Electrochemically Promoted Fluoroalkylation—Distal Functionalization of Unactivated Alkenes

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Supporting Information

ABSTRACT: Difunctionalization of olefins represents a powerful synthetic tool and yet a challenging task. This work describes an electrochemically enabled fluoroalkylation—migration reaction of unactivated olefins in the absence of a strong oxidant or heavy metal catalyst, affording fluorinated (hetero)aryl ketones in good yields and excellent regioselectivities. The efficient and sustainable electrochemical strategy provides a rapid access to a dual functionalized fluorine-containing heterocyclic manifold.

The vicinal difunctionalization of olefins represents an attractive and versatile method for the rapid transformation of a complex scaffold.1 Considerable progress has been made with fluorinated radicals to provide divergent approaches for the difunctionalization of olefins, especially difluromethylation,2 trifluoromethylation,3 and perfluoralkylation.4 However, a majority of the studies concentrated on the modification of styrene and other activated alkenes.5 In the matter of distal unsubstituted olefins, the lack of π−π conjugation increases the lability of carbon radicals and frustrates the functionalization of unactivated olefins.6 Recently, dual functionalizations of unactivated alkenes through radical fluoroalkylation with subsequent intramolecular formyl, vinyl, alkynyl, cyano, aryl, and heteroaryl functional group migrations have been reported.7 In particular, the radical trifluoromethylation—distal migration procedure has been documented by Zhu, Studer, and Yu independently. These protocols provide rapid access to fluoroalkylated ketones with a variety of vicinal β-functionalization in a radical cascade fashion. However, a number of those examples required the use of excess oxidants6a,b,7d,8 and/or noble heavy metals.6c−h The development of a sustainable and effective approach to realize such a fluoroalkylation—distal functionalization sequence still represents an unmet challenge and is in urgent demand.

Electrochemistry utilizes direct interaction of electrons from the anode and cathode with the nucleus instead of a chemical oxidant or reductant.9 The redox efficiency, innate scalability, and sustainability of such a process prompted the investigation of electrochemical olefin difunctionalization reactions.10 The combination of the electrochemical catalytic cycle with a radical mechanism has currently emerged as a new approach for olefin dual activation that maximizes substrate generality, avoids using strong oxidants, and minimizes byproduct formation. So far, several electrochemically enabled strategies have been developed for radical trifluoromethylation—functionalization of olefins (Scheme 1). The most popular method is through radical addition of styrene followed by anodic oxidation to form carbocation and nucleophilic addition to install the second functionality.11 However, an unstabilized carbocation often leads to intricate side reactions such as hydration and overoxidation. An alternative strategy is using preformed metal—halogen radical species to capture the carbon radical intermediate and anodically coupled electrolysis to generate the CF3-halogen difunctionalized product. The pioneering work on Mn-catalyzed electrochemical fluoroalkylation—difunctionalization of olefins represents a new approach for olefin dual activation that maximizes substrate generality.

Received: February 4, 2019

Scheme 1. Electrochemically Enabled Alkene Difunctionalization: Radical Trifluoromethylation Strategies

DOI: 10.1021/acs.orglett.9b00444
Org. Lett. XXXX, XXX, XXX−XXX

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migration/halogenation of terminal alkenes was achieved by the Lin group. In their case, a preformed Mn–X adduct is required for electrochemical dual functionalization. We speculated that a synthetically more convenient protocol might be realized via a radical addition procedure with concomitant functional group migration to alkenes. Through a selection of suitable fluoroalkylating reagents in combination with remotely functionalized unactivated alkenes, radical cascades of 5-exo cyclizations with subsequent ring opening might be realized via a radical addition procedure with a portfolio of fluorinating sources. This electrochemically enabled dual functionalization process can be precisely initiated and ceased by fine-tuning of the cell voltage to avoid overoxidation of the olefins and regulate subsequent chemical steps. Surprisingly, despite the potential utility of such a transformation, very few examples of electrochemical distal migration have previously been described.

Inspired by recent developments in the area of remote functionalization, we herein reported an electrochemical radical fluoroalkylation–distal functionalization reaction of unactivated olefins with a portfolio of fluorinating sources. This reaction could be conducted at room temperature without an oxidative reagent or metal catalyst. Furthermore, this powerful and green strategy exhibited a wide substrate scope, broad functionalization,16 we herein reported an electrochemical reaction that could be conducted at room temperature without an oxidative reagent or metal catalyst. Furthermore, this powerful and green strategy exhibited a wide substrate scope, broad functionalization,16 we herein reported an electrochemical reaction that could be conducted at room temperature without an oxidative reagent or metal catalyst. Furthermore, this powerful and green strategy exhibited a wide substrate scope, broad functionalization.

