg, 0.004 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 60 W was used, the temperature being ramped from room temperature to 150 °C. Once 150 °C was reached, the reaction mixture was held at this temperature for 5 min. After the mixture was allowed 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 was extracted and removed. After further extraction of the aqueous layer with ether, combining of the organic washings and drying over MgSO_4 , the ether was removed in vacuo, leaving the crude product. In optimizing experiments the ^1H NMR spectrum of the product mixture was recorded and the product yield determined by integration of the peaks due to biaryl and aryl halide starting material taking $[\text{I}(\text{biaryl})/\text{I}(\text{biaryl} + \text{aryl halide})] \times 100$. In the screening experiments, 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 whilst under a vacuum on a Schlenk line. ^1H and ^{13}C NMR spectra of the products were obtained and found to be identical to authentic samples.

(22) This is the largest scale reaction possible using the 10-mL sealed glass tubes.