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An expeditious aqueous Suzuki–Miyaura method for the arylation of bromophenols

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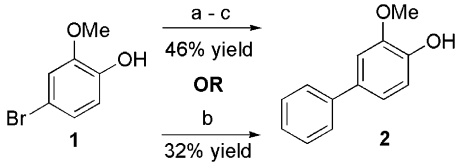
Abstract—The development of a novel Suzuki–Miyaura method has been achieved to allow the efficient arylation of bromophenols. A range of functionality is tolerated with regard to the boronic acid coupling partner and the reaction exhibits complete chemoselectivity for the C_{aryl}–Br bond versus the C_{aryl}–Cl bond in the aryl halide input. The experimental protocol features a short reaction time of 15 min, utilizes inexpensive Pd/C as a catalyst, and is conducted with water as the solvent.

The venerable Suzuki–Miyaura reaction,[1,2] along with other palladium-mediated carbon–carbon bond formation reactions, has experienced an explosion in utilization in the field of organic synthesis in recent years.[3,4] Applications of this catalytic reaction firmly grounded in the tenants of organometallic chemistry have been supported by catalyst system improvements that have allowed an expansion in the reaction scope and efficiency.[5–8] The Suzuki–Miyaura reaction may be found as a key reaction step in a number of elegant total syntheses of natural products.[9]

Our interest in the Suzuki–Miyaura reaction began with the optimization of a series of diaryl ether phenols based on the promise of triclosan as an antimalarial.[10] A straightforward approach to the functionalization of 4-bromo-2-methoxyphenol (**1**) to provide a small family of *m*-arylphenols is shown in Scheme 1. To the best of our knowledge, the literature provides little if any precedent for the utilization of the Suzuki–Miyaura reaction to functionalize this electron-rich bromophenol.[11] Our first inclination was to avoid the potentially complicating presence of the phenol[12] in this metal-catalyzed reaction by protecting it as the benzyl ether. The



Scheme 1. First generation routes to target arylated phenol. Reagents and conditions: (a) BnBr, K_2CO_3, EtOH, 50 °C (91%); (b) $Pd(PPh_3)_4$, $PhB(OH)_2$, aq Na_2CO_3, DME, 80 °C (53%); (c) H_2, Pd/C, MeOH (96%).

Suzuki–Miyaura reaction, conducted under standard conditions,[13] of the intermediate benzyl ether proceeded only in 53% yield and the overall desired transformation occurred in three steps in 46% yield. Without protection of the phenol, the aryl bromide cross-coupled in a slightly decreased overall yield of 32%. Clearly, a more optimal way of conducting the Suzuki–Miyaura reaction was needed, and a one step transformation from **1** to provide the target class of arylated phenols was deemed most desirable.

At the outset of this effort, we were cognizant of literature precedent for the Suzuki–Miyaura reaction of the regioisomeric parent bromophenols[8,14–18] and bromosalicylaldehydes,[19,20] which may exhibit different reactivity due to the presence of an intramolecular hydrogen bond masking the phenolic hydrogen. All of these reported substrates are less electron-rich than

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1. We contemplated an exhaustive survey of these and other published protocols, but instead opted for the development of a novel Suzuki–Miyaura method that would offer short reaction times and high yields of the desired coupling product while utilizing a catalyst system that was inexpensive and environmentally-benign.

We were fascinated by the report of Hirao that offered the promise of a green protocol.[14] Hirao demonstrated the Pd/C catalyzed coupling of some arylboronic acids with a series of iodophenols in the presence of 3 equiv of aqueous potassium carbonate at room temperature for 12 h. While the functionalizations of the iodophenols were high-yielding, the one example of coupling a bromophenol—4-bromophenol—with phenylboronic acid afforded only 35% of the desired product at room temperature over 12 h and a 76% yield at 50 °C over 12 h. Also, the number of functionalized arylboronic acids explored was limited to five. Hirao's method is a worthwhile extension of work in the literature examining the Pd/C catalyzed Suzuki–Miyaura reaction dating back to Buchecker's 1994 publication.[21] Clearly, this type of Suzuki–Miyaura method has the benefits of using Pd/C, an easily removed and cost-effective catalyst that does not require a phosphine ligand,[22] and water as an inexpensive, environmentally-benign, and readily-available solvent.[23]

We, thus, chose to explore a Pd/C catalyzed aqueous method and were struck by the potential for an application of microwave reactor technology[24–26] to arrive at a cleaner and more rapid reaction. The literature precedents are highlighted by contributions from Leadbeater where his system is characterized by a very low loading of a Pd source, an excess of aqueous sodium carbonate, and the use of a phase transfer catalyst such as tetrabutylammonium bromide.[27–31] Leadbeater, however, has only reported the Suzuki–Miyaura coupling of 4-iodo- and 4-bromophenol.[29] Our approach was to explore a variant of the Hirao method, incorporating the benefit of microwave reactor technology, while expanding on their substrate scope to include a variety of bromophenols and arylboronic acids.

