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Exploiting the sp^2 character of bicyclo[1.1.1]pentyl radicals in the transition metal-free multi-component difunctionalization of [1.1.1]propellane

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Abstract

Strained bicyclic substructures are increasingly relevant in medicinal chemistry discovery research because of their role as bioisosteres. Over the last decade, the successful use of bicyclo[1.1.1]pentane (BCP) as a *para*-disubstituted benzene replacement has made it a highly valuable pharmacophore. However, various challenges, including limited and lengthy access to useful BCP building blocks, are hampering early discovery research. Herein we report a single-step, transition metal-free, multi-component approach to synthetically versatile BCP boronates. Radicals derived from commonly available carboxylic acids and organohalides perform additions onto [1.1.1]propellane to afford BCP radicals, which then engage in polarity-matched borylation. A wide array of alkyl-, aryl-, and alkenyl-functionalized BCP boronates were easily prepared. Late-stage functionalization performed on natural products and approved drugs proceeded with good efficiency to generate the corresponding BCP conjugates. Various photoredox transformations forging C–C and C–N bonds were demonstrated by taking advantage of BCP trifluoroborate salts derived from the BCP boronates.

Editorial Summary:

Methods to access bicyclo[1.1.1]pentane building blocks are limited, with current routes requiring multiple steps. Now, a diverse array of bicyclo[1.1.1]pentane boronates can be accessed via a multi-component reaction in a single step. Alkyl-, aryl- and alkenyl substructures can be installed onto bicyclo[1.1.1]pentane boronates by the use of carboxylic acids and organohalides.

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Author Contributions Statement

W.D., E.Y., L.L. and A.B. performed the laboratory experiments. W.D. and G.A.M conceived the project. W.D., A.J. and G.A.M directed the investigations. W.D., E.Y., L.L. and G.A.M analyzed the experimental data and prepared the manuscript.

Supplementary Information General information, experimental procedures, extended optimizations, synthesis and characterization data, mechanistic studies, discussion, X-ray crystallographic data, references, NMR spectra, Supplementary Scheme S1, Figures S1–16 and Tables S1–13.

Competing Interests Statement

The authors declare no competing interest.

Successful drug discovery efforts rely on potent drugs presenting good activity/affinity toward the target of interest as well as satisfactory ADMET parameters.¹ If unmet, these requirements spell the demise of clinical drug candidates.² Modern medicinal chemistry has embraced the concept of “escaping from flatland” as a powerful tenet to circumvent toxicity and poor pharmacokinetics. To improve the physicochemical properties of drug candidates, practitioners are increasingly turning to bioisostere replacements to increase the proportion of sp³-hybridized carbon centers.^{3–7} Among the more prevalent pharmacophores, *para*-disubstituted aryl rings suffer from undesired metabolism to the corresponding quinones *in vivo*, and additionally such arenes are associated with low solubility in physiological media.⁸ The strategy of increasing three-dimensional space to alleviate these shortcomings has led to the incorporation of cubanes, adamantanes, and bicyclo[1.1.1]pentanes (BCPs), which, among others, have a demonstrated ability to fulfill all the requirements of good bioisosteres of arenes.^{9,10} Indeed, this strategy is becoming increasingly rewarding as demonstrated by a flow of reports, beginning with the seminal work from Pfizer.¹¹ Since this pioneering effort, the number of patents published with BCP-containing drugs has skyrocketed, along with synthetic methods to incorporate this motif into scaffolds of interest using commercial feedstocks (Fig. 1a).

Over the decades since the first synthesis of [1.1.1]propellane by Wiberg,¹² numerous efforts have been devoted to its functionalization by radical and anionic pathways.^{13–15} Although highly useful difunctionalizations of [1.1.1]propellane have been developed, especially in recent years by Knochel,^{16,17} Uchiyama,^{18,19} Anderson,^{20,21} Aggarwal,²² Leonori,²³ MacMillan²⁴ and others,^{25–27} the availability of versatile BCP building blocks that would allow late-stage functionalizations for medicinal chemistry studies remains limited. State-of-the-art appendages to elaborate BCPs include carboxylic acids, iodides, and boronates. Of the three, BCP boronates have proven particularly versatile for their ability to be functionalized in a wide range of bond-forming events.^{19,25,28–33} For example, the bridgehead hydroxy BCP synthesis can currently only be accomplished via BCP boronates. Though endowed with enormous and unique synthetic potential, the challenges of efficient access to BCP boronate derivatives are currently limiting their practicability in medicinal chemistry.

Decarboxylative borylation of BCP carboxylates, pioneered by Aggarwal, is currently the standard,³⁴ but is limited by the lengthy synthesis of BCP carboxylates from [1.1.1]propellane. Furthermore, radical chain borylation using the Suginome borane reported by the Uchiyama group¹⁹ and the stepwise addition-borylation process reported by the Walsh group²⁵ provide direct access to BCP boronic acid pinacol ester (Bpin) in one-pot, but these methods only address the synthesis of specific classes of BCP-Bpins, and the requirement for functional group-limiting organometallic reagents is also non-ideal. Finally, the Qin group came up with a modular access to BCP-Bpin by a cyclization approach,³³ providing a versatile way to access bridge-substituted BCP boronates. However, a platform that allows rapid access to BCP-Bpin while incorporating diverse structural motifs simultaneously onto the BCP substructure is still elusive. Its development would greatly benefit medicinal chemists, facilitating therapeutic discoveries with BCP by adopting this versatile building block.

In recent years, the rapid development of transition metal-free radical borylation, especially using alkyl radicals, has allowed an expansive range of organoboron compounds to be prepared in a facile manner.³⁵ A bifunctional boron reagent is usually used, with one handle functioning as activator of the radical precursor, while the other serves as the radical acceptor for borylation. Generally, trapping of nucleophilic alkyl radicals is accomplished with a (catecholato)boronate (Bcat) acceptor, which is more electron-poor than a Bpin acceptor. Similarly, trapping of the more electrophilic aryl radicals is usually achieved by using Bpin acceptors because they are relatively more electron-rich. We postulated that polarity matching between radicals and boronate acceptors could play an important role in three-component functionalizations of [1.1.1]propellane using organic radical and boronate partners, and that bridgehead BCP radicals, which display partial sp^2 character,³⁶ could be preferentially trapped by a more electron-rich Bpin-type acceptor instead of a Bcat-type acceptor (Fig. 1b).^{37–39} As evidence, computational studies have shown that the kinetic barrier of alkyl radical borylation with a Bpin acceptor is ~15 kcal/mol,³⁸ which is higher than the barrier for addition onto [1.1.1]propellane (11–13 kcal/mol).^{20,21} Thus, we envisioned leveraging this difference in energy barriers to perform radical addition onto [1.1.1]propellane by strain-released C_1 – C_3 bond cleavage to generate a BCP radical, which would then be trapped by a Bpin acceptor. In this manner, BCP-Bpins could be made in the simplest imaginable one-step manner. The generality of this approach was expected to depend largely on the diversity of radical progenitors, and because carboxylic acids (**1**) and organohalides (**2**) are among the most prevalent building blocks, we reasoned that they would allow access to the broadest range of chemical space. Herein, we report a general approach to substituted BCP-Bpins in a single step using [1.1.1]propellane and two different Bpin acceptors in which redox active esters (RAEs)^{40,41} derived from carboxylic acids or organohalides serve as radical precursors in conjunctive C–C/C–B couplings featuring easy setup, mild conditions, and broad scope (Fig. 1c).

