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Organic Chemistry

Metal-Free Electrochemistry-Driven Decarboxylative Primary Alkyl-Alkoxylation of Olefins

Meiqun Lu, Kailun Chen, Tao Wu, and Hu Cai**

Abstract: Here, a primary alkylative difunctionalization of olefins based on the decarboxylation of carboxylate ions to obtain alkyl radicals by electrochemical anodic oxidation is reported. The reaction employs quaternary ammonium carboxylates as the source of alkyl radicals and does not require additional oxidizing agents or electrolytes. The reaction exhibits a broad substrate range and functional group compatibility. It gently converts mono- or disubstituted styrene substrates and alkyl carboxylate anions of various carbon chain lengths and substituents to products under the reaction conditions. Furthermore, it is important to note that not only alcohols but carboxylic acids and water can also serve as nucleophilic reagents to participate in the reaction and yield the corresponding products. Preliminary mechanistic studies have demonstrated that the reaction is enabled by the lower oxidation potential of the carboxylate anion compared to that of the olefin. The anodic oxidation of the carboxylate anion occurs prior to the oxidation of the olefin, followed by decarboxylation to obtain alkyl radicals.

Alkyl functional groups, including methyl, ethyl, and longer carbon chain variants, are nonpolar and exhibit strong lipophilicity. Adding these groups to drug molecules can significantly boost their lipid solubility, which in turn enhances biofilm penetration, increases intracellular permeability, and improves bioavailability. Additionally, the incorporation of long alkyl chains markedly enhances their lipophilicity and hydrophobic characteristics, influencing the pharmacokinetics of drug molecules, including their distribution and metabolism within the body (Scheme 1a).[1–6] Traditional methods of introducing these groups use electrophilic halides or alcohol derivatives, or organometallic compounds such as nucleophilic Grignard reagents, which are often pre-synthesized, under harsh reaction conditions, and accompanied by by-products such as elimination and hydrolysis.[7–12] The thriving development of photochemistry and electrochemistry in organic synthesis has provided new source compounds for alkylation reactions, such as former electrophilic halides, alcohols, and amines that can appear as radicals in alkylation reactions.[13–26] Carboxylic acids can also be decarboxylated to obtain alkyl radicals for application in organic synthesis, and they are cheap and readily available, which makes them more advantageous compared to the previous halides or Grignard reagents.[27–33]

The difunctionalization of olefins can start from cheap and readily available olefin substrates and build two new chemical bonds in one step to increase the complexity and added value of the original molecule.[34–40] However, olefin difunctionalization reactions initiated with the addition of alkyl radicals principally focus on more stable radicals (Scheme 1b),[41–52] such as nucleophilic isopropyl radicals, tert-butyl radicals,[42–46] and primary carbon radicals stabilized by adjacent conjugate groups or atoms (for example *a*-amino radicals or *a*-alkoxyl radicals),[47–49] or electrophilic perfluoroalkyl or polyfluoroalkyl radicals.[50–52] This is primarily due to the large polarity effect between these radicals and olefins, which facilitates the addition step.[53–59] In contrast, another class of primary carbon radicals and methyl radicals, characterized by their diminished stability and nucleophilicity,[60–64] are less frequently employed in olefin difunctionalization reactions, owing to the absence of the aforementioned effects which make the addition to be thermodynamically unfavorable or reversible process.[65–70]

However, the traditional Kolbe reaction is an electrochemical process in which alkyl carboxylic acids are decarboxylated to produce free radicals and then dimerize to obtain long-chain alkanes, many of which are primary carbon alkyl radical involved (Scheme 1c).[71–78] We imagine whether olefins can be introduced into the Kolbe reactions, so that the primary carbon alkylation of olefins can be achieved with cheap and readily available primary carbon alkyl carboxylic acids as the source of methyl or long-chain alkyl groups (Scheme 1d). We not only hope to achieve decarboxylation of alkyl carboxylic acids to obtain primary alkyl radicals through anodic oxidation,[79–82] but also hope that the anode can quickly oxidize new carbon radical to carbocation after the addition of primary alkyl groups to olefins, thereby promoting the equilibrium shift of the radical addition step and combining with nucleophiles to achieve the primary alkyl difunctionalization reaction of olefins.

