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Electrochemically Driven Cross-Electrophile Coupling of Alkyl Halides

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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[1]. 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[2]. Owing to the broad availability of alkyl halides, their direct cross coupling—commonly known as cross-electrophile-coupling (XEC)—provides a promising route toward this objective[3,4,5]. Such transformations circumvent the preparation of carbon nucleophiles used in traditional cross-coupling reactions as well as stability and functional group tolerance issues that commonly associate with these reagents. 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 efficient XEC of a variety of functionalized and unactivated alkyl electrophiles and exhibits 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[6]. 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 (Fig. 1A). Due to the inherent limitations associated with the use of preformed carbon nucleophiles, reaction methods

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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[3,4,5] (Fig. 1B). 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[7,8,9]. 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[10]. Nonetheless, a highly selective and broadly applicable protocol for the C(sp^3)-C(sp^3) XEC remains elusive[11,12,13]. Using Ni catalysis, the Gong and MacMillan groups have independently provided critical advances toward solving this synthetic problem[14,15,16] (Fig. 1C). However, the reliance on a Ni catalyst imparts innate limitations. For example, competing homocoupling remains a major competing pathway even when one of the coupling partners is used in large excess observation, which has been attributed to the similar reactivity of Ni toward different types of alkyl halides[17]. Furthermore, tertiary electrophiles have rarely been shown to be compatible with existing protocols[18,19] due to various undesired side reactions such as protodehalogenation and elimination.[20]

Among the most well-established methods for the construction of C(sp^3)-C(sp^3) bonds is the S_N2 reaction[21]. 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[22], whereas alkyl halides with fewer substituents are superior electrophiles in S_N2 reactions owing to their smaller steric profiles[21] (Fig. 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**).

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[23,24]. 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 β-H elimination. The electrochemistry of alkyl halides has been well studied in both analytical[25] and synthetic contexts[26]. Related to our work, Périchon and co-workers reported an early example of the electroreductive C(sp^3)-C(sp^3) XEC[27], albeit with a limited reaction scope featuring only strongly activated alkyl halides (e.g., α-haloesters and polyhalogenated alkanes) (Fig. 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 (ECEC) steps (Fig. 1D). To achieve this ECEC mechanism requires the second reduction event to take place at a 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. However, literature data suggested that for simple tertiary alkyl halides such as *tert*-butyl bromide, the reduction of *tert*-butyl radical is typically more difficult than the initial alkyl halide reduction[28], and this finding is supported by our own experimental and computational evidence (see SI sections 7 and 8). The challenging second reduction 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 suggested that a variety of functional groups such as boryl, aryl, vinyl, alkynyl, and silyl could facilitate the desired $2e^-$ reduction of alkyl halides (see SI sections 8 and 12.3) by forming p-p or p-π 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 α-halo pinacol boronate ester (Bpin) substrates[29,30,31,32]. Upon systematic optimization, we found that the electrolysis of a mixture of tertiary α-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 (Fig. 2A). Electrode screening showed that graphite and Mg are the optimal cathode and anode materials, respectively, which are superior to various other metal-based electrodes. A time course study showed that this e-XEC reaction exhibits excellent chemoselectivity with only traces (≤5%) of hydrodehalogenation and elimination products (**4**–**6**) and no dimerization observed (Fig. 2A). Importantly, although employing three equivalents of **2** was desirable to ensure high reaction efficiency, only one equivalent was consumed with the excess material nearly fully remained. When the loading of **2** was decreased to 1.05 equivalents, good yield and high chemoselectivity were maintained for the reaction. Importantly, secondary α-bromo Bpin **7-Br** can also undergo XEC with **2** to afford **8** in 65% isolated yield, in addition to <5% of dimer **10** and ≤10% protodebromination products **6** and **9**. Replacing **7-Br** with chlorinated congener **7-Cl** also provided good yield in the presence of 30 mol% tetrabutylammonium bromide (TBAB), which promoted in-situ halogen exchange.

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[14–16]. The

desired cross-coupling products were obtained in ≤5% yield in all cases along with substantial amounts of hydrodehalogenation and dimerization products (see SI). Thus, our electrochemical approach provides a complementary and fundamentally distinct solution to the longstanding challenge of $C(sp^3)$-$C(sp^3)$ XEC with broadened substrate scope and improved selectivity.

