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, Massachusetts 02139, United States

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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 analogues 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] 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.[3−6] 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.

Chart 1. Boronic Acids That Easily Undergo Protodeboronation in Aqueous Base To Give the Parent Arene
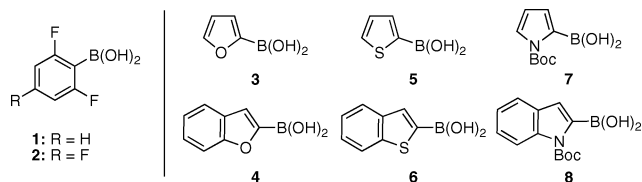

One viable solution to this problem is the masking of the boronic acids as MIDA boronates,[7] cyclic triolborates,[8] or trifluoroborate salts[9,10] which slowly hydrolyze[11] to the free boronic acid under the reaction conditions. The ratio of the concentration of catalyst and the boronic acid is relatively 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 efficient coupling. Another solution, albeit limited to aryl bromides and iodides, allows the coupling of **2** and pentafluorophenylboronic acid by using stoichiometric amounts of Ag_2O 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 min to 2 h. 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 K_3PO_4 (Scheme 1). Rapid formation of product **10** demonstrated that transmetalation and reductive elimination occur with **1** at room temperature.[15]

Scheme 1. Initial Observation of the Coupling of **1** with a Stoichiometric Amount of an Oxidative-Addition Complex **9**
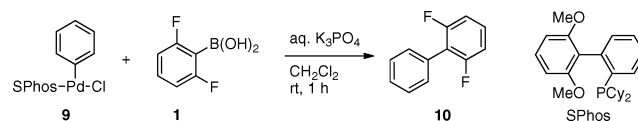
Using 2 mol % of **9** as precatalyst, 4-chloroanisole was coupled with **1** to give the desired product in 93% yield in less than 30 min using a 1:2 mixture of THF and 0.5 M aqueous K_3PO_4. Kinetics studies showed that product formation stopped abruptly, indicating that the remainder of **1** was 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).

**Chart 2.** XPhos-Containing Precatalysts Used in This Study
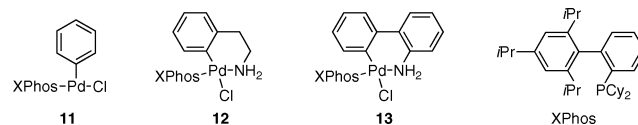
The syntheses of complexes **9** and **11** are difficult, and their use as precatalysts for the SMC of **1** with any aryl halide necessarily results in the formation of biaryl **10** in addition to the desired product. The preparation and isolation of an individual oxidative-addition complex for each 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]

Scheme 2. Synthesis of Precatalyst **13**
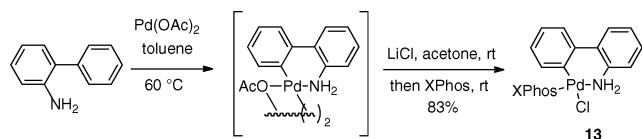
For the SMC reaction between 4-chloroanisole and **1** in the presence of aqueous 0.5 M K$_3$PO$_4$ as base, the use of precatalysts **12** and **13** was tested. As expected, only the latter promoted the reaction, leading to full conversion to product.

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 iodides[18] (Table 1). Substrates with coordinating groups in the ortho position, such as esters or ketones, could also not be coupled efficiently. However, even large noncoordinating 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.

Table 1. Coupling of Polyfluoroboronic Acids to Aryl Chlorides, Bromides, and Triflates[a]
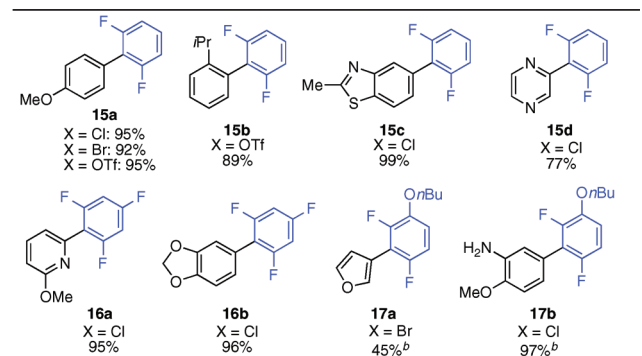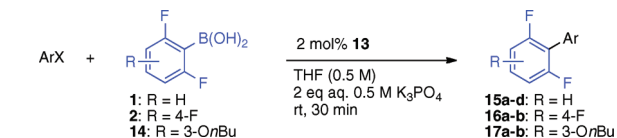
[a] ArX (1 mmol), ArB(OH)$_2$ (1.5 mmol), **13** (2 mol %), degassed THF (2 mL), degassed 0.5 M aq K$_3$PO$_4$ (4 mL), rt, 30 min; isolated yields, average of two runs. [b] **13** (3 mol %).

