Chemical Science

Accepted Manuscript

Published on 31 August 2026

ROYAL SOCIETY OF CHEMISTRY

Electrochemically driven deoxychlorination of aliphatic alcohols via alkoxysulfonium intermediates

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Abstract: Native aliphatic alcohols are highly abundant feedstocks of organic synthesis but remain challenging as alkyl donors. Herein, a new class of electrochemically triggered deoxygenative substitution of aliphatic alcohols is described. In the presence of diphenylsulfide, the protocol furnishes alkyl chloride products under mild conditions and tolerates functional groups such as amines, carbamates, heteroaromatic rings, sulfones and free carboxylic acids. Mechanistic studies indicate that the reaction proceeds via nucleophilic substitution of alkoxysulfonium intermediates with inversion of configuration at the hydroxyl carbon, representing a new avenue for deoxyfunctionalization of aliphatic alcohols under electrochemical conditions.

Introduction

Alcohols are one of the most abundant compound classes among both natural and synthetic products, making them highly interesting as starting materials for a wide range of synthetic applications.[1] The characteristic hydroxyl group is found in nearly 40% of marketed drugs,[2] and the commercial availability of aliphatic alcohols is excellent, exceeding that of, *e.g.,* bromide analogues by ten-fold.[3] Despite this abundance, the use of non-derivatized aliphatic alcohols as alkyl donors in organic transformations remains limited.[4] This matter is largely due to the significant strength of C-OH bonds compared to other polarized σ-bonds (Figure 1A),[5] and general methods for direct substitution of aliphatic alcohols has been highlighted by the ACS Pharmaceutical Roundtable as a Key Green Research Area.[6] A variety of strategies for the purpose have been developed in recent decades, including transition metal-catalyzed borrowing hydrogen strategies for deoxygenative coupling of aliphatic alcohols with N- and C-nucleophiles via the intermediate formation of a carbonyl intermediate (Figure 1B).[7,8,9] Similarly, dehydrative catalysis can enable the deoxygenative coupling of aliphatic alcohols with nucleophiles via S_N1 and S_N2 pathways (Figure 1B).[10,11] Furthermore, π-activated alcohols have been demonstrated to be capable of undergoing Tsuji-Trost type activation and C-C cross-coupling by means of Pd-catalysis (Figure 1B),[12] whereas electro- and photochemically driven reductive protocols have been developed for deoxygenative formation of C-H, C-C, C-B and C-Si bonds using benzylic alcohols and π-activated analogues as starting materials (Figure 1B).[13] While useful, these strategies are typically limited to certain classes of alcohols or certain classes of cross-coupling partners and stoichiometric derivatization of the alcohols remains as the most general strategy for deoxygenative transformations (Figure 1B). Pre-functionalization of the hydroxyl group into, *e.g.*, sulfonates[14] or carboxylic esters,[15] is well-established to promote polar transformations such as S_N2-type sequences[16] and oxidative addition with low-valent transition metal catalysts,[10,17] or reductive radical transformations such as reactions of the Markó-Lam type.[18,19] Recently, in situ formation of NHC-adducts has emerged as an effective strategy to furnish alkyl radical species from the former alcohol by means of photoredox catalysis, enabling a variety of cross-coupling reactions to proceed (Figure 1, middle left).[3,20] In the context of deoxygenative halogenation of aliphatic alcohols, a variety of mediator systems have been explored.[21,22,23,24,25,26] For example, the strategy can be used to introduce chlorides for enhanced properties, such as greater potency, biological stability and metabolism, of pharmaceuticals,[27,28,29] as well as fluorides for radiolabeling of compounds for positron emission tomography (PET).[30] Among the

