

# 1

## Methods to Investigate Mechanisms of Electroorganic Reactions

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## 1.1 Introduction

### 1.1.1 Scope: Methods of Molecular Electrochemistry

Reaction mechanisms divide the transformations between organic molecules into classes that can be understood by well-defined concepts. Thus, for example, the  $S_N1$  or  $S_N2$  nucleophilic substitutions are examples of organic reaction mechanisms. Each mechanism is characterized by transition states and intermediates that are passed over while the reaction proceeds. It defines the kinetic, stereochemical, and product features of the reaction. Reaction mechanisms are thus extremely important to optimize the respective conversion for conditions, selectivity, or yields of desired products.

Reaction mechanisms are also defined for *electroorganic* reactions, induced by or including an electron transfer at an electrode. Knowledge of such electrode reaction mechanisms includes, preferably but not exclusively, the potential at which the reaction proceeds, the proof of intermediates, the electron stoichiometry, the kinetics of the various reaction steps, and the transport properties of the species involved. Recently, the terms

*molecular electrochemistry* [1] or *dynamic electrochemistry* [2] have been used for that part of electrochemistry that studies the mechanistic events at or near an electrode on a molecular level.

There are a large number of methods (often also called *electroanalytical methods*) for such studies of which only the most important ones can be covered in this chapter. Moreover, technical details of the methods cannot be described, and emphasis will be placed on their use in mechanistic electroorganic chemistry.

### 1.1.2 Historical Development

Although organic electrochemistry had already been established in the nineteenth century, only the 1960s saw the advent of detailed electroorganic mechanistic studies.

Most of the techniques employed can be traced back to polarography, which was already in use in 1925, to determine the concentrations of organic molecules [3]. Technical developments in instrumentation (potentiostats) [4], the use of nonaqueous electrolytes [5], and the digital control of experiments [6] led to the spread of electroanalytical techniques. For example, cyclic voltammograms are frequently and routinely used today to define the redox

properties of newly synthesized organic compounds similar to the use of NMR spectra for structural characterization.

Numerical simulation of the experiments [7] became increasingly available during the 1980s, and ultramicroelectrodes [8] opened the way not only to ever-faster timescales but also to finer lateral resolution when characterizing electrode processes. Finally, combinations with spectroscopic and mass-sensitive devices opened new ways to augment information available from molecular electrochemical experiments.

This development contributes to a still-increasing body of knowledge about the fate of organic molecules upon oxidation and reduction.

## 1.2

### Why and How to Investigate Mechanisms of Electroorganic Reactions

#### 1.2.1

##### Steps of Electrode Reaction Mechanisms

##### 1.2.1.1 General

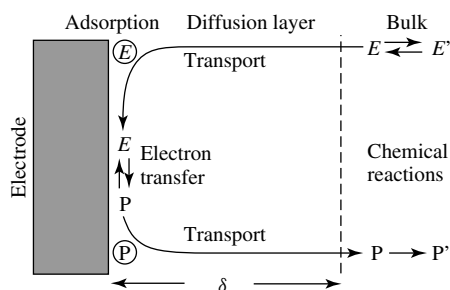
As heterogeneous reactions at the interface electrode–electrolyte, electrochemical reactions are intrinsically more complex than typical (thermal) chemical transformations (Figure 1). We mostly neglect the exact structure of the interface in the following description. Transport of the educt

(substrate) from the bulk of the electrolyte to the electrode plays an important, often rate-determining role. The electron transfer step occurs at the interface. The product of the redox reaction is transported back to the bulk. Purely chemical reactions may precede or follow these steps. Specific interactions of any species present in the electrolyte with the electrode surface leads to adsorption, which may considerably influence the overall process.

##### 1.2.1.2 Transport

Three types of mass transport are important at an electrode:

1. *Diffusion* (along a concentration gradient) is observed if the solution near the electrode is depleted from a substrate or a product is accumulated. Diffusion is characterized by a diffusion coefficient  $D$  (typical value:  $10^{-5}$  cm<sup>2</sup>/s) and extends over a diffusion layer (thickness:  $\delta$ ) that develops from the electrode into the electrolyte. At the outward boundary the concentrations approach their bulk values.
2. *Migration* (in the electrical field between the anode and the cathode) contributes to the movement of charged species. In most practical experiments, however, the concentration of supporting electrolyte ions is much higher (100–1000:1) than that of other ions.



**Fig. 1** Steps constituting a typical organic electrode reaction; E, E': educt, P, P': product; circles indicate adsorbed molecules.

Hence, migration of the latter is suppressed. On the other hand, migration becomes important at modified electrodes or in electrolytes of low ion concentration [9].

3. *Convection* (of the electrolyte liquid phase as a whole) can be natural (due to thermal effects or density gradients) or forced (principal mass transport mode in hydrodynamic techniques). Still, however, close to the electrode surface a diffusion layer develops.

If we neglect migration, experiments can be performed under conditions of minimal convection, which are thus dominated by diffusion. Since  $\delta$  increases with time  $t$  in such a case, *nonstationary conditions* exist. On the other hand, if convection dominates in the electrolyte bulk,  $\delta \neq f(t)$ , and we approach *stationary conditions*, as far as diffusion is concerned.

### 1.2.1.3 Electron Transfer

The electron transfer (ET) at the interface between electrode and electrolyte is central to an electrode reaction. Electrons pass through the interface. Macroscopically we observe a current  $i$ .

The transfer of an electron to (reduction) or from (oxidation) the substrate is an activated process, characterized by a rate constant  $k_s$ , defined as the standard (or formal) potential  $E^0$ , and the transfer coefficient  $\alpha$ . The three situations mentioned below can be distinguished:

1. ET much faster than transport (transport control). Electrochemical equilibrium is attained at the electrode surface at all times and defined by the electrode potential  $E$ . The concentrations  $c_{\text{ox}}$  and  $c_{\text{red}}$  of oxidized and reduced forms of the redox couple, respectively, follow the Nernst equation (1) (*reversible ET*)

$$\frac{c_{\text{ox}}}{c_{\text{red}}} = \exp \left[ \frac{nF}{RT} (E - E^0) \right] \quad (1)$$

( $n$  = number of electrons transferred,  $F$  = Faraday constant,  $R$  = gas constant,  $T$  = temperature). The current is proportional to the amount of material transported to the electrode in a time unit.

2. ET much slower than transport (ET control). The current follows the Butler–Volmer equation (2)

$$i = i_0 \left\{ \exp \left[ \frac{-\alpha nF}{RT} (E - E^0) \right] - \exp \left[ \frac{(1 - \alpha)nF}{RT} (E - E^0) \right] \right\} \quad (2)$$

where  $i_0$  defines the exchange current at  $E = E^0$  (*irreversible ET*). A physical interpretation of  $\alpha$  is related to the ET transition state (see the comprehensive discussion in ref. [10]). It is furthermore expected that  $\alpha$  is potential dependent and important mechanistic conclusions follow [11, 12].

3. ET and transport have comparable rates. This mixed-control situation is characterized as *quasi-reversible*.

A given electrode reaction may correspond to any of these situations depending on the experimental conditions, in particular on the external control of mass transfer.

### 1.2.1.4 Chemical Kinetic Steps

Most electrode reactions of interest to the organic electrochemist involve chemical reaction steps. These are often assumed to occur in a homogeneous solution, that is, not at the electrode surface itself. They are described by the usual chemical kinetic equations, for example, first- or second-order reactions and may be reversible (*chemical reversibility*) or irreversible.

Chemical steps may precede or follow the transport and ET processes. In the former case, the electroactive species is formed in a preequilibrium. In the latter case, we produce by ET some reactive species, which undergoes a (possibly complex) chemical transformation to a more stable product.

#### 1.2.1.5 Adsorption

The involvement of specific attractive interactions of molecules with the electrode surface (adsorption) makes the electrode process even more complex. The intensity of such interactions ranges from weak (physisorption) to strong (chemical bonds formed between adsorbate and electrode).

For some common organic electrochemical reactions, for example, the Kolbe electrolysis of carboxylates [13], the adsorption of intermediates has been discussed.

### 1.2.2

#### Organic Electrode Reaction Mechanisms

##### 1.2.2.1 Electron Transfer Initiates Chemistry

The majority of organic electrode reactions is characterized by the generation of a reactive intermediate at the electrode by ET and subsequent reactions typical for that species. Thus, the oxidation or reduction step initiates the follow-up chemistry to the reaction products ("doing chemistry with electrodes" [14]).

Species with electron deficiency (e.g. carbocations), unpaired electrons (e.g. radicals, radical ions), electron excess (e.g. carbanions), or those with unusual oxidation states (e.g. metal complexes with low- or high-valent central atoms) are produced at the electrode. Electrochemical generation of such intermediates may be advantageous because of the mild reaction conditions employed (room temperature,

strong acids or bases are not necessary) and/or the additional selectivity introduced in controlled-potential experiments.

The reaction mechanisms of organic electrode reactions are thus composed of at least one ET step at the electrode as well as preceding and follow-up bond-breaking, bond-forming, or structural rearrangement steps. These chemical steps may be concerted with the electron transfer [15, 16]. The instrumental techniques described in this chapter allow the investigation of the course of the reaction accompanying the overall electrolysis.

##### 1.2.2.2 Nomenclature of Electrode Reaction Mechanisms

In order to classify the various mechanisms of organic electrode reactions, a specific nomenclature has been developed [17]. It is often extended in an informal way to accommodate particular reaction features, and one may find additional or deviant symbols.

Usually, however, electron transfers at the electrode are denoted by "E", while chemical steps not involving the electrode are denoted by "C". The ET may further be characterized as "E<sub>r</sub>", "E<sub>qr</sub>", or "E<sub>i</sub>" in the reversible, quasi-reversible, or irreversible case. It is usually not indicated how transport occurs. If the C-step is a dimerization, the symbol "D" is common, while an ET between two species in a (homogeneous) solution is denoted "SET" (for solution electron transfer) [18] or "DISP" (see, e.g. [19]).

For more complex mechanisms, picturesque names such as square, ladder, fence [18] or cubic schemes [20] have been selected. In redox polymer films, additional transport of counterions, solvation, and polymer reconfiguration are important and four-dimensional hyper-cubes are needed to describe the reactions [21].

## 1.2.3

**Formal Description of Events at an Electrode**1.2.3.1 **Current-Potential-Time Relationships**

The equations given in Section 1.2.1 include the most important quantities for understanding a reaction mechanism at an electrode: current  $i$ , potential  $E$ , and time  $t$ . Consequently, most techniques to investigate electroorganic reaction mechanisms involve the determination of  $i$  or  $E$  as a function of time (while the other one of these quantities is kept constant) or as a function of each other (while one is varied with  $t$  in a defined manner).

Similar  $i-E-t$  relationships are derived theoretically from basic equations (simulation, see Section 1.4.1), on the basis of a hypothesis for the reaction mechanism, and the experimental and the theoretical results are compared. In this way, the hypothesis is either disproved, or proven to be consistent with the events at the electrode.

1.2.3.2 **Concentration Profiles**

The current through the electrode is proportional to the flux of redox-active material to the surface, which, in turn is related to the concentrations  $c$  of various species near the interface. Thus, an equivalent description is based on the dependence of  $c$  on space  $x$  and  $t$ . Often a single space-coordinate suffices. More complex systems (e.g. ultramicroelectrodes) may require up to three space-coordinates.

Although it is difficult to determine the spatial distribution of species experimentally, it provides an illustrative view of the electrode reaction. Simulations usually provide values of  $c = f(x, t)$  for each species as the primary result. The space dependence of  $c$  is termed a *concentration*

*profile*. In general, the electrode is located at  $x = 0$ , and the electrolyte extends into the positive  $x$  half-space. The bulk of the solution is assumed at the right-hand side of the profile. Often, concentration values are normalized with respect to the bulk concentration of one species, and space coordinate values are normalized with respect to the extension of the diffusion layer  $\delta$ . Such concentration profiles will be used in the following discussion.

## 1.2.4

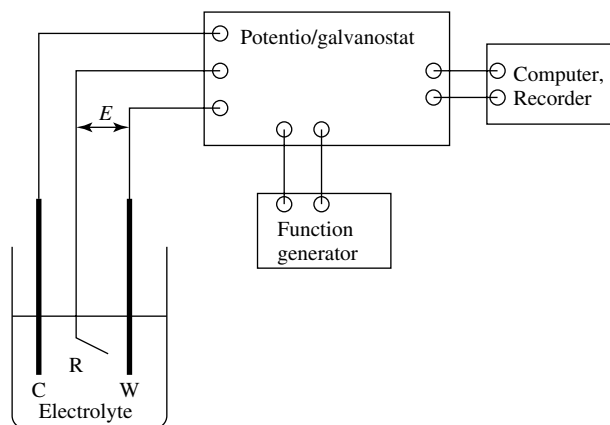
**Methods of Mechanistic Electroorganic Chemistry**1.2.4.1 **Classification**

One of several possibilities to classify electroanalytical methods is based on the quantity that is controlled in the experiment, that is, current or potential. Alternatively, since diffusion is an important mode of mass transport in most experiments, we distinguish techniques with stationary or nonstationary diffusion. Finally, transient methods are different from those that work in an exhaustive way.

Only a small selection of the variants in the electrochemical literature can be mentioned here. Thus, impedance techniques (small amplitude sinusoidal perturbation at the electrode with observation of the system's response [22]) as well as polarographic methods (at mercury electrodes) will not be described. Since the notion of a reaction mechanism requires consumption of substance, equilibrium techniques (such as potentiometry) will also not be discussed here.

1.2.4.2 **Controlled-Potential Techniques**

Control of the potential  $E$  of that electrode where the electrode reaction occurs (working electrode) is accomplished by a



**Fig. 2** Schematic representation of experimental set-up for controlled-potential experiments; W: working, C: counter, R: references electrodes.

potentiostat in a three-electrode arrangement (Figure 2). The current is passed through the working (W) and counter (C) electrodes, while  $E$  is measured with respect to a currentless reference (R) electrode. Often, a recording device and a function generator complement the experimental setup.

We will assume a simple reversible one-electron redox process  $A \xrightleftharpoons{\pm e^-} B$  in all cases to introduce the techniques.

An important property of the solution to be investigated is the *rest* or *open-circuit potential*  $E_R$ . This is the potential that the working electrode develops in the solution at equilibrium, that is, when no current flows through the electrode. The value of  $E_R$  depends on the components of the solution and the electrode itself.

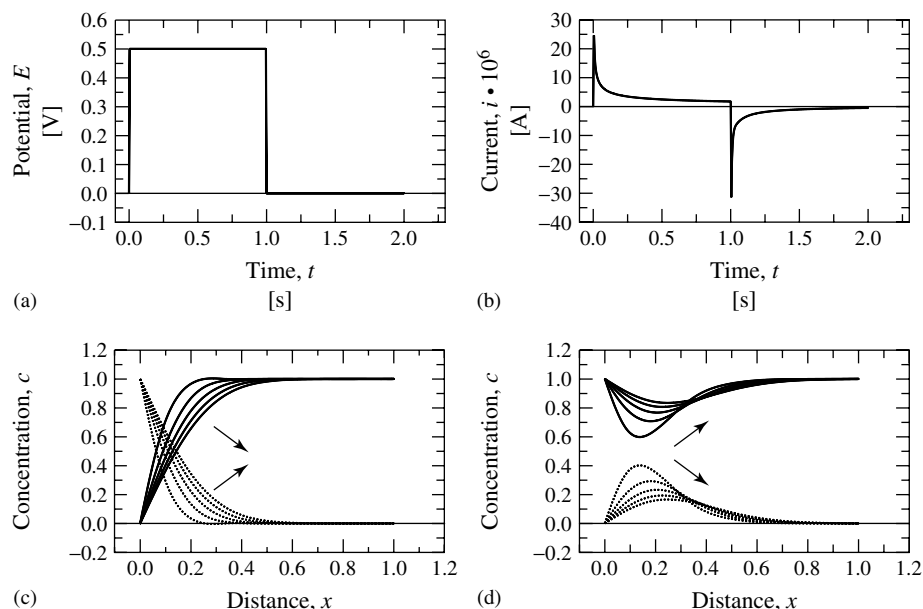
*Chronoamperometry* is a technique in which a potential step is applied to the working electrode in a quiet solution at  $t = 0$  (Figure 3). Initially ( $t < 0$ ), the electrode attains  $E_R$ . For  $t > 0$ , a potential is selected, which drives the desired electrode reaction. Often, but not necessarily (see, e.g. References [23–25]) the latter is in the

transport (diffusion) limited region. After some (pulse) time  $\tau$ ,  $E$  may be switched back to  $E_R$  or another appropriate value (double-step chronoamperometry).

Starting at  $E_R$  guarantees that at  $t < 0$ , the concentration of the redox-active compound A,  $c_A$ , equals  $c_A^0$  at all  $x$ . The product concentration  $c_B$  is usually assumed to be zero. After  $E$  is stepped, the concentrations of A and B at  $x = 0$  adjust to conform to equation (1). These concentrations deviate from the bulk concentrations that remain at their initial values throughout the experiment, and a concentration gradient develops. As a result, A diffuses to the electrode, while B is produced at  $x = 0$  and diffuses to the bulk. The resulting diffusion layer grows into the solution with  $t$  (typically  $10^{-2}$  cm after 10 s in common organic solvents). The steepness of the concentration gradient is high shortly after  $t = 0$ , and decreases thereafter. This is reflected in the current response given by the Cottrell equation (3)

$$i = \frac{nFAc_A^0\sqrt{D}}{\sqrt{\pi t}} \quad (3)$$





**Fig. 3** Chronoamperometry: (a) typical excitation signal; (b) current response; and concentration profiles [(c) first step; (d) second step; educt: solid lines, product: dotted lines; five

profiles respectively at various times, increasing time shown by arrows] for a double-step chronoamperometric experiment (pulse time  $\tau = 1$  s).

in the most simple case (with  $A$  = electroactive area of the electrode). Thus,  $i\sqrt{t}$  is a constant, and a plot of  $i$  vs.  $t^{-1/2}$  is a straight line.

Switching back  $E$  to  $E_R$  causes the concentrations at  $x = 0$  to return to their original values with the concentration profiles changing accordingly. Now, B, which has accumulated in the diffusion layer, diffuses toward the electrode and is transformed back to A. We observe a current in the opposite direction.

Any reaction that removes B from the solution will influence the current response, allowing qualitative mechanistic conclusions. Furthermore, quantitative analysis of chronoamperometric curves includes determination of  $n$ ,  $A$ , or  $D$ , provided two of these quantities are known.

*Chronocoulometry* is similar to chronoamperometry, but the time integral of  $i$ ,

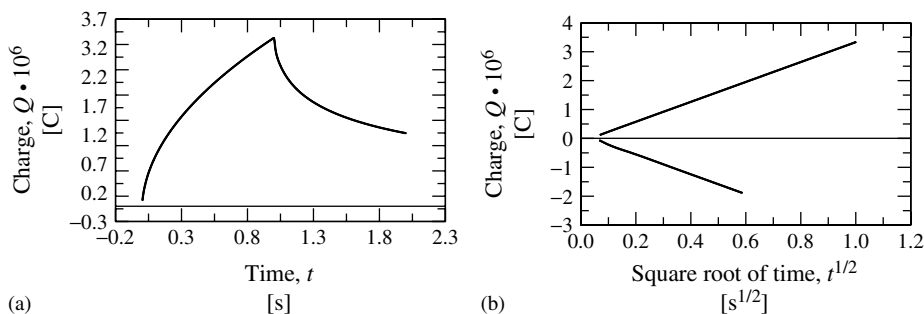
the charge  $Q$ , is recorded (Figure 4). This quantity continuously increases during the first part of the experiment ( $0 < t < \tau$ ). Integration of equation (3) yields

$$Q = \frac{2nFAc_A^0\sqrt{D}}{\sqrt{\pi}}\sqrt{t} \quad (0 < t < \tau) \quad (4)$$

As soon as the potential is stepped back such that a current in the reverse direction flows, the accumulated charge decreases as shown:

$$Q = \frac{2nFAc_A^0\sqrt{D}}{\sqrt{\pi}}(\sqrt{t} - \sqrt{t - \tau}) \quad (\tau < t < 2\tau) \quad (5)$$

Thus, a plot of  $Q$  vs.  $\sqrt{t}$  for the first, and  $Q$  vs.  $\sqrt{t} - \sqrt{t - \tau}$  for the second part of the curve results in two straight lines ("Anson plot" [26]). Adsorption of redox active species can simply be diagnosed



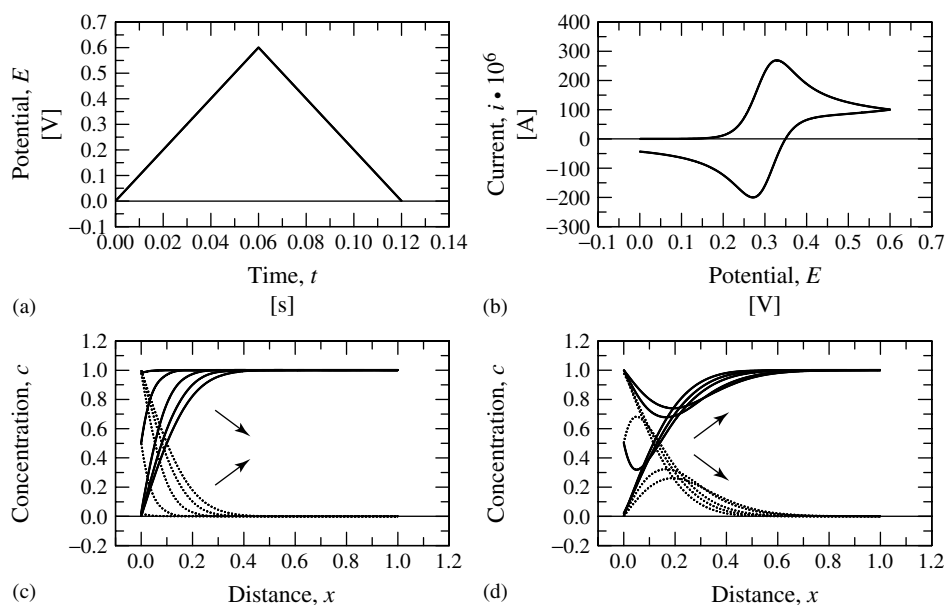
**Fig. 4** Chronocoulometry: (a) typical charge response; (b) Anson plot for a double-step chronocoulometric experiment.

if the extrapolated Anson plot lines do not cross close to the origin [27]. An interesting characteristic of the chronocoulometric curve is that  $Q(2\tau)/Q(\tau) = 0.414$ , if no follow-up reaction destroys B. If B reacts, however, this charge ratio increases.

Because of its integral nature, chronocoulometry is less susceptible to noise

than chronoamperometry. Again,  $n$ ,  $A$ , or  $D$  are accessible from chronocoulometric data.

*Linear sweep* and *cyclic voltammetry* (LSV and CV) are probably the most widely used techniques to investigate electrode reaction mechanisms. They are easy to apply experimentally, readily available in



**Fig. 5** Linear sweep and cyclic voltammetry: (a) typical excitation signal; (b) current response; and concentration profiles [(c) forward scan; (d) reverse scan; educt: solid lines, product: dotted lines; five profiles respectively at various times, increasing time shown by arrows] for a cyclic voltammetric experiment.

educt: solid lines, product: dotted lines; five profiles respectively at various times, increasing time shown by arrows] for a cyclic voltammetric experiment.

commercial instruments, and provide a wealth of mechanistic information. In such experiments, the potential of the working electrode is controlled by a potential ramp (LSV) or one or more potential triangle(s) (CV, Figure 5, see also Volume 3, Chapter 2).

The potential changes with a scan (or sweep) rate  $v = dE/dt$ . This quantity is easily variable and is one of the most important parameters for mechanistic analysis, defining the timescale of the experiment.

In these techniques, the concentrations at the electrode do not immediately attain their extreme values after the start of the experiment. Rather, they change with  $E$  or  $t$  according to equation (1). While the steepness of the concentration profiles increases with  $E$  (forward scan), simultaneously  $\delta$  increases in the quiet solution. The latter effect slows down the increase of  $i$  with  $E$ , and finally (close to the limiting current region) leads to the formation of a peak with a characteristic asymmetric shape. On the reverse scan (after switching the scan direction at  $E_\lambda$ ), products formed in the forward scan can be detected (B, in the case discussed).

The peak current in the forward scan is given by [28]

$$i_p = 0.4463nFAc_A^0 \sqrt{\frac{nF}{RT}} vD \quad (6)$$

or, for  $T = 298 \text{ K}$ ,

$$i_p = (2.69 \times 10^5)n^{3/2}Ac_A^0\sqrt{vD} \quad (7)$$

(Randles-Sevcik equation). The peak potential in the forward scan,  $E_p^f$ , is related to  $E^0$  of the redox couple by  $E_p^f = E^0 + 28 \text{ mV}$ , and  $E^0 = (E_p^f + E_p^b)/2$ , where  $E_p^b$  is the potential of the peak on the reverse scan.

Besides determination of  $n$ ,  $A$ , or  $D$ , follow-up kinetics are accessible from the influence on the position of the peaks, and in particular, the intensity of the reverse peak. Formation of products that are electroactive within the potential window scanned causes the appearance of additional peaks. Furthermore, the shape of the peaks allows conclusions to be drawn about the involvement of adsorption processes.

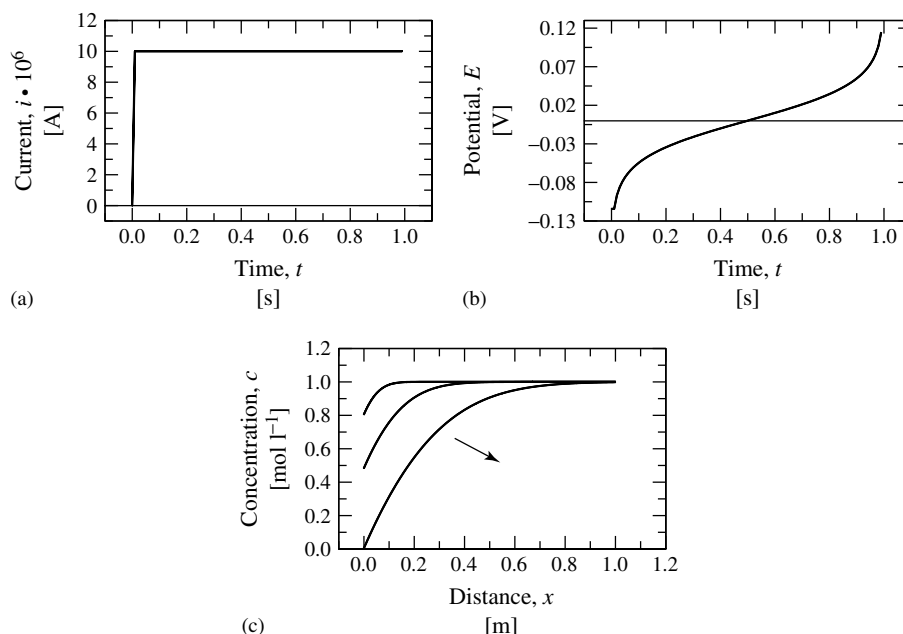
#### 1.2.4.3 Controlled-Current Techniques

Current control of an electroanalytical experiment is accomplished by a galvanostat or amperostat [29].

*Chronopotentiometry* is a transient constant-current technique in which the potential of the electrode is followed, as a function of time, in a quiet solution (Figure 6). Double-step applications [30], as well as programmed current experiments [31] have been described.

Starting at  $E_R$ , as soon as a current  $i$  is imposed, the equivalent flux of redox-active substrate A to the electrode is established. Since  $i$  is constant, the slope of the concentration profile must also be constant. Thus, depletion of the substrate causes an increase in the diffusion layer thickness, while the steepness of the profile does not change. The concentration of A at  $x = 0$  necessarily decreases. Simultaneously,  $c_B(x = 0)$  increases. As a consequence,  $E$  adjusts according to equation (1).

After some *transition time*  $\tau$ ,  $c_A(x = 0)$  reaches a value of zero and no more decrease is possible. Since  $\delta$  still keeps increasing, the concentration gradient becomes less steep. The current can no longer be maintained by the redox reaction of A. Now,  $E$  increases steeply until another electrode process is possible (not shown in Figure 6).



**Fig. 6** Chronopotentiometry: (a) typical excitation signal; (b) potential response; (c) concentration profiles of educt for a chronopotentiometric experiment (three profiles at various times, increasing time shown by arrow).

The relation between  $i$  and  $\tau$  is given by the Sand equation (8)

$$i\tau^{1/2} = \frac{nFAc_A^0\sqrt{\pi D}}{2} \quad (8)$$

Again,  $n$ ,  $A$ , or  $D$  can be determined from chronopotentiometric experiments.

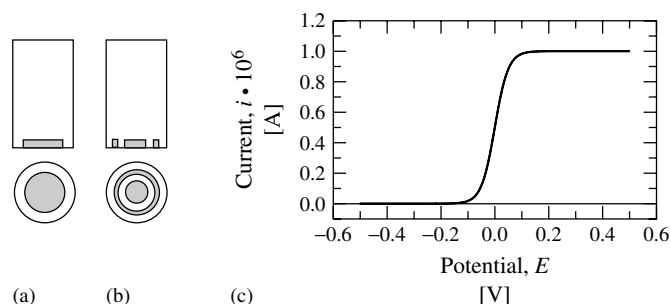
#### 1.2.4.4 Hydrodynamic Voltammetry

In hydrodynamic techniques, convection is the principal mode of mass transport, and is brought about by the controlled movement of the electrode in the solution or by pumping the electrolyte through a pipe or channel.

In a simple model, one assumes that convective mass transport keeps the concentration constant at some fixed distance  $\delta$  from the solid wall. Thus, the diffusion layer thickness is constant.

*Rotating disk voltammetry* uses a potential scan to control the potential of a specially designed working electrode, consisting of a disk embedded into the lower cross section of a perpendicularly mounted insulating shaft. The shaft is inserted into the electrolyte and rotated around its vertical axis with an angular velocity  $\omega$  (RDE [32], Figure 7). The electrolyte is set into a circular motion and moves centrifugally along the electrode surface. It is replenished by fresh solution dragged up vertically from the bulk.

Diffusion occurs across a distance of  $\delta = 1.61D^{1/3}\omega^{-1/2}\nu^{1/6}$  ( $\nu$  is the kinematic viscosity of the electrolyte). At  $E_R$ ,  $c_A(x=0) \approx c_A^0$ , diffusion is negligible and no current flows. Scanning  $E$  causes  $c_A(x=0)$  to change, and a current results. Eventually,  $c_A(x=0) = 0$  and a limiting



**Fig. 7** Construction [section and bottom view, (a) RDE; (b) RRDE] of rotating disk electrodes; and (c) typical RDE response.

current

$$i_{\text{lim}} = 0.620nFAc_A^0 D^{2/3} \omega^{1/2} \nu^{-1/6} \quad (9)$$

is reached [Levich equation (9)].

Since products of the electrode process are quickly transported out of the vicinity of the electrode disk, use of the rotating disk electrode complements the more complex rotating ring disk electrode (RRDE) [32]. Here, redox active products can be detected at the ring electrode, which is held at a separately controlled potential.

*Channel techniques* employ rectangular ducts through which the electrolyte flows. The electrode is embedded into the wall [33]. Under suitable geometrical conditions [2] a parabolic velocity profile develops. Potential-controlled steady state (diffusion limiting conditions) and transient experiments are possible [34]. Similar to the Levich equation at the RDE, the diffusion limiting current is

$$i_{\text{lim}} = 1.165nFc_A^0 D^{2/3} \bar{U}^{1/3} h^{-1/3} w x_E^{2/3} \quad (10)$$

(with  $\bar{U}$  = mean solution velocity,  $x_E$  = electrode length,  $h$  = half-height of channel,  $w$  = width of the electrode). Experimental variables include  $\bar{U}$  and  $x_E$  (arrays of microbands) [35, 36].

The fact that transport limits the rate of the overall electrode reaction affects the fastest timescale accessible. Once transport controls the rate, faster reaction steps cannot be characterized. It is thus important to enhance mass transfer, for example, by increased convection with high flow rates [37, 38].

#### 1.2.4.5 Exhaustive Electrolysis Techniques

In contrast to the techniques discussed up to now in which only a small part of the substrate present in the electrolyte is consumed, we will now consider approaches that exhaustively convert the substrate to the product. Typically, the electrodes used have a comparatively large area, and the electrolyte is stirred in order to increase mass transport. Exhaustive electrolyses can be performed potentiostatically or galvanostatically.

In *potentiostatic exhaustive electrolysis*, the potential of the working electrode is constant throughout the experiment. The substrate is transported by convection and diffusion to the working electrode surface. The current decreases with the bulk concentration of the substrate, if no further electron transfers occur. The charge transferred is

$$Q = \int_0^{t_{\text{end}}} i \, dt \quad (11)$$

with  $t_{\text{end}}$  denoting the time when the experiment is stopped. A frequent, but not unique stopping criterion is the remaining current, for example, 1% of the initial  $i$ . One could also test for disappearance of the substrate or some intermediate, *in situ* or in samples taken from the electrolyte. Typically, the duration of a potentiostatic electrolysis is much larger than that of a transient experiment as discussed above.

$Q$  can be related to the amount  $m$  of substrate with molecular mass  $M$  consumed. From Faraday's first law ( $Q = nFm/M$ ),  $n$  is available.

From an exhaustive potentiostatic electrolysis, the product(s) formed at the selected electrode potential can be *isolated*. Preparative and analytical techniques are available to determine the composition of the product mixture and the structure of its components. Mechanistic reasoning will often allow defining the reaction steps. Even more information about the reaction can be gained from electrolysis experiments at various defined potentials, for example, after each peak in the cyclic voltammogram of the substrate.

In contrast, in *galvanostatic exhaustive electrolysis* the current through the working electrode is kept constant. As in chronopotentiometry, this will result in a constant flux of electroactive material to the surface. Consequently, the electrode potential will vary during the experiment. As a result, at different times various electrode processes may be induced. Hence, the results of galvanostatic and potentiostatic electrolyses will not necessarily be identical.

The determination of charge in galvanostatic electrolysis is particularly simple, since  $i \neq f(t)$ :  $Q = it$ . Again, a suitable protocol for endpoint detection must be defined [39], and product isolation is possible.

### 1.3

#### How to Gain Access to Kinetics, Thermodynamics, and Mechanisms of Electroorganic Reactions

##### 1.3.1

##### Qualitative and Quantitative Investigation of Electrode Reaction Mechanisms

Two extreme forms of mechanistic investigations in organic electrochemistry are frequently applied:

1. *Qualitative analysis* has the main objective of confirming a given mechanistic hypothesis by rejection of conflicting alternatives. This may be applied to single elementary steps, the intermediates, or how the steps are linked together.
2. *Quantitative analysis* relies on a highly probable mechanistic hypothesis and determines as many as possible kinetic, thermodynamic, and/or transport parameters for the various steps. This is often a complex problem, since the values of the parameters are usually correlated, their relation to experimental data is nonlinear, and the data contain artifacts and statistical errors [40, 41].

Both types of mechanistic analysis are supported by the instrumental techniques discussed here.

##### 1.3.2

##### General Recommendations for Mechanistic Analysis

In general, for a mechanistic analysis, as many facets as possible of the investigated electrode reaction should be taken into account and the various experimental parameters be varied as widely as possible. Among these are

- *Time scale*: This is particularly important for kinetic studies and the determination of rate constants.

- **Concentration:** The dependence of results on concentration indicates chemical reactions of an order higher than unity.
- **Presence of reagents:** Formation of intermediates may be proven by their reaction with intentionally added reagents, for example, nucleophiles to quench electrogenerated carbenium ions. Characteristic changes are expected, for example, peaks in CV may disappear.

Usually, the experimental results are compared with the theoretical model simulations. Again, it is important to consider wide ranges of experimental conditions that have to be adequately modeled using a single set of parameters. Comparison is done by

- **data transformation.** Suitable transformations of the experimental data lead to straight lines (e.g. Anson plot in chronocoulometry) or similar simple curves (semi-integration or differentiation [42]).
- **feature analysis.** The experimental curves exhibit features (e.g. peaks in CV) that change characteristically with the experimental conditions. The results are usually compared to working curves [28] or surfaces [43, 44].
- **full curve analysis.** Global analysis of experimental and theoretical data is applied by comparing entire curves. This is used to great advantage in simulation procedures [45, 46].

Of course, experimental artifacts should be avoided. In particular, in mechanistic electroorganic work these are

- **Background currents** are current components not related to the ET of substrates or products, but rather to impurities

or are caused by non-Faradaic processes (charging of the double layer). They are at least approximately corrected by subtraction of a blank curve recorded in the electrolyte without substrate.

- **$iR$  drop** is caused by the resistance  $R$  between the reference and the working electrode in a three-electrode cell. It is particularly awkward in low-conductivity electrolytes and distorts curves in a nonlinear way. Compensation in commercial instruments is often possible, and procedures for correction have also been given [47, 48]. However, it is best to avoid an  $iR$  drop by decreasing  $i$  [decreasing  $c$  or  $A$  (ultramicroelectrodes, Section 1.4.2)] or  $R$  (increasing conductivity or decreasing distance between reference and working electrodes).

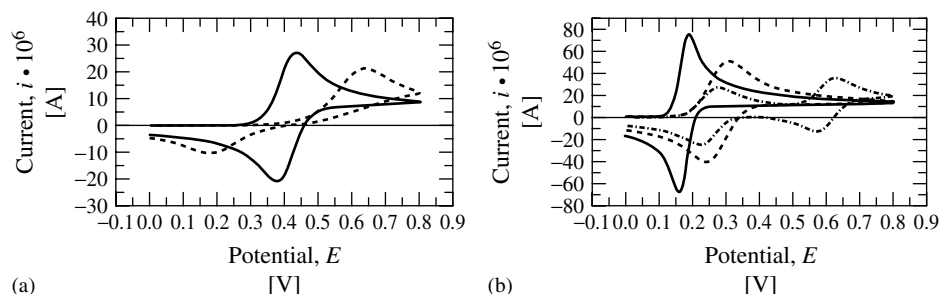
### 1.3.3

#### Some Mechanistic Examples

##### 1.3.3.1 Pure ET Reactions

If no chemical steps are coupled to the ET at the electrode, the reaction mechanism is fully described by  $E^0$  (thermodynamics),  $n$  (stoichiometry),  $D$  (transport), as well as  $k_s$ , and  $\alpha$  (kinetics). It is characteristic to find a fully developed reverse peak in the cyclic voltammogram [49]. Qualitatively, it is important to diagnose full diffusion control ( $E_r$ ). Cyclic voltammetry allows this by inspection of the peak potential difference  $\Delta E_p = E_p^f - E_p^b$ . For  $E_r$ ,  $\Delta E_p$  is independent of  $v$ , while for  $E_{qr}$  an increase of  $v$  (faster timescale) causes  $\Delta E_p$  to increase (Figure 8a) [50].

While  $E^0$  follows from CV directly (Section 1.2.4), determination of the other parameters is more complex. For diffusion-controlled ETs,  $n$  follows from  $\Delta E_p = 58/n$  mV, and  $D$  is calculated from



**Fig. 8** Typical cyclic voltammograms of pure electron transfer reactions; (a) effect of quasi-reversibility ( $k_s$  decreases from solid to dashed line); (b) effect of relative values of

formal potentials in an  $E_rE_r$  reaction (difference of formal potentials,  $\Delta E^0$ , decreases from dash-dotted through dashed to solid line; in the latter case, potential inversion occurs).

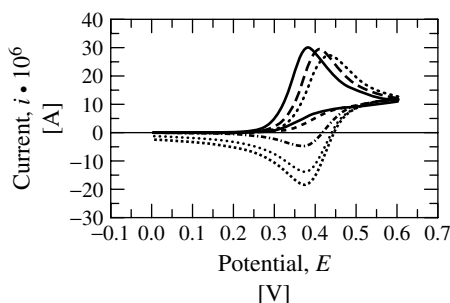
equation (7). Alternatively, a combination of equations (7) and either (3) or (4) yields  $n$  [51]. Exhaustive electrolyses also give  $n$  and allow product generation. Because of the longer timescale as compared to transient methods, the results may differ from the CV or potential step techniques. Often, starting with stable organic molecules, radical ions are produced, which can be investigated by ESR spectroelectrochemistry (Section 1.4.4). Note, that  $n$  must be an integer value.

Kinetic information for  $E_{qr}$  reactions is not available from techniques that work in the diffusion-controlled regime. However, again, CV allows determination of  $k_s$  from the dependence of  $\Delta E_p$  on  $v$  [50, 52, 53]. The transfer coefficient is also accessible from cyclic voltammograms [53]. Often  $\alpha$

is assumed to be 0.5 in organic electrode reactions, but clearly this is only a rough approximation.

Transfer of several electrons yields  $n > 1$  from the above procedures, but CV additionally shows the relative thermodynamics and depending on the individual  $E^0$  values, various shapes of  $i/E$  curves are obtained (Figure 8b). If the two  $E^0$  are sufficiently different ( $\Delta E^0 > 100$  mV), two separated peak couples occur (dash-dotted line). On the other hand, if  $\Delta E^0$  decreases below  $\approx 100$  mV, the voltammetric signals merge (dashed line).

Further, interesting cases are encountered in “inverted potential” [54] situations (solid line in Figure 8b, second ET thermodynamically easier than the first one), and for dendrimers with a large number of



**Fig. 9** Typical cyclic voltammograms of an EC reaction system; rate of follow-up reaction increases from short-dashed through dotted, dash-dotted and long-dashed to solid curve.



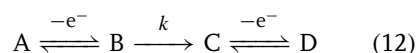
redox-active units, which undergo ET at approximately the same potential [55].

### 1.3.3.2 Follow-up Reactions

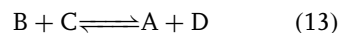
Irreversible follow-up reactions (most simple case: EC mechanism) decrease the concentration of the primary redox product. This is again diagnosed in CV (Figure 9) and also in chronocoulometry. Timescale variation in CV allows to modulate the importance of the C-step: at fast  $v$  the chemical reaction will have no influence on the curves, while at slower  $v$  all product has reacted and the reverse peak disappears. A governing factor is  $k/a$  ( $k$  = rate constant of C-step,  $a = nFv/RT$ ). Thus, for a qualitative interpretation, the peak current ratio in CV is evaluated as a function of  $v$  (and  $E_\lambda$ ) in order to calculate  $k$  [49]. Also,  $E_p$  and  $i_p$  depend on  $k/a$  [28].

Reversible follow-up reactions may just shift the entire voltammetric signals (fast equilibration) on the  $E$  axis, or lead to effects approaching those of the irreversible case [28].

The most important are cases in which the product of the C-step is again electroactive [ECE mechanism, Reaction (12)]:



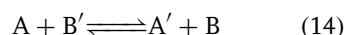
(for an oxidation; extension to reduction is obvious). In such cases, homogeneous ETs [disproportionation, Reaction (13)] have also to be considered:



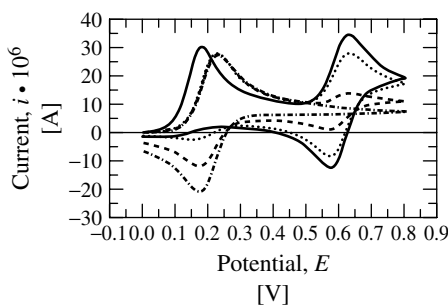
where the equilibrium constant is related to the  $E^0$  of the two heterogeneous ETs.

Several variants are discussed in the literature [18, 56, 57]. Figure 10 shows some cyclic voltammograms. The height of the second peak depends on the rate of the C-step. In chronoamperometry, the formation of a redox-active product leads to an increase in the apparent  $n$  during the experiment (e.g. from  $n = 1$  to  $n = 2$ ). A plot of  $i$  vs.  $t^{-1/2}$  switches from a straight line for  $n = 1$  at small  $t$  to the one for  $n = 2$  at large  $t$ .

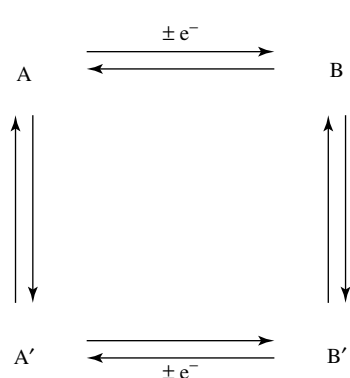
If, for an oxidation step, the chemical reaction of B leads to the oxidized form of the second redox couple B' (and not the reduced one as in the earlier case) and a second chemical transformation from A' leads back to A [reaction (14)], we arrive at a square scheme (Figure 11), which forms the basis for many important redox systems [18, 58]. Again SET steps



can be involved, resulting in rather unusual voltammograms under certain conditions [18, 59].



**Fig. 10** Typical cyclic voltammograms of ECE reaction systems; rate of C-step increases from dash-dotted through dashed and dotted to solid curve.



**Fig. 11** The square scheme reaction mechanism.

### 1.3.3.3 Preequilibria to ETs

The square scheme discussed above already includes a further common motif in electroorganic mechanisms: reaction  $A \rightleftharpoons A'$  forms a preequilibrium to both ETs in the scheme. The response of such a system in CV depends particularly on the equilibrium constant  $K = [A]/[A']$  and the rate constants  $k_{A \rightarrow A'}$  and  $k_{A' \rightarrow A}$ . If the  $k$  are large (reaction at equilibrium), only that ET will occur, which is thermodynamically easier (smaller  $E^0$ ). All material consumed by that ET will immediately be replenished through the equilibrium reaction. On the other hand, if the  $k$  are small, two peaks will be observed with their relative heights proportional to the equilibrium concentrations of A and A', thus allowing determination of  $K$ .

Both partners of the preequilibrium are not always electroactive (CE mechanism).

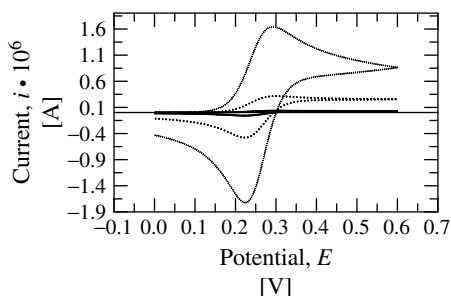
Kinetics and thermodynamics will influence the exact appearance of the concentration profiles. Figure 12 shows some CE voltammograms. In particular, chronopotentiometry was used for analyses [60, 61], since for high  $i$

$$i\tau^{1/2} = \frac{\sqrt{\pi}}{2} nFAc^0 \sqrt{D} \frac{K}{1+K} \quad (15)$$

(with total concentration  $c^0 = c_A^0 + c_{A'}^0$ ) [62]. Furthermore, hydrodynamic techniques were also employed [63, 64].

### 1.3.3.4 Catalytic Reactions

In some reactions the product of an ET at the electrode reacts back to the starting compound:  $A \xrightleftharpoons[\pm e^-]{k} B \xrightarrow{k} A$ . This mechanistic motif is found in mediated electrode reactions [65] or in sensor applications [66]. The reformation of



**Fig. 12** Typical cyclic voltammograms of preequilibrium systems; kinetics of preequilibrium become slower from dotted through dashed to solid curve.

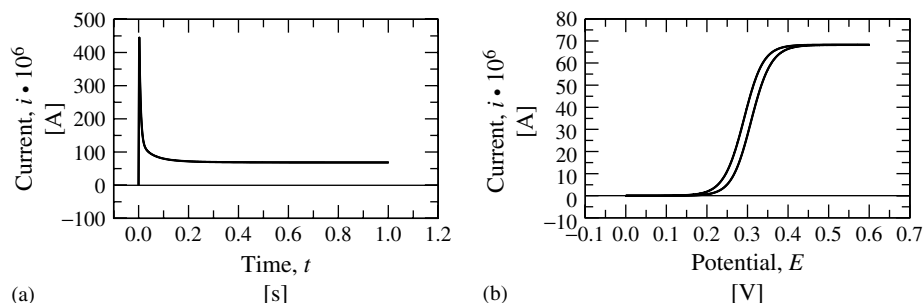


Fig. 13 Typical (a) chronoamperogram and (b) cyclic voltammogram of a catalytic system.

the electroactive A leads to an increase in current and a decrease of diffusional effects. Thus, in chronoamperometry,  $i$  reaches a nonzero limiting value (Figure 13a), while in CV the peak disappears in favor of an S-shaped  $i/E$  curve (Figure 13b). From the limiting CV current, the rate constant  $k$  is accessible from [28, 67]

$$i = nFAc^0\sqrt{Dk} \quad (16)$$

#### 1.4

##### How to Gain Additional Information about Electroorganic Reaction Mechanisms

###### 1.4.1

###### Simulation

A simulation (Volume 3, Chapter 3.1) is the reproduction of an electroanalytical experiment in the form of a set of mathematical equations and their solutions, usually on a digital computer [7]. The equations express a physical model of the real experiment. Thus, the main steps of the electrode process (see Section 1.2.1) are included.

Various numerical techniques are employed, and commercial programs are available, mostly for the CV technique [7]. For the elucidation of electrode reaction

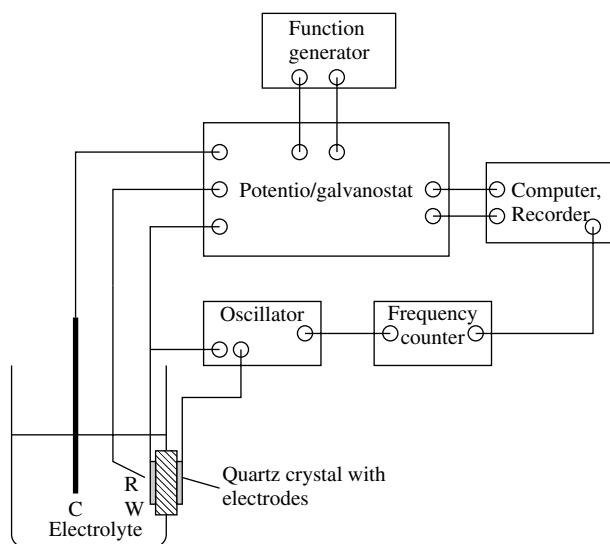
mechanisms, simulation is an indispensable tool for both types of analyses described in Section 1.3.1. For a simulation, one needs a mechanistic hypothesis that in some programs is translated into the governing equations automatically [45, 68, 69]. There are various parameters defining the reaction steps in detail, for example, rate constants or formal potentials. One solves the equations for given values of these parameters and compares the results to experimental curves in an iterative process, until a “best fit” is obtained. Automatic fitting is also available [45]. Alternatively, it is illustrating to see how variations in mechanism and/or parameters change the resulting curves.

It is of particular importance to follow the guidelines provided in Section 1.3.2 in comparing experiments and simulations.

###### 1.4.2

###### Ultramicroelectrodes

In previous sections we have implicitly assumed that diffusion occurs perpendicular to the electrode surface (semi-infinite linear diffusion). If we decrease the size of the electrode to values roughly in the order of the size of diffusion layers, this assumption becomes invalid. Now, additional



**Fig. 14** Set-up of an electrogravimetric experiment with an electrochemical quartz crystal microbalance.

diffusion components parallel to the surface become important. Thus, the current densities are increased. It is common to call disk electrodes with radii  $\leq 20 \mu\text{m}$  “ultramicroelectrodes” (UMEs) [8].

UMEs decrease the effects of non-Faradaic currents and of the  $iR$  drop. At usual timescales, diffusional transport becomes stationary after short settling times, and the enhanced mass transport leads to a decrease of reaction effects. On the other hand, in voltammetry very high scan rates ( $v$  up to  $10^6 \text{ Vs}^{-1}$ ) become accessible, which is important for the study of very fast chemical steps. For organic reactions, minimization of the  $iR$  drop is of practical value and highly nonpolar solvents (e.g. benzene or hexane [8]) have been used with low or vanishing concentrations of supporting electrolyte. In scanning electrochemical microscopy (SECM [70]), the small size of UMEs is exploited to localize electrode processes in the  $\mu\text{m}$  scale.

#### 1.4.3

##### Electrogravimetry

If the electrode process results in the deposition of some product at the electrode surface, or in changes of composition of a precipitate or film on the electrode, mass changes are coupled to the ET. Usually, these changes are small (ng– $\mu\text{g}$ ) and special techniques are necessary for their exact determination.

A technique for such measurements is the electrochemical quartz crystal microbalance (EQCM; Figure 14) [71]. Here, the working electrode is part of a quartz crystal oscillator that is mounted on the wall of the electrochemical cell and exposed to the electrolyte. The resonance frequency  $f$  of the quartz crystal is proportional to mass changes  $\Delta m$ :  $\Delta f \sim \Delta m$ . With base frequencies around 10 MHz, the determination of  $\Delta m$  in the ng range is possible.

Electrogravimetric experiments lead to a mechanistic understanding of polymer

film formation on electrodes, support the study of film morphology and the diffusional as well as the migrational transport into and within such films [72].

#### 1.4.4

#### Spectroelectrochemistry

Although the instrumental techniques described here give detailed mechanistic information, they do not provide an insight into the structure of intermediates. If we, however, combine electrochemical and spectroscopic methods, this is advantageously accomplished (spectroelectrochemistry) [73]. Various spectroscopies have been coupled with electrochemical experiments, among them ESR [74], optical [75], and NMR spectroscopy [76, 77], as well as mass spectrometry [78, 79].

Three types of spectroelectrochemical experiments are useful for mechanistic studies:

- *Spectral* resolution records spectra at different potentials, for example, during a CV scan. This allows structural characterization of intermediates.
- *Temporal* resolution records the intensity of a spectroscopic signal with  $t$ , giving access to formation and decay kinetics.
- *Spatial* resolution [80] leads to information on the distribution of species within the diffusion layer. Distinction between alternative mechanisms has been reported [81].

#### 1.5

#### Conclusion

This chapter discussed some of the more important electroanalytical techniques with particular emphasis on their

use in electroorganic chemistry. These techniques greatly help determine and understand the mechanistic course of electrode reactions in a qualitative and quantitative way. Besides briefly describing the methods themselves, the chapter provides examples for their application for some frequently encountered reaction mechanisms. In particular, cyclic voltammetry is probably the most often used of these techniques, but other methods should also be applied if necessary, and extensions, as discussed in Section 1.4, are expected to gain additional importance in the future.

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## 2

### Practical Aspects of Preparative Scale Electrolysis

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## 2.1 Introduction

The success of an electrolysis process depends on the choice of a suitable electrochemical cell and optimal operation conditions because there is a widespread variety of electrolyte composition, cell constructions, electrode materials, and electrochemical reaction parameters.

The objective of this chapter is to study some essential practical aspects, which have to be considered. First, as necessary background information, the different alternatives for electrochemical cell operation are discussed in general. Then follows an overview of properties of electrode materials, electrolyte components, and cell separators. Finally, examples of cell constructions are shown.

A precondition for an appropriate decision in the planning of a preparative electroorganic synthesis is sufficient information about the electrochemical reaction. As far as possible, knowledge about the influence of parameters such as temperature, solvent, pH value, and stirring rate should be included. Electroanalytical standard methods to acquire such data have been discussed in Chapter 1: cyclic voltammetry as an especially valuable tool and its combination with the rotating disk electrode method for additional knowledge. At

the beginning, literature data about comparable reactions are very helpful. A wide overview about reported electroorganic reactions is given as a basic information source in the following chapters.

The considerations, prior to beginning, must include special characteristics of electrochemical reactions and their practical consequences in a preparative scale electrolysis:

- The first fundamental decision is to use one of the following alternatives
  - direct electroorganic reaction at an inert or electrocatalytic active electrode surface, which needs no additional agent in the electrolyte,
  - indirect electrolysis, that is, the electrochemical regeneration of a conventional oxidizing or reducing agent,
  - application of a “mediator”, which is present like a homogeneous catalyst and is continuously regenerated in situ at an electrode (see Chapter 15).

Many examples of these ways are shown in this volume, discussing their advantages and drawbacks.

- The principle of electrochemistry is to replace the direct electron transfer between atoms or molecules of a conventional redox reaction by separating

the oxidation at the anode and the reduction at the cathode. Even though in most cases only one of these reactions is intended (at the “working electrode”), the other one unavoidably has to be carried out (at the “counter electrode”), at least without detrimental effects on the desired reaction. In consequence, the selection of optimal electrode materials and of a suitable cell – undivided or divided by a separator – will be essential. Recent developments aim at conversions that produce useful products simultaneously at the anode and cathode (“paired electrolyses”, see Chapter 3).

- A typical advantage of electrochemistry in comparison to conventional chemical reactions is the possibility to control the reaction by electrical parameters. The choice of the alternatives using a constant cell current (galvanostatic operation) or using a constant electrode potential (potentiostatic operation) generally has a significant influence on the results of electroorganic syntheses (see Sect. 2.3.2.2 and 2.3.2.3 and Chapter 3).
- An electrochemical reaction needs the transfer of ions between the electrodes. Therefore, the solution in the cell requires usually at least minimal ion conductivity. In most cases, a supporting electrolyte has to be added, and after the reaction it is separated and reused.
- Electrochemical reactions proceed, in principle, heterogeneously at the electrode surfaces. Hence, the mass transfer has a major influence, especially on the selectivity of the electrode reactions. Therefore, the mixing conditions in the cell have to be optimized, considering also the operation mode as batch or as flow-through reactor.

## 2.2

### Target and Scale of the Investigations

Prior to beginning it is necessary to evaluate the aim and the scale of the planned investigations because many particular aspects, discussed in this chapter, are dependent on this decision. There may be a wide range of intentions for preparative electrolysis investigations, demonstrated here by two borderline cases:

- If the target is to find new electrochemical conversions – perhaps of expensive compounds – then the products only have to be accessible in small amounts for their identification. A high yield concerning the reactants is required but technical aspects such as energy consumption are not interesting. In this case, a small volume will probably be the most important feature of the electrochemical cell.
- If the investigations are intended to develop an industrial production, the focus will be to optimize the operation conditions and to get base data for scale-up. In this case, the electrochemical properties of the experimental cell have to be equivalent with the planned technical cell. Thus, it is necessary to carry out experiments on a sufficient large scale, including lifetime tests of cell components. For industrial and engineering aspects, see for example, [1, 2, 3b, 4] (overview), [5c] (detailed), and [6, 7] (including theory).

For numerous research intentions, an average scale will be chosen, considering on the one hand, the costs of chemicals and on the other, the easier experimental work and better reproducibility of results, using a cell of medium – but not too small – dimensions.

## 2.3 Principles of Electrochemical Cell Operation

### 2.3.1

#### Essential Definitions for Electroorganic Reactions

Fundamental criteria to evaluate the results of any organic synthesis are the “yield”, being the fraction of the entire supplied reactant, which has formed the product, and the “selectivity”, being the fraction of the converted reactant, which has been used to generate the product.

In addition, the “current efficiency” (“current yield”) is typical for an electrolysis process, the fraction of the electrical cell current – or (integrated over the time) the fraction of the transferred charge – which is used to form the product. The theoretical charge transfer for one mol product is given by the Faraday constant  $F$ , the charge of one mol electrons,  $F = 96\,485\text{ As/mol} = 26,8\text{ Ah/mol}$ , multiplied by the number of transferred electrons.

Of general importance for reactions is the “degree of conversion” (short: “conversion”), being the fraction of a reactant that has been removed because of the reaction. Because the concentrations of reactants are decreased and that of products increased with rising conversion, the selectivity of the desired reaction mostly becomes smaller during the course of the reaction owing to a decrease of the desired reaction of the reactants and enhancement of consecutive reactions of the products.

If the reaction conditions are changing with time, (especially during batch operation, see Sect. 2.3.4), it is necessary for yield, selectivity, and current efficiency to distinguish between the actual values and the summarized (integrated) values from the start to the end of the reaction.

### 2.3.2

#### Controlling of the Electrochemical Reaction Rate by Electrode Potential and Cell Current

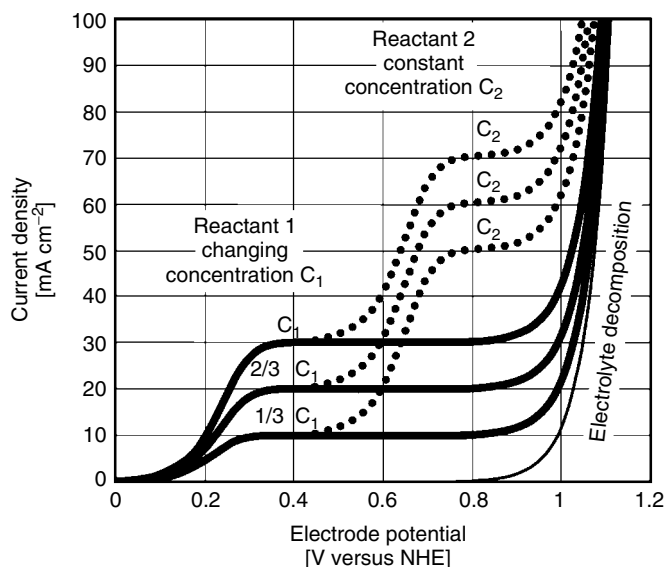
For choosing a suitable cell construction and optimal reaction conditions in the cell, it is inevitable to consider the fundamental correlations between electrode potential and cell current and their influence on selectivity and yield of the electrochemical reactions. Therefore, a simplified overview is given here. The detailed theory is elucidated in Chapter 1.

The electrochemical reaction rate and thus the speed of production in the cell are proportional to the cell current. The current density – the cell current divided by the electrode area – is dependent on the potential of the working electrode.

To achieve a large production rate, the current density should be as high as possible. Particularly, industrial cells need a satisfactory current density and “space–time yield”, that is, production per time and cell volume, because the investment costs and consequently the production costs are enlarged with increasing electrode area and cell volume. But, naturally, the current density is limited by different reasons that have to be considered.

##### 2.3.2.1 General Correlations between Electrode Potential and Current Density

Figure 1 shows typical current density–potential curves of an electroorganic reaction. In this example, the thin line represents the anodic oxidation of the electrolyte without reactants at a higher potential, here at more than 0.8 V versus NHE. If the reactant 1 is present, it can be converted according to the thick compact lines at lower potentials above 0.2 V versus NHE, and this selectively can occur up to 0.5 V versus NHE. Over 0.5 V versus NHE also, an additional reactant



**Fig. 1** Current density–potential curves for the anodic oxidation of two various reactants and finally of the solvent. The electrode potential is measured against a “reference electrode” (RE), here for example, the “normal hydrogen electrode” (NHE).

2 can be oxidized, increasing the current consistent with the thick dotted lines (a constant concentration of reactant 2 is assumed). An analogous correlation has to be considered for the counter electrode (here the cathode).

**2.3.2.1.1 Equilibrium Potential** The minimum potential, which is necessary to perform a (reversible) reaction, is the equilibrium potential  $E$ , defined for zero cell current. It is typical for a given reaction. By definition, it is related to the NHE, which represents the potential zero. If the electrode reaction is coupled with the reaction  $2\text{H}^+ + 2e^- \rightleftharpoons \text{H}_2$  at the NHE, theoretically  $E$  can be calculated using the free reaction enthalpy  $\Delta G$  (Gibbs energy) of the total reaction divided by the charge transfer of the reaction:  $E = -\Delta G/(z \cdot F)$  [ $V$ ] ( $z$  = number of transferred electrons,

$F$  = Faraday constant). The equilibrium potential  $E$  is dependent on the temperature and on the concentrations (activities) of the oxidized and reduced species of the reactants according to the Nernst equation (see Chapter 1). In practice, electroorganic conversions mostly are not simple reversible reactions. Often, they will include, for example, energy-rich intermediates, complicated reaction mechanisms, and irreversible steps. In this case, it is difficult to define  $E$  and it has only poor practical relevance. Then, a suitable value of the “redox potential” is used as a base for the design of an electroorganic synthesis. It can be estimated from measurements of the “peak potential” in cyclic voltammetry or of the “half-wave potential” in polarography (see Chapter 1). Usually, a common RE such as the calomel electrode is applied (see Sect. 2.5.1.6.1). Numerous literature data are available, for example, in [5b, 8, 9].

**2.3.2.1.2 Overvoltage** To obtain a cell current, an “overvoltage”, a potential difference additional to the equilibrium potential, has to be applied. Thus, the overvoltage – consisting of different components – is the deciding parameter to control the speed of an electrochemical reaction. The energy demand due to the overvoltages at both electrodes is lost completely as heat.

**Charge transfer overvoltage** The “charge transfer overvoltage” is necessary to overcome the kinetic hindrance of the electrochemical reaction, that is, to surpass the activation energy of the charge transfer at the electrode. The current density increases exponentially with this overvoltage (see the thin line for the electrolyte in Fig. 1), frequently by a factor of about ten with additional 120 mV overvoltage (for one electron in the transfer step; this is quantified analogous to the Arrhenius law of chemical reactions by the Butler–Volmer equation, see Chapter 1).

**Concentration overvoltage (reaction overvoltage and diffusion overvoltage)** If a significant current is flowing, the concentrations of reactants will be lower and those of products higher at the electrode surface than in the bulk electrolyte. Hence, consistent with the Nernst equation, the electrode potential is shifted by the “concentration overvoltage”. Partially, it can be caused by slow chemical reaction steps before and/or after the charge transfer (“reaction overvoltage”). Additionally, an unavoidable part of the concentration overvoltage is the “diffusion overvoltage” due to concentration differences in the “diffusion layer” that is formed in the electrolyte adjacent to the electrode surface. In this layer, a mass transfer is possible

only by diffusion and not by convection (see Chapter 1). Usually, these concentration differences increase proportional to the current density, according to the first Fick’s law.

**2.3.2.1.3 Limiting Current Density** The diffusion overvoltage hinders the current density to rise continuously with increasing potential, especially in case of low reactant concentrations. The “limiting current density” for a reaction is reached when the current density becomes equivalent to the maximally accessible diffusion rate of a required reactant, see the horizontal sections of the thick curves in Fig. 1. Here, the reactant concentration at the electrode surface tends to zero and the diffusion overvoltage can reach very high values. The limiting current density usually – in consequence of the first Fick’s law – is proportional to the reactant concentration, as shown for reactant 1 by the different thick compact curves in Fig. 1. Thus, the limiting current density can be improved by an increased reactant concentration, for example, due to choosing a reduced degree of conversion. There are further methods to enhance the diffusion rate, such as intensified stirring (i.e. thinner diffusion layer), elevated temperature, and/or reduced viscosity (i.e. increased diffusion coefficient). For the electrolyte decomposition (thin line in Fig. 1), the diffusion overvoltage is negligible in the considered range of current density due to the excess concentration of the solvent, and no limiting current density is observed.

**2.3.2.1.4 Side-reactions** As soon as the cell current density surpasses the limiting current density of one reaction, the electrode potential rises until additionally another reaction takes place (in Fig. 1

oxidation of reactant 2, thick dotted lines, finally the oxidation of the electrolyte). Consequently, the current efficiency for the desired product 1 is lowered and the specific energy consumption for the production increases (it is additionally enlarged because of the simultaneously rising cell voltage).

If there are no detrimental organic side reactions, a cell current density in excess of the limiting current density – and as result a loss of current efficiency – may be acceptable for laboratory scale experiments. For example, a hydrogen evolution parallel to an electroorganic cathodic reduction can even be advantageous as it improves the mass transfer by moving gas bubbles and thus enhances the organic cathodic reduction.

But if reactants or products of the desired reaction are lost and/or if undesired compounds are formed by side reactions (i.e. yield and selectivity will be reduced), it is necessary to avoid any overstepping of the limiting current density. Especially in case of changing conditions (batch operation) with a rising degree of conversion – here, the most significant parameter will be the decreasing reactant concentration – a continuous adjustment of the current density is indispensable. Then it will be better to work at a constant electrode potential than at constant cell current (see Sect. 2.3.2.3).

In the example of Fig. 1, the potential differences are so large that clearly discriminated reactions can be realized. At a potential of 0.3 V, only reactant 1 is active, even at low concentrations for high degrees of conversion.

There are also some reactions known, which need – contrary to the normal case – a high current density for a sufficient selectivity, for example, the Kolbe reaction (see Chapter 6).

**2.3.2.1.5 Possible Problems in Electroorganic Reaction Systems** Unfortunately, electroorganic reactions do not always display clearly defined potential conditions, like those in Fig. 1. Typical reasons may be:

- For many organic reactions, the Gibbs energies are similar and consequently there are only little differences in the equilibrium potentials, which cannot be used to achieve a selective reaction.
- Frequently, reactions consist of a chain of consecutive reaction steps, including species, which need a very high energy, for example, energy-rich radical ions. This causes an effect similar to a large activation energy, and the overall reaction runs irreversible. A significant charge transfer overvoltage – up to 1 Volt or more – can be observed, which is much higher than the equilibrium electrode potential  $E$ . Consequently, the smaller differences in  $E$  cannot be used to run reactions selectively, different from Fig. 1, where large potential differences are available.
- Additionally, complicated and only partially understood influences may be found, for example, of the electrode material (possibly including its history) or of the electrolyte composition.

Under such conditions – that is, missing clearly separated electrode potentials – concurrent reactions will occur. In consequence, only a poor selectivity of the electrode reactions is to be expected and well-optimized reaction conditions will be indispensable.

**2.3.2.1.6 Overvoltage Due to Electrolyte and Cell Separator Resistance** The different overvoltages, discussed above, influence the correlation between electrode



potential and current density. Additional overvoltages are caused by the resistance of the electrolyte and of the separator in a divided cell. Although these overvoltages are not parts of the electrode potentials, they have to be surpassed in order to enable a current in the cell and they enhance the heat evolution in the cell. They increase linearly with rising current due to the ohmic resistance (in case of strong gas evolution, the increase may be steeper because the resistance increases). These overvoltages can be lowered by taking electrolytes with higher conductivity, for example, solvents with higher dielectric constants and the use of sufficiently dissociated supporting electrolytes. These overvoltages can be furthermore lessened by decreasing the distance between the electrodes and by using diaphragms of medium to high porosity (see Sect. 2.4.3.1).

**2.3.2.1.7 Cell Voltage** Figure 2 shows schematically the cell voltage as summation of the above discussed equilibrium

potentials and overvoltages and of the ohmic voltage drops in the electrodes (electron conductors) and in the electrolytes, including cell separators (ion conductors).

### 2.3.2.2 Operation with Constant Cell Current (Galvanostatic Operation)

Constant current electrolysis is an easy way to operate an electrochemical cell. Usually, it is also applied in industrial scale electrolysis. For laboratory scale experiments, inexpensive power supplies for constant current operation are available (also a potentiostat normally can work in galvanostatic operation). The transferred charge can be calculated directly by multiplication of cell current and time (no integration is needed).

The electrode potentials (exactly the overvoltages) are dependant on the current density. Thus, using the galvanostatic operation mode, optimal results are attained only if a well-defined current density can be chosen with a clear difference between desired and undesired reactions, as in Fig. 1. This precondition is favored

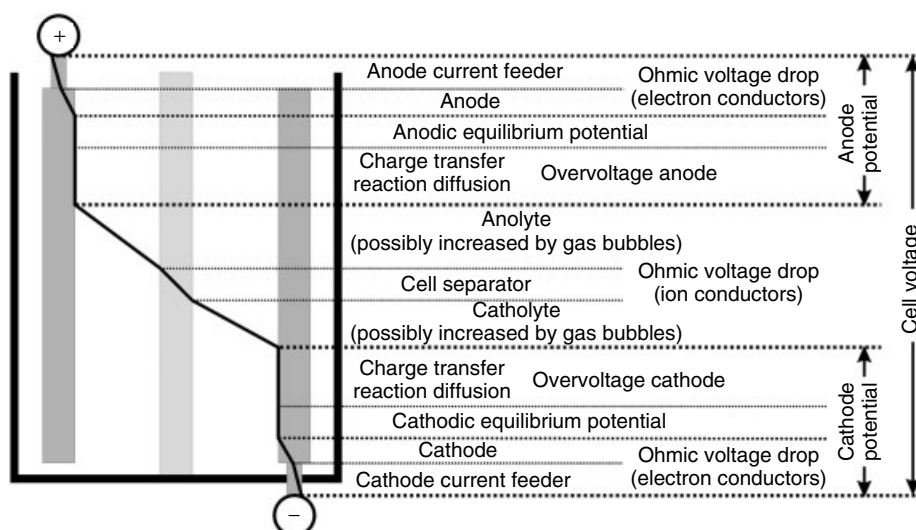


Fig. 2 Composition of the cell voltage (not in real scale).

especially at constant concentrations owing to continuous addition of reactant and removal of product in a flow-through cell (steady state).

For batch operation (see Sect. 2.3.4), the limiting current density is going to zero for increasing degree of conversion (see reactant 1 in Fig. 1). Here, the galvanostatic operation may only be acceptable if exclusively unproblematic side reactions occur, such as water electrolysis as solvent decomposition. In all other cases, better results can be expected using the potentiostatic operation (see next section).

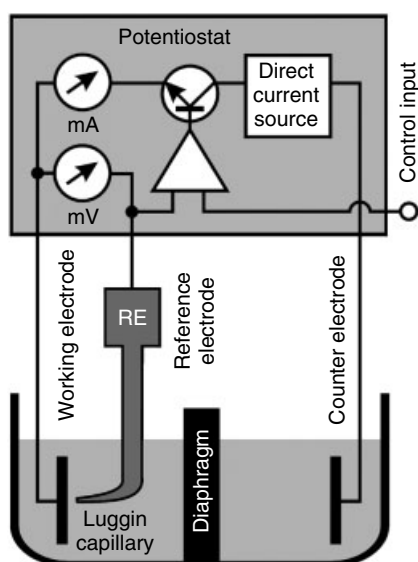
In some problematic cases, there will be no obvious limits available for the choice of the current density in galvanostatic operation. Concurrent reactions take place, resulting in a poor selectivity. But here the potentiostatic operation also cannot demonstrate its advantages, and probably the simpler galvanostatic operation may be applied. To find relatively suitable operation conditions, an experimental optimization of the current density should be carried out, perhaps including parameters

such as concentrations of reactants and products, degree of conversion, temperature, and so on.

### 2.3.2.3 Operation with Constant Electrode Potential (Potentiostatic Operation)

As discussed in Sect. 2.3.2.1, electroorganic reactions can often be selectively controlled by a constant potential of the working electrode, even at decreasing reactant concentrations (see Fig. 3). A precondition of this operation mode is a suitable potential-measuring equipment in the cell (special practical aspects of potential measurement are discussed in Sect. 2.5.1.6). The optimal potential can be chosen using a current density–potential curve (see Fig. 1), available by cyclovoltammetry with a very low scan rate.

A potentiostat is relatively expensive, especially if high power is needed. A cheaper method is to use the galvanostatic operation and to measure continuously the potential and to adapt the cell current manually (or using a computer data acquisition system) in order to adjust the



**Fig. 3** Scheme of potentiostatic operation for a preparative electrolysis, using in principle a simplified cyclovoltammetry equipment. The potential of the working electrode is measured by a Luggin capillary, coupled with a reference electrode (RE, see Sect. 2.5.1.6). The control circuit in the potentiostat adjusts the cell current until the potential of the working electrode is equal to the voltage at the control input.

electrode potential as accurately as possible at the desired value. This technique may be applicable even in cases where it is difficult to measure the potential correctly, for example, in nonaqueous solvents of poor conductivity. Then, the control circuit of a potentiostat cannot properly work, but it is much easier to measure than to control a potential.

Because the current is not constant during the potentiostatic operation, it has to be integrated during the experiment for calculating the charge transfer and the current efficiency. Coulometers or electronic integrators are commercially available. If a computer data acquisition system is used, the current integration is possible by software.

In principle, a further inexpensive method is to work at constant cell voltage. But here the potentials of the working and of the counter electrode, and all voltage drops of the electrolytes and of the cell separator are included (see Fig. 2). Thus, in most cases, clearly defined conditions at the working electrode cannot be adjusted using this operation mode (nevertheless, because of its uncomplicated realization, it is applied in most technical electrolyses to achieve approximately the desired cell current).

### 2.3.3

#### Undivided or Divided Cells

Because of the low-cost construction and simple operation, an undivided cell is always desired but it cannot be realized in all cases. A precondition for electrolysis in an undivided cell is that disadvantageous reactions and reaction products at the counter electrode can be avoided, for example, by selection of the electrode material and/or of the electrolyte composition.

For instance, graphite has a higher hydrogen overvoltage than platinum and its catalytic activity for hydrogenation is low. Thus, a graphite counter electrode may be useful for hydrogen evolution without further electroorganic reactions. Another example is the addition of a “depolarizer,” which enables an innocuous reaction at the counter electrode before an essential compound in the solution can be attacked. Special depolarized electrodes are “gas diffusion electrodes” (GDE), known from fuel cells, or “sacrificial electrodes,” which are dissolved during the reaction (see Sect. 2.4.1.2).

A typical counter electrode reaction is the electrolysis of water. Here the cathodic evolution of hydrogen is coupled with the formation of base, the anodic development of oxygen produces acid additionally. Frequently, acid and base formation at both electrodes will be balanced. Otherwise, a buffer solution or a (continuous) base/acid addition, for example, by a pH-controlling system, can enable the application of an undivided cell.

In many cases, it will be impossible to prevent unwanted reactions at the counter electrode. Then a separation of the anolyte and catholyte is needed. An optimal compromise has to be found for the separator between separation effectiveness and ion conductivity, that is, minimized electrical resistance and low energy consumption. Moreover, chemical, thermal, and mechanical stability and price of the separator have to be considered. Naturally, a complete separation is impossible, because a slight diffusion rate is inevitable. In laboratory scale experiments, probably a high cell voltage is acceptable in order to realize a maximal separation.

Two basically different types of cell separators are available: porous separators

with unselective ion transport and “ion-exchange membranes,” which support the selective transport of either cations or anions (see Sect. 2.4.3).

#### 2.3.4

##### **Batch Operation or Flow-through Cells**

Batch operation is the simplest way of electrolysis and, therefore, mostly applied for electroorganic syntheses. The reactant concentration decreases with rising degree of conversion (see reactant 1 in Fig. 1). The selectivity of the reaction can be maintained in spite of a decline of the limiting current density by potentiostatic cell operation. Usually, the reaction is carried out up to a selected conversion or transferred charge, respectively. Owing to the continuously changing conditions, much information about the reaction is available by analysis of samples, extracted in suitable intervals during the experiment. A plot of all concentrations of reactants and products versus time or transferred charge gives information about reaction rate, yield, selectivity, current efficiency, and also about any by-product formation in parallel and/or consecutive reactions.

Constant process conditions – as well of concentrations as of other parameters – are realized using a flow-through cell in steady state operation. Into the cell continuously reactants are added and products are removed to maintain constant concentration and conversion. Additional expenses, especially pumps, are needed, however. This continuous operation will be applied, for example, if optimal results only are achievable using well-defined process conditions. Another example is the application of cell components – such as ion-exchange membranes – that need constant concentrations and a long time after

start-up for optimal working. Large-scale industrial cells are often operated under steady state conditions.

Batch operation in a larger scale – in laboratory or even industrial applications – frequently is realized using a flow-through cell with optimized flow characteristics, which is coupled by circulating pumps with reservoirs that contain the reaction solutions.

## 2.4

### **Components of Electroorganic Reaction Systems**

The following short overview can only give an impression of some usual or innovative cell components and materials (a more detailed overview is given, for example, in [3a, 3b, 10, 11]).

Particular attention should be paid to toxic materials. Electroorganic synthesis will become increasingly of interest in the preparation of speciality chemicals, for example, food additives and pharmaceuticals. Thus, toxic materials should be avoided as far as possible, for example, for electrodes, solvents, or supporting electrolytes. At least, it has to be guaranteed that toxic materials in the products can be separated or removed below the official threshold values.

Precondition of a successful electroorganic synthesis is an optimal arrangement of all incorporated components. Therefore, all available information from literature, supplemented, if possible, by results of own experiments, should be considered. The best way to get actual information about suppliers of materials and equipment – that probably may be very quickly changing – is the Internet via a search engine.

## 2.4.1

**Electrodes**

The electrodes are the typical and most important components of an electrochemical cell – especially the working electrode – which usually decide about the success of an electroorganic synthesis. Electrode materials need a sufficient electronic conductivity and corrosion stability as well as, ideally, a selective electrocatalytic activity which favors the desired reaction. The overvoltages for undesired reactions should be high, for example, for the decomposition of the solvent water by anodic oxygen or cathodic hydrogen evolution. But, additionally, the behavior of electrodes can show unexpected and incomprehensible effects, which will cause difficulties to attain reproducible results.

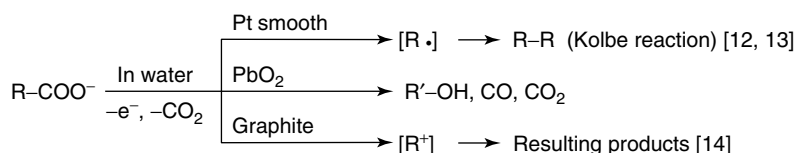
The electrode reaction typically includes a lot of steps, such as adsorption and desorption, one or several electron transfer steps, preceding, and/or

subsequent chemical reactions. All these steps, and consequently the selectivity of the reactions, will be influenced by properties of the electrode surface, for example, by chemical composition, morphology, and porosity, which may also be dependent on the history of the electrode. Usually, there is a significant interdependency between the electrode properties and the electrolyte composition, that is, reactants, products, solvents, and supporting electrolytes, including impurities.

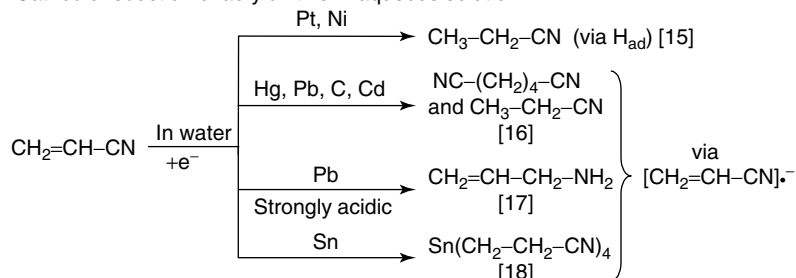
This shall be elucidated by two examples for the influence of the electrode material on the product spectrum of well-known electrochemical reactions [4], see Scheme 1 below.

A special problem can be the passivation of the electrode surface by insulating layers, for example, formation of oxides on metals at a too high anodic potential or precipitation of polymers in aprotic solvents from olefinic or aromatic compounds by anodic oxidation. As a result, the effective surface and the activity of the

- Anodic oxidation of carboxylates in aqueous solution via decarboxylation



- Cathodic reduction of acrylonitrile in aqueous solution



**Scheme 1** Influence of the electrode material on the product spectrum of an electrochemical reaction.

electrode are diminished. To avoid an increasing of the local current density and consequently a reduced reaction selectivity, the cell current should be decreased (automatically achieved by potentiostatic operation). A periodical change of the polarity of the electrodes for regeneration of the activity can be helpful (then a symmetrical construction of the cell will be suitable). Also, additives to the electrolyte with better dissolving power for polymers can be beneficial.

Electrodes may consist of a homogeneous material – frequently, with an in situ formed active layer on the surface – or of a carrier material with an active coating. A proper connection to the current feeder and a suitable assembling of the cell must be enabled; often, a leakproof installation of electrodes in the cell body is required. Therefore, the mechanical properties of the electrode material have to pass practical selection criteria:

- strength, hardness, elasticity, brittleness, and so on.
- possibility to be converted to wires, sheets, grids, expanded metal sheets, porous plates, such as sintered metal, felt, or foamed material, and so on.
- possibilities of cutting, machining, welding, or soldering, and so on.

A very important aspect is corrosion, concerning a possible contamination of electrolyte and products – particularly in case of toxic materials – and with respect to the electrode lifetime. Last, not least, the price can be decisive, especially if a commercial application is planned.

In the following section, examples of electrode materials for application as anode and/or as cathode, and then some electrode types of practical interest are discussed. A comprehensive overview

about electrodes is given, for example, in [10, 11].

#### 2.4.1.1 Examples of Electrode Materials

**2.4.1.1.1 Anode Materials: General Requirements** A major problem and thus a decisive factor for the choice of anode materials is corrosion, except when the dissolution of a metal is the desired reaction (“sacrificial anodes”, see Sect. 2.4.1.2.4). The stability of anode materials is extremely dependent on the composition of the anolyte (e.g. pH value, aqueous or non-aqueous medium, temperature, presence of halogenides, etc.).

In aqueous electrolytes, frequently the oxygen overvoltage is an essential aspect. If the anode is the working electrode and a strong oxidation power is desired, special materials with a high oxygen overvoltage are needed in order to reduce concurrent oxygen production. If the anode is the oxygen evolving counter electrode it is mostly difficult to avoid disadvantageous oxidation reactions, due to the high potential of the oxygen formation, further increased by the oxygen overvoltage. There are no anode materials with a real low oxygen overvoltage. Thus, in most cases, the anode as counter electrode has to work in a divided cell within a separate compartment, unless a depolarized anode can be used (see Sect. 2.3.3).

**2.4.1.1.2 Cathode Materials: General Requirements** Cathodes usually have no corrosion problem. If the cathode is the working electrode, a main selection criterion of the materials is the hydrogen overvoltage, that is, the accessible reduction power, which may vary in a wide range (e.g. hydrogen overvoltage at  $1 \text{ mA cm}^{-2}$  very low  $\eta_{\text{H}} < 0.1 \text{ V}$ : Pt, platinum metals;

low  $\eta_{\text{H}} < 0.2$  V: Ni, Au; medium  $\eta_{\text{H}}$  0.2–0.6 V: Cu, Ag, Fe, Al, Ti, Cr, Mo, W, Bi, stainless steels (Cr-Ni-Fe), brass (Cu-Zn), Monel<sup>®</sup> (Cu-Ni); high  $\eta_{\text{H}} \approx 1.0$  V: Hg, Pb, Cd, Sn, Zn, graphite) [4]. A principally high hydrogen overvoltage of a pure cathode material can be decreased – that is, the cathode will be poisoned and hydrogen evolution occurs – even by very small amounts of other metals, for example, dissolved from a noble metal anode (this has to be considered in the selection of the anode material).

A further argument for the choice of the cathode material may be the catalytic activity for hydrogenation reactions. Vice versa, this is also important if the cathode is the counter electrode – usually evolving hydrogen – where hydrogenation reactions are undesired.

**2.4.1.1.3 Platinum, Platinum Metals or their Alloys, and Other Noble Metals** Platinum, platinum metals or their alloys, and other noble metals are classical electrode materials, and much literature about these is available. Though the orientation of single crystals has a considerable influence, for synthetic applications, only polycrystalline materials are suitable. The metals show significant differences in their electrocatalytic and additionally in their chemical catalytic activity. Owing to the high price of the metals, it may be interesting to use them as a coating on a carrier (see Sect. 2.4.1.1.10).

**Anode** Investigations using cyclic voltammetry confirm an important effect of surface oxides (see Vols. 3, 4). A known example of the different anodic activity is the poisoning of platinum by adsorbed carbon monoxide species, for example, in the direct methanol fuel cell (DMFC),

which can be overcome by alloying with ruthenium [19].

Anodic corrosion in case of platinum metals mostly is insignificant or at least small for most anolyte compositions and conditions. But it may be an economic problem for industrial applications. Furthermore, as aforementioned, it can be the reason of cathode poisoning. The corrosion rate of gold, and especially of the less noble metals, is very dependent on the pH value of the anolyte.

**Cathode** Platinum metals, especially platinum and palladium, achieve the lowest known overvoltages for hydrogen. Moreover, they are effective catalysts for hydrogenation reactions [15].

#### 2.4.1.1.4 Nickel

**Anode** A nickel anode forms in aqueous alkaline solutions a layer of Nickel(III)-oxide NiOOH. Owing to its application in nickel cadmium and nickel metal hydride accumulators, it is much investigated [20]. It is stable for oxygen evolution and very interesting for selective oxidation reactions ([21] see Chapters 6, 15), an industrial application is one step of the vitamin C production [22]).

**Cathode** Nickel may be an alternative for platinum metals in alkaline solutions due to its low hydrogen overvoltage and catalytic activity. The activity is especially high at the very fine dispersed “Raney nickel”, which is available from a layer of a nickel alloy on the cathode surface by dissolving the alloy metal (aluminum or zinc) in alkaline solution prior to use (e.g. [23, 24]. Raney nickel usually is not stable against oxygen and self-ignition in air may be possible).

#### 2.4.1.1.5 Iron, Stainless Steel

**Cathode** Iron is a very cheap cathode material with a relatively low hydrogen overvoltage (e.g. [25]). It is of interest for industrial applications. In order to avoid corrosion during interruption of the current, stainless steel may be suitable, especially in laboratory cells where the increased electrical resistance and hydrogen overvoltage are irrelevant.

**2.4.1.1.6 Lead** About lead much literature is available due its technical application in the “lead-acid-battery”. Pure lead is very soft and has a poor mechanical stability. Therefore, often it is applied as a coating on a carrier or alloys are used, for example, with antimony (“type metal”).

**Anode (lead dioxide)** On lead as anode material in aqueous solutions (for example, [26]) usually a lead dioxide layer is formed and continuously regenerated at high anodic potentials, but in longer operation the lead is destroyed by this process.  $\text{PbO}_2$  is an anode material with a very high oxygen overvoltage and therefore it offers a high anodic potential and a strong oxidation effect in aqueous acidic solutions, especially in sulfuric acid (industrial utilization e.g. for chromic acid regeneration [27]). Because  $\text{PbO}_2$  is a strong chemical oxidation agent too, its application as anode material is restricted if a spontaneous reaction with a reactant is possible.

$\text{PbO}_2$  is also applicable as a coating on a suitable carrier material (see Sect. 2.4.1.1.10).  $\text{PbO}_2$ -coated titanium anodes with good stability are commercially available. On platinum or platinum-coated titanium a coating of  $\text{PbO}_2$  for laboratory use can easily be prepared electrochemically (e.g. [28]).

The corrosion rate of  $\text{PbO}_2$  – often enhanced by mechanical erosion – is relatively high and may be a problem due to the toxicity of lead.  $\text{PbO}_2$  can be stabilized by modification with, for example, silver, antimony, tin, cobalt oxides (or by alloying of the lead base metal with these metals, respectively) [29].

**Cathode** The hydrogen overvoltage on lead is especially high, but this can be realized only with very pure lead. Other metals with a lower hydrogen overvoltage must not be present, for example, in the electrolyte or from the anode. In the negative electrode of lead-acid-batteries, antimony as alloying metal is replaced with calcium in order to achieve a high hydrogen overvoltage (“maintenance-free battery”) [30].

#### 2.4.1.1.7 Mercury

**Cathode** Mercury is a classical cathode material for electroorganic reductions due to its extraordinarily high hydrogen overvoltage in aqueous solutions. Because it is liquid, it needs special cell constructions (see e.g. Fig. 8). By stirring, its surface can be continuously renewed so that reduced metals – including even alkali metals from a supporting electrolyte – will be dissolved as amalgam and thus will not decrease the hydrogen overvoltage at the surface. For many applications also, an amalgamated metal electrode such as copper, which is easier to handle, may be sufficient. The toxicity of mercury restricts its applicability for technical syntheses.

**2.4.1.1.8 Carbon** Carbon is a common electrode material (e.g. [31]) that is much cheaper than noble metals. Its conductivity is by a factor of about 100 lower than that of metals, but this will be no problem using



suitable electrode constructions. Its technical applications include current feeders of batteries, anodes for chlorine evolution, bipolar electrodes for industrial scale electroorganic syntheses (see Fig. 12), and anodes in the molten-salt electrolysis for aluminum winning.

Carbon is available in a large variety of qualities. Electrode carbon is produced with different percentages of crystalline graphite (as a consequence, for example, different conductivities and stabilities are resulting). It is usually highly porous and not leakproof against gases and fluids. It can also be impregnated with resins, even using fluorinated resins, in order to realize tight materials of high chemical stability. All these materials can be easily machined but their solidity is limited and they are somewhat brittle. Graphite fiber reinforced graphite with a very high mechanical strength is obtainable for special applications (e.g. SGL-Carbon Group).

Graphite is offered moreover in flexible sheets (e.g. Sigraflex® of the SGL-Carbon Group). This is primarily a sealing material, but it is suitable also as electrode or corrosion resistant current feeder (erosion in case of gas evolution is possible).

Carbon fiber or graphite fiber materials, available, for example, as felt, clothes, or paper, and so on, are state of the art for realizing conductive diffusion zones in fuel cells but also they can be used as electrodes. They attain a very high porosity (free space volume up to 80%) and a surprisingly good elasticity.

Glassy carbon (vitreous carbon) is a further modification. It is a smooth and tight material of high corrosion resistance and for many reactions it may be a suitable alternative of platinum. It is relatively expensive, but much cheaper than noble metals. It is very hard and brittle and allows only limited possibilities for

machining (diamond tools necessary). It is additionally available as a foamed material.

Carbon- or graphite-filled polymers or a carbon paste, which can easily be regenerated by removing a surface layer, are also possible electrode materials.

Generally, carbon materials show a low electrocatalytic activity. But often it is very dependent on the history of the electrode, for example, due to removing of a surface coverage or due to roughening of the surface. Thus it may be difficult to get reproducible results, and frequently a long time of changing conditions after start of the electrolysis is observed.

**Anode** In aqueous anolytes, under conditions which favor the oxygen evolution, carbon is attacked under carbon dioxide formation, this is increasingly encountered with more porous materials. Glassy carbon will be relatively stable. A low pH value may retard the oxygen reaction, but carbon remains a problematic anode material in aqueous solutions. Additionally, it can be attacked because of intercalation of anions.

In nonaqueous media, carbon (graphite) frequently is an optimal anode material, for example, for methoxylation reactions, even in an industrial scale (capillary gap cell, see Fig. 12). It shows an appreciable overvoltage for the oxidation of methanol compared to platinum.

**Cathode** The hydrogen overvoltage of carbon is relatively high. Thus, if the cathode is the working electrode, a lot of reduction reactions is enabled. On the other hand, the catalytic activity for hydrogenation reactions is low. This is advantageous if the cathode is the counter electrode: cathodic side-reactions are avoided besides hydrogen evolution,

and therefore carbon can be a useful cathode material, even though the energy consumption is increased because of the hydrogen overvoltage.

**2.4.1.1.9 Ceramic Materials** An example of a sufficiently conductive metal oxide is magnetite  $\text{Fe}_3\text{O}_4$ , which has been used, for example, in the past as corrosion resistant anode material for industrial chlorine evolution (it can be smelted and casted at  $1500^\circ\text{C}$ , but it is a very brittle material).

The modern material Ebonex<sup>®</sup> is a mixture of substoichiometric titanium oxides  $\text{Ti}_4\text{O}_7$ ,  $\text{Ti}_5\text{O}_9 \dots \text{Ti}_n\text{O}_{2n-1}$  ("Magnéli phases" [32]). It offers a unique combination of electrical conductivity and corrosion resistance. Primarily, Ebonex<sup>®</sup> is produced as a powder. As is usual for ceramics, the ready-formed material is hard and brittle, the possibilities of machining are restricted (diamond tools).

The electrocatalytic activity of Ebonex<sup>®</sup> is low, the overvoltages for oxygen and hydrogen are very high. Additionally, to its direct application as electrode material, it is an interesting carrier material for electrode coatings. Even very thin layers of the coating show only the electrochemical properties of the coating but not of the carrier [32–34].

**2.4.1.1.10 Coated Electrodes and Carrier Materials** Numerous interesting electrode materials are applicable exclusively in the form of a coating on a carrier material. Besides the electrocatalytic coatings listed below the use of precious metal electrodes as a thin layer on a cheaper carrier material will be attractive.

Common carrier materials will be, for example, carbon, glassy carbon, or Ebonex<sup>®</sup>, but for practical and industrial

applications especially metals such as titanium are appropriate.

**Titanium as a carrier metal** Titanium (or a similar metal such as tantalum, etc.) cannot work directly as anode because a semiconducting oxide layer inhibits any electron transport in anodic direction ("valve metal"). But coated with an electrocatalytic layer, for example, of platinum or of metal oxides (see below), it is an interesting carrier metal due to the excellent corrosion stability in aqueous media, caused by the "self-healing" passivation layer (e.g. stability against chlorine in the large scale industrial application of "Dimension Stable Anodes" DSA<sup>®</sup>, see below).

A cathodic current is in principle possible, but in case of hydrogen evolution, titanium will be destroyed by hydride formation.

Protection layers between the titanium metal and the electrocatalytic coating, for example, of substoichiometric titanium oxides (see Ebonex<sup>®</sup> above), increase the stability by shielding the metal, for example, to avoid the formation of insulating titanium dioxide layers on the metal [35]. The preparation of such electrodes with optimal properties usually needs the special know-how of commercial suppliers.

It has to be considered that titanium – at least without special protection layers – will be attacked by several chemicals: for example, fluorides, fluorine-containing substances, such as tetrafluoroborates  $\text{BF}_4^-$ , or oxalates, and possibly by other organic acids, which may be formed during anodic oxidation reactions. An application of titanium in nonaqueous media is not suitable (instability of the passivating oxide layer).

**Metal oxide coatings** Commercial lead dioxide coatings, for example, on titanium, have a higher stability compared with lead or lead alloy anodes with their in situ formed oxide layer. A secure contact between  $\text{PbO}_2$  and titanium has to be guaranteed, for example, by a platinum layer or at least by a sufficiently large number of platinum crystallites.

Also, other metal oxide coatings are possible, for example, electrochemically deposited manganese dioxide. Moreover, further electrocatalytically active oxides are research objectives, for example, oxides with spinel structure such as  $\text{CoMn}_2\text{O}_4$  [36].

**Dimension stable anodes (DSA®)** These titanium anodes with platinum metal oxide coatings have revolutionized the industrial chlor-alkali electrolysis [37] (about 10% energy saving compared to graphite anodes that corrode continuously by oxygen/carbon dioxide formation). Ruthenium as active catalyst metal – with its easy  $\text{Ru}^{4+}/\text{Ru}^{3+}$  changing for the oxidation of chloride ions to chlorine – is optimally fixed in an electrically conductive mixed crystal structure with titanium dioxide. A simple DSA for laboratory use is easy to prepare according to [38] (example I: painting and thermal decomposition of a solution of  $\text{RuCl}_3 \cdot x\text{H}_2\text{O}$ , a titanium alcoholate and  $\text{HCl}$ ). But DSA's of optimized stability, including the above-mentioned protection layers, are only available from commercial suppliers (complex coating compositions and production processes, for example, plasma spraying too, at exactly defined conditions).

Ruthenium will be dissolved by oxygen evolution (volatile  $\text{RuO}_4$ ). Coatings based on iridium/tantalum oxides are stable for oxygen evolving anodes, even with simultaneous chlorine evolution in the presence of chlorides.

The application of a DSA for electroorganic oxidations [39] may possibly be disturbed because of corrosion of the active layer and/or the titanium carrier by organic reactants and products. If significant advantages using a DSA are expected, stability tests of the DSA under the special conditions have to be performed.

Analogous to the DSA manufacture, a pure titanium dioxide coating can be prepared, which shows a high activity and stability (also against titanium hydride formation), for electroorganic cathodic reductions (e.g. [40], see Chapter 7).

**Diamond coating (boron doped)** A new unconventional electrode material with very interesting properties is diamond, electrically conductive by doping with boron (e.g. [41, 42]). It can be applied on various carriers – for example, silicon, carbon, tantalum, titanium – by chemical vapor deposition (CVD). It has a low catalytic activity and the highest known overvoltages for oxygen and also a high one for hydrogen evolution. Therefore, the potential range and the electrochemical power for oxidation as well as for reduction is extraordinarily high. A possible application is the electrochemical detoxification of waste (e.g. [43, 44]).

#### 2.4.1.2 Examples of Electrode Types and their Special Properties

##### 2.4.1.2.1 Smooth or Porous Electrodes

The porosity of an electrode surface will significantly influence its electrochemical behavior, especially because of a considerable decrease of the effective current density in case of materials with a high microporosity and consequently a large effective surface area. A well-known example is platinized platinum that can enable

reactions that are impossible at smooth platinum. A similar material is Raney nickel. But also a simple roughening of an electrode surface, for example, by etching, may be advantageous.

Dimensions and structures of pores in electrode materials will vary in an extremely wide range. The influence of the porosity on the electrode properties includes also mass-transfer effects.

In order to extend the effective electrode area in principle three-dimensional electrodes are possible, for example, by using a packed particle bed, a sintered or foamed metal, or a graphite fiber felt. But the depth of the working electrode volume usually is only small (it is dependent on the ratio of the electrode and electrolyte conductivity, for example, [45]).

**2.4.1.2.2 Gas Evolving Electrodes** Gases, for example, hydrogen, oxygen, or carbon dioxide, are often formed in the main reaction or as a by-product (caution: the possibility of explosive gas mixtures and of an ignition by a shortcut between the electrodes has to be taken into consideration). An advantageous effect of the moving gas bubbles is the increase of the mass transfer at the electrode surface [46]. On the other hand, the gas has to be removed as fast as possible from the current path in front of the electrode, in order to prevent a too large decrease of the electrolyte conductivity and a perturbation of the uniform current density on the electrodes, up to a (temporarily) blocking of the electrode surface. Especially big gas bubbles must be avoided. An optimally perforated structure of the electrode is desired, for example, expanded metal sheets. A horizontal electrode arrangement can be suitable for undivided cells or if a gas evolution only is possible at the upper electrode. If there is a

formation of gas at both electrodes in divided cells, mostly vertical electrodes will be necessary. Then a possible decrease of the current density in the upper part of the cell has to be considered (see Sect. 2.5.1.1).

**2.4.1.2.3 Gas Diffusion Electrodes** Gas diffusion electrodes (GDE's) are well known from fuel cells, for example, [47]. The function of gas consuming GDE's is based on "three phase zones", where the gas, the electrolyte and the electrocatalyst, that needs a sufficient electrical connection to the current feeder, are simultaneously in contact. The electrocatalyst, usually platinum metals, should be located in the three phase zones, realizing a maximal surface that is the effective electrode area. A duplicate pore system must be established: on the one hand, for the electrolyte, usually by hydrophilic carbon black, which is also the electronically conducting carrier of the catalyst, and, on the other hand, for the gas, typically by addition of hydrophobic polytetrafluoroethylene (PTFE). In consequence, common GDE's only can work in aqueous electrolytes without components that impede the hydrophobic rejection of the electrolyte from the gas pores.

GDE's may be interesting for synthesis cells as depolarized electrodes (e.g. [48]). A hydrogen-consuming anode will work at a low potential that avoids undesired anodic oxidations (e.g. no chlorine evolution in presence of chlorides). In order to reject an excess of the electrolyte from the GDE structure, a proton-conducting membrane (Nafion®) between the GDE and the electrolyte can be used ("Hydrina®", De Nora Spa. [49]).

A fascinating option is offered by carbon-based oxygen-consuming cathodes, which can reduce oxygen into hydrogen peroxide (e.g. [50]). Thus, an oxidizing agent is produced at the cathode! In combination

with the anodic oxidation, a “200% cell” may be possible (e.g. [51, 52]).

**2.4.1.2.4 Sacrificial Anodes** A special type of a depolarized electrode is a sacrificial anode – often as counter electrode – where the electrode material is dissolved during the reaction (e.g. [53]). Typical are very electronegative metals, such as magnesium, aluminum, or zinc, which avoid – because of their low potential – any anodic oxidation and therefore allow the application of undivided cells. Frequently, this technique is utilized in nonaqueous media, also in industrial reactions (continuous operation in “pencil sharpener cells”, using conic cathodes that form a conic shape of the anodes too [54]). Ideally, the metal generates a salt that increases the conductivity of the electrolyte and is not too soluble so that it can be easily removed by precipitation. There are also conversions where the dissolved anode material is used as reactant, for example, different metals for production of metalorganic compounds or sulfur for organic polysulfides (mixed with carbon powder for sufficient conductivity [55]).

## 2.4.2 Electrolytes

In addition to the function as reaction medium – as in all chemical reactions – in electrochemical processes, the electrolyte has to provide the transport of ions between the electrodes. An optimal combination of solvent and supporting electrolyte has to be found, considering the reaction conditions and the properties of reactants, products, and electrodes. A short overview of usual electrolytes – and some examples of unconventional electrolytes as thought-provoking impulse for research – is given

here; a more detailed discussion is available, for example, in [3, 5] (comprehensive data of nonaqueous electrolytes in [56]).

### 2.4.2.1 Solvents

The significant, often decisive, influence of the solvent in chemical reactions similarly is valid for electrochemical reactions too, for example, due to protic or aprotic and electrophilic or nucleophilic properties. If an excess of reactants can be used as solvent, a particularly uncomplicated operation will be possible. An additional solvent should be inert. The requirements for the solvent in dissolving power for reactants and products and the criteria regarding an easy separation of the products from the reaction mixture, for example, the boiling point, are comparable for chemical and electrochemical conversions. Generally, there is an interest to use, as far as possible, inexpensive, nontoxic, and easy to handle solvents.

But in electrochemistry additional properties of the solvent are essential:

- the ability to solvate ions – dissociated as cations and/or anions – in order to achieve a sufficient conductivity of the electrolyte (this is often, but not exclusively, coupled with the polarity of the solvent),
- an advantageous or at least innocuous influence on the electrode reactions, for example, by adsorption at the electrode surface – probably in concurrence to reactants – or by interaction with intermediates such as radical ions,
- the usable potential range (“potential window”) in which the solvent itself does not react at the electrodes, at the anode as well as at the cathode (in Table 1 a practically acceptable solvent decomposition of  $0.1 \text{ mA cm}^{-2}$  is assumed, see the thin line in Fig. 1).

**Tab. 1** Potential limits of some solvents at 0.1 mA cm<sup>-2</sup> and 25 °C [4] sorted according to increasing dielectric constant  $\epsilon$  (with 0.1 m [NBu<sub>4</sub>]ClO<sub>4</sub> and platinum electrodes if not otherwise stated)

Solvent	Abbreviation	$\epsilon$	Potential limit [V]	
			Cathodic	Anodic
1,2-Dimethoxyethane	–	3.5	–3.0 <sup>a</sup>	+0.7 <sup>a</sup>
Acetic acid (water free)	HAc	6.2	–1.7 <sup>a</sup>	+2.0 <sup>b</sup>
Tetrahydrofuran	THF	7.6	–3.3 <sup>c</sup>	+2.1 <sup>c</sup>
Dichloromethane (methylene chloride)	MC	9.1	–1.7	+1.8
Pyridine	Py	12.0	–2.2	+3.3
Acetone	–	21.0	–1.6	+1.6
Hexamethylphosphoric acid triamide	HMPA	30	–3.3 <sup>c</sup>	+1.1 <sup>c</sup>
Methanol	MeOH	31.5	–2.2 <sup>a</sup>	+1.3
N-methylpyrrolidone	NMP	32	–3.3 <sup>a</sup>	+1.4 <sup>c</sup>
Nitromethane	–	35.7	–2.4 <sup>c</sup>	+3.0 <sup>c</sup>
Acetonitrile	ACN	36.2	–2.6	+2.7
N,N-dimethylformamide	DMF	36.7	–2.7	+1.5
N,N-dimethylacetamide	DMA	38	–2.6	+1.3
Sulfolane (tetramethylenesulfone)	–	44	–2.3 <sup>a</sup>	+3.3
Dimethylsulfoxide	DMSO	46.6	–2.7	+1.3
Propylenecarbonate	PC	65.2	–1.9	+1.7
Water	–	80	–2.9 <sup>a</sup>	+1.4
85–96 wt-% sulfuric acid	–	100	–1.0 <sup>a</sup>	+2.1
Tetrahexylammoniumbenzoate (molten at 25 °C)	–	–	–1.2	+0.3
AlCl <sub>3</sub> /NaCl/KCl (molten at 150 °C)	–	–	–1.9	+1.0

<sup>a</sup>Mercury electrode.

<sup>b</sup>Sodium acetate.

<sup>c</sup>Lithium perchlorate.

$\epsilon$  = dielectric constant.

#### 2.4.2.2 Supporting Electrolytes

The solute–solvent mixture in electroorganic conversions frequently is not conductive enough and a supporting electrolyte has to be added. If an acidic or basic reaction medium is used, the needed acid or base may be sufficient to increase the conductivity of the electrolyte. This is an inexpensive way, and after the reaction, mostly a simple neutralization is possible. If in special cases a mediator is applied – for example, a bromide for the industrial anodic methoxylation of furan [57] – this can provide an adequate conductivity.

But usually an inert supporting electrolyte, which does not react anyway, is needed. Important properties for its selection are

- sufficient solubility and conductivity in the applied solvent,
- easy separation and recycling,

and similar criteria as for the solvents such as

- sufficient stability against oxidation and reduction (see Table 2),
- optimal interaction with the electrode reactions, especially adsorption effects,

**Tab. 2** Potential limits of some anions and cations of supporting electrolytes [4] (concentration 0.1 m in water and acetonitrile at 0.1 mA cm<sup>-2</sup> and 25 °C)

Ion	Electrode	Potential limit [V]	
		In water	In acetonitrile
I <sup>-</sup>	Pt anode	0.30 <sup>a</sup>	0.20
Br <sup>-</sup>	"	0.85 <sup>a</sup>	0.70
Cl <sup>-</sup>	"	1.10 <sup>a</sup>	1.15
F <sup>-</sup>	"	(2.6) <sup>a,b</sup>	–
ClO <sub>4</sub> <sup>-</sup>	"	(1.5)	2.6
[BF <sub>4</sub> ] <sup>-</sup>	"	–	3.1
[PF <sub>6</sub> ] <sup>-</sup>	"	–	3.2
Li <sup>+</sup>	Hg cathode	–2.16	–1.8
Na <sup>+</sup>	"	–1.95	–1.7
K <sup>+</sup>	"	–2.03	–1.8
Rb <sup>+</sup>	"	–1.98	–1.8
NH <sub>4</sub> <sup>+</sup>	"	–2.00	–1.7
N(CH <sub>3</sub> ) <sub>4</sub> <sup>+</sup>	"	–2.65	–2.4
N(C <sub>2</sub> H <sub>5</sub> ) <sub>4</sub> <sup>+</sup>	"	–2.78	–2.5
N(C <sub>4</sub> H <sub>9</sub> ) <sub>4</sub> <sup>+</sup>	"	–2.87	–2.6
N(C <sub>2</sub> H <sub>5</sub> ) <sub>3</sub> H <sup>+</sup>	"	–1.83	–

<sup>a</sup>Resulting from standard potentials.

<sup>b</sup>Oxygen evolution already at a lower potential.

- low toxicity,
- low prize.

#### 2.4.2.3 Examples of Electrolytes

**2.4.2.3.1 Aqueous Electrolytes** Generally, water is the first choice as solvent for electrochemistry due to the optimal solvation of ions in consequence of its high dielectric constant. In aqueous electrolytes, a large variety of suitable salts is available which leads to a high conductivity. Also, concerning the low costs and the environmental protection, water will be the most attractive solvent. But, on the other hand, the reactivity of water is relatively high and frequently it obstructs the intended electroorganic conversion, forming undesired by-products.

Using an optimal combination of supporting electrolyte, electrode materials,

and operation conditions, it may be possible to use the advantages of an aqueous electrolyte, while avoiding undesired side-reactions. An example is the cathodic hydrodimerization of acrylonitrile to adipodinitrile, the largest industrial electroorganic process [16]. The best results are obtained with a strongly hydrophobic cation of the supporting electrolyte (hexamethylenebis(ethyltributyl)ammonium phosphate), because it is adsorbed at the cathode and rejects maximally the undesired hydrogenation to propionitrile in presence of water [58] (see the reaction scheme at the beginning of Sect. 2.4.1).

For reactants (solid or liquid), which are not sufficiently soluble in water, additional cosolvents can be used in order to obtain a homogeneous solution. Examples are alcohols, such as ethanol or 2-propanol,

and ethers, such as dioxane, but also quaternary ammonium salts as shown in Table 2 as supporting electrolytes.

**2.4.2.3.2 Electrochemistry Using Emulsions** The electrochemical conversion of a reactant, which is not sufficiently soluble in water, may also be possible in emulsion, formed by an aqueous electrolyte and the liquid reactant or an organic solvent containing the reactant. This enables to convert compounds with a very low dielectric constant, for example, aromatic hydrocarbons, simultaneously using the high conductivity of an aqueous electrolyte. A “phase-transfer agent” (“phase-transfer catalyst”) such as, for example, a tetraalkylammonium salt, polyethyleneglycol, or a crown ether, can enhance the transport of the reactant between the organic and aqueous phase (e.g. [59–61]). Also, ultrasound has been used to enhance an electrosynthesis in emulsion [62].

**2.4.2.3.3 Electrolytes Based on Nonaqueous Protic Solvents** Particularly methanol is very often used as solvent. Its high dielectric constant and general similarity to water enables a good solvation of ions and high dissolving power for salts. The low boiling point simplifies the product separation by distillation. Especially interesting is methanol simultaneously as reactant and solvent, for example, for methoxylations (see Chapter 6). The dual methoxylation, for example, of toluene derivatives, results in the selective synthesis of acetals, which can be hydrolyzed to aldehydes, under recycling of the methanol. There are various examples of industrial applications (e.g. [3b, 63]).

**2.4.2.3.4 Electrolytes Based on Aprotic Solvents** Aprotic electrolytes are usually

needed if reactants or especially basic intermediates would be protonated by a protic solvent. Additionally, very high electrode potentials are accessible (see Table 1). Owing to the small dielectric constant of aprotic solvents it is difficult to provide a sufficient conductivity. The supporting electrolyte has not only to be soluble, but must dissociate also into ions. Typical compounds are lithium or tetraalkylammonium cations and tetrafluoroborate or hexafluorophosphate anions (perchlorate salts are in principle possible but as explosive compounds might be formed their application is restricted).

Aprotic electrolytes of an adequate high conductivity are necessary for lithium batteries and supercapacitors. Therefore, recently, much industrial research has been done in this area and highly sophisticated electrolyte systems have been developed (e.g. [64]). The supporting electrolytes for aprotic solvents generally are more or less expensive and toxic. After the reaction, their separation and recycling is inevitable and frequently needs considerable efforts.

A standard aprotic electrolyte system with general applicability for electroorganic syntheses is acetonitrile with  $\text{Bu}_4\text{NBF}_4$  as supporting electrolyte. It shows a wide potential window  $-2.6$  to  $+2.7$  V, a low reactivity (nucleophilicity and electrophilicity) and a relatively high dielectric constant and conductivity. The low boiling point allows an easy separation after the reaction. The toxicity of acetonitrile has to be considered, however (maximum allowable concentration at the working place 20 ppm).

The application of aprotic electrolytes usually requires that water traces are carefully removed and therefore needs much effort for purification steps in an inert gas atmosphere. It has to be



considered that water may be the product of (side-)reactions at the electrodes.

**2.4.2.3.5 Molten Salts as Electrolytes** In the bottom of Table 1, examples of salts are shown, which are liquids at room temperature or at moderately higher temperatures. Recently, “ionic liquids”, for example, based on imidazolium salts, have found interest as solvents in lab scale reactions (e.g. [65]). In electrochemistry, they may be used as solvent and supporting electrolyte simultaneously. Because they are not volatile, an easy separation from products by distillation is possible.

**2.4.2.3.6 Liquefied or Supercritical Gases as Solvents for Electrolytes** For very special applications, where the increased efforts for low temperature and/or pressurized cells are acceptable, liquefied gases, for example, sulfur dioxide or ammonia, can be interesting solvents for electrolytes (see e.g. [3a]). Supercritical fluids show remarkable properties that are very different from other solvents. Detrimental to electrochemistry is that especially the dielectric constant in the supercritical state becomes low. For supercritical carbon dioxide, no supporting electrolyte with sufficient conductivity is known.

Various fluorinations, which need principally much energy for the generation of the reagent fluorine, are carried out electrochemically in liquid hydrogen fluoride, even in an industrial scale [66]. Owing to the extreme toxicity and the corrosive medium, special precautions are necessary.

**2.4.2.3.7 Solid Polymer Electrolyte Technology** Ion-exchange membranes, often used as cell separators (see Sect. 2.4.3.2),

in principle, are ion conductors and can work as electrolyte even in the absence of a conductive solution. This “solid polymer electrolyte technology” (SPE) actually is well known for fuel cells (PEMFC = proton-exchange membrane fuel cell and DMFC = direct methanol fuel cell) [47]. It also enables electroorganic syntheses without any supporting electrolyte. If the application is possible – a precondition is a sufficient conductivity of the membrane in the reaction system (see Sect. 2.4.3.2) – the operation is easy and saves expenses for separating and recycling of a supporting electrolyte ([67], overview in [68]). Advantages of the SPE technology have been verified for different reactions using cation- and anion-exchange membranes in combination with various electrode materials in aqueous and nonaqueous media. A successful example is the methoxylation of amides, such as *N,N*-dimethylformamide (DMF), which runs nearly perfectly with graphite felt electrodes, pressed on the surfaces of a cation-exchange membrane (Nafion®) in a pure mixture of methanol and DMF without any additive. Approximately 100% selectivity and current efficiency at a low cell voltage [68] is better than reported for Bu<sub>4</sub>NBF<sub>4</sub> as supporting electrolyte [69].

### 2.4.3 Cell Separators

As discussed in Sect. 2.3.3, the in principle desirable application of an undivided cell will be impossible if a reaction at the counter electrode results in unacceptable consequences, for example, impurities of the product and/or considerable losses in yield and current efficiency. There is a large variety of cell separators available, but none of them can work ideally.

The task of a cell separator is to impede a direct mixing of anolyte and catholyte and to decrease diffusion, but at the same time the migration of ions has to be possible without a too high voltage drop. Naturally, a compromise of these requirements has to be found.

The functioning of a separator will be the more difficult, the more different both electrolytes are. With increasing concentration gradients diffusion will be enhanced. It can be reduced using a less porous and/or thicker separator, but then the voltage drop increases. A special problem, that has to be avoided, is a precipitation at the surface or within the separator if the solubility of a compound is smaller in one solution compared with the other.

If for laboratory experiments an optimal separation of anolyte and catholyte is needed, and a high voltage is acceptable, two separators can be used. The volume between these can additionally be rinsed with a solution for removing compounds that have been transferred through the separators but are not allowed to arrive in the opposite cell chamber.

#### 2.4.3.1 Porous Materials

Decisive characteristics of porous separators ("diaphragms") are porosity, pore diameter, and thickness. For practical use, other aspects such as mechanical strength (brittle or flexible), constant dimensions (swelling in the solvent), and chemical stability are important.

The mostly applied porous separator in laboratory cells is sintered glass ("fritted glass"). It can be simply and leakproof mounted by the glassblower into the walls of glass cells and then it is very easy to handle. It is available – like similar ceramic materials, for example, sintered aluminum oxide or unglazed porcelain

or pottery – with various porosity, pore diameter, and thickness. As glass or ceramic diaphragms are rigid and brittle, for adequate mechanical solidity in larger cells they need an increased thickness, causing a high voltage drop. Glass and some ceramic materials will be attacked by strongly alkaline media.

In aqueous solutions, glass or ceramic surfaces adsorb  $\text{OH}^-$  ions. Thus, they are negatively polarized and consequently the solution close to the surface is positively charged ("ζ-potential"). Therefore, in such diaphragms with small pores and consequently a large surface, the solution significantly is moved in the electric field towards the cathode. This "electroosmotic" transfer can produce an undesired transport through the diaphragm.

Flexible porous diaphragms, available also as thin foils, can be applied up to large dimensions. They can be produced, for example, from fiber materials (as paper, felt or woven fabric) or together with a soluble filler that is subsequently removed. In chemically not aggressive solutions, even simple materials such as filter paper or regenerated cellulose film ("cellophane") may be usable. Diaphragm materials with very good technical properties formerly have been made of asbestos, but its application is obsolete due to its danger in causing cancer. Various new alternative materials, that are asbestos free, are available.

Porous diaphragms are also made of diverse polymers, for example, as separators for batteries. Polymers can be attacked by organic solvents and a swelling of the polymer material may clog a diaphragm. The stability of a polymer is very dependent on all compounds in an electrolyte mixture and thus the combination of diaphragm and electrolyte has to be carefully selected, especially if a long-term application is needed. Diaphragms

of polyethylene or polypropylene are cheap and show a good stability under manifold conditions. A universal stability is guaranteed with polytetrafluoroethylene (PTFE, Teflon<sup>®</sup>), porous diaphragms of this material are available, for example, from W. L. Gore & Associates). Owing to the hydrophobic properties of these polymers it is not possible to use them directly in aqueous solutions. But, if they are wetted previously with an alcohol (e.g. 2-propanol), aqueous electrolytes can be applied after replacement of the alcohol.

#### 2.4.3.2 Ion-exchange Membranes

Ion-exchange membranes are interesting as cell separators that are selective for cations or anions. They show a high conductivity, at least in aqueous solutions. But they are not “simple” separators due to their special characteristics, which have to be discussed here.

An ion-exchange membrane consists of an “ionomer,” which contains “fixed ions” that are covalently bound to the polymer backbone. It is electrically neutral because of included “counterions”. If water – or probably another sufficiently polar solvent – is absorbed and if the fixed and counterions can be separately solvated to an adequate degree, the counterions become mobile and the ion-exchange membrane can work as an ion conductor. Owing to the electric field of the fixed ions “coions” with the same charge as the fixed ions are rejected and are typically absent inside the membrane. Thus the membrane is selective for the transfer of counterions (“permselectivity” = permeation selectivity, e.g. [70]).

A cation-selective membrane (cation-exchange membrane) contains negatively charged fixed ions, mostly sulfonic acid groups, and cations as counterions, for example,  $H^+$  or  $Na^+$ . In an anion-selective

membrane (anion-exchange membrane), typically positively charged quaternary ammonium groups are the fixed ions and anions such as  $Cl^-$  are the counterions. Usually, one of the ions of the supporting electrolyte will be the charge carrier in the ion-exchange membrane. The selectivity will be nearly 100% in diluted aqueous solutions, but it can strongly decrease, depending on the composition and the concentration of the electrolytes on both sides of the membrane and additionally be influenced by the current density.

An ion-exchange membrane does not contain macroscopic pores and the transport channels for the migration of ions are of molecular dimensions. Nevertheless, as in the case of porous separators, diffusion occurs if there are concentration gradients between both sides of the membrane. But an additional transport effect is typical for ion-exchange membranes. Because predominantly one type of ions is mobile, the molecules in the solvation shells of these ions are completely transferred through the membrane. This transport is equivalent to the above-mentioned “electroosmotic stream” (here it cannot be suppressed, not even with a high pressure difference). All uncharged compounds such as solvents, reactants, and products are unselectively transferred. In a cation-exchange membrane, this transport is directed to the cathode and in an anion-exchange membrane to the anode. Its quantity is very dependent on the membrane type and on the composition and concentration of the solutions. Up to several molecules per migrating ion can be transferred, that is, a significant convective flow through the membrane occurs. Therefore, this effect has to be considered if the application of ion-exchange membranes is planned. Possibly, the electroosmotic stream can be used to

push back an undesired diffusion through the membrane.

Ion-exchange membranes are primarily designed for aqueous solutions. In organic solvents (e.g. [71]), their swelling may be very strong, perhaps up to dissolution. Another precondition for their use is that the solvent is able to solvate the ions inside the membrane to permit a sufficient conductivity. In aprotic solvents, the membrane voltage drop will be unacceptably high. Possibly, in such cases a membrane can be used in combination with a solvent on the other side that enables a good conductivity (e.g. an aqueous electrolyte).

The properties of the polymer backbone in an ion-exchange membrane determine its stability against solvents and chemically aggressive conditions. The most used polymer is polystyrene, crosslinked with divinylbenzene. But also many other polymers and polymer composites are applied in order to achieve an increased stability. A cation-exchange membrane of nearly universal chemical stability is Nafion® (Du Pont), a perfluorinated sulfonic acid ionomer (industrially used e.g. for chlor-alkali electrolysis), but it is expensive and its swelling in organic solvents is high. Anion-exchange membranes are commonly less resistant than cation-exchange membranes, especially at elevated temperatures and against oxidizing and alkaline conditions. Most membranes include a woven fabric as mechanical reinforcement. The optimal membranes – cation- or anion-exchange membranes – should be selected for the specified application from the large number of membrane types, using the technical advice of the suppliers.

An additional interesting application of ion-exchange membranes for the treatment of electroorganic product solutions is the “electrodialysis” (e.g. [70, 72]). It

allows, using a cell stack with a combination of cation- and anion-exchange membranes, to remove or concentrate ionic compounds (salts, acids, bases) in solutions. In “bipolar membranes”, laminated layers of a cation and an anion-exchange membrane, water can be dissociated into  $H^+$  and  $OH^-$  ions (e.g. [73]). Therefore, an electrodialysis stack with integrated bipolar membranes enables to split up salts into their corresponding acids and bases.

## 2.5

### Electrochemical Cells

The electrochemical cell is the apparatus, which is finally needed to realize the desired electroorganic conversion, and, therefore, its design has to consider, as far as possible, all the aspects discussed in this chapter. Furthermore, an uncomplicated and inexpensive manufacturing and an effective and easy handling of the cell will be important.

#### 2.5.1

##### Requirements in Electrochemical Cells

The following items generally will be essential, but their importance depends on the individual reaction system and on the intention of the investigations such as the following:

- uniform current density (i.e. uniform current distribution),
- uniform mixing and mass transfer,
- constant temperature,
- construction materials, that do not corrode.

Successful handling of the cell and performance of the electrolysis requires:

- uncomplicated and leakproof mounting,
- error-free sampling,
- exact mass and charge balancing.

Possible further requirements are as follows:

- reliable potential measurement,
- inert gas atmosphere,
- balancing of a gas evolution,
- reflux condenser to avoid a loss of solvent (this can be important especially in case of gas evolution, an additional low-temperature cold trap may be suitable).

Additional qualifications may be necessary for special intentions.

#### 2.5.1.1 Uniform Current Density

The decisive influence of the current density on the electrode reactions – including their selectivity – has been discussed in Sect. 2.3.2.1. Therefore, a uniform current density on the entire electrode area usually is indispensable. Precondition is a sufficiently constant overall cell resistance – of the electrodes, the electrolytes, and the cell separator – for every point of the electrode area. This needs satisfactory conductivities of the electrode materials and adequately dimensioned, symmetrical current feeders. For a constant electrolyte resistance, the electrodes have to be mounted parallel. This becomes more and more important

- with increasing current density,
- with decreasing electrolyte conductivity,
- with decreasing electrode distance (for reduced cell voltage).

Examples of cell constructions, which provide a uniform current density, will be shown in Sect. 2.5.2. A significant disturbance of the current density distribution can be produced by gas evolution, especially in case of vertical electrodes in the

upper part of the cell. Thus, the cell construction has to enable a fast displacement of gases from the electrolyte between the electrodes or between the separator and the electrodes (see Sect. 2.4.1.2.2). The current density has to be limited so that the gases can be discharged without problems.

#### 2.5.1.2 Uniform Mixing and Mass Transfer

The significance of mass transfer for the electrode reactions, that are in principle heterogeneous, has been discussed in Sect. 2.3.2.1, especially important at low reactant concentrations. Therefore, local differences in the movement within the electrolytes should be avoided and a uniform mixing is desired. In a number of cases, a gas evolution at the electrode may be sufficient. Frequently, especially in cells for batch operation, a (magnetic) stirrer can be used (see Fig. 8).

In flow-through cells, a design for optimal fluid distribution may be suitable (see Figs. 9 and 10a). A further enhanced mixing is attained using a “turbulence promoter”, for example, a coarse woven mesh of polymer wires (see e.g. in Fig. 13). The permanent shift in direction during the flow within the plane of the mesh results in a strong agitation. By this way, also electrolyte chambers of small thickness can be realized in flow-through cells. As an example, typically, the chambers between the membranes of electrodialysis stacks are built up by spacers of such a mesh, ca. 0.5 to 2 mm thick, with integrated elastomer sealing gaskets (the inlet and outlet channels are formed by punched holes in the gaskets, see Fig. 11). The optimal mixing increases the limiting current density and the minor distance prevents a too high voltage, so that even very diluted solutions can be electrolyzed. Gases may be problematical

for turbulence promoters as gas bubbles can adhere to the mesh.

### 2.5.1.3 Temperature Control

The rate of electrochemical reactions is given by the cell current, that is, in principle, it can be controlled independent of the temperature (the required overvoltages are influenced by the temperature, however). But usually, electroorganic conversions include chemical reaction steps and therefore the temperature influence, especially on reaction kinetics and selectivity, is frequently similar to that of pure chemical reactions. Consequently, a constant temperature is desirable to achieve clearly defined conditions for the investigations.

Typical for electrochemical systems is the increasing conductivity of electrolytes and the reduced cell voltage with increasing temperature. Therefore, an elevated temperature may be suitable, as high as the chemistry of the reaction system allows. An additional limit is the boiling temperature of the electrolyte. Vapor bubbles will increase the resistance and the voltage drop of the electrolyte so that additional heat will be evolved and the temperature will further increase, that is, an instable situation will occur. Such effects especially may be expected at locations of lower conductivity, for example, in a diaphragm. Any local overheating ("hot spot") will cause a loss of yield and selectivity and probably a damage of cell components. Therefore, this has to be prevented by temperature controlling in combination with the mixing of the electrolytes and by choosing suitable operation conditions.

The consumed electrical energy is  $U \cdot I$  ( $U$ , cell voltage [V],  $I$ , cell current [A]). The part  $U \cdot I - \Delta H$ , that exceeds the enthalpy of the cell reaction  $\Delta H = \Delta G + T \cdot \Delta S$  ( $\Delta G$ , reaction free enthalpy (Gibbs energy)

[J],  $T$ , absolute temperature [K],  $\Delta S$ , reaction entropy [J K<sup>-1</sup>]) is converted into heat and has to be dissipated from the cell. Substantially, it is the consequence of the overvoltages (see Sect. 2.3.2.1), the part that is caused by ohmic voltage drops is the "Joule heat". Small cells usually need a heating for applications at elevated temperature, but for larger cells and high cell currents a sufficient heat dissipation is required.

The easiest temperature controlling method for small cells is a jacket round the cell that is connected to the fluid circulation of a thermostat (see Fig. 8). For flow-through cells, especially when they are running in batch operation with circulation through a reactant reservoir, a heat exchanger (e.g. of glass) should be included into the cell liquid loop. Probably, the backsides of the electrodes can be used as heat-exchanger area for temperature controlling (caution: without additional protection, e.g. by insulating, it is not allowed to bring the backsides of both electrodes in contact with a noninsulating temperature bath fluid (e.g. water), because the potential difference will initiate severe damages by (pitting) corrosion, probably even in the thermostat, that is electrically connected to earth). More sophisticated temperature controlling methods, for example, using temperature sensors in the cell, electronic controllers and electrical quartz heaters, are practically proven.

### 2.5.1.4 Construction Materials

Glass will be the most applied material for small cells (see e.g. Fig. 8). It is insulating and resistant against most electrolytes, except strongly alkaline and fluoride-containing media, and it can be used up to high temperatures. An important advantage is the possibility to observe reactions directly, for example,

gas evolution, color changes, formation of two phases, or precipitation of solids. Complex constructions can be realized by a glassblower. Coupling devices such as ground-glass equipment, flanged joints, and screw cap connections for easy handling are available in a large variety and different diameters. Glass is completely tight, any diffusion into and out of the cell is impossible (e.g. of oxygen or solvent vapor). If necessary, for example, in case of extremely oxygen-sensitive compounds, the glassblower can substitute coupling devices by direct connections. But the problem of glass, particularly for enlarged cells, is its breakability.

Mechanically robust materials are metals, for example, different chromium-nickel steels, or titanium. Their use in electrochemical cells is limited because they are conductive and may corrode. The corrosion is significantly influenced when the metal is insulated or connected to the anode or to the cathode (see Fig. 9).

Polymers, for example, polypropylene or polymethylmethacrylate (PMMA, "Plexiglas<sup>®</sup>" transparent) and many others, may be interesting materials of easy machinability. But their chemical stability, especially against organic solvents, has to be tested individually.

Chemically universally stable is polytetrafluoroethylene (PTFE, "Teflon<sup>®</sup>"), but it is relatively expensive. A problem is the "cold flow", that is, the polymer is slowly deformed under the mechanical stress of the pressure on the gaskets and a leakage of the cell can occur (PTFE compounds, e.g. with glass powder or graphite, show a better behavior.)

It has to be considered that polymers – different from glass and metals – generally are more or less permeable for gases and vapors, mainly

in thin layers such as films or tube walls. Especially PTFE, which cannot be molten but only sintered, is always porous. If this is a problem, fusible but more expensive fluorinated polymers can be used, such as perfluoroalkylvinylether (PFA) or fluorinated ethylene-propylene (FEP). A thin FEP film, for example, is useful for insulating and shielding of metal surfaces.

Materials for gaskets have to be chemically stable and should be elastic in order to reduce the required force for sealing. Frequently, O-rings, that need a groove for fixing, or flat gaskets, which can be cut from sheet material, are applied. Unfortunately, common elastomers, also for example, silicon rubber or ethylene-propylenediene copolymer (EPDM), are attacked by many organic solvents (swelling) and have to be tested for each case in detail. Fluorinated elastomers, for example, "Viton<sup>®</sup>" or "Kalrez<sup>®</sup>", may be suitable but are expensive. Probably, O-rings with an elastic silicon rubber core and a resistant FEP jacket can be helpful. A paste of pure PTFE is available that can be used like joint grease for sealing.

An all-purpose gasket material is expanded PTFE ("Gore-Tex<sup>®</sup>" and similar products, but expensive and only usable once). It is available as a cord of various diameters  $\geq 1$  mm or as sheet material. Initially, it is very soft and can be adapted to each surface (it is, for example, even possible to mount a metal mesh electrode tightly between glass flanges and to connect the edges outside with a current feeder). The cord will be formed to a closed loop by inclined cutting and overlapping. It can be fixed for mounting by an integrated adhesive stripe or by the above-mentioned PTFE paste. During mounting, the gasket will be strongly compacted.

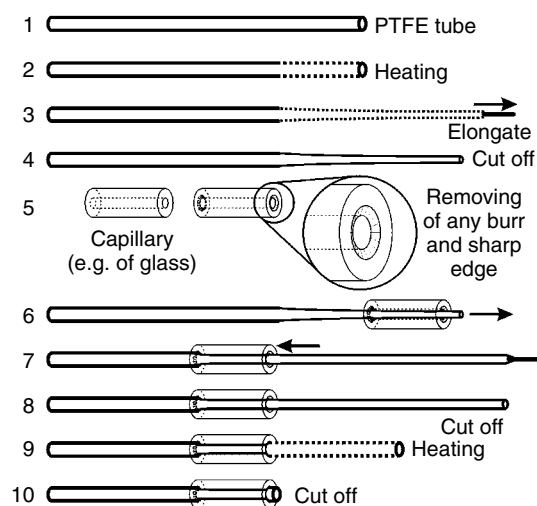
With a small pressing force, a leakproof sealing for aqueous solutions is possible. To become tight against gases and vapors, an increased force is required (by strong pressing, up to a translucent appearance, even applicable for high-pressure cells). No could flow as in case of common PTFE occurs. If vulnerable materials, such as a membrane or mesh, have to be mounted, a preforming of the gaskets is suitable, that is, preliminary mounting of the cell at reduced force with a plastic film instead of these sensitive materials.

Generally, a constant, sufficiently strong pressure on the gaskets is necessary, but it must not be too high so that, for example, gaskets or membranes, and cell parts, for example, of glass or PTFE, could be damaged. Therefore, an elastic construction is suitable. This function may be performed by the gaskets themselves, if they are sufficiently thick and elastic. Probably, a (silicon) rubber sheet of some millimeters thickness can be added between the first cell part and the fixing plate. Also, cup springs as washers at the screwing of the cell are practically proven.

Various fluoropolymer equipment, for example, connectors and valves, is available from laboratory suppliers (at a high price). The principle of a simple, quick, and inexpensive method for connections of electrochemical cells using PTFE tubes is shown in Fig. 4.

A PTFE tube (1), for example, with an outer diameter of 3 mm and an inner diameter of 2 mm, is cut some centimeters longer than finally needed. Tubes from 0.5 mm up to 6 mm outer diameter have been successfully applied with this method. The tube is heated at the end (ca. 2–3 cm) with a hot air blower until it becomes clearly transparent (2, ca. 250 °C, using a gas flame includes the risk of overheating and decomposition of the polymer). Then the tube is quickly stretched so that the diameter becomes smaller than the borehole (3). The squeezed end is cut off (4).

A capillary of glass or another material, for example, PTFE or metal, is cut to about 2 cm (5). It can be part of a larger device too. The method can also use any other cylindrical borehole of sufficient length



**Fig. 4** Leakproof fixing of PTFE tube in a borehole, here in a glass capillary, that can be linked to a common screw cap connection (borehole diameter about 20% lesser than the original outer diameter of the tube, length of the borehole at least three times the diameter).



(at least about three times the diameter) in any material, for example, polymers, metals, or also glass. For the chosen tube of this example, the diameter should be 2.4 mm. Any burr or sharp edge has to be removed (see enlarged picture (5); in case of the glass capillary this is possible using a file or hard-metal tool or by melting). The elongated end of the tube is drawn through the capillary (6) and fixed in a vice. Then the capillary – or the device with the borehole – is moved on the tube to the desired position (7). A considerably strong and constant force during this movement shows that a leakproof connection between the tube and the capillary can be expected. Again the squeezed end is cut off (8). The part of the tube, that has been drawn through the capillary, will be largely elongated. Its original length and diameter can be reestablished by heating to clear transparency (9, a heating of the capillary itself should be avoided). If the tube is then cut off at about 2 mm (10), this is a protection against pulling out. For building up a further connection, the process can be repeated with the reestablished PTFE tube. The practicability of this method has been proven even in a pressure electrolysis cell at 5 bar.

#### 2.5.1.5 Mass and Charge Balancing

At a first glance, it may be sufficient to detect the desired product but a comprehensive information about the investigated conversion needs mass and charge balancing.

- Total mass balance, that is, the sum of inputs has to be equal to the sum of outputs. This will be particularly interesting for long term and generally for continuously operated investigations in order to detect a possible leakage

(otherwise, a loss of vaporized liquids is difficultly observable).

- Partial balances of all compounds, that is, the individual reactants have to be found in the products, considering stoichiometry.

This will be helpful to detect the reason if there is a loss of single compounds.

- Charge (current) balance and calculation of the current efficiency (see Sect. 2.3.1), that is, the electrochemical products on both electrodes, including product gases, have to be equivalent to the consumed electrical charge.

This can also detect a partial electrical shortcut or, more probable, an “electrochemical shortcut”, that is, the consumption of a product of an electrode at the other one, for example, anodic oxidation of hydrogen, that has been evolved at the cathode.

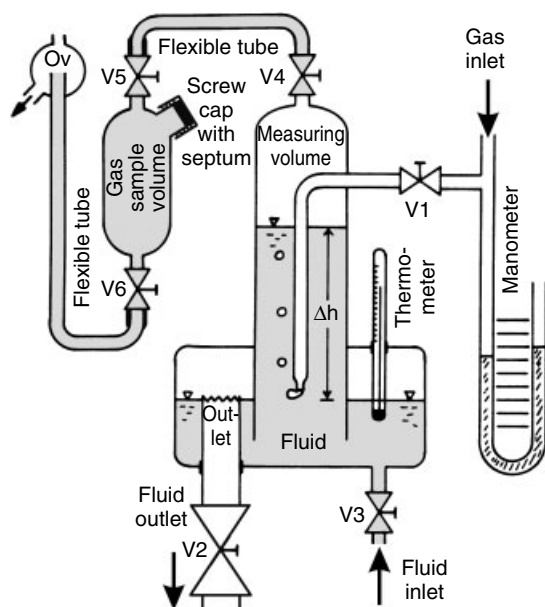
The effort to carry out all these balances is high, but it significantly increases the reliability of the results, that should be based not only on single measurements (analyses). Usually, incorrect data are only detectable on the basis of at least two independent values or balances. If various balances are found, often an error can be identified as a false measurement or analysis mistake and not a real failure. As far as possible, several samples should be taken during each experiment for improved reliability. For continuous operation under stationary conditions, the average of some measurements and analyses will be used (any tendency in the individual values shows that the stationary state is not yet achieved). In case of batch operation a consistent change with time confirms reasonable results (here, in the mass balance the decrease of the cell liquid by the sampling has to be considered).

An easy way for sampling of the cell fluid is to mount a screw cap with a septum at a suitable place of the cell (the cell fluid should not permanently be in contact with the septum and a loss out of the gas-phase through the perforated septum should be avoided). The cheap common medical disposable syringes, which are available in various types with needles of different diameter and length, can be used. The coupling of the cell with a syringe is also possible using PTFE tubes according to Fig. 4 (direct fixing in the connector of the syringe or via a capillary that includes the conic adaptor for the syringe).

As mentioned above in Sect. 2.4.1.2.2, frequently gases are evolved during electrochemical reactions, especially at the counter electrode. Information about volume and composition of one or both of these gases can be necessary to clarify the electrochemical process. Probably small gas amounts have to be sampled. The gas sampling device in Fig. 5, made of glass,

has proved its practicability [74] (caution: explosive gas mixtures can be formed in electrochemical cells; an antisplinter protection has to be provided!). The fluid has to be selected for minimal solubility of the gas, for example, for carbon dioxide containing gases an acidified, saturated salt solution. Solvent vapors must be condensed previously. Addition of a detergent facilitates a uniform overflow at the fluid outlet. The valves may be simple hose cocks. The level of the fluid outlet is adjusted so that the gas can stream in nearly without pressure (observable at the manometer).

The overflowing fluid is equivalent to the gas volume. If the measurement has to be more exact than about 3%, corrections concerning the actual atmospheric pressure, the decreased pressure due to the height  $\Delta h$  of the fluid and the vapor pressure of the fluid are possible [74]. Additional errors can occur if the gas is significantly soluble in the fluid.



**Fig. 5** Gas sampling device

Filling with fluid: V1 and V2 are closed, V4, V5, and V6 are opened, V3 is opened until the device is filled completely and the fluid runs over at Ov; Operation: V3 and V4 are closed, V2 is widely opened, when the overflow at the fluid outlet is finished, V1 can be opened for the gas; Gas transfer: like filling with fluid until the gas is transferred into the gas sample volume.

The level of the overflow  $O_v$  should be elevated for transferring the gas into the sample volume for realizing a slight excess pressure. Then the sample volume, after closing of  $V_5$  and  $V_6$ , can be carried away (probably with a residue of fluid) and samples for gas chromatography can be taken through the septum with a gas-tight syringe, without the risk of contamination due to immigration of air. Nevertheless, the samples should be analyzed as soon as possible because a diffusion of air into the sample volume is practically inevitable (shown by the presence of nitrogen in the analysis).

Generally, a continuous recording of electrically available data – for example, current, cell voltage, electrode potentials, temperatures – is beneficial to supervise the proper procedure of each experiment. Especially in case of a failure this will be a valuable help to find the reason. Today, the best way is to use a data acquisition system in a computer that offers the results directly for further calculations, for example, integration of the consumed current (converted charge). For continuously operated experiments the addition of scales, which acquire the weight of input and output reservoirs, will be advantageous in order to supervise the mass balances continuously.

#### 2.5.1.6 Electrode Potential Measurement

The central importance of the electrode potential has been discussed in Sect. 2.3.2. The potentiostatic operation mode evidently requires a reliable potential measurement. Only experiments at constant current can operate without knowledge of the potential. But here too the potential of the working electrode imparts interesting information, for example, a change in this potential – probably not detectable in the

entire cell voltage – can indicate a variation of the electrode reaction.

An exact potential measurement is difficult – particularly in organic electrochemistry – and probably requires very sophisticated techniques to avoid a variety of possible errors (e.g. [75]). Fortunately, for practical applications in electroorganic synthesis, it will usually be sufficient to get reproducible potentials for the current density–potential curves (see Fig. 1) as well as for the synthesis cell. A constant deviation in both measurements may be acceptable, even though the accurate value may be unknown. Some aspects will be discussed here, a more detailed overview is given, for example, in [3a].

**2.5.1.6.1 Reference Electrodes** By definition, the normal hydrogen electrode (NHE) is the reference for electrode potentials (see Sect. 2.3.2.1), but practically it is scarcely usable. A reference electrode (RE) has to provide a well-defined potential between the electrolyte and its electric connector, joined with the input of the measuring instrument. Usually, a metal and a slightly soluble salt of this metal is applied (secondary electrode) [76, 77]. The electrolyte in the RE is connected to the electrolyte in the electrochemical cell via a diaphragm, which has to separate both electrolytes, as far as possible without a potential difference (see below).

A classical system is the saturated calomel electrode, SCE ( $\text{Hg}/\text{Hg}_2\text{Cl}_2/\text{saturated KCl in H}_2\text{O}$ ) with a potential of  $E = +242 \text{ mV}$  versus NHE ( $25^\circ\text{C}$ ). The disadvantage is the sensitivity against a current flow through the system (generally, potentials should be measured only using instruments with a very high input resistance, that is, nearly currentless with maximally  $1 \text{ nA}$ ). The systems  $[\text{Hg}/\text{Hg}_2\text{SO}_4/\text{sat. K}_2\text{SO}_4 \text{ in H}_2\text{O}]$   $E = +650 \text{ mV}$  versus

NHE (25 °C) or [Hg/HgO/1n NaOH in H<sub>2</sub>O]  $E = +140$  mV versus NHE (25 °C) are, for example, interesting if chloride ions are not allowed. A problem of all mercury containing systems is the toxicity. A nontoxic system is [Ag/AgCl/sat. KCl in H<sub>2</sub>O]  $E = +197$  mV versus NHE (25 °C). It is nearly temperature independent and insensitive against current flow. It can be easily prepared by anodic oxidation of a silver wire in KCl solution (coating with an AgCl layer, subsequently an excess of solid KCl is added to the electrolyte round the silver wire). But, diffusion of silver ions out of the partially soluble AgCl can be a problem.

The potential of the RE may be changed by infiltration from the cell electrolyte. Thus, the combination of cell electrolyte and RE has to be carefully selected [3a, 76, 77]. Probably, a reference system in the same solvent as in the cell will be suitable, for example, Ag/0.01 m AgNO<sub>3</sub>/0.1 m NaClO<sub>4</sub> in acetonitrile,  $E \approx +500$  mV versus NHE (25 °C) [78].

**2.5.1.6.2 Diffusion Potentials** At the interface between two different solutions – here, between the electrolyte of the reference system and the cell electrolyte – significant potential differences can occur. The “diffusion potential” is caused by a different diffusion velocity of cations and anions, as it is evident for acids and bases due to the extraordinary high mobility of H<sup>+</sup> and OH<sup>−</sup> ions. In strongly acidic or alkaline aqueous electrolytes, several ten millivolts may be obtained. This can be reduced using a “salt bridge” with a high concentrated electrolyte, whose cations and anions have the same mobility, for example, potassium chloride (KCl is often contained in RE systems). Additionally, the potential difference may be dependent on the type

of the separator and on the flow rate of KCl solution through the separator. Usual separators are sintered glass or ceramic diaphragms or, for example, a plug of agar. In practical applications, mostly a contamination of the cell electrolyte with chloride ions is undesired (probably formation of chlorine at the anode). But, a poorly permeable separator can produce high potential differences. An alternative is the change to the inert K<sub>2</sub>SO<sub>4</sub> solution. In contact with an organic electrolyte, indefinable conditions with significant potential differences are possible. Also, a transfer of water may be detrimental in this case. As mentioned above, an RE system, that is compatible with the cell electrolyte, should be used, even though the potential could be problematically to define.

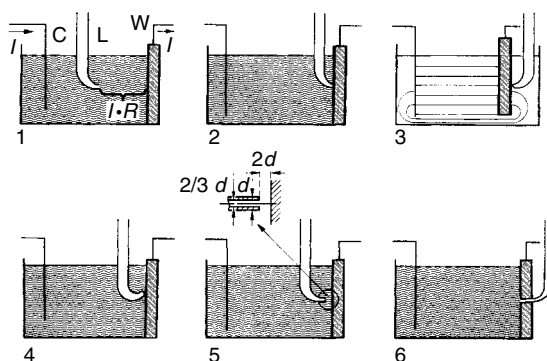
All these possible difficulties show that an accurate potential measurement is mainly possible in uncomplicated aqueous solutions. In electrolytes, for electroorganic syntheses, especially in aprotic solutions, significant deviations are to be expected. But, as mentioned above, this is no problem for practical applications if it can be verified that the acquired potential values are reproducible.

**2.5.1.6.3 Luggin Capillaries** The location, where the potential of the electrolyte should be measured, is connected to the RE by the Luggin (Haber–Luggin) capillary. Its design can significantly influence the accuracy of the acquired potential values. Requirements are

- optimal position in front of the electrode,
- sufficiently low resistance,
- undisturbed operation.

Different positions of the Luggin capillary are shown in Fig. 6 [4]. In example 1, a too large distance between the working

**Fig. 6** (From Ref. [4]) Positioning of the Luggin capillary. problematic: 1–3; suitable: 4–6; W: working electrode; L: Luggin capillary; C: counter electrode;  $I$ : cell current,  $R$ : electrolyte resistance.



electrode and the tip of the capillary causes a considerable voltage drop due to the resistance  $R$  of the electrolyte layer and the cell current  $I$ . This voltage drop increases linearly with rising  $I$  and can overlay the current density potential curve (see Fig. 1), so that changes in the overvoltages, which are important for the electrode reactions, may not be detectable. In example 2, there is no distance so that at the location of the capillary tip the current is interrupted and the measured potential is incorrect. A recommended position is shown in example 5: the distance is equal to the twofold outer diameter  $d$  ( $d \approx 1$  mm, inner diameter  $2/3 d$ ). It is difficult to fix this position; thus, the tip of the capillary is turned up in example 4, and the edge can be placed directly on the electrode. No disturbance is to be expected in example 6, but this design is not realizable everywhere. The position behind the electrode in example 3 is sometimes reported in the literature, but the uneven current density distribution may initiate deviations.

The voltage drop  $I \cdot R$  should be estimated and eliminated from the measured potential. It can be directly determined by fast current interruption measurements: about  $1 \mu\text{s}$  after shutting down the current, the potential is already decreased by all ohmic voltage drops while all other

overvoltages are remaining at the stationary value. Comfortable potentiostats include automatic potential correction possibilities (e.g. [79, 80]).

An adequately high input resistance is ensured using a potentiostat (other instruments probably need an additional amplifier like for pH electrodes). Nevertheless, the resistance of the Luggin capillary has to be sufficiently low. This is unproblematic using the classical glass capillary, filled with high concentrated KCl solution (see part 10 of Fig. 8b, combined with a container for the RE). For reducing the effective resistance – especially, if a longer capillary is needed and/or if electrolytes of lower conductivity have to be used in the capillary – a thin wire of a noncorroding metal (e.g. platinum) can be inserted into the capillary (no contact to the electrode!). Additionally, it will be favorable to guide the wire outside the capillary and to connect it via a high insulating capacitor parallel to the RE with the input of the potentiostat (no influence on the stationary potential value, but stabilization of the potentiostat in the higher frequency range [81]).

Penetration of gas bubbles into the Luggin capillary can disturb the steady operation. In the worst case, the control circuit of the potentiostat will be interrupted and the cell current can increase

uncontrollably up to the positive or negative maximum value (a damage of cell components can be possible). The turned up tip of the capillary in example 4 of Fig. 6 is a possibility to avoid this. Also, the platinum wire within the capillary, mentioned above, increases the security against perturbation by gas bubbles. Even a PTFE tube, otherwise extremely sensitive to blocking by gas bubbles due to its hydrophobic properties, can be used as a Luggin capillary with a platinum wire inside (easy mounting through the cell wall like in Fig. 4).

## 2.5.2

### Examples of Electrochemical Cells

The equipment for electroanalytical methods usually includes the required cells, but standardized preparative scale electrochemical cells are scarcely available (some equipment is offered, for example, by the Electrosynthesis Company Inc., Lancaster, USA). Most of the electrochemical cells, used for the investigations in the literature, are made in the facilities of the institutes, especially by glassblowers. This

allows to easily modify the design for special requirements. The following examples are presented to give some ideas for own constructions. The chosen industrial cell designs include a commercial cell that is available also on a small scale and therefore can be used in the laboratory.

#### 2.5.2.1 “H-cell”

The classical H-cell (Fig. 7, with a shape similar to the letter “H”) is, for example, suitable for demonstration of simple electrochemical experiments, such as water electrolysis. In the vertical containers, the electrodes can easily be mounted; the horizontal connection between anode and cathode compartment is divided by a diaphragm. This cell can have a large energy loss due to a high cell voltage, and the current density at the electrodes is very unevenly distributed. As discussed above, these problems may be disadvantageous for electroorganic conversions in this cell type. Nevertheless, there are many examples of the successful application of similar cells, also using a mercury cathode (e.g. [82, 83]).

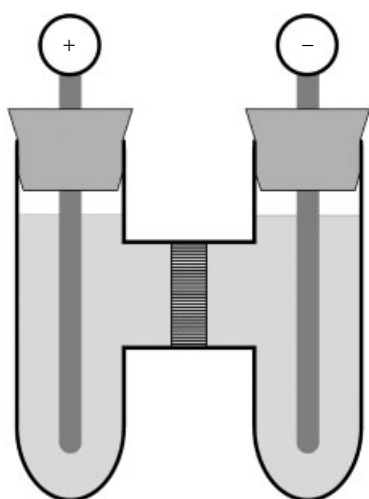


Fig. 7 H-cell.

A comparable cell design – but with flat, solid, or perforated electrodes, mounted parallel nearby the diaphragm – avoids the above-mentioned problems and can work with optimal current distribution [84].

