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Radical Borylative Cyclization of Isocyanoarenes with N-Heterocyclic Carbene Borane: Synthesis of Borylated Aza-arenes

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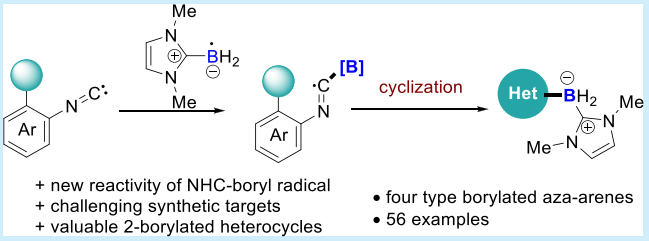
ABSTRACT: Borylated aza-arenes are of great importance in the area of organic synthesis. A radical borylative cyclization of isocyanoarenes with N-heterocyclic carbene borane (NHC-BH_3) under metal-free conditions was developed. The reaction allows the efficient assembly of several types of borylated aza-arenes (phenanthridines, benzothiazoles, etc.), which are difficult to access using alternative methods. Mild reaction conditions, a good functional-group tolerance, and generally good efficiencies were observed. The utility of these products is demonstrated, and the mechanism is discussed.



Organoborons are among the most useful building blocks in organic synthesis due to the versatility of the C−B bond, which is involved in diverse chemical transformations.[1] Interestingly, however, while phenyl-based boronic acids (or their derivatives) have been met with tremendous success, the application of heteroaromatic boron reagents is often troublesome.[2] This is mainly due to their instability, which is derived from undesired protodeboronation and causes their preparation to be less efficient.[3] For the same reason, their involvement in cross-coupling reactions is generally less productive. These statements are particularly true for the preparation and coupling reactions of 2-heteroaromatic boronic acids.[4] One viable strategy to solve these problems is to mask the sp^2-B boronic acids as tetra-coordinated sp3-hybridized surrogates. In this regard, MIDA boronates,[5a,b] cyclic triolborates,[5c] and trifluoroborate salts[5d] display improved stabilities and are known to undergo efficient coupling reactions by virtue of the slow-releaseof the free boronic acids.

For the preparation of heteroaromatic borons, the general and widely applied method relies on the reaction of a heteroaromatic metallic reagent (prepared by deprotonation or metal−halogen exchange) with trialkylborate, wherein a poor functional group tolerance can be found.[6] The direct C−H borylation of heteroaromatics that was developed in recent years represents an appealing alternative.[7] The prediction of the regioselectivity, however, remains a challenge. Another useful strategy is to start with borylated building blocks. By heterocyclization, the heteroaromatic ring is formed, and the boryl moiety is retained in the product.[8] This strategy offers a more flexible and diverse synthesis of heteroaromatic borons, but the availability of borylated building blocks is often limiting (Figure 1a).

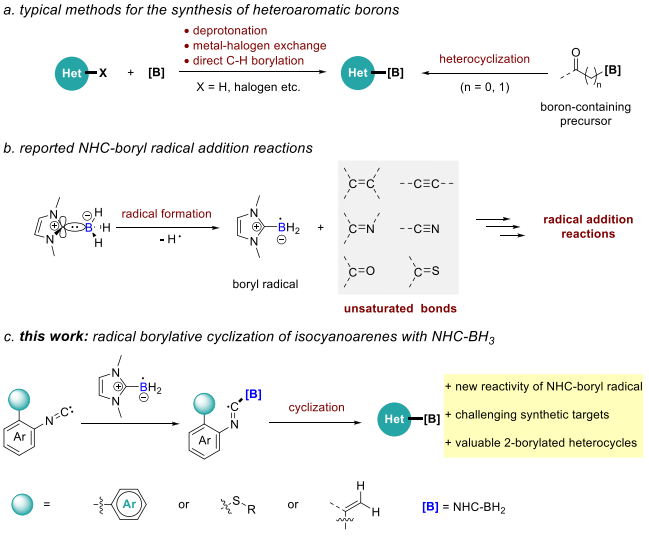


Figure 1. Radical borylative reaction of N-heterocyclic carbene boranes.

