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Photoinduced decarboxylative borylation of carboxylic acids

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The conversion of widely available carboxylic acids into versatile boronic esters would be highly enabling for synthesis. Here we report 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 not just primary, secondary, and tertiary alkyl carboxylic acids but also a diverse range of natural product carboxylic acids, thereby demonstrating its broad utility and functional-group tolerance.

Carboxylic acids are among the most prevalent of organic molecules found in nature (*1*). In 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. Specifically, they share a number of features with carboxylic acids that make them potent bioisosteres in medicinal chemistry (*5*). For example, 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.

Up until very recently, only the decarbonylative 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 sp^2 carbon centers (Fig. 1A). Applying these conditions to simple carboxylic acid derivatives bearing sp^3 carbon centers gives low yields of the desired boronic esters. Seeking a complementary method that would allow the transformation of sp^3 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 either low-valent Ni or Fe, or photoexcited Ru(I), 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 coupling reaction (*16*). We wondered whether diboron reagents, such as bis(pinacolato)diboron (B_2pin_2) 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 sp^3 and sp^2 *N*-hydroxyphthalimide esters by using such diboron species were disclosed (*17*–*19*). Use of a Ni(II) precatalyst in the presence of a bipyridine ligand, $MgBr_2.OEt_2$, and MeLi-activated B_2pin_2 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 iridium catalysis by using a large excess of tetrahydroxydiboron ($B_2(OH)_4$) or B_2pin_2 (*18*), the proposed mechanism involving reaction of the putative alkyl

radical with nucleophile-activated sp^2–sp^3 diboron species (*20*, *21*) to give the desired organoboron compound. The substrate scope for this photoexcited-Ir-mediated process was narrower than the Ni-mediated process; B_2pin_2 could only be used to form the primary boronic esters, with other more substituted products requiring the use of $B_2(OH)_4$ and isolation as the trifluoroborate salts. A similar photomediated process for the decarboxylative borylation of aryl *N*-hydroxyphthalimides that does not require a transition-metal photocatalyst has also been disclosed (*19*). For that process, LED illumination (400 nm), excess B_2pin_2 (3.0 equivalents), a catalytic amount of Cs_2CO_3, 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 *N*-hydroxyphthalimide ester **1** with a slight excess of the diboron reagent, bis(catecholato)diboron (B_2cat_2; 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 NEt_3, 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, for example, EtOAc, CH_2Cl_2, MeCN, and Et_2O, did not lead to any of the desired product (Fig. 1C, entry 5). Increasing the amount of B_2cat_2 in increments from 1.00 equivalent to 2.00 equivalents revealed that a slight excess of the reagent (1.25 equivalents; 91% yield; Fig. 1C, entry 4 versus 1) was optimal; 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 O_2 was detrimental and therefore conducting the reaction under an inert atmosphere (N_2 or Ar) was important for maintaining high yields. Cognizant of the cost of B_2cat_2, we discovered that replacing it by a 1:1 mixture of $B_2(OH)_4$ and catechol gave similar yields (Fig. 1C, entry 8). For our process, the use of the more Lewis acidic diboron reagent, B_2cat_2 (Fig. 1C, compare entry 2 with entry 3), was crucial, and the addition of Cs_2CO_3 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, carbon–bromine 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 being sufficient for providing material of high purity. Secondary carboxylic acids, either appended to acyclic chains or to a variety of rings (cyclohexyl, cyclopentyl, cyclopropyl, 2,2,2-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 carbocyclic substrates containing two stereogenic centers, at least one of which bore the carboxylic acid moiety. Here, the boronic ester products were obtained with varying diastereomeric ratios (d.r.), depending on the relative position of substituents and ring size. Although the 1,3-substituted cyclopentane, **18**, was obtained with low levels of diastereoselectivity, the 1,2-subsitututed 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 into 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, for example 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 α-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) **40** in 41% yield. To demonstrate the utility of the transformation for medicinal chemistry applications, fenbufen, a protected form of glu-

tamic acid, and indometacin were converted into the corresponding boronic esters in moderate to good yields. These examples highlight that the transformation is also tolerant of free hydroxy groups, silyl ethers, and ketones.

