Paired Oxidative and Reductive Catalysis: Breaking the Potential Barrier of Electrochemical C(sp³)−H Alkenylation

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ABSTRACT: Due to the intrinsic inertness of alkanes, strong oxidative conditions are typically required to enable their C(sp³)−H functionalization. Herein, a paired electrocatalysis strategy was developed by integrating oxidative catalysis with reductive catalysis in one cell without interference, in which earth-abundant iron and nickel are employed as the anodic and cathodic catalysts, respectively. This approach lowers the previously high oxidation potential required for alkane activation, enabling electrochemical alkane functionalization at the ultra-low oxidation potential of ~0.25 V under mild conditions. Structurally diverse alkenes, including challenging all-carbon tetrasubstituted olefins, can be accessed via this electrochemical C(sp³)−H alkenylation using readily available alkenyl electrophiles.

Methods for the selective conversion of abundant alkanes into higher-value, functionalized chemical feedstocks are highly desired.[1] However, the high redox potentials (often above 3.0 V vs SCE) and strong bond-dissociation energy (BDE ~96−101 kcal/mol) of aliphatic C−H bonds in alkanes lead to extreme difficulty in controlling reaction chemoselectivity, where oxidative degradation of other functionalities and solvent functionalization is likely to occur prior to the desired C(sp³)−H functionalization,[2] leading to minimal functional group tolerance (Figure 1a). In this content, electrochemistry, in which electrons are used as a sustainable and inherently safe redox reagent, offers an attractive alternative for oxidative activation of alkanes.[3] More specifically, the use of redox mediators to achieve indirect processes has been envisioned as a milder and more practical alternative to overcome the extremely high oxidation potentials of alkanes. In this regard, research into electrochemically driven C(sp³)−H functionalization is mostly focused on relatively activated C−H bonds based on low bond-dissociation energies and/or polarity effects (α-heteroatom, benzylic, and allylic).[4] In contrast, the direct functionalization of strong, neutral C(sp³)−H bonds in inert alkanes has rarely been explored(Figure 1b). In 2017, Baran and co-workers reported an electrochemical oxidation of unactivated C−H bonds using quinuclidine as a redox mediator, in which the working potential of the reaction was measured to be around +1.8 V vs. Ag/AgCl.[2a] Later, they reported an alkyl C−H fluorination using a simple nitrate additive (E$_p$ = 2.2 V vs. Ag/AgCl).[5] Subsequently, Xu et al. developed a photoelectrochemical Minisci alkylation of N-heteroarenes with aliphatic C−H bonds employing the chloride anion as an anodic redox mediator, where the anode potential is approximately +0.92 V to +1.04 V vs. Fc⁺/Fc.[6] Afterwards, tetrabutylammonium decatungstate (TBADT), sulfonamide and cerium chloride were also employed in Minisci alkylation reaction.[7] Furthermore, Lei et al. developed a Mn-catalyzed

oxidative azidation of C(sp³)−H bonds, in which the anodic oxidative potential ranges from 1.9 to 2.2 V vs. Ag/AgCl.[8] Very recently, Ritter-type amination of C(sp³)−H bonds using sulfate (E$_o$ = 2.6 V vs NHE) as stoichiometric mediator was also acheievd.[9] In all of these cases, strong oxidative conditions and/or stoichiometric mediators, and high oxidative potential at the anode with H$_2$ evolution at the cathode are required. In addition, the use of expensive mediators (e.g., quinuclidine) limits their further application. Thus, the development of efficient catalytic systems based on earth-abundant catalyst for alkane functionalization that operate under ultra-low oxidation potentials and mild conditions is highly desired.
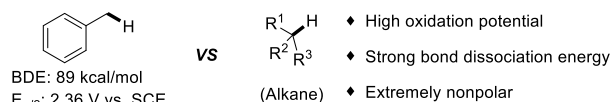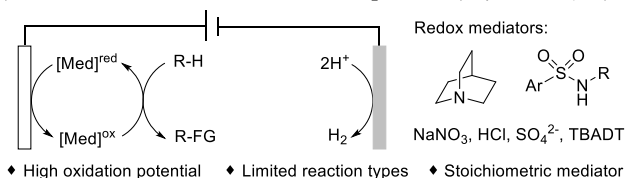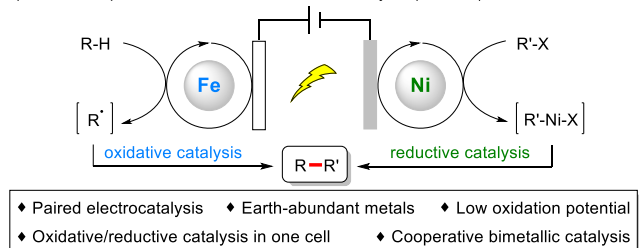

