Electrosynthesis Using Carboxylic Acid Derivatives – New Tricks for Old Reactions.

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CONSPECTUS

Electrosynthetic organic chemistry is an old discipline that takes its root in Faraday's seminal works. The field has a rich history and is in the midst of a renaissance, due to the growing impetus of the chemical community to develop greener, more economical, and more efficient synthetic methodologies. Indeed, electrosynthesis relies on one of the greenest and cheapest reagents in the world: the electron itself.

In this account, the recent developments in the use of carboxylic acid derivatives in electrosynthesis are summarised. Until lately, the fate of the mono-electronic reduction of aromatic esters in non-protic solvents remained unclear. Recent investigations have shown that aromatic esters are reduced and form surprisingly long-lived radical-anions. Under the right conditions, these radical-anions decompose into the corresponding carboxylates and alkyl radicals. These principles have been used to develop a novel electrochemical alcohol deoxygenation reaction using aromatic esters as stable and versatile radical precursors.

In contrast to esters, the electrochemistry of carboxylic acids has been intensively studied. Pioneering works by Faraday and Kolbe in the late 1800s have revealed that the anodic oxidation of carboxylic acids leads to a radical decarboxylation. Interestingly, radical recombination is observed due to the very high concentration of radicals in the vicinity of the electrode. Such radical recombination is rarely observed during classical homogenous radical reactions. The "Kolbe" reaction and its carbocationic variation have been intensively used across the fields due to their versatility. As we will develop in this account, almost two hundred years after its discovery, the anodic decarboxylation of carboxylic acids is still relevant to modern organic chemists. For instance, we will examine how the non-decarboxylate Kolbe reaction of aromatic acids to form aroyloxy radicals and how oxycarbonyl radicals could be generated from hemioxalates. Finally, the carbocationic variant of the Kolbe reaction, known as the Hofer-Moest reaction, will be examined in the context of two newly developed reactions: a green MOM-type ether formation and the use of malonic acid derivatives as carbonyl synthons.

Electrosynthesis is a powerful synthetic tool. Even if it might still be underutilised at the moment, there is little doubt that it will become one of the "classic" methods to activate small organic molecules in a very near future.
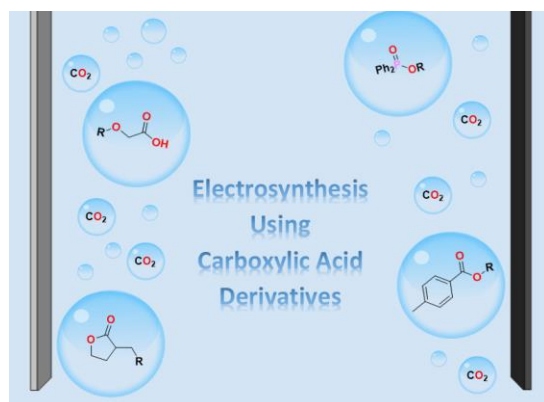
1. INTRODUCTION

The field of electrosynthetic organic chemistry had an extensive and rich history before interest began to wane. Today, the field is in the midst of a renaissance, as the chemical community continues to strive towards greener, more economical, and more efficient synthetic methodologies. Initial forays into organic electrosynthesis can be found as early as 1832,[1] however, it is only with the advent of simpler and more readily-available electrochemical setups that the technique has started to become a valuable tool to the modern synthetic chemist.[2–5]

Not only are previously reported methods being improved, but new procedures formerly believed to be implausible by conventional means are becoming more widely available through the use of electrochemistry. Indeed, electrosynthesis has proven to possess a wide range of applications including cathodic radical deoxygenation,[6] oxidative decarboxylation,[7] allylic oxidation of alkenes,[8] electrochemical methoxymethylation,[9,10] and decarboxylative etherification.[11] Moreover, these transformations have also shown promise at an industrial scale.[12,13] The case studies reported herein demonstrate the versatility of synthetic electrochemistry, alongside its potential to provide a greener and more economical alternative to more traditional procedures, the majority of which rely on the use of toxic transition metals, inherently unstable intermediates, or harsh reaction conditions.

Although this account does not intend to be a comprehensive review, a summary of the previous salient results in the field will help to put the recent advances into context.

1.1. Monoelectronic reduction of aromatic esters

Investigations into the monoelectronic reduction of aromatic esters are scarce within the chemical literature. Moreover, while there is a general agreement regarding the initial formation

of the corresponding radical anion, there remains significant controversy surrounding their fate upon decomposition. Two possible pathways have been proposed for the decomposition of the aromatic ester's radical-anion (**Scheme 1**). Pathway A leads to the formation of a carboxylate and an alkyl radical,[14,15] while pathway B results in an acyl radical and an alkoxide through a proposed carbonyl-oxygen scission.[16] In order to address this dichotomy, additional studies were required, which will be discussed later in this account.
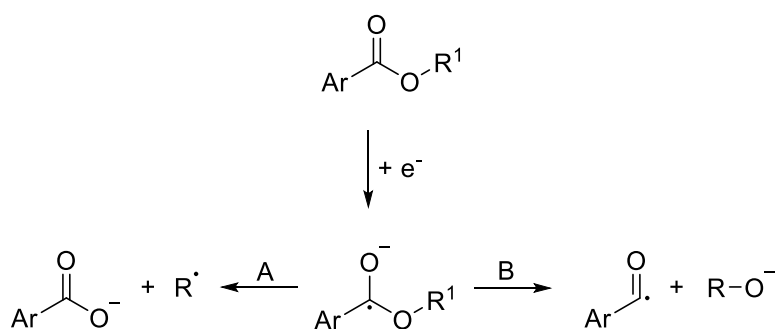
Scheme 1. Possible decomposition pathways of aromatic esters upon one-electron reduction

1.2. Kolbe Electrolysis

In stark contrast to their ester analogues, the electrochemistry of the carboxylic acids has been intensively explored. The anodic oxidation of carboxylates (also known as the Kolbe reaction; **Scheme 2**[17]) is among the first reported organic electrosynthesis[1] and several reviews have been prublished on the topic.[18–22]
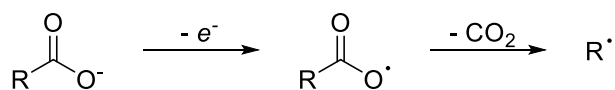
Scheme 2. General Scheme for the Kolbe decarboxylation

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During the Kolbe decarboxylation, a carboxylate is oxidised into its corresponding carboxyl radical. When the R group is an alkyl, a decarboxylation occurs very rapidly and lead to the formation of an alkyl radical R•. As we will see later, the fate of the reaction is slightly different when R is an aromatic group.[23] The Kolbe electrolysis has been found to possess a wide range of applications, some of which are summarised in **Scheme 3**.
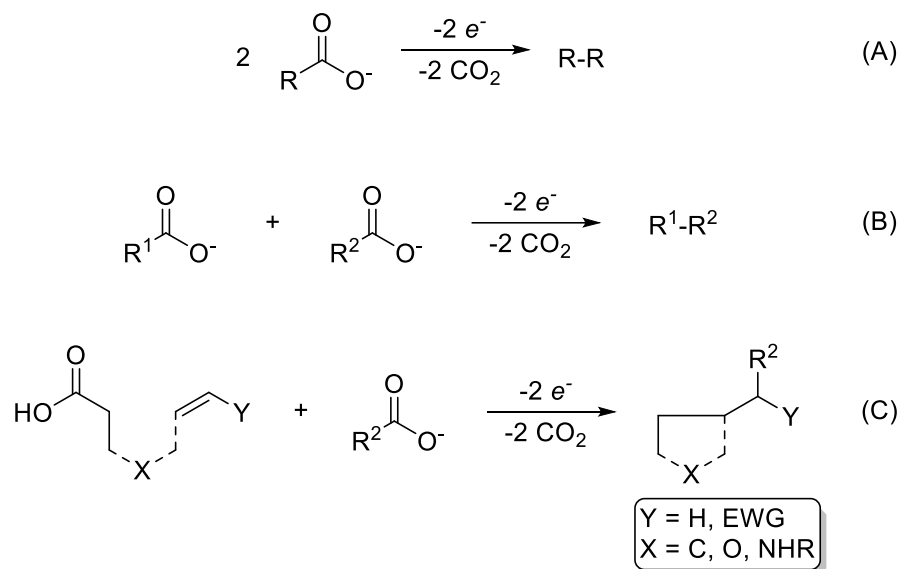
Scheme 3. Applications of the Kolbe reaction

One of the most common uses of the Kolbe reaction remains the preparation of homo-dimers (Scheme 3, A).[19,24–27] Typically, an alcoholic solution of the carboxylic acid is partially neutralised (usually up to 25%) and electrolysed in a beaker-type cell using platinum electrodes. The key of the Kolbe reaction is the use of high current densities (usually higher than 100mA.cm^{-2}) which not only favours the absorption of the negative carboxylate on the positive anode but also generates a high concentration of radicals that favours their recombination on or near the electrode's surface.[28]

Kolbe electrolysis has also been employed to perform unsymmetrical radical sp^3-sp^3 couplings (Scheme 3, B). To do so, a carboxylic acid (R^{1}COOH) is electrolysed in presence of an excess of

a co-acid (R^2COOH) in order to obtain the cross-coupling product (R^1-R^2). [29] That methodology has been intensively used for the synthesis of pheromones derivatives among other applications.[19,30–34] Unfortunately, the formation of the dimer of the co-acid (R^2-R^2) is unavoidable. Therefore, the method is restricted to co-acids that lead to the formation of volatile or easily removable dimers.

