

# Biaryl Coupling Reactions



## Transition-Metal-Free Suzuki-Type Coupling Reactions\*\*

Nicholas E. Leadbeater\* and Maria Marco

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 C–C bonds, in particular for the formation of biaryl compounds.<sup>[1]</sup> 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 ten 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. In addition to a range of organic solvents, there has been considerable recent interest in the use of water as a reaction medium. Water, which is cheap, readily available, nontoxic, and nonflammable, has clear advantages as a solvent for use in chemistry.<sup>[2,3]</sup> Suzuki coupling reactions of water-soluble aryl iodides have been performed in water with simple palladium salts<sup>[4,5]</sup> or amphiphilic polymer-supported palladium catalysts.<sup>[6]</sup> Badone and co-workers have investigated the effects of solvent, including water, on the rate of the ligand-free palladium acetate catalyzed Suzuki reaction of a range of aryl bromides, iodides, and triflates.<sup>[7]</sup> They report that when using water as a solvent, the addition of 1 equivalent of tetrabutylammonium bromide (TBAB) to the reaction mixture greatly accelerates the reaction.<sup>[8]</sup> They find

that aryl bromides can be coupled with phenylboronic acid to yield biaryl compounds 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 thought to be twofold: 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  $[\text{ArB}(\text{OH})_3]^- [\text{R}_4\text{N}]^+$ . TBAB has been used recently in conjunction with a palladium oxime catalyst for the Suzuki coupling of aryl chlorides with phenylboronic acid in water.<sup>[9]</sup> We 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.<sup>[10]</sup> The total reaction time is between 5 and 10 min, and low palladium loadings are used. Like Badone and co-workers, we attribute much of the success of our methodology to the use of TBAB as additive. In our studies to understand further the role of this additive, we have found that, using the appropriate conditions, it is possible to perform Suzuki-type coupling reactions without the need for a transition-metal catalyst, which we report herein.

As a starting point for the development of our transition-metal-free aryl-coupling methodology, we chose to study the microwave-promoted coupling of phenylboronic acid with 4-bromoacetophenone, as this would act as a sharpening stone for optimizing reaction conditions. The results from our optimization studies are presented in Table 1.

Performing the reaction at 150 °C in a sealed tube, we found that optimum yields of product are obtained when a ratio of aryl bromide to boronic acid of 1:1.3 is used. The reason that excess boronic acid is required is because, at the elevated temperatures used in the reactions, there is competitive protodeboronation of the boronic acid to produce benzene. We found that a microwave power of 100 W is optimum. Since we were not concerned about deactivation of a metal catalyst, we used a higher power than that normally

**Table 1:** Microwave-promoted Suzuki-type coupling of 4-bromoacetophenone and phenylboronic acid in water.<sup>[a]</sup>

Entry	Reaction conditions <sup>[b]</sup>						Yield <sup>[d]</sup> [%]
	PhB(OH) <sub>2</sub> [equiv]	TBAB [equiv]	Na <sub>2</sub> CO <sub>3</sub> [equiv]	Power [W]	T [°C]	t [min]	
1	1.3	1.0	3.8	60	150	5	97
2	1.3	1.0	3.8	<b>150</b>	150	5	100
3	1.3	1.0	3.8	<b>100</b>	150	5	100
4	<b>1.0</b>	1.0	3.8	<b>100</b>	150	5	82
5	<b>1.1</b>	1.0	3.8	<b>100</b>	150	5	95
6	<b>1.2</b>	1.0	3.8	<b>100</b>	150	5	100 (98) <sup>[d]</sup>
7	<b>1.2</b>	<b>0.5</b>	3.8	<b>100</b>	150	5	58
8	<b>1.2</b>	1.0	<b>1.9</b>	<b>100</b>	150	5	84 <sup>[d]</sup>
9	<b>1.2</b>	1.0	3.8	<b>oil bath</b>	150	120	94 <sup>[d]</sup>

[a] Aryl halide (1 mmol), water (2 mL). 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 <sup>1</sup>H NMR spectroscopic analysis. [d] Yield of isolated product.