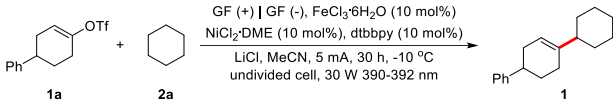**Figure 1.** Electrochemically driven alkane functionalization

In contrast to single half-electrode reactions, simultaneous activation of both alkanes and electrophiles on both electrodes via paired electrolysis is more energy efficient, synthetically useful, and would greatly increase the functional complexity and synthetic value of the cross-coupling products available.[10] However, owing to the large electrode separation in electrolytic cells, which typically ranges from millimeters to centimeters, the highly reactive intermediates generated simultaneously at the anode and cathode are usually not stable enough to migrate from one side to the other, so the selective cross-coupling of reactive intermediates is hindered by their decomposition due to inefficient interelectrode transport.[11] To address this challenge, we reasoned that the distinctively separated oxidative and reductive centers in electrolysis also provide an opportunity to develop paired electrocatalysis with merged oxidative catalysis and reductive catalysis in one cell, in which paired anodic/cathodic catalysts could serve as stable shuttles to transport electrons from a heterogeneous process occurring at an electrode to a homogeneous process occurring in the solvent (Figure 1c). Thus, highly reactive intermediates with short lifetimes could be generated and interact with each other in solvent rather than being generated on the electrode surface, enabling the selective coupling of highly reactive intermediates without limitation by molecular diffusion and interelectrode transport rates.

To achieve this paired electrocatalysis, the major challenge is the regeneration of different catalysts through oxidation and reduction in one system, in which the high-valent metals generated from oxidative catalysis are prone to reduction and the low-valent metals generated from reductive catalysis are prone to oxidation. On this basis, the key to achieving this novel strategy is identifying a couple of non-interfering paired catalysts. Bearing these challenges in mind, we wondered whether $FeCl_3$ could be exploited to render an alternative electrophotocatalyst for the proposed paired electrocatalysis. Previous studies have demonstrated that tetrahedral $[FeCl_4]^-$ is readily formed in solution by the reaction of $FeCl_3$ and chlorine salts.[12] Although reduction of Fe^{3+} is thermodynamically favored on the cathode, the anion $[FeCl_4]^-$ could efficiently move to the anode region driven by an oriented electric field, thus having its effective concentration selectively increased near the surface of the anode and preventing its electroreduction on the cathode. Moreover, highly electrophilic chloride radicals, which effectively activate alkanes, can be generated through ligand-to-metal charge transfer (LMCT) by light irradiation of $[FeCl_4]^-$,[13] and the formed Fe^{2+} can be recycled to $[FeCl_4]^-$ on the anode. Furthermore, owing to the ultra-low oxidative potential required to recycle of Fe^{2+} to Fe^{3+}, earth-abundant metal ions, such as Ni^{2+}, which have higher oxidation potentials, can be applied as cathodic catalysts without competitive oxidation at the anode, leading to orthogonal oxidative and reductive catalysis and enabling alkane functionalization at ultra-low potential.