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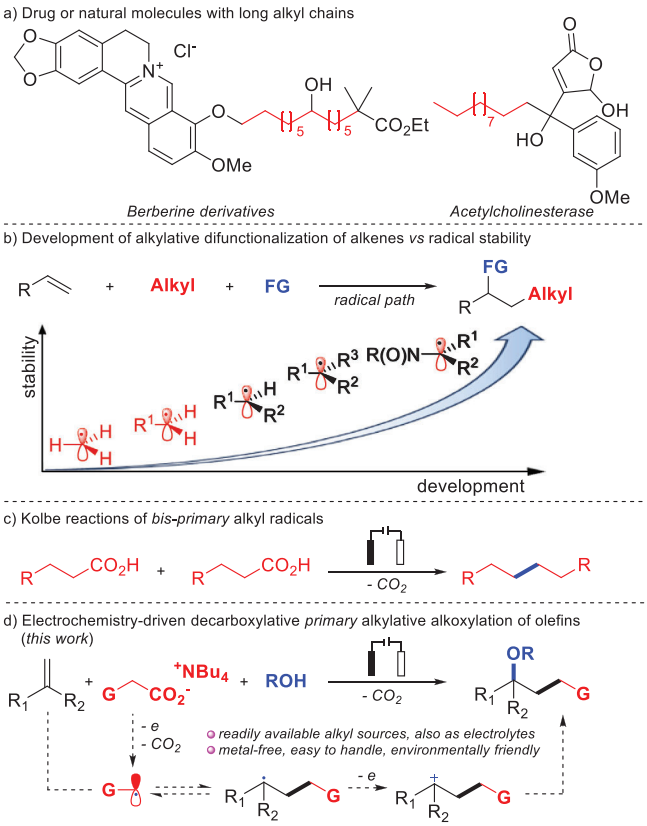
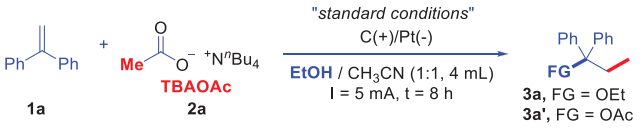
Additional supporting information can be found online in the Supporting Information section



Scheme 1. Alkylated drug and alkylation of alkenes.

Table 1: The optimization process.[a]

