

# Electrochemically Driven Cross-Electrophile Coupling of Alkyl Halides

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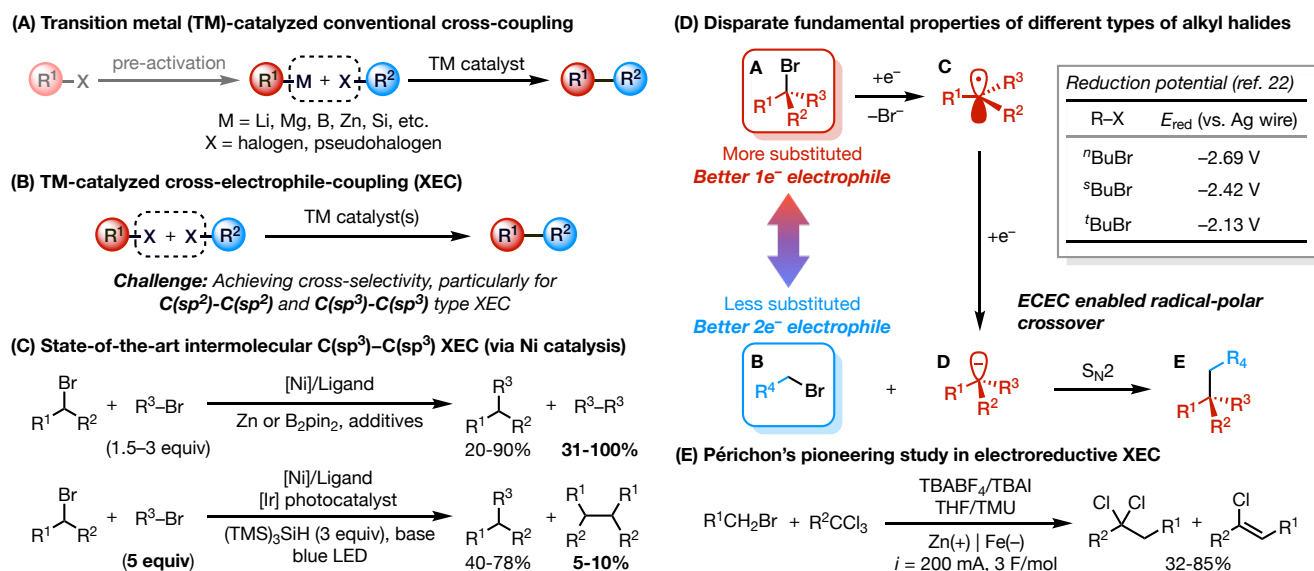
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**Abstract:** Recent research in medicinal chemistry suggests a correlation between an increase in the fraction of  $sp^3$  carbons in drug candidates with their improved success rate in clinical trials<sup>1</sup>. As such, the development of robust and selective methods for the construction of  $C(sp^3)-C(sp^3)$  bonds remains a critical problem in modern organic chemistry<sup>2</sup>. Owing to the broad availability and synthetic accessibility of alkyl halides, their direct cross coupling—commonly known as cross-electrophile coupling (XEC)—provides a promising route toward this objective<sup>3,4,5</sup>. However, achieving high selectivity in  $C(sp^3)-C(sp^3)$  XEC remains a largely unmet challenge. Herein, we employ electrochemistry to achieve the differential activation of alkyl halides by exploiting their disparate electronic and steric properties. Specifically, the selective cathodic reduction of a more substituted alkyl halide gives rise to a carbanion, which undergoes preferential coupling with a less substituted alkyl halide via bimolecular nucleophilic substitution ( $S_N2$ ) to forge a new C–C bond. This transition-metal free protocol enables the efficient XEC of a variety of functionalized and unactivated alkyl electrophiles and exhibits substantially improved chemoselectivity versus existing methodologies.

Transition-metal catalyzed cross-coupling represents one of the most reliable approaches toward the formation of C–C bonds in organic synthesis<sup>6</sup>. These transformations typically involve the coupling between an electrophilic organohalide and a nucleophilic organometallic agent (e.g., organomagnesium, organozinc, or organoboron), the latter of which is often prepared from the corresponding organohalide (Figure. 1A). Due to the inherent limitations associated with the use of preformed carbon nucleophiles, reaction methods that cross-couple two different carbon electrophiles (e.g., two organohalides)—commonly known as cross-electrophile coupling (XEC)—represent an attractive alternative to the canonical cross coupling<sup>3,4,5</sup> (Figure. 1B). In fact, the development of Cu-mediated homocoupling between aryl halides dates back to the early 1900s. Recent advances have enabled selective XEC of two organohalides with distinct carbon hybridization states (e.g.,  $sp^2-sp^3$ ) by using transition-metal catalysts that exhibit different reactivity towards each electrophile<sup>7,8,9</sup>. In contrast, the selective coupling of electrophiles with same hybridization states remains a significant challenge. Recently, Weix reported an elegant bimetallic strategy to successfully address the XEC between two aryl electrophiles<sup>10</sup>. Nonetheless, a highly selective and broadly applicable protocol for the  $C(sp^3)-C(sp^3)$  XEC remains elusive<sup>11,12,13</sup>. With the use of Ni catalysis, the Gong and MacMillan groups have independently provided a critical first step toward solving this synthetic problem<sup>14,15,16</sup> (Figure. 1C). In these systems, however, the reliance on a Ni catalyst imparts innate limitations. For example, competing homocoupling remains a major competitive pathway even when one of the coupling partners is used in large excess; this observation has been attributed to the similar reactivity of Ni toward different types of alkyl halides<sup>17</sup>. Furthermore, tertiary electrophiles have rarely been shown to be compatible with existing protocols,<sup>18,19</sup> due to various undesired side reactions such as protodehalogenation and elimination.<sup>20</sup>

