Cu-catalyzed cross-coupling of benzylboronic esters and epoxides

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ABSTRACT

A reaction between epoxides and benzylboronic acid pinacol esters is described. CuI was found to be an effective catalyst of this transformation upon activation of the benzylboronic ester with an alkyllithium reagent. The reaction was very efficient and a variety of substituted epoxides were found to be good substrates with good regioselectivity for substitution at the less substituted side of the epoxide. A reaction using an enantioenriched secondary benzylboronic ester was found to not be stereospecific.

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Introduction

Organoboron reagents are compounds of great importance to organic synthesis that have received much interest in recent years [1-8]. Reactions involving alkylboronic esters provide an excellent example for the versatility of organoboron reagents. Beyond participating in transition metal-catalyzed cross-coupling reactions, these reagents are known to react stereospecifically in oxidations, conversions to heteroatoms, protodeboronation, homologations, olefinations, and alkynylations, to name a few [7]. The precedent for participating in new organic transformations as well as the moisture and air stability of these compounds make boronic esters attractive reagents for further development.

Lewis base activation of alkylboronic esters with an organolithium reagent render the subsequent alkylboronate species nucleophilic and these have been used in numerous reactions, including in some enantiospecific transformations [9-11]. In our laboratory, we have found the activation of benzylboronic esters with an alkyllithium reagent forms a boronate intermediate capable of adding to various electrophiles including carbonyls, imines, and alkyl halides [12-15]. We sought to expand this reactivity to epoxides as well as determine if an activated dialkylboronate could participate in a stereospecific addition reaction.

There are several previous examples of cross-coupling reactions between epoxides and boronic acids and esters. Pd catalysts have been used in the cross coupling between vinyl epoxides and aryl and vinylboronic acids [16]. Nickel catalysts have facilitated cross-coupling between epoxides with arylboronic acids [17,18]. Copper catalysts have been employed with epoxide couplings with arylboronic acids and *gem*-diborylmethane (pinBCH₂Bpin) [19-21]. Aside from reactions with pinBCH₂Bpin [20], there are no other examples of the addition of alkylboronic esters to epoxides to the best of our knowledge.

Results and discussion

Investigation began with examining styrene oxide as a model substrate. Using similar reaction conditions that had been effective for the addition of benzylboronates to aldehydes and imines, we observed no desired reactivity (Table 1, entry 1) [12,13]. Previously, Schomaker and coworkers had shown alkoxide base activation of benzylboronic esters had been effective at forming stabilized benzyl carbanions that were shown to react with heteroallene electrophiles and alkyl halides [22]. Activation of the benzylboronic ester with lithium *tert*-butoxide instead of *s*-butyllithium was also ineffective under our conditions for addition to epoxides (entry 2). We examined copper salts as additives and found that CuI was an effective catalyst (entries 4–5) [19,20,23]. Brief examination of other metal catalysts including Sc(OTf)₃, NiCl₂ with bipyridine as a ligand provided none of the desired product. Notably, a mixture of regioisomers was observed with our reaction conditions favoring the linear product. The preference for the linear product is consistent with a previous example of Cu-catalyzed addition of arylboronic esters to styrene oxide [19]. In related work, Weix reported a mixture of regioisomers in a Ni-catalyzed addition of aryl nucleophiles to styrene oxide where addition to the benzylic carbon was the major regioisomer observed [24]. In

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Table 1
Optimization of Reaction Conditions.
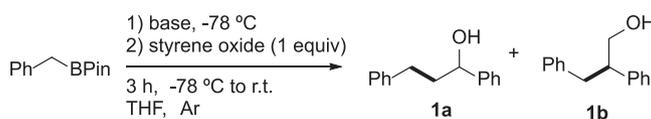
Entry	Additive	Reaction stoichiometry and base	Yield (**1a:1b**) %[a]
1	none	1.6 equiv BnBpin, 1.4 equiv s-BuLi	0
2	none	1.6 equiv BnBpin, 1.6 equiv LiO*t*-Bu	0
3	CuI (5 mol%)	1.6 equiv BnBpin, 1.6 equiv LiO*t*-Bu	0
4	Cu(OTf)$_2$ (10 mol%)	1.6 equiv BnBpin, 1.4 equiv s-BuLi	28 (6:1)
5	CuI (10 mol%)	1.6 equiv BnBpin, 1.4 equiv s-BuLi	65 (5:1)
6	CuI (10 mol%)	2.5 equiv BnBpin, 2.0 equiv s-BuLi	89 (4:1)
7	CuI (5 mol%)	2.5 equiv BnBpin, 2.0 equiv s-BuLi	94 (4:1)

[a] Yields determined by NMR using an internal standard.

an effort to improve the reaction efficiency, more intermediate boronate nucleophile was generated in the reaction, leading to an increase in product yield and complete consumption of the starting epoxide (entry 6). Finally, it was found that 5 mol% CuI was also effective, providing the product in 94% as a 4:1 mixture of regioisomers (entry 7).