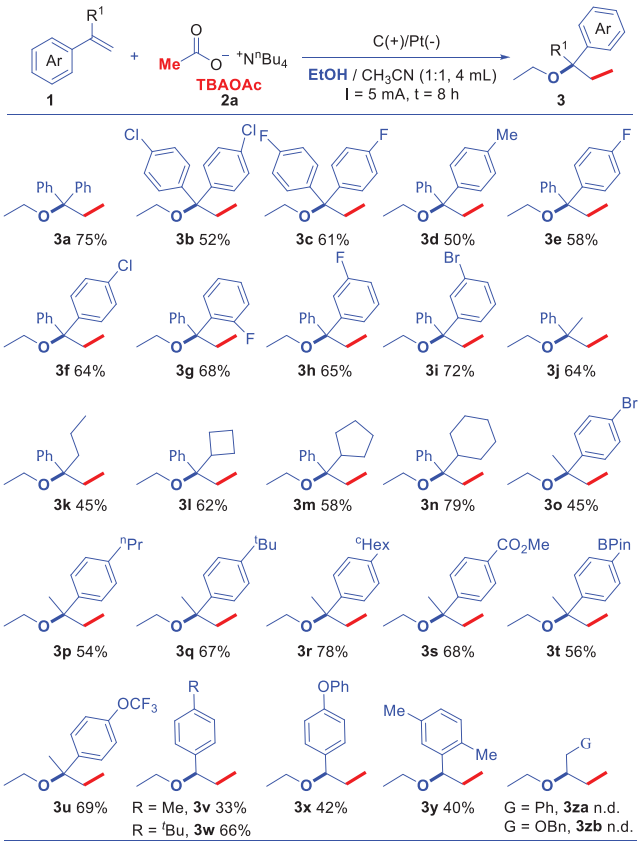


Entry	Deviations from standard conditions	Yield (%) [b]
1	None	75
2	1.0 eq $TBABF_4$ and 5.0 eq CsOAc	40
3	1.0 eq $TBAPF_6$ and 5.0 eq CsOAc	48
4	1.0 eq TBACl and 5.0 eq CsOAc	9
5	1.0 eq CTAB and 5.0 eq CsOAc	N.D.
6	1.0 eq TBAOAc and 3.0 eq CsOAc	65
7	1.0 eq TBAOAc and 5.0 eq CsOAc	73
8	1.0 eq TBAOAc	70
9	1.2 eq TBAOAc	72
10	5.0 eq TBAOAc	64
11	1.5 eq TMAOAc	57
12	1.5 eq TBAOAc and 1.0 eq $TBABF_4$	56
13	$I = 7$ mA, $t = 6$ h	68
14	$I = 3$ mA, $t = 13$ h	71
15	5.0 eq EtOH and 4 mL CH_3CN	13
16	0.1 mL EtOH and 4 mL CH_3CN	16
17	0.5 mL EtOH and 4 mL CH_3CN	46

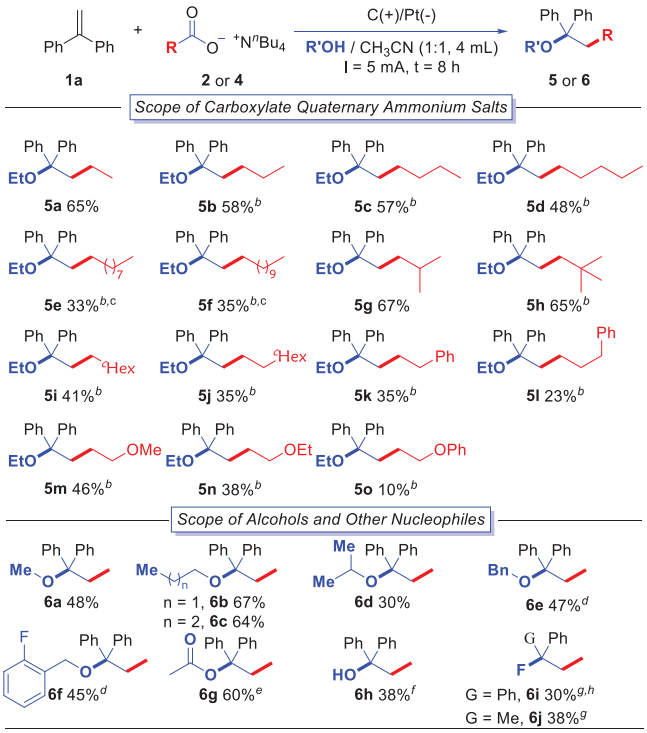
[a] Reaction Condition: **1a** (0.2 mmol), **2a** (1.5 equiv), EtOH/CH_3CN (1/1, 4 mL), Graphite cloth anode (10 mm x 15 mm) and Pt plate cathode (7.5 mm x 15 mm x 0.1 mm) at r.t. [b] The yield of **3a** was determined by ^1H NMR with Mesitylene as internal standard.

1,1-stilbene **1a** was selected as the model substrate and various acetate salts as the methyl source, and initial experiments were performed in the presence of common electrolytes, such as tetrabutylammonium tetrafluoroborate, under an undivided electrolysis cell (Table 1). When a large excess (5 equiv) of cesium acetate was used, olefinic methyl-ethoxylated products were detected in a yield of 40% (Entry 2). Other electrolytes, such as tetrabutylammonium hexafluorophosphate, tetrabutylammonium chloride, and hexadecyltrimethylammonium bromide, were tested in combination with cesium acetate, but they did not improve the reaction efficiency (Entry 3–5). In some cases, they even inhibited it. To improve the yield of the product and considering the solubility of cesium acetate, tetrabutylammonium acetate was used instead of cesium acetate (Entry 6–10). The product yield increased to 75% when only 1.5 equiv of this methyl source was used, and no additional electrolyte was needed (Entry 1). The optimization process revealed that the amount of tetrabutylammonium acetate has an effect on the substrate conversion. A 70% yield can be achieved with 1 equiv, but yields decrease beyond 2 equiv due to the occurrence of methyl-acetoxylation by-products **3a'** (Entry 8–10). Tetramethylammonium acetate, which serves as a source of decarboxylative methyls, also produces the target product, but with decreased yield (Entry 11). Additional electrolytes are harmful to the reaction conversion (Entry 12). The reaction current can be adjusted without significantly affecting the yield of **3a**, but it will impact the reaction time (Entry 13 and 14). The quantity of the nucleophilic reagent, ethanol, is a crucial factor in the reaction and therefore is increased to a level comparable to that of the solvent in order to obtain an optimized yield (Entry 15–17).