One of the most well-established methods for the construction of  $C(sp^3)-C(sp^3)$  bonds is the  $S_N2$  reaction<sup>21</sup>. In such a reaction, a carbanion equivalent in the form of an organometallic reagent (e.g., Grignard or organocuprate reagents) reacts directly with an alkyl electrophile via bimolecular substitution to form a new  $C-C$  bond. On this basis, we envisioned a new strategy for the cross-coupling of two alkyl halides via an  $S_N2$  mechanism by exploiting the disparate electronic and steric properties of differentially substituted alkyl halides. Specifically, alkyl halides bearing more substituents undergo single electron reduction at lower potentials owing to the enhanced stability of the resultant C-centered radicals<sup>22</sup>, whereas alkyl halides with fewer substituents are superior electrophiles in  $S_N2$  reactions owing to their smaller steric profiles<sup>21</sup> (Figure 1D). Thus, the desired XEC can be envisioned via a radical-polar crossover pathway consisting of the selective reduction of a more substituted alkyl halide (A) to a C-centered radical (C) followed by a second reduction to a carbanion (D) and subsequent chemoselective nucleophilic substitution on a less hindered alkyl halide (B).



**Figure 1. Cross-coupling and cross-electrophile-coupling for  $C(sp^3)-C(sp^3)$  bond formation.** (A) Transition-metal-catalyzed conventional cross-coupling. (B) Transition-metal catalyzed cross-electrophile-coupling. (C) State-of-the-art Ni-catalyzed  $C(sp^3)-C(sp^3)$  XEC. (D) Proposed reaction strategy for the electrochemical XEC (*this work*). (E) Périchon's pioneering study on electroreductive XEC.

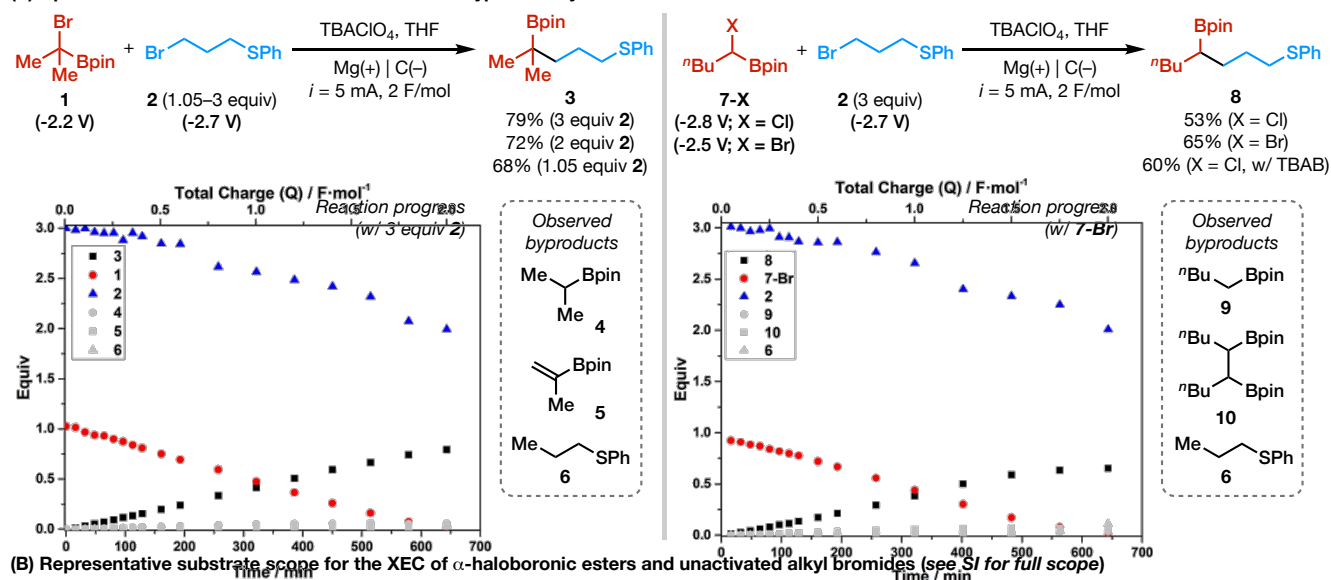
Owing to its ability to distinguish between two functional groups with minute differences in redox potential, electrochemistry constitutes an ideal means to achieve this reaction strategy<sup>23,24</sup>. Importantly, the use of direct electrolysis as opposed to transition metal catalysis enables a different mechanism for the activation of alkyl halides, which could circumvent undesired side reactivities such as unselective alkyl halide reduction and  $\beta$ -H elimination. The electrochemistry of alkyl halides has been well studied in both analytical<sup>25</sup> and synthetic contexts<sup>26</sup>. Related to our work, Périchon and co-workers reported an early example of the electroreductive  $C(sp^3)-C(sp^3)$  XEC<sup>27</sup>, albeit with a limited reaction scope featuring only strongly activated alkyl halides (e.g.,  $\alpha$ -haloesters and polyhalogenated alkanes) (Figure. 1E). Against this backdrop, we envision that an electrochemically driven, transition-metal-free XEC could offer a new paradigm for the construction of  $C(sp^3)-C(sp^3)$  bonds and thus enable greater efficiency, sustainability, and diversity in chemical synthesis.