### 2.5.2.2 Beaker Glass Cells

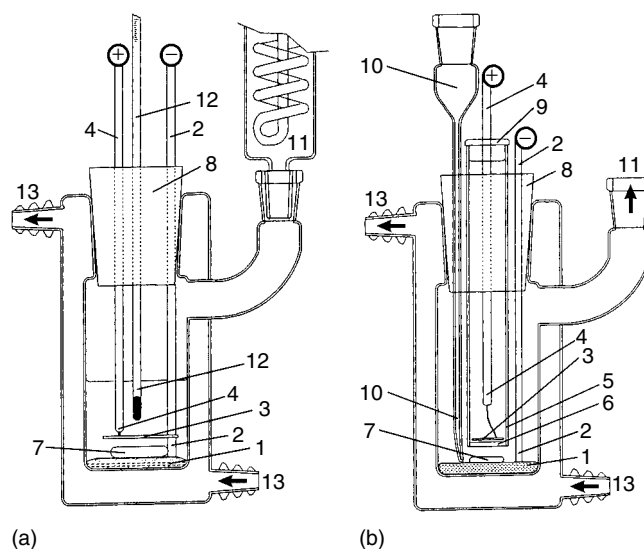
For investigations in batch operation, using a small reactant volume, a beaker glass cell like the one in Fig. 8 is optimal [85]. The reaction is directly observable. In the example, a mercury cathode and a platinum mesh anode (with a platinum wire ring as current feeder) are used. A magnetic stirrer provides the mixing of the electrolyte and renewal of the mercury surface. The parallel mounting of the electrodes enables a uniform current density. If the cell has to be divided (Fig. 8b), the anode is enclosed in a glass tube with a diaphragm. An RE with an integrated Luggin capillary can be added. A jacket for

heating or cooling is connected to a thermostat. Similarly, in an undivided cell, vertical, parallel, or concentric electrodes can be used.

### 2.5.2.3 Flow-through Cells

Flow-through cells enable optimal flow conditions. They can work in continuous operation at stationary conditions as well as in batch operation if they are coupled by a circular flow to a reactant reservoir (see Sect. 2.3.4).

In Fig. 9, the cathode block (4) of stainless steel includes inlet and outlet channels (6) that are each connected by 6 boreholes for uniform flow distribution to the cathode surface (details see cross section 7). The anode (2) is a platinum foil of 18 cm<sup>2</sup> active area with the brass cover plate (1) as current feeder. The electrode distance is given by the sealing gasket (3), for example, silicon rubber of 0.2–1 mm [85].



**Fig. 8** Beaker glass cells (a) undivided, (b) divided. 1 mercury cathode, 2 cathode current feeder, 3 platinum mesh anode, 4 anode current feeder, 5 anolyte tube with, 6 diaphragm, 7 magnetic stirrer, 8,9 PTFE stopper, 10 reference electrode with Luggin capillary, 11 reflux condenser, 12 thermometer, 13 connection to thermostat.

A similar design with a second block as anode, for example, of coated titanium or graphite, can be used as divided cell with a flexible diaphragm or an ion-exchange membrane.

If both electrodes have to be made of materials, that are available only as foils or sheets or are not machinable, or for example, for materials, such as graphite felt, a cell design like the one in Fig. 9 is not realizable. Inlet and outlet systems have to be integrated in the electrolyte compartments. The “parallel-plate and frame” design of a laboratory flow-trough cell in Fig. 10 consists of easy-to-produce parts, using the fixing method for PTFE tubes in Fig. 4.

The rectangular frame in Fig. 10a enables a similar mixing quality in the cell chamber as in the cell of Fig. 9 (for reduced mixing requirements less tubes are sufficient). Ring-shaped frames as shown in Fig. 10b can be particularly easy machined by turning, or simply can be cut from thick-walled tubes, including glass.

A cell design like the one in Fig. 10 is very flexible concerning material, shape,

dimensions, thickness, and required connections of the cell compartments. The desired electrodes, diaphragms, and/or ion-exchange membranes and the necessary cell chambers between – also for example, gas supplying chambers for GDEs or heating/cooling chambers – can simply be combined and mounted by fixing plates and screws. Electrode plates or foils – even of large dimensions – can be applied without any machining like the cathode in Fig. 10b, using the edges as current feeders (electrode distance from the membrane = frame + sealing gaskets thickness). If a reduced electrode distance for low cell voltages is needed, a perforated electrode of a suitable material can be connected in an adequate distance in front of a current feeder plate (“preelectrode”), like the anode in Fig. 10b.

The cell design in Fig. 10 can be applied without flow-through in batch operation too, for example, for easy testing of electrode or separator materials. Then, the frame thickness is chosen for the desired cell compartment volume (for a thickness

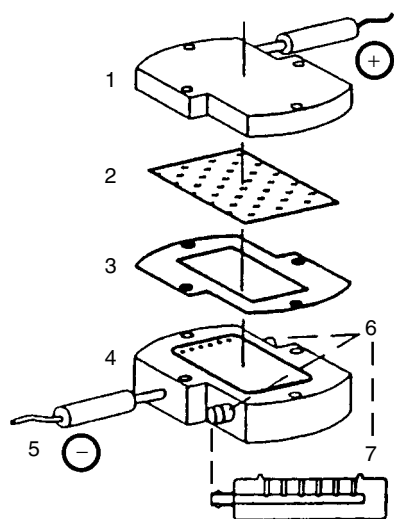
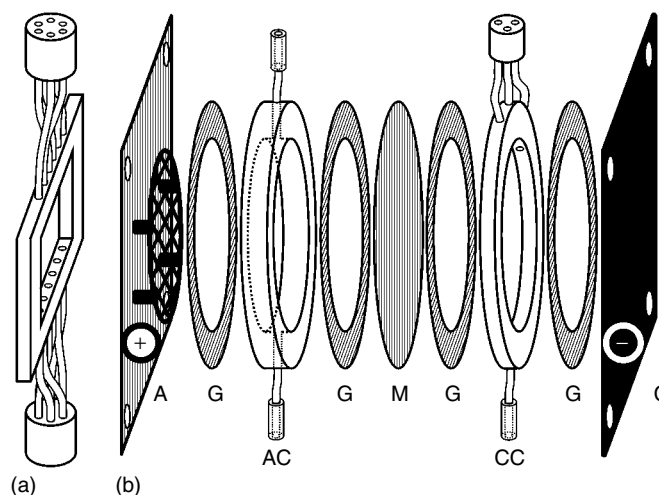


Fig. 9 Example of a laboratory flow-through cell.





**Fig. 10** Examples of parallel-plate and frame designs for laboratory flow-through cells (a) cell chamber for strong mixing and (b) various parts of a cylindrical cell. A: anode (with preelectrode); G: sealing gaskets; AC: anode compartment (glass ring, reduced mixing requirements); M: membrane (diaphragm); CC: cathode compartment (three tubes for gas outlet, sufficient mixing by gas evolution); C: cathode (current feeders outside the cell at the four corners).

above ca. 15 mm, also a magnetic stirrer can be used).

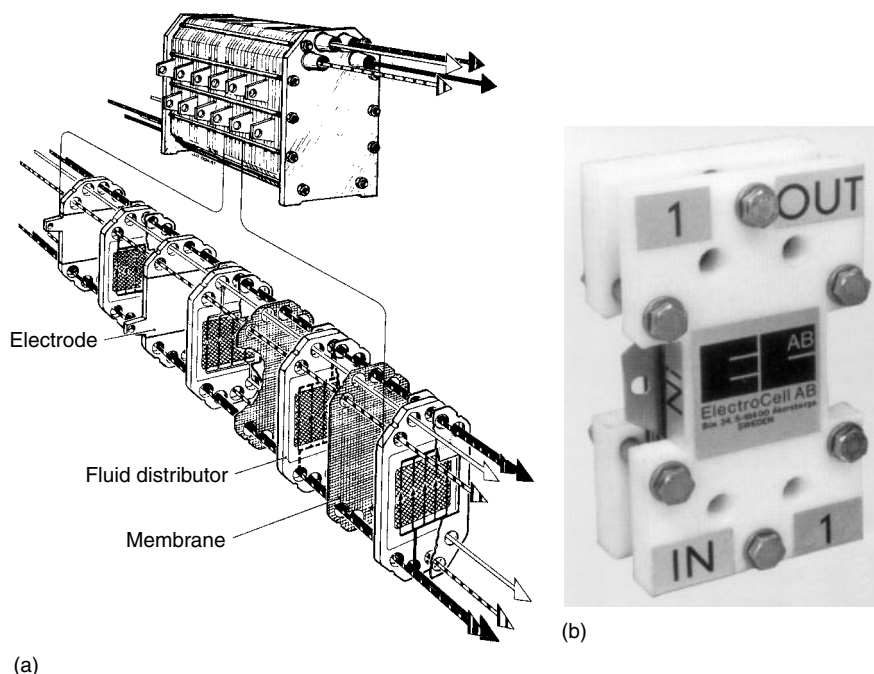
#### 2.5.2.4 Industrial Scale Cells

**2.5.2.4.1 Parallel-plate and Frame Cells (Filter Press Cells)** The design of industrial cells has to combine many cell units in a cell stack with a sufficient electrode area. The optimized supplying of reactants and the draining of products, probably including gases and/or circulation streams, is a special challenge. Owing to the large variety of requirements for electroorganic syntheses, a modular system is needed (“building blocks”). Figure 11 shows an example of a commercial cell that is available in different dimensions, including a laboratory scale cell.

The exploded view in Fig. 11 elucidates the function of this parallel-plate and

frame design (“filter press cell”, in principle comparable to Fig. 10b). All components – electrodes (plates), fluid distributors (frames), membranes or diaphragms, and sealing gaskets – have punched holes at the same position so that different channels are formed through the entire stack (here eight channels). The fluid distributors – for example, cathode and anode compartments or electrodialysis chambers – are connected to the appropriate channels by boreholes in the frames, for example, the cathode compartments at the bottom with the catholyte inlet channel and at the top with the catholyte outlet channel. Various fluid distributors are possible (e.g. different thickness and fluid distribution, probably turbulence promoters).

Two electrical connection modes for the electrodes in a cell stack are possible:



**Fig. 11** Examples of commercial cells (ElectroCell AB, Sweden) (a) Parallel-plate and frame industrial scale cell (area of one electrode:  $0.001 \text{ m}^2$  (laboratory);  $0.01 \text{ m}^2$  (pilot plant);  $0.04\text{--}0.4 \text{ m}^2$  (production); up to  $16 \text{ m}^2$  in one cell stack). (b) Laboratory scale cell.

- “monopolar”, all anodes and cathodes are connected in parallel to the current feeders (see Fig. 11a); this requires high current at low voltage,
- “bipolar”, the cell units are connected in series, that is, cathode and anode of adjacent cell units are combined, ideally one side of the electrode works as cathode and the other one as anode, the current feeders are connected only to the electrodes at the ends of the cell stack; this requires high voltage at low current.

Cell construction, current feeders and power supply are less expensive for the bipolar connection (see also Fig. 12), but the different potentials of all electrodes can be problematical (e.g. shunt currents, additional by-products, and corrosion in the channels).

**2.5.2.4.2 Capillary Gap Cells** The capillary gap cell in Fig. 12 [4] is used in various industrial electroorganic syntheses, for example, [57, 63], including a “paired electrosynthesis” for generating useful products at both electrodes [86] (BASF AG, Germany). The distances in a stack of circular graphite plates (1) are fixed to about 1 mm by plastic stripes, forming the capillary gaps (2). The cell fluid is pumped into the central channel (3) and streams radially outside where it runs down and is recycled and cooled (4). The graphite plate at the top is connected to the cathodic (6) and that at the bottom to the anodic current feeder (5).

In this undivided, bipolar cell, the top-sides of all the graphite plates are working as anodes and the bottom sides as

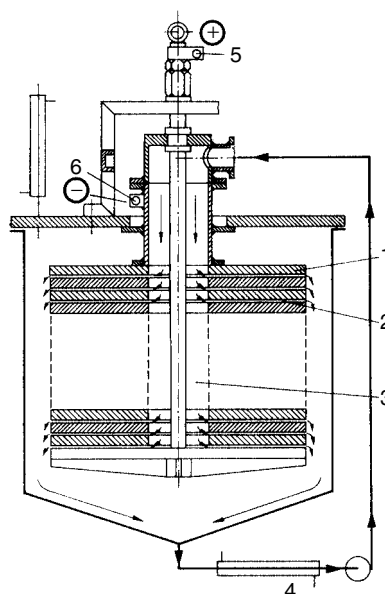
**Fig. 12** Capillary gap cell (From Ref. [4]): 1 bipolar electrode plates, 2 capillary gap, 3 electrolyte channel, 4 heat exchanger, 5, 6 current feeders.

cathodes. The small electrode distance enables the use of low conductive electrolytes.

A concentric capillary gap cell (up to 800 cm<sup>2</sup> active area) is described in [87].

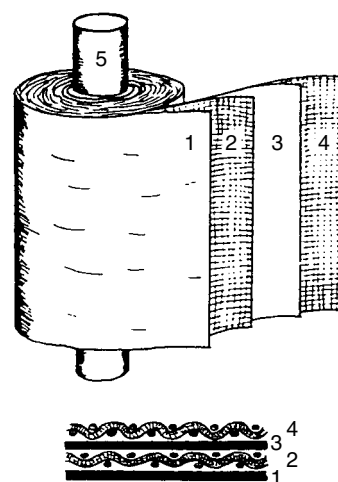
A modified cell design like the one in Fig. 12 uses, instead of the rigid graphite plates, graphite felt, which is passed by the liquid, and instead of the gaps, diaphragms or ion-exchange membranes (solid polymer electrolyte technology) [88, 51].

**2.5.2.4.3 Swiss Roll Cell** This cell has been developed in Switzerland [89]. A commercial application is one oxidation step at a NiOOH anode in alkaline solution for the vitamin C production [22]. Mesh electrodes of stainless steel (cathode 1) and nickel (anode 3) are rolled up together with spacers of polypropylene mesh (2,4) on the central current feeder (5) and mounted in a cylinder (cells up to 1 m diameter, 200 m<sup>2</sup> active area). The electrolyte streams axially through the cell.



Advantages of this cell design are as follows:

- the small electrode distance enables application of poorly conductive electrolytes;
- the high electrode area per volume unit results in a high space-time



**Fig. 13** Swiss roll cell. (From Ref. [89].)

yield, even at very low current densities;

- the high turbulence due to the mesh structure (increased limiting current density) allows an extensive reactant depletion (high conversion).

#### 2.5.2.4.4 Innovative Cell Constructions

There are a lot of further innovative cell constructions in the literature that may also be suitable for electroorganic syntheses, from laboratory up to industrial scale. Examples are rotating electrodes, application of ultrasound, and packed or fluidized particle bed three-dimensional electrodes for increasing the active electrode area and enhancing the mass transfer. A short overview is given, for example, in [1, 2].

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### 3

## Comparison of Chemical and Electrochemical Methods in Organic Synthesis

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### 3.1 Introduction

When a chemist wants to synthesize an organic compound he uses a familiar set of equipment and methods. Familiarity and experimental skills are attained to a large degree by his basic and advanced laboratory training and the methods he used in his master's and Ph.D. theses. Knowledge of reliable methods is developed at these instances by reading about and applying reactions from tested procedures, for example, from organic synthesis and literature reports on frequently applied reagents of good selectivity and broad scope. Organic electrochemistry belongs to the category of less common methods in a chemist's experimental training. Consequently, the techniques and reactions of this field tend to be used only in special cases. Lack of experience and less developed experimental skills may lead to disappointment, which can cause a prejudice against the method. Often heard statements, which originate mostly from hearsay rather than experience, are: the restricted scope of reactions, limited mechanistic knowledge, necessity of special equipment, which is expensive and difficult to acquire, long reaction times, and low yields and selectivities.

This chapter is aimed at providing a more realistic picture of the general scope of electroorganic synthesis by giving a survey of favorable C,C-bond forming reactions and functional group interconversions (FGIs) at the electrode and pointing to the advantages of electrochemical methods compared to purely chemical ones in these cases. Furthermore, some hints on the equipment used are given for beginners in the field. These points are dealt with in more detail in other chapters of this volume.

### 3.2 General Aspects of Organic Synthesis

Organic synthesis is focused on the preparation of a given target molecule [1–4]. Targets can arise from the structure proofs for new compounds, the generation of biological activities or material properties, the support of a theoretical prediction, the challenge to prepare a complex molecule, or the extension of chemical methodology. A good synthesis should fulfill a number of the following requirements: it should involve few steps; provide a high selectivity; use cheap, readily available, nontoxic reagents and solvents; allow the recycling of expensive reagents;

apply nonhazardous reaction conditions; exhibit a good atom economy, that is, it should transfer a maximum number of atoms of starting material and reagents into the product, which also means a low production of waste; and finally it should provide a broad scope for converting readily available starting materials into a large variety of product structures.

Synthesis consists of (1) planning the reaction sequence with respect to the given conditions, (2) executing the optimal reaction path, (3) isolating the product and workup, and (4) improving yield and selectivity of the conversion by changing reagents and reaction conditions. The difference between chemical and electrochemical reactions lies mainly in the set of available reactions for points (1) and (2) and the equipment used in (2). These points will be addressed in Sects. 3.4–3.6.

Organic synthesis applies, in general, two types of reactions: C,C-bond forming reactions (C,C) for the construction of larger molecules from smaller units and FGIs for the installation of the required functionality (e.g. hydroxy, amino, keto, carboxyl, double bond) into the target molecule or for the activation of the synthetic subunits. The C,C-bond forming reactions can be classified as *polar reactions*, in which an activated donor reacts selectively with an acceptor or vice versa; as *radical reactions*, which are increasingly applied in synthesis because they do not interfere with polar groups in the molecule [5]; and as *pericyclic reactions*, especially cycloadditions, for the construction of ring compounds with high stereoselectivity [6] and transition metal-catalyzed reactions [7].

Polar reactions in chemical synthesis involve reactive intermediates such as

carbocations and carbanions, or more generally, electrophiles and nucleophiles. Radicals for chemical synthesis are generated mostly by radical transfer reactions initiated by thermolysis or photolysis of peroxides or azocompounds. This way a large variety of very selective radical chain additions are available [5].

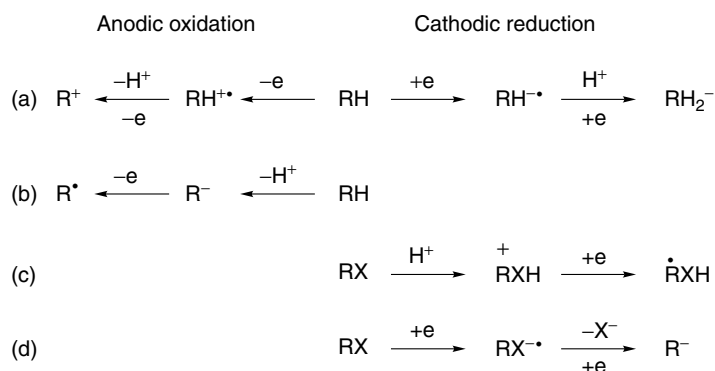
### 3.3

#### The Reactive Intermediates in Organic Electrosynthesis

In electroorganic synthesis, radical ions preponderate as useful intermediates (Scheme 1a). Radical cations can, in subsequent deprotonations and further electron transfers (ET), be transformed into carbocations or vice versa as radical anions can be converted by protonation and further reduction into carbanions. Carbanions can also be generated by reductive cleavage of R–X (X = Cl, Br, I, OTos), and subsequent reduction of the intermediate radical R<sup>•</sup> (Scheme 1d). Radical anions can also be used as electrogenerated bases (EGBs, see Chapter 14) for the deprotonation of C–H bonds to form carbanions.

Electrogenerated radical ions nicely supplement the methodology of chemical synthesis, whose reactions are less suited to generate and use radical ions, but rather apply polar substitution and addition reactions.

Radicals are generated at the anode by oxidation of carbanions (Scheme 1b), for example, alkoxides and carboxylates (see Chapter 5, 6), and at the cathode by reduction of protonated carbonyl compounds or onium salts (Scheme 1c) (see Chapter 7). Thereby, a wide choice of different radical structures can be mildly and simply



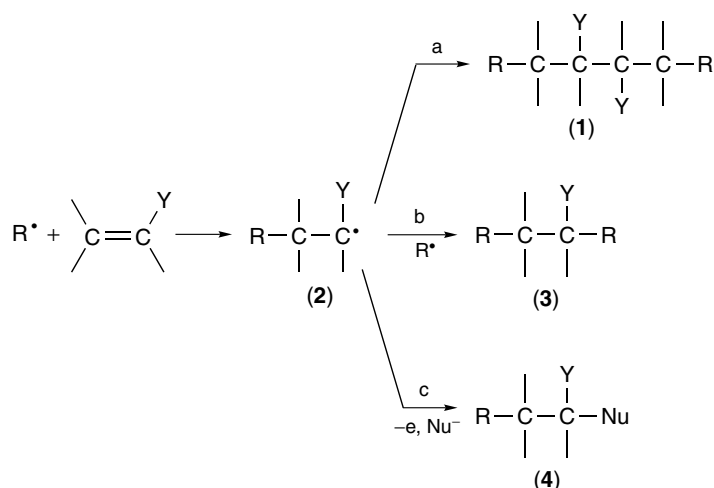
**Scheme 1** Electrochemical generation of reactive intermediates for polar reactions.

obtained from readily available precursors. These radicals are especially suited for coupling and additive-coupling reactions in nonchain processes because they are favored by the high radical concentrations at the electrode. The electrogenerated radicals can be trapped by olefins to yield additive dimers (**1**) (Scheme 2) and additive monomers (**3**), or the adduct radical can be further oxidized to a carbocation that reacts with a nucleophile to form (**4**). In additive dimers (**1**), two radicals and two olefins are joined in a one-pot reaction with a specific head-to-head connection of the olefins. This is a unique structure pattern that is nearly exclusively available only by electrogenerated radicals. It is a consequence of the high radical concentration in the reaction layer at the electrode surface. The product ratio (**1**):(**3**) can in part be controlled by the current density and olefin concentration (Scheme 2, paths a and b), and the formation of (**4**) by the electrode potential and the substituent of the olefin (Scheme 2, path c) (see Chapter 5).

Pericyclic reactions belong to the most powerful methods for C,C-bond forming reactions, especially for the stereo- and regioselective construction of polycyclic ring

systems [4, 6]. After the Grignard reaction, the Diels–Alder cycloaddition ranks second among the most applied methods in organic synthesis. It plays a minor role in electrosynthesis; however, electrochemically initiated cycloadditions have been described recently [8, 9]. They involve chain reactions with a radical cation as the chain transferring step or the generation of reactive dienophiles (see Chapter 5). Transition metal complexes are powerful catalysts for C,C-bond forming reactions. By way of in situ generation, they are increasingly applied in electrochemistry as electrocatalysts for cathodic coupling [10], reductive carboxylation [11], acylation or alkylation [12], activation [13], and cofactor regeneration in electroenzymatic reactions [14].

A synthetically very potent and unique feature of organic electrosynthesis is the oxidative or reductive ‘Umpolung’ of reactivity. Reactive acceptors are anodically available as radical cations in a wide variety by the oxidative ‘Umpolung’ of donors. This way two donors can be coupled in one step if one of them is converted to an acceptor at the electrode. Chemically, at least two additional



**Scheme 2** Reactions of electrogenerated radicals.

steps are needed for this operation. Thus, electrochemistry saves steps in synthesis and allows the use of synthetic building blocks in several reactivities, namely as donors, acceptors, and radicals. Of general synthetic value is the generation of latent immonium ions for electrophilic addition (see Chapter 6) and the oxidative coupling of olefins (see Chapter 5). In common chemical synthesis, there is, on the other hand, a highly developed experience and a large arsenal of reagents to execute selective electrophilic, nucleophilic, and radical substitutions and additions.

Reactive donors can be generated cathodically by reductive cleavage of halides to carbanions or by reduction of double bonds to radical anions. Using these methods, two acceptors can be dimerized in one step by reductive ‘Umpolung’, for example, two molecules of acrylonitrile to adipodinitrile – a reaction, which normally needs two or more steps.

On the other hand, highly developed chemical techniques are available

to generate activated donors with different functional groups and carbon structures by hydrogen–metal, halide–metal, or metal–metal exchanges. Furthermore, in these cases, the low temperatures and inert solvents, which are necessary to handle reactive and labile carbanions and to achieve high selectivities, can be applied. For practical use, the lower temperature limit for preparative scale electrolysis is, in general, at  $-50^\circ\text{C}$ , because of the decreased ion conductivity at lower temperatures. Furthermore, the inert, but unpolar solvent, petroleum ether, widely used in alkali organic chemistry, cannot be applied in electrochemistry owing to its missing dissociation power for supporting electrolytes.

The principle of electrochemical redox-‘Umpolung’ has been uniquely applied in cyclization. Thereby, one of two donors in the acyclic precursor is oxidized to an acceptor, whose reaction with the donor leads to cyclization. The same holds for the cyclization by way of reduction of one out of two acceptors [15].

## 3.4

**Selection of Advantageous Electrochemical C,C-Bond Forming Reactions and Functional Group Interconversions**

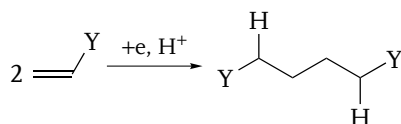
Organic electrochemistry should preferentially be used for those conversions, where the method has advantages over purely chemical reactions. In the following section, a selection of such conversions with yields that are mostly higher than 50% are given.

## 3.4.1

**C,C-Bond Formation**

There is a large variety of polar and radical reactions, transition metal-catalyzed and pericyclic conversions, that have been carefully developed with regard to scope, selectivity, and yield. They are compiled in large compendia, for example, in [16–19], and in series, for example [20, 21], and are continuously improved and extended in timely research papers. This literature should be consulted in parallel with suggestions taken from electrosynthesis. Electrosynthesis is a clear alternative to chemical synthesis, when reactive intermediates (see Sect. 3.3) such as radical ions, radicals, carbanions, or carbocations are involved. The more advantageous are summarized in the following sections.

At the cathode, olefins with electron deficient double bonds can be hydrodimerized (Eq. 1). This reaction has been developed for acrylonitrile [22] in a technical adipodinitrile synthesis [23] with a scale of more than 300.000 tons per year. The scope of this hydrodimerization has been substantiated with many examples [24–33].

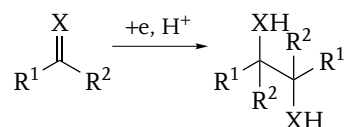


Y = CN, CO<sub>2</sub>Me, SO<sub>2</sub>Aryl, COR, NO<sub>2</sub>

Yields: 28–95%

(1)

Aldehydes and ketones can be hydrodimerized to pinacols (Eq. 2) [34–37]. With aromatic carbonyl compounds, the yields and selectivities are mostly higher than with aliphatic ones. The reaction has been extended to imines (Eq. 2, X = NAr, N-Bn) [38–41] and to heterohydrodimerizations affording, for example,  $\gamma$ -lactones (Eq. 3) [42–44].



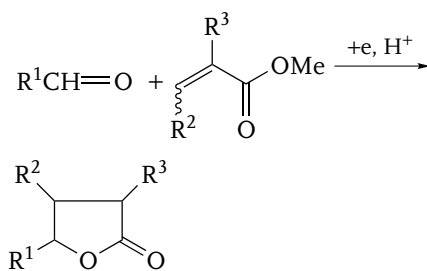
R<sup>1</sup> = aryl, alkyl, vinyl;

R<sup>2</sup> = H, aryl, alkyl;

X = O, N-aryl, N-benzyl.

Yields: 40–90%

(2)



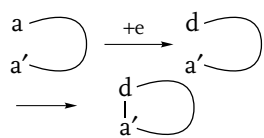
R<sup>1</sup> = alkyl; R<sup>2</sup>, R<sup>3</sup> = H, alkyl;

Yields: 30–90%

(3)

Reductive “Umpolung” of acyclic compounds with two acceptors allows efficient single-step cyclizations by converting one of the acceptors into a donor (Eq. 4) [15].

This has been applied to the cyclization of dihalides [45, 46], nonconjugated, unsaturated ketones [47] and esters [48], oxoalkylpyridinium salts [49], aldehydes and unsaturated nitriles [50], halides, and unsaturated esters [51]. The ‘unpoled’ acceptors, mostly radical anions or carbanions (see Scheme 1), can also be used in intermolecular reactions such as acylation, alkylation, or carboxylation (Eq. 5).



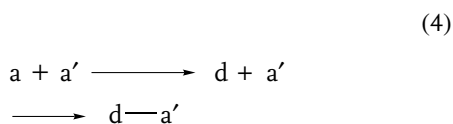
a: C-halide [45, 46],  $\text{C}=\text{O}$  [47, 52],

$\text{C}=\text{N}^+$  [49],  $-\text{CH}=\text{CHCO}_2\text{Me}$  [53];

a': C-halide [45, 46],  $-\text{CH}=\text{CH}-$  [47],

$\text{C}=\text{O}$  [49, 54],  $-\text{CH}=\text{CHCO}_2\text{Me}$  [53];

Yields: 23–100%



a:  $\text{CH}_2=\text{CHCO}_2\text{Me}$  [55], aryl [56],

$-\text{N}=\text{N}-$  [57],  $\text{C}=\text{N}^+$  [58],

$\text{R}-\text{CCl}_3$  [59, 60];

a':  $(\text{RCO})_2\text{O}$  [55],  $^+\text{BuNMe}_3$  [56],

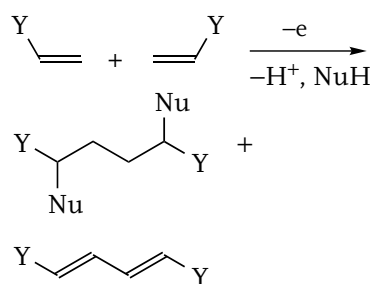
$\text{Br}(\text{CH}_2)_n \text{Br}$  [57],  $\text{BuBr}$  [58],

$\text{RCH}=\text{O}$  [59],  $\text{CO}_2$  [61–63].

Yields: 40–83%

(5)

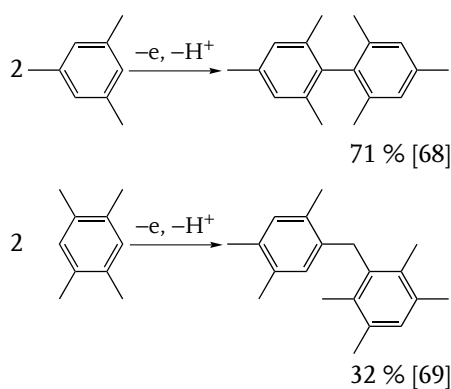
Electron-rich olefins with substituents  $\text{Y} = \text{phenyl}$ , vinyl, amino, or alkoxy can be coupled by anodic oxidation to tail–tail dimers being either deprotonated to dienes and/or substituted  $\alpha$  to  $\text{Y}$ , depending on  $\text{Y}$  and the reaction conditions (Eq. 6). Alkyl substituted arenes can be dehydrodimerized to diphenyls or diphenylmethanes depending on the kind of substitution (Eq. 7).



Y: aryl [64], vinyl [65], OR [66],

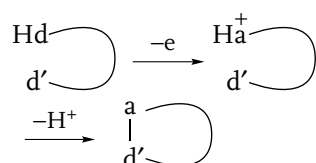
$\text{RNH}$  [67]; Nu: OMe; Yields 45–67%

(6)



(7)

A mirror image to the cyclization in Eq. (4) can be achieved by reversing the polarity of one from two connected donors by anodic oxidation (Eq. 8) [15].



d: aryl [70, 71, 72, 75],  
 $\text{CH}=\text{CHOEt}$  [73, 76, 77],  
 $\text{R}'\text{CH}=\text{CH}-\text{NR}_2$  [74],

d': aryl [70, 71, 72, 74],  
 enol ether [76, 77], vinyl [75];

Yields: 45–95%

(8)

The application of radicals for C,C-bond formation by way of coupling and addition is shown in Scheme 2. Carboxylates are precursors for the anodically generated radical  $\text{R}^\bullet$ , see also Chapter 5 [78]. There, R can bear different substituents; limitations arise when they are in the  $\alpha$ -position. Furthermore, anions of CH-acidic compounds have been applied with pKs-values up to 14 [79], because with this acidity they can be fairly simply handled with methanol as solvent; furthermore, Grignard reagents have been oxidized to alkyl radicals in diethyl ether [80]. For intermolecular additions, fairly reactive olefins, such as styrene, butadiene [79, 81], electron deficient alkenes [82], or mediation with  $\text{Mn}^{3+}$  have to be used to overcome the competing coupling of the radicals [83]. These reactions afford synthetically interesting additive dimers, where four building blocks can be joined in one step with specific head-to-head coupling of the olefins. Intramolecular addition also tolerates less reactive alkenes as long as the double bond is three atoms apart from the radical to form a five-membered ring [84].

### 3.4.2

#### Functional Group Interconversions

There are a large variety of methods for different FGIs in chemical synthesis that lead to the wanted products with high yield and selectivity. Many of them are compiled in [18, 19] and they are continuously improved, extended, and supplemented in timely communications.

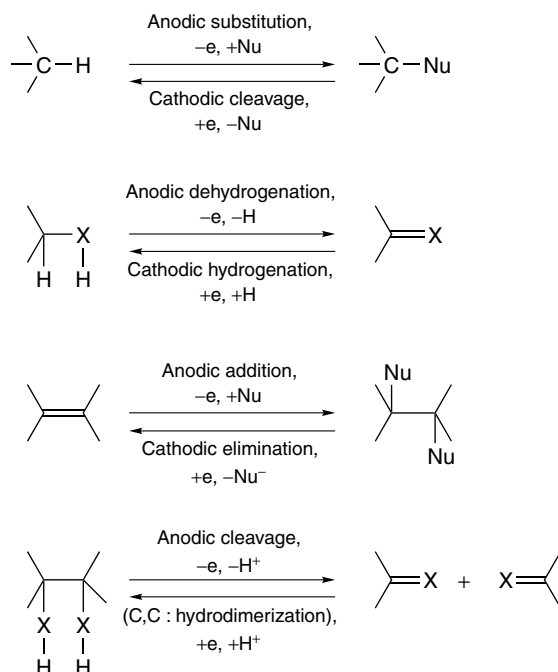
Electrochemical FGIs can be classified into four groups (Scheme 3):

1. anodic substitution and its cathodic counterpart, cathodic cleavage;
2. anodic dehydrogenation and cathodic hydrogenation;
3. anodic addition and cathodic elimination; and
4. anodic cleavage, where the cathodic reversal is a C,C-bond forming reaction, for example, hydrodimerization.

CH-bonds for anodic substitution can be those in alkanes and aryl compounds as well as those activated by an aryl, alkoxy, thio, amino group, or a double bond.

For the anodic substitution of unactivated CH-bonds, some fairly selective reactions for tertiary CH-bonds in hydrocarbons and  $\gamma$ -CH-bonds in esters or ketones are available [85–87]. However, in some cases, a better control of follow-up oxidations remains to be developed. Chemically, a number of selective reactions are available, such as the ozone on silica gel for tertiary CH-bonds [88], the Barton or Hoffmann–Loeffler–Freitag reaction for  $\gamma$ -CH-bonds [89], and for remote CH-bonds,  $(i\text{-prop})_2\text{NCl}/\text{H}^+$  [90, 91], photochlorination of fatty acids adsorbed on alumina [92] or template-directed oxidations [93].

For activated CH-bonds, a wealth of chemical methods are available, such



**Scheme 3** Classification of electrochemical functional group interconversions (FGI's).

as singlet oxygen, *N*-bromosuccinimide,  $\text{Br}_2/h\nu$ ,  $\text{Pb}(\text{OAc})_4$ , or  $\text{SeO}_2$  [94]. Anodically, fair yields are obtained for CH-bonds activated by a vinyl, phenyl, or alkoxy group [95–99], although sometimes problems of regioselectivity occur. The oxidation of *N*-acyl-*N*-alkylamines, which leads to synthetically very interesting precursors of iminium cations [100–104], is a unique electrochemical reaction. For the nucleophilic substitution of aromatic CH-bonds, electrochemistry has a clear advantage over chemical conversions. At the anode nucleophiles like OR, OCOR, and CN can be introduced simply and in one step [105–109], while chemically, multi-step procedures are necessary to achieve this goal.

Carboxylic acids can be regarded as compounds having a CH-bond with an inserted  $\text{CO}_2$ -group. They can be converted

by non-Kolbe electrolysis into products in which the  $\text{CO}_2\text{H}$  group is regioselectively replaced by a nucleophile or a double bond (see Chapter 6) [110–113]. This conversion can be combined with specific rearrangements or fragmentations [110, 114]. The comparable chemical conversions, such as the Kochi reaction [115] or the Hofmann rearrangement [116], are more limited in scope.

The cathodic cleavage of CX- to CH-bonds can be achieved with a variety of substituents X, such as Hal,  $\text{NR}_3^+$ ,  $\text{PR}_3^+$ , OTos, or epoxides. Generally, good yields, a high potential selectivity, and often good stereoselectivities are encountered (see also Chapter 8) [117–123]. Chemical reactions for similar conversions, which are well worked out, especially with regard to yield and selectivity, are the reduction of tosylates with  $\text{LiAlH}_4$  and halides with



Bu<sub>3</sub>SnH [124] or radical deoxygenations of alcohols [125].

For the dehydrogenation of CH–XH structures, for example, of alcohols to ketones, of aldehydes to carboxylic acids, or of amines to nitriles, there is a wealth of anodic reactions available, such as the nickel hydroxide electrode [126], indirect electrolysis [127, 128] (Chapter 15) with I<sup>−</sup>, NO<sub>3</sub><sup>−</sup>, thioanisole [129, 130], or RuO<sub>2</sub>/Cl<sup>−</sup> [131]. Likewise, selective chemical oxidations (Cr(VI), MnO<sub>2</sub>, MnO<sub>4</sub><sup>−</sup>, DMSO/Ac<sub>2</sub>O, Ag<sub>2</sub>O/Celite<sup>®</sup>, and O<sub>2</sub>/Pt) [94] are available for that purpose. The advantages of the electrochemical conversion are a lower price, an easier scale-up, and reduced problems of pollution.

The hydrogenation of C=X and C=C double bonds can be achieved cathodically and with a number of chemical reagents, such as catalytic hydrogenation, metal hydrides, and dissolving metals [19]. Here, the best method must be selected for each individual case. The advantages of the electrochemical method are the potential selective conversion at the cathode, the possibility of reducing carbon–heteroatom double bonds in the presence of C=C bonds [132], the *trans*-hydrogenation of C=C bonds via radical anions [133] in contrast to the *cis*-hydrogenation with catalytically transferred hydrogen, or the potential selective reduction of the phenyl group in the presence of an isolated double bond [134].

Anodic addition converts enolacetates into  $\alpha$ -acetoxyketones or enones, depending on the reaction conditions [135], conjugated dienes into 1,2- or 1,4-dimethoxy alkenes [65], and hydroquinone dimethyl ethers into quinone bisketals [136, 137]. Anodic addition also affords products, some of which are of industrial interest, such as propylene oxide [138a] or 1,4-dimethoxydihydrofuran [138b]. To

improve the selectivity in anodic addition, sometimes mediators like Pd<sup>2+</sup>, Ce<sup>4+</sup>, or Ru<sup>3+</sup> are used (see Chapter 15) [127, 128]. Chemical reagents that lead to similar conversions include MnO<sub>4</sub><sup>−</sup>, OsO<sub>4</sub>/*N*-methyl morpholin oxide, Hal<sub>2</sub>, and peracids [139].

Cathodic elimination can remove a variety of vicinal nucleophiles (X = Br [140], Cl [141], S-C<sub>6</sub>H<sub>5</sub> [142], or oxalate [143]) to form a double bond. Controlled potential cathodic reduction allows the selective elimination of vic-dihalides depending on the degree of alkylation [144]. Chemically, these reductions are more limited in scope; they can be conducted with I<sup>−</sup> in DMF, with Zn, Mg, or Cr<sup>2+</sup> [145].

The cleavage of 1,2-diols can be inexpensively achieved at a nickel hydroxide electrode [126], while chemically more expensive reagents such as Pb(OAc)<sub>4</sub> or IO<sub>4</sub><sup>−</sup> must be used. The latter can be used as mediator for the indirect anodic cleavage of starch [146]. Double bonds can be cleaved at the anode to carboxylic acids by applying the double mediator: RuCl<sub>3</sub>, IO<sub>4</sub><sup>−</sup> [147].

The conversion of heteroatoms to different oxidation states, for example, NH<sub>2</sub> → NO<sub>2</sub>, -S- → -SO-, -SO<sub>2</sub>- or NO<sub>2</sub> → NHOH, NH<sub>2</sub> is possible at the electrode. Of advantage, especially in the reduction of nitro functions, is the potential selective conversion to certain oxidation states such as the hydroxylamino or amino group (see Chapters 7, 9, 10) [148–150].

Cathodic cleavage and elimination combined with the possibility of varying the reduction potential of protecting groups have proved to be mild and selective methods for deprotection. This way the tritylone group, which blocks alcohols with similar chemoselectivity as the trityl group, but has a higher stability against acids, can be cathodically removed [151]. The

$\beta$ -polyhaloethyl group is cleaved at different potentials depending on the kind and number of halogens [152]. *N*-benzoyl or *N*-phenylsulfonyl protected amino acids can be deblocked at the cathode [153]. Non-conjugated dienes having double bonds with a different degree of alkylation can be selectively blocked with pyridinium hydroperbromide at the higher alkylated double bond [154], and by potential selective reduction of the tetrabromide at the less alkylated one [144]. By controlled potential electrolysis, protecting groups can be selectively removed. This makes electrochemical deprotection [155, 156] a valuable supplement to chemical deprotection [157, 158]. Additionally, less interference with other functional groups is encountered than in chemical deprotection.

Each oxidation generates at the anode, electrophiles or protons, respectively, and each reduction vice versa generates nucleophiles or bases. With such electrochemically generated acids or bases, EGAs or EGBs, acid- or base-catalyzed reactions can be initiated (see chapter 14). EGBs from probases, for example, azobenzene, tetralkyl ethene tetracarboxylate, fluorenes, or radical anions have been used for deprotonation of aromatic hydrocarbons and subsequent carboxylation [159], or of a phosphonium salt to produce an ylide for a Wittig reaction [160]. EGAs produced in solvents of low nucleophilicity as conjugated acids of the supporting electrolyte anion have been used for the generation of acetals from epoxides or ketones [161, 162].

Organometallic compounds can be generated at the electrode in three ways. An alkyl halide is reduced at an active cathode, for example, Pb, Sn, which reacts with the intermediate radical [163, 164]. A Grignard reagent or an  $\alpha$ -complex is oxidized at an active anode and the intermediate radical reacts with the anode

metal, for example, Pb, Mg, Al, Hg, In, Bi [165, 166]. Finally, a metal ion can be reduced to a highly reactive metal that forms complexes with olefins or other ligands [167].

Electrochemical and chemical oxidative or reductive FGIs and C,C-bond forming reactions differ in some aspects. The first are heterogeneous reactions and mostly outer-sphere ET processes. The second ones are mostly homogeneous reactions and inner-sphere processes. Outer-sphere ET mostly leads to more or less free reactive intermediates, for which the stereoselectivity of the following bond forming process is harder to control. In inner-sphere ETs, the substrate forms simultaneously, with the change of the oxidation state, a bond to the hetero- or carbon atom of the oxidizing or reducing agent. These ETs are more sensitive to steric and electronic influences, which often leads to higher selectivities. This feature is exploited in indirect electrochemical oxidations or reductions, where selective chemical oxidants/reductants are used as mediators (see Chapter 15). Thereby, selectivities can be improved, follow-up ETs suppressed, and second-order reactions shifted to first-order ones [168]. The smooth regeneration of the active mediator has been resolved in many cases (see Chapter 15); in others, for example,  $\text{SmI}_2$  [169], it is a matter of intense ongoing research. In heterogeneous electrochemical processes, the reaction is confined to a more or less thin reaction layer (0.1  $\mu\text{m}$  to 0.1 cm depending on the reactivity of the intermediate). This leads to a higher concentration of the reactive intermediate ( $10^2$  to  $10^5$  times higher), compared to the homogeneous reactions of chemical redox reagents, and thus favors second-order reactions.

### 3.5

#### Working Out An Electroorganic Synthesis

First, one should determine how well electrochemistry is suited for the planned synthetic step. For C,C-bond formations, this can be deduced from Schemes 1 and 2 (Sects. 3.3 and 3.4 of this article). According to this information, electroorganic synthesis should be considered as favorable for reductive and oxidative inter- and intramolecular coupling reactions as well as additions via radical ions, radicals, or anions. Each FGI fitting into Scheme 3 is, in principle, suited for an electrochemical conversion. After this selection, a literature search is made in the table of contents of this book, in [170–174], and in an electronic search system to find timely communications for reactions similar to the given conversion. A closely related, reported procedure should then be accurately reproduced. The conditions of the examined reaction are then applied to the given problem. In general, the following conditions are favorable: high substrate concentration ( $\sim 0.5 \text{ mol l}^{-1}$ ), undivided cell (provided substrate and product are fairly stable against the counter electrode), current controlled electrolysis at 50 to  $100 \text{ mA cm}^{-2}$ , a temperature of  $0^\circ$  to  $50^\circ\text{C}$ , and in the first electrolysis only a 50% conversion to suppress reductive or oxidative follow-up reactions. For oxidations, the materials suitable for the working electrode are graphite, glassy carbon, and platinum; and for reductions, the suitable materials are graphite, glassy carbon, or a mercury pool. The materials that can be used as counter electrodes are graphite or platinum as cathode or as anode, steel as cathode, and aluminum as consumable anode. For oxidations, it is suitable to start with the solvents: methanol, acetonitrile, or  $\text{CH}_2\text{Cl}_2/\text{CF}_3\text{CO}_2\text{H}$ , and

for reductions with methanol, tetrahydrofuran, or dimethylformamide. TEATos and  $\text{Bu}_4\text{NBF}_4$  (tetraethyl tosylate, tetrabutylammonium tetrafluoroborate) have proved to be useful as supporting electrolytes. For a thorough treatment of this topic, see Chapter 2.

Products are then identified and roughly quantified by TLC, HPLC, GC, IR, ESI/MS, GC/MS, and  $^1\text{H-NMR}$ .

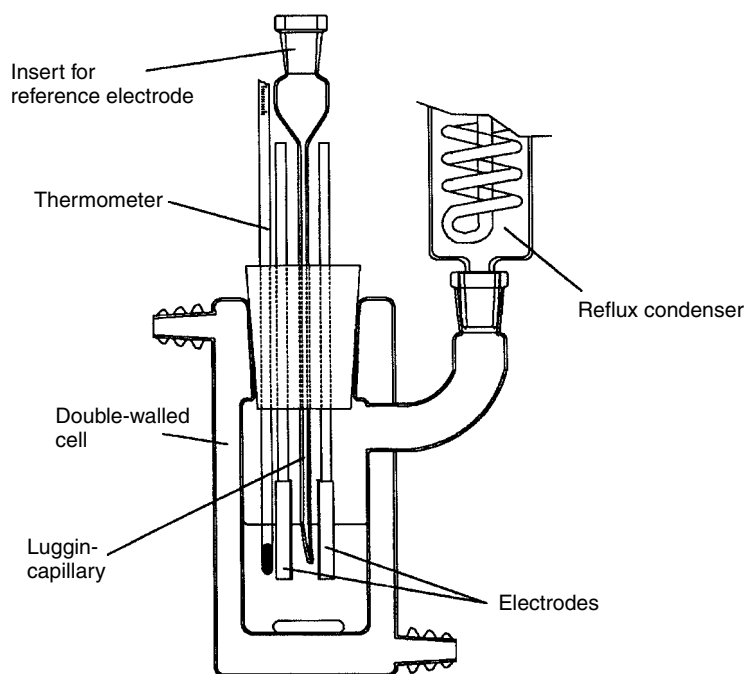
For optimization, the temperature is extended down to  $-30^\circ\text{C}$  and up to  $80^\circ\text{C}$ , and the current density down to  $1 \text{ mA cm}^{-2}$ . If unwanted oxidative or reductive conversions have occurred, a potential controlled electrolysis (to prevent over-oxidation or reduction) and a divided cell or a consumable anode (to prevent unwanted conversions at the counter electrode) should be applied. If passivation (blocking of the surface of the working electrode by insulating films) is suspected, a more porous material for the working electrode, reversal of electrode polarity or frequent cleaning of the electrode surface by polishing or heating to a red glow should be employed. These are just some hints; the topic is covered in depth in Chapter 2.

### 3.6

#### Equipment

For the electrolyses, a cell and a DC power supply are needed. For a thorough coverage, see again Chapter 2. For most conversions, especially the exploratory ones, the author has used a double-walled beaker-type cell (Fig. 1).

The cell is closed with a teflon stopper with small holes for the two current feeders, the Luggin capillary (to establish an electrolyte bridge between the reference electrode and the working electrode



**Fig. 1** Undivided beaker-type cell for potential controlled electrolysis.

in potential controlled electrolysis), a thermometer, and gas inlet tube [not shown] (for purging the electrolyte with nitrogen). These parts are fastened in the stopper with viton rings that are held in place by teflon plates, which are screwed to the top and the bottom of the stopper. V2A steel rods, screwed into the graphite plates ending in a holder for glassy carbon electrodes or screwed in a teflon frame that supports thin platinum foils, served as current feeders. A platinum wire sealed into a glass tube served as current feeder to the mercury pool electrode.

For current-controlled conversions, a current-regulated DC source (up to 50V and 2A, with voltage and current display) [175] or one or two car batteries (12 to 24V) with a volt and ampere meter [176] or a regulated AC power source with a rectifier are sufficient as the power supply.

The current consumed (measured in faradays [F]) corresponds to  $F = \text{current (in ampere)} \times \text{electrolysis time (in hours)} \times 0.0374$ .

For a potential controlled electrolysis, one needs a potentiostat [177] and a reference electrode. The Ag/AgCl electrode can be used as a reference electrode with a fixed potential. It is prepared from a silver wire, which is covered with AgCl, when employed as the anode in 2N HCl.

The reference electrode is connected with the cell via a glass tube (Luggin capillary) filled with electrolyte, and the narrowed orifice of the tube is placed about 0.1 to 0.3 mm in front of the side of the working electrode that faces the counter electrode. The potential between this point and the surface of the working electrode is measured with a high resistance voltmeter that makes contact with the silver wire of

the reference electrode and the current feeder of the working electrode. It is this potential that the substrate and the intermediates experience at the electrode surface. The regulated DC source can be used as a potentiostat, when the current is manually adjusted in such a way during the electrolysis that the potential of the working electrode (against the reference electrode) maintains a given value. This set-up can also be used to obtain current/voltage ( $i/U$ ) curves in the electrolysis cell by changing the voltage stepwise and recording the current. The voltage at the current steps in this curve indicates at what potential the substrate is converted and at what potential unwanted oxidations/reductions occur. This is the potential range in which the electrolysis should be conducted. The consumed current is recorded with a chemical or electronic coulometer [178]. This chapter is written for organic chemists who have not used electroorganic synthesis before. It aims to facilitate the integration of the reagent electron into synthesis by using equipment that is either around in each laboratory or can be prepared readily in the workshop and by a glassblower or is commercially available at a reasonable price. For a detailed introduction, see Chapter 2.

### 3.7 Some General Comments

Organic electrochemistry fulfills favorably the requirements defined for a good synthesis (see Sect. 3.2). The “Umpolung” of reactivity by ET saves steps because it allows a one-step coupling of two donors or two acceptors. In comparable chemical conversions, two or more steps are necessary for that purpose. The selectivity

of electrochemical reactions with regard to a potential selective conversion of an electrophore is much better than that of chemical reactions. However, the chemoselectivity, the regioselectivity, and especially the stereoselectivity are often inferior to those of chemical reactions. The reasons are that chemical reactions proceed mostly in a concerted way and are thus by nature more sensitive to steric and electronic interactions than reactive intermediates in electrode processes. Furthermore, the lower temperatures that increase the selectivity are better attainable in chemical conversions, and a much more profound knowledge of the control of chemical reactions has been accumulated. The reagent electron is cheap and readily available. Two moles of electron (2F) for the conversion of 1 mole of substrate in a 2-electron conversion at a cell voltage of 5 volt corresponds to 0.27 kWh, which costs 0.03 Euro. Prices of chemical reagents, on the other hand, are much higher except for oxygen, whose use, however, is limited due to its comparatively low oxidation potential.

The investment for equipment is somewhat higher than for chemical reactors, but an electrochemical reactor can be applied to many more reaction types than a chemical one. Technical electrolyses are mostly run in continuous flow reactors, sometimes for years without change of the electrodes, which saves personnel, maintenance, and solvent costs as compared to chemical conversions, which are often performed in batch reactors.

Electrochemical preparations are often easier to conduct than chemical conversions. Solubility problems, which frequently occur with inorganic redox reagents in organic solvents, are not encountered. On the other hand, the inertness of the solvents and the lower attainable temperatures in chemical reactions

cannot be achieved to this extent in electrolysis. To reach a sufficient electric conductivity, polar and, thus, more reactive solvents are necessary for the electrolytes, and the temperatures for practical reasons cannot be lowered much below  $-40^{\circ}\text{C}$  in preparative scale electrolyses.

Workup of electrolyses is often easier as no products of chemical oxidants or reactants need to be separated. Additionally, in electrolysis a similar workup can be used for a wide number of applications. Furthermore, the scale-up of electrochemical reactions is often easier to achieve than for chemical conversions. The electron is a nontoxic reagent, which is not the case for many chemical reagents. Often used solvents and supporting electrolytes in electrosynthesis such as methanol, water, and alkali or tetraalkylammonium salts are nontoxic. Expensive reagents are recycled in catalytic amounts as mediators in indirect electrolyses. Reaction conditions for electroorganic synthesis are, in general, harmless. They are mostly conducted at room temperature and at normal pressure. Reactive intermediates that undergo exothermic reactions are not accumulated, but are immediately consumed after generation.

Atom economy is high. As a reagent, no compounds are needed and consequently none are produced as the electron is immaterial. This results in a greater advantage of electrochemical reactions compared to chemical conversions, namely, an effective contribution to pollution control. The direct ET from the electrode to the substrate avoids the problem of separation and waste treatment of the, frequently, toxic end products of chemical reductions or oxidations. Furthermore, by electrodialysis, organic acids or bases can be regenerated from their salts without the use of, for example, sulfuric acid or

sodium hydroxide, which leads to the coproduction of sodium salts or sulfates as waste [179, 180]. At the same time, inorganic acids and bases, necessary for chemical production, are provided by this process. An application of electrodialysis has been demonstrated in the preparation of methoxyacetic acid by oxidation of methoxyethanol at the nickel hydroxide electrode [181]. Additionally, unwanted side products can be converted into the wanted product. The economy of the process reduces the problem of waste separation and treatment. This is accomplished in the manufacture of chloroacetic acid by chlorination of acetic acid. There, the side product, dichloroacetic acid, formed by overchlorination, is cathodically converted to chloroacetic acid [182].

Also, the substrate in general needs no additional atoms for activation because the potential of the working electrode can be adjusted by the power supply to each electrophore for the activation of the substrate by electron transfer.

The broad scope of electrochemical C,C-bond forming reactions and FGIs is demonstrated in many chapters of Volume 8 and partly summarized in Sect. 3.4. Furthermore, it should be mentioned that at the electrode a synthetic building unit can be used with several reactivities, because this can be changed via electron transfer. In chemical preparation, building units are usually designed for only one reactivity. While the reagent electron can be applied to many diverse reactions, a chemical reducing or oxidizing reagent is mostly limited to a narrow selection of very similar conversions. So for a chemical synthesis, a number of different reagents have to be either prepared in mostly multistep procedures or have to be bought, mostly at high cost.

Finally, the equipment to generate the reagent electron for the majority of conversions in the milligram- to 100-gram scale consists (as shown in Sect. 3.6) of a readily available and inexpensive, simple cell and power supply.

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## 4

### Cathodic Reactions of Hydrocarbons, Olefins, and Aromatic Compounds

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#### 4.1 Introduction

The electrochemical reduction of pure hydrocarbons without functional groups is almost exclusively restricted to unsaturated compounds. The reason is that aliphatic hydrocarbons have extremely low electron affinities that render their reduction impossible, despite a gain of solvation energy within the stability limits of conventional solvent-electrolyte systems.

Thus, electrochemical data involving both thermodynamic and kinetic parameters of hydrocarbons are available for only olefinic and aromatic  $\pi$ -systems. The reduction of aromatics, in particular, had already attracted much interest in the late fifties and early sixties. The correlation between the reduction potentials and molecular-orbital (MO) energies of a series of aromatic hydrocarbons was one of the first successful applications of the Hückel molecular orbital (HMO) theory, and allowed the development of a coherent picture of cathodic reduction [1]. The early research on this subject has been reviewed several times [2–4].

Later, during the golden age of mechanistic chemistry, interest focused on the elucidation of reaction paths of cathodically generated species, including disproportionations [5] and chemical follow-up

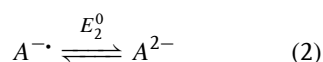
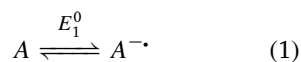
processes [6]. Techniques were developed and improved to measure both the kinetics of coupled chemical reactions [7] and thermodynamic parameters such as redox potentials of higher-charged aromatics [8, 9]. The discovery of the redox properties of conducting polymers in the year 1977 and later of the fullerenes [10, 11], gave new impetus to the electrochemistry of unsaturated hydrocarbons, initiating extended studies on the redox properties of these species [12–14].

#### 4.2 Reductive Generation of Anionic Species

##### 4.2.1 Experimental Background

Thermodynamic reduction potentials of numerous aromatics were first measured by Hoijsink and van Schooten in 96% aqueous dioxane, using polarography [15, 16]. These fundamental works were decisive tests of the HMO theory, showing that the polarographic half-wave potentials vary linearly with the HMO energies of the lowest unoccupied molecular orbitals (LUMO) of the hydrocarbons [1]. Hoijsink et al. had already noticed that most aromatics can be further reduced to their respective dianions [17]. They proposed a

two-step reduction scheme, where both redox potentials 1 and 2 are, on average, separated by about 500 mV:



However, their careful analysis also showed that most of the dianions were not stable in the polarographic or voltammetric timescale, and even less so after bulk electrolysis, and underwent follow-up reactions with water or other electrophilic impurities, details of which are discussed in Sect. 4.3.

Aprotic solvents such as acetonitrile [18, 19] or dimethylformamide (DMF) [20–22] considerably improved the stability of the radical anions but normally had little effect on the reactions of the more basic dianions [22, 23]. The increased irreversibility of the dianion formation is probably because of the ability of dianions to abstract protons even from the solvent, or, by Hoffmann elimination, from the tetraalkylammonium salts that are common supporting-electrolytes in aprotic solvents [24].

Progress in electrochemical instrumentation soon stimulated the application of more elaborated measurement methods than simple dc polarography, which facilitated studies of heterogeneous kinetics and detection of follow-up reactions of the electrogenerated species. Thus, conclusions originally drawn from the shape and height of polarographic curves have been amply confirmed by straightforward diagnostic criteria in cyclic voltammetry [7, 25, 26], nowadays the standard method for mechanistic studies in organic electrochemistry [27, 28].

A fundamental improvement in the facilities for studying electrode processes of reactive intermediates was the purification technique of Parker and Hammerich [8, 9]. They used neutral, highly activated alumina suspended in the solvent-electrolyte system as a scavenger of spurious impurities. Thus, it was possible to generate a large number of dianions of aromatic hydrocarbons in common electrolytic solvents containing tetraalkylammonium ions. It was the first time that such dianions were stable in the timescale of slow-sweep voltammetry. As the presence of alumina in the solvent-electrolyte systems may produce adsorption effects at the electrode, or in some cases chemisorption and decomposition of the electroactive species, Kieseles constructed a new electrochemical cell with an integrated alumina column [29].

Heinze modified the technique by purifying the solvent by transferring it under high vacuum from the electrochemical cell to superactive alumina in a separate vessel [27, 28]. Such sophisticated methods made it possible to generate reversible polyanions up to octaanions of aromatic and olefinic hydrocarbons [27, 28, 30–33].

Further progress in stabilizing highly charged anions was achieved by the application of unconventional solvents such as ammonia or dimethylamine at low temperatures. Using these solvents it was possible to observe the reversible generation of supercharged anions at low scan rates in voltammetric experiments [34, 35].

#### 4.2.2

##### Redox Properties

For the purpose of description, the electrochemistry of hydrocarbons may usefully be classified in three categories: benzenoid, nonbenzenoid, and olefinic hydrocarbons,

each of which exhibit characteristic properties upon reduction.

Benzenoid hydrocarbons have been studied in the greatest detail [2, 4, 36]. In aprotic solvents they can be reversibly reduced to their respective anions without difficulties. Even the electrochemical reduction of benzene in dimethoxyethane has been described [37, 38]. In many cases the electrogenerated radical anions are stable enough to allow the simultaneous measurements of their extent solvent reorganization (ESR) spectra [39–41]. The most striking feature of benzenoid hydrocarbons is the excellent correlation between their thermodynamic reduction potentials and the predictions of semiempirical  $\pi$ -electron theories, especially of the Hückel approximation (HMO). As the thermodynamic reduction potentials are a measure of the electron affinities of the respective compounds, they can be compared with the theoretically calculated energies in the simple MO picture, where additional electrons have been added to antibonding MOs of the  $\pi$ -systems. Therefore, assuming that the solvation energies for a series of aromatic hydrocarbons are constant, there should be a linear correlation between the thermodynamic reduction potentials (half-wave potentials  $E_{1/2}$ ) and the calculated energies  $m_{m+1}$  of the lowest unoccupied MO (LUMO) in units of an effective  $\beta$  in the HMO approximation:

$$E_{1/2} = -bm_{m+1} + C \quad (3)$$

where  $b$  corresponds to an effective value of the resonance integral  $\beta$  and  $C$  is a constant within a series of hydrocarbons. Independent voltammetric and polarographic measurements carried out in different solvents such as 2-methoxyethanol, 96% dioxane and DMF confirm the relationship through excellent linear correlations with slopes  $b$  of approximately 2.40 [1, 20,

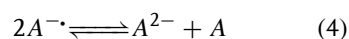
42, 43]. Rather surprisingly, the differences in half-wave potentials of hydrocarbons from one solvent to another are very small. This constancy in energy values as well as slopes of correlation lines in widely varying solvents and supporting electrolytes implies that solvation energies, provided they are not small, change in the same way from system to system.

As already observed by Hoijsink [17], nearly all benzenoid hydrocarbons can be reduced to their respective dianions – only benzene and naphthalene are exceptions. In all experiments, these second reduction steps appear approximately  $-0.55 \pm 0.10$  V negatively to the first reduction, provided that the supporting electrolytes used were tetraalkylammonium salts. Therefore, these reduction potentials were also correlated with the LUMO energies of the HMO model [3]. It was suggested that the energy difference of 0.55 eV corresponds to the repulsion energy between both electrons in the LUMOs of the dianions [1], despite the differences in their structures. On the other hand, quantum-mechanical calculations show that the repulsion energies are much larger. Dewar has calculated values in the range of 5 eV [44]. The discrepancy between experiment and theory results from the fact that ion-pairing effects and solvation influences have been neglected in the calculation. Experimental data clearly reveal that counterion effects that efficiently shield the negative excess charge have in the past been underestimated and are considerably stronger for di- and polyanions than for radical anions [44–47].

In polar solvents such as DMF or acetonitrile, the interaction increases in the order tetrabutylammonium < K < Na < Li and, consequently, reduction potentials shift in a positive direction [6, 48]. Obviously, ion pairing is greatest for the

small lithium ions in agreement with the prediction of Born's equation [49]. In the case of solvents with low dielectricity constants the pattern is different, and ion pairing becomes dominant as the radius of alkali cations increases [47, 50, 51]. The reasons for this behavior have not yet been studied in detail, but it has been proposed that in ethereal solvents the solvation of small cations remains stronger than that of larger ones, and therefore ion pairing of potassium should be more pronounced than that of lithium.

Ion-pairing effects may considerably influence disproportionation mechanisms that involve homogeneous redox reactions of anions to their respective dianionic and neutral species (Eq. 4) [52, 53].



Disproportionation mechanisms have been proposed for protonation reactions and intramolecular rearrangements (see Sects. 4.3.2 and 4.3.3) [54]. The prominent feature is that follow-up processes at the level of the dianion can already take place at potentials corresponding to radical anion formation. In order to evaluate data for disproportionation reactions it is necessary to know the value of the disproportionation equilibrium constant,

$$K_D = \frac{[A^{2-}][A]}{[A^{\cdot-}]^2} \quad (5a)$$

$$\frac{RT}{nF} \ln K_D = E_2^0 - E_1^0 \quad (5b)$$

This can be determined from the difference in reversible potentials of the couples  $A/A^{\cdot-}$  and  $A^{\cdot-}/A^{2-}$  (Eq. 5).

In the case of benzenoid aromatics,  $K_D$  values range between  $10^{-9}$  and  $10^{-13}$  provided tetraalkylammonium salts have been used as supporting electrolytes [9]. In solvents of low dielectricity constant,

additional effects are observed, showing influences of the supporting electrolyte concentration and of the nature of the cations [6]. In the tetraalkylammonium series the strongest (contact) ion pairs are formed by  $Et_4 N^+$ , and  $K_D$  is largest for that cation [9, 55].

Drastic changes in the disproportionation constants occur when alkali cations are used instead of tetraalkylammonium ions. Typically, the potentials of the radical anion formation are less affected than that of the dianion formation. In the presence of alkali cations,  $\Delta E^0$  shifts may reach values of more than 600 mV, which correspond to an increase in the  $K$  constant of more than 10 orders of magnitude [52, 53].

The electrochemistry of nonbenzenoid hydrocarbons has attracted much interest because their structures offer unusual insights into  $\pi$ -electron systems, which undergo geometric changes upon reduction and obey both the Hückel  $4n$  and  $4n + 2$  rules (Table 2).

The most widely studied examples are cyclooctatetraene (COT, **1**) and its derivatives. In such conventional aprotic solvents as DMF, dimethyl sulfoxide (DMSO), or acetonitrile containing tetraalkylammonium salts, two distinct one-electron reduction waves are observed at approximately  $-1.64$  V and  $-1.80$  V vs. saturated calomel electrode (SCE), with  $\Delta E^0$  separations varying from  $-130$  mV to  $-240$  mV. [46, 56–60] In tetrahydrofuran (THF) and  $NH_3$ , this separation reduces further [61], and in the presence of all alkali salts [62, 63] even two-electron reduction waves with positive  $\Delta E^0$  differences were obtained, indicating large disproportionation constants. The unusually small separation of the two redox steps in comparison to the data of benzenoid aromatics was ascribed to the fact that the planar COT dianion forms a  $4n + 2$   $\pi$ -electron system that is



stabilized by its gain in Hückel resonance energy [64]. Obviously, strong ion-pairing effects additionally favor the formation of the dianion [62, 63]. On the other hand, it was argued that a negative shift of the first reduction step, leading to small  $\Delta E^0$  values, is caused by energy requirements accompanying the transition from the tube-shaped to the planar molecule. This is supported by electrochemical results obtained with methyl-substituted COT derivatives. Thus, all methyl-substituted derivatives due to a steric barrier are harder to reduce than (1) itself, and in 1,2,3,4-tetramethylcyclooctatetraene (2) reduction occurs at the extremely negative potential of  $-3.6$  V (hexamethyl phosphoric acid triamide, HMPA vs. SCE) [65]. In the case of phenyl-substituted COTs, the steric demand is by and large energetically compensated through the planarization of the system and the subsequent resonance interaction between the phenyl moieties and the COT ring. Therefore, the reduction potentials are similar to that of an unsubstituted (1). In addition, the resonance-stabilizing effect upon the dianion is sufficient to shift the second redox potential  $E_2^0$  positively to  $E_1^0$ , thus producing a single two-electron reduction wave [59]. It is interesting to note that the electrochemistry of the doubly decked [8]annulene ( $=[2_2]$  (1,5)-cyclooctatetraenophane) also indicates some sterical strain [66]. The formation of the monoanion occurs at a potential of  $-2.43$  V (DMA, vs. Ag/AgCl). It can be reduced up to its tetraanion at a potential of  $-3.22$  V.

The redox behavior of a number of higher annulenes than (1) has been studied during the past twenty-five years. The evaluation of their electronic properties has attracted much interest because it offers a good comparison of the fundamental differences between  $4n$  and

$4n + 2$   $\pi$ -systems. As predicted by the simple MO theories, the transfer of an electron to a  $[4n]$ annulene should be energetically favorable because the electron is inserted into a low-lying nonbonding orbital. The further reduction to the dianion leads to a stabilized (aromatic)  $4n + 2$   $\pi$ -system, which therefore should also be easily accessible. In contrast, during the reduction of an aromatic,  $[4n + 2]$ annulene electrons are injected into a LUMO with high energy, and in the second reduction step an unstable  $4n$  dianion is generated.

Consequently, the reduction of  $[4n]$ annulenes should be observed at relatively positive potentials with small  $\Delta E^0$  separations for the dianion formation, while the reduction of the  $[4n + 2]$ annulenes should occur at more negative potentials with large  $\Delta E^0$  separations for the dianion formation. This is exactly what is observed in (see Table 1). Although benzene [37, 38], the classical Hückel aromatic with  $4 \times 1 + 2 = 6$   $\pi$ -electrons, is reduced at  $-3.42$  V (vs. Ag/AgCl), the reduction of the [8]annulene COT occurs at  $-1.81$  V. Similarly, the [16]annulene (3) [67, 68] is more easily reduced than the corresponding [18]annulene (4) [69], although the reduction of the larger  $\pi$ -systems should be more favorable for electrostatic reasons.

For larger annulenes, even the reduction to tetraanions is possible [47, 75–77]. This is especially favorable for the neutral  $4n + 2$  species, which, after the injection of four electrons, reform a stabilized  $4n + 2$   $\pi$ -system. On the other hand, the existence of four excess charges in one molecule gives rise to strong electron repulsion. It can only be shielded by ion pairing that drives the formation of the tetraanion to a potential sufficiently positive for reduction to occur within the stability range of the solvent-electrolyte system. Thus, the electrochemical reduction of

Tab. 1 Redox potentials  $E^0$  (in volt) for the reduction of aromatic and olefinic hydrocarbons

Compounds	$E^0_{R/R^-}$	$E^0_{R^-/R^{2-}}$	$E^0_{R_2^{2-}/R_3^{3-}}$	$E^0_{R^{3-}/R_4}$	References
Benzene <sup>a</sup>	−3.42	—	—	—	35, 37
Naphthalene <sup>a</sup>	−2.53	—	—	—	35
Anthracene <sup>a</sup>	−2.04	−2.64	—	—	35
Chrysene <sup>b</sup>	−2.27	−2.77	—	—	9
Corenene <sup>b</sup>	−2.07	−2.72	—	—	9
1,2-benzanthracene <sup>b</sup>	−2.05	−2.67	—	—	9
Phenanthrene <sup>a</sup>	−2.49	−3.13	—	—	35
Triphenylene <sup>a</sup>	−2.42	−2.97	—	—	35
Pyrene <sup>a</sup>	−2.29	−2.91	—	—	35
Biphenyl <sup>c</sup>	−2.68	−3.18	—	—	12
<i>p</i> -terphenyl <sup>a</sup>	−2.40	−2.70	—	—	35
<i>o</i> -terphenyl	−2.62	−2.72	—	—	70
Quaterphenyl <sup>a</sup>	−2.28	−2.455	—	—	35
Stilbene <sup>a</sup>	−2.26	−2.72	—	—	35
Bianthryl <sup>a</sup>	−1.92	−2.14	−2.82	−3.17	35
Biphenanthryl <sup>a</sup>	−2.35	−2.51	−3.23	—	35
Decacyclene <sup>c</sup>	−1.74	−2.14	−2.35	−2.68 (−2.88)	27
2,2'-distyryl-biphenyl <sup>a</sup>	−2.12	−2.21	−2.81	−3.13	71
4,4'-distyryl-biphenyl <sup>c</sup>	−2.30	−2.52	−3.06	—	71
<i>p</i> -oligophenylenevinylene ( <i>n</i> = 1) <sup>a</sup>	−2.00	−2.24	—	—	31
( <i>n</i> = 2) <sup>a</sup>	−1.86	−1.97	−2.79	−3.10	226
( <i>n</i> = 3) <sup>a</sup>	−1.85	−1.91	−2.46	−2.88	31
Acepleiadylene <sup>c</sup>	−1.85	−2.51	−3.11	−3.14	47
COT <sup>d</sup>	−1.81	−1.94	—	—	59
[12]annulene <sup>e</sup>	−1.35	−2.00	—	—	72
1,7-methano[12]annulene <sup>f</sup>	−1.51	−1.84	—	—	73
15,16-dihdropyrene[14]annulene) <sup>g</sup>	−2.22	−3.01	—	—	64
[16]annulene <sup>f</sup>	−1.27	−1.56	—	—	67
[18]annulene <sup>f</sup>	−1.60	−1.94	—	—	69
Heptalene <sup>f</sup>	−1.49	−2.19	—	—	74
C <sub>60</sub> <sup>h</sup>	−0.98	−1.37	−1.87	−2.35 (−2.85, −3.26)	14
C <sub>70</sub> <sup>h</sup>	−0.97	−1.34	−1.78	−2.21 (−2.70, −3.10)	14

<sup>a</sup> Cyclic voltammetry was performed at a Pt electrode with solutions of  $10^{-3}$ – $10^{-4}$  M in substrate. All potentials are expressed in V versus Ag/AgCl; solvent: dimethylamine-TBABr, temperature between −40 and −65 °C.

<sup>b</sup> DMF-Me<sub>4</sub>NBr, potentials versus Ag/AgCl (corrected from SCE).

<sup>c</sup> THF-NaBPh<sub>4</sub> or LiBPh<sub>4</sub>, potentials versus Ag/AgCl, in brackets potentials for penta- and hexaanion formation.

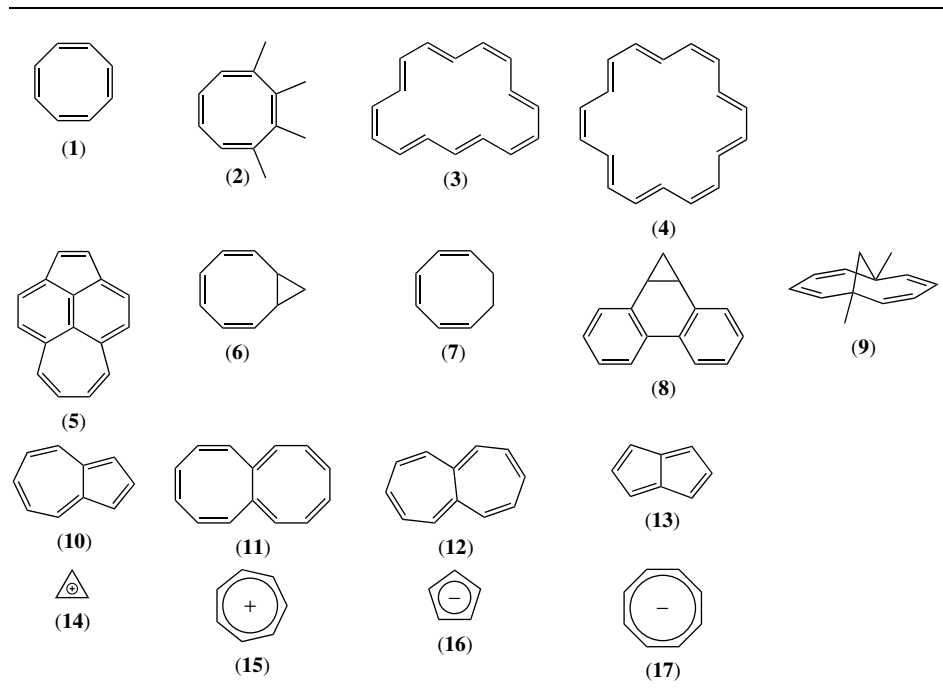
<sup>d</sup> ACN-TEAP, potentials versus Ag/AgCl (corrected from SCE).

<sup>e</sup> THF-TBAClO<sub>4</sub>, potentials versus Hg pool.

<sup>f</sup> DMF-TBAClO<sub>4</sub>, potentials versus Ag/AgCl (corrected from SCE).

<sup>g</sup> DMF-TBAClO<sub>4</sub>, potentials versus Ag/0.1 M AgNO<sub>3</sub>.

<sup>h</sup> Toluene/ACN-TBAPF<sub>6</sub>, potentials vs. Fc/Fc<sup>+</sup> at −10 °C, in brackets potentials for penta- and hexaanion formation.

**Tab. 2** Structure formula of annulenes and cyclic conjugated systems (1–17)

acepleiadylene (5) to its tetraanion was only achieved in THF in the presence of LiBPh<sub>4</sub> as a supporting electrolyte [47]. Attempts to generate the same species in the presence of tetrabutylammonium ions were unsuccessful.

Several studies have been published concerning the problem of homoaromaticity and its influence on reduction potentials. The term “homoaromaticity” is applied to cyclic resonance-stabilized systems where a carbon–carbon double bond is replaced by a cyclopropane ring, or a saturated carbon atom is introduced into the conjugated chain. Paquette et al. investigated the reduction of *cis*-bicyclo- [6.1.0]-nona-2,4,6-triene (6) and similar derivatives [73]. They found that it is reduced (–2.59, –2.79 V) more negatively than (1) but more easily than cyclooctatriene (7) (–2.77 V), thus proving a degree of homoconjugative

stabilization in the radical anion of (6). Analogously, dibenzonorcoradiene (8) is easier to reduce than biphenyl, but harder to reduce than phenanthrene [41]. The electrochemical reduction of 1,6-dimethylbicyclo[4.4.1]undeca-2,4,7,9-tetraene (9) was also interpreted in terms of homoconjugation in the anions. The reduction appears to proceed via an ECE scheme where the initial reduction produces an unstable radical anion, which undergoes a structural change, producing another radical anion with a conjugatively stabilized *p*-system. The second electron transfer (ET) occurs more easily than the first one, thus producing a typical “two-electron” reduction [78, 79].

Of the condensed nonbenzenoid aromatics, azulene (10) has gained greatest popularity [80]. Although it is an isomer of naphthalene, its electrochemical behavior

differs markedly from its benzenoid counterpart. Azulene is reversibly reduced at  $-1.62$  V (vs. Ag/AgCl), while the reduction of naphthalene takes place at  $-2.53$  V [35, 81]. Furthermore, the anion of azulene is extremely stable against the attack of protons [81]. The bicyclus octalene (11) has 14  $\pi$ -electrons.  $H^1$ -NMR data show that it possesses a nonplanar structure with polyolefinic properties and therefore resembles its monocyclic relative COT. Polarography and cyclic voltammetry reveal that it is reversibly reduced to the radical anion at  $E_{1/2} = -1.67$  V and, rather surprisingly, in a three-electron process at  $E_{1/2} = -1.70$  V to its stable tetraanion [82, 83]. This unusual behavior can be only explained by assuming that the energy gain from delocalization in the planar 18  $\pi$ -system is higher than torsional and electronic repulsions. Other bicyclic systems such as heptalene (12) [74] and pentalene (13) [84] can also be reduced to their respective anions. Nevertheless, in comparison with equivalent monocyclic  $p$ -systems such as (1), their reduction behavior is still not properly understood.

A further group of nonbenzenoid aromatics is the series of odd-membered cations and anions such as cyclopropenium (14) and tropylium cations (15) as well as cyclopentadienyl (16) and cyclononatetracenyl anions (17). Regarding the arguments for the properties of Hückel-like  $4n + 2$   $\pi$ -systems, all these molecules should be energetically stabilized. Obviously, this is not fulfilled in all cases. The tropylium cation (15) can be reduced in a one-electron step to the tropyli radical even at  $E = +0.06$  V vs. SCE [85, 86]. The radical is unstable and rapidly dimerizes to bitropyl. The heptaphenyl tropylium radical is stable on the voltammetric timescale, but decays

slowly producing a dimeric-species involving coupling via the phenyl groups [87]. Similarly, 2,3 diphenylethyl-cyclopropenyl is irreversibly reduced in  $CH_3CN$  at  $E_p = -0.04$  V. On the other hand, the reduction of trimethylcyclopropenyl occurs at  $-1.32$  V, which is in better agreement with the prediction of the Hückel theory [88–91]. Otherwise, relatively positive reduction potentials seem to be typical for most carbocations [92, 93]. The easy reducibility is probably caused by the excess positive charge.

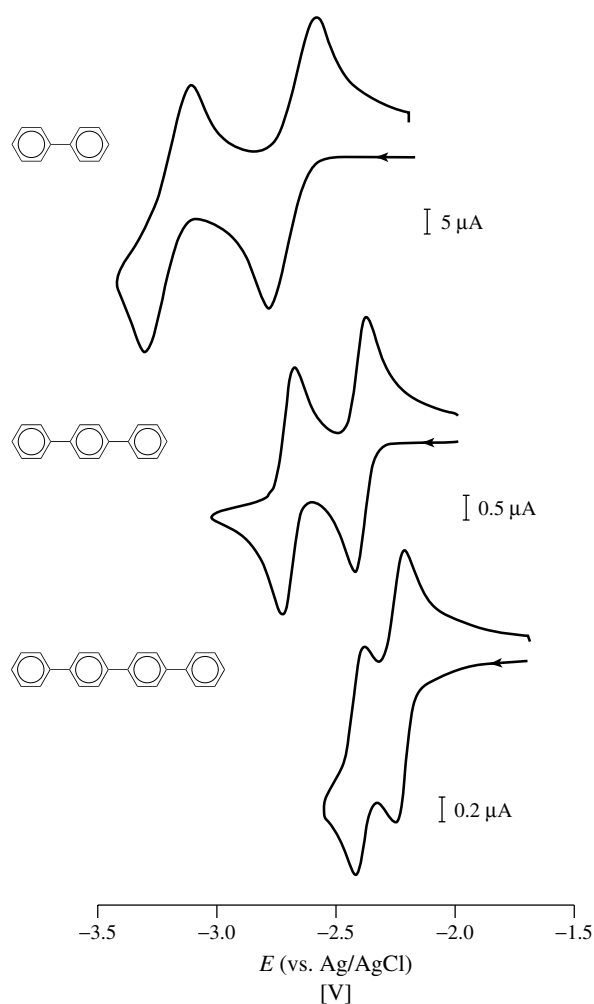
The discovery of the metal-like properties of conducting polymers has once again focused attention on the oxidation and reduction characteristics of aromatic systems. It turns out that most of these conducting materials consist of chainlike connected carbocyclic or heterocyclic aromatics [94–97].

The simplest molecules in these series are dimers, followed by oligomers of increasing chain length and polymers. As the current–voltage curves of polymers are difficult to interpret, quantitative information on the redox properties of such systems was preferentially obtained from reduction experiments with dimers and defined oligomers. Redox data on dimers are available for biphenyl [12–14], bianthryl [53, 98, 99], biazulenyl [100] bicyclooctatetraenyl [101], and dimeric [19] annulenes [102]. All species can be reduced to at least their respective dianions. In the case of bianthryl and bicyclooctatetraene, even the formation of tetraanions has been observed. In general, the observed redox potentials of the monoanion formation differ significantly from those of the monomeric parent compounds and shift to less negative values. This is evidence of conjugative stabilization in the charged oligomeric unit [103]. On the other hand, large  $\Delta E^0$  separations

between the redox potentials of the respective mono- and dianions indicate strong electron repulsion between both electrophores. A typical example is biphenyl, which is reduced to the radical anion at  $-2.68$  V and to the dianion at  $-3.18$  V (Fig. 1) [12–14, 35], whereas the reduction of the monomeric benzene occurs at  $-3.42$  V [37, 38]. Obviously, the biphenyl

anion has gained a considerable amount of conjugative stabilization energy, while in the dianion, strong electron–electron repulsion dominates.

During the last decade, the concept of the oligomeric approach has been developed, which includes electrochemical studies of a great number of monodisperse chainlike hydrocarbons. Voltammetric

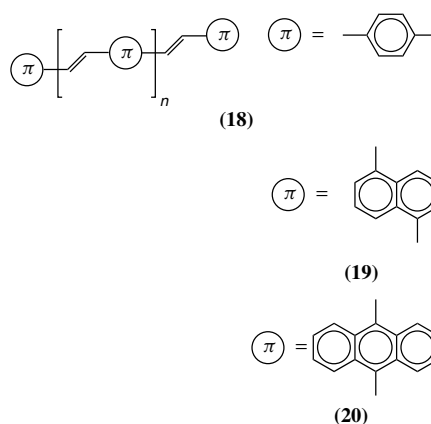


**Fig. 1** Cyclic voltammograms for the reduction of biphenyl ( $T = -70^\circ\text{C}$ ,  $\nu = 2\text{ Vs}^{-1}$ ); terphenyl ( $T = -40^\circ\text{C}$ ,  $\nu = 100\text{ mVs}^{-1}$ ); and quaterphenyl ( $T = -5^\circ\text{C}$ ,  $\nu = 100\text{ mVs}^{-1}$ ) in dimethylamine/0.1 M TBABr.

measurements carried out with several oligomers of the *p*-phenylenevinylene (18,  $n = 1 - 6$ ) [30, 31] and the *p*-phenylene [35] series, respectively, clearly demonstrate that the reduction properties of such oligomers and polymers depend on the chain length of the systems. Three effects are especially significant. First, the potentials of already existing redox states shift to less negative values when the next higher homologue is reduced. Obviously, the redox energies of different states gradually approach a common convergence limit with increasing chain length. Second, the redox states degenerate pairwise with increasing chain length, and third, in agreement with expectations, adding successive monomeric subunits in the molecular chain enlarges the number of accessible redox states (Fig. 1). However, the energetic gap increases strongly between the lowest and the highest charged states. From these results, it becomes clear that in conducting polymers like poly-*p*-phenylene, a reasonable number of energetically low-lying redox states are degenerated, followed by redox states with increasingly higher energies [12]. This explains the broad, plateaulike waves that are so often characteristic of the potential range following the peaklike main wave in voltammetric experiments.

Quite a large number of publications that have appeared since that time support these findings, but have also introduced new aspects that show the complexity of redox mechanisms in such systems [104]. Very systematic studies have been carried out by Müllen et al., who have varied, in chainlike oligomers, the type and coupling position of the electroactive monomeric building blocks and the modes of linkage, using both saturated and unsaturated species with different lengths [105, 106]. Their results clearly show that the size

of the aromatic subunit, the overall number of  $\pi$ -electrons, the  $\pi$ -topology, and steric effects are important factors for the redox behavior of all these species. Thus in the series of oligoarylenevinylenes, replacement of the phenylene unit by larger arylene units enlarges the charge capacity of the respective systems. While the *p*-oligophenylenevinylene (18) ( $n = 1$ ) with three phenylene units can be electrochemically reduced up to a dianion, the corresponding naphthalene derivative (19) ( $n = 1$ ) reaches a trianion level and the anthracene derivative (20) ( $n = 1$ ) reaches even a hexaanion state [105–108].

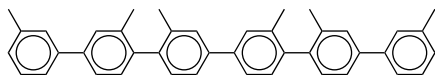


An important reason for this phenomenon is the fact that the better the excess charges in condensed aromatic units are stabilized, the larger the  $\pi$ -structure is. Of course, the energetic stabilization of an excess charge in a large aromatic unit diminishes the trend for its delocalization and Coulombic repulsion effects along the chain. Therefore, the shift of the first redox potential dependent on the chain length is less pronounced for the naphthalene and anthracene derivatives than for the phenylene system or the pure oligoene chain, and, the separation between successive redox steps becomes substantially smaller as the number of

**Fig. 2** Reduction of *p*-oligophenylenevinylenes (**18**),  $T = -65^\circ\text{C}$ ,  $\nu = 100\text{ mVs}^{-1}$ ;  $n = 3$  in DMA/TBABr,  $n = 4, 5$  in THF/TBAPF<sub>6</sub>, (dashed line: background current). (From Ref. [31].)

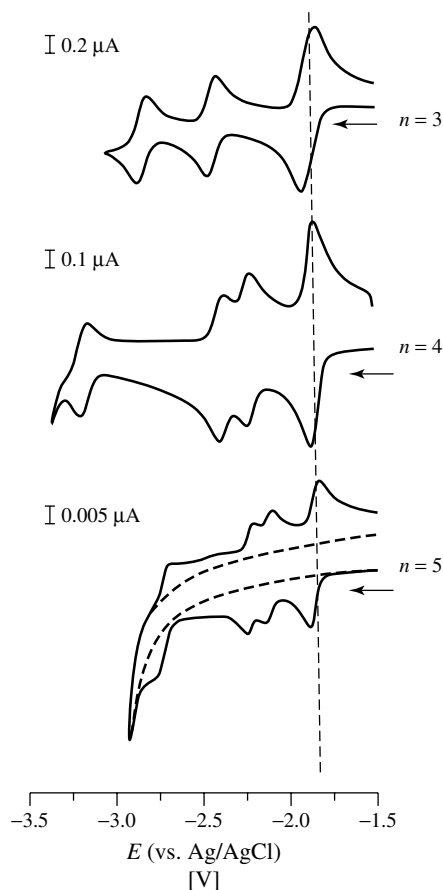
$\pi$ -subunits increases (Fig. 2). A further influence on the redox properties results from the coupling pattern between the vinylene and the arylene units. Measurements on para-, meta-, and ortho-coupled phenylenevinylenes reveal that it is more difficult to charge meta- and ortho-homologues than the corresponding para-homologues. However, the conjugative uncoupling of two metagroups in a phenylene ring diminishes Coulombic repulsion, and therefore the energetic separation between successive redox steps decreases.

The redox properties of oligo-*p*-phenylenes change when sterically relevant methyl groups exist in the central rings. Thus, in comparison with the unsubstituted oligomers in methyl-substituted homologues, for example (**21**), with four or more phenylene units, the first reductive redox step is shifted to a more negative potential and a two-electron wave appears in the voltammetric response [109]. This can be interpreted by assuming that, because of steric hindrance, additional energy is needed to planarize the phenylene chain for the first electron transfer, and that the second electron is able to enter the then flattened system at the same or even a more positive potential.



(**21**)

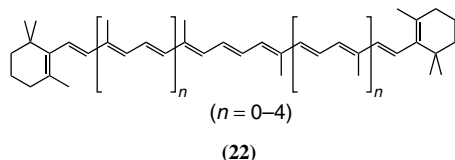
Within the hydrocarbons containing olefinic double bonds, polyacetylene (PA) is the most thoroughly studied system. The great interest results from its extremely



high conductivity, up to  $100\,000\text{ S cm}^{-1}$ , which emerges on oxidative or reductive charging of the polymer [94–96, 110]. As already found by MacDiarmid [10], PA can be reversibly reduced to a polyanionic material.

Despite the great interest in PA, there are only a few electrochemical studies of monodisperse oligoene systems. The reason is the high reactivity of doped alkyl-substituted oligoenes in the presence of nucleophiles or electrophiles. Normally, these oligomers consist of a carbon chain with alternating single and double bonds and two terminating groups, which are

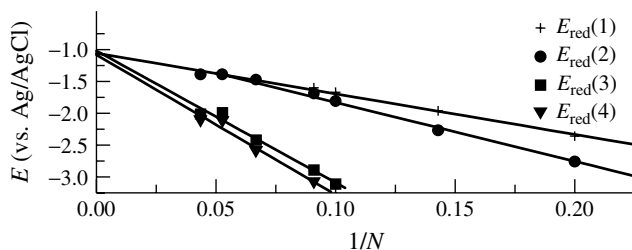
equal in most cases. Thus, a *t*-butyl group [111–114] or, in the case of  $\alpha$ - and  $\beta$ -carotenoids, a cyclohexenyl group [115, 116], has been used, while phenyl or other aromatic substituents have been used as end groups in the so-called arylpolyenes [117]. The chain length  $n$  ( $n$  = number of double bonds in the conjugated system) again determines the electronic properties of the oligomers.



A series of carotenes [118, 119] (22) (number of double bonds  $N = 5$  and higher) may serve as an illustration of this redox behavior. For all related states within the series, a strictly linear dependence of the redox potentials versus the chain length of the oligomers is observed (Fig. 3). As can be seen, the reduction for the oligomer with  $N = 5$  starts with two well-separated one-electron redox steps. With increasing chain length, there are additional weakly separated redox pairs. The potential gaps in the single pairs and between them decrease. Thus, two-electron transfer steps are most

likely to occur for the longer polyenes ( $n \geq 19$ ).

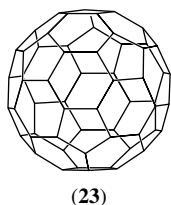
A further interesting point concerns unusually small differences between the reduction potentials of mono- and dianions of some molecules containing olefinic double bonds. Although in *trans*-stilbene the formation of the dianion occurs approximately 500 mV negatively to the radical anion formation [35, 120], for tetraphenylethylene the standard potentials for the  $R/R^-$  couple ( $E_{R/R^-}^0$ ) and the  $R^-/R^{2-}$  couple ( $E_{R^-/R^{2-}}^0$ ) are very closely spaced. The  $\Delta E^0$  separation amounts in HMPA to –138 mV, in DMF to –35 mV, and in ACN reaches even positive values of approximately 150 mV [121–123]. Consequently, the disproportionation constant  $K$  varies within five orders of magnitude, a phenomenon mainly ascribed to increasing ion pairing ongoing from HMPA to ACN [123]. Nevertheless, intermolecular phenomena alone are not sufficient to explain the dramatic decrease of the  $\Delta E^0$  separation in tetraphenylethylenes in comparison to stilbene. It is now generally accepted that structural changes involving twisting of the ethylenic bond and accompanying the dianion formation are the main reasons for the energetic stabilization of the dianion of tetraphenylethylene [124].



**Fig. 3** Apparent reduction potentials of (22) vs.  $1/N$  ( $N$ : number of double bonds), from CV measurements in dimethylamine/TBABr,  $T = -60^\circ\text{C}$ ,  $\nu = 100 \text{ mVs}^{-1}$ .



Similar effects are also observed with 9,9'-bifluorenylidene [125].



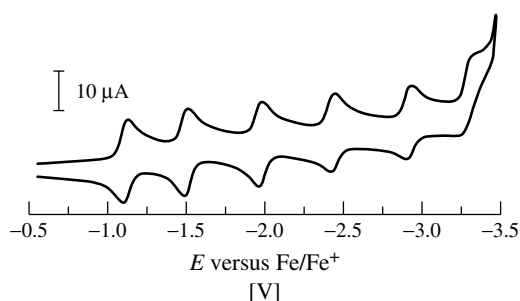
A new class of conjugated hydrocarbons is that of the fullerenes [11], which represent an allotropic modification of graphite. Their electrochemistry has been studied in great detail during the last decade [126]. The basic entity within this series is the  $C_{60}$  molecule (23). Because of its high electron affinity, it can be reduced up to its hexaanion (Fig. 4) [14, 127]. Solid-state measurements indicate that the radical anion of  $C_{60}$  reversibly dimerizes. NMR measurements confirm a  $\sigma$ -bond formation between two radical anion moieties [128, 129].

#### 4.2.3

##### Electron-transfer Kinetics

Conversion of an oxidized species into the reduced form and vice versa requires the reorganization of the solvent in the immediate neighborhood of the reactant, together with some structural changes within the reactant. In the case

of heterogeneous charge transfer, additional double layer effects are operative, which depend, inter alia, on type and concentration of the supporting electrolyte, but may also be influenced by the electrode material used as well as adsorption phenomena. Theoretical concepts have been developed by Hush, Marcus, and Dogonadze [130–134]. Applications of the Marcus theory to problems in organic electrochemistry have been discussed by Eberson [135]. As most studies on the reduction of hydrocarbons were carried out in aprotic solvents in the presence of excess supporting electrolyte, double-layer influences on electron-transfer kinetics were usually regarded as less important [2, 136]. Normally, the rates of heterogeneous ET to aromatic and olefinic hydrocarbons are high. It is assumed that the activation barrier is mainly caused by the solvent reorganization. Such reactions are termed outer-sphere processes. Reductions of systems that require in addition a large conformational energy change in the transition state are rare [137]. The most widely discussed example from this class is the COT molecule (1), which exhibits a slow heterogeneous ET for the anion formation, while the rate between the anion and the dianion is significantly faster [56–58, 63]. In the literature it has been suggested that upon reduction the tube-shaped ring passes through



**Fig. 4** Voltammogram for the reduction of  $C_{60}$  in toluene/acetonitrile 0.1 M TBABr;  $\nu = 100 \text{ mVs}^{-1}$ ,  $T = -10^\circ\text{C}$ . (From Ref. [14].)

at least a partially flattened transition state to form a planar anion radical. The experimentally determined activation energy (10–11 kcal mole<sup>-1</sup>), which is similar to the activation energy of ring inversion (13.7 kcal mole<sup>-1</sup>), has been interpreted as supporting evidence [136]. However, independent studies by Fry et al. [46] and Parker et al. [138] have shown that the rate constant for the first reduction step increased as the cation size of the supporting electrolyte decreased from tetraheptylammonium to tetramethylammonium. This contradicts the assumption of pure structural reorganization effects during the reduction of (1) and points to adsorption phenomena of the electrolyte cations. Moreover, in a very recent EPR investigation, homogeneous rate constants for the COT<sup>-</sup>/COT electron self-exchange process were found to be close to the diffusion limit ( $\sim 10^9$  M<sup>-1</sup>s<sup>-1</sup>) [139]. It seems that the influence of structural reorganization on the activation process was overestimated in earlier works. In a recent paper, Evans discussed electron-transfer reactions of some fully  $\alpha$ -methylated cycloalkane-1,2-diones in which the contributions of internal reorganization are substantial [140]. In that case, both homogeneous (self-exchange) and heterogeneous electron-transfer rate constants are affected by the structural differences among these diketones.

Tetraphenylethylene is another example of a slow charge transfer. Here, the radical anion formation is fast, whereas the second charge transfer is slow [121]. In agreement with the thermodynamic findings, the second charge transfer suggests that considerable structural reorganization occurs at the activation barrier of the second reduction step. Nor is it yet clear as to what extent solvent reorganization also influences the activation energy [121].

### 4.3

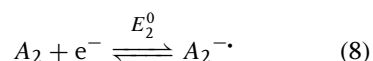
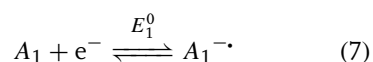
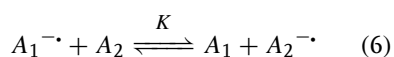
#### Chemical Reactions of Electrogenerated Anions

With one or more electrons in antibonding orbitals, reduced hydrocarbons are a highly reactive species capable of both inter- and intramolecular reactions. The preferred pathway of the follow-up reaction depends not only on the electronic and steric structure of the reduced species but also on its chemical environment, especially on the counterion and the solvent.

##### 4.3.1

#### Homogeneous Electron Transfer

The most elementary follow-up reaction is the homogeneous ET to another solution species, which may be identical with the donor molecule itself [52]. The equilibria of homogeneous ET reactions are governed by the standard potentials of the involved redox couples and are easily calculated with given data according to Eqs. (6–9):

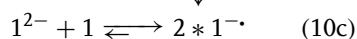
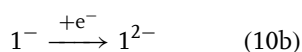
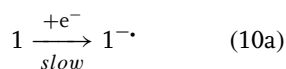


$$\frac{RT}{F} \ln K = E_2^0 - E_1^0 \quad (9)$$

The kinetics are much more complex and depend on the reorganization of the molecular framework [141], the solvation shell, and the electrostatic interaction. A semi-quantitative estimation of rate constants may be obtained with the well-known Marcus equation [142]. The calculated data compare quite well with experimental values. Most of the experimental hydrocarbon

data have been provided by Szwarc and his school [5]. The state of the art has been discussed in an excellent review [135].

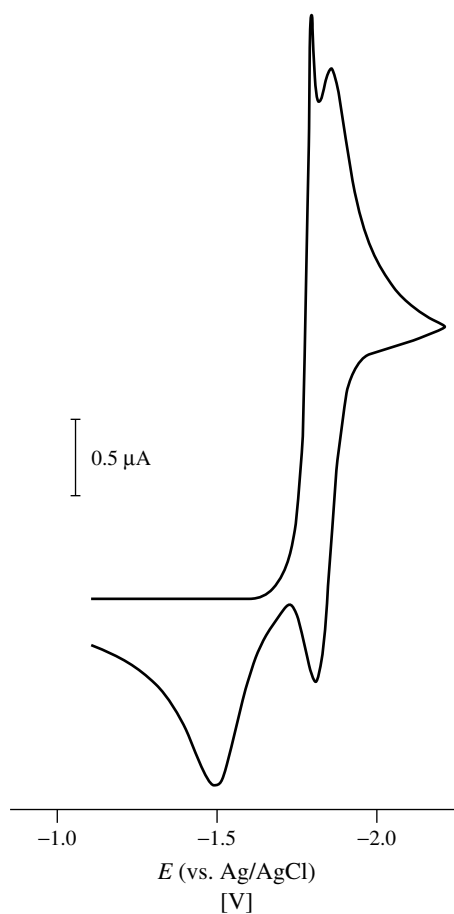
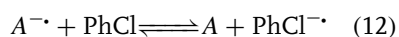
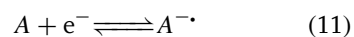
Homogeneous ET has to be taken into account whenever dealing with electrode reactions, as was pointed out by Marcoux [143]. It is of special importance when the heterogeneous ET is slow, providing an additional and more effective pathway to reduced species.



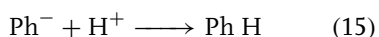
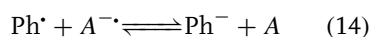
The homogeneous rate constant for the second charge transfer in (1), similar to the heterogeneous charge transfer, is considerably larger than the first one. The difference greatly depends on the experimental conditions. It has been shown by cyclic voltammetry in super-dry THF/TBAPF<sub>6</sub> that the first ET can be catalyzed by the dianion of COT itself in a homogeneous synproportionation (Eq. 10), giving rise to a catalytic spike (Fig. 5). The mechanism has been confirmed by digital simulation [144].

Quite often the resulting anionic species undergoes a fast follow-up reaction. Thus, homogeneous ET becomes a crucial step in many electrode reactions: a well-known example is the cathodic reduction of organic halides. In mercury, heterogeneous ET to most halides is slow. This kinetic

barrier may be circumvented by addition of aromatic hydrocarbons such as phenanthrene [145], anthracene [146], and naphthalene [145]. These compounds are easily reduced at the cathode and transfer their excess electron to the organic halide. The resulting halide anion radical undergoes a fast follow-up reaction. The whole reaction sequence is as follows:



**Fig. 5** Spike effect during the reduction of (1) indicating an (autocatalytic) homogeneous generation of the radical anion of (1), cyclic voltammetry in THF/0.1 M TBAPF<sub>6</sub>,  $T = 20^\circ\text{C}$ ,  $\nu = 100 \text{ mVs}^{-1}$ .



Regeneration of hydrocarbon in Eqs. (12 and 14) makes the process catalytic.

The reduction of organic halides in the presence of aromatic hydrocarbons, the subject of detailed kinetic studies, provide rate constants for the homogeneous ET [147–150] and the follow-up reaction [151]. The theoretical basis for this kind of experiment (“homogeneous redox catalysis”) was laid by Savéant’s group in a series of papers during the years 1978–80 [152–157]. Homogeneous ET also plays an important role in the protonation of anion radicals [158].

When an anion radical undergoes heterogeneous ET, formation of the neutral molecule in the ground state is strongly favored over formation of an excited state [159, 160]. No such restriction applies to homogeneous ET, which, if sufficiently exothermic, may yield excited states of hydrocarbons. One may naively suppose that an electron is removed from the bonding molecular orbital of highest energy to give either the first excited singlet or triplet; electrochemiluminescence [161] may then occur.

The emission observed is usually the fluorescent band of the hydrocarbon, corresponding to the decay of the first excited singlet. The energy released by homogeneous electron transfer is given by the difference between the redox potentials of donor and acceptor plus a small entropy term [162], and in many cases of electrochemiluminescence falls short of the energy needed to populate the singlet state directly. In these “energy-deficient” cases, there is sufficient energy to populate the lowest triplet state, and singlets can

then be produced by diffusion-controlled triplet–triplet annihilation. Emissions observed at wavelengths other than that of the main singlet have been ascribed to excited dimers (excimers) [163, 164], excited charge-transfer complexes (exciplexes) [165–167], and fluorescent products of radical-ion decay. Acceptors in electrochemiluminescence may be the corresponding hydrocarbon radical cations, added alkyl halides [168] or benzoyl peroxide [169, 170], or adventitious impurities, which need be present at only  $10^{-7}$  M levels. The experimental technique for the method is demanding [171].

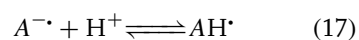
#### 4.3.2

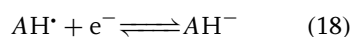
##### Electrophilic and Related Reactions

##### 4.3.2.1 Protonation

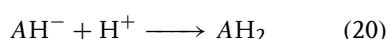
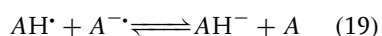
Under protic conditions, aromatic hydrocarbons and compounds with activated double bonds usually undergo Birch-like reactions [172]. The reaction sequence has been elucidated by the classical work of Hoijsink [15–17, 173, 174], who used the HMO theory to rationalize both chemical and electrochemical steps.

The anion radical produced by homogeneous ET is monoprotonated to give a Wheland-like  $\pi$ -radical. It readily accepts another electron because its bonding or nonbonding SOMO (single occupied molecular orbital) always has a lower energy than the antibonding LUMO of the parent hydrocarbon. The second ET preferably occurs by disproportionation [158]. In a fast follow-up reaction, the resulting carbanion takes another proton to eventually yield the final dihydroproduct (Eqs. 16–20):





or



If the reduction potential of the resulting dihydroproduct is sufficiently positive, it can undergo another reduction cycle. One of many examples is provided by the reduction of benz[a]anthracene in 75% aqueous dioxane [15–17, 175].

Because of its general importance to organic electrochemistry, the reaction scheme just outlined has been the subject of detailed mechanistic studies [21, 176–182, 183]. As a model reaction, protonation of anthracene anion radicals by phenol in DMF has been selected. Of five limiting kinetic variants,  $\text{ECE}_{\text{rev}}$ ,  $\text{ECE}_{\text{irr}}$ ,  $\text{DISP1}$ ,  $\text{DISP2}$ , and  $\text{DISP3}$ , the favored pathway was found to be  $\text{DISP1}$  [158]. It involves the protonation of the anion radical as the rate-determining step (Eq. 17), followed by homogeneous ET between the anion radical and the protonated anion radical (Eq. 19), yielding the monohydrogenated anion, which is itself rapidly and irreversibly protonated to the final dihydrogenated product. This mechanism has been disputed because of apparent deviations from predicted reaction orders [176–179]. Recently, it turned out that the inconsistencies are largely due to the formation of homoconjugated complexes between phenol and the phenolate anion [181]. Thus,  $\text{DISP1}$  now seems to be generally accepted.

The rate-determining step of the  $\text{DISP1}$  mechanism, the protonation of the radical anion, largely depends on its electronic structure. As a guideline, LUMO energies of the parent hydrocarbon may

be used [42, 184]. The attempt to correlate rate constants with highest local charge densities failed [185]. Therefore, Eberson suggested the application of the Dewar–Zimmermann rules [186].

Under highly protic conditions, the major products of cathodic reductions of cyclic conjugated hydrocarbons are usually dihydro derivatives [56, 57, 187]. In 2-methoxyethanol, for example, naphthalene yields 1,4-dihydronaphthalene [187] and COT mainly provides 1,3,6-cyclooctatriene [56, 57].

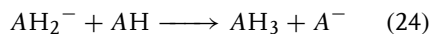
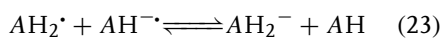
These findings are in contrast to thermodynamics favoring, in the case of naphthalene, the formation of conjugated 1,2-isomers. Therefore, kinetic control has to be assumed. The site selectivity for the first as well as the second protonation step has been predicted by HMO theory. One approach refers to local charge densities [188]; the other one uses localization energies as a reactivity index [189]. In any event, the inductive effect of the methylene group, formed in the first protonation step, has to be taken into account if two sites provide comparable reactivity indices.

These techniques proved to be successful for the majority of the hydrocarbons, but they failed for some compounds such as phenanthrene, terphenyl, or quaterphenyl. The failure has been interpreted by the effect of the electric field on the charge distribution [190]. Actually, these molecules have strongly anisotropic polarizabilities. In a more recent study, it was demonstrated that the isomeric ratio also depends on the counterion [191].

Under nominally aprotic conditions, 1,2-protonation dominates in naphthalene. Reduction of naphthalene in anhydrous acetonitrile containing tetraethylammonium *p*-toluenesulfonate yields 1,2-dihydronaphthalene, which is subsequently

reduced to tetralin [192]. Similarly, reduction of (1) in anhydrous DMF gives 1,3,5-cyclooctatriene almost exclusively [56, 57]. The formation of the thermodynamically more stable products is most probably because of base-catalyzed isomerization.

An interesting situation arises from the reduction of CH-acidic hydrocarbons because these compounds can undergo self-protonation. Actually, a voltammetric investigation of 1,3-diphenyl-2-methylindene and 4,5-methylenepheneanthrene in DMF/TBAP or DMSO/TBAP clearly indicated a DISP1 mechanism, analogous to that described earlier [193]. Similar results have been obtained for variously substituted indenenes in which the stoichiometry is in perfect agreement with a two-electron, two-proton reduction process involving one-third starting material under self-protonation conditions, the remaining two-thirds acting as a proton donor [194]. Generally, under self-protonation conditions the DISP1 pathway operates (Eqs. 21–24) in which the protonation reaction between the radical anion ( $AH^{\cdot-}$ ) and the neutral species ( $AH$ ) is the rate-determining step.



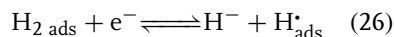
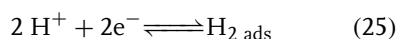
On the other hand, reduction of fluorene [195, 196] results in a homolytic cleavage of the CH bond (discussed in Sect. 4.3.4.2).

To study the stereochemistry of protonation reactions, substituted indenenes have been cathodically reduced in DMF/TBAP with water or phenol being added [194, 197, 198]. In the presence of water, a

formal “anti” addition of protons was observed, whereas addition of phenol led to the prevalent formation of products, formally derived from “syn” protonation. Obviously, steric effects and/or acidities of the proton donor and the dihydropyridine product play an important role.

Quite often, ion pairing causes a substantial positive shift of the reduction potential. For electrostatic reasons, the shift is especially large for the formation of higher valency ions. Therefore, with increasing interaction of the counterion, di- and polyanion formation becomes thermodynamically more favorable. Under these conditions, cathodic reduction immediately produces dianions via disproportionation and heterogeneous ET. Because of their high basicity, the dianions readily undergo protonation. Such a dianion mechanism was observed when tetraphenylethylene was reduced in acetonitrile-TEAP in the presence of water or alcohols. Kinetic measurements led to a mixed-order rate law, rationalized by the existence of a hydrogen-bonded complex between the ion-paired dianion and the proton donor [123, 124].

The classical Hoijsink mechanism and the dianion mechanism have been observed at electrodes with a high hydrogen overvoltage, such as mercury. If mercury is replaced by platinum with its low hydrogen overvoltage, a radical pathway seems to be favored [199], which is closely related to catalytic hydrogenations of hydrocarbons. Spectroelectrochemical experiments provided evidence for an additional hydride mechanism (Eqs. 25–27) [200].:



These results illustrate that the reaction sequence and the stereochemistry of

cathodic hydrogenations are controlled by the solvent, electrolyte, proton donor, electrode material, and so on. Thus, with increasing mechanistic knowledge, electrochemistry offers the chance to realize highly selective hydrogenations.

The addition of protons is certainly the most common “nucleophilic” reaction of reduced hydrocarbon species due to the almost ubiquitous availability of proton donors, which may or not be wanted. However, under strictly aprotic conditions it is also possible to add other electrophilic reagents such as alkyl halides, acyl halides, CO<sub>2</sub>, and SO<sub>2</sub>.

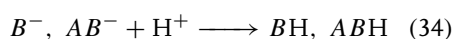
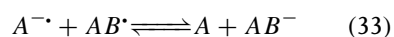
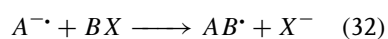
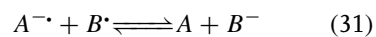
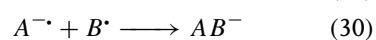
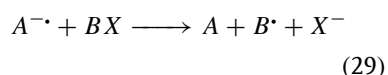
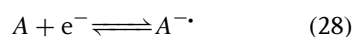
#### 4.3.2.2 Alkylation

The addition of alkyl halides to aromatic anion radicals, generated by alkalimetal reduction in ethereal solvents, was already known in the 1950s [201] and was reviewed by Garst in 1971 [202]. The first electrochemical analogue was observed by Lund et al. [203]. These authors cathodically reduced hydrocarbons such as naphthalene, anthracene, stilbene [145, 146], and perylene [147–150] in the presence of alkyl halides and isolated hydrogenated and alkylated products. Similar reactions are observed when the halides are replaced by ammonium or sulfonium [204].

These alkylations can be looked upon as aliphatic nucleophilic substitutions, usually thought to proceed via S<sub>N</sub>1, S<sub>N</sub>2, or hybrids of these mechanisms. However, in recent years more and more evidence for a single-electron transfer (SET) mechanism, represented in Eqs. (28–31), was obtained, and it was suggested that S<sub>N</sub>2 and SET are just limiting cases of the same single-electron transfer mechanism [205, 206]. The SET pathway involves first a transfer of an electron from the nucleophile to the electrophile followed by bond formation, whereas the S<sub>N</sub>2 reaction involves a

synchronous shift of a single electron and bond formation (Eqs. 32 and 33). In addition, the generated anions may be protonated (Eq. 34).

Because of these fundamental aspects, the mechanism of cathodically induced alkylations has been the subject of detailed studies [147–150, 207]. In a stereochemical investigation it was found that racemization is much more effective than inversion. This result was interpreted as evidence of competition between the SET pathway and the S<sub>N</sub>2 mechanism, with SET being the more important route [207]. The SET mechanism is represented in Eqs. (28–34):



The rate-determining step (Eq. 29) of the SET mechanism consists of an ET concerted with a cleavage of the carbon–halide bond in the alkyl halide, and resulting in the generation of an alkyl radical. Numerous investigations have focused on the measurement of these rate constants [147–150]. As expected, the rate constant increases when the redox potential of the aromatic compound becomes more negative. The coupling step between alkyl radicals and aromatic anions is fast, with rate constants at the level of diffusion control. This indicates the lack of significant activation barriers, which consequently results in insensitivity to structural differences in the alkyl radical

and in the aromatic radical anion [208]. Moreover, radical anions with very different redox potentials ( $\Delta E_A^0 = 0.9$  V) couple with primary radicals with approximately the same rate constant. The competing  $S_N2$  mechanism Eqs. (32 and 33) may be favored if the reacting species are not too sterically hindered, and the driving force for an electron-transfer reaction is low. In general, the more positive the redox potential of the aromatic compound is or the poorer the alkylhalide is an electron acceptor, the more important the  $S_N2$  mechanism becomes [209].

#### 4.3.2.3 Acylation

Formally related reactions are observed when anthracene [210] or arylolefins [211–213] are reduced in the presence of carboxylic acid derivatives such as anhydrides, esters, amides, or nitriles. Under these conditions, mono- or diacylated compounds are obtained. It is interesting to note that the yield of acylated products largely depends on the counterion of the reduced hydrocarbon species. It is especially high when lithium is used, which is supposed to prevent hydrodimerization of the carboxylic acid by ion-pair formation. In contrast to alkylation, acylation is assumed to prefer an  $S_N2$  mechanism. However, it is not clear if the radical anion or the dianion are the reactive species. The addition of nitriles is usually followed by hydrolysis of the resulting ketimines [211–213].

#### 4.3.2.4 Addition of $CO_2$ and $SO_3$

In the pioneering papers of Wawzonek et al. [18, 214] it was demonstrated that  $CO_2$  can be added to cathodically reduced hydrocarbons to yield dihydrodicarbonylates. Examples of this kind of reaction include naphthalene [215–220], anthracene [18], 9,10-diphenylanthracene [18], phenanthrene [215, 216], butadiene [217–220], stilbene [18], and diphenyl

acetylene [217–220]. The mechanism is assumed to be analogous to that for protonation, the essential steps being nucleophilic addition by an anion radical and subsequently by an anion [221]. 1,4-Addition to naphthalene suggests that carboxylation is kinetically controlled; formation of dihydromonocarboxylates indicates competition with protonation. Mechanisms involved have  $CO_2^{\cdot-}$  to be considered for those hydrocarbons that are reduced at more negative potentials than  $CO_2$  [222], and for the electroinactive norbornadiene, which gives 3-nortricyclenecarboxylic acid [223]. Chemically  $CO_2^{\cdot-}$  formed is known to undergo typical radical addition reactions [222, 224]. Like  $CO_2$ ,  $SO_3$  adds to reduced anthracene to give 9,10-dihydroanthracenebissulfonate [215, 216].

#### 4.3.3

##### Reductive Coupling

Cathodically reduced hydrocarbons not only undergo homogeneous ET and nucleophilic attack but also coupling reactions resulting in hydrodimerization and polymerization.

Reduction of stilbene [18] or diphenylacetylene [214] in DMF yields 1,2,3,4-tetraphenylbutane, whereas phenanthrene [214] provides 9,9',10,10'-tetrahydro-9,9'-biphenanthrene. Hydrodimerization was also observed with benzalfluorene [225]. If DMF is replaced by acetonitrile, protonation completely dominates hydrodimerization [18]. In carefully dried ethers, using alkali or alkaline earth metals salts as supporting electrolyte, 1,1-diphenylethylene can be reduced cathodically to give stable solutions of 1,1,4,4-tetraphenylbutane dianions [226]. These dianions can be cleaved by flash



photolysis in the presence of excess 1,1-diphenylethylene to give transient anion radicals of 1,1-diphenylethylene. Kinetic analysis of the subsequent recombination confirmed the postulated radical–radical mechanism; the rate constant was found to be  $0.5 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$  [227]. 9-Cyanoanthracene undergoes a reversible electrodimersation with almost no side reactions, making a perfect model compound [228–233]. Again, it turned out that the dimerization follows a radical–radical mechanism. It is also interesting to note that water accelerates the dimerization. This effect was rationalized by specific solvation [233]. A careful study of the dimerization kinetics of 9-cyanoanthracene in different solvents and at low temperatures gives evidence that the coupling reaction is diffusion controlled and that its rate constant increases with increasing polarity of the solvent as predicted by the Debye–Smoluchovsky theory [234, 235]. It should be noted that several authors have suggested a more complex reaction pattern, which at least involves a two-step mechanism [236, 237]. A final decision on the validity of these different reaction paths will be a task of future research.

Many alkenes, activated by electron-withdrawing groups, readily undergo hydrodimerizations. The best-known example is the electrodimersation of acrylonitrile, the base of the commercial Monsanto process [238–240]. Evidence is presented there that the essential step is a coupling of two radical anions (radical–radical route). In a very recent study, A. J. Bard has shown, using the scanning electrochemical microscope (SECM) technique (see Volume 3, Chapter 3.3), that only the radical anions of acrylonitrile dimerize (radical–radical route) [241]. Sterically less demanding arylalkenes and dienes undergo not only dimerization but also

polymerization. Styrene is polymerized in ethers by alkali metal reduction [242] or addition of cumyl potassium [243]. The mechanism of ET-induced polymerization was extensively studied by Szwarc and his school [244–246]. It turned out that the first step is dimerization of the styrene anion radical, usually obtained by addition of sodium naphthalene. Under aprotic conditions, the resulting dianion adds to monomers, forming polymeric “living anions.” It is interesting to note that the rate of the polymerization largely depends on the counterion.

With conventional techniques and electrolytes, it was not possible to obtain living anions because they are rapidly protonated by tetraalkylammonium salts and residual water. The first report of the production of living polymers by an electrolytic method has to be attributed to Yamazaki et al. [247], who used tetrahydrofuran as solvent, and  $\text{LiAlH}_4$  or  $\text{NaAl}(\text{C}_2\text{H}_5)_4$  as electrolyte for the polymerization of  $\alpha$ -methylstyrene. A similar technique was used to polymerize styrene as well as derivatives [248–252]. The suggested mechanism agrees with the pathway described earlier.

#### 4.3.4

##### Intramolecular Reactions

For many years, intramolecular reactions such as conformational changes, bond cleavage, bond formation, and valence isomerizations have been observed only when hydrocarbons were reduced with alkali metals in ethereal solvents. In most electrochemical experiments, these reactions were dominated by the electrophilic processes already described. However, progress in experimental techniques [8, 9, 27–29] has made these reactions accessible to electroanalytical investigations, providing new mechanistic insight.

#### 4.3.4.1 Conformational Changes

In recent years it has become increasingly obvious that ET is frequently accompanied by conformational changes. The interconversion may precede or follow ET; the majority of these processes have to be classified as CE (as yet this mechanism has not been observed in the hydrocarbon series), EC, EEC, or ECE mechanisms, whereas only a few systems follow an EE pathway. An example for an EC process is the interconversion of the anion radical of *cis*-stilbene, which is quite slow on the voltammetric timescale [120], whereas *cis*-azobenzene anion radicals isomerize very rapidly [253, 254]. Tetraphenylethylene undergoes two closely separated reversible additions of one electron [122, 255, 256]. The small difference of standard potentials, equivalent to a high disproportionation constant (see Eq. 5), has been interpreted as interconversion from an almost planar to an orthogonal conformation when going from the neutral molecule to the dianion [257]. The thermodynamics and kinetics of ET-induced interconversions of substituted tetraphenylethylenes have been studied in great detail [141]. Reduction of 1,6-dimethylbicyclo[4.4.1]undeca-2,4,7,9-tetraene appears to proceed via an ECE scheme where the initial reduction gives an unstable radical anion, which undergoes a structural change, giving another anion with a conjugatively stabilized  $\pi$ -system [78, 79]. Conformational changes concurrent with ET (EE pathway) are observed upon reduction of (1), as cited earlier. This emerging field was reviewed by Evans and O'Connell [141].

#### 4.3.4.2 Bond-breaking and Bond-making Reactions

Reductive cleavage of carbon–carbon bonds upon alkali metal reduction of

diarylalkanes in ethereal solvents was already observed by Ziegler and Thielmann in the 1920s [258]. As was shown by Lagendijk and Szwarc [259] for 1,2-di( $\alpha$ -naphthyl)ethane, the primary anion radical undergoes homogeneous disproportionation that is supported by ion pairing. The resulting dianion decomposes by the fission of the CH<sub>2</sub>–CH<sub>2</sub> bonds into the salts of  $\alpha$ -naphthylmethyl carbanions. Similarly, 9,9'-bianthryl can be cathodically cleaved into anthracene and 9,9'-dihydroanthracene plus small amounts of reduced dimers. The dianion mechanism is quite slow, whereas the tri- and tetraanions are supposed to decay rapidly [260].

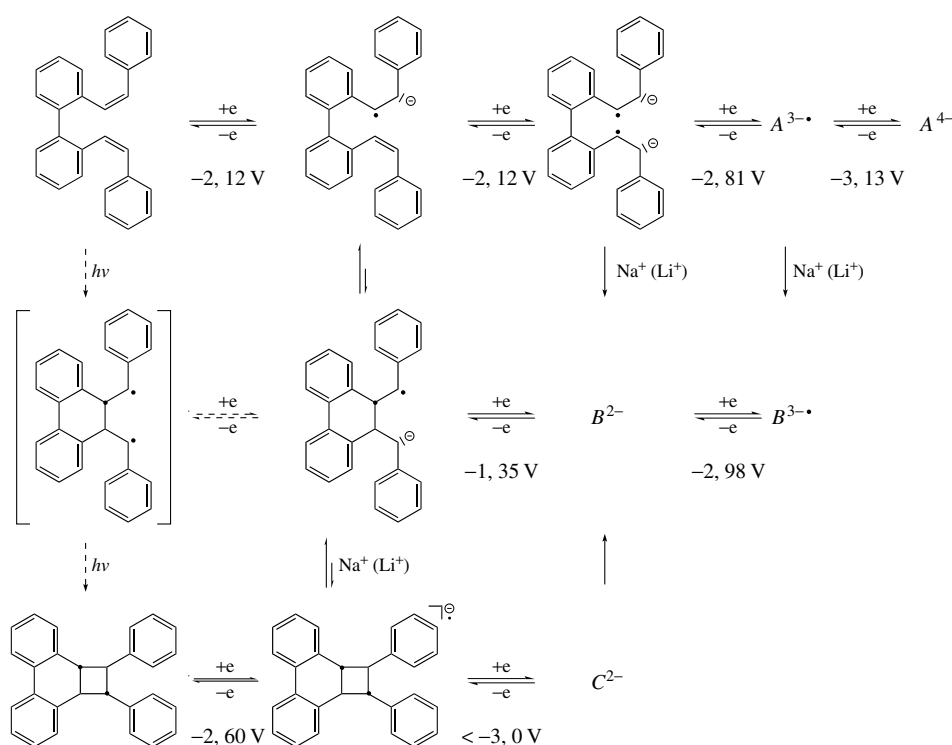
ESR spectroscopical investigations of the anion radical of fluorene indicated a first-order decay, and it was concluded that the CH bond undergoes homolytic cleavage [261]. Voltammetric studies of fluorene in DMF reached the same conclusion [195].

The thermal and photochemical ring opening reactions of cyclobutene are the classical examples of pericyclic processes [262]. In 1976, Bauld et al. described an ET-induced analog [263]. They observed that benzo- and phenanthrocyclobutene undergoes ring opening upon alkali metal reduction and suggested an ECE pathway. A voltammetric study of 1,2-tetrahydro-1,2-diphenylcyclobutanepheneanthrene in THF-NaBPh<sub>4</sub> confirmed this mechanism. However, it turned out that the rate of the ring opening largely depends on the counterion. If ion pairing is prevented by addition of 15-crown-5, the reaction rate slows down dramatically. At –50 °C the anion radical of the Z isomer becomes stable on the voltammetric timescale, whereas the dianion exhibits a fast ring opening [71, 264]. Two-electron reduction [61] or oxidation [265] of 1,3-dimethylenecyclobutanes yields

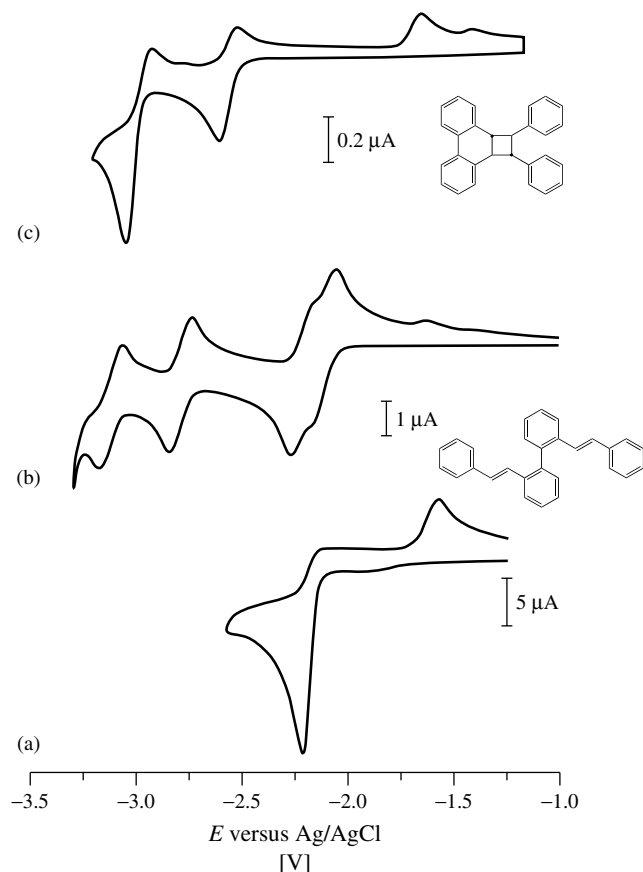
bicyclo[1.1.0]butanes. Cyclic voltammetry of 2,4-di-9H-fluoren-9-yliden-1,1,3,3-tetramethylcyclobutane in DMF at low temperatures demonstrated that bond formation proceeds via an EEC mechanism; the rate constant was found to be  $20 \text{ s}^{-1}$  [264].

ET-induced cycloadditions of polycyclic olefins and cycloreversions of cyclobutane species have been studied by ESR spectroscopy [266]. Upon chemical and electrochemical reduction, 2,2'-distyrylbiphenyl rearranges by intramolecular coupling into a "bis-benzylic" dihydrophenanthrene dianion  $B^{2-}$  (Scheme 1), which can be either protonated to a 9,10'-dibenzyl-9,10-dihydrophenanthrene or oxidatively coupled to a cyclobutane species. It is interesting to note that the intramolecular bond

formation takes place at the di- and tri-ionic level, which is comparable with a radical–radical coupling (RR route, EEC mechanism) [71]. The experiments are evidence that RS (radical substrate) coupling is generally improbable for ionic dimerization reactions. At low temperatures, the coupling rate between the negatively charged styryl units slows down and the tetraanion of the starting species can be obtained. Again, it turns out that ion-pairing effects favor the formation of the bis-benzylic intermediate. Thus, the first-order intramolecular coupling step between the negatively charged styryl units is significantly faster in THF/NaBPh<sub>4</sub> than in the presence of additional 15-crown-5 or in DMA/TBABr [71] (Scheme 1, Fig. 6).



**Scheme 1** ET-induced cycloaddition of 2,2'-distyrylbiphenyl.



**Fig. 6** Reduction of 2,2'-distyrylbiphenyl (a, b) and 1,2-tetrahydro-1,2-diphenylcyclobutanephenanthrene (c) see [Ref. [71]; (a) in THF/ $\text{NaBPh}_4$ ,  $\nu = 200 \text{ mVs}^{-1}$ ,  $T = 0^\circ\text{C}$  (b, c) in DMA/TBABr,  $\nu = 100 \text{ mV s}^{-1}$ ,  $T = -60^\circ\text{C}$ .

1-Arylindenes undergo sigmatropic 1,5-shifts, induced oxidatively [267], thermally [268], photochemically [269], and reductively [270]. The reductive rearrangement of 1,1,3-triphenylindene, yielding the dianion of 1,2,3-triphenyl-2H-indene, has been the subject of voltammetric investigations in DMF-TBAP [271]. The reaction follows an EEC or EDisp C pathway.

At room temperature in the presence of  $\text{Na}^+$  cations, the rearranging

dianion is formed via homogeneous disproportionation, thermodynamically favored by ion pairing and kinetically supported by the fast follow-up reaction. When ion pairing is suppressed by an application of low temperatures or the addition of sodium complexing 15-crown-5, the anion radical becomes persistent and the reactive dianion species has to be generated via heterogeneous ET at much more negative potentials. The same results are obtained when the bulky tetrabutylammonium

ion is used as a counterion [271]. Replacing 1,1,3-triphenylindene with 1-methyl-1-phenylindene or 1,2-dihydro-1,1'-spirobiindene, the anion radical undergoes quite an unusual cleavage of the alkyl-aryl bond, whereas the dianion rearranges in the same manner as triphenylindene [272].

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## 5

### Anodic Reactions of Alkanes, Alkenes, and Aromatic Compounds

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## 5.1 Introduction

This chapter deals with anodic oxidation of saturated hydrocarbons, olefins, and aromatic compounds. Substituted hydrocarbons are included, when the substituents strongly influence the reactivity. Anodic functional group interconversions (FGI) of the substituents are covered in Chapters 6, 8–10 and 15.

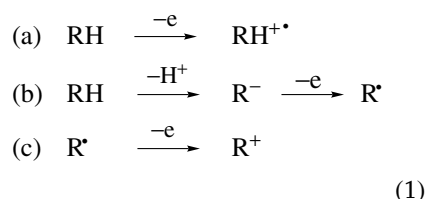
The principal reactions encountered in anodic reactions of hydrocarbons involve

1. substitution of a hydrogen atom in a C–H bond for a heteroatom,
2. addition of carbon or heteroatoms to a C,C double bond,
3. coupling of alkenes or aromatic compounds,
4. dehydrogenation,
5. C,C bond cleavage and
6. rearrangement.

Mechanistically, there are several pathways leading to the products. Such mechanisms are, however, only in a limited number of cases, clearly established and can furthermore change depending on the reaction conditions.

The pathways consist mostly of successive reactions being chemical- and electron-transfer steps (C and E steps)

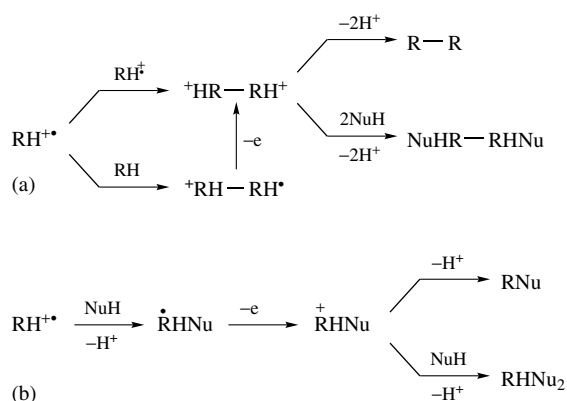
and involve radical cations, radicals, and cations. At the anode, these intermediates are generated in the following way (Eq. 1):



Transfer of an electron from a  $\sigma$ - or  $\pi$ -bond leads to a radical cation (Eq. 1a), oxidation with a preceding (Eq. 1b) or a succeeding deprotonation generates a radical, and oxidation of the radical forms a cation (Eq. 1c). The radical cations can react according to Scheme 1 [1, 2].

Radical cations can dimerize in a radical–radical coupling reaction (Scheme 1a) to afford dimer dication. An alternative pathway to form the dimer dication is a radical–substrate coupling in an electrophilic addition of the radical cation to the nucleophilic substrate. The dimer dication can lose two protons to form a *bis*-dehydro dimer or react with two nucleophiles to yield a disubstituted dimer.

The radical cation can alternatively react with a heteroatom nucleophile (Scheme 1b) and after deprotonation lead to a radical bound to the nucleophile. This radical can be further oxidized to



**Scheme 1** Reactions of radical cations (a) C,C-bond formation, (b) substitution and addition.

a cation, that is, deprotonated to a substituted alkene or reacts with a second nucleophile to an addition product. The cationic intermediates can also rearrange in this sequence.

The radicals undergo the usual reactions as dimerizations, disproportionations, atom-transfer reactions, or additions [3]. Compared to homogeneous radical reactions, bimolecular dimerizations and disproportionations are favored at the electrode. Stationary radical concentrations are higher in heterogeneous electrochemical conversions because the radicals are confined to a narrow reaction layer at the electrode surface. This layer arises from the slow diffusion of the radicals generated in high concentration at the electrode surface into the bulk of the solution and their fast reaction on this way. The more reactive the radical is, the narrower the reaction layer will be and thus the higher is the concentration of the radical.

Carbocations also react as usual by solvolysis, deprotonation, and rearrangement [4].

These general reactions will be illustrated by representative examples from the aforementioned groups of hydrocarbons.

## 5.2

### Anodic Oxidation of Alkanes

#### 5.2.1

##### Anodic Substitution of CH Bonds

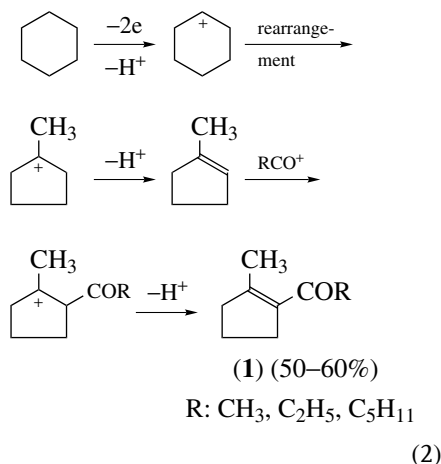
The nonactivated CH bond in aliphatic hydrocarbons is oxidized at a potential that lies mostly more anodic than 2.5 V [vs. SCE (saturated calomel electrode)] [5, 6]. This necessitates electrolytes with high anodic decomposition potentials.

In fluorosulfonic acid the anodic oxidation of cyclohexane in the presence of different acids ( $\text{RCO}_2\text{H}$ ) leads to a single product with a rearranged carbon skeleton, a 1-acyl-2-methyl-1-cyclopentene (**1**) in 50 to 60% yield (Eq. 2) [7, 8]. Also other alkanes have been converted at a smooth platinum anode into the corresponding  $\alpha,\beta$ -unsaturated ketones in 42 to 71% yield (Table 1) [8, 9]. Product formation is proposed to occur by oxidation of the hydrocarbon to a carbocation (Eq. 1 and Scheme 1) that rearranges and gets deprotonated to an alkene, which subsequently reacts with an acylium cation from the carboxylic acid to afford the  $\alpha,\beta$ -unsaturated ketone (**1**) (Eq. 2) [8–10]. In the absence of acetic acid, for example, in fluorosulfonic acid/sodium

**Tab. 1** Anodic oxidation of alkanes in fluorosulfonic acid, 1.1 M acetic acid

Alkane	Product	Current yield [%]
(CH <sub>3</sub> ) <sub>3</sub> CH	(CH <sub>3</sub> ) <sub>2</sub> C=CHCOCH <sub>3</sub>	64
<i>n</i> -C <sub>5</sub> H <sub>12</sub>	C <sub>2</sub> H <sub>5</sub> (CH <sub>3</sub> )C=CHCOCH <sub>3</sub>	40
	C <sub>5</sub> H <sub>9</sub> COCH <sub>3</sub>	18
<i>n</i> -C <sub>6</sub> H <sub>14</sub>	C <sub>6</sub> H <sub>11</sub> COCH <sub>3</sub>	51
<i>n</i> -C <sub>7</sub> H <sub>16</sub>	C <sub>7</sub> H <sub>13</sub> COCH <sub>3</sub>	56
Cyclohexane	2-Methyl-1-acetyl-1-cyclopentene	71
Cyclooctane	C <sub>8</sub> H <sub>13</sub> COCH <sub>3</sub>	42

fluorosulfonate, only oligomeric products are isolated even at  $-20^{\circ}$  [8]. The carbenium ions formed can also be trapped by carbon monoxide under pressure to yield highly selective carboxylic acids with cyclic hydrocarbons but less selective with acyclic ones [11].



Electrochemical fluorination in anhydrous hydrogen fluoride (Simons process) involves electrolysis of organic compounds (aliphatic hydrocarbons, haloalkanes, acid halides, esters, ethers, amines) at nickel electrodes. It leads mostly to perfluorinated compounds, but is accompanied to a high extent by cleavage and rearrangement reactions. The mechanism of the formation of carbocations according to Eq. (1) and Scheme 1 is assumed

through oxidation of the CH bond by higher-valent nickel fluorides. Partial fluorination can be achieved by electrolysis in molten  $\text{KF} \cdot 2\text{HF}$  in the Phillips process at porous carbon electrodes [12–15].

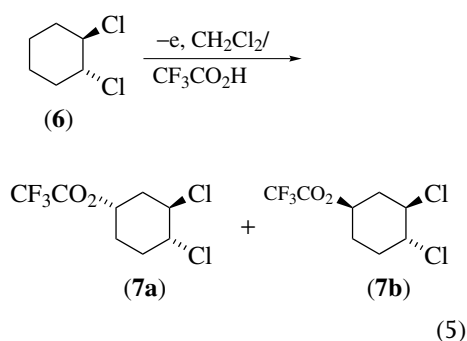
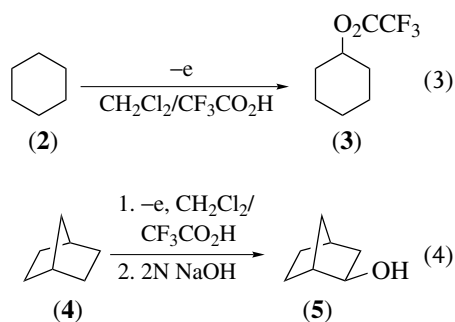
In trifluoroacetic acid [0.4 M TBABF<sub>4</sub> (tetrabutyl ammonium tetrafluoroborate)] unbranched alkanes are oxidized in fair to good yields to the corresponding trifluoroacetates (Table 2) [16]. As mechanism, a 2e-oxidation and deprotonation to an intermediate carbenium ion, that undergoes solvolysis is proposed. The isomer distribution points to a fairly unselective CH oxidation at the methylene groups. Branched hydrocarbons are preferentially oxidized at the tertiary CH bond [17].

Dichloromethane/trifluoroacetic acid appears to be the solvent mixture of choice for these substitutions. Dichloromethane dissolves sufficiently the hydrocarbon and can be easily removed by distillation. Trifluoroacetic acid is a nucleophile with a fairly high resistance towards oxidation. Platinum is the only suitable anode material, while gold, glassy carbon, graphite, and lead dioxide corrode heavily. Electrolysis of cyclohexane (2) in  $\text{CH}_2\text{Cl}_2/20\% \text{CF}_3\text{CO}_2\text{H}/4\% (\text{CF}_3\text{CO})_2\text{O}/0.05 \text{ M TBABF}_4$  at  $0^{\circ}\text{C}$  in an undivided cell at controlled current afforded 92% cyclohexyl trifluoroacetate (3) (Eq. 3). While cyclohexane and

**Tab. 2** Yields and isomer distribution of trifluoroacetates in the oxidation of alkanes in  $\text{CF}_3\text{CO}_2\text{H}/0.4 \text{ M TBABF}_4$ 

Alkane	Current yield [%]	Isomer distribution [%]		
		2-isomer	3-isomer	4-isomer
<i>n</i> -Octane	75	33	33	33
<i>n</i> -Heptane	75	45	45	10
<i>n</i> -Hexane	60	Not resolved		
<i>n</i> -Pentane	50	Not resolved		

cyclopentane (84%) lead to high yields of the cycloalkyl trifluoroacetates, those of medium-sized rings are low (8-ring: 30%, 10-ring: 6%, 12-ring: 9%) within a complex product mixture. The electrolysis of norbornane (4) (Eq. 4) leads in dichloromethane/trifluoroacetic acid to 83% *exo*-2-norbornanol (5) after hydrolysis of the trifluoroacetate [16]. The stereochemistry of (5) indicates that possibly a nonclassical norbornyl cation is involved. Oxidation of *trans*-1,2-dichlorocyclohexane (6) produces in  $\text{CH}_2\text{Cl}_2/20\% \text{CF}_3\text{CO}_2\text{H}$ , 0.05 M TBABF<sub>4</sub> at 0 °C (7a,b) as main product in 49% yield (Eq. 5) [16]. The inductive effect of the two chlorine atoms directs the oxidation mainly to C(4) and C(5). Thus the reaction provides a synthetically useful route from olefins to homoallylic alcohols via protection of the double bond, anodic oxidation, hydrolysis, and deprotection.



*Trans*-decalin tends to form oligomers as major products in  $\text{CH}_2\text{Cl}_2/\text{CF}_3\text{CO}_2\text{H}$ . In the less acidic solvent,  $\text{CH}_2\text{Cl}_2/\text{HOAc}$  with  $\text{Bu}_4\text{NPF}_6$ , the oligomerization can be suppressed and 67% decalyl acetates together with 10% fluorodecalins are formed. The chemoselectivity of the acetoxylation is for C(4a):C(1):C(2) = 12:1:1. With  $\text{Bu}_4\text{NOAc}$  as supporting electrolyte, 77% decalyl acetate is obtained in equal chemoselectivity but without fluorination products. However, 35 to 40 F  $\text{mol}^{-1}$  are required in this case for complete conversion [18, 19].

The CH bonds of steroids surprisingly can be oxidized even in methanol as a solvent. The electrolysis of androstane in 0.1 M  $\text{NaClO}_4$  methanol/dichloromethane at a glassy carbon anode produces after 53% conversion 14% 6-methoxyandrostane and 27% 6-(methoxymethoxy) androstane [18, 19]. This remarkable regioselectivity is possibly

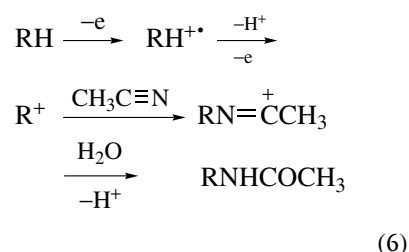


**Tab. 3** Yields and isomer distribution of acetamidoalkanes obtained by cpe of alkanes at a Pt-anode in CH<sub>3</sub>CN/0.1 M TBABF<sub>4</sub>

Alkane	Yield [%]	Isomer distribution [%]		
		2-isomer	3-isomer	4-isomer
<i>n</i> -Octane	45	33	35	32
<i>n</i> -Heptane	48	45	45	10
<i>n</i> -Hexane	45	55	45	
<i>n</i> -Pentane	50	Not resolved		

due to the stacking of steroid molecules at the electrode surface.

Controlled potential electrolysis (cpe) of alkanes in acetonitrile/0.1 M TBABF<sub>4</sub> yields acetamidoalkanes (Table 3). Voltammetry and coulometry indicate a 2e-oxidation to a carbenium ion that subsequently reacts with the nitrogen atom of acetonitrile in a Ritter reaction (Eq. 6) [20].



The oxidation of substituted adamantanes has been studied in detail by Miller [21, 22] and Mellor [23–25]. Cpe in a divided cell produces two types of products by substitution at the tertiary carbon atom: substitution of hydrogen for acetamide with retention of the substituent X in the adamantane molecule [substituent X (yield in %): H (90), Cl (91), F (65), CH<sub>3</sub> (91), CO<sub>2</sub>CH<sub>3</sub> (64), CN (41)] and substitution of X for acetamide [Br (89), CH<sub>2</sub>OH (37), COCH<sub>3</sub> (44), OH (41), OCH<sub>3</sub> (58)] [22]. Cleavages of 1-acetyl-, 1-bromo-

and 1-hydroxymethyladamantane are of interest because they mimic the results in mass spectrometry. Comparison of the oxidation of substituted adamantanes with lead (IV), cobalt (III) and manganese (III) trifluoroacetates and with anodic oxidation in acetonitrile or trifluoroacetic acid, shows that the anodic oxidation proceeds via a radical cation intermediate, while the metal salts form products by CH abstraction [22]. As a preparative result, the anodic oxidation yields mainly fragmentation products, while with metal salts, hydrogen substitution is achieved preferentially.

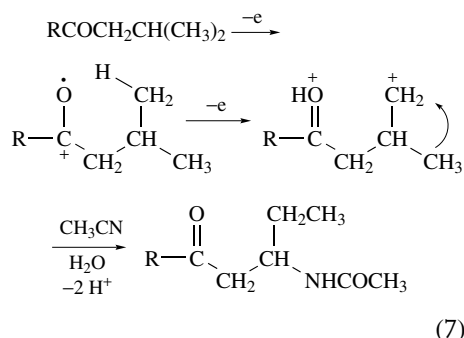
### 5.2.2 Oxidation of Remote CH Bonds in Ketones, Carboxylic Acids, and Steroids

Ketones that lack  $\alpha$ -branching are oxidized in acetonitrile/0.1 N LiClO<sub>4</sub> at a platinum anode to afford acetamido ketones with the acetamido group in remote position (Table 4) [26, 27]. The products can be rationalized via oxidation of the carbonyl group to a radical cation. This initiates a  $\gamma$ -hydrogen abstraction that is analogous to this, found in mass spectrometry and photochemistry. The formed radical is oxidized to a carbenium ion which possibly rearranges and undergoes a Ritter reaction

Tab. 4 Remote oxidation of ketones in acetonitrile/lithium perchlorate

Ketone	Product [% yield]
2-Hexanone	5-Acetamido-2-hexanone (40)
2-Heptanone	6-Acetamido-2-heptanone (30)
2-Octanone	7-Acetamido-2-octanone (21)
	6-Acetamido-2-octanone (30)
	5-Acetamido-2-octanone (7)
4-Heptanone	2-Acetamido-4-heptanone (31)
2-Methyl-4-pentanone	2-Acetamido-2-methyl-4-pentanone (20)
	4-Acetamido-2-hexanone (20)
2,6-Dimethyl-4-heptanone	2-Acetamido-2,6-dimethyl-4-heptanone (20)
	6-Acetamido-2-methyl-4-octanone (20)
2,5-Dimethyl-3-hexanone	5-Acetamido-2-methyl-3-heptanone (25)
	5-Acetamido-2,5-dimethyl-3-hexanone (35)
4,4-Dimethyl-2-pentanone	4-Acetamido-4-methyl-2-hexanone (50)

with acetonitrile (Eq. 7).



In  $\text{CH}_2\text{Cl}_2/\text{CF}_3\text{CCO}_2\text{H}$  dodeca- and tetradecanoic acid are preferentially tri-fluoroacetoxylated at the ( $\omega$ -2) to ( $\omega$ -4) positions in 40 to 15% yield; no or only very minor attack is found at C-2 to C-6 [18]. The remarkable regioselectivity is assumed to be due to the inductive effect of the carboxylic group, which can be protonated in the more acidic region close to the anode surface. Esters with an acyclic alkyl chain have been oxidized by cpe in a divided cell in  $\text{CH}_3\text{CN}/\text{LiClO}_4$  or  $\text{TEABF}_4$  at a platinum anode with a high selectivity for the ( $\omega$ -1)-position (Table 5) [28].

### 5.2.3

#### C,C Bond Cleavage in Hydrocarbons

By analogy with their behavior in mass spectrometry, branched hydrocarbons are cleaved when oxidized in  $\text{CH}_3\text{CN}/\text{TEABF}_4$  at  $-45^\circ\text{C}$ . The resulting acetamides of the fragments (Table 6) are formed by cleavage of the initial radical cation at the C,C bond between the secondary and tertiary C atom, to afford after a second electron transfer, carbocations, which react in a Ritter reaction with acetonitrile [29].

Anodic oxidation of alkyl substituted cyclopropanes and spiroalkanes in methanol/TEATos (tetraethyl ammonium tosylate) affords monomethoxy and dimethoxy products in yields ranging from 6 to 86% [30, 31]. The products result from the cleavage of the most highly substituted C,C bond. In contrast to the anodic cleavage the acid-catalyzed cleavage occurs selectively at the less substituted carbon. The cleavage of hetero-substituted cyclopropanes is reported in Ref. [32–35].

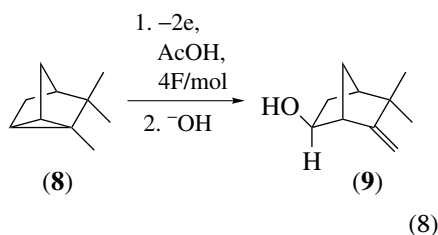
Tab. 5 Remote oxidation of esters in acetonitrile/LiClO<sub>4</sub> or TEABF<sub>4</sub>

<i>Ester</i>	<i>Acetamido ester [% yield]</i>
Ethyl butanoate	Ethyl 3-acetamidobutanoate (70)
Methyl hexanoate	Methyl 5-acetamidohexanoate (42)
	Methyl 4-acetamidohexanoate (11)
Methyl nonanoate	Methyl 8-acetamidononanoate (25)
Methyl 3-methylbutanoate	Methyl 3-acetamido-3-methylbutanoate (68)
Methyl 2-methylpropanoate	Methyl 2-acetamido-2-methylpropanoate (58)
	Methyl 3-acetamidobutanoate (4)

Tab. 6 Anodic oxidation of branched hydrocarbons in acetonitrile/TEABF<sub>4</sub>

<i>Hydrocarbon</i>	<i>Products</i>
2,3-Dimethylbutane	2-Propylacetamide
2,2,4-Trimethylpentane	<i>t</i> -Butylacetamide, 2-propylacetamide, 2-butylacetamide
2,2-Dimethylbutane	<i>t</i> -Butylacetamide, <i>t</i> -pentylacetamide, isopentylacetamide
<i>t</i> -Butylcyclohexane	<i>t</i> -Butylacetamide, cyclohexylacetamide
<i>n</i> -Octane	2-Octylacetamide, 3-octylacetamide, 4-octylacetamide

Tricyclene (**8**) has been oxidized in acetic acid/Et<sub>3</sub>N to the Nojigiku alcohol (**9**) in 77% yield (Eq. 8) [36]. The reaction was also conducted in a 2.25-kg scale to afford pure (**9**) in 65% yield from crude (**8**) containing alkenes. The olefins remained unconverted due to their higher oxidation potential.



By indirect oxidation with electro-generated NO<sub>3</sub><sup>•</sup> radicals in *t*-butanol/water/HNO<sub>3</sub>/O<sub>2</sub>, saturated hydrocarbons were oxidized to ketones with a statistical H-abstraction at the methylene

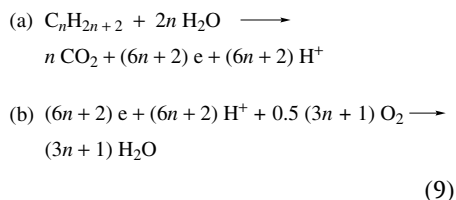
groups [37]. With Co(OAc)<sub>2</sub> the hydrocarbons: cyclohexane and norbornane have been indirectly oxidized in CF<sub>3</sub>CO<sub>2</sub>H/CH<sub>3</sub>CO<sub>2</sub>H to the corresponding ketones in 47 to 52% yield [38].

#### 5.2.4

#### Oxidation of Hydrocarbons in Fuel Cells

In fuel cells, the combustion energy of hydrocarbons can be converted directly into electrical energy. At the fuel cell anode, the hydrocarbon is in most cases converted to carbon dioxide because the intermediates are more easily oxidized than the starting hydrocarbon (Eq. 9a); at the fuel cell cathode oxygen is reduced to water (Eq. 9b). Most fuel cell research has involved the use of hydrogen as fuel. However, solid oxide fuels cells (SOFCs) can operate at higher temperature and can

use dry hydrocarbons as fuels [39, 40].



Only in few cases, substitution, dehydrogenation, or coupling products of the hydrocarbon are obtained. The selective dehydrogenation of short-chain hydrocarbons is reported for higher temperatures. Ethane is dehydrogenated at 700 °C in the presence of oxygen to ethene with 10.6% conversion and 96.9% selectivity [41]. In a mixed oxide consisting of Mo/Bi/Ni/Fe Si/K/Na, a propene has been oxidized to acroleine [42]. The dehydrodimerization of short-chain hydrocarbons has also been achieved. The oxidative coupling of methane at an Ag/Bi<sub>2</sub>O<sub>3</sub> electrode in a solid electrolyte yielded at 700 °C and 2% conversion in 72% selectivity ethane and in 18% selectivity ethene [43]. Further dehydrodimerizations of methane at 500 to 900 °C are reported for a Y<sub>2</sub>O<sub>3</sub>/ZrO<sub>2</sub> solid electrolyte and different anode materials like Ag, Ni, Cu, Bi, Pt, Sm, and Mn [44–46].

