

Organic electrosynthesis: a promising green methodology in organic chemistry†

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Over the last decade, organic electrosynthesis has become recognized as one of the methodologies that can fulfill several important criteria that are needed if society is to develop environmentally compatible processes. It can be used to replace toxic or dangerous oxidizing or reducing reagents, reduce energy consumption, and can be used for the *in situ* production of unstable and hazardous reagents. These are just a few of the most important attributes that render electrochemistry environmentally useful. In this review the main characteristics of electrochemistry as a promising green methodology for organic synthesis are described and exemplified. Herein we provide basic information concerning the nature of electrosynthetic processes, paired electrochemical reactions, electrocatalytic reactions, reactions carried out in ionic liquids, electrogeneration of reactants, electrochemical reactions that use renewable starting materials (biomass), green organic electrosynthesis in micro- and nano-emulsions, the synthesis of complex molecules using an electrosynthetic key step, and conclude with some insights concerning the future. Throughout the review the “green aspects” of these topics are highlighted and their relationship with the twelve green chemistry principles is described.

1.0 Introduction

Why is electrosynthesis a green methodology?

Electrochemistry may be used for the development of new methods and processes focused on the improvement of the quality of our environment. There are several ways in which electrochemistry can help to preserve the environment:

- Sustainable energy production.^{1,2} There are important research projects focused upon the development of solar cells, hydrogen combustion cells and storage systems (*e.g.*, batteries).
- Electrosynthesis of chemical products.^{3–5} Electrons are inherently clean reactants that can be used to achieve oxidation and reduction reactions.
- Real-time monitoring of the electrochemical process. Compared to traditional chemical analyses, electrochemistry can provide a rapid feedback of the chemistry that is taking place

during a process, thereby minimizing errors and costs associated with it.

d) Treatment of pollutants. The processes called electro-incineration provides an option to eliminate pollutants that are difficult to destroy by chemical or biological routes, and which are dangerous or require expensive processes.^{6–8}

The first three topics are closely related to the postulates of green chemistry;^{1,9,10} the purpose is to design chemical processes that reduce or eliminate the use or generation of dangerous substances. Therefore, for an electrochemical process to be completely green, the electricity employed in it should also be of a sustainable origin, and be ecologically compatible. Worldwide, the electricity that is currently generated is obtained primarily from the combustion of carbon-based compounds, such as natural gas, diesel fuel, or coal. This cannot be supported indefinitely. Promising modern alternative technologies are under development (Fig. 1).¹¹

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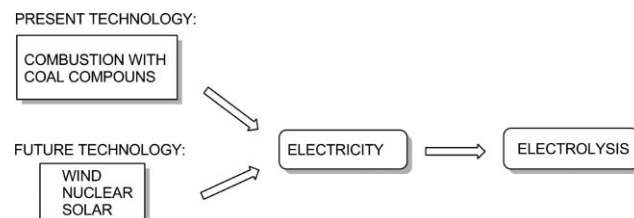


Fig. 1 Comparison of the present and future scenarios for obtaining electricity.

Fig. 2 depicts how organic electrosynthesis relates to at least 9 of the 12 postulates of sustainable or green chemistry as follows:

- When green solvents, such as ionic liquids or microemulsions are used in electrosynthesis, the method becomes more ecologically sound.

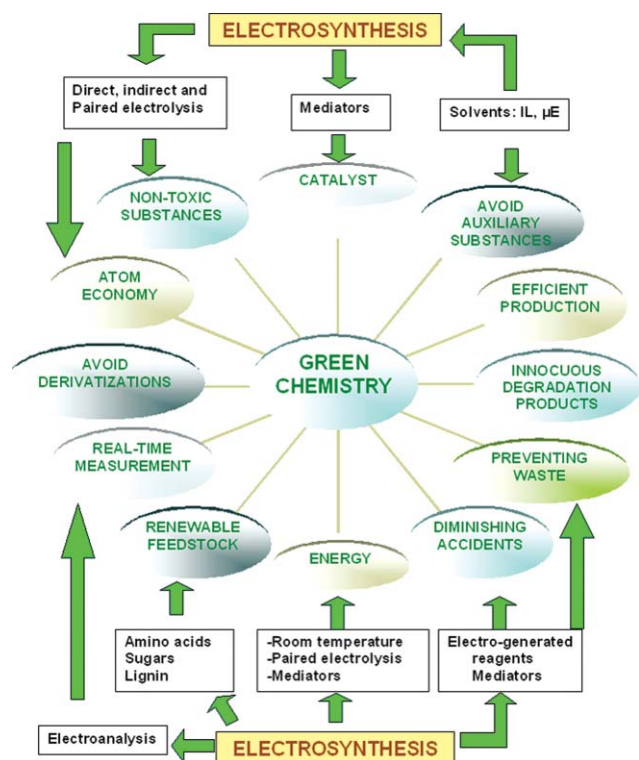


Fig. 2 Organic electrochemistry and its direct relationship to the green chemistry postulates.

b) The use of mediators provides an important option to create catalytic synthetic processes with decreased energy consumption and chemical waste.

c) The possibility to perform direct, indirect or paired electrolysis can significantly improve atom economy.

d) The use of renewable starting materials is entirely consistent with the green chemistry philosophy.

e) The energetic aspect is positively impacted when operations are conducted at room temperature or when mediators are the electron carriers in the transformations; paired electrochemical syntheses have great impact on this point.

f) Real-time monitoring can be easily achieved thanks to the possibility of coupling electroanalytical control methods during the electrolysis.

g) Safety is improved and the chance of an accident is reduced by *in situ* electrogenerating or recycling reactive species or dangerous toxic reactants.

h) Waste production can be prevented when reagents are stoichiometrically electrogenerated in the electrochemical cell.

Green organic electrochemistry

Several characteristics make the electrochemical production of organic compounds less polluting than classical methods.¹² Since electrons can be considered as redox reactants, it is possible to substitute an electric current in place of dangerous and polluting reducing and/or oxidizing reagents (*e.g.*, OsO₄, Pb(OAc)₄, NaH, Na⁰ and K⁰). Furthermore, since the energy of the electrons can be controlled through the applied voltage most of the electrochemical reactions take place at room temperature.⁴ The electrodes can also be considered as heterogeneous catalysts that

can simply be physically removed at the end of the reaction. In many instances, classical procedures take place using organic solvents of low volatility; nowadays electrochemistry conducted in ionic liquids (IL's) can be an alternative to these solvents. These IL's can be recovered in order to eliminate pollution risks and reduce costs. The use of redox catalysts and electron-mediated reactions allows one to decrease the concentration of the reactants used in traditional organic chemistry, and still preserve the selectivity of the reaction. As a consequence, it is fair to consider electrochemistry as a tool for green chemistry.

While electrochemistry has been widely studied within the electrochemical community, many organic chemists are not completely convinced of its utility as a routine tool in synthesis, in the same way that microwaves or photochemistry now are. As a result, there are currently only a few processes at the industrial or pilot-plant scale for the electrochemistry of organic molecules. We firmly believe that organic electrochemistry, particularly those aspects associated with green processes, should be more widely known and utilized by the synthetic community.

A brief historical summary of organic electrochemistry

The use of electricity in organic synthesis is not new. The first experiments reported go back to the middle of the 19th century. In 1834, Faraday performed pioneering experiments designed to demonstrate the validity of the then recently postulated transformation law that now bears his name *i.e.*, Faraday's law ($Q = nNF$, where Q = charge consumed, n = moles of electrons involved per mole of compound being transformed, N = moles of the compound being transformed, F = Faraday's constant). He observed that ethane was generated when a solution of sodium acetate was electrolyzed, and thereby performed the first electroorganic synthetic transformation.¹³

This reaction was later studied in detail by Kolbe who in 1849–1854 understood, interpreted and performed the synthesis of dimeric alkanes using organic acid carboxylates as starting materials.¹⁴ The reaction $2RCOO^- \rightarrow R-R + 2CO_2 + 2e^-$ is now referred to as the Kolbe reaction. It was used on an industrial scale until the middle of the 1980's in countries including the former USSR, Japan, India, and West Germany. In another historically important event (1890), Haber selectively prepared phenylhydroxylamine and aniline from the electrolytic reduction of nitrobenzene, and examined the effect of using different potential values upon product composition. He concluded that the nature of the product was a function of the potential applied to the working electrode.¹⁵ During the years 1960–1970, Baizer developed at Monsanto the electrohydrodimerization process of acrylonitrile on a large scale to produce Nylon fibers.¹⁶ This was the first commercially successful electrochemical reaction that catapulted the interest of industrial companies into the use of organic electrochemical processes. The most outstanding developments in organic electrochemistry were performed during the 20th century and have been thoroughly described in a historical review by Lund.¹⁷

Basic principles of organic electrochemistry

During an organic electrochemical reaction, organic molecules are activated by the addition or removal of electrons at the surface of an electrode through a heterogeneous process. The

energy of the electrons at the electrode can be modified at will by using a power supply. The addition of an electron from the cathode into the molecule's LUMO (lowest unoccupied molecular orbital), results in a reduction. The inverse process occurs at the anode, *i.e.*, the removal of an electron from the HOMO (highest occupied molecular orbital) triggers an oxidation. The electrochemical reactions of organic compounds are typically a combination of two basic events: a heterogeneous electron transfer process with the molecule (abbreviated by the symbol E) occurring at the electrode surface that leads to the formation of a reactive intermediate (radical-cation or radical-anion), and a chemical process (C) that occurs in solution. The processes can be repeated and/or combined to afford different kinetic sequences such as EE, EC, CE and ECE (Fig. 3).⁴

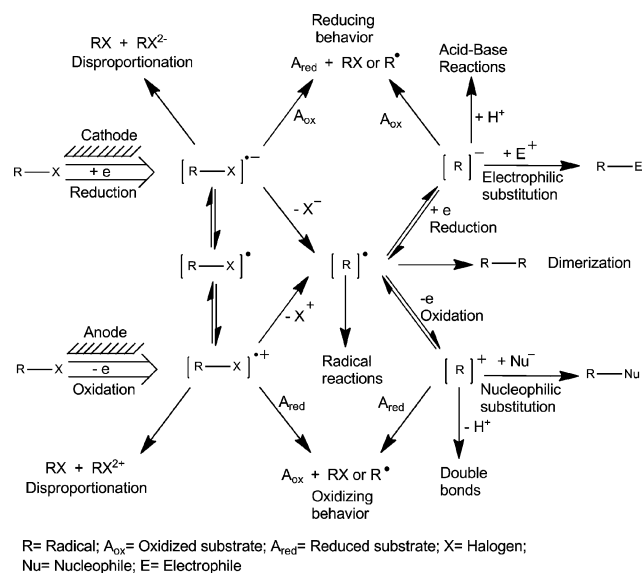


Fig. 3 Reactive intermediates formed electrochemically and subsequent chemical reactions that afford the final products during an electrochemical reaction.

Another advantage of organic electrochemistry is that a preliminary electroanalytical study of the reactivity of the molecules of interest can be simply and quickly performed using cyclic voltammetry (CV) and coulometry.¹⁸ From these studies it is relatively easy to foresee which functional groups may be oxidized or reduced. To propose a redox transformation mechanism, it is necessary to perform complementary studies that use analytical techniques that are commonly used in the field of physical organic chemistry.^{19,20,21}

Electron transfer in electrochemical processes may result in an inversion of the reactivity of a functional group (*umpolung*);²² when oxidized, electron-rich compounds become electron-deficient, and nucleophiles are converted to electrophiles. Similarly, reduction converts electron-deficient centers into nucleophilic reactive sites. This feature of organic electrochemistry is not easy to achieve by traditional organic chemistry, and is one of the most important and powerful electrochemical strategies in the synthesis of complex molecules. Hence, it is possible to propose synthetic routes that differ from those of traditional organic chemistry.

