Carboranes

Electrochemical Cage Activation of Carboranes

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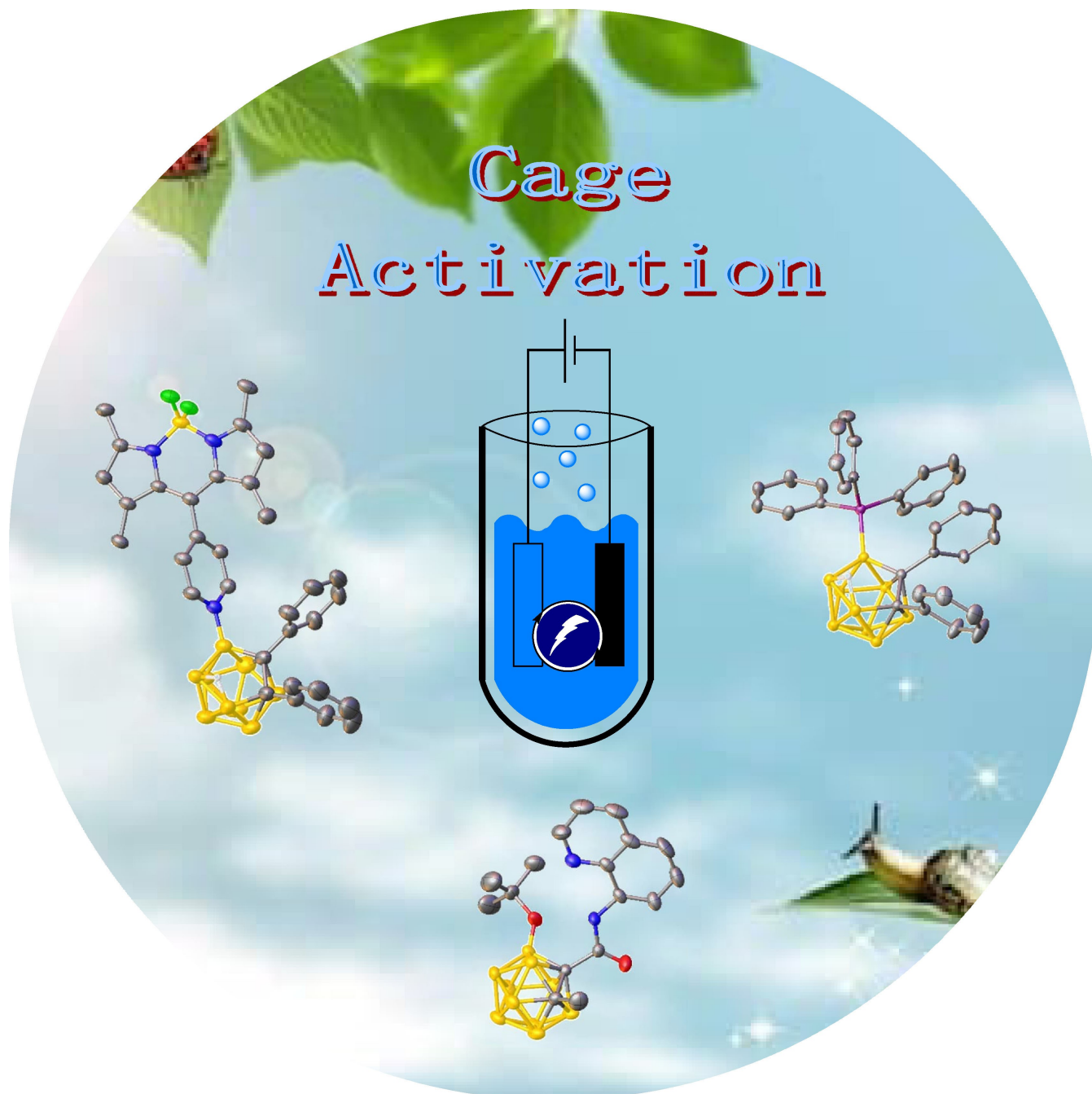
Abstract: Carboranes are boron–carbon molecular clusters that possess unique properties, such as their icosahedron geometry, high boron content, and delocalized three-dimensional aromaticity. These features render carboranes valuable building blocks for applications in supramolecular design, nanomaterials, optoelectronics, organometallic coordination chemistry, and as boron neutron capture therapy (BNCT) agents. Despite tremendous progress in this field, stoichiometric chemical redox reagents are largely required for the oxidative activation of carborane cages. In this context, electrosyntheses represent an alternative strategy for more sustainable molecular syntheses. It is only in recent few years that considerable progress has been made in electrochemical cage functionalization of carboranes, which are summarized in this Minireview. We anticipate that electrocatalysis will serve as an increasingly powerful stimulus within the current renaissance of carborane electrochemistry.
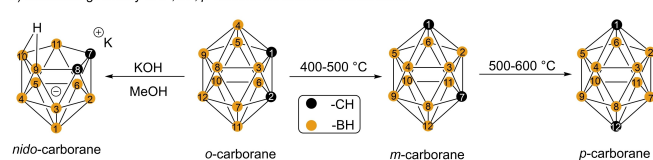
1. Introduction

Carboranes, polyhedral boron–carbon molecular clusters, have one or more of the B–H vertices replaced by C–H units.[1] Among them, icosahedral 1,2-dicarba-*closo*-dodeca-borane (o-$C_2B_{10}H_{12}$), which was reported as early as 1963,[2] has attracted significant attention because of its high symmetry, remarkable stability, and subsequent commercial availability. This cluster comprises ten boron atoms and two neighboring carbon atoms, thus enabling further transformation to *meta*-, *para*-, and *nido*-carboranes, while each atom is hexacoordinated, with 26 delocalized electrons over the entire structure of the cluster (Scheme 1a).[3] Over the past few decades, o-carboranes have been extensively studied and have found wide applications as useful functional building blocks in supramolecular design and nanomaterials,[4] in medicine as boron neutron capture therapy (BNCT) agents or pharmacophores,[5] and in organometallic/coordination chemistry,[6] among others. Owing to the strongly electron-withdrawing character of the o-carborane unit toward carbon substituents, the C–H bonds are weakly acidic in this cage ($pK_a \approx 23$)[7] and can be deprotonated with strong bases, such as alkyl lithium or Grignard reagents. Thus, a large number of carbon-substituted o-carboranes have been prepared by the reaction of negatively charged carbon atoms with electrophilic reagents, such as alkyl halides, carbonyl derivatives, and chlorosilanes. In sharp contrast, the selective functionalization of the ten B–H vertices with very similar chemical