N-heterocyclic carbene boranes (NHC-BH_3) have a rich chemistry and have attracted considerable attention from organic chemistry community.[9] They can seve as precursors of borenium ions[10] and boryl anions.[11] Additionally, the ligation of N-heterocyclic carbenes significantly reduces the bond

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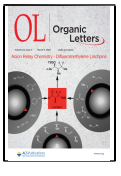

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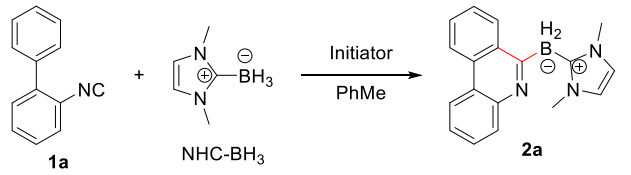
dissociation energy of the B−H bond, thus rendering NHC-BH_3 as ideal reagents to generate boryl radicals.[12] In this regard, a variety of carbon−carbon and carbon−heteroatom multiple bonds, including alkenes,[13] alkynes,[14] imines,[15a] nitriles,[15b] esters,[15c] and xanthates,[15d] are known to undergo radical addition reactions with NHC-boryl radicals. These protocols offer convenient access to novel and valuable borylated building blocks, some of which are otherwise difficult to prepare (Figure 1b). Nevertheless, although isocyanides are frequently utilized in radical reactions,[16] their application in the boryl radical-addition reaction is unprecedented. Inspired by the recent advances of nitrogen heterocycle synthesis via a radical cascade reaction using isocyanides as radical acceptors,[17] we envisioned that the NHC-boryl radical may also be added to isocyanide to form an imidoyl radical, thereby leading to the synthesis of borylated heteroaromatics. Herein, we show that the strategy is viable in the synthesis of borylated phenanthridine, benzothiazole, quinolone, and isoquinoline (Figure 1c). The azo-arenes were constructed with the concomitant incorporation of a boryl atom. All these heterocycles are important in functional molecules,[18] but the synthesis and application of their borylated derivatives have seldom been realized.

To start, we investigated the borylative cyclization of 2-isocyano-1,1′-biphenyl (**1a**) with 1,3-dimethylimidazol-2-ylidene borane (NHC-BH_3, 1.5 equiv) (Table 1). The use of di-

Table 1. Optimization of the Reaction Conditions[a]



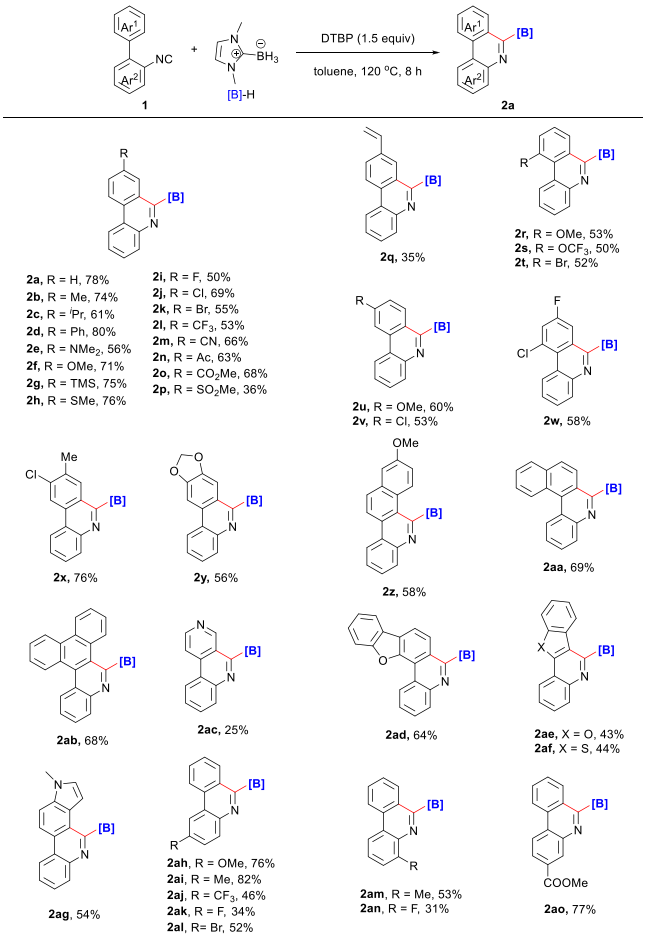
entry	initiator (equiv)	solvent	temperature (°C)	yield (%)
1	DTBP	toluene	100	30
2	DTBP	toluene	120	74
3[b]	DTBP	toluene	120	78
4	DTBP[c]	toluene	120	57
5	DCP	toluene	120	45
6	BPO	toluene	120	35
7	LPO	toluene	120	50
8	TBPB	toluene	120	16