We subsequently employed the e-XEC to synthesize a diverse collection of coupling products from α-haloboronate esters and unactivated alkyl halides (Fig. 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 (**17**, **20**–**24**,), are compatible with the reaction conditions. α-Haloboronic esters derived from drug molecules were readily converted to coupling products (**26**, **27**). Finally, we demonstrated the sequential synthesis of secondary and tertiary alkylboronic esters **32** and **35** from *n*-butyl Bpin (**30**) via iterative e-XEC in combination with Matteson and halogenation reactions (Fig. 2C)[30]. Alkylboronate esters are valuable synthetic intermediates that can undergo a diverse range of transformations[33], but a general protocol that grants access to primary, secondary, *and* tertiary alkyl boronic esters remains rare[34,35]. The e-XEC thus provides a modular approach to the synthesis of such compounds from simple alkyl halides (see SI for comparison with the Matteson reaction)[36,37,38,39,40].

We further expanded the scope of the e-XEC to various alkyl halides with stabilizing π-systems (Fig. 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: substrates with bulky silyl groups preferentially gave alkyne products via direct alkylation (**58**, **59**), whereas those featuring alkyl substituents afforded isomerized allenes as major products (**60**–**62**).

α-Silyl groups can also facilitate the reduction of alkyl halides by stabilizing the resultant radical and anion intermediates. Various α-halosilanes[41] (**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, chlorogermanes, or carbon dioxide as the coupling partner (**68**–**75**). While prior work to synthesize *gem*-silylboryl and *gem*-disilyl products required the use of esoteric silylboronate ester reagents (e.g., Me_2PhSi-Bpin) with limited availability[42,43], our method used readily available alkyl halides and chlorosilanes, thus granting convenient access to a diverse range of value-added synthetic intermediates. Finally, we demonstrated the synthetic utility of the e-XEC in a two-step C–H methylation of drug derivatives[44] (Fig. 3B). Starting from methyl dehydroabietate (**76**), a sequence of photochemical benzylic C–H chlorination[45] and e-XEC using methyl tosylate gave rise to methylated product **77**. In a similar fashion, d_3-methylation of ibuprofen methyl ester (**78**) and a retinoic acid agonist (**79**) was achieved using CD_3OTs from readily available d_3-methanol.

Control experiments lent strong support to the proposed radical-polar crossover mechanism for the e-XEC reaction. First, starting from radical probe substrate **80**, ring-opened product **81** was obtained (Fig. 4A, left), which arose from a sequence of single-electron reduction, cyclopropane ring-opening, and second reduction prior to nucleophilic subsitution with **31**[38]. In a second experiment, we carried out the e-XEC of **1** with chiral secondary alkyl bromide **82** and observed that the enantiomeric excess of **82** was largely preserved in the coupling product **83** (Fig. 4A, right). This finding is consistent with a concerted bimolecular substitution mechanism. The identity of the reduced nucleophile that participates in the S_N2 step is likely a solvated anion rather than an organomagnesium complex (with Mg^{2+} from oxidation of the sacrificial anode), as conducting the reaction in a divided cell that separates the cathode and anode also led to the desired product in 72% yield (Table S2). In fact, a Mg anode is not necessary in a divided cell, as using a graphite anode along with 1,2,2,6,6-pentamethylpiperidine as sacrificial reductant also proved productive.

Finally, we attempted to augment the synthetic utility of the e-XEC 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 (Fig. 4B, left), 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 reaction (Fig. S29). 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 electrolysis, revealing an increase in the interfacial resistance from 239.5 ± 1.5 Ω to 710.6 ± 3.3 Ω (Fig. 4B, left). The composition of the passivation layer was investigated by energy-dispersive X-ray spectroscopy (EDS), showing Mg, Br, Cl, O, C, and a trace amount of S (Fig. 4C). Further characterization of the passivation layer using FT-IR and X-ray photoelectron spectroscopy (XPS) confirmed the presence of $MgBr_2$ along with $Mg(ClO_4)_2$,[46] both of which are poorly soluble in THF.[47, 48] Drawing inspiration from Mg electrolytes for Mg batteries, we used ethereal solvents to help solubilize Mg salts through chelation to stabilize the Mg anode and allow for longer electrolysis.[49, 50] After surveying several cosolvents, we discovered that the solvent system of THF/dimethoxyethane (DME) reduced the Mg electrode passivation (Fig. S29). The thin passivation layer formed under the new reaction condition had a substantially lower interfacial resistance (321.5 ± 3.6 Ω at 20 h), allowing the voltage at the Mg anode to stabilize at ~1 V for prolonged time (Fig. 4B, right). The anodic potential eventually increased after *ca.* 20 h, forming a thinner film with largely the same composition (Figs. S33, S34, S36, S37) but reduced resistance. Applying this new protocol enabled the reaction to be readily scaled up with a decreased electrolyte loading, generating up to 3 g of desired products in high yield (Fig. 4D).

