Published in final edited form as:

Angew Chem Int Ed Engl. 2013 July 15; 52(29): . doi:10.1002/anie.201302660.

Boron-Substituted 1,3-Dihydro-1,3-azaborines: Synthesis, Structure, and Evaluation of Aromaticity

Senmiao Xu,

Department of Chemistry and Biochemistry, University of Oregon Eugene, Oregon 97403-1253, United States, Fax: (+1)-541-346-0487

Tanya C. Mikulas,

Department of Chemistry, The University of Alabama, Tuscaloosa, AL, 35487-0336

Lev N. Zakharov,

Center for Advanced Materials Characterization in Oregon, University of Oregon, Eugene, Oregon 97403-1253, United States

David A. Dixon, and

Department of Chemistry, The University of Alabama, Tuscaloosa, AL, 35487-0336

Shih-Yuan Liu

Department of Chemistry and Biochemistry, University of Oregon Eugene, Oregon 97403-1253, United States, Fax: (+1)-541-346-0487

David A. Dixon: dadixon@as.ua.edu; Shih-Yuan Liu: lsy@uoregon.edu

Abstract

We describe the first general synthesis of *B*-substituted 1,3-dihydro-1,3-azaborines. Experimental structural analysis combined with NICS and resonance stabilization energy calculations suggest that the 1,3-dihydro-1,3-azaborine heterocycle exhibits aromatic character that is intermediate between benzene and 1,2-dihydro-1,2-azaborine. The synthetic methods presented in this work represent a significant advance in realizing the potential of the 1,3-dihydro-1,3-azaborine heterocycle as an emerging arene BN isostere in potential biomedical and materials science applications.

Keywords

Boron; Azaborines; Heterocycles; Aromaticity

BN/CC isosterism has emerged as an attractive strategy to expand the chemical space of compounds relevant to biomedical research and materials science.^[1] Among the three BN

Correspondence concerning X-ray crystallography should be directed to Lev Zakharov (lev@uoregon.edu)., Correspondence concerning electronic structure calculations should be directed to David Dixon.

Supporting information for this article is available on the WWW under <http://www.angewandte.org> or from the author.

isosteres of benzene (i.e., 1,2-dihydrido-1,2-azaborine,^[2] 1,3-dihydrido-1,3-azaborine, and 1,4-dihydrido-1,4-azaborine;^[3] see Scheme 1), 1,3-dihydro-1,3-azaborine (from hereon abbreviated as 1,3-azaborine) is thermodynamically the least stable isomer.^[4] Not surprisingly, its development has lagged the other azaborines in the series. The first synthetic example of a 1,3-azaborine debuted in late 2011,^[5] and the diversity of synthetically accessible 1,3-azaborines remains very limited to date.

1,3-Azaborines exhibit electronic structures that are very distinct from their 1,2-azaborine and carbonaceous analogues.^[6] In order to exploit the unique properties of this family of heterocycles in materials and biomedical applications, new synthetic tools need to be developed. Late-stage functionalization strategies are arguably the most efficient approach to generate an array of derivatives from an assembled BN heterocyclic core. We envisioned that the boron position in 1,3-azaborines could be utilized as a straightforward point of attachment for a variety of functional substituents at a late stage. For 1,3-azaborines, however, a general method for substitution at boron has yet to be developed. In this communication, we describe protocols for the synthesis of a diverse array of *B*-substituted 1,3-azaborines using *B*-N(*i*-Pr)₂-substituted 1,3-azaborine **1** as a universal precursor. Furthermore, we provide evidence that 1,3-azaborines are more aromatic than corresponding 1,2-azaborines based on structural, magnetic, and energetic considerations.

Recently, we disclosed that 1,3-azaborine **1** was inert towards anionic and neutral nucleophiles.^[5] On the other hand, we showed that treatment of **1** with acetic acid readily furnished the *B*-OAc-substituted product.^[6] Encouraged by this preliminary finding, we envisioned that 1,3-azaborine **1** could be converted to *B*-substituted derivatives under acidic conditions. Scheme 2 illustrates that reaction of precursor **1** with 2 equiv. of HCl produced the *B*-Cl substituted 1,3-azaborine **2** in 52% yield. Full and clean conversion from **1** to **2** was observed by ¹¹B NMR under the optimized reaction conditions. We believe that the moderate isolated yield is due to loss upon purification via silica gel chromatography. It is worth noting that the relative stability of 1,3-azaborine **2** toward silica gel treatment is in stark contrast to the *B*-Cl substituted 1,2-azaborine, which undergoes complete degradation upon exposure to silica gel.

