Boronic Acids

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Palladium-Catalyzed Direct Synthesis of Organoboronic Acids**

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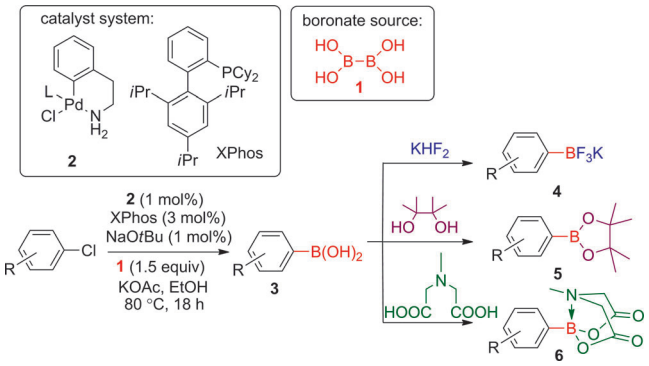
Organoboronic acids and their derivatives have become established as incomparably useful reagents in organic synthesis,[1] particularly as nucleophilic coupling partners in the catalytic formation of C–C bonds, such as the Suzuki–Miyaura coupling[2] or the allylation of aldehydes.[3] Accordingly, the development of synthetic methods for the generation of organoboron species has attracted considerable interest. Several excellent and important approaches to this challenge have emerged, including the palladium-catalyzed borylation of haloarenes[4] and iridium-catalyzed aryl C–H borylation.[5] Unfortunately, however, these methods typically employ boronate esters as the boron source (most usually the pinacol derivatives pinacolborane (HBpin) or bis(pinacolato)diborane (B_2pin_2)) and therefore produce the corresponding boronate ester products. More traditional stoichiometric approaches to the problem of boronic acid synthesis also rely on boronate ester starting materials with the additional disadvantages of requiring the use of harsh metalating reagents and having limited substrate scope.[6] The products of these processes must then be subjected to further manipulation if other derivatives are desired. This necessitates the removal of stoichiometric quantities of pinacol (or other alcohol), for example by using $NaIO_4$ and/or acid-induced hydrolysis to obtain the corresponding boronic acid.[5e] Such requirements place limitations on both the step- and atom-economy of the syntheses and raise concomitant environmental concerns. These considerations serve to highlight how inherently attractive the prospect of direct, catalytic generation of boronic acids is, particularly given their near ubiquity in coupling protocols.

One answer to the challenge lies in the direct exploitation of diboronic acid[7] (also called tetrahydroxydiboron), $[B(OH)_2]_2$ (**1**). However, despite the associated advantages, development of methodology based around this reagent has been limited.[8] This is accounted for by the hitherto considerably lower price and greater commercial availability of boronate esters (such as B_2pin_2) and the fact that diboronic acid is relatively unstable in the presence of palladium(0) species, which can lead to its decomposition before useful catalysis can take place.

In light of the above, a recent report from Molander et al. comes as a timely and important development.[8a] The authors of the study have shown that aryl boronic acids may be accessed directly from aryl chloride substrates, and either isolated or derivatized further in situ to easy-to-handle trifluoroborate salts[9] **4** or corresponding boronate esters, such as **5** or **6** (Scheme 1). Thus, by slight variation of the



Scheme 1. Palladium-catalyzed direct formation of aryl boronic acids from chloroarenes and example derivatizations. Cy = cyclohexyl.

reaction conditions different boronates (**3**–**5**) can be obtained for Suzuki–Miyaura coupling reactions,[2] and if necessary, the boronate group can be protected as a MIDA boronate[10] (**6**; MIDA = *N*-methyliminodiacetic acid) too.

Aryl chloride substrates proved superior to their bromide counterparts; the former were required to circumvent the formation of homoaryl products arising from the coupling of **3** with remaining haloarene substrates in the reaction mixture. The XPhos ligand, which has previously proved successful in the palladium-catalyzed activation of aryl chlorides,[11] was chosen alongside the recently reported palladium complex **2**.[11c] The latter eliminates indoline under basic conditions to give Pd^0 species without requiring other additives.

