Article

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Electrochemical Oxidation of Alcohols and Aldehydes to Carboxylic Acids Catalyzed by 4-Acetamido-TEMPO (ACT): An Alternative to "Anelli" and "Pinnick" Oxidations

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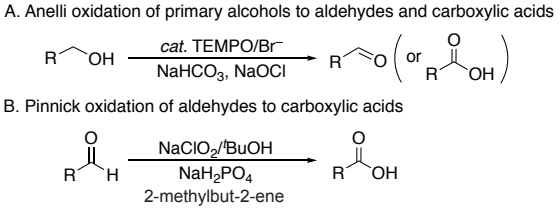
ABSTRACT: An electrocatalytic method has been developed to oxidize primary alcohols and aldehydes to the corresponding carboxylic acids, using 4-acetamido-2,2,6,6-tetramethylpiperidine 1-oxyl (ACT) as a mediator. The method successfully converts benzylic, aliphatic, heterocyclic and other heteroatom-containing substrates to the corresponding carboxylic acids in aqueous solution at room temperature. The mild conditions enable retention of stereochemistry adjacent to

the site of oxidation, as demonstrated in a 40 g-scale synthesis of a precursor to levetiracetam, a medication used to treat epilepsy.

KEYWORDS: alcohols, aldehydes, carboxylic acids, oxidation, electrocatalysis, electrochemistry, nitroxyl, aminoxyl

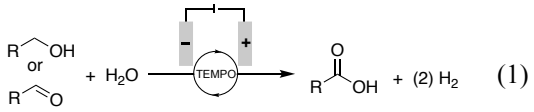
Introduction

Oxidations of alcohols and aldehydes to carboxylic acids are widely used transformations in organic chemistry.[1-4] They are commonly featured in the synthesis of pharmaceuticals and other industrial chemicals,[5-8] and they are the focus of considerable attention for the conversion of carbohydrates, sugars, and other biomass-derived feedstocks to value-added products.[9-14] Classical oxidation methods feature chromium and manganese oxide reagents;[2,5] however, methods employing organic aminoxyls in catalytic reactions used extensively,[15-18] including applications to the synthesis of complex molecules, such as natural products and pharmaceuticals. Methods employing bleach (NaOCl) and TEMPO (2,2,6,6-tetramethylpiperidine *N*-oxyl) are especially effective for alcohol oxidation, and a prominent example is the biphasic Anelli-Montonari oxidation method that uses TEMPO and bromide as cocatalysts (Scheme 1A).[19-25] Most of the latter applications focus on production of aldehydes and ketones, but they have also been used to prepare carboxylic acids.[26-30] Sodium chlorite ($NaClO_2$) has been shown to be an especially effective oxidant for conversion of aldehydes to carboxylic acids.[2] One of the most prominent examples of this reactivity is the so-called "Pinnick oxidation",[31] which adapted from earlier precedents by Kraus[32] and Lindgren and Nilsson[33] (Scheme 1B).[34-37] A sacrificial alkene is often included in these reactions to scavenge the hypochlorite byproduct of the reaction.



Scheme 1. Common protocols for oxidation of aldehyde to carboxylic acid (1) and alcohol to aldehyde.

Electrochemical alcohol oxidation methods using organic aminoxyl mediators (i.e., electrocatalysts) have advanced considerably in recent years, and they provide a compelling alternative to the more-traditional chemical methods.[38] These methods are appealing, in part, because they generate hydrogen gas as the sole byproduct of the reaction (eq 1).[39] Electrochemical methods for the oxidation of primary alcohols to carboxylic acids have been investigated primarily for the conversion of mono/polysaccharides and other biomass-derived precursors.[40-47] To our knowledge, there are no reports of electrochemical aminoxyl-mediated methods for oxidation of aldehydes. Moreover, preparative-scale oxidation of alcohols and aldehydes to carboxylic acids with substrates bearing heterocycles and adjacent stereocenters that are commonly encountered in pharmaceutical applications have not been investigated.



