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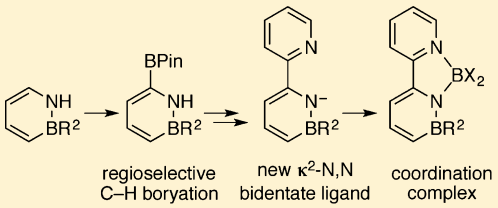
Late-Stage Functionalization of 1,2-Dihydro-1,2-azaborines via Regioselective Iridium-Catalyzed C–H Borylation: The Development of a New N,N-Bidentate Ligand Scaffold

Andrew W. Baggett,[†,‡] Monica Vasiliu,[§] Bo Li,[†] David A. Dixon,[§] and Shih-Yuan Liu*[,†,‡]

[†]Department of Chemistry, Boston College, Chestnut Hill, Massachusetts 02467-3860, United States
[‡]Department of Chemistry and Biochemistry, University of Oregon, Eugene, Oregon 97403-1253, United States
[§]Department of Chemistry, The University of Alabama, Tuscaloosa, Alabama 35487-0036, United States

Supporting Information

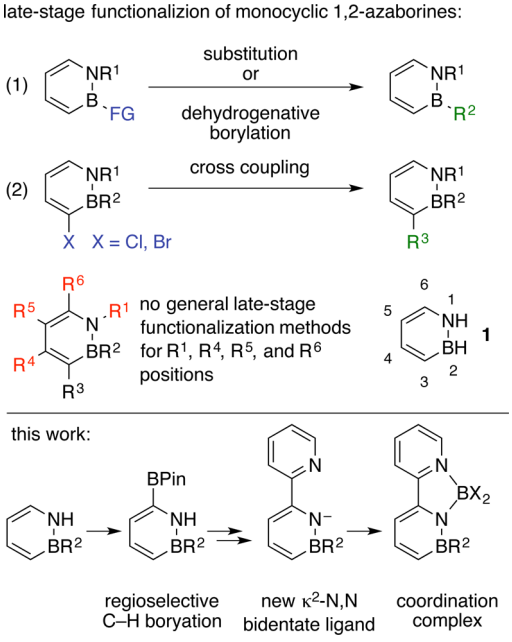
ABSTRACT: The first general late-stage functionalization of monocyclic 1,2-azaborines at the C(6) position is described. Ir-catalyzed C–H borylation occurs regioselectively at the C(6) position of *B*-substituted 1,2-azaborines and is compatible with a range of substitution patterns at boron (e.g., hydride, alkoxide, alkyl, and aryl substituents). Subsequent Suzuki cross coupling with aryl- and heteroaryl bromides furnishes 1,2-azaborine-based biaryl compounds including 6-[pyrid-2-yl]-1,2-azaborines that represent novel κ^2-N,N-bidentate ligands. The 6-[pyrid-2-yl]-*B*-Me-1,2-azaborine ligand has been demonstrated to form an emissive coordination complex with dimesitylboron that exhibits bathochromically shifted absorption and emission maxima and a higher photoluminescence quantum yield compared to its carbonaceous analogue.



