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Oxidative Generation of Boron-Centered Radicals in Carboranes

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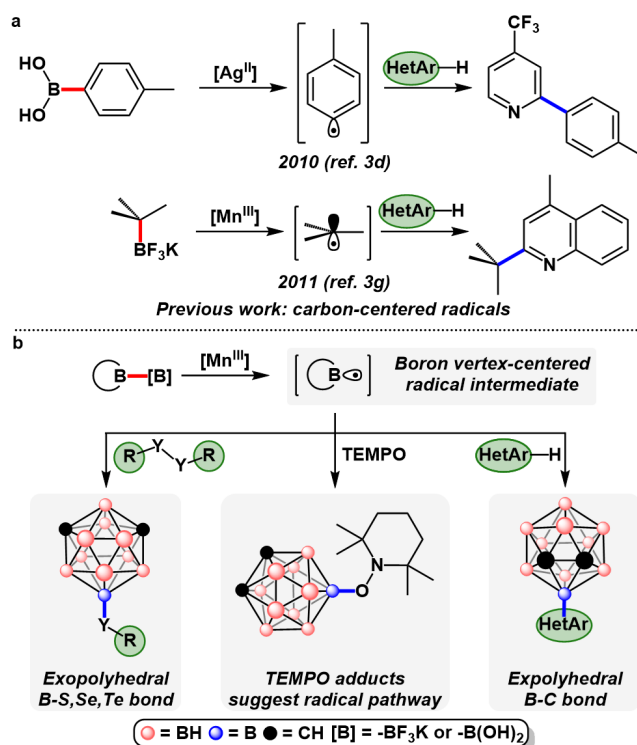
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Supporting Information Placeholder

ABSTRACT: We report the first indirect observation and use of boron vertex-centered carboranyl radicals generated by the oxidation of modified carboranyl precursors. These radical intermediates are formed by the direct oxidation of a B–B bond between a boron cluster cage and an exopolyhedral boron-based substituent (e.g., $-\text{BF}_3\text{K}$, $-\text{B}(\text{OH})_2$). The *in situ* generated radical species are shown to be competent substrates in reactions with oxygen-based radicals, dichalcogenides, and N-heterocycles, yielding the corresponding substituted carboranes containing B–O, B–S, B–Se, B–Te, and B–C bonds. Remarkably, this chemistry tolerates various electronic environments, providing access to facile substitution chemistry at both electron-rich and electron-poor B–H vertices in carboranes.

Carbon centered radicals are ubiquitous in chemistry and have garnered significant interest due to their utility in building complex organic molecules.^{1,2} Particularly, methods utilizing carbon-centered radical intermediates have made use of stable radical precursors containing cleavable C–X bonds (X: $-\text{COOH}$ ^{3a}, $(-\text{SO}_2)_2\text{Zn}$ ^{3b,c}, $-\text{B}(\text{OH})_2$ ^{3d-f}, $-\text{BF}_3\text{K}$ ^{3f-i}) that undergo homolytic C–X bond scission in the presence of oxidants. These radical intermediates have subsequently been used to substitute various substrates including N-heterocycles^{3a-d,f,g,i}, extended aromatic systems^{3e}, and oxygen-based radical traps (Figure 1a).^{3h}

Icosahedral carboranes ($\text{C}_2\text{B}_{10}\text{H}_{12}$)⁴ are molecular clusters that exist as three distinct isomers (*ortho*-, *meta*-, *para*-) that feature a steric profile similar to that of adamantane.⁵ Due to inherent asymmetry of the electronic structure, various vertices in these species feature orthogonal chemical reactivity. For example, C–H vertices (pKa: 22–27)^{4a} exhibit nucleophilic reactivity after deprotonation with base. Conversely, B–H vertices in these molecules have been classically amenable to electrophilic substitution on the electron-rich boron vertices furthest away from the carbon sites.⁴ Most recently, new methods have enabled metal-catalyzed cross-coupling^{6a}, metal-catalyzed B–H activation^{6b,c}, and nucleophilic substitution^{6d} strategies at most B–H vertices in carboranes. While the majority of the above methods rely on two-electron transformations, one-electron chemistry has remained underexplored.⁷



This work: boron vertex-centered radicals of *ortho*- and *meta*-
Figure 1. (a) Literature examples of carbon-centered radicals generated by the oxidation of C–B bonds. (b) This work, oxidation of carboranes containing exopolyhedral B–[B] bonds.