(1)

In a recent study, we demonstrated that the electrocatalytic activity of aminoxyl radicals is more strongly affected by the redox potential of the aminoxyl than by its steric properties.[48] Specifically, higher catalytic activity was observed for aminoxyls with higher potentials, and this trend was evident even when comparing sterically hindered TEMPO derivatives to less-hindered

aminoxyls such as ABNO (9-azabicyclo[3.3.1]nonane *N*-oxyl) and AZADO (2-azaadamantane *N*-oxyl).[49] In electrocatalytic applications, the electrode potential may be tuned to match the redox potential of the aminoxyl mediator, and the catalytic rate is controlled solely by the reactivity of the oxoammonium species with the substrate. With chemical oxidants, such as bleach, the catalytic rate is often controlled by the rate of catalyst reoxidation.[48] The low-cost aminoxyl, 4-acetamido-TEMPO (ACT) was found to be a highly effective mediator for electrocatalytic oxidation of a various simple alcohols. In the present study, we expand on these fundamental observations and demonstrate the preparative-scale utility of ACT-mediated oxidation of primary alcohols and aldehydes to carboxylic acids. Noteworthy outcomes include demonstration of the compatibility of the reaction with pyridine-containing substrates and retention of stereochemical configuration adjacent to an alcohol in the oxidation of a chiral alcohol to a carboxylic acid. The latter reactivity is showcased in the oxidation of a key intermediate in the generic drug, levetiracetam.

Results and Discussion

For electrochemical oxidation by ACT and other aminoxyl radicals, aqueous carbonate buffer (pH 8 to 11) is a suitable reaction medium that avoids the need for more-costly organic electrolytes and makes the solution sufficiently basic to allow for fast oxidation of alcohols.[48] In an effort to explore an electrochemical aldehyde oxidation, we considered ACT under the same conditions. Cyclic voltammetry and chronoamperometry methods were used for the initial evaluation of the catalytic activity. Figure 1 shows the cyclic voltammograms (CVs) and chronoamperograms of ACT in the absence and presence of 4-pyridinecarboxaldehyde (**1b**). In the absence of **1b**, the CV of ACT exhibits one anodic peak and a related cathodic peak (Figure 1, black trace a). The anodic peak corresponds to the one-electron oxidation of ACT to the oxoammonium species ACT^+, while

the cathodic peak corresponds to the one-electron reduction of the electrochemically generated ACT^+ to ACT. The ratios of the cathodic-to-anodic peak currents are near unity, consistent with the good stability of the ACT^+ under these conditions.[48] In the presence of **1b**, ACT^+ mediates catalytic oxidation of the aldehyde substrate to the corresponding carboxylic acid **1c** (Figure 1, blue trace b), resulting in a significant increase in the anodic peak current and a disappearance of the cathodic peak. Complementary data were obtained by chronoamerometry. A chronoamperogram of ACT in the absence of **1b** (Figure 1, black trace c) shows a diffusion-controlled oxidation current corresponding to the oxidation of ACT to ACT^+ at the electrode. The presence of **1b** leads to a >10-fold increase in the oxidation current (Figure 1, blue trace d) due to the catalytic turnover of ACT.[50]

