A Practical Guide to Electrosynthesis

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Abstract | Organic Electrosynthesis is an old and rich discipline. By exploiting the cheapest and greenest source of electrons, electricity itself, electrolysis has been shown to be a powerful method to perform redox reactions under mild, safe and green conditions. The field is in the midst of a renaissance and there is little doubt that it will become one of the classic methods to activate small organic molecules in the very near future. Nevertheless, electrosynthesis can be rather daunting for a beginner. In this review, we will guide synthetic chemists through their first organic and organometallic electrosyntheses by reviewing the essential aspects of the field and by sharing practical tips. We will also cover the fundamentals of electroanalytical techniques, such as cyclic voltammetry since they are powerful methods to investigate mechanisms. Finally, these concepts will be examined in practice through three case studies.

[H1] Introduction

On March 20, 1800, Count Alessandro Volta sent a letter to the then President of The Royal Society, Joseph Banks, including a first description of a battery. It would not be exaggerating to say that it shocked the scientific world of the time; the first source of direct current was born. It did not take long for two chemists to find a synthetic use for this discovery. A little under two months later, on May 2, 1800, Sir Anthony Carlisle and William Nicholson performed the first electrolysis of water (to produced hydrogen and oxygen). Following this discovery, the electrolyses of many inorganic compounds were performed with varying degrees of success. It was not until the early 1830s, however, that Michael Faraday became interested in the electrolysis of organic compounds. In 1834, he published the following observation: "The electrolysis of a solution of sodium acetate gives rise to the formation of a gas (ethane)”.[1] The very first example of what is now known as the Kolbe decarboxylation had just been performed and the field of organic electrosynthesis was born.[2] Though the field proved to be highly popular at that time, by the middle of the 20th century, the general interest in organic electrochemistry had begun to fade. This might be partly attributed to a lack of understanding of the processes — the field has been regarded as something of a black box — but also a high entry barrier with the need to build sophisticated equipment. In addition, there was little concern at the time for the development of green or more sustainable processes. Recent technological developments in electroanalytical methods and the greater availability of standardized electrosynthetic equipment has led to a renaissance of the discipline and a resurgence of interest from the synthetic community.[3]

[H1] Basic electrosynthetic concepts

We will here discuss the basic concepts of electrosynthesis focusing mostly on practical aspects. We have deliberately kept the discussion of theoretical concepts that underly the practical to a minimum. There are several textbooks and reviews dedicated to the topic.[4–6]

[H2] Current

The easiest way to understand, intuitively, the concepts of current and potential difference is by analogy to a river.

The potential difference can be compared to the elevation of a waterfall. The river's water loses potential energy when it falls, and in the same way, an electron loses energy when moving from a high potential point to a low potential point within an electrical circuit. The electrical current is similar to the flow of a river. A high current means a rapid flow of electrons in the circuit — a high number of electrons per unit time (Eqn 1).

$$i(t) = \frac{dQ}{dt} \ (1)$$

During an electrolysis, oxidation occurs at the positively charged anode, while reduction occurs at the negatively charged cathode. Per IUPAC convention, reductions lead to negative currents while oxidations lead to positive currents. A source of potential confusion for novices here is that US chemists use the opposite convention, so one must take note of an authors affiliation before attempting to understand their discussion — especially if comparing work from two or more different labs (NB: USA use the opposite convention).

[H2] Potential

A redox couple is defined by an equilibrium between an oxidized species (O) and a reduced species (R) — with the chemical equation (Eqn 2) balanced by a number of electrons.

$$O + ne^- \rightleftharpoons R \ (2)$$

The potential (E) of a redox couple (O/R) is a thermodynamic value that reflects the oxidising or reducing power of a given species and is given by the Nernst equation, which describes the electrochemical potential of the couple at the equilibrium (**Error! Reference source not found.**), where R is ideal gas constant, T is temperature, F: Faraday constant, a_{red}: activity in reductant, a_{ox}: activity in oxidant :

$$E = E^0 - \frac{RT}{nF} \ln \frac{a_{red}}{a_{ox}} \ (3)$$

The absolute potential cannot be measured directly and is thus always given as a relative value with respect to a a reference electrode, the potential of which is set by convention. Colloquially the concepts of "potential" and "difference of potential" are used interchangeably although they are, strictly speaking, different. By convention, the standard hydrogen electrode (SHE) has a potential of 0.0 V. Electrons (from an electrode or a redox reagent) will flow from the lowest potential to the highest one. Thus, a species with a negative redox potential is one that is more difficult to reduce than a proton. To draw an analogy between electrochemical potential and a concept perhaps more familiar to synthetic chemists, an electrode with a slightly negative potential could be compared to a mild reducing agent while an electrode with a highly negative potential could be compared to a strong reducing agent.

However, the standard hydrogen electrode is rarely used in laboatories because of the safety issues posed by working with hydrogen gas and thus is complex and time-consuming to install. For studies conducted in aqueous solution, the use of an Ag/AgCl or calomel reference electrode is often preferred to the use of the SHE.[7]

In organic solvents meanwhile, the use of commercial Ag/AgCl or calomel electrodes is frequently impractical — most are aqueous references and water may contaminate the organic electrolytic solution. In addition the high electrical resistance of organic solvents is problematic. Most commerical reference electrodes have onlysmall, sintered glass dividers to enable ion mobility which dramatically increases the resistance of the system.

One solution to these issues is the use of a quasi-reference electrode, for example, a silver wire coated with AgCl (easily prepared by the electrolysis of 0.1 M aqueous HCl with an Ag anode). Such a quasi-reference can be directly immersed into the solution or separated by a highly porous sintered glass divider. The potential of such a quasi reference is unknown, and the IUPAC recommendation is to add ferrocene (Fc) as an internal standard at the end of a set of experiments and to express the measured potentials versus that of the Fc^+/Fc couple.

It is essential to appreciate the extremely narrow action range of the electrochemical potential. During an electrosynthesis, knowing the composition of the layer in the immediate vicinity of the electrode is more important than the composition of the bulk solution.