Our experiments began with a brief survey of benzothiazole-substituted tertiary alcohol and Langlois’ reagent (CF3SO2Na) in different electrolytes and solvents under constant voltage. This study revealed that n-Bu4NBf4 in DCM/H2O was able to promote the desired migration sequence using an undivided cell at 3.0 V (Table 1, entry 11). Other ammonium halide electrolytes and LiClO4 delivered poor conversions (entries 1–5). Increasing or decreasing the voltage of the cell afforded poor yields (entries 12 and 13). Under the optimized conditions, we investigated the substrate scope of this reaction by using various alkyl and aryl substituted alkenes 1 (Scheme 2). The electrochemically generated trifluoromethyl radical reacted with 1 and induced the migration of the benzothiazole to provide 3. Alcohols bearing substituted aryl functionalities (R2), such as methyl, methoxy, and halogen on the benzene ring, resulted in the corresponding benzothiazole-migrated products in good yields (3a–3n). Reactions of alkyl- and cyclic alkyl-substituted alcohols also proceeded smoothly to furnish the desired ketones (3o–3t). A sterically more hindered substrate could also be tolerated to furnish the multisubstituted product in moderate yield (3u). Thiophene and furan functionalities could be tolerated under the reaction conditions (3v–3w). Next, we examined the scope of this electrochemical trifluoromethylation–arylation reaction. Intriguingly, substitu-
tuted benzothiazole and thiazole could migrate to the alkene to realize the difunctionalized ketones (3x−3aa). Considerably lower yields were obtained with pyridine-, imidazole-, and benzoimidazole-bearing alcohols (3bb−3dd).

We then sought to demonstrate the generality of this approach with other fluoroalkylating sources (Scheme 3). The CF2H-analogue of Langlois’ reagent NaSO2CF2H, which was readily prepared according the elegant method reported by Hu,18 has been subjected to the electrochemical conditions. Such CF2H radical addition to unsaturated substrate has rarely been achieved under electrochemical conditions.19 Limited examples have been demonstrated on the addition of unactivated alkenes.2c−e,20 Gratifyingly, by using 3 equiv of NaSO2CF2H, the corresponding CF2H-bearing ketones 4a−4e were afforded in moderate yields at 2.5 V cell voltage in MeCN/H2O. When NaSO2CF3 (0.4 mmol) in acetonitrile (5.4 mL) and water (0.6 mL) was charged at 3.0 V cell voltage.

To gain insight into this electrochemical migration reaction, a series of mechanistic studies were conducted. In the radical-trapping experiment, by adding 3 equiv of TEMPO to the standard conditions, this reaction was inhibited (Scheme 5a). Using diphenylethylene 9 as a trapping reagent, the CF3-adduct 10 was detected by GC-MS (Scheme 5b). Thus, radical intermediates are possibly involved in this electrochemical system. The utility of an aryl migrated product was demonstrated (Scheme 5c). Under simple reducing/oxidising conditions, 3y was converted to the corresponding aldehyde 12 in 68% yield. Next, we studied the redox potentials of three fluoroalkylating reagents by cyclic voltammetry (CV) experiments in MeCN (10−4 M) with n-Bu4NBF4 (0.2 M) at a scan rate of 0.2 V·s−1 (Figure 1). The oxidation peak of NaSO2CF2H was observed at the very low point of 0.590 V, 0.814V, 0.742V, 0.590V.

Figure 1. Cyclic voltammetry studies. Cyclic voltammetry of 2 (10−4 M in MeCN) with n-Bu4NBF4 (0.2 M) using glassy carbon working electrode, Pt wire counter electrode, SCE reference electrode, scan rate = 0.2 V·s−1.
while NaSO₂CF₃ and NaSO₂C₆F₁₃ displayed adjacent oxidizing peaks at 0.814 and 0.742 V, respectively. This observation indicated that NaSO₂CF₂H was much more easily oxidized on the anode than trifluoromethyl and perfluoroalkyl reagents, which quickly decomposed on electrodes. This could explain the unusual high activity of the CF₂H radical and yet low conversion in the electrochemical olefin functionalization. Overall, the relative reactivity of these fluoroalkanesulfinites in oxidative radical fluoroalkylation decreases in the following order: CF₅SO₂Na > C₆F₁₃SO₂Na > CF₃HSO₂Na. This reactivity sequence is consistent with their innate nucleophilicity, but different from the relative reactivities of their fluoroalkyl radicals.¹⁸

Based on the previous reports¹⁰ and the above experimental evidence, a possible mechanism for the electrochemical radical fluoroalkylation—distal migration reaction is illustrated in Scheme 6. Initially, the CF₃ radical is generated from

Scheme 6. Proposed Mechanism for the Electrochemical Migration Reaction

anodic oxidation and addition of the tertiary alcohol I affords the carbon radical intermediate A, which rapidly attacks the heteroarene to generate cyclic nitrogen radical intermediate B. The fast ring opening followed by radical β-cleavage furnishes a stabilized radical intermediate C, which is oxidized to carbocation D at the anode. Finally, deprotonation of D affords the heteroaryl migrated product 3y.

In conclusion, we have developed an electrochemical difunctionalization of olefins by a radical fluoroalkylation—distal migration pathway. This method enables the fast modification of olefins via cascade dual anodic oxidations under catalyst-free conditions. Excellent substrate generality was demonstrated with consistent fluoroalkylating reagent tolerance. This radical sequence provides a highly valuable methodology for the fluorinated ketone synthesis and could be further elaborated to access more functionalized carbonyls.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00444.
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