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# Decarboxylative Borylation of Aliphatic Esters under Visible-Light Photoredox Conditions

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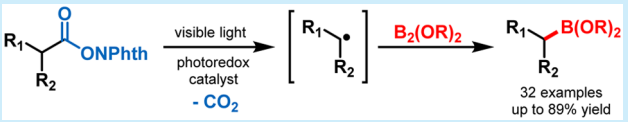
Supporting Information

**ABSTRACT:** The conventional methods for preparing alkyl boronates often necessitate anhydrous and demanding reaction conditions. Herein, a new, operationally simple decarboxylative borylation reaction of readily available aliphatic acid derivatives under additive-free visible-light photoredox conditions in nonanhydrous solvents has been described. Primary and secondary alkyl boronates or tetrafluoroborates with various functional groups were prepared accordingly. A catalytic cycle involving alkyl radical reaction with base-activated diboron species has been proposed.




Alkylboron compounds represent an important class of reagents in organic synthesis of bioactive molecules and functional materials.[1] The most common methods to access alkylboranes or boronates include transmetalation from highly reactive organolithium or organomagnesium[2] and the hydroboration of olefins.[3] $\beta$-Borylation is another effective method but largely limited to $\alpha,\beta$-unsaturated carbonyls.[4] Transition-metal-catalyzed direct C−H borylation of alkanes has also been reported for terminal methyl groups of simple alkanes or with certain directing groups.[5] A more general approach has been the Miyaura borylation-type reaction of alkyl (pseudo)halides,[6] and to date, several effective catalyst systems based on Pd,[7] Ni,[8] Cu,[9] Zn,[10] and Fe[11] have been reported. Although these methods have been successful, they usually require strictly anhydrous conditions, and many of them are incompatible with highly polar or protic groups.

Aliphatic carboxylic acids are abundant and inexpensive basic chemicals. Reactions involving a decarboxylative process and an ensuing C−X bond formation process would produce various functionalized aliphatic compounds.[12] Indeed, since the discovery of Hunsdiecker halogenation, many other decarboxylative reactions have been disclosed, including fluorination,[13] (hetero)arylation,[14] and addition reactions.[15] In sharp contrast, however, the synthetically versatile C−B bond has not been introduced in the same vein.[16] The key challenge might be the incompatibility between the reducing property of organoboranes[17] and most oxidizing reaction conditions that are necessary for inducing decarboxylation.

Recently, our group and the Larionov group have independently discovered that aryl halides can react with diboron reagents to form aryl boronate compounds under UV light irradiation.[18] The mechanistic studies revealed that highly reactive aryl radicals were involved. Based on these observations, we were interested in the possibility of making alkyl boronates via alkyl radicals that may be generated from readily available aliphatic acid derivatives.

*N*-Acyloxyphthalimides can be prepared from the acids and *N*-hydroxyphthalimide in one step and have been used for decarboxylative C−C bond formation reactions under both visible-light photoredox conditions and non-photochemical conditions.[19] The decarboxylative reactions were initiated by a single-electron reduction process of *N*-acyloxyphthalimides, which is different from most oxidizing decarboxylative reactions. Therefore, we hypothesized that *N*-hydroxyphthalimides might be amenable to generation of organoboron compounds.

To test our hypothesis, we used *N*-acyloxyphthalimide **1a** as a model substrate and tetrahydroxydiboron $B_2(OH)_4$[17a,18a] as the borylating reagent to screen various reaction parameters under visible-light photoredox conditions (Table 1). After extensive experimentation, we found that a simple parameter combination could already provide satisfactory results. Thus, a solution of **1a** and $B_2(OH)_4$ (4.0 equiv) in DMF ($c$[**1a**] = 0.3 M) together with the catalyst $[Ir(ppy)_2dtbpy]PF_6$ (1 mol %) was placed in a glass test tube and irradiated with a 45 W compact fluorescent lamp (CFL, maximum at 465 nm) at room temperature for 12 h. NMR analysis of the crude product indicated formation of the expected boronic acid in 85% yield. After treatment with aqueous $KHF_2$ to facilitate the isolation, the expected alkyltrifluoroborates **2a** was isolated in 83% yield by filtration (entry 1). Remarkably, different from many other visible light photoredox decarboxylative reactions, no sacrificial additives were needed to regenerate the active catalyst.[19f−i] This reaction did not require anhydrous solvent, but addition of more water led to lower yields of **2a** (entries 2 and 3). Other solvents were inferior (entries 4 and 5). Using a higher concentration (entry 6) or less $B_2(OH)_2$ (entry 7) all led to lower yields. In all cases, the main side product was the decarboxylation/hydrogenation product. Lastly, no reaction occurred in the absence of light or the catalyst.