When heterocycle **1** was treated with MeOH, no reaction was observed. However under acidic conditions, i.e., when a 1:1 mixture of MeOH and HCl was reacted with **1**, the *B*-OMe-substituted 1,3-azaborine **3** was generated in 70% isolated yield. Similarly, treatment of **1** with 1.0 equiv. of HF•pyridine gave the fluoride-substituted 1,3-azaborine **4**. When 1.5 equiv. of HF•pyridine was used, the substitution reaction was complete within six minutes as determined by ¹¹B NMR. To the best of our knowledge, this is the first isolated example of a *B*-F substituted azaborine.^[7] The *B*-CN-substituted 1,3-azaborine **5** was synthesized upon exposure of **1** to a 1:1 mixture of MeOH and TMSCN, presumably via the *in situ* generated HCN.^[8] The *B*-CN connectivity (vs. *B*-NC) in **5** was confirmed by ¹³C NMR (broad peak at 128.8 ppm (CN)), which is consistent with the data reported for the *B*-CN-substituted 1,2-azaborine analogue.^[9]

Despite the successful examples shown in Scheme 2, the acid promoted *B*-substitution has significant limitations. For instance, carbon-based substituents with high p*K*_a C–H bonds (e.g., alkyl, aryl, vinyl, alkynyl) cannot be accessed. A method that would allow nucleophilic substitution at boron under neutral or basic conditions would significantly expand the diversity of 1,3-azaborines. We already determined that heterocycle **1** did not react with a number of anionic nucleophiles due to the weak leaving group ability of the diisopropylamino group.^[5] Thus, our strategy was to convert **1** into a 1,3-azaborine intermediate **I** bearing a good leaving group which in turn can readily undergo nucleophilic substitution (Scheme 3).

With this strategy in mind, we focused our initial attention on developing *B*-OAc-substituted 1,3-azaborine **6** as a precursor for nucleophilic substitution reactions based on our prior success in using **6** and LiAlH₄ to produce *N*-Me-1,3-BN toluene.^[6] However, treatment of **6** with the stronger base *n*-BuLi gave only a trace amount of desired substitution product (Scheme 4, top). For compound **6**, we realized that in addition to the desired nucleophilic attack at boron (path a) two possible side reactions may be competitive with a strong nucleophile/base such as *n*-BuLi: 1) attack at the carbonyl carbon (path b) and 2) deprotonation (path c). Introducing a bulky carboxylate as a leaving group with a quaternary α -carbon could potentially mitigate the problem. Indeed, when 1,3-azaborine **7**, which features the bulky pivalate as the leaving group at boron, was reacted with *n*-BuLi at room temperature, the desired *B*-*n*-Bu-substituted compound was formed in 83% yield (Scheme 4, middle). The overall yield over two steps from starting material **1** is 72% due to potential loss of material associated with an additional isolation process. In order to improve the overall efficiency of the substitution protocol starting from 1,3-azaborine **1**, we envisioned that the conversion from **1** to **7** and the subsequent nucleophilic substitution reaction could be performed in one single pot with the only operation between the two reactions being the removal of the diisopropylamine byproduct under vacuum. Gratifyingly, we determined that the two-step one-pot process resulted in 80% overall isolated yield of the *B*-*n*-Bu substituted heterocycle, an improvement of 8% over the step-by-step procedure (Scheme 4, bottom).

With an optimized general protocol in hand, we then investigated the scope of the substitution reaction. As can be seen from Table 1, the one-pot displacement of the diisopropylamino group in **1** occurs readily in the presence of alkyl- (entry 1), vinyl- (entry 2), aryl- (entry 3), and alkynyl-based (entry 4) nucleophiles. Sterically hindered aryl nucleophiles such as mesityllithium also readily undergo substitution (entry 5). Interestingly, without first converting the diisopropylamino group to *B*-pivalate-substituted intermediate **7**, phenol and *t*-butyl alcohol failed to react with 1,3-azaborine **1** even in the presence of HCl.

