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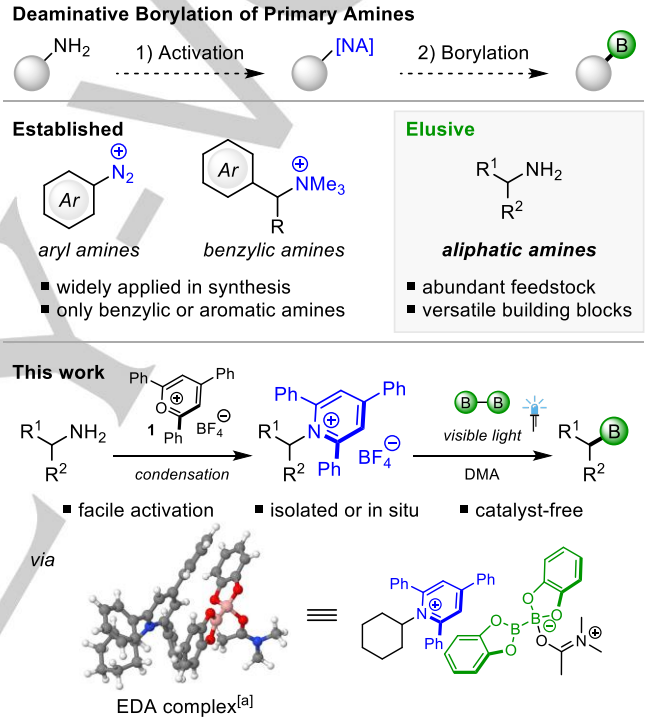
Deaminative Borylation of Aliphatic Amines Enabled by Visible Light Excitation of an Electron-Donor-Acceptor Complex

Frederik Sandfort[+], Felix Strieth-Kalthoff[+], Felix J. R. Klauck, Michael J. James, and Frank Glorius*

Abstract: A deaminative strategy for the borylation of aliphatic primary amines is described. Alkyl radicals derived from the single-electron reduction of redox-active pyridinium salts, which can be isolated or generated in situ, were borylated in a visible light-mediated reaction with bis(catecholato)diboron. No catalyst or further additives were required. The key electron-donor-acceptor complex was characterized in detail by both experimental and computational investigations. The synthetic potential of this mild protocol was demonstrated through the late-stage functionalization of natural products and drug molecules.

Organoboronic acids and their esters are among the most prominent molecules used in organic chemistry. Their value as synthetic intermediates, as well as target molecules, has been proven over the last decades, emphasized by the Nobel prize for the Suzuki-Miyaura coupling in 2010. While the synthesis of aromatic boronic acids has been widely established,[1] chemists have recently turned their focus towards the development of methods for the synthesis of aliphatic boronates.[2] Besides their use in organic synthesis, these molecules may also possess biological activity and have consequently been utilized in medicinal chemistry programs.[3,4] Traditionally, C_{sp3}–B bonds are formed either by trapping of organometallic intermediates with borates, or from the corresponding olefins via hydroboration.[1] More recent borylation methods have sought to use milder conditions and precursors derived from naturally abundant and inexpensive feedstock chemicals. In this context, radical-mediated processes, in which alkyl radicals are borylated with (activated) diboranes, have become increasingly important.[5] A number of prominent examples of this approach using activated carboxylic acids, namely redox-active *N*-hydroxyphthalimide esters, as precursors for borylation have been independently reported by the groups of Baran, Li and Aggarwal.[6] In this regard, primary aliphatic amines also present a potentially interesting precursor for borylation (Scheme 1), as they are a natural feedstock of similar abundance to carboxylic acids and are present in numerous natural products and drugs.[7] Thus, their synthesis and use as versatile building blocks in organic synthesis has already been widely explored.[8] The borylation of primary amines has previously been reported for aromatic and benzylic amines through the use of the corresponding diazonium or trimethylammonium salts.[9] However, the borylation of simple aliphatic amines remains an unresolved challenge in organic synthesis.[10] One method to activate aliphatic primary amines is via the formation of redox-active pyridinium salts (Katritzky salts), which were originally used in two-electron pathways.[11] These salts are readily formed by simple condensation of the corresponding primary amine with the commercially available pyrylium salt **1** and can usually be isolated by filtration. The synthetic use of Katritzky salts has recently been demonstrated by the Watson group in the context of Nickel catalysis,[12] as well as under photocatalytic conditions by our group.[13] In both cases, single-electron reduction of the Katritzky salt is proposed to give rise to an alkyl radical intermediate.



