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Electrooxidative *o*-carborane chalcogenations without directing groups: cage activation by copper catalysis at room temperature†

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Copper-catalyzed electrochemical direct chalcogenations of *o*-carboranes was established at room temperature. Thereby, a series of cage C-sulfonylated and C-selenylated *o*-carboranes anchored with valuable functional groups was accessed with high levels of position- and chemo-selectivity control. The cupraelectrocatalysis provided efficient means to activate otherwise inert cage C–H bonds for the late-stage diversification of *o*-carboranes.

Carboranes are polyhedral molecular boron–carbon clusters, which display unique properties, such as a boron enriched content, icosahedron geometry and three-dimensional electronic delocalization.¹ These features render carboranes as valuable building blocks for applications to optoelectronics,² as nanomaterials, in supramolecular design,³ organometallic coordination chemistry,⁴ and boron neutron capture therapy (BNCT) agents.⁵ As a consequence, considerable progress has been witnessed in transition metal-catalyzed regioselective cage B–H functionalization of *o*-carboranes⁶ and different functional motifs have been incorporated into the cage boron vertices.^{7–10} However, progress in this research arena continues to be considerably limited by the shortage of robust and efficient methods to access carborane-functionalized molecules. While C–S bonds are important structural motifs in various biologically active molecules and functional materials,¹¹ strategies for the assembly of chalcogen-substituted carboranes continue to be scarce. A major challenge is hence represented by the strong coordination abilities of thiols to most transition metals, which often lead to catalyst deactivation.¹² While copper-catalyzed B(4,5)–H disulfonylation of *o*-carboranes was achieved,^{7e} elevated reaction temperature was required, and 8-

aminoquinoline was necessary as bidentate directing group. The bidentate directing group¹³ needs to be installed and removed, which jeopardizes the overall efficacy. Likewise, an organometallic strategy was recently devised for cysteine bor-ylation with a stoichiometric platinum(II)-based carboranes.¹⁴ Meanwhile, oxidative cage B/C–H functionalizations largely call for noble transition metal catalysts¹⁵ and stoichiometric amounts of chemical oxidants, such as expensive silver(I) salts.¹⁶

In recent years, electricity has been identified as an increasingly viable, sustainable redox equivalent for environmentally-benign molecular synthesis.^{17,18} While significant advances have been realized by the merger of electrocatalysis with organometallic bond activation,¹⁹ electrochemical carborane functionalizations continue unfortunately to be underdevelopment. In sharp contrast, we have now devised a strategy for unprecedented copper-catalyzed electrochemical cage C–H chalcogenations of *o*-carboranes in a dehydrogenative manner, assembling a variety of C-sulfonylated and C-selenylated *o*-carboranes (Fig. 1a). It is noteworthy that our electrochemical cage C–S/Se modification approach is devoid of chemical oxidants, and does not need any directing groups, operative at room temperature.

We commenced our studies by probing various reaction conditions for the envisioned copper-catalyzed cage C–H thiolation of *o*-carborane in an operationally simple undivided cell setup equipped with a GF (graphite felt) anode and a Pt cathode (Fig. 1b and Table S1†). After extensive experimentation, we observed that the thiolation of substrate **1** proceeded efficiently with catalytic amounts of CuOAc and 2-phenylpyridine, albeit in the presence of 2 equivalents LiOtBu as the base, and 2 equivalents *n*-Bu₄Ni as the electrolyte at room temperature under a constant current of 2 mA (entry 1). The yield was reduced when other copper sources or additives were used (entries 2–5). Surprisingly, *n*-Bu₄NPF₆ as the electrolyte failed to facilitate the