On the other hand, using the optimized one-pot substitution protocol, heteroatom-based nucleophiles become suitable as reaction partners. Use of phenoxide (entry 6) and *t*-butoxide (entry 7) resulted in the formation of the corresponding products **8f** and **8g** in high yields. The diisopropylamino substituent in **1** can be readily converted to another amino functionality such as bis(trimethylsilyl)amino group employing KN(SiMe₃)₂ as the nucleophile, furnishing **8h** in 69% yield (entry 8). Notably, in addition to the HF•pyridine reagent, the *B*-F substituted 1,3-azaborine **4** can also be formed via a nucleophilic protocol using CsF (entry 9). Finally, the one-pot protocol converts 1,3-azaborine **1** to the *B*-OMe derivative **3** with MeOH/NEt₃ (entry 10).

Among the azaborine series (1,2-, 1,3-, and 1,4-azaborines), the 1,3-isomer is the only family that cannot not be satisfactorily represented by a Lewis structure without invoking formal charges (Figure 1). Because the chemistry of 1,3-azaborines is just emerging, structural information on this family of heterocycles is very limited. Compound **1** is the only reported example that has been characterized by single-crystal X-ray analysis.^[5] A larger structural database should facilitate the development of a better understanding of the bonding and electronic structure for this family of compounds.

With a library of 1,3-azaborines now readily accessible, we have crystallographically characterized compounds **8c**, **8d**, and **8f**.^[10] 1,3-Azaborine **8f** is the 1,3-BN isostere of a diphenylether (specifically, 1-methyl-3-phenoxybenzene). The observed bonding between the boron and exocyclic oxygen in **8f** is revealing (Figure 1): The exocyclic oxygen atom of **8f** is mostly sp²-hybridized, with $\text{B-O-C} = 123.8(2)^\circ$. The C-O-B-C(2) torsion angle of $170.4(2)^\circ$ and the B-O bond distance of $1.422(3) \text{ \AA}$ suggest some double-bond character between oxygen and boron (sum of single-bond covalent radii = $1.48 \text{ \AA}$).^[11] However,

compared to a typical *B*-alkoxide-substituted 1,2-azaborine ($B-O = 1.389(2) \text{ \AA}$),^[12] the observed $B-O$ distance in **8f** is longer (by $0.03 \text{ \AA}$), indicating a weaker $B-O$ bonding in a 1,3-azaborine vs. a 1,2-azaborine. In a more direct comparison of diphenylether structures, we prepared 1,2-azaborine **9**^[10] and determined its corresponding $B-O$ distance, which is $1.392(1) \text{ \AA}$ (Figure 2). The weaker $B-O$ bonding in 1,3-azaborines in comparison to 1,2-azaborines is consistent with the electrostatic potential map calculations^[6] in which a highly delocalized intra-ring electron system renders the boron atom relatively less capable of accepting electrons from exocyclic substituents.

Another striking feature of the solid-state structure of **8f** is the short $B-C(2)$ distance of $1.476(5) \text{ \AA}$.^[13,14] However, the crystallographically determined short $B-C(2)$ distance is not predicted by gas-phase density functional theory (DFT) calculations at B3LYP/DZVP2^[15] level ($B-C(2) = [1.516 \text{ \AA}]$).^[16] The observed $B-C(2)$ distance for the *B*-diisopropylamino-substituted 1,3-azaborine **1** is $1.525(2) \text{ \AA}$ and that for **8c** and **8d** are $1.508(3) \text{ \AA}$ and $1.498(2) \text{ \AA}$, respectively, and the calculated DFT values are consistent with these (See Supporting Information). Thus, the observed *B*-substituent-dependent intra-ring solid-state $B-C(2)$ bond distances range from $1.476 \text{ \AA}$ to $1.525 \text{ \AA}$ (i.e., a difference of $\sim 0.05 \text{ \AA}$), which is relatively large and distinct from 1,2-azaborines and arenes.^[17]

