Borylation

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Deoxygenative Borylation of Secondary and Tertiary Alcohols

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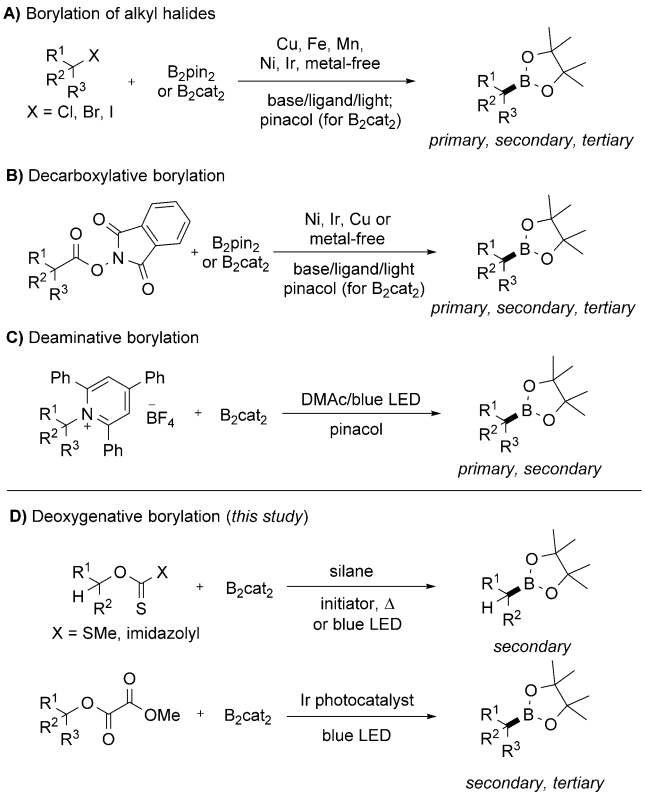
Abstract: *Two different approaches for the deoxygenative radical borylation of secondary and tertiary alcohols are presented. These transformations either proceed through a metal-free silyl-radical-mediated pathway or utilize visible-light photoredox catalysis. Readily available xanthates or methyl oxalates are used as radical precursors. The reactions show broad substrate scope and high functional-group tolerance, and are conducted under mild and practical conditions.*

Alkyl boronic esters are highly valuable building blocks in chemical synthesis since the C–B bond is easily transformed into a great variety of useful functional groups. Moreover, these boronic esters are good substrates in transition-metal-catalyzed C–C coupling reactions.[1] Therefore, synthetic methods for their preparation are required. Along these lines, methods for the borylation of alkyl halides,[2] carboxylic acids,[3] and amines[4] using diboron reagents by applying either radical chemistry or transition-metal catalysis have been reported recently (Scheme 1 A–C). Surprisingly, despite the easy accessibility and abundance of alcohols, their deoxygenative borylation remains underdeveloped. Metal-catalyzed borylation of primary and secondary alkyl tosylates has been disclosed[5,2i] but borylation of tertiary alcohols is unknown to our knowledge.

We therefore decided to focus on the deoxygenative borylation of secondary and tertiary alcohols using a radical approach. The borylation of alkyl radicals by B_2cat_2 in the presence of a Lewis base (commonly an amide used as the solvent) has already been documented to be a very efficient reaction.[2h,3a,6] Encouraged by these studies, we envisioned a similar radical strategy using a suitable alcohol activating group and show herein that xanthates, which are readily prepared from alcohols and widely applied in the Barton–McCombie deoxygenation reaction,[7] can be converted into the corresponding alkyl boronic esters using silanes as radical mediators (Scheme 1 D). Since tertiary xanthates are not stable, we also introduce a second method to prepare tertiary alkyl boronic esters from easily accessible *tert*-alkyl oxalates[8] using redox catalysis.



Scheme 1. Borylation of alkyl halides, carboxylic acids, amines, and alcohols with diboron reagents. B_2pin_2 = bis(pinacolato)diboron, B_2cat_2 = bis(catecholato)diboron.