General description of the experimental method in organic electrochemistry

The aim in this section is to give a brief, non comprehensive review of the key definitions and experimental methods used in organic electrochemistry. Appropriate references complement this discussion.²³

An electrochemical reaction typically requires two electrodes (anode and cathode) in contact with a solution that contains an electrolyte. An electrolyte is a salt that provides ions to improve the conductivity of the solution. The cathode is connected to the negative pole of a direct current (DC) power source, and the anode to the positive pole (Fig. 4A). One or more electrons get removed at the anode from the compound that oxidizes most easily, and then transported through a wire (electronic conductor) to the power source and onto the cathode where, by means of another electrochemical reaction, they are transferred to the compound that is easiest to reduce. The electrode where the desired reaction takes place is called the working electrode (WE). To prevent the products obtained at one electrode from interfering with the reaction occurring at the other electrode, it is occasionally necessary to place the electrodes in separate compartments (*i.e.*, a divided cell). The division is achieved using an appropriate separator (*e.g.*, a porous material like a glass frit or a ceramic, or an ion exchange membrane such as Nafion®). Ideally the separator should easily transport ions in order to maintain a high conductivity and a low working voltage between the electrodes when using high currents, all with a minimal exchange of solvent and neutral molecules (*i.e.*, low permeability). Furthermore, it must be stable under the electrolysis conditions, and be chemically compatible with the solvent(s) and organic molecules involved in the process. For laboratory scale processes, the simplest divided cell is the H-cell (Fig. 4B).^{3,4,18}

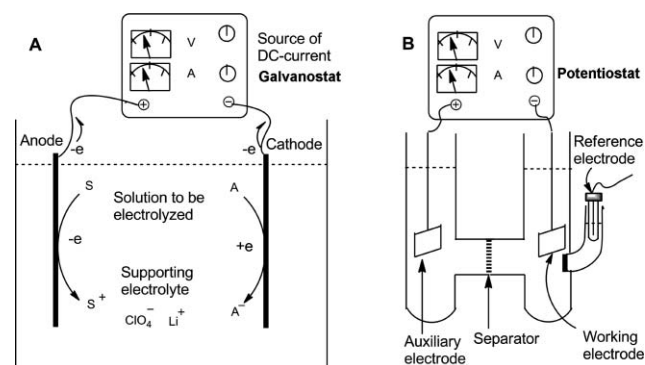


Fig. 4 A) Scheme of a galvanostatic, non divided cell for electrolysis using two electrodes. B) Potentiostatic, divided cell using three electrodes.

There are cases where the desired molecular transformation requires that the potential at the working electrode be controlled in order to selectively attack a functional group and not others that have a slightly different standard potential. This can be achieved by controlling the potential of the WE with respect to that of a reference electrode (RE) (*i.e.*, an electrode with a constant and known potential like the saturated calomel electrode – SCE). Such processes are called potentiostatic electrolyses and can produce very selective transformations. A potentiostat achieves this by employing a three electrode cell (Fig. 4B), where

current only flows between the WE, which has a fixed and stable potential, and the counter- or auxiliary-electrode (CE or AE). In most cases, the latter is used only to close the electric circuit, but we shall see later that this reaction can be useful to achieve coupled electrolyses. The potentiostat is indispensable in research laboratories and is relatively inexpensive. However, it is not practical for industrial scale processes due to the increase in cost associated with a potentiostat that could operate at the current values required in large scale transformations. In these cases, galvanostatic electrolysis is the best choice. This method only requires a two electrode cell (Fig. 4A) and controls the electrical current that flows through the cell using a DC power source or a galvanostat, either of which is much cheaper than a high current potentiostat; here, the potential of the electrodes changes in response to the electrochemical reaction occurring on them. Early during a reaction, the potentiostated and galvanostated processes produce similar transformations; however, at later stages the selectivity of a galvanostatic process is often lower than that achieved by using a potentiostat since the potential is not fixed in the former.¹⁹ Nonetheless, simpler conditions can be employed to try an electrolysis reaction for the first time; the selectivity can then be checked before going to the more complicated setup by running to partial conversion. For example, the electrolysis of 1 to 10 grams of starting material can typically be accomplished using an ordinary commercial DC power source, with a capacity of 30 to 100 V and 1 to 5 A depending on the electrode area. Some authors report the use of simple, readily available and low cost materials in order to interest those persons who might be reluctant to use electrochemistry.²⁴ The use of rechargeable lantern batteries, battery eliminators or AC-DC voltage transformers as the DC power source along with inexpensive electrodes (*e.g.*, graphite, stainless steel) and standard glassware provide examples of this approach. This tactic promises to assist organic chemists to exploit the great advantages of successful organic electrosyntheses.

Advantages and disadvantages of organic electrosynthesis

Advantages:

- The *reaction selectivity* can be controlled with the potential applied at the working electrode. Thus, the selection of one electrophore as opposed to another with a similar structure can be achieved. Unlike with the use of redox reagents, the potential can be modified at will.

- The *reaction rate* can be controlled by adjusting the current density or applied potential.²⁵

- As in classical organic chemistry, the *degree of transformation* of a molecule (regarding its oxidation state) can be controlled by managing the charge consumption.

- The *nature of the electrode* and the *composition* of the electrolyte can be used as reaction parameters to control selectivity and reaction rate.

- The electrosynthetic experimental conditions and pathway can be predicted on the basis of electroanalytical techniques.²¹

- The reaction conditions are typically mild since in general, electrolysis is performed at room temperature and atmospheric pressure.

- The electrons are environmentally-friendly reagents.

Disadvantages and possible solutions:

- Electrolysis cells are required. Fortunately, nowadays it is possible to perform reactions with materials and glassware easily found in a common organic chemistry laboratory. In addition, the use of batteries and other DC power sources provides a practical means of accessing galvanostatic techniques.

- Electrochemical reactions occur at the electrodes and are therefore heterogeneous processes. Since they typically take place at the interface between an electrode (limited in area and movement) and the electrolyte, they can be slower than homogeneous reactions. In order to improve this situation, high surface area electrodes are used (*e.g.*, felt or sponge type electrodes). Also moving electrodes offer larger mass-transport parameters. In other cases, it is possible to use mediators that act as electron carriers between the electrode and the substrate (*i.e.*, indirect electrolysis), leading to an increase in the reaction rate. In this way, the reaction of interest is performed in a homogeneous phase.

- Charge transport through the solution requires an ionic medium of high conductivity, for which the use of a supporting electrolyte is indispensable. Nowadays, ionic liquids offer an interesting alternative since the solvent is also the electrolyte and it can be composed exclusively of organic ions. The use of aqueous emulsions is also a promising strategy for organic electrochemical transformations.

- The recovery of the supporting electrolyte can cause technical difficulties and increase costs. This problem can be minimized by using micro flow cells, which have a very small distance between the electrodes.²⁶ This approach also increases the mass transport and enhances the rate of the chemical reactions that follow the electron transfer.²⁷ In this way, lower concentrations of the supporting electrolyte can be used; it can even be generated *in situ* (*e.g.*, with a sacrificial anode,²⁸ or solid-supported acids²⁹ or bases³⁰ in the electrochemical cell).

- In some of the electrochemical reactions, cells divided by a separator are used thereby leading to a higher resistance to charge transport. However, the separator can be omitted if sacrificial anodes are used. Alternatively, conductive membranes of low resistance can be employed (*e.g.*, NafionTM).

Some examples of organic electrosynthesis are described next. In each instance several postulates of green chemistry are illustrated including, for example, the use of renewable raw materials, high atom economy, substitution or decrease in the amount of toxic substances, the use of redox electrocatalysts, and new electrolysis media.

2.0 Examples of green organic electrosynthesis methods

Of the many known electrochemical transformations, those portrayed below were selected because they are clear examples of green electrochemistry, *i.e.*, they illustrate green organic synthesis or sustainable reactions using an electron as the reactant.

2.1 Paired electrochemical reactions

(Relationship to the principles of green chemistry: ENERGY, NON TOXIC SUBSTANCES, ATOM ECONOMY, Fig. 2)

When an electrochemical reaction takes place at the working electrode there must be simultaneously another electrochemical reaction occurring at the counter-electrode. This fact offers the opportunity to reduce energy and time by “pairing” the two processes so that the compounds formed at each electrode are valuable/useful and both electrodes are considered working electrodes. In most cases, only the electrochemical reaction occurring at the working electrode is considered useful, but the possibility to also use the counter electrode for the synthesis of products of interest can, in an ideal case, achieve a combined electrochemical yield (understood in this context as moles of products per unit of charge moved in the cell) of up to 200%.[§] Thus, when a mole of electrons is moved through the electrochemical cell and both electrodes perform useful chemical transformations, the total yield is simply the sum of the respective yields of the reactions that occur at each electrode (Fig. 5).

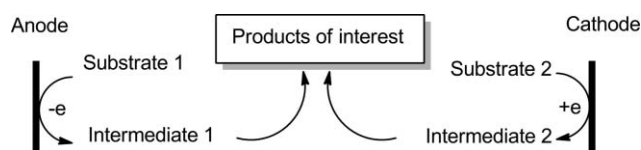


Fig. 5 General process for a paired electrochemical synthesis.

There are different types of paired reactions that differ according to the reactant source and the products obtained at the electrodes. The terms *parallel*, *convergent*, *divergent*, and *linear* are used when referring to electrochemical paired reactions.³¹

Parallel paired electrochemical processes use different starting materials, each reacting at one of the electrodes to generate different products with no chemical interaction between them during the course of the electrolysis. One example is the simultaneous production of phthalide from phthalic acid dimethyl ester, and the dimethylacetal of *t*-butylbenzaldehyde obtained from the electrolysis of *t*-butyltoluene in a non divided cell.^{12,32} This global process is used commercially to afford 4000 metric ton/year of *t*-butyldimethylaldehyde dimethylacetal. In this process, methanol (MeOH) serves both as one of the starting materials and as the solvent. Furthermore, as MeOH is released during the diester reduction at the cathode, it is also consumed by the *t*-butylbenzaldehyde generated at the anode to produce the dimethylacetal (Fig. 6). Furthermore, the protons generated at the anode are consumed at the cathode. In this ingenious process, the total atom economy[¶] is 100%.

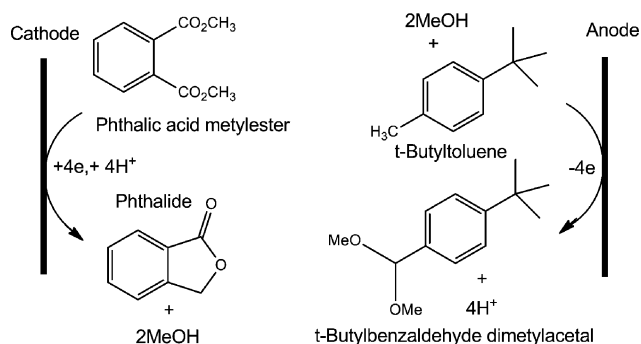


Fig. 6 Parallel paired electrochemical synthesis of phthalide and dimethylacetal from *t*-butylbenzaldehyde as starting material.

Convergent paired processes involve two different substrates undergoing either oxidation or reduction to afford products that react among themselves to generate a single product. One example is the electrochemical synthesis of cyanoacetic acid (Fig. 7).³³ The conventional synthesis—an established industrial process—is performed by mixing chloroacetic acid and a source of cyanide ions. This process is very dangerous and not environmentally friendly and can be replaced by a more ecological electrochemical method, which uses CO₂ and acetonitrile as substrates. Other examples of convergent synthesis include: a) the production of glyoxalic acid from the cathodic reduction of oxalic acid and from the anodic oxidation of glyoxal³⁴ and the nitroalkylation of thiophenols, where the electrooxidation of a thio-compound yields a sulfur-based cation. This cation reacts with the carbanion generated at the cathode by the reduction of the acidic protons of the nitroalkane.³⁵

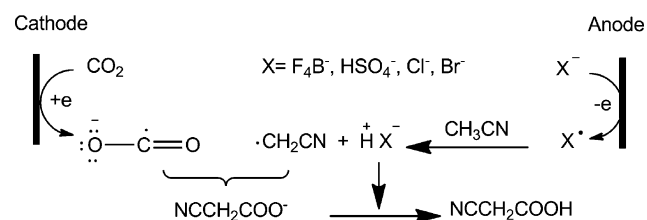


Fig. 7 Convergent paired electrochemical synthesis of cyanoacetic acid.