In summary, we report a new electrochemical protocol for the XEC of alkyl halides under simple, transition-metal-free conditions. This selective $C(sp^3)$-$C(sp^3)$ 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 myriad unactivated and functionalized alkyl electrophiles and α-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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data availability:

All data supporting the findings of this work are available within the paper and its Supplementary Information.

References

1. Lovering F, Bikker J, Humblet C Escape from Flatland: Increasing Saturation as an Approach to Improving Clinical Success. J. Med. Chem. 52, 6752–6756 (2009). [PubMed: 19827778]
2. Choi J, Fu GC Transition metal–catalyzed alkyl-alkyl bond formation: Another dimension in cross-coupling chemistry. Science 356, eaaf7230 (2017). [PubMed: 28408546]
3. Everson DA, Weix DJ Cross-Electrophile Coupling: Principles of Reactivity and Selectivity. J. Org. Chem. 79, 4793–4798 (2014). [PubMed: 24820397]
4. Wang X, Dai Y, Gong H Nickel-Catalyzed Reductive Couplings. Top. Curr. Chem. 374, 43 (2016).
5. Lucas EL; Jarvo ER Stereospecific and stereoconvergent cross-couplings between alkyl electrophiles. Nat. Rev. Chem. 1, 0065 (2017).
6. Jana R, Pathak TP, Sigman MS Advances in Transition Metal (Pd,Ni,Fe)-Catalyzed Cross-Coupling Reactions Using Alkyl-organometallics as Reaction Partners. Chem. Rev. 111, 1417–1492 (2011). [PubMed: 21319862]
7. Weix DJ Methods and Mechanisms for Cross-Electrophile Coupling of Csp^2 Halides with Alkyl Electrophiles. Acc. Chem. Res. 48, 1767–1775 (2015). [PubMed: 26011466]
8. Cherney AH, Reisman SE Nickel-Catalyzed Asymmetric Reductive Cross-Coupling between Vinyl and Benzyl Electrophiles. J. Am. Chem. Soc. 136, 14365–14368 (2014). [PubMed: 25245492]
9. Zhang P, Le CC, MacMillan DWC Silyl Radical Activation of Alkyl Halides in Metallaphotoredox Catalysis: A Unique Pathway for Cross-Electrophile Coupling. J. Am. Chem. Soc. 138, 8084–8087 (2016). [PubMed: 27263662]
10. Ackerman LKG, Lovell MW, Weix DJ Multimetallic catalysed cross-coupling of aryl bromides with aryl triflates. Nature 524, 454–457 (2015). [PubMed: 26280337]
11. Sanford AB et al. Nickel-Catalyzed Alkyl−Alkyl Cross-Electrophile Coupling Reaction of 1,3-Dimesylates for the Synthesis of Alkylcyclopropanes. J. Am. Chem. Soc. 142, 5017–5023 (2020). [PubMed: 32129601]
12. Qian X, Auffrant A, Felouat A, Gosmini C Cobalt-Catalyzed Reductive Allylation of Alkyl Halides with Allylic Acetates or Carbonates. Angew. Chem. Int. Ed. 50, 10402–10405 (2011).
13. Liu J-H et al. Copper-Catalyzed Reductive Cross-Coupling of Nonactivated Alkyl Tosylates and Mesylates with Alkyl and Aryl Bromides. Chem. Eur. J. 20, 15334–15338 (2014). [PubMed: 25308802]

