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Letter

Aromatic Metamorphosis of Indoles into 1,2-Benzazaborins

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Supporting Information

ABSTRACT: Among the plethora of aromatic compounds, indoles represent a privileged class of substructures that is ubiquitous in natural products and pharmaceuticals. While numerous exocyclic functionalizations of indoles have provided access to a variety of useful derivatives, endocyclic transformations involving the cleavage of the C2–N bond remain challenging due to the high aromaticity and strength of this bond in indoles. Herein, we report the "aromatic metamorphosis" of indoles into 1,2-benzazaborins via the insertion of boron into the C2–N bond. This endocyclic insertion consists of a reductive ring-opening



using lithium metal and a subsequent trapping of the resulting dianionic species with organoboronic esters. Considering that 1,2-azaborins have attracted increasing academic and industrial attention as BN isosteres of benzene, the counterintuitive aromatic metamorphosis presented herein can feasibly be expected to substantially advance the promising chemistry of 1,2-azaborins.

A mong aromatic compounds, indoles have received particular attention due to their prevalence in natural products and pharmaceuticals,¹ and numerous methods have been developed for the functionalization of indoles.² However, almost all these reactions are limited to the exocyclic functionalization of indoles, which has been attributed to the exceptional robustness of the indole skeleton (Figure 1a, left). Conversely, endocyclic functionalizations such as atom insertion and removal/substitution of endocyclic atoms have not been accomplished (Scheme 1a, right), except for Studer's ring-opening silylation with silyllithium.³

Recently, we have become interested in the development of endocyclic transformations of aromatic compounds, which we



Figure 1. Functionalization of indoles. (a) Conventional exocyclic and elusive endocyclic functionalization. (b) Insertion of boron into the C2–N bond of indoles to generate benzo[e][1,2]azaborins.

Scheme 1. Optimization Study for the Insertion of Boron into Indole 1a

(a) Yus's reductive ring-opening of benzofuran



have coined "aromatic metamorphosis".^{4,5} We envisioned that the endocyclic functionalization of indoles could become a game-changing method for the synthesis of nitrogencontaining cyclic molecules using readily available indoles as a common platform. In particular, the insertion of a boron atom into the C2–N bond would be interesting, considering that the resulting benzo[e][1,2]azaborins are attractive BN isosteres of naphthalenes.^{6,7} Over the past decade, 1,2azaborins,⁸ in which one of the C==C units in the benzene ring is replaced with a B–N unit, and their derivatives have

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Scheme 2. Reaction Scope



^{*a*}10 mmol of **1a** was used. ^{*b*}1.0 mmol of **1** was used. ^{*c*}Determined by NMR spectroscopy. ^{*d*}0.50 mmol of **1d**, 2.5 mmol of Li, and 0.25 mmol of 1,4bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzene (**2u**) were used. ^{*c*}10 mmol of **1d**, 50 mmol of Li, and 5.0 mmol of 1,4-dibromo-2,5bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzene (**2v**) were used. ^{*f*}1.0 mmol of **1d**, 5.0 mmol of Li, and 0.20 mmol of 1,3,5-tris(4,4,5,5tetramethyl-1,3,2-dioxaborolan-2-yl)benzene (**2w**) were used.

attracted increasing attention as promising functional molecules with potential applications in bioactive molecules^{7,9} and optoelectronic materials.¹⁰ The B–N unit induces local dipole moments and/or polarization of the frontier orbitals, which dramatically changes the optical and electronic properties of the parent aromatic compounds.

Generally, benzo[e][1,2] azaborins are synthesized from the corresponding o-vinyl-6,11 or -alkynylanilines¹² via Dewar's bora-Friedel-Crafts reaction, which intrinsically suffers from the instability of the aniline substrates and the laborious preparation of the starting materials.¹³ A synthetic route to benzo[e][1,2]azaborins from stable and easily accessible indoles should thus represent an attractive research target and diversify the accessibility of the chemical space. Herein, we report a new method for the synthesis of benzo[e][1,2]azaborins via the insertion of boron into the C2-N bond of indoles. This transformation consists of two consecutive reactions: a reductive ring-opening of indoles with lithium metal that affords dianionic intermediates A (Figure 1b, step a) followed by a trapping reaction with boron electrophiles such as the commercially available organoboronic pinacol esters (Figure 1b, step b).

We have previously accomplished the insertion of boron into benzofurans via nickel- or manganese-catalyzed ring-opening reactions.^{5d,e} Unfortunately, these catalyst systems are ineffective for the insertion of boron into indoles, and the indole substrates were recovered in most cases. In general, indoles should be expected to be less susceptible to ring-opening than benzofurans, considering that the aromatic stabilization energy of the pyrrole ring is higher than that of the furan ring.¹⁴ Moreover, given that strongly basic amide anions would be formed as leaving groups, the cleavage of C–N bonds remains considerably challenging.

