ORGANOMETALLICS

Article

Cite This: *Organometallics* XXXX, XXX, XXX–XXX

Chemoselective Benzylation of Aldehydes Using Lewis Base Activated Boronate Nucleophiles

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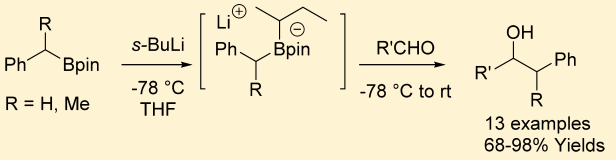
Supporting Information

ABSTRACT: A benzylation of aldehydes using primary and secondary benzylboronic acid pinacol esters is reported. Activation of the boronic ester with *s*-butyllithium rendered it nucleophilic toward aldehydes. The activated nucleophile chemoselectively transfers the benzyl group over the *sec*-butyl group, providing excellent yields of the benzylated products. ^{11}B NMR experiments were performed to study the mechanism of this transformation.

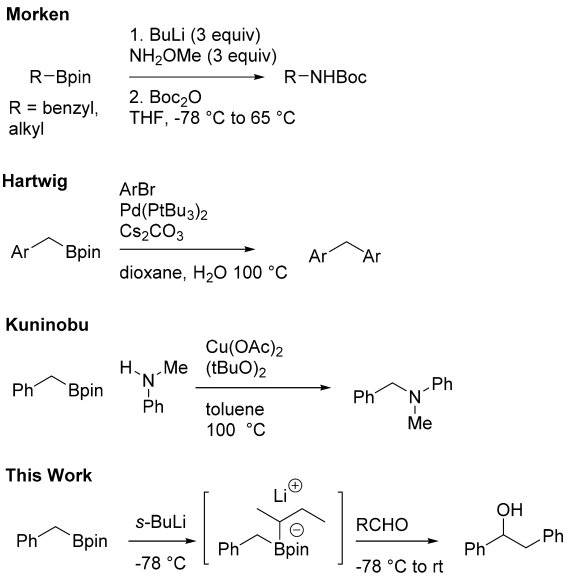


Organoboron reagents are useful intermediates in organic synthesis.[1] The boronic acid pinacol ester functional group has been exploited in natural product synthesis through the Suzuki–Miyaura cross-coupling reaction.[1a] Benzylboronic esters are a subclass of organoboron reagents that are less developed in their synthetic applications than the widely used arylboronic acids.[2] Traditionally, benzylboronic esters are synthesized from the corresponding alkyl halide through either Grignard formation[3] or the use of a transition-metal catalyst.[4−6] More recently, these compounds have been prepared through C–H activation using transition-metal catalysts[7−10] or other methods.[11−14]

While our interests were in developing a reaction between the primary benzylboronic acid pinacol ester and aldehydes, the use of secondary and tertiary benzylic boronic esters has received much attention in the development of stereospecific transformations employing enantioenriched benzylic boronic esters.[15] Stereospecific synthesis and subsequent oxidations of tertiary boronic esters have provided tertiary alcohols[16] and amines.[17,18] Numerous other stereospecific reactions have provided arylation,[19] protodeboronation,[20] halogenation,[21] and various carbon homologations of secondary and tertiary benzylic boronic esters.[15a] There are examples of Rh-catalyzed addition of secondary benzylboronic esters to aldehydes[22] and imines;[23] however, electrophiles required electron-withdrawing groups to obtain good yields.

In contrast, there are only a few reported examples of primary benzylboronic esters as reactants (Scheme 1). Previous reports have demonstrated the oxidation of benzylboronic acid pinacol ester (BnBpin) to the corresponding alcohol, iodide, and amine compounds.[8,17] Additionally, BnBpin has been employed in Pd-catalyzed cross-coupling reactions as well as Cu-catalyzed Chan–Lam type couplings with anilines and phenols.[8,24] BnBpin is commercially available and not moisture sensitive, making it an attractive reagent for further development. We sought to develop a reaction using BnBpin as a nucleophile with aldehydes.

