Nickel-catalyzed switchable asymmetric electrochemical functionalization of alkenes

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The development of general electrocatalytic methods for the diversity-oriented regio- and stereoselective functionalization of alkenes remains a challenge in organic synthesis. We present a switchable electrocatalytic method based on anodic oxidative activation for the controlled liberation of chiral α-keto radical species toward stereoselective organic transformations. Electrogenerated α-keto radical species capture alkene partners, allowing switchable intermolecular alkene difunctionalization and alkenylation in a highly stereoselective manner. In addition to acting as proton donors to facilitate H₂ evolution at the cathode, the unique properties of alcohol additives play an important role in determining the distinct outcomes for alkene functionalization under electrocatalytic conditions.

INTRODUCTION

Electrosynthesis provides an enabling and environmentally sustainable tool to drive chemical transformation in modern chemistry (1–13). Advances made by using chiral catalysts in the field of electrosynthesis (14–16) to form new carbon-carbon bonds with high levels of stereoselectivity (17–26) have provided access to chiral scaffolds that are ubiquitous in medicines and functionalized materials of great importance (27, 28). Over the last decade, Lewis acid catalysis has received much attention in organic synthesis and serves as a platform for the identification of new asymmetric synthetic reactions (29). The creation and implementation of enantioselective radical modes that offer access to hitherto inaccessible reaction pathways is thus a key goal for further growth in the field of electrocatalysis (30–34). Different from classical enolate chemistry, merging stereoselective Lewis acid catalysis with electrochemistry could provide anodic oxidation–triggered electrophilic α-keto radical based on a single-electron transfer (SET) process, thus offering a unique opportunity to access modular structural complexity with predictable reactivity (Fig. 1A) (35–38).

Alkenes are common functional groups for the chemo-, regio-, and stereoselective incorporation of C–C and C–X bonds in organic molecules (39). The electrochemical functionalization of alkenes with respect to carbonyls and other polar functional groups offers unique potential for the late-stage diversification of complex compounds sustainably (40). Mechanistically, alkenes undergo electrochemical oxidation via the SET process to create radical cation intermediates (Fig. 1B, type a) and would create massive space for further synthetic elaborations of alkenes with external nucleophiles (41–43). Alternatively, the direct activation of nucleophilic species forms the appropriate radical intermediate to initiate subsequent alkene addition (Fig. 1B, type b) (44–51). In this regard, the Meggers group reported elegant asymmetric electrocatalytic oxidation cross-coupling reactions with an innovative chiral-at-rhodium Lewis acid catalyst to afford enantioenriched 1,4-dicarbonyl compounds (35). Lin and co-workers reported seminal asymmetric electrocatalytic cyano-functionalization and hydrocyanation of alkenes through the enantioselective capture of carbon-centered radicals by chiral copper-cyano complexes to furnish chiral nitriles (52, 53). Recently, we developed asymmetric electrosynthesis leading to intermolecular alkylation (36) and arylation (37) reactions. However, the electrochemical α-alkenylation of ketones has been sluggish to develop and thus is difficult for the development of chemo- and enantioselective carbon-carbon bond formation reactions with high efficiency (38, 54, 55). Furthermore, despite the immense synthetic potential of these reactions in organic synthesis, the discovery of divergent catalytic procedures from a common precursor rationally and predictably under electrolytic circumstances remains a formidable challenge.

From the viewpoint of high-step economy and versatility (56), the diamine-based nickel complex (57, 58) can serve as the chiral catalyst to trigger anodic SET activation of an enolate species to generate α-keto radicals (36, 37), which might be intercepted by a variety of alkenes. In addition, we hypothesized that the nucleophilicity of alcohol additives would play a vital role in controlling the reaction pathways, thus offering a unique opportunity for individual access to diverse products rationally and predictably. Here, we describe the successful development of such a switchable electrocatalytic system through a stereoselective radical addition pathway to achieve asymmetric difunctionalization and alkenylation reactions with excellent chemo- and enantioselectivities by chiral Lewis acid catalysis (Fig. 1C).

