BN heterocycles

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A Modular Synthetic Approach to Monocyclic 1,4-Azaborines

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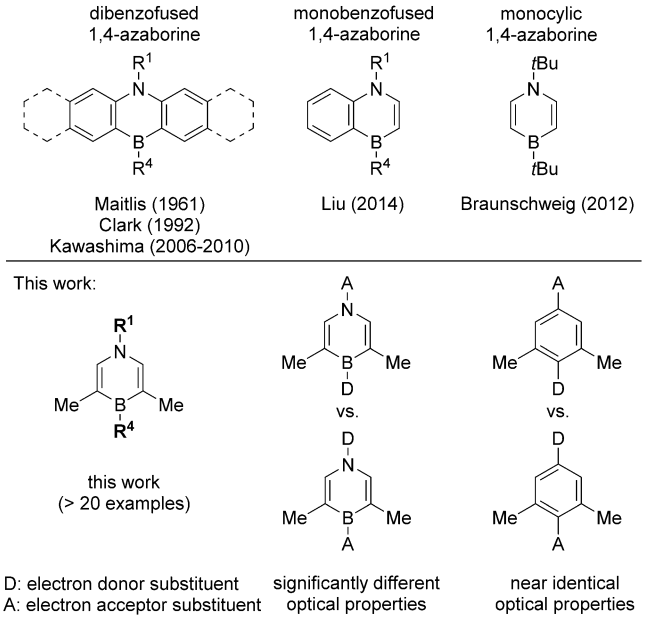
Abstract: *A simple and general method for the synthesis of a wide range of monocyclic 1,4-azaborines, including the first examples containing B heteroatoms is described. Post-heterocycle-formation olefin isomerization was employed as a key strategy. This new synthetic method provides fundamental insight into the resonance stabilization and photophysical properties of 1,4-azaborines.*

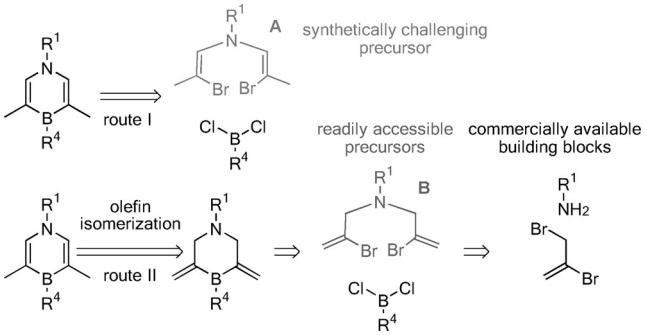
BN/CC isosterism, which is the replacement of a CC unit with the isoelectronic and isostructural BN unit, has emerged as a viable strategy to increase the chemical space of compounds relevant to materials science and biomedical research.[1] The application of BN/CC isosterism to the benzene motif leads to three structural isomers: 1,2-dihydrido-1,2-azaborine, 1,3-dihydrido-1,3-azaborine, and 1,4-dihydrido-1,4-azaborine (from hereon, abbreviated as 1,2-azaborine, 1,3-azaborine, and 1,4-azaborine, respectively). While significant advances have been made in the development of 1,2-azaborine derivatives,[1,2] less progress has been reported for 1,3-[3] and 1,4-azaborine[4] derivatives, which is arguably due to a lack of general synthetic access to these families of compounds. For 1,4-azaborines, most of the pioneering work has centered on polycyclic dibenzofused derivatives (Scheme 1), which can be prepared from stable halogenated diarylamines.[5] Recently, we reported the synthesis of monobenzofused 1,4-azaborines and described their potential application in coordination chemistry and catalysis.[6,7] However, the chemistry of the simplest monocyclic 1,4-azaborine has remained virtually unexplored. Braunschweig and co-workers reported the only synthesis and isolation of a monocyclic 1,4-azaborine to date, which involves Rh-mediated cyclization of *N*-*t*Bu-*B*-*t*Bu iminoborane with acetylene.[8] Although elegantly simple, the reported synthetic scope was limited to one example, namely, *N*-*t*Bu-*B*-*t*Bu-1,4-azaborine (Scheme 1).



