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C-H Functionalization of BN-aromatics Promoted by Addition of Organolithium Compounds to the Boron Atom

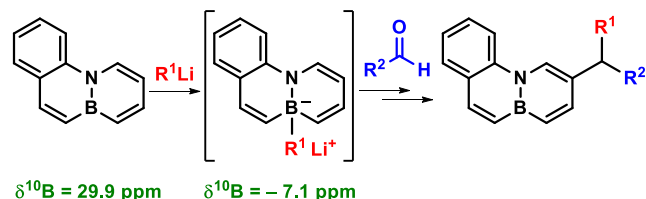
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Supporting Information Placeholder



ABSTRACT: Addition of an organolithium compound to a BN-phenanthrene with embedded B and N atoms is proposed to result in coordination of RLi to the boron atom. This coordination, supported by NMR spectroscopy and DFT calculations, increases the nucleophilicity of the system in the β position to the N atom, and is therefore a useful tool for promoting regioselective C–H functionalization of BN aromatics.

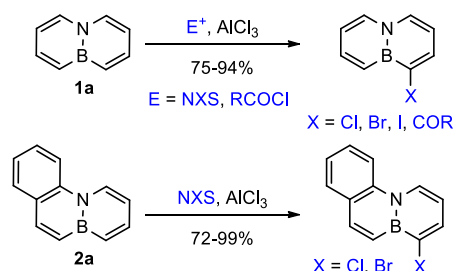
BN-aromatic compounds, i.e., isosteres of arenes in which a C=C bond has been formally replaced by a B–N bond, have emerged in recent years as a novel class of organic compounds with a wide range of applications.^[1] The modulation of the properties induced in the molecule by the presence of a polarized BN unit has prompted significant advances in materials science,^[2] medicinal chemistry^[3] and catalysis.^[4]

The synthesis of BN-aromatic compounds has also progressed significantly over the last few years, and a number of different BN-heterocyclic cores are currently accessible.^[5] Despite this, late-stage functionalization, which could be considered the most versatile strategy to access families of substituted derivatives with modulated properties for a given BN-aromatic core is still relatively unexplored. In particular, procedures for the functionalization of carbon atoms,^[6,7] which become the only possibility for late-stage functionalization in BN-polycyclic aromatic hydrocarbons (BN-PAHs) with embedded boron and nitrogen atoms, are very limited, and remain essentially limited to the halogenation of a few particular substrates, generally

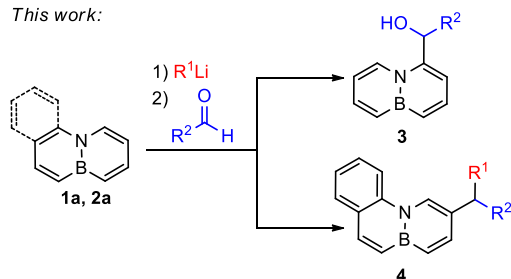
followed by cross-coupling reactions.^[8,9] In order to establish late-stage functionalization as a routine tool in the synthesis of BN-PAHs, a systematic study of the reactivity of the simplest BN-PAHs is highly desirable. This would allow acquisition of fundamental knowledge that could help to predict the behavior of more complex systems and therefore the design of efficient synthetic routes based on reliable late-stage functionalizations. In this sense, BN-naphthalene **1a** and BN-phenanthrene **2a** are two of the simplest polycyclic BN-aromatic compounds containing embedded B and N atoms and could therefore serve as useful model systems. The known reactivity of these compounds is thus far limited to regioselective electrophilic aromatic substitutions taking place in the position α to the boron atom (Scheme 1).^[10,11] It is worth noting that these are classical reactions of aromatic compounds whose regioselectivity is biased by the presence of the B–N bond. In contrast, although reactions of BN-aromatic compounds containing embedded B and N atoms with organolithium compounds are completely unexplored,^[12] we considered that they could provide an interesting approach for accessing alternative modes of functionalization.

