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Development of *N*-centered radical scavengers that enables photoredox-catalyzed transition-metal-free radical amination of alkyl pinacol boronates

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In recent years, amination of alkylboronates through ionic copper catalysis or boron-ate complex 1,2-metalation has been well established, but complementary radical processes remain less studied before. Herein, based on rational design, we develop several imine-type *N*-centered radical scavengers and apply them to the radical amination of alkylboronates. The reaction proceeds under mild photoredox-catalyzed transition-metal-free conditions and features excellent functional group tolerance. It also enables the preparation of a range of medicinally valuable amine derivatives from complex natural products. Further application of this reagent in C-H amination, deoxygenative amination, decarboxylative amination and three component trifluoromethylative/sulfonylative aminations are also realized. Further mechanistic studies and DFT calculations are conducted to provide detailed evidence for the mechanism.

Organoboron compounds are some of the most useful compounds in synthetic chemistry because of the versatile reactivity of carbon–boron bonds[1–4]. Among them, boronic acid pinacol esters have received a great deal of attention from the synthetic community due to their stability, which facilitates their handling and allows them to be used for a broad range of reactions. Amines and other nitrogen-containing functional groups are highly important and can be found in many bioactive alkaloids, small molecule pharmaceuticals, and agrochemicals[5]. Thus, transformations of pinacol boronates to corresponding amines are highly valuable, especially for medicinal chemistry.

Since 1964, amination of organoboranes (such as trialkylboranes, dichloroboranes, and dialkylborinates) has been well studied[6]. But until recent decades, the amination of bench-stable boronic acids or boronic esters has been reported. Among them, since 1998, the copper-promoted C-N bond formation of arylboronic acids with amines and amides (Chan–Lam coupling) is an attractive method[7–11]. Later, the substrate scope has been expanded to arylboronates, alkyl boronic acids, alkylboronates and potassium organotrifluoroborates[12–17]. Besides copper catalysis, an alternative strategy is the conversion of a boron reagent to a boron 'ate' complex, mediated by the aminating reagent, followed by a 1,2-metalate rearrangement that establishes a C-N bond and yields the amination product.[18–24]. Those aminations are generally transition-metal-free and stereospecific. From 2012, the groups of Morken[19,21,23], Kürti[20], and Liu[22,24] have made great contributions to this area. Very recently, an enzymatic process has also been reported[25].

Ionic amination of alkylboronates usually requires high temperature for copper catalysis or a strong base (e.g. *n*-BuLi, *t*-BuOK etc.) for boron-ate complex formation, which has resulted in limited

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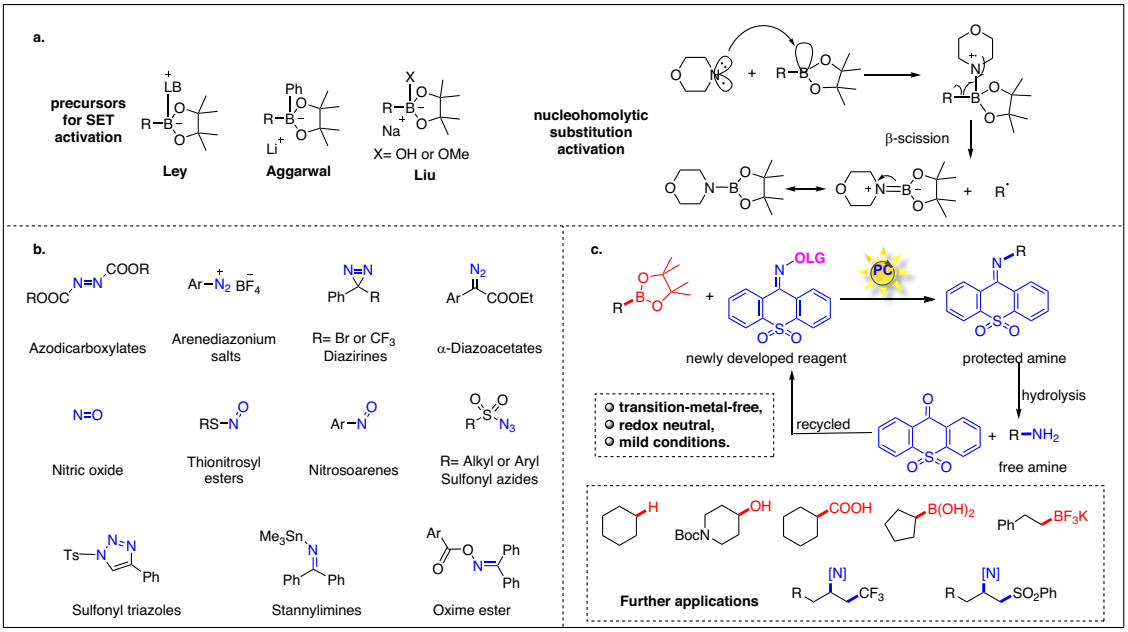

Fig. 1 | Introduction of *N*-centered radical scavengers and our strategy. a Activation of C-B bond through SET and nucleohomolytic substitution pathways. **b** Summary of the reported *N*-centered radical scavengers. **c** This work, development of imine-type *N*-centered radical scavengers and application in deboronative amination reaction.

