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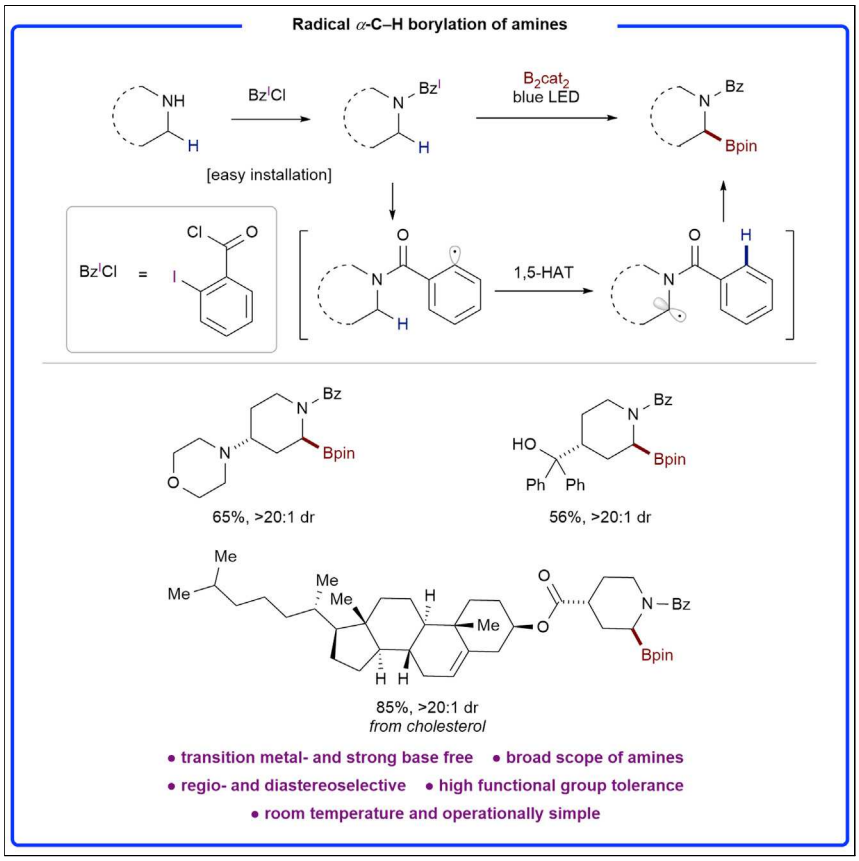
General and selective metal-free radical α-C–H borylation of aliphatic amines



General access to highly valuable α-aminoboronates via late-stage C–H borylation of amines remains a formidable challenge. To this end, a general, mild, and photoinduced transition-metal- and strong-base-free radical borylation method has been developed. This operationally simple method afforded highly regio- and diastereo-selective late-stage α-borylation products with high functional group tolerance.

Sumon Sarkar, Sidhant Wagulde, Xiangqing Jia, Vladimir Gevorgyan

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Highlights

General, mild, transition-metal-free method for α-C(sp^3)–H borylation of amines

Highly regio- and diastereo-selective radical borylation

Operationally simple method with broad scope and high functional group tolerance

Late-stage borylation of complex amines and drugs

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General and selective metal-free radical α-C–H borylation of aliphatic amines

Sumon Sarkar,[1] Sidhant Wagulde,[1] Xiangqing Jia,[1] and Vladimir Gevorgyan[1,2,*]

SUMMARY

Despite recent developments, selective C(sp^3)–H borylation of feedstock amines remains a formidable challenge. Herein, we have developed a general, mild, and photoinduced transition-metal- and strong-base-free method for α-C(sp^3)–H borylation of amines. This protocol features a regioselective 1,5-hydrogen atom transfer process to access key α-aminoalkyl radical intermediate using commercially available easy-to-install/remove iodobenzoyl radical translocating group. Remarkably, this general, efficient, and operationally simple method allows activation of primary and secondary α-C–H sites of a broad range of acyclic and cyclic amines toward highly regio- and diastereo-selective syntheses of valuable α-aminoboronates. Utility of this protocol has been demonstrated by its employment in late-stage borylation of structurally complex amines and formal C–H arylation reaction of amines. Thus, it is expected that this operationally simple, general, and practical method will find broad application in organic synthesis and drug discovery.

INTRODUCTION

α-Aminoboronic acids enjoy numerous applications in organic synthesis,[1] material science,[2] and drug discovery[3] (Figure 1). Traditionally, aminoboronate synthesis relies on pre-functionalized starting materials or multistep routes.[4–8] Undeniably, more attractive approach would be α-C–H borylation of feedstock amines; however, this remains a formidable challenge.[9–12] Despite recent developments,[13–25] examples of direct α-C–H borylation of amines are extremely scarce in literature and mostly provide products of terminal- or β-site borylation.[16,20,26] Existing directed methods typically include transition-metal (TM)-catalyzed guided C–H activation or deprotonation under strongly basic conditions; thus, both cases involve carbometallation intermediates (**A**, **B**; Scheme 1A).[27–35] TM-catalyzed thermal conditions often employ amines as a reagent or difficult-to-install/remove directing groups (DG), such as 2-pyridyl group, on amines. Moreover, positions of functionalization are often limited to terminal or activated secondary sites.[33,34] The latter approach requires use of strong base for the deprotonation step and offers α-*N*-borylation only at tertiary benzylic sites.[30] Thus, a general C–H borylation method operating under mild conditions is highly desirable. Herein, we report TM- and strong-base-free, mild C(sp^3)–H borylation protocol of feedstock amines under operationally simple, photoinduced conditions operating through radical mechanism (via intermediate **C**).

