LETTER

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Hindered dialkyl ether synthesis with electrogenerated carbocations

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Hindered ethers are of high value for various applications; however, they remain an underexplored area of chemical space because they are difficult to synthesize via conventional reactions[1,2]. Such motifs are highly coveted in medicinal chemistry, because extensive substitution about the ether bond prevents unwanted metabolic processes that can lead to rapid degradation in vivo. Here we report a simple route towards the synthesis of hindered ethers, in which electrochemical oxidation is used to liberate high-energy carbocations from simple carboxylic acids. These reactive carbocation intermediates, which are generated with low electrochemical potentials, capture an alcohol donor under non-acidic conditions; this enables the formation of a range of ethers (more than 80 have been prepared here) that would otherwise be difficult to access. The carbocations can also be intercepted by simple nucleophiles, leading to the formation of hindered alcohols and even alkyl fluorides. This method was evaluated for its ability to circumvent the synthetic bottlenecks encountered in the preparation of 12 chemical scaffolds, leading to higher yields of the required products, in addition to substantial reductions in the number of steps and the amount of labour required to prepare them. The use of molecular probes and the results of kinetic studies support the proposed mechanism and the role of additives under the conditions examined. The reaction manifold that we report here demonstrates the power of electrochemistry to access highly reactive intermediates under mild conditions and, in turn, the substantial improvements in efficiency that can be achieved with these otherwise-inaccessible intermediates.

The Williamson ether synthesis[3,4] is a long-established method by which to synthesize primary alkyl ethers via S_N2 substitution (Fig. 1a). However, in contexts involving secondary or tertiary alkyl halides the reaction often derails, leading to elimination byproducts or to no reaction at all. Hindered ether **1**, which is a key intermediate in 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 made in facilitating access to them. The alternative workhorse method, the Mitsunobu reaction, also fails in such settings owing to the steric demands of the S_N2 process and the pK_a requirements of the nucleophile[5]. To the best of our knowledge, the most frequently used method for the synthesis of hindered dialkyl ether bonds still uses carbocation chemistry accessed from olefins (hydroalkoxylation) under strongly acidic conditions[6]. Although this transformation has been known for nearly a century, its use is substantially limited in scope owing to sluggish reactivity and a lack of chemoselectivity[7]. For example, in order to prepare hindered ether **1**, a multi-step route via 4-hydroxyproline **2** (R = CO_2Me) was used. The synthesis required over 6 days of reaction time and gave the required product in less than 4% overall yield; the key C–O bond-forming reaction—the treatment of methylenecyclobutane with $BF_3{\cdot}Et_2O$ 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, there is a third class of ether synthesis that has been known for many years but has remained largely underexplored. This class (Fig. 1a, yellow inset) stems from the oldest synthetic organic electrochemical reaction, the Kolbe dimerization, which was discovered[9] in 1847. 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 reaction is the non-acidic generation of high-energy carbocations directly from carboxylic acids.

We were therefore surprised to find a dearth of applications of the Hofer–Moest reaction in synthetic contexts (Fig. 1b). Indeed, much more complex catalytic systems that take advantage of photolytic conditions have been developed to make alkyl–aryl ethers[19]. There are probably two reasons for the limited exploration of electrolytic decarboxylative ether synthesis: first, the barrier to entry into electrosynthesis has traditionally been high for a practicing synthetic organic chemist[20]. Second, all Hofer–Moest systems known so far have 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 hydrogen gas.

Herein, we report how the generation of carbocations from unactivated, aliphatic carboxylic acids—and their subsequent capture by heteroatom nucleophiles—can be leveraged to provide a wide array of hindered C–X bonds.

Several key literature precedents can be highlighted that aided this development. It is known that carbon-based electrodes favour the desired carbocation generation, whereas platinum electrodes favour unproductive radical (Kolbe-type) dimerization[21]. It is also known that inert, non-oxidizable anions (for example, ClO_4^-) enhance cation-like reactivity in the Hofer–Moest reaction[22]. Mildly alkaline conditions are known to be beneficial for the desired carbocation formation[22,23]. Finally, simple undivided cells are generally used in this process, which suggests that cathodic reduction would not interfere substantially with the reaction.