Scheme 1. Functionalization of BN-phenanthrene **1a** and BN-naphthalene **2a**

Previous work:



This work:



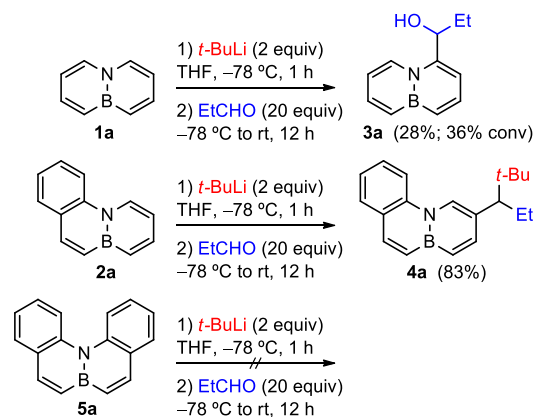
Herein we report the reactivity of BN-naphthalene **1a** and BN-phenanthrene **2a** upon the sequential addition of organolithium compounds and carbonyl derivatives (Scheme 1), which leads to functionalization of these systems complementary to that previously reported, and the discovery of a novel transformation in which the B–N bond plays a key role.

We began our investigation by exploring the reactivity of BN-naphthalene **1a**, BN-phenanthrene **2a** and BN-benzo[*c*]phenanthrene **5a**^[13] (Scheme 2). At the outset, 2 equiv of *t*-BuLi were added to the corresponding substrate and the mixture was stirred at $-78^\circ C$ for 1 h. An excess of propanal (20 equiv) was then added and the temperature was slowly raised to room temperature. Under these initial conditions, **1a** yielded alcohol **3a**, presumably via a classical mechanism consisting of deprotonation of **1a** and addition of the BN-aryllithium generated to the aldehyde. Although conversion is low, this result was promising, as the reaction is completely selective and gives rise to a functionalization complementary to that observed for electrophilic aromatic substitutions (see Scheme 1). Surprisingly, under the same conditions, **2a** furnished a completely different product, namely BN-phenanthrene **4a**, which is selectively functionalized in the β position to the N atom and includes both the aldehyde and the *tert*-butyl moiety from the organolithium compound in its structure in high yield. This absolutely different outcome suggests totally different mechanisms in the reactions of **1a** and **2a**. Finally, BN-benzo[*c*]phenanthrene **5a** was recovered unchanged when subjected to identical conditions.

These results reveal the tremendous influence of relatively small structural changes on the reactivity of PAHs with embedded B and N atoms. As a better understanding of the behavior of these simple systems would provide useful information when trying to functionalize higher PAHs,

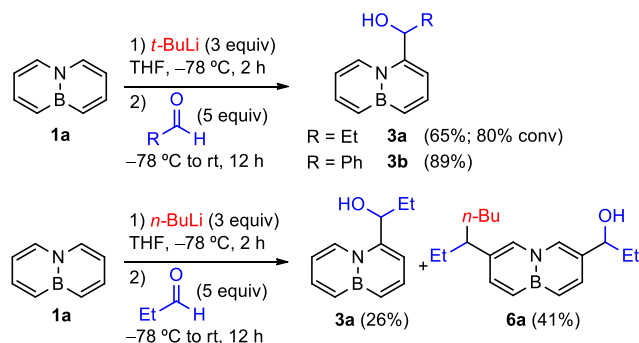
we embarked on a detailed study of the reactions that lead to **3**, and in particular, the unexpected functionalization of **2a** to obtain **4**.

Scheme 2. Reaction of **1a**, **2a** and **5a** with *t*-BuLi and propanal



After some optimization, we found that high conversion of **1a** and a good isolated yield of **3a** could be obtained when increasing the number of equiv of *t*-BuLi to 3 and lowering the amount of propanal to 5 equiv (Scheme 3). Under these conditions an aromatic aldehyde, such as benzaldehyde, also played a role in the reaction, leading to BN-naphthalene **3b** in high yield. In contrast, when more nucleophilic and less basic *n*-BuLi was used instead of *t*-BuLi, **3a** was formed in only 26% yield, and **6a** was additionally obtained in 41% yield. Compound **6a** is a difunctionalized BN-naphthalene whose structure seems to be related to that of compound **4a** observed in the reaction of BN-phenanthrene **2a**: the positions β to the N atom are functionalized, and the *n*-butyl moiety is incorporated into the final product. The observed results suggest that the RLi is acting as a base in the mechanism leading to the formation of **3**, whereas in the reaction giving rise to **4** or **6** it acts as a nucleophile.