[a]General reaction conditions are as follows: **1a** (0.2 mmol), NHC-BH_3 (0.3 mmol, 1.5 equiv), initiator (1.5 equiv), and solvent (2.0 mL) in a sealed tube for 12 h under N_2. DTBP, di-(*tert*-butylperoxy)-2-methylpropane; DCP, dicumyl peroxide; BPO, benzoyl peroxide; LPO, dilauroyl peroxide; TBPB, *tert*-butyl peroxybenzoate. [b]NHC-BH_3 (2.0 equiv) was used. [c]Initiator (3.0 equiv) was used.

(*tert*-butylperoxy)-2-methylpropane (DTBP, 1.5 equiv) as initiator and oxidant in toluene at 100 °C produced the desired borylated phenanthridine (**2a**) in a 30% yield (Table 1, entry 1), and with a large amount of NHC-BH_3 remained intact.[17,19] Elevating the temperature to 120 °C led to a higher conversion, and the yield was improved to 74% (Table 1, entry 2). While increasing the loading of NHC-BH_3 to 2.0 equiv further increased the yield to 78% (Table 1, entry 3), the use of an excess amount of DTBP (3.0 equiv) resulted in a lower yield (Table 1, entry 4). Other commonly used peroxides, such as DCP, BPO, LPO, and TBPB, were less effective in promoting the reaction (Table 1, entries 5−8, respectively).

With the optimized reaction conditions in hand (Table 1, entry 3), we next evaluated the substrate scope of this borylated phenanthridine synthesis. The functional group compatibility on Ar1 was first investigated. As shown in Scheme 1, both electron-donating (**2b−2h**) and electron-

Scheme 1. Scope of Borylated Phenanthridines Synthesis



withdrawing (**2i−2p**) substituents were well tolerated, giving the corresponding products in moderate to good yields. 4-Cyano- and 4-vinyl-substituted isocyanides were also suitable substrates (**2q** and **2m**, respectively), suggesting a preferential addition of the NHC-boryl radical to isocyanide and thus a high chemoselectivity of this protocol.[14b,15b] Substituents at the *ortho*-position did not hamper the reactivity (**2r−2t** and **2w**). The *meta*-substituted substrates, with two possible reaction sites, cyclized only at the less sterically congested position, highlighting a high level of regioselectivity (**2u**, **2v**, **2x**, and **2y**). This could probably be a result of the large steric-shielding effect of the NHC-boryl radical. Substrates bearing a fused arene or heteroarene, such as naphthalene (**2z** and **2aa**), phenanthrene (**2ab**), pyridine (**2ac**), benzofuran (**2ad** and **2ae**), benzothiophene (**2af**), and indole (**2ag**), were also viable for cyclization. The low yield of **2ac** might be caused by the electron- deficiency of pyridine ring compared with the benzene ring. Interestingly, the reactions of **2z** and **2ag** occurred preferentially at the electron-rich position. The substituent tolerance on Ar2 was also good, as a number of functional groups with diverse electron properties at different positions were generally tolerated (**2ah−2ao**).