When a carboxylate is submitted to the Kolbe electrolysis in presence of an alkene, the radical addition product is obtained (Scheme 3, C). The methodology was extensively used to rapidly access complex carbo and heterocyclic compounds through a Kolbe-intramolecular cyclisation tandem reaction.[19,35–37]

1.3. Hofer-Moest Electrolysis

Hofer and Moest have shown that when platinum electrodes are substituted for carbon graphite electrodes, the Kolbe-produced radical gets overoxidised into the corresponding carbocation (**Scheme 4**).[18,19,38] This simple modification of the Kolbe electrolysis has been used to perform classic cationic reactions.

$$R\text{-}COO^- \xrightarrow[\;-CO_2\;]{-2\,e^-} R^+ \xrightarrow{NuH} R\text{-}Nu$$
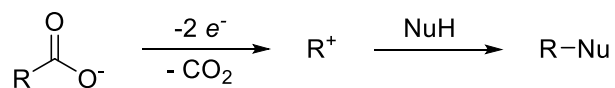
Scheme 4. Hofer-Moest reaction and subsequent application

The most common use of the Hofer-Moest reaction is depicted in **Scheme 4**. A carbocation is generated through the decarboxylation of a carboxylic acid, and the generated carbocation is trapped by a nucleophile. Carboxylic acids,[39] alcohols,[40] water[41] and nitriles[42] have been found to be suitable nucleophiles. The methodology has shown to be particularly useful for the modification

of carbohydrates.[43] The Hofer-Moest reaction has also been applied to other classical carbocation transformation such as eliminations[44] or rearrangements.[45]

Besides the advances in the field that will be developed in this account, more recent applications of the Hofer-Moest include the mild formylation of amine[46] as well as its very promising use in the synthesis of biofuels.[47–50]

2. Electrolysis of carboxylic acid derivatives

2.1. Aromatic Esters, Toluates and diphenylphosphinates

2.1.1. Chemical and Electrochemical Radical Deoxygenation

The Barton-McCombie reaction is the acme among the synthetic tools available for the deoxygenation of alcohols. However, the use of toxic tin reducing agents, expensive silicon hydrides or the exploitation of light-sensitive intermediates make it a less than ideal methodology.[51,52]

The monoelectronic reduction of aromatic and aliphatic esters is well established in the literature in presence of a proton source but,[53] as discussed in the introduction, the fate of the reaction remains unclear in absence of proton. Thanks to their low reduction potential, aromatic esters are ideal systems to study mechanistically using electroanalytical methods. Furthermore, the possibility of selectively reducing different functionalised esters, based on their unique reduction potential, is an attractive prospect to synthetic chemists. It is therefore surprising that only a few studies of these systems have been undertaken.[14,16,54–56]

Coulometric studies (bulk electrolysis at -2.9V *vs* Fc^+/Fc during which the charge was measured) on a series of alkyl benzoates and toluates have confirmed the monoelectronic nature of the

reduction of their reduction. Cyclic voltammetry studies have shown an almost completely reversible chemical behaviour (cathodic peak's current $\approx$ anodic peak's current) for ethyl toluate. This demonstrates the surprisingly high stability of the radical-anion under the cyclic voltammetry conditions (Figure 1). On the other hand, allyl toluate displayed a completely irreversible chemical behaviour when submitted to similar cyclic voltammetry conditions, showing the rapid decomposition of the radical-anion in this case.[57] Lifetimes of radical-anions could easily be measure from cyclic voltammograms recorded at different scan rates.[58,59]
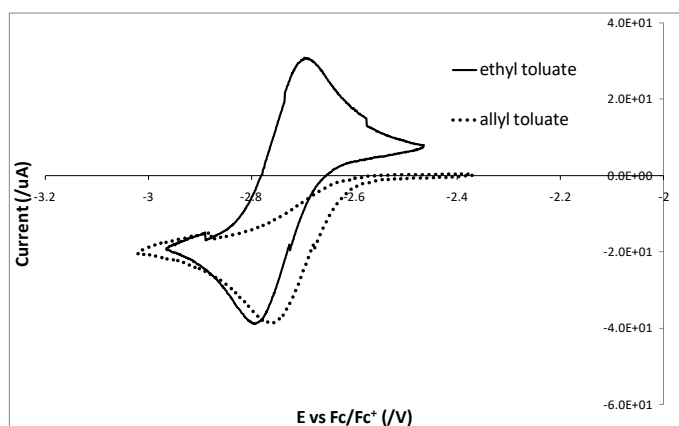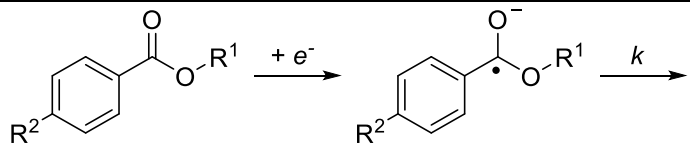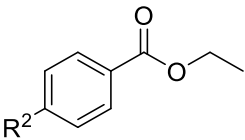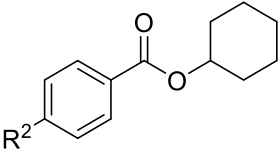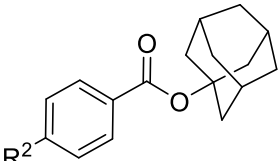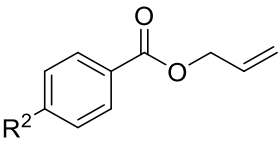

Figure 1. Cyclic voltammogram of ethyl toluate (thick line) (10^{-3} M) and allyl toluate (dotted line) (10^{-3} M) in DMF containing 0.1 M NBu$_4$BF$_4$. Glassy carbon working electrode / Platinum foil counter electrode / Pt wire pseudo reference electrode. Sweeping rate 150 mV/s

The lifetimes of several benzoate's radical-anion were measured using cyclic voltammetry and are summarised in Table 1. Benzoate has shown to be reduced at -2.68V *vs* Fc$^+$/Fc. An increase in radical stabilisation ability of the alkyl part R^1 of the esters (Cy < ^{t}Bu < allyl) leads to an increase in the rate of decomposition *k*. Such an observation strongly supports Wagenknecht's mechanism (Scheme 1, pathway A) where the radical-anion intermediate decomposes into an alkyl radical and

an aromatic carboxylate. Interestingly, a similar observation was made upon replacement of benzoate ($R^2 = H$) with toluate ($R^2 = Me$;

Table 1).[57] The addition of a methyl group in the *para* position resulted in a more negative reduction potential of the aromatic esters by approximately, 0.1 V which is indicative of an increase in the electron density of the aromatic group.[14] Consequently, this leads to a destabilisation of the intermediate radical-anion and accelerates its decomposition.

Table 1. Comparative rates of decomposition rates of aromatic esters' radical anions

R^1 = alkyl, allyl, R^2 = H, Me

Entry	Ester	k/s^{-1} in MeCN	
		$R^2 = H$	$R^2 = Me$
1		0.012	0.013
2		0.025	0.049
3		0.39	0.81
4		2809	6455

Rates (k) measured using DigitalSimulation based on CVs of aromatic esters (10^{-3} M) recorded in MeCN containing 0.1 M NBu$_4$BF$_4$. Using a glassy carbon working electrode / Platinum foil counter electrode / Pt wire pseudo reference electrode. Sweeping rate 150 mV/s, 250mV/s and 500mV/s

The long lifetime of the radical-anion was found to be detrimental to the reaction since this leaves enough time for the radical-anion to decompose following multiple and uncontrolled pathways. Heating was found to be beneficial by speeding up the decomposition of the radical-anion. Consequently, the deoxygenation of toluates was first investigated using samarium(II) iodide since, at that time, our goal was to develop conditions that could be reproduced easily in standard synthetic laboratories.

When toluate **1** was heated under reflux in THF in presence of HMPA and samarium(II) iodide, the corresponding deoxygenated product, **2**, was obtained with good yields and in few minutes (Scheme 5). This deoxygenation was found to tolerate a wide variety of functional groups, as summarised in Table 2.
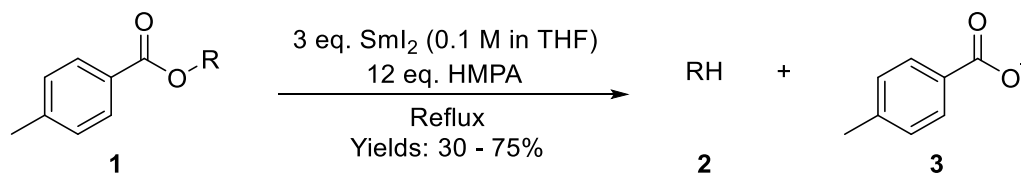
Scheme 5. Chemical radical deoxygenation of **1**, affording **2** and **3**

The confirmation of a radical-based reaction pathway was supported by the synthesis and subsequent reduction of **4**, which bears a suitably placed alkyne group (Scheme 6). Indeed, in the presence of SmI$_2$/HMPA, the generated radical underwent a five-*exo*-dig cyclisation to form the expected tetrahydrofuran **5**. Interestingly, the origin of the final hydrogen atom remains unclear.

