

# The State of the Art in Azaborine Chemistry: New Synthetic Methods and Applications

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**ABSTRACT:** Boron–nitrogen heteroarenes hold great promise for practical application in many areas of chemistry. Enduring interest in realizing this potential has in turn driven perennial innovation with respect to these compounds’ synthesis. This Perspective discusses in detail the most recent advances in methods pertaining to the preparation of BN-isosteres of benzene, naphthalene, and their derivatives. Additional focus is placed on the progress enabled by these syntheses toward functional utility of such BN-heterocycles in biochemistry and pharmacology, materials science, and transition-metal-based catalysis. The prospects for future research efforts in these and related fields are also assessed.

## ■ INTRODUCTION

The replacement of two carbon atoms in a benzene ring with one boron and one nitrogen atom can proceed according to three permutations to produce 1,2-dihydro-1,2-azaborine (**1**), 1,3-dihydro-1,3-azaborine (**2**), or 1,4-dihydro-1,4-azaborine (**3**) (Figure 1).<sup>1</sup> These benzenoid BN-isosteres exhibit many of the

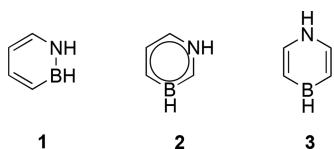


Figure 1. Three possible boron–nitrogen isosteres of benzene.

hallmark properties and reactivity patterns of aromatic hydrocarbons, though often modulated in ways reflective of the azaborines’ unique polarization.

The first wave of BN-heteroarene research began in the late 1950s with Dewar’s studies of polycyclic derivatives of **1**, e.g., BN-naphthalenes,<sup>2</sup> phenanthrenes,<sup>3</sup> and tetraphenes (Figure 2).<sup>4,5</sup> The early syntheses of these compounds often employed harsh conditions and afforded products in low overall yields. Efforts to further functionalize their base structures were confined to select substitutions at boron<sup>6</sup> and nitrogen,<sup>7</sup> and simple, substrate-controlled S<sub>E</sub>Ar reactions at various carbon

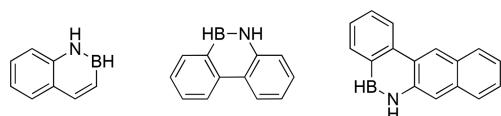


Figure 2. Examples of BN-polyaromatic compounds synthesized by Dewar.

positions.<sup>2b,8</sup> Experimental characterization of basic molecular properties was similarly limited to analysis of UV absorbance spectra and <sup>11</sup>B NMR shifts.<sup>9</sup> Dewar’s sole investigation into the biological activity of several BN-naphthalenes and phenanthrenes found only that they exhibited little antibacterial activity *in vitro*, but high toxicity in mice.<sup>7</sup>

The field lay essentially dormant from 1970 until 2000, when Ashe’s ring-closing metathesis (RCM) synthetic strategy<sup>10</sup> ushered in a revival of interest in azaborines<sup>11</sup> that has persisted to this day. While research of the current era has so far focused on 1,2-BN-isomers, efforts by the Liu and Braunschweig groups have also resulted in progress in gaining synthetic access to 1,3- and 1,4-azaborines. This critical development has enabled sophisticated interrogation of the fundamental properties of azaborines through comparative study of their electronic structures. Overall, synthetic access to azaborines has sufficiently advanced to now also support investigations into their functional properties in biomedical research and materials science.

This Perspective aims to highlight the advancements made in the past five years along these fronts so as to emphasize the incredible range of possible avenues for scientific engagement with azaborines.<sup>12</sup> Due to similarities in their manner of synthesis, derivatization, and application, a discussion of modern developments in BN-naphthalene chemistry is also included herein. Content is organized by structural motif in the following order: 1,2-azaborine, 1,2-BN-naphthalene, 1,3-azaborine, 1,4-azaborine, and 1,4-BN-naphthalene. Readers interested in higher order BN-polyaromatics are encouraged to consult recent reviews.<sup>13</sup>

## ■ 1,2-AZABORINES

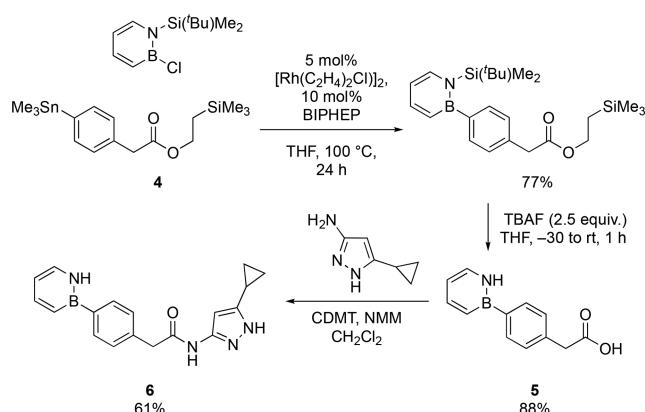
A suite of methods to elaborate the functionalization at each individual position of a 1,2-azaborine is a long-standing aspiration of chemists in the field. Recent progress toward this goal includes a series of versatile coupling reactions at boron, C(3), and C(6). Specifically, a rhodium-catalyzed coupling of aryl stannanes with *B*-chloroazaborines leads to formation of B–C<sub>aryl</sub> linked biphenyl units.<sup>14</sup> Use of stannane **4** in particular allowed for preparation of an azaborine-containing variant (**5**) of felbinac (4-biphenylacetic acid), which itself served as a precursor to a BN-isostere (**6**) of a known<sup>15</sup> CDK2 inhibitor (Scheme 1).<sup>16</sup>

Notably, **6** demonstrated greater potency against CDK2 than its carbonaceous antecedent (**6-c**) ( $IC_{50}(6) = 87$  vs  $IC_{50}(6\text{-c}) = 320$  nM). Docking models of **6** in the ATP binding site of CDK2 indicated the possible presence of hydrogen bonding

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**Scheme 1.** Synthesis of an Azaborine-Containing CDK2 Inhibitor (**6**) through Rh-Catalyzed *B*-arylation<sup>14,16,a</sup>

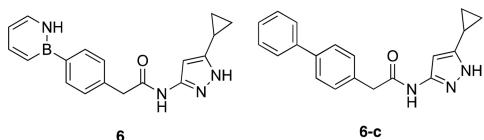


<sup>a</sup>Abbreviations: BIPHEP = 2,2'-bis(diphenylphosphino)-1,1'-biphenyl; CDMT = 2-chloro-4,6-dimethoxy-1,3,5-triazine; NMM = *N*-methylmorpholine; TBAF = tetra-*n*-butylammonium fluoride.

between the azaborine NH and the Ile10 carbonyl oxygen, which would obviously be absent in the case of **6-c**; given an approximate strength of 1 kcal mol<sup>-1</sup>,<sup>17</sup> this additional favorable interaction may account for the improved inhibitory activity of **6**.

Additional *in vitro* and *in vivo* studies of **6** provided further insight into the physicochemical and pharmacokinetic behavior of an azaborine-containing compound *vis-à-vis* its all-carbon analogue.<sup>16</sup> The ADMET profiles of **6** and **6-c** in fact proved

**Table 1.** ADMET Profiles of **6** and **6-c** As Originally Reported in Ref 16<sup>a</sup>



parameter	<b>6</b>	<b>6-c</b>
aq solubility (mM; pH = 6.8)	0.013	<0.004
FASSIF solubility (mM)	0.03	0.006
log D	3.9	4.4
PAMPA	-4.5	-3.9
RLM CL (mL min <sup>-1</sup> kg <sup>-1</sup> )	48	48
CYP3A4 IC <sub>50</sub> (mM)	>20	>20
hERG IC <sub>50</sub> (mM)	>30	>30

<sup>a</sup>Abbreviations: ADMET = absorption, distribution, metabolism, excretion, and toxicity; FASSIF = fasted and fed state simulated stomach and intestinal fluids; PAMPA = parallel artificial membrane permeability assay; RLM CL = rat liver microsome clearance; CYP3A4 IC<sub>50</sub> = cytochrome P450 3A4 inhibition; hERG IC<sub>50</sub> = human ether-*à*-go-go-related gene ion channel inhibition.