Recently, an example showcasing the possibility of efficiently generating boron vertex-centered radicals in carboranes was accomplished by Xie and coworkers.^{7d} In their elegant report, Xie *et al.* utilized the reduction of *ortho*-carboranyl diazonium salts to generate boron-centered radical intermediates. Subsequently, the generated radical intermediates exhibited reactivity towards five-membered heterocycles and simple arenes. We hypothesized that, complimentary to the reductive approach for generating boron vertex-centered radicals, one could develop oxidative chemistry, akin to chemistry developed with borylated aryl and alkyl-based species (*vide supra*, Figure 1).

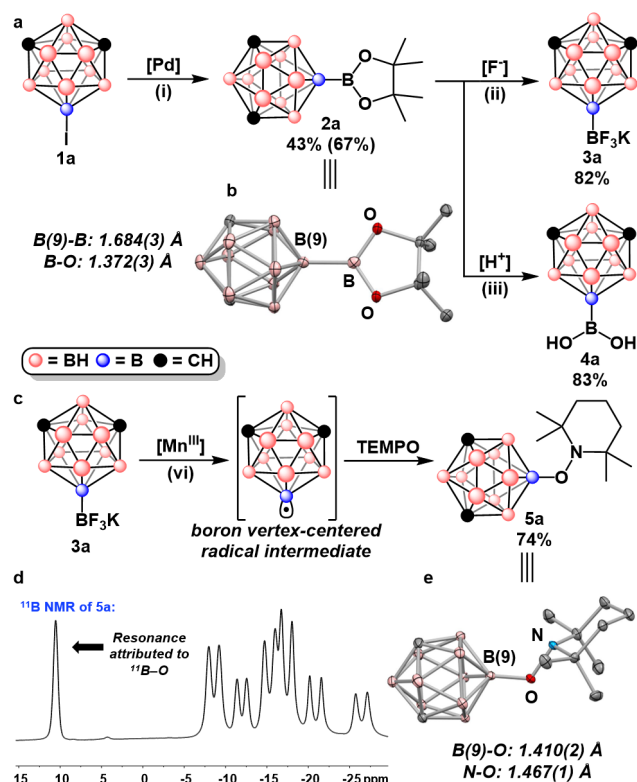


Figure 2. (a) Synthesis of substituted carboranes containing exopolyhedral boron-based substituents. (i) 5 mol% [dppf-Pd-G3], 1.5 eq B₂Pi₂, 2.5 eq Cs₂CO₃, DMF (5% H₂O v/v), 50 °C, 2 h. (ii) 1. 4.1 eq of KF in H₂O, 1:1 MeOH:MeCN, 45 °C, 0.5 h; 2. 2.05 eq Tartaric Acid in THF, 45 °C, 0.5 h. (iii) HCl (conc.), EtOH, 80 °C, 8 h. (b) Single-crystal X-ray structure of **2a**. (c) Oxidation **3a** in the presence of TEMPO. (iv) 1.5 eq **3a**, 1.5 eq Mn(OAc)₃·2H₂O, acetic acid. (d) ¹¹B NMR spectrum of **5a**. (e) Single-crystal X-ray structure of **5a**. Isolated yields are given as percentages and conversion by GC-MS is in parenthesis. Thermal ellipsoids are drawn at 50% probability and hydrogens are omitted for clarity.