Results and discussion

Visible-light mediated difunctionalization of [1.1.1]propellane with redox-active ester.

To realize the desired transformations, the reactivity of different alkyl radicals with a Bpin acceptor was first examined by competition experiments (Fig. 2). Five alkyl radicals derived from **1a–e** were reacted competitively with the BCP radical from **1f** together with bis(pinacolato)diboron (B_2pin_2) **3a**.⁴² For alkyl radicals derived from sp^3 -hybridized precursors, only primary alkyl radical **1c** shows competitive reactivity to form alkyl-Bpin product.⁴³ We reasoned that the higher inherent reactivity of primary radicals, as well as their minimal steric footprint, make them more favorable partners in this borylation event in comparison with the more stabilized radicals from **1a** and **1b**. Interestingly, the degree of angle strain was found to correlate positively with the Bpin product formation. Cyclopropyl (**1d**) radical shows similar reactivity to BCP radicals, giving equal formation of alkyl-Bpin product, while the highly distorted cubyl radical (**1e**) outcompeted BCP radical, forming predominantly cubyl-Bpin. Additionally, the degree of s character was also found to correlate positively with the borylation yield when using B_2pin_2 **3a** (See Supplementary Section 8.1 for details). These results indicate that a polarity match between sp^2 -like alkyl radicals and Bpin acceptors allows efficient borylation. Moreover, this implies that B_2pin_2

3a can serve as a less expensive and more robust surrogate for borylation of sp^2 -like alkyl radicals in place of B_2cat_2 .

Encouraged by this promising reactivity pattern, we explored the possibility of achieving a multi-component reaction forging a C–C and C–B bond in a single operation using [1.1.1]propellane as a linchpin (Table 1). Preliminary studies were carried out with RAE **1b** as the radical precursor, [1.1.1]propellane as the BCP precursor, and B_2pin_2 **3a** as radical acceptor as well as the activator for the RAE. The multicomponent reaction performed with **1b** (1 equiv.), [1.1.1]propellane (1.5 equiv.), and **3a** (3 equiv.) in DMA (0.1 M) under irradiation of a 52 W Kessil 390 nm LED lamp provided the desired three-component product in 89% yield (entry 1). Furthermore, **3a** is not the only acceptor capable of executing this transformation, as BCP boronic acid can be made in the same manner simply by using tetrahydroxydiboron [$B_2(OH)_4$] as the acceptor (entry 2). An attempt to improve the yield of the latter by increasing the loading of $B_2(OH)_4$ results in more direct alkyl-borylation product and a lower yield of the desired product (Supplementary Table S1). Not surprisingly, B_2cat_2 , a reactive alkyl radical acceptor, exhibits undesired chemoselectivity, with the two-component alkyl-borylation being the dominant reaction (entry 3). Lowering the loading of **3a** to 1.2 equivalents still allows good reactivity (entry 4). A non-amide type solvent was also suitable for the process, providing a slightly diminished yield, indicating the reaction is not mediated by DMA (entry 5).³⁴ Moreover, the poor reactivity under 456 nm light irradiation (entry 6) and the fact that the reaction does not yield any product under thermal conditions in the absence of light (entry 7) indicates the importance of lower wavelength (390 nm) irradiation.

After demonstrating the feasibility of the process, we next began to examine the scope of this transformation (Table 1). A wide variety of alkyl radicals derived from RAEs can be incorporated despite their dramatically different electrophilicities and steric encumbrances. Unactivated primary alkyl radicals bearing various functional groups afforded the desired BCP-Bpins in good to excellent yields (**4a–e**). Notably, **4c** and **4d**, derived from aspartic acid and glutamic acid, serve as unnatural amino acids by simple modifications. An alkyl bromide handle is also tolerated, thus enabling further modification by substitution (**4e**). Activated α -thioxy- (**4f**) and benzylic radicals (**4g**, **4h**) also delivered BCP boronates in moderate to good yields. Secondary radicals proved to be highly efficient (**4i–p**). Notably, nucleophilic radicals, which are under-exploited in reactions with [1.1.1]propellane, were converted to the desired products in good yields (**4l–p**), demonstrating the generality of this method. Also of note, the reaction is scalable without significant loss of efficiency (**4k**). Somewhat surprisingly, the use of more sterically hindered tertiary radicals did not lead to a drop in yields (**4q–x**), even though the formation of vicinal quaternary centers is challenging. Radicals with significant sp^2 character (**4u**, **4v**) and electronically similar BCP radicals (**4w**) maintained good chemoselectivity. Notably, the radical precursor leading to **4x**, which has low reactivity as a result of stabilization by a captodative effect, can be trapped by [1.1.1]propellane to deliver the corresponding product, showing the strong thermodynamic driving force accompanying the strain-release effect. Beyond alkyl radicals, an electron-deficient hetaryl radical was also found to be amenable as a result of fast decarboxylation (**4x**). To demonstrate the robustness of this method, various carboxylate-containing natural

products and drug scaffolds were incorporated, and the results show no significant loss of efficiency (**4ad-an**) (Fig. 3c). Unsurprisingly, the radical derived from citronellic acid underwent 5-exo-trig cyclization to give product **4ad**.²¹

Because boronic acids are more reactive than boronate esters in select transformations, thus providing beneficial advantages for further functionalization, several BCP boronic acids were accessed directly in the same manner using $B_2(OH)_4$ as the borylating agent (Table 1). Generally, the BCP boronic acids were synthesized in comparable yields to those of the boronate esters (**4k**, **4t**, **4ae**, **4af**, **4ai-al**), but tertiary radicals tended to perform better by using $B_2(OH)_4$ (**4r**, **4am**). Moreover, ortho/meta mimics (**4z-4ac**) can also be synthesized using this method by using C_2 -substituted [1.1.1]propellane, albeit the less hindered $B_2(OH)_4$ is needed in place of B_2pin_2 because of steric effects exerted by the C_2 -substituent. Furthermore, as we realized the synthesis of RAE requires an extra step from the widely available carboxylic acid, we showcased a telescoped process by generating RAEs *in situ*, then demonstrated that the same reaction can be carried out with increased efficiency (**4k**, **4ao**, **4ap**) (Table 2). Remarkably, the *in situ* transformation is not only applicable in simple carboxylic acids, but more complex structures bearing multiple different functional groups as well (**4aq**, **4ar**).

Difunctionalization of [1.1.1]propellane with organohalides.

