1,2-Azaborolyls, Isoelectronic Analogues of the Ubiquitous Cyclopentadienyl Ligand: Synthesis of *B*-Heteroatom-Substituted 1,2-Azaborolyl Complexes and an Assessment of Their Electronic Features**

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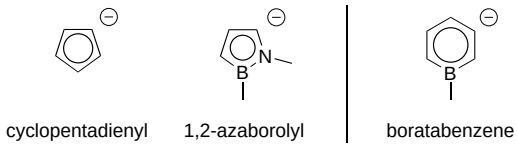
The cyclopentadienyl group is one of the most widely used ligands in organometallic chemistry, and metal complexes that bear cyclopentadienyl (Cp) ligands have been applied across a broad spectrum of fields.[1] One particularly noteworthy use of cyclopentadienyl complexes (e.g., zirconocene- and titanocene-based systems) is as catalysts for Ziegler–Natta polymerizations of olefins.[2]

The desire to modulate the reactivity of Ziegler–Natta catalysts has led to growing interest in the development of variations of Cp-based Group 4 metallocenes.[2, 3] For example, a number of recent studies have pursued the use of boron-based heterocycles as alternatives to cyclopentadienyl.[4] Particularly noteworthy are the investigations of Bazan and Ashe, who have shown that boratabenzene–zirconium complexes can furnish reactivity distinct from cyclopentadienyl-zirconium complexes and that the electronic nature of the boron substituent dictates the catalyst's course of action.[5–8]

1,2-Azaborolyls are isoelectronic with cyclopentadienyls (Scheme 1). As with boratabenzenes,[9] the boron of azaborolyls provides a potentially straightforward point of attachment for substituents that can modulate the electronic nature of the boron heterocycle.[10]

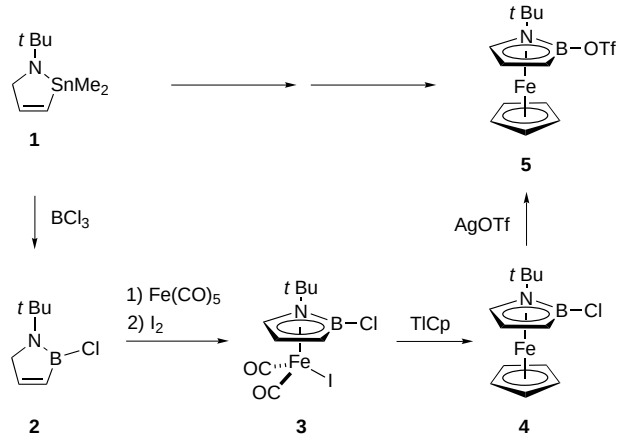


Scheme 1. Cyclopentadienyl and related ligands.

Surprisingly, 1,2-azaborolyls have not been widely investigated. Nearly all of the work to date is due to Schmid, whose pioneering studies of azaborolyls were initiated two decades ago.[11, 12] Only two substituents on boron, both of which are carbon-based (methyl and phenyl), have been described.

In 1998, we initiated a program directed at expanding the diversity of accessible 1,2-azaborolyls, with a particular focus on the boron substituent. Herein, we demonstrate that, from a single precursor, we can synthesize azaborolyl complexes that bear a wide array of substituents (hydrogen, carbon, nitrogen, oxygen, fluorine, phosphorus, and sulfur). We have structurally characterized a B–OR adduct, and through electrochemical studies we have established that the group on boron exerts a significant impact on the electronic nature of the metal complex.

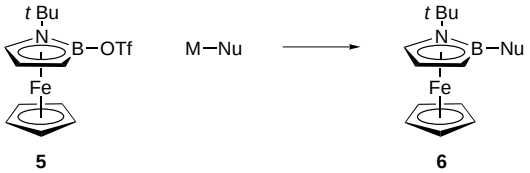
In our initial investigation, we chose to focus on the synthesis of azaborolyl–iron complexes, thereby allowing direct comparison with much-studied, isoelectronic ferrocenes.[1b] Transmetalation of the previously reported stannacycle **1**[13] with BCl_3 affords the *B*-chloroboracycle **2**, which is then complexed to iron (Scheme 2).[14] Treatment of this η^5-(1,2-azaborolyl) adduct **3** with TlCp[15] furnishes ferrocene analogue **4**, the chloride of which is then abstracted by AgOTf ($OTf = OSO_2CF_3$) to provide the more reactive triflate complex **5**.[16]



Scheme 2. Synthesis of *B*-heteroatom-substituted η^5-(1,2-azaborolyl) complexes.