Scheme 1. Development of 1,4-azaborines.

In order to unleash the full potential of the chemistry of 1,4-azaborines as a new benzene isostere, a more versatile synthesis needs to be developed that can access a wide range of substituted monocyclic 1,4-azaborine derivatives. In this work, we disclose a modular synthetic approach to the preparation of N- and B-substituted monocyclic 1,4-azaborines.

Scheme 2 illustrates our retrosynthetic analysis for the assembly of the 1,4-azaborine ring. In analogy to the synthesis of dibenzofused 1,4-azaborines,[4,5] a monocyclic 1,4-azaborine could potentially be prepared through coupling of the dilithium reagent produced from the dibromide **A** with a boron electrophile (Scheme 2, route I). However, in con-



Scheme 2. Retrosynthetic analysis.

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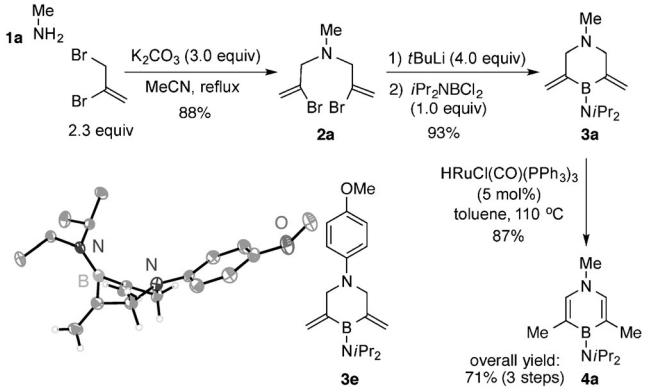
trast to brominated diaryl anilines (precursors to dibenzo-fused 1,4-azaborines), bis-Z-β-halo-enamine **A**[9] suffers from potential stability issues and the need to precisely control the olefin geometry, thus rendering route I synthetically very challenging. We envisioned a strategy involving post-heterocycle-formation olefin isomerization to circumvent the challenges associated with enamine precursor **A**. The design involves readily accessible allylamine **B** as an intermediate, which upon heterocycle formation and olefin isomerization[10] should produce the targeted aromatic 1,4-azaborine heterocycle (route II, Scheme 2). Allylamine **B** can in turn be easily accessed from commercially available amines and 2,3-dibromopropene.

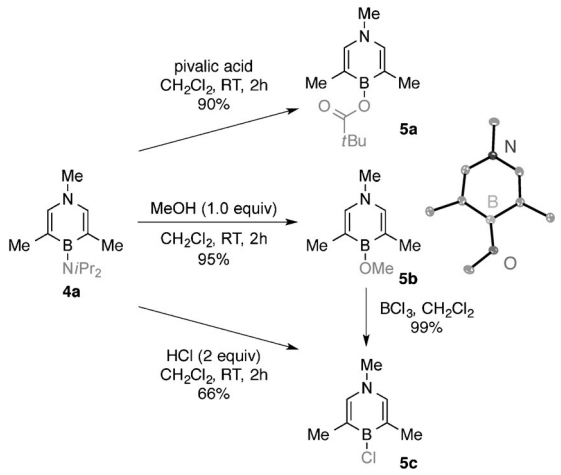
To demonstrate the feasibility of our synthetic strategy, methylamine (**1a**) was first coupled with 2,3-dibromopropene to furnish **2a** in 88% yield (Scheme 3). Subsequent metal–halogen exchange[11] followed by quenching with iPr_2NBCl_2,



Scheme 3. A three-step synthetic sequence for monocyclic 1,4-azaborines.

