Three-Component Cross-Electrophile Coupling: Regioselective Electrochemical Dialkylation of Alkenes

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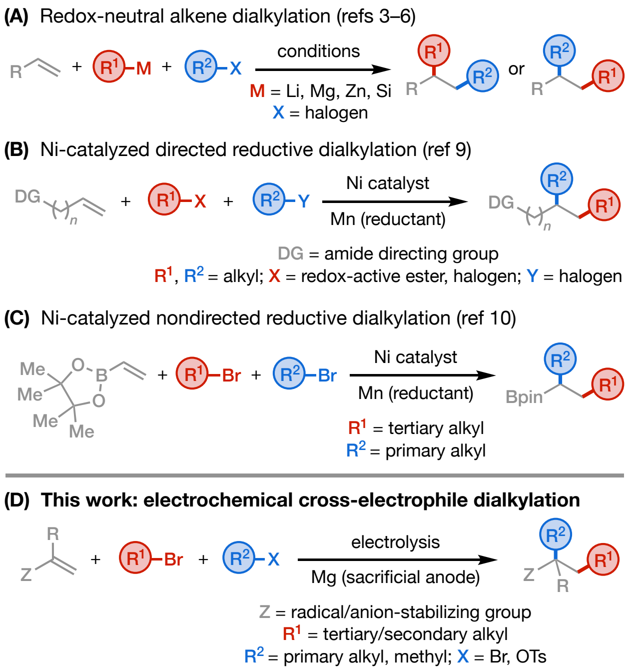
ABSTRACT: The cross-electrophile dialkylation of alkenes enables the formation of two C(sp^3)–C(sp^3) bonds from readily available starting materials in a single transformation, thereby providing a modular and expedient approach to building up structural complexity in organic synthesis. Herein, we exploit the disparate electronic and steric properties of alkyl halides with varying degrees of substitution to accomplish their selective activation and addition to alkenes under electrochemical conditions. This method enables regioselective dialkylation of alkenes without the use of a transition-metal catalyst and provides access to a diverse range of synthetically useful compounds.

The development of new methodologies for C(sp^3)–C(sp^3) bond formation continues to be a prominent objective in modern organic synthesis.[1] In this regard, the dialkylation of alkenes is a particularly modular and expedient strategy that can construct two C(sp^3)–C(sp^3) bonds in a single operation, rapidly increasing molecular complexity from readily accessible alkene feedstocks. Over the past decade, significant progress has been made in this area.[2] Such reactions typically proceed in a redox-neutral fashion using an alkyl electrophile and an alkyl organometallic reagent and often also require a transition-metal catalyst and a directing group on the alkene (Scheme 1A).[3–6] However, the reliance on potent organometallic reagents such as organolithium,[3] -magnesium,[4] and -zinc[5] complexes can limit the functional group compatibility and broader applicability of this approach.

Examples of reductive dialkylation using two alkyl electrophiles are now emerging, although this approach is less well-developed. Of note, initial efforts to achieve this transformation date back to the 1970s, when highly reactive metallic lithium[7] or Grignard reagents[8] were employed as the reductant to dialkylate unfunctionalized hydrocarbon alkenes. Toward discovering milder and more broadly applicable strategies, Koh and Shu independently reported elegant Ni-catalyzed alkene dialkylation methods with alkyl halides and aliphatic redox-active esters in the presence of a directing auxiliary group (Scheme 1B),[9] and Fu demonstrated a nondirected, Ni-catalyzed dialkylation with a variety of tertiary and primary alkyl halides using vinylboronic acid pinacol ester as the sole substrate (Scheme 1C).[10] Despite these seminal advances,[11] the reliance on Ni catalysts presents inherent limitations on substrate scope. Indeed, directing groups are often needed to suppress β-hydride elimination,[12] while the use of 1,1-disubstituted alkenes to access tetrasubstituted carbon centers has traditionally been challenging due to the steric hindrance of the proposed tertiary alkyl nickel intermediates.[13]