## 5.3

### Anodic Oxidation of Alkenes

#### 5.3.1

##### General Reaction Behavior

Alkenes are in general oxidized easier than the corresponding alkanes because the HOMO of the  $\pi$ -bond from which the electron is transferred to the anode has a higher energy than the HOMO of the  $\sigma$ -bond in the corresponding alkane. Depending on the substituents at the olefinic carbon atom, the oxidation

potential of alkenes can vary from less than 0 V (vs. Ag/AgCl) for strong electron-donating substituents, like the dimethylamino group, till up to 2.5 V for hydrogen and electron withdrawing groups as the ester group. A selection of oxidation potentials for substituted alkenes is found in Refs. [5, 47, 48].

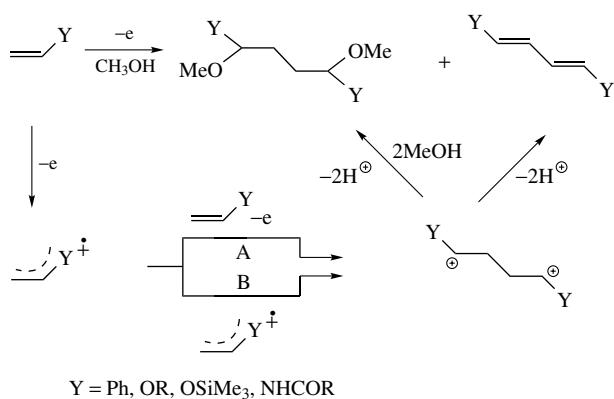
Electron transfer from the alkene leads to a radical cation that can undergo coupling (Scheme 1a). The radical cation can also react with the nucleophilic heteroatom of a reagent to afford addition or substitution products (Scheme 1b). Adducts can be likewise obtained by oxidation of the nucleophile to a radical that undergoes radical addition. Reactions between alkenes and nucleophiles can be realized too with chemical oxidants that are regenerated at the anode (mediators) (see Chapter 15). Finally, cycloadditions between alkenes can be initiated by a catalytic anodic electron transfer. These principal reaction modes are subsequently illustrated by selected conversions.

#### 5.3.2

##### Anodic Coupling of Alkenes by Way of Radical Cations

#### 5.3.2.1 Intermolecular Coupling

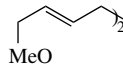
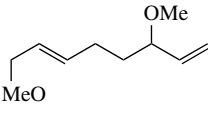
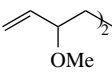
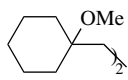
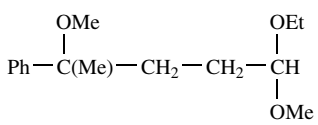
Olefins with electron-donating substituents as the alkoxy, acylamino, phenyl, or vinyl group can be coupled in methanol to give 1,4-dimethoxy dimers and/or dienes (Scheme 2). The first intermediate in this coupling reaction is a radical cation, which either by electrophilic addition to the olefin and subsequent 1e-oxidation (path A) [49] or by radical dimerization (path B) [50, 51] leads to a dimer dication that undergoes methanolysis or deprotonation. Representative examples of this coupling reaction are summarized in Table 7.

**Scheme 2** Anodic coupling of alkenes.**Tab. 7** Anodic oxidation of ethylenic compounds

Nr.	Substrate	Conditions	Products	Yield [%]	Refs.
1	Styrene	MeOH, NaOAc, NaClO <sub>4</sub> , C	$\text{Ph}-\underset{\text{OMe}}{\text{CH}}-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{Ph}$	64	52
2	$\alpha$ -Methylstyrene	MeOH, NaOAc, NaClO <sub>4</sub> , C	$\text{Ph}-\underset{\text{Me}}{\text{C}}=\text{CH}-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{Ph}$	64	52
3	Styrene	CH <sub>2</sub> Cl <sub>2</sub> -H <sub>2</sub> O, TBAHSO <sub>4</sub>	$\text{Ph}-\text{CH}(\text{O})-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{Ph}$	52	53, 54
4	Vinyl ethyl ether	MeOH, NaI, C	$\text{MeO}-\underset{\text{EtO}}{\text{CH}}-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{Ph}$	51	56, 58
5	1-Ethoxycyclohexene	MeOH, NaClO <sub>4</sub> , 2,6-lutidine, C	$\text{Cyclohexyl}-\text{CH}(\text{O})-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{Cyclohexyl}$	48	58
6		CH <sub>2</sub> Cl <sub>2</sub> , MeOH, Bu <sub>4</sub> NBF <sub>4</sub>		50	59
7		MeCN, MeOH, LiClO <sub>4</sub>		78	59

(continued overleaf)

Tab. 7 (continued)

Nr.	Substrate	Conditions	Products	Yield [%]	Refs.
8	1,1-Bis(dimethyl-amino)-ethylene	DMF, Et <sub>4</sub> NClO <sub>4</sub>	$((\text{Me}_2\text{N})_2\text{CH}=\text{CH})_2$	–	60, 61
9	Butadiene	C, MeOH, NaClO <sub>4</sub>		17	65
				16	
				16	
10	Methylenecyclohexane	C, MeOH, NaClO <sub>4</sub>		38	67
11	$\alpha$ -Methylstyrene, vinyl ethyl ether	C, MeOH, NaClO <sub>4</sub>		32	68

Styrene and indene derivatives (Scheme 2, Y = Ph) are dimerized to 1,4-dimethoxy-1,4-diphenylbutanes or 1,4-diphenylbutadienes (Table 7, numbers 1 and 2) [52]. The product distribution is in some cases strongly dependent on the anode potential and the supporting electrolyte. Dimerization is promoted by  $\alpha$ -substituents that stabilize the intermediate radical cation, for example, phenyl, vinyl, alkoxy, dialkylamino groups.  $\beta$ -Alkyl substituents strongly decrease the yield of dimers and favor formation of dimethoxylated monomers.

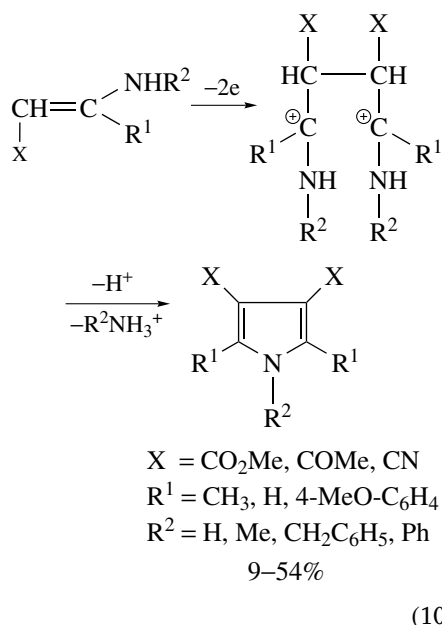
Enol ethers (Scheme 2, Y = OR) with half-wave potentials between  $E_{1/2} = +1.2$  and  $+1.8$  V (Ag/AgCl) couple in methanol with 2,6-lutidine as base at a graphite anode to give the acetals of 1,4-dicarbonyl

compounds in 30 to 60% yield (Table 7, numbers 4, 5) [55–57].

Silyl enol ethers (Scheme 2, Y = OSi(CH<sub>3</sub>)<sub>3</sub>) can be dimerized to 1,4-dicarbonyl compounds in good yields. To suppress the methanolysis of the silyl enol ethers, MeCN-5% MeOH is used as solvent and the electrolysis is conducted within one hour by the use of a capillary gap cell, which allows high currents (Table 7, numbers 6 and 7) [59].

Examples of the coupling of enamines are rare [60]. In most cases, the enamines undergo methanolysis to form electroinactive aminoacetals prior to the coupling reaction. Enamino ketones or enamino esters, however, yield via dimerization of the radical cations and subsequent ring closure pyrrole derivatives

(Eq. 10) [62–64].

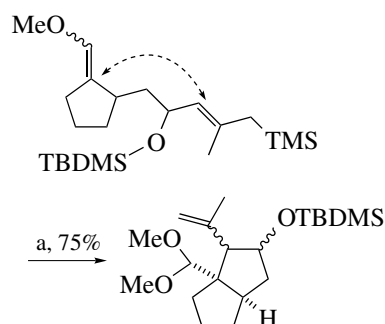


Dienes [Scheme 2, Y = vinyl] are dimerized to dimethoxyoctadienes or are dimethoxylated to dimethoxybutenes at graphite, platinum, or glassy carbon anodes in an electrolyte consisting of methanol–sodium perchlorate (Table 7, number 9) [55, 65]. Dimerization is favored by graphite or carbon cloth anodes, by high olefin concentrations and by terminally unsubstituted dienes [65, 66]. The ratio of monomer to dimer is determined mainly by the anode material. Anodes with a smooth surface, such as platinum, gold, and glassy carbon, promote the formation of monomers; porous materials, such as soft graphite or carbon cloth, favor the dimers. Alkenes without (+)-M substituents can be coupled if they are dialkylated at one carbon atom of the double bond and are unsubstituted at the other (Table 7, number 10). This is a further indication that the dimerization of radical cations responds sensitively to steric hindrance.

Unsymmetrical dimers are accessible through the coelectrolysis of different olefins (Table 7, number 11). Coupling can also be achieved by the addition of anodically generated radicals with subsequent dimerization of the adduct radicals (additive dimerization, see Section 5.3.3).

#### 5.3.2.2 Intramolecular Coupling

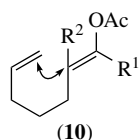
The intramolecular coupling of enolethers with enolethers, styrenes, alkyl-substituted olefins, allylsilanes, and vinylsilanes was systematically studied by Moeller [69]. Many of these coupling reactions turned out to be compatible with the smooth formation of quaternary carbon atoms (Eq. 11) [70], which were formed diastereoselectively and led to fused bicyclic ring skeletons having a *cis*-stereochemistry [71]. The cyclization is compatible with acid-sensitive functional groups as the allylic alkoxy group. Moeller has demonstrated in some cases that these reactions can be run without loss of selectivity and yield in a simple beaker with either a carbon rod or reticulated carbon as anode without potential control and a 6-V lantern battery as power supply [71].



a : C-anode, 1 M LiClO<sub>4</sub>, MeOH/THF, lutidine

(11)

Unsaturated enol acetates (**10**) have been cyclized to cyclohexenylketones [72].



Swenton has explored the dependence of yield and selectivity in the intramolecular coupling between phenols and olefins on the substituents in the aryl ring and the olefin (Scheme 3) [73, 74].

Oxidation of the phenol (**11**), deprotonation and a further electron transfer leads to (**13**), which undergoes an electrophilic

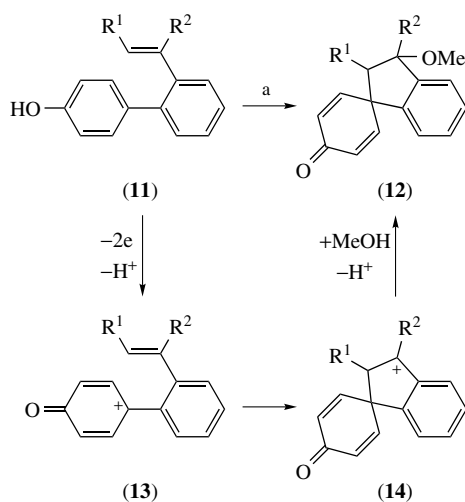
addition to the double bond and the resulting cation (**14**) is subsequently trapped by methanol to afford (**12**).

Further examples of intramolecular coupling have been summarized in the literature [75, 76].

### 5.3.3

#### Anodic Substitution and Addition via Radical Cations

Anodic addition of nucleophiles to olefins can be achieved via oxidation of the alkene to a radical cation. This means that a nucleophile can be added to a nucleophilic alkene by reversing its polarity to an electrophilic radical cation



R <sup>1</sup>	R <sup>2</sup>	Yield (%)
H	H	16
H	CH <sub>3</sub>	85
H	Ph	65
CH <sub>3</sub>	H	35
-(CH <sub>2</sub> ) <sub>3</sub> <sup>-</sup>		69

a: Pt anode, CH<sub>3</sub>CN/MeOH/AcOH, LiClO<sub>4</sub>

**Scheme 3** Intramolecular coupling between phenol and alkene.

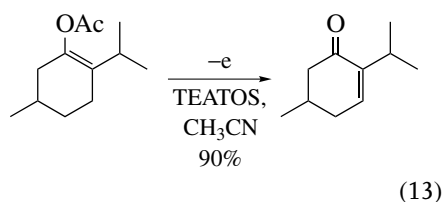
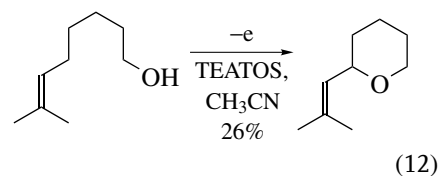


at the anode. In the usual additions to olefins an electrophile is added in the first step. The anodic addition of methanol to cyclohexene (**15**, Nu = CH<sub>3</sub>O, Scheme 4) to afford (**21**)–(**23**) illustrates well the competing pathways. The first formed radical cation (**16**) can react with the nucleophile to form via (**17**) the carbenium ion (**19**). In competition (**16**) can be deprotonated and the formed radical oxidized to the allyl cation (**18**). Methanolysis of (**18**) leads to (**21**) as does the deprotonation of (**19**). The carbocation (**19**) can furthermore undergo a 1,2-carbon shift to form via (**20**) the acetal (**23**). Furthermore, (**19**) reacts in a minor pathway with a second nucleophile to yield the bisadduct (**22**) [77].

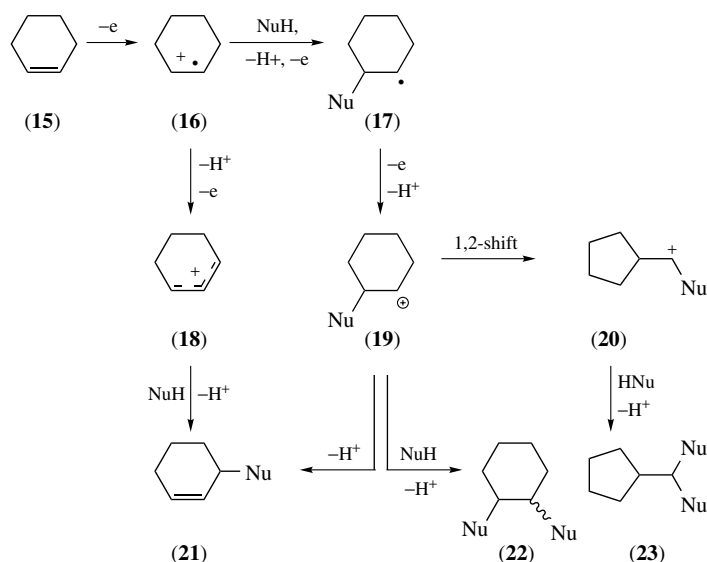
The basicity or acidity of the electrolyte, and in particular, the methanol concentration, strongly influences the product distribution. With an equimolar mixture of cyclohexene and methanol in tetrahydrofuran, 81% of 3-methoxycyclohexene

(Scheme 4, (**21**), Nu = OCH<sub>3</sub>) are formed nearly exclusively. In acetic acid, the corresponding acetate is found and in acetonitrile an *N*-acetyl amine via reaction of (**18**) with the nitrogen of acetonitrile is obtained [78, 79].

Allylic CH bonds can be substituted fairly regioselectively by using an intramolecular reaction (Eq. 12) [80] or suitable substitution (Eq. 13) [81].



Generation of hypochloric acid at the anode allows allyl substitution via an

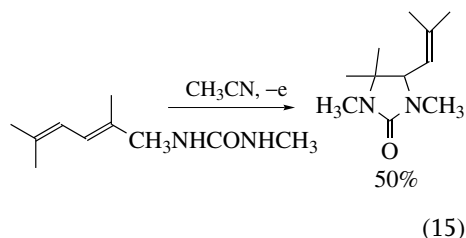
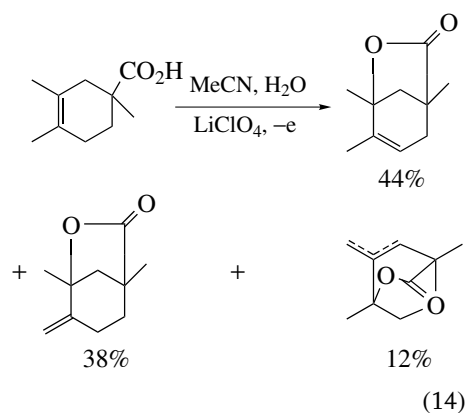


**Scheme 4** Anodic substitution and addition with cyclohexene (**15**) via a radical cation.

ene-reaction in high regioselectivity and yield [82].  $\beta$ -Ionone has been acetoxylation in the allylic C4 position in excellent yield [83]. With  $\alpha$ - and  $\beta$ -pinene anodic allylic methoxylation is achieved by cleavage of the four-membered ring [84]. Enamines afford mixtures of allylic and vinylic methoxylation in 74 to 76% yield [85]; besides, methanol also enolates from CH-acidic compounds, for example, methyl acetoacetate, can be introduced (Table 8, number 3).

Bisalkoxylations are rare with alkyl-substituted alkenes, but can become a major portion of the products with enolethers [55, 56, 58], 1,3-dienes [55, 65, 86, 87] or arylolefins [52, 53], especially, when the terminal position of the alkene bears alkyl substituents that disfavor dimerization.

Intramolecular addition can occur when nucleophilic substituents are suitably positioned as in Eq. 14 [88]. When the latter electrolysis is conducted in  $\text{CH}_2\text{Cl}_2/\text{Bu}_4\text{NCl}$ , 75% of the chloro- $\gamma$ -lactone are obtained. Electrolysis of (*E*)-5-phenyl-4-pentenoic acid affords a 4-(phenylmethoxymethyl)-4-butanolide [89].



Dienes can undergo 1,2- and/or 1,4-addition [65]. 1,3-Bisnucleophiles, as 1,3-dimethylurea, favor 1,2-addition due to the formation of a five-membered ring (Eq. 15) [90]. Furan and its derivatives undergo a clean 1,4-addition, which is mediated by  $\text{NH}_4\text{Br}$  [91] and has been also used for a technical scale conversion [92]. *N*-Acetylindole reacts in a 1,2-bisacetoxylation because the phenyl ring wants to regain aromaticity [93].

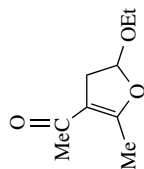
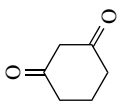
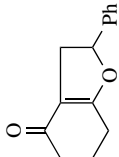
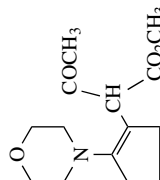
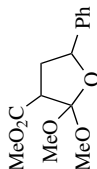
#### 5.3.4

##### Addition via Oxidation of Nucleophiles to Radicals

If anions  $\text{R}^-$  are oxidized in the presence of olefins, additive dimers (**24**) and substituted monomers (**26**) are obtained (Scheme 5, Table 8, and Ref. [94]). The products can be rationalized by the following pathway: the radical  $\text{R}^\bullet$  obtained by a 1e-oxidation from the anion  $\text{R}^-$  adds to the alkene to give the primary adduct (**25**), which dimerizes to afford the additive dimer (**24**) with regiospecific head-to-head connection of the two olefins, or couples with  $\text{R}^\bullet$  to form the additive monomer (**26**). If the substituent Y in the olefin can stabilize a carbenium ion, (**25**) is oxidized to the cation (**27**), which reacts intra- or intermolecularly with nucleophiles to give (**28**) or (**29**).

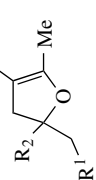
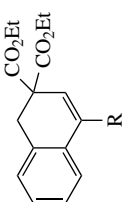
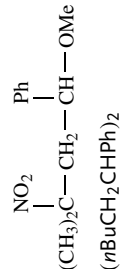
Satisfactory to good yields of adducts have been found for styrenes (Scheme 5, Y = phenyl), conjugated dienes (Y = vinyl), enamines (Y =  $\text{NR}_2$ ), and enol ethers (Y = alkoxy), particularly if they are

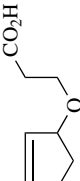
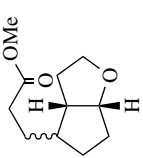
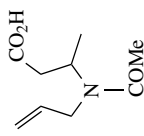
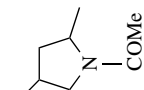
Tab. 8 Addition of Anodically Generated Radicals to Alkenes

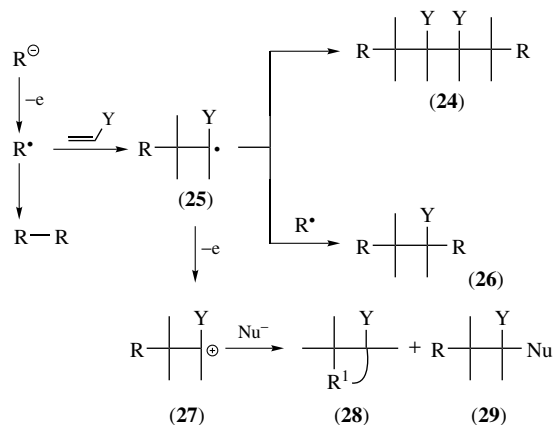
Nr.	Radical precursor, Olefin	Conditions	Product	Yield [%]	Refs.
<i>Anions of 1,3-dicarbonyl compounds</i>					
1	$\text{MeO}_2\text{CCH}_2\text{COMe}$ $\text{H}_2\text{C}=\text{CHOEt}$	$\text{MeOH}$ , $\text{MeONa}$ , Pt		36	95
2	 $\text{PhCH}=\text{CH}_2$	$\text{MeCN}$ , $\text{Et}_4\text{NOTos}$		85	96
3	$\text{CH}_3\text{COCH}_2\text{CO}_2\text{CH}_3$ Morpholino- cyclopentene	$\text{CH}_3\text{ONa}$ , $\text{MeOH}$		67	97
4	$(\text{MeO}_2\text{C})_2\text{CH}_2$ Styrene	$\text{MeOH}$ , $\text{MeONa}$ , Pt		40	95

(continued overleaf)

Tab. 8 (continued)

Nr.	Radical precursor, Olefin	Conditions	Product	Yield [%]	Refs.
<i>Anions of 1,3-dicarbonyl compounds</i>					
5	(MeO <sub>2</sub> C) <sub>2</sub> CH <sub>2</sub> Butadiene	MeOH, MeONa, Pt	[(MeCO) <sub>2</sub> CHCH <sub>2</sub> CH=CHCH <sub>2</sub> ] <sub>2</sub> + isomers	46	95
6	CH <sub>3</sub> COCH <sub>2</sub> CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub> 	HOAc/EtOAc NaOAc, 0.1 eq. Mn(OAc) <sub>2</sub> C-anode		80–86	98
7	 R: C <sub>6</sub> H <sub>13</sub> , (CH <sub>3</sub> ) <sub>3</sub> Si, Ph	KOAc/HOAc, 0.25 eq. Mn(OAc) <sub>2</sub> C-anode		40–91	99
8	(CH <sub>3</sub> ) <sub>2</sub> CHNO <sub>2</sub> , Styrene	MeOH, MeONa, Pt		43	100
9	<i>n</i> BuMgBr, Styrene	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> O, LiClO <sub>4</sub> , Pt	( <i>n</i> BuCH <sub>2</sub> CHPh) <sub>2</sub>	29	101
10	EtO <sub>2</sub> CCO <sub>2</sub> H, Butadiene	MeOH, Pt	<i>Carboxylates</i> (EtO <sub>2</sub> CCH <sub>2</sub> CH=CHCH <sub>2</sub> ) <sub>2</sub> + isomers EtO <sub>2</sub> CCH <sub>2</sub> CH=CHCH <sub>2</sub> CO <sub>2</sub> Et	66 4	102

11	$\text{MeO}_2\text{C}(\text{CH}_2)_4\text{CO}_2\text{H}$ Ethylene	MeOH, Pt	$\text{MeO}_2\text{C}(\text{CH}_2)_{12}\text{CO}_2\text{Me}$	92–95	103
12	$\text{MeO}_2\text{CCH}_2\text{CO}_2\text{H}$ Styrene	MeOH, Pt	$\text{MeO}_2\text{C}(\text{CH}_2)_{10}\text{CO}_2\text{Me}$ $[\text{MeO}_2\text{C}(\text{CH}_2)_2\text{CHPh}]_2$	38	102
13	$\text{MeO}_2\text{C}(\text{CH}_2)_4\text{CO}_2\text{H}$ Butadiene	MeOH, Pt	$[\text{MeO}_2\text{C}(\text{CH}_2)_5\text{CH}=\text{CHCH}_2]_2$	4747	104
14	$\text{F}_3\text{CCO}_2\text{H}$ , $\text{CH}_2=\text{CH}i\text{Pr}$	MeCN, NaOH, Pt	$\text{MeO}_2\text{C}(\text{CH}_2)_5\text{CH}=\text{CH}(\text{CH}_2)_5\text{CO}_2\text{Me}$	40	105
15	$\text{CH}_3\text{CO}_2\text{H}$ Methacroleine	MeCN, $\text{H}_2\text{O}$ , Pt	$[\text{CF}_3\text{CH}_2\text{CH}(\text{HPr})]_2$ $[\text{CH}_3-\text{CH}_2\text{C}(\text{CH}_3)(\text{CHO})]_2$	80 80	106, 107
16	$\text{CF}_3\text{CO}_2\text{H}$ , Vinyl acetate	MeCN, $\text{H}_2\text{O}$ , NaOH	$[\text{CF}_3\text{CH}_2\text{CH}(\text{OAc})]_2$	14	108
17	$\text{CH}_3\text{CO}_2\text{H}$ , Dimethyl fumarate	MeCN, $\text{H}_2\text{O}$	$[\text{MeO}_2\text{C}(\text{CH}_3)\text{CH}]_2$	80	109
18	 $\text{MeO}_2\text{C}(\text{CH}_2)\text{CO}_2\text{H}$	5% MeONa, MeOH		41	110
19	 $\text{MeO}_2\text{C}(\text{CH}_2)_4\text{CO}_2\text{H}$	5% MeONa, MeOH	$\text{MeO}_2\text{C}(\text{CH}_2)_4$ 	53	111



**Scheme 5** Addition of anodically generated radicals to alkenes.

unsubstituted at the carbon atom in  $\beta$ -position to  $Y$ . Nonactivated alkenes react less satisfactorily.

In the oxidation of anionized 1,3-dicarbonyl compounds (Table 8, numbers 1–7) at potentials between 0.6 and 1.4 V (sce) and in the presence of butadiene, mainly the additive dimer (24) is obtained; in the presence of ethyl vinyl ether chiefly the disubstituted monomers (28) or (29) arise.

In the addition to nonactivated alkenes, where the direct anodic oxidation is less, satisfactorily good yields can be achieved when  $Mn(OAc)_2$  is used as mediator (Table 8, entries 6, 7). Sorbic acid precursors have been obtained in larger scale and high current efficiency by a Mn(III)-mediated oxidation of acetic acid/acetic anhydride in the presence of butadiene [112].

Also other anions, such as the 2-nitropropanate anion, Grignard reagents (Table 8, numbers 8 and 9), and borates [113], can be added to olefins.

Also azide radicals generated by anodic oxidation of sodium azide in the presence of olefins afford in acetic acid additive dimers, products of allylic substitution and

additive monomers [114].  $NO_3^\bullet$ -radicals can be prepared by anodic oxidation of nitrate anion. In the presence of terminal and *vic*-disubstituted olefins, nitrate esters are obtained [115]. With an aldehyde and nitrate anion, acyl radicals are generated that afford 1,2-bisadducts with activated olefins [116].

If carboxylates are subjected to Kolbe electrolysis in the presence of olefins, the generated Kolbe radicals add to the double bonds to afford mainly additive dimers (Table 8, entries 10–17).

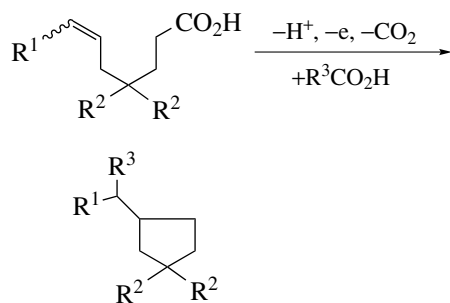
Upon electrolysis of trifluoroacetate in  $MeCN-H_2O$ -(Pt) in an undivided cell in the presence of an electron, deficient olefins additive dimers and additive monomers are obtained. The selectivity can be controlled by current density, temperature, and the substitution pattern of the olefin [117].

The influence of mechanism and kinetic data on yields and selectivities in addition reactions of anodically generated radicals to olefins has been calculated and the predictions tested in preparative electrolyses [118].

Good yields can be obtained with nonactivated alkenes, when the reaction

is conducted intramolecularly.  $\beta$ -Allyloxy- and  $\beta$ -allylaminopropionates cyclize in a mixed Kolbe electrolysis by way of an intramolecular addition (5-*exo-trig* cyclization) and a subsequent heterocoupling of the exocyclic radical to form 3-substituted tetrahydrofurans and pyrrolidines (Table 8, numbers 18 and 19). This intermolecular addition has been used to synthesize a precursor of prostaglandin PGF<sub>2 $\alpha$</sub>  [119, 120].

The extension of the cyclization from tetrahydrofurans and pyrrolidines to carbocycles leads to a sharp decrease in the yield of cyclized product. This is due to the slower cyclization rate of 5-hexenyl radicals compared to 5-(3-oxahexenyl) radicals, which favors the competing bimolecular coupling to the acyclic product. Three measures help to increase the yield in these cyclizations.



R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	yield (%)
CN	CH <sub>3</sub>	(CH <sub>2</sub> ) <sub>4</sub> CO <sub>2</sub> CH <sub>3</sub>	75
CO <sub>2</sub> Et	CH <sub>3</sub>	(CH <sub>2</sub> ) <sub>4</sub> CO <sub>2</sub> CH <sub>3</sub>	76
CN	H	(CH <sub>2</sub> ) <sub>4</sub> CO <sub>2</sub> CH <sub>3</sub>	71
COCH <sub>3</sub>	H	CH <sub>3</sub>	71

(16)

These are the use of the *geminal* dialkyl effect, the decrease of the current density and especially the use of an electrophilic double bond that increases the addition

rate of the mostly nucleophilic Kolbe-radical. With electron-attracting groups at the double bond, the yield of cyclized product increases from 21% to more than 70% (Eq. 16) [121]. For a more detailed discussion, see the literature [122].

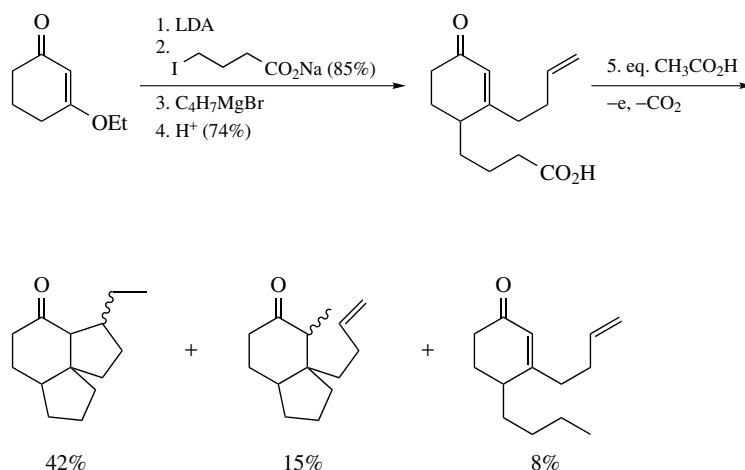
A radical tandem cyclization, consisting of two radical carbocyclizations and a heterocoupling reaction, has been achieved by electrolysis of unsaturated carboxylic acids with different coacids. This provides a short synthetic sequence to tricyclic products, for example, triquinanes, starting from carboxylic acids which are accessible in few steps (Scheme 6) [123]. The selectivity for the formation of the tricyclic, bicyclic, and monocyclic product depending on the current density could be predicted by applying a mathematical simulation based on the proposed mechanism.

Radical cyclizations of this type can be also achieved in chemical radical chain reactions [124, 125], often in a wider scope. The anodically initiated cyclization, however, has advantages. It avoids tin hydride, which is mostly used as coreagent in chemical radical chain cyclizations and because the toxicity of tin organics makes these reactions less attractive for the synthesis of pharmaceuticals. In chemical radical chain reactions, which involve in most cases an addition and an atom-transfer reaction, one C,C- and one C,H- or C,X bond is being formed, while in anodic addition followed by heterocoupling two C,C bonds are being formed, where the second one is established simply and in wide variety by the appropriate choice of the coacid.

### 5.3.5

#### Mediated Oxidation of Alkenes

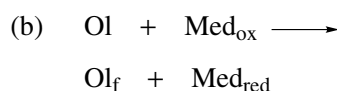
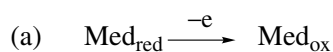
Alkenes, as other organic substrates, can be converted by indirect anodic oxidation.



2 diastereomers 2.7 : 1

**Scheme 6** Radical tandem cyclization to tricyclic compounds.

Here a mediator serves as an oxidant that enables the selective introduction of a functional group. The mediator is thereby reduced and can be regenerated at the anode, so that it acts as a redox catalyst (Eq. 17). The method is very powerful, as very selective oxidants, whose use is limited to smaller amounts due to their price, can be applied in catalytic quantities amounts for larger scale conversions.



Med = mediator,

Ol<sub>f</sub> = functionalized ofefin

(17)

This wide field is covered separately in Chapter 15 of this book. Further reviews to this topic can be found in Ref. [126–128].

In enzymatic syntheses, the use of mediated reactions for the regeneration of enzymes and cofactors becomes increasingly important [129].

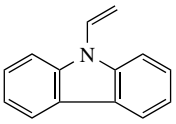
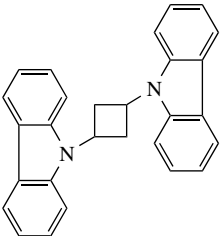
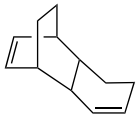
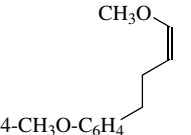
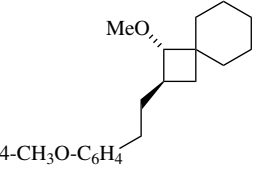
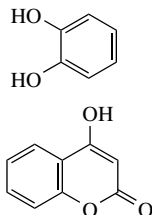
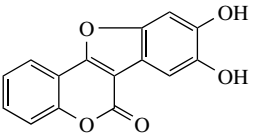
### 5.3.6

#### Anodically Induced Cycloadditions

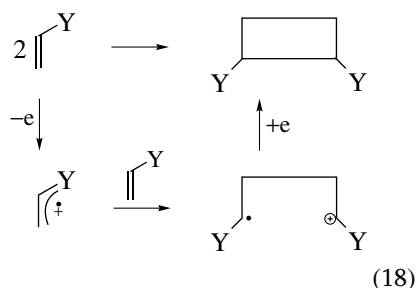
[4 + 2]- and [2 + 2]-cycloadditions can be induced by electron transfer. In a radical chain reaction, the olefin is oxidized to its radical cation, which undergoes a cycloaddition. The distonic dimer radical cation then accepts an electron from the olefin to undergo ring closure and to initiate a new cycle (Eq. 18) [130]. This way vinyl carbazole (Table 9, number 1) and 5,6-dimethoxyindene [131] have been cyclized. Indenone also reacts in an electrocatalyzed [4 + 2]- and [2 + 2]-cycloaddition with styrene derivatives [132]. Furthermore, a series of dienes has been subjected to [4 + 2]- and [2 + 2]-cycloadditions with Ar<sub>3</sub>N<sup>+</sup> as mediator (Table 9, numbers 2



Tab. 9 Cycloadditions of anodically generated intermediates

Nr.	Olefin	Conditions	Product	Yield [%]	Ref.
1		Fe(NO <sub>3</sub> ) <sub>3</sub> , MeOH		80	130
2	1,3-Cyclohexadiene	MeCN, CH <sub>2</sub> Cl <sub>2</sub> lutidine, Ar <sub>3</sub> N		24	133
3	 4-CH <sub>3</sub> O-C <sub>6</sub> H <sub>4</sub>	LiClO <sub>4</sub> CH <sub>3</sub> NO <sub>2</sub>		73	134
4		H <sub>2</sub> O, NaOAc		95	135

and 3).



In other cases, the cycloadditions are not electrocatalytic. The reactive intermediates

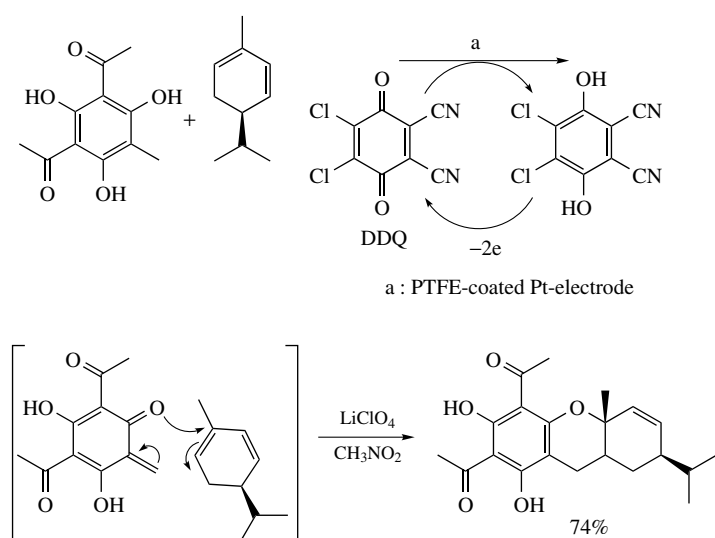
are generated electrochemically and then react with the olefin to form an adduct that stabilizes itself by reaction with a nucleophile or by deprotonation. This way, *ortho*-phenols react with enols presumably via an *ortho*-quinone as intermediate (Table 9, number 4).

In the synthesis of an euglobal skeleton, a quinone methide has been generated in situ by anodic oxidation mediated by DDQ. The cycloaddition with unactivated alkenes was promoted by the use of lithium perchlorate/nitromethane

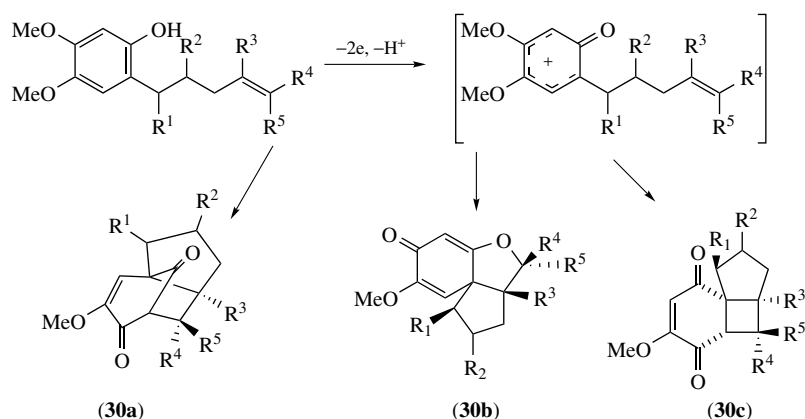
and a hydrophobic PTFE-coated electrode (Scheme 7) [136].

The intramolecular coupling of phenol derivatives with olefins is a very useful C,C bond-forming reaction. Yamamura has shown that this reaction can lead to three different product types (30a–c) (Scheme 8) [137, 138].

The three pathways depended strongly on the configuration of the double bond and the nature of the functional groups attached to the double bonds. The synthetic possibilities have been nicely summarized with some retrosynthetic analyses of the target molecules by Moeller [139].



**Scheme 7** [4 + 2] – Cycloaddition with anodically generated quinone methide.



**Scheme 8** Anodic intramolecular coupling of phenols with olefins.

## 5.4 Anodic Oxidation of Aromatic Compounds

### 5.4.1

#### General Principles of Reaction

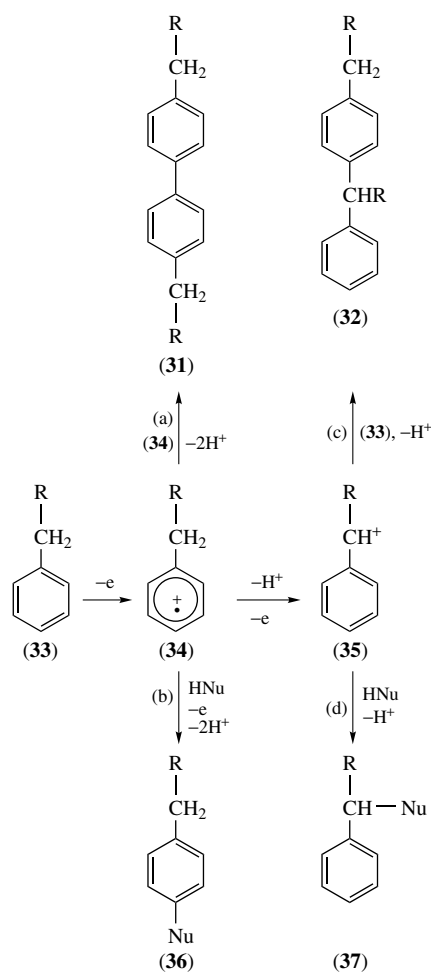
Anodic conversion of aromatics proceeds in most cases by 1e-transfer to the anode to form a radical cation (34) (Scheme 9). Oxidation is facilitated by extension of the  $\pi$ -system ( $E_{1/2}$  vs. Ag/Ag<sup>+</sup> benzene 2.08 V, pyrene 0.86 V) and by electron donating substituents ( $E_{1/2}$  vs. Ag/Ag<sup>+</sup> *p*-phenylenediamine  $-0.15$  V). Oxidation potentials of polycyclic aromatics and substituted benzenes are collected in Ref. [140–142].

The radical cation (34) can react along the following pathways:

- It can undergo a radical–radical coupling reaction with subsequent rearomatization by deprotonation to form biphenyl compounds (31) (Scheme 9). This pathway is supported by electron-donating substituents that stabilize the coupled  $\sigma$ -intermediate.
- The radical cation can react with a nucleophile to afford a nuclear substitution product.
- It can be deprotonated in the benzylic position to form, after a further electron transfer to the anode, a benzyl cation (35), which can undergo an electrophilic aromatic substitution at (33) to yield a diphenylmethane derivative.
- The benzyl cation can react with a nucleophile to lead to a side chain substitution product.

The product distribution between reaction in the nucleus or in the side chain depends

among others on the charge distribution in the radical cation. A high positive charge density at the unsubstituted aromatic carbon atom favors products (31) and (36), while a high positive charge density at an aromatic carbon atom adjacent to an alkyl substituent supports the formation of (32) or (37) [143]. The selectivity, however, is not always pronounced. Investigations on the mechanism of these reactions and the evolving general as well as individual patterns can be found in Ref. [144–146].



**Scheme 9** Reaction pathways of anodically generated aromatic radical cations.

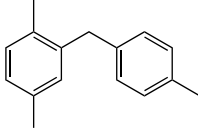
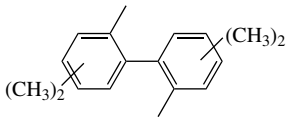
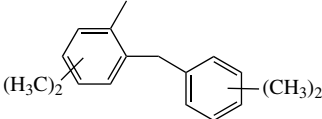
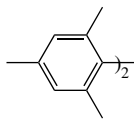
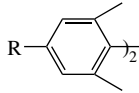
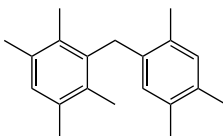
## 5.4.2

**Anodic Coupling**

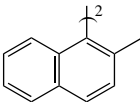
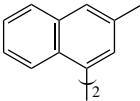
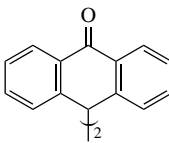
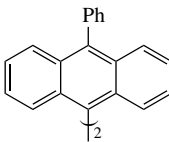
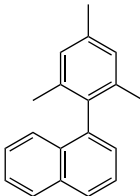
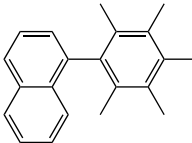
Representative couplings of aromatic hydrocarbons are summarized in Table 10. Alkyl-substituted aromatic hydrocarbons can be coupled to diphenyls and/or diphenylmethanes depending on their substitution pattern (Table 10, numbers 1–6). Reactions occur according to Scheme 9, paths (a) and (c).

For mesitylene and durene, the kinetics have been followed by specular reflectance spectroscopy [159]. The results indicated that mesitylene produces a fairly stable radical cation that dimerizes. That of durene, however, is less stable and loses a proton to form a benzyl radical, which subsequently leads to a diphenylmethane. The stability of the radical cation increases with increasing charge delocalization, blocking of

**Tab. 10** Anodic coupling of aromatic hydrocarbons

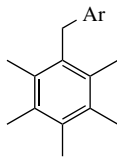
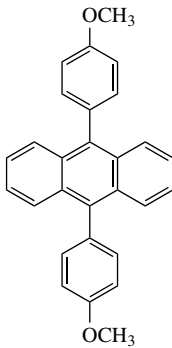
Nr.	Substrate	Conditions	Products	Yield [%]	Ref.
1	<i>p</i> -Xylene	C, CH <sub>2</sub> Cl <sub>2</sub> , TFA, TBABF <sub>4</sub>		22	147
2	1,2,4-Trimethylbenzene	C, CH <sub>3</sub> NO <sub>2</sub> , Bu <sub>4</sub> NBF <sub>4</sub>		17	148
				21	
3	1,3,5-Trimethylbenzene	Pt, Bu <sub>4</sub> NBF <sub>4</sub> , CH <sub>3</sub> CN		71	149
4	5-Alkyl-substituted <i>m</i> -xylenes		 R = Me, Et, <i>i</i> -Pr, <i>t</i> -Bu	4–82	150
5	1,2,4,5-Tetramethylbenzene	C, CH <sub>2</sub> Cl <sub>2</sub> , TBABF <sub>4</sub>		85	147

Tab. 10 (continued)

Nr.	Substrate	Conditions	Products	Yield [%]	Ref.
6	2-Methyl-naphthalene	C, CH <sub>3</sub> CN/H <sub>2</sub> O NaBF <sub>4</sub>		45	151
				28	
7	Anthracene	MeCN, EtOH, LiClO <sub>4</sub>		91	152
8	9-Phenyl-anthracene	TEAClO <sub>4</sub> , MeCN		37	153
9	1,5-Dichloro-anthracene	MeCN, EtOH	1,1',5,5'-Tetrachlorobianthrone	75	154
	<i>Mixed coupling</i>				
10	Naphthalene, mesitylene	Pt, Bu <sub>4</sub> NBF <sub>4</sub> , MeCN, AcOH	1, 1'-Binaphthyl	22	155
				19	
11	Naphthalene, pentamethyl-benzene	Pt, Bu <sub>4</sub> NBF <sub>4</sub> , MeCN, AcOH	1, 1'-Binaphthyl	1.6	156
				64	

(continued overleaf)

Tab. 10 (continued)

Nr.	Substrate	Conditions	Products	Yield [%]	Ref.
12	Hexamethylbenzene and aromatic hydrocarbons (benzene, toluene, <i>p</i> -xylene, mesitylene)	Pt, CH <sub>2</sub> Cl <sub>2</sub> : TFA (9:1), TBABF <sub>4</sub>		8–66	157
13	Anthracene, anisole	Pt, Bu <sub>4</sub> NBF <sub>4</sub> , CH <sub>2</sub> Cl <sub>2</sub> -TFA-TFAn (47:2:1)		70	158

reactive sites, and stabilization by specific functional groups (phenyl, alkoxy, and amino) [160]. The complex reaction mechanisms of radical cations and methods of their investigation have been reviewed in detail [161].

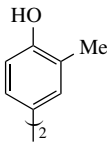
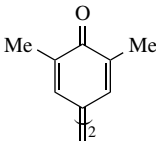
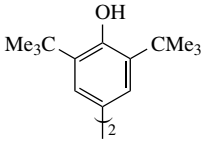
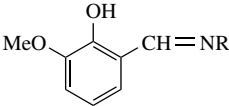
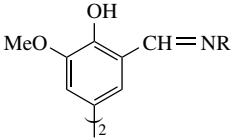
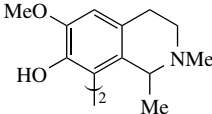
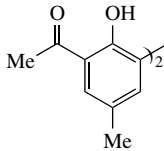
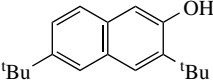
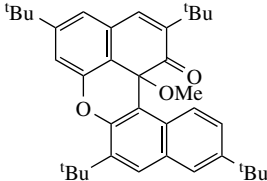
To favor the coupling reaction, the competing side reaction of the radical cation with nucleophiles must be suppressed by the use of a medium of low nucleophilicity. The solvent of choice is dichloromethane. Especially in electroanalytic studies, neutral alumina is frequently added to suppress hydroxylation of the radical cation [162]. The reversible cyclic voltammetric behavior of radical cations is also enhanced in mixtures of methylene dichloride, trifluoroacetic acid, and trifluoroacetic anhydride (TFAn) with TBABF<sub>4</sub> as supporting electrolyte. With acetonitrile as solvent

acetamides, which are formed in a Ritter reaction, are often the major products. The selective dimerization of mesitylene in acetonitrile is exceptional (Table 10, number 3).

*Mixed coupling* between naphthalene and alkyl benzenes has also been demonstrated (Table 10, numbers 10–13). The relative yield of mixed coupling products increases with the basicity of the alkyl benzene; with mesitylene 19%, with tetramethylbenzene 42%, and with pentamethylbenzene 64%. This suggests an electrophilic reaction between naphthalene cation radicals and alkylbenzenes. The mixed coupling reaction of phenanthrene with anisole has been studied kinetically [163].

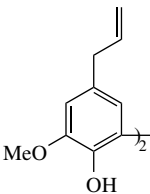
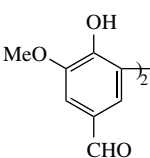
Bibenzyls can be obtained in a remarkable reaction from toluene, *p*-xylene or ethylbenzene in 60 to 100% yield [164]. For

Tab. 11 Anodic coupling of phenols

Nr	Phenol	Conditions	Products	Yield [%]	Ref.
1	<i>o</i> -Cresol	PbO <sub>2</sub> , H <sub>2</sub> SO <sub>4</sub>		5	171
2	2,6-Dimethyl-phenol	Pt, MeCN, NaClO <sub>4</sub> , 2,6-lutidine		90	172
3	2,6-Di- <i>t</i> -butyl-phenol	MeOH/CH <sub>2</sub> Cl <sub>2</sub> , LiClO <sub>4</sub> , Pt, periodic current reversal in divided cell		93	173
4	 R = <i>i</i> -Pr, <i>t</i> -But, CH <sub>2</sub> CH(CH <sub>3</sub> )CO <sub>2</sub> H, Me, Et, Benzyl	Glassy carbon, MeCN, NaClO <sub>4</sub>		41–100	174
5	1,2-Dimethyl-7-hydroxy-6-methoxy-1,2,3,4-tetrahydroisoquinoline	Graphite felt, MeONa, MeCN, TEAClO <sub>4</sub>		69 <sup>a</sup>	175
6	2-Acetyl-4-methyl-phenol	0.1 M NaOH, H <sub>2</sub> O, MeOH, Pt		26	176
7		CH <sub>3</sub> OH-ether, 1% KOH		65	177

(continued overleaf)

Tab. 11 (continued)

Nr	Phenol	Conditions	Products	Yield [%]	Ref.
8	2-Methoxy-4-allyl-phenol	Pt, MeOH-LiClO <sub>4</sub> , NaOH		100	178
9	Vanillin	Pt, MeCN, NaClO <sub>4</sub> , Et <sub>4</sub> NOH, 0.25 V (SCE)		65	179

<sup>a</sup>Only one of three possible diastereomers is obtained; additionally, 7% O-C coupling product is found.

this reaction catalytic amounts of quinones are irradiated in the presence of the alkylbenzenes, and the anode potential is held at that of the quinone–hydroquinone couple. The photo-excited quinone abstracts a benzylic hydrogen to form a radical that dimerizes. The resulting hydroquinone is reoxidized to the quinone.

Cyanation of aromatic hydrocarbons, also a carbon–carbon coupling reaction, is achieved in the case of anthracene in MeCN-Et<sub>4</sub>NCN to yield 54% 9,10-dicyanoanthracene [165]. The cyanation is simplified when it is carried out in an emulsion system (aqueous sodium cyanide, dichloromethane, and TBAHSO<sub>4</sub>). Its synthetic utility in this mode has been demonstrated for the preparation of 4-alkoxy-4-cyanobiphenyls, a class of liquid crystals [166].

Anions of CH-acidic compounds (dimethyl malonate and nitromethane) can be linked to aromatics (benzene, toluene, naphthalene, and 1,4-dimethoxybenzene) when they are coelectrolyzed in methanol–sodium methoxide [167].

The earlier literature on oxidative coupling of phenols is reviewed in Ref. [168] and that on anodic coupling in Ref. [169, 170]; some examples of the coupling reactions are summarized in Table 11, see also Chapter 6.

Phenols are coupled mostly in alkaline media by oxidation of the phenolates to phenoxy radicals. However, coupling in neutral or acidic medium by way of phenoxy radical cations and phenoxonium cations as intermediates is also known. To generate the phenolate ion, bases as alkali hydroxides, Et<sub>4</sub>NOH or 2,6-lutidine are used. The anodically generated phenoxy radicals react by carbon–carbon and carbon–oxygen coupling to dimers, which additionally can be further oxidized. This frequently leads to product mixtures that are synthetically not very useful. Blocking of the 2-, 4- or 6-position makes the coupling reaction more selective. Phenols with unsubstituted *para*-position usually form *para*, *para*-coupling products as the major dimer (Table 11, numbers 1–4). If the 4-position is blocked *ortho*, *ortho*-coupling



is the main reaction (Table 11, numbers 5–9).

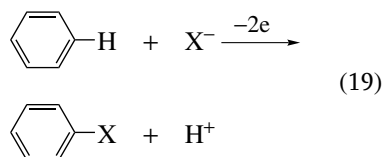
The anodic coupling of aryl ethers is reviewed in Ref. [180]. Aryl ethers are more selectively coupled than phenols for the following reasons: The carbon–oxygen coupling is made impossible and the *ortho*-coupling and the oxidation to quinones become more difficult. A mixture of trifluoroacetic acid (TFA) and dichloromethane proved to be the most suitable electrolyte [181]. TFA enhances the radical cation stability and suppresses the nucleophilicity of water. Of further advantage is the addition of alumina or trifluoroacetic anhydride [182]. Table 12 compiles representative examples of the aryl ether coupling.

The trimethylsilyloxy (TMSO) group is stable under the coupling conditions in acetonitrile (Table 12, number 6). After oxidative dimerization the TMS-ether can be mildly hydrolyzed ( $H^+$  and  $H_2O$ ) to the phenol or converted to a dibenzofuran. 1,2-Dialkoxybenzenes have been trimerized to triphenylenes (Table 5, numbers 7, 8). The reaction product is the triphenylene radical cation, which is reduced to the final product either by zinc powder or in a flow cell consisting of a porous anode and cathode [188]. Anodic trimerization of catechol ketals yields triphenylene ketals, which can function as a platform for receptors, for example, in an artificial caffeine receptor [190].

#### 5.4.2.1 Nuclear Aromatic Substitution

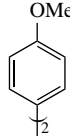
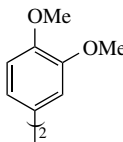
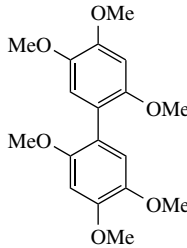
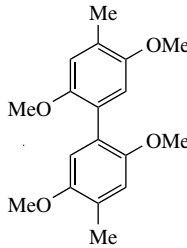
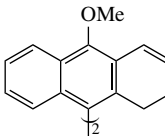
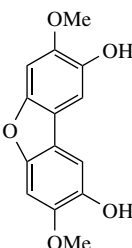
Nuclear aromatic substitution occurs by way of an  $EC_NEC_B$ -sequence as shown in Scheme 9, path (b). It occurs at the carbon atom with the highest positive charge density and in alkylbenzenes competes with side chain substitution via an  $EC_BEC_N$  process by deprotonation of the radical cation to form a benzyl radical.

(Scheme 9, path d). An increasing number of alkyl substituents at the benzylic carbon (toluene 28.6%, ethyl benzene 50.5%, isopropylbenzene 46.7% [191]) and electrolytes of lower nucleophilicity (TBAOAc, HOAc [192]) favor side chain substitution. Table 13 presents some selected examples of aromatic nuclear substitution with different nucleophiles  $X^-$  or  $HX$  (Eq. 19).

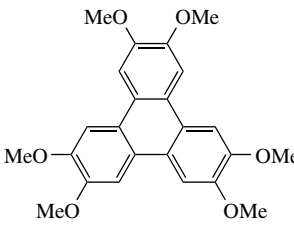
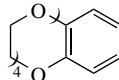


Nuclear methoxylation of substrates with high oxidation potentials proceeds unsatisfactorily because the product with the electron-donating methoxy group is easier to oxidize than the starting compound. With naphthalene and anthracene, this drawback is less pronounced (Table 13, number 1). For the methoxylation of methyl cinnamates that already bear methoxy substituents in the aromatic ring, substitution has been investigated in neutral and basic medium with regard to ring substitution (major product) and double-bond addition whose ratio depends on current density, cell type, electrode material, solvent, substrate, and base concentration [206]. Phenols have been converted to quinones (Table 13, number 2) and these by subsequent cathodic reduction to hydroquinones [194]. The direct oxidation of naphthalenes yields naphthoquinones in 20 to 30% yield; better results (up to 95%) are obtained using indirect methods [197, 207]. Acetoxylation is a more favorable general route to produce phenols by anodic substitution; they can be easily hydrolyzed to phenols and are less susceptible to further oxidations than

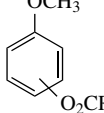
Tab. 12 Anodic coupling of arylothers

Nr.	Aryl ether	Conditions	Products	Yield [%]	Ref.
1	Anisole	Pt, CF <sub>3</sub> CO <sub>2</sub> H-CH <sub>2</sub> Cl <sub>2</sub> (1 : 2), Bu <sub>4</sub> NBF <sub>4</sub>		63	181
2	1,2-Dimethoxybenzene	CF <sub>3</sub> CO <sub>2</sub> H-CH <sub>2</sub> Cl <sub>2</sub> (1 : 2), Bu <sub>4</sub> NBF <sub>4</sub>		86	181
3	1,2,4-Trimethoxybenzene			85	183
4	2,5-Dimethoxytoluene	MeCN, water, TEAClO <sub>4</sub>		No yield given	184
5	9-Methoxyanthracene	MeCN, TFA, Bu <sub>4</sub> NBF <sub>4</sub>		95	185
6	2-Methoxy-1,4-bis(trimethylsiloxy)benzene	CH <sub>3</sub> CN, LiClO <sub>4</sub>		65	186

Tab. 12 (continued)

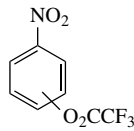
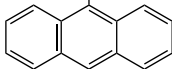
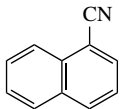
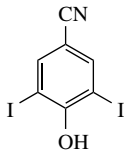
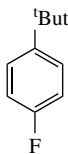
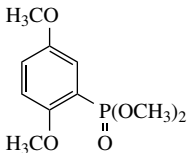
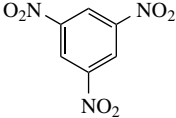
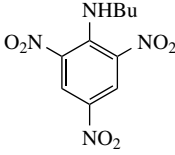
Nr.	Aryl ether	Conditions	Products	Yield [%]	Ref.
7	1,2-Dimethoxybenzene	CH <sub>2</sub> Cl <sub>2</sub> , TFA, Bu <sub>4</sub> NBF <sub>4</sub>		50	187
8		MeCN or CH <sub>2</sub> Cl <sub>2</sub> , TFA	Cyclotrimer	30	188, 189

Tab. 13 Anodic nuclear substitution of aromatic compounds

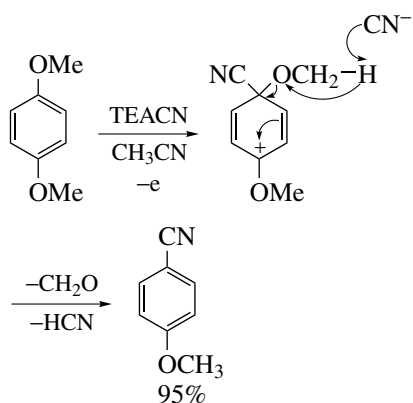
Nr.	Aromatic Compound	X <sup>-</sup> or HX (eq. 19)	Products	Yield [%]	Refs.
1	Naphthalene	CH <sub>3</sub> OH/KOH	1-methoxy-naphthalene, 1,4-dimethoxy-naphthalene, 1,2-dimethoxy-naphthalene, 1,2,4-trimethoxy-naphthalene	21 49 20 6	193
2	2,3,6-Trimethylphenol	H <sub>2</sub> O, acetone, H <sub>2</sub> SO <sub>4</sub> , PbO <sub>2</sub>	2,3,6-trimethylbenzoquinone	85	194
3	Anisol	CH <sub>2</sub> Cl <sub>2</sub> , H <sub>2</sub> O, RCO <sub>2</sub> H, Bu <sub>4</sub> N <sup>+</sup>	 <i>o</i> : <i>m</i> : <i>p</i> = 51 : 1 : 48	51–63	195
4	Naphthalene	NaOAc, HOAc	1-naphthylacetate	22 70–85	196 197

(continued overleaf)

Tab. 13 (continued)

Nr.	Aromatic Compound	$X^-$ or $HX$ (eq. 19)	Products	Yield [%]	Refs.
5	Nitrobenzene	$CF_3CO_2Na/CF_3CO_2H$	 $o : m : p =$ $22 : 59 : 19$	60	198
6	Anthracene	$CH_3CN, (CF_3CO)_2O$ $Bu_4NBF_4$		85	199
7	Naphthalene	Aqueous $NaCN, CH_2Cl_2$ , emulsion		69	166, 200, 201
8	4-Cyanophenol	$H_2O, NaHCO_3, KI$		97	202
9	4- <i>t</i> -Butyl- <i>t</i> -butylbenzene	$CH_3CN, Et_4NF \cdot 3HF$		63	203
10	Hydroquinone dimethyl ether	$CH_3OH, (CH_3O)_3P,$ $(CH_3)_4NSO_4CH_3$		90	204
11		$BuNH_2, DMF, Et_4NBF_4$		30	205

alkoxy products. (Table 13, number. 3–5). Emulsion electrolysis has been successfully applied with phase-transfer catalysts (Table 13, number 3), which allows the conversion of salts that are not or only slightly soluble in organic solvents and which needs only small cell voltages due to the high conductivity of the electrolyte. The acetoxylation is also of technical interest because it affords in good regioselectivity,  $\alpha$ -naphthol (Table 13, number 4). With  $\text{CF}_3\text{CO}_2\text{H}/(\text{CF}_3\text{CO}_2)_2\text{O}$  also acceptor substituted aromatic compounds can be acetoxylation (Table 13, number 5). Further examples of the trifluoroacetoxylation to suppress follow-up reactions are presented in Ref. [208, 209]. A way to retard side chain acetoxylation in alkyl benzenes is by electrolysis in an undivided cell in the presence of Pd on charcoal. By hydrogenolytic cleavage of the benzyl acetate, the unwanted competition product is reconverted into starting material [210]. As substituents also the acetamido (Table 13, number 6) [211], thio [212], cyano [165, 166, 213, 214], halo (Table 13, Nr. 9) [215] and phosphite (Table 13, Nr. 10) can be introduced. With the cyano group, an *ipso* substitution of the methoxy group is observed (Eq. 20) [165].



(20)

The anodic chlorination in some cases allows one to achieve better regioselectivities than chemical alternatives (*p/o* ratio of chlorotoluene in chlorination of toluene: anodic 2.2, chemical alternative 0.5–1.0) [215]. Anodic oxidation of iodine in trimethyl orthoformate afforded a positive iodine species, which led to a more selective aromatic iodination than known methods [216]. Aryliodination is achieved in good yield, when an aryl iodide is oxidized in HOAc, 25%  $\text{Ac}_2\text{O}$ , 5%  $\text{H}_2\text{SO}_4$  in the presence of an arene [217, 218]. Alkyl nitroaromatic compounds, nitroaromatic ketones, and nitroanilines are prepared in good yields and regioselectivity by addition of the corresponding nucleophile to a nitroarene and subsequent anodic oxidation of the  $\sigma$ -complex (Table 13, number 11) [219, 220].

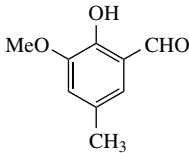
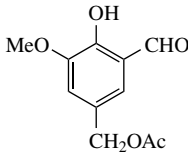
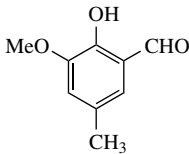
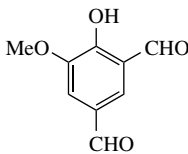
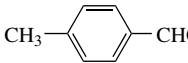
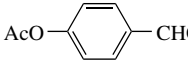
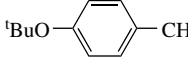
#### 5.4.2.2 Anodic Side Chain Substitution of Aromatic Compounds

Anodic side chain substitution is a competing reaction to nuclear substitution of aromatic compounds. In side chain substitution, the first formed acidic radical cation is deprotonated at the  $\alpha$ -carbon atom of an alkyl group to form a radical. This is further oxidized to a benzyl cation, which reacts with a nucleophile (Scheme 9, path d). The factors that influence the ratio of nuclear to side chain substitution have been described in 5.4.1.

The conversion to the monosubstitution product can in some cases be controlled by the oxidation potential or the substituent at the aryl group (Table 14, number 1–3). Further examples of technical interest can be found in Ref. [221].

In the case of the steroid (38), anodic substitution allowed the selective substitution of the benzylic hydrogen atom by a methoxy group, whose elimination afforded (39) and overall led in a three

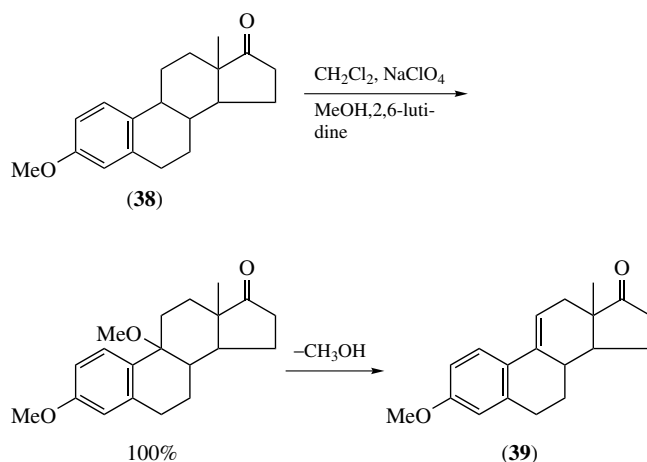
Tab. 14 Anodic side chain substitution

Nr.	Aromatic Compound	$X^-$ or $HX$	Products	Yield [%]	Ref.
1	4-Acetoxy-toluene	HOAc, $t$ BuOH Et <sub>4</sub> NOTos, Cu(OAc) <sub>2</sub>	4-acetoxy-benzylacetate, 4-acetoxy-benzaldehyde, 4-acetoxy-benzaldehyde diacetate	69 8 3	222
2		MeCN, AcOH (3 : 1) NaOAc, NaClO <sub>4</sub> 0.65 V		75	223
3		MeCN, AcOH (3 : 1) NaOAc, NaClO <sub>4</sub> 0.8 V		73	223
4	<i>p</i> -Xylene	CH <sub>3</sub> OH, AcOH, NaBF <sub>4</sub>		86	226
5	<i>p</i> -Cresyl-acetate	CH <sub>3</sub> OH, AcOH, NaBF <sub>4</sub>		72	226
6	<i>p</i> -Cresyl- $t$ butyl ether	MeOH, KF		80–85	227

step reaction to a corticoid with the last step being a hydroboration/oxidation (Scheme 10) [224]. Oxidation of toluene in CH<sub>3</sub>CN/LiClO<sub>4</sub> with traces of water affords *N*-acetyl benzylamine in nearly quantitative yield [225].

Oxidation of substituted toluenes to substituted benzaldehydes or their acetals is a reaction that is of high technical interest. It is performed by direct as well as indirect anodic oxidation. A number of direct oxidations is shown in Table 14, Nr. 4 to 6.

Some of these processes have been developed for technical conversions and have been summarized in Ref. [228, 229]. The anodic technical production of *t*-butylbenzaldehyde has been coupled with the cathodic reduction of phthalic anhydride to phthalide in a paired electrosynthesis in a capillary gap cell [230]. Indirect oxidations with Mn<sup>2+</sup>/Mn<sup>3+</sup> or Ce<sup>3+</sup>/Ce<sup>4+</sup> as mediators are reported in [231–234]. With tris(2,4-dibromophenyl)amine as mediator, different substituted toluenes are converted



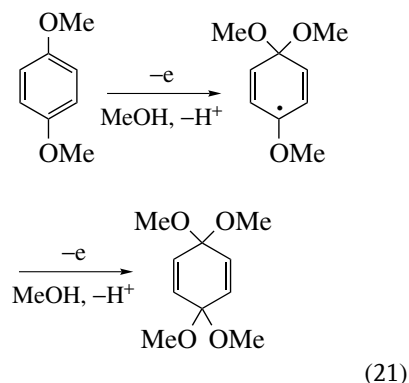
**Scheme 10** Synthesis of a corticoid precursor (39) by anodic substitution.

in a 6e-oxidation in good yields to trimethyl orthoesters of substituted benzoic acids [235].

#### 5.4.3

##### Anodic Addition

Aromatic compounds, substituted in 1,4-position with methoxy or hydroxy groups, undergo 1,4-addition with loss of the aromaticity (Eq. 21) (Table 15, numbers 1,2).



A synthon for an “unpoled” quinone has been prepared by anodic

addition of methanol to 2-bromo-1,4-dimethoxybenzene (Table 15, number 3). Anodic oxidation of catechols leads to reactive 1,2-quinones, which can be trapped with 1,3-dicarbonyl compounds or dienes (Table 15, numbers 4,5).

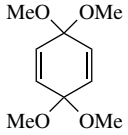
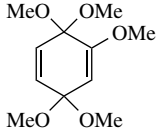
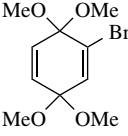
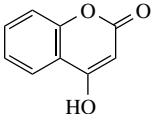
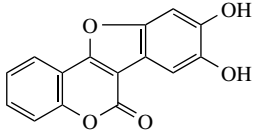
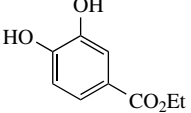
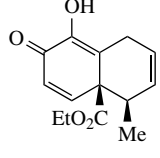
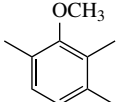
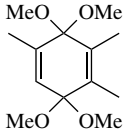
The conversion to quinones is of technical interest (Vit. E, K) starting from phenol ethers or naphthalines (Table 15, number 6) is compiled in Ref. [242]. For the oxidation to naphthoquinones, indirect methods proved to be superior [243].

#### 5.5

##### Comparison of Anodic Conversions of Alkanes, Alkenes, and Aromatic Compounds with their Chemical Transformations

Conversion of alkanes means substitution of a hydrogen atom for a heteroatom. This is achieved at the anode by transfer of two electrons from a C–H bond to the electrode and reaction of the intermediate carbocation with a nucleophile. Chemically in most cases either a chlorine or bromine

Tab. 15 Anodic addition to aromatic compounds

Nr.	Aromatic Compound	$X^-$ or HX	Product	Yield [%]	Ref.
1	Hydroquinone dimethyl ether	CH <sub>3</sub> OH/KOH		75	236
2	1,2,4-Trimethoxybenzene	CH <sub>3</sub> OH, KOH		91	237
3	2-Bromo-1,4-dimethoxybenzene	MeOH, MeONa		75	238
4	Catechol + 	cpe(1.1 V vs. sce), aq. NaOAc		95	239
5	 + 1,3-pentadiene	CH <sub>3</sub> NO <sub>2</sub> , LiClO <sub>4</sub> 0.5%, HOAc		92	240
6		CH <sub>3</sub> OH, KF		77	241

atom is introduced via a radical chain substitution. The halide is subsequently exchanged for other nucleophiles in a  $S_N1$  or  $S_N2$  reaction. The electrochemical reaction has the advantage that oxygen and nitrogen groups can be introduced directly

in one step, while the chemical version in general needs two steps. On the other side, the regioselectivity is presently better to control in chemical reactions and competing side reactions as C,C bond cleavage or skeletal rearrangements are less frequent.



Conversion of alkenes comprehends dimerization, substitution, and addition. Dehydrodimerization and additive dimerization can be achieved at the anode with different sorts of alkenes in one step. Such reactions are rare in chemical conversions and mostly multistep sequences are needed. Such couplings are, for example, the transition metal-catalyzed Heck- [244] or metathesis-reaction [245]. They require mostly more reaction steps and expensive catalysts but lead to homo- and heterocoupling with high selectivity. Substitutions of allylic hydrogen can be achieved at the anode with a fairly large variety of heteroatom groups, as the halo, hydroxy, oxo or amino group, in a one-pot reaction. Chemically, this is achieved mostly in a radical chain substitution of hydrogen for chloride or bromide and a subsequent nucleophilic substitution of the halide against other heteroatoms. The advantage of the anodic conversion is the one-pot conversion, while the chemical transformations need several steps. This is compensated frequently by a higher selectivity in the chemical reaction. Anodic addition is a unique conversion because it allows the addition of two nucleophiles to the double bond in one step. In chemical additions, mostly a nucleophile and an electrophile are added. In anodic additions, however, the regio- and stereoselectivity is often less developed than in chemical additions.

The conversion of aromatic compounds comprises coupling, nuclear and benzylic substitution, and in some cases, addition. Homo- and in a more limited scope, heterocoupling is achieved for unsubstituted and substituted aromatic compounds in direct or indirect anodic processes. Chemically, there is a limited variety of expensive oxidation reagents available, but a large scope of transition

metal-catalyzed selective heterocouplings, as the Kumada-, Heck- [246], Stille- and Suzuki [247]-coupling, is described. Again the higher selectivity in chemical versus electrochemical coupling has to be paid for by expensive catalysts or reagents and more reaction steps. Anodic oxidation offers a fairly large potential for oxidation of the benzylic position to alcohols, ketones, aldehydes, and carboxylic acids and is in this respect superior to a chemical reaction also because selectivity plays a minor role in these conversions. Anodic nuclear substitution allows the one-step introduction of the hydroxy, amino or cyano group, while in chemical nuclear substitution, the groups that can be directly introduced are confined to the bromo, chloro, nitro, and sulfonyl group, while other substituents have to be introduced in multistep conversions. There the anode has a fairly large not yet fully exploited potential. Addition reactions rely mainly on oxidations and are preferably done directly at the anode or mediated with a selective oxidant in catalytic amounts in an indirect electrolysis.

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## 6 Oxidation of Oxygen-containing Compounds (Alcohols, Carbonyl Compounds, Carboxylic Acids)

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## 6.1 Introduction

The anode is an ideal reagent to oxidize organic substrates such as oxygen-containing compounds (alcohols, carbonyl compounds, and carboxylic acids). Thereby these substrates can be converted avoiding chemical reagents, which simplifies the reaction conditions and the work-up. Additionally, the electron transfer leads selectively to a variety of reactive species, which can find further use in organic synthesis.

The reactions can be classified into two categories, direct and indirect oxidation methods, which are schematically represented in Figs. 1 and 2.

In the direct method substrates are oxidized by electron transfer from the substrate to the anode, while in the indirect method they are oxidized in solution by the oxidized form of a mediator that is generated from the reduced form at the anode. Thus, efficiencies in direct and indirect methods are largely dependent on the oxidation potentials of substrates and mediators, respectively.

Since alcohols and ketones generally possess high oxidation potentials, the indirect method is often applied to those compounds, while phenols and carboxylic acids are mainly oxidized by

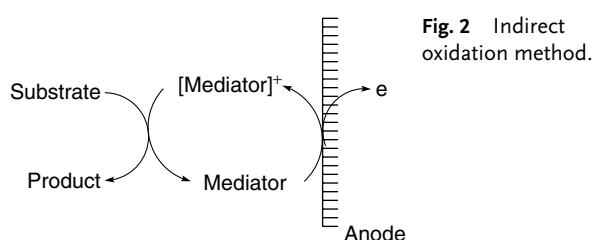
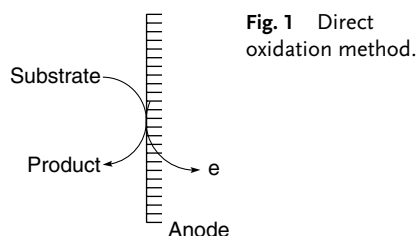
the direct method, though there have been exceptions.

Both direct and indirect anodic oxidation have a variety of advantages over chemical oxidation methods.

This article shows a variety of patterns of electrochemical oxidation of oxygen-containing compounds (alcohols, carbonyl compounds, and carboxylic acids), aiming to be helpful for both electroorganic and organic chemists to cover this field from a synthetic viewpoint. Since there have been excellent books [1–5] published on the subject, this article quotes only some typical and important papers from before 1990.

## 6.2 Oxidation of Alcohols

Direct electrochemical oxidation is not a convenient way for a preparative production of carbonyl compounds from alcohols due to the unselectivity caused by the high oxidation potentials of alcohols. Thus, there have been only a few compounds (some aliphatic alcohols, glycols, and related alcohols) that have been oxidized by the direct method, while the indirect method has often been used to oxidize selectively a variety of alcohols, since it does not



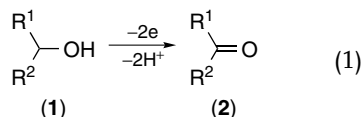
depend on the oxidation potentials of the substrates.

#### 6.2.1

##### Direct Oxidation of Alcohols

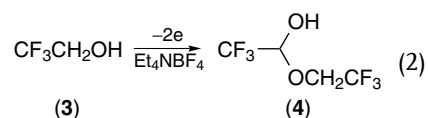
###### 6.2.1.1 Aliphatic Alcohols

The direct electrochemical oxidation of aliphatic alcohols (1) to carbonyl compounds (2) (Eq. 1) is not a convenient way for synthesis because of the high oxidation potentials of alcohols. The oxidation always competes with the oxidation of a solvent and supporting electrolyte, leading to low current efficiencies and side products.



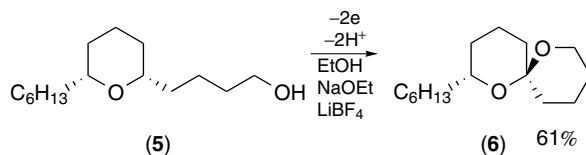
Although the lower alcohol homologues such as MeOH and EtOH can be oxidized electrochemically in aqueous solution, the mechanism is complex and barely investigated [6]. Electrolysis of the neat liquid is one way to achieve the direct oxidation of MeOH and EtOH [7].

Another recently reported example is the electrochemical oxidation of 2,2,2-trifluoroethanol (3) to trifluoroacetaldehyde 2,2,2-trifluoroethyl hemiacetal (4), which can be used as an equivalent of trifluoroacetaldehyde (Eq. 2) [8]. The yield of (4) was 70 to 75% at a current consumption of 1.5 F mol<sup>-1</sup>.



Higher alcohols, however, cannot be used as neat liquids in electrolysis. For anodic oxidation those alcohols must be dissolved in appropriate solvents. Acetonitrile is the most frequently used solvent for that purpose. Electrochemical oxidation of *n*-butyl alcohol to *n*-butyraldehyde was achieved in moderately dilute acetonitrile solution in a current yield of 77% [9].

The oxidation of alkoxides instead of alcohols is an alternative to achieve the desired oxidation. A spiro-cyclization of (5) occurred, when it was electrolyzed in EtOH containing both EtONa and LiBF<sub>4</sub> to afford 61% of the spiroacetal (6)

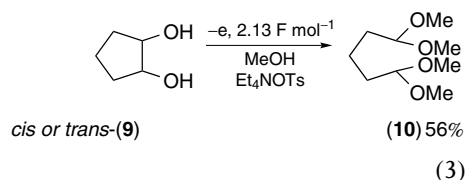


**Scheme 1** Anodic conversion of ether to ketal.

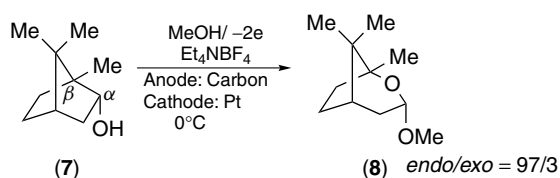
(Scheme 1) [10]. The choice of solvent and supporting electrolyte was important for the selectivity.

Alcohols with ring strain can be oxidized by the direct method. Borneol (7) was electrochemically oxidized in MeOH with cleavage of the  $C_\alpha-C_\beta$  bond to afford (8) with an *endo/exo* ratio of 97/3 in more than 70% yield at 5 F mol<sup>-1</sup> (Scheme 2) [11].

**Glycols and related alcohols:** In contrast to aliphatic monoalcohols (1), 1,2-glycols and related compounds (2-methoxy alcohols, 1,2-amino alcohols) can be easily oxidized by the direct electrochemical method [12]. For example, 1,2-cyclopentanediol (9) affords diacetal (10) in 56% yield as the main product (Eq. 3).

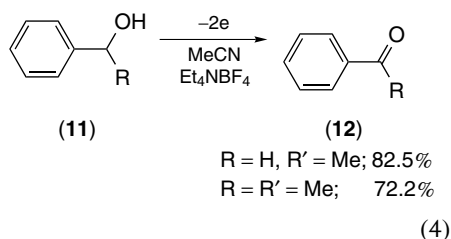


Similarly, the electrooxidation of alcohols carrying a  $\beta$ -methoxy or  $\beta$ -diethylamino group leads to the corresponding cleavage products in high yields [13].



**Scheme 2** Conversion of alcohol into cyclic acetal by anodic oxygen insertion.

**Benzyl alcohols:** Aryl alkyl carbinols (11) can be oxidized to ketones (12) by the direct electrochemical method (Eq. 4) since they possess their oxidation potentials at around 2.0 V versus SCE (saturated calomel electrode); however, cleavage products decrease the selectivity [14].



### 6.2.2

#### Indirect Oxidation of Alcohols

The direct electrochemical oxidation of alcohols is in many cases unselective because of the high oxidation potentials of the alcohols. One possible way to avoid this disadvantage is the use of a mediatory system (an indirect oxidation). Thereby a mediator is converted to its oxidized form at a less positive potential than that required for the direct oxidation of the alcohol, and the oxidized form of the

mediator oxidizes the alcohol (see also Chapter 15).

Mediators can be classified into two categories: (1) mediators fixed to the electrode surface and (2) mediators that dissolve in the solution. A representative of the first category is the nickel hydroxide electrode (NHE) and the second category involves inorganic (metal and halide ions) and organic mediators.

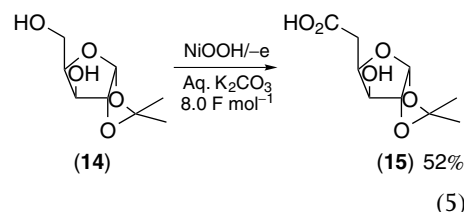
#### 6.2.2.1 Mediators Fixed to the Electrode Surface

A variety of alcohols can be oxidized at the nickel hydroxide electrode. The mediator is presumably a nickel oxide hydroxide, which is fixed to the electrode surface and is continuously reformed at the electrode surface.

Primary and secondary alcohols (**1**) were converted to carboxylic acids (**13**) and ketones (**2**), respectively, in excellent yields when the electrolysis was carried out using the nickel hydroxide electrode in aqueous solution (Scheme 3) [15].

Primary hydroxyl groups are more easily oxidized than secondary ones. The different reactivity of secondary and primary

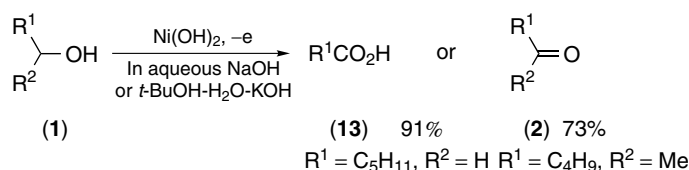
hydroxyl groups allowed the chemoselective oxidation of 1,2-*O*-isopropylidene- $\alpha$ -D-xylofuranose (**14**) to the carboxylic acid (**15**) (Eq. 5) [16].



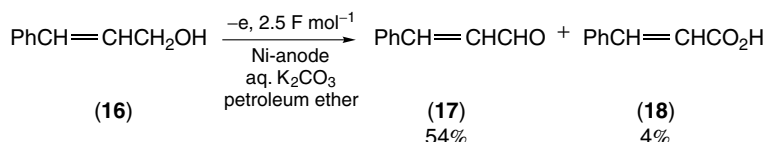
$\alpha,\beta$ -Diols were oxidatively cleaved at the  $C_\alpha-C_\beta$  bond [16].

The conversion of primary alcohols to aldehydes was achieved by using a biphasic system consisting of water and a nonpolar organic solvent such as petroleum ether. Under these conditions, benzylic and allylic alcohols were oxidized with high selectivity to the aldehydes (for example, (**16**) to (**17**) in Scheme 4), while aliphatic alcohols were converted to aldehydes with poor selectivity [17].

Other examples of conversion using a nickel oxide electrode are the oxidation of benzyl alcohols. A nickel foam electrode was used for oxidation [18] in this case and the mechanism was studied by



**Scheme 3** Oxidation of aliphatic alcohol at the nickel oxide electrode.



**Scheme 4** Oxidation of allyl alcohol at the nickel oxide electrode.

means of cyclic voltammetry and polarization curves [19].

#### 6.2.2.2 Mediators Dissolved in the Electrolyte

**6.2.2.2.1 Metal Ion Mediators** A variety of metal salts and complexes have often been used as soluble mediators for the indirect electrochemical oxidation of alcohols. In particular, there have been many studies on the oxidation of benzyl alcohols to benzaldehydes.

– *Ru complexes*: Redox couples of Ru(II)/Ru(IV) [20–22], Ru(IV)/Ru(V) [23], and Ru(IV)/Ru(VII) [24] were used for the oxidation of alcohols (1) to carbonyl compounds (2) or carboxylic acids (13). A double mediatory system consisting of Ru(IV)/Ru(VIII) and  $\text{Cl}^-/\text{Cl}^+$  redox couples has been developed for the oxidation of alcohols and aldehydes [25–28].

–  $\text{Co}_2(\text{SO}_4)_3$ : Electrochemical oxidation of  $\text{CoSO}_4$  generated  $\text{Co}_2(\text{SO}_4)_3$  that reacted with 1-naphthylmethanol in tri-butyl phosphate to give 1-naphthaldehyde in 66% yield [29, 30].

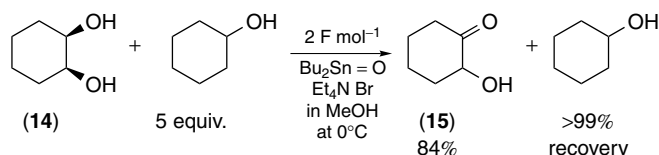
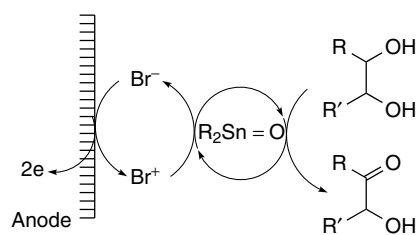
–  $\text{H}_2\text{CrO}_4$ : Propargylic acid was prepared from propargylic alcohol by oxidation with chromic acid ( $\text{H}_2\text{CrO}_4$ ) in  $\text{H}_2\text{SO}_4$ , and the resultant  $\text{Cr}_2(\text{SO}_4)_3$  was electrochemically regenerated to  $\text{H}_2\text{CrO}_4$  [31, 32]. This mediator reaction is an example of the excellent method, that is, a system consisting of an electrochemical cell and a chemical reactor.

–  $\text{K}_6\text{SiW}_{11}\text{O}_{39}\text{Mn(II)}$ : Manganese ion-substituted silicon polyoxotungstate can be used as a mediator for alcohol oxidation. Constant potential electrolysis of 1-phenylethanol at 1.25 V in the presence of 5 mol% of the catalyst gave acetophenone in 61% yield [33].

–  $\text{Bu}_2\text{Sn}=\text{O}$ : Selective oxidation of 1,2-diols to  $\alpha$ -hydroxy ketones was electrochemically achieved in a double mediatory system consisting of dialkyl tin oxide and the bromide ion (Fig. 3) [34].

The most interesting point in this oxidation was the high chemoselectivity. For example, 1,2-diol (14) was selectively oxidized to give  $\alpha$ -hydroxy ketone (15) in 84% yield at a current consumption of  $2 \text{ F mol}^{-1}$ , even though the electrolysis was carried out in the presence of

Fig. 3 Mediated oxidation of diols.



Scheme 5 Selective anodic oxidation of diol to  $\alpha$ -hydroxyketone.

cyclohexanol (5 equiv. to **14**) and in MeOH as a solvent (Scheme 5).

#### 6.2.2.2.2 Halide Ion Mediators

–  $I^-$ : Secondary alcohols are oxidized to ketones and primary alcohols are oxidized to esters, when iodonium ion is used as a catalytic mediator as shown in Fig. 4 [35]. This method may have high potentiality in organic synthesis, since it requires only a catalytic amount of KI, whereas most of the hitherto known oxidations usually require more than one equivalent of the oxidizing agent.

–  $IO_3^-/IO_4^-$ : The periodate/iodate redox mediatory system was applied to the conversion of 2,3-butanediol to acetaldehyde in 80% current efficiency [36].

–  $Br^-$ :  $\alpha$ -Hydroxy-arylacetic acid esters were oxidized with bromide ion as a mediator to give  $\alpha$ -oxo-arylacetic acid esters [37].

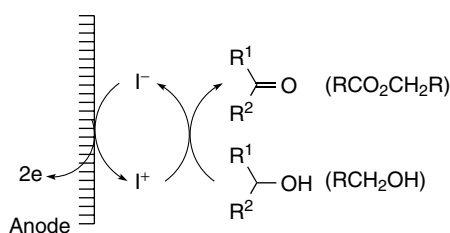
–  $Cl^-$ :  $Cl^-$  is in general not as good as  $Br^-$  and  $I^-$  as a mediator, but it worked well for the conversion of

aldoximes ( $R-CH=N-OH$ ) to nitriles ( $R-CN$ ). The intermediates were nitrile oxides ( $R-CN-O$ ), which were reduced at the cathode to nitriles. The yields decreased in the order of  $Cl^- > Br^- > I^- > ClO_4^-$  [38].

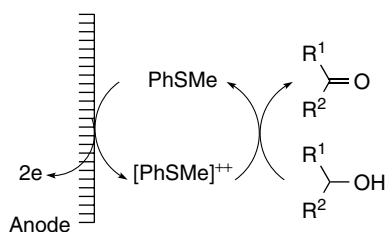
–  $Cl^-/ClO^-$ : In the presence of polymer-supported phase transfer catalyst and redox mediator  $Cl^-/ClO^-$ , the oxidation of benzyl alcohol to benzaldehyde or benzoic acid was achieved [39–41].

–  $NO_3^-$ : Nitrate ion worked as a mediator to oxidize simple alkanols to the corresponding ketones [42].

**6.2.2.2.3 Organic Mediators** Organic mediators are very useful in electroorganic chemistry since their structural modification may increase the selectivity of the oxidation. The first organic mediator exploited for oxidation in synthesis was thioanisole. Since then, there appeared a variety of other organic mediators such as tri-arylamines, tetramethylpiperidiny-1-oxyl (TEMPO), and *N*-hydroxyphthalimides (NHPIs).



**Fig. 4** Iodide-mediated oxidation of alcohols.



**Fig. 5** Thioanisole-mediated oxidation of alcohols.



– *Thioanisole*: A system utilizing thioanisole as an organic mediator was developed for the oxidation of secondary alcohols to ketones (Fig. 5; 2-octanol to 2-octanone; 99%, menthol to menthone; 92%, cyclododecanol to cyclododecanone; 75%) [43]. The use of 2,2,2-trifluoroethanol as a solvent in the mediatory system improved the yields [44].

Furthermore, a double mediatory system consisting of alkyl methyl sulfide and bromide ion was developed, which made the oxidation of alcohols feasible at a lower potential (1.1 V vs SCE) than that of thioanisole (1.60 V vs SCE) [45]. Both the alkyl methyl sulfide and the bromide ion act together as mediators. Under this condition 2-octanol was oxidized to 2-octanone in 85% yield.

Other organic mediators are as follows:

– *Trisarylaminines*: Trisarylaminines have been successfully used as redox catalysts in many indirect electrochemical oxidations. Their advantage is the possibility to adjust their oxidation potential by selection of the substituents on the aromatic rings.

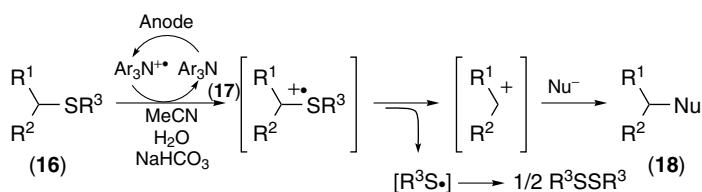
The compounds so far exploited cover a potential range from 0.8 to about 2.0 V versus NHE [46].

Oxidation reactions using mediators are possible under very mild conditions with high selectivity. In fact, the oxidative cleavage of the carbon–sulfur bond of thio ether (16) was easily possible by using mediator (17) (Scheme 6) [46].

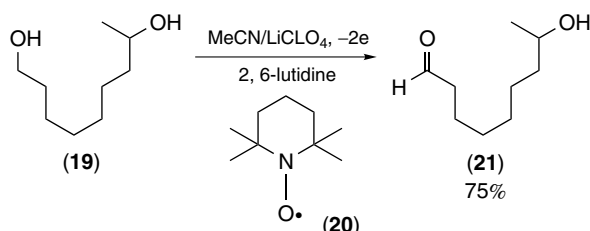
Furthermore, the mediator has been used for the bond cleavage of benzyl ethers, the oxidation of benzyl alcohol to benzaldehyde, the oxidation of toluene derivatives to benzoic acid esters, and the oxidation of aliphatic ethers [47].

– *TEMPO*: 2,2,6,6-Tetramethylpiperidiny-1-oxy (20: TEMPO) works as a mediator for the oxidation of primary alcohols to aldehydes. The oxidation of secondary alcohols is much slower than that of primary alcohols as exemplified by the oxidation of (19) to (21) (Scheme 7) [48]. Active species is the oxo-ammonium generated from TEMPO.

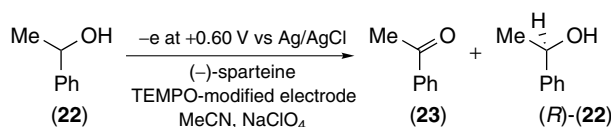
TEMPO has been structurally modified to bring about new selectivities [49, 50].



**Scheme 6** Indirect anodic cleavage of thioethers with trisarylaminines.



**Scheme 7** Selective anodic oxidation of diols with TEMPO as mediator.

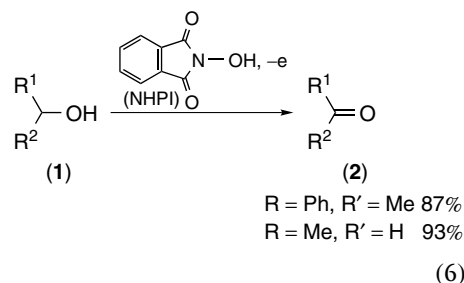


**Scheme 8** Enantioselective oxidation of alcohols with TEMPO/sparteine.

As a result, a highly enantioselective oxidation of (22) was achieved by using a TEMPO-modified graphite felt electrode in the presence of (–)-sparteine, where the enantiopurity of the remaining (22) was >99% and the current efficiency for (23) was >90% (Scheme 8) [51]. However, this selectivity has been questioned [52].

A double mediatory system consisting of modified TEMPO and halide ion or metal ion was also exploited for the oxidation of alcohols [53–55]. A number of carbohydrates have been chemoselectively oxidized at the primary hydroxyl group to uronic acids [56].

– *N*-Hydroxyphthalimide: *N*-Hydroxyphthalimide (NHPI) was shown to be a mediator for the electrochemical oxidation of (1) to (2) (Eq. 6) [57, 58], although the yields of (2) were not always satisfactory. A large deuterium isotope effect ( $k_H/k_D = 10.6$ ) was observed in the oxidation of benzhydrol [59]. Recently, tetrafluoro-NHPI was found to be efficient for the oxidation of borneol [60].



– *Flavin*: Riboflavin-2',3',4',5'-tetraacetate works as a mediator in the photoinduced

electrochemical oxidation of benzyl alcohol to benzaldehyde [61].

### 6.3 Oxidation of Phenols

Phenols (1.8 V vs Ag/Ag<sup>+</sup>) [62], in particular phenolate ion (0.55 V vs Ag/Ag<sup>+</sup>) [63], are easily oxidized by the electrochemical method to give cationic intermediates, which react with nucleophilic solvents such as MeOH, MeCN, or H<sub>2</sub>O or with the phenol itself, yielding dimers.

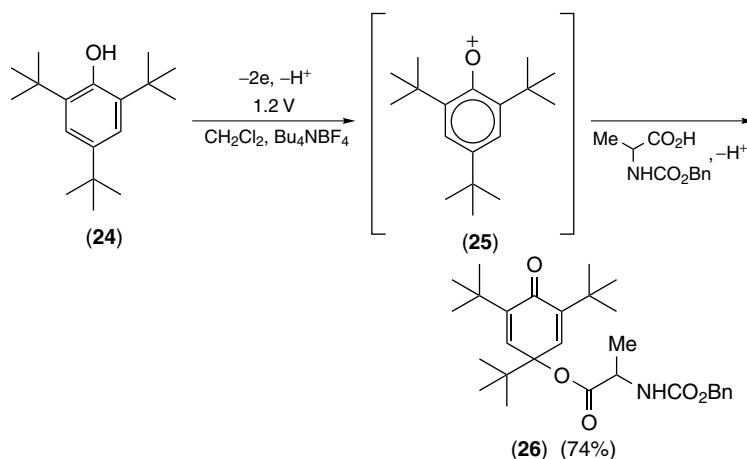
#### 6.3.1 Oxidation of Phenols to Quinones

Sterically hindered phenol (24) was electrochemically oxidized to afford a phenoxenium ion (25) that reacted with *O*- and *N*-nucleophiles to yield a cyclohexadienyl-protected amino acid (26) (Scheme 9) [64].

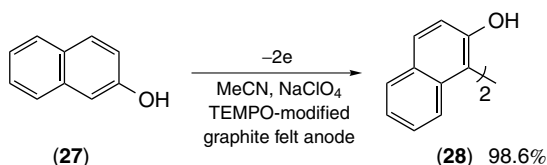
Similarly, 2,6-di-*t*-butyl-phenol was oxidized to 2,6-di-*t*-butyl-*p*-quinone in 60% yield under conditions of MeOH–AcOH containing NaBF<sub>4</sub> [65].

#### 6.3.2 C, C–Bond Formation

A variety of phenol couplings have been described. Those reported before 1991 have been reviewed [66]. 2-Naphthol (27) was oxidized to 1,1'-binaphthol (28) in high current efficiency on a graphite felt electrode coated with a thin poly(acrylic acid) layer immobilizing 4-amino-2,2,6,6-tetramethylpiperidiny-1-oxy (4-amino-TEMPO) (Scheme 10) [67].



**Scheme 9** O-protection of amino acids by oxidative coupling with phenols.



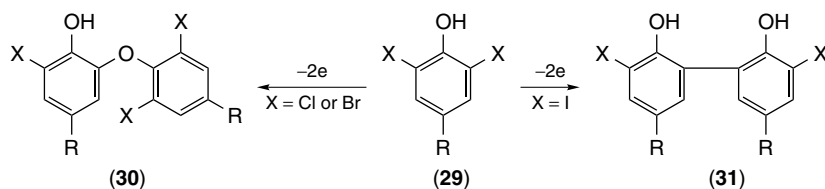
**Scheme 10** Anodic coupling of  $\beta$ -naphthol mediated by TEMPO.

Phenols (**29**) substituted with bromo- and chloro-atoms in the *o*, *o'*-positions were oxidized to diaryl ethers (**30**), while the iodo-substituted phenols (**29**) provided the diaryls (**31**) as major products (Scheme 11) [68].

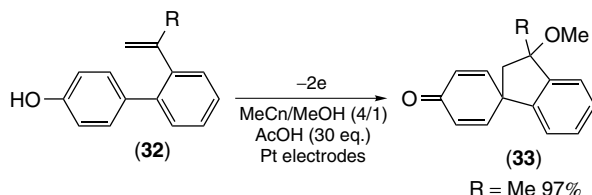
The electrochemical oxidation of 4-(2'-alkenylphenyl)phenols (**32**) in MeCN/MeOH affords spirodienones (**33**) arising from cyclization by the intramolecular addition of the 4-position of the phenol to the olefinic side chain and

the reaction of the resulting benzylic cation with MeOH (Scheme 12) [69–71]. The efficiency of this C–C bond forming reaction depends on the olefinic substituents R.

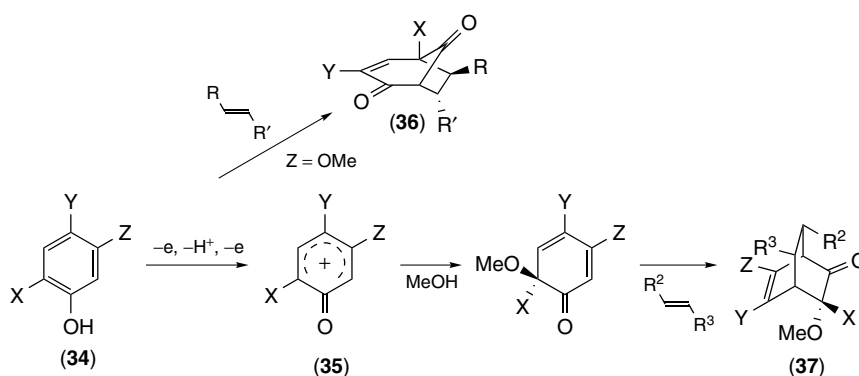
Phenoxy cations (**35**) electrochemically generated from phenols (**34**) react with olefins to afford two types of bicyclic compounds (**36**) and (**37**), depending on the substituents (X, Y, Z), the solvent used for electrolysis, and the structure of the olefin (Scheme 13) [72].



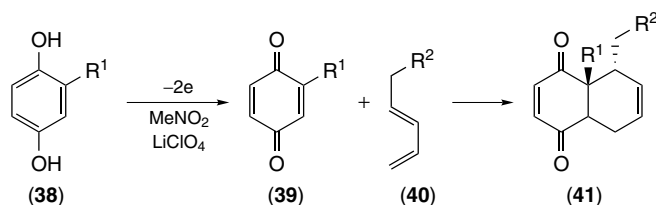
**Scheme 11** Anodic C,C- and C,O-coupling of phenols.



**Scheme 12** Spirodienones by intramolecular phenol–alkene coupling.



**Scheme 13** Anodic cycloadditions with phenols and alkenes.



**Scheme 14** Anodic cycloadditions with hydroquinone and dienes.

Similarly, an intramolecular C–C bond formation was observed in the electrolysis of other phenols with olefinic functionality in the side chain [73–76].

The electrochemical oxidation of phenols produces quinones that can be used as dienophiles for the Diels–Alder reaction. A typical example is shown in Scheme 14, where a lithium perchlorate/nitromethane system and an electrode coated with a PTFE [poly-(tetrafluoroethylene)] fiber, to create a hydrophobic reaction layer,

supported the Diels–Alder reaction between in situ generated quinone (39) and diene (40) to give the adduct (41) [77, 78].

#### 6.4

#### Oxidation of Carbonyl Compounds

The electrochemical oxidation of carbonyl compounds is achieved by direct and indirect methods.

## 6.4.1

**Direct Oxidation of Carbonyl Compounds**

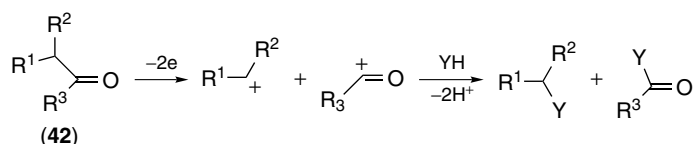
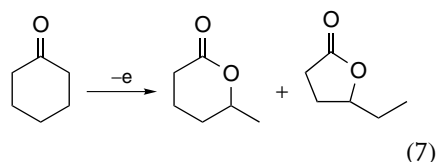
$\alpha$ -Cleavage was observed as the main route in the electrochemical oxidation of aliphatic  $\alpha$ -branched ketones (42) (Scheme 15) [79, 80].

For example, acetyladamantane and isopropyl methyl ketone gave 1-adamantyl-acetamide in 85% yield and *N*-acetyl-isopropylamine in 46% yield, respectively [79]. A similar  $\alpha$ -cleavage was observed in the electrochemical oxidation of the  $\alpha$ -branched cyclic ketone (43) using Et<sub>3</sub>N-5HF as an electrolyte (Scheme 16) [81].

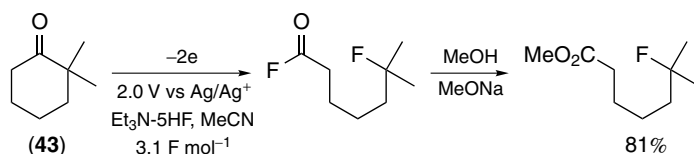
On the other hand, acyclic ketones, when oxidized in trifluoroacetic acid [82] or in MeCN [83], gave dehydrogenated ketones and products substituted at the remote ( $\gamma$ ,  $\delta$ , or  $\varepsilon$ ) positions.

For example, 2-hexanone in MeCN gave 5-acetamino-2-hexanone (44) in 40% yield (Scheme 17) [82], and 2-pentanone was oxidized in trifluoroacetic acid to give a mixture of 4-trifluoroacetoxy-2-pentanone (24%) and 3- and 4-penten-2-one (6%) [83]. A mechanism involving intramolecular hydrogen abstraction by a ketone cation radical that forms a carbenium ion via a [1,5]-hydrogen shift was proposed.

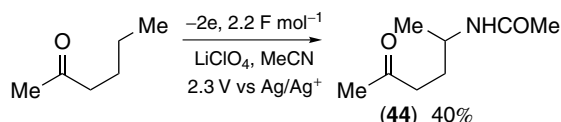
An  $\alpha$ -cleavage with subsequent [1,2]-hydrogen shifts was observed in the electrochemical oxidation of cyclohexanone (Eq. 7) [84].



**Scheme 15** Anodic  $\alpha$ -cleavage of acyclic ketones.



**Scheme 16** Anodic  $\alpha$ -cleavage of cyclic ketones.



**Scheme 17**  $\gamma$ -Acetamidation of ketones via a ketone radical cation and a [1,5]-hydrogen shift.

## 6.4.2

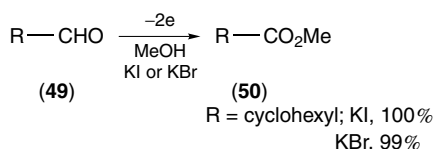
**Indirect Oxidation of Carbonyl Compounds**

Indirect oxidation of carbonyl compounds using mediators leads to better results than the direct oxidation.

– *PbO<sub>2</sub> anode*: Camphor was electrochemically oxidized at Pb/PbO<sub>2</sub> as an anode material in 1 M H<sub>2</sub>SO<sub>4</sub>/MeCN to give 1,2-campholide (45) as the main product (88%) and 6% (46) (Scheme 18) [85].

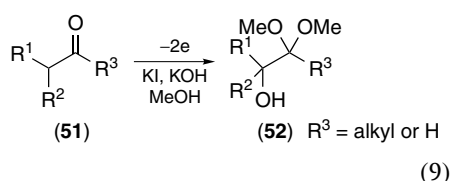
– *Ni electrode*: The nickel hydroxide electrode was nicely used for the oxidation of aldehyde (47) to carboxylic acid (48) (Scheme 19) [15].

– *Halide ion*: Aldehydes (49) were transformed to methyl esters (50) by way of electrolysis in MeOH containing an alkali metal halide as shown in Eq. (8) [86]. KI and KBr gave satisfactory results. In a two-phase system consisting of water and *n*-BuOH, aldehydes were converted to *n*-Bu esters.



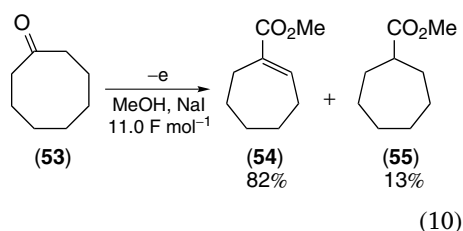
A similar electrochemical oxidation of aromatic aldehydes to their corresponding methyl esters was achieved by using flavo-thiazolio-cyclophane as a mediator [87].

Ketones and aldehydes (51) are oxidized to  $\alpha$ -hydroxy ketals and acetals (52) by electrolysis in MeOH containing halide ion under basic conditions (Eq. 9) [88].

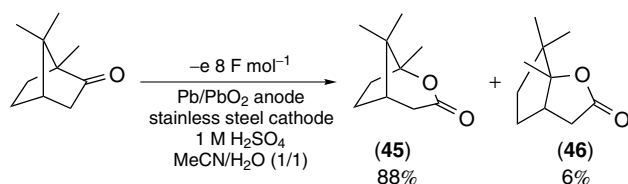


A reaction mechanism as described in Scheme 20 was proposed.

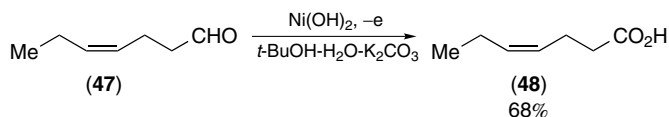
Under similar reaction conditions, some ketones such as (53) gave products via an electrochemically induced Favorskii rearrangement (Eq. 10) [89, 90].



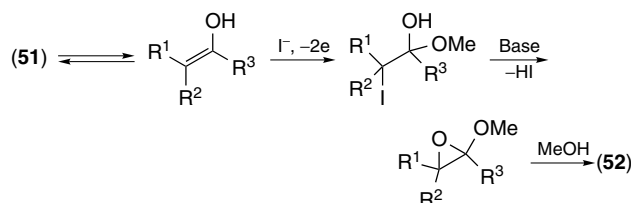
Electrochemical oxidation of higher aldehydes (56) in the presence of secondary



**Scheme 18** Anodic Bayer-Villiger oxidation.



**Scheme 19** Anodic oxidation of aldehydes to carboxylic acids at the nickel oxide electrode.



**Scheme 20** Anodic conversion of ketones to  $\alpha$ -hydroxy ketals.

amines in a mixed solvent of water and *t*-BuOH containing KI gave  $\alpha$ -amino ketones (57) (Scheme 21) [91]. The reaction involves enamines as intermediates.

Electrochemical oxidation of easily accessible alkyl aryl ketones (58) in trimethyl orthoformate containing a small amount of iodine or organo-iodo compounds gave methyl  $\alpha$ -alkylalkanoates (59) in high yields (Scheme 22) [92]. The products (59) are precursors for drugs possessing anti-inflammatory and analgesic activities.

still a widely applied method because of its specificity and versatility, which cannot be achieved by other chemical methods. The reaction is initiated by a one-electron transfer from a carboxylate ion (60) to the anode, yielding a radical (61) that dimerizes to a homocoupling product (62) (path a, Scheme 23, termed Kolbe reaction) [94–96]. The reaction is very useful for the preparation of higher alkanes or 1,*n*-diesters. In addition to the Kolbe reaction, it has been found in the beginning of 20th century that depending on the reaction conditions and the structure of carboxylic acid, a carbenium ion (63) can be formed in a two-electron oxidation (path b, Scheme 23), which is termed non-Kolbe reaction or Hofer–Moest reaction [94–97].

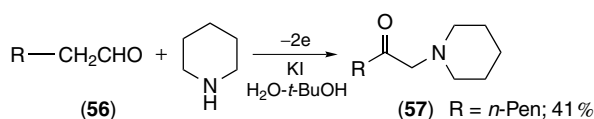
Both types of reaction are applied in organic synthesis. Some representative examples are given below.

## 6.5 Oxidation of Carboxylic Acids

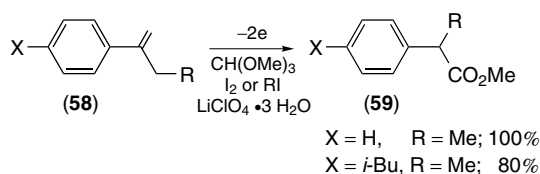
### 6.5.1

#### The Kolbe Reaction

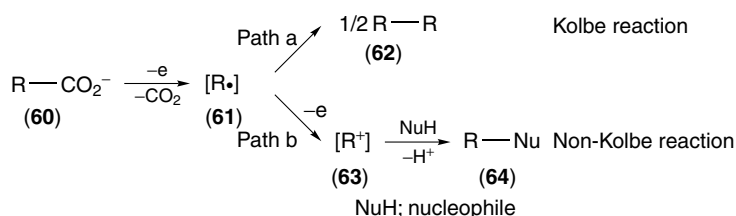
The Kolbe reaction is the oldest electroorganic reaction, discovered in the middle of the 19th century [93], but is



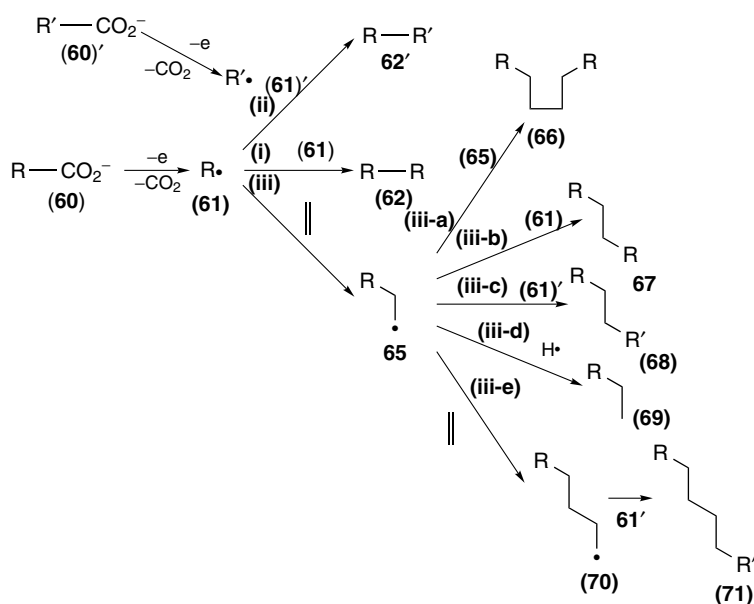
**Scheme 21** Anodic conversion of ketones to  $\alpha$ -aminoketones.



**Scheme 22** Anodic conversion of aryl alkyl ketones to methyl phenyl acetates.



**Scheme 23** Anodic decarboxylation of carboxylic acids.



**Scheme 24** Reaction of radicals generated by anodic decarboxylation of carboxylic acids.

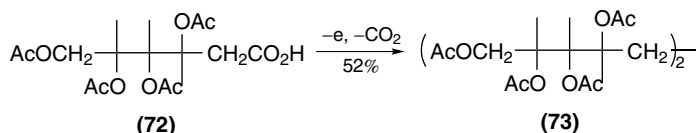
The Kolbe coupling reaction and its modifications are schematically summarized in Scheme 24. The Kolbe coupling reaction produces dimer (62) through a radical (61) generated from carboxylate ion (60) (type i). Modified Kolbe reactions are the cross-coupling reactions between  $[\text{R}\cdot]$  (61) and  $[\text{R}'\cdot]$  (61') generated from a co-acid (60') (type ii), and the reaction through trapping of (61) with olefins (type iii). The reaction of type iii can be further subdivided into five types iii-a-e according to the subsequent reaction of

radical (65) formed by the addition of (61) to olefins.

The reaction of type i is utilized for the preparation of a variety of dicarboxylic acids. Scheme 25 shows the synthesis of a C-disaccharide (73) from a carbohydrate carboxylic acid (72) [98].

In order to obtain the coupling product (62) in good yield, factors such as anode material, solvent, pH, and structure of the substrate are critical. In general, the following conditions are recommended for the Kolbe reaction; solvent: MeOH containing





**Scheme 25** C-disaccharides by anodic decarboxylation of carbohydrate carboxylic acids.

a small amount of water (0.25–2.5%), or pure MeOH, in a few cases, *N,N*-dimethylformamide (DMF) or MeCN have also been used; current density: 0.1 to 1.0 A cm<sup>-2</sup>; supporting electrolyte: alkali metal hydroxide (2–5%), in some cases, trialkylamines or pyridine have been applied; anode materials: platinum, platinized titanium, or glassy carbon. The use of soft carbon anode results in the formation of carbenium ion (63).

The coupling reactions are in general limited to primary carboxylic acids (RCH<sub>2</sub>CO<sub>2</sub>H).  $\alpha$ -Branched carboxylic acids lead to non-Kolbe products. However, carboxylic acid (74) with the electron-attracting trifluoromethyl group in the  $\alpha$ -position yields the Kolbe coupling product (75) (Scheme 26) [99, 100].

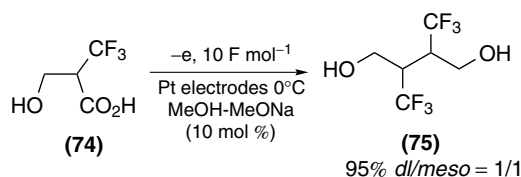
A reaction of type ii (heterocoupling) occurred for (74) in satisfactory yield when

an excess amount of a co-acid (76) was used (Scheme 27) [99, 100].

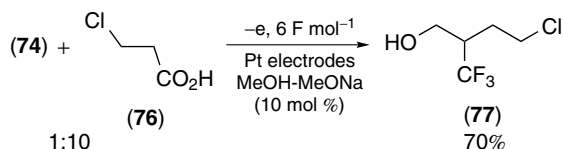
The addition reaction of type iii can be further subdivided into type iii-a–e.

– *Type iii-a*: The formation of (66) is found in the electrolysis of partially neutralized trifluoroacetic acid in the presence of diallylamine (78). It provides the crystalline hydrochloride of *cis*-3,4-bis-(2,2,2-trifluoroethyl)pyrrolidine (79) in 8% yield (Scheme 28) [101].

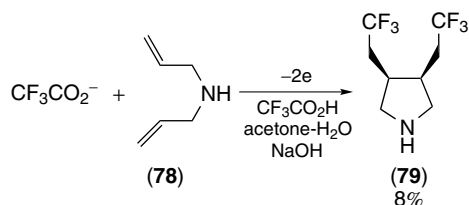
Another example of type iii-a is the trifluoromethylation of double bonds by electrolysis of trifluoroacetic acid in the presence of olefins. Methyl vinyl ketone, vinyl acetate, diethyl fumarate, diethyl maleate, *N*-ethylmaleimide, and 2,5-dihydrothiophene-1,1-dioxide were examined as olefins. The products were bis-trifluoromethylated additive dimers (66) (type iii-a) and monomers (67) (type



**Scheme 26** Anodic homocoupling by Kolbe electrolysis.



**Scheme 27** Anodic heterocoupling by Kolbe electrolysis.



**Scheme 28** Anodic additive coupling by Kolbe electrolysis.

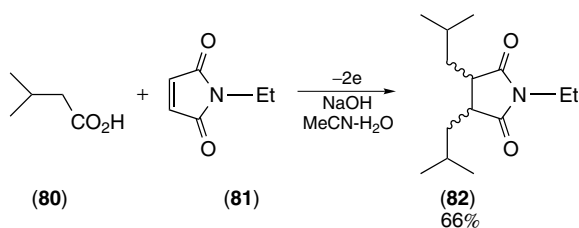
**iii-b)** [102–104]. Electrooxidation of trifluoroacetic acid in the presence of acrylonitrile in an MeCN-water solution gave 2,3-bis(2,2,2-trifluoroethyl)succinonitrile in 20 to 25% yield with a 1:1 ratio of the diastereoisomers [105].

– *Type iii-b:* This reaction leads to products (67). The electrochemical oxidation of the sodium salts of acetic, propionic, and isovaleric acids in the presence of ethylenic compounds bearing electron-withdrawing substituents gives 1,2-dialkylated adducts as the main products. A methyl radical generated from an acetate ion reacts with diethyl fumarate to give diethyl 2,3-dimethylsuccinate in 80% yield [106].

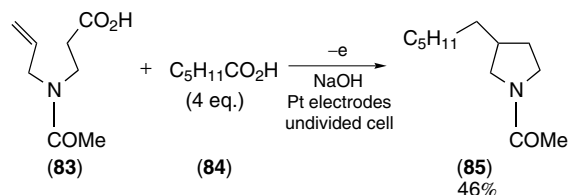
Similarly, dialkylated succinimide (82) was obtained in the electrolysis of acid (80) with maleimide (81) (Scheme 29) [107].

Electrochemical trifluoromethylation of 3-sulfolene in a  $\text{CF}_3\text{CO}_2\text{H}/\text{CF}_3\text{CO}_2\text{Na}/\text{CH}_3\text{CN}/\text{H}_2\text{O}$  system gave a complex mixture consisting of *meso*- and *dl*-3,4-bis(trifluoromethyl)sulfolanes as the major components [108].

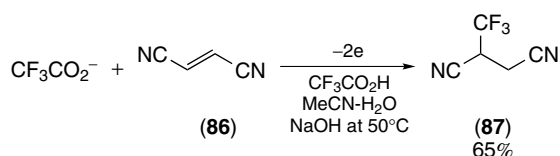
*Type iii-c* reaction leads to the formation of (68). In the case of 6-alkenoic acids an intramolecular addition takes place. The Kolbe electrolysis of  $\beta$ -(*N*-allylamino)alkanoate (83) in the presence of a co-acid (84) gave 3-alkyl-substituted pyrrolidine (85) through an intramolecular



**Scheme 29** Addition of radicals generated by Kolbe electrolysis.



**Scheme 30** Additive cyclization by way of Kolbe electrolysis.



**Scheme 31** Addition of radicals generated by Kolbe electrolysis.

addition of the initially generated radical, followed by a heterocoupling with a pentyl radical (Scheme 30) [109].

A type **iii-d** reaction leads to the formation of (69). Trifluoromethyl radicals generated electrochemically from trifluoroacetate can attack electron-deficient olefins leading to trifluoromethylated carbon radicals whose chemical and electrochemical follow-up reactions can be controlled by current density, reaction temperature, and substituents of the olefins. With fumaronitrile (86) at 50 °C the monotrifluoromethylated compound (87) was obtained in 65% yield (Scheme 31) [110].

With type **iii-e** reactions compounds (71) are formed. A radical tandem reaction initiated by the Kolbe electrolysis of (88) gave tricyclic compounds (89) in a one pot reaction (Scheme 32) [111]. The electrochemical decarboxylation avoids the usually applied toxic tin hydride as reagent and

allows the introduction of different substituents R by varying the co-acid RCO<sub>2</sub>H.

## 6.5.2

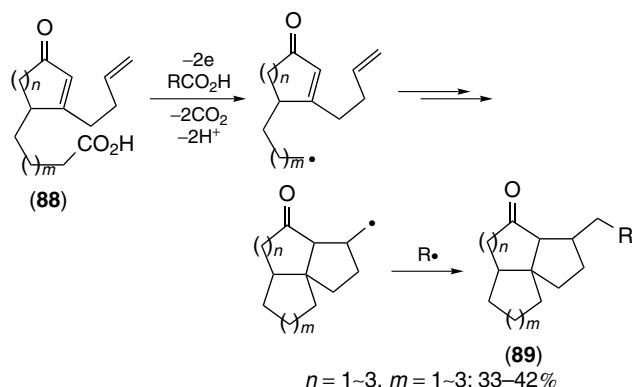
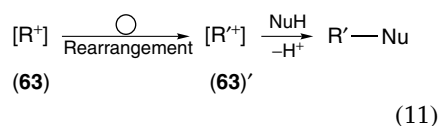
### The Non-Kolbe Reaction

#### 6.5.2.1 Reaction with Nucleophiles

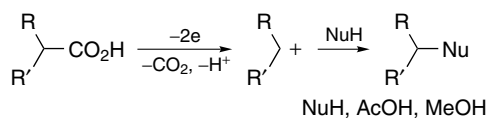
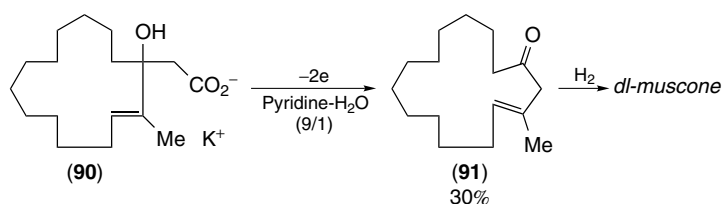
Depending on the anode material used, the oxidation of a carboxylic acid can lead to a carbenium ion [R<sup>+</sup>], which is trapped by a nucleophile (NuH) to afford a one-carbon-shortened product (Scheme 33) [112].

#### 6.5.2.2 Rearrangement

The intermediate cation [R<sup>+</sup>] (63) often rearranges to a more stable cation [R'<sup>+</sup>] (63') that is trapped by NuH (Eq. 11).



**Scheme 32** Radical tandem cyclization initiated by Kolbe electrolysis.

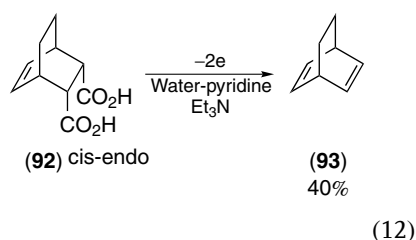
**Scheme 33** Anodic substitution by way of the Non-Kolbe reaction.**Scheme 34** 1,2-Rearrangement induced by the Non-Kolbe reaction as key step for a muscone synthesis.

Electrolysis of  $\beta$ -hydroxy carboxylic acid (90) gave ketone (91) as the main product, which was converted to *dl*-muscone (Scheme 34) [113]. The migratory aptitude of alkyl substituents at the  $\beta$ -position in the intermediate  $\beta$ -hydroxy carbenium ion was scrutinized to show that vinyl, cyclopropyl, and benzyl groups rearrange predominantly.

Several similar rearrangements starting from  $\gamma$ -hydroxy [114] and  $\beta$ -alkoxy acids [115] were reported.

#### 6.5.2.3 Olefin Formation

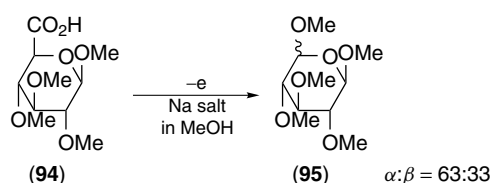
Electrochemical oxidation of 1,2-dicarboxylic acids provides an easy route to olefins [116–118]. For example, 1,2-dicarboxylic acid (92) was decarboxylated by electrochemical oxidation to give olefin (93) as the 1,2-elimination product (Eq. 12) [116, 117].

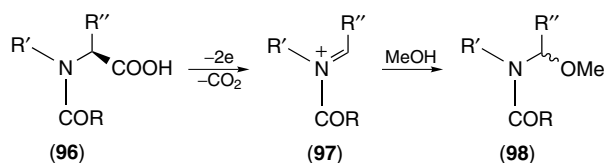


On the other hand, 1,1-dicarboxylic acids gave ketones as 1,1-elimination products [119].

#### 6.5.2.4 Oxidative Decarboxylation of $\alpha$ -heteroatom-substituted Carboxylic Acids

*Oxidative decarboxylation of  $\alpha$ -oxy-carboxylic acids:* 2,3,4-tri-*O*-methyl- $\beta$ -D-glucopyranosiduronic acid (94) was electrolyzed under several reaction conditions to give a mixture of stereoisomers (95) as shown in Scheme 35 [120].

**Scheme 35** Anodic decarboxylation of a hexose to a pentose.



**Scheme 36** Anodic decarboxylation of *N*-acyl  $\alpha$ -amino acids to a *N*-acyl iminium intermediates.



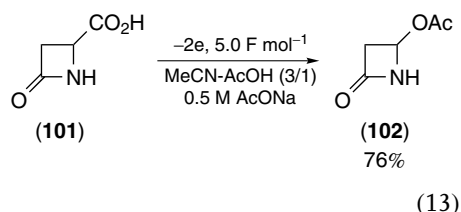
**Scheme 37** Anodic decarboxylation of a dipeptide.

*Oxidative decarboxylation of  $\alpha$ -amino carboxylic acid:* The electrochemical oxidation of *N*-acyl- $\alpha$ -amino acids (**96**) in MeOH affords *N*, *O*-acetals (**98**) through acyliminium intermediates (**97**) (Scheme 36) [121].

This reaction has been applied to the synthesis of a variety of pharmaceutically interesting compounds.

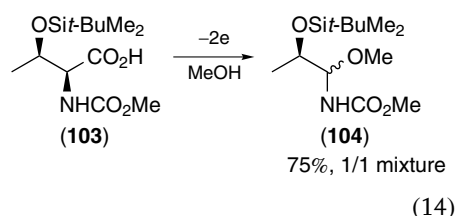
$\alpha$ -Amino acid (**99**) possessing two stereogenic centers was electrolyzed in MeOH to produce *N*-acyl-*N*, *O*-acetal (**100**) (Scheme 37) [122].

Correspondingly, 4-acetoxy-2-azetidinone (**102**) was prepared from 4-carboxy-2-azetidinone (**101**) by a non-Kolbe reaction (Eq. 13) [123].

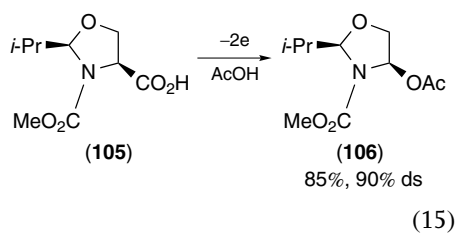


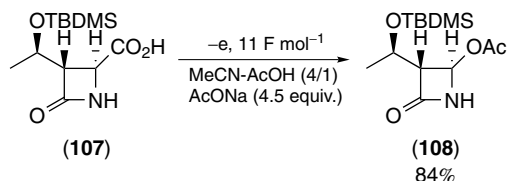
The stereochemistry in the electrochemical oxidation of (**96**) yielding *N*, *O*-acetals (**98**) is of timely interest. The electrochemical oxidation of acyclic threonine derivative

(**103**) gave a *N*, *O*-acetal (**104**) with a 1 : 1 mixture of diastereoisomers in 75% yield (Eq. 14) [124]. In general, the diastereoselectivity (ds) observed in the electrochemical oxidation is lower than that in the Lewis acid-catalyzed replacement of the methoxy group with nucleophiles. This is exemplified by the introduction of an allyl group into (**104**) with a diastereoselectivity of 4/1.

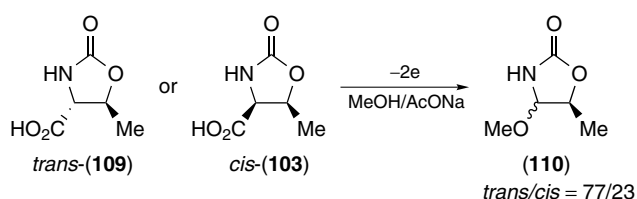


For the cyclic compound (**105**) derived from serine methyl ester, a high diastereoselectivity was observed (85% yield, 90% ds) (Eq. 15) [124].





**Scheme 38** Diastereoselective anodic decarboxylative substitution of a  $\beta$ -lactam.



**Scheme 39** Diastereoselective anodic decarboxylative substitution of a threonine derivative.

However, electrolysis of *N*-methoxycarbonyl-*O*[(*t*-butyl)dimethylsilyl]hydroxyproline in MeOH also led to a substitution of the CO<sub>2</sub>H group by the MeO group with no diastereoselectivity [125].

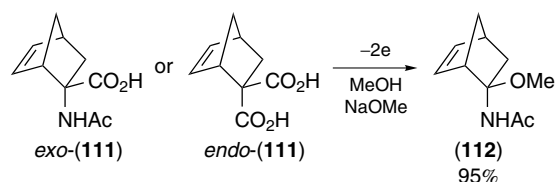
On the other hand the electrolysis of (107) afforded optically pure (108) in 84% yield (Scheme 38) [123]. Thus the stereochemistry differs strongly depending on the kind of carboxylic acid used.

The electrochemical substitution of either stereoisomer of the *N*-acyl- $\alpha$ -amino carboxylic acid (109) led to product (110) in 75% yield with a *trans/cis* ratio of 77/23 (Scheme 39) [126, 127], which is in contrast to the stereoselectivity (>97.5% ds) observed in the substitution of the methoxy group of (110) with dibenzoylmethane in trifluoroacetic acid.

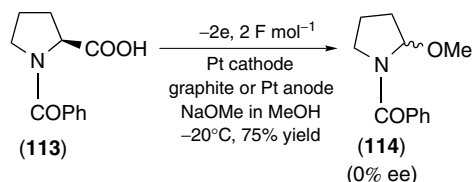
Electrochemical oxidation of *exo*- or *endo*-carboxylic acid (111) gave only 2-*exo*-methoxynorbornene derivative (112) in 95% yield (Scheme 40) [128].

Since the oxidation of (96) proceeds through the acyliminium ions (97) (Scheme 36), where the positive charge is stabilized by the adjacent nitrogen atom, it should lead to racemic acetals (98) from enantioenriched acids (96). In fact, the electrolysis of *N*-benzoylated L-proline (113) gave racemic *N*, *O*-acetal (114) regardless of the anode material used (Scheme 41) [129].

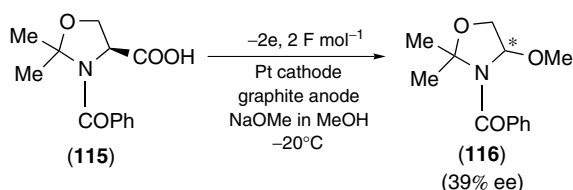
On the other hand, in contrast with the non-Kolbe reaction of (113), that of L-serine derivative (115) gave an optically active  $\alpha$ -methoxylated product (116) with 39% ee when graphite was used as the anode



**Scheme 40** Anodic decarboxylation of a norbornene carboxylic acid.



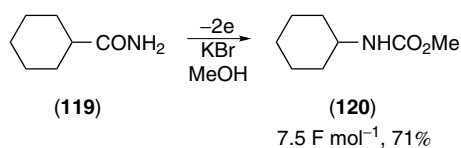
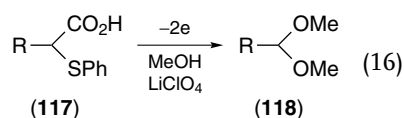
**Scheme 41** Anodic decarboxylation of a *N*-phenacyl proline.



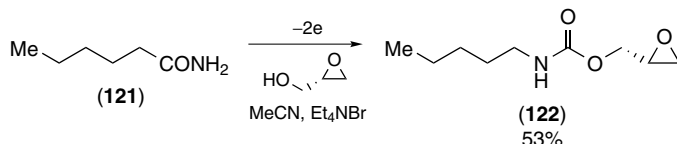
**Scheme 42** Anodic decarboxylation of a substituted *N*-phenacyl oxazolidinecarboxylic acid with partial retention of configuration.

material (Scheme 42) [129]. The absolute configuration of the enriched enantiomer of **(116)** was made probable to be *S*. This is the first example of memory of chirality in carbenium ion chemistry.

The electrolysis of  $\alpha$ -phenylthiocarboxylic acids (**(117)**) in MeOH containing  $LiClO_4$  gave the corresponding aldehyde acetals (**(118)**) (Eq. 16) [130].



**Scheme 43** Electrochemically induced Hofmann rearrangement.



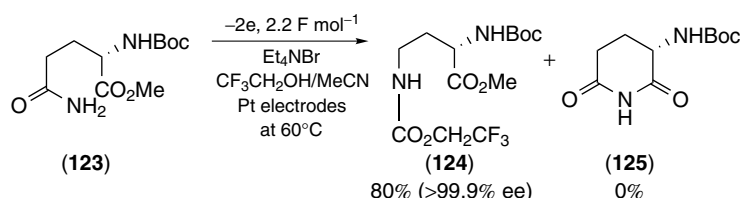
**Scheme 44** Electrochemically induced Hofmann rearrangement with insertion of an epoxy alcohol.

### 6.5.3

#### Oxidation of Amides

Electrolysis of amides in MeOH containing the bromide ion efficiently led to products of the Hofmann rearrangement (for example, **(119)** to **(120)**; Scheme 43) [131]. This reaction, named the electrochemically induced (E-I) Hofmann rearrangement, is achieved without any bromine and base under mild and neutral reaction conditions.

Thus, for example, an epoxy functional group in the alcohol part remained intact



**Scheme 45** Electrochemically induced Hofmann rearrangement of N-Boc glutamine with retention of configuration.

during the conversion of (121) to (122) (Scheme 44) [132, 133].

However, the conditions of the E-I Hofmann rearrangement are not yet suitable for substrates that are unstable under weakly basic conditions, since the electrochemically generated bases (EGB) may be present in the vicinity of the cathode. For example, the E-I Hofmann rearrangement of (2*S*)-*N*<sup>2</sup>-Boc-protected glutamine methyl ester (123) in MeOH containing the bromide ion yielded the desired Hofmann rearrangement product in only a low yield (28%) and a by-product (125) that might be generated by a base-catalyzed cyclization of (123). On the other hand, the transformation of (123) to (124) was successfully achieved without any formation of (125) and no loss of the optical purity by electrolysis using the CF<sub>3</sub>CH<sub>2</sub>OH/MeCN solvent system in which CF<sub>3</sub>CH<sub>2</sub>OH might play an important role to control the basicity caused by the EGB (Scheme 45) [134].

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## 7 Reduction of Oxygen-containing Compounds

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## 7.1 Introduction

This chapter is concerned with the electroreduction of oxygen-containing compounds, that is, the cathodic reduction of alcohols, ethers, esters, amides, carboxylic acids, aldehydes, and ketones. The reduction potentials of these oxygen-containing compounds depend highly on their structures. In general, oxygen-containing aromatic compounds are rather easily electroreducible because aryl groups act as electron-withdrawing substituents and facilitate the electron transfer from the cathode to the substrates. The electroreduction of aliphatic ketones and aldehydes has long been known and has been well established from the synthetic and mechanistic viewpoints [1–3], because these compounds are electrochemically reducible under mild reaction conditions. On the other hand, the reduction potentials of other oxygen-containing aliphatic compounds such as aliphatic alcohols, ethers, carboxylic acids, and esters are highly negative and their electroreduction has proved to be difficult until recently. In the last few years, some new electroreductive methods, which enable reduction of alcohols, aliphatic esters, and carboxylic acids, have been reported and now almost all oxygen-containing compounds

can be electrochemically reduced under mild reaction conditions.

Numerous studies concerning the electroreduction of oxygen-containing compounds have been reported so far and our knowledge in this field is far from complete. However, previous studies in this area until 1990, have been well summarized in the literature [1–3]. Thus, this chapter mainly deals with studies after 1990 along with some typical examples reported until 1990. In addition, many studies in this field have been carried out from both the synthetic and mechanistic point of view; however, the main contents of this chapter focus on the modern synthetic reactions using electrochemical reduction.

## 7.2 Cathodic Reduction of Alcohols

Cleavage of C–O bonds by direct electron transfer from a cathode is usually difficult because of the negative reduction potential of the bond. Therefore, the reduction of aliphatic alcohols (R–OH) to the corresponding hydrocarbons (R–H) is often carried out by the transformation of hydroxyl groups to good leaving groups such as halides (X = Br, I), methanesulfonates (OMs), and

*p*-toluenesulfonates (OTs) followed by electroreduction (Scheme 1) [4, 5]. The details of the electroreduction of halides are given in Chapter 8 (oxidation and reduction of halogen-containing compounds) and that of methanesulfonates and *p*-toluenesulfonates is summarized in Chapter 9 (electrochemistry of sulfur-containing compounds).

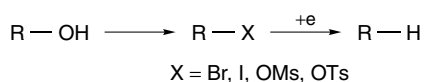
Aromatic hydroxyl groups are also difficult to reduce; however, the transformation of hydroxyl groups to phosphonate esters followed by electroreduction affords the corresponding hydrocarbons (Scheme 2) [6].

Although the electroreduction of nonactivated alcohols requires appropriate activation of hydroxyl groups as mentioned above, activated ones such as allylic and benzylic alcohols can be reduced by direct electroreduction (Scheme 3) [1, 7–9].

Electrolysis of alcohols in an undivided cell and in the presence of trialkyl phosphine is recently reported, and this is one of the most simple and

reliable methods for the reduction of alcohols to the corresponding hydrocarbons. In this reaction, the role of the anode and the cathode is as follows: trialkyl phosphine is anodically oxidized to the corresponding cation radical, which reacts with the alcohol to form a phosphonium salt. The electroreduction of the phosphonium salt leads to the formation of a hydrocarbon (Scheme 4) [10, 11].

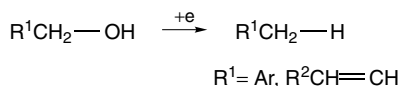
The cleavage of C–O bonds under usual conditions of electroreduction is rather difficult. However, 1,2-elimination and 1,3-elimination of hydroxyl groups initiated by the electron transfer to neighboring groups such as SPh, SO<sub>2</sub>Ph takes place under mild reaction conditions and leads to the cleavage of C–O bonds. Usually, 1,2-elimination needs no activation of the hydroxyl group (Scheme 5), whilst for 1,3-elimination, an appropriate activation of the hydroxyl group is required (Scheme 6) [12–14].



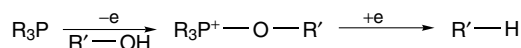
**Scheme 1** Cathodic desoxygenation of aliphatic alcohols; yields, e.g. for X = OMs: 63–85%.



**Scheme 2** Cathodic desoxygenation of phenols; yields: in general, 40–70%.

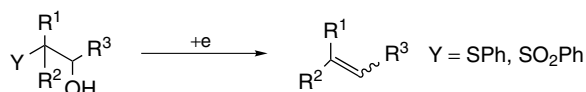


**Scheme 3** Cathodic desoxygenation of allylic and benzylic alcohols via *in situ* formed iodides; yields: up to 95%.

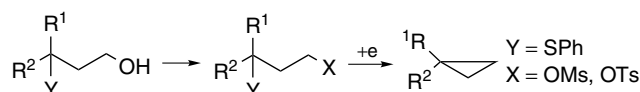


**Scheme 4** Cathodic desoxygenation of alcohols via phosphonium salts; R': aliphatic, benzylic, yields: 48–96%.





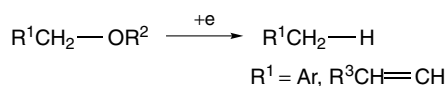
**Scheme 5** Cathodic 1,2-elimination of  $\beta$ -arylthio- and  $\beta$ -arylsulfonyl-substituted alcohols;  $\text{R}^1, \text{R}^2, \text{R}^3$ : aliphatic, H, yields: 50–96%.



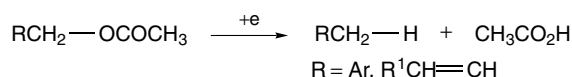
**Scheme 6** Cathodic 1,3-elimination of  $\gamma$ -substituted alcohols;  $\text{R}^1, \text{R}^2$ : aliphatic, H, yields: 65–75%.

### 7.3 Cathodic Reduction of Ethers

Because the reduction potential of ether is usually more negative than that of halides, examples that belong to this category are rather rare. Generally, cathodic reduction of ethers is similar to that of alcohols, and nonactivated ethers are not reducible under the conditions of electroreduction. Activated ethers such as benzylic and allylic ethers are electrochemically reduced to a limited extent (Scheme 7) [1, 15, 16]. Reduction of epoxides is usually difficult; however, electroreductive cleavage of activated epoxides to the corresponding alcohols is reported [17, 18]. The cleavage of the C–O bond of ethers is more easily accomplished in anodic oxidation than in cathodic reduction, which is stated in Chapter 6.



**Scheme 7** Cathodic cleavage of benzyl ethers.



**Scheme 8** Cathodic cleavage of benzyl- and allylesters; e.g. benzyl carbamate, yields: 90–99%.

### 7.4 Cathodic Reduction of Esters and Amides

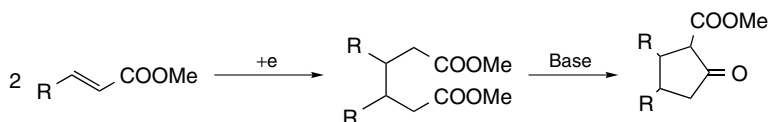
Electroreduction of esters ( $\text{R}^1\text{COOR}^2$ ) is classified into three types of reaction. The first type of reaction is the reductive cleavage of a bond between oxygen and  $\text{R}^2$ . This type of reaction is similar to the cathodic reduction of alcohols (Sect. 7.2) and ethers (Sect. 7.3). That is, activated esters such as allylic and benzylic esters are electrochemically reduced to the corresponding hydrocarbons and acids (Scheme 8) [1, 16, 19–21].

Cathodic 1,2-elimination of activated esters leads to the cleavage of the C–O bond and this method is useful for the deprotection of protected carboxyl groups (Scheme 9) [22, 23].

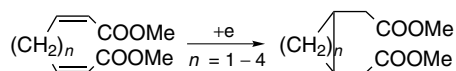
The second type of reaction is the reductive coupling of  $\alpha, \beta$ -unsaturated esters. These reactions are well documented



**Scheme 9** Cathodic deprotection of esters; R: phenyl, phenylNH, benzyl, polyene, yields: 45–90%.



**Scheme 10** Intermolecular cathodic coupling of  $\alpha,\beta$ -unsaturated esters; R: subst. phenyl, yields: 50–60%.



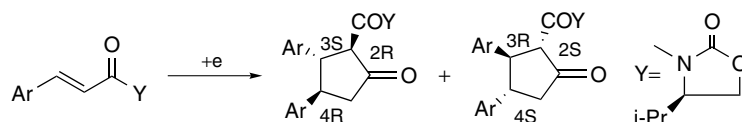
**Scheme 11** Intramolecular cathodic coupling of  $\alpha,\beta$ -unsaturated esters; yields: 40–100%.

in the literature [1], and hence, typical examples of intermolecular and intramolecular coupling reactions are exemplified in Schemes 10 and 11, respectively [24, 25].

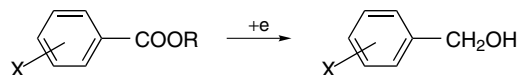
$\alpha,\beta$ -Unsaturated amides show similar reactivities as the corresponding esters. For example, electroreduction of chiral  $\alpha,\beta$ -unsaturated amides affords chiral-coupling products in partially high diastereoselectivity (Scheme 12) [26–28].

A third type of reaction is the reduction of the C=O bond of esters. Until recently, electroreduction of esters to the corresponding alcohols has been limited to that of aromatic compounds as shown in Scheme 13 [1, 29, 30].

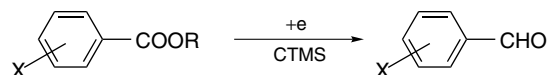
Electroreduction of aromatic esters to the corresponding aldehydes is accomplished by the reduction of esters in the presence of chlorotrimethylsilane (CTMS) (Scheme 14) [31].



**Scheme 12** Diastereoselective intermolecular cathodic coupling of  $\alpha,\beta$ -unsaturated esters; yields: 70–98%, *de*: 0 to >95%.



**Scheme 13** Cathodic reduction of aromatic esters to benzyl alcohols; e.g. X: 3-OH, yield: 91.5%.



**Scheme 14** Cathodic reduction of aromatic esters to aromatic aldehydes; X = H, alkyl, yields: 0–70%.

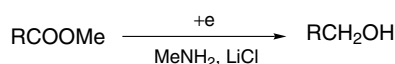
Because of the highly negative reduction potentials ( $\sim -3.0$  V vs. SCE) [32], the electroreduction of esters of aliphatic carboxylic acids to primary alcohols by direct electron transfer from the cathode is very difficult and the electrochemical Birch-type reduction of aliphatic esters in MeNH<sub>2</sub> or liquid NH<sub>3</sub> has not been reported until recently (Scheme 15) [33, 34]. This reaction is not a reduction by direct electron transfer from the cathode to the C=O bonds of the ester but the reduction by a solvated electron.

Electroreduction of aliphatic esters has been recently achieved by using a Mg electrode [35]. When the reduction of

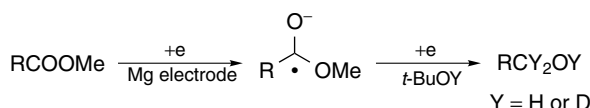
aliphatic esters with the Mg electrode is performed in the presence of *t*-BuOH as a proton source, the corresponding primary alcohols are obtained in high yield. The use of *t*-BuOD instead of *t*-BuOH yielded deuterated alcohols with high deuterium incorporation (Scheme 16).

This method is also applicable to the reduction of amides to the corresponding aldehydes and alcohols by controlling the amount of *t*-BuOH and supplied electricity. The reduction in the presence of *t*-BuOD gives deuterated aldehydes (Scheme 17).

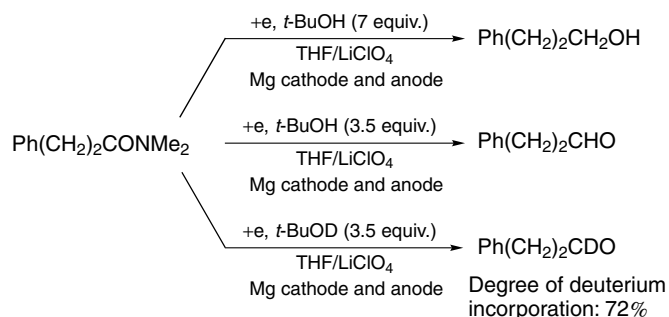
Electroreduction of aliphatic esters with an Mg electrode, under aprotic conditions, leads to dimerization



**Scheme 15** Cathodic Birch-type reduction of aliphatic esters to alcohols; R: alkyl, yields: 95%.



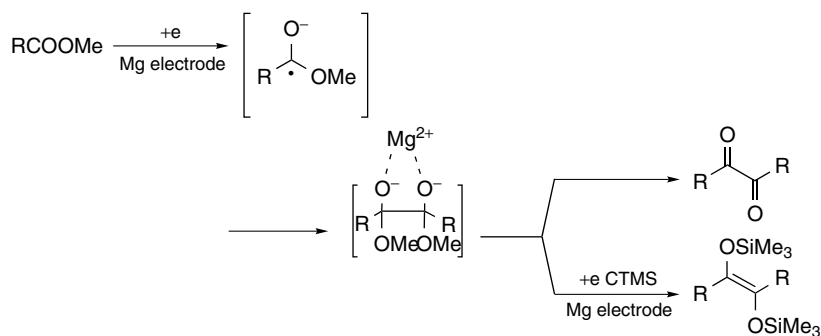
**Scheme 16** Deuterated alcohols by cathodic reduction in the presence of *t*-BuOD.



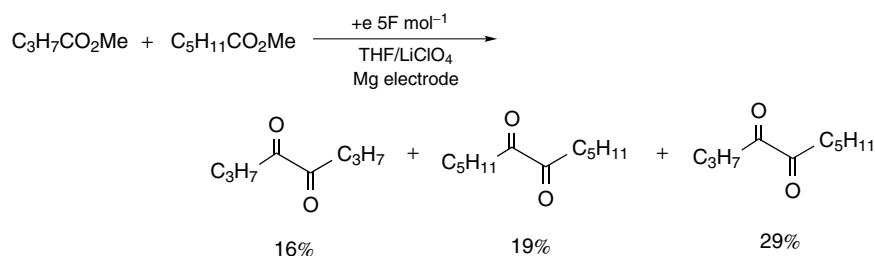
**Scheme 17** Cathodic reduction of amides to alcohols and aldehydes; yields (alcohol): 70–82%, yields (aldehyde): 65%.

affording the corresponding 1,2-diketone whereas a *bis*-(trimethylsilyloxy)alkene is obtained on reduction in the presence of chlorotrimethylsilane (Scheme 18) [36]. Electroreduction of aromatic esters under aprotic conditions leads to the corresponding 1,2-diketones [37]. The crucial factor in generating the 1,2-diketone is the formation of the Mg salt that is insoluble in the solvent (THF).

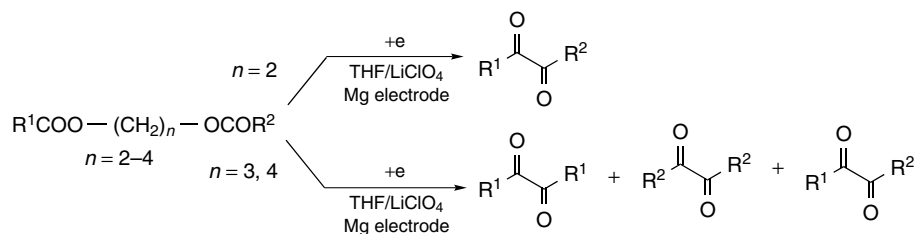
Although electroreduction of a mixture of esters with an Mg electrode gives a mixture of symmetrical and unsymmetrical 1,2-diketones (Scheme 19), the reduction of diesters affords unsymmetrical 1,2-diketones as the single product (Scheme 20) [38, 39]. The selectivity of the reaction shown in Scheme 20 is highly dependent on the value of  $n$  and the best result is obtained when  $n = 2$ .



**Scheme 18** Cathodic dimerization of esters to 1,2-diketones; R: alkyl, aryl; yields (diketone): 33–65%, yields (endioldiether): 55–78%.



**Scheme 19** Symmetrical and unsymmetrical 1,2-diketones from mixtures of esters.



**Scheme 20** Selectivity of unsymmetrical 1,2-diketone formation from unsymmetrical diesters of 1, $n$ -diols.

The anion radical species formed by the electroreduction of aliphatic esters show interesting reactivities, and the reduction of olefinic esters gives bicyclic products with high regio- and stereoselectivity. The electroreduction of the ester in the presence of chlorotrimethylsilane affords a tricyclic product (Scheme 21) [35, 40]. The mechanism of this cyclization reaction seems to be the addition of anion radical species, formed by the reduction of the ester group, to the carbon–carbon double bond.