Our initial reaction development was guided by cyclic voltammetry (CV) and density functional theory (DFT) computation. The desired reaction pathway involves a sequence of electrochemical-chemical-electrochemical-chemical steps (i.e., an ECEC mechanism; Figure 1D). To achieve this ECEC mechanism requires the second reduction event to take place at a substantially faster rate than the initial reduction of alkyl halide **A** to minimize diffusion of reactive intermediates away from the cathode. In addition, the reduction of alkyl radical **C** at the applied potential needs to be sufficiently fast to outcompete undesired side reactions such as radical dimerization and hydrogen-atom abstraction. CV data revealed that the reduction of simple tertiary alkyl halides, such as *tert*-butyl bromide, occurs at  $-2.0$  V (vs. saturated calomel electrode, SCE), whereas the resultant *tert*-butyl radical is reduced at  $-2.2$  V<sup>28</sup>. The very negative second reduction potential suggests that generation of the carbanion is difficult, and thus, the desired XEC will be accompanied by radical side reactions. Indeed, electrolysis of *tert*-butyl bromide or (3-bromo-3-methylbutyl)benzene in the presence of a simple primary alkyl bromide gave rise to only traces of the desired product, along with substantial quantities of protodebromination and elimination side products (see SI).

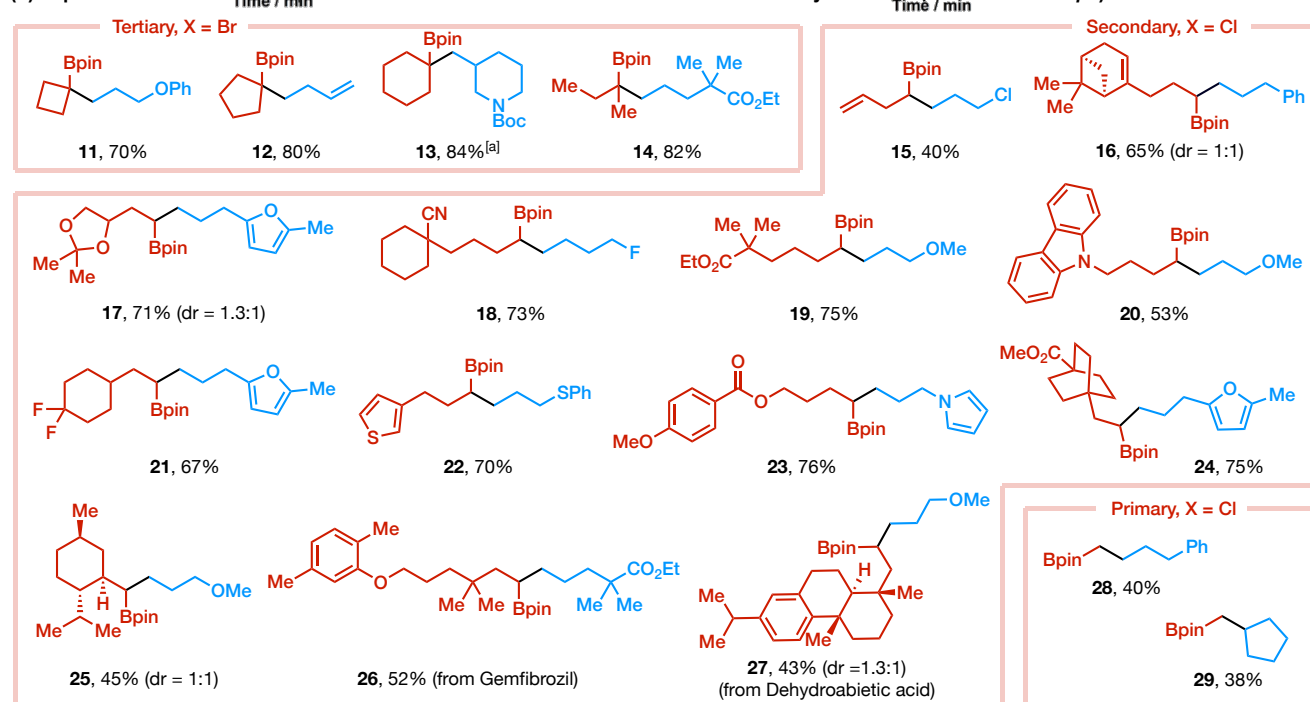
To address this issue, we sought to lower the potential for the second reduction event by introducing an anion-stabilizing substituent. CV and DFT data (see SI) suggested that a variety of functional groups such as boryl, aryl, vinyl, alkynyl, and silyl could facilitate the desired  $2e^-$  reduction of alkyl halides by forming p-p or p- $\pi$  conjugation with the resultant carbanion. This stabilization effect also further augments the reduction potential difference between the two alkyl halide coupling partners and, thus, ensures high chemoselectivity. Importantly, the inclusion of such substituents also increases the functional complexity and synthetic value of the cross-coupling products.

