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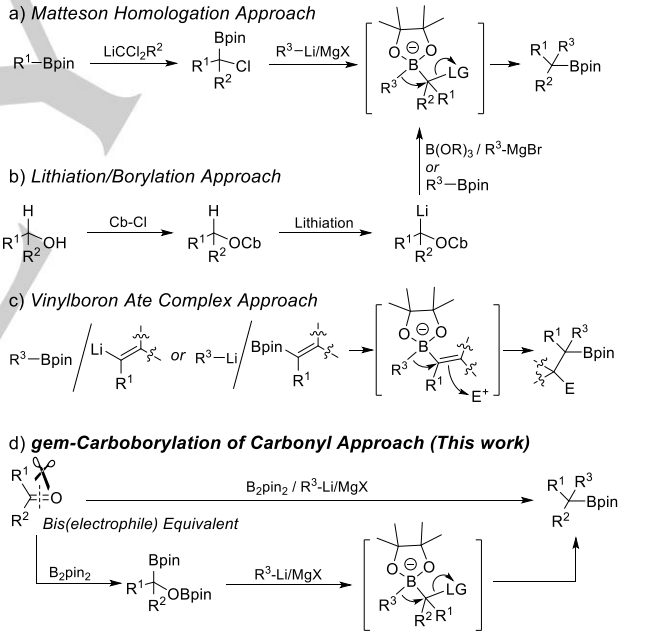
Access to Secondary and Tertiary Alkyl Boronic Esters via *gem*-Carboborylation using Carbonyl as Bis(electrophile) Equivalent

Dunfa Shi, Lu Wang, Chungu Xia and Chao Liu*

Abstract: An unprecedent *gem*-carboborylation of aldehydes and ketones was demonstrated. Various secondary and tertiary alkyl boronic esters were conveniently obtained. The addition of B_2pin_2 to carbonyls provides α-oxyl containing alkylborons. Organolithiums and Grignard reagents were applied as the *C*-nucleophiles for the 1,2-metallate rearrangement process. Organolithiums could be generated from C-H lithiation or halogen/lithium exchanges. Utilizing chiral ligand generated chiral alkyl boronic ester, demonstrating the catalyst-controlled enantioselectivity for this transformation.

Alkyl boronic esters are of increasing importance to many fields across chemical science, not only due to the versatile transformation of their C-B bonds but also because of their applications in medicinal chemistry.[1] However, the preparation of alkyl boronic esters is still unable to meet their rapid growing demands. Especially, the synthesis of secondary and tertiary alkyl boronic esters still remains great challenges to date. Many efforts have been devoted to their syntheses through the borylation of alkenes, alkyl (pseudo)halides, *etc*.[2] Since the poineering research by Matteson and Mah, the 1,2-metalate rearrangement of α-leaving group containing tetracoordinated boron chemistry has been developed as a versatile strategy for the synthesis of alkyl boronic esters.[3] The essence for such strategy is to find a proper way to build up those α-leaving group containing tetracoordinated boron species. In the classic Matteson homologations, the α-halo boronic esters were not easily accessible. One feasible approach is the reaction of a *pre*-prepared organoboronic ester with dihalomethyl lithium reagent (R^2 = H, Scheme 1a).[3a] However, any other *gem*-dihalo organolithium ($R^2 \neq H$) are uneasy to access. As a result, only secondary alkyl boronic esters can be facilely obtained via this approach. Recently, the lithiation/borylation approach has been developed as a versatile method for the synthesis of various secondary and tertiary alkyl boronic esters.[4] This approach generally started with the formation of carbamates or benzoates from alcohols, followed by lithiation to afford an α-leaving group (*O*-type) containing lithium reagent. Consequently, the resulted lithium reagent reacted with a *pre*-prepared organoboronic ester to give the key tetracoordinated boron species (Scheme 1b). Obviously, the formation of carbamates or benzoates from alcohols and the *pre*-prepared organoboronic esters requires extra synthetic procedures. The recently developed electrophile-induced 1,2-metalate rearrangement of vinylboron ate complexes also showed powerful ability for the synthesis of secondary and tertiary alkyl boronic esters (Scheme 1c).[5] However, either vinylboronic esters or vinyl lithium reagents are not easily accessible. Since the initial discovery by Sadighi, the 1,2-addition of B_2pin_2 to aldehydes and ketones have been demonstrated as a practical method for the synthesis of α-oxyl boronates.[6] The use of the α-oxyl as a leaving group with a carbon nucleophile will directly achieve the synthesis of secondary and tertiary alkyl boronic esters from aldehydes and ketones. Such hypothesis will exhibit that carbonyls can be used as bis(electrophile) equivalents to react with one *B*-nucleophile and one *C*-nucleophile to achieve a *gem*-carboborylation. The wide availability of B_2pin_2 and aldehydes/ketones makes this strategy appealing. Herein, we demonstrated our recent progress on this unprecedented *gem*-carboborylation of aldehydes and ketones for the synthesis of secondary and tertiary alkyl boronic esters, in which carbonyls were used as bis(electrophile) equivalents (Scheme 1d).