Based upon the above results and further control experiments (see below), we believe that the transformation proceeds through a radical chain process that is initiated through either a photochemical event or a less-efficient thermal event, both of which operate in parallel (Fig. 3A). For the photochemical process, the *N*-hydroxyphthalimide substrate and a DMAc solvent molecule bind to the boron centers of B_2cat_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_2cat_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_2cat_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. That the transformation is not diastereospecific (Fig. 2B, products **16**, **18**, and **22**), supports the intermediacy of an alkyl radical. 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 (1.3×10^8 s^{-1}, *23*). We also prepared 5-hexenyl *N*-hydroxyphthalimide **54** and subjected it to the reaction conditions, knowing that the putative intermediate, 5-hexenyl radical, undergoes cyclization to the more thermodynamically stable cyclopentyl methyl primary radical with a rate constant of 1.0×10^5 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 ca. 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 where 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 (DMAc, DMF) is evidence to support the involvement of boryl radicals, which are extremely unstable unless coordinated to a Lewis base, especially those that allow 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 carbenes (*26*, *27*) and pyridines (*28*, *29*) are among the best Lewis bases for stabilizing boryl radicals. We therefore subjected our standard substrate, **1**, and B_2cat_2 as a solution in CH_2Cl_2 (a solvent that does not promote decarboxylative borylation), together with two equivalents of *N*,*N*-dimethylamino pyridine (DMAP), to blue LED illumination. We obtained the desired pinacol boronic ester **2** in 10% yield (13% yield 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 DMAP-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 ^{11}B NMR spectrum of B_2cat_2 in CH_2Cl_2 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 CH_2Cl_2 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(catecholato) boronate $B(cat)_2^-$ (*31*); 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*-hydroxyphthalimide substrate **1** and the B_2cat_2 reagent in DMAc solution show bands exclusively in the 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 supporting 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 can be useful precursors to alkyl radicals in the presence of either in-situ generated oxygen-centered radicals (*34*–*36*) or good Lewis bases such as DMAP (*37*). However, we only observed consumption of product upon conducting the reaction at high concentrations of reaction partners (~1 m) or by conducting the reaction at elevated temperatures. The distinct structural features of the substrates that did not give the desired boronic ester products, namely, flexible tertiary, secondary benzylic, and α-heteroatom carboxylic acids, suggest that the putative intermediate alkyl radicals probably underwent single-electron oxidation to the stable carbenium ions rather than borylation.

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number: GB 1705897.5).

SUPPLEMENTARY MATERIALS
www.sciencemag.org/cgi/content/full/science.aan3679/DC1
Materials and Methods
Figs. S1 to S7
Tables S1 and S2
References (*37*–*67*)
NMR Spectra

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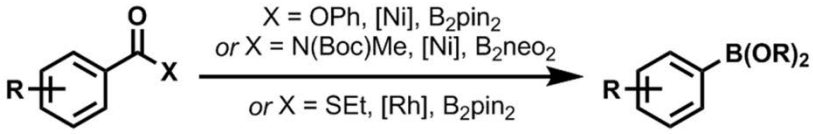
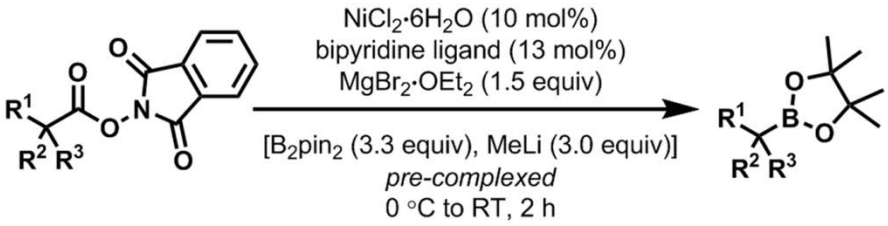
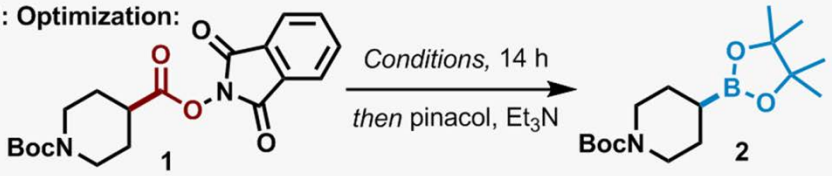
A: Previous Decarbonylative Borylations:



B: Baran's Ni-catalyzed Decarboxylative Borylation:



C: Optimization:



Entry	Conditions	Yield/ %
1	1.00 equiv B_2cat_2, DMF, blue LEDs	69
2	1.00 equiv B_2cat_2, DMAc, blue LEDs	71
3	1.00 equiv B_2pin_2, DMAc, blue LEDs	14
4	**1.25 equiv B_2cat_2, DMAc, blue LEDs**	**91**
5	1.00 equiv B_2cat_2, other solvents (e.g. CH_2Cl_2), blue LEDs	<2
6	1.25 equiv B_2cat_2, DMAc, Dark	36
7	1.25 equiv B_2cat_2, DMAc, Dark, 70 h	63
8	1.00 equiv $B_2(OH)_4$, 1.00 equiv catechol, DMAc, blue LEDs	77

Fig. 1. Reaction development. (**A**) Transition-metal-catalyzed decarbonylative borylation reactions of aryl carboxylic acid derivatives. These reactions proceed through oxidative addition of the metal into the C–X bond, extrusion of CO, σ-bond metathesis with the diboron species, and reductive elimination to form the C–B bond. (**B**) Baran's Ni-catalyzed decarboxylative borylation. (**C**) Optimization of reaction conditions for the visible-light-activated decarboxylative borylation of *N*-hydroxyphthalimide ester **1** in the presence of diboron species, bis(catecholato)diboron (B_2cat_2). The reaction conditions highlighted in yellow (entry 4) are optimal.