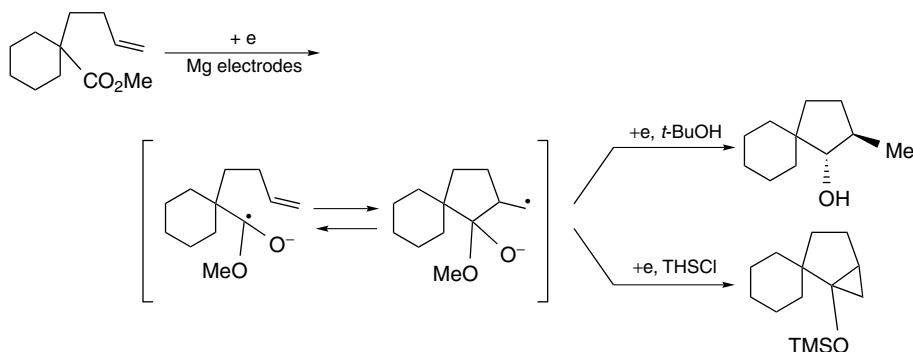
Electroreduction of aliphatic amides in the presence of chlorotrimethylsilane gives coupling products and this reaction is useful for the synthesis of  $\alpha$ -amino ketones (Scheme 22) [41]. In this reaction, the formation of an Mg salt promotes the coupling of two anion radical centers.

## 7.5

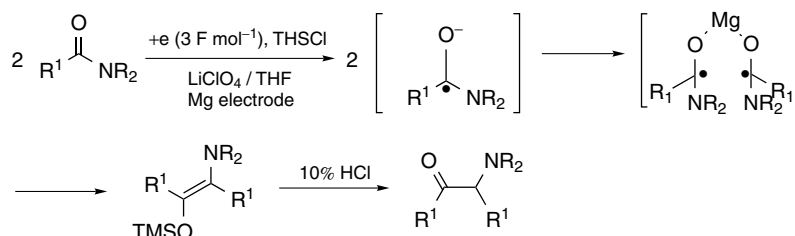
### Cathodic Reduction of Carboxylic Acid

Electroreduction of aromatic carboxylic acid to the corresponding aldehydes and alcohols has been well studied [1], however, examples of the reduction of aliphatic carboxylic acids are rare. The aromatic carboxylic acids are usually reduced to the corresponding benzylic alcohols under acidic conditions (Scheme 23) [42–46]. Substitution of an electron-withdrawing group on the aromatic ring further facilitates the electron transfer from the cathode to the carboxyl group. Selectivity of electroreduction of aromatic carboxylic acids to the corresponding aldehydes can be achieved by controlling the reaction medium [47].

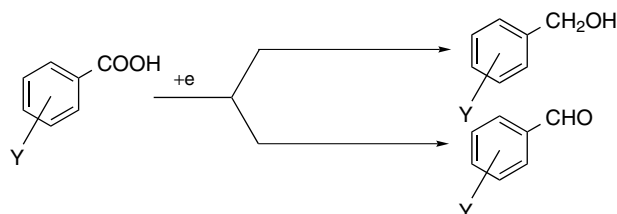
Although some electroreduction of aliphatic acids are reported in the older



**Scheme 21** Cathodic cyclization of unsaturated esters; yield (alcohol): 60%, yield (TMS ether): 67%.



**Scheme 22** Cathodic coupling of amides;  $R^1$ : alkyl,  $R^2$ : methyl, yields: 63–70%.



**Scheme 23** Cathodic reduction of aromatic carboxylic acids to benzyl alcohols or benzaldehydes.

literature [48], the yields are very low. Electroreduction of aliphatic carboxylic acids under usual anhydrous reaction conditions does not lead to electron transfer to the C=O group but leads to a deprotonation reaction through the reduction of the proton. This deprotonation reaction can be applied to the preparation of esters under mild reaction conditions (Scheme 24) [49].

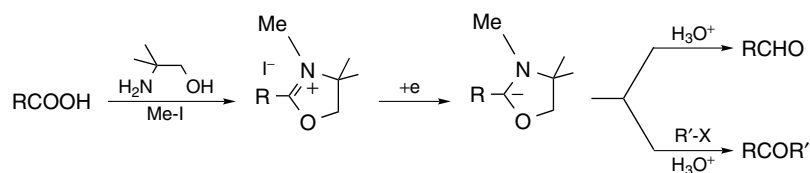
Appropriate activation of carboxyl groups enables reduction of aliphatic carboxylic acids to the corresponding aldehydes. The electroreduction of iminium salts prepared from aliphatic carboxylic

acids gives acyl anion equivalents. The hydrolysis of the anion yields the corresponding aldehyde, and the reaction of the anion with alkyl halide followed by hydrolysis affords a ketone (Scheme 25) [50, 51].

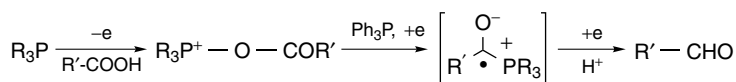
Recently, the electrolysis of aliphatic carboxylic acids in an undivided cell and in the presence of triphenyl phosphine has been reported, which turned out to be one of the most reliable methods for the reduction of aliphatic carboxylic acids to the corresponding aldehydes (Scheme 26) [11, 52]. In this reaction,



**Scheme 24** Cathodic alkylation of carboxylic acids to esters; R: alkyl, aryl, R': alkyl, yields: 24–96%.



**Scheme 25** Cathodic reduction of activated aliphatic carboxylic acids to aldehydes (R: alkyl, yields: 70–82%) and ketones (R': benzyl, yields: 66–72%).



**Scheme 26** Cathodic reduction of aliphatic carboxylic acids in the presence of triphenylphosphine to aldehydes; R': alkyl, aryl, yields: 36–100%.

triphenyl phosphine is anodically oxidized to the corresponding cation radical, which reacts with carboxylic acids to form acyl phosphonium salts. These salts are electroreduced to aldehydes.

This reaction is applicable to the reduction of  $\alpha$ -amino acids to optically active  $\alpha$ -amino aldehydes with high yields (Scheme 27) [53].

The acyl radical equivalents formed by the electroreduction of acyl phosphonium salts have an interesting reactivity and the electroreduction of nonconjugated olefinic acids yields intramolecular coupling products (Scheme 28) [11, 54, 55].

## 7.6

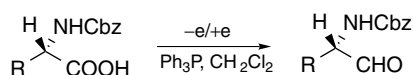
### Cathodic Reduction of Ketones, Aldehydes, and Carbon Dioxide

Reduction potentials of ketones and aldehydes are effected by the substituents. Electron-withdrawing groups usually facilitate the electroreduction of these compounds [1, 2]. Electroreduction of aliphatic and aromatic ketones and aldehydes generally takes place under mild reaction conditions; however, the nature

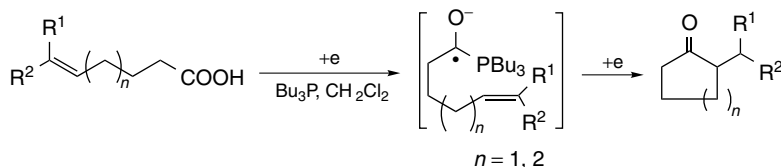
of the products often depends on the reaction conditions. The mechanism of the electroreduction of ketones and aldehydes is similar to that of esters though the reduction potentials of esters are much more negative than those of ketones. One electron transfer from the cathode to the substrates forms anion radical species. The fate of the anion radical depends on the reaction conditions and radical coupling products are often formed under aprotic conditions [1, 56, 57], while further reduction of the anion radical to the corresponding alcohols takes place under protic conditions (Scheme 29) [1, 58–61].

Since the electroreduction of ketones shown in Scheme 29 has been well established [1–3, 12, 62–65], one more recent interest in the electroreduction of carbonyl compounds is focused on the stereo-selective reduction of ketones. For example, the diastereo-selective cathodic coupling of aromatic ketones has been reported. In the presence of a chiral-supporting electrolyte, a low degree of enantioselectivity has been found [66] (Scheme 30).

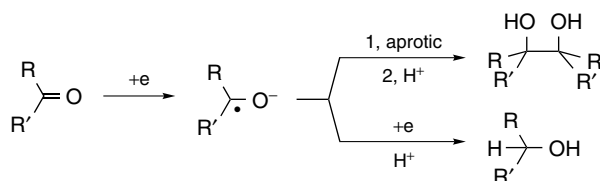
Electroreduction of carbonyl compounds under irradiation of ultrasound is another



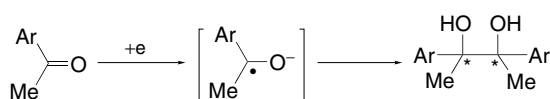
**Scheme 27** Cathodic reduction of amino acids in the presence of triphenylphosphine to amino aldehydes; R: alkyl, yields: 81–84%.



**Scheme 28** Cathodic cyclization of unsaturated acids in the presence of triphenyl phosphine; R<sup>1</sup>: alkyl, H, aryl, R<sup>2</sup>: H, aryl, yields: 11–49%.



**Scheme 29** Cathodic reduction of ketones; diols  $R^1$ : aryl,  $R^2$ : H, yields: in general 45–100%; alcohols:  $R^1$ ,  $R^2$ : alkyl, yields: in general, 45–100%.



**Scheme 30** Diastereoselective cathodic coupling of aromatic ketones in the presence of chiral supporting electrolyte, yield: 91%, 25% *ee*.

new technique of electrochemistry. For instance, electroreductive-coupling reactions under ultrasonic irradiation remarkably increase the selectivity of the coupling (Scheme 31) [67].

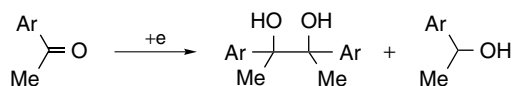
Asymmetric electroreduction of ketones to the corresponding chiral alcohols has recently been reported. Typical examples are the reduction of ketones bearing chiral auxiliaries [68, 69], and the indirect reduction of ketones with alcohol dehydrogenase (ADH), as a mediator (Scheme 32) [70].

Anion radical species formed by electroreduction of carbonyl compounds show interesting reactivities. In some cases, the

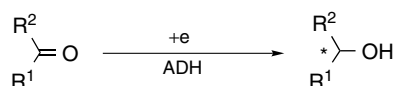
anion radical species may act as an electro-generated base (EGB) (details of EGB are shown in Chapter 14) and promotes the base-catalyzed condensation reaction of ketones and aldehydes (Scheme 33) [71–73].

In another case, the anion radical species undergoes regio- and stereoselective intermolecular coupling reactions with carbon–carbon double bonds (Scheme 34) or triple bonds [74]. This reaction is useful for the regio- and stereo-selective formation of cyclic alcohols having a 5-membered ring [75, 76].

The radical cyclization reaction shown in Scheme 34 exclusively takes place at the higher substituted carbon atom of the

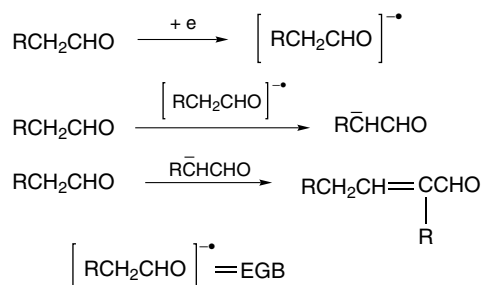


**Scheme 31** Influence of sonication on the selectivity in the cathodic reduction of aromatic ketones: diol 10–23% (without sonication), 36–42% (with sonication).

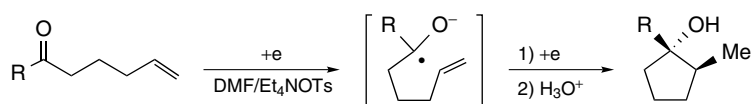


**Scheme 32** Electroenzymatic reduction of ketones with alcohol dehydrogenase;  $R^1$ : aryl,  $R^2$ : alkyl, CHO, CO<sub>2</sub>H, yields: 92–100%, 0–100% *ee*.





**Scheme 33** Base catalyzed condensation of aldehydes by electrogenerated bases (EGB's); R: alkyl, yields: 72–77%, very high current efficiency.



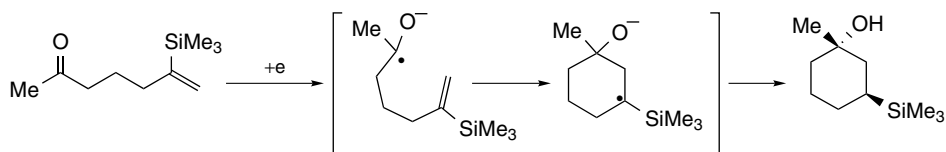
**Scheme 34** Cathodic cyclization of unsaturated ketones; R: alkyl, yields: 75–98%.

double bond and forms a 5-membered ring, whilst the similar cyclization reaction to the silyl substituted carbon–carbon double bond predominantly occurs at the lower substituted carbon atom of the double bond and forms a 6-membered ring (Scheme 35) [77].

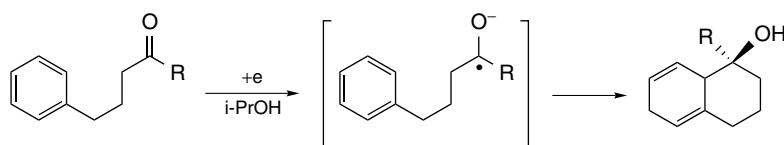
The addition of cathodically generated butyl radicals to aromatic rings forms cyclic alcohols with high stereoselectivity (Scheme 36) [78].

The anion radical species also adds to a carbon nitrogen triple bond and affords cyclic ketones (Scheme 37) [79, 80].

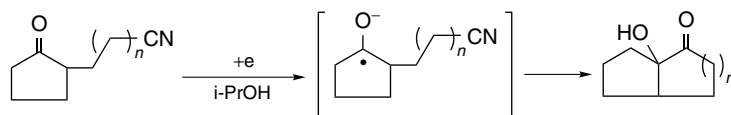
In contrast to the high regioselectivity and good yields of electroreductive intramolecular coupling reactions of ketones with multiple bonds shown in Schemes 34 to 37, the yields of intermolecular coupling reactions have been very low until recently. However, by using carbon fiber electrodes, intermolecular coupling reactions have



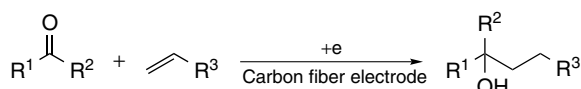
**Scheme 35** Intramolecular cathodic coupling of vinylsilanes with ketones; yields: 55%.



**Scheme 36** Intramolecular cathodic cyclization of ketones with aryl rings; R: alkyl, yields: 21–74%.



**Scheme 37** Intramolecular cathodic cyclization of ketones with nitriles;  $n$ : 1,2, yields: 55–76%.



**Scheme 38** Cathodic intermolecular coupling of ketones with alkenes;  $R^1$ ,  $R^2$ ,  $R^3$ : alkyl, yield: 52–82%.

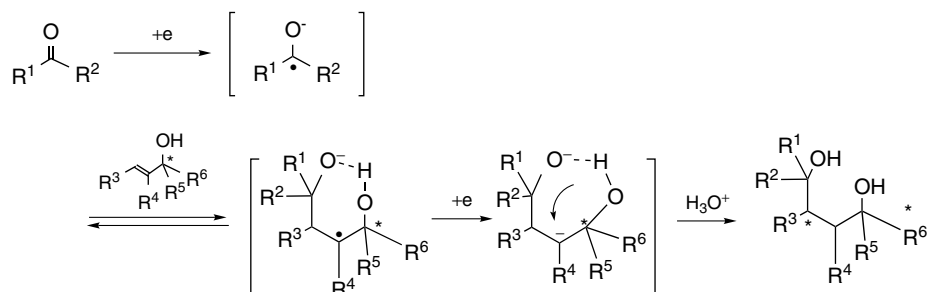
now attained in reasonable yields ( $\sim 80\%$ ) (Scheme 38) [81].

In the cathodic intermolecular coupling of ketones with optically active allylic alcohols, the hydroxyl group plays an important role in promoting the stereoselective coupling reaction, and the formation of a cyclic intermediate is suggested to be the reason for a high diastereoselectivity ( $de = \sim 95\%$ ) (Scheme 39) [82]. For example, the cathodic coupling of acetone ( $R^1 = R^2 = \text{CH}_3$ ) with *trans*-( $R$ )-2-octen-4-ol ( $R^3 = \text{CH}_3$ ,  $R^4 = R^5 = \text{H}$ ,  $R^6 = \text{C}_4\text{H}_9$ ) and *trans*-( $R$ )-5-methyl-2-hexen-4-ol ( $R^3 = \text{CH}_3$ ,  $R^4 = \text{H}$ ,  $R^5 = \text{CH}_3$ ,  $R^6 = \text{C}_2\text{H}_5$ ) gave the corresponding (3*S*,5*R*)-2,3-dimethyl-2,5-nonanediol and (3*S*,5*R*)-2,3,6-trimethyl-2,5-heptanediol, respectively, with excellent diastereoselectivity. Also, the coupling

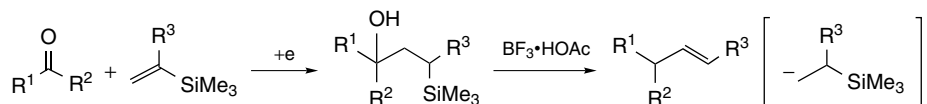
of acetone with *cis*-( $R$ )-2-octen-4-ol gave (3*R*,5*R*)-2,3-dimethyl-2,5-nonanediol with high diastereoselectivity.

Electroreductive coupling of ketones with silyl-substituted olefins promotes interesting reactions that are useful for organic synthesis. For example, coupling of ketones with trimethylvinylsilanes affords  $\beta$ -trimethylsilyl alcohols, which are easily transformed to the corresponding olefins (Scheme 40). This reaction is interesting from the synthetic point of view since vinylsilane behaves as the equivalent to a  $\beta$ -trimethylsilyl group-substituted anion [77, 83].

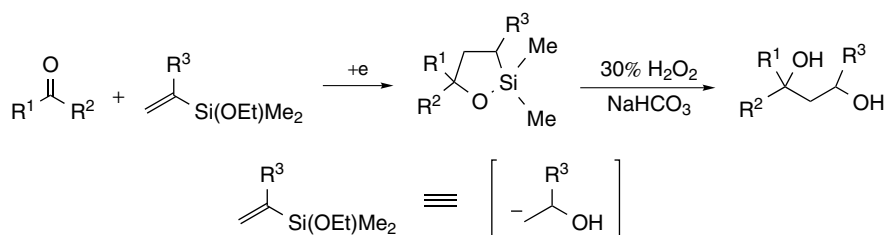
Cathodic coupling of ketones with an ethoxydimethylsilyl-substituted olefin affords oxasilacyclopentanes with excellent yield. This coupling is synthetically valuable as the coupling product is a



**Scheme 39** Diastereoselective cathodic coupling of ketones with allylic alcohols; yields: 60–90%.



**Scheme 40** Cathodic intermolecular coupling of ketones with vinyl trimethylsilane;  $R^1, R^2$ : alkyl,  $R^3$ : prim. sec. alcohol, yields: 35–96%.



**Scheme 41** Cathodic intermolecular coupling of ketones with vinyl ethoxy dimethylsilane;  $R^1, R^2$ : alkyl,  $R^3$ : H, alkyl, yields: 62–79%.

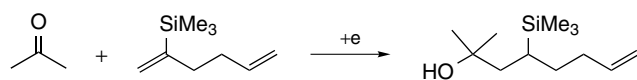
useful key intermediate for the preparation of a 1,3-diol. In this reaction, the ethoxydimethylsilyl-substituted olefin acts as the equivalent of a  $\beta$ -hydroxy substituted anion (Scheme 41) [84].

The existence of a trimethylsilyl group on the carbon–carbon double bond seems to activate the double bond towards radical addition since the electroreductive intermolecular coupling of ketones with carbon–carbon double bond predominantly takes place at the

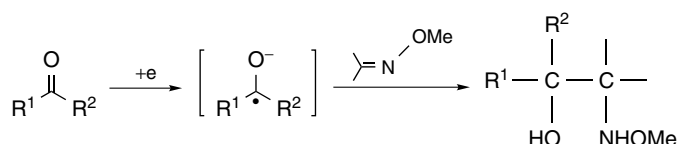
trimethylsilyl-substituted carbon of the double bond (Scheme 42) [77].

Anion radical species formed by the electroreduction of ketones also intermolecularly add to a carbon–nitrogen double bond and form derivatives of an  $\alpha$ -amino alcohol (Scheme 43) [85].

Carbon dioxide ( $\text{CO}_2$ ) is another reducible species with a carbon–oxygen bond. The electroreduction of  $\text{CO}_2$  is well established in the literature [1], however, the nature of the product highly depends



**Scheme 42** Selectivity in the intermolecular coupling of ketones with vinyl trimethylsilanes; yields: 86%.



**Scheme 43** Intermolecular cathodic heterocoupling of ketones with oximes;  $R^1, R^2$ : alkyl, cycloalkyl, yields: 43–98%.

on the reaction conditions. The formation of formic acid, oxalic acid, glyoxylic acid, glycolic acids, carbon monoxide, methanol, and ethylene glycol has been reported so far. Recently metal catalysts effective for the reduction of carbon dioxide have been reported. Typical examples are the reduction of carbon dioxide using Co [86], Re [87], Ru [88], and Ni [89].

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## 8 Oxidation and Reduction of Halogen-containing Compounds

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## 8.1 Introduction

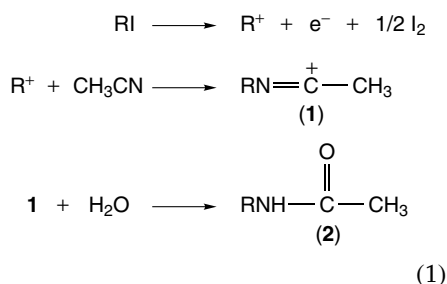
Among many classes of organic compounds, halogen-containing species is one of the most thoroughly investigated. This chapter offers a brief overview of both the oxidation and reduction of halogenated organic compounds. Limitations of space preclude a comprehensive bibliography; mainly, the most important and recent publications are cited here. Where the same author or authors have published a series of papers on a subject, often only the most recent reference is given. Additional information can be obtained from other more expansive treatments [1–3]. By consulting references cited within the articles listed at the end of this chapter, the interested reader can gain an even more complete picture of this subject.

## 8.2 Anodic Processes

As revealed in the following three sections, work dealing with the electrochemical oxidation of halogenated organic compounds is centered largely on the behavior of alkyl, alicyclic, and aryl halides. A review by Becker [4] provides an especially good perspective of developments in these areas.

### 8.2.1 Halogenated Alkanes

At a platinum anode in acetonitrile, a primary alkyl iodide undergoes oxidation to give a carbocation that reacts with the solvent to give an intermediate (1), and the latter species is converted to an *N*-alkylacetamide (2) during an ether–water workup [5]:



where, among other groups,  $\text{R}=\text{CH}_3$ ,  $\text{C}_2\text{H}_5$ ,  $(\text{CH}_3)_2\text{CH}$ ,  $\text{C}_4\text{H}_9$ , and  $(\text{CH}_3)_3\text{CCH}_2$  (Eq. 1). However, other evidence [6] suggests that a cation radical ( $\text{RI}^{\cdot+}$ ) is initially generated at the anode. Polyfluoroalkyl iodides can be transformed anodically into amides, esters, and ethers [7]. Secondary alkyl iodides afford *N*-alkylacetamides (2) upon oxidation at platinum in acetonitrile [8], and various mechanistic features of the oxidation of both primary and secondary alkyl iodides have been probed [9].

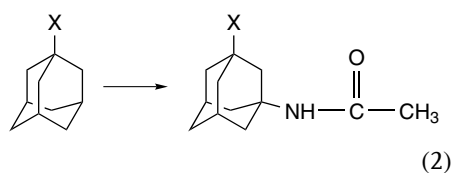


Controlled-potential oxidations of a number of primary, secondary, and tertiary alkyl bromides at platinum electrodes in acetonitrile have been investigated [10]. For compounds such as 2-bromopropane, 2-bromobutane, *tert*-butyl bromide, and neopentyl bromide, a single *N*-alkylacetamide is produced. On the other hand, for 1-bromobutane, 1-bromopentane, 1-bromohexane, 1-bromo-3-methylbutane, and 3-bromohexane, a mixture of amides arises. It was proposed that one electron is removed from each molecule of starting material and that the resulting cation radical ( $\text{RBr}^{+\bullet}$ ) decomposes to yield a carbocation ( $\text{R}^+$ ). Once formed, the carbocation can react (either directly or after rearrangement) with acetonitrile eventually to form an *N*-alkylacetamide, as described above for alkyl iodides. In later work, Becker [11] studied the oxidation of 1-bromoalkanes ranging from methyl to heptyl bromide. He observed that, as the carbon-chain length is increased, the coulombic yield of amides decreases as the number of different amides increases.

### 8.2.2

#### Alicyclic Halides

Koch and Miller [12] reported that oxidation of 1-chloro- and 1-fluoroadamantane at a platinum anode in acetonitrile is a two-electron process leading to the formation of the corresponding *N*-(3-halo-1-adamantyl)acetamide in yields of 91 and 65%, respectively (Eq. 2):



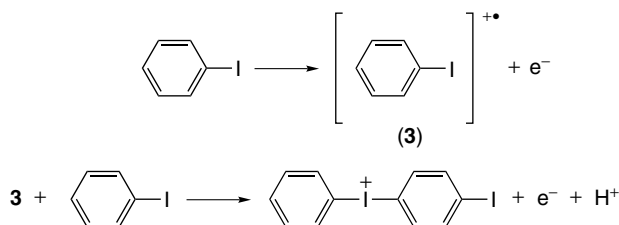
However, electrooxidation of 1-bromoadamantane involves the transfer of more than three electrons to afford *N*-(1-adamantyl)acetamide. In a comparable study of the oxidation of 2-haloadamantanes and their methyl-substituted analogues [13], it was observed that the products depend upon the identity of the halogen atom as well as the number of bridgehead methyl groups.

Oxidation of either cyclopropyl methyl iodide or cyclobutyl iodide at platinum in acetonitrile, followed by an aqueous workup, leads to a mixture of *N*-(cyclopropyl methyl)acetamide and *N*-cyclobutylacetamide, presumably because the intermediate cyclopropylmethyl cations can rearrange partially to a cyclobutyl cation; both react with acetonitrile to form immonium cations that are hydrolyzed to the isomeric acetamides [14]. Cyclopentyl, cyclohexyl, and cycloheptyl bromides have been oxidized to afford a mixture of the corresponding *N*-cycloalkylacetamide and cycloalkene, whereas cyclobutyl bromide gives only *N*-cyclobutylacetamide, and bromocyclopropane is converted into *N*-allylacetamide [15]. Polycyclic bridgehead iodides undergo electrooxidation at glassy carbon in acetonitrile to form *N*-alkylacetamides [16]; for example, *N*-(1-bicyclo[2.1.1]hexyl)acetamide was obtained in 55% yield from 1-iodobicyclo[2.1.1]hexane.

### 8.2.3

#### Aryl Halides

In early work, the oxidation of iodobenzene at platinum in acetonitrile was shown to give a cation radical (3), which reacts with excess starting material to yield the 4-iododiphenyliodonium cation [5] (Scheme 1).



**Scheme 1** Anodic coupling of iodobenzene to the 4-iododiphenyliodonium cation [5].

Parker and Eberson [17] demonstrated that the oxidation of 9,10-dibromoanthracene in the presence of a nucleophile (e.g. 3,5-lutidine) results in the replacement of a bromine by the nucleophile. In a series of papers [18], various polyfluoroaromatic amines were oxidized at platinum in an acetone–water mixture; for example, octafluoroacridone was synthesized from 2-aminononafluorobenzophenone (Scheme 2).

In a potassium acetate–acetic acid medium, 2-fluoro- and 4-fluoroanisole can be oxidized at platinum to afford 2-acetoxy- and 4-acetoxyanisole, respectively [19]. Using a platinum anode in a trifluoroacetic acid–potassium trifluoroacetate solution, Blum and Nyberg [20] electrooxidized hexafluorobenzene to tetrafluorobenzoquinone in 75% yield, and octafluoronaphthalene was converted into hexafluoronaphthoquinone in 60% yield.

### 8.3 Cathodic Processes

In this part of the chapter, the discussion is focused on the direct cathodic reduction of halogenated organic compounds, although the last section will address the increasingly active area of catalytic reductions of carbon–halogen bonds.

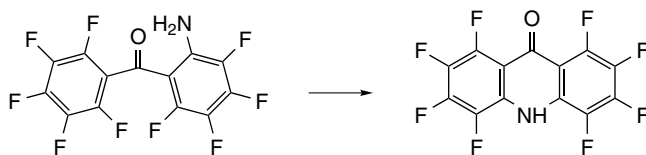
#### 8.3.1 Halogenated Alkanes

Depending on the electrode material, the potential, the solvent, and the supporting electrolyte, the reduction of an alkyl monohalide (RX) at an inert cathode can lead to a radical ( $R^\bullet$ ) or a carbanion ( $R^-$ ) intermediate, as shown in the following mechanistic Scheme 3.

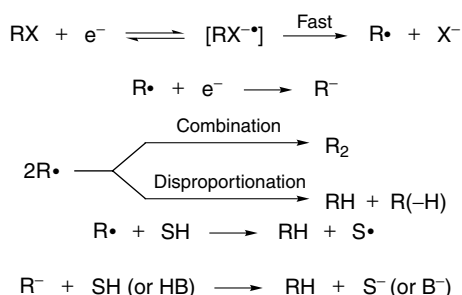
Once formed, the radical intermediate ( $R^\bullet$ ) can couple to afford a dimer ( $R_2$ ), can disproportionate to give an alkane (RH) and an olefin ( $R(-H)$ ), or can accept a hydrogen atom from a donor (such as the solvent, SH) to give an alkane. A carbanion ( $R^-$ ) can be protonated by the solvent (or a deliberately added acid, HB) to yield an alkane. In addition, RX can undergo E2 and  $S_N2$  reactions with  $B^-$ , and  $R^-$  can attack RX to form a dimer.

Tertiary alkyl halides are easier to reduce than secondary alkyl halides, which are easier to reduce than primary alkyl halides. Carbon–iodine bonds are easier to reduce than carbon–bromine bonds, which are easier to reduce than carbon–chlorine bonds [1–3].

Primary [21] and secondary [22] alkyl iodides are reduced in a stepwise fashion at mercury cathodes to form alkyl radicals and alkyl carbanions; the alkyl radicals undergo coupling and disproportionation as well as interaction with the electrode to yield diorganomercury compounds, and



**Scheme 2** Octafluoroacridone by way of anodic nuclear substitution [18].

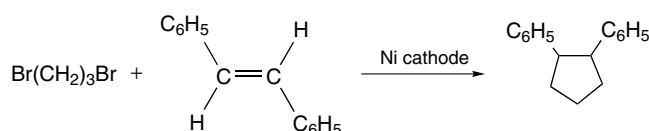


**Scheme 3** Mechanism of cathodic cleavage of halogenated alkanes.

the alkyl carbanions afford mainly alkanes and olefins. However, the reduction of primary and secondary alkyl bromides at mercury gives alkyl carbanions only [21, 22], whereas *tert*-butyl bromide exhibits a stepwise reduction [23]. An investigation of the reduction of primary, secondary, and tertiary alkyl iodides and bromides at glassy carbon has revealed the formation of alkanes, olefins, and coupling products [24].

Electrochemical reduction of a variety of polyhalogenated alkanes has been undertaken. Stepwise dechlorination of *gem*-dichloro- and *gem*-trichloroalkanes occurs. Dichloromethane can be reduced in the presence of an olefin to form a cyclopropane [25], and

reductive coupling of 1,1,1-trichloro-2,2,2-trifluoroethane with aldehydes [26] and of *gem*-polyhalo compounds with activated olefins [27] is possible. Several studies have involved the electrogeneration of the trichloromethyl anion, which reacts with a number of substrates [28]. Vicinal dihalides, such as 1,2-dibromo-1,2-diphenylethane, undergo a two-electron reduction with loss of two halides to yield an olefin [29]. Electrochemical reduction of  $\alpha,\omega$ -dihaloalkanes at both mercury and carbon cathodes has been extensively investigated [30, 31]; from starting materials with short carbon chains, for example, 1,3-dibromopropane and 1,4-dibromobutane, the corresponding cycloalkane can be prepared. Reduction



**Scheme 4** Cathodic alkylation of *trans*-stilbene [32].

of 1,3-dibromopropane at a nickel cathode in the presence of an arylalkene affords the cyclopentane adduct (Scheme 4) [32].

### 8.3.2

#### Halogenated Alkenes and Alkynes

Vinyl halides, such as *cis*- and *trans*-3-iodo-3-hexene [33], undergo a one-electron reduction with expulsion of a halide ion to give a vinyl radical that is further reduced and protonated. When vinyl halides are electrolyzed in the presence of trimethylchlorosilane, silylated products are obtained [34].

A classic paper by Baizer and Chroma [35] describes synthetic applications based on the reduction of allyl halides. Electrolyses of 4-bromo- and 4-chloro-2-butene can be employed for the allylation of acetone and benzaldehyde [36], and the reduction of allyl halides in the presence of trimethylchlorosilane affords silylated compounds [34].

Several publications deal with acetylenic halides that can undergo reductive intramolecular cyclization [37]. For example, electrolysis of 6-iodo-1-phenyl-1-hexyne at a carbon cathode gives benzyldenecyclopentane in 36% yield.

### 8.3.3

#### Benzyl Halides

Mechanistic aspects of the reduction of benzyl halides at mercury have been extensively investigated [35, 38]. From the reduction of benzyl iodide at platinum, Koch and coworkers [39] obtained toluene, bibenzyl, and hydrocinnamionitrile. Electrolysis of benzyl chloride in the presence of acyl chlorides can be used to synthesize alkyl benzyl ketones [40], whereas alcohols are formed by electrolysis of

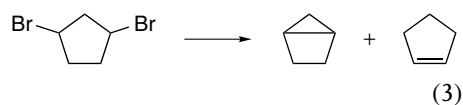
benzyl chloride in the presence of ketones and aldehydes [28]. Steric effects on the reductive coupling of  $\alpha$ -substituted benzyl bromides have been probed [41]. Reduction of trichloromethylbenzene in the presence of acetic anhydride gives 2-acetoxy-1-chloro-1-phenyl-1-propene and 1,2-diacetoxy-1-phenyl-1-propene [42], and cathodic addition of trichloromethylbenzene to ketones yields  $\alpha,\beta$ -unsaturated ketones [43]. Amino acids can be obtained via the coupling of Schiff bases with electrogenerated benzyl carbanions [44].

### 8.3.4

#### Alicyclic Halides

Mann and Barnes [45] have discussed the mechanism of reduction of substituted and optically active 1-bromo- and 1-iodocyclopropanes, and Hazard and coworkers [46] have investigated the reduction of 1-bromo-1-carboxy-2,2-diphenylcyclopropane. At mercury cathodes, electrolyses of 1-bromo- and 1-iodonorbornane proceed via two-electron cleavage of the carbon-halogen bond to give mainly norbornane, plus a small amount of bis(1-norbornyl)mercury [47].

Electrochemical reduction of 2,2-dichloronorbornane, 2-*exo*-bromo-2-*endo*-chloronorbornane, and 2-*endo*-bromo-2-*exo*-chloronorbornane gives mixtures of nortricyclene and *endo*-2-chloronorbornane [48]. Electrolysis of 1-bromo-3-chlorocyclobutane at mercury yields bicyclo[1.1.0]butane, cyclobutane, and cyclobutene [49]. Hoffmann and Voss [50] observed that 1,3-dibromocycloalkanes can undergo ring-closure at a platinum cathode (Eq. 3):

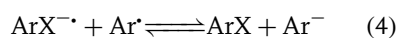


Reduction of 1-bromo-4-chlorobicyclo[2.2.0]hexane affords  $\Delta^{1,4}$ -bicyclo[2.2.0]hexane [51]. Wiberg and coworkers [52] electrolyzed 1,4-dibromobicyclo[2.2.2]octane and obtained evidence that [2.2.2]propellane is a transient intermediate, and electrolysis of 1,5-dibromobicyclo[3.2.1]octane leads to [3.2.1]propellane [49]. Studies of the reductions of 1,3-dihaloadamantanes, 1,4-dihalobicyclo[2.2.2]octanes, and 1,3-dihalobicyclo[1.1.1]pentanes have been reported [53]. When 1,4-dihalonorbornanes are electrolyzed at mercury, norbornane and bis(1-norbornyl)mercury are produced, along with small quantities of 1,1'-binorbornyl, and [2.2.1]propellane is an intermediate [54]. Selective electrochemical trimethylsilylation of tetrachlorocyclopropane to afford 1-(trimethylsilyl)trichlorocyclopropane has been described [55]. Chlordane, aldrin, and alodan (chlorinated insecticides) can be electrochemically dechlorinated [56], and lindane ( $\gamma$ -hexachlorocyclohexane) can undergo stepwise dechlorination [57].

### 8.3.5

#### Aryl Halides

Earlier, in Sect. 8.3.1, a generalized mechanistic scheme for the reduction of simple alkyl halides was presented. What distinguishes aryl halides ( $\text{ArX}$ ) from alkyl halides ( $\text{RX}$ ) is the finite lifetime of the initially electrogenerated anion radical ( $\text{ArX}^{\cdot-}$ ). Thus, although  $\text{ArX}$  exhibits the same kinds of reactions as  $\text{RX}$ , a key difference is that the transient anion radical ( $\text{ArX}^{\cdot-}$ ) can undergo a homogeneous electron-transfer reaction with the aryl radical ( $\text{Ar}^{\cdot}$ ) (Eq. 4):



Savéant and coworkers [58] have played a central role in characterizing the behavior of aryl halides.

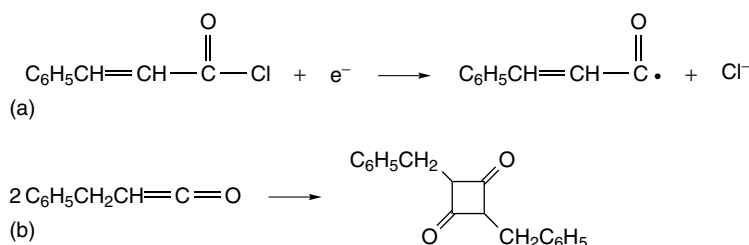
Iodobenzene and bromobenzene [59], as well as *p*-iodoanisole [60], can be electrolyzed at mercury cathodes in the presence of carbon dioxide to give carboxylic acids. Reduction of various aryl halides in the presence of trimethylchlorosilane affords silylated products [61]. Kariv-Miller and Vajtner [62] converted fluorobenzene to benzene by carrying out electrolyses at mercury cathodes in diglyme containing the dimethylpyrrolidinium cation ( $\text{DMP}^+$ ); the latter behaves catalytically by being reduced to an amalgam that reacts with fluorobenzene to form the anion radical ( $\text{C}_6\text{H}_5\text{F}^{\cdot-}$ ), which undergoes a carbon-fluorine bond scission, followed by reduction and protonation to yield benzene. Reduction of an aryl halide gives an aryl carbanion, which, by deprotonating an appropriate nitrile, can lead to coupling of the nitrile with esters, aldehydes, and ketones [63].

Dihalobenzenes, such as *p*-bromiodobenzene, can be reduced in a stepwise manner [64]. An investigation of the electrochemistry of the entire family of chlorinated benzenes has been reported [65], and the dechlorinations of 1,2,3,5-tetrachlorobenzene [57] and of 2,4-dichlorophenoxyacetic acid (a herbicide) have been accomplished [66]. Several papers dealing with the reduction of chlorinated biphenyls have appeared [67–69].

### 8.3.6

#### Acyl and Phenacyl Halides

Reduction of benzoyl chloride at mercury yields an acyl radical that dimerizes to form benzil. As quickly as it forms, benzil accepts an electron to form an anion radical that is acylated by a molecule of benzoyl



**Scheme 5** Cathodic reduction of cinnamoyl chloride to the corresponding ketene dimer [70b].

chloride; most probably, the resulting intermediate is reduced again and acylated one more time to afford a mixture of *cis*- and *trans*-stilbenediol dibenzoate [70, 71]. An analogous set of reactions can be proposed for the reduction of both 1-naphthoyl chloride and 2-naphthoyl chloride [70]. Cinnamoyl chloride undergoes a one-electron reduction at mercury to give a radical (Scheme 5a). This radical gains a hydrogen atom from the medium to form a ketene, which immediately undergoes dimerization (Scheme 5b).

In addition to studying the behavior of benzoyl chloride, Cheek and Horine [72] have examined the reduction of benzoyl fluoride; electrolysis of the latter compound affords benzyl benzoate, diphenylacetylene, stilbenol benzoate, and some polymers. Another feature of the reduction of benzoyl chloride is the possibility that both acyl radicals and acyl anions are involved as intermediates [71].

Glutaryl dichloride undergoes reduction at mercury to give 5-chlorovalerolactone and valerolactone; a polymeric solid, possibly  $\text{X}[(\text{CH}_2)_3\text{CHCl}-\text{O}-\text{C}=\text{O}]_n(\text{CH}_2)_3\text{X}$  (where  $\text{X} = \text{CHO}$  or  $\text{CO}_2\text{H}$ ), is additionally produced [73]. Heptanoyl chloride [71], trimethylacetyl chloride [74], and cyclohexanecarbonyl chloride [75] can be reduced at carbon or mercury cathodes to form the corresponding aldehydes; in addition, the anhydride (and sometimes

the carboxylic acid) is obtained as a by-product of hydrolysis involving adventitious water.

Phenylacetyl chloride and hydrocinnamoyl chloride are reduced at mercury to form both acyl radicals and acyl anions as intermediates [76]. From electrolyses of phenylacetyl chloride, the products include 1,4-diphenyl-2-butene-2,3-diol diphenylacetate, phenylacetaldehyde, toluene, 1,3-diphenylacetone, and 1,4-diphenyl-2,3-butanediol, and analogous species arise from the reduction of hydrocinnamoyl chloride. Reduction of phthaloyl dichloride is a more complicated system [77]; the electrolysis products are phthalide, bipthalyl, and 3-chlorophthalide, but the latter compound undergoes further reduction to give phthalide, bipthalyl, and dihydrobipthalide.

Electrolysis of 2-furoyl chloride at mercury affords mainly 1,2-di(2-furyl)ethene-1,2-diol di(2-furoate); however, an interesting pair of minor products are 1,2-di(2-furyl)-2-hydroxy-3-cyanopropanone and 3-(2-furyl)acrylonitrile, in which a fragment of the solvent (acetonitrile) is incorporated [78]. When 2,4,6-trimethylbenzoyl chloride is reduced at carbon or mercury cathodes in acetonitrile, the major products are 2,4,6-trimethylbenzaldehyde and 3-(2,4,6-trimethylphenyl)acrylonitrile,

along with traces of 3-(2,4,6-trimethylphenyl)glutaronitrile and 3-(2,4,6-trimethylphenyl)propionitrile [79].

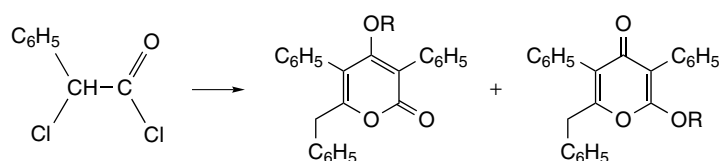
Reduction of 1-adamantanecarbonyl chloride at carbon or mercury leads to the quantitative formation of 1-adamantanecarboxaldehyde [80]. Mubarak [81] investigated the reduction of 2-thiophenecarbonyl chloride at both carbon and mercury; the starting material appears to undergo a two-electron reduction to form an acyl anion, which leads to 1,2-di(2-thienyl)ethene-1,2-diol di(2-thiophenecarboxylate) as the major product and to 2-thiophenecarboxaldehyde as the minor product.

Lozano and Barba [82] electrolyzed 2-chloro-2-phenylacetyl chloride at mercury in methylene chloride and obtained derivatives of pyran-2-one and pyran-4-one, where R is H and  $\text{C}_6\text{H}_5\text{CH}_2\text{CO}$ , respectively, at high and low current density (Scheme 6). In later work [83], the same workers reduced 2-bromo-2,2-diphenylacetyl bromide in methylene dichloride saturated with hydrogen sulfide gas; three sulfur-containing

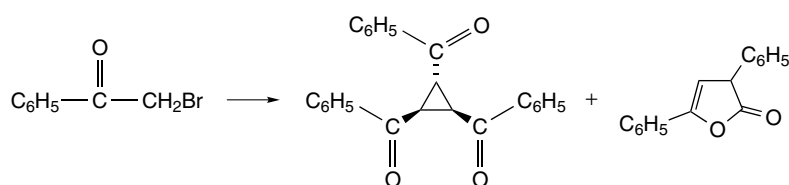
products were formed – *S*-methylidene bis(diphenylthioacetate), *S*-chloromethyl diphenylthioacetate, and *S*-methyl diphenylthioacetate.

Barba and coworkers [84–91] have published a number of papers dealing with novel syntheses based on the reduction of phenacyl bromides. Electrolysis of phenacyl bromide at a mercury cathode leads to an intermediate, which reacts to give 2,4-diphenylfuran [84]. However, when a proton donor ( $\text{CH}_3\text{OH}$ ) is present, the reduction of phenacyl bromide yields acetophenone and 2-bromo-1,3-diphenyl-3,4-epoxy-butan-1-one. Interestingly, if phenacyl bromide is slowly introduced into an electrolysis cell so that the unreduced starting material is maintained at a low concentration, the products are different [85] (Scheme 7).

It is also possible to protect the carbonyl moiety of a phenacyl bromide via the reaction with semicarbazide hydrochloride; then the semicarbazone can be electrolytically dimerized, ultimately to afford a 2,5-diarylfuran [86]. Alternatively, the electrolytically formed dimer can be converted



**Scheme 6** Cathodic reduction of 2-chloro-2-phenylacetyl chloride to pyran-2-one and pyran-4-one derivatives [82].



**Scheme 7** Cathodic reduction of phenacylbromide to trimer and dimer [85].

(via refluxing in dimethylformamide) to a 3,6-diphenylpyridazine [87]. Reduction of  $\alpha$ -bromopropiophenone at mercury gives 1,4-diphenyl-2,3-dimethylbutan-1,4-dione [88], and the reduction of phenacyl bromides provides a synthetic pathway to 4-aryl-2-methylfurans [89] and enol carbonates [90]. Finally, 3,7-diaryl-2H-imidazo[2,1-b] [1, 3, 4]oxadiazines can be prepared via reduction of the semicarbazones of phenacyl bromide [91].

### 8.3.7

#### Aliphatic $\alpha$ -Halocarbonyl Compounds

Studies of aliphatic  $\alpha$ -haloaldehydes in water–dioxane have shown that the electrochemical behavior of these compounds is affected by the equilibrium between the hydrated and unhydrated forms of the aldehyde [92]. Each carbon–halogen bond is broken in a two-electron, one-proton process, and the resulting nonhalogenated aldehyde undergoes reduction at a more negative potential [93].

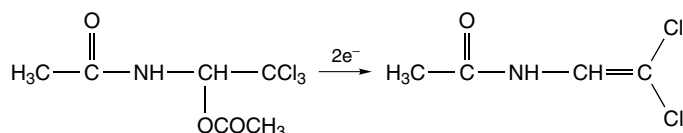
Reduction of 2-bromo-3-pentanone at mercury affords a mixture of 3-pentanone and 1-hydroxy-3-pentanone, whereas electrolysis of  $\alpha,\alpha'$ -dibromoacetone in the presence of benzoate gives a mixture of products arising from both a carbon–bromine bond cleavage and an  $S_N2$  displacement of bromide by benzoate [94]. In an acetic acid–acetate buffer, branched dibromo ketones, such as 2,4-dibromo-2,4-dimethyl-3-pentanone, are reduced to  $\alpha$ -acetoxy ketones; however, less highly substituted compounds, such as 4,6-dibromo-5-nonanone, undergo simple cleavage of both carbon–bromine bonds [95]. Other work dealing with the reduction of  $\alpha,\alpha'$ -dibromoketones has been described [96].

Reduction of bis( $\alpha$ -bromocyclopropyl) ketone in an aqueous acetic acid–acetate

buffer gives a mixture of dicyclopropyl ketone and  $\alpha$ -bromocyclopropyl cyclopropyl ketone, whereas only the latter product is obtained for the same buffer in dimethylformamide [97]. Low-temperature reduction of alkylated  $\alpha,\alpha'$ -dihaloketones to cyclopropanones (isolated as hemiacetals or hemiacylals) can be performed with highly alkylated starting compounds [98]. Electrolysis of  $\alpha,\alpha'$ -dichloroketones at mercury in the presence of carboxylic acids, phenols, and diethyl malonate leads to the formation of Favorskii-rearrangement products, dechlorinated ketones, and addition products [99]. In the presence of amines or phenols, 1,1,3-tribromo- or 1,1,3-trichloro-3-methyl-2-pentanone can be reduced to the corresponding  $\alpha,\beta$ -unsaturated amides or esters [100].

In aqueous media,  $\alpha$ -halocarboxylic acids and their esters undergo two-electron, one-proton reductive cleavage [101]. Electrolysis of ethyl bromoacetate at mercury affords mainly ethyl acetate and diethyl succinate, along with small amounts of diethyl fumarate, 1,2,3-tricarbethoxycyclopropane, and 1,2,3-tricarbethoxypropane [35]. Electrolysis of a solution containing  $\alpha$ -chloro-*N*-benzylacetamide, carbon dioxide, and a probase (e.g. tetraethyl ethylenetetra-carboxylate) has been used to synthesize *N*-benzyloxazolidine-2,4-dione (a biologically active compound) [102]. Maran [103] has examined the reduction of  $\alpha$ -haloamides at mercury; for example, electrolysis of (*S*)-(-)-2-bromo-*N*-phenylpropanamide yields propananilide, 2-(dimethylamino)-5-methyl-3-phenyloxazolidin-4-one, and *cis*-1,4-diphenyl-3,6-dimethyl-2,5-dioxopiperazine. Casadei and coworkers [104] investigated the following process (Scheme 8).





**Scheme 8** Cathodic  $\beta$ -elimination from  $\beta$ -haloacetate [104].

Reductions of ethyl  $\alpha,\beta$ -dibromopropionate, ethyl  $\alpha,\gamma$ -dibromobutyrate, and methyl  $\alpha,\delta$ -dibromovalerate at mercury have been characterized [105].

### 8.3.8

#### Halogenated Heterocyclic Compounds

Halogenated heterocyclic compounds exhibit a behavior similar to that of aryl halides. Accordingly, at mercury in aqueous media, monohalogenated pyridines, in either their unprotonated or protonated forms, undergo a two-electron cleavage of the carbon-halogen bond, followed by protonation to yield pyridine [106]. Redox catalysis has been used to probe the reduction of 2-bromo-, 3-bromo-, 2-chloro-, and 3-chloropyridine at mercury [58]. Reduction of 2,5-dibromo-, 2,3-dichloro-, and 2,6-dichloropyridine in ethanol-water has been studied polarographically [107], and the electrochemical behavior of mono- and dihalopyridines at carbon cathodes has been characterized [108]. Chambers and coworkers [109] have studied the reduction of some polyhalopyridines at mercury. There is a patent describing the electrosynthesis of 2,3,5-trichloropyridine from pentachloropyridine [110, 111], and two patents deal with the reduction of pentachloropyridine to 2,3,5,6-tetrachloropyridine [112–115].

Two papers concerning the reduction of chlorinated quinolines have been published [116, 117]. Electrolysis of 3,4,5,6-tetrachloro-2-picolinic acid at a silver

cathode affords 3,4,6-trichloro-2-picolinic acid, which can be further reduced to 3,6-dichloro-2-picolinic acid [118, 119].

Studies of the behavior of heterocyclic compounds possessing two nitrogen atoms are rare. There is a survey of the reduction of 6-haloquinoxalines and 2-halophenazines [116], and a report about the reduction of 4-chloroquinazoline [120].

Halogenated thiazoles are reduced at mercury in a process involving two electrons and a proton to give thiazole [121]. By electrolyzing 2-bromothiazole in an acidic water-ethanol mixture, Iversen [122] obtained thiazole in 88% yield. Reduction of 2-bromothiazole at carbon involves both radical and carbanion intermediates, and thiazole is formed quantitatively [123].

For the reduction of bromo- and iodothiophenes in both aqueous and nonaqueous media, cleavage of each carbon-halogen bond is a two-electron, one-proton process [124]. Pletcher and Razaq [125] prepared 3-bromothiophene by electrolyzing 2,3,5-tribromothiophene, and Gedye and coworkers [126] investigated the reduction of tetrabromo-, tetraiodo-, 2,3,4-tribromo-, and 3,4-dibromothiophene at various cathodes. Procedures for the electrosynthesis of brominated thiophenes have been reported [127]. Reduction of several dihalothiophenes at carbon gives rise to an electrolytically induced halogen dance [128] and, by reducing a substituted 3-chlorobenzo[*b*]thiophene, Justice and Hall [129, 130] obtained 3-hydrobenzo[*b*]thiophene.

## 8.3.9

**Catalytic Reduction of Carbon–Halogen Bonds**

Although an up-to-date review [3] of this subject has recently appeared, a summary is presented here. In many instances, a carbon–halogen bond can be cleaved chemically with an electron-transfer mediator (catalyst) that is electrogenerated at potentials more positive than those required for the direct reduction of the carbon–halogen bond. Electrogenerated anion radicals of aromatic hydrocarbons were the first mediators to be used, but in recent years electrogenerated low-valent transition-metal complexes and other organometallic species have enjoyed increasing popularity as catalysts.

Lund and coworkers [131] pioneered the use of aromatic anion radicals as mediators in a study of the catalytic reduction of bromobenzene by the electrogenerated anion radical of chrysene. Other early investigations involved the catalytic reduction of 1-bromo- and 1-chlorobutane by the anion radicals of *trans*-stilbene and anthracene [132], of 1-chlorohexane and 6-chloro-1-hexene by the naphthalene anion radical [133], and of 1-chlorooctane by the phenanthrene anion radical [134]. Simonet and coworkers [135] pointed out that a catalytically formed alkyl radical can react with an aromatic anion radical to form an alkylated aromatic hydrocarbon. Additional, comparatively recent work has centered on electron transfer between aromatic anion radicals and 1,2-dichloro-1,2-diphenylethane [136], on reductive coupling of *tert*-butyl bromide with azobenzene, quinoxaline, and anthracene [137], and on the reactions of aromatic anion radicals with substituted benzyl chlorides [138], with

vinyl bromides, 2-bromoindene, and 7,7-dichlorobicyclo[4.1.0]heptane [139], and with bornyl, isobornyl, and *exo*- and *endo*-norbornyl bromides [140].

Two reviews provide important information about the use of transition-metal complexes as mediators [141] and about catalytic processes involving a wider variety of metal species [142].

Catalytic processes based on the use of electrogenerated nickel(0) bipyridine complexes have been a prominent theme in the laboratories of Nédélec, Périchon, and Troupel; some of the more recent work has involved the following: (1) cross-coupling of aryl halides with ethyl chloroacetate [143], with activated olefins [144], and with activated alkyl halides [145], (2) coupling of organic halides with carbon monoxide to form ketones [146], (3) coupling of  $\alpha$ -chloroketones with aryl halides to give  $\alpha$ -arylated ketones [147], and (4) formation of ketones via reduction of a mixture of a benzyl or alkyl halide with a metal carbonyl [148].

Nickel(0) triphenylphosphine can be used to couple aryl halides and alkenes to synthesize substituted olefins [149], 1,2-bis[(di-2-propylphosphino)benzene]nickel(0) can be used to couple aryl halides [150], and 1,2-bis[(diphenylphosphino)ethane]nickel(0) can be used to prepare benzoic acid from bromobenzene in the presence of carbon dioxide [151].

Electrogenerated nickel(I) salen has been employed catalytically for the reduction of benzal chloride [152] and for the reductive coupling of 2-bromo- and 2-iodoethanol to prepare 1,4-butanediol [153]. Electrogenerated nickel(I) cyclams have been used as catalysts for the reductive intramolecular cyclizations of *o*-haloaryl

compounds possessing unsaturated side chains [154], of 2-bromoalkyl- and 3-bromoalkyl-2-cyclohexen-1-ones [155], of *o*-bromoacryloylanilides to give five-membered lactams [156], of acetylenic halides to prepare functionalized (methylene)cyclopentanes [157], and of 2-bromo- and 2-iodoethanol to afford ethylene oxide [158].

Cobalt(I) salen has been employed as a catalyst for the reduction of the following species: benzal chloride [159]; benzotrichloride [160]; 1-bromobutane, 1-iodobutane, and 1,2-dibromobutane [161]; iodoethane [162], benzyl chloride [163], and ethyl chloroacetate [164]. Rusling and coworkers have investigated the use of cobalt(I) salen, as well as vitamin B<sub>12</sub>s and cobalt(I) phthalocyanine, in both homogeneous phase and bicontinuous microemulsions for the catalytic reduction of vicinal dibromides [165] and 1-bromobutane, 1-bromododecane, and *trans*-1,2-dibromocyclohexane [166].

Electrogenerated samarium(II) catalyzes the reduction of organic halides [167] and the reductive coupling of 3-chloropropanoate or of allyl chloride with ketones [168, 169]. Reactions of iron(II) porphyrin with vicinal dihalides and various organic monohalides have been examined [170], and iron(II) myoglobin immobilized in biomembrane-like surfactant films on graphite electrodes catalytically dehalogenates ethylene dibromide and trichloroacetic acid [171]. Yoshida and coworkers reduced mixtures of organic halides and iron pentacarbonyl, followed by addition of an electrophile, to prepare carbonyl compounds [172] and, in related work, iron pentacarbonyl served as a catalyst for the conversion of alkyl halides into aldehydes [173, 174].

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## 9

### Electrochemical Reactions of Sulfur Organic Compounds

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## 9.1 Introduction

Sulfur organic compounds were among the first that attracted the attention of electrochemists about a century ago. Since that time, great progress has been made in this field and it will not be an exaggeration to say that synthetic and theoretical studies in sulfur electrochemistry account for a great part of the progress in organic electrochemistry.

An enormous amount of work has been done in this wide field and a number of excellent reviews on different aspects of sulfur electrochemistry has been published [1–7], so here we confine our attention to some principal reactions and interesting applications of both anodic and cathodic activation of sulfur-containing molecules. Compared to other chalcogenides, sulfur has frontier orbitals that have volume, symmetry, and energy more suitable for efficient interaction with adjacent carbon atoms. The ionization of molecular sulfur requires about 10 eV. Conjugation of the  $p_z$  orbitals of sulfur with a  $\pi$ -system lowers the ionization potential by ca. 2 eV. For this reason, compounds of divalent sulfur undergo oxidation rather easily often giving rise to cation radicals or dications. The stability of this species is in line with the

conjugation or other interactions affecting the delocalization of a charge on the sulfur atom. The HOMO of such intermediates still controls their reactivity, which is the tendency to dimerization or other second-order orbital-controlled interactions. The lack of conjugation, for example, in aliphatic sulfur derivatives, causes sulfur-centered charge-controlled reactions and often results in scission of bonds formed by sulfur. If sulfur does not form multiple bonds or has no vacant or half-filled orbitals, like in sulfonium salts, the reduction of such compounds is usually accompanied by reductive cleavage.

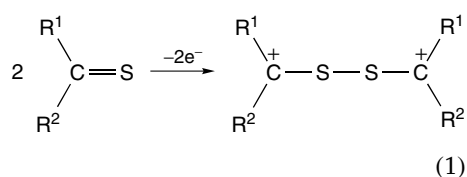
The review below deals with anodic and cathodic reactions of organic derivatives of sulfur, which have interesting potentialities for the electrosynthesis and electrochemically initiated functionalization of organosulfur and related organic compounds.

## 9.2 Electrooxidation

### 9.2.1 Thiones

The HOMO of thiocarbonyl compounds corresponds to the  $n$ -electrons of sulfur; the  $\pi$ -orbitals of the C=S bond usually

have a lower energy. However, both chemical (shown for thioureas, thiocarbonates, and thiocarbamates) and electrochemical oxidation (tested for aromatic thiocarbonyl derivatives in poorly nucleophilic media) show reaction of C=S double bond opening and formation of dicationic dimers (Eq. 1) [8].



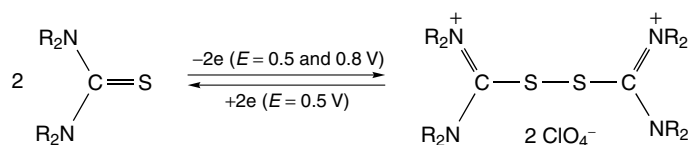
The oxidation step of thioureas can be reversed, as was shown by cyclic voltammetry to regenerate thiourea from anodically produced dimeric salt (in AN/Bu<sub>4</sub>NClO<sub>4</sub>, potentials vs Ag/Ag<sup>+</sup>) (Scheme 1).

The anodic oxidation of alkyl isothiocyanates RNCS in wet acetonitrile (AN) involves the formation of two possible

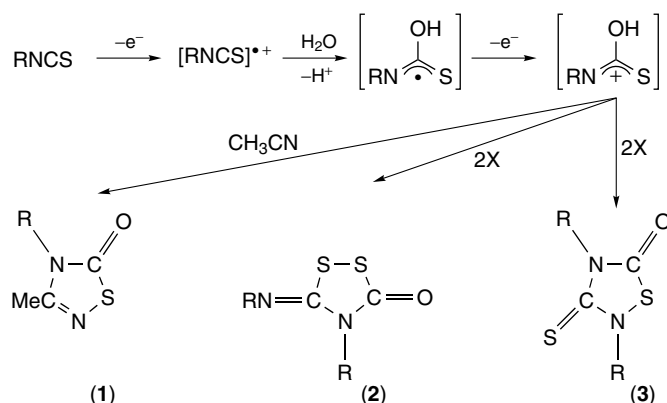
intermediates (a free radical and the corresponding highly reactive cation). The anodic behavior of alkyl isothiocyanates appears to be strongly dependent on the bulkiness of the alkyl group R. As a matter of fact, the exclusive formation of five-membered heterocyclic compounds as shown in Structures (1), (2), and (3) implies reactions of transient(s) with the starting compound or the nucleophilic solvent (in the example quoted above, acetonitrile will favor formation of structure (1)) (Scheme 2).

The anodic oxidation of 1,2-dithiole-3-thiones (R<sup>1</sup>, R<sup>2</sup> = H, Ph, respectively) was reported [9, 10] to yield disulfide-linked bis(dithiole-3-thione) dication (Scheme 3).

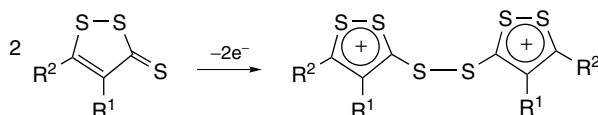
Homogeneous oxidation of substituted thiobenzamides and *N,N'*-diphenylthiourea in aqueous AN/Bu<sub>4</sub>NOAc or in aqueous EtOH/Et<sub>4</sub>NOTs, mediated by the organotellurium species



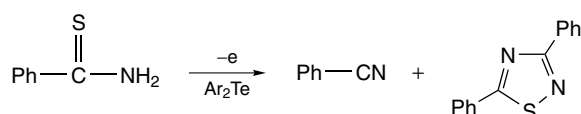
**Scheme 1** Anodic dimerization of thiourea and cathodic cleavage of the dimer.



**Scheme 2** Anodic oxidation of alkyl isothiocyanates.



**Scheme 3** Anodic oxidation of 1,2-dithiole-3-thiones.



**Scheme 4** Oxidation of substituted thiobenzamides.

generated by the electrooxidation of diorganyltellurides, results in substituted benzonitrile and 3,5-diaryl-1,2,4-thiadiazole [11]. The use of the first solvent favors the formation of nitriles whereas by using the second electrolyte, the corresponding thiadiazoles were selectively obtained in a 71–77% yield (Scheme 4).

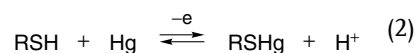
The oxidation of thioesters of phosphorus(III) acids (*S*-ethyldiphenylphosphinite, *S,S*-diethylphenylphosphonite and triethylthiophosphite) in AN/NaClO<sub>4</sub> occurs at potentials characteristic for thioethers with substituents other than for phosphorus(III) groups, which suggests the contribution of the lone pair of sulfur to the HOMO to be predominant. The process is thought to proceed via an intermediate cation radical with the number of electrons *n* varying from 0.65 to 0.85, which suggests a catalytic mechanism [12–15].

### 9.2.2

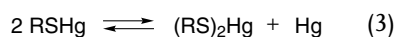
#### Thiols

In aqueous solutions, the peak potentials of the oxidation of thiols vary with pH ( $\Delta E_p/\Delta \text{pH} \cong 60 \text{ mV}$ ), reflecting the position of the acid-base equilibrium affecting the SH group. In basic solutions,

when  $\text{pH} > \text{pK}_a$  (RSH), the only form,  $\text{RS}^-$ , is present, and the  $E_p$  remains constant. The oxidation of thiols at a Hg electrode occurs reversibly (in acid media) and involves the formation of a metastable intermediate of Hg(I) (Eq. 2):



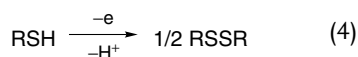
Then mercury thiolate transforms into a more stable Hg(II) derivative (Eq. 3) [16, 17].



The oxidation of thiols on mercury and some other metals ( $\text{M} = \text{Zn}, \text{Cd}$ ) can be used for the preparation of different bis-thiolate complexes  $\text{M}(\text{SR}_2)$  [18].

Under aprotic conditions, prototropic transformations of thiols are relatively slow, so one can observe distinct waves of the oxidation of the protonated form and of its parent base [19, 20]. Normally, the oxidation of thiols (aliphatic, aromatic, and heteroaromatic) affords diorganyl-disulfides. So various aliphatic and aromatic thiols are easily converted into the corresponding disulfides upon oxidation in MeOH/MeONa with the yields ranging

from 65 to 95% (Eq. 4) [21].



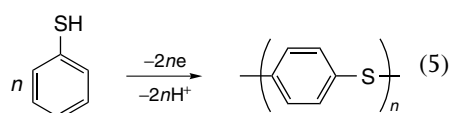
The electrooxidation of thiophenol [19], 2-mercaptobenzothiazole [22], 6- and 2-thiopyridine [23], 2-thiopyridine [24] results in their disulfide derivatives in good yields. Bifunctional compound, 2,6-purinedithiol [23] can form first a 6,6'-disulfide (4), and then, by subsequent oxidation of the latter, give a cyclic product with two S-S bridges (Scheme 5).

In the anodic process of another bifunctional thiol, 1,3-propanedithiol, all three forms – a neutral molecule, its mono-, and dianion undergo oxidation. The addition of  $\text{HO}^-$  ions to the solution or a cathodic preelectrolysis (due to the reduction of protons), shift the equilibrium toward

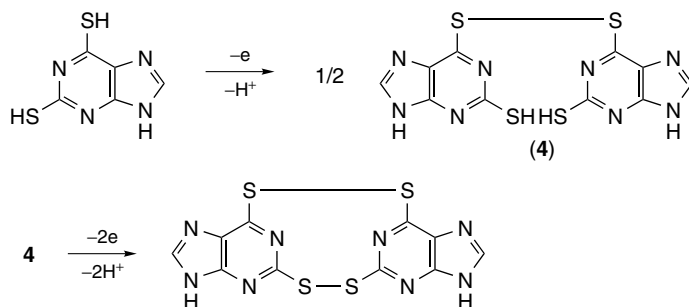
the deprotonated form [25]. The overall process can be depicted by the following Scheme 6.

The system lipoic-dihydrolipoic acid behaves in a similar way.

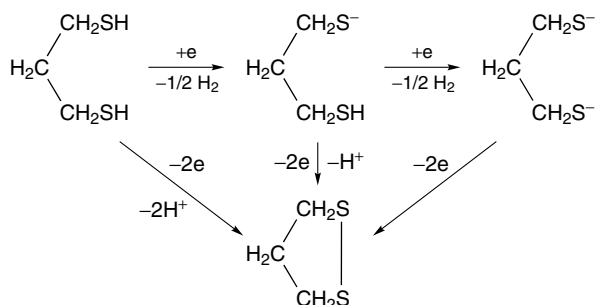
Although thiophenol, like other thiols, normally forms diphenyldisulfide upon oxidation [19], in the presence of a strong proton-donor ( $\text{CH}_3\text{NO}_2/\text{CF}_3\text{COOH}$ ) it can undergo anodic polymerization to give poly-*p*-phenylene sulfide (Eq. 5) [26].



Another example of a polymer formation is the oxidation of 1,3,4-thiadiazole-2,5-dithiol [27] including the formation of an intermediate disulfide (5). As the latter is



**Scheme 5** Anodic cyclodimerization of 2,6-purinedithiol.



**Scheme 6** Anodic cyclization of 1,3-propanedithiol.

easier to oxidize than the starting thiol, it forms a polymer in the presence of 2-chloro-pyridine or lutidine (Scheme 7).

Anodic fluorination of thiols was reported [28] providing a route to perfluoroalkyl derivatives of sulfur hexafluoride though the yields of products are not high. The process, achieved in a system of HF/NaF at a Ni anode with helium bubbling through the solution, leads to different perfluorinated products (Scheme 8).

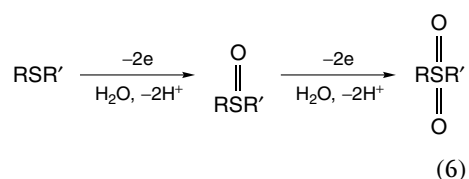
The high tendency of thiols to form sulfur-gold bonds upon oxidation on a gold electrode was used in numerous investigations to modify gold electrodes for different analytical and synthetic purposes. Nonanethiol [29], butanethiol and octanethiol [30], hexadecanethiols [31], octadecanethiol [32], ferrocene-terminated alkanethiol ( $\text{FcCO}_2\text{C}_{11}\text{H}_{22}\text{SH}$ ) [33], 2-mercaptobenzothiazole and 2-mercaptobenzimidazole [34], 3-mercaptopropionic acid or bis(4-pyridyl) disulfide and *n*-alkanethiols having various chain lengths [35], 4-aminothiophenol [36], 1-undecanethiol and 3-mercaptopropionic acid (the latter can be selectively removed by controlling the electrode potential, and replaced with 1-hexadecanethiol

or 11-mercaptoundecanoic acid) [37], a viologen derivative of *N*-(*n*-octyl)-*N'*-(10-mercaptodecyl)-4,4'-bipyridinium dibromide [38], and 3,3'-thiodipropionic acid [39] form monolayers on the gold electrodes by self-assembly. Polybithiophene films were electrochemically grafted onto titanium electrodes as well [40].

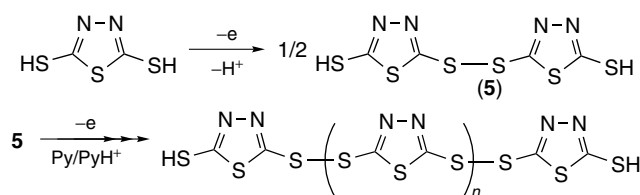
### 9.2.3

#### Sulfides

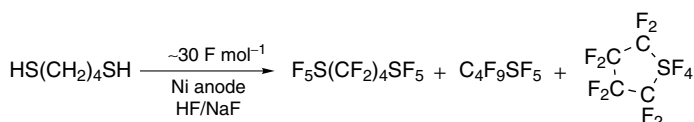
First reported by Fichter in the year 1910 [41–52], and improved later on as described in many papers and patents, the oxidation of diorganysulfides in aqueous and organo-aqueous media occurs in two steps, providing first sulfoxides and then sulfones in yields close to quantitative (Eq. 6).



Diverse products were obtained when performing this process under water-free conditions. The fact that the removal



**Scheme 7** Anodic polymerization of 1,3,4-thiadiazole-2,5-dithiol.

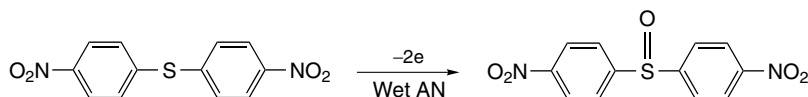


**Scheme 8** Anodic perfluorination of 1,4-butane-dithiol.

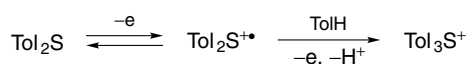
of an electron from organic sulfides normally provides intermediate sulfur cation radicals helps to better understand the nature of the transformations leading to these products.

The reactions of electrogenerated cation radicals of diarylsulfides are mainly orbital-controlled and at this level the electronic structure of their frontier orbitals (HOMO–SOMO) has very interesting synthetic consequences. The 3p orbitals of sulfur are conjugated with only one aromatic ring even if there are two aryls bound to sulfur. Therefore, only one ring can be activated electrochemically. The degree of the charge delocalization in the ArS moiety of a cation radical on the one hand, and the availability of *p*- and *o*-positions for the substitution on the other, determine quite different reactivity of such species.

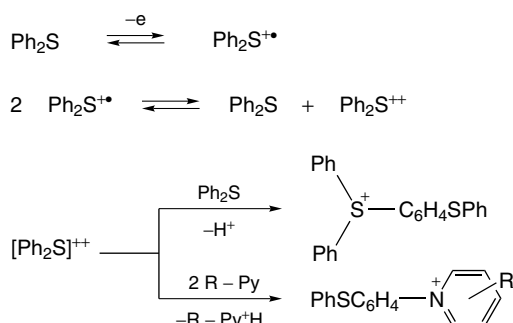
The cation radicals of the compounds with electron-withdrawing substituents undergo first-order sulfur-centered reactions (Scheme 9) [48–50], those with neutral or weak donor substituents (Scheme 10) react with  $\pi$ -nucleophiles such as styrene, anisole [51, 52] to give trisarylsulfonium salts (if the *p*-position is substituted [52]) or  $\text{Ph}_2\text{S}^{+\bullet}$  can disproportionate (Scheme 11). The cation radicals of arylsulfides bearing electron-donating substituents can form more reactive dications by disproportionation, which, in turn, can react with nucleophiles [52, 53]. In the absence of an external nucleophile, the sulfides produce sulfonium products by self-coupling (Scheme 11) [48, 52–56]. When the *para*-position of an aromatic ring is substituted, *ortho*-products can be obtained, the regioselectivity of their



**Scheme 9** Oxidation of diorganylsulfides in organo-aqueous media.



**Scheme 10** Generation of sulfonium salts from thioethers.



**Scheme 11** Formation of sulfonium and pyridinium products by anodic oxidation of  $\text{Ph}_2\text{S}$ .

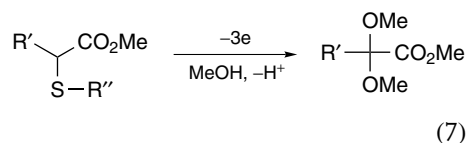
formation is controlled by the combined electron-donating effects of the *para*-substituents [57].

The sulfonium dimer can in turn be oxidized at a higher potential, which is the diffusion-limited oxidation current of Ph<sub>2</sub>S. For this reason, the concentration of the latter in the reaction layer closer to the electrode is practically zero, so a dimeric dication radical formed from [(Ph)<sub>2</sub>S-C<sub>6</sub>H<sub>4</sub>SPh] can only react with this cation. Thus, no trimers but only tetramers are obtained under such conditions (Scheme 12) [52, 54, 55].

Alkyl aryl sulfides [48, 56–59] follow the same scheme of oxidation, that is, sulfonium dimers are the main products unless the alkyl group is a stable-leaving group (*i*-Pr, CH<sub>2</sub>Ph, CPh<sub>3</sub>), in the last case, an S–C(sp<sup>3</sup>) bond cleavage occurs (Scheme 13).

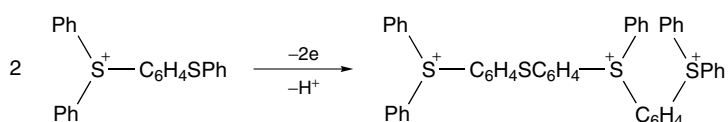
Oxidative S–C bond cleavage, followed by the attack of a nucleophile on the carbocation formed, is a classical anodic substitution reaction. In this way, OH [60], AcNH [61], AcCH<sub>2</sub> [62], and CH<sub>2</sub>=CHCH<sub>2</sub> [63] groups were introduced to replace the RS fragment.

Different nucleophiles such as methanol, allylsilanes, silyl enol ethers, trimethylsilylcyanide, and arenes can be used in this process [62]. When the sulfide itself contains an unsaturated or aromatic fragment and the process is carried out in the absence of a nucleophile, an intramolecular anodic substitution/cyclization might occur [61–63]. Methyl esters of 2-benzothiazolyl-2-alkyl or aryl-acetic acid, oxidized in MeOH/Et<sub>4</sub>NClO<sub>4</sub> or H<sub>2</sub>SO<sub>4</sub> in the presence of CuCl<sub>2</sub>, form 2,2-dimethoxy products (Eq. 7) [64].

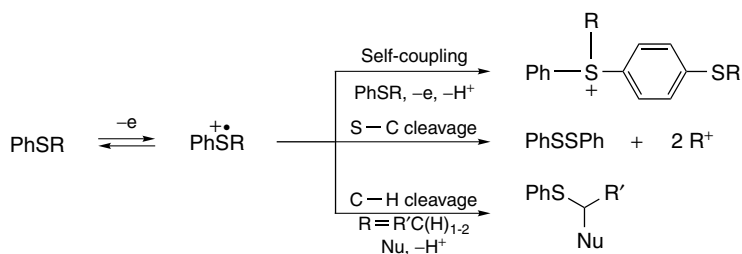


Oxidation of  $\alpha$ -organythiocarbamates in a MeOH/Et<sub>4</sub>NOTs system smoothly affords the substitution of the ArS-group with MeO; the yields of such a process are close to quantitative [62]. The eliminating ArS<sup>•</sup> fragment dimerizes to end up as a corresponding disulfide (Scheme 14).

Anodic elimination (oxidative desulfanylation–deprotonation) occurs when a carbonyl or CN group (X) is attached

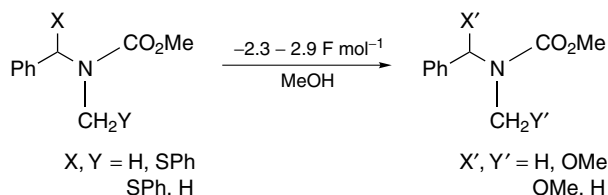


**Scheme 12** Anodic coupling of a sulfonium dimer.

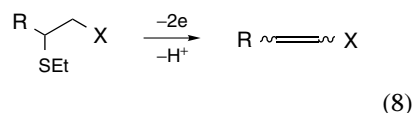


**Scheme 13** Different pathways of oxidation of alkyl aryl sulfides.



**Scheme 14** Anodic oxidation of thiocarbamate.

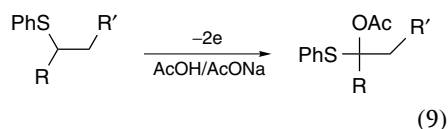
to the  $\beta$ -carbon rendering its proton(s) more acidic.  $\alpha,\beta$ -Unsaturated carbonyl or cyano derivatives can thus be obtained (Eq. 8) [65].



A simultaneous cleavage of both C–S and C–C bonds was observed during the oxidation of  $\beta$ -hydroxysulfides [66] resulting in two different ketones (Scheme 15).

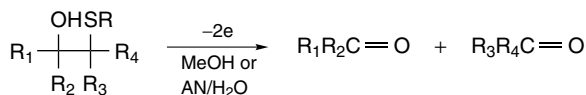
The last reaction in Scheme 13 becomes possible when the sulfide has a  $\text{CH}_2$  or  $\text{CH}$  fragment, adjacent to the sulfur atom whose protons are getting more acid when the molecule is oxidized. Electron-withdrawing groups (EWGs) increase the ease of deprotonation of this site even more. Thus,  $\alpha$ -MeO-,  $\alpha$ -AcO-, and  $\alpha$ -F-sulfides were prepared (Eq. 9) [67–70]. When the nucleophilic attack is sterically hindered or  $\alpha$ -protons are absent, products acetoxyated in the phenyl ring are

observed [67].



When there is an  $\text{Me}_3\text{Si}$  group at the  $\alpha$ -position of an alkyl aryl sulfide, which is known to leave more easily than a proton, the cleavage of the  $\text{C}_{\text{sp}^3}$ –Si bond gives access to different  $\alpha$ -functionalized products ( $\text{R}=\text{RCO}$ , or,  $\text{RR}^1\text{C}=\text{CHCHR}^2$ ) (Scheme 16) [71–73]. However, in a low-nucleophilic media, it is the rupture of the S–C( $\text{sp}^3$ ) bond that takes place leading to corresponding disulfides in an  $\text{EC}_2\text{C}_1$  process [73].

Both the second and third processes in Scheme 13 can also be used for the functionalization of  $\alpha$ -silylated alkyl phenyl sulfides [74] when oxidizing the latter in the presence of primary alcohols. First, the cleavage of the C–Si bond (equivalent to deprotonation) and then that of the S–C bond occurs to give

**Scheme 15** Anodic oxidation of  $\beta$ -hydroxysulfide.**Scheme 16** Anodic oxidation of  $\alpha$ -trimethylsilylmethylene aryl sulfide.

either 1-methoxy-1-phenylthioacetone or its acetal (Scheme 17).

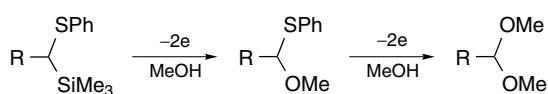
Anodic nucleophilic functionalization of an  $\alpha$ -carbon turned out to be particularly efficient for the fluorination of organic sulfides. The introduction of one or two fluorine atoms at the  $\alpha$ -carbon was reported in several papers for sulfides bearing EWGs = CN, COMe, CPh, CF<sub>3</sub>, CO<sub>2</sub>Et, CONEt<sub>2</sub>, PO(OEt)<sub>2</sub> (Scheme 18) [75–78]. Two systems are mainly used as the supporting electrolyte and fluorine source at a time namely, Et<sub>3</sub>N·3HF and Et<sub>4</sub>NF.

Both mono- and difluorination of aromatic thioethers can be achieved for compounds bearing an electron acceptor group, not only at the  $\alpha$ -methylene carbon but also in the aromatic ring (EWG = CN, NO<sub>2</sub>, RSO<sub>2</sub>) (Scheme 19) [79].

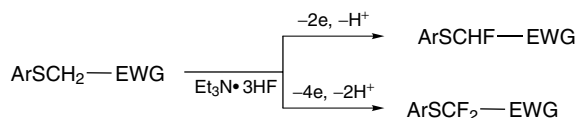
Anodic regioselective fluorination of  $\alpha$ -phenylsulphenylated ethyl acetates, 1-naphthalene and 2-pyridine derivatives [80], 1-aryl-3-(phenylthio)oxindoles and 2-substituted-3-oxo-4-(phenylthio)-1,2,3,4-tetrahydroisoquinolines [81], 2-benzothiazolyl and 5-chloro-2-benzothiazolyl sulfides [82],  $\alpha$ -(phenylsulfonyl)lactams [83], as well as various heterocycles such as thiolanones, oxathiolanones, dithiolanones, 3H-1,4-benzoxathian-2-ones [84] in Et<sub>3</sub>N·3HF or Et<sub>4</sub>NF·*n*HF (*n* = 3,4), has been reported.

The anodic fluorination of 2-phenylthiochromen-4-one under similar conditions provides 3-monofluoro- and 2,3,3-trifluoro-products (Scheme 20) [85].

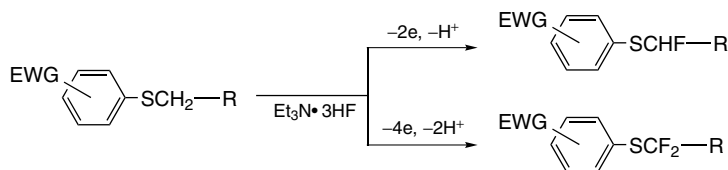
Recent developments in anodic fluorination were reviewed in Ref. [86].



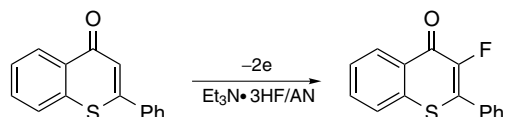
**Scheme 17** Anodic substitution of  $\alpha$ -silylated alkyl phenyl sulfides.



**Scheme 18** Anodic fluorination of sulfides.



**Scheme 19** Anodic fluorination of sulfides.



**Scheme 20** Anodic fluorination of thiochromen-4-one.

The preparative oxidation of vinyl sulfides is thought to proceed via an intermediate bridged sulfonium cation that can be attacked by an external nucleophile from the less encumbered side to give two isomers (Scheme 21) [87].

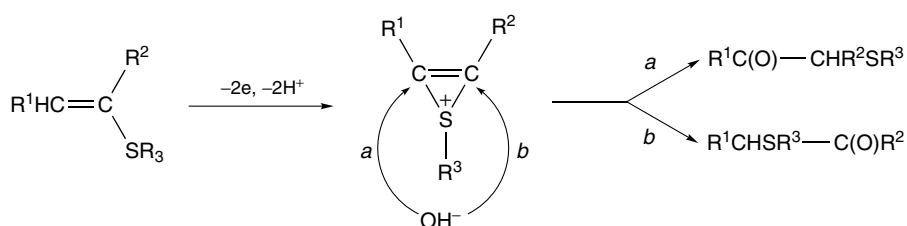
As performed in AN, with either H<sub>2</sub>O or MeOH added [87, 88], this process can afford different products, for example  $\alpha$ -thioaryl aldehydes or their dimethyl acetals. Similar products were shown to form in systems AN/Et<sub>3</sub>N·3HF, MeOH/Et<sub>3</sub>N·3HF, and AcOH/AcOK, the nucleophiles being F, MeO, and AcO, respectively. In the last two cases both vicinal and geminal adducts were obtained (Scheme 22).

In order to rationalize the product distribution, a mechanism analogous to

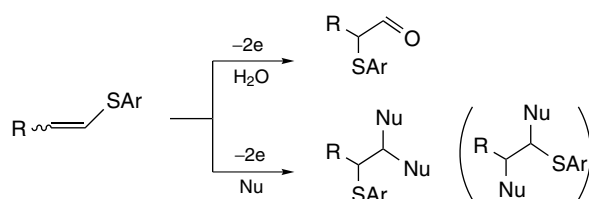
that described in Ref. [87] was proposed involving a thiiran intermediate, formed upon addition of a first Nu to the vinylic cation radical, which can then be attacked by a second Nu from either side to give either gem- or vic-adducts.

Oxidative electrophilic activation of  $\alpha,\beta$ -unsaturated phenylsulfides, carried out in an AcOH/AcONa solution results in products of the addition of a nucleophile to the multiple bonds,  $\alpha,\beta$ -diacetoxysulfides or, as a result of a further oxidation, that eliminates the PhS group, in  $\alpha$ -acetoxo ketones (Scheme 23) [89].

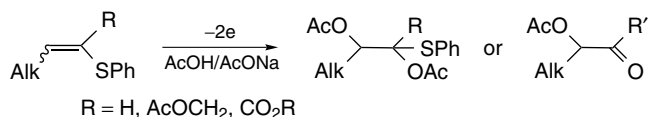
Although the oxidation of arylsulfides, as determined by their HOMO's structure, is expected to involve cation radical species, these latter reactions are not always detectable by voltammetry at reasonable



**Scheme 21** Anodic oxidation of vinyl sulfides.



**Scheme 22** Anodic oxidation of vinyl sulfides.



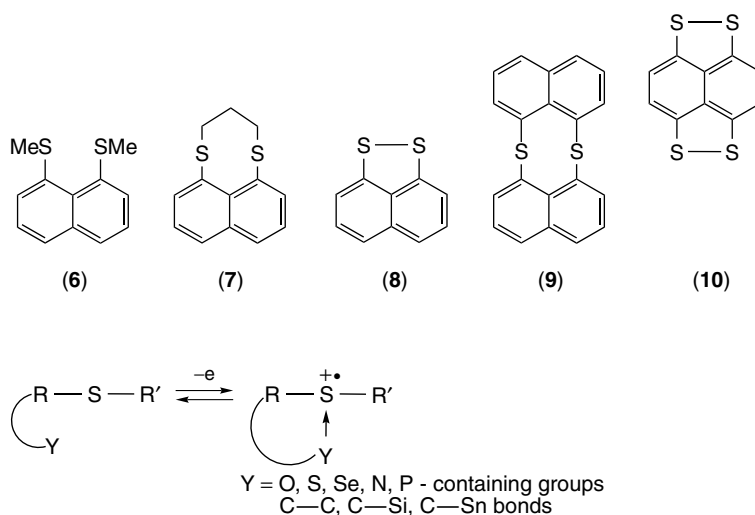
**Scheme 23** Anodic oxidation of vinyl sulfides.

sweep rates. The presence of an extended conjugated system is crucial for the stability and hence the observation of such cation radicals: for example, the reversibility was not seen for the oxidation of the first two naphthalene derivatives (6) and (7) depicted below [90], whereas it was observed for derivatives (8) to (10) [91, 92]. In some cases, even if at moderate scan rates the reduction signals of cation radicals or dications from PhSR (R = Me, Et, *i*-Pr, *t*-Bu, Ph) are not seen; these species, however, were successfully used to mediate the oxidation of secondary alcohols to ketones [93].

The assistance of some electron-rich groups [94–96], heteroatoms [90, 97, 98] or filled  $\sigma$ -orbitals [99, 100] in the oxidation of organic sulfides was studied in a series of papers (Scheme 24). Since the 3p orbitals of sulfur are quite compact compared to those of Se, the mentioned electronic and stereoelectronic effects are rather remarkable. These interactions (discussed in terms of a trans-annular

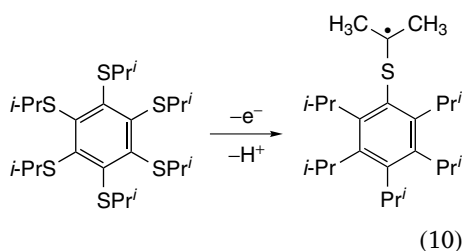
effect, anchimeric assistance or interaction through space) are repulsive and destabilizing for the starting molecule so they lower its oxidation potential by splitting the levels of the occupied frontier orbitals. On the other hand, they strongly stabilize the corresponding cation radicals due to the interaction that can vary from almost purely electrostatic to two center, three electron [2c3e]- or 2e-bonds. The formation of stable dithiadication of 1,5-dithiacyclooctanes is, probably, the best illustration of this [90, 101, 102].

Anodic oxidations of hexathioalkyl benzene asterisk compounds were achieved at a Pt anode in AN. In particular, hexa-*iso*-propylthio-benzene afforded both the primary cation radical and the free radical obtained from the deprotonation (Eq. 10). The radical was found to exist in two forms (one progressively transformed into another as evidenced by ESR spectroscopy). The observation of both forms was possible because of a sterically caused hindered rotation. The produced free radical has



**Scheme 24** Neighbouring group assistance of sulfide oxidation.

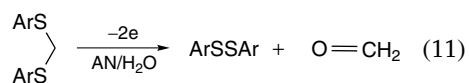
quite a long half-time life ( $\tau_{1/2} > 200$  s) at room temperature [103].



#### 9.2.4

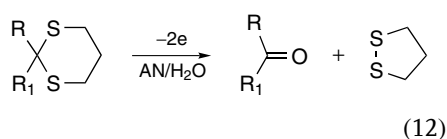
##### Thioketals and Thioacetals

The oxidation of geminal dithioethers usually results in the removal of both organylthio groups affording a disulfide and regenerating a ketone or an aldehyde. Since the thioprotection of carbonyl groups is a common tool in organic synthesis, this process received special attention as a general and selective way of deprotection of various carbonyl compounds. Open-chain bis(diorganylthio)methanes, substituted 1,3-dithianes, and related compounds [104–109] can be converted into corresponding carbonyl compounds (Eq. 11); it is also possible to deprotect a ketone thioacetal in preference to an aldehyde thioacetal [108].



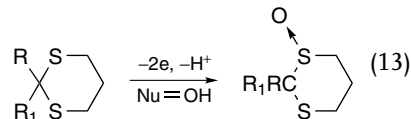
In dry AN, the oxidation was shown to follow an EEC scheme (electrochemical, electrochemical, chemical reaction) and is thought to involve an intermediate

dimeric dication. In the presence of water, an ECE process takes place involving the cleavage of two S–C bonds and leading to a disulfide and a carbonyl compound (Eq. 12) [107].



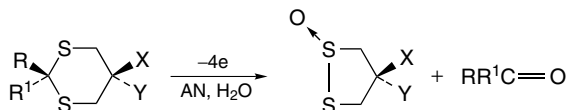
This process is more efficient when being redox-catalyzed [110, 111]. Thus the use of electrogenerated cation radicals of some triarylaminines (Ar = Tol, *p*-Br-C<sub>6</sub>H<sub>4</sub> [112]) as mediators provides even higher yields of the corresponding carbonyl compounds.

In wet acetonitrile, 1,3-dithiane-1-oxides can be formed from 1,3-dithianes (Eq. 13) [105, 107].

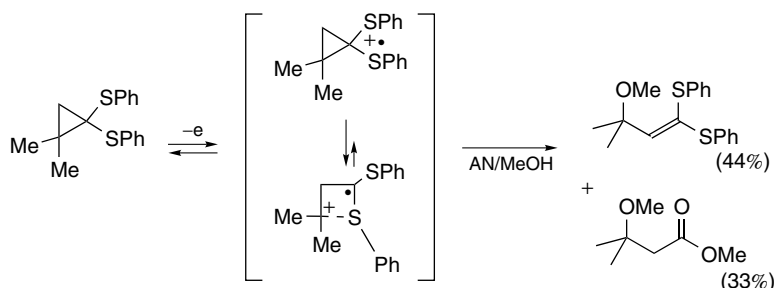


The formation of S-oxides has also been observed when oxidizing a variety of 5-substituted 2-tert-butyl-1,3-dithianes in wet acetonitrile. In an undivided cell, 4-substituted 1,2-dithiolane-1-oxides were obtained (Scheme 25) [113]. A coupled cathodic process, in this case, was the reduction of protons formed in the anodic reaction.

Under the conditions of electrochemical carbonyl deprotection, some strained cyclic systems like 2-, 2,2-, and



**Scheme 25** Conversion of 1,3-dithianes into 1,2-dithiolane-1-oxides.



**Scheme 26** Anodic ring opening of 1,1-bis(phenylthio)-cyclopropanes.

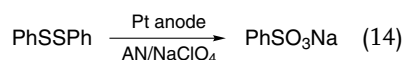
2,3-methylsubstituted 1,1-bis(phenylthio)-cyclopropanes undergo ring opening to give methanol-addition products (Scheme 26) [114]. The process is thought to include an intermediate equilibrium of two distinct cation radicals, so the presence of donor methyl groups at the C(2) atom, stabilizing the cation radical, is critical for the ring opening.

### 9.2.5

#### Disulfides

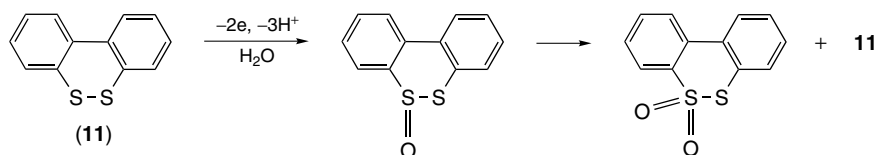
Being oxidized in the presence of oxygen donors such as  $\text{ClO}_4^-$  or in aqueous solutions, diorganyldisulfides often cleave the S–S bond to form corresponding sulfonic acids. In wet acetonitrile (AN), other oxygen containing products, for example, sulfones, were obtained as well. However, under dry aprotic and low-nucleophilic conditions, the rupture of the S–S bridge occurs to produce  $\text{RS}^+$  species that can react with a variety of C-nucleophiles providing a convenient route to different organo-sulfur derivatives.

The oxidation of diphenyldisulfide in  $\text{AcOH/HCl}$  or  $\text{AN/NaClO}_4$  [115] solution gives benzenesulfonic acid or its sodium salt (Eq. 14) [116, 117].



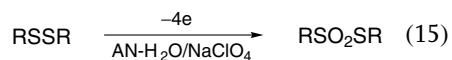
Using this reaction, 1-cystine was converted to 1-cysteic acid; the process gives better yields when mediated by bromide ion oxidation [118].

In wet acetonitrile, the oxidation of diaryldisulfides [119] and dialkyldisulfides ( $\text{Alk} \neq t\text{-Bu}$ ) [120] affords the corresponding aryl and alkylthiosulfonates in good synthetic yields (Eq. 15). Thus, the oxidation of a cyclic disulfide, dibenzo(*c,e*)-1,2-dithiin (1,1) does not affect the S–S bond and results in a corresponding thiosulfonate, dibenzo(*c,e*)-1,2-dithiin-1,1-dioxide (Scheme 27) [121]. Such oxidized products can form in wet acetonitrile as well as in a dry solvent, but in the latter case this is probably a result of disproportionation of the primarily



**Scheme 27** Oxidation of disulfide to diaryl thiosulfonate.

formed sulfoxide.



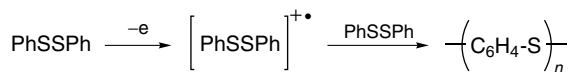
When neither solvent nor supporting salt can provide oxygen (e.g. in a system  $\text{CH}_2\text{Cl}_2/\text{Bu}_4\text{NBF}_4$ ) and a strong proton donor is present in the solution, the oxidation of diphenylsulfide yields oligo(*p*-phenylene)sulfides (Scheme 28) [122].

In an aprotic solution, the mechanism of oxidation of diaryl disulfides was shown to be more complex than a direct cleavage of the S–S linkage [116, 117, 123]. The occurrence of two consecutive reactions being of second kinetic order if potential-determined and of first order if current-determined, was established for the two-electron transfer steps. Dimerization of the cation radicals occurs on the  $\text{ArS}$  fragment, whose contribution to the HOMO is more important, and produces an intermediate disulfonium dication. The subsequent cleavage of the latter results in two  $\text{ArS}^+$  cations and a molecule of a disulfide (the same as a starting disulfide in the case of symmetrical compounds). This mechanism,  $\text{EC}_2\text{C}_1\text{E}$  ( $\text{E}$  = electrochemical,  $\text{C}$  = Chemical), has

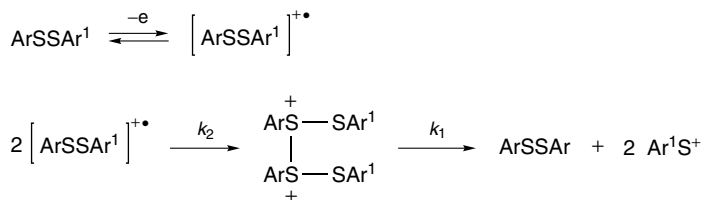
been illustrated by the oxidation of unsymmetrical dichalcogenides (both due to the different substitution at the aromatic rings or to the different nature of heteroatoms forming the dielement bridge). It was shown that unsymmetrical diaryl disulfides, like 4-bromo-4'-nitrodiphenyldisulfide, or a heterodielement compound like phenylselenenylthiobenzene,  $\text{PhSSePh}$ , undergo symmetrization to give a mixture of two symmetrical diaryl disulfides, 4,4'-dibromo and 4,4'-dinitrodiphenyldisulfide (in a total yield 80%) or, respectively, diphenylsulfide and diselenide (Scheme 29) [116, 117].

Owing to a very dissymmetric  $\pi$ -charges distribution on the S–S bridge in aryl methyl disulfides, 4- $\text{RC}_6\text{H}_4\text{SSMe}$ , the cation radicals of these compounds behave like those of alkyl aryl selenides, undergoing a potential-determined cleavage of the S–S bond or a deprotonation of the methyl group [124, 125].

Electrogenerated organysulfenium cations  $\text{RS}^+$ , being strong electrophiles, provide interesting synthetic opportunities for the sulfur functionalization of organic compounds. First reported by Bewick [126] for  $\text{Me}_2\text{S}_2$ , the oxidation of diorganyldisulfides in an appropriate aprotic solvent (AN,



**Scheme 28** Anodic oligomerization of diphenyldisulfides.



**Scheme 29** Anodic symmetrization of unsymmetrical dichalcogenides.

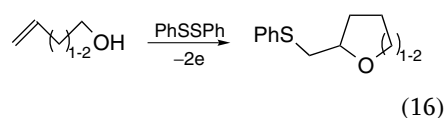
$\text{CH}_2\text{Cl}_2$ , sulfolane, THF) in the presence of alkenes, whose oxidation potential is lower than that of the disulfide, results in the addition of the MeS group on the double bond. Since then, the anodic sulfenylation of multiple bonds received many synthetic applications.

High selectivity of the addition and the formation of trans-products (with an external nucleophile added to the vicinal position to RS group) suggest that the process occurs via an intermediate episulfonium complex or an ylide (Scheme 30).

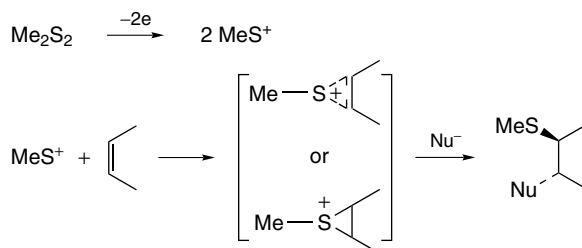
The nucleophilic properties of the media are crucial for the nature of the methylthio products formed. With pyridine, a product of vicinal methylthiation-pyridination was obtained. In pure acetonitrile the solvent itself plays the role of a nucleophile [127], whereas in a low-nucleophilic liquid  $\text{SO}_2$  a product of

1,2-dimethylthiation was obtained in a quantitative yield (Scheme 31) [128].

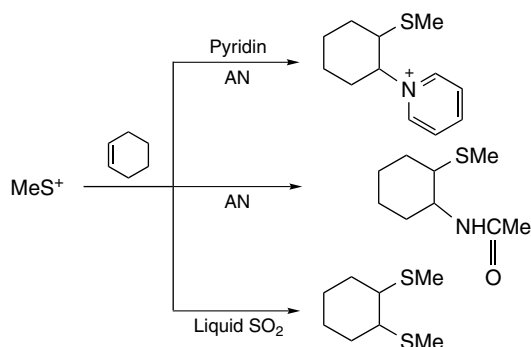
Terminal alkenes, containing  $\omega$ -OH or  $\omega$ -COOH functionalities, may undergo cyclization [129] with different orientation of the intramolecular attack of the nucleophilic end of the molecule on the intermediate episulfonium ion (Eq. 16).



Usually, 5- and 6-membered Markovnikov-type products are formed; in other cases the process results in various open-chain products. The formation of an anti-Markovnikov adduct from 2-cyclohex-1-enyl-ethanol was explained by the cyclization of an episulfonium intermediate



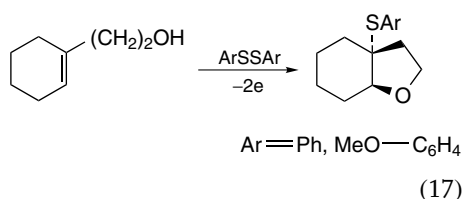
**Scheme 30** Sulfenylation of double bonds.



**Scheme 31** Addition of the methylthiogroup and nucleophiles to alkenes.

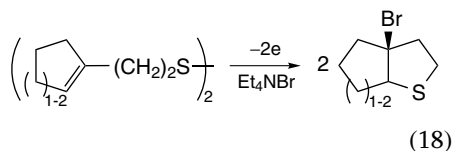


into a spiro compound with a 4-membered O-containing ring, which then rearranges to the more stable 5-membered product (Eq. 17) [129].



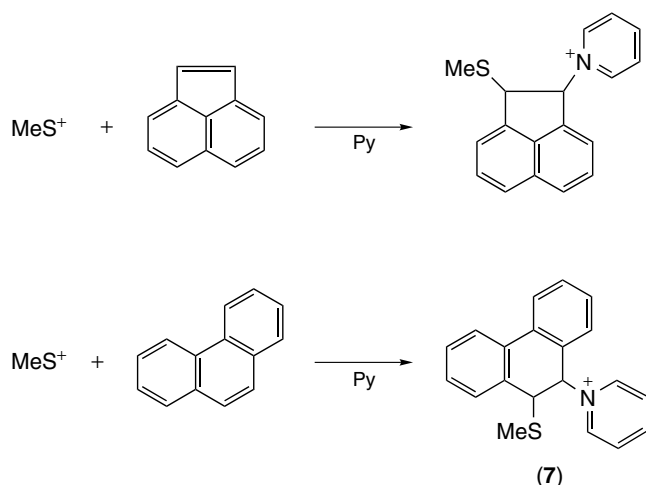
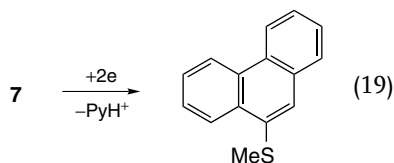
The process was shown to be more efficient when performed in the presence of some bromide salts whose oxidation allows lowering of the working potential and favors the S–S bond scission. Bromide mediated oxidation of bis(2-cyclopent-1-enylethane) and bis(2-cyclohex-1-enylethane)disulfide in AN/ $\text{Et}_4\text{NClO}_4$ / $\text{Et}_4\text{NBr}$  [130] undergoes the S–S bond cleavage followed by an intramolecular attack of the sulfenium cation on the double bond to give [3.3.0] and [4.4.0] bicyclic products. The anion  $\text{Br}^-$  also serves in the process as an

external nucleophile (Eq. 18).

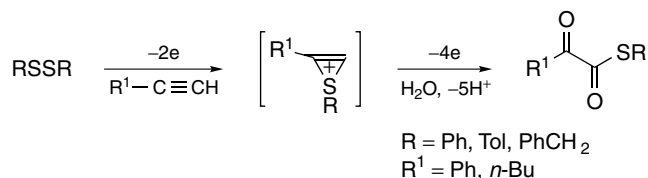


The oxidation of  $\text{Me}_2\text{S}_2$  in the presence of aromatics with an increased electron density at several carbons, such as acenaphthylene or phenanthrene, and pyridine leads to similar products of vicinal functionalization (Scheme 32) [128].

The feasibility of a one-pot consecutive removal of the pyridinium moiety by reducing the products electrochemically in the same cell has been shown, thus providing a convenient synthetic route to 1-methylthio-acenaphthylene and 9-methylthio-phenanthrene (Eq. 19) [128].



**Scheme 32** Addition of the methylthiogroup and nucleophiles to aromatic compounds.

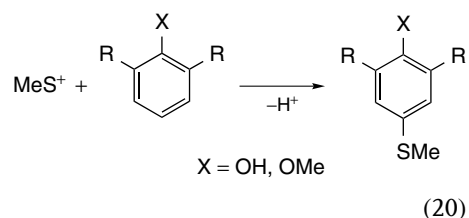


**Scheme 33**  $\alpha$ -Oxothioesters by addition of electrogenerated  $\text{RS}^+$  electrophiles to alkynes.

$\text{RS}^+$  electrophiles that are electrogenerated in a  $\text{CH}_2\text{Cl}_2/\text{Bu}_4\text{NClO}_4$  solution readily attack even less reactive triple bonds of terminal alkynes [123] and result, after further oxidation and hydrolysis, in  $\alpha$ -oxothioesters (Scheme 33). Under acidic conditions, it is possible to direct the reaction to the formation of an oligomer, cyclohexa-1,4-phenylene sulfide, or a conductive poly(*p*-phenylene)sulfide [131, 132].

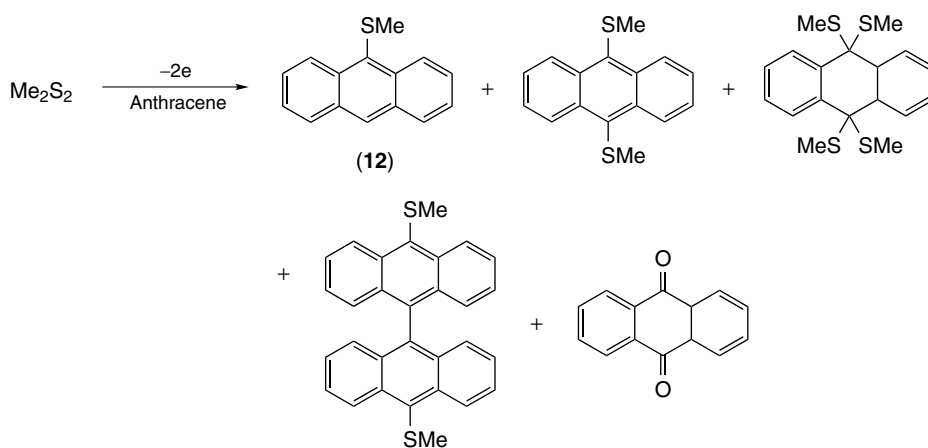
For electrogenerated sulfenium cations, not only the addition to multiple carbon-carbon bonds was shown but also examples of electrophilic aromatic substitution. Carried out in a low-nucleophilic media ( $\text{CH}_2\text{Cl}_2$ ), this process provides a new route to arylthio derivatives allowing methylthiation of diverse phenols and

anisoles in 26 to 77 and 11 to 35% yields, respectively (Eq. 20) [133].



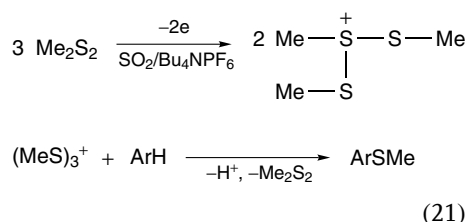
When anthracene was used as an arene under similar conditions, a mixture of methylthiated products was obtained, among them 9-methylthio-anthracene (**12**) in 74% yield, and the dimer of (**12**) (Scheme 34) [128].

To circumvent the limitation caused by the oxidation of aromatic substrates, a two-step process was designed in



**Scheme 34** Methylthiation of anthracene.

such a way that  $\text{Me}_2\text{S}_2$  is first oxidized in liquid sulfur dioxide to generate a potent methylthiating agent, supposedly  $(\text{MeS})_3^+$ , which can be isolated as a solid with an appropriate counterion or stocked in the solution for several weeks. This reagent regioselectively reacts with various strongly to weakly activated arenes to afford their methylthiation in good to excellent yields (Eq. 21) [134]. Thus, anthracene and 2,6-dimethylphenol give 9-methylthioanthracene and 6-methylthio-2,6-dimethylphenol in 78% and 97% isolated yields, respectively. Polymethylthiation was also observed and, with thiophene as a substrate, the bis-methylthiated product was formed predominantly (Scheme 35).

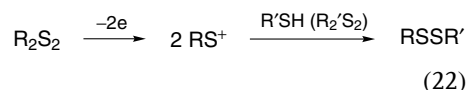


When both *para*- and *ortho*-positions of the arene are available for substitution, a mixture of *ca.* 9:1 *p*- and *o*-methylthioproducts was obtained.

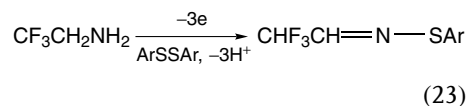
It is interesting that dialkyldisulfides ( $\text{Alk} \neq t\text{-Bu}$ ) usually cleave on the S—S bond to produce corresponding sulfenium cations, whereas di-*t*-butyldisulfide undergoes the S—C bond cleavage [135].

The resulting *t*-BuSS $\cdot$  radicals dimerize to the tetrasulfide, and *t*-Bu $^+$  carbocation can be trapped by different nitriles to afford, after workup, corresponding *N*-(*t*-Bu)amides [135]. In liquid  $\text{SO}_2$ , the products of the oxidation of *t*-Bu $_2\text{S}_2$  react with phenol yielding  $\text{S}_8$  and 4-*t*-butyl phenol almost quantitatively [136].

The molecule of a thiol or a disulfide can serve as a nucleophile for  $\text{RS}^+$  cations. Thus the reaction of sulfenium cations, electrogenerated in  $\text{CH}_2\text{Cl}_2/\text{Bu}_4\text{NClO}_4$ , with these substrates results in unsymmetrical diorganyldisulfides in 47 to 90% yields (Eq. 22) [137].



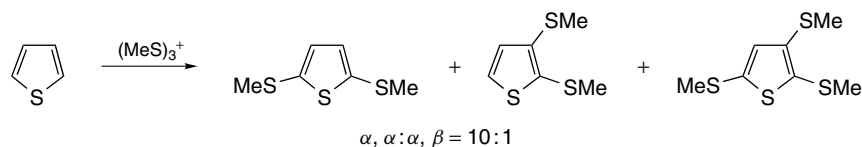
The oxidation of a mixture of aromatic disulfides,  $\text{Ph}_2\text{S}_2$  or  $\text{Tol}_2\text{S}_2$ , with 2,2,2-trifluoroethylamine affording arylsulfanylation of the amino group was reported (Eq. 23) [138].



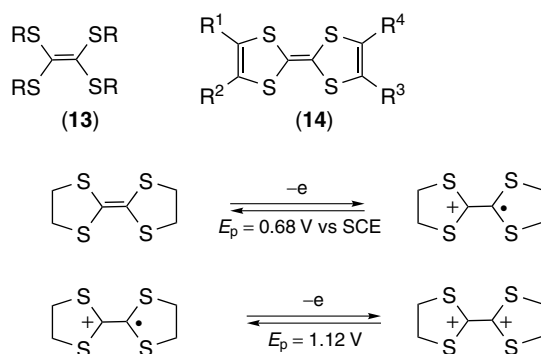
#### 9.2.6

##### Tetrathiofulvalenes

Electrooxidation of tetraorganyltioethylenes (**13**) ( $\text{R} = \text{Me}, \text{Et}, \text{Ph}$ ) [139–142] and bicyclic tetrathiofulvalenes (**14**) [143] occurs in two reversible one-electron steps (Scheme 36).



**Scheme 35** Bismethylthiation of thiophene.

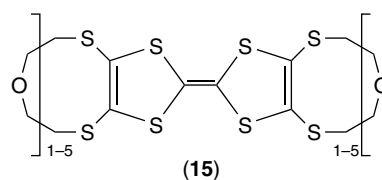


**Scheme 36** Reversible 1e-oxidations of tetrathiofulvalenes.

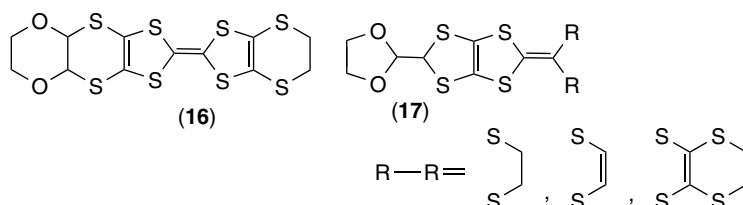
Authors [143] suppose that sulfur atoms are not affected by oxidation and only act as activating double bond substituents. However, the analysis of the electronic structure of tetrathiofulvalene shows that, resulting from the interaction of  $\pi(\text{CC})$  and  $\pi(\text{S})$  orbitals, HOMO of this molecule is an antibonding combination of  $\pi$  and  $n_\pi$  orbitals with the predominant contribution being from the latter. Indeed, the substitution of one or more S atoms with Se results in a less conjugated system and, as a consequence, in higher oxidation potentials [144].

Other conditions being equal, the first oxidation potentials of tetrathiofulvalenes are usually less positive than those of tetrathioethylenes [141–151]. The first reversible oxidation of tetrathiofulvalenes normally occurs at 0.2–0.8 V versus SCE, whereas the second occurs at 0.6–1.2 V

with a gap between the potentials of formation of a cation radical and of a dication of about 0.27–0.46 V depending on the nature of the substituents at S atoms. Similarly, crown ether derivatives of tetrathiofulvalene (15) undergo two consecutive reversible oxidations ( $E_{1/2}^1 = 0.48$  and  $E_{1/2}^2 = 0.64$  V vs SCE [152]), the potential of the first of which shifts anodically in the presence of several ions ( $\text{Li}^+$ ,  $\text{Na}^+$ ,  $\text{K}^+$ ,  $\text{Ag}^+$ ) in solution.



The redox properties of bis-fused TTF derivatives and unsymmetrical TTF derivatives (16) and (17) were reported [153, 154].



An extensive review on bis-tetrathiofulvalenes in which the TTF moieties are separated by several spacers was recently published [155].

### 9.2.7

#### Sulfur-containing Polymers

Because of a remarkable  $n$ - $\pi$  conjugation in aromatic sulfides, and hence an extended charge delocalization in their  $p$ - or  $n$ -doped forms, sulfur-containing polymers have good potentialities for use in many fields dealing with conductive polymers. Such polymers are usually obtained by anodic oxidation of corresponding monomers and oligomers under low-nucleophilic conditions [156, 157]. Because of the above-mentioned conjugation, the oxidation of the polymer is easier than that of the starting material, so the polymer formed is obtained in its doped form as exemplified below for the polythiophene formation (Scheme 37).

Thus, many polymers with different conductivity were synthesized. To cite a few, these are polythiophene [158], 3-methylthiophene [159], polymers of 3-thiophene-acetic acid and methyl 3-thiophene-acetate [160], poly(2,5-thienylenevinylene) [161], poly(benzo[*b*]thiophene) [162], poly(naphtho[2,3-*c*]thiophene) [163], poly(dithieno[3,2-*b*;2',3'-*d*]thiophene) [164], poly(3-*n*-hexylthiophene) [165], poly(2,5-di-(2-thienyl)-thiophene) [166], copolymers of thiophene and

1-methylpyrrole [167], polyethers possessing two 3-thienyl units [168], polythiophenol [26], polymers of 3-thienyltrifluoroacetamide and 3-thienylheptafluorobutyramide [169], poly(4-*R*-2,2'-bithiophenes) ( $R = \text{Oct}, \text{CH}_2\text{OH}, \text{CO}, \text{CO}_2\text{Me}$ ) [170], poly(3-butylthiophene-co-3-bromothiophene) [171], disulfide-containing polymer of 2,5-dimercapto-1,3,4-thiadiazole [27], poly(3,4,3',4'-tetraoctyl-[2,2']bithienyl) [172], polymers produced by anodic coupling of a series of dipyrrolyl-ethylenes, -thiophenes, -phenylenes, and -diethylene-thiophenes [173], poly *p*-nitrophenyl-functionalyzed thiophenes [174], poly(2,5-bis(3,4-ethylenedioxy-2-thienyl)pyridine) exhibiting multicolor electrochromism for neutral,  $p$ - and  $n$ -type doped forms [175], and many others.

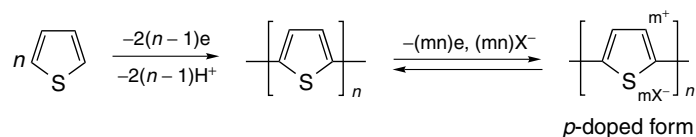
## 9.3

### Reduction

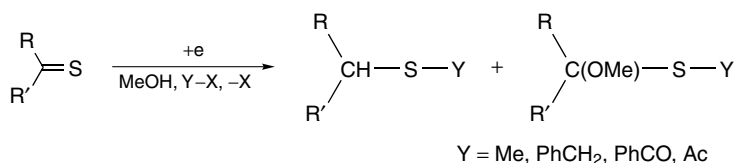
#### 9.3.1

##### Thiones

In general, it may be expected that thiocarbonyl compounds are easier to reduce cathodically than the corresponding carbonyl structures. There are a few examples dealing with the cathodic reduction of thiones. Let us quote the case of thiobenzophenone, which affords readily a rather stable radical anion at a potential that is +0.5 V more positive than that of benzophenone, when

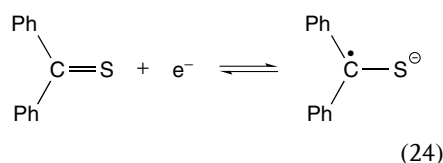


**Scheme 37** Oxidation of thiophene to  $p$ -doped polythiophene.



**Scheme 38** Cathodic alkylation of thiones.

reduced in dimethylformamide (Eq. 24).



Such anion radicals derived from thiones were shown to play the role of nucleophiles as well as that of reducing agents towards alkyl halides [176–178], tosylates [178], and acetylchloride [176]. This way, thiobenzophenone could be cathodically converted in the presence of benzyl chloride and benzoic anhydride to afford the corresponding products in good yields (Scheme 38).

Similarly, aliphatic thiones are also readily reduced at microcathodes in DMF. Thus, thiocamphor exhibits a one-electron reversible step at  $-1.88$  V versus SCE, which is about  $0.9$  V more positive than the potential of the reduction of camphor under the same experimental conditions.  $\alpha,\beta$ -unsaturated thiones such as (18) were also investigated polarographically in protic media. Similarly [179–182], reduction of  $\alpha,\beta$ -ethylenic ketones and aldehydes in acidic media yielded dimers.

Electrochemical investigations of 3-heterosubstituted 2-cyclohexene-1-thiones of the general formulae (19) are available in a recent literature [183, 184].

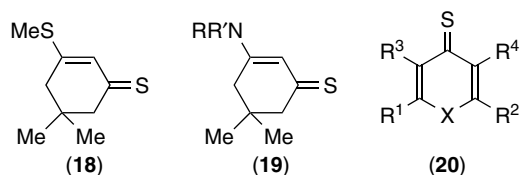
The cathodic coupling of 4H-pyran 4-thiones (20) in nonaqueous media was achieved in good or even high yields [185, 186] to afford  $\pi$ -donors like bipyranlydenes.

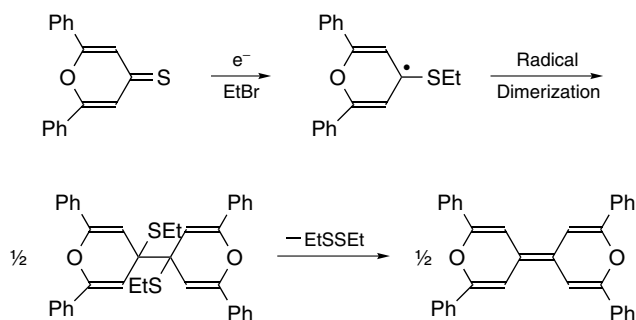
To allow anion radicals generated from structure (20) to dimerize more rapidly, this reaction was carried out in the presence of an electrophile. For example, in the presence of EtBr as electrophile, the cathodic coupling of structure (20) ( $X = \text{O}$ ,  $R^1 = R^2 = \text{Ph}$ ,  $R^3 = R^4 = \text{H}$ ) may be depicted as follows (Scheme 39).

Such a coupling reaction when achieved in electrophilic media was shown to be of a general character. Thus, thiocoumarines could be also converted into corresponding  $\pi$ -donor dimers in one step and in good yields.

The coupling of strongly activated thiones (20) ( $X = \text{S}$  and  $\text{NR}$ ), was also achieved, however, in much lower yields [187].

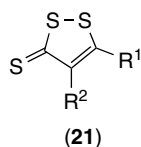
1,2-Dithioles-3-thiones (21) were – and continue to be – frequently studied





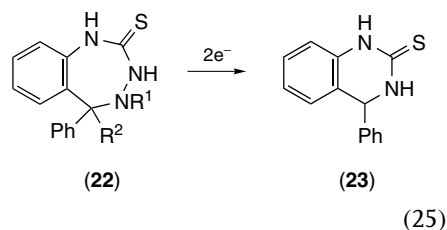
**Scheme 39** Cathodic dimerization with subsequent disulfide elimination of pyran-4-thiones.

[188–196] in electrochemistry.



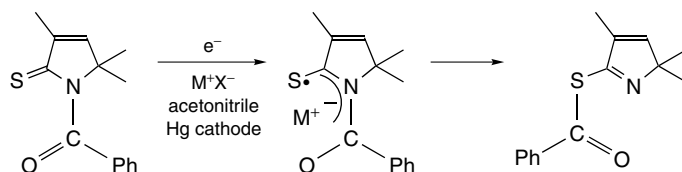
Many papers deal with both analytical determination and cathodic transformations of thiones (21). Thus, a four-electron reduction of OLTIPRAZ<sup>R</sup> [4-methyl-5-(2-pyrazinyl)-1,2-dithiole-3-thione] produces several species that could account for the schistosomicidal activity of metabolites of the starting compound. The first two-electron reduction (in aqueous media) affords the scission of the S–S linkage and the thus formed dianion can be readily [197] alkylated by common alkyl halides. Let us note that the cathodic behavior of structure (21) was shown to be strongly influenced by the nature of substituents and particularly [198] by the electron-donating ability of R<sup>1</sup>.

Thiourea and related compounds like thioamides have been studied polarographically in alcoholic buffered media. Being cathodically reduced, benzotriazepine (22) undergoes a ring contraction affording the corresponding quinazoline (23) (Eq. 25) [194, 195].



Lastly, the electrochemical reduction of 3-imidazolin-5-thiones in an AN solution showed a rather unexpected migration of the aryl group from nitrogen to sulfur [196] occurring under electron transfer, although the mechanism was not strictly proven by the authors (Scheme 40).

Thioesters and dithioesters are readily reduced at a mercury cathode. In the



**Scheme 40** Reductive 1,3-benzoyl migration.

presence of electrophiles [199–201] (e.g. primary alkyl halides, dimethylsulfate), corresponding alkylated compounds can be formed (Scheme 41).

Benzenecarbodithioesters and carbodithio-S-esters were shown to yield diphenylacetylene by the cathodic reduction in aprotic media. Thus, the formation of diphenylacetylene involves [202] two molecules of a substrate. The cathodic reactivity of thioamides involving a similar alkylation of the C=S group in the presence of primary alkyl halides was reviewed [199–201].

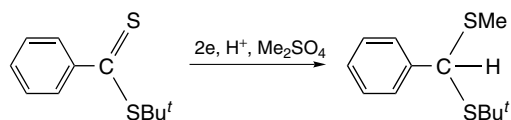
One-electron reversible reduction of triarylphosphine sulfides in DMF/Et<sub>4</sub>NI leads to an anion radical [198, 203, 204]. The second step of the reduction, occurring at slightly more negative potentials, results in different products of cleavage of P–S or P–C bonds – triphenylphosphine, benzene, and diphenylthiophosphinic acid (Scheme 42).

Tetraorganyldiphosphine sulfides, R<sub>2</sub>P(S)-PR<sub>2</sub> (R = Ph, Me) can be reduced in DMF/Et<sub>4</sub>NI at about –1.8 V versus the Hg pool [197]. The process is supposed to occur with the two-electron reductive cleavage of one of the bonds formed by sulfur. Under similar

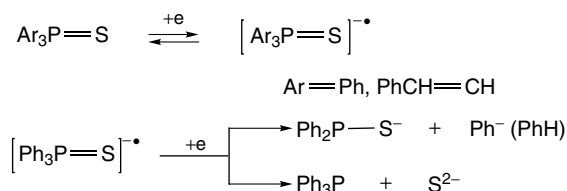
conditions, tetraorganyldiphosphine disulfides, RR'P(S)-P(S)RR' (R, R' = Ph, Bz, Me, Et, Pr, *i*-Pr, Bu), undergo the electroreduction within the interval of potentials from –1.54 to –2.48 V versus the Hg pool [197]. The process is supposed to occur with the two-electron reductive cleavage of one of the bonds formed by sulfur.

### 9.3.2 Sulfides

Dialkyl sulfides RSR' are known [205] to be electrochemically inactive in all cathode materials and solvents considered. On the contrary, arylalkylsulfides ArSR and diarylsulfides ArSAr', in general, can exhibit [206] an irreversible two-electron cathodic step at fairly negative potentials. As a matter of fact, diphenylsulfide was reported to be polarographically reduced in DMF at a potential of  $E_{1/2} = -2.549$  V versus the Ag<sup>+</sup>/Ag electrode. Phenyl methyl sulfide was found to be even more difficult to reduce under the same experimental conditions: a wave at  $E_{1/2} = -2.751$  V was observed. Such negative potentials preclude the use of hydroorganic solvents and platinum electrodes. The assumed

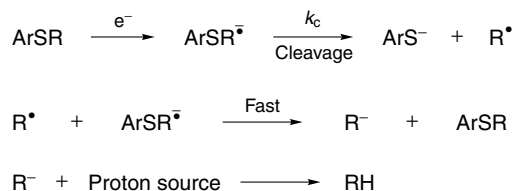


**Scheme 41** Reduction of dithioester.



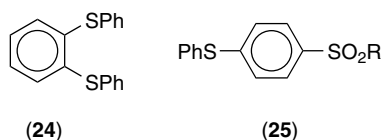
**Scheme 42** Reduction of triarylphosphine sulfides.



**Scheme 43** Reductive cleavage of arylsulfides.

mechanism would correspond to a Disproportionation scheme as shown above (Scheme 43).

To date, few quantitative studies are available on sulfides. However, the rates  $k_c$  are probably very high when weakly activated ArSR are considered.

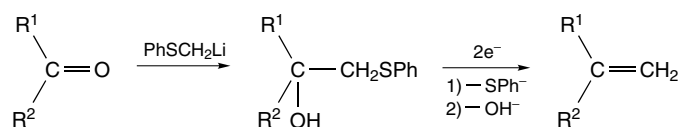
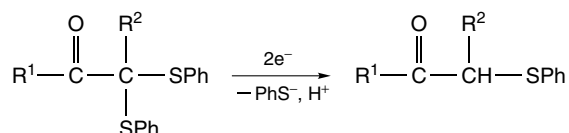


With 1,2-di(phenylthio)benzene (24), two successive two-electron steps [207] can be observed in aprotic DMF ( $E_1 = -1.82$  V and  $E_2 = -2.11$  V vs Ag/AgI 0.1 M /I<sup>-</sup> reference system). On the other hand, substitution by efficient electron-withdrawing groups might change dramatically the cathodic behavior of ArSR-type compounds. Apparently, the captodative character of substituents attached to the phenyl ring (see Structure 25) strongly

reinforced the stability of the primary anion radical while the cleavage rate ( $\text{PhS}^{\cdot-}$  was proven to be the leaving group) decreased ( $k_c \leq 1 \text{ s}^{-1}$ ). Transient arylsulfonyl  $\sigma$  radicals of structure (25) were shown to act as electrophiles [208] and therefore used as intermediates in  $\text{S}_{\text{RN}}1$  reactions when electro-inactive nucleophiles were added to the electrolysis solution.

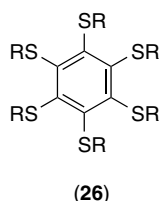
The reduction of sulfides bearing a vic-OH group involves a fast cleavage of the C–S bond accompanied by a simultaneous elimination of the hydroxyl group. This process can be efficiently used as a mild method to create double bonds, for example, from ketones [209–211]. The yields of such a process are fairly high (Scheme 44).

The reduction of  $\alpha$ -carbonyl diphenyldithioacetals [212] was reported to be self-catalyzed (with formation in the course of the cathode process of the couple

**Scheme 44** Cathodic elimination of vic-hydroxy-arylsulfides.**Scheme 45** Cathodic cleavage of a  $\alpha$ -carbonyl arylsulfide.

PhS-SPh/PhS<sup>•</sup> that acts as a redox catalyst at the potential of  $-0.63$  V vs NHE) (Scheme 45).

Hexathioalkyl-substituted benzenes are considered as new  $\pi$ -acceptors [213].



Structures such as (26) were demonstrated [103] to be fairly easily reduced at a Pt electrode. Thus, when R = Ph, an anion radical ( $E^\circ = -1.26$  V vs Ag/AgI/I<sup>−</sup> 0.1 M) of high stability is formed. However, macroelectrolyses of the compounds (26) could not be achieved at all since whatever the amount of electricity passed through the cell, the starting material was totally recovered. The compounds (26) are expected to react slowly with the tetraalkylammonium salt R<sub>4</sub>N<sup>+</sup> and the reaction would correspond to an indirect reduction of the electrolyte. Compounds (26), with R = primary alkyl groups, led – even in DMF – to strong self-inhibition explained by the adsorption of produced

phenylthiolate onto the mercury electrode. With R = *t*-Bu, the bulkiness of the thiolate forbids that and the cleavage reaction could be evidenced (by the detection of an anion radical of very short lifetime) (Scheme 46).

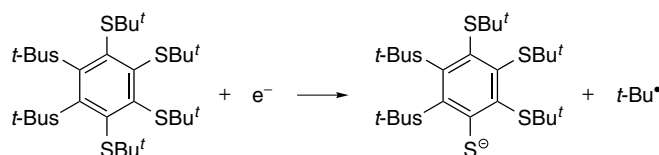
The electroreduction of benzothiophene presents an example when the saturation of a double bond can compete with the S–C bond cleavage and the chemoselectivity depends on the experimental conditions (Scheme 47) [214].

Unlike oxygen derivatives, thioesters of phosphor(III) acids (S-ethyldiphenylphosphinite, S,S-diethylphenylphosphonite and triethylthiophosphite) undergo electroreduction at DME (dropping mercury electrode) in DMF or AN [215]. An irreversible two-electron process results in the P–S bond scission.

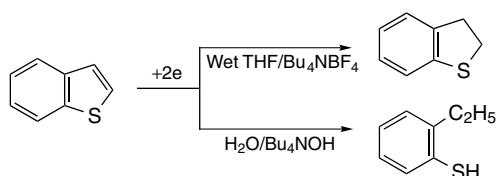
*p*-Diphenylarylsulfophosphamides exhibit facile cathodic cleavage reaction yielding, after quenching, diphenylphosphinic acid and aryl sulfide [216].

### 9.3.3 Disulfides

The reduction of disulfides is a reverse reaction of thiol oxidation and, under protic

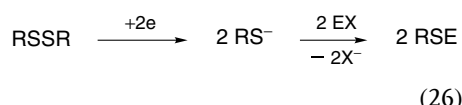


**Scheme 46** Cathodic cleavage of hexa(thio-*t*-butyl)benzene.



**Scheme 47** Two pathways for the reduction of benzothiophene.

conditions, many reactions discussed in Sect. 9.2.2 can be effected in the back direction. Since the process involves a thiolate-anions formation, it can be used for in situ generation of S-nucleophiles reacting with appropriate electrophilic partners to give alkylated or acetylated products (Eq. 26) [217].



The electroreduction of disulfides  $\text{R}_2\text{S}_2$  ( $\text{R} = \text{Ar}, \text{Alk}$ ), in the presence of carbonyl compounds and  $\text{Me}_3\text{SiCl}$ , includes the formation of intermediate thiosilanes and results in trimethylsilyl ethers of hemithioacetals of ketones and aldehydes or in full thioacetals depending on whether a two-compartment (a) or an undivided (b) cell was used (Scheme 48) [218].

The above process carried out without a carbonyl compound is probably the best means to smoothly obtain thiosilanes [219].

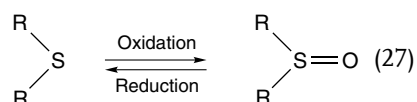
Upon activation of disulfides ( $\text{R} = \text{Bz}, \text{Pr}, t\text{-Bu}$ ) by electrogenerated anion radicals of some activated olefins [220] the formation of a saturated thioalkyl product

takes place along with the homogeneous reduction of the disulfide (Scheme 49).

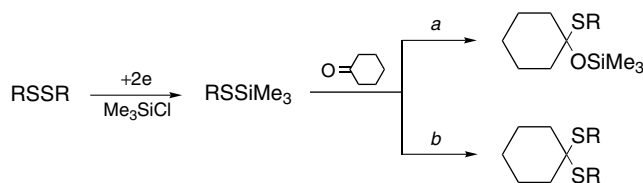
Diaryldisulfides can as well act as electrophiles toward electrogenerated nucleophiles [221].

### 9.3.4 Sulfoxides

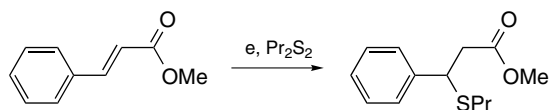
Since diorganyl sulfides and sulfoxides can be mutually interconverted electrochemically [222] (for the oxidation of sulfides to sulfoxides and further to sulfones, see Sect. 9.2.3), sulfoxides take an intermediate position between sulfides and sulfones (Eq. 27).



Chemical reduction of sulfoxides can be carried out in aprotic solvents according to several routes. It formally deals with an exchange of oxygen atoms using trivalent derivatives of phosphorus ( $\text{PI}_3, \text{PCl}_3$ ), boron ( $\text{BBr}_3$ ) as well as derivatives of silicon ( $\text{MeSiCl}_3$ ). Other methods consist in the use of reducing reagents in the



**Scheme 48** Hemithioacetals and thioacetals via reduction of disulfides in the presence of ketone.



**Scheme 49** Reductive thioalkylation of methyl cinnamate with disulfide.

presence of Lewis acids (like  $\text{NaBH}_4 + \text{TiCl}_4$ ).

Electrochemically, the reduction of activated sulfoxides (unsaturated or aromatic) in protic media exhibits a specific step leading to corresponding sulfides. However, in acidic solutions of sulfoxides a hydrogen reduction wave can be seen [223, 224] because of the reduction of their protonated form. On the contrary, in the absence of electrophiles (in aprotic DMF), the reduction of aromatic sulfoxides was reported to afford [225] a complex between the reduced form and the substrate (the process therefore would be analogous to

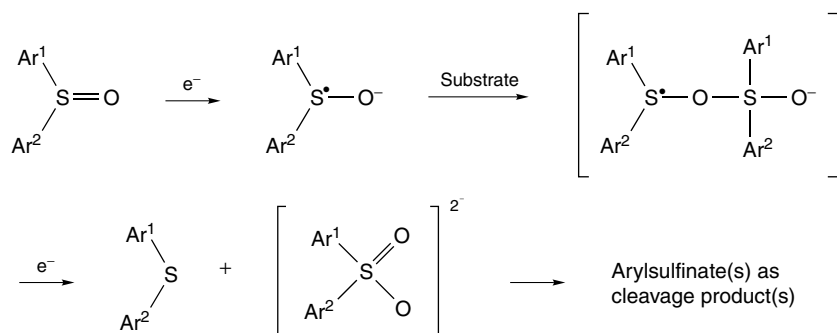
a disproportionation induced by electron transfer) (Scheme 50).

$\alpha,\beta$ -Ethylenic sulfoxides were shown to behave similarly. However, cleavage reactions (partial formation of sulfonate ion) as well as a coupling reaction (the behavior similar to that of  $\alpha,\beta$ -ethylenic ketones) could clearly be demonstrated (Scheme 51) [226].

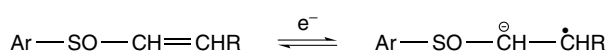
### 9.3.5

#### Sulfones

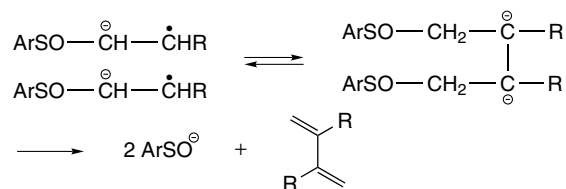
Most sulfones are known to react with chemical reagents (dissolved metals,



**Scheme 50** Disproportionation of sulfoxide by electron transfer.



High concentration (coupling)



Low concentration

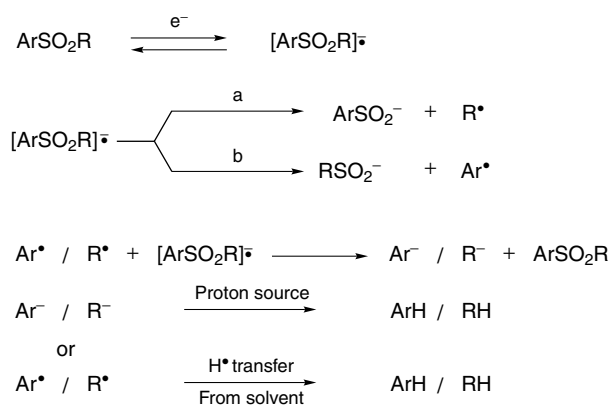


**Scheme 51** Cathodic cleavage and coupling competing in reduction of  $\alpha,\beta$ -ethylenic sulfoxides.

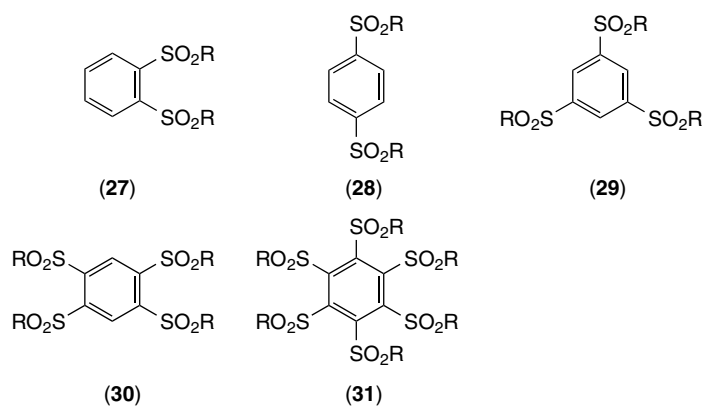
amalgams) via electron transfer. Such reactions can be successfully mimicked by using electrochemistry with cathodes (Hg, Pt, glassy carbon) whose potentials can be adjusted to fit the level of the LUMO of a considered sulfone. Generally speaking, phenyl alkyl sulfones  $\text{PhSO}_2\text{R}$  (taken as model molecules) are electroactive (with the standard potential  $E^\circ$  in the range from  $-2.2$  V to  $-2.4$  V vs SCE) while dialkyl sulfones are not sufficiently activated to exhibit *any* felt electron transfer up to  $-3.0$  V versus SCE. Since phenyl alkyl sulfones are weakly electroactive [227, 228], electrochemical steps are only visible in aprotic organic solvents. The reductive cleavage

of aromatic sulfones is depicted in the Scheme 52 below:

The above mechanism underlines the sulfone anion radical as an obligatory intermediate. The lifetime of such species depends on the nature of substituent(s) on the Ar group. Thus, with a strongly electron-withdrawing substituent in position 4 or/and 2 (like  $\text{NO}_2$  and CN groups), highly stable free radicals can be obtained [229, 230]. Note also that two cleavage routes (a) or/and (b) can be observed according to the nature of Ar and R and the position of substituents on the aromatic ring [231, 232].



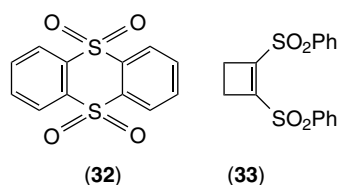
**Scheme 52** Sulfone anion radical in the reductive cleavage of arylsulfones.



Thus (29) and (30) at the level of the first one-electron transfer will lead to dimers [233] while cleavage reactions will occur only after the disproportionation or an electrolyses at the level of the second electron-transfer step [6] (producing a dianion). Bulky hexasulfones (31) with different R (Alk, Ar) undergo a conformational change through electron transfer [234]. Separate redox systems were clearly evidenced for a sterically congested structure (presumably possessing a chair form) of low  $E^\circ$  and for an unstable one (produced by electron transfer and of a short lifetime) with a much higher  $E^\circ$  since it is more conjugated. Lastly, disulfones (27) and (28) appear to be cleaved. Both undergo an *ipso* substitution with formation of an  $R^\bullet$  radical and a subsequent coupling with the substrate anion radical [235]. Sterical hindrance in (27) makes ortho-coupling unfavorable. However, the disulfone (27) shows an interesting case of a reversible cleavage according to route (a) (see general reduction Scheme 52 of aromatic sulfones) and a reorganization of the substrate, which can cleave to a phenoxy derivative (Scheme 53) [236].

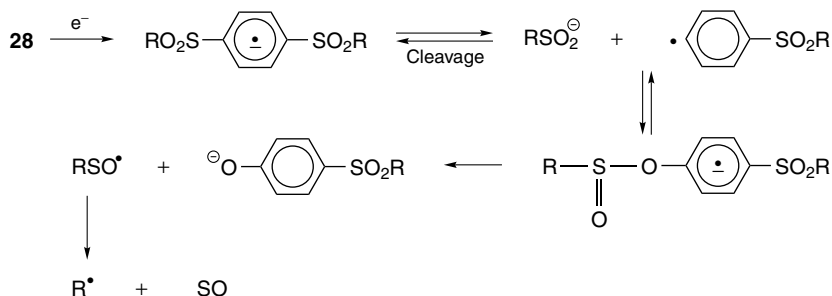
Thus, the progressive accumulation of alkyl and/or arylsulfonyl groups onto a benzene ring (in the aromatic polysulfones (27)–(31)) led to an increasing stabilization of the corresponding anion radicals.

Other disulfones like (32) and (33) were studied (see Ref. [6]). They exhibit surprisingly stable anion radicals (and even a stable dianion with (32)). Such charged species could be used as redox mediators. However, reduction of alkyl halides RX by (33) did not permit the formation of alkylated products presumably because of the strong steric strain induced by alkylation of the corresponding carbon atoms in the cyclobutene ring.

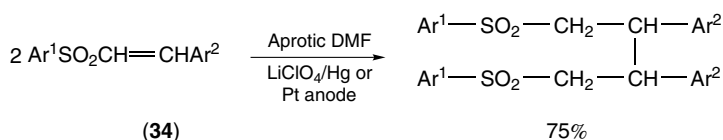


$\alpha,\beta$ -Ethylenic sulfones exhibit a behavior that could be considered as specific and totally different from that of  $\alpha,\beta$ -ethylenic ketones or nitriles. Thus, with the present series, there is practically no case of dimerization or double-bond saturation. This seems to be because of the fact that reduction of compounds of this series cannot be completed neither in acidic nor in aqueous solutions because a fast cleavage occurs at the level of the anion radical.

Consequently, the reaction given below could be regarded as an exception (reduction in a DMF/LiClO<sub>4</sub> system). Aromatic



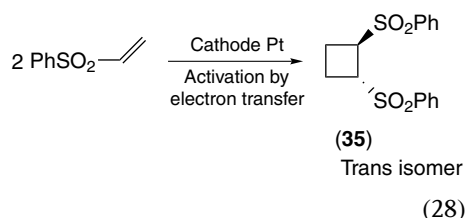
**Scheme 53** Reversible cleavage and reorganization of disulfone.



**Scheme 54** Cathodic coupling of  $\alpha,\beta$ -ethylenic sulfone.

ethylenic sulfones (34) were found [237] to lead selectively to the corresponding  $\delta$ -disulfones with a high ratio of the *d,l* isomer (*d,l*/meso > 10) (Scheme 54).

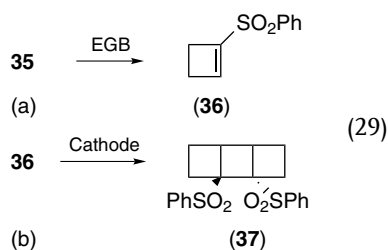
Such a behavior, however, was not found with vinyl arylsulfones: studies in aprotic organic solvents revealed the existence of electrocatalytic cyclodimerizations. Thus, sulfones  $\text{ArSO}_2\text{CH}=\text{CHR}$  afford corresponding cyclodimers [238], often, almost quantitatively (in constant current electrolyses in DMSO/ $\text{LiClO}_4$  solution, the catalytic amount of electricity does not exceed  $0.1 \text{ F mol}^{-1}$ ) (Eq. 28).



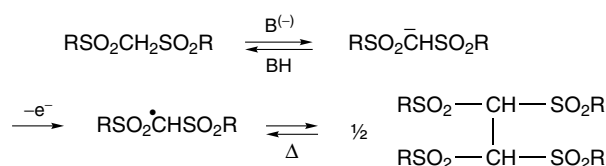
Cyclobutane (35) and its analogs were not described in literature so far. They can be regarded as an easy source both of a cyclobutyl radical [239] (by cleavage of C–S bond under electron transfer) and a dienophile [240]. Thus, (35) readily yields the corresponding cyclobutene (36) in the presence of electrogenerated bases (EGB)

like superoxide or acridine anion radical (Eq. 29). The product (36), unknown until now, could be efficiently used in Diels–Alder synthesis.

It was checked to undergo the cathodic cyclodimerization, thus providing a route [241] to ladderanes (37) (Eq. 29). However, this process could not be generalized by transfer to other unsaturated sulfones, because the double bond can readily migrate to the  $\beta,\gamma$ -position, where it favors the cleavage of the concerned anion radical.



Lastly, the anodic oxidation of sulfone anions could be achieved. Examples of the dimer formation are available in a recent paper [242]. The activity of  $\alpha$ -sulfonyl anions at a positively polarized electrode was pointed out. The coupling of  $\alpha,\alpha$ -bissulfonyl anions by anodic oxidation was also achieved. These coupling reactions



**Scheme 55** Anodic coupling of  $\alpha,\alpha$ -bissulfonyl anions.

leading to their formation, the mechanism of the heterogeneous (direct) reduction is strongly expected to be ECE (two heterogeneous electron transfers E associated with an extremely fast chemical reaction C). To illustrate the influence of the nature of substituents R on the ease of the electroreduction in the series of organyl(1-naphthyl)methyl sulfonium salts (**39**), some reduction potentials are collected in Table 1.

C[S+](R)c1ccc2ccccc2c1.[X-]

(39)

**Tab. 1** Potentials of reduction ( $E_p$ , vs SCE) of sulfonium salts (**39**) at a Pt microelectrode in AN/ $\text{Bu}_4\text{NBF}_4$ ;  $C = 10^{-3}$  M (from Ref. [243–246].)

<i>R</i>	<i>X</i>	<i>E<sub>p</sub></i> (V)
—CH <sub>3</sub>	CF <sub>3</sub> SO <sub>3</sub>	—1.51
—CH(CH <sub>3</sub> ) <sub>2</sub>	BF <sub>4</sub>	—1.49
—CH <sub>2</sub> —C <sub>6</sub> H <sub>5</sub>	BF <sub>4</sub>	—1.23
—CH <sub>2</sub> COC <sub>6</sub> H <sub>5</sub>	CF <sub>3</sub> SO <sub>3</sub>	—0.74
—CH <sub>2</sub> C(C <sub>6</sub> H <sub>5</sub> )=C(CN) <sub>2</sub>	CF <sub>3</sub> SO <sub>3</sub>	—0.17

$$\text{R}^1\text{R}^2\text{R}^3\text{SR}^+ \xrightarrow[-\text{X}^-]{\text{e}^-} [\text{R}^1\text{R}^2\text{R}^3\text{S}]^\bullet \begin{cases} \rightarrow (\text{R}^1)^\bullet + \text{R}^2\text{SR}^3 \\ \rightarrow (\text{R}^2)^\bullet + \text{R}^1\text{SR}^3 \\ \rightarrow (\text{R}^3)^\bullet + \text{R}^1\text{SR}^2 \end{cases} \quad (38)$$



Lastly, let us emphasize the large difference of reducibility ( $E_p$  vs SCE) between sulfoxonium, sulfonium, and its corresponding ylide.

The nature of the cleavage and the possible stability of sulfuranyl radicals formed after electron transfer could be advantageously revealed by ESR and the associated technique of spin trapping as well [247, 248]. Spin traps such as *t*-butylphenylnitron and nitrosodurene could contribute to demonstrate the structure of the leaving radical formed by cathodic decomposition of the sulfonium substrate.

#### 9.3.7

##### Sulfonamides and Deprotection to Amines

In nonaqueous media, the cathodic cleavage of N–S bonds occurs according

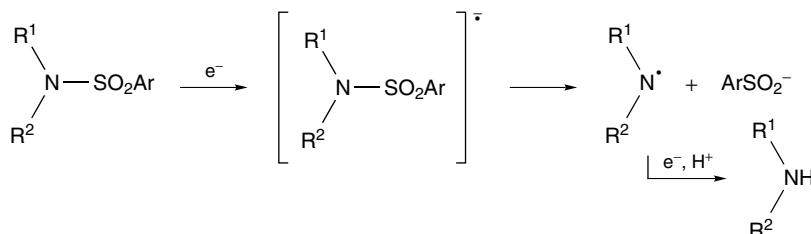
to an overall two-electron process (Scheme 57).

Reduction potentials are much too cathodic to allow reaction in aqueous solvents. This reaction is efficient for the deprotection of the amine function. It is then particularly well adapted to achieve the deprotection in a very mild and selective manner [249], and to allow the synthesis of macrocycles in high yield (Scheme 58) [250]. Note that mesitylates are not electrochemically active.

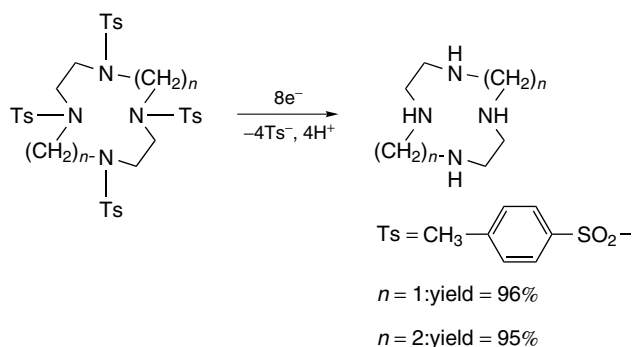
#### 9.4

##### Sacrificial Sulfur Electrodes

Although it does not deal with the direct redox processes of sulfur organic compounds, the use of sacrificial electrodes, both cathodes and anodes producing



**Scheme 57** Cathodic cleavage of sulfonamide for deprotection of amines.



**Scheme 58** Cathodic deprotection of macrocyclic polyamines.

under polarization  $S_x^{2-}$  or  $S_y^{2+}$  species, turned out to be a very convenient electrochemical way to obtain various organosulfur products. Usually made of a molten mixture of elemental sulfur and a carbon powder, these electrodes behave like conventional inert electrodes in the range of potentials between  $-0.6$  and  $1.6$  V vs. SCE; at these potentials, sulfur is not involved in the formation of products. At potentials below  $-0.6$  V or above  $1.6$  V, the reduction or oxidation of sulfur takes place, respectively. The cathodic dissolution of the sulfur electrode produces  $S_3^{2-}$ ,  $S_4^{2-}$ , and  $S_8^{2-}$  species, whereas its anodic process mainly generates  $S^{2+}$  cations. When using sacrificial sulfur electrodes, a general rule applies: the higher the corresponding potential (cathodic or anodic), the more reduced/oxidized (and hence containing less S atoms) S-species are produced, for example,  $S_4^{2-} > (S_6^{2-} \leftrightarrow 2S_3^{2-}) > S_8^{2-}$  in the cathodic and  $S^{2+} > S_2^{2+}$  in the anodic process.

#### 9.4.1

##### Sacrificial Anodes

Diorganyltrisulfides ( $RS_3R$ ,  $R = \text{Alk}, \text{Ar}$ ) can be obtained by the reaction of electrogenerated  $S^{2+}$  cations with thiols in good synthetic yields [251]. When the potential of the electrolysis shifts to higher potentials ( $2.3$  V vs SCE), trisulfides are preferentially formed; as the potential is set at about  $1.8$  V, a rise of the

yield of tetrasulfides is observed owing to the formation of the less oxidized form  $S_2^{2+}$ .  $\alpha,\omega$ -Terminal dithiols, used in this process, give cyclic products. A cyclic sulfide, 2-[1,3]-benzothiadiazole, was obtained when using *o*-phenylenediamine in a similar process [252]. With aniline, one obtains the ortho-substituted product, 2,2'-diaminodiphenylsulfide. It is interesting that when a secondary or a tertiary aromatic amine is taken, the formation of a para-substituted diarylsulfide takes place exclusively.