Borylation of xanthates was studied first. It is well known that silanes can act as radical-chain reducing reagents for the reduction of xanthates.[9] In contrast to tin hydrides, they are non-toxic and the rate constant k for the reduction of a C-radical by a silane is around one order of magnitude smaller than that for the same reduction with a tin hydride. Moreover, from our previous studies, we knew that C-radical borylation with B_2cat_2 is a very fast transformation[2h] that should outcompete the direct slower C-radical reduction by a silane. Therefore, silanes were considered as radical mediators in the targeted deoxygenative borylation.

Xanthate **1a**, which was selected as the model substrate, was reacted with B_2cat_2 in DMF using 2,2′-azobis(2-methylpropionitrile) (AIBN) in the presence of different silanes at 70 °C. Reaction optimization revealed that the best result is obtained when using commercial tris(trimethylsilyl)silane (TTMSS)[9] as the reducing reagent. With Ph_3SiH, Ph_2MeSiH, and Ph_2SiH_2, deoxygenative borylation did not occur. We also found that the xanthate functionality as compared to the

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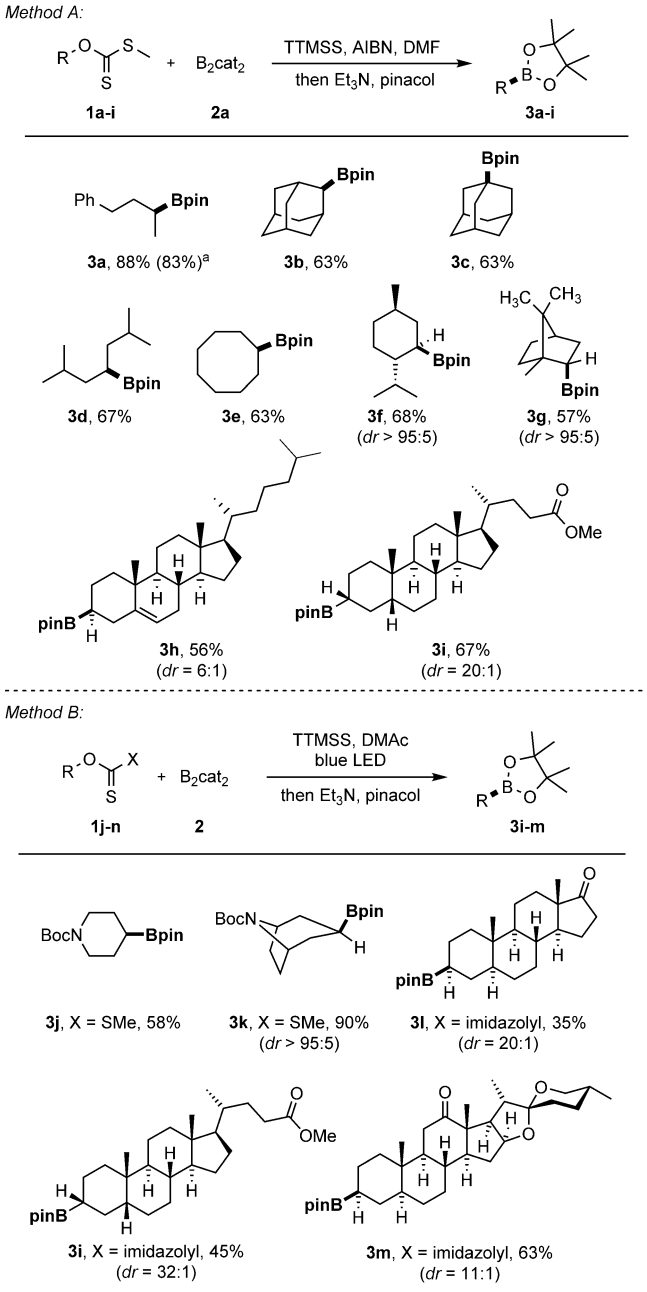
thionocarbamate (X = imidazolyl, see Scheme 1D) or thionocarbonate (X = OPh) entity is the best C-radical precursor for this transformation. Notably, there is likely no radical chain and the highest yield was achieved by using a stoichiometric amount of AIBN at 70 °C in DMF (see the Supporting Information). The competing direct alkyl radical reduction by TTMSS was prevented by using the diboron reagent in excess (4.0 equiv). Due to the instability of the catechol boronic ester, the crude product was transesterified with pinacol and Et_3N to give the alkyl boronic ester **3a** in 88% isolated yield (Method A, Scheme 2). Reducing the amount of B_2cat_2 to 2.0 equiv led to a slightly lower yield (75%, see Table S1 in the Supporting Information) and therefore all further experiments were conducted using 4.0 equiv of the diborane.