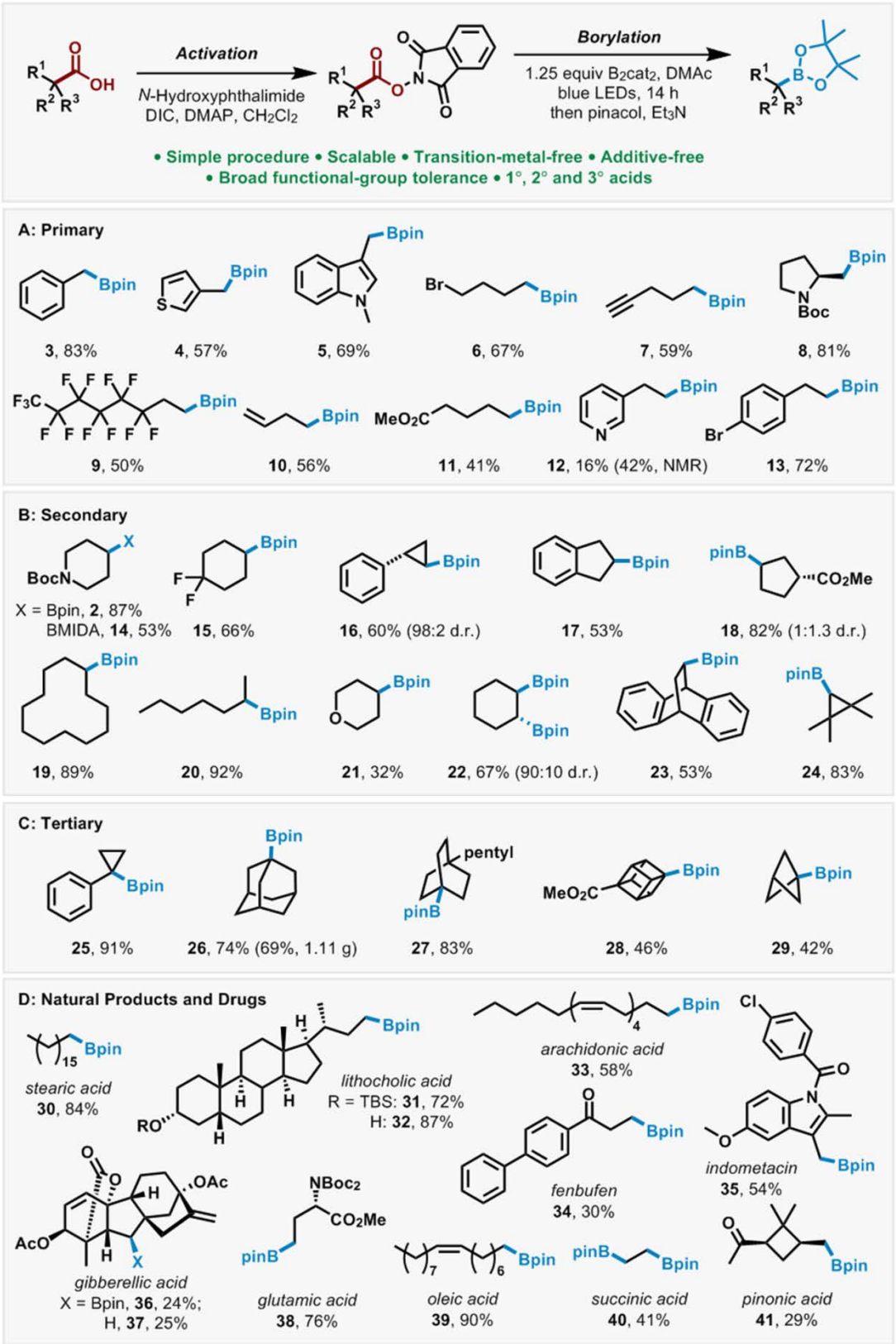


Fig. 2. Exploration of substrate scope. Decarboxylative borylation of (**A**) primary, (**B**) secondary, (**C**) tertiary and (**D**) drug and natural-product-derived *N*-hydroxyphthalimide esters.

