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Communication

Electrochemical Borylation of Alkyl Halides: Fast, Scalable Access to Alkyl Boronic Esters

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ABSTRACT: Herein, a fast, scalable, and transition-metal-free borylation of alkyl halides (X = I, Br, Cl) enabled by electroreduction is reported. This process provides an efficient and practical access to primary, secondary, and tertiary boronic esters at a high current. More than 70 examples, including the late-stage borylation of natural products and drug derivatives, are furnished at room temperature, thereby demonstrating the broad utility and functional-group tolerance of this protocol. Mechanistic studies disclosed that B_2cat_2 serves as both a reagent and a cathodic mediator, enabling electroreduction of difficult-to-reduce alkyl bromides or chlorides at a low potential.

Alkylboron compounds are highly important synthetic precursors that can readily be transformed to incorporate a wide range of valuable functional groups; these borylated compounds are extensively used in fields such as materials science and medicinal chemistry.[1] In recent decades, transition-metal catalyzed and photoinduced borylation of alkyl halides has emerged as a versatile approach for the synthesis of alkylboron compounds.[2] However, each of these strategies relies mostly on transition-metal catalysts, ligands, stoichiometric quantities of activators, and/or long reaction times.[2] Therefore, the development of simpler, milder, and more efficient approaches to the synthesis of alkylboron compounds is desirable.

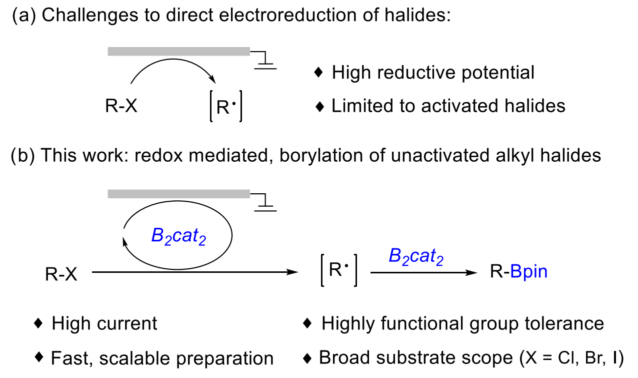

Figure 1. Electroreduction of alkyl halides.

Electrochemistry, in which an electron is utilized as a sustainable and inherently safe redox reagent, represents an environmentally benign method in organic synthesis.[3] Moreover, energetic chemical reductants, transition-metal catalysts, and ligands that preclude large-scale synthesis can be eliminated from electrochemical reactions. Therefore, direct electrochemical borylation of unactivated alkyl halides should provide a practical and appealing pathway for the construction of alkylboron compounds.[4] Notably, metal-catalyzed hydroboration of alkenes is one of the most important methods for preparing organoboranes;[5] in comparison, electrochemical borylation of alkyl halides features *ipso*-selectivity as well as transition-metal-free and sustainable conditions. However,

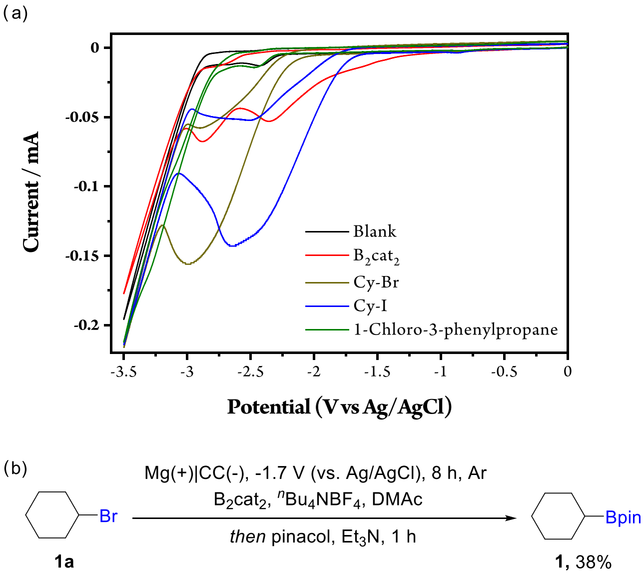

Figure 2. (a) CV experiments for different alkyl halides. (b) Preliminary investigation.

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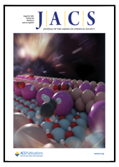

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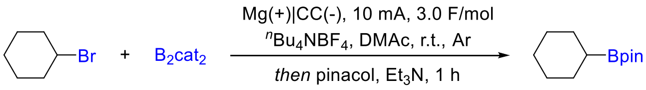
Table 1. Optimization of the Reaction Conditions[a]



1a **1**

Entry	Variation from conditions	Yield (%)[b]
1	none	83
2	MeCN	59
3	**150 mA**	**82**
4	200 mA	77
5	150 mA, under air	80
6	H_2O (1.0 equiv)	64
7	Entry 3 without electricity	n.d.

[a] CyBr (0.6 mmol), B_2cat_2 (4.0 equiv), $^nBu_4NBF_4$ (0.3 mmol), DMAc (6.0 mL), n.d. = not detected. [b] GC yields using biphenyl as an internal standard.

unactivated alkyl halides, especially the bromides and chlorides, are unreactive and difficult to reduce. To date, electroreduction of unactivated alkyl halides has rarely been explored (Figure 1a).[6]

Mediators serve crucial roles in enhancing reaction efficiency, controlling reaction selectivity, and avoiding over-reduction of products and electrode passivation.[3,7] Accordingly, we conceived that the above-mentioned challenges may be circumvented through a mediator-assisted strategy. With respect to this point, boron compounds, such as B_2cat_2, which not only constitutes vacant p-orbital on the boron atom for accepting electrons but also possesses good stability, might offer such an opportunity.[7,8] Of note, B_2cat_2 is also a readily available boron source, and it can efficiently trap the carbon-centered radical generated from the reduction of alkyl halides,[2k,n,o] thus offering a new channel for the preparation of alkylboron compounds (Figure 1b).

To probe the feasibility of our proposed assumption, cyclic voltammetry (CV) experiments were first conducted. Clearly, the onset potential for B_2cat_2 reduction is approximately −1.3 V (Figure 2a). This potential is significantly more positive than the onset potential needed for the reduction of alkyl halides; for example, the onset reductive potentials for CyI, CyBr, and 1-chloro-3-phenylpropane are around −1.65 V, − 2.1 V, and −2.6 V, respectively. Furthermore, a controlled potential experiment showed that alkylboron product **1** was obtained in 38% yield when the potential of the working cathode was set to −1.7 V (Figure 2b). Notably, the potential selected for this experiment is more positive than the potential needed for the reduction of CyBr but is sufficient to directly reduce B_2cat_2. These results show that the reduction of B_2cat_2 occurs

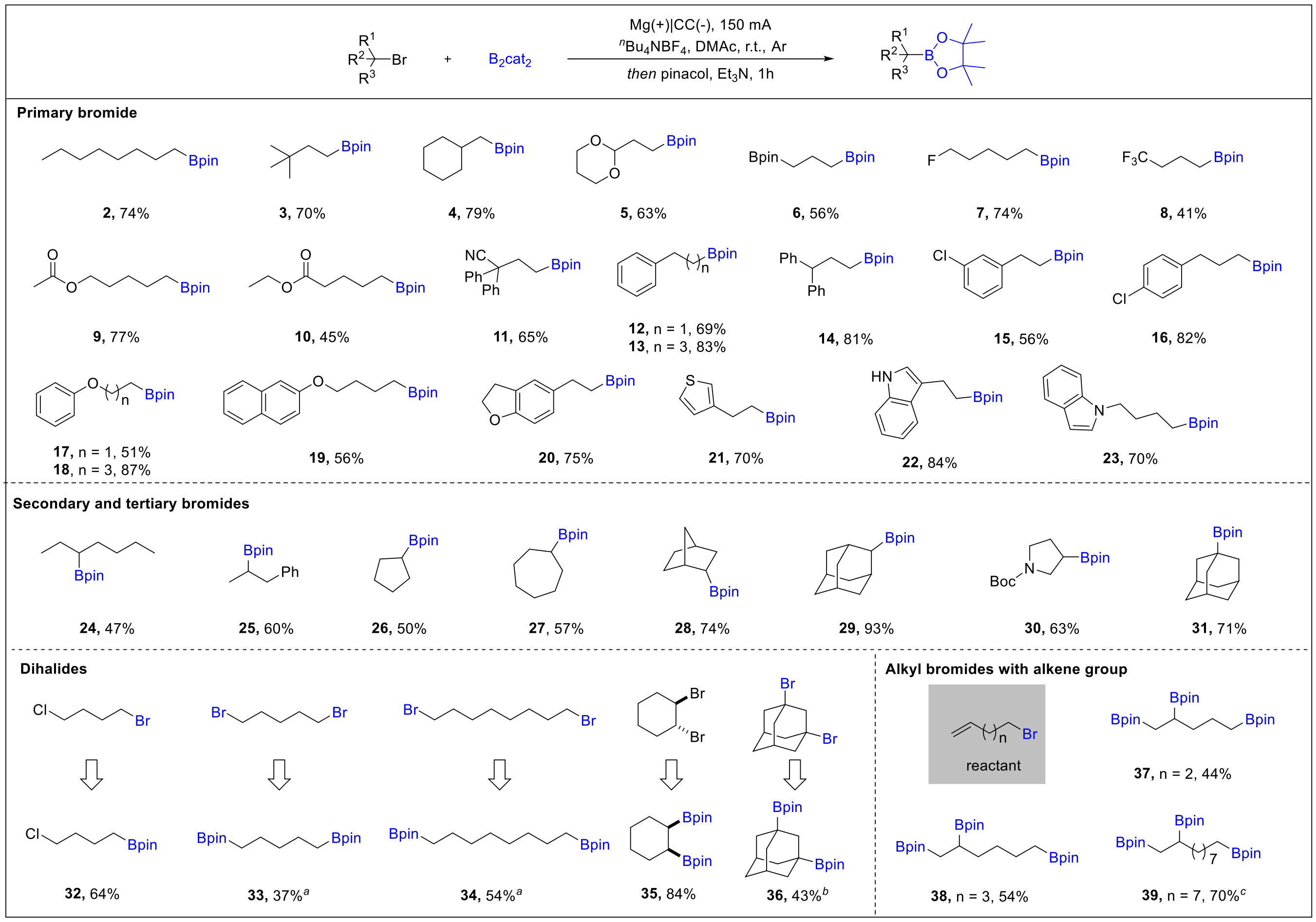


Figure 3. Reaction conditions: alkyl bromide (0.6 mmol), B_2cat_2 (4.0 equiv), $^nBu_4NBF_4$ (0.3 mmol), DMAc (6.0 mL), Mg plate anode and carbon cloth cathode, undivided cell, constant current I = 150 mA, 3.0 F/mol, 19 min, room temperature; pinacol (8.0 equiv), Et_3N (1.5 mL), 1 h. Isolated yields are reported. [a] B_2cat_2 (8.0 equiv), 7.0 F, 45 min; pinacol (16.0 equiv), Et_3N (1.5 mL), 1 h. [b] B_2cat_2 (8.0 equiv), 3.0 F, 19 min; pinacol (16.0 equiv), Et_3N (1.5 mL), 1 h. [c] 4.0 F, 25 min, 150 mA.

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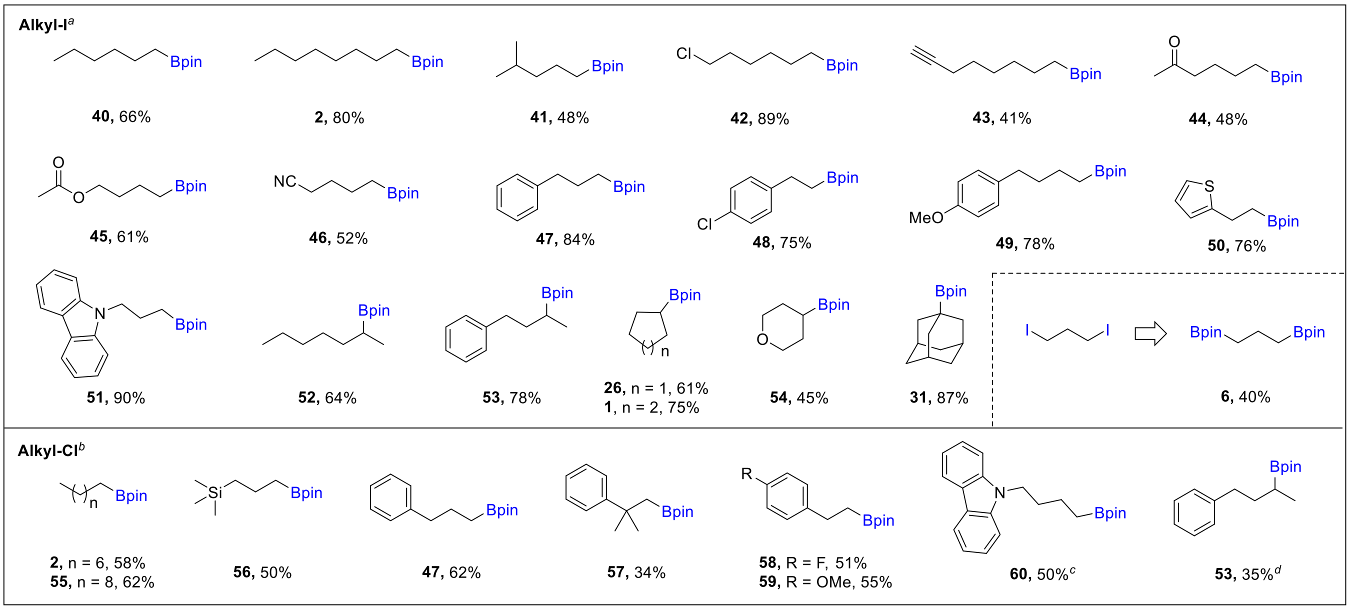

Figure 4. ^a Reaction conditions: alkyl iodides (0.6 mmol), B_2cat_2 (4.0 equiv), $^nBu_4NBF_4$ (0.3 mmol), DMF (6.0 mL), Mg plate anode and carbon cloth cathode, undivided cell, constant current $I = 200$ mA, 2.5 F/mol, 12 min, room temperature; pinacol (8.0 equiv), Et_3N (1.5 mL), 1 h. Isolated yields are reported. ^b Reaction conditions: alkyl chloride (0.6 mmol), B_2cat_2 (4.0 equiv), $LiClO_4$ (0.3 mmol), DMAc:TPPA (3:1, 6.0 mL), Mg plate anode and carbon cloth cathode, undivided cell, constant current $I = 60$ mA, 4.0 F/mol, 64 min, room temperature; pinacol (8.0 equiv), Et_3N (1.5 mL), 1 h. Isolated yields are reported. ^c 30 mA, 128 min. ^d 20 mA, 193 min.

preferentially, which could mediate electron transfer between the cathode and alkyl halides.

Subsequently, after extensive evaluation of key parameters including solvent, electrode, and electrolyte, we discovered that the desired alkylboron product **1** can be obtained in 83% yield using magnesium as the anode and carbon cloth as the cathode (Table 1, entry 1). The cell voltage in this condition is only around 1.1 V, which implies that a higher current can be applied for this electroreductive process. We found that the current can increase even further, from 10 mA to 200 mA, with only a slight reduction in the product yield (entries 3 and 4), highlighting the efficient electron transfer between the cathode and substrate. Even so, cathodic electron transfer is still the rate-determining step under these conditions. This reaction could also work well when open to the air (cap removed, entry 5); however, water has a detrimental impact on the reaction efficiency (entry 6). Finally, electricity was proved to be essential for this transformation, as no product was detected in its absence (entry 7). As high current densities are particularly important for chemical throughput, therefore, this method provides a fast and practical approach for the synthesis of alkylborons.

With the optimized reaction conditions in hand, the scope of alkyl bromides was investigated. As shown in Figure 3, a wide range of primary, secondary, and tertiary alkyl bromides were viable in this reaction, furnishing the desired alkyl boronic esters (**1**−**31**) in moderate to excellent yields. Of note, a broad range of functional groups, including acetal (**5**), boronate ester (**6**), halides (**7**, **15**, **16**), trifluoromethyl group (**8**), esters (**9**, **10**), cyanide (**11**), arenes and heterocycles (**11**−**23**), ethers (**17**−**20**), and carbamate (**30**), were all compatible with this transformation, which demonstrates the robustness of this electrochemical protocol. Both monocyclic and polycyclic bromides were also transformed efficiently into alkyl boronic esters in good yields (**26**−**31**). Notably, the highly chemoselective borylation of an alkyl bromide in the presence of a chloride was obtained (**32**). Additionally, Polyboron compounds have emerged as versatile reagents, but straightforward approaches to their synthesis are limited.[9] We describe herein the preparation of various diborylated and triborylated compounds by employing dibromides or alkene-bearing monobromides (**33**−**39**), respectively.

We next extended this borylation reaction to alkyl iodides. This electroreductive borylation occurs with a high preference for the C−I bond in the presence of various reducible functional groups, including chloro- (**42**), alkynyl- (**43**), ketone- (**44**), ester- (**45**), and nitrile- (**46**) (Figure 4); the corresponding products were isolated in moderate to excellent yields (41%−89% yields). The representative heterocycles thiophene and carbazole, which usually are sensitive to oxidative conditions, remained intact after reaction, affording the desired products **50** and **51** in 76% and 90% yield, respectively. Cyclic and acyclic secondary iodides were borylated in 45%−78% yields (**1**, **26**, **52**−**54**). Tertiary alkyl iodides were also amenable to this protocol, as exemplified by 1-iodoadamantane, which gave product **31** in 87% yield. As an example of the application of the protocol to diiodides, 1,3-diiodopropane delivered the diborylated product **6** in 40% yield.

Encouraged by these results, we further attempted to apply our developed approach to unactivated alkyl chlorides. More inert and challenging unactivated alkyl chlorides could also be boronated in acceptable yields (**55**−**60**). Silyl groups (**56**), aryl fluoride (**58**), aryl ether (**59**), and carbazole (**60**) examples were well tolerated. Compared with bromides and iodides, organochlorides offer the following advantages: (1) abundant and diverse structures in both commercial and natural sources; (2) reduced toxicity compared with most available electrophiles; (3) low sourcing and production costs on a large scale; and (4) reasonable chemical stability in multistep sequences.[10]

The synthetic application of our developed method was further demonstrated by the late-stage borylation of a series of

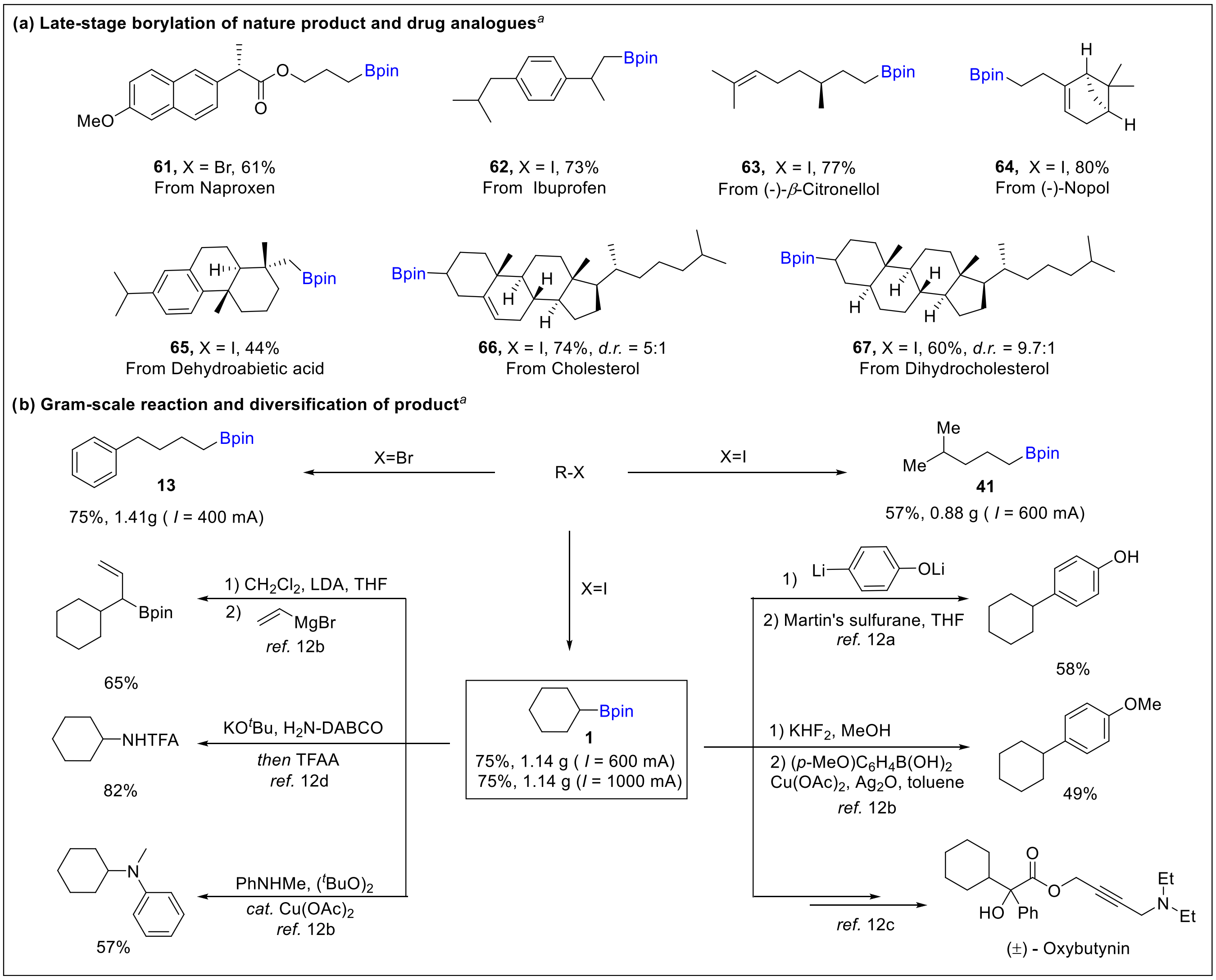

Figure 5. (a) Late-stage borylation of natural products and drug analogues. (b) Gram-scale reactions and diversity of products. ^{a}For details, please see the Supporting Information.

natural products and pharmaceutical derivatives (Figure 5a). Naproxen and ibuprofen, which are nonsteroidal anti-inflammatory drugs commonly used for the reduction of pain and inflammation, produced the borylated compounds **61** and **62** in 61% and 73% yields, respectively. (−)-*β*-Citronellol, (−)-nopol, dehydroabietic acid, cholesterol, and dehydrocholesterol were all successfully borylated in 44%−80% yields (**63**−**67**). Furthermore, this electroreductive borylation could readily be scaled up to gram quantities with high efficiency. For example, 1.41 g of the alkylboronic ester **13** was isolated in 75% yield from its bromide. The alkylboronic ester **41**, a key intermediate in the synthesis of the natural product 7-deoxy-7,14-didehydrosydonol,[11] was prepared on a 7.2 mmol scale with 57% yield from 1-iodo-4-methylpentane. The cyclohexylboronate ester **1** was synthesized efficiently from cyclohexyl iodide at a high current up to 1000 mA on a gram scale. The C−B bond in **1** can be further transformed into various C−C bonds, C−O bonds, and C−N bonds, as in previous reports (Figure 5b).[12]

To gain insight into the reaction mechanism, a series of experiments were conducted. A radical clock experiment supported the radical mechanism, as the borylated ring-opening product **68** was isolated as the major product (Figure 6a). Comparing the ^{11}B NMR spectrum of B_2cat_2 in $CDCl_3$ with that in a mixed-solvent system of DMAc and $CDCl_3$ reveals that the presence of DMAc led to a chemical shift from 31.0 ppm (a single signal) to 27.6 ppm (a broad signal; for details, please see the Supporting Information), illustrating the existence of ligated diboron.[13]

On the basis of our results and previous studies,[2,13] a plausible mechanism as exemplified for the reaction of alkyl bromides and B_2cat_2 is depicted in Figure 6b. The reaction begins with a single-electron reduction of B_2cat_2 to generate the B_2cat_2 radical anion **II**, which further helps mediate the reduction of the alkyl bromide to generate an alkyl radical. The calculated reaction free energy suggests that the electron transfer between **II** and cyclohexyl bromide (**1a**) is thermodynamically feasible ($\Delta G_{rxn} = -22.4$ kcal/mol, Figure 6b). The alkyl radical generated through the halogen atom transfer mechanism is also possible.[14] Afterward, there are two possible ways for the further transformation of the alkyl radical. In path a, the alkyl radical reacts with complex **I**, affording an alkyl boronate ester, and the DMAc-stabilized boryl radical **III**/**IV**, which could either reduce alkyl halides and initiate a

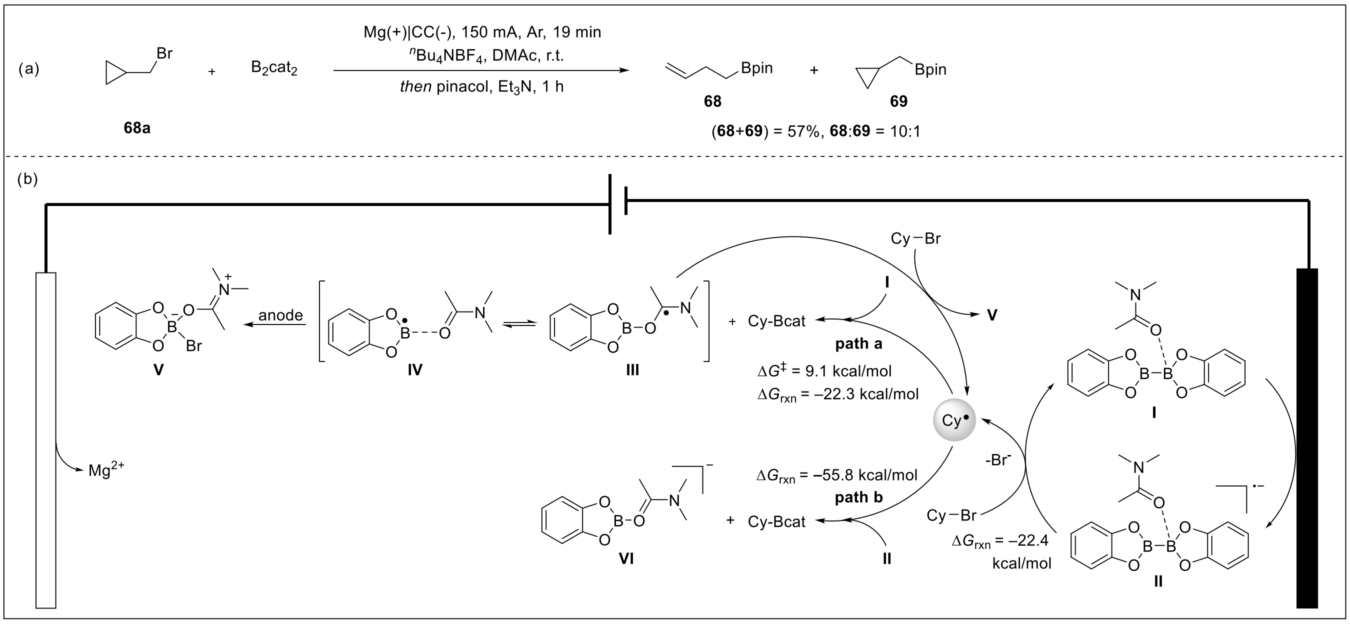

Figure 6. (a) Radical clock experiment. (b) Proposed possible mechanism.

slow radical chain process to regenerate the alkyl radical or be oxidized on the anode to form complex **V** eventually. In path b, the alkyl radical reacts with intermediate **II** through radical−radical cross-coupling, furnishing alkyl boronate esters, and complex **VI**, which might be further stabilized by the metal cation generated from anode.[15] Herein, density functional theory (DFT) calculations suggest that path a requires an activation free energy of 9.1 kcal/mol and is exergonic by 22.3 kcal/mol, whereas the radical−radical cross-coupling step in path b is barrier-less and highly exergonic (ΔG_{rxn} = −55.8 kcal/mol, for details; see the Supporting Information). These kinetic and thermodynamic characteristics imply that this borylation reaction occurs rapidly through path b.

In conclusion, an electrochemical borylation of unactivated alkyl halides at high current was reported for the first time, which provides a general and practical method for the preparation of primary, secondary, and tertiary alkyl boronic esters in good to excellent yields with a good tolerance for a broad range of functional groups. The particularly unusual feature of this transformation is that B_2cat_2 is reduced preferentially at the cathode, which further mediates the reduction of alkyl halides.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.1c06473.

> Experimental procedure, characterization data, and copies of ^1H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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(15) Boryl anion **VI** is speculated to be stabilized by combining with anode-generated Mg^{2+}; DFT calculations support that this process is highly exergonic. For details, please see the Supporting Information.