To explore the feasibility of our proposed system, the reaction of alkenyl triflate 1a and cyclohexane 2a in the presence of commercially available $FeCl_3·6H_2O$ and $NiCl_2·DME$ under irradiation by purple LEDs was investigated. Outcomes from the screening of catalysts, ligands, and halide salts are shown in Table 1. The desired cross-coupling product 1 can be isolated in 75% yield under the optimized conditions, with none providing

the reductive coupling products. Unsurprisingly, the choice of anodic and cathodic catalysts has a profound influence on the reaction. Anodic catalysts, such as $CuCl_2$, which can be easily deposited on the surface of the cathode, even at a low reduction potential, or $CeCl_3/BiCl_3$, leads to low conversion of electrophiles and low yields (entries 2–4). Cathodic catalysts such as $CoCl_2$, which have a much lower reactivity in comparison to that of $NiCl_2·DME$, failed to afford the desired product (entry 5). These results demonstrate the importance of the correct choice of paired catalysts. Ligands for the nickel also play a crucial role in the reaction. The commercially available 4,4'-di-tert-butyl-2-2'-bipyridine (dtbbpy) gave the best yields among ligands such as 1,2-bis(diphenylphosphino)ethane (dppe), phenanthroline, and other bipyridine-type ligands (entries 6–9). Furthermore, the addition of chlorine salts that increase the concentration of the anion $[FeCl_4]^-$, is crucial for reaction efficiency, and LiCl provides the best outcome (entry 10). A current that matches the anodic and cathodic reaction rates was required for high yields, and an optimal current of 5 mA was identified (entry 11). Control experiments indicated that paired catalysts, electric current, and light irradiation are all essential, as reactions performed in their absence provided poor results (entries 12–13).

Table 1. Optimization of the reaction conditions.[a]

GF (+) | GF (-), $FeCl_3·6H_2O$ (10 mol%)
$NiCl_2·DME$ (10 mol%), dtbbpy (10 mol%)
LiCl, MeCN, 5 mA, 30 h, -10 °C
undivided cell, 30 W 390-392 nm

1a + 2a → 1

Entry	Variation from standard conditions	Yield (%)[b]
1	none	78 (75)
2	$CuCl_2$ instead of $FeCl_3·6H_2O$	6
3	$CeCl_3$ instead of $FeCl_3·6H_2O$	n.d.
4	$BiCl_3$ instead of $FeCl_3·6H_2O$	27
5	$CoCl_2$ instead of $NiCl_2·DME$	n.d.
6	dppe instead of dtbbpy	n.d.
7	phenanthroline instead of dtbbpy	15
8	tpy[c] instead of dtbbpy	n.d.
9	bpy instead of dtbbpy	66
10	nBu_4NCl instead of LiCl	22
11	I = 10 mA	57
12	w/o $FeCl_3·6H_2O$ or $NiCl_2·DME$	n.d.
13	w/o electricity or light	n.d.

[a]Reaction conditions: 1a (0.6 mmol), 2a (10.0 equiv.), $FeCl_3·6H_2O$ (10 mol%), $NiCl_2·DME$ (10 mol%), dtbbpy (10 mol%), LiCl (2.0 equiv.), anhydrous MeCN (6.0 mL), 5 mA, 30 h, 30 W 390-392 nm, -10 °C, argon, graphite felt (GF) as electrodes, undivided cell. [b]GC yields using biphenyl as an internal standard, isolated yields in parentheses. [c]2,6-bis(2-pyridyl)pyridine.