With the optimization conditions in hand, we turned to substrate evolution (Scheme 2). We examined a wide variety of olefinic substrates for the reaction, most of which yielded moderate to good yields for alkyl-ethoxylation. In the examination of various symmetric 1,1-diaryl-substituted ethenes, including *para*-chloro **1b**, fluoro **1c**, as well as unsymmetric 1-aryl-substituted styrenes exemplified by *para*-methyl **1d**, fluoro **1e**, chloro **1f**, *ortho*-fluoro **1 g**, and *meta*-fluoro **1 h**, bromo **1i** derivatives, the electrochemical decarboxylation reactions were successfully conducted using the tetrabutylammonium acetate system. These reactions typically yielded methyl-ethoxylated products with efficiencies ranging from 50 to 72%. Subsequent investigations focused on 1-alkyl-substituted styrenic substrates, incorporating *n*-alkyl groups with varying carbon chain lengths **1j-1k** and various cycloalkyl substitutions **1l-1n**, resulted in the formation of olefin difunctionalized products. Further exploration involved various 1-aryl-substituted 1-methyl olefins, which proved to be compatible with the existing decarboxylative alkylation framework, producing the anticipated products **3o-3u** with yields between 45% and 78%. Additionally, it is noteworthy that monoaryl-substituted vinyl substrates were mildly converted into 1-ethoxy-1-arylpropane products **3v-3y**, albeit in relatively lower yields. This reduced efficiency may be attributable to a heightened susceptibility to radical polymerization. Despite extensive efforts, unactivated alkenes like 3-phenylpropene and 3-benzyloxypropene failed



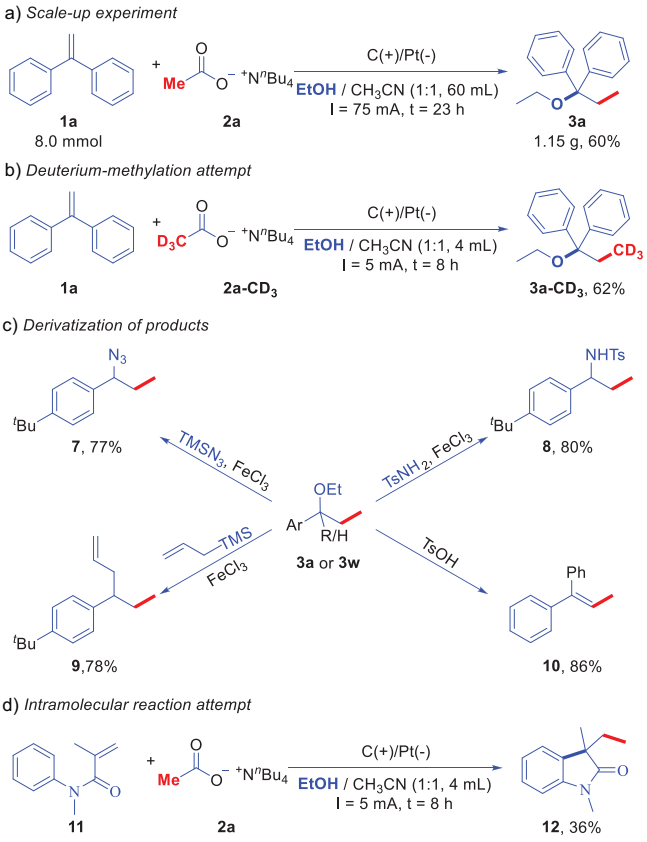
Scheme 2. The scope of alkenes.[a)]
[a)] Reaction Condition: **1** (0.2 mmol), **2a** (1.5 equiv), EtOH/CH_3CN (1/1, 4 mL), Graphite cloth anode (10 mm x 15 mm) and Pt plate cathode (7.5 mm x 15 mm x 0.1 mm) at r.t., $I = 5$ mA, $t = 8$ h, Average isolated yield of two runs.



