The conversion of widely available carboxylic acids into versatile boronic esters would be highly enabling for synthesis. We found that this transformation can be effected by illuminating the N-hydroxyphthalimide ester derivative of the carboxylic acid under visible light at room temperature in the presence of the diboron reagent bis(catecholato)diboron. A simple workup allows isolation of the pinacol boronic ester. Experimental evidence suggests that boryl radical intermediates are involved in the process. The methodology is illustrated by the transformation of primary, secondary, and tertiary alkyl carboxylic acids as well as a diverse range of natural-product carboxylic acids, thereby demonstrating its broad utility and functional group tolerance.

A straightforward method for converting libraries of bioactive carboxylic acids into the corresponding boronic esters in a Suzuki-Miyaura-type coupling reaction (16). We wondered whether diboron reagents such as bis(pinacolato)diboron (B2pin2) could take the place of these carbon-based nucleophiles to instead effect C–B bond formation. Very recently, reaction conditions that allow the decarboxylative borylation of sp2 and sp3 N-hydroxyphthalimide esters by using such diboron species were disclosed (17–19). Baran and colleagues reported that the use of a Ni(II) pre-catalyst in the presence of a bipyridine ligand, MgBr2·OEt2, and MeLi-activated B2pin2 (Et, ethyl; Me, methyl) led the putative alkyl radical intermediate to combine with a Ni–boryl intermediate, which underwent reductive elimination to give the alkyl boronic ester (Fig. 1B) (17). The substrate scope (which encompassed amino acid–derived and peptidic N-hydroxyphthalimide esters) and functional group tolerance of these reaction conditions were very broad. The same transformation can be carried out under visible light–mediated iodiridium catalysis by using a large excess of B2(OH)4 (tetrahydrox ydiboron) or B2pin2 (18); the proposed mechanism involves reaction of the putative alkyl radical with nucleophile-activated sp2-sp2 diboron species (20, 21) to give the desired organoboron compound. The substrate scope for this photoexcited Ir–mediated process was narrower than for the Ni-mediated process; B2pin2 could only be used to form the primary boronic esters, with other more substituted products requiring the use of B2(OH)4 and isolation as the trifluoroborate salts. A similar photomediated process for the decarboxylative borylation of aryl N-hydroxyphthalimides

**Photoinduced decarboxylative borylation of carboxylic acids**

Alexander Fawcett, Johan Pradeilles, Yahui Wang, Tatsuya Mutsuga, Eddie L. Myers, Varinder K. Aggarwal

Carboxylic acids are among the most prevalent of organic molecules found in nature (7). By contrast, the isoelectronic boronic acids are scarcely found in nature at all, yet serve as precursors to a vast array of molecules containing different functional groups (2) through single-step, transition metal–mediated coupling reactions (3), 1,2-metallate rearrangements, or deborylative nucleophilic addition (4). Therefore, the conversion of the ubiquitous carboxylic acid group into the highly versatile boronic acid moiety would facilitate more rapid diversification of this important class of feedstock molecules. Also, boronic acids are important target molecules in their own right because they share a number of features with carboxylic acids that make them potent bioisosteres in medicinal chemistry (5). Specifically, boronic acids form hydrogen bonds of similar geometries to carboxylic acids (6), despite their lower acidity, and they can switch reversibly between stable tricoordinate and tetracoordinate forms, thus mimicking the tetrahedral intermediates involved in, for example, the enzymatic hydrolysis of amide groups (7). A straightforward method for converting libraries of bioactive carboxylic acids into the corresponding boronic acids would lead to enhanced screening libraries and would facilitate bioisosteric lead optimization.

Until very recently, only the decarboxylative borylation of carboxylic derivatives was known. These transformations involved the oxidative addition of a catalytically active Ni(0) or Rh(I) species into the C–O (8), C–S (9), or C–N (10) bond of an ester, thioester, or amide derivative, respectively, and only gave high yields for carboxylic acid derivatives bearing sp2 carbon centers (Fig. 1A). Applying these conditions to simple carboxylic acid derivatives bearing sp3 carbon centers gives low yields of the desired boronic esters. Seeking a complementary method that would allow the transformation of sp3 carboxylic acids, we considered N-hydroxyphthalimide esters, which have recently been used in the decarboxylative functionalization of alkyl groups under mild conditions (11–15). In the presence of photoexcited Ru(I) or low-valent Ni or Fe, these esters are known to undergo facile single-electron reduction followed by rapid decarboxylative fragmentation to an alkyl radical. The alkyl radical then reacts to form a carbon-carbon bond with either an electrophilic olefin or, through mediation by a transition metal, a carbon-centered organometallic nucleophile, including boronic esters in a Suzuki-Miyaura–type

---

**Fig. 1. Reaction development.**

**A** Transition metal–catalyzed decarboxylative borylation reactions of aryl carboxylic acid derivatives. These reactions proceed through oxidative addition of the metal into the C–X bond, extrusion of CO, e–bond metathesis with the diboron species, and reductive elimination to form the C–B bond.