We then moved on to examine the scope of this new decarboxylative borylation reaction, and the results are summarized in Scheme 1. Overall, both secondary and primary carboxylic acid derived *N*-acyloxyphthalimides could smoothly

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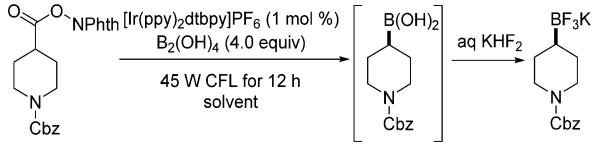
**Table 1. Reaction Optimization of the Decarboxylative Borylation with Tetrahydroxydiboron**[a]

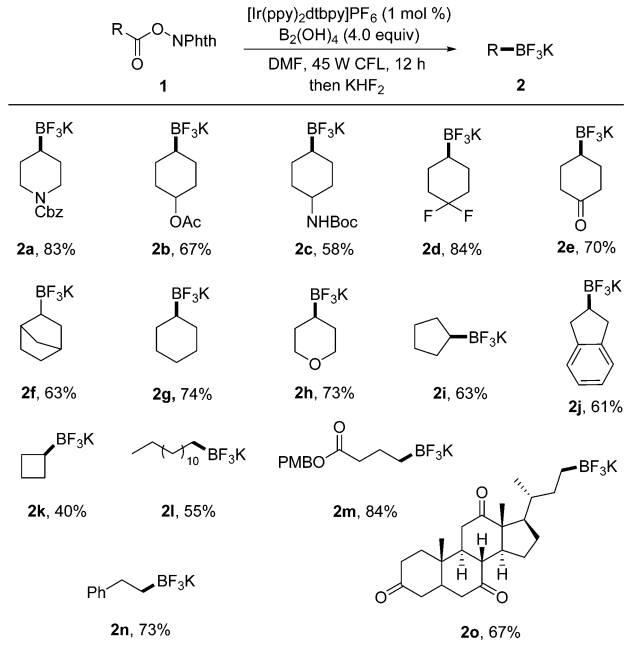



1a 2a

| entry | conditions | yield[c] (%) |
|---|---|---|
| 1 | **DMF (0.3 M)** | **85 (83[d])** |
| 2 | **DMF/$H_2O$ = 10:1** (0.3 M) | 76 |
| 3 | **DMF/$H_2O$ = 4:1** (0.3 M) | 69 |
| 4 | **MeCN** (0.3 M) | 47 |
| 5 | **MeOH** (0.3 M) | 11 |
| 6 | DMF (**0.4 M**) | 60 |
| 7[b] | DMF (0.3 M) | 60 |
| 8 | DMF (0.3 M), **dark** | NR |
| 9 | DMF (0.3 M), **no catalyst** | NR |

[a]Reaction conditions: *N*-acyloxyphthalimide **1** (0.6 mmol), $B_2(OH)_4$ (2.4 mmol), $[Ir(ppy)_2(dtbpy)]PF_6$ (0.006 mmol) in solvent (2 mL) was irradiated with a 45 W CFL for 12 h. [b]3.0 equiv of $B_2(OH)_4$ was used. [c]Yields of the intermediate boronic acids determined by crude $^1H$ NMR with 1,3,5-trimethoxybenzene as an internal standard. [d]Isolated yield of the tetrafluoroborate. NR: no reaction.

**Scheme 1. Substrate Scope of the Decarboxylative Borylation with Tetrahydroxydiboron**[a]

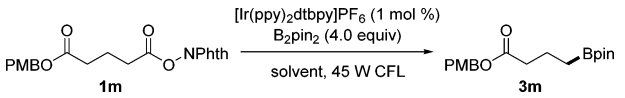



[a]Reaction conditions: *N*-acyloxyphthalimide **1** (0.6 mmol), $B_2(OH)_4$ (2.4 mmol), $[Ir(ppy)_2dtbpy]PF_6$ (0.006 mmol) in 2 mL of DMF, 45 W CFL for 12 h.

undergo decarboxylative borylation to afford the corresponding alkyl tetrafluoroborates in moderate to good yields without changing the standard conditions. Tertiary carboxylic acid derived *N*-acyloxyphthalimides, however, led to only decarboxylation/hydrogenation product. A variety of functional groups, including ester (**2b**, **2m**), ketone (**2e**, **2o**), carbamate (**2a**, **2c**), and ether (**2h**) were well tolerated. The mild reaction conditions and excellent functional group compatibility allowed the late-stage borylation of complex molecules. For example, the decarboxylative borylation of the dehydrocholic acid derivative successfully provided the corresponding product **2o** in 67% yield.