Scheme 1. General outline of deaminative borylation protocols and the deaminative borylation of aliphatic primary amines (this work). [a] Geometry determined by DFT calculations.

In modern organic synthesis, single-electron-transfer processes are often mediated by photoredox catalysis.[14] Whilst these methods have been used to enable a number of challenging transformations, the photocatalysts are still typically based on expensive transition metal complexes. Thus, photocatalyst-free methods, which can directly use visible light as one of the mildest, cheapest and greenest forms of energy available, are highly desirable.[15] To meet this end, single-electron-transfer processes can be promoted in the absence of a photocatalyst if either one reaction partner or an encounter complex of two or more molecules is excited. The latter is generally described as an electron-donor-acceptor (EDA) complex.[16,17]

Considering the above, and based on our previous work, we questioned whether Katritzky salts could serve as acceptors in EDA-promoted reactions to enable challenging functional group interconversions under catalyst-free conditions. Herein, we describe the visible light-mediated deaminative borylation of primary aliphatic amines under catalyst- and additive-free

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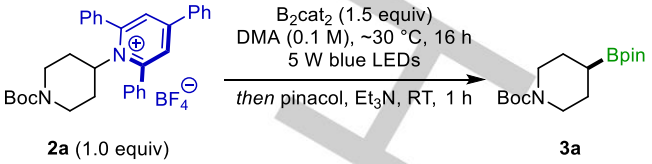
conditions. This reaction was enabled by the formation and irradiation of a ternary EDA complex of the Katritzky salt, bis(catecholato)diboron (B_2cat_2) and DMA (*N,N*-dimethylacetamide). A range of primary, benzylic and secondary Katritzky salts, including those derived from natural products, were all converted into high value aliphatic boronic esters.

Our studies began by examining known boron-based EDA complex donors in combination with Katritzky salt **2a**.[6c,6d] Pleasingly, we observed the appearance of a significant color change when dissolving Katritzky salt **2a** and B_2cat_2 in DMA, which was a strong indicator that the Katritzky salts could indeed undergo the desired EDA complex formation. Through optimization studies we found that the desired borylated product **3a** could be isolated in 94% yield by irradiating a mixture of Katritzky salt **2a** and 1.5 equivalents of B_2cat_2 in DMA (0.1 M) under an atmosphere of argon with visible light (λ_{max} = 455 nm, 5 W blue LEDs) for 16 h followed by transesterification with pinacol and Et_3N (table 1, entry 1). Other boron sources such as B_2pin_2, or the use of non-coordinating solvents such as CH_2Cl_2, did not lead to any product formation (table 1, entries 2,3). However, when adding 5.0 equivalents of DMA to the reaction mixture in CH_2Cl_2 the desired product could still be formed in 77% yield (table 1, entry 4). Through further optimization we found that both the amount of B_2cat_2 and the reaction time could also be decreased to only 1.2 equivalents and 6 h, respectively (table 1, entry 5). A control experiment without light revealed formation of the desired product in 60% yield after 16 h reaction time (table 1, entry 6). However, further studies showed that the thermal reactivity was strongly substrate-dependent.[18]