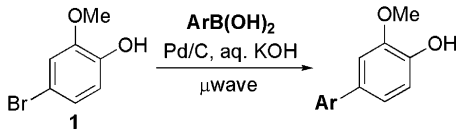
Our explorations began with an optimization of the Suzuki–Miyaura coupling of commercially available **1** with phenylboronic acid in a CEM Discovery/Explorer microwave system. It must be noted that all reactions were performed in air with commercial grade solvents and reagents used without further purification. The reaction variables explored[32] were reaction time (10–60 min), temperature (80–170 °C), reactor wattage (25–300 W), amount of commercially available 10 wt % Pd/C catalyst (0–5 mol %), type of base added as a solid or aqueous solution, number of equivalents of base (0–4), and total reaction volume (1–4 mL). An HPLC assay allowed the determination of the yield of desired 4-phenyl-2-methoxyphenol **2**.[32]

Reaction temperatures of 110–170 °C afforded assay yields above 90%. Base was necessary for the reaction to occur and could be added as a solid or a 1 M aqueous solution. With regard to potassium carbonate, 0.5–3.0 equiv afforded assay yields >90%, with 2.0 equiv being optimal. Potassium hydroxide provides slightly higher yields than potassium carbonate and sodium hydroxide. Significantly lower HPLC assay yields were determined when utilizing Na_2CO_3 (Leadbeater protocol),[31] Cs_2CO_3, CsF, KF, and K_3PO_4. An overall reaction volume of ca. 3 mL (2.0 mL 1 M aq base + 1.0 mL water) was optimal, compared to volumes of 1–4 mL. The assay yield and purity showed little dependence on microwave power, but did decrease slightly, due to the formation of small amounts of unidentifiable by-products, as the reaction time was increased from 15 to 60 min.

Experimental investigations, thus, afforded an optimized protocol that differed from Hirao's in terms of the reaction time, temperature, catalyst loading, amount and nature of base, and the use of microwave reactor technology. The optimum protocol was determined to be as follows: 1 mol % 10 wt % Pd/C, 1.1 equiv $PhB(OH)_2$, 2.0 equiv 1 M aq KOH, 1.0 mL H_2O, 120 °C, and 150 W for a reaction time of 15 min. This protocol afforded a 99% HPLC assay yield of **2** with a purity of 97%. The reaction product upon typical extractive workup was suitable for subsequent synthetic transformations or could be further purified via silica gel chromatography to afford spectroscopically pure material with a yield of 83% (average of three independent runs). Interestingly, when conducted under these optimum conditions in a pre-equilibrated oil bath,[33] the reaction was characterized by a 96% HPLC assay yield of the desired product with a purity of 98%. It appears reasonable that our Suzuki–Miyaura method does not rely on non-thermal microwave effects[34] and is transferable between the microwave and conventional oil bath.

An investigation was conducted on the scope of arylboronic acids tolerated by this novel Suzuki–Miyaura protocol (Table 1). The method performed well for the tolylboronic acids (*o*-, *m*-, *p*-; entries 2–4). It is interesting to note that whereas the reaction with *o*-tolylboronic acid (entry 2) proceeded in 91% yield, the reaction with the more sterically-encumbered 2,6-dimethylphenylboronic acid (entries 5 and 6) occurred in negligible yield. The catalyst system allowed coupling of the 1- and 2-naphthyl groups (entries 7 and 8, respectively) to the phenol scaffold in moderate yields. The introduction of heteroatoms to the arylboronic acid resulted in lower isolated yields of the desired Suzuki–Miyaura product (entries 9–13 and 18–19). It is interesting to note that utilization of both electron-rich (entry 9) and electron poor (entries 10–19) arylboronic acids led to lower isolated yields than when using electron-neutral arylboronic acids (entries 1–4). While by-products such as a homocoupled bis(phenol) were not detected, we cannot rule out the degradation of the boronic acids via protodeboronation[30,35,36] or homocoupling.[37] These types of arylboronic acid decomposition pathways could occur in the presence of a strong base at elevated temperatures. In the instances where the functional group (i.e., cyano, carbomethoxy, and acetamide) on the arylboronic acid itself could be hydrolyzed, the use