In order to test our hypothesis, we set out to prepare potassium 9-*meta*-carboranyltrifluoroborate (**3a**, Figure 2a). Importantly, **3a** would provide similar steric and electronic environments to alkyl trifluoroborates, which have been widely studied as radical precursors.^{3b-4} To prepare **3a**, we first developed borylation conditions to transform 9-iodo-*meta*-carboranyl (**1a**, Figure 2a) into the corresponding 9-*meta*-carboranyl boronic ester (**2a**, Figure 2a, SI sec. 4) while monitoring the progress of the reaction by HRGC-MS. Through optimization of the catalytic transformation, we found that Cs₂CO₃ and N,N-dimethylformamide (DMF) were critical to achieve high conversion efficiency for the borylation (up to 72%). With these conditions, we were able to synthesize and isolate **2a** in 42% yield on a 5 mmol scale. ¹¹B NMR spectroscopy of **2a** revealed two diagnostic resonances corresponding to the substituted ¹¹B site of the boron cage and the ¹¹B of the boronic ester in a 1:1 ratio. To confirm the placement of the boronic ester on the carborane cage, single-crystals of **2a** suitable for X-ray crystallography were grown from a concentrated solution of **2a** in pentane. The crystallographically derived structure of **2a** was found to be consistent with its proposed structural formulation (Figure 2b), featuring an exopolyhedral B(9)–Bpin bond. The measured exopolyhedral B(9)–Bpin bond length (1.684(3) Å) for **2a** is consistent with the previously studied electron-poor, 3-*ortho*-carboranyl boronic

ester obtained *via* direct B–H borylation (1.680(6) Å).⁸ Notably, similar to alkyl and aryl boronic esters,⁹ **2a** undergoes deprotection in the presence of fluoride or acid, yielding the corresponding trifluoroborate salt (**3a**) and boronic acid (**4a**) derivatives in 82% and 83% yields, respectively (Figure 2a, SI sec. 5). Additionally, it was possible to prepare the analogous 9-*ortho*-carboranyl boronic ester and acid, **2b** and **4b**, though the fluoride-sensitivity¹⁰ of *ortho*-carborane prevented the synthesis of the 9-*ortho*-carboranyltrifluoroborate derivative (see SI for full experimental details).

With a library of carborane clusters featuring exopolyhedral boron-based substituents (**3a** and **4a-b**) in hand, we commenced our studies to probe the propensity of these B–borylated carboranes to undergo oxidative B–[B] ([B]: –BF₃K, or –B(OH)₂) bond cleavage. We first performed the oxidation of **3a** in acetic acid with manganese (III) acetate dihydrate (Mn(OAc)₃·2H₂O) in the presence of (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO, Figure 2c, SI sec. 6,9) with the intent of trapping any radical intermediates formed *in situ*. During the course of the reaction, we observed the exclusive formation of a boron cluster-containing species corresponding to a TEMPO adduct of *meta*-carborane (**5a**) by HRGC-MS that could be isolated *via* silica gel column chromatography in 74% yield. ¹¹B NMR spectroscopy of purified **5a** revealed a ¹¹B resonance within a chemical shift range indicative of an exopolyhedral ¹¹B–O bond (Figure 2d), which was subsequently confirmed by single-crystal X-ray crystallography (Figure 2e).

Isolation of **5a** suggested the intermediacy of the boron vertex-centered radical, which could be trapped by other reagents besides TEMPO. To explore this generality, we evaluated a series of dichalcogenides as trapping agents under similar oxidizing conditions (Figure 3, SI sec. 9). First we performed the oxidation of **3a** in the presence of diphenyl disulfide. This reaction generated a product mixture containing a species corresponding to **5b** by HRGC-MS. Compound **5b** was isolated from the product mixture as an air-stable solid *via* silica gel column chromatography in 56% yield and its identity was confirmed by ¹H, ¹³C, and ¹¹B NMR spectroscopy. The ¹¹B NMR spectrum of **5b** featured a diagnostic ¹¹B resonance consistent with the formation of an exopolyhedral ¹¹B–S bond and is in agreement to the proposed structural formulation (Figure 3).

