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Photoinduced Deaminative Borylation of Alkylamines

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Supporting Information Placeholder

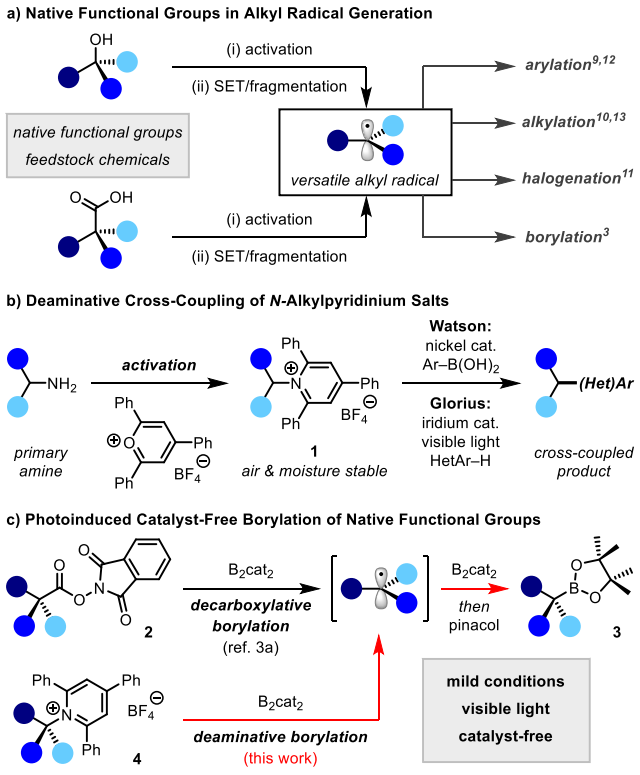
ABSTRACT: An operationally simple deaminative borylation reaction of primary alkylamines has been developed. The formation of electron-donor-acceptor complexes between *N*-alkylpyridinium salts and bis(catecholato)diboron enables photoinduced single-electron transfer and fragmentation to carbon-centered radicals, which are subsequently borylated. The mild conditions allow a diverse range of readily available alkylamines to be efficiently converted into synthetically valuable alkylboronic esters under catalyst-free conditions.

Boronic esters are arguably the most versatile functional groups available.[1,2] Traditionally, aliphatic organoborons were prepared from petrochemically-derived olefins but recent developments have provided new routes to these important molecules from sustainable chemical feedstocks.[3] Strategies that can transform readily available native functional groups,[4] such as carboxylic acids,[5] alcohols[6] and amines,[7] into valuable building blocks are highly attractive. While such approaches are well-established for substitution and cross-coupling reactions at sp^2 carbon centers,[5–7] related transformations at unactivated sp^3 positions have only recently gained significant attention from the synthetic community.[8] This has largely resulted from an increased interest in radical chemistry, which has provided innovative methods that use carboxylic acids[9–11] and alcohols[12–13] in a variety of transformations, including borylations,[3] proceeding through single-electron transfer (SET)-induced fragmentations to generate alkyl radical intermediates (Scheme 1a).

In contrast, alkylamines, which are another class of readily available feedstock chemicals, have barely been utilized. There are only two reports detailing the application of unactivated primary alkylamines in cross-coupling reactions by the groups of Watson and Glorius.[14] These used easily prepared Katritzky pyridinium salts **1**,[15] which undergo facile single-electron reduction and fragmentation, catalyzed by nickel or photoexcited iridium complexes (Scheme 1b).[16] The resulting alkyl radicals were demonstrated to participate in cross-coupling reactions with aryl boronic acids or homolytic substitutions with heteroaromatic rings.