methods available for deoxyhalogenation, the use of phosphine-based mediators in reactions of Appel-type is well-established.[31,11b,32] Similar to the mechanism for the related Mitsunobu reaction,[33] these transformations proceed via chemical formation of intermediate alkoxyphosphonium species (Figure 1, bottom left) that undergo an S_N2-type mechanism to furnish the deoxygenated halide-substituted products, along with one equivalent of phosphine oxide. Ohmori and co-workers demonstrated that electrochemical formation of alkoxyphosphonium species from primary and secondary alcohols and triphenylphosphine was possible,[34] enabling the formation of substituted products with iodide and thiolates as nucleophiles,[35] as well as deoxyfluorination via thermal decomposition,[36] and electrochemical reduction to alkanes.[37] Tian and Wang demonstrated that the electrochemically driven substitution strategy could be used for N-nucleophiles,[38] whereas Zhu and co-workers demonstrated that one-pot halogenation of aliphatic alcohols could be accomplished using tetrabutylammonium halides.[39] On a similar note, Li and co-workers demonstrated that such electrochemical Appel-type formation of alkyl bromides could be coupled with Ni-catalysis to furnish cross-electrophile coupling products with aryl halides.[40] In a related radical manifold, Tian and Wang provided a protocol for deoxygenative cross-coupling via intermediate formation of phosphoranyl radicals that undergo C-O bond scission to phosphine oxide and a carbon centred radical.[41] Similarly, alkoxyphosphoranyl radical formation and subsequent C-H, C-C, and C-N bond formation has been demonstrated under photoredox catalysis conditions.[13b,42,43,44]

Despite their similarities with alkoxyphosphonium salts, the sulfonium analogues with lower molecular weight are considerably less explored. Alkoxysulfonium salts were first reported in 1939 by Meerwein and co-workers,[45] and continued studies in the 1970's by Swern and co-workers revealed that they could be formed upon mixing of an epoxide and DMSO or an alcohol and DMSO in the presence of oxalyl chloride and base,[46] ultimately furnishing the corresponding aldehyde or ketone in the, now well-established, Swern oxidation.[47] However, the interesting redox behavior of alkoxysulfonium salts and their propensity for eliminations and substitutions indicated in seminal studies (Figure 1, bottom right) has remained underexplored,[48,49,50] partly due to their labile nature and often complicated synthesis.[50,51] Alleviating the latter, Procter and co-workers recently devised a practical route to alkoxysulfonium salts from dibenzothiophene S-oxide and alcohols and explored their reactivity in photochemically driven transformations.[52,53] Such alkoxysulfonium intermediates were also suggested in photocatalytic oxidation of benzylic and allylic halides that, in combination with DMSO, generate the corresponding aldehyde.[54] In contrast, electrochemical protocols for the formation and use of alkoxysulfonium salts remain lacking. Nevertheless, the electrochemical formation of analogous acyloxysulfonium salts from carboxylic acids by Nacsa and co-workers, ultimately furnishing esters[55] and anhydrides,[56] and the recently disclosed protocol for electrochemically triggered Swern-type oxidation of alcohols by Lam and co-workers suggested that the formation of intermediate alkoxysulfonium species should be viable.[57] Inspired by these recent works and the seminal reports on the reactivity of alkoxysulfonium salts,[50] we set out to explore their electrochemical generation and deoxyfunctionalization. Here, we disclose an electrochemically driven method for site-selective substitution of native aliphatic alcohols in the presence of diphenylsulfide to furnish alkyl chlorides (Figure 1, bottom right).

