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Synthesis and Suzuki Reactions of N-Heterocyclic Carbene Difluoro(aryl)-boranes

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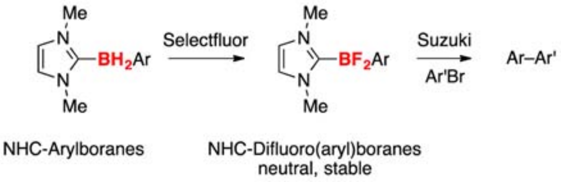
Supporting Information

ABSTRACT: Readily available NHC-arylboranes (NHC-BH_2Ar) are converted in high yield to stable NHC-difluoro(aryl)boranes (NHC-BF_2Ar) by treatment with 2 equiv of 1-chloromethyl-4-fluoro-1,4-diazonia-bicyclo[2.2.2]octane bis(tetrafluoroborate) (Selectfluor). In turn, the NHC-difluoro(aryl)boranes participate directly in Suzuki reactions under conditions previously used for anionic trifluoroborate salts. Accordingly, NHC-difluoroboranes are a new class of stable precursors for Suzuki reactions.



The ease of handling of N-heterocyclic carbene boranes (NHC-boranes) has facilitated the recent exploration of the reagent chemistry of this interesting class of ligated boranes.[1] NHC-boranes with B–H bonds serve as reducing agents in both radical[2] and ionic[3] reactions. They are also valuable co-initiators in photopolymerizations,[4] and they are precatalysts for borenium-catalyzed hydrogenations.[5] NHC-boryl sulfides,[6,7] halides, triflates, and related species are useful reagents.[1,8] Though much of this chemistry is based on 1,3-imidazol-2-ylidene boranes, an assortment of newer classes of NHC-boranes also show promise.[9]

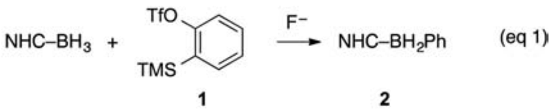
Furthermore, it is increasingly possible to make carbon-substituted NHC-boranes. NHC-boranes with B–C bonds can be made either by direct complexation of NHCs and boranes[1] or by functionalization of simple NHC-boranes by catalyzed hydroborations,[10] substitutions,[11] and carbene BH insertion reactions.[12] The carbon-substituted NHC-boranes formed in these reactions often have favorable physical properties (stable, easy to isolate), but little is presently known about their chemistry.

Recently, we have found in collaboration with Taniguchi that NHC-arylboranes are readily made by the hydroboration reaction of arynes.[13] In the parent example shown in Scheme 1 (eq 1), generation of benzyne from *o*-silyl triflate **1** and fluoride ion[14] in the presence of NHC-boranes (NHC-BH_3) results in spontaneous hydroboration to provide robust, stable products like **2**. This aryne hydroboration is so far unique to NHC-boranes,[13] which are stable enough to survive the conditions of benzyne generation yet reactive enough to add spontaneously to benzyne as it forms.

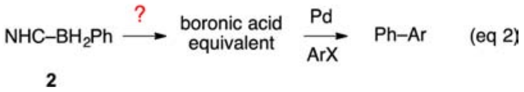
As a first step toward increasing the synthetic utility of carbon-substituted NHC-boranes, we set out to bridge the gap between NHC-borane chemistry and boronic acid chemistry.[15] Within boronic acid chemistry, we targeted the Suzuki–Miyaura reaction[16,17] as job-one (Scheme 1, eq 2). Here we report that NHC-arylboranes are readily fluorinated to give NHC-difluoro(aryl)boranes.[18] In turn, these difluoro(aryl)-boranes are boronic acid equivalents that partner directly with aryl bromides in Suzuki reactions under standard conditions. After summarizing the results of the two new reactions, we briefly compare and contrast the new NHC-difluoro(aryl)-boranes with other common precursors for Suzuki reactions.

