

## Development of Transition-Metal-Free Carbon–Carbon and Carbon-Boron Bond-Forming Reactions by Utilizing 1,1-Bis[(Pinacolato)Boryl]Alkanes

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Organoboranes are one of the most versatile reagents and intermediates in organic synthesis, enabling a wide variety of synthetic transformations.<sup>1</sup> Due to their stability, easy accessibility and environmentally benign nature, numerous classes of organoboron reagents have been prepared and utilized under both stoichiometric and catalytic conditions ever since the laboratory preparation of triethylborane by Frankland in 1859.<sup>2</sup> In particular, the boron reagents have enjoyed widespread use as coupling partners in palladium-, nickel-, or copper-catalyzed cross coupling reactions such as Suzuki-Miyaura reaction<sup>3</sup> and Chan-Evans-Lam reaction.<sup>4</sup>

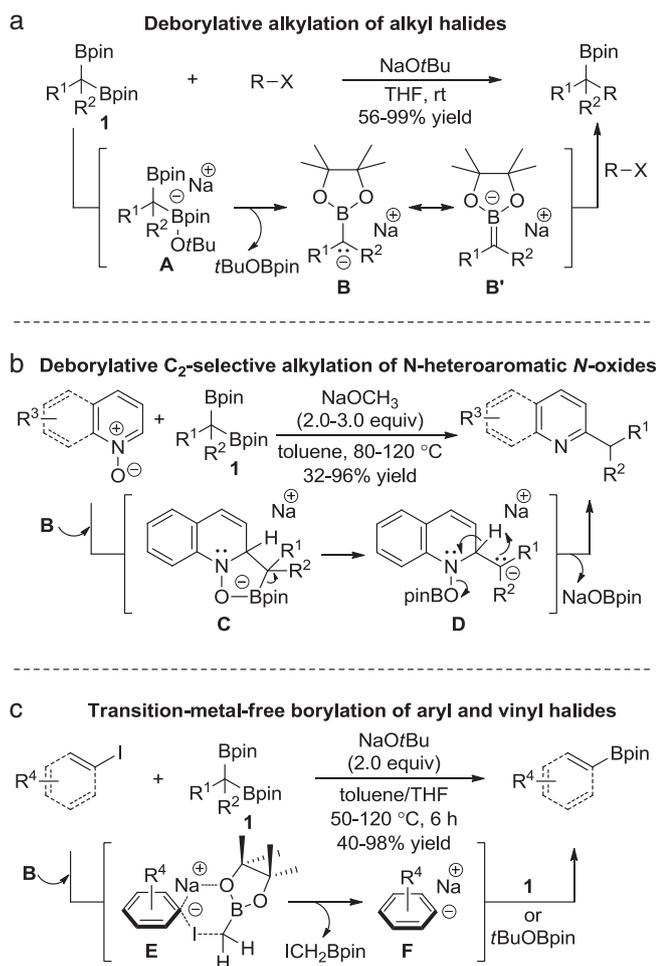
In 2010, Shibata and Endo elegantly introduced 1,1-bis[(pinacolato)boryl]alkanes (**1**) as a new class of boron-based coupling reagent in their chemoselective and regioselective Suzuki-Miyaura reaction of aryl halides, which operate under palladium catalysis.<sup>5</sup> Following this seminal work, **1** have attracted considerable attention from the synthetic community and various catalytic and non-catalytic, chemo- and enantioselective C–C bond-forming reactions have been developed, using **1** as the key reagent.<sup>6</sup>

Moriken and co-workers in 2014 reported the first example of the alkoxide-promoted deborylative alkylation of **1** with alkyl halides (Scheme 1(a)).<sup>7a</sup> This transformation provided access to primary, secondary, and tertiary alkylboronic esters in good to excellent yields with high chemo- and diastereoselectivity, and features broad substrate scope including tolerance for geminal bis(boryl)cyclopropanes. Remarkably, an intramolecular version of this deborylative alkylation provides an efficient route to carbocyclic organoboronates with three to seven-membered ring sizes, which are not readily accessible by other means. Mechanistic studies indicated that an  $\alpha$ -boryl carbanion **B** could be generated *in situ* upon reaction of **1** with the metal alkoxide through chemoselective mono deborylation of an *ate* complex **A**, accompanied by liberation of *t*BuOBpin (Scheme 1(a)). The intermediary presence of boron alkylidene **B'** specie, which formed presumably due to the enhanced  $\pi$ -bonding interaction between the negatively

charged carbon atom and the Lewis-acidic three-coordinated boron, was also supported by spectroscopic studies. Very recently, the same group also disclosed deborylative cyclization reaction of **1** bearing a tethered alkene. It was proposed that this unusual transformation proceeds via a non-concerted stepwise [2 + 2] cycloaddition reaction between the tethered alkene and a boron alkylidene.<sup>7b</sup>