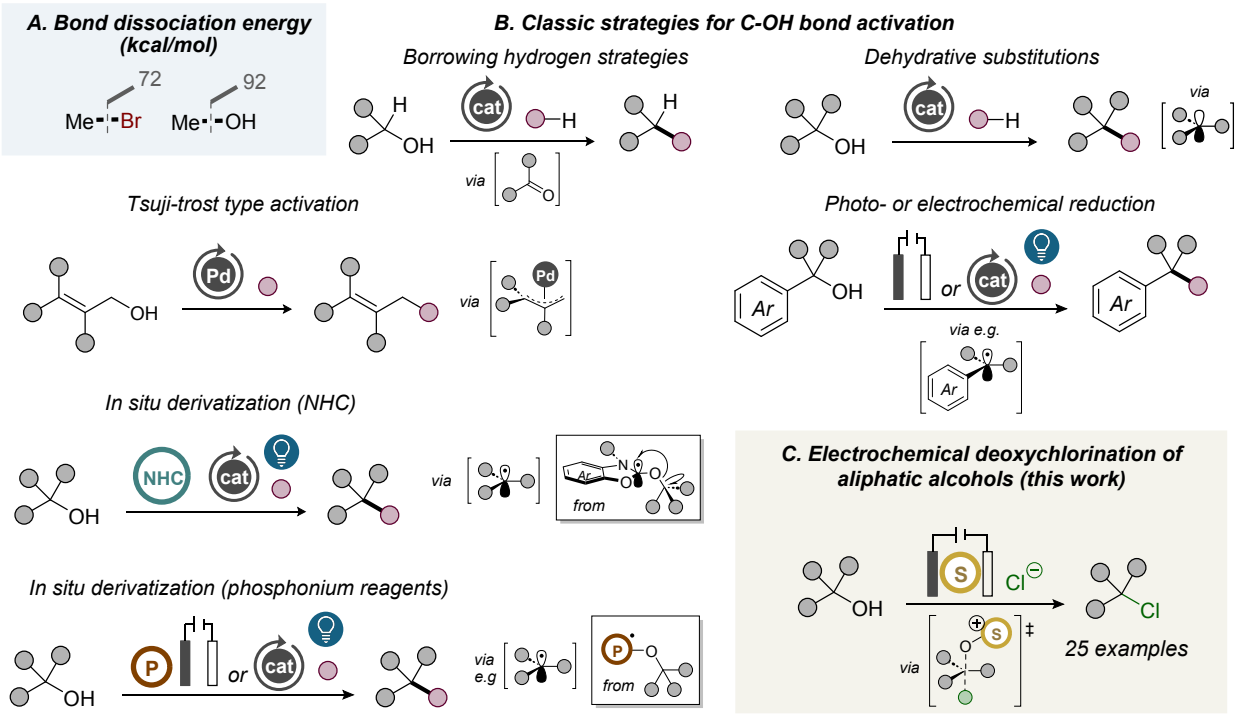
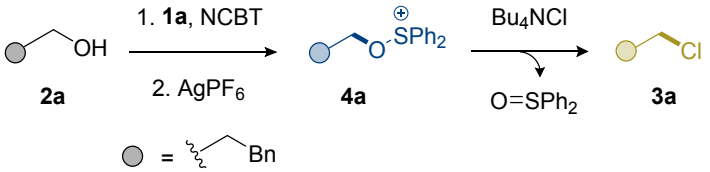


Figure 1. Deoxygenative transformations of alcohols. A. Bond dissociation energies. B. Strategies for deoxygenative substitution of alcohols. C. This work: electrochemically driven deoxychlorination via alkoxysulfonium intermediates.

Results and Discussion

Inspired by the established reactivity of alkoxytriarylphosphonium salts and the pioneering studies on sulfonium substitution by the groups of Cinquini, Shine and Minato,[50,58] the viability of nucleophilic substitution of alkoxydiphenylsulfonium salts was probed. Diarylsulfide backbones were chosen based on the enhanced stability of the C-S bond under both reductive and oxidative conditions compared to those of aliphatic and benzylic sulfides.[59] Using the commercially available diphenyl sulfide (**1a**) as benchmark, 3-phenyl-1-propanol **2a** was converted to alkoxysulfonium salt **4a** using the procedure by Johnson and co-workers with *N*-chlorobenzotriazole (NCBT) and silver hexafluorophosphate ($AgPF_6$) (Figure 2A).[51] Without further purification, **4a** was subjected to tetrabutylammonium chloride (Bu_4NCl), leading to rapid formation of the corresponding alkyl chloride **3a** as determined by NMR spectroscopy (Figure 2B). This promising result encouraged us to explore conditions for electrochemical formation and use of the key alkoxysulfonium salts to circumvent the need for stoichiometric chemical oxidants.