gave BN heterocycle **3a** in 93% yield. Finally, isomerization of the exocyclic double bonds of **3a** in the presence of a Ru^{II} catalyst[12] produced the desired target. Thus, the monocyclic 1,4-azaborine **4a** can be prepared from commercially available materials in a straightforward three-step sequence with an overall yield of 71%. In addition to methylamine (**1a**), benzylamine (**1b**), allylamine (**1c**), aniline (**1d**), *para*-methoxyaniline (**1e**), and *para*-trifluoromethylaniline (**1f**) are also suitable amines for our reaction sequence to furnish corresponding diisopropylamino-substituted 1,4-azaborines **4b**–**f** (see the Supporting Information for details; for **4c**, an *E*/*Z* mixture of *N*-prop-1-en-1yl) isomers was obtained). For *para*-methoxyaniline, we were able to obtain a crystal structure for the non-aromatic BN hetercocyle **3e**, which shows a boat-like conformation in the solid state (Scheme 3). While the boron atom in **3e** is trigonal planar (sum of the bond angles = 360.0°), the intraring nitrogen atom is pyramidalized (sum of the bond angles = 347.5°).

Having demonstrated an efficient route to a variety of monocyclic 1,4-azaborine derivatives with different substituent on the nitrogen atom, we were interested in investigating the chemistry at boron. We determined that the diisopropylamino group at the boron atom in 1,4-azaborine **4a** can be

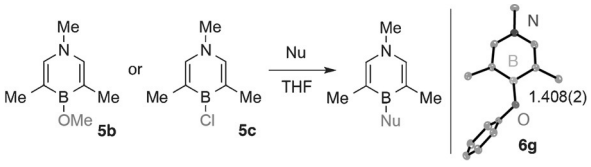


Scheme 4. Functionalization chemistry at the boron atom of 1,4-azaborines.

readily exchanged with substituents that can serve as good leaving groups for further functionalization [e.g., pivalate (**5a**), OMe (**5b**), Cl (**5c**); Scheme 4].[3c,13]

We then used compounds **5b** and **5c** as precursors for the synthesis of a variety of B-substituted 1,4-azaborines through a simple nucleophilic substitution reaction. As can be seen from Table 1, a variety of nucleophiles produce the corresponding B-substituted 1,4-azaborines (entries 1–9). We were able to obtain the crystal structures for 1,4-azaborines **6d**, **6f**, and **6g** (see the Supporting Information for details). The structure of the B-phenoxy-substituted 1,4-azaborine **6g** is noteworthy because the B–O distances of phenoxy-substituted 1,2- and 1,3-azaborines have been successfully correlated with the extent of intraring electron delocalization of the BN heterocycles.[3c] It is believed that the longer the exocyclic B–O distance, the stronger the extent of the intraring electron delocalization.

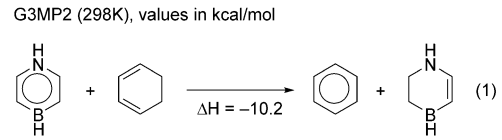
Table 1: Versatile synthesis of B-substituted 1,4-azaborines.



Entry	Nucleophile (Nu)	Product	Yield [%][a] From **5b**	Yield [%][a] From **5c**
1	EtMgBr	**6a**	70	67
2	CH_2=CHMgBr	**6b**	68	67
3	CH_2=$CHCH_2$MgBr	**6c**	77	75
4	Ph–≡–MgBr	**6d**	83	73
5	PhMgBr	**6e**	79	71
6	mesitylithium	**6f**	74	72
7	PhOLi	**6g**	NR[b]	72
8	Et_3BLiH	**6h**	60[c]	80
9	iPr_2NLi	**4a**	85	77

