The application of cathodic reductions and anodic oxidations in the synthesis of complex molecules

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This *tutorial review* surveys the recent advances in electrochemical transformations as they pertain to the synthesis of complex organic molecules. Electrochemistry has emerged as a powerful tool to synthetic chemists, yet many have never considered electrochemical methodology as a means for synthesis. Here, an introduction to electrochemistry and voltammetry will be provided with descriptions of the four types of electrochemical cells. In addition, recent examples of both anodic oxidations and cathodic reductions will be discussed, along with the experimental setups for carrying out each reaction.

Introduction

Although synthetic chemists have long appreciated the value of electrochemistry as a tool for numerous organic transformations (often on an industrial-scale), the use of electrochemical methods in complex molecule synthesis remains rare. Terms like "cyclic voltammetry," "reduction potential," and "current density" are rarely associated with typical synthetic transformations. Preparative electrolyses involve the irreversible reduction or oxidation of a substrate at an electrode which is often followed by secondary reactions. In this *tutorial review*, an introduction to synthetic electrochemistry will be presented that will highlight the scope of transformations possible and detail the experimental design and set-up for many electrochemical reactions. Since several excellent comprehensive reviews and texts already exist,[1] this article will showcase a range of methodologies with emphasis on how each particular application was carried out. This review will focus on the synthetic aspects of preparative electrochemistry[2] while the in-depth physical-organic and mechanistic considerations are beyond the scope of this article. There are a number of excellent texts that cover many of these aspects in detail.[3]

Synthetic electrochemistry is a rapidly growing area of interest within the synthetic community although it is far from being a routine technique. Despite the fact that many oxidative and reductive conversions are known, electrochemical methods are often only considered after all other methods have been exhausted. However, the past several years have witnessed an explosion of literature involving electrochemical methodology, specifically the use of these reactions as key steps *en route* to complex natural products. Baizer, Fry, Little, Moeller, Schäfer, Shono and others have made significant contributions to the electrochemical field, describing advanced synthetic and mechanistic aspects of organic electrochemistry. Herein, the basics will be described,[4] including an introduction to the terms that are most commonly used during the course of a synthetic electrochemical experiment. There exist more detailed descriptions[5] of the theory and mechanistic aspects behind the introduction for continued reading.

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Introduction to synthetic electrochemistry

Organic electrochemical reactions (electrolyses) can be classified as either oxidations or reductions with the reaction being comprised of the substrate, electrodes, electrolyte, solvent and various additives. In a galvanic cell (two electrodes connected by a salt bridge composed of a solution of an electrolyte), oxidations take place at the anode and reductions at the cathode. What makes electrochemical reactions unique from many ionizing reactions is that they take place *on the surface* of the electrode[6] and produce highly reactive intermediates such as radical-cations (*via* oxidation) and radical-anions (*via* reduction) that diffuse into solution. A variety of secondary reactions can ensue from the initial radical-ion species.

Electrolyses take place in an electrochemical reactor, simply referred to as the *cell*. The term cell is used to describe any setup that contains an electroactive species, solvent, electrolyte and at least two electrodes, the cathode and anode. The range of acceptable solvents is fairly broad and includes methanol, acetonitrile, dichloromethane, or tetrahydrofuran. Many different electrolytes (typically salts that dissociate into ions and make the solution conductive) have been used in electrochemical reactions, but generally the list includes lithium perchlorate, tetrabutylammonium tetrafluoroborate, tetraethylammonium tosylate, tetrabutylammonium acetate, or any other tetraalkyl ammonium salt. Electrodes can be built from any material that allows for the transfer of electrons in solution so long as they are stable to the reaction conditions. These typically include platinum (wire, mesh, or foil), carbon rods, carbon plates, magnesium, stainless steel, or reticulated vitreous carbon[7] (RVC). RVC is a unique glass-like carbon that combines the properties of carbon with glass. It has a high void volume, high surface area, and chemical resistance, making it an attractive choice for many electrochemical transformations. In addition, many electrochemical reactions utilize sacrificial electrodes. The electrodes are generally made of metals such as zinc or lead and are consumed during the course of the reaction. Some reactions are sensitive to the current density at the surface of the electrode (as given in mA cm^{-2}). If this is the case, electrodes that provide an easy way to determine the surface area, such as carbon rods or plates, are often employed. As with any chemical reaction, the choice of solvent, electrolyte, electrode, and current density often need to be optimized as these parameters have a marked effect on the reaction outcome.

In addition to all of the above, a potentiostat must be used to apply a potential. Consider a potentiostat as a variable battery. Whereas a 9 V battery can apply 9 V across an electrode, the potentiostat can be used to select any potential, relative to a reference electrode. In addition, a potentiostat can be used to control the current during a constant current experiment. The ability to choose a given potential or current to effect selective oxidation or reduction is what makes electrochemical methodologies unique. Many different types of potentiostats are available, from basic models to top-of-the-line hand-held models. The more advanced models allow for cyclic voltammetry (CV) and linear sweep voltammetry (LSV) studies (discussed later) and are considerably more expensive.

Although the principle components of the cell are constant, there are alternative arrangements for the construction and operation of the electrochemical reactor. There are two basic choices for construction of the electrochemical reactor: an undivided cell or a divided cell. Typically, undivided cells are used for constant current experiments and divided cells for constant potential experiments, but there exist examples for the contrary. Either divided or undivided cells can be used for electrochemical oxidations and reductions. The cell can be operated in two different manifolds with either the potential (in Volts) or current (in Amps) being held constant while the other parameter varies. The setups will be discussed in the following order: (1) constant current/undivided cells; (2) controlled potential/undivided cells; (3) controlled potential/divided cells; and (4) constant current/divided cells.

Due to their ease of construction, constant current/undivided cell experiments are most often encountered in the literature. Beginning with a typical undivided electrochemical cell in Fig. 1, a potentiostat is connected to two electrodes, one acting as a cathode and one as the anode. The two electrodes are submerged into a solution containing the electroactive species, electrolyte, and solvent. Once submerged, the cell behaves as a broken circuit until a potential is applied across the electrodes. In a constant current experiment, as the name implies, a current is set at the potentiostat and the potential at the electrode surface begins to rise. For an anodic oxidation, the potential will continue to rise until the oxidation potential is reached for the electroactive species. Once this potential is reached, it stabilizes until all of the material at this oxidation potential is consumed. Once consumed, the potential climbs to a point where either a second electroactive species or the solvent is oxidized. When performing constant current anodic oxidations, it is critical that the oxidation potential of the electroactive species be known, so as to ensure the first oxidation does not involve the solvent or additives. Oxidation occurs at the anode by transfer of electrons from a molecule to the electrode. At the cathode, molecules are reduced by transfer of electrons from the electrode to the species being reduced. The overall process results in transfer of electrons

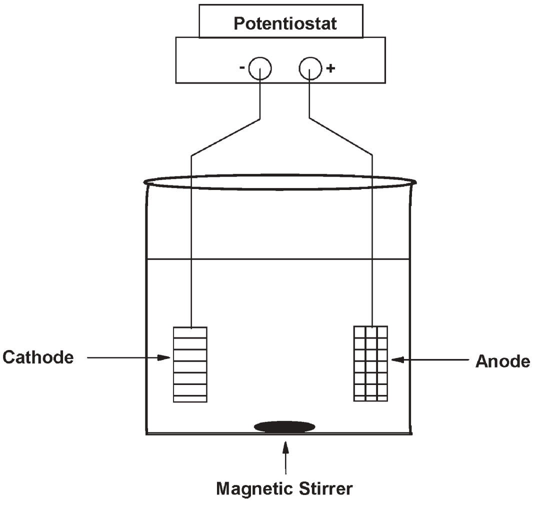


Fig. 1 Schematic of a typical undivided cell.

from the cathode to the anode, thus completing the circuit and allowing for electrons to flow through the cell.

The undivided cell setup allows for both reduction and oxidation to happen within the same compartment such that the substrate of interest is exposed to all species present in the reaction. A consequence of this arrangement is that consideration needs to be given to the chemistry occurring at the auxiliary electrode (the auxiliary electrode is the cathode for an oxidation, and *vice versa* for a reduction). The auxiliary electrode does not play a direct role in producing the desired products; however, the by-products generated during the course of an electrochemical reaction can affect non-reacted starting materials or the products themselves. For example, during anodic oxidation reactions acid is typically generated during the course of the experiment. Protic additives such as methanol or isopropanol are often included and allow for the generation of alkoxide at the cathode by reduction to form hydrogen. The generated alkoxide can neutralize the acid liberated at the anode and prevent undesired side reactions. Additives such as amine bases can also be used to help preserve the neutrality of the cell. Although the graphic in Fig. 1 resembles a beaker, the actual apparatus itself may be a round-bottom flask, vial, or other custom-designed glassware.

One of the powerful features of electrochemical reactions is the ability to tightly control the reaction potential and effect selective redox reactions in the presence of multiple functional groups. If the potential during a given electrochemical oxidation or reduction must be at or below a certain value, a controlled potential experiment will allow for selective oxidation or reduction. The potential of the cell can be set at a given value relative to a reference electrode and only those electroactive species below the set potential will be oxidized or reduced. Since the potential will be set relative to a reference electrode, a third electrode will be required in addition to the anode and cathode. Although constructing a reference electrode requires little work, many are commercially available, reusable and relatively cost efficient. Standard reference electrodes are a Ag/Ag^+ or a saturated calomel electrode (SCE).

Controlled potential experiments allow for selective oxidation/reduction by keeping the potential at the electrode surface at a set value. However, as the electroactive species is consumed, the current decreases. As the current drops, it takes longer to oxidize or reduce the starting material. Often times, it becomes hard to drive a controlled potential experiment to completion, and the time required to complete the reaction increases dramatically.

An alternative, but more complex, arrangement is the divided cell which physically separates the anodic and cathodic compartments by means of a small, porous frit. Although divided, the frit does allows for the transfer of charge such that the electrolysis can occur. No substrates ever move between compartments. This setup is extremely useful if the side reactions that occur at the auxiliary electrode affect either the starting materials or the products. As seen in Fig. 2, this setup is considerably more complicated than the undivided cell although there are commercial sources of divided cells. Many are marketed with all necessary components for performing reactions and can be customized for almost any scale. Divided cells can be employed in either constant current or controlled potential experiments. Again, for controlled potential experiments, a reference electrode is necessary and is generally placed into the compartment with the working electrode (the anodic compartment for an oxidation or the cathodic compartment for a reduction). The electroactive species is placed into the appropriate compartment along with solvent and the desired electrolyte. In the compartment with the auxiliary electrode is placed the solvent, electrolyte, and a species that can partake in the opposite electrochemical reaction. In some instances, sacrificial electrodes are used and their reduction/oxidation is used to complete the circuit (see below). Constant current electrolyses (oxidations and reductions) are conducted identically to that in an undivided cell. The species to be oxidized is placed into the anodic compartment along with the anode, solvent, and electrolyte. The cathodic compartment contains the species to be reduced and the solvent, electrolyte, and cathode. Standard electrodes, electrolytes, and solvents can be used; the only difference here from an undivided cell is that the two half-cells are separated by a porous frit.