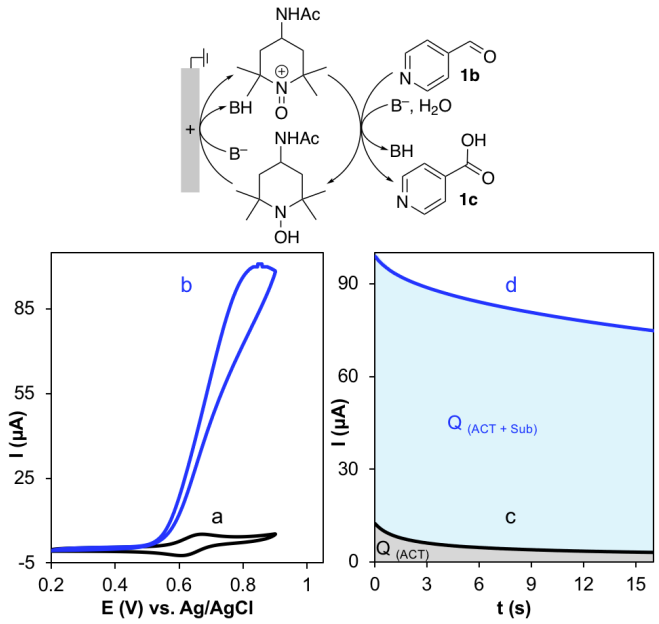


Figure 1. ACT-catalyzed electrochemical oxidation of **1b** (top), cyclic voltammograms (left) and chronoamperograms (right) of 1 mM ACT in the absence (a and c) and presence (b and d) of 20 mM **1b**. Scan rate is 10 mVs^{-1} for cyclic voltammetry and applied potential is 0.70 V vs. Ag/AgCl for chronoamperometry. Reaction conditions: aqueous carbonate buffer, $NaHCO_3$:Na_2CO_3 (0.1 M each), pH 10.

The area under the chronoamperogram traces corresponds to the charge consumed during the experiment, as depicted by the shaded regions in Figure 1, and the turnover frequency of the reaction (TOF = 1770) was derived from the ratio of consumed charge in the absence and presence of **1b**.[51] This analysis accounts for the fact that oxidation of ACT in the absence of aldehyde is a one-electron process, while ACT-mediated aldehyde oxidation is a two-electron process, corresponding to oxidation of the hydroxylamine to the oxoammonium (cf. Figure 1). A similar approach was then applied to various other alcohols and aldehydes (Figure 2). The relative reactivity of alcohols and aldehydes is different for different substrates. For example, as shown in Figure 2a, the catalytic activity of ACT is lower for the oxidation of the solketal (**2a**) than for oxidation of the corresponding aldehyde **2b**. The relative reactivity of **2a** and **2b** is manifested in the time course of a bulk electrolysis reaction (Figure 3), which shows formation of the carboxylic acid product even at early time periods, with only a small build-up of the aldehyde during the reaction. In contrast, ACT shows considerably higher activity with cyclopentanemethanol (**3a**) than with the corresponding aldehyde **3b** (Figure 2b). A quantitative comparison of several substrate pairs analyzed in this manner is presented in Figure 2c.

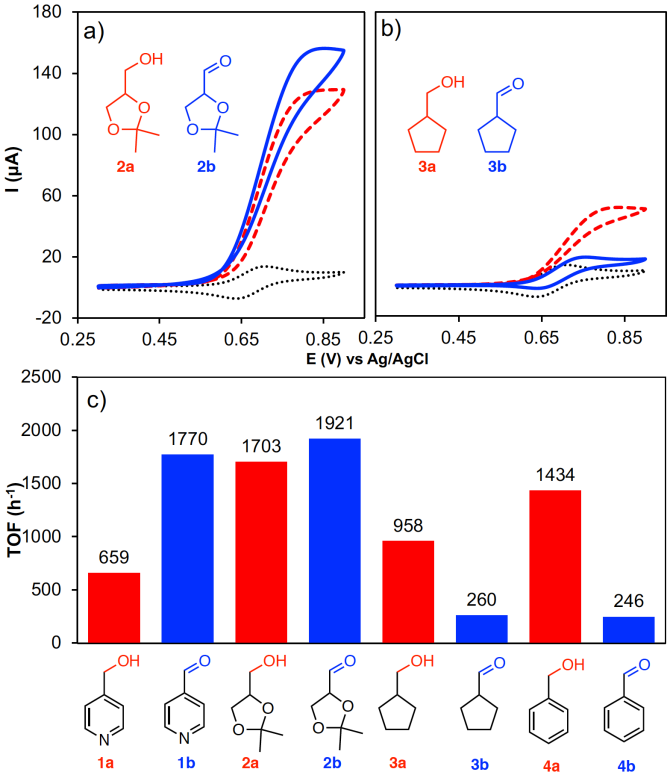


Figure 2. Cyclic voltammograms of 1 mM ACT in the absence (dotted line) and presence of 20 mM **2a** (a, dashed line), 20 mM **3a** (b, dashed line), 20 mM **2b** (a, solid line) and 20 mM **3b** (b, solid line), scan rate 10 mVs^{-1}. TOF of ACT toward oxidation of alcohols and aldehydes (c), applied potential 0.7 V vs. Ag/AgCl. Reaction conditions: H_2O/CH_3CN (50:50) 0.05 $NaHCO_3$, 0.05 M Na_2CO_3.