Scheme 2. Method A: Deoxygenative borylation of alkyl xanthates using AIBN/TTMSS. Reaction conditions: **1a–i** (0.2 mmol), B_2cat_2 (0.8 mmol), TTMSS (0.23 mmol), AIBN (0.2 mmol), DMF (0.6 mL), 70 °C, 15 h; pinacol (0.8 mmol), Et_3N (0.7 mL), 1 h; yields of isolated product are shown. Method B: Light-mediated borylation. Reaction conditions: **1j–n** (0.2 mmol), B_2cat_2 (0.8 mmol), TTMSS (0.23 mmol), DMAc (0.6 mL, + dioxane in some cases, see the Supporting Information), 35 °C, 24–48 h; pinacol (0.8 mmol), Et_3N (0.7 mL), 1 h; yields of isolated product are shown. [a] Reaction was performed on a 1.0 mmol scale.

Under optimized conditions, the secondary alcohol derived xanthates **1b**, **1d**, and **1e** were successfully borylated using Method A (**3b**,**d**,**e**, 63–67%). The tertiary adamantyl xanthate **1c**, which cannot undergo *syn*-elimination, was an eligible substrate to provide **3c** in 63% yield. Notably, deoxygenative borylation of L-menthol (**3f**) and isoborneol (**3g**) was accomplished with complete stereocontrol. The reaction tolerates internal alkenes and ester moieties since both cholesterol and lithocholic acid methyl ester were borylated with good to excellent diastereoselectivity (**3h**,**i**). The relative stereochemistry was assigned by oxidation and subsequent NMR experiments (see the Supporting Information). The scalability was evaluated by performing the reaction on a 1.0 mmol scale, providing **3a** in 83% yield.

During these investigations, we realized that irradiation of the reaction mixture with blue LEDs in the absence of AIBN in dimethylacetamide (DMAc) also gave access to the borylated products in good to excellent yields (Method B). Moreover, if the synthesis of the xanthate derivative is challenging (e.g., for ketones **3l**,**m**), the corresponding O-thionocarbamate has to be selected as the C-radical precursor. Functional groups like Boc-protected amines, esters, ketones, and acetals, as found in hecogenin (**3m**), tropine (**3k**) and epiandrosterone (**3l**), were tolerated by this method and good to excellent stereocontrol was achieved. For some examples, solubility issues were solved by addition of either DMAc or 1,3-dioxane (see the Supporting Information).

We next searched for a suitable activating group for the deoxygenative borylation of tertiary alcohols. Due to undesired side reactions, xanthates are not eligible *tert*-alkyl radical precursors and oxalates were selected instead.[10] Oxalates have been used in combination with Barton-PTOC esters (PTOC = pyridine-2-thione-N-oxycarbonyl) for *tert*-alkyl radical generation,[11] and recent examples have also documented the feasibility of a reductive cleavage of alkyl oxalates using either activated Zn in a Ni-promoted process or a strongly reducing photocatalyst at elevated temperatures.[8]

We chose the readily prepared methyl oxalate **4a** as a model substrate and C-radical generation was tested using photoredox catalysis. To our delight, formation of product **5a** was observed with tris[2-phenylpyridinato-C^2,N]iridium(III) (fac-Ir(ppy)$_3$) as the catalyst. Optimization of the reaction conditions revealed DMF to be the ideal solvent (see the Supporting Information) and the alkyl boronic ester **5a** was obtained in 85% yield of isolated product (Scheme 3). Various *tert*-alkyl boronic esters could be prepared in good yields by using this method (**5b–e**). Internal alkenes are tolerated, as demonstrated by the transformation of α-terpineol into **5f**, which represents a valuable building block in organic synthesis. Furthermore, benzylic amines and esters