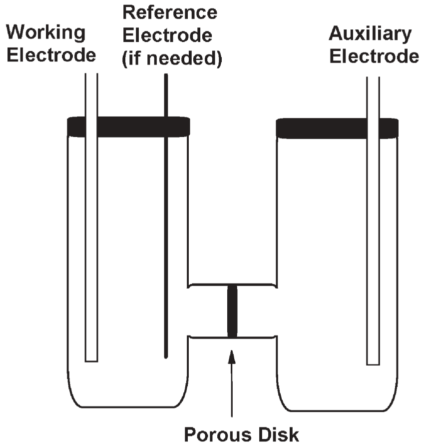


Fig. 2 Schematic of a divided cell (H-cell).

For any electrochemical reaction taking place within a cell, the potential, V of the cell is given by the formula:

$$V = iR \tag{1}$$

where i is the current and R is the resistance of the cell, given in Ohms (Ω). The resistance of a cell is directly related to the concentration of the electrolytes in solution. As the concentration of these electrolytes decreases, the resistance increases. This accounts for the drop in current during a constant potential experiment. Likewise, for a constant current experiment, as the resistance increases, the potential also increases.

The electrical double layer

The primary reason that the choice of the electrode material can be so critical in designing a successful process is that the reaction takes place exclusively on the surface of the electrode and not in the bulk solution. Seminal work by Helmholtz, Grahame and others (see refs. 1–4) described what happens when charge is applied to an electrode (in this case when a positive charge is applied). A strong electrical field is generated in solution at the surface of the anode from the high concentration of negatively charged ions being attracted to the positively charged electrode. These negatively charged ions, in turn, attract more positively charged ions from the solution and form another electrical field on the solution side. This newly formed second electrical field is significantly weaker, since the anode compensates for most of the field generated from the negative ions. This process is repeated throughout the solution. As the layers of electrical charge progress further and further away from the electrode, the effective potential of the field diminishes. The innermost layer (shown in Fig. 1 as the distance from the electrode to d_1) is termed the compact inner layer and is typically only a few Ångstroms wide. The potential of this layer decreases linearly with increasing distance from the electrode. As a result, at the end of the compact layer, or outer Helmholtz plane, most of the potential difference between the electrode and the solution is lost. Once d_1 is reached, the potential drops exponentially through the diffuse layer (d_1 to d_2). This diffuse layer can be anywhere from a few tens to hundreds of Ångstroms away from the surface of the electrode. Both the compact layer and diffuse layer constitute the electrical double layer. Once the outermost region of the diffuse layer is reached, the potential is identical to the bulk of the solution. It is generally accepted that the oxidation/reduction of the electroactive species takes place on the electrode surface in the compact inner layer. For reactions that involve cyclizations, the cyclization itself is accepted to be kinetically faster than diffusion through the inner layer. This is the reason that highly reactive radical-cations and radical-anions can be generated in the presence of nucleophilic and protic solvents (Fig. 3).

Oxidation/reduction potentials and voltammetry

The transfer of electrons between an electrode and an organic substrate is a heterogeneous process. What determines if there is sufficient energy to accomplish this transfer is the potential of the electrode. Electrode potentials are always given as the difference between the potential at the electrode of interest and a carefully selected reference electrode. In addition, the electrode potential (E) can be related to the free energy change of a reversible reaction by:

$$\Delta G = -nFE \tag{2}$$

or related to the standard state free energy by:

$$\Delta G^\circ = -nFE^\circ \tag{3}$$

where F is Faraday's constant (96,485 C mol^{-1}) and is defined as the quantity of electricity needed to effect the reaction with 1 equivalent of an electroactive compound, and n is the number of electrons involved in the overall reaction. From a synthetic viewpoint, a Faraday can be viewed as a molar equivalent of electrons and sets up simple stoichiometry for the reaction. Just as the reduction of an alkyl halide by magnesium requires one molar equivalent of magnesium but in reality requires two molar equivalents (or two Faraday's) of electrons.

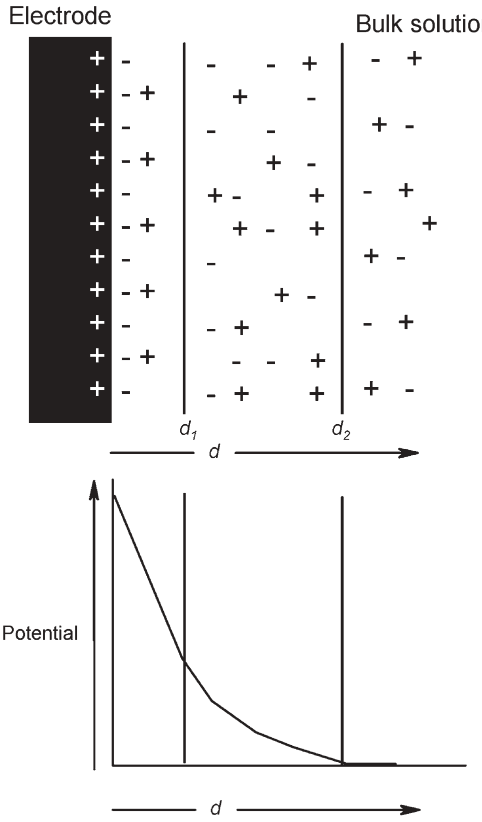


Fig. 3 Representation of the electrical double layer.

Using thermodynamic definitions, the free energy change can be expressed as:

$$\Delta G = \Delta G^\circ + RT\ln Q \tag{4}$$

where R is the ideal gas constant (8.314 J K^{-1} mol^{-1}), T is the temperature expressed in K, and Q is the activity quotient and is expressed as the ratio of the activities of products to reactants. Substituting eqn (2) and eqn (3) into eqn (4), we get:

$$E = E^\circ + \frac{RT}{nF}\ln Q \tag{5}$$

Eqn 5 is known as the Nernst equation and for any reversible electrochemical reaction given by:

$$\mathrm{Ox} + ne^- \rightleftharpoons \mathrm{Red} \tag{6}$$

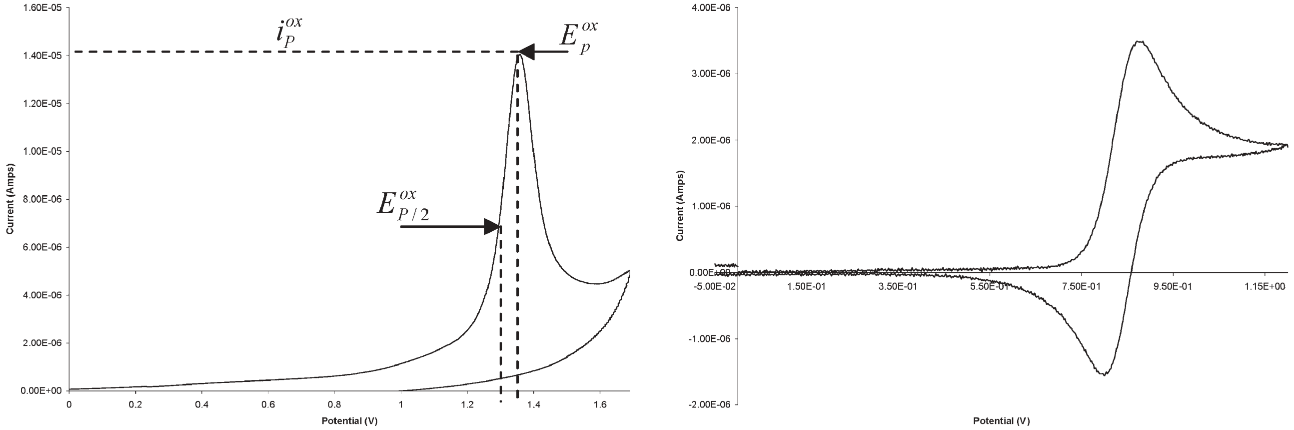
the Nernst equation becomes:

$$E = E^\circ + \frac{RT}{nF}\ln\frac{a_{\mathrm{Ox}}}{a_{\mathrm{Red}}} \tag{7}$$

where a_{Ox} and a_{Red} are the activities of the oxidative and reductive species at the surface of the electrode. Since activities are rarely used for synthetic applications, substituting the concentrations for activities gives the Nernst equation in the form:

$$E = E^\circ + \frac{RT}{nF}\ln\frac{C_{\mathrm{Ox}}}{C_{\mathrm{Red}}} \tag{8}$$

Where C_{Ox} and C_{Red} are the concentrations of the oxidized and reduced species at the electrode and at 25 °C the standard



Irreversible **Reversible**

Fig. 4 CV plots showing an irreversible and reversible oxidation.

form of the Nernst equation most often encountered is:

$$E = E^\circ + \frac{0.059}{n}\log\frac{C_{\mathrm{Ox}}}{C_{\mathrm{Red}}} \tag{9}$$

Unlike many chemical reactions, the magnitude of the free energy necessary to induce an electron transfer in an electrochemical process can be measured directly by the use of voltammetry. In practice the oxidation or reduction potential of the electrolysis substrate is determined experimentally and used to guide the reaction parameters. Cyclic voltammetry (CV) is a method by which the current response of a small electrode is measured when that electrode is subjected to a triangular waveform. Usually, the triangular waveform begins with the initial potential (E_{initial}) and ends with the same potential (E_{final}). Going from E_{initial} to E_{final}, the waveform should contain two equal and opposite slopes and begin positive for oxidations and negative for reductions. The results are plotted in a current/potential curve and called a voltammogram. Fig. 4 shows two CV curves, an irreversible plot and a reversible plot. The resulting voltammogram contains information about the behavior of a substrate under an applied potential. The voltammogram can show whether the oxidation (or reduction) is reversible, quasireversible, or irreversible. In most instances, reversible or irreversible curves will be generated. In a irreversible oxidation (as seen in Fig. 4), the forward scan shows an anodic oxidation potential ($E_{\mathrm{p}}^{\mathrm{ox}}$) of approximately 1.35 V and a half-peak oxidation potential ($E_{\mathrm{p}}^{\mathrm{ox}}/2$) of around 1.30V. Although the principles of reversibility and irreversibility are quite complex,[3] the presence of a second peak in the reverse scan beneath the oxidation peak is generally considered diagnostic of a reversible process (as seen in the reversible CV). Typically, the value reported for a given substrate is the half-peak potential. The half-peak potential is defined as the value of E where $i = i_{\mathrm{p}}/2$. Many electrochemical reactions involving organic molecules produce highly reactive intermediate radical-ions that undergo further reaction upon formation. Irreversible CV plots are characteristic of these types of electrochemical processes and are at the heart of most preparative organic electrolyses (Fig. 4). As defined earlier, the reverse scan does not show another peak and the current drops to 0, hence the irreversible oxidation.

Since the majority of organic electrochemical reactions involve species that quickly react in an irreversible manner, there is no need to study the reverse wave function. In this case, only the oxidation or reduction wave is studied. This procedure is called linear sweep voltammetry (LSV) and is often encountered. The setup is identical to CV studies and the generated CV plot would contain only the forward scan.