Divergent paired electrochemical reactions are those where two different products are obtained from the same substrate by means of different electrochemical reactions. For example, the oxidation of glucose to sorbitol is accompanied by reduction of glucose to gluconate is accompanied by reduction of glucose to sorbitol (Fig. 8). Thus, the same substrate (namely glucose) is converted into two different products by the reagents produced at the electrodes. This process is used on an industrial scale.^{36,37} The energy savings and the use of safe renewable starting materials clearly satisfy several of the postulates of green chemistry.¹⁰

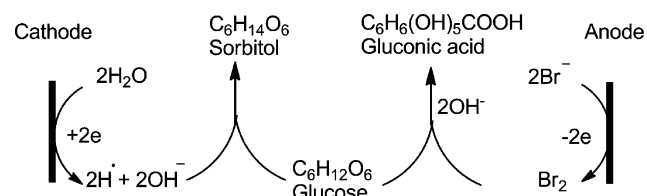


Fig. 8 Divergent paired electrochemical synthesis of sorbitol and gluconic acid, using glucose as the starting material.

Linear paired electrochemical reactions are designed to convert one substrate into one product in a system where the electrochemical reactions that take place at the anode and the cathode are different. If the current efficiency of each reaction taking place at each electrode were 100%, the theoretical electrochemical yield (see above) of the electrogenerated products would be 200%. For each mole of electrons moving through the electrochemical cell, one mole of the product is produced at each electrode. This type of process has been used for the conversion of dibutyl *N*-hydroxylamine to *N*-butyldibutylamine *N*-oxide thanks to the possibility of generating hydrogen peroxide as an oxidant from the cathodic reduction of dioxygen (Fig. 9).

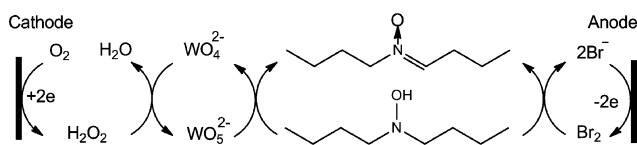


Fig. 9 Linear paired electrocatalysis of *N*-butyldenbutylamine *N*-oxide, using as a starting material dibutyl *N*-hydroxylamine.

Hydrogen peroxide reacts with a redox catalyst (WO_4^{2-}) to form the final oxidizing reagent (WO_5^{2-}) which oxidizes the substrate to the *N*-oxide. The substrate is simultaneously oxidized by Br_2 electrogenerated at the anode. In the present instance, an electrochemical yield higher than 180% was achieved for this process.³⁸

Other examples of linear paired electrocatalysis include:

- The formation of *p*-benzoquinone from benzene. Benzene is oxidized by Ag^{2+} produced at the anode by oxidizing Ag^+ , while at the cathode the $\text{Cu}^+/\text{Cu}^{2+}$ mediator system in the presence of dioxygen produces H_2O_2 that also oxidizes benzene.³⁹

- The electrocatalysis of sulfones is a similar process to that described in Fig. 9, but using a thioether.⁴⁰

- The generation of 2,5-dimethoxy-2,5-dihydrofuran involves the formation of bromine at both electrodes. Bromine then acts as a selective oxidant for the furan ring.¹²

In summary, paired reactions provide an environmentally friendly electrochemical methodology. They not only avoid the generation of toxic wastes, but also allow a more efficient use of electrical current when using the semi-reactions taking place at both electrodes to achieve specific outcomes. Energy costs are reduced and a high atom economy is achievable.

2.2 Electrocatalytic reactions

(Relationship to the principles of green chemistry: ENERGY, NON TOXIC SUBSTANCES, ATOM ECONOMY, CATALYST, PREVENT WASTE, Fig. 2)

A redox chemical reaction can take place by one of the following three processes:

a) Conventional homogeneous oxidation (Fig. 10 A) wherein the reagent is used in at least a stoichiometric amount. This leads to the formation of large quantities of the reduced form of the oxidant, which is frequently a toxic metal salt that requires further treatment and disposal.

b) Direct electrolysis (Fig. 10 B). When the electroactive substrate is transformed by means of a direct electrolysis, the electrode replaces the redox reagent. Electrolysis occurs at the electrode surface in a heterogeneous electron transfer process.

c) Indirect electrolysis or electrocatalytic reaction (Fig. 10 C).^{41,42} In the event that a direct electrolysis fails to produce the desired level of selectivity or yield, it is often replaced by an indirect process that requires the use of an *in situ* electrogenerated redox catalyst. The catalyst is regenerated at the electrode and only small quantities of the redox reagent are used. In this way, it is possible to use redox reactants that in stoichiometric amounts would be considered dangerous or toxic. A great deal of research has focused on the development of electrocatalytic methods with an environmental perspective. This redox catalyst is also known as the mediator (*Med*) or electron carrier. To be useful for indirect electrocatalysis, mediators must possess certain characteristics: the ability to be recycled, good stability in

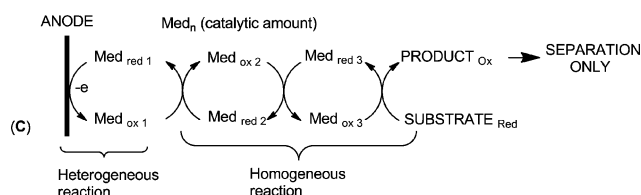
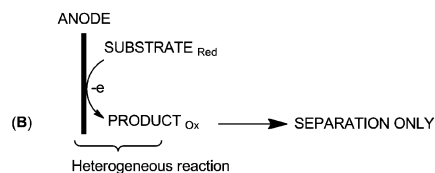
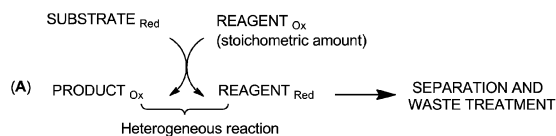


Fig. 10 Diverse pathways for redox processes in a synthetic reaction: (A) conventional homogeneous reaction, exemplified by an oxidation; (B) direct electrolysis, heterogeneous reaction; (C) indirect catalytic electrocatalytic process, heterogeneous-homogeneous.

both oxidation states, facile electron transfer from the electrode to the mediator (*i.e.*, fast electrochemical kinetics), fast electron-transfer from the mediator to the reactant, and ease of separation from the products. The mediator couple can participate in only one or in a cascade of homogeneous processes that eventually lead to the formation of the product (Fig. 10 C). This allows the development of a system where the redox couples that participate can in principle be recycled indefinitely.

As stated earlier, an inherent property of electrochemistry is that the initial redox process involves a heterogeneous step wherein electron transfer occurs at an electrode. In many electrochemical processes, this step requires the application of high voltage to obtain reasonable current densities in order to achieve useful rates of transformation. In contrast, electrocatalysis allows one to decrease the redox potential needed for a functional group transformation and also to considerably increase the reaction rate. Reactions carried out in this way may have large savings in energy consumption, a fundamental aspect within the green chemistry philosophy. Fig. 10 C shows that the indirect electrolysis combines an electrochemical step—which generates the *Med* in its active form—with homogeneous redox reaction(s) involving the active form of other *Med* and the substrate to be transformed into the product of interest.

Some of the classical organic methodologies involve the use of toxic Cr(VI) compounds. The oxidation of a primary hydroxyl group to the corresponding aldehyde is a good example. When a direct electrooxidation like in Fig. 10 B was used, it did not proceed satisfactorily.⁴³ However, when a double mediated system consisting of Br^-/Br_2 and $\text{TEMPO}_{(\text{red})}/\text{TEMPO}_{(\text{ox})}$ (TEMPO = free radical 2,2,6,6-tetramethyl-1-piperidin-1-oxo, $\text{R}_2\text{N}-\text{O}^\bullet/\text{R}_2\text{N}=\text{O}^+$) is used in the process, it proceeds efficiently (Fig. 11).⁴⁴ This electrocatalytic process has gained considerable interest and is frequently used in synthetic organic electrochemistry. Here, the selectivity of the oxidation is achieved by the redox potential of the oxoammonium salt obtained from the

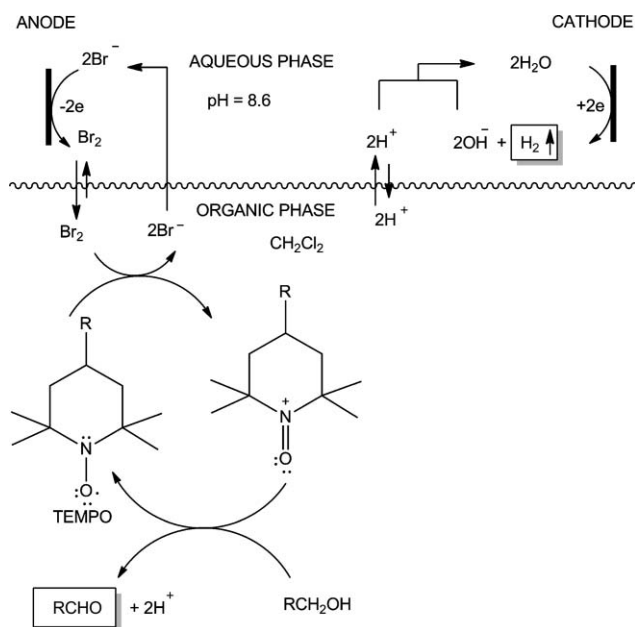


Fig. 11 General mechanism for the electrooxidation of alcohols with a double mediator $R_2N=O^+/R_2N-O^-$ and Br_2/Br^- in a two-phase system.

bromine-mediated oxidation of the free radical. Azabicyclic *N*-oxyls^{45,46} can serve as mediators in the selective oxidation of secondary hindered alcohols with better yields than with the classical non electrochemical methods. Phthalimide-*N*-oxyl radical (PINO \cdot) has a functional group similar to that of the nitroxyl radicals of TEMPO, and can be obtained readily from the electrooxidation of *N*-hydroxyphthalimide (NHPI). It is also an effective electrochemical mediator for the electrocatalytic oxidation of benzyl alcohols.^{47–49} New greener methodologies like the use of water soluble ionic TEMPO derivatives,⁵⁰ ionic liquids⁵¹ or emulsions⁵² overcome the initial disadvantage of the biphasic medium ($H_2O-CH_2Cl_2$) containing chlorinated solvents.

The most important advantages of this two-phase double mediator electrooxidation over the classical Cr(vi) methods employed in organic synthesis are:

- It minimizes pollution. By means of the electrochemical method, the TEMPO mediator is used in catalytic amounts (*ca.*, 0.01 equiv.), while in the conventional process a stoichiometric amount is the minimum quantity of oxidant required (which is often a highly toxic chromium(vi) salt). In the electrochemical process the aldehyde and hydrogen are the final products, while when Cr(vi) is used, chromium(III) compounds are generated and must be disposed of.

- The pH is not modified since the protons released during the oxidation are neutralized by the hydroxide ion generated at the cathode.

- Anhydrous conditions are not required, since oxidation is performed in a two-phase system.

- Good yields are obtained. For example a yield between 85 and 98% of the product is obtained when no double bonds nor activated aromatic rings are present in the substrate,⁵³ this is better than the yield obtained when using the conventional method (*ca.* 50%, see section 3.0).

- Simple purification. The product is concentrated in the organic phase, which contains a small quantity of the redox catalyst. Removal of the solvent affords the product.

- Low energy consumption. The indirect electrolysis increases selectivity of the reactions at the electrode.

- The end of the reaction can be visualized by the appearance of a permanent red color (due to bromine in the organic phase). It is not necessary to follow the course of the reaction by analytical techniques.

Other mediators used to carry out selective oxidation of alcohols include: iodonium ion obtained from electrooxidation of iodide ions,⁵⁴ hypobromous acid generated from bromide ion oxidation,⁵⁵ and electrogenerated bromonium ion (Br^+) obtained from the oxidation of *N*-bromosuccinimide (NBS).⁵⁶ Another significant example of this methodology is the electrochemical regeneration of chromium(vi) for the synthesis of 1,4-naphthoquinone using naphthalene as the starting material.⁵⁷

Table 1 lists several examples where electrocatalytic reactions have been used to perform redox transformations of organic molecules. As the preceding examples showed, it is clear that electrochemical methods are environmentally friendly either by using the direct or the indirect electrochemical routes. Indirect electrolysis using mediators is one of the greatest contributions of organic electrochemistry to green organic chemistry. Ongoing research focuses on the discovery of more selective and accessible mediators, from both the chemical and the economical points of view.⁵⁸ Nevertheless, there are still electrocatalytic reactions that do not meet the principles of green chemistry (for example, the use of organic amalgams)⁵⁹ and active research is carried out in this field to overcome these restrictions.