In recent years, metal-free borylation reactions using diboron reagents as radical trapping agents have gained increasing interest in organic synthesis.[36–51] Thus, we hypothesized that if α-aminoalkyl radical could be accessed via selective hydrogen atom transfer (HAT),[52–60] it could be trapped with diboron reagent to afford desired

THE BIGGER PICTURE

Boronic acid is a functional group of paramount importance in organic synthesis, material science, and drug discovery due to various cross-coupling strategies employing boron compounds to construct complex structures. Moreover, α-aminoboronic acid motif, a bioisostere of amino acid, enjoys increasing abundance in drugs and drug candidates. However, synthesis of many such compounds remain challenging. Undoubtedly, the most straightforward approach is the late-stage C–H borylation of feedstock amines and bioactive molecules, which will also enable rapid derivatization of pharmaceutical candidates. Herein, we report a general, easy-to-use, mild, metal-free method for α-C–H borylations of amines that is highly regio- and diastereoselective and broadly applicable in late-stage borylation of complex amine-containing molecules.

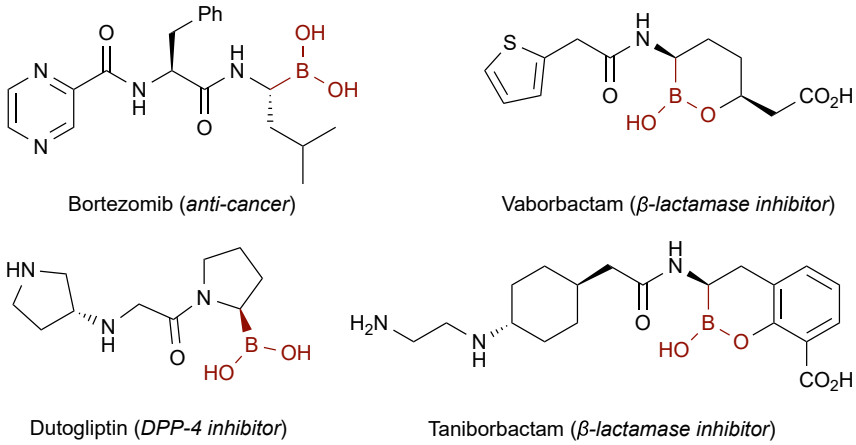

Figure 1. α-Aminoboronic acid-containing drugs

aminoboronate.[37] Inspired by our previous works[61–68] on selective activation of C(sp^3)–H bonds using radical translocating groups,[69–83] we envisioned that easy-to-install and remove and commercially available 2-iodobenzoyl (Bz^I)-tethered amines could be employed for α-C–H borylation reaction. Photoinduced single-electron reduction would generate aryl radical on a DG (**D**). The followed favored 1,5-HAT at the proximal α-C(sp^3)–H site would result in the key aminoalkyl radical **E**, thus obviating the requirement of TM or strong base for the C–H bond activation. TM-catalyzed C–H activation favors primary sites, whereas radical pathway favors activation of weaker C–H bonds; thus, successful borylation at previously underdeveloped aliphatic secondary C–H sites was anticipated. The major challenges could involve premature borylation of more reactive aryl radical **D**,[36,39] cyclization or desaturation of the translocated α-aminoalkyl radical **E**,[37,67] and hydrodehalogenation via intermolecular HAT of radical **D** or **E**.[68] Although guided hydrogen abstraction of amine provides efficient access to α-aminoalkyl radical **E**, intermolecular radical trapping of the corresponding α-aminoalkyl radical remains elusive.[68–70] Moreover, despite recent developments, metal-free borylation of less reactive alkyl radicals, such as α-aminoalkyl radical, remains mostly unsuccessful.[37,46] Thus, a general protocol involving diboron-mediated trapping of α-aminoalkyl radical is yet to be uncovered.[46]

RESULTS AND DISCUSSION

Gratifyingly, optimization studies[84] on borylation of 2-iodobenzoyl (Bz^I) protected dibutyl amine **2c** allowed to obtain targeted product **3c** in 80% isolated yield. The reaction proceeds with bis(catecolato)diboron (B_2cat_2, 3.5 equiv) under 427 nm light irradiation and features simple workup procedure upon reaction completion (Figure 2, entry 1). The reaction is only slightly less efficient with lower excess of B_2cat_2 or without triethylamine (entries 2 and 3). Control experiments indicated no reaction with other diboron reagents, such as bis(pinacolato)diboron (B_2pin_2) or under dark (entries 4 and 5). More practically, borylation of dibutyl amine can be performed with respectable efficiency in a semi-one-pot fashion without isolating the tethered amine intermediate **2c** (entry 6). Cyclic piperidine substrate **2j** also underwent smooth borylation with 72% of isolated yields (entry 7). Of note, different radical translocating groups were also tested under these borylation conditions. Substrates with 2-iodothiobenzoyl (**2am**), 2-iodobenzenesulfonyl (**2an**), and 2-iodobenzyl (**2ao**, **2ap**) groups mostly resulted in corresponding reduction (**3-A**) and desaturation (**3-B**) side products with trace or no desired borylation product (**3**) formation (entries 8–11).[84]