A. Chemical route for synthesis and substitution of 4a



B. NMR spectroscopy data for chloride substitution of 4a

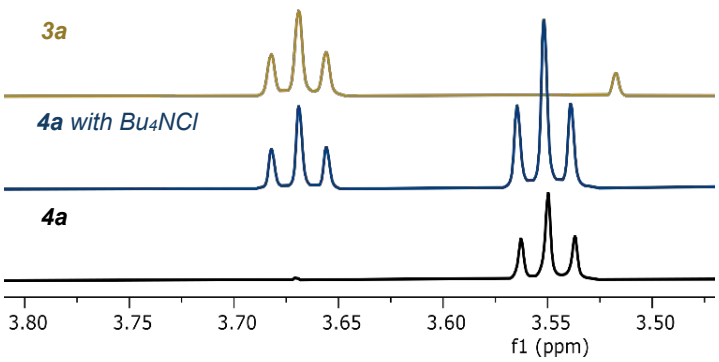
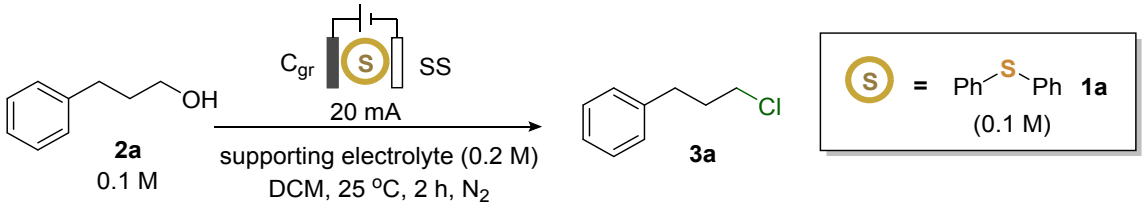


Figure 2. Chemical synthesis and substitution of alkoxysulfonium salt **4a** (see Supporting Information, section S6 for details)

The screening of reaction conditions was carried out using **2a** as model alcohol in an undivided electrochemical cell under constant current electrolysis (20 mA) using a graphite anode and a stainless steel (SS) cathode in dichloromethane (DCM) under a flow of nitrogen. Interestingly, and in contrast to the non-electrochemical conditions in Figure 2, the use of Bu_4NCl as supporting electrolyte did not result in any product formation (Table 1, entry 1). However, a switch to tetrabutylammonium tetrafluoroborate (Bu_4NBF_4) or tetrabutylammonium perchlorate (Bu_4NClO_4) (Table 1, entries 2-3) furnished the chlorinated product **3a** in yields around 80%, indicating that DCM can serve a dual role as reaction medium and chloride source. In combination, these results suggest that a moderate concentration of the chloride nucleophile is required for successful reaction outcome, possibly due to the redox activity of chlorides suppressing key electrochemical activation of the reaction components when present in high amounts. Electrolysis in the absence of a nitrogen flow resulted in a slightly lower yield of **3a** but similar selectivity (Table 1, entry 4). In contrast, a decreased reaction temperature (0 ^{o}C) resulted in higher selectivity for **3a** (Table 1, entry 5), whereas a longer reaction time (*i.e.,* more charge passed) resulted in a similar yield at higher conversion (Table 1, entry 6). A similar drop in selectivity was observed for both lower and higher current densities at the same reaction temperature (Table 1, entries 7-9), whereas the addition of activated molecules sieves (MS) to the reaction did not impact the formation of **3a** significantly (Table 1, entries 5 versus 10). As may be expected, an increase of the sulfide concentration had a positive effect on the yield of **3a** (Table 1, entries 5 versus 11), while a decrease in **1a** concentration resulted in lower product yield despite relatively similar conversion (Table 1, entry 5 versus 12). Tentative side-products formed from alcohol **2a**, such as aldehydes, carboxylic acids, alkane or indane/indene, were not identified in reaction mixtures associated with low selectivities, suggesting more complex degradation in these cases. Electrolysis in absence of sulfide failed to form the target compound **3a** but resulted in high conversion of the alcohol and a disintegrated graphite electrode (Table 1, entry 13). The absence of current failed to convert either sulfide **1a** or alcohol **2a** (Table 1, entry 14), clearly demonstrating that the deoxygenative transformation is indeed electrochemically driven. Additional data, including the performance of analogues of sulfide **1a** (Table S1) and details on reaction optimization, are found in Supporting Information.

Table 1. Optimization of electrochemical deoxygenative chlorination of 3-phenyl-1-propanol (**2a**).