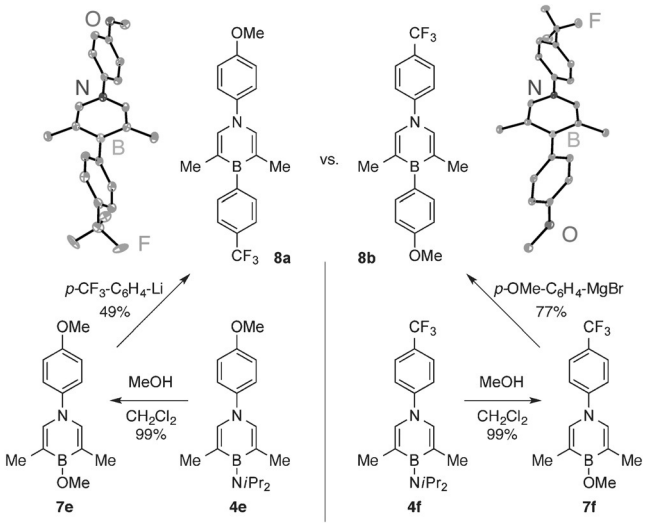
[a] Yield of isolated product. [b] No reaction. [c] Conversion based on ^{11}B NMR.

The observed B–O distance in **6g** is 1.408(2) Å (Table 1), which is between those of 1,2-azaborine (1.392(1) Å) and 1,3-azaborine (1.422(3) Å). Additionally, we predicted the resonance stabilization energy (RSE) of the parent 1,4-azaborine to be approximately 22 kcal mol^{-1}. This value was derived computationally (G3MP2)[14] through Equation (1), which

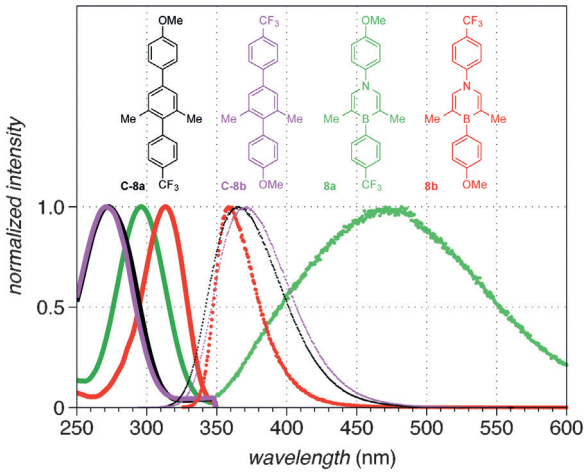


reveals that the RSE of the parent 1,4-azaborine is approximately 10 kcal mol^{-1} less than that of benzene (RSE = 32.6 kcal mol^{-1}). Compared to a similar analysis for the parent 1,2- and 1,3-azaborine (RSE = 20 and 31 kcal mol^{-1}, respectively), the parent 1,4-azaborine exhibits an intermediate RSE.[15] Overall, our observations are consistent with the following resonance stabilization trend: 1,3-azaborine > 1,4-azaborine > 1,2-azaborine.[16]

To investigate 1,4-azaborines in the context of potential materials applications, we investigated 1,4-azaborine analogues of donor/acceptor-substituted *para*-terphenyls.[17] We are particularly interested in the photophysical effects resulting from donor/acceptor substitution[18] featuring 1,4-azaborine as the linking core. Scheme 5 illustrates the synthesis of donor/acceptor-substituted 1,4-azaborines **8a** and **8b**, which exhibit opposite polarity [**8a**: (N)donor/(B)acceptor, **8b**: (N)acceptor/(B)donor]. Treatment of the corresponding *B*-N*i*Pr$_2$ 1,4-azaborine precursors **4e** or **4f** with MeOH produces the corresponding *B*-OMe-substituted 1,4-azaborines **7e** and **7f** in quantitative yield. Subsequent displacement of the *B*-OMe group with the corresponding aryl nucleophiles produces the desired target compounds **8a** and **8b**. Compounds **6d**, **6e**, **6f**, **8a**, and **8b** do not appear to decompose when stored as solids in air over a 24 h period based on NMR. In solution,



Scheme 5. Synthesis of donor/acceptor-substituted 1,4-azaborine analogues of *p*-terphenyl.