environments in o-carboranes is very challenging and underdeveloped.[8]
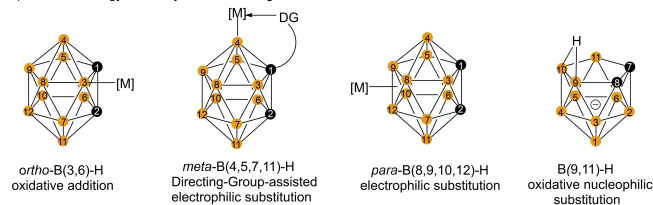
In general, as a result of differences in electronegativity and the distance between the boron and carbon atoms, the 10 B–H bonds of o-carboranes have different electron density, which leads to the electrophilic substitution reactions of carborane derivatives with decreasing reaction rates in the order: B(9,12)–H > B(8,10)–H > B(4,5,7,11)–H > B-(3,6)–H, which also corresponds to the calculated charge distributions on the cage.[9] As the charge differences are very small, achieving high regioselectivity in these substitution reactions is usually very challenging.

A general strategy for the transition-metal-catalyzed selective B–H functionalization of o-carborane cages involves predominately three principles:[10] 1) electron-rich transition-metal catalysts preferably functionalize the most electron-deficient B(3,6)–H bonds, which are bonded to the two cage carbon atoms; 2) electrophilic transition-metal catalysts are appropriate for the functionalization of electron-rich B(8,9,10,12)–H bonds (not bonded to cage carbon atoms); and 3) directing groups in combination with electrophilic transition-metal catalysts are essential for B-(4,5,7,11)–H functionalizations proximal to only one cage carbon atom (Scheme 1b). However, an oxidative nucleo-
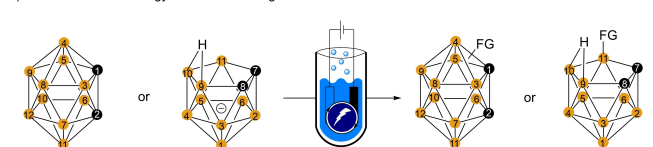
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a) Molecular geometry of o-, m-, p-carboranes and *nido*-carboranes.

nido-carborane o-carborane m-carborane p-carborane

b) General strategy for catalytic selective cage B-H functionalization.

ortho-B(3,6)-H oxidative addition

meta-B(4,5,7,11)-H Directing-Group-assisted electrophilic substitution

para-B(8,9,10,12)-H electrophilic substitution

B(9,11)-H oxidative nucleophilic substitution
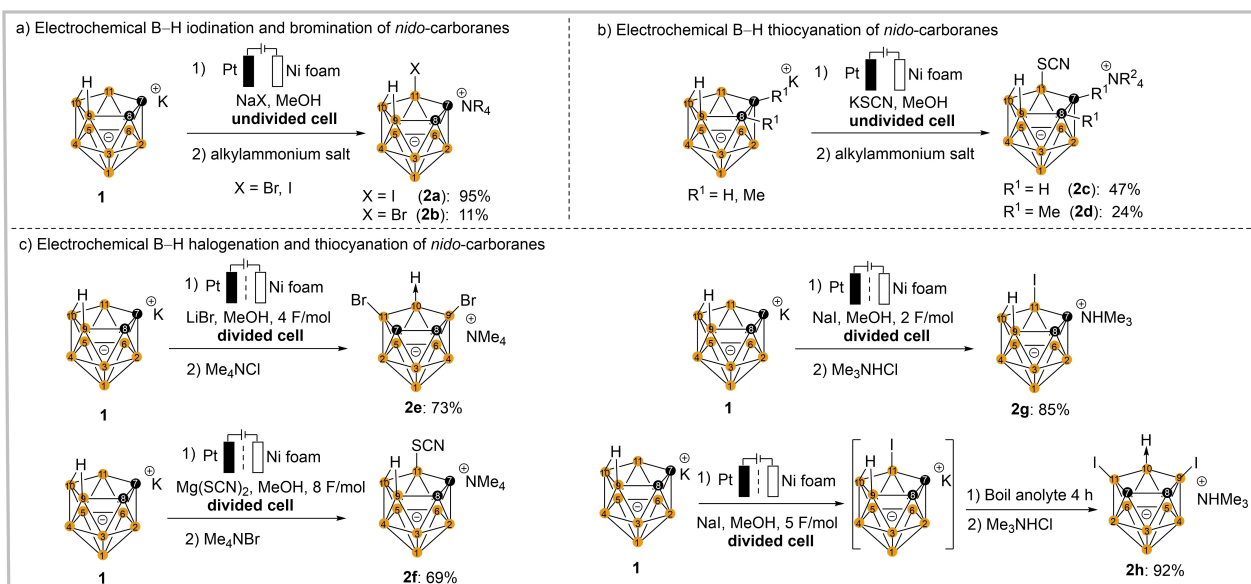
c) Electrochemical strategy for carborane cage activation.

Scheme 1. B–H functionalization of carborane cages.

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Scheme 2. Electrochemical B–H halogenation and thiocyanation of *nido*-carboranes.

philic substitution strategy is generally employed for the *nido*-carboranes to achieve the B(9,11)–H functionalizations.

Despite indisputable advances in the cage activation of carboranes,[6,10,11] oxidative carborane cage functionalizations[12] unfortunately often suffer from the need for stoichiometric amounts of toxic and/or expensive chemical oxidants, such as copper(II)[13] or silver(I) salts,[14] thus limiting the inherently sustainable nature and generality of the cage activation approach. The direct exploitation of electric current for the development of new redox strategies in synthetic organic transformations is on the verge of a
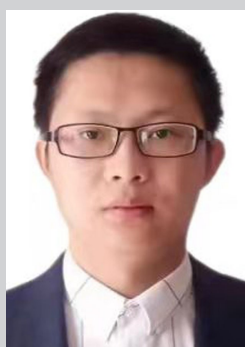
Long Yang received his MChem in 2017 from Fuzhou University (China), where he worked in the area of C–H activation under the supervision of Prof. Gang Li. Then, he moved to Germany and received his PhD at Georg-August-University Göttingen under the supervision of Prof. Lutz Ackermann in October 2021, where he worked on metalla-electrocatalyzed C–H activation and electrochemical cage activation of carboranes.

