Paired Electrolysis Enables Reductive Heck Coupling of Unactivated (Hetero)Aryl Halides and Alkenes

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ABSTRACT: The formation of carbon-carbon (C–C) bonds is a cornerstone of organic synthesis. Among various methods to construct Csp^2–Csp^3 bonds, the reductive Heck reaction between (hetero)aryl halides and alkenes stands out due to its potential efficiency and broad substrate availability. However, traditional reductive Heck reactions are limited by the use of precious metal catalysts and/or limited aryl halide and alkene compatibility. Here, we present an electrochemically mediated, metal- and catalyst-free reductive Heck reaction that tolerates both unactivated (hetero)aryl halides and diverse alkenes such as vinyl boronates. Detailed electrochemical and deuterium-labeling studies support that this transformation likely proceeds through a paired electrolysis pathway, in which acid generated by the oxidation of *N*,*N*-diisopropylethylamine (DIPEA) at the anode intercepts an alkyl carbanion formed after radical-polar crossover at the cathode. As such, this approach offers a sustainable method for the construction of Csp^2–Csp^3 bonds from (hetero)aryl halides and alkenes, paving the way for the development of other electrochemically mediated olefin difunctionalization reactions.

Introduction

The emergence of cross-coupling reactions, particularly those that facilitate C–C bond formation, has garnered considerable traction within the realm of chemical synthesis.[1–5] In particular, intermolecular Csp^2–Csp^3 coupling reactions have been instrumental in accessing natural products and other bioactive molecules (Figure 1a).[6,7] Despite their efficacy, traditional methodologies for Csp^2–Csp^3 bond formation possess significant drawbacks. For example, transition metal-catalyzed Negishi couplings[8,9] between aryl (pseudo)halides and alkylzinc reagents or Friedel–Crafts reactions[10,11] between arenes and alkyl (pseudo)halides suffer from the need to handle air-sensitive organometallic reagents, poor atom economy, low yields, and/or limited functional group tolerance. As such, new, straightforward methods for the construction of Csp^2–Csp^3 bonds from easily handled starting materials would have significant utility in medicinal chemistry and beyond.

Recently, the 1,2-difunctionalization of olefins has emerged as a powerful approach for the synthesis of diversely functionalized complex molecules, driven largely by the ubiquity of alkenes as building blocks in organic synthesis.[12–15] For example, the anti-Markovnikov 1,2-hydroarylation of olefins, referred to as the reductive Heck reaction, is a promising platform for the construction of Csp^2–Csp^3 bonds due to its lack of waste and the potential for simple handling of all three reaction components (Ar, H, alkene).[16–20] Current approaches for the reductive Heck reaction largely rely on transition metal catalysts (Figure 1b). Various Pd catalysts have been developed, which generally require the use of specialized hydride sources to bypass the formation of the traditional Heck coupling product.[17,20–23] To circumvent the use of Pd due to its cost and availability constraints, Ni catalysts have been developed in recent years, but they tend to suffer from limited alkene scopes and the need for superstoichiometric amounts of strong reductants such as Zn metal.[18,24–26] Recently, specialized photoredox catalysts capable of directly reducing unactivated haloarenes have been developed;[27–33] some of these catalysts have been employed in reductive Heck reactions between haloarenes and alkenes (Figure 1b).[28,34,35] Despite their potential, the scopes of these transformations tend to be much narrower with respect to both the alkene and aryl halide coupling

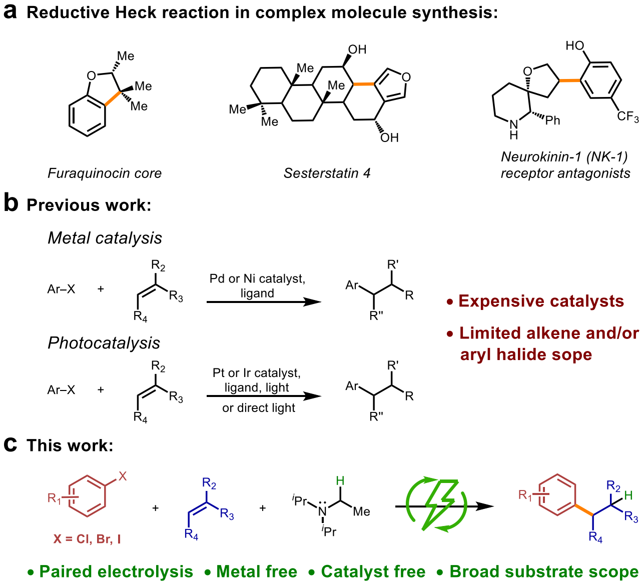


Figure 1. a) Examples of reductive Heck reactions in complex molecule synthesis. b) Traditional reductive Heck couplings through transition metal catalysis or photocatalysis. c) Reductive Heck reaction via paired electrolysis (this work).