INTRODUCTION

BN/CC isosterism has emerged as a viable strategy to expand the structural diversity of organic molecules.[1] Our group has been focusing on the development of 1,2-dihydro-1,2-azaborines (hereafter abbreviated as 1,2-azaborines) as a BN isostere of the ubiquitous monocyclic arene motif. Despite recent achievements in the assessment of aromaticity[2] as well as the understanding of the electronic structure of 1,2-azaborines,[3] the development of applications of this basic heterocyclic motif in medicinal chemistry[4] and in materials science[5] has been significantly hampered by the lack of available synthetic tools that enable the access of substituted derivatives. Selective late-stage functionalization is arguably the most general and efficient approach to generate an array of derivatives from an assembled 1,2-azaborine core. Due to the electrophilic nature of boron and the versatile reactivity of the B–H bond, functionalization at the boron position has been established via nucleophilic substitution[6] and dehydrogenative borylation chemistry,[7] respectively (Scheme 1, eq 1, FG = leaving group, H). The successful regioselective halogenation of 1,2-azaborines at the C(3) position[2d,8] should set up its further derivatization via cross-coupling chemistry (Scheme 1, eq 2).[9] In contrast to the above-mentioned examples, no general solutions for the late-stage installation of substituents at the R[1],[10] R[4], R[5],[11] and R[6] positions have been reported (Scheme 1).[12−14] The selective late-stage functionalization at the C(6) position piqued our interest in particular, as the ready incorporation of coordinating substituents at this position would enable the straightforward construction of a library of novel anionic κ^2 bidentate ligands. For instance, the installation of the 2-pyridyl group at the C(6) position would result in novel azaborine-containing ligands closely related to the privileged classes of 2,2-bipyridine[15] and 2-phenylpyridine[16] ligands.

Scheme 1. State-of-the-Art in the Late-Stage Functionalization of Monocyclic 1,2-Azaborines



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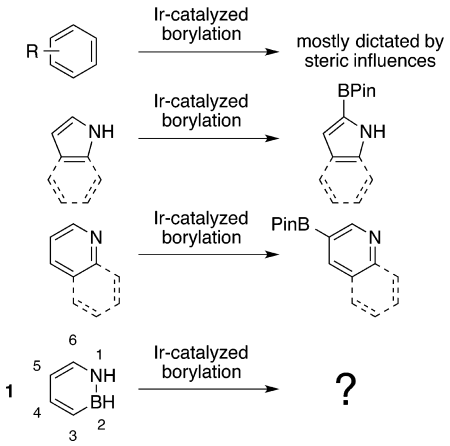
In this work, we establish that selective late-stage functionalization at the C(6) position of a 1,2-azaborine can be achieved via iridium-catalyzed C−H borylation followed by Suzuki cross coupling. Furthermore, we demonstrate that this new synthetic tool can be used to prepare new κ^2-N,N-bidentate ligands capable of forming coordination complexes (Scheme 1, bottom).

RESULTS AND DISCUSSION

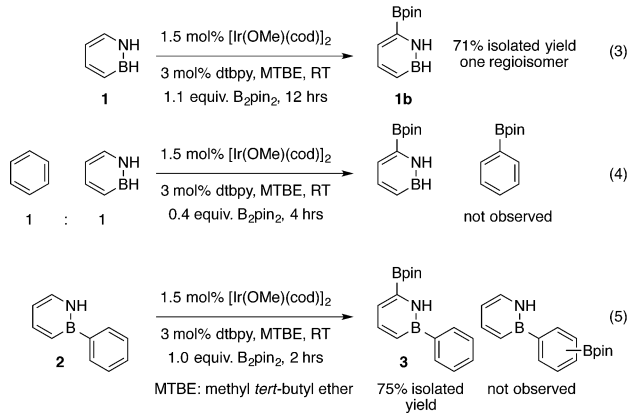
The iridium-catalyzed C−H borylation[17] represents a powerful synthetic tool to prepare aryl and heteroaryl boronate esters. It has been established that borylation regioselectivities for arenes are largely dictated by steric effects.[18] However, electronic influences on the selectivity of this reaction have also been observed. In particular, distinct borylation selectivities have been determined for nitrogen heterocycles related to 1,2-azaborine (i.e., pyrrole and pyridine). In the presence of the $[IrCl(cod)]_2$/4,4′-di-*tert*-butyl-2,2′-bipyridine (dtbpy) catalyst system, pyrrole and indole undergo a regioselective borylation at the 2-position whereas pyridine and quinolines are

Scheme 2. Regioselectivity in Ir-Catalyzed Borylation



preferentially borylated at the C(3) position (Scheme 2).[19] ^{1}H and ^{13}C NMR chemical shift and pK_a values of the C−H bond have been successfully correlated with borylation regioselectivity, predicting preferential borylation at the position bearing the most acidic[20] and most downfield ^{1}H chemical shift.[21]