Similarly, oxidation of **3a** in the presence of diphenyl diselenide and subsequent purification produced **5c** in 57% isolated yield. Consistent with the presence of an exopolyhedral B–Se bonding interaction in **5c**, one can observe a ⁷⁷Se–¹¹B quartet resonance in the ⁷⁷Se NMR of **5c** (Figure 3). When the oxidation of **3a** is performed under inert atmosphere in the presence of diphenyl ditelluride, a species containing an exopolyhedral B–Te bond (**5d**) is formed, as suggested by HR-GCMS. This species could be isolated *via* a similar purification protocol (*vide supra*), albeit in a lower isolated yield (27%), likely due to the poor oxidative stability of telluroether compounds.¹¹ NMR spectroscopy experiments of **5d**, including ¹¹B and ¹²⁵Te NMR spectra, are fully consistent with its proposed structural formulation. Finally, utilizing this approach, we were able to demonstrate the formation of a selenoether species (**5e**) containing two boron-connected substitutions, and the first example of a mixed-isomer dicarboranyl selenide (See SI for full experimental details). Interestingly, given the dramatic electron donating capabilities of the B(9) position of *ortho*- and *meta*-carboranes, **5e** exhibits the most downfield ⁷⁷Se NMR chemical shift (Figure 3, δ = –284.0 ppm) for any known selenoether-type compound reported to date.¹¹ Overall, formation of products **5b-5e** further reinforces our hypothesis of the intermediacy of the boron vertex-centered radicals during the course of **3a** oxidation.