It became immediately apparent that limiting the amount of alcohol posed several considerable challenges: the decomposition of the carbocation due to the low nucleophilicity of alcohols; the competitive trapping of the carbocation by water; the consumption of alcohols by anodic oxidation; and the necessity of an external electron-acceptor in order to balance electrons. Figure 1c summarizes the results of around 1,000 experiments (see Supplementary Information for an extensive sampling) that were undertaken in order to solve these problems. Not surprisingly, initial exploratory experiments using the proposed

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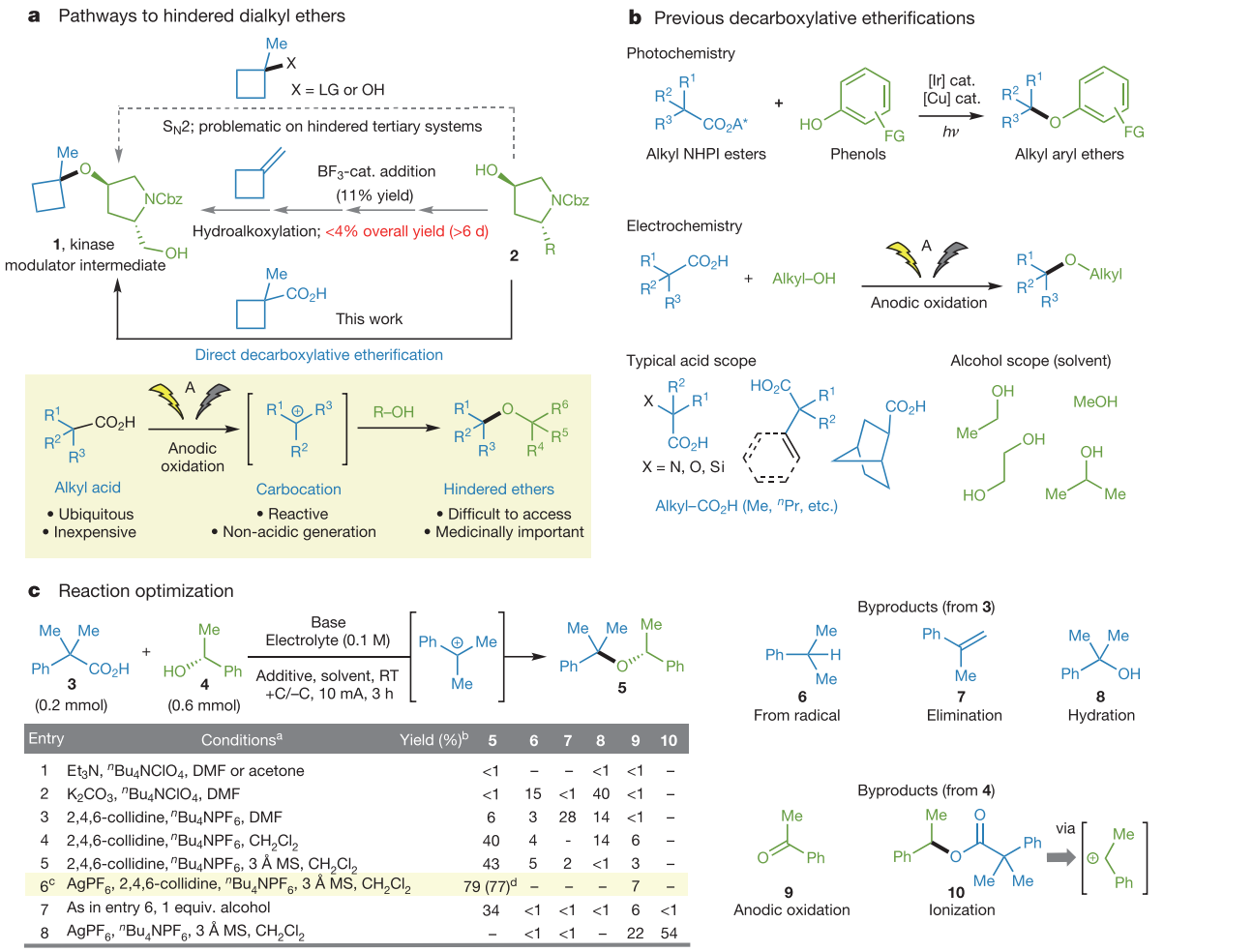