Experimental setup for voltammetry

In order to obtain CV data, an electrochemical cell setup needs to be constructed as in Fig. 5. An electrode system consisting of working, reference, and counter electrodes is submerged into a solution of the substrate and an inert electrolyte. Although the setup requires three electrodes, many are commercially available. In fact, the electrochemical cell can now be purchased as a package that includes everything needed to obtain CV data and perform other electrochemical experiments.[8]

The cell consists of a glass compartment and a Teflon stopper with four holes, one each for the reference electrode, working electrode, counter electrode, and an inert gas purge line. Working electrodes typically consist of a glassy carbon or platinum electrode. Counter electrodes are typically platinum

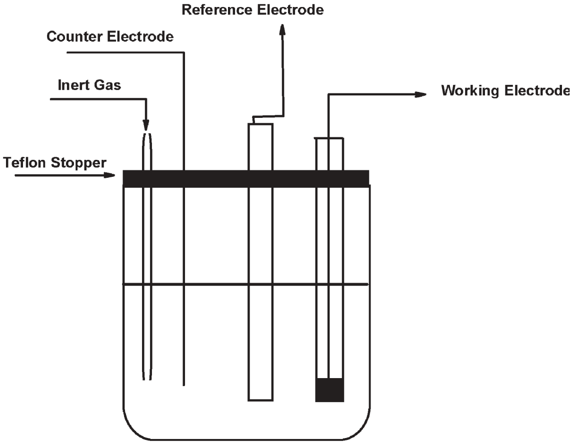


Fig. 5 Standard setup for voltammetry studies.

wires. Reference electrodes can be a Ag/AgCl electrode or an SCE (Fig. 5). Before CV data is obtained, the solution must be purged with an inert gas to remove dissolved oxygen, whose reduction can be observed in the CV plot. Solvents are usually chosen to be the same as the actual reaction. Solvents should be of the highest purity to ensure accurate data are obtained. Electrolytes chosen for electrochemical reactions and CV studies are generally the same as other electrochemical reactions: $LiClO_4$, Bu_4NOTs, Bu_4NClO_4, or many other tetraalkyl ammonium salts. Electrolytes and solvents should be chosen that will not oxidize/reduce during the course of the experiment. For example, solvents containing hydroxyl or nitro groups are generally not used due to the possibility of side reactions resulting from oxidation of the hydroxyl moiety or reduction of the nitro functional group. As there is considerable variation in the protocol used to obtain CV data (solvent system, electrolyte, *etc.*), it is valuable to report as many parameters as possible such as the electrode material, the electrolyte and the scan rate (typically in mV s^{-1}). Oxidation and reduction potentials are dependent on the conditions by which they were obtained and changing variables can affect the observed potentials.

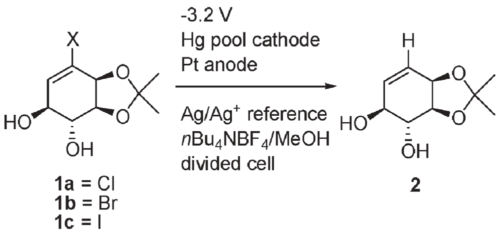
Table 1 shows representative oxidation potentials of various functional groups.[9] A trend can be seen in entries 1–3. Structural features that stabilize the adjacent radical-cation, such as neighboring electron donating substituents, lower the oxidation potential of the substrate. However, in the case of benzene, the oxidation disrupts aromaticity, hence the increase in oxidation potential relative to 1,3-cyclohexadiene. Many of the features seen in the oxidation potential are familiar trends in electrophilic aromatic substitution chemistry. For example, substitution of the aromatic ring (entries 4–6) with electron-donating functionality decreases the oxidation potential by stabilizing the intermediate radical-cation. Furan and thiophene show similar half-wave oxidation potentials, although furan oxidizes at a slightly lesser potential due to decreased aromaticity.

Synthetic applications of electrochemistry

In recent years, there has been a considerable increase in the use of electrochemical reactions in organic synthesis. For this review, we have chosen several different applications that are meant to illustrate the wide diversity seen both in experimental design and in available reaction manifolds. The reactions can be conveniently grouped into the following classifications : (1) cathodic reductions; (2) cathodic cyclizations; (3) anodic oxidations; and (4) anodic cyclizations.

Table 1 Selected oxidation potentials

Entry	Compound	Oxidation potential /V
1	Cyclohexene	1.98
2	1,3-Cyclohexadiene	1.60
3	Benzene	2.04
4	Phenol	1.04
5	Anisole	1.40
6	1,4-Dimethoxybenzene	1.04
7	Aniline	0.70
8	Pyridine	1.82
9	Thiophene	1.70
10	Furan	1.55



Scheme 1 Cathodic reduction of vinyl halides.

Cathodic reduction reactions

The electrochemical reduction of various functional groups has been shown to be an effective method for initiating anionic reactions. Electrochemical reductions do not require stoichiometric metal or metal hydride sources which has strong economic and environmental implications. For metal-mediated synthetic transformations, electrochemistry can be used to regenerate the reactive oxidation state of a given metal complex.

Hudlicky and coworkers demonstrated that the cathodic reduction of vinyl halides could be utilized in the synthesis of inositols.[10] Beginning with **1a–c**, reduction of the vinyl halide was studied both chemically by means of Bu_3SnH reduction and by cathodic reduction. Linear sweep voltammetry showed broad reduction peaks in the range of −3.0 to −3.2 V (*vs* Ag/Ag^+) for the vinyl halide substrates. As such, this was the potential chosen to study the reduction of the various vinyl halides. In all instances, similar yields were obtained with cathodic reduction as with tributyltin hyride; however, this example demonstrates how electrochemical methodology can be substituted for metal reagents (Scheme 1).

The mercury pool electrode used in this case is unique in the fact that the mercury sits at the bottom of the electrochemical cell, hence the term “pool.” The schematic of the setup is seen in Fig. 6. The mercury is placed in the bottom of the beaker

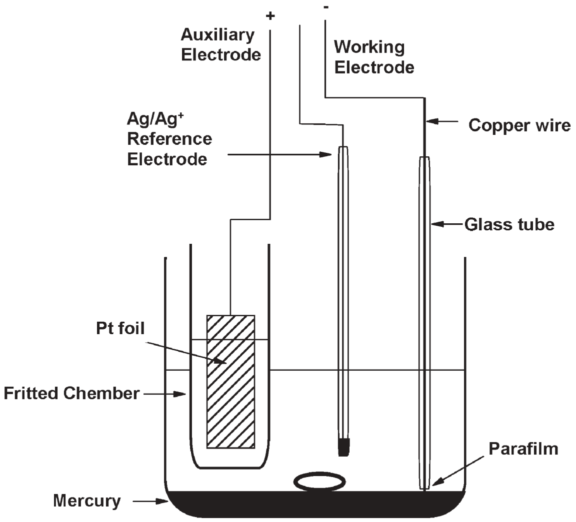


Fig. 6 Divided cell setup for cathodic reduction of vinyl halides.

and is connected to the potentiostat *via* a copper wire protected from the bulk solution by a glass tube and sealed at the end with parafilm. The mercury pool acts as the working cathode. The anode in this case is platinum foil in a fritted disk chamber that allows for charge transfer and completion of the circuit. The reference electrode was a simple Ag/Ag$^+$ electrode. A constant potential in the range of -2.8 V to -3.2 V was applied and facilitated the cathodic reduction of the vinyl halides.

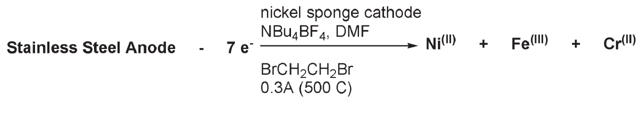
Although replacing metal reagents entirely is possible as in the above example, electrochemistry can also be used in conjunction with catalytic quantities of metal additives to retain desired reactivity profile of a particular metal.

Durandetti *et al.* recently reported an electrochemical variant of the Nozaki–Hiyama–Kishi (NHK) reaction in which two sacrificial anodes were used.[11] This is an excellent example of integrating electrochemical methods into pre-existing reaction manifolds. An NHK coupling reaction requires Cr^{II} and Ni^{II} and the source of these ions is generally CrCl$_2$ and NiCl$_2$. The reaction requires these particular metals to mediate various insertion, transmetallation and addition steps. In their modification of the classic NHK reaction, Durandetti first generated these ions electrochemically through a commercially available sacrificial stainless steel anode composed of iron, chromium, and nickel in a 72/18/10 ratio. Oxidation of the sacrificial anode led to the generation of the needed Ni^{II} and Cr^{II} species in solution. The amount of chromium and nickel generated during pre-electrolysis was determined by weighing the anode before and after the oxidation process (Scheme 2).

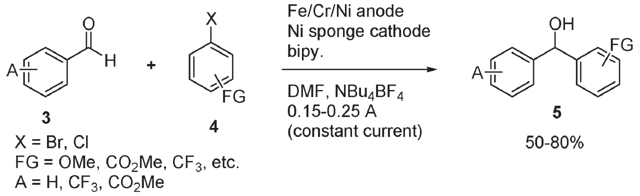
The second part of this sequence is the electroreductive cross-coupling reaction between aryl or vinyl halides and aromatic aldehydes. Once the pre-electrolysis was judged complete, the stainless steel anode was replaced with an iron rod and a constant current of 0.15 to 0.25 A was applied. Switching to the iron rod kept the chromium content of the solution at the minimum (determined to be 7%).

This reaction was performed on aromatic halides containing various electron-withdrawing and electron-donating groups and proved efficient with both. Most importantly, the catalytic amount of Cr^{II} required was only 7%. Chromium salts are not only expensive, but also poisonous. In addition, some examples use up to 400 mol% of chromium. This inexpensive, catalytic variant of the NHK couplings could even have applications in industrial processes. These reactions were carried out in a four-neck flask with the two electrodes, an argon inlet, and one neck was used to hold the reference electrode when the potential of the cell was measured (Scheme 3).

Very recently, Barba reported the facile conversion of *o*-quinones into 1,3-dioxolanes *via* an electroreduction in dichloromethane.[12a] Cyclic voltammetry showed two one-electron reduction peaks, both reversible. This, along with an intensely colored solution, suggests the presence of a radical anion and a dianion.



Scheme 2 Pre-electrolysis of stainless steel anode generating active ions for NHK coupling.

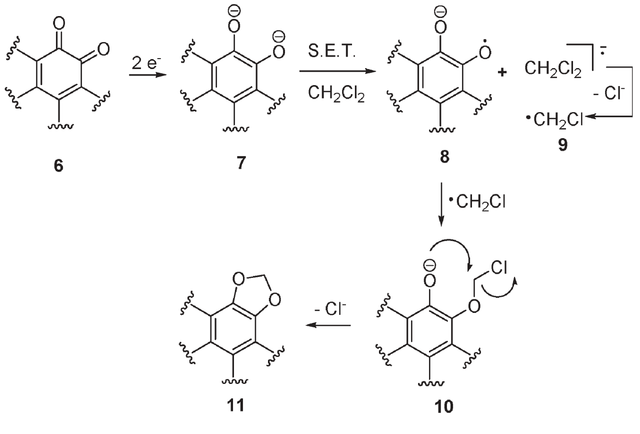


Scheme 3 Electrochemical NHK coupling between aryl halides and aromatic aldehydes.

