

PRF# 54825-UR3

Phosphine-Directed C-H Borylation of Arenes: Facile Access to Ambiphilic Phosphine Boronate Esters

Timothy B. Clark, University of San Diego

Progress Report

Over the past year of the granting period, the focus has been on completing the final experiments and characterization of compounds required for publication. There have been a number of complications that have arose during this process that have resulted in not completing the manuscript for publication. At this point, however, the manuscript is about 95% complete and I intend to submit it to the *Journal of the American Chemical Society* in the next two weeks. The major tasks that remain are to catalogue the characterization data for about 5 compounds. For 2–3 of these compounds, additional spectral data is required because the initial data was insufficient.

One major challenge that was faced during the reporting period was in the deprotection of the borane-protected phosphine boronates (see Scheme 1 for big picture of reaction sequence, deprotection is boxed). Because the final products are not readily purified upon deprotection (due to air- and moisture-sensitivity), the starting material must be highly pure and no side reactions can take place during the deprotection. The most common side reaction is the protodeboration of the C–Bpin bond, providing the starting phosphine with the desired phosphine boronate. There is still a class of protected phosphine boronates that we have not been able to deprotect cleanly (those containing indoles), but examples from the remaining classes of borylated compounds have been demonstrated (see Figure 1 for the successful deprotected products).

Scheme 1. General Reaction Scheme of Phosphine-Directed C-H Borylation

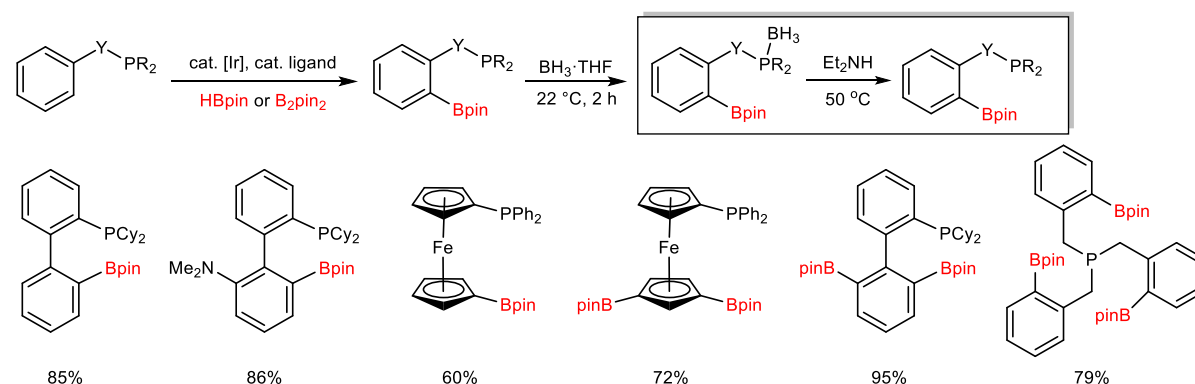
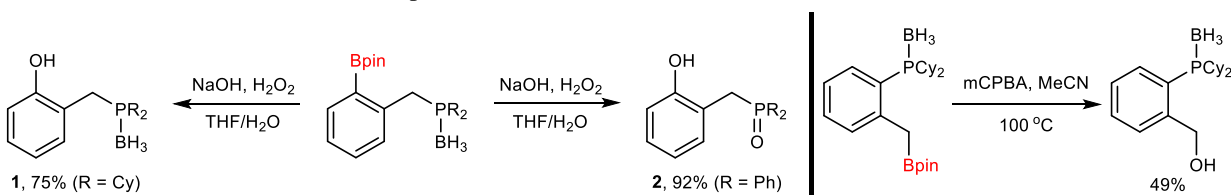


Figure 1. Deprotected Phosphine Boronates (see boxed reaction in Scheme 1 for general reaction)