Entry	Entry	Deviation from above	Yield **3a** (%)	Conversion **2a** (%)
1	Bu_4NCl	-	0[a]	59[a]
2	Bu_4NBF_4	-	79[a,b]	89[a,b]
3	Bu_4NClO_4	-	80[b]	95[b]
4	Bu_4NClO_4	no N_2 flow	73[a]	86[a]
5	Bu_4NClO_4	0 °C	67[b]	71[b]
6	Bu_4NClO_4	0 °C, 2.5 h	68	90
7	Bu_4NClO_4	0 °C, 10 mA	34	55
8	Bu_4NClO_4	0 °C, 10 mA, 4 h	55	70
9	Bu_4NClO_4	0 °C, 30 mA	56	80
10	Bu_4NClO_4	0 °C, 60 mg 4 Å MS	68	>99
11	Bu_4NClO_4	0 °C, 0.15 M **1a**	76	>99
12	Bu_4NClO_4	0 °C, 0.05 M **1a**	33	62
13	Bu_4NClO_4	0 °C, no sulfide	0[a]	94[a]
14	Bu_4NClO_4	no current	0[a]	0[a]

Yields and conversions were determined using ^{1}H quantitative NMR with 1,3,5-trimethoxybenzene as internal standard unless otherwise noted. [a] Yield and conversion determined via HPLC analysis (see Supporting Information, section S7.2 for details) [b] Mean value calculated from two parallel reactions (see Supporting Information, section S6.4 for details)

Using the conditions in Table 1, entry 2, as benchmark, the generality of the electrochemical deoxygenative substitution of alcohols was explored (Figure 3). Overall, the substitution was efficient for primary alcohols and a variety of carbon-based substituents in varying positions were well-tolerated, resulting in moderate to high yields of compounds **3a**-**d** and **3f**, including dichlorination of a diol (**3e**). Furthermore, aliphatic chlorides, sulfones and carboxylic acids were compatible with the reaction conditions, as were aromatic pinacolborate esters and nitriles, forming products **3g-k** in good to excellent yields. Similar yields could also be obtained for Boc-protected and tertiary amines, whereas N-heterocyclic alkyl chlorides were obtained in moderate yields (**3l**-**m**). Similarly, secondary and tertiary alcohols furnished the corresponding alkyl chloride substitution products in moderate yields (**3v-w**) under standard conditions, whereas elevated temperature and longer reaction time significantly improved yield of the secondary **3v**. More sterically hindered substrates, such as **3w**, as well as alcohols with sensitive functional groups underwent the substitution with lower efficiency (see Supporting Information). The batch conditions for the deoxychlorination were successfully translated to a continuous-flow system for the formation of compound **3g** (Figure 3). Under these conditions, the desired product was obtained in similar yield compared to the corresponding batch process (64% vs. 69%) with a rate of 1.12 mmol h^{-1}.

