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Generation of 3-Pyridyl Biaryl Systems via Palladium-Catalyzed Suzuki Cross-Couplings of Aryl Halides with 3-Pyridylboroxin

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Abstract: The synthesis of 3-pyridyl biaryl systems can be readily achieved by means of palladium-catalyzed Suzuki cross-coupling reactions between aryl halides and 3-pyridylboroxin. A series of cross-couplings were conducted in order to investigate the scope and limitations of this protocol.

The palladium-catalyzed Suzuki cross-coupling reaction between boronic acids/esters and aryl halides is a powerful carbon−carbon bond-forming tool in organic synthesis and is widely used in the construction of biaryl systems.[1] In our laboratories, we sought to utilize this reaction for the preparation of a key heterobiaryl scaffold that contained a 3-pyridyl connectivity by a cross-coupling reaction between pyridine-3-boronic acid (**2**)[2−4] and a proprietary aryl halide. The scale of our preparation required multigram amounts of the boronic acid **2**, but due to the high cost (∼$100/g) of **2** (and the scarce commercial availability of the pinacol ester surrogate), we sought to prepare it ourselves following the procedure recently reported by Li and co-workers[3,4] using the relatively inexpensive reagent 3-bromopyridine (∼$1/g). We were also hoping that our application to large-scale preparation of the simple reagent **3** would also circumvent the use of the reagent diethyl(3-pyridyl)borane[5] which, although less expensive than **2** (∼$10/g), was limited to smaller amounts commercially available.

Li's reported method for the preparation of pyridine-3-boronic acid (**2**) involves the low-temperature lithium−halogen exchange of 3-bromopyridine (**1**) using *n*-butyllithium followed by an in situ quench of the lithio species with triisopropylborate.[4] Hydrolysis of the boronate adduct with aqueous acid provides the free boronic acid **2**. To isolate and purify the reagent, the authors chose to heat a mixture of **2** in acetonitrile, resulting in the formation of the stable 3-pyridylboroxin (**3**), a dehydrated trimer (Scheme 1). The authors then converted boroxin **3** to the corresponding pinacol ester, which was fully characterized. Boroxin **3** itself is a bench-stable compound that can be easily hydrolyzed[6] to provide pure boronic acid **2** prior to subjection to the Suzuki cross-coupling conditions. In our hands, this protocol worked quite well to provide **3** in good yield (90% over three steps) and was amenable to multigram-scale preparation of our desired biphenyl target. The boroxin was substantially more pure than the boronic acid adduct (>95% versus ∼85% by ^{1}H and ^{13}C NMR analyses) due to the crystallization of **3** from acetonitrile after the trimer formation. We have observed that **3** can be stored on the benchtop for more than two months without any detectable decomposition (analysis by ^{1}H NMR and LC MS). In our experience, this method constituted a vast improvement over the previously reported methods for generating **2**.[7]

It is not as well-known that some boroxins can serve as boronic acid surrogates for Suzuki cross-coupling reactions.[8] Although the use of aryl boroxins is well documented in the literature,[9] their primary application has been a means by which boronic acids can be purified and characterized.[10] With **3** in hand, we decided to try to use it as is in our cross-coupling reaction instead of

† Undergraduate Summer Research Intern, Summer 2002.

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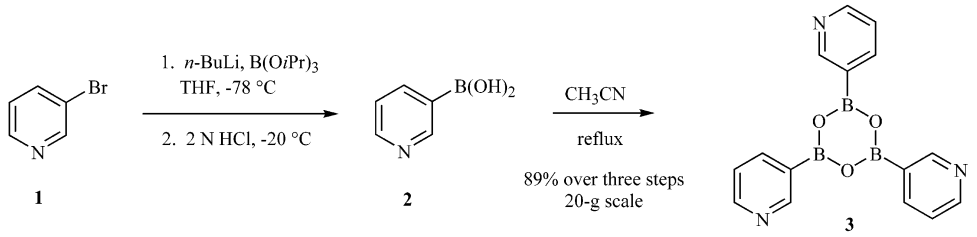
SCHEME 1



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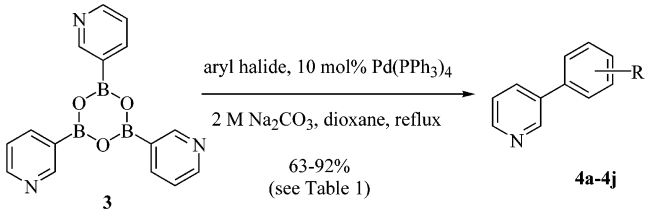
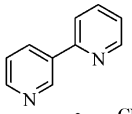
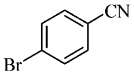
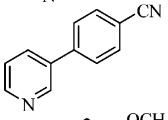
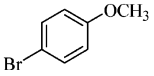
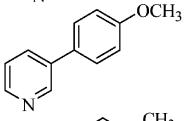
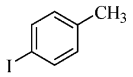
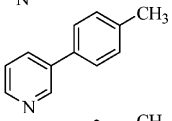
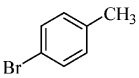
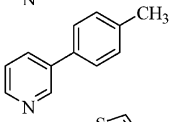
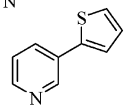
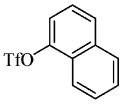
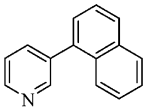
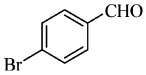
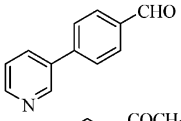
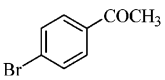
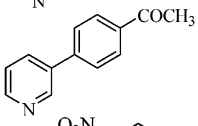
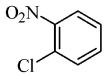
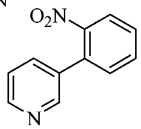


