Here, we describe a protocol for the metal-free, photo-induced borylation of unactivated C(sp³)–H bonds distal to an O-oxalate hydroxamic ester functionality. The methodology requires only substrate and bis(catecholato)diboron under light irradiation to effect the desired transformation. A range of linear and cyclic tertiary and secondary borylation products are obtained in good yields and high site-selectivity enabling the late-stage C(sp³)–H borylation of natural product derivatives and drug-like compounds.

Despite the progress in the borylation of C(sp²)–H bonds, the site-selective borylation of C(sp³)–H bonds is far less advanced. Transition-metal-catalyzed C–H borylation represents the most common strategy, and impressive progress has been achieved with various transition metals such as Ir, Rh, Co, Ru, and Pd (Scheme 1a). While synthetically attractive, these methods often target activated C–H bonds, rely on heteroatom directing groups, sometimes require harsh reaction conditions, and employ excess alkanes, thereby limiting scope. Moreover, the targeting of tertiary C(sp³)–H bonds is especially difficult due to both steric hindrance and the potential of β-hydride elimination with the late, noble transition metals.

A less-explored approach is the borylation of carbon-based radicals generated by hydrogen atom transfer (HAT). In 2020, the Aggarwal group employed a Cl⁻-assisted HAT strategy to achieve the primary-selective C(sp³)–H borylation of alkanes and silanes in the presence of B₂Cat₃ and alkoxypthalimide under mild conditions (Scheme 1b). Later, Xia, Dai, and Aggarwal groups reported an iron/copper-catalyzed C(sp³)–H borylation enabled by photoinduced ligand-to-metal charge transfer (LMCT). Gevorgyan group also achieved a metal-free radical α-C–H borylation of aliphatic amines (Scheme 1b). By
employing iodobenzoyl radical translocation group, \(\alpha\)-amino-alkyl radical intermediates are generated via 1,5-hydrogen atom transfer (1,5-HAT). This method allows activation of primary and secondary \(\alpha\)-C–H sites of a broad range of acyclic and cyclic amines. Despite recent developments, metal-free borylation of tertiary \(\text{C}^{\text{sp}^3}\)-H bonds remains an unsolved problem. Therefore, a general approach that expands the scope, works with a common functional group, and site-selectively targets tertiary sites fills an important gap.

Recently, our group achieved the nickel-catalyzed reductive arylation of remote \(\text{C}^{\text{sp}^3}\)-H bonds with aryl electrophiles by using the \(\text{O}\)-oxalate hydroxamic ester (Oohe) moiety as the N-radical precursor.\(^\text{14}\) In 2020, the Gong group found, under light irradiation, \(\text{B}_2\text{cat}_2\) can activate the carbonyl oxygen of tertiary alkyl methyl oxalates, facilitating the formation of tertiary alkyl radicals via C–O bond fragmentation.\(^\text{15}\) Encouraged by these results, we hypothesized that N-radicals could be generated by irradiating \(\text{O}\)-oxalate hydroxamic esters in the presence of \(\text{B}_2\text{cat}_2\). Subsequently, carbon radicals at the \(\gamma\) site would be formed via 1,5-HAT, chemoselectively affording alkyl boric esters through \(\text{B}_2\text{cat}_2\) capture (Scheme 1c). During the preparation of this manuscript, Mo and co-workers disclosed a metal-free borylation of \(\text{O}\)-benzoyl hydroxamic ester with \(\text{B}_2\text{cat}_2\),\(^\text{16}\) however, a photoredox catalyst and amine additive are necessary. An excited \([\text{EY}^2–]^*\) intermediate is proposed as a powerful reducing reagent that undergoes single-electron transfer to \(\text{O}\)-benzoyl hydroxamic ester, leading to the homolytic cleavage of the N–O bond and formation of N-based radicals. The amine additive is proposed to regenerate the photoredox catalyst. Here, we demonstrate that by using an \(\text{O}\)-oxalate hydroxamic ester, the \(\text{C}^{\text{sp}^3}\)-H borylation reaction can proceed with visible light irradiation only—without the need for a photoredox catalyst or amine additive.