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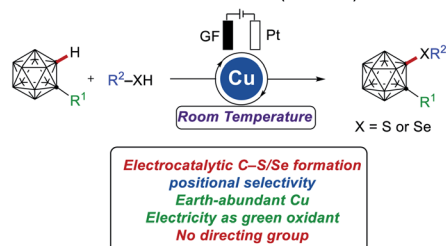
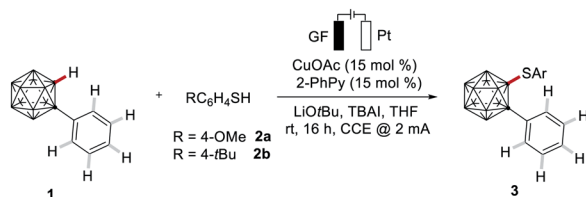
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† Electronic supplementary information (ESI) available. CCDC 2049567 (**3aa**), 2049566 (**3am**), 2049564 (**3ao**), 2065339 (**4br**), 2049565 (**4av**) and 2063919 (**5b**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d1sc02905c

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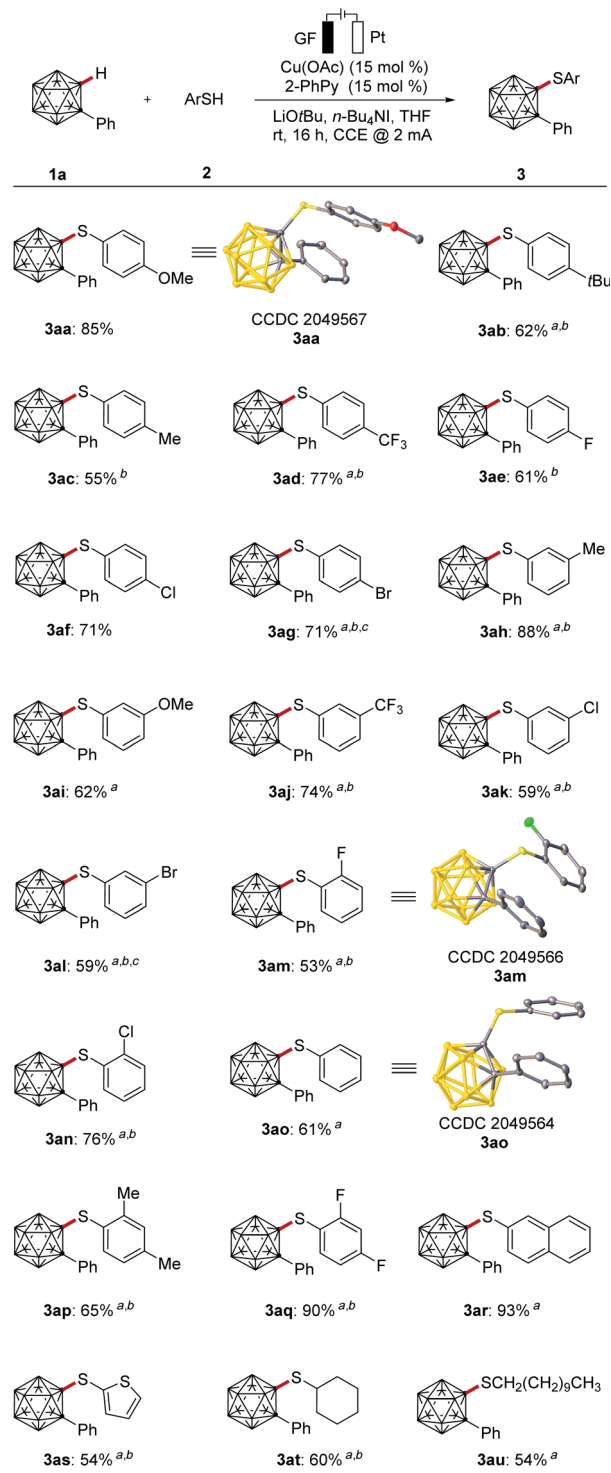


a) Electrochemical diversification of *o*-carboranes (this work)b) Optimization of reaction conditions^a

| Entry | Deviation from standard conditions | Yield [%] ^b |
|-------|---|--------------------------|
| 1 | None | 90% (85%) ^c |
| 2 | Cu(OAc) ₂ instead of CuOAc | 51% |
| 3 | CuI instead of CuOAc | 43% |
| 4 | 2,6-Lutidine instead of 2-PhPy | 71% |
| 5 | 1,10-Phen instead of 2-PhPy | 16% |
| 6 | TBAPF ₆ instead of TBAI | --- |
| 7 | TBAI (3 equiv) | 49% |
| 8 | KI (1 equiv) as additive | 67% |
| 9 | DCE instead of THF | --- |
| 10 | CH ₃ CN instead of THF | 49% |
| 11 | No electricity | 14% ^d |
| 12 | No [Cu] | --- |
| 13 | Procedure B (2b) | 66% (62%) ^{e,d} |
| 14 | Procedure B: second step without electricity (2b) | --- |
| 15 | Procedure B (2a) | 92% ^e |