**B** Baran’s Ni-catalyzed decarboxylative borylation. The reaction conditions for the visible light–activated decarboxylative borylation of N-hydroxyphthalimide ester 1 in the presence of the diboron species bis(catecholato)diboron (B2cat2). The reaction conditions highlighted in yellow (entry 4) are optimal.

---

**Entry Conditions**

<table>
<thead>
<tr>
<th></th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>69</td>
</tr>
<tr>
<td>2</td>
<td>71</td>
</tr>
<tr>
<td>3</td>
<td>14</td>
</tr>
<tr>
<td>4</td>
<td>91</td>
</tr>
<tr>
<td>5</td>
<td>&lt;2</td>
</tr>
<tr>
<td>6</td>
<td>36</td>
</tr>
<tr>
<td>7</td>
<td>63</td>
</tr>
<tr>
<td>8</td>
<td>77</td>
</tr>
</tbody>
</table>
that does not require a transition metal photocatalyst has also been disclosed (9). For that process, LED illumination (400 nm), excess B2pin2 (3.0 equivalents), a catalytic amount of Cs2CO3, and stoichiometric amounts of pyridine were required for high yields.

Our exploration of this transformation led us to identify much simpler reaction conditions. Specifically, treatment of 1-N-hydroxyphthalimidine ester 1 with a slight excess of the diboron reagent bis(catechol)diboron (B2cat2; 1.25 equivalents) in N,N-dimethylacetamide (DMAc) solvent at ambient temperature under illumination by blue LEDs, followed by a workup that involved adding pinacol and NEt3, so as to effect ligand exchange to form the more stable pinacol boronic ester, gave the desired boronic ester 2 in 91% yield (Fig. 1C, entry 4). A solvent screen revealed that amide-based solvents were uniquely effective for the transformation, with DMAc performing marginally better than N,N-dimethylformamide (DMF) (Fig. 1C, entry 1); the use of other standard organic solvents such as EtOAc, CH2Cl2, MeCN, and Et2O did not lead to any of the desired product (Fig. 1C, entry 5). Increasing the amount of B2cat2 in increments from 1.00 equivalent to 2.00 equivalents revealed that a slight excess of the reagent (1.25 equivalents; Fig. 1C, entry 4 versus 1) was optimal, with 91% yield; there was a slight drop in yield with larger amounts. The transformation was promoted by light, as a reaction conducted in the dark generated the desired product at a much lower rate: 36% yield after 14 hours, and 63% yield after 70 hours (Fig. 1C, entries 6 and 7). Light from a regular white bulb placed in the vicinity of the reaction vessel was equally effective (91% yield), although ambient light led to a less efficient reaction (43% yield). The transformation was moderately sensitive to concentration (0.1 M being optimal), and investigation of the progress of the reaction showed that it was complete within 4 hours (for operational reasons, a reaction time of 14 hours was used for the exploration of substrate scope). Although the reaction was tolerant of small amounts of water, the presence of O2 was detrimental; therefore, conducting the reaction under an inert atmosphere (N2 or Ar) was detrimental; therefore, conducting the reaction under blue LEDs was required for high yields.