Having assessed the feasibility of the paired redox strategy, we next evaluated its generality with regard to alkenyl electrophiles. As shown in Figure 2, a broad range of structurally diverse mono-, di-, and tri-substituted alkenyl triflate/bromides are viable in this reaction, delivering the corresponding alkenes in good to excellent yields (1–13). Di-substituted alkenyl

electrophiles proved to be suitable for this transformation, providing the desired alkenylation products in 56%–79% yields (1–5). Interestingly, the benzo-fused vinyl triflate provides higher efficiency, as exemplified by product 5. Most encouragingly, highly sterically demanding tri-substituted alkenyl triflates were also found to be amenable to this protocol, affording the desired olefins 6 and 7 in 51% and 67% yields, respectively, demonstrating the utility of this system for rapid synthesis of all-carbon tetrasubstituted alkenes.[14] In addition, mono-substituted alkenyl halides, such as β-bromostyrene derivatives, also participate in this reaction to give 1,1-di-substituted alkenes in moderate to good yields (8–10), and the stereochemistry of the alkenyl electrophiles is reliably translated into the products. The easily reducible nitrile group survives well during electrolysis, providing significant opportunities for downstream preparation of more complex molecules. Intriguingly, bromoethene, which is a colorless and flammable gas, was also found to be a suitable substrate for this reaction, giving the desired allylbenzenes (11 and 12) and but-3-en-1-ylbenzene (13) in moderate yields.
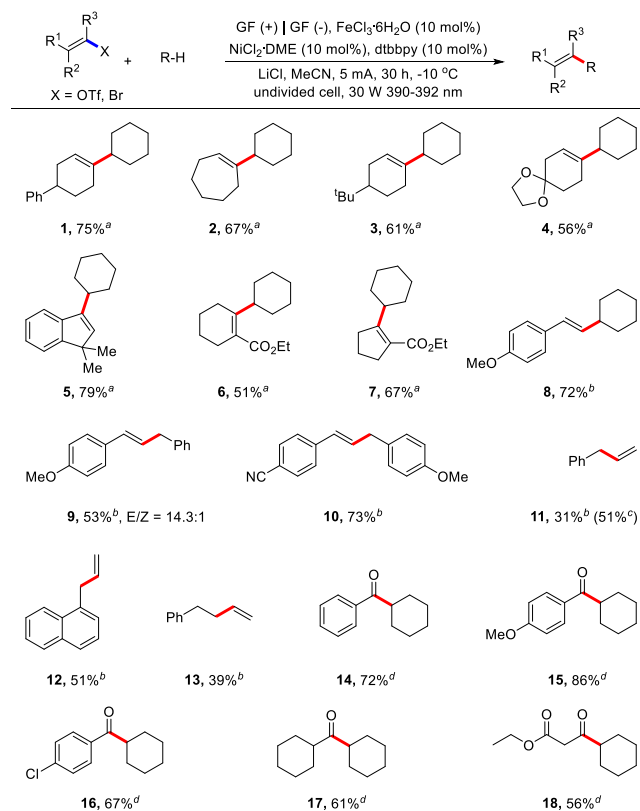
Figure 2. Substrate scope for electrophiles. [a]Unless otherwise specified, all reactions were performed under standard conditions (entry 1, table 1). [b]Reaction performed using the corresponding alkenyl bromide. [c]GC yields using biphenyl as an internal standard [d]Reaction performed using the corresponding acyl chlorides.