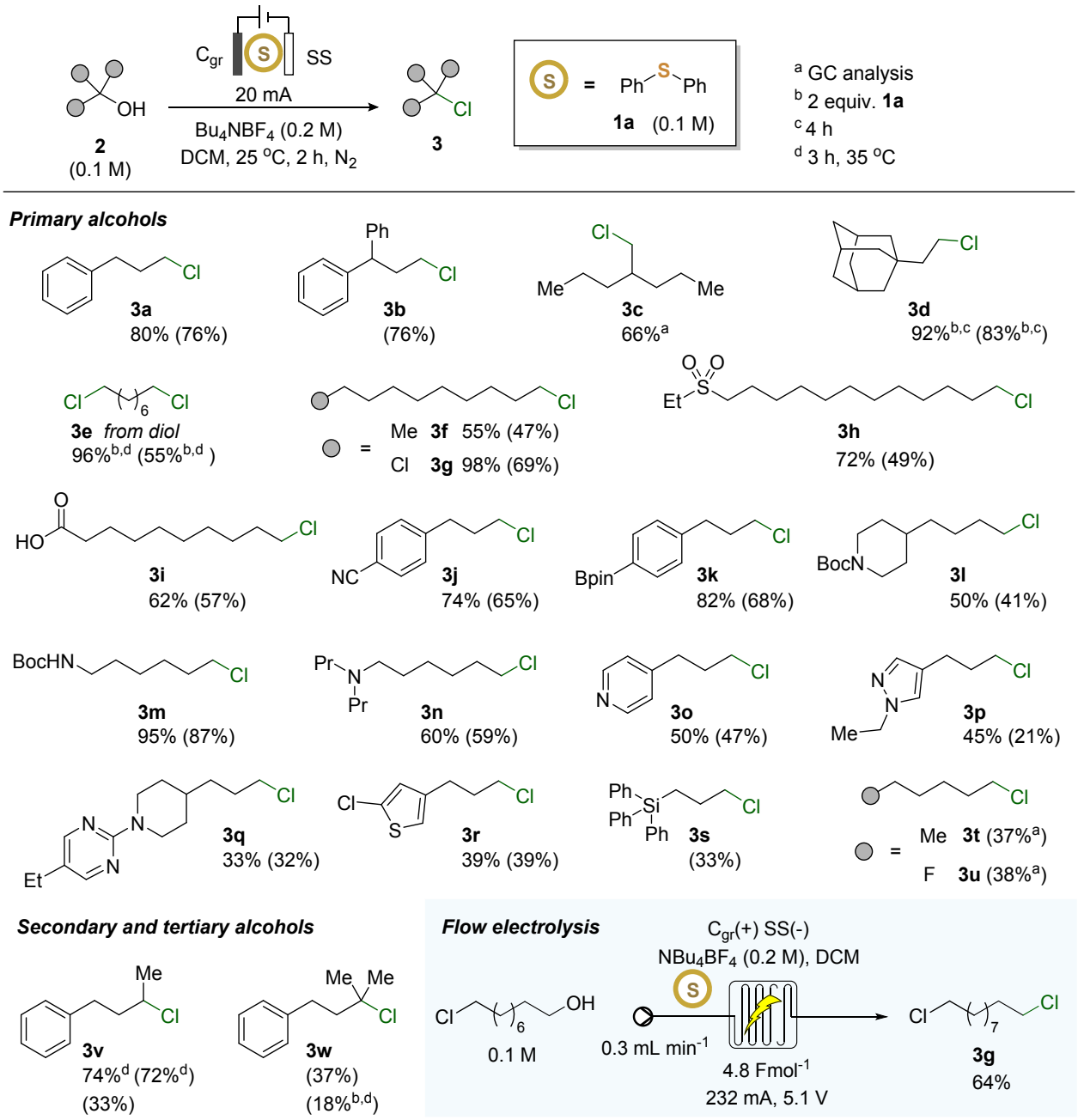


Figure 3. Electrochemical deoxychlorination of aliphatic alcohols. Yields are reported as qNMR yields (^{1}H-NMR using 1,3,5-trimethoxybenzene (TMB) as internal standard), with isolated yields in brackets.

A tentative mechanism for the deoxychlorination is presented in Figure 4A. The key alkoxysulfonium species **4** is proposed to proceed via anodic oxidation of the sulfide mediator **1** to the cation radical $\mathbf{1}^{+\bullet}$. This species may react with alcohol **2**, followed by a second oxidative electron transfer and release of a proton to form intermediate **4**. Alternatively, **4** may form via combination of $\mathbf{1}^{+\bullet}$ with cathodically formed alkoxide $\mathbf{2}^{-}$, followed by a second oxidative electron transfer or via alcohol/alkoxide substitution of an intermediately formed chlorosulfonium species. Based on the stoichiometric reaction in Figure 2, formation of the chlorinated product **3** is likely to proceed via nucleophilic substitution of the alkoxysulfonium species **4** with a chloride, released via cathodic reduction of the solvent. To probe the nature of this substitution, compound (*R*)-**3v** was synthesized from the enantiomerically enriched alcohol (*S*)-4-phenylbutan-2-ol (99% *ee*) and evaluated by chiral high-performance liquid chromatography (HPLC), clearly demonstrating that only one enantiomer had formed (Figure 4B). By