When the reduction was carried in THF-d_8 or in glassware that had been pre-treated with DCl, only a minor amount of deuterium was incorporated in the final deoxygenated product.
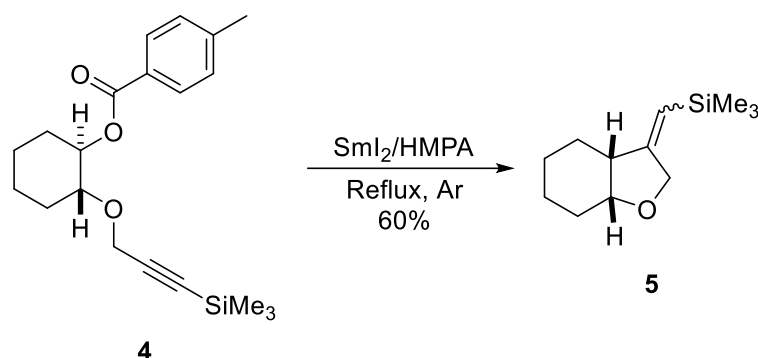

Scheme 6. Chemical radical cyclisation of **4**, affording tetrahydrofuran **5**

Due to the success of this chemical methodology, it was envisaged that an electrochemical method would hold promise and avoid the use of the toxic and expensive SmI$_2$/HPMA system. Electrosynthesis does not suffer from these drawbacks, with initial screenings identifying NMP as the best solvent. Indeed, it was possible to successfully deoxygenate toluates in good yields using simple and economically-relevant graphite electrodes in NMP at higher temperatures.[60]
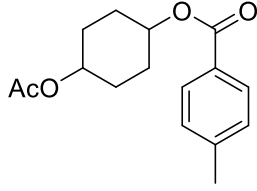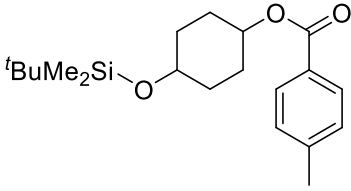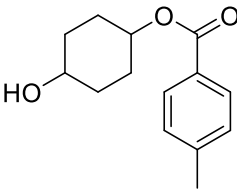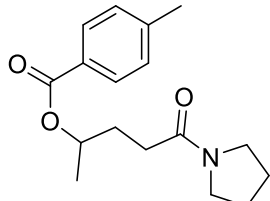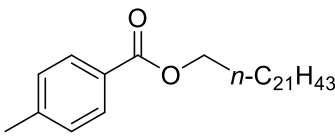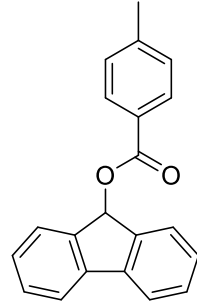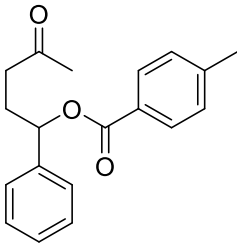
Further studies demonstrated the high functional group tolerance of this method. As it can be seen from Table 2, esters (entry 4), silyl ethers (entry 5), unprotected alcohols (entry 6) and amides (entry 7) are well tolerated by both the chemical and electrochemical methodologies. Ketones (entry 10), however, are only compatible with the electrochemical methodology. Unfortunately, significantly lower yields were obtained for the deoxygenation of primary alcohols when compared to secondary and tertiary alcohols, mirroring the results obtained with the samarium-based method. Moreover, the *in-situ* generated radical could be captured intramolecularly *via* a five-*exo*-dig cyclisation, as previously mentioned for the SmI$_2$/HMPA system.

Table 2. Substituent scope of the chemical and electrochemical deoxygenation of toluates
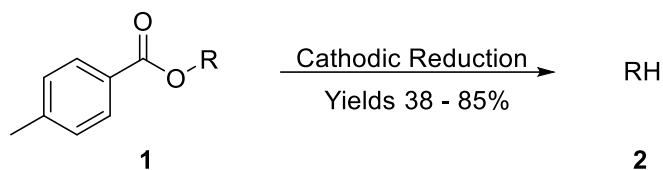
Electrolysis mode: Galvanostatic, $J= 15$ mA.cm^{-2}
Electrodes type: Carbon graphite
Cell type: Divided
Substrate concentration: 6 mM
Supporting electrolyte/solvent/temperature: [^{n}Bu$_4$N][BF$_4$] (0.15 M) in NMP at 130°C

Entry	Esters	Yield in alkane / %	
		Chemical Reduction	Electrochemical Reduction
1		73	85
2		64	75
3		30	38

4		62	72
5		60	83
6		59	64
7		69	70
8		63	41
9		30	50
10		0%	67%

Issues were encountered upon deoxygenation of the primary alcohol **6** due to the production of a long-lived radical anion, **6⁻**. This radical-anion could then undergo the desired deoxygenation pathway (A) or follow numerous undesired decomposition pathways, the most common being depicted in Scheme 7 (Pathway B). The radical-anion, due to its long lifetime, is reprotonated by adventitious protons (solvent, residual moisture, etc.) and undergoes a second reduction to form the hemiacetal **7**. The later one decomposes, during the workup, into the initial primary alcohol. Indeed, experimentally, the main by-product of the reduction of primary compounds was found to be the corresponding alcohol.
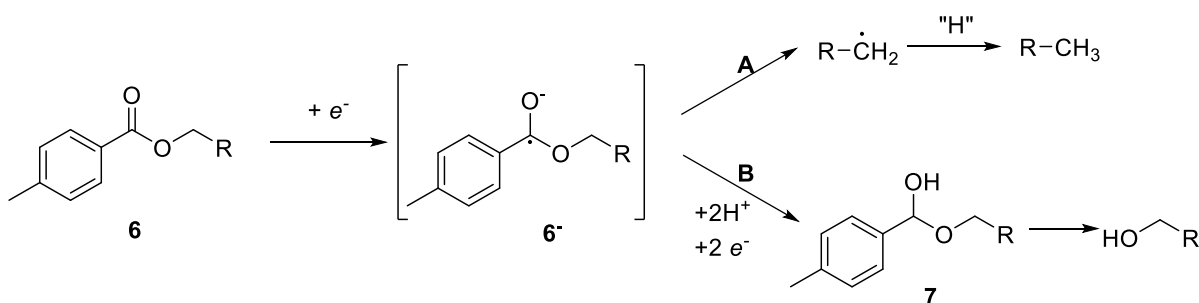
Scheme 7. Electrochemical deoxygenation of primary toluate **6**

In an attempt to improve the deoxygenation of primary alcohols, the possibility of a similar reaction where the primary alcohol could be esterified *in-situ* during the electrolysis was investigated. It was envisaged that, in the presence of an excess of methyl toluate, the electrolysis of the desired alcohol would first lead to transesterification and then afford the corresponding alkane *via* the mechanism illustrated in Figure 2.[61]

First, the primary alcohol is reduced at the cathode into hydrogen and a highly nucleophilic tetrabutylammonium alkoxide. In the presence of an excess of methyl toluate the alkoxide is

transformed into the corresponding primary toluate, which is subsequently reduced into its radical-anion. As discussed previously, the radical-anions of primary aromatic esters are relatively long-lived and will decompose either *via* the desired deoxygenation pathway or through the capture of a hydrogen atom/proton to reform the starting alkoxide through hydrolysis of the hemiacetal. This alkoxide would then go through a new transesterification/reduction cycle, which eventually results in deoxygenation.
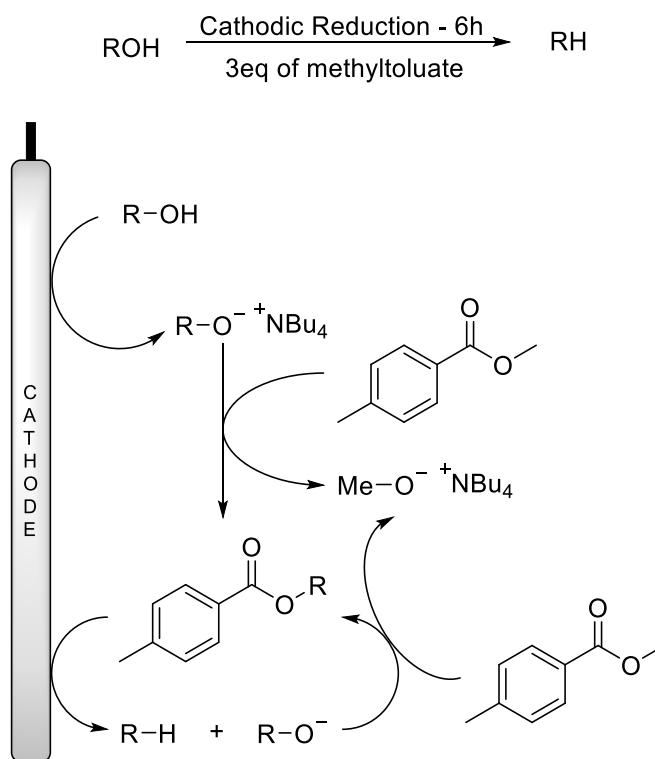

Figure 2. Mechanism for the electrochemical deoxygenation of alcohols

In contrast to precedent methods, excellent results were obtained for the electrolysis of primary alcohols which could now be deoxygenated with excellent yields (Table 3); however, secondary and tertiary alcohols showed little to no reactivity, presumably due to their steric hindrance precluding the transesterification process.[61]

Table 3. Substituent scope of the electrochemical deoxygenation of primary alcohols.
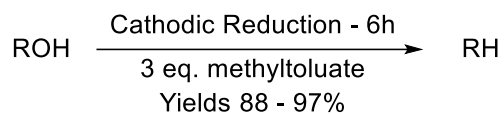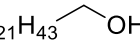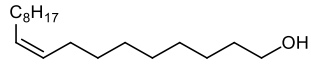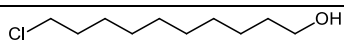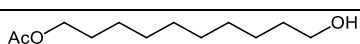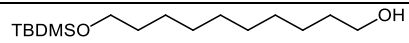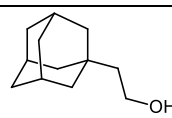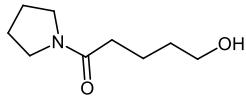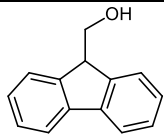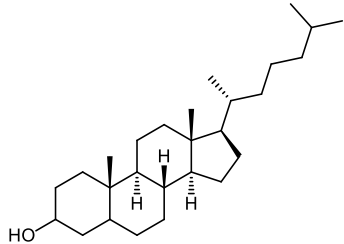
$$ROH \xrightarrow[\substack{\text{3 eq. methyltoluate} \\ \text{Yields 88 - 97\%}}]{\text{Cathodic Reduction - 6h}} RH$$
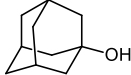
Electrolysis mode: Galvanostatic, J= 100 mA.cm^{-2}
Electrodes type: Carbon graphite
Cell type: Divided
Substrate concentration: 3 mM
Supporting electrolyte/solvent/temperature: [^{n}Bu$_4$N][BF$_4$] (0.15 M) in DMF at 60°C