[H2] Kinetic Aspects

Just like conventional reactions, electron transfers can be analysed in terms of kinetics. The relationship between the rate (intensity of electric current) and the potential depends on both the rate of the charge transfer reaction and the rate of mass transport. As with thermal reactions, the limiting step will impose its rate on the electrochemical reaction. Unlike conventional reactions, however, the temperature is not the only factor influencing the kinetics; in electrochemical reactions, the electrode potential is the main influential kinetic factor (Butler–Volmer model).

The overpotential is an essential kinetic component. Consider an ideal electrolytic cell, with no resistance, containing an acidic aqueous solution. In theory, immersing an electrode in the solution and adjusting its potential to a slightly negative value should be sufficient to generate hydrogen gas. In reality, however, under such conditions, no hydrogen evolution occurs. A potential more negative than that predicted by thermodynamics is required before hydrogen bubbles are noticeably formed on the surface of the electrode. The difference between this potential and the theoretical potential is called the overpotential (η). It relates to the additional energy needed to compensate for the slow charge transfers. To state it differently, the need for overpotential is the result of the kinetics involved in the electronic transfer as well as from the ohmic drop (resistance). Applying a surplus of potential can accelerate these different equilibria.

[H2] Electrolysis Potential

Having reviewed the various factors that influence the electrolysis, it is now possible to establish the equation that links these factors to the applied potential of an electrolysis (**Error! Reference source not found.**) in which E_{anode} and $E_{cathode}$ are the potentials, determined by the Nernst equation, of the redox couples found at the anode and cathode respectively; R is the resistance of the solution; i the current and $\Sigma\eta$ the sum of the moduli of the cathodic and anode overpotentials. (The cathodic overpotentials are always negative).

$$\Delta E_{elec} = E_{anode} - E_{cathode} + Ri + \Sigma\eta \ (4)$$

[H1] Cyclic Voltammetry

Here we describe the main technique used in electroanalytical chemistry, in particular its use in the elucidation of electroorganic mechanisms.

[H2] Principle

The equipment needed to run cyclic voltammetry experiments consists of a potentiostat **[G]** connected to an electrochemical cell (Figure 1). Convection effects are detrimental to electrochemical measurements and must thus be avoided. The cell must therefore be placed on a vibration-free surface and the temperature carefully controlled with a thermostat.

The basic set up consists of the following:

1. A working electrode — the potential ramp is applied to this electrode and current recorded.
2. A reference electrode with a constant potential —the potential applied to the working electrode is expressed in relation to this reference electrode.
3. A counter-electrode — the potential of this electrode is adjusted using the potentiostat such that the potential difference measured between the reference electrode and the working electrode matches the desired applied potential: $\Delta E_{applied} = E_{work}(t) - E_{ref}$. The counter electrode is also essential to close the electrochemical circuit.

Cyclic voltammetry cells are standard 3-electrode setups. From a practical perspective, one selects a cell that allows the three electrodes to be immersed in a minimum of solution in order to minimise the amount of chemical needed to run the experiments. As a rule of thumb, the three electrodes should be less than 1cm apart to minimise the impedance of the system especially if, for fear of possible contamination, one decides to separate the counter and reference electrodes from the bulk of the solution, using a porous sintered glass filter. Typically, the cell is filled with 0.1M solution of support electrolyte. Oxygen is then removed and excluded from the system by sparging the solution with argon or nitrogen gas. The analyte is then added in order to produce a 1mM solution. It is crucial to have 10–100 times more supporting electrolyte **[G]** than analyte. With a lower ratio, the analyte becomes a current carrier it's resulting migration leading to ohmic drop and a biased response. Organic species tend to adsorb rapidly onto electrodes — particularly carbon electrodes — therefore it is advisable to polish the electrode between measurements to avoid a loss of sensitivity and an altered signal. This is easily achieved by immersing the electrode in an aqueous suspension of either nanometric alumina or diamond. Commercially available, disposable, screen-printed 3-electrodes setups are more expensive but avoid the need for polishing because a fresh setup is used for each experiment. Cyclic voltammetry relies on diffusion; it is therefore it is important to make sure that the solution is 'quiet'. Indeed, the solution should only be stirred between, rather than during, CV scans. With this set up in place, a linearly increasing or decreasing potential (E) ramp is applied on the working electrode with a precise sweeping rate ν (V s^{-1}) and the current (I) response of the system is recorded (I vs E; Figure 2).

From a practical perspective, the potential is increased at a defined scan rate from an initial potential (E_i) to a final potential (E_f). Until the oxidation potential (E) of the analyte is reached, the recorded current is merely a capacitive current. However, once the critical oxidation potential is reached, the analyte is oxidized and a positive current is recorded. The local electrolysis leads to a rapid depletion of the analyte from the area near the electrode and a decrease of current is observed until a plateau is reached (diffusion current). At this point, in absence of stirring, the electrolysis rate is controlled by the diffusion of the analyte from the bulk of the solution to the electrode. The potential sweep is then reversed and, depending on the system under investigation, a reductive current might be observed during the back scan giving rise to the classic "duck" shaped CV curve.

Figure 2e shows a typical example of a cyclic voltammogram. The analyte is oxidized and shows an anodic peak (E_{pa} and I_{pa}). Assuming the oxidized form of the analyte is stable and does not undergo any further chemical or electrochemical reaction, it will be reduced back during the back scan and an opposite current, I_{pc}, will be recorded. The system is then said to be chemically reversible. In a chemically reversible system, I_{pc} must be equal to the anodic I_{pa}. The number of exchanged electrons can also be determined by measuring the difference of potential between the cathodic peak and the anodic peak using **Error! Reference source not found.** in which R: ideal gas constant, T: temperature, F: Faraday constant, n: number of electrons, E_{pc}: cathodic process potential, E_{pa}: anodic process potential

$$\left|E_{pc} - E_{pa}\right| = 2.2\frac{RT}{nF} \approx \frac{56.5\mathrm{mV}}{n} \text{at } 25°\mathrm{C}\ (5)$$

If the electrolysis products are unstable and undergo a rapid chemical reaction on the cyclic voltammetry experiment time scale, no opposite current will be recorded during the back scan. The system is then said to be chemically irreversible. Equations to describe such systems are more complex and will not be discussed here. For more complex systems, Digital Simulation packages can help beginners (as well as more experienced users) to extract the thermodynamic and kinetic information out of a single voltammogram.