We began our investigation by studying the reaction between Oohe 1 and \(\text{B}_2\text{cat}_2\) in \(\text{N},\text{N}\)-dimethylformamide (DMF) under blue LEDs irradiation (Table 1). Pلسaingly, the conditions provided targeted alkyl pinacol boronic ester 11 in 98% isolated yield after treating the crude reaction with pinacol and triethylamine. Increasing the concentration led to lower yields, likely because higher concentrations favored N–B bond formation over 1,5-HAT resulting in reduced product formation. The N-Bcat product can undergo hydrolysis to form the N–H during work-up to provide the formal hydrogenation product (Table 1, entries 2–4). Evaluation of the solvent revealed that amide-based solvents were uniquely effective for the transformation, likely due to the stabilization of the boryl radical involved in the radical chain process (see ESIT)\(^\text{17}\). The crucial effect of light was confirmed by the absence of desired product 11 when the reaction was performed in the dark (Table 1, entry 6). The conditions previously reported\(^\text{14}\) by our group provided 11 in only 6% yield (Table 1, entry 7). Composed to blue light, white light and green light provided the product in lower yields, 42% and 23%, respectively. The important role of the catechol ligand on the diboron reagent was highlighted by no reactions with bis[pinacolato]diboron (\(\text{B}_2\text{pin}_2\)) and \(\text{B}_2\text{OH}_4\) (Table 1, entries 10 and 11). Replacing \(\text{B}_2\text{cat}_2\) with a 1 : 1 mixture of \(\text{B}_2\text{OH}_4\) and catechol also gave the desired product in moderate yield (Table 1, entry 13). Reducing the amount of \(\text{B}_2\text{cat}_2\) to 1.5 equiv. resulted in a decrease in the reaction yield (Table 1, entry 13), from 98% to 60%. A series of amidyl-radical precursors 2–8 were also tested, the reaction did not work under the developed conditions. Interestingly, 61% yield could be achieved when \(\text{O}\)-benzoyl hydroxamic ester 9 (ref. 16 and 18) was used as starting material, without the use of a photocatalyst.

With the optimized reaction conditions in hand, we next evaluated a range of substrates with tertiary and secondary \(\text{C}^{\text{sp}^3}\)-H bonds (Table 2). Various methine C–H borylation worked successfully with excellent yields including cyclic congeners and sterically hindered adamantyl, which is typically difficult to access. For all cases, only a single regioisomer was observed. Notably, the borylation occurred site-selectively for

<table>
<thead>
<tr>
<th>Entry</th>
<th>Deviation</th>
<th>Yield(^b) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>None</td>
<td>98</td>
</tr>
<tr>
<td>2</td>
<td>0.4 M DMF</td>
<td>26</td>
</tr>
<tr>
<td>3</td>
<td>0.25 M DMF</td>
<td>65</td>
</tr>
<tr>
<td>4</td>
<td>0.1 M DMF</td>
<td>96</td>
</tr>
<tr>
<td>5</td>
<td>0.1 M DMA</td>
<td>45</td>
</tr>
<tr>
<td>6</td>
<td>No light</td>
<td>Trace</td>
</tr>
<tr>
<td>7</td>
<td>Cook’s conditions(^c)</td>
<td>6</td>
</tr>
<tr>
<td>8</td>
<td>White light</td>
<td>42</td>
</tr>
<tr>
<td>9</td>
<td>Green light</td>
<td>23</td>
</tr>
<tr>
<td>10</td>
<td>3 equiv. (\text{B}_2\text{Pin}_2)</td>
<td>Trace</td>
</tr>
<tr>
<td>11</td>
<td>3 equiv. (\text{B}_2\text{OH}_4)</td>
<td>Trace</td>
</tr>
<tr>
<td>12</td>
<td>3 equiv. (\text{B}_2\text{OH}_4) + 3 equiv. catechol</td>
<td>63</td>
</tr>
<tr>
<td>13</td>
<td>1.5 equiv. (\text{B}_2\text{Cat}_2)</td>
<td>60</td>
</tr>
</tbody>
</table>

\(^a\) Performed on 0.1 mmol scale (0.1 mmol 1) in 0.05 M solvent. \(^b\) Yields were determined using \(^1\)H NMR analysis with 1,3,5-trimethoxybenzene (Ar–H) as internal standard. \(^c\) Performed with 0.1 mmol 1, 15 mol% \(\text{Ni(bfaccac)}_2\text{H}_2\text{O}, 0.8\) equiv. pyridine, 1.5 equiv. \(\text{Zn}\) and 1.2 equiv. \(\text{MgCl}_2\), in 0.2 M DMA/THF [3/1], 16 h.\(^\text{11}\)
corresponding amines (see ESI†). The starting materials were readily prepared from the
can apply to
functionalization, we became interested in whether our strategy
0.025 M DMF.
crude reaction mixture.
value of this method for the late-stage functionalization of
could be successfully borylated, thereby demonstrating the
acid (\(\text{HAT}\)).