2.3 Reactions in ionic liquids

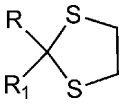
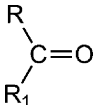
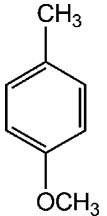
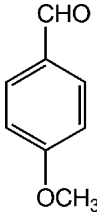
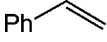
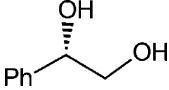
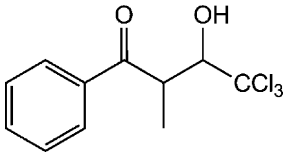
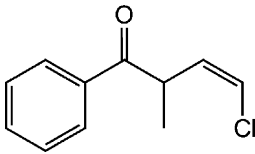
(Relationship to the principles of green chemistry: AVOID AUXILIARY SUBSTANCES, Fig. 2)

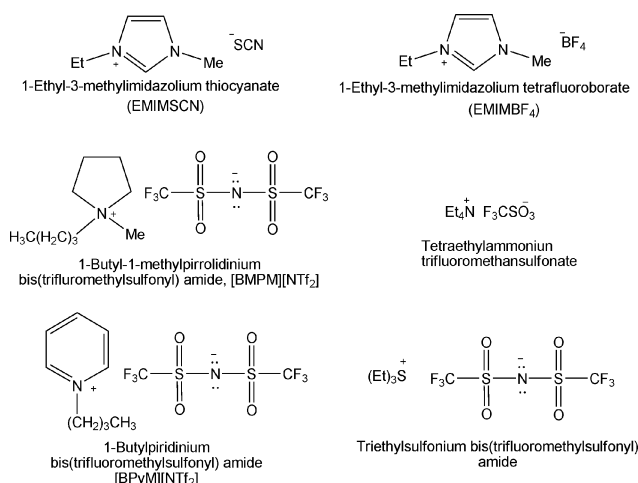
One of the major recent developments in chemistry that has transcended to the synthetic electrochemical area is the switch to ecological and easily recyclable solvents; one option involves the use of room temperature ionic liquids (RTIL's or IL's).^{65,66} Ionic liquids, as their name indicates are salts (normally organic) that exist as liquids at room temperature. Hence, their physical and chemical properties are completely different from the solutions that contain solvated ions (Fig. 12). Table 2 summarizes the principal characteristics of these liquids.

There are some properties of ionic liquids that are particularly interesting insofar as they apply to electrochemistry. These include their high ionic conductivity, non volatility and low flammability. Each of these factors provides advantages for electrochemical investigations relative to the use of standard organic solvents. The low dielectric constant of the organic solvents restricts their use in electrochemistry, while their volatility and flammability constitute safety hazards when used in large scale. Thanks to the very active research in this field observed in the last few years, there are many potentially useful ionic liquids for electrochemistry.^{67,68}

Ions dissolved in aqueous solutions constitute the most economical and practical electrolytic mixtures. Unfortunately, such media are not commonly used for organic electrochemistry, since most organic substances are not soluble in water. To generate

Table 1 Examples of electrocatalytic reactions used for redox transformations of organic molecules

Substrate	Mediator	Product	Yield (%)	Ref.
	$\text{Ar}_3\text{N}^{+}/\text{Ar}_3\text{N}^{*}$		80–90	[60]
	$\text{Ce}^{4+}/\text{Ce}^{3+}$		94	[61]
	$[\text{Fe}(\text{CN})_6]^{3-}/[\text{Fe}(\text{CN})_6]^{4-}$ $\text{OsO}_4\text{L}_2/\text{OsO}_4\text{H}_2\text{L}_2$		88	[62]
	$\text{Cr}^{3+}/\text{Cr}^{2+}$		62	[63]
ArNO_2	$(\text{C}_5\text{H}_5)\text{TiOH}^{+}/(\text{C}_5\text{H}_5)_2\text{Ti}^{+}$	ArNH_2	95–99	[64]

**Fig. 12** Structures of some ionic liquids used in electrochemistry.

a compatible conducting medium, polar organic solvents are used with dissolutions of large amounts (*ca.* 0.05 to 0.5 M) of quaternary ammonium salts. Nevertheless, the large currents required in large scale processes overheat the solutions due to the limited conductivity of these organic electrolytes. The expensive organic salts used as supporting electrolytes are not needed with ionic liquids due to the intrinsic ionic conductivity of the latter.

Another advantage of using an ionic liquid is the time saved during the purification process and the fact that a simpler separation step is used after the electrolysis. Most of the organic molecules are soluble in organic ionic liquids and the substitution of volatile organic solvents does not affect the amount of material that can be transformed during the

Table 2 The main properties of room temperature ionic liquids

Property	Advantage
Low melting-point	· Liquids at room temperature · Large temperature window
Non volatile	· High chemical and electrochemical stability · Thermal stability, non flammable · Possible recyclability
Consists of ions	· High viscosity · High ionic density · High ionic conductivity
Composed of organic or organic-inorganic ions	· Different choices of anions and cations · Synthesis by design · Varied options for their composition

electrolysis because they maintain a high solubility. The ionic liquids can be recovered efficiently because they are non volatile, and can be recycled and reused in subsequent future reactions. This option is most often not available when working with traditional organic solvents. The technical aspects of the use of ionic liquids in electrochemistry have been reviewed.⁶⁸ Their electro-activity range usually covers several volts either in the anodic or cathodic direction, and in most cases it is limited by the presence of water or impurities.⁶⁹ This wide potential range is also an advantage in electrosynthesis, since many of the functional groups of interest require high voltages.

A particularly interesting example is the selective anodic fluorination of organic molecules. The pharmacological importance of fluorinated compounds has been recognized for many decades. For this reason, it is desirable to develop an ecological and safe alternative to avoid the manipulation of hydrofluoric acid. The use of ionic liquids to achieve selective electrochemical

fluorinations has been useful in the preparation of fluorinated molecules (Fig. 13).⁷⁰ To do so, the ionic liquids $\text{Et}_3\text{N}\cdot 3\text{HF}$, $\text{Et}_3\text{N}\cdot 5\text{HF}$ or $\text{Et}_4\text{NF}\cdot 3\text{HF}$ are used not only as solvents, but also as safe and readily available sources of the fluoride ion. This ion attacks the radical-cation intermediate that is electrogenerated at the anode. The use of these materials in combination with another ionic liquid based on the imidazolium cation structure improves reactivity and increases the yield. In this mixture the nucleophilicity of the fluoride ion is improved and the electrogenerated cationic intermediate is stabilized; both factors are beneficial for the reaction.

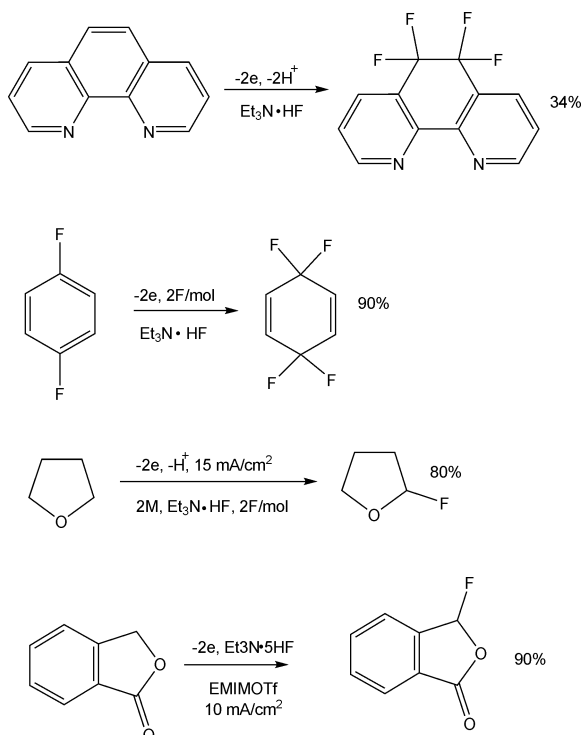


Fig. 13 Examples of selective anodic fluorinations using the ionic liquids $\text{Et}_3\text{N}\cdot 3\text{HF}$, $\text{Et}_3\text{N}\cdot 5\text{HF}$ or $\text{Et}_4\text{NF}\cdot 3\text{HF}$.⁷³⁻⁷⁶

Another important example related to green chemistry is the fixation of CO_2 into organic molecules. When CO_2 is reduced in an ionic liquid that contains an epoxide, it is possible to prepare carbonates with current efficiencies that vary from 32 to 87% (Fig. 14).⁷¹ At least in $[\text{EMIM}][\text{BF}_4]$, $[\text{BMIM}][\text{PF}_6]$ (1-butyl-3-methylimidazolium hexafluorophosphate) and $[\text{BPyM}][\text{BF}_4]$ (1-butylpyridinium tetrafluoroborate) the reaction proceeds satisfactorily. Even though a high potential is required, only a “catalytic amount” of electricity is needed, and hence very low power is consumed. This is a radical anion-initiated chain reaction where a reactive radical reduces the next equivalent of CO_2 . These reactions provide a clear example of green organic electrosynthesis. Following the same principle, the electrochemical synthesis of carbonates has also been described using alcohols as starting materials.⁷² The reaction involves the reductive activation of CO_2 using $[\text{BMIM}][\text{BF}_4]$ as the ionic liquid and an organoiodine compound. Cu was the best cathode material and the chemical yield gave 33–73% of the desired organic carbonate (Fig. 14).

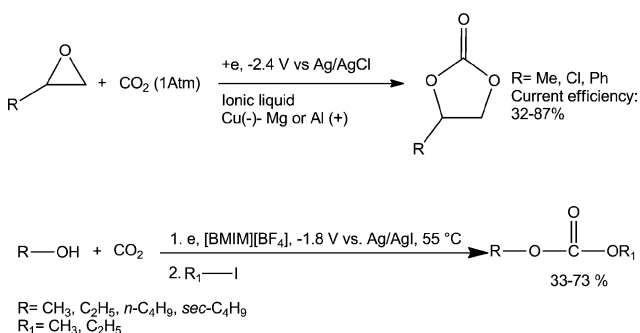


Fig. 14 Production of carbonates from the electroreduction of CO_2 in the presence of epoxides and alcohols in an ionic liquid.

For the efficient production of carbamates from amines *via* the electroreduction of CO_2 in $[\text{BMIM}][\text{BF}_4]$, it was necessary to use a higher potential than that used in the previous case. In addition, more energy was consumed (at least 2 F/mol). At the end of the reaction the carboxylate anion generated during the reaction was trapped using EtI . Both consecutive reactions were conducted in the same reaction cell (Fig. 15). Here, the use of catalysts and toxic volatile solvents—used in the classic synthetic route—is avoided.⁷⁷ Table 3 exemplifies some organic transformations carried out using ionic liquids.



Fig. 15 Production of carbamates from the electroreduction of CO_2 in the ionic liquid $[\text{BMIM}][\text{BF}_4]$.

2.4 Reactions using electrogenerated reactants

(Relationship to the principles of green chemistry: DIMINISHING ACCIDENTS, PREVENTING WASTE, Fig. 2)

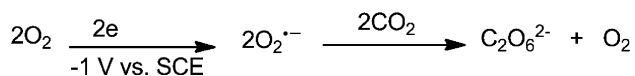
Electrolysis can lead to a variety of different reactive intermediates to be used in synthetic reactions which are not accessible by conventional methods. Some of these species have very short half-lives, and the chemical reactions that lead to them generally take place at the interface between the electrode and the solution, immediately after the electron transfer reaction. In this section, besides the electrogeneration of acids and bases, the generation and use of three electrogenerated species of synthetic interest is described as well as their relationship to green chemistry. In the case of electrogenerated acids the area around the anode is acidic, while the bulk of the solution remains essentially neutral. A larger variety of useful electrochemically generated intermediates have been reported,^{83,84} but due to space limitations these will not be discussed here.