The chemical reversibility of a system depends on the scanning rate at which the analysis is performed. A system that appears to be irreversible at a low scan rate might become reversible, or at least partially reversible, at a higher scan rate. Therefore, by recording cyclic voltammograms at different scan rates, it is very often possible to study the different chemical kinetics that accompany the electron transfers.

The concept of "reversibility" often refers specifically to "chemical reversibility" (i.e. the stability of the electrolysed product). However, the concept of "electrochemical reversibility" also exists. An electrochemically irreversible system implies a slow electron transfer while fast electron transfers lead to "electrochemically reversible" system (also called Nernstian systems).

[H2] Chronoamperometry and chronocoulometry

Studying electrochemical changes with respect to time can provide valuable information about the kinetics of different electrochemical phenomena. The basic principle and equipment needed to perform chronoamperometry and chronocoulometry are substantially similar to those for cyclic voltammetry. During a chronoamperometric experiment, however, an initial applied potential is chosen so that no redox reaction occurs and is then quickly pulsed to a value where the redox species is active, and the resulting current vs time plot is recorded. The mathematical analysis of these currents makes it possible to extract valuable information about the kinetics of the different phenomena that occur during the electrochemical process and is especially useful to study adsorption **[G]** of the analyte on the electrode surface.[8] Although chronoamperometric methods offer some advantages over cyclic voltammetry, it comes at the cost of a loss of signature in "potentials" since discreet potentials are selected during chronoamperometry while a potential range is scanned during cyclic voltammetry analysis so the two methods are often combined.

Coulometry is the measurement of the number of charges involved in an electrochemical reaction. In other words, by using coulometry, one is able to determine the number of electrons transferred per molecule of substrate. To do this, a voltammetry is carried out beforehand in order to determine the reduction or oxidation potential of the compound under investigation. Once this value is known, the working electrode is set to this potential and, unlike in voltammetry or chronoamperometry experiment, the solution is vigorously stirred and electrolysed until the current value has fallen to 0.1% of its initial value. During this operation, the number of coulombs is recorded by integrating the current value with respect to time (**Error! Reference source not found.**), where i: the current in A, t: the time in s and Q: the total charge in C.

$$Q = \int_{t_0}^{t_{fin}} i(t)\,dt \quad (6)$$

Electronic integrators are now available which, when placed in series in the electrolysis circuit, directly measure the number of charge consumed during electrolysis.

A word of caution is necessary here. It is frequently observed that the number of exchanged electrons measured by cyclic voltammetry or chronoamperometry differs from the one found by coulometry. The difference is to the result of the time scale of the different analyses. While voltammetries and chronoamperometries are transient methods performed in less than a second, coulometry is performed over a time range from a few minutes to several hours. It is not uncommon for side chemical reactions to take place over such a long time period and, if the products are electroactive at the applied potential, they will have an impact on the final charge count.

[H2] Electrochemical parameter measurement

Here we briefly explain how the previously discussed analytical methods can be used to extract important electrochemical parameters. In order to determine the redox potential of a redox couple, voltammetry is the method of choice. It does not provide the value of the standard potential, which is essential for theoretical calculations, but fortunately it is not required for the purposes of electrosynthesis. For an electrochemically reversible system one can measure, from a voltammogram, the half-wave potential ($E_{1/2}$) — the potential at which the current is half that at the apex of the cathodic or anodic peak. In the case of an electrochemically non-reversible system, there is only one peak, and either the cathodic or the anodic peak potential is reported (E_{pc} or E_{pa}) keeping in mind that this value depends on the parameters of the CV system such as the scan rate and the concentration of the analyte.

The next question is: 'how many electrons have been exchanged?' The question may seem trivial but it is challenging to determine the number of electrons exchanged for an unknown system.

As we have seen earlier, in the case of a reversible system, it is easy to determine the number of exchanged electrons by cyclic voltammetry, whereas for a chemically non-reversible system the same task is more complex. Coulometry also allows for the determination of exchanged electrons. However, if the oxidized or reduced analyte generates a new electroactive species at the electrolysis potential, then this will impact the final electron count as further reactions occur. Coulometry thus measures the number of electrons exchanged during the global electrolysis and not necessarily the number of electrons exchanged in a specific process. Both the Compton[9] and Amatore[10] groups have developed advanced methods to measure the number of exchanged electrons using voltametric and other transient methods.

Finally, in order to propose a plausible reaction mechanism, it is often interesting to know the kinetic parameters of the system, for instance the kinetic rate constant of a chemical reaction that occurs following the initial electron transfer. For simple systems, such as an electron transfer followed by a unique chemical reaction, one can rely on the use of Shain and Nicholson's semiempirical method.[11] However, for more complex systems and in order to obtain more accurate data, the use of a softward package such as DigitalSimulation is often necessary to extract the kinetic and thermodynamic parameters from a chronoamperogram or cyclic voltammogram.[12]

[H1] Electrosynthesis

In literature descriptions of electrosynthesis, technical terms such as H-cell, standard cell or quasi-reference cell, are frequently used without proper definition and without describing the construction of the apparatus. Our aim here is to provide a practical guide such that anyone can attempt to apply organic electrolysis.

[H2] Constant potential vs constant current

Electrolysis can be conducted under two different regimes: with constant current or with constant/controlled potential. To explain the fundamental difference between the two see the general reaction scheme in Figure 3 | **(a) General reaction scheme for a reduction at constant current or potential. (b) Examples of different electrochemical cells**. Left | divided cell with removable divider. Right | Jacketed, water-cooled non-divided cell. Figure adapted from Ref. 13 with permission from The Royal Society of ChemistryFigure 3**Error! Reference source not found.**a**Error! Reference source not found.**.

Constant current electrolysis requires only a simple source of direct current (i.e. a battery) to be effective.

At the beginning of the electrolysis, **A** is available in sufficient quantity to ensure the entire current is carried by its electrolysis alone. Over time, however, the concentration of species **A** gradually decreases until there is insufficient quantity for it to provide the entire current on its own. At this point, the working electrode's potential will drift until electrolysis of species **B** begins (assuming it is electroactive) and at this point selectivity issues may arise. For example, stopping the reaction at B when it can be further reduced to C would be challenging even though some A remains)

By contrast, constant potential electrolysis makes high selectivity possible by keeping the working electrode's potential constant during the electrolysis. The drawbacks of this methods are that a longer electrolysis time is necessary and it may be necessary to use a more sophisticated electrochemical setup.