Our exploration of this transformation led us to identify much simpler reaction conditions. Specifically, treatment of 1-N-hydroxyphthalimidine ester 1 with a slight excess of the diboron reagent bis(catechol)diboron (B2cat2; 1.25 equivalents) in N,N-dimethylacetamide (DMAc) solvent at ambient temperature under illumination by blue LEDs, followed by a workup that involved adding pinacol and NEt3, so as to effect ligand exchange to form the more stable pinacol boronic ester, gave the desired boronic ester 2 in 91% yield (Fig. 1C, entry 4). A solvent screen revealed that amide-based solvents were uniquely effective for the transformation, with DMAc performing marginally better than N,N-dimethylformamide (DMF) (Fig. 1C, entry 1); the use of other standard organic solvents such as EtOAc, CH2Cl2, MeCN, and Et2O did not lead to any of the desired product (Fig. 1C, entry 5). Increasing the amount of B2cat2 in increments from 1.00 equivalent to 2.00 equivalents revealed that a slight excess of the reagent (1.25 equivalents; Fig. 1C, entry 4 versus 1) was optimal, with 91% yield; there was a slight drop in yield with larger amounts. The transformation was promoted by light, as a reaction conducted in the dark generated the desired product at a much lower rate: 36% yield after 14 hours, and 63% yield after 70 hours (Fig. 1C, entries 6 and 7). Light from a regular white bulb placed in the vicinity of the reaction vessel was equally effective (91% yield), although ambient light led to a less efficient reaction (43% yield). The transformation was moderately sensitive to concentration (0.1 M being optimal), and investigation of the progress of the reaction showed that it was complete within 4 hours (for operational reasons, a reaction time of 14 hours was used for the exploration of substrate scope). Although the reaction was tolerant of small amounts of water, the presence of O2 was detrimental; therefore, conducting the reaction under an inert atmosphere (N2 or Ar) was important for maintaining high yields. Cognizant of the cost of B2cat2, we discovered that replacing it with a 1:1 mixture of B2(OH)4 and catechol gave similar yields (Fig. 1C, entry 8). For our process, the use of the more Lewis-acidic diboron reagent B2pin2 (Fig. 1C; compare entry 2 with entry 3) was crucial, and the addition of Cs2CO3 had an inhibitory effect (see supplementary materials). The substrate scope of the transformation was broad. Primary carboxylic acids, including a benzylic substrate and substrates bearing heteroatoms, heterocycles (thiophene, indole, pyridine), β-positioned alkenes, alkynes, esters, carbonobromine bonds, and perfluoroalkyl chains, were converted into the corresponding primary pinacol boronic esters in good to high yields (Fig. 2A). The isolation of these products was extremely facile; a quick filtration through a plug of silica gel was sufficient to provide material of high purity. Secondary carboxylic acids, either appended to acyclic chains or to a variety of rings (cyclohexyl, cyclopentyl, cyclopropyl, 1,2,2-bridged bicyclic, pyranyl) and paired with functional groups such as difluoromethylene, a carbamate, and an ester, were converted into the corresponding boronic esters in good to high yield (Fig. 2B). We also investigated carbonyl substrates containing two stereogenic centers, at least one of which bore the carboxylic acid moiety. Here, the boronic ester products were obtained with varying diastereomic ratios (d.r.), depending on the relative position of substituents and ring size. Whereas the 1,3-substituted cyclopentane 18 was obtained with low levels of diastereoselectivity, the 1,2-substituted cyclohexane 22 (derived from the corresponding dicarboxylic acid) and 1,2-disubstituted cyclopropane 16 were obtained in 90:10 and 98:2 d.r., respectively (Fig. 2B). Tertiary carboxylic acids in which the three carbon atoms were tied back to a ring structure—for example, adamantyl, cubyl, and bicyclo[1.1.1]pentyl carboxylic acids—were transformed into the corresponding boronic esters in good yield (Fig. 2C). Gram quantities of adamantyl pinacol boronic ester 26 could be prepared in a single reaction. However, the use of N-hydroxyphthalimide esters of more flexible
tertiary carboxylic acids (e.g., 1-methyl-cyclohexyl carboxylic acid) did not provide the desired boronic ester, although the starting material was completely consumed under the reaction conditions. Other substrates that did not lead to the desired boronic ester included secondary benzylic substrates, allylic substrates, and substrates containing $\alpha$-heteroatoms (including amino acids).

To showcase the utility of the transformation for diversifying natural-product carboxylic acids, we prepared a diverse collection of $N$-hydroxyphthalimide esters and subjected them to the optimized reaction conditions. Boronic esters derived from stearic, oleic, lithocholic, pinonic, gibberellic, and arachidonic acids were obtained in moderate to good yields (Fig. 2D). Transformation of the bis($N$-hydroxyphthalimide ester) of succinic acid gave the corresponding 1,2-bis(boronic ester) in 41% yield. To demonstrate the utility of the transformation for medicinal chemistry purposes, we converted fenbufen, a protected form of glutamic acid, and indometacin (Fig. 2D, products 34, 38, and 35), into the corresponding boronic esters in moderate to good yields. These examples show that the transformation is also tolerant of free hydroxy groups, silyl ethers, and ketones.