14. Yu X, Yang T, Wang S, Xu H, Gong H Nickel-Catalyzed Reductive Cross-Coupling of Unactivated Alkyl Halides. Org. Lett. 13, 2138–2141 (2011). [PubMed: 21434609]
15. Xu H, Zhao C, Qian Q, Deng W, Gong H Nickel-catalyzed cross-coupling of unactivated alkyl halides using bis(pinacolato)diboron as reductant. Chem. Sci. 4, 4022–4029 (2013).
16. Smith RT et al. Metallaphotoredox-Catalyzed Cross-Electrophile Csp^3−Csp^3 Coupling of Aliphatic Bromides. J. Am. Chem. Soc. 140, 17433–17438 (2018). [PubMed: 30516995]
17. Diccianni JB, Katigbak J, Hu C, Diao T Mechanistic Characterization of (Xantphos)Ni(I)-Mediated Alkyl Bromide Activation: Oxidative Addition, Electron Transfer, or Halogen-Atom Abstraction. J. Am. Chem. Soc. 141, 1788–1796 (2019). [PubMed: 30612428]
18. Wang J, Gong Y, Sun D, Gong H Nickel-catalyzed reductive benzylation of tertiary alkyl halides with benzyl chlorides and chloroformates. Org. Chem. Front. 8, 2944–2948 (2021).
19. Chen H, Jia X, Yu Y, Qian Q, Gong H Nickel-Catalyzed Reductive Allylation of Tertiary Alkyl Halides with Allylic Carbonates. Angew. Chem. Int. Ed. 56, 13103–13106 (2017).
20. Xue W et al. Nickel-catalyzed formation of quaternary carbon centers using tertiary alkyl electrophiles. Chem. Soc. Rev. 50, 4162–4184 (2021). [PubMed: 33533345]
21. Clayden J, Greeves N, Warren S Organic chemistry (2nd ed.). Oxford: Oxford University Press. (2012).
22. Vasudevan D Direct and indirect electrochemical reduction of organic halides in aprotic media. Russ J Electrochem, 41, 310–314 (2005).
23. Yan M; Kawamata Y; Baran PS Synthetic Organic Electrochemical Methods Since 2000: On the Verge of a Renaissance. Chem. Rev. 117, 13230–13319 (2017). [PubMed: 28991454]
24. Moeller KD Synthetic Applications of Anodic Electrochemistry. Tetrahedron 56, 9527–9554 (2000).
25. Cleary JA, Mubarak MS, Vieira KL, Anderson MR, Peters DG Electrochemical Reduction of Alkyl Halides at Vitreous Carbon Cathodes in Dimethylformamide. J. Electroanal. Chem. Interfacial Electrochem 198, 107–124 (1986).
26. Chaussard J et al. Use of Sacrificial Anodes in Electrochemical Functionalization of Organic Halides. Synthesis 1990, 369–381 (1990).
27. Nedelec JY, Ait-Haddou-Mouloud H, Folest JC, Perichon J Electrochemical cross-coupling of alkyl halides in the presence of a sacrificial anode. J. Org. Chem. 53, 4720–4724 (1988).
28. Andrieux CP, Gallardo I, Saveant JM Outer-Sphere Electron-Transfer Reduction of Alkyl Halides. A Source of Alkyl Radicals or of Carbanions? Reduction of Alkyl Radicals. J. Am. Chem. Soc. 111, 1620–1626 (1989).
29. Knochel P New Approach to Boron-Stabilized Organometallics. J. Am. Chem. Soc. 112, 7431–7433 (1990).
30. Matteson DS α-Halo Boronic Esters: Intermediates for Stereodirected Synthesis. Chem. Rev. 89, 1535–1551 (1989).
31. Schmidt J, Choi J, Liu AT, Slusarczyk M, Fu GC A general, modular method for the catalytic asymmetric synthesis of alkylboronate esters. Science 354, 1265–1269 (2016). [PubMed: 27940868]
32. Sun S-Z, Börjesson M, MartinMontero R, Martin R Site-Selective Ni-Catalyzed ReductiveCoupling of α-Haloboranes with Unactivated Olefins. J. Am. Chem. Soc. 140, 12765–12769 (2018). [PubMed: 30244574]
33. Sandford C, Aggarwal VK Stereospecific functionalizations and transformations of secondary and tertiary boronic esters. Chem. Commun. 53, 5481–5494 (2017).
34. Li C et al. Decarboxylative borylation. Science 356, eaam7355 (2017). [PubMed: 28408721]
35. Fawcett A et al. Photoinduced decarboxylative borylation of carboxylic acids. Science, 357, 283–286 (2017). [PubMed: 28619717]
36. Yang Y et al. Practical and Modular Construction of C(sp3)−Rich Alkyl Boron Compounds. J. Am. Chem. Soc. 143, 471–480 (2021). [PubMed: 33347297]
37. Bera S, Mao R Hu X Enantioselective C(sp3)–C(sp3) cross-coupling of non-activated alkyl electrophiles via nickel hydride catalysis. Nat. Chem13, 270–277 (2021). [PubMed: 33380741]