Scheme 1. Strategies for the synthesis of secondary and tertiary alkyl boronic esters via 1,2-metalate rearrangement.

Hydrocinnamaldehyde (**1aa**) was initially applied to test the hypothesis shown in Scheme 1d. With ICyCuCl (ICy = 1,3-dicyclohexylimidazol-2-ylidene) as the catalyst, the addition of B_2pin_2 to **1aa** can easily occur to give α-OBpin alkyl boronic ester **1aa-I** which contains one *C*-Bpin and one *O*-Bpin.[6a] Then, MeLi was added as the model *C*-nucleophile. Two experiments were first carried out by using one or two equivalents of MeLi, respectively. MeLi was added at -30 °C and the reaction mixtures were then heated at 80 °C for 6 hours. As a result, the experiment with one equivalent of MeLi afforded 30% of the desired **2aa**, while two equivalents of MeLi only afforded trace amount of **2aa**. It has been demonstrated that the energy difference between the interaction of *C*-nucleophile with *C*-Bpin

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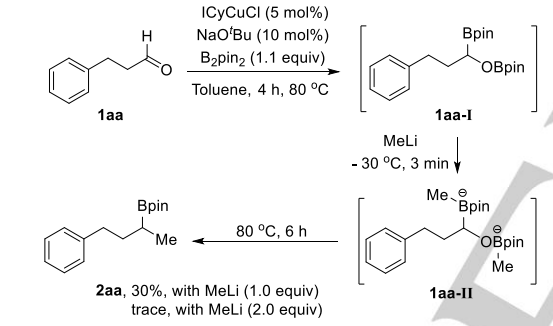
and with *O*-Bpin is small.[7] Therefore, adding MeLi to **1aa-I** will have two possibilities to form *C*-B-Me or *O*-B-Me moiety (as shown in **1aa-II**). The formation of *O*-B-Me will obviously reduce the leaving ability of OBpin group. Those results suggested that 1) one equivalent of MeLi would not exclusively form *C*-B-Me to keep the OBpin as the leaving group; 2) two equivalents of MeLi would fully convert **1aa-I** to **1aa-II**,[6f] while the formation of *O*-B-Me in **1aa-II** blocked the 1,2-migration, as a result to decrease the yield of **2aa**.

The key to solve this problem is to find a way to make the α-oxyl of **1aa-II** a better leaving group under the reaction condition. Very recently, acyl chloride has been applied by Aggarwal and coworkers to increase the leaving ability of amino group.[8] Inspired by this report, some acyl chlorides were tested in this transformation to increase the leaving ability of α-oxyl group in **1aa-II** (Scheme 2). To our delight, the use of benzoyl chloride remarkably increased the yield of **2aa** to 85%. Benzyl chloroformate gave 84% yield. Both phenyl chloroformate (ClCOOPh) and methyl chloroformate (ClCOOMe) afforded almost quantitative yields of the desired **2aa**. It was observed that a slight amount of diphenyl carbonate was generated in the reaction with ClCOOPh, which made the separation of the desired product troublesome, thus, ClCOOMe was finally used for further studies.