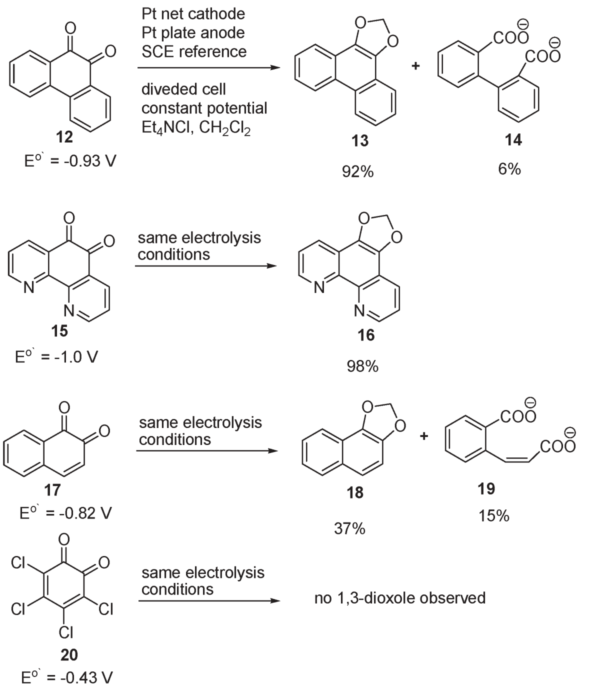
Mechanistically, the two-electron reduction would provide a dianion **7** that can undergo a single electron transfer reaction with dichloromethane. In solution, the single electron transfer to dichloromethane is concerted[12b] with the C–Cl bond cleavage to generate the monochloromethane radical **9**. This radical can couple with the radical anion of the quinone **8** to form the new C–O bond. An intramolecular nucleophilic substitution provides the 1,3-dioxolane **11** (Scheme 4).

A number of *o*-quinones were subjected to constant potential electrochemical reduction. As seen in Scheme 5, the formation of the desired 1,3-dioxole is highly dependent on the *o*-quinone, in particular, on the formal potential ($E^{\circ\prime}$, defined as the average of the cathodic and anodic peak potentials). Substrates **12** and **15** with $E^{\circ\prime}$ of -0.93 V and -1.0 V, form the dioxoles in 92% and 98%, respectively. However, for substrate **17**, ($E^{\circ\prime} = -0.82$ V) only 37% was formed along with 15% of **19**. The formation of **19** is from electron transfer from the dianion to oxygen, which occurs during workup. When tetrachloro-*o*-quinone **20** ($E^{\circ\prime} = -0.43$ V) was subjected to electrolysis, no dioxole was observed. In conclusion, the more negative the $E^{\circ\prime}$ value for the *o*-quinone, the higher the percent yield of the 1,3-dioxole (Scheme 5).

Not only does the chemistry demonstrate a nice application of the cathodic reduction methodology, but the setup also is unique. The setup is a standard divided cell with a SCE reference electrode, a platinum plate auxiliary electrode, and a 12 cm^2 platinum net as the working electrode. The cell is also cooled by circulating water that passes through the outer walls of the cell. The cathodic compartment contains the platinum



Scheme 4 Mechanism for the electroreductive formation of 1,3-dioxolanes from *o*-quinones.



Scheme 5 Cathodic reduction of quinones to 1,3-dioxolanes.

net, dichloromethane, the electroactive species, and the electrolyte (Et$_4$NCl). The anodic compartment contains the platinum plate auxiliary electrode, dichloromethane, and the electrolyte. This compartment is separated form the cathodic compartment by a low porosity glass frit diaphragm (Fig. 7).

Little[13] recently reported the electrochemical formation of glycals *via* a cathodic reduction of glycosyl bromides. This methodology utilizes an undivided cell and a sacrificial zinc anode. Glycals are useful synthons and have found wide application in total synthesis, *C*-glycoside formation, and oligosaccharide formation. Standard methods for the synthesis of glycals involve metallic or organometallic reagents. As a result, electrochemistry provides another alternative for the use of metal reagents in organic synthesis.

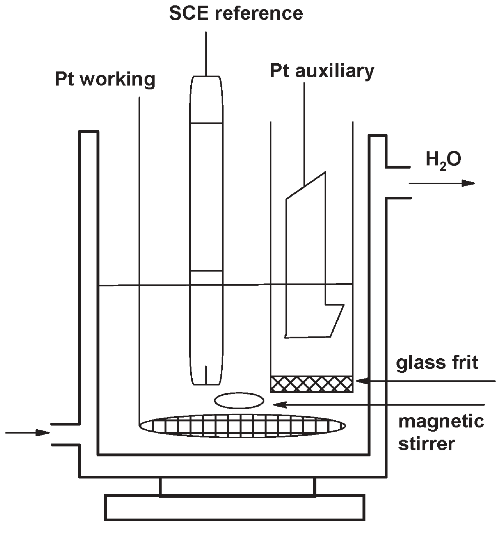
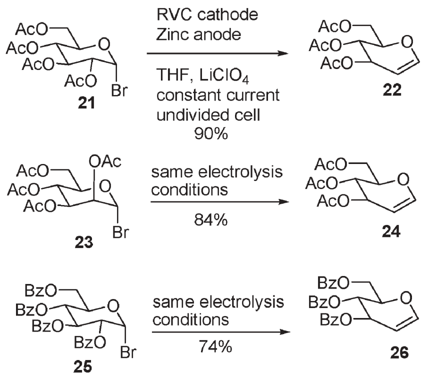


Fig. 7 Schematic of electrochemical cell for reduction of *o*-quinones to 1,3-dioxoles.



Scheme 6 Electrochemical reduction of glycosyl bromides.

Various glycosyl bromides were subjected to electrolysis conditions, outlined in Scheme 6. The reaction most likely involves direct reduction of the carbon–bromine bond followed by elimination of the neighboring acetate group. The reactions were performed in a 30 mL undivided cell utilizing an RVC cathode and a sacrificial zinc anode. The electrolyte was LiClO$_4$ and the reductions were carried out in freshly distilled and thoroughly degassed THF. The electrolyses were conducted under constant current conditions (400–500 mA) and proceeded to give moderate to high yields of variously protected glycals (Fig. 8).

The reduction of the carbonyl group is one of the most common and important synthetic transformations. Most of the common reducing agents involve the direct transfer of hydride from a metallohydride species. However, from the viewpoint of electrochemistry, an even more direct method involves the reduction of the carbonyl group with electrons themselves. The next two examples show how electrochemistry can be utilized to reduce carbonyl compounds to their corresponding alcohols or amines.

Schäfer reported on the transformation of ketones to their corresponding amines through electrochemical reduction of the *in situ* generated Schiff base.[14] This example demonstrates,

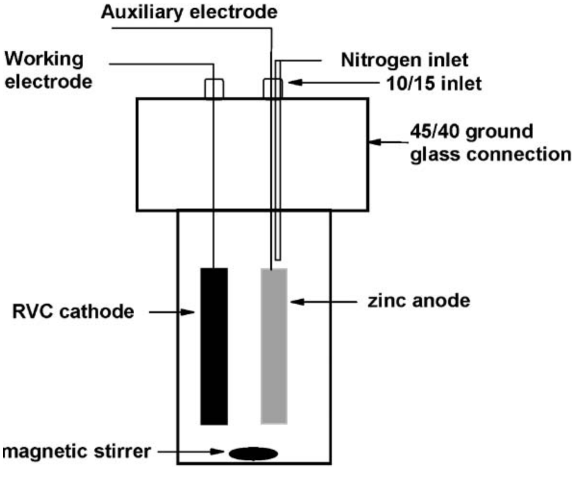
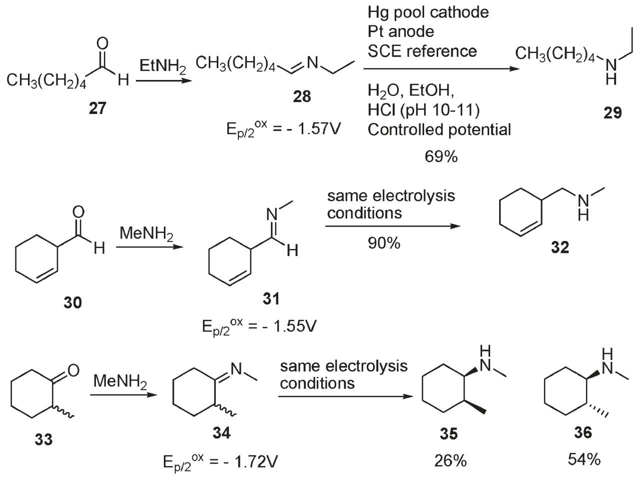


Fig. 8 Experimental setup for electrochemical reduction of glycosyl bromides.

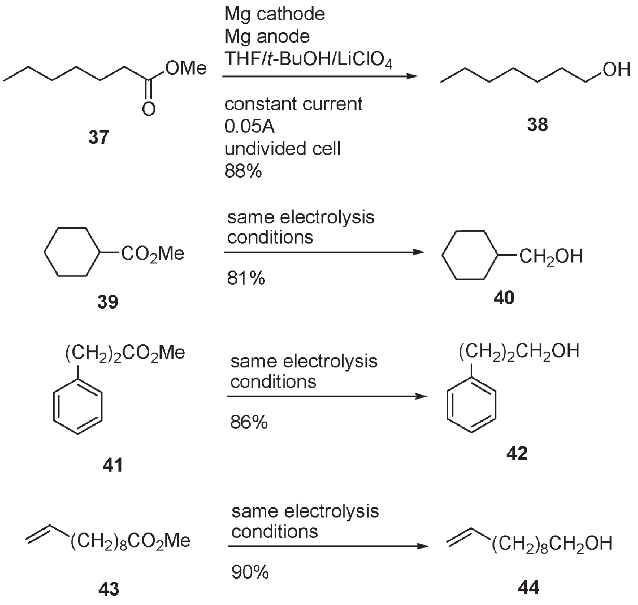
again, how electrochemical methods can be used for selective functional group interconversions. Reductive amination conditions typically use sodium cyanoborohydride or catalytic hydrogenation over palladium, platinum, or nickel. Catalytic hydrogenations are sometimes disadvantageous due to hydrogenation of other functional groups, such as alkenes, aromatic rings, or benzyl protecting groups. Platinum and nickel catalysts are also expensive and can be incompatible with sulfur-containing molecules.

Schäfer's methodology relies on the fact that Schiff bases reduce at potentials ~1.0–1.5 V less negative than their corresponding ketones. Using a divided cell identical to that in Fig. 2, the potential is set high enough to selectively reduce the Schiff base and not the ketone. The only major change is that the pH of the cell is held between pH 10 and 11. This methodology was applied to a number of cyclic and acyclic ketones and the corresponding secondary amines were all attained in high yields. In the two listed cases where diastereomers are possible, the thermodynamically favored *trans*-amines predominated. It is also noted that changing methylamine to isopropylamine increased these ratios up to five-fold (Scheme 7).

