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Photoredox Catalysis Enables Access to *N*-Functionalized 2,1-Borazonaphthalenes

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Abstract

The synthesis and utilization of a class of 2,1-borazonaphthyltrifluoroborate reagents that provide a general solution to the challenge of *N*-functionalization of the 2,1-borazonaphthalene core is described. By adorning the nitrogen of this core with a trifluoroboratomethyl unit, a suite of odd-electron processes can be executed, installing motifs that would otherwise be inaccessible using a two-electron approach. In addition, this process enables rapid annulation, furnishing a heretofore unknown polycyclic B–N species.

Graphical Abstract

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ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. Experimental procedures and characterization data for all compounds (PDF).

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Entry into new chemical space is important for identifying novel pharmacophores and granting “freedom to operate” from patent infringement. The identification of new bioisosteres with good drug-like properties (good bioavailability, appropriate lipophilicity, chemical stability, etc.) is therefore of high interest. Because of the ability of B–N bonds to mimic C=C bonds, B–N heterocycles have emerged as attractive isosteres. These “azaborines” bear striking structural resemblances to their carbon variants with a fundamentally different set of rules that govern their reactivity. Indeed, this is exemplified *in vivo* by an azaborine antibacterial agent. The activity of this agent stems from its fit in the binding pocket of the target enzyme as well as an important dative boron-tyrosine interaction. Additionally, Liu and co-workers have shown that the azaborine variant of a CDK2 inhibitor had both better *in vitro* aqueous solubility and *in vivo* oral availability.

Similarly, 2,1-borazaronaphthalenes have shown promise as medicinally relevant agents that serve as bioisosteric replacements of naphthalene with isoelectronic correlations to indole. Recently, we developed a rapid synthetic route to prepare these polycyclic species in addition to synthetic strategies for their elaboration (Figure 1). Such strategies include halogenation (and subsequent cross-coupling), nucleophilic substitution, and, most recently, C–X borylation and regioselective C–H functionalization. Although routes to functionalize several positions now exist, elaboration of the azaborinyl nitrogen is typically programmed before annulation. That is, *N*-substituted azaborines are typically prepared from *N*-monosubstituted 2-aminostyrenes and organotrifluoroborates *via* defluorinative annulation. Post-annulative modifications at nitrogen *via* N–H activation remain challenging despite the traditional ease of N–H functionalization. As part of a program to elaborate this azaborinyl core, a simple strategy for *N*-alkylation was pursued. Notably, this transformation is wholly unique to the 2,1-borazaronaphthalenes and would not be possible in the analogous naphthalene isostere.

Based on prior studies, KHMDs efficiently deprotonates the 2,1-borazaronaphthyl nitrogen. Thus, we initially sought to assay the nucleophilicity of the corresponding anion. Reaction of **1** with KHMDs followed by treatment with an electrophile did furnish some *N*-alkylated azaborines (Scheme 1). However, these reactions were sluggish, often requiring a second addition of base and alkyl halide. In addition, this approach was restricted to 1° alkyl electrophiles. Attempts to alter reactivity by examining bases or other anionic HMDS variants (LiHMDS, NaHMDS, etc.) were met with similar or worse results. In several cases, the desired alkylated product was not observed at all (Scheme 1). Similarly, attempts to execute Michael-type addition failed. The poor reactivity of this anion may relate to the inherent redistribution of electron density from nitrogen onto boron.

To overcome these limitations, the possibility of appending the azaborinyl nitrogen with a functional handle that would allow further C–C bond construction was considered. Specifically, the envisioned handle would generate a carbon-centered radical α to nitrogen by the action of a visible light-activated catalyst. Visible light photoredox catalysis provides a reliable, controlled means to access odd-electron reactivity under mild conditions. These radicals can be harnessed for bond-forming processes simply not available in two-electron chemistry, resulting in a shortened path to molecular complexity. Recently, our group and others have developed powerful methods for generating and engaging C-centered radicals

via Ni/photoredox dual catalysis. Ultimately, this allows C_{sp^3} – C_{sp^2} bonds to be forged under remarkably mild conditions. This has even been extended to C_{sp^2} –Y bond construction (Y = N, O, S, and P). Given that organotrifluoroborates are excellent radical feedstocks, we attempted to prepare **3a** by way of its Bpin precursor. Treatment of the corresponding azaborinyl anion with iodomethylpinacolboronate did furnish the desired Bpin **2i** (not shown). Subsequent treatment with KHF_2 resulted in facile conversion to the trifluoroborate salt. The two steps could be performed as a telescoped process, giving **3a** in 70% overall yield (Table 1). This two-step sequence was used to assemble a library of azaborinyl trifluoroborates (Scheme 2). In general, changes in the substitution pattern of the azaborinyl core had little impact on the reaction outcome. Alkyl, alkenyl, and aryl substituents on boron were all tolerated, as were modifications to the adjoining all-carbon ring. In select cases, diminished yields were obtained, presumably because of the poor nitrogen nucleophilicity (**3j**–**3k**). Although higher order azaborinyltrifluoroborates with branching at the α -amino carbon would be attractive, alkylation of more substituted α -halo- α -boryl electrophiles was not examined because of the aforementioned failure of secondary electrophiles, combined with the lack of commercial availability of the requisite boryl electrophiles.