**Table 2.** Pharmacokinetic Properties of **6** and **6-c** Observed in Male Sprague–Dawley Rats after Either Intravenous or Oral Administration As Originally Reported in Ref 16<sup>a</sup>

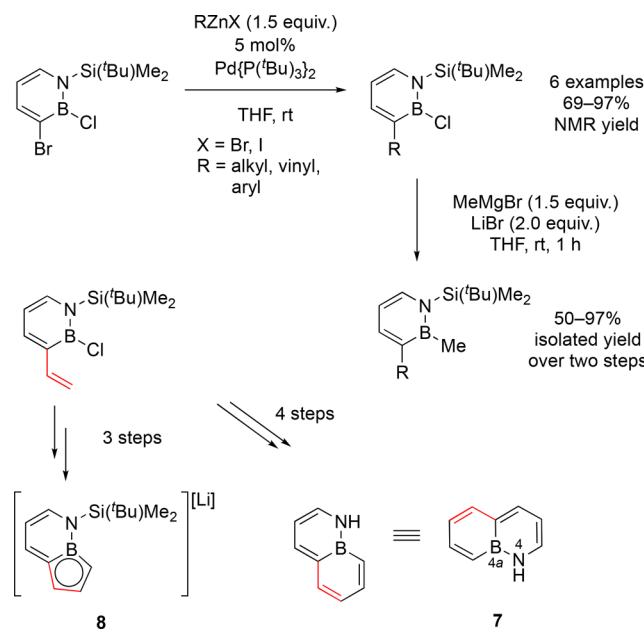
compd	dose (mg kg <sup>-1</sup> )		AUC (nMh)		<i>F</i> (%)	CL (mL min <sup>-1</sup> kg <sup>-1</sup> )	<i>t</i> <sub>1/2</sub> (h)	<i>t</i> <sub>max</sub> (h)	MRT (h)	<i>C</i> <sub>max</sub> (nM)
	IV	PO	IV	PO						
<b>6-c</b>	0.5	5.0	1261	283	22.5	39.2	10.5	0.5	0.8	692
<b>6</b>	1.0	5.0	2092	613	29.3	23.7	11.6	1.5	2.7	746

<sup>a</sup>Abbreviations: AUC = area under the curve (IV, intravenous, or PO, oral) normalized to 1 mg kg<sup>-1</sup> dose; *F* = bioavailability; CL = clearance; MRT = mean residence time.

quite similar, save for **6** demonstrating significantly higher solubility and slightly lower membrane permeability (Table 1); these differences were attributed to the greater polarity of the azaborine unit in **6** compared to that of the isosteric phenyl group in **6-c**. In *in vivo* experiments, however, **6** consistently outperformed **6-c**, exhibiting slower clearance rates (CL) and greater bioavailability (*F*) when dosed intravenously, and a higher maximum concentration (*C*<sub>max</sub>) when dosed orally (Table 2).

Diverse substitution at C(3) has been achieved through a Negishi coupling reaction that is remarkably tolerant of a labile B–Cl bond (Scheme 2).<sup>18</sup> The ability to install a vinyl group at

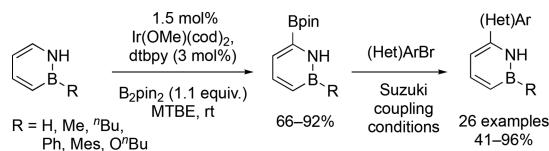
**Scheme 2.** Negishi Cross-Coupling of C(3)-Brominated Azaborine (Top) and Derivatization of a C(3)-Vinylated Azaborine into BN-Naphthalene **7** and BN-Indenyl Anion **8** (Bottom)<sup>18</sup>



C(3) notably afforded the opportunity to synthesize previously uncharacterized BN-isosteres of naphthalene (**7**) and the indenyl anion (**8**).

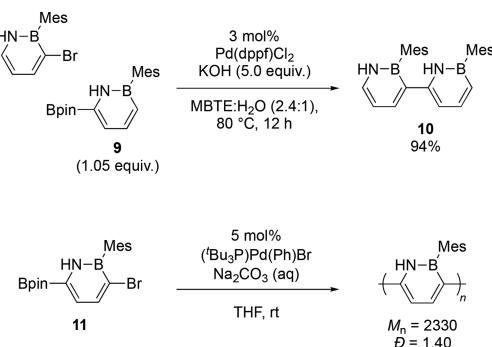
Finally, C(6) functionalization has been realized through iridium-catalyzed borylation, followed by palladium-catalyzed (hetero)arylation (Scheme 3).<sup>19</sup> Intriguingly, a C(3)-brominated azaborine can serve as a coupling partner to the borylated azaborine **9** in the latter step, leading to formation of dimer **10** (Scheme 4).<sup>20</sup> Furthermore, subjecting bis-functionalized azaborine **11** to Suzuki–Miyaura polycondensation conditions produced short polymer chains (*M*<sub>n</sub> = 2330, ~12 azaborine units per chain). Based on the crystal structure obtained for **10**,

**Scheme 3. Ir-Catalyzed C(6)-Selective Borylation, Followed by Pd-Catalyzed (Hetero)arylation<sup>19,a</sup>**



<sup>a</sup>Abbreviations: cod = 1,5-cyclooctadiene; dtbpy = 4,4'-di-*tert*-butyl-2,2'-bipyridine; MTBE = methyl *tert*-butyl ether.

**Scheme 4. Dimerization (Top) and Polymerization (Bottom) of Azaborine Monomers through Suzuki–Miyaura Coupling<sup>20,a</sup>**

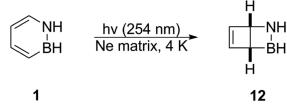


<sup>a</sup>Abbreviations: dppf = 1,1'-bis(diphenylphosphino)ferrocene; MTBE = methyl *tert*-butyl ether.

the azaborine units in these oligomers were presumed to adopt a nearly coplanar, all-*syn* conformation; this orientation appears to be enforced by favorable N—H···π interactions. As a result, the azaborine polymers exhibit an effective conjugation length ( $n_{ECL}$ ) of 14, which is reflected by a massive bathochromic shift between the  $\lambda_{abs,max}$  of the monomer **11** (277 nm) and the polymer (up to 475 nm).

In addition to devising routes to increasingly complex azaborine-containing structures, Liu and collaborators have continued to pursue studies of the fundamental chemistry of **1** itself. For example, in 2012, an initial probe of the photochemical behavior of **1** in a neon matrix by the Bettinger group revealed, based on IR measurements, selective valence isomerization to the Dewar form (**12**; Scheme 5).<sup>21</sup>

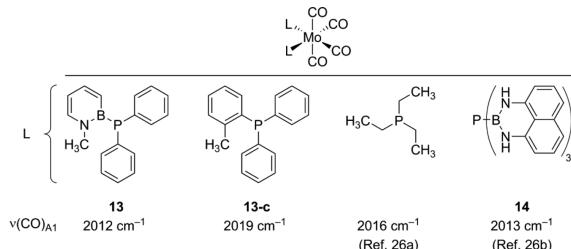
**Scheme 5. Selective Photoisomerization of Azaborine **1** Conducted in a Neon Matrix (4 K)<sup>21</sup>**



Preliminary forays into the similarly underexplored field of azaborine surface chemistry have also been conducted recently by the Sykes group. Temperature-programmed desorption studies of **1** on Au(111) and Cu(111) surfaces allowed characterization of three distinct adsorption states: a monolayer, a bilayer, and a multilayer.<sup>22</sup> Additionally, at sub-monolayer coverage, predominantly trimeric magic clustering was observed for **1** on Au(111), due in part to favorable N—H···H—B dihydrogen bonding interactions.<sup>23</sup> On Cu(111), however, more significant charge-transfer between the adsorbed molecules and the metal surface increases the strength of

repulsive Coulombic intermolecular forces, such that **1** persists as isolated monomers at low to near-monolayer coverages.