The final example in the cathodic reduction section illustrates the first cathodic reduction of aliphatic carboxylic esters (and *N*,*N*-dimethylformamides) to their corresponding primary alcohols. Although electrochemical reactions have been studied since the 1800s, the cathodic reduction of these types of esters and amides wasn't described until 1992 by the Shono group.[15] The arduous task of reducing esters and amides electrochemically is attributed to their relatively high negative reduction potentials (~ −3.0 V *vs* SCE). Through much trial and error, Shono found that a magnesium cathode must be used. Other cathodes such as Zn, Pb, Ni, Cu, Pt, or C were ineffective in promoting the reduction of esters or amides. In addition to the magnesium cathode, a protic solvent such as *tert*-butyl alcohol was needed. Other alcohols such as methanol, ethanol or isopropanol led to a significant decrease in the yield. An overall four-electron reduction, the reaction was allowed to proceed until 7 F mol^{-1} were consumed (for a four-electron reduction, the theoretical charge required would be 4 F mol^{-1}) (Scheme 8).



Scheme 7 Cathodic reduction of enamines.

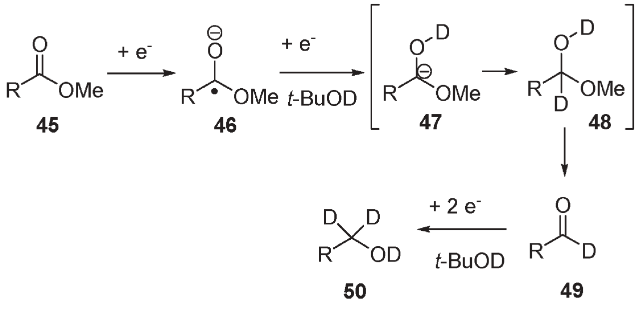


Scheme 8 Cathodic reduction of esters to their corresponding alcohols.

An informative mechanistic study on the reduction was performed with *t*-BuOD. It was found that the source of protons came exclusively from the *t*-BuOH. Not only does this serve as an informative mechanistic investigation, but it also provides an economical way to access deuterated species. Typically the reduction of carbonyls to the deuterated carbinols involves lithium aluminium deuteride, an expensive reagent. Typical deuterium incorporation with this methodology yielded 89–93% deuterium incorporation (Scheme 9).

Electroreductive cyclization reactions

All of the previous examples have demonstrated useful intermolecular reactions between an electrochemically generated anion or radical anion. The next section comprises some of the most interesting recent disclosures of how these highly reactive radical anions or anions can undergo intramolecular reactions. The electroreductive cyclization (ERC) reaction is becoming widely employed as a versatile means for intramolecular anionic cyclizations. The benefits of using the electrochemical methodology here is the same as in the prior electroreductive reactions: mild conditions, selective reduction abilities and applicability to a wide range of functionalities.



Scheme 9 Mechanism of cathodic reduction of esters in the presence of *t*-BuOD.

Ohmori *et al.* reported on the intramolecular cyclization reaction of acyl anion equivalents generated by *in situ* cathodic reduction of tributylphosphonium ions.[16] What makes this case even more impressive is that the tributylphosphonium ions are generated at the anode prior to reduction. Ohmori previously reported the electrochemical conversion of acids to aldehydes through oxidation of triphenylphosphine and cathodic reduction of the acyloxytriphenylphosphonium ions, however he extended this methodology to include the use of the generated acyl anion equivalent in intramolecular cyclization reactions by simply adding one more equivalent of phosphine.

In describing the reduction of acids to aldehydes, the sequence begins with the anodic oxidation (to be discussed later) of triphenylphosphine. The generated phosphine radical cation **52** then undergoes a second oxidation and reaction with a carboxylic acid. The newly formed acyloxyphosphonium ion **53** can migrate to the cathode where it will be first reduced to expel triphenylphosphine oxide and the acyl radical **55**. The highly reactive acyl radical quickly undergoes a second reduction to the acyl anion **56**, which becomes protonated in solution to yield the corresponding aldehyde **57** (Fig. 9). This methodology was used to synthesize a number of α-amino aldehydes from their α-amino acids. This process even worked with methionine, whose thioether sidechain is susceptible to oxidation (Table 2).

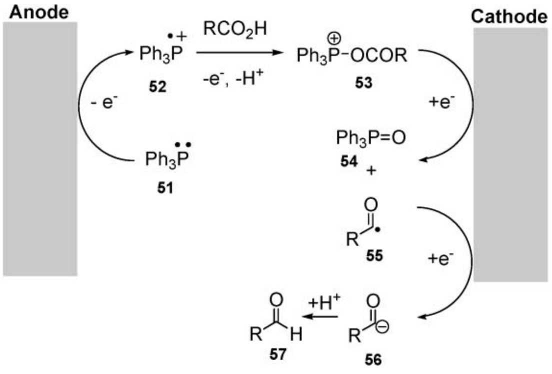
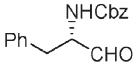
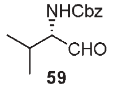
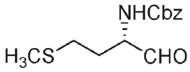
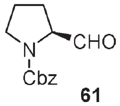


Fig. 9 Electrochemical reduction of acids to aldehydes.

Table 2 Cathodic reduction of amino acids

$$Ph_3P\ (2\ eq.) + RCO_2H \xrightarrow[\substack{Ph_3PHClO_4 \\ \text{undivided cell} \\ \text{constant current}}]{\substack{\text{Graphite anode} \\ \text{Graphite cathode} \\ CH_2Cl_2}} RCHO$$

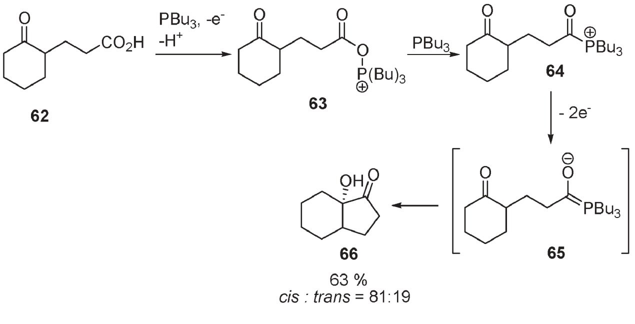
Entry	Aldehyde	Yield (%)
1	 **58**	83
2	 **59**	81
3	 **60**	84
4	 **61**	81

Ohmori later utilized this strategy to generate acyl anion equivalents to facilitate intramolecular cyclizations.[17] With the addition of a third equivalent of phosphine (in this case tributylphosphine), the acyloxyphosphonium ion undergoes attack by the excess phosphine to produce an acyltributylphosphonium species. Electroreduction of this acyltributylphosphonium ion generates an α-oxy ylide, the synthetic equivalent of an acyl anion. Ohmori utilized this approach to facilitate intramolecular cyclizations to produce 5- and 6-membered rings (Scheme 10).

These reactions were carried out in an undivided cell with a carbon plate anode and cathode, each 12 cm^2. The plates were separated by 1 cm and submerged into a solution of the keto acid, PPh_3, $MeSO_3H$, and $PhCH_2(Et)_2NCl$. These cells can be constructed in many ways. A Teflon® spacer can be used to separate the cathode and anode or any other insulating, chemically inert material. The carbon plates can be assembled together with a Teflon® "cap" and connected to the potentiostat by means of copper screws passing through the Teflon® and into the carbon. This setup is particularly useful when air and/or moisture sensitive reactions need to be carried out. The Teflon® can be machined to fit snug inside of the electrochemical cell and a hole drilled to allow an inert atmosphere to be introduced (Fig. 10).

One of the unique characteristics of cathodic reductions is that some can be classified as umpolung reactions. An umpolung reaction is any transformation that effects a reversal of polarity in a functional group, changing a normally nucleophilic site into an electrophilic one, and *vice versa* (Scheme 11).

Little[18] reported the cathodic reduction of α,β-unsaturated esters to undergo an umpolung transformation that creates a nucleophilic β-carbon. This nucleophilic β-carbon was used to facilitate ring-closing reactions on various ketones and aldehydes in good yields (70–79%). In addition, CV studies were undertaken to prove that of the two possible functional groups for electrochemical reduction, the ketone or the α,β-unsaturated ester, it was the α,β-unsaturated ester that



Scheme 10 Intramolecular cyclizations from electrochemically generated acyl anion equivalents.

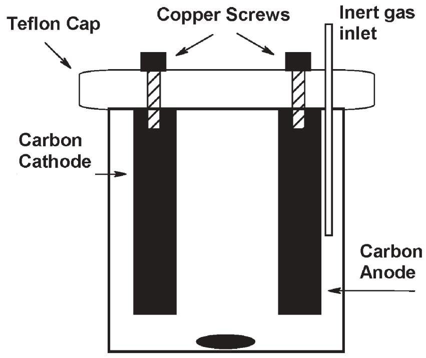
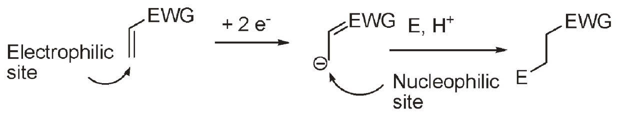


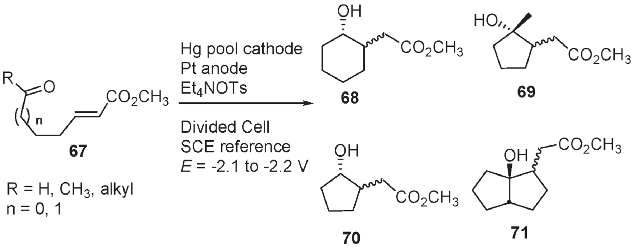
Fig. 10 Cell schematic.



Scheme 11 Some cathodic reductions resulting in a normally electrophilic site becoming nucleophilic, or an umpolung transformation.

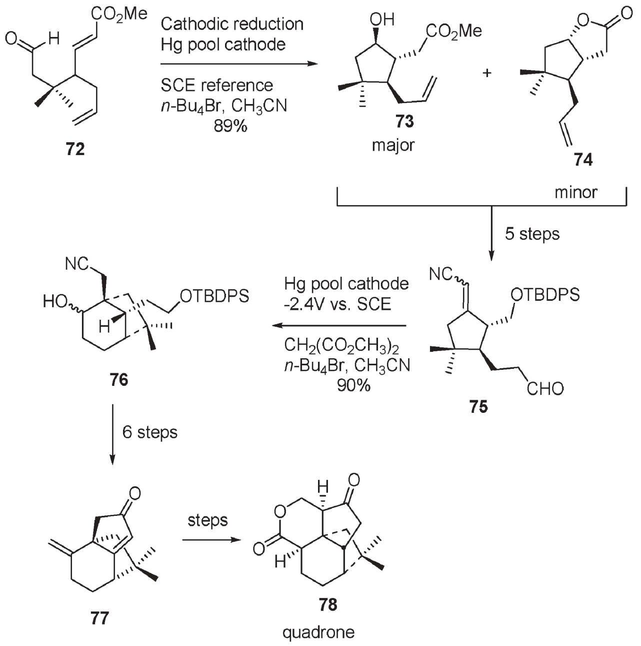
indeed was reduced first. With the α,β-unsaturated ester present, only one reduction wave was observed with $E_{pc} = -2.14$ V (*vs* SCE). After hydrogenation of the α,β-unsaturated ester, the CV displayed no such reduction wave. Little went on to study how temperature and different proton sources effect not only the yield, but also the *cis* : *trans* ratio (Scheme 12).