[H2] The cell

The construction of an electrolysis cell is relatively simple and is within the reach of any competent glassblower.

Depending on the reaction to be performed, it is possible to use a divided or undivided cell (Figure 3b). In the simplest of configurations, in an undivided cell, molecules are free to move to the cathode or the anode. This is not a problem if the reactant in question can only be reduced or oxidized and the product is not electroactive. However, in many cases, such a cell configuration is not appropriate. For example, in the event that the initial product may undergo a further reduction or oxidation, or if the initial electrolysis product may react with the counter electrode or one of the products generated at the counter electrode. In this case, a divided cell, equipped with a diaphragm **[G]** , should be used to separate the catholyte **[G]** from the anolyte **[G]**. The shape of the latter type of cell often resembles the letter H and as a result it is generally referred to as "H cell."

[H2] The electrodes

The electrode material undeniably plays a key role in electrolysis and the importance of choosing the right material has been reviewed elsewhere.[14,15]

The construction of an electrode remains a trivial step that consists of cutting a piece of metal or carbon and drilling into its upper part in order to attach a copper wire that will be connected to a current generator. For safety reasons, it is recommended that users insulate copper-electrode connections with Teflon. This is especially important if the electrode is used as anode since the slightest copper surface exposed to the solution will oxidize until the connections dissolve. An alternative is to use wires made from a nickel-chrome alloy. These are more resistant to corrosion and can be connected to the electrodes using an epoxy resin. The different cathode and anode materials are summarized in

Table 1.

[H2] The solvent

Electrolysis can only occur at the interface between electrode and a conducting solvent. The nature of the solvent will therefore play an important role in electrolysis and several factors must be considered.

1. The proton activity. Related to the "acidity" of the solvent in question. A solvent with a strong proton activity may facilitate the reduction of a radical anion by protonating it. It can also prevent a proton elimination reaction from an oxidation-generated radical-cation.
2. The electrochemical window. This is the range of potentials accessible to an electrochemical system. The latter depends on several factors, such as temperature, solvent, supporting electrolyte or electrode.
3. The dielectric constant **[G]**. This has direct influence on the value of the ohmic drop **[G]** (resistance) because it controls the dissociation of the electrolytes. It is therefore wise to use solvents with a strong dielectric constant.

Protic acidic solvents such as sulfuric, fluorosulfonic, trifluoroacetic and acetic acids have been used historically owing to their ability to dissolve both organic and inorganic compounds. However, their strong corrosivity and their incompatibility with certain organic compounds means they have fallen into disuse.

Neutral protic solvents are very often preferred to the previous category. Indeed, alcoholic solvents, such as methanol and ethanol, have been found to be excellent solvents to carry out oxidations in undivided cells with the reduction of the alcohol solvent occurring at the cathode. High molecular weight alcohols are typically unsuitable as electrolytic solvents owing to their poor conductivity. Hexafluoroisopropanol (HFIP), however, has recently been shown to be an ideal solvent for many electrosynthetic transformations.[16] Interestingly, water can be used as solvent for electrolysis, unless it is incompatible with the expected reaction mechanism. The main problem with water is, nevertheless, that it is a poor solvent for many organic species. A practical trick consists of using a "hydrotropic" supporting electrolyte, such as tetrabutylammonium tosylate, to increase the solubility of organic substances.[17,18] Another solution is to run an emulsion-type electrolysis by adding a phase-transfer catalyst to the cell.[19–21]

Basic amine-based solvents such as ammonia, methyl amine or ethylene diamine, have been used mostly to perform reductions and to study highly basic species such as dianions.[4] Another useful property specific to these solvents is their ability to generate solvated electrons at the cathode that can be put to use in reactions similar to the well-known Birch reduction.[22]

Aprotic polar solvents are the ideal candidates for electrosynthesis when trace amounts of protons would be detrimental to the desired reaction. In addition, it is often easier to study the mechanism of electrochemical reactions in aprotic solvents since mechanisms can vary as a function of the pH.[23] However, one must keep in mind that these solvents are usually difficult to dry and may contain residual water alongside other nucleophilic impurities. These can easily be removed by passing the solvent through a column of activated alumina immediately prior to the electrolysis.

Acetonitrile is one of the most popular aprotic solvents, whether for reductions or oxidations, owing to its large electrochemical window. In addition, the conductivity of the electrolyte solutions in acetonitrile are improved. The solvent is water soluble, and is easily removed during the workup.

Interestingly acetonitrile, unlike *N*,*N*-dimethylformamide (DMF), is a poor hydrogen atom donor in radical processes.

DMF is an excellent choice for organic electrolysis since it can dissolve a wide range of organic and inorganic compounds. The major drawback with this solvent is that it slowly breaks down into dimethylamine and formic acid. *N*-methylpyrrollidine (NMP) is a more stable alternative to DMF but is more difficult to remove at the end of the reaction.

DMSO is equally an excellent solvent that dissolved many inorganic and organic compounds. It is relatively resistant to oxidation but is easily cathodically decomposed. DMSO is not always chemically inert and can take an active role during electrolysis when it is reduced into dimethylsulfide or methylsulfinylmethylide (dimsyl) anion.

Less conductive solvents such as nitromethane, ethers and dichloromethane have been used to carry out anodic oxidations even though a large amount of supporting electrolyte had to be used.[24] Ethers are poor oxidation solvents because they are themselves easily oxidized into their corresponding oxonium, while dichloromethane releases chloride ions as a result of cathodic decomposition.

Ionic liquids have been introduced into organic electrochemistry with mixed success.[25,26] Indeed, these salts, liquids at room temperature, have large electrochemical windows. However, they are very resistant and viscous. One way to alleviate this problem is to add a small amount of DMF to the medium.[27] This solvent seems to disturb the stacking of ions and facilitates their mobility, leading to a significant increase in conductivity.