We recently reported a photoinduced decarboxylative borylation for the synthesis of alkylboronic esters **3** from carboxylic acids (Scheme 1c).[3a] The reaction proceeds under catalyst- and additive-free conditions due to the efficient photoexcitation of an electron-donor acceptor (EDA) complex between an *N*-hydroxyphthalimide ester **2** and bis(catecholato)diboron (B_2cat_2).[17] Inspired by the works of Watson and Glorius,[14] we questioned whether this type of reactivity could be extended to a deaminative borylation, wherein Katritzky's *N*-alkylpyridiniums **4** could act as acceptors for the formation of EDA complexes with B_2cat_2. This would provide a catalyst-free photoinduced C–N bond activation to transform readily available primary amines into boronic esters. Herein, we describe the successful application of Katritzky's pyridinium salts in deaminative borylations that proceed under mild, operationally simple, catalyst- and additive-free conditions, promoted by irradiation with visible light. Notably, this is the first example of a borylation reaction of unactivated $C(sp^3)$–N bonds.[18]

Scheme 1. Native Functional Groups as Alkyl Radical Precursors

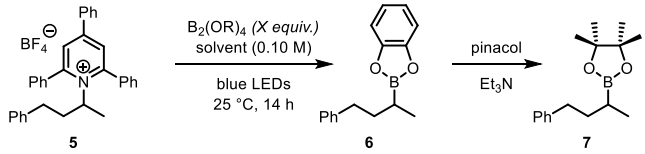


We began our investigations by studying the reaction between *N*-alkylpyridinium **5** and B_2cat_2 in *N*,*N*-dimethylacetamide (DMA) under irradiation with blue LEDs (Table 1). To our delight, these simple conditions led to the formation of the desired boronic ester in 89% yield, after transesterification of the initially generated catechol boronic ester **6** to the stable pinacol boronic ester **7** (entry 1). The important role of the electron-rich aromatic diol ligand,

catechol, on the boron reagent was highlighted by the failure of bis(pinacolato)diboron (B_2pin_2) or tetrahydroxydiboron [$B_2(OH)_4$] to give more than trace amounts of **7** (entries 2 and 3). Interestingly, the borylation reaction could be performed with $B_2(OH)_4$ if catechol was also added to the reaction, albeit with slightly lower yield (entry 4). The benficial effect of light was demonstrated by the significantly lower yield obtained when the reaction was performed in the dark (entry 5). However, the reactivity could be restored by heating for prolonged periods (entry 6). Evaulating various solvents indicated that those with Lewis basic sites, such as DMA and DMF were required for the reaction. The use of Lewis basic solvents was also found to be crucial in our previously reported decarboxylative borylation reaction, which was attributed to the stabilization of the boryl radical involved in the chain process.[3a] Finally, reducing the amount of B_2cat_2 to 1.5 equivalents resulted in a small decrease in yield (entry 12), which was subsequently improved by increasing the concentration to 0.20 M (entry 13).

With the optimum conditions in hand, the scope of this deaminative borylation reaction was explored (Table 2). A range of secondary alkylamines were efficiently transformed into the corresponding pinacol boronic esters **7**–**14**, including those possessing carbamate- or phthalimide-protected amines (**12**–**13**) and free alcohols (**14**). The reaction was also found to be scalable, as demonstrated by the preparation of boronic ester **7** on a 2.0 mmol scale, providing almost identical yield to that obtained on small-scale. Unfortunately, amines bearing tertiary alkyl groups could not be utilized in this borylation protocol due to the inability of these more sterically hindered amines to form the requisite pyridinium salts. On the other hand, primary alkylamines proved to be viable substrates, with the corresponding *N*-alkylpyridiniums undergoing efficient deaminative borylation to afford primary alkylboronic esters **15**–**32**. Aromatic rings bearing ether, cyano, and primary sulfonamide groups were tolerated (**18**–**20**), as were various heteroaromatics (**21** and **22**). A variety of other useful motifs could also be incorporated into the amine substrates, such as silyl ethers (**23**), carboxylic acids (**24**), alkyl and benzoyl esters (**25**–**27**), secondary amides (**28**), alkynes (**29**), and olefins (**30**). In addition, diamine substrates, including 1,8-diaminooctane and a diamino disiloxane underwent double deaminative borylation to afford the bis(boronic ester) products **31** and **32**, repectively. The excellent functional group tolerance of the mild reaction conditions also enabled the preparation of boronic ester derivatives of a number of complex natural products, including those derived from amino acids ornithine (**33**) and lysine (**34**), terpines pinanamine (**35**) and