Scheme 1. Approaches for Dialkylation of Alkenes

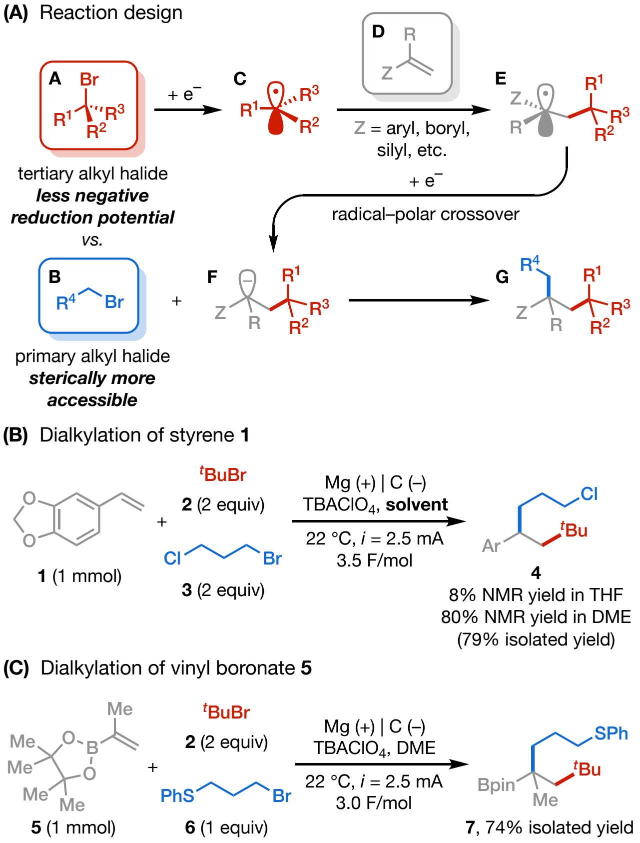


Considering these limitations, we were interested in developing a fundamentally different strategy relying on the use of electrochemistry[14] to accomplish the reductive dialkylation of alkenes in a selective and generalizable manner (Scheme 1D).[15] Electrochemical alkyl halide reduction has been well studied using analytical techniques,[16] although the scope of explored reactivity remains limited.[17] We recently established electrochemistry as an efficient tool for the reductive cross-electrophile coupling (XEC) of a variety of functionalized and unactivated alkyl electrophiles, and we found that under these conditions, alkyl halides display disparate reactivities depending on their degree of substitution.[18] We envisioned that a similar strategy could be exploited to accomplish the electroreductive dialkylation of alkenes (Scheme 2A). For example, in a reaction involving tertiary and primary alkyl halides, the tertiary alkyl halide (**A**) would be preferentially reduced, yielding a nucleophilic tertiary alkyl radical (**C**), which would add across a radical-acceptor alkene (**D**) to generate a new C–C bond and an adjacent alkyl radical (**E**). Further reduction of **E** at the cathode would yield a carbanion (**F**),[19] which would selectively attack the sterically more accessible primary alkyl halide (**B**) to afford the desired dialkylation product (**G**). To facilitate this mechanism, it is critical that the chosen alkene possesses a substituent that can help stabilize the key radical and anionic intermediates (**E**/**F**) via conjugation, hyperconjugation, or inductive effects, to ensure efficient radical–polar crossover. Based on the literature[19,20] and results from DFT calculations (Table S2), a variety of functional groups in principle would satisfy this criterion, such as π-systems (e.g., aryl, vinyl, alkynyl), boryl, silyl, and sulfide groups. Such functionalities would also constitute useful handles for further synthetic elaboration. More broadly, electrochemistry is a powerful tool for promoting the desired transformation, given that it can selectively activate structurally similar molecules on the basis of potential differences and readily support multiple electron transfer events in a net-reductive manifold. Here, we show that such an electroreductive cross-electrophile dialkylation offers a modular, efficient, and selective approach to construct C(sp^3)–C(sp^3) bonds from a diverse range of alkenes and alkyl halides.