Scheme 1. Reactions with BnBpin



Primary benzylboronic esters are more challenging substrates in comparison to substituted benzylboronic esters. Mayr and Aggarwal have combined BnBpin and phenyllithium to form a boronate nucleophile and measured its nucleophilicity in reactions with dibenzylic carbocations.[25] These studies found the boronate species generated from BnBpin to be less nucleophilic than boronates from secondary benzylboronic esters. We anticipated that using an alkyllithium to generate the boronate nucleophile would increase the nucleophilicity of the benzyl moiety, opening a new class of reactivity.

We began our investigations with examining the nucleophilic addition of BnBpin to benzaldehyde (Table 1). Activating

Received: February 8, 2018

DOI: 10.1021/acs.organomet.8b00085
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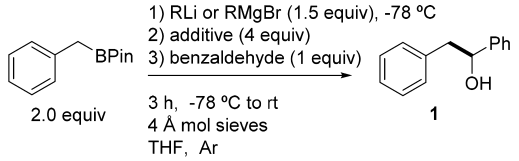
Table 1. Optimization of Reaction Conditions



entry	change from standard conditions	yield, %[a]
1	*n*-BuLi	38
2	*n*-BuLi with NMP	82
3	*n*-BuLi with DMPU	71
4	*n*-BuLi with TMEDA	74
5	*s*-BuLi with NMP	82
6	*s*-BuLi with no additives	100 (98)[b]
7	MeLi	54
8	PhLi	6
9	MeMgBr	20

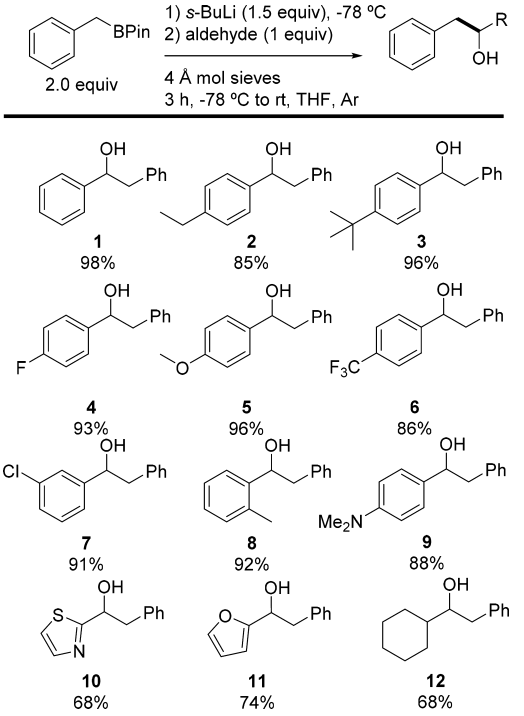
[a]Yields determined by NMR using an internal standard. [b]Isolated yield in parentheses.

BnBpin with *n*-BuLi and no additives provided a 38% yield of the desired product along with benzyl alcohol and trace amounts of benzoic acid (entry 1). Formation of benzyl alcohol can be formed by β-hydride transfer from the butyl group when it is attached to the boronate,[26] a Cannizzaro side reaction catalyzed by Li ions,[27] or air oxidation of BnBpin.[28] The inclusion of polar aprotic additives was then pursued to favor nucleophilic benzyl addition over formation of benzyl alcohol.[29] The addition of NMP was effective, providing the desired product in 82% yield (entry 2). Use of DMPU and TMEDA as additives also showed an improvement in the yield (entries 3 and 4). *s*-BuLi was found to be equally effective as *n*-BuLi with NMP as an additive (entry 5). A control experiment revealed NMP was not necessary when *s*-BuLi was used (entry 6). *s*-BuLi has previously been used to activate alkylboronic esters for Pd-catalyzed cross-coupling.[30] Examination of other organometal activating agents, including PhLi, found *s*-BuLi to be the most effective (entries 7–9).

It is significant that no butyl addition to the aldehyde was observed, indicating that a chemoselective transfer of the benzyl group is possible with alkyllithium activation of BnBpin. This result was consistent across all organometallic Lewis base reagents examined, with the benzyl group always being selectively transferred with no evidence of the other group being transferred during the optimization. Control experiments confirmed that there was no reaction observed between BnBpin and benzaldehyde in a variety of solvents with heating. Activation of BnBpin with metal alkoxides also provided none of the desired reactivity, suggesting that irreversible coordination of a Lewis base was necessary to obtain the desired reactivity.