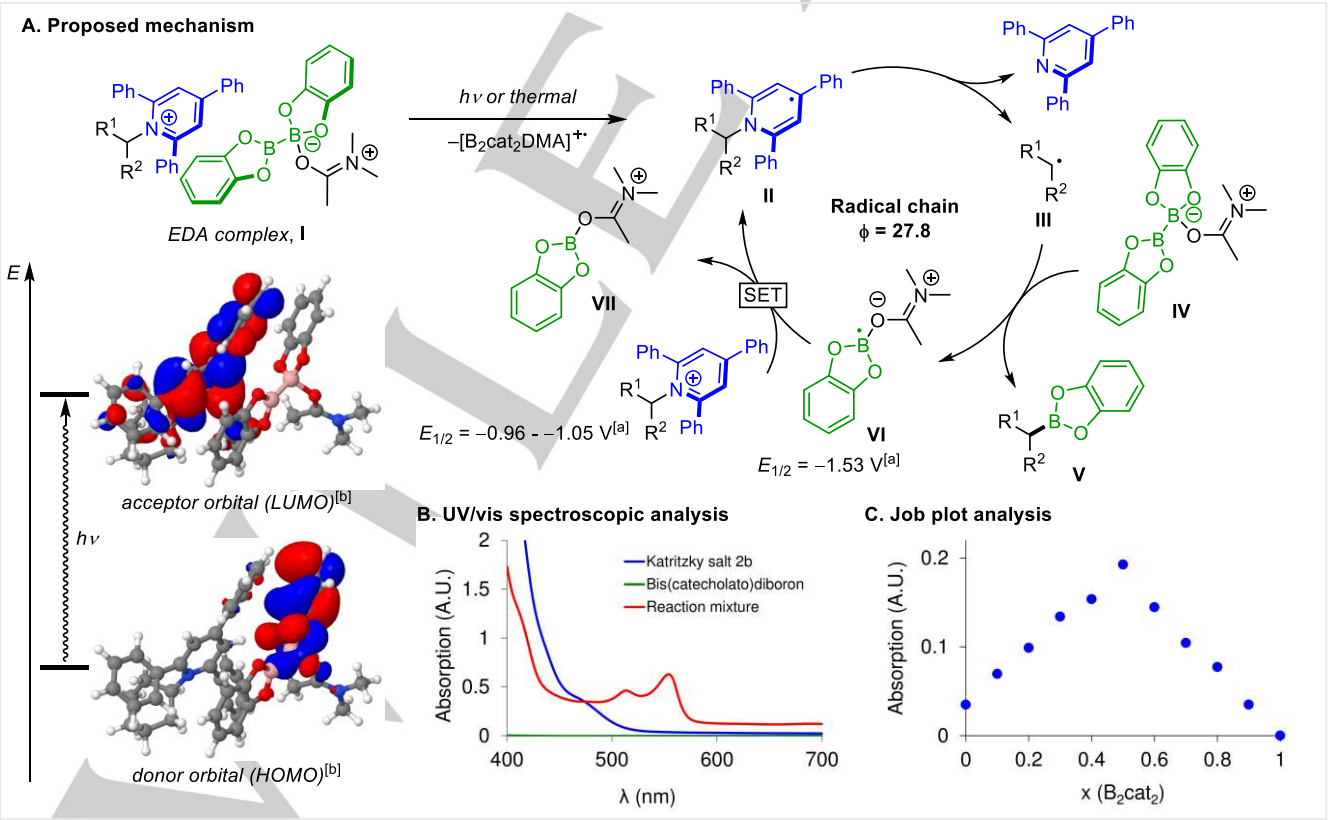
Table 1. Visible light-mediated deaminative borylation of Katritzky salt **2a**.



2a (1.0 equiv) **3a**

Entry	Variation from standard conditions[a]	Yield [%][b]
1	none	94
2	B_2pin_2 (1.5 equiv) instead of B_2cat_2	0
3	CH_2Cl_2 instead of DMA	0
4	CH_2Cl_2 + DMA (5.0 equiv)	77
5	**B_2cat_2 (1.2 equiv), 6 h reaction time**	**95 (91)[c]**
6	no irradiation	60
7	under air	0
8	TEMPO (2.0 equiv)	0

[a] Conditions: **2a** (0.10 mmol), B_2cat_2 (0.15 mmol) and DMA (0.1 M) under argon. [b] Yields determined by ^{1}H NMR spectroscopic analysis using 1,3,5-trimethoxybenzene as internal standard. [c] Isolated yield on a 0.3 mmol scale in parentheses.