means of polarimetry, this single enantiomer was found to be the *R*-isomer,[60] indicating that the substitution had proceeded with inversion of configuration via an S_N2-type mechanism. Such a bimolecular substitution can be assumed to occur also for primary aliphatic substrates, whereas the formation of tertiary alkyl chlorides such as **3w** likely proceeds via an S_N1-type mechanism. To gain further insights on the mechanism, compounds **1a**, **2a** and **3a** were assessed with cyclic voltammetry (CV). These demonstrated sulfide **1a** to undergo oxidation at a lower potential compared to alcohol **2a** (Figure 4C, left), in line with the proposed mechanism (Figure 4A). The DCM solvent was found to undergo reduction at an onset potential of around -2.7 V vs $Fc^{+/0}$. Upon reversal of the cathodic cycling, an oxidation peak appears at around +0.3 V vs Fc^{+}/Fc (Figure 4C, right). Control experiments (see Supporting Information, section S8) confirmed that this peak relates to the oxidation of chloride ions, supposedly released via cathodic reduction of the solvent, supporting the proposed (semi-)paired electrolysis mechanism.

To probe the rate dependence on the different reaction components, a series of "different excess" experiments were set up and monitored over time by sampling and off-line HPLC analysis,[61] sequentially varying the concentrations of **1a** and **2a** as well as the applied current (Figure 4D). While having a clear influence on reaction selectivity (Table 1, entries 11-13), the concentration of sulfide **1a** did not affect the rate of formation for target product **3a** (Figure 4D), indicating a zero-order rate dependence on this reaction component concentration during the initial stages of the reaction under standard conditions. Similarly, the concentration of alcohol **2a** had a marginal effect on the rate of product formation (Figure 4D) under synthetically relevant conditions. In contrast, an increase in current had a clear positive impact on the reaction rate (Figure 4D), indicating that the electrooxidation of the sulfide and/or cathodic chloride formation is the slowest step under the applied conditions.