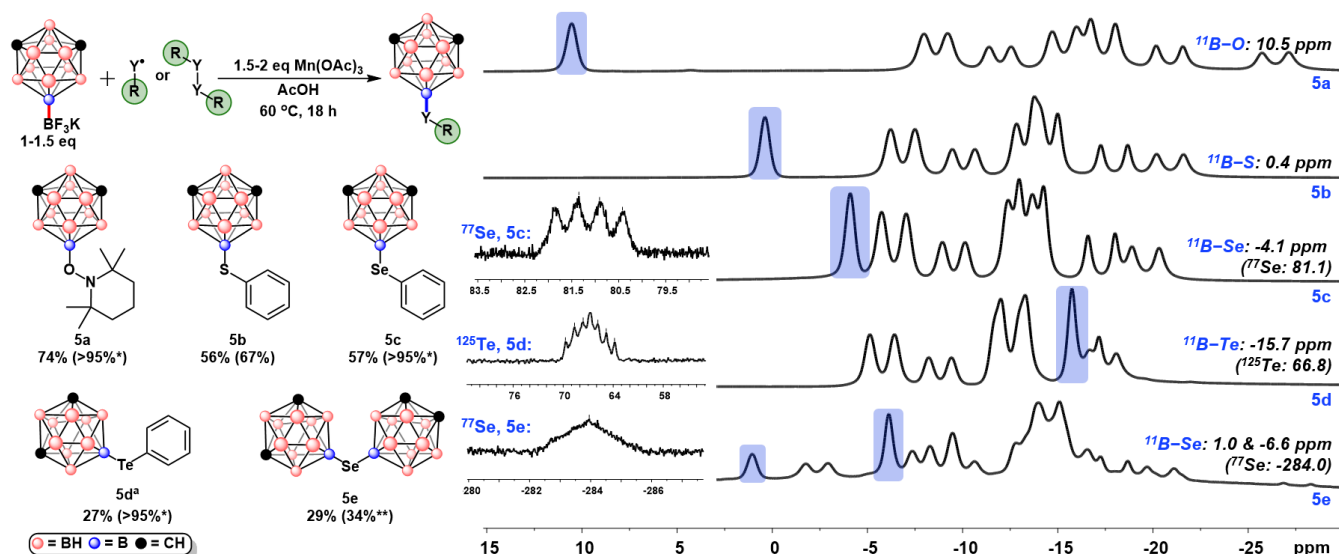


Figure 3. Oxidation of **3a** and reaction with TEMPO and dichalcogenides. ^{11}B NMR (and heteronuclear NMR, where relevant) spectra of compounds **5a-5e**. Resonances highlighted in blue are attributed to the exopolyhedral ^{11}B -Y bond. Isolated yields are given as percentages and conversion by HRGC-MS in parenthesis. *No starting material was observed by HRGC-MS. **Conversion was determined by ^{11}B NMR spectroscopy. ^aReaction was performed under an atmosphere of argon.

Carbon-centered radical intermediates have been known to undergo C-H activation processes with N-heterocycles, thereby allowing the formation of C-C bonds. We therefore hypothesized that the oxidatively generated boron vertex-centered radical intermediate could undergo a similar C-H activation mechanism, forming the desired exopolyhedral B-C bond (SI sec. 9). To investigate the potential for the carboranyl radical intermediate to participate in C-H activation mechanisms with N-heterocycles, we chose 4-methyl-quinoline^{3g} as a model substrate. 4-methyl-quinoline was treated with an excess of $\text{Mn}(\text{OAc})_3 \cdot 2\text{H}_2\text{O}$ (3 eq) and **3a** (1.5 eq) in acetic acid (1 mL). Monitoring of this reaction by HRGC-MS suggested partial conversion (17%) of 4-methyl-quinoline to a carborane-containing heterocyclic product. Increasing the stoichiometric ratio of $\text{Mn}(\text{OAc})_3 \cdot 2\text{H}_2\text{O}$ and **3a**, however, resulted in a substantial increase of the product formation (up to 32% conversion, SI sec. 7). When this reaction is performed on a larger scale (0.25 mmol), the product mixture can be subjected to purification *via* silica gel column chromatography to produce **5f** as suggested by diagnostic ^1H , ^{13}C , and ^{11}B NMR spectroscopy in 30% isolated yield. Notably, the efficiency of the carboranyl radical-heterocycle coupling is limited in this case, and is consistent with the sterically hindered nature of carborane. Similar reactions utilizing sterically hindered carbon-based substrates (e.g. tert-butyl radical synthons) usually exhibit conversions up to 58%.^{3g} Previous mechanistic studies into the C-H activation of N-heterocycles by carbon-centered radicals highlighted the innate reactivity of certain positions in pyridines that could, in theory, be extended to other heterocyclic systems.^{3c} To confirm the paralleled reactivity between boron vertex- and carbon-centered radicals further, we employed benzothiazole as a model five-membered heterocycle with innate reactivity towards carbon-centered radicals at C(2). When the oxidation of **3a** is performed in a 1:1 mixture of acetic acid:water with benzothiazole as a trapping reagent, formation of a carborane-containing heterocyclic product was possible as indicated by HRGC-MS. Compound **5g** was isolated from the product mixture *via* a similar purification protocol (*vide supra*) and obtained in 41% yield. ^1H , ^{13}C , and ^{11}B NMR spectroscopy of **5g** suggested likely C-H activation by the carboranyl radical at C(2) of benzothiazole, and single-crystals of **5g** suitable for X-ray crystallography were subsequently grown from an acetone:pentane mixture.