Becky Bongsuiru Jei studied chemistry at the University of Buea, Cameroon, and obtained her MSc in 2018 under the supervision of Dr. Chi Jovita. She then commenced her doctoral studies in the group of Prof. Lutz Ackermann. Currently, her research is focused on the sustainable use of transition metals in the functionalization of carboranes.
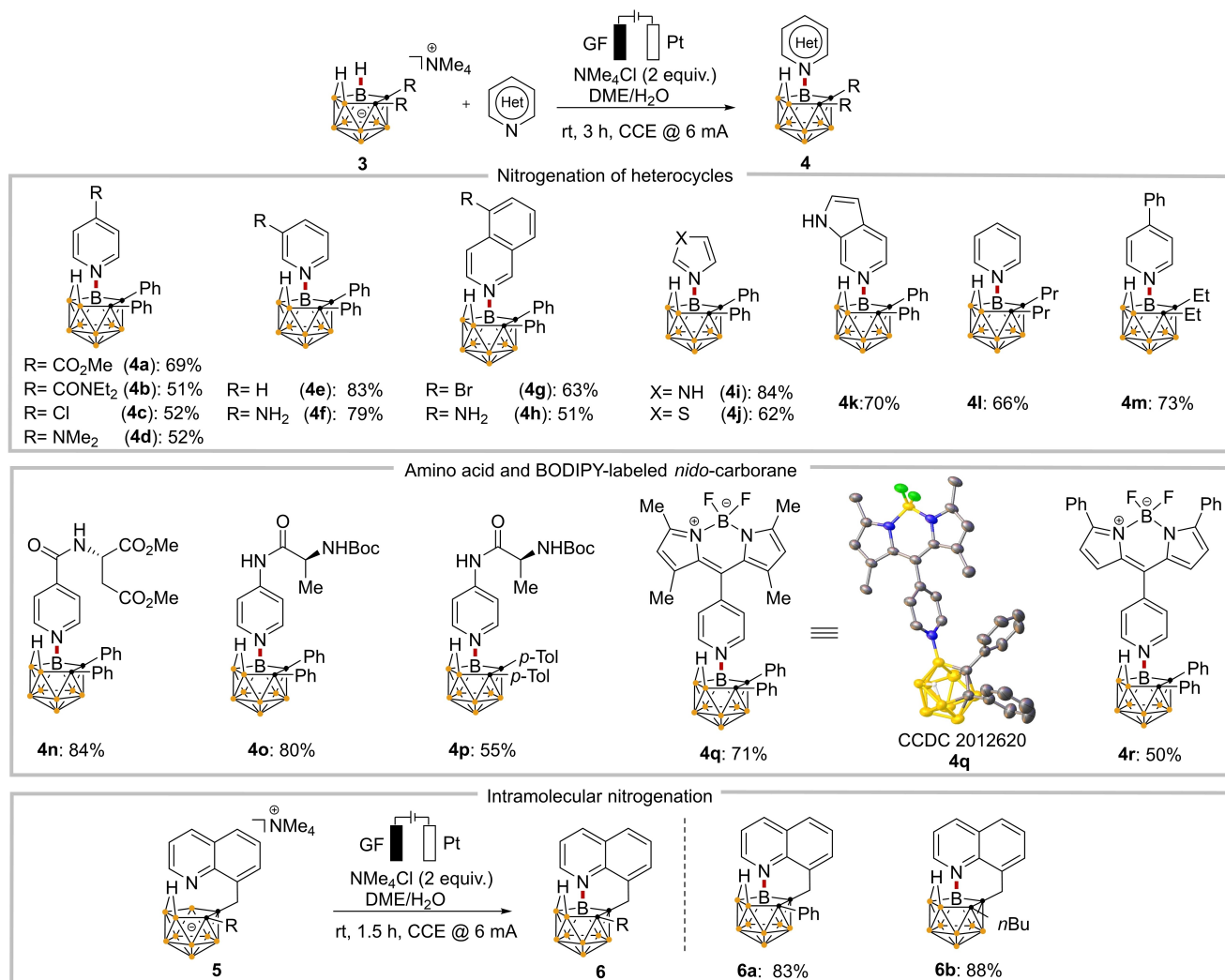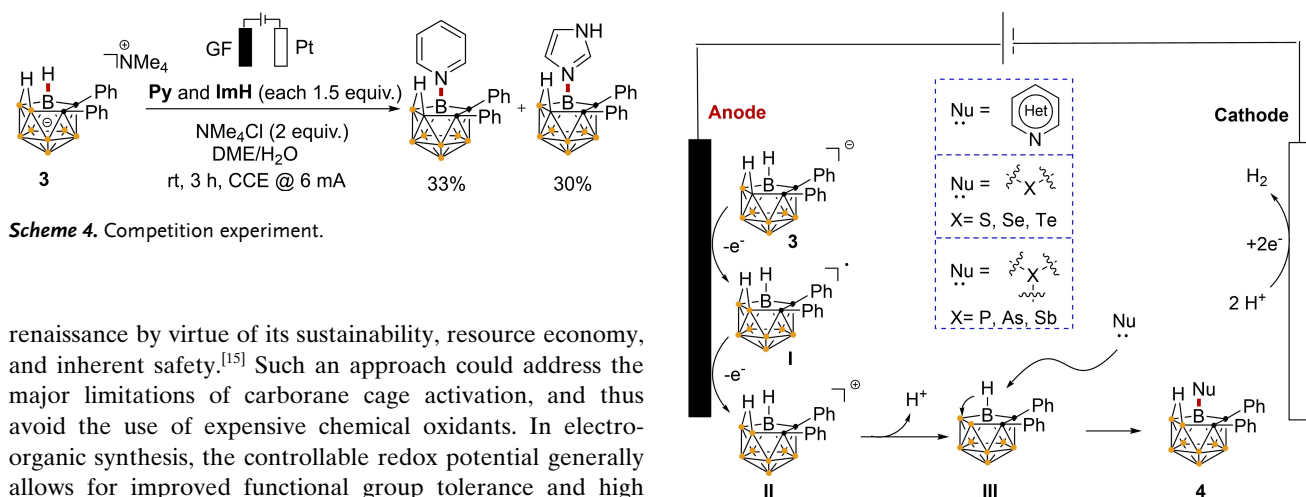
Zi-Jing Zhang was born in 1995 in Anhui (China). He obtained his BSc from Lanzhou University in 2016. In 2021, he received his PhD from the University of Science and Technology of China under the supervision of Prof. Liu-Zhu Gong, where he focused on metal and Lewis base cooperative catalysis. He then joined the group of Prof. Lutz Ackermann at Georg-August-University Göttingen as a postdoctoral researcher, working on asymmetric C–H functionalization.