Cyclic voltammetry of **3a** revealed it is well-within the range of standard photocatalysts used in the dual catalytic process ($E_{1/2}^{ox} = +1.07$ V vs SCE, see Supporting Information for details), indicating oxidative fragmentation should indeed be possible. Thus, attempts to perform C_{sp^3} – C_{sp^2} coupling with this functional handle were initiated. Typical conditions for Ni/photoredox cross-coupling resulted in good baseline reactivity when attempting to cross-couple 4-bromobenzonitrile with **3a** (Table 1, entry 1). Control experiments confirmed this was indeed proceeding through the expected dual catalytic pathway (entries 2–4). Because conversion was incomplete under these initial conditions, a brief optimization of the process was next pursued. The components of the catalytic system (nickel catalysts, photocatalysts, bases, and solvents) were systematically modified. In general, other nickel complexes were inferior to $[Ni(dtbbpy)(H_2O)_4]Cl_2$ (entries 5–6). Whereas $[Ru(bpy)_3](PF_6)_2$ led to poor conversion (entry 7), the inexpensive organic photocatalyst 4CzIPN could be used with similar results (entry 8). 2,6-Lutidine afforded the best results among the bases examined. Alternative solvents did not improve the yield of the reaction (entries 9–10). Although not giving the highest P/IS ratio observed, a combination of 4CzIPN, 2,6-lutidine, and $[Ni(dtbbpy)(H_2O)_4]Cl_2$ in dioxane was advanced as suitable conditions for practical reasons (4CzIPN can be prepared for ~\$6 per gram). These conditions were scaled up, giving an 80% yield of azaborine **4a**.

With the conditions established for the cross-coupling process, the scope of the transformation was next explored. Using **3a** as a representative azaborinyltrifluoroborate, application of the process was examined in the context of various aryl halide coupling partners (Scheme 3). In general, the mild reaction conditions accommodated various aryl- and heteroaryl bromides. Indeed, a range of electronically disparate aryl bromides were coupled with ease. Nitrogen- (**4d**–**4f**), oxygen- (**4c**, **4g**), and sulfur-based (**4h**, **4i**) heterocycles were amenable to cross-coupling in moderate to good yield. Additionally, two azaborines can be linked *via* a methylene linker using this approach (**4j**), illustrating how

one azaborinyl core can serve as either a nucleophilic or electrophilic partner. A representative alkenyl electrophile was amenable to these conditions (**4k**). Finally, acylation of **3a** was achieved by cross-coupling with an *in situ* generated mixed-anhydride to give **4l**.

The accessible chemical diversity was further evaluated using various azaborinyltrifluoroborates with representative aryl- and heteroaryl bromides (Scheme 4). The reaction was compatible with many azaborinyltrifluoroborates, giving the cross-coupled products in moderate to good yield. The reaction appeared to be insensitive to changes in the boryl substituent and the adjacent ring. Because of their excellent photophysical properties, there is growing interest in the properties of BN-polycyclic aromatic hydrocarbons. However, the synthetic strategies are still quite limited because of the tailored, lengthy routes needed to effect annulation. As an example, Vaquero recently reported a synthetic route for synthesizing 4a-aza-10a-boraphenanthrenes, relying on pre-functionalization of the azaborinyl nitrogen prior to construction of the azaborine core. Although an innovative achievement and the first route to such a core, the scope is quite narrow, in part hampered by the synthetic limitations of the route. Thus, in an effort to access new azaborinyl cores from these trifluoroborates, we attempted intramolecular coupling *via* Ni/photoredox chemistry of **3f**. This strategy gave what is, to the best of our knowledge, the first azaborinyl benzo[*a*]fluorene analogue (**4v**).