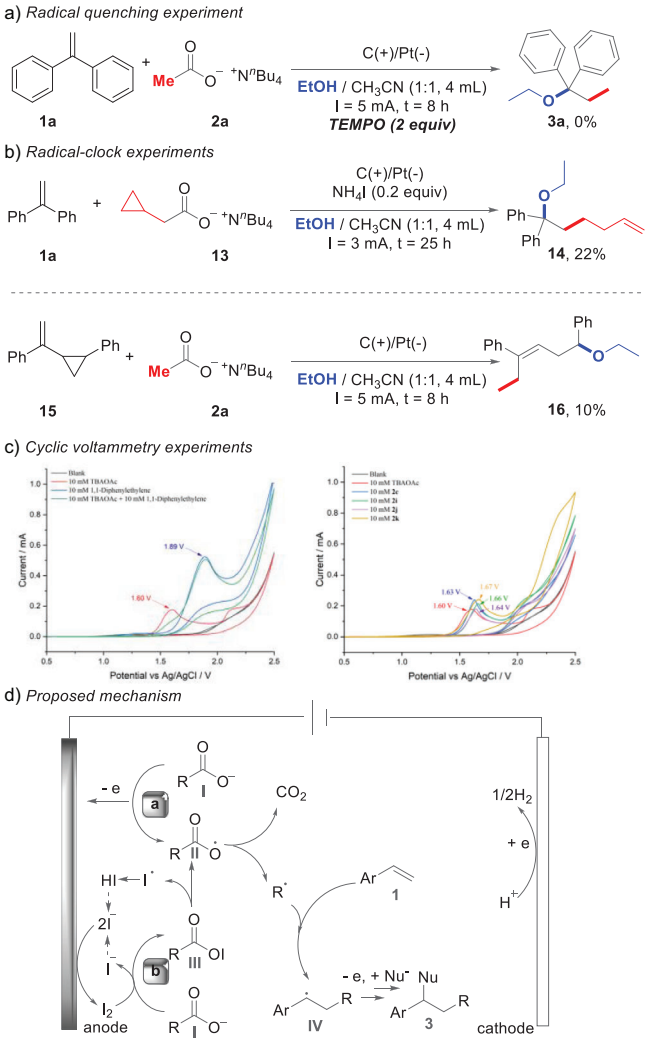
Scheme 3. The scope of carboxylate quaternary ammonium salts and alcohols.[a)]
[a)] Reaction Condition: **1a** (0.2 mmol), **2** (1.5 equiv), EtOH/CH_3CN (1/1, 4 mL), Graphite cloth anode (10 mm x 15 mm) and Pt plate cathode (7.5 mm x 15 mm x 0.1 mm) at r.t., $I = 5$ mA, $t = 8$ h, Average isolated yield of two runs. [b] 20 mol% NH_4I was added. $I = 3$ mA, $t = 23$ h [c] EtOH:CH_3CN: *n*-Hexane 3:3:2, 4 mL as solvent. [d] CH_3CN:R'OH 3:1, 4 mL as solvent, $I = 5$ mA, $t = 15$ h. [e] CH_3CN 4 mL as solvent, HOAc (3.0 equiv), $I = 5$ mA, $t = 8$ h. [f] CH_3CN:H_2O 7:1, 4 mL as solvent, $I = 5$ mA, $t = 8$ h. [g] TBAF (0.6 mmol), CH_3CN:^{t}BuOH 7:1, 4 mL as solvent. [h] ^{19}F NMR yield.

to yield products **3za**/**3zb** due to unfavorable alkyl radical addition.The compatibility of diverse functional groups, such as sp^2-hybridized C─Br, C─Cl, C─F bonds, cyclobutyl, ester, pinacol boronate (Bpin) and trifluoromethoxy groups, with the current conversion process was also confirmed, underscoring the versatility and robustness of this chemical transformation strategy.

