

# eEtherification: An electrochemical strategy towards the synthesis of sterically hindered dialkyl ethers from activated alcohols

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**KEYWORDS** Etherification; Alcohols; Electrochemistry; Activation; Ether; Synthesis; Carbocation; Decarboxylation

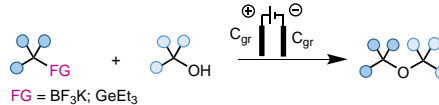
**ABSTRACT:** Traditional etherification methods, although staples in synthetic chemistry, often fall short in the efficient construction of sterically hindered dialkyl ethers, especially under mild and practical conditions. Recent advances have attempted to address these limitations, typically relying on transition metal catalysts, external reductants or harsh reaction conditions. In this article, we disclose a novel electrochemical approach that enables the synthesis of sterically hindered ethers from economically relevant and readily accessible alcohols without the need for sacrificial oxidants. Our protocol exploits mild conditions to generate reactive carbocations, which are subsequently captured by alcohol nucleophiles to yield the desired ethers. This method is cost-effective, practical and broad in scope, providing a valuable addition to chemists' synthetic toolkit for ether synthesis.

Throughout history, ethers have played an essential role in society. Their widespread use as anaesthetics in the 19th century<sup>1</sup> and their diverse applications in fields as diverse as cosmetics, fuels, pharmaceuticals and agrochemicals highlight their ubiquity.<sup>2-5</sup> This widespread use has led chemists to develop numerous protocols for ether synthesis.<sup>6</sup> One method is the Williamson etherification reaction, in which an alcohol is deprotonated with a strong base such as sodium hydride to form the corresponding alkoxide. This alkoxide is then reacted with an alkyl halide to give the desired ether product.<sup>7</sup> While this method allows the rapid synthesis of both symmetric and asymmetric ethers, their effectiveness is significantly reduced when synthesising sterically hindered ethers, often resulting in unwanted elimination products. To address this challenge, acid-catalysed hydroalkoxylation of alkenes is a promising solution for accessing hindered ethers. In this approach, an alkene is treated with a strong acid to generate a carbocation, which is then trapped by alcohols.<sup>8</sup> Despite the advantages, this transformation often requires harsh conditions that can limit the functional group compatibility and requires unhindered substrates to avoid competition with  $\beta$ -H elimination. Despite significant efforts to develop milder versions of traditional etherification methods, including transition metal catalysis,<sup>9-15</sup> and reductive etherification (which involves coupling an aldehyde or ketone with an alcohol in the presence of a silane reductant and a Lewis acid catalyst),<sup>16,17</sup> the synthesis of sterically hindered ethers without relying on large quantities of alcohol nucleophiles or external redox agents remains a challenging and underexplored area. This highlights the need for developing more practical methods, particularly as interest grows in preparing bioactive substrates<sup>18,19</sup> to address new challenges in pharmaceutical<sup>20</sup> and agrochemical<sup>21</sup> development. Although electrochemistry has been known for centuries, it now enables novel reactivity and the design of unorthodox retrosynthetic pathways by using electricity as a cheap electron source.<sup>22-25</sup> Electrochemistry

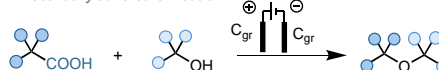
offers a sustainable alternative under mild conditions and has proven

## A. Previous electrochemical methodologies

*Electrochemical functionalisation via electroauxiliaries*



*Decarboxylative etherification*



- Multistep synthesis requiring high temperatures and/or a glovebox for starting material preparation