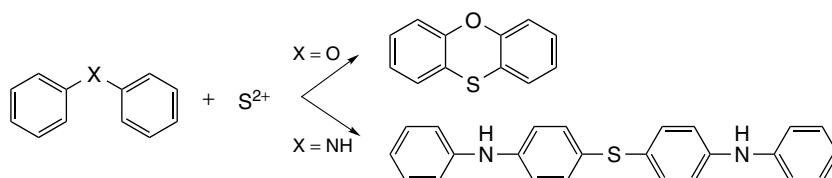
Another point worth mentioning is the selectivity of the electrogenerated electrophilic sulfur species toward aromatic substrates in the reaction with diphenylether and diphenylamine. In the first case, an internal ortho-cyclization yields in phenoxathiin, in the second, a para-substitution occurs [252] giving a linear product (Scheme 59).

More activated substrates such as thiophene, produce a mixture of  $\alpha,\alpha'$ -dithiophene mono-, di-, tri-, tetra-, and polysulfides. When both  $\alpha$ -positions of thiophene are taken by methyl groups, a  $\beta,\beta'$ - and a fused tricyclic product were obtained.

#### 9.4.2

##### Sacrificial Cathodes

Cathodic generation of  $S_x^{2-}$  species in the presence of alkylhalogenides provides polysulfides  $\text{Alk-S}_x\text{-Alk}$  ( $x = 2, 3, 4$ ). At more negative potentials



**Scheme 59** Anodic substitution of aromatic compounds with electrogenerated  $S^{2+}$ .

(−1.5 V vs SCE) one obtains equal quantities of di-, tri-, and tetrasulfides, at less negative potentials (−0.9 V), tri- and tetrasulfides are obtained almost exclusively [253]. Substituted monohalobenzenes such as 4-bromobenzophenone and 2-chloronitrobenzene give corresponding diaryldisulfides [254–256]. The addition of MeI in the last case, resulting in methyl-(2-nitrophenyl)disulfide, allowed to suppose the process to occur via an intermediate 2-nitrophenyl disulfide anion.

1,4- and 1,2-dinitrobenzene react with polysulfide ions ( $S_3^{2-} \leftrightarrow S_6^{2-}$ ) or aryl-disulfide anions  $ArS_2^{2-}$ , obtained by adding sulfur to the solution of electrogenerated 4-methylphenyl or 4-fluorophenyl thiolates, affording the products of nucleophilic aromatic substitution of *ortho* or *para* nitro groups – nitroarylthiolate, nitroaryl disulfide ions, or an equilibrium mixture of nitroaryl mono- and disulfide ions [257] or  $NO_2C_6H_4S_2Ar$  [258], respectively.

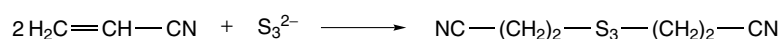
In an  $S_{RN}1$  process with polysulfide anions, 3-bromoquinoline afforded a mixture of diquinolinyl mono-, di- and trisulfide, all in similar yields

of about 22% [259]. Cumulene derivatives such as 1,1-di-*p*-chlorophenylbuta-1,2,3-triene, 1,1-di-*p*-chlorophenyl-4,4-di-*p*-methylphenylbuta-1,2,3-triene, and 1,1,4,4-tetraphenylbuta-1,2,3-triene produced 7-membered pentathiepins with 5 sulfur atoms [260].

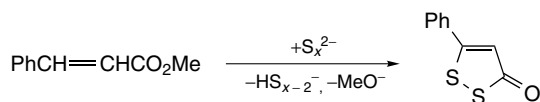
Activated unsaturated compounds react with  $S_x^{2-}$  species as well [261]. Thus, acrylonitrile gives bis(2-cyanoethyl)trisulfide as a main product along with some amount of 6-amino-5-cyano-7,8-dihydro-4*H*-1,2,3-trithiocine, if the reaction was carried out in strong basic media (Scheme 60).

When 3-chloro-3-phenyl acrylonitrile was involved in this reaction, a bicyclic product, 6,6'-diphenyl-4,4'-bis(1,2,3-dithiazine) was formed in good yield [262]. Five-membered cyclic disulfides were obtained in this reaction when ethylenic esters or ketones were taken as an unsaturated substrate (Scheme 61) [263].

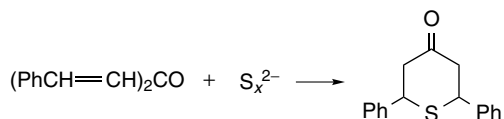
An example of the formation of a cyclic product, containing only one sulfur atom, is the reaction of  $S_x^{2-}$  anions with activated double bonds of 1,5-diphenyl-1,4-pentadiene-3-one yielding in a substituted oxotetrahydrothiopyran (Scheme 62) [253].



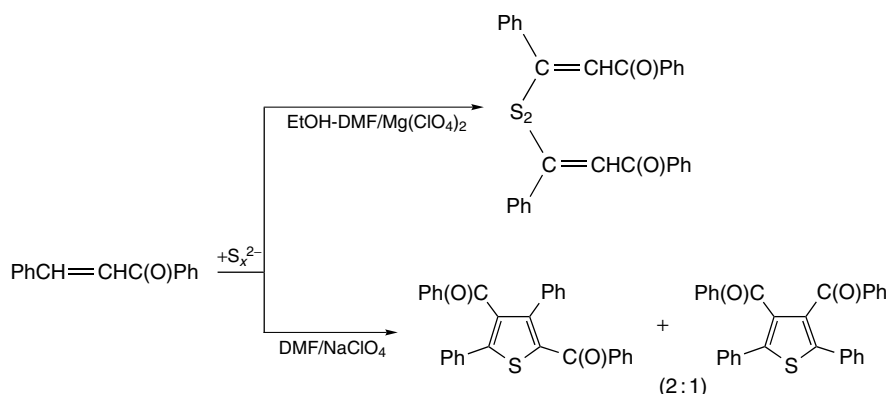
**Scheme 60** Michael addition with electrogenerated  $S_3^{2-}$ .



**Scheme 61** Cyclic disulfides by reaction of  $S_x^{2-}$  with methyl cinnamate.



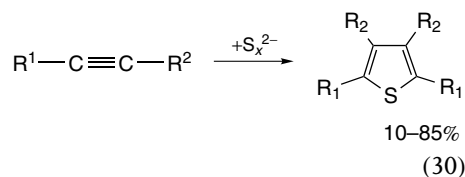
**Scheme 62** Double Michael addition of electrogenerated  $S_x^{2-}$  to a divinylketone.



**Scheme 63** Michael addition of  $\text{S}_x^{2-}$  to benzalacetophenone.

A similar process with benzalacetophenone results in different products, the chemoselectivity being controlled by the experimental conditions, namely the solvent and the supporting electrolyte used [261]. Either an acyclic disulfide, bis(2-benzoyl-1-phenylvinyl) disulfide (in EtOH-DMF/ $\text{Mg(ClO}_4)_2$ ), or two isomeric thiophenes (in DMF/ $\text{NaClO}_4$ ) can thus be obtained (Scheme 63). Upon the substitution of a vinylic proton at C(2) with Br, the reaction becomes more regioselective and the only product now formed is an  $\alpha, \alpha'$ -dibenzoyl thiophene derivative.

The reaction of  $\text{R}^1\text{-C}\equiv\text{C-R}^2$  with the electrogenerated  $\text{S}_x^{2-}$  ions provides a convenient method for the synthesis of substituted thiophenes (Eq. 30) [263]. Besides thiophenes, some dithiols, divinylsulfides and 2,4,6-tricarboxyethyl-1,3,5-trithiophenol were formed, the product distribution being governed by the nature of the substituents in the starting acetylenic substrate.



The triple bond of the cyano group in benzonitrile is also affected by  $\text{S}_x^{2-}$  anions; thiobenzamide was formed in this case in a 40% yield [255, 256]. An interesting example of a simultaneous introduction of both sulfur and carbon using a sacrificial carbon-sulfur cathode is the formation of 4-morpholino- $\alpha$ -thioxoethanedithioate from morpholine [264].

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## 10 Electrochemistry of Nitrogen-containing Compounds

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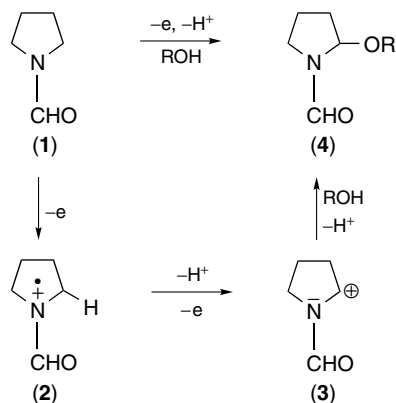
## 10.1 Introduction

From a synthetic perspective, the anodic oxidation of molecules that contain amines and amides remains one of the most important classes of electrochemical reactions studied to date. The value of these reactions is derived from the vast number of biologically active molecules that contain nitrogen atoms and also from the often unique opportunity electrochemistry offers for rapidly building these molecules by selectively functionalizing readily available amine and amide starting materials. In many cases, chemical alternatives to the electrochemical approach are not available. Hence, the electrochemical oxidation of amines and amides provides an outstanding backdrop for illustrating the synthetic potential electrochemistry has for “opening up” entirely new pathways for the construction of molecules.

This idea is perhaps easiest to illustrate for the oxidation of an amide (Scheme 1). Amide oxidation reactions are of tremendous synthetic interest because they can provide an oxidative alternative to the synthesis of reactive *N*-acyliminium ion intermediates (**3**). Such a route would complement well the existing reductive and condensation-based approaches [1–3]. However, because amides

have high-oxidation potentials, they are often difficult to oxidize using chemical reagents [4]. In addition, the alkoxy products (**4**) typically generated have oxidation potentials that are only 150 to 200 mV higher than that of the initial amide starting materials. Hence, a selective oxidation is needed in order to avoid overoxidation of the product. For chemical oxidants, this selectivity can be difficult to achieve, especially in the context of developing a generally useful synthetic method. For example, consider a chemical oxidant having the appropriate window of reactivity such that an amide substrate (**1**) can be oxidized without overoxidizing the alkoxy product (**4**). If an electron-donating substituent is added to the substrate that lowers its oxidation potential by 200 mV (an alkyl group), the required selectivity for the reaction would be lost and the product oxidized. The addition of an electron-withdrawing group to the substrate would render the oxidation potential of the substrate too high for use by the chemical reagent. The result is that chemical reagents that can affect the selective oxidation of an amide are by their nature limited in scope.

Electrochemical oxidations have no such difficulty. The potential of an anode surface can be varied widely without losing the selectivity of the oxidation. In the scenario outlined above, the potential



**Scheme 1** Anodic alkoxlation of *N*-formyl pyrrolidine.

would be lowered for a substrate having the electron-donating group and raised for the substrate having the electron-withdrawing group. In both cases, the difference in oxidation potential between the substrate and the alkoxy product would ensure that overoxidation of the product could be avoided. As outlined in Sects. 10.4 to 10.7 below, this is not simply a theoretical argument. Anodic amide oxidations have proven to be very useful synthetic tools and can provide new and powerful strategies for constructing complex organic molecules.

While anodic amide oxidations have found the most synthetic use to date, the oxidation of nitrogen-containing molecules is not limited to amide substrates. A variety of amine oxidations have been studied, and the Kolbe electrolysis of carboxylic acids has been used to generate nitrogen-based reactive intermediates. Many of these reactions also offer unique synthetic advantages (Sects. 10.2 and 10.3).

For any synthetic method, it is important to define the experimental setup required for the reactions so that new users can take advantage of the chemistry. This is especially important for electrochemistry in which misgivings about the need for

complicated equipment, the complexity of the reaction setups, and the generality of the reactions studied often limit acceptance of the methodology developed by the larger synthetic community. In practice, these concerns rarely represent insurmountable barriers. The equipment necessary for trying the majority of electrochemical synthetic methods can be very simple [5], the concepts needed for conducting the vast majority of synthetic experiments can be readily explained [6], and the generality of the reactions are often superb (vide infra). Since detailed discussions of these topics can be found elsewhere [7, 8], they will not be discussed here. Instead, the review that follows will seek to place the oxidation of nitrogen compounds into a synthetic context. In doing so, it is hoped that this work will enable readers to identify not only what reactions are available but also identify how the reactions can be utilized to develop new strategies for synthesis.

## 10.2

### Oxidation of Amines

The formation of a radical cation intermediate normally initiates reactions that

fall into one of three main categories. In the first category, the radical cation intermediate generated oxidizes a second substrate in the reaction medium. This results in a mediated oxidation of the second substrate. In the second category, the radical cation generated undergoes an additional reaction with either an olefin or a nucleophile. In the third category, the elimination of a neighboring group of the radical cation leads to the formation of an electrophile that either traps a nucleophile or undergoes a second elimination reaction in order to generate an unsaturated product. All three of these reaction types have been triggered by the oxidation of an amine to form a nitrogen-based radical cation.

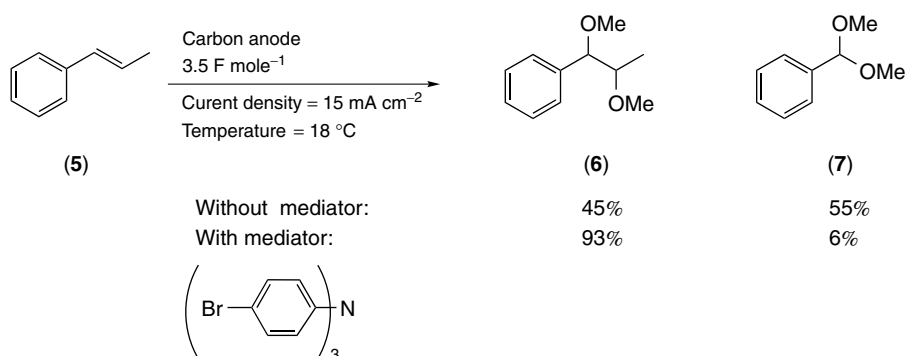
### 10.2.1

#### Amine Radical Cations as Electrochemical Mediators

A variety of amines have been used as mediators for electrochemical oxidation reactions. In these reactions, the amine is oxidized at an anode surface to form a radical cation. The amine radical cation then oxidizes a second substrate triggering a reaction of synthetic interest. The regenerated amine is then reoxidized at the anode

surface and the cycle continues. These reactions have been reviewed previously [9]. However, a pair of recent experiments deserves comment here because they illustrate the potential utility of these reactions.

The use of a chemical mediator can alter the chemoselectivity of an electrochemical reaction. In the reaction illustrated in Scheme 2,  $\beta$ -methylstyrene was oxidized using both direct electrolysis and mediated conditions [10]. The current density, amount of charge passed, temperature, and other variables were all kept constant. The only difference was the addition of 6.4 mole percent of tris(4-bromophenyl)amine to the mediated reaction. The direct electrolysis tended to afford the product of a four-electron oxidation (7). When 3.5 F mole<sup>-1</sup> of electricity was passed, a 55% yield of (7) was obtained along with a 45% yield of (6). With additional current (6.4 F mole<sup>-1</sup>), a 75% yield of (7) was obtained. The mediated process led to a preponderance of the product from the two-electron oxidation. When 3.5 F mole<sup>-1</sup> of electricity was passed in the experiment using the triarylamine mediator, a 93% yield of (6) was obtained along with only 6% of the four-electron oxidation product.



**Scheme 2** Anodic methoxylation of  $\beta$ -methylstyrene without and with an amine radical cation as mediator.

In many cases, mediators are used to regenerate chemical reagents. Such reactions are advantageous because they capitalize on the advantages of electrochemistry and the selectivity associated with the chemical reaction. For example [11], a tris(4-bromophenyl)amine-mediated reaction has been utilized to effect the Wacker process (Scheme 3). The reactions were conducted using either a divided cell with 5 mole percent  $\text{Pd}(\text{OAc})_2$  catalyst or an undivided cell with 5 mole percent  $\text{PdCl}_2$  catalyst. In both cases, the  $\text{Pd}(0)$  generated from the reaction was reoxidized to the  $\text{Pd}(II)$  species required for the reaction by two equivalents of the amine radical cation. The amine radical cation was then regenerated using a platinum anode. Both reaction setups used 20 mole percent of the mediator along with a 0.5 M  $\text{Et}_4\text{NOTs}$  in a 7:1 acetonitrile/water electrolyte solution. Two to three  $\text{F mole}^{-1}$  of electricity was passed in each case. Using these conditions, a series of nine monosubstituted olefins were converted into the corresponding methyl ketones. The reactions tolerated the presence of aryl rings, ethers, ketones, esters, carbamates, and alcohols and afforded yields that ranged from 66 to 93%. Two

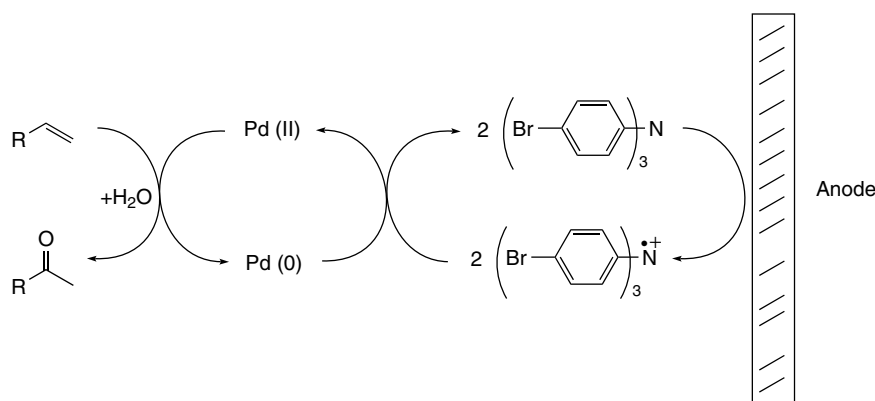
representative examples are illustrated in Scheme 4.

### 10.2.2

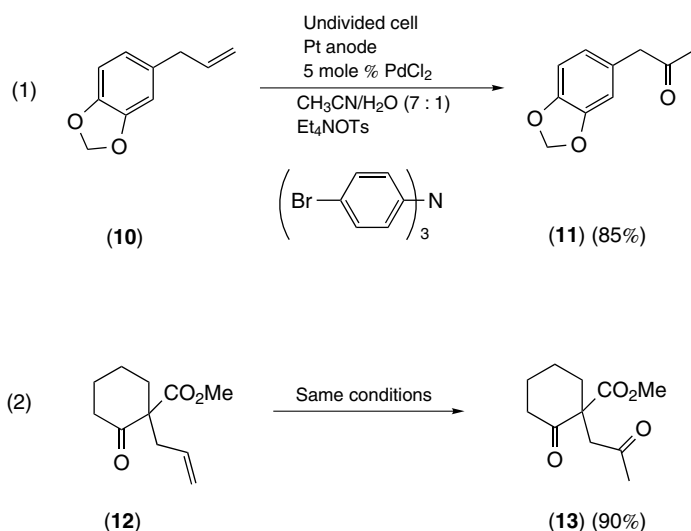
#### Functionalization Reactions

In addition to using amine oxidation products as mediators, anodic oxidation reactions can be used to functionalize amine compounds. These reactions include both – examples that generate imines and nitriles, as well as examples that lead to the addition of nucleophiles to the carbon alpha to the nitrogen.

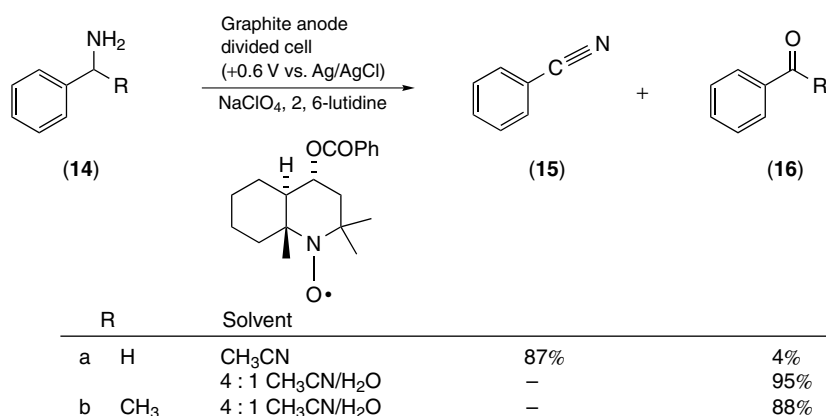
The electrochemical oxidation of amines to imines and nitriles typically utilize a chemical mediator. The use of both *N*-oxyl radicals [12, 13] and halogens has been reported for this process [14]. For example, the conversion of benzyl amine (**14a**) into nitrile (**15a**) and aldehyde (**16a**) has been accomplished using the *N*-oxyl radical of a decahydroquinoline ring skeleton as the mediator (Scheme 5). The use of acetonitrile as the solvent for the reaction generated the nitrile product. The addition of water to the reaction stopped this process by hydrolyzing the imine generated. A high yield of the aldehyde was obtained. In the case of a secondary amine, the aqueous



**Scheme 3** Electrochemical Wacker process with amine radical cation-mediated  $\text{Pd}(II)$  regeneration.



Scheme 4 Electrochemical Wacker processes.



Scheme 5 Mediated anodic oxidation of amine to nitrile and carbonyl compound.

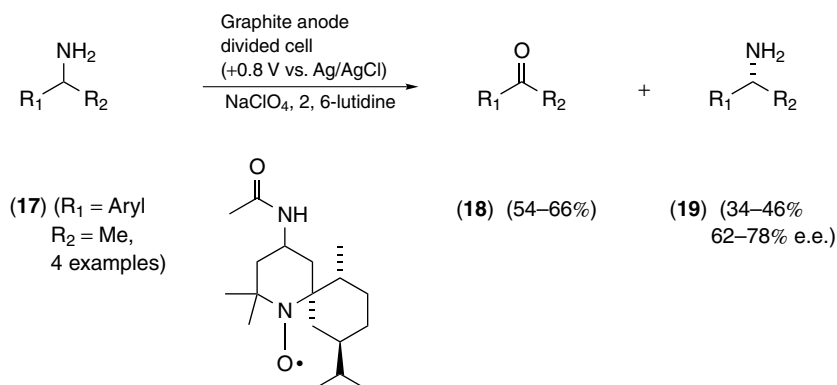
conditions were used to generate a ketone product. Several examples were reported including the oxidation of both the primary and the secondary aliphatic amines.

Recently, a similar reaction has been shown to affect the kinetic resolution of racemic secondary amines (Scheme 6) [15]. In this example, *N*-oxyl radical (20) was utilized as the mediator. The rest of the reaction conditions remained the

same as in the aqueous cases illustrated in Scheme 5. The reactions were run to partial conversion and then the chirality of the recovered amine-starting material was measured. Enantiomeric excesses of 62 to 78% were obtained. The turnover number for the *N*-oxyl radical ranged from 21.7 to 26.5.

The direct oxidation of tertiary amines leads to the formation of an iminium





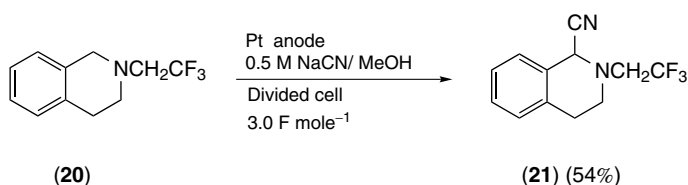
**Scheme 6** Kinetic resolution in the oxidation of a *rac*-sec amine with a non racemic nitroxyl mediator.

ion followed by subsequent trapping with a nucleophile. As illustrated in Scheme 7, Fuchigami and coworkers reported the anodic cyanation of 2,2,2-trifluoroethylamines [16]. In these experiments, no oxidized product was obtained alpha to the trifluoromethyl group. This result was curious since  $\alpha$ -methoxylation reactions showed the exact opposite selectivity and favored methoxylation on the carbon alpha over the trifluoromethyl group [17]. The mechanism of the cyanation reaction clearly proceeded through the formation of an iminium ion. However, it was not clear why this reaction differed so dramatically from the methoxylation process.

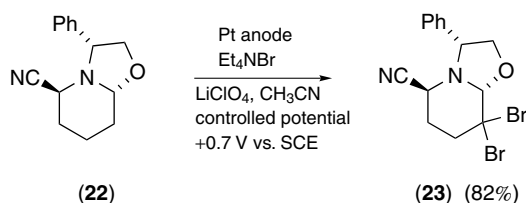
Similar oxidations also occurred with enamine substrates. In the reaction outlined in Scheme 8 [18], the formation of a dibrominated product arose because of the initial oxidation of an enamine

substrate that resulted from the opening of the tetrahydrofuran ring in the substrate. The oxidation led to the radical cation of the enamine that underwent a subsequent reaction with an oxidized bromide (Br<sup>•</sup>) to generate an  $\alpha$ -brominated iminium ion. Elimination of a proton to regenerate the enamine, oxidation to reform the enamine radical cation, and trapping of a second bromine radical again led to an iminium ion. Recyclization afforded the bicyclic product.

The oxidation of an amine can benefit from the use of an electroauxiliary [19–28]. Electroauxiliaries are substituents that both lower the initial oxidation potential of the substrate and control the formation of the subsequent reactive intermediates. To this end, the anodic oxidation of the 6-membered ring  $\alpha$ -silyl amines in the presence of cyanide was shown to afford a net displacement of the silyl



**Scheme 7** Anodic  $\alpha$ -cyanation of amine.



**Scheme 8** Anodic conversion of an amine to an enamine with subsequent anodic bromination.

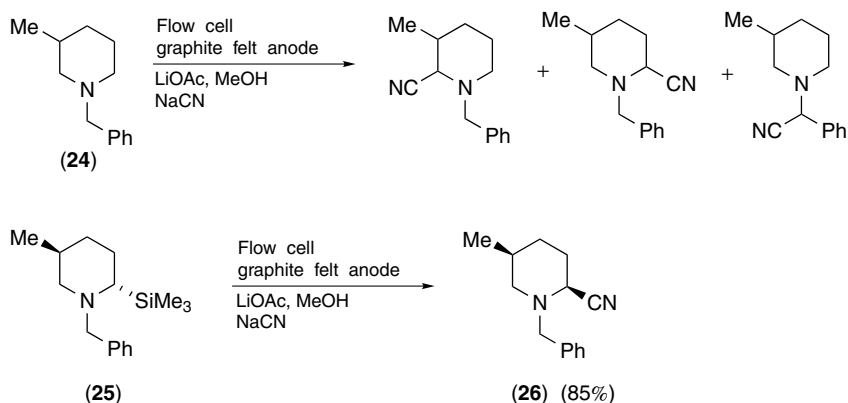
group by cyanide (Scheme 9) [29]. Both aliphatic and aromatic cases were studied. The reactions were much more selective than the cyanations involving the direct oxidations of amines. For example, when (24) was oxidized at an anode surface an inseparable mixture of three products was obtained. In contrast, the oxidation of (25) led to the formation of just one product. Three items concerning this reaction deserve further comment. First, substrate (25) was readily available by metallation and silylation of the *t*-butyliminomethyl-protected 3-methylpiperidine. The reaction led to an 85% isolated yield of the product silylated at the 6-position of the piperidine ring. Second, the stereochemistry of the cyanation reaction arose because of a stereoelectronic addition of cyanide to the iminium ion generated from the elimination of the silyl group from the

initial amine radical cation followed by a second oxidation. Finally, the conversion of the silylated amine to the  $\alpha$ -cyanoamine required only 2 F mole<sup>-1</sup> of electricity. Earlier direct oxidations required up to 4 F mole<sup>-1</sup> due to a homogenous electron transfer between the cyanide anion and the radical cation in solution. The authors argued that the increase in efficiency arose because of the ability of the cyanide anion to accelerate the elimination of the silyl group from the radical cation. This decreases the lifetime of the radical cation and reduces the chance for a homogenous electron transfer.

### 10.2.3

#### N-centered Radicals and Cycloadditions

In addition to generating amine radical cation mediators and functionalizing



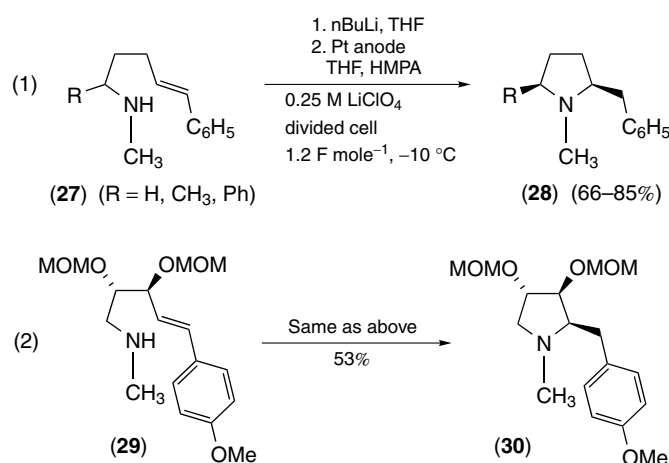
**Scheme 9** Regioselective anodic cyanation of amine (25) by way of an electroauxiliary.

amine substrates, anodic oxidation reactions can be used to trigger nitrogen-based radical chemistry. An example of this chemistry is illustrated in Scheme 10 [30, 31]. In both the reactions illustrated, the amines were treated with *n*-BuLi and the resulting anion oxidized at a platinum anode using constant current conditions, a divided cell, and a lithium perchlorate in THF/HMPA (30:1) electrolyte solution. The one-electron oxidation led to the formation of the nitrogen-based radical that then added to the olefin to form a cyclic product. Abstraction of a hydrogen atom from the solvent afforded products (28) and (30). Oxidation of the amines without prior treatment with *n*-BuLi failed to afford cyclic products. In cases where *n*-BuLi was used, the reactions were both stereo- and regioselective. For reactions originating from (27) only *cis*-pyrrolidine products were obtained. The product (30) was used further to complete the synthesis of (+)-*N*-methylanisomycin [31].

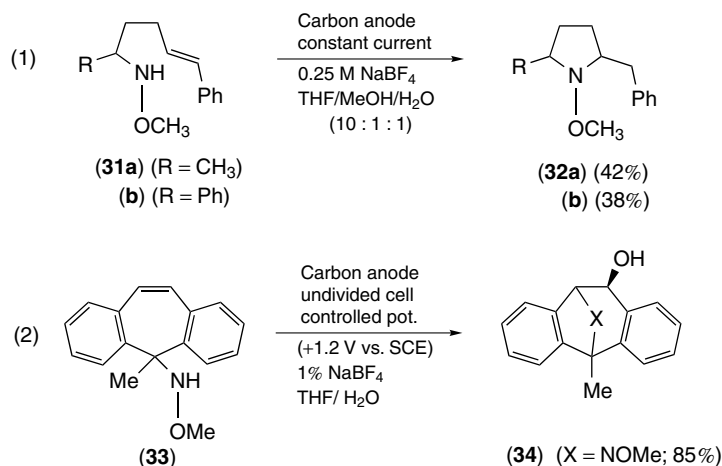
The direct oxidation of unsaturated *N*-methoxy amines also leads to the formation of cyclic products (Scheme 11) [30].

For cases directly comparable to the cyclization originating from (27) above, the yields of the product were not as high. However, a related reaction used in the synthesis of an 11-substituted dibenzo[*a,d*]-cycloheptenimine derivative was very successful as shown in Scheme 11 (Eq. 2) [32]. In this reaction, a controlled potential electrolysis of (33) led to the formation of the tetracyclic (34) in an 85% isolated yield. The reaction was performed on a 1 g scale using an undivided cell, a graphite felt anode, a stainless steel cathode, a saturated calomel reference electrode, and a 1% NaBF<sub>4</sub> in 70:30 THF/water electrolyte solution. The electrolysis was scaled up further with the use of a flow cell. In this experiment, 200 g of (33) were oxidized in order to afford a 75% isolated yield of (34).

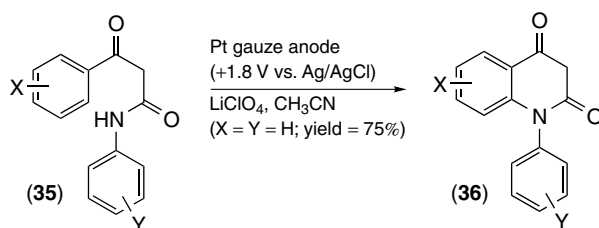
Another oxidative cyclization to afford a nitrogen heterocycle is illustrated in Scheme 12 [33]. This reaction was accomplished using a platinum gauze electrode at a controlled potential of +1.8 V versus Ag/AgCl. The reaction proceeded through the initial oxidation of the amide. Evidence



**Scheme 10** Regio- and stereoselective anodic cyclization of amides.



**Scheme 11** Regioselective anodic cyclization of *O*-Methyl hydroxylamines.

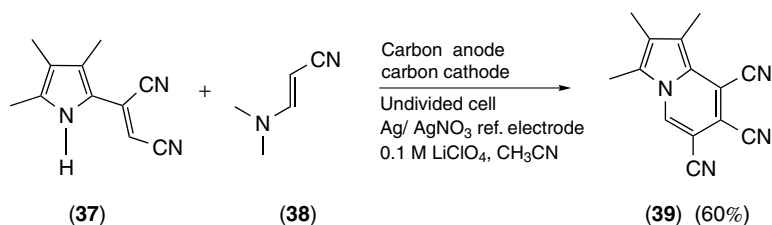


**Scheme 12** Intramolecular anodic amination of aromatics.

for this conclusion was obtained by placing substituents on the two phenyl rings of the substrate. It was found that substituents in position X did not influence the initial oxidation wave obtained for the substrate, while substituents in position Y did. Electron-withdrawing groups in this position raised the oxidation potential for the substrate, while electron-donating groups in position Y lowered the observed oxidation potential. Formation of the nitrogen-based radical was followed by the cyclization reaction. A second oxidation reaction followed by loss of a proton and reestablishment of the aromatic ring afforded the cyclic product.

Amine-based radical cations have also served as participants in cycloaddition

reactions (Scheme 13) [34]. In these experiments, a LiClO<sub>4</sub> in acetonitrile solution containing a 2-vinylpyrrole and a  $\beta$ -acceptor substituted enamine was electrolyzed at a controlled potential in an undivided cell. As in the case illustrated, it was not always clear which substrate underwent the oxidation. Both (37) and (38) have similar oxidation potentials ( $E_p = +0.85$  and  $+0.86$  respectively). The result was a [4+2]-cycloaddition reaction between two substrates having nearly identical HOMO energies. Cyclic voltammetry data indicated that the cycloaddition reactions were diffusion-controlled processes. In all cases, the product generated was a single regioisomer. The yield for the reaction varied from 23 to 66% (10 cases).



Scheme 13 Anodic cycloaddition.

It is important to note that the reactions are fundamentally different from similar radical cation Diels–Alder reactions initiated with the use of a photochemical electron-transfer reaction [35, 36]. In photochemical reactions, a one-electron oxidation of the substrate leads to a cycloaddition that is then terminated by a “back electron transfer”. No net change is made in the oxidation state of the substrate. However, the reaction outlined in Scheme 13 involves a net two-electron oxidation of the substrate. Hence, the two pathways are complementary.

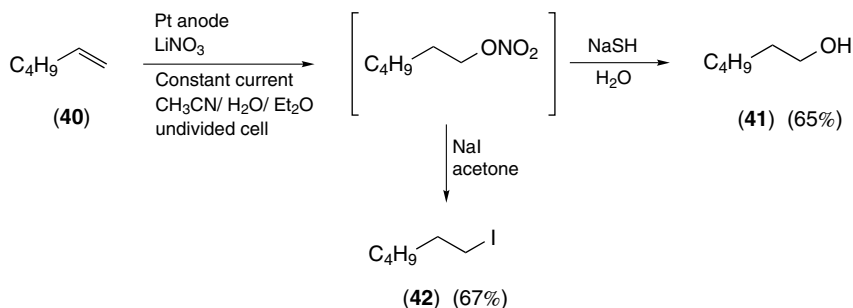
Finally, the oxidation of nitrate anions leads to nitrate radicals ( $\text{NO}_3^\bullet$ ) that add to olefins (Scheme 14) [37]. These oxidations were carried out at a platinum anode using constant current conditions, an undivided cell, a mixed  $\text{MeCN}:\text{H}_2\text{O}:\text{Et}_2\text{O}$  solvent system, and  $\text{LiNO}_3$  as the electrolyte. The initial oxidation led to a nitrate product that was not stable and hence

converted immediately to either an alcohol or an iodide secondary product. The reactions worked well with either mono-substituted or disubstituted olefins. Interestingly, when 1,1-disubstituted olefins were used the reactions led to the formation of substituted oxazoles in good yields (Scheme 15). These products formed from an initial addition of the nitrate radical to the olefin, oxidation of the resulting tertiary radical to a cation, and the trapping of the cation with acetonitrile. A loss of  $\text{NO}_2^+$  led to the observed cyclic product.

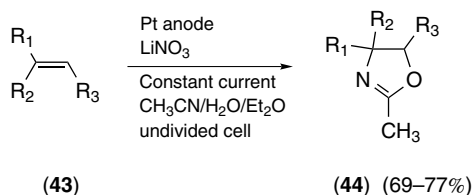
### 10.3

#### Kolbe Oxidations and the Formation of *N*-Acyliminium Ions

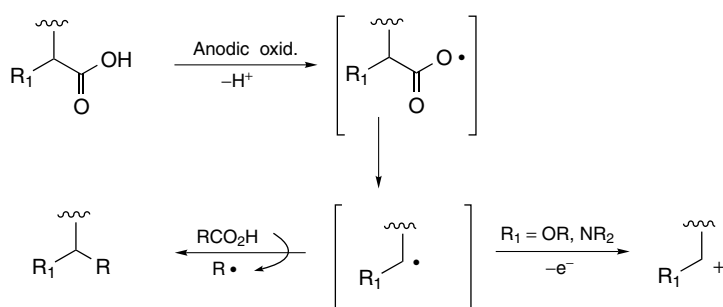
One of the best-known anodic oxidation reactions is still the Kolbe electrolysis [38]. These reactions typically involve the decarboxylation of a carboxylic acid and



Scheme 14 Anodic addition of nitrate anions to double bonds.



**Scheme 15** Anodic addition of a nitrate anion and acetonitrile to a double bond.

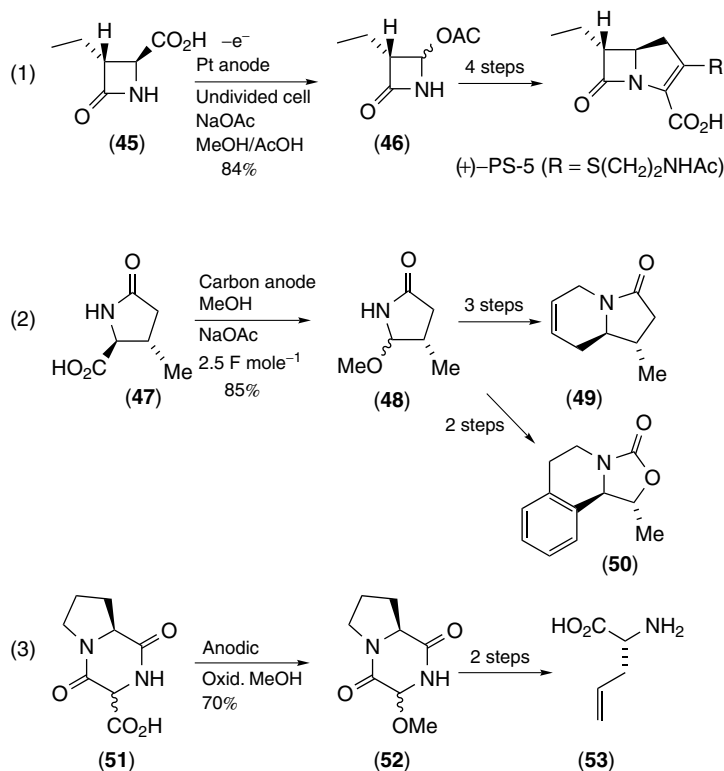


**Scheme 16** Anodic decarboxylation: radical and cationic pathway.

the formation of a radical intermediate (Scheme 16). The radical intermediates have been used to trigger a wide variety of both intermolecular and intramolecular coupling reactions. However, the formation of the radical intermediate and subsequent coupling reactions can be dramatically altered by the nature of the substrate. If a heteroatom is present on the alpha carbon of the original acid, then the reactions lead to cationic intermediates. For example, the anodic oxidation of *N*-acyl protected amino acids leads to the formation of *N*-acyliminium ion intermediates.

Because of the efficiency of this process, the anodic oxidation of amino acid precursors can serve as an excellent method for generating chiral building blocks for synthesis. For example (Scheme 17, Eq. 1) [39], the anodic oxidation of (45) was accomplished at a platinum anode using an undivided cell. An acetate nucleophile was used to trap

the *N*-acyliminium ion intermediate generated. The resulting product (46) was then used as a key intermediate in the asymmetric synthesis of the  $\beta$ -lactam natural product (+)-PS-5. In the second example [40] (Scheme 17, Eq. 2), the oxidation of (47) in methanol solvent led to the formation of the methoxylated amide (48) in high yield. In this case, the product was converted into a variety of functionalized products. Along these lines, bicyclic (49) was formed by allylating (48) with allylbromide, treating the resulting product with allylsilane and  $\text{BF}_3 \cdot \text{Et}_2\text{O}$ , and then effecting an olefin metathesis reaction. Tricyclic (50) was generated by treating the methoxylated amide (48) with 1-bromo-2-phenylethane and then effecting an intramolecular cyclization reaction with  $\text{TiCl}_4$ . Finally, the oxidation of (51) afforded the chiral cationic glycine equivalent (52) (Scheme 17, Eq. 3) [41]. This intermediate was useful for the synthesis of amino acid derivatives.



**Scheme 17** Generation of *N*-acyliminium ions by anodic decarboxylation.

In a related series of reactions, Seebach and coworkers decarboxylated amino acids to make peptide-based building blocks (Scheme 18) [42, 43]. In this work, 13 examples were tried with yields ranging from 25 to 98%. Treatment of the methoxylated products with Lewis acid was used to introduce both allyl and phosphonate-based nucleophiles into the molecules.

## 10.4

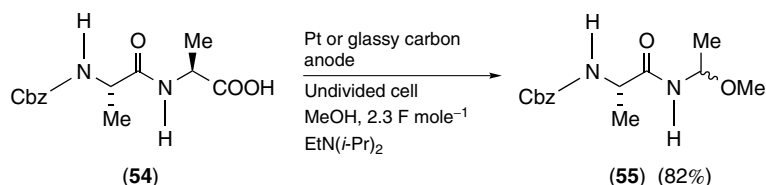
### The Anodic Oxidation of Amides

#### 10.4.1

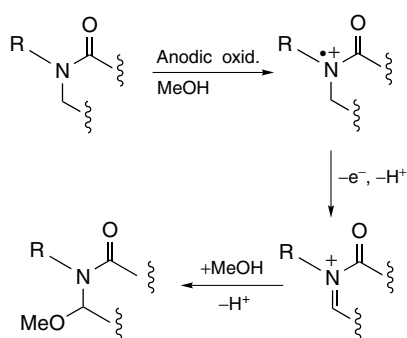
##### General Reaction

As mentioned in the introduction, one of the most synthetically useful anodic

oxidation reaction involves the direct conversion of amides to *N*-acyliminium ions (Scheme 19). This reaction, initially discovered by Ross, Finkelstein, and Peterson [44–46], complements existing chemical methods that employ either the reduction of an imide or the condensation of an amide and an aldehyde to make *N*-acyliminium ions. The power of the oxidative method lies in its ability to quickly make reactive intermediates from known amine and amino acid starting materials. Because of the reactions utility, the early work concerning the synthetic potential of anodic amide oxidation reactions has been extensively reviewed [47]. Since the appearance of that review, the anodic amide oxidation reaction has continued to



**Scheme 18** *N*- $\alpha$ -methoxylation in peptides by anodic decarboxylation.



**Scheme 19** Anodic conversion of amides to *N*-acyliminium ions.

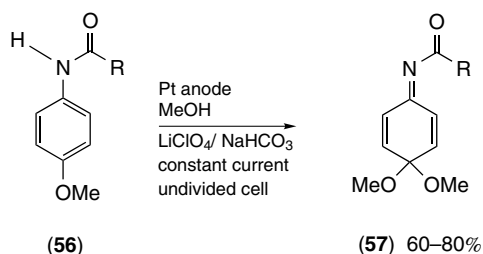
be effectively utilized for the synthesis of complex organic molecules. This work falls into three main categories; the construction of small molecule building blocks, the synthesis of natural products, and the synthesis of constrained peptidomimetics.

#### 10.4.2

##### Adding Functionality to Synthetic Starting Materials

One of the most practical applications of the anodic amide oxidation reaction

involves the conversion of readily available starting materials into useful synthetic building blocks. This is accomplished by using the oxidation reaction to selectively functionalize the starting material. For example, the conversion of *p*-methoxyanilide derivatives into quinone *N*-acylimine ketals has been effected at a platinum anode (Scheme 20) [48]. Related efforts have explored the compatibility of the oxidations with both substituents on the aromatic ring and a variety of protecting groups on nitrogen. In this work, the quinone imine



**Scheme 20** Anodic conversion of *p*-methoxyanilide to quinone imine.

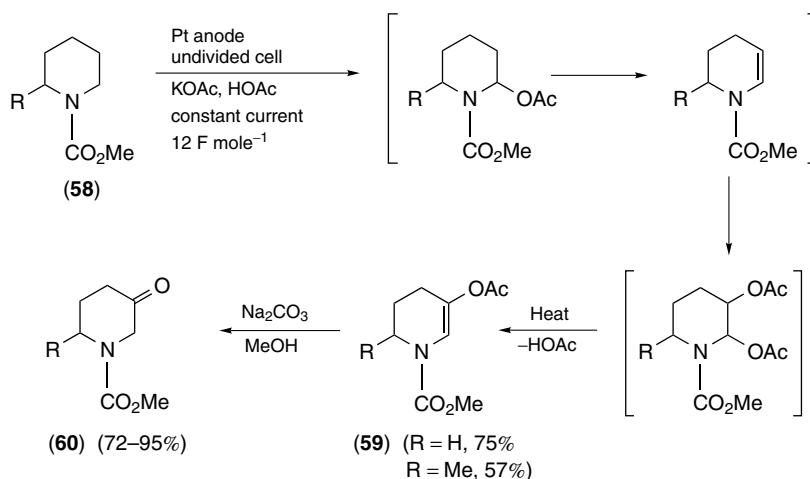


acetals (57) were obtained in yields ranging from 62 to 97% [49].

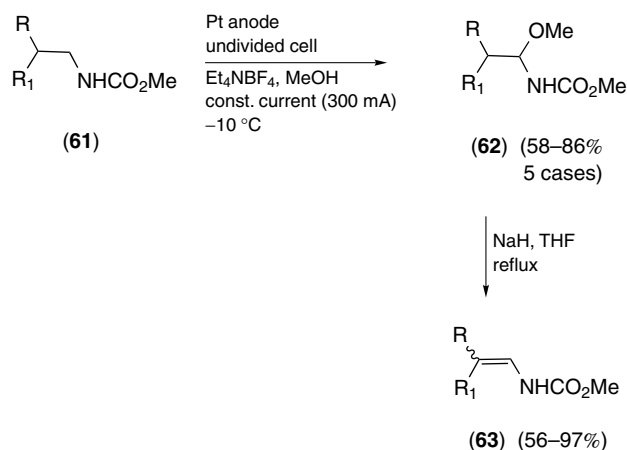
Anodic amide oxidations have also proven useful for selectively converting amides into enamides that have in turn been used to functionalize the carbon beta to nitrogen. For example, the four-electron oxidation of carbamates was used to introduce a carbonyl beta to a nitrogen (Scheme 21) [50]. In this example, the starting carbamate was oxidized at a carbon

anode in acetic acid using an undivided cell and constant current conditions. Oxidation led initially to the  $\alpha$ -acetoxy amide that then underwent elimination to the enamide. Anodic oxidation of the enamide then led to the diacetoxy compound that upon heating afforded the  $\beta$ -acetoxy enamide (59). Hydrolysis then afforded the desired  $\beta$ -ketoamide.

In a related set of reactions, anodic amide oxidation reactions have been



**Scheme 21** Anodic  $\beta$ -oxidation of amides via enamides.



**Scheme 22** Enecarbamates by anodic oxidation of amides.

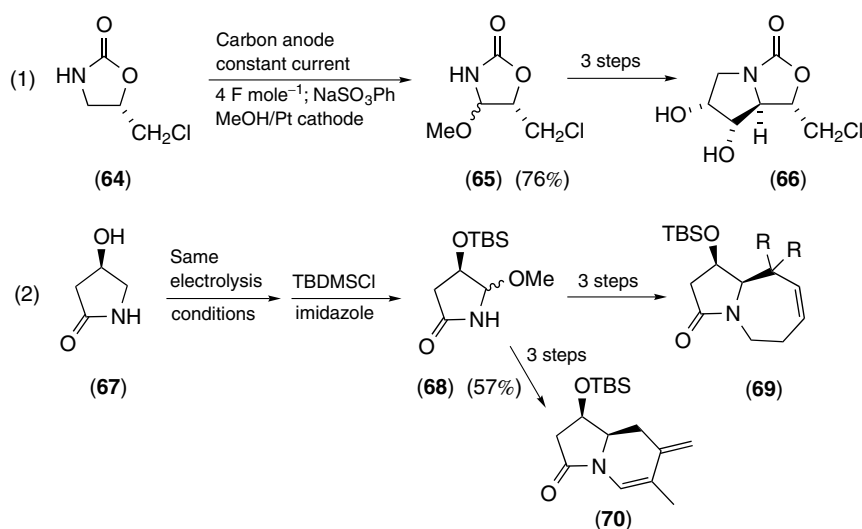
used to make enecarbamates in acyclic systems (Scheme 22) [51]. The oxidation reactions were typically done on a 6-g scale. The desired enecarbamate products were then formed using a base-catalyzed elimination of the methoxy group. In this work, the enecarbamate products were subsequently hydroborated in order to form  $\beta$ -hydroxy carbamates.

In addition to elimination reactions, the methoxylated amide products from electrolysis reactions have been treated with a variety of nucleophiles [47]. In recent studies, these efforts have been utilized to expand the chiral pool of starting materials available to synthetic chemists. For example, consider the reactions illustrated in Scheme 23 [52, 53]. In these efforts, Steckhan and coworkers have used the oxidation reaction to make a stable *N*- $\alpha$ -methoxy amide that was stored for future use. The oxidation of (64) is representative of this family of reactions [52]. The oxidation was performed at a carbon anode using constant

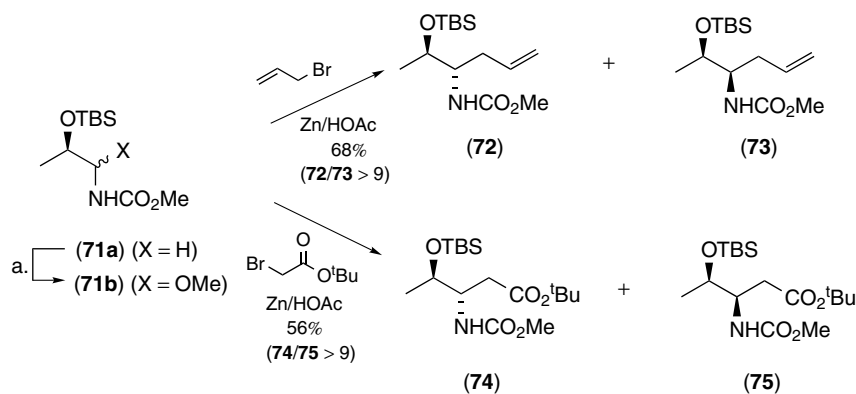
current conditions and enabled the synthesis of 12 g of product. The methoxylated amide obtained was used to generate precursors of pyrrolidine azasugar derivatives (66) [54]. Using the same conditions, the methoxylated amide (68) could be made on a 5-g scale [53]. Compound (68) was used as a precursor of the series of bicyclic lactam intermediates (69) and (70) [55].

Kise and coworkers have shown that organozinc reagents can be added to electrochemically derived *N*-acyliminium ions. These reactions have been used to synthesize  $\beta$ -amino acid derivatives (Scheme 24) [56].

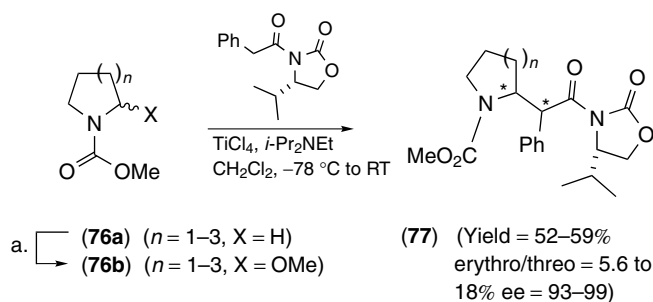
In another analogous set of reactions, Matsumura and coworkers have shown that electrochemically derived *N*-acyliminium ions can serve as electrophiles in asymmetric alkylation reactions (Scheme 25) [57]. In this case, the methoxycarbamate of a series of cyclic amines was oxidized in order to generate the *N*- $\alpha$ -methoxy carbamates,



**Scheme 23** Building blocks for the chiral pool by anodic  $\alpha$ -methoxylation of amides.



**Scheme 24** *N*-α-methoxylation of carbamates and further conversion of the methoxy products.



Reagents: a) Carbon anode, MeOH, Et<sub>4</sub>NBF<sub>4</sub>, 2.3 F mole<sup>-1</sup>, 85% (*n* = 2)

**Scheme 25** *N*-α-methoxylation of carbamates and diastereoselective substitution of the methoxy group.

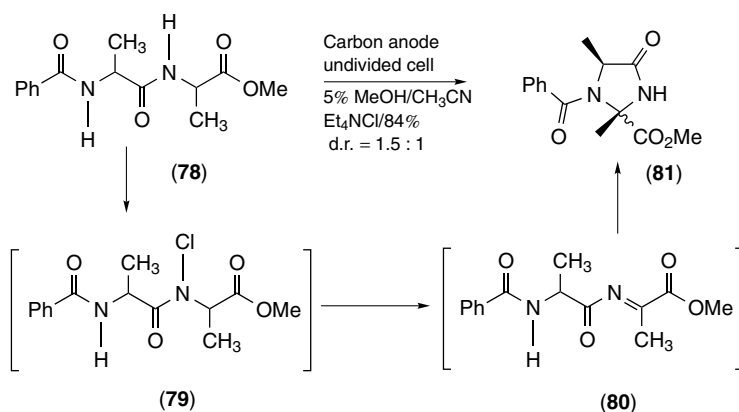
which were treated with a chiral enolate equivalent. The reactions resulted in the formation of enantiomerically enriched methylphenidate precursors (77).

#### 10.4.3

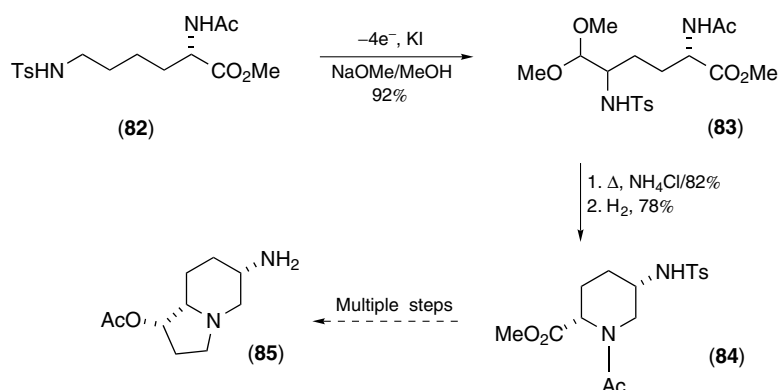
##### Mediated Reactions and the use of Electroauxiliaries

In addition to the direct oxidation of simple amides, indirect oxidations of amides have proven useful for synthesizing chiral starting materials. Such reactions are often employed when direct electrolyses

prove problematic. Typically, they utilize a halogen electrolyte that is oxidized at the anode surface to form a reactive “X<sup>+</sup>” species. The X<sup>+</sup> intermediate then reacts with the amide nitrogen. A subsequent elimination reaction generates the desired *N*-acyliminium ion. Reactions of this type have been used to functionalize amino acid derivatives (Scheme 26) [58], as well as to initiate oxidation – rearrangement sequences for building bicyclic amines (Scheme 27) [59]. In the second example, the initial oxidation of (82) led to the formation of an enamine. The enamine



**Scheme 26** Cl<sup>−</sup>-mediated *N*- $\alpha$ -substitution of a dipeptide.

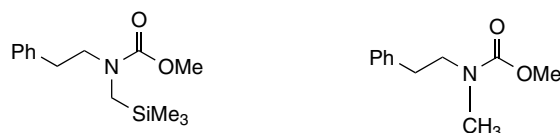


**Scheme 27** I<sup>−</sup>-mediated regioselective conversion of a diamide to an enamide with subsequent aziridine formation and methanolysis.

then underwent a second oxidation to form an alkoxy aziridine intermediate. Trapping with methanol afforded the product (**83**). Finally, compound (**83**) was subjected to an intramolecular reductive amination reaction before being converted into the bicyclic (**85**) using a multistep procedure.

In addition to using indirect oxidation reactions, electroauxiliaries have been used to circumvent problems with problematic amide oxidations. As mentioned in Sect. 10.2.2, an electroauxiliary is a group that is added to a molecule in order to reduce the oxidation potential of the

starting material [19–28]. The electroauxiliary works by donating electron density to the group being oxidized, raising the energy of the HOMO and lowering the oxidation potential. In the case of an amide oxidation, silicon groups can serve as very effective electroauxiliaries (Scheme 28) [60]. For example, the oxidation potential (measured using a Ag/AgCl reference electrode in a LiClO<sub>4</sub> in acetonitrile electrolyte solution) of (**86**) is half a volt lower than the oxidation potential of (**87**). In addition to lowering the oxidation potential of the substrate, the presence of the electroauxiliary

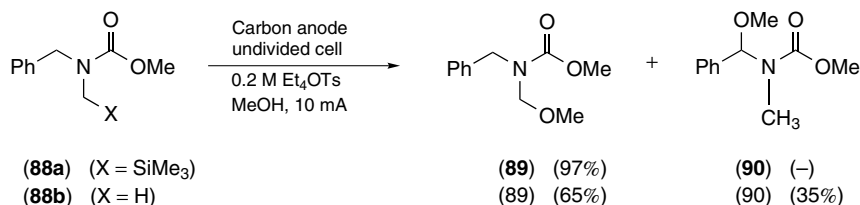
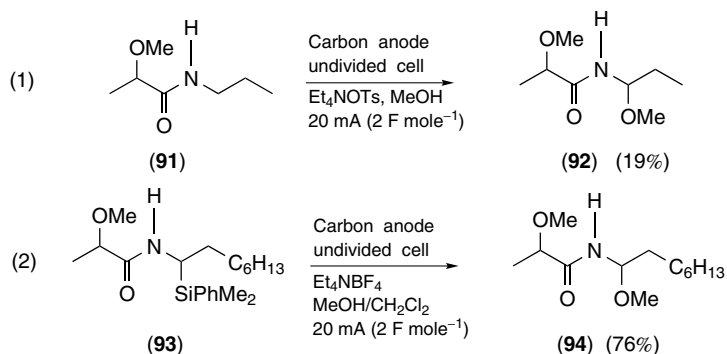
(86) ( $E_p = +1.45$  V (Ag/AgCl))(87) ( $E_p = +1.95$  V (Ag/AgCl))**Scheme 28** Lowering the oxidation potential of amide by an electroauxiliary.

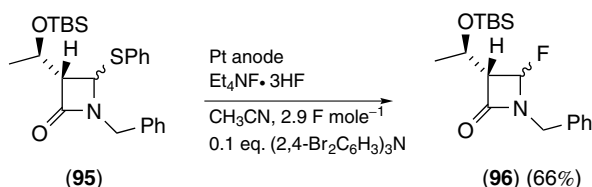
controls the formation of the subsequent reactive intermediate and thus channels the reaction toward the formation of a particular product. For example, the oxidation of (88a) led to the exclusive formation of the methoxymethyl-substituted amide (89) (Scheme 29) [60]. Without the electroauxiliary, a similar reaction originating from (88b) led to a mixture of products.

In a related set of reactions, Oku and coworkers have been investigating the anodic oxidation of acyclic amides having alkoxy groups on the carbon alpha to the amide carbonyl (91) [61]. The direct

oxidations of these substrates typically lead to poor yields of the methoxylated product (Scheme 30, Eq. 1) [61, 62]. However, when the amides are substituted with a silyl group on the carbon alpha to the amide nitrogen (93), the oxidation proceeds smoothly (Scheme 30, Eq. 2).

In addition to silicon, sulfur groups have been used as auxiliaries for amide oxidation reactions (Scheme 31) [63]. However, in these cases the mechanism of the reaction is different. The sulfur is oxidized to form a sulfur radical cation that is then eliminated from the molecule in order to

**Scheme 29** Regioselective *N*- $\alpha$ -methoxylation of amides using an electroauxiliary.**Scheme 30** Selective *N*- $\alpha$ -methoxylation of amides using an electroauxiliary.



**Scheme 31** Anodic substitution of an *N*- $\alpha$ -thiogroup with fluoride.

generate an *N*-acyliminium ion. In the example illustrated, the iminium ion was trapped with fluoride. For this example, a triarylamine was used as a mediator for this reaction in order to avoid passivation of the electrode surface by the liberated sulfur species [64].

## 10.5

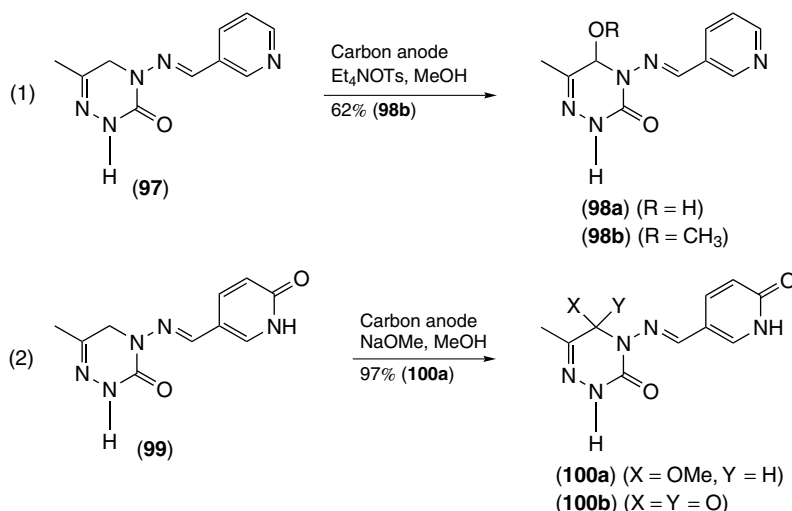
### The Application of Amide Oxidations to the Synthesis of Natural Products

#### 10.5.1

#### The Synthesis of Azathymine Derivatives

Because anodic amide oxidation provides an excellent method for functionalizing

molecules, it has proven to be a very useful tool for constructing natural products. For example, Hudlicky and coworkers have used an anodic amide oxidation in the synthesis of a series of azathymine derivatives [65]. In this work, the authors utilized the anodic amide oxidation reaction in order to circumvent problems with an anionic oxygenation reaction (Scheme 32). When substrate (**97**) was treated with *sec*-butyllithium and then oxygen, a 10 to 35% yield of the hydroxylated product (**98a**) was isolated. The reaction could not be run on a large scale due to safety issues. The authors recommend that the reaction be run on not more than 2 mmol of material due to the potential for explosion. For comparison, the anodic oxidation of (**97**)



**Scheme 32** Anodic *N*- $\alpha$ -methoxylation as superior route to azathymine derivatives.

led to a 62% isolated yield of the methoxylated product (**98b**). The anodic reaction could be run on a 20-g scale.

In a similar experiment, the anionic oxygenation of the substrate (**99**) failed to generate the desired hydroxylated product. In this case, a small-scale (721 mg) anodic oxidation reaction led to a 97% yield of the methoxylated product. For larger scale reactions, it was important to force the reaction to completion because (**99**) was difficult to remove from product (**100a**). The overoxidized material (**100b**) could be separated from the product by recrystallization. With this in mind, large-scale reactions of (**99**) (10–15 g) were pushed to a point where they led to 45 to 50% yields of the desired product along with 25% of the overoxidized (**100b**).

Both the methoxylated products could be hydrolyzed using citric acid in water/THF or KOH in water to afford the initially desired alcohol compounds. In this chemistry, it was clear that the electrochemical protocol offered distinct advantages over the more traditional chemical route.

#### 10.5.2

##### Octahydroisoquinolines

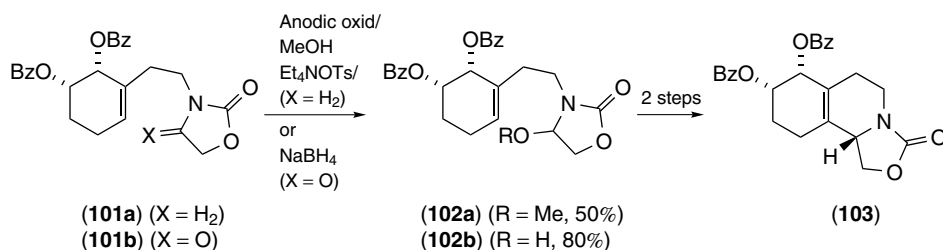
In addition to their work concerning the synthesis of azathymine derivatives, Hudlicky and coworkers have also explored

the synthetic utility of anodic amide oxidations in the synthesis of the octahydroisoquinolines needed for the synthesis of morphine [66]. In this case, an electrochemical route to the *N*- $\alpha$ -alkoxyamide (**102a**) was used in order to provide a complementary route to a reductive approach to (**102b**) originating from the imide (**101b**) (Scheme 33). The yield of the *N*- $\alpha$ -alkoxyamide obtained from the electrochemical route was not as high (50%) as the yield obtained using the reductive approach. However, the use of the anodic oxidation reaction did allow for flexibility in terms of when the alkoxy functionality was introduced into the molecule and did avoid the use of base-sensitive intermediates like imide (**101b**).

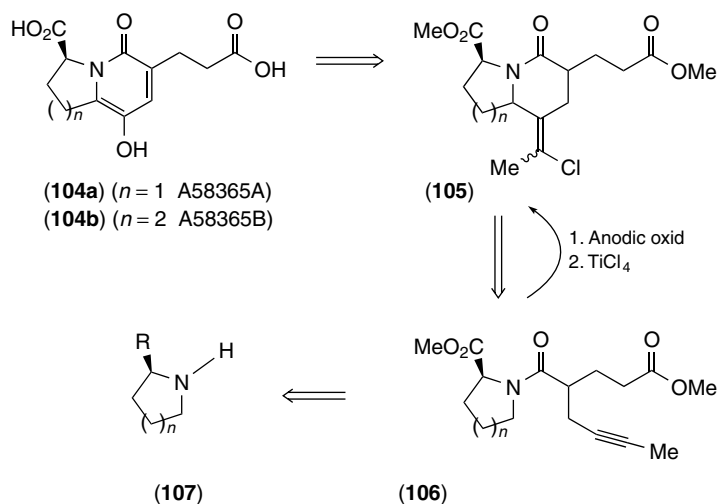
#### 10.5.3

##### ACE Inhibitors A58365A and A58365B

As seen in Scheme 33, the ability of anodic amide oxidations to functionalize amines opened up the possibility for developing annulation strategies for fusing rings onto amines and amino acid derivatives [67–69]. This approach was used to synthesize the ACE inhibitors A58365A and A58365B [70]. As illustrated in Scheme 34, these two natural products differed only in the size of their nonaromatic rings. For this reason, it was suggested that nearly identical routes



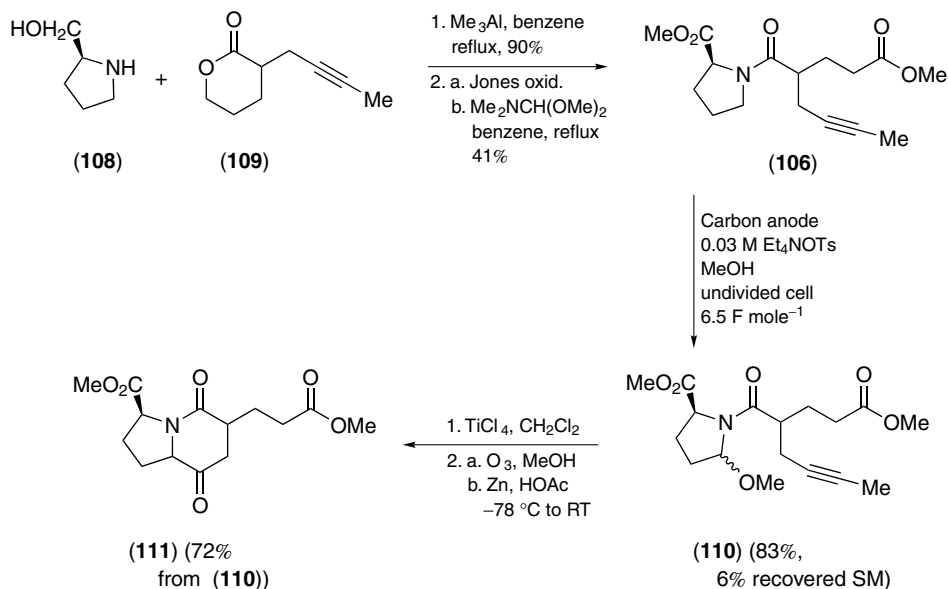
**Scheme 33** Anodic *N*- $\alpha$ -methoxylation *en route* to octahydroisoquinolines.



**Scheme 34** Retrosynthesis of ACE inhibitors using an *N*- $\alpha$ -methoxylation as key step.

could be used to make the two molecules if a procedure was found for annulating the aromatic ring onto the starting amine. For A583655A, this was accomplished by first converting prolinol into the substituted

proline derivative (109) (Scheme 35). The carbon  $\alpha$  to the nitrogen was then functionalized using a carbon anode, a 0.03 M  $\text{Et}_4\text{NOTs}$  in methanol electrolyte solution, and an undivided cell. After  $6.5 \text{ F mole}^{-1}$ ,



**Scheme 35** Synthesis of an ACE inhibitor using an *N*- $\alpha$ -methoxylation as key step.



an 83% isolated yield of the methoxylated amide was obtained. Treatment of this product with  $\text{TiCl}_4$  then afforded a cyclized product (**105**) that upon ozonolysis led to the formation of the bicyclic amide derivative (**111**). The bicyclic amide was converted into A58365A in four steps.

Using an identical process, the pipecolic acid derivative (**112**) was converted into a bicyclic amide derivative as shown in Scheme 36. In this case, the methoxylated amide proved to be unstable in the crude electrolysis reaction and was taken directly into the cyclization–ozonolysis sequence. A 74% yield of the bicyclic ketone was obtained over three steps. Compound (**114**) was converted into A58365B demonstrating that the anodic oxidation reaction allowed for rapid access to both natural products.

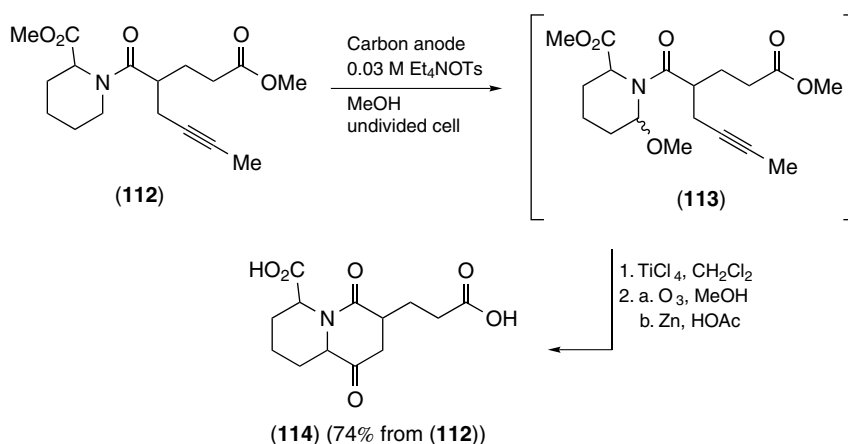
#### 10.5.4

##### (3*R*, 5*R*, 8*aR*)-3-*n*-Butylindolizidine

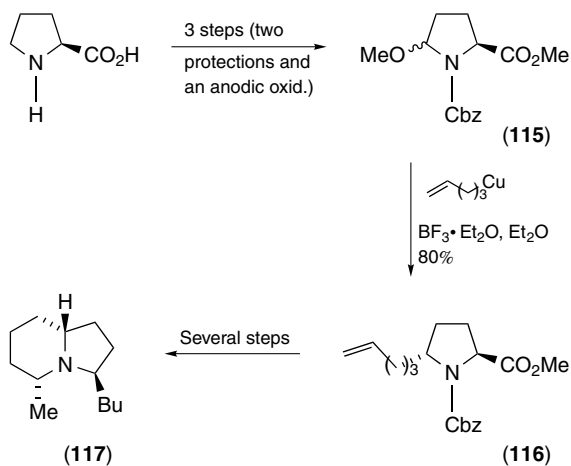
The functionalization of proline has been used to synthesize natural products from the indolizidine alkaloid family [71]. To this end, Lhommet and coworkers utilized

an anodic oxidation reaction to form the methoxylated carbamate (**115**) from proline (Scheme 37). This transformation was done by protecting the acid as a methyl ester, protecting the proline amine with a Cbz group, and then utilizing an anodic amide oxidation to methoxylate the  $\text{C}_5$  position. The three-step procedure led to a 69% overall yield of (**115**). The methoxylated amide was then treated with a cuprate reagent in the presence of  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  in order to produce (**116**). As with other cuprate additions to *N*-acyliminium ions, the stereochemistry obtained for the reactions placed the incoming nucleophile trans to the methyl ester [72–74]. The rationale for this stereochemistry is that the methyl ester complexes a cuprate along with the pi-system of the iminium ion. This effectively blocks the face of the iminium ion that is syn to the methyl ester (Fig. 1), and forces the nucleophile to approach from the opposite face.

Once the functionalized proline (**116**) was in place, it could be converted to the desired indolizidine ring system using several steps, which included a Wacker oxidation, to generate a methyl ketone

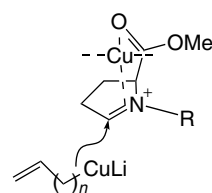


**Scheme 36** Synthesis of an ACE inhibitor using an *N*- $\alpha$ -methoxylation as key step.



**Scheme 37** Synthesis of an indolizidine precursor using an *N*- $\alpha$ -methoxylation.

**Fig. 1** Transition state for the cuprate addition.



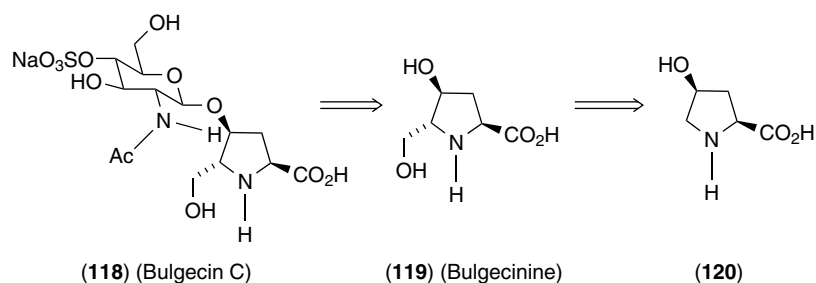
and a subsequent intramolecular reductive amination reaction.

#### 10.5.5

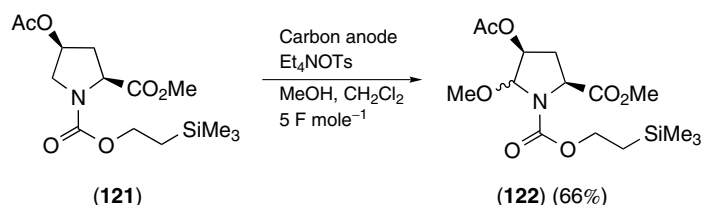
##### Bulgecin C

Anodic oxidation reactions have also been used to functionalize substituted proline derivatives. For example, an anodic amide

oxidation was employed in the synthesis of Bulgecin C (Scheme 38) [75]. In this work, a 4-hydroxyproline derivative was functionalized at C<sub>5</sub> using the electrochemical methodology (Scheme 39). It was found that both the group at the four-position of the ring and the protecting group on the nitrogen had an impact on the oxidation reaction. In the best case, the 4-hydroxy



**Scheme 38** Retrosynthesis of Bulgecinine.



**Scheme 39** Anodic  $N$ - $\alpha$ -methoxylation as key step to a Bulgecinine precursor.

group was protected as an acetate and the nitrogen of the proline ring protected with a trimethylsilylcarboxy group. The anodic oxidation reaction then afforded a 66% isolated yield of the methoxylated product. The methoxylated product was converted into bulgecinine (119) in five steps.

A similar series of reactions have been studied by Thaning and Wistrand [73, 76]. In these experiments, the acetoxy-protected proline derivatives were oxidized using constant current conditions, a platinum anode, tetrabutylammonium tetrafluoroborate as electrolyte, and a methanol solvent (Scheme 40).

#### 10.5.6

##### ( $\pm$ )-Anatoxin A

Shono and coworkers have used a pair of amide oxidation reactions to synthesize the naturally occurring alkaloid Anatoxin A [77]. As illustrated in Scheme 41, the synthesis used the first anodic amide oxidation to functionalize

the methoxycarbamate protected proline (125) and the second to initiate the formation of the bridged bicyclic ring skeleton. In a reaction typical of anodic amide oxidations, the second methoxylation reaction occurred regioselectively at the least-substituted carbon.

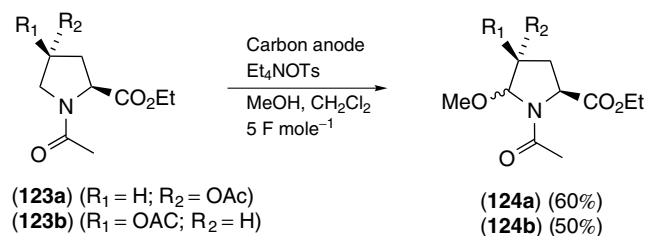
#### 10.6

##### The Synthesis of Constrained Peptidomimetics

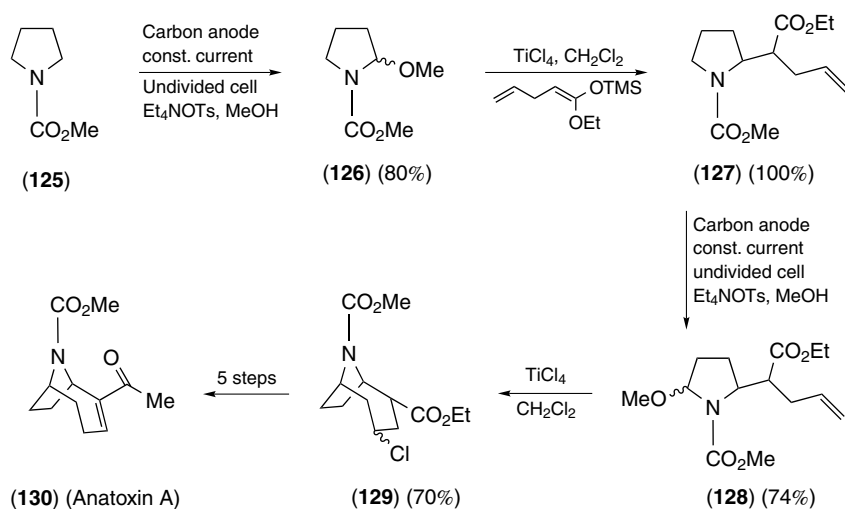
#### 10.6.1

##### Introduction

In many of the direct amide oxidations illustrated above, the reactions were used to functionalize amino acid derivatives. Because of the reactions effectiveness in this area, anodic electrochemistry has proven to be an outstanding tool for building constrained peptidomimetics [78–81]. In this work, a series of constrained peptide analogs were designed by replacing spatially close hydrogens in a proposed



**Scheme 40** Anodic  $N$ - $\alpha$ -methoxylation as key step to a Bulgecinine precursor.



**Scheme 41** A double  $N$ - $\alpha$ -methoxylation for the synthesis of the  $\alpha,\alpha'$ -disubstituted proline: Anatoxin.

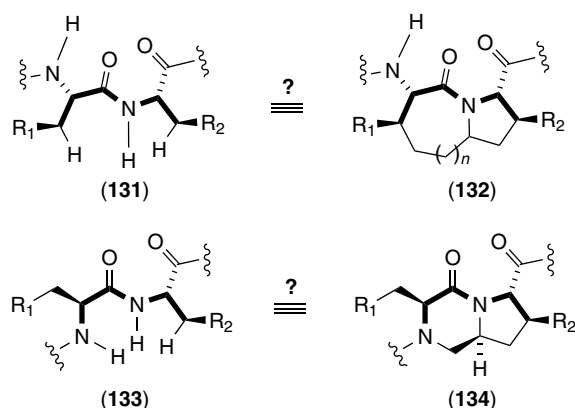
active peptide conformation with carbon-based bridges. This resulted in molecules that fixed both the peptide backbone conformation and the amino acid side chains in place with a polycyclic ring skeleton. Two such constrained analogs are illustrated in Scheme 42. While analogs of this nature are simple to design, they can be difficult to synthesize. How does one “simply” replace spatially close hydrogens with carbon bridges in a real molecule

in the lab? The key is to recognize that such transformations require the selective oxidation of the initial amino acid starting material. Therefore, they are ideally suited for use in anodic electrochemistry.

#### 10.6.2

##### The Synthesis of Constrained TRH Analogs

The thyrotropin-releasing hormone (TRH) is the hypothalamic tripeptide that releases



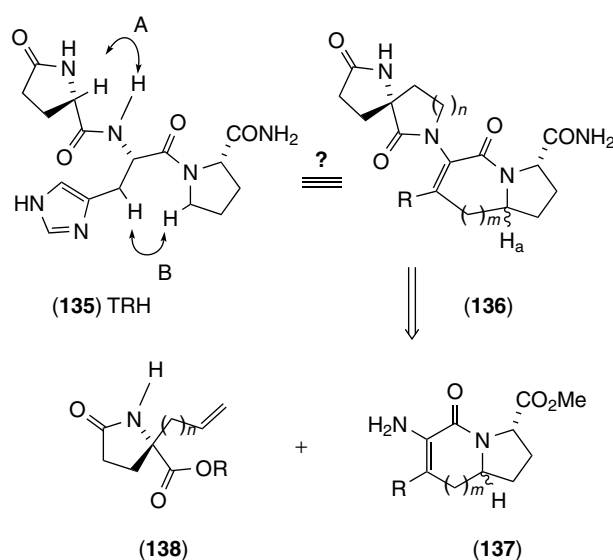
**Scheme 42** Constrained peptidomimetics.

the thyroid-stimulating hormone from the anterior pituitary gland [82, 83]. In addition to this endocrine behavior, TRH displays effects in the brain, blood, spinal cord, and gut. Because of its biological relevance, a large effort has been made to probe conformation of TRH responsible for binding to its endocrine receptor. As part of this effort, the constrained analogs (**136**) of TRH illustrated in Scheme 43 were designed [84, 85]. The retrosynthesis of the constrained analogs called for the initial synthesis of two building blocks, each of which could be envisioned as arising from an initial amino acid starting material by the use of an anodic amide oxidation. The first building block (**137**) would be used to constrain the two right-hand amino acids and would be made by using an anodic amide oxidation to functionalize a proline derivative. The second building block (**138**) would be used to constrain the pyroglutamate portion of the ring and would be made by using

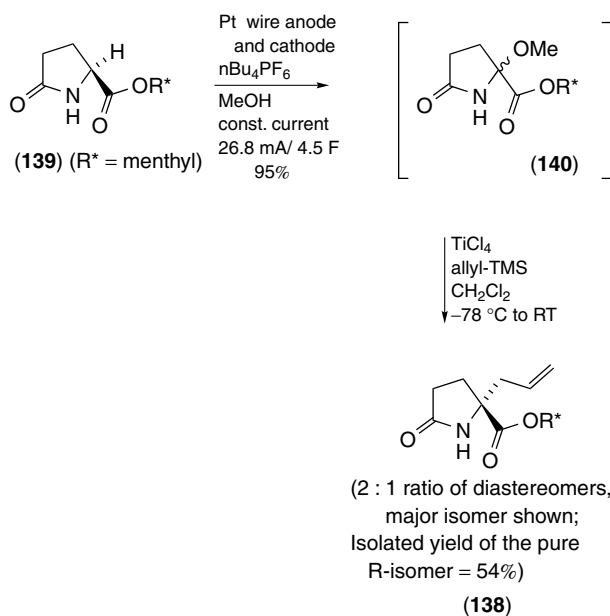
an anodic oxidation to functionalize a pyroglutamate derivative.

Both anodic oxidation reactions proceeded well. As illustrated in Scheme 44, an anodic methoxylation of menthyl pyroglutamate followed by the trapping of an incipient *N*-acyliminium ion with allylsilane in the presence of Lewis acid led to (**138**) [86]. While the stereoselectivity of this reaction was not high, the major product from the reaction could be fractionally crystallized from hexane and the route used to conveniently prepare (**138**) on a scale of 10 g. In this case, a platinum wire anode was used in order to keep the current density high. This was required because of the high oxidation potential of the secondary amide relative to the methanol solvent used in the reaction.

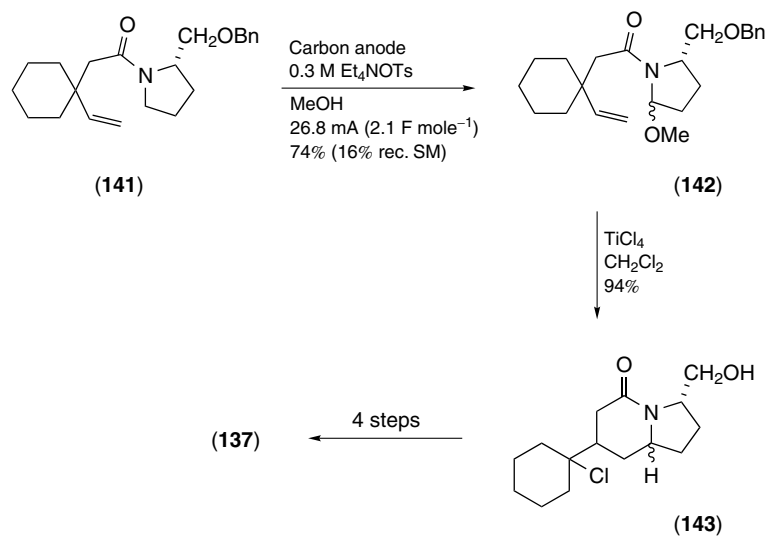
The anodic oxidation utilized in the synthesis of (**137**) proved equally effective. In this example, the electrochemical step was used to functionalize the amide substrate (**141**) (Scheme 45) [87, 88]. A



**Scheme 43** Retrosynthesis of constrained TRH analogs.



**Scheme 44** Synthesis of a TRH analog building block by anodic  $N$ - $\alpha$ -methoxylation.



**Scheme 45** Synthesis of a TRH analog building block by anodic  $N$ - $\alpha$ -methoxylation.

74% isolated yield of the methoxylated product was obtained along with 16% of the recovered starting material. Treatment of the methoxylated product

with titanium tetrachloride and methylene chloride then led to a cyclization – rearrangement sequence that generated the bicyclic amide (143). Intermediate

(143) was converted into the desired peptide building block in four steps. Once the building blocks were available, the fully constrained analogs (136,  $n = m = 1$ ) were synthesized in a straightforward fashion [89].

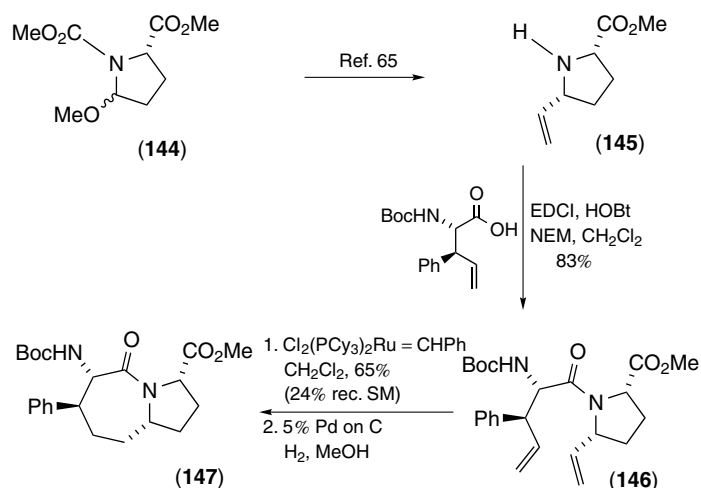
### 10.6.3

#### Sequential Amide Oxidation – Olefin Metathesis Strategies

While the sequence to synthesize (137) as outlined above proved effective for obtaining initial biological testing data on the analogs, it suffered from several major weaknesses. First, the oxidation reaction did not allow the presence of either an oxygen or a nitrogen functional group on the carbon alpha to the amide carbonyl. The presence of such a group stopped the electrolysis, presumably because the oxidation potential of the substrate became higher than the methanol solvent. The result was the need to functionalize the molecule late in the synthesis following construction of the bicyclic ring skeleton. Such an approach made it difficult to build bicyclic

analogs with stereocenters in the lactam ring. Second, the cyclization reaction to form (143) led to a mixture of stereoisomers at the bridgehead carbon. For the purpose of initially screening analogs this was fine. Both isomers were desired. But once a biological preference was found for the isomer having an *R*-configuration at the bridgehead, a more selective route became highly desirable. Finally, the rearrangement reaction encountered during the synthesis of (143) rendered it difficult to make seven-membered ring lactam analogs. Such analogs were needed in order to reintroduce a degree of flexibility into the analogs.

In order to address these issues, a strategy for effecting the anodic oxidation reaction earlier in the synthesis was designed. This plan called for functionalizing a proline derivative and then using the resulting methoxylated amide to introduce a vinyl group to the carbon alpha to the nitrogen (Scheme 46) [72–74]. The resulting vinyl proline derivative would be coupled to a second vinyl-substituted amino acid building block and an olefin



**Scheme 46** Sequential amide oxidation–olefin metathesis strategy.

metathesis reaction used to complete the synthesis of the building block [90–93]. In the synthesis illustrated, methyl proline was protected as a carbamate and then oxidized at an anode to form starting material (144). This starting material was converted into a vinyl-substituted amino acid derivative (145) [94–96] that was then coupled to a known carboxylic acid [97] in order to form diene (146). Olefin metathesis followed by hydrogenation of the double bond resulted in the synthesis of the desired building block (147). This route proved very effective and has now been used to synthesize a series of constrained TRH analogs [98].

#### 10.6.4

#### Substance P Analogs and an Approach to Piperazinone Rings

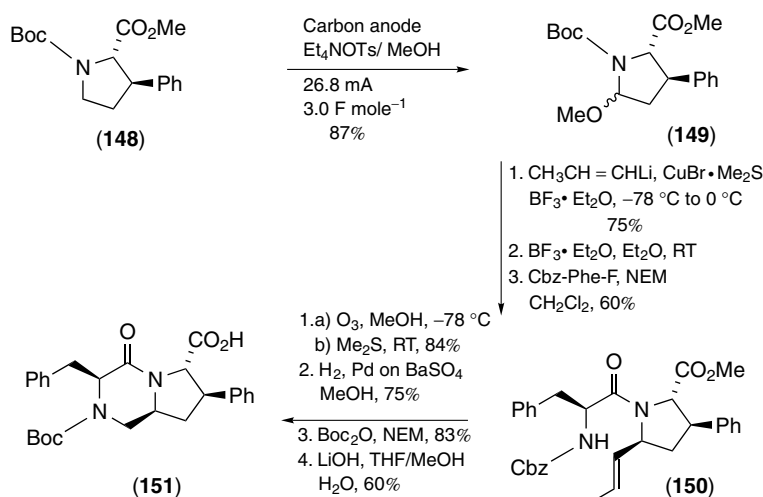
The use of an anodic amide oxidation to introduce a vinyl group to the C<sub>5</sub> position of a proline derivative has proven to be an effective strategy for building other constrained peptidomimetics as well. For example, a variation on the approach has

been utilized to synthesize the second family of analogs illustrated in Scheme 42 (134) [99, 100]. Analogs of this family were designed as mimics for the Phe<sup>7</sup>Phe<sup>8</sup> region of substance P [101–104]. In this work, an anodic oxidation of the known 3-phenyl-substituted proline [105] methyl ester led to a methoxylated amide (149) that was treated with a cuprate reagent, deprotected, and coupled to a Cbz-protected phenylalanine in order to afford (150) (Scheme 47). Ozonolysis and a reductive amination reaction led to the formation of a bicyclic derivative that was subsequently converted into a building block for solid-phase peptide synthesis (151) by reprotecting the nitrogen with a *t*-Boc group and saponifying the methyl ester with lithium hydroxide.

#### 10.7

#### Amide Oxidations and the Construction of Combinatorial Libraries

In addition to demonstrating the utility of anodic amide oxidations as a tool for



**Scheme 47** Piperazinone ring by *N*-α-methoxylation of a proline derivative.

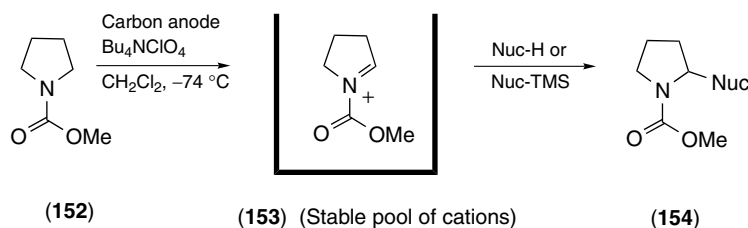


constructing complex natural products and peptidomimetics, recent work has been focusing on developing the reaction as a tool for synthesizing libraries of molecules. Yoshida and coworkers have recently reported that anodic amide oxidation can be used to make a stable “cation pool” of iminium ions (Scheme 48) [106]. Once generated, the cation pool was directly trapped with nucleophiles in order to generate new carbon–carbon bonds. This development was interesting because it has the potential to overcome many of the synthetic problems that can complicate the direct trapping of oxidatively generated electrophiles with nucleophiles. Since cationic intermediates are generally not stable in oxidation conditions, the nucleophile for such a reaction normally needs to be present during the oxidation so that it can trap the electrophile as it is generated. This creates problems since most nucleophiles are also sensitive to oxidation. For example, an allylsilane oxidizes at a potential lower than that of an amide. Therefore, the oxidative generation of an iminium ion in the presence of an allylsilane nucleophile is not possible. It was for this reason that the amide oxidations, described in the sections above, were normally done in a methanol solvent. The solvent trapped the iminium ion affording an *N*- $\alpha$ -alkoxyamide product that was isolated. In the second step, the iminium

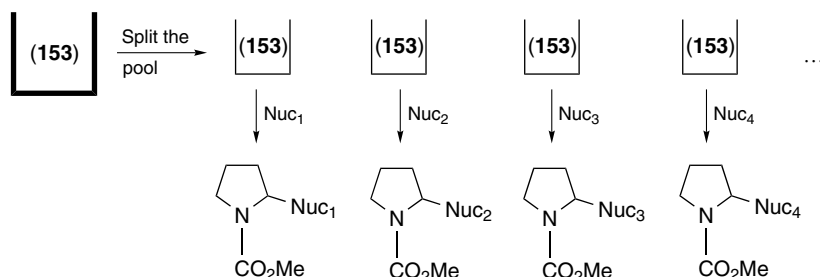
ion was regenerated in the presence of the nucleophile with the use of an acid. With the use of the cation pool method, both, the need for methanol trapping and the need for regenerating the iminium ion with a Lewis acid can be avoided. The oxidation reaction is conducted at a low temperature using dichloromethane as the solvent. No nucleophile is present. Under these conditions, the *N*-acyliminium ion is stable; even to temperatures up to zero degrees. Adding the nucleophile to the cation pool then completes the reaction. Allylsilanes, 1,3-dicarbonyl equivalents, and electron-rich aromatic rings have all been used as nucleophiles for this process.

Recently, Yoshida and coworkers demonstrated that the cation pool method can be used to make available *N*-acyliminium ion intermediates for parallel synthesis approaches to molecular libraries [106]. In this work, the cation pool was split into separate flasks following the electrolysis reaction. Different nucleophiles were then added to each flask in order to form a series of products (Scheme 49).

Direct electrochemical amide oxidation reactions have also been employed in parallel synthesis using a spatially addressable electrochemical platform [107]. In this work, an electrolysis platform was set up so that 16 electrochemical reactions could be run in parallel at the same time. The cells were set up in a 4 by 4 array in which each cell was equipped with a



**Scheme 48** Cation pool method for *N*- $\alpha$ -substitution.



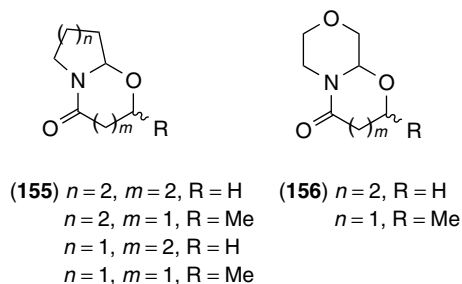
**Scheme 49** Parallel synthesis for *N*- $\alpha$ -substituted proline derivatives.

stainless steel cathode and a graphite rod anode. The cathodes were welded into a stainless steel plate that then served as a common terminal for the connection to the current source. The graphite electrodes served as the working electrodes and were isolated from each other and the cathodes with the use of a Teflon plate. The 16 anodes were then connected in a parallel circuit so that a constant current reaction could be performed in each cell. In a typical experiment, one of four carbamates was added to each cell along with one of four different alcohols. The reaction cells were charged with a 0.5 M Bu<sub>4</sub>NBF<sub>4</sub> in 1 : 1 acetonitrile/alcohol electrolyte solution, and then a constant current applied until 2.0 F mole<sup>-1</sup> of electricity had been passed through each cell. The reactions afforded the 16 *N*- $\alpha$ -alkoxyamides in yields that ranged from 61 to 95%. In another experiment,

trapping the incipient *N*-acyliminium with an intramolecular alcohol nucleophile generated a small library of bicyclic amide products (Scheme 50). The intramolecular reactions proceeded in yields of 80 to 95%.

## 10.8 Conclusions

The anodic oxidation of nitrogen compounds provides an excellent example of how the use of electrochemistry can alter the way in which we view the syntheses of complex organic molecules. Currently, there are two main thrusts to these efforts. First, the oxidation reactions allow for a reversal in the polarity of known functional groups, and therefore molecules with nucleophilic nitrogens can be converted into electrophiles. Second, the oxidation reactions allow for the selective



**Scheme 50** Electrogenenerated library of bicyclic amides.

functionalization of amine and amino acid starting materials. The addition of functionality to these molecules enables their use as building blocks for constructing a variety of more complex structures. The result has been the simplified construction of synthetically useful chiral starting materials, biologically relevant natural products, and conformationally constrained peptidomimetics.

Finally, it is important to note that many of the anodic reactions discussed above cannot be duplicated with traditional chemical oxidants. For this reason, the anodic oxidation of nitrogen-containing compounds represents a powerful class of reactions that has the potential to open up entirely new synthetic pathways to complex molecules. From the work already accomplished, it is clear that employing such an approach is both feasible and beneficial, and that the ability to selectively oxidize amines and amides is a valuable "tool" for any synthetic chemist to have at their disposal.

### Acknowledgment

This chapter is dedicated to the memory of Professor Eberhard Steckhan (9/12/43–2/10/2000).

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## 11 Electrosynthesis of Natural Products, Fine Chemicals, and Pharmaceuticals

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### 11.1 Introduction

The utility of the electrode to promote bond formation between functional groups of the same polarity provides researchers with an opportunity to explore the chemistry of interesting intermediates, and synthetic strategies that are based on their intermediacy [1, 2]. Reduction at a cathode, or oxidation at an anode, renders electron-poor sites rich, and electron-rich sites, poor. For example, the reduction of an  $\alpha$ ,  $\beta$ -unsaturated ketone leads to a radical anion in which the  $\beta$ -carbon possesses nucleophilic, rather than electrophilic character. Similarly, oxidation of an enol ether affords a radical cation wherein the  $\beta$ -carbon displays electrophilic, rather than its usual nucleophilic behavior [3].

Electrochemical processes are conducted under what one refers to as either “constant current” (CC) or “controlled potential” (CP) conditions [1, 2]. The constant current electrolysis (CCE) is often preferred; it is less expensive to implement since it does not require the acquisition of a potentiometer, is readily amenable to scale-up, and reaction times are often short. The disadvantage is that in order to maintain a constant current, the potential changes, become more negative or positive, depending on whether

a reduction or an oxidation is being investigated. Controlled potential methods allow one to set the potential to a value corresponding to that of the electrophore (the unit undergoing redox chemistry), in much the same way that a light filter allows one to selectively irradiate a particular chromophore in a photochemical process. Just as one should record an ultraviolet (UV) spectrum to determine the appropriate filter prior to conducting a photolysis, one ought to obtain the analogous cyclic voltammogram (CV) of the material to be studied electrochemically. The voltammogram describes how the current changes as a function of potential and allows one, therefore, to select the potential best suited to the redox transformation of interest.

The following presentation focuses upon redox processes that lead to the production of natural products, fine chemicals, and pharmaceuticals. Rather than providing an exhaustive coverage of the literature, our intent is to provide the reader with the general flavor of the transformations that can be conducted as well as their utility within the context of organic synthesis. Our coverage merely skims the surface of this rich and fertile area of investigation. Excellent treatises and reviews exist, and the interested reader is referred to them for greater detail [1–12].



## 11.2 Reduction

As indicated, the reduction of an electron-deficient alkene renders a formally electropositive carbon center nucleophilic. The fields of electrohydrodimerization and electrohydrocyclization are a direct consequence of this realization [1, 2]. The former corresponds to the dimerization of an electron-deficient alkene *via* a process that couples the electron-deficient  $\beta$ -carbons of the substrate. Overall, two electrons and two protons are consumed. Electrohydrocyclization is the intramolecular counterpart of this process.

### 11.2.1 Electrohydrocyclization

This transformation is undoubtedly the best-known cathodically initiated cyclization. Substrates consist of two electron deficient alkenes tethered to one another. As illustrated in Table 1, the methodology is exceptionally useful for the construction of three-, five-, and six-membered

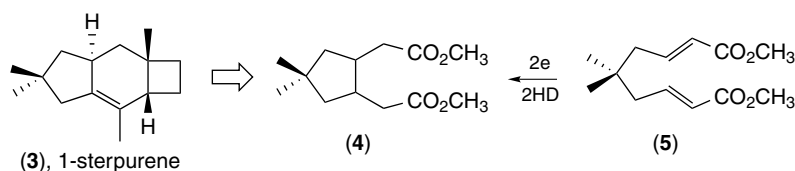
rings, but not for rings of sizes seven and eight [13, 14].

The utility of the electrohydrocyclization reaction to assemble natural products remains essentially untapped. It has, however, been used in the synthesis of the tricyclic sesquiterpene 1-sterpurene (3), the presumed causative agent of the so-called “silver leaf disease” that affects certain species of scrubs and trees in Western North America [15]. As is illustrated in Scheme 1 and in Table 2, the electrohydrocyclization reaction of bisenoate (5) was used to create the five-membered ring of the natural product.

The reaction was investigated under a variety of conditions. As noted in Table 2, both the yield and stereo-selectivity varied in response to changes in the electrode and proton donor (HD). Environmental factors clearly make the use of a glassy carbon electrode preferable to mercury or lead electrodes. Yields range from 58 to 87%, and the stereo-selectivity from a low of 2.6 : 1 *trans/cis* (6a/6b) to as high as 14.8 : 1 when the reaction is conducted in the presence of cerium (III) chloride.

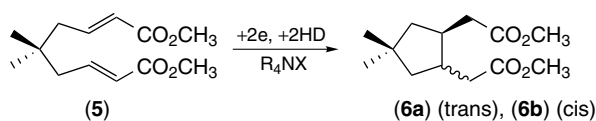
**Tab. 1** Ring sizes accessible using electrohydrocyclization

$n$	Ring size	$R$	$X$	Yield (%)
1	3	Et	CO <sub>2</sub> Et	98
2	4	H	CO <sub>2</sub> Et	41
2	4	H	CN	15
3	5	H	CO <sub>2</sub> Et	~quant
4	6	H	CO <sub>2</sub> Et	90
5	7	H	CO <sub>2</sub> Et	~10
6	8	H	CO <sub>2</sub> Et	0



**Scheme 1** Electrohydrocyclization en route to 1-sterpurene.

**Tab. 2** Effect of proton donor and electrode material



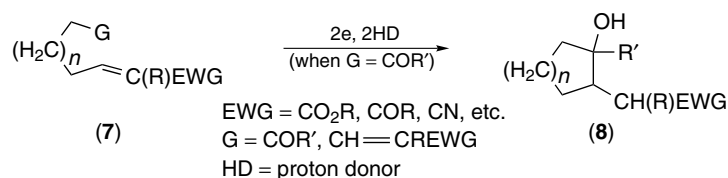
Electrode	Proton source	trans/cis ratio	Yield (%)	Additive
Hg	AcOH, H <sub>2</sub> O	2.6 : 1	82–87	none
Hg	CH <sub>2</sub> (CO <sub>2</sub> Et) <sub>2</sub>	7.5 : 1	66	none
Glassy carbon	CH <sub>2</sub> (CO <sub>2</sub> Et) <sub>2</sub>	7.1 : 1	73	none
Cu	CH <sub>2</sub> (CO <sub>2</sub> Et) <sub>2</sub>	11.6 : 1	58	none
Hg	CH <sub>2</sub> (CO <sub>2</sub> Et) <sub>2</sub>	14.8 : 1	73	CeCl <sub>3</sub>

### 11.2.2

#### Electroreductive Cyclization

Many reductive cyclizations, including many of those that are not initiated electrochemically, correspond to variations on the electrohydrocyclization theme. The so-called electroreductive-cyclization reaction, for example, involves cyclization between the  $\beta$ -carbon of an electron-deficient alkene and an aldehyde or ketone tethered to it, to form a new  $\sigma$ -bond between these formally electron deficient centers (Scheme 2).

Like the electrohydrodimerization and electrohydrocyclization reactions, this process also requires the consumption of two electrons and two protons. It has been shown to occur *via* a sequence consisting of electron transfer followed by a rate-determining protonation of the resulting radical anion, addition of a second electron to generate a carbanion, cyclization of the carbanion onto the carbonyl acceptor unit and the addition of the second proton [16]. Carbon acids like dimethyl malonate and malononitrile are often used as a proton source. The course of this and other



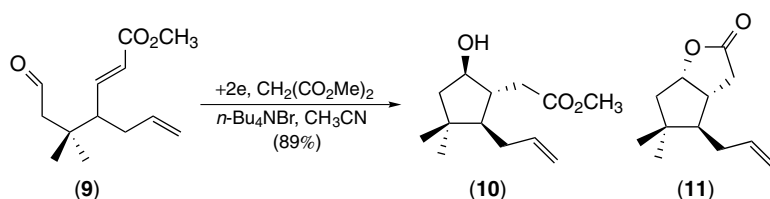
**Scheme 2** General reaction of an electroreductive cyclization.

electrochemical reactions is conveniently monitored using a variety of standard techniques including coulometry. The latter provides a straightforward means of determining when the theoretical amount of charge has been consumed. For each of the reactions discussed thus far, this corresponds to 2 Faradays of charge per mol of substrate.

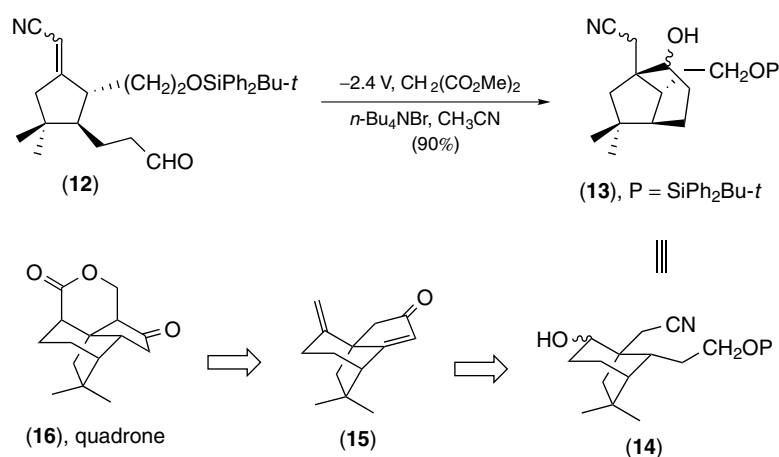
A demonstration of the utility of the electroreductive cyclization reaction is provided by the formal total synthesis of the antitumor agent quadrone (**16**, Scheme 4) [17]. The first stage of the synthesis involved a controlled potential reduction of (**9**) in the presence of dimethyl malonate as the proton donor. An efficient cyclization ensued, leading to the formation of the  $\gamma$ -hydroxy ester (**10**)

and lactone (**11**) in a combined yield of 89% (Scheme 3).

Adducts (**10**) and (**11**) were each converted to the unsaturated nitrile (**12**) that is shown in Scheme 4. Electroreductive cyclization of (**12**) presented a major challenge given the highly hindered nature of the fully substituted  $\beta$ -carbon of the  $\alpha, \beta$ -unsaturated subunit. Many organic transformations fail to occur when presented with a similarly crowded environment. Thus, it is significant that the controlled potential electroreductive cyclization reaction of (**12**) afforded a 90% isolated yield of the requisite [3.2.1] adduct (**13**). Steric factors clearly did not hinder this reaction, a result that is presumed to be generalizable to other electroreductive cyclizations. Cycloadduct (**13**) was



**Scheme 3** Electroreductive cyclization to  $\gamma$ -hydroxyester and a lactone.



**Scheme 4** Steric factors do not prohibit electroreductive cyclization.

subsequently converted to enone (15) [18], a point that converged with an existing synthesis of quadrone (16).

### 11.2.3

#### Reductive Cyclization of Ketonitriles

Ketones tethered to nitriles also function admirably as substrates in reductive cyclizations [19, 20]. As illustrated by the example portrayed in the equation in Table 3, reduction leads to the formation of an  $\alpha$ -ketol (18) as the major product. That this functionality is present in many natural products and that it can be constructed by coupling two very common functional groups, adds interest to the transformation [21]. Both controlled potential and constant current conditions have been utilized. Of the electrodes examined (Ag, Cd, Pb, Zn, C-fiber, and Sn), tin was generally

the most effective. Using it, for example, allowed the controlled potential reduction of (17) to proceed in a respectable 76% yield. As illustrated in Table 3, the preference for ketol formation drops when carried out at constant current or without using a diaphragm to separate the anode and cathode chambers of the electrolysis cell.

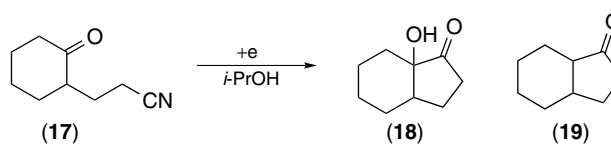
The transformation has been employed extensively in the preparation of precursors to a number of natural products including dihydrojasnone, rosaprostol, valeranone, and hirsutene [20]. Its use en route to guaiazulene (23) is illustrated in Scheme 5.

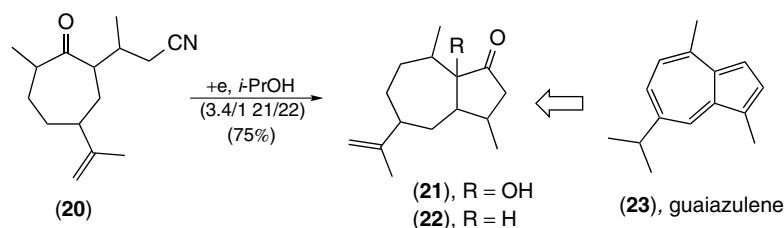
### 11.2.4

#### Reductive Cyclization of Pyridinium Salts

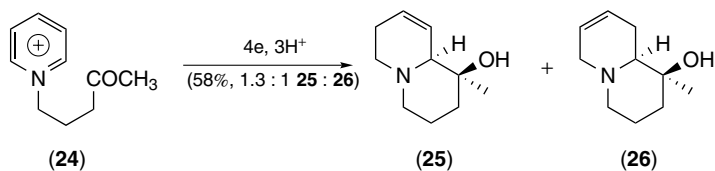
Pyridinium salts tethered to ketones also undergo reductive cyclization (Schemes 6

Tab. 3 Reductive cyclization of ketonitriles

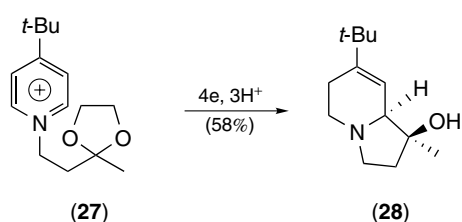
		
Conditions	$F \text{ mol}^{-1}$	Yield (% 18, % 19)
<i>i</i> -PrOH, 25 °C, −2.8 V (SCE; Sn) divided cell, ceramic diaphragm	3	76, 2
<i>i</i> -PrOH, 25 °C, constant current of 0.2 A, divided cell, ceramic diaphragm	3.5	63, 16
<i>i</i> -PrOH, 25 °C, −2.8 V (SCE; Sn) divided cell, no diaphragm	4	65, 11



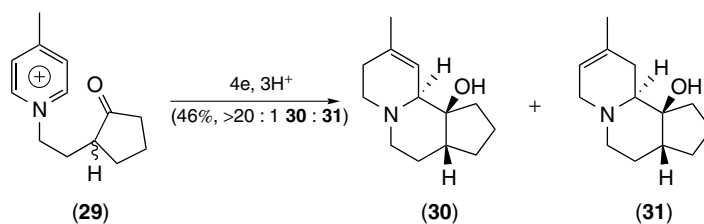
Scheme 5 Reductive cyclization of ketonitriles an route to guaiazulene.



**Scheme 6** Reductive cyclization of an oxoalkyl pyridinium salt to a quinolizidine.



**Scheme 7** Reductive cyclization of an oxoalkyl pyridinium salt to an indolizidine.



Hg (constant current of  $4.2 \text{ mA cm}^{-2}$ , charge  $8 \text{ F mol}^{-1}$ ), 10%  $\text{H}_2\text{SO}_4$ , 0.2 M in pyridinium salt,  $20^\circ\text{C}$ )

**Scheme 8** Reductive cyclization of an oxoalkyl pyridinium salt to a quinolizidine.

to 8) [22]. The reaction provides a convenient, diastereo-selective route to quinolizidine derivatives such as (25, 26, 30), and (31), as well as to indolizidine derivatives, (28). In each instance, the product corresponds to that diastereomer wherein the hydroxyl group and ring junction hydrogen are trans to one another. The transformation holds significant promise as a route to alkaloids. A mercury cathode is preferred; passivation occurs when lead is used. Interestingly, the reaction does not occur using either graphite or glassy carbon electrodes. This observation points out the need to treat the choice of

electrode material as a reaction parameter that may need to be adjusted in order to determine optimal reaction conditions in an electrochemical transformation. To the inexperienced practitioner, this may seem like an undesirable burden. One should pause, however, to reflect upon the many experimental parameters that require adjustment in experiments that do not use electrochemistry. With experience, one becomes as comfortable with having to spend a bit of time selecting the most useful electrode as one does with having to vary other reaction parameters in an effort to achieve optimization.

## 11.2.5

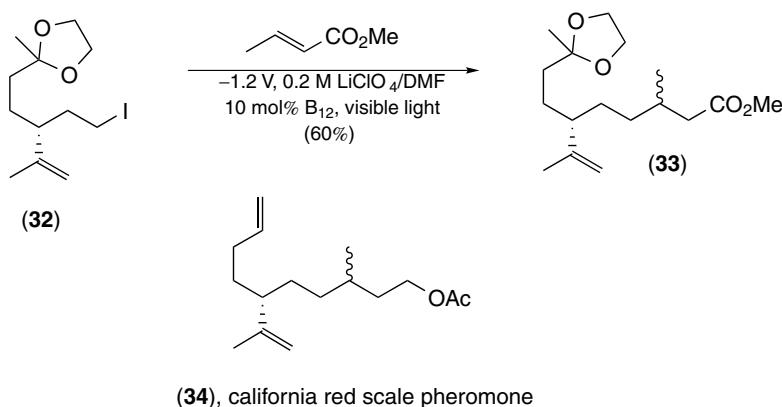
**Vitamin B<sub>12</sub>-mediated Cyclizations**

Vitamin B<sub>12</sub> reacts with alkyl halides to form a cobalt (III) alkyl intermediate. Irradiation with visible light leads to the expulsion of a carbon-centered radical and a cobalt (II) species. The latter is easily reduced at  $-0.8$  V to reconvert it to a cobalt (I) intermediate that reenters the catalytic cycle by reacting with a second molecule of the halide. The radical is capable of undergoing a number of interesting transformations, including conjugate addition to a Michael acceptor. The example illustrated in Scheme 9 provided a straightforward route to ester

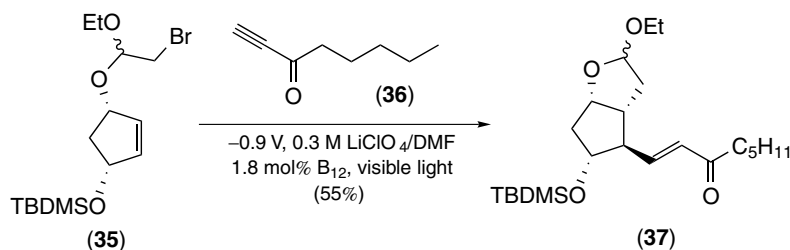
(33), and ultimately to the California red scale pheromone (34) [23].

Another illustration of the utility of this chemistry is provided by its use as the key step in a synthesis of prostaglandin PGF<sub>2 $\alpha$</sub>  [24]. In this case, the radical formed from bromoacetal (35) undergoes an *intramolecular 5-exo-trig* cyclization onto the olefin of the cyclopentene ring, thereby generating a new radical capable of undergoing another reaction. When it was intercepted *intermolecularly* by ynone (36), enone (37) was produced in a 55% yield (Scheme 10).

The chemistry takes place *via* the reduction of vitamin B<sub>12</sub> or a similar cobalt (III) species (38) in a process that



**Scheme 9** Vitamin B<sub>12</sub>-mediated Michael addition.



**Scheme 10** Vitamin B<sub>12</sub>-mediated cyclization and conjugate addition to prostaglandin PGF<sub>2 $\alpha$</sub> .

sees the conversion of cobalt from the +3 to the +1 oxidation state, and the opening of two sites of unsaturation (Scheme 11) [25]. This nucleophilic intermediate reacts rapidly with the alkyl halide to form the octahedral complex (39) and reestablish a +3 oxidation state on cobalt. Reduction of (39) expels either a radical or a carbanion and regenerates the nucleophilic cobalt (I) intermediate.

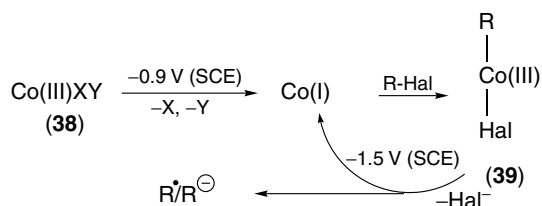
Typically, the reactions are carried out using a controlled potential, with the potential set to a value that allows the selective reduction of Co(III) in the presence of the alkyl halide and Michael acceptor [26]. Only 1–20 mol % of the cobalt mediator is needed. The reactions are conducted in a medium in which lithium perchlorate

serves as the supporting electrolyte, DMF as solvent, and ammonium bromide as the proton donor.

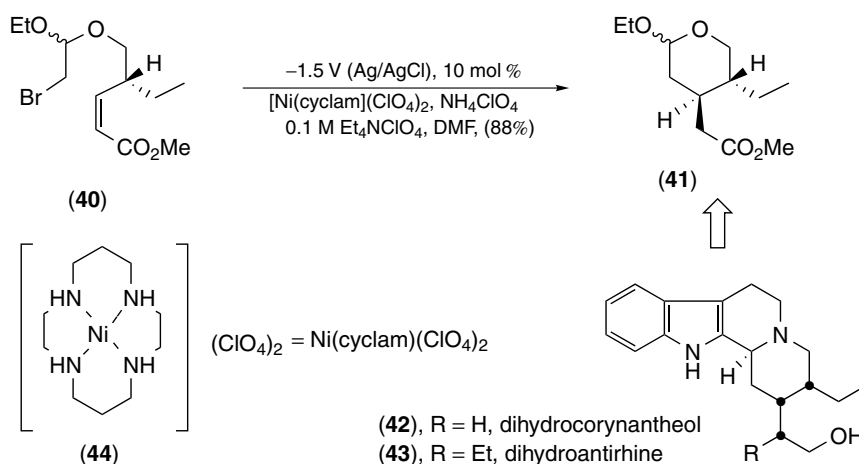
#### 11.2.6

#### Organonickel and Organopalladium Reagents

$\beta$ -Bromoacetals and  $\beta$ -bromoacetates readily undergo nickel (II) catalyzed cyclization onto alkenes [6, 7]. The process, illustrated in Scheme 12, has its nonelectrochemical counterpart in free radical chemistry as well as in the vitamin B<sub>12</sub>-mediated chemistry discussed previously. It provides an exceptionally powerful method for the construction of six-membered rings under “environmentally friendly” conditions,



**Scheme 11** Carbanion formation from alkyl halides and cobalt (III) species.



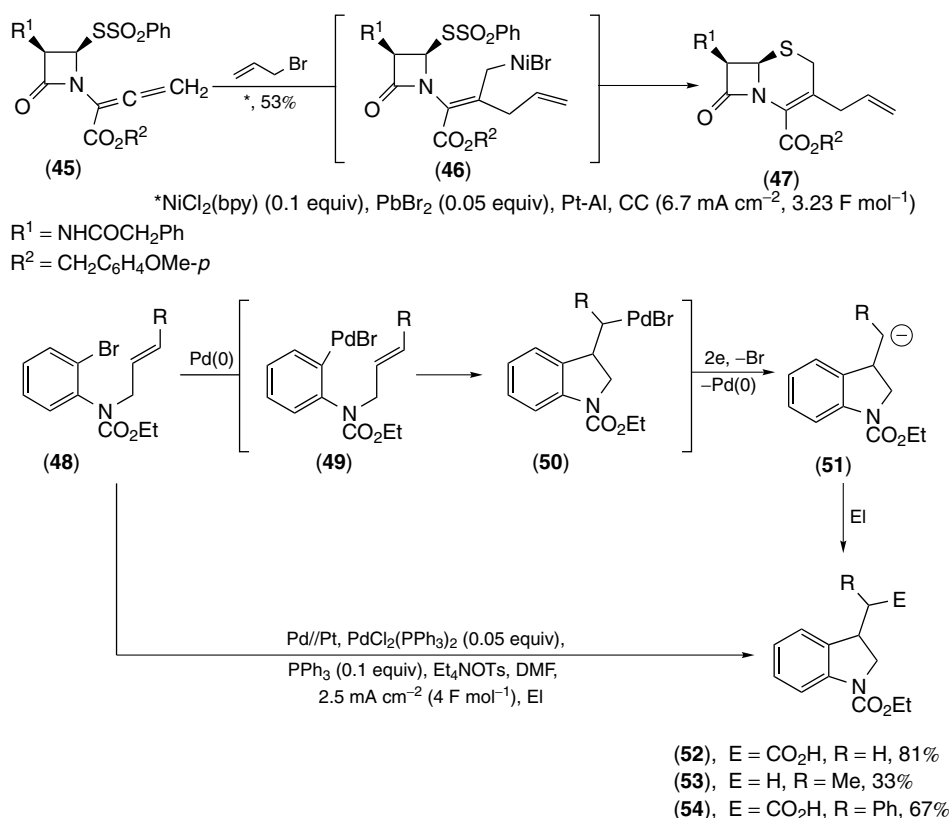
**Scheme 12** Nickel cyclam mediated intramolecular reductive cyclization.

requiring only 10 mol % of the nickel cyclam complex (**44**) to be effective. Use of this complex to mediate the process avoids the use of high dilution that is often required of organotin-promoted radical reactions. Cyclization is most effective when an electron-deficient alkene is utilized. The product of the reaction of bromoenone (**40**) is the tetrahydropyranyl ester (**41**), an intermediate that has been used in a synthesis of *Ipecac* and *Corynanthe* alkaloids (**42**) and (**43**).

In the presence of certain metals, particularly nickel and palladium, allylic and aryl halides serve as convenient sources of

electrogenerated organometallics [27]. Elegant mechanistic studies of several very important palladium-catalyzed reactions, including the Heck reaction, have been described within the last five years. The reader is referred to the original literature for insight concerning the beautiful way in which the tools common to the field of electrochemistry can be used to elucidate reaction mechanism [8].

The first example illustrated in Scheme 13 portrays a novel route to the cephalosporin derivative (**47**) [28, 29] through the intermediacy of the allyl nickel species (**46**). The second example provides



**Scheme 13** Organonickel and organopalladium mediated routes of cephalosporin analogs and indoles.



a convenient means of synthesizing indoles using a transformation that is reminiscent of a Heck reaction [30].

### 11.3

#### Oxidation

##### 11.3.1

#### Kolbe Oxidation

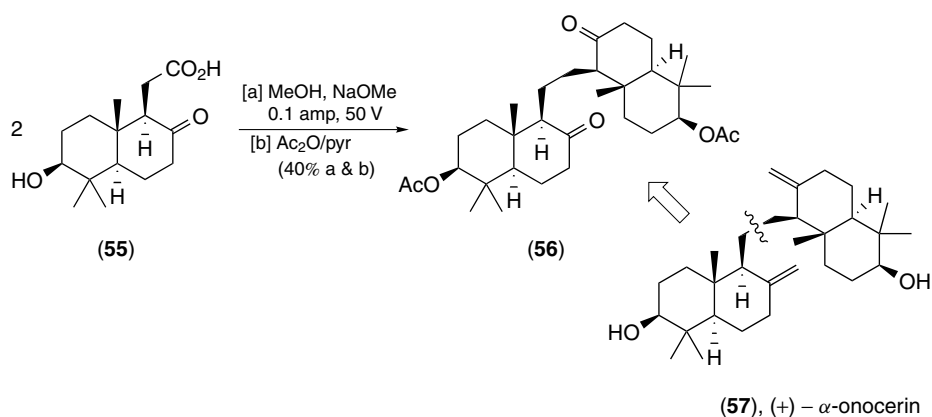
Perhaps the best-known and most widely appreciated electrochemical transformation is the Kolbe oxidation (see also Chapter 6) [1, 2, 31]. The process involves the one electron oxidation of the salt of a carboxylic acid, and the loss of carbon dioxide to afford a radical,  $R^\bullet$ , that subsequently engages in coupling reactions. Both symmetrical ( $R^\bullet + R^\bullet$ ) and nonsymmetrical ( $R^\bullet + R'^\bullet$ ) radical couplings are known and are illustrated in the following discussion. The nonsymmetrical variety (often referred to as a mixed or hetero coupling) is remarkable given that it requires the cogeneration and reaction of more than one reactive intermediate.

A typical Kolbe electrolysis experiment calls for the constant current electrolysis of

an alkaline alcoholic solution (5–10% neutralized carboxylic acid) between platinum electrodes in an undivided cell. Further oxidation of the radical leads to a carbocation that is typically intercepted by the alcoholic solvent to give rise to the so-called non-Kolbe product. The latter pathway is favored by low current density, the use of graphite electrodes, salt additives, and an alkaline medium [32]. Conversely, high current density, the use of platinum electrodes, an acidic medium, and electron-releasing groups favor the Kolbe pathway [32].

A good example of the simplicity and power of the chemistry to rapidly construct complex systems is provided by the Kolbe dimerization of (55) as the key step of a total synthesis of the triterpene (+)- $\alpha$ -onocerin (57; Scheme 14) [33]. Thus, oxidation of (+)-hydroxy keto acid (55) in methanol containing a trace of sodium methoxide and at a temperature of 50 °C, followed by acylation and chromatography, provided (+)-diacetoxydione (56) in a 40% yield.

Nonsymmetrical coupling reactions have been used extensively to generate natural products [32, 34–41]. A typical procedure calls for the use of a large excess



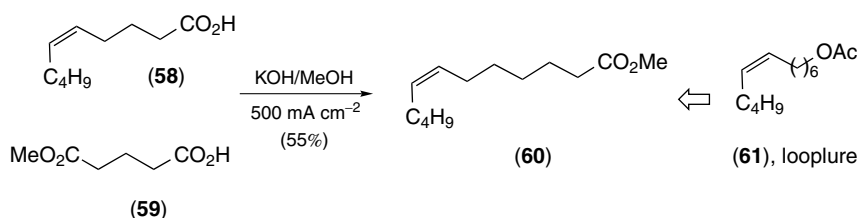
**Scheme 14** Kolbe oxidation en route to onocerin.

(5–10 equivalents) of one of the acids. The insect pheromone looplure (**61**) was synthesized by using the nonsymmetrical coupling illustrated in Scheme 15 [35]. Electrolysis of (**58**) and (**59**) (1:2 ratio) provided only moderate yields of the desired coupling product (**60**) (26–35%), but the use of a tenfold excess of monomethyl glutarate (**59**) increased the yield to 55%.

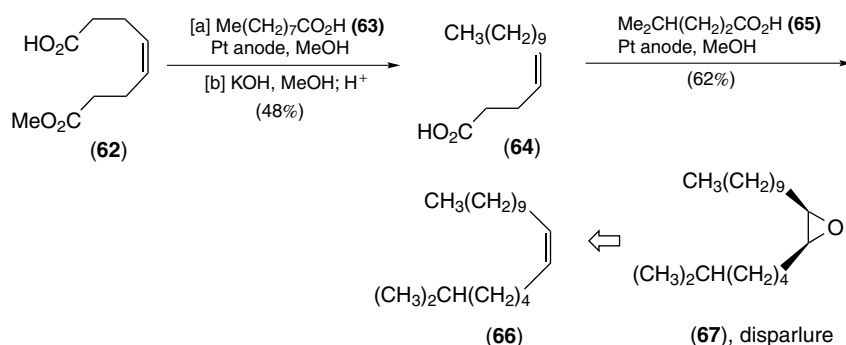
Of interest is the fact that one of the coupling partners in the looplure synthesis was the half acid-half ester (**59**). Since the ester was untouched in the coelectrolysis, it could potentially function as a site for a second Kolbe oxidation and subsequent coupling. This strategy was utilized in the synthesis of disparlure (**67**; Scheme 16) [36]. A mixed coupling between the half-acid ester (**62**) and nonanoic acid (**63**) (1:10 ratio) proceeded smoothly to afford (**64**). Saponification

unmasked the second carboxylic acid unit, which served nicely in a mixed coupling reaction with (**65**) (1:10 **64/65**) to provide a rapid and efficient (62%) access to the alkene (**66**); epoxidation afforded the insect pheromone disparlure (**67**).

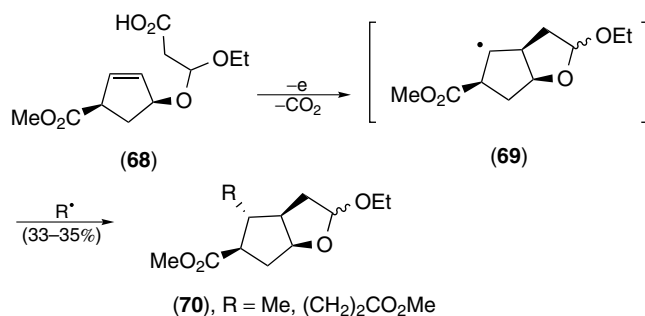
The radical produced from the oxidative decarboxylation may also be trapped *intramolecularly* to form five- and six-membered rings (Scheme 17). The Kolbe protocol avoids the use of the toxic organotin reagents that are commonly used in the formation of radicals. Moreover, when alkyltin hydride reagents are used, a C–H bond is formed. The Kolbe reaction protocol, on the other hand, allows the radical formed after cyclization to be captured by a different radical in a coelectrolysis experiment, rather than being reduced. This tandem sequence of events has been exploited in the construction of prostaglandin precursor (**70**) [37–41]. Here, the cyclized



**Scheme 15** Mixed Kolbe oxidation as a route to an insect pheromone.



**Scheme 16** Mixed Kolbe electrolysis route to disparlure.



**Scheme 17** Tandem Kolbe electrolyses.

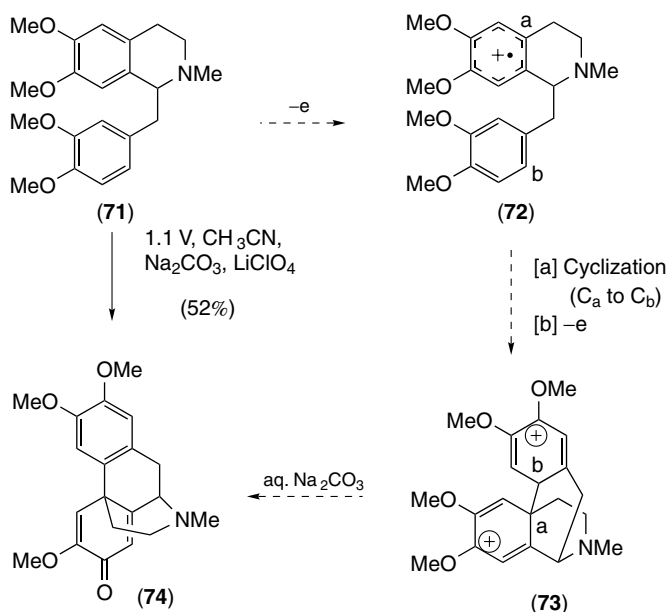
radical (69) is intercepted by an alkyl radical, R<sup>•</sup>, generated by the oxidation of a fourfold excess of co-acid.

### 11.3.2

#### Arene Oxidations

The power and utility of the anode as a selective oxidant is highlighted beautifully by the electrooxidative cyclization of 1-benzyl-tetrahydroisoquinolines (Scheme 18) [42].

These substrates possess several oxidizable sites. Racemic laudanosine (71), for example, could be oxidized at nitrogen or in one or both of the electron-rich aromatic rings. In fact, it displays *five* volta-metric peak potentials at 0.63, 0.81, 1.13, 1.30, and 1.47 V (vs Ag/AgNO<sub>3</sub>). Yet, using potential control, it proved a simple matter to oxidize a dimethoxyaryl unit in the presence of the *N*-methylamine subunit.



**Scheme 18** Intramolecular oxidative coupling of laudanosine.

The preparative scale oxidation of laudanosine (**71**) at +1.1 V led to the isolation of a 52% yield of *O*-methylflavinantine (**74**) [42, 43]. The mechanism for this exceptionally useful means of synthesizing the morphine class of alkaloids is illustrated in Scheme 18.

Several elegant syntheses of anthracyclinone aglycons are based on the ability to intercept the intermediate radical cation (**76**) formed from the oxidation of aromatic ethers (**75**) and (**79**) *in situ* with alkanols [9, 44, 45]. Inter- and intramolecular capture can occur. As illustrated in Scheme 19, the methodology leads to the facile construction of substituted quinone mono- and bisketals.

Substituted quinone ketals, prepared in this manner, serve nicely in annelation strategies leading to natural products. Two are illustrated, one in Scheme 20 leading to (+)-4-demethoxydaunomycinone (**87**) and (+)-daunomycinone (**88**) [46–48], the other in Scheme 21 serving as a pathway to  $\alpha$ -citromycinone (**94**). The first calls for a Michael addition of (**84**) to quinone ketal (**83**) followed by capture of the intermediate enolate, and leads to annelated

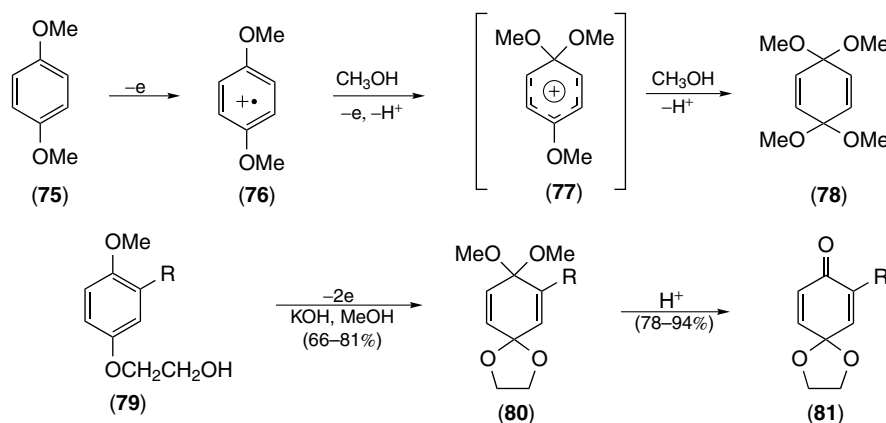
product (**85**) when R = H, and to (**86**) when R = OMe. These materials were converted to the natural products (**87**) and (**88**) in the manner shown in Scheme 20 [48].

In the second instance, the electrochemically generated bromoquinone monoketal (**90**) was converted to the organolithium reagent (**91**) (Scheme 21) [46, 47]. Its reaction with ketal (**92**), a synthon for the 1,4-dipole (**93**) [49, 50], proceeded smoothly to afford, after sequential treatment with aqueous acid and boron tribromide, a 60% yield of  $\alpha$ -citromycinone (**94**).

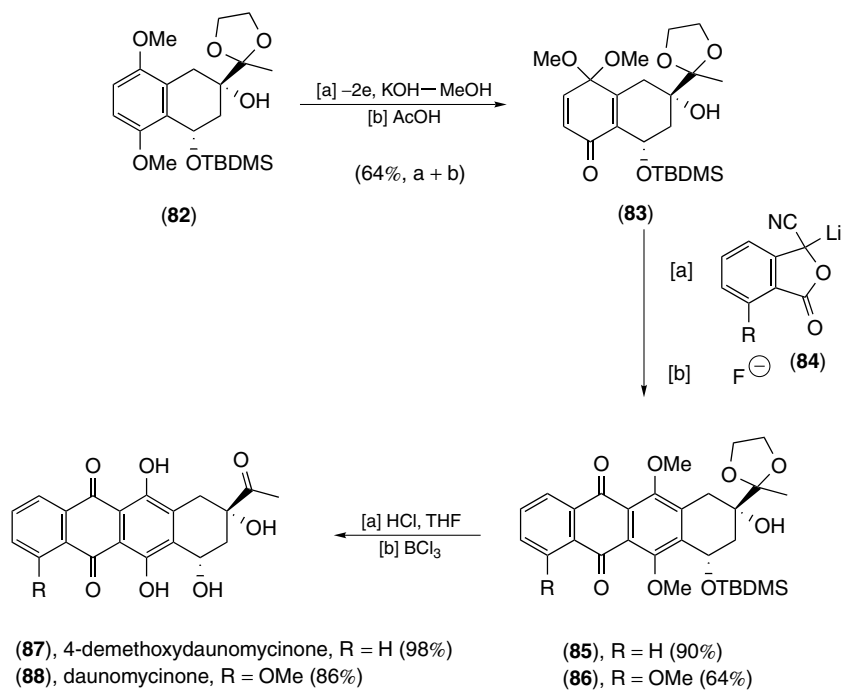
### 11.3.3

#### [5 + 2] Cycloadditions to Oxidized Aromatics

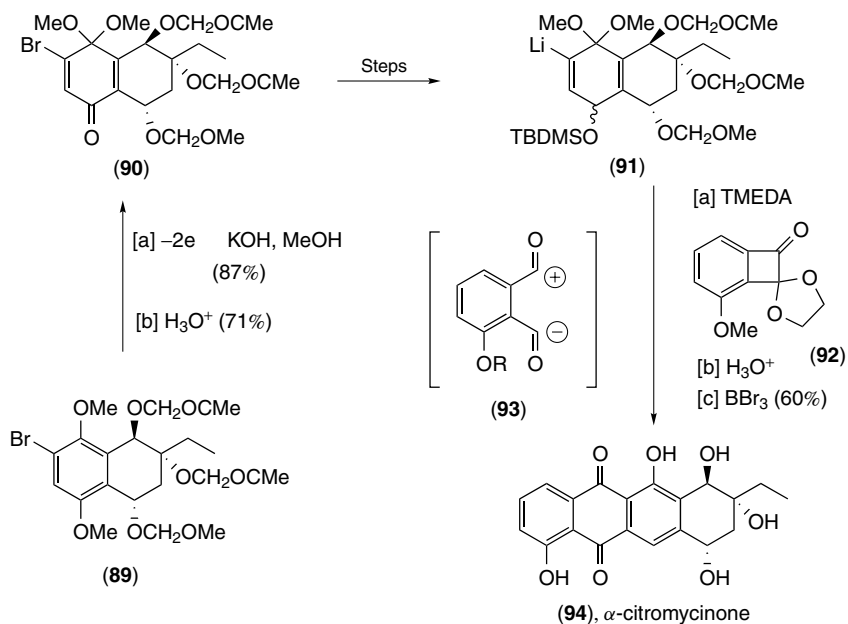
The oxidative electrochemistry of phenols has been developed elegantly [51, 52]. The key intermediate is often the pentadienyl cation (**96**) that is formed after the loss of two electrons and one proton from (**95**) (Scheme 22). It can be intercepted by alkenes, at the terminal carbons of the pentadienyl array, to achieve a [5 + 2] cycloaddition (e.g. (**96**) to **97**), or by a nucleophilic solvent such as methanol, leading to a conjugated diene (**99**). The



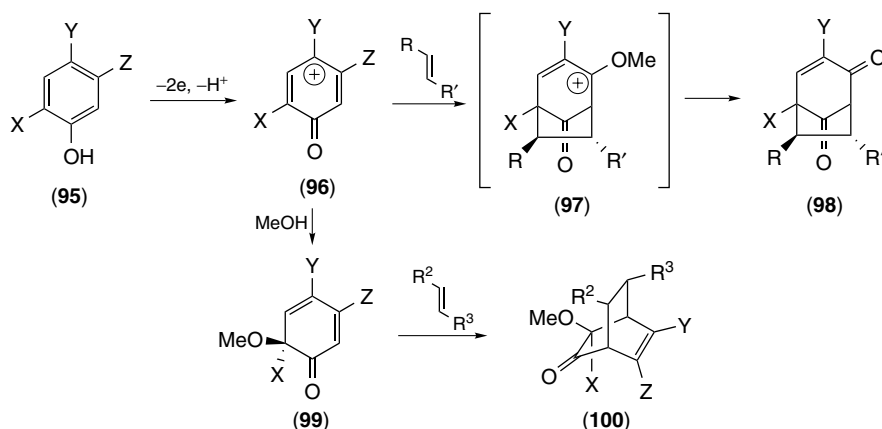
**Scheme 19** An expeditious synthesis of quinone ketals.



**Scheme 20** An elegant route to anthracycline antibiotics.



**Scheme 21** Electrooxidation and annelation en route to  $\alpha$ -citromycinone.



**Scheme 22** Opportunities for [5 + 2] and [4 + 2] cycloaddition.

latter constitutes a useful and a novel route to Diels–Alder dienes.

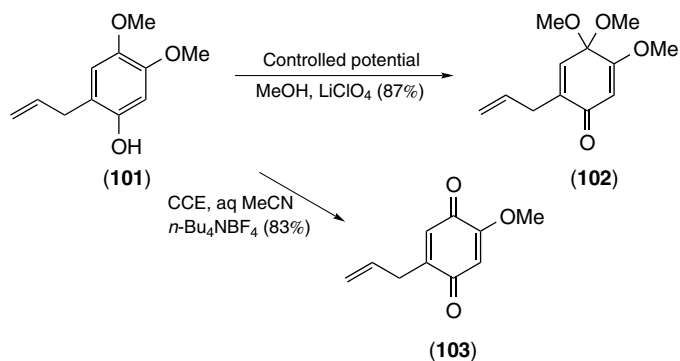
Both inter- and intramolecular [5 + 2] cycloaddition modes have been utilized in the synthesis of natural products. Successful intermolecular cycloaddition depends on making an appropriate selection of solvent, supporting electrolyte, oxidation potential, and current density. This is nicely illustrated in Schemes 23 to 25. For example, in methanol the controlled potential oxidation of phenol (**101**) affords a high yield (87%) of (**102**), the adduct wherein methanol has intercepted the reactive intermediate [51]. In contrast, a constant current electrolysis conducted in acetonitrile rather than methanol, led to an 83% yield of quinone (**103**).

As the examples portrayed in Scheme 24 show [51], cycloaddition is often carried out in mixed solvent systems consisting of either methanol/acetic acid (2 : 1) or acetic acid/trifluoroacetic acid (4 : 1) with lithium perchlorate as supporting electrolyte. Cycloaddition between the oxidized form of (**101**) and alkene (**104E**) leads to the neolignan (**105a**) in high yield, and with preservation of the olefin geometry. When the *Z*-isomer (**104Z**) is used, the chemistry

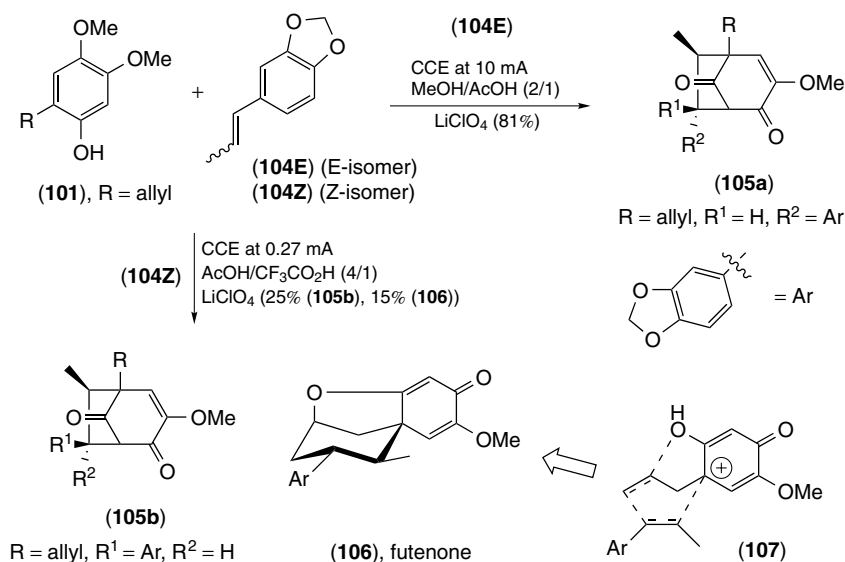
is not nearly as efficient. Two products, (**105b**) and (**106**) (futenone) are produced in a yield of 25 and 15%, respectively. Notice the different current densities that are associated with these transformations, 10 mA cm<sup>-2</sup> for the reaction conducted in MeOH/AcOH, 0.27 mA cm<sup>-2</sup> in AcOH/TFA (trifluoroacetic acid). It turns out that the success of many of the cycloadditions depends on finding the optimal current density.

Asatone (**110**; Scheme 25), a neolignan, was quickly assembled by capitalizing upon the ability of a nucleophilic solvent to intercept the intermediate cation formed upon the electrooxidation of (**108**); in this instance the conjugated 1,3-diene (**109**) was produced. This result contrasts with the oxidation of 4,5-dimethoxyphenol (**101**) (Scheme 23) wherein the *nonconjugated* 1,4-diene (**102**) was generated. Diene (**109**) served admirably as both the diene and the dienophile in an intermolecular Diels–Alder reaction leading to asatone (**110**) [51].

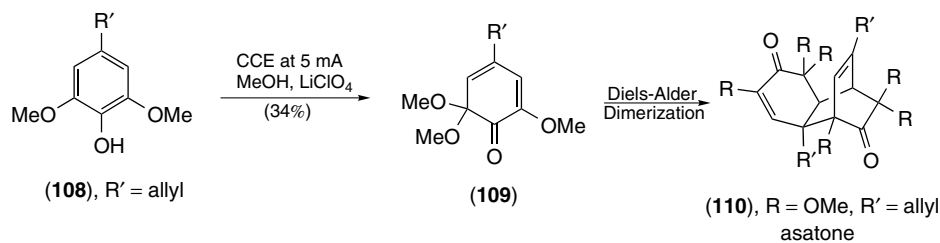
The *intramolecular* [5 + 2] cycloaddition mode has been studied extensively. The chemistry bears a remarkable similarity to the arene-olefin photocycloaddition [53] reaction (e.g. 114



**Scheme 23** The influence of reaction conditions upon the oxidation of phenols.



**Scheme 24** The [5 + 2] cycloaddition approach to natural product skeletons.



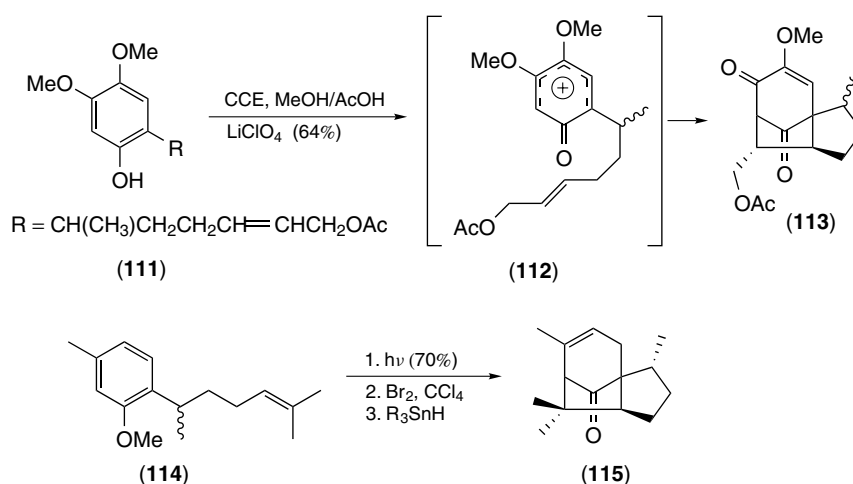
**Scheme 25** The [4 + 2] cycloaddition approach to natural product skeletons.

to **115**) that has frequently been used in the synthesis of complex bioactive natural products. While different intermediates are involved, the photo- and electrochemical reactions provide access to many of the same ring systems. The similarity is nicely illustrated in Scheme 26 by comparing key steps of an electrochemical approach to the total synthesis of the angularly fused sesquiterpene pentalene [54], and a photochemical pathway that ultimately led to the sesquiterpene cedrene.

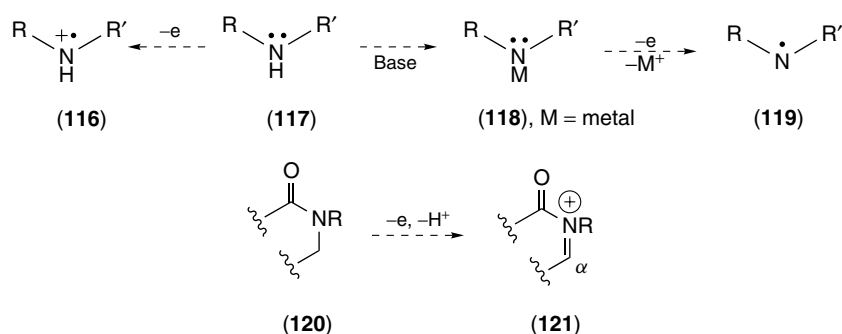
#### 11.3.4

#### Oxidation at and Adjacent to Nitrogen

Amines and amides undergo oxidation at or adjacent to nitrogen (Scheme 27). A neutral amine, for example, can be oxidized to afford a cation radical (**117** to **116**). Similarly, electrooxidation of the anion produced via deprotonation of a secondary amine leads to an aminyl radical (**119**) that is capable of participating in carbon–nitrogen bond-forming reactions with remotely tethered alkenes.



**Scheme 26** Comparison of electrochemical and photochemical strategies.



**Scheme 27** Oxidation at and adjacent to nitrogen.

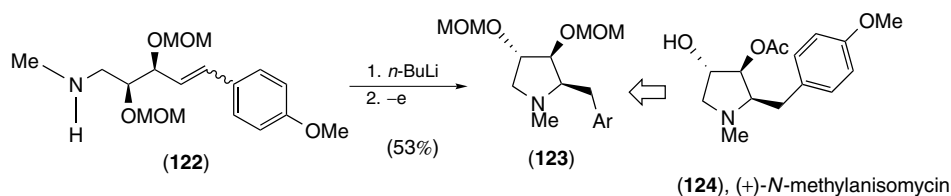


Amides (carbamates) (**120**) are susceptible to oxidation at alkyl centers adjacent to nitrogen.

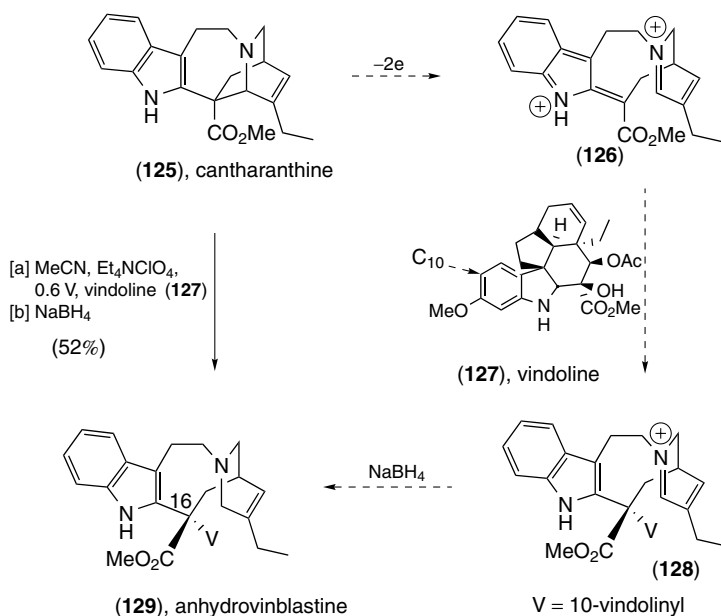
Indicative of the chemistry of the aminyl radical (**119**) is a synthesis of the *N*-methyl derivative of the antibiotic (–)-anisomycin (**124**; Scheme 28) [55]. Pyrrolidine (**123**) was obtained by treating (*E*)- $\delta$ -alkenylamine (**122**) with *n*-butyllithium at  $-78^\circ\text{C}$ , followed by oxidation at a constant current ( $17.5\text{ mA cm}^{-2}$ ) in a 100:1 mixture of THF and HMPA containing 0.25 M lithium perchlorate as the supporting electrolyte at  $-10^\circ\text{C}$ .