In contrast to benzene (D_{6h} point group), which possesses six symmetry (and electronically)-equivalent hydrogens, the parent 1,2-azaborine **1** (C_s point group) bears six electronically distinct hydrogens. Due to the absence of any steric influence, a regioselective borylation of **1** would thus necessarily depend solely on electronic directing effects. We were very pleased to discover that borylation of **1** under catalytic conditions developed by Ishiyama, Hartwig, and Miyaura ($[Ir(OMe)(cod)]_2$/dtbpy)[22] gave selectively the C(6)-borylated regioisomer **1b** in 71% isolated yield (eq 3). An intermolecular competition experiment between benzene and 1,2-azaborine **1** reveals that the 1,2-azaborine heterocycle is preferentially borylated over the corresponding arene (eq 4). Similarly, an intramolecular competition experiment using the *B*-Ph-substituted 1,2-azaborine **2** as the substrate shows C(6)-borylation adduct **3** as the exclusively observed borylation product (eq 5).



In order to understand the observed preference of the borylation reaction, we calculated the gas-phase acidity, ΔG_{gas}, at the G3MP2 level[23] (Gaussian09),[24] the solution-phase pK_a (H_2O) values using the self-consistent reaction field approach (SCRF)[25] with the COSMO parameters[26,27] as implemented in the Gaussian03,[28] and the bond dissociation energies (BDE) of

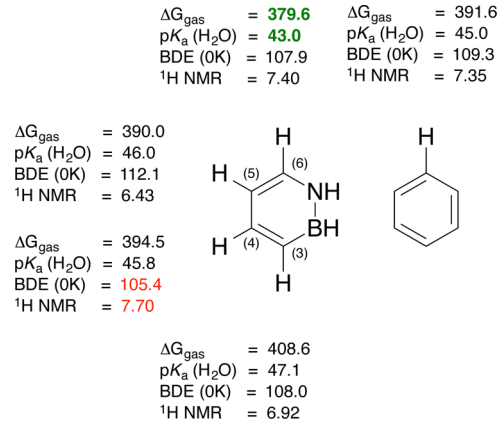


Figure 1. Calculated G3MP2 gas-phase acidities (ΔG_{gas}), pK_a (B3LYP/DZVP2) values in H_2O, G3MP2 bond dissociation energies (BDE) for the corresponding C−H bonds, and experimentally observed ^{1}H NMR chemical shifts of the hydrogen atoms. Energy values are in kcal/mol. Chemical shift values are in ppm in CD_2Cl_2. ΔG_{gas} is defined as the free energy of the following reaction in the gas phase at 298 K: X−H → X^- + H^+.

the four C−H bonds of **1** (Figure 1), also at the G3MP2 level. ^{1}H NMR chemical shifts obtained from a solution of 1,2-azaborine **1** in CD_2Cl_2 are also shown. As shown in Figure 1, the C(6)−H bond, i.e., the site of selective borylation, is the most acidic among the C−H bonds in **1** (Figure 1, green numbers). This is consistent with the reported hypothesis that the transition state for the C−H activation involves significant proton-transfer character.[20] Conversely, the observed borylation selectivity for heterocycle **1** does not correlate with the hydrogen exhibiting the most downfield ^{1}H NMR chemical shift or the weakest C−H bond dissociation energy, which would have predicted C(4) borylation (Figure 1, red numbers). Using the same level of theory, the gas-phase acidity ΔG_{gas}, the pK_a, and the BDE of the C−H bond in benzene were predicted to be 391.6 kcal/mol, 45.0, and 109.3 kcal/mol, respectively.[29] The reduced acidic character of benzene's C−H bond in comparison to 1,2-azaborine's C(6)−H bond is consistent with

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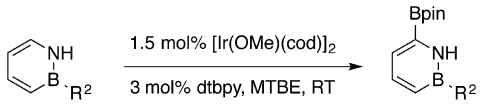
the outcome of the intermolecular competition experiment shown in eq 4, which shows selective borylation of the 1,2-azaborine heterocycle.

