Published in final edited form as:

J Am Chem Soc. 2010 October 13; 132(40): 14073–14075. doi:10.1021/ja1073799.

A New Palladium Precatalyst Allows for the Fast Suzuki-Miyaura Coupling Reactions of Unstable Polyfluorophenyl and 2-Heteroaryl Boronic Acids

Tom Kinzel, Yong Zhang, and Stephen L. Buchwald*

Department of Chemistry, Massachusetts Institute of Technology, 77 Massachusetts Avenue, Cambridge, MA 02138

Abstract

Boronic acids which quickly deboronate under basic conditions, such as polyfluorophenylboronic acid and five-membered 2-heteroaromatic boronic acids, are especially challenging coupling partners for Suzuki-Miyaura reactions. Nevertheless, being able to use these substrates is highly desirable for a number of applications. Having found that monodentate biarylphosphine ligands can promote these coupling processes, we developed a precatalyst that forms the catalytically active species under conditions where boronic acid decomposition is slow. With this precatalyst, Suzuki-Miyaura reactions of a wide range of (hetero)aryl chlorides, bromides, and triflates with polyfluorophenyl, 2-furan, 2-thiophene and 2-pyrroleboronic acids and their analogs proceed at room temperature or 40 °C in short reaction times to give the desired products in excellent yields.

The Suzuki-Miyaura cross-coupling (SMC) reaction is arguably the most important and widely used method for the construction of sp^2 - sp^2 carbon-carbon bonds.¹ However, since SMCs are typically performed at elevated temperatures and require several hours reaction time, the scope of usable boronic acids is limited to those that do not significantly decompose under standard conditions. Consequently, the SMCs of quickly deboronating 2,6-difluorophenylboronic acid (**1**) and analog **2** as well as the SMCs of five-membered 2-heterocyclic boronic acids **3–8** (Chart 1) are problematic.^{3–4,5–6} Being able to couple these boronic acids with functionalized aryl and heteroaryl substrates would be of great interest for the synthesis of pharmaceutical and agrochemical candidates, natural products, and materials.

One viable solution to this problem is the masking of the boronic acids as MIDA boronates,⁷ cyclic triolborates,⁸ or trifluoroborate salts^{9–10} which slowly hydrolyze¹¹ to the free boronic acid under the reaction conditions. The ratio of the concentration of catalyst and the boronic acid is relatively high and, as a result, transmetalation is favored over protodeboronation. Nevertheless, these surrogates are typically prepared from the free boronic acids, and often, high palladium loadings and/or long reaction times are required for

sbuchwal@mit.edu.

Supporting Information Available. Complete ref. 4a and 4b, experimental procedures and product characterization. This material is available free of charge via the Internet at <http://pubs.acs.org>.

efficient coupling. Another solution, albeit limited to aryl bromides and iodides, allows the coupling of **2** and pentafluorophenylboronic acid by using stoichiometric amounts of Ag₂O in addition to the palladium catalyst.^{12,13}

Herein, we report the fast and efficient SMC of the free boronic acids **1–8** at room temperature or 40 °C in short reaction times of 30 minutes to 2 hours. Key to the success was the development of a new precatalyst that generates the catalytically active LPd(0) species quickly under mild conditions under which the deboronation of the boronic acid is significantly slowed down.

In the course of mechanistic investigations, we prepared complex SPhosPdPhCl (**9**) that results from oxidative addition of SPhosPd(0) with chlorobenzene,¹⁴ and treated it with **1** in the presence of aqueous K₃PO₄ (Scheme 1). Rapid formation of product **10** demonstrated that transmetalation and reductive elimination occur with **1** at room temperature.¹⁵

Using 2 mol% of **9** as precatalyst, 4-chloroanisole was coupled with **1** to give the desired product in 93% yield in less than 30 minutes using a 1:2 mixture of THF and 0.5 M aqueous K₃PO₄. Kinetics studies showed that product formation stopped abruptly, indicating that the remainder of **1** was consumed by competing base- and/or metal-catalyzed deboronation.² Increasing the temperature resulted in a lower conversion. However, full conversion of 4-chloroanisole at room temperature was achieved by using the oxidative-addition complex **11** in which the SPhos ligand is replaced by XPhos (Chart 2).

The syntheses of complexes **9** and **11** are difficult, and their use as precatalysts for the SMC of **1** with any aryl halide necessarily results in the formation of biaryl **10** in addition to the desired product. The preparation and isolation of an individual oxidative-addition complex for each substrate is clearly impractical and often impossible. Because using Pd(OAc)₂ or Pd(dba)₂ with XPhos gave unsatisfactory results, we sought another solution to provide the catalytically active XPhosPd(0) species which undergoes oxidative addition *in situ*.