Soon after the disclosure of this methodology, Little and coworkers published the formal total synthesis of quadrone, **78**.[19] This approach uses two electroreductive cyclizations previously described. The first ERC involves the reduction of the α,β-unsaturated ester **72** to yield an isomeric mixture of **73** and **74**, in an impressive 89% yield. Although a mixture is produced, both isomers can be carried forward to **75** after 5 steps. With **75**, another ERC, this time utilizing an α,β-unsaturated nitrile, cyclized smoothly to produce **76** with a 90% yield. After 6 additional steps, **77** was obtained, thus completing the formal total synthesis of quadrone. This is an excellent example of how ERCs can be applied toward total synthesis and nicely demonstrates the synthetic utility of electrochemical key steps (Scheme 13).



Compound	Yield (%)	*cis* :*trans*
68	72	1.8:1
69	70	1.4:1
70	76	5.1:1
71	79	11.4:1

Scheme 12 Reductive cyclizations of α,β-unsaturated esters.

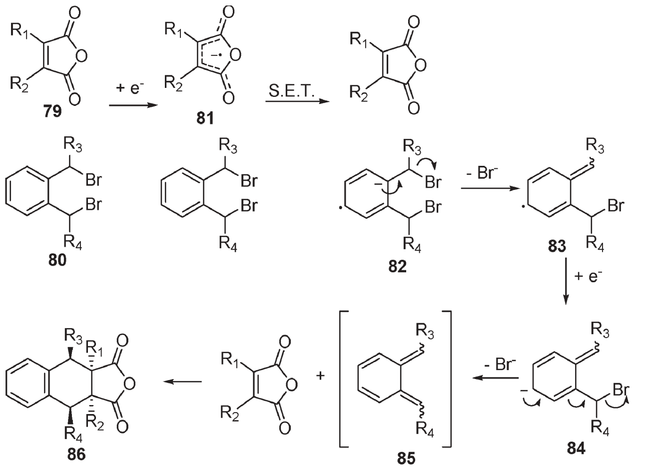


Scheme 13 Little's formal synthesis of quadrone utilizing two electroreductive cyclization reactions.

Utley and Wyatt disclosed the *in situ* generation of *o*-quinodimethanes from the cathodic reduction of α,α′-dibromo-1,2-dialkylbenzenes in the presence of dienophiles, such as maleic anhydride.[20] Yields were moderate to good, depending on substitution, and the electrochemical studies also revealed interesting mechanistic details. It was found, again through CV studies, that the dienophile possesses a higher negative reduction potential, implying that the first reduction takes place here to generate the radical anion at maleic anhydride. As the alkene is electron deficient, the role as an electron acceptor is reasonable. Mechanistically, once the radical ion is generated, it quickly undergoes electron transfer to the dibromide. Once the radical anion is generated in the aromatic ring, loss of bromide is fast to generate the aryl radical. The aryl radical can then undergo reduction to the anion, followed by loss of the second bromide to generate the *o*-quinodimethane species. These intermediates are highly reactive and undergo rapid dimerizations if no species is present to further any reaction. In this case, the maleic anhydride traps the *o*-quinodimethane and forms the Diels–Alder adducts (Scheme 14). These reactions were carried out with a standard mercury pool electrode (see Fig. 6) in a divided cell with a Ag/Ag$^+$ reference electrode.

Anodic oxidation reactions

The anodic oxidation of organic molecules has also developed significantly over the past few decades, and includes two well-known named reactions, the Kolbe electrolysis reaction and the Shono oxidation. The majority of anodic oxidations involve cyclization reactions, and as such, many of the following examples involve ring closures initiated by an oxidation at the anode. The transition from cathodic reductions to anodic oxidations switches the focus from the cathode to the anode with the reactive species being either radical-cations or formal



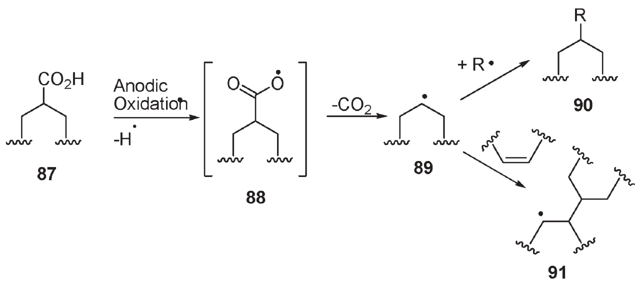
Scheme 14 Electrochemical generation of *o*-quinodimethanes.

cations. It is also important to note that the majority of anodic oxidations will take place in undivided cells as constant current experiments. Many of the setup diagrams have already been shown and, for simplicity, will not be pictured unless significant changes have been made. Due to the existence of many reviews on anodic oxidations, including a recent comprehensive review,[1c] only a few recent examples have been chosen to illustrate the potential synthetic applications.

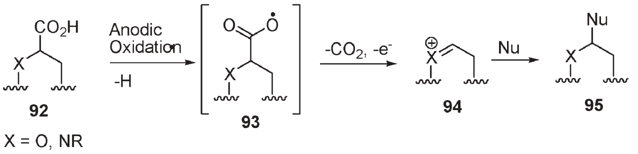
Anodic oxidations

As previously mentioned, the Kolbe electrolysis (or Kolbe oxidation) is one of the most popular and well-known electrochemical reactions. As a result, it has been extensively studied and reviewed.[1a] The Kolbe electrolysis is the electrochemical decarboxylation of an organic acid to generate a carbon-centered radical. As with standard radical chemistry, these radicals can undergo dimerization, addition to alkenes, or facilitate radical chain reactions. A general scheme can be seen in Scheme 15.

An extension of the Kolbe oxidation has been deemed the non-Kolbe oxidation. The difference here is the carboxylic acid is positioned α to a heteroatom, such as nitrogen or oxygen. The donating power of the adjacent heteroatom lowers the oxidation potential of the initial radical species such that a second, rapid electron loss ensues to yield oxonium or iminium ions with a formal positive charge. These species are susceptible to nucleophilic attack and have become highly regarded as a means of forming new carbon–carbon, carbon–oxygen, and carbon–nitrogen bonds (Scheme 16).



Scheme 15 The Kolbe electrolysis forming carbon-centered radicals.



Scheme 16 The non-Kolbe oxidation followed by nucleophilic trapping.

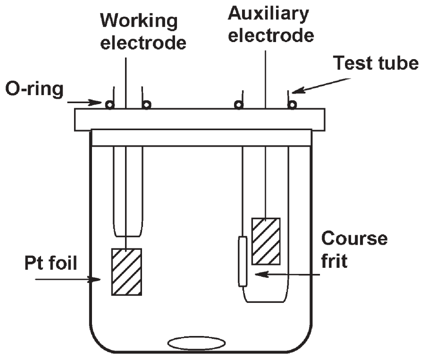
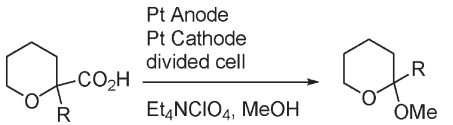


Fig. 11 Electrochemical cell setup for non-Kolbe oxidation.

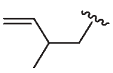
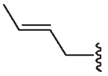
A potentially useful example of the non-Kolbe oxidation was performed by the lab of Wuts several years ago.[21] Wuts showed that spiroketals could be synthesized through an electrochemical decarboxylation reaction involving tetrahydropyrans with carboxylic acids substituted at the 2-position. The decarboxylation took place in methanol, K_2CO_3, and Et_4NClO_4 as the supporting electrolyte in a divided cell with a platinum anode and platinum cathode (Fig. 11). The decarboxylation proceeded smoothly and was high yielding in all examples (Table 3).

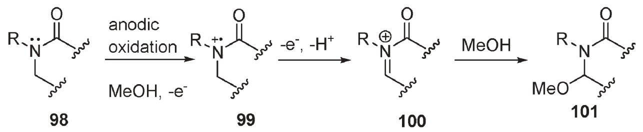
Another well-known electrochemical oxidation is the Shono oxidation. Shono's protocol generates *N*-acyliminium ions from the oxidation of amides. The popularity of this method has led to its application to the total synthesis of natural products, asymmetric building blocks for organic synthesis, and many other applications in medicinal chemistry. Since a comprehensive review already exists covering these

Table 3 Non-Kolbe oxidation in the synthesis of ketals



96 97

Entry	R	Yield (%)
1		87
2		75
3		90



Scheme 17 The mechanism for the Shono oxidation *via* direct oxidation of the amide.

applications,[1b] a general overview will be presented along with a recent example from the literature applying the Shono oxidation toward a total synthesis.

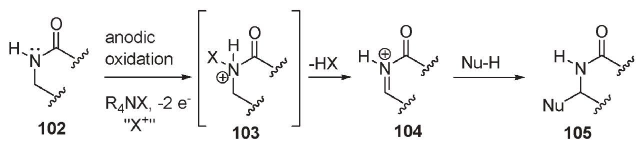
The oxidation of amides to *N*-acyliminium ions can be performed in two ways: direct oxidation and indirect oxidation. The true Shono oxidation is an example of a direct oxidation. Here, the *N*-acyliminium ion is generated by the electrochemical oxidation of the amide, followed by nucleophilic trapping. The trapping moiety is generally the protic solvent in which the reaction was carried out (Scheme 17).

The second method for generating *N*-acyliminium ions electrochemically is through the oxidation of a halogenated electrolyte to form the highly reactive “X^{+}” species. This species can in turn react with the amide nitrogen and through loss of HX form an *N*-acyliminium ion. This process is also often used to functionalize positions α to amines (Scheme 18).

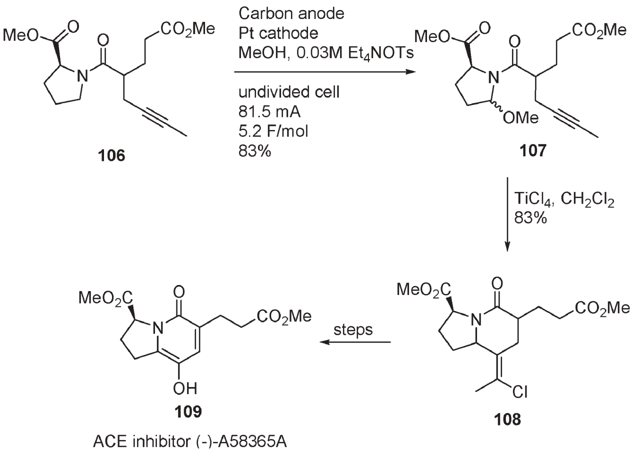
Moeller used the Shono oxidation in the total synthesis of the ACE inhibitor (−)-A58365A.[22] Amide **106** was electrochemically oxidized in an undivided cell with a carbon anode, platinum cathode, and in 0.03M Et_4NOTs in methanol. A constant current of 81.5 mA was passed until 5.2 F mol^{-1} were consumed. An 83% yield of **107** was isolated and was successfully treated with $TiCl_4$ to provide the bicyclic adduct **108**. This adduct was carried forward in the synthesis of **109** (Scheme 19).