Entry	Alcohol	Yield in alkane / %
1	C$_{21}$H$_{43}$ ⌒ OH	92
2	C$_8$H$_{17}$ ... OH	90
3	Cl ... OH	91
4	AcO ... OH	89
5	TBDMSO ... OH	90
6	(adamantyl) OH	97
7	(pyrrolidinyl-C(=O)) ... OH	95
8	(fluorenyl) OH	88
9	(cholesterol, HO-)	< 3% conversion

| 10 | | 0% conversion |

While the previous methodology has demonstrated significant versatility, the electroreduction often required temperatures of up to 130°C and a low current density, resulting in long electrolysis periods (up to 12 h for the conversion of less than 10mmol of substrate). The use of diphenylphosphinates as an alternative to toluates was considered, since the formation of a P=O bond during the decomposition step would be a major driving force for the deoxygenation reaction.[6] The reduction potential of ethyldiphenylphosphinate (−2.4 V *vs* Ag/AgCl or -2.83V *vs* Fc$^+$/Fc) is slightly more negative than that of the corresponding toluate (−2.3 V *vs* Ag/AgCl or -2.73V *vs* Fc$^+$/Fc), and thus chemical reduction by SmI$_2$/HMPA is no longer possible (Figure 3).
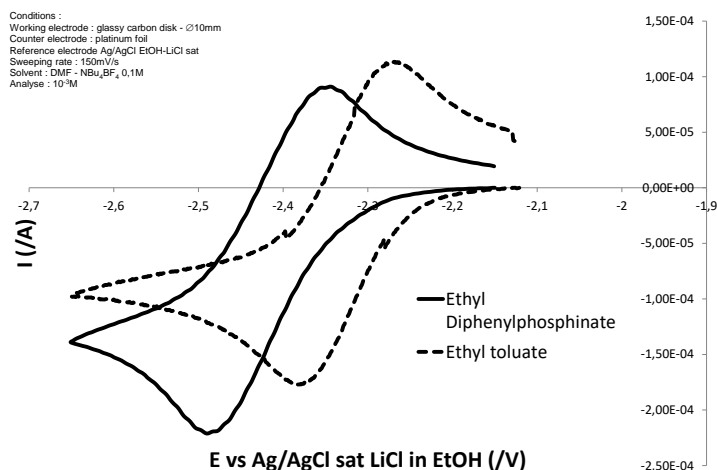
Figure 3. Cyclic voltammogram of ethyl diphenylphosphinate (thick line) (10^{-3} M) and ethyl toluate (dotted line) (10^{-3} M) in DMF containing 0.1 M NBu$_4$BF$_4$. Glassy carbon working electrode / Platinum foil counter electrode / Pt Ag/AgCl reference electrode. Sweeping rate 150 mV/s

Moreover, coulometric and cyclic voltammetric studies revealed that this reduction proceeds *via* a mechanism similar to the one postulated for the monoelectronic reduction of aromatic esters. A radical-anion is formed and ultimately decomposes to give diphenylphosphinate and an alkyl

radical. As with the toluate systems, it was again found that the stability of the formed alkyl radical was intrinsically linked to the rate of decomposition of the parent radical anion. (Table 4).

Table 4. Comparative rates of decomposition of radical anions

		$R^1-OR^2 \xrightarrow{+\ e^-} \left[R^1-OR^2\right]^{\cdot-} \xrightarrow{k} R^1-O^- + \cdot R^2$ $R^1 = p$-tolyl or Ph_2PO	
		k/s^{-1} in MeCN	
Entry	R^2	$R^1 = p\text{-}tolyl$	$R^1 = Ph_2PO$
1		0.012	0.013
2		0.025	0.049
3		0.39	0.81
4		2809	6455

Reduction of 1-adamantyldiphenylphosphinate was initially achieved in moderate yields (44%) in a divided cell using graphite electrodes at 110 °C in DMF. However, upon reduction of the reaction temperature to ca. 60 °C, significantly higher yields (90%) could be obtained, which is in sharp contrast to the reduction of the corresponding toluates which require temperatures up to 130 °C. Yields could be further improved by increasing the current density to 100 mA.cm^{-2}, however, densities above this were found to be detrimental.

Primary, secondary, and tertiary phosphinates were found to undergo reductive deoxygenation with ease. Strikingly, in direct contrast with the previously reported toluate methodology, excellent

yields were obtained for primary phosphinates (> 60%), while retaining a high functional group tolerance (Table 5).

Table 5. Substituent scope of the electrochemical deoxygenation of diphenylphosphinates.
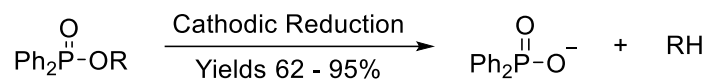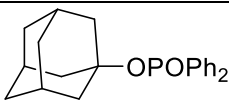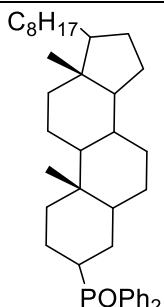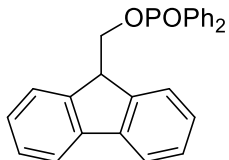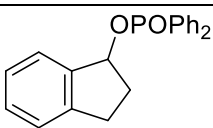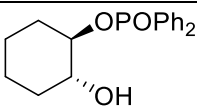
$$\text{Ph}_2\overset{\overset{\displaystyle O}{\|}}{\text{P}}\text{-OR} \xrightarrow[\text{Yields 62 - 95\%}]{\text{Cathodic Reduction}} \text{Ph}_2\overset{\overset{\displaystyle O}{\|}}{\text{P}}\text{-O}^- \quad + \quad \text{RH}$$
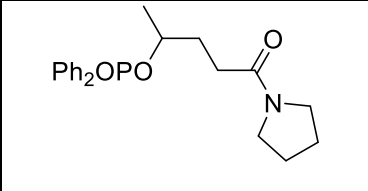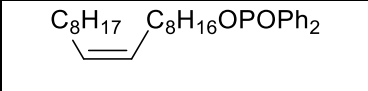
Electrolysis mode: Galvanostatic, J= 100 mA.cm^{-2}
Electrodes type: Carbon graphite
Cell type: Divided
Substrate concentration: 17 mM
Supporting electrolyte/solvent/temperature: [^{n}Bu$_4$N][BF$_4$] (0.15 M) in DMF at 60°C

Entry	Diphenylphosphinate	Yield in alkane / %
1		92
2		95
3		70
4		78
5		81

6	Ph$_2$OPO	78
7	C$_8$H$_{17}$ C$_8$H$_{16}$OPOPh$_2$	67
8	^{n}Bu ... OPOPh$_2$	62
9	OTBDMS ... OPOPh$_2$	90
10	OAc ... OPOPh$_2$	74

In order to confirm that a radical pathway was in operation, **8** was synthesised and subsequently electrolysed (Scheme 8), with the expected bicyclic system **9** arising from a five-*exo*-dig cyclisation on the pendant alkyne. Interestingly, the loss of the SiMe$_3$ group was apparent by ^{1}H NMR spectroscopy, but the exact mechanism for this is remains unclear.
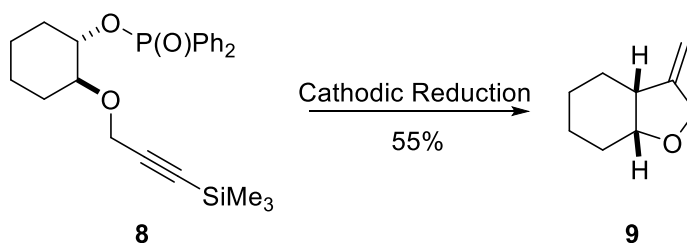
Scheme 8. Electrochemical deoxygenation of **8**, affording tetrahydrofuran **9**

2.1.2. Electrochemical Deprotection of Aromatic Esters

As mentioned previously, aromatic esters have shown remarkable versatility in synthetic electrochemistry,[15] and this is further demonstrated by their use as electrochemically-labile protecting groups.[62,63] Electrocleavable aromatic esters provide an appealing alternative to classical acidic and basic ester deprotection, especially since the reducing power of the electrode can be easily tuned.

As mentioned previously (Scheme 7, pathway B), the addition of a proton source to the reduction medium should quench the intermediate radical-anion. This was indeed observed by cyclic voltammetry. The reduction of the ethyl toluate became completely irreversible in presence of methanol, indicating that the radical-anion is quenched by the proton source (**Figure 4**).
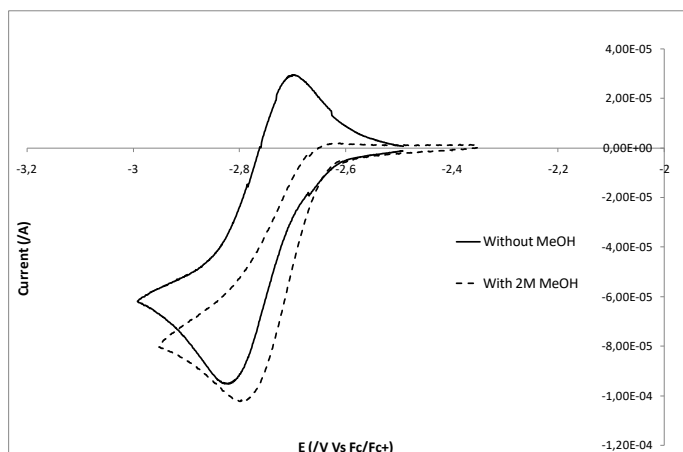
Figure 4. Influence of the addition of methanol on the reduction of ethyl toluate (10^{-3} M in NMP containing 0.1 M NBu$_4$BF$_4$. Glassy carbon working electrode / Platinum foil counter electrode / Pt wire pseudo reference electrode. Sweeping rate 150 mV/s

For instance, when toluates were reduced by SmI$_2$ and HMPA in the presence of a proton source such as methanol, the free alcohol was obtained with exceptionally fast reaction times (< minutes) in almost quantitative yields.[62] This was believed to occur *via* a mechanism similar to the

Bouveault-Blanc reaction,[53] a re-protonation of the radical-anion intermediate followed by a second electron transfer and protonation to form the corresponding acetal, which then decomposes to afford the desired alcohol (Scheme 9). These yields were readily reproduced electrochemically in NMP, utilising graphite electrodes and ^{i}PrOH as a proton source.
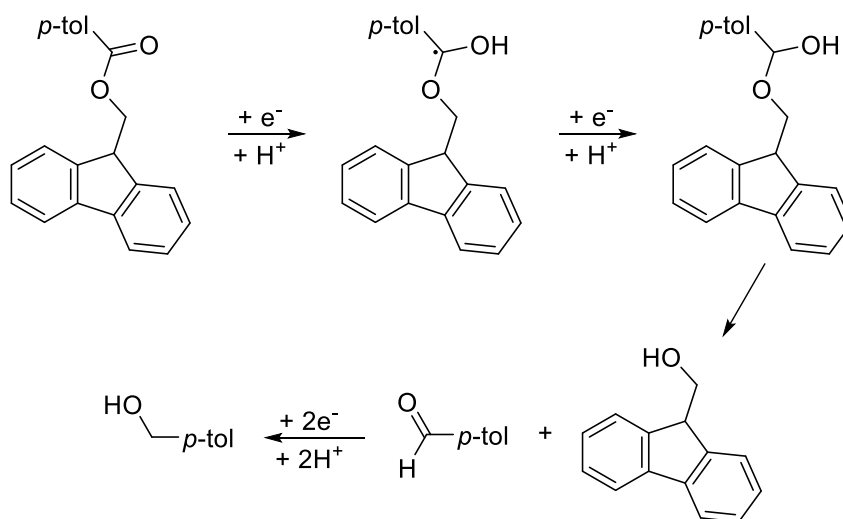
Scheme 9. Electrochemical deprotection of toluates.