We first tested our hypothesis with  $\alpha$ -halo pinacol boronate ester (Bpin) substrates<sup>29,30,31,32</sup>. Upon systematic optimization, we found that the electrolysis of a mixture of tertiary  $\alpha$ -bromo Bpin **1** and an unactivated primary alkyl bromide **2** gave rise to the desired product **3** in 79% isolated yield under simple electrolysis conditions after passing 2 F/mol of charge (Figure. 2A). Electrode screening showed that graphite (C) is the optimal cathode material and superior to various metal-based electrodes. CV and DFT data revealed that graphite imparts a substantial overpotential for the initial reduction of **1**, thereby rendering the first electron transfer in the ECEC mechanism slower than the second and ensuring high reaction selectivity (*vide supra*). Indeed, a time course study showed that the e-XEC reaction between **1** and **2** exhibits excellent chemoselectivity with only traces ( $\leq 5\%$ ) of hydrodehalogenation and elimination products (**4–6**) and no dimerization observed (Figure. 2A). Importantly, although employing three equivalents of **2** was desirable to ensure high reaction efficiency, only one equivalent was consumed with the remaining material nearly fully recovered. When the loading of **2** was decreased to 1.05 equivalents, good yield and high chemoselectivity were maintained for the reaction.

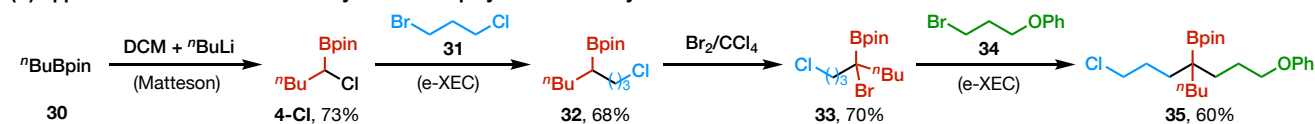
(A) Optimized conditions for the XEC of two distinct types of alkyl bromides



(B) Representative substrate scope for the XEC of  $\alpha$ -haloboronic esters and unactivated alkyl bromides (see SI for full scope)



(C) Application: Iterative XEC for the synthesis of a polysubstituted alkylboronic ester



**Figure 2. Electroreductive coupling of  $\alpha$ -halo pinacol boronic ester with alkyl halides.** (A) Electrochemical XEC between  $\alpha$ -halo Bpin and primary alkyl bromides: chemoselectivity test. (B) Substrate scope for the e-XEC. Reaction conditions:  $\alpha$ -halo Bpin (1.0 mmol, 1 equiv), primary alkyl bromide (3.0 mmol, 3 equiv), TBAClO<sub>4</sub> (3 equiv), THF (2.5 mL), Mg anode, graphite cathode, undivided cell (5 mL, ElectraSyn 2.0), constant current  $i = 5 \text{ mA}$  (current density  $j = 1.03 \text{ mA/cm}^2$ ),  $Q = 2 \text{ F/mol}$ , 22 °C. See

SI for experimental details. (C) Iterative e-XEC for the synthesis of a polysubstituted alkylboronic ester.  
[a]Yield of the alcohol after oxidation of Bpin. Bpin, pinacol boronate ester.

