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C-N Borylation

Lewis Base Promoted Selective C-N Borylation of Alkyl Amines

Jiefeng Hu[+], Guoqiang Wang[+], Shuhua Li, and Zhuangzhi Shi**

Abstract: *An efficient method for metal-free deaminative borylation of alkylamines using bis-(catecholato)diboron as the boron source to directly synthesize various alkyl potassium trifluoroborate salts is introduced. The key to this high reactivity is the utilization of pyridinium salt-activated alkylamines, with a catalytic amount of a bipyridine-type Lewis base as a promoter. This transformation shows good functional group compatibility (e.g., being unimpeded by the presence of a ketone, indole, internal alkene, or unactivated alkyl chloride) and can serve as a powerful synthetic tool for borylation of amine groups in complex compounds. Mechanistic experiments and computations suggest a mechanism in which the Lewis-base activated B_2cat_2 unit intercepts an alkyl radical generated by single-electron transfer (SET) from a boron-based reductant.*

Boronic acids and their derivatives play important roles in a variety of fields ranging from material science to drug discovery and organic synthesis.[1] They are usually prepared by either lithium compounds or Grignard reagents, processes which are not compatible with many functional groups.[2] The Miyaura-type[3] and radical-mediated[4] borylation methods developed over the past decades have enabled efficient approaches to build these useful compounds, which features a broad substrate scope and good functional group compatibility. Specifically, the selective borylation of unreactive chemical bonds has shown promise because it confers the synthetic versatility of inert functional groups.[5] However, these methods are usually well appreciated in the construction of arylboronic esters, and applying these strategies to synthesize alkylboronic esters[6] has yet to be broadly recognized. Very recently, Baran and coworkers reported the Ni-catalyzed decarboxylative borylation of alkyl *N*-hydroxyphthalimide esters from alkyl carboxylic acids with bis(pinacolato)diboron (B_2pin_2) to alkyl boronic esters through alkyl radical intermediates.[7] Later, Aggarwal et al. also uncovered that this transformation could also be promoted by visible light at room temperature in the presence of bis(catecholato)diboron (B_2cat_2).[8] Similar to alkyl carboxylic acids in terms of natural abundance, alkylamines have received less attention, and their deaminative borylation has been virtually unexplored.

Amines are known to be poor electrophiles because of the resonance stability of the C-N bond. Therefore, the selective break the C-N bond of an amine to build C-B bond is a very valuable transformation in organic chemistry. In 2010, Wang et al. developed a novel metal-free method for the synthesis of arylboronates from

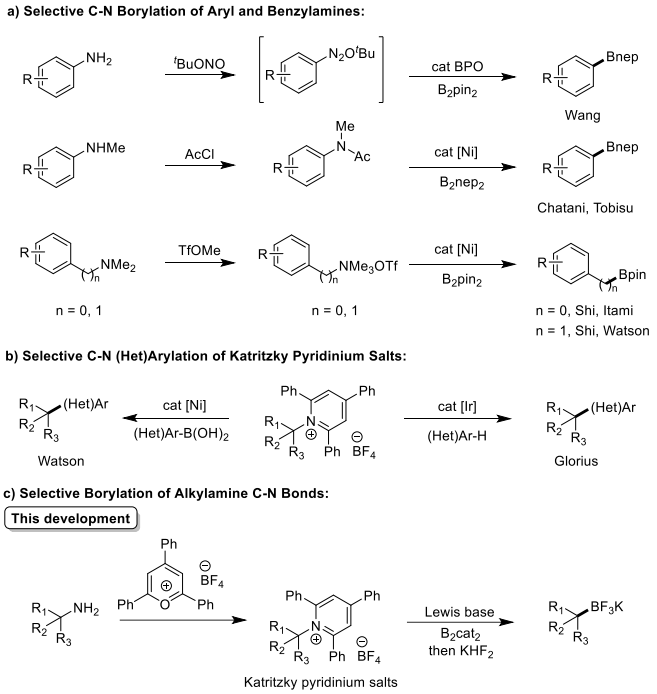

Figure 1. Selective borylation of alkylamine C-N bonds.