It is worth noting that, under the employed reaction conditions, activation of the N–H and B–H bonds of the parent 1,2-azaborine **1** is not observed. This observation is consistent with the work of Suginome, who demonstrated that arene borylation using the structurally somewhat similar 1,8-naphthalenediaminatoborane H-Bdan requires significant modifications of both the reaction conditions and the catalyst system to effect B–H activation in appreciable amount.[30]

The borylation regioselectivity is independent of the substituent at boron. In addition to **1** (*B*–H) and **2** (*B*–Ph) (*vide supra*), Table 1 shows that exclusive C(6)-borylation is

Table 1. Ir-Catalyzed Borylation of *B*-Substituted 1,2-Azaborines



4 **5**

entry	substrate	product	yield[a] (%)
1	**4a** (R^2 = Me)	**5a**	67[b]
2	**4b** (R^2 = *n*-Bu)	**5b**	86
3	**4c** (R^2 = Mes)	**5c**	92
4	**4d** (R^2 = O-*n*-Bu)	**5d**	66

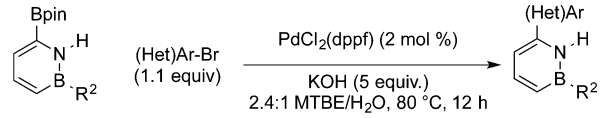
[a]Isolated yield (average of two runs). [b]Yield over two steps starting from the *N*-TBS-*B*-Me-1,2-azaborine precursor (see Supporting Information).

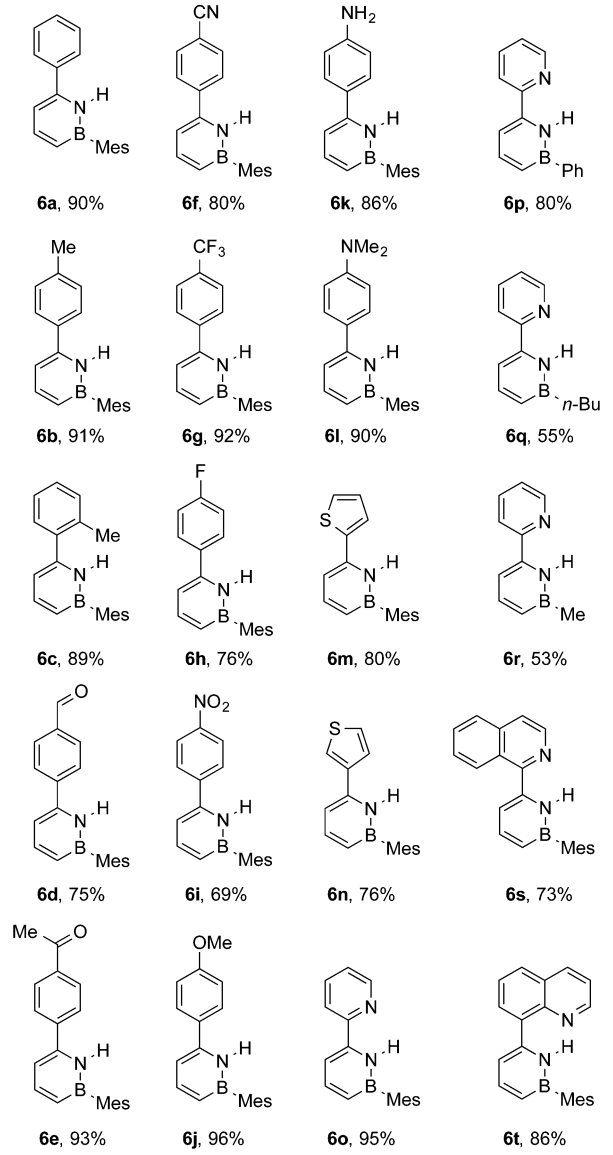
observed for *B*-alkyl- (entries 1 and 2), bulky *B*-mesityl- (entry 3), and *B*-alkoxide- (entry 4) substituted 1,2-azaborines. The compatibility of a boron substituent such as a *B*-alkoxide that is capable of serving as a leaving group enables the development of strategies that involve multiple late-stage functionalizations (e.g., C(6) functionalization followed by functionalization at boron).