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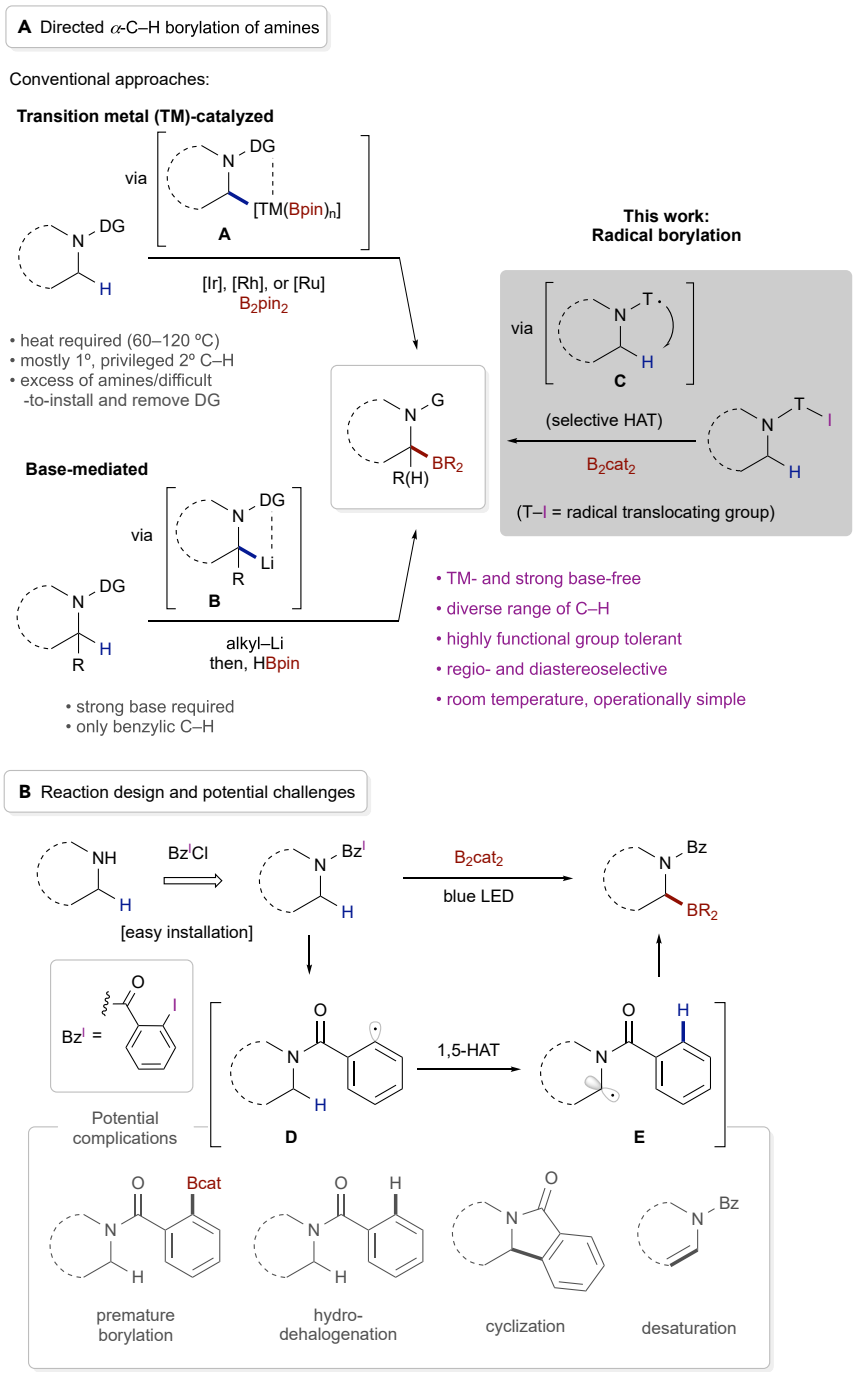
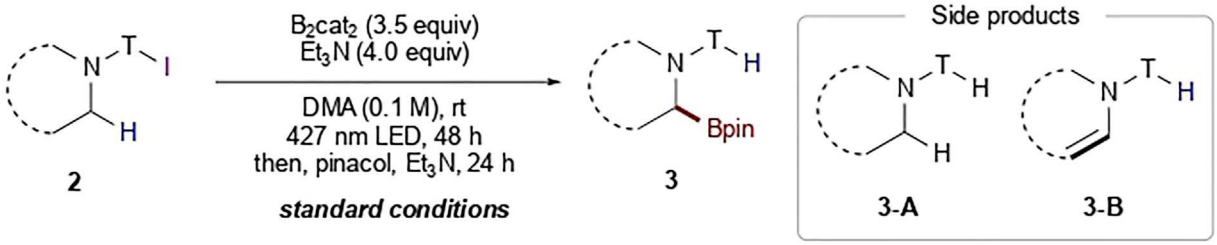
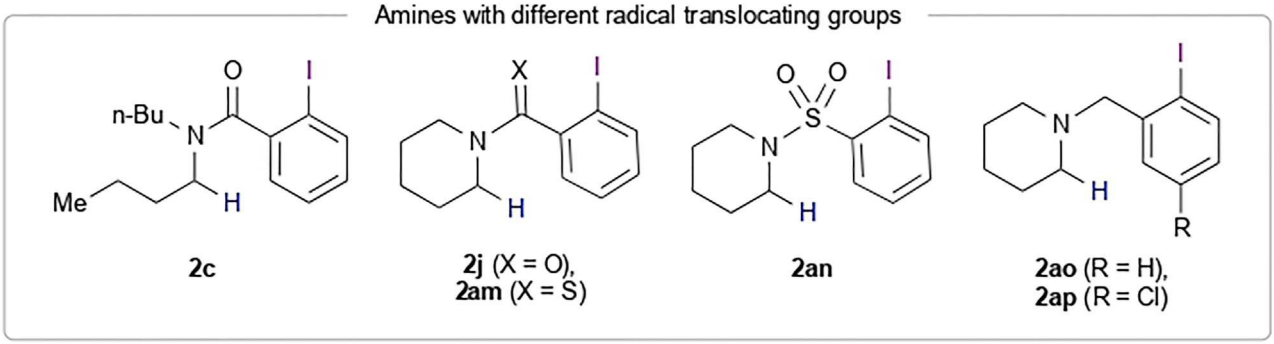