RESULTS

Design of the switchable electrosynthesis

To test the feasibility of our plan, 2-acylimidazole 1a and diphenylethylene 2a were used as the model substrates containing 2,6-diter-butylpyridine as a basic additive in an undivided cell equipped with a boron-doped diamond (BDD) anode and a platinum plate cathode (Table 1). In an initial experiment, the desired product 3a was obtained in 55% yield with a marginal enantiomeric excess (ee) by using a constant current of 2 mA with methanol (MeOH) as both a cosolvent and a trapping reagent (entry 1; see the Supplementary Materials for details). We next tested a series of diamine ligands for the nickel catalyst to determine their influence on the enantioselectivity of the transformation, and large variations in the ee values and yields were observed in these reactions (entries 1 to 8). Pleasingly, we found that the use of chiral diamine ligand L8 could lead to desired...
product 3a in 74% yield with 93% ee under the electrolytic conditions (entry 8). Further attempts to achieve enantioselective switchable electrochemical alkenylation processes were carried out by manipulating the reaction conditions. We reasoned that the generation of 4a through the electrocatalytic alkenylation pathway would benefit from the introduction of less nucleophilic polyfluorinated alcohols, such as 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) or 1,1,1-trifluoroethanol (TFE), under otherwise identical reaction conditions [N = −4.23 (HFIP), −2.78 (TFE), and 0.01 (MeOH)] (59). Therefore, we investigated the effect of polyfluorinated alcohol additives, and the use of HFIP or TFE instead of methanol led to the switchable formation of the targeted alkenylated product 4a over 3a, albeit with moderate enantiocontrol (entries 9 and 10). A slight increase in enantioselectivity was observed when the reaction temperature was decreased to 0°C along with Pt as electrodes (60% ee, entry 11). To our delight, the stereoselectivity was enhanced with a mixed solvent of MeCN/TFE (86% ee, entry 12). Further exploration revealed that the enantioselectivity was increased with TBACl as a supporting electrolyte (entry 13, 40% yield, 93% ee). Ultimately, the desired product 4a could be obtained in 56% yield with 95% ee in a solvent mixture of MeCN/DCM/TFE at a 1:1:1 ratio (entry 14).

**Substrate scope**

With the optimal reaction conditions established, we next investigated the substrate scope of the asymmetric difunctionalization of alkenes (Fig. 2). As shown in Fig. 2A, the method was compatible with a different class of N-substituted imidazole moieties, giving the desired products 3a to 3d in good yields and excellent enantioselectivities. The absolute configuration of the resulting molecules was assigned by single-crystal x-ray diffraction analysis. Both electron withdrawing and electron-donating groups at the para position attached to the benzene ring of 2-acylimidazoles performed well under the optimized reaction conditions (3e to 3k). Furthermore, substituents at the meta or ortho positions on the aryl moiety of 2-acyl imidazoles 1 were also well tolerated (3l to 3n). Disubstituted-phenyl and (hetero)aromatic substitution gave the desired products in moderate yields with high enantioselectivities (3o and 3p). Moreover,

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**Fig. 1. Overview of the asymmetric switchable electrochemical transformations of alkenes.** (A) Electrogenerated α-keto radical species via nickel catalyst. (B) Electrochemical alkenylation: type a, direct electrolytic activation of alkene; type b, direct electrolytic activation of reagent. (C) This work: Ni-catalyzed enantioselective switchable electrochemical alkenylation (path I) and alkenylation (path II).
the reaction of alkyl-substituted acyl imidazole also proceeded successfully, providing the product with 74% yield and 88% ee (3q).

The generality of the reaction with respect to the substituents on the alkene coupling partners was also investigated (Fig. 2B). Various diversely functionalized 1,1-diarylethylenes were found to be suitable substrates to afford the expected products (3r to 3w) in good yields with satisfactory enantioselectivities. 1-Alkyl-substituted styrenes could be tolerated without notable influence on the outcome of the reactions (3x to 3z), albeit with poor diastereoselectivities. Monosubstituted alkenes and 1,3-diene derivatives proved to be suitable substrates for the formation of the corresponding products with excellent enantioselectivities (3aa to 3af). N-Vinylcarbazole and vinyl ether also successfully participated in the stereocontrolled process (3ag and 3ah). Further studies revealed that the electrochemical alkene difunctionalization reaction was also compatible with other alcohol nucleophiles (Fig. 2C), delivering corresponding products in excellent enantioselectivities (3ai to 3ak). Notably, in the presence of Et3N·3HF as the fluorine source (Fig. 2D), the fluorinated adduct was obtained in 57% yield and 84% ee (3al).