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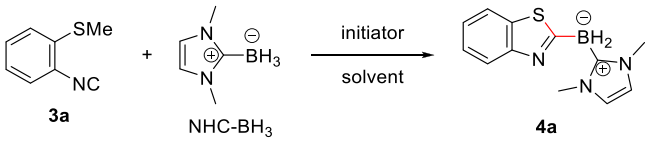
The above success encouraged us to explore the applicability of a similar protocol to other borylated heteroarene syntheses. Benzothiazoles are a privileged structural motif in medicinal chemistry.[20] The construction of 2-borylated benzothiazoles would therefore set the stage for the flexible and diverse synthesis of a benzothiazole-containing small-molecule library.[21] For this purpose, 2-isocyanoaryl thioethers were chosen as starting materials for cyclization. As a model reaction, 2-isocyanoaryl thioether (**3a**, 0.2 mmol, 1.0 equiv) was reacted with NHC-BH_3 (1.5 equiv) in the presence of different initiators. With DTBP (1.5 equiv), the desired borylated benzothiazole (**4a**) was indeed formed in a 23% yield when the reaction was heated in toluene at 120 °C (Table 2, entry 1). Varying the dosage of DTBP, however, did not increase the yield (Table 2, entries 2 and 3). Changing the initiator from DTBP to AIBN in acetonitrile at 80 °C was proved to be unfruitful (Table 2, entry 4). Nevertheless, the introduction of *tert*-dodecanethiol (0.5 equiv) as a polarity-reversing catalyst gave a significantly enhanced yield of 58% (Table 2, entry 5).[14b,22] Toluene was a better solvent for this transformation (Table 2, entry 6). Interestingly, decreasing the loading of *tert*-dodecanethiol to 0.2 equiv gave an improved yield of 69%, while the use of a stoichiometric amount of it was found to be detrimental to the reaction (Table 2, entries 7 and 8, respectively). Finally, the yield was improved to 75% (Table 2, entry 9) when 2.0 equiv of NHC-BH_3 was employed.

Table 2. Optimization of the Reaction Conditions[a]



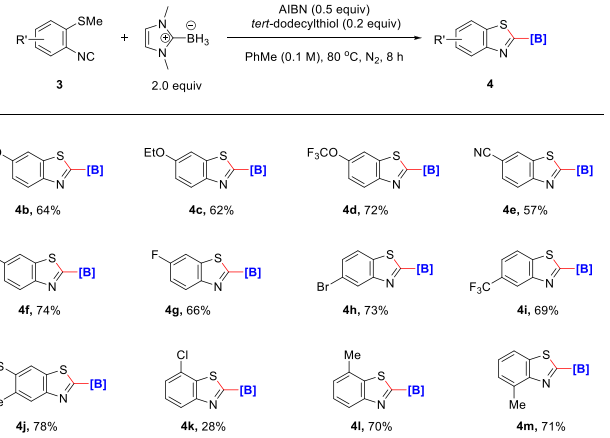
entry	initiator (equiv)	additive (equiv)	solvent	temperature (°C)	yield (%)
1	DTBP (1.5)		toluene	120	23
2	DTBP (0.5)		toluene	120	22
3	DTBP (3.0)		toluene	120	7
4	AIBN (0.5)		MeCN	80	5
5	AIBN (0.5)	RSH (0.5)	MeCN	80	58
6	AIBN (0.5)	RSH (0.5)	toluene	80	63
7	AIBN (0.5)	RSH (0.2)	toluene	80	69
8	AIBN (0.5)	RSH (1.0)	toluene	80	39
9[b]	AIBN (0.5)	RSH (0.2)	toluene	80	75

[a]General reaction conditions are as follows: **3a** (0.2 mmol, 1.0 equiv), NHC-BH_3 (0.3 mmol, 1.5 equiv), initiator, and additive in solvent (2.0 mL) in a sealed tube for 8 h. AIBN, 2,2-azobis(isobutyronitrile); RSH, *tert*-dodecylthiol. [b]NHC-BH_3 (2.0 equiv) was used.

The substrate scope of this radical borylative cyclization of 2-isocyanoaryl thioethers was also explored (Scheme 2). A number of commonly encountered functional groups, such as ether (**4b**–**4c**), cyano (**4e**), methylsulfonyl (**4f**), halide (**4g**, **4h** and **4k**), trifluoromethyl (**4i**), and thioether (**4j**) groups, were well tolerated, generally giving the target products in moderate to good yields. The low yield of **4k** is due to the rapid decomposition of the isocyanide starting material. The *ortho*-methyl substituent did not hamper the reactivity (**4l** and **4m**).