In 2016, the group of Cho independently developed regioselective alkylation of quinoline and pyridine *N*-oxides using **1** ( $R^1 = \text{alkyl}$ ,  $R^2 = \text{H}$ ) as alkylating agents (Scheme 1(b)).<sup>8a</sup> The optimal conditions for methylation included the use of NaOCH<sub>3</sub> as base and toluene as the solvent in presence of an excess amount of **1** ( $R^1 = R^2 = \text{H}$ ) at an elevated temperature of 80 °C. Instead of expected 2-(borylmethyl)heteroarenes, the deoxygenated 2-methylated quinoline and pyridine derivatives were obtained as a single product under these conditions. It was found that this protocol was also applicable to a broad range of 1,1-diborylalkanes as well as other heterocyclic *N*-oxides. The same group also reported secondary alkylation of *N*-heteroaromatic *N*-oxides under slightly modified reaction conditions using internal *gem*-bis[(pinacolato)boryl]alkanes **1** ( $R^1 = R^2 = \text{alkyl}$ ).<sup>8b</sup> On the basis of mechanistic studies, a stepwise mechanism was proposed for this deborylative alkylation of *N*-heterocyclic *N*-oxides (Scheme 1(b)).<sup>8</sup> As exemplified for quinoline *N*-oxide ( $R^3 = \text{H}$ ), the nucleophilic attack of the boron-stabilized carbanion **B** at the 2-position of the heteroarene leads to the formation of tricyclic intermediate **C**, which is then rearranged to the carbanion **D**. Subsequent intramolecular proton transfer in **D** and concurrent elimination of NaOBpin furnishes the alkylated heterocycle.

Arylboronic acids and esters have become the coupling reagents of choice in a wide range of transition-metal-catalyzed cross coupling reactions.<sup>3,4</sup> Typically, the arylboronic acid derivatives are prepared by the reaction of trialkylboronates with nucleophilic aryl organometallic reagents (*e.g.*, Grignard and organolithium reagents) or the catalytic cross coupling reaction of aryl halides or *pseudo*-



**Scheme 1.** C–C and C–B bond-forming reactions by utilizing 1,1-bis[(pinacolato)boryl]alkanes.

halides with  $B_2pin_2$ . However, a major drawback of these methods is the requirement of rigorous anhydrous solvents under cryogenic conditions and use of expensive and toxic transition-metal catalysts, respectively. In recent years, primarily due to its cost-effectiveness and operational simplicity, transition-metal-free borylation has emerged as a promising alternative.<sup>9</sup>

In line with their continuous endeavor utilizing **1** in organic synthesis, the groups of Cho and Baik investigated the chemoselective borylation of aryl and vinyl halides (I, Br) employing **1** ( $R^1 = R^2 = H$  or  $R^1 = H, R^2 = CH_3$ ) as the source of boron (Scheme 1(c)).<sup>10</sup> As a rare example of a transition-metal-free borylation reaction, Cho and Baik's method exhibited good compatibility with the presence of a broad range of organohalides. It should also be noted that the borylated products are obtained as a sole product in all cases and no alkylated products are detected under the optimal conditions. Noteworthy is that this report is the first example of C–B bond-forming reaction of aryl halides by using **1**. Based on the experimental and DFT calculation studies, a mechanistic proposal for this novel transformation was presented, as shown in Scheme 1(c). Nucleophilic

attack of the  $\alpha$ -boryl carbanion **B** on the halogen atom of the iodoarene generates sodium aryl anion species **F** via the transition state **E** with concurrent formation of  $ICH_2Bpin$ . Subsequently, the aryl anion in **F** undergoes a rapid carbon-boron bond-forming reaction with **1** or  $tBuOBpin$  to give the borylated arene.

In summary, 1,1-diborylalkanes (**1**) have recently gained much attention in many transition-metal-free C–C and C–B bond-forming reactions because of their versatility as a coupling partner. Their ability to generate boron-stabilized carbanion (*i.e.*, **B**) under mild conditions has proven crucial in most transformations. We are convinced that further applications of **1** are forthcoming.

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## Highlights

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