converting it to boronic acid **2** prior to reaction. Our reasoning was that the basic aqueous conditions in the Suzuki protocol would be sufficient for hydrolysis of **3** to boronic acid **2** in situ.[8] We attempted the first Suzuki cross-coupling reaction between **3** and 4′-bromoacetophenone using aqueous 2 M sodium carbonate as base and 10 mol % of tetrakis(triphenylphosphine)palladium(0) as catalyst and discovered that the cross-coupling produced the desired biaryl **4i** in 86% yield (Scheme 2 and Table 1, entry 9). We initially attempted this reaction using 1 molar equiv of **3**, but it was later confirmed that the theoretical amount of 0.3 molar equiv was sufficient for complete conversion to cross-coupled product. In direct comparison, the cross-coupling reaction between the boronic acid **2** with 4′-bromoacetophenone under the same conditions produced **4i** in 74% yield. In the latter case, the crude product was accompanied by larger amounts of undetermined impurities, presumably arising from the impure nature of the prepared reagent **2**. These discoveries prompted us to investigate the scope and limitations of this protocol.

We discovered that **3** undergoes palladium-catalyzed Suzuki cross-coupling with a wide variety of aryl halides and an aryl triflate in acceptable to excellent yields (**4a**−**j**, Table 1). For reasons of comparison to the bulk of the reported literature, we decided to employ the "standard" Suzuki reaction conditions in all cases using 10 mol % of the zerovalent catalyst tetrakis(triphenylphosphine)-palladium in a refluxing mixture of 2 M sodium carbonate and dioxane.[1] Not unlike the corresponding reaction with boronic acids, this transformation appears to be quite general, with the usual variety of functional groups tolerated under these conditions. Aryl halides with either electron-donating or -withdrawing substituents couple readily with boroxin **3**, and cross-coupling with some heteroaryl halides to form heterobiaryl systems was also readily achieved (Table 1, entries 1 and 6). Direct comparisons to the same transformations using diethyl-(3-pyridyl)borane show the transformations are quite comparable. For instance, the respective yields for the cross-coupling utilizing **3** versus diethyl(3-pyridyl)borane are 72% (entry 1) versus 85%[5a] to prepare **4a**, 63% (entry 3) versus 75%[5b] to prepare **4c**, 69% (entry 4) versus 84%[5b] to prepare **4d**, 91% (entry 6) versus 76%[5a] to prepare **4f**, 86% (entry 9) versus 73%[5b] to prepare **4i**, and 79% (entry 10) versus 75%[5b] to prepare **4j**. Interestingly, there are not very many examples in the literature for which pyridylboronic acids are cross-coupled with aryl halides and triflates, but instead a wealth of examples exist in which pyridyl halides are cross-coupled with the boronic acid moiety borne on the other aryl substrate partner.

TABLE 1. Suzuki Cross-Coupling Reactions of Aryl Halides with 3-Pyridylboroxin (3)

Entry	Substrate	Coupling Product	Yield[a]
1			**4a**, 72%
2			**4b**, 89%
3			**4c**, 63%
4			**4d**, 69%
5			**4d**, 67%
6			**4f**, 91%
7			**4g**, 83%
8			**4h**, 92%
9			**4i**, 86%
10			**4j**, 79%

[a] Isolated yields following chromatography.

Attempts to cross-couple **3** with 4′-bromoacetophenone to provide **4i** using anhydrous conditions reported by Buchwald[11] and Fu[12] did not provide the desired product. We believe that formation of an active boronate species of **3** does not readily occur under anhydrous conditions that employ fluoride salts (KF or CsF). Rather, it is necessary that **3** undergo initial in situ hydrolysis to the boronic acid **2** prior to coupling. While it was found that it was possible to utilize 0.3 equiv of **3** per equivalent of aryl halide substrate in this reaction, we found that the slight "excess" of 0.5 equiv of **3** was satisfactory to achieve respectable results overall, not unlike the process using a boronic acid.

In conclusion, this work demonstrates that 3-pyridylboroxin **3** may act as a suitable synthetic equivalent of pyridine-3-boronic acid for the palladium-catalyzed Suzuki cross-coupling reaction with a variety of aryl halides and an aryl triflate. Boroxin **3** is a bench-stable compound that can be readily prepared from 3-bromopyridine **1** in good yield and in relatively large scale. We believe that these attractive features make **3** a viable replacement for the expensive commercial reagent 3-pyridylboronic acid **2**.

Acknowledgment. We acknowledge and thank Professors Victor Snieckus of Queen's University and Thomas Hoye of University of Minnesota for many helpful discussions and suggestions.

Supporting Information Available: Experimental procedures, spectral and analytical data, and literature references for all reaction products. This material is available free of charge via the Internet at http://pubs.acs.org.

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