[H2] The supporting electrolyte

The passage of current through a solution depends directly on the mobility of ions found in the solution. The choice of electrolyte depends on its solubility, its dissociation in the solvent, and its chemical compatibility with the reaction one wishes to perform. If the electrolysis is being carried out in a divided cell, it is essential that both the catholyte and anolyte contain the broadly similar concentrations of supporting electrolyte. Otherwise, the solvent may migrate from one compartment to the other one during the electrolysis.

In this section we will broadly discuss the main anions and cations used in supporting electrolytes, more in-depth information, such as the solvent windows for various solvent and supporting electrolyte combinations can be found elsewhere.[24]

Perchlorates are very difficult to oxidize and therefore offer an excellent oxidation window. While lithium or sodium perchlorates are relatively stable at room temperature, even in presence of organic compound, tetrabutylammonium perchlorates should always be vacuum-dried without ever being heated. Tetrafluoroborates offer a slightly wider anodic window than that of perchlorates and importantly are much more stable. Hexafluorophosphates are also highly stable and even more resistant to oxidation than tetrafluoroborates or perchlorates. Trifluoromethanesulfonates are much more stable than perchlorates and more difficult to oxidize than hexafluorophosphates. Tetrabutylammonium triflate is also much more soluble in organic solvents than perchlorate or the corresponding tetrafluoroborate. Finally, this quaternary ammonium salt is easily prepared, in one step, from tributylamine and butyl triflate. Tosylates are so-called "hydrotropic" salts. Once dissolved in water (up to 1M), their hydrophobic properties facilitate the dissolution of organic species. The effect is even more pronounced when partnered with a tetraalkylammonium cation.

Lithium cations can be reduced into metallic lithium when a platinum electrode is used. The presence of traces of water can then lead to the passivation of the electrode through the formation of an insulating layer of lithium hydroxide.Sodium salts are rarely soluble in organic solvents and thus, with the exception of sodium perchlorate are rarely used. Tetraalkylammoniums are the most commonly employed cations in organic electrosynthesis. The halides of these cations are sometimes used, but tetrafluoroborate and hexafluorophosphate anions are usually preferred due to their large anodic window. The presence of a strong base in the medium tends to degrade tetraalkylammonium salt into trialkylamine via a Hoffmann-type degradation.

[H1] Case Studies

Here we use three case studies that illustrates three key concepts associated with electrosynthesis: The impact of the nature of the electrodes, the influence of the supporting electrolyte and the importance of the electroanalytical studies to elucidate a redox mechanism and developing a new reactivity.

[H2] Importance of the electrode material

Here we will describe how the nature of the working electrode could dramatically change the outcome of an electrosynthetic reaction in this case an anodic decarboxylation of carboxylic acids.

In contrast to most organic electrosyntheses, the electrochemical behaviour of carboxylic acids has been thoroughly studied. The Kolbe reaction or anodic oxidation of carboxylates[2] was among the first reported organic electrosyntheses,[1] if not the first, with many articles published on the topic.[28–32]

In the Kolbe reaction, a carboxylate anion RCO_2^- is oxidized at the anode to produce the corresponding carboxyl radical ($RCO_2^{\bullet}$). When R is an alkyl group, a decarboxylation occurs very rapidly and leads to the formation of an alkyl radical $R^{\bullet}$. The outcome of the reaction is slightly different when R is aromatic. Although an aroyloxy radical is still produced, its decarboxylation is much slower than for the aliphatic analogues.[33] Typically, the reaction is carried out on an alcoholic solution of the carboxylic acid that has been partially neutralized (usually up to 25%) and the electrolysis is performed in an undivided cell using platinum electrodes. Interestingly, CV experiments show that the solvent is actually easier to oxidize than the carboxylate! One might then wonder how the reaction could still proceed. The key to understanding this is that, during an electrolysis, composition of the electrode and the layer of solution surrounding it very often matters more than the composition of the bulk of the solution. Indeed, the use of high current densities (usually higher than 100 $mAcm^{-2}$) during the electrolysis helps to ensure the adsorption of the negatively charged carboxylates on the positive anode such that solvent molecules are excluded. Such high current densities also lead to a high concentration of alkyl radicals produced by the anodic decarboxylation of the carboxylic acids and favours their combination on or near the electrode's surface.[34] Finally, another key element of the reaction is the use of "smooth" anode materials such as precious metals (Pt, Au, Ir, etc.) or glassy carbon electrodes. As we will see, electrodes made from porous materials such as graphite induce a very different result.

The Kolbe electrolysis is a highly versatile method to generate radicals from simple, unactivated and readily available carboxylic acids. The method has been found to possess a wide range of applications, some of which are summarized in Figure 4.

One of the most common uses of the Kolbe reaction is the preparation of homo-dimers (Figure 4a).[29,35–38] Kolbe electrolysis has also been employed to perform unsymmetrical radical sp^3–sp^3 couplings (Figure 4b). To achieve this, a carboxylic acid (R^1COOH) 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).[39] This method has been intensively used for the synthesis of pheromone derivatives among other applications.[29,40–44] 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 (Figure 4c). The methodology was extensively used to rapidly access complex carbo- and heterocyclic compounds through a Kolbe-intramolecular cyclization tandem reaction.[29,45–47]

As noted above, when traditional Pt electrodes are substituted for graphite electrodes, the fate of the anodic oxidation is very different. In the Hofer–Moest variation of the Kolbe reaction, the radical ($R^•$), initially produced via the usual Kolbe decarboxylation is further oxidized to produce the corresponding carbocation (R^+) (Figure 4d).[28,29,48] Although other factors such as the temperature and the nature of the solvent–electrolyte system have been found to favour suchmultielectron oxidation, the nature of the anode remains the most important. The exact reason for this dramatic change in mechanism remains poorly understood. One plausible hypothesis would be that organic molecules tend to adsorb more strongly on graphite than on platinum, thus allowing enough time for further oxidation to the cation to occur.