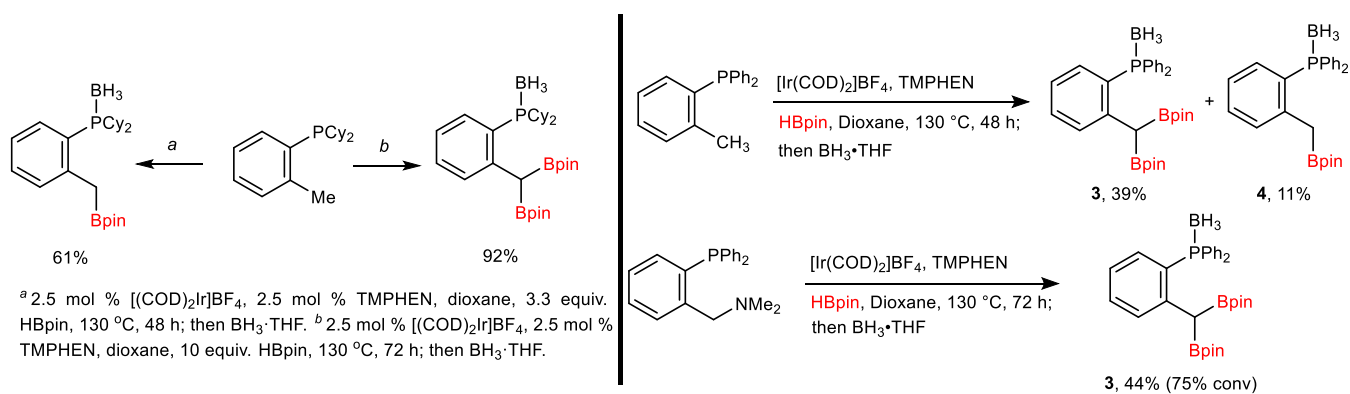
Another area of focus during the granting period was on the functionalization of the protected phosphine boronates. After the last reporting period, High Resolution Mass Spectrometry revealed that some of the oxidations of the carbon–boron bond to carbon–oxygen bonds also resulted in deprotection and oxidation of the phosphine. As shown in Scheme 2, the diphenylphosphine was readily deprotected leading to phosphine oxide **2**, whereas the dicyclohexyl version (**1**) remained protected. Attempts to improve the oxidation conditions to selectively obtain the protected phenol in place of **2** were unsuccessful, also providing **2**. During these studies, however, mCPBA was identified as a viable oxidant for these transformations (though still deprotecting the phosphine as in the case of **2**). These additional conditions led to the oxidation of a benzylic boronate, which was not successful under the traditional hydrogen peroxide conditions (Scheme 2, right). Further optimization and determination if the protecting group is retained is currently underway. An additional functionalization that was targeted for further optimization for publication was the amination of protected phosphine boronates. The initial aminations were reported in the previous report and also resulted in deprotection with diphenylphosphines and did not deprotect with dicyclohexylphosphines. Attempts to improve the yield of those examples, however, failed and no progress has been made on this aspect of the project.

Scheme 2. Oxidation of Protected Phosphine Boronates to Alcohols



A final area of new exploration has been to extend the phosphine-directed C–H borylation of benzylic C–H bonds to additional substrates. In the previous report, the benzylic C–H borylation was shown, which provides mono- or bis-borylation of benzylic methyl groups adjacent to phosphines (Scheme 3, left). Benzylic C–H borylation has not been extensively reported in the literature and there are no such examples of phosphine-directed C–H borylation. To begin examining the scope of this transformation, a series of phosphines was examined under the reaction conditions with the goal of determining the scope of the phosphine substituents and the ability to functionalize secondary benzylic C–H bonds. The relatively successful examples are shown in Scheme 3 (right). The diphenyl-substituted *o*-tolylphosphine was less reactive than the dicyclohexyl version of this substrate. A 39% isolated yield of bis-borylated product **3** was obtained accompanied by 11% of mono-borylation product **4**. Further optimization is required to access each of these products in good yield. A similar substrate possessing a benzylic amine was examined with the goal of secondary benzylic C–H borylation. Surprisingly, efficient formation of bis-borylated product **3** was obtained. Some borodeaminations have been reported in the literature, but not of this type. Further exploration is required to understand the nature of this reaction.

Scheme 3. Exploration of the Scope of Benzylic C–H Borylation



Impact of Award

This ACS-PRF award has catalyzed this project into a robust research project in the PI's lab. When the proposal was submitted this was a new direction for the PI's research group with limited results that led to one publication. This funding has allowed the PI to expand the application of the methodology to a wide range of phosphine substrates. Furthermore, the results obtained from this grant were used to secure a National Science Foundation Research at Undergraduate Institutes grant that started on September 1, 2018, after the ACS-PRF grant was complete. The future directions of the grant are expanding with the expanded funding. Overall, this ACS-PRF grant has provided the needed seed funding to pursue this line of work, which is now quite robust.