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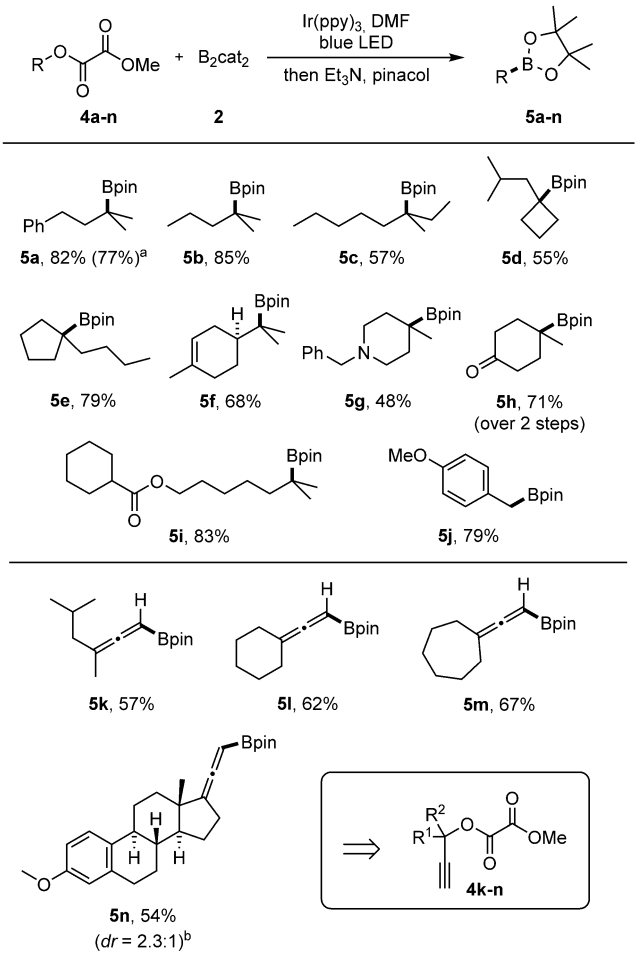
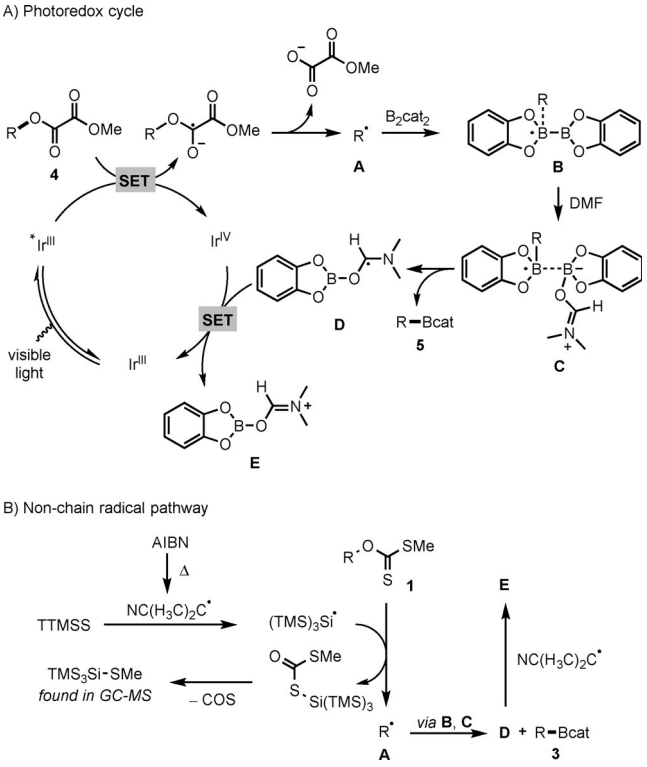


Scheme 3. Deoxygenative borylation of tertiary alkyl oxalates through reductive C–O bond cleavage. Reaction conditions: **4a–n** (0.2 mmol), B_2cat_2 (0.6 mmol), $Ir(ppy)_3$ (1.0 mol%), DMF (0.6–1.2 mL), rt, 24 h; pinacol (0.8 mmol), Et_3N (0.7 mL), 1 h; yields of isolated product are shown. [a] Reaction was performed on a 1.0 mmol scale; [b] The relative stereochemistry could not be assigned.