Having established a method utilizing B_2pin_2 **3a** and taking advantage of a boryl radical as a reductant, we sought to leverage complementary modes of activation that would engage other types of radical precursors to expand the BCP-Bpin library. Organohalides have been demonstrated to react with [1.1.1]propellane to afford BCP halides under thermal and light activation *via* an ATRA mechanism.^{20,21} Given the success realized with the RAE radical precursors, we hypothesized that we could also take advantage of abundant organohalides to accomplish BCP-Bpin synthesis. Suginome borane **3b** (Table 3), an unsymmetrical reagent with silyl- and boryl handles, is an under-explored reagent in radical processes. The Uchiyama group has shown the possibility of using **3b** to undergo Si–B bond homolytic cleavage to generate a silyl radical. This provided the inspiration to leverage the silyl radical as a halogen atom transfer (XAT) reagent to activate organohalides, while using its Bpin handle as a BCP radical acceptor.¹⁹ This unexplored mode of reactivity was expected to allow advantage to be taken of abundant organohalides as radical precursors to expand the chemical space of BCP-Bpin substructures (Table 3). Based on our established experience, we quickly discovered that the target product could be accessed in 66% yield using alkyl bromide **2a** (1 equiv.) as a radical precursor, [1.1.1]propellane as a BCP linchpin, with Suginome borane **3b** acting as an activator and BCP radical acceptor (entry 1). Similarly, alkyl iodide **2b** is also compatible and gives a similar yield (entry 2). Control studies using B_2pin_2 **3a** give only a trace amount of product (entry 3), showing the necessity of having a strong silyl XAT reagent. The Bpin radical appears to be too sluggish to undergo XAT or single electron transfer (SET) with alkyl halides to generate radicals. The inclusion of a base (K_3PO_4) to neutralize the acidic byproducts is crucial for this reaction (entry 4). Irradiation at 390 nm works better than 456 nm because of the poor absorption of alkyl halides in the blue region (entry 5). Interestingly, the reaction carried out without light gives a detectable

amount of product, which is likely induced by trace amounts of O₂ in the reaction (entry 6).¹⁹

With suitable conditions in hand, we then turned to investigate the scope of this transformation with various organohalides (Table 3). The first class of substrates we examined was alkyl halides, and overall, many types of alkyl halides were found to be compatible in this reaction. Notably, an electron-deficient alkyl radical with an electron-withdrawing group alpha to the radical gives higher yields by using an organobromide than using the carboxylic acid (**4u**), showing that the two methods are complementary. Also, a chloride handle (**5a**) and hydroxy group (**5d**) are tolerated, enabling the potential for post-functionalizations. The reaction was shown to be scalable by carrying out the gram-scale synthesis of **4k** using an alkyl iodide.

The abundance of structurally diverse aryl- and heteroaryl halides provided another compelling rationale for using halides as radical precursors, allowing installation of (het)aryl substructures onto the BCP scaffold that were unsuccessful previously using (het)aryl RAEs owing to the challenging decarboxylation. Fortunately, various aryl iodides bearing electronically diverse *para* substituents were found to react under suitable conditions (**5k-s**). Moreover, aryl groups bearing many functionalizable handles can be used in the transformation (**5p**, **5q**, **5u**, **5w**). The ability to incorporate multiple practical subunits on the various substrates in the reactions will facilitate customizable post-functionalizations on the BCP-Bpin platform. Furthermore, *meta* (**5t**), *ortho* (**5u**), and multi-substituted aryl units (**5w**, **5x**) do not lead to drops in efficiency. Next, we moved on to evaluate the scope of heteroaryl iodides, which are of immense interest in medicinal chemistry. Both electron-deficient (**4y**, **5y-aa**) as well as electron-rich heteroaryls (**5ab-ae**) delivered the corresponding BCP-Bpins. Notably, 1-benzothiazole and pyrazole have proven challenging to install onto BCP using cross-coupling strategies.⁴⁴ Although **5ad** and **5ae** were obtained in moderate yields, access to such substructures demonstrates that the method provides a complementary pathway to high-value targets. Somewhat unusually, an alkenyl fragment could also be incorporated into the BCP substructure in modest yield (**5af**).

Photoredox functionalization of the boron handles.

The applicability of BCP boronates in subsequent functionalization has been demonstrated by many pioneering works. Numerous transformations have been shown to be successful on BCP boronates, including oxidation to alcohols, Suzuki-Miyaura coupling, and more.^{19,25,28,33} Thus, after exploiting the potential of the multicomponent reaction to access a wide array of BCP boronates, we sought to demonstrate the synthetic utility of the boron handle by taking advantage of BCP radicals generated from the boronate precursors. Our group is actively engaged in photoredox-mediated transformations using organotrifluoroborate salts, and the lack of reports on using BCP-containing boron compounds in photoredox transformations prompted us to pursue their applications using light-mediated reactions (Fig. 3). To showcase the feasibility of post-functionalizations, we first developed a straightforward process accessing BCP potassium trifluoroborate (BF₃K) salt **6** in a one-pot procedure without the need of chromatography. The process can be run on gram-scale, demonstrating its practicality. Cyclic voltammetry was conducted on **6**,

revealing that even though a high *s* character is imparted by the strained BCP scaffold, **6** has a favorably low oxidation potential ($E_{1/2} = +1.36$ V vs SCE) that is similar to that of sp^3 tertiary alkyl BF_3Ks ($E_{1/2} = +1.26$ V vs SCE)⁴⁵ and much lower than aryl BF_3Ks ($E_{1/2} = +1.84$ V vs SCE),⁴⁶ revealing the alkyl-like properties of the BCP substructure. The Anderson group recently reported a diverse array of BCP radical additions to vinylic acceptors by silyl radical-mediated XAT on BCP halides,⁴⁷ and we envisioned BCP radicals generated under reductive quenching of a photocatalyst from **6** could also perform additions to electron-deficient alkenes (**7**, **8**). The BCP radical was shown to undergo a smooth polarity-matched addition onto acrylonitrile (i) and dehydroalanine (ii). With the success of implementing these two net-neutral transformations with **6**, the feasibility of a late-stage Minisci reaction, a net-oxidative transformation, was investigated.⁴⁸ Importantly, the BCP radical was found to be modestly effective in this net-oxidative event, providing the Minisci product **9** in a 30% unoptimized yield (iii). Next, we moved on to a metal catalyzed transformation by investigating the feasibility of a photoredox Chan-Lam C–N coupling via a dual catalytic manifold. The Chan-Lam coupling is one of the more important transformations for organoboron compounds, and the C–N linkage is also a high-value bond connection in medicinal chemistry. However, engaging alkylboron compounds in Chan-Lam coupling has been challenging, with only sporadic reports and limited scope.^{30,49} We hypothesized that one of the challenges for alkylboron substrates in these reactions is the difficult two-electron transmetalation to Cu(II), which is often resolved by elevating the reaction temperature.^{50,51} Thus, we surmised we could leverage alkyl radical generation to perform a single-electron transmetalation to Cu(II), which would bypass the sluggish, more traditional two-electron transmetalation. Inspired by the work of the MacMillan group,⁵² we quickly identified suitable conditions for this photoredox-type Chan-Lam coupling, leading to a high yield of the desired product (**10**) (iv). Finally, the BCP trifluoroborate formed in a conjunctive, multicomponent transformation from readily available materials was subjected to another multicomponent reaction involving addition of the BCP radical to (vinyl)Bpin to form an α -boryl-stabilized radical. The displaced radical generated in this process was subsequently funneled into a Ni-catalyzed Csp^2 – Csp^3 cross-coupling reaction with an aryl halide, providing the desired product **11** in 41% yield (v).⁵³ The two-step process (1,3-difunctionalization of propellane followed by difunctionalization of the vinylboronate) thus dramatically increases molecular complexity by bringing together four very unique components in two simple transformations, with enormous flexibility for even further elaboration as a result of incorporating diverse functional groups from these subunits.

Mechanistic investigations of radical nature and origin of selectivity.