Next, we examined various alkylcarboxylate quaternary ammonium salts as sources of different alkyl radicals (Scheme 3). Various straight-chain alkyl radical precursors are available for the corresponding alkylation products. For example, tetrabutylammonium propionate can be used to obtain the target product in a 65% yield with **1a**. Similarly, *n*-butyric acid ammonium can be oxidatively decarboxylated and then added to the olefin, resulting in the formation of the *n*-propylation product **5b** with a yield of 58%. However, catalytic amounts of ammonium iodide are necessary to facilitate the conversion process of these reactions. The product **5c** or **5d**, which lengthens one or two methylene group, is also obtained in a similar way with the pentanoate or hexanoate salt, at a similar yield. Acids with much longer carbon chains, such as arachidonic acid and lauric acid, are derivatives or by-products of natural plant oils. Fortunately, their quaternary ammonium salts can also be used in the current reaction to supply much longer carbon chain primary alkyl radicals to gain long-chain alkyl ethers **5e** and **5f**. In addition, branched chain alkylation, for example, isopropyl **5 g**, neoamyl **5 h**, cyclohexylmethyl **5i**, and 2-cyclohexylethyl **5j** could also be achieved by adding alkyl radicals to olefins resulting from the oxidative decarboxylation of the corresponding carboxylic acid quaternary ammonium salts. Terminal aryl-substituted alkylcarboxylic acid anions are also compatible with our system. The corresponding radicals involved in the reaction were obtained by the loss of carbon dioxide via single electron intermediates and delivered the difunctionalization products of olefins **5k** and **5l** in yields of 35% and 23%, respectively. Under the present reaction conditions, it is possible to obtain alkylation products of the primary carbon that are substituted with methoxy **5m**, ethoxy **5n**, and even phenoxy groups **5o**. However, it is important to note that the corresponding yields would be significantly reduced. The array of nucleophiles was finally considered. Alcohols of various types can be utilized to capture carbocation intermediates and participate in reactions. Among the bulk reagents, methanol, *n*-propanol,



Scheme 4. Scale-up of experiment and products derivatization.



Scheme 5. Mechanistic studies.

n-butanol, isopropanol, benzyl alcohol, or substituted benzyl alcohol can be introduced into the three-component reaction to form the corresponding ether products **6a–6f**. Additionally, other oxygen nucleophiles, such as acids, can be used to give alkyl-acetyloxy products **6g** of alkenes; water is also introduced into the system to give an alcohol product **6h** in synthetically meaningful yields. It is particularly encouraging to observe that within the tetrabutyl fluoride-tert-butyl alcohol system, the fluoride anion is capable of functioning as a nucleophile, thereby facilitating the synthesis of fluoromethylation products **6i** and **6j**, although the yield is low, which is due to the instability of the products.

We investigated the synthetic applications of this reaction (Scheme 4). Since the conditions of this reaction are simple, green, and environmentally friendly, and do not require the addition of additional electrolytes usually required in electrochemistry, this reaction has practical application value. We scaled up the reaction to 8 mmol by simply increasing the current of the reaction to 75 mA and prolonging the reaction time to 23 h to easily obtain a gram-scale product **3a** in 60% yield (Scheme 4a). Deuteration may enhance the pharmacokinetic and/or toxicity profile of drugs, thus the "deuterium switch" has emerged as a novel avenue in drug development research.[83–87] Given the limited availability of deuterium, it is more advantageous to synthesize potential molecules from inexpensive and readily available deuterated starting materials. Deuterated acetic acid is such a raw material, and the conversion to a quaternary ammonium salt, followed by the introduction of a fully deuterated methyl functional group into the olefin molecule **3a-CD$_3$**,[88–93] can be readily achieved through the described methodology (Scheme 4b). Furthermore, alkoxy-alkylation products can be converted to higher synthetic value molecular entities, such as azides, sulfonamides, allyls, or olefins via cleavage of C─O bonds under Lewis acid or Brønsted acid catalysis (Scheme 4c).[94,95] Oxindoles represent pivotal natural product and medicine scaffolds.[96–98] We hypothesized that the current system could be applied to unsaturated amide substrates to synthesize such derivatives via decarboxylative alkylarylation of alkenes. This hypothesis was verified, resulting in the successful conversion of amide **11** to oxindole **12** under optimized conditions, achieving a yield of 36% (Scheme 4d).

In order to examine the mechanism of the reaction, we designed some control experiments and electrochemical detection procedures (Scheme 5). First, we utilized TEMPO to verify the free radical process of the reaction.[99–101] When 2 equiv of TEMPO were added to the reaction, the reaction was completely inhibited and no target product was detected (Scheme 5a). Surprisingly, we likewise did not observe any