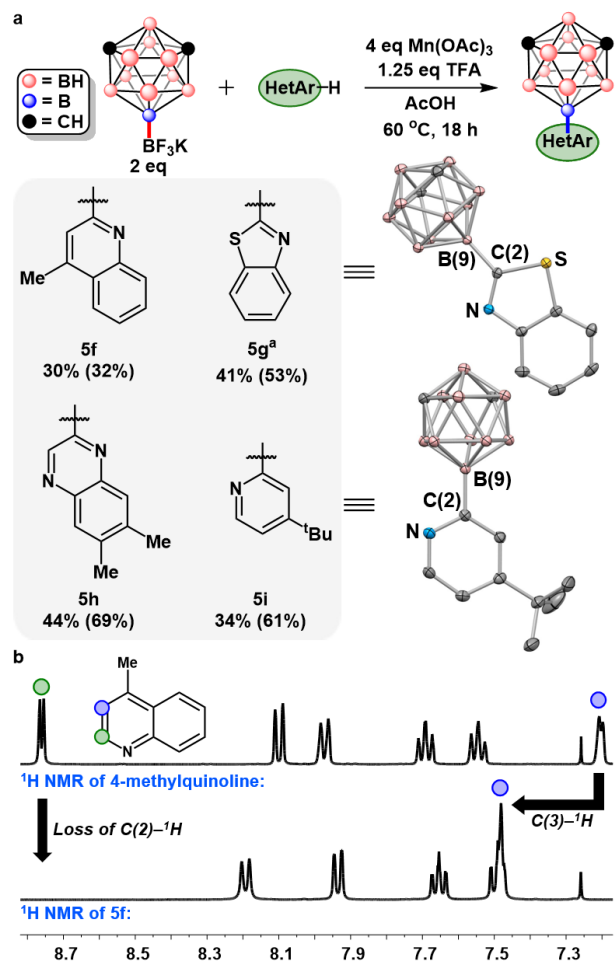


Figure 4. (a) Oxidation of **3a** and reaction with N-heterocycles. (b) ^1H NMR experiments of 4-methylquinoline and **5f** show C-H activation at C(2). ^aReaction was performed in 1:1 $\text{AcOH}:\text{H}_2\text{O}$. Isolated yields are given as percentages and conversion by HRGC-MS in parenthesis. Thermal ellipsoids are drawn at 50% probability and hydrogens are omitted for clarity.

The crystallographically derived structure of **5g** (Figure 4a) is in agreement with the proposed structural formulation and definitively indicates substitution at C(2) position of the heterocycle leading to the formation of an exopolyhedral B(9)–C(2) bond. Furthermore, reactivity towards pyridines and pyrazines was tested to further confirm that the regioselective substitution of the carboranyl radical onto the N-heterocycle is consistent with proposed radical-promoted C–H functionalization mechanisms.^{3c} Under identical oxidation conditions and following similar isolation procedures used in the synthesis of **5f**, the radical-heterocycle coupling works comparably well with pyridines and pyrazines, affording **5h** and **5i** in 44% and 34% isolated yields, respectively. Single-crystal X-ray crystallography of **5i** (Figure 4a) confirms the anticipated regioselectivity of the C–H functionalization. Importantly, formation of products **5f–i** are indicative of the paralleled reactivity between oxidatively generated boron vertex- and carbon-centered radicals when participating in analogous C–H functionalization mechanisms (Figure 4b).