We initially investigated this approach using styrene **1**, ^{t}BuBr (**2**), and 1-bromo-3-chloropropane (**3**) adopting conditions previously optimized for electroreductive XEC (Scheme 2B).[18] After electrolysis in THF, more than 95% of **1** was consumed although the desired product **4** was obtained in only 8% yield. We attributed this low yield to unwanted reactivity arising ultimately from severe passivation of the sacrificial Mg anode (Figure S5), which led to a rapidly rising and unstable anodic potential to compensate for the increasing electrode resistance (Figure 1a). In previous work,[18] we determined that the passivation layer formed under similar conditions is a mixture of magnesium salts—predominantly $MgBr_2$ and $Mg(ClO_4)_2$—formed from Mg^{2+} generated at the anode and Br^- and ClO_4^- in solution. These salts are poorly soluble in THF but will dissolve in coordinating solvents.[21] Positing that magnesium salts were also causing the observed electrode fouling in the dialkylation reaction, we surveyed additional solvents such as ^{t}BuCN and 1,2-dimethoxyethane (DME). Indeed, the thickness of the passivation layer was significantly reduced in DME (Figure S5), and correspondingly a low and steady electrode potential is maintained throughout electrolysis (Figure 1b).

Under optimized conditions with DME as solvent, product **4** was isolated in a significantly improved yield of 79% using 2 equiv of each alkyl bromide.[22] Finally, the conditions developed above also proved to be suitable for the dialkylation of vinyl boronate **5** (Scheme 2C), thus providing a modular and expedient approach for the synthesis of polysubstituted alkylboronic esters, a class of highly versatile synthetic intermediates. In this case, the reaction reached high yield using only 1 equiv of primary alkyl halide **6** and 2 equiv of its tertiary coupling partner **2**. In both cases, the products **4** and **7** were formed with high chemoselectivity, and importantly the formation of the opposite dialkylated regioisomer was not observed.

Scheme 2. Reaction Design and Development[a]



[a]All reactions were performed in an undivided cell using a sacrificial magnesium anode and a graphite cathode. TBA, tetrabutylammonium.