Table 1. Coupling of **1** with arylboronic acids

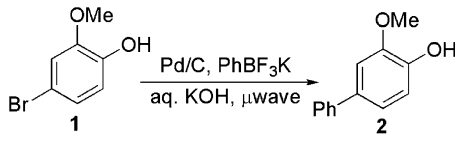


Entry	Ar	% Yield[a]
1[b]	Ph	83
2	*o*-Tolyl	91
3	*m*-Tolyl	90
4	*p*-Tolyl	89
5[c]	2,6-$Me_2C_6H_4$	4
6[c,d]		7
7	1-Naphthyl	58
8	2-Naphthyl	48
9	*p*-$MeOC_6H_4$	31
10	4-ClC_6H_4	35
11[e]		16
12	2,4-$Cl_2C_6H_4$	0
13[f,g]		2
14	3-CNC_6H_4	39
15[e]		70
16[h]	4-$MeO_2CC_6H_4$	10
17[e,i]		36
18	4-Ac(H)NC_6H_4	4
19[e]		10

[a] Isolated yield obtained of chromatographically and spectroscopically homogeneous material using standard conditions (1 mol % 10 wt % Pd/C, 1.1 $ArB(OH)_2$, 2.0 equiv 1 M aq KOH, 1.0 mL H_2O, 120 °C, 150 W, 15 min, microwave), unless noted otherwise.
[b] Yield represents mean for three independent trials.
[c] Yield approximated by HPLC.
[d] Reaction time of 1 h.
[e] Use of 1.0 equiv KOH (1 M aq soln).
[f] Yield determined by ^1H NMR integration.
[g] 2.2 equiv boronic acid, 1.0 equiv K_2CO_3 (1 M aq soln), 50 W.
[h] 48% isolated yield of corresponding benzoic acid hydrolysis product.
[i] 12% isolated yield of corresponding benzoic acid hydrolysis product.

of only 1 equiv of potassium hydroxide led to improved yields.

Given the lower yields observed with heteroatom functionalized arylboronic acids, we were interested in exploring the use the corresponding potassium aryltrifluoroborates, which appear to be less susceptible to protodeboronation than their boronic acid counterparts.[38,39] We briefly examined the coupling of **1** with potassium phenyltrifluoroborate (Scheme 2). Clearly, the phenyltrifluoroborate salt is less reactive than phenylboronic acid under our experimental conditions and further optimization will be necessary to expand our method to include these intriguing salts. It should be noted that Molander recently published $Pd(OAc)_2$ catalyzed ligandless conditions for coupling the less electron-rich 4-bromophenol with potassium phenyltrifluoroborate with an 82% overall yield.[40] Kabalka and Al-Masum are to be credited with the first examples of microwave promoted Suzuki–Miyaura couplings with potassium aryltrifluoroborates.[41]

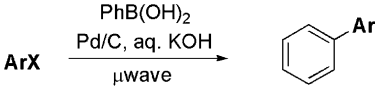


t = 15 min (isol. yield = 64%, 89% brsm)
t = 30 min (isol. yield = 72%, 88% brsm)
t = 60 min (isol. yield = 68%, 88% brsm)

Scheme 2. Attempted Suzuki–Miyaura couplings with potassium phenyltrifluoroborate.

An examination of the reaction scope in terms of aryl bromides is shown in Table 2 and serves to benchmark our optimized protocol versus those previously reported in the literature. As expected, the regioisomers of bromophenol (entries 1–3) reacted in high yield with phenylboronic acid under the standard reaction conditions. It is noteworthy that the isolated yield of the 4-phenylphenol (entry 3) is comparable to those obtained with the elegant, but more elaborate catalyst systems of both Buchwald[5,6] and Fu and co-workers.[8] Selectivity for the C_{aryl}–Br bond versus the C_{aryl}–Cl bond was achieved when reacting 2-bromo-4-chlorophenol (entries 4 and 5). A slight increase in the number of equivalents of phenylboronic acid (1.1–>1.5) was necessary to consume all of the starting material phenol. It is interesting to note that 4-chloro-2-methoxyphenol (entries 6–9) did not react to any significant extent as judged by LC–MS analysis of the crude reaction mixture. With this substrate, the temperature was increased to 190 °C and the reactor power was elevated to 300 W,