Entry	Conditions[a]	Yield (%)[b]	5	6	7	8	9	10
1	Et_3N, $^nBu_4NClO_4$, DMF or acetone		<1	–	–	<1	<1	–
2	K_2CO_3, $^nBu_4NClO_4$, DMF		<1	15	<1	40	<1	–
3	2,4,6-collidine, $^nBu_4NPF_6$, DMF		6	3	28	14	<1	–
4	2,4,6-collidine, $^nBu_4NPF_6$, CH_2Cl_2		40	4	-	14	6	–
5	2,4,6-collidine, $^nBu_4NPF_6$, 3 Å MS, CH_2Cl_2		43	5	2	<1	3	–
6[c]	$AgPF_6$, 2,4,6-collidine, $^nBu_4NPF_6$, 3 Å MS, CH_2Cl_2	79 (77)[d]	–	–	–	7	–	
7	As in entry 6, 1 equiv. alcohol		34	<1	<1	<1	6	<1
8	$AgPF_6$, $^nBu_4NPF_6$, 3 Å MS, CH_2Cl_2		–	<1	<1	–	22	54

Fig. 1 | Background and reaction development. a, The synthesis of hindered ethers is a long-standing challenge in organic synthesis. A; constant-current electrolysis; cat., catalyst; Cbz, carboxybenzyl; LG, leaving group. **b**, Historical context and previous strategies for decarboxylative etherification. FG, functional group; NHPI, *N*-hydroxyphthalimide. **c**, Development and optimization of hindered ether synthesis depicted through electromechanistic analysis. [a]Compound **3** (0.2 mmol), 3.0 equiv. of alcohol **4** (except where designated). [b]Yield based on gas chromatography. All entries were 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), 3 Å molecular sieves (150 mg), dichloromethane (CH_2Cl_2; 3 ml), current (I) = 10 mA, 3 h. [d]Isolated yield. DMF, *N*,*N*-dimethylformamide; RT, room temperature; +C/−C represents the graphite electrodes.

conversion of **3** and **4** to **5** as an example—based on the literature precedent available[11,22]—led to only trace amounts of product (entry 1). The conversion of the carboxylate was improved by choosing potassium carbonate or 2,4,6-collidine as a non-oxidizable base (entries 2, 3), although **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 the solvent to dichloromethane (entry 4), which resulted in a large increase of the desired ether product. In dichloromethane, hydration of the carbocation (leading to **8**) persisted (entry 4), which was suppressed by the addition of 3 Å molecular sieves (entry 5). It was also found that dichloromethane was apparently reduced at the cathode (Supplementary Fig. 2), acting as an electron sink. Past approaches using water or simple alcohols as the solvent did not need to address this issue, as the solvent can serve as both the reagent and an electron sink (via proton reduction). Accordingly, the addition of a better sacrificial oxidant (silver hexafluorophosphate, $AgPF_6$) considerably improved the yield of **5**, leading to our optimized conditions (entry 6). The addition of $AgPF_6$ also completely suppressed the formation of **6** and **7**, although this effect was found to vary by substrate and—in some cases—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 in various pharmaceutical and materials applications. Although carbocation-based routes from olefins predominate in the literature, electrochemical access to such valuable entities has notable advantages in terms of the time required, the step count and the overall yield. Figure 2 shows an abbreviated depiction of six such applications as well as the more than 80 ethers prepared (see Supplementary Information for a full listing of substrates as well as a comparison to previous 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 various functional groups are tolerated, such as Boc-protected amines (**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 alcohols (**50**), protected sugars (**53**) and olefin-containing alcohols (**48**, **51**, **59**), as well as alcohols containing 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, because acidic methods for ether synthesis using such alcohols would