A quantitative measure of the relative electron-richness of 1,2-azaborines has been reported by Liu in the form of a Tolman-type electronic parameter for the azaborine-bearing phosphine ligand **13**.<sup>24</sup> Preparation of a bis-13 molybdenum tetracarbonyl complex enabled determination of the relevant carbonyl vibrational IR frequency;<sup>25</sup> comparisons of this value to those of several other like complexes indicate the electron-donating ability of **13** is greater than that of both its direct *o*-tolyl analogue (**13-c**) and triethylphosphine, and is in fact on par with the donating strength of the tris-borylated phosphine **14** (Figure 3).<sup>26</sup> Notably, however, the possible tunability of

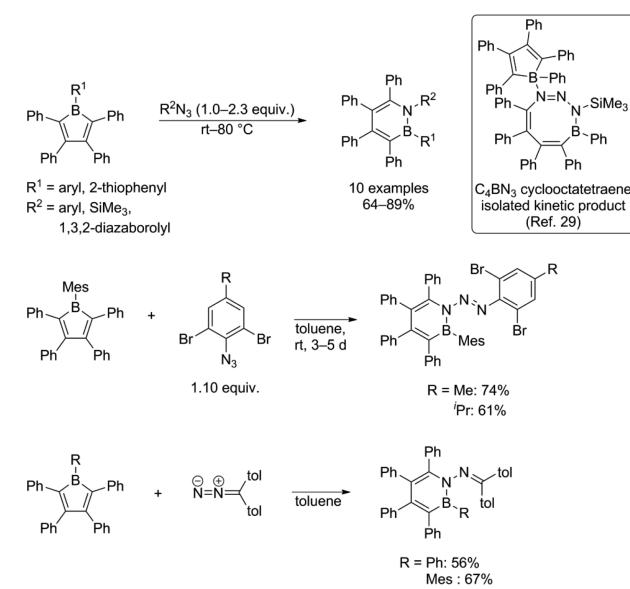


**Figure 3.** Carbonyl A<sub>1</sub> vibrational IR frequencies for various bis-phosphine-ligated molybdenum complexes.

this property by additional substitution on the azaborine group in **13** was not examined as part of the above work. Likewise, to our knowledge, the actual catalytic performance of any 1,2-azaborine-containing phosphine–metal complex also has yet to be evaluated.

Complementing the studies of unsubstituted **1** discussed above, Braunschweig has conducted investigations of the properties of various *per*-substituted 1,2-azaborines. Such compounds are synthetically accessible through ring expansions of boroles mediated by either azides or diazoalkanes (Scheme 6).<sup>27</sup> (The common tetrahomaryl C-substitution of the products is dictated by the nature of the available starting boroles.) With azides, incorporation of either the α- or γ-

**Scheme 6. Ring Expansion of Boroles into Hexasubstituted 1,2-Azaborines<sup>27</sup>**

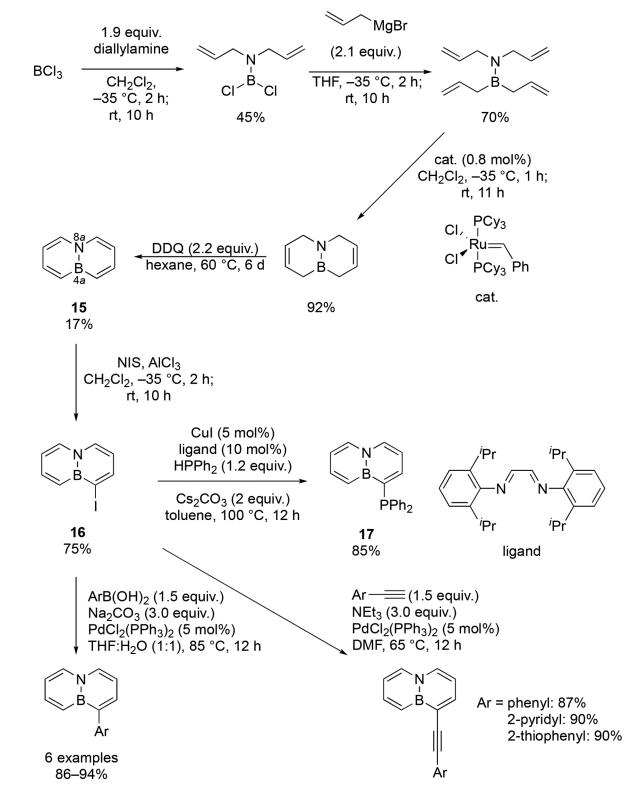


nitrogen into the product azaborine ring proceeds selectively depending on the sterics associated with both the azide and the borole: increased steric bulk generally favors  $\gamma$ -nitrogen incorporation, which notably leads to formation of 1,2-azaborine analogues of traditional diaryl azo dyes (**Scheme 6**, middle).<sup>28</sup> In contrast, Martin found that attack by the azide  $\alpha$ -nitrogen on the borole actually generates a  $C_4BN_3$  cyclooctatetraene derivative as an isolable kinetic product.<sup>29</sup> Preliminary calculations indicated, however, that formation of the hexasubstituted 1,2-azaborines ultimately obtained by Braunschweig does not proceed through this species; subsequent computations predicted they instead form through a single transition state from the initial azide–borole adduct.<sup>27d</sup>

## ■ 1,2-BN-NAPHTHALENE

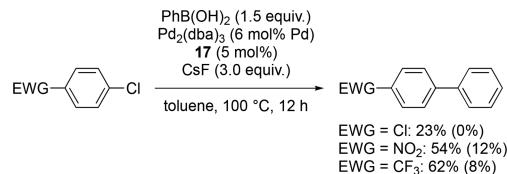
Of a possible 23 isosteric BN-naphthalene motifs, just six have been synthesized so far. Moreover, five of these belong to the subset in which the boron and nitrogen atoms are adjacent. 8a-Azonia-4a-boratanaphthalene (15) was originally prepared by Dewar back in 1968, although in such low yield as to render the route impractical.<sup>2b</sup> Fang has since demonstrated the greater effectiveness of a modern ring-closing metathesis/oxidation protocol for obtaining 15 in higher yields (**Scheme 7**).<sup>31</sup>

**Scheme 7.** Fang's Synthesis and Subsequent Derivatization of 8a-Azonia-4a-boratanaphthalene (15)<sup>31,32</sup>



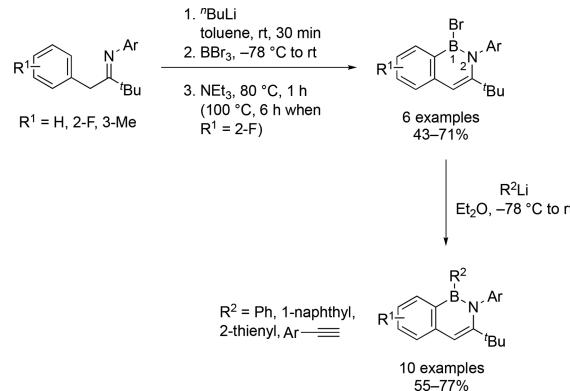
Iodination of 15 through electrophilic aromatic substitution was found to occur with complete regioselectivity at C(4); the resulting halogenated BN-naphthalene (16) proved a viable substrate for Suzuki–Miyaura and Sonogashira cross-coupling reactions. Additionally, copper-catalyzed phosphination produced 17, which served as an effective ligand for difficult Suzuki–Miyaura coupling reactions involving electron-deficient aryl chlorides (**Scheme 8**).<sup>32</sup>

**Scheme 8.** Palladium-Catalyzed Suzuki–Miyaura Coupling Reactions of Electron-Deficient Aryl Chlorides Using 17 as a Ligand<sup>32,a</sup>

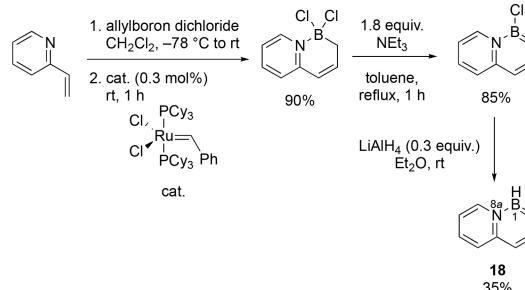


<sup>a</sup>Yields in parentheses are from reactions using 5 mol %  $PPh_3$  as a ligand.