Scheme 3. Reaction of **1a** with RLi and aldehydes

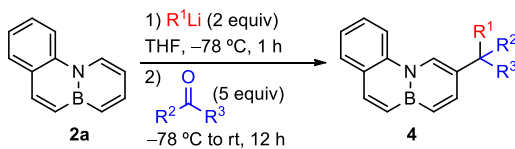


Next, we focused on exploring the scope of the reaction discovered upon sequential treatment of **2a** with *t*-BuLi and propanal to yield **4a** (Table 1).^[14] Gratifyingly, we found that, besides *t*-BuLi (entry 1), other organolithium compounds such as *n*-BuLi (entry 2) or MeLi (entry 3) followed

an analogous reaction pathway with propanal as the aldehyde counterpart, thus leading to the corresponding functionalized BN-phenanthrenes **4a-c** in good yields.

In regard to the scope of the carbonyl derivative, a β -branched aldehyde provided **4d** in excellent yield (entry 4) whereas decomposition was observed in the presence of α -branched aldehydes. In addition, aromatic (entries 5-9) and heteroaromatic aldehydes (entries 10-12) were found to be suitable reagents for this transformation, and in this case the amount of aldehyde could be reduced to five equiv. Notably, aliphatic ketones were also appropriate partners for this transformation, leading to the corresponding BN-phenanthrenes functionalized with tertiary alkyl groups in moderate to good yields (entries 13, 14). In contrast, the use of Michael acceptors, acyl chlorides or isocyanates as electrophiles was unsuccessful.

Table 1. Scope of the reaction of **2a** with RLi and carbonyl derivatives

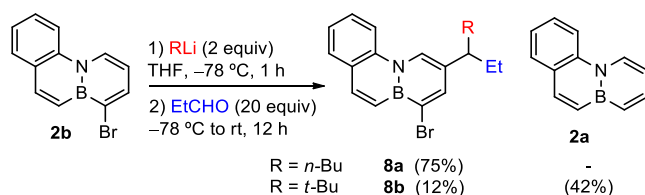


entry	R ¹	R ²	R ³	4	yield(%)
1 ^a	<i>t</i> -Bu	Et	H	4a	83
2 ^a	<i>n</i> -Bu	Et	H	4b	76
3 ^a	Me	Et	H	4c	63 ^b
4 ^a	<i>n</i> -Bu	CH ₂ (CH ₃) ₂	H	4d	99
5	<i>n</i> -Bu	Ph	H	4e	99
6	<i>t</i> -Bu	Ph	H	4f	62
7	<i>n</i> -Bu	<i>p</i> -CF ₃ -C ₆ H ₄	H	4g	55
8	<i>t</i> -Bu	<i>p</i> -CF ₃ -C ₆ H ₄	H	4h	97
9	<i>n</i> -Bu	<i>p</i> -MeO-C ₆ H ₄	H	4i	83
10	<i>n</i> -Bu	2-pyridyl	H	4j	65
11	<i>n</i> -Bu	2-thienyl	H	4k	60
12	<i>n</i> -Bu	2-quinolyl	H	4l	88
13 ^a	<i>n</i> -Bu	Me	Me	4m	62
14 ^a	<i>n</i> -Bu	-(CH ₂) ₅ -		4n	41 ^c

^aUsing 20 equiv of aldehyde. ^b85% conv. ^c87% conv.

Moreover, brominated BN-phenanthrene **2b** underwent an analogous transformation when sequentially treated with *n*-BuLi and propanal, thus allowing the isolation of selectively difunctionalized BN-phenanthrene **8a** in good yield (Scheme 4).

Scheme 4. Reaction of **2b** with RLi and propanal

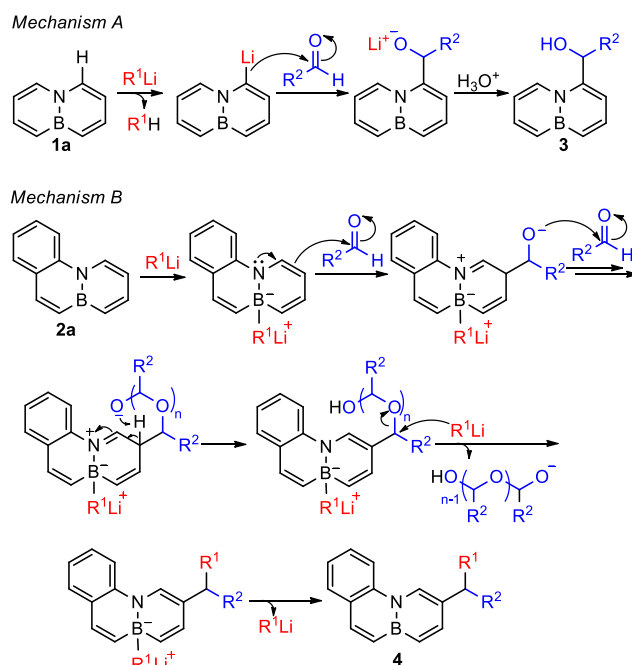


It should be noted that bromine-lithium exchange was not observed under these reaction conditions. However,