Lutz Ackermann studied chemistry at Christian-Albrechts-University Kiel (Germany) and received his PhD in 2001 with Prof. A. Fürstner at the Max-Plank-Institut für Kohlenforschung in Mülheim/Ruhr. After postdoctoral research with Prof. R. G. Bergman at UC Berkeley, he started his independent research career in 2003 at the Ludwig-Maximilians-University München supported by the Emmy Noether program of the DFG. In 2007, he was appointed Full Professor at the Georg-August-Universität Göttingen. His recent awards include an ERC Advanced Grant (2021) and a Gottfried-Wilhelm-Leibniz-Preis (2017) as well as visiting professorships at the Universitàdegli Studi di Milano, the University of Wisconsin at Madison, and the Università di Pavia.

Scheme 3. Electrochemical B–H nitrogenation of *nido*-carboranes.

Scheme 4. Competition experiment.

renaissance by virtue of its sustainability, resource economy, and inherent safety.[15] Such an approach could address the major limitations of carborane cage activation, and thus avoid the use of expensive chemical oxidants. In electro-organic synthesis, the controllable redox potential generally allows for improved functional group tolerance and high levels of chemo- and regioselectivities.[16] In this Minireview, we summarize the key developments in the area of electro-chemical carborane cage activation up to January 2022 (Scheme 1c).

Scheme 5. Proposed mechanism.

Scheme 6. Electrochemical B–H functionalization with various heteroatoms bearing a lone pair of electrons.
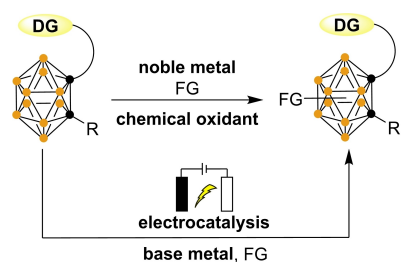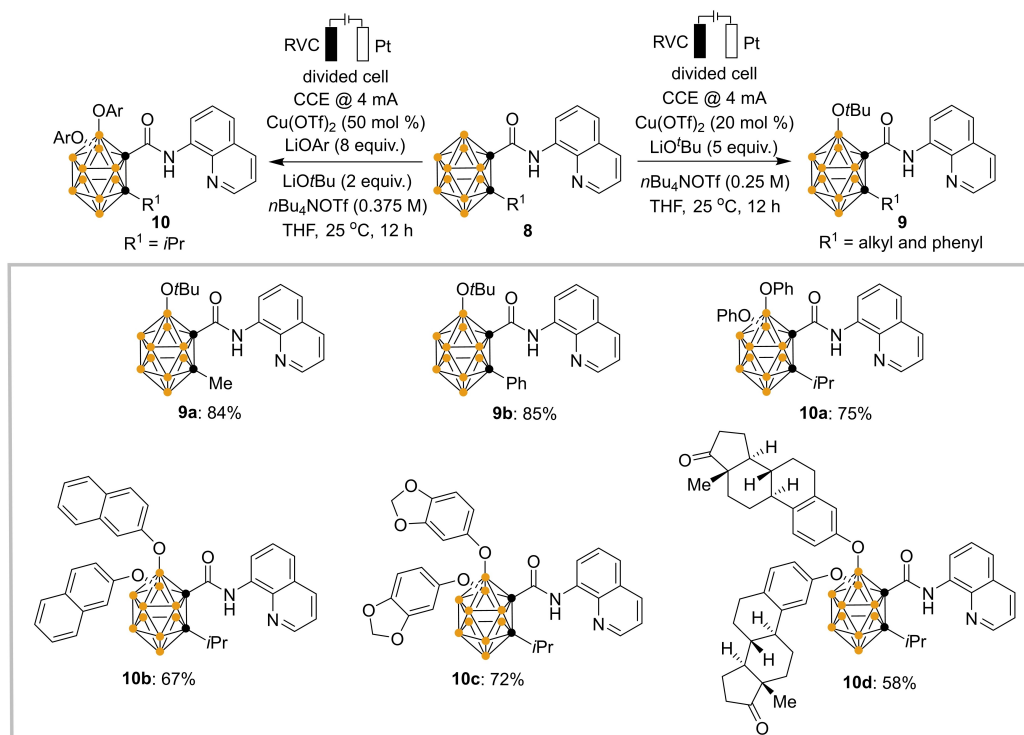

Scheme 7. Metal-catalyzed electrochemical B–H functionalization.

## 2. Electrochemical Activation of the nido-Carborane Cage

Since its discovery, the 7,8-dicarba-*nido*-undecaborate anion (*nido*-carborane) and its derivatives have attracted consid-

erable attention as unusual three-dimensional π-ligands[17] as well as water-solubilizing boron moieties for the design of potential drugs towards boron neutron capture therapy for cancer.[18,19] In sharp contrast to *closo*-carboranes, *nido*-carboranes are typically more reactive species, which can react with transition metals to form stable metallacarboranes,[20] or undergo cage decomposition in the presence of strong oxidants[21] or electrophiles.[22] However, the introduction of substituents containing functional groups into the 7,8-dicarba-*nido*-undecaborate anion skeleton considerably expands the possibility to bind this anion with different compounds that provide selective delivery of the agent to a tumor, for example, to monoclonal antibodies.[23]

In 2004, Shirokii et al. first reported the electrochemical halogenation of potassium dodecahydro-7,8-dicarba-*nido*-undecaborate to achieve monoiodide and monobromide *nido*-carborane derivatives in the form of their alkyl

Scheme 8. Copper-catalyzed electrochemical B—H oxygenation of *o*-carboranes.
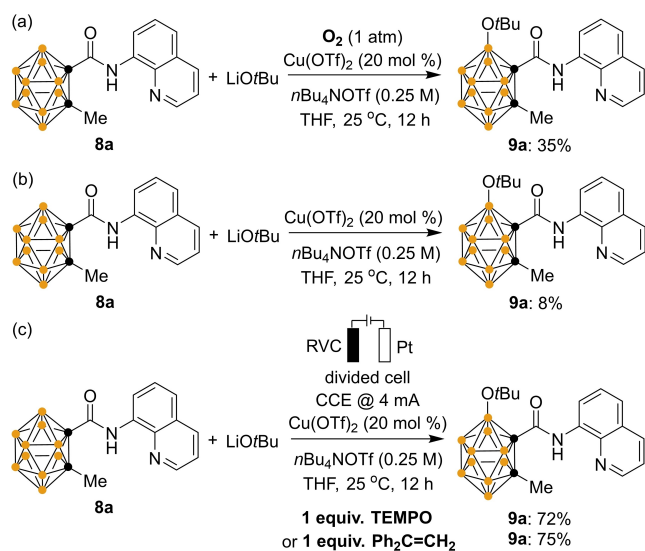
**Scheme 9.** Control experiments for copper-catalyzed electrochemical B—H oxygenation.