partners compared to traditional Pd-catalyzed methods. Additionally, the need for efficient light penetration into solution and the use of Ir or Pt photocatalysts in many cases hinders the scalability of these reactions.

Electrochemistry has (re)emerged as a powerful tool for organic synthesis, leveraging its inherent sustainability and complementary selectivity compared to traditional methods.[36,37] Recently, we[38] and others[39–44] have shown that electroreductive couplings (i.e., without light irradiation or transition metal catalysts) can enable the radical functionalization of unactivated haloarenes, but the scope of reactivity, especially in terms of C–C bond-forming reactions, remains limited. Additionally, such organoelectrochemical transformations tend to focus on reactions occurring at only one electrode (working electrode), resulting in significant waste from byproducts generated at the other electrode (counter electrode). This waste limits the true sustainability of electrochemical methods. Paired electrolysis, which involves harnessing both cathodic and anodic reactions to minimize the formation of undesirable byproducts, presents a promising approach to maximize the efficiency of electrochemical methods.[36,45–49] However, rationally designed paired electrolysis reactions remain relatively rare.

Herein, we report an electrochemically mediated reductive Heck coupling of unactivated haloarenes and alkenes that proceeds without the need for any catalysts or photoirradiation (Figure 1c). In-depth electrochemical and deuterium-labeling studies support that this transformation likely proceeds through a paired electrolysis mechanism, in which acid generated at the anode quenches the anion formed after radical-polar crossover from addition of the cathodically generated aryl radical to the alkene partner. Critically, our approach demonstrates remarkable efficiency even with challenging substrates such as heteroaryl halides and relatively unactivated alkenes, including vinyl boronates. Our work lays the groundwork for a sustainable new platform in olefin difunctionalization, in which cationic species generated at the anode quench anionic species generated at the cathode.

Results and Discussion

To investigate the feasibility of the proposed electrochemically driven reductive Heck reaction, the coupling of methyl 3-chlorobenzoate (**1**) and 1,1-diphenylethylene (**2**) was selected as a model reaction (Figure 2, left). After optimization, the use of 6 equiv. of **2**, 4 equiv. of *N,N*-diisopropylethylamine (DIPEA) as an inexpensive sacrificial reductant, tetrabutylammonium hexafluorophosphate ($TBAPF_6$) as the electrolyte, porous carbon as both the cathode and the anode, acetonitrile (MeCN) as the solvent, and an applied current of 10 mA (7 F/mol) at room temperature was found to afford the corresponding product **4** in 92% yield (Figure 2, SI Table S1). The use of other tertiary amines, including Et_3N (57%) and $(nBu)_3N$ (64%), leads to lower yields of **4** (entries 27–28, SI Table S1). As expected, the reaction does not proceed in the absence of electricity (entry 29, SI Table S1). Higher currents (up to 30 mA) can be used to further shorten the reaction time (2.5 h) as desired without compromising the reaction yield (entries 19–21, SI Table S1). Notably, neither catalysts nor redox mediators are needed to drive this reaction to completion, in contrast to most other reported electroreductive couplings of chloroarenes.[38–40,42,50]

Further optimization revealed that the ratio of **2** and DIPEA relative to **1** plays a pivotal role in achieving a high reaction yield. Through systematic variation, we observed that a 6:4 ratio of **2**:DIPEA is optimal, although similar yields could be obtained with slightly less DIPEA (3 equiv.) and/or slightly more **2** (7 equiv.). We hypothesized that the alkene:DIPEA ratio may be critical to pushing other, less-activated alkenes to couple as well. As such, the coupling of **1** and styrene (**3**) to yield **5** was optimized by varying the ratio of **3** and DIPEA as well (Figure 2, right). A similar ratio of **3**:DIPEA (7:4) to that used for the coupling with **2** (6:4) was found to provide the highest efficiency, furnishing **5** in 75% yield (Figure 2). It should be noted that fewer equivalents of alkene can be employed, if necessary, with reactions employing 2 equiv. of **2** still proceeding with good yields (up to 61%, entry 18, SI Table S1). A slight excess of alkene relative to the haloarene is likely needed to suppress the formation of the corresponding reduction (Ar–H) product (SI Table S4). In some other electro(photo)reductive couplings,[28,29,41] up to 50 equiv. of the radical trap are needed to obtain good yields, highlighting the efficiency of the present transformation.