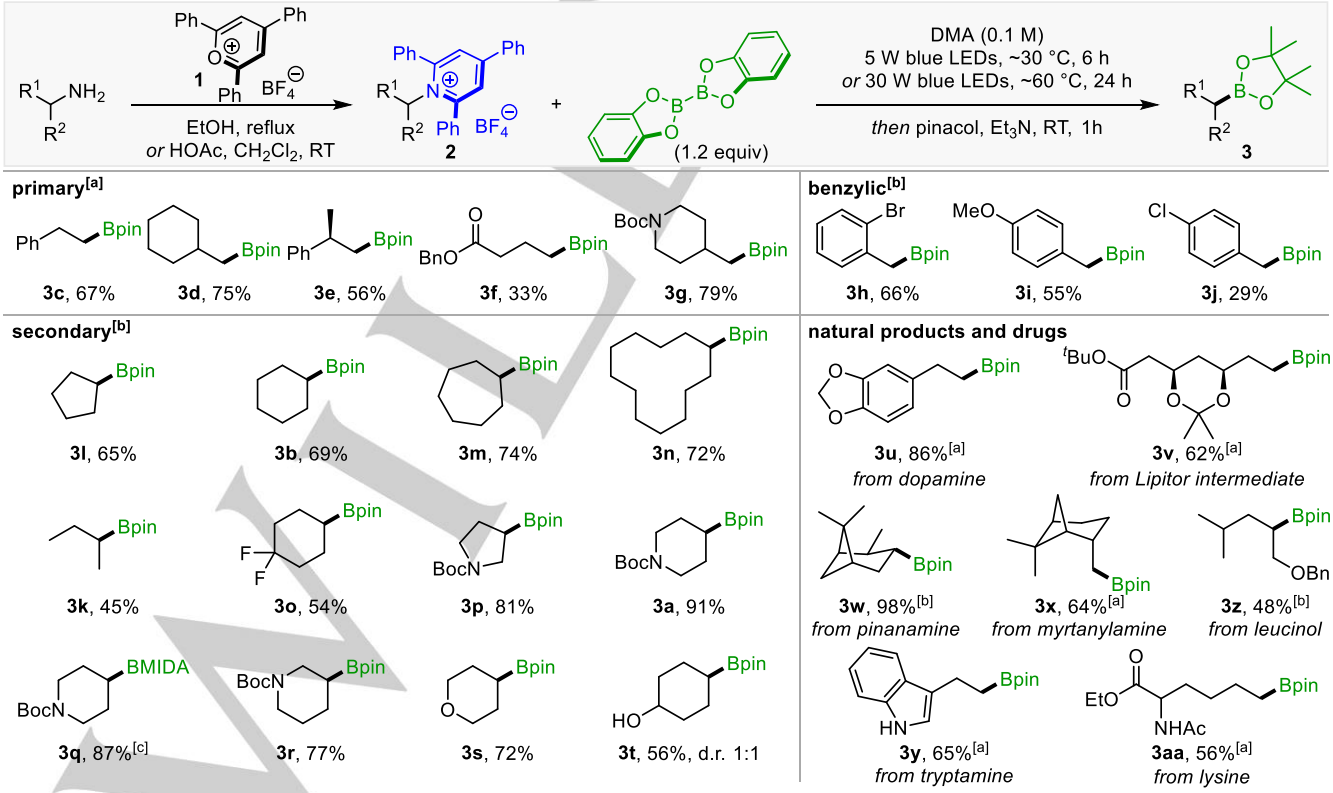


Scheme 2. A. Proposed reaction mechanism. B. UV/vis spectra of Katritzky salt **2b**, B_2cat_2 and the reaction mixture in DMA. C. Job plot of Katritzky salt **2b** and B_2cat_2 in DMA. [a] Calculated redox potentials in MeCN vs SCE. [b] TDDFT-computed donor and acceptor orbitals of a charge transfer transition in the EDA complex.