Overall, the observed intra-ring bond distances in 1,3-azaborines **1**, **8c**, **8d**, and **8f** are not consistent with a single Lewis structure description, which corroborates previous theoretical predictions of a significantly electron-delocalized structure.^[4]

To more quantitatively evaluate the aromatic character of 1,3-azaborines, we calculated the nucleus-independent chemical shift NICS(0) and NICS(1) values^[18] for the BN-heterocyclic portion of compounds **1**, **8c**, **8d**, and **8f** (Figure 3). Without exception, the NICS values for the illustrated 1,3-azaborines are more negative than the corresponding *B*-substituted 1,2-azaborines but less negative than the corresponding carbonaceous arenes.^[19] Thus, based on the NICS values, 1,3-azaborine exhibits aromaticity that is intermediate between benzene and 1,2-azaborine.

Finally, we have predicted the resonance stabilization energy (RSE) of the parent 1,3-azaborine to be approximately 29 kcal/mol . This value was derived computationally (G3MP2)^[20] through equations (1) and (2), which reveal that the RSE of the parent 1,3-azaborine is ca. 5 kcal/mol (average of 3.5 and 6.6 kcal/mol) less than that of benzene (RSE = 34.1 kcal/mol). Compared to a similar analysis for the parent 1,2-azaborine (RSE = 21 kcal/mol),^[21] the parent 1,3-azaborine exhibits a RSE that is higher, which is consistent with the structural analysis and NICS calculations.

G3MP2 (298K), values in kcal/mol

Thus, in terms of structure, magnetism, and resonance energy stabilization presented in this work, we conclude that 1,3-azaborines should be considered more aromatic than 1,2-azaborines.^[22] It appears that the crucial factors governing the relative aromaticity between 1,2- and 1,3-azaborines originate in the extent of electron delocalization as well as the lack of a $B-N$ bond in the 1,3-isomer. The stronger capability for the 1,2-azaborine to localize its

electrons in the BN bond region^[23] may disrupt electron delocalization and result in a relatively lower aromatic character.

In summary, we developed the first general synthetic toolbox for the synthesis of *B*-substituted 1,3-azaborines. As part of the scope of our method, we synthesized and isolated the first example of a *B*-F substituted azaborine. Structural analysis in the solid state revealed a *B*-substituent dependent intra-ring bond distance for the B–C(2) bond. The relatively long B–O distance, the calculated NICS values for 1,3-azaborines **1**, **8c**, **8d**, and **8f**, and the resonance stabilization energy evaluation suggest that 1,3-azaborines are highly aromatic. In view of the ubiquity and importance of arenes in biomedical research and materials science, the synthetic methods presented in this work represent a significant advance in realizing the potential of BN/CC isosterism, specifically the use of 1,3-azaborines, in these important areas of research.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This research was supported by the National Institutes of Health (National Institute of General Medical Sciences, Grant R01-GM094541). Funding for the University of Oregon Chemistry Research and Instrumentation Services has been furnished in part by the NSF (CHE-0923589).

