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A 1,3-Dihydro-1,3-azaborine Debuts

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Supporting Information

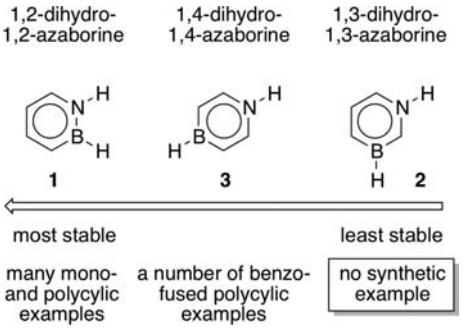
ABSTRACT: We present the first synthesis and characterization of a 1,3-dihydro-1,3-azaborine, a long-sought BN isostere of benzene. 1,3-Dihydro-1,3-azaborine is a stable structural motif with considerable aromatic character as evidenced by structural analysis and its reaction chemistry. Single crystal X-ray analysis indicates bonding consistent with significant electron delocalization. 1,3-Dihydro-1,3-azaborines also undergo nucleophilic substitutions at boron and electrophilic aromatic substitution reactions. In view of the versatility and impact of aromatic compounds in the biomedical field and in materials science, the present study further expands the available chemical space of arenes via BN/CC isosterism.

The expansion of structural diversity beyond what can be achieved by Nature is one of the main goals of organic synthesis. The BN/CC isosterism has emerged as a viable strategy to increase the chemical space of compounds relevant to biomedical research and materials science.[1,2] When applied to the quintessential aromatic compound benzene, BN/CC isosterism results in three structural isomers (Scheme 1): 1,2-dihydro-1,2-azaborine **1**, 1,3-dihydro-1,3-azaborine **2**, and 1,4-dihydro-1,4-azaborine **3** (from hereon, abbreviated as 1,2-azaborine, 1,3-azaborine, and 1,4-azaborine, respectively). Computational predictions suggest that the 1,2-isomer is thermodynamically most stable followed by the 1,4- then the 1,3-isomer.[3] This stability trend tracks with the number of published reports on these BN heterocycles. While many mono- and polycyclic 1,2-azaborine[4] compounds and a number of benzo-fused polycyclic 1,4-azaborines[5,6] have been synthesized and characterized,[1] the synthesis of a 1,3-azaborine derivative has remained elusive to date. In this communication, we disclose the first synthetic example of a 1,3-azaborine. We demonstrate that a 1,3-azaborine is a stable structural motif with considerable aromatic character as evidenced by structural analysis and its reaction chemistry.

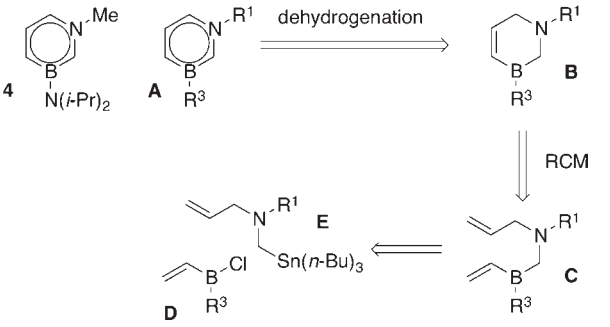
Scheme 2 illustrates our retrosynthetic analysis for a 1,3-azaborine. We envisioned that *B*-vinyl heterocycle **B** could potentially be poised to undergo dehydrogenation to furnish the target 1,3-azaborine **A**. Intermediate **B** could be prepared via ring closing metathesis (RCM) of diene **C**,[7] which in turn should be accessible from the coupling of vinyl boron chloride **D** and allylamine **E**.