2.4.1 Superoxide electrogeneration ($\text{O}_2^{\cdot-}$). The superoxide ion ($\text{O}_2^{\cdot-}$) can be generated by reducing dioxygen electrochemically and is a synthetically useful reagent.⁸⁵ This ion can act either as a nucleophile, a reducing agent, or a base. Its nucleophilic character is observed clearly when it is generated in the presence of CO_2 , giving rise to the formation of peroxodicarbonate, $\text{C}_2\text{O}_6^{2-}$. This electrochemical CO_2 activation is of interest due

Table 3 Examples of the use of ionic liquids in organic electrochemistry

Reaction	Yield (%)	Reference
$\text{PhCOCOOH} \xrightarrow[\text{[EMIM][Br], -1.3 V vs SCE, CG(-)-Pt(+), 80 }^\circ\text{C}]{2e} \text{PhCH(OH)COOH}$	91	[78]
$\text{RCHOHR}_1 \xrightarrow[\text{1-2 F / mol, 2, 6-Lutidine, 0.55 V vs Fc}^+ / \text{Fc (ferricinium / ferrocene)}]{\text{TEMPO cat., [bmpy][NTf}_2\text{]}} \text{RCOR}_1$	35–98	[79]
$2 \text{ PhCOCH}_3 \xrightarrow[\text{[BMIM][NTf}_2\text{]}]{2e, 1.1 \text{ F / mol}} \text{PhC(OH)(Ph)C(OH)(Ph)}$	92	[80]
$\text{PhHC=NPh} \xrightarrow[\text{Et}_4\text{N}^+ \cdot \text{p-TsO}^- \text{ (l), (Tetraethylammonium p-toluenesulfonate)}]{+2e, \text{CO}_2, 2\text{H}^+, 40^\circ\text{C}} \text{PhHC(NHPh)COOH}$	60	[81]
$\text{PhCH}_2\text{OH} \xrightarrow[\text{TEMPO, -2e}]{\text{[BMIM][PF}_6\text{]}} \text{PhCHO}$	90	[82]

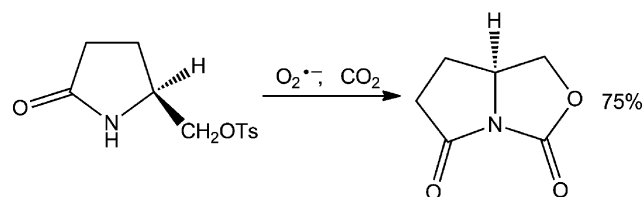
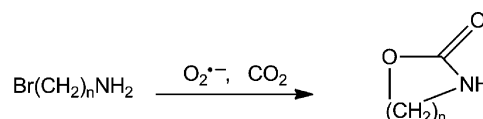
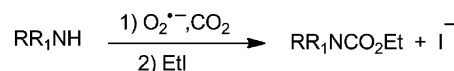
to the possibility of using this polluting greenhouse gas as a source of carbon (Fig. 16).

**Fig. 16** Electrochemical generation of the superoxide ion and reaction with CO_2 .

The indirect electrochemical synthesis of carbamides uses a system based on $\text{O}_2^{\cdot-}/\text{CO}_2$ to convert primary or secondary amines into carbamides (Fig. 17).⁸⁶ The commercial synthesis of these compounds involves the ammoniolysis of chloroformates or the addition of alcohols to isocyanates, and the use of phosgene. The electrochemical synthetic route avoids phosgene, turning it into an attractive environmentally friendly option.

2.4.2 Electrogeneration of intermediates that contain S^{2+} .

This synthetically useful but unstable sulfur species can be electrogenerated either by oxidation or reduction of elemental sulfur (S^0 as S_8). The electroreduction of sulfur generates nucleophilic species like the polysulfide anion S_4^{2-} which can participate in substitution reactions of alkyl halogens or Michael-like conjugate additions. A particularly interesting example is the

**Fig. 17** Conversion of primary or secondary amines into carbamides, using a $\text{O}_2^{\cdot-}/\text{CO}_2$ system.

synthesis of thiophenes, from the reaction between conjugated alkenes or alkynes and the anion S_4^{2-} (Fig. 18).⁸⁷

The electrooxidation of sulfur generates the species S^{2+} , while the oxidation of diphenyl disulfide (PhSSPh) produces the PhS^+ . Both electrogenerated intermediates are synthetically useful in aromatic electrophilic substitution reactions (Fig. 19).

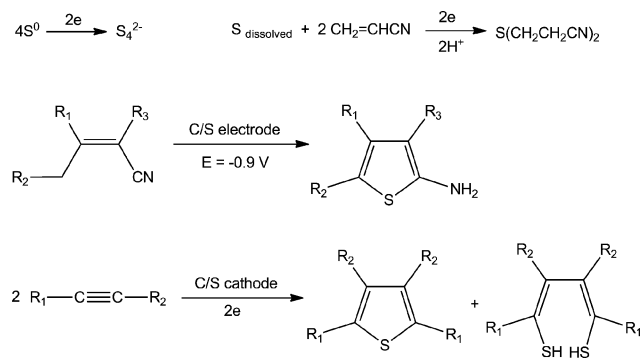


Fig. 18 Electrochemical generation of S_4^{2-} anion and its reactions with conjugated alkenes or alkynes.

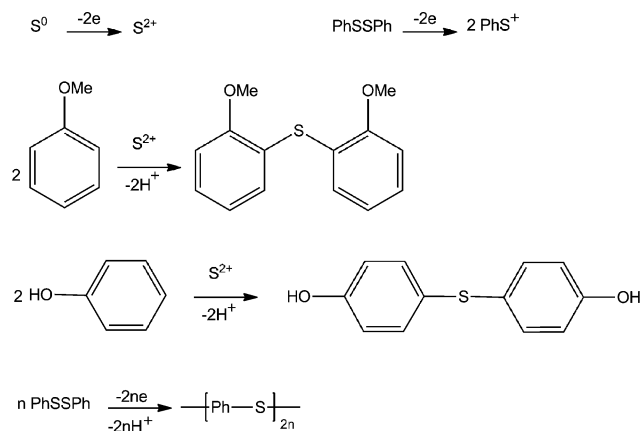
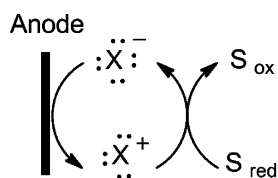


Fig. 19 Synthesis of aromatic thioethers by means of sulfur or PhSSPh electrooxidation.

2.4.3 The use of halogenonium ions (X^+) as oxidants in synthesis. The synthetically useful species chloronium (Cl^+),⁸⁸ chlorine atom (Cl^\cdot),⁸⁹ bromonium (Br^+),⁹⁰ or iodonium (I^+),⁹¹ can be electrogenerated at the anode in an electrochemical cell using the corresponding anions as starting materials. These free radical or positively charged intermediates can participate in halogenation, oxidation or cleavage reactions regenerating the starting anions, which are then reoxidized in an electrocatalytic cycle (Fig. 20). These species are selective, soft oxidants and their electrogeneration allows one to control the amount of oxidant used in the reaction.



X = Halogen; S = Organic substrate

Fig. 20 Anodic electrogeneration of halogenonium ions.

The conversion of furans to 2,5-dimethoxy-2,5-dihydrofurans can be achieved by using the oxidizing properties of these halogenonium reagents. This reaction was applied to hispanolone, a natural product that contains a furan ring in its structure (Fig. 21).⁹² When one equivalent of *N*-bromosuccinimide was added as the oxidizing agent the degra-

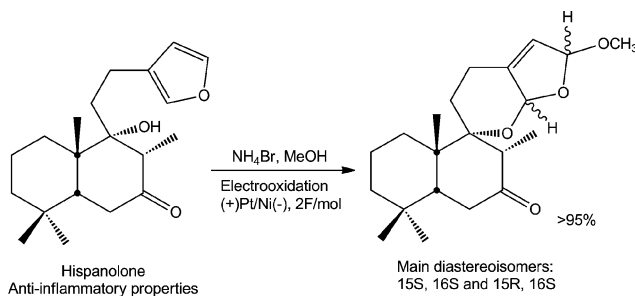


Fig. 21 Electrosynthesis of 2,5-dialcoxy-2,5-dihydrofuran derivatives of hispanolone by means of the electrogeneration of bromonium ions.

gradation of the starting material was observed; this confirms the selectivity and mild nature of the electrogenerated bromonium agent. Another option uses bromine; this dangerous oxidant is difficult to handle since its vapor pressure is low. Its electrochemical production is safer and has been applied, for example, to estrogen bromination.⁹³ Hence, the electrochemical method provides a more convenient and safer means of generating bromonium ion instead of bromine as oxidizing species.

2.4.4. Electrogenerated acids. During most electrolyses an acidic medium is generated near the anode due to the oxidation of water or traces of it that happen to be present in the solvent (Fig. 22). This has been used gainfully by organic electrochemists since the electrogenerated acid can catalyze reactions that occur near the electrode. This is referred to as functionalization, catalyzed by an *electrogenerated acid* (EGA). The ensuing acidity depends on the supporting electrolyte and the solvent used during the electrolysis. One of the most acidic systems can be obtained with $LiClO_4/CH_2Cl_2$.⁹⁴ Here metallic Li is deposited on the cathode, and in the absence of a source of protons (*i.e.*, an aprotic solvent) the metal cannot react; the perchlorate anions diffuse into the bulk of the solution. At the anode, the proton is obtained from the oxidation of traces of water; both ions generate perchloric acid which is completely dissociated due to its low concentration in the electrolytic cell.

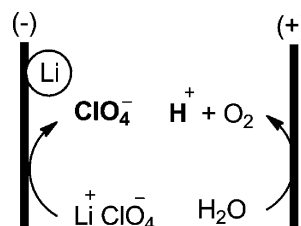


Fig. 22 Electrogeneration of an acid.

EGAs are excellent catalysts for the transformation of epoxides to ketones or acetonides (Fig. 23)⁹⁵ and also have been used in the conversion of *DL*-nerolidol to *DL*-bisabolol (Fig. 24).⁹⁶ In this system, commercial grade acetone and small amounts of $LiClO_4$ are used. When distilled acetone is used the yield decreases to 35%, which suggests that the electrolysis of traces of water is the source of protons that catalyze the reaction.

The Diels–Alder reaction of cyclopentadiene and a ketal-protected α,β -unsaturated ketone or aldehyde occurs very smoothly and efficiently in the presence of an EGA (Fig. 25).⁹⁷ The corresponding thermal process conducted using the ketal

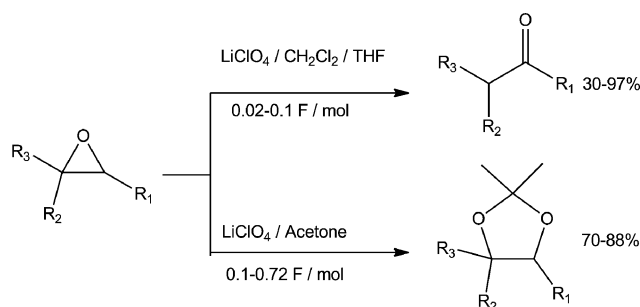


Fig. 23 An EGA acting as catalyst for the transformation of epoxides.

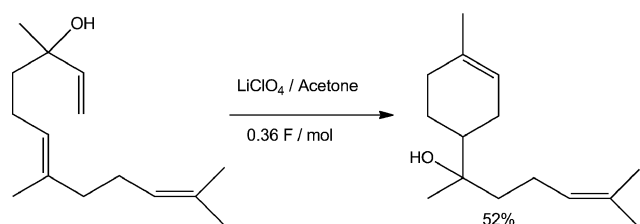


Fig. 24 Synthesis of DL-bisabolol from DL-cis-nerolidol by means of EGA.

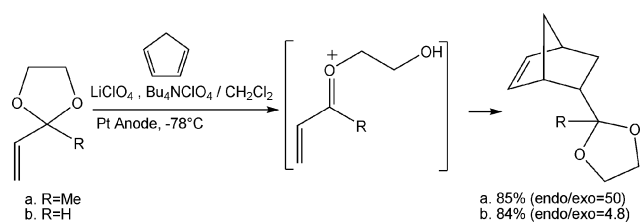


Fig. 25 Diels–Alder reaction in the presence of an EGA.

of methyl vinyl ketone in the absence of EGA gives an *endo/exo* isomer ratio of 0.7 : 1. In dramatic contrast, the presence of EGA increases this ratio to 50 : 1 and also avoids polymerization problems.