To cleave the robust indole cores, we focused on the strong reducing ability of lithium metal. Yus has reported the reductive cleavage of the C2–O bond in benzofuran using an excess of lithium powder to furnish the corresponding dianionic species of the type **A** that can be subsequently trapped with electrophiles (Scheme 1a).¹⁵ Based on this precedent, we began our investigation by establishing the optimal conditions for the lithium-mediated reductive ring-opening of *N*-phenylindole (1a). According to Yus' method, we conducted the ring opening of **1a** at 0 °C using 10 equiv of lithium powder and a catalytic amount of 4,4'-di-*tert*-butylbiphenyl (DTBB) as an electron-transfer mediator. After quenching with H₂O, the ring-opened *o*-vinylaniline was obtained in 51% yield. Optimization of the reaction conditions (cf. Tables S1 and S2) revealed an increased yield (84%) when

the reaction was conducted at -30 °C. It should also be noted that the reaction proceeded smoothly even in the absence of DTBB. The (*Z*)-configured dianionic intermediate was generated in a stereoselective manner, and a subsequent treatment with D₂O exclusively provided (*Z*)-*N*-phenyl-2-(vinyl-2-*d*)aniline in 95% yield with 100% deuterium incorporation (Scheme 1b).

We then attempted the synthesis of benzazaborin **3aa** via the electrophilic trapping of the dianionic species **A** with commercially available phenylboronic acid pinacol ester (PhB(pin), **2a**). However, a simple addition of **2a** to the reaction mixture afforded a complex product mixture, and **3aa** was not observed (Scheme 1c), which we tentatively attributed to the potential decomposition of the in situ generated **3aa** by the excess lithium powder. Therefore, we removed the remaining lithium powder by filtration under an atmosphere of argon using an H-type Schlenk tube, in which two glass chambers are separated by a glass filter (Figure S2). Removing the remaining lithium after the ring opening, before addition of a solution of **2a** in THF, afforded benzazaborin **3aa** in 82% yield (Scheme 1c).¹⁶

With the optimal conditions in hand, we explored the substrate scope (Scheme 2). A variety of arylboronates 2 can be used in the present method (Scheme 2a). The formation of the C–B–N linkage between the dianionic intermediate A and 2 should be expected to be fast, and various functional groups such as benzoyl, ester, amide, and cyano groups in 3ae-ah were well tolerated. Halogen and triflyloxy substituents at the *ortho* positions of the B(pin) unit did not hamper the electrophilic trapping to afford the corresponding benzazaborins (3ai-al) in high yield. The remaining halogen moieties in 3ai-al can be used for further derivatization into, e.g., BN-containing polyaromatic compounds (vide infra; Scheme 3b). Interestingly, this boron-insertion method can also be scaled

Scheme 3. Derivatization of 3 into Further π -Extended Molecules

(a) 3-Arylation via a bromination/Suzuki–Miyaura coupling sequence





(b) Synthesis of BN-embedded PAHs via an intramolecular C-H arylation

up: for example, 2.6 g (72% yield) of **3ak** was obtained from 10 mmol of **1a**. Moreover, naphthyl-, 3-thienyl-, and 4-pyridylboronic acid esters 2m-p could be used as the boron electrophiles to smoothly furnish 3am-ap. Apart from arylboronic acid esters, alkynyl, alkenyl, and even alkylboronic acid esters (2q-t) could be used to generate the corresponding benzazaborins (3aq-at) in 80%, 82%, 81%, and 82% yield, respectively.

We then investigated the scope of this reaction with respect to indoles 1 (Scheme 2b). The reactions of 5-butyl- and 5-(trimethylsilyl)indole 1b and 1c with 2a afforded 3ba and 3ca in good yield. The ring-opening of 5-fluoro-N-phenylindole did not proceed; given that N-phenylindole was obtained after the reaction, it seems feasible to conclude that a reductive lithiation of the C-F bond occurs. Similarly, 5-methoxy- and 5-phenyl-substituted indoles did not undergo the ring-opening. Instead of the targeted cleavage of the C2-N bond, Birch-type reduction of their aromatic rings afforded complex product mixtures (Figure S1). Substituents at the 2-position hamper the ring opening of the corresponding 2-substituted indoles. However, we found that the 2-position can be functionalized after the insertion of boron into the C2-N bond (vide infra; Scheme 3a). Subsequently, we explored the scope of this transformation with respect to N-substituted indoles. Alkyl and silyl substituents on the N-aryl ring did not hamper the insertion of boron. On the other hand, methoxy groups lowered the efficiency of the ring opening, which is reflected in the low yields of benzazaborins 3ga (39%) and 3ja (21%). Electron-withdrawing trifluoromethyl-substituted indole 1h decomposed in the presence of lithium metal under the conditions applied. The presence of an aryl ring on the nitrogen atom seems to be indispensable, and a replacement with alkyl or benzyl groups prevents the initial ring-opening step (Figure S1).