by-products of TEMPO trapping the alkyl radicals. We then synthesized two specific substrates for radical-clock experiments to further demonstrate the generation of radical intermediates (Scheme 5b).[102–104] We used cyclopropyl-substituted tetrabutyl quaternary ammonium acetate **13** as a source of alkyl radicals to probe the radical decarboxylation process. Analysis of the products showed that we harvested the ternary ring-opening to obtain the ethoxylated product of the terminal olefin **14** in 22% yield. This suggests that the alkyl radicals may be generated by decarboxylation to obtain the cyclopropylmethyl radical with a lower rate of addition to **1a** than its ring-opening isomerization rate. When we used ternary ring-substituted styrene **15** as a substrate, 10% cyclopropyl ring-opening was detected by analyzing the reaction mixture under optimal conditions to obtain the product of the internal olefin **16**. This predicts that this methyl radical addition to the olefin yields a similar carbon-centered radical species to the cyclo-propyl substituent described above, and that it is anodically oxidized to the carbocation at a rate lower than that of the ring-opening step of the cyclopropyl ring.

Finally, we performed cyclic voltammetry experiments under a range of conditions (Scheme 5c).[105–107] We measured the oxidation potential of tetrabutylammonium acetate at 1.60 V, while the substrate olefin **1a** was around 1.89 V, which indicates that **2a** is oxidized preferentially over the substrate, which is the key to making the present reaction possible. Meanwhile, we measured the oxidation potentials of alkyl carboxylic acid quaternary ammonium salts with different carbon chain lengths, which require higher voltages to be oxidized as the carbon chain lengthens. We also conducted preliminary research on the fact that the addition of catalytic amounts of ammonium iodide can promote the decarboxylative alkylation of long-chain carboxylates. Cyclic voltammetry experiments showed that the addition of ammonium iodide significantly reduced the oxidation potential of the original carboxylate anion; in addition, an equivalent amount of iodine can achieve the decarboxylation reaction of quaternary ammonium carboxylates (See Supporting Information).[108]

Based on the above experimental results and relevant literature,[109–112] we propose a possible mechanism for the reaction (Scheme 5d). Alkyl carboxylate **I** are initially oxidized to carboxylate radicals **II** by the anode of the cell (path a). The radicals are then decarboxylated to gain primary alkyl radicals, added to olefins **1** to form new benzyl radicals **IV**, and rapidly oxidized to carbocation by the anode. The ions are captured by alcohols or other nucleophiles to afford the final products, while hydrogen release occurs at the cathode of the cell to achieve electronic equilibrium. However, an alternative pathway for the generation of alkyl carboxylate radicals via the homolytic cleavage of acyl hypoiodides cannot be completely ruled out in some conditions refer to adding NH_4I (path b).[113–115]

In conclusion, we present a metal-free electrochemically mediated decarboxylation of tetrabutylammonium alkyl carbonylates, enabling the generation of primary alkyl radicals that facilitate the alkyl-alkoxylation of olefins. This approach effectively transforms a wide range of substrates into tertiary or secondary ethers while demonstrating excellent compatibility with diverse functional groups. The scalability of the reaction has been validated, and the resulting C─O bonds can be further diversified into C─C or C─N bond derivatives. Notably, this method enables the incorporation of fully deuterated methyl groups using cost-effective and readily available deuterated acetic acid, offering a practical strategy for synthesizing CD_3-modified pharmaceuticals. To confirm radical formation and clarify the catalytic role of NH_4I in this process, we conducted a series of controlled experiments. We envision extending this electrochemical decarboxylation strategy to a broader range of substrates and developing innovative methodologies in the future.

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Alkoxy-alkylation · Carboxylate quaternary ammonium salts · Decarboxylation · Diflunctionlization of alkenes · Electrochemistry-driven

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Communication

Organic Chemistry

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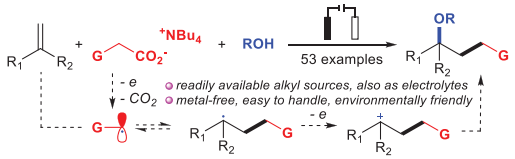
Metal-Free Electrochemistry-Driven Decarboxylative Primary Alkyl-Alkoxylation of Olefins



Here, we report the first successful primary alkylation (or methylation) bifunctionalization reaction of olefins through sequential anodic oxidation in a simple electrochemical system, utilizing quaternary amine salts of acetic or long chain carboxylic acids as both methyl or primary alkyl radical precursors and electrolytes. ((The Table of Contents text should give readers a short preview of the main theme of the research and results included in the paper to attract their attention into reading the paper in full. The Table of Contents text should be different from the abstract and should be no more than 450 characters including spaces.))