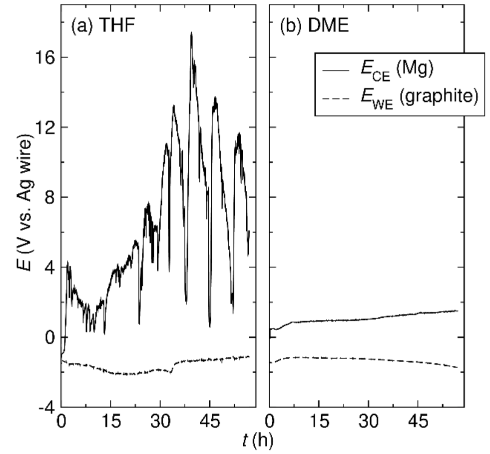
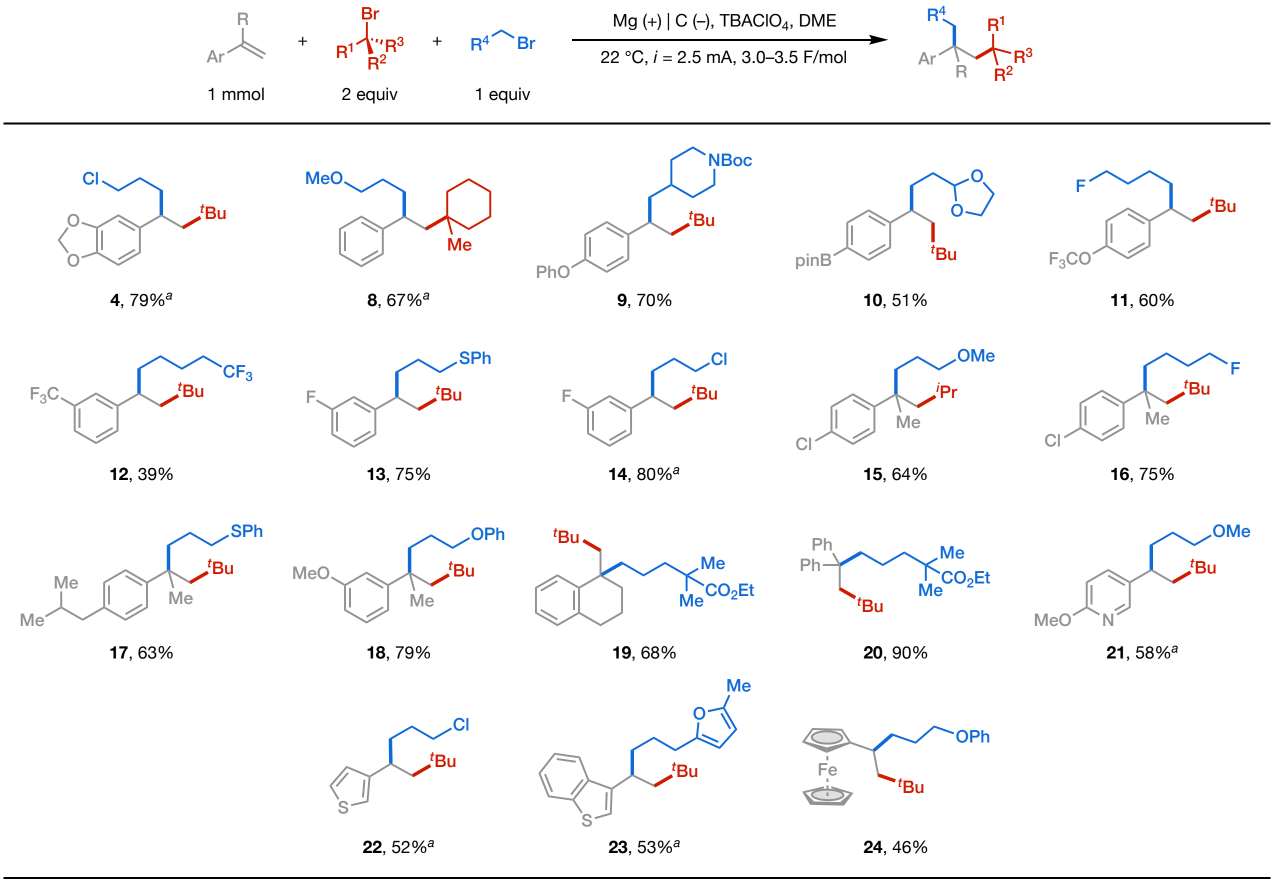


Figure 1. Voltage profiles of the Mg counter electrode (E_{CE}) and graphite working electrode (E_{WE}) during the electrochemical dialkylation reaction in either (a) THF or (b) DME. Ferrocenium/ferrocene redox couple ($Fc^{+/0}$) is +0.91 V versus Ag wire in $TBAClO_4$/THF (0.5 M).