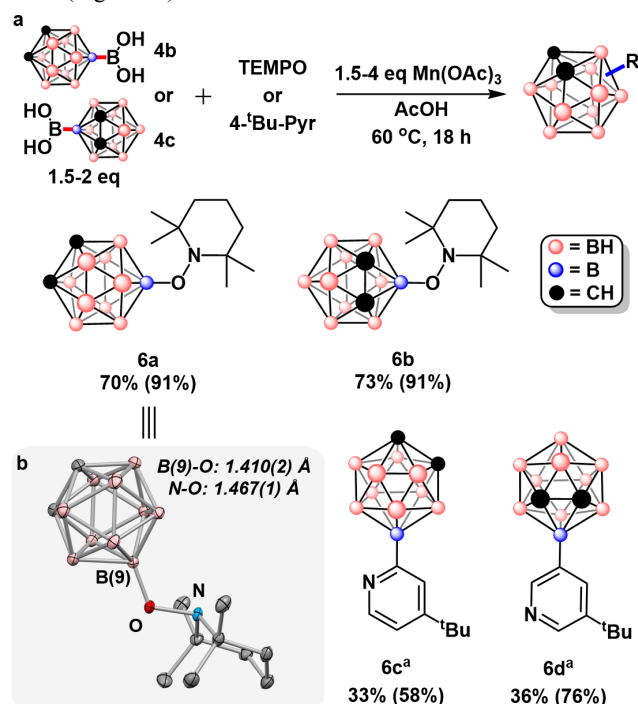


Figure 5. (a) Oxidation of **4b–c**. (b) Single-crystal X-ray structure of **6a**. ^aReaction also included 1.25 eq of TFA. Isolated yields are given as percentages and conversion by HRGC-MS in parenthesis. Thermal ellipsoids are drawn at 50% probability and hydrogens are omitted for clarity.

In order to determine the accessibility of other carboranyl radical intermediates, we probed the susceptibility of **4b** and 3-*ortho*-carboranyl boronic acid (**4c**) to undergo homolytic B–B(OH)₂ bond scission in the presence of Mn(OAc)₃·2H₂O (Figure 5a, SI sec. 10). Initially, **4b** was treated with identical oxidation conditions used in the preparation of **5a** (Figure 5a), and the formation of **6a** was monitored by HR-GCMS. After 18 hours, **6a** was isolated from the reaction mixture *via* silica gel column chromatography in a similar yield to that of **5a** (70%). Analogous to **5a**, ¹¹B NMR spectroscopy of **6a** revealed a diagnostic ¹¹B resonance typical of the formation of an exopolyhedral ¹¹B–O bond and can be crystallographically characterized. Likewise, when using **4c** as a radical precursor, it was possible to synthesize and isolate **6b** in 73% yield following the same procedure (*vide supra*). Carboranyl radical intermediates from the oxidation of **4b** and **4c** formed in the presence of 4-^tBu-pyridine also participate in the anticipated C–H

functionalization pathway. As a result, products **6c** and **6d** were prepared and isolated in comparable yields to **5i** (33% and 36%, respectively). Surprisingly, compounds **6c–d** are the first known examples of substituted *ortho*-carboranes containing pyridyl groups at any boron vertex of the cluster. The synthesis of compounds **6a–d** suggests that the reactivity of the carboranyl radical intermediates are independent of any perceivable difference in the electronic nature of the exopolyhedral boron-based substituent.

In conclusion, we report the first example of boron vertex-centered carboranyl radicals generated *via* oxidative exopolyhedral B–[B] bond scission. Once generated, the carboranyl radical intermediates have been observed to participate in a similar substitution chemistry with carbon-centered radicals, as manifested by both the chemoselectivity for chalcogen-based radical traps (TEMPO, dichalcogenides) and the regioselectivity of heterocycle substitution. The use of reactive, boron-centered carboranyl radical intermediates, has afforded new avenues to forge exopolyhedral B–X bonds with boron-rich clusters. Additionally, this new method for carboranyl radical generation expands upon the existing repertoire of reactive boron cluster species¹² and main group-centered radicals.¹³

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available upon request from A. M. S. Full procedures and additional data (PDF) Crystallographic data (CIF).

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Notes

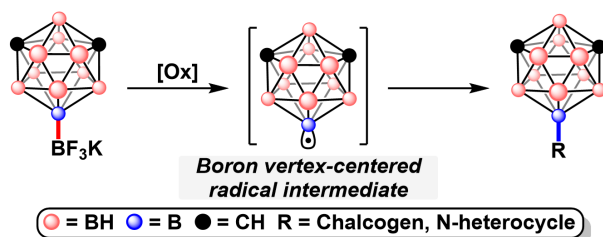
The authors declare no competing financial interests.

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