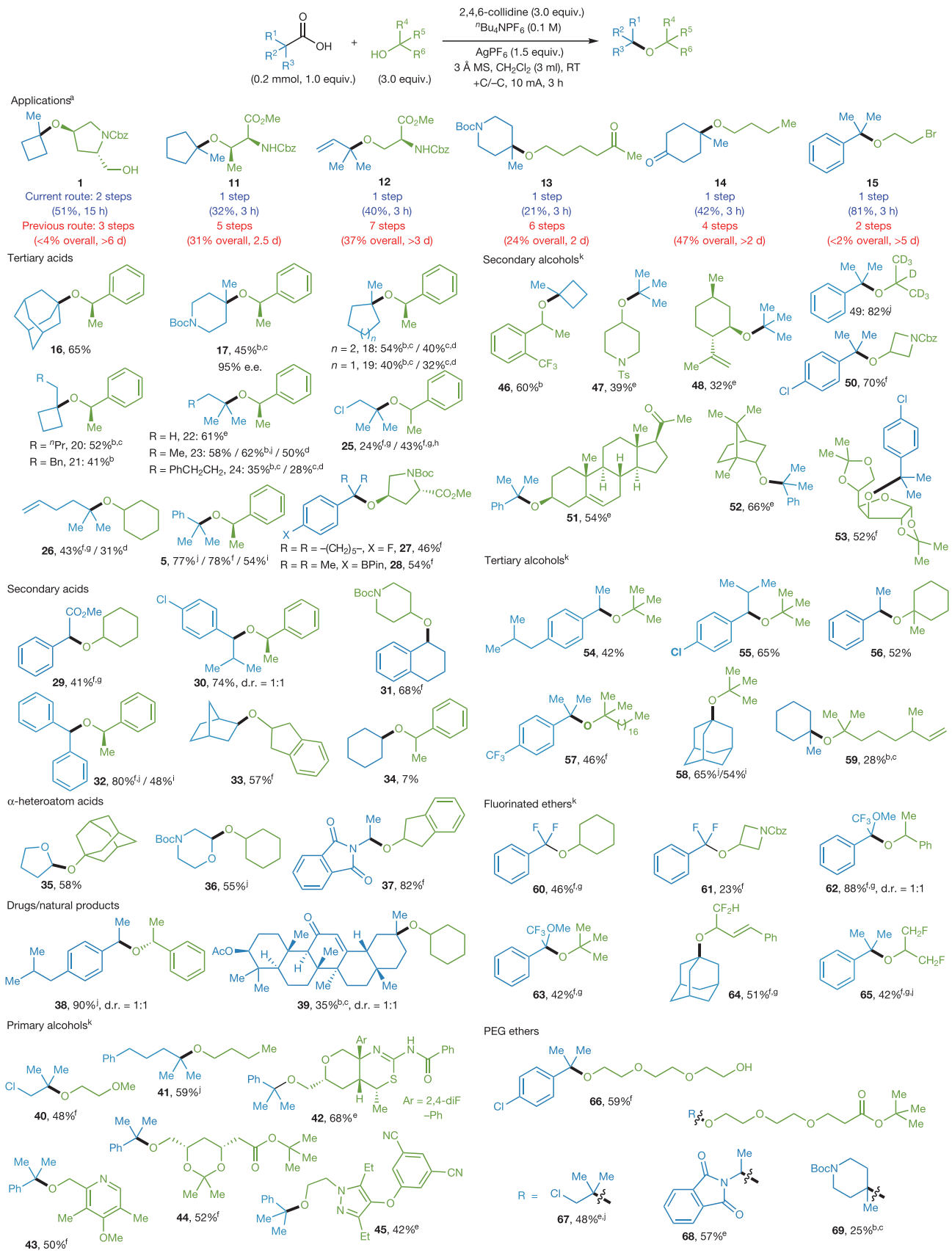

Fig. 2 | Applications, and partial scope of hindered ether synthesis via electrochemical decarboxylation. [a]See Supplementary Information for literature routes. [b]$AgSbF_6$ (0.3 mmol) instead of $AgPF_6$. [c]DBU (1,8-diazabicyclo[5.4.0]undec-7-ene; 0.6 mmol) instead of 2,4,6-collidine. [d]$KSbF_6$ (0.3 mmol) instead of $AgPF_6$. [e]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), 3 Å molecular sieves (100 mg), CH_2Cl_2 (2 ml), $I = 10$ mA, 3 h. [f]$AgClO_4$ (0.6 mmol) instead of $AgPF_6$, $^nBu_4NClO_4$ (0.1 M) instead of $^nBu_4NPF_6$. [g]4.0 or 6.0 equiv. alcohol. [h]1.5 ml CH_2Cl_2, $I = 7.5$ mA, 4 h. [i]$^nBu_4NClO_4$ (0.1 M) instead of $^nBu_4NPF_6$, no $AgPF_6$. [j]Reaction performed in triplicate; yield is average of three runs. [k]See Supplementary Information for more examples. Boc, *tert*-butyloxycarbonyl; d.r., diastereomeric ratio; MS, molecular sieves; Ts, tosyl.