ammonium salts in an undivided cell (Scheme 2a).[24] Later, the same group extended their research to the thiocyanation of *nido*-carborane, by employing electricity as a green oxidant, although the yield was moderate (Scheme 2b).[25] To improve the efficiency of the bromination and the thiocyanation, they further carried out this electrosynthesis with a divided cell setup (Scheme 2c),[26] which led to B(9)-monosubstituted derivatives [9-X-7,8-$C_2B_9H_{11}$]$^-$ (X=I, SCN) and unprecedented disubstituted derivatives [9,11-X_2-

7,8-$C_2B_9H_{10}$]$^-$ (X=Br, I) being obtained as their alkyl ammonium salts. As a consequence of the relatively low oxidation potential of the bromine and iodine anions, an accumulation of bromine and iodine was visually observed at the surface of the anode during the electrolysis. Selective mono- and difunctionalization could be accomplished by controlling the quantity of charge. Since bromine is a more powerful halogenating agent in electrophilic substitution reactions, the electrochemical bromination proceeded rapidly, with the formation of the dibromo-substituted compound **2e** as the predominant product.

Although the electrochemical B—H iodination and bromination of *nido*-carborane were successfully achieved, the electrochemical chlorination of the cage did not proceed either in a divided or undivided cell, arguably because of the high oxidation potential of the chlorine anion.

Recently, a breakthrough in electrochemically catalyzed B—H activation was established by the Ackermann group.[27] In their approach, the electrocatalyzed oxidative B—H nitrogenation of *nido*-carborane (*nido*-7,8-$C_2B_9H_{12}^-$) with N-heterocycles was achieved at room temperature, thereby enabling the preparation of various N-substituted *nido*-carboranes without chemical oxidants, such as DDQ[28a,b] and FeCl$_3$[28e] (Scheme 3). The optimized reaction conditions involved the use of NMe$_4$Cl as the electrolyte and a mixture of DME and H$_2$O as the best solvent system, which delivered the desired products **4** in a user-friendly undivided cell setup.

Initially, various substituents in the *meta*- and *para*-positions of pyridines were employed to probe the robustness of the electrocatalyzed B—H transformation, which
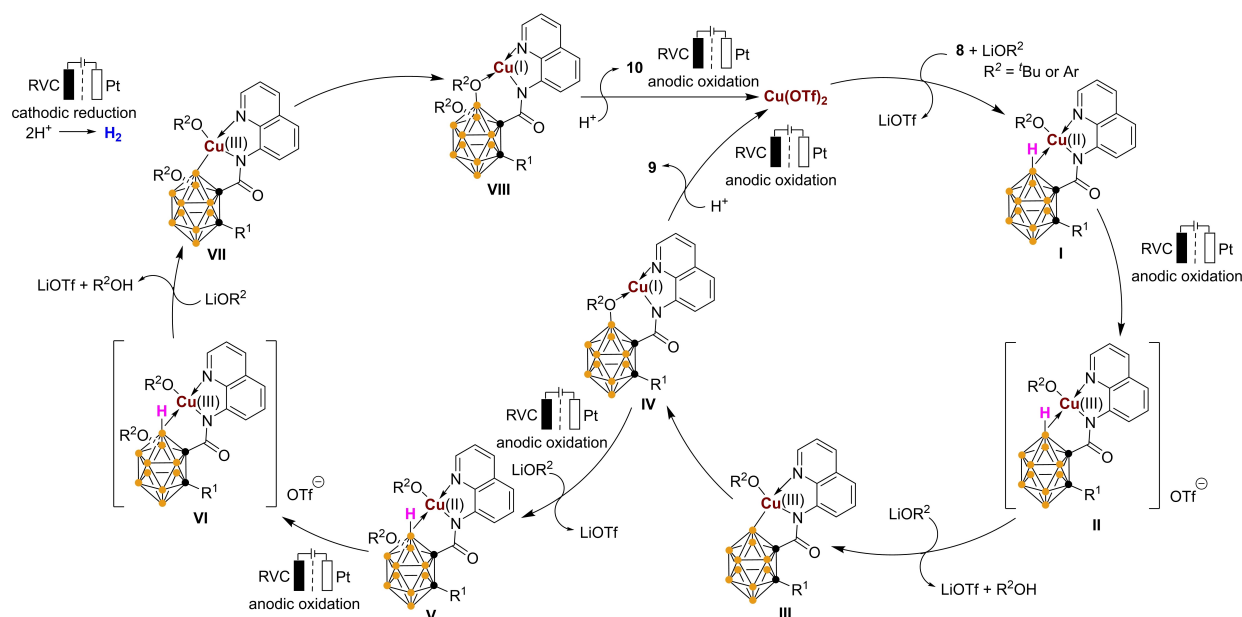
Scheme 10. Plausible reaction mechanism of the copper-catalyzed electrochemical B–H oxygenation.
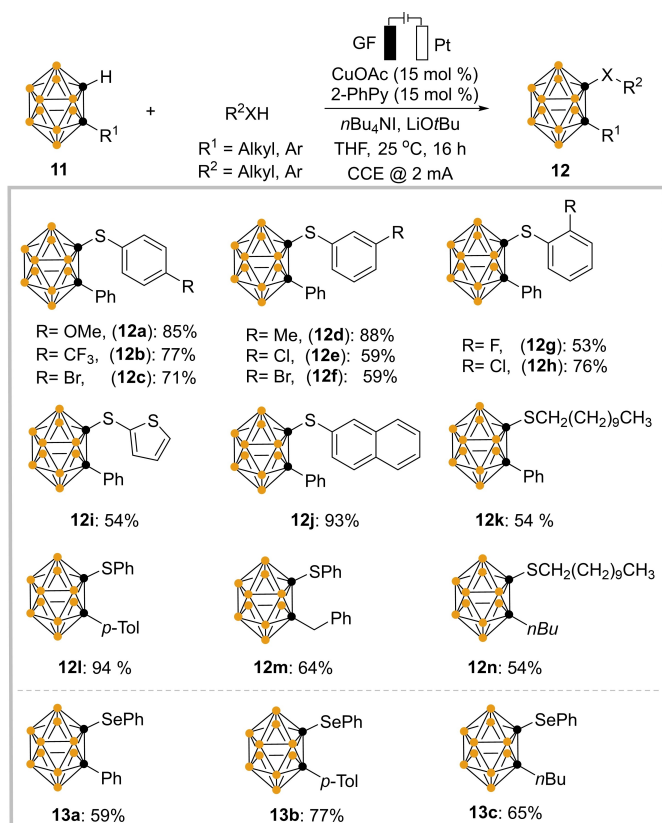
Scheme 11. Electrochemical C–H chalcogenation of *o*-carboranes.