Scheme 3. Electroreductive Dialkylation of Styrenes



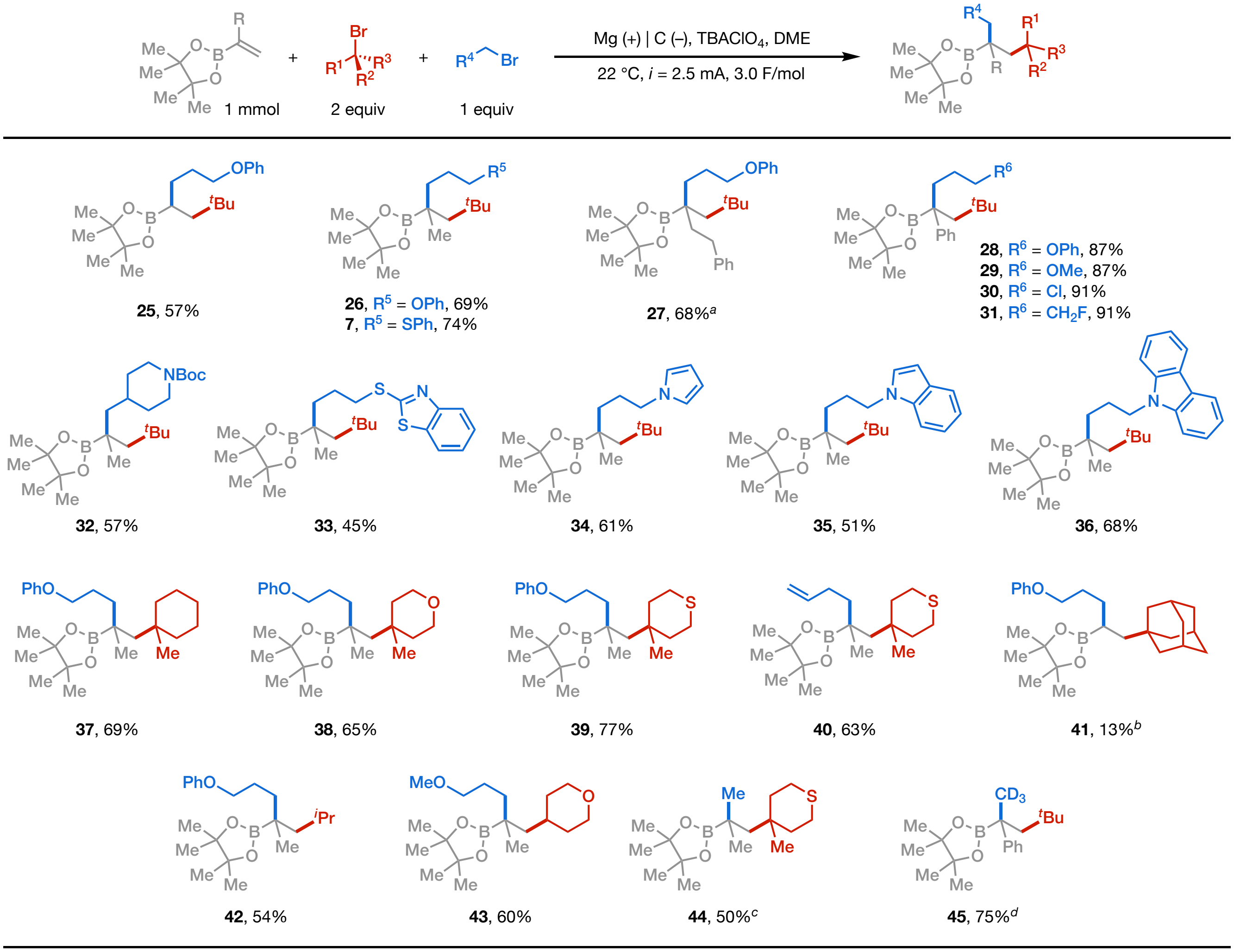
[a]2.0 equiv of primary alkyl bromide. Boc, *tert*-butyloxycarbonyl.

As shown in Scheme 3, a diverse array of styrenes and unactivated alkyl halides also underwent the desired transformation in good to excellent yields. Styrenes with distinct electronic properties (i.e., electron-rich and -deficient) and double-bond substitution (e.g., mono- and 1,1-disubstitued) proved to be suitable substrates. Of note, our approach successfully transformed 1,1-disubstituted alkenes—a traditionally challenging class of substrates in Ni-catalyzed dialkylation methods—to products with skipped quaternary carbon centers (**15**–**20**). In addition to ^{t}BuBr (**2**), other tertiary (e.g., 1-methylcyclohexyl; **8**) and secondary electrophiles (e.g., isopropyl; **15**) were successfully installed onto styrenes with high regioselectivity; however, activated radical precursors, such as perfluoroalkyl bromides and iodoacetates, were currently not tolerated (Figure S8). Despite requiring relatively negative cathodic potentials (−1.2 to −1.7 V versus Ag wire for product **4**; Figure 1b), our approach is compatible with a diverse panel of functional groups that are inert to single-electron reduction on graphite, such as carbamate (**9**), acetal (**4**, **10**), trifluoromethyl (**11**, **12**), sulfide (**13**, **17**), and ester (**19**, **20**). Aryl boronic ester (**10**) and alkyl/aryl chloride (**4**, **14**–**16**) remain intact during electrolysis, providing additional scaffolds for orthogonal cross-coupling reactions. Furthermore, alkenes and alkyl halides containing electron-rich and -deficient heteroarenes, including pyridine, (benzo)thiophene, and furan were readily converted to the desired products in good yields (**21**–**23**), and vinylferrocene was transformed into product **24**.