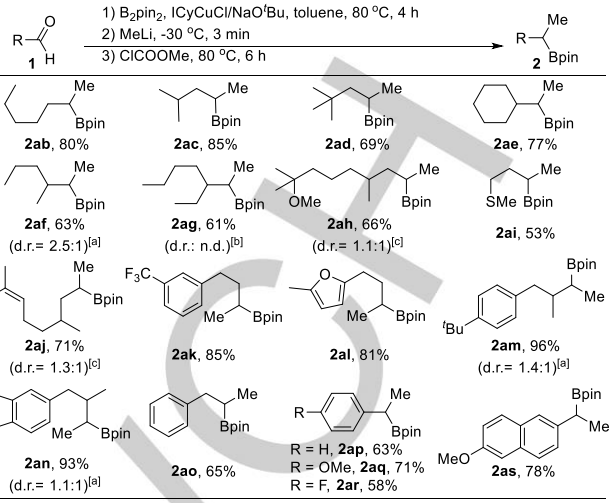
1) B_2pin_2 (1.1 equiv), ICyCuCl (5 mol%)
NaO^{t}Bu (10 mol%), toluene, 80 °C, 4 h
2) MeLi (2.2 equiv), -30 °C, 3 min
3) **R-Cl** (1.2 equiv), 80 °C, 6 h

1aa → **2aa**

R-Cl		Yield[a]
PhCOCl	benzoyl chloride	85%
BnOCOCl	benzyl chloroformate	84%
PhOCOCl	phenyl chloroformate	99%
MeOCOCl	methyl chloroformate	96% (88%)[b]

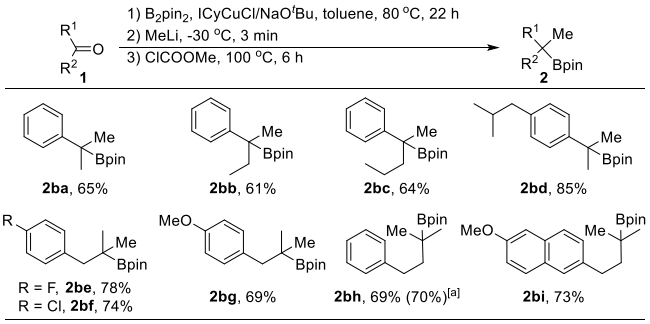
Scheme 2. Initial investigation on *gem*-carboborylation of aldehyde. [a] The yield was determined by NMR analysis with CH_2Br_2 as the standard. [b] Yield of isolated product.

With the optimal conditions in hand, various aldehydes were first tested in this *gem*-carboborylation protocol with B_2pin_2 and MeLi as the nucleophiles to access secondary alkyl boronic esters (Scheme 3). Simple aliphatic aldehydes afforded their corresponding secondary alkyl boronic esters in good yields (**2ab**-**2ag**). Functional groups, such as OMe, SMe, alkenyl and aromatic CF_3, were well tolerated (**2ah**-**2ak**). Aliphatic aldehydes, which contains aromatic groups (including furyl), were also tested and good to excellent yields were obtained (**2ak**-**2ao**). Aromatic aldehydes gave their corresponding secondary benzylic boronic esters in good yields (**2ap**-**2as**).



Scheme 3. Access to secondary alkyl boronic esters via *gem*-carboborylation of aldehydes with B_2pin_2 and MeLi as the nucleophiles. Reaction conditions: 1) **1** (0.50 mmol), B_2pin_2 (0.55 mmol), ICyCuCl (5 mol%), NaO^{t}Bu (10 mol%), toluene (2.0 mL), 80 °C, 4 h, 2) MeLi (1.1 mmol), -30 °C, 3 min, 3) ClCOOMe (0.60 mmol), 80 °C, 6 h. Yields based on isolated products; [a] Determined by NMR analysis; [b] n.d.= not determined; [c] Determined by GC-MS analysis.