arylamines with B_2pin_2 *via* the Sandmeyer reaction process.[9] In 2014, Tobisu and Chatani developed Ni-catalyzed borylative cleavage of sp^2 C-N bonds in *N*-aryl amides and carbamates.[10] In 2016, we and other groups also reported Ni-catalyzed aryl and benzyl C-N bond borylation *via* ammonium salts under mild conditions (Figure 1a).[11] Inspired by recent progress from Watson[12] and Glorius[13] groups, the Katritzky salts[14] generated from alkylamines can act as alkylating agents in radical induced deaminative arylation (Figure 1b). Moreover, we[15] first uncovered the B-B bond cleavage by a Lewis base, 4-cyanopyridine, to produce a pyridine-stabilized boryl radical.[16] We envisioned that if the transient alkyl radical generated from Katritzky pyridinium salts and the stabilized boryl radical were formed in one reaction system, selective cross-coupling of these two species might build sp^3 C-B bonds.[17] Herein, we report our results on the utilization of pyridinium salt-activated alkylamines as the electrophilic component in a Lewis base-promoted deaminative borylation reaction (Figure 1c).

We began the investigations by monitoring the reactivity of the pyridinium salt **1b** derived from a primary amine **1a** with B_2cat_2. The reaction was found to be facile, with 1.5 equiv of B_2cat_2 in the presence of a Lewis base, dtbpy (10 mol %), in DMA after 6 h at 100 °C. Since the catechol boronate product is not stable, the crude product can transfer to potassium trifluoroborate salt **1c** with KHF_2 in 62% yield by trituration with hot acetone or transesterification with pinacol to boronic ester **1c'** in 72% yield (entry 1). Significantly, dtbpy can accelerate the C-N borylation process (entries 2-4) and other Lewis bases, such as py and bpy, were also effective for this transformation albeit with lower yields (entries 5-6). Other diboron reagents, such as B_2pin_2, did not provide the corresponding carboboration product (entry 7). The use of Lewis basic solvents, such as DMA or DMF (entry 8), was required for the reaction, and using toluene as a solvent led to a very low yield (entry 9). At a lower temperature (80 °C), the results were found to be slightly inferior to those observed under the optimal conditions

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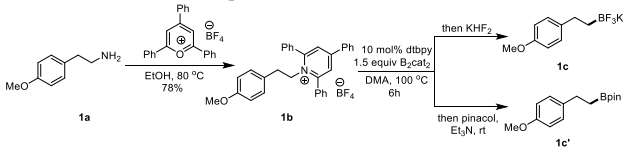
Table 1. Reaction development.[a]