	C-8a	C-8b	8a	8b
λ_{abs}	272 nm	270 nm	296 nm	313 nm
λ_{em}	365 nm	370 nm	482 nm	359 nm
Stokes shift	9367 cm^{-1}	10010 cm^{-1}	13037 cm^{-1}	4094 cm^{-1}
Φ_{PL}	0.82	0.78	0.09	0.66

Figure 1. Normalized absorption (solid lines) and emission (dotted traces) spectra for **8a** (green) and **8b** (red) and their carbonaceous analogues **C-8a** (black) and **C-8b** (purple) in THF at 1×10^{-5} M. Photoluminescene quantum yields were determined using the comparative method (see the Supporting Information for details).

less than 5% decomposition was observed for compound **8a** over a 24 h period.

Figure 1 shows the normalized absorption and emission spectra of **8a** and **8b**, along with those of their corresponding carbonaceous counterparts **C-8a** and **C-8b** in THF solution. It is evident that the carbonaceous terphenyls **C-8a** (black) and **C-8b** (purple) exhibit very similar absorption and emission profiles. On the other hand, significant differences in both the absorption and emission spectra can be observed between **8a** (green) and **8b** (red). Thus, in contrast to carbon-based terphenyls, the specific orientation of the donor/acceptor placement on 1,4-azaborines has a dramatic impact on the resulting optical properties. The table in Figure 1 lists the observed photophysical parameters for **8a**, **8b**, **C-8a**, and **C-8b**. Particularly striking is the difference in the Stokes shift between **8a** (13037 cm^{-1}) and **8b** (4097 cm^{-1}). The Stokes shift exhibited by BN terphenyl **8b** is uniquely small among the terphenyl compounds shown in Figure 1. This suggests a relatively small structural reorganization between the ground state and the excited state.

To address whether the N substituent or the B substituent is causing the large discrepancy of the observed Stokes shift between **8a** and **8b**, we prepared the 1,4-azaborine-based biphenyl compounds **9a** and **9b** and their corresponding carbonaceous analogues **C-9a** and **C-9b** (Figure 2). Consistent with our observations for the terphenyl series, 1,4-azaborine biphenyl **9b**, which has an electron-withdrawing aryl substituent on the nitrogen atom, also exhibits the smallest Stokes shift among the biphenyl series (see the Supporting Information).

In summary, we have developed a general method for the synthesis of a wide range of monocyclic 1,4-azaborines. From

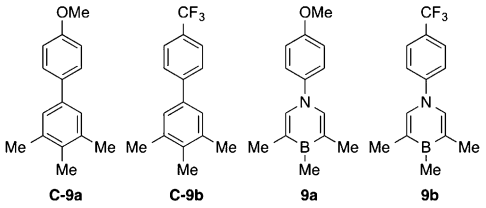


Figure 2. 1,4-Azaborine biphenyl series **9a** and **9b**, and their carbonaceous isosteres **C-9a** and **C-9b**.

commercially available amines and 2,3-dibromopropene, the 1,4-azaborine ring structure can be assembled in three synthetic steps. Structural analysis of the **B**-OPh-substituted 1,4-azaborine is consistent with a 1,4-azaborine that exhibits resonance stabilization between that of 1,3-azaborine and 1,2-azaborine. We have also prepared 1,4-azaborine-based terphenyl and biphenyl compounds and demonstrated that in contrast to their carbonaceous analogues, the specific orientation of the placement of donor and acceptor substituents has a dramatic impact on the optical properties of the resulting 1,4-azaborines. The availability of a simple and modular synthesis of monocyclic 1,4-azaborines should open up new avenues for the exploration of this family of compounds as benzene isosteres in biomedical and materials applications.

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