Previously, we developed precatalyst **12** which, upon deprotonation by a base, forms XPhosPd(0) and indoline via C–N reductive elimination.¹⁶ While it is an excellent source of the catalytically active Pd species, its activation with weak bases is slow and occurs only at elevated temperatures. Moreover, its synthesis requires several steps. In the process of addressing these issues, we found that both drawbacks could be overcome with a new class of precatalysts where the parent aliphatic amine in **12** is replaced by 2-aminobiphenyl in **13**: First, the higher acidity of the palladium-bound aromatic amine compared to the aliphatic amine allows activation of **13** to occur almost instantaneously with weak base at room temperature. Second, **13** is easily obtained in a one-pot procedure by combining Pd(OAc)₂ with 2-aminobiphenyl, followed by addition of LiCl and the ligand (XPhos) (Scheme 2).¹⁷

For the SMC reaction between 4-chloroanisole and **1** in the presence of aqueous 0.5 M K₃PO₄ as base, the use of precatalysts **12** and **13** was tested. As expected, only the latter promoted the reaction, leading to full conversion to product.

Initially, several aryl halides or pseudohalides were subjected to the SMC reaction with polyfluorophenylboronic acids. We observed that aryl chlorides, bromides, and triflates are good substrates for the coupling with **1** while only low conversions were observed with aryl iodides¹⁸ (Table 1). Substrates with coordinating groups in the ortho position, such as esters or ketones, could also not be coupled efficiently. However, even large non-coordinating ortho substituents, as in **15b**, were well tolerated. Heteroaromatic compounds readily underwent the SMC to form the desired products in excellent yields, but five-membered chloro- or bromoheteroarenes with multiple heteroatoms remained problematic.

Interestingly, we found that while trisubstituted polyfluorophenylboronic acids **2** and **14** could be employed to give products **16** and **17**, very low conversion was observed with 2,3,6-trifluorophenylboronic acid. To understand this result, we studied both the deboronation rates¹⁹ and apparent transmetalation rates²⁰ of (poly)fluorophenylboronic acids (Table 2). Transmetalation efficiency increases with the number of fluorine substituents, with ortho substitution having the greatest impact. Thus, **1** reacts about 150 times faster than simple phenylboronic acid, and almost 4 times faster than 2-fluorophenylboronic acid. In the series of **1**→**2**→**14**, the loss in stability is counterbalanced by higher transmetalation rates, thus allowing the coupling of **2** and **14** under essentially the same reaction conditions. In contrast, the coupling of 2,3,6-trifluorophenylboronic acid is more problematic because the deboronation rate is dramatically increased while transmetalation rate does not change relative to **1**.²¹

It is important to note that the coupling of these polyfluorophenylboronic acids proceeds using established ligands (SPhos, XPhos) that exhibited excellent results in other SMC reactions. Thus, the previously reported unsuccessful attempts³ to couple **1** and **2** in the presence of these ligands were not due to their structure, but to the reaction conditions which were necessary to provide the active catalytic species. Using precatalyst **13**, the catalytically active XPhosPd(0) species is formed rapidly at room temperature, thereby allowing the successful coupling of these unstable boronic acids.

Next, we turned our attention to heteroaryl boronic acids and found that by using 2 mol% of **13**, 2-heterocyclic boronic acids **3–8** could be coupled efficiently with a wide array of aryl and benzyl halides, mostly within 30 minutes at room temperature or 40 °C (Table 3). The higher stability of the 2-heterocyclic boronic acids relative to the polyfluorophenylboronic acids allowed the transformations of challenging substrates that could not be used with the latter. Therefore, performing the reaction at 40 °C for 2 h allowed the conversion of 4- and 5-halopyrazoles, 2-chlorobenzoxindole as well as 2-chloroacetanilide to give the coupled products **19a**, **20c**, **22b**, and **20b** in excellent yields.

The fast generation of XPhosPd(0) from precatalyst **13** is a prerequisite for the successful coupling of unstable boronic acids **1–8**, but also increases the rate of reaction for other SMC reactions, as illustrated by the fast coupling of 3-furan and 3-thiopheneboronic acids to give **24** and **25**.

In summary, we have developed a procedure for very fast SMC reactions at room temperature or 40 °C that allows the coupling of a wide range of (hetero)aryl halides and triflates with excellent functional group tolerance. The fast catalytic process and the extremely mild reaction conditions make the coupling of unstable polyfluorophenyl and five-membered 2-heterocyclic boronic acids with a wide range of aryl (pseudo)halides possible. The rate increase in comparison to typical SMC reactions relies on fast generation of the catalytically active species from an easy to prepare, air- and moisture-stable precatalyst.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank the NIH for financial support of this project (GM46059) and BASF for a gift of palladium compounds. T.K. thanks the Alexander von Humboldt Foundation for a Feodor Lynen postdoctoral fellowship. We also thank Dr. Jaclyn Henderson for assistance with some experiments. The Varian NMR instrument used was supported by the NSF (grants CHE 9808061 and DBI 9729592).