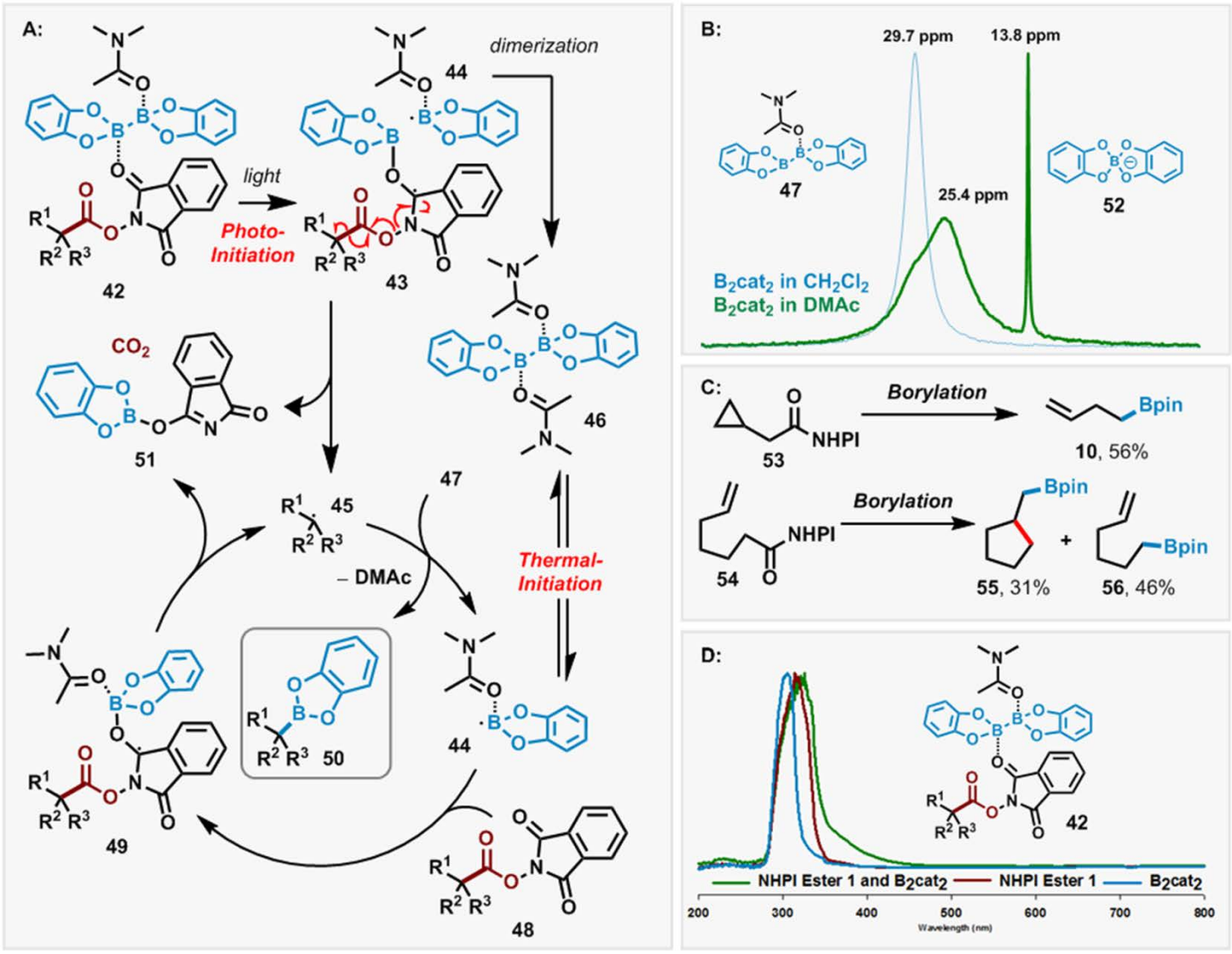


Fig. 3. Mechanistic studies. (**A**) Proposed mechanism for the decarboxylative borylation of *N*-hydroxyphthalimide esters. (**B**) ^{11}B NMR spectra of DMAc and CH_2Cl_2 solutions of B_2cat_2 (**C**) The decarboxylative borylation of cyclopropylmethyl *N*-hydroxyphthalimide ester **53** leads to homoallyl 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/Vis absorption spectra (normalized) of DMAc solutions of *N*-hydroxyphthalimide ester **1** (red trace), B_2cat_2 (blue trace) and a 1:1.25 mixture of ester **1** and B_2cat_2 (green trace).

Photoinduced decarboxylative borylation of carboxylic acids

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