Scheme 1. Directed α-C–H borylation of amines

With optimized conditions in hand, the generality of this protocol was explored (Figure 3). To our delight, acyclic amines with primary and secondary C–H sites delivered borylation product (**3a–3e**) with up to 93% yield. Acyclic substrates with competitive α- primary and secondary C–H sites provided regioisomeric mixtures (**3f**/**3f′** and **3g**/**3g′**), which can be separated by column chromatography. Expectedly, preference toward the secondary sites was observed. Likely due to steric reasons, primary (**3h**) or secondary (**3i**) C–H sites were preferentially





Entry	Substrates	Deviation from standard conditions	Yield of **3** (%)[a]
1	**2c**	None	84 (80)[b]
2	**2c**	B_2cat_2 (2 equiv)	70
3	**2c**	Without Et_3N	60
4	**2c**	B_2pin_2 as boron reagent	0
5	**2c**	No light, 80 °C	0
6	**2c**	Directly from dibutyl amine, without isolation of **2c**	58
7	**2j**	None[c]	72[b]
8	**2am**	None	0[d]
9	**2an**	None	0[d]
10	**2ao**	None	trace[e]
11	**2ap**	None	trace[e]

Figure 2. Optimization of reaction conditions

[a]0.2 mmol scale GC-MS yields. [b]Isolated yield. [c]Transesterification required 48 h. [d]Only reduction by-product (**3-A**) formed. [e]Mixture of corresponding reduction (**3-A**) and desaturation (**3-B**) by-products formed.

borylated in the presence of tertiary sites with lower C–H bond dissociation energy (BDE).[85] Next, the scope of the cyclic amines was explored. Azacycles with different ring sizes (**3j**–**3l**) underwent borylation with 61%–82% yields. A broad