Primary, secondary, and tertiary toluates can be deprotected with equal efficiency, with typically encountered functionalities tolerated (e.g. esters, silyl ethers, and amide moieties; Table 6).

Table 6. Substituent scope of the electrochemical deprotection of toluates.
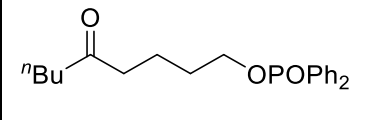

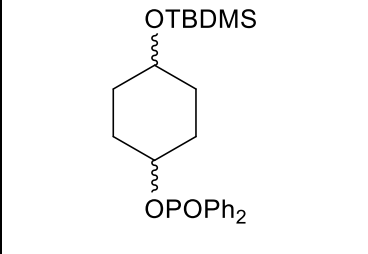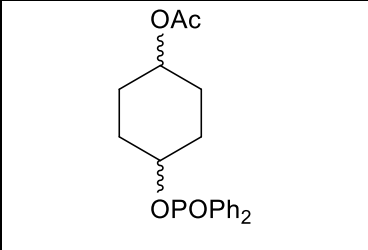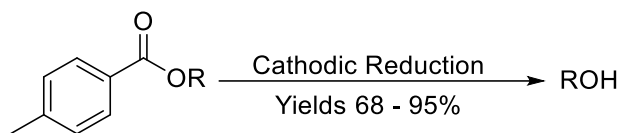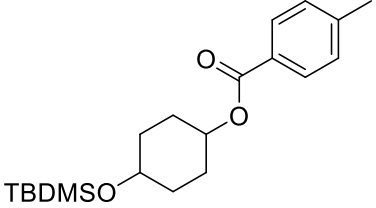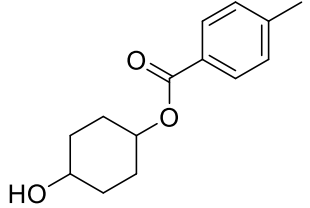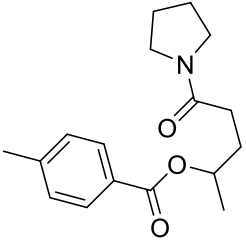Electrolysis mode: Galvanostatic, J= 15 mA.cm^{-2}
Electrodes type: Carbon graphite
Cell type: Divided
Substrate concentration: 5 mM
Supporting electrolyte/solvent/temperature: [^{n}Bu$_4$N][BF$_4$] (0.15 M) in NMP/^{i}PrOH 93/7 at 90°C

Entry	Toluate	Yield in alcohol / %
1		95
2		81
3		76
4		83

5		72
6		68
7		89

Furthermore, as the reduction potential of an aromatic ester can be altered by modifying the substituents on the aromatic ring, chemoselective transformations are possible. To make an analogy with classical chemistry, being able to control the reduction potential of the electrode would be similar to having an unlimited range of reducing reagents, all with slightly different reducing activities.[64] The cyclic voltammogram of compound **10** perfectly illustrates this principle (Figure 5). The compound exhibits three distinct reductions at -1.51V, -1.80V and -2.5V *vs* Ag/AgCl. A fourth, unresolved, reduction at -2.6V *vs* Ag/AgCl is due to a second reduction of the di-trifluoromethyl ester.
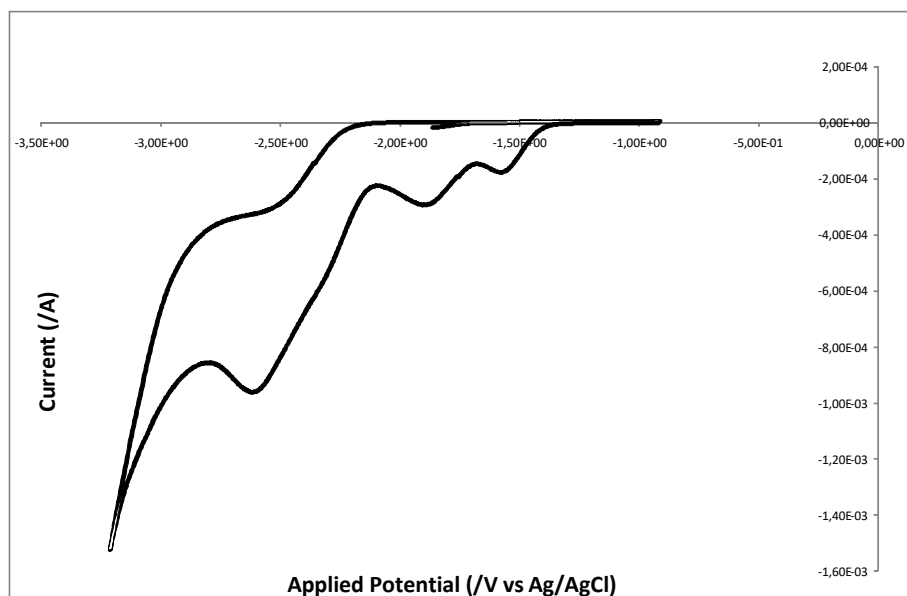
Figure 5. Cyclic voltammogram of **10** (10^{-3} M in DMF containing 0.1 M NBu$_4$BF$_4$. Glassy carbon working electrode / Platinum foil counter electrode / Ag/AgCl reference electrode. Sweeping rate 150 mV/s)

Single, double, and total deprotection of compound **10** could be achieved through careful control of electrode potential (Scheme 10). Such transformations are not possible using chemical methodologies (i.e. SmI$_2$/HMPA), which are unable to discriminate between different aromatic esters.
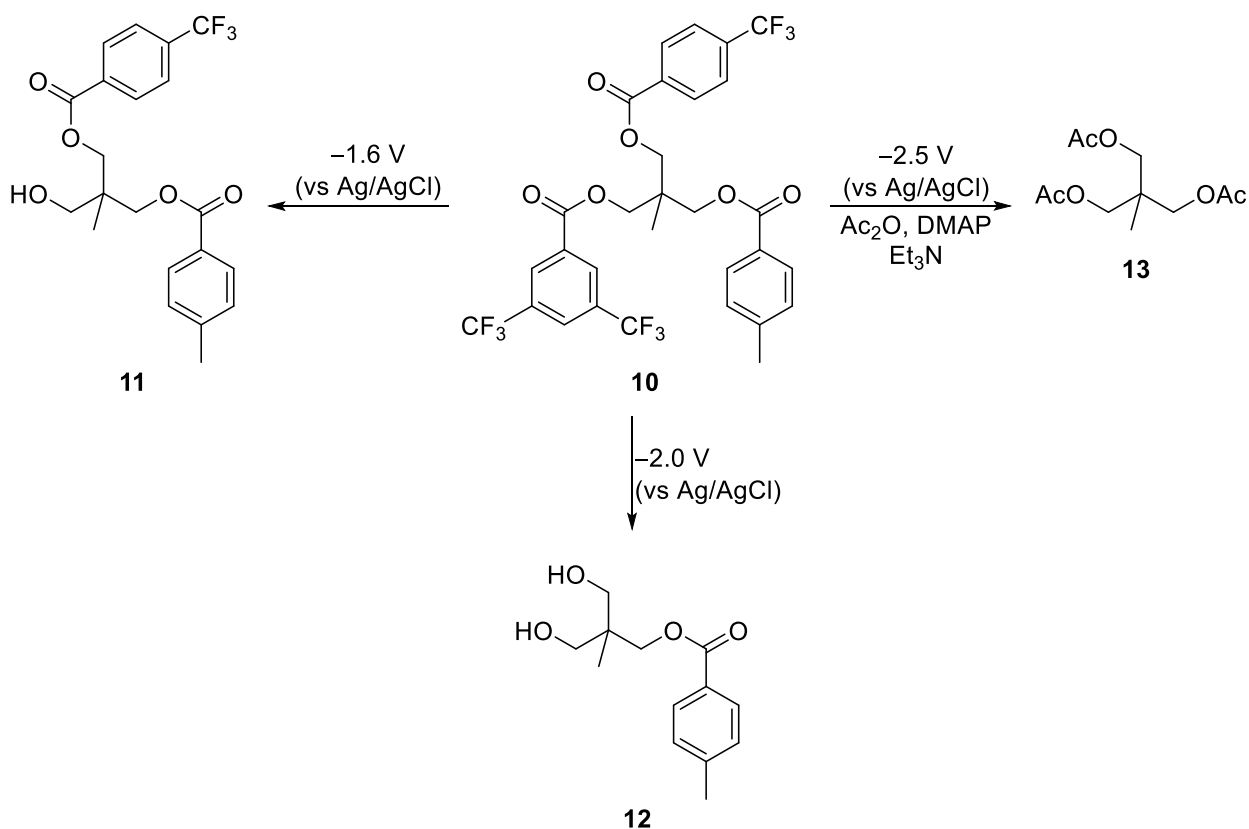
Scheme 10. Chemoselective deprotection of **10**, affording **11**, **12**, or **13** depending on the applied potential

2.2. Electrochemical Lactonisation

The intramolecular addition of an electrochemically-generated carbon-centred radical, followed by intermolecular trapping of the newly formed radical by another carbon-centred radical is well known for the formation of 5- and 6-membered carbo- and heterocycles.[65,66] Building on this work, the plausibility of trapping electrogenerated oxygen-centred radicals with a suitably positioned electron-deficient double bond was investigated.[23] Aroyloxy radicals are known to decarboxylate at a much slower rate than their aliphatic counterparts and therefore represent a suitable starting point towards the synthesis of substituted phthalides. This was confirmed upon electrolysis of

various benzoic acid derivatives under standard Kolbe conditions in the presence of sodium methoxide and aliphatic carboxylic co-acids, which led to the formation of the desired lactone in good yields, with the non-alkylated lactone (R=H) as the sole side product (Scheme 11). Interestingly, these reactions could be performed under ambient conditions and did not require the use of dry or deoxygenated solvents.