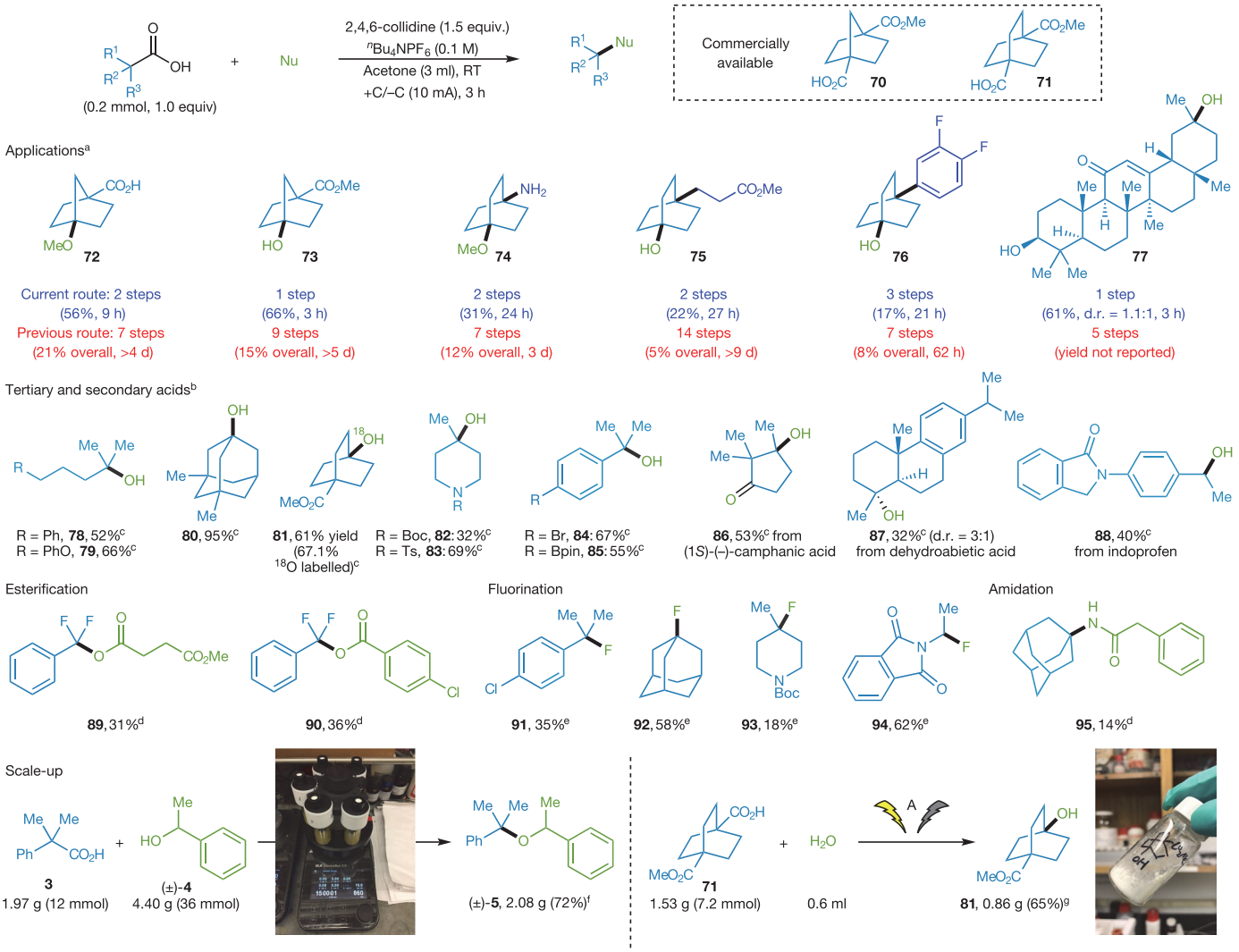

Fig. 3 | Applications and partial scope of trapping electrogenerated carbocations with other nucleophiles along with scalability demonstration. [a]See Supplementary Information for literature routes. [b]See Supplementary Information for more examples. [c]H_2O (0.1 ml) as nucleophile. [d]Carboxylic acid or phenylacetonitrile as nucleophile (0.6 mmol, 3 equiv.), conditions: $AgClO_4$ (0.6 mmol, 3 equiv.), 2,4,6-collidine (0.6 mmol, 3 equiv.), $^nBu_4NClO_4$ (0.1 M), 3 Å molecular sieves (150 mg), CH_2Cl_2 (3 ml). [e]KF (0.72 mmol, 3.6 equiv.) as nucleophile, conditions: 18-crown-6 (0.72 mmol, 3.6 eq), $AgClO_4$ (0.6 mmol, 3 equiv.), 2,4,6-collidine (0.6 mmol, 3 equiv.), $^nBu_4NPF_6$ (0.1 M), 3 Å MS (150 mg), CH_2Cl_2 (3 ml). [f]Conditions for scale-up to (±)-**5** (each reaction): **3** (2.4 mmol), (±)-**4** (7.2 mmol), 2,4,6-collidine (3.6 mmol), $^nBu_4NClO_4$ (0.1 M), 3 Å molecular sieves (450 mg), CH_2Cl_2 (9 ml) +C/−C (10 mA), RT, 15 h. [g]Conditions for scale-up to **81** (each reaction): **71** (1.2 mmol), H_2O (0.1 ml), 2,4,6-collidine (1.8 mmol), $^nBu_4NPF_6$ (0.02 M), acetone (9 ml), +C/−C (10 mA), RT, 12 h. Nu, nucleophile; pin, pinacolato.

lead to elimination or racemization (**17** is formed in 95% enantiomeric excess (e.e.)). Electrogenerated cations bearing fluorine atoms can also be intercepted, opening up a range of organofluorine-containing ether systems that were previously either difficult to access or unknown (see Supplementary Information for full listing of fluorinated ethers). Finally, the synthesis of polyethyleneglycol (PEG) ethers—which historically has been laborious—can be achieved in a modular fashion using this process (no PEG ethers analogous to **66**–**69** are known). To ensure the robustness of the process, ten randomly selected examples in Fig. 2 were run in triplicate, with yields varying by no more than 5% between runs.

As mentioned above, the use of simple alcohols such as methanol—as well as water—is already known in electrochemical decarboxylative processes[10–18] (Fig. 1b). However, the scope of such processes is quite limited. The conditions developed here were therefore adapted for these related reactions (Supplementary Information). In order to render this reaction general, the choice of electrolyte (tetrabutylammonium hexafluorophosphate, $^nBu_4NPF_6$) and base (2,4,6-collidine) was crucial, whereas silver additives were found to be unnecessary. As with the synthesis of hindered ethers, the most convincing case for the use of this reaction stems from its ability to substantially truncate synthetic pathways. Six such examples (**72**–**77**) are illustrated in Fig. 3 (see Supplementary Information).