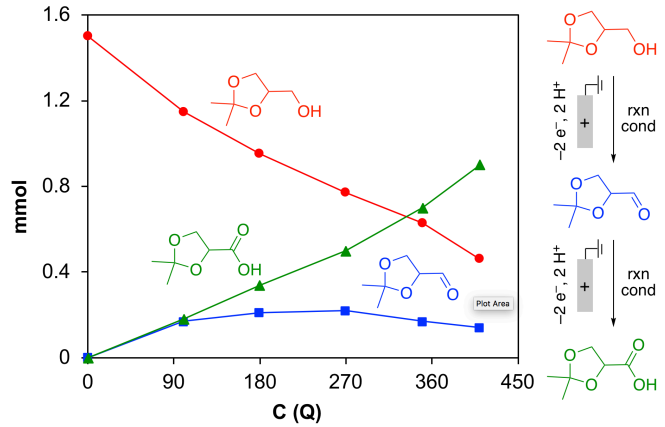
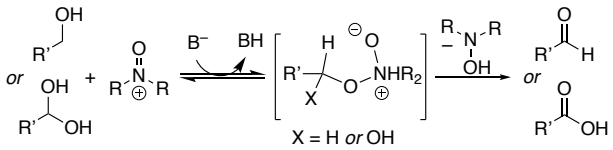


Figure 3. Concentration profiles of alcohol, aldehyde and carboxylic acid in the course bulk electrolysis of **2a**. Reaction Conditions: 1.5 1mmol and 5mol% ACT in aqueous carbonate buffer (15 mL), $NaHCO_3$ (0.1 M) Na_2CO_3 electrolyte (0.1 M), pH 10, applied potential is 0.75 V vs. Ag/AgCl.

There is no clear trend for electronic effects on the rate of alcohol oxidation. For example, 4-hydroxymethylpyridine **1a** is less reactive than benzyl alcohol **4a**, thus favoring the more electron-rich alcohol. The opposite trend is observed with solketal/cyclopentanemethanol (**2a**/**3a**), for which the electron-deficient derivative **2a** is more reactive. This discrepancy may be rationalized by the multi-step mechanism involved in oxoammonium-mediated alcohol oxidation (Scheme 2), in which electron-deficient substitutions should facilitate alcohol deprotonation during adduct formation with the oxoammonium species, while the same substituents should have the opposite effect on the hydride transfer step.[2,52,53] For the aldehyde substrates, however, both substrate pairs, **1b**/**4b** and **2b**/**3b**, show a higher rate with the more electron-deficient derivative (**1b** and **2b**). These observations are readily rationalized by the need to generate the aldehyde hydrate in order to oxidize the aldehyde to the carboxylic acid. The hydration equilibrium is strongly favored by the presence of electron-withdrawing substituents.[54] For example, hydration constants for aldehydes **1b** and **4b** have been reported to be 50 and 0.01, respectively, under neutral conditions.[55] To probe the latter effect further, electrochemical oxidation of **1b** and **4b** were compared at different pH values. High catalytic TOFs were observed for ACT-catalyzed oxidation of **1b**, with the electron-withdrawing pyridyl group (Figure 4a). On the other hand, little catalytic activity was observed for oxidation of **4b** at pH 8.4 and 10. Only upon increasing the solution pH to 11.5 was significant catalytic current observed (Figure 4b), albeit still much lower than that observed with **1b** at similar pH (Figure 4c).



Scheme 2. Oxidation of primary alcohol and aldehyde hydrate by oxoammonium.