Anodic Oxidation
0.3 eq. NaOMe
5 eq. RCOOH
Yields 31 - 58%
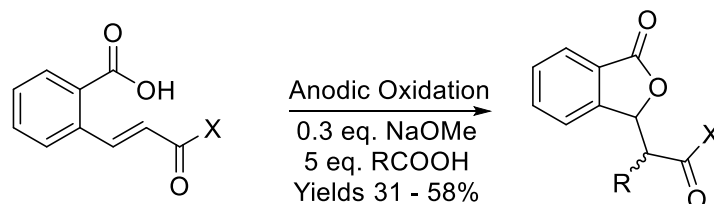
Electrolysis mode: Galvanostatic, J= 100 mA.cm^{-2}
Electrodes type: Platinum
Cell type: Undivided
Substrate concentration: 40 mM
Solvent/temperature: MeOH at room temperature

58%	45%	46%	31%

42%	65%	43%	33%
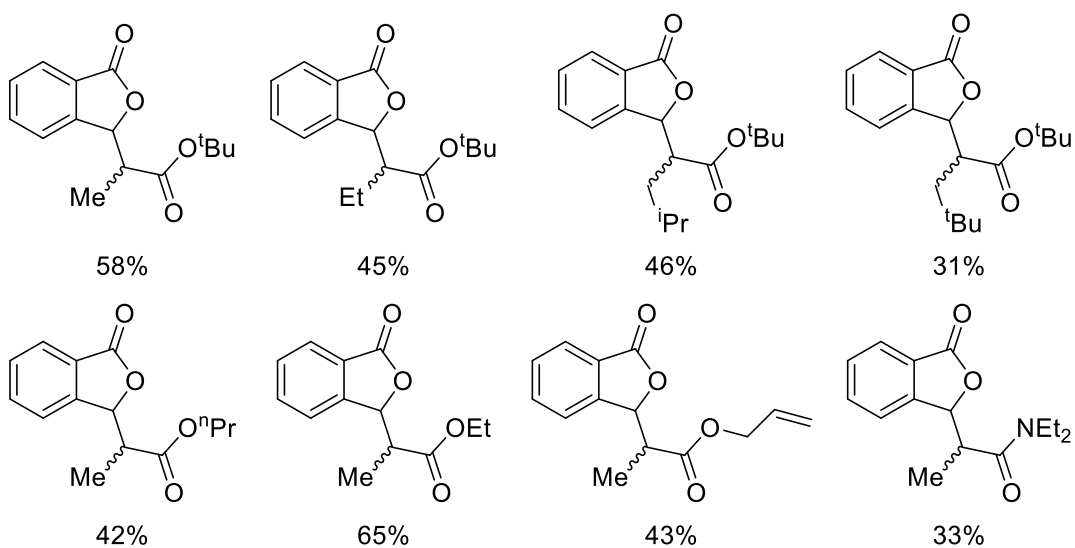
Scheme 11. General scheme and scope of the electrochemical lactonisation procedure

The lactonisation tolerates a wide variety of functional groups. However, electrolysis of 2-vinylbenzoic acid tended to result in polymerisation, and only afforded traces of the desired

phthalide. Moreover, secondary and tertiary aliphatic carboxylic co-acids failed to produce the desired compounds, presumably due to the ease with which their associated radicals are overoxidised into their corresponding carbocations.

Optimal yields were obtained when using a current density of 100 mA.cm^{-2} and, although slightly better yields could be obtained using a mixture of MeCN and water as the solvent, an increase in side-product formation was observed, thus complicating purification. No notable decrease in yield was observed upon increasing the scale to using 2 g of substrate.

Events occurring during the initial electron transfer remain unclear since benzoic acid derivatives have been reported to be inert towards Kolbe electrolytic conditions,[18] possibly due to their higher oxidation potential (1.9 *vs* SCE for benzoic acid[67] and 1.24V *vs* SCE for acetic acid[68]) or a probable different mode of adsorption on the electrode.

A possible mechanism for this reaction begins with the oxidation of the aliphatic co-acid and the formation of an alkyl radical which could then oxidise the aromatic carboxylate (Figure 6). The newly generated aroyloxy radical would then undergo a five-*exo*-trig cyclisation leading to the formation of a phthalide ring and a new carbon-centred radical. Finally, this radical is trapped by recombination with a second equivalent of alkyl radical to afford the desired functionalised phthalide. A direct addition of the co-acid radical on the alkene was ruled out since the electrolysis of ethyl cinnamate in presence of acetic acid did not lead to any significant amount of radical addition product under the electrochemical conditions used for the generation of phthalides.
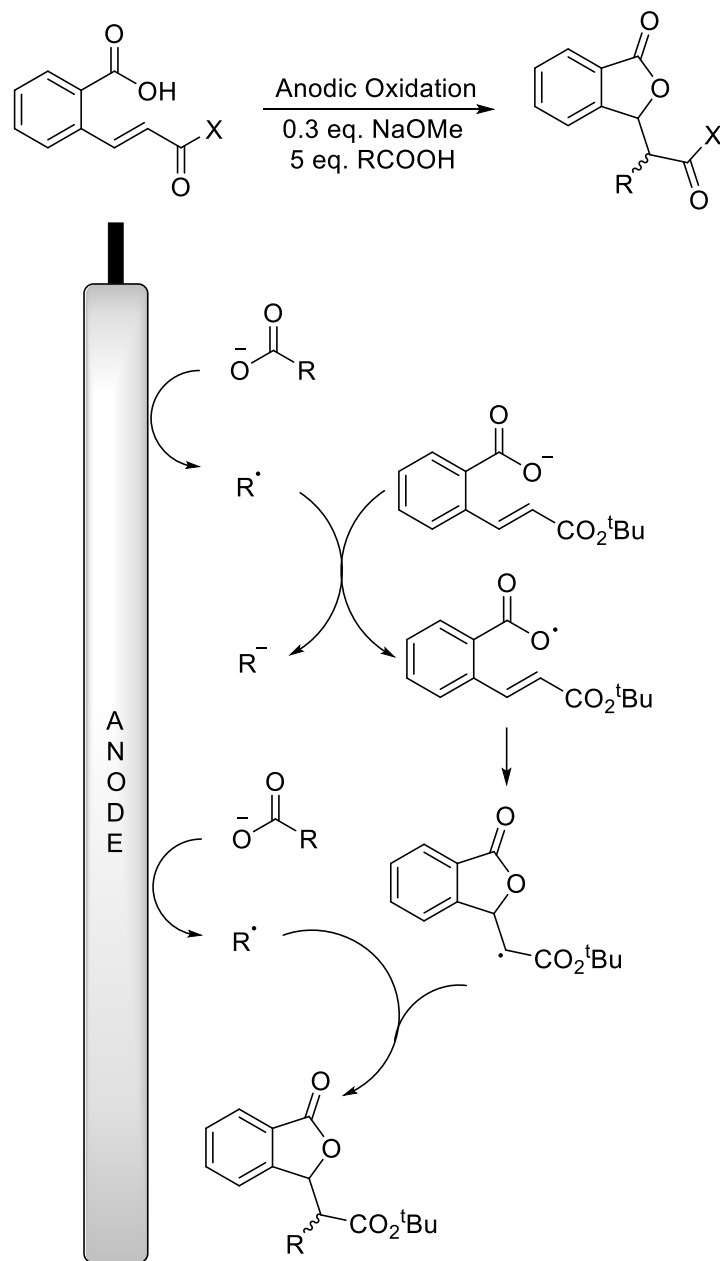
Figure 6. Mechanism for the synthesis of functionalised phthalides