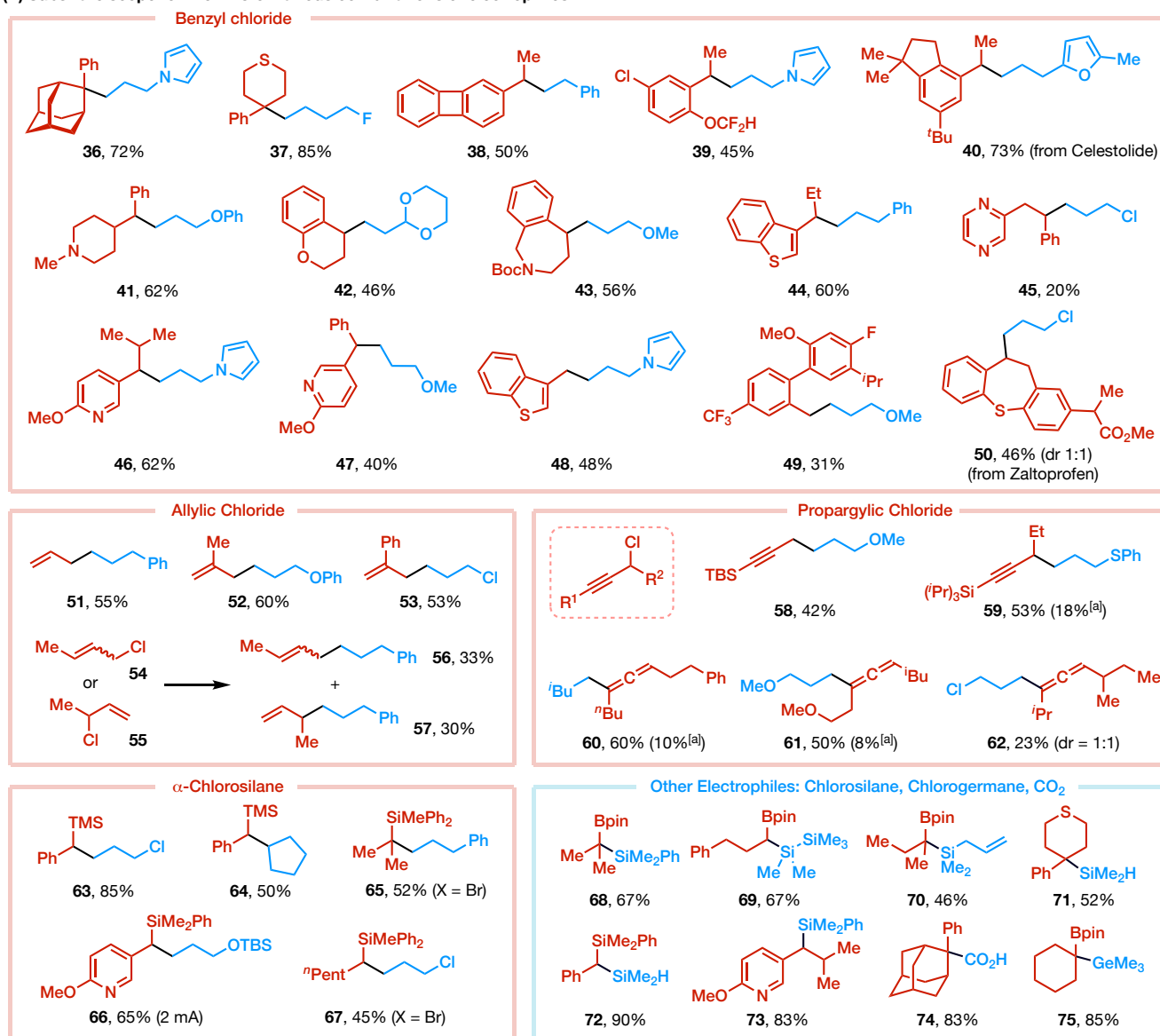
Importantly, secondary  $\alpha$ -chloro Bpin **7-Cl** can also undergo XEC with **2** to afford **8** in 53% isolated yield, in addition to <5% of dimer **10**. However, we also obtained a significant amount (~20%) of alkane **6** from hydrodehalogenation of **2**. During the reaction course, we observed an induction period, as well as the formation of halogen-exchange product **7-Br** (see SI). Further CV study revealed that substrate **7-Cl** shows a similar reduction potential to its coupling partner **2**, whereas the corresponding bromide **7-Br** is substantially easier to reduce than **7-Cl** (by ~400 mV). These findings suggest that **7-Br** is likely the actual reactant in the e-XEC, with the observed induction period stemming from slow generation of **7-Br** upon unproductive consumption of **2** to release the required Br<sup>-</sup>. Guided by this information, we further obtained optimal conditions by either adding a catalytic amount of tetrabutylammonium bromide (TBAB) or using **7-Br** directly as the substrate, which led to improved yield ( $\geq 60\%$  **8**) and chemoselectivity ( $\leq 12\%$  **6**).

To directly compare our reaction protocol to literature alternatives for XEC, we subjected substrates **1** or **7-Cl** with **2** to various known systems using Ni catalysis<sup>14-16</sup>. The desired cross-coupling products were obtained in  $\leq 5\%$  yield in all cases along with substantial amounts of hydrodehalogenation and dimerization products (see SI). Thus, our electrochemical approach provides a fundamentally distinct solution to the longstanding challenge of C(sp<sup>3</sup>)-C(sp<sup>3</sup>) XEC with substantially broadened substrate scope and improved selectivity.