The addition of water to generate various tertiary and secondary alcohols is a broadly applicable process, with selected examples depicted in Fig. 3 (for additional examples, see Supplementary Information). Again, the chemoselectivity is on par with that observed in the synthesis of hindered ethers: aryl bromides (**84**), boronic esters (**85**), electron-rich aromatics (**87**), lactams (**88**), ethers (**79**) and esters (**81**) are tolerated. In preliminary studies, the possibility of adding other nucleophiles to the putative electrogenerated carbocations was also studied. Carboxylates that are not capable of decarboxylation under these conditions could act as nucleophiles, thus providing hindered esters (**89**, **90**)[24]. Useful organofluorine building blocks could also be accessed (**91**–**94**) in a process that might be of use in radiolabelling studies, because the fluorine source used (the inexpensive salt potassium fluoride) 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 by the gram-scale preparation of **5** and **81** through etherification and hydroxylation processes, respectively. In the case of

large-scale etherification, the silver salt additive could be left out with a only minimal effect on yield (78% in the presence of silver salt, compared with 72% when this additive is omitted).

Extensive mechanistic studies were also undertaken in order to understand the role of the additives and the nature of the reactive intermediate. In summary, the mechanism is likely to involve 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 in which standard S_N2 and carbocation-based approaches are unsuccessful in forming hindered functionalized carbogenic frameworks.

Online content

Any methods, additional references, Nature Research reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41586-019-1539-y.

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METHODS

Here we describe a typical procedure for the decarboxylative etherification. Further experimental details are provided in the 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 min, the reaction mixture was electrolysed at a constant current of 10 mA for 3 h. 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 2 M 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 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.

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Author contributions J.X., M.S. and P.S.B. conceived the project. J.X., M.S., Y.K., H.L., D.G.B. and P.S.B. designed the experiments and analysed 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 the 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.

Competing interests The authors declare no competing interests.

Additional information

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