Interestingly, lactones could also be formed by a less obvious disconnecting approach, which relies on the formation of oxycarbonyl radicals. While hemioxalic acids are unstable, their corresponding ammonium salts are easily prepared by treatment of the corresponding acid with a methanolic ammonia solution. Electrolysis of easily-prepared hemioxalate ammonium salts in the

presence of inexpensive aliphatic co-acids led to the formation of a range of γ-substituted butyrolactones, with the sole by-products being the dimer of the decarboxylated co-acid, carbon dioxide and ammonia (Figure 7).[69]
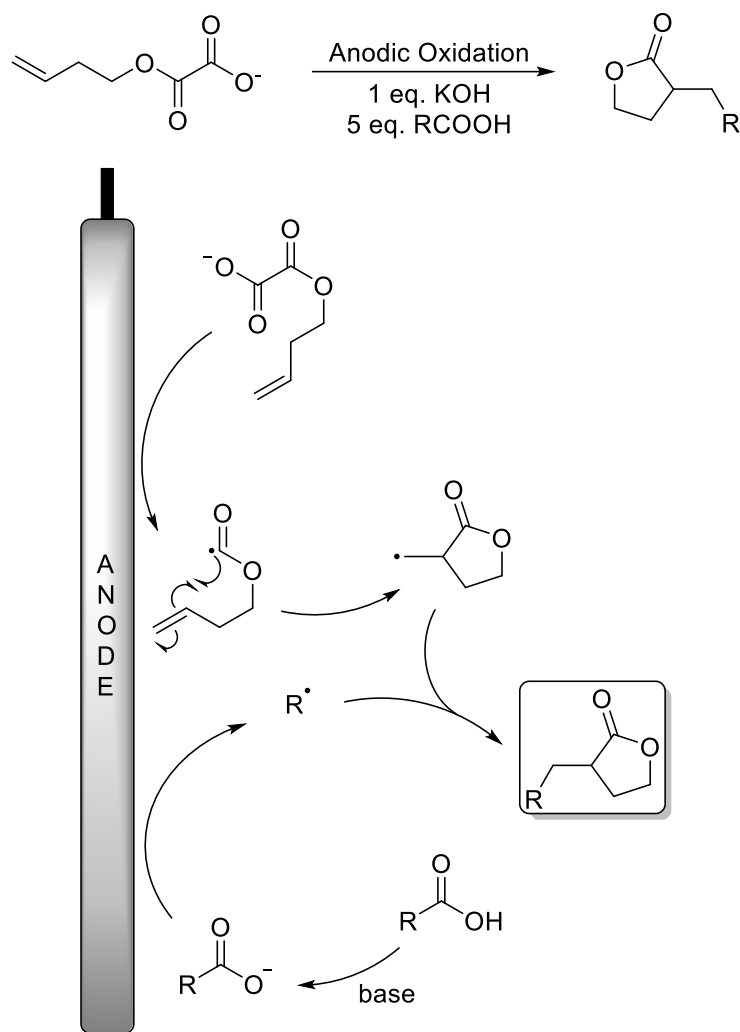
Figure 7. Mechanism for the anodic lactonisation of hemioxalate salts

The length of the co-acid alkyl chain had little effect on the outcome of the coupling, nor did its steric bulk (Scheme 12). This methodology was tolerant of both secondary co-acids and those containing halogens, both of which are not usually feasible by radical-based electrochemical methodologies.
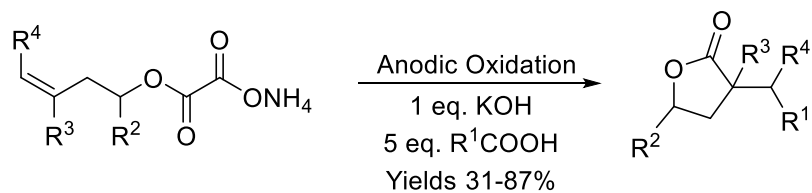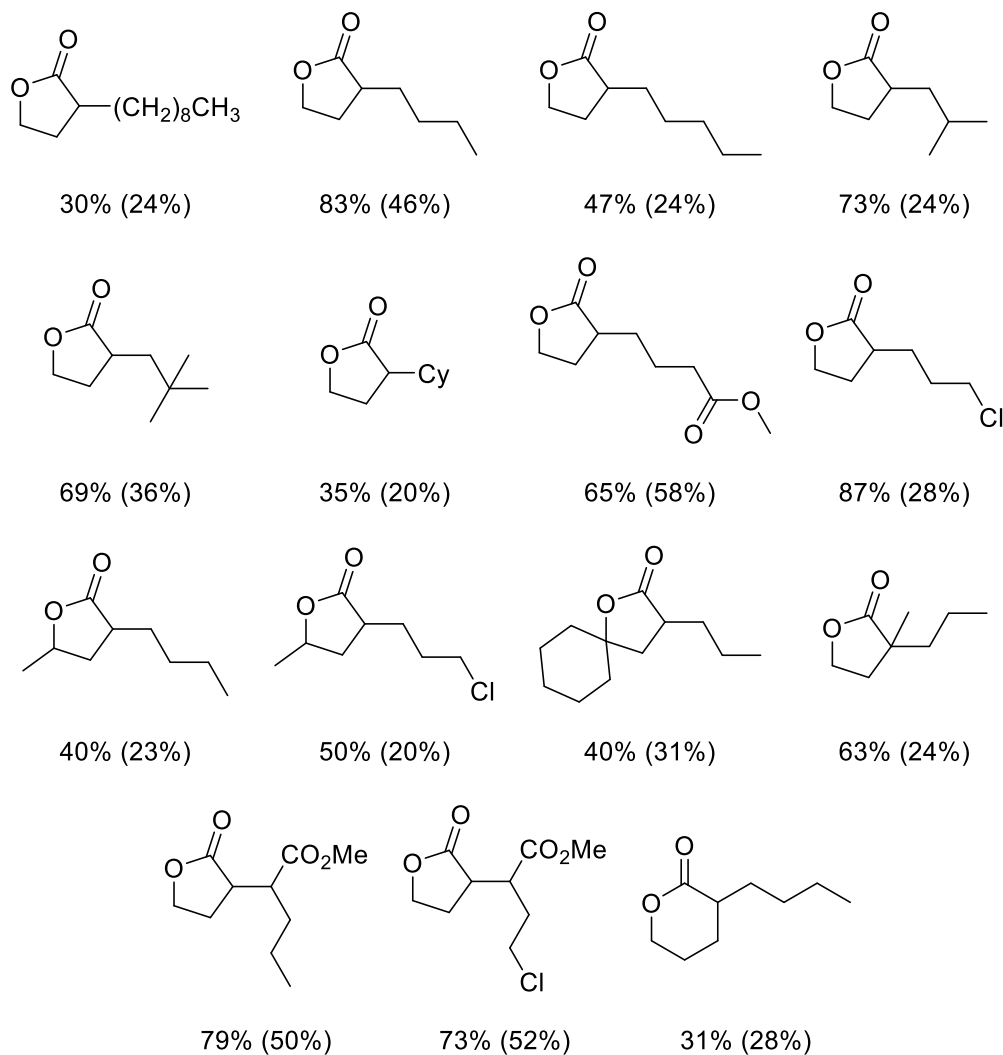
Scheme 12. General scheme and scope of the electrochemical lactonisation of hemioxalate salts.

NMR yields are reported due to the volatility of the compounds (isolated yields are in quotes).

Modification of the hemioxalate salt in either the α-, γ-, or terminal-position allowed for further functionalisation, with these substituents retained in the final lactone product. Furthermore, increasing the length of the carbon chain of the hemioxalate provided access to δ-valerolactones under similar electrochemical conditions. While the reaction conditions are similar to those used for the synthesis of phthalides, the outcome and mechanism are significantly different (Figure 7). Oxidation of the hemioxalate salt results in a decarboxylation to afford an oxycarbonyl radical, which rapidly undergoes a five-*exo*-trig cyclisation and forms a carbon-centred CH_2 radical. This radical is then trapped with alkyl radicals, which are generated concurrently *via* the decarboxylation of aliphatic carboxylates, to afford the desired γ-butyrolactone. This new methodology offers a new, practical and economical way to access functionalised lactones.

2.3. Electrochemical Methoxymethylation

Methoxymethyl (MOM) ethers are often used to protect alcohols and phenols due to their high tolerance toward a range of reaction conditions.[9,70–72] However, these are often generated using an excess of the highly carcinogenic chloromethyl methyl ether (MOMCl) under basic conditions.[9,73–75] Common alternatives, such as those employing formaldehyde dimethyl acetal are not always practical due to its inherently low reactivity. The electrochemical methoxymethylation of alcohols can circumvent these typically encountered problems and represents a green and safe approach for the synthesis of MOM-type ethers.[9,76,77] The electrolysis of α-alkoxy carboxylic acids, which were prepared by Williamson etherification of the desired alcohol, under Hofer-Moest conditions using graphite electrodes in methanol afforded high yields of the desired MOM-type ether in excess of 75% (Scheme 13).[38,78] When a high current density was used (100 mA.cm^{-2}), subsequent

purification was no longer necessary. Additionally, the electrolytic reaction has shown to be extremely robust since it does not require the use of dry or deoxygenated solvents.

$$R^1O\text{-}CH(R^2)\text{-}COO^- \xrightarrow[-CO_2]{-e^-} R^1O\text{-}\overset{\bullet}{C}(R^2) \xrightarrow{-e^-} R^1O^+{=}CHR^2 \xrightarrow{MeO^-} R^1O\text{-}CH(R^2)\text{-}OMe$$
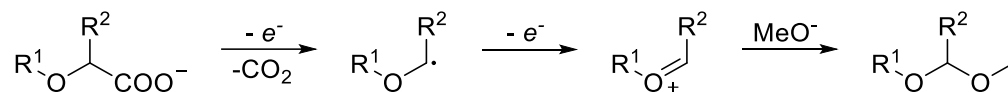
Scheme 13. General scheme for the electrochemical methoxymethylation of α-alkoxy carboxylic acids under Hofer-Moest conditions

First, the carboxylate undergoes a one-electron oxidation and decarboxylation to form a carbon-centred radical. The presence of an adjacent oxygen atom and the use of carbon electrodes rapidly promotes a second oxidation to form the corresponding oxonium. The oxonium is then trapped by the solvent to form the desired MOM-type ether.

Neither the current density nor the nature of the base, which is used to afford the small amounts of carboxylates and therefore facilitate conductivity, were found to have an impact on the reaction outcome. Steric hindrance has little impact on the reaction, the electrolysis conditions are compatible with a wide range of functional groups, and no decrease in yield was observed upon scaling-up to reactions using 5 g of substrate.