Fig. 1 Electrochemical diversification of *o*-carboranes and optimization of reaction conditions. ^aReaction conditions: procedure A: **1a** (0.10 mmol), **2a** (0.3 mmol), CuOAc (15 mol%), 2-PhPy (15 mol%), LiOtBu (0.2 mmol), TBAI (2.0 equiv.), solvent (3 mL), platinum cathode (10 mm × 15 mm × 0.25 mm), graphite felt (GF) anode (10 mm × 15 mm × 6 mm), 2 mA, under air, r.t., 16 h. ^bYield was determined by ¹H NMR with CH₂Br₂ as the internal standard. ^cIsolated yields in parenthesis. ^dKI (1.0 equiv.) as additive. ^eProcedure B: **2** (0.3 mmol), LiOtBu (0.2 mmol), TBAI (2.0 equiv.), solvent (3.0 mL), 2 mA, r.t., 3 h, then adding **1a** (0.10 mmol), 2-PhPy (15 mol%), CuOAc (15 mol%), 2 mA, r.t., 16 h. ^f**2b** (0.3 mmol), LiOtBu (0.2 mmol), KI (1.0 equiv.), TBAI (2.0 equiv.), solvent (3.0 mL), 2 mA, r.t., 3 h, then adding **1a** (0.10 mmol), 2-PhPy (15 mol%), CuOAc (15 mol%), r.t., 16 h. TBAI = tetrabutylammonium iodide, TBAPF₆ = tetrabutylammonium hexafluorophosphate. DCE = 1,2-dichloroethane, THF = tetrahydrofuran.

carborane modification, indicating that *n*-Bu₄Ni operates not only as electrolyte, but also as a redox mediator (entry 6). Altering the stoichiometry of the electrolyte or using KI did not improve the performance (entries 7–8). Product formation was not observed, when the reaction was conducted with DCE as the



Scheme 1 Electrochemical C–H thiolation of *o*-carborane **1a**. (a) Procedure A. (b) KI (1 equiv.). (c) CuI as the catalyst.



solvent, while CH₃CN resulted in a drop of the catalytic performance (entries 9–10). Control experiments confirmed the essential role of the electricity and the catalyst (entries 11–12), while a sequential procedure was found to be beneficial (entries 13–15).

