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Diversity through Isosterism: The Case of Boron-Substituted 1,2-Dihydro-1,2-azaborines

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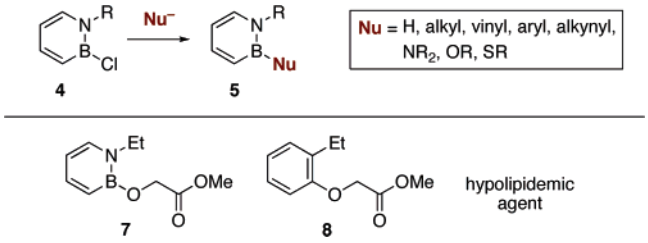
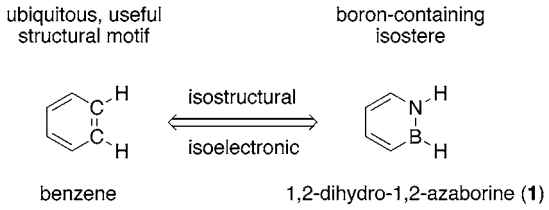
ABSTRACT



The first general synthesis of boron-substituted 1,2-dihydro-1,2-azaborines is described. The versatile 1,2-dihydro-1,2-azaborine precursor 4 is synthesized through a ring-closing metathesis–oxidation sequence. Treatment of 4 with a wide range of anionic nucleophiles furnishes the desired adducts 5 in good yields. The scope includes hydrogen- and a variety of carbon- and heteroatom-based nucleophiles. Furthermore, the boron-containing isostere (7) of the potent hypolipidemic agent, methyl 2-ethylphenoxyacetate (8), is readily prepared through our method.

Although boron is not an element commonly found in living systems, there has been burgeoning interest in incorporating boron into biologically active molecules.[1] Over the past decades, boron-containing compounds have been utilized as potent antimicrobial agents,[2] protease inhibitors,[3] and anticancer agents as part of boron neutron capture therapy (BNCT).[4] We have initiated a program directed toward the development of boron-containing aromatic heterocycles that mimic ubiquitous natural structures. Specifically, we are interested in the 1,2-dihydro-1,2-azaborine core[5] (from now on abbreviated as 1,2-azaborine) as it relates to the quintessential aromatic compound, benzene, by substitution of one of benzene's C=C bond units with an isoelectronic and isostructural B−N bond. The application of the B−N vs C=C isosterism[6] to benzene, and its many useful derivatives could open unexplored opportunities in the development of new drugs as well as provide new directions in the area of conjugated organic materials.[7]



In contrast to polycyclic boron-nitrogen heterocycles (e.g., borazarophenanthrene,[7b,8] borazaronaphthalene,[9] borazaro-

[†] Correspondence concerning X-ray crystallography should be directed to L.N.Z.

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pyrene,[7a] borazaroindene,[10] and borazarotriphenylene[11]), the chemistry of the biologically more relevant monocyclic 1,2-azaborines has not been extensively explored, presumably due to limited synthetic access. Dewar and White pioneered the first syntheses of 1,2-azaborines in the early 1960s and demonstrated that these compounds have substantial aromatic character.[12] More recently, Ashe has developed two complementary synthetic strategies for 1,2-azaborines: (1) a ring expansion of lithium azaborolides[13] and (2) a ring-closing metathesis (RCM)−oxidation sequence.[14] Ashe's elegant preparative routes established a more general approach to BN-containing aromatic ring structures.

Despite the groundbreaking advances made to date, significant synthetic challenges remain. For instance, the simplest member in the family of 1,2-azaborines, compound **1**, is still elusive. More generally, the scope with respect to the boron substituent (R^2 in Figure 1) provided by current

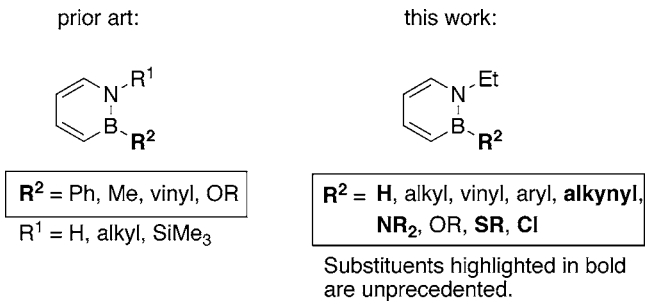
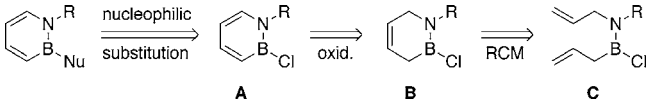


Figure 1. Scope of boron substituents in 1,2-azaborines.