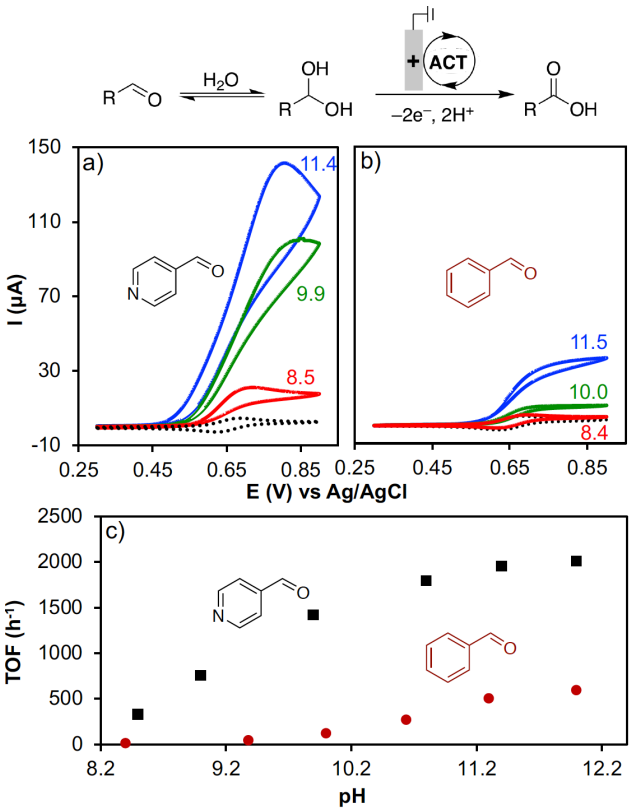
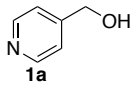
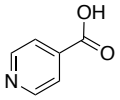
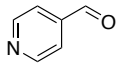
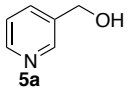
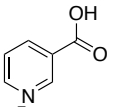
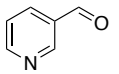
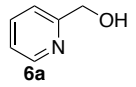
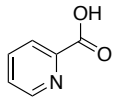
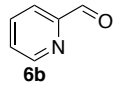
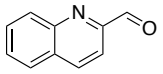
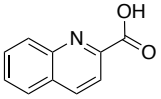
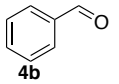
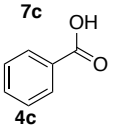
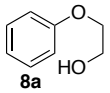
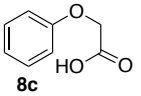
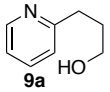
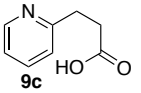
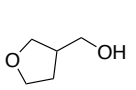
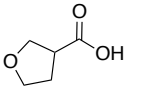
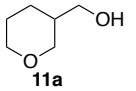
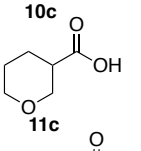
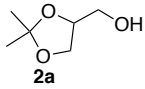
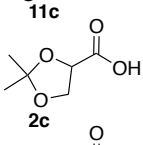
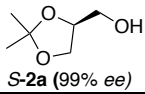
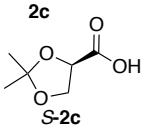


Figure 4. Cyclic voltammograms of ACT in the absence (dotted line) and presence of 20 mM **1b** (a) and 20 mM **4b** (b) at different pH values. The TOF of ACT for oxidation of **1b** and **4b** as a function of pH (c). Solution conditions: CH_3CN/H_2O (70:30), change in pH was obtained by varying the ratio of the $NaHCO_3$ to Na_2CO_3 electrolyte (total concentration 0.14 M). Scan rate is 10 mVs^{-1}.