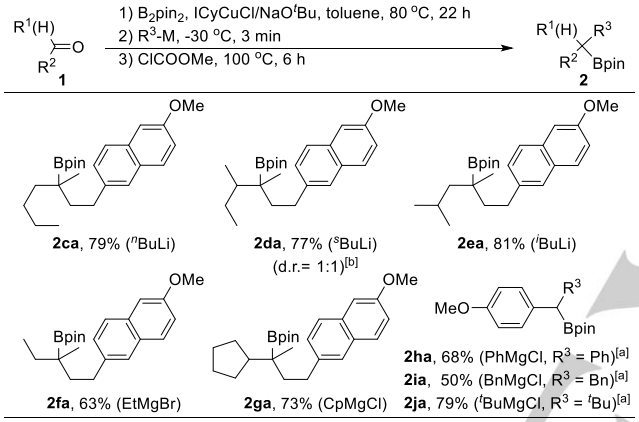
When ketones were applied in this transformation, various tertiary alkyl boronic esters were easily obtained (Scheme 4). As demonstrated by the Clark group, the addition of B_2pin_2 to ketones is relatively sluggish than that of aldehydes.[6c] Therefore, a prolonged reaction time is required to complete this addition step. Aromatic ketones such as acetophenone and propiophenone gave benzylic tertiary alkyl boronic esters in moderate to good yields (**2ba**-**2bd**). Aliphatic ketones afforded their corresponding tertiary alkyl boronic esters in good yields (**2be**-**2bi**). Aromatic C-F, C-Cl and C-OMe were well tolerated (**2be**-**2bg**). Moreover, the reaction temperature of the last substitution step was raised to 100 °C, which benefited to the completion of the reaction. In these transformations, α-OBpin alkyl boronic esters were initially generated for the following homologative carbonation. A free α-OH alkyl boronic ester **2bh-OH** derived from benzylacetone was also tested and it was successfully methylated with MeLi by using ClCOOMe as a promotor and the desired **2bh** was obtained in 70% yield (See details in supporting information), illustrating that the free α-OH alkyl boronic ester was competent in the homologation step under this esterification condition with ClCOOMe.



Scheme 4. Access to tertiary alkyl boronic esters via *gem*-carboborylation of ketones with B_2pin_2 and MeLi as the nucleophiles. Reaction conditions: 1) 1 (0.50 mmol), B_2pin_2 (0.55 mmol), ICyCuCl (5 mol%), NaO^{t}Bu (10 mol%), toluene (2.0 mL), 80 °C, 22 h, 2) MeLi (1.3 mmol), -30 °C, 3 min, 3) ClCOOMe (0.80 mmol), 100 °C, 6 h. Yields based on isolated products; [a] α-OH alkyl

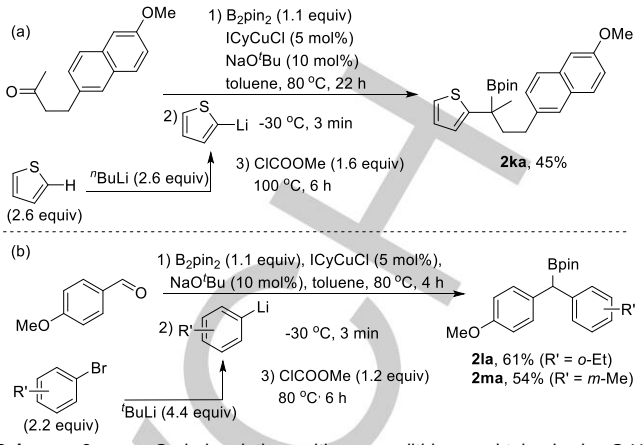
boronic ester **2bh-OH** derived from benzylacetone was directly used for methylation.