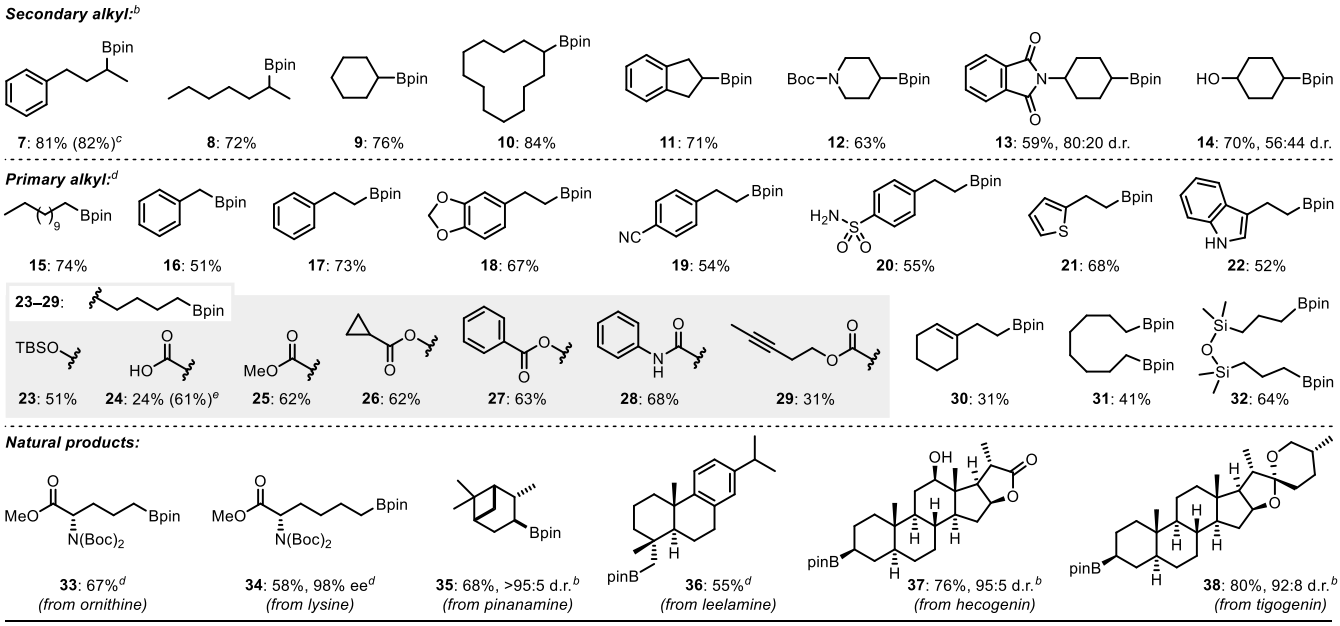
Table 1. Optimization Studies[a]



entry	$B_2(OR)_4$ (equiv.)	solvent	Modifications	**7** (%)[b]
1	B_2cat_2 (2.0)	DMA	-	89
2	B_2pin_2 (2.0)	DMA	-	0
3	$B_2(OH)_4$ (2.0)	DMA	-	1
4	$B_2(OH)_4$ (2.0)	DMA	with 2.0 equiv. catechol	70
5	B_2cat_2 (2.0)	DMA	no light	35
6	B_2cat_2 (2.0)	DMA	no light, 65 °C, 24 h	72
7	B_2cat_2 (2.0)	DMF	-	84
8	B_2cat_2 (2.0)	MeCN	-	2
9	B_2cat_2 (2.0)	EtOAc	-	7
10	B_2cat_2 (2.0)	THF	-	41
11	B_2cat_2 (2.0)	DCE	-	3
12	B_2cat_2 (1.5)	DMA	-	81
13	B_2cat_2 (1.5)	DMA	0.20 M concentration	91

[a]All reactions were carried out using 0.10 mmol of pyridinium **5**. [b]Yields are of the pinacol boronic ester after transesterification and were determined by GC using biphenyl as internal standard. DMA = *N*,*N*-dimethylacetamide; DMF = *N*,*N*-dimethylformamide; DCE = 1,2-dichloroethane; cat = catecholato; pin = pinacolato.

Table 2. Substrate Scope[a]



[a]Reactions were carried out with 0.30 mmol of the pyridinium salt. Yields are of isolated products after purification. [b]Reactions performed using conditions from Table 1, entry 13. [c]Reaction performed on a 2.0 mmol scale. [d]Reactions carried out at 0.25–0.75 M with 1.1–3.0 equiv. of B_2cat_2 at 45 °C. See Supporting Information for exact experimental procedures. [e]NMR yield shown in parenthesis. TBS = *tert*-butyldimethylsilyl.

leelamine (**36**), and steroids hecogenin (**37**) and tigogenin (**38**) in high diastereoselectivity. It should be noted that under the deaminative cross-coupling conditions developed by Watson and co-workers (Scheme 1b), a lysine derivative underwent partial racemization to give the product in low ee.[14a] However, under our deaminative borylation conditions, lysine derivate **34** was isolated in 98% ee.

To gain further insight into the mechanism of this photoinduced deaminative borylation reaction, we began by investigating the formation of the proposed EDA complex between *N*-alkylpyridinium **5** and B_2cat_2 by UV/Vis absorption spectroscopy (Figure 1).[19] When a DMA solution of pyridinium was treated with B_2cat_2, a dramatic color change was observed (Figure 1A), and this was accompanied by a bathochromic shift in the absorption spectrum, which is diagnostic of an EDA complex (Figure 1B). The nature of this interaction was further investigated by employing Job's method of continuous variation, which confirmed the stoichiometry of the complex as 1:1.[20] Additional insight into the mechanism was obtained from the borylation of cyclopropyl substrate **39**, which yielded the ring-opened product **40** (Figure 1C); and alkynyl substrate **42**, which gave the exocyclic alkenyl boronic ester **43** (Figure 1D), thereby confirming the formation of radical intermediates.[21,22] This was also supported by the generation of diastereomeric mixtures of borylated products **13** and **14** from single diastereomers (*trans*) of the amine substrates (Table 2). Finally, the quantum yield for the borylation of **5** was determined to be Φ = 7.0, indicating that a radical chain process is operative.

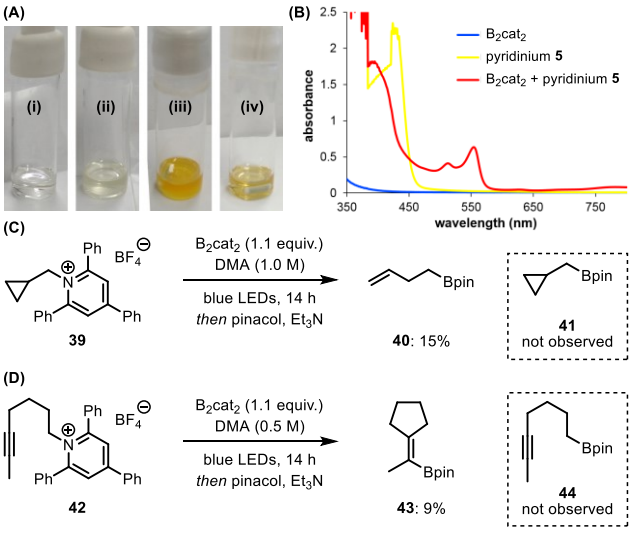
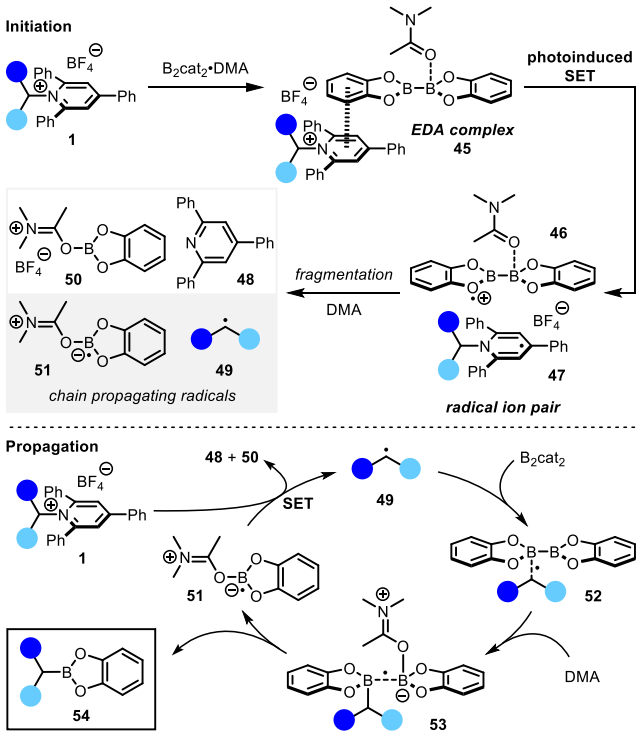


Figure 1. Mechanistic Studies. (A) Comparison of the colors of DMA solutions of B_2cat_2 (i), pyridinium (ii), and mixtures of B_2cat_2 and pyridinium prior to irradiation (iii) and after 14 h irradiation (iv). (B) UV/Vis absorption spectra of DMA solutions of B_2cat_2 (0.15 M), **5** (0.10 M), and a mixture of B_2cat_2 (0.15 M) and **5** (0.10 M). (C) Radial-mediated cyclopropane ring-opening. (D) Radical-mediated 5-*exo-dig* cyclization.

Based on the above observations, we propose the mechanism outlined in Scheme 2. Initiation of the radical chain begins with formation of EDA complex **45** between *N*-alkylpyridinium **1** and the B_2cat_2•DMA adduct.[3a] Photoexcitation of **45** triggers a SET to form a radical ion pair comprised of radial cation **46** and dihydropyridine radical **47**. Fragmentation of **47** generates pyridine **48** and the alkyl radical **49**, whereas **46** fragments to form the cationic DMA–Bcat adduct **50** and the DMA-stabilized boron-centered radical **51**.[23] In a recent report by Studer and co-workers, the lowest energy pathway for formal homolytic substitution at boron of B_2cat_2 by a carbon-centered radical was calculated to proceed via initial reaction of the radical with B_2cat_2, followed by complexation with a Lewis base (DMF) prior to fragmentation.[24] As such, propagation of the deaminative borylation likely proceeds via reaction of alkyl radical **49** with B_2cat_2 to generate radical **52**. After complexation with DMA, forming **53**, fragmentation provides the alkylboronic ester product **54** and boryl radical **51**. Lewis base-stabilized boron-centered radicals have recently been demonstrated to be strong single-electron reductants,[25] thus we propose that SET from **51** to *N*-alkylpyridinium **1** ($E_{1/2}$ = –0.93 V vs. SCE in DMF)[26] regenerates alkyl radical **49** to propagate the radical chain.

Scheme 2. Proposed Mechanism



In conclusion, we have developed the first deaminative borylation reaction of unactivated aliphatic primary amines, proceeding via the reaction of *N*-alkylpyridinium salts with B_2cat_2. The reaction proceeds under mild, catalyst-free conditions, promoted by irradiation with visible light. Key to the success of the reaction was the use of B_2cat_2, whose electron-rich aromatic diol ligands enabled efficient formation of EDA complexes with the electron-deficient pyridiniums. Given the ready availability of primary amines from feedstock chemicals, we anticipate that this operationally simple deaminative borylation will find widespread application for the preparation of synthetically and biologically important boron-containing molecules.

ASSOCIATED CONTENT

Supporting Information.
The Supporting Information is available free of charge on the ACS Publications website.

Detailed experimental procedures and characterization of all products (PDF).

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Notes

The authors declare no competing financial interests.

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