proceeded with excellent levels of regio- and chemoselectivity (**4a–4f**). Notably, a variety of valuable synthetically meaningful functional groups, such as ester (**4a**), amide (**4b**), chloro (**4c**), amino (**4f**, **4h**), and bromo (**4g**), were fully tolerated in these metal-free electrooxidatively cata-

lyzed B–H nitrogenations, which should prove instrumental for further late-stage manipulations. Specifically, the Steglich catalyst 4-dimethylaminopyridine (DMAP) could be efficiently converted into the desired DMAP-decorated *nido*-carborane product (**4d**) by electrochemical nitrogenation. The procedure proved to be applicable to further N-heterocyclic substrates, such as isoquinoline (**4g**, **4h**), imidazole (**4i**), thiazole (**4j**), and azaindole (**4k**). It is worth noting that dialkyl-substituted *nido*-carboranes at the C-(cage) site were also functionalized, thereby furnishing the corresponding B–N coupling products (**4l**, **4m**).

The metal-free electrocatalytic B–H activation of *nido*-carborane proved to be a broadly applicable strategy and gave access to synthetically useful amino acid and fluorogenic boron-dipyrrin (BODIPY) labeled *nido*-carborane hybrids (**4n–4r**). In addition, not only intermolecular transformations proved to be viable, but the intramolecular B–N coupling reactions of *nido*-carborane were efficiently accomplished. Both aryl and alkyl substituents at the cage-carbon site afforded comparable results (**6a**, **6b**).

Competition experiments showed a slight preference in favor of the more nucleophilic N-heterocycles (Scheme 4). Cyclovoltammetric analysis of the *nido*-carborane showed an irreversible oxidation of the *nido*-carborane at $E_{p/2} = 0.56$ V vs. Ag/Ag$^+$ at ambient temperature (Figure 1), which is indicative of a direct oxidation of the *nido*-carborane.

UV/Vis absorption and fluorescence spectroscopy studies of the thus-obtained novel BODIPY-labeled *nido*-carboranes **4q** and **4r** in various solvents showed a very intense absorption in the UV as well as visible region with a high Stokes shift, thereby resulting in an intense red to purple color. These spectroscopic data indicated the unique potential applications of the BODIPY-labeled *nido*-carborane compounds in pharmaceuticals, luminescent materials, and bioimaging.

a) Late-stage diversification

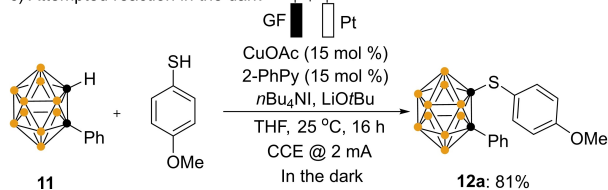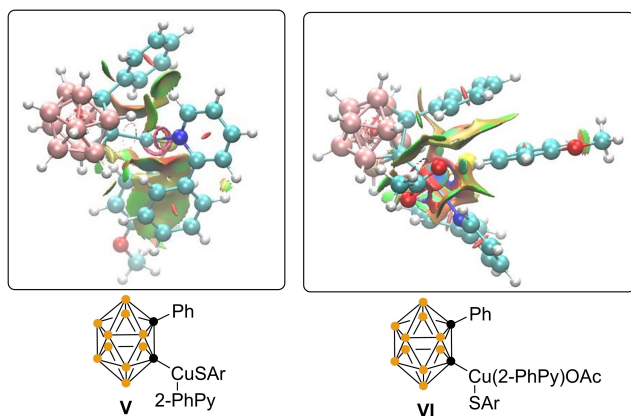b) Radical inhibitors

Reaction Inhibitor	**12a** Yield
TEMPO	75%
Ph$_2$C=CH$_2$	72%
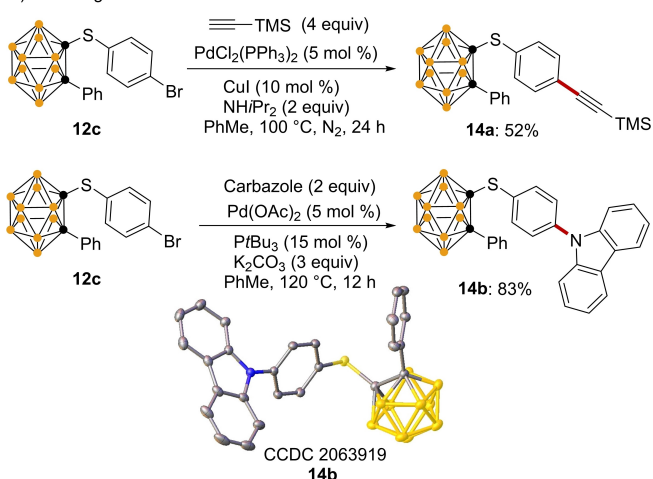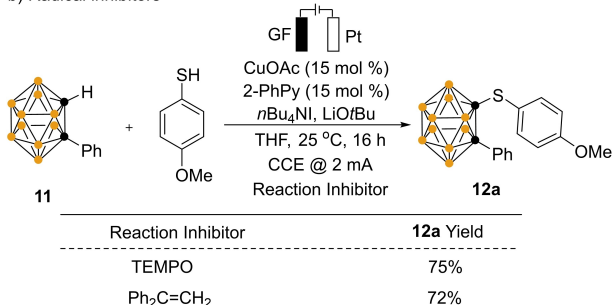
c) Attempted reaction in the dark

Scheme 12. Late-stage diversification and control experiments of cupra-electrocatalyzed C–H chalcogenation.