We next turned our attention to investigate the mechanism of this transformation, hoping to shed light on the radical intermediacy under light irradiation and the origin of the selectivity of this well-orchestrated, multi-component transformation. First, TEMPO trapping experiments were performed with both reactions (Fig. 4a). None of the reactions afforded the BCP-Bpin product, but rather the TEMPO adducts **12**, which were derived from the radical precursors. Next, a RAE **11**-derived radical clock gives only ring-opened product **13**, while 5-hexenyl radical from alkyl halide **2c** undergoes 5-exo-trig cyclization to give ring-closing product **15** exclusively (Fig. 4b). Therefore, the radical nature of both

reactions with RAE and organohalides were confirmed. Further, elaborations on different radical clocks showed that the time-scale for alkyl radical addition onto [1.1.1]propellane is significantly slower than addition onto electron-deficient alkenes, which is similar to what has been observed in alkyl-iodination of [1.1.1]propellane²¹ (Supplementary Section 8.3).

With the radical nature of the reactions in mind, the genesis of the radicals was investigated. The involvement of O₂ in radical generation was first ruled out by carefully degassing the reactions before subjecting the reaction to light irradiation – the results show no loss in reactivity by rigorous exclusion of O₂. Thermal activation was also ruled out, because little to no product was observed in the absence of light (Supplementary Tables S1 & S3). UV-Vis studies suggest the only absorbing species are the radical precursors, and there is no bathochromic shift evident for electron donor-acceptor (EDA) complex formation, indicating that radical generation is accomplished by direct excitation of radical precursors (Fig. 4c). The above results support the formation of radicals via light-irradiation. Although numerous studies have demonstrated that the unsubstituted BCP radical is relatively slow to add to [1.1.1]propellane to form [2]staffanes,^{19,20,23} there is a lack of evidence on how the through-space interaction of substituted BCPs affects the staffane formation. Intriguingly, we observed that the C₁-C₃ field effect has a dramatic impact on [2]staffane formation (Fig. 4d). Two electronically different BCP radicals with ester (**1f**) and hydrogen (**1h**) substituents on C₁ were generated from their corresponding RAEs. When the BCP radical bearing an electron-withdrawing group (ester) on C₁ was subjected to the standard conditions, we observed a mixture of BCP monomer (**17**) and [2]staffane oligomer (**4w**), whereas BCP radicals with a more electron-neutral substituent only affords monomer **18**. This explains the observation that multi-component reactions with alkyl radicals always afford BCP-Bpin exclusively, while engaging electrophilic aryl- as well as alkenyl radicals results in formation of a small amount (<20%) of [2]staffane byproducts. We reason that the origin of the phenomenon is variation of the electrophilicity and geometry in the BCP radicals. C₁ substituents are known to have a significant impact on the BCP electrophilicity and geometry.²³ The increase of electrophilicity favors the addition onto another [1.1.1]propellane instead of B₂pin₂ because of the electron-rich nature of [1.1.1]propellane, which causes the formation of [2]staffane product. Interestingly, kinetic and NMR studies suggest that phthalimide, a by-product from the RAE, serves as a Lewis base to stabilize the boryl radical, while control studies exclude the involvement of DMA-boryl radical in the chain propagation (See Supplementary Section 8.6 and 8.7 for details). Finally, we conducted quantum yield (Φ) studies with RAE and organohalide systems, and both quantum yields were measured to be larger than 1, indicating chain mechanisms in both cases (See Supplementary Section 8.8).

Based on the combined evidence in hand and previous literature, a mechanism that accounts for this multi-component borylation is proposed (Fig. 4e). In the initiation phase, the RAE is photoexcited by 390 nm irradiation, which then becomes a strong oxidant ($E_{1/2} = +1.6$ V)⁵⁴ that can undergo SET with phthalimide-B₂pin₂ adduct, generating radical **20**. Similarly, organohalide can be excited by 390 nm irradiation, leading to homolysis with generation of **20**.^{39,55} Intermediate **20** is then funneled into the propagation phase by first being intercepted by [1.1.1]propellane (step i). The highly exothermic strain release leads to BCP

radical **21**, which then engages in borylation with boryl acceptor $B_2pin_2/Me_2PhSi-Bpin$ (step ii/ii') to form a radical complex **22/22'**. The B-B/Si-B bond is then cleaved to form BCP boronates (step iii/iii') with the corresponding boryl/silyl radical **23/23'** activating another radical precursor by the corresponding SET/XAT event to sustain the chain propagation (step iv/iv').

Conclusion

In summary, the transition metal-free, multi-component BCP-Bpin synthesis reported herein enables rapid access to a diverse array of BCP building blocks. The radical approaches allow incorporation of two widely available materials, carboxylic acids and organohalides, ensuring access to a broad expanse of novel chemical space. The excellent chemoselectivity enables various motifs, including α -heteroalkyls, strained alkyls, alkenyl- and (het)aryl groups, to be installed easily on the BCP scaffolds. The usefulness of this method is further boosted by direct access to stable BCP BF_3K salts and the ability to engage them in photoredox-mediated transformations to build valuable C–C and C–N linkages. We anticipate more functional groups can be introduced into this new platform for BCP boron compound synthesis, and alternative radical acceptors could replace the boron acceptors to generate other BCP motifs, further leveraging the sp^2 character of BCP radicals.

Methods

General Procedure for the preparation of [1.1.1]propellane-diethyl ether solution.

To an appropriately-sized round bottom flask is added 1,1-dibromo-2,2-bis(chloromethyl)cyclopropane (5.0 g, 16.8 mmol) and Et_2O (10–12 mL) under an inert atmosphere. Once the reactants are dissolved, the reaction is cooled to $-78\text{ }^\circ\text{C}$ in a Dry Ice-acetone bath. The reaction turns into a slurry at $-78\text{ }^\circ\text{C}$. To the light brown slurry is added PhLi (20 mL, 38.0 mmol, 2.3 equiv., 1.9 M solution in *n*-Bu₂O) dropwise over 10 to 15 min. The reaction is then stirred at $-78\text{ }^\circ\text{C}$ for another 30 min and then is allowed to warm to $0\text{ }^\circ\text{C}$ using an ice-water bath. After 2 h, the reaction turns into a dark-brown slurry, which indicates the reaction is finished. The product propellane is co-distilled with Et_2O by house vacuum (ca. 4 Torr) as a clear, colorless solution. The receiving flask was submerged in a $-78\text{ }^\circ\text{C}$ bath or liquid nitrogen bath. The concentration of the [1.1.1]propellane-diethyl ether solution is determined by ¹H NMR using 100 μL of the solution and 0.100 mmol of 1,3,5-trimethoxybenzene as an internal standard in $CDCl_3$.

General procedure for the preparation of BCP Bpin with redox-active esters and B_2pin_2 .

To an 8 mL reaction vial equipped with a stirrer bar is added redox-active ester (1 equiv.) and dry B_2pin_2 (3 equiv.). The reaction vessel is sealed with a cap containing a TFE-lined silicone septum and then is evacuated and backfilled with argon three times. When done, degassed DMA (0.1 M) is added. Next, freshly prepared and titrated [1.1.1]propellane (1.5–3 equiv., 0.8–1.3 M solution in Et_2O) is then added, and the vial is quickly sealed with Parafilm®. The reaction mixture is then irradiated under vigorous stirring at 390 nm irradiation using a 52 W Kessil® PR160L-390 nm lamp at 1 inch distance for 16 h. Room temperature is maintained by the use of two fans. After 16 h, the deep red reaction mixture

is partitioned between Et₂O and saturated aqueous NH₄Cl. The organic layer is washed with brine twice, dried (MgSO₄), filtered, and then concentrated under reduced pressure. The product is purified by flash column chromatography.