38. Hong K, Liu X, Morken JP Simple Access to Elusive α-Boryl Carbanions and Their Alkylation: An Umpolung Construction for Organic Synthesis. J. Am. Chem. Soc. 136, 10581–10584 (2014). [PubMed: 25019925]
39. Kischkewitz M, Okamoto K, Mück-Lichtenfeld C, Studer A Radical-polar crossover reactions of vinylboron ate complexes. Science 355, 936–938 (2017). [PubMed: 28254937]
40. Collins BSL, Wilson CM, Myers EL, Aggarwal VK Asymmetric Synthesis of Secondary and Tertiary Boronic Esters. Angew. Chem. Int. Ed. 56, 11700–11733 (2017).
41. Hofstra JL, Cherney AH, Ordner CM, Reisman SE Synthesis of Enantioenriched Allylic Silanes via Nickel-Catalyzed Reductive Cross-Coupling. J. Am. Chem. Soc. 140, 139–142 (2018). [PubMed: 29202243]
42. Wang L et al. C–O Functionalization of α-Oxyboronates: A Deoxygenative gem-Diborylation and gem-Silylborylation of Aldehydes and Ketones. J. Am. Chem. Soc. 139, 5257–5264 (2017). [PubMed: 28306251]
43. Hazrati H, Oestreich M Copper-Catalyzed Double C(sp3)–Si Coupling of Geminal Dibromides: Ionic-to-Radical Switch in the Reaction Mechanism. Org. Lett. 20, 5367–5369 (2018). [PubMed: 30095263]
44. Vasilopoulos A, Krska SW, Stahl SS C(sp3)–H Methylation Enabled by Peroxide Photosensitization and Ni-Mediated Radical Coupling. Science 372, 398–403 (2021). [PubMed: 33888639]
45. McMillan AJ et al. Practical and Selective sp^3 C−H Bond Chlorination via Aminium Radicals. Angew. Chem. Int. Ed. 60, 7132–7139 (2021).
46. Bishop JL, Quinn R, Dyar MD Spectral and Thermal Properties of Perchlorate Salts and Implications for Mars. Am Mineral. 99, 1580–1592 (2014). [PubMed: 32042202]
47. Xue W, Shishido R, Oestreich M Bench-Stable Stock Solutions of Silicon Grignard Reagents: Application to Iron- and Cobalt-Catalyzed Radical C(sp3)–Si Cross-Coupling Reactions. Angew. Chem. Int. Ed. 57, 12141–12145 (2018).
48. Chan C-Y, Lepeshkov IN, Khoo KH Ed. Alkaline Earth Metal Perchlorates. In Solubility Data Series (Pergamon, 1989).
49. Okoshi M; Yamada Y; Yamada A; Nakai H Theoretical Analysis on De-Solvation of Lithium, Sodium, and Magnesium Cations to Organic Electrolyte Solvents. J. Electrochem. Soc. 160, A2160–A2165 (2013).
50. Shao Y et al. Coordination Chemistry in Magnesium Battery Electrolytes: How Ligands Affect Their Performance. Sci. Rep. 3, 3130–3136 (2013). [PubMed: 24185310]

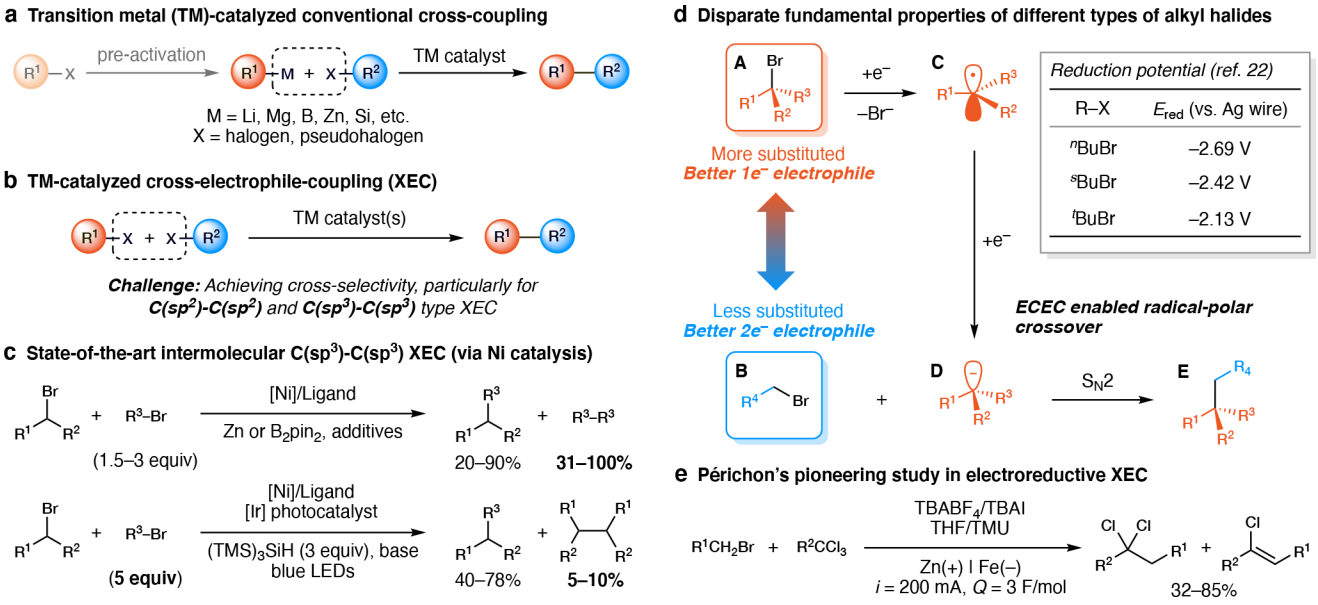

Fig 1. Cross-coupling and cross-electrophile-coupling for C(sp^3)-C(sp^3) bond formation.

(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. TBA = tetrabutylammonium, TMU = tetramethylurea.

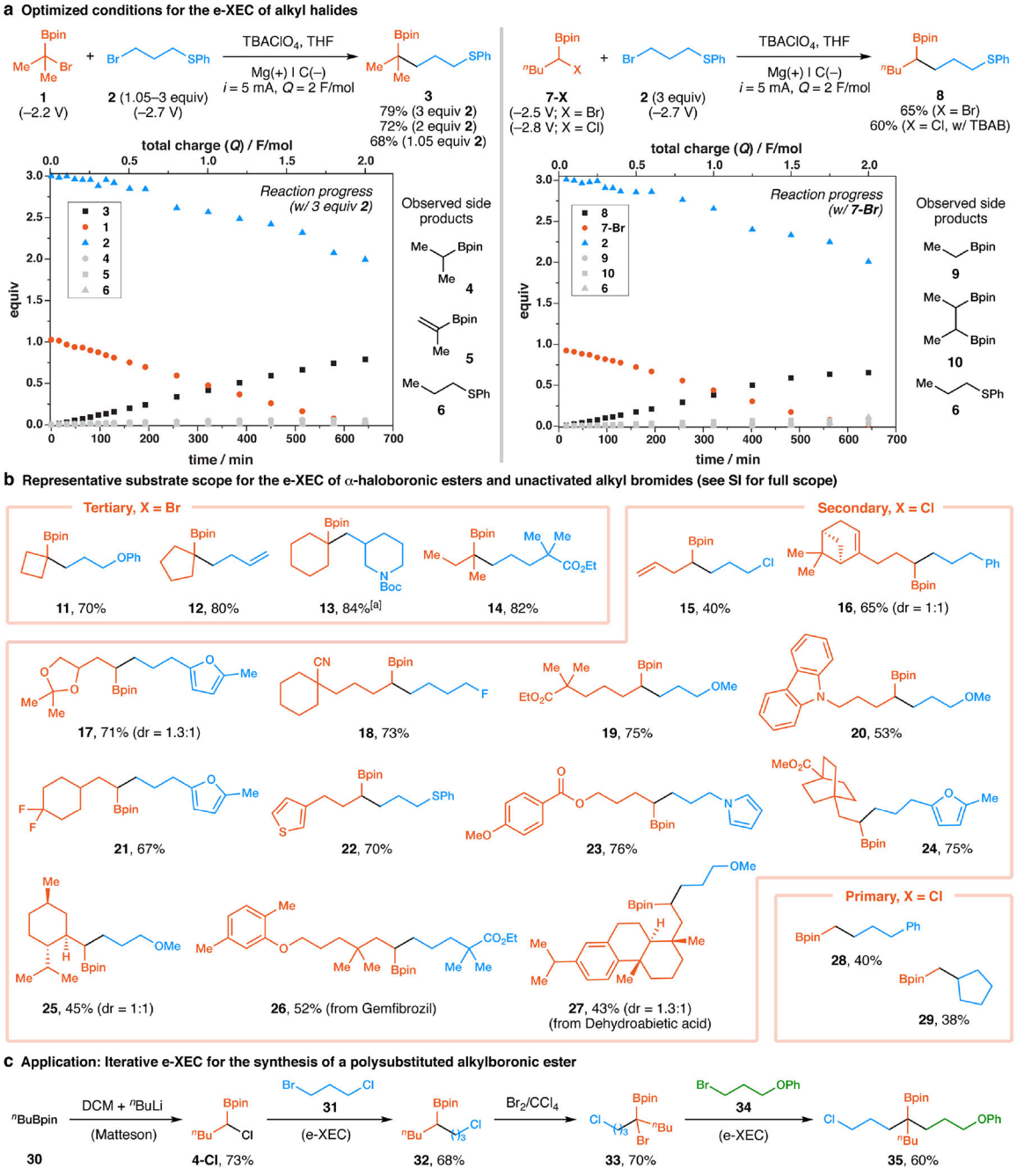

Fig 2. Electroreductive coupling of α-halo pinacol boronic ester with alkyl halides.

(**A**) Electrochemical XEC between α-halo Bpin and primary alkyl bromides: chemoselectivity test. Potential values in parentheses under alkyl halide substrates are presented against ferrocene/ferrocenium reference and are current onset potentials (see SI). (**B**) Substrate scope for the e-XEC. Reaction conditions: α-halo Bpin (1.0 mmol, 1 equiv), primary alkyl bromide (3.0 mmol, 3 equiv), $TBAClO_4$ (3 equiv), THF (2.5 mL), Mg anode, graphite cathode, undivided cell (5 mL, ElectraSyn 2.0), constant current $i = 5$ mA (current density $j = 1.03$ mA/cm^2), $Q = 2$ 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.

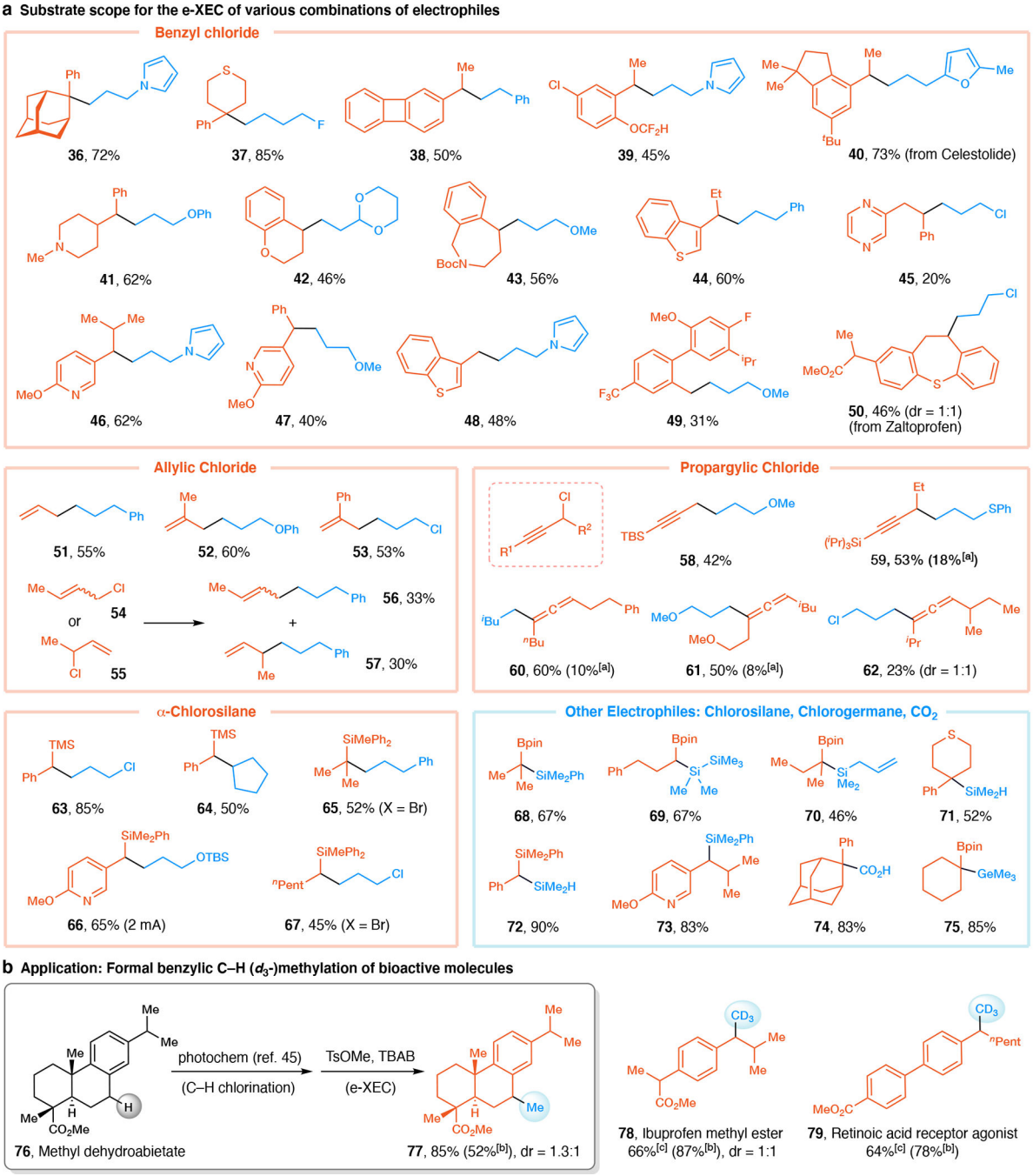

Fig 3. Substrate scope and synthetic application.

(A) Substrate scope of benzyl-, allyl-, propargyl chloride, α-chlorosilane and other electrophiles. Reaction conditions: α-functionalized alkyl halide (1.0 mmol, 1 equiv), primary alkyl bromide (3.0 mmol, 3 equiv), $TBAClO_4$ (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^2), $Q = 2$ F/mol, 22 °C. See SI for experimental details. (**B**) Formal late-stage benzylic C–H (d_3-)methylation of bioactive molecules.[a]Yield of

minor regioisomer. [b]Yield of benzylic C–H chlorination. [c]Using CD_3OTs prepared from CD_3OD.