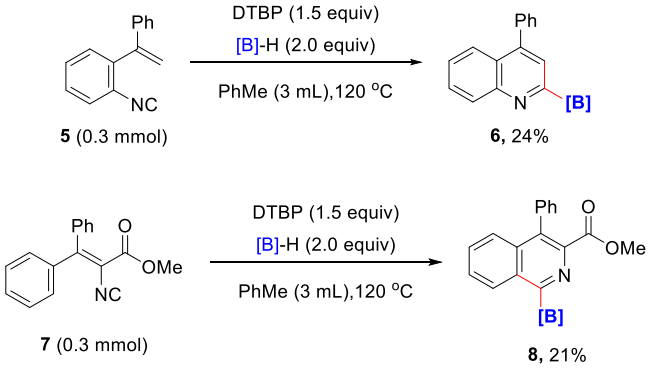
Following a similar strategy, isocyanides **5** and **7** were subjected to the radical cyclization reaction, using DTBP as both the initiator and the oxidant.[23] The 2-borylated quinolone **6** and 1-borylated isoquinoline **8** were successfully constructed, but in low yields (Scheme 3).

Scheme 2. Scope of the Synthesis of 2-Borylated Benzothiazoles[a]



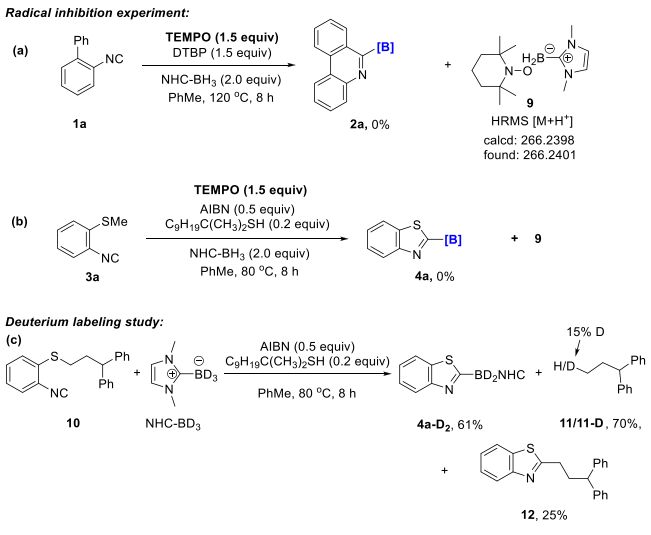
[a]See the Supporting Information.

Scheme 3. Synthesis of Borylated Quinolone and Isoquinoline



To provide insight into the possible mechanism of the radical borylative cyclization of isocyanoarenes, several experiments were conducted (Scheme 4). First, control experiments

Scheme 4. Mechanistic Studies



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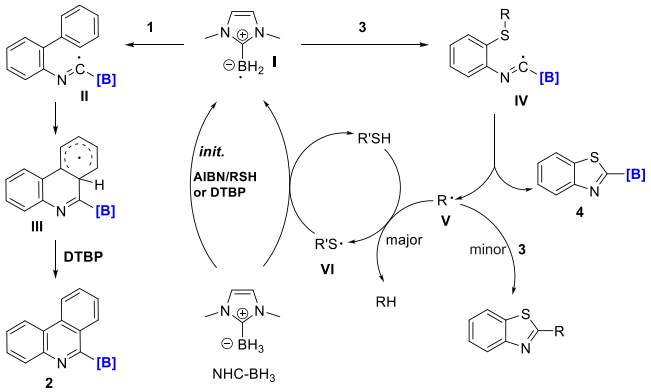
showed that both reactions were shut down in the absence of initiators (DTBP or AIBN). TEMPO inhibited both reactions completely, and a TEMPO-borane (**9**) adduct was detected (Scheme 4a and b). These results clearly pointed to a radical reaction pathway. Unlike the phenanthridine protocol, no additional oxidant was used for the benzothiazole synthesis. We were thus interested in the fate of the methyl group in the 2-isocyanoaryl thioethers. To make the detection easier, compound **10** with a heavier alkyl substituent was prepared and allowed to react with deuterated NHC-borane (NHC-BD_3). In addition to the desired borylative cyclization product (**4a-D_2**, 61% yield), an alkylative cyclized benzothiazole **12** was also formed in a 25% yield (Scheme 4c). Alkane **11** with partial deuterium incorporation was isolated as the byproduct in a 70% yield. Taken together, these results indicated the formation of an alkyl radical, probably via homolytic cleavage of the C−S bond.