**Scheme 9.** Cui's Synthesis of 2-Azonia-1-boratanaphthalenes Starting from Aryl Ketimines<sup>33</sup>



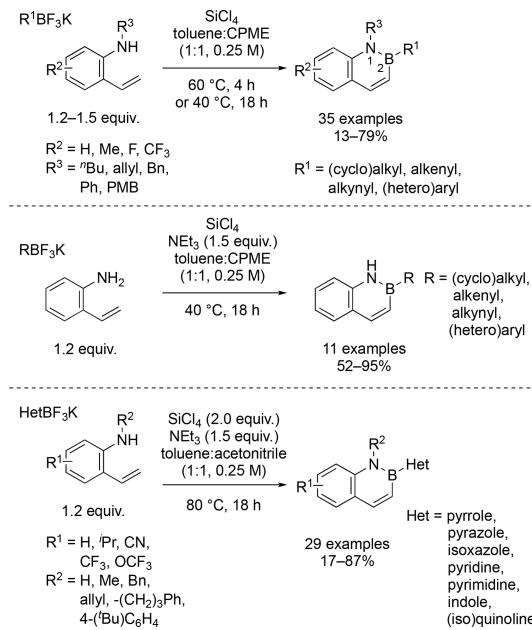
**Scheme 10.** Liu's Synthesis of 8a-Azonia-1-boratanaphthalene (18) Starting from 2-Vinylpyridine<sup>34</sup>



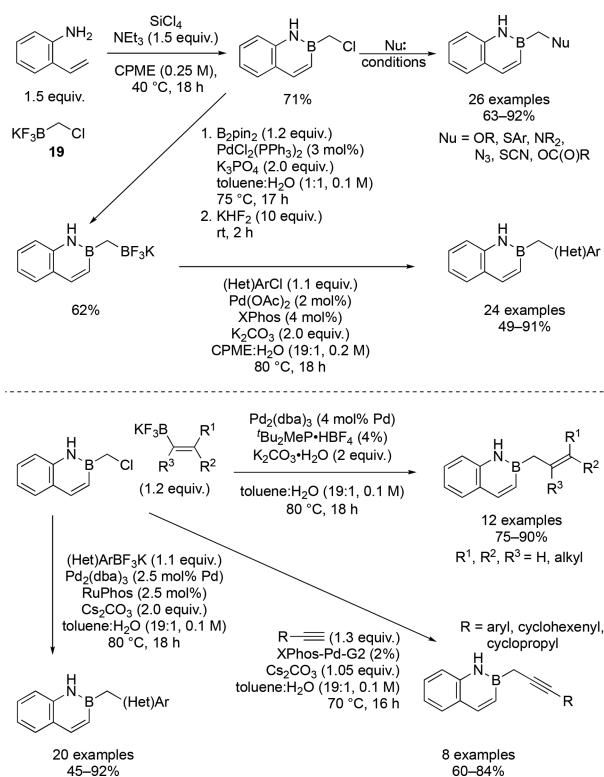
Other known BN-naphthalene frameworks include 4-azonia-4a-boratanaphthalene (7; *vide supra*), 2-azonia-1-boratanaphthalenes (**Scheme 9**),<sup>33</sup> and 8a-azonia-1-boratanaphthalene (18; **Scheme 10**).<sup>34</sup> The vast majority of recent work conducted in this field, however, has centered around 1-azonia-2-boratanaphthalenes. Since 2014, Molander has generated a considerable number of these compounds through a  $SiCl_4$ -promoted<sup>35</sup> cyclization reaction of 2-aminostyrenes with potassium trifluoroborate salts (**Scheme 11**).<sup>36,37</sup> The key to this method's versatility lies in the use of trifluoroborate salts over traditional chloroborane electrophiles,<sup>38</sup> as this confers the twin advantages of broader commercial availability and greater ease of handling and storage.

1-Azonia-2-boratanaphthalenes derived in this manner specifically from potassium (chloromethyl)trifluoroborate (19) present a pseudobenzylic halide handle well-disposed to further functionalization, either through simple substitution reactions, direct cross-couplings, or a two-step borylation/cross-coupling sequence (**Scheme 12**).<sup>39</sup>

**Scheme 11.** Molander's Synthesis of 1-Azonia-2-boratanaphthalenes from 2-Aminostyrenes and Potassium Trifluoroborate Salts<sup>36,a</sup>

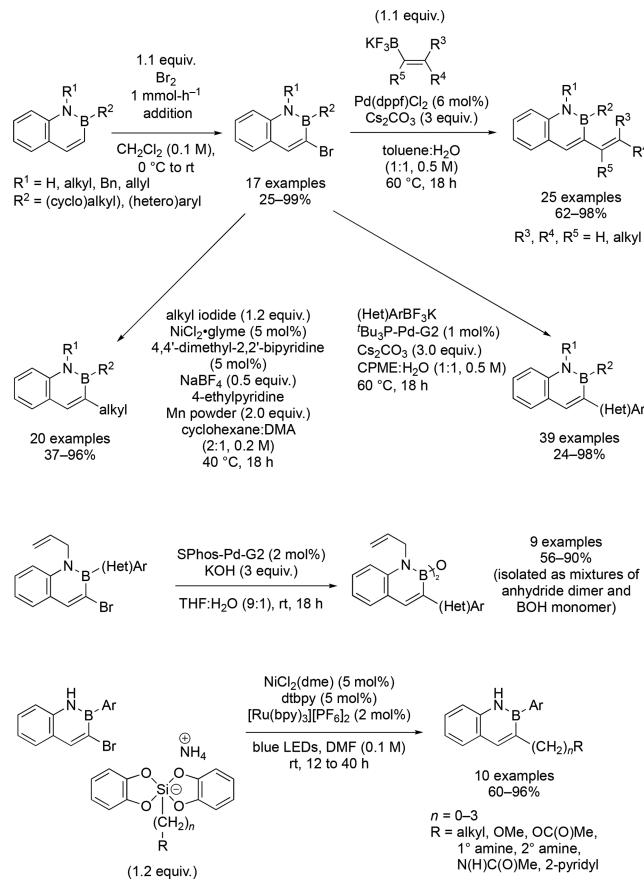


**Scheme 12.** Synthesis and Derivatization of 2-(Chloromethyl)-1-azonia-2-boratanaphthalenes<sup>39,a</sup>



Diverse substitution at C(3) was likewise achieved by initial bromination of this position, followed by a variety of cross-

**Scheme 13.** C(3)-Selective Bromination of 1-Azonia-2-boratanaphthalenes and Subsequent Functionalization<sup>41,a</sup>



coupling reactions, including an intriguing "self-arylation"<sup>40</sup> process (**Scheme 13**).<sup>41</sup>

Other groups have used Molander's cyclization procedure to prepare BN-analogues of known biologically active molecules. Rombouts, for example, synthesized two BN-isosteres of the well-known  $\beta$ -blocker propanolol and screened them against a panel of 26 receptors.<sup>42</sup> While ineffective against the majority of the panel, BN-propanolol **20** did exhibit significant inhibitory activity against the  $\beta_2$  adrenergic receptor, with near equal potency as that of propanolol itself; Rombouts also found the pharmacokinetic profile of **20** to be similarly comparable to that of the all-carbon system (**Table 3**).