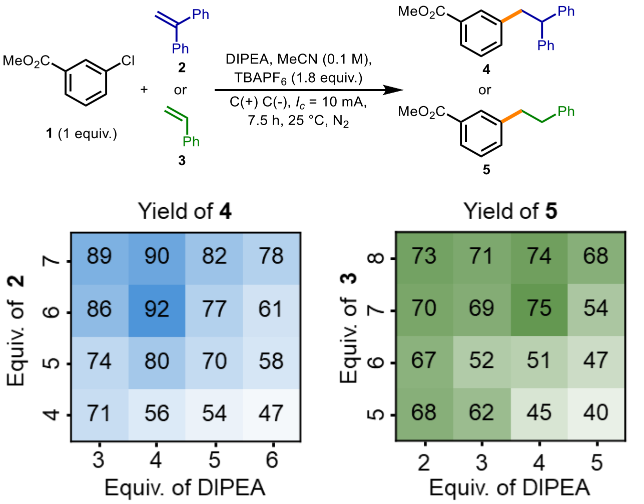
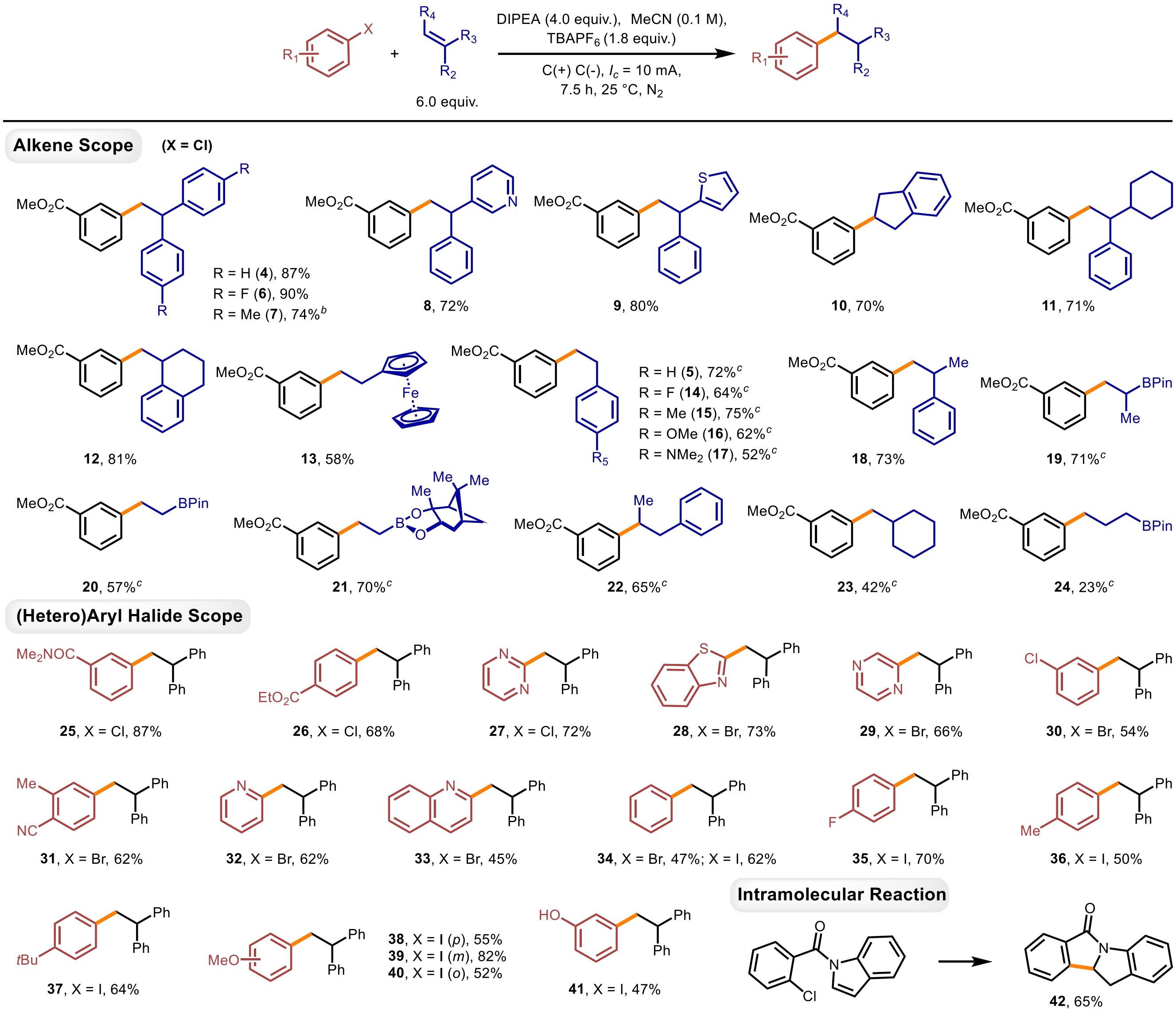