From a synthetic perspective, this paired redox system offers a modular synthetic route for the coupling of more challenging electrophiles with alkanes. For example, acyl chlorides, which are very sensitive to electroreductive conditions, also serve as suitable reaction partners in this protocol. A range of benzoyl chlorides, with either electron-rich or electron-deficient
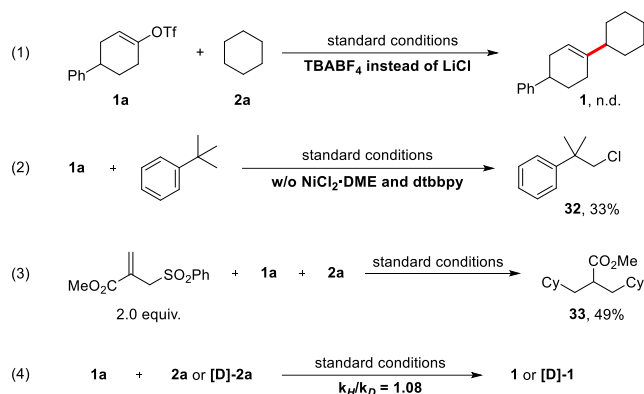
substituents on aromatic ring, were viable in this transformation, affording the corresponding ketones (14–18) in 56%–86% yields. Interestingly, both secondary and primary acyl chlorides derived from the corresponding alkyl carboxylic acids with multiple C(sp³)–H moieties also serve as suitable reaction partners, yielding the desired ketones (17 and 18) in 56%–61% yields without functionalizing other C–H bonds within the molecular scaffold.
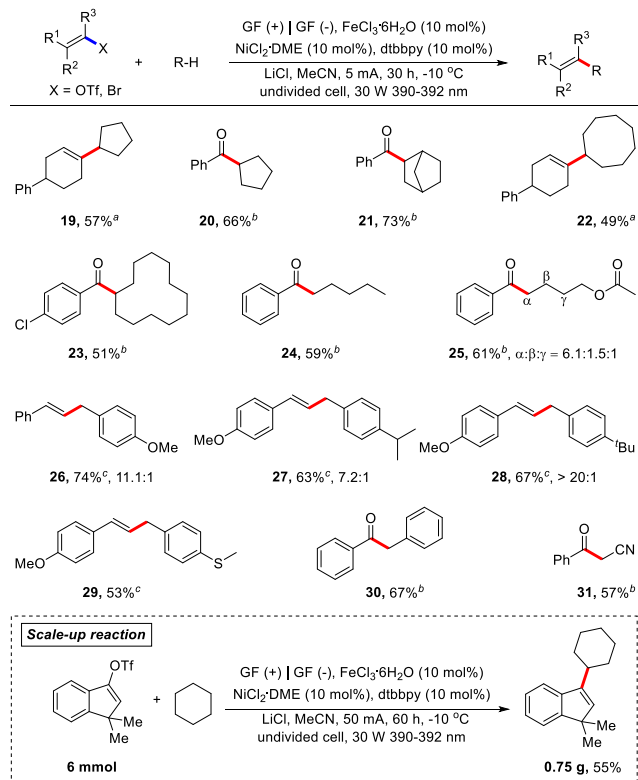
Figure 3. Substrate scope for C(sp³)–H moieties. [a]Unless otherwise specified, all reactions were performed under standard conditions (entry 1, table 1). [b]Reaction performed using the corresponding acyl chlorides. [c]Reaction performed using the corresponding alkenyl bromide. For details, see the Supporting Information.

Subsequently, the reaction scope with respect to alkanes was evaluated. Cycloalkanes of various ring sizes ranging from five to twelve carbon atoms afforded the desired products 19–23 in moderate to good yields (49%–73%). For acyclic alkanes bearing multiple reactive sites, such as *n*-pentane and butyl acetate, C(sp³)–H functionalization proceeded preferentially at the methyl group (24–25), which is probably due to steric effects. The reaction of benzylic C(sp³)–H bonds was also efficient, delivering the desired products in 53%–74% yields. Interestingly, in the case of substrates with multiple hydridic C–H bonds, the reaction proceeded predominantly at the primary and less sterically hindered C(sp³)–H bond (27–28), with the sterically hindered C–H bonds remaining intact. Furthermore, the methylthio group, which is very sensitive to oxidative conditions, was also amenable to this protocol and an example reaction gave the desired product 29 in 53% yield, highlighting the utility of very mild 'redox-neutral' electrosynthesis. Electron-withdrawing groups, such as nitrile, renders the adjacent hydrogen atoms both stronger and less hydridic,

resulting in a significantly lower reactivity. Intriguingly, this protocol can also be used as a modular synthetic route for the functionalization of less hydridic and more challenging C–H bonds. For example, acetonitrile was also tolerated in this reaction, affording the corresponding product **31** in 57% yield. Furthermore, this protocol can be readily scaled up with high efficiency. For example, 0.75 g of **5** was isolated in 55% yield.