Starting from vinyl boronates, secondary and tertiary alkyl boronic esters **25**–**45** were synthesized (Scheme 4); these versatile building blocks can be readily converted to a variety of functionalities through known transformations.[23] Various *N*-heterocycles that are common pharmaceutical fragments[24] including piperidine (**32**), benzothiazole (**33**), pyrrole (**34**), indole (**35**), and carbazole (**36**) were also well-tolerated, and a suite of tertiary and secondary alkyl halides were used to construct dialkylated products in moderate to high yields (**37**–**43**). Notably, homoallyl bromide can be incorporated to form product **40** with the unactivated terminal alkene intact. Methylation (**44**) and trideuteromethylation (**45**) were also achieved when the corresponding tosylates were used in lieu of primary alkyl bromides, providing a convenient route for the installation of methyl groups—a transformation of increasing importance in medicinal chemistry.[25]

We further applied this method to the dialkylation of other categories of activated alkenes (Scheme 5A). For instance, vinyl silanes (**46**, **47**), phosphines (**48**), and sulfides (**49**, **50**) were dialkylated with high regioselectivity. Of note, thioether products **49** and **50** could be further hydrodesulfurized,[26] the cumulative electrochemical/chemical approach effectively achieving dialkylation of simple alkenes (i.e., dialkylation of ethylene and propylene). In the formation of product **52**, diene substrate **51** underwent 1,4-dialkylation.[19] Similarly, 1,4-addition on enyne substrate **53** resulted in the generation of tetrasubstituted allene **54**,[27] which is a versatile building block in organic synthesis.[28] Our ongoing efforts are now being directed toward improving the product yield achieved with each substrate class and using these products for complex target synthesis.

Scheme 4. Electroreductive Dialkylation of Vinyl Boronates



[a] 1.2 equiv of primary alkyl bromide and 3.5 F/mol. [b] 2.2 F/mol. [c] 3.0 equiv of MeOTs. [d] 1.0 equiv of CD_3OTs. Ts, 4-toluenesulfonyl.

Compared with tertiary alkyl bromides, chlorosilanes are excellent electrophiles in nucleophilic substitution, but they are poor single-electron acceptors. For example, the onset potential of ^{t}BuBr and chlorotrimethylsilane is −2.4 V (Figure S2) and < −3 V[29] versus $Fc^{+/0}$, respectively. Therefore, we envisioned that chlorosilanes could be used in place of primary alkyl bromides to forge $C(sp^3)$–Si bonds (Scheme 5B). Thus, we used our protocol to synthesize benzylsilane **55**, which could in principle undergo electrochemical benzylic substitution with suitable nucleophiles by oxidatively cleaving the newly formed C–Si bond.[30] We also achieved the regioselective silyl/germanyl alkylation of vinyl boronates by utilizing chlorosilanes and chlorogermanes as electrophiles, respectively, offering an efficient route to access *gem*-silylboronates (**56**, **57**) and *gem*-germylboronates (**58**). Reagents containing geminated main group elements could be used as a modular platform for the synthesis of complex molecules.[31]