Kilburn has likewise generated a series of BN-naphthalene derivatives to test as inhibitors of phosphodiesterase 10A (PDE10A), an enzyme localized in human brain tissue and a target for treatment of various neurological diseases.<sup>43</sup> Two members of the series (**21** and **22**) displayed markedly greater activity against PDE10A than their all-carbon equivalents (although quinoline-based variants proved the most potent overall) (**Table 4**). While these results, in conjunction with those reported by Zécri and Liu (*vide supra*), are indeed encouraging, much further study is likely required before BN-isosterism becomes a standard tool of drug discovery efforts.

**Table 3. Select Physicochemical and Pharmacokinetic Properties of 20 versus Propanolol, Excerpted from Ref 42**

parameter	20	propanolol
$\beta_2 \text{ pIC}_{50}^a$	7.0	7.3
$\log D$ ( $\text{pH} = 7.4$ )	1.81	1.62
$\text{CL}_{\text{int}}^b$ ( $\mu\text{L min}^{-1} \text{mg}^{-1}$ )	11.0	28.8
$f_w$ brain (rat, %)	1.9	2.8
$C_{\text{max}}$ brain (mouse, $\mu\text{M}$ ) <sup>c</sup>	62	16
$f_w$ plasma (human, %)	36.7	42.1
cytotoxicity <sup>d</sup> ( $\mu\text{M}$ )	59.0	>100

<sup>a</sup>cAMP quantification in  $\text{h}\beta 2\text{-CHO}$  cells. <sup>b</sup>In vitro clearance determined by incubation in human liver microsomes, expressed per milligram of protein. <sup>c</sup>Formulated with 20% HP $\beta$ CD(aq) for 20 and dosed at 5  $\text{mg kg}^{-1}$  sc. <sup>d</sup>Evaluated as the lowest concentration for 20% maximal effect (LTC,  $\text{EC}_{20}$ ) in a HepG2 cell line.

**Table 4. Comparison of Properties of Select BN-, Naphthyl-, and Quinoline-Based PDE10A Inhibitors, Excerpted from Ref 43<sup>a</sup>**

<b>21</b>	$\text{IC}_{50} = 64 \text{ nM}$ $\text{cLogP} = 4.18$ $\text{CL}_{\text{int}} = 2.1$	$\text{IC}_{50} = 4\% \text{ inh.}^b$ $\text{cLogP} = 4.87$ $\text{CL}_{\text{int}} = 1.5$	$\text{IC}_{50} = 12 \text{ nM}$ $\text{cLogP} = 3.58$ $\text{CL}_{\text{int}} = 1.8$
<b>22</b>	$\text{IC}_{50} = 330 \text{ nM}$ $\text{cLogP} = 3.95$ $\text{CL}_{\text{int}} > 17$	$\text{IC}_{50} = 2\% \text{ inh.}^b$ $\text{cLogP} = 4.64$ $\text{CL}_{\text{int}} > 17$	$\text{IC}_{50} = 170 \text{ nM}$ $\text{cLogP} = 2.35$ $\text{CL}_{\text{int}} > 17$

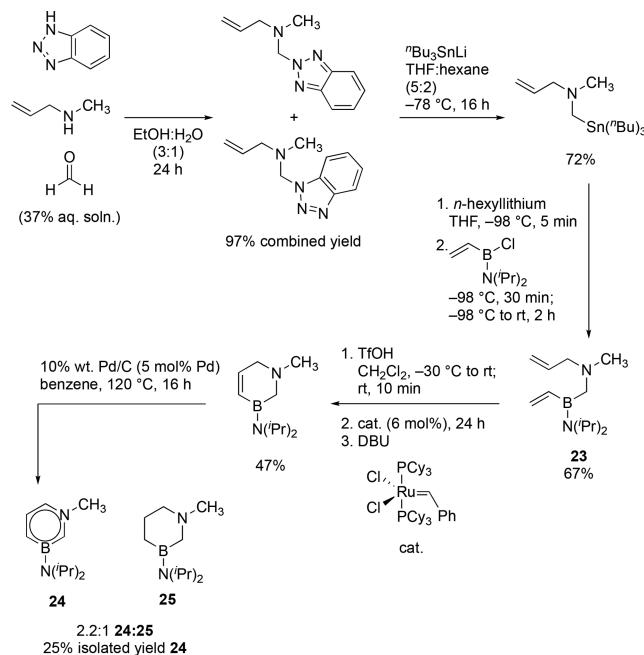
<sup>a</sup>Abbreviations:  $\text{cLogP}$  = calculated Log P;  $\text{CL}_{\text{int}}$  = microsomal intrinsic clearance ( $\text{L kg}^{-1} \text{ h}^{-1}$ ). <sup>b</sup>At 10  $\mu\text{M}$ .

## ■ 1,3-AZABORINES

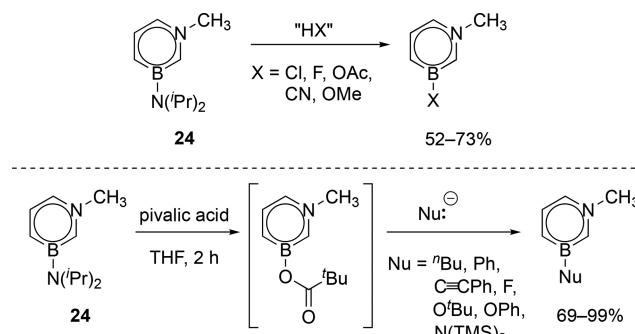
Only a single synthetic route to the 1,3-azaborine core has been reported to date (Scheme 14).<sup>44,45</sup> As in the majority of modern syntheses of 1,2-azaborines (*vide supra*), cyclization is achieved through ring-closing metathesis, specifically in this case between the *N*-allyl and *B*-vinyl groups of intermediate 23. Catalytic dehydrogenation then affords 1,3-azaborine 24, albeit with concomitant formation of significant (but fortunately, separable) amounts of the azaborinane side product 25.

The suboptimal results of its final step notwithstanding, the above route furnished 24 in sufficient quantities to enable development of several reaction protocols to subsequently diversify the boron substituent.<sup>46</sup> Direct displacement of the *N,N*-diisopropylamino group is effective only under acidic conditions (Scheme 15, top); preceding exchange with pivalic acid, however, facilitates substitution with a variety of basic, anionic nucleophiles, including organolithiates and Grignard reagents (Scheme 15, bottom). Methods to similarly modify any of the other positions of the 1,3-azaborine ring have not

**Scheme 14. Synthesis of 1,3-Azaborine 24<sup>44</sup>**



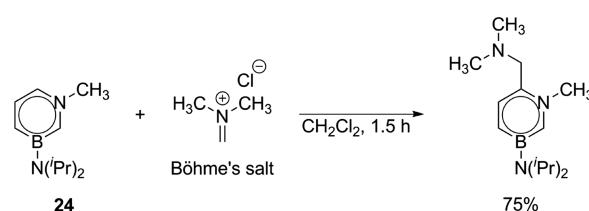
**Scheme 15. 1,3-Azaborine Boron Substituent Exchange under Acidic (Top) and Basic (Bottom) Conditions<sup>46,a</sup>**