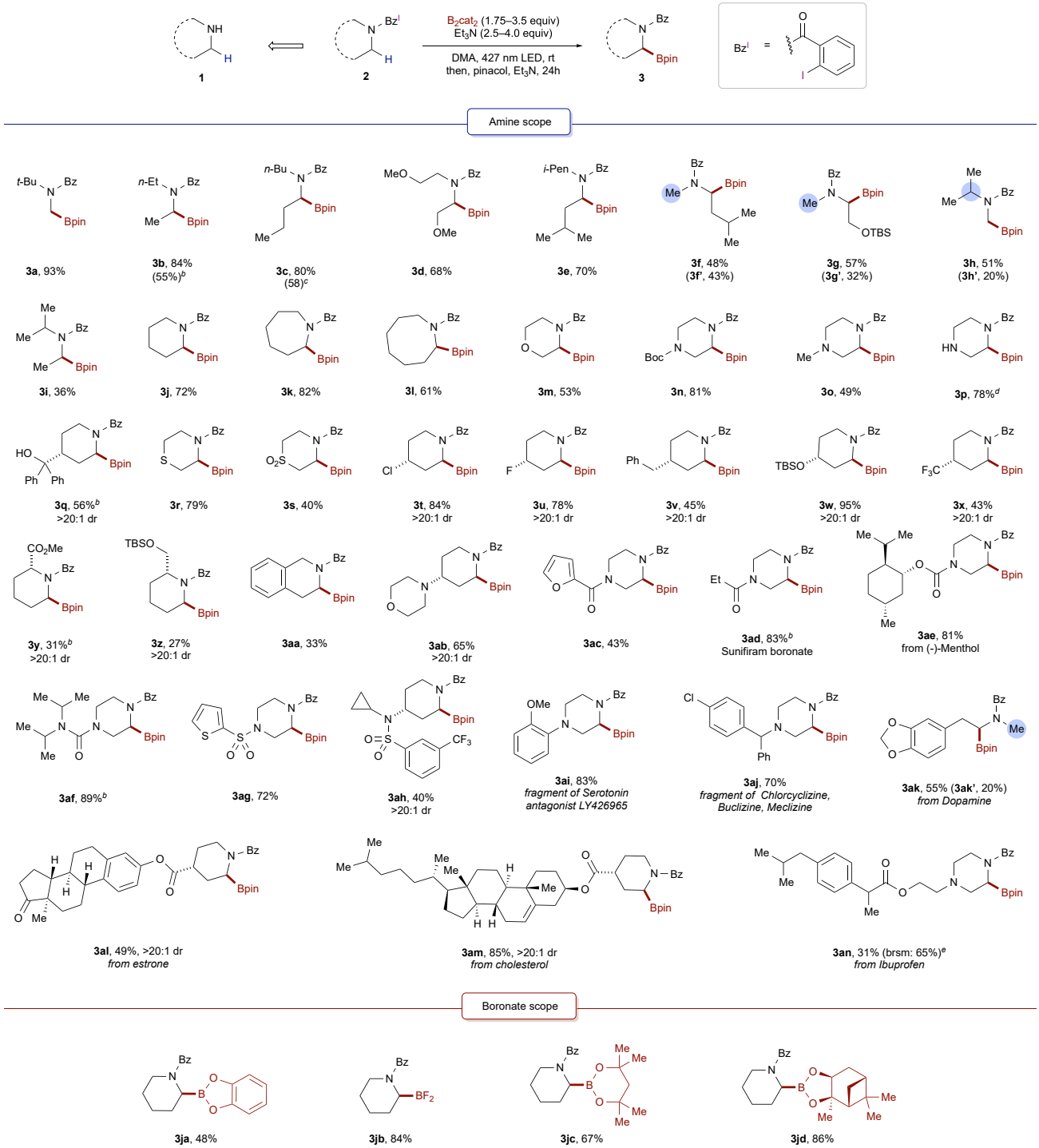


Figure 3. Scope of radical α-C(sp^3)–H borylation of amines[a]

[a]0.2 mmol scale, isolated yields of **3** from corresponding **2**.[84] [b]1.75 equiv of B_2Cat_2 was used. [c]GC-MS yields for semi-one pot borylation from the corresponding amine. [d]Isolated after Boc protection. [e]Yield based on recovered starting materials.

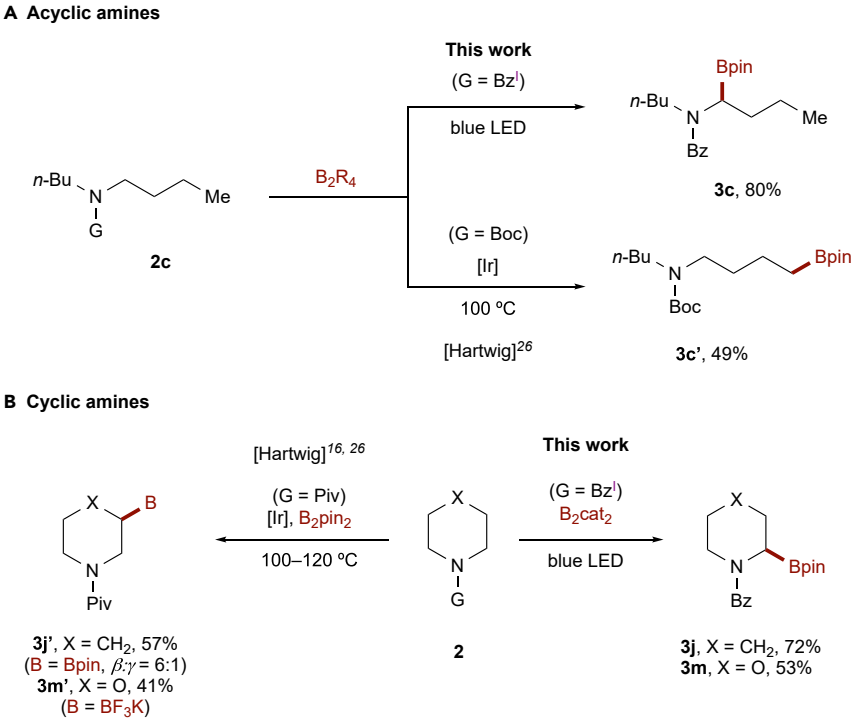
range of heterocycles (**3m**–**3x**) containing various functional groups, such as ether (**3m**), Boc-protected amine (**3n**), thioether (**3r**), sulfone (**3s**), and halides (**3t**, **3u**, and **3x**), were found to be competent substrates. Notably, substituted piperidines