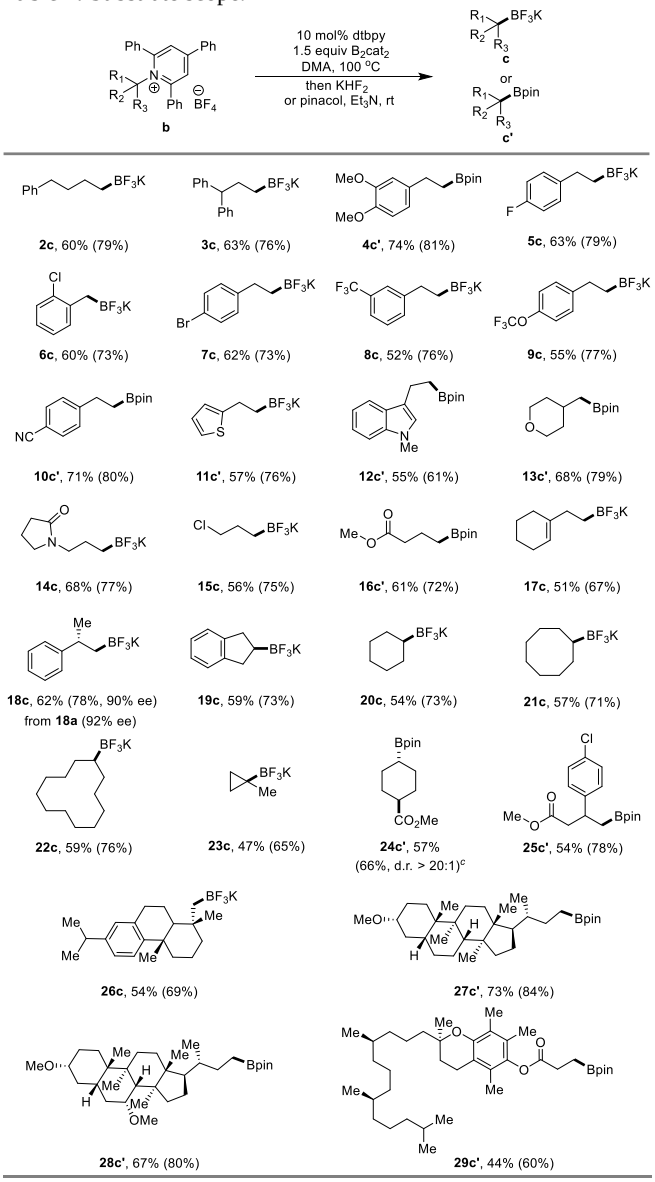
Entry	Variation from the standard conditions	Yield of **1c'** (%)[b]
1	none	84 (72[c], 62[d])
2	without Lewis base	28
3	without Lewis base, 12 h	41
4	without Lewis base, 24 h	49
5	using py instead of dtbpy	39
6	using bpy instead of dtbpy	69
7	B_2pin_2 instead of B_2cat_2	0
8	DMF	67
9	toluene	17
10	at 80 °C	78
11	at room temperature, 48 h	34
12	in the dark	80

[a] Reaction conditions: **1b** (0.40 mmol), B_2cat_2 (0.60 mmol), 10 mol% of dtbpy in DMA (1.0 mL), 100 °C, 6 h, under Ar. [b] Determined by crude ^{1}H NMR analysis based on **1c'**. [c] Isolated yield of **1c'**. [d] Isolated yield of **1c**. dtbpy = 4,4'-di-*tert*-butyl-2,2'-bipyridine; py = pyridine; bpy = 2,2'-bipyridine.

(entry 10), and the reaction at room temperature resulted in poor conversion, even with a prolonged time period (entry 11). Finally, the reaction could be conducted well in the dark, indicating it is not a visible-light-driven borylation (entry 12).

With the optimized reaction conditions in hand, we then examined the scope of this transformation (Table 2). To facilitate purification, we converted most products to the corresponding potassium trifluoroborate salts. Deaminative borylation of primary amine derivatives **2-10b** with different aryl moieties on the carbon chain proceeded smoothly. It should be noted that the chemoselectivity of the C-N borylation process was not affected by halo substituents such as F (**5c**), Cl (**6c**) and Br (**7c**) on the substrates, highlighting the potential of this process in combination with subsequent cross-coupling transformations. The couplings of substrates with heterocyclic aromatic motifs, such as thiophene (**11c'**) and indole (**12c'**), were also tolerable. Borylation of substrates containing ether (**13b**) and amide groups (**14b**) generated products **13c'** and **14c** in modest yields. Notably, substrate **15b**, with a primary alkyl chloride motif, was also found to be compatible with the reaction conditions. Amino acid derivative **16b** produced product **16c'** in 61% yield. Substrate **17b** with an internal alkenyl motif worked well under the optimized procedure. Furthermore, (R)-2-phenyl-1-propylamine (**18a**) with a preexisting stereocenter was preserved during the reaction (**18c**). A range of secondary alkylamines were also efficiently transformed into the corresponding potassium trifluoroborate salts **19-22c**. Importantly, tertiary amine **23b** could also be converted into the desired product **23c** in modest yield. Unfortunately, pyridinium salts from sterically hindered tertiary amines such as adamantyl amine can't be prepared. To further explore functional group compatibility of this method, an additive-based robustness screen was also performed (see Scheme S4 in SI for details).[18] The screen indicated the tolerance of the reaction to alcohols, epoxides, acetals, ketones, carboxylic acids, secondary amines, lactams, pyridines, silanes, internal alkynes and *α,β*-unsaturated esters. Aldehydes, terminal olefins, and alkynes as well as aziridines that likely underwent boron addition under the reaction conditions were predicted to be unsuitable substrates.

