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Electrosynthesis

Electrochemical B–H Nitrogenation: Access to Amino Acid and BODIPY-Labeled *nido*-Carboranes

*Long Yang[+], Becky Bongsuiru Jei[+], Alexej Scheremetjew, Rositha Kuniyil, and Lutz Ackermann**

Dedicated to Professor Pierre H. Dixneuf

Abstract: *Electrocatalyzed oxidative B–H nitrogenations of nido-carborane (nido-7,8-$C_2B_9H_{12}^-$) with N-heterocycles have been established, enabling the preparation of various N-substituted nido-carboranes without chemical oxidants or metal catalyst under ambient conditions. The electrolysis manifold occurred with high levels of efficiency as well as chemo- and position- selectivity, employing sustainable electricity as the sole oxidant. The strategy set the stage for a user-friendly access to novel amino acid and fluorogenic boron-dipyrrin (BODIPY)-labeled nido-carborane hybrids.*

Introduction

Carboranes—polyhedral boron-carbon molecular clusters—possess unique properties, such as the icosahedron geometry, enriched boron content and delocalized three-dimensional aromaticity.[1] These features render carboranes valuable building blocks for applications to supramolecular design or nanomaterials,[2] optoelectronics,[3] boron neutron capture therapy (BNCT) agents[4] and organometallic coordination chemistry.[5] As a consequence, a variety of transition metal-catalyzed regioselective B–H functionalization has emerged as a useful tool for the derivatization of *closo*-carboranes.[6] Despite considerable progress, B–H functionalization of *nido*-carborane (7,8-$C_2B_9H_{12}^-$) remain in its infancy.[7] One major challenge is represented by the negatively charged cluster, which prevents the B–H bond from undergoing nucleophilic substitutions. In recent years, nitrogen-containing carboranes have received increasing attention, since they bear major potential in drug discovery[8] as well as catalysis,[9] with key contributions by the groups of Spokoyny,[10] Xie,[11] Teixidor[12] and Yan,[13] among others.[14] Inspite of indisputable advances, oxidative cage B–H functionalizations largely require transition metal catalysts[15] and stoichiometric amounts of chemical oxidants, such as toxic and/or expensive copper(II) or silver(I) salts,[16] which compromises the sustainable nature and generality of this approach.

In recent years, the use of electricity as a redox agent to facilitate chemical reactions has been recognized as an increasingly viable, environmentally-friendly strategy.[17] While significant recent impetus was gained by the merger of electrocatalysis with organometallic C–H activation,[18] electrochemical regioselective cage B–H functionalization continues to be scarce, with one electrochemical thiocyanation of *nido*-carboranes and one very recently reported example of copper-catalyzed electrochemical B–H oxygenation of *o*-carborane.[19] Within our program on sustainable electrochemical bond activation,[20] we have now devised a strategy for unprecedented electrochemical regioselective cage B–H nitrogenation of *nido*-carborane in a dehydrogenative manner, assembling a variety of N-heterocycle-, amino acid- and BODIPY-labeled *nido*-carboranes (Figure 1). Notable features of our findings include 1) electrochemical B–N coupling, 2) effective B–H nitrogenation devoid of chemical oxidants, 3) amino acid- and BODIPY-labeled *nido*-carborane, 4) H_2O as the reactant for hydrogen evolution reaction (HER) and 5) selective B–H nitrogenations with electricity as the sole oxidant.

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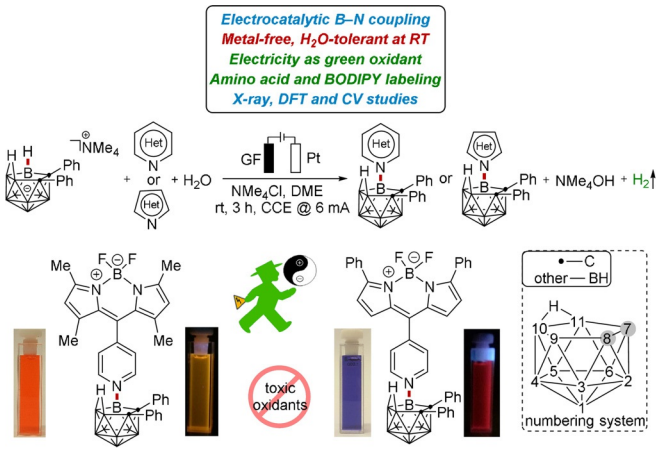