With various C(6)-borylated 1,2-azaborines in hand, we then investigated their suitability toward Suzuki cross-coupling reactions. As can be seen from Table 2,[31] coupling of borylated 1,2-azaborine substrates with electron-neutral (entries **6a–c**), electron-poor (entries **6d–6i**), and electron-rich (entries **6j–6l**) aryl bromides proceed in good yields. Heteroaryl bromides including thiophene (entries **6m**, **6n**), pyridine (entries **6o–6r**), isoquinoline (**6s**), and quinoline (**6t**) bromides serve as suitable cross-coupling partners as well.

Conversely, the reaction of **1b** (containing the *B*–H) and **5d** (containing the *B*–O-*n*-Bu) under the cross-coupling conditions shown in Table 1 led to decomposition of the starting material, presumably due to the sensitivity of the *B*–H and *B*–O-*n*-Bu bonds toward water under strongly basic conditions.[32] Gratifyingly we were able to determine that boronate ester **5d**, and to a more limited extent **1b**, are suitable Suzuki cross-coupling substrates under conditions that utilize a weaker base.[33] As can be seen from Table 3, coupling of **5d** with a number of aryl and heteroaryl bromides can be achieved in the presence of $Pd(OAc)_2$/SPhos as a catalyst and K_3PO_4 as the base additive (entries **6w**, **6y**, **6z**) or using the combination of Pd_2dba_3/P(*o*-tol)$_3$ and Na_2CO_3 (entry **6x**). Similarly, boronate ester **1b** engages in Suzuki cross coupling with simple aryl bromides (entries **6u** and **6v**). It is worth noting that product

Table 2. Suzuki Cross Coupling of Borylated 1,2-Azaborine Substrates[a]





[a]Percent numbers are isolated yields and represent an average of two runs.

6u (the result of the reaction between bromobenzene and **1b**) represents a new BN isostere of biphenyl. The substrate scope with regard to substrate **1b** remains still somewhat limited, however, as all attempts to couple **1b** with heteroaryl bromides (including 2-bromopyridine) have not succeeded in our hands.[34]

The successful development of cross-coupling conditions for **5d** is significant from a synthetic strategy point of view: The capability to functionalize the boron position post C–H borylation/Suzuki coupling (enabled by the relatively labile *B*-O-*n*-Bu functionality in **5d**) should allow access to 1,2-azaborine derivatives that would have been challenging to access otherwise. For instance, disubstituted 1,2-azaborine **X**