| Table 2 Substrate scope for \(\gamma\)-C–H borylation of acid derivatives** |
|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|
| **R^1** | **R^2** | **R^3** | **H** | **Product** |
| R = Bu, 11, 98% | 12, 57% | 13, 70% | 14, 53% | 15, 67% | 16, 62% | 17, 81% |
| R = Me, 18, 74% | 19, 51% | 20, 51% | 21, 46% | 22, 56% | 23, 54% |
| R = Ph, 24, 58% | 25, 75% | 26, 75% | 27, 71% | 28, 69% | 29, 58% |
| R = Br, 30, 51% | 31, 78% | From Stearic acid (32, 54%) | From Oleic acid (33, 28%) | From Dihydrocholesterol (34, 54%) |

**Performed on 0.1 mmol scale with 3 equiv. of \(\text{B}2\text{Cat}_{2}\), in 0.05 M DMF. The reaction time was 24 h. Isolated yields are shown.

substrates that contain more than one tertiary C–H bond (18 and 21), demonstrating the advantage of the intramolecular
HAT-strategy. Various functional groups, such as halides (22 and 30), ketone (23), and alkene (33), are all amenable to the
reaction conditions. Substrates containing oxygen atom adjacent
to the reaction site also afforded desired products 24, 25 and 34.

Compared to the methine borylation, yields for the less
activated secondary C–H bonds were slightly lower. The reaction
provided exclusive \(\gamma\)-borylation even in the presence of tertiary
C(sp^3)–H bonds (28). While \(\text{O-oxide}\) hydroxamic ester failed to
target benzylic sites, we turned to \(\text{O-benzoyl}\) hydroxamic ester,
which allowed the formation of benzylic boronates, as exemplified by 29–31. Aryl rings substituted with methoxy and bromo
groups also proved to be suitable substrates. The methodology
failed to produce primary boronic esters due to unidentifiable
side product formation. Encouraged by the broad scope of our
method, we next targeted the site-selective C–H borylation of
drug derivatives and biologically relevant compounds. Stearic
acid (32), oleic acid (33) and dihydrocholesterol (34) substrates
could be successfully borylated, thereby demonstrating the
value of this method for the late-stage functionalization of
complex alkanes.

While the primary goal of this work targeted \(N\)-directed C–H
functionalization, we became interested in whether our strategy
can apply to \(\delta\)-C–H bond borylation of amine derivatives
(Table 3). The starting materials were readily prepared from the
Corresponding amines (see ESI†). While \(tert\) butyl \(\text{O-benzoyl}\) hydroxamic ester 35 only provided trace yields, the adamantoyl-based \(\text{O-benzoyl}\) hydroxamic ester 36 produced the desired boronic esters in 58% yield. Additionally, we observed the desired borylation of
benzoyl-based \(\text{O-hydroxamic ester}\) substrates bearing either
electron-withdrawing or electron-donating groups on the
aromatic ring, providing good yields of the target boronic esters (37–41). Notably, borylation of the aliphatic C–H bond
predominated over that of the benzylic C–H bond in substrates
having two possible 1,5-HAT pathways (42). Product 43 was
obtained in lower yield compared to product 38, likely due to
the Thorpe–Ingold effect.** Again, the method provided a broad
substrate scope with excellent regioselectivity.

Compounds 44–47 were formed as mixture of the two dia-
stereoisomers. Transannular borylation occurred with complete
regioselectivity to produce 47 as the sole product. The bory-
lation protocol was successfully applied to an amine-derived
from germifibril, affording product 48 in a synthetically
useful yield.

Performing the reaction on 1.0 mmol also produced the
desired product in good yield, demonstrating the practicality of
this method (Scheme 2a). As expected, the boronic ester pro-
ducts can be easily transformed into other synthetically useful
motifs (Scheme 2b). For example, the transition-metal-free
cross-coupling** between 11 and furan furnished the \(\gamma\)aryl-
lated derivative 49. Mild oxidation and Zweifel olefination** of
11 provided the corresponding products, 50 and 51, respec-
tively. Additionally, Matteson homologation** of the obtained
product provided boronate, which was further transformed into alcohol derivate 52.

To gain insight into the reaction mechanism, several control experiments were performed (Scheme 3). Only trace of the desired product was detected when the reaction was performed in the presence of TEMPO. Other radical scavengers such as BHT also significantly diminish the yield (Scheme 3a). The reaction of unsaturated the O-oxalate hydroxamic ester 53a as a radical probe afforded the cyclized product 53 (Scheme 3b). Additionally, a substrate containing cyclopropyl methyl moiety undergoes ring-opening to result primary borylated product 54 (Scheme 3c). Together, the results in Scheme 3 suggest that the reaction proceeds via a radical H-atom abstraction mechanism. Additionally, we investigated the photoinitiation process by measuring absorption spectra of the reaction components.