Nitrate ions can also participate in a wide array of electrochemical oxidation reactions that include addition to double bonds and oxidation of alcohols.[23] The oxidation of nitrate (NO_3^-) leads to the highly reactive nitrate radical that has been shown by Shono to effect the formation of an acyl radical that can add to an activated olefin and form potentially useful synthons.[24] The reactions were carried out in an undivided cell with two platinum electrodes in a 10 : 1 MeCN : H_2O solution with $LiNO_3$ as the electrolyte. The reaction was carried out at a constant current of 200 mA and was judged complete when 10 F mol^{-1} had passed through the solution (Scheme 20).

Electrooxidative cyclizations



Scheme 18 Shono oxidation *via* oxidation of electrolyte to form “X^{+}”.

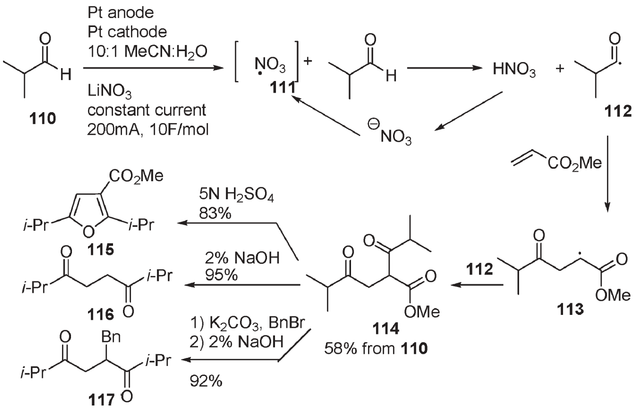


Scheme 19 The total synthesis of (−)-A58365A utilizing a Shono oxidation.

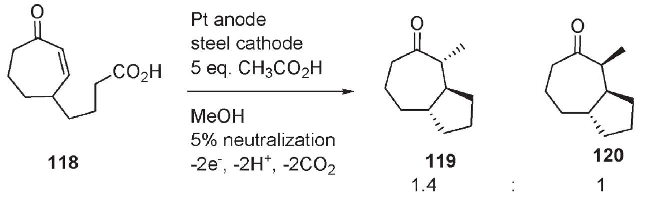
The use of electrochemically generated radical-cations has received much attention over the past few decades. Electrooxidative cyclizations (EOCs) are tolerable of most functionalities and have also been applied to the synthesis of complex natural products. The next examples will introduce the most recent examples of EOCs and highlight how EOCs can be incorporated into everyday synthetic transformations.

EOCs are all based on the same general principle: electrooxidation to form a radical-cation, followed by intramolecular trapping of a nucleophile. What makes these reactions unique is that they take place in highly nucleophilic solvents, such as isopropanol or methanol. This again stresses the fact that these reactions take place at the surface of the electrode in the electrical double layer. This allows for the intramolecular reaction to be kinetically faster than diffusion though the double layer, followed by nucleophilic attack of solvent. Popular functional groups involved in EOCs are electron-rich alkyl enol ethers,[25] silyl enol ethers,[32,33] ketene dithioacetals,[26] and phenols.[27] Nucleophiles can be electron-rich aryl- or hetero-aryl rings, enol ethers, hydroxyls, or most other nucleophilic functional groups. In addition, the Kolbe electrolysis is often used as a means for initiating radical cyclizations. All of the above-mentioned examples will be covered briefly.

Schäfer and co-workers have elegantly applied the Kolbe electrolysis to the synthesis of complex organic molecules.



Scheme 20 Electrochemical generation of nitrate radical and its use to facilitate the formation of acyl radicals.



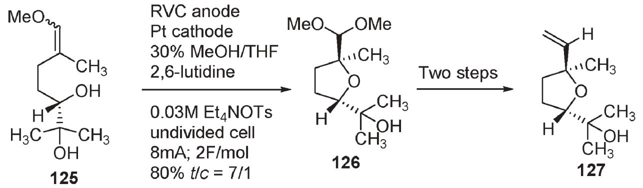
Scheme 21 Kolbe electrolysis used to initiate radical cyclization.

Schäfer used this methodology to construct perhydroazulenes, a class of compounds notoriously difficult to make.[28] Beginning with acid **118**, electrochemical oxidation in an undivided cell with a platinum anode and steel cathode initiated the radical decarboxylation that led to the cyclized perhydroazulene. This reaction sequence took place in acetic acid (called co-electrolysis), which also undergoes radical decarboxylation to form a methyl radical that couples to the radical from the cyclization. The reaction proceeded in a 72% overall yield, producing a 1.4 : 1 mixture at the methyl at C(2) (Scheme 21).

Moeller and Wright have carried out extensive studies on the electrochemical coupling of electron-rich enol ethers with various nucleophiles. These reactions are another example of how electrochemistry facilitates the reversal of polarity (umpolung) of electron-rich olefins and changes them into electrophilic sites. Two applications of this methodology that resulted in the total synthesis of natural products will be discussed, along with the methodology itself.

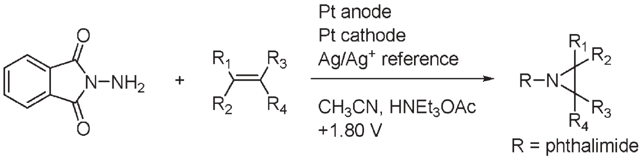
Moeller has reported on the use of anodic oxidations to generate radical cations of alkyl enol ethers, followed by nucleophilic trapping with a pendant hydroxyl to form tetrahydrofuran-containing molecules.[29] The electrochemical oxidation of the electron-rich enol ether provides a radical-cation that is quickly trapped by the pendant hydroxyl group. A second one-electron oxidation generates the stabilized oxonium ion, which is trapped by the nucleophilic solvent to form the dimethoxy ketal. To further demonstrate the ease with which these reactions can be carried out, this methodology was also performed using a 6 volt lantern battery as the power supply (Scheme 22).[30]

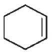
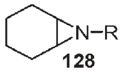
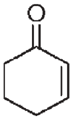
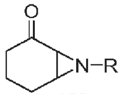
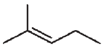
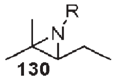
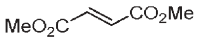
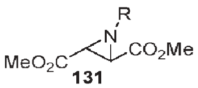
This novel methodology was used by Moeller to synthesize the natural product (+)-linalool oxide **127**. The methoxy enol ether **125** (produced in two steps from commercially available material) is electrochemically oxidized to generate the dimethoxy acetal **126**. The electrolysis was carried out in an undivided cell with an RVC anode, and a Pt cathode, in a solution of 0.03M Et_4NOTs in methanol. The addition of 2,6-lutidine was necessary to neutralize the generated acid. This sequence consumed 2 F mol^{-1} and produced the desired *trans* orientation at the 2- and 5-positions of the tetrahydrofuran ring as the major isomer (7 : 1). The stereochemistry is believed to be controlled by stereoelectronic factors because the incoming hydroxyl attacks the π* orbital of the radical cation (for a more in-depth discussion, see ref. 29). The newly formed tetrahydrofuran is transformed into (+)-linalool oxide in just two additional steps (Scheme 23).



Scheme 23 The use of an anodic oxidation in the total synthesis of (+)-linalool oxide.

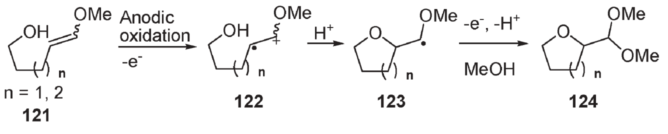
Table 4 Electrochemical aziridination of olefins



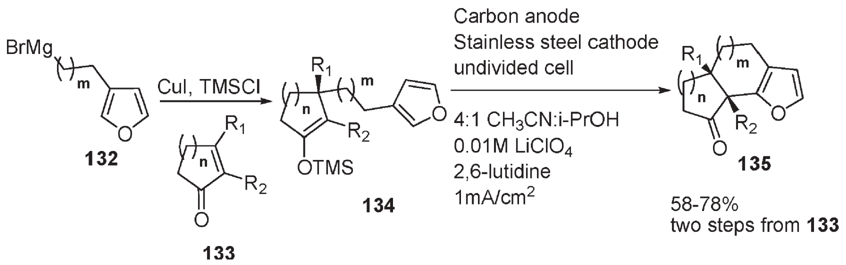
Entry	Substrate	Product	Yield (%)
1		 **128**	85
2		 **129**	78
3		 **130**	91
4		 **131**	92

Yudin and Siu reported on the electrochemical aziridination of olefins.[31] This process again eliminates the use of $Pb(OAc)_4$, a highly toxic chemical oxidant typically used in aziridination processes. This application was applied to the aziridination of a number of alkenes by phthalimide with the majority producing high yields of aziridines (Table 4).

These reactions were carried out in a divided cell with a platinum anode and cathode with a Ag/AgCl reference electrode. The value of +1.60 V was initially chosen due to the fact that the oxidation potential of $Pb(OAc)_4$ was determined by CV studies to be +1.60 V. However, through optimization, +1.80 was the optimal oxidation potential. The anodic compartment contained the two substrates, CH_3CN, the reference and anode electrodes, and the electrolyte



Scheme 22 Anodic oxidation of electron-rich alkyl enol ethers and intramolecular trapping of hydroxyl.



Scheme 24 Two-step construction of annulated furans.

(NEt_3OAc). The cathodic compartment contained the auxiliary electrode and the electrolyte in CH_3CN. The experimental setup is identical to that in Fig. 2. It should also be noted that these reactions failed when the Pt anode was replaced with graphite. Although difficult to explain, this is an excellent example of how some electrochemical reactions are sensitive to electrode materials.

Wright and coworkers have developed a two-step, conjugate addition/anodic oxidation sequence to gain access to annulated heterocycles, particularly furans.[32] The sequence begins with the conjugate addition of a furyl-appended cuprate **132** to an α,β-unsaturated enone **133**, with *in situ* trapping of the enolate as a silyl enol ether **134**. As with the case of the alkyl enol ethers, the silyl enol ether will undergo electrochemical oxidation to generate a radical cation that will undergo nucleophilic attack by the appended heterocycle. After a second one-electron oxidation and trapping with the nucleophilic solvent (iPrOH), the annulated heterocycle **135** is formed after acidic workup (Scheme 24). In this case, isopropanol must be used instead of methanol to prevent methanolysis of the silyl enol ether. This methodology has been used to form 5-, 6-, and 7-membered rings and has been performed on various 2- and 3-substituted cyclopentenones, cyclohexenones, cycloheptenones, and acyclic enones. Enones containing functionality such as phenolic ethers, carbamates, esters, ketals, and terminal vinyl groups were also studied and found to be highly tolerable of this methodology. Through optimization, it was found that the optimal current density was 1 mA cm^{-2} at the anode (Scheme 24).