Complex **5** reacts with anionic nucleophiles to produce a wide array of *B*-substituted adducts **6** in good to excellent yields (Table 1). Organometallic reagents (Table 1, entries 1 and 2), hydride (Table 1, entry 3),[17] alkoxides and thiolates

Table 1. Synthesis of a diverse array of *B*-substituted 1,2-azaborolyl complexes by nucleophilic substitution.



Entry	M–Nu	Yield [%][a]
1	Li-*n*Bu	84
2	MgBr	88
3	$LiAlH_4$	91
4	Na-OMe	83[b]
5	Na-SBn	89
6	Li-NMe_2	85
7	K-PPh_2	75
8	K-F	87

[a] Yield of isolated product (average of two runs). [b] 95% purity.

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(Table 1, entries 4 and 5), amides and phosphides (Table 1, entries 6 and 7), as well as fluoride (Table 1, entry 8) all cleanly displace the triflate, presumably via an addition–elimination pathway. The syntheses illustrated in Table 1 and Scheme 2 describe the first examples of heteroatom-substituted 1,2-azaborolyls.

To gain insight into how the boron substituent affects the electronic nature of the iron, we have measured the oxidation potential of these new azaborolyl complexes (Table 2).[18] As expected, the NMe_2 and OMe groups are the best donors among those that we have examined (Table 2, entries 1 and 2). The *n*Bu, SBn, F, and allyl substituents appear to be modestly electron-donating (Table 2, entries 3–6) relative to H (Table 2, entry 7), whereas PPh_2 is electron-withdrawing (Table 2, entry 8).

Table 2. Oxidation potential of 1,2-azaborolyliron complexes as a function of the substituent on boron (0.0026 M; 0.10 M Bu_4NPF_6; CH_2Cl_2; 20 mV s^{-1}; potentials relative to Ag/Ag^+ with $E_{1/2} = 0.23$ V for Fc/Fc^+).

Entry	Boron substituent Nu on **6**	E_{pa} [V][a]
1	NMe_2	−0.26
2	OMe	−0.08
3	*n*Bu	0.07
4	SBn	0.08
5	F	0.08
6	allyl	0.13
7	H	0.20
8	PPh_2	0.29

[a] E_{pa} = anodic peak potential.

Using the data in Table 2 and a two-parameter Hammett analysis (σ_I = inductive component; σ_R = resonance component),[19, 20] we have determined an excellent correlation between observed and calculated oxidation potentials for these substituted 1,2-azaborolyl complexes (Figure 1; $E_{pa} = 0.42\sigma_I + 0.94\sigma_R + 0.20$).

We have confirmed our structural assignment for azaborolyl complexes **6** through an X-ray crystallographic study of the *B*-OMe adduct (Figure 2). As expected on the basis of our electrochemical investigations, the OMe group adopts a geometry consistent with π bonding between oxygen and boron (Figure 2).[21]

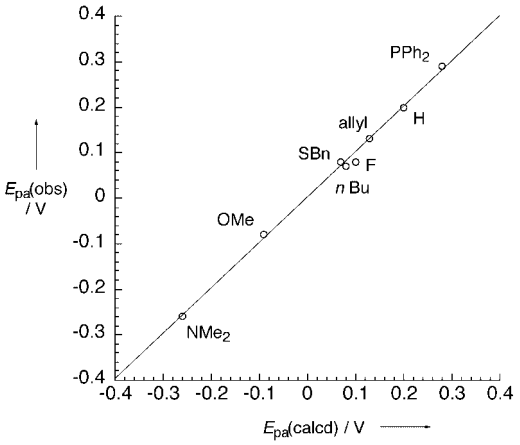


Figure 1. Observed and calculated (by Hammett analysis) oxidation potentials for substituted 1,2-azaborolyl complexes (E_{pa}(calcd) = 0.42 σ_I + 0.94 σ_R + 0.20).