References

1. For an overview, see: Campbell PG, Marwitz AJV, Liu S-Y. *Angew. Chem. Int. Ed.* 2012; 51:6074–6092. Bosdet MJD, Piers WE. *Can. J. Chem.* 2009; 87:8–29. Liu Z, Marder TB. *Angew. Chem. Int. Ed.* 2008; 47:242–244.
2. For leading references on 1,2-azaborines, see: Knack DH, Marshall JL, Harlow GP, Dudzik A, Szaleniec M, Liu S-Y, Heider J. *Angew. Chem. Int. Ed.* 2013; 52:2599–2601. Marwitz AJV, Lamm AN, Zakharov LN, Vasiliu M, Dixon DA, Liu S-Y. *Chem. Sci.* 2012; 3:825–829. Lamm AN, Garner EB, Dixon DA, Liu S-Y. *Angew. Chem. Int. Ed.* 2011; 50:8157–8160. Campbell PG, Abbey ER, Neiner D, Grant DJ, Dixon DA, Liu S-Y. *J. Am. Chem. Soc.* 2010; 132:18048–18050. [PubMed: 21141893] Liu L, Marwitz AJV, Matthews BW, Liu S-Y. *Angew. Chem. Int. Ed.* 2009; 48:6817–6819. Abbey ER, Zakharov LN, Liu S-Y. *J. Am. Chem. Soc.* 2008; 130:7250–7252. [PubMed: 18479099] Hatakeyama T, Hashimoto S, Oba T, Nakamura M. *J. Am. Chem. Soc.* 2012; 134:19600–19603. [PubMed: 23167918] Wang X-Y, Lin H-R, Lei T, Yang D-C, Zhuang F-D, Wang J-Y, Yuan S-C, Pei J. *Angew. Chem. Int. Ed.* 2013; 52:3117–3120.
3. For leading references on 1,4-azaborines, see: Braunschweig H, Damme A, Jimenez-Halla JO, Pfaffinger B, Radacki K, Wolf J. *Angew. Chem. Int. Ed.* 2012; 51:10034–10037. Agou T, Sekine M, Kobayashi J, Kawashima T. *Chem. Commun.* 2009:1894–1896. Kranz M, Hampel F, Clark T. *J. Chem. Soc., Chem. Commun.* 1992:1247–1248.
4. (a) Matus MH, Liu S-Y, Dixon DA. *J. Phys. Chem. A.* 2010; 114:2644–2654. [PubMed: 20112904] (b) Kranz M, Clark T. *J. Org. Chem.* 1992; 57:5492–5500.
5. Xu S, Zakharov LN, Liu S-Y. *J. Am. Chem. Soc.* 2011; 133:20152–20155. [PubMed: 22091703]
6. Chrostowska A, Xu S, Lamm AN, Mazière A, Weber CD, Dargelos A, Baylère P, Graciaa A, Liu S-Y. *J. Am. Chem. Soc.* 2012; 134:10279–10285. [PubMed: 22616808]
7. The preparation of *B*-F substituted 1,2-azaborines has thus far been challenging.
8. Negru M, Schoollmeyer D, Kunz H. *Angew. Chem. Int. Ed.* 2007; 46:9339–9341.
9. Marwitz AJV, McClintock SP, Zakharov LN, Liu S-Y. *Chem. Commun.* 2010; 46:779–781.
10. Crystallographic data for **8f**: C₁₁H₁₂BNO, *Mr* = 185.03, crystal size 0.40 x 0.19 x 0.01 mm³, Orthorhombic, space group *Pca* 2₁, *a* = 11.230(12), *b* = 11.861(13), *c* = 7.474(9) Å, *V* = 995.5(19) Å³, *Z* = 4, ρ_{calc} = 1.234 g cm⁻³, μ = 0.077 mm⁻¹, F(000) = 392, MoK α - radiation = 0.71073 Å, *T* = 173(2) K, 2 θ max = 50.00°, 7967 reflections measured [*R*_{int} = 0.0544], 1748 reflections

observed, 175 refined parameters, $R_1 = 0.0485$, $wR_2 = 0.1017$, and $GOF = 1.072$ for reflections with $I > 2 \sigma(I)$, $R_1 = 0.0660$, $wR_2 = 0.1097$, and $GOF = 1.072$ for all data, max/min residual electron density $+0.130/-0.180 \text{ e } \text{\AA}^{-3}$. CCDC 930426 (**8f**), CCDC 930428 (**8c**), CCDC 930427 (**8d**), and CCDC 931041 (**9**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