On the basis of the above results and literature precedents,[24] a possible reaction mechanism was proposed and is outlined in Scheme 5. The boryl radical **I** is initially generated via

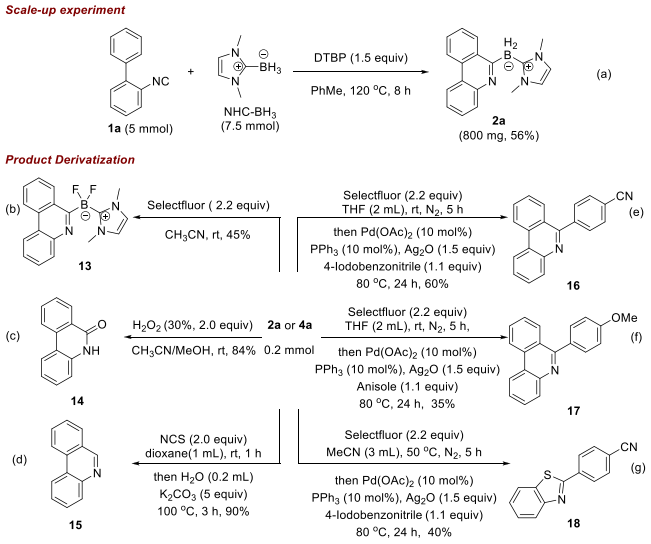
Scheme 5. Proposed Mechanism



hydrogen abstraction under the assistance of initiator DTBP or AIBN/RSH. For the synthesis of phenanthridine, the boryl radical **I** adds to isocyanide **1** to form a borylimidoyl radical **II**,[17] which then undergoes intramolecular radical cyclization to form intermediate **III**. Finally, the deprotonation and oxidation of **III** provide the borylated phenanthridine **2**. Likewise for the benzothiazole synthesis, the borylimidoyl radical **IV** is initially formed.[22,25] Subsequently, homolytic substitution (S_H2) at the sulfur atom delivers the product **4** and releases an R radical, which in turn serves as the radical initiator for another cycle of the reaction.

The synthetic value of the products was also demonstrated (Scheme 6). First, the efficiency of the multi-millimolar reaction was not significantly compromised (Scheme 6a). The oxidation of **2a** with Selectfluor (2.2 equiv) gave a difluoroborate product **13** (Scheme 6b).[26] Treating **2a** with hydrogen peroxide gave a C−B bond-oxidized phenanthridin-6(*5H*)-one product **14** in good yields (Scheme 6c).[27] Interestingly, the reaction of **2a** with NCS, followed by an aqueous workup, led to the formation of the deboron hydrogenation product **15** (Scheme 6d).[26] The palladium-catalyzed Suzuki−Miyaura coupling reactions of **2a** or **4a** with aryl iodides were successful, leading to an extended π-system (**16**, **17**, and **18**) in reasonable yields (Scheme 6e−g, respectively).[26]

Scheme 6. Gram-Scale Synthesis and Synthetic Applications



In summary, the synthesis of heteroaromatic boron reagents, especially the 2-heteroaromatic ones, tremendously challenging. Reported herein is a radical borylative cyclization of functionalized isocyanides toward the synthesis of 2-borylated phenanthridines and benzothiazoles. The sp^3-B N-heterocyclic carbene borane (NHC-BH_3) is utilized as the boryl source and offers a high stability to the products. A good functional group tolerance and moderate to good efficiencies were observed. The synthetic utilities of the borylated products were demonstrated. Mechanistic studies suggested a radical reaction pathway was involved.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00309.

Complete experimental procedures, characterization of new products, NMR spectra, HRMS data, and melting point data (PDF)

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Notes

The authors declare no competing financial interest.

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