A 5-*exo-trig* cyclization of the metalated aminyl radical provided pyrrolidine (**123**) as a single isomer in a 53% yield. A routine series of transformations converted it to the target structure (**124**).

The vinblastine alkaloids are important chemotherapeutic materials, and are well known for their antitumor properties. A two-electron oxidation of alkaloid cantharanthine (**125**) followed by nucleophilic capture of the resulting imminium ion (**126**) by C<sub>10</sub> of vindoline (**127**), afforded (**128**) and provided access to this important class of materials (Scheme 29) [56].



**Scheme 28** Aminyl radical cyclization.



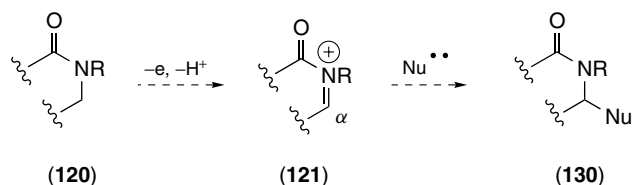
**Scheme 29** An elegant electrochemical route to the vinblastine alkaloids.

Oxidation was carried out at a potential that allowed the selective oxidation of cantharanthine (**125**). The overall process was shown to occur in a stepwise manner with vindoline (**127**) intercepting the putative dication (**126**). Reduction of (**128**) with sodium borohydride afforded anhydrovinblastine (**129**) in a 52% yield accompanied by 12% of the material epimeric at C<sub>16</sub>.

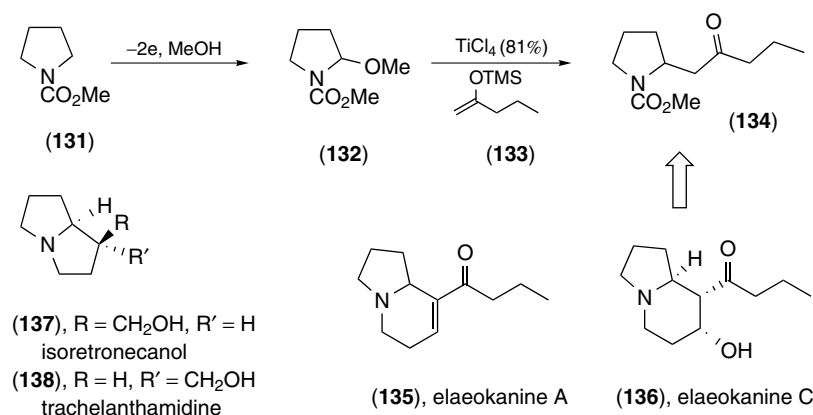
As indicated previously, amides (carbamates) (**120**) are susceptible to oxidation at an alkyl center adjacent to nitrogen. The resulting acyl imminium ion (**121**) can be intercepted by a variety of nucleophiles in a process that sets the stage for subsequent carbon–carbon formation (Scheme 30). As the following discussion illustrates, the creative utilization of this protocol provides an exceptionally useful entry to a host of alkaloids.

Both pyrrolizidine and indolizidine alkaloids can be synthesized by taking advantage of the anodic  $\alpha$ -alkoxylation of *N*-alkoxycarbonylpyrrolidines (e.g. (**131**) to (**132**), Scheme 31). The method has been utilized to synthesize isoretronecanol (**137**), trachelanthamidine (**138**), elaeokanine A (**135**), and elaeokanine C (**136**) [57]. Once the methoxy group has been installed and nucleophilic capture of the intermediate has occurred, the product (**132**) can be treated with an enol ether (e.g. **133**) and titanium tetrachloride to affect C–C bond formation adjacent to nitrogen. This sequence served nicely in syntheses of both indolizidine alkaloids elaeokanine A (**135**) and C (**136**).

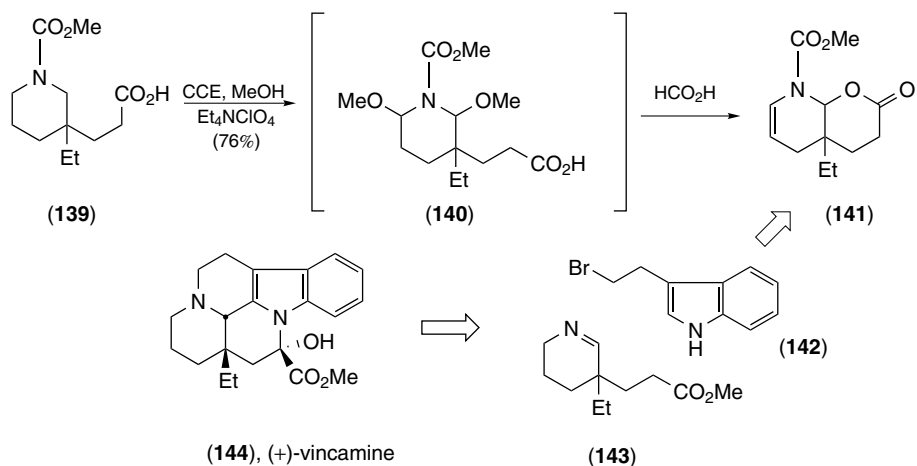
A formal total synthesis of vincamine (**144**) was achieved, once again by capitalizing upon the ability to affect oxidation



**Scheme 30** Nucleophilic addition to an electrochemically generated acyl imminium ion.



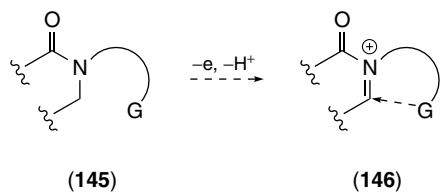
**Scheme 31** Indolizidine and pyrrolizidine alkaloid synthesis.



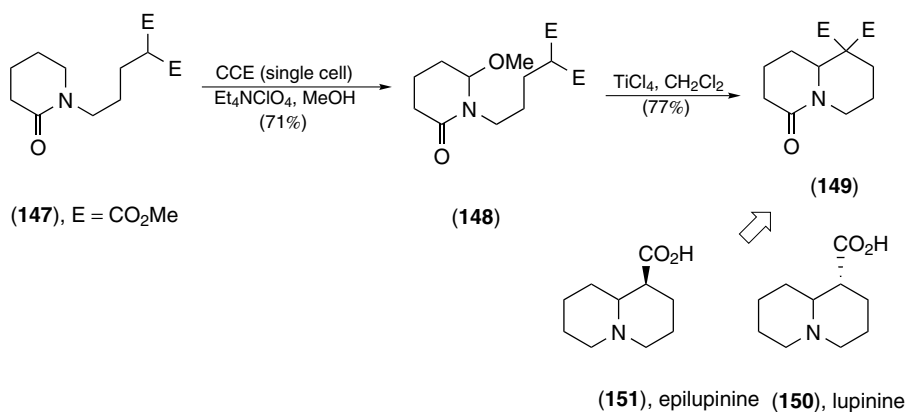
**Scheme 32** An ingenious synthesis of vincamine.

$\alpha$  to nitrogen [58, 59]. Thus, when the piperidine carboxylic acid ester (139) was oxidized at a constant, it was efficiently converted to methyl ether (140). When

treated with formic acid, (140) transformed to lactone (141) in a 76% yield after chromatography. Hydrogenation, hydrolysis, and esterification afforded ester (143).



**Scheme 33** Anodic cyclization of lactams.



**Scheme 34** Intramolecular cyclization onto an acyl imminium ion.

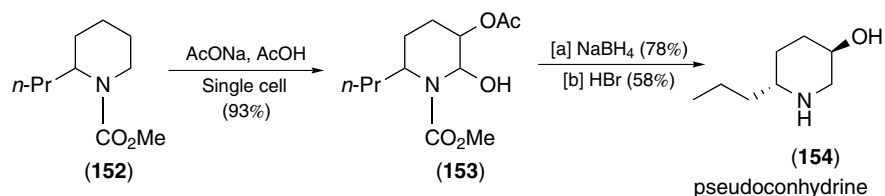
The latter served as a key-coupling partner with tryptophyl bromide (**142**) en route to the assembly of vincamine (**144**).

Another useful route to alkaloids involves the electrochemical oxidation of lactams (**145**) bearing functionality on nitrogen that can be used to intramolecularly capture an intermediate acyl iminium ion (**146**). The concept is portrayed in Scheme 33 and is highlighted by the synthesis of alkaloids lupinine (**150**) and epilupinine (**151**) shown in Scheme 34 [60]. Thus, the electrooxidation of lactam (**147**) provided a 71% yield of ether (**148**). Subsequent treatment with titanium tetrachloride affected cyclization and afforded the [4.4.0] bicyclic adduct (**149**). Krapcho decarbomethoxylation followed by hydride reduction of both the

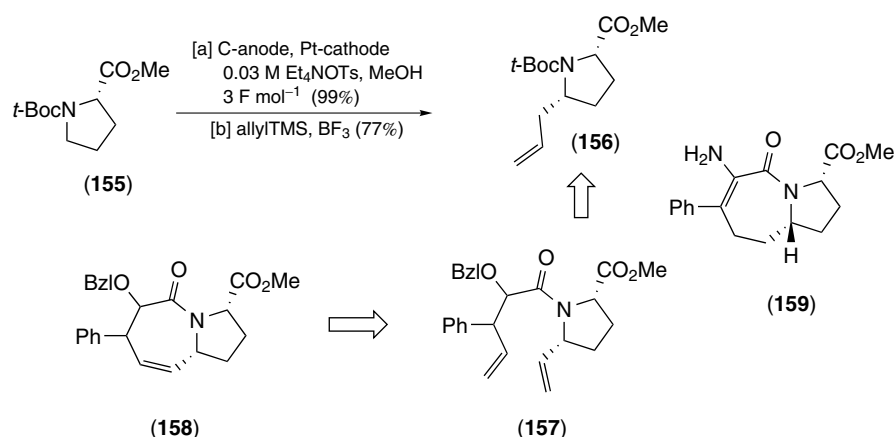
amide and ester units of the resulting epimeric esters provided the natural products (**150**) and (**151**).

A convenient method to affect the oxidation  $\beta$ - to nitrogen in piperidines is based on the anodic oxidation of *N*-carboalkoxy piperidines (Scheme 35). The electrochemical oxidation of piperidine (**152**) in the presence of acetic acid and potassium acetate, for example, afforded a mixture of isomeric 2-hydroxy-3-acetoxypiperidines (**153**) in a combined yield of 93%, following an aqueous workup [61]. Reduction with sodium borohydride severed the C–OH bond. Treatment with acid and then base completed a synthesis of pseudoconhydrine (**154**).

The anodic  $\alpha$ -alkoxylation of amides [10–12, 62–65] has been used extensively



**Scheme 35** Synthesis of pseudoconhydrine.



**Scheme 36** An elegant synthesis of a peptide mimetic.

in the construction of peptide mimetics. Much of the work has focused upon the synthesis of conformationally restricted systems in an effort to ascertain the relationship between the bioactivity of the parent peptide and a specific conformer of it. The example illustrated in Scheme 36 portrays an exceptionally clever synthesis of (**158**), a key substance en route to the Phe-Pro-building block (**159**) [10–12]. Both the electrooxidation and ring-forming metathesis (**157** to **158**) reactions are of special note.

#### 11.4

##### Concluding Remarks

It is hoped that the examples cited have provided the reader with a sense of the wide range of exceptionally useful transformations that can be carried out electrochemically. It is hoped that some day this protocol will be routinely considered, evaluated for its unique merits, and widely adopted as a tool that is to be used to solve problems in organic synthesis.

##### Acknowledgment

We are grateful to the National Science Foundation for supporting our research efforts in the field of organic electrochemistry.

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## 12

### Electrochemistry of Heterocycles

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## 12.1

### Overview on the Electrochemistry of Heterocycles

Heterocycles are of great interest in organic chemistry due to their specific properties. Many of these cycles are widely present in natural and pharmaceutical compounds. Electrochemistry appears as a powerful tool for the preparation and the functionalization of various heterocycles because anodic oxidations and cathodic reductions allow the selective preparation of highly reactive intermediates (radicals, radical ions, cations, anions, and electrophilic and nucleophilic groups). In this way, the electrochemical technique can be used as a key step for the synthesis of complex molecules containing heterocycles. A review of the electrolysis of heterocyclic compounds is summarized in Ref. [1].

#### 12.1.1

##### Electrosyntheses of Heterocycles

Ring-closure reactions occur either by intramolecular coupling when the electrogenerated center and the other reactive center are in appropriate positions within the molecule, or by intermolecular coupling. In this latter case, the ring formation involves the creation of two bonds either simultaneously or in

two separated steps. Coupling reactions can occur by either direct electrolysis or by using transition metal complexes as catalysts. Bond formations result from carbon–carbon, carbon–heteroatom, or heteroatom–heteroatom coupling reactions.

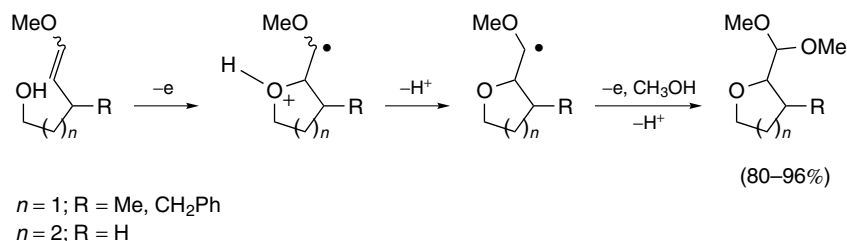
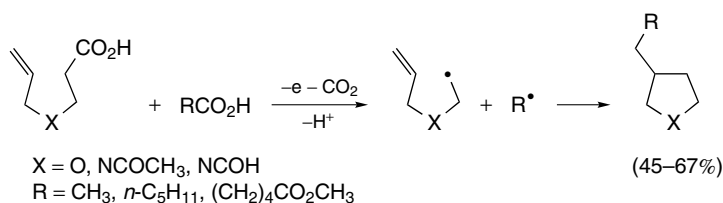
It is worth noting that anodic oxidations often give electrophilic and/or acidic centers, whereas cathodic reductions lead to nucleophilic and/or basic centers. Moreover, we must keep in mind that the mechanisms of many anodic and cathodic cyclizations are not accurately known.

##### 12.1.1.1 Anodic Cyclizations

Various reactive intermediates have been postulated in the formation of heterocycles by anodic oxidation.

Radical cations resulting from oxidation of olefins, aromatic compounds, amino groups, and so on, can react by electrophilic addition to a nucleophilic center as shown, for example, in Scheme 1 [2, 3]. The double bond activated by an electron-donating substituent is first oxidized leading to a radical cation that attacks the nucleophilic center. The global reaction is a two-electron process corresponding to an ECEC mechanism.

Radicals prepared by anodic oxidation of anions or by the Kolbe reactions can couple with other radicals or add to double bonds. For instance in Scheme 2 [4, 5], the

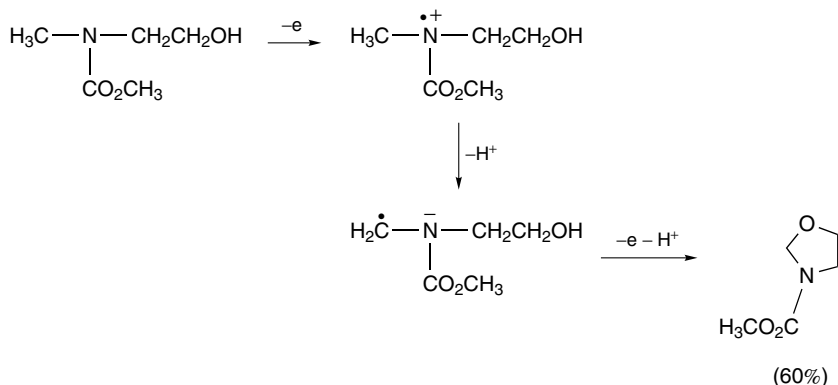
**Scheme 1** Intramolecular reaction of a radical cation with a nucleophile.**Scheme 2** Intramolecular addition of a Kolbe radical to a double bond.

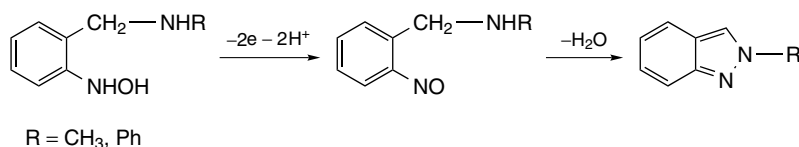
initial radical generated by a Kolbe reaction adds to a double bond within the molecule prior to trapping the radical from a second carboxylic acid.

Cations resulting from a two-electron oxidation of carboxylic acids (non-Kolbe electrolysis) or from compounds having protons in the  $\alpha$ -position to heteroatoms as shown in Scheme 3 [6] react with nucleophilic centers. In the last case,

deprotonation reactions are favored by the presence of bases in the medium.

More generally, electrolytically formed electrophilic centers react with nucleophilic centers. For example, in Scheme 4 [7], an electrogenerated nitroso group leads to a nitrogen–nitrogen bond formation after reaction with an amino group. When the electrolysis is performed in a batch cell, a rapid cyclization

**Scheme 3** Intramolecular reaction of an electrogenerated carbocation with a nucleophile.



**Scheme 4** Intramolecular reaction of an electrogenerated electrophile with a nucleophile.

is necessary to avoid a coupling reaction between the starting hydroxylamino compound (previously produced by the cathodic reduction of the corresponding nitro compound) and its nitroso derivative.

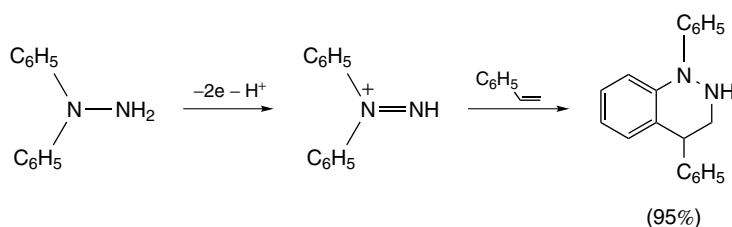
Anodically electrogenerated species can undergo cycloaddition reactions with other reagents. For example, in Scheme 5 a diazenium cation reacts with styrene [8, 9].

#### 12.1.1.2 Cathodic Cyclizations

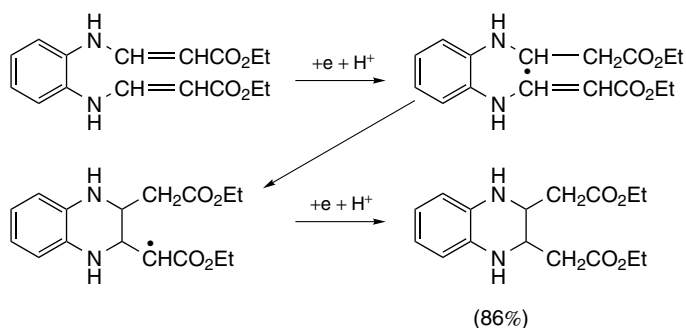
Cathodic cyclizations also involve various reactive intermediates.

Radicals can be obtained from reduction of molecules followed either by protonation or departure of a nucleophile as illustrated in Schemes 6 [10] and 7 [11], respectively. In the first example, a generally accepted mechanism involves a reduction of a double bond activated by an electron-withdrawing group to a radical anion followed by protonation and cyclization of the resulting radical. The addition of a second electron and proton completes the process.

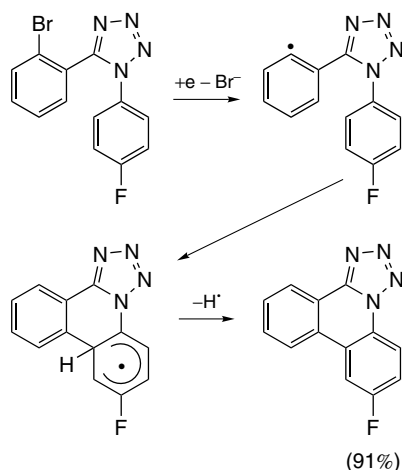
In the second example, the aryl radical obtained after cleavage of the



**Scheme 5** Cycloaddition of an electrogenerated electrophile.



**Scheme 6** Intramolecular reaction of a radical anion with an electrophile.



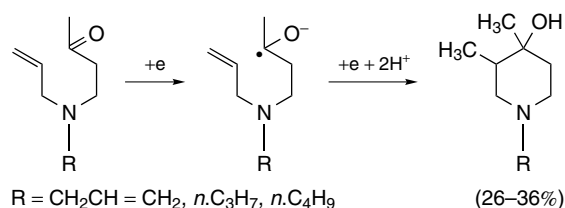
**Scheme 7** Intramolecular addition of an electrogenerated radical to an aryl ring.

carbon–halogen bond leads to a fast intramolecular cyclization.

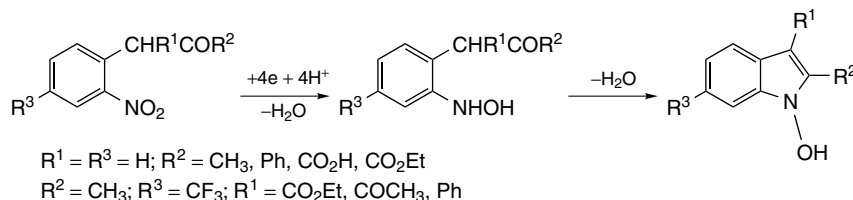
Radical anions resulting from cathodic reductions of molecules react with electrophilic centers. As an example (Scheme 8), the reduction of compounds in which a double bond is not conjugated with a carbonyl group, involves an intramolecular coupling reaction of radical anion with alkene [12].

More generally, electrolytically produced nucleophilic centers (amine, hydroxylamine, hydrazine, alcohol) react with electrophilic centers (carbonyl group, cyano group, nitroso group) as illustrated in Scheme 9 for the synthesis of *N*-hydroxyindoles [13].

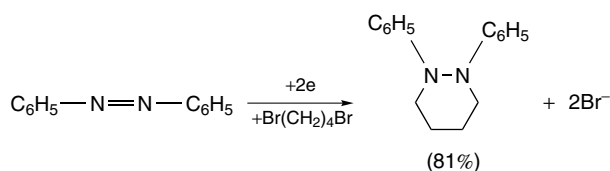
Cathodically electrogenerated species can give cycloaddition reactions with other reagents. This can be illustrated



**Scheme 8** Intramolecular addition of a radical anion to an alkene.



**Scheme 9** Intramolecular reaction of a cathodically generated nucleophile with an electrophile.



**Scheme 10** Cathodic bisalkylation of azobenzene with 1,4-dibromobutane.

by the cathodic reduction of azobenzene in the presence of 1,4-dibromobutane (Scheme 10) [14, 15].

### 12.1.2

#### Electrochemical Behavior of Heterocycles

Electrochemistry is also a powerful means of modifying heterocycles. According to the electrochemical process (oxidation or reduction) several types of reactions can take place: unsaturation or saturation of the cycle, substitution, addition, ring expansion, ring contraction or ring opening.

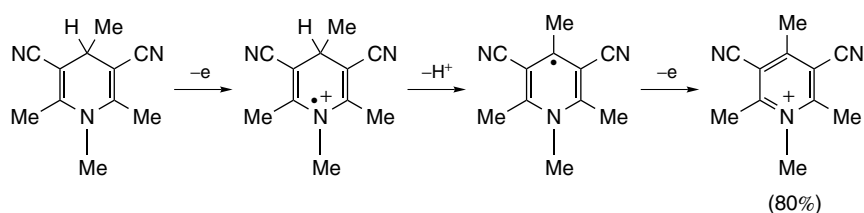
##### 12.1.2.1 Oxidation of Heterocycles

The presence of electron-donating substituents generally favors oxidation of heterocycles.

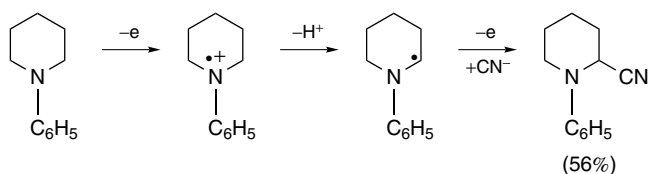
Oxidations of heterocycles can afford formations of double bonds. This is illustrated by the anodic oxidation of dihydropyridines (Scheme 11) [16] for which pyridinium cations are produced according to an ECE mechanism. Unsubstituted dihydropyridines at carbon 4 give pyridines.

Anodic oxidations can produce cationic species that react with nucleophiles. For example, the oxidation of *N*-phenylpiperidine performed in the presence of cyanide ions affords an  $\alpha$ -aminonitrile according to an ECEC mechanism (Scheme 12) [17].

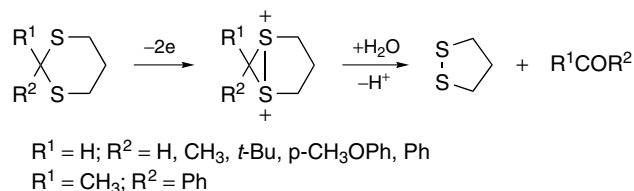
The oxidation of dithianes (Scheme 13) leads to a dicationic species that reacts with water affording aldehydes or ketones and 1,2-dithiolane, which undergoes further oxidation to the sulfoxide (20–74% yields) [18].



**Scheme 11** Anodic dehydrogenation of dihydropyridine.



**Scheme 12** Anodic cyanation of *N*-phenylpiperidine.



**Scheme 13** Anodic deprotection of dithianes.

#### 12.1.2.2 Reduction of Heterocycles

The presence of an electron-withdrawing substituent can favor reductions of heterocycles. In this way, the electroreduction of an activated thiopyran affords a dihydrothiopyran with elimination of dimethylamine (Scheme 14) [19].

### 12.2

#### Oxidative Cyclizations at the Anode

##### 12.2.1

##### Intramolecular Cyclizations

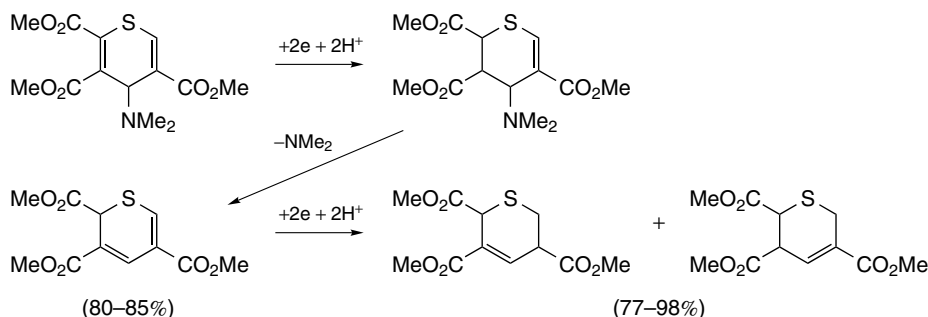
##### 12.2.1.1 Carbon–Carbon Bond Formation

The Kolbe electrolysis has been used by Schäfer and coworkers to synthesize substituted furans or pyrrolidines in good yields by a carbon–carbon coupling reaction after co-oxidations of 6-alkenoic acids and various carboxylic acids [4, 5, 20, 21] (Schemes 2 and 15). In Scheme 15, the

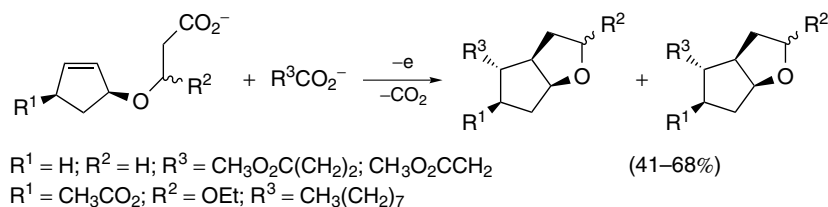
bicyclic tetrahydrofurans produced from 3-cyclopentenyl oxypropionates can be used as intermediates for the synthesis of prostaglandines.

Diarylamides with arenes activated by electron-donating substituents can be converted to azacycles by anodic oxidation through phenolic oxidative coupling reactions that can be a key step in the synthesis of alkaloids (Schemes 16 and 17). According to the nature of substituents and the experimental conditions, either spiro compounds [22] or non-spiro compounds [23, 24] were obtained.

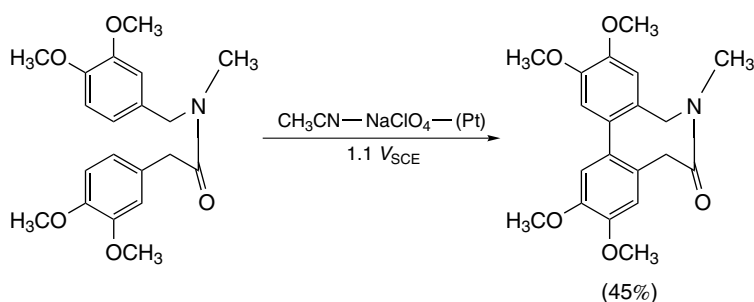
Carbon–carbon bond formation has also been achieved using electroauxiliaries. The method developed by Yoshida and coworkers uses an auxiliary (silicon, tin, sulfur), which when added to a molecule, decreases the oxidation potential of the starting compound. Thus the chance of overoxidation can be avoided. The anodic oxidation of compounds having a



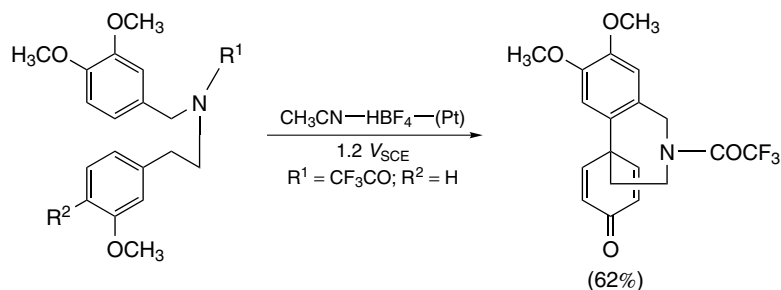
**Scheme 14** Cathodic partial hydrogenation and deamination of a thiopyran.



**Scheme 15** Intramolecular addition of Kolbe radicals.



**Scheme 16** Anodic aryl-aryl coupling.



**Scheme 17** Anodic aryl-aryl coupling.

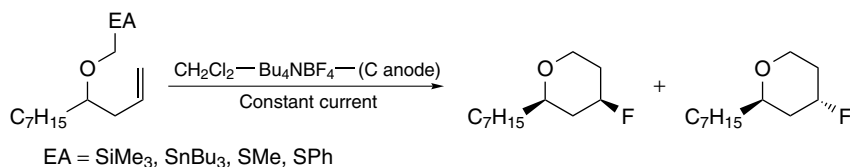
carbon-carbon double bond leads to the selective cleavage of the carbon-auxiliary bond, and the effective intramolecular carbon-carbon bond formation leads to one of the olefinic carbons and the introduction of fluoride to the other in good yield (61–84%) (Scheme 18) [25–27].

The stereoselectivity of the reaction is higher with a sulfur auxiliary (cis/trans: 87/13) and lower with a silicon auxiliary (cis/trans: 55/45).

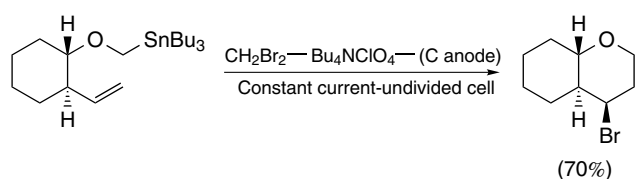
A bromide was introduced in the reaction instead of a fluoride in performing the anodic oxidation of  $\alpha$ -stannyl ethers in dibromomethane solvent with tetrabutylammonium perchlorate as the electrolyte (Scheme 19) [28]. The bromide ion was generated by the reduction of the solvent at the cathode of an undivided cell.

Cyclizations involving aromatic rings can also be obtained in good yield (54–80%) after anodic oxidations of





**Scheme 18** Selective anodic cyclization assisted by an electroauxiliary.



**Scheme 19** Selective anodic cyclization assisted by an electroauxiliary.

$\alpha$ -stannyl ethers and carbamates [28] or  $\alpha$ -organothiocarbamates [29] having an aromatic ring in the appropriate position (Scheme 20).

#### 12.2.1.2 Carbon–Heteroatom Bond Formation

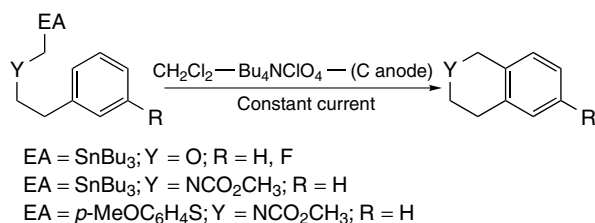
**12.2.1.2.1 Carbon–Oxygen Bond Formation** Hydroxyl or carboxylate groups can participate in a ring-closure reaction by an intramolecular nucleophilic attack to a generated electrophilic center as already described in Schemes 1 and 3.

The process described in Scheme 3 was previously observed by Weinberg and coworker [30] for the anodic oxidation of *N*-benzyl,*N*-methylethanolamine in basic

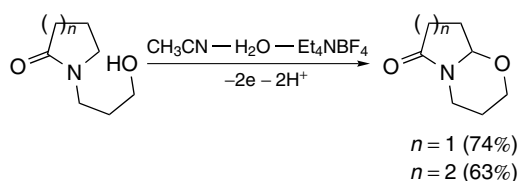
media (methanol–KOH). A mixture of two oxazolidines resulting from two *N*-alkyliminium intermediates was obtained.

The same mechanism can be proposed for the intramolecular alkoxylation of conveniently substituted lactams (Scheme 21) [31, 32].

The oxidation of enol ethers at a reticulated vitreous carbon anode [2, 3] (Scheme 1) in a mixture of methanol/THF containing tetraethylammonium tosylate as the electrolyte and 2,6-lutidine as the base leads to substituted tetrahydrofuran and tetrahydropyran rings in good yields (51–96%). The major product obtained had a *trans*-stereochemistry. The cyclization failed to make seven-membered ring products. In order to determine the



**Scheme 20** Intramolecular cyclization to ethers and carbamates.



**Scheme 21** Intramolecular alkoxylation of lactams.

reactivity of a terminating group for the enol ether radical cation, Moeller and coworkers [2] used a cyclization reaction to form a five or six-membered ring and a quaternary carbon (Scheme 22).

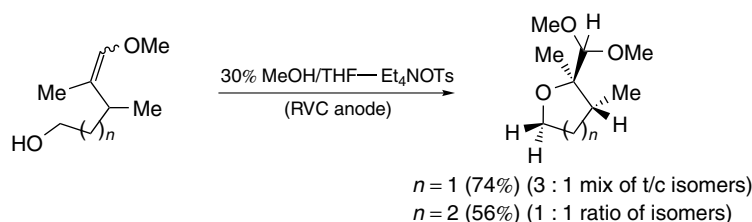
The reaction can also be initiated by the oxidation of a ketene acetal equivalent (Scheme 23).

6,5-Bicyclic [33] and 7,5-bicyclic [34, 35] dipeptides (Scheme 24) have been synthesized by a one-step electrochemical cyclization from various dipeptides. The selective anodic amide oxidation

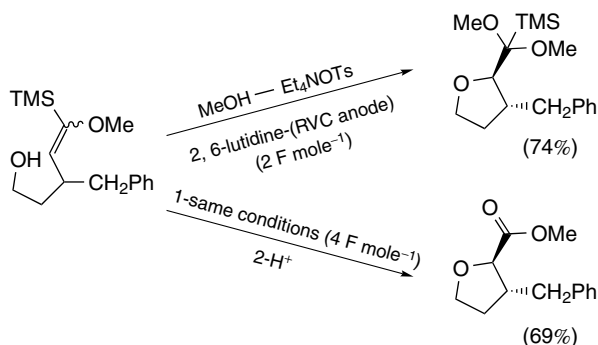
generates an *N*-acyliminium cation, which is trapped by an intramolecular hydroxyl group, for oxidation of *N*-benzyl, *N*-methylethanolamine [30].

The anodic oxidation of (*S*)-2-acetamido-2-(3,4-dimethoxybenzyl)propionitrile (Scheme 25) [36] probably proceeds *via* formation of a benzyl cation.

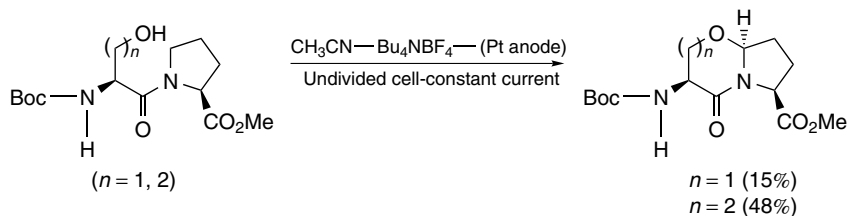
Substituted spiroketals can be prepared in good yields (51–61%) by the electrochemical oxidative cyclization of  $\omega$ -hydroxytetrahydropyrans in anhydrous ethanol containing lithium



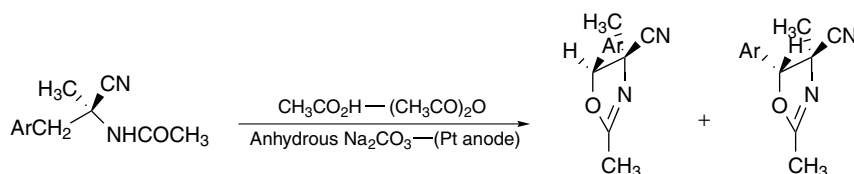
**Scheme 22** Cyclization of enolethers.



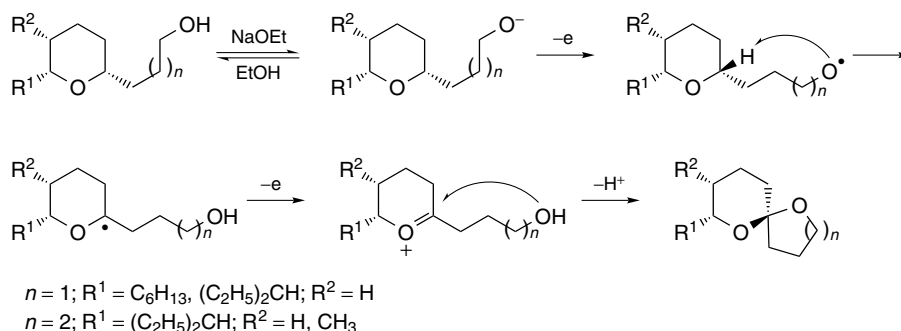
**Scheme 23** Cyclization of a ketene acetal equivalent.



Scheme 24 Cyclization of dipeptides.



Scheme 25 Cyclization of a benzyl cation.

Scheme 26 Cyclization of  $\omega$ -hydroxytetrahydropyrans.

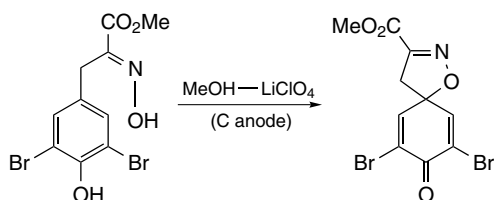
tetrafluoroborate as the electrolyte and sodium ethylate as the base [37]. The proposed mechanism described in Scheme 26 assumes, after a first-electron transfer, an intramolecular hydrogen abstraction followed by a second-electron transfer leading to the selective formation of a cyclic oxonium cation. The process was completed by a subsequent cyclization.

The anodic oxidation of methyl-3,5-dibromo-4-hydroxyphenylpyruvate oxime affords a spiroisooxazole in almost quantitative yield (Scheme 27) [38].

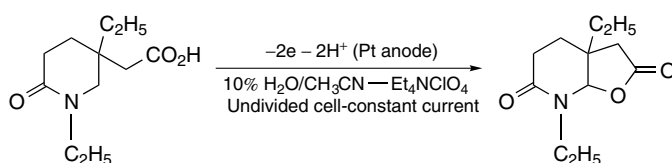
The anodic lactonization of a 2-piperidinone carboxylic acid (Scheme 28) [39] results from a coupling reaction between the nucleophilic carboxylate and the electrogenerated iminium intermediate.

#### 12.2.1.2.2 Carbon–Nitrogen Bond Formation

A carbon–nitrogen bond can result either from the reaction between an anodically produced cationic center and an amino group or from the reaction between a nucleophilic center and an electrogenerated electrophilic nitrogen



**Scheme 27** Cyclization to a spiroisooxazole.



**Scheme 28** Lactonization from an iminium intermediate.

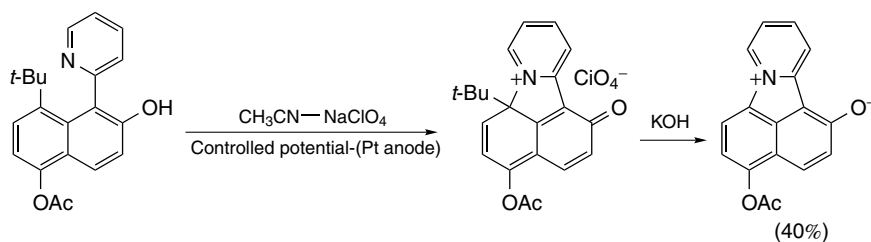
obtained after oxidation of the amino or the hydroxylamino groups.

The oxidation of 8-*t*-butyl-1-(2-pyridyl)-2-naphthol illustrates the reaction between a produced cationic center and a tertiary amine (Scheme 29) [40]. The produced pyridinium salt reacts in a basic medium with loss of isobutylene.

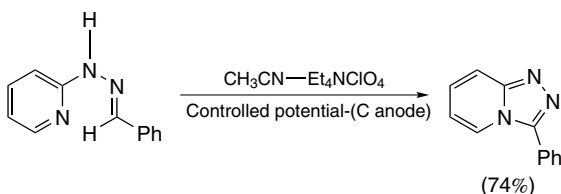
Electrochemical syntheses of triazoles, imidazoles, and pyrazoles can involve

anodic oxidations of various phenylhydrazones or equivalent species. In this way, electrochemical oxidations of benzylidene 2-pyridylhydrazone and chalcone phenylhydrazone [41–43] lead to 3-phenyl-*s*-triazolo[4,3a]pyridine (Scheme 30) and 1,3,5-triphenylpyrazol (Scheme 31), respectively.

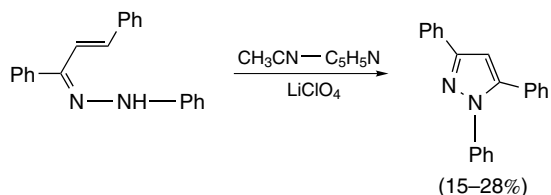
Anodic oxidations of secondary amines can provide radicals or radical cations.



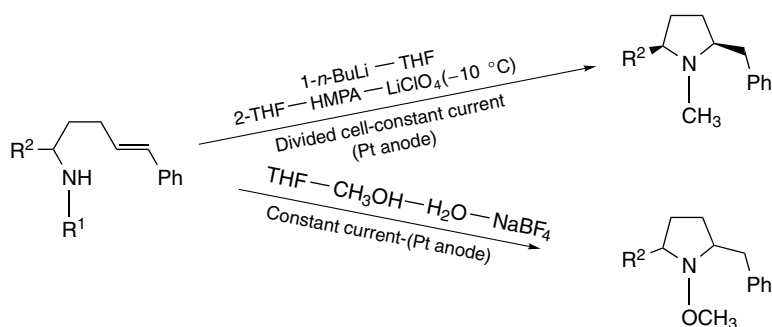
**Scheme 29** Intramolecular cyclization to a pyridinium salt.



**Scheme 30** Cyclization of a benzylidene 2-pyridylhydrazone.



**Scheme 31** Cyclization of phenylhydrazones.



**Scheme 32** Cyclization of unsaturated amines.

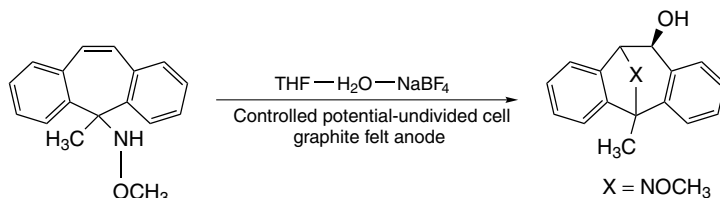
In the presence of a double bond in an appropriate position, a radical coupling can take place as shown in Scheme 32.

For  $R^1 = \text{CH}_3$ , the amines are first treated with  $n\text{-BuLi}$  in order to generate the corresponding nitrogen anions, which undergo a one-electron oxidation, affording nitrogen radicals. After radical coupling followed by hydrogen abstraction from the solvent, pyrrolidines with a *cis*-stereochemistry are obtained in good yields (66–85%) [44, 45].

For  $R^1 = \text{OCH}_3$ , the direct oxidation of the amines led to pyrrolidines in

lower yields (38–42%) [44]. However, the presence of a methoxy group bonded to the nitrogen atom does not prevent good yields as observed in Scheme 33, where the product was isolated in 85% yield [46].

Nitroso groups are well known as good electrophilic reagents and can be used to prepare various heterocycles. However, a direct electrochemical access to nitroso derivatives from the corresponding nitro compounds is not usual. Generally, nitroso compounds are obtained in two consecutive steps as summarized in Scheme 34.



**Scheme 33** Cyclization of *O*-methylhydroxylamines.



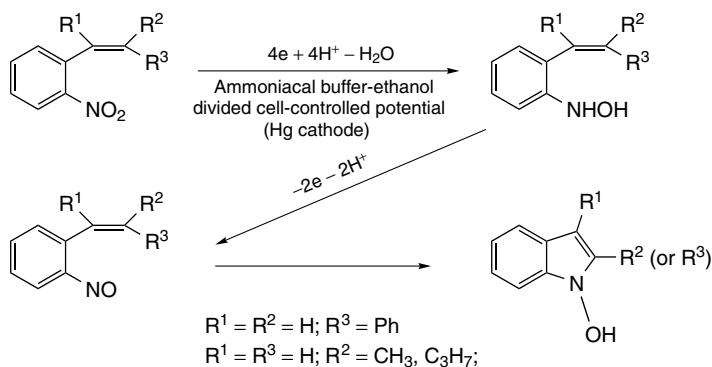
**Scheme 34** Nitroso group generation by reduction – oxidation.

Electrosyntheses of heterocycles from nitroso derivatives prepared in a batch cell according to Scheme 34 need two conditions. The first one is a good stability of the hydroxylamine intermediate and the second one is a very fast cyclization of the nitroso compound to avoid the formation of an azoxy compound by condensation of the generated nitroso and the hydroxylamine. Electroanalytical studies using cyclic voltammetry can give information on the rate of cyclization.

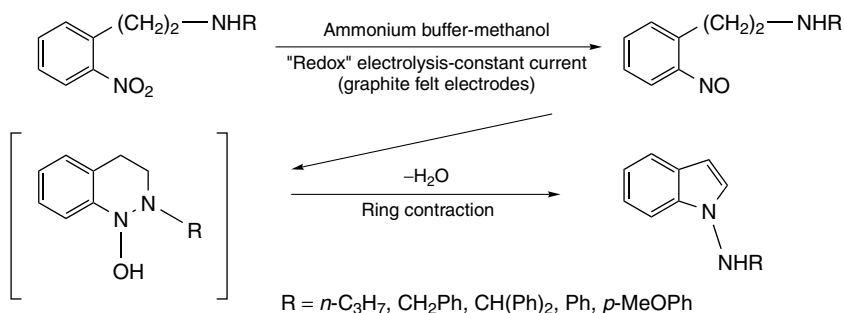
Some *N*-hydroxyindoles were prepared from *o*-nitrophenyl alkenes according to

Scheme 35 [47]. However, with electron-withdrawing substituents in  $\beta$  position ( $R^2 = \text{CN}$  or  $\text{CO}_2\text{Et}$ ), only the azoxy compound was obtained because of a slow cyclization.

However, an improved electrochemical “redox” methodology using a flow cell fitted with two consecutive porous electrodes of opposite polarities (cathode then anode), allows a rapid and total oxidation at the anode of the hydroxylamine intermediate produced at the cathode. Various nitroso compounds may be obtained in high yields without



**Scheme 35** Cyclization of an electrogenerated nitroso compound.



**Scheme 36** Cyclization of an electrogenerated nitroso compound.

formation of azoxy compounds [48–54]. This methodology has been developed for the synthesis of 1-aminoindoles (25–71% yields) from N-substituted 2-(*ortho*-nitrophenyl)ethylamines as depicted in Scheme 36 [53]. The intramolecular cyclization involves hydrocinnoline-type intermediates that, under slightly basic conditions, undergo a spontaneous ring contraction.

Indirect oxidations of amides by electro-generated “Cl<sup>+</sup>”, which gives an adduct with the amide nitrogen, has been used to synthesize chiral building blocks (Scheme 37) [55].

#### 12.2.1.2.3 Carbon–Sulfur Bond Formation

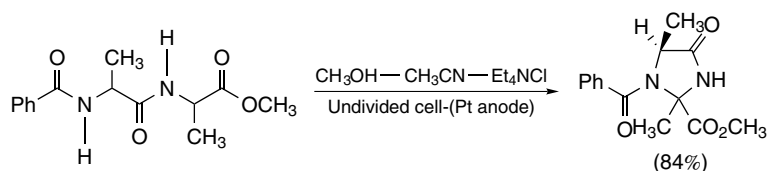
1,3-Thiazole derivatives can be obtained in good yields (60–95%) by intramolecular electrocyclization of thiocarboximides. The mechanism involving a two-electron process is shown in Scheme 38 [56]. After the second-electron transfer, the thiocarbonyl group attacks the cationic site located in the *ortho* position of the aromatic nucleus.

#### 12.2.1.3 Heteroatom–Heteroatom Bond Formation

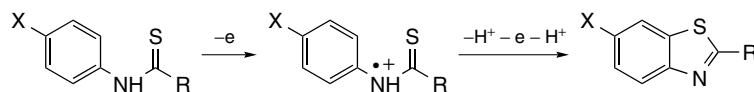
##### 12.2.1.3.1 Nitrogen–Nitrogen Bond Formation

Triazole derivatives may be obtained by the electrooxidation of molecules containing several nitrogen atoms as illustrated in Scheme 39 [57].

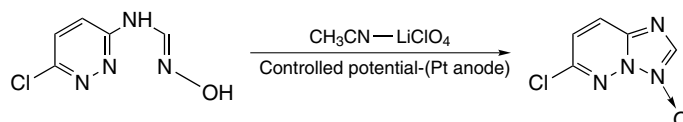
In order to prepare 2-substituted indazoles, electrolyses (Scheme 40) of *ortho*-nitrobenzylamines in two steps were performed in a batch cell [7] and in a flow cell, equipped with two consecutive porous electrodes of opposite polarities (*vide supra*) [52]. Only benzylamines bearing an electron-donating group were successfully cyclized in a batch cell because an electron-withdrawing substituent dramatically decreased the rate of the intramolecular cyclization. On the contrary, indazoles substituted either by the electron-donating or the electron-withdrawing group were obtained in good yields (70–85%) in a “redox” cell.



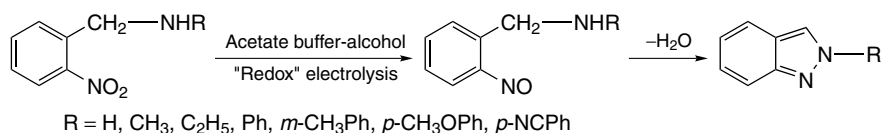
**Scheme 37** Cl-mediated cyclization of a dipeptide.



**Scheme 38** Electrocyclization of a thiocarboximide.



**Scheme 39** Synthesis of a triazol.



**Scheme 40** Cyclization by way of an electrogenerated NO-group.

In the same way, cinnoline and 1,4-dihydrocinnoline were prepared from *ortho*-nitrophenyl ethylamine by a two-step electrolysis performed either in a batch cell [58] or in a flow cell [53] (Scheme 41).

**12.2.1.3.2 Nitrogen–Oxygen Bond Formation** The anodic oxidation of vicinal dioximes gives 3,4-diphenylfurazan-2-oxide by intramolecular ring formation (Scheme 42) [59].

#### 12.2.2 Intermolecular Coupling

Intermolecular coupling reactions can take place either through a reaction between an electrogenerated reagent and another suitable species (heterocoupling reaction)

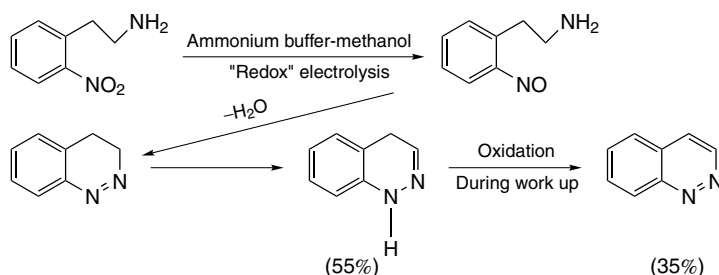
or by the “dimerization” of the electrogenerated reagent (homocoupling reaction).

#### 12.2.2.1 Heterocoupling Reactions

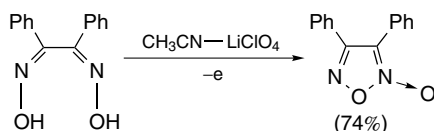
**12.2.2.1.1 Cycloaddition Reactions with Alkenes** Olefins can react with electrogenerated radicals, cationic species or dienophiles.

Electrochemical oxidations of anions lead to radicals that may add to the carbon–carbon double bonds. In this way, the oxidation of anions of dimethyl malonate or methyl acetylacetate in the presence of olefins gives di- or tetrahydrofurans derivatives in moderate yields (Scheme 43) [60].

The same reaction can occur during the anodic oxidation of the enolate of

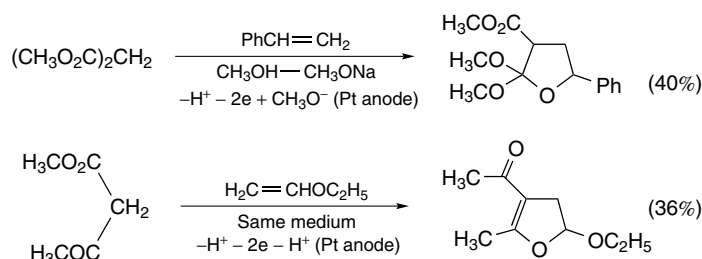


**Scheme 41** Cinnolines via cyclization with an electrogenerated NO-group.

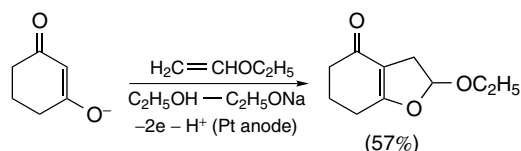


**Scheme 42** Anodic cyclization of *vic*-dioximes.





**Scheme 43** Anodic addition of anions of 1,3-dicarbonyl compounds to electron-rich olefins.



**Scheme 44** Anodic addition of the anion of a 1,3-dicarbonyl compound to vinyl ethyl ether.

cyclohexan-1,3-dione in a basic media (Scheme 44) [61, 62].

Yoshida and coworkers [63, 64] studied the oxidative cycloaddition of cyclic 1,3-dione (1,3-cyclopentanedione and some 1,3-cyclohexanediones) and olefins in various solvents and electrolytes. The best results were obtained in acetonitrile containing tetraethylammonium tosylate as electrolyte (97% yield with 5,5-dimethyl-1,3-cyclohexadione and styrene) (Scheme 45).

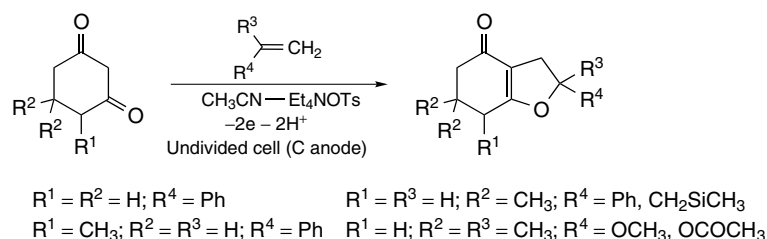
A mechanism involving attack of a radical intermediate to olefin has been proposed (Scheme 46) [64].

An electrochemical oxidation of hydroquinones can be used to initiate [3 + 2] cycloaddition reactions with alkenes. The

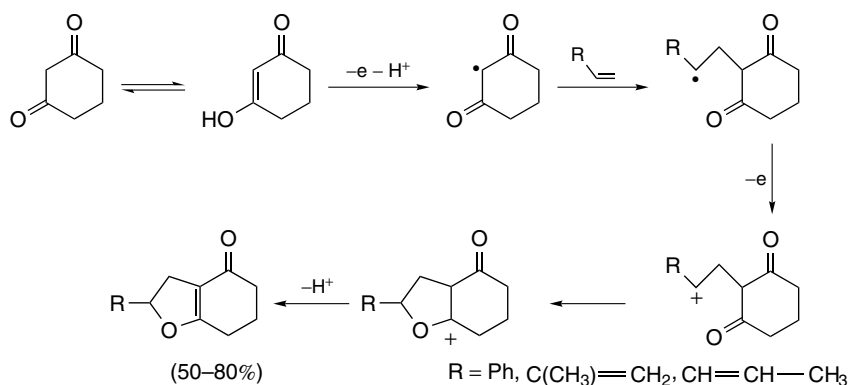
reaction, first studied by Swenton and coworkers [65, 66], was recently performed at a PTFE-coated carbon anode in a highly polar electrolyte solution affording dihydrobenzofurans in good yields (60–99%) (Scheme 47) [67].

The electrochemical oxidation of *N,N*-diarylhydrazines affords diazenium cations that undergo cycloadditions with olefins (*vide supra* Scheme 5) [8, 9, 68–70]. Acetonitrile can participate in the formation of cycloadducts.

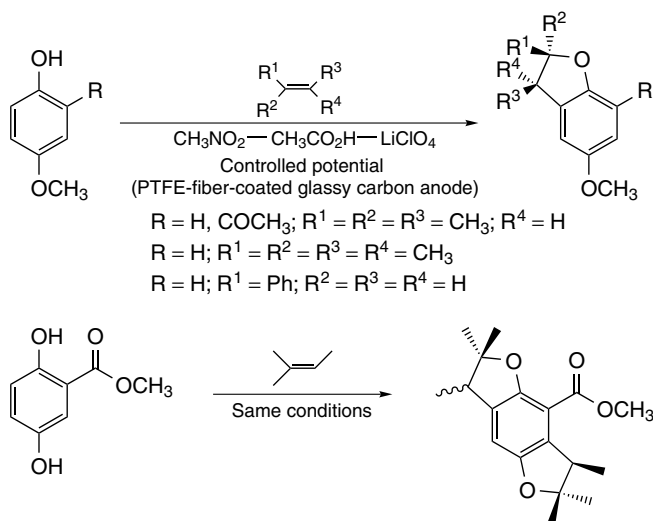
The electrochemical oxidation of *N,N*-dibenzyl, *N'*-arylhydrazines gives carbocations that react with alkenes affording five-membered heterocycles (Scheme 48) [70].



**Scheme 45** Anodic addition of the anion of 1,3-cyclohexanedione to electron rich olefins.



**Scheme 46** Mechanism of anodic addition with subsequent cyclization.



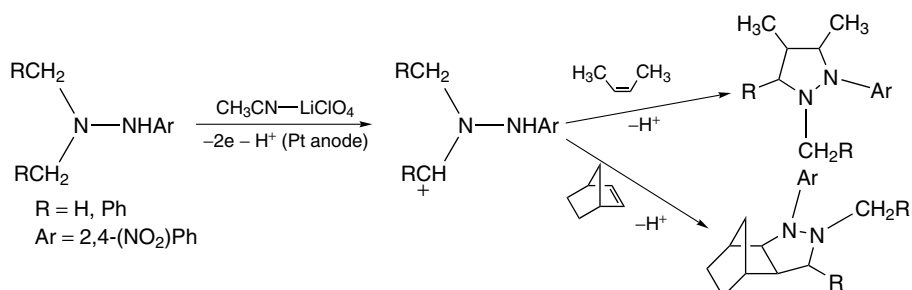
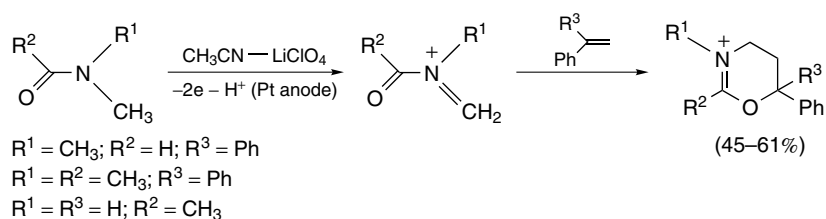
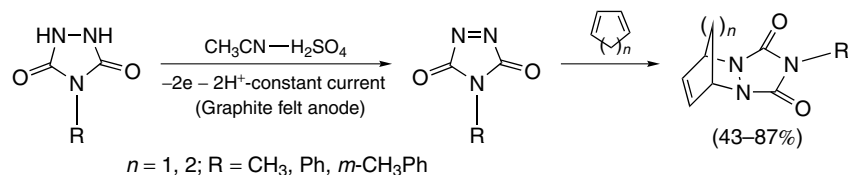
**Scheme 47** Phenols in anodic addition with subsequent cyclization.

The anodic oxidation of *N*-methylamides leads to *N*-acyliminium intermediates that may react with olefins (Scheme 49) [71].

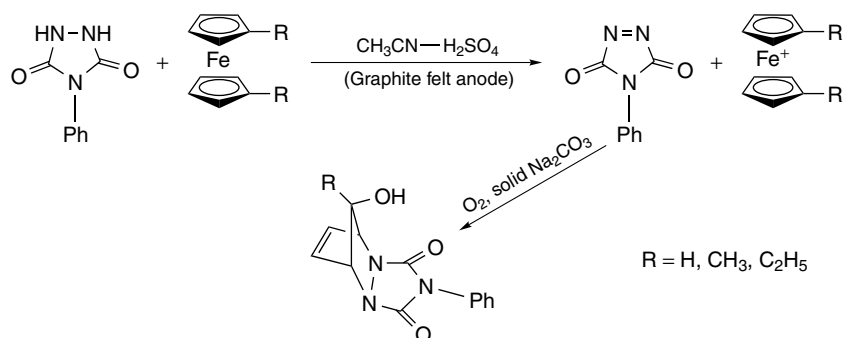
Dienophilic cyclic  $\alpha$ -carbonylazo compounds (triazoline diones, indazolone, phthalazine dione) prepared in a flow cell, by anodic oxidation of the corresponding hydrazino compounds in acidic methanol or acetonitrile, react with dienes (Scheme 50) [72, 73].

The coupling reaction is very fast because unstable cyclopentadienols resulting from the decomposition of ferrocenium cations can be trapped, in good yields (80%), by triazoline diones [73]. The cycloadduct is obtained with totally regio and stereo selectivities (Scheme 51).

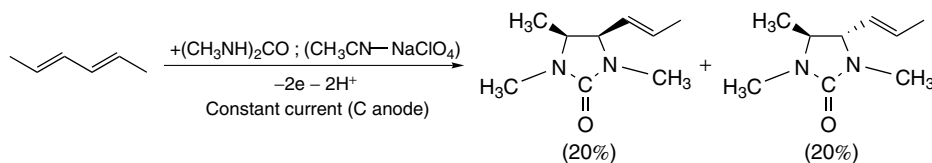
The oxidative addition of *N,N'*-dimethylurea to 2,4-hexadiene gives imidazolinones (Scheme 52) [74].

Scheme 48 Cycloaddition with *N,N*-dibenzylhydrazines.Scheme 49 Cycloaddition with *N*-acyliminium ions.

Scheme 50 Cycloaddition with hydrazino compounds.



Scheme 51 Anodic cycloaddition of a hydrazino compound to cyclopentadiene from ferrocene.



**Scheme 52** Anodic addition of dimethylurea to 2,4-hexadiene.

#### 12.2.2.1.2 Cycloaddition Reactions with Other Nucleophiles

The anodic two-electron oxidation of catechol affords *o*-quinone that may react with the enolates of 4-hydroxycoumarin or 5,5-dimethyl-1,3-cyclohexanedione (dimedone). The resulting adducts undergo a second anodic oxidation leading to benzofuran derivatives in good yields (90–95%) (Scheme 53) [75, 76].

The oxidation of *N*-phenylhydrazones in the presence of pyridine leads to the formation of *s*-triazolo[4,3a]pyridinium salts by attack of pyridine as a nucleophile on the nitrilimine intermediate (Scheme 54) [77].

Conveniently, ortho-substituted nitroso-benzenes prepared in a “redox” cell (*vide supra*) from the corresponding

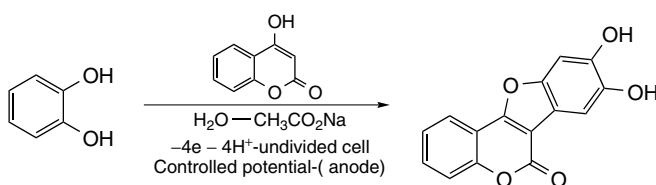
nitrobenzenes react with sulfinic acids affording *N*-sulfonylated hydroxylamines that may undergo cyclization into *N*-sulfonylated benzisoxazolones in moderate yields (50–79%) (Scheme 55) [49–51].

#### 12.2.2.2 Homocoupling Reactions

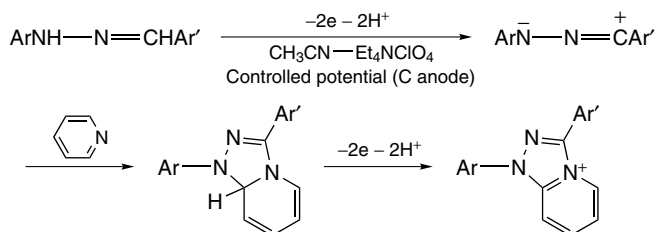
Anodic dimerizations of enamino esters (Scheme 56) or ketones may give symmetrically substituted pyrroles [78].

Dimerizations can also be observed from the anodic oxidations of ketene imines (Scheme 57) [79] or alkylisothiocyanates (Scheme 58) [80].

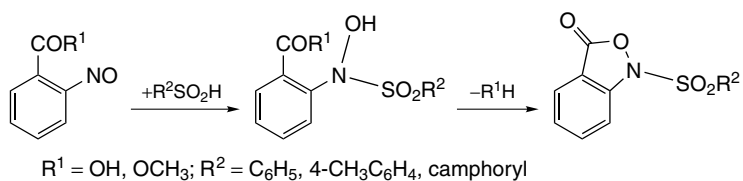
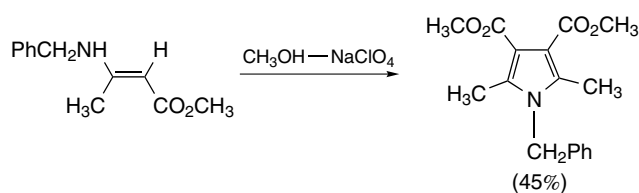
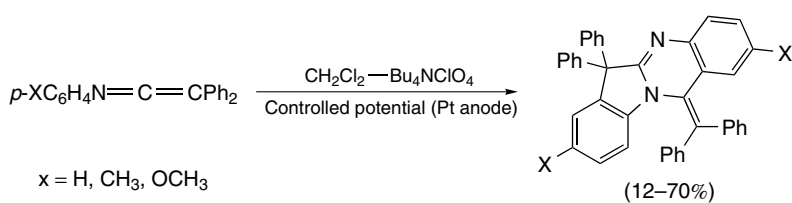
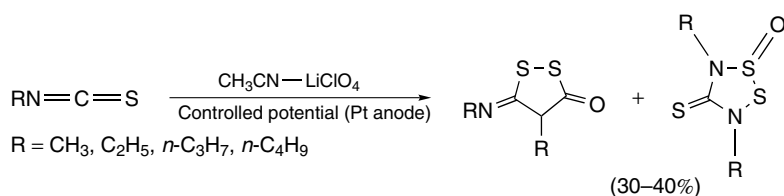
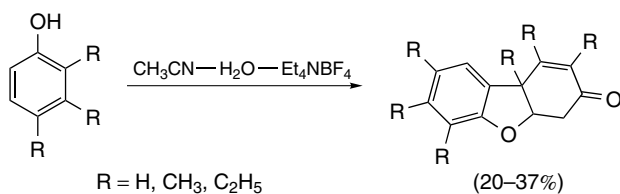
Derivatives of dihydrofurans are produced in limited yields (20–37%) after the anodic oxidations of phenols (Scheme 59) [81].



**Scheme 53** Anodic cycloaddition with catechol.



**Scheme 54** Anodic cycloaddition between pyridine and *N*-phenylhydrazones.

**Scheme 55** Cycloaddition with electrogenerated nitrosobenzenes.**Scheme 56** Anodic dimerization of enamino esters.**Scheme 57** Anodic coupling of ketenimines.**Scheme 58** Anodic coupling of alkylisothiocyanates.**Scheme 59** Dihydrofurans by anodic coupling of phenols.

## 12.3 Reductive Cyclization at the Cathode

### 12.3.1 Intramolecular Cyclization

#### 12.3.1.1 Carbon–Carbon Bond Formation

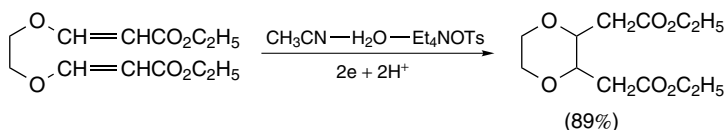
Electrohydrodimerization is well known for its application in the preparation of adiponitrile [82]. The method was successfully used in the preparation of heterocycles from reductions of activated bis-alkenes (Scheme 60 and *vide supra* Scheme 6) [10, 83] or bis-imines affording substituted piperazines in good yields, in the presence of proton donors (Scheme 61) [84].

Reductive cyclizations of nonconjugated olefinic ketones (see Scheme 8) [12] or

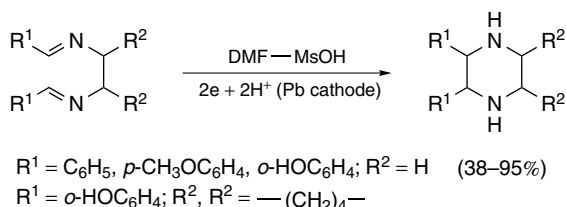
pyridinium salts N-substituted by a non-conjugated keto group (Scheme 62) [85], afford cyclic tertiary alcohols.

The cathodic cleavage of dihalides may be a powerful route to a variety of heterocycles (Schemes 63 and 64) [86–88].

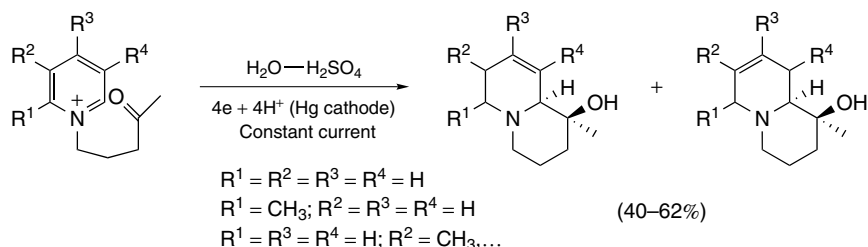
Organic electroreductive coupling reactions using transition-metal complexes as catalysts have been widely investigated. Reviews on the subject have been published [89, 90]. The method involving the most common transition-metal complexes (nickel, cobalt, palladium) appears to be a useful tool to synthesize heterocycles from organic halides *via* radical intermediates. Nickel catalyst precursors are nickel(II) salts that are cathodically reduced either to nickel(I) or to nickel(0) and cobalt catalyst



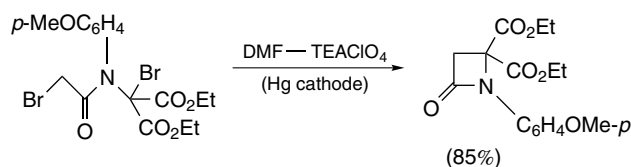
**Scheme 60** Cathodic cyclization of activated bis-alkenes.



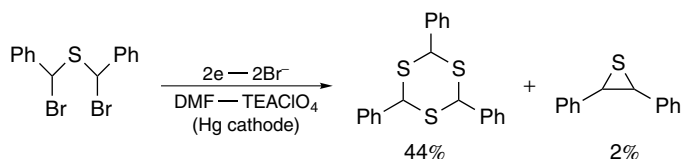
**Scheme 61** Cathodic cyclization of activated bis-imines.



**Scheme 62** Cathodic cyclization of *N*-ketoalkyl pyridinium salts.



**Scheme 63**  $\beta$ -Lactams by cathodic elimination of dihalides.

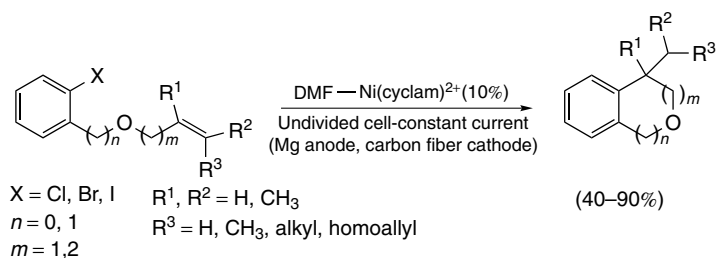


**Scheme 64** Trithiacyclohexane by cathodic elimination of  $\alpha, \alpha'$ -dibromothioether.

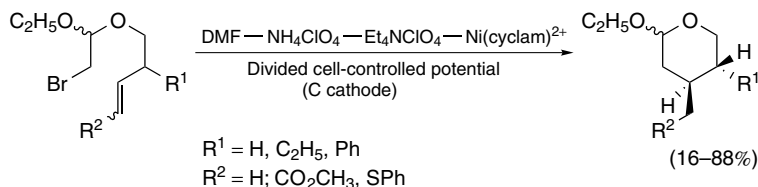
precursors are cobalt(III) or cobalt(II) that are reduced to cobalt(I). Phosphino complexes of palladium(II) undergo a two-electron reduction to active palladium(0). The reduced complexes react rapidly with insertion in the carbon–halogen bond of the organic substrate, and simultaneous oxidation of the metallic center. After a second electron transfer, the cleavage of

the carbon–metal bond regenerates the active form of the catalyst and gives an alkyl, alkenyl, or aryl radical, which adds intramolecularly to a double or a triple bond. In some cases, a carbanion is obtained, which can react with electrophiles. Some examples are given below.

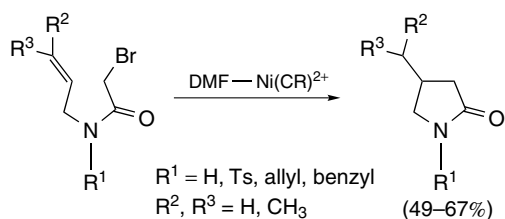
Catalytic electroreductions involving nickel complexes produced five [91–95] or



**Scheme 65** Heterocycles by Nickel catalyzed intramolecular cathodic addition of halides to double bonds.



**Scheme 66** Heterocycles by Nickel catalyzed intramolecular cathodic addition of halides to double bonds.

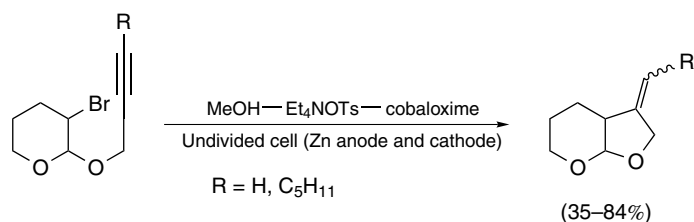


**Scheme 67** Heterocycles by Nickel catalyzed intramolecular cathodic addition of halides to double bonds.

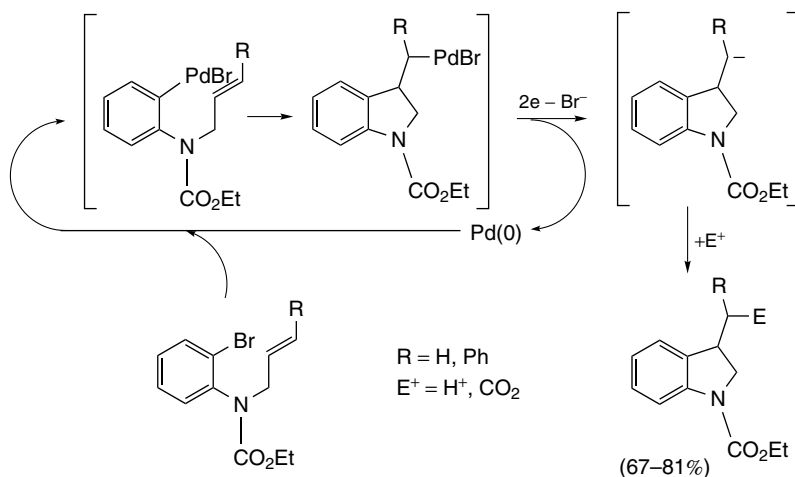
six-membered [96, 97] rings in low to high yields from conveniently available unsaturated halides (Schemes 65, 66 and 67).

Similar cyclizations can be performed using cobalt complexes (vitamin B<sub>12</sub> and B<sub>12</sub> analogs) as mediators [97–100] (Scheme 68).

Palladium complexes have been used for the electroreductive cyclization of *N*-alkenyl-2-bromoanilines to the corresponding indoline derivatives (Scheme 69) [101]. The postulated carbanion intermediate undergoes a reaction with the electrophiles ( $\text{H}^+$ ,  $\text{CO}_2$ ).



**Scheme 68** Vitamin B<sub>12</sub>-catalyzed cyclization of alkyl bromides with alkynes.



**Scheme 69** Palladium(0) catalyzed cathodic cyclization of aryl bromides and double bonds.



### 12.3.1.2 Carbon–Heteroatom Bond Formation

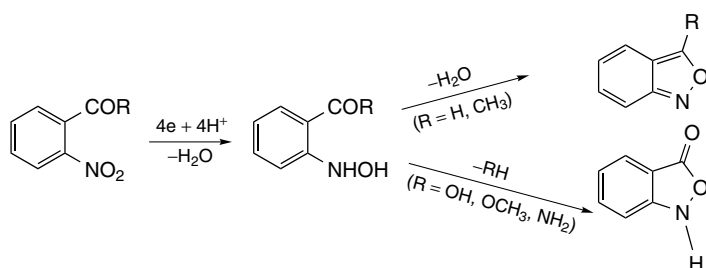
**12.3.1.2.1 Carbon–Oxygen Bond Formation** The cathodic reduction of some nitrocarbonyl compounds in aqueous acidic medium gives the hydroxylamino derivatives that can undergo a ring-closure reaction affording anthranilic compounds or isoxazolones [102–104] (Schemes 70 and 71).

Butenolides can be produced after cathodic reduction involving an electron-deficient allene and a ketone (Scheme 72) [105].

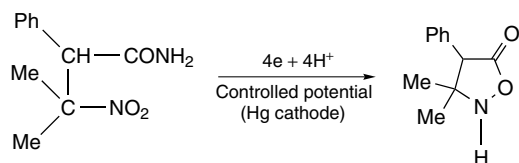
**12.3.1.2.2 Carbon–Nitrogen Bond Formation** The cathodic reduction, in protic media, of aromatic nitro compounds produces nucleophilic centers, either

hydroxylamino groups (four-electron reduction) or amino groups (six-electron reduction, in a sufficiently acidic medium, at a more negative potential than the first four-electron wave). In the presence of a suitable electrophilic substituent (keto, ester or cyano group), a cyclization can occur with a carbon–nitrogen bond formation leading to the heterocyclic *N*-hydroxy compounds, *N*-oxides or hydroxamic acids.

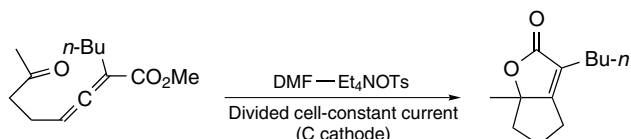
In acidic or slightly basic aqueous media, *N*-hydroxyindoles can be prepared after electrolysis of  $\alpha$ -(*o*-nitrophenyl) ketones (*vide supra* Scheme 9) [13], at a working potential corresponding to the first cathodic wave. In an acidic medium, indoles are directly obtained at a working potential corresponding to the second cathodic wave.



**Scheme 70** Cathodic reduction of nitrocarbonyl compounds to anthranilic derivatives.



**Scheme 71** Cathodic reduction of nitrocarbonyl compounds to isoxazolones.



**Scheme 72** Butenolides by cathodic cyclization of allene and ketone.

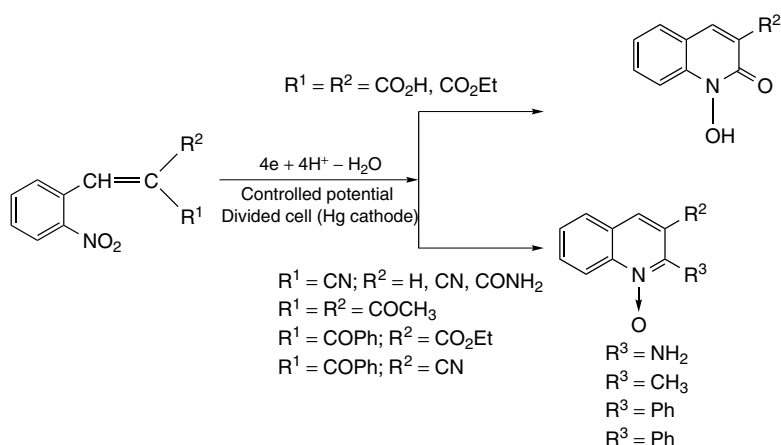
Electrochemical reductions of several *ortho*-substituted nitro compounds of the general formula  $o\text{-O}_2\text{NC}_6\text{H}_4\text{CH}=\text{CR}^1\text{R}^2$  (Scheme 73) [47, 106, 107] or  $o\text{-O}_2\text{NC}_6\text{H}_4\text{COCHR}^1\text{R}^2$  (Scheme 74) [108], in which  $R^1$  and  $R^2$  are electron-withdrawing substituents, have been performed in acidic media leading to various quinoline derivatives.

2-*H*-1,4-Benzoxazine and 2-*H*-1,4-benzothiazine derivatives have been

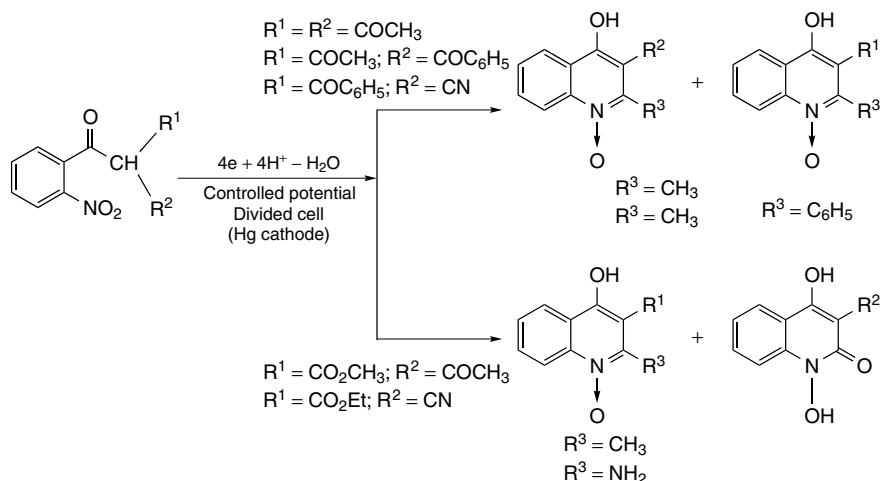
prepared after a cathodic reduction of *o*-nitrophenoxy and *o*-nitrophenylthioacetic compounds, respectively (Scheme 75) [109–111].

A benzothiazine derivative can be also obtained after a four-electron reduction of an *o*-nitrobenzyl thiocyanate in an acidic medium (Scheme 76) [112].

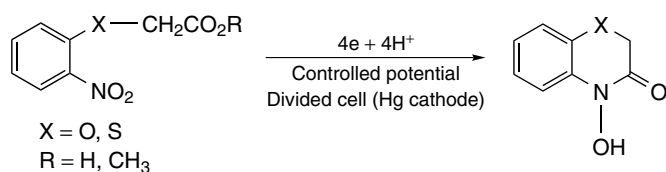
The cathodic reduction of substituted nitrophenylpyridines, pyridiniums or dihydropyridines gives naphthyridine



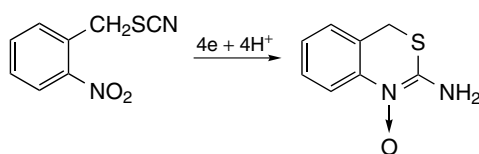
**Scheme 73** Cyclization of *o*-substituted nitroaryl compounds.



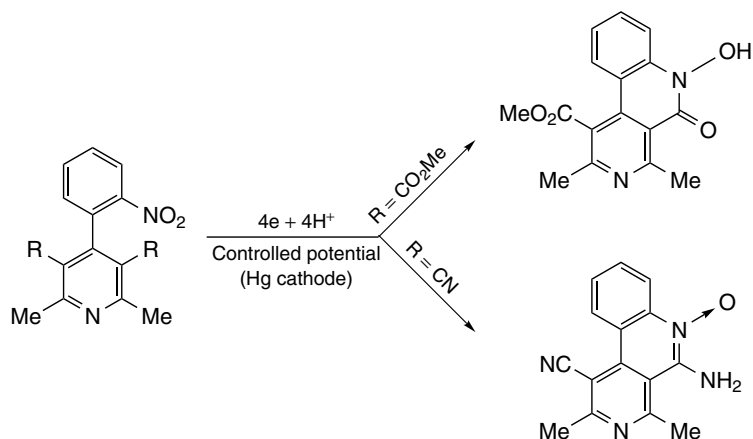
**Scheme 74** Cyclization of *o*-substituted nitroaryl compounds.



**Scheme 75** Benzoxazines and benzothiazines by cathodic cyclization.



**Scheme 76** Benzothiazine by cathodic cyclization of *o*-nitrobenzylthiocyanate.



**Scheme 77** Naphthyridines by cathodic cyclization.

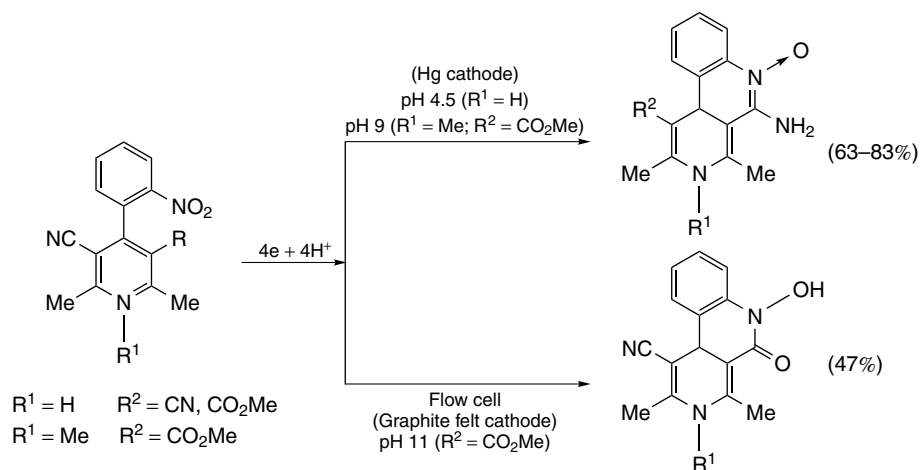
derivatives in good yields (Schemes 77 and 78) [113–115].

The four-electron reduction of symmetrical ( $\text{R}^2 = \text{CN}$ ; Scheme 78) [114] or unsymmetrical ( $\text{R}^2 = \text{CO}_2\text{Me}$ ) [115] 4-(*o*-nitrophenyl)-1,4-dihydropyridines leads to aminobenzonaphthyridine N-oxide when the electrolysis is performed in slightly acidic or slightly basic medium; in higher basic medium, the reduction of the unsymmetrical compound gives a cyclic hydroxamic acid.

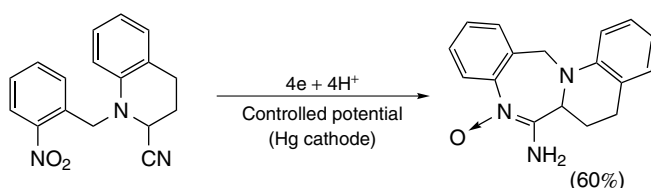
The electrochemical reduction of the corresponding nitrophenylpyridine or pyridinium derivatives only produces cyclic hydroxamic acids.

In the same way, a benzodiazepine ring can be obtained after cathodic reduction of an anodically cyanated 2-nitrobenzyl tetrahydroquinoline (Scheme 79) [115].

According to the working potential, the medium, and the nature of substituents, the cathodic reduction of aliphatic  $\gamma$ -nitroketones leads to pyrroline



**Scheme 78** Naphthyridines by cathodic cyclization.



**Scheme 79** Cathodic cyclization to the benzodiazepine ring.

N-oxide, pyrrolines, and pyrrolidines (Scheme 80) [116, 117].

In the same way, the four-electron cathodic reduction of  $\gamma$ -nitroesters gives *N*-hydroxypyrrolidinones (Scheme 81) [118].

### 12.3.1.3 Heteroatom–Heteroatom Bond Formation

**12.3.1.3.1 Nitrogen–Nitrogen Bond Formation** The cathodic reduction of *o*-nitroazobenzenes in a basic medium leads to benzotriazole N-oxides (Scheme 82) [119–121].

2,2'-Dinitrobiphenyl, in an alkaline solution, is reduced to benzo[*c*]cinnoline N-oxide (Scheme 83) [122, 123].

### 12.3.2

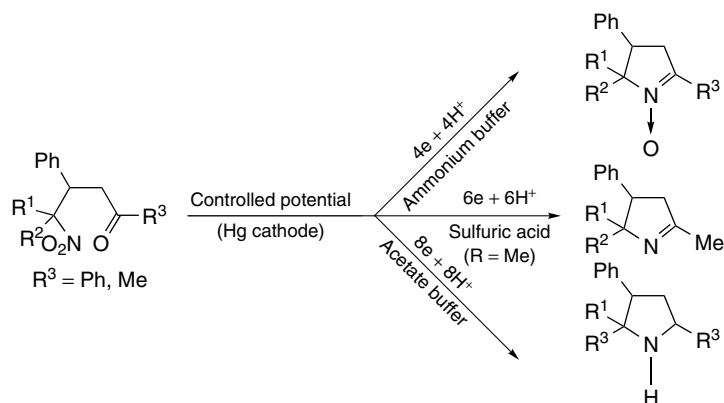
#### Intermolecular Cyclization

##### 12.3.2.1 Heterocoupling Reactions

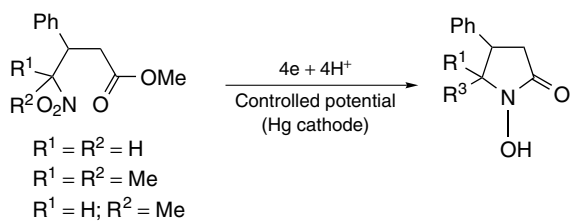
The electrochemical reduction of 2,2-dibromo-1,3-diones in the presence of various olefins (styrene, indene) affords the [3 + 2] cycloadducts, 2,3-dihydrofuran derivatives in moderate to good yields (37–94%) (Scheme 84) [124].

The cathodic reduction of 2-bromo-2-nitropropane in the presence of dimethyl acetylene dicarboxylate leads to 5,5-dimethyl-2,3,4-trimethoxycarbonyl-5-hydropyrrole as the major product (64% yield) (Scheme 85) [125].

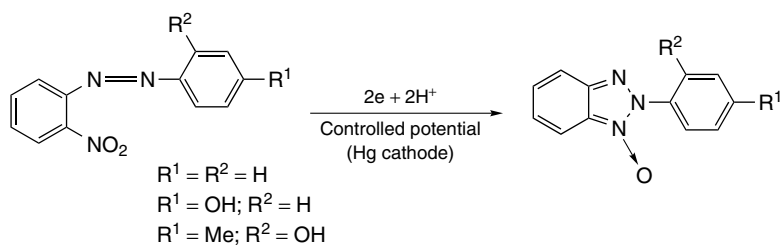
The reduction of acrylic ester in the presence of aldehydes or ketones and trimethylsilyl chloride affords



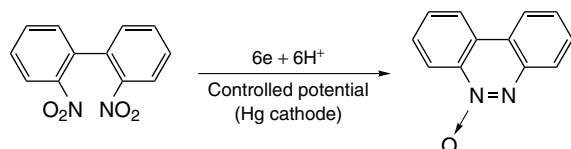
**Scheme 80** N-Heterocycles by cathodic reduction of  $\gamma$ -nitroketones.



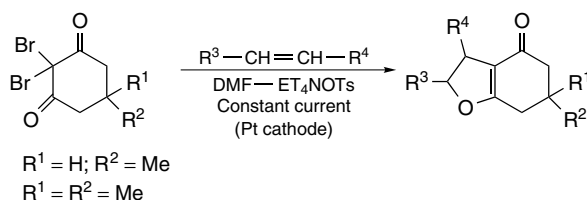
**Scheme 81** N-Heterocycles by cathodic reduction of  $\gamma$ -nitroesters.



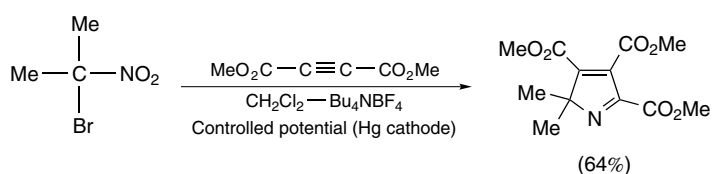
**Scheme 82** Benzotriazoles by cathodic cyclization.



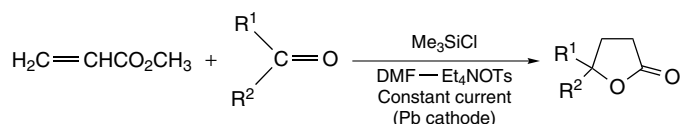
**Scheme 83** Benzo[c]cinnoline by cathodic cyclization of 2,2'-dinitrobiphenyl.



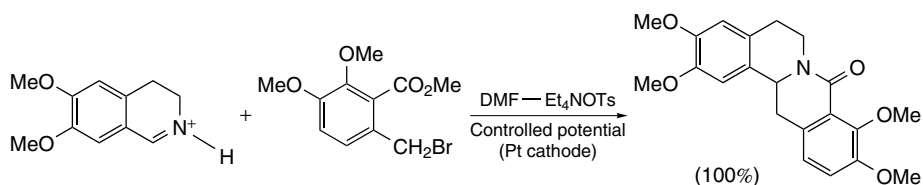
**Scheme 84** [3 + 2]-Cycloaddition with 2,2-dibromo-1,3-diones and alkenes.



**Scheme 85** Cathodic cycloaddition of 2-bromo-2-nitropropane to dimethyl acetylenedicarboxylate.



**Scheme 86** Cathodic heterocoupling of ketones with methyl acrylate.



**Scheme 87** Alkaloid-type compounds by reductive alkylation of iminium salts.

5-substituted tetrahydrofuran-2-one in moderate to good yields (51–86%) (Scheme 86) [126].

The electroreduction of iminium salts in the presence of alkyl halides has been applied to the synthesis of alkaloid-type compounds as depicted in Scheme 87 [127, 128].

#### 12.3.2.2 Homocoupling Reaction

The cathodic reduction of phenyl bromide in an aprotic medium gives substituted furan as summarized in Scheme 88 [129–133].

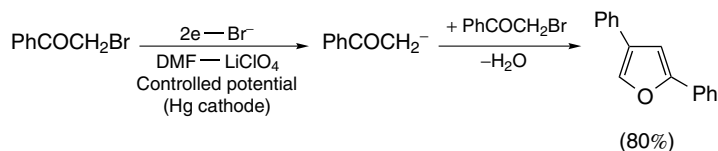
## 12.4

### Anodic Oxidation of Heterocycles

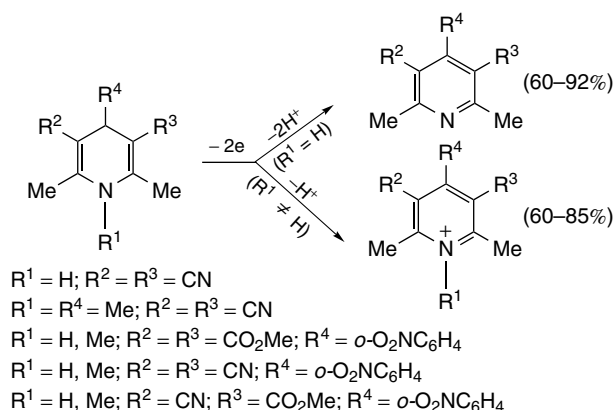
#### 12.4.1

##### Double Bond Formation

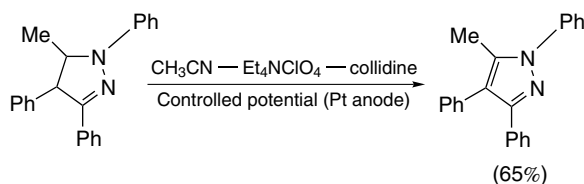
The formation of a double bond during anodic oxidations can result from eliminations of protons, carbon dioxide or acylium cations. The electrooxidative aromatization of dihydropyridine derivatives and heterocycles containing nitrogen atom (dihydroquinoxalines, tetrahydrocinnolines) involves an ECE mechanism as previously



**Scheme 88** Cathodic cyclization of a  $\alpha$ -bromoketone to a furan.



**Scheme 89** Anodic dehydrogenation of dihydropyridines.



**Scheme 90** Anodic dehydrogenation of pyrazolines.

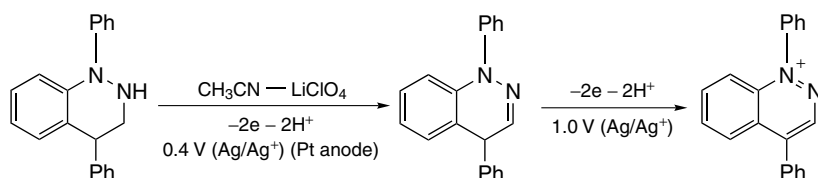
depicted in Scheme 11. The anodic oxidation of substituted 1,4-dihydropyridines can be performed in acetonitrile, at a platinum anode [16, 134] or in slightly acidic hydroalcoholic media, at a graphite felt anode in a flow cell (Scheme 89) [113, 114].

The electrooxidation of substituted pyrazolines in the presence of a base (pyridine, collidine), which facilitates deprotonation from the pyrazoline ring, gives the corresponding pyrazoles (Scheme 90). In the absence of a base, an Ar–Ar coupling product is obtained [135–138].

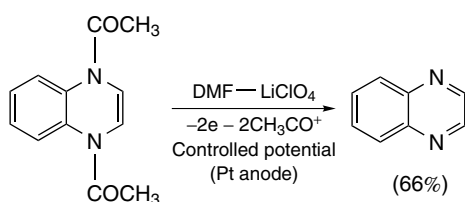
The anodic oxidation of 1,4-diphenyl-1,2,3,4-tetrahydrocinnoline, leads to the corresponding 1,4-dihydrocinnoline and cinnolinium salt, at a more anodic potential (Scheme 91) [8].

The electrooxidation of *N,N*-diacetyldihydroquinoxaline involves a cleavage of the nitrogen–acylcarbon bonds according to an ECEC mechanism (Scheme 92) [139].

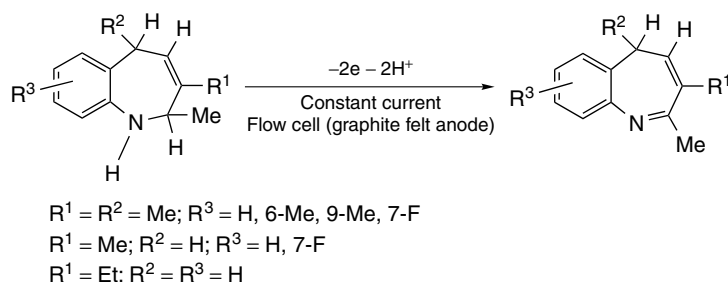
The anodic oxidation of 2,5-dihydro-1*H*-1-benzazepines in slightly acidic hydroalcoholic medium gives 5*H*-1-benzazepines in moderate yields



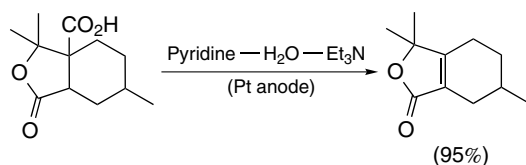
**Scheme 91** Anodic dehydrogenation of tetrahydrocinnoline.



**Scheme 92** Anodic deacylation of *N,N*-diacetyldihydroquinoxaline to quinoxaline.



**Scheme 93** Anodic dehydrogenation of dihydrobenzazepine.



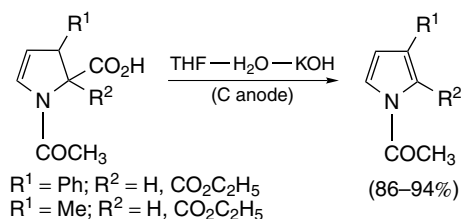
**Scheme 94** Dehydrogenation by way of anodic decarboxylation.

(35–45%) (Scheme 93) [140]. In a slightly basic medium, an intermolecular coupling reaction is observed (*vide infra* Scheme 128).

The formation of a double bond can also be performed either by direct

electrodecarboxylation corresponding to a discharge of a carboxylate ion as shown in Scheme 94 [141], or by an indirect electrodecaboxylation involving the oxidation of a heteroatom in the  $\beta$ -position (Scheme 95) [142–144].





**Scheme 95** Dehydrogenation-decarboxylation to pyrroles.

Various intermediates (uracil, thymine, pyrazoline,  $\beta$ -carboline, and dihydroquinoline derivatives) have been prepared in this way [142–147].

#### 12.4.2

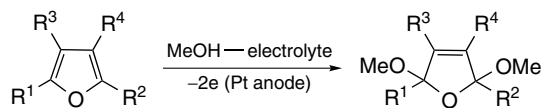
##### Functionalization of Heterocycles

The anodic functionalization of heterocycles, which generally results from a nucleophilic attack of reagents to the oxidized heterocycle, is of great interest in synthetic organic chemistry. In particular,

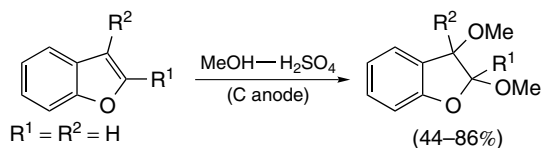
the anodic methoxylation or cyanation of heterocycles can produce powerful synthons.

##### 12.4.2.1 Methoxylation Reactions

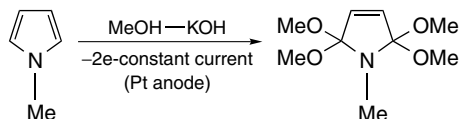
Anodic oxidations of heteroaromatic cycles (furans, pyrroles, benzofurans) in the presence of methanol have been extensively studied [148–165]. The electromethoxylation of differently substituted furans gives 2,5-dimethoxy-2,5-dihydrofurans in moderate to good yields (Scheme 96) [148–159, 166–170].



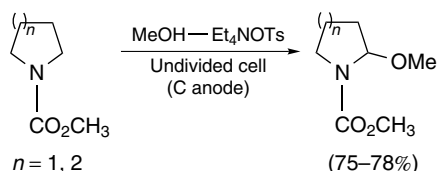
**Scheme 96** Anodic methoxylation of furan.



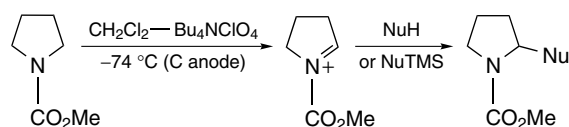
**Scheme 97** Anodic methoxylation of benzofuran.



**Scheme 98** Anodic tetramethoxylation of *N*-methylpyrrol.



**Scheme 99** Anodic methoxylation via an iminium cation.



**Scheme 100** Preparation of stable iminium carbamates at low temperature and trapping with nucleophiles.

In a similar way, benzofurans and *N*-methylpyrrole afford 2,3-dimethoxylated derivatives (Scheme 97) [160] and 2,5-tetramethoxy-2,5-dihydro-*N*-methylpyrrole, respectively (Scheme 98) [57, 161, 162].

A nucleophilic attack of methanol in the  $\alpha$ -position to a nitrogen atom can take place through an electrochemically generated iminium cation from substituted pyrrolidine [171, 172], piperidine [173–180] or oxazolidinone [181, 182] derivatives, as illustrated in Scheme 99 for *N*-carbomethoxypyrrolidine [163] and *N*-carbomethoxypiperidine [174].

The corresponding methoxylated products are equivalents of iminium cations and consequently, can be very versatile synthetic intermediates that can undergo a substitution of the methoxylated group by nucleophiles under Lewis acid conditions.

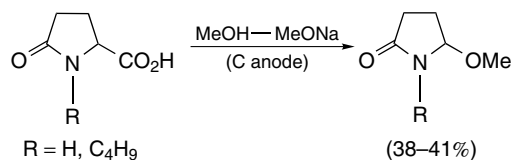
In addition to this method, Yoshida and coworkers [183] have electrochemically prepared, at low temperatures, stable *N*-substituted cations (Scheme 100) that can directly react with various nucleophiles after electrolysis.

Using this method, a first trapping of the iminium cation with methanol followed by a regeneration of this cation with a Lewis acid is avoided.

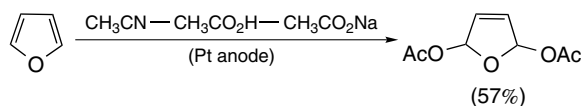
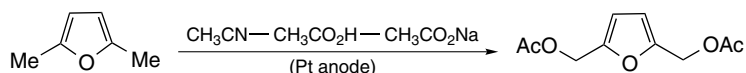
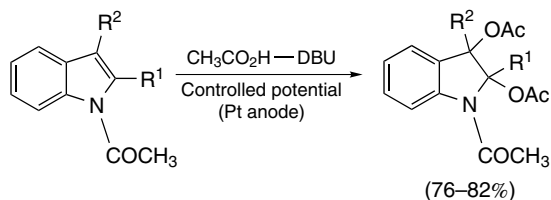
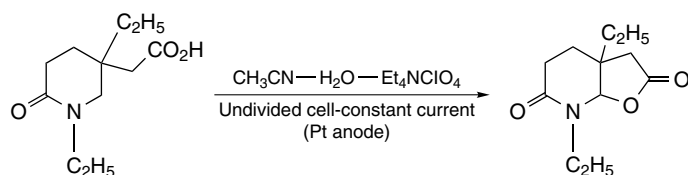
The electrodecarboxylation of heterocycles having a carboxylic group in  $\alpha$ -position to an heteroatom (oxygen, nitrogen) can lead to the corresponding methoxylated product when the electrolysis is performed in methanol [143, 184–189], as shown in Scheme 101.

#### 12.4.2.2 Acetoxylation Reactions

The electroacetoxylation of furan proceeds in a way similar to electromethoxylation (Scheme 102) [190], but by a different



**Scheme 101** Methoxylation via anodic decarboxylation.

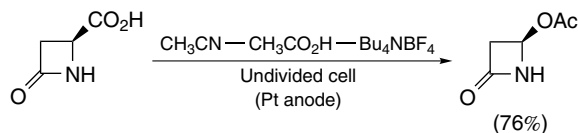
**Scheme 102** Anodic nuclear diacetoxylation of furan.**Scheme 103** Anodic side chain diacetoxylation of furan.**Scheme 104** Anodic diacetoxylation of an indole derivative.**Scheme 105**  $\gamma$ -Lactone by intramolecular acyloxylation.

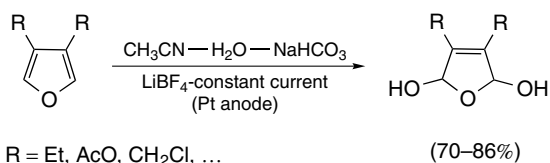
method for 2,5-dimethylfuran for which an acetoxylation of the side chain is observed (Scheme 103) [170].

The anodic diacetoxylation of *N*-acetylindoles (or *N*-acetylindoline) in acetic acid and in the presence of a base affords the corresponding 2,3-diacetoxyindoline (Scheme 104) [191]. A 2,3-diacetoxylation of *N*-carbomethoxypiperidine is also observed [192].

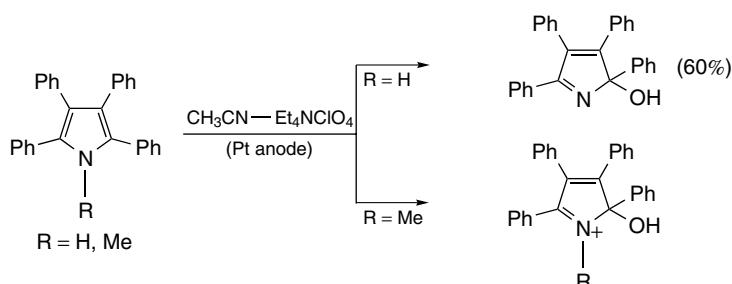
Lactones can be produced by intramolecular acetoxylation of piperidine (Scheme 105) [177].

A monoacetoxylation may be obtained *via* an electrodecaboxylation of heterocycles ( $\beta$ -lactam [193, 194] or oxazolidine derivatives [195]) having a carboxylic group in  $\alpha$ -position, as shown in Scheme 106 for the preparation of 4-acetoxy-2-azetidinones.

**Scheme 106** Decarboxylative acetoxylation of a  $\beta$ -lactam.



**Scheme 107** Anodic dihydroxylation of furan.



**Scheme 108** 2-Hydroxylation of pyrrole.

#### 12.4.2.3 Hydroxylation Reactions

A 2,5-dihydroxylation can be obtained by anodic oxidation of furan derivatives under suitable experimental conditions (Scheme 107) [149, 196].

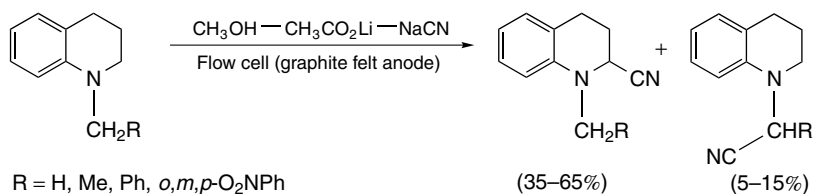
Anodic oxidations of 2,3,4,5-tetraphenylpyrrole in an organic solvent (nitromethane, acetonitrile) containing trace amounts of water afford 2-hydroxy derivatives (Scheme 108) [197–199].

The electrohydroxylation of tetrahydrofuran [200, 201] and *N*-carbomethoxypyrrolidine [202, 203], in the presence of water, gives the corresponding 2-hydroxy derivatives.

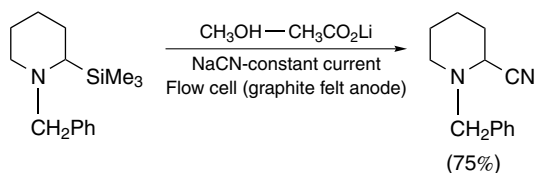
#### 12.4.2.4 Cyanation Reactions

$\alpha$ -Aminonitrile derivatives can be prepared by anodic oxidations of *N*-substituted tertiary cyclic amines (pyrrolidines [204], piperidines [17, 115, 204–208], tetrahydroquinolines [17, 115, 205–207], tetrahydroisoquinolines [206], azepane, morpholine, thiomorpholine, piperazine [207], benzazepines [115]), in the presence of cyanide ions as depicted in Scheme 12 for *N*-phenylpiperidine and Scheme 109 for *N*-alkyltetrahydroquinolines [17].

The anodic cyanation of *N*-alkyl tertiary cyclic amines can give a mixture of regioisomers as observed in Scheme 109.



**Scheme 109** Cyanation of tetrahydroquinoline.



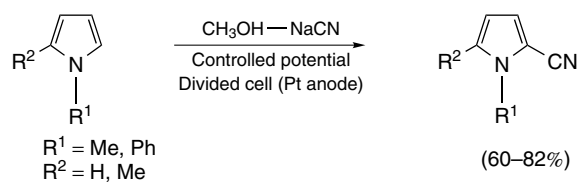
**Scheme 110** Regioselective  $\alpha$ -cyanation of piperidine by replacement of a trimethylsilyl group.

The problem of regioselectivity can be avoided by using a trimethylsilyl group in the  $\alpha$ -position to the nitrogen atom (Scheme 110) of *N*-benzyltetrahydroquinoline and piperidine derivatives [205]. The trimethylsilyl group

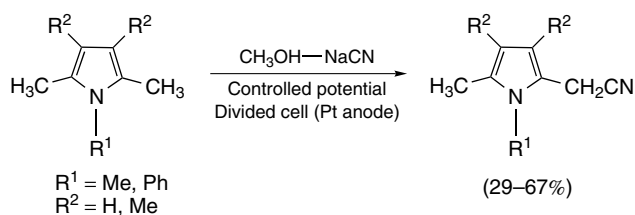
1. directs the iminium formation through a preferential desilylation reaction *versus* deprotonation; and

2. lowers the oxidation potential of tertiary amines compared to non-silylated species.

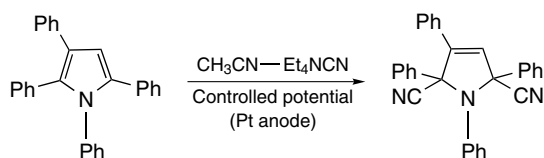
Anodic cyanations of *N*-substituted pyrrole or 2-methylpyrrole derivatives take place in the  $\alpha$ -position to the nitrogen atom (Scheme 111) [209] and at the side chain with 2,5-dimethyl or 2,3,4,5-tetramethylpyrrole derivatives (Scheme 112).



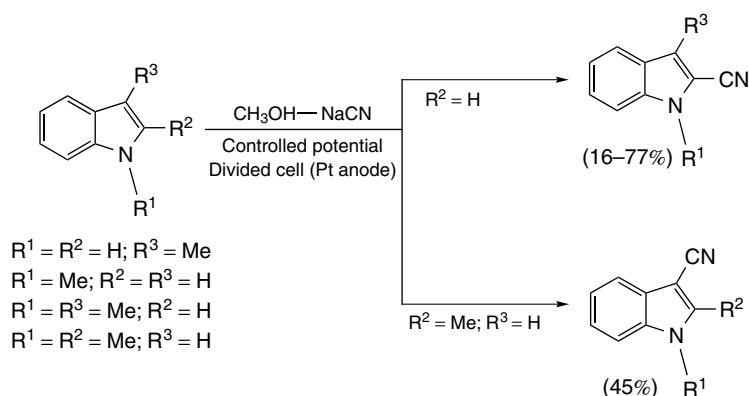
**Scheme 111** Nuclear cyanation of pyrrole.



**Scheme 112** Side-chain cyanation of pyrrole.



**Scheme 113** 1,4-Addition of cyanide to pyrrole.



**Scheme 114** Nuclear cyanation of indole.

However, a dicyanation can be observed for 1,2,3,5-tetraphenylpyrrole leading to 1,2,3,5-tetraphenyl-2,5-dicyanopyrroline (Scheme 113) [210].

In contrast, the cyanation of the side chain is not observed for indole derivatives (Scheme 114) [209].

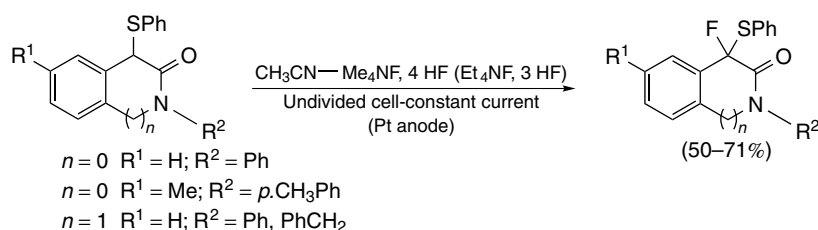
#### 12.4.2.5 Halogenation Reactions

Anodic oxidations of thioethers such as 3-phenylthiooxindole derivatives ( $n = 0$ ) or 3-oxo-4-phenylthiotetrahydroisoquinoline derivatives ( $n = 1$ ) in the presence of

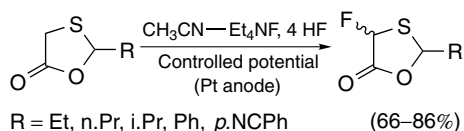
fluoride anions lead to a deprotonation at the  $\alpha$  carbon, followed by addition of a fluoride ion to the intermediate cation (Scheme 115) [211].

In a similar way, a monofluorination of various phenylthio derivatives of lactams [212, 213], lactones [214] and dioxolanones [215] was achieved.

A monofluorination of 2-substituted-1,3-oxathiolan-5-ones (Scheme 116) [216], 2-substituted dithiolanones [217], thiazolidinones [218], and dihydrochromanone or thiodihydrochromanone



**Scheme 115** Monofluorination of tetrahydroisoquinoline.



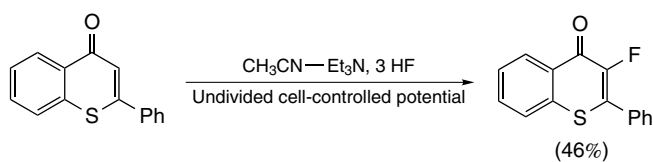
**Scheme 116** Monofluorination of oxathiolanone.

derivatives [219–221] occurs at the position  $\alpha$  to the heteroatom.

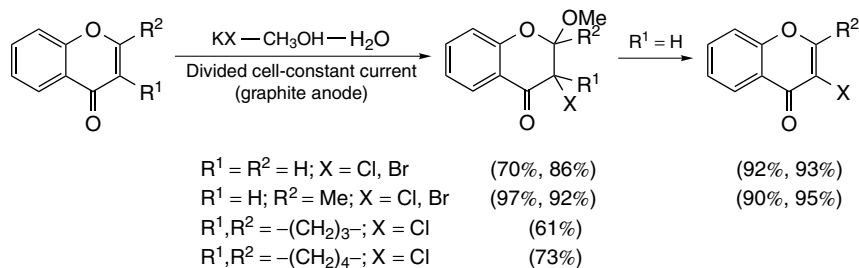
In contrast, the anodic fluorination of  $\alpha,\beta$ -unsaturated cyclic heterocycles such as flavone [222] or thioflavone

derivatives [223] takes place at the position  $\beta$  to the heteroatom as shown in Scheme 117.

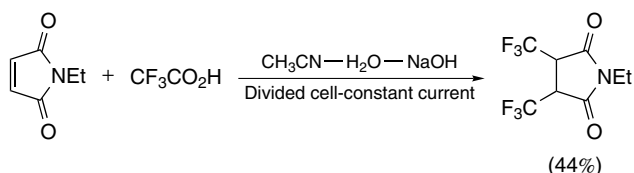
The regioselective electrohalomethoxylation of chromone derivatives is followed



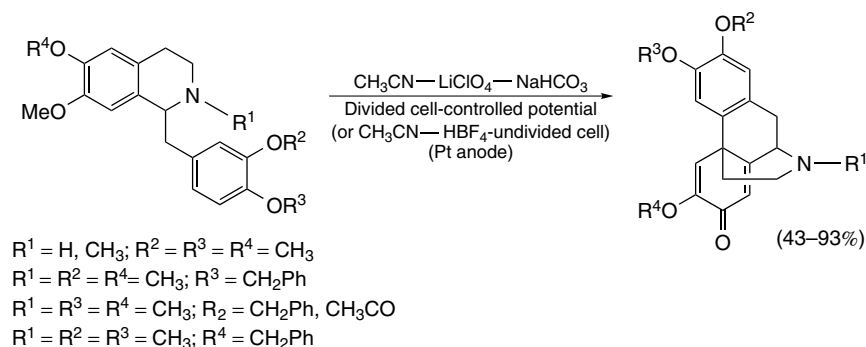
**Scheme 117**  $\beta$ -Monofluorination of a thioflavone.



**Scheme 118** Halomethoxylation of chromene.



**Scheme 119** Trifluoromethylation by anodic decarboxylation of trifluoroacetic acid in the presence of double bonds.



**Scheme 120** Intramolecular coupling of 1-benzyltetrahydroisoquinolines.

in some cases by a demethoxylation to afford chloro and bromochromones (Scheme 118) [224].

#### 12.4.2.6 Trifluoromethylation Reactions

The anodic oxidation of trifluoroacetic acid affords the trifluoromethyl radical  $\text{CF}_3\cdot$ . Addition of this radical to unsaturated heterocycles can produce bis(trifluoromethylated) compounds (Scheme 119) [225].

#### 12.4.2.7 Intramolecular Coupling Reactions

The anodic oxidation of 1-benzyltetrahydroisoquinoline derivatives produces morphinandienones according to Scheme 120 [81, 226–233].

A similar intramolecular coupling is observed for isochroman analogs of 1-benzylisoquinoline alkaloids (Scheme 121) [234].

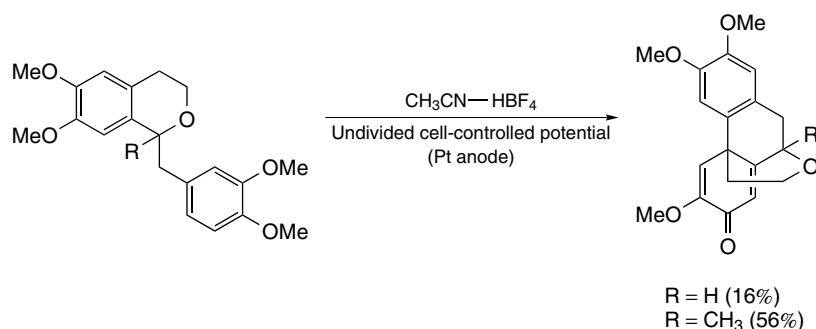
Intramolecular anodic olefin coupling reactions involving heteroatomic aromatic rings were used to prepare fused, bicyclic ring skeletons (Scheme 122) [159].

#### 12.4.2.8 Dimerization Reactions

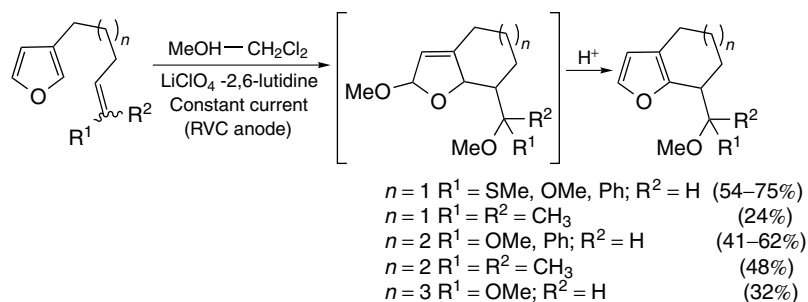
Anodic oxidations of heterocycles can produce symmetrical dimers *via* carbon–carbon coupling.

The anodic dimerization of 1,2,3,5-tetraphenylpyrrole occurs at the C-3 position (Scheme 123) [210].

5,5'-Substituted hydrylic acids can be obtained from 5-substituted barbituric acids as shown in Scheme 124 [159].

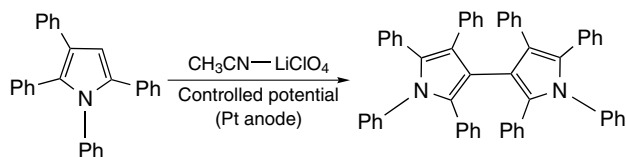
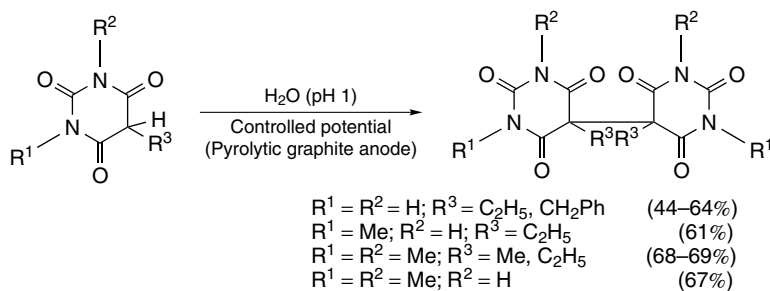
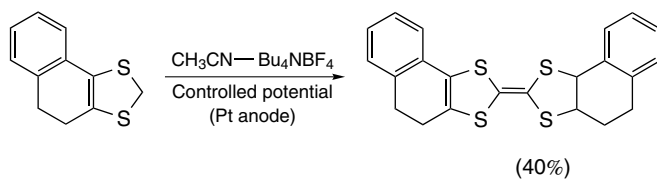
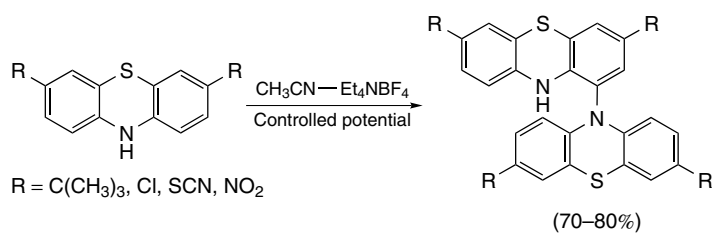
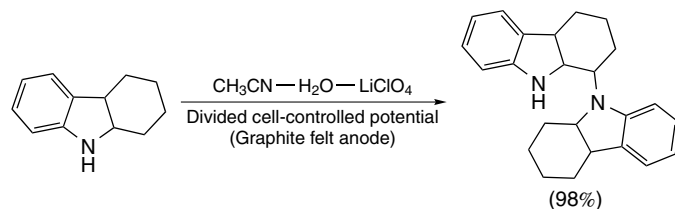


**Scheme 121** Intramolecular coupling of isochromane and aryl.



**Scheme 122** Intramolecular coupling of furan and alkene.



**Scheme 123** Anodic dimerization of pyrrole.**Scheme 124** Anodic dimerization of barbituric acid.**Scheme 125** Anodic dimerization of dithioles to tetrathiofulvalene.**Scheme 126** Unsymmetrical dimer by anodic coupling of a phenothiazine.**Scheme 127** Unsymmetrical dimer by anodic coupling of a tetrahydrocarbazole.

Tetrathiafulvalenes can be produced by an oxidative electrodimerization of 1,3-dithiole derivatives (Scheme 125) [235].

Unsymmetrical dimers may also be electrochemically produced as illustrated in Schemes 126, 127, and 128 respectively, from phenothiazine derivatives [236], tetrahydrocarbazole [146] and dihydrobenzazepine derivatives [140].

In addition, anodic oxidations, at a platinum or glassy carbon electrode, of heterocycles such as pyrrole or thiophene derivatives in organic solvents (acetonitrile, propylene carbonate, dichloromethane) were widely used to

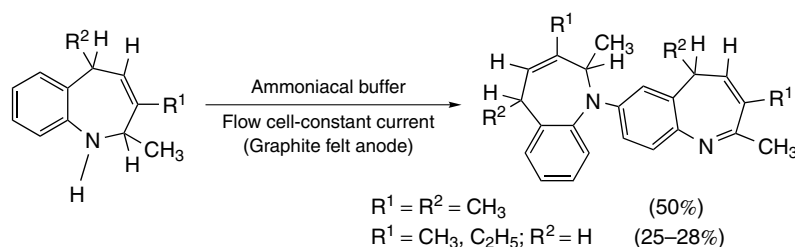
produce conducting polymer films coating the electrode (Scheme 129). A review of electropolymerized films is summarized in Refs. [237, 238], also see Chapter 16.

#### 12.4.3

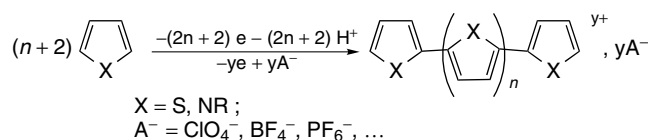
##### Ring Expansions

Anodic decarboxylations of  $\beta$ -carboxylate ethylene acetals afford 2-methoxy-1,4-dioxan derivatives.

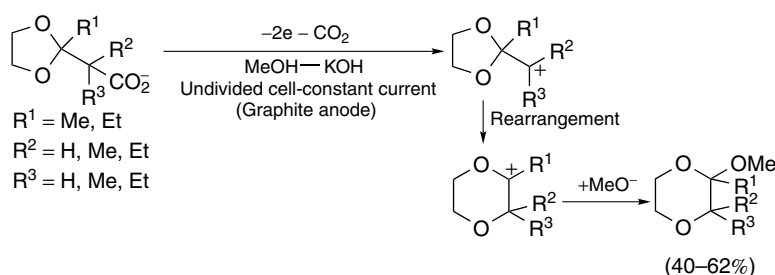
The mechanism involves a rearrangement of the electrogenerated cation with an expansion of heterocycles (Scheme 130) [239, 240].



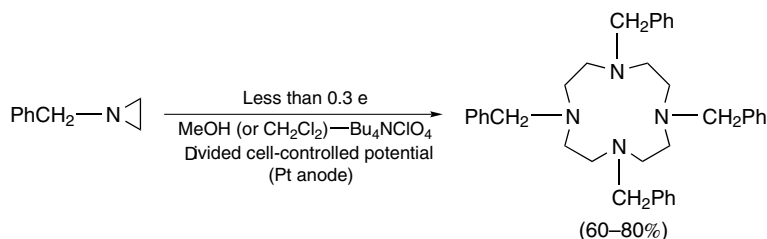
**Scheme 128** Unsymmetrical dimer by anodic coupling of a dihydrobenzazepine.



**Scheme 129** Anodic polymerization of pyrrole and thiophene.



**Scheme 130** Rearrangement of electrogenerated cation.



**Scheme 131** Tetramerization of benzylaziridine.

A particular ring expansion corresponding to a tetramerization of 1-benzylaziridine may be induced anodically leading to a tetraazacyclododecane (Scheme 131) [241].

However, it is worth noting that anodic oxidations of aziridine derivatives can give a mixture of opened compounds [242].

#### 12.4.4

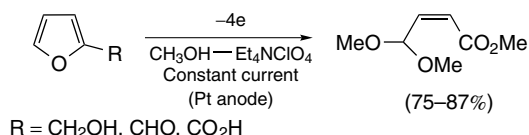
##### Ring Contractions

As previously illustrated in Scheme 13, the anodic oxidation of dithianes involves a ring contraction affording 1,2-dithiolane [18].

#### 12.4.5

##### Ring Opening

As an example, a convenient preparation of methyl (*E*) and (*Z*)-4,4-dimethoxybutenoates can be performed by anodic oxidation of furfuryl alcohol, furfural or furoic acid *via* a dimethoxylated dihydrofuran intermediate (Scheme 132) [157].



**Scheme 132** Ring opening of furan derivatives.

## 12.5

### Cathodic Reduction of Heterocycles

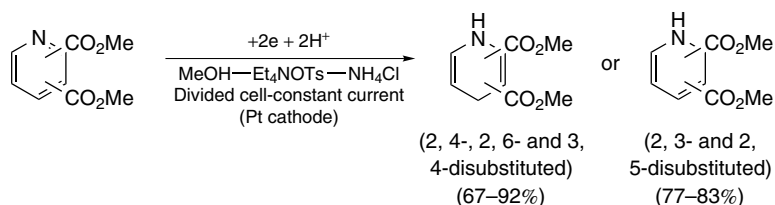
#### 12.5.1

##### Electroreductive Hydrogenation of Double Bonds

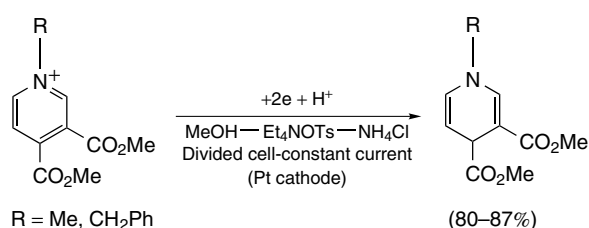
The hydrogenation of a double bond during cathodic reductions generally results from addition of protons to an electrogenerated basic species. It is worth noting that partial and selective hydrogenation can take place according to the nature of the heterocycles and the experimental conditions.

The electroreduction of deactivated pyridines or pyridinium salts affords selectively the corresponding 1,2- or 1,4-dihydropyridine derivatives according to the position of the substituents (Schemes 133 and 134) [243]. In the same experimental conditions a monoactivated pyridine is not reducible.

*N*-Methyl and *N*-benzylpyridinium salts in an aqueous acidic medium (HCl), can be reduced, at high current densities, into *N*-methyl and *N*-benzylpyridines in good yields (87–98%) [244].



**Scheme 133** Cathodic hydrogenation of pyridine.

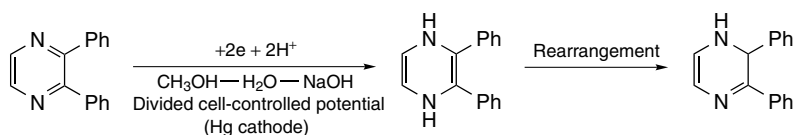


**Scheme 134** Cathodic hydrogenation of pyridinium salt.

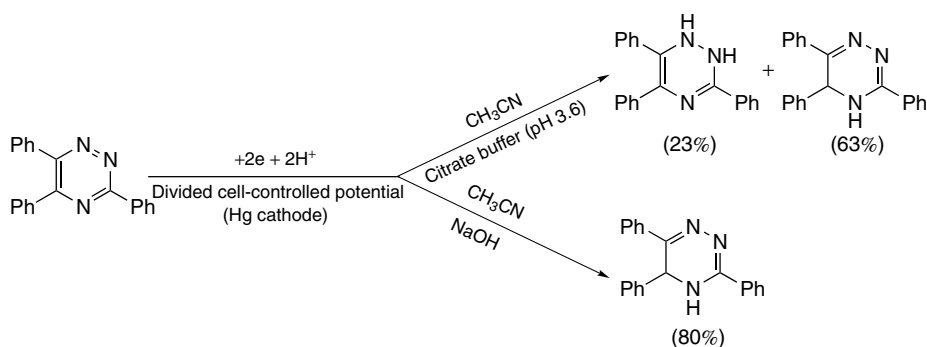
The electrochemical reduction of pyrazines in an alkaline hydroorganic medium gives the corresponding 1,4-dihydropyrazines that are easily reoxidizable. Generally, 1,4-dihydropyrazines isomerize into 1,2- or 1,6-dihydropyrazines (Scheme 135) [245].

Similar behaviors were observed for quinoxaline [246, 247] and pyridopyrazine derivatives [248, 249].

Triazines are reducible in two 2-e steps in slightly acidic media [250]. The first reduction leads to a mixture of two



**Scheme 135** Cathodic hydrogenation of pyrazines.



**Scheme 136** Cathodic hydrogenation of a triazine.

dihydro compounds (Scheme 136). A ring contraction is observed at a more cathodic potential (*vide infra* Scheme 160).

Only one isomer is produced in good yields (80%) in a basic medium. The latter is further reducible in a slightly acidic medium in the tetrahydro derivative (Scheme 137).

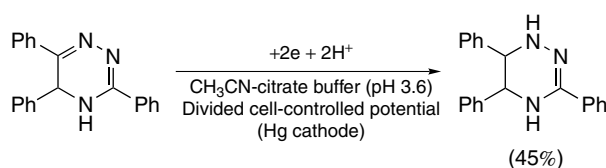
Triazine-3-ones and triazine-3-thiones can also be reduced in two consecutive steps leading to the corresponding dihydro and tetrahydro derivatives. However, according to the experimental conditions, a ring contraction can occur at the second step [250].

The electrochemical reductions of purine, adenine, and related compounds involve two consecutive steps as shown in Scheme 138 for adenine [251].

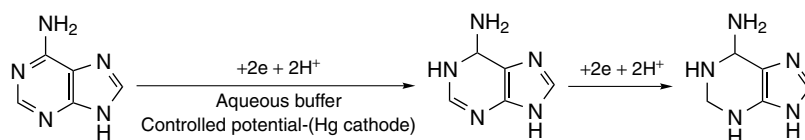
The electroreductive hydrogenation of pyridazine-3-ones performed at the first wave, in acidic or basic medium, takes place at the 4,5-double bond. A further reduction of 4,5-dihydropyridazin-3-ones in basic media, affords the corresponding tetrahydro derivatives (Scheme 139) [252].

A ring contraction (*vide infra* Scheme 161) or a ring opening of electrogenerated tetrahydro derivatives can be observed in sulfuric acid.

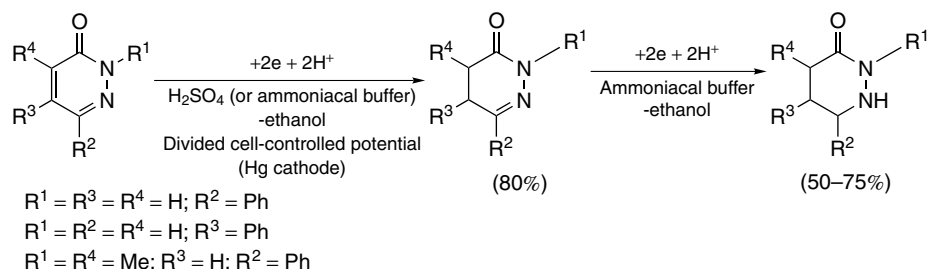
The cathodic reduction of 4-carboethoxycoumarin in the presence of a catalytic amount of various chiral alkaloids can afford 4-carboethoxydihydrocoumarin in low enantiomeric excess ( $ee \leq 20\%$ ) (Scheme 140) [253]. In the case of 4-methyldihydrocoumarine, the



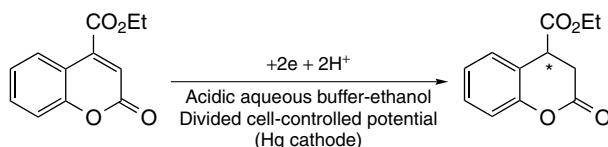
**Scheme 137** Cathodic hydrogenation of a dihydrotriazine.



**Scheme 138** Cathodic hydrogenation of adenine.



**Scheme 139** Cathodic hydrogenation of pyridazine-3-one.



**Scheme 140** Enantioselective cathodic hydrogenation of coumarine in the presence of an alkaloid.

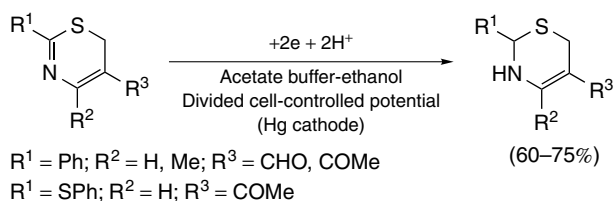
enantio-selectivity has been increased to 67% *ee* [254].

Monoactivated and diactivated substituted 6*H*-1,3-thiazines can be reduced in a slightly acidic hydroorganic medium [255–258]. In the case of thiazines monoactivated at carbon 5, an electrolysis performed at the plateau of the two-electron wave gives the 2,3-dihydro compounds (Scheme 141).

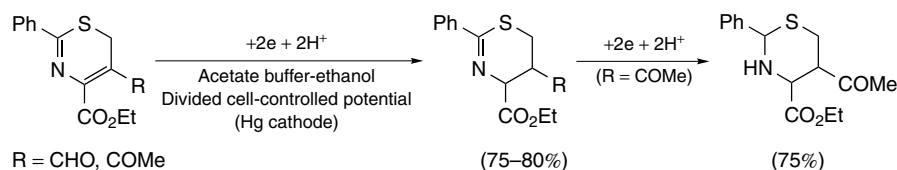
2-Phenylthiazines diactivated at C-4 and C-5 positions are reducible in two 2-*e*

steps. An electrolysis carried out at the plateau of the first wave yields the 5,6-dihydro compounds. The tetrahydro derivatives can be prepared at more cathodic potentials (Scheme 142).

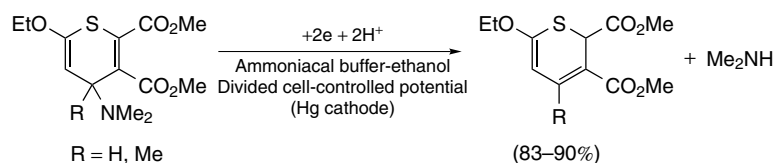
2-Ethoxy-4*H*-1,3-thiazines bearing an NMe<sub>2</sub> substituent at carbon 4 are reducible in two 2-*e* steps in slightly basic media. An electroreduction performed at the first wave is followed by a dimethylamine elimination (Scheme 143) [259, 260]. The electrolysis carried out at the second



**Scheme 141** Partial hydrogenation of a thiazine.



**Scheme 142** Partial and full hydrogenation of a thiazine.



**Scheme 143** Hydrogenation and elimination of a thiazine.

wave involves a ring opening (*vide infra* Scheme 167). A ring contraction is observed in acidic medium (*vide infra* Scheme 162).

Functionalized dihydrothiopyran derivatives can be obtained by electroreduction of triactivated [19] (*vide supra* Scheme 14) and tetraactivated 4*H*-thiopyrans [261].

### 12.5.2

#### Functionalization of Heterocycles

The cathodic reduction of heterocycles generally affords nucleophilic species that can react with electrophilic reagents.

##### 12.5.2.1 Addition Reactions

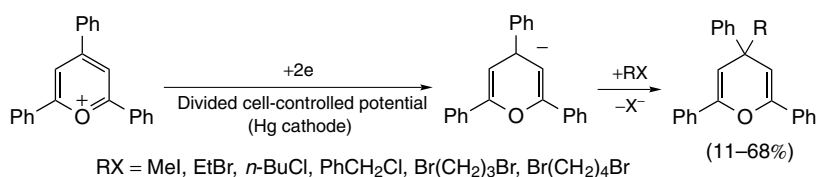
The two-electronic cathodic reduction of some 2,4,6-triarylpyrylium cations

in the presence of aliphatic chlorides, bromides or iodides leads to the formation of 2,4,6-triaryl-4-alkyl-4*H*-pyrans (Scheme 144) [262].

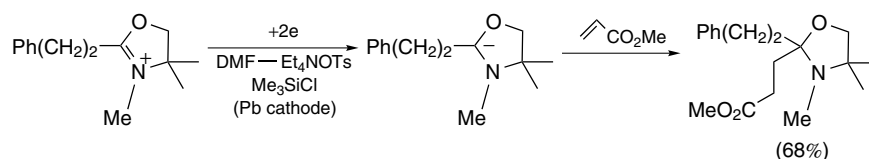
A mixture of 2,4,6-triphenyl-4-(4-bromobutyl)-4*H*-pyran (28%) and 1,4-bis-(2,4,6-triphenyl-4*H*-pyran-2-yl)-butane (6%) is obtained when 1,4-dibromobutane is used as the electrophile.

The electroreduction of oxazolinium salts gives acylanion equivalents that react in a Michael addition with activated olefins as shown for methylacrylate in Scheme 145 [263].

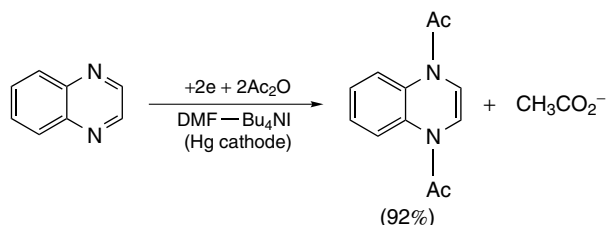
The cathodic reduction of quinoxaline in the presence of acetic anhydride affords diacetylated products [264] as depicted in Scheme 146 for quinoxaline.



**Scheme 144** Cathodic alkylation of triarylpyrylium cations.



**Scheme 145** Cathodic Michael addition of an oxazolinium salt.



**Scheme 146** Cathodic diacetylation of quinoxaline.

A tetraacetylation with cleavage of the N–N bond can take place as observed for 3,6-diphenylpyridazine (Scheme 147)

A monoacetoxylation of 2,3-diphenylpyrido[3,4b]pyrazine at position 5 has been observed (Scheme 148) [249].

However, 3-Phenylpyrido[3,4b]pyrazine in acetonitrile can be diacetylated at the 1,4-positions in low yields (19%).

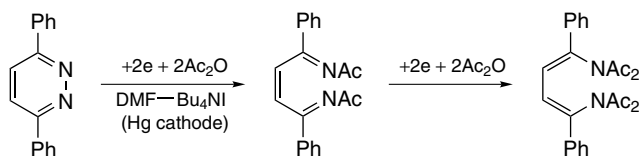
#### 12.5.2.2 Substitution Reactions

2-Arylpyridines can be obtained by the electrochemical reduction of the corresponding aryl and pyridyl halides using a sacrificial anode (Mg, Zn or Fe) in the presence of  $\text{NiBr}_2\text{bpy}$  as a catalyst (Scheme 149) [265, 266].

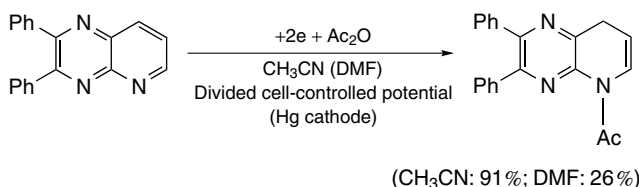
The electroreductive coupling process can also be performed with heteroaryl halides as 2- or 3-bromothiophene or 3-bromofuran instead of aryl halides.

In a similar way, 2-arylpyrimidines and 2-arylpyrazines have been prepared from 2-chloropyrimidine and 2-chloropyrazine and various functionalized aryl halides. An iron anode is used in order to generate iron salts that allow the desired coupling reaction (Scheme 150) [267].

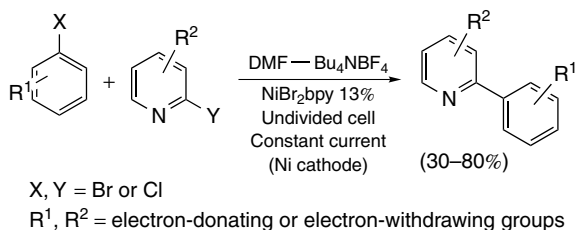
4-Phenylquinoline derivatives can also be prepared by an electrochemical cross-coupling of functionalized phenyl halides with 4-chloroquinoline derivatives in the presence of a cobalt catalyst (Scheme 151) [268].



**Scheme 147** Cathodic tetraacetylation of diphenylpyridazine.

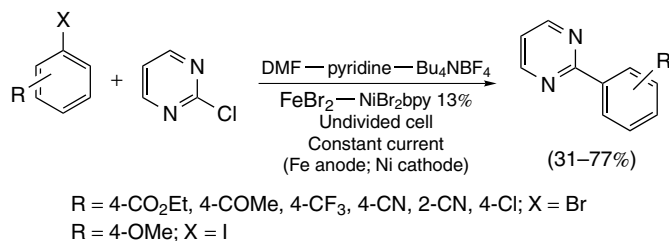


**Scheme 148** Monoacetylation of pyridopyrazine.

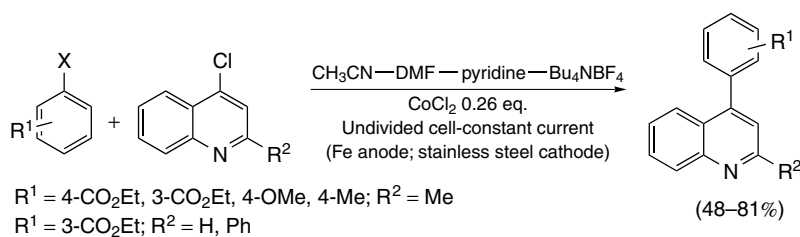


**Scheme 149** Cathodic heterocoupling of aryl halides and pyridyl halides.





**Scheme 150** Cathodic heterocoupling of aryl halide and pyrimidine halide.



**Scheme 151** Cathodic heterocoupling of aryl halide and chloroquinoline.

### 12.5.2.3 Intramolecular Coupling

#### Reactions

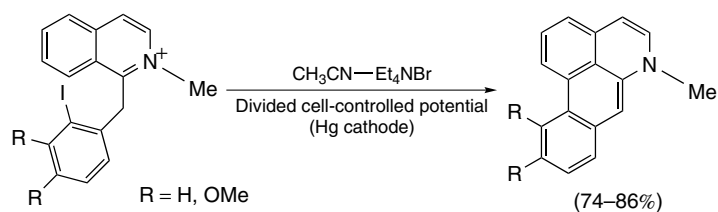
An electrochemical synthesis of aporphines *via* cathodic cyclization of iodo benzylisoquinolinium salts has been reported (Scheme 152) [269].

Diastereoselective cathodic cyclizations of 1-(4-oxoalkyl) and 1-(3-oxoalkyl)

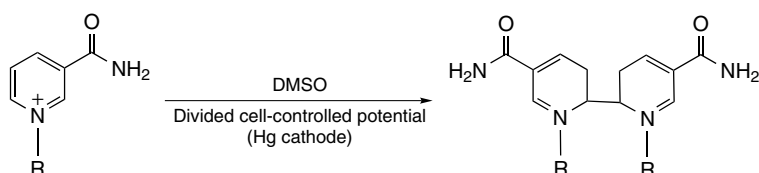
pyridinium salts lead to quinolizidine (*vide supra* Scheme 62) and indolizidine derivatives [85].

### 12.5.2.4 Dimerization Reactions

Cathodic reductions of 1-substituted-3-nicotinamides (1-methylnicotinamide,



**Scheme 152** Aporphine by cathodic cyclization of a iodobenzylisoquinolinium salt.



**Scheme 153** Cathodic dimerization of nicotinamide.

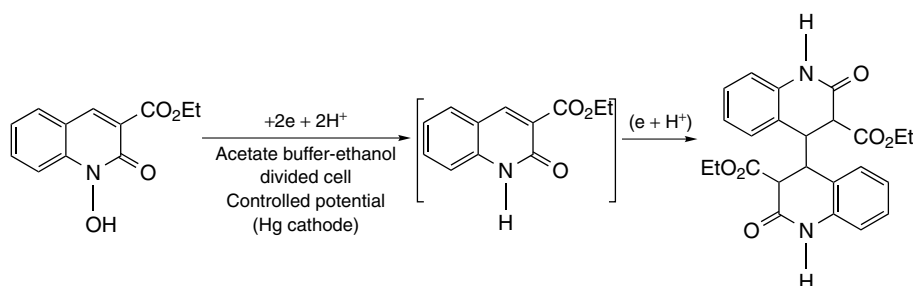
$\text{NAD}^+$ ,  $\text{NMN}^+$ ,  $\text{NADP}^+$ ) in nonaqueous media (acetonitrile, DMSO) involve  $1 \text{ F mol}^{-1}$  to form neutral free radicals that dimerize at the 6-position (Scheme 153) [270].

Anodic oxidations of the dimers produce the dehydridimers.

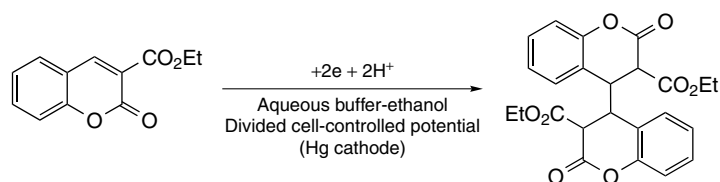
The cathodic dimerization of 1-hydroxy-3-carboethoxy-2-quinolone occurs at the C-4

position with consumption of  $3 \text{ F mol}^{-1}$ . An intermediate resulting from reduction of the N—OH bond has been postulated (Scheme 154) [107].

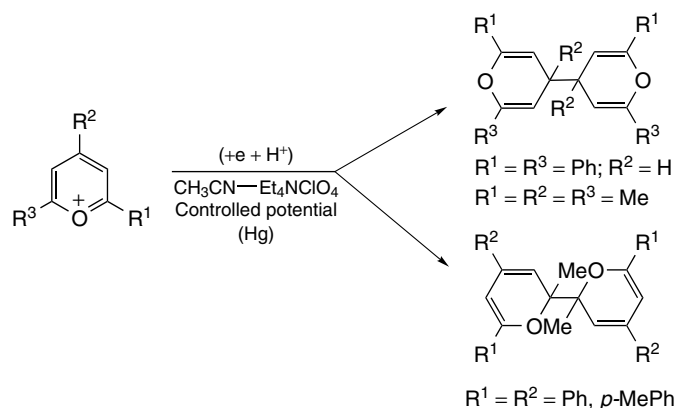
The electrochemical behavior of this intermediate and that of coumarin derivatives can be similar [271–273], as shown in Scheme 155 for 3-carboethoxycoumarin.



**Scheme 154** Cathodic dimerization of a quinolone.



**Scheme 155** Cathodic dimerization of a coumarine.



**Scheme 156** Cathodic dimerization of pyrylium salts.

An asymmetric induction can be performed during the cathodic reduction of various substituted coumarins in the presence of chiral alkaloids. A mixture of dimers and dihydrocoumarins is obtained in various yields according to the nature of the alkaloids (31–89% of dimer and 5–67% of dihydrocoumarin with unsubstituted coumarin) [273].

Bipyrans can be prepared by quantitative cathodic reductions of the corresponding pyrylium and benzopyrylium salts. According to the nature of the substituents, dimerizations obtained from pyrylium salts take place at the C-2 or C-4 positions (Scheme 156) [274].

The major compound obtained from the electrolysis of 3-phenyl-2*H*-1,4-benzoxazine results from a 1-e reductive dimerization with the coupling taking place at the C-3 position (Scheme 157) [109].

When the cathodic reduction of 2-phenyl-6*H*-1,3-thiazines monoactivated at the C-5 position is carried out at the foot of the first wave, hydrodimers resulting from coupling at the C-2 position were obtained in relatively good yields (Scheme 158) [255, 256].

### 12.5.3

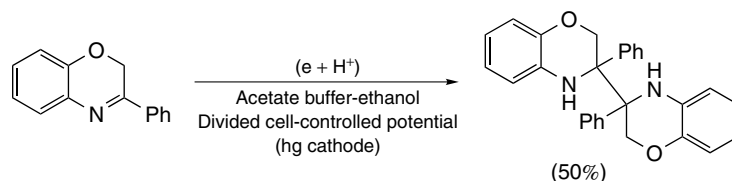
#### Ring Expansions

The electrochemical reduction of various bicyclic  $\alpha$ -amino ketones such as quinolizidinone ( $n = 2$ ) (Scheme 159) can involve a cleavage of the carbon–nitrogen bond giving a ring enlargement [275, 276].