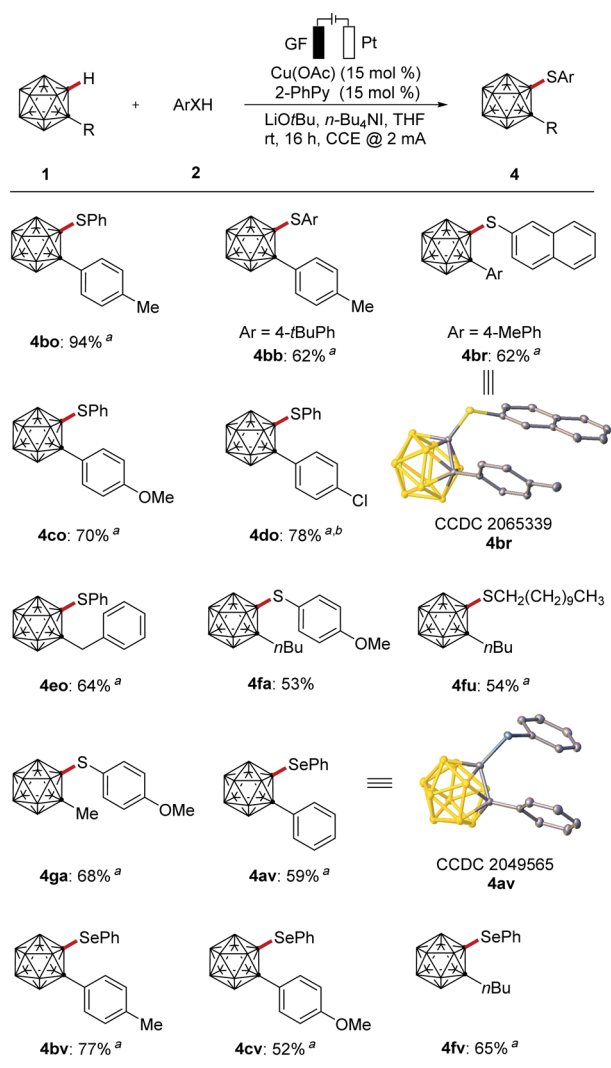
With the optimized reaction conditions in hand, we explored the versatility of the cage C–H thiolation of *o*-carborane **1a** with different thiols **2** (Scheme 1). Electron-rich as well as electron-deficient substituents on the arenes were found to be amenable to the electrocatalyzed C–H activation, providing the corresponding thiolation products **3aa–3ao** in good to excellent yields. Thereby, a variety of synthetically useful functional groups, such as fluoro (**3ae**, **3am**), chloro (**3af**, **3ak**, **3an**) and bromo (**3ag**, **3al**), were fully tolerated, which should prove instrumental for further late-stage manipulations. Various disubstituted aromatic and heterocyclic thiols afforded the corresponding cage C–S modified products **3ap–3as**. Notably, aliphatic thiols efficiently underwent the electrochemical

transformation to provide the corresponding cage alkylthiolated products **3at–3au**. Notably, the halogen-containing thiols (**2e–2f**, **2k–2n** and **2q**) reacted selectively with *o*-carboranes to deliver the desired products without halide coupling byproducts being observed. The connectivity of the products **3aa**, **3am** and **3ao** was unambiguously verified by X-ray single crystal diffraction analysis.²²

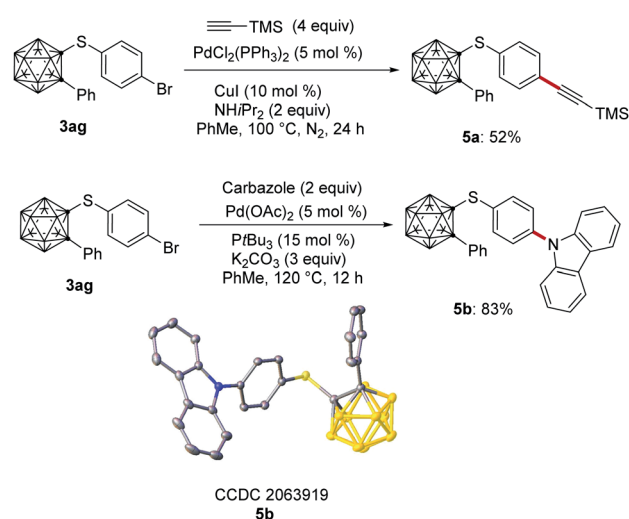
Encouraged by the efficiency of the cupraelectro-oxidative cage C–H thiolation, we became intrigued to explore the chalcogenation of differently-decorated *o*-carboranes **1** (Scheme 2). Electronically diverse carboranes **1** served as competent coupling partners, giving the corresponding thiolation products **4bo–4do** with high levels of efficacy in position-selective manner. The strategy was not restricted to phenyl-substituted *o*-carboranes. Indeed, substrates bearing benzyl and even alkyl groups also performed well to deliver the desired products **4eo–4ga**. It is noteworthy that the C–H activation approach was also compatible with selenols to give the *o*-carboranes **4av–4fv**. The molecular structures of the carborane **4br** and **4av** were unambiguously verified by single-crystal X-ray diffraction.²²