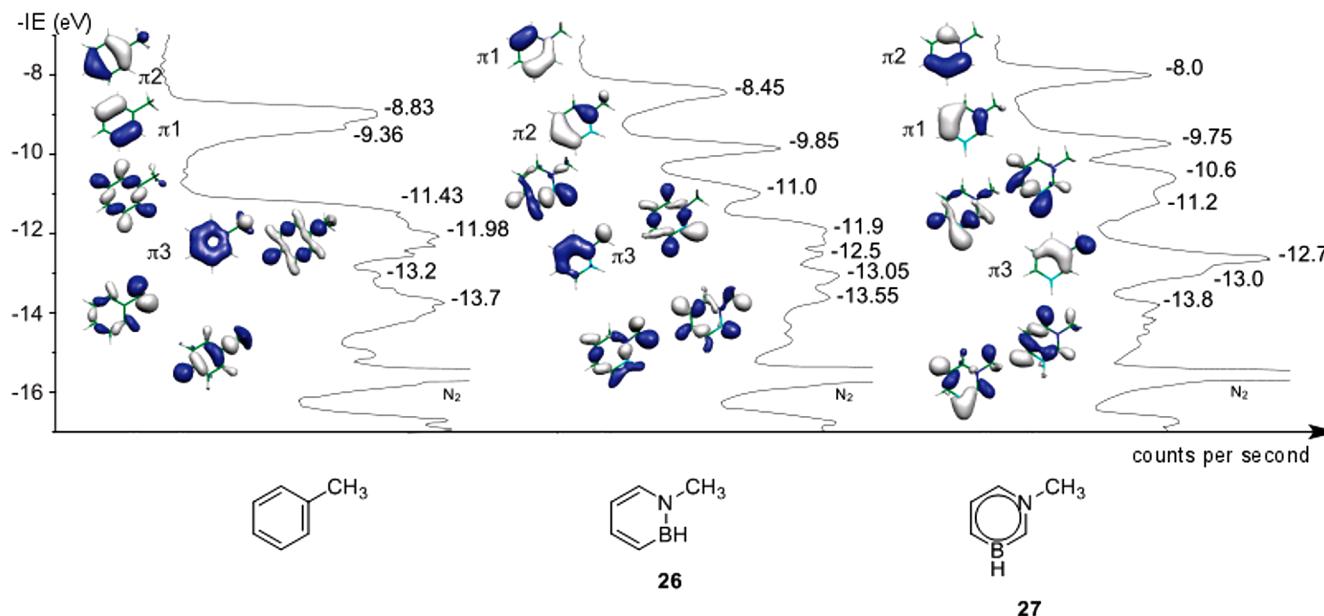
<sup>a</sup>Abbreviations: TMS = trimethylsilyl.

been reported, save for an isolated example of electrophilic aromatic substitution at C(6) using Böhme's salt (Scheme 16).<sup>44</sup>

**Scheme 16. Regioselective Electrophilic Aromatic Substitution of 24 with Böhme's Salt<sup>44</sup>**



With the establishment of reliable synthetic routes to both 1,2- and 1,3-azaborines, Chrostowska and Liu undertook a direct comparative electronic structure analysis of BN isosteres 26 and 27 *vis-à-vis* their all-carbon equivalent, toluene.<sup>47</sup> Specifically, UV-photoelectron spectroscopy (UV-PES) coupled with calibrated computational modeling granted insight into the relative energies of the occupied molecular



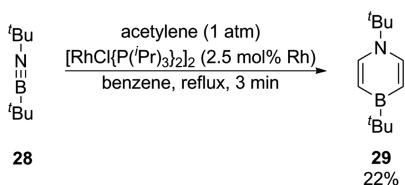
**Figure 4.** UV-PE spectra of toluene (left), **26** (middle), and **27** (right). Energy values are reported as the negative of the experimentally determined ionization energy ( $-IE$ ). The depicted molecular orbitals are the top seven occupied orbitals associated with the energy levels observed for each molecule. Spectral data and orbital calculations originally reported in ref 47.

orbitals of the three species (Figure 4). The key trend to emerge from this analysis was an increase in HOMO energy going from toluene ( $-8.84$  eV) to **26** ( $-8.45$  eV) to **27** ( $-8.0$  eV). Oxidation potentials measured in separate cyclic voltammetry experiments were notably consistent with the UV-PES results in that **27** exhibited the lowest potential ( $0.94$  V), followed by **26** ( $1.31$  V), and finally toluene ( $2.1$  V). It largely remains to be seen, however, the extent to which the difference in HOMO energies between 1,2- and 1,3-azaborines affects their relative reactivities, for, as alluded to above, the chemistry of 1,3-azaborines is markedly unexplored.

## ■ 1,4-AZABORINES

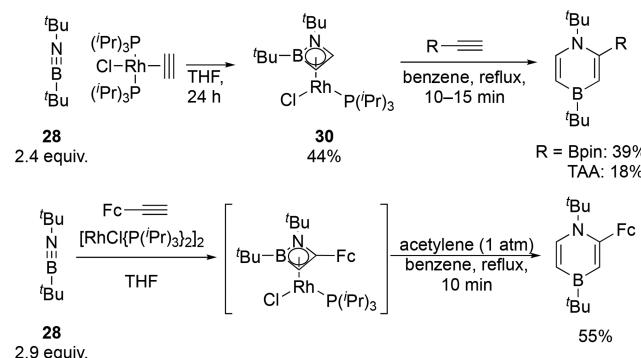
Inspired by [2+2+2] alkyne cyclotrimerization reactions to form substituted benzenes, in 2012 Braunschweig investigated the analogous combination of an iminoborane with two alkyne units as a possible method to generate 1,2-azaborines. The reaction of di-*tert*-butyliminoborane (**28**) with excess acetylene in the presence of a rhodium catalyst, however, selectively produced 1,4-azaborine **29** instead (Scheme 17).<sup>48,49</sup>

**Scheme 17. Rhodium-Catalyzed Cycloaddition of Iminoborane **28** with Acetylene<sup>48</sup>**



Identification and isolation of a rhodium  $\eta^4$ -1,2-azaborete intermediate (**30**) eventually led to an expansion of the method to a two-step protocol (necessarily stoichiometric in rhodium) for preparing 1,4-azaborines diversely substituted at C(2) (Scheme 18).<sup>50</sup> (Continued use of **28** as the requisite iminoborane component effectively precluded variation of the

**Scheme 18. Synthesis of C(2)-Substituted 1,4-Azaborines through Stoichiometric  $\eta^4$ -1,2-Azaborete Rhodium Complexes<sup>50,a</sup>**



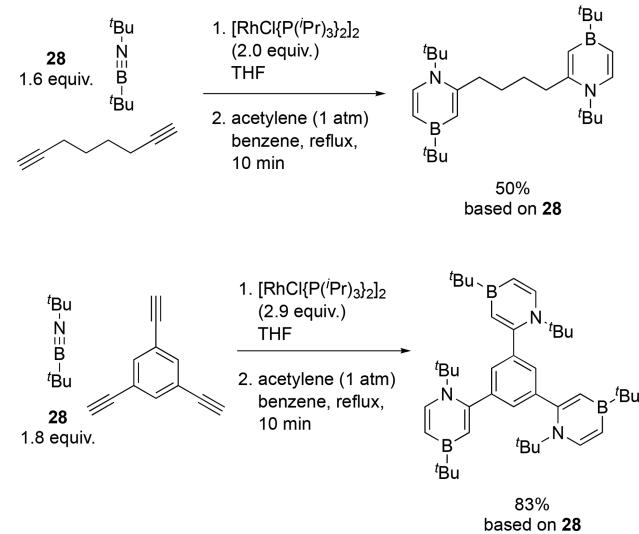
<sup>a</sup>Abbreviations: Fc = ferrocenyl; TAA = 4-(*N,N*-bis(4-methoxyphenyl)amino)phenyl.

nitrogen and boron substituents.) Interestingly, when diyne or triyne starting materials were used, products bearing correspondingly either two or three discrete 1,4-azaborine rings were formed (Scheme 19).<sup>50</sup>