To our delight, *p*-diborylbenzenes 2u and 2v reacted with 2 equiv of dianionic **A**, which was derived from indole 1d, to afford 3du and 3dv in 86% and 51% yield, respectively (Scheme 2c). Moreover, 1,3,5-triborylbenzene 2w reacted with 3 equiv of dianionic **A** to furnish 3dw in 56% yield.

As previously mentioned, we failed to convert 2-substituted indoles into the corresponding 3-substituted benzazaborins using the method presented herein. However, the 3-position of benzazaborin can be readily functionalized via bromination and subsequent cross-coupling with a modification of the procedure reported by Molander.¹⁷ Benzazaborin **3da** underwent an electrophilic bromination with *N*-bromosuccinimide (NBS) and AlCl₃ to afford 3-brominated 1,2-benzazaborin **4da**, and a subsequent Suzuki–Miyaura coupling afforded 1,2,3-triarylbenzazaborin **5da** in 74% yield over two steps (Scheme 3a). This bromination/Suzuki–Miyaura coupling sequence represents a powerful tool for the subsequent decoration of benzazaborins **3**.

Next, we attempted the synthesis of BN-embedded polyaromatic hydrocarbons (PAHs) via further cyclization of 1,2-diarylbenzazaborins 3. PAHs have garnered increasing attention as intriguing π -conjugated molecules in materials science, and replacement of a C=C bond in PAHs with a B-N bond should represent an effective means to modulate their original properties while maintaining structural similarity.^{8c,d,10h-w,18} With these considerations in mind, we decided to synthesize BN-embedded PAHs 6 via cyclization of 1,2-diarylbenzazaborins 3.

Initially, we attempted a Scholl-type dehydrogenative cyclization of 3aa, as fused PAHs are often synthesized via oxidative intramolecular reactions.¹⁹ However, the azaborin scaffold is generally incompatible with oxidative conditions, and complex mixtures were obtained from all reactions. We thus focused on the redox-neutral palladium-catalyzed intramolecular C-H arylation of 2-bromophenyl-substituted benzazaborin 3ak.²⁰ After extensive screening, we identified the optimal reaction conditions: treatment of benzazaborin **3ak** with 5 mol % of $Pd(OAc)_2$, 10 mol % of PPh_3 , and 1 equiv of K₂CO₃ in toluene (0.04 M) at 120 °C for 14 h furnished a BN isostere of benzo[g]chrysene **6ak** in 95% yield (Scheme 3b). Using phosphine ligands other than PPh₃ induced undesired Suzuki-Miyaura coupling between the C-Br and the peripheral C-B bonds, which prevented the formation of 6ak (Table S4). Yet, the present palladium-catalyzed intramolecular C-H arylation can be used for a 2-fold cyclization: under more dilute conditions (0.01 M in toluene), 3dv underwent cyclization to furnish B2N2-embedded PAH 6dv in 83% yield. The fused structures of 6ak and 6dv were unambiguously determined by single-crystal X-ray diffraction analysis (Figures S3 and S5).

The photophysical properties of 1,2-diphenylbenzazaborin **3aa** and BN-embedded PAHs **6ak** and **6dv** are summarized in Figure S7. Planar **6ak**, which exhibits an extended π -conjugation, showed bathochromically shifted longest wavelength absorption ($\lambda_{max} = 337 \text{ nm}$) and emission ($\lambda_{em} = 401 \text{ nm}$) bands relative to those of **3aa** ($\lambda_{max} = 316 \text{ nm}$; $\lambda_{em} = 367 \text{ nm}$), while the fluorescence quantum yields (Φ_F) of **3aa** and **6ak** are comparable (**3aa**: $\Phi_F = 7\%$; **6ak**: 9%). Doubly BN-embedded **6dv** exhibited even further red-shifted longest-wavelength absorption ($\lambda_{max} = 387 \text{ nm}$) and emission maxima ($\lambda_{em} = 400$ and 419 nm; Stokes shift: 840 cm⁻¹; $\Phi_F = 19\%$). A carbonaceous analogue of **6dv** shows its longest-wavelength absorption at $\lambda_{max} = 374 \text{ nm}$, which is slightly blue-shifted relative to that of **6dv**.²¹

In conclusion, we have developed a synthetic route to benzazaborins from ubiquitous indoles that proceeds via the reductive cleavage of the π -aromaticity and the strong C2–N σ -bond to subsequently insert a boron unit. As a demonstration of the synthetic utility of the thus-obtained benzazaborin products, we subjected bromo-containing 1,2diarylbenzazaborins to palladium-catalyzed intramolecular C– H arylations, which furnished the corresponding BNembedded fused polyaromatic hydrocarbons. Considering that 1,2-azaborins have acquired increasing academic and industrial recognition as polar BN isosteres of benzene, the future of BN-embedded compounds seems promising. Our aromatic metamorphosis should thus represent a reliable and useful addition to the synthetic toolkit of contemporary organic chemistry.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.or-glett.9b01353.

Experimental procedures, X-ray crystallographic analysis, photophysical properties, and spectral data (PDF)

Accession Codes

CCDC 1885774–1885775 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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