Scheme 1. Formation and Proposed Suzuki Reactions of B-Aryl NHC-Boranes

(a) New formation on B-aryl NHC-boranes



(b) Goal: bridge NHC-borane and boronic acid chemistry by engaging B-aryl NHC boranes in Suzuki reactions



We hypothesized that NHC-dihalo(aryl)boranes would liberate boronic acids on exposure to water. In practice, this reaction occurred easily, indeed too easily, for boryl iodides, bromides, and chlorides as shown by the results in Scheme 2. Treatment of NHC-phenylborane **3** with diiodine (1 equiv), dibromine (1 equiv), or *N*-chlorosuccinimide (NCS, 2 equiv) resulted in rapid formation of the corresponding NHC-dihaloboranes **4–6** as assessed by ^{11}B NMR spectroscopy.[8,13] The iodide **4** and bromide **5** were very sensitive to water, quickly liberating phenylboronic acid **7** ($PhB(OH_2)$), as assessed by ^{11}B NMR spectroscopy) and the corresponding imidazolium halide salt (as assessed by ^{1}H NMR spectroscopy). The dichloroborane **6** was more stable, yet still gradually produced phenylboronic acid **7** over a few hours on exposure to water at 25 °C.

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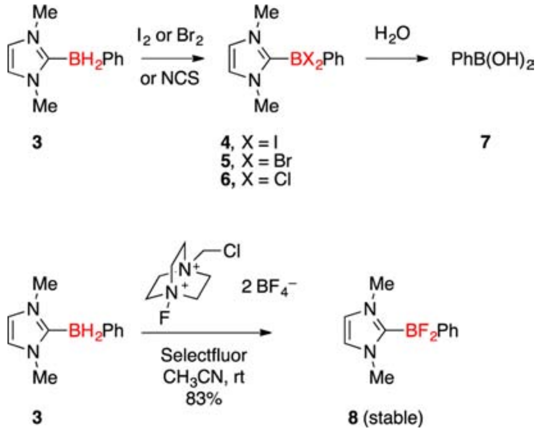
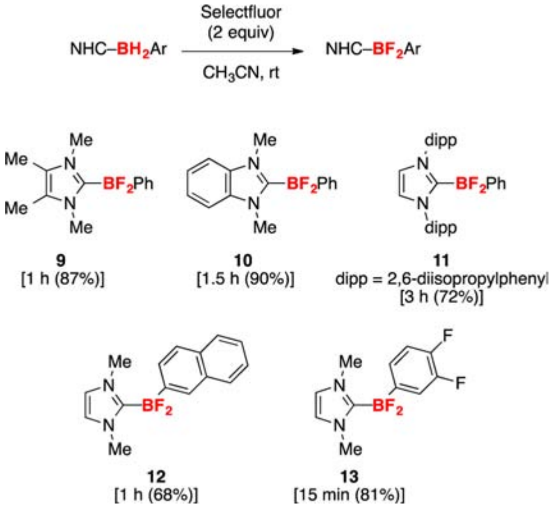
Scheme 2. Halogenation Reactions of an NHC-Phenylborane



Scheme 3. Selectfluor Difluorination Reactions



These rapid halogenation reactions are potentially useful for making boronic acids from NHC-boranes. However, boronic acids themselves[16d] are often not the preferred precursors for Suzuki reactions. Instead, stable precursors such as pinacol boranes, trifluoroborate salts, and MIDA boronates (MIDA is *N*-methyliminodiacetate) are commonly used because they are easy to handle.[19]

We found the sweet spot between stability for ease of handling and reactivity in Suzuki reactions with NHC-difluoro(aryl)boranes. We recently described several such difluoroboranes that had promising stability but were not convenient to prepare.[18] We now find that NHC-difluoro(aryl)boranes can be easily made by reaction of NHC-arylboranes with Selectfluor.[20,21]

In a typical example, reaction of **3** with 2 equiv of Selectfluor at room temperature in acetonitrile cleanly provided difluoroborane **8** in 1.5 h as followed by ^{11}B NMR spectroscopy (4.6 ppm, t, J_{BF} = 62.4 Hz). Simple evaporation of the acetonitrile and direct purification of the crude product by automated flash chromatography provided the robust difluoroborane **8** as a white solid (mp 80–83 °C) in 83% yield. This is a significant improvement over the prior fluorination procedure (Ph_3CBF_4, PhOH),[18] both in practice (Selectfluor is cheaper and easier to handle than Ph_3CBF_4) and in outcome (Ph_3CBF_4 often provides side products). Unlike the other dihaloboranes **4**–**6**, difluoroborane **8** is stable to exposure to water for long periods at room temperature and even on heating (as long as base is excluded).