functional group compatibility. A radical protocol through photoredox catalysis may provide an alternative milder pathway. However, the development of such a protocol is not straightforward due to the challenges in achieving single-electron oxidation of alkylboronates, so further activation is necessary. In 2017, the Ley group reported that a weak Lewis base could act as an activator to promote this process (Fig. 1a), but this protocol is limited to benzylic boronates and α-heteroatom-substituted primary alkyl boronates[26]. Soon after, the Aggarwal group realized the activation of general alkyl boronic esters with PhLi as the activator[27–30], and recently the Liu group reported single-electron oxidation of alkylboronates with NaOMe or NaOH as the activator, however strong bases were required[31]. In contrast, in 2022, Maier reported a milder amino radical transfer (ART) activation strategy, where alkylboronates could be activated by an in situ generated amino radical[32]. Recently, the Studer group also applied this strategy to generate alkyl radicals, and further pointed out that this process proceeded through a nucleohomolytic substitution mechanism (Fig. 1a)[33]. Since no further activation step was required, and the boronic esters could be activated by the amino radical generated from a weak organic base[34–36], we decide to apply this strategy into our transformations.

In recent years, radical amination has attracted much attention. Several different strategies for radical C-N couplings have been reported[37–40], for example, the reaction of *N*-centered radical addition to olefins and aromatics has been well established, whereas the development of transition-metal-catalyzed strategies and radical-radical coupling strategies have been fast growing[38–40]. However, the research field of *N*-centered radical scavengers has suffered from slow development[41]. Although different reagents (Fig. 1b), such as nitric oxide[41], azodicarboxylates[42–46], diazonium salts[47–49], diazirines[50], nitrosoarenes[51] and sulfonyl azides[52,53], have been used as *N*-centered radical scavengers for many years, there are only few reagents developed in the recent 20 years, such as α-diazoacetates[54–56] and sulfonyl triazoles[57–59]. After carefully analysis, we note that most of these reagents contain N–N or N–O multiple bonds, so that subsequent reduction is required to obtain the free amine, which reduces the redox economy of the process. Until 2010, the Studer group applied stannylimine as the scavenger to give an imine as the final product, which only requires hydrolysis to give the corresponding amine[60]. This synthetic approach is redox-economical, but due to the high toxicity of stannylimine, further application is limited. Very recently, the research groups of Cho[61,62], Glorius[63–69], Prieto[70] and others[71–74] have developed an oxime ester derivative as the amination reagent. For this reagent, through photoinduced triplet energy transfer (EnT) pathway, a persistent iminyl radical was generated as the *N*-centered radical scavenger.

In this study, inspired by the works of Studer[60,75], Cho[61,62] and Glorius[63–69], we decide to develop an imine-type *N*-centered radical scavenger that benefits from stability, convenient scale-up preparation, and properties that traditional reagents lack, such as non-explosivity (compared to azide reagents) and low toxicity (compared to stannylimines). We also want the resulting imines to be easily hydrolyzed to access free amines while the by-product ketone could be recovered and recycled (Fig. 1c). Based on the development of this reagent, we would then investigate the visible-light photoredox-catalyzed radical amination of alkyl pinacol boronates, and application of this method in the synthesis of several functional molecules. Once this is successfully achieved, we aim to show the generality of the developed reagent in more challenging C-H aminations, deoxygenative aminations and some other transformations.

Results

Reaction development

We began our studies by rational design and synthesis of imine derivatives as potential *N*-centered radical scavengers. Firstly, we synthesized **2a** and **2b**[61]. Our hypothesis is that if the photo-oxidation step to generate an alkyl radical is quicker than triplet energy transfer (EnT), the newly formed radical will add to **2a**/**2b** to generate a more thermodynamically stabilized radical intermediate **INTa**/**INTb**, which will promote the progression of the reaction. Then, considering the polarity of the C=N bond in imines, N is more electronegative than C, so any (partial) negative charge would localize on the N atom. As most alkyl radicals are nucleophilic radicals, which prefer addition to electropositive sites, thus umpolung natural polarity of the imines is required to revert its reactivity (Fig. 2a). Inspired by the creative work from Kurti[76], oxime tosylate **2c** was synthesized. We then synthesized **2d** and **2e** with two aromatic rings to help stabilize the anticipated radical center and a ketone to induce umpolung. Similarly, oxime