Finally, we have determined the impact that replacing two carbons of a cyclopentadienyl ligand with the corresponding isoelectronic B–N unit has on a metal. Thus, electrochemistry indicates that 1,2-azaborolyl is somewhat more electron-donating than cyclopentadienyl (Scheme 3).[22]

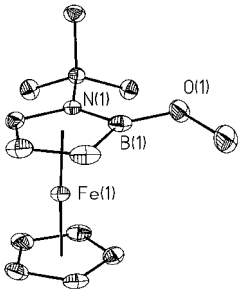
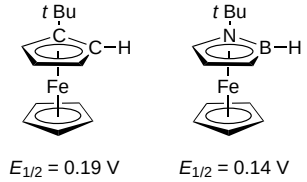


Figure 2. Molecular structure of azaborolyl complex **6** (Nu = OMe) (ORTEP illustration, with thermal ellipsoids drawn at the 35% probability level).

In summary, we have developed a synthetic route that provides access to a diverse array of the first *B*-heteroatom-substituted (H, N, O, F, P, S, and Cl) 1,2-azaborolyl complexes. In addition, we have established that the substituent on boron can modulate the reactivity of the complexes, specifically, their susceptibility to one-electron oxidation. Furthermore, we have determined that a 1,2-azaborolyl is more electron-rich than an isostructural cyclopentadienyl ligand. In view of the ubiquity and the utility of cyclopentadienyl–metal complexes, we anticipate that the observations described in this study will stimulate the development of applications of η^5-(1,2-azaborolyl) ligands in metal-catalyzed processes.



Scheme 3. Direct electrochemical comparison between a 1,2-azaborolyl and a cyclopentadienyl complex (0.0026 M; 0.10 M Bu_4NPF_6; CH_2Cl_2; 20 mV s^{-1}; potentials relative to Ag/Ag^+ with $E_{1/2} = 0.23$ V for Fc/Fc^+).

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[21] The short B–O bond length (1.384 Å) is consistent with a significant π interaction (sum of covalent radii: 1.47 Å).

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Total Synthesis of Ambruticin**

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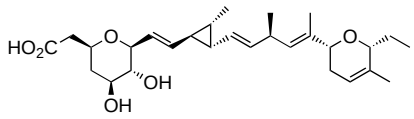
Ambruticin (**1**) was isolated from fermentation extracts of the Myxobacteria species *Polyangium cellulosum* var. *fulvum*. It is an orally active antifungal agent showing in vitro and in vivo activity against a variety of pathogenic fungi, including *Histoplasma capsulatum*, *Coccidioides immitis*, and *Blastomyces dermatitides*, as well as the dermatophytic filamentous fungi.[1] Ambruticin features unique *cis*-2,6-disubstituted tetrahydropyran and dihydropyran ring systems together with a methylcyclopropane moiety. In spite of considerable interest



1 (+)-Ambruticin

in the preparation of **1**,[2] we found in the literature only one total synthesis, reported by Kende in 1990,[3] and the difficulty in designing a stereoselective total synthesis is manifested in recent reports dealing with partial syntheses of the molecule.[4] In our continuing search for new applications of stereoselective radical cyclization reactions of β-alkoxyacrylates,[5] we examined the efficacy of these reactions in a stereocontrolled synthesis of **1**.

In our retrosynthetic analysis, the tetrahydropyran aldehyde **B** was to be prepared from a β-alkoxyacrylate precursor **C**, which may be obtained from L-arabinose (**2**). The dihydropyran derivative **E** was envisaged to arise from the diene **F** by olefin metathesis.[6] Connection of the parts **A** and **D** by Julia-type olefination would then complete the construction of the carbon framework (Scheme 1).

Selective acetonide protection of the dithioacetal derivative of L-arabinose (**2**) and benzylation of the remaining hydroxy groups gave the acetonide **4** (Scheme 2).[2a] The β-alkoxyacrylate **5** was obtained from **4** by acetonide deprotection, regioselective TBS protection of the primary hydroxy group, and reaction with methyl propiolate. The aldehyde group generated from the dithioacetal moiety in **5** was reduced with $NaBH_4$, and bromide substitution led to the primary bromide **6**, which was then stereoselectively transformed into the

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