Selected examples from the scope of this methodology (Scheme 2) illustrate its value; electron-rich (**4a**) and electron-poor (**4b**–**c**) aryl derivatives are efficiently converted into trifluoroborates, including aldehydes (**4c**), which do not

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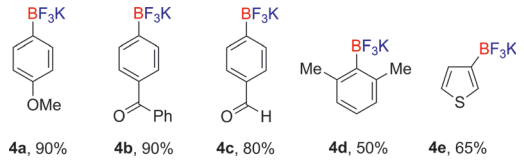
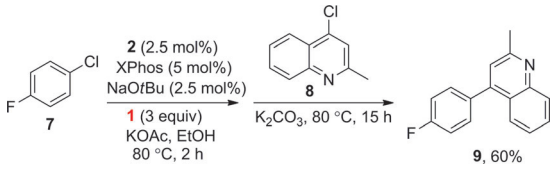


Scheme 2. Example trifluoroborates obtained from a one-pot conversion of aryl chlorides into boronic acids and subsequent reaction with KHF_2 (see Scheme 1).

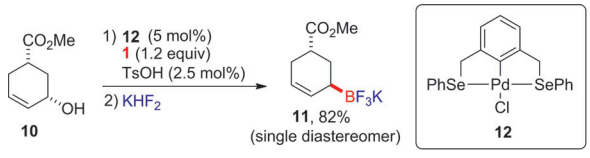
undergo further attack. Notably, even 2,6-disubstituted aryl chlorides performed well (**4d**) compared to the corresponding iodides or bromides under Miyaura conditions, although to achieve this result twice the usual amount of **1** had to be employed. The efficient conversion of 3-chlorothiophene into **4e** hints at a promising outlook for heteroaromatic chlorides; however, a general procedure for their borylation using **1** remains to be reported. Impressively, scale-up to 6 mmol was demonstrated in the case of **4a**.

The one-pot Suzuki–Miyaura coupling of products **3** can also be carried out without changing the catalyst system. The addition of K_2CO_3 base appears to decompose excess **1** from the initial reaction, after which efficient conversion into biaryl products can proceed when the desired aryl chloride partner is introduced (Scheme 3).



Scheme 3. Example of a one-pot generation of arylboronic acid and subsequent conversion into biaryl products by Suzuki–Miyaura coupling.

Although Molander's borylation of aryl chlorides marks the first foray diboronic acid **1** has made into the area of aryl borylation reactions, its use in palladium-catalyzed allylic $C(sp^3)$–B bond formation has previously been described in a handful of reports by the Szabó research group.[8b–d] A variety of allylic substrates, including alcohols, were functionalized in a process proposed to be redox neutral with respect to palladium. Diboronic acid (**1**) was proposed to play a role in the activation of the alcohol groups as well as providing the boron source for the formation of the final product. As with the work on aryl chlorides, alcohol solvent—in this case methanol—proved the most efficient, either on its own or with DMSO. Scheme 4 illustrates this approach to allylic



Scheme 4. Diboronic acid in the palladium-catalyzed allylic borylation. TsOH = *para*-toluenesulfonic acid.

boronates with a palladium pincer complex catalyzed[12] example wherein the boronic acid intermediate is generated as a single diastereomer and trapped as the trifluoroborate salt **11** (Scheme 4).[8c]

The prospect of synthesizing diverse boronic acids directly from readily available starting materials is inherently attractive. Catalytic methods offering this option appear to be slowly emerging as viable and more atom-economical alternatives to both stoichiometric methods and those able to utilize only preformed boronate esters. Molander's method can easily be integrated into one-pot procedures to generate trifluoroborates and various boronates from aryl chlorides. Thus, a broad array of organoboronate reagents can be obtained, thereby offering a flexible strategy for subsequent coupling reactions. This strategy is likely to contribute significantly to the way in which C–B bond preparation is approached and positively impact on the preparation of substrates for a considerable proportion of catalyzed coupling reactions. The only existing catalytic protocols exploiting diboronic acid have used palladium. Given that various other d-block metals (e.g. Ir, Rh, and Ni) are known to be effective borylation catalysts, it is reasonable to anticipate their application to syntheses using diboronic acid (**1**) in the near future. Similarly, C–H borylation using diboronic acid can be envisaged, as can an increase in the number of methods exploiting the boronic acid group in novel transformations.

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