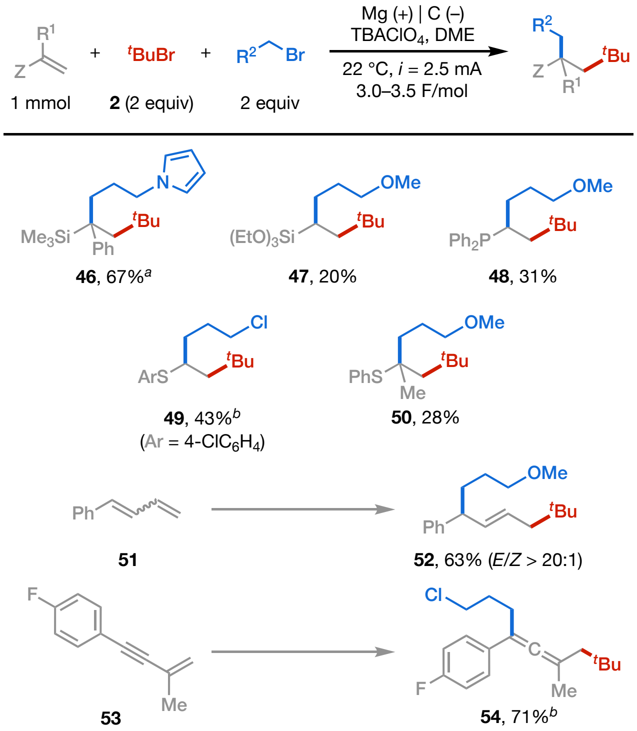
We further carried out cyclic voltammetry (CV), DFT calculations, and control experiments to assess the proposed reaction mechanism (Scheme 2A). CV data revealed that tertiary alkyl bromides (**A**) are typically easier to reduce comparing with primary alkyl bromides (**B**). For example, ^{t}BuBr (**2**) showed an irreversible reduction wave with a half-peak potential ($E_{p/2}$) at −2.77 V versus $Fc^{+/0}$, whereas primary alkyl bromide **3** displayed an $E_{p/2}$ at −3.00 V versus $Fc^{+/0}$, which is 0.23 V more difficult to reduce than **2** (Figure S2). Upon selective reduction of **A**, the resulting tertiary alkyl radical (**C**) could undergo a second reduction to form the corresponding carbanion intermediate (e.g., ^{t}Bu$^-$) but the potential of this process is rather negative due to the electron-rich nature of **C** (the computed standard reduction potential, $E°$, of *tert*-butyl radical is −3.54 V versus $Fc^{+/0}$). Instead, its addition to relatively electrophilic styrene or vinyl boronate is expected to be facile to form radical **E** (computed Gibbs energy of activation for *tert*-butyl radical addition: 12.6 kcal/mol when R = H, Z = Ph; 12.1 kcal/mol when R = H, Z = Bpin; Scheme 6A). Ring-opening dialkylation of radical probe **59** further supported the intermediacy of radical intermediate **E** (Scheme 6B). Compared with **C**, **E** with an anion-stabilizing group is predicted to undergo electroreduction at a more favorable potential ($E°$ = −2.80 V versus $Fc^{+/0}$ when R = H, Z = Ph; $E°$ = −2.63 V versus $Fc^{+/0}$ when R = H, Z = Bpin), giving rise to carbanion **F**. To verify the presence of carbanion intermediate **F**, D_2O was added to electrolysis under standard conditions, and deuteroalkylation product **61** was observed with significant deuterium incorporation (Scheme 6C). This reaction is unlikely to undergo deuterium atom transfer from D_2O to benzyl radical **E**, as the O–D bond in D_2O (computed bond dissociation energy: 118.3

kcal/mol) is substantially stronger than the benzylic C–D bond that would form in this process (89.3 kcal/mol). Instead, the deuteration took place via reaction of carbanion **F** with D_2O. Finally, the substitution of **B** with **F** is estimated to feature a low barrier (Scheme 6D), furnishing product **G**.

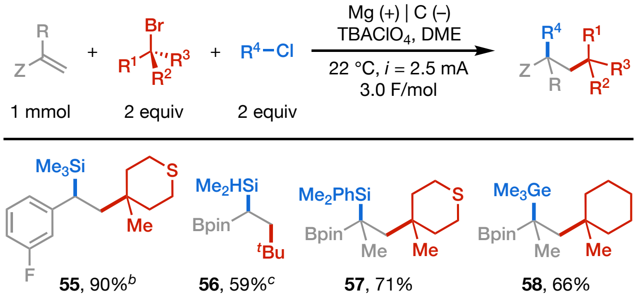
In summary, we have developed an electroreductive approach for the cross-electrophile dialkylation of alkenes that boasts broad reaction scope and delivers products with high chemo- and regioselectivity. We envision that this radical–polar crossover design will significantly enhance the ability of synthetic chemists to forge C(sp^3)–C(sp^3) bonds in the preparation of complex molecules and provide a general strategy for the discovery of new electrosynthetic transformations.