References

1. (a) Miyaura N, Yamada K, Suzuki A. *Tetrahedron Lett.* 1979; 36:3427. (b) Miyaura N. J. *Organomet. Chem.* 2002; 653:54. (c) Miyaura, N. *Metal-Catalyzed Cross-Coupling Reactions*. Diederich, F.; de Meijere, A., editors. New York: Wiley-VCH; 2004.
2. Both base- and metal-catalyzed deboronation of boronic acids may occur under typical SMC reactions. (a) Kuivila HG, Reuwer JF, Mangravite JA. *Can. J. Chem.* 1963; 41:3081. (b) Kuivila HG, Reuwer JF, Mangravite JA. *J. Am. Chem. Soc.* 1964; 86:2666.
3. While 2,3- and 2,4-difluorophenylboronic acids could be coupled using ligand SPhos at 80–90 °C, these conditions did not allow the efficient coupling of **1** or **2**: Barder TE, Walker SD, Martinelli JR, Buchwald SL. *J. Am. Chem. Soc.* 2005; 127:4685. [PubMed: 15796535]
4. For some examples for the coupling of 2,6-difluorophenylboronic acid with vinyl triflates and aryl bromides, see: (a) Antonow D, et al. *J. Med. Chem.* 2010; 53:2927. [PubMed: 20218628] (b) Schmidt D, et al. *Bioorg. Med. Chem. Lett.* 2009; 19:4768. [PubMed: 19592242] (c) Palmer BD, Smaill JB, Rewcastle GW, Dobrusin EM, Kraker A, Moore CW, Steinkampf RW, Denny WA. *Bioorg. Med. Chem. Lett.* 2005; 15:1931. [PubMed: 15780636]
5. (a) Knapp DM, Gillis EP, Burke MD. *J. Am. Chem. Soc.* 2009; 131:6961. [PubMed: 19405470] (b) Billingsley KL, Buchwald SL. *J. Am. Chem. Soc.* 2007; 129:3358. [PubMed: 17326639] (c) Billingsley KL, Anderson KW, Buchwald SL. *Angew. Chem. Int. Ed.* 2006; 45:3484. (c) Tyrell E, Brookes P. *Synthesis*. 2003:469.
6. For some representative examples of the coupling of five-membered 2-heteroaromatic boronic acids, see: (a) Kabri Y, Gellis A, Vanelle P. *Eur. J. Org. Chem.* 2009; 2009:4059. (b) Gill GS, Grobelny DW, Chaplin JH, Flynn BL. *J. Org. Chem.* 2008; 73:1131. [PubMed: 18177049] (c) Organ M, Çalimsiz S, Sayah M, Hoi K, Lough A. *Angew. Chem. Int. Ed.* 2009; 48:2383. (d) Dang Y, Chen Y. *J. Org. Chem.* 2007; 72:6901. [PubMed: 17685657] (e) Maeda H, Haketa Y, Nakanishi T. *J. Am. Chem. Soc.* 2007; 129:13661. [PubMed: 17927182] (f) James CA, Coelho AL, Gevaert M, Forgione P, Snieckus V. *J. Org. Chem.* 2009; 74:4094. [PubMed: 19441801]
7. 2-heterocyclic MIDA boronates were successfully employed for SMCs (See Ref. 4a), but polyfluorophenyl MIDA boronates were not described. MIDA = *N*-methyliminodiacetic acid.
8. Yamamoto Y, Takizawa M, Yu X, Miyaura N. *Angew. Chem. Int. Ed.* 2008; 47:928.
9. Polyfluorophenyl BF₃K salts were coupled to 4-bromobenzonitrile: Molander GA, Biolatto B. J. *Org. Chem.* 2003; 68:4302. [PubMed: 12762730]
10. Coupling of 2-heterocyclic BF₃K salts: Molander GA, Canturk B, Kennedy LE. *J. Org. Chem.* 2009; 74:973. [PubMed: 19105735]
11. The hydrolysis of BF₃K salts to the free boronic acid likely occurs prior to cross-coupling: Butters M, Harvey JN, Jover J, Lennox AJJ, Lloyd-Jones GC, Murray P. *Angew. Chem. Int. Ed.* 2010; 49:5156.
12. (a) Chen J, Cammers-Goodwin A. *Tetrahedron Lett.* 2003; 44:1503. (b) Korenaga T, Kosaki T, Fukumura R, Ema T, Sakai T. *Org. Lett.* 2005; 7:4915. [PubMed: 16235921] (c) Adonin NY, Babushkin DE, Parmon VN, Bardin VV, Kostin GA, Mashukov VI, Frohn H. *Tetrahedron*. 2008; 64:5920.
13. It should be mentioned that with copper or palladium catalysts, aryl bromides and chlorides can be directly coupled to polyfluorobenzenes via C-H activation processes, but high temperatures and long reaction times are required: (a) Lafrance M, Shore D, Fagnou K. *Org. Lett.* 2006; 8:5097. [PubMed: 17048852] (b) Do H, Daugulis O. *J. Am. Chem. Soc.* 2008; 130:1128. [PubMed: 18181627]
14. Barder TE, Biscoe MR, Buchwald SL. *Organometallics*. 2007; 26:2183.
15. The reductive elimination of 4-methoxy-2',6'-difluorobiphenyl from an isolated Pd(II) complex has been reported: Osakada K, Onodera H, Nishihara Y. *Organometallics*. 2005; 24:190.
16. Biscoe MR, Fors BP, Buchwald SL. *J. Am. Chem. Soc.* 2008; 130:6686. [PubMed: 18447360]
17. Albert J, Granell J, Zafrilla J, Font-Bardia M, Solans X. *J. Organomet. Chem.* 2005; 690:422.
18. The rate of the SMC reaction under the described conditions decreases in the order ArCl > ArBr > ArI. This order is reproduced in stoichiometric transmetalation studies starting from oxidative-