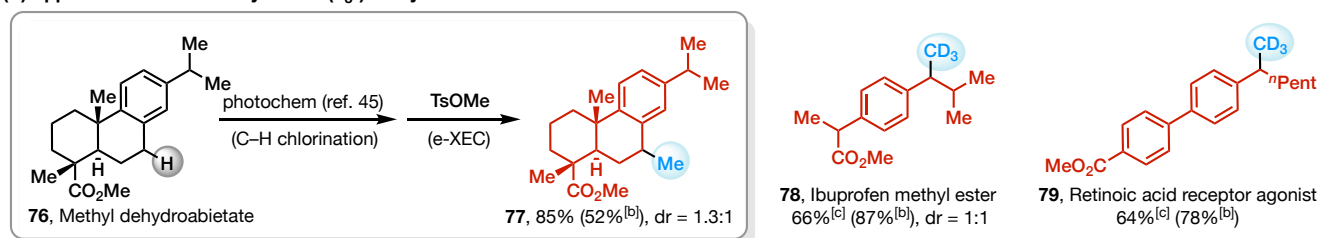
With the optimal conditions in hand, we then expanded the scope of the e-XEC to synthesize a diverse collection of C(sp<sup>3</sup>)-C(sp<sup>3</sup>) coupling products from  $\alpha$ -haloboronate esters and unactivated alkyl halides (Figure. 2B). Various functional groups, such as alkyl chloride (**15**), alkene (**12**, **15-16**), carbamate (**13**), acetal (**17**), ester (**14**, **19**, **23-24**, **26**), nitrile (**18**), difluoromethylene (**21**), thioether (**22**), and heteroarenes (furan (**17**, **21**, **24**), thiophene (**22**), pyrrole (**23**) and carbazole (**20**)), are compatible with the reaction conditions.  $\alpha$ -Haloboronic esters derived from drug molecules were readily converted to coupling products (**26**, **27**). Finally, we demonstrated the synthesis of tertiary alkylboronic ester via iterative e-XEC in combination with Matteson and halogenation reactions (Figure. 2C)<sup>30</sup>. Starting from commercially available *n*-butyl Bpin (**30**), we demonstrated the sequential synthesis of both a secondary (**32**) and a tertiary (**35**) alkylboronate ester via a series of halogenation and e-XEC reactions. Alkylboronate esters are valuable synthetic intermediates that can undergo a diverse range of transformations<sup>33</sup>, but a general protocol that grants access to primary, secondary, and tertiary alkyl boronic esters remains rare<sup>34,35</sup>. The e-XEC thus provides a modular approach to the synthesis of such compounds from simple alkyl halides<sup>36,37,38,39,40</sup>.

We further expanded the scope of the XEC to various alkyl halides with stabilizing  $\pi$ -systems (Figure. 3A). For example, a suite of tertiary, secondary, and primary benzyl chlorides with diverse functional groups, such as fluoroalkyl (**39**, **49**), amine (**41**), ester (**50**), and heterocycles (**37**, **41**, **42-48**, **50**), proved suitable substrates. Further, allylic and propargylic chlorides are also compatible with our electrochemical method. Owing to charge delocalization, reactions starting from isomeric allylic chlorides **54** and **55** provided a mixture of linear (**56**) and branched (**57**) products in identical ratios. For propargylic substrates, the substituents on the alkyne influenced the constitution of the product: the presence of bulky silyl groups preferentially led to formation of alkyne products from directly alkylation (**58**, **59**), whereas substrates featuring alkyl substituents afforded isomerized allenes as major products (**60-62**).