On the basis of the above results and further control experiments (see below), we believe that the transformation proceeds through a radical chain process that is initiated by both a photochemical event and a less efficient thermal event (Fig. 3A). For the photochemical process, the $N$-hydroxyphthalimide substrate and a DMAc solvent molecule bind to the boron centers of $B_2$cat$_2$, forming heteroleptic ternary complex 42. This species, which is formed in low concentration, absorbs light to form an excited state that ultimately leads to cleavage of the B–B bond, thus forming the DMAc-stabilized boryl radical 44 and the O-boryl-$N$-hydroxyphthalimide ester radical 43, which subsequently undergoes rapid decarboxylation to form the alkyl radical 45 and O-boryl phthalimide 51. The alkyl radical then reacts with DMAc-ligated $B_2$cat$_2$ 47, thus generating the desired boronic ester 50 and DMAc-stabilized boryl radical 44. The resulting boryl radical can then either propagate a radical chain process through reaction with one of the imidyl oxygen atoms of the $N$-hydroxyphthalimide ester, thus leading to homolytic decarboxylation, or else terminate the chain through radical-radical dimerization with another boryl radical (22). Alternatively, the 2:1 DMAc/$B_2$cat$_2$ complex 46 undergoes thermal homolytic fragmentation to give two equivalents of the DMAc-stabilized boryl radical 44, which propagate the chain as described above.

We inferred the existence of an alkyl radical intermediate because the transformation is not diastereospecific (Fig. 2B, products 16, 18, and 22). This possibility was probed further by subjecting methyl cyclopropyl $N$-hydroxyphthalimide 53 to the reaction conditions (Fig. 3C); the isolation of the homoallylic pinacol boronic ester 10 (56% yield) confirmed the intermediacy of the methylcyclopropyl radical, which is known to undergo rapid ring opening to the homoallylic radical (rate constant = $1.3 \times 10^8$ s$^{-1}$) (23). We also prepared 5-hexenyl $N$-hydroxyphthalimide 54 and subjected it to the reaction conditions, knowing that the putative 11B NMR spectra of DMAc and CH$_2$Cl$_2$ solutions of $B_2$cat$_2$. (C) Decarboxylative borylation of cyclopropylmethyl $N$-hydroxyphthalimide ester 53 leads to homoallyl boronic ester 10. Decarboxylative borylation of 5-hexenyl $N$-hydroxyphthalimide ester 54 leads to a mixture of the 5-hexenyl 56 and the cyclopentyl methyl boronic ester 55. (D) UV/visible absorption spectra (normalized) of DMAc solutions of $N$-hydroxyphthalimide ester 1 (red trace), $B_2$cat$_2$ (blue trace), and a 1:1.25 mixture of ester 1 and $B_2$cat$_2$ (green trace).
intermediate 5-hexenyl radical undergoes cyclization to the more thermodynamically stable cyclopentyl methyl primary radical (rate constant = 1.0 × 10^9 s^-1) (23). We obtained a mixture of the 5-hexenyl 56 (linear) and the cyclopentyl methyl boronic ester 55 (cyclic) in a ratio of ~1.5:1 (Fig. 3C). This ratio was dependent on the concentration of the reaction components, the cyclic product being favored under more dilute conditions (see supplementary materials). The dependence of the linear/cyclic ratio on concentration supports the operation of a chain process, such as the one proposed above, rather than a process in which the desired boronic ester is formed through radical-radical coupling of the alkyl radical and DMAc-stabilized boryl radical within the solvent cage (19).