underwent radical borylation with high diastereocontrol. Azacycles with C-4 substitution (**3q**, **3t–3x**) were isolated as single diastereomers.[84] This method demonstrated high functional group tolerance. Thus, sensitive functional groups, including free amine (**3p**) and free alcohol (**3q**), were tolerated under these borylation reaction conditions. Next, the scope of complex and densely functionalized molecules was investigated. Similarly, highly regio- and diastereo-selective borylation was accomplished with C-2 substituted piperidines, such as amino acid **3y** and amino alcohol **3z**, albeit with diminished yields. This could be due to a non-selective HAT followed by selective trapping of the unactivated secondary α-aminoalkyl radical over its less reactive and sterically hindered counterpart. Likewise, tetrahydroisoquinoline provided regioselective borylation (**3aa**) with non-typical regioselectivity.[32] Expectedly, piperidine derivative with multiple types of weak C–H bonds produced single regioisomer **3ab** due to a directed nature of this transformation. α-C–H borylation works smoothly with complex azacycles tolerating additional amide (**3ac**, **3ad**), carbamate (**3ae**), carbamoyl (**3af**), and sulfonamide (**3ag**, **3ah**) functionalities, which serve as common DGs under TM-catalyzed C–H borylation and other C–H activation reactions.[27,31–34] Importantly, boronate analog of Sunifiram **3ad** was accessed with good yield. Likewise, amine-containing drug fragments of serotonin antagonist LY426965 (**3ai**) and chlorcyclizine, buclizine, and meclizine (**3aj**) underwent radical borylation in good yields. Expectedly, dopamine derivative delivered secondary site-selective borylation product (**3ak**) in good yields. Likewise, α-aminoboronates obtained from the substrates containing biologically active motif and drug molecules, such as estrone (**3al**), cholesterol (**3am**), and ibuprofen (**3an**), showcased the viability of employing this protocol for a late-stage functionalization of complex amines. Estrone (**3al**) and cholesterol (**3am**) substrates also underwent highly diastereo-selective borylation.

In addition to the pinacol esters, other boronates could also be obtained. Thus, catechol boronate (**3ja**) can be isolated directly upon reaction, however, with diminished yields. Quenching reaction with fluoride salt afforded fluoroborate **3jb** in good yield.[84] Other *in situ* transesterifications of catecolboronates led to propanediol- (**3jc**) and (+)-pinanediol (**3jd**) boronates. Notably, (+)-pinanediol boronates are commonly used in stereoselective synthesis.[86]

Expectedly, this directed borylation method provided complementary regioselectivity (**3c**, **3j**, and **3m**) to that under direct borylation approach, which offers terminal selectivity in case of acyclic amines (**3c′**; Scheme 2A) and β-selectivity in case of cyclic amines (**3j′** and **3m′**; Scheme 2B).[16,20,26]

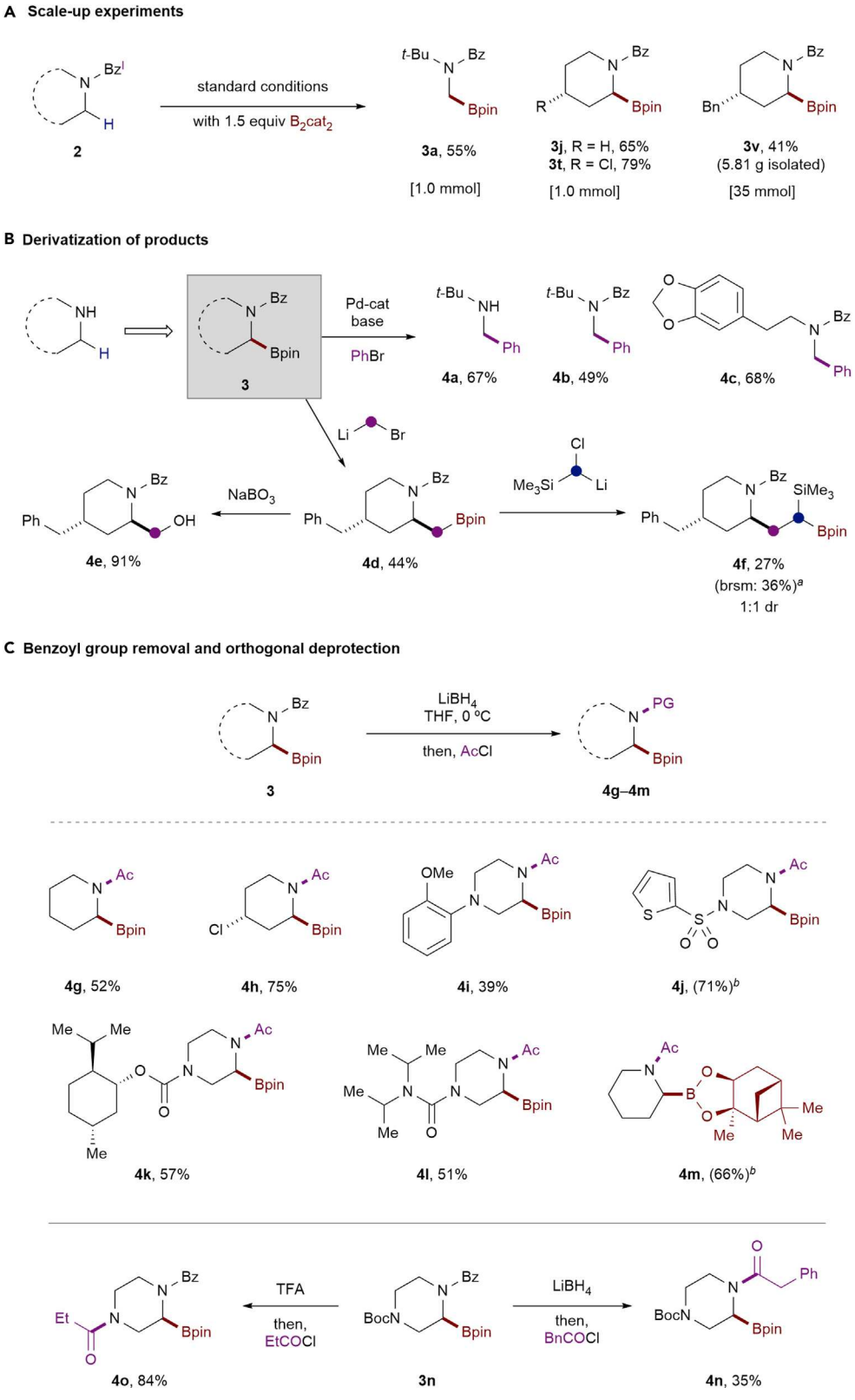
The practicality of this method was highlighted by the scale-up experiments performed with 1.5 equiv of B_2cat_2, which afforded acyclic (**3a**) and cyclic (**3j**, **3t**, **3v**) aminoboronates in good yields (Scheme 3A). Expectedly, methylamine-derived **3a** and **3ak′** underwent smooth Suzuki-Miyaura cross-coupling reaction[87,88] to afford arylated products (**4a–4c**) in good overall yield, including the *in situ* arylation and benzamide deprotection product **4a** (Scheme 3B). Moreover, Matteson homologation of the obtained product provided β-aminoboronate **4d**, which was further transformed into β-amino alcohol derivative **4e** and functionalized γ-aminoboronate **4f**.[89–91] Notably, we have developed $LiBH_4$-mediated mild deprotection of Bz radical translocating group, which tolerates a broad range of functional groups, such as alkyl halide (**4h**), electron-rich arene (**4i**), amide derivatives (**4j–4n**), and different boronates (**4m**) (Scheme 3C). Moreover, orthogonal deprotection of amides was showcased with piperazine derivative **3n**.[92]