## B. This work

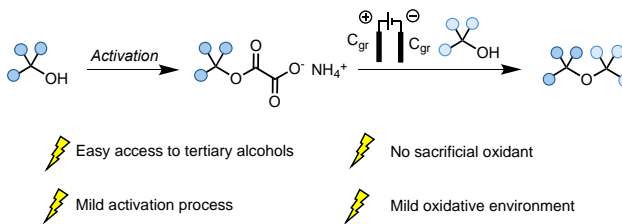


Figure 1. Summary of methodologies its effectiveness in preparing ethers.<sup>26-28</sup> Recently, Phil Baran and co-workers published an elegant Hofer-Moest-type decarboxylation approach for synthesising hindered dialkyl ethers.<sup>29</sup> This straightforward method represents a significant advance in accessing sterically hindered ethers. However, the limited availability of commercially available tertiary acids, coupled with the challenges in their synthesis, remains a significant limitation. This simple approach to generate a stable carbocation, which is then attacked by an alcohol is used by Chung, Lee and

their team who successfully achieved the electrochemical preparation of hindered ethers by anodic generation of carbocations from potassium trifluoroborate salts.<sup>30</sup> More recently, Shoenebeck and co-workers developed a similar transformation but from alkyl germanes (Figure 1, A).<sup>31</sup>

While these methods provide access to tertiary ethers, they typically require lengthy syntheses to obtain the starting materials necessary for electrolysis, and the use of a glove box is sometimes required (see Figure S6). This highlights the need for more straightforward methods that use stable and readily available starting materials.<sup>32</sup> In this vein, our group has recently developed a method to generate carbocations from easily accessible alcohol derivatives such as hemioxalate salts.<sup>33</sup> Unlike tertiary carboxylic acids, trifluoroborate salts, and germanium derivatives, hemioxalate salts can be easily prepared from tertiary alcohol derivatives in a single step under non-strict anhydrous and oxygen-free conditions without the need for purification. Tertiary alcohol derivatives are readily available commercially or can be easily synthesised by adding an organometallic reagent to ketones. We now report the anodic oxidation of hemioxalate salts in the presence of an alcohol as an expedient, mild, green, and practical method for accessing hindered ethers (Figure 1, B). The overall strategy involves the anodic generation of carbocations under neutral and mild conditions by oxidation and double decarboxylation of hemioxalates salts and their *in situ* capture by the desired alcohol.

As a starting point, we adapted the conditions previously developed for our deoxyfluorination methodology to the preparation of 1-(cyclohexyloxy)adamantane (**1**) from the ammonium hemioxalate salt of 1-adamantanol (**a**) using cyclohexanol as the nucleophile (Table 1, Entry 1)(see Supplementary Information for the full optimisation table). Electrolyses were monitored by TLC, GC-MS or HPLC-MS and continued until the starting material was consumed entirely. For such transformations, carbon graphite electrodes are ideal, not only because of their low cost but also because they enhance the adsorption of organic molecules, which promotes the overoxidation of alkyl radicals into their corresponding carbocations.<sup>23</sup> In addition, using two carbon electrodes allows for alternating the current polarity during the electrolysis in order to avoid any passivation of the electrodes. Dichloromethane (DCM) was chosen as the solvent owing to its low coordinating properties, which minimised competition with the nucleophilic alcohol in trapping the generated carbocation. Adding 3 Å molecular sieves to the reaction mixture was beneficial in preventing adventitious water from quenching the anodically generated carbocation. However, the poor solubility of the ammonium hemioxalate salt in DCM was a significant challenge (Table 1, Entry 3). To overcome this problem, 2,4,6-collidine was added to the reaction medium to generate the corresponding collidinium hemioxalate salt *in situ*, which is soluble in DCM. The protonated collidine adduct is then deprotonated at the cathode, generating hydrogen and preventing the reduction of DCM and the associated generation of chloride anions. We then screened various supporting electrolytes and found that NBu<sub>4</sub>ClO<sub>4</sub> gave the highest yield of the desired ether. Its concentration proved to have little impact; therefore, 0.5 equivalent of supporting electrolyte was found to be enough to provide enough conductivity. For the current density, 8.33 mA/cm<sup>2</sup> was found to be optimal; lower current densities resulted in similar yields when pushed to full conversion but resulted in lengthier electrolysis time. A concentration of 40 mM in hemioxalate salts was found to be ideal for the reaction. Higher concentrations led to lower yields. Full conversion of

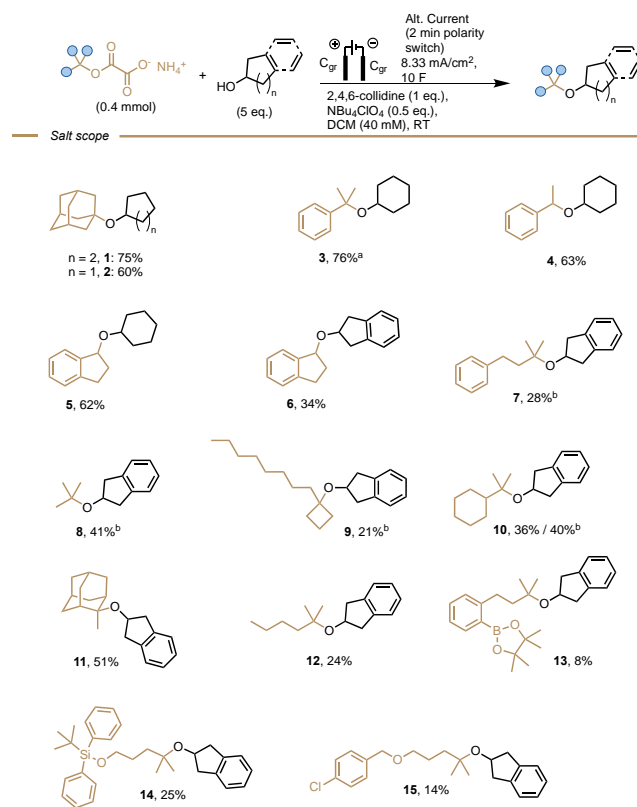
the starting material was achieved after 10 F. Unfortunately, a stoichiometric excess of the alcohol nucleophile was required; attempts to reduce its amount below 5 equivalents in order to develop a more economical process resulted in significantly lower yields of the desired ether. Finally, it was confirmed that no reaction took place in the absence of electrolytic current. With the optimal conditions established, we explored the scope and limitations of the methodology (Scheme 1).

**Table 1. Summary of optimisation**

Entry	Deviation from standard conditions	Yield <sup>a</sup>
1	None	54%
2	No electricity	N/O
3	No base	11%
4	Coll•HOTf as supporting electrolyte	19%
5	Coll•HPF <sub>6</sub> as a supporting electrolyte	38%
6	10 F	77%
7	10 F + 5 eq. of Cyclohexanol	38%
8	8.33 mA/cm <sup>2</sup>	59%
9	8.33 mA/cm <sup>2</sup> , 10 F, NBu <sub>4</sub> ClO <sub>4</sub> (0.5 eq.), 5 eq. of Cyclohexanol	89% (68%) <sup>b</sup>
10	8.33 mA/cm <sup>2</sup> , 10 F, NBu <sub>4</sub> ClO <sub>4</sub> (0.5 eq.), 5 eq. of Cyclohexanol, 40 mM	Quant. (75%) <sup>b</sup>

<sup>a</sup> GC-MS yield, <sup>b</sup> Isolated yield

**Scheme 1. Etherification of activated alcohols – Salt variation**



<sup>a</sup> Reaction conditions: hemioxalate salt (0.4 mmol), alcohol (5 eq.), collidinium tetrafluoroborate (1 eq.), DCM (5 mL), 3 Å molecular sieves (300 mg), room temperature, C<sub>gr</sub> (+) C<sub>gr</sub> (-), 4.17 mA/cm<sup>2</sup>, 5 F, Alternative current (2 min polarity switch). <sup>b</sup> The reaction was done with 5 mL of DCM

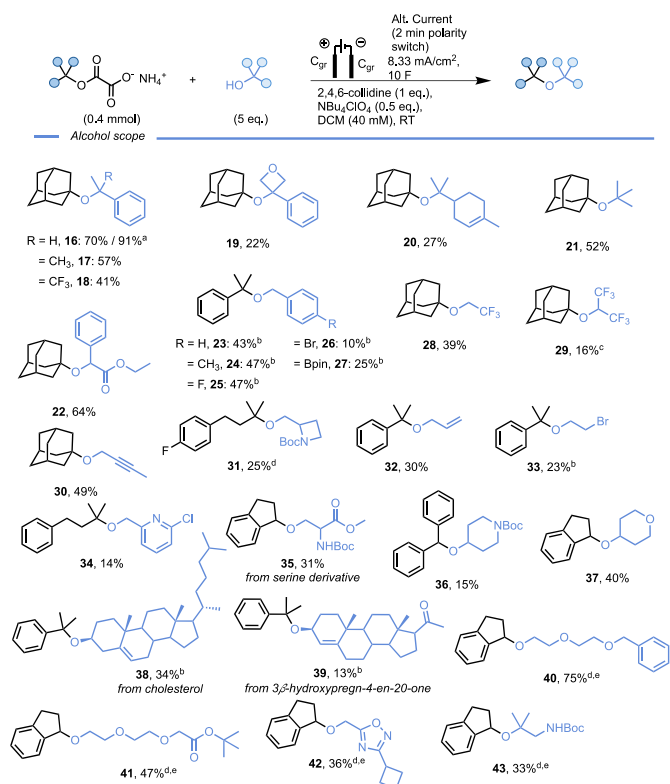
First, the scope of the hemioxalate salts was investigated. The adamantyl group was successfully added to cyclohexanol and cyclopentanol to yield ethers **1** and **2** in good yields. When the tertiary benzylic salt of 2-phenyl-2-propanol was subjected to

electrolysis to form the cumyl cation, unsurprisingly, an increase in the elimination product was observed under the present conditions. To overcome this, the conditions for this salt had to be reoptimised (Table S2), giving the product **3** in good yields. Salts from secondary benzylic alcohols were also tested, resulting in products **4-6**. While product **4** was obtained in satisfactory yields, the carbocation derived from 2-indanol spontaneously rearranged, suggesting a 1,2-hydride shift, producing a benzylic carbocation, which was then captured by the nucleophile to give products **5** and **6**. Aliphatic salts, including those involving the transformation of a cyclobutane ring, were also screened (products **7-12**), resulting in moderate to good yields (21%-51%). The new anodic transformation was compatible with boronate ester, leading to the corresponding ether **13**, albeit in low yields. Silyl ethers were also compatible, and the ether **14** bearing a TBDMS was obtained in 25% yield, while the oxidation-prone chlorobenzyl ether gave product **15** in 14% yield. Unfortunately, the electrolysis of saturated heterocyclic salts (including protected piperidines) often resulted in low yields due to substrate decomposition (see Figure S7). As expected, secondary and primary aliphatic salts did not yield the desired ethers, presumably due to the greater difficulty forming their highly unstable corresponding carbocations than their tertiary analogues. Yet, this does not represent a significant limitation, as unhindered ethers can be readily synthesised using the traditional Williamson ether synthesis method.

The scope of the alcohol nucleophile was then investigated (Scheme 2), starting with (*S*)-phenylethanol, which afforded product **16** in satisfactory yields. As expected, increasing the steric hindrance of the coupling alcohol led to a decrease in the yield of the desired ethers **17** and **18**. The synthesis of  $\alpha,\alpha'$ -bis-tertiary ethers (**19-21**), which are known to be highly challenging to access via Williamson etherification, proceeded smoothly and gave moderate to good yields (22%-52%). In particular, the med-chem-relevant oxetane (**19**) and terpene (**20**) derivatives were well tolerated under the electrolytic conditions. Ester groups were also well tolerated, with product **22** obtained in good yield without ester hydrolysis.

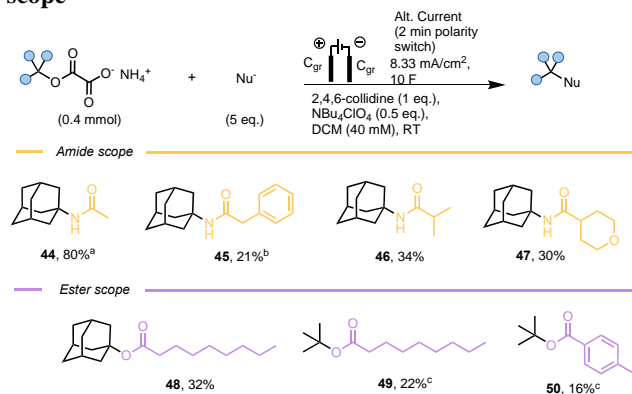
Easily oxidisable benzyl alcohols were found to be compatible with this methodology, and products **23** to **25** were obtained in satisfactory yields. Bromobenzyl alcohol was tolerated, yielding product **26**, albeit in modest yields. Boronic acid ester was also compatible with this protocol, giving product **27**. Weaker nucleophiles were also tested, forming fluorinated ethers **28** and **29** in moderate yields. Finally, The novel methodology proved to be robust enough to be rapidly scaled up. Indeed, product **16** was obtained in excellent yield after scale-up (1 mmol reaction). Etherification using alcohols bearing alkyne and alkene gave products **30** and **32**, respectively in satisfactory yields. Pharmaceutically relevant moieties such as azetidine, an alcohol-bearing halide susceptible to rapid ring-closure and formation of ethylene oxide under basic conditions, and an amino acid were well tolerated (**31**, **33** and **35**, respectively). Heterocycles (**34**, **36** and **37**) were also compatible with this method and gave moderate results. Further etherifications using pharmaceutically relevant steroids such as cholesterol (**38**) and a progesterone derivative (**39**) were successful. PEG ethers were also tested, and good yields of **40** and **41** were obtained. The biologically active 1,2,4-oxadiazole was compatible with this method and gave

**Scheme 2. Etherification of activated alcohols - Alcohol scope**



<sup>a</sup> Scale-up reaction: hemioxalate salt (1 mmol), alcohol (5 eq.), TBAP (0.5 eq.), DCM (20 mL), 3Å molecular sieves (600 mg), room temperature, C<sub>gr</sub> (+) C<sub>gr</sub> (-) 8.33 mA/cm<sup>2</sup>, 10 F, Alternative current (2 min polarity switch). <sup>b</sup> Reaction conditions: hemioxalate salt (0.4 mmol), alcohol (5 eq.), collidinium tetrafluoroborate (1 eq.), DCM (5 mL), 3Å molecular sieves (300 mg), room temperature, C<sub>gr</sub> (+) C<sub>gr</sub> (-) 4.17 mA/cm<sup>2</sup>, 5 F, Alternative current (2 min polarity switch). <sup>c</sup> Reaction done with HFIP as solvent (10 mL). <sup>d</sup> Reaction done in 5 mL of DCM. <sup>e</sup> Ammonium hemioxalate salt used for this transformation was derived from 1-indanol (0.4 mmol).