Many other reactions have taken place in the presence of EGAs, such as the acylation of aromatic rings using acetic anhydride,⁹⁴ epoxide rupture⁹⁸ and aldol condensations.⁹⁹ The use of EGA is an excellent example of how the anodic oxidation can be used to catalyze and initiate new reactions. Electrolysis offers an opportunity to keep the vicinity of the anode acidic, while the bulk of the solution remains essentially neutral. Hence, molecules sensitive to an acid medium can be used. Since the acid is generated during the electrochemical reaction, it is not necessary to manipulate or transport it, which makes this a green technique with respect to safety.

2.4.5 Electrogenerated bases. The cathodic reduction of organic compounds whose structures possess acidic protons generates anions and/or radical-anions and hydrogen. These intermediates can act as bases, nucleophiles, and/or reducing agents (Fig. 3). Compounds that produce bases by electroreduction of their acidic protons are called *pro-bases* (PBH) and the bases obtained by this method are called *electrogenerated bases* (EGB) (Fig. 26).^{36,83,100,101} The EGBs can be generated *in situ* in aprotic solvents. In this way, problems associated with the handling of strong bases (*e.g.*, corrosion, stability, *etc.*) are avoided. The correct selection of the PBH and of the counter-ion

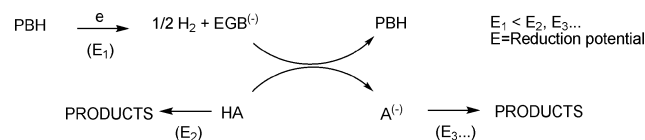


Fig. 26 Electrogeneration of a base and subsequent acid–base reaction.

used in the electrolysis¹⁰² allows one to control the strength of the EGB. Additionally, control of the amount of charge that flows through the solution assures an adequate base concentration. In this way only the necessary amount is produced, thereby avoiding waste and pollution. There are several requirements for the efficient generation of EGBs using the cathodic reduction of a PBH.^{103,83}

a) The reduction potential of the PBH (E_1) must be less negative than that of the other components present in solution and that of the electrolyte. This includes that of acidic protons of other molecules (E_2) and of the subsequent reduction of products formed during the reaction (E_3).

b) EGBs must be strong bases and at the same time weak nucleophiles and reducing agents.

c) In the cases where the PBH cannot be regenerated, a stoichiometric amount of this PBH must be used.

d) If one is interested in obtaining an anionic product (*e.g.*, enolate) the cell must be divided or use the sacrificial anode methodology.

Under certain conditions, the nucleophilicity of these anionic intermediates predominates; for this reason, the experimental conditions used for electrochemically generating the bases (*vide infra*) must be carefully selected. For example, the electroreduction of triethyl phosphonoacetate in the presence of aldehydes produces unsaturated esters with good stereoselectivity (Fig. 27).¹⁰⁴

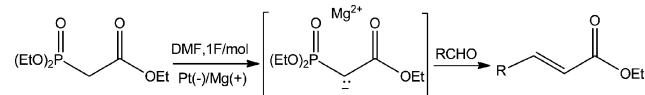


Fig. 27 Electrochemical synthesis of α,β -(*E*)-unsaturated esters in a single compartment cell (Horner–Emmons reaction) through the electrogeneration of the triethyl phosphonoacetate anion.

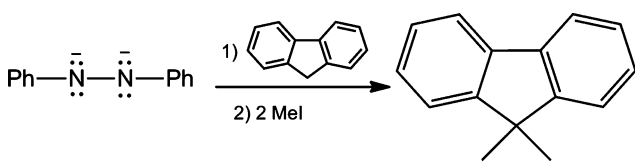
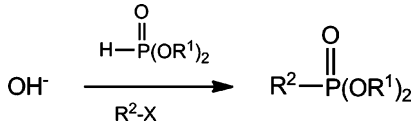
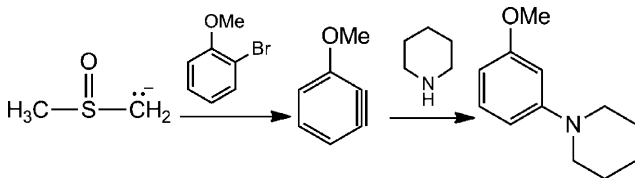
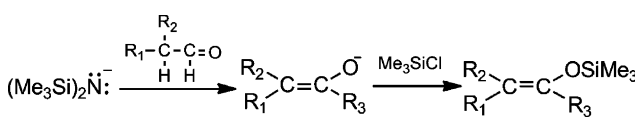
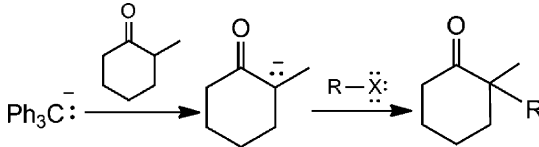
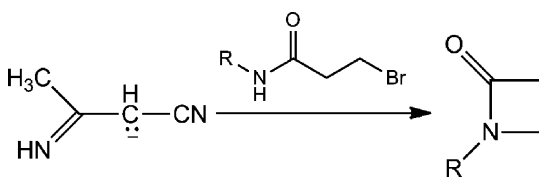
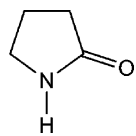
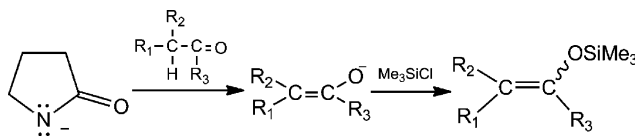
Some examples of the use of EGBs in organic synthesis are given in Table 4. These reactions show the possibility of generating strong bases in aprotic polar solvents, thus avoiding the use of potentially dangerous reactants such as K, Li, KH, alkoxides, sodamide, *etc.* Precise control of the required amounts of these species generated *in situ* reduces risks associated with their transportation and manipulation to a minimum. In summary, EGBs meet many of the requirements of sustainable or green chemistry, most of them related to safety and waste generation.

2.5 Electrochemical reactions that use renewable starting materials (biomass)

(Relationship to the principles of green chemistry: RENEWABLE FEEDSTOCK, Fig. 2)

Of great importance to research in sustainable chemistry is the use of renewable starting materials. In this manner, the synthetic

Table 4 Some examples of the use of EGBs in organic synthesis

PBH	EGB	Reaction	Yield (%)	Ref.
PhN \equiv NPh			90–98	[105]
H ₂ O			49–76	[106]
DMSO			45	[107]
(Me ₃ Si) ₂ NH			71–95	[108]
Ph ₃ CH			22–84	[109]
2CH ₃ CN			28–98	[110]
			88–82	[111]

capacity of Nature is exploited to provide useful materials (biomass). One of the 12 postulates of green chemistry indicates that the reactant (*viz.*, a substrate) must be renewable if this is to be technically and economically viable.¹⁰ This postulate has been proposed because:

1. The gradual decrease of the supply of natural reserves and the high costs of non renewable starting materials (*e.g.*, carbon and petroleum).¹¹² Hence, a progressive change in the chemical industry is suggested towards the use of renewable starting materials (raw materials).

2. The addition of oxygen to hydrocarbons to generate useful organic products has been historically one of the most polluting steps used in organic synthesis. Since naturally-occurring carbohydrates are highly oxygenated, their use in place of petroleum derivatives could eliminate this step.¹¹³

Biomass, composed of the material produced from plant growth on soil or in water, is a result of direct photosynthesis. It consists of monomers and polymers, the latter occurring in the largest amount in Nature. The most important polymers are proteins and carbohydrates. For example, cellulose is the

most abundant polymeric carbohydrate in biomass and it can be hydrolyzed to glucose by means of an electrogenerated acid in a divided cell (Fig. 28), with an excellent yield between 90–98%.¹¹⁴

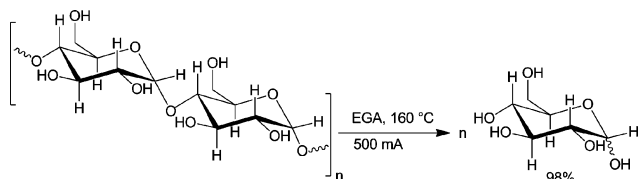


Fig. 28 Formation of glucose from the hydrolysis of carbohydrates with EGA.

Wood also contains the aromatic polymer lignin, which is the most available and renewable source of aromatic compounds.¹¹⁵ The monomers of lignin are derivatives of phenylpropene. Fig. 29 shows some of the aromatic compounds obtained by lignin electrolysis. The products of lignin reduction are used as adhesives, stabilizers, resins, and plastics.¹¹⁶ More than 20 compounds have been reported from lignin oxidation, including methyl ethyl ketone, catechol and vanillinic alcohol.¹¹⁷

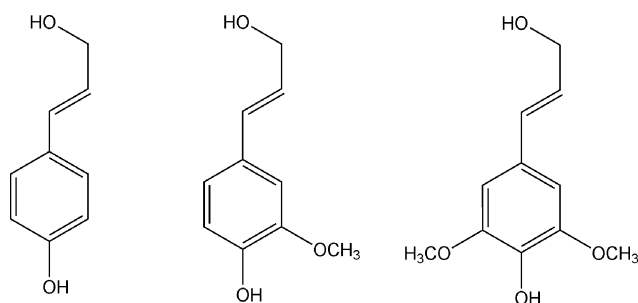


Fig. 29 Aromatic compounds present in lignin from wood.

Furfural is considered a renewable substance since it can be obtained from the hydrolysis of pentoses found in cereals. Furfural can be reduced at Cu cathodes in aqueous solution at pH 10, obtaining 90% conversion and 80% selectivity towards the formation of furfuryl alcohol.¹¹⁸ Furfural also can be electrolyzed in an electrochemical flow cell fitted with carbon felt electrodes. In this case, the paired electrolysis technique is used to produce furoic acid and furfuryl alcohol (Fig. 30).¹¹⁹ When the electrode surface area is increased, the electrochemical reaction rate is increased. In this way, two desirable characteristics for sustainable organic electrosynthesis are met, *i.e.* low energetic consumption and renewable starting materials. Both, furfuryl alcohol and furoic acid are important intermediates in industry, perfumery, and the polymer industry. A similar example is the production of L-cysteic acid and L-cystein from the paired electrolysis of L-cystine that is obtained abundantly from the feathers of farm birds (Fig. 31).¹²⁰

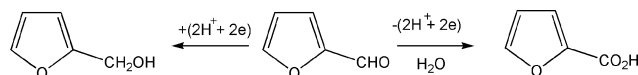


Fig. 30 Paired electrosynthesis of furoic acid and furfuryl alcohol from furfural.

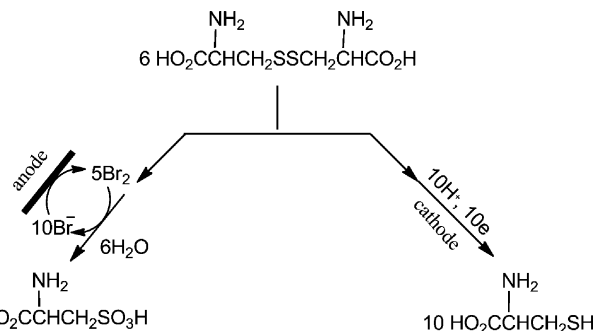


Fig. 31 Production of L-cysteic acid and L-cystein by means of the paired electrolysis of L-cystine.

An important industrial process which uses biomass is the production of carboxylic acids by the acid hydrolysis of wax esters. The whitening step involves oxidation with chromic acid of the alcohols generated during the hydrolysis to the corresponding carboxylic acids. To decrease the stoichiometric amounts of Cr(VI), the metallic salt is used in catalytic quantities and the Cr(III) produced is electrochemically oxidized to regenerate the oxidant (Fig. 32). More information about biomass electrochemical transformations can be found in the specialized literature.^{116,121}

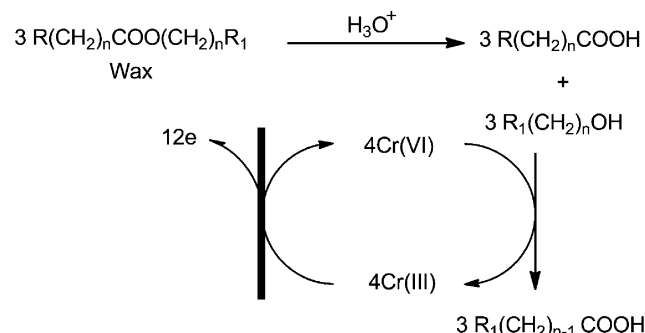


Fig. 32 Electrochemical regeneration of Cr(VI) for the whitening of waxes.