Scaffold functionalization of the thus obtained carborane **3ag** provided the alkynylated derivative **5a** and amine **5b** (Scheme 3), giving access to carborane-based host materials of relevant to phosphorescent organic light-emitting diodes.²⁰

Next, we became attracted to delineating the mode of the cupraelectro-catalyzed cage C–H chalcogenation. To this end, control experiments were performed (Scheme 4a). First, electrocatalysis in the presence of TEMPO or Ph₂C=CH₂ gave the desired product **3aa**. EPR studies of thiol **2a**, LiOtBu and THF under the electrochemical conditions showed a small radical signal, which might be attributed to a thiol radical.²¹ Second, the cupraelectrocatalysis occurred efficiently in the dark. Third, detailed cyclic voltammetric analysis of the thiol and iodide mediator (Scheme 4b and ESI†)²¹ revealed an irreversible oxidation of the thiol anion at $E_p = -0.62$ V vs. Ag/Ag⁺ and two oxidation events for the iodide, including an irreversible oxidation at $E_p = 0.12$ V vs. Ag/Ag⁺ and a reversible oxidation at

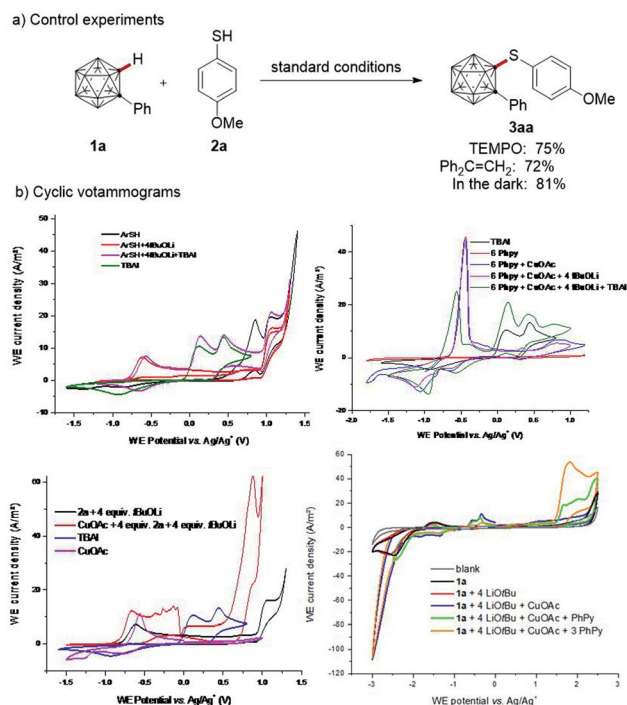


Scheme 2 Electrochemical cage C–H chalcogenation of *o*-carboranes. (a) Procedure B. (b) KI (1 equiv.).



Scheme 3 Late-stage diversification.





Scheme 4 Control experiments and cyclic voltammograms.

$E_p = 0.44$ V vs. Ag/Ag⁺, which is in good agreement with the literature reported iodide oxidation potentials,^{18c,d} and is suggestive of the preferential oxidation of the iodide as a redox mediator. In this context, the use of *n*-Bu₄N⁺I⁻ as a redox mediator to achieve copper-catalyzed electrochemical arene C–H aminations had been documented.^{18d} Furthermore, we calculated the redox potential of complex C by means of DFT calculations at the PW6B95-D4/def2-TZVP + SMD(MeCN)//TPSS-D3BJ/def2-SVP level of theory.²¹ These studies revealed a calculated oxidation half-wave potential for complex C is $E_{1/2}^{o,calc} = -0.08$ V vs. SCE. Hence, iodide is a competent redox mediator to achieve the transformation from complex C to complex D. Analysis of non-covalent interactions²¹ in complex C (Fig. 2) show the presence