The requirement of using an amide-based solvent (e.g., DMAc or DMF) is evidence to support the involvement of boryl radicals, which are extremely unstable unless coordinated to a Lewis base, especially one that allows delocalization of the unpaired electron residing formally on the boron center (24). A recent computational investigation suggests that Lewis bases, such as DMF and DMAc, do provide substantial stabilization to boryl radicals (25). Recent investigations have shown that N-heterocyclic carbene (26, 27) and pyridine (28, 29) are among the best Lewis bases for stabilizing boryl radicals. We therefore subjected our standard substrate, 1, and B(cat)2 as a solution in CH2Cl2 (a solvent that does not promote decarboxylative borylation), together with two equivalents of N,N-dimethylamino pyridine (DMA), to blue LED illumination. We obtained the desired pinacol boronic ester 2 in 10% yield (13% for the reaction conducted in the dark), thus strongly suggesting that DMAc solvent takes on the additional role of stabilizing a boryl radical. That the DMAc-mediated transformation proceeds equally well in the dark supports thermal fragmentation of the doubly ligated diboron species as a possible chain process–initiating event. Furthermore, comparing the 13C nuclear magnetic resonance (NMR) spectrum of B(cat)2 in CH2Cl2 with that in DMAc (Fig. 3B), the former shows a single signal at 29.7 ppm, whereas the latter shows two more upfield signals, one broad (25.4 ppm) and one sharp (13.8 ppm). The upfield shifting and broadening of the peak in going from CH2Cl2 to DMAc supports the existence of ligated diboron species (30). Intriguingly, the sharp signal at 13.8 ppm is consistent with the presence of the previously reported cubically symmetrical bis(catchelatato) boronate B(cat)2− (32); the identity of this species was confirmed through independent synthesis. This species could be formed through a process initiated by homolytic cleavage of the B–B bond, thus lending further credence to the above mechanistic proposal.

That the transformation was promoted by visible light was initially intriguing because the independent absorption spectra of both the N-hydroxypythalimide substrate 1 and the B(cat)2 reagent in DMAc solution show bands exclusively in the ultraviolet (UV) region (maxima at 314 and 303 nm, respectively), with no features in the visible region. However, a DMAc solution of a mixture of these components, at the concentration relevant to the process (0.1 M), shows a shoulder on the bathochromic side that extends into the region that overlaps with the band of wavelengths emitted by the blue LEDs (maxima at 450 nm). These data provide strong evidence for the presence of ternary complex 42, which is proposed to absorb light and undergo fragmentation to the alkyl radical and the DMAc-stabilized boryl radical. It is conceivable that upon excitation of ternary complex 42 (32), intracomplex electron transfer from a catechol moiety to the phthalimide moiety would immediately precede decarboxylative fragmentation (19, 33). We also wondered about the reversibility of the C–B bond formation and thus the stability of the boronic esters under the reaction conditions, as it has been shown that they are extremely unstable unless coordinated to a Lewis base, especially one that allows delocalization of the unpaired electron residing formally on the boron center (24). A recent computational investigation suggests that Lewis bases, such as DMF and DMAc, do provide substantial stabilization to boryl radicals (25). Recent investigations have shown that N-heterocyclic carbene (26, 27) and pyridine (28, 29) are among the best Lewis bases for stabilizing boryl radicals. We therefore subjected our standard substrate, 1, and B(cat)2 as a solution in CH2Cl2 (a solvent that does not promote decarboxylative borylation), together with two equivalents of N,N-dimethylamino pyridine (DMA), to blue LED illumination. We obtained the desired pinacol boronic ester 2 in 10% yield (13% for the reaction conducted in the dark), thus strongly suggesting that DMAc solvent takes on the additional role of stabilizing a boryl radical. That the DMAc-mediated transformation proceeds equally well in the dark supports thermal fragmentation of the doubly ligated diboron species as a possible chain process–initiating event. Furthermore, comparing the 13C nuclear magnetic resonance (NMR) spectrum of B(cat)2 in CH2Cl2 with that in DMAc (Fig. 3B), the former shows a single signal at 29.7 ppm, whereas the latter shows two more upfield signals, one broad (25.4 ppm) and one sharp (13.8 ppm). The upfield shifting and broadening of the peak in going from CH2Cl2 to DMAc supports the existence of ligated diboron species (30). Intriguingly, the sharp signal at 13.8 ppm is consistent with the presence of the previously reported cubically symmetrical bis(catchelatato) boronate B(cat)2− (32); the identity of this species was confirmed through independent synthesis.
Photoinduced decarboxylative borylation of carboxylic acids
Alexander Fawcett, Johan Pradeilles, Yahui Wang, Tatsuya Mutsuga, Eddie L. Myers and Varinder K. Aggarwal

Science 357 (6348), 283-286,
DOI: 10.1126/science.aan3679originally published online June 15, 2017

Lighting the way to carbon borylation
Boron substituents provide versatile reactivity, and their utility has been emerging in pharmaceutical contexts. Fawcett et al. show that visible light can induce replacement of carboxylic acid groups with boronate esters, which will ease their introduction into a wide variety of compounds. Once the acids are activated with phthalimide substituents, they can react with catecholborane dimers under illumination in amide solvents, with no need for catalysts or other additives. The reaction appears to proceed by radical chain propagation after photoinitiation.

Science, this issue p. 283