Recognizing a potentially detrimental Lewis acid (boron)−Lewis base (nitrogen lone pair) interaction in precursors **B** and **C**, we chose compound **4** (R^1 = Me, R^3 = $N(i\text{-Pr})_2$, see Scheme 2) as our initial 1,3-azaborine target to mitigate this issue. Scheme 3 illustrates our synthesis of the penultimate compound **9**. The

Scheme 1. The Three BN Isosteres of Benzene



Scheme 2. Retrosynthetic Analysis



reaction of *N*-methylallylamine with formaldehyde and 1,2,3-benzotriazole afforded intermediates **5** and **5′** (as a 4:1 mixture) in 97% yield.[8] Deprotonation of *n*-Bu_3SnH with LDA followed by addition of the mixture of **5** and **5′** furnished **6** in 72% yield, with the 1,2,3-benzotriazole serving as a leaving group.[9] Our initial attempts using direct transmetalation between stannane nucleophile **6** and the vinylboron chloride **7**[10] were unsuccessful. However, lithium−tin exchange of **6** with *n*-hexyllithium followed by addition of electrophile **7** afforded the desired coupling product **8** in 67% yield. Grubbs first generation and Schrock catalysts were then screened to examine the RCM reaction of **8**. Disappointingly, these initial cyclization attempts met with failure, presumably due to degradation of RCM catalysts by the relatively nucleophilic amine group in **8**.[11] It has been demonstrated that the Grubbs first generation catalyst is compatible with an ammonium salt.[12] After screening a number of Brønsted acids, we found triflic acid to be the most suitable protection

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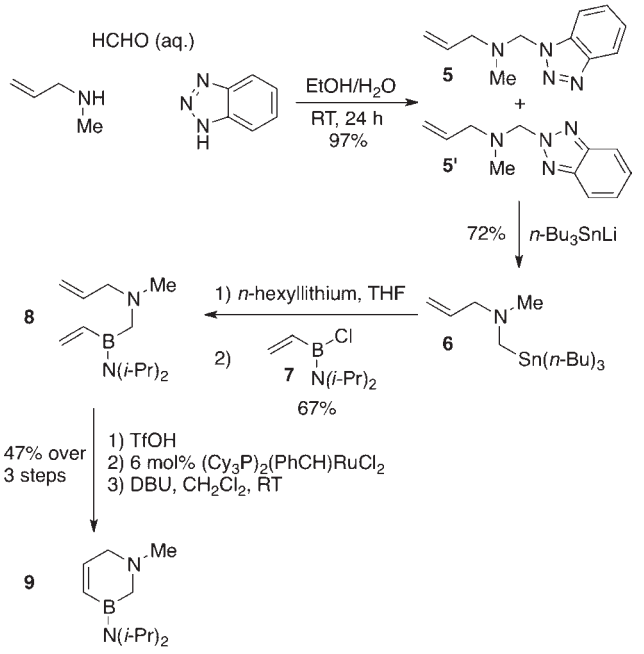
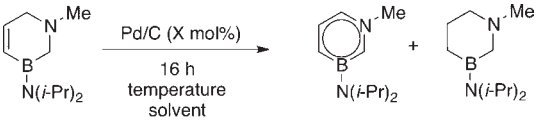
Scheme 3. Synthesis of Precursor 9



agent for the nitrogen lone pair in **8**. Thus, RCM reaction of **8**·TfOH complex followed by deprotonation with DBU produced the desired heterocycle **9** in 47% overall yield (over 3 steps from **8**).