To explore further the usefulness of the decarboxylative borylation, we also examined bis(pinacolato)diboron ($B_2pin_2$) as the borylating reagent. However, we did not succeed with secondary carboxylic acid derivatives such as **1a**. Only a small amount (less than 10%) of the expected boronate could be observed, and the mass balance was mostly the corresponding hydrogenated product. In contrast, primary carboxylic acid derived *N*-acyloxyphthalimide **1m**[14,16] was a viable substrate and converted to the desired boronate **3m**. Thus, a solution of **1m**, $B_2pin_2$, and the catalyst in DMF ($c$[**1m**] = 0.1 M) was irradiated for 16 h, and **3a** was formed in 41% yield on the basis of the $^1H$ NMR analysis of the crude product (Table 2, entry 1).

**Table 2. Reaction Optimization of the Decarboxylative Borylation with Bis(pinacolato)diboron $B_2pin_2$**[a]




1m 3m

| entry | solvent | concn (M) | NMR yield[d] (%) |
|---|---|---|---|
| 1 | DMF | 0.1 | 41 |
| 2 | MeCN | 0.1 | 37 |
| 3 | DMF/$H_2O$ = 1:1 | 0.1 | 54 |
| 4 | MeCN/$H_2O$ = 1:1 | 0.1 | 58 |
| 5 | DMF/MeCN/$H_2O$ = 1:1:1 | 0.1 | 62 |
| 6 | DMF/MeCN/$H_2O$ = 1:1:1 | 0.2 | 69 |
| 7 | **DMF/MeCN/$H_2O$ = 1:1:1** | **0.3** | **86** |
| 8[b] | DMF/MeCN/$H_2O$ = 1:1:1 | 0.3 | 61 |
| 9[c] | DMF/MeCN/$H_2O$ = 1:1:1 | 0.3 | 34 |

[a]Reaction conditions: *N*-acyloxyphthalimide **1** (0.3 mmol), $B_2pin_2$ (1.2 mmol), $[Ir(ppy)_2(dtbpy)]PF_6$ (0.003 mmol), 45 W CFL, 16 h. [b]3.0 equiv of $B_2pin_2$ used. [c]2.0 equiv of DMAP added. [d]Determined by $^1H$ NMR with 1,3,5-trimethoxybenzene as an internal standard.

Acetonitrile as the solvent led to slightly lower yield (entry 2). Screening various solvent combinations revealed that a ternary solvent mixture could improve the yield to 62% (entries 3–5). Increasing the concentration of **1m** from 0.1 to 0.3 M further improved the yield to 86% by decreasing the hydrogenated side product (entries 6 and 7). By comparison, decreasing the equivalents of $B_2pin_2$ led to an inferior result (entry 8). Finally, various amines or pyridine-based additives were not helpful. For example, addition of 2 equiv of DMAP led to significantly lower yield (entry 9).

With the above optimized conditions in hand, we examined the substrate scope of this reaction with $B_2pin_2$, as summarized in Scheme 2. Primary *N*-acyloxyphthalimides with various electron-donating, electron-neutral, and electron-withdrawing groups were all efficiently converted to the corresponding alkyl pinacol boronates in good to excellent yields. A (*Z*)-double bond in oleic acid (**3f**) or a terminal alkyne (**3j**) could be tolerated, which is interesting considering that the reaction might involve a reactive carbon-centered radical. An aryl bromide (**3e**) and an alkyl chloride (**3g**) also survived, demonstrating the orthogonal reactivity of this reaction with previous alkyl metallic reagents-based or metal-catalyzed borylation of halides. Again, dehydrocholic acid was successfully used in the reaction, providing a highly functionalized alkyl boronate **3o**.

Stimulated by the success of aliphatic decarboxylative borylation, we also tested an aryl acid-derived *N*-acyloxyphthalimide **1k**. Under similar conditions, however, the expected



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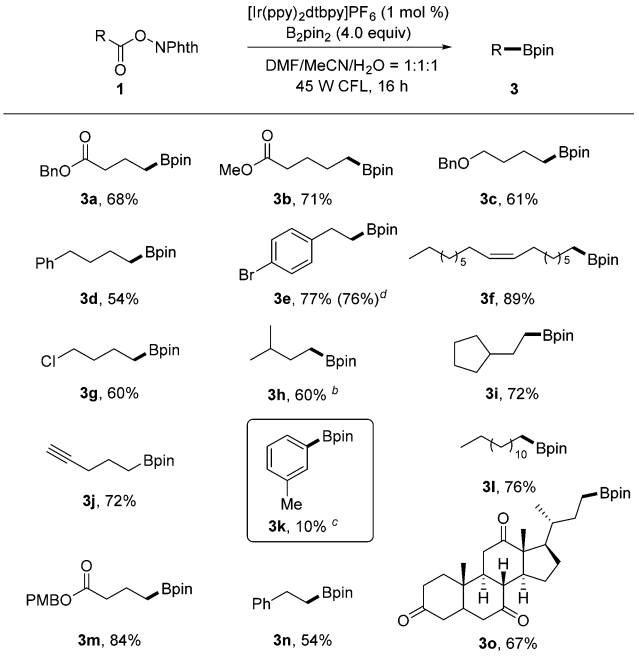
**Scheme 2. Substrate Scope of the Decarboxylative Borylation with Bis(pinacolato)diboron $B_2pin_2$**[a]