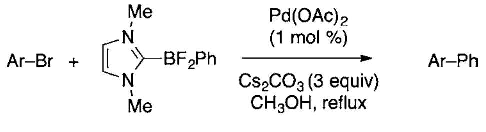
Reaction of **3** with only 1 equiv of Selectfluor provided mainly difluoroborane **8** with only a small resonance observed for the corresponding monofluoroborane (NHC-BHFPh, at −11 ppm). For this representative double fluorination reaction at least, the second fluorination step is faster than the first one.

Scheme 3 shows the structures of several other NHC-difluoro(aryl)boranes made by reactions with Selectfluor along with reaction times and isolated yields. We varied both the NHC-borane ylidene substituent while keeping the B-substituent as phenyl (**9**–**11**; 72–87% yield), and the B-substituent while keeping the NHC-borane as 1,3-dimethylimidazol-2-ylidene (**12**, 68% yield, and **13**, 81% yield).

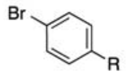
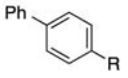
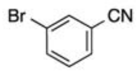
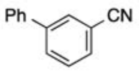
It is possible to release boronic acids from the difluoro(aryl)boranes by heating with water and base (see Supporting Information), but it is easier to use them directly in Suzuki reactions. To this end, we tried Molander and Bialatto's conditions for low palladium loading in reactions of potassium trifluoroborates ($Pd(OAc)_2$ and a carbonate base in methanol).[22] We varied only the base, looking at both cesium carbonate (Cs_2CO_3) and potassium carbonate (K_2CO_3). Both worked, but the former gave faster conversions in scouting reactions (see Supporting Information) so it was selected for the scope study.

In the typical reaction shown in entry 1 of Table 1, a methanol solution of **8** (1 equiv), 4-bromobenzonitrile **14a** (1 equiv), $Pd(OAc)_2$ (1 mol %), and cesium carbonate (Cs_2CO_3, 3 equiv) was refluxed for 3 h. Standard workup and flash chromatography provided 4-phenylbenzonitrile **15a** in 87% yield.

Table 1. Suzuki Coupling Reactions of 8 with Aryl Bromides



14a–g **8** **15a–g**

entry	ArX	time	ArPh	yield[a]
				
1	**14a**, R = CN	3 h	**15a**	87%
2	**14b**, R = CF_3	2 h	**15b**	72%
3[b]	**14c**, R = CHO	2 h	**15c**	68%
4	**14d**, R = NO_2	1 h	**15d**	84%
5	**14e**, R = CO_2Me	2 h	**15e**	81%
6	**14f**, R = OMe	4 h	**15f**	82%
				
7	**14g**	3 h	**15g**	81%

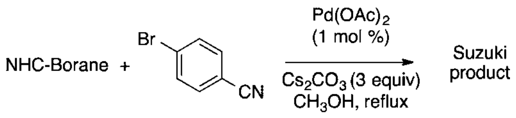
[a]Isolated yield after flash chromatography. [b]Small amounts of methyl esters **14e** and **15e** resulting from Cannizzaro reactions with the solvent were also formed.

Entries 2–7 in Table 1 show the results of additional Suzuki coupling reactions of the partner NHC-difluoro(aryl)borane **8** with assorted aryl bromides **14b**–**g** under the same conditions.

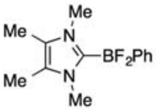
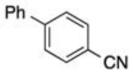
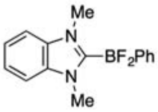
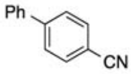
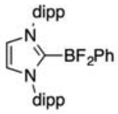
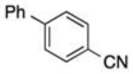
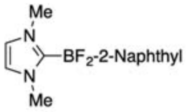
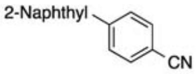
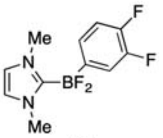
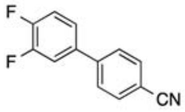
All of the reactions produced good yields of Suzuki coupling products **14b−g** (68−84%) over the course of 1−4 h. Reaction progress can be monitored by standard TLC analysis.