Table 2. Substrate scope.[a]



[a] Reaction conditions: A mixture of compound **b** (0.40 mmol), B_2cat_2 (0.60 mmol), and 10 mol% of dtbpy in THF (1 mL) was stirred for 6 h at 100 °C under Ar, for product **c**: saturated KHF_2 (4.5 M) at 0 °C, 3 h, isolated yields by trituration with hot acetone; for product **c'**: pinacol (1.2 mmol), Et_3N (1.0 mL), 1 h, isolated yields by column chromatography. Yields given within parentheses were determined by ^{1}HNMR analysis of crude product **c'**.

To showcase the utility of the transformation for diversifying natural-product amines, we prepared a diverse collection of Katritzky pyridinium salts and subjected them to the optimized reaction conditions. For example, the reaction of cyclic substrate **24b** only gave **24c'** in high diastereoselectivity. Product **25c'** is derived from a commercially available drug baclofen, a medication used to treat spasticity. Leelamine derivative **26b** could undergo C-N borylation with B_2cat_2 to produce product **26c** in 54% yield. Steroids **27-28b** were also readily transformed into boronates **27-28c'** in 67-73% yields. In addition, a vitamin E derivative **29b** was borylated with excellent chemoselectivity.

To investigate the reaction mechanism, we explored a radical clock experiment by performing the reaction on a cyclopropyl-containing substrate **30**. Under the standard conditions, we obtained ring-opening products **32** and **33**[19], and normal borylation product **31** was not detected (Scheme 1a). Additionally, the cross coupling of **34**, prepared from (S)-2-aminooctane, resulted in racemic **35**

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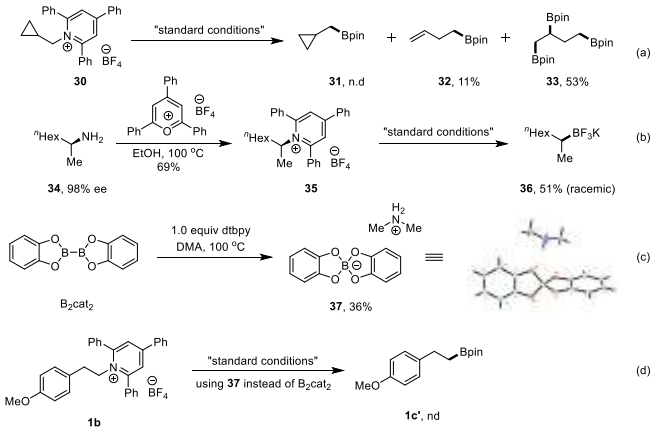
(Scheme 1b). These results indicate that this deaminative borylation undergo a radical-mediated pathway. In our system, we isolated a symmetrical tetraorganoborate complex **37**, likely by homolytic cleavage of the B–B bond, which was confirmed through X-ray (Scheme 1c). However, this complex could not transfer to the desired product, confirming that it was not a viable intermediate in this deaminative borylation process (Scheme 1d).



Scheme 1. Mechanistic experiments.

