

## Microwave-promoted Suzuki coupling reactions with organotrifluoroborates in water using ultra-low catalyst loadings

Riina K. Arvela, Nicholas E. Leadbeater,\* Tamera L. Mack and Chad M. Kormos

*Department of Chemistry, University of Connecticut, 55 North Eagleville Road, Storrs, CT 06269-3060, USA*

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**Abstract**—The Suzuki reaction in water using parts per million concentrations of palladium is reported using potassium trifluoroborates as alternatives to boronic acids as substrates.

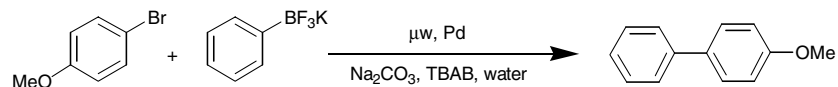
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The Suzuki reaction (palladium-catalyzed cross-coupling of an organoboron compound with an electrophile) is one of the most versatile and utilized reactions for the selective construction of carbon–carbon bonds, in particular for the formation of biaryls.<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. In general, it is boronic acids or esters that are used in the reaction. However, more recently alternative boron reagents have been developed for use in Suzuki reactions. Of these, potassium organotrifluoroborate salts have shown particular potential.<sup>2</sup> They are easily prepared and purified and thus offer ease of handling. Genet and co-workers,<sup>3</sup> and Chen and Xia<sup>4</sup> have demonstrated the use of aryl- and heteroaryl-trifluoroborates as substrates in couplings with aryldiazonium and diaryliodonium ions, respectively, using palladium catalysts. Batey and Quach reported the synthesis and cross-coupling of tetrabutylammonium organotrifluoroborate salts with a range of aryl and alkenyl halides using a mixture of palladium acetate and dppb as the catalyst and  $\text{Cs}_2\text{CO}_3$  as base.<sup>5</sup> More recently, Molander and co-workers have published a range of procedures for the coupling of potassium organotrifluoroborate salts with a range of electrophiles and have shown the great scope of these reagents and simplified the coupling protocols.<sup>6–9</sup> The reactions can be performed in methanol or water, in

the open air, using  $\text{Pd}(\text{OAc})_2$  as the catalyst and  $\text{K}_2\text{CO}_3$  as base. As well as working with aryl- and alkenyl-halides and triflates,<sup>10</sup> the methodology can be applied to couplings involving acetates.<sup>11</sup> By using a dialkylphosphanylbiaryl ligand, aryl chlorides can be coupled with aryl trifluoroborates.<sup>12</sup>

We have studied the Suzuki reaction extensively and found that it is possible to perform couplings of aryl bromides in neat water using very low catalyst concentrations.<sup>13,14</sup> Key to the success of the reaction is microwave heating and the use of water as solvent.<sup>15</sup> Microwave heating has found a valuable place in the synthetic chemist's toolbox. This is evidenced by the large number of papers and reviews currently appearing in the literature.<sup>16,17</sup> As well as being energy efficient, microwave heating can enhance the rate of reactions and in many cases improve product yields.<sup>18</sup> Water is an excellent solvent for microwave-promoted synthesis. Although it has a dielectric loss factor, which puts it into the category of only a medium absorber, even in the absence of any additives it heats up rapidly upon microwave irradiation. Using a sealed vessel it is possible to heat water to well above its boiling point. Water also offers practical advantages over organic solvents. It is cheap, readily available, and non-flammable. Our reactions were performed using a scientific microwave apparatus, using between 50 ppb and 2.5 ppm palladium, and are complete in 5 min. This therefore offers an easy, fast, and efficient route to biaryl-functionalized products.<sup>19</sup> Following the recent publication by Kabalka and Al-Masum on microwave-promoted cross-couplings involving potassium organotrifluoroborates using 2 mol %  $\text{PdCl}_2(\text{dppf})$ ,<sup>20</sup> we were keen to see if our

\* Corresponding author. Tel.: +1 860 486 5076; fax: +1 860 486 2981; e-mail: [nicholas.leadbeater@uconn.edu](mailto:nicholas.leadbeater@uconn.edu)



Scheme 1.

**Table 1.** Coupling of aryl halides with potassium organotrifluoroborates<sup>a</sup>

Entry	Aryl halide	Borate	Yield (%)	Entry	Aryl halide	Borate	Yield (%)
1			96	15 <sup>b</sup>			75
2			95	16			0
3			95	17			96
4			93	18			85
5			87	19			82
6			90	20			85
7			97	21			60
8			24	22			87
9			78	23			8
10			11	24			12
11			98	25			77
12			93	26 <sup>c</sup>			87
13			86	27 <sup>d</sup>			77
14			4	28			0

<sup>a</sup> Reactions were run in a sealed tube, using 1 mmol aryl halide, 1.0 mmol potassium organotrifluoroborate, 2.5 ppm Pd, 3.7 mmol of Na<sub>2</sub>CO<sub>3</sub>, 1 mL ethanol, and 1 mL water. An initial microwave irradiation of 300 W was used, the temperature being ramped from rt to 150 °C where it was then held for 5 min. Temperature was measured with a fiber-optic device inserted into the reaction vessel.

<sup>b</sup> Mixture of cis and trans products (cis:trans = 10:90).