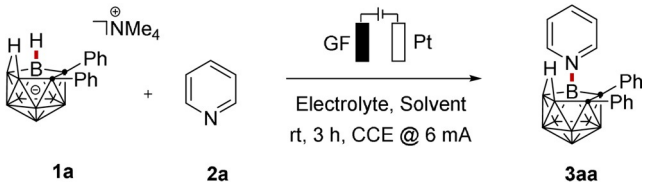
Figure 1. Electrooxidative cage B–H nitrogenation of *nido*-carborane.

Results and Discussion

We initiated our studies by probing various reaction conditions for the envisioned electrochemical-catalyzed B–N coupling of *nido*-carborane **1a** with pyridine **2a** at room temperature in an operationally simple undivided cell setup equipped with a GF (Graphite Felt) anode and a Pt-plate cathode (Table 1 and Table S1). After considerable preliminary experimentation, we were delighted to observe that the desired B-pyridine *nido*-carborane product **3aa** was obtained in 60% yield in DME/H_2O as the reaction medium (entries 1–4). Further electrolyte optimization indicated that NMe_4Cl was best (entries 5–7). Increasing the amount of H_2O to 1 mL led to a significant decrease in the yield (entries 8–9), while reducing it to 0.2 mL increased the efficiency to 83% isolated yield of product **3aa** (entry 10). Control experiments confirmed the essential role of the H_2O, the electricity, the NMe_4Cl additive and the GF anode (entries 11–16).

With the optimized reaction conditions in hand, we probed its versatility for the B–N coupling of *nido*-carboranes **1** with different N-heterocyclic substrates **2** (Scheme 1). Electron-rich as well as electron-deficient groups on the pyridine **2** were amenable to the electrocatalyzed B–H oxidation coupling, providing the corresponding products in good to excellent yields (**3aa**–**3am**). Thereby, a variety of synthetically useful functional groups, such as ester (**3ah**), amide (**3ai**), chloro (**3aj**) and bromo (**3ak**), were fully tolerated, which could prove instrumental for further late-