**(A) Substrate scope for the XEC of various combinations of electrophiles**

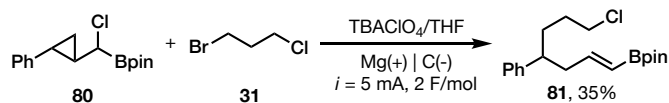


**(B) Application: Formal benzylic C-H ( $d_3$ -)methylation of bioactive molecules**

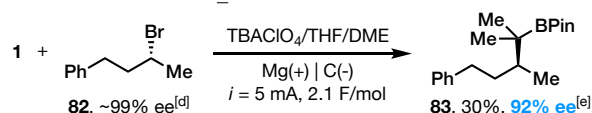


**(C) Mechanistic experiments**

**Radical probe experiment:**



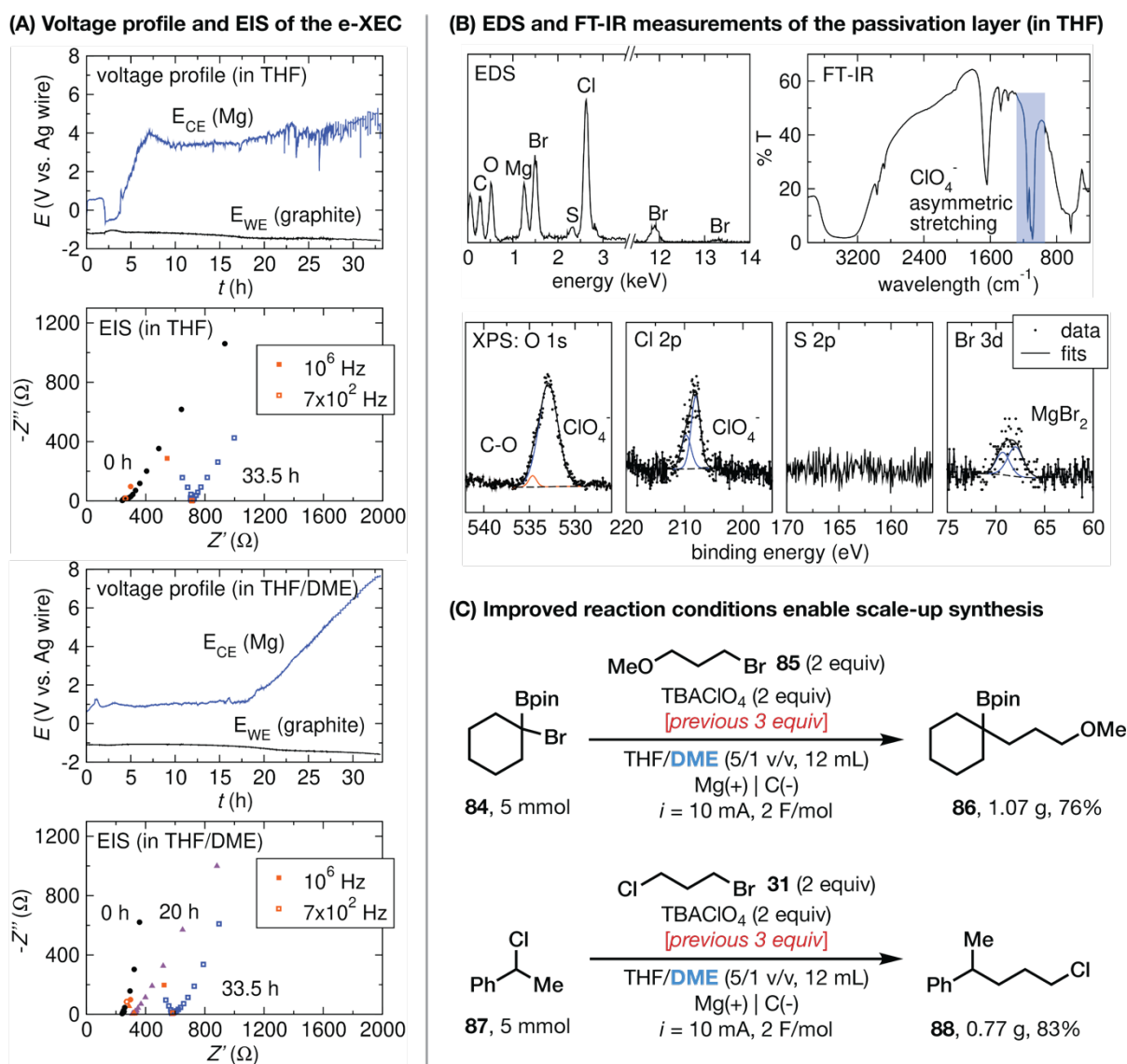
**Stereochemistry test ( $S_N2$  probe):**



**Figure 3. Substrate scope and synthetic application.** (A) Substrate scope of benzyl-, allyl-, propargyl chloride,  $\alpha$ -chlorosilane and other electrophiles. Reaction conditions:  $\alpha$ -functionalized alkyl halide (1.0 mmol, 1 equiv), primary alkyl bromide (3.0 mmol, 3 equiv), TBAClO<sub>4</sub> (3 equiv), THF (2.5 mL), Mg anode, graphite cathode, undivided cell (5 mL, ElectraSyn 2.0), constant current  $i = 5$  mA (current density = 1.03 mA/cm<sup>2</sup>),  $Q = 2$  F/mol, 22 °C. See SI for experimental details. (B) Formal late-stage benzylic C–H ( $d_3$ -)methylation of bioactive molecules.<sup>[a]</sup>Yield of minor regioisomer. <sup>[b]</sup>Yield of benzylic C–H chlorination. <sup>[c]</sup>Using CD<sub>3</sub>OTs prepared from CD<sub>3</sub>OD. (C) Mechanistic experiments. <sup>[d]</sup>Ee of the starting alcohol before bromination. <sup>[e]</sup>Absolute stereochemistry could not be determined and was assumed based on proposed mechanism.

$\alpha$ -Silyl groups can also facilitate the reduction of alkyl halides by stabilizing the resultant radical and anion intermediates. Various  $\alpha$ -halosilanes<sup>41</sup> (**63–67**) were transformed into cross coupling products in high efficiency. Notably, the scope of the e-XEC was further expanded to the formation of various distinct types of C–C, C–Si, and C–Ge bonds using chlorosilanes, chlorogermenes, or carbon dioxide as the coupling partner (**68–75**). Notably, while prior work to synthesize *gem*-silylboryl and *gem*-disilyl products required the use of esoteric silylboronate ester reagents (e.g., Me<sub>2</sub>PhSi-Bpin) with limited availability<sup>42,43</sup>, our method used readily available alkyl halides and chlorosilanes, thus granting convenient access to a diverse range of value-added synthetic intermediates. Finally, we further demonstrated the synthetic utility of our XEC protocol in the context of a two-step C–H methylation of drug derivatives<sup>44</sup> (Figure 3B). For example, starting from methyl dehydroabietate (**76**), a sequence of photochemical benzylic C–H chlorination<sup>45</sup> and e-XEC using methyl tosylate (with TBAB as an additive) gave rise to the methylated product **77**. In a similar fashion,  $d_3$ -methylation of ibuprofen methyl ester (**78**) and a retinoic acid agonist (**79**) were achieved in good yield using CD<sub>3</sub>OTs from readily available  $d_3$ -methanol as the deuterium source.