<sup>c</sup> Mixture of cis and trans products (cis:trans = 13:87).

<sup>d</sup> Mixture of cis and trans products (cis:trans = 19:81).

ultra-low metal catalyzed Suzuki coupling protocol could be extended to use with these versatile substrates and our initial results are reported here.

In order to gauge the potential of our already established Suzuki coupling methodology for use with organotrifluoroborates, we decided to take the coupling of 4-bromoanisole and potassium phenyltrifluoroborate as a test case, working on a 1 mmol scale (Scheme 1). We first attempted the coupling using sodium carbonate (3.7 mmol) as a base for the reaction, tetrabutylammonium bromide (TBAB) (1 mmol) as phase-transfer agent, 2 mL water and 50 ppb palladium as the catalyst. We obtained a 15% yield of the desired biaryl product. The reaction mixture was heated to 150 °C where it was held for 5 min before cooling back to room temperature. We found that if the palladium concentration was increased to 2.5 ppm, a more respectable 82% product yield could be obtained.

As a point of note, when working in water, a major problem can be precipitation of palladium from a stock solution, particularly when working with a salt such as palladium acetate. This is avoided by using an acid stabilized stock solution such as that purchased as an ICP standard for palladium.<sup>†</sup> This can be diluted accordingly to give solutions of the desired concentrations. For low concentrations, a couple of drops of HCl can be added to avoid precipitation of palladium from solution.

When developing our ultra-low palladium concentration Suzuki couplings using boronic acids as substrates, we found that a 1:1 (vol) ethanol/water mixture worked just as well with the water/TBAB combination and has the added advantage of ease of work-up at the end of the reaction. We therefore screened this in our test reaction with potassium phenyltrifluoroborate. We found that using a palladium concentration of 2.5 ppm and keeping all other conditions the same, ethanol/water solvent mixture gave us a 96% yield of the desired product. Reduction of the base from 3.7 to 3 equiv has a deleterious effect on product yield as does decreasing the reaction temperature from 150 to 135 °C. Thus, our optimal conditions were 1 equiv 4-bromoanisole, 1 equiv potassium phenyltrifluoroborate, 3.7 equiv Na<sub>2</sub>CO<sub>3</sub>, 1:1 water/ethanol as solvent, 2.5 ppm palladium as catalyst, heating to 150 °C, and holding at this temperature for 5 min. With our optimal conditions in hand, we decided to explore the substrate scope of the reaction by performing the couplings of ranges of aryl halides and potassium organotrifluoroborates. Our results are shown in Table 1.<sup>21</sup>

In couplings with potassium phenyltrifluoroborate, a range of functionalities are tolerated on the aryl bromide component (Table 1, entries 1–7) although our results hint at the fact that sterically demanding aryl bromide substrates could prove problematic (Table 1,

entry 8). Although 2-bromothiophene can be used as a substrate with success (Table 1, entry 9), 2-bromopyridine gives much less promising results (Table 1, entry 10). This mirrors our work on Suzuki couplings in water using boronic acids where again we find that halopyridines cannot be coupled effectively due to competitive decomposition of the heterocyclic substrate.<sup>14</sup> Representative aryl iodides and a chloride were screened in the coupling with potassium phenyltrifluoroborate. Whilst the iodo-functionalized substrates could be effectively coupled (Table 1, entries 11–13) 4-chloroacetophenone could not (Table 1, entry 14). Again, this is not unexpected in the light of our work using boronic acids as coupling partners in ultra-low Pd-catalyzed Suzuki reactions. Looking at other halide substrates, we find that whilst an alkenyl bromides such as  $\beta$ -bromostyrene can be coupled efficiently with potassium phenyltrifluoroborate (Table 1, entry 15), the sp<sup>2</sup>–sp<sup>3</sup> coupling of this borate with 1-bromohexane was unsuccessful (Table 1, entry 16). We have screened representative potassium organotrifluoroborates. Aryl trifluoroborates couple effectively with 4-bromoanisole and 4-bromotoluene under our conditions (Table 1, entries 17–22). Potassium 3-thiophene trifluoroborate couples with aryl bromides with higher yields being obtained with substrates bearing electron-withdrawing substituents (Table 1, entries 23–25). The vinyl substrate potassium *trans*-styryltrifluoroborate can be used as a coupling partner, a mixture of *cis* and *trans* alkenes being formed in the reaction with 4-bromoanisole and 4-bromotoluene, the *trans*-isomer being predominant in both cases (Table 1, entries 26 and 27). This is in contrast to our results obtained using the boronic acid equivalent of this (*trans*-2-phenylvinylboronic acid) where the *trans*-product is formed exclusively.<sup>14</sup> Attempts to use an alkyltrifluoroborate as a coupling partner were unsuccessful (Table 1, entry 28). This is not surprising given that Molander and co-workers found that it took 9 mol % PdCl<sub>2</sub>(dppf) to couple these substrates.<sup>7</sup>

In summary, we have shown here that by using microwave promotion and water as a solvent, it is possible to couple a range of potassium organotrifluoroborates with aryl bromides and iodides efficiently, quickly, and using low catalyst loadings. The ease of purification of potassium organotrifluoroborates makes them valuable starting materials for Suzuki couplings and addition of this range of substrates to our ultra-low palladium loading methodology increases their versatility.

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