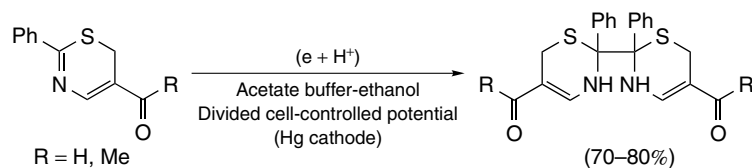
### 12.5.4

#### Ring Contractions

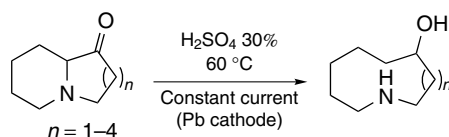
A ring contraction can be obtained by heteroatom (sulfur, nitrogen) extrusion from



**Scheme 157** Cathodic dimerization of benzoxazines.



**Scheme 158** Cathodic dimerization of thiazines.



**Scheme 159** Cathodic ring expansion.

heterocycles. The first process generally involves a ring opening.

Electrolyses at the second reduction step of triazine derivatives in acidic medium, can produce substituted imidazole derivatives as illustrated in Scheme 160 for 2,4,5-triphenylimidazole [250].

The cathodic reduction in acidic medium, of 4,5-dihydropyridazine-3-ones unsubstituted at the N-2 position gives 1-aminopyrrolidin-2-ones *via* the corresponding tetrahydropyridazine-3-ones. 4,5-Dihydropyridazine-3-ones substituted at the N-2 position afford pyroline-2-ones derivatives [252] (Scheme 161).

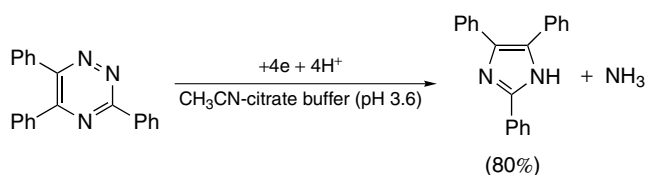
Activated pyrroles can be prepared by the cathodic reduction of 4*H*-1,3-thiazines (Scheme 162) [259, 260] or pyridazines (Scheme 163) [277].

### 12.5.5

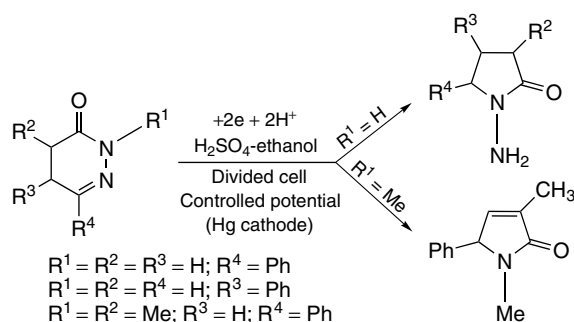
#### Ring Opening

The cathodic reduction of cyclic quaternary ammonium compounds can involve a cleavage at the N atom with ring opening as observed for anilinium salts (Scheme 164) [244].

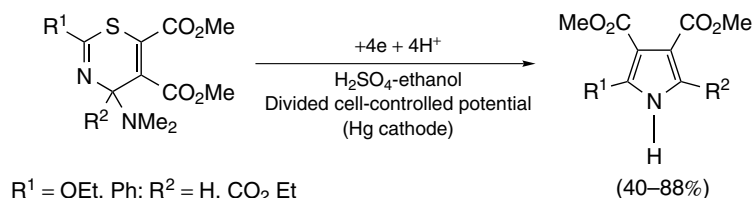
The electrochemical reduction of heterocyclic enammonium salts can give



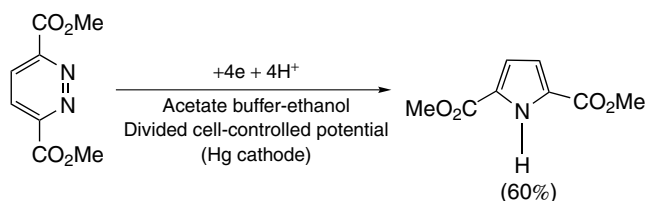
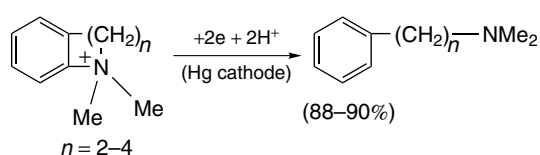
**Scheme 160** Cathodic ring contraction.



**Scheme 161** Cathodic ring contraction.



**Scheme 162** Cathodic ring contraction.

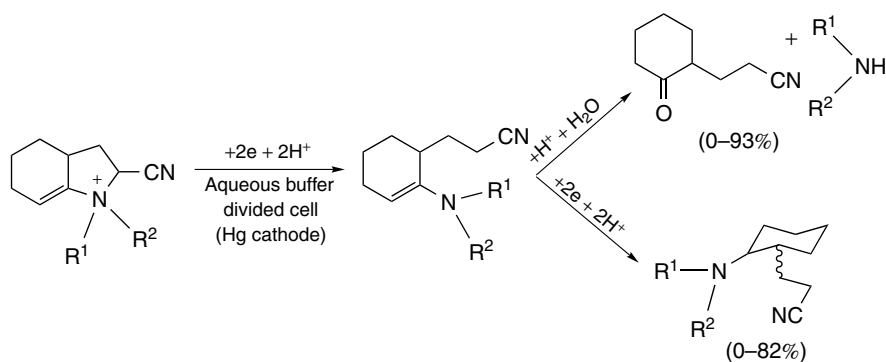
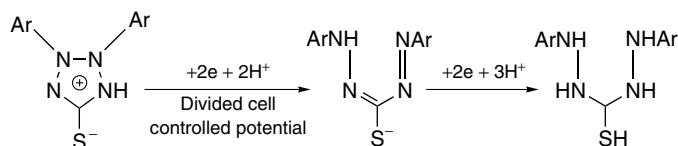
**Scheme 163** Cathodic ring contraction.**Scheme 164** Ring opening of anilinium salts.

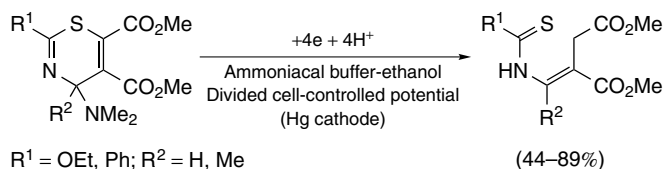
a mixture of products in different yields depending on the pH value (Scheme 165) [278].

A N–N bond cleavage can be obtained by the cathodic reduction of some mesoionic

2,3-diaryl-2*H*-tetrazolium-5-thiolate compounds (Scheme 166) [279].

The four-electronic cathodic reduction of 4-*H*-1,3-thiazine derivatives in a slightly basic medium leads to a ring

**Scheme 165** Ring opening of enammonium salts.**Scheme 166** Cathodic N–N bond cleavage.



**Scheme 167** Cathodic C–S bond cleavage.

opening by cleavage of a C–S bond (Scheme 167) [260].

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## 13

### Selectivity in Electrochemical Reactions

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### 13.1 Introduction

In an electrochemical reaction, a compound is converted by an electron transfer at the electrode. This step is mostly followed by a chemical reaction of the generated intermediate and possibly by further electron transfers (see Chap. 1). Selectivity tells us how the main product is formed preferentially. The favored introduction of a substituent into one out of several positions is termed as *regioselectivity* [1]. The different reactivities of similar functional groups toward a reagent are designated as *chemoselectivity*. The preferred formation of one out of several stereoisomers is named *stereoselectivity*. The latter can be further differentiated into diastereoselectivity, in which one out of several diastereomers is formed selectively from a prostereogenic center, and enantioselectivity, in which one out of two enantiomers is generated preferentially from a prostereogenic center.

The selectivity of reactions can be controlled thermodynamically or kinetically. In the first case, the pathways leading from a starting material or a common intermediate to the products are reversible. Here, the relative portion of the products is determined by their different heats of formation. This constitutes the minor

part of reactions, while the major part is irreversible and kinetically controlled. In this case, the product distribution depends on the activation energies of the competing reactions. In electrochemical conversions, mostly reactive intermediates such as radical ions, radicals, carbanions, or carbocations are involved. Owing to their reactivity, the selectivity of the reactions can be lower as these are concerted processes that constitute a large part of pure chemical reactions. However, the nature of the electrode reaction provides other means of controlling the selectivity. While chemical reactions are mostly homogeneous processes, electroorganic reactions are heterogeneous, involving an electron transfer at the electrode surface and mass transport to and from the electrode. This results in the formation of a reaction layer near the electrode surface, where the concentration of reactive intermediates is higher compared with homogeneous reactions. This allows to influence reaction orders. As each electron transfer results in the generation of protons at the anode and bases at the cathode, their concentration near the electrode is often different from that in the bulk of the electrolyte. Additionally, substrates, intermediates, or products can be adsorbed at the electrode, which can induce activation or deactivation, whose

extent is often controlled by the electrode material and potential. The rate of substrate conversion depends on the rate of electron transfer, which is related to the reduction or oxidation potential of the electrophore. This can be exploited for the potential-selective conversion of substrates as the oxidation or reduction power of the working electrode can be more precisely adjusted and controlled via its potential as is possible with the limited number of chemical reductants or oxidants. Electronic and steric factors that influence activation energies can be enhanced or diminished by the large potential gradient at the electrode and the bulkiness of the electrode that can shield parts of the reacting molecule. Furthermore, the electrode can be used to regenerate selective chemical oxidants or reductants that can then be used catalytically in indirect electrolyses (see Chap. 15).

Selectivity in homogeneous reactions is treated in Refs. [2–6], while the selectivities that are influenced in heterogeneous reactions by diffusion and adsorption are dealt with in Refs. [7, 8]. Kinetics and mechanisms of electrochemical reactions are covered in Chap. 1 of this volume and in Refs. [9–11].

In electroorganic conversions, the knowledge of the mechanism is mostly

incomplete. Therefore, the selectivities can at best be correlated with the limited set of available mechanistic data, and explanations must be adjusted when new information arrives.

## 13.2 Regioselectivity

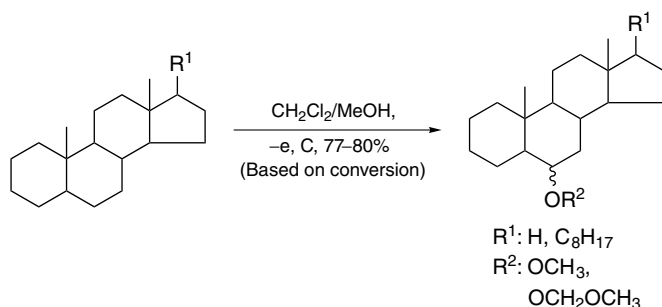
A major part of regioselective conversions comprises additions to unsymmetrically substituted alkenes, substitutions in allylic positions or in aromatic compounds, conversions of anions, radicals, or carbocations with two reactive sites, and reactions at different CH bonds.

### 13.2.1

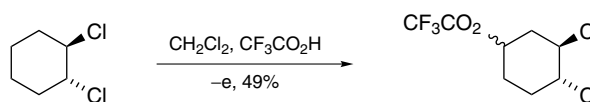
#### Regioselectivity at the Anode

##### 13.2.1.1 Regioselective Substitution of CH Bonds

**13.2.1.1.1 Regioselective Substitution of Unactivated CH Bonds** CH bonds in cycloalkanes (decaline, steroids) and alkanes bearing electron-deficient groups in remote positions (1,2-dichlorocyclohexane, decanoic acid) can be regioselectively substituted at the anode by trifluoroacetate, acetate, or methoxide (Figs. 1, 2) [12–14].



**Fig. 1** Regioselective C6-methoxylation and methoxymethoxylation of steroids [12].



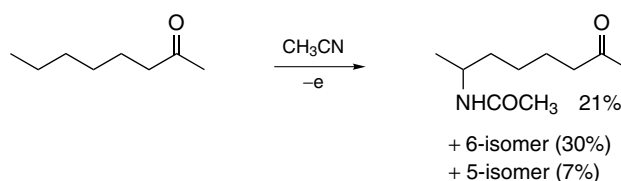
**Fig. 2** Regioselective trifluoroacetoxylation of 1,2-dichlorocyclohexane [13, 14].

The reaction occurs by oxidation of the CH bond to a radical cation that is deprotonated to a radical. This is further oxidized to a carbocation that reacts with the nucleophiles in the electrolyte. The regiochemistry is controlled by inductive deactivation ( $-I$ -substituents) as well as by activation ( $+I$ -substituents), which leads to a reactivity:  $\text{tert.H} > \text{sec.H} > \text{prim.H}$ . In steroids, a preferential adsorption appears to play a role.

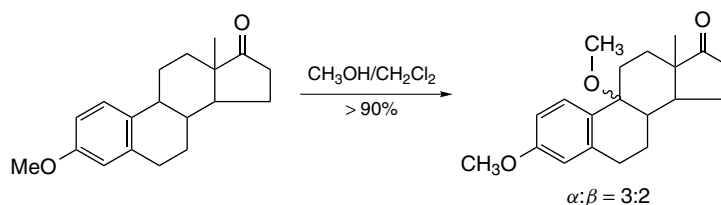
With ketones, a remote regioselective acetamidation is found. This result is mechanistically in accordance with the oxidation of the oxygen atom to a radical cation that abstracts a hydrogen from a remote CH bond. The generated radical is then oxidized to a cation, that reacts with acetonitrile to get the acetamide (Fig. 3) [15].

### 13.2.1.1.2 Regioselective Substitution of Activated CH Bonds

**Benzylic CH bonds** Benzylic CH bonds can be preferentially substituted at the anode by oxidation of the aromatic ring to a radical cation, which can undergo side-chain substitution at the benzylic carbon atom and/or nuclear substitution. Benzylic substitution preponderates, when there is an alkyl substituent at the aromatic carbon bearing the highest positive charge density in the radical cation, while a hydrogen at this position leads to a nuclear substitution [16]. Anodic benzylic substitution is used in technical processes for the conversion of alkyl aromatics into substituted benzaldehydes [17, 18]. Anodic benzylic substitution has been used for the regioselective methoxylation of estratrienone at C9 (Fig. 4) [19].



**Fig. 3** Remote acetamidation of ketones [15].



**Fig. 4** Regioselective methoxylation of 3-methoxy-estratrienone at C9 [19].



Anodic oxidation of *p*-methylbenzyl-sulfonic ester, -carboxylic ester, and -nitrile in  $\text{Et}_3\text{N}\cdot 3\text{HF}/\text{CH}_3\text{CN}$  affords fluorides and acetamides at the methyl (Me) and substituted ( $\text{CH}_2\text{E}$ ) benzyl position:  $\text{Me}/\text{CH}_2\text{E} = 24/76$  ( $\text{E} = \text{CO}_2\text{Et}$ ),  $9/91(\text{CN})$ ,  $69/31$  ( $\text{SO}_3\text{Et}$ ). In the radical bromination of these compounds, substitution at  $\text{CH}_3$  is enhanced [20].

**Allylic CH bonds** Aliphatic alkenes frequently undergo allylic substitution by oxidation of the double bond to a radical cation that undergoes deprotonation at the allylic position and subsequent oxidation of the resulting allyl radical to a cation, which finally combines with the nucleophiles from the electrolyte [21, 22]. The selectivity is mostly low. Regioselective allylic substitution or dehydrogenation is, however, found in some cases with activated alkenes, for example,  $\beta$ -ionone that reacts to (1) (Fig. 5) as a major product [23], menthone enolacetate that yields 90% (2) [24], and 3,7-dimethyl-6-octen-1-ol

(citronellol) is converted, possibly by intramolecular assistance, to 26% (3) [25] or 56% (4) [26] in the key step of a rose oxide synthesis. Regioselective electrochemical chlorination of the methyl group in the 3-methyl-3-butenolate moiety of penicillin derivatives was found in dichloromethane:water:sodium chloride:sulfuric acid as electrolyte [27]. The reaction possibly involves a chloro-ene reaction.

**CH bonds  $\alpha$  to an amino group** Anodic methoxylation of unsymmetrical tertiary amines takes place preferentially at the methyl group (Fig. 6) [28–30]. Substitution at a CH bond  $\alpha$  to an amino group proceeds by oxidation of the amino group to a radical cation, followed by deprotonation at the adjacent CH bond to a radical. This is oxidized to a cation, which undergoes solvolysis, in this case, methanolysis. The regioselectivity has been explained by assuming that an adsorbed amine from which the intermediate cation is formed is as distant as possible from the anode

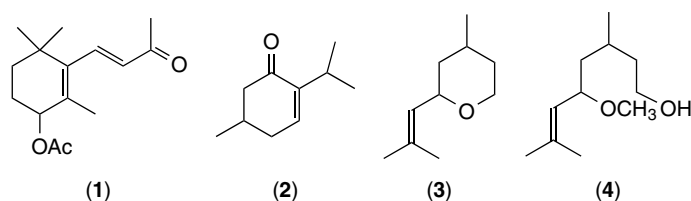


Fig. 5 Examples of regioselective allylic substitution [23–26].

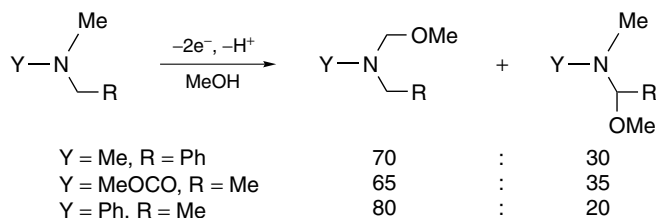
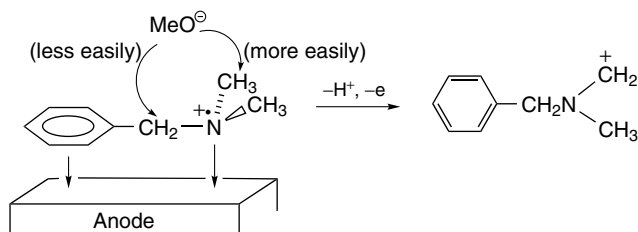


Fig. 6 Anodic methoxylation of tertiary amines and carbamates [28–30].



**Fig. 7** Proposed explanation for the regioselectivity in methoxylation of *N*-benzyl-*N*, *N*-dimethylamine [28].

(Fig. 7) [28]. However, other explanations for this unexpected regioselectivity have also been proposed [31, 32].

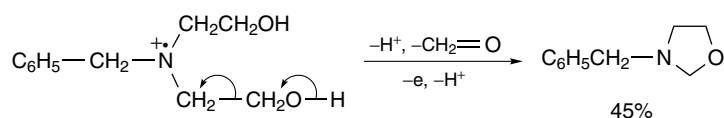
The oxidation of *N*-benzyl-diethanolamine afforded 45% 3-benzyl-oxazolidine as the major product. This was attributed to the fragmentation of the intermediate radical cation, a 1e oxidation of the radical, and the intramolecular combination of the cation with the hydroxyl group (Fig. 8) [28].

A different regioselectivity has been reported in the anodic methoxylation of *N*-(fluoroethyl) anilines as shown in Fig. 9 [33]. Since in this case, the regioselectivity decreases with the decreasing electron-withdrawing ability of the  $R_f$  groups ( $-I$ -effect), it can be explained in

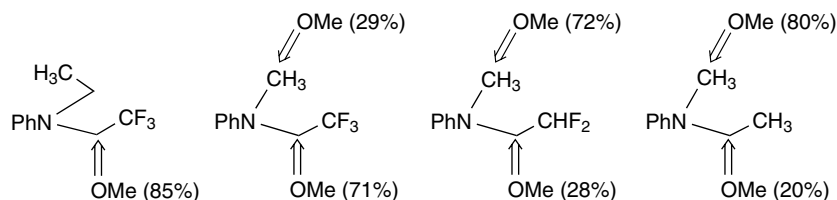
terms of the different deprotonation rates of the radical cation intermediate.

Anodic methoxylation of 2,3-dimethyl-1-phenyl-5-pyrazolone (antipyrine) occurs regioselectively at the *N*-methyl group, leading to a selective demethylation [34]. Anodic methoxylation of unsymmetrical carbamates affords a mixture of regioisomers (Fig. 6) [29]. However, the regioselectivity can be completely controlled by an electroauxiliary [35]. This is achieved by prior introduction of a trimethylsilyl or phenylthio group at one of the  $\alpha$ -carbon atoms; selectivity arises because the silyl cation or thiyl radical are better leaving groups than the proton (Fig. 10) [36, 37].

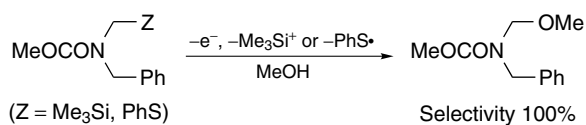
Direct anodic methoxylation of biscarbamates of a methyl  $\alpha$ ,  $\omega$ -diaminocarboxylate



**Fig. 8** 3-Benzyl-oxazolidine formation from *N*-benzyl-diethanolamine by fragmentation and intramolecular alkoxylation [28].



**Fig. 9** Regioselectivity in anodic methoxylation of *N*-(fluoroethyl)anilines [33].



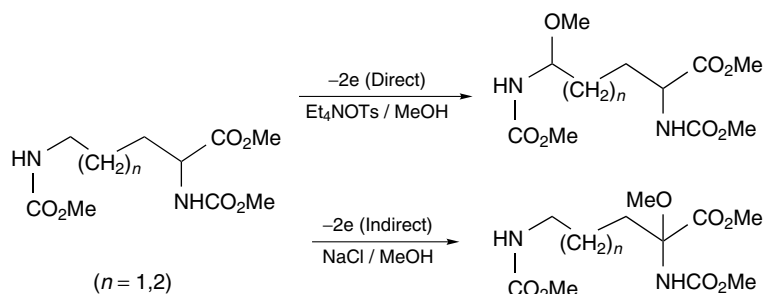
**Fig. 10** Regioselective anodic methoxylation of unsymmetrical carbamates using electroauxiliaries [36, 37].

takes place predominantly at the  $\omega$ -position, while indirect anodic methoxylation occurs selectively at the  $\alpha$ -position (Fig. 11) [38–40]. In indirect chloride-mediated methoxylation, methyl hypochlorite is formed as the reactive intermediate that generates the *N*-chloro compound. HCl elimination forms the intermediate *N*-acylimino acid ester that adds methanol. The chloride-mediated anodic methoxylation of protected dipeptide esters shows a high regioselectivity. It is influenced by the *N*-protecting groups and the amino acid side chains and can be directed towards the selective oxidation of the *C*-terminal amino acid [41]. Regioselective oxidation of the *N*-terminal amino acid is achieved by the direct electrolysis of *N*-(2-nitrophenylsulfenyl)-protected dipeptides with the intermediate formation of the sulfenimino dipeptide [42].

Anodic methoxylation of conformationally biased 2-substituted *N*-acyl piperidines leads regioselectively to 6-methoxy products owing to the steric constraints

imposed by the slowly rotating *N*-acyl group [43]. Similar results were found in the cyanation of 2-alkyl-*N*-phenylpiperidines, in which the major isomer has a *trans* configuration with an axial cyano group and an equatorial alkyl substituent. 4-Methyl-6-pentyl-*N*-phenyl piperidine afforded the trisubstituted *ax*-6-cyano compound as a single diastereomer [44]. Anodic cyanation of *N*-ethyl-*N*-methylaniline proceeds with a regioselectivity similar to that of anodic methoxylation [45]. With cyclic *N*-alkyl amines, the cyano group is preferentially introduced into the 5- or 6-membered ring  $\alpha$  to the nitrogen atom. This selectivity increases with increasing bulkiness of the *N*-alkyl group [46].

A silyl group  $\alpha$  to the nitrogen atom in tetrahydroisoquinolines and piperidines governs the regiochemistry, leads to an exclusive cyanation at this position, and additionally lowers the oxidation potential compared to the nonsilylated analogs [47]. Anodic cyanation of *N*-2,2,2-trifluoroethyl



**Fig. 11** Regioselective methoxylation of *N*, *N*-biscarbamates of methyl  $\alpha$ ,  $\omega$ -diaminocarboxylates [38–40].

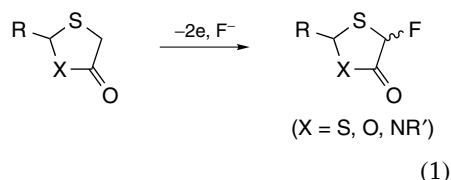
amines occurs with fair yield and selectivity at the positions  $\alpha$  to nitrogen that are not adjacent to the  $\text{CF}_3$  group [48].

**CH bonds  $\alpha$  to an oxy group** The oxygen atom of an alkoxy group directs substitution to the  $\alpha$ -carbon atom, because oxygen is oxidized to a radical cation that leads, as in the case of amines, to the generation of a carbocation in the  $\alpha$ -position. Tetrahydrofuran (THF) and other ethers have been hydroxylated and alkoxy-lated at the  $\alpha$ -carbon atom in medium to good yields [49–52]. Cyclic ethers, lactones, and a cyclic carbonate are regioselectively monofluorinated in  $\text{Et}_3\text{N}\cdot 5\text{HF}$  [53]. For the methoxylation of unsymmetrical ethers, the indirect oxidation with tris(2,4-dibromophenyl)amine as mediator proved to be favorable. With this procedure, secondary carbon atoms in the presence of primary and tertiary ones  $\alpha$  to the oxygen atom can be selectively methoxylated [54]. The oxidation of hydroxy groups to oxo groups in cholic acid proceeds at different rates, namely, at  $\text{C7} > \text{C12} > \text{C3}$  [55]. In polyhydroxylated triterpenes, the 3-OH group has been regioselectively oxidized by indirect oxidation with KI as the mediator [56].

**CH bonds  $\alpha$  to a sulfur or seleno group**

Anodic methoxylation and acetoxylation of alkyl and phenyl sulfides and selenides, bearing at the  $\alpha$ -carbon atom beside hydrogen and an electron-withdrawing group, such as CN or  $\text{CF}_3$ , proceed highly regioselectively at this site to afford  $\alpha$ -methoxy or acetoxy products [57–60]. The regioselectivity is controlled by the deprotonation rate of the sulfur or selenium radical cations as in the case of the fluoroalkylamines. Also, highly regioselective anodic mono- and difluorination of sulfides and

selenides have been achieved [61–63]. The monofluorination of heterocycles also proceeds regioselectively (Eq. 1) [64–66].



Partial fluorination of 4-arylthio-1,3-dioxolan-2-ones occurs preferentially at the carbon atom adjacent to the thio group [67]. However, a remarkable solvent effect is encountered. In the more polar solvent, dimethoxyethane substitution occurs, while in the less polar dichloromethane a larger portion of the desulfurization with cleavage of the phenylthio group takes place. This is attributed to the fact that the intermediate radical cation is more stable in the polar solvent and undergoes deprotonation, while in the less polar solvent, the less stabilized radical cation dissociates into a dioxolane cation and a phenylthio radical.

**Anodic substitution of aromatics** Anodic nuclear methoxylation of arenes occurs predominantly at the carbon bearing the highest positive charge density in the intermediate radical cation. If this position is occupied by a poor leaving group, for example, an alkyl group, a side-chain substitution occurs [16], with better leaving groups an ipso-substitution is found. Regioselective side-chain substitution of alkylarenes is a method that is also of technical importance for their conversion to acetals of benzaldehydes [17, 18, 68, 69]. Methoxycycloheptatrienes undergo a regioselective methoxylation at the carbon atom bearing the methoxy group, finally leading to substituted

tropones [70, 71]. Presumably by way of an ECE (electrochemical, chemical, electrochemical)-process, a tropylium cation is formed, which undergoes methanolysis at the methoxylated carbon atom. Anodic cyanation of dibenzofuran in MeOH/NaCN leads via an intermediate radical cation predominantly to the 3-isomer, while in electrophilic cyanation with BrCN/AlCl<sub>3</sub> the 2-isomer is obtained regioselectively [72]. Anodic cyanation of 1,4-dimethoxybenzene and 1,2,3-trimethoxybenzene affords in an ipso-substitution 4-methoxy- and 2,6-dimethoxybenzonitrile, respectively [45]. Pyrrole and indol undergo a highly regioselective anodic cyanation to provide 2-cyano products [73]. Anodic oxidation of dialkyldisulfides in SO<sub>2</sub> and in the presence of arenes, such as anthracene, phenol, and xylene, yields alkyl aryl sulfides predominantly in the *p*-position of the electron-donating substituent in good to excellent yield [74]. Anodic oxidation of terminal alkynes in NaI/MeOH affords 1-iodoalkynes exclusively [75].

#### 13.2.1.2 Regioselective Addition to Double Bonds

Substituted 1,4-dimethoxybenzenes [76], furan [77], and dienes [78] undergo exclusively to predominantly 1,4-dialkoxylation upon electrolysis in alcohol or an inert solvent with alcohol added. The reaction proceeds via an intermediate radical cation that undergoes solvolysis at the positions of the highest positive charge density. Anodic selenoalkoxylation proceeds regioselectively

via an intermediate selenium cation that undergoes methanolysis at the higher alkylated carbon atom (Fig. 12) [79]. For further regioselective oxy-, hydroxy-, and acetamido-selenations of olefins, see Ref. [80].

Anodic regioselective acetamidossulfonylation of alkenes is similarly achieved by oxidation of diphenyldisulfide in acetonitrile [81]. Cyclic enamines, which are intermediates in the oxidation of cyclic *N*-methoxycarbonyl amines, react in aqueous acetonitrile that contains chloride ions to  $\alpha$ -hydroxy- $\beta$ -chloro compounds via intermediate chloronium ions [82]. Enoethers undergo a regioselective azidomethoxylation to yield acetals of  $\alpha$ -azido carbonyl compounds upon electrolysis in methanol containing sodium azide [83]. The reaction proceeds possibly via addition of an anodically generated azide radical.

Lithium (*E*)- or (*Z*)- $\delta$ -alkenylamides are converted regio- and stereoselectively in a 5-*exo-trig*-cyclization of an intermediate amide radical to substituted pyrrolidines [84].

#### 13.2.1.3 Anodic Cleavage

By analogy with their behavior in mass spectrometry, branched hydrocarbons are cleaved upon oxidation in acetonitrile/TEABF<sub>4</sub> to afford acetamides of fragments that originate from an intermediate radical cation by cleavage between the secondary and tertiary carbon atoms [85]. Anodic cleavage of cyclopropanes can proceed quite regioselectively depending on the reaction conditions and the kind of substituents (Fig. 13)

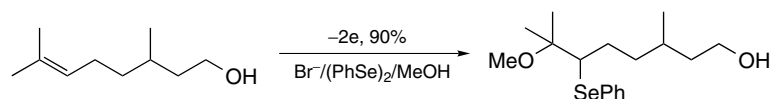


Fig. 12 Regioselective anodic selenoalkoxylation [79].

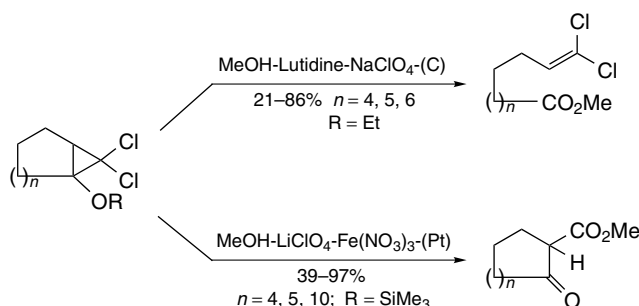


Fig. 13 Anodic cleavage of cyclopropanes [86, 87].

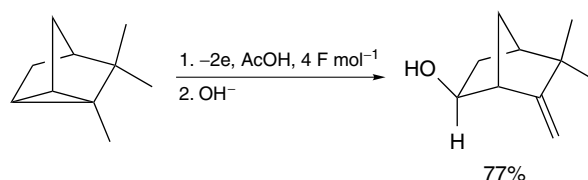


Fig. 14 Anodic cleavage of a tricyclene [88].

[86, 87]. A tricyclene has been converted in acetic acid/ $\text{Et}_3\text{N}$  to Nojigiku alcohol with a 77% yield by regioselective cleavage at the external cyclopropane C–C bond (Fig. 14) [88].

#### 13.2.1.4 Anodic C,C-Coupling

Anodic C, C-coupling is a very powerful tool to synthesize cyclic compounds with high regio- and stereoselectivity. It involves inter- and intramolecular coupling of arylolefins, dienes, enoethers, phenol ethers, and aromatic amines and often opens a quick entry into complex natural products in a few steps. Although the mechanism is fully established in only a few cases, it does appear to involve the coupling of two radical cations at the site of their highest radical density and is further controlled by steric constraints. This important type of reaction is reviewed in Chap. 5 and in Refs. [89, 90].

### 13.2.2

#### Regioselectivity in Cathode Reactions

##### 13.2.2.1 Regioselective Substitution

Cathodic substitution stands for C,C bond or C, heteroatom bond formation with cathodically generated anions. The question of regioselectivity is encountered in the reaction of such anions with allyl halides (path a) or in the reaction of allyl anions generated in an ECE process from allyl halides (path b). Cathodic reductive silylation of an allyl halide proceeds regioselectively at the less substituted position (Fig. 15) [91]. From the reduction potentials of the halides it is proposed that the reaction follows path b.

Regioselectivity in the cathodic allylation of ketones and aldehydes is greatly affected by the relative ease of the reduction of the allyl halide compared with that of the carbonyl compound. When the carbonyl compound is more easily reduced than the allyl halide, the allylation takes

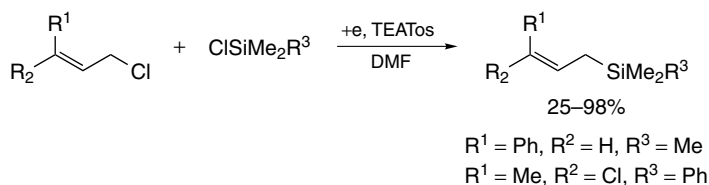


Fig. 15 Regioselective cathodic silylation of allyl chlorides [91].

place preferentially at the less substituted carbon atom to give homoallyl alcohols, which are not so easily obtained by chemical methods. When, however, the allyl halide is more easily reduced than the carbonyl compound, the allylation happens preferentially at the more highly substituted carbon atom of the allyl group, which would be the addition of a cathodically generated allyl anion at the carbonyl group (see Sect. 13.2.2.2, Fig. 16, and [92, 93]). In this case, the regioselectivity is additionally greatly influenced by the cathode material, where platinum, zinc, nickel, and

aluminum afforded chiefly allylation at the more substituted allylic carbon, while with carbon or mercury, allylation took place at both termini of the allyl group.

The cathodic coupling of prenyl chloride with diethyl fumarate and methyl crotonate proceeds with different regioselectivities as shown in Fig. 17 [94]. Also in this case, the change in the regioselectivity appears to be due to the reduction of the diethyl fumarate to a radical anion that undergoes a nucleophilic substitution at the prenyl chloride, and in the other case there is a 2e reduction of the prenyl

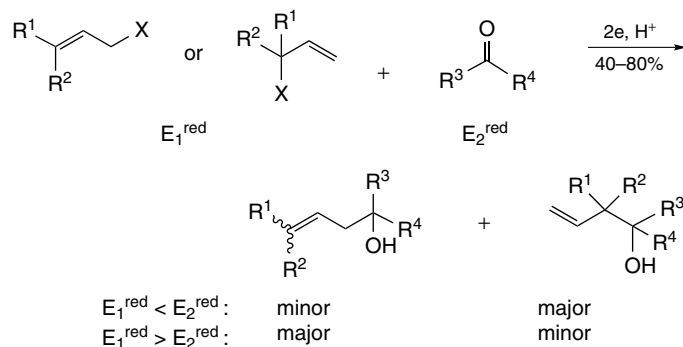


Fig. 16 Regioselective cathodic addition of allyl substituted allyl halides to carbonyl compounds [93].

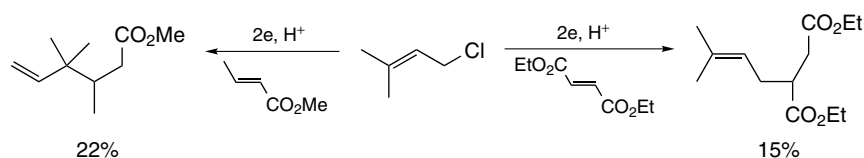
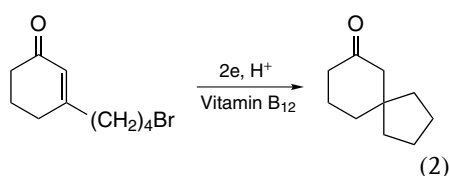


Fig. 17 Regioselective cathodic addition of prenyl chloride to  $\alpha$ ,  $\beta$ -unsaturated esters [94].

chloride to an allyl anion with a subsequent Michael addition.

Vitamin B<sub>12</sub>-catalyzed intramolecular cathodic coupling leads to a regioselective 1,4-addition with formation of a spirocompound (Eq. 2) [95]. This chain reaction is initiated by the reduction of Co(III) to a Co(I) species, which reacts in an oxidative addition with the alkyl bromide. The resulting alkyl-Co(III)-Br species is then reduced to an alkyl anion that undergoes a Michael addition and yields Co(I) for the next cycle.



An interesting case of a cathodic substitution is the EuCl<sub>3</sub>-mediated reduction of oxygen that reacts with aliphatic CH bonds. The selectivity of 1-H:2-H:3-H being 1:6:19 was attributed to a radical intermediate, while in the aromatic substitution the preferred ortho- and para-substitution points to an electrophilic oxygen species [96]. In the FeCl<sub>3</sub>-mediated oxygenation of *n*-hexane in a fuel cell, the addition of  $\alpha$ - and  $\beta$ -cyclodextrins improved the selectivity toward oxygenation of the terminal CH<sub>3</sub>-groups due to inclusion of the *n*-hexane in the cyclodextrin cavity [97].

### 13.2.2.2 Cathodic Addition

Cathodic addition involves either the reduction of a  $\pi$ -system in an ECEC process (electrochemical, chemical, electrochemical, chemical) and the chemical reaction (C) of the intermediates with a carbon or heteroatom electrophile or the cathodic conversion of a C–X bond in an ECE process into an anion that adds to an electrophilic  $\pi$ -system. The electrochemical Birch reduction of arenes

to 1,4-cyclohexadienes [98] belongs to the first type, in which the proton from an appropriate donor acts as the electrophile. Possibly, Li<sup>+</sup> from the supporting electrolyte operates as a mediator [99]. Cathodic reduction of substituted 1-methoxy-cycloheptatrienes in the presence of *isopropyl*chloride was found to be an effective method for regioselectively introducing the *isopropyl* group at C6 of the seven-membered ring system [100]. An example of the cathodic addition of allyl halides to aliphatic aldehydes and ketones has already been given in Sect. 13.2.2.1. Correspondingly, homoallylic alcohols were synthesized in the coupling of aromatic aldehydes and ketones with allylic acetates catalyzed by iron(I) complexes generated from FeBr<sub>2</sub> and a sacrificial Fe anode. The regioselectivity with unsymmetrical allyl groups was in favor of the branched product in a ratio of 96:4 to 100:0 versus the linear product [101]. With the activated zinc obtained by the cathodic reduction of ZnBr<sub>2</sub>, an unusual regioselectivity was found in the reaction of the trifluorinated analogs of prenyl bromide with carbonyl compounds [102]. When the aldehyde was sterically hindered  $\alpha$ -alkylation occurred and with an unhindered aldehyde  $\gamma$ -allylation was observed.  $\gamma$ -Allylation is always found with prenyl bromide. In the nickel-catalyzed intramolecular transfer of allyl moieties from substituted allyl ethers to a carbonyl group a regioselectivity toward the branched isomer was found [103]. Electrolysis of 3-mono and 3,3-disubstituted allylic bromides in the presence of carbon dioxide (1 atm) at a Pt cathode and a Mg anode gave regioselectively the corresponding 4-mono and 4,4-disubstituted 3-alkenoic acids with a 34 to 71% yield [104]. Reduction of vinyl phosphonates at a Mg cathode in the presence of acid anhydrides brought

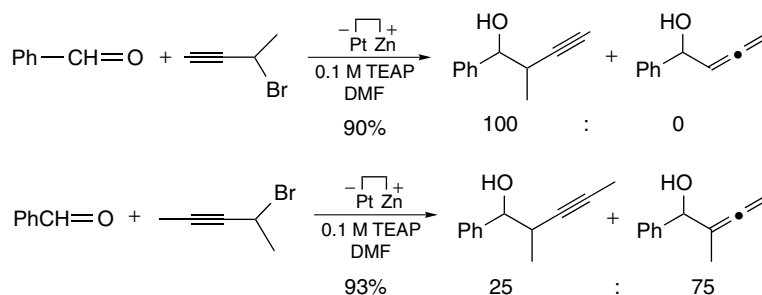


about the regioselective *C*-acylation to the corresponding  $\beta$ -acyl phosphonates. The reaction may proceed via the radical anion of the vinyl phosphonate that undergoes acylation [105]. Electrolysis of unsubstituted or  $\alpha$ -substituted propargylic bromides in the presence of aldehydes gave exclusively homopropargylic alcohols in high yields, while with  $\gamma$ -substituted propargylic bromides the homoallenyl alcohols were obtained as major products (Fig. 18) [106]. Regioselectivity was controlled via the material of the sacrificial anode (zinc, aluminum). This was explained with the preferred formation of  $\gamma$ -substituted propargyl- $\alpha$ -zinc bromides and  $\gamma, \gamma$ -disubstituted allenyl- $\alpha$ -zinc bromides, which reacted with the aldehyde in a six-membered transition state.

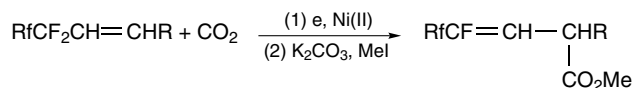
The nickel-catalyzed electrochemical carboxylation of 1-(perfluoroalkyl) alkenes proceeds regioselectively to afford 4-fluoro-4-perfluoroalkyl-3-alkenoic acids via a Ni(II)-allyl complex and a final  $F^-$  elimination (Fig. 19) [107]. Electrochemical carboxylation of alkynes in the presence of

$Ni(bipy)_3(BF_4)_2$  is a regioselective process, in which carboxylation takes place mainly at the 2-position of terminal alkynes [108]. The regioselective carboxylation of nonconjugated diynes has also been reported [109]. In the electrocarboxylation of several allenes with nickel(II) complexes and a sacrificial Mg anode, unsaturated carboxylic acids are obtained. The regioselectivity of the carbon dioxide incorporation in the central or terminal position of the allene depends on steric and electronic effects [110]. Cathodic intramolecular coupling of nonconjugated enones proceeds both in a regioselective 5-*exo-trig* cyclization and with high diastereoselectivity (Fig. 20) [111].

Also, intermolecular coupling with dienes has been satisfactorily accomplished using a carbon fiber cathode. In the case of unsymmetrically substituted dienes, a high regioselectivity toward the less substituted terminal double bond was found [112]. Electroreduction of nonconjugated enones and ynones containing a sulfur or a nitrogen atom in the

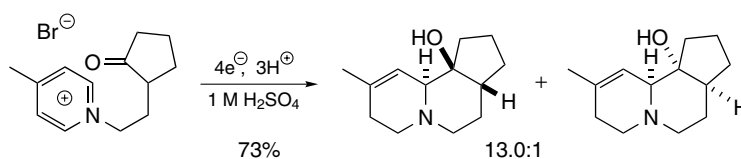
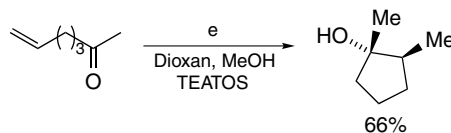


**Fig. 18** Regioselective cathodic addition of propargyl bromides to aldehydes [106].



**Fig. 19** Cathodic carboxylation of perfluoroalkyl olefins with subsequent fluoride elimination [107].

**Fig. 20** Regio- and stereoselective cathodic intramolecular coupling of nonconjugated enones [111].



**Fig. 21** Regio- and stereoselective cathodic cyclization of a 4-oxoalkyl pyridinium salt [114, 115].

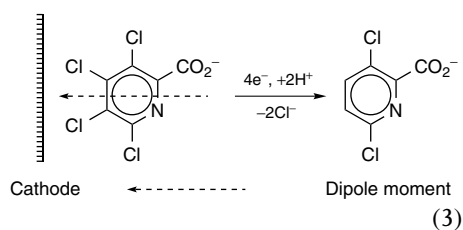
connecting chain brought about regio- and stereoselective cyclization to afford heteroatom containing cyclic alcohols in moderate to good yields [113]. Regioselective intramolecular coupling is also found in the cathodic reduction of oxoalkyl pyridinium salts to yield polycyclic pyrrolidines and piperidines (Fig. 21) [114, 115]. The reaction proceeds presumably via reduction of the hydrogen-bonded carbonyl group to a nucleophilic hydroxyalkyl radical that undergoes addition to the electrophilic C=N double bond of the pyridine. With 3-substituted pyridines, a preferential orthocoupling against a paracoupling occurs (see also Sect. 13.4.2).

Cathodic reduction of *N*-(2-iodophenyl)-*N*-alkylcinnamides under deaerated conditions forms 1-alkyl-3-benzylindolin-2-ones regioselectively (70–85%), presumably in a radical or anionic 5-*exo-trig* process. The mechanism has been explored by the use of cyclic voltammetry, controlled-potential electrolysis (cpe), and deuterium labeling [116].

#### 13.2.2.3 Cathodic Cleavage

In cathodic cleavage, a C–X bond is reductively converted to a C–H bond.

Thereby, either a localized or delocalized radical anion is formed in the first step that undergoes cleavage to a radical and X<sup>−</sup>. The radical is further reduced to an anion that is finally protonated. Tetrachloropicolinate is regioselectively dechlorinated at the 4- and 5-position, which is attributed to the controlled orientation of the substrate at the electrode surface owing to the dipole moment of the molecule (Eq. 3) [117].



Pentachloropyridine undergoes a regioselective dechlorination to give 2,3,5,6-tetrachloropyridine [118]. The reduction of 1- and 2-phenoxy-naphthalene at the cathode or by an alkali metal afforded phenol and naphthalene. The intermediacy of the naphthalene radical has been made probable by the use of an internal radical trap [119]. 5-Aryloxy-1-phenyltetrazoles cleave reductively predominantly at the tetrazolyl-O bond. The relative rates of

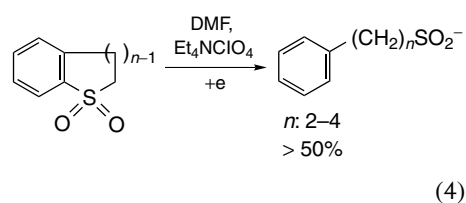
differently substituted aryloxy rings are roughly related to the  $pK_a$  values of the corresponding phenols [120]. The regioselective cleavage of a hydroxyl group is possible in hydroxymethyl pyridines since the electron-withdrawing pyridine ring selectively activates the 4-position (Fig. 22) [121].

Reductive ring opening of cyclic *N*-alkyl anilinium salts happens regioselectively at the *N*-aryl bond to form an *N*, *N*-dialkyl amine. A  $2e$  reduction has been proposed, followed by cleavage to the most stable carbanion (Fig. 23) [122].

Acyclic alkyl phenyl sulfones undergo an alkyl-sulfur bond cleavage [123]; however, in cyclic arylsulfones the aryl-sulfur

bond cleavage takes place selectively (Eq. 4) [124].

The allylic sulfonyl group is regioselectively cleaved in the presence of the alkyl-sulfonyl group by indirect reduction with anthracene as a mediator (Fig. 24) [125].



(4)

#### 13.2.2.4 Cathodic Coupling

Cathodic coupling involves C, C bond formation by reduction of an activated

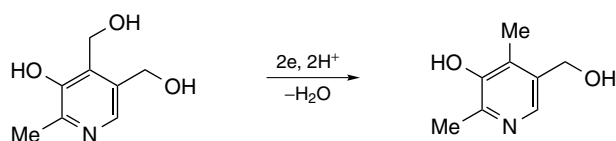


Fig. 22 Regioselective cleavage of a hydroxyl group [121].

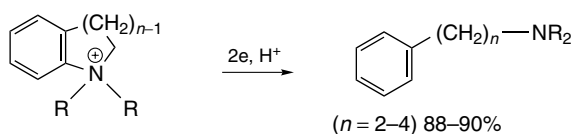


Fig. 23 Reductive cleavage of cyclic anilinium salts [122].

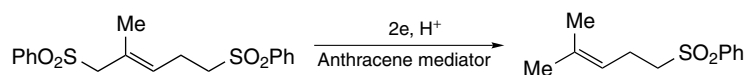


Fig. 24 Regioselective cleavage of allyl sulfones [125].

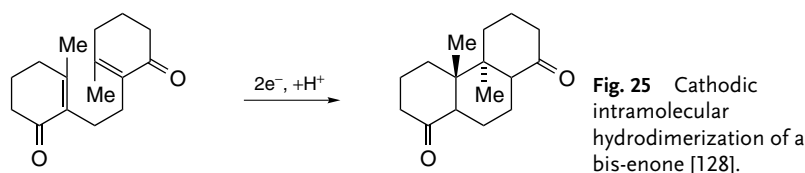


Fig. 25 Cathodic intramolecular hydrodimerization of a bis-enone [128].

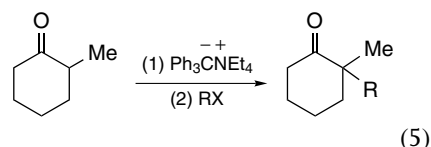
C=C or a C=X double bond. Thereby, in most cases radical anions or radicals, the latter produced in an EC process, couple. Activated olefins such as acrylonitrile and alkyl acrylates undergo regioselective  $\beta,\beta$ -coupling to form the corresponding hydrodimers [126]. On the other hand, cathodic coupling of  $\alpha,\beta$ -unsaturated carbonyl compounds yields mixtures of 1,1'-, 1,3'- and 3,3'- regioisomers depending on electronic and steric factors. With vinyl alkyl ketones all three isomers are formed, while with styryl alkyl ketones exclusively the 3,3'-isomer is obtained [127]. The intramolecular coupling of enones proceeds highly regioselectively owing to steric constraints (Fig. 25) [128].

Cathodic reduction of retinal leads to a regioselective coupling in the presence of malonic ester to produce the corresponding pinacol (Fig. 26) [129]. Chromium(III) ions facilitate the reduction and favor the regioselective coupling of conjugated dienones to pinacols. A Cr(III)-carbonyl compound complex is evidenced as the reason for the selectivity [130].

#### 13.2.2.5 Electrogenerated Bases

Electrogenerated bases (see Chap. 14) can be prepared in situ and tailored for regioselective deprotonation. Regioselective alkylation of an unsymmetrical cyclic ketone was achieved by using an electrogenerated triphenylmethyl anion (Eq. 5,  $RX = CH_3I$ ,

BuI,  $C_6H_5CH_2Br$ , 38–84%) [131, 132].



As an entry into O-functionalized disaccharides, the cathodic deprotonation of hydroxy groups and the subsequent trapping of the alkoxide with suitable reagents were evaluated. The regioselectivity was correlated by way of computer simulations to electrostatic potential profiles of the relevant conformers of sucrose [133].

### 13.3

#### Chemoselectivity

##### 13.3.1

##### General

Chemoselectivity describes the preferred formation of one out of several products due to the selective interaction of a reagent with the substrate. In electroorganic conversion, the electrode is the reagent that can influence the reaction course in several ways: The electrode material can form immobilized organometallics or oxides that can shift the conversion like mediators from an outer sphere electron transfer to a more selective inner sphere electron transfer [134]. Overvoltages can suppress the hydrogen evolution in cathodic reduction

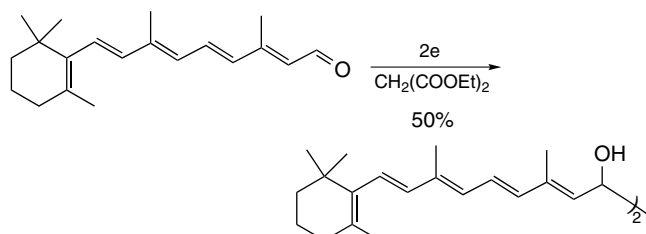


Fig. 26 Cathodic hydrodimerization of retinal [129].

at mercury or graphite in protic electrolytes [135] or the anodic oxygen generation at graphite. By appropriate treatment the electrode surface can be made more hydrophilic [136] or more hydrophobic [137]. The roughness of the electrode surface influences the concentration of the reactive intermediates formed by electron transfer. A large real electrode surface inherent to the material, e.g. pyrolytic graphite, promotes first-order reactions owing to a lower concentration of reactive intermediates, while a smooth surface, e.g. platinum, favors second-order conversions, for example, in the Kolbe reaction [138]. Likewise, the current density can favor first-order (low current density) or second-order conversions of the electrogenerated intermediate (high current density). The kind of supporting electrolyte can create a hydrophilic electrode surface, for example, hydrated  $\text{Li}^+$  favors hydrogenation in the cathodic reduction of activated olefins, while the tetrabutylammonium cation can make the electrode surface more hydrophobic than the bulk electrolyte, thus promoting hydrodimerization in the reduction of activated olefins [139]. Redox catalysts (mediators) (see Chap. 15 and Ref. [140]) can change the reaction course by decreasing overvoltages that may occur in direct electron transfer and by proceeding via more selective inner sphere transfer routes.

The substrate can change the reactivity in the interaction with the reagent by means of its electrophilicity, nucleophilicity, and hardness [4, 141]. These properties can be accentuated by electroauxiliaries [35] that facilitate electron transfer and direct follow-up reactions. A powerful control is the potential of the electrophore that is determined by electronic factors, steric accessibility, and intramolecular electron transfer. This potential can

be accurately set by electronically adjusting the potential of the working electrode and holding it constant throughout the whole electrolysis (cpe). This allows the potential-selective conversion of one out of several electrophores.

### 13.3.2

#### Chemoselectivity in Anode Reactions

##### 13.3.2.1 Anodic Dehydrogenation

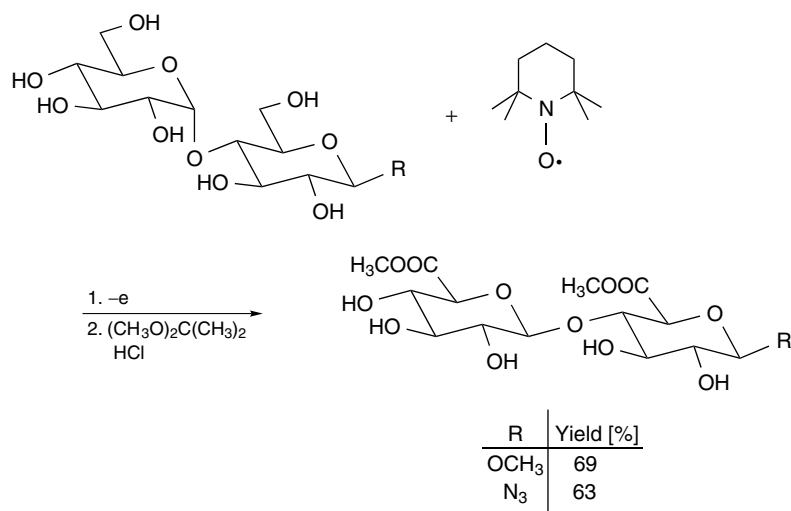
Partially protected carbohydrates can be selectively oxidized at the primary hydroxy group to uronic acids at the nickel hydroxide electrode. At the same electrode, in polyhydroxy steroids, a preferential oxidation of the sterically better accessible hydroxyl groups is achieved [142]. By way of the mediator, TEMPO, carbohydrates that are only protected at the anomeric hydroxyl group are selectively oxidized at the primary hydroxyl group (Fig. 27) [143–145].

Anodic oxidation of a mixture of *cis*-cyclohexane-1,2-diol and cyclohexanol in methanol containing dibutyltin oxide and  $\text{Et}_4\text{NBr}$  provides 2-hydroxycyclohexanone selectively, while cyclohexanol is recovered almost completely (Fig. 28) [146]. The cyclic intermediate dibutyl-(1,2-dioxycyclohexyl)stannan is oxidized indirectly by  $\text{Br}^+$ .

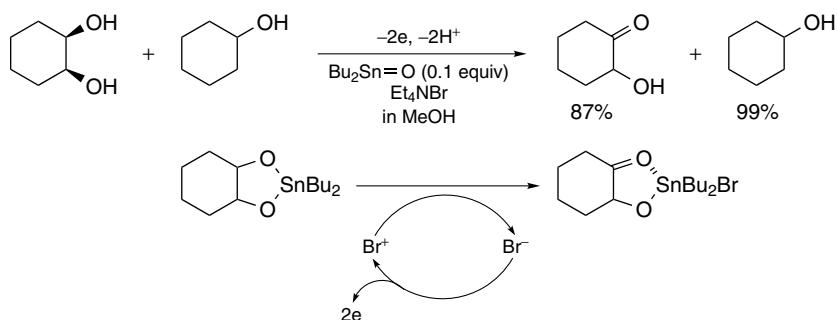
The chemoselectivity can be strongly changed by the anode material. The oxidation of glycolaldehyde at a platinum anode affords mainly glyoxal while the conversion with a platinum anode modified by antimony or bismuth *ad*-atoms provides mainly glycolic acid (Fig. 29) [147].

##### 13.3.2.2 Anodic Cleavage

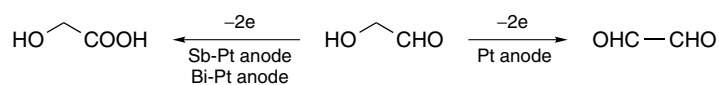
Potential-selective cleavage is a powerful method for potential-selective deprotection. Benzyl ethers can be cleaved to benzaldehyde and alcohol via oxidation of the benzyl group to a radical cation (Fig. 30) [148]. With the radical cation of



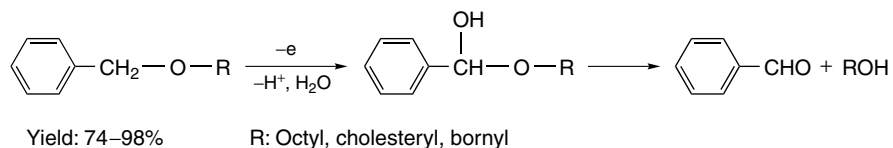
**Fig. 27** Chemoselective oxidation of primary OH-groups in carbohydrates with TEMPO as mediator [143–145].



**Fig. 28** Chemoselective oxidation of 1,2-cyclohexandiol in the presence of cyclohexanol [146].



**Fig. 29** Chemoselective oxidation of glycolaldehyde [147].



**Fig. 30** Anodic deprotection of benzyl ethers [148].

tris(*p*-bromophenyl)amine in the presence of 2,6-lutidine the cleavage occurs under even milder conditions than can be used for a mediated process [149]. By variation of the oxidation potential of the radical cation owing to a different substitution of the trisarylamine, a selective deprotection of diols protected with a benzyl and a *p*-methoxybenzyl group becomes possible [150, 151].

### 13.3.2.3 Anodic Substitution and Addition

Chemoselective oxidation of 3-arylsulfenylmethyl- $\Delta^3$ -cephem affords 3-methoxymethyl- $\Delta^3$ -cephem in an anodic substitution. From the two thioethers, the arylthio group is more easily oxidized to a radical cation, that then undergoes cleavage to a thiyl radical and a carbocation (Fig. 31) [152].

In the case of anodic oxidation of geranyltrimethylsilane, the C=C double bond

of the allylsilane moiety is selectively oxidized owing to the electron-donating effect of the  $\beta$ -silyl group (Fig. 32) [153].

Unsaturated  $\alpha$ -heteroatom organosilicon, organotin, and organosulfur compounds undergo selective cleavage of the C–Si, C–Sn, and C–S bond respectively, with the subsequent intramolecular addition of the generated carbocation to the double bond (Fig. 33) [154, 155].

Chemoselective anodic methoxylation at a distinct carbon atom in the  $\alpha$ -position to an amino group in a polypeptide was achieved by prior introduction of a silyl group as an electroauxiliary at this carbon atom [156]. Amide oxidation in *N*-acetylpyrrolidines substituted with electron-rich phenyl rings led to either methoxylation  $\alpha$  to the nitrogen atom or in the benzylic position. Mechanistic studies indicate that both the amide and the phenyl oxidation compete, but intramolecular electron transfer leads to

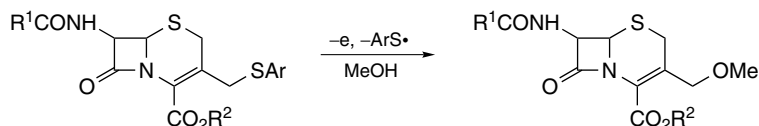


Fig. 31 Chemoselective anodic substitution of an arylthio group [152].

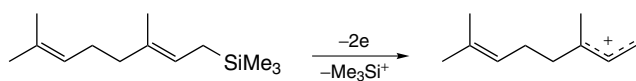


Fig. 32 Chemoselective cleavage of the allylsilane moiety [153].

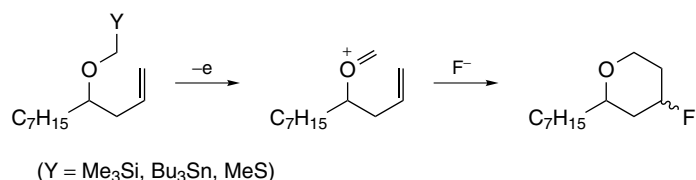


Fig. 33 Selective cleavage of C–Si, C–Sn, and C–S bonds [154, 155].

the selective formation of an amide oxidation product [157].

### 13.3.3

#### Chemoselectivity in Cathode Reactions

##### 13.3.3.1 Cathodic Hydrogenation

Electrocatalytic hydrogenation has the advantage of milder reaction conditions compared to catalytic hydrogenation. The development of various electrode materials (e.g., massive electrodes, powder cathodes, polymer film electrodes) and the optimization of reaction conditions have led to highly selective electrocatalytic hydrogenations. These are very suitable for the conversion of aliphatic and aromatic nitro compounds to amines and  $\alpha, \beta$ -unsaturated ketones to saturated ketones. The field is reviewed with 173 references in [158]. While the reduction of conjugated enones does not always proceed chemoselectively at a Hg cathode, the use of a carbon felt electrode coated with polyviologen/Pd particles provided saturated ketones exclusively (Fig. 34) [159].

Solvents exert control on the chemoselective hydrogenation of alkenes bearing a benzyloxy protecting group [160]. In the unpolar solvent benzene, only the double bond is hydrogenated, while in methanol, acetone, and ethyl acetate, the benzyloxy group is also removed. Selective

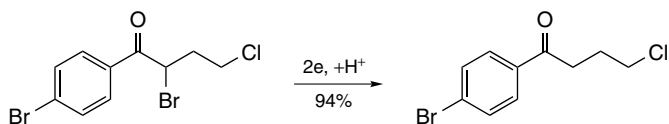
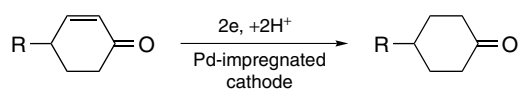
electrohydrogenation of the nitroaromatic and nitroaliphatic functional groups in molecules that contain other groups that are easy to hydrogenate (e.g., activated double bond, carbon–iodine bond, nitrile) was carried out in slightly acidic (pH 3) or near neutral MeOH–H<sub>2</sub>O solutions at Devarda Cu and Raney Co electrodes [161]. Electrochemical and chemical reduction of multifunctional molecules can proceed with different chemoselectivities. While in nitroketones the carbonyl group is selectively reduced with NaBH<sub>4</sub> [162], in nitroesters the nitro group is preferentially reduced at the cathode [163].

##### 13.3.3.2 Cathodic Cleavage and Elimination

In polyfunctional molecules, the electrophore with the least negative reduction potential is selectively cleaved [164]. A bromine atom at a carbon atom  $\alpha$  to a carbonyl group is fairly easily reducible; therefore, cpe at the potential in which this C–Br bond is reduced proceeds highly chemoselectively (Fig. 35) [164].

Potential selective cathodic bond cleavage is of considerable importance for deprotection [165–174]. As shown in Fig. 36, the C–X bond can be easily cleaved with a high selectivity, when an unsaturated group Y is attached in the  $\alpha$ -position to the carbon.

**Fig. 34** Chemoselective electrocatalytic hydrogenation of conjugated enones [159].



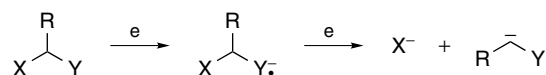
**Fig. 35** Chemoselective cathodic cleavage in polyfunctional molecules [164].



Some further examples of selective deprotection in the presence of other reducible functional groups are shown in Figs. 37–40.

In the tetrabromide of 4-vinyl-1-cyclohexene, the higher alkylated double bond could be selectively deprotected by cpe [177].

Carboxylic acids can be protected as 2-haloethyl derivatives. These are reducible at different potentials depending on the kind and the number of halogen substituents at C2 (Fig. 40) [178]. This kind of protecting group has been employed in a nucleotide synthesis using the triester method [179].



X,Y: SR, C<sub>6</sub>H<sub>5</sub>CO; CH<sub>2</sub>CO<sub>2</sub>Et, SO<sub>2</sub>C<sub>6</sub>H<sub>5</sub>; OR, pyridyl; SBT, CO<sub>2</sub>Me; O<sub>2</sub>CC<sub>6</sub>H<sub>5</sub>, CN; OAc, C=C-CO<sub>2</sub>R; OR, 10-oxo-9-anthracenyl.

Fig. 36 Chemoselective cathodic deprotection [165–173].

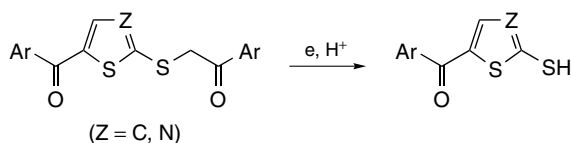


Fig. 37 Chemoselective cathodic deprotection [174].

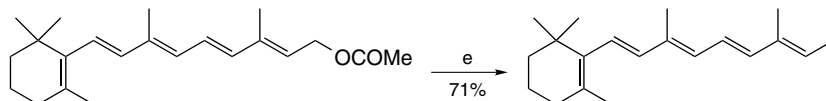


Fig. 38 Selective cathodic deprotection [175].

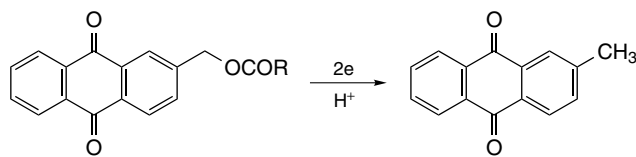


Fig. 39 Selective cathodic deprotection [176].

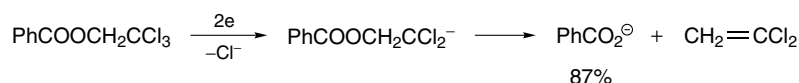


Fig. 40 Potential-selective deprotection of esters [178].

### 13.4 Stereoselectivity

#### 13.4.1 General

In coupling, substitution, or addition reactions, stereogenic centers are transformed into other ones or generated from prostereogenic groups. This creates stereoisomers that have the same constitution, but different configurations. A molecule with  $n$  stereogenic centers can form  $2^n$  stereoisomers (diastereomers and enantiomers). Stereoselectivity means that one out of several possible stereoisomers is preferentially formed. Diastereoselectivity designates the preferred formation of one diastereomer; enantioselectivity of one major enantiomer. Stereochemistry in organic reactions and the stereoselective construction of new stereogenic centers is one of the central and very lively topics in organic chemistry today, as was demonstrated by the Nobel prize of 2001 dedicated to this field. Control of stereoselectivity means to channel a reaction predominantly to one stereoisomer, which increases its yield and avoids the often very difficult separation of stereoisomers. The topics of stereochemistry, stereoselectivity, and stereoselective synthesis are covered, for example, in Refs. [180–182]. Diastereoselective synthesis with chiral auxiliaries [183] and catalytic enantioselective syntheses [184, 185] are efficiently and increasingly used to prepare complex molecules in high enantiomeric purity. These are applied, for example, in research in the life sciences and in the synthesis of pharmaceuticals and agrochemicals.

Stereoselectivity arises from small differences in the activation energies of competing reactions leading to different stereoisomers. These differences originate

from variations in transition state energies due to spatially directed steric and electronic interactions between the reactants. In organic electrochemistry, the mechanism and control of the stereochemical course has not been studied in such width and depth as in organic chemistry. However, in these cases of electrochemistry, in which the factors influencing the stereochemistry have been studied in some detail, the same controls have been found as in homogeneous chemical reactions. There are, however, some additional effects inherent to the electrochemical reaction that are frequently found in mechanistic discussions. They arise from the heterogeneous nature of the electrochemical process and the vicinity of the reaction layer to the electrode surface, which creates conditions that are different from these in homogeneous reactions. Furthermore, the intermediate may be absorbed by noncovalent forces or bound covalently to the electrode. The substrate may be converted in an inner sphere electron transfer by immobilized metal oxides in anode processes or transition metal complexes in cathodic conversions. These factors, however, have to be identified in the individual case by comparing the stereoselectivity of the same conversion by chemical and electrochemical means, which has not as yet been rigorously done. In the meantime, the advanced knowledge about factors that increase the diastereo- and enantioselectivity in homogeneous reactions has to be used to improve the stereoselectivity in electrochemical conversions. To exploit the controls that are in principle offered by the electrochemical reaction layer and adsorption, the knowledge about these phenomena has to be extended by fundamental research on this topic applied to organic molecules and their reactions. In the meantime, the usual approach to

complex systems, namely, optimization via systematic variation of the reaction conditions has to be applied.

### 13.4.2

#### Diastereoselectivity

Diastereoselectivity denotes the preferential formation of one out of several diastereoisomers. Selected examples are presented in the following text for anodic and cathodic C, C bond formations and for functional group interconversions.

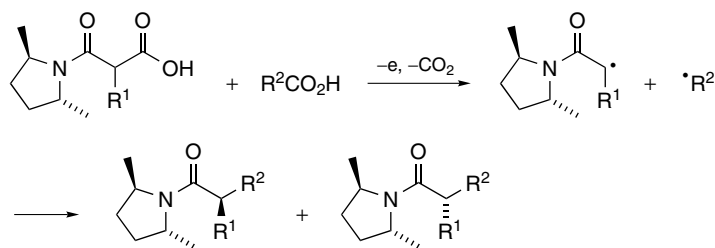
#### 13.4.2.1 Diastereoselectivity at the Anode

**13.4.2.1.1 Coupling** Anodic decarboxylation of carboxylic acids (Kolbe electrolysis) generates alkyl radicals that can couple, disproportionate, or be further oxidized [138]. The first route leads to homo- and heterocoupling products, which are treated in this section, the last route generates substitution products (see Sect. 13.4.2.1.2). Enantioenriched 2-alkyl substituted alkyl malonates yield racemic heterocoupling products [186, 187]. The same holds for the homocoupling of *trans*- and *cis*-4-*t*-butylcyclohexanecarboxylates [188]. In the

case of *trans*-4-phenylcyclohexanecarboxylates and of *cis*-4-phenyl-2-cyclohexenecarboxylates, the distribution of stereoisomeric dimers indicates that adsorption might slightly influence the product distribution.

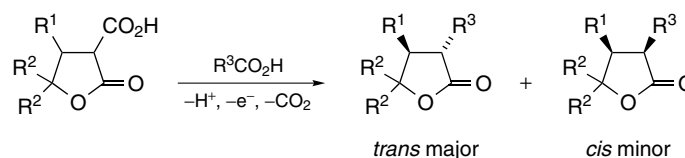
Carboxylates with different nonracemic chiral auxiliaries have been anodically decarboxylated to explore the *face*-selective heterocoupling of the intermediate radicals. With (2*R*, 5*R*)-2,5-dimethylpyrrolidine as the chiral amido group and an increasing size of the substituents R<sup>1</sup> and R<sup>2</sup> selectivities up to 86% de (diastereomeric excess) have been obtained (Fig. 41) [189, 190]. The results point to an increasing portion of an intermediate radical with *Z*-conformation and a growing steric hindrance for the *si*-approach. With oxazolidine, 2,10-camphersultame, and menthol auxiliaries, the diastereoselectivity is lower. Heterocoupling of 2-carboxy-butyrolactones with a stereogenic center in the  $\alpha$ -position to the intermediate radical leads to 2-substituted butyrolactones with a 33 to 43% yield and up to 88% de (Fig. 42) [191].

The results show that, in the coupling of anodically generated radicals, good diastereoselectivities can only be achieved when the intermediate radical



R<sup>1</sup> = CH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>, C(CH<sub>3</sub>)<sub>3</sub>, C(CH<sub>3</sub>)<sub>2</sub>Et      R<sup>2</sup> = C<sub>4</sub>H<sub>9</sub>, CH<sub>2</sub>C(CH<sub>3</sub>)<sub>3</sub>, C(CH<sub>3</sub>)<sub>2</sub>Et  
16–69% yield, 20–86% de

**Fig. 41** Diastereoselective coupling of radicals in the Kolbe electrolysis [189, 190].



$\text{R}^1 = \text{Ph}, i\text{-Pr}, t\text{-Bu}$        $\text{R}^2 = \text{Me}, \text{H}$        $\text{R}^3 = \text{CH}_3, \text{C}(\text{CH}_3)_2 \text{CO}_2\text{Et}$   
 33–43% yield, 0–88% de

**Fig. 42** Diastereoselective coupling of radicals in the Kolbe electrolysis [191].

adopts a preferred conformation and the substituents efficiently shield one face of the radical. These observations correspond to those found in homogeneous radical reactions [192]. Stereogenic centers at the  $\beta$ -carbon atom of the acid and more remote positions retain their configuration as expected. The same holds for double bonds except for the (*Z*)-4-enoic acids that partially isomerize to (*E*)-products via a reversible ring closure to cyclopropylcarbinyl radicals [193].

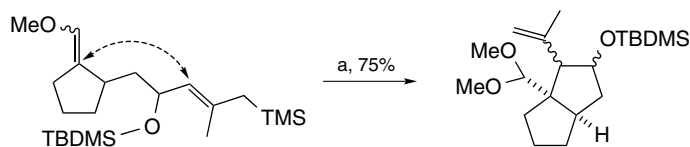
The anion of methyl phenylacetate, formed by an electrogenerated base, was homocoupled with iodine or anodically mediated by iodide to afford dimethyl 2,3-diphenylsuccinate in high yield and high *d, l*-selectivity. This reaction probably does not involve free radicals but an iodination-nucleophilic substitution sequence [194, 195].

Oxidation of arylolefins, enolethers, or dienes yields intermolecular homocoupling products in moderate to good yield (see Sect. 13.2.1.4); however, no pronounced diastereoselectivity was observed. This is also due to the fact that the coupling sites do not tolerate substituents that would make up a prostereogenic center. Furthermore, the fairly stable cations of the dimerized radical cation solvolyze stereounselectively. The same holds for the intermolecular coupling of aromatic compounds, in

which the diastereoselective formation of *atropo*-isomers has been observed only in a few cases. There the TEMPO/sparteine-mediated enantioselective homocoupling of 2-naphthol has been described (see Sect. 4.3.2.1). Furthermore, the oxidative coupling of 1,2-dimethyl-7-hydroxy-6-methoxy-1,2,3,4-tetrahydroisoquinoline at a graphite felt anode yielded an 8,8'-coupling product that had the *R, R* and *S, S* but not the *R, S* configuration at C1 [196]. An aspidosperma class alkaloid has been regio- and diastereoselectively dehydrodimerized by the anodic coupling of an aryl with an enaminoester moiety [197].

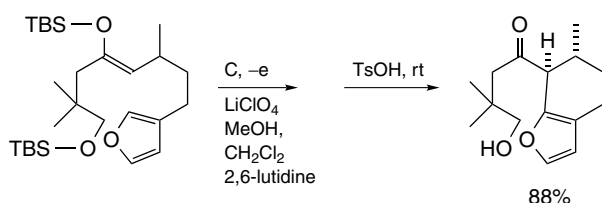
The intramolecular coupling of enolethers with enolethers, styrenes, dienes, alkyl-substituted olefins, allylsilanes, and vinylsilanes was systematically studied by Moeller [90, 198–200]. These couplings allow the smooth formation of quaternary carbon atoms in fused bicyclic rings having a *cis* stereochemistry (Fig. 43) [201, 202].

Ketene dithioacetal enolethers underwent stereoselective intramolecular coupling to yield *trans*- or *cis*-disubstituted five- or six-membered cycloalkanes in high stereoselectivity and yield [203]. In the intramolecular coupling of an allylsilane, a five-membered ring with three contiguous stereogenic centers was stereoselectively formed without loss of a very acid sensitive allylic, alkoxy group [204]. The intramolecular coupling of a furan



a : C-anode, 1 M LiClO<sub>4</sub>, MeOH/THF, lutidine

**Fig. 43** Stereoselective intramolecular coupling of enoether with allylsilane [201, 202].



**Fig. 44** Stereoselective cyclization of a silyl enoether and a furan [205].

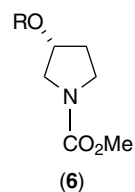
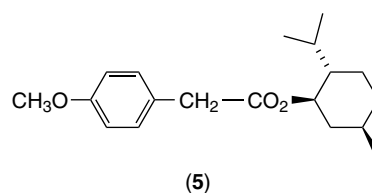
ring with a silylenoether was used to stereoselectively assemble the tricyclic core ring system of alliacol A (Fig. 44) [205]. The electrolysis proceeded in high yield and could be accomplished with the use of a 6-V lantern battery.

For further examples of the stereoselective synthesis of ring systems, see anodically initiated cycloadditions in Sect. 13.4.2.1.3.

**13.4.2.1.2 Substitution** Anodic substitution designates the oxidative replacement of a hydrogen atom, a silyl, or a carboxyl group (non-Kolbe electrolysis) by a nucleophilic carbon or heteroatom.

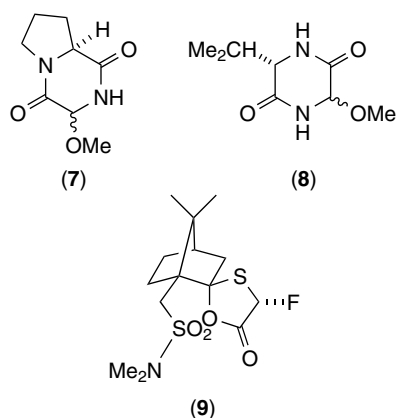
Anodic oxidation of 2-*t*-butylindan in acetic acid led predominantly to side-chain acetoxylation at a Pt or PbO<sub>2</sub> anode. The *cis*/*trans* ratio of the two acetates is significantly higher in the anodic process than in the related homogeneous reactions, indicating that adsorption at least partially controls the anodic reaction [206, 207]. Menthyl 4-methoxyarylate (5) could be

diastereoselectively fluorinated in the  $\alpha$ -position by anodic oxidation with Et<sub>3</sub>N, 3HF/MeCN as electrolyte. The observed diastereoselectivities are discussed in connection with the chiral auxiliary and the role of the anode [208].



Anodic  $\alpha$ -methoxylation of (3-*R*)-1-methoxycarbonylpyrrolidinol derivatives (6) (*R* = H, Ac, SiMe<sub>2</sub>*t*-butyl) displays a modest stereoselectivity. However,

substitution of the anodically introduced methoxy group with a cyano group leads with  $R = \text{TBDMSi}$  to a stereoselectivity of up to 86% de [209]. Anodic methoxylation of conformationally biased 4-*t*-butylpiperidine-1-carboxaldehyde gave axial 2-substitution owing to the steric constraints imposed by the *N*-acyl group [210]. In anodic cyanation of *N*-alkyl-substituted tetrahydroquinolines and *N*-phenylpiperidines, the cyano group was selectively introduced at C2 in the axial position [211]. Chiral electrophilic glycine equivalents (7) and (8) were generated by anodic methoxylation of heterocycles that incorporated L-proline and L-leucine as chiral auxiliaries [212].



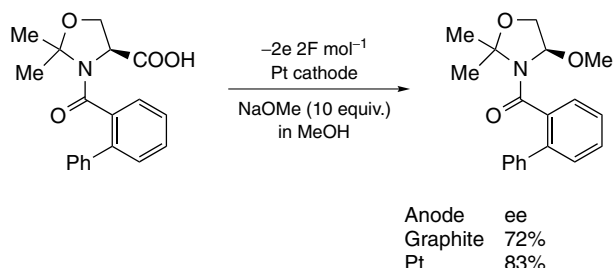
$\beta$ -Hydroxypiperidine alkaloids have been synthesized via anodic methoxylation that allowed the regio- and stereoselective introduction of substituents [213]. A highly diastereoselective fluorination was achieved with chiral 1,3-oxathiolan-5-ones derived from camphorsulfonamide. In dimethoxyethane containing  $\text{Et}_4\text{NF} \cdot 4\text{HF}$ , the monofluorinated product (9) was obtained as a single diastereomer [214].

Anodic substitution of a carboxylic acid involves decarboxylation to an alkyl radical

that is further oxidized to a carbocation, which reacts with nucleophiles present in the electrolyte (non-Kolbe electrolysis) [215]. Decarboxylation of *exo*- and *endo*-bicycloalkane carboxylic acid, depending on the electrolyte, leads to methoxylation, hydroxylation, or acetamidation in low diastereoselectivity [216, 217]. Cyclopropyl carboxylic acids, besides radical coupling, undergo a ring cleavage to allyl methyl ethers, whose stereochemistry points to a concerted electrocyclic ring opening of a cyclopropyl cation [218, 219]. Electrochemical decarboxylation of L-threonine and oligopeptide derivatives forms *N*-acyl-*N*,*O*-acetals with a moderate diastereoselectivity. These can be further converted by reaction with organometallics or trialkylphosphites and the resulting diastereomers can be separated by HPLC (high performance liquid chromatography) [220]. *Trans*-4-hydroxy-L-proline was converted by anodic decarboxylation and  $\text{TiCl}_4$  mediated reaction with nucleophiles to enantiomerically pure pyrrolidines [221] or (3*R*)-3-hydroxy-4-aminobutyric acid (GABOB) [222]. A very interesting retention of configuration (91.5%) is found in the anodic decarboxylative methoxylation of serine derivatives (Fig. 45) [223]. The restricted rotation of the bulky *o*-phenylbenzoyl protecting group preserves the stereochemical information in the intermediate iminium cation and leads by facial shielding to a high degree of retention in the cation-methanol recombination.

#### 13.4.2.1.3 Addition and Cycloaddition

**Addition** In anodic addition, either the olefin is oxidized to a radical cation that reacts with the nucleophilic species in the electrolyte or the nucleophile is oxidized to a radical that adds to the double bond.

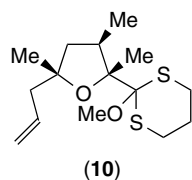


**Fig. 45** Stereoselective methoxylation of serine derivatives by anodic decarboxylation [223].

The route that is taken depends on the oxidation potential of the nucleophile and the olefin.

Acetoxylation proceeds mostly via the radical cation of the olefin. Aliphatic alkenes, however, undergo allylic substitution and rearrangement predominantly rather than addition [224, 225]. Aryl-substituted alkenes react by addition to vic-disubstituted acetates, in which the diastereoselectivity of the product formation indicates a cyclic acetoxonium ion as intermediate [226, 227]. In acenaphthenes, the *cis* portion of the diacetoxo product is significantly larger in the anodic process than in the chemical ones indicating that some steric shielding through the electrode is involved [228].

The stereoselective intramolecular coupling of a ketene dithioacetal to an oxygen nucleophile to afford (**10**), was used as a key step in the total synthesis of (+)-nemorensic acid [229].

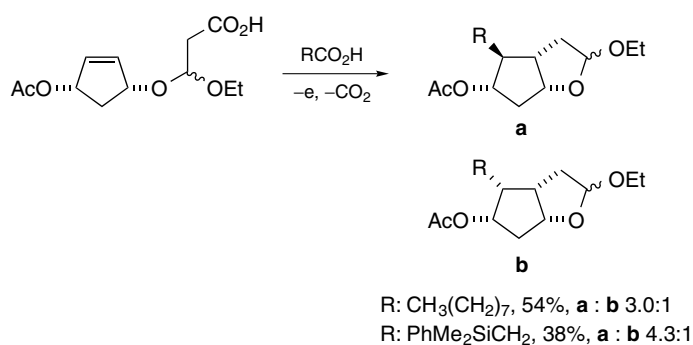
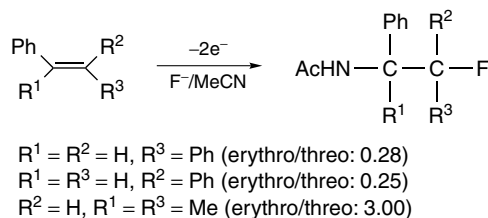


Aliphatic cyclic olefins form the *trans*-dimethoxy compound in anodic methoxylation; however, only as a minor

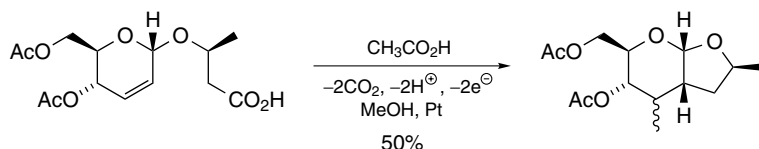
side product, while the major products arise from allylic substitution and rearrangement [225, 230]. Furans react in a 1,4-addition to 2,5-dimethoxy-2,5-dihydrofurans, in which the *trans* diastereomer predominates [231]. Anodic methoxylation of benzothiophenes proceeds with a low diastereoselectivity of *cis:trans* = 4:3 indicating some shielding effect of the anode [232]. A larger shielding effect in the anodic addition of methanol to (*E, E*)-1,4-diphenyl-1,3-butadiene with a *syn:anti* ratio of 8.9:1 has been observed for the 1,4-adduct [233]. The aromatic compound pseudocumene affords in a 1,4-addition with a 30% yield *trans*-3,6-dimethoxy-1,3,6-trimethylcyclohexa-1,4-diene as the major product [234]. The stereoselectivity of the fluoroacetamidation of a variety of olefins has been rationalized as due to the adsorption of the olefin, fluoride anion, and the resulting oxidized olefinic species on the anode surface (Fig. 46) [235–237].

Chloroacetamidation of unsaturated carbohydrates occurs with substrate dependent stereoselectivity [238]. For iodoacetamidation of cyclohexene [239], a *trans* selectivity has been reported. Nitroacetamidation of the conjugated dienes that were electrolyzed in acetonitrile-containing  $N_2O_4$ , showed a good regio- and a poor stereoselectivity [240]. Anodic

**Fig. 46** Stereoselective anodic fluoroacetamidation of arylelefins [235–237].



**Fig. 47** Stereoselective 5-*exo-trig*-cyclization and heterocoupling to a prostaglandine precursor [246].



**Fig. 48** Stereoselective 5-*exo-trig*-cyclization and heterocoupling to a branched carbohydrate [247].

acetamidosulfenylation occurs stereoselectively to form the trans product in acetonitrile-containing disulfides [241, 242]. The selenoalkoxylation of cyclic olefins stereoselectively affords the trans product with a 56 to 98% yield [243]. Optically active 2-fluoro-1-tetralones (with >95% *ee*) were prepared by anodic fluorination of camphanyl enolester derivatives and subsequent hydrolysis of the fluorinated electrolysis products [244]. The transformation of alkenes by direct and indirect anodic oxidation and the effect of substrate, of structure, and of electrolysis

conditions on the regio- and stereoselectivity has been reviewed recently [245].

Unsaturated carboxylic acids can be decarboxylated to alkyl radicals that undergo an intramolecular addition. The 5-*exo-trig*-cyclization of  $\beta$ -allyloxy radicals, generated from an appropriate carboxylic acid, combined with a final heterocoupling has been applied to synthesize a precursor of prostaglandine PGF<sub>2</sub> $\alpha$  (Fig. 47) [246] and a branched carbohydrate (ratio of diastereomers 1.8:1) (Fig. 48) [247]. A radical tandem cyclization of a doubly unsaturated monocyclic carbocyclic acid provides a



short synthetic entry to tricyclic products, for example, triquinanes [248]. In all these reactions, the cyclization proceeds highly stereoselectively as an intramolecular *cis* addition, while the concluding intermolecular heterocoupling has a low stereoselectivity.

Neutral aminyl radicals generated by anodic oxidation of lithium alkenyl amides undergo a stereoselective cyclization to *cis*-1-methyl-2,5-disubstituted pyrrolidines [249].

**Cycloaddition** Anodically generated phenoxy cations, *o*-quinones, and *o*-quinone methides react with olefins to bicyclic and tricyclic annelated compounds in stereoselective cycloadditions [250–252]. In the synthesis of a Euglobin skeleton, a quinone methide has been generated *in situ* by anodic oxidation mediated by DDQ. The cycloaddition was promoted by the use of lithium perchlorate

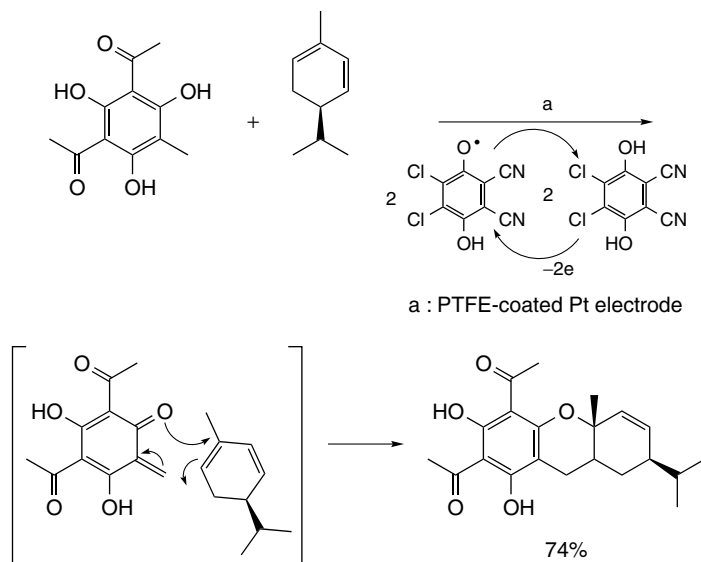
and a hydrophobic PTFE-coated electrode (Fig. 49) [253–256].

The intramolecular cycloaddition of phenol derivatives can lead stereoselectively to three different product types (Fig. 50) [257–259]. The competition of the three pathways depends strongly on the configuration of the double bond and the nature of the functional groups attached to it. The different products can be formed quite selectively [260]; the synthetic possibilities have been summarized in Ref. [261].

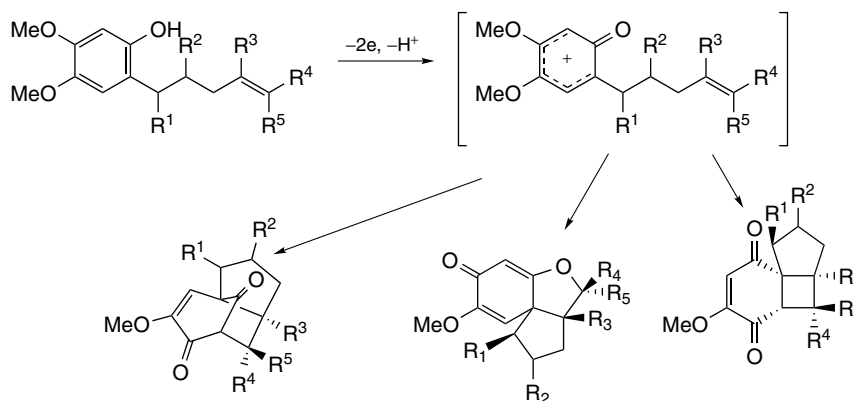
#### 13.4.2.2 Diastereoselectivity at the Cathode

##### 13.4.2.2.1 Coupling

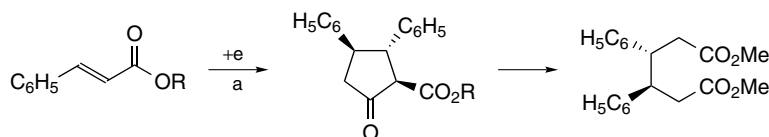
**Activated olefins** The scope of electrohydrodimerization of activated olefins with regard to the different structures and functional groups has been thoroughly explored since the discoveries



**Fig. 49** Cycloaddition of an electrogenerated *o*-quinone methide to  $\alpha$ -phellandrene [255, 256].



**Fig. 50** Stereoselective intramolecular addition of anodically generated phenoxy cations [257–259].



a: Hg, DMF, TEAB yield: 69–98% R: different chiral auxiliaries, borneol > 95% de.  
b: 1. NaOH, 2. HCl, MeOH, 62–88%.

**Fig. 51** Stereoselective hydrodimerization of methyl cinnamate [264–270].

of M. M. Baizer [262, 263] and is presently still extended (see Chaps. 4 and 7). The strong interest in the stereochemistry of these coupling reactions, however, started only a decade ago. In this connection, the stereochemistry of the hydrodimerization of cinnamic acid esterified with chiral auxiliaries has been investigated. It proceeds smoothly via coupling and intramolecular condensation. Thereby, highly simple diastereoselectivities to *all-trans*-2-methoxycarbonyl-3,4-diphenylcyclopentanone and, in some cases, highly facial diastereoselectivities (>95% de with bornyl ester) have been found (Fig. 51) [264].

A well-supported mechanism for a radical anion–radical anion coupling as the key step has been proposed. The relative

stereochemistry at C3 and C4 is fixed irreversibly at the coupling stage, and there is strong evidence that templating in the complex between the two radical anions and water determines the stereochemistry [265, 266].

With diphenylmethylborneol as the chiral auxiliary high face selectivities have been achieved and the *all-trans*-2-alkoxycarbonyl-3,4-diphenylcyclopentanone has been converted to dimethyl (3*R*, 4*R*)-3,4-diaryladipate with 87 to 95% ee [267, 268]. With an isopropylloxazolidinone as the chiral auxiliary the stereoselectivity in the *all-trans* cyclized hydrodimer was strongly affected by the electrolyte employed [269, 270].

A mechanism similar to that for  $\alpha$ ,  $\beta$ -unsaturated esters has been worked out

for the stereoselective coupling of  $\alpha$ ,  $\beta$ -unsaturated ketones [271].

Methyl 4-*t*-butylcyclohex-1-enecarboxylate forms as the major single product upon cathodic reduction in DMF (dimethylformamide) a hydrodimer in which the cyclohexyl rings are joined axially and the methoxycarbonyl groups are also axial. kinetics and force-field calculations indicate a radical anion–radical anion coupling, whose stereoelectronic control dictates diaxial coupling of the cyclohexyl rings. Protonation of the dimer dianion is under thermodynamic control [272]. The cathodic coupling of 2-aryl-1-arylsulfonylethylenes leads in aprotic media and in the presence of lithium salts almost exclusively to D,L-hydrodimers. The coupling reaction often competes with cleavage reactions and depends on the proton donating ability of the solvent [273]. 3-(2-Furyl)propennitrile yields a mixture of D,L- and *meso*-hydrodimers, from which the latter undergoes an in situ Thorpe–Ziegler reaction to a cyclic enamionitrile [274]. A tetracyclic hydrodimer is obtained highly stereoselectively from

dimethyl benzene-1,2-diacrylate by cathodic coupling and subsequent Michael addition [275].

Methyl abscisic acid undergoes an intramolecular cyclization affording with a 51% yield a mixture of diastereomers (Fig. 52) [276].

Cathodic reduction of 1,3-diphenylpropenone leads to 1-hydroxy-2-benzoyl-3,4-diphenyl cyclopentanes with exclusive *cis* configuration of the two phenyl groups. With 1-phenyl-1-pentene-3-one the cyclodimer 2-methyl-3,5-diphenyl-4-(1-propionyl)-cyclohexanone is formed with a 100% yield in an intramolecular Michael addition via an electrogenerated base. The substituents are all in the most stable equatorial position [277].

Intramolecular hydrodimerization of activated olefins has been exploited for elegant one-step cyclizations and heterocouplings (Fig. 53) [263, 278, 279].

A variety of intramolecular cathodic homo- and heterocouplings and their stereochemistry also with regard to the synthesis of complex natural products is shown in Fig. 54, and has been compiled in Chap. 11 and in Ref. [280].

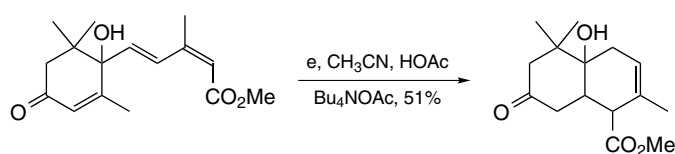


Fig. 52 Intramolecular cyclization of methyl abscisic acid [276].

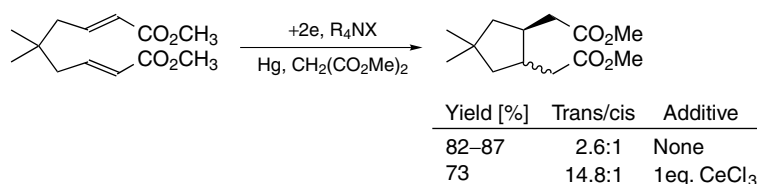


Fig. 53 Stereoselective intramolecular coupling of  $\alpha$ ,  $\beta$ -unsaturated esters [279].

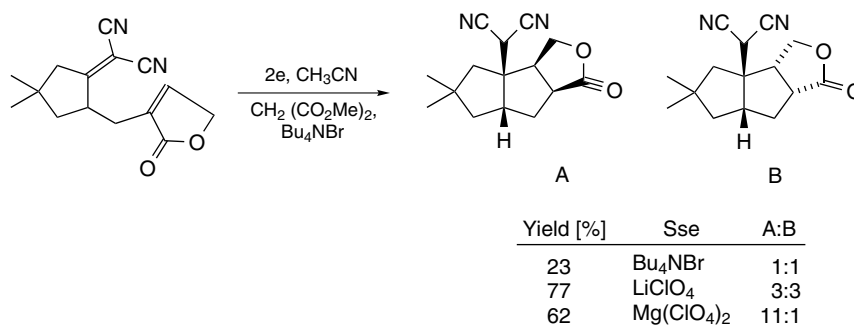


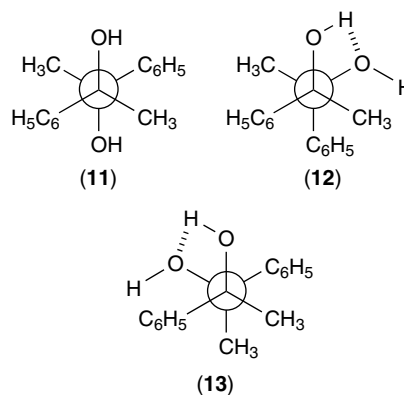
Fig. 54 Stereoselective cyclization of activated olefins [281].

Trimethyl aconitate can be cyclodimerized in 75% yield and a high stereoselectivity to a pentamethyl 1-(2-methoxy-2-oxoethyl)-1,2,3,4,5-cyclopentane pentacarboxylate. Product formation is initiated by an electrogenerated base that induces a catalytic cycle of two successive Michael additions. The most stable out of 16 possible diastereomers is formed, which indicates that the tandem Michael addition is thermodynamically controlled [282].

### Carbonyl compounds

**Intermolecular coupling** Many papers on hydrodimerization of aromatic carbonyl compounds have appeared indicating the importance of this reaction. The rac/meso ratio for the pinacolization of acetophenone in aqueous ethanol ranges between 0.9 and 1.4 in acidic medium and between 2.5 and 3.2 in basic medium. The diastereoselectivity is independent of the cathode material mercury, tin, or copper. Electrolysis conditions such as current density, potential, or current-controlled electrolysis also do not influence the diastereoselectivity. The same holds for propiophenone. For benzaldehyde, the rac/meso ratio is 1.1 to 1.2 in acidic as well as in basic media [283]. In the presence

of adsorbable ions such as  $I^-$  and  $Et_4N^+$ , the rac/meso ratio for benzaldehyde can decrease to 0.5 [284]. In dry DMF/LiClO<sub>4</sub>, the rac/meso ratio for acetophenone increases up to between 12.5 and 19 [285]. It was proposed that in acidic solutions, two ketyl radicals couple and in alkaline solution a ketyl radical and a radical anion couple. There is one transition state (11) leading to a meso product and two (12) and (13) forming a rac product. (11) minimizes steric interactions, while in (12) and (13) hydrogen bonding is involved. The latter is more or less pronounced in acidic and basic protic media. In aprotic media with the complexing  $Li^+$  ion, bridging is maximized leading to high rac selectivity.



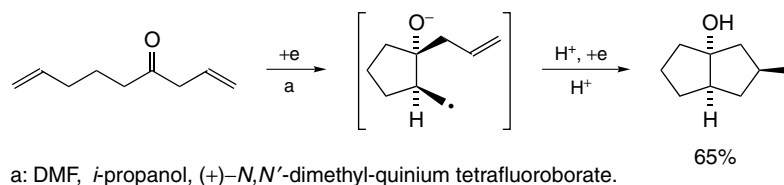
For further contributions on the diastereoselectivity in electropinacolizations, see Ref. [286–295]. Reduction in DMF at a Hg cathode can lead to improved yield and selectivity upon addition of catalytic amounts of tetraalkylammonium salts to the electrolyte. On the basis of preparative scale electrolyses and cyclic voltammetry for that behavior, a mechanism is proposed that involves an initial reduction of the tetraalkylammonium cation with the participation of the electrode material to form a catalyst that favors 1e reduction routes [296, 297]. Stoichiometric amounts of ytterbium(II), generated by reduction of Yb(III), support the stereospecific coupling of 1,3-dibenzoylpropane to *cis*-cyclopentane-1,2-diol. However, Yb(III) remains bounded to the pinacol and cannot be released to act as a catalyst. This leads to a loss of stereoselectivity in the course of the reaction [298]. Also, with the addition of a Ce(IV)-complex the stereochemical course of the reduction can be altered [299]. In a weakly acidic solution, the *meso*/*rac* ratio in the EHD (electrohydrodimerization) of acetophenone could be influenced by ultrasonication [300]. Besides phenyl ketone compounds, examples with other aromatic groups have also been published [294, 295, 301, 302].

There is insufficient information on the stereochemistry of the experimentally less simple hydrodimerization of aliphatic carbonyl compounds in a protic

medium. These couplings need more negative reduction potentials than aromatic carbonyl compounds and suffer from competing aldol reactions.

Unconjugated unsaturated aliphatic ketones undergo a regio- and diastereoselective intramolecular heterocoupling involving the addition of a ketyl to the double bond (Fig. 20) [111]. An interesting extension is the twofold cyclization of unconjugated dienones to form bicyclic alcohols in high yield and stereoselectivity (Fig. 55) [303]. (+)-*N,N*-dimethylquinium tetrafluoroborate causes an anodically shifted catalytic current and is essential for double cyclization. It is proposed that it is adsorbed at the cathode and facilitates reduction and *exo-trig*-cyclization by hydrogen bonding.

Imines can be stereoselectively hydrodimerized to 1,2-diamines with *rac*/*meso* ratios of 0.9 to 1.1 similar to the cathodic coupling of carbonyl compounds to pinacols in an acidic medium [304]. With 4,6-dimethylpyrimid-2-one only the *meso*-diamine was obtained [305]. Electroreduction of diimines prepared from 1,2-diamines and aromatic aldehydes gave 2,3-diaryl piperazines in DMF/TEATos and MSA (methane sulfonic acid) in high yield and with stereoselectivity. Chiral piperazines were prepared from chiral 1,2-diamines [306]. With a steel cathode and a sacrificial Al anode in TFA (tetrafluoroacetyl), PbBr<sub>2</sub>, and Bu<sub>4</sub>NBr/THF as electrolyte with a 65 to 77% yield, and



**Fig. 55** Stereoselective twofold cyclization of unconjugated dienones to bicyclic alcohols [303].

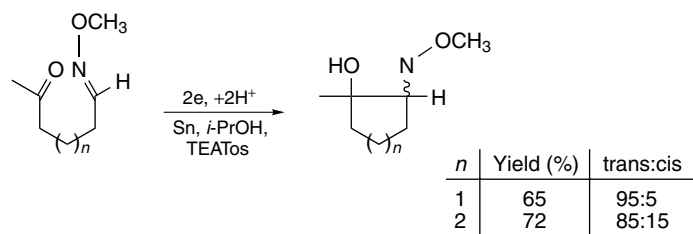
1,2-diamines were obtained with rac:meso ratios >99:1 by using the sterically demanding *N*-benzhydryl-*N*-benzylidene amines [307].

Reductive cross-dimerization has been established with ketones and *O*-methoximes upon reduction in isopropanol with a Sn cathode as a convenient route to  $\beta$ -amino alcohols, diastereoselectivities of up to 85:15 were obtained. A chiral ligand was obtained this way from the coupling of (–)-menthone with *O*-methyl acetaldoxime. Similarly, ketones could be coupled to hydrazones and nitrones. Also, intramolecular couplings were achieved with good yields and diastereoselectivity (Fig. 56) [308].

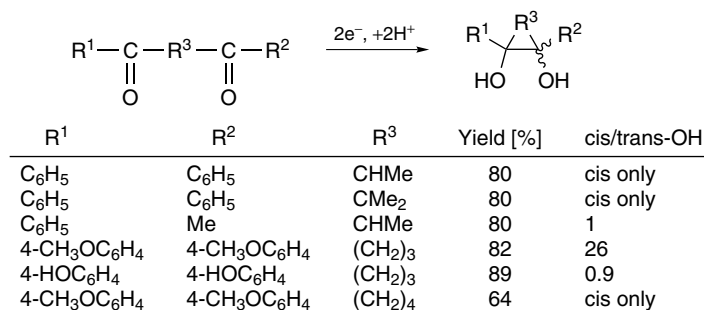
Cathodic heterocoupling of ketones with allylic alcohols takes place at a carbon fiber cathode with high regio- and diastereoselectivity to afford the corresponding

1,4-diols with a good yield (78–79%). The use of a chiral allyl alcohol gave the diol with a high diastereomeric excess (de > 85%). The diastereoselectivity is explained as being due to hydrogen bonding between the hydroxyl group of the alcohol and the ketyl derived from the ketone [309].

**Intramolecular coupling** Some aromatic diketones have been stereoselectively cyclized under various electrolysis conditions, which, together with the substrate structure, strongly influence the stereochemistry of the formed cyclic diol. Reductive cyclization of 1,8-diaroylnaphthalenes led to trans-diols, 2,2'-diaroylbiphenyls and  $\alpha, \omega$ -diaroylalkanes yielded cis-diols with different stereoselectivities depending on substrate structure and electrolysis conditions (pH, cosolvent) (Fig. 57) [310–312].



**Fig. 56** Stereoselective intramolecular coupling of a carbonyl group with an *O*-methyl oxime [308].



**Fig. 57** Stereoselective intramolecular coupling of ketones to cyclic diols [313, 310].

2-Substituted 1,3-diphenyl-1,3-propanediols afforded in high yield and *cis* selectivity 3-methyl substituted 1,2-diphenyl-1,2-cyclopropanediols [313]. 1-Acyl-9-benzoylnaphthalenes were cyclized to 1,2-acenaphthenediols with a 50 to 100% yield and a *cis:trans* ratio ranging from 100:0 (preferably in an acidic medium) to 0:100 (preferably in a basic medium), which is also dependent on the kind of acyl group, supporting electrolyte, cosolvent, and cathode potential. The preferable formation of the *cis*-diol in an acidic medium is rationalized as due to cyclization in a radical–radical coupling, while in an alkaline medium, the *trans*-diol is formed by intramolecular nucleophilic addition of the radical anion to the carbonyl group [314].

Electroreduction of  $\gamma$ - and  $\delta$ -cyano ketones in *iso*PrOH with a Sn cathode gave  $\alpha$ -hydroxyketones with good diastereoselectivities as cyclization products. The reaction has been used as a key step for the synthesis of, for example, guaiazulene, triquinanes, and dihydrojasnone. Similarly, the corresponding intermolecular couplings were realized [315].

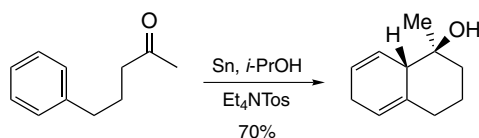
Nonconjugated enones and ynones that contain a sulfur or nitrogen bridge could be regio- and diastereoselectively hydromerized to cyclic alcohols [316].

Reduction of nonconjugated aromatic ketones gave at metal cathodes (e.g., tin, copper, silver, palladium, zinc) the *cis* isomers (*cis*-H/OH) of cyclized products in high diastereoselectivity. The electroreduction of 5-phenylpentan-2-one led to 70% of an exclusively *cis*-hexahydronaphthalene

using a Sn cathode and tetraalkylammonium salts in *iso*PrOH (Fig. 58). A variety of new bi- and polycyclic tertiary alcohols were prepared this way. Mechanistic studies point to a reduction of the carbonyl group to a radical anion that attacks the aromatic ring in such a way that the negatively charged oxygen atom avoids electronic repulsion with the  $\pi$ -electrons of the aromatic ring leading this way to the product with H and OH being *cis* to each other. Reduction with Na in HMPA (hexamethyl phosphoric acid triamide)-THF gave the same cyclized product; however, in lower yield than in the electroreduction [317, 318].

1-(Oxoalkyl)pyridinium salts can be cyclized to quinolizidine and indolizidine derivatives upon reduction in aqueous sulfuric acid at a Hg cathode. The cyclization occurs in some cases with high stereoselectivity. The stereochemistry of the products, cyclic voltammetry, and quantum chemical calculations point to a reduction of the protonated carbonyl group forming a nucleophilic radical that adds to the electrophilic C=N bond of the pyridinium moiety. The cyclized radical cation is further reduced to the products. The stereoselectivity can be correlated with the energies of the cyclized diastereoisomeric radical cations, which indicates that the cyclization is reversible (Fig. 21) [115].

**Halides** The nickel-catalyzed cathodic addition of (*Z*)- or (*E*)-alkenylhalides to electron-deficient olefins in the presence of a sacrificial iron rod anode proceeds with complete retention of



**Fig. 58** Cathodic stereoselective cyclization of nonconjugated aromatic ketones [317, 318].

the stereochemistry in the alkenyl part and affords isomerically pure (*Z*)- and (*E*)-olefins in high yield [319]. Aryl-O-glycosides have been prepared diastereoselectively by cathodic reduction of glycosyl halides at a Ag cathode with a set of phenols and polyhydroxyphenols [320].

#### 13.4.2.3 Hydrogenation

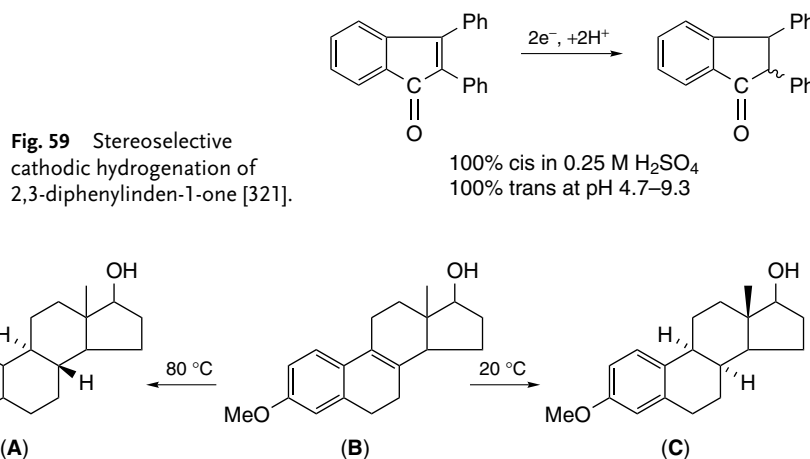
**C, C double and triple bonds** C=C double bonds can be stereoselectively hydrogenated with *cis* or *trans* addition of the hydrogen atoms. 2,3-Diphenylindenone underwent a selective *cis* addition in 0.25 M sulfuric acid, while a *trans* addition was found at higher pH values (Fig. 59) [321]. For the corresponding methyl-phenyl- and dimethylindenone, the diastereoselectivity was low.

The *cis/trans* ratio of 1,4-disubstituted cyclohexanes formed from activated cyclohexenes at a Hg cathode depends on the solvent and proton source and shows a low diastereoselectivity. Protonation of the first formed radical anion is kinetically

controlled and occurs with little face selectivity [322].

The stereochemical outcome of cathodic hydrogenation of acetylenes to the corresponding alkenes changes strongly with the reaction conditions, such as supporting electrolyte, solvent, and cathode material. A Ag/Pd-cathode hydrogenates 2-butyne-1,4-diol and acetylene dicarboxylic acid exclusively to the *cis*-olefin [323]. Similar results were obtained at a Cu net covered with spongy silver [324]. With dimethyl butynedioate the *cis/trans* ratio of the product dimethyl butenedioate on a Pd black cathode decreased with increasing pH both in electrolytic and catalytic hydrogenation [325]. On the other side at a Hg cathode a *trans* addition to alkynes occurs [326]. In methylamine/LiCl, dialkylacetylenes are reduced to *trans*-olefins. Nonconjugated aromatic internal acetylenes are selectively reduced to aromatic *trans*-olefins [327].

Electrolysis of estratetraene (**B**) (Fig. 60) in acidic EtOH at 20 °C and a catalytically active electrode (Pd on Pt cathode) gives 8 $\alpha$ -estradiol methyl ether (**C**)





stereoselectively. At a higher temperature (80 °C) and otherwise identical conditions, the 8- $\beta$ -product (**A**) is formed stereoselectively, which results from the acid catalyzed isomerization of the 8,9-double bond at the higher temperature. Also, nonconjugated double bonds are reduced, while carbonyl groups are not attacked [328].

Reduction in liquid  $\text{NH}_3$  and NaCl at Pt electrodes gives a 90% yield of a mixture consisting of 85% (**A**) (Fig. 60) and 14% (**C**) [329]. The hydrogenations in methylamine or ammonia are cathodic Birch reductions in which the final protonation of the intermediate anion leads to the thermodynamically more favorable trans product.

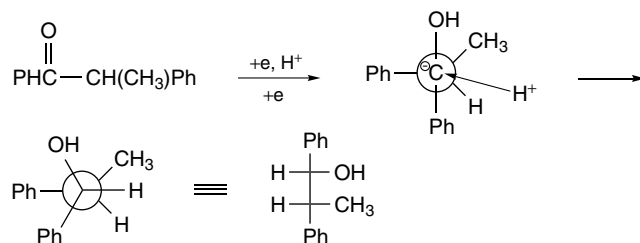
A benzene ring without electron-withdrawing substituents is hydrogenated by using hydrogen active cathodes in an acidic solution. For example, *O*-methylphenol is stereoselectively hydrogenated on a Rh/C cathode to give *cis*-2-methylcyclohexanol (*cis*/*trans* ratio 2.3–6.7) as the major isomer. 2,6-Dimethylphenol affords *cis,cis*-2,6-dimethylcyclohexanol [330]. Enantioenriched substituted (*R*)-4-phenylpyridine has been reduced to the corresponding (*S*)-4-phenyl-1,4-dihydropyridine with partially high retention of configuration depending on the substituents [331]. Methyl 4-*t*-butylcyclohex-1-enecarboxylate leads to *cis*

and *trans* isomers of the corresponding cyclohexanecarboxylate. The isomer ratio depends on the reaction conditions and is under kinetic control. Protonation of the first formed radical anion occurs probably at C1 with little stereoselectivity [322].

**C=X bonds** The stereochemistry of the reduction of carbonyl compounds has been intensely studied with regard to synthetic and mechanistic aspects. The reduction of 1,2-diphenyl-1-propanone at a Hg cathode in aqueous EtOH and pH 8 affords the erythro alcohol as the major diastereomer (erythro:threo = 5 to 1.4:1) [332]. This selectivity is in accord with a protonation of the intermediate anion, formed in an ECE sequence, from the least hindered side (Fig. 61).

The cathodic reduction of ketones ( $\pm$ )- $\text{RCHMeC(O)R}^1$  ( $\text{R} = \text{Ph}$ ,  $\text{R}^1 = \text{Ph}$ ,  $\text{Me}$ ;  $\text{R} = \text{cyclohexyl}$ ,  $\text{R}^1 = \text{Me}$ ) afforded mixtures of diastereomeric alcohols. The origin of the diastereoselectivity, which depends on  $\text{R}^1$  and  $\text{R}$  and the electrolysis conditions, is discussed [333]. Acyclic and cyclic ketones with a chiral center in the  $\beta$ -position yielded diastereomers in a ratio different from that obtained by  $\text{LiAlH}_4$ -reduction [334].

4-*t*-Butylcyclohexanone is reduced at a Pt black cathode to 4-*t*-butylcyclohexanol



**Fig. 61** Stereoselective reduction of 1,2-diphenyl-1-propanone to erythro-1,2-diphenyl-1-propanol as the major diastereomer (other enantiomer not shown) [332].

with a cis/trans ratio of 0.9 in acidic and 1.0 in basic media. At a Hg cathode the corresponding ratios are 0.2 and 0.4 [335]. For 2-methylcyclohexanone, the cis/trans ratio of the formed 2-methylcyclohexanol depends on the electrode material, current density, cosolvents and pH of the electrolyte. In a basic medium, the best yields were obtained with a cis/trans ratio of 35 : 65 [336]. For 4-*t*-butylcyclohexanone and 3,3,5-trimethylcyclohexanone at a Pt cathode in LiCl, EtOH, and HMPA, a good yield of the alcohol with a eq/ax ratio of 95 : 5 was obtained, while at a Pb cathode in NaOAc, HOAc, MeOH a lower yield and a eq/ax ratio of 44/56 was observed [337]. A series of cyclic ketones was reduced in *isopropanol* and in H<sub>2</sub>SO<sub>4</sub>, H<sub>2</sub>O, and MeOH. It was found that in *isopropanol* the ratio of diastereomers was approximately equal to their relative thermodynamic stabilities, while in an acidic medium, the less stable epimeric alcohols were formed to a higher extent. This result was taken as an indication that in an acidic medium an adsorbed intermediate is rapidly protonated, while in the poor proton donating *isopropanol*, this intermediate can diffuse into solution and equilibrate in this way [338]. A very profound study gives further insight into the mechanism [339, 340]. Conformationally rigid ketones, for

example, 4-*t*-butylcyclohexanone, *trans*-decalin-2-one and others have been investigated looking particularly at factors (e.g., cathode material, solvent, proton donor, cathode potential, current density, and supporting electrolyte) that influence the ratio of ax:eq alcohol. The highest stereoselectivity in favor of the axial alcohol (98% cis alcohol from 4-*t*-butyl-cyclohexanone) is obtained using doubly charged electrolyte cations (Mg<sup>2+</sup>, Zn<sup>2+</sup>). The control of stereochemistry is explained in terms of ion-pairing of the key carbanionic intermediate that is formed in an ECE process. Further investigations of the stereoselective reduction of ketones are found in [341, 342].

For steroidal ketones and  $\alpha$ -ketols, stereoselective cathodic reductions have been described [343]. The stereoselective reductive ring opening of epoxyketones to a ketoalcohol has been used in the conversion of the corresponding steroids [344, 345].

The reduction of 2-oxoacids bound to different chiral auxiliaries gave the 2-hydroxyacid derivatives in a 64 to 76% yield and 42 to 86% de depending on solvent, proton donor, supporting electrolyte, temperature, and substituent R in the oxoacid. The results are in accordance with an ECE reduction of the 2-oxoamide to an enolate anion, which subsequently undergoes a face-selective protonation to the hydroxy acid [346, 347].

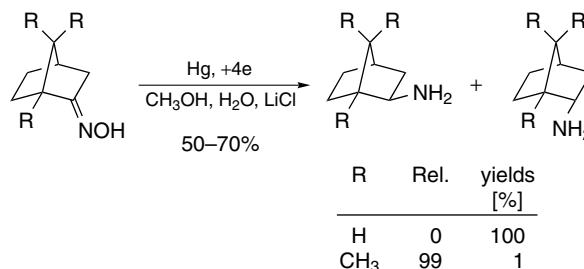


Fig. 62 Stereoselective reduction of camphor- and norcamphoroxime [348].

Electrochemical reduction of camphor- and norcamphoroxime at a Hg cathode proceeds with a high degree of stereoselectivity to give products of opposite stereochemistry to those formed in the dissolving metal (Na-alcohol) reduction of the oximes. The electrolyses are proposed to proceed by a kinetically controlled attack by the electrode on each oxime from the less hindered side (Fig. 62) [348]. In contrast, the corresponding *N*-phenyl imines yield products of the same stereochemistry as those isolated from a dissolving metal reduction. Cyclic voltammetry and polarographic data point to  $\text{RH}^-$  and  $\text{R}^{2-}$  intermediates in this case that are protonated from the least hindered side [349].

Reductive cathodic amination of 2,5-hexanedione with ammonia and 1-phenylethylamine at the Hg cathode gave 2,5-dimethylpyrrolidines with satisfactory yields and excellent *cis* selectivity (90–98%). Other amines reacted less selectively to afford mixtures of pyrroles and diastereoisomeric pyrrolidines. A mechanism is proposed that involves the reduction of iminium ions, in which the stereoselectivity is controlled after the two 1e reductions of the cyclic iminium ion by the final protonation [350].

#### 13.4.2.4 Cleavage

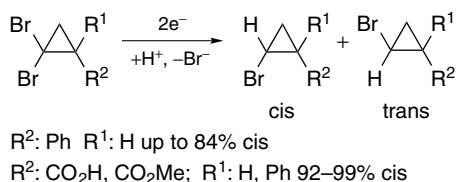
In cathodic cleavage, a C–X bond is mostly reduced to a radical anion that dissociates into a radical and an anion  $\text{X}^-$ . The radical is further reduced to an anion and protonated in the final step.

Cathodic deprotection of tosylates of chiral alcohols was achieved without racemization by cleavage of the O– $\text{SO}_2$  bond [351]. Optically active quaternary arsonium [352, 353] and phosphonium salts [354] are cathodically cleaved to tertiary arsines and phosphines respectively, with retention of the configuration. The first enantiomer enriched chiral phosphines have been prepared this way.

1-Substituted 2,2-dibromocyclopropanes are stereoselectively reduced to the corresponding diastereomeric monobromides in good yields (Fig. 63) [355].

Bicyclic *gem*-dihalocyclopropanes lead predominantly to the corresponding *endo*-monohalocyclopropanes, which are formed by reduction of the *exo*-halogen, whose approach to the cathode is less hindered [356, 357].

Cathodic reduction of bicyclic *gem*-dibromocyclopropane in the presence of chlorotrimethylsilane provides the *exo*-silylated isomer selectively. With a sacrificial Mg anode the current efficiency can be increased by sonication as the anode acts additionally as a chemical reducing agent [358]. The 2e reduction of (*S*)-(+)-1-bromo-1-carboxy-2,2-diphenylcyclopropane showed that the stereoselectivity at a Hg cathode was strongly determined by the supporting electrolyte cation. With  $\text{NH}_4^+$ , a preferential retention of configuration was observed, which increased with a more negative reduction potential. By contrast, a  $\text{R}_4\text{N}^+$  cation gives rise to a major inversion, which increases with the bulkiness



**Fig. 63** Diastereoselective debromination of substituted *gem*-dibromocyclopropanes [355].

of the organic cation. The stereochemistry is thought to be determined by the facial selective protonation of the final anion, whose orientation and shielding is also controlled by the nature of the interface [359]. Cyclic quaternary ammonium salts undergo a electroreductive ring opening to enamines, that are further reduced to cyclic amines, whose stereoselectivity is affected by the pH of the electrolyte [360].

#### 13.4.2.5 Elimination

Cathodic elimination occurs with vicinal C–X bonds that can act both as an electron acceptor and as a leaving group. Vic-dihaloalkanes were stereoselectively reduced at a Hg cathode to the corresponding olefins. *Meso*-1,2-dibromo-1,2-diphenylethane gave *trans*-stilbene only. The rac compound afforded *cis*- and *trans*-stilbene, with the *cis* portion increasing with size and concentration of the supporting electrolyte cation. This has been interpreted as being caused by interaction of this cation with an anionic intermediate [361]. 2,3-*Meso*-dibromosuccinate has been reduced stereoselectively to fumarate and maleates. The rac form selectively produced fumarate at low and high pHs, while between pH 0.4 and 6.9, up to 70% maleate is formed. A mechanism explaining this behavior is presented [362]. The cathodic reduction of the *meso* and *rac* forms of EtCHBrCHBrEt and Me<sub>2</sub>CHCHBrCHBrCHMe<sub>2</sub> was carried out in liquid ammonia and DMF. The *cis*/*trans* ratio of the products EtCH=CHEt and Me<sub>2</sub>CHCH=CHCHMe<sub>2</sub> varied with the electrode potential. Elimination of two bromide anions occurred preferentially by a concerted mechanism, except for the *rac* diastereomer of the latter dibromide, which was unable to attain the

*anti*-configuration. At sufficiently negative potentials, all rotamers were reduced under diffusion control such that the product ratio reflected the distribution of the conformers in the dibromide [363]. The double bond in unsaturated carboxylic acids and alcohols was protected by bromination with pyridinium hydrobromide perbromide under mild conditions. Deprotection was achieved by cathodic reduction at –1.4 V. At overall yields of 68 to 99%, the configuration of the double bond was retained by >96% [364]. The reductive elimination of the cyclic sulfate of 1,2-butanediol led to *trans*-2-butene selectively. Aromatic vicinal dioxalates underwent fragmentation and elimination on cathodic reduction to give alkenes. *Meso*-(EtO<sub>2</sub>COCH(C<sub>6</sub>H<sub>5</sub>))<sub>2</sub> gave 80% *trans*-stilbene [365].

### 13.4.3

#### Enantioselectivity

##### 13.4.3.1 General

A reaction is termed *enantioselective* when a new stereogenic center is generated and one enantiomer is formed in excess. This occurs through a chiral inductor that is in a reversibly formed complex attached to the molecule that bears the prostereogenic center. The chiral inductor can be in the reagent, the solvent, in additives, or, in the case of heterogeneous reactions, at a surface. Best suited are enantioenriched catalysts, whose stereochemical information is transferred to the substrate in the rate-determining step. A large number of efficient enantioselective catalysts have been developed in organic chemistry that lead to enantioselectivities >95% *ee* for functional group interconversions, especially hydrogenations, and many types of C, C – bond-forming reactions [184, 185]. In organic

electrochemistry, enantioselective conversions are much less developed than those in chemical synthesis. Nevertheless, there are some methods and potential developments that are outlined below.

#### 13.4.3.2 Anode

**13.4.3.2.1 Coupling** A graphite felt electrode chemically modified with TEMPO led to the enantioselective electrocatalytic coupling of 2-naphthol, 2-methoxynaphthalene and 10-hydroxyphenanthrene with high enantioselectivity (up to 98% *ee*) in the presence of (–)-sparteine as a chiral base [366].

**13.4.3.2.2 Addition** Anodic oxidation of enolacetates, for example, 1-acetoxy-3,4-dihydronaphthalene and  $\alpha$ -acetoxy- $\beta$ -alkylstyrene, afforded at  $-78^{\circ}\text{C}$  in acetonitrile/THF/HOAc containing tetraethylammonium (*S*)-camphorsulfonate as supporting electrolyte, enantioenriched acetoxylation products with 44 and 21% *ee* (enantiomeric excess) respectively [367].

**13.4.3.2.3 Heteroatom Oxidation, Dehydrogenation** Electrooxidative kinetic resolution of *rac* alcohols mediated with a catalytic amount of an optically active *N*-oxyl was performed in an undivided cell at constant current conditions. A high enantiomeric purity for the recovered alcohol was found, which could be increased by electrolysis at lower temperatures. The optically active *N*-oxyl was recovered and used repeatedly without change in efficiency and selectivity [368]. Cyclovoltammetry with the *N*-oxyl: (6*R*, 7*S*, 10*R*)-4-oxo-2,2,7-trimethyl-10-isopropyl-1-azaspiro[5.5]undecane-*N*-oxyl as catalyst showed for *rac*-1-phenylethanol a highly enhanced catalytic

current for (*R*)-1-phenylethanol compared with a small enhancement for the (*S*)-isomer [369]. This oxidation was also performed free of organic solvents in an aqueous silica gel disperse system to afford enantioenriched *sec*-alcohols and  $\gamma$ -lactones [370].

In an enantiomer-differentiating oxidation at a poly-(L-valine)-coated  $\text{PbO}_2$  anode, *rac*-2,2-dimethyl-1-phenyl-1-propanol was partially oxidized leaving 43% optically pure (*S*)-alcohol [371]. At a TEMPO-modified graphite felt anode *rac*-1-phenylethanol has been enantioselectively oxidized in the presence of (–)-sparteine leaving 46% of the (*R*)-alcohol with 99.6% *ee* [372]. However, under the same conditions, an exclusive dehydrogenation of (–)-sparteine to the iminium salt without oxidation of the alcohol was found [373].

Alkyl aryl sulfides were anodically oxidized to the corresponding chiral sulfoxides by using poly(amino acid)-coated electrodes. Partially very high enantioselectivities (93% *ee*) were reported [374, 375]; however, the reproducibility depended strongly on the lot of the poly(amino acid) used [376]. Earlier, with a similar approach, by using an edge surface graphite anode that was chemically modified with (*S*)-phenylalanine, an enantioselectivity of 0.5 to 2.5% was found in the oxidation of methyl *p*-tolyl sulfide to the sulfoxide [377].

#### 13.4.3.3 Cathode

**13.4.3.3.1 Hydrogenation** The enantioselective reduction of prochiral ketones to chiral alcohols has been intensely investigated. The highest enantioselectivity has been found for 2-acetylpyridine, which was reduced in buffered EtOH (pH 4.5), in the presence of strychnine to 1-(2-pyridyl)-ethanol with 48% *ee*. The selectivity was

assumed to arise by enantioselective protonation of  $(\text{PyrC}(\text{OH})\text{CH}_3)^-$  formed in an ECE process from 2-acetylpyridine [378]. For enantioselective conversions involving intermediate carbanions, the influence of the chiral inductor acting as proton donor and the potential that controls adsorption of the inductor are discussed for the electroreduction of *syn*- and *anti*- $\text{HON}=\text{CPhCO}_2\text{H}$ ,  $\text{PhCOCO}_2\text{H}$ , and  $\text{PHNHN}=\text{CPhCO}_2\text{H}$  in the presence of strychnine [379]. The *ee* depended on the alkaloid concentration [380–382].

The HOPG (highly oriented pyrolytic graphite) carbon electrode chemically modified with (*S*)-phenylalanine at the basal surface led to 2% *ee* in the reduction of 4-acetylpyridine [377]. A cathode modified with a chiral poly(pyrrole) reduced 4-methylbenzophenone or acetophenone in DMF/LiBr and phenol as proton donor to 1-phenylethanol with up to 17% *ee* [382]. Alkyl aryl ketones have been reduced to the corresponding alcohols at a Hg cathode in DMF/water in the presence of (1*R*, 2*S*)-*N,N*-dimethylephedrinium tetrafluoroborate (DET), producing (*S*)-1-phenylethanol with 55% *ee* from acetophenone. Cyclovoltammetry supports an enantioselective protonation of the intermediate  $(\text{PhCOH}(\text{CH}_3))^-$  [383].

The asymmetric reduction of C=N double bonds in prochiral oximes afforded a maximum of 18% *ee* [380, 384, 385]. Prochiral azomethines were reduced to the corresponding 1,2-diamines and secondary amines using 36 optically active supporting electrolytes. The dimers were optically inactive, while the monomers showed low optical inductions ( $\leq 11\%$  *ee*). The effect of electrolyte, substrate concentration, temperature, pH, and cathode potential on the induction was studied. It was proposed that the enantioselectivity

arises among others from a specifically adsorbed supporting electrolyte that forms H-bonds with the substrate. The highest optical inductions were obtained with certain diquaternary salts [386]. Low enantioselectivities have been obtained in the reduction of aryl alkyl ketones in the presence of chiral supporting electrolytes derived from, for example, ephedrine [387].

The C=C double bond in 4-methylcoumarin has been hydrogenated at a Hg cathode in the presence of alkaloids with 17% *ee* [388]. By systematic variation of pH, supporting electrolyte, working potential, substrate, and alkaloid (yohimbine) concentration, the enantioselectivity has been increased to 67% *ee*. A mechanism supported by electroanalytical data and preparative scale electrolysis is proposed. The main features are a 1e reduction of the hydrogen-bonded enone leading to an enol radical that tautomerizes to a more easily reducible keto radical or dimerizes. The keto radical is reduced and further protonated. The function of yohimbine- $\text{H}^+$  is to catalyze the tautomerization and to enantioselectively protonate the final carbanion. It is also concluded that the hydrophobic yohimbine is enriched near the hydrophobic cathode surface. Quantum chemical calculations demonstrate that *si* protonation of the intermediate anion by yohimbine- $\text{H}^+$  to give the (*R*)-dihydroproduct is energetically favored [389, 390]. Similarly, 3-methylinden-1-one in the presence of strychnine yields 71% 3-methylindan-1-one with 35% *ee* (*S*-enantiomer). An analogous mechanism, such as for 4-methylcoumarin, is supported by preparative scale electrolysis and cyclovoltammetry. The mechanistic model enabled the synthesis of simple nonracemic catalysts, from which (*S*)-*N*-methylprolinooctadecylester leads to

66% 3-methylindan-1-one with 26% *ee*(S) [391].

The enzymatic enantioselective hydrogenation of enoates has been achieved with an enoate reductase and a cathodically regenerated methyl viologen radical cation as cofactor [392]. This way sodium (*E*)-2-methylcinnamate was reduced to (*R*)-2-methyl-3-phenylpropionic acid with 95% *ee*. A number of chiral compounds were correspondingly prepared via biocatalytic reduction with hydrogenases or reductases or microbial cells containing those and mediators as cofactors, which were regenerated at the cathode [393]. Similarly, electroenzymatic reduction of ketones and aldehydes using alcohol dehydrogenase afforded almost optically pure chiral alcohols in high yields [394]. A high enantioselectivity was also achieved using Baker's yeast and the viologen radical cation as mediator [395]. Electroenzymatic syntheses are reviewed in Ref. [396].

**13.4.3.3.2 Cleavage** Gem-dihalides and monohalides have been dehalogenated to chiral monohalides in the presence of alkaloids [397, 398]. 1,1-Diphenyl-2-bromo-2-carboxyl (bromo or methyl carboxylate) cyclopropanes are cathodically debrominated in the presence of alkaloid cations with enantioselectivities up to 45% *ee*. A mechanism is proposed whereby the alkaloid is adsorbed at the Hg cathode, which protonates face selectively the carbanion generated by 2e reduction from the bromide [399].

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## 14

### Electrogenerated Acids and Bases

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It is well known that when electrolysis is carried out in a divided cell, the acidity of the anolyte and the basicity of the catholyte increase unless special precaution is taken. These medium changes may induce acid–base reactions of substrates and/or products leading to unintended final products or mixtures of products. However, electrochemical formation of strongly acidic or basic species may also be used deliberately as alternatives to conventional strong acids or bases. The use of electrogenerated bases (EGBs) has been particularly explored, and a range of well-defined EGBs with different basicities have been developed and used synthetically. In comparison, the use of electrogenerated acids (EGAs) has received less attention. Both subjects – electrogenerated acid (EGA) [1], electrogenerated base (EGB) [2, 3] – have previously been reviewed.

## 14.1

### Electrogenerated Acids

#### 14.1.1

##### General Concepts

Electrogenerated acids (EGAs) are strong Brønsted acids arising from protons produced directly or indirectly in an anodic

process. Reactions induced by protons formed directly in an anodic process are almost exclusively catalytic. The reactions do not involve oxidation of the substrates and only a catalytic amount of the EGA is required.

Protons, generated indirectly by deprotonation of an intermediate during anodic oxidation of an organic substrate, are obviously produced in stoichiometric amounts. Reactions induced by these protons are typically acid-catalyzed conversions of the initial oxidation product or proton-induced reactions/deactivation of unconverted substrate.

Direct formation of protons by anodic oxidation of dihydrogen,  $H_2$ , on activated Pt anodes allows the formation of well-defined quantities of acid [4, 5]. However, this method of proton generation has not been used in typical EGA-induced reactions.

In the absence of more easily oxidized substrates, residual water in aprotic solvents will undergo oxidation at platinum anodes. However, the mechanism of proton formation is not necessarily by simple water oxidation with the evolution of  $O_2$  but may involve radical reactions of the solvent or oxidation of supporting electrolyte anions [6, 7]. The protons produced, together with the most basic species in solution, form

the EGA. Proton activity can be measured by indicators such as nitroanilines [8].

#### 14.1.2

##### **Influence of the Solvent-electrolyte System**

The successful formation of protons by anodic oxidation obviously requires the absence of a supporting electrolyte with easily oxidized anions. Anions such as  $\text{PF}_6^-$ ,  $\text{BF}_4^-$ , and  $\text{ClO}_4^-$  fulfill the requirement, whereas, for example, halide anions and  $\text{CH}_3\text{COO}^-$  normally prevent production of the EGA.

The ability of the supporting electrolyte anion to stabilize the intermediate carbocations in only moderately polar solvents such as  $\text{CH}_2\text{Cl}_2$  or THF may play an important role for product formation. The  $\text{ClO}_4^-$  ion is known to stabilize carbocations in ether [9] and in alcoholic solutions [10], whereas the tosylate anion ( $\text{TsO}^-$ ) has been suggested to add to reactive carbocations [11] (see Sect. 14.3.1). It is unfortunate that in many cases  $\text{ClO}_4^-$  has proven to be superior in EGA-catalyzed reactions, since the known safety risks of organic perchlorates (explosive) prevent the general use of metal perchlorates as the supporting electrolyte.

The significance of the supporting electrolyte cation depends crucially on whether a divided or an undivided cell is used. In a divided cell, the choice of cation is of minor importance but in an undivided cell the cathode process should not lead to formation of base and thereby to buffering of the solution. Metal cations such as  $\text{Li}^+$ ,  $\text{Na}^+$  or  $\text{Mg}^{2+}$  are often the choice since in aprotic solvents the metal cation may be the most easily reduced component. This has been observed as deposits of metal on the surface of the cathode arising from

reduction of the metal cation [1, 8, 12]. Tetraalkylammonium cations, on the other hand, may, in aprotic solvents, give rise to the formation of amines upon reduction, and the solution becomes buffered. In an undivided cell, the difference in proton activity of an electrolyzed MeCN solution containing  $\text{NaClO}_4$  and of one containing  $\text{Bu}_4\text{NBF}_4$  was found to be of almost two orders of magnitude after passage of the same amount of charge, the MeCN- $\text{NaClO}_4$  solution being the more acidic [8]. This was taken as evidence for the buffering effect offered by the  $\text{Bu}_4\text{N}^+$  ion, since independently prepared standard solutions of  $\text{HClO}_4$  and  $\text{HBF}_4$  in MeCN showed similar proton activity [8].

The choice of solvent plays a role for (1) the proton activity of the medium and (2) the involvement of solvent molecules in the follow-up reaction of the intermediate carbocations. Most EGA-catalyzed reactions are carried out in fairly unpolar solvents such as  $\text{CH}_2\text{Cl}_2$ ,  $\text{ClCH}_2\text{CH}_2\text{Cl}$ , THF or mixtures of these. Catalytic reactions that involve trapping of a carbocation intermediate by solvent are typically carried out in acetone, MeCN, or MeOH. In protic solvents such as MeOH, the bulk solution does not become acidic in undivided cells, since base ( $\text{MeO}^-$ ) is produced at the cathode. However, in the vicinity of the anode the acidity may be sufficiently high for ketones to undergo acid catalyzed hemiacetal formation [13], see Sect. 14.2.2. Where the EGA is formed via elimination of protons during the oxidative conversion of an organic substrate, the more polar MeCN is normally used.

#### 14.1.3

##### **In situ Versus Ex situ Formation of the EGA**

For acid catalyzed reactions, formation of the EGA *ex situ* by electrolysis of the

solvent-electrolyte system in the absence of a substrate (typically in a divided cell) is commonplace. After electrolysis, samples of the anolyte may be added to a solution of the substrate, and the reaction carried out as a conventional reaction in a homogeneous solution. One advantage of an ex situ operation is that substrates, which may undergo direct anodic oxidation, can be subject to an EGA-catalyzed conversion without interference from substrate oxidation. The ex situ formation of EGA has also been crucial as evidence for the EGA catalysis of a given substrate conversion as opposed to a chain mechanism involving radical cations of the substrate. In situ formation of the EGA obviously takes place in reactions involving oxidative conversion of the substrate but is also used for purely EGA-catalyzed reactions.

#### 14.1.4

##### Comparison of EGAs with Conventional Acids

The major advantages of EGAs compared to conventional acids relate to their application in catalytic reactions, Sect. 14.3; strongly acidic conditions are obtained in the vicinity of the anode although the bulk solution is kept essentially neutral. The successful replacement of often expensive and/or moisture-sensitive Lewis acids with an EGA is a promising strategy, especially because stoichiometric amounts of Lewis acids may, in some cases, be substituted with catalytic amounts of the EGA. Similarly, the use of an EGA offers an attractive alternative to anhydrous  $\text{HClO}_4$  that may be difficult to prepare in small amounts without being contaminated with  $\text{HCl}$ .

## 14.2

### Charge-consuming Reactions

#### 14.2.1

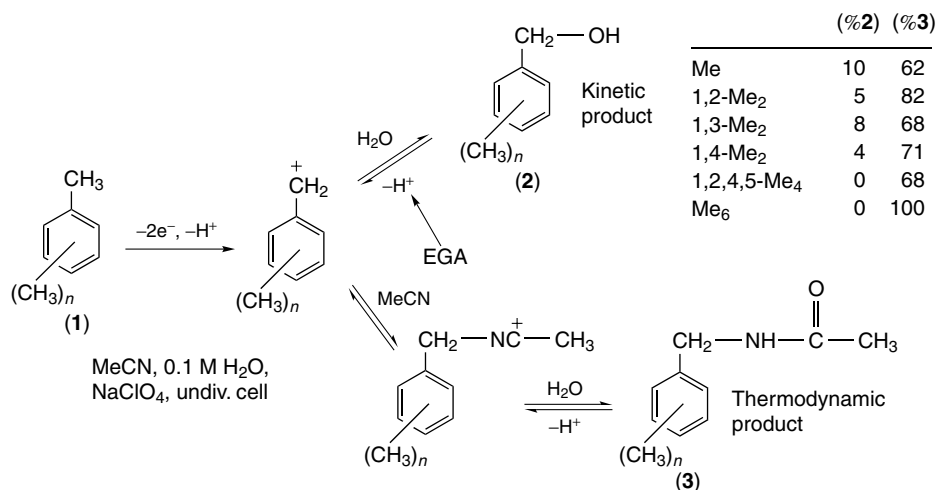
##### EGA Catalyzed Follow-up Reaction of the Product of Anodic Oxidation

One of the first notions of EGA-catalyzed reactions was the rationalization [8, 14] of the unexpected outcome of anodic oxidation of methyl arenes, (1), in MeCN containing various amounts of water. Preferentially *N*-benzyl acetamides, (3), rather than the benzyl alcohols, (2), were formed [15, 16] (with increasing amounts of water, increasing amounts of aldehyde was formed as a side product [16]). Since water is a more powerful nucleophile than MeCN, it is reasonable to believe that the carbocation formed by overall two-electron oxidation and deprotonation is initially trapped by water. However, the process is reversible in the presence of a strong EGA (protons liberated from the oxidized substrate), and the carbocation is eventually trapped by the excess MeCN, Scheme 1.

It was demonstrated that in the acidic conditions prevailing after electrolysis, benzyl alcohol added to the anolyte was quickly converted to the acetamide [8]. The more methyl substituents there were in the benzene ring, the more stable the carbocation intermediate became and the higher the ratio (3):(2).

Similarly, anodic oxidation of bibenzyl ether in wet MeCN leads to benzaldehyde and (3) rather than to benzaldehyde and (2), since (2) in this case also undergoes EGA-catalyzed reaction with MeCN [14].

Transformation of amines to aldehydes or ketones can be carried out via the anodic  $\alpha$ -methoxylation of the corresponding carbamates, (4), followed by an acid-catalyzed conversion of the  $\alpha$ -methoxylated



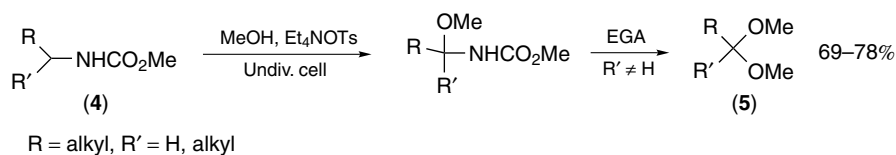
**Scheme 1** EGA catalysis in side-chain oxidation of methyl arenes.

carbamates into the dimethyl acetals, (5), Scheme 2 [17]. When R' ≠ H, the anodic oxidation of (4) leads directly to (5).

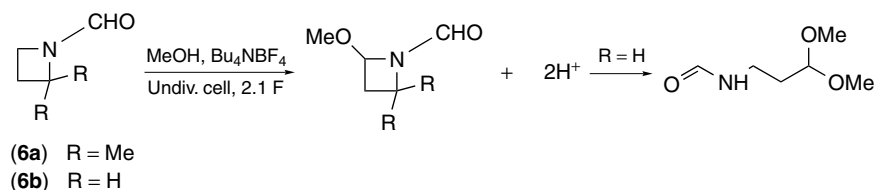
Oxidation of *N,N*-dialkylamides in MeOH normally gives  $\alpha$ -methoxylated amides in high yields. The reaction also works well for *N*-formyl-2,2-dimethylazetidine, (6a), but in the absence of the methyl groups, (6b), the primary product undergoes EGA-catalyzed

solvolysis, Scheme 3 [18]. The EGA-catalyzed reaction could not be suppressed by the addition of a base. The more strained ring system, *N*-acetylaziridine, does not undergo methoxylation, but only EGA-catalyzed solvolysis (0.5 F), Scheme 4 [18].

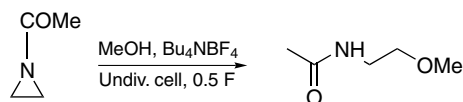
Oxidation of a 5,8-dihydro-1,4-naphthalenediol derivative, (7), leads in a 2 F process to the dihydronaphthoquinone, (8), but in a divided cell EGA-catalyzed



**Scheme 2** EGA-catalyzed conversion of  $\alpha$ -methoxy carbamates into acetals.



**Scheme 3** EGA-catalyzed methanolysis of *N*-formyl- $\alpha$ -methoxyazetidine.



**Scheme 4** EGA-catalyzed methanolysis of *N*-acetylaziridine.

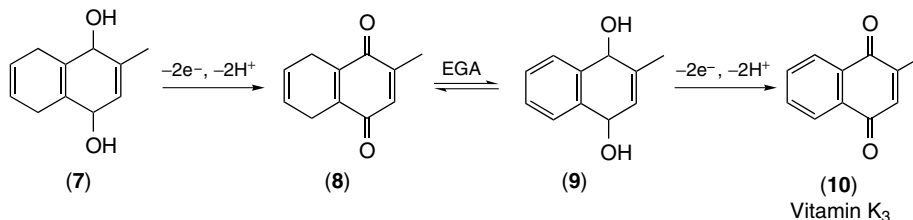
conversion to the hydroquinone, (9), takes place, and (9) is then further oxidized (2 F) to the naphthoquinone, (10), Scheme 5 [19]. The EGA is formed during the initial oxidation of (7) by loss of protons, which are not neutralized in the divided cell. Using 7.5 to 9 F, good chemical yields (>90%) of (10) are obtained in MeCN, AcOH or AcOEt containing 10% *t*-BuOH with LiClO<sub>4</sub>, Bu<sub>4</sub>NClO<sub>4</sub> or LiBF<sub>4</sub> as the supporting electrolyte. The presence of an alcohol (*t*-BuOH) seems necessary in order to prevent formation of oligomeric material.

In MeOH-Et<sub>4</sub>NOTs, oxidation (4 F) of (7) leads exclusively to (8). Subsequent oxidation of (8) in MeCN-LiClO<sub>4</sub> leads to (10) in 90% yield (3.5 F) [19].

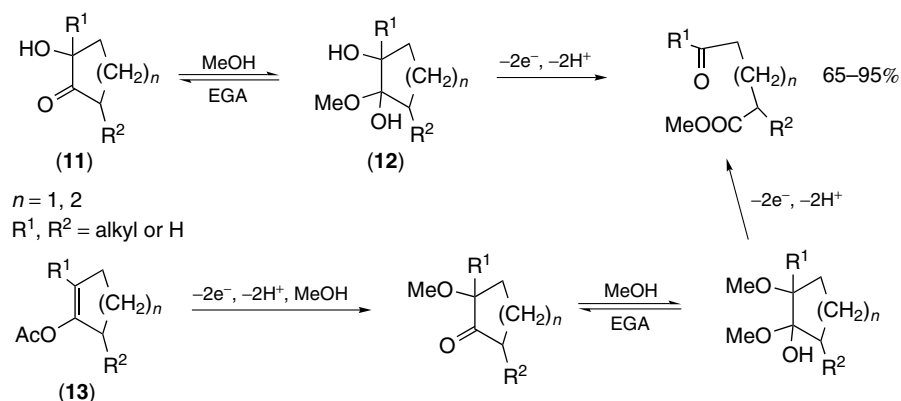
#### 14.2.2

##### EGA Induced Conversion of Substrate

Oxidative cleavage of  $\alpha$ -hydroxycycloalkanones, (11), in MeOH-LiClO<sub>4</sub> at a Pt anode in a divided cell, [13, 20] has been suggested to take place via the hemiacetal, (12), formed in situ by EGA catalysis [13], Scheme 6.



**Scheme 5** EGA-catalyzed double bond migration.



**Scheme 6** EGA-catalyzed hemiacetal formation.

The reaction requires 4 to 5 F, and parallel, direct oxidation of (11) cannot be excluded.  $\alpha$ -Acetoxycycloalkanones undergo similar cleavage reactions in MeOH-LiClO<sub>4</sub>. Bond cleavage does not occur for (11) in MeOH-Et<sub>4</sub>NOTs [13], that is, conditions in which less EGA production is expected (cf. Sect. 14.1.2), whereas cleavage of 1,2-diols does take place [21].

Similarly, oxidation of cycloalkanone enol acetates, (13), in MeOH/AcOH(10:1)-LiClO<sub>4</sub> at a Pt anode in a divided cell leads to oxidative cleavage to the (same) oxoalkanoates as the corresponding (11), Scheme 6, [13]. In this case, EGA-catalyzed conversion into a hemiacetal has also been suggested, Scheme 6, [13]. Using AcOH-Et<sub>4</sub>NOTs in an undivided cell (13) gives a mixture of  $\alpha,\beta$ -cycloalkenones and  $\alpha$ -acetoxycycloalkanones [22, 23].

Unintended EGA-catalyzed rearrangement of substrates during anodic oxidation has been reported in a number of cases, for example, rearrangement of strained polycyclic hydrocarbons upon oxidation in MeCN-LiClO<sub>4</sub> [24].

Unintended deactivation of substrates during proton-producing anodic processes such as couplings or substitutions is common. For coupling reactions carried out in polar aprotic solvents, electron-rich substrates (typically *N*-, *O*- or *S*-compounds) may be the most basic species in solution. In divided cells, it is therefore often observed that (1) the charge consumption in an exhaustive electrolysis is lower than expected, (2) the chemical yield of the product is low, and (3) some substrate is recovered after addition of the base or during workup, since a considerable part of the substrate is deactivated by protonation during electrolysis. For example, deactivation of the substrate takes place during anodic coupling of aryl-substituted 1,4-dithiines

in MeCN/CH<sub>2</sub>Cl<sub>2</sub> [25] and during the anodic dimerization/oligomerization of substituted pyrroles in MeCN [26]. The undesired deactivation of the substrate may be avoided by addition of base (competing reaction of the base as nucleophile is possible) or by using an undivided cell (competing reduction of substrate or product is possible).

### 14.3

#### Acid Catalyzed Reactions

A number of reactions that are traditionally carried out using either Brønsted or Lewis acids as catalysts have been shown to take place in the presence of EGA formed either in situ or ex situ. The reactions do not involve charge-consuming conversions of the substrates.

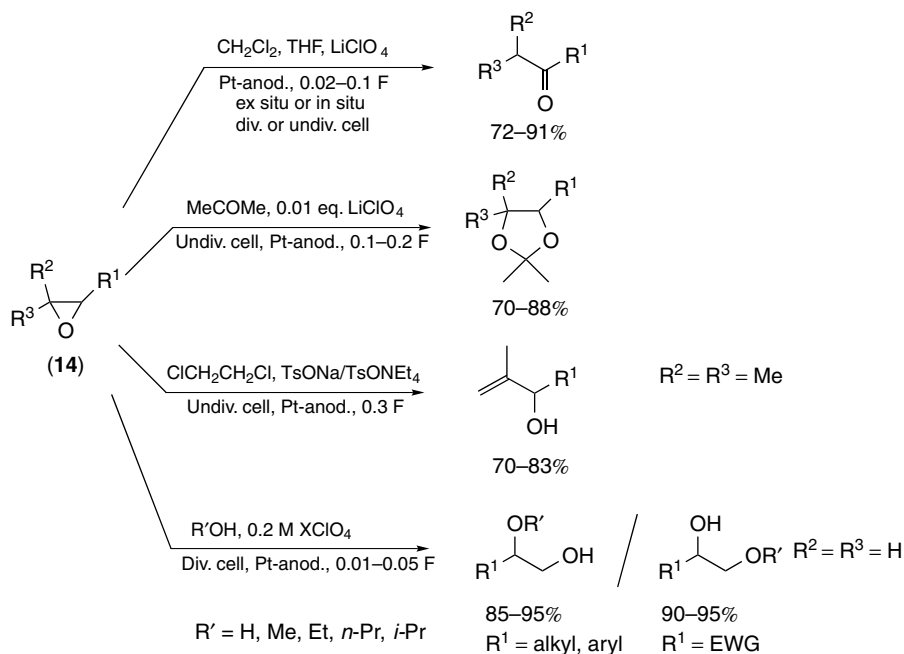
##### 14.3.1

#### Ring Opening of Epoxides

EGA-catalyzed ring opening of epoxides, (14), is one of the most-studied catalytic EGA reactions. The proper choice of solvent and supporting electrolyte allows selective formation of a ketone, an allylic alcohol, an acetonide, or an  $\alpha$ -hydroxy ether, Scheme 7.