(1) [1a structure: Ph-cyclohexene-OTf] + [2a cyclohexane] → standard conditions, TBABF$_4$ instead of LiCl → [product] **1**, n.d.

(2) **1a** + [tert-butylbenzene] → standard conditions, w/o NiCl$_2$·DME and dtbbpy → [product] **32**, 33%

(3) MeO$_2$C–[acrylate]–SO$_2$Ph + **1a** + **2a** (2.0 equiv.) → standard conditions → Cy–[CO$_2$Me]–Cy **33**, 49%

(4) **1a** + **2a** or [D]-**2a** → standard conditions, k_H/k_D = 1.08 → **1** or [D]-**1**

Figure 4. Mechanistic study reactions.

A series of experiments were performed to gain insight into the reaction mechanism. First, as shown in Figure 4, no desired product was detected when TBABF$_4$ was employed as the electrolyte instead of LiCl (Eq. 1). In addition, the control experiments detailed in Table 1 (entry 12) already proved that the iron catalyst is essential for this transformation. These results reveal the importance of the formation of [FeCl$_4$]$^-$ *in situ* and the direct anodic oxidation of chloride to give the electrophilic chloride radical to initiate the reaction can be excluded. Furthermore, when *tert*-butylbenzene was employed to replace **2a** under standard conditions in the absence of nickel catalyst (Eq. 2), the corresponding (1-chloro-2-methylpropan-2-yl)benzene was isolated in 33% yield, which might be generated via an anodic chlorination process. Moreover, the model reaction was completely inhibited if the radical acceptor methyl 2-((phenylsulfonyl)methyl)acrylate was added to the standard reaction (Eq. 3), where the cyclohexyl radical substitution/addition product **33** was isolated in 49% yield. These results demonstrate that a highly electrophilic chloride radical is generated *in situ* via an anodic catalytic process, which effectively activates alkanes through hydrogen abstraction to afford the corresponding carbon radical. In addition, parallel reactions of **1a** with **2a** or [D]-**2a** (cyclohexane-d_{12}) showed that k_H/k_D = 1.08, which suggests that cleavage of the C(sp^3)–H bond is not involved in the rate-determining step (Eq. 4).[15]