Figure 2. Reaction optimization by varying the ratio of alkene to DIPEA. Yields based on ^1H NMR analysis of the crude product mixtures using CH_2Br_2 as an internal standard.

With optimized conditions in hand, the scope of the electroreductive coupling of alkenes and haloarenes was investigated (Table 1). First, a variety of alkenes were coupled with **1**. 1,1-Diarylethylenes bearing various substituents (H, F, CH_3) were subjected to the standard conditions and produced the corresponding 1,1,2-triarylethane derivatives (**4**, **6**, **7**) in excellent yields. For the coupling to produce **7**, *N,N*-dimethylformamide (DMF) was used as the reaction solvent in place of MeCN due to the poor solubility of the alkene substrate in MeCN. The standard coupling to produce **4** also proceeds well in DMF (entry 23, SI Table S1). 1,1-Diarylethylene derivatives with

Table 1. Scope of reductive Heck coupling via paired electrolysis.



[a]Isolated yields are shown. [b]DMF as solvent. [c]7.0 equiv. alkene.

two different aryl groups were also suitable reaction partners (**8, 9**). These include alkenes containing heteroaryl groups, such as pyridine (**8**) and thiophene (**9**), which are widely present in drug-like molecules. 1-Alkyl-1-arylethylene derivatives also produce the corresponding products (**11**, **12**, **18**) in good yields, regardless of the steric bulk of the alkyl group. Indene (**10**) is also an efficient coupling partner to produce 2-arylindanes, which are a core of some terpenoid natural products such as quadrangularin A.[51]

Certain vinylarenes, such as vinylferrocene (**13**), can be engaged under the standard reaction conditions to produce the corresponding 1,2-diarylethane derivatives in good yields. Using an alkene:DIPEA ratio of 7:4 relative to the chloroarene starting material, styrenes bearing different functional groups, including electron-donating amine groups, react smoothly to afford the corresponding hydroarylated products (**14–17**) in good yields as well. Additionally, vinyl boronates proved to be suitable substrates under these modified conditions (**19–21**). The synthesized alkylboronates are versatile building blocks for organic synthesis and have also found recent application in medicinal chemistry.[52] Vinylboronates would likely not be suitable substrates for transition metal-catalyzed reductive Heck reactions due to competing Suzuki-Miyaura coupling with the aryl halide partner.[53] As such, 1,2-difunctionalizations of vinyl boronates remain relatively rare and complement existing transition metal-catalyzed methods for the arylborylation of alkenes.[54–56] This protocol is also applicable to β-methylstyrene (**22**), reflecting the generally good tolerance of radical reactions towards steric hindrance. Simple aliphatic olefins can be converted to the corresponding products (**23**, **24**, SI Figure S21) in moderate to low yields, likely due to the lack of radical/anion-stabilizing substituents on these substrates. Other unactivated alkenes provided moderate yields of the desired products but could not be separated from the corresponding reduction (Ar–H) side products, representing a current limitation of this method (SI Figure S21).