With precursor **9** in hand, we were one dehydrogenation step away from the desired target 1,3-azaborine **4**. However, to the best of our knowledge, there are no reported examples of aromatization by eliminating two hydrogen atoms from meta positions in a six-membered ring system.[13] Indeed, our first attempts employing DDQ resulted in intractable mixtures. Further examination using Pd/C-mediated dehydrogention of heterocycle **9** afforded what appears to be the desired 1,3-azaborine **4** (^{11}B at δ 29.7 ppm) with good conversion (**4**/**9** > 19:1), albeit along with an appreciable amount of reduced byproduct **10** (^{11}B at δ 43.6 ppm, **4**/**10** = 1.1:1) (Table 1, entry 1). Notably, Pd black performed poorly compared to Pd/C under otherwise identical reaction conditions.[14] These results prompted us to screen for better reaction conditions using Pd/C. The **4**/**10** ratio is strongly dependent on the solvents used. Among the variety of the solvents examined, benzene was the best solvent in providing the highest **4**/**10** ratio (Table 1, entry 6 vs entries 2−5). However, the overall yield of **4** and **10** is only moderate (46−65%) in the presence of 20 mol % of Pd/C regardless which solvent was used (Table 1 entries 1−6). The effect of catalyst loading is significant. The ratio of **4**/**10** was increased to 11.5:1 when 50 mol % of Pd/C was used (Table 1, entry 7). However, a concomitant reduction in the overall yield (36% for **4** + **10**) was observed. Although only moderate selectivity was achieved in the presence of 5 mol % Pd/C (**4**/**10** = 1.8:1), the total yield (93% for **4** + **10**) and the absolute yield of **4** (ca. 60%, Table 1, entry 9) are superior to those entries with higher catalyst loadings. With 5 mol % Pd/C, the ratio of **4**/**10** can be further improved to 2.2:1 with conservation of total yield when the reaction was carried out at 120 °C (Table 1, entry 10). A further increase in temperature did not result in a better **4**/**10** ratio (Table 1, entry 11). Thus, under our optimized conditions, the desired product 1,3-azaborine **4**

Table 1. Optimization Survey for Dehydrogenation of 9



entry	catalyst loding X	solvent	T (°C)	**4**/**9**[a]	**4**/**10**[a]	yield[b] (%) of **4** + **10**
1	20	cyclohexene	85	>19:1	1.1:1	52
2	20	pentane	85	>19:1	1.2:1	65
3	20	Et_2O	85	>19:1	2.9:1	46
4	20	THF	85	>19:1	3.3:1	56
5	20	toluene	85	>19:1	2.5:1	62
6	20	benzene	85	>19:1	3.5:1	52
7	50	benzene	85	>19:1	11.5:1	36
8	10	benzene	85	>19:1	2.1:1	78
9	5	benzene	85	>19:1	1.8:1	93
10	5	benzene	120	>19:1	2.2:1	94
11	5	benzene	160	>19:1	1.6:1	89

[a] Determined by ^{1}H NMR. [b] Yield of crude material.

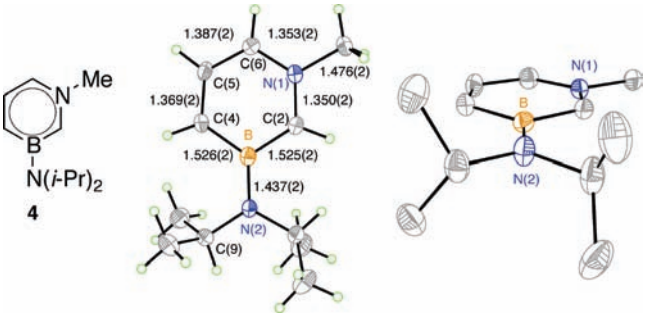


Figure 1. ORTEP illustrations, with thermal ellipsoids drawn at the 35% probability level, of compound **4**.

was finally isolated in 25% yield by distillation as a pale yellow liquid.

We were able to obtain crystals of **4** suitable for single crystal X-ray diffraction analysis by slow evaporation of a saturated pentane solution of **4** at −30 °C. The structure of **4** shown in Figure 1 unambiguously confirms our structural assignment and provides the first glimpse into the bonding of the 1,3-azaborine motif. The 1,3-azaborine ring is completely planar with 0.01 Å root-mean-square deviation of the ring atoms from the plane. The exocyclic nitrogen atom N(2) in **4** adopts trigonal planar geometry, with sum of the angles around N(2) being 360 ± 0.1°. The C(9)−N(2)−B−C(2) torsion angle of 178.57° and N(2)−B bond distance of 1.437(2) Å suggest significant π-bonding between N(2) and B (sum of sp^3 single-bond covalent radii = 1.56 Å;[15] the B(sp^2)−N(sp^2) single bond distance (i.e., perpendicular orientation) is ca. 1.47 Å).[16] Compared to known boron- and/or nitrogen-containing heteroaromatic compounds, all the intra-ring bond distances in **4** are consistent with electron delocalization. For example, the B−C(2) and B−C(4) distances in **4** (1.525(2) and 1.526(2) Å, respectively) are significantly shorter than the sum of B(sp^3)−C(sp^3) single-bond covalent radii of 1.6 Å,[15,17] but significantly longer than a B(sp^2)═C(sp^2)