In contrast to the prevalence of electrochemical difunctionalization of alkenes, processes that undergo direct asymmetric electrocatalytic alkenylation have been much less studied. Using TFE as an alcohol additive, we were able to switch the difunctionalization pathway to the nickel-catalyzed asymmetric electrochemical alkenylation process to access alkenylation product 4 (Fig. 3). Under the optimized reaction conditions (Table 1, entry 14), a broad range of 2-acylimidazoles and alkenes were investigated. The electronic nature of the substituents on the benzene ring of 2-acylimidazole 1a (0.2 mmol, 1.0 equiv) and 2a (1.2 mmol, 6.0 equiv), 2,6-di-tert-butylpyridine (0.1 mmol, 0.5 equiv), NiCl2 (10 mol %), L (20 mol %), tBu4NPF6 (0.06 M), and DCM/alcohol = 1:1 (10 ml) at 10°C under constant-current conditions in an undivided cell.

Table 1. Optimization of the reaction conditions. Unless otherwise specified, all reactions were carried out using 2-acylimidazole 1a (0.2 mmol, 1.0 equiv) and 2a (1.2 mmol, 6.0 equiv), 2,6-di-tert-butylpyridine (0.1 mmol, 0.5 equiv), NiCl2 (10 mol %), L (20 mol %), tBu4NPF6 (0.06 M), and DCM/alcohol = 1:1 (10 ml) at 10°C under constant-current conditions in an undivided cell.

| Entry | L   | Solvent     | Yield (%) of 3a* | ee of 3a (%) † | Yield (%) of 4a* | ee of 4a (%) † |
|-------|-----|-------------|------------------|----------------|------------------|----------------|
| 1     | L1  | DCM/MeOH    | 55               | 3              | –                | –              |
| 2     | L2  | DCM/MeOH    | 34               | 21             | –                | –              |
| 3     | L3  | DCM/MeOH    | 32               | 51             | –                | –              |
| 4     | L4  | DCM/MeOH    | 54               | 80             | –                | –              |
| 5     | L5  | DCM/MeOH    | 55               | 82             | –                | –              |
| 6     | L6  | DCM/MeOH    | 60               | 81             | –                | –              |
| 7     | L7  | DCM/MeOH    | 61               | 90             | –                | –              |
| 8     | L8  | DCM/MeOH    | 74               | 93             | –                | –              |
| 9     | L8  | DCM/HFIP    | –                | –              | 31               | 51             |
| 10    | L8  | DCM/TFE     | –                | –              | 42               | 55             |
| 11†   | L8  | DCM/TFE     | –                | –              | 63               | 60             |
| 12‡   | L8  | MeCN/TFE    | –                | –              | 31               | 86             |
| 13§   | L8  | MeCN/TFE    | –                | –              | 40               | 93             |
| 14‡§  | L8  | MeCN/DCM/TFE| –                | –              | 56               | 95             |