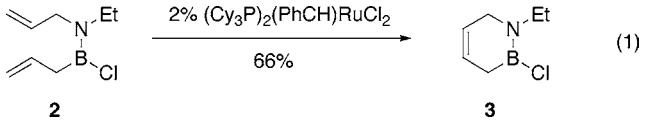
synthetic methods is fairly limited. To the best of our knowledge, carbon-[9a,13] and oxygen-based[15] groups are the only boron substituents in all of the monocyclic 1,2-azaborines that have been isolated to date. In order to take full advantage of the BN-isosterism of the ubiquitous benzene core, we set out to address this synthetic limitation. In this paper, we establish the first general synthesis of *B*-substituted 1,2-azaborines that includes not only a variety of carbon-based substituents but also a number of unprecedented examples of *B*-heteroatom substitutions (Figure 1).

We envisioned that an intermediate bearing a good leaving group on boron, e.g., **A** in Scheme 1, could serve as a

Scheme 1. Synthetic Strategy

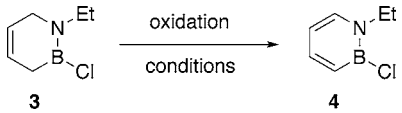


versatile precursor toward a wide range of *B*-substituted 1,2-azaborines via nucleophilic substitution.[16] Heterocycle **A** could be approached from the ring-opened precursor **C** via RCM followed by dehydrogenation. However, neither the RCM nor the oxidation have been performed in the presence of the reactive and labile B−Cl bond. Gratifyingly we determined that RCM of precursor **2** proceeds smoothly in the presence of 2% first-generation Grubbs catalyst to generate heterocycle **3** (eq 1), which is a testimony to the robustness and the versatility of modern RCM protocols.[17]



The aromatization of **3** proved to be more challenging.[18] Our initial attempts using DDQ[14] met with failure (Table 1, entry 1). However, optimization of conditions showed that palladium can serve as a catalyst for this transformation (entry 2).[11,12b] The presence of a hydrogen acceptor (i.e., cyclohexene) further improves the yield (entry 3). A survey

Table 1. Aromatization of Heterocycle **3**: Optimization Survey



entry	conditions	yield[a] (%)
1	1 equiv of DDQ, pentane, 35 °C, 24 h	14
2	Pd/C (20 mol %), pentane 80 °C, 16 h	31
3	Pd/C (20 mol %), cyclohexene, 80 °C, 16 h	43
4	Ru/C (20 mol %), cyclohexene, 80 °C, 16 h	1
5	Rh/Al_2O_3 (20 mol %), cyclohexene, 80 °C, 16 h	23
6	**Pd black (20 mol %), cyclohexene, 80 °C, 16 h**	**75 (57)[b]**
7	$Pd(PPh_3)_4$ (10 mol %), benzene, 80 °C, 16 h	0

[a] Determined by ^{11}B NMR analysis versus a calibrated internal standard. [b] Isolated yield in parentheses (see the Supporting Information for details).

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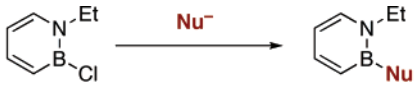
of transition metals reveals that Pd black catalyzes the aromatization of **3** most efficiently (entries 3−6). Finally, we determined that a homogeneous Pd source is ineffective in mediating this transformation (entry 7).

Heterocycle **4** serves as a general precursor to *B*-substituted 1,2-azaborines (Table 2). Displacement of the chloride in **4** occurs readily in the presence of alkyl- (entry 1), vinyl- (entry 2), aryl- (entry 3), and alkynyl-based (entry 4) nucleophiles. Moreover, heteroatom substitution also proceeded smoothly, resulting in the isolation of unprecedented nitrogen- (entry 5) and sulfur-substituted (entry 6) 1,2-azaborines. Potassium *tert*-butoxide reacts readily with **4** to provide the alkoxy adduct (entry 7). Treatment of **4** with Superhydride furnishes a 1,2-azaborine containing the unique B−H bond (**5h**, entry 8). Compound **5h** is stable toward purification by silica gel chromatography, which stands in stark contrast to prior failed attempts to isolate 1,2-azaborines bearing the B−H substitution.[15,19] The successful preparation of **5h** opens new opportunities for the synthesis of the ultimate parent azaborine **1**.