Next, this protocol also allowed the application of various *C*-nucleophiles to form C-C bonds to give various secondary and tertiary alkyl boronic esters. First, commercially available organolithiums and Grignard reagents were tested (Scheme 5). Nabumetone and anisic aldehyde were selected as the tentative carbonyl compounds. With nabumetone as the substrate, ^{n}BuLi, ^{s}BuLi and ^{t}BuLi afforded their corresponding tertiary alkyl boronic esters in good yields (**2ca**, **2da**, **2ea**). Whilst, primary (EtMgBr) and secondary (CpMgCl, Cp = cyclopentyl) alkyl Grignard reagents afforded good yields of the desired tertiary alkyl boronic esters (**2fa**, **2ga**). With anisic aldehyde as the substrate, PhMgCl, BnMgCl and ^{t}BuMgCl gave the desired secondary benzylic boronic esters in moderate to good yields (**2ha**, **2ia**, **2ja**).



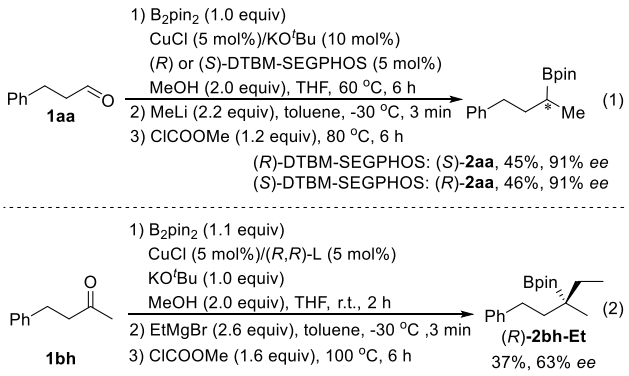
Scheme 5. Substrate scope of organometal reagents. Reaction conditions: 1) **1** (0.50 mmol), B_2pin_2 (0.55 mmol), ICyCuCl (5 mol%), NaO^{t}Bu (10 mol%), toluene (2.0 mL), 80 °C, 22 h, 2) MeLi (1.3 mmol), -30 °C, 3 min, 3) ClCOOMe (0.80 mmol), 100 °C, 6 h. Yields based on isolated products; [a] 1) reaction time: 4 h, 2) R^3-M (1.1 mmol), 3) ClCOOMe (0.60 mmol), 80 °C; [b] Determined by NMR analysis.

Besides, organolithiums could also be obtained via C-H lithiation or halogen/lithium exchange. It will greatly enlarge the scope of nucleophiles for this *gem*-carboborylation process. Selected examples were presented in Scheme 6. The *in situ* C-H lithiated thiophene was subjected to the reaction with nabumetone, as a result, the desired tertiary alkyl boronic ester **2ka** was obtained in 45% yield (Scheme 6a). The halogen/lithium exchange of aryl bromides with butyllithium was applied to react with anisic aldehyde. The corresponding diaryl methylboronic esters were obtained in moderate yields (Scheme 6b, **2la**, **2ma**).



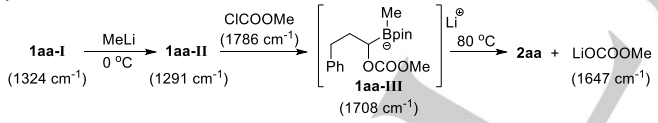
Scheme 6. *gem*-Carboborylation with organolithiums obtained via C-H lithiation and halogen/lithium exchange.