<table>
<thead>
<tr>
<th>Scheme 2</th>
<th>The method offers value in both laboratory scalability and synthetic utility.</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) 1 mmol scales:</td>
<td></td>
</tr>
<tr>
<td>b) Follow-up chemistry:</td>
<td></td>
</tr>
<tr>
<td>a) Reaction with radical scavengers:</td>
<td></td>
</tr>
<tr>
<td>b) Cyclization Experiment:</td>
<td></td>
</tr>
<tr>
<td>c) Radical-Clock Experiments:</td>
<td></td>
</tr>
</tbody>
</table>

| Scheme 3 | Mechanistic studies. (a) Reaction with radical scavengers; (b) radical-mediated cyclization; (c) radical-mediated cyclopropane ring-opening. |

Table 3  Substrate scope for δ-C–H borylation of amine derivatives

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Isolated Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 equiv B2Cat2, 0.05 M DMF</td>
<td>24 h</td>
</tr>
<tr>
<td>Isolated yields are shown.</td>
<td></td>
</tr>
<tr>
<td>B2Cat2, 0.025 M DMF</td>
<td></td>
</tr>
<tr>
<td>dr was calculated by 1H NMR analysis of the crude reaction mixture.</td>
<td></td>
</tr>
<tr>
<td>B2Cat2, 0.025 M DMF</td>
<td></td>
</tr>
<tr>
<td>dr was calculated by 1H NMR analysis of the crude reaction mixture.</td>
<td></td>
</tr>
<tr>
<td>Signal overlap in the 1H NMR, unambiguous determination of the selectivity failed.</td>
<td></td>
</tr>
</tbody>
</table>

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The lack of change in the UV/Vis spectrum suggested that an electron donor–acceptor complex between O-oxalate hydroxamic ester and B\textsubscript{2}cat\textsubscript{2} does not occur, is fast on the UV/Vis timescale, or is generated in small amounts (Fig. S1).\textsuperscript{15} A weak absorption at ∼430 nm suggests the formation of a DMF-B\textsubscript{2}cat\textsubscript{2} adduct.\textsuperscript{15} Likely, photoexcitation of the DMF-B\textsubscript{2}cat\textsubscript{2} complex generates a DMF-stabilized boryl radical, which can further initiate a radical chain process.\textsuperscript{15,16} Interestingly, a bathochromic shift in the absorption spectrum was observed when O-benzoyl hydroxamic ester 9 was treated with B\textsubscript{2}cat\textsubscript{2} in DMF (Fig. S3†), suggesting the formation of an electron–donor–acceptor (EDA) complex.

Based on the combination of mechanistic results and literature reports, a proposed mechanism is shown in Scheme 4. Under light irradiation, the formation of a (DMF)\textsubscript{2}B\textsubscript{2}cat\textsubscript{2} A will give a DMF-stabilized Bcat radical B to activate the oxalate. Then, radical fragmentation of the N–O bond generates the corresponding amidenyl radical C, followed by 1,5-HAT to give a C-centered alkyl radical D. Radical D is then trapped by diboron B\textsubscript{2}cat\textsubscript{2} A to yield the adduct E, with subsequent B–B bond cleavage facilitated by complexation with DMF to form F. The weak B–B bond homolyzes to give the borylated product G along with DMF-Bcat radical B.

In conclusion, we have developed a photoinduced remote C(sp\textsuperscript{3})–H bond borylation of O-oxalate hydroxamic esters. The reaction does not require a photocatalyst, transition metal catalyst, or additional radical initiator. Remarkably, this method enables the targeting of an impressive array of aliphatic C–H bonds (2° and 3°) with broad functional group tolerance and highly site-selectivity and can be used in the late-stage borylation of bioactive molecules. Key to the success of the reaction was the use of O-oxalate hydroxamic esters, which efficiently reacted with B\textsubscript{2}cat\textsubscript{2} in a photoinitiated radical chain mechanism.

Scheme 4 Proposed reaction mechanism.

Author contributions
J. H. and S. P. C. designed the experiments. J. H. performed the experiments. J. H. and S. P. C. wrote the manuscript.

Conflicts of interest
The authors declare no conflicts of interest.

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Notes and references