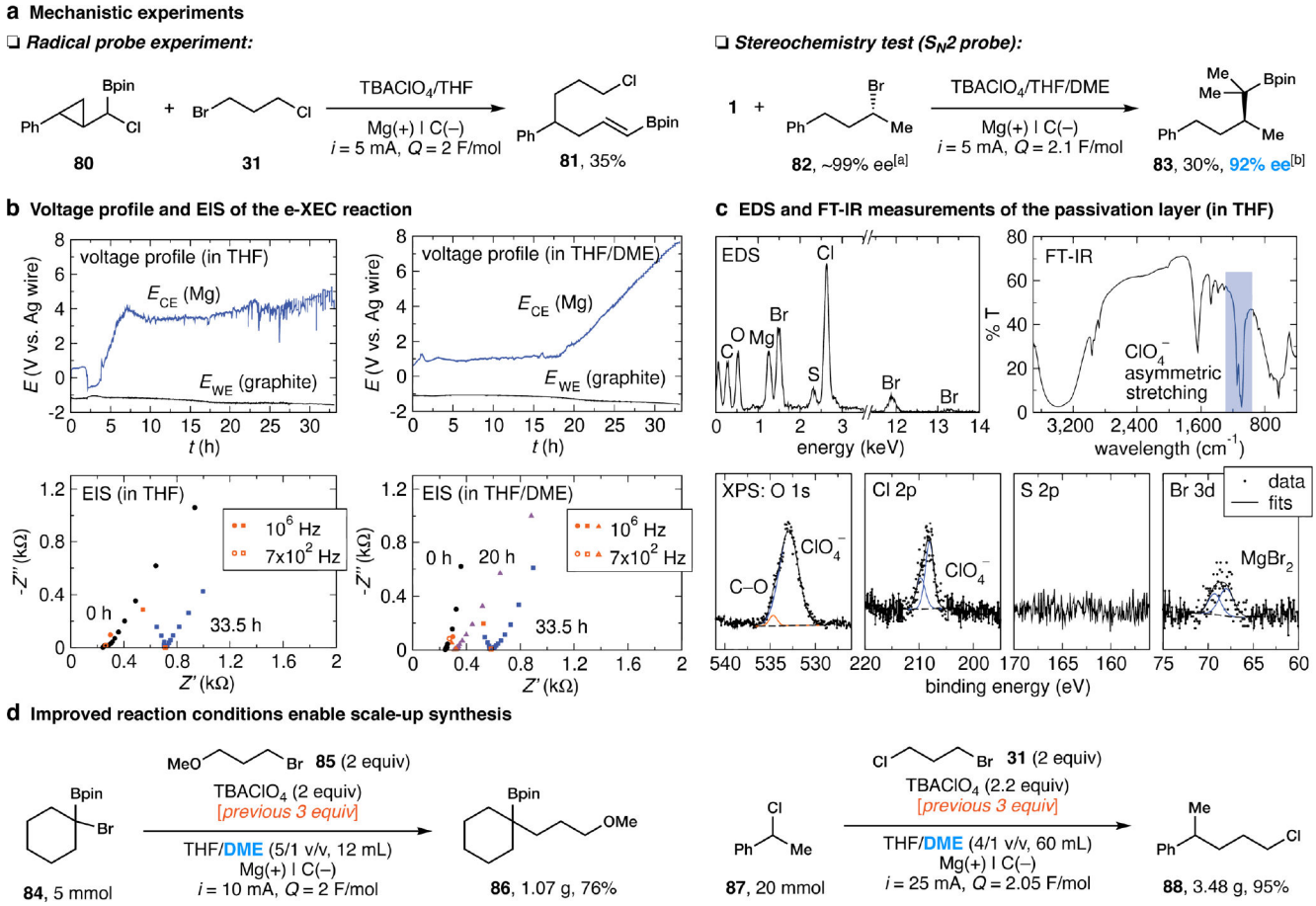

Fig 4. Anode passivation analysis and gram-scale synthesis.

(**A**) Mechanistic experiments. [a]Ee of the starting alcohol before bromination. [b]Absolute stereochemistry could not be determined and was assumed based on proposed mechanism. (**B**) The voltage profile and EIS of the e-XEC reaction. E_{CE} and E_{WE} are the potentials on the counter electrode (Mg) and working electrode (graphite), respectively. Z' and Z'' are the real and imaginary parts of the impedance, respectively. The complete EIS data can be found in the SI. (**C**) Characterization of the passivation layer formed on Mg anode after e-XEC in THF. (**D**) Scale-up synthesis.