These voltammetric studies were then extended to bulk electrochemical oxidation of a variety of other alcohols and aldehydes, using ACT as the catalyst (2.5 or 5 mol% loading) (Table 1). The optimized conditions employ aqueous bicarbonate/carbonate solution, avoiding the need for tetraalkylamonium salts or related less desirable electrolytes. A number of different benzylic and aliphatic alcohols and aldehydes were converted to the corresponding carboxylic acids, including a number of examples containing pyridine or quinoline units. For water-insoluble substrates, a mixture of acetonitrile/water was used (entries 7 and 8). The only undesirable byproduct observed from these reactions was a small amount of benzil (approx. 10% yield) in the oxidation

Table 1. The substrate scope for ACT mediated formation of carboxylic acids.[a]

entry	substrate	product	time (h)	yield[b]
1	 **1a**	 **1c**	13	97%
2	 **1b**		8	95%
3	 **5a**	 **5c**	12	96%
4	 **5b**		8	86%[c]
5	 **6a**	 **6c**	12	83%
6	 **6b**		10	86%
7[d]	 **7b**	 **7c**	8	91%
8[d]	 **4b**	 **4c**	8	87%[e]
9	 **8a**	 **8c**	5	91%
10	 **9a**	 **9c**	8	97%
11	 **10a**	 **10c**	3	96%
12	 **11a**	 **11c**	5	99%
13	 **2a**	 **2c**	2	99%
14	 *S*-**2a** (99% *ee)*	 *S*-**2c**	2	99% 99% *ee*

[a] Conditions: 1 mmol alcohol with 5 mol % ACT or 2 mmol aldehyde with 2.5% ACT, in 10 mL aqueous carbonate buffer 0.1 M $NaHCO_3$, 0.1 M Na_2CO_3, pH 9.8-10.1, electrolysis at 0.7 V vs. Ag/AgCl. [b] Isolated yield. [c] 0.2 M Na_2CO_3, pH 11.5; 6% diketone (dimer) observed. [d] 40% acetonitrile was used for substrate solubility. [e] 0.2 M Na_2CO_3, pH 11.5; 6% benzil observed.

benzaldehyde and the analogous diketone in the oxidation of 3-pyridinecarboxaldehyde. By running the reaction at higher pH, for example, using only Na_2CO_3 as the electrolyte (pH 11.5), the yield of these dimeric side products decreased to approximately 6% (entries 4 and 8; see Section 4 of the Supporting Information for details).

The effect of pH on electrochemical aminoxyl-mediated alcohol oxidation has been investigated in previous voltammetric studies,[48,56,57] and faster rates are typically observed at higher pH. Similar behavior was observed in the present reactions, as revealed by voltammetric and chromonamperometric analysis of the pH dependence of ACT-mediated oxidation of substrates **1a**, **1b**, **4a**, and **4b** (see Figure 4 and Figures S11 and S12 in the Supporting Information). More thorough analysis of ACT-mediated oxidation of *S*-**2a** reveals the pH effects under bulk electrolysis conditions (Figure 5). Higher current and more-rapid conversion of the substrate were observed at pH 9.8 relative to the reaction conducted at pH 8.5; however, both experiments led to high yields of product (97% and 99% at pH 8.5 and 9.8, respectively) and complete retention of enantioselectivity (>99% *ee*). The latter observation is rationalized by the relatively short lifetime and/or build-up of the aldehyde intermediate during the reaction (cf. Figure 3).