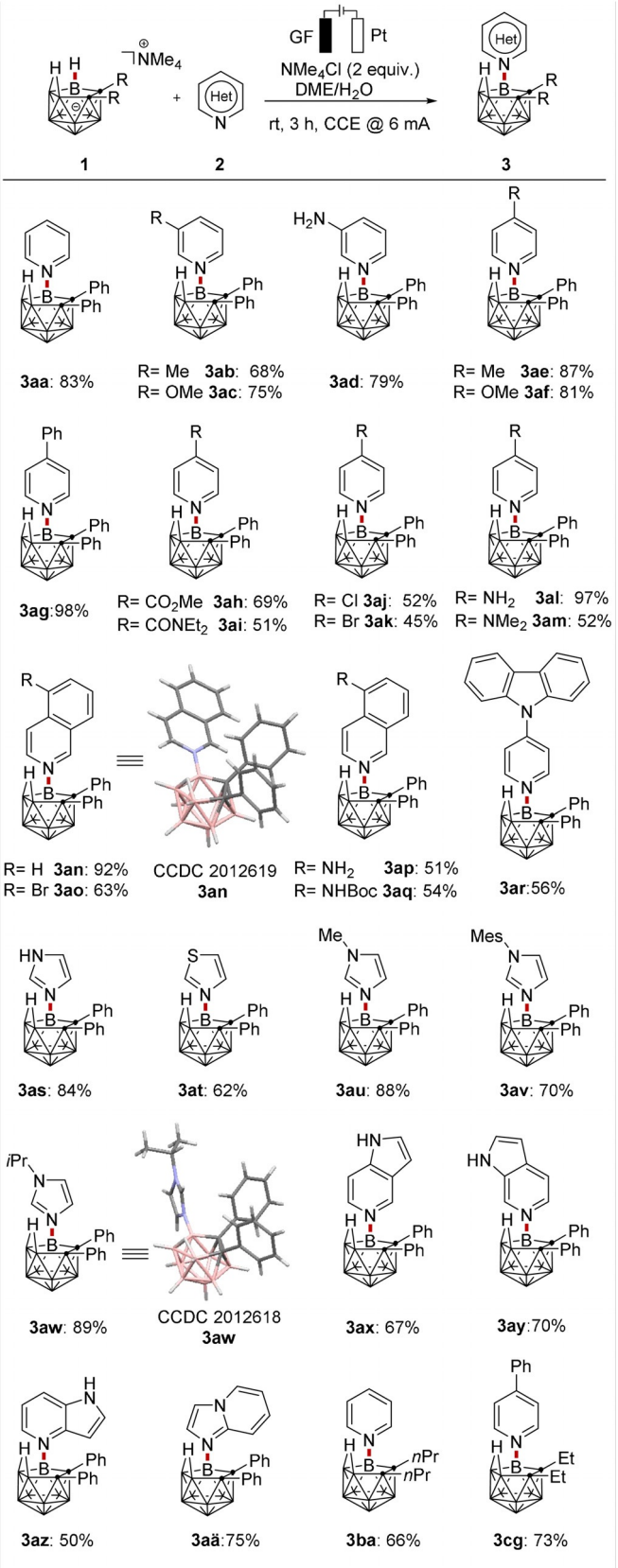
Table 1: Optimization of reaction conditions.[a]



1a **2a** **3aa**

Entry	Electrolyte	Solvent	Yield [%][b]
1	–	MeOH/H_2O	8%[c]
2	–	THF/H_2O	36%[c]
3	–	CH_3CN/H_2O	40%[c]
4	–	DME/H_2O	60%[c]
5	$nBuNPF_6$	DME/H_2O	20%[c]
6	$nBuNBF_4$	DME/H_2O	63%[c]
7	NMe_4Cl	DME/H_2O	65%[c]
8	NMe_4Cl	DME/H_2O	32%[d]
9	NMe_4Cl	DME/H_2O	50%[e]
10	**NMe_4Cl**	**DME/H_2O**	**87% (83%)[f]**
11	NMe_4Cl	DME	10%
12	NMe_4Cl	DME/H_2O	–[g]
13	–	DME/H_2O	67%
14	KCl	DME/H_2O	75%
15	NaCl	DME/H_2O	70%
16	NMe_4Cl	DME/H_2O	73%[h]

[a] Reaction conditions: **1a** (0.10 mmol), **2a** (0.30 mmol), electrolyte (2 equiv.), DME (4.0 mL), H_2O (0.2 mL), 25 °C, 3 h. [b] Yield was determined by ^1H NMR with CH_2Br_2 as the standard. [c] H_2O (0.5 mL). [d] H_2O (1.0 mL). [e] DME (5.0 mL), H_2O (1.0 mL). [f] Isolated yields in parenthesis. [g] No electricity. [h] Pt-plate as anode. DME = 1,2-Dimethoxyethane, THF = Tetrahydrofuran.



Scheme 1. Electrooxidative B–H nitrogenation of *nido*-carborane **1** with N-heterocycles **2**.