Table 2. Coupling of aryl halides with phenylboronic acid



Entry	ArX	% Yield[a]
1	2-Bromophenol	96
2	3-Bromophenol	88
3	4-Bromophenol	94
4[b]	2-Bromo-4-chlorophenol	40
5[c]		88
6	4-Chloro-2-methoxyphenol	0
7[d]		0
8[e]		0
9[f]		0
10[g,h]	3-Bromoanisole	46
11[g,i,j]		65
12	3-Bromobenzoic acid	81

[a] Isolated yield of chromatographically and spectroscopically homogeneous material obtained using standard conditions (1 mol % 10 wt % Pd/C, 1.1 equiv $PhB(OH)_2$, 2.0 equiv 1 M aq KOH, 1.0 mL H_2O, 120 °C, 150 W, 15 min, microwave), unless noted otherwise.
[b] Yield approximated by HPLC, which demonstrated the presence of 68% desired product and 18% starting material phenol.
[c] Standard protocol except for use of 1.5 equiv $PhB(OH)_2$.
[d] Standard protocol except for usage of 300 W power.
[e] Standard protocol except for usage of 300 W power with continuous cool setting.
[f] Standard protocol except for use of 300 W power and $T = 190$ °C.
[g] Yield determined by ^1H NMR integration.
[h] 29% starting material anisole recovered.
[i] Standard protocol except for use of 1.5 equiv $PhB(OH)_2$ and $t = 30$ min.
[j] 25% starting material anisole recovered.

with and without simultaneous cooling of the reaction vessel with a stream of compressed air to allow for increased levels of microwave irradiation. Consistent with these results is the observation that 3-chlorophenol did not react under our standard reaction conditions with phenylboronic acid. During the preparation of this manuscript, Leadbeater reported the productive Suzuki–Miyaura reaction of aryl chlorides, but not chlorophenols, using his standard phase-transfer protocol with the alterations of 300 W of reactor power and simultaneous cooling.[42]

It is interesting to note that 3-bromoanisole (entries 10 and 11) was partially converted to the desired product while 3-bromobenzoic acid (entry 12) coupled quite efficiently with $PhB(OH)_2$. The observations support our hypothesis that the success of our reaction protocol is dependent on the production of significant amounts of a water-soluble anion. This can be achieved either by deprotonation of the phenol or carboxylic acid (in the case of entry 12) moiety. The reactions of 3-bromoanisole are, thus, expected to be much more sluggish. Leadbeater's protocol addresses this issue by utilization of tetra-*n*-butylammonium bromide, which in one role serves as a phase transfer catalyst for non-ionizable substrates.[31]

In conclusion, we have reported a novel Suzuki–Miyaura method that addresses the need for a facile and rapid synthesis of arylated phenols from their bromophenol precursor. The method also accepts bromobenzoic acids as substrates and holds promise for the implementation of potassium aryltrifluoroborates. The protocol exhibits complete chemoselectivity for arylbromides versus arylchlorides and is thus complementary to Leadbeater's method. We believe the use of the cost-effective and simple catalyst system composed of Pd/C is also complementary to the highly evolved Suzuki–Miyaura methods that rely on a ligated Pd(0) or Pd(II) precatalyst and oftentimes a phosphine ligand. For example, during the preparation of this manuscript, Anderson and Buchwald reported a significant contribution to the Suzuki–Miyaura reaction method utilizing catalytic $Pd(OAc)_2$ and a sulfonate-derivatized aryldicyclohexylphosphine ligand to perform the aqueous coupling of a wide range of arylboronic acids with arylchlorides and bromides, including 5-chloro-2-hydroxybenzoic acid.[5] Clearly, some cases such as those documented in this report may benefit from a simple and cost-effective catalyst system whereas others may necessitate the more complex, expensive, and evolved catalyst systems. We will report in due course the utilization of our Pd/C catalyzed Suzuki–Miyaura coupling to prepare a range of biologically-active small molecules that may serve as leads in the development of next-generation antimalarials.

Acknowledgments

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Supplementary data

Experimental details and characterization data for all new compounds reported. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.04.027.