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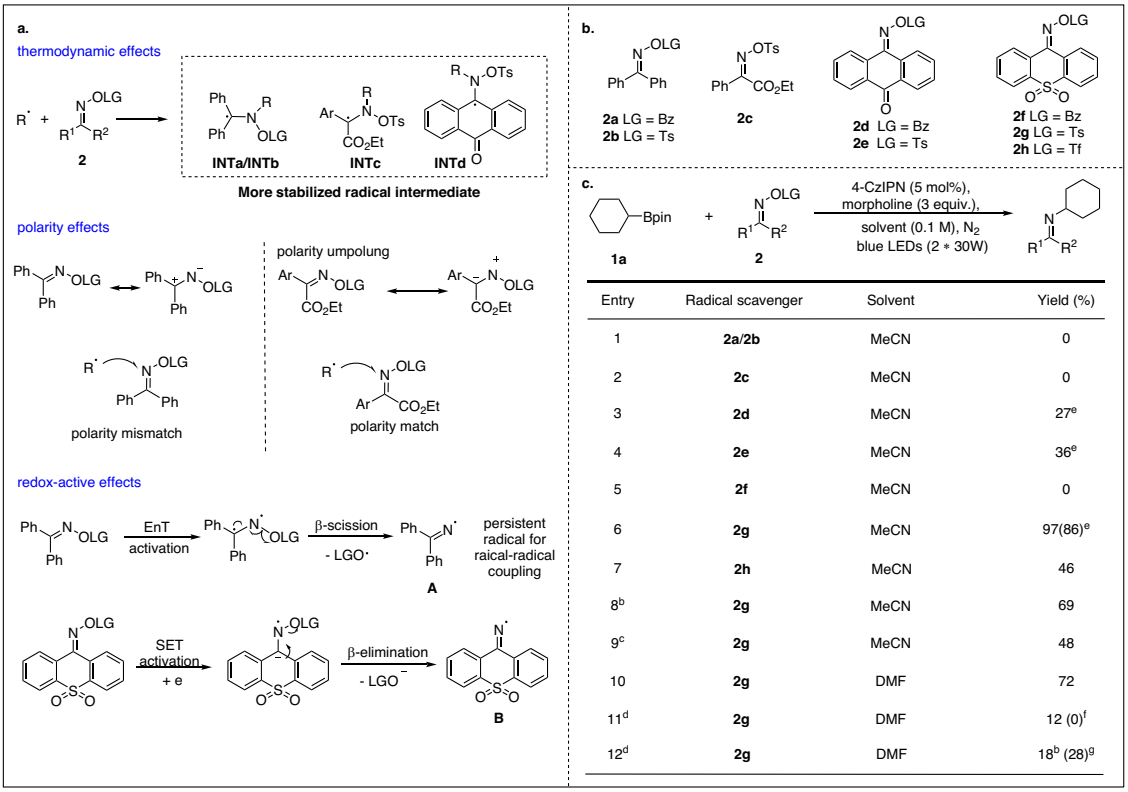

Entry	Radical scavenger	Solvent	Yield (%)
1	**2a/2b**	MeCN	0
2	**2c**	MeCN	0
3	**2d**	MeCN	27[e]
4	**2e**	MeCN	36[e]
5	**2f**	MeCN	0
6	**2g**	MeCN	97(86)[e]
7	**2h**	MeCN	46
8[b]	**2g**	MeCN	69
9[c]	**2g**	MeCN	48
10	**2g**	DMF	72
11[d]	**2g**	DMF	12 (0)[f]
12[d]	**2g**	DMF	18[b] (28)[g]

Fig. 2 | Rational design of imine-type *N*-centered radical scavengers and their reactivity in the deboronative amination reactions. a Rational design of the imine-type *N*-centered radical scavengers. **b** Different *N*-centered radical scavengers been designed and synthesized. **c** Optimization of the reactions, standard reaction conditions: **1a** (0.2 mmol), **2** (0.4 mmol), morpholine (0.6 mmol), 4-CzIPN (5 mol%), MeCN (0.1 M), blue LEDs, 16 h. Yields were determined by ^{1}H NMR analysis with CH_2Br_2 as an internal standard. [a]morpholine (0.4 mmol). [b]Photocatalyst = Ir[(dFCF$_3$ppy)$_2$(dtbbpy)]PF$_6$ (1 mol%). [c]Without photocatalyst. [d]Isolated yield. [e]MeCN as solvent. [f]With 390 nm LEDs.

derivatives with a sulfone group **2f, 2g** and **2h** were synthesized (Fig. 2b). It should be noted that, putting an electron-withdrawing group on the carbon side of the imines would not only invert the polarity of the C=N bond, but also make the molecules redox-active. As traditional oxime derivatives (like **2a**/**2b**) are well known for EnT activation to generate a persistent iminyl radical for radical-radical coupling reactions; our newly developed reagent **2d** to **2h** would be much easier for single-electron transfer (SET) activation to generate corresponding persistent iminyl radicals[77–80].

With these potential scavengers in hand, we proceeded to investigate the reactivity of aminating reagents **2** with alkyl boronic ester **1a**. Unsurprisingly, **2a** and **2b** failed to give any desired product (Fig. 2c, entry 1). Scavenger **2c** also showed no reactivity (entry 2). Delightfully, employing **2d** gave the desired product in 27% yield (entry 3), whereas **2e** resulted in a slight improved yield (entry 4). Much to our surprise, **2f** showed no reactivity (entry 5), but when we switched to **2g**, the desired product was obtained in excellent yield (entry 6), whereas reagent **2h** gave a much lower yield (entry 7). When morpholine was reduced to 2 equivalents, the yield decreased significantly (entry 8). Using 1 mol% Ir[(dFCF$_3$ppy)$_2$(dtbbpy)]PF$_6$ instead of 4-CzIPN as the photocatalyst resulted in a significantly lower yield (entry 9). Switching the solvent to DMF resulted in a decreased yield (entry 10). Interestingly, irradiation without a photocatalyst in DMF also afforded the desired product in 12% yield, but in contrast, when MeCN was used as the solvent under photocatalyst-free conditions, no desired product was obtained, which could be due to poor solubility (entry 11). Further optimization results showed that irradiation with 390 nm LEDs in DMF without a photocatalyst could give the desired product in 28% yield (entry 12). However, we could not obtain any better results under photocatalyst-free conditions.