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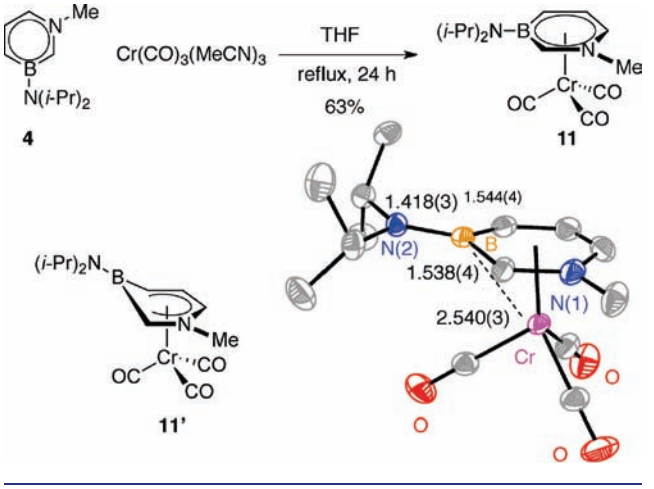
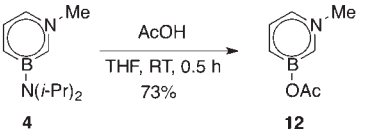
Scheme 4. Synthesis and Characterization of Piano Stool Complex 11



double bond (ca. 1.45 Å).[18] The N(1)−C(2) (1.350(2) Å) and N(1)−C(6) (1.353(2) Å) distances are similar to those in pyridine (1.347 Å).[19] The C(4)−C(5) (1.369(2) Å) and C(5)−C(6) (1.387(2) Å) distances are slightly shorter than those in benzene (1.40 Å) but longer than an average $C(sp^2)=C(sp^2)$ double bond of ca. 1.34 Å.[15] Notably, there is a smaller difference in the CC bond distances (i.e., difference between the longest and shortest intra-ring C−C bonds) in 1,3-azaborine **4** (0.018 Å) compared to an 1,2-azaborine (ca. 0.056 Å).[16b] Overall, the observed bonding in **4** indicates delocalized features and is consistent with computationally predicated values.[3]

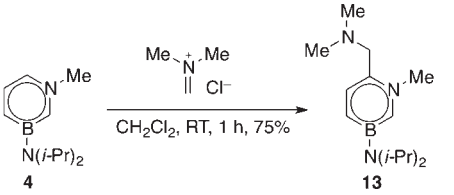
We are interested in the reaction chemistry of 1,3-azaborine **4**, in particular as it pertains to the aromatic character of this new heterocycle. We determined that 1,3-azaborine **4** reacts with $Cr(CO)_3(MeCN)_3$ to form the corresponding piano stool complex **11** in 63% yield (Scheme 4). A closer inspection of the structure suggests that compound **11** may be best characterized as an η^5 π-complex in which the boron atom does not significantly participate in π bonding with the Cr metal (e.g., structure **11′**).[20] The six-membered BN heterocycle is not planar in **11**; the boron atom is 0.21 Å above the root-mean-square plane containing the other five ring atoms. Compared to the structure of free heterocycle **4** (1.437(2) Å), the B−N(2) distance in **11** (1.418(3) Å) is shortened with significant double-bond character. Furthermore, the B−C distances in **11** (1.538(4) and 1.544(4) Å) are lengthened compared to **4** (1.525(2) and 1.526(2), respectively). Striking is the long Cr−B bond in **11** (2.540(3) Å), which is much longer than that of the parent 1,2-azaborine−$Cr(CO)_3$ complex (2.301(2) Å).[21] The observed bonding in **11** is similar to other metal complexes of *B*-amino-substituted boron heterocycles.[22]

To explore the substitution chemistry of 1,3-azaborine **4**, we treated it with a variety of nucleophiles (e.g., vinylmagnesium bromide, CsF, $LiAlH_4$, LiOAc, MeOH). Somewhat surprisingly, under those basic and neutral conditions, very little reactivity was observed. The diisopropylamino group might be too strong of a donor to serve as a leaving group. However, we were pleased to see that substitution at boron occurred readily with acetic acid, furnishing a *B*-OAc substituted 1,3-azaborine **12** in 73% yield (eq 1). We postulate that under acidic conditions, protonation of nitrogen lone pair renders the diisopropylamino substituent a much better leaving group, thus, promoting the substitution reaction.