Table 2. Synthesis of *B*-Substituted 1,2-Azaborines through Nucleophilic Substitution of **4**



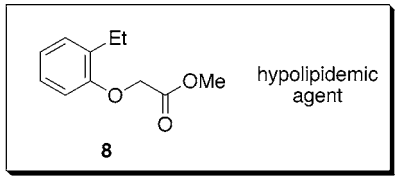
4 **5**

entry	nucleophile (Nu)	product	yield (%)[a]
1	Li–Bu	**5a**	79
2	Li–vinyl	**5b**	50
3	BrMg–Ph	**5c**	76
4	BrMg—≡—Ph	**5d**	83
5	Li–NMe_2	**5e**	66
6	K–SBn	**5f**	80
7	K–O*t*Bu	**5g**	71
8	$LiBEt_3$–H	**5h**	92

[a] Isolated yield.

A number of the compounds in Table 2 resemble aromatic structures of significance in chemistry. For instance, the vinyl-substituted 1,2-azaborine **5b** is a heteroaromatic derivative of styrene. The alkyne adduct **5d** is isoelectronic with tolan. Thus, our synthetic method can provide ready access to boron-containing heteroaromatics relevant to materials science.

To further demonstrate the utility of our synthetic method, we have prepared **7**, which is the elemental isomer of methyl 2-ethylphenoxyacetate **8**. Compound **8** and its derivatives have demonstrated potent hypolipidemic activity in animal studies.[20] Treatment of 1,2-azaborine precursor **4** with methyl glycolate **6** in the presence of triethylamine furnishes **7** in a straightforward manner (eq 2).



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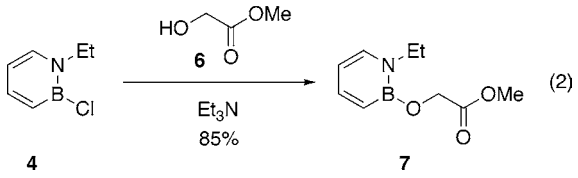
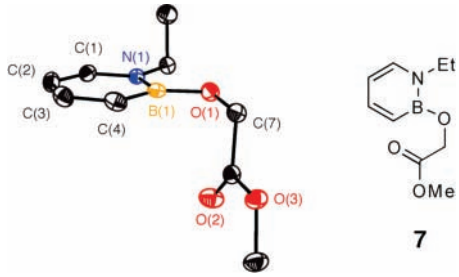


4 **7**

We have characterized compound **7** by single-crystal X-ray crystallography (Figure 2). There are only two reported crystal structures of metal-free 1,2-azaborines (i.e., not π-bound to a transition metal),[21] and to the best of our knowledge, the structure illustrated in Figure 2 is the first containing an exocyclic *B*-heteroatom bond.



7

Figure 2. ORTEP illustrations, with thermal ellipsoids drawn at the 35% probability level, of compound **7**.

The exocyclic oxygen atom O(1) of **7** is trigonal (i.e., sp^2-hybridized), with ∠B(1)−O(1)−C(7) = 118.6(1)°. The C(7)−O(1)−B(1)−N(1) torsion angle of −172.9(1)° and the B(1)−O(1) bond distance of 1.389(2) Å suggest significant π-bonding between oxygen and boron (sum of covalent radii = 1.55 Å).[22] The 1,2-azaborine ring is completely planar within 0.003 Å. The bond distances in the 1,2-azaborine ring (in Å), B(1)−N(1) = 1.436(2), N(1)−C(1) = 1.370(2), C(1)−C(2) = 1.355(2), C(2)−C(3) = 1.413(2), C(3)−C(4) = 1.363(2), and C(4)−B(1) = 1.518(2), are similar to the reported ones with *B*-Ph substitution.[21] Thus, the oxygen heteroatom does not appear to significantly affect the aromatic delocalization of the 1,2-azaborine heterocycle.

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In summary, we have developed a general method for the synthesis of a wide range of *B*-substituted 1,2-azaborines, including the first examples containing *B*-heteroatoms. Because 1,2-azaborines are isostructural and isoelectronic to the ubiquitous benzene motif, our study provides new opportunities in the areas of drug discovery and material science by increasing the diversity of biologically active molecules and conjugated materials through BN-isosterism.

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Supporting Information Available: Experimental procedures and compound characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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