Scheme 13. Noncovalent interaction plots for the complex **V** and **VI**. Here, strong attractive interactions are given in blue, weak attractive interactions are given in green, and red corresponds to strong repulsive interactions. Ar = 4-MeOC$_6$H$_4$.
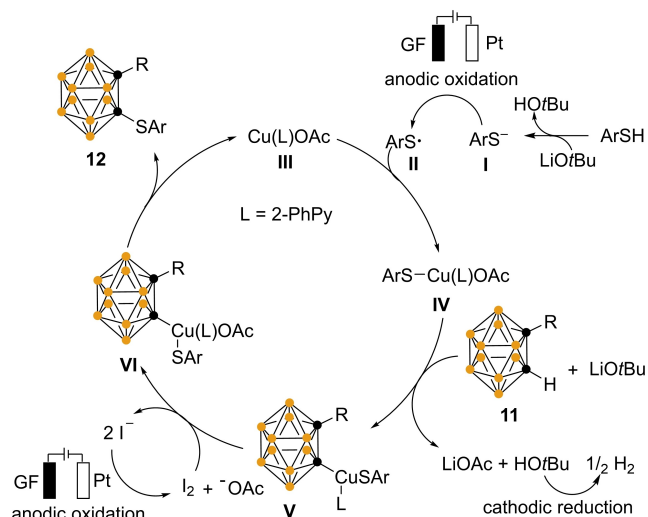
Scheme 14. Plausible mechanism of cupra-electrocatalyzed cage C–H chalcogenation.
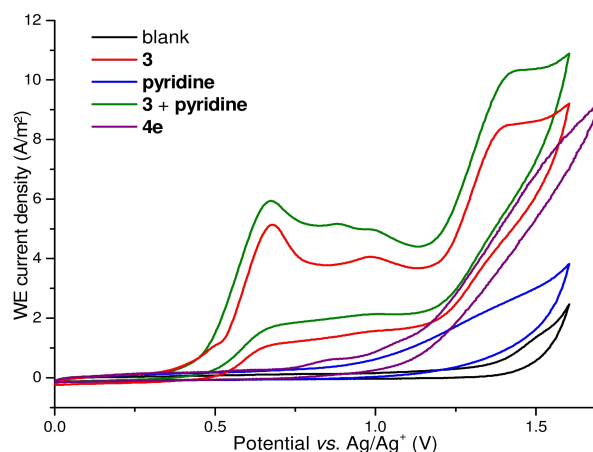
Figure 1. Cyclic voltammetry in DME with 0.1 M nBu$_4$NPF$_6$ under N$_2$ at a scan rate of 100 mV s^{-1}. A glassy carbon working electrode (disk, diameter: 3 mm), a coiled platinum wire counter electrode, and a non-aqueous Ag/Ag$^+$ reference electrode were employed. The Ag/Ag$^+$ reference electrode was a silver wire in a MeCN solution of 100 mM TBAPF$_6$ and 10 mM AgNO$_3$.

On the basis of the mechanistic findings and literature reports,[28] the catalytic cycle depicted in Scheme 5 was proposed.[27] Initially, successive single-electron transfers (SET) deliver intermediates **I** and then **II**. Next, deprotonation of the bridge proton results in the formation of cage-open carborane intermediate **III**. A subsequent nucleophilic substitution and B–H hydrogen-atom transfer (HAT) then generates the desired nitrogenation product. The formation of hydrogen as a by-product through cathodic proton reduction was confirmed by headspace gas chromatographic analysis.

In contrast to the nitrogenation of *nido*-carboranes under electrocatalysis, Yan and co-workers recently reported a similar electrooxidative cage B–H functionalization of *nido*-carboranes with various heteroatoms bearing a lone

pair of electrons (Scheme 6).[29] This electrochemical oxidation method enabled site-selective B–S, B–Se, B–Te, B–N, B–P, B–As, and B–Sb coupling with wide scope and high functional group tolerance in a user-friendly undivided cell setup (**7a–7q**). Although diphenyl sulfide was unreactive under identical conditions (**7g**), selenides and tellurides were amenable substrates in the electrooxidative cage B–H functionalization (**7h**, **7j**), with the reaction efficiency increasing in the series Te > Se ≫ S, which corresponds with the respective nucleophilic substitution reactions. A gram-scale reaction illustrated the synthetic utility of the electro-catalyzed cage B–H activation (Scheme 6a).

Furthermore, when the deuterated *nido*-carborane with a bridging B–D–B bond was used as the starting material, the product contained a normal hydrogen atom in the B–H–B bond, which suggests a B–H hydrogen-atom transfer (HAT) process occurred before the B–H bond was attacked by the nucleophilic agents (Scheme 6b). In addition, this electrooxidative strategy was further applied to give rise to B–S-containing products with highly functionalized sulfides (Scheme 6c), which are of great importance for the development of carborane-based drugs, namely BNCT. Based on these results, the authors also proposed a related reaction mechanism, which is depicted in Scheme 5.

3. Electrochemical Activation of the *o*-Carborane Cage

In recent years, the transition-metal-catalyzed B–H functionalization of *o*-carborane has witnessed major momentum, with a strong incentive being the synthesis of new *o*-carborane-containing materials and drug molecules; this has been summarized in a recent review.[30] However, most of the established oxidation reactions require noble transition metal catalysts and an excess amount of chemical oxidants, which compromises the resource economy.[13,14] In sharp contrast, the combination of base-metal catalysis and electrochemistry for the B–H functionalization of carboranes represents an attractive and environmentally friendly alternative to traditional methods, and avoids the use of harsh oxidizing agents and noble transition metal catalysts (Scheme 7).

In 2020, the Xie research group developed a copper-catalyzed electrochemical selective B–H oxygenation of *o*-carboranes, by merging base-metal catalysis and electrochemistry[31] in a divided cell setup equipped with a RVC (reticulated vitreous carbon) anode and a Pt cathode, which led to the facile synthesis of a series of B(4)-monooxygenated and B(4,5)-diphenolated carborane derivatives (Scheme 8).[32] This process employed electric energy instead of harsh chemical oxidants, and an earth-abundant copper catalyst at room temperature instead of a noble transition metal catalyst.