11. (a) Pyykkö P, Atsumi M. *Chem. Eur. J.* 2009; 15:12770–12779. [PubMed: 19856342] (b) Allen FH, Kennard O, Watson DG, Brammer L, Orpen AG, Taylor R. *J. Chem. Soc., Perkin Trans.* 1987; 2:S1–S19.
12. Marwitz AJV, Abbey ER, Jenkins JT, Zakharov LN, Liu S-Y. *Org. Lett.* 2007; 9:4905–4908. [PubMed: 17944483]
13. A B–C bond distance of 1.476 Å is consistent with substantial double bond character. The sum of B–C single-bond covalent radii = 1.60 Å, and the sum of B=C double-bond covalent radii = 1.45 Å, see reference 13a.
14. For an excellent discussion on the structural changes accompanying the stepwise population of a B–C bond, see: Chiu CW, Gabbai FP. *Angew. Chem. Int. Ed.* 2007; 46:6878–6881.
15. (a) Becke AD. *J. Chem. Phys.* 1993; 98:5648–5652. (b) Godbout N, Salahub DR, Andzelm J, Wimmer E. *Can. J. Chem.* 1992; 70:560–571.
16. This may suggest a potential origin of the observed B–C distances in crystal packing forces in the solid state.
17. A CCDC search (version 2011) of monosubstituted benzenes (> 1900 datapoints) revealed that ipso CC bond lengths for PhOR, PhNR₂, PhCR₃ range from 1.376–1.384 Å, 1.376–1.408, and 1.381–1.400, respectively (i.e., an overall range of 0.032 Å). The B–C distance in reported 1,2-azaborines range from 1.486–1.518 Å (i.e., an overall range of 0.032 Å).
18. Chen Z, Wannere CS, Corminboeuf C, Puchta R, Schleyer PR. *Chem. Rev.* 2005; 105:3842–3888. [PubMed: 16218569]
19. See Supporting Information for details.
20. Curtiss LA, Redfern PC, Raghavachari K, Rassolov V, Pople JA. *J. Chem. Phys.* 1999; 110:4703–4709.
21. Marwitz AJV, Matus MH, Zakharov LN, Dixon DA, Liu S-Y. *Angew. Chem. Int. Ed.* 2009; 48:973–977.
22. This conclusion is not inconsistent with the fact that 1,3-azaborines are thermodynamically less stable than 1,2-azaborines. The crucial factors determining the relative thermodynamic stabilities originate in the strength of the bonds, see reference 4.
23. Grant DJ, Dixon DA. *J. Phys. Chem. A.* 2006; 110:12955–12962. [PubMed: 17125312]

Figure 1.
Lewis structures for the azaborine series.

Figure 2. ORTEP illustrations, with thermal ellipsoids drawn at the 35% probability level, of **8f** and **9**. Numbers in brackets are optimized gas-phase bond distances calculated at the B3LYP/DZVP2 level.

		 <chem>CN1C=CC(BN(C)C)C1</chem> 1	 <chem>CN1C=CC(Bc2ccccc2)C1</chem> 8c	 <chem>CN1C=CC(BC#Cc2ccccc2)C1</chem> 8d	 <chem>CN1C=CC(BOc2ccccc2)C1</chem> 8f
	NICS(0)/NICS(1)				
increasing aromatic character	arene	−8.3/−9.0	−7.8/−9.6	−8.3/−9.5	−9.2/−9.5
	1,3-azaborine	−5.2/−6.6	−5.9/−7.9	−6.5/−8.2	−6.6/−7.6
	1,2-azaborine	−3.4/−4.5	−4.4/−6.0	−5.1/−6.5	−4.7/−5.4

Figure 3.

Calculated NICS(0) and NICS(1) values for 1,3-azaborines **1**, **8c**, **8d**, **8f** and their corresponding 1,2-azaborine and carbonaceous (arene) counterparts.

Scheme 1.
The three BN isosteres of benzene.

Scheme 2.
Substitution reactions of precursor **1** under acidic conditions.

Scheme 3.
Development of a nucleophilic substitution strategy for **1**.

Scheme 4.
Optimization of a nucleophilic substitution protocol.

Table 1Synthesis of *B*-Substituted 1,3-Azaborines through Nucleophilic Substitution

entry	nucleophile (Nu)	product	yield (%) ^a
1	Li- <i>n</i> -Bu	8a	80
2	BrMg-vinyl	8b	76
3	BrMg-Ph	8c	94
4	BrMg—≡—Ph	8d	89
5	Li-Mesityl	8e	87
6	Li-OPh	8f	99
7	K- <i>Ot</i> -Bu	8g	99
8	K-N(SiMe ₃) ₂	8h	69
9	Cs-F	4	81
10	Et ₃ N/HOMe ^b	3	96

^a Isolated yield.^b Vacuum was not applied after treatment of **1** with pivalic acid.