(1)

Electrophilic aromatic substitution (EAS) reactions are a hallmark feature for aromatic compounds.[23,24] 1,3-Azaborine **4** resembles an electron rich aromatic nucleus capable of undergoing EAS reactions. We were happy to determine that treatment of 1,3-azaborine **4** with dimethyl(methylene)ammonium chloride produced the EAS product **13** regioselectively in 75% yield (eq 2).



(2)

In summary, we synthesized the first example of a 1,3-azaborine. We determined 1,3-azaborines are a thermally stable and isolable family of heterocycles with considerable aromatic character. Single crystal X-ray diffraction analysis is consistent with significant electron delocalization within the six-membered heterocyclic ring. We also demonstrated that 1,3-azaborine **4** undergoes nucleophilic substitutions at boron and electrophilic aromatic substitution reactions. In view of the recent resurgence of interest in developing BN heterocycles as arene mimics, our work opens up a new dimension of structural diversity that we envision will impact research in the biomedical field and materials science.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures, spectroscopic data, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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■ REFERENCES

(1) For an overview, see: (a) Bosdet, M. J. D.; Piers, W. E. *Can. J. Chem.* **2009**, *87*, 8–29. (b) Liu, Z.; Marder, T. B. *Angew. Chem., Int. Ed.* **2008**, *47*, 242–244.

(2) Fore recent references on potential biomedical applications, see: (a) Liu, L.; Marwitz, A. J. V.; Matthews, B. W.; Liu, S.-Y. *Angew. Chem., Int. Ed.* **2009**, *48*, 6817–6819. (b) Abbey, E. R.; Zakharov, L. N.; Liu, S.-Y. *J. Am. Chem. Soc.* **2010**, *132*, 16340–16342. (c) Abbey, E. R.; Zakharov, L. N.; Liu, S.-Y. *J. Am. Chem. Soc.* **2011**, *133*, 11508–11511.