Under galvanostatic conditions and with 8-aminoquinoline as the directing group and Cu(OTf)$_2$ as the catalyst, B(4)-oxygenated *o*-carboranes **9** were obtained from carboranyl amides **8** using LiO*t*Bu as a strong base. In addition,

B(4,5)-dioxygenated *o*-carboranes **10** were formed when lithium phenolates were employed as the coupling partners. The electrochemical cage B–H oxygenation was demonstrated to proceed with high levels of chemo- and regioselectivity as well as good functional group tolerance, such as of naphthalene (**10b**), benzodioxole (**10c**), and estrone (**10d**). The authors proposed that the steric hindrance of the substituents determined the mono- versus diselectivity. In addition, the use of K$_2$CO$_3$ was shown to effectively remove 8-aminoquinoline directing groups at high temperature.

To gain insight into the reaction mechanism, the authors performed control experiments (Scheme 9). When employing oxygen as the sole oxidant or without electric current conditions, 35% and 8% of product **9a** was obtained, respectively (Scheme 9a,b). These results indicated a high-valent copper(III) species may be involved in the reaction, arguably generated by oxidation by oxygen or disproportionation[33] of the copper(II) salt. Reactions in the presence of the radical scavenger TEMPO (2,2,6,6-tetramethylpiperidin-1-oxyl) or Ph$_2$C=CH$_2$ produced the desired product **9a** in good yield, which suggests that the B–H oxygenation is less likely to involve radical intermediates (Scheme 9c).

On the basis of the experimental results, a plausible catalytic cycle was proposed by Xie and co-workers (Scheme 10). Bidentate chelation of carboranyl amides **8** with Cu(OTf)$_2$ followed by salt metathesis and anodic oxidation generated the active copper species **II**. Electrophilic attack of the copper(III) center at the relatively electron-rich B(4)–H bond generates the copper(III) intermediate **III**. A facile B–O bond formation through reductive elimination and protonation generates the B(4)-oxygenated *o*-carboranes **9**, and the catalytically competent copper(II) complex is regenerated by anodic oxidation. Such a cycle occurs once more to generate the B(4,5)-dioxygenated *o*-carboranes **10**.

In contrast to the oxygenation of *o*-carboranes, Ackermann and co-workers reported an intriguing copper-catalyzed electrochemical cage C–H chalcogenations of *o*-carboranes through a dehydrogenative pathway, notably without a directing group.[34] This approach constitutes an unprecedented strategy for the assembly of a variety of C-sulfenylated and C-selenylated *o*-carborane derivatives **12** under mild conditions (Scheme 11). This electrochemical cage functionalization approach was demonstrated to proceed with good substrate scope and outstanding levels of chemo- and regioselectivity. Different thiols/selenols bearing electron-donating or electron-withdrawing groups, aliphatic thiols, as well as other derivatized *o*-carboranes were well-tolerated.

Further transformation of the thus-obtained bromothiolated *o*-carborane (**12c**) into alkynylated derivative **14a** and amine **14b** proved viable (Scheme 12a), which offers a new route to cage C-substituted carborane-based host materials for applications in phosphorescent organic light-emitting diodes.[35] The structure of the carbazole-thiolated *o*-carborane product **14b** was unambiguously confirmed by X-ray diffraction analysis.

To establish the mode of action of the cupra-electro-catalysis, the authors performed control experiments, which revealed that the reaction proceeds successfully in the presence of TEMPO or $Ph_2C=CH_2$ as well as in the dark (Scheme 12b,c). EPR studies showed a small radical signal, which might be attributed to a thiol radical. Cyclic voltammetric analysis of the thiol and n-Bu_4NI revealed an irreversible oxidation of the thiolate anion at $E_p = -0.62$ V vs. Ag/Ag^+ and two oxidation events for the iodide, which is indicative of the preferential oxidation of the thiolate anion, along with iodide serving as a redox mediator. In addition, DFT calculations were also supportive of iodide serving as a competent redox mediator to achieve the transformation from complex **V** to complex **VI** (Scheme 13).[34]

From the findings of the control experiments and mechanistic studies, a plausible catalytic cycle (Scheme 14) was proposed to feature an anodic single-electron-transfer (SET) oxidation of the thiol anion **I** to deliver the sulfur-centered radical **II**, which further reacts with the copper(I) species **III** to form copper(II) complex **IV**. Thereafter, carborane cage activation and anodic oxidation by the anodically generated redox mediator I_2 furnishes the copper-(III) species **VI**, which subsequently undergoes reductive elimination to afford the final product **12** and regenerate the catalytically active complex **III**.

4. Summary and Outlook

Given the rising demand for sustainable strategies for molecular syntheses, resource economy in molecular syntheses has gained significant momentum in recent years.[36] In this context, electrochemistry is considered as a green tool, promoting organic reactions under mild conditions without the necessity for chemical oxidants, thereby preventing undesired waste formation. In particular, electricity from renewable energy sources, such as solar and wind power,[37] has the unique potential for an ideal step and redox economy. In recent years, significant progress has been witnessed by the merger of electrochemistry with transition-metal catalysis for the construction of challenging C–C and C–heteroatom bonds for the synthesis of complex organic molecules in a sustainable fashion under exceedingly mild reaction conditions.[15]

Concurrently, the transition-metal-catalyzed B–H activation of carboranes has emerged as a transformative platform for molecular syntheses during the last decade.[8] However, despite significant advances in carborane cage activations, the quest for sustainable and environmentally benign strategies continue to be of central importance for resource-economical carborane cage activations. Herein, we have highlighted key contributions in the electrochemical functionalization of *nido*-carboranes and *o*-carboranes, including, B–O, B–S, B–Se, B–Te, B–N, B–P, B–As, B–Sb, B–Br, B–I, B–SCN, C–S, and C–Se bond formation, which should provide guidance towards more sustainable cage activation in the future. Despite this notable progress, electrochemical cage activations of carboranes continue to be underdeveloped, probably because of the electron-deficient character of the carboranes. However, electron-rich ligands or directing groups can likely enable challenging electrochemical cage functionalizations in the future. Given the environmentally friendly nature of electrocatalytic oxidations, further exciting developments are expected in this rapidly evolving research arena of carborane cage activation, such as the direct use of renewable forms of energy, photo-electrocatalysis, earth-abundant electrocatalysis, continuous-flow electrocatalysis, and enantioselective electrochemical transformations. By reviewing the exciting recent developments in the areas of carborane electrochemistry, we hope to highlight the numerous opportunities that lie ahead for us in terms of carborane functionalization.

Acknowledgements

Conflict of Interest

The authors declare no conflict of interest.

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