Oxidative Generation of Boron-Centered Radicals in Carboranes

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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., −BF₃K, −B(OH)₃). The in situ generated radical species are shown to be competent substrates in reactions with oxygen-based radicals, dichalogenides, 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. Particularly, methods utilizing carbon-centered radical intermediates have made use of stable radical precursors containing cleavable C–X bonds (X: −COOH, (−SO₂)₂Zn, −B(OH)₃, −BF₃K) 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, extended aromatic systems, and oxygen-based radical traps (Figure 1a). Icosahedral carboranes (C₈B₉H₁₂) are molecular clusters that exist as three distinct isomers (ortho-, meta-, para-) that feature a steric profile similar to that of adamantane. 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) 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. Most recently, new methods have enabled metal-catalyzed cross-coupling, metal-catalyzed B–H activation, and nucleophilic substitution 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.

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. 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 amines. 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).
the previously studied electron-hedral B consistent with its proposed structural formulation (Figure 2a, SI sec. 6). To confirm the placement of the boronic ester on the B site of the boron cage and the presence of TEMPO. (iv) 1.5 eq Mn(OAc)\(_2\)O, acetic acid. (d) \(^{11}B\) 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. 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 Cs\(_2\)CO\(_3\) 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. \(^{11}B\) NMR spectroscopy of 2a revealed two diagnostic resonances corresponding to the substituted \(^{11}B\) site of the boron cage and the \(^{11}B\) 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). Notably, similar to alkyl and aryl boronic esters, 2a undergoes deprotection in the presence of fluoride or acid, yielding the corresponding tri- fluoroborate 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-sensitivity 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]\(_2\) \(\rightarrow [\text{BF}_2\text{K}]_2\) or –[B(OH)]\(_2\) \(\rightarrow [\text{BF}_2\text{K}]_2\) bond cleavage. We first performed the oxidation of 3a in acetic acid with manganese (III) acetate dihydrate (Mn(OAc)\(_2\)\(\cdot\)2H\(_2\)O) in the presence of (2,2,6,6-tetramethylpiperidin-1-yl)oxy (TEMPO, Figure 2c, SI sec. 6,9) with the intent of trapping any radical intermediates formed \(\textit{in situ}\). 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. \(^{11}B\) NMR spectroscopy of purified 5a revealed a \(^{11}B\) 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 \(^1H\), \(^{13}C\), and \(^{11}B\) NMR spectroscopy. The \(^{11}B\) NMR spectrum of 5b featured a diagnostic \(^{11}B\) 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 5e in 57% isolated yield. Consistent with the presence of an exopolyhedral B–Se bonding interaction in 5e, one can observe a \(^{77}Se\)–\(^{11}B\) quartet resonance in the \(^{77}Se\) NMR of 5e (Figure 3). When the oxidation of 3a is performed under inert atmosphere in the presence of diphenyl disulfide, 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 \(\textit{vide supra}\), albeit in a lower isolated yield (27%), likely due to the poor oxidative stability of telluroether compounds. \(^11\)NMR spectroscopy experiments of 5d, including \(^{11}B\) and \(^{125}Te\) 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 \(^{77}Se\) NMR chemical shift (Figure 3, \(\delta = -284.0 \text{ ppm}\) for any known selenoether-type compound reported to date. 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. Reaction 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-methylquinoline 3g as a model substrate. 4-Methylquinoline was treated with an excess of Mn(OAc)$_2$·2H$_2$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-methylquinoline to a carborane-containing heterocyclic product. Increasing the stoichiometric ratio of Mn(OAc)$_2$·2H$_2$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 $^1$H, $^{13}$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%. 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. 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 similar purification protocol (vide supra) and obtained in 41% yield. $^1$H, $^{13}$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) $^1$H NMR experiments of 4-methylquinoline and 5f show C−H activation at C(2). Reaction was performed in 1:1 AcOH:H$_2$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 carboryl radical onto the N-heterocycle is consistent with proposed radical-promoted C−H functionalization mechanisms. Under identical oxidation conditions and following similar isolation procedures used in the synthesis of 5i, 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 5j (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).

In order to determine the accessibility of other carboryl radical intermediates, we probed the susceptibility of 4b and 3-ortho-carboryl boronic acid (4c) to undergo homolytic B−B(OH)₂ bond scission in the presence of Mn(OAc)₂·2H₂O (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). Carboryl radical intermediates from the oxidation of 4b and 4c formed in the presence of 4-²Bu-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 carboryl 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 carboryl radicals generated via oxidative exopolyhedral B−[B] bond scission. Once generated, the carboryl 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 carboryl radical intermediates, has afforded new avenues to forge exopolyhedral B−X bonds with boron-rich clusters. Additionally, this new method for carboryl radical generation expands upon the existing repertoire of reactive boron cluster species and main group-centered radicals.

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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REFERENCES


BF₃K $\xrightarrow{[\text{Ox}]} \text{Boron vertex-centered radical intermediate} \rightarrow R$

○ = BH ○ = B ● = CH R = Chalcogen, N-heterocycle