[\*] Dr. N. E. Leadbeater, M. Marco  
Department of Chemistry, King's College London  
Strand, London, WC2R 2LS (UK)  
Fax: (+44) 20-7848-2810  
E-mail: nicholas.leadbeater@kcl.ac.uk

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used in the palladium-mediated couplings (60 W). We found that the amount of base used in the reaction affects the yield considerably, the optimum quantity being 3.8 equivalents. The reaction reaches completion in 5 min. To show that the reaction is indeed metal-free, we used new glassware, apparatus, and reagents and analyzed the entire crude product mixture for palladium content. We found that there was no palladium in the product mixture to the level of detection of the analysis apparatus.<sup>[11]</sup> This, and the fact that the reaction is reproducible argues against catalytic contaminants. We also checked the levels of other metals in the product mixture that could possibly be acting as catalysts by inductively coupled plasma atomic absorption (ICP AA) spectroscopy. None of them were present in the product mixture in concentrations above the level of detection of the apparatus of 0.5–1 ppm.<sup>[12]</sup>

In an attempt to broaden the scope of the methodology, we investigated the possibility of performing the reaction with conventional heating. We found that placing a sealed tube in an oil bath at 150 °C offers an easy way to perform the reaction with 4-bromoacetophenone, a 91 % yield of product being obtained after heating for 2 h. However, the reaction of unactivated and deactivated aryl bromide substrates is not so efficient under conventional heating, even after heating for extended periods of time (16 h).

The methodology is applicable to a wide range of aryl bromide substrates (Table 2, entries 1–15), with good yields being obtained in the reaction with phenylboronic acid. A wide range of functional groups are tolerated in the reaction and are not affected by the high temperature and aqueous conditions used. Furthermore, sterically demanding aryl bromides can be coupled with phenylboronic acid to give good yields of product (Table 2, entries 8 and 13). To show that the reaction is regiospecific with respect to both the aryl bromide and the boronic acid, we screened the reaction of 4-bromoacetophenone with 4-methylbenzeneboronic acid and obtained the desired coupling product in excellent yield (Table 2, entry 15). Representative aryl iodides were also screened in the coupling reaction using our methodology (Table 2, entries 16–18), but product yields were lower those

**Table 2:** Suzuki-type coupling of aryl halides and aryl boronic acids in water.<sup>[a]</sup>

X = Cl, Br, I

Entry	Aryl halide	Yield [%]	Entry	Aryl halide	Yield [%]
1		90 <sup>[b]</sup>	11		71 <sup>[c]</sup>
2		99 <sup>[b]</sup>	12		99 <sup>[b]</sup>
3		98 (91) <sup>[b]</sup>	13		50 <sup>[b]</sup>
4		82 <sup>[b]</sup>	14		76 <sup>[c]</sup>
5		61 <sup>[b]</sup>	15		99 <sup>[b,d]</sup>
6		53 <sup>[c]</sup>	16		3 <sup>[c]</sup>
7		73 <sup>[b]</sup>	17		79 <sup>[c]</sup>
8		55 <sup>[b]</sup>	18		25 <sup>[c]</sup>
9		82 <sup>[c]</sup>	19		0 <sup>[c]</sup>
10		96 <sup>[c]</sup>	20		0 <sup>[c]</sup>

[a] Aryl halide (1 mmol), boronic acid (1.3 mmol), Na<sub>2</sub>CO<sub>3</sub> (3.8 mmol), TBAB (1.0 mmol), water (2 mL). Yields quoted are for microwave promotion using a microwave power of 100 W. The temperature was ramped to 150 °C and held for 5 min. The yield quoted in parentheses was obtained when using conventional heating. The sealed tube was placed in an oil bath at 150 °C and held for 5 h. [b] Yields of isolated product. [c] Determined by <sup>1</sup>H NMR spectroscopic analysis. [d] Reaction using 4-methylbenzeneboronic acid as the coupling partner.

with their bromo counterparts. Aryl chlorides cannot be coupled by this method (Table 2, entries 19 and 20).

In conclusion, we have shown that the Suzuki-type coupling of boronic acids and aryl halides is possible without the need for a transition-metal catalyst. The methodology is immediately viable for use both in small research and larger industrial scales. Since the use of transition metals leads to the generation of waste and has a number of hazards associated with it, such as the handling of toxic, air- and moisture-sensitive complexes, the eradication of the transition-metal catalyst from the Suzuki reaction offers significant advantages. Work is currently underway to investigate the mechanism of the coupling reaction.

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