Scheme 2. Complementarity of the developed approach with existing direct borylation methods

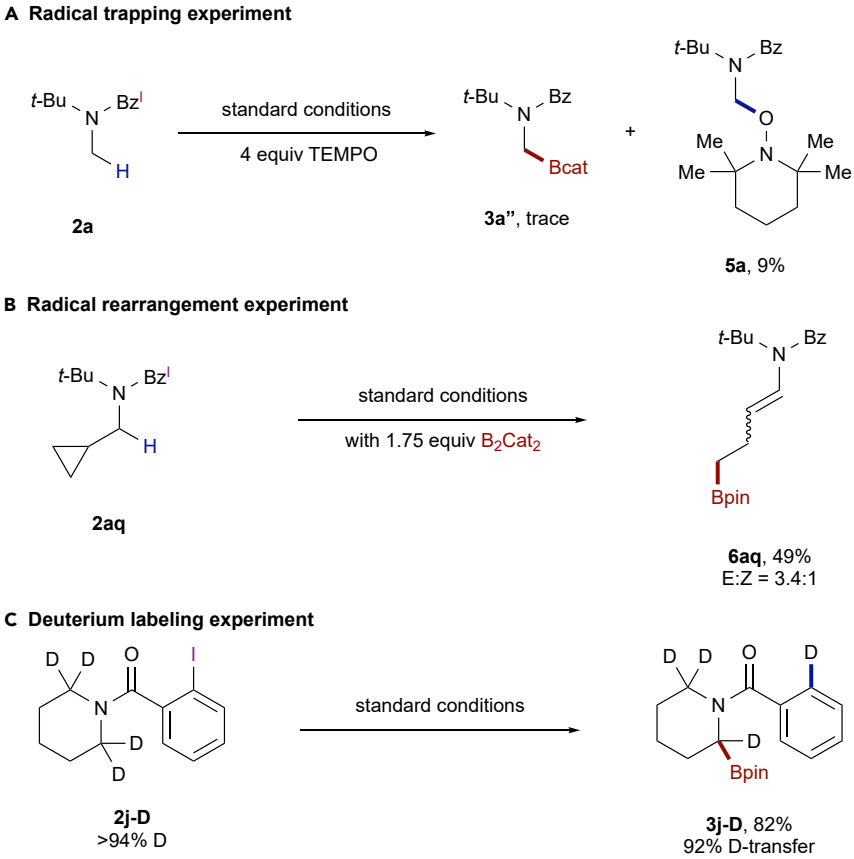
Next, a series of mechanistic studies were performed to gain insight into the mechanism of this reaction. First, radical trapping experiment with 2,2,6,6-Tetramethylpiperidin-1-yl)oxyl (TEMPO) led to trace amount of the borylation product **3a''** and notable amounts of the TEMPO-trapping adduct **5a** (Scheme 4A). The radical nature of the transformation was further supported by radical rearrangement experiment with the substrate containing a cyclopropyl group at the α-position to amine (**2aq**), which produced the ring-opening borylation product **6aq** (Scheme 4B). The selective 1,5-HAT process was validated by the deuterium labeling studies, which confirmed the complete D-atom transfer (**2j-*D*** → **3j-*D***; Scheme 4C). The results of the light on/off experiment, taken together with the value of the obtained quantum yield (φ = 2.6), indicate the involvement of the radical chain mechanism.[84]