Substrate scope

With the optimized conditions in hand, we investigated the scope of the deboronative amination (Fig. 3). Cyclic secondary alkyl-Bpin (**1a**-**1f**) were converted effectively and delivered the corresponding imines in moderate to good yields. Interestingly, we found that substrates with a non-strained 6-membered or 5-membered ring (**1a**-**1d**) could give the desired product in good yield, however much lower yields were obtained from substrates with a 4-membered or 12-membered ring (**1e, 1f**). Acyclic substrates (**1g**-**1m**) were also efficiently transformed to the desired products. It should be noted, substrates with a cyclic ether (**1c**), Boc-protected amine (**1d**), acetate (**1i**), ester (**1j**), alkyne (**1l**) or nitrile (**1m**) all gave the desired products in good yields, demonstrating excellent functional group tolerance. However, the substrate with an amide group (**1k**) resulted in a lower yield. Primary alkyl-Bpin (**1n**-**1v**) were smoothly transformed into the desired alkyl imines (**3n**-**3t**) in moderate yields. A range of functional groups were tolerated, including bromide (**1o**), silyl ether (**1p**), ketal (**1q**), indole (**1t**), carbazole (**1u**) and sulfonamide (**1v**). Much to our surprise, under the standard conditions, tertiary substrates (**1w**-**1y**) could not give the corresponding imine products but instead afforded saturated amines in moderate yields. We believed these saturated amines were produced from further reduction of the corresponding imines by the excess morpholine under the photoredox-catalyzed conditions[81]. Notably, derivatives of drug molecules and natural products, such as gemfibrozil (**3y**), cedrol (**3z**), dehydroabietic acid (**3aa**), santonin (**3ab**), diosgenin (**3ac**), vespertilin (**3ad**), and oleanolic acid (**3ae**) could be obtained in moderate to good yields, demonstrating that this method can be used for late-stage installation of C-N bonds from corresponding boronic esters in complex molecules.

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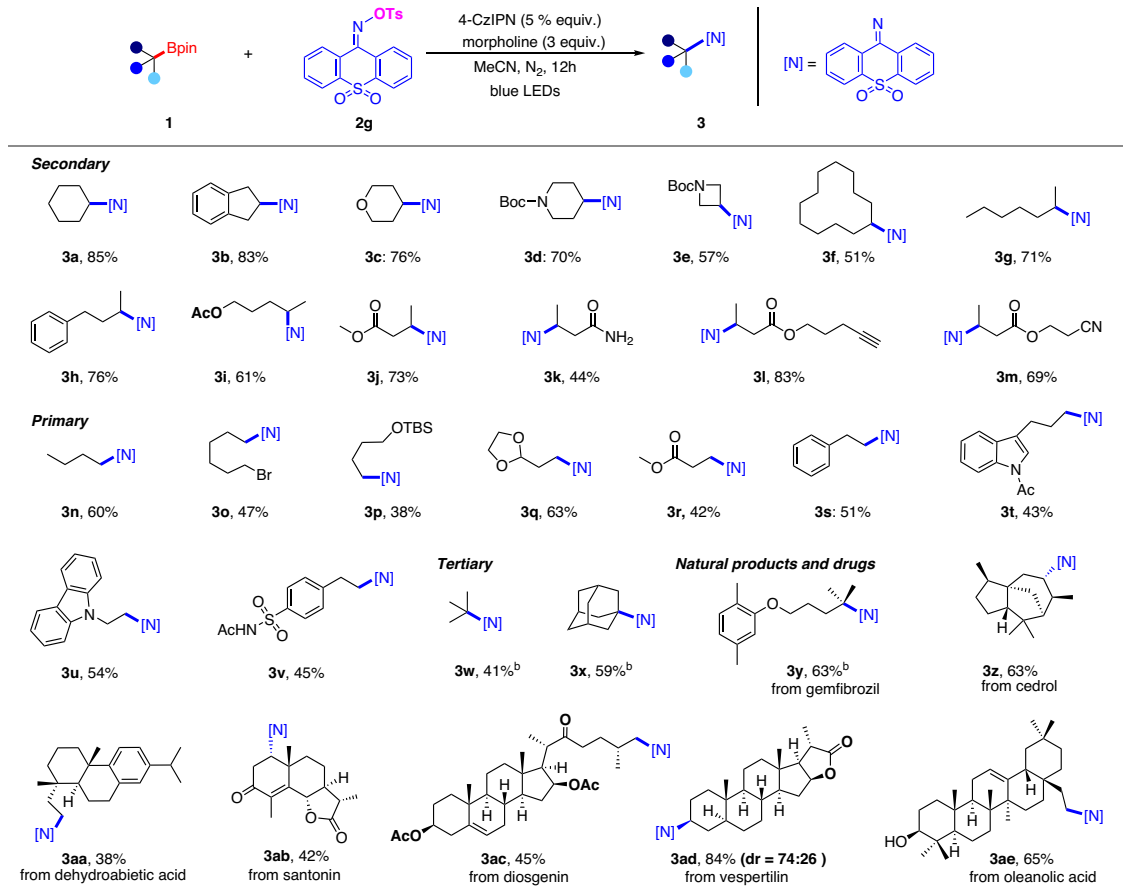