It is worth noting that dtbpy is crucial to accelerate the reaction of Katritzky salts and B_2cat_2. Therefore, we performed the density functional theory (DFT) calculations using the M06-2X functional[20] (see SI for details) to investigate the role of dtbpy in this radical process (Figure 2). The association of two N atoms of dtbpy with

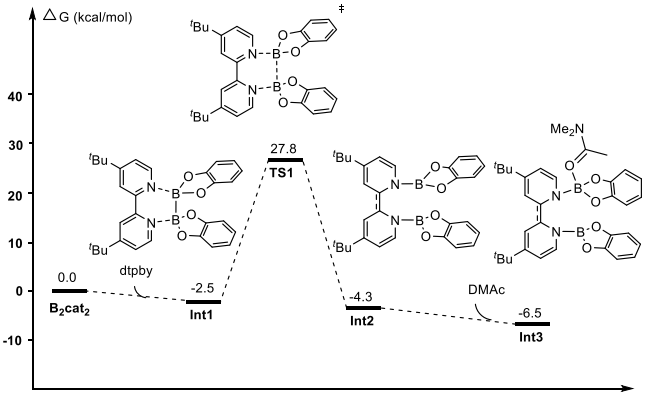


Figure 2. Gibbs free energy profile for the dtpby induced cleavage of the B-B bond of B_2cat_2 (all energies are given in kcal mol^{-1}).

B_2cat_2 forms a Lewis adduct **Int1**, which is exergonic by 2.5 kcal mol^{-1}. Then, the cleavage of B-B in **Int1** generates the bipyridinylidene intermediate **Int2**, and the corresponding barrier is 27.8 kcal mol^{-1} (with respect to separated B_2cat_2 and dtbpy). The **Int2** could be associated with the solvent DMAc to provide DMAc-**Int2** adduct (**Int3**). The formation of **Int3** is exergonic by 6.5 kcal mol^{-1}, suggesting the generation of **Int3** is possible under the experimental conditions. As demonstrated by ^{11}B NMR, the calculated ^{11}B NMR chemical shift (δ_B = 22.0 ppm) of **Int2** is in good agreement with the experimental ^{11}B NMR shift at ~20 ppm found in a 1:1 mixture of dtbpy and B_2cat_2 (Figure 3), which indicates that the association of **Int2** and DMAc is reversible at 100 °C. The bipyridinylidene derivative has recently been demonstrated to be a strong organic single electron reductant.[21] The calculated HOMO energy of **Int3** (-4.9 ev) is comparable to the bipyridinylidene derived from 4-DMAP[20] (-4.6 ev) (see Scheme S8 in SI for details). Thus, the species **Int3** may act as an electron donor. We speculate that SET from **Int3** to Katritzky salts (**a**) leads to the C-N fragmentation, generating the alkyl radical. This pathway is exergonic by 1.7 kcal mol^{-1} (see Scheme S9 in SI for details).

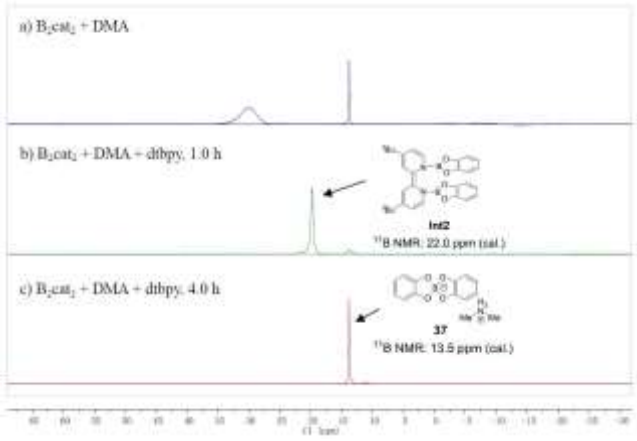


Figure 3. ^{11}B NMR studies of the reaction intermediates.