With optimal conditions in hand, the substrate scope with respect to the aldehyde was examined. Excellent yields were obtained with aromatic aldehydes (Table 2). Both electron-donating and electron-withdrawing substituents performed well under these reaction conditions, with all of these reactions going to completion in 3 h. This benzylation proved to be very tolerant of electronic changes on the aldehyde.[22a] Given the lack of difference in reaction efficiency with electronically differentiated para substituents, a competition experiment was performed that found *p*-trifluoromethylbenzaldehyde reacted more quickly than *p*-methoxybenzaldehyde as would be

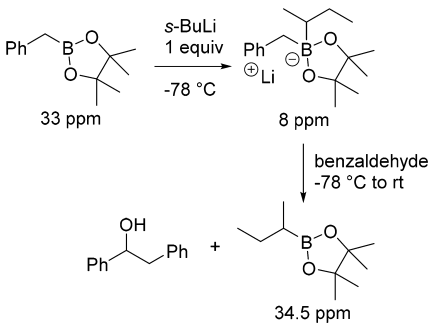
Table 2. Aldehyde Substrate Scope



expected.[31] Reactions with heterocyclic aldehydes also gave respectable yields under these reaction conditions (**10** and **11**). A reaction with cyclohexylcarboxaldehyde resulted in a 68% yield of **12**, providing an example of an aliphatic aldehyde substrate.

^{11}B NMR was used to support the proposed intermediates in the mechanism (Scheme 2). BnBpin has a ^{11}B NMR resonance

Scheme 2. ^{11}B NMR of Reaction



at 33 ppm. Addition of 1 equiv of *s*-BuLi resulted in the appearance of a resonance at 8 ppm, consistent with the chemical shift of LiArBnBpin intermediates previously observed by Aggarwal.[32] At the conclusion of the reaction, a new resonance was observed at 34.5 ppm, which matches the reported data for *s*-BuBpin.[33]

A secondary benzylic boronic acid pinacol ester was also examined as a nucleophile (Scheme 3). With benzaldehyde as the electrophile, the secondary alcohol was isolated in a 79% yield. The efficiency of this reaction compares favorably to a previously reported Rh-catalyzed addition of secondary benzylic trifluoroborate salts to aldehydes that required an electron-withdrawing substituent on the aldehyde to obtain yields above 50%.[22a] A 1:1 mixture of diastereomers was isolated. This result

DOI: 10.1021/acs.organomet.8b00085
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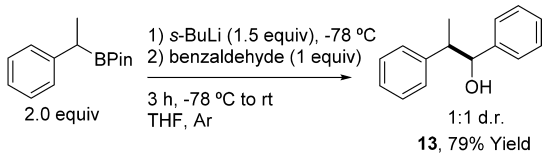
Scheme 3. Secondary Benzyl Boronate Nucleophile



was not surprising, since this addition is presumed to go through an open transition state.

In summary, a method for the benzylation of aldehydes using Lewis base activated boronate nucleophiles has been described. Activation of BnBPin by an alkyllithium reagent was necessary to render the benzyl group nucleophilic. An important discovery was the chemoselective transfer of the benzyl group over butyl substituents of the activated boronate nucleophile under the reaction conditions, allowing for formation of the benzylation products in excellent yields, especially with aryl aldehydes. The presence of electron-donating or electron-withdrawing substituents on the aldehyde did not affect the efficiency of the reaction. In our laboratory we plan to pursue the benzylation of other electrophiles using this methodology.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.organomet.8b00085.

Experimental procedures and ^{1}H, ^{13}C, ^{19}F, and ^{11}B NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The College of Charleston is acknowledged for financial support. M.R.H. acknowledges support for a summer stipend funded by the Howard Hughes Medical Institute to the College of Charleston as part of their 2012 Undergraduate Science Education Competition and the National Center for Research Resources (5 P20 RR016461) and the National Institute of General Medical Sciences (8 P20 GM103499) from the NIH. The NMR spectrometer at the College of Charleston was supported by the National Science Foundation under Grant No. 1429308.

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DOI: 10.1021/acs.organomet.8b00085
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