Next, a range of haloarenes were coupled with **2** under the standard reaction conditions (Table 1). Traditionally, purely electroreductive couplings (i.e., without light irradiation, redox mediators, or catalysts) require electron-deficient aryl iodides or bromides to proceed efficiently and show limited functional group tolerance.[43,44,57] The successful coupling of a moderately activated chloroarene bearing a reactive ester group (**1**) led us to hypothesize that the present reaction should show a much-improved scope. Indeed, electrophilic functional groups, including amides (**25**, **42**), esters (**26**), and nitriles (**31**) are tolerated under these conditions. More easily reduced carbonyl groups such as aldehydes and ketones are not tolerated, as they likely undergo competitive reduction over the chloroarene substrate.[58] N-containing heterocycles are ubiquitous in drug-like molecules but can present a challenge for traditional transition metal catalysis due to catalyst inhibition.[59] In contrast, a range of heteroaryl chlorides and bromides were viable substrates for reductive coupling with **2**, including those bearing pyrimidine (**27**), benzothiazole (**28**), pyrazine (**29**), pyridine (**32**), and quinoline (**33**) groups. A substrate bearing both an aryl chloride and an aryl bromide underwent selective debromination to furnish the chloroarene product (**30**), demonstrating that the cleavage of C–Br bonds occurs selectively over C–Cl bonds. This is likely due to the faster mesolytic cleavage of aryl bromide radical anions (see mechanistic discussion below).[60] The chloroarene functionality can be engaged in subsequent transition metal-catalyzed transformations, allowing for rapid product elaboration.

Electroreductive couplings involving electron-neutral and electron-rich chloroarenes generally proceed in poor yields, likely due to the inherent difficulty of reducing these substrates.[61] As such, bromide or iodide leaving groups are preferred for these substrates. Consistently, electron-neutral bromobenzene and iodobenzene (**34**) could be efficiently coupled with **2** under the standard reaction conditions. Electron-rich aryl iodides bearing fluorine (**35**), alkyl (**36**, **37**), and methoxy (**38–40**) groups afford the corresponding products in decent yields. This includes an *ortho*-methoxy group (**40**), demonstrating that this transformation tolerates steric hindrance on the haloarene partner (**22**). Notably, 3-iodophenol also produces the corresponding product in moderate yield (**41**), suggesting that this electroreductive coupling is tolerant of some acidic functional groups. In addition to intermolecular reactions, this method could also be applied to an intramolecular coupling to produce an indolinone (**42**), which is a common heterocyclic backbone in bioactive compounds.[62]

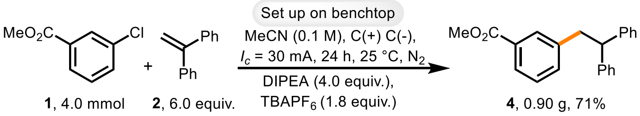


Figure 3. Large-scale synthesis of **4** from **1** and **2**.

Given its simplicity, this electroreductive coupling can easily be conducted on gram-scale in a 3-neck round-bottom flask (Figure 3, SI Figure S3). The large-scale experiment was set up on the benchtop under N_2 and the reaction time was kept short by increasing the current to 30 mA. Under these conditions, nearly 1 g of **4** could be produced in just 24 h of reaction time, supporting the scalability of this reaction.

The mechanism of the electroreductive Heck coupling of **1** and **2** was studied to understand the underpinnings of its operational simplicity (Figures 4–5). Based on previous electrochemical studies,[44,63,64] we hypothesized that, at the cathode, the haloarene substrate likely undergoes reduction to the corresponding radical anion, which would undergo rapid mesolytic cleavage to the corresponding aryl radical.[60] This radical would be trapped by the alkene substrate and then undergo either hydrogen atom transfer (HAT) or radical-polar crossover to produce a carbanion that would undergo rapid protonation (Figure 5, left).[44] While the source of H in the final product was initially unclear, the two most likely sources are the solvent (MeCN) or DIPEA after electrochemical oxidation.[65–67]