As shown in Figure 4, the homolytic cleavage of the B-N bond in **Int3** could generate the radical species dtbpy-Bcat (**Int3″**) and DMAc-Bcat (**Int4**), which is predicted to be only endergonic by 3.7 kcal mol^{-1}, suggesting that this process is also possible. It has been reported that the Lewis base-stabilized boron centered radicals can be considered as strong single-electron reductants.[6u, 16a] The calculated HOMO energy of **Int3″** and **Int4** is -4.7 ev and -5.6 ev, respectively. Thus, we proposed that the resulting Lewis base stabilized boron radical could also react with Katritzky salts *via* the SET process to form the alkyl radical **b'**. Hence, the *in situ* generated bipyridinylidene analogue (**Int3**) using dtbpy and B_2cat_2, or its fragmented species (**Int4**, **Int3″**), might be possible for single electron donors to initiate this radical process for subsequent borylation reaction. It has been demonstrated that alkyl *N*-hydroxyphthalimide ester could form an alkyl radical with B_2cat_2-DMAc adduct to trigger a SET process *via* a thermal or photochemical event.[8] However, the calculated HOMO energy of B_2cat_2-DMAc complex is -6.7 ev, which indicates that this complex is a weaker single electron reductant compared with **Int3**. These results are in accord with the experimental result that in the absence of dtbpy, the borylation product was obtained in a lower yield. The generated alkyl radical **b'** could couple with **Int4** to form the desired boronic ester **c**[16a]. Alternatively, radical **b'** could also react with B_2cat_2 to generate the final product **c**. [6u]

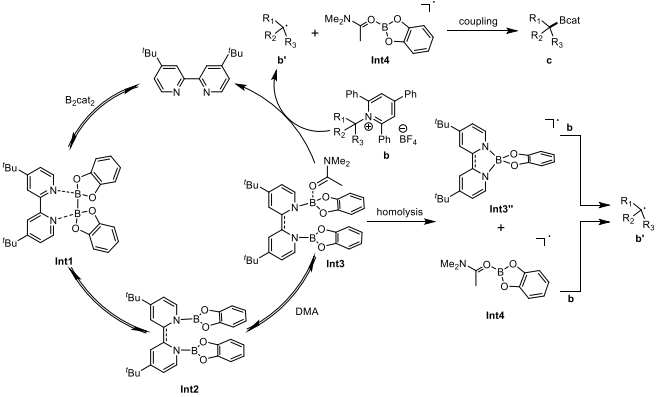


Figure 4. Plausible mechanism.

In summary, we have developed an efficient transitionary, metal-free system that can activate the C–N bonds of Katritzky pyridinium salts derived from diverse alkylamines *via* a deaminative process to produce a series of alkyl potassium trifluoroborate salts. In view of the widespread amine group and its precursors in chemicals, this method offers a meaningful tool to enable them as valuable building blocks. This transformation showed exceptional functional group tolerance, high efficiency and excellent chemoselectivity. Due to these advantages, this reaction should be of high synthetic value.

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Keywords: metal-free ·borylation ·alkylamine ·radical ·C-N activation

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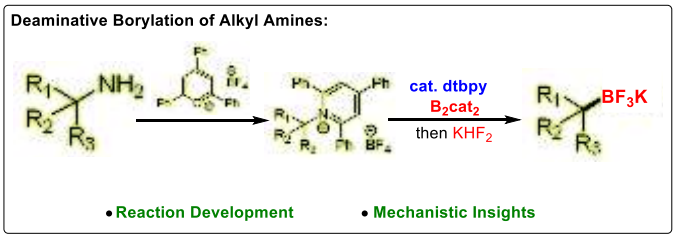
Layout 2:

C-N Borylation

Jiefeng Hu, Guoqiang Wang, Shuhua Li*, and Zhuangzhi Shi*___ **Page – Page**

Lewis Base Promoted Selective C-N Borylation of Alkyl Amines



N to B: A mild catalytic system was developed for the preparation of alkyl potassium trifluoroborate salts via C-N bond cleavage. This method has good functional group compatibility and can serve as a powerful synthetic tool for late-stage borylative cleavage C-N bonds in complex compounds.