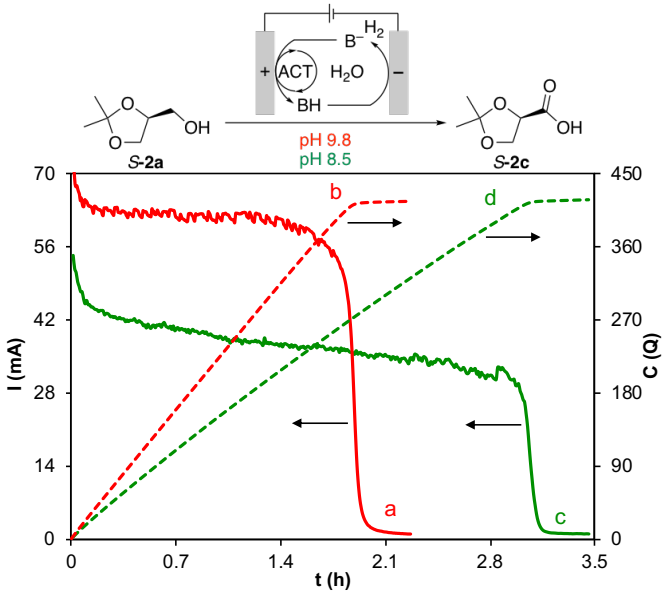


Figure 5. Current traces observed (a and c) and associated charge consumed (b and d) during the bulk electrolysis of solketal at pH 9.8 (0.1 M $NaHCO_3$, 0.1 M Na_2CO_3 for a) and 8.5 (0.2 M $NaHCO_3$ for c). Reaction condition: 1 mmol solketal with 5 mol% ACT in 10 mL aqueous solution, applied potential 0.7 V vs. Ag/AgCl.

In order to demonstrate the synthetic utility and larger-scale viability of this approach, we targeted the preparation of the carboxylic acid precursor to levetiracetam [(2*S*)-2-(2-oxo-1-pyrrolidinyl)butanamide], a generic drug commonly used to treat epilepsy and potentially beneficial for other central nervous system disorders like Alzheimer's and autism.[58] The chiral alcohol **12a** is readily obtained via condensation of the corresponding aminoalcohol and butyrolactone, and oxidation of **12a** to carboxylic acid **12c** is one of several efficient routes that has been demonstrated for the synthesis of levetiracetam.[59-61] Under the pH 9.8 conditions identified for the oxidation of solketal, voltammetric studies of **12a** showed that ACT exhibits high catalytic activity (Figure 6, trace b), and the carboxylic acid **12c** was obtained in 87% isolated yield and 87% *ee* following a 2 h bulk electrolysis (Figure 6, traces c and d).

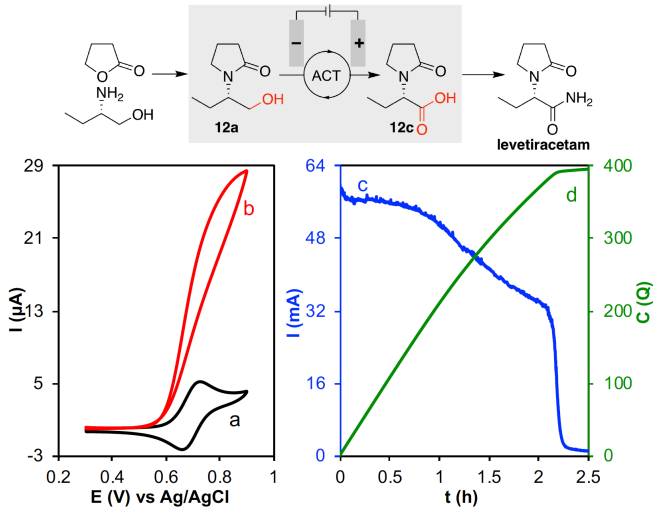
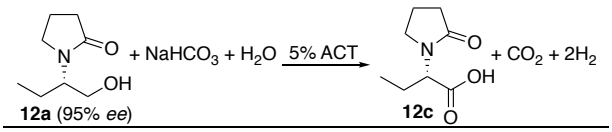


Figure 6. Possible synthetic route for the synthesis of levetiracetam and cyclic voltammograms of ACT in the absence (a) and presence of **13a** (b). Conditions: 1 mM ACT, 20 mM substrate, scan rate 10 mV s^{-1}.

The current (c) and consumed charge (d) for the ACT catalyzed electrochemical oxidation. Reaction condition: 1 mmol **12a**, 5 mol% ACT in 10 mL aqueous solution, applied potential 0.7 V vs. Ag/AgCl. Aqueous carbonate buffer, 0.1 M $NaHCO_3$ and 0.1 M Na_2CO_3 (pH 9.8), was used for both voltammetric and electrolysis experiments.