The electrochemical processes occurring at the cathode and anode were first interrogated using cyclic voltammetry (CV) with ferrocene (Fc) as an internal reference (Figure 4a–b). CV revealed that **2** undergoes irreversible reduction to **2**$^{\cdot-}$ at a much more negative potential ($E_{p/2}$ = −2.92 V vs. Fc/Fc$^+$) than that at which **1** is reduced to **1**$^{\cdot-}$ ($E_{p/2}$ = −2.45 V vs. Fc/Fc$^+$, Figure 2a, SI Section 7). Similar CV profiles were observed for mixtures of **1** and **2** or **1** and **2** and DIPEA, indicating that neither **2** nor DIPEA exert a discernible influence on the reduction of the aryl chloride substrate (Figure 4a). Comparing the $E_{p/2}$ of **1** with the cathode potential measured during a reaction in progress using a 3-electrode setup (−2.62 V vs. Fc/Fc$^+$, Figure 4c, SI Section 5), we conclude that the dominant cathodic reaction is likely the reduction of **1** to **1**$^{\cdot-}$. Despite the absence of catalysts or redox mediators under these conditions, the measured cathode potential herein (−2.62 V vs. Fc/Fc$^+$) is not that much more negative than related reactions conducted with redox mediators (approximately −2.35 V vs Fc/Fc$^+$)[38] or electrophotocatalysts (approximately −2.57 V vs Fc/Fc$^+$).[29] At the anode, DIPEA likely undergoes oxidation to maintain charge balance during the reaction.[65–67] Indeed, CV revealed that DIPEA undergoes oxidation to DIPEA$^{\cdot+}$ with an $E_{p/2}$ value of +0.60 V vs. Fc/Fc$^+$ (Figure 4b, SI Section 6), which is comparable to the measured anode potential during the reaction (+0.74 V vs. Fc/Fc$^+$, Figure 4c). Notably, CV measurements at different scan rates support that the species generated upon reduction of **1** exhibits ~25-fold faster diffusion away from the electrode than that generated upon oxidation of **2** (SI Section 11), which helps to minimize overreduction to the corresponding aryl anion and subsequent protonation to form the reduced (Ar–H) side product.[68]

Deuterium labeling experiments were next conducted to identify the source of H in the final product (Figure 4d, SI Section 10). Surprisingly, conducting the reaction in CD_3CN as the solvent did not lead to any detectable deuterium incorporation into the final product. This result suggests that the solvent does not undergo HAT or deprotonation under the standard reaction conditions. In contrast, the addition of a small amount of D_2O to the reaction mixture (1:50 relative to CH_3CN) led to 66% deuterium incorporation into the product, as confirmed by ^{1}H NMR and gas chromatography-mass spectrometry (GC-MS) (SI Figures S10–S11).