are tolerated (see **5g** and **5i**). When the 1,3-dioxolane-protected ketone **4h** was used as the substrate, partial deprotection was observed during the reaction, likely do to the presence of the Lewis acidic B_2cat_2. Therefore, the product was fully deprotected upon treatment of the product mixture with catalytic quantities of sodium tetrakis(3,5-trifluoromethylphenyl)borate ($NaBAr^F_4$) in water[12] to give the ketone **5h** in good yield (71%). The reaction also proceeds well for benzyl methyl oxalates, as exemplified by the preparation of **5j** (79%). However, non-activated *sec*-alkyl methyl oxalates are not good substrates for this deoxygenative borylation. For example, boronic ester **3a** was obtained in low a yield of 25% when using the oxalate route (see the Supporting Information). On a 1.0 mmol scale, **5a** was obtained in 77% yield, thus demonstrating the robustness of the process.

We were very pleased to find that this strategy can be used to convert tertiary propargylic alcohols into allenyl boronic esters, which are highly valuable reagents for the synthesis of homopropargylic alcohols and amines,[13a,b] with complete regiocontrol. Notably, this process represents the first radical approach towards this important compound class.[13a,c–e] Branched propargylic alcohols performed well and the boronic esters **5k–m** were isolated in 57–67% yield. The reaction was also applied to biologically active mestranol to provide the allene **5n** in 54% yield. Unfortunately, substituted alkynes targeting tetrasubstituted allenes led to complex reaction mixtures.

A suggested mechanism for the photoredox process is presented in Scheme 4A. Alkyl radical **A** is generated by electron transfer from the photoexcited $Ir(ppy)_3$ catalyst ($Ir^{III}*$) to the methyl oxalate **4** and subsequent C–O bond



Scheme 4. Proposed reaction mechanisms for the radical borylation of xanthates, O-thionocarbamates, and methyl oxalates.

cleavage. **A** then adds to B_2cat_2 to give adduct radical **B**, which is trapped by the solvent to give intermediate **C**.[2h] The weak B–B one electron σ-bond readily homolyzes to give the alkyl catechol boronic ester **5** along with **D**. Radical **D** is oxidized by the photocatalyst (Ir^{IV}) to give cation **E**, thereby regenerating Ir^{III}. The proposed mechanism for the non-chain radial TTMSS process (method A) is depicted in Scheme 4B. The radical nature of these transformations was supported by a radial-probe experiment (cyclopropane ring opening, see the Supporting Information). The TTMSS radical, generated from the silane by hydrogen atom transfer to a 2-cyano-isopropyl radical derived from AIBN, reacts with xanthate **1** in an addition fragmentation sequence to give radical **A** and $(Me_3Si)_3SiSCOSMe$. Radical **A** is borylated via **B** and **C** as described before. Radical **D** is eventually oxidized by another

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2-cyanoprop-2-yl radical to give **E**. Due to the stability and nucleophilicity of radical **D**, its direct reduction by TTMSS is likely an inefficient step, thus explaining the necessity of using a stoichiometric amount of AIBN. The mechanism of the light-mediated borylation with TTMSS (method B) remains unclear.

In conclusion, two novel approaches for the radical borylation of secondary and tertiary alcohols via their xanthates, O-thionocarbamates, or methyl oxalates were developed. For secondary alcohols, a metal-free reaction using TTMSS as a radical mediator was developed. For tertiary alcohols, where xanthates and their derivatives cannot be accessed, deoxygenative borylation can be achieved via their methyl oxalates by using Ir photordeox catalysis without any additional radical mediator. These processes deliver a great variety of alkyl boronic esters in good to excellent yields under mild conditions. Importantly, propargylic alcohols are converted with complete regioselectivity into the corresponding allenyl boronic esters, which are valuable reagents in organic synthesis.

Acknowledgements

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Conflict of interest

The authors declare no conflict of interest.

Keywords: alcohols · borylation · deoxygenation · photoredox catalysis · radical reactions

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