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Communication

Cu-catalyzed deoxygenative *gem*-hydroborylation of aromatic aldehydes and ketones to access benzylboronic esters

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ABSTRACT

Organoboron compounds are widely used in synthetic chemistry, pharmaceutical chemistry and material chemistry. Among various organoboron compounds, benzylboronic esters are unique and highly reactive, making them suitable benzylation reagents. At present, the synthetic methods for the syntheses of benzylboronic esters are still insufficient to meet their demands. It is necessary to develop novel and practical methods for their preparation. In this work, a novel copper-catalyzed deoxygenative *gem*-hydroborylation of aromatic aldehydes and ketones has been developed. This direct and operationally simple protocol provides an effective approach for the synthesis of a variety of primary and secondary benzylboronates, in which broad functional group tolerance was presented. Widely available B₂pin₂ (pin = pinacol) was used as the boron source and alcoholic proton was applied as the hydride source.

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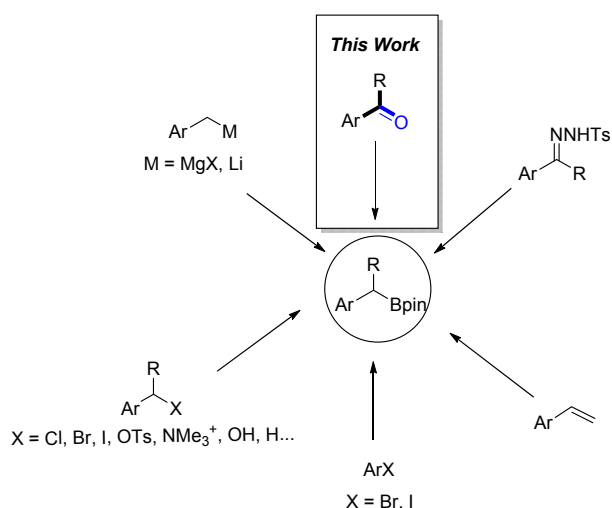
Organoboron compounds represent significant structural motifs in organic synthesis [1–6], developing novel and practical strategies for the synthesis of organoboron compounds is highly demanding in nowadays chemical society. Among various organoboron compounds, benzylboronic esters are unique alkylboron compounds. They are relatively reactive and can be a practical benzylation reagent in the presence of transition metal catalysts [7–14]. Up to date, tremendous efforts have been made for the synthesis of benzylboronic esters. In general, benzylboronic esters are often synthesized by the borylation of Grignard or lithium reagents [15]. However, this method shows poor functional group compatibility and the difficult preparation of benzylic Grignard and lithium reagents make this classic approach less practical. Recently, transition metal (including

Pd, Cu, Ni, Fe, *et al.*) catalyzed borylation of benzyl (pseudo)halides has been reported for the synthesis of benzylboronic esters [14,16–22]. Moreover, the cross-coupling of aryl halides [23,24] or sulfonates [25] with 1,1-diborylalkanes under palladium catalysis is also an effective method. Benzylic alcohols have also been utilized as electrophiles for the synthesis of primary benzylic boronic esters in the presence of palladium or copper catalyst [26,27], in which secondary benzylic alcohols cannot be compatible in those catalytic system. Directly utilizing benzylic C–H as the electrophile under the transition metal catalyzed borylation condition is an ideal approach, while it currently still suffers from the chemoselectivity issues on benzylic or aromatic C–H borylation and mono- or di-borylation [28–30]. Styrenes could also be used for the syn-

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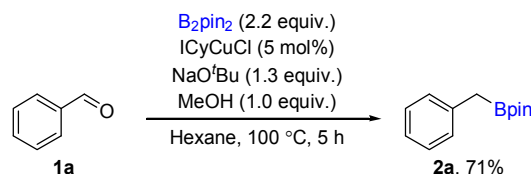


Scheme 1. Strategies for the synthesis of benzylboronic esters.

thesis of benzylboronic esters via unusual transition metal catalyzed Markovnikov selective hydroborations [31–37]. Through 1,2-metallate rearrangement, benzylboronic esters could be synthesized from tosylhydrazones and HBpin or B₂pin₂ under a metal-free condition [38]. Tosylhydrazones are usually prepared from carbonyl compounds. The direct utilization of aromatic carbonyls for the synthesis of benzylboronic esters would be more step-economy [39]. Herein, we describe the first deoxygenative *gem*-hydroborylation of aromatic aldehydes and ketones under copper catalysis to access both primary and secondary benzylboronic esters (Scheme 1).

In 2017, we have demonstrated a deoxygenative *gem*-diborylation of aliphatic aldehydes and ketones [40]. During this study, when benzaldehyde (**1a**) was utilized as the substrate, a significant amount of *gem*-hydroborylation product benzylboronic ester (**2a**) was obtained instead of *gem*-diboron product. These initial results promoted us to further improve the preparative procedure by using MeOH as the [H] source for achieving the catalytic synthesis of benzylboronic esters from aromatic aldehydes. As a result, **2a** was isolated with 71% yield under an optimal catalysis system: ICyCuCl (5 mol%), B₂pin₂ (2.2 equiv.), NaO^tBu (1.3 equiv.), with MeOH (1.0 equiv.) as the proton source in hexane at 100 °C for 5 h (Scheme 2).

With the optimized conditions in hand, a wide range of aromatic aldehydes were first examined for its generality in this transformation. As shown in Scheme 3, the reaction system is efficient for substrates containing various functional groups and afford the corresponding products in moderate to good



Scheme 2. The deoxygenative *gem*-hydroborylation of benzaldehyde.

yields. For instance, the reaction of substrates with electron-donating groups (–OMe, –tBu or other oxygen-containing groups) and substrates with electron-withdrawing groups (–F and –Cl) all proceeded well, affording the corresponding products in moderate to good yields (**2b–2e**, **2g**, **2i–2m**). The sulfur-containing group –SMe was also tolerated under standard condition (**2f**). It was noteworthy that steric effect did not have a strong influence on the reactivity. For instance, when 2,4,6-trimethylbenzaldehyde was used as the substrate, the corresponding product **2h** was isolated in 52% yield. Moreover, other aromatic aldehyde such as 2-naphthaldehyde and hetero-aromatic aldehyde such as 2-thienaldehyde proceeded smoothly to generate the corresponding products (**2n**, **2o**).

However, when extending the catalytic system to aromatic ketones, problem occurred and only trace amounts of products were detected, in which most of the starting ketones were reduced to their corresponding alcohols. The generation of alcohols indicated the presence of hydride species in this catalytic system. It has been demonstrated that proton could be used as hydride source in the presence of B₂pin₂ [41–49]. Furthermore, Clark et al. [50] has shown that the addition rate of a copper-boron species to ketone C=O group was slower than that of aldehydes. Therefore, the addition of hydride species to ketone carbonyls dominated the transformation of ketones. As a result, alcohols were produced as the major products. In order to solve this problem, a more reactive KO^tBu was applied to activate B₂pin₂ instead of NaO^tBu, for which we expected to increase the nucleophilicity of boryl group for the addition to ketone carbonyl groups. Meanwhile, a less acidic alcohol was utilized as the proton source instead of MeOH, for which we expected to slower down the generation of hydride species. To our delight, after a series of attempts, when the reaction was carried out in the presence of 1.0 equiv. KO^tBu as base and EtOH as the proton source, the aromatic ketones were successfully transformed to their corresponding secondary benzylboronic esters.

Subsequently, a series of aromatic ketones were investigated under the optimized conditions (Scheme 4). Aromatic ketones, such as acetophenone, propiophenone and butyrophe-



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