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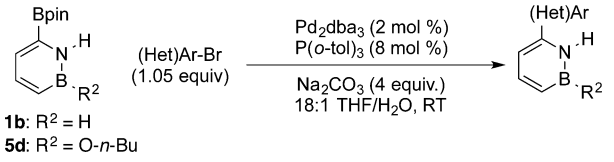
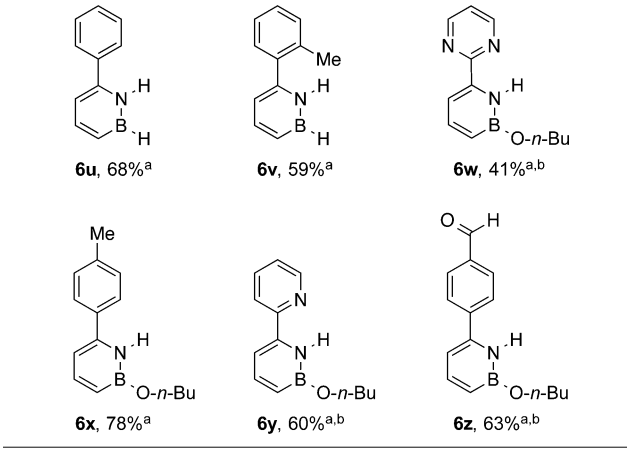
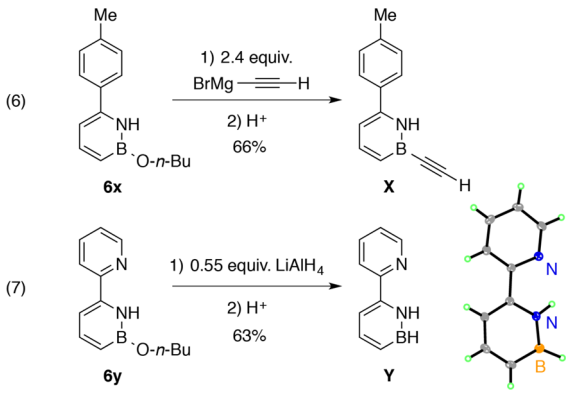
Table 3. Suzuki Cross Coupling of Borylated 1,2-Azaborine Substrates 1b and 5d





[a]Isolated yield, average of two runs. [b]Conditions: 1 mol % of $Pd(OAc)_2$, 2 mol % of SPhos, 1.3 equiv of K_3PO_4, 30:1 *n*-BuOH/H_2O, 10 h, 60 °C.

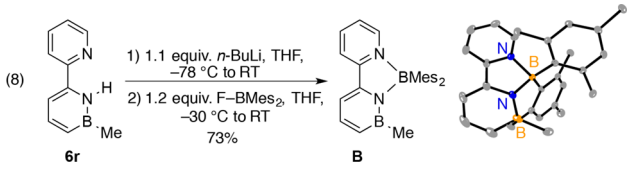
bearing a *B*-ethynyl group, which is a problematic functional group for the Ir-catalyzed borylation reaction,[35] can now be synthesized from **6x** through a simple substitution reaction with ethynylmagnesium bromide (eq 6). Similarly, the "parental"



structure of our κ^2-N,N-bidentate ligands, compound **Y**, which was previously inaccessible from the cross-coupling reaction with **1b** (*vide supra*), can now be prepared from **6y** upon treatment with $LiAlH_4$ (eq 7). We obtained the X-ray structure for compound **Y**, which shows a syn-coplanar conformation with respect to the nitrogen atoms (∠NCCN = 1.1°).[36]

A one-pot borylation/Suzuki cross-coupling sequence is a favorable method to quickly obtain biaryl compounds from unactivated arenes. Using a similar one-pot protocol reported by Marder et al.,[31] we prepared **6a**, **6j**, and **6q** directly from 1,2-azaborines **4b** and **4c**.[37] The one-pot isolated yields for **6a** (74%) and **6j** (80%) were slightly below the overall yields obtained via the two-step procedure (83% and 88%, respectively). On the other hand, the one-pot protocol resulted in a significant increase in the isolated yield for *B*–*n*-Bu 1,2-azaborine biaryl compound **6q** (75% vs 47%).

Table 2 illustrates a collection of C(6)-substituted 1,2-azaborines (**6o**–**6t**) that have the potential to serve as precursors to anionic κ^2-N,N-bidentate ligands. In our initial effort, we chose to investigate the coordination ability of the ligand derived from **6r**. Deprotonation of **6r** with *n*-butyllithium and subsequent quenching with dimesitylboron fluoride[38] led to the formation of its corresponding κ^2-N,N complex **B** in 73% yield, which we were able to structurally characterize via single-crystal X-ray diffraction (eq 8).