This simple modification of the Kolbe electrolysis has been used to perform classic cationic reactions. The most common use of the Hofer–Moest reaction is depicted in Figure 4d. A carbocation is generated through the decarboxylation of a carboxylic acid, and the generated carbocation is trapped with a nucleophile. Carboxylic acids,[49] alcohols,[50] water,[51] and nitriles[52] have been found to be suitable nucleophilic partners. The methodology has been shown to be particularly useful for the modification of carbohydrates.[53] The Hofer–Moest reaction has also been applied to other classical carbocation transformations such as eliminations[54] or rearrangements.[55]

The structure of the carboxylic acid itself also has a dramatic impact on the outcome of the anodic oxidation. Oxidation of allylic, benzylic and tertiary carboxylic acids results in overoxidation of the alkyl radical to form the corresponding stabilized carbocation independent of the electrode material employed. Anodic oxidation of secondary carboxylic acids generates a mixture of carbocations and radicals.

Besides the advances in the field discussed here, more recent applications of the Hofer–Moest reaction include the mild formylation of amines[56] as well as its very promising use in the synthesis of biofuels.[57–60]

[H2] From mechanism to a new reaction

Here we will discuss how the use of electroanalytical methods helped to elucidate the mechanism of disulfide oxidation and how this ultimately led to the development of new methodology.[61] The reader will have to keep in mind that the USA current-potential convention will be used for the CV analysis (negative oxidative current, positive reduction current).

The oxidation of disulfides (R^1SSR^2) is an important biological process and has, unsurprisingly, attracted a lot of attention. For a long time, the monoelectronic oxidation of disulfides was thought to lead to the rupture of the S-S- bond and to the formation of a thionium (RS^+) and of a radical ($RS^•$) even though the sulfur-centred radical was never observed nor trapped. The radical-cation of the disulfide was also thought to be too unstable to be observed by CV. Indeed, a cyclic voltammogram of *para*-fluorobenzenedisulfide ($(p\text{-}FC_6H_4S)_2$) (dashed lines) in a dichloromethane (DCM) solution containing $[NBu_4][PF_6]$ as supporting electrolyte shows a chemically irreversible oxidation at E_{pa}= 1.29 V vs $Fc^{+/0}$ (Figure 5a). However, the reductive return scan shows a reduction at E_{pc}= −0.25V vs $Fc^{+/0}$. Although the PF_6^- anion is very often considered unreactive, it remains quite coordinating in presence of a strong electrophilic cation such as a disulfide radical-cation. When PF_6^- was substituted by a weakly coordinating anion such as $B(C_6F_5)_4^-$, a very different oxidative behaviour is observed. The oxidation of the disulfide is now chemically reversible ($E_{1/2}$=1.21 V vs $Fc^{+/0}$) and no reduction is observed on the backscan.

These two simple experiments immediately begin to shed light on the mechanism of disulfide oxidation. In the presence of PF_6^-, a coordinating anion, a chemically irreversible oxidation is observed indicating that as soon as it is formed, the disulfide radical-cation undergoes a rapid follow-up chemical reaction that leads to the formation of a new electroactive compound that could be reduced at E_{pc}= 0.25V vs $Fc^{+/0}$. In the presence of $B(C_6F_5)_4^-$, however, the radical-cation is surprisingly stable at room temperature.

The next step is to perform bulk electrolysis and coulometry of this oxidation. After bulk electrolysis in DCM containing $[NBu_4][PF_6]$ at 1.38V vs $Fc^{+/0}$, no disulfide radical cation remains. Its total consumption is confirmed by the absence of current at 1.21V vs $Fc^{+/0}$ (dashed line, Figure 5b). In this same reductive scan, the only observed reduction is that at E_{pc}= 0.25V vs $Fc^{+/0}$ (a reduction of the the product previously observed). Interestingly, this reduction is also chemically irreversible, and on the back scan a peak at around 1.21V vs $Fc^{+/0}$ indicates regeneration of the starting disulfide. Coulometry shows that ⅔ $e^-$are consumed per mole of disulfide in this reduction. When the same experiment is performed in DCM in the presence of $[NBu_4][B(C_6F_5)_4]$, a solution of the disulfide radical-cation can be obtained and no other chemical reaction is observed. The solution can be reduced to reform the original disulfide. In this case, the number of exchanged electrons per mole of disulfide is close to one. This confirms that in the presence of a weakly coordinating anion, the radical-cation of the disulfide is quite stable and only traces of the new reducible product are formed. Additional CV experiments, using different concentrations of disulfides and experimenting at different temperatures in DCM/$[NBu_4][B(C_6F_5)_4]$ show that higher concentrations of disulfide and lower temperatures both favour the formation of the reducible product.

We now have more clues about the possible nature of the reducible product. Indeed, the fact that only ⅔ e^- are consumed during the anodic oxidation of the disulfide in DCM/$[NBu_4][PF_6]$ suggests that one neutral disulfide has combined with two disulfide radical-cations to form a new compound that can be reduced back into the starting disulfide. Combined with the knowledge that radical-cations dimerize easily and that the reducible product formation is favoured at high concentration of disulfide and low temperatures we are able to propose a plausible mechanism for the reaction:

a. The formation of the disulfide radical-cation (as seen by the oxidation wave at 1.21V vs $Fc^{+/0}$ on the CV experiments)
b. The dimerization of two radical-cations (suggested by CV experiments at various concentrations and temperatures)
c. The formed dimer then reacts with one molecule of neutral disulfide (as suggested by the ⅔e^- per molecule of disulfide measured by coulometry) to form a compound that regenerates the initial disulfide when reduced.

Taken together this suggested that the identity of the new reducible compound was a trisulfide cation. Indeed, the dimer of the disulfide radical-cation would be highly electrophilic and would be attacked by a nucleophilic disulfide rapidly upon its formation. The reduction of the trisulfide cation would also be in good agreement with the formation of the initial disulfide.

The proposed mechanism (Figure 5c) was supported by chemical oxidation of the disulfide with $SbCl_5$, which was found to result in the trisulfide cation. CV of this trisulfide cation confirmed its reduction at 1.21V vs $Fc^{+/0}$ to reform the disulfide.