Unfortunately, this methodology possesses several drawbacks, including low current efficiency and possible overoxidation of the MOM-type ether. Using flow electrosynthesis would circumvent these problems, however, flow systems remain expensive and space-consuming. Like several groups before us,[12,79,80] we decided to develop a space and cost-efficient flow system by converting a commercially available batch-based system into a continuous-flow reactor.[10] This was easily achieved with 3D printing, whereby carbon electrodes were incorporated into a 3D printed polypropylene flow cell designed to fit into commercially available electrosynthesis equipment (Figure 8). In order to prevent passivation of the electrodes, their polarity was alternated, and the

starting material exchanged for the corresponding potassium salt, with the latter also conveniently removing the need for a supporting electrolyte and helped to monitor the passage of the compound within the flow cell.
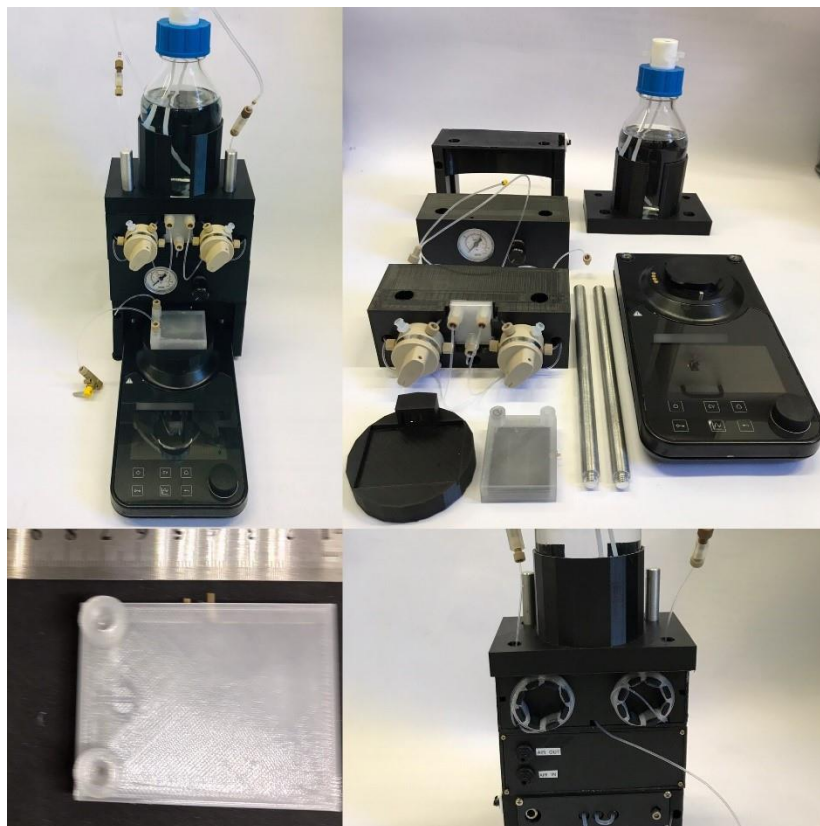
Figure 8. 3D Printed electrochemical flow experimental setup

When compared to batch experiments,[9] the flow experiments lead to either a similar or slightly higher yield (Table 7). As expected, easily oxidisable compounds (e.g. those bearing benzylic functionalities, entry 3), which are incompatible with batch electrolysis conditions, were tolerated, and excellent current efficiencies in the range of 75-80% were observed.

Table 7. Scope of methoxymethylation protocol

Anodic Oxidation
Yields 45-95%

Y = H or K
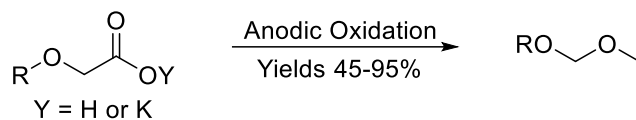
Batch (Y=H)
Electrolysis mode: Galvanostatic, J= 100 mA.cm^{-2}
Electrodes type: Carbon graphite
Cell type: Undivided
Substrate concentration: 37.5 mM + 0.25eq. NaOMe
Solvent/temperature: MeOH at room temperature

Flow (Y=K)
Electrolysis mode: Galvanostatic, J= 5 mA.cm^{-2}
Electrodes type: Carbon graphite
Cell type: Undivided
Flow rate: 0.15mL.min^{-1}
Solvent/temperature: MeOH at room temperature

Entry	Starting Material	Product	Yield / %	
			Batch (Y = H)	Flow (Y = K)
1			84	95
2			-	95
3			< 5	80
4			90	93
5			0	98
6			45	83

2.4. Electrochemical Oxidative Decarboxylation of Malonates

While the synthesis of 1,5-dicarbonyls is easily achieved through well-established chemistry,[81–83] 1,4-dicarbonyls require much more elaborate umpolung strategies.[64,84,85] It is now possible to electrochemically synthesise di- and poly-ketones and ketoesters from malonic acid derivatives using a practical and versatile umpolung strategy.[7,86,87] Malonyl anions readily undergo Michael-type addition on acrylic derivatives. The electrolysis of the Michael adducts was undertaken using graphite electrodes in methanol containing 2.1 eq. of ammonia, which afforded a complex mixture of products. Treatment of this mixture with hydrochloric acid resulted in the clean formation of the desired 1,4-diketones in high yields (Table 8).

Table 8. General scheme and scope of the synthesis of 1,4-diketones
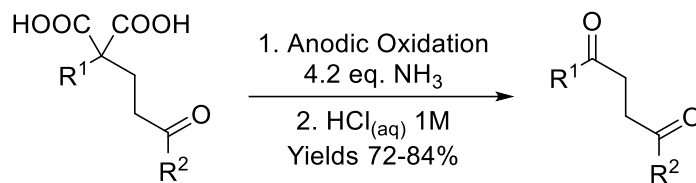
Electrolysis mode: Galvanostatic, J= 60 mA.cm^{-2}
Electrodes type: Carbon graphite
Cell type: Undivided
Substrate concentration: 12.5 mM
Solvent/temperature: MeOH at room temperature

Entry	Starting Material	Product	Yield / %
1			83
2			84
3			83
4			72

The length of the aliphatic chain has very little effect on the efficiency of the reaction, while aromatic and cyclic ketones are also tolerated. This protocol could also be employed for the electrochemical decarboxylation of tetracarboxylic acids to form both diketones and tetraketones in high yields (ca. 80%; Table 9).[7] Although the electrolysis times required are long (between five and ten hours), the ease of use and high yields counter this inconvenience.

Table 9. General scheme and scope of the electrolysis of tetracarboxylic acids

Entry	Malonic Acid Derivative	Ketone Product	Yield / %
1			85
2			82
3			77
4			86

The synthetic utility of this methodology was exemplified through the total synthesis of *cis*-jasmone, which could be prepared *via* an intramolecular aldol condensation from a diketone precursor.[88] Indeed, under electrochemical conditions, the desired diketone could be synthesised in 90% yield from the corresponding malonate derivative (Scheme 14).
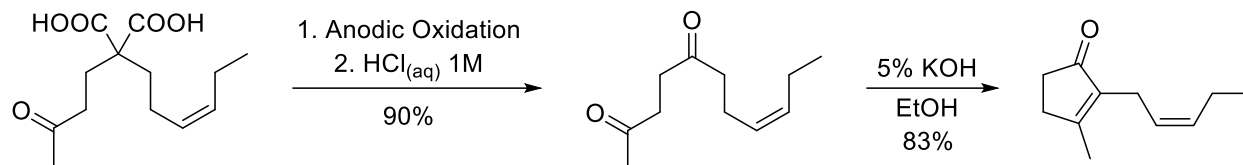
Scheme 14. Synthesis of *cis*-jasmone from an electrochemically synthesised precursor

3. SUMMARY

As we continue to strive for more efficient, cost-effective, and environmentally friendly synthetic methodologies, the revitalisation of the synthetic electrochemistry field will endure. In this account, we have shown how carboxylic acid derivatives could be used as economically-relevant, green and stable precursors to radicals and carbocations.

Aromatic esters have been shown to act as easily accessible and stable radical precursors, which facilitate both deoxygenation reactions and deprotections under both chemical and electrochemical conditions.[15] Being able the finely tune the potential of an electrode is perhaps the greatest advantage of electrochemistry, as it offers an unprecedented chemoselectivity when it comes to selectively deprotect esters as a function of their reduction potentials.[62]

It has been shown that, while reported almost two centuries ago, the use of Kolbe electrolysis conditions is still relevant to the modern chemist. The intramolecular addition of electrochemically-generated carbon centred radicals has been employed, resulting in the ability to synthesise a library of functionalised phthalides,[23] alongside 5- and 6-membered lactones under ambient conditions without the need for meticulous control of moisture and or oxygen within the electrochemical setup.[69]

Similarly, the use of graphite electrodes to promote multi-electron transfer processes has resulted in the development of both batch and continuous-flow approaches towards the synthesis of a wide

variety of methoxymethyl ethers, thus reducing our reliance on procedures which necessitate the use of highly carcinogenic reagents.[9,10] Furthermore, similar conditions have also been found to be extremely useful for the synthesis of 1,4-dicarbonyl compounds, which typically require umpolung strategies.[7]

The growing impetus of the chemical community for the development of greener alternatives to classical reactions and the increasing availability of electrochemical equipment means that electrosynthesis is on its way to becoming a "classic" method to activate molecules.

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Notes

The authors declare no competing financial interest.

Biographies

Matthew Leech received his MChem in Chemistry (2014) and PhD in Organometallic Chemistry (2019) from the University of Sussex, where he was tasked with investigating the synthesis, reactivity, and electrochemical behaviour of transition metal cyaphide complexes. He is currently a Postdoctoral Research Associate in the laboratory of Dr Kevin Lam, with his research focussed

on the electrochemical synthesis and subsequent utility of oxygen- and nitrogen-centred radical-containing compounds. His research interests include organic and organometallic electrosynthesis, molecular materials, and the chemistry of low coordinate, main group elements.

Kevin Lam received his MSc in Chemistry (2006) and PhD in Medicinal Organic Chemistry (2010) from the Catholic University of Louvain in Belgium under the supervision of Professor István E. Markó. Following a postdoctoral research stay at the University of Vermont with William E. Geiger Jr. in the field of Organometallic electrochemistry, he joined the faculty of Nazarbayev University in Kazakhstan as an Assistant Professor in 2013. In 2017, he moved to the University of Greenwich in the UK, where he is a Reader/Associate Professor in Medicinal Chemistry. His current research interests include electrosynthesis, medicinal electrochemistry, electrode surface modification and the use of analytical electrochemistry to elucidate reaction mechanisms.

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