addition complexes. Furthermore, we found an inhibiting effect on the transmetalation rate by additional halide ions, in the order $I^- > Br^- > Cl^-$.

19. The deboronation rates of some polyfluorophenylboronic acids in a D_2O /pyridine mixture at elevated temperatures were reported: Frohn H, Adonin NY, Bardin VV, Starichenko VF. *Z. Anorg. Allg. Chem.* 2002; 628:2834.
20. Apparent relative transmetalation rates were determined by competition experiments using an excess of a mixture of 2-methoxyphenylboronic acid and a second boronic acid with 4-chloroanisole as substrate in the presence of 20 mol% **13**. The obtained product ratios were normalized to the product ratio found for the competition experiment between 2-methoxyphenylboronic acid and phenylboronic acid. To ensure that the measured values reflect the transmetalation of the free boronic acids and not of boronic acid anhydrides or boroxines present in the starting material, we modified the experiment involving phenylboronic acid by premixing the boronic acid mixture with aqueous K_3PO_4 solution prior to addition of the precatalyst and aryl chloride, and we found the same ratio of products as before.
21. The attempted coupling of 2,3,6-trifluorophenylboronic acid with 4-chloroacetophenone under microwave irradiation led exclusively to the deboronated compound, trifluorobenzene: Clarke ML, France MB, Fuentes JA, Milton EJ, Roff JR. *Beilstein J. Chem.* 2007; 3:18.

Scheme 1.

Initial observation of the coupling of **1** with a stoichiometric amount of an oxidative-addition complex **9**.

Scheme 2.
Synthesis of precatalyst **13**.

Chart 1.
Boronic acids that easily undergo protodeboronation in aqueous base to give the parent arene.

Chart 2.
XPhos-containing precatalysts used in this study.

Table 1

Coupling of polyfluoroboronic acids to aryl chlorides, bromides, and triflates.^a

^aArX (1 mmol), ArB(OH)₂ (1.5 mmol), **13** (2 mol %), degassed THF (2 mL), degassed 0.5 M aq. K₃PO₄ (4 mL), rt, 30 min; isolated yields, average of two runs.

^b**13** (3 mol%).

Table 2

Deboronation rates and apparent relative transmetalation rates of polyfluorophenylboronic acids.

Entry	Boronic acid	Deboronation rate, $t_{1/2}$ (min) ^a	Relative transmetalation rate, k_{rel}
1	PhB(OH) ₂		1
2	2-F		42
3	3-F		2
4	4-F		5
5	2,6-F ₂ (1)	28	155
6	2,4,6-F ₃ (2)	10	202
7	2,6-F ₂ -3- <i>On</i> Bu (14)	6	536
8	2,3,6-F ₃	2	156

^aDeboronation due to the presence of base was measured via calorimetry at room temperature in a mixture of THF and 0.5 M K₃PO₄. The values in the column are the half-lives of the observed first-order kinetic profiles.

Table 3

Coupling of 2- and 3-heterocyclic boronic acids to aryl and benzyl chlorides and aryl bromides.^b

^a ArX (1 mmol), ArB(OH)₂ (1.5 mmol), **13** (2 mol %), degassed THF (2 mL), degassed 0.5 M aq. K₃PO₄ (4 mL), rt, or 40 °C, 30 min or 2 h; isolated yields, average of two runs.