2.6 Organic electrosynthesis in micro- and nano-emulsions

(Relationship to the principles of green chemistry: AVOID AUXILIARY SUBSTANCES, Fig. 2)

2.6.1. Microemulsions. Water provides an economical and environmentally friendly medium for industrial electrolyses. However, only a few organic reagents are soluble in aqueous solutions. A viable alternative to solving this problem is to produce an emulsion that consists of the organic reactant and water. In 1950, Schulman added long chain alcohols to an oil–water emulsion stabilized by a surfactant in order to obtain stable fluids that he called *microemulsions* (μE).¹²² These μE are prepared by mixing a surfactant, a co-surfactant, oil, and water.¹²³ The diameter of these emulsions is generally around 10 to 50 nm, which is much smaller than that in conventional emulsions where it can be up to 100 μm . These μE are of great interest because of their low toxicity and cost. The surfactant molecules are found at the interface of the oil–water partition. The polar or charged groups of the surfactant (hydrophilic) are

oriented towards the aqueous side of the interface and the non polar chain (hydrophobic) is oriented towards the oily phase. In an electrochemical cell the conductivity of the μE is due to the ionic surfactant and its counter-ion dissolved in the continuous aqueous phase. In this way, the surfactant simultaneously serves the role of supporting electrolyte and of μE generator.¹²⁴ Two kinds of μE are useful in electrochemistry (Fig. 33):

- Oil–water microemulsions, in which the oil drops are surrounded by water molecules. The resulting diameters range between 10 and 100 nm.

- Bicontinuous microemulsions, characterized by the existence of continuous oil and water phases intermixed to create a so-called dynamic network in the medium.

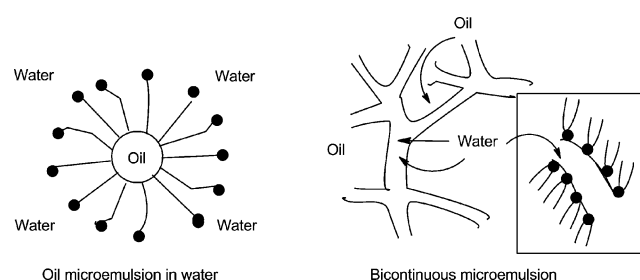


Fig. 33 Schematic representation of the structures of useful microemulsions in electrochemistry.

The most common surfactants used for the preparation of microemulsions are quaternary ammonium salts that possess long aliphatic chains (Fig. 34).

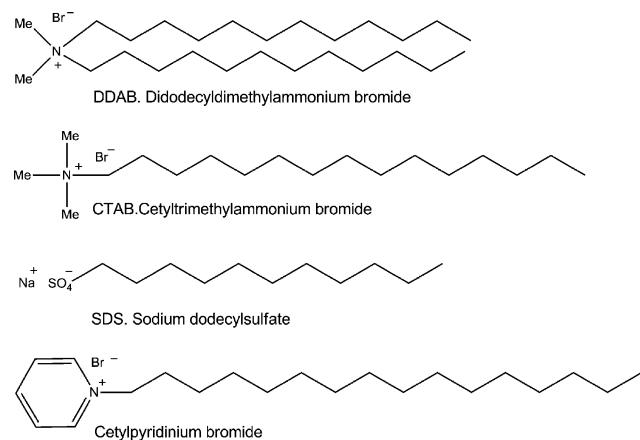


Fig. 34 Surfactants used for the preparation of microemulsions.

Monsanto's process for synthesizing adiponitrile provides an excellent example of the use of μE ; the process typically produces 270,000 ton/year of adiponitrile by the electrohydrodimerization of acrylonitrile (Fig. 35). Adiponitrile is the precursor of the hexamethylenediamine monomer which is used in the manufacture of Nylon 6,6. As stated earlier, the sequence constituted the most successful process in the history

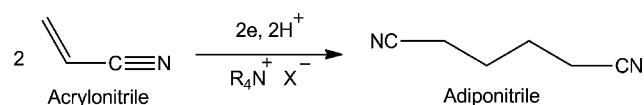


Fig. 35 Electrohydrodimerization of acrylonitrile.

of organic electrochemistry until the end of the last century. In this process, the μE is generated in water and is composed of acrylonitrile, adiponitrile and a quaternary ammonium salt.¹²⁵

The direct electroreduction of the nitro group is another process where microemulsions prove to be useful. For example, the conventional electrolysis of nitrobenzene, generates hydroxylamine or aniline. However, in the presence of microemulsions, dimers corresponding to the lower reduction state (nitroso) are obtained (Fig. 36). Clearly, an electrochemistry performed in the presence of a microemulsion can modify the reaction pathways.

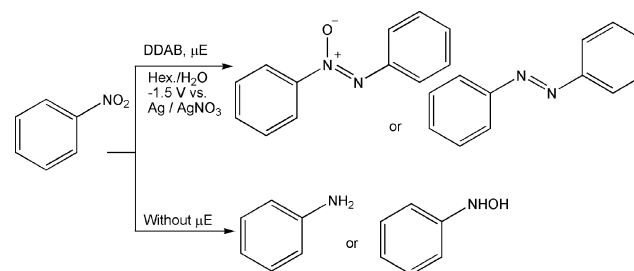


Fig. 36 The reduction of nitrobenzene with and without microemulsions (μE). The product depends on salt conc. and pH.

Microemulsions that incorporate mediators have been used effectively in electrochemical reactions. One example is the use of the system that uses cobalt macrocyclic complexes shown in Fig. 37, where the electrochemical reduction of the Co^{II} complex generates the active Co^{I} species. The latter reacts with the alkyl halide producing an organometallic intermediate that initiates the alkylation reaction. In this way carbon–carbon (C–C) bonds can be formed in an aqueous medium, a reaction that is difficult to carry out by conventional organic chemistry in this medium. The best yields are obtained when $\text{Co}^{\text{I}}\text{L}$ is generated electrochemically and visible light is used to break the alkyl–cobalt bond in the presence of a CTAB microemulsion (Fig. 34).¹²⁶

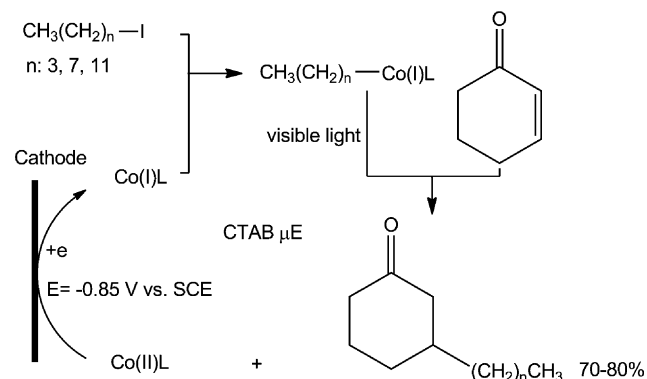


Fig. 37 C–C bond generated by electrocatalysis using a CTAB μE (CTAB: pentanol:tetradecane: H_2O ratio = 17.5 : 35 : 12.5 : 35 wt%).

Another way to generate microemulsions is to apply ultrasound. This process is called *acoustic emulsification*.^{127,128} These emulsions are generated by a cavitation phenomenon at the liquid–liquid interface. The advantages of using μE s obtained in this way are:

· They are highly stable and therefore the use of a surfactant can be eliminated.

· The phases and compounds are easily separated when the ultrasound is turned off. The product is found in the organic phase.

· The electrochemical reaction takes place on a larger surface, since ultrasound cleans the electrode's surface.

· The solubility of the organic compounds is enhanced.

· Mass transfer towards the electrodes is favored by the cavitation phenomenon.

Ultrasound-assisted emulsification was applied to the electrosynthesis of *leuco*-methylene green (Fig. 38).¹²⁹ This is a dye used in the textile industry and can be obtained from methylene green, which has low solubility in water. When no ultrasound is applied, the product covers the surface of the electrode blocking its electron transfer capability (*i.e.* passivation); this is a common problem in organic electrosynthetic processes and hence ultrasound can be very useful. Here, the μE traps the product in the organic phase microdroplets without signs of electrode passivation.

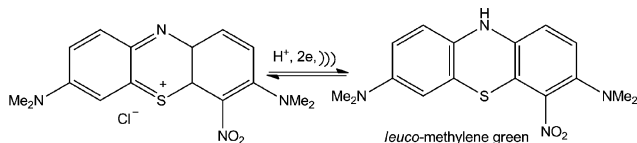


Fig. 38 Electrosynthesis of *leuco*-methylene using acoustic emulsification.

2.6.2. Nanoemulsions. A nanoemulsion (nE) is a thermodynamically stable isotropic liquid dispersion of water, oil, and a surfactant.¹³⁰ In addition to μE properties, this medium can provide a higher active surface area where reactions are faster. TEMPO-mediated electrooxidation of alcohols using an electrolysis system containing a nanoemulsion has been achieved successfully.^{131,132} This electrooxidation is carried out under constant current in an undivided cell, using Br^- ions as a second water-soluble mediator (see Fig. 11). Amphiphilic alcohols such as sugars and polyethylene glycols efficiently formed nanoemulsions in water and were smoothly oxidized, whereas alcohols that did not form nanoemulsions were not efficiently oxidized. Water-soluble TEMPO (WS-TEMPO) derivatives have been synthesized by attaching an ammonium group (cationic WS-TEMPO) or a sulfonic acid group (anionic WS-TEMPO). The formation of a nanoemulsion with the WS-TEMPO and the amphiphilic alcohol enhances the reactivity of alcohol electrooxidation in water. The mediator remains intact in the aqueous solution after extraction and can be reused.¹³³

Electrolyses performed in microemulsions and nanoemulsions hold much promise as environmentally friendly synthetic processes, since the main solvent in the reaction is water. In this way the use of large amounts of non aqueous solvents can be avoided, costs can be lowered, and accident risks can be minimized.

3.0 Preparation of complex molecules using electrosynthesis

Ecological regulations and rising financial costs have prompted those in the chemical industries to examine the potential savings

and environmental advantages that electrochemical processes can provide. In this way, some laboratories that specialize in the synthesis of complex organic molecules have started to explore the methods described earlier and have done so with an eye towards possible commercial interest.^{134–136} This has led to the search for synthetic procedures where electrochemical reactions provide a key component in the synthetic pathway.^{137,138} Of the many examples illustrating the application of electrochemistry to the synthesis of natural products, we cite only a few in an effort to give the reader a feeling for the rather broad range of structures that can be accessed using the electrochemical tools previously described throughout this perspective article.

A recent example illustrating the use of a mediator in natural product synthesis focused upon the sesquiterpene called daucene (Fig. 39).¹³⁹

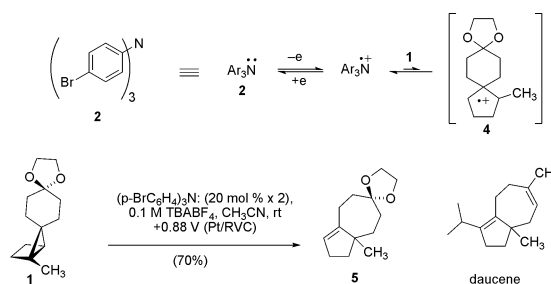


Fig. 39 Use of a redox mediator in the electrosynthesis of daucene.

Tris(4-bromophenyl)amine (**2**) was used as the mediator; its oxidation at *ca.* 0.9 V ($\text{Ag}/0.1 \text{ M AgNO}_3$) afforded the aminium radical cation **3** which in turn served as the oxidizing agent for the strained hydrocarbon **1**, leading to the formation and subsequent rearrangement of cation radical **4**. Even though the mediator oxidizes at a potential that is *ca.* 0.5 V more negative than that needed for the direct oxidation of the substrate, it satisfactorily served its role as a hole carrier and oxidant. Mediators in general are reduced (or oxidized) at a potential that is less than that needed were a direct reduction (oxidation) of the substrate to be carried out, and therefore mediated processes require the consumption of less energy. The conversion of **1** to **5** took place in a yield of 70%; the product **5** was then transformed to daucene. In the present instance, a much larger amount of mediator was needed in order to completely convert the strained hydrocarbon **1** to the rearranged product **5**.¹⁴⁰ As indicated above, catalytic quantities should have sufficed. Efforts are currently underway to achieve this level of efficiency.