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 rates[19] and apparent transmetalation rates[20] 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, whereas the transmetalation rate does not change relative to that of **1**.[21]

Table 2. Deboronation Rates and Apparent Relative Transmetalation Rates of Polyfluorophenylboronic Acids

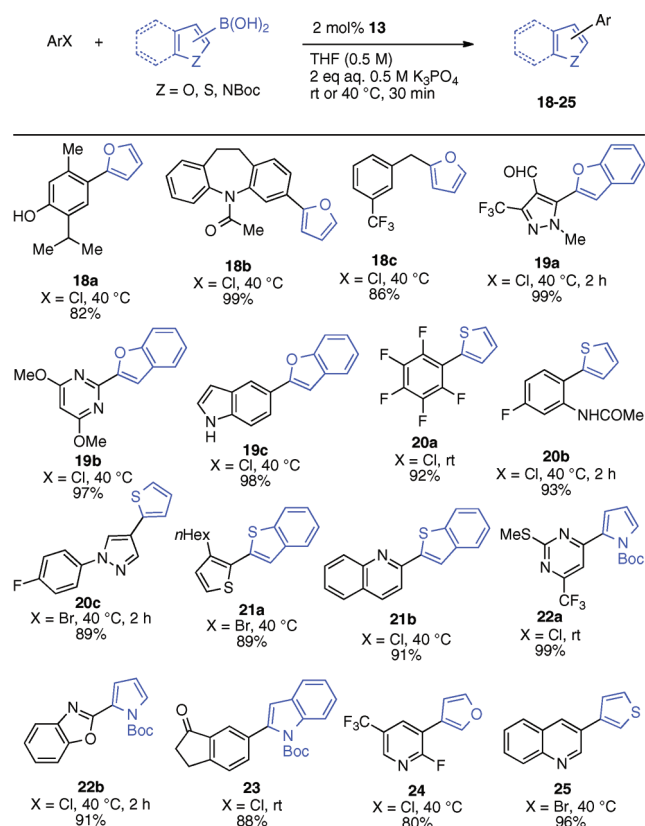| entry	boronic acid	deboronation rate, $t_{1/2}$ (min)[a]	relative transmetalation rate, k_{rel}
1	PhB(OH)$_2$		1
2	2-F		42
3	3-F		2
4	4-F		5
5	2,6-F$_2$ (**1**)	28	155
6	2,4,6-F$_3$ (**2**)	10	202
7	2,6-F$_2$-3-OnBu (**14**)	6	536
8	2,3,6-F$_3$	2	156

[a] Deboronation due to the presence of base was measured via calorimetry at room temperature in a mixture of THF and 0.5 M K$_3$PO$_4$. The values in the column are the half-lives of the observed first-order kinetic profiles.

It is important to note that the coupling of these polyfluorophenylboronic acids proceeds by using established ligands (SPhos, XPhos) that exhibited excellent results in other SMC reactions. Thus, the previously reported unsuccessful attempts[3] 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 min at room temperature or 40 °C (Table 3). The higher stability of the 2-heterocyclic boronic acids relative to that of 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-chloro-benzoxindole 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 prerequesite 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

Table 3. Coupling of 2- and 3-Heterocyclic Boronic Acids to Aryl and Benzyl Chlorides and Aryl Bromides[a]

ArX + (heterocyclic)B(OH)$_2$ (Z = O, S, NBoc) →[2 mol% **13**, THF (0.5 M), 2 eq aq. 0.5 M K$_3$PO$_4$, rt or 40 °C, 30 min] **18-25**

18a
X = Cl, 40 °C
82%

18b
X = Cl, 40 °C
99%

18c
X = Cl, 40 °C
86%

19a
X = Cl, 40 °C, 2 h
99%

19b
X = Cl, 40 °C
97%

19c
X = Cl, 40 °C
98%

20a
X = Cl, rt
92%

20b
X = Cl, 40 °C, 2 h
93%

20c
X = Br, 40 °C, 2 h
89%

21a
X = Br, 40 °C
89%

21b
X = Cl, 40 °C
91%

22a
X = Cl, rt
99%

22b
X = Cl, 40 °C, 2 h
91%

23
X = Cl, rt
88%

24
X = Cl, 40 °C
80%

25
X = Br, 40 °C
96%

[a] Reagents and conditions: ArX (1 mmol), ArB(OH)$_2$ (1.5 mmol), **13** (2 mol %), degassed THF (2 mL), degassed 0.5 M aq K$_3$PO$_4$ (4 mL), rt or 40 °C, 30 min or 2 h; isolated yields, average of two runs.

with a wide range of aryl (pseudo)halides possible. The rate increase in comparison to that of typical SMC reactions relies on fast generation of the catalytically active species from an easy-to-prepare, air- and moisture-stable precatalyst.

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

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