and not surprisingly, when *t*-BuLi is used BN-phenanthrene **2a**, presumably coming from bromine-lithium exchange followed by hydrolysis, becomes the major product, although compound **8b** could also be isolated in 12% yield.

We propose the mechanisms shown in Scheme 5 to explain the different reaction pathways observed in the sequential reaction of BN-PAHs with organolithium compounds and carbonyl derivatives. Mechanism A would account for the formation of **3**. Thus, treatment of BN-phenanthrene **1a** with RLi results in an acid-base reaction in which the more acidic position of **1a** is deprotonated. The BN-aryllithium species generated then acts as a nucleophile, adding to the electrophilic aldehyde to yield **3** upon hydrolysis.

Scheme 5. Proposed mechanisms



In contrast, mechanism B would explain the formation of derivatives **4**. In this case, the reaction would start with attack of the RLi at the electrophilic boron atom rather than with deprotonation. Upon addition, donation of the nitrogen electron pair to the empty boron orbital, thus contributing to the aromaticity of the azaborine ring, would be hampered, and this electronic reorganization would increase the nucleophilicity of the nitrogen atom and allow the system to act as an enamine, which attacks the aldehyde. Subsequent addition to one or more aldehyde units would facilitate the next step, namely intramolecular proton abstraction. Addition of RLi^[15] to the electrophilic carbon atom bearing the oxygen substituent, followed by decoordination of the RLi from the boron atom, would finally lead to functionalized BN-phenanthrenes **4**. A related mechanism would explain the formation of **6a** from **1a**.

Monitoring by ¹⁰B and ¹H NMR spectroscopy the addition of *t*-BuLi to **1a** and **2a** supported the proposed mechanisms.^[16]

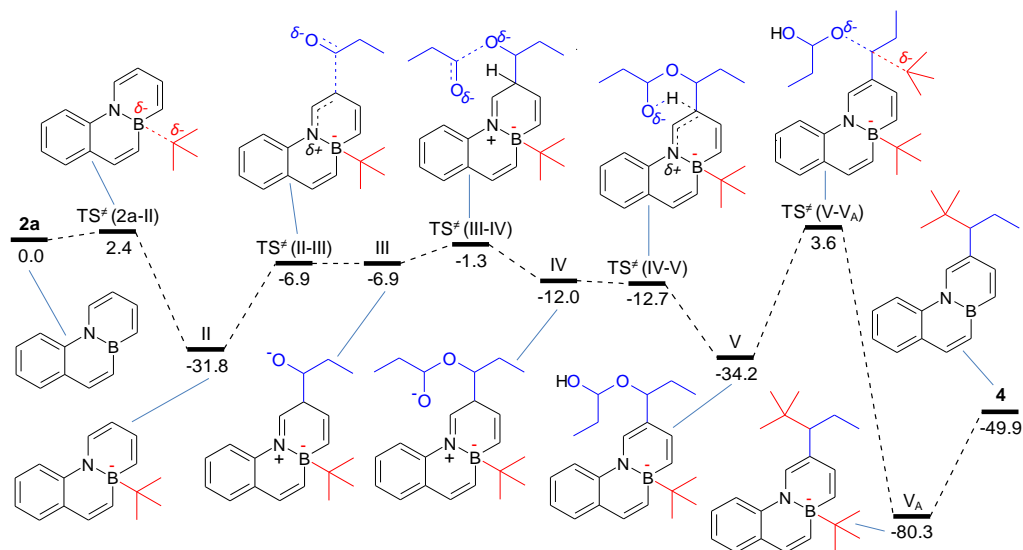


Figure 1. The energy profile for the proposed reaction mechanism, showing relative Gibbs energies (kcal/mol) of each intermediate and transition state (TS*) computed at 195K in THF solvent.