General procedure for the preparation of BCP Bpin with organohalides.

To an 8 mL reaction vial equipped with a stirrer bar is added organohalide (1 equiv.) and K₃PO₄ (0.5 equiv.). The vial is then transferred to a nitrogen-filled glovebox. Me₂PhSi-Bpin (2 equiv.) is added, and then the vial is sealed with a cap containing a TFE-lined silicone septum and transferred out of the glovebox. MeOH (0.1 M) is added. Next, [1.1.1]propellane (1.5 – 3 equiv., 0.8 – 1.3 M solution in Et₂O) is added, and the vial is quickly sealed with Parafilm®. The reaction mixture is then irradiated under vigorous stirring at 390 nm irradiation using a 52 W Kessil® PR160L-390 nm lamp at 1 inch distance for 16 h. Room temperature is maintained by the use of two fans. After 16 h, the crude material is passed through a pad of Celite® and eluted with another 10 mL of acetone. The filtrate is concentrated under reduced pressure and purified by flash column chromatography.

Data Availability

All data supporting the findings of this study are available in this article and its Supplementary Information. Crystallographic data for the structure **4ar** reported in this Article have been deposited at the Cambridge Crystallographic Data Centre, under the deposition number CCDC 2105768. Copies of the data can be obtained free of charge via <https://www.ccdc.cam.ac.uk/structures/>.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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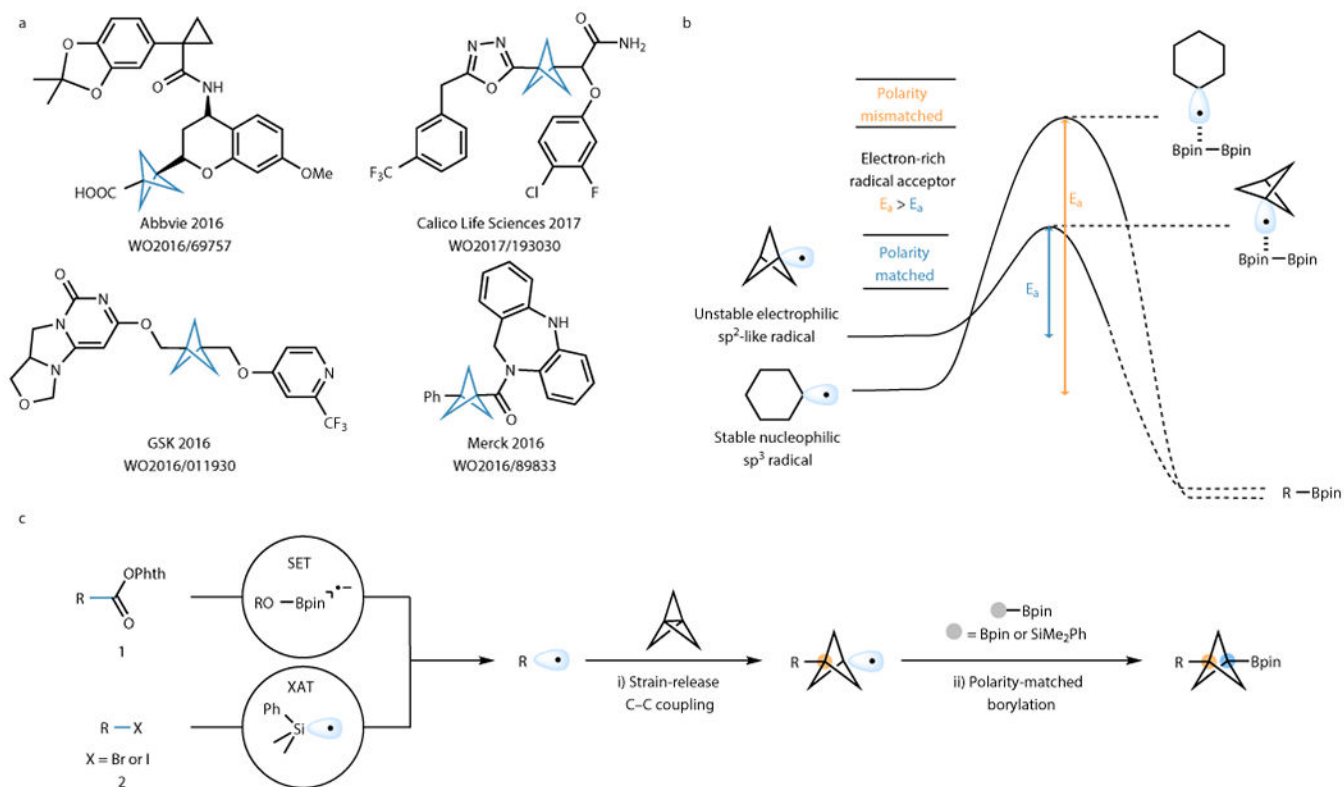


Figure 1. One-step, multi-component access to diverse BCP boronates.

a. Representative BCP-containing drug candidates reported in recent years. **b.** Proposed kinetic barriers: polarity-matching requirement leads to favorable reactivity between strained sp^2 -like alkyl radicals with Bpin acceptors. **c.** This work: Leveraging lower kinetic barrier of radical addition to [1.1.1]propellane and favorable borylation reactivity between BCP radicals and Bpin acceptors to accomplish a simple transition metal-free multi-component reaction to afford the synthetically useful BCP boronates.