We also prepared complex **A**[39] as the carbonaceous isostere of **B** to facilitate investigation of the effects of BN/CC isosterism on the optoelectronic properties in this system.[40] Figure 2 shows the normalized absorbance and emission

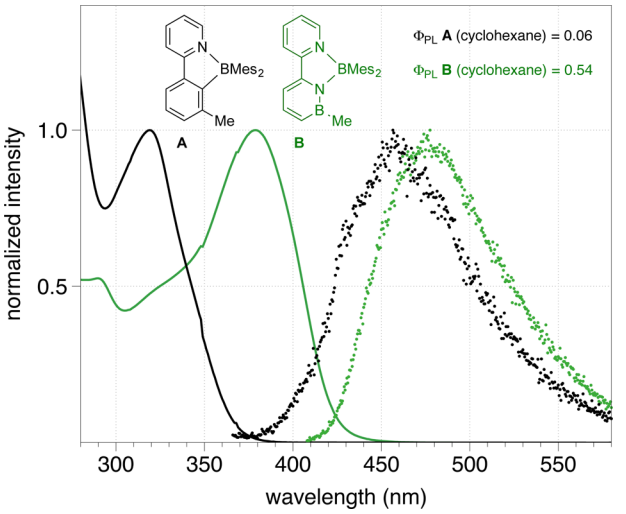


Figure 2. Normalized absorption and emission spectra of complexes **A** and **B** measured in THF at 1.3 × 10^{-4} M concentration. Quantum yields were determined in cyclohexane solutions.

spectra of **A** and **B**. A bathochromic shift of 4963 cm^{-1} is observed for the lowest-energy absorbance peak of **B** compared to that of **A**. Similarly, the emission peak for **B** is also bathochromically shifted versus that of **A**, although to a lesser extent (by 940 cm^{-1}). The photoluminescence quantum yield of **B** is 0.54, nearly an order of magnitude greater than that of its carbonaceous isostere **A** (~0.06). The Stokes shift for **A** is ~9,300 cm^{-1} (~27 kcal/mol), and for **B** it is 5,400 cm^{-1} (~15 kcal/mol). The substantial difference in the Stokes shift between **A** and **B** is due to the difference in the lowest-energy absorption peaks of **A** and **B**, which is predicted by TD-DFT calculations (see Supporting Information for details).

CONCLUSION

We have developed the first general solution for the late-stage functionalization of monocyclic 1,2-azaborines at the C(6) position via an approach involving a regioselective iridium-catalyzed C–H borylation followed by Suzuki cross coupling. We successfully applied this method to install a wide range of

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arenes and heteroarenes at the C(6) position of a 1,2-azaborine, including nitrogen heterocycles that produce novel 1,2-azaborine-based κ^2-N,N-bidentate ligands. The 6-[pyrid-2-yl]-*B*-Me-1,2-azaborine ligand has been demonstrated to form an emissive coordination complex with dimesitylboron that exhibits bathochromically shifted absorption and emission maxima and a higher photoluminescence quantum yield compared to its carbonaceous analogue. The described synthetic method significantly expands the synthetic toolbox for the 1,2-azaborine motif, and current efforts are directed toward its application in 1,2-azaborine-based coordination chemistry as well as in the development of biologically active compounds.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, spectroscopic data, additional computational details, complete refs 24 and 28, and crystallographic information. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*shihyuan.liu@bc.edu

Notes

The authors declare no competing financial interest.

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(13) Braunschweig and co-workers reported rhodium-catalyzed cycloaddition reactions of di-*tert*-butyliminoborane with ethynylferrocene or 4,4,5,5-tetramethyl-2-(phenylethynyl)-1,3,2-dioxaborolane followed by acetylene to produce highly functionalized 1,2-di-*tert*-butyl-4,6-diferrocenyl-1,2-azaborine and 1,2-di-*tert*-butyl-6-phenyl-5-pinacolato-1,2-azaborine, respectively; see: Braunschweig, H.; Geetharani, K.; Jimenez-Halla, J. O. C.; Schäfer, M. *Angew. Chem., Int. Ed.* **2014**, *53*, 3500−3504.

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