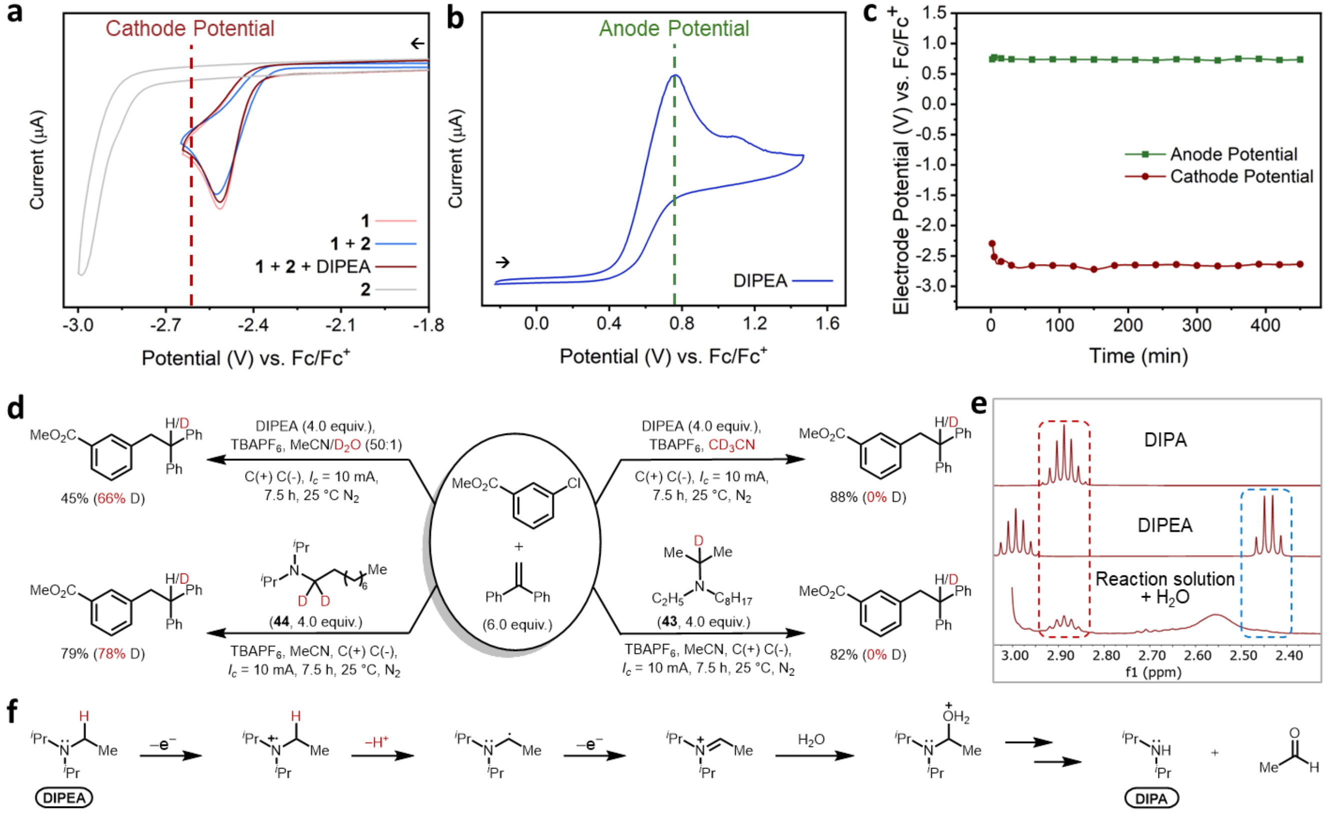


Figure 4. Mechanistic studies. a). CVs of methyl 3-chlorobenzoate (**1**), 1,1-diphenylethylene (**2**), a mixture of **1** and **2**, and a mixture of **1** and **2** and DIPEA. Chemicals dissolved in an electrolyte solution of $TBAPF_6$ (0.1 M) in MeCN in a N_2-filled glovebox, with Fc as an internal reference. Scan rate: 100 mV/s. $E_{p/2}$ of **1** = −2.45 V vs. Fc/Fc^+; $E_{p/2}$ of **2** = −2.92 V vs. Fc/Fc^+. b) CV of DIPEA dissolved in an electrolyte solution of $TBAPF_6$ (0.1 M) in MeCN in a N_2-filled glovebox, with Fc as an internal reference. Scan rate: 100 mV/s. $E_{p/2}$ = +0.60 V. c) Anode (green) and cathode (red) potentials during a reaction in progress measured using a Ag/Ag^+ reference electrode. d) ^1H NMR spectra of DIPA (top), DIPEA (middle), and the crude reaction mixture after mixing with DI H_2O (bottom). e) Deuterium labeling experiments. f) Proposed mechanism for the formation of DIPA and H^+ from DIPEA at the anode.

Trace deuterium incorporation into the product (5%) was also observed when *t*-BuOD was added to the reaction mixture (SI Figure S12). Together, these findings support a mechanistic scenario involving radical-polar crossover to produce a carbanionic intermediate that is ultimately trapped by protonation (Figure 5, left).[44]

DIPEA has been reported to function as a 2-electron terminal reductant in electrocatalytic reactions while also generating H^+ upon oxidation (Figure 5, right).[65–67] We hypothesized that this process could serve as the H^+ source under the standard reaction conditions through a paired electrolysis pathway. To verify this hypothesis, additional isotope labeling experiments were designed. We synthesized selectively deuterated DIPEA analogues with deuterium incorporated only on the secondary (**43**) or primary (**44**) alkyl groups.[69] When employing deuterated amine **43** instead of DIPEA under the standard reaction conditions, the desired product **4** was obtained without any deuterium incorporation, as confirmed by ^1H NMR and GC-MS (SI Figures S15–S16). This observation indicates that the α-hydrogens of the isopropyl groups on DIPEA are likely not functioning as H sources under the standard reaction conditions. In contrast, replacing DIPEA with **44** yielded **4** with significant (78%) deuterium incorporation (SI Figures S17–S18). As such, these findings suggest that the α-hydrogens on the ethyl group of DIPEA are the dominant H source for incorporation into the final product.