To fully confirm and establish the use of Katritzky salts as acceptors in EDA complexes, we next sought to characterize the true nature of the complex and the reaction mechanism itself. While neither Katritzky salt **2b**, derived from cyclohexylamine, nor B_2cat_2 showed significant UV/vis absorption at 550 nm, an absorption shoulder appeared in the spectrum of the reaction mixture, supporting the formation of an EDA complex (Scheme 2, **B**). However, this shoulder was not present when the reagents were dissolved in CH_2Cl_2, but appeared and grew stronger upon the successive addition of DMA,[18] suggesting the formation of a ternary EDA complex. A subsequent Job plot analysis revealed a 1:1 adduct formation of Katritzky salt **2b** and B_2cat_2 in DMA (Scheme 2, **C**). Based on these results we propose EDA complex **I**, primarily stabilized by π-π interactions. Computational investigations using time-dependent density functional theory (TDDFT) calculations revealed three significant excitations with $\lambda > 400$ nm, which can all be assigned to charge-transfer-type transitions.[18] The involved molecular orbitals (HOMO & LUMO) are depicted in Scheme 2. A transition between these orbitals directly corresponds to the proposed single-electron transfer from the B_2cat_2 to the Katritzky salt.

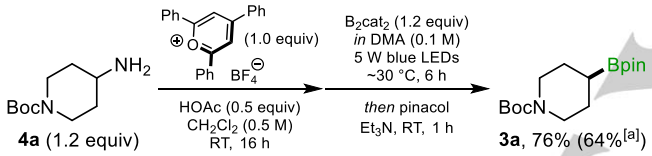
Further evidence for the radical nature of the reaction was obtained when all product formation was inhibited by the presence of air or TEMPO (table 1, entries 7,8). Next, quantum yield determination (Φ = 27.8) suggested a radical chain mechanism to be operative. Consequently, we propose the following mechanistic scenario (Scheme 2, **A**): First, the radical chain is initiated by photochemical or thermal electron transfer within EDA complex **I** to form pyridinyl radical **II**. Fragmentation of intermediate **II** leads to the formation of alkyl radical **III**, which then undergoes borylation with DMA-activated B_2cat_2 **IV** to form boronic ester **V** and open-shell boron species **VI**. Finally, electron transfer from open-shell species **VI** to the Katritzky salt enables chain propagation. Computationally determined redox potentials suggest that this electron transfer step is thermodynamically feasible.

Having concluded mechanistic investigations, we began scoping studies for this deaminative borylation reaction (Scheme 3). Pleasingly, we found a variety of previously unreactive sterically different primary Katritzky salts[13] could all undergo borylation in good yield (**3c**–**e**).[18] Different functional groups, such as carboxylic acid esters or protected amines were well-tolerated (**3f**–**g**). Benzylic boronic esters were also isolated in moderate to good yield (**3h**–**j**). Notably, aryl bromides and aryl chlorides were tolerated, providing opportunity for further functionalization. However, when electron poor benzylic Katritzky salts were used, dimerization of the corresponding benzylic radical was observed as a major byproduct. Acyclic and cyclic secondary Katritzky salts with varying ring sizes all underwent borylation efficiently (**3k**–**o**). Furthermore, pharmaceutically relevant saturated heterocyclic amines afforded the desired products in generally very good yield (**3p**–**s**). The facile transesterification to a MIDA boronate was also demonstrated (**3q**) and even a free alcohol could be tolerated in this reaction process (**3t**). Having demonstrated the effectiveness of this borylation protocol for a variety of primary and secondary Katritzky salts, we sought to explore the late-stage functionalization of natural products and drugs. Pleasingly then, dopamine derivative **3u** as well as the highly functionalized boronic ester **3v** derived from a Lipitor intermediate were both isolated in good to excellent yield.