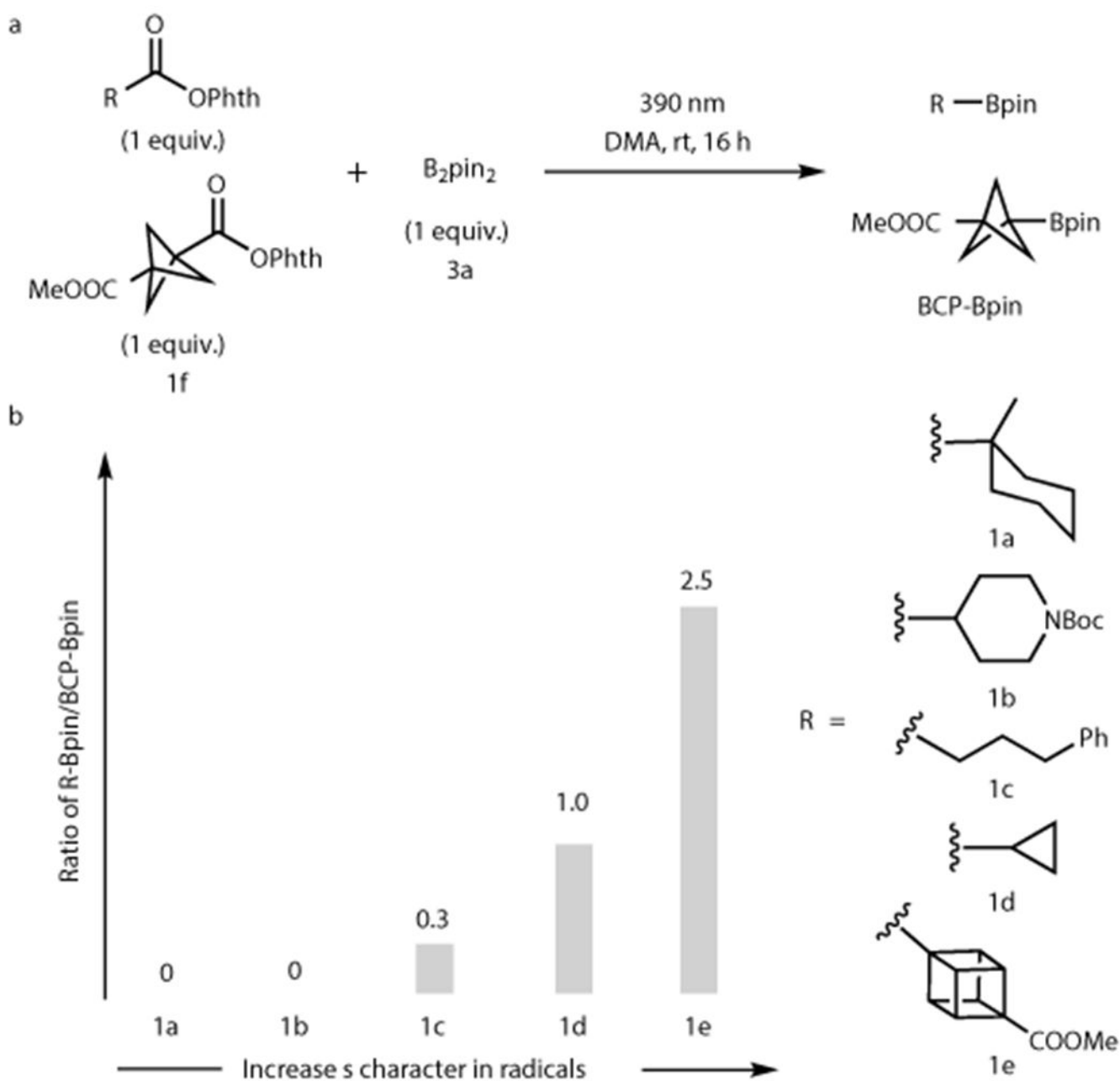


Figure 2. Strain-induced increase in *s* character in alkyl radicals leads to favorable borylations in competition experiments.

A positive correlation between the degree radical *s* character and borylation efficiency is demonstrated by competition experiments between radicals with varies *s* characters. See supplementary information section 8.1 for more details and discussion. **a.** Competition experiments were performed between BCP redox-active ester **1f** and other alkyl bearing redox-active esters with B_2pin_2 in DMA under 390 nm light irradiation. **b.** Results indicate that higher *s* character in the radical leads to more favorable borylation with B_2pin_2 .

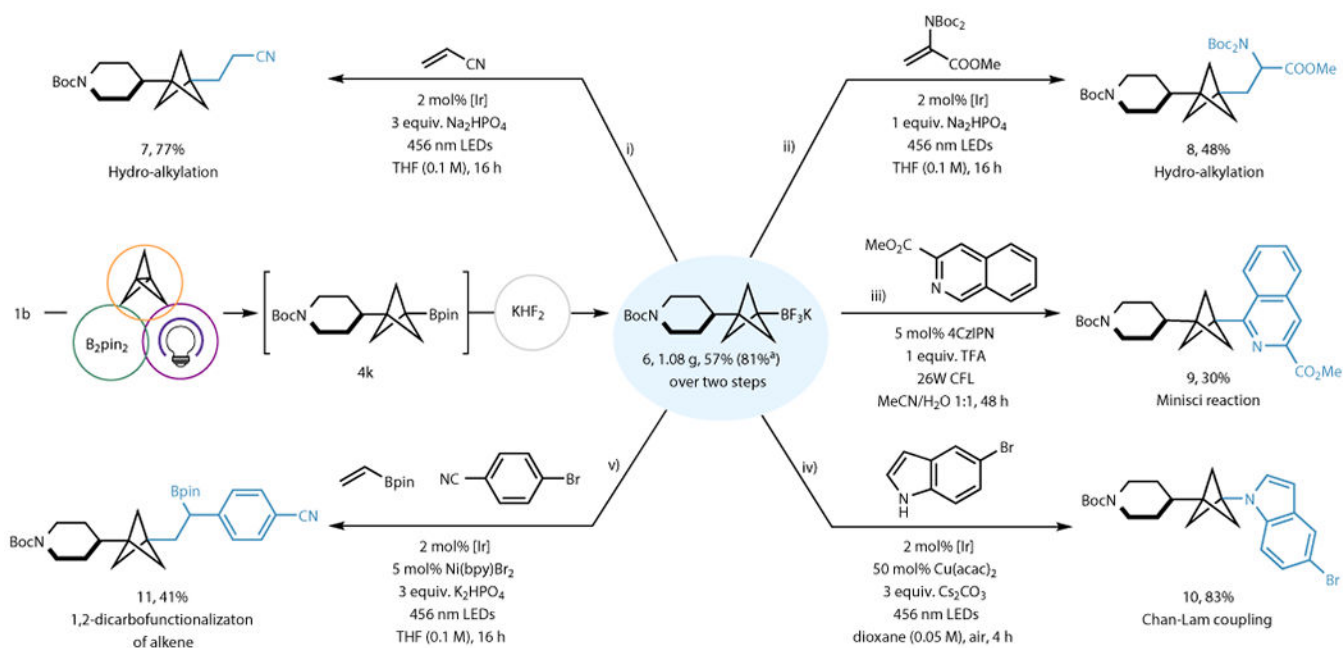


Figure 3. One-pot synthesis of BCP-BF₃K **6 and its diversification by photoredox-mediated processes.**

BCP trifluoroborate **6** can be synthesized in a one-pot manner from RAE without the need of column chromatography. The synthetic applications of **6** is demonstrated by several photoredox transformation: (i) hydroalkylation with acrylonitrile; (ii) hydroalkylation with dehydroalanine to yield an amino acid derivative; (iii) Minisci heteroarylation; (iv) single-electron mediated Chan-Lam C–N coupling; (v) 1,2-dicarbofunctionalization of vinyl boronic pinacol ester. See supplementary information section 7 for details on reaction conditions. [Ir] = Ir[dF(CF₃)ppy]₂(bpy)PF₆. ^aYield by using isolated **4k**.