*Isolated yields after chromatography are shown. †Enantiomeric excess (ee) was analyzed by chiral HPLC. ‡With Pt(+) / Pt(−) at 0°C. §Tetrabutylammonium hexafluorophosphate; HFIP, hexafluoro-2-propanol; TFE, 2,2,2-trifluoroethanol.
Fig. 2. Nickel-catalyzed asymmetric electrochemical difunctionalization of alkenes. Unless otherwise specified, all reactions were carried out using 2-acylimidazole 1 (0.2 mmol, 1.0 equiv) and 2 (1.2 mmol, 6.0 equiv), 2,6-di-tert-butylpyridine (0.1 mmol, 0.5 equiv), NiCl₂ (10 mol %), L₈ (20 mol %), and DCM/alcohol = 1:1 (10 ml) at 10°C under constant-current conditions in an undivided cell. (A) Substrate scope of 2-acylimidazoles. *2 (0.5 mmol, 2.5 equiv) and Cp₂Fe (10 mol %) with a Pt anode and a Pt cathode. †Diphenylethylene 2a (12.0 equiv) was used. (B) Substrate scope of alkenes. ‡(0.2 mmol, 1.0 equiv), quinuclidine (0.2 mmol, 1.0 equiv), NiCl₂ (10 mol %), L₅ (20 mol %), and TBAPF₆ (0.06 M) were used at 20°C with an RVC anode and an RVC cathode. (C) Substrate scope of alcohol additives. (D) Vicinal carbofluorination of alkenes. ‡Et₃N·3HF (5.0 equiv) was used in MeCN (8 ml) with a foam Ni anode and a platinum cathode.
suitable substrates to afford the desired products in good yield with excellent enantioselectivities (4g to 4k).

**Synthetic application**

To demonstrate the practicality of the current methodology, the di-functionalized product 3a can be readily elaborated in different ways (Fig. 4A). First, the treatment of 3a with MeOTf, followed by the addition of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and water, afforded lactone 5 in 74% yield and 92% ee. Subsequently, the di-functionalized product 3a can be easily transformed into the corresponding ketones 6 and 7 in high yields, thereby confirming the synthetic utility of the current protocol. In addition, the imidazole moiety was readily removed to generate ester 8 in 81% yield with maintained enantioselectivity. Reduction of the ester group of 8 in the presence of LiAlH₄ afforded the corresponding alcohol 9 in 93% yield and 92% ee (Fig. 4B). Hydrogenolysis of benzyl ether and removal of the imidazole moiety gave rise to desired acid 10 in good yield (Fig. 4C). Carboxylic acid 10 was subsequently treated with trimethylsilyl azide to generate the corresponding amide 11. After intramolecular oxidative coupling of 11, (−)-N-acetylcocbinol 12 was obtained in 42% yield and 86% ee.

**Plausible mechanism**

A series of experiments were conducted to shed light on the mechanism of the asymmetric electrolytic transformation (Fig. 5). Initially, cyclic voltammetry experiments of reaction components were conducted. As shown in Fig. 5A, the onset oxidative potential of 2-acylimidazole 1a decreased notable from 1.1 to 0.3 V (versus SCE) after the chiral nickel catalyst was added, suggesting that the anodic oxidation of the nickel-bound enolate intermediate was quite facile. In contrast, the onset oxidation potentials for alkenes...
2a, 2b, 2e, 2f, and 2k are approximately +1.75, +1.60, +1.79, +1.72, and +1.28 V versus SCE, respectively (Fig. 5B). It can be seen from the above results that the nickel-mediated anodic oxidative reaction operates at much lower electrode potentials than the onset potential required for the direct oxidation of different alkenes, showing that the direct oxidation of alkenes on the anode was difficult and unlikely to happen under our reaction conditions.

To gain deeper insight into the mechanism of this process, several control experiments verified the necessity of each reaction component (Fig. 5C). No desired product was observed in the absence of the nickel salt (entry 1), diamine ligand (entry 2), or electric current (entry 3). It should be noted that no transformation occurred when exposed to air (entry 4). Notably, 3a was obtained in only 21% yield and 12% ee with Mn(OAc)₃ as chemical oxidation in the absence of electric current (entry 5). To further confirm the pathway of this reaction, a controlled potential experiment was conducted with a constant anodic potential of 1.0 V (versus SCE), which is higher than the potential needed for the oxidation of nickel-bound enolate but insufficient for the direct oxidation of alkenes (Fig. 5, A and B). We observed the formation of difunctionalization product 3a in 65% yield.
Fig. 5. Mechanistic proposal for asymmetric switchable electrosynthesis. (A) Cyclic voltammetry (CV) of 1a in the absence or presence of Lewis acid catalyst. The oxidation peak of the nickel catalyst was observed at +1.48 V (versus SCE). CV of nickel-bound enolate intermediate [1a (0.01 M)] and nickel catalyst (0.05 M), green line] with an electrolyte of nBu4NPF6 (0.1 M) in MeCN (5 mL). The onset potential of the nickel-bound enolate intermediate was measured at approximately +0.49 V (versus SCE). (B) CV of alkenes. CV of different alkenes 2 (0.01 M) with an electrolyte of nBu4NPF6 (0.1 M) in MeCN (5 mL). (C) Control experiments. (D) Radical clock experiment. (E) Proposed catalytic cycle.