Fig. 3 | Substrate scope of alkyl pinacol boronates. Standard reaction conditions: **1** (0.2 mmol), **2g** (0.4 mmol), morpholine (0.6 mmol), 4-CzIPN (5 mol%), MeCN (0.1 M), 12 h, blue LEDs. [b]Isolated as saturated amine.

Mechanistic studies and DFT calculations

Mechanistic studies were conducted to provide evidence for the proposed radical pathway. Radical clock experiments with substrate **1af** provided the corresponding ring-opening product **3af** in 43% yield, indicating that a cyclopropylmethyl radical intermediate was involved in the reaction (Supplementary Fig. S1a). Then, a series experiments of **2g** with different photocatalysts were conducted to investigate how much starting material would remain (Supplementary Fig. S1b). We chose four photocatalysts which differs in both triplet energies and reduction potentials[82–87]. DFT calculations indicated that the triplet energy of **2g** was 43.6 kcal/mol, while the excited energy of 4-CzIPN is 59.7 kcal/mol, which means triplet 4-CzIPN is strong enough to consume **2g** in the absence of a reductant. However, our experiments showed that most of the starting material remained in each case for all four photocatalysts. Although through these experiments we cannot completely rule out the triplet EnT pathway, however, it does indicate that an EnT pathway is not likely to be the major pathway. Another strong evidence is that, in DMF, 12% yield of desired product was still obtained without a photocatalyst (Fig. 2c, entry 11). In this case, as blue light could not excite **2g** directly, a triplet EnT pathway could be ruled out, and we believe that, in the absence of a photocatalyst, there may be an EDA complex that initiates the reaction. This was further confirmed by UV-Vis experiments (Supplementary Fig. S1c). Besides, the quantum yield of our deboronative amination reaction under the standard conditions with **1a** was determined to be 0.674, indicating that radical chain processes are not supported (see Supplementary Information for details).

To gain further understanding of the mechanism, DFT calculations for the deboronative imination reaction were performed (Fig. 4). Firstly, morpholine **INT1** could be oxidized by the excited photocatalyst through a SET process to give a radical cation species **INT2** and the reduced $PC^{\cdot-}$ species. Next, **INT2** could be converted to an *N*-centered radical **INT3** via proton transfer with another morpholine molecule. Then, the yielded *N*-centered radical **INT3** could attack the B-site of **1a** via **TS1** to generate a cyclohexyl radical **INT4**. The predicted activation barrier for this step is 8.5 kcal/mol relative to **1a** + **INT3**. Subsequently, the yielded cyclohexyl radical **INT4** could attack the C=N moiety of **2g**. Computational results show that it is more likely for **INT4** to attack the N-site of **2g** via **TS2a**, than the C-site via **TS2b**, to afford the radical adduct **INT5**. For the following transformations, there are two possible pathways. In pathway a (black in Fig. 4), **INT5** is further reduced by the reduced photocatalyst to form the anionic intermediate, which undergoes β-elimination through transition state **TS3a** to give desired product **3a**. Alternatively, in pathway b (red in Fig. 2), **INT5** could undergo β-scission directly through transition state **TS3b** to give **3a** and release the radical intermediate **INT6b**, which could be further reduced by the reduced photocatalyst to give a tosylate anion. The transition state energy barrier for the β-elimination step (**TS3a**) is 1.3 kcal/mol lower than that for the β-scission step (**TS3b**), indicating that pathway a is more favorable. On the other hand, the reduced $PC^{\cdot-}$ species might undergo SET with **2g** to give the corresponding radical anion. The predicted energy barrier for this SET process is 6.9 kcal/mol (Supplementary Fig. S2). Next, a β-elimination step could follow via **TS-S1** to give an iminyl radical and tosylate anion. The calculated activation barrier for this step is only 5.8 kcal/mol. The cross-coupling between the iminyl radical and the cyclohexyl radical could also give the desired product **3a**, so may not be ruled out.