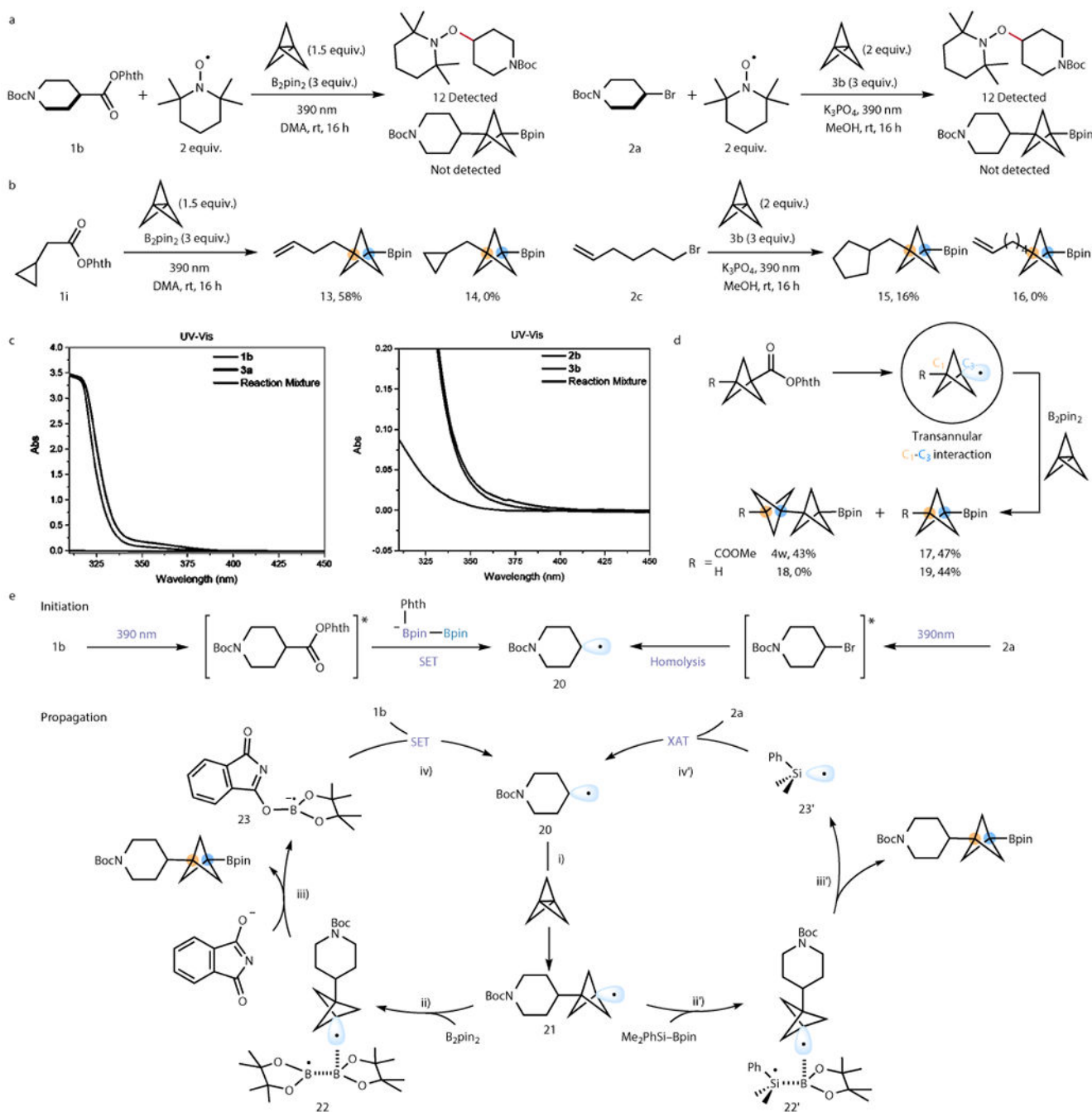


Figure 4. Mechanistic investigations into the radical intermediacy and origin of chemoselectivity. **a.** Addition of TEMPO completely shut down product formation, and TEMPO-adducts were formed. **b.** Radical clock experiments confirmed the radical nature of the two reactions and suggested slow addition between radical and [1.1.1]propellane. **c.** UV-vis studies indicate that at 390 nm, radical precursors are the only absorbing species, and there is no noticeable formation of an EDA complex. Thus, initiation is carried out by excitation of the RAE/organohalides. **d.** Electronic effect on BCP radical borylation vs. oligomerization: significant through-space effect on the BCP radical such that electron-rich BCP radical tends to undergo

borylation whereas electron-poor BCP tends to oligomerize to form [2]staffane as the major product. **e.** Proposed mechanism based on literature and observations. The chain initiation involves light-mediated excitation of the radical precursor. Chain propagation involves four steps: i) radical addition to [1.1.1]propellane; ii) and ii') the BCP radical formed coordinates to the Bpin acceptor; iii) and iii') B–B/Si–B bond undergoes homolytic cleavage to generate BCP-Bpin; iv) and iv') B/Si radical from the bond cleavage event initiates the next chain cycle.

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Table 1.

BCP Bpin and boronic acid synthesis by utilization of carboxylic acids as radical precursors

Entry	Deviation from standard condition	Yield(%)	Primary radical	Tertiary radical	Aryl radical
1	None	89			
2	B ₂ (OH) ₄ (1.2 equiv.) instead of B ₂ pin ₂	64	4a , 40%	4b , 46%	4c , 72%
3	B ₂ cat ₂ (1.2 equiv.) instead of B ₂ pin ₂	10			4d , 48%
4	1.2 equiv. of B ₂ pin ₂	60			
5	MeCN (0.1 M) instead of DMA	59			
6	34 W 456 nm LED as light source	30	4e , 76%	4f , 60%	4g , 45% ^b 4h , 36% ^b
7	No light (rt and 60 °C)	0			

Secondary radical	Tertiary radical	Aryl radical
4i , 58%	4j , 52%	4k , 89% (64% ^a) [642 mg, 64%]
4l , 63%	4m , 58% > 20:1 d.r.	4n , 67%
4o , 61%	4p , 84%	4q , 71%
4r , 52(68% ^a)	4s , 60%	4t , 51% ^a
4u , 41% ^b	4v , 42% ^b	4w , 43% ^{b,c}
4x , 41% ^b	4y , 42% ^b (62% ^{b,d})	

C ₂ -Substituted BCP	Late-stage drug/natural product modification
4z , 48% ^e	4ad , 85% 1:1 d.r. from Citronellonic acid
4aa , 38% ^e	4ae , 43% (27% ^a) from Mycophenolic acid
4ab , 38% ^e	4af , 71% (55% ^a) from Fenbufen
4ac , 23% ^e	4ag , 41% ^b from Indomethacin
	4ah , 48% ^b from 2,4-D
	4ai , 34% (21% ^a) from Camphanic acid
	4aj , 60% (55% ^a) from Gibberellic acid
	4ak , 60% (58% ^a) from Dehydrocholic acid
	4al , 58% (54% ^a) 2:1:1 d.r. from Glycyrrhetic acid
	4am , 80% (82% ^a) from Gemfibrozil
	4an , 35% ^b from Flurbiprofen

Optimization was performed on 0.3 mmol scale of **1b** (See Supplementary Section 3.1 for details). Standard conditions for the scope study: RAE substrate (0.3 mmol, 1 equiv.), [1.1.1]propellane (0.45 mmol, 1.5 equiv.), B₂pin₂ (0.9 mmol, 3 equiv.), DMA (3 mL, 0.1 M), 16 h irradiation with 52 W 390 nm LEDs. All yields are isolated unless otherwise noted.

^aB₂(OH)₄ (1.2 equiv.) was used, and the yield was calculated by converting to the pinacolboronate by addition of pinacol (See Supplementary Section 4 for details).

^b3 equiv. of propellane were used.

^c1.2 equiv. of B₂pin₂ were used.

^d¹H NMR yield using 1,3,5-trimethoxybenzene as internal standard

^e1.5 equiv. C₂-substituted [1.1.1]propellane and 2 equiv. B₂(OH)₄ was used instead of [1.1.1]propellane and B₂pin₂. Products are racemic. (See Supplementary Section 4 for details).