Previous studies suggest that, upon oxidation, DIPEA forms an iminium ion at the ethyl group, leading to *N,N*-diisopropylamine (DIPA) upon hydrolysis (Figure 4f).[65–67] To further support the proposed anodic reaction, we compared the ^1H NMR spectrum of a crude reaction after addition of deionized H_2O with those of DIPEA and DIPA (Figure 4e). After the reaction, only DIPA was detected. This observation further supports that DIPEA undergoes the loss of two electrons and a proton to produce an iminium ion at the anode during the reaction.

These collective findings suggest that the oxidation of DIPEA plays a pivotal role in generating the acid required to complete the electroreductive coupling of haloarenes and alkenes via a paired electrolysis mechanism (Figure 5). Consistently, conducting the coupling between **1** and **2** in a divided cell produced a low yield (21%) of **4**, supporting the need to reduce the haloarene and oxidize DIPEA in the same chamber to obtain high yields (entry 31, SI Table S1). We cannot rule out the possibility that HAT from DIPEA or an oxidized intermediate occurs to the initially generated alkyl radical, although this mechanistic scenario does not account for deuterium incorporation in the presence of D_2O, a source of D^+ but not $D\cdot$.[70–72] Overall, these mechanistic studies support that DIPEA serves a dual role as terminal reductant (allowing for electrolysis to occur) and H source for completing the radical-polar crossover reaction pathway.

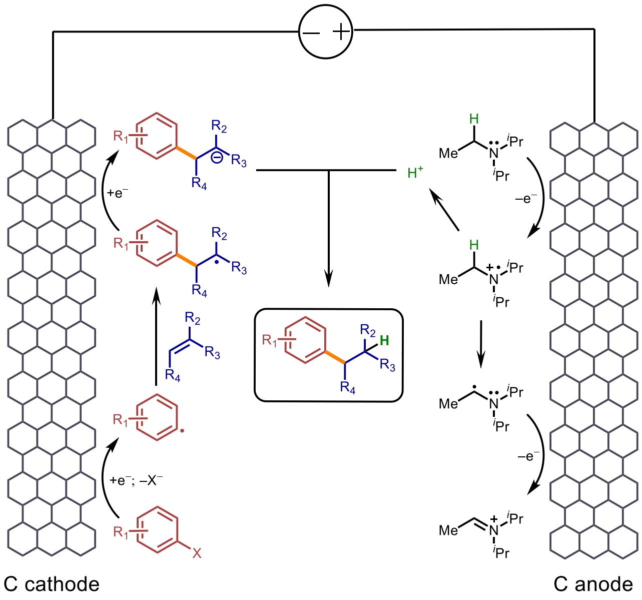


Figure 5. Proposed paired electrolysis mechanism.

Conclusion

Herein, we present a metal- and catalyst-free method for the reductive coupling of (hetero)aryl halides and alkenes, both widely available substrates in organic synthesis. This electrochemically promoted reaction proceeds smoothly in an undivided cell and generally affords good yields with various substrates, including (hetero)aryl halides and vinyl boronates. In-depth mechanistic studies support that this transformation likely proceeds through a rare paired electrolysis mechanism.[45–49] Specifically, the aryl halide undergoes cathodic reduction, followed by addition to the alkene substrate to form an alkyl radical that is subsequently reduced through a radical-polar crossover pathway. The resultant alkyl anion reacts with H⁺ generated by oxidation of DIPEA at the anode to form the desired product. The use of deuterated alkyl amines allows for selective deuteration of the final product.

Our work demonstrates that paired electrolysis offers a sustainable platform for olefin difunctionalization, in which one alkene coupling partner is generated at the cathode (e.g., aryl radical) and one alkene coupling partner is generated at the anode (e.g., H⁺). In future work, we will explore the scope of reaction partners that can be efficiently added across alkenes using this simple electrochemical protocol.

ASSOCIATED CONTENT

Experimental procedures and all characterization and electrochemistry data.

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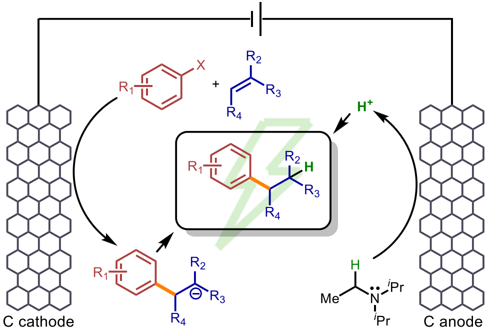

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