Further control experiments lent strong support to the proposed radical-polar crossover mechanism of the e-XEC reaction. First, when radical probe substrate **80** was subjected to the XEC conditions, the ring-opened product **81** was obtained in 35% yield (Figure. 3C, left), which likely arose from a sequence of single-electron reduction, cyclopropane ring-opening, and second reduction prior to nucleophilic substitution with **31**<sup>38</sup>. In a second experiment, we carried out the e-XEC using substrate **1** together with chiral secondary alkyl bromide **82** and observed that the enantiomeric excess of **82** was largely preserved in the coupling product **83** (Figure. 3C, right). Together, these findings suggest that substrate **1** readily undergoes two-electron reduction in our e-XEC system (see SI section 12.3). The identity of the reduced nucleophile that participates in the subsequent S<sub>N</sub>2 step is likely a solvated anion rather than an organomagnesium complex (with Mg<sup>2+</sup> from oxidation of the sacrificial anode), as conducting the electrolysis in a divided cell that separates the cathodic and anodic events also led to the desired cross coupling, albeit with lower yield (55%) due to high cell resistance (see SI).



**Figure 4. Anode passivation analysis and gram-scale synthesis.** (A) The voltage profile and EIS of the e-XEC reaction (B) Characterization of the passivation layer formed on Mg anode after e-XEC in THF. (C) Scale-up synthesis.

Finally, we attempted to further augment the synthetic utility of the e-XEC reaction by developing a gram-scale procedure. Our effort was initially hampered by the high overall cell voltage during electrolysis, which caused the reaction to stop prematurely. By monitoring the potential at both working and counter electrodes (Figure. 4A), we attributed the high cell voltage to a sudden potential increase at the Mg anode due to the formation of a visible passivating film during the first few hours of the e-XEC reaction (Figure. S28). Meanwhile, the potential at the carbon working electrode remained stable. Electrochemical impedance spectroscopy (EIS) of the Mg anode was measured at the beginning and end of the reaction, revealing an increase in the interfacial resistance from  $239.5 \pm 1.5 \Omega$  to  $710.6 \pm 3.3 \Omega$  (Figure. 4A). The composition of the passivation layer was investigated by energy-dispersive X-ray spectroscopy (EDS), revealing Mg, Br, Cl, O, C, and a trace amount of S (Figure 4B, top). Further characterization of the passivation layer using FT-IR and X-ray photoelectron spectroscopy (XPS)



(Figure. 4B) confirmed the presence of dihalide salt  $\text{MgBr}_2$  along with  $\text{Mg}(\text{ClO}_4)_2$ ,<sup>46</sup> both of which are poorly soluble in THF.<sup>47, 48</sup> Drawing inspiration of Mg electrolytes for Mg batteries, we attempted to use ethereal solvents to help solubilize Mg salts through chelation to stabilize the Mg anode and allow for longer electrolysis.<sup>49, 50</sup> After surveying several cosolvents, we discovered that the solvent system of THF/dimethoxyethane (DME; 5:1 mixture) reduced the Mg electrode passivation (Figure. S28). The thin passivation layer formed under the new reaction condition had a substantially lower interfacial resistance ( $321.5 \pm 3.6 \, \Omega$  at 20 h) (Figure 4A, bottom), allowing the voltage at the Mg anode to stabilize at  $\sim 1$  V for prolonged time (Figure 4A). The anodic potential eventually increased after *ca.* 20 h, forming a film with largely the same composition (Figures. S32, S33, S35, S36). Thus, the reduced resistance of the film is a result of its smaller thickness. Applying this new protocol enabled the reaction to be scaled up smoothly with a decreased electrolyte loading, generating  $\sim 1$  g of the desired products in high yield (Figure. 4C).

In summary, we report a new electrochemical protocol for the XEC of alkyl halides under simple, transition-metal-free conditions. This selective  $\text{C}(\text{sp}^3)\text{-C}(\text{sp}^3)$  coupling reaction was achieved with high chemoselectivity and broad functional group compatibility, granting access to a diverse array of cross-coupled products from the combination of unactivated alkyl electrophiles with myriad functionalized alkyl halides and  $\alpha$ -halosilanes. Given its broad reaction scope, high chemoselectivity, and operational simplicity, we anticipate this new XEC protocol will find widespread application in synthetic and medicinal chemistry.

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