Subsequently, the dependence of the average rate on current was evaluated, and the model reaction shows a first-order dependence on current (Figure 5a), suggesting that electron transfer at the electrodes is still the rate-determining step in this reaction under these conditions. Furthermore, the electrode voltage over the course of electrolysis was monitored under standard conditions. Anodic oxidation was kept around 0.25 V, while the cathodic reduction was kept around −1.5 V (Figure 5b). Cyclic voltammetry (CV) experiments further confirmed that anodic oxidation is in accordance with the Fe^{II}/Fe^{III} oxidative catalytic cycle, while the cathodic reduction corresponds to the Ni^{III}/Ni^{II} or Ni^{II}/Ni^{I} reductive catalytic cycle (Figure 5c-d).[16]
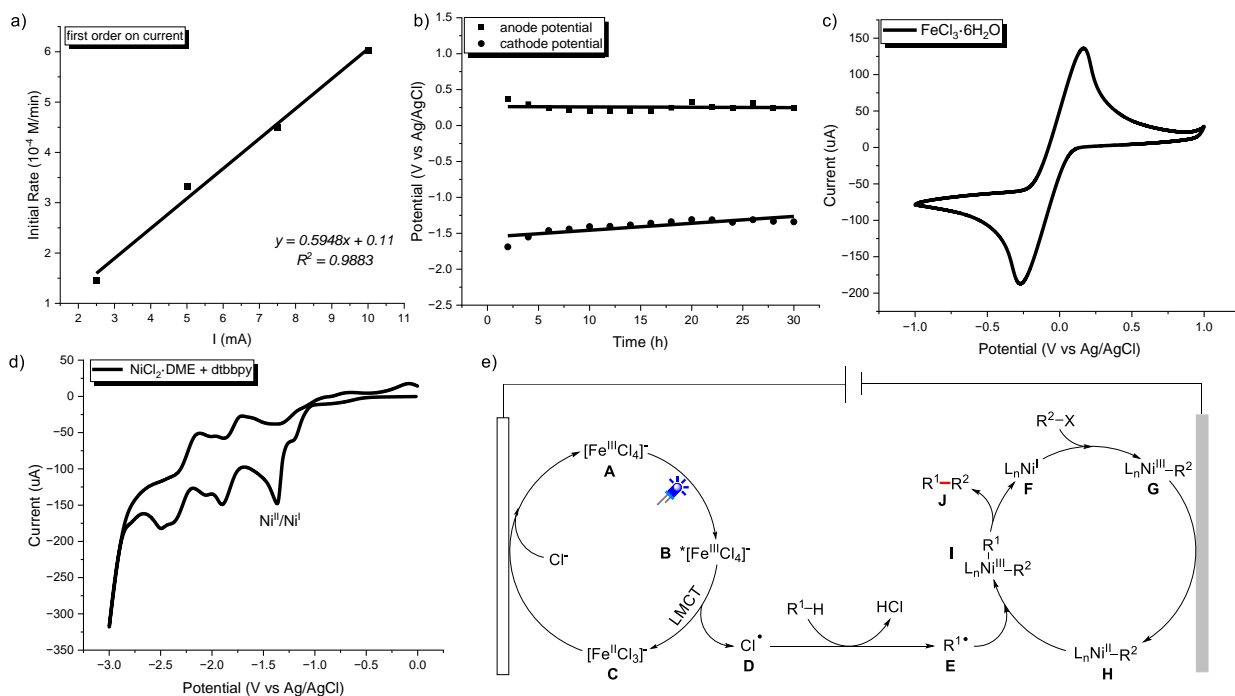
Figure 5. a) Plot showing first-order rate dependence on current. b) Electrode voltage over the course of electrolysis. c) CV of FeCl$_3$·6H$_2$O. d) CV of the mixture of NiCl$_2$·DME and dtbbpy. e) Proposed mechanism.

On the basis of our results and previous studies,[1b, 12-13, 16-17] a plausible mechanism is shown in Figure 5e. The process begins with electrophilic chloride-radical formation via ligand-to-metal charge transfer of the excited $[FeCl_4]^-$ catalyst. This chlorine radical would undergo hydrogen abstraction with alkane to a reactive alkyl radical, and the $[FeCl_3]^-$ was oxidized on anode to recycle $[FeCl_4]^-$. Concomitantly, the catalyst precursor of Ni^{II} is reduced on the cathode, affording a Ni^I species. The Ni^I species undergoes further oxidative addition with alkenyl electrophiles to generate an alkenyl-Ni^{III} complex, which is subsequently electrochemically reduced to an alkenyl-Ni^{II} species. Then, this alkenyl-Ni^{II} species intercepts the alkyl radical to generate the high-valent Ni^{III}-alkenyl, alkyl species **I**. **I** then undergoes further reductive elimination to furnish the cross-coupling products and regenerate the Ni^I catalyst.

In conclusion, a paired electrocatalysis strategy for alkane functionalization is reported for the first time, in which paired earth-abundant iron and nickel catalysts serve as electron shuttles to activate anodic and cathodic reactants, respectively, in one cell without interference. Importantly, $C(sp^3)$–H alkenylation and acylation of alkanes with ultra-low oxidation potential is achieved using this protocol, providing a modular method for versatile mono- or muti-substituted olefins and ketones under mild conditions. Mechanistic studies showed that iron is recycled at the anode, while nickel is recycled at the cathode. Furthermore, chloride anions play an important role in reaction efficiency, possibly by promoting the formation of $[FeCl_4]^-$ *in situ*.

ASSOCIATED CONTENT

Supporting Information

Experimental procedure, characterization data, and copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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