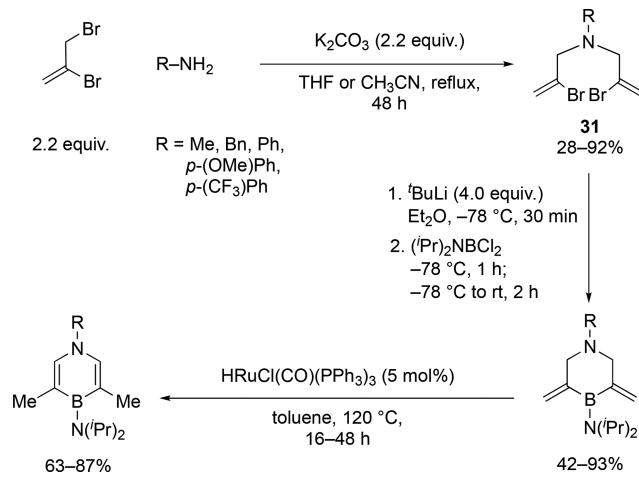
As a complement to the method described above, Liu has also recently reported a synthetic route to 1,4-azaborines that is amenable to facile variation of both the nitrogen and boron substituents.<sup>51</sup> Starting with dialkylation of a suitable primary amine, cyclization is then effected by double lithiation of intermediate **31** and subsequent trapping with (diisopropylamino)boron dichloride (Scheme 20). Ruthenium-catalyzed isomerization of the exocyclic alkenes then generates the 1,4-azaborine core.<sup>52</sup>

Similar to the case of 1,3-azaborine **24**, the *N,N*-diisopropylamino group of **32** can be directly displaced with methanol, and the resulting *B*-methoxy group can be further exchanged with a series of anionic nucleophiles (Scheme 21).<sup>51</sup> Notable among the 1,4-azaborines prepared in this manner are

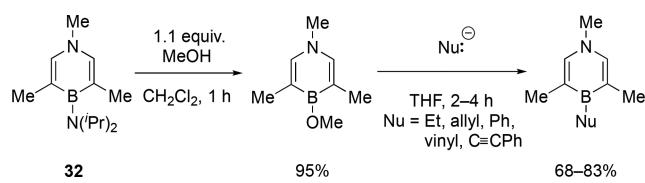
**Scheme 19. Synthesis of Bis- and Tris-1,4-azaborines Using Diyne (Top) and Triyne (Bottom) Starting Materials<sup>50</sup>**



**Scheme 20. Synthesis of 3,5-Dimethyl-1,4-azaborines<sup>51</sup>**

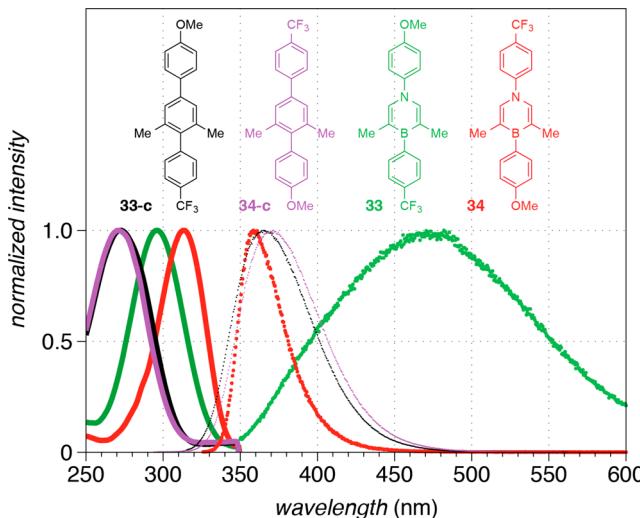


**Scheme 21. Diversification of the B(4) Substituent Starting from 32<sup>51</sup>**



33 and 34, in which the azaborine ring is disubstituted with an electron-donating aryl group on nitrogen and an electron-withdrawing group on boron and *vice versa*, respectively. The absorption and emission spectra of these two compounds provides a demonstrative example of the power of C=C/ $\text{B}=\text{N}^+$  isosterism to amplify chemical diversity within a given structural framework: as shown in Figure 5, the  $\lambda_{\text{abs}}$ ,  $\lambda_{\text{em}}$ , and Stokes shifts of 33 and 34 are distinctly different, whereas those of the two all-carbon analogues 33-c and 34-c are nearly identical.

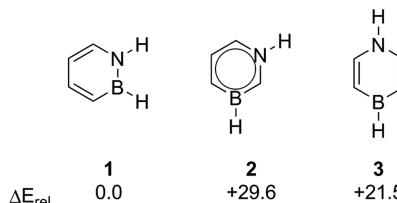
Despite the emergence of these new synthetic routes, a lightly substituted 1,4-azaborine *à la* 26 or 27 continues to elude.<sup>53</sup> As a result, comparisons of the fundamental properties



**Figure 5.** Normalized absorption (solid lines) and emission (dotted traces) spectra for 33 (green) and 34 (red) and their carbonaceous analogues 33-c (black) and 34-c (purple) in THF at  $1 \times 10^{-5}$  M. Spectral data originally reported in ref 51.

of the three azaborine isomers has largely remained confined to high-level computational studies. Significantly, these have all affirmed early predictions by Clark that 1 is considerably more thermodynamically stable than either 2 or 3 (Scheme 22).<sup>54</sup>

**Scheme 22. Calculated Relative Thermodynamic Stabilities of 1, 2, and 3<sup>a</sup>**



<sup>a</sup>ΔE<sub>rel</sub> values (kcal mol<sup>-1</sup>) are from ref 54b.

The trend with respect to aromatic character, however, is somewhat less clear-cut: while an apparent consensus supports 2 as the most aromatic isomer, the current literature features discrepant evaluations of the relative aromatics of 1 and 3 (Table 5). On the basis of different indicators of  $\pi$  electron cyclic delocalization, Pati,<sup>54c</sup> Baranac-Stojanović,<sup>54d</sup> and Siga-

**Table 5. Various Calculated Measures of the Aromaticity of 1, 2, and 3<sup>a</sup>**

parameter	1	2	3
HOMA <sup>b</sup>	0.71	0.74	0.51
PDI <sup>b</sup>	0.06	0.07	0.04
FLU <sup>b</sup>	0.015	0.014	0.019
ECRE <sup>c</sup> (kcal mol <sup>-1</sup> )	55.69 <sup>f</sup>	76.66 <sup>f</sup>	33.51
RSE <sup>d</sup> (kcal mol <sup>-1</sup> )	19.8	31.1	22.4
NICS(0) <sub>xxz</sub> <sup>e</sup>	-26.3	-31.1	-25.8

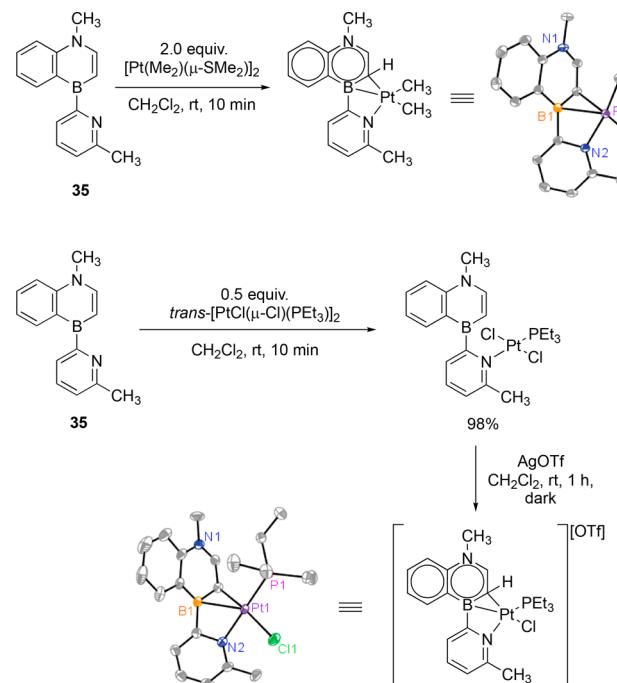
<sup>a</sup>Abbreviations: ECRE = extra cyclic resonance energy; FLU = fluctuation index; HOMA = harmonic oscillator model of aromaticity; NICS = nuclear independent chemical shift; PDI = *para*-delocalization index; RSE = resonance stabilization energy. <sup>b</sup>From ref 54c. <sup>c</sup>From ref 54d. <sup>d</sup>From ref 51. <sup>e</sup>From ref 54e. <sup>f</sup>Weighted average based on two possible resonance structures.