Scheme 5. Extended Scope

(A) Electroreductive dialkylation of other types of alkenes



(B) Electroreductive alkyl silyl/germylation of alkenes



[a] 1.0 equiv of primary alkyl bromide. [b] Yields determined by ^{1}H NMR analysis. [c] i = 5 mA.

Scheme 6. DFT Calculations and Control Experiments

(A) Geometries of *tert*-butyl radical addition transition states

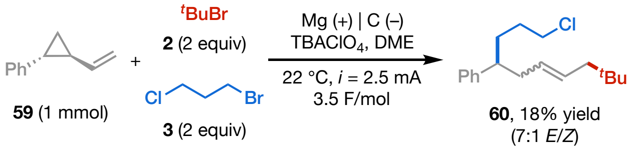
with styrene

$\Delta G^\ddagger$ = 12.6 kcal/mol

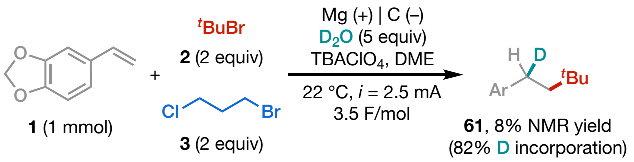
with vinylboronic acid pinacol ester

$\Delta G^\ddagger$ = 12.1 kcal/mol

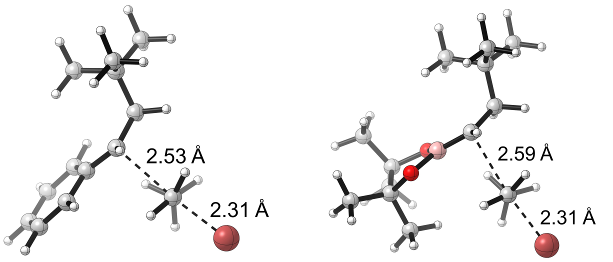
(B) Radical probe experiment



(C) Evidence for carbanion intermediate **F**



(D) Geometries of S_N2 transition states



with styrene

$\Delta G^\ddagger$ = 14.5 kcal/mol

with vinylboronic acid pinacol ester

$\Delta G^\ddagger$ = 14.2 kcal/mol

ASSOCIATED CONTENT

Supporting Information

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

Experimental procedures, characterization data, copies of NMR spectra, and computational details (PDF)

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

Financial support was provided by NIGMS (R01GM130928; to S.L.) and NSF Center for Synthetic Organic Electrochemistry (CHE-2002158; to K.A.S.). S.L. is grateful to FMC Corporation for a New Investigator Award and the Camille and Henry Dreyfus Foundation for a Camille Dreyfus Teacher-Scholar Award. We thank K. R. Meihaus, L. F. T. Novaes, J. I. Martinez Alvarado, and J. Rein for manuscript editing, I. Keresztes and D. Wood for assistance in mass spectrometry data collection and analysis, A. J. Ressler, S. J. Lee, and Z. Lu for assistance in substrate synthesis, and J. Liu for reproducing experiments.

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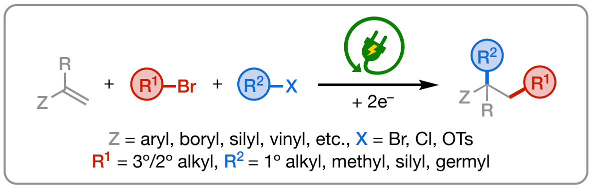
TOC GRAPHIC



Z = aryl, boryl, silyl, vinyl, etc., X = Br, Cl, OTs
R^1 = 3°/2° alkyl, R^2 = 1° alkyl, methyl, silyl, germyl

Representative products: