HHS Public Access

Author manuscript

Nature. Author manuscript; available in PMC 2020 March 09.

Published in final edited form as:

Nature. 2019 September ; 573(7774): 398–402. doi:10.1038/s41586-019-1539-y.

Hindered Dialkyl Ether Synthesis with Electrogenerated Carbocations

Jinbao Xiang[1,2,†], **Ming Shang**[1,†], **Yu Kawamata**[1], **Helena Lundberg**[1,3], **Solomon H. Reisberg**[1], **Miao Chen**[1], **Pavel Mykhailiuk**[1,7], **Gregory Beutner**[4], **Michael R. Collins**[5], **Alyn Davies**[6], **Matthew Del Bel**[5], **Gary M. Gallego**[5], **Jillian E. Spangler**[5], **Jeremy Starr**[6], **Shouliang Yang**[5], **Donna G. Blackmond**[1], **Phil S. Baran**[1,*]

[1]Department of Chemistry, Scripps Research, 10550 North Torrey Pines Road, La Jolla, CA 92037, USA.

[2]The Center for Combinatorial Chemistry and Drug Discovery of Jilin University, The School of Pharmaceutical Sciences, Jilin University, 1266 Fujin Road, Changchun, Jilin 130021, P. R. China.

[3]Department of Chemistry, KTH Royal Institute of Technology, Teknikringen 30, 10044 Stockholm, Sweden.

[4]Chemical and Synthetic Development, Bristol-Myers Squibb, One Squibb Drive, New Brunswick, NJ 08903, USA.

[5]Department of Chemistry, La Jolla Laboratories, Pfizer Inc., 10770 Science Center Drive, San Diego, CA 92121, USA.

[6]Pfizer Medicinal Sciences, Eastern Point Road, Groton, CT 06340, USA.

[7]Enamine Ltd., Chervonotkatska 78, 02094 Kyiv, Ukraine; and Taras Shevchenko National University of Kyiv, Chemistry Department, Volodymyrska 64, 01601 Kyiv, Ukraine.

Abstract

Hindered ethers represent an underexplored area of chemical space due to the difficulty and inoperability associated with conventional reactions, despite the high-value of such structural motifs in a variety of societal applications[1–2]. For example, such motifs are highly coveted in medicinal chemistry, as extensive substitution about the ether bond prevents unwanted metabolic processes that can lead to rapid *in vivo* degradation. Demonstrated herein is an exceptionally simple solution to this problem that leverages the power of electrochemical oxidation to liberate

*Correspondence and requests for materials should be addressed to P.S.B. (pbaran@scripps.edu).

Author contributions J.X., M.S. and P.S.B. conceived of the project. J.X., M.S., Y.K., H.L., D.G.B. and P.S.B. designed the experiments and analyzed the data. J.X. and M.S. developed the electrochemical decarboxylative methods and performed their applications. H.L. and Y.K. carried out the mechanistic study. J.X., M.S., S.H.R., M.C., P.M., G.B., M.R.C., A.D., M.D.B., G.M.G., J.E.S., J.S. and S.Y. conducted experiments to demonstrate substrate scope. P.S.B. wrote the manuscript. J.X., M.S., Y.K., S.H.R., P.M., H.L. and D.G.B. assisted in writing and editing the manuscript.

†These authors contributed equally to this work.

Supplementary information is available in the online version of the paper.

Competing interests The authors declare no competing interests.

Readers are welcome to comment on the online version of the paper.

high-energy carbocations from simple carboxylic acids. The controlled formation of these reactive intermediates takes place with low electrochemical potentials under non-acidic conditions to capture an alcohol donor thereby producing a range (>80) of ethers that would be extremely difficult to otherwise access. Simple nucleophiles can also intercept such cations, leading to hindered alcohols and even alkyl fluorides. This method has been field tested to solve the synthetic bottlenecks encountered on twelve real-world chemical scaffolds with documented societal impact, resulting in a dramatic reduction in step-count and labor required, accompanied with higher yields. Finally, the use of molecular probes coupled to kinetic studies support the proposed mechanism and role of additives in the conditions employed.

Students of organic chemistry are taught the Williamson ether synthesis[3–4] as a classic way to make primary alkyl ethers via S_N2 substitution (Fig. 1A), but in contexts involving secondary or tertiary alkyl halides the reaction often derails, leading to elimination byproducts or no reaction at all. Hindered ether **1**, a key intermediate for the synthesis of an aurora kinase modulator, exemplifies this commonly-faced challenge. Despite the documented utility of hindered ethers[1–2], very little progress has been registered to bridge this gap in reactivity. The alternative workhorse method, the Mitsunobu reaction, also fails in such settings due to steric demands of the S_N2 process and pK_a requirements of the nucleophile[5]. To the best of our knowledge, the most often-employed method for the synthesis of hindered dialkyl ether bonds still uses carbocation chemistry accessed from olefins (hydroalkoxylation) under strongly acidic conditions[6]. While this transformation has been known for nearly a century, its use is drastically limited in scope due to a lack of chemoselectivity and sluggish reactivity[7]. Indeed, in preparing hindered ether **1**, a multi-step route via 4-hydroxyproline **2** (R = CO_2Me) was employed, requiring over 6 days of reaction time (<4% overall yield), wherein the key C–O bond-forming reaction—the treatment of methylenecyclobutane with BF_3•Et_2O in the presence of the requisite secondary alcohol—provides the ether in only 11% yield[8].

Distinct from sterically-sensitive S_N2 and strongly acidic carbocation pathways, a third class of ether synthesis has been known for many years, but has remained largely underexplored. This third reaction paradigm (Figure 1A, yellow inset) stems from the oldest synthetic organic electrochemical reaction, the Kolbe dimerization, discovered in 1847[9]. In the so-called interrupted Kolbe variant, known as the Hofer-Moest reaction[10], electrolytic oxidation of a carboxylic acid under mildly alkaline conditions generates a carbocation that can be captured by incipient nucleophiles[10–18]. A distinct advantage of this reactivity paradigm is the *non-acidic* generation of high energy carbocations directly from ubiquitous carboxylic acids.

Based on this apparent advantage, we surveyed the literature, and were startled to observe an extremely limited application of the Hofer-Moest reaction in synthetic contexts (Figure 1B). Indeed, rather than using this reaction, much more complex catalytic systems that take advantage of photolytic conditions have been developed to make alkyl-aryl ethers[19]. There are likely two reasons for the limited exploration of electrolytic decarboxylative ether synthesis: First, the barrier to entry for electrosynthesis has traditionally been high for a practicing synthetic organic chemist[20]. Second, all Hofer-Moest systems known to date

required solvent-quantities of the alcoholic nucleophile, which is untenable for complex ethereal substrates. The alcoholic solvent, in addition to functioning as a reagent, permits current to pass and also acts as an electron-sink to balance the electrochemical process (liberating H_2 gas).

Herein, we report how the generation of carbocations from unactivated, aliphatic carboxylic acids, and their subsequent capture with heteroatom nucleophiles can be leveraged to provide a wide array of hindered C–X bonds. The reaction exhibits remarkable scope (>100 examples) across a range of valuable substrate classes (including previously inaccessible fluorinated ethers), is easily scalable in an undivided cell using inexpensive graphite electrodes, and has been studied in detail mechanistically.

The development of a practical electrochemical decarboxylative etherification was predicated on the valuable examples that preceded this work. Specifically, we set out to invent a set of Hofer-Moest conditions that were amenable to the needs of an organic chemist working on elaborate substrates (using a practical commercial setup with simple electrodes, mild conditions to tolerate sensitive functionality, and non-solvent quantities of alcohol donor). To achieve these goals, the extensive body of electrochemical literature[10–18, 20] around this reaction gave us key clues for initial reaction development. Specifically, it was known that carbon-based electrodes favored the desired carbocation generation, while platinum electrodes favored unproductive radical (Kolbe-type) dimerization[21]. It was also known that inert, non-oxidizable anions (e.g., ClO_4^-) enhance cation-like reactivity in the Hofer-Moest reaction[22]. Third, literature precedent showed that mildly alkaline conditions would be beneficial for the desired carbocation formation[22,23]. Finally, simple undivided cells are generally used in this process, suggesting that cathodic reduction would not significantly interfere with the reaction.

It became immediately apparent that limiting the amount of alcohol posed a number of significant challenges: decomposition of carbocation due to the low nucleophilicity of alcohols, competitive trapping of carbocation by water, consumption of alcohols by anodic oxidation and necessity of external electron-acceptor to balance electrons. Figure 1C summarizes the results of *ca.* 1000 experiments (see Supplementary Information for an extensive sampling) to solve all of these problems. Not surprisingly, initial exploratory experiments using the proposed conversion of **3** and **4** to **5** as an example, based on the literature precedent available (*vide supra*)[11,22], led to only trace amounts of product (entry 1). The conversion of the carboxylate was improved by choosing K_2CO_3 or 2,4,6-collidine as a non-oxidizable base (entries 2,3), though **6** and **7** were identified as major byproducts due to the presence of radical intermediate[22] and elimination pathways, respectively. These problems were effectively suppressed by changing solvents to CH_2Cl_2 (entry 4), resulting in the large increase of the desired ether product. In CH_2Cl_2, hydration of the carbocation (leading to **8**) persisted (entry 4), which was suppressed with the addition of 3Å molecular sieves (entry 5). It was also found that CH_2Cl_2 was apparently reduced at the cathode (see Figure S2 of Supplementary Information), acting as an electron-sink. Past approaches using water or simple alcohols as solvent did not need to address this issue, as the solvent can serve as the reagent and an electron sink (*via* proton reduction). Accordingly, adding a better sacrificial oxidant ($AgPF_6$) significantly improved the yield of **5**, leading to our optimized

conditions (entry 6). Addition of $AgPF_6$ also completely suppressed the formation of **6** and **7**, though this effect varies by substrate and, in some cases (*vide infra*), silver additives are not necessary at all. Negative controls confirmed the necessity of a slight stoichiometric excess of the alcoholic partner (entry 7). In the absence of base, no desired product was observed, with the major products being the ketone **9** and the ester **10** (entry 8).

The patent literature is replete with examples of hindered ethers of use in a variety of pharmaceutical and materials applications. While carbocation-based routes from olefins predominate in literature, electrochemical access to such compounds has notable advantages on the time, step count and overall yield to access such valuable entities. Illustrated in Table 1 is an abbreviated depiction of six such applications as well as the 80+ ethers prepared (see Supplementary Information for full listing of substrates as well as comparison to prior routes). Primary carboxylic acids and certain secondary systems are not compatible with electrochemical etherification, because the resultant carbocations are not sufficiently stable. However, this limitation is inconsequential from a synthetic perspective, as those ethers can be easily prepared through standard S_N2-type approaches[3–5]. Acids bearing a variety of functional groups are tolerated such as Boc-protected amine (**17**), aryl and alkyl halides (**25**, **27**, **30**), olefins (**26**), esters (**29**, **39**), enones (**39**), ethers (**35**, **36**, **62**), and even oxidation-prone boronic esters (**28**). Similarly, the scope of alcohol coupling partners is vast and includes acid-labile and oxidation-prone chiral secondary benzylic alcohols (**17**), deuterated systems (**49**), azetidinyl (**50**), protected sugars (**53**), olefin-containing (**48, 51, 59**), acetals and esters (**44**), halides (**15**), nitriles (**45**), nitro groups (see Supplementary Information), and even Lewis-basic heterocycles (**42**, **43**, **45**). The ability to tolerate chiral, ionizable secondary alcohols is worth emphasizing, as acidic methods for ether synthesis would lead to elimination or racemization (**17** is formed in 95% *ee*). Electrogenerated cations bearing fluorine atoms can also be intercepted, opening up a range of new organofluorine-containing ether systems that were either difficult to access or unknown (see Supplementary Information for full listing of fluorinated ethers). Finally, the synthesis of polyethyleneglycol (PEG) ethers, historically laborious, can be modularly produced through this process (no PEG ethers analogous to **66–69** are known). To ensure the robustness of the process, ten randomly selected examples in Table 1 were run in triplicate and exhibited no more than 5% yield variance between runs.

As mentioned at the outset, the use of simple alcohols such as methanol and water itself is already known in electrochemical decarboxylative processes (Figure 1B)[10–18]. However, the scope of such processes is quite limited. The conditions developed above were therefore adapted for these related reactions (see Supplementary Information). In order to render this reaction general, the choice of electrolyte ($^nBu_4NPF_6$) and base (2,4,6-collidine) was crucial while silver additives were found to be unnecessary. As with hindered ether synthesis, the most convincing case for the use of this reaction stems from its ability to dramatically truncate synthetic pathways. Six such examples are illustrated in Table 2 (see Supplementary Information).

The addition of water to generate various tertiary and secondary alcohols is a broadly applicable process with selected examples depicted in Table 2 (for additional examples, see Supplementary Information). Again, the chemoselectivity is on par with that observed

above; aryl bromides (**84**), boronic esters (**85**), electron rich aromatics (**87**), lactams (**88**), ethers (**79**), and esters (**81**) are tolerated. In preliminary studies, the potential of adding other nucleophiles to the putative electrogenerated carbocations was also studied. Carboxylates not capable of decarboxylation under these conditions could act as nucleophiles, to provide hindered esters (**89** and **90**)[24]. Useful organofluorine building blocks could also be accessed (**91**-**94**) in a process that might be of use in radiolabeling studies, since the fluorine source utilized (inexpensive KF) is preferred in such situations[25]. Finally, using benzonitrile as a nucleophile led to the expected Ritter-type product (**95**), albeit in lower yield[26]. The robust and practical nature of this process was also demonstrated with the gram-scale preparation of **5** and **81** through etherification and hydroxylation processes. In the case of large-scale etherification, the silver salt additive could be left out with a minimal effect on yield (72 vs 78% yield).

Extensive mechanistic studies were also undertaken to understand the role of additives and the nature of the reactive intermediate. In summary, the mechanism is likely to be the rate-limiting oxidation of a carboxylate on the anode to generate a carbocation, followed by nucleophilic attack by an alcohol to afford the ether product (See Supplementary Information for full details).

It is anticipated that the mild electrogeneration of carbocations reported herein will find use in numerous settings where standard S_N2 and carbocation-based approaches for forming hindered functionalized carbogenic frameworks fail.

METHODS

Here we describe a typical procedure for the decarboxylative etherification, and further experimental details are provided in Supplementary Information.

General procedure for decarboxylative etherification.

With no precautions to exclude air or moisture, the ElectraSyn vial (5 mL) with a stir bar was charged with carboxylic acid (0.2 mmol, 1.0 equiv.), alcohol (0.6 mmol, 3.0 equiv.), 2,4,6-collidine (0.6 mmol, 3.0 equiv.), $^{n}Bu_4NPF_6$ (0.3 mmol, 1.5 equiv.), 3 Å molecular sieves (150 mg), $AgPF_6$ (0.3 mmol, 1.5 equiv.), and CH_2Cl_2 (3.0 mL). The ElectraSyn vial cap equipped with anode (graphite) and cathode (graphite) were inserted into the mixture. After pre-stirring for 15 minutes, the reaction mixture was electrolyzed at a constant current of 10 mA for 3 hours. The ElectraSyn vial cap was removed, and electrodes were rinsed with Et_2O (2 mL), which was combined with the crude mixture. Then, the crude mixture was further diluted with Et_2O (30 mL). The resulting mixture was washed with 2N HCl (20 mL) and $NaHCO_3$ (aq) (20 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The crude material was purified by preparative thin-layer chromatography (PTLC) to furnish the desired product. Full experimental details and characterization of new compounds can be found in the Supplementary Information.

Data availability.

The data that support the findings of this study are available within the paper and its Supplementary Information. Metrical parameters for the structures of (2*R*)-**77** and

(11*R*)-**138** are available free of charge from the Cambridge Crystallographic Data Centre (https://www.ccdc.cam.ac.uk/) under reference numbers 1918528 and 1903823, respectively.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

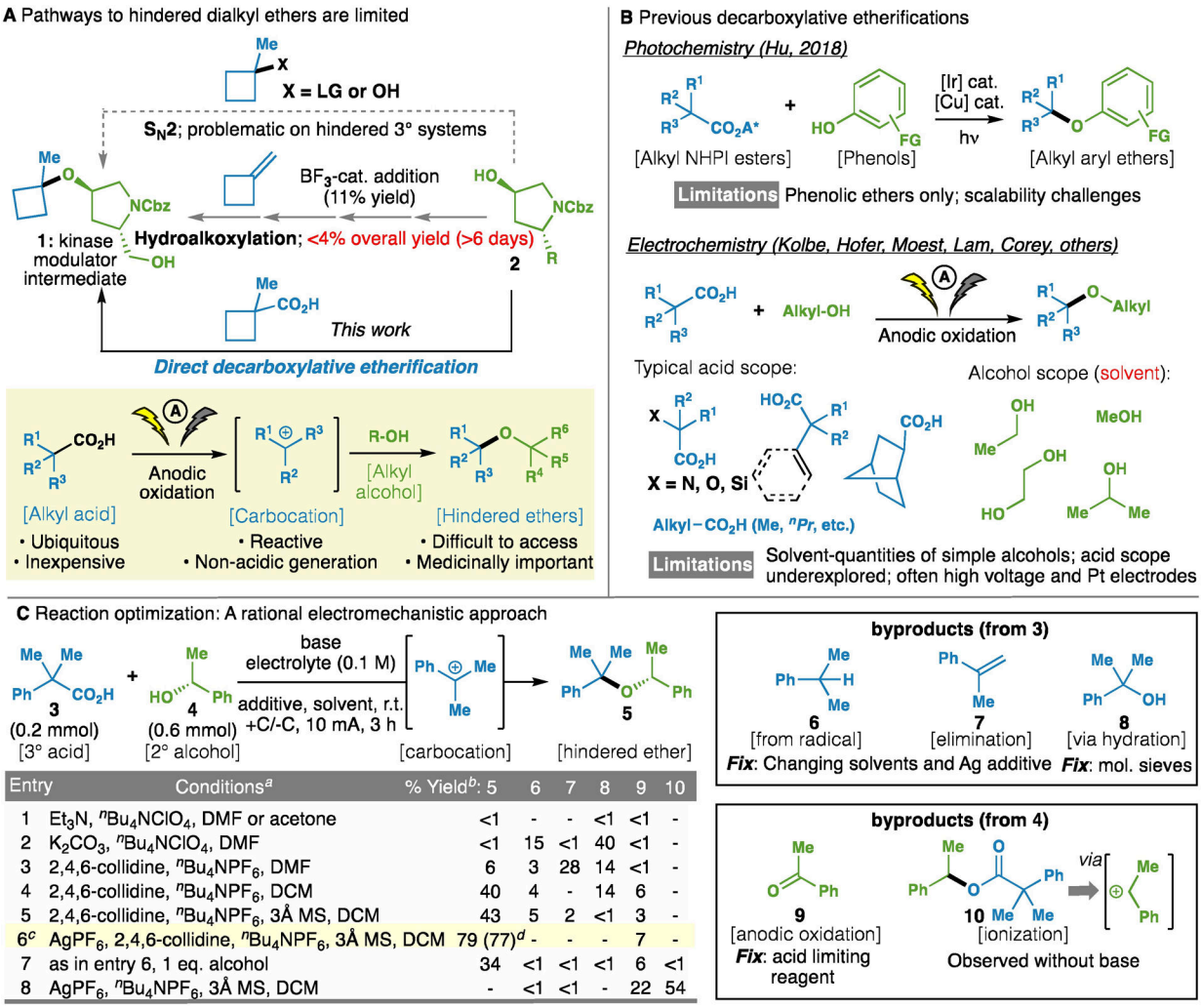
Acknowledgments

Financial support for this work was provided by Pfizer, Inc., NSF (CCI Phase 1 grant 1740656), and the National Institutes of Health (grant number GM-118176). China Scholarship Council and Jilin University supported a fellowship to J.X., Zhejiang Yuanhong Medicine Technology Co. Ltd. supported a fellowship to M.S., The Hewitt Foundation supported a fellowship to Y.K., The Swedish Research Council supported a fellowship to H.L., Fulbright Fellowship supported a fellowship to P.M., S.H.R. acknowledges an NSF GRFP (#2017237151) and a Donald and Delia Baxter Fellowship. We thank D.-H. Huang and L. Pasternack (Scripps Research) for assistance with NMR spectroscopy; J. Chen (Automated Synthesis Facility, Scripps Research); A. Rheingold, C. E. Moore, and M. A. Galella (UCSD) for x-ray crystallographic analysis.

References:

1. Roughley SD & Jordan AM The medicinal chemist's toolbox: An analysis of reactions ssed in the pursuit of drug candidates. J. Med. Chem 54, 3451–3479 (2011). [PubMed: 21504168]
2. Fischer J & Ganellin CR Analogue-based drug discovery, pp 206–217 (Wiley, 2006).
3. Williamson W Ueber die theorie der aetherbildung. Justus Liebigs Ann. Chem 77, 37–49 (1851)
4. Kürti L & Czakó B Strategic applications of named reactions in organic synthesis, pp 484–485. (Elsevier, 2005).
5. Swamy KCK, Kumar NNB, Balaraman E & Kumar KVPP Mitsunobu and related reactions: Advances and applications. Chem. Rev 109, 2551–2651 (2009). [PubMed: 19382806]
6. Beyerman HC & Heiszwolf GJ Reaction of steroidal alcohols with isobutene. Usefulness of *t*-butyl as a hydroxyl-protecting group in a synthesis of testosterone. Rec. Trav. Chim. Pays-Bas 84, 203–212 (1965).
7. Smith MB & March J March's advanced organic chemistry, pp 1037–1041 (Wiley, 2007).
8. Abraham S et al. Aurora kinase compounds and methods of their use. WO2011088045 A1 (2011).
9. Kolbe H Beobachtungen über die oxydirende Wirkung des Sauerstoffs, wenn derselbe mit Hülfe einer elektrischen Säule entwickelt wird. J. Prakt. Chem 41, 137–139 (1847).
10. Hofer H & Moest M Mittheilung aus dem elektrochemischen Laboratorium der Königl, Technischen Hochschule zu München. Justus Liebigs Ann. Chem 323, 284–323 (1902).
11. Corey EJ, Bauld NL, La Londe RT, Casanova J Jr & Kaiser ET Generation of cationic carbon by anodic oxidation of carboxylic acids. J. Am. Chem. Soc 82, 2645–2646 (1960).
12. Luo X, Ma X, Lebreux F, Markó IE & Lam K Electrochemical methoxymethylation of alcohols – A new, green and safe approach for the preparation of MOM ethers and other acetals. Chem. Commun 54, 9969–9972 (2018).
13. Bunyan PJ & Hey DH The electrolysis of some aryl-substituted, aliphatic acids. J. Chem. Soc 1360–1365 (1962).
14. Iwasaki T, Hrorikawa H, Matsumoto K & Miyoshi M Electrochemical synthesis and reactivity of α-alkoxy α-amino acid derivatives. Bull. Chem. Soc. Japan 52, 826–830 (1979).
15. Tajima T, Kurihara H & Fuchigami T Development of an electrolytic system for non-Kolbe electrolysis based on the acid−base reaction between carboxylic acids as a substrate and solid-supported bases. J. Am. Chem. Soc 129, 6680–6681 (2007). [PubMed: 17477529]
16. Shtelman AV & Becker JY Electrochemical synthesis of 1,2-disilylethanes from α-silylacetic acids. J. Org. Chem 76, 4710–4714 (2011). [PubMed: 21495731]
17. Torii S, Inokuchi T, Mizuguchi K & Yamazaki M Electrolytic decarboxylation reactions. 4. Electrosyntheses of 3-alkyl-2-cycloalken-1-ol acetates from 1-alkyl-2-cycloalkene-1-carboxylic acids. Preparation of *dl*-muscone from cyclopentadecanone. J. Org. Chem 44, 2303–2307 (1979).

18. Coleman JP, Lines R, Utley JHP & Weedon BCL Electro-organic reactions. Part II. Mechanism of the kolbe electrolysis of substituted phenylacetate ions. J. Chem. Soc., Perkin Trans. 2, 0, 1064–1069 (1974).
19. Mao R, Balon J & Hu X Decarboxylative C(sp^3)–O cross-coupling. Angew. Chem. Int. Ed 57, 13624–13628 (2018).
20. Yan M, Kawamata Y & Baran PS Synthetic organic electrochemical methods since 2000: On the verge of a renaissance. Chem. Rev 117, 13230–13319 (2017). [PubMed: 28991454]
21. Ross SD & Finkelstein M Anodic oxidations. V. The Kolbe oxidation of phenylacetic acid and 1-methylcyclohexaneacetic acid at platinum and at carbon. J. Org. Chem 34, 2923–2927 (1969).
22. Schäfer HJ Recent contributions of Kolbe electrolysis to organic synthesis. Top. Curr. Chem 152, 91–151 (1990).
23. Koehl WJ Anodic oxidation of aliphatic acids at carbon anodes, J. Am. Chem. Soc 86, 4686–4690 (1964).
24. Iwasaki T, Horikawa H, Matsumoto K & Miyoshi M An electrochemical synthesis of 2-acetoxy-2-amino acid and 3-acetoxy-3-amino acid derivatives. J. Org. Chem 42, 2419–2423 (1977). [PubMed: 874616]
25. Huang X, Liu W, Hooker JM & Groves JT Targeted fluorination with the fluoride ion by manganese-catalyzed decarboxylation. Angew. Chem. Int. Ed 54, 5241–5245 (2015).
26. Eberson L & Nyberg K Studies on the Kolbe electrolytic synthesis. V. An electrochemical analogue of the Ritter reaction. Acta Chem. Scand 18, 1567–1568 (1964).



Entry	Conditions[a]	% Yield[b]: 5	6	7	8	9	10
1	Et_3N, $^nBu_4NClO_4$, DMF or acetone	<1	-	-	<1	<1	-
2	K_2CO_3, $^nBu_4NClO_4$, DMF	<1	15	<1	40	<1	-
3	2,4,6-collidine, $^nBu_4NPF_6$, DMF	6	3	28	14	<1	-
4	2,4,6-collidine, $^nBu_4NPF_6$, DCM	40	4	-	14	6	-
5	2,4,6-collidine, $^nBu_4NPF_6$, 3Å MS, DCM	43	5	2	<1	3	-
6[c]	$AgPF_6$, 2,4,6-collidine, $^nBu_4NPF_6$, 3Å MS, DCM	79 (77)[d]	-	-	-	7	-
7	as in entry 6, 1 eq. alcohol	34	<1	<1	<1	6	<1
8	$AgPF_6$, $^nBu_4NPF_6$, 3Å MS, DCM	-	<1	<1	-	22	54

Figure 1.

(A) The synthesis of hindered ethers is a long-standing challenge in organic synthesis; (B) Historical context and prior strategies for decarboxylative etherification; and (C) Development and optimization of hindered ether synthesis depicted through electromechanistic analysis. [a]Compound **3** (0.2 mmol), 3.0 eq. alcohol **4** was used (except where designated). [b]GC yield. All entries performed in triplicate. [c]Conditions: acid **3** (0.2 mmol), alcohol **4** (0.6 mmol), $AgPF_6$ (0.3 mmol), 2,4,6-collidine (0.6 mmol), $^nBu_4NPF_6$ (0.1 M), 3Å MS (150 mg), CH_2Cl_2 (3 mL), I = 10 mA, 3 h. [d]Isolated yield. DMF, *N,N*-dimethylformamide; DCM, dichloromethane; 3Å MS, 3Å molecular sieves.

Table 1.

Applications, and partial scope of hindered ether synthesis via electrochemical decarboxylation (see Supplementary Information for full scope).

[a]$AgSbF_6$ (0.3 mmol) instead of $AgPF_6$. [b]DBU (0.6 mmol) instead of 2,4,6-collidine. [c]$KSbF_6$ (0.3 mmol) instead of $AgPF_6$. [d]Alcohol as limiting reagent, conditions: alcohol (0.15 mmol), carboxylic acid (0.45 mmol), $AgClO_4$ (0.6 mmol), 2,4,6-collidine (0.675 mmol), $^nBu_4NClO_4$ (0.2 M), 3Å MS (100 mg), CH_2Cl_2 (2 mL), I = 10 mA, 3 h. [e]$AgClO_4$ (0.6 mmol) instead of $AgPF_6$, $^nBu_4NClO_4$ (0.1 M) instead of $^nBu_4NPF_6$. [f]4.0 or 6.0 eq.

alcohol. [g]1.5 mL CH_2Cl_2, I = 7.5 mA, 4 h. [hn]$^nBu_4NClO_4$ (0.1 M) instead of $^nBu_4NPF_6$, no $AgPF_6$. [i]Reaction performed in triplicate; yield is average of three runs.

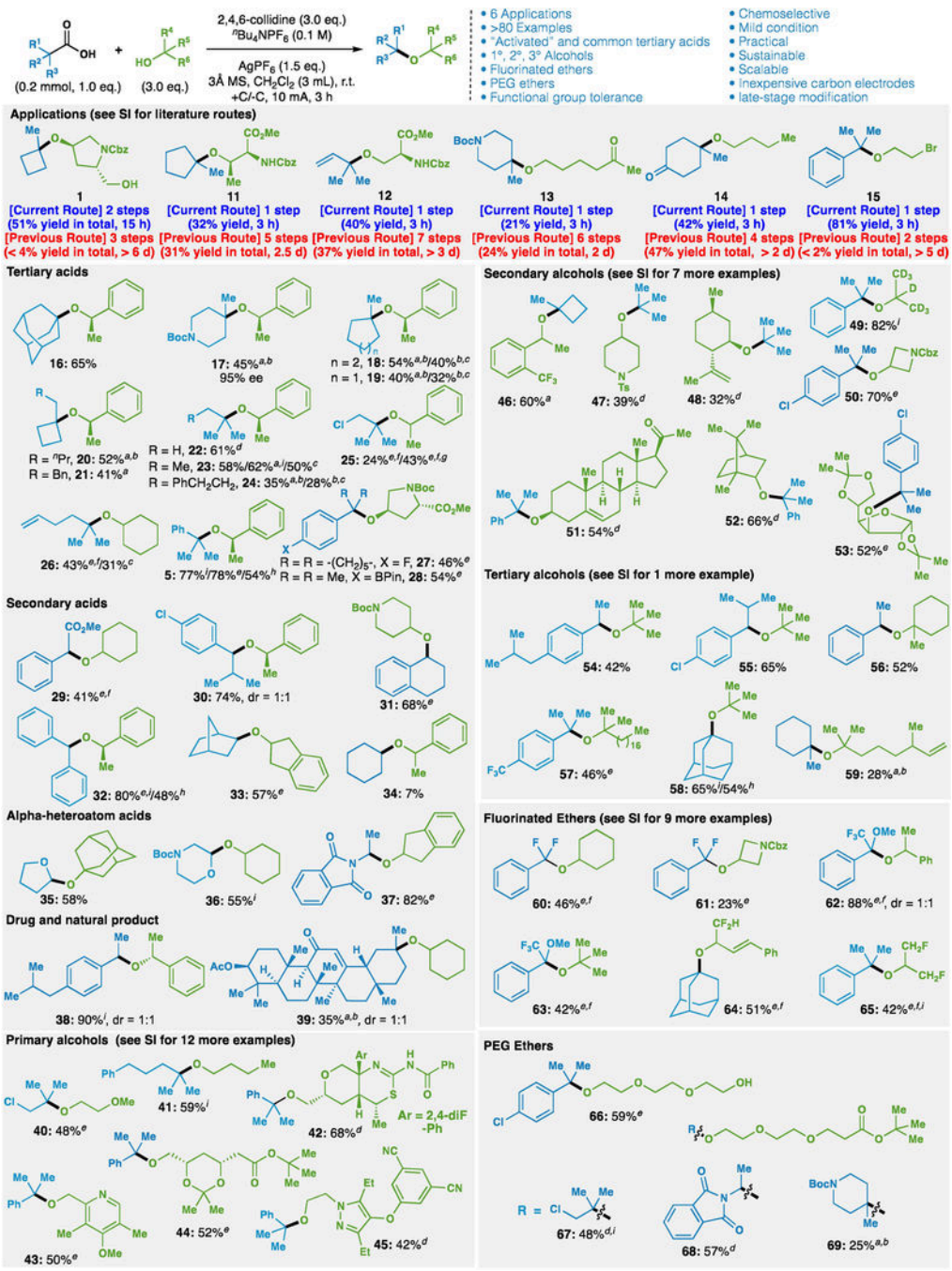


Table 2.

Applications and partial scope of trapping electrogenerated carbocations with other nucleophiles along with scalability demonstration (see Supplementary Information for full scope).

[a]H_2O (0.1 mL) as nucleophile. [b]Carboxylic acid or phenylacetonitrile as nucleophile (0.6 mmol, 3 eq.), conditions: $AgClO_4$ (0.6 mmol, 3 eq.), 2,4,6-collidine (0.6 mmol, 3 eq.), $^nBu_4NClO_4$ (0.1 M), 3Å MS (150 mg), CH_2Cl_2 (3 mL). [c]KF (0.72 mmol, 3.6 eq.) as nucleophile, conditions: 18-Crown-6 (0.72 mmol, 3.6 eq), $AgClO_4$ (0.6 mmol, 3 eq.), 2,4,6-collidine (0.6 mmol, 3 eq.), $^nBu_4NPF_6$ (0.1 M), 3Å MS (150 mg), CH_2Cl_2 (3 mL).