(3) Kranz, M.; Clark, T. *J. Org. Chem.* **1992**, *57*, 5492–5500.
(4) For recent work, see: (a) Lepeltier, M.; Lukoyanova, O.; Jacobson, A.; Jeeva, S.; Perepichka, D. F. *Chem. Commun.* **2010**, *46*, 7007–7009. (b) Taniguchi, T.; Yamaguchi, S. *Organometallics* **2010**, *29*, 5732–5735. (c) Pan, J.; Kampf, J. W.; Ashe, A. J., III. *Organometallics* **2008**, *27*, 1345–1347. (d) Pan, J.; Kampf, J. W.; Ashe, A. J., III. *J. Organomet. Chem.* **2009**, *694*, 1036–1040. (e) Pan, J.; Kampf, J. W.; Ashe, A. J., III. *Organometallics* **2009**, *28*, 506–511. (f) Lamm, A. N.; Garner, E. B., III; Dixon, D. A.; Liu, S.-Y. *Angew. Chem., Int. Ed.* **2011**, *50*, 8157–8160. (g) Campbell, P. G.; Abbey, E. R.; Neiner, D.; Grant, D. J.; Dixon, D. A.; Liu, S.-Y. *J. Am. Chem. Soc.* **2010**, *132*, 18048–18050. (h) Daly, A. M.; Tanjaroon, C.; Marwitz, A. J. V.; Liu, S.-Y.; Kukolich, S. G. *J. Am. Chem. Soc.* **2010**, *132*, 5501–5506. (i) Marwitz, A. J. V.; McClintock, S. P.; Zakharov, L. N.; Liu, S.-Y. *Chem. Commun.* **2010**, *46*, 779–781. (j) Marwitz, A. J. V.; Jenkins, J. T.; Zakharov, L. N.; Liu, S.-Y. *Angew. Chem., Int. Ed.* **2010**, *49*, 7444–7447. (k) Lamm, A. N.; Liu, S.-Y. *Mol. BioSyst.* **2009**, *5*, 1303–1305.
(5) For early work, see: (a) Maitlis, P. M. *J. Chem. Soc.* **1961**, 425–429. (b) Kranz, M.; Hampel, F.; Clark, T. *J. Chem. Soc., Chem. Comm.* **1992**, 1247–1248.
(6) Fore recent work, see: (a) Agou, T.; Arai, H.; Kawashima, T. *Chem. Lett.* **2010**, *39*, 612–613. (b) Agou, T.; Kojima, T.; Kobayashi, J.; Kawashima, T. *Org. Lett.* **2009**, *11*, 3534–3537. (c) Agou, T.; Sekine, M.; Kobayashi, J.; Kawashima, T. *Chem.—Eur. J.* **2009**, *15*, 5056–5062. (d) Agou, T.; Sekine, M.; Kobayashi, J.; Kawashima, T. *Chem. Commun.* **2009**, 1894–1896.
(7) Ashe, A. J., III; Fang, X. *Org. Lett.* **2000**, *2*, 2089–2091.
(8) Katritzky, A. R.; Rachwal, S.; Wu, J. *Can. J. Chem.* **1990**, *68*, 446–455.
(9) Katritzky, A. R.; Chang, H.-X.; Wu, J. *Synthesis* **1994**, 907–908.
(10) Ashe, A. J., III; Fang, X.; Kampf, J. W. *Organometallics* **2000**, *19*, 4935–4937.
(11) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199–2238.
(12) Fu, G. C.; Nguyen, S. B. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1993**, *115*, 9856–9857.
(13) For examples of aromatization by eliminating two hydrogen atoms from meta positions in five-membered ring systems, see: Donohoe, T. J.; Orr, A. J.; Bingham, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 2664–2670.
(14) Poor conversion was observed (**4**/**9** = 1:2.1).
(15) Pyykkö, P.; Atsumi, M. *Chem.—Eur. J.* **2009**, *15*, 12770–12779.
(16) (a) Ostby, K. A.; Haaland, A.; Gundersen, G.; Nöth, H. *Organometallics* **2005**, *24*, 5318–5328. (b) Abbey, E. R.; Zakharov, L. N.; Liu, S.-Y. *J. Am. Chem. Soc.* **2008**, *130*, 7250–7252.
(17) Buehl, M.; Steinke, T.; Schleyer, P. v. R.; Boese, R. *Angew. Chem., Int. Ed.* **1991**, *30*, 1160–1161.
(18) Chiu, C. W.; Gabbaï, F. P. *Angew. Chem., Int. Ed.* **2007**, *46*, 6878–6881.
(19) Mootz, D.; Wussow, H. G. *J. Chem. Phys.* **1981**, *75*, 1517–1522.
(20) For an overview of ring-slippage in the 1,2-azaborolyl ligand system, see: Schmid, G. *Comments Inorg. Chem.* **1985**, *4*, 17–32.
(21) Marwitz, A. J. V.; Matus, M. H.; Zakharov, L. N.; Dixon, D. A.; Liu, S.-Y. *Angew. Chem., Int. Ed.* **2009**, *48*, 973–977.
(22) For an example, see: Ashe, A. J., III; Al-Ahmad, S.; Fang, X.; Kampf, J. W. *Organometallics* **1998**, *17*, 3883–3888.
(23) Taylor, R. *Electrophilic Aromatic Substitution*; Wiley & Sons: West Sussex, U.K., 1990.
(24) 1,2-Dihydro-1,2-azaborines have been demonstrated to undergo EAS reactions, see: Pan, J.; Kampf, J. W.; Ashe, A. J., III. *Org. Lett.* **2007**, *9*, 679–681.