Based on the literature reports[37,39,41,43,49] and the above-mentioned preliminary studies (Scheme 4),[84] the following mechanism for this novel α-borylation reaction is proposed (Scheme 5). First, a photoinduced homolysis of the C–I bond in **F***, the electron donor-acceptor (EDA) complex of **2** with boron reagent (**F**), leads to electrophilic aryl radical **D** likely via a single-electron transfer (SET) mechanism.[93,94] A subsequent polarity-matched 1,5-HAT generates nucleophilic α-aminoalkyl radical **E**, followed by radical addition to a ligated B_2cat_2 providing **G** and boryl radical **H**, which propagates the radical chain via halogen-atom transfer (XAT) or HAT with substrate **2**. *In situ* transesterification of catecolboronate **G** provides isolable reaction product, pinacol boronate **3**. Importantly, *N*-benzoyl group plays a key role in the success of this reaction. First, it provides sufficient Thorpe-Ingold effect. Second, it provides a polarity matching for efficient 1,5-HAT for the generation of nucleophilic α-aminoalkyl radical. Finally, the presence of *N*-benzoyl group suppresses the undesired radical polar crossover (RPC) of α-aminoalkyl radical into iminium species, leading to desaturation byproduct (**3-B**), thus favoring efficient



Scheme 3. Further transformations of obtained boronates[84]

[a]Yield based on recovered starting materials. [b]NMR yields.



Scheme 4. Mechanistic studies[84]

trapping with diboron reagent. This was supported by the results with benzyl radical translocating groups (Figure 2, **2an**, **2ao**), where *N*-benzyl employment of which provided a mixture of desaturation and reduction side products.

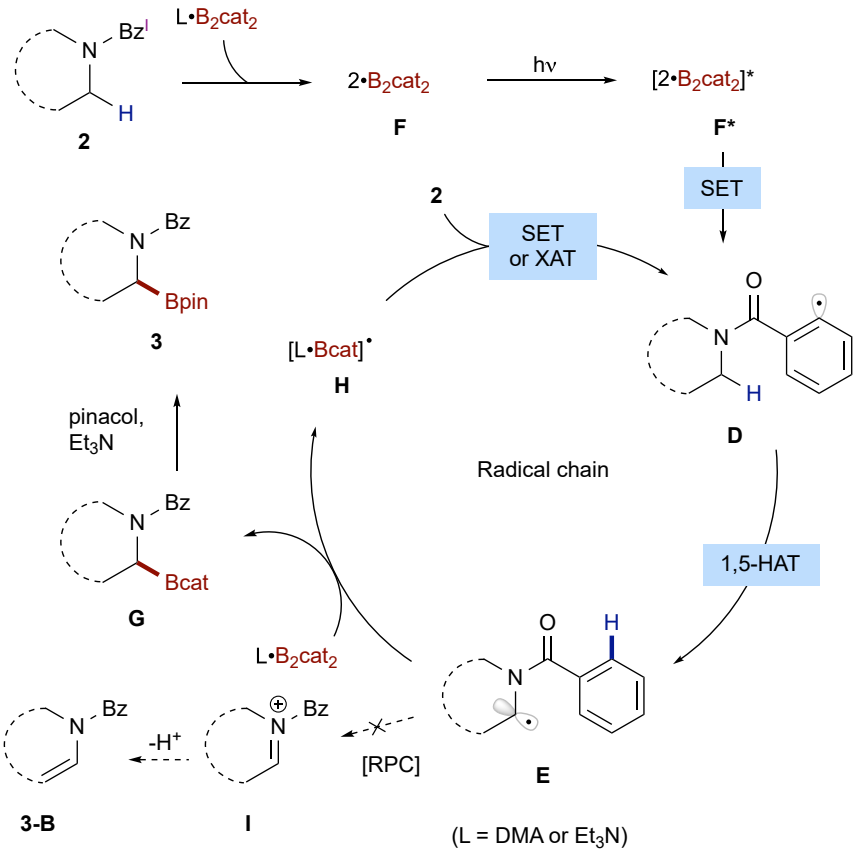
In conclusion, the first radical α-C(sp^3)–H borylation of amines has been developed. This protocol features photoinduced diboron reagent-mediated mild generation of aryl radical and selective 1,5-HAT event generating the key α-aminoalkyl radical intermediate employing a commercially available, easily installable/removable 2-iodobenzoyl radical translocating group. Remarkably, this method does not require use of photosensitizer, TM catalyst, or a strong base and allows for efficient, site-selective C–H activation of broad range of amines, including complex and pharmaceutically relevant amines. This highly site- and diastereo-selective α-borylation method is broadly applicable for late-stage functionalization of complex amine-containing molecules and drugs. It is expected that this operationally simple, general, and practical method will find broad application in organic synthesis and drug discovery.

EXPERIMENTAL PROCEDURES

Resource availability

Lead contact

Further information and requests for resources should be directed to and will be fulfilled by the lead contact, Vladimir Gevorgyan (vald@utdallas.edu).



Scheme 5. Proposed reaction mechanism

Materials availability

This study did not generate new unique reagents.

Data and code availability

This study did not generate any datasets or code. All relevant procedures and experimental data are provided in the supplemental information.

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.chempr.2022.07.022.

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AUTHOR CONTRIBUTIONS

V.G. supervised the project. S.S. designed the strategy. S.S., S.W., and X.J. designed, performed, and analyzed all experiments. S.S. and V.G. wrote this manuscript with input from all authors.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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