### Table 1: Variation from the standard conditions

| Entry | Variation from the standard conditions | Results |
|-------|---------------------------------------|---------|
| 1     | Without NiCl2                          | No reaction |
| 2     | Without L8                            | No reaction |
| 3     | In the absence of electric current    | No reaction |
| 4     | Under air                             | No reaction |
| 5     | Mn(OAc)2 (2 equiv), without electricity | 21%, 12% ee |
| 6     | constant potential versus SCE: +1.0 V | 65%, 92% ee |
and 92% ee (entry 6); therefore, the direct anodic generation of alkene radical cations is unlikely to contribute to the observed asymmetric difunctionalization.

When the alkene bearing a cyclopropyl moiety (19) as a radical clock was subjected to electrolytic reaction conditions, cyclopropane ring-opening products 20 and 21 were obtained, indicating the intermediacy of the α-keto radical in the transformation (Fig. 5D). The collective data shown in Fig. 5 (A to D) are consistent with our assumption that the electrochemical functionalization reaction is mediated by an electrogenerated radical-based mechanism.

Taking into account the combined results of mechanistic studies, a plausible mechanistic cycle is outlined in Fig. 5E. The divergent functionalization reactions begin with the addition of the chiral Lewis acid catalyst I to 2-acylimidazole I and generate nickel-bound enolate intermediate (62), which is oxidized to α-keto radical species II on the anode surface. Consequently, radical species II reacts efficiently with electron-rich alkenes to form carbon-centered radical III, followed by anodic oxidation to produce carbocation intermediate IV and regenerate nickel catalyst I. Crucially, the original selectivity between the competing difunctionalization and alkenylation pathways was determined by the nucleophilicity of the alcohol used in the reaction. Nucleophilic alcohols (such as MeOH) react with nascent carbocation IV to generate difunctionalized product 3, while with less nucleophilic alcohols (such as TFE), β-H elimination predominates to furnish the final alkenylation product 4.

**DISCUSSION**

In conclusion, we used Ni-catalyzed enantioselective electrochemical coupling of 2-acylimidazoles with alkenes. This operationally simple and modular protocol, ensuring the SET event under electrolytic conditions, used readily available alkenes as coupling partners to offer chiral functionalization products with high efficiency, as well as excellent chemo- and enantioselectivity. Mechanistic investigations revealed that an electrogenerated chiral α-keto radical species is involved in the stereodetermining step. Manipulation of the switchable difunctionalization and alkenylation transformations could be governed by the nucleophilicity of alcohol additives. We believe that in the near future, the realization of enantioselective electrochemical transformations will improve the scope of electrochemistry and pave the way for exploring new chemical spaces and developing solutions to challenging synthetic problems.

**MATERIALS AND METHODS**

**General information**

Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. The instrument for electrolysis is a dual display potentiostat (DJS-292B) (made in China). The anodic electrode was a platinum plate (20 mm by 20 mm by 0.2 mm), and the cathodic electrode was a platinum plate (20 mm by 20 mm by 0.2 mm). Electrolysis was carried out at 10°C until complete consumption of the starting material (monitored by thin-layer chromatography (TLC)). The solution was diluted with ethyl acetate and washed with saturated NH4Cl aqueous solution followed by distilled water washes. The aqueous phase was then extracted three times with ethyl acetate. The combined organic phase was dried over anhydrous MgSO4 and concentrated under reduced pressure. The residue was purified by short silica gel chromatography to afford the desired products 3.

**Supplementary materials**

Supplementary material for this article is available at https://science.org/doi/10.1126/sciadv.6add7134

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