las<sup>54e</sup> have all designated **1** as more aromatic than **3**. Liu and Dixon, however, have calculated from hypohomodesmotic reactions the resonance stabilization energy (RSE) of **3** to be slightly larger than that of **1** ( $\Delta$ RSE = 2.6 kcal mol<sup>-1</sup>).<sup>51</sup>

## ■ 1,4-BN-NAPHTHALENES

In 2014, Liu prepared 1,4-BN-naphthalene **35** and found it to coordinate to neutral and cationic platinum(II) metal centers in a unique  $\kappa^2$ -*N*, $\eta^2$ -BC mode (Scheme 23).<sup>55,56</sup> Additionally, use

**Scheme 23. Complexation of 1,4-BN-Naphthalene **35** with Neutral and Cationic Platinum(II) Sources<sup>a</sup>**



<sup>a</sup>Crystal structure information originally provided in ref 55.

of a triarylphosphine variant of **35** as a ligand for Pd-catalyzed 1,3-enyne hydroboration led to a relatively rare observation of selectivity for formation of the *trans* addition product (12:82:6 cis:*trans*:allene).

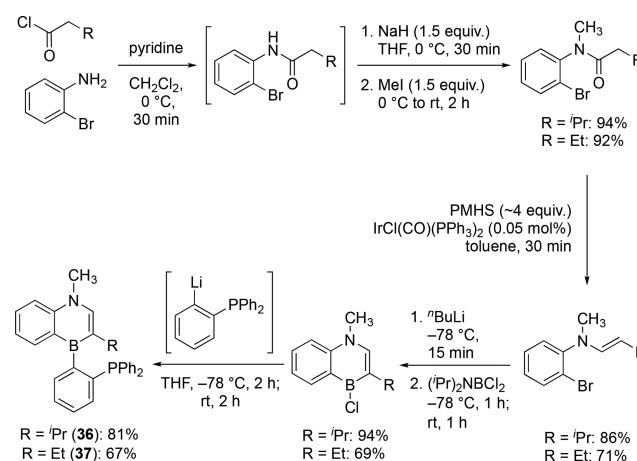
In order to expand on this preliminary result, a new synthetic strategy to access the requisite 1,4-BN-naphthalene ligands was devised (Scheme 24); this sequence notably supersedes the original 2014 route both in terms of scalability and support of substitution at C(3).<sup>57</sup> Indeed, this latter feature proved critical to maximizing the *trans* selectivity of 1,3-enyne hydroboration, with C(3)-*i*Pr ligand **36** affording the highest selectivity for terminal enynes, and C(3)-Et ligand **37** yielding similar results for internal enynes (Scheme 25).

## ■ PERSPECTIVE

BN/CC isosterism has tremendous potential to expand the chemical space of organic compounds. When applied to the ubiquitously useful arene motif in particular, BN/CC isosterism will undoubtedly help advance contemporary research in areas such as biomedical research, materials science, and catalysis.

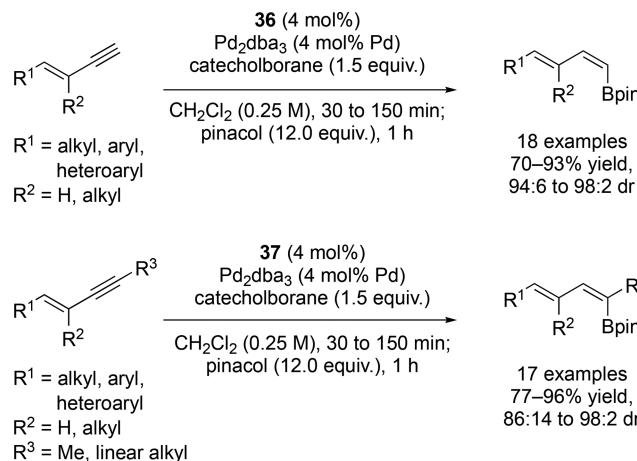
The field of azaborine chemistry has already undergone considerable growth in the past five years. Access to several key structural motifs, namely 1,3- and 1,4-azaborines, has been achieved, and a key building block for 1,2-azaborines is now

**Scheme 24. Synthesis of  $\kappa^2$ -*P*, $\eta^2$ -BC Ligands **36** and **37**<sup>57,a</sup>**



<sup>a</sup>Abbreviations: PMHS = polymethylhydrosiloxane.

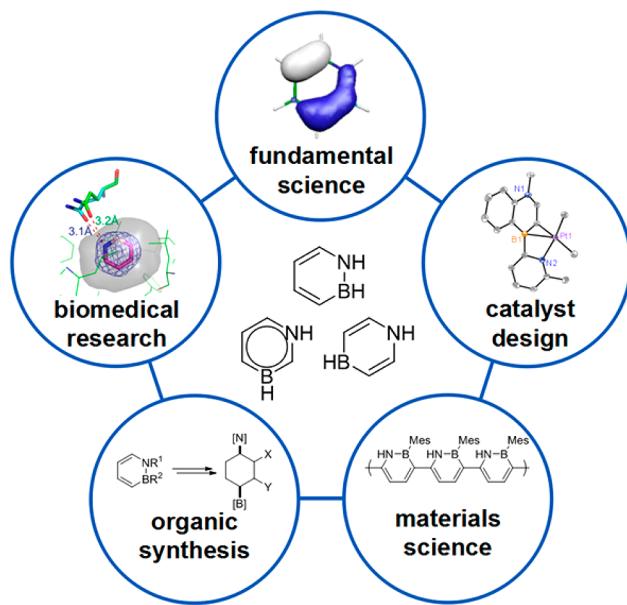
**Scheme 25. Palladium-Catalyzed *trans*-Hydroboration of Terminal (Top) and Internal (Bottom) 1,3-Enynes Using **36** and **37**, Respectively, as Ligand<sup>b</sup>**



commercially available.<sup>58</sup> New late-stage functionalization methods, particularly for 1,2-azaborines and 1,2-BN-naphthalenes, have also expanded the scope of these compounds' potential utility. Concomitant with the new expanded *chemical space* made available by BN/CC isosterism, new *functional space* is being created. The introduction of boron–nitrogen units to the vast space of polyaromatic hydrocarbons (PAHs) is now being intensively explored to modulate the properties of these materials. The azaborine unit is also being investigated in medicinal chemistry as a new pharmacophore with unique pharmacokinetic profiles. Azaborine-containing ligands have also recently been shown to support distinct modes of reactivity and selectivity in transition-metal-based catalysis.

Thus, the outlook for future studies of azaborines is indeed an exciting one. While initial applications in biomedical research, materials science, and catalysis appear promising, extensive additional groundwork is still required before the field as a whole can be considered to have reached a state of maturity. In addition to continued progress in the aforementioned areas, a need also persists for development of new synthetic methodologies to access BN-containing structures.

One emerging application of azaborine chemistry that perhaps has been overlooked up to this point is the use of



**Figure 6.** Frontiers for future discoveries in azaborine chemistry.

this BN-heterocycle motif as a carbon–boron–nitrogen synthon in organic synthesis. The photoisomerization<sup>21</sup> and Diels–Alder cycloaddition<sup>59</sup> of 1,2-azaborines to form heteroatom-substituted cyclobutane and cyclohexane derivatives, respectively, represent promising initial leads toward this development. Translating the unique electronic structure features of azaborines to organic synthesis applications will result in further expansion of the field beyond its already far-ranging frontiers (Figure 6).

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### Notes

The authors declare no competing financial interest.

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