Ultimately a methodology for the addition of disulfides across double bonds was developed based on this mechanistic investigation.[61]

[H2] Importance of the supporting electrolyte

The choice of an appropriate supporting electrolyte is frequently overlooked in the development of electrosynthetic reactions, as it is often believed to be present solely to improve conductivity of the reaction medium and to have no influence on the reactions performed. This is not always the case, however, as exemplified by the electrochemical studies conducted by Geiger and co-workers on ruthenocene (the second-row analogue of ferrocene).[62]

Ferrocene and the ferrocenium ion exhibit almost ideally reversible redox behavior in non-aqueous media, so much so that this redox couple has been designated by IUPAC as the internal reference of choice for electrochemical studies. The electrochemical behavior of ruthenocene is far more complex.

It was initially reported that the anodic oxidation of ruthenocene using a mercury electrode was a reversible one-electron process. However, isolation of the oxidized product revealed a Hg(I) adduct, $Hg[(RuCp_2)_2]^+$, instead of the expected ruthenocenium. Oxidation (either chemical or electrochemical) of ruthenocene (Ru^{II}) was known to produce Ru^{IV} complexes although this had been attributed to disproportionation of ruthenocenium (Ru^{III}).

Instead, it was suggested that the oxidation of ruthenocene was a two-electron process when conducted in media containing traditional supporting electrolytes (i.e. $[BF_4]^-$, $[PF_6]^-$, $[ClO_4]^-$). However, this assertion could not be reconciled with the reversible one-electron process observed when oxidation was conducted in molten salts, nor with the fact that the decamethylruthenocenium ion was not observed to disproportionate under similar conditions. It was thus postulated that the supporting electrolyte, specifically its anionic component, was responsible for promoting the two-electron oxidation as a result of nucleophilic attack at the in situ generated Ru^{III} centre. A simple (reversible) one-electron oxidation could be observed when oxidation was performed in solutions containing weakly-coordinating anions at room temperature (i.e. $BArF_{24}$; Figure 6**Error! Reference source not found.**).

When electrochemical studies were carried out in low-donor solvents with supporting electrolytes comprising of weakly-coordinating anions (e.g. TFAB; $[B(C_6F_5)_4]^-$, tetrakis(perfluoroaryl)borate anion) the voltametric response observed was consistent with reversible formation of the desired ruthenocenium ion ($E_{½}$ = 0.4 V vs Fc). Slower scan rates gave little indication of dimerization, with near-reversible behaviour consistently observed. However, at high scan rates or at low temperatures, the reversibility of the voltammogram was reduced, with a cathodic wave observed at ca. −0.06 V (vs Fc at 243K; $\nu = 0.2$ V s^{-1}), which was attributed to formation of the bis(ruthenocenium) dication by analogy to the corresponding osmium system.

After exchanging the TFAB counterion for $BArF_{24}$, the reversible one-electron process corresponding to the ruthenocene/ruthenocenium redox couple appeared at a more positive potential ($E_{½}$ = 0.57 V vs Fc). Moreover, two additional cathodic product peaks were observed, with their relative amounts dependent upon the CV scan rate and temperature. An additional consequence arising from the use of $BArF_{24}$ counterions is that the electrogenerated species possessed a much greater solubility when compared to their TFAB counterparts, thus facilitating characterization using NMR spectroscopy.

Reducing the supporting electrolyte concentrations enabled NMR shimming of samples of ruthenocene that had been electrolysed at low temperatures in CD_2Cl_2 at a concentration appropriate for NMR studies (~10 mM in the metal complex). In addition to one Ru(IV) side-product, it was possible to identify three different Ru(III) species, which co-exist in a temperature sensitive equilibrium. Formation of the metal–metal dimer is disfavoured at high temperatures, as evidenced by the broadening and eventual disappearance of the Cp-H resonance at 5.38 ppm at higher temperatures. Similarly, the appearance of a pair of triplets at 5.53 and 5.02 ppm in addition to a singlet at 5.14 ppm, which integrate to 2:2:5 respectively is indicative of the formation of the dinuclear C−H activated species. The generation of $[Cp_2RuH]^+$ was evident through the presence of a hydride resonance between −7.1 and −7.3 ppm. The expected CpH resonance was highly temperature sensitive, appearing between 1.8 (298 K) and 3.7 ppm (228 K). The formation of these complexes is summarized in Figure 6**Error! Reference source not found.**.

When small quantities of $[NBu_4][PF_6]$ were added to solutions of ruthenocene containing either TFAB- or $BArF_{24}$-based supporting electrolytes the reversibility of the ruthenocene oxidation was immediately changed. When 10 equivalents of $[NBu_4][PF_6]$, were added, the reversibility of the oxidation had been completely quenched, with a shift of the oxidative process to more negative potential. This is consistent with either increased ion-pairing of the ruthenocenium with the $[PF_6]^-$ or a coupled follow-up reaction, such as the formation of a metal-fluoride or metal-F-PF_5 Ru(IV) species.

[H1] Conclusions

In this article, we have introduced organic electrosynthesis, its history, and the essential aspects of the method. An overview of the theoretical and experimental aspects has been discussed, alongside practical advice for those seeking to undertake their first electrosyntheses. Key parameters such as cell design, electrode material, solvent, and supporting electrolyte choice have been reviewed in order to demystify some of the most overlooked factors by those taking their first steps into the field. In combination with organic and organometallic electrosynthesis case studies, we have shown the dramatic effects that these parameters can have, including their ability to dramatically alter the fate of an electrosynthetic reaction.

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[H1] Competing interests statement

The authors declare no competing interests.

Table 1 | **Advantages and disadvantages of different electrode materials**

Material	Pro	Con
Mercury (cathode)	Large H_2 overpotential (can access very negative potentials) Renewable surface	Highly toxic (can form organomercurial compounds) Rarely used anymore
Lead (cathode)	Large H_2 overpotential	Easily passivated by organic compounds (needs cleaning during the electrolysis)
Silver (plated) (cathode)	Excellent for the reduction of organic halides	High cost
Nickel (anode)	Forms the strongly oxidizing agent NiOOH in basic conditions	High cost
Magnesium, aluminium, iron, zinc (sacrificial anodes)	Avoids the need for a large excess of supporting electrolyte Avoids the need for a divided cell Generates Lewis acids in-situ	Corrosion of the electrode during the electrolysis
Carbon (cathode and anode)	Highly versatile Large H_2 overpotential (as a cathode) Low cost Wide varieties available (graphite, glassy carbon, pyrolytic carbon, etc.) Easily chemically modified	Can be brittle Difficult to clean
Platinum (cathode and anode)	Highly versatile High stability Easy to clean	Low H_2 overpotential (as a cathode) High cost

Figure 1 | **An electrochemical cell used for cyclic voltammetry.** A standard 3-electrode setup comprising of a working, counter, and reference electrode, immersed in a solution of supporting electrolyte (0.1 M) and analyte (1 mM). An inert gas inlet provides a means to sparge the system with dinitrogen or argon.