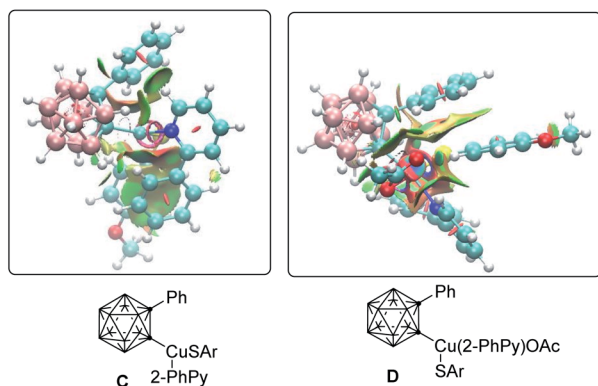
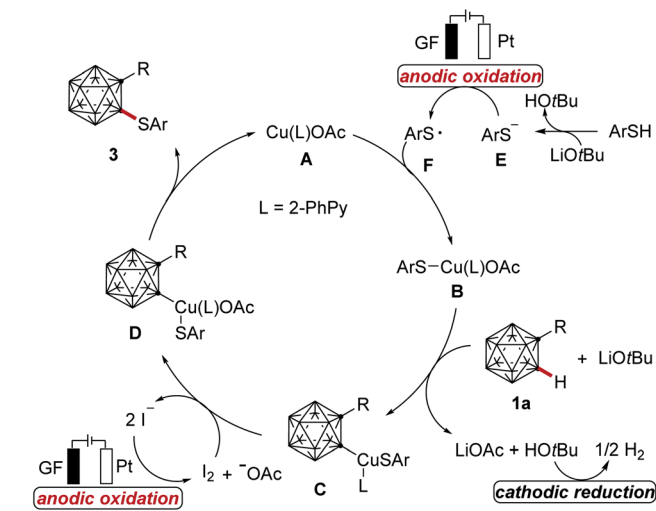


Fig. 2 Non-covalent interaction plots for the complexes C and D. Strong attractive interactions are shown in blue, weak attractive interactions are given in green, while red corresponds to repulsive interactions. Ar = 4-MeOC₆H₄.



Scheme 5 Proposed reaction mechanism.

of a weak stabilization interaction between the chalcogen's anisole group and the 2-phenylpyridine. In contrast, in complex D these interactions were found more relevant between the *o*-carborane phenyl group and the chalcogen aromatic motif.

On the basis of the aforementioned findings,¹⁸ a plausible reaction mechanism is proposed in Scheme 5, which commences with an anodic single electron-transfer (SET) oxidation of the thiol anion E to form the sulfur-centered radical F. Subsequently, the copper(I) species A reacts with the sulfur radical F to deliver copper(II) complex B, which next reacts with *o*-carborane 1 in the presence of LiOtBu to generate a copper(II)-*o*-carborane complex C. Thereafter, the complex C is oxidized by the anodically generated redox mediator I₂ to furnish the copper(III) species D,^{18d} which subsequently undergoes reductive elimination, affording the final product and regenerating the catalytically active complex A. Alternatively, the direct oxidation of copper(II) complex C by electricity to generate copper(III) species D can not be excluded at this stage.^{18a,b}

In conclusion, a sustainable electrocatalytic C–H chalcogenation of *o*-carboranes with thiols and selenols was realized at room temperature by earth abundant copper catalysis. The C–H activation was characterized by mild reaction conditions and high functional group tolerance, leading to the facile assembly of various *o*-carboranes. Thereby, a transformative platform for the design of cage C–S and C–Se *o*-carboranes was established that avoids chemical oxidants by environmentally-sound electricity in the absence of directing groups. A plausible mechanism of paired electrolysis was established by detailed mechanistic studies.

Data availability

All experimental data, procedures for data analysis and pertinent data sets are provided in the ESI.†

Author contributions

L. Y. and L. A. conceived the project. L. Y. and B. B. J. performed the experiments. A. S. performed CV studies. B. Y. performed



DFT calculations. A. C. S. performed EPR studies. L. Y. and L. A. wrote the manuscript. All of the authors discussed the results and contributed to the preparation of the final manuscript.

Conflicts of interest

The authors declare no conflict of interest.

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- 22 Deposition numbers 2049567 (**3aa**), 2049566 (**3am**), 2049564 (**3ao**), 2065339 (**4br**), 2049565 (**4av**) and 2063919 (**5b**) contain the supplementary crystallographic data for this paper.