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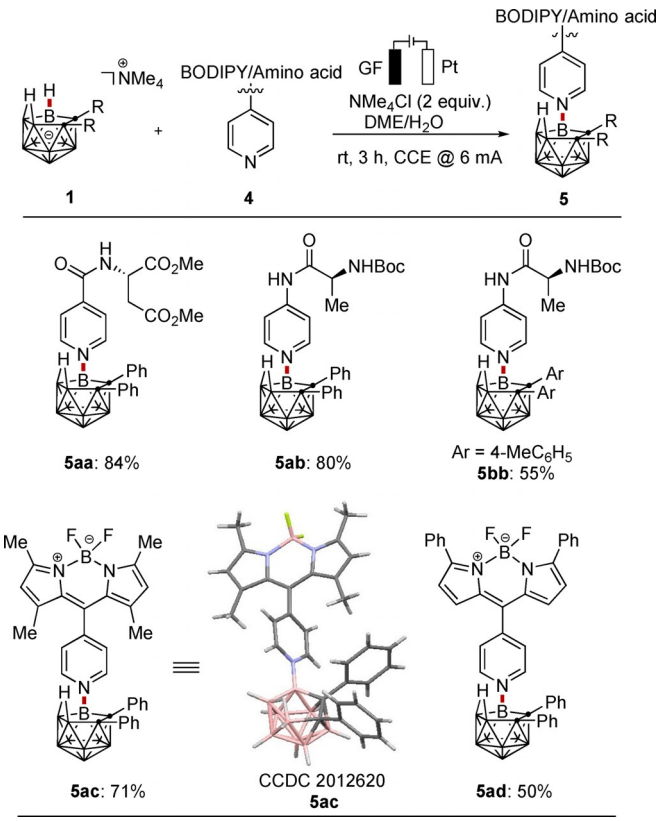
stage manipulations. In addition, various isoquinolines (**2n**–**2q**) and even the carbazole-substituted pyridine (**2r**), afforded the corresponding electro-oxidative B–N coupling product in good to excellent yields (**3an**–**3ar**). Notably, the free NH_2-amino group (**2d**, **2l**) was also tolerated under the mild electro-oxidative conditions, athough the amine-substituted and *Boc*-protected amino isoquinoline products (**3ap**–**3aq**) were isolated in somewhat lower yields. Interestingly, the Steglich catalyst 4-dimethylaminopyridine (DMAP) was also a competent pyridine derivative in the electrochemical reaction, providing the DMAP decorated *nido*-carborane product (**3am**) with good efficacy.

The robustness of the electrocatalyzed B–N bond formation at room temperature was next evaluated by other N-heterocyclic substrates, such as imidazole with $N = 11.47$ in MeCN according to Mayr's scale,[21] N-substituted derivatives of imidazoles, thiazole and azaindoles, giving the corresponding B–N products in good to excellent yields (**3as**–**3aä**). In addition, dialkyl substituted *nido*-carboranes also efficiently underwent the electrochemical transformation to provide the corresponding B–N coupling products **3ba**–**3cg**. Thus, the oxidant- and catalyst-free electrochemical oxidative B–N coupling provides a new route to a convenient and versatile synthesis of N-heterocycle-substituted *nido*-carboranes. The connectivity of the products (**3an** and **3aw**) was unambiguously verified by X-ray single crystal diffraction analysis.[23]

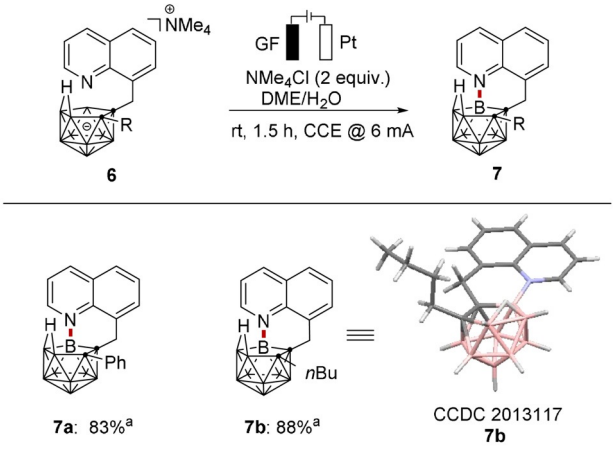
Encouraged by the unique efficiency of the electrocatalyzed metal-free B–N oxidative coupling with various N-heterocyclic substrates, we became intrigued to explore the late-stage amino acid and BODIPY diversification of structurally complex *nido*-carboranes (Scheme 2). Both amino acid- and BODIPY-labeled pyridine proved to be suitable substrates (**5aa**–**5ad**).

The strategy was not restricted to intermolecular transformations. Indeed, the intramolecular B–N couplings of *nido*-carborane **6** was likewise accomplished (Scheme 3), and either aryl or alkyl substituents at the cage-carbon site afforded comparable results (**7a**–**7b**). Moreover, the molecular structure of the products (**5ac** and **7b**) was again unambiguously verified by single-crystal X-ray diffraction.[23]

The high efficacy of the electrocatalyzed B–H activation for the synthesis of N-heterocyclic *nido*-carboranes motivated us to delineate its mode of action. To this end, an intermolecular competition experiment between pyridine and imidazole revealed a slight preference for pyridine, likely due to the higher nucleophilicity of pyridine when compared to imidazole (pyridine: $N = 11.05$ in H_2O, imidazole: $N = 9.63$ in H_2O)[21] (Scheme 4). Furthermore, we probed the electrochemical B–H activation by means of cyclovoltammetric analysis of the *nido*-carborane (Figure 2). Thus, we observed an irreversible oxidation of the *nido*-carborane at $E_{p/2} = 0.56$ V vs. Ag/Ag^+ at ambient temperature, which is indicative of a direct oxidation of the *nido*-carborane under electrochemical condition. Furthermore, the calculated half-wave oxidation potential of **1a** using DFT computation at the B97D3/def2-QZVP + CPCM(DME)//B97D3/def2-TZVP level of theory is in good agreement with the one obtained by our CV studies (exp: $E_{p/2} = 0.87$ V vs. SCE, calc: $E_{1/2} = 0.86$ V vs. SCE).[22] Subsequently, we analyzed the thermal and



Scheme 2. Electrooxidative B–N nitrogenation with amino acids and BODIPY pyridines.



Scheme 3. Electrooxidative intramolecular B–N annulation of **6**.

chemical stability of product **3aa**. Thus, we found that compound **3aa** (0.4 mL [D_6]DMSO) was rather stable, when being heated to 120 °C for 10 h with only minor decomposition. Likewise, a solution of product **3aa** featured excellent stability in aqueous media as judged by ^{11}B NMR spectroscopy, while showing reduced stability in strongly acidic or alkaline environments (SI Figure S1–S5).

The optical properties of the thus-obtained novel BODIPY-labeled *nido*-carborane **5ac** and **5ad** were studied in detail by UV/Vis absorption and fluorescence spectroscopy in

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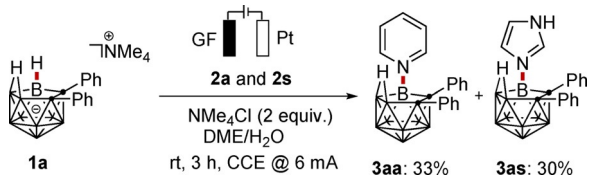


Scheme 4. Competition experiments.

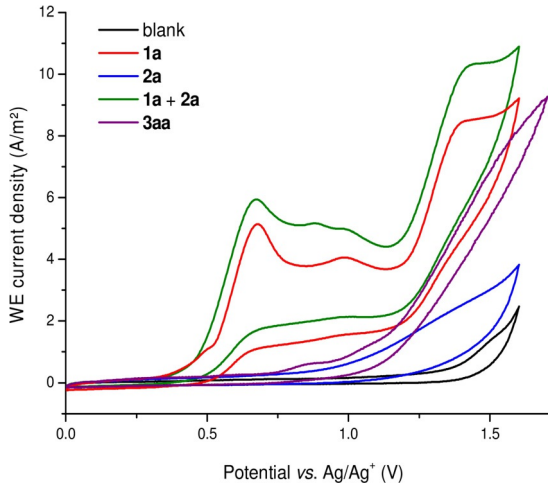


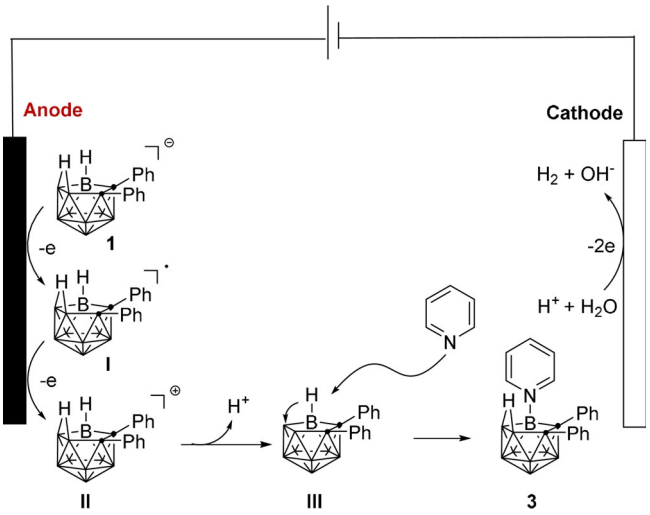
Figure 2. Cyclic voltammograms at 100 mVs^{-1}, nBu_4NPF_6 (0.1 M in DME), concentration of substrates 1 mM.

various solvents (Table 2). The unprecedented BODIPY-labeled *nido*-carboranes exhibited very intense absorption in the UV and visible region, with an absorption maxima between 507–582 nm and high Stokes shift, resulting in an intense red to purple color. This could be rationalized by a possible donor-acceptor-donor structure of the compounds **5ac** and **5ad**, with the *nido*-carborane core being a considerable electron acceptor. These spectroscopic data indicated the unique potential applications of the BODIPY-labeled *nido*-carborane compounds in pharmaceuticals, luminescent materials and bioimaging.

Based on DFT, CV studies and literature reports,[13] a plausible reaction mechanism is proposed in Scheme 5,

Table 2: Spectroscopic data of BODIPY-labelled *nido*-carborane **5ac** and **5ad**.

Compd	Solvent	$^{Max}\lambda_{abs}$ [nm]	$^{Max}\lambda_{em}$ [nm]	Stokes shift [cm^{-1}]	ε_{max} [M^{-1} cm^{-1}]
5ac	DCM	512	569	1956	68812
	$CHCl_3$	513	567	1856	69790
	Actone	507	559	1834	73746
	DMF	509	561	1821	69557
	THF	509	562	1852	72549
5ad	DCM	577	634	1558	63459
	$CHCl_3$	582	640	1557	60882
	Actone	570	623	1492	65681
	DMF	574	602	810	58557
	THF	575	630	1518	67718



Scheme 5. Proposed reaction mechanism.

which commences with an anodic single electron-transfer (SET) process from *nido*-carborane ainon to form intermediate **I**, followed by the oxidation to generate intermediate **II**. Subsequently, deprotonation of the bridge proton results in the formation of cage-open carborane intermediate **III**. Finally, the pyridine undergoes nucleophilic attack on the electron deficient B(9/11)-H site of the intermediate **III** with consecutive transfer of H to the B(10) and B(11) forming a new bridge proton. In addition, molecular H_2 is generated as the by-product through cathodic proton reduction, which was confirmed by head-space GC analysis.[22]

Conclusion

In summary, reagent and catalyst-free electrocatalyzed direct B–N oxidative couplings of *nido*-carborane with N-heterocyclic compound have been achieved at room temperature with molecular hydrogen as the sole by-product. This approach features mild reaction conditions and high tolerance of functional groups leading to various amino acid- and BODIPY-labeled *nido*-carboranes, thereby offering a new platform for the design and synthesis of N-substituted *nido*-carborane by environmentally-benign electricity. A plausible mechanism was established by cyclic voltammetry studies and computation. The thus-obtained BODIPY-labeled *nido*-carborane displayed improved spectroscopic features.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: B-H nitrogenation · electrochemistry · *nido*-carborane · regioselective · room temperature

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[22] For detailed information, see the Supporting Information.

[23] Deposition numbers 2012618 (**3aw**), 2012619 (**3an**), 2012620 (**5ac**) and 2013117 (**7b**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.

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