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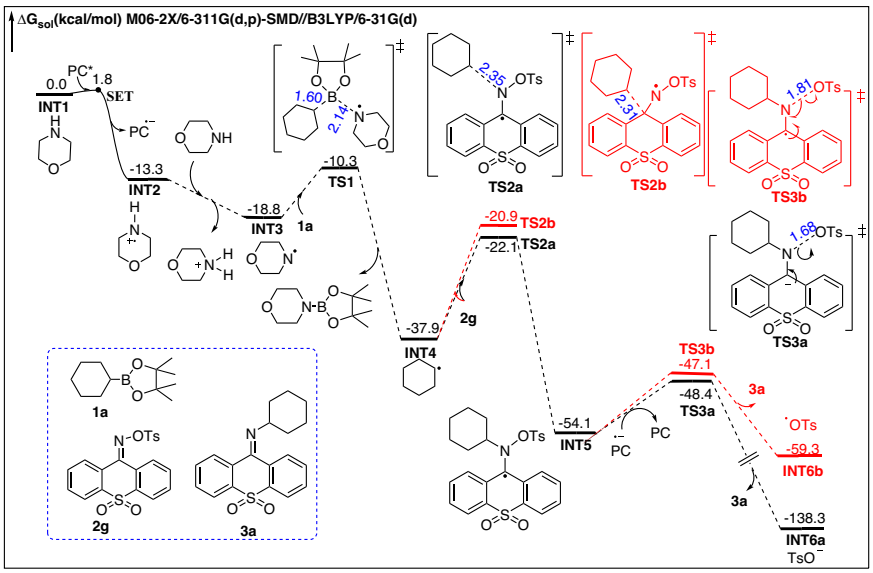

Fig. 4 | DFT calculations for the deboronative imination reaction. Steps of cyclohexyl radical formation, radical addition, and β-elimination to afford the final product.

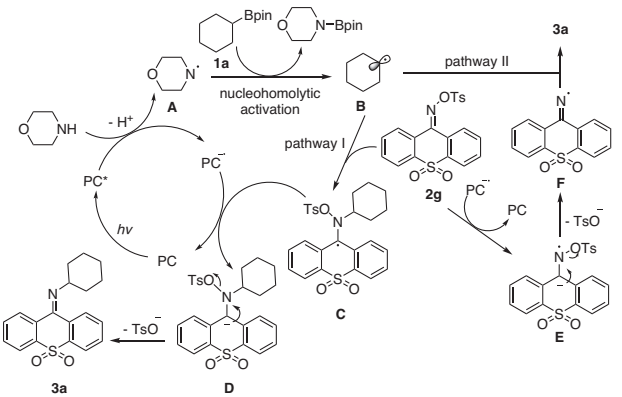

Fig. 5 | Proposed mechanism. Radical addition followed by reduction, β-elimination pathway (pathway I) and radical-radical coupling pathway (pathway II).

One may wonder whether an EnT pathway is feasible for this reaction. The predicted singlet-triplet energy gap of **2g** is 43.6 kcal/mol. Nevertheless, the excited **2g*** needs to overcome a barrier of 10.1 kcal/mol to undergo homolytic cleavage to give the iminyl radical (Supplementary Fig. S2), which is less favorable than the SET process.

Based on the mechanistic studies and DFT calculations, a possible mechanism was proposed (Fig. 5). Firstly, morpholine is oxidized by an excited photocatalyst (PC*) and undergoes deprotonation by another morpholine molecule to generate radical **A**. Radical **A** then activates substrate **1a** through nucleohomolytic substitution to generate cyclohexyl radical **B**, which in turn adds to aminating reagent **2g** and give intermediate **C**. Then **C** is reduced by the reduced photocatalyst to give anionic intermediate **D**, which undergoes β-elimination to give the desired product **3a**. Also, there is another possible mechanism (Fig. 5, pathway II), where after cyclohexyl radical **B** is generated, **2g** could be further reduced by the reduced photocatalyst to give intermediate **E**. This in turn generates iminyl radical **F** after β-elimination of a tosylate anion. Finally, cyclohexyl radical **B** undergoes cross coupling with the iminyl radical **F** to give desired product **3a**. Since reagent **2g** is present in large excess, whereas iminyl radical **F** is generated in low concentration in the reaction system, we still believe that pathway I is more probable than pathway II, but we cannot rule out the latter.

Application in functional molecules syntheses and other transformations

The excellent functional group tolerance of the mild reaction conditions further encouraged us to apply our method in the synthesis of functional molecules. In recent years, the cedrol derivatized amine **8** was found to have interesting anti influenza virus activity[88]. But starting from cedrene (**4**), the traditional synthetic route required 4 steps (Fig. 6a), including hydroboration-oxidation to give alcohol **5**, then oxidation to give ketone **6**, followed by further transformation into oxime **7**, and finally reduction to give amine **8**. It is worth noting that, unfortunately, this route affords product **8** as an inseparable mixture. Recently, the Shu group reported an improved synthesis of **8**, through direct radical hydroamination of cedrene (**4**), where the desired product **8** could be obtained in a single step with 95% yield[89]. Unfortunately, with his method, **8** was still obtained as an inseparable mixture (d.r. = 1.6:1). Now, using our method, we have demonstrated that it only requires 2 steps (hydroboration and deboronative amination) to synthesise the desired product **3z** as a single diastereomer. After hydrolysis, the desired free amine **8** was obtained as a single diastereomer with a yield of 68%. We then applied our method into the synthesis of (*S*)-phenibut, starting from boronic ester **9**. Previously, the Yun group transformed the pinacol boronate into dichloroborane **10**[90], and then reacted it with benzyl azide to obtain protected phenibut **11**. Through our method, pinacol boronate **9** could be transformed into protected phenibut **12** in a single step, with 100% es. Our method was further applied to the synthesis of a chiral amino alcohol[91]. Starting from boronic ester **13**, desired product **14** was obtained with good es. Interestingly, in this reaction we also obtained side-product **15**, possibly through a radical 1,2-aryl migration process.