Secondary and tertiary alkyl boronic esters are closely related to enantioselective synthesis.[2b, 9] The enantioselectivity of those classic Matteson homologations are usually substrate-control with the embeddedness of a chiral auxiliary in the diol moiety of the boronic ester. Those lithiation/borylation approaches are reagent-control with the addition of stoichiometric amounts of chiral amines.[4] Catalyst-controlled enantioselectivity is an appealing strategy for the synthesis of chiral alkyl boronic esters.[2b] Unsaturated double bonds are ideal prochiral moieties in organic transformations. The recent development of enantioselective nucleophilic addition of B_2pin_2 to aldehydes and ketones by the Ito group provided us an opportunity to achieve a catalyst-controlled enantioselective *gem*-carboborylation of carbonyls.[6g, 6h] Aldehyde **1aa** and ketone **1bh** were used to verify this hypothesis (Scheme 7). When (*R*)-DTBM-SEGPHOS was used as the chiral ligand and MeLi as the *C*-nucleophile, the desired (*S*)-**2aa** was obtained with a 91% *ee* value in 45% yield. When (*S*)-DTBM-SEGPHOS was used, the desired (*R*)-**2aa** was obtained with a 91% *ee* value in 46% yield (Scheme 7, eq. 1). Moreover, Applying Ito's asymmetric 1,2-borylation of ketones[6g] in this transformation successfully resulted in asymmetric tertiary alkyl boronic ester (Scheme 7, eq. 2). These results elucidated that the enantioselectivity of the product was controlled by the catalyst. Furthermore, according to the report by the Ito group, (*R*)-DTBM-SEGPHOS afforded *S*-isomer of the addition product α-oxyl alkylboronic ester.[6h] The obtained (*S*)-configuration of **2aa** is consistent with the inversion process of 1,2-metallate rearrangement, verifying the mechanistic insight of our initial proposal of this transformation in Scheme 1d.



Scheme 7. Catalyst-controlled enantioselectivity.

To probe the insightful information of this transformation, in situ IR spectroscopy technique was applied to monitor the reaction course of **1aa-I** with MeLi and ClCOOMe (Scheme 8, See 3D spectra in SI). Upon the addition of MeLi, the specific absorbance of **1aa-I** at 1324 cm^{-1} disappeared immediately, meanwhile, a new peak at 1291 cm^{-1} appeared. This phenomenon indicated an immediate interaction of MeLi with **1aa-I** to generate **1aa-II**. As ClCOOMe was added, this peak gradually shifted to 1309 cm^{-1}. Meanwhile, the specific absorbance of ClCOOMe at 1786 cm^{-1} gradually decreased and the specific absorbance of **1aa-III** at 1708 cm^{-1} appeared. When heating the mixture at 80 °C, the peaks at 1786 cm^{-1} and 1708 cm^{-1} immediately decreased together with an observation of a strong and broad absorbance at 1647 cm^{-1}. At the same time, suspension was observed in the reaction mixture. By comparison with its standard IR spectrum, the 1647 cm^{-1} was assigned to be the absorbance of LiOCOOMe. These observations indicated that high temperature was beneficial to both the acylation of α-oxyl group of **1aa-I** with ClCOOMe and the 1,2-metalate rearrangement of **1aa-III** to afford the desired product **2aa** and LiOCOOMe.



Scheme 8. Reaction course monitored by in situ IR

In summary, we have demonstrated a *gem*-carboborylation of aldehydes and ketones using carbonyl group as bis(electrophile) equivalent to synthesize various secondary and tertiary alkyl boronic esters. The 1,2-addition of B_2pin_2 to carbonyls provides α-oxyl alkylboronates. Organolithiums and Grignard reagents were applied as the *C*-nucleophiles for the 1,2-metallate rearrangement process. ClCOOMe was used to increase the leaving ability of α-oxyl group. Catalytic amount of chiral ligand could promote to form chiral alkyl boronic ester, which supported the catalyst-controlled enantioselectivity for this transformation.

Acknowledgements

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Keywords: *gem*-Carboborylation • Alkyl Boronic Esters • Bis(electrophile) Equivalent • 1,2-Metallate Rearrangement • Catalyst-Control Enantioselectivity

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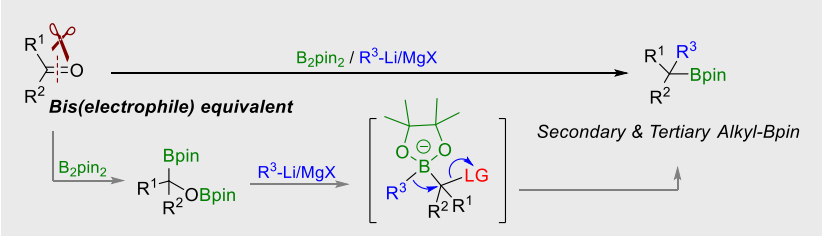

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