We next sought to examine the substrate scope of this reaction. Monosubstituted, 1,1-disubstituted, and 1,2-disubstituted epoxides were examined in this reaction, providing the desired product in good to excellent isolated yields (Table 2). A regiospecific addition to the less substituted side of the epoxide was observed in all cases except with styrene oxide, consistent with previous reported cuprate additions to epoxides [25]. Ethers (**4**), aryl bromides (**6**), and silyl-protected alcohols (**8**) were found to be compatible functional groups in this reaction. Use of the 1,2-disubstituted cyclohexene oxide afforded the desired product in a 64% yield (**9**). A reaction with an epoxide containing a pyridine moiety did not provide the desired reactivity with starting material observed after the

Table 2
Epoxide Substrate Scope.

1
80%[a]

2
89%

3
91%

4
91%

5
70%

6
91%

7
85%

8
73%

9
64%

10
0%
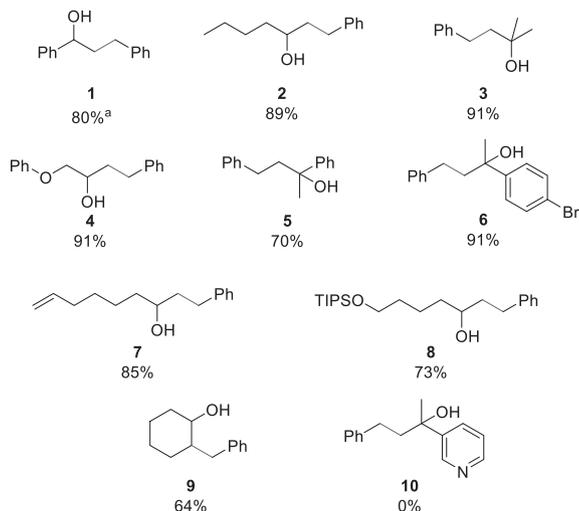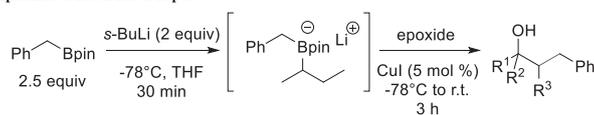
[a] A 4:1 mixture of regioisomers **1a** and **1b** as shown in Table 1.

reaction (**10**). A control experiment where one equivalent of pyridine was added to a reaction with styrene oxide also provided only recovered starting material, suggesting the pyridine interferes with the Cu catalyst. Less that 7% of bibenzyl as determined by NMR internal standard of the unpurified reaction mixture was observed under these Cu-catalyzed conditions. Activation of other alkylboronic acid pinacol esters including hexylBpin, isopropylBpin, and cyclopropylBpin with *sec*-butyllithium provided no desired product under the standard reaction conditions, showing the limits of this reaction.

Next, a reaction with an enantioenriched epoxide was examined (Scheme 1). Commercially available (*S*)-propylene oxide reacted smoothly to provide the desired product in a 91% yield. Analysis of the reaction's stereospecificity was done by forming the Mosher's ester of **11**. [1]H and ^{19}F analysis of the Mosher ester product revealed only one diastereomer of product. These results and comparing the optical rotation of the alcohol product **11** to literature values, confirmed the reaction was stereospecific with respect to the epoxide as expected due to substitution at the less substituted carbon of the epoxide [26-29].

Finally, an enantioenriched benzylboronic ester was prepared and employed to determine if the reaction was stereospecific with respect to the nucleophile (Scheme 2). Using racemic, branched benzylboronic ester with (*S*)-propylene oxide, a 60% yield with a 56:44 diastereomeric ratio. Switching to a reaction with enantioenriched branched benzylboronic ester, the same 56:44 diastereomeric ratio was observed. Since identical diastereomeric ratios were observed, it can be concluded that the reaction is not stereospecific with respect to the boronate nucleophile under our reaction conditions.

To probe the mechanism of the reaction, radical trap experiments with (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) were performed as shown in Scheme 3. In these experiments, the inhibited yields of **7** were similar with both 1 and 2.5 equivalents of TEMPO added. Additionally, there was a 40% and 126% yield (based on the amount of starting epoxide) of the benzyl TEMPO adduct **13** in those experiments.