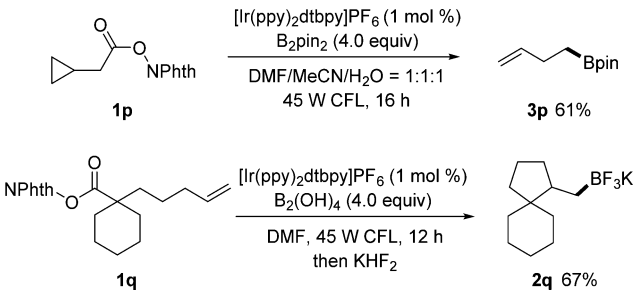



[a]Reaction conditions: *N*-acyloxyphthalimide **1** (0.3 mmol), $B_2pin_2$ (1.2 mmol), $[Ir(ppy)_2(dtbpy)]PF_6$ (0.003 mmol) in 1 mL of DMF/MeCN/$H_2O$ (1/1/1), 45 W CFL for 16 h. [b]Reaction time for 20 h. [c]Reaction time for 48 h. [d]Yield of 1 mmol scale.

reaction with $B_2pin_2$ only provided arylboronic ester **3k** in 10% yield, and the most mass balance was *m*-methyl benzoic acid, probably due to slow decarboxylation and competitive hydrogen trapping.

To shed light on the mechanism of the present decarboxylative borylation, we conducted two radical cascade experiments (Scheme 3). The reaction of **1p**,[20] containing a cyclopropyl

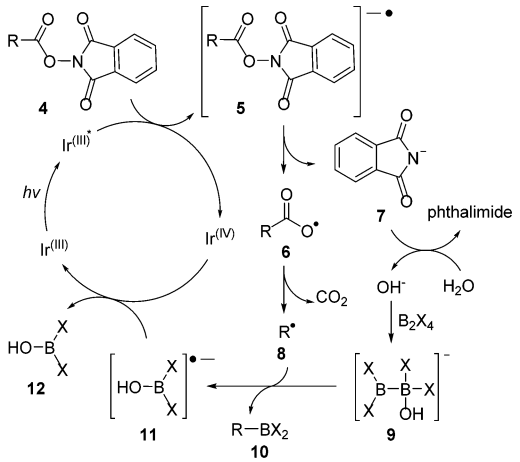
**Scheme 3. Reactions Probing the Mechanism**




group, with $B_2pin_2$ afforded the ring-opening product **3p** in 61% yield. In the case of **1q**, the decarboxylation was followed by 5-*exo* cyclization prior to borylation, and **2q** was thus obtained in 67% yield. These results all support the involvement of an alkyl radical and its reaction with the boron species.

A plausible mechanism for the visible-light photoredox decarboxylative borylation reported herein is outlined in Scheme 4. Single-electron transfer from visible light-excited photocatalyst $Ir^{(III)}$* to the *N*-acyloxyphthalimide **4** generates a radical anion **5** that undergoes homolytic cleavage of the N−O bond, leading to carboxyl radical **6** and phthalimide anion **7**. Subsequent decarboxylation of **6** generates alkyl radical R• (**8**). In the

**Scheme 4. Proposed Mechanism of Decarboxylative Borylation**




R = alkyl, $BX_2$ = $B(OH)_2$ or Bpin

presence of water, the weakly basic **7** may generate hydroxide that can react with a diboron reagent $B_2X_4$ to generate a $sp^3$−$sp^2$ diboron species (**9**).[18a,21−23] Alkyl radical **8** then reacts with **9** to form the desired product alkyl boronate **10** and concomitantly boryl radical anion **11**.[18a] Finally, the $Ir^{(IV)}$ species was reduced by **11** to regenerate catalyst $Ir^{(III)}$ to complete the catalytic cycle.

In summary, we have developed a new method to prepare alkyl boronates from readily available carboxylic acids via a novel visible-light photoredox decarboxylative borylation reaction. This reaction is operationally simple, works under mild reaction conditions, and tolerates nonanhydrous solvents and polar functional groups. This reaction represents a complementary approach to the existing C($sp^3$)−B bond formation methods. Further studies on the detailed mechanism and scope and synthetic applications are ongoing.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01181.

Detailed experimental procedures; spectral data of products (PDF)

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### Notes

The authors declare no competing financial interest.

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