### Scheme 3. Etherification of activated alcohols - Nucleophile scope



<sup>a</sup> Reaction conditions: Collidinium adamantyl oxalate salt (0.2 mmol), no supporting electrolyte, MeCN (3 mL), 3Å molecular sieves (300 mg), room temperature, C<sub>gr</sub> (+) C<sub>gr</sub> (-) 4.17 mA/cm<sup>2</sup>, 4 F, Alternative current (2 min polarity switch). <sup>b</sup> Reaction done in 5 mL of DCM. <sup>c</sup> Collidinium tert-butyl oxalate salt (0.4 mmol) was used for this transformation product **42**. Finally, a sterically hindered alcohol bearing a protected amine was etherified to afford product **43** in moderate yields (see Figure S7 for the full list of unsuccessful substrates). Encouraged by these results, trapping the generated carbocation

with various nucleophiles was investigated (Scheme 3). Nitriles were tested as nucleophiles in Ritter-type transformations. Amide **44** was successfully obtained in good yields by changing the solvent to acetonitrile. Returning to DCM and using 5 equivalents of nitrile also gave satisfactory results with benzylic nitriles (**45**), aliphatic nitriles (**46**) and nitriles containing a saturated heterocycle (**47**), all of which were tolerated. This opens up avenues for mild alcohol to amide transformation that can be added to the synthetic chemist's toolbox. Using carboxylic acids as nucleophiles to form sterically hindered esters proved more challenging due to their relatively low nucleophilicity and tendency to undergo competitive decarboxylation under electrochemical conditions. Nevertheless, adamantyl esters **48** and *tert*-butyl esters **49** and **50** were obtained in moderate yields.

A plausible mechanism for electrochemical etherification is shown in Scheme S8. First, the collidinium hemioxalate salt, obtained by cation exchange with the ammonium hemioxalate salt, undergoes a first anodic oxidation to form the hemioxalate radical. This species then spontaneously undergoes two successive decarboxylations to form an alkyl radical. Subsequent anodic oxidation of the radical produces the carbocation, which is then captured by the alcohol nucleophile. Deprotonation of the oxonium ion by the non-oxidisable base 2,4,6-collidine gives the desired ether. 2,4,6-collidinium is reduced at the cathode, regenerating the active base. Cyclic voltammetry curves for the anodic oxidation of the ammonium hemioxalate salt can be found in the Supporting Information (Figures S3-S5).

An electrochemically irreversible oxidation occurs at 1.20 V vs  $\text{Fc}^{+/0}$  likely corresponding to the generation of the oxalyl radical at the anode. No reduction events were recorded during reverse scans. This profile suggests an EC-type mechanism where an electron transfer reaction is then followed by a chemical reaction, specifically, the decomposition of the oxalyl radical to the alkyl radical.

**In summary, we have developed a practical, inexpensive and mild electrochemical method for the synthesis of sterically hindered dialkyl ethers, amides and esters from activated alcohols. This approach exploits the generation of reactive carbocations under mild conditions, which are subsequently trapped by various nucleophiles. The versatility of this methodology, demonstrated by the successful incorporation of various alcohols, nitriles and carboxylic acids, makes it a valuable addition to the synthetic chemist's toolkit.**

## ASSOCIATED CONTENT

### Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures, spectral data, and characterisation of compounds (PDF)

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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. / ‡These authors contributed equally.

## Notes

The authors declare no competing financial interest.

## ACKNOWLEDGMENT

The authors are grateful to GlaxoSmithKline, and the University of Greenwich (PhD Scholarship to C.K.). C.K and D.L.P thanks Dr. Steve Besley (GSK) for HRMS analysis work and Dr. Steve Richards (GSK) for NMR compound elucidation work. C.K and S.K. thanks Kiel university, Prof. Manuel van Gemmeren (Otto-Diels-Institut für Organische Chemie, Christian-Albrechts-Universität zu Kiel, Otto-Hahn-Platz 4, 24098 Kiel, Germany) and the Studienstiftung des deutschen Volkes for supporting and funding the research stay abroad with K.L. C.K and D.R thanks Dr. Maria Manuel Marques (LAQV-REQUIMTE, Department of Chemistry, NOVA School of Science and Technology, Universidade Nova de Lisboa, 2829-516 Caparica, Portugal) for supporting and funding the research stay abroad with K.L. K.L. also thanks IKA for material support.

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