To gain insight into the reaction of **2a**, we investigated its mechanism using Density Functional Theory (DFT) methods (see Supporting Information for details). With regard to **1a**, its reactivity with RLi is determined by the first step of the reaction, which could follow either mechanism A or mechanism B. The energy stability of the first intermediate (i.e., deprotonated species for A and coordinated system for B) explains the different reactivity of **1a** with *n*-BuLi and *t*-BuLi. Thus, for *t*-BuLi, formation of the first intermediate via mechanism A is favored by ca. 3 kcal/mol, thus meaning that mechanism B is disfavored under equilibrium conditions at 195K (coordination product <0.1%). In contrast, both mechanisms are predicted to be experimentally observed for *n*-BuLi due to the similar intermediate energies (less than 1 kcal/mol of difference between them). Consequently, the calculated coordination/deprotonation product ratio is 90/10 at 195K, in qualitative agreement with experimental findings.

The reaction of **2a**, in contrast, exclusively proceeds via mechanism B. Deprotonation is energetically disfavored, predicting a 95/5 coordination/deprotonation product ratio, which is also compatible with the experimental absence of deprotonation product. We have therefore focused on the study of mechanism B for **2a**. The free energy profile determined (Figure 1) indicates that the first reaction step, i.e., the coordination of the carbanion to the boron atom, is thermodynamically and kinetically favored. The very low activation energy leads to the rapid formation of intermediate **II**, which, in the absence of other reagents, is stable, and is in fact experimentally detectable by NMR spectroscopy. Attack to the other β - and δ -positions (respect to N atom) are not favored due to loss of aromaticity, as has been previously observed in electrophilic attack for BN-phenanthrenes.^[10a] Formation of the carbanion induces chemical activation of the external azaborine ring, which promotes the reaction with one aldehyde molecule at a position β to the N atom. Formation of the C-C bond occurs

on the opposite face of the ring, where the *t*-Bu is coordinated, due to steric repulsion between the *t*-Bu fragment and the aldehyde. The intermediate (**III**) formed can subsequently react with a second aldehyde molecule, proceeding with a low activation energy (i.e., fast reaction), to generate the unstable intermediate **IV**, which reacts instantaneously (i.e., virtually negligible activation energy) to give rise to intramolecular abstraction of a hydrogen atom, and formation of intermediate **V**.

Subsequent reaction with a second carbanion may lead to the thermodynamically stable intermediate **VA**, being the reaction thermodynamically favored due to energetic stabilization resulting from C-C bond formation and the entropic contribution of the leaving group. The large energy barrier of this step is due to the steric repulsive interaction between the carbanion attached to the boron and the incoming carbanion or alternatively with the leaving group, making this the rate-determining step for the whole mechanism.

Finally, intermediate **VA** can release the carbanion attached to the boron to give the final product **4**, in a thermodynamically disfavored process. However, the global Gibbs energy is still significantly negative (c.a. -50 kcal \cdot mol $^{-1}$), therefore the whole reaction is a spontaneous process, even at -78 °C.

In conclusion, a new insight into the reactivity of BN-aromatics with organolithium compounds has been gained. For BN-PAHs with embedded B and N atoms, either deprotonation or addition of the organolithium to the boron atom are possible initial steps, and the reaction outcome depends mainly on the particular structure of the BN-aromatic compound, as evidenced experimentally and supported by NMR studies and DFT calculations. The findings concerning the reactivity of BN-phenanthrene **2a**, which allowed a method for the selective late-stage functionalization of this BN-PAH to be established, are particularly interesting. Thus, reaction of **2a** with RLi proceeds

via coordination of the organolithium to the boron atom. This intermediate, which has been detected by NMR spectroscopy, evolves after addition of a carbonyl compound to finally yield a BN-phenanthrene functionalized in the position β to the N atom. This transformation is unprecedented and constitutes a novel reaction pathway specific for BN-aromatics as it relies upon the presence of the B–N bond. We hope that these findings may establish addition of organolithium compounds as a useful tool for the late-stage functionalization of higher BN-PAHs.

ASSOCIATED CONTENT

Supporting Information

Experimental and computational details, and NMR spectra for all new compounds (PDF)

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

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(14) For the optimization of this reaction see SI.

(15) Although it has been represented as a free RLi for simplicity, this step could also involve RLi coordinated to a boron atom, either in the starting material, the final product or any of the intermediates.

(16) Use of ^{10}B NMR instead of ^{11}B NMR was crucial, see SI for details.