A possible catalytic cycle for this reaction is shown in Scheme 4. Coordination of two benzyl groups to the Cu catalyst would form a dibenzylcuprate intermediate that could then react with the epoxide. The results from the TEMPO experiments suggest a SET alkyl transfer between the boronate nucleophile and the copper is occurring, resulting in racemization of the enriched benzylic nucleophile employed in Scheme 2 [7]. Previously, we have proposed the presence of radical intermediates being involved in our transition metal-free coupling between the benzylboronates and alkyl bromides [15].
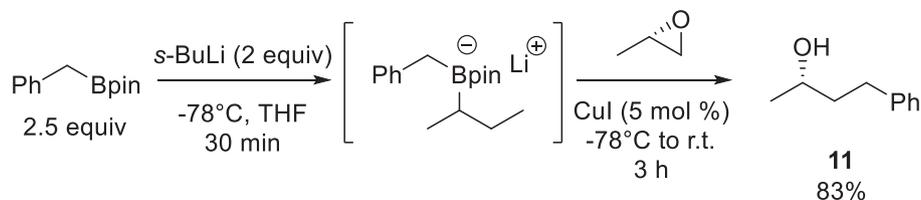
Scheme 1. Stereospecific Reaction with an Enantioenriched Epoxide.
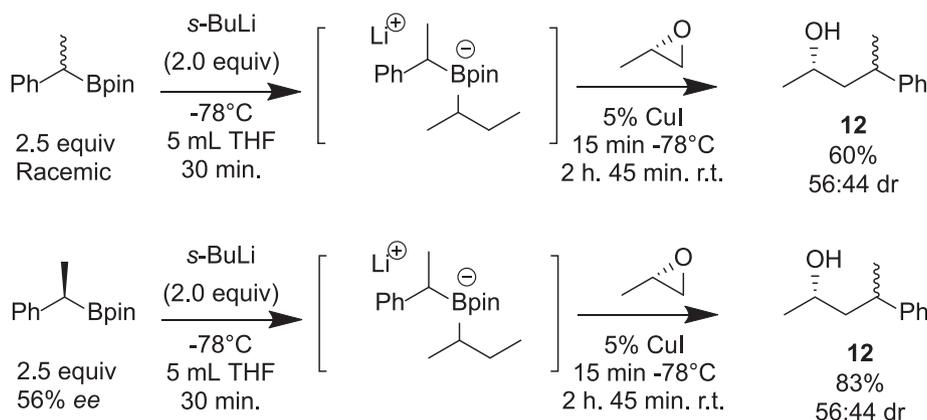
Scheme 2. Reaction with an Enantioenriched Benzylboronic Ester.
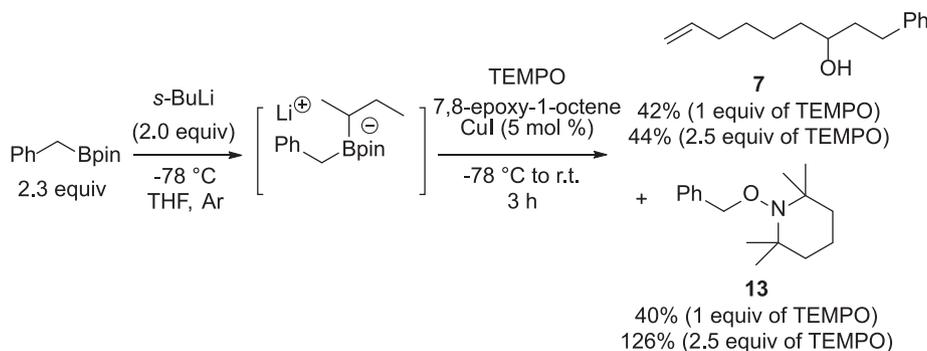
Scheme 3. Reaction with TEMPO.
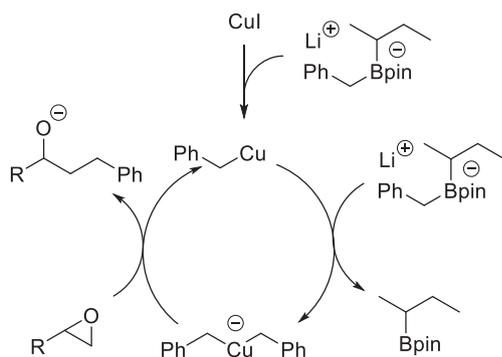
Scheme 4. Proposed Catalytic Cycle.

Conclusions

In conclusion, a Cu-catalyzed benzylation of epoxides has been developed using benzylboronic esters. The represents the first example of an alkyl-monoboronic ester coupling to an epoxide. Excellent regioselectivity was observed for the addition to the epoxides for all substrates except styrene oxide. The reaction was found to be enantiospecific when using an enantioenriched epoxide. The reaction was not enantiospecific with respect to the boronate nucleophile.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2021.153369.

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[29] See Supporting Information for synthesis and NMR spectra of the Mosher's ester of 11.