Radical alkylation strategies have been identified as viable means for introducing complex, functionally dense fragments and are the type of efficient late-stage functionalization reactions that are attractive to medicinal chemists. The reagents described here provide azaborine “radicals in a bottle”, and thus opportunities for further non-nickel-mediated diversification modes exist. Thus, a range of reactions that either provided structures that would be otherwise inaccessible *via* an anionic route and/or that complemented the described Ni/photoredox process were pursued (Scheme 5). Photoredox-mediated radical cyanation provided a compound that was simply not accessible *via* anionic displacement (see Scheme 3). Minisci-type alkylation was used to prepare **6a** in fair yield. This complements the Ni/photoredox approach in that the azaborinyl unit can be installed at a wholly different location than in **4f** while retaining the bromine functional handle. Using a vinyl sulfone, an alkenyl moiety could be installed *via* a radical addition–elimination process. In contrast to the poor reactivity of the azaborinyl anion toward Michael addition, radical trapping of the azaborinyl radical with acrylonitrile was reasonably fruitful. The success of this latter reaction prompted us to explore radical defluorinative alkylation via a radical/polar crossover pathway. This proceeded smoothly and installed another type of bioisotere (*gem*-difluoroalkenes are carbonyl mimics) onto the existing azaborinyl scaffold.

In summary, an odd-electron strategy to access a diverse set of *N*-functionalized 2,1-borazaronaphthalenes is reported. Pre-functionalization of the azaborinyl nitrogen with a trifluoroboratomethyl unit allows facile generation of an α -amino radical under photoredox conditions. This radical enables new, previously unattainable disconnections on this core to be established and thus allows the rapid diversification of these naphthalene isosteres under mild conditions. Moreover, it has enabled heretofore unknown azaborine cores to be accessed with ease. Ultimately, this approach is ideal for late-stage integration of B-N heterocycles into complex molecules, thus facilitating entry into new chemical space.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Outline of functionalization processes of the 2,1-borazonaphthalene core and the strategy pursued here.

Scheme 1. Anionic Approach to N-Functionalization of 2,1-Borazonaphthalenes ^a

^aReagents and conditions: **1** (0.5 mmol, 1.0 equiv), alkyl bromide (2.0 equiv), KHMDS (2.0 equiv), THF (0.5 m), rt, 24 h.

Scheme 2. Synthesis of an Azaborinyltrifluoroborate Library^a

^aReagents and conditions: 1) Azaborine (1 mmol, 1.0 equiv), ICH_2BPin (2.0 equiv), KHMDS (2.0 equiv), THF (0.5 M), -78°C to rt, 30 h; 2) KHF_2 (6.0 equiv, 4.5 M), K_2CO_3 (1.5 equiv), MeCN (0.3 M), 0°C to rt, 12 h. ^bThe intermediate was directly converted into trifluoroborate **3** without isolation and characterization. ^c5 mmol scale.

Scheme 3. Scope of Ni/Photoredox Cross-Coupling with **3a**^a

^aUnless otherwise noted, reactions were performed using **3a** (0.5 mmol) at rt for 36 h; all yields are isolated yields after purification. ^cIn 0.2 mmol scale, see Supporting Information for experimental details.

Scheme 4. Azaborinyl Trifluoroborates as Nucleophiles in Ni/Photoredox Cross-Coupling^a

^aUnless otherwise noted reactions were performed using *N*-trifluoroboratomethyl azaborines (0.5 mmol) at room temperature for 36 h; ^bAll yields are isolated yields after purification.

Scheme 5. Diversification of **3a** via Radical Alkylation^a

^aFor full synthetic details, see the Supporting Information; all yields are isolated yields after purification.

Table 1.

Optimization of Cross-Coupling of 3a with 4-Bromobenzonitrile^a

entry	Dev from std cond	P/I/S Ratio
1	none	3.21
2	no light (dark)	0.00
3	no Ir photocatalyst	0.00
4	No Ni catalyst	0.00
5	[Ni(diOMebpy)(H ₂ O) ₄]Cl ₂	0.74
6	Ni(NO ₃) ₂ • 6H ₂ O, Ligand L1	1.78
7	Ru(bpy) ₃ (PF ₆) ₂	0.18
8	4CzIPN ^b	2.80
9	MeCN	1.03
10	CPME	0.00
11	2,6-lutidine	4.87
12	K ₃ PO ₄	3.57
13	2,6-lutidine, 36 hours ^c	5.46
14	4CzIPN, 2,6-lutidine, 36 hours	4.98

4CzIPN
E_{1/2} (*P/P[•]): +1.35 V
E_{1/2} (P/P[•]): -1.21 V

[Ni(dtbbpy)(H₂O)₄]Cl₂

L1:

^aProduct ratios determined by HPLC using 4,4'-di-*tert*-butylbiphenyl as internal standard. ^b4CzIPN = 2,4,5,6-tetra-9H-carbazol-9-yl-1,3-benzenedicarbonitrile. ^cIsolated yield is 87% on 0.2 mmol scale.