To further demonstrate the generality of this developed reagent, more challenging transformations (such as, deoxygenative amination, C-H amination and three-component radical relay aminations) and other radical precursors (such as carboxylic acid, boronic acid, and potassium organotrifluoroborate) were tested (Fig. 7). Delightfully, under slightly optimized conditions (see Supplementary Information for details), the use of an NHC activation strategy developed by the MacMillan group[92–95] enabled the conversion of alcohol **16** into imine **3d** in 15% yield (Fig. 7a). Additionally, cyclohexane **17** could be transformed into imine **3a** in 19% yield (Fig. 7b). Starting from carboxylic

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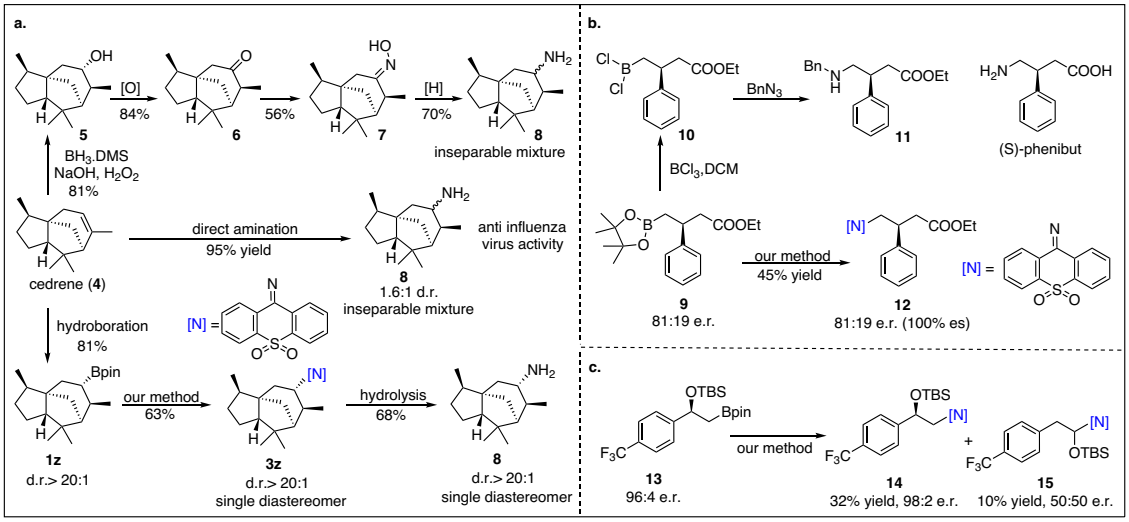

Fig. 6 | Application of our method in the syntheses of functional molecules. a Application in the synthesis of cedrol-derivatized amine. **b** Application in the synthesis of (*S*)-phenibut. **c** Application in the synthesis of chiral amino alcohol.

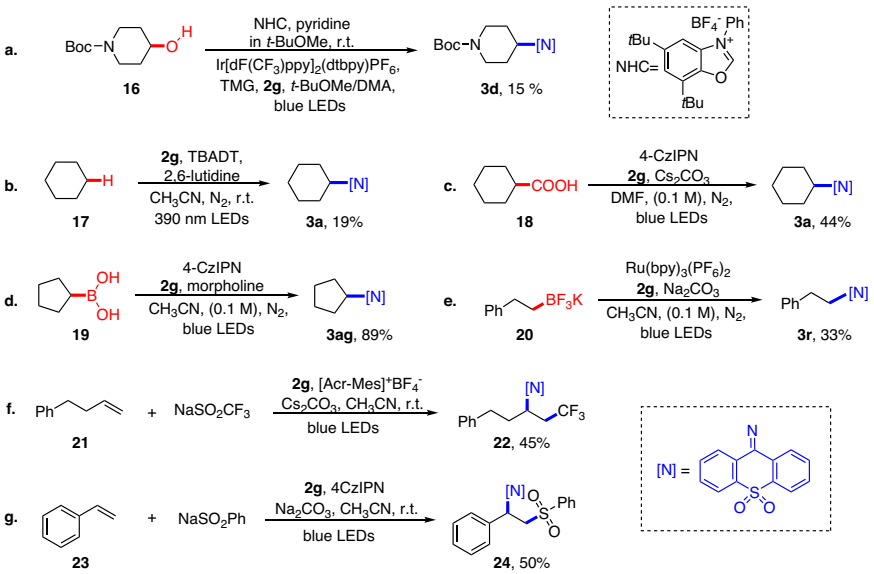

Fig. 7 | Further applications of reagent 2g. a Deoxygenative amination. **b** C-H amination. **c** Decarboxylative amination. **d** Amination of alkyl boronic acid. **e** Amination of alkyl potassium trifluoroborate. **f** Three-component trifluoromethylative amination. **g** Three-component sulfonylative amination.

acid **18**, the corresponding decarboxylative amination product **3a** was obtained in 44% yield (Fig. 7c). With our standard conditions, boronic acid **19** could be converted into imine **3ag** in 89% yield (Fig. 7d). With slightly optimized conditions, potassium trifluoroborate **20** could be transformed to imine **3r** in 33% yield (Fig. 7e). Also, three-component trifluoromethylative amination[96] of unactivated olefin **21** could deliver the desired difunctionalized product **22** in 45% yield (Fig. 7f), and three-component sulfonylative amination of styrene **23** successfully afforded desired product **24** in 50% yield (Fig. 7g).