Electrochemical oxidative cyclization reactions have been impressively developed into a very useful tool, and have been successfully applied to the synthesis of natural products.¹⁴¹ Here we draw attention to an asymmetric synthesis of (–)-alliacol **A**,¹⁴² a substance that displays anticancer activity and that has been the subject of many synthetic endeavors (Fig. 40).¹⁴³ This route features a constant current intramolecular oxidative cyclization of furan **6**, leading to the formation of **8**, a substance that was subsequently transformed into the natural product. Interestingly, the oxidation of the silyl enol ether is better achieved by electrochemistry than by using other

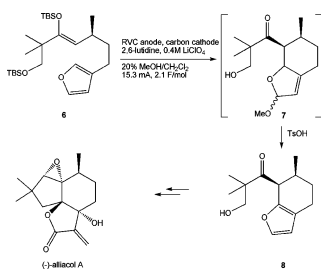


Fig. 40 Key electrochemical oxidative cyclization en route to (-)-alliacol A.

chemical oxidants, some of them very toxic and expensive, rendering this transformation into an environmentally friendly reaction.¹⁴⁴

Electrochemistry also played a seminal role in the total synthesis of the complex diterpene natural products, (-)-guanacastepene E and (-)-heptemerone B (Fig. 41).¹⁴⁵ Of particular note was the conversion of the furan **9** to the tetracyclic structure **10**, a transformation that was achieved by oxidizing the silyl enol ether **9** at a reticulated vitreous carbon (RVC) working electrode. The reaction possesses the same ecological attributes described for the synthesis of (-)-alliacol A. Of practical interest is the fact that the reaction was done using the simplest of reaction setups, *viz.*, a 3-neck round-bottom flask and carbon electrodes. As the figure shows, the process proceeded efficiently (81%) with the consumption of 2.6 F/mol, despite the complexity of the starting material. The simplicity of the reaction setup as well as the efficiency of the transformation, argue convincingly for the more widespread use of electrochemistry in organic synthesis.

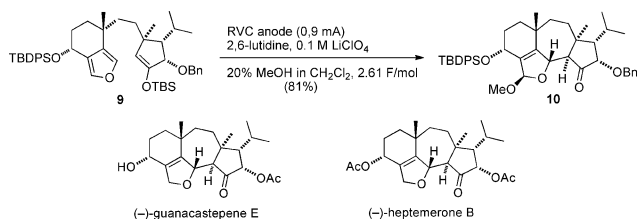


Fig. 41 Use of an electrooxidative cyclization in a structurally complex setting.

The electrochemical oxidation of amides is of relatively common usage.¹⁴⁶ The process has been studied in detail and has been elegantly applied to the total synthesis of a substance that is referred to as A58365A, an inhibitor of the angiotensin-converting enzyme (Fig. 42).¹⁴⁷ In that investigation, oxidation of the proline derived amide **11** led to the *in situ* formation and capture of an acyl iminium ion **12** by the solvent (MeOH) to generate **13**. Subsequent Lewis acid-promoted cyclization and oxidative cleavage of the resulting exocyclic π -bond in structure **14** formed the diketo diester **15**, a substance that was subsequently transformed to the natural product.

The preceding examples feature oxidative processes. Two examples that feature electroreduction steps are now described. One was used to complete the formal total synthesis of the antitumor agent called quadrone (Fig. 43),¹⁴⁸ and the other

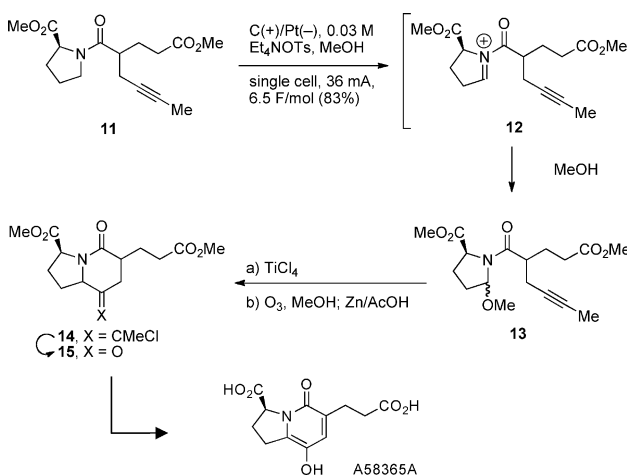


Fig. 42 Amide oxidation – an electrochemical key step in the construction of the bioactive amide called A58365A.

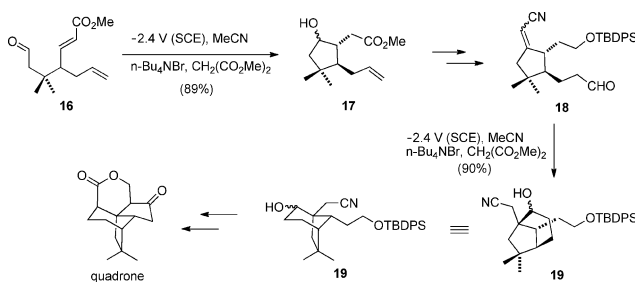


Fig. 43 Application of the electroreductive cyclization reaction to a formal total synthesis of the antitumor agent, quadrone.

culminated in the first total synthesis of the sesquiterpene called sterpurene¹⁴⁹ (Fig. 44).

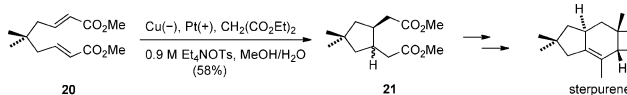


Fig. 44 Application of the electrohydrocyclization reaction to the synthesis of sterpurene.

The quadrone synthesis utilized two electroreductive cyclization reactions, the first converting aldehyde **16** to the cyclopentanol **17** and the second transforming the unsaturated nitrile **18** to the bicyclo[3.2.1] framework found in structure **19**. As these transformations show, electroreductive cyclization reactions lead to the formation of a σ -bond between the β -carbon of an electron-deficient alkene and a pendant carbonyl. When reduced, the β -carbon undergoes an *umpolung*, changing its electronic character from deficient to rich. Detailed mechanistic studies have shown that cyclization occurs *via* the carbanion intermediate that is generated following protonation and addition of a second electron to the initially formed radical anion.¹⁵⁰

An interesting example of an intramolecular electrohydrocyclization is the sterpurene synthesis by means of the conversion of the bisenoate **20** to the cyclopentane diester **21**.¹⁵¹ Hg was used initially as the cathode. Clearly, its use is in violation of the principles of green chemistry. As a result, other cathode materials were examined. The results shown here portray the outcome when Cu was used. Future efforts to “green-up”

the processes may benefit from recent results showing that both electroreductive cyclization and electrohydrocyclization reactions occur in the presence of 6 mol% Ni-salen complex, the latter serving as a mediator.¹⁵²

In order to show the advantages and limitations of organic electroynthesis in the total synthesis of a natural product and to compare the green chemistry potential, the synthesis of *N*-isobutyl-(2*E*,6*Z*)-dodecadienamide **22** was performed and the chemical and electrochemical approaches were compared; both methodologies involved the same intermediates, produced by different chemical pathways (Fig. 45).¹⁵³ It is clear that other chemical methodologies exist for preparing some of the compounds, but the pathways that were adopted assure that one can closely compare the two general methodologies. Four reactions were compared from the point of view of yield and adherence to the principles of green chemistry: (a) the oxidation of an alcohol to an aldehyde, (b) a Horner–Emmons olefination reaction, (c) a carboxylic acid amidation with triphenylphosphonium ions, and (d) a Wittig reaction. Overall, the electrochemical approach proved to be much more effective, affording an overall yield of 22% for the synthesis of **22**, instead of the very low 5% that was obtained by the alternative non electrochemical approach. Unfortunately, the pure electrosynthetic method did not work for the last reaction in the sequence. This study demonstrated that organic electrochemistry can be a reliable method for the synthesis of important intermediates, but not all electrochemical reactions can compete with all of the well-established methods of organic synthesis. Nevertheless, organic electroynthesis can

be combined with traditional methods in order to obtain the best results in complex total syntheses while always striving to keep the foundations of green chemistry in mind.

4.0 Concluding remarks

The application of electrochemical methodologies to organic synthesis is receiving significant attention from industry and research centers worldwide, not only because transformations can often be conducted more efficiently, but also because electrochemical processes can decrease pollution and make the chemistry environmentally friendly. Fig. 46 compares a conventional chemical process with its electrochemical counterpart. In the latter the waste treatment is simple since there is no need to treat the redox reactants as they are simple electrons. Furthermore, the use of redox reactants can be avoided when electron transfer is involved. Elimination of even one operation in industry decreases energy consumption and helps make the process more economically feasible. As a result of these considerations, it is expected that in the near future more large-scale processes will use organic electroynthesis to perform key reactions. All the advantages of using organic electroynthesis that have been mentioned in this article and the direct relationship with green chemistry (9 of the 12 principles are involved, Fig. 2), will hopefully encourage organic chemists to think seriously about using it to solve important problems in synthesis. It provides a reliable and valuable synthetic tool that is well suited for constructing interesting molecules.

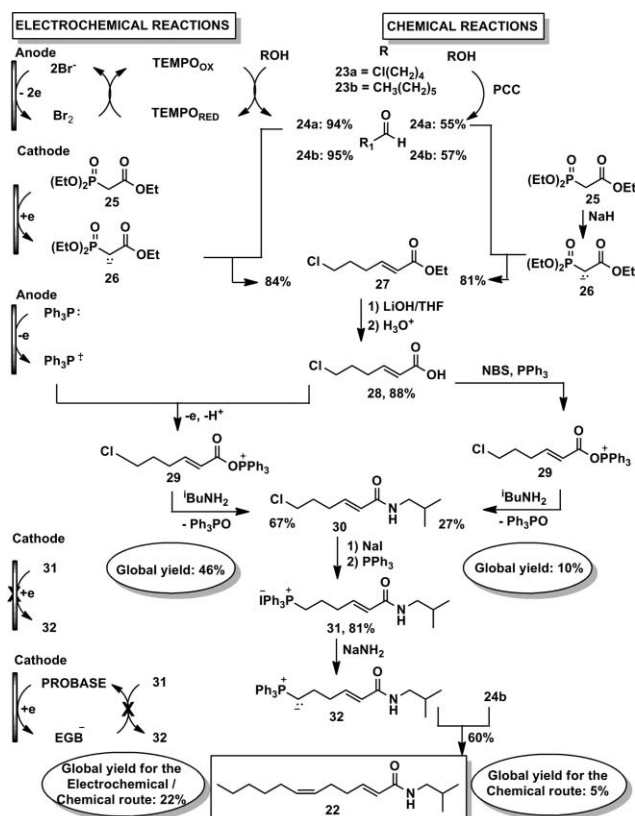


Fig. 45 Electrochemical (left) and chemical (right) routes used for the synthesis of *N*-isobutyl-(2*E*, 6*Z*)-dodecadienamide **22**. From reference 153.

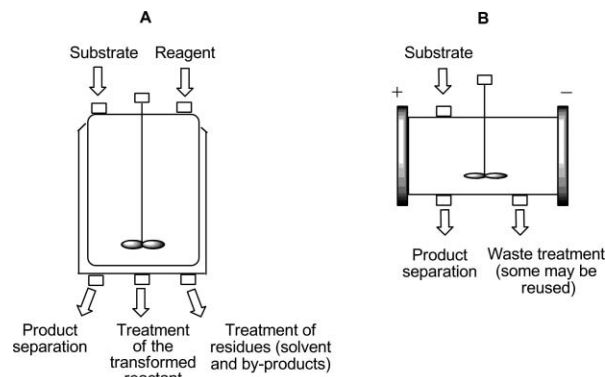


Fig. 46 Comparison between a conventional chemical process (A) and an electrochemical process (B).

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§ It is important to differentiate from current efficiency, a parameter that informs how efficiently the electrical charge is used in the reaction of interest (pure electrical value). The classical chemical yield definition does not apply here because both mass and charge are required to obtain the electrochemical yield in a paired reaction.

¶ This term describes the efficiency of a chemical process in terms of all of the atoms involved. In an ideal chemical process, the number of atoms found in the starting materials or reactants equals the number found in the products generated and no atoms are wasted.

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