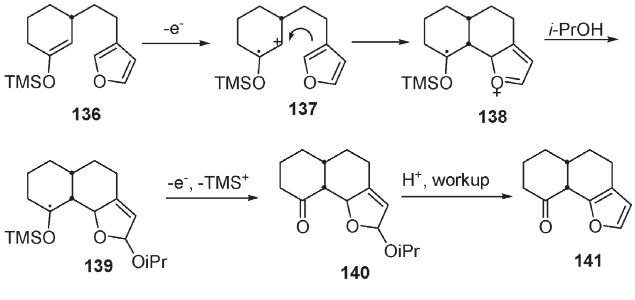
Mechanistically, the electrochemical oxidation could take place at one of two sites: the silyl enol ether or the furan ring. CV studies were undertaken and it was found that a TMS enol ether had an oxidation potential of 0.87V (*vs* Ag/Ag^+) and a monosubstituted furan had an oxidation potential of 1.31 V (*vs* Ag/Ag^+). The difference suggests that the oxidation first takes place at the enol ether to generate the radical cation **137** that is trapped by the furan to generate **138**. Quenching of the oxonium ion with *i*-PrOH followed by a second oxidation and loss of TMS^+ generates the acetal **139**. Upon acidic workup, the annulated furan is generated as a single *cis*-fused isomer **141** (Scheme 25).

These reactions were carried out using electrodes fashioned from carbon and stainless steel plates. Since it was found that the current density was one of the critical factors in the success of these reactions, the plates were chosen to allow for easy calculation and for high surface area. Carbon rods were initially used as both the anode and cathode, but the low surface area caused long reaction times and lower yields. Typical reaction times for carbon rod experiments were 18–20 hours and for the new electrodes the reaction times were reduced to 1.5–3 hours, independent of the scale. These electrodes can be fashioned by an apparatus shop and all materials are commercially available. The design was made adaptable to scales ranging from 150 mg to 15 g of enol ether and, as a result, made to fit 50 mL, 250 mL, 600 mL and 4 L beakers (the electrode for the 4 L beaker must be supported on an iron ring and stand to prevent collapse of the beaker). The schematic shown in Fig. 12 was made to fit into a 250 mL beaker.

Moeller recently utilized a silyl enol ether anodic oxidation/furyl trap in his total synthesis of (−)-alliacol A.[33] Beginning with **142**, anodic oxidation on an RVC anode, carbon cathode, in 30% $MeOH/CH_2Cl_2$ with $LiClO_4$ and 2,6-lutidine produced the annulated furan **143**. After deprotection of the TBS ether and conversion of the alcohol to the primary iodide, the newly formed annulated furan underwent silver-promoted nucleophilic displacement of the iodide in methanolic THF to provide the acetal **144**. This acetal was converted to (−)-alliacol A **145** in just 12 more steps (Scheme 26).

Chemically modified electrodes

One of the most promising areas for advancement of electrochemical methodology in organic synthesis lies in the development of chemically modified electrodes. Polymers can be deposited onto the surface of the electrode and modified thereafter. Solutions of monomers can also be electrochemically polymerized onto the surface and modified further. Osa's group has made many promising advances in the past couple of decades on the TEMPO-modified graphite felt electrodes.[34] Osa has shown these modified electrodes can be used to effect oxidations of alcohols and induce lactonization reactions. These modified electrodes may appear complex, but their



Scheme 25 Mechanism of annulated furan formation.

construction is straightforward and can be performed in any synthetic laboratory.

These electrodes can be prepared according to the method of Osa *et al.* A carbon felt electrode (5 × 2 × 0.5 cm, 450 mg) is dipped into a 2.5 wt% solution of polyacrylic acid (PAA) in methanol and dried under vacuum. The coated amount of PAA was determined to be about 3 wt%. Next, the polymer was crosslinked with hexamethylenediamine in DMF with dicyclohexylcarbodiimide (DCC). The electrode was then treated with a solution of 4-amino-2,2,6,6-tetramethylpiperydinyl-1-oxyl (4-amino-TEMPO) in DMF and DCC. To "cap" the remaining free carboxylic acids, dibutyl sulfate was reacted with the electrode to form the butyl esters (Scheme 27).

A nice application of these chemically modified electrodes was published by the Osa group and involved the electrocatalytic oxidation of methyl-substituted diols to form optically pure lactones, with (−)-sparteine as a chiral base. The electrochemical oxidation of the alcohols **146**, **148**, and **150**, produced optically pure lactones in both high yield and enantiomeric excess. It is believed that the lower yield of **151** is due to the selective oxidation of only the *S*-isomer (Table 5). These reactions were carried out in a divided H-cell separated by a cation-exchange membrane (Naflon 117). The anode compartment contained the TEMPO-modified electrode, $NaClO_4$, CH_3CN, (−)-sparteine, and a Ag/Ag^+ reference electrode. The cathode compartment contained CH_3CN, $NaClO_4$, and an unspecified counter electrode. Although not specified, this could be either a platinum wire or a carbon rod (Table 5). See Fig. 2 for setup.

The mechanism of this transformation involves electrochemical oxidation of the polymer-bound TEMPO to the oxoammonium salt. This salt (2 equivalents) reacts with the (−)-spartenine–diol complex to form the monoaldehyde, which forms an enantiomerically enriched lactol. The lactol is oxidized by a second equivalent of the oxoammonium salt to produce the enantiomerically pure lactone. The oxidation of

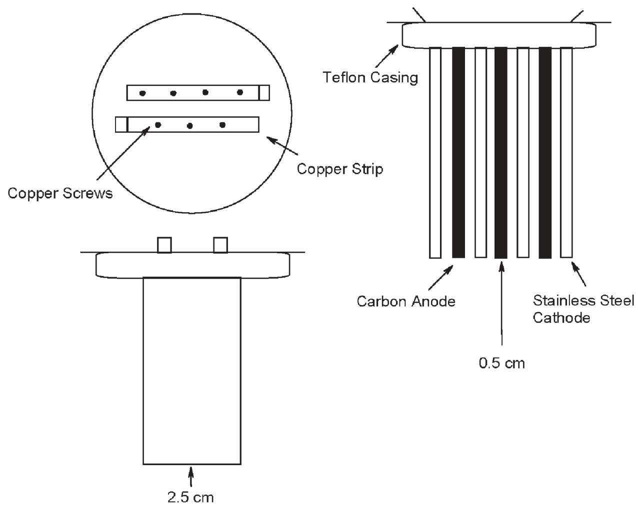
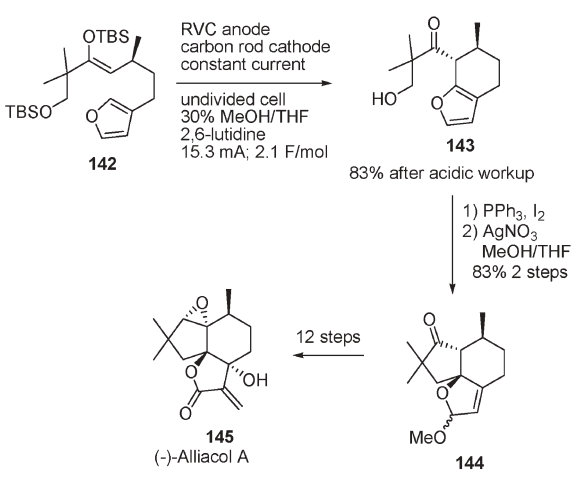
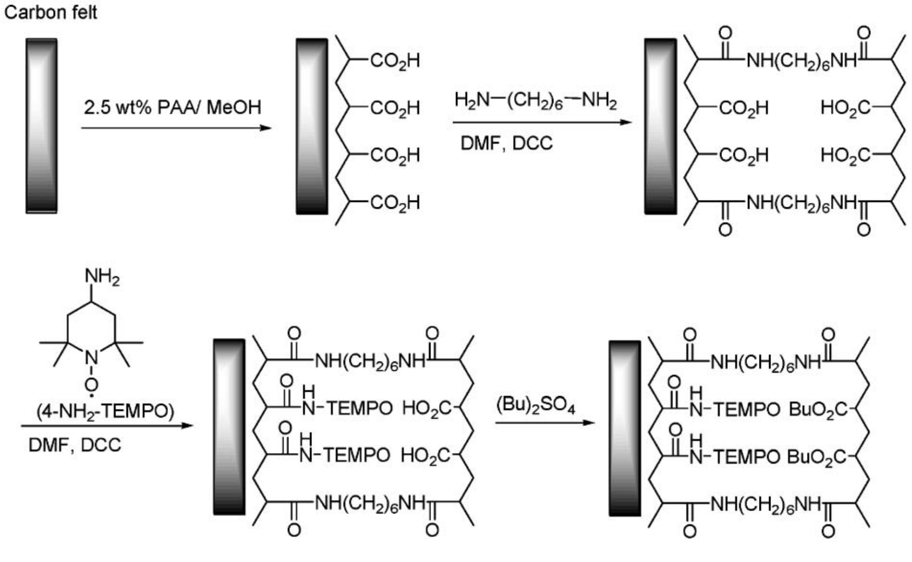


Fig. 12 Schematic of electrodes.

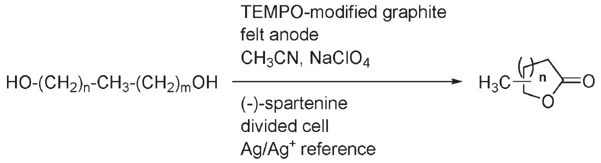


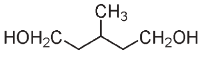
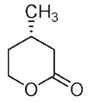
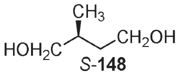
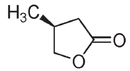
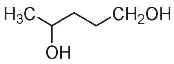
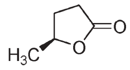
Scheme 26 Total synthesis of (−)-alliacol A.



Scheme 27 Construction of TEMPO modified carbon felt electrodes.

Table 5 TEMPO modified electrode oxidation of alcohols to lactones



Entry	Substrate	Product	Yield (%)	*ee* (%)
1	 **146**	 *S*-**147**	94	98
2	 *S*-**148**	 *S*-**149**	97	100
3	 (±) **150**	 *S*-**151**	48	99

the polymer-bound TEMPO electrodes was found to be reversible when subjected to CV studies and the electrodes could be easily recovered and reused.

Conclusions

It is clear that the growing interest of synthetic chemists in electrochemical methodology is related to the wide applicability and utility of these methods. In this tutorial review, numerous transformations were discussed that involved either cathodic reductions or anodic oxidations, many on functionally-rich substrates. These reactions can be highly selective and many replace or dramatically reduce the need for toxic, expensive metals. Although many examples could not be covered, the cited references will point the interested reader to further discussions. Most of the equipment required for electrochemical transformations is now commercially available or can easily be constructed with the help of a skilled apparatus shop. It is the belief of the authors that many more electrochemical transformations will be disclosed and this method will continue to evolve into a widely used and accepted method for synthetic chemists.

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