The reaction was then tested under different conditions and reaction scales (Table 2). Changes to the electrolyte concentration and reaction scale (1–14 mmol; entries 1–8) led to some variation in the reaction time, but quantitative conversion of alcohol to carboxylic acid was observed in all reactions. The alcohol **12a** has good solubility in aqueous solution, allowing the concentration to be increased up to 0.6 M (≅ 10 wt%) (entry 4). Both controlled current and controlled potential electrolysis were effective, and the reaction completion was indicated by either a sharp drop in the current during controlled potential operation (cf. Figure 6, trace c) or a jump in the potential during controlled current operation (see Figure S14 in Supporting Information). The reaction was also effective using the commercially available ElectraSyn 2.0 apparatus (entry 6).[62] At pH 9.8, with a 1:1 ratio of $NaHCO_3$ and 0.1 M Na_2CO_3 (0.1 M each) as the electrolyte, a small drop in enantioselectivity was observed during oxidation of the substrate **12a** (95% *ee*) to the product **12c** (87% *ee*). Therefore, the reaction was re-optimized by using 1.1 equiv of $NaHCO_3$ as the electrolyte (pH 8.5). (Note: Oxidation of H^+ to H_2 at the cathode counter electrode maintains the pH during the reactions.) This less basic medium led to higher retention of enantioselectivity, and oxidation of **12a** on 40 g scale led to formation of **12c** in 91% yield and 92% *ee* (Table 2, entry 9).[51]

Table 2. Different reaction conditions for the oxidation of **13a** to **13c**.



12a (95% *ee*) **12c**

entry	mmol	V (mL)	base (equiv)	t (h)	yield[a] *(ee)*
1	1	10	HCO_3^- (1), CO_3^{2-} (1)	2.5	87% (87%)
2	3	10	HCO_3^- (1), CO_3^{2-} (1)	5.5	91%
3	3	10	HCO_3^- (0.33), CO_3^{2-} (0.33)	8.5	93%
4	6	10	HCO_3^- (0.5), CO_3^{2-} (0.5)	14	96%
5	1	10	HCO_3^- (1.1)	4	88%
6	1	10	HCO_3^- (1.1)	4	91%[b]
7	3	10	HCO_3^- (1.1)	11	94%
8	14	70	HCO_3^- (1.1)	14	93%
9	245	1000	HCO_3^- (1.1)	29	91%[c] (92%)[d]

[a] NMR yield, trimethoxybenzene was used as internal standard. [b] The reaction was performed using ElectraSyn 2.0. [c] Isolated yield, [d] enantiomeric excess was determined using chiral HPLC.

Conclusion

The results described herein show that ACT-mediated electrochemical oxidation of alcohols and aldehydes provides an effective and scalable route to generate carboxylic acids, including substrates that contain heterocycles and stereocenters adjacent to the alcohol. The protocol is quite practical, as it uses aqueous reaction media, carbonate/bicarbonate base as the electrolyte, proceeds at room temperature, uses an inexpensive catalyst, and is amenable to larger scale applications. These features, combined with the environmentally benign nature of electrosynthesis, make it highly appealing approach for the preparation of carboxylic acids, for example, in the pharmaceutical industry. This feature is evident in the 40 g scale oxidation of 1-[(2S)-1-hydroxy-2-butanyl]-2-pyrrolidinone.

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ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: xxx.

Experimental details, description of electrochemical reactions, additional electrochemical studies, derivation of turnover frequencies (TOFs), NMR spectra of the products, and the chromatographic characterization of enantiomeric excess, including Figures S1–S14. (PDF)

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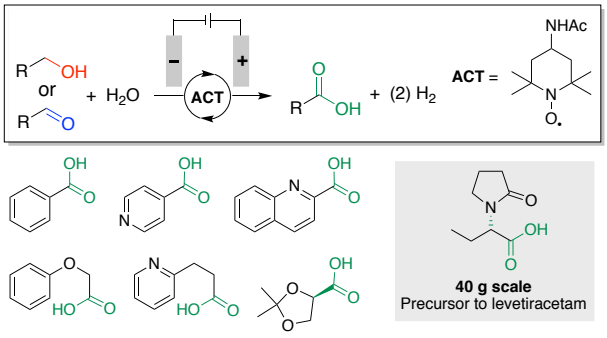
TOC Graphic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or
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+ H2O
ACT
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ACT =
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Precursor to levetiracetam