Figure 2 | **Principles of cyclic voltammetry. a** | Initial sweep with potential increased linearly up to a set point. **b** | Observed current response of the initial sweep shown in part a vs potential. **c** | Reverse sweep with potential returning to intial level linearly (at the same rate as initial sweep over time). **d** | Observed current response of the reverse sweep vs potential **e** | typical cyclic voltammogram with important parameters annotated. E_{pa}: anodic peak potential, E_{pc}: cathodic peak potential, I_{pa}: anodic peak current, I_{pc}: cathodic peak current.

Figure 3 | **(a) General reaction scheme for a reduction at constant current or potential. (b) Examples of different electrochemical cells**. Left | divided cell with removable divider. Right | Jacketed, water-cooled non-divided cell. Figure adapted from Ref. 13 with permission from The Royal Society of Chemistry

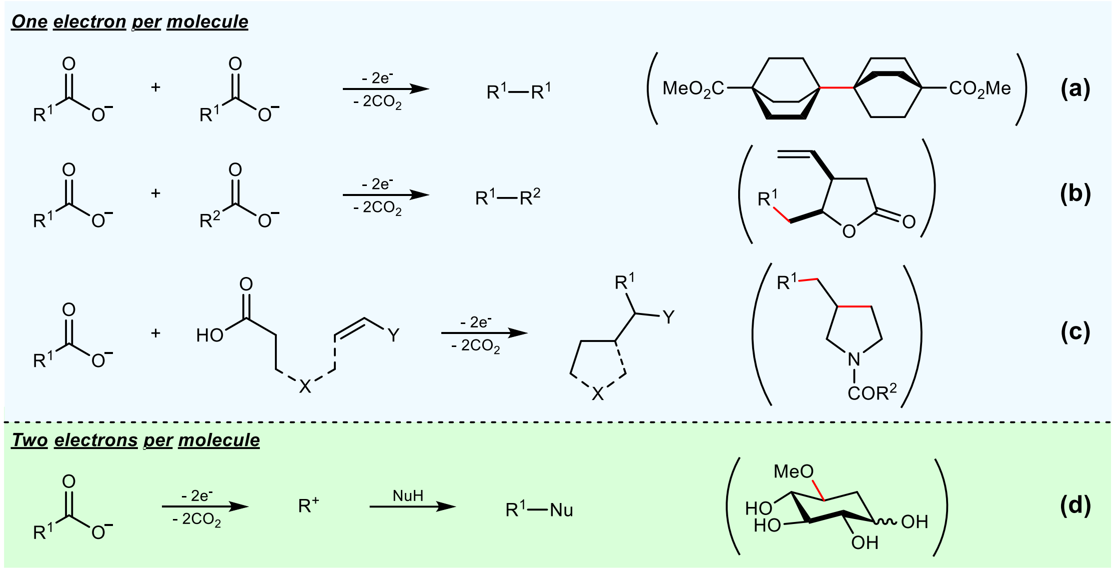

Figure 4 | **Applications of the Kolbe reaction**. **a** | Homocoupling of two carboxylates. **b** | Heterocoupling of two carboxylates. **c** | Formation of substituted carbo- and heterocycles. **d** | Hofer-Moest decarboxylation and subsequent trapping with a nucleophile. R^1 and R^2: aliphatic chains. Examples taken from references 36, 44, 45, and 53, with the formed bond(s) highlighted in red

Figure 5 | **Experimental cyclic voltammograms and proposed mechanism for the oxidation of (p-F-$C_6H_4S)_2$.** **a** | CV of (p-F-$C_6H_4S)_2$ in CH_2Cl_2/0.05 M $[Bu_4N][PF_6]$ (dashed) and CH_2Cl_2/0.05 M $[Bu_4N][B(C_6F_5)_4]$ (solid) and, scan rate = 0.2 V s^{-1}. In the presence of PF_6^- the oxidation is irreversible; the radical cation (red circles) is thus understood to have reacted further as soon as it is formed. In the presence of $B(C_6F_5)_4^-$, however, the radical cation is stable and the oxidation is seen to be reversible. **b** | CV of (p-F-$C_6H_4S)_2$ in CH_2Cl_2/0.05 M $[Bu_4N][B(C_6F_5)_4]$ before (solid) and after (dashed) bulk electrolysis, scan rate = 0.2 V s^{-1}. After bulk electrolysis no disulfide cation remains but a new product has been formed that is itself irreversibly reduced at 0.25 V vs $Fc^{+/0}$. This new product can be oxidized back to the starting disulfide. **c |** Proposed new mechanism for disulfide oxidation. Parts (a) and (b) adapted from Ref. 61 with permission from The American Chemical Society

Figure 6 | **Proposed reaction pathways after electrochemical oxidation of ruthenocene**

[H1] Glossary terms

Adsorption: The adhesion of a chemical substance (known as the adsorbate) onto a surface.
Anolyte: The electrolyte in the presence of the anode in an electrochemical cell.
Catholyte: The electrolyte in the presence of the cathode in an electrochemical cell.
Diaphragm: Alternatively a membrane or frit, a semi-permiable material which allows the flow of ions between the anolyte and catholyte compartments in a divided cell without mixing the two solutions.
Dielectric constant: A measure of the polarity of an organic solvent and its ability to insulate charge.
Ohmic drop: Also known as IR drop, a potential drop caused by the inherent resistance of the solvent, which can cause shifts in peak potential, reduce observed currents, and increase the separation between anodic and cathodic peaks.
Potentiostat: An electronic instrument which controls the voltage difference between two electrodes.
Supporting electrolyte: A chemical species that is not electroactive in the range of the applied potentials being studied, which is added to a solvent medium in order to increase its conductivity ideally without affecting the electrochemical behaviour of the analyte.