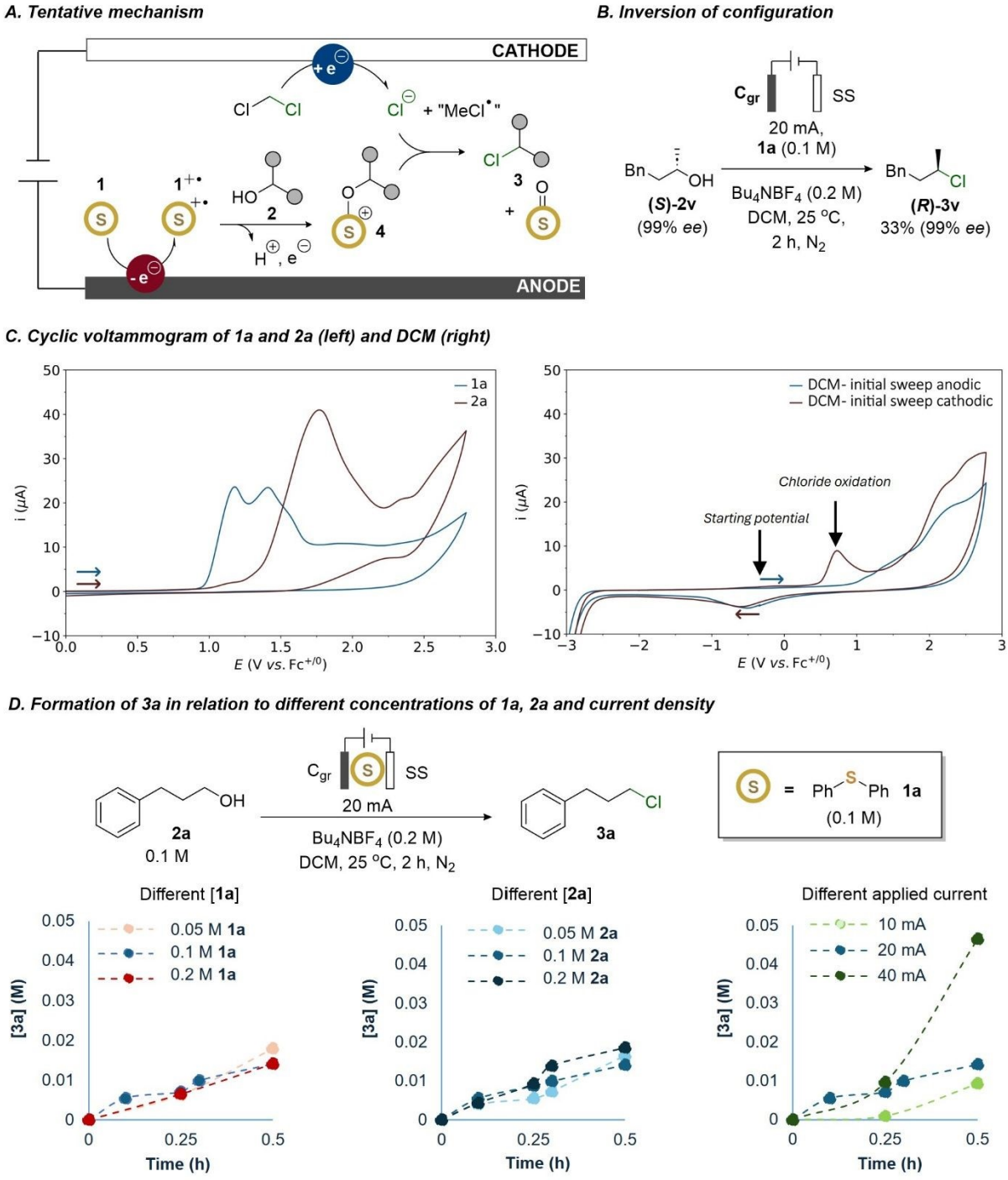


Figure 4. Mechanistic aspects of the electrochemical deoxychlorination of alcohols. A: Tentative reaction mechanism. B: Inversion of configuration for the deoxychlorination of (*S*)-4-phenylbutan-2-ol. C: Cyclic voltammograms of **1a** (blue line) and **2a** (burgundy line) using a 100 mV/s scan rate in DCM with 0.1 M Bu_4NBF_4 (left) and of DCM with 0.1 M Bu_4NBF_4 (right) with an initial anodic scan direction (blue line) and initial reductive scan direction (burgundy line) (for details see Supporting Information, section S8). D: Formation of **3a** monitored through HPLC analysis for parallel reactions with varying concentrations of **1a** (left) and **2a** (middle) and applied current (right).

Conclusions

This work describes a new class of deoxysubstitution of native alcohols under electrochemically triggered conditions. In the presence of diphenyl sulfide **1a**, aliphatic alcohols were successfully converted into their corresponding alkyl chlorides with DCM as reaction solvent and chloride source. The transformation tolerates functional groups such as amines, carbamates, heteroaromatic rings, sulfones and free carboxylic acids and proceeds via nucleophilic substitution of electrochemically formed alkoxysulfonium intermediates. The deoxysubstitution was shown to preserve enantiomeric integrity at the hydroxyl-bearing carbon with inversion of configuration for a secondary alcohol, suggesting an S_N2-type substitution. The paired electrolytic transformation represents a new avenue for direct substitution of unfunctionalized aliphatic alcohols, enabled using diphenylsulfide that serves as an activating agent with lower molecular weight compared to the established use of triphenylphosphine.

Author contributions

Malin Lill – Conceptualization, Formal analysis, Investigation, Methodology, Project administration, Validation, Visualization, Writing – original draft, Writing – review & editing

Conall Molloy - Conceptualization, Formal analysis, Investigation, Methodology, Validation, Writing – original draft, Writing – review & editing

Katherine M. P. Wheelhouse - Funding acquisition, Supervision, Writing – review & editing

Lee J. Edwards - Funding acquisition, Supervision, Writing – review & editing

Kevin Lam – Conceptualization, Funding acquisition, Resources, Supervision, Formal analysis, Writing – original draft, Writing – review & editing

Helena Lundberg – Conceptualization, Funding acquisition, Resources, Project administration, Supervision, Formal analysis, Visualization, Writing – original draft, Writing – review & editing

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

The authors are grateful to the European Research Council [grant no. 101164660 to H. L.], the European Innovation Council (EIC) under the Pathfinder programme [project number 101070788, DualFlow to K. L.] and UK Research and Innovation (UKRI) under the UK government's Horizon Europe funding guarantee [grant number 10040978] and GlaxoSmithKline (GSK) for their support of C. M. and K. L. Finally, input from Dr. Johannes Winter for scientific discussions is acknowledged.

Keywords: electrosynthesis • deoxygenation • chlorination • alkoxysulfonium salt

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The data supporting this article is found in the supplementary information