Table 2 shows examples of Suzuki reactions of the other difluoroboranes **9−13**, this time all with 4-bromobenzonitrile **14a**. Again Molander's conditions for trifluoroborate couplings were used with Cs_2CO_3, and isolated yields of products **15a**, **16**, and **17** are uniformly good, 68−84%. Analysis of several crude products by ^1H NMR spectroscopy showed resonances of the 1,3-dimethylimidazolium salt by protonation of the NHC. This salt and the inorganic products are readily removed by silica gel filtration.

Table 2. Suzuki Reactions with NHC-Difluoro(aryl)boranes



14a

entry	NHC-borane	Suzuki product (time, yield[a])
1	 **9**	 **15a**, (3 h, 84%)
2	 **10**	 **15a**, (3 h, 83%)
3	 **11**	 **15a**, (6 h, 72%)
4	 **12**	 **16**, (4 h, 70%)
5	 **13**	 **17**, (4 h, 68%)

[a] Isolated yield after flash chromatography.

What happens to the difluoro(aryl)boranes under the reaction conditions is currently unclear, but we speculate that they mimic other Suzuki precursors by slowly producing either boronates or reactive equivalents of boronates throughout the course of the reaction.[22,23]

The significance of this preliminary work is 3-fold. First, the immediate goal to build a bridge between NHC-borane chemistry and Suzuki chemistry has been met. Second, the bridge is built upon NHC-difluoro(aryl)boranes. These neutral compounds, usually white solids, are convenient to chromatograph, easy to identify, largely insoluble in water, and soluble in a wide range of organic solvents. These favorably properties bode well for future applications in boronic acid chemistry, both in and beyond Suzuki reactions.

Finally, third, the fluorination of NHC-boranes provides an entry to boronic acid chemistry that differs from current stable precursors. The other main classes of stable Suzuki precursors shown in Figure 1, potassium trifluoroborates,[24] pinacol boranes, and MIDA boronates,[25] usually come from precursors in the boronic acid oxidation state. These are in a way protecting groups.

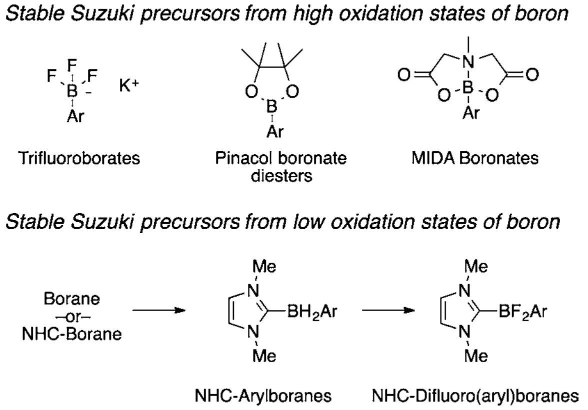


Figure 1. Comparing and contrasting stable precursors for Suzuki reactions.

NHC-difluoro(aryl)boranes differ because they are produced by fluorination, not functional group exchange. Thus, the run up to Suzuki chemistry in the NHC-borane approach is based on low oxidation states of boron. The stability of both the parent NHC-boranes and their difluoro derivatives coupled with their access from reduced boron chemistry will in the long run provide added flexibility in diverse synthetic settings including multistep total synthesis and selective cross coupling reactions.

In summary, we have bridged the budding chemistry of NHC-boranes with well established boronic acid chemistry by a two-step sequence of fluorination and Suzuki reaction. Currently, the simplest N-heterocyclic carbene, 1,3-dimethylimidazol-2-ylidene, looks attractive for this chemistry because it is readily available and has a relatively low molecular weight (96 g mol^{-1}). Looking beyond Suzuki reactions, the observations suggest that substituted NHC-difluoro(aryl)boranes may serve as boronic acid precursors or equivalents in other types of reactions as well.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details, compound characterization data, and copies of NMR spectra of all products. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01101.

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Notes

The authors declare no competing financial interest.

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