In order to demonstrate the accessibility of the aminating reagent, we performed a large scale synthesis of **2g** in single sequence and obtained 19.4 g of reagent **2g** (Fig. 8a). To demonstrate the practical use of our deboronative amination reaction, we also carried out a scale up experiment, starting from 841 mg (4 mmol) boronate **1a**, where desired product **3a** was obtained in 53% yield (Fig. 8b). It should be highlighted that our imine products can be treated as protected amines, which can be easily converted into the corresponding amines through simple hydrolysis. In order to demonstrate the advantage of our method (Fig. 8c), we hydrolyzed product **3b** with HCl to provide amine-HCl salt **25** in 55% yield, meanwhile recycling ketone **26** in 79% yield. After neutralizing **25** with NaOH, free amine **27** was obtained in 75% yield. The recycled ketone **26** could be further transformed into aminating reagent **2g**.

Discussion

In conclusion, based on rational design, we have developed several imine-type *N*-centered radical scavengers and successfully applied them in visible-light photoredox-catalyzed transition-metal-free radical amination of alkyl pinacol boronates. The reaction proceeds under mild conditions, features excellent functional group tolerance, and enables the preparation of medicinally valuable imine derivatives of a range of complex natural products. Detailed mechanistic studies and DFT calculations has shown that a photoinduced EnT process is unlikely to be the major pathway; this reaction most likely proceeds through a photoredox-catalyzed SET process. Furthermore, DFT calculations support a radical addition, reduction, then anionic β-elimination pathway rather than a radical addition, β-scission pathway. To demonstrate the generality of these developed reagents,

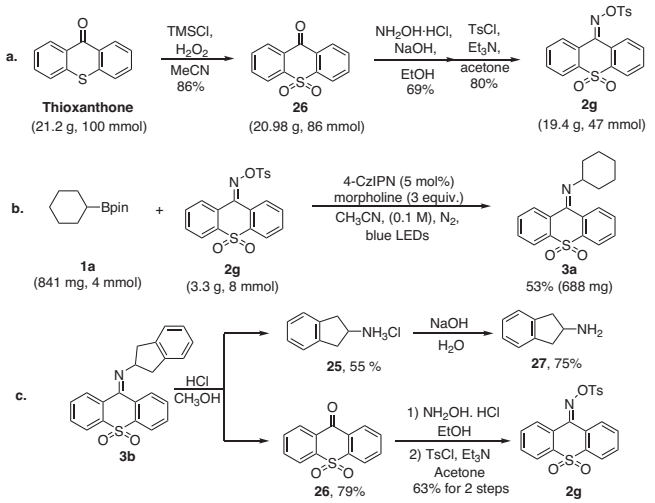

Fig. 8 | Scale-up reaction for reagent synthesis, deboronative aminations and hydrolysis experiment. a 19-gram scale synthesis of reagent **2g**. **b** 800-mg scale deboronative amination reaction. **c** Hydrolysis experiment to give free amine and recovery of ketone.

further application in C-H amination, deoxygenative amination, decarboxylative amination and three component trifluoromethylative/sulfonylative aminations were also realized. Given the importance of amination of organoboron compounds, we believe our radical process will be an important addition to this research area.

Methods

General procedure for deboronative amination reactions

An oven-dried vial (12 mL) equipped with a magnetic stirrer bar was sequentially charged with alkyl pinacol boronate (0.2 mmol, 1.0 equiv.), **2** (0.4 mmol, 2.0 equiv.), 4-CzIPN (4.0 mg, 0.01 mmol, 0.05 equiv.). The vial was evacuated and back-filled with nitrogen three times before CH_3CN (1.0 mL, 0.2 M) and morpholine (52.3 mg, 0.6 mmol, 3.0 equiv.) were added. Then, the vial was irradiated under blue LEDs for 16 h. After the reaction was completed, the solution was concentrated under reduced pressure. The residues were directly purified by column chromatography to give the desired product (notably, the silica gel used here was pre-neutralized with 5% triethylamine in petroleum ether solution prior to the usage, in order to minimize the product loss).

Data availability

The authors declare that the data supporting the findings of this study are available within the paper and its Supplementary Information files. Should any raw data files be needed in another format they are available from the corresponding author upon request. Source data are provided with this paper.

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Author contributions

J.W. conceived and directed the project. C.Z. performed the experiments and collected the data. X.B., J.L. conducted the DFT calculations. J.W., X.B., C.Z., and J.L. discussed the results. J.W. wrote the manuscript with contributions from all authors. All authors have read and approved the final version of the manuscript.

Competing interests

The authors declare no competing interests.

Additional information

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