References and notes

1. Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2483.
2. Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147–168.
3. *Handbook of Organopalladium Chemistry for Organic Synthesis*; John Wiley & Sons: New York, 2002; Vol. 1.
4. *Handbook of Organopalladium Chemistry for Organic Synthesis*; John Wiley & Sons: New York, 2002; Vol. 2.
5. Anderson, K. W.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2005**, *44*, 6173–6177.
6. Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685–4696.
7. Altenhoff, G.; Goddard, R.; Lehmann, C. W.; Glorius, F. *J. Am. Chem. Soc.* **2004**, *126*, 15195–15201.
8. Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020–4028.
9. Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4442–4489.
10. Freundlich, J. S.; Anderson, J. W.; Sarantakis, D.; Shieh, H.-M.; Yu, M.; Lucumi, E.; Kuo, M.; Schiehser, G. A.; Jacobus, D. P.; Jacobs, W. R., Jr.; Fidock, D. A.; Sacchettini, J. C. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 5247–5255.
11. A search of the literature for cross-couplings of **1** resulted in only one hit—a Stille reaction of 4-(tri-*n*-butylstannyl)-2-methoxyphenol: Pouységu, L.; Avellan, A.-V.; Quideau, S. *J. Org. Chem.* **2002**, *67*, 3425–3436.
12. Liu, B.; Moffett, K. K.; Joseph, R. W.; Dorsey, B. D. *Tetrahedron Lett.* **2005**, *46*, 1779–1782.
13. Alo, B. I.; Kandil, A.; Patil, P. A.; Sharp, M. J.; Siddiqui, M. A.; Snieckus, V.; Josephy, P. D. *J. Org. Chem.* **1991**, *56*, 3763–3768.
14. Sakurai, H.; Tsukuda, T.; Hirao, T. *J. Org. Chem.* **2002**, *67*, 2721–2722.
15. Heidenreich, R. G.; Köhler, K.; Krauter, J. G. E.; Pietsch, J. *Synlett* **2002**, *7*, 1118–1122.
16. Botella, L.; Nájera, C. *J. Organomet. Chem.* **2002**, *663*, 46–57.
17. Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9550–9561.
18. Bumagin, N. A.; Bykov, V. V. *Tetrahedron* **1997**, *53*, 14437–14450.
19. Zhuravel, M. A.; Nguyen, S. T. *Tetrahedron Lett.* **2001**, *42*, 7925–7928.
20. Morris, G. A.; Nguyen, S. T. *Tetrahedron Lett.* **2001**, *42*, 2093–2096.
21. Marck, G.; Villiger, A.; Buchecker, R. *Tetrahedron Lett.* **1994**, *35*, 3277–3280.
22. Novak, B. M.; Wallow, T. I. *J. Org. Chem.* **1994**, *59*, 5034–5037.
23. Shaughnessy, K. H.; DeVasher, R. B. *Curr. Org. Chem.* **2005**, *9*, 585–604.
24. Roberts, B. A.; Strauss, C. R. *Acc. Chem. Res.* **2005**, *38*, 653–661.
25. Kappe, C. O. *Angew. Chem., Int. Ed.* **2004**, *43*, 6250–6284.
26. Larhed, M.; Moberg, C.; Hallberg, A. *Acc. Chem. Res.* **2002**, *35*, 717–727.
27. Leadbeater, N. E. *Chem. Commun.* **2005**, 2881–2902.
28. Leadbeater, N. E.; Marco, M. *J. Org. Chem.* **2003**, *68*, 5660–5667.

29. Leadbeater, N. E.; Marco, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 1407–1409.
30. Leadbeater, N. E.; Marco, M. *Org. Lett.* **2002**, *4*, 2973–2976.
31. Leadbeater, N. E.; Marco, M. *J. Org. Chem.* **2002**, *68*, 888–892.
32. Please see Supplementary information for details.
33. **CAUTION**: Due to the heating of water significantly above its boiling point, a safety shield was used during the reaction and upon its completion, the reaction mixture was immediately immersed in a ~20 °C water bath.
34. Strauss, C. R. *Angew. Chem., Int. Ed.* **2002**, *41*, 3589–3590.
35. Kuivila, H. G.; Reuwer, J. F., Jr.; Mangravite, J. A. *J. Am. Chem. Soc.* **1964**, *86*, 2666–2670.
36. Kuivila, H. G.; Nahabedian, K. V. *J. Am. Chem. Soc.* **1961**, *83*, 2159–2163.
37. Wong, M. S.; Zhang, X. L. *Tetrahedron Lett.* **2001**, *42*, 4087–4089.
38. Molander, G. A.; Figueroa, R. *Aldrichim. Acta* **2005**, *38*, 49–56.
39. Darses, S.; Genet, J.-P. *Eur. J. Org. Chem.* **2003**, 4313–4327.
40. Molander, G. A.; Biolatto, B. *Org. Lett.* **2002**, *4*, 1867–1870.
41. Kabalka, G. W.; Al-Masum, M. *Tetrahedron Lett.* **2005**, *46*, 6329–6331.
42. Arvela, R. K.; Leadbeater, N. E. *Org. Lett.* **2005**, *7*, 2101–2104.