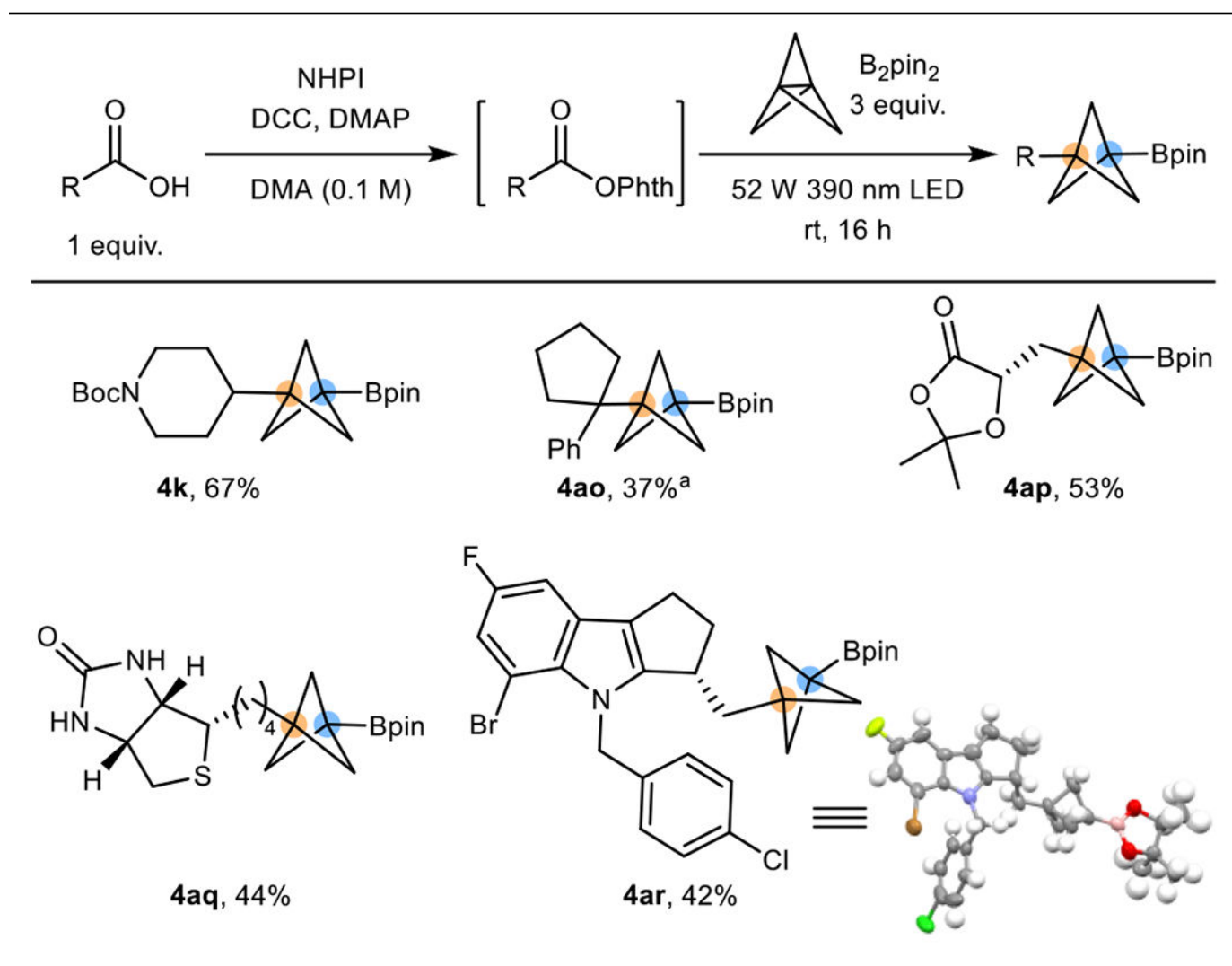
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Table 2.

BCP Bpin synthesis by activating carboxylic acids *in situ*

Standard conditions: alkyl carboxylic acid (0.3 mmol, 1 equiv.), NHPI (0.33 mmol, 1.1 equiv.), DCC (0.33 mmol, 1.1 equiv.), DMAP (0.015 mmol, 5 mol %), DMA (3 mL, 0.1 M), room temperature 4 h. Borylation; then [1.1.1]propellane (0.45 mmol, 1.5 equiv.), B₂pin₂ (0.9 mmol, 3 equiv.), 16 h irradiation with 52 W 390 nm LEDs.

^a 3 equiv. of propellane were used.

Table 3.

XAT mediated BCP boronate synthesis from organohalides

Reaction Scheme			Reaction Conditions					
			K_3PO_4 (0.5 equiv.) 52 W 390 nm LED MeOH (0.1 M), rt, 16 h					
Entry	Deviation from standard condition	Yield/(%)	Alkyl scope					
1	None (X = Br)	66						
2	None (X = I)	72						
3	B ₂ pin ₂ 3a (3 equiv.) instead of 3b	Trace	4k , 52% ^a (65% ^b) [1.24 g, 68% ^b]	4u , 50% ^a	5a , 52% ^b	5b , 46% ^b		
4	No K ₃ PO ₄	Trace						
5	34 W 456 nm LED as light	27						
6	No light (rt and 60 °C)	Trace						
			5c , 42% ^b	5d , 46% ^b	5e , 51% ^b	5f , 34% ^a	5g , 59% ^a > 20:1 d.r.	
							5h , 44% ^a	
							5i , 41% ^b	
							5j , 42% ^a	
			5k , 68% ^{b,d}	5l , 51% ^{b,d}	5m , 53% ^{b,c}	5n , 48% ^{b,c}	5o , 53% ^{b,c} (59% ^{b,c,e})	
			5p , 38% ^{b,c}	5q , 43% ^{b,c}	5r , 42% ^{b,c}	5s , 34% ^{b,c}	5t , 32% ^{b,c}	
			5w , 38% ^{b,c}	5x , 20% ^{b,c,f}				
			5y , 48% ^{b,d}	5z , 43% ^{b,d} (62% ^{b,d,e})				
			5aa , 67% ^{b,d}	5ab , 34% ^{b,c}	5ac , 38% ^{b,c}	5ad , 30% ^{b,c}	5ae , 25% ^{b,c}	
			5af , 32% ^{b,c} 1:1 E/Z					

Optimization was performed using 0.1 mmol scale of **2a** (See Supplementary Section 3.2 for details). Standard conditions for the scope study: organohalide substrate (0.3 mmol, 1 equiv.), [1.1.1]propellane (0.6 mmol, 2.0 equiv.), Me₂PhSi-Bpin (0.6 mmol, 2 equiv.), K₃PO₄ (0.15 mmol, 0.5 equiv.), MeOH (3 mL, 0.1 M), 16 h irradiation with 52 W 390 nm LEDs. All yields are isolated unless otherwise noted.

^aThe organobromide was used.

^bThe organoiodide was used.

^c3 equiv. of propellane were used.

^d1.5 equiv. of propellane were used.

^e¹H NMR yield using 1,3,5-trimethoxybenzene as an internal standard.

^f2:1 MeOH-acetone (0.1 M) mixed solvent was used.