Scheme 3. Scope of the deaminative borylation. Conditions: **2** (0.30 mmol), B_2cat_2 (0.36 mmol) and DMA (0.1 M) under argon. [a] Irradiation with 30 W blue LEDs for 24 h at ~60 °C. [b] Irradiation with 5 W blue LEDs for 6 h at ~30 °C. [c] Transesterification: Methyliminodiacetic acid (MIDA), 60 °C, 24 h.

Furthermore, sterically demanding natural products pinanamine and myrtanylamine were also efficiently borylated as was unprotected tryptamine containing a free N–H group (**3w**–**y**). From natural amino acids derived protected leucinol and lysine afforded the corresponding products **3z** and **3aa** in moderate yield. As mentioned previously, the Katritzky salts are formed via a simple and efficient condensation reaction, which can also be carried out at room temperature in CH_2Cl_2, if acetic acid is used as a Brønsted acid catalyst.[19] However, in some cases isolation can be difficult if the Katritzky salt does not precipitate. Thus, we sought to develop a one-pot procedure in which the Katritzky salt is generated and reacted in situ. As a solvent mixture of CH_2Cl_2 and DMA was already successful for borylation during the optimization process, we were confident that such a protocol could be realized. Pleasingly, we found that simply through the addition of a solution of B_2cat_2 in DMA to a pre-formed Katritzky salt solution in CH_2Cl_2, followed by the standard borylation procedure, the desired product **3a** could be isolated in 76% yield directly from amine **4a** (Scheme 4). Compared to isolation of Katritzky salt **2a** (70%)[13] and successive borylation with our method, the one-pot borylation even offers a slight increase in yield over two steps (76% vs. 64%). This one-pot protocol is significant for enabling the first direct deaminative borylation of primary amines.



Scheme 4. One-pot borylation procedure via in situ generation of Katritzki salt **2a**, performed on a 0.3 mmol scale. [a] Performed on a 2.5 mmol scale.

In summary, we report the deaminative borylation of primary aliphatic amines via the use of Katritzky salts as acceptors in EDA complexes. The reaction proceeds under mild visible light-mediated conditions and requires only a coordinating solvent and no further catalysts or additives. We propose a radical chain mechanism initiated by an EDA complex based on experimental and computational studies. The method efficiently converts primary, benzylic and secondary amines into the corresponding borylated products. The synthetic value of this methodology is further demonstrated through the late-stage functionalization of natural products and drug molecules. Notably, direct amine to boronate interconversion can also be performed in a one-pot process, whereby the Katritzky salt is not isolated but reacted in situ. Further studies into the full synthetic potential and use of Katritzky salts as acceptors in EDA complexes are ongoing in our laboratory.

Acknowledgements

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Keywords: borylation • deaminative strategy • visible light • electron-donor-acceptor • DFT calculations

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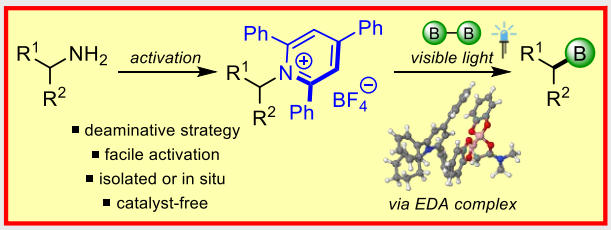

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Deaminative Borylation. A deaminative strategy for the borylation of aliphatic amines is described. Alkyl radicals derived from redox-active pyridinium salts were borylated in a visible light-mediated reaction with bis(catecholato)diboron. The synthetic potential of this method was demonstrated by late-stage functionalization of natural products and drug molecules. The key electron-donor-acceptor complex is characterized in detail by various experiments as well as computational investigations.

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