Nonnucleophilic solvents such as ClCH<sub>2</sub>CH<sub>2</sub>Cl, CH<sub>2</sub>Cl<sub>2</sub> or THF with perchlorate supporting electrolytes favor the formation of ketones [12]. In general, EGA-catalyzed reactions give higher yields (70–90%) and shorter reaction times than reactions carried out with conventional acid catalysts in CH<sub>2</sub>Cl<sub>2</sub> or with BF<sub>3</sub> · Et<sub>2</sub>O in benzene [12, 27].

Formation of the acetonides, Scheme 7, takes place in an acetone containing small amounts (0.01 eq.) of a metal perchlorate. Higher concentration of the perchlorate



**Scheme 7** EGA-catalyzed ring opening of epoxides.

salt decreases the yield of acetonide and increases the yield of ketone, which has been interpreted as a competition between trapping the carbocation with the nucleophile (acetone) and stabilization/ion-pair formation with  $\text{ClO}_4^-$  [12]. Acyclic  $\alpha,\beta$ -diols may be converted to acetonides using similar experimental conditions but with less current efficiency (85% yield, 0.3 F for a substrate analogous to (14)) [12].

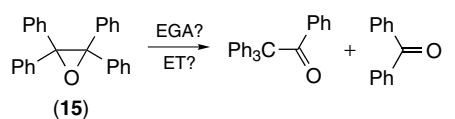
Formation of allylic alcohols is favored by supporting electrolytes with tosylate anions, Scheme 7, [11]. Under these conditions, only small amounts of ketone were produced. It has been suggested that the role of the tosylate is as a nucleophile that traps the carbocation. Elimination from this intermediate then leads to the allylic alcohol. This explanation is supported by isolation of the

tosylated intermediate in 8% yield at 5 °C [11].

The EGA-catalyzed alcoholysis of substrates of monosubstituted oxiranes takes place according to Scheme 7 with either  $\text{NaClO}_4$  or  $\text{Bu}_4\text{NClO}_4$  as supporting electrolyte [28]. Ring opening to the more stable carbocation determines the site of alcohol attack. For styrene oxide, the EGA-catalyzed reaction was compared with reactions using  $\text{AcOH}$ ,  $\text{HCOOH}$ ,  $\text{Cl}_3\text{CCOOH}$ , 60%  $\text{HClO}_4$  or  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  as catalysts, and the EGA-catalyzed reaction was found to be superior with respect to yield and reaction time [28]. For cyclohexene epoxide and other cycloalkene epoxides, the reaction was shown to be highly selective giving exclusively the product with OH and OR' *trans*. For example, cyclohexene epoxide gives exclusively (96%) the *trans* product upon electrolysis in MeOH (0.003 F) [28].

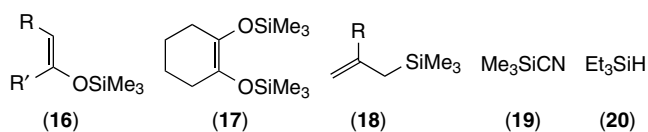


Ring opening and ketone formation from the tetrasubstituted oxirane, (15), upon anodic oxidation in poorly nucleophilic solvents in a divided cell takes place according to Eq. (1) [29]. In solvents containing water (conditions A), C–C-bond cleavage takes place and benzophenone is the main product, whereas substrate rearrangement preferentially takes place in dry conditions (B and C). Two mechanisms have been suggested for the reaction in dry conditions: (1) formation of the radical cation followed by ring opening, migration, and electron transfer from the rearranged radical cation to another substrate molecule (0.05 F), that is, by electron-transfer catalysis [29] and (2) EGA-induced ring opening followed by migration and deprotonation, that is, by acid catalysis [12]. That EGA catalysis *can* take place is evident from conditions B in which 97% of the rearranged ketone was obtained without passage of current but simply by adding the substrate to the preelectrolyzed “wet” solution [12]. For conditions C, parallel reaction pathways via electron-transfer catalysis and EGA catalysis cannot be ruled out.

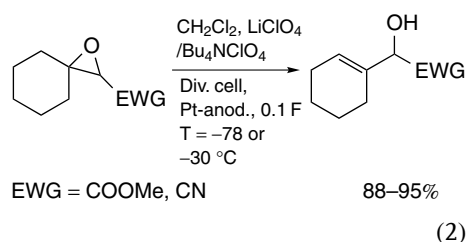


A: in situ “wet” CH <sub>2</sub> Cl <sub>2</sub> /THF, LiClO <sub>4</sub> /Et <sub>4</sub> NClO <sub>4</sub> , 1.2 F	30%	69%
B: ex situ “wet” CH <sub>2</sub> Cl <sub>2</sub> /THF, LiClO <sub>4</sub> /Et <sub>4</sub> NClO <sub>4</sub> , 2.5 F	97%	–
C: in situ dry MeCN, LiClO <sub>4</sub> , 0.05 F	90%	10%

(1)



For substrates with strongly electron withdrawing substituents, formation of the allylic alcohol in good yields takes place under conditions otherwise favoring ketone formation, Eq. (2) [30].



#### 14.3.2

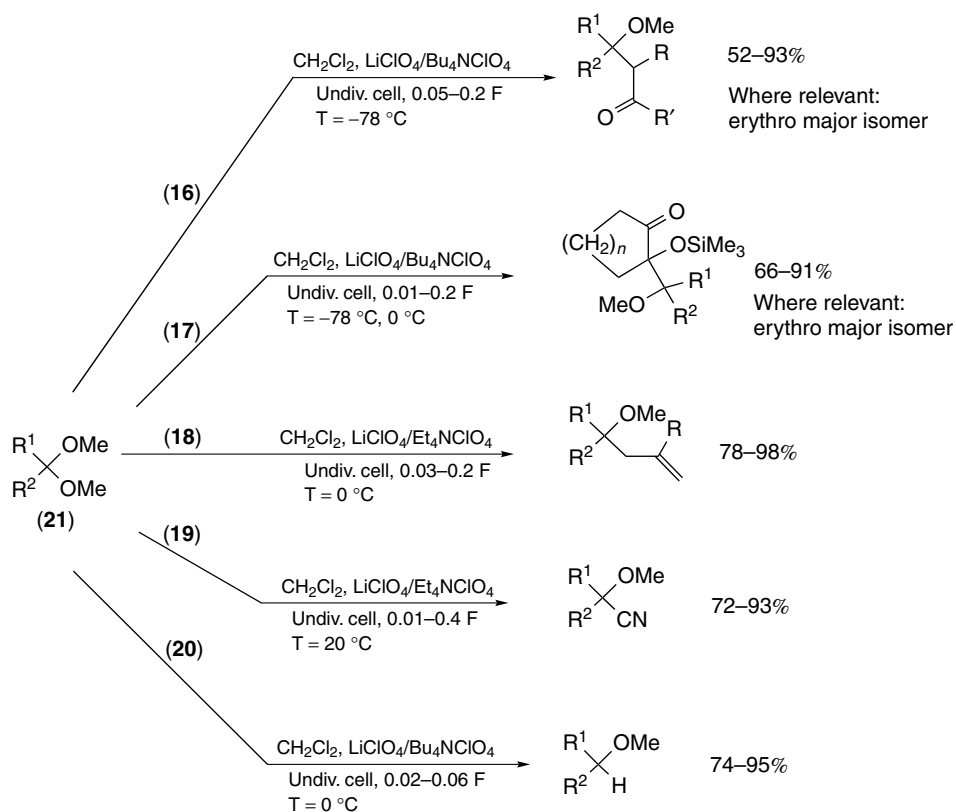
##### Reaction of Acetals, Ketones, and Aldehydes with Nucleophiles

Another reaction type for which EGA catalysis has been thoroughly explored is the reaction between organo-silicon nucleophiles and acetals or unprotected aldehydes and ketones [31–33]. The reaction types are aldol condensation, allylation, cyanation, and hydride reductions depending on which of the nucleophiles (16) to (20) is used.

Typical reaction conditions, products, and yields are depicted in Scheme 8 for acetals [32, 33].

In general, acetals derived from aldehydes (21, R<sup>1</sup> = alkyl, R<sup>2</sup> = H) are more reactive than those derived from ketones (21, R<sup>1</sup>, R<sup>2</sup> = alkyl), and, for example, allylations of the latter are carried out at 0 °C rather than at –78 °C.

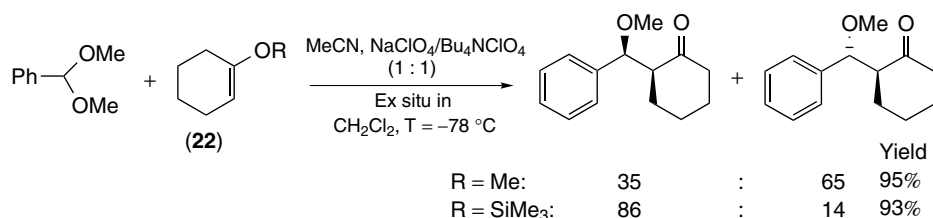
The aldol reactions of enol silyl ethers, (16), with unprotected aromatic aldehydes also give good yields of the adducts (isolated as the silyl ether) but with



**Scheme 8** EGA-catalyzed addition of C-nucleophiles to acetals.

a lower erythro:threo ratio than the corresponding acetal. For reaction of benzaldehyde with cyclohexanone enol trimethylsilyl ether, a ratio of 69:31 was obtained whereas the corresponding acetal gave a ratio of 86:14 [33].

Acetals of benzaldehydes may undergo EGA-catalyzed aldol reactions also with alkyl enol ethers, (22) (R = alkyl), as nucleophiles [31] but in contrast to the reaction with enol silyl ethers the threo isomer is favored in this case,



**Scheme 9** EGA-catalyzed diastereoselective aldol reaction of acetal with an enolether.

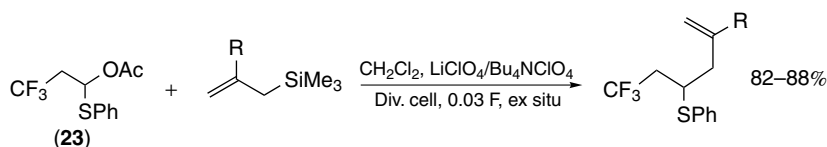
Scheme 9. Reaction with alkyl enol ethers is unsuccessful for acetals of aliphatic aldehydes [31].

The cyanation reactions with (19) (extremely toxic and requires essentially nonacidic reaction conditions) can also be carried out with unprotected aldehydes in good yields but with higher charge consumption (88–97%, 0.15–0.45 F). For ketones, the products are isolated as trimethylsilyl ethers, whereas for aldehydes the silyl ethers are hydrolyzed to alcohols [33].

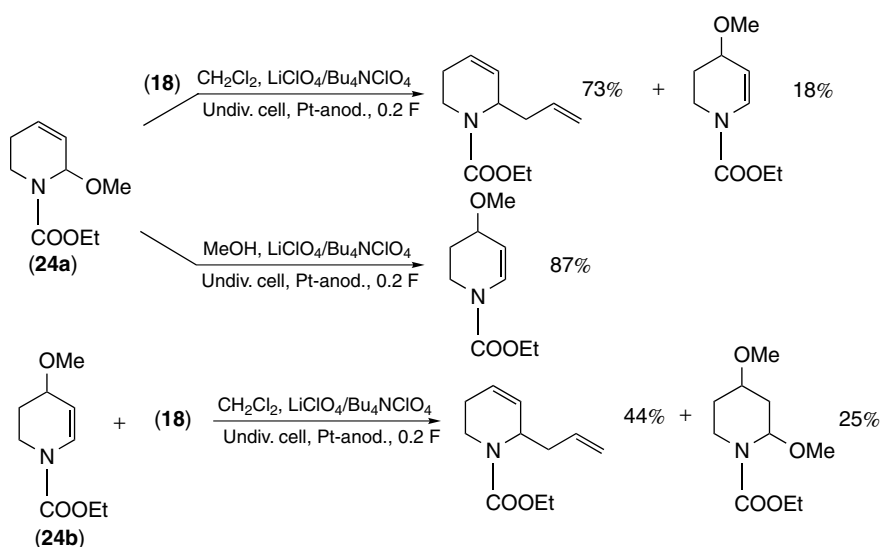
Allylations do not work for unprotected aldehydes, and reactions with (20) have only been reported for acetals of aromatic aldehydes [33]. For

CF<sub>3</sub> compounds like (23) in which the sulfur substituent stabilizes the carbocation,  $\beta$ -allylation and -cyanation is possible, Scheme 10. Normally,  $\beta$ -substitution of CF<sub>3</sub> compounds is problematic because of competing elimination [34].

Reaction of (24a) or (24b) with (16), (18) or (19) under the conditions of EGA catalysis leads selectively to substitution in the 2-position, Scheme 11, via the common cationic intermediate. Reaction with *O*- (or *S*-) nucleophiles such as MeOH, Scheme 11, exclusively gives substitution in the 4-position [35]. The difference in regioselectivity has been interpreted as 2-substitution arising from



Scheme 10 Allylation of  $\alpha$ -phenylthio acetates.



Scheme 11 Regioselective EGA-catalyzed allylic substitution.

kinetic control and 4-substitution from thermodynamic control [35]. The MeOH (or Me<sub>3</sub>SiOMe) liberated during the reaction with Me<sub>3</sub>SiNu in CH<sub>2</sub>Cl<sub>2</sub> gives rise to the 4-methoxy-substituted side product.

Reductive cleavage of glycosides is conventionally carried out using moisture-sensitive Lewis acids such as BF<sub>3</sub> · Et<sub>2</sub>O, BuSnCl<sub>3</sub> or Me<sub>3</sub>SiOTf. The EGA equivalent does not work with Et<sub>3</sub>SiH as the H-donor but good yields are obtained using the conditions of Scheme 12. Small amounts of water decelerate the reaction but the products are identical [36].

#### 14.3.3

##### 1,4-Addition to Enones

Selective formation of 1,5-dicarbonyl compounds by 1,4-addition (Michael addition) of enolates to enones is facilitated by the use of enol silyl ethers as enolate equivalents [37]. The reaction is catalyzed by

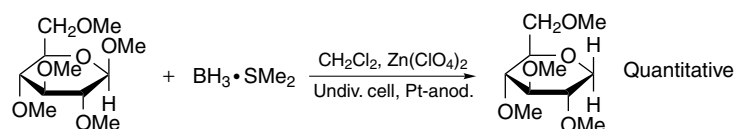
stoichiometric amounts of Lewis acids such as TiCl<sub>4</sub>, Ti(O-<sup>i</sup>Pr)<sub>4</sub>, SnCl<sub>4</sub> or trityl salts but catalytic amounts of EGA can be used instead, Scheme 13. The silyl adducts formed are easily hydrolyzed to ketones and the threo/erythro ratios are similar to those obtained using Lewis acid catalysts. Ketene silyl acetals may be used as nucleophiles with similar yields under identical conditions [37].

#### 14.3.4

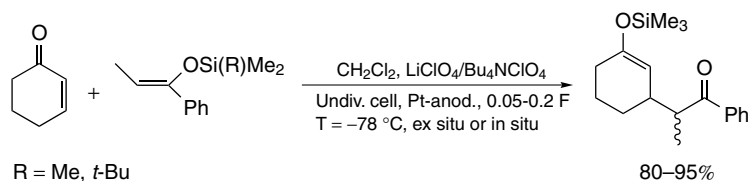
##### Functional Group Protection

Protection of a carbonyl function as the 1,3-dioxolane can be efficiently carried out with 1,2-bis(trimethylsiloxy)ethane and EGA catalysis, Scheme 14 [38]. Application to 1-menthone leads to 91% of the acetal without epimerization at C-2. The reaction is not efficient for conjugated enones [38].

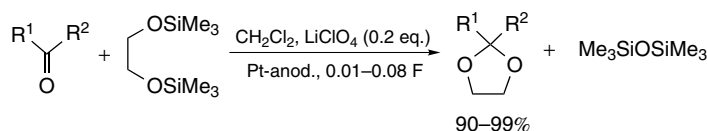
Protection of alcohols with 3,4-dihydro-2H-pyran can be carried out by EGA



**Scheme 12** EGA-catalyzed reductive cleavage of glycosides.



**Scheme 13** EGA-catalyzed Michael addition of enolethers.



**Scheme 14** Protection of a carbonyl group as 1,3-dioxolane.

catalysis by passing very small amounts of charge, Scheme 15 [39]. The procedure also works nicely for compounds containing protected carbonyl groups. The corresponding deprotection, Scheme 15, is not selective when other ether functions are present in the molecule. The conditions used for deprotection can be used as a general method for trans-esterification, for example, conversion of glycerides into simple alkyl esters of fatty acids in high yields [39].

#### 14.3.5

##### Electrophilic Aromatic Substitution

Instead of stoichiometric amounts of Lewis acids ( $\text{ZnCl}_2$ ,  $\text{FeCl}_3$ ), small amounts of EGA (0.003–0.03 F) may catalyze acylation of electron-rich arenes when the electrophile precursor is used as solvent/co-solvent [40]. Yields in the range 22 to 95% are obtained, lowest when *o*-substitution has to take place as in 1,4-dimethoxybenzene. The regioselectivity is 75 to 98% [40].

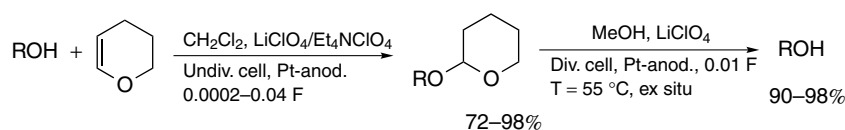
The involvement of EGA as a catalyst in the nitration of naphthalene by  $\text{NO}_2$

in  $\text{MeCN-LiBF}_4$  has been suggested [41]. In a divided cell, a small amount of charge was passed (0.015 F) and the reaction monitored thereafter. The rate of reaction increased by 40 to 60% compared to the rate of reaction observed under identical conditions but without passage of charge [41].

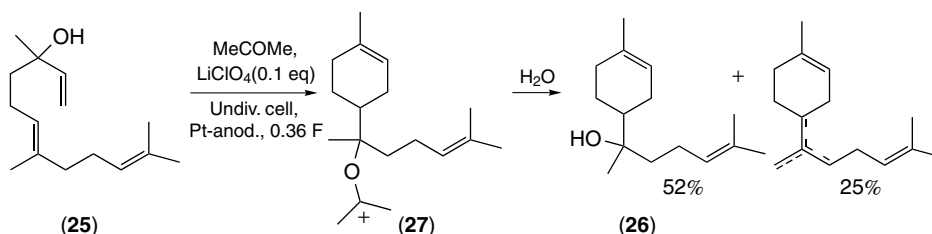
#### 14.3.6

##### Cyclizations

Most attempted conversions of (25) to (26) by conventional acid catalysis (e.g.  $\text{HCOOH}$  in pentane,  $\text{AlCl}_3$  in ether or  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  in  $\text{CH}_2\text{Cl}_2$ ) lead predominantly to mixtures of the alkenes rather than the desired (26) (<30%) [42]. Under these conditions, deprotonation of the cyclic carbocation species takes precedence over return of the OH-group or – if formed – (26) is unstable under the reaction conditions. A rationalization of the successful conversion by EGA catalysis in acetone is the trapping of the cyclized carbocation by acetone giving (27), which is hydrolyzed to (26) (52%, 0% *de*), Scheme 16. Other solvents gave none of



**Scheme 15** Protection of alcohols.



**Scheme 16** EGA-catalyzed cyclization.

(26), and only metal perchlorates were effective in the conversion of (25) to (26) [42].

Cyclizations of the type in Scheme 17 can be carried out in concentrated sulfuric acid, and workup, therefore, requires large amounts of base. The EGA-catalyzed cyclization can be carried out in solutions that can be neutralized by a few drops of pyridine, since only a very small amount of charge is necessary to complete the cyclization process under optimal conditions [43].

#### 14.3.7

##### Diels–Alder Reactions

Diels–Alder reactions between dienes and highly reactive dienophiles such as alkyl vinyl ketones can be carried out using the corresponding acetals in order to prevent polymerization of the dienophile. Activation of the masked dienophiles to undergo ionic [4 + 2] cycloadditions with dienes can be by EGA using the conditions in Scheme 18 [44]. Yields in the range 20 to 85% were obtained depending on the

reactants [44]. In all cases, higher endo/exo ratios were obtained than those obtained by the thermal Diels–Alder reactions of the corresponding enones. For (28) ( $R = \text{Me}$ ) with cyclopentadiene, a ratio of 50:1 was obtained, which should be compared to 3.9:1 for a thermal reaction of the enone [44].

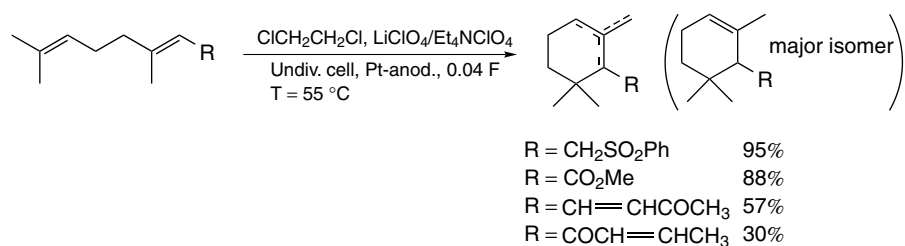
#### 14.4

##### Electrogenerated Bases

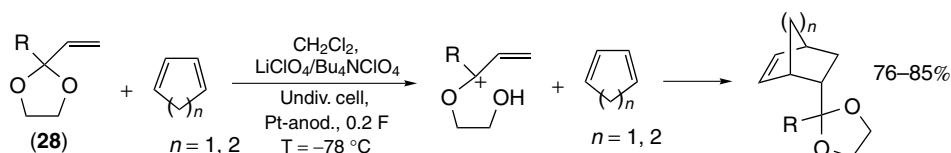
#### 14.4.1

##### General Concepts

Electrogenerated bases (EGBs) can be radical anions, anions or dianions. However, basicity is not the only general property of these species, and competing reactions of EGBs are as nucleophiles or as single electron-transfer agents. As with conventional bases, sterically hindered EGBs are useful because proton abstraction becomes favored over nucleophilic substitutions and additions. In contrast to



**Scheme 17** EGA-catalyzed cyclization.



**Scheme 18** EGA-catalyzed cycloaddition.

reactions involving EGAs that are mostly catalytic, many reactions involving EGBs require stoichiometric amounts of base.

Historically, the concept of EGBs was developed in relation to electrochemically induced Wittig reactions [45]. Co-electrolysis of the phosphonium salt and the carbonyl compound was carried out using the carbonyl compound as the solvent and gave reasonable yields of the alkene [45]. Most of these reactions can be rationalized within Scheme 19, in which the phosphonium ion participates both as the probase (PB) and as the acidic substrate [46].

Ylide formation by electrochemical reduction of onium ions [47–53] can in general be rationalized as resulting from an EGB reaction. A major disadvantage in using the substrate as the PB is that only half the substrate undergoes the desired base-induced reaction (except in cases that are catalytic, see Sect. 14.9). Of the more synthetic usefulness for reactions requiring stoichiometric amounts of base are the EGBs generated from PBs, which are different from the acidic substrates as demonstrated first for the Wittig reaction using azobenzene as the PB [46].

The ideal EGB should be (1) formed by reduction of a cheap, nontoxic PB at modest potential, (2) nonnucleophilic in order to avoid side reactions, (3) easily separated from the reaction mixture, and (4) recyclable. No single compound or class of compounds fulfill these requirements.

#### 14.4.2

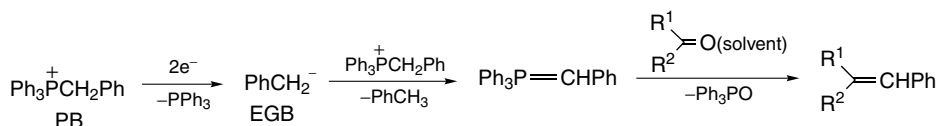
##### In situ Versus Ex situ Formation of the EGB

Formation of EGBs from deliberately added PBs may be carried out in two ways: (1) in situ where generation of the EGB by reduction of the PB takes place in the presence of the reactant(s), or (2) ex situ where the EGB is generated by exhaustive reduction of the PB followed by subsequent addition of the reactant(s). The most frequently used method is in situ generation of the EGB. The advantages of in situ generation are that the EGB can be short lived, and that the applied current can control the amount of base present. The major disadvantage is that the PB must be more easily reduced than the reactant(s). The use of an ex situ formed EGB is similar to the use of an ordinary base. The advantage of ex situ formation is that easily reduced reactants can be used in combination with EGBs generated from PBs, which are difficult to reduce. A disadvantage is that the EGB has to be stable in the solvent-electrolyte system for a longer time.

#### 14.4.3

##### Kinetic Versus Thermodynamic Basicity

One way to classify EGBs is according to the atom to which proton transfer takes place, typically nitrogen, oxygen or carbon. As in other proton transfer reactions, proton transfer to/from heteroatoms (*N* or *O*) is generally much faster than to/from carbon when comparing reactions



**Scheme 19** Wittig reaction with a phosphonium ion as probase and as substrate.

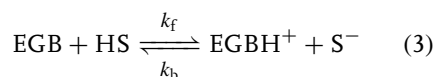
of similar driving forces. Often, proton transfer to anions or dianions is faster than proton transfer to radical anions (assuming equal thermodynamic basicity and the same type of atom) due to the fact that radical anions, which are feasible as EGBs, generally are extensively delocalized. Within different classes of EGBs there is, therefore, no simple relationship between thermodynamic and kinetic basicities. The kinetics of proton transfer to typical EGBs from different types of acids is not discussed here; references can be found in Refs. [3, 54].

The reactions discussed in the following sections take place in aprotic solvents, and reference to known or estimated thermodynamic basicities will relate to DMSO unless otherwise noted, since DMSO is the polar aprotic solvent in which most thermodynamic acidities have been measured [55–58]. Values of pK determined in DMSO can usually be assumed to parallel values in DMF [59, 60], MeCN, and other polar aprotic solvents whereas pK values (and *relative* pK values) related to water and other hydroxylic solvents can be *very* different.

#### 14.4.4

##### Efficiency of the Proton Transfer Reaction

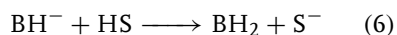
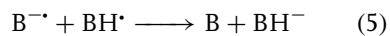
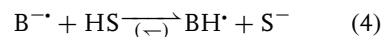
For an EGB to work efficiently on a synthetic scale, the proton transfer reaction (Eq. 3) has to appear essentially irreversible.



Irreversibility can be obtained if (1) the equilibrium constant for reaction (3),  $K = k_f/k_b$ , is large, that is, the EGB is a thermodynamically much stronger base than the deprotonated substrate,  $\text{S}^-$ . If that is the case, the substrate may be

quantitatively deprotonated either by an *in situ* or an *ex situ*-formed EGB, and  $\text{S}^-$  converted to the product by addition of another reactant in a subsequent step; (2)  $\text{EGBH}^+$  or  $\text{S}^-$  (or both) are removed from the equilibrium in an irreversible follow-up reaction. If that is the case, the formation of products may, as with ordinary bases, be efficient even when  $K \ll 1$ .

Using a radical anion,  $\text{B}^{\cdot-}$ , as the EGB normally ensures that the protonated EGB [in this case a radical,  $\text{BH}^{\cdot}$ , Eq. (4)], is quickly removed from the equilibrium, since neutral radicals formed by protonation of radical anions normally are more easily reduced than the precursor B, Eq. (5).



The anion  $\text{BH}^-$  formed in Eq. (5) is thermodynamically a stronger base than  $\text{B}^{\cdot-}$ , and  $\text{BH}^-$  will react with another molecule of substrate, Eq. (6). Each PB will therefore consume a total of two protons (and two electrons). Radical anion EGBs are normally produced *in situ*.

When the EGB is an anion or a dianion, irreversible follow-up reaction of the deprotonated substrate,  $\text{S}^-$ , is the only way by which an unfavorable proton transfer equilibrium can be driven toward products. A disadvantage is that when the follow-up reaction of  $\text{S}^-$  is with an added electrophile, competing reaction between the EGB and the electrophile is often observed. Or – if the EGB is a dianion – the monoprotonated form may react with the electrophile.



## 14.4.5

**Comparison of EGBs with Conventional Bases**

In contrast to EGAs, most of the synthetically useful reactions involving EGBs are reactions requiring stoichiometric amounts of the electrogenerated reagent, Sect. 14.8, and the major advantage of strong EGBs compared to strong conventional bases is the recycling aspect. Whereas strong conventional bases typically are expensive reagents that can be used only once, many of the strong EGBs are converted directly into their PB, or the PB can be obtained rather easily by reoxidation. For base-catalyzed reactions, Sect. 14.9, particularly the recent, elegant uses of dioxygen,  $O_2$ , as a PB are promising.

## 14.5

**Nitrogen Bases**

## 14.5.1

**Azo Compounds and Nitrogen Heteroaromatics as Probases**

Azobenzenes, (29), and analogous heteroaromatic azo compounds, (30), are in aprotic solvents reduced in two sequential one-electron steps to the radical anion and the dianion [61–66]. Disproportionation of the radical anion to the dianion is favored by the presence of  $Li^+$  [67]. The dianion is considerably more basic than the radical anion, and the dianion is only stable in very dry nonacidic solvents [64, 65, 67, 68]. Both the dianion and the radical anion derived from (29) have been used as EGBs. The anion resulting from protonation of the dianion is less basic (by several pK units) than the dianion but more basic than

the radical anion [65], [ $pK(Ph-NH-NH-Ph)$  26.1,  $pK(Ph-NH-N^--Ph) \approx 31$ ,  $pK(Ph-NH-N^{\cdot-}-Ph) < 20$ ]. Azopyridines, (30), are in general more easily reduced to dianions than (29) but the dianions are also less basic [64, 66, 69].

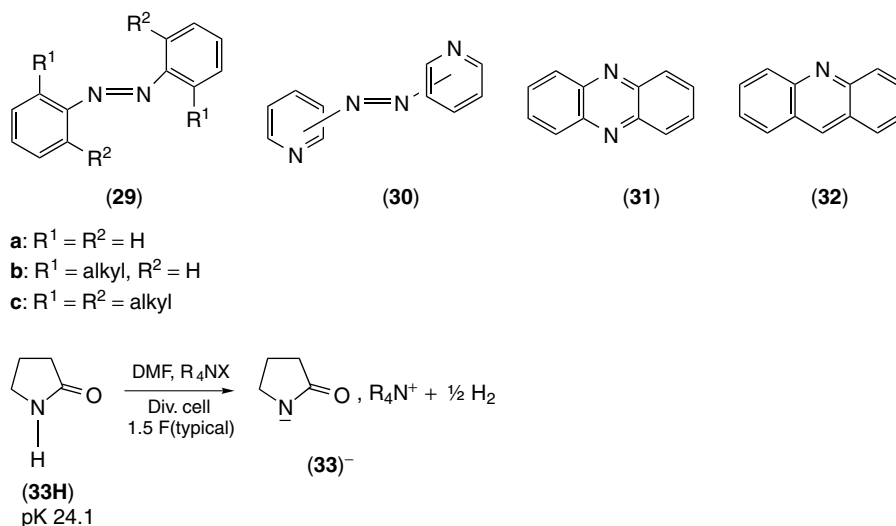
Using the dianion as an EGB may result in mono- or diprotonation depending on the strength of the acid, whereas the radical anion EGB always results in diprotonation, cf. Eqs. (4 to 6). Upon workup, the resulting species is always the dihydro product, and a disadvantage of (29a) as a PB on a multigram scale is the conversion of its dihydro product, hydrazobenzene, into the carcinogenic benzidine on acidic aqueous workup. This inconvenience is avoided by using (29b–c) that also show enhanced basicity of the EGBs (radical anions or dianions). Another disadvantage of (29a) as a PB is that both  $(29a)^{\cdot-}$  and  $(29a)^{2-}$  are good nucleophiles (see Sect. 14.8.5 for an example).

Nitrogen heteroaromatics are expected to be useful probases. The cathodic reduction of phenazine, (31), resembles closely that of (29a) [70, 71], and the kinetic basicity of  $(31)^{\cdot-}$  is comparable to that of  $(29a)^{\cdot-}$  [54]. However, application of (31) as a PB in electrosynthesis has not been reported, and there is only a single report concerning the use of the radical anion of acridine, (32), as an EGB [72].

## 14.5.2

**Amides as Probases**

The application of 2-pyrrolidone, (33H), as a PB is widespread (see Sects. 14.8 and 14.9). The 2-pyrrolidone anion,  $(33)^-$ , is formed by direct cathodic reduction ( $\approx -2.5$  V), Scheme 20, and therefore necessarily has to be used as an *ex situ*



**Scheme 20** 2-Pyrrolidone as probase.

reagent. The anion is a strong base,  $pK(2\text{-pyrrolidone})$  24.1.

An alternative procedure (constant current, undivided cell, stainless steel cathode, sacrificial magnesium anode) has later been developed for ex situ preparation of  $(33)^-$  from  $(33H)$  [73]. The solution of the  $Mg^{2+}$ -stabilized  $(33)^-$  may be stored at room temperature for up to 10 h. The solvent used, dimethoxyethane with 10% v/v HMPA, raises problems since in many laboratories HMPA is a banned substance because of its carcinogenicity. The HMPA is required to give acceptable conductivity in the preparation of the EGB but is also crucial in avoiding strong ion pairing between  $Mg^{2+}$  and the EGB (which decreases the reactivity of the EGB) [73]. However, it is reported that HMPA may be replaced with  $Me_2N(CH_2)_2NMe_2$  as a complexing agent [73].

The advantages of polymer-supported reagents have been exploited for EGBs in the form of EGBs generated from polyacrylamides [74]. The effective base is in all cases an amide anion similar to  $(33)^-$ .

The polyacrylamides could be repeatedly reused [74].

A stronger base and notably weaker nucleophile is the anion of hexamethyldisilazane  $(Me_3Si)_2NH$ ,  $(34H)$ . The anion,  $(34)^-$ , is electrogenerated ex situ, similarly to  $(33)^-$ , as its magnesium salt in dimethoxyethane with 15% v/v HMPA [75]. The PB  $(34H)$  is commercially available, relatively cheap, and in many respects behaves very much like lithium diisopropylamide (LDA). Substitution of HMPA with *N*-methyl-2-pyrrolidone was not successful [75].

Since formation of EGBs from amides, in all cases, is the result of direct reduction and  $H_2$  formation (and has to be done ex situ), the monomeric as well as the polymeric EGBs are recovered as the PB. Their reactions as bases have to be driven either by a thermodynamically favored proton transfer reaction or by a fast follow-up reaction of the deprotonated substrate, which – particularly for  $(33)^-$  – is difficult, since  $(33)^-$  is a good nucleophile.

## 14.6 Oxygen Bases

### 14.6.1

#### Dioxygen as Probase

Dioxygen is conveniently reduced to the superoxide anion,  $O_2^{\cdot-}$ , by reduction at about  $-1.0$  V (vs. SCE) in MeCN or DMF. The properties of  $O_2^{\cdot-}$  have been reviewed [76–78]. Its basic properties stem from the driving force of the disproportionation [78], Eq. (5). The  $O_2^{\cdot-}$  is a relatively weak base ( $pK(HO_2^{\cdot}) \approx 12$  in DMF) [79] but the overall equilibrium constant for reaction (7) is in the order of  $10^5$  for simple alcohols and water ( $pK \approx 30$ ) in DMF [79]. However, for such highly endergonic reactions, the rate-determining protonation of  $O_2^{\cdot-}$  is a slow reaction with a second order rate constant of around  $10^{-3} \text{ M}^{-1} \text{ s}^{-1}$  [79].



The common method of  $O_2^{\cdot-}$  generation is by bubbling  $O_2$  through the catholyte during reduction, and an excess of  $O_2$  is therefore present. Carbanions formed by proton transfer to  $O_2^{\cdot-}$  may therefore react with  $O_2$ , and many synthetically interesting reactions involve not only deprotonation but also oxidative follow-up reactions of the deprotonated substrate (cf. Sect. 14.8.7). For several base-catalyzed reactions (Sect. 14.9) the  $O_2$  present in

air-saturated solutions serves as the PB source. This approach prevents oxidative follow-up reactions.

### 14.6.2

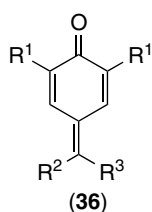
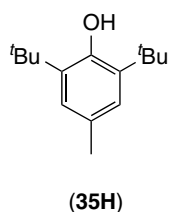
#### Phenols as Probases

Hindered phenolates have low nucleophilicity and may in aprotic solvent act as EGBs. The tetraethylammonium phenolate of (35H), ( $pK \approx 16.8$ ) can be formed ex situ by direct reduction of (35H) [80, 81], similar to Scheme 20. Since the thermodynamic basicity is low, the applicability as an EGB is entirely dependent on the removal of deprotonated substrate by further reaction.

### 14.6.3

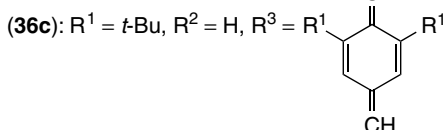
#### Carbonyl Compounds as Probases

An alternative route to phenolate-like EGBs is through the cathodic reduction of quinonemethides, (36), [82, 83]. The advantage of these PBs is that they are reduced at modest potentials, which allow EGB formation to take place in situ, and they are ultimately converted into phenols that are easily reoxidized to (36) either by air or by anodic oxidation (60–70% yield) [82]. The radical anion (36a) $^{\cdot-}$  is expected to have basicity similar to that of (35) $^{\cdot-}$ , whereas the  $pK$  of the conjugate acid of the dianion formed by further reduction can be assumed close to that of triphenylmethane, 30.6.



(36a):  $R^1 = t\text{-Bu}$ ,  $R^2 = R^3 = \text{Ph}$

(36b):  $R^1 = t\text{-Bu}$ ,  $R^2, R^3 = 9\text{-fluorenylidene}$



The electrochemical behavior of (36a) has been studied in some detail [83]. Protonation of (36a)<sup>•−</sup> (at oxygen) gives a radical, which in contrast to the radicals formed by protonation of (29)<sup>•−</sup>–(32)<sup>•−</sup>, is more difficult to reduce (by ca. 0.1 V) than (36a) [83]. The reaction sequence in Eqs. (5) and (6) is therefore not followed for (36a).

Radical anion EGBs derived from aromatic carbonyl compounds are expected to be relatively weak bases but since the radical anions undergo dimerization, the more basic dimer dianions may be active as EGBs for substrates with pK values in the range 20 to 23. Aromatic carbonyl compounds have primarily been used as PBs in catalytic reactions in which the PB also functions as an electrophile (cf. Sect. 14.9.2).

## 14.7 Carbon Bases

Two types of electrogenerated carbon bases have commonly been used: (1) dianions derived from activated alkenes, and (2) carbanions formed by reductive cleavage of halogen compounds or by direct reduction of weak carbon acids. In both cases, the efficiency of the proton transfer reaction relies on a thermodynamically favored proton transfer or a fast follow-up reaction of the deprotonated substrate.

### 14.7.1

#### Activated Alkenes as Probases

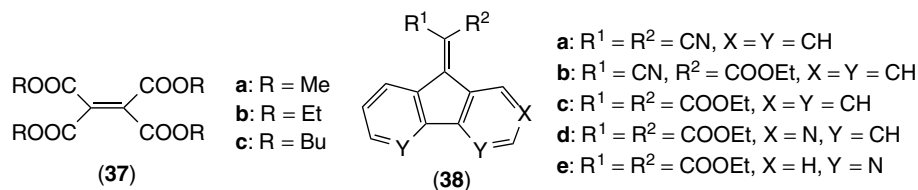
Esters of ethenetetracarboxylic acid, (37), and disubstituted (fluoren-9-ylidene)methane derivatives, (38), are reduced sequentially to radical anions and dianions [2, 68, 84, 85]. Only the dianions are sufficiently basic to be useful as EGBs [53, 86]. For (37), the two reduction potentials are separated by 0.2 V [68], and even with a working potential allowing formation only of the radical anion, the dianion can be formed by disproportionation. The protonated form of the dianionic EGBs, (37H)<sup>−</sup> and (38H)<sup>−</sup>, will normally be stable in solution since the pK values of the dihydro products are expected to be in the range 12 to 16.

The more hindered (37c) is to be preferred; the PB is less susceptible to Michael addition and (37c)<sup>2−</sup> as well as (37cH)<sup>−</sup> are less nucleophilic than those of the lower esters (see Sect. 14.8.5 for an example). In the absence of side reactions these PBs are, upon workup, converted into the dihydro derivatives that can be reoxidized back to the PBs by bromine or by anodic oxidation [68, 87, 88]. The base strength of (38)<sup>2−</sup> can be modified either by substitution [89] or by complexation with alkali metal counterions [86, 89].

### 14.7.2

#### Carbanions as EGBs

Like the formation of anionic EGBs by direct reduction of weak nitrogen or oxygen



acids, formation of carbanion EGBs by direct reduction of weak carbon acids normally requires *ex situ* conditions, since most reactants are reducible at the required potentials. Triphenylmethane, (**39**), a very weak acid ( $pK$  30.6), is directly reducible to the corresponding strongly basic and nonnucleophilic triphenylmethyl carbanion in dry conditions at low temperature [80, 90].

The phenyl  $\sigma$ -anion is strongly basic but may be obtained at relatively modest potentials by reductive cleavage of halobenzenes when the right cathode material is chosen [63]. Typically, the reactions are carried out at constant current in undivided cells using Cd-coated Ni-cathodes, Al or Mg sacrificial anodes, DMF (or MeCN for cyanomethylation) as the solvent and  $Bu_4NBF_4$  as the electrolyte. Under these conditions, iodobenzene is reduced at  $-1.6$  V versus SCE and bromobenzene at  $-1.9$  V, which may allow their use *in situ* [63, 91–93].

In most other cases, direct reduction of carbon acids has been used as a pathway for generation of nucleophiles and not EGBs. Easily reduced halogen compounds have occasionally been used as PBs. The EGBs are identical to those obtained by direct reduction of the conjugated acid; an advantage being that reduction and cleavage of the halocompound normally is easier and therefore may allow *in situ* formation. However, these EGBs are only moderately basic.

#### 14.7.3

##### Other Electrogenated Carbon Bases

Cathodic reduction of aromatic hydrocarbons gives  $\pi$ -radical anions, which are possible EGBs. However, the PBs normally have low solubilities in polar aprotic solvents, relatively low reduction potentials,

and proton transfer to carbon in a delocalized radical anion is normally slow (cf. Sect. 14.4.3). There are very few cases of aromatic hydrocarbons being deliberately used as PBs in electrosynthesis but an interesting analogue involves reduction of the fullerene  $C_{60}$  [94]. This compound can fairly easily be reduced sequentially to mono-, di-, and tri-anions of increasing basicity. The fullerene is in principle recyclable but may also be reused *in situ* since the partially hydrogenated forms can also work as PBs [94]. However,  $C_{60}$  is very poorly soluble in polar solvents and the practical use of  $C_{60}$  as PB is limited to base-catalyzed reactions in which only very small amounts of PB is required, see Sect. 14.9.1.

#### 14.8

##### Reactions Consuming Stoichiometric Amounts of Base

#### 14.8.1

##### Wittig Reactions

Wittig reactions have frequently been used to test and compare new EGBs, typically stilbene formation in the EGB-induced Wittig reaction of the relatively acidic  $Ph_3P^+CH_2Ph$  ( $pK$  17.4) with  $PhCHO$ . A selection of results is shown in Table 1, and there appears to be large inconsistencies in the yields and in the *trans/cis* ratios obtained under apparently identical conditions. The effect of changing the supporting electrolyte cation from  $Bu_4N^+$  to  $Li^+$  also appears to be nonsystematic.

The easy formation of (**38**)<sup>2−</sup> has (particularly in the presence of  $Li^+$ ) been shown to be useful for the synthesis of *cis*-rich mixtures of alkenes whilst stronger bases such as  $KOBu^t$  or  $BuLi$  essentially give the *trans* product [86].

**Tab. 1** Yields and stereochemistry of stilbene as a function of the EGB and the reaction conditions in the Wittig reaction of  $\text{Ph}_3\text{P}^+\text{CH}_2\text{Ph}$  with  $\text{PhCHO}^{\text{a}}$ 

EGB	Supporting electrolyte	Yield ( <i>trans/cis</i> )	References
$(29\text{a})^{\text{--}\cdot}/(29\text{a})^{2-\text{b}}$	LiCl	98% (0.66)	46
$(29\text{a})^{\text{--}\cdot}$	$\text{Bu}_4\text{NBF}_4$	79% (0.5), 78% (0.5) <sup>c</sup> , 96% (0.5) <sup>d</sup>	95
$(36\text{a})^{\text{--}\cdot}$	$\text{Bu}_4\text{NClO}_4$	99% (1.9)	82
	$\text{Bu}_4\text{NBF}_4$	58% (0.59)	95
$(36\text{b})^{2-}$	$\text{Bu}_4\text{NClO}_4$	48% (1.0)	82
$(36\text{c})^{2-}$	$\text{Bu}_4\text{NClO}_4$	84% (1.3)	82
$(38\text{a})^{2-}$	$\text{Bu}_4\text{NBF}_4$	80% (0.63), 46% (1.6)	95, 86
	$\text{LiClO}_4$	74% (0.69), 74% (1.44)	86, 53
$(38\text{b})^{2-}$	$\text{Bu}_4\text{NBF}_4$	68% (1.0)	86
	$\text{LiClO}_4$	94% (1.2)	86
$(38\text{c})^{2-}$	$\text{Bu}_4\text{NClO}_4$	80% (9.0)	89
$(38\text{d})^{2-}$	$\text{Bu}_4\text{NClO}_4$	91% (1.0)	89
$(38\text{e})^{2-}$	$\text{Bu}_4\text{NClO}_4$	87% (4.0)	89

<sup>a</sup>General conditions: DMF as solvent and in situ formation of the EGB by constant potential electrolysis (CPE) at the potential of EGB-formation in a divided cell.

<sup>b</sup>Disproportionation of  $(29\text{a})^{\text{--}\cdot}$  to  $(29\text{a})^{2-}$  in the presence of  $\text{Li}^+$  cannot be excluded.

<sup>c</sup>Constant current electrolysis (CCE).

<sup>d</sup>CCE in DMSO as solvent.

Wittig–Horner reactions between alkyl phosphonates and aldehydes can be carried out similar to the Wittig reaction but the phosphonates are much weaker acids than the phosphonium cations [by 9–10 pK units when comparing  $\text{Ph}_3\text{P}^+\text{CH}_2\text{X}$  with  $(\text{EtO})_2\text{P}(\text{O})\text{CH}_2\text{X}$ ], and, therefore, stronger electron-withdrawing substituents, X, [96] or more basic EGBs are required. Using (29) as a PB in situ gives, in the presence of *p*-methoxybenzaldehyde, the alkene in 60 to 80% yield for phosphonates  $(\text{EtO})_2\text{P}(\text{O})\text{CHXY}$  with Y = H, X = COOEt, CN, Ph, and Y = Me, X = COOEt, Y = X = Cl, exclusively (or almost exclusively) as the *E* isomer [96]. This approach may be compared to the direct reduction (at Pt or GC cathodes) of the phosphonates to give  $\text{H}_2$  and the anion, followed by addition of an aldehyde, which

gives similar yields of the alkene [97]. The successful use of (36a) as a PB for deprotonation of  $(\text{EtO})_2\text{P}(\text{O})\text{CH}_2\text{Ph}$  (pK 27.6) and formation of stilbene (*trans/cis* = 9) in the presence of benzaldehyde [82] is hardly due to  $(36\text{a})^{\text{--}\cdot}$ . More likely, initial *O*-protonation of  $(36\text{a})^{\text{--}\cdot}$  by an acidic impurity gives the radical that is further reduced at the working potential (lower than that of  $36\text{a}^{\text{--}\cdot}$  formation), and the much more basic substituted triphenylmethyl anion deprotonates the phosphonate. The reaction is then sustained by the protonation of a new  $(36\text{a})^{\text{--}\cdot}$  by the dihydro product,  $(36\text{aH}_2)$ .

Only low yields (10%) of coumarin were obtained by the intramolecular Wittig–Horner reaction of 2-(diethoxyphosphorylacetoxy)benzaldehyde using  $(35)^-$  as an EGB (formed ex situ in MeCN) [98].

## 14.8.2

**Addition to Aldehydes and Ketones**

Ex situ formation of  $(33)^-$  followed by addition to a mixture of  $\text{CHCl}_3$  and aldehyde (aliphatic or aromatic) in DMF at low temperature leads to deprotonation of  $\text{CHCl}_3$  but not of the aldehyde, and formation of the trichlorocarbonol takes place without formation of side products by aldol condensation, Scheme 21 [99]. The reaction could also be carried out (75–86% yield for butanal) using polymeric amides as a PB and with similar conditions [74].

The relatively easy formation of  $\text{Ph}^-$  from  $\text{PhI}$  (cf. Sect. 14.7.2) allows EGB formation in situ and gives trichloromethylation of aldehydes in 48 to 61% yield at room temperature [91]. A similar procedure was used for reaction of  $\text{CF}_3\text{CCl}_2\text{H}$  and  $\text{CCl}_3\text{CCl}_2\text{H}$  with aldehydes [91].

Trifluoromethylation of carbonyl compounds could be carried out by a procedure similar to Scheme 21, the only differences being that the reaction was carried out at  $-50^\circ\text{C}$ ,  $\text{CF}_3\text{H}$  (gas, very weak acid, estimated  $\text{pK}$  25–28) was added in a larger excess, and  $\text{Bu}_4\text{N}^+$  or  $\text{Oct}_4\text{N}^+$  counterions rather than  $\text{Et}_4\text{N}^+$  were necessary [100]. Yields were good (60–92%) with aromatic aldehydes. For ketones, good yields (60–85%) were only obtained when the alcoholate was trapped as the trimethylsilyl ether by hexamethyldisilazane. Aliphatic aldehydes gave poor yields [100]. Trifluoromethylation of aromatic aldehydes has

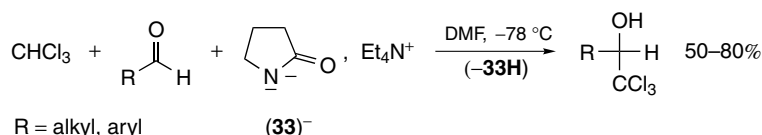
also been carried out using in situ generated  $\text{Ph}^-$  as the EGB in  $\text{DMF-Bu}_4\text{NBF}_4$ . The PB had to be present in excess to achieve full conversion of the aldehyde. Moderate to good yields were obtained [93]. DMF as a solvent seems to be crucial for the stability of “ $\text{CF}_3^-$ ”, and trapping of  $\text{CF}_3^-$  by DMF to form an aminoalcoholate has been suggested as the initial step in the mechanism. Thereafter, the “ $\text{CF}_3^-$ ” is transferred to the more powerful electrophile, the aldehyde or the ketone [101, 102].

## 14.8.3

**Alkylation of Activated Methylen Compounds**

In general, deprotonation of the substrate by reaction with an EGB has to take place in a separate step before addition of the alkylating agent, since competing alkylation of the EGB may otherwise take place. In order to minimize the time between deprotonation and alkylation, a three-step procedure is often used: (1) ex situ formation of a strongly basic EGB, (2) addition of the EGB to the substrate, which is quantitatively deprotonated, and (3) trapping of the deprotonated substrate with the alkylating agent.

Selective monoalkylation of methyl arylacetates by alkylhalides is difficult with conventional bases. It may be achieved by application of the three-step procedure outlined above adding  $(33)^-$  to the methyl arylacetates at a low temperature



**Scheme 21** Trichloromethylation of aldehydes with 2-pyrrolidone as probase.

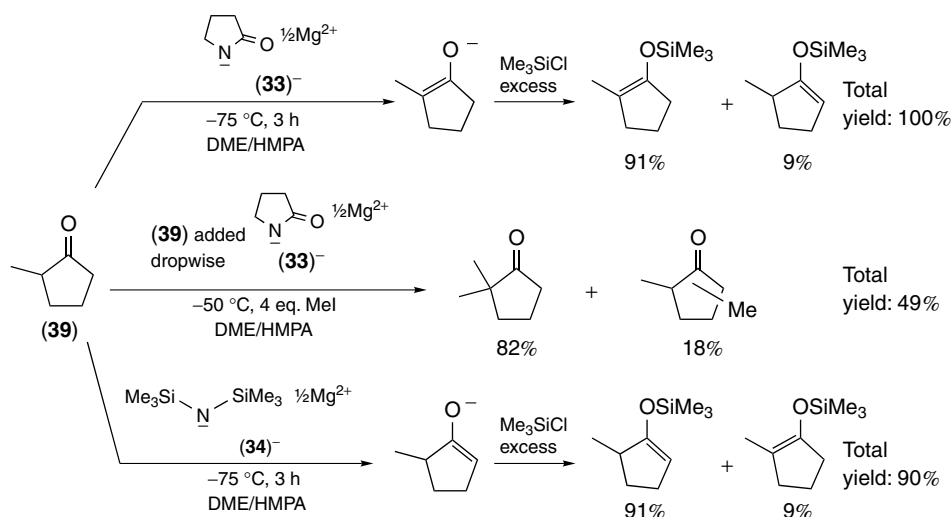
( $-78^{\circ}\text{C}$ ). The substrate is deprotonated [ $\text{pK}(\text{PhCH}_2\text{COOMe})$  22.7] and trapped by an alkyl iodide ( $-78^{\circ}\text{C}$ ). This procedure leads selectively to mono  $\alpha$ -alkylation (81–99%) [103]. Selective monoalkylation of  $\beta$ -diketones in 70 to 95% yield was obtained by a similar procedure, and only in a few cases (bulky secondary alkylhalides) were the  $O$ -alkylated substrate found as a side product. Tetraalkylammonium counter cations were necessary in stabilizing the enolate;  $\text{Na}^+$  counter cations did not give selective  $C$ -alkylation [104].

It may be difficult to alkylate  $\alpha$ - $\text{CF}_3$  enolates since they easily undergo defluorination prior to trapping with the alkylating reagent. The enolate of dimethyl trifluoromethylmalonate generated by  $(33)^{-}/\text{Et}_4\text{N}^{+}$  was shown to be stable towards defluorination and could be alkylated in 30 to 80% yield depending on the alkyl halide [105].

Less reactive compounds such as alkyl benzyl ketones and cycloalkanones ( $\text{pK}$  20–26) may be deprotonated by *ex situ*

generated  $(33)^{-}$  with  $\text{Mg}^{2+}$  as counterions forming enolates stabilized by  $\text{Mg}^{2+}$ , whereas dialkyl ketones ( $\text{pK}$  27–28) do not react [73, 106]. Under the conditions in Scheme 22, the enolates equilibrate to the more stable *Z*-enolates that can be trapped by an excess  $\text{Me}_3\text{SiCl}$ . The presence of HMPA is crucial for the equilibration [73]. The regioselective monoalkylation of 2-methylcyclopentanone, (39), via the enolate is difficult to achieve with conventional bases but can be carried out using a slightly modified procedure, where 4 eq. of  $\text{MeI}$  is added to the EGB solution and (39) is added dropwise at  $-50^{\circ}\text{C}$ . Formation of the 2,2-dimethylcyclopentanone takes place but conversion is low since some of the EGB is methylated [106], Scheme 22. The conversion may be improved by subjecting the product mixture to another cycle of reaction since the product is too weakly acidic to be deprotonated by the EGB.

Using the more basic and less nucleophilic EGB  $(34)^{-}$  also leads to deprotonation, Scheme 22, but trapping with  $\text{Me}_3\text{SiCl}$  predominantly gives products



**Scheme 22** C- or O-alkylation of an enolate formed by an EGB.



arising from the removal of the most acidic hydrogen (kinetic control). Equilibration of the enolate to the more substituted isomer does not take place [75], probably because of the fast, quantitative deprotonation leaving no unreacted ketone as is necessary for equilibration.

Alkylation of 2-methylcyclohexanone could not be achieved by the procedure used for (39) since it is a weaker acid. Good yields (38–84%) of the 2-alkyl-2-methylcyclohexanone were obtained from 2-methylcyclohexanone using the strongly basic trityl anion as an EGB (generated *ex situ* by reduction of  $\text{Ph}_3\text{CH}$ , in  $\text{DMF-Bu}_4\text{NBF}_4$  at  $-50^\circ\text{C}$ ) followed by addition of alkyl or benzyl iodide or bromide [80, 90]. This EGB is a stronger base than  $(33)^-$  and the enolates formed (with  $\text{R}_4\text{N}^+$  counterions) are more reactive than those stabilized by  $\text{Mg}^{2+}$  in Scheme 22. Only with  $\text{MeI}$  as the alkylating reagent, 2,5-dimethylcyclohexanone was the dominating regioisomer [90]. Monoalkylation of cyclohexanone and fluorene could be carried out using the same procedure [90].

A one-pot conversion of  $\text{EtOOCCH}_2\text{CN}$  and  $\text{ClCOOEt}$  initially to  $(\text{EtOOC})_2\text{CHCN}$  using (29a) as PB, and then to  $(\text{EtOOC})_2\text{C=O}$  (77%) by  $\text{O}_2^{\cdot-}/\text{O}_2$  according to the third reaction in Scheme 28 (Sect. 14.8.7) has been reported [107].

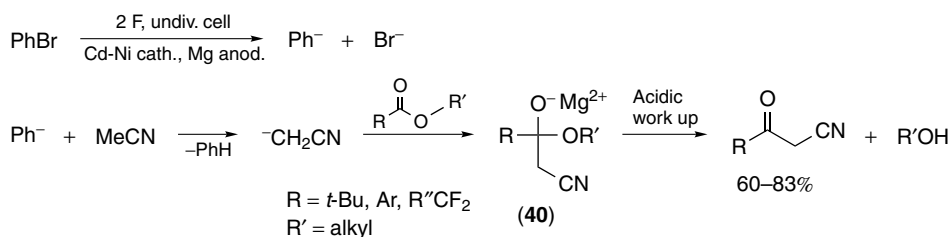
#### 14.8.4

##### Cyanomethylation

Formation of  $\beta$ -oxonitriles by cyanomethylation of esters requires that the ester contains no  $\alpha$ -hydrogens since the acidity of  $\text{MeCN}$  ( $\text{pK}$  31.3) is comparable to the acidity of the  $\alpha$ -hydrogens of the ester. A strong EGB such as  $\text{Ph}^-$  produced *in situ* using  $\text{MeCN}$  as the solvent and in the presence of esters lacking  $\alpha$ -hydrogens leads to nucleophilic acyl substitution [63, 92], Scheme 23. It is crucial that the anionic intermediate, (40), is stabilized by the anodically produced  $\text{Mg}^{2+}$ , since the final  $\beta$ -oxonitrile is far more acidic ( $\text{pK} \approx 12$ ) than  $\text{MeCN}$ . The same procedure could be used for cyanomethylation of ketones and aldehydes to give  $\beta$ -hydroxynitriles (55–74%) [92].

Attempts to prepare  $^-\text{CH}_2\text{CN}$  before adding the electrophile did not lead to cyanomethylation since  $^-\text{CH}_2\text{CN}$  reacts with  $\text{MeCN}$  prior to addition of the electrophile, and the type of products isolated (20–88%) depended on the electrophile [92].

When more acidic nitriles such as  $\text{PhCH}_2\text{CN}$  ( $\text{pK}$  21.9) are used (in  $\text{DMF}$ ) with *in situ* produced  $\text{Ph}^-$  as the EGB, esters with  $\alpha$ -hydrogens can also be used as electrophiles. Formation of  $\beta$ -oxoesters may be carried out in a similar



**Scheme 23** Cyanomethylation using  $\text{Ph}^-$  as EGB.

fashion using, for example,  $\text{PhCH}_2\text{COOEt}$  ( $\text{pK } 22.7$ ) instead of  $\text{PhCH}_2\text{CN}$  or  $\text{MeCN}$  [63].

Whether the dianion of azobenzene is able to deprotonate  $\text{MeCN}$  ( $\text{pK } 31.3$ ) has been discussed [62, 64, 68]. However, on a preparative scale generation of  $^-\text{CH}_2\text{CN}$  takes place at the potential of the second reduction of azobenzene, and reactions initiated by cyanomethylation of benzamide [108], carbonyl compounds (or their Schiff bases) or  $\alpha,\beta$ -unsaturated nitriles either present in situ [69, 109] or added subsequently [110–112] have been studied. A mixture of products is normally obtained.

#### 14.8.5

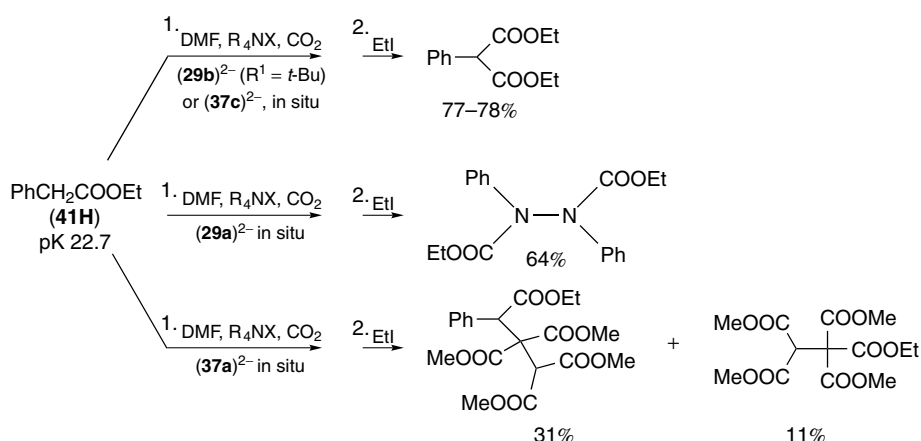
##### Carboxylation

The advantages of sterically hindered PBs have been demonstrated for the series (37a–c). The dianionic EGBs are all able to deprotonate ethyl phenylacetate, (41H), ( $\text{pK } 22.7$ ), and the anion (41) $^-$  is carboxylated in the presence of  $\text{CO}_2$  [68]. Using (37a) $^{2-}$  as an EGB, the product of Michael addition of (41) $^-$  to (37a) is formed

as well, and the subsequent alkylation of the carboxylated ethyl phenylacetate also leads to alkylation of (37aH) $^-$ , Scheme 24. Smaller amounts of the side products are obtained using the more bulky (37b) $^{2-}$  as an EGB and using (37c) $^{2-}$  effects clean carboxylation and alkylation of (41H), Scheme 24, [68]. In none of the cases, products derived from carboxylation of the EGBs were found. This, however, was the case using (29a) as a PB. Although (29a) $^{2-}$  is able to deprotonate (41H), the only product isolated was dicarboxylated and alkylated azobenzene. The more sterically hindered (29b) ( $\text{R}^1 = t\text{-Bu}$ ) used as a PB gave the intended product [68]. Both (29a) $^{--}$  and (29a) $^{2-}$  are also easily alkylated by  $\text{MeI}$  [67].

In the carboxylation of the less acidic diglycolic acid *N*-methylimide, (37b) $^{2-}$  was found to be superior to (29b) $^{2-}$  ( $\text{R}^1 = t\text{-Bu}$ ) as an EGB since the latter partially underwent cleavage of the *N*-*N*-bond [113].

A surprising *N*-carboxylation of amines and anilines using (33) $^-$  as EGB in  $\text{MeCN-Et}_4\text{NClO}_4$  has been reported [114]. Despite the fact that amines and anilines have  $\text{pK}$



**Scheme 24** Advantage of a sterically hindered probase in carboxylation of ethyl phenylacetate.

values in the range 30 to 40 (while **33H** has  $pK$  24.1), a yield of 30 to 90% of the alkyl or aryl carbamates were obtained by stepwise addition of the amine,  $CO_2$ , and EtI to the ex situ formed EGB [114].

The acidity of the *N*-protons in amides is considerably higher ( $pK$  typically in the range 20–26) than those of amines, and  $(37b)^{2-}$  has been successfully used as in situ formed EGB for *N*-carboxylation and subsequent cyclization of amides with leaving groups in the  $\alpha$ -position according to Scheme 25 [115].

#### 14.8.6

##### Cyclizations

Formation of 12 to 16-membered lactones in 66 to 75% yield from the corresponding  $\omega$ -bromo carboxylic acids can be carried out by addition of a solution of ex situ formed  $(33)^-$  to a dilute solution of the carboxylic acid at low temperature ( $-60^\circ C$ ) [116]. A crucial point in the selective reaction seems to be  $R_4N^+$ , which stabilizes the carboxylate ion and slows down bimolecular reactions for steric reasons. The yield of the cyclic product increases with increasing size of *R* [116].

Formation of cyclopropane derivatives by reaction between an  $\alpha,\beta$ -dihalo compound and an acidic methylene compound can, in principle, be initiated by direct cathodic formation of the anion

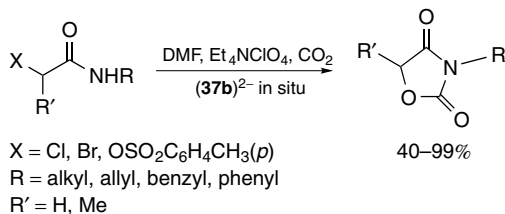
of the methylene compound but competing reduction of the halogen compound normally leads to low yields [117]. Higher yields are obtained using an easily formed EGB for the deprotonation step. Using **(29a)** as the PB in  $MeCN-Bu_4NClO_4$   $\alpha,\alpha$ -diactivated methylene compounds ( $XCH_2COOEt$ ,  $X = Ac, CN, COOEt$ ) gave, in the presence of 1,2-dibromoethane, 80 to 85% of the cyclopropane product [117]. An intramolecular version of the same reaction type using **(29a)** as the PB in  $DMF-Bu_4NBr$  gave 80 to 82% yield of the 1,1-dicarbomethoxycycloalkanes when  $Br(CH_2)_nCH(COOMe)_2$  ( $n = 4, 5$ ) were used as substrates [118].

Direct reduction of *O*-tosylglycolamides leads to cleavage and loss of the tosyl group but in situ formation in DMF of EGBs derived from **(29a)** or from  $Me_2CBrCOOEt$  leads to deprotonation of the amide nitrogen. The amide anion acts as a nucleophile toward unreacted starting material; further deprotonation takes place followed by cyclization to the diketopiperazine. However, small amounts of the oxazolidinone arising by nucleophilic attack on DMF is also formed, Scheme 26 [119].

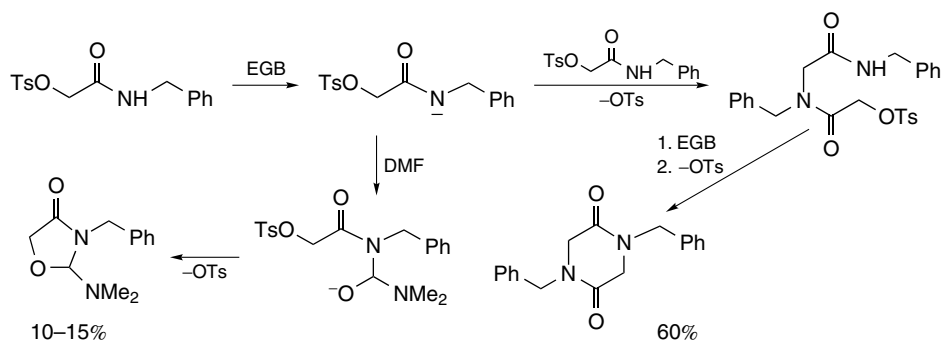
#### 14.8.7

##### Oxidative Conversions

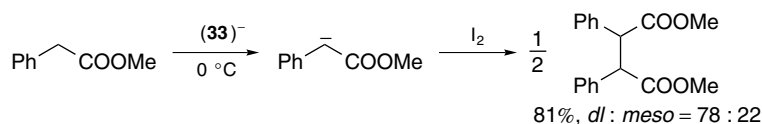
Homocoupling of aryl acetic acid derivatives has been achieved by deprotonation and oxidation by  $I_2$  as outlined



**Scheme 25** *N*-carboxylation of amides using EGB.



**Scheme 26** Dimerization and cyclization initiated by deprotonation of an amide by EGB.

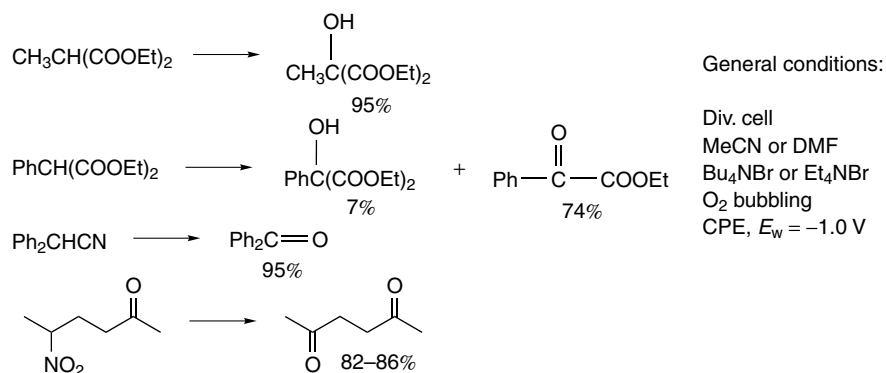


**Scheme 27** Oxidative homocoupling of anions formed by an EGB.

in Scheme 27 [120]. The EGB  $(33)^-$  was formed ex situ in  $\text{DMF}\cdot\text{Bu}_4\text{NClO}_4$  and gave much higher yields than when the reaction was carried out using conventional bases with metal counterions [120]. Good yields but lower *dl*:*meso* ratios were obtained for other aryl groups than for Ph. Nonstoichiometric amounts of  $\text{I}_2$  could be used in combination with anodic regeneration. An optically active oxazolidinone

derivative of phenyl acetic acid gave selectively the *R,R*-dimer [120].

Deprotonation of carbon acids by  $\text{O}_2^{\cdot-}$  in the presence of  $\text{O}_2$  (i.e. when  $\text{O}_2^{\cdot-}$  is formed in situ by bubbling  $\text{O}_2$  through the catholyte) can lead to oxidative conversion of the carbon acid by reaction between the deprotonated substrate and the excess  $\text{O}_2$  [107, 121–123], in some cases by consumption of less than stoichiometric



**Scheme 28** Oxidative conversion of carbon acids initiated by deprotonation by superoxide.

amounts of charge. Examples are given in Scheme 28, and more can be found in Ref. [123]. The product anion, may to some extent, deprotonate the acidic substrate whereby the reaction becomes partially catalytic. Monoactivated methylene compounds give lower yields, typically 5 to 50% [123, 124].

The mechanism by which the hydroperoxide intermediate, (42) (Scheme 29) is converted into the products of Scheme 28 is not clear. The follow-up reaction of (42) may be diverted by reaction with an enone that undergoes epoxidation in 85 to 90% yield, Scheme 29, [121]. The epoxidation reaction does not take place directly from  $O_2$  and  $O_2^{\cdot-}$  but requires the formation of an intermediate of type (42) derived either from the enone or from an external carbon acid as in Scheme 29. Yields are considerably improved using an external carbon acid since the Michael addition between the enone and its anion otherwise competes with the epoxidation. For

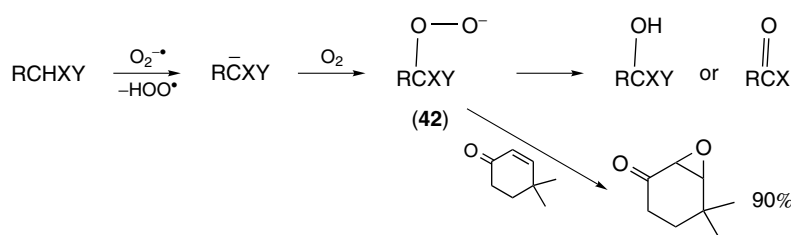
slowly reacting enones, two- or four-fold excess of the carbon acid may be required since the “normal” oxidative conversion of (42) competes with the reaction with the enone [121].

#### 14.8.8 Condensations

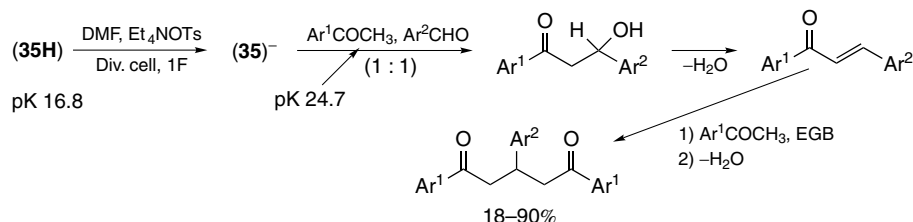
Despite a very unfavorable proton transfer using  $(35)^-$  as an EGB, condensation of acetophenone with an aromatic aldehyde took place within a matter of hours. The reaction led to  $\alpha,\beta$ -unsaturated ketones, which underwent the Michael addition with a second equivalent of deprotonated ketone, Scheme 30, [80, 81]. The EGB was generated ex situ.

#### 14.8.9 Miscellaneous Reactions

A very efficient pathway to formation of esters by reaction of a carboxylic acid



**Scheme 29** Reaction of deprotonated carbon acids with oxygen.



**Scheme 30** EGB-initiated aldol condensation between benzaldehyde and acetophenone.

with an alkylhalide is by use of  $(33)^-$  as EGB. Yields were generally between 80 and 100% using a three-step procedure: formation of the EGB *ex situ*, addition of the acid, and addition of the alkyl halide, all reactions carried out in DMF at room temperature [116]. This may be compared to the simpler two-step procedure [81] in which the carboxylate ions are formed by direct reduction of the acids followed by addition of the alkyl halide leading to somewhat lower yields.

Formation of 1-arylsulfonylcyclobutenes via  $\beta$ -elimination from *trans* 1,2-diarylsulfonylcyclobutane takes place in low yields (<25%) using conventional bases [72]. Using either  $O_2$  or  $(32)$  as a PB in DMF- $Et_4NClO_4$  gave the cyclobutenes in 50 to 70% yields. Workup was facilitated using  $O_2$  as the PB [72].

The detailed mechanism of the Favorskii rearrangement in Scheme 31 is not clear. Equimolar amounts of the carbon acid and the ketone are used, and initial

deprotonation of the carbon acid has to take place. Of the two PBs applied,  $(29a)$  was superior and both were superior to  $NaCH(COOEt)_2$  as a base (40%) [125].

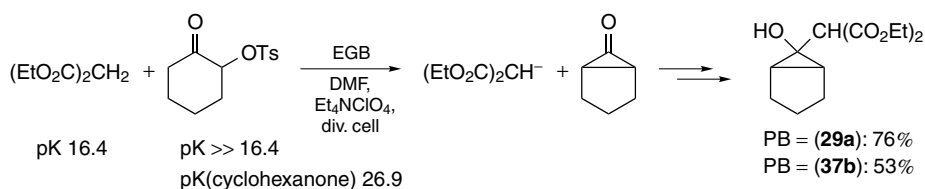
Using  $O_2$  as the PB (and in the absence of diethyl malonate) 2-tosyloxycyclohexanone gave, after 2 F reduction at the potential of  $O_2^{\cdot-}$ -formation, exclusively methyl cyclopentanecarboxylate (75%) when MeI was added after the electrolysis [126, 127].

## 14.9 Base-Catalyzed Reactions

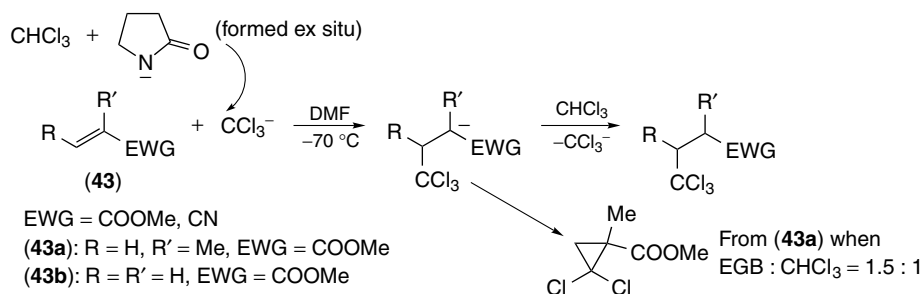
### 14.9.1

#### Michael Additions

Addition of  $CCl_3^-$  to  $\alpha,\beta$ -unsubstituted esters or nitriles,  $(43)$ , can be carried out using less than stoichiometric amounts of  $(33)^-$ , since the anion formed by addition is sufficiently basic to deprotonate  $CHCl_3$  [128]. Yields in the range 70 to 80% are obtained when  $R = H, Me$ . The acidic



**Scheme 31** EGB-initiated Favorskii rearrangement.



**Scheme 32** Catalytic vs. stoichiometric amounts of EGB.

$\text{HCCl}_2\text{COOMe}$  could be used instead of  $\text{CHCl}_3$  with similar results [128]. For (**43a**), cyclization by intramolecular  $\text{S}_{\text{N}}2$  reaction competes with protonation, and when stoichiometric amounts of EGB and  $\text{CHCl}_3$  were used, the cyclopropane derivative was the main product, Scheme 32, since protonation of the intermediate anion now has to be from (**33H**), which is less acidic than  $\text{CHCl}_3$  [128].

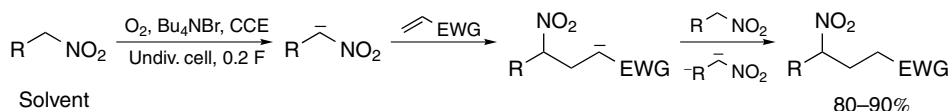
The trichloromethylation of (**43b**) has also been carried out using polyacrylamides as PBs [74]. Copolymers of *N*-methylacrylamide (57% of the monomer units) and styrene ( $M_n \approx 4000$ ) gave the best result (94%) using  $\text{CHCl}_3$ :(**43b**) = 3:1 with addition of the polymeric EGB in an amount of reduced *N*-methylacrylamide units corresponding to the amount of (**43b**) (i.e. *not* a catalytic reaction) in DMF. Lower yields (72% and 89%) were obtained with a homopolymer of *N*-methylacrylamide and with a copolymer of *N*-methylacrylamide and *N,N*-dimethylacrylamide [74].

Typical acceptors in Michael additions are reducible and their radical anions often undergo dimerization (hydrodimerizations). Either the radical anions or more likely the dimer dianions can act as EGBs toward the donor in the Michael addition. Since the reaction is catalytic in base when the product anion is more basic than the donor anion, the Michael addition can take place by reduction of a small fraction (2–10%) of the acceptor [129]. The reaction takes place in 20 to 77% yield

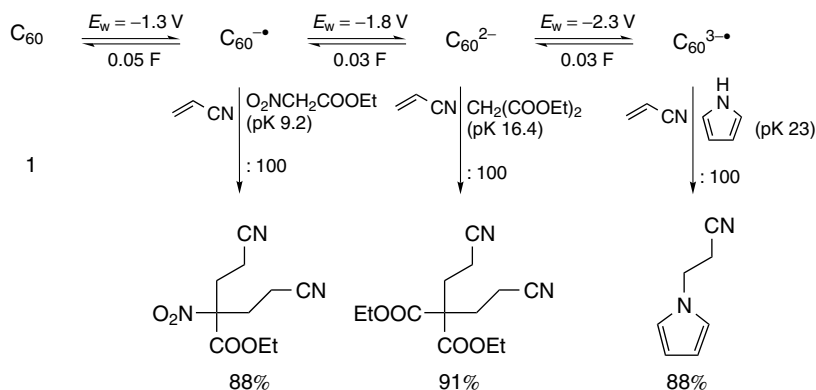
using  $\text{CH}_2=\text{CHX}$  ( $\text{X} = \text{CN}, \text{COOEt}$ ) as acceptors and dialkyl malonates as donors in  $\text{DMF-Pr}_4\text{NBF}_4$ . The susceptibility of the PBs (**37a** and **b**) toward the Michael addition (cf. Sect. 14.8.5) resulted in 60 to 93% yield of the addition product when subjected to a similar procedure [129].

Superoxide anion formed *in situ* in a solution exposed to air (i.e. with only a small concentration of  $\text{O}_2$ ) has been used as an EGB to generate nitroalkane anions that may add to activated alkenes or to carbonyl compounds [130, 131]. An example is shown in Scheme 33. The reaction is catalytic since the product anion can act as a base toward the nitroalkane. Using the nitroalkane as the solvent favors the proton transfer pathway over the competing addition of the product anion to a second molecule of activated alkene, a pathway that may lead to polymerization [130]. In some cases, better yields of the Michael addition product were obtained if a stoichiometric amount of the anion was formed *ex situ* (with  $\text{O}_2$  as the PB), and the activated alkene added subsequently [130, 132].

A catalytic amount (0.001 eq.) of (**29a**) can also be used as the PB for the conversion in Scheme 33 [122], and a one-pot conversion of the addition product (formed within 4–22 h) to the corresponding ketone could be performed by letting  $\text{O}_2$  into the solution and generating  $\text{O}_2^{\cdot-}$ . Conversion of the nitro group into the ketone then took place according to the last reaction in Scheme 28 with an overall yield of 46 to 62% [122].



**Scheme 33** Superoxide-catalyzed Michael addition.



**Scheme 34** Michael additions catalyzed by one-, two- or threefold reduced fullerene.

Application of the increasingly basic EGBs formed by the consecutive one-electron reductions of the fullerene,  $C_{60}$ , is illustrated in Scheme 34 (potentials vs.  $Fc/Fc^+$ ) [94]. The reactions in Scheme 34 are catalytic since the addition products are less acidic than the carbon acids used, and the reactions can therefore be carried out using very small amounts of the PB. The reactions were carried out in a divided cell using MeCN/PhMe (2 : 3)- $Bu_4NBr$ .

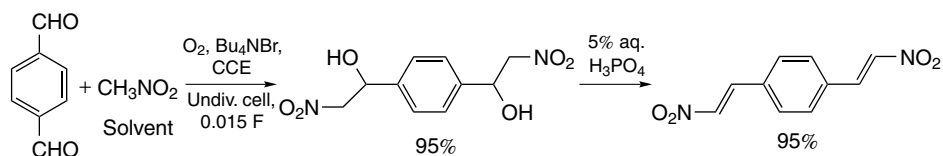
#### 14.9.2

##### Reactions Involving Aldehydes and Ketones

The procedure described in Sect. 14.9.1 for addition of nitroalkane anions to activated alkenes can also be used for addition to aldehydes. The nitroalcohol formed can be dehydrated in almost quantitative yields in dilute  $H_3PO_4$  in a subsequent step [130, 131]. Starting with

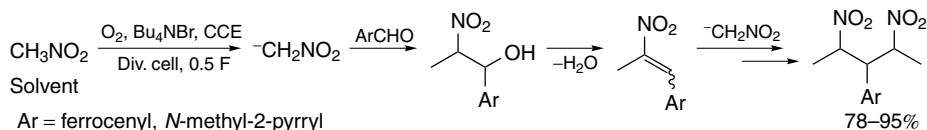
terephthalaldehyde, this process provides a convenient route to the highly electron deficient 1,4-bis(nitroethene) derivative, Scheme 35. This bis(activated alkene) could be used as the Michael acceptor in a superoxide anion-initiated reaction with a (strong) carbon acid in MeCN, cf. Scheme 33. A strong carbon acid,  $EtOOCCH_2NO_2$  (pK 9.2) is required for protonation of the addition product which is also necessary for preventing polymerization.

For aromatic or heteroaromatic monoaldehydes,  $ArCHO$ , an efficient procedure has been developed for synthesis of 1,3-dinitro compounds [132]. Rather than in situ reduction of  $O_2$ , the  $O_2$  reduction is carried out in a divided cell with the aliphatic nitro compound as the solvent. Charge corresponding to 0.5 F with respect to the aldehyde is passed through the cell, the current is switched off



**Scheme 35** Superoxide-catalyzed formation of nitroalcohols.





**Scheme 36** EGB-catalyzed formation of dinitro compounds.

and the aldehyde added. Using these conditions, elimination of water from the addition compound takes place almost quantitatively for aldehydes with an electron-donating substituent. Addition of the second nitronate anion then takes place giving the 2-aryl-1,3-dinitro compound, Scheme 36 [133]. When Ar = phenyl, 9-anthryl, 2-furyl and 2-thienyl nitroalcohols were formed together with 30 to 53% of the 2-aryl-1,3-dinitro compound. Aldehydes with strongly electron withdrawing groups (2- or 4-pyridinecarbaldehyde, 3-nitrobenzaldehyde or 5-nitro-2-furaldehyde) gave only the nitroalcohols [132].

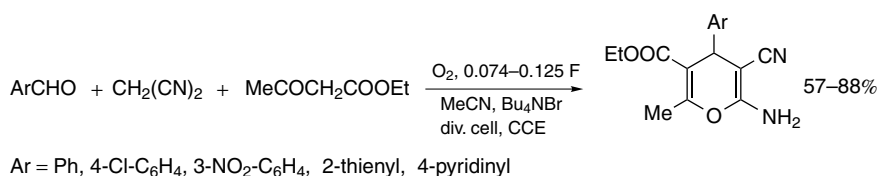
Dehydration of the alcohol is suppressed when the reaction is carried out in DMF-Et<sub>4</sub>NOTs containing 1.85 M water at  $-40^\circ\text{C}$  [134]. Under these conditions, aromatic or heteroaromatic aldehydes react with PhCH<sub>2</sub>CN, PhCH<sub>2</sub>COOEt or PhSCH<sub>2</sub>CN to give the corresponding alcohols in 52 to 90% yield using 0.04 to 0.12 F [134]. It is not clear whether O<sub>2</sub> was present in the catholyte or reduction products derived from the aldehydes served as the EGB.

A one-pot reaction of aromatic or heteroaromatic aldehydes with equimolar

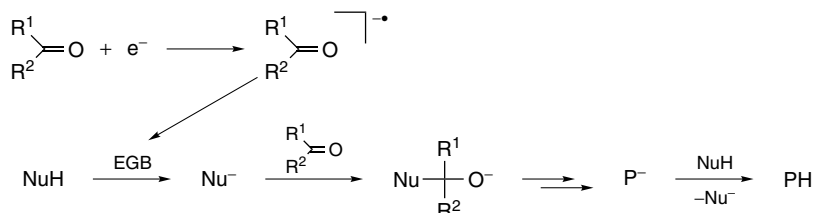
amounts of malonitrile and ethyl acetoacetate to give as final product substituted 2-amino-4*H*-pyranes, Scheme 37, has been reported [135]. The reaction is catalyzed by in situ formed O<sub>2</sub><sup>•−</sup>, and product formation has been rationalized as consisting of EGB-catalyzed Knoevenagel condensation of the aldehyde and malonitrile followed by the EGB-catalyzed Michael addition of the ethyl acetoacetate, and finally the Thorpe-Ziegler cyclization to give the pyran [135].

A number of electrocatalytic reactions have been reported in which the EGB is derived by initial reduction of an aldehyde or a ketone that at the same time functions as the electrophile in a coupling reaction [136–139]. It is likely that the actual EGB is a dimer dianion of the carbonyl compound or a dianion of the carbonyl compound formed by disproportionation. The general principle is outlined in Scheme 38. The reactions become catalytic when the product anion, P<sup>−</sup>, is protonated by the weak acid, NuH, whereby the nucleophile, Nu<sup>−</sup>, is regenerated.

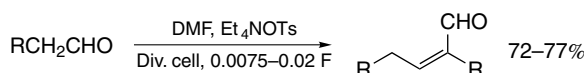
One example is cathodically induced aldol condensation of aliphatic aldehydes, Scheme 39, [138]. In contrast to the



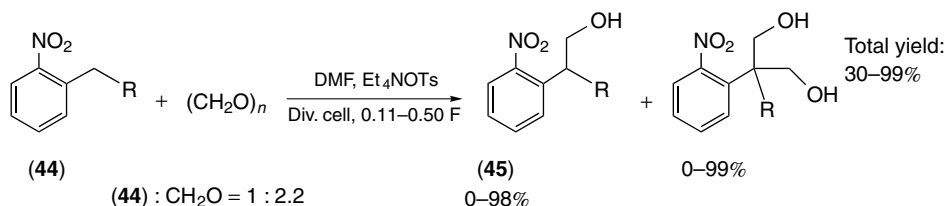
**Scheme 37** EGB-catalyzed condensation and subsequent Michael addition.



**Scheme 38** EGB-catalyzed addition of a nucleophile to a carbonyl compound using the carbonyl compound as probase.



**Scheme 39** EGB-catalyzed aldol condensation with the aldehyde as probase.



**Scheme 40** EGB-catalyzed hydroxymethylation of nitroalkylbenzenes.

noncatalytic mixed condensations of acetophenones with aromatic aldehydes using (35H) as a PB, [81] (Sect. 14.8.8) the reaction in Scheme 39 was not followed by a Michael addition.

Another example is the electrocatalytic reaction between aromatic carbonyl compounds and dialkyl phosphonates. Here, rearrangement of the product anion leads to a phosphate as the product [136].

Hydroxymethylation of 2- or 4-nitroalkylbenzenes, (44), takes place by passing a catalytic amount of charge through a solution of (44) and  $(\text{CH}_2\text{O})_n$  Scheme 40 [140]. (44) is reduced at the electrode and electron transfer from (44) $^{\cdot-}$  to  $\text{CH}_2\text{O}$  is envisaged [140]. The resulting formyl radical anion then acts as an EGB toward

unreduced (44), and the carbanion adds to  $\text{CH}_2\text{O}$  giving the hydroxymethylated product in the anionic form. The chain reaction is then sustained by proton transfer from (44) to give the neutral product, (45). In most cases, the reaction goes on to give the bis(hydroxymethylated) substrate as the main product by deprotonation of (45), Scheme 40, [140].

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## 15

### Indirect Electrochemical Reactions

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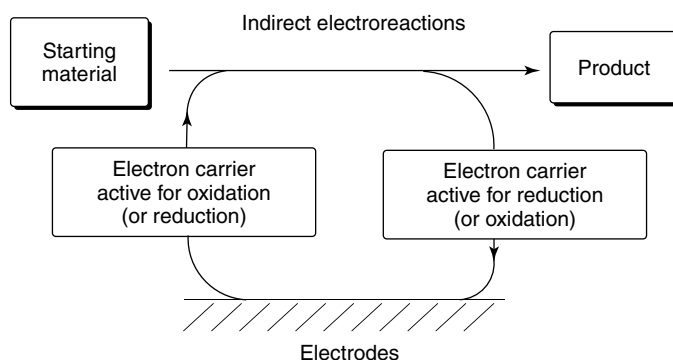
### 15.1 Introduction

Indirect electrochemical methods have been intensively studied, especially from the viewpoint of development of innovative synthetic methods in industrial organic chemistry. The indirect procedure is required when the direct method is unsuitable because (1) the desired reaction does not proceed sufficiently because of an extremely slow reaction or a very low current efficiency; (2) the electrolysis lacks product-selectivity and thus offers only a low yield; (3) tar and products cover the surface of the electrode, interrupting the electrolysis. Indirect electrochemical techniques involve the recycling of mediators (or electron carriers) in a redox system, as depicted in Fig. 1 [1–24].

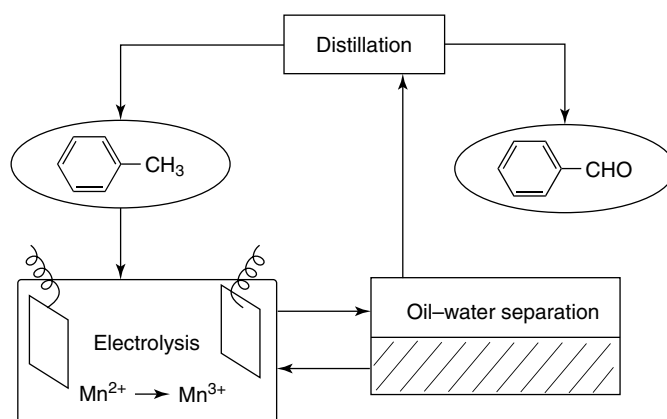
The redox electron carrier produced at the electrode can react homogeneously with organic substrates that may be dissolved, suspended, or emulsified, to provide the desired oxidized (or reduced) products as well as the regenerated redox electron carrier. The cycle is completed when the reduced (or oxidized) electron carrier is reoxidized (or rereduced) at the anode (or cathode) to regenerate the original oxidizing (or reducing) redox electron carrier. The recycling of a suitable redox electron carrier in this way is referred to as

an “indirect electrochemical reaction”. For example, the oxidation consists of two well-defined processes: (1) electrooxidation of the mediator to a higher oxidation state; (2) chemical oxidation of the organic substrate with the mediator. The technique in which these two processes are carried out together in a single electrolysis is called the “in-cell method,” while the process involving separated electrochemical and chemical steps is called the “ex-cell method.” Generally, redox electron carriers include a variety of metals, nonmetals, and organic redox systems. For example, the indirect oxidation of toluene using Mn(III) gives a quantitative yield of benzaldehyde. Mn(III) can be regenerated through electrolysis of the Mn(III) species [25]. The direct oxidation of toluene produces benzaldehyde together with many by-products. The flow diagram for benzaldehyde production from toluene (in-cell method) by indirect electrolysis is presented in Fig. 2. A schematic layout of an indirect ex-cell method is shown in Fig. 3 [1]. A large-scale preparation of anisaldehyde from *p*-methoxytoluene illustrates this idea. The ex-cell method can also be used for the manufacture of anthraquinone from anthracene [1]. The process involves a two-step reaction. The reaction conditions for the first step must permit a sufficiently fast electrochemical reaction of the carrier.





**Fig. 1** Recycling of a mediator (electron carrier) for indirect electroreaction.



**Fig. 2** Indirect electrooxidation of toluene by an in-cell method.

Additionally, the rate of the homogeneous reaction of the carrier with the substrate must be considered.

Also important is the choice of a suitable redox system for the indirect electroreduction of particular substrates. For instance, toluene can be oxidized with  $\text{Mn(III)}$  or  $\text{Ce(IV)}$  to benzaldehyde, whilst with  $\text{Cr(VI)}$  benzoic acid is obtained. On the other hand, anthraquinone is commercially prepared from anthracene by employing chromic acid oxidation.

The feasibility of the indirect redox process strongly depends on whether the product can be readily separated

from a highly acidic media after the electrolysis [3]. The selection of electrode materials is also very important. In most cases, lead is used as the electrode material for both the anode and the cathode. An improvement in its corrosion resistance [26] as well as in its overvoltage characteristic has been made by alloying it with a small amount of a second metal such as silver or antimony [27]. Lead dioxide-coated carbon or graphite electrodes can be used as anodes. In place of platinum electrodes, platinum-coated titanium electrodes are used in some cases [28].

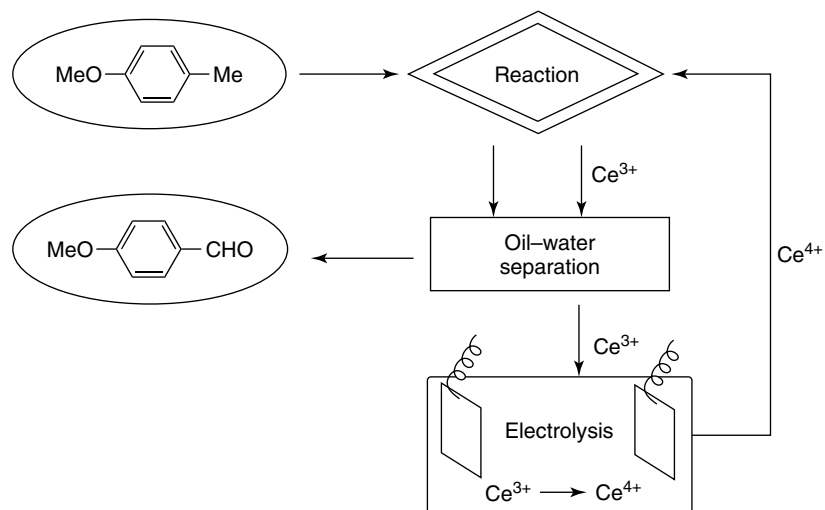


Fig. 3 Electrooxidation of *p*-methoxytoluene with cerium salt by an ex-cell method.

As mentioned above, the critical feature of indirect electrochemical reactions is the correct choice of a redox system. Specific examples of indirect electrochemical reactions with a great variety of redox carriers are presented in the following sections.

## 15.2

### Indirect Electrooxidation

#### 15.2.1

##### Indirect Oxidation with Halide Ions

Nonmetal oxidizing redox systems that involve halide ions and organic compounds as electron carriers play an extremely important role for functionalization of organic molecules.

Halide ions, in general, are typical nonmetal type electron carriers. The following halogen redox systems for indirect electrooxidation are well established;  $\text{Cl}^-/[\text{Cl}]^+$ ,  $\text{Br}^-/[\text{Br}]^+$ ,  $\text{Br}^-/\text{BrO}^-$ ,  $\text{I}^-/[\text{I}]^+$ ,  $\text{IO}_3^-/\text{IO}_4^-$ , and so on [29, 30]. The oxidation potentials ( $E^\circ$ ) of halogen redox

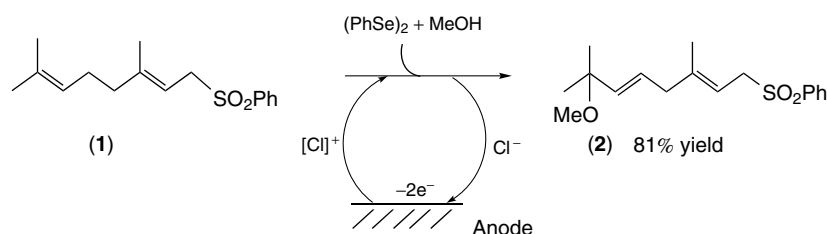
systems under basic and acidic conditions are listed in Table 1 [31]. The combination of these redox systems with a suitable substrate has been shown to be extremely effective in organic synthesis. Thus, by considering such novel combinations, there are numerous possibilities of finding new types of electrosynthetic reactions.

##### 15.2.1.1 Chloro Cation $[\text{Cl}]^+$ -assisted Indirect Oxidation

The combination of the electrogenerated chloro cation  $[\text{Cl}]^+$  with diphenyldiselenide is a typical example of the functionalization of an olefin. The electrochemical oxyselenation-deselenation of (1) to (2) proceeds in a  $\text{MeOH}\text{-NaCl}\text{-(Pt)}$  system (Scheme 1) [32]. The bromide salt-promoted oxyselenation of olefins is discussed in Sect. 15.2.2. Penicillin (3) can be converted into the oxazoline-azetidinone (4) by a chloride salt-promoted paired reaction in a  $\text{MeOH}\text{-}t\text{-BuOH}(5:1)\text{-MgCl}_2\text{-(Pt)}$  system at  $-40^\circ\text{C}$  in 74~93% yield (Scheme 2) [33, 34]. This conversion probably involves an initial attack of an

**Tab. 1** Electrode reactions of  $X^-$  and their redox potentials ( $E^\circ$ ) in basic and acidic solutions

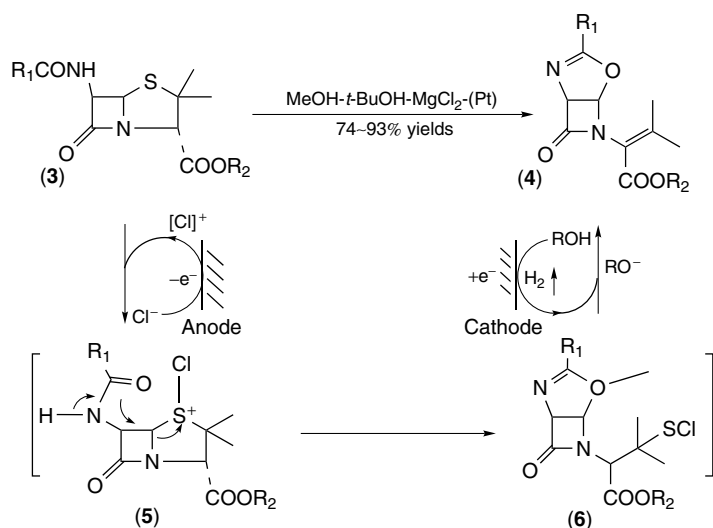
Electrode reaction under basic conditions	$E^\circ$	Electrode reaction under acidic conditions	$E^\circ$
$\text{Cl}^- + 2\text{OH}^- \xrightarrow{-2e^-} \text{ClO}^- + \text{H}_2\text{O}$	0.89	$\text{Cl}^- (2\text{Cl}^-) \xrightarrow{-2e^-} [\text{Cl}]^+ (\text{Cl}_2)$	1.39
$\text{ClO}^- + 2\text{OH}^- \xrightarrow{-2e^-} \text{ClO}_2^- + \text{H}_2\text{O}$	0.66	$1/2\text{Cl}_2 + \text{H}_2\text{O} \xrightarrow{-e^-} \text{HClO} + \text{H}^+$	1.59
$\text{ClO}_2^- + 2\text{OH}^- \xrightarrow{-2e^-} \text{ClO}_3^- + \text{H}_2\text{O}$	0.33	$\text{HClO} + \text{H}_2\text{O} \xrightarrow{-2e^-} \text{HClO}_2 + 2\text{H}^+$	1.64
$\text{ClO}_3^- + 2\text{OH}^- \xrightarrow{-2e^-} \text{ClO}_4^- + \text{H}_2\text{O}$	0.36	$\text{HClO}_2 + \text{H}_2\text{O} \xrightarrow{-2e^-} \text{ClO}_3^- + 3\text{H}^+$	1.21
		$\text{ClO}_3^- + \text{H}_2\text{O} \xrightarrow{-2e^-} \text{ClO}_4^- + 2\text{H}^+$	1.19
$\text{Br}^- + 2\text{OH}^- \xrightarrow{-2e^-} \text{BrO}^- + \text{H}_2\text{O}$	0.76	$\text{Br}^- (2\text{Br}^-) \xrightarrow{-2e^-} [\text{Br}] + (\text{Br}_2)$	1.087
$\text{Br}^- + 6\text{OH}^- \xrightarrow{-2e^-} \text{BrO}_3^- + 3\text{H}_2\text{O}$	0.61	$1/2\text{Br}_2 + 3\text{H}_2\text{O} \xrightarrow{-5e^-} \text{BrO}_3^- + 6\text{H}^+$	1.52
$\text{I}^- (2\text{I}^-) \xrightarrow{-2e^-} [\text{I}] + (\text{I}_2)$	0.536	$1/2\text{I}_2 + 3\text{H}_2\text{O} \xrightarrow{-5e^-} \text{IO}_3^- + 6\text{H}^+$	1.195
$3\text{I}^- \xrightarrow{-2e^-} \text{I}_3^-$	0.536	$1/2\text{I}_2 + \text{H}_2\text{O} \xrightarrow{-e^-} \text{HIO} + \text{H}^+$	1.45
$\text{I}^- + 2\text{OH}^- \xrightarrow{-2e^-} \text{IO}^- + \text{H}_2\text{O}$	0.49		

 $E^\circ$ : Standard redox potential (25 °C).**Scheme 1** Electrochemical oxyselenation-deselenation.

activated chlorine atom on divalent sulfur, giving an intermediate (5), which may suffer an intramolecular nucleophilic attack of the amide group at the C(7) position to produce the oxazoline ring compound (6). Subsequent reaction with the base produced at the cathode gives (4).

Oxidative cleavage of the C(1)–C(2) bond of aziridines and 2-amino-1-cycloalkanols, giving the corresponding keto

nitriles, has been performed by oxidation with electrogenerated reactive-halogen species (e.g.  $[\text{Cl}^+]$  and  $[\text{Br}^+]$ ) [35]. Indirect electrooxidation using sodium chloride as a redox catalyst is equally effective for  $\alpha$ -methoxylation of dipeptide esters. Application for the synthesis of chiral heterocyclic compounds along with their usage as synthetic building blocks has been investigated [36].



**Scheme 2** Conversion of penicillin into a oxazoline-azetidinone.

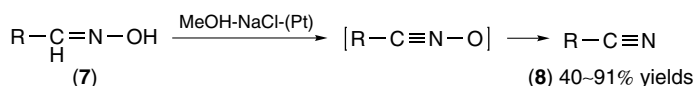
Aldoximes (7) are converted into the corresponding nitriles (8) by using halogen ions as mediators (Scheme 3). Sodium chloride affords the best result among the supporting electrolytes ( $\text{Cl}^- > \text{Br}^- > \text{I}^- > \text{ClO}_4^- > \text{TsO}^-$ ) [37].

Hypervalent iodobenzene chlorofluorides, a useful fluorinating reagent, has been used for indirect anodic gem-difluorination [38, 39].

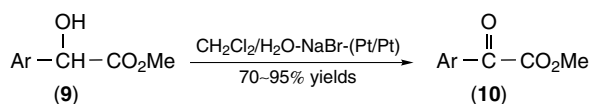
#### 15.2.1.2 Bromo Cation $[\text{Br}]^+$ -assisted Indirect Oxidation

The conversion of  $\alpha$ -hydroxyketones and aliphatic  $\alpha$ -hydroxy esters (9), with

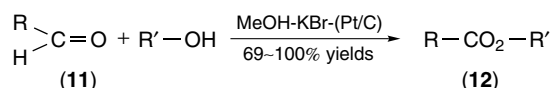
bromide as mediator, leads to the corresponding  $\alpha$ -keto carbonyl compounds (10) in good yields (Scheme 4) [40]. Hemiacetals formed *in situ* from aldehydes (11) can be oxidized indirectly to the corresponding esters (12) (Scheme 5) [41]. Electrochemical deacetylation of 3-oxobutanoate derivatives leads to substituted esters [42]. The reaction is initiated by the bromination of the active methylene group by an electrogenerated bromonium ion followed by base-catalyzed deacetylation, and terminated by reductive dehalogenation of the  $\alpha$ -bromo carbonyl compound at the cathode.



**Scheme 3** Conversion of aldoximes into nitriles.



**Scheme 4** Conversion of  $\alpha$ -hydroxyesters into  $\alpha$ -ketoesters.

**Scheme 5** Conversion of aldehydes into esters.

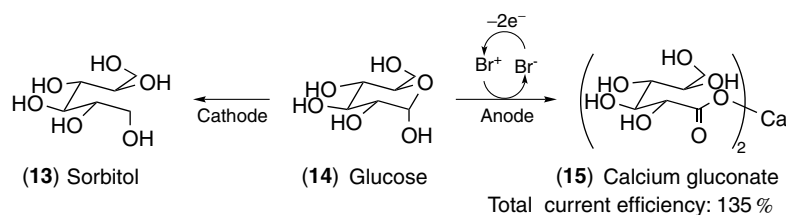
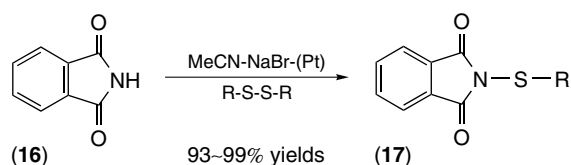
The conversion of glucose (**14**) into both sorbitol (**13**) and gluconic acid (**15**) has been realized in an aq. NaBr/CaCO<sub>3</sub>/Na<sub>2</sub>SO<sub>4</sub>-(C/Pb) system (Scheme 6) [43, 44]. *O*-Glycosylation of thioglycosides with alcohol is successfully performed by electrooxidation, in the presence of catalytic amounts of ammonium or alkali bromide, to afford *O*-glycosides [45]. In a similar way, [Br]<sup>++</sup>-assisted electrochemical *N*-glycosylation of silylated pyrimidines with protected arylthioriboses has been attained [46]. Pyrimidine bases and their nucleosides have been indirectly brominated, in chlorinated, and iodinated to their 5-bromo(or halo) derivatives [47].

Deprotection of thioesters under neutral conditions has been achieved by electrooxidative cleavage of the carbon–sulfur

bond in an aq. MeCN-Bu<sub>4</sub>NBF<sub>4</sub>-(Pt) system [48].

The combination of the electrogenerated bromo cation [Br]<sup>+</sup> with diphenyldisulfide is a typical example of hetero–hetero bonds.

The direct electrosynthesis of S–N bonds from disulfides and amines has been shown to occur through a reaction of the amine with the oxidized disulfide being a strong electrophile. In contrast to the results, the cross-coupling of phthalimide (**16**) with disulfide does not proceed in a direct electrolysis. However, the electrosynthesis of sulfenimides (**17**) can be achieved by a [Br]<sup>+</sup>-mediated cross-coupling reaction of imides with disulfides (Scheme 7). The electrolysis of a mixture of (**16**) and dicyclohexyl disulfide in an MeCN-NaBr-(Pt) system affords

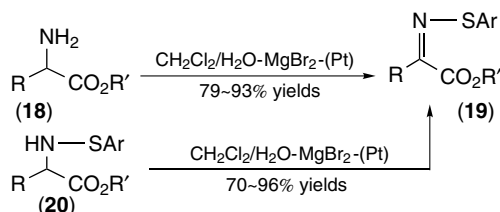
**Scheme 6** Simultaneous oxidation of glucose to gluconic acid and reduction to sorbitol.**Scheme 7** Br<sup>+</sup>-mediated cross coupling to form S–N bonds.

the corresponding (17) ( $R = \text{cyclohexyl}$ ) in quantitative yield [49].

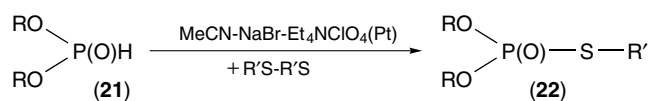
The direct electrosynthesis of sulfenimines (19) from  $\alpha$ -aminoalkanoates (18) and diaryl disulfides proceeds in a  $\text{CH}_2\text{Cl}_2\text{-H}_2\text{O-MgBr}_2\text{-(Pt)}$  system in 70~96% yields (Scheme 8) [50]. Electrolysis of sulfenamides (20) is considered to be the intermediates in the direct conversion of (18)  $\rightarrow$  (19).

The P-S bond formation of dialkyl (or diaryl) phosphites (21) with disulfide proceeds in an  $\text{MeCN-NaBr/Et}_4\text{NClO}_4\text{-(Pt)}$  system at 20~25 °C, giving phosphorothiolates (22) in 72~91% yields (Scheme 9) [51]. In this reaction, both sodium iodide and sodium chloride are less effective than sodium bromide. Depending on the nature of the cation, the yields of (22) decrease in the order of  $\text{Na}^+$  (91%) >  $\text{K}^+$  (76%) >  $\text{Li}^+$  (69%) >  $\text{Et}_4\text{N}^+$  (46%).

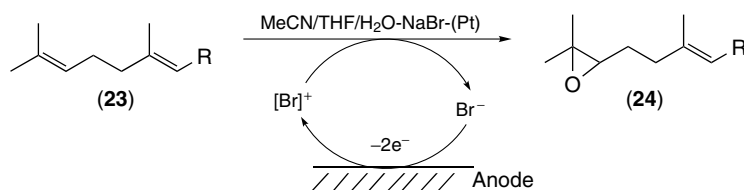
Electrochemical epoxidation of olefins has been developed for the production of ethylene and propylene oxides in aqueous sodium chloride or bromide solution. However, associated with these electrolyses are difficulties in achieving product selectivity as well as in obtaining high yields of the epoxides. Recently, a regioselective  $\omega$ -epoxidation of polyisoprenoids (23) to (24), promoted by electrooxidation in an  $\text{MeCN/THF/H}_2\text{O-NaBr-(Pt)}$  system, has been achieved (Scheme 10) [52]. The electrochemical conversion of (21) ( $R = \text{CH}_2\text{SO}_2\text{Ph}$ ) to (22) (88% yield) is superior to the NBS method (69%) or to *m*-CPBA oxidation (72%). Other bromides are also effective for epoxidation in the following order:  $\text{NaBr}$  (91%) >  $\text{Et}_4\text{NBr}$  (82%) >  $\text{KBr}$  (78%) >  $\text{LiBr}$  (75%) >  $\text{NH}_4\text{Br}$  (13%). The utility of the method is exemplified by the facile syntheses of *dl*-iron [53]



**Scheme 8** Sulfenimines from  $\alpha$ -aminoalkanoates.



**Scheme 9** Phosphorothiolates from dialkyl- and diaryl phosphites.

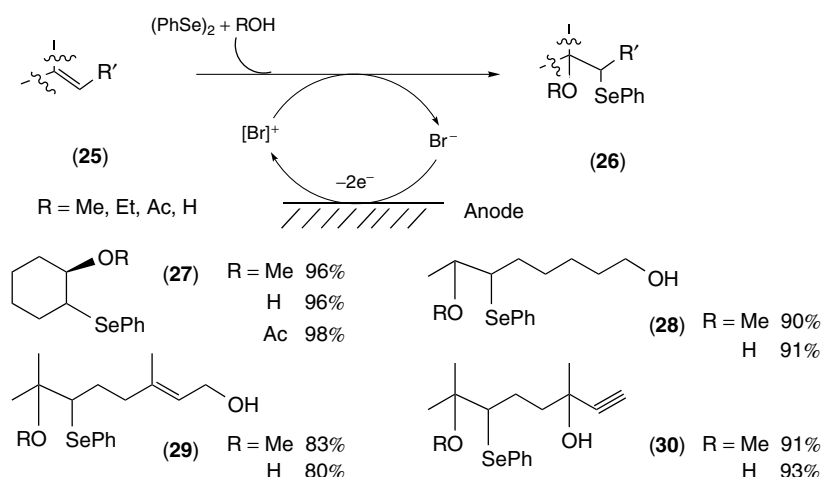


**Scheme 10** Regioselective  $\omega$ -epoxidation of polyisoprenoids.

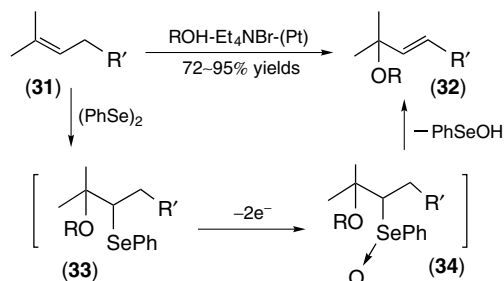
and piperonal [54]. The use of polymeric quaternary ammonium bromide as a precursor of a polymeric reagent for electroepoxidation of olefins has been recently reported [55].

Oxyselenation is a powerful tool for functionalization in synthetic organic chemistry. Electrochemically generated  $[\text{Br}]^+$  or bromine reacts with  $(\text{PhSe})_2$ , producing  $\text{PhSeBr}$ . Attack of  $\text{PhSeBr}$  on the olefin (**25**) gives a selenated intermediate followed by solvolysis to provide (**26**) and a bromide ion (Scheme 11). A typical electrolysis is carried out in a  $\text{MeOH-Et}_4\text{NBr}/\text{H}_2\text{SO}_4$  (trace)/ $(\text{PhSe})_2$ -(Pt) system in an undivided cell. Some results

(**27**, **28**, **29**, and **30**) are presented below. The electrochemical hydroxyselenation proceeds readily in an  $\text{MeCN-H}_2\text{O}(3:1)$ - $\text{NaBr-Pt}$  system. A similar method is employed in the conversion of various olean-12-ene sapogenols into olean-11-en-28,13b-olides [56]. One-step conversion of olefins (**31**) into allylic alcohols (**32**) ( $\text{R} = \text{H}$ ) and ethers (**32**) ( $\text{R} = \text{alkyl}$ ) can also be performed by an electrooxidative oxyselenation-deselenation sequence via (**33**)  $\rightarrow$  (**34**) (Scheme 12) [57, 58]. The reaction proceeds preferentially in an  $\text{ROH-Et}_4\text{NBr-(PhSe)}_2$ -(Pt) system without using sulfuric acid. In this manner, *dl*-rose oxide (**37**) can be prepared from citronellol (**35**)



Scheme 11 Oxyselenation of alkenes.

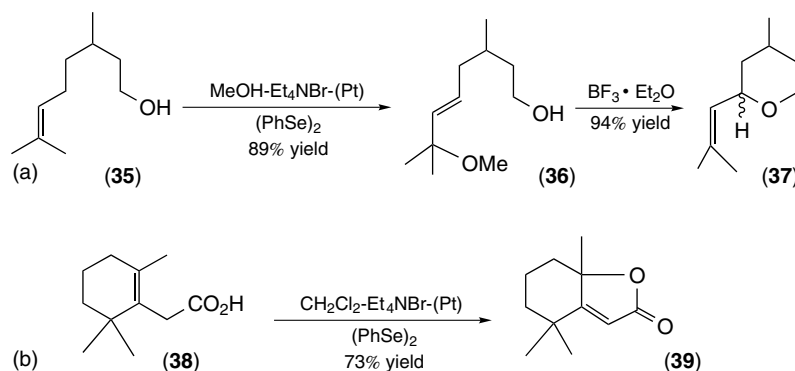


Scheme 12 Oxyselenation-deselenation of alkenes to allyl alcohols.

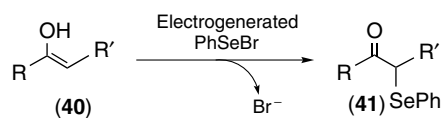
by electrochemical allyloxylation *via* oxy-selenation followed by a demethoxylation cyclization of (36) by treatment with  $\text{BF}_3$ -etherate in 85% overall yield (Scheme 13a). Similarly, a one-step synthesis of *dl*-dihydroactinidiolide (39) can be performed by electrochemical intramolecular oxy-selenation-deselenation of (38) (Scheme 13b).  $\alpha$ -Phenylselenoketones are valuable precursors to  $\alpha$ ,  $\beta$ -unsaturated and  $\alpha$ -exo-methylene carbonyl compounds. A facile access to  $\alpha$ -phenylselenenyl carbonyl compounds (41) by electrooxidation of the ketone (40) is available in an MeCN(or AcOH)- $\text{MgBr}_2/(\text{PhSe})_2\text{-Et}_4\text{NBr}$ -(Pt) system (Scheme 14) [59]. The effect of halide ions is remarkable. The bromide ion is the most effective and the iodide

ion is the least. Magnesium ion seems to be essential for promoting enolization (40  $\rightarrow$  41). The method can also be applied to alicyclic systems.

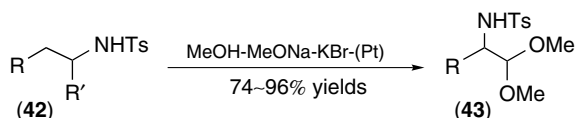
Benzyl alcohol can be smoothly converted to benzaldehyde by electrochemically recycled  $\text{BrO}^-$  as an oxidizing catalyst in an emulsion system prepared from a mixture of water, amyl acetate, and 2%  $\text{Bu}_4\text{NHSO}_4$  [60]. A different hypobromite reagent is provided by an electrochemical oxidation of a cross-linked poly-4-vinylpyridine in an MeCN- $\text{H}_2\text{O}$ -HBr-(Pt) system [61]. Secondary alcohols can be oxidized by this method to give ketones in high yields. The electrooxidation of *N*-monoalkyltosylamides (42) in a two-phase system consisting of cyclohexane



**Scheme 13** Cyclic ethers and lactones by allyloxylation-cyclization of unsaturated alcohols and carboxylic acids.



**Scheme 14**  $\alpha$ -Phenylselenenyl carbonyl compounds from ketones.



**Scheme 15** Conversion of alkyltosylamides into  $\alpha$ -tosylamino aldehyde acetals.

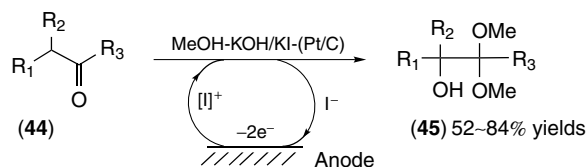


and water containing KOH and KBr under heating yields pyrrolidine derivatives in 52~100% yields [62]. Employing different oxidation conditions such as the MeOH-MeONa/KBr-(Pt) system results for (42) in  $\alpha$ -(tosylamino) aldehyde acetals (43) in 74~96% yields (Scheme 15) [62].

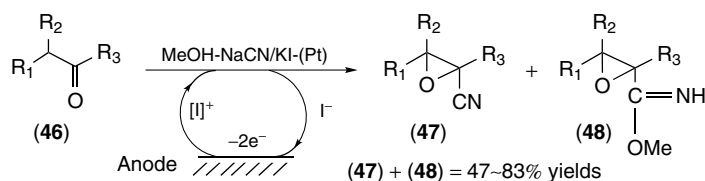
### 15.2.1.3 Indirect Oxidation with $[I]^+$ and $IO_4^-$ as Electron Carriers

The transformation of aldehydes (44) ( $R_3 = H$ ) and ketones (44) ( $R_3 = \text{Alkyl}$ ) to the corresponding  $\alpha$ -hydroxylated acetals (45) has been performed in an MeOH-KOH/KI-(Pt/C) system. The first step of the oxidation is considered to proceed by the attack of an electrogenerated active iodine species  $[I]^+$  to an enolized carbonyl group (Scheme 16) [63]. The electrochemical dimethoxylation of cyclic ketones proceeds by indirect

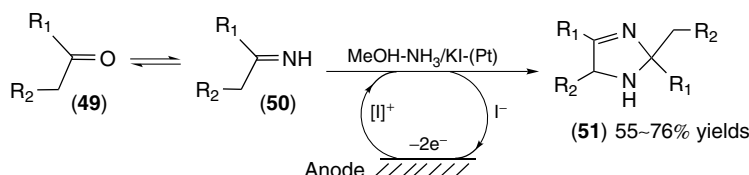
electrooxidation in an MeOH-NaI-(C/Pt) system in an undivided cell [64–66]. The iodine-assisted methoxylation would take place in the following way: (1) initial iodination by the reaction of electrogenerated iodine yields  $\alpha$ -iodocycloketone that undergoes a second iodination to give diiodocycloketone; (2) the substitution of the iodo group by electrogenerated methoxyl anion affords the dimethoxide. The conversion of alkyl aryl ketones to methyl  $\alpha$ -arylalkanoates is achieved in a TMOF(trimethyl orthoformate)-LiClO<sub>4</sub>/I<sub>2</sub>-(Pt) system. Use of a *commutator* is essential to suppress the deposition of nonconducting materials on the surface of the cathode [67]. Oxiranes (47) and (48) are produced in fairly good yields when ketones are electrooxidized in an MeOH-NaCN/KI-(Pt) system (Scheme 17) [68]. In an



**Scheme 16** Transformation of aldehydes and ketones to  $\alpha$ -hydroxy acetals.



**Scheme 17** Oxiranes from ketones.



**Scheme 18** 2,2-Dihydro-1H-imidazoles from ketones.

ammonia-methanol solution, ketones (49) can be transformed into the corresponding 2,5-dihydro-1H-imidazoles derivatives (51) *via* imines (50). The electrolysis is carried out in an MeOH-MeONa/NH<sub>3</sub>/KI-(Pt) system (Scheme 18) [69].

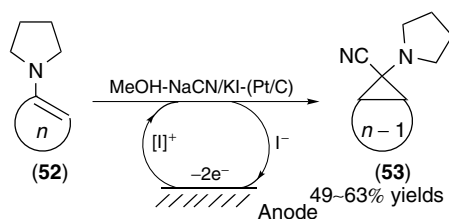
Ring construction of pyrrolidinoenamines (52) of alicyclic ketones, giving the bicyclo compound (53), has been attained by using the iodide ion as a mediator in an MeOH-NaCN-(Pt) electrolysis system [70] (Scheme 19).

Oxidation of alcohols (54) with the iodo cation [I]<sup>+</sup> as an electron carrier yields ketones (55) in 52~84% yields in an aqueous (*t*-BuOH)-KI-(C or Pt) system in an undivided cell (Scheme 20) [71]. The electrogenerated iodo cation is considered to behave as an oxidizing agent. Indirect

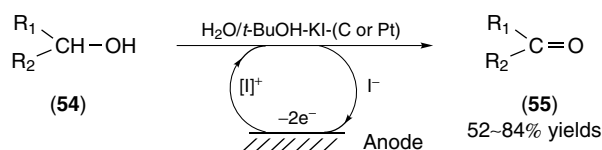
electrooxidation of D-glucitol 1,3,4,6-diacetals can lead to 2-keto-L-gluconic acid 3,5,4,6-diacetals by using sodium iodide as a mediator [72].

The Ritter reaction [6] proceeds by the electrooxidation of alkyl iodides (56) in an MeCN-(Pt) system to form *N*-alkyl acetamides (58) (Scheme 21). Attack of carbenium ion intermediate – from dissociation of the initially formed alkyl cation radical – to acetonitrile would give the iminium cation (57). However, a different mechanism is proposed, whereby the alkyl iodide reacts with the electrogenerated iodo cation [I]<sup>+</sup> [73].

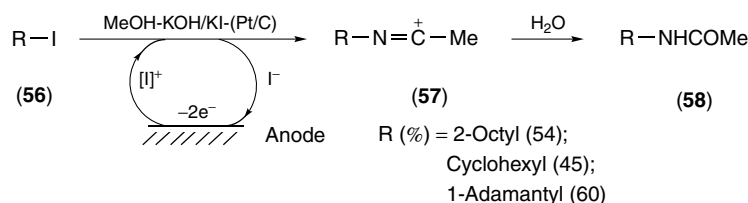
Formation of *N,N*-dialkylformamides occurs successfully by electrolysis of a mixture of *sec*-amines and formaldehyde in an aqueous KI-(Pt/C) system in 57~93%



**Scheme 19** Cyclopropanation of enamines.



**Scheme 20** Iodide-mediated oxidation of alcohols.



**Scheme 21** Conversion of alkyl iodides into acetamides.

yields. In this system, the electrooxidation of  $I^-$  probably provides an active  $[I]^+$  species that associates with the lone-pair electron on the nitrogen atom. Electrooxidation of enamines in similar conditions affords the corresponding  $\beta$ -keto amines in 31~60% yields [74]. Iodo cation  $[I]^+$ -assisted electrooxidative preparation of nitrones has been performed in an MeOH-NaI-(Pt) system in good yields [75].

Formation of the P–N bond has been observed when the cross-coupling of dialkylphosphites (59) with amines (60) proceeds by an iodo cation  $[I]^+$ -promoted electrooxidation, affording *N*-substituted dialkylphosphor-amidates (61) (Scheme 22) [76]. Lack of alkali iodide in the electrolysis media results in the formation of only a trace of (61), indicating that the iodide plays an important role in the P–N bond-forming reaction. In contrast, usage of sodium bromide or sodium chloride brings about inferior results since the current drops to zero before the cross-coupling reaction is completed.

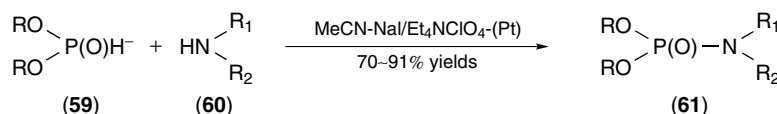
Iodine-assisted cleavage of the vicinal diol group of dextran has been investigated [77]. Dialdehyde starch (63) can

be produced readily by oxidative cleavage of a vicinal diol of starch (62) with periodic acid regenerated by electrolysis (Scheme 23) [78]. 2,3-Butanediol can be cleaved anodically by using a periodate/iodate redox mediatory system to give acetoaldehyde [79]. The electrolytic conversion of iodic acid to periodic acid occurs in a 5%  $H_2SO_4$ -( $PbO_2$ -Pb) system at pH 0.7~2.0 at 7% iodic acid concentration. The transformation of (62) to (63) by electro-regenerated periodic acid proceeds in more than 90% conversion yields. The cleavage of electron-rich double bonds of (64) to the corresponding aldehydes (65) using a ruthenium-silicon-tungstate  $[(Bu_4N)_5(H_2O)RuSiW_{11}O_{39}]$  and  $IO_4^-/IO_3^-$  double redox system has been developed. The electrolysis of aryl substituted olefins yields the corresponding aldehydes in 59~79% yields (Scheme 24) [80].

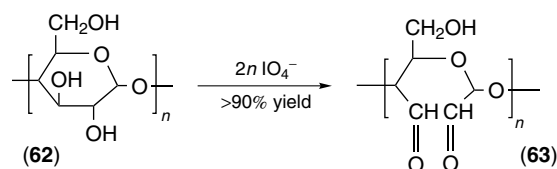
### 15.2.2

#### Indirect Oxidation with Organic Mediators

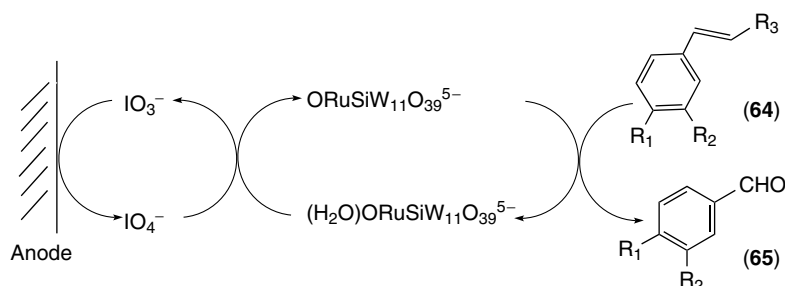
Besides metal and nonmetal redox systems, organic redox systems are also important electron carriers for indirect electrooxidation.



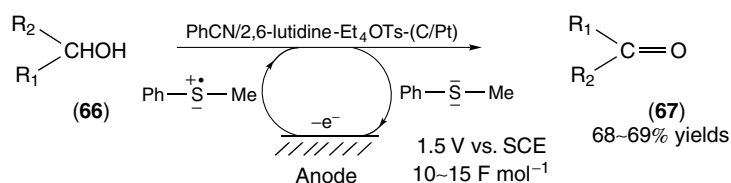
**Scheme 22** Cross coupling of dialkylphosphites with amines to dialkylphosphor-amidates.



**Scheme 23** Dialdehyde starch by oxidative cleavage.



**Scheme 24** Mediated cleavage of aryl olefin to aryl aldehyde.



**Scheme 25** Oxidation of secondary alcohols with thioanisole as organic redox catalysts.

#### 15.2.2.1 Mediators Containing Sulfur and Selenium Elements

The oxidation of secondary alcohols (**66**) to (**67**) is possible by indirect electrooxidation utilizing thioanisole as an organic redox catalyst in a PhCN-2,6-lutidine-Et<sub>4</sub>NOTs-(C/Pt) system at 1.5 V vs. SCE [81] and is also performed in the presence of 2,2,2-trifluoroethanol [82]. It is suggested that the initially formed cation radical sulfide species derived from the direct discharge of the sulfide provides phenylmethyl-alkoxysulfonium ions, which are transformed to (**67**) and thioanisole.

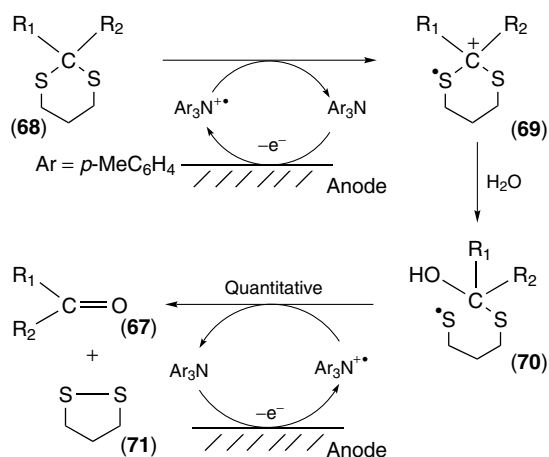
A novel electron carrier-mediator system has been devised by employing a PhCN-2,6-lutidine-Et<sub>4</sub>NBr-(C/Pt) system in the presence of *n*-octyl methyl sulfide as a mediator. The reaction is probably initiated by the discharge of the bromide ion, which provides bromo cation or bromine. Alkoxysulfonium ions produced by the reaction of the sulfide with bromo cation

are also considered to be key intermediates [83]. Synthesis of chromans by photosensitized electrooxidation of sulfides mediated by methylene blue has also been achieved [84]. Electrosynthesis of  $\alpha$ -keto acetals by a selenium-catalyzed transformation of aryl methyl ketones has been accomplished [85].

#### 15.2.2.2 Mediators Containing Nitrogen

An effective and mild electrocatalytic procedure for the deprotection of the 1,3-dithiane group of (**68**), giving the ketone (**67**), has been developed by using a small amount of tris(*p*-tolyl)amine as a homogeneous electron-transfer catalyst (Scheme 26) [86]. The scope and limitations are discussed in detail [87]. The method can be applied also for oxidative removal of the 4-methoxybenzyl thioether protecting group from poly-cystinyl peptides [88].

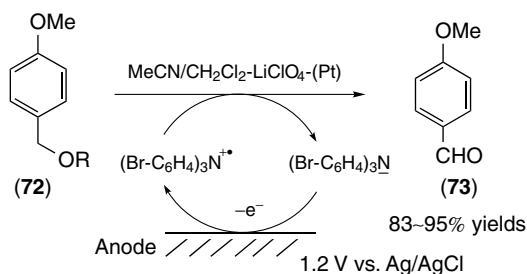
The brominated triaryl amines have been shown to be good mediators for



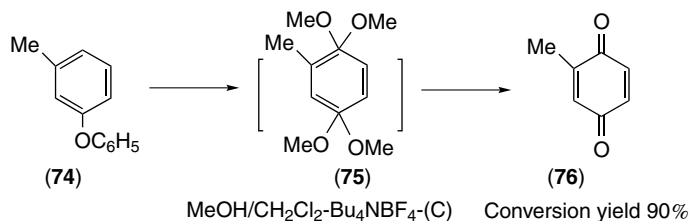
**Scheme 26** Electrocatalytic deprotection of 1,3-dithianes.

the indirect electrooxidation of organic compounds [89]. The stable cation radical of tris(*p*-bromophenyl)amine can be used as a homogeneous electron-transfer catalyst for the mild oxidative removal of the *p*-methoxybenzyl ether-protecting group [90–92]. The electrolysis of (72) is

carried out in an MeCN/CH<sub>2</sub>Cl<sub>2</sub>(5:1)-LiClO<sub>4</sub>-(Pt) system in a divided cell at an anode potential of +1.2 V versus Ag/AgCl to generate (73) in 83–95% yields (Scheme 27) [93–96]. The reversible potential of the redox couple (Br-C<sub>6</sub>H<sub>4</sub>)<sub>3</sub>N<sup>+</sup>•/(Br-C<sub>6</sub>H<sub>4</sub>)<sub>3</sub>N (*E*<sup>o</sup> = +1.05 V vs. SCE) is



**Scheme 27** Oxidative cleavage of the benzyl ether-protecting group.



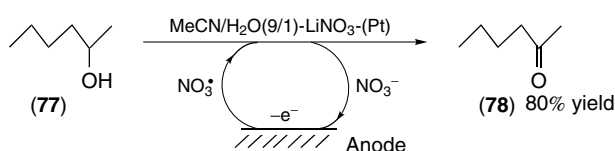
**Scheme 28** Oxidation of *m*-phenoxytoluene to 2-methylbenzoquinone.

about 550 mV more negative than the irreversible oxidation potentials of (72). The method usually gives 75~95% yields of R-OH. Tris(*p*-bromophenyl)amine and can also be used as an organic mediator for the oxidation of *m*-phenoxytoluene (74), giving 2-methylbenzoquinone (76) (Scheme 28) [97] and also for benzyl alcohols in high yield [98]. It is found that the amine also proves to be an effective mediator for the indirect oxidation of amines. Benzyl amines can be converted to the corresponding Schiff base in excellent yield [99].

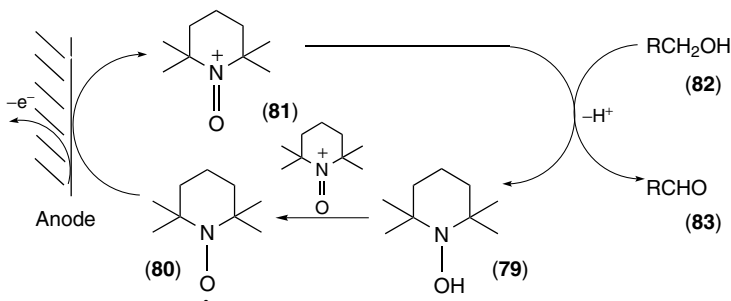
Nitrogen compound-mediated electrooxidations of alcohols to aldehydes and ketones have recently been developed. The nitrate radical-mediated oxidation of secondary alcohols (77)→(78) occurs in an MeCN-H<sub>2</sub>O(9:1)-LiNO<sub>3</sub>-(Pt) system (Scheme 29) [100]. Primary alcohols are also electrooxidized indirectly by using electrogenerated nitrate radicals as a mediator in an MeOH-LiNO<sub>3</sub>/H<sub>2</sub>SO<sub>4</sub>-(Pt) system to give the corresponding

acetals as major products [101]. The indirect electrooxidation of ethers with nitrate radicals proceeds smoothly in an aq. MeCN-LiNO<sub>3</sub>-(Pt) system to afford the corresponding acids and/or ketones in good yields [102]. Recently, addition of nitrate radicals to a C≡C triple bond in the alkynyl ethers, as *cis*(or *trans*)-alkoxy-2-(hex-1-ynyl)-cyclopentanes (or cyclohexanes) yields anellated tetrahydrofuran derivatives with high diastereoselectivity, including oxidative, self-terminating radical cyclizations [103]. Hydroxylamines can be converted into the corresponding nitrones by electrooxidation with bromocation mediators [104].

Nitroxyl radicals can be oxidized to *N*-oxo ammonium salts that are themselves useful oxidants for primary and secondary alcohols. Recently, the behavior of different nitroxides as catalysts for alcohol oxidation has been studied by quantum chemical calculations [105]. Generally, 2,2,6,6-tetramethylpiperidine *N*-oxyl (TEMPO) (80) is used for the



**Scheme 29** Nitrate-mediated oxidation of alcohols.



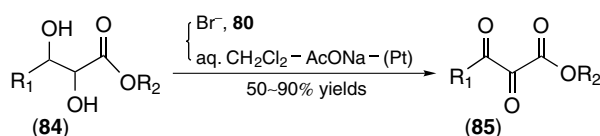
**Scheme 30** Nitroxyl-radical-mediated selective oxidation of primary alcohols.

indirect electrooxidation of alcohols (**82**) (Scheme 30) [106]. The nitroxyl-mediated oxidation of alcohols to aldehydes (**83**) and ketones is achieved in an MeCN-LiClO<sub>4</sub>-2,6-lutidine-(Pt) system in the presence of (**80**) in a divided cell. Primary alcohols are selectively oxidized at  $-60^{\circ}\text{C}$  and secondary alcohols react more slowly than primary ones.

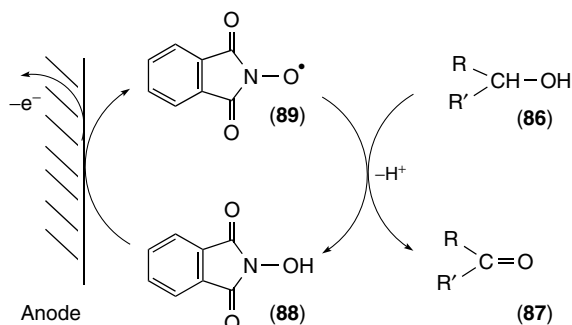
A double mediatory system consisting of *N*-oxoammonium salts and active bromine species, generated from 2,2,6,6-tetramethylpiperidine-1-oxyl derivatives and bromide ions as recyclable reagents is shown to be useful for the selective electrooxidation of primary and secondary alcohols to aldehydes and ketones, in an aqueous-organic two-phase system [107]. The double mediatory system is superior to both direct oxidation and combinations [108]. Such a double-mediatory system is found to be effective for the preparation of vicinal tricarbonyl compounds (**85**) from 2,3-dihydroxyalkanoates

(**84**) (Scheme 31) [109]. 4-Chlorobutanal, cyclopropylaldehyde, and *m*-phenoxybenzaldehyde are also prepared in the two-phase system [110]. Indirect electrooxidation of 6 $\beta$ -methyl-3 $\beta$ , 5 $\alpha$ -dihydroxy-16 $\alpha$ , 17 $\alpha$ -cyclohexanopregnan-20-one are indirectly electrooxidized to the corresponding 5 $\alpha$ -hydroxy-3,20-dione using sodium bromide and substituted TEMPO as the mediating couple [111].

A graphite felt electrode bearing the cross-linked 4-amino-TEMPO for alcohol oxidation has been prepared and the modified electrode can be used for the conversion of nerol to neral selectively with a turnover number higher than 1560 [112]. 4-Amino-TEMPO, immobilized through an amide linkage to poly(acrylic acid), can be used for the electrocatalytic oxidation of thiols [113]. Methyl-substituted diols on a TEMPO-modified graphite felt electrode in the presence of (–)-sparteine undergo enantioselective, electrocatalytic lactonization in good enantiomeric excess



**Scheme 31** Oxidation of 2,3-dihydroxyesters to vicinal tricarbonyl compounds with bromide and **80**.



**Scheme 32** Oxidation of alcohols with *N*-hydroxyphthalimides as mediator.

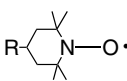
more than 95% in acetonitrile [114, 115]. However, the kinetic resolution of 2-phenylethanol by indirect oxidation with TEMPO in the presence of sparteine has been questioned [115].

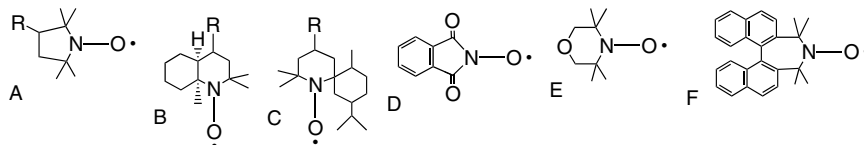
(*d,l*)-*cis,cis*-4-Benzoyloxy-2,2,8 $\alpha$ -trimethyldecahydroquinolinyl-*N*-oxyl is found to be a good mediator for selective electrooxidation of primary and secondary alcohols [116]. The first example of the electrochemical method for the efficient, enantioselective oxidation of racemic *sec*-alcohols using a chiral nitroxyl radical, for example, (6*S*,7*R*,10*R*)-4-acetylamino-2,2,7-trimethyl-10-isopropyl-1-azaspiro[5.5]un-

decane-*N*-oxyl, has been reported [117]. A preparative electrocatalytic oxidation of racemic 1-phenylethanol on the chiral *N*-oxyl catalyst yields 50~70% of enantiopurity (*S* values: 4.1~4.6). Several examples of *N*-oxyl derivatives are listed in Table 2.

*N*-Hydroxyphthalimide (**88**) has also been shown to be an effective mediator for the oxidation of alcohols [120]. The oxidation process depicted in Scheme 32 is suitable for the oxidation of secondary alcohols (**86**). *N*-Hydroxyphthalimide also plays an important role as a mediator for deprotection of the 4-phenyl-1,3-dioxolane

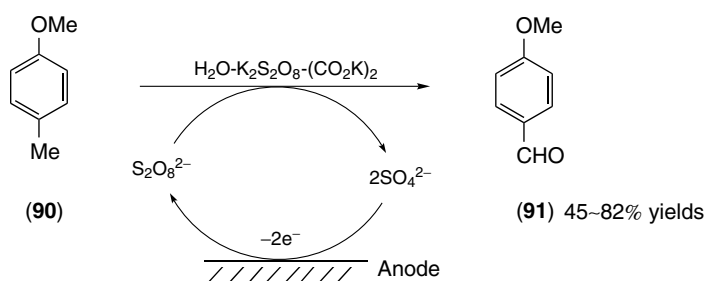
Tab. 2 *N*-Oxyl derivatives used for electrooxidation of alcohols as mediators

Mediator system <i>N</i> -Oxyl	R	Electrolysis conditions	Product yield [%]	References
 (4-R-TEMPO)	H	aq.CH <sub>2</sub> Cl <sub>2</sub> -NaBr/NaHCO <sub>3</sub> -(Pt)	90	108
		aq.CH <sub>2</sub> Cl <sub>2</sub> -Bu <sub>4</sub> NPF <sub>6</sub> -(Pt)	—	105
	CN	aq.CH <sub>2</sub> Cl <sub>2</sub> -NaBr/NaHCO <sub>3</sub> -(Pt)	91	108
	OMe	aq.CH <sub>2</sub> Cl <sub>2</sub> -NaBr/NaHCO <sub>3</sub> -(Pt)	93	105, 108
	PhCO <sub>2</sub>	aq.CH <sub>2</sub> Cl <sub>2</sub> -NaBr/NaHCO <sub>3</sub> -(Pt)	90~98	108
		aq.CH <sub>2</sub> Cl <sub>2</sub> -NaBr/NaHCO <sub>3</sub> -(Pt)	70	110
			61~93	107, 109
	NHAc	aq.CH <sub>2</sub> Cl <sub>2</sub> -NaBr/NaHCO <sub>3</sub> -(Pt)	—	111
	<i>p</i> -Bu-C <sub>6</sub> H <sub>4</sub> CO <sub>2</sub>	aq.CH <sub>2</sub> Cl <sub>2</sub> -NaBr/AcONa-(Pt)	93	108
	Polymer-CONH	MeCN-NaClO <sub>4</sub> /2,6-Lutidine-(C)	90*	112~115
A	PhCO <sub>2</sub> CH <sub>2</sub>	MeCN/H <sub>2</sub> O(7/1)-Et <sub>4</sub> NBF <sub>4</sub> -(Pt)	33*	118
B	PhCO <sub>2</sub>	MeCN-NaClO <sub>4</sub> /2,6-Lutidine-(C)	75	119
C	NHAc	MeCN-NaClO <sub>4</sub> /2,6-Lutidine-(C)	82.7~96.7	116
D	—	MeCN-NaClO <sub>4</sub> -(C)	51.4~63.9	117
E, F	—	MeCN-NaClO <sub>4</sub> -(C)	54~81	120~122
	—	aq.CH <sub>2</sub> Cl <sub>2</sub> -Bu <sub>4</sub> NPF <sub>6</sub> -(Pt)	—	105



\*Current efficiency.





**Scheme 33** Oxidation of *p*-methoxytoluene to anisaldehyde with peroxodisulfate as mediator.

protecting group as well as the vicinal position to amides and lactams in 54~81% yields [121, 122].

### 15.2.3

#### Indirect Oxidation with Other Redox Systems

Redox systems other than halide salts are also used for catalytic indirect electrooxidation. For instance, *p*-methoxytoluene (90) can be oxidized in an aqueous  $\text{K}_2\text{S}_2\text{O}_8\text{-(CO}_2\text{K)}_2$  system to give anisaldehyde (91)

in 45~82% yield (Scheme 33) [123]. Silver salts, cupric sulfate, copper(II) oxide, and copper metal can be used in place of  $(\text{CO}_2\text{K})_2$ . The quinone/hydroquinone redox systems also play an important role for the electrooxidative conversion of alcohols to aldehydes. Conversions have been achieved in a solvent-free system [124]. A glassy carbon electrode with modified quinone/hydroquinone has also been used for the oxidation [125]. Flavin analogs proved to be useful for the photoinduced oxidation of benzyl alcohols [126].

**Tab. 3** Metal in redox systems and their oxidation-reduction potentials ( $E^\circ$ )

Redox system	$E^\circ$ (N.H.E.) value in acidic media
$\text{Co}^{3+} + e^- \longrightarrow \text{Co}^{2+}$	2.00
$\text{Ce}^{4+} + e^- \longrightarrow \text{Ce}^{3+}$	1.81
$\text{MnO}_4^- + 8\text{H}^+ + 5e^- \longrightarrow \text{Mn}^{2+} + 4\text{H}_2\text{O}$	1.51
$\text{Mn}^{3+} + e^- \longrightarrow \text{Mn}^{2+}$	1.51
$\text{PbO}_2 + 4\text{H}^+ + 2e^- \longrightarrow \text{Pb}^{2+} + 2\text{H}_2\text{O}$	1.46
$\text{Cr}_2\text{O}_7^{2-} + 14\text{H}^+ + 6e^- \longrightarrow 2\text{Cr}^{3+} + 7\text{H}_2\text{O}$	1.33
$\text{Ti}^{3+} + 2e^- \longrightarrow \text{Ti}^+$	1.25
$\text{MnO}_2 + 4\text{H}^+ + 2e^- \longrightarrow \text{Mn}^{2+} + 2\text{H}_2\text{O}$	1.23
$\text{Fe}^{3+} + e^- \longrightarrow \text{Fe}^{2+}$	0.77
$\text{Fe}(\text{CN})_6^{3-} + e^- \longrightarrow \text{Fe}(\text{CN})_6^{4-}$	0.69
$\text{Sn}^{4+} + 2e^- \longrightarrow \text{Sn}^{2+}$	0.15
$\text{TiO}^{2+} + 2\text{H}^+ + e^- \longrightarrow \text{Ti}^{3+} + \text{H}_2\text{O}$	0.10
$\text{Ti}^{3+} + e^- \longrightarrow \text{Ti}^{2+}$	-0.37
$\text{Cr}^{3+} + e^- \longrightarrow \text{Cr}^{2+}$	-0.41

## 15.2.4

**Metal Ion-assisted Indirect Oxidation****15.2.4.1 Indirect Oxidation with Metal Ion Redox Systems**

Metal ions that are suitable as oxidizing or reducing agents are listed in Table 3 together with their oxidation potentials [1]. After oxidizing organic substrates, the resulting metal ions in a low-valent state may be reoxidized by electrolysis and this way converted to oxidants in a high oxidation state, thus forming the redox loop shown in Fig. 1.

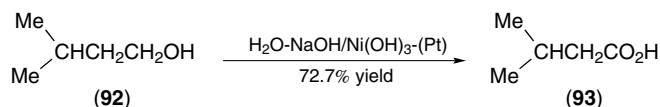
Success in indirect electrooxidation with a metal redox carrier depends on the choice of a metal ion (1) that is best suited for the desired functionalization; (2) that is soluble in the electrolysis media in both the high and the low oxidation states; (3) that is expected to undergo electrooxidative regeneration with high current efficiency as well as to react with the substrate in a high yield; (4) that can be readily separated from the products;

(5) that can be used without further purification before and after electrolysis; and (6) that can preferably be used in the in-cell method.

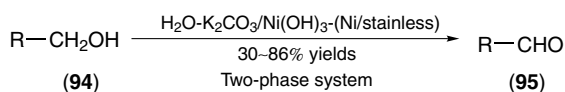
**15.2.4.2 Indirect Oxidation with Nickel (Ni) and Cobalt (Co) Compounds**

Primary alcohols are readily oxidized to acids by Ni(III) hydroxide as the electron carrier. An example is the electrooxidation of isoamyl alcohol (**92**) in H<sub>2</sub>O-NaOH/Ni(OH)<sub>3</sub>-(Pt) to give isovaleric acid (**93**) in a good yield (Scheme 34) [127]. A Ni metal complex is also effective for methanol oxidation [128]. The intermediary aldehydes (**95**) are isolable by employing a two-phase system in 30~86% yields (Scheme 35) [129]. Under basic conditions, secondary alcohols are readily oxidized into the corresponding ketones [130].

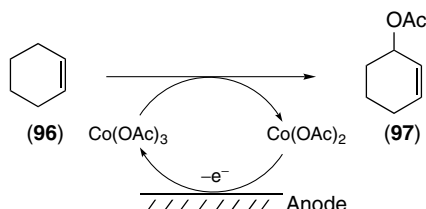
Co(III)(OAc)<sub>3</sub> can be used as a mediator in an AcOH-AcONa/Bu<sub>4</sub>NBF<sub>4</sub>-(C) system at high current density [131].



**Scheme 34** Oxidation of primary alcohols to carboxylic acids with nickel(III) as mediator.



**Scheme 35** Oxidation of primary alcohols to aldehydes with nickel(III) as mediator.



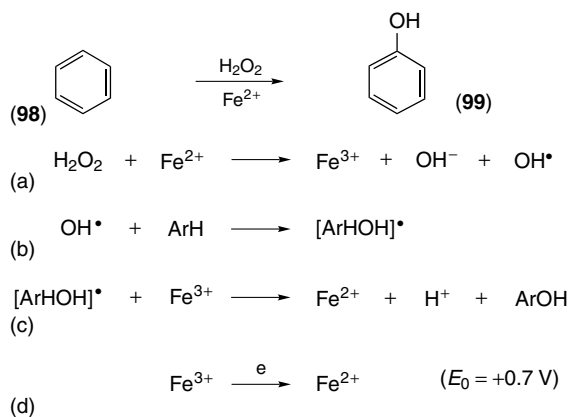
**Scheme 36** Allylic acetoxylation of cyclohexene with cobalt(III) triacetate.

Allylic acetoxylation of cyclohexene (**96**) at 80 °C affords 3-acetoxycyclohexene (**97**) in 67% yield (Scheme 36). It was found that the catalytic double-bond isomerization of 3-phenylpropene proceeds by the action of an electrochemically generated 17-electron Co(II) species [132]. The cobalt(III)-mediated electrooxidative decomposition of chlorinated organics, that is, 1,3-dichloro-2-propanol, 2-monochloropropanol, and so on, has been performed

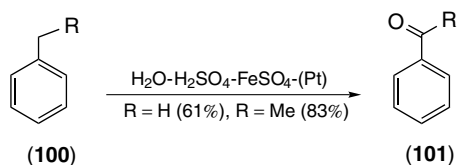
at ambient temperatures [133]. The migration of the phenyl group in 1-bromo-2,2-bis(ethoxycarbonyl)-2-phenylethane is catalyzed by the action of cobalt in vitamin B<sub>12</sub> derivatives [134].

#### 15.2.4.3 Iron (Fe) Complex-assisted Oxidation

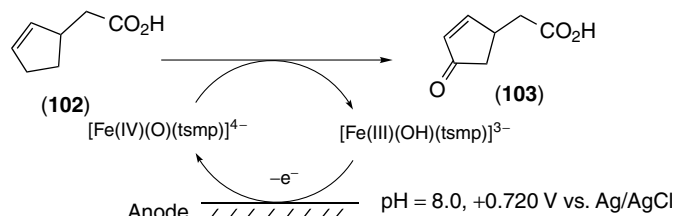
Fenton's reagent [ $\text{H}_2\text{O}_2 + \text{Fe(II)}$ ] can be used as a redox carrier for the indirect hydroxylation of aromatic



**Scheme 37** Hydroxylation of aromatic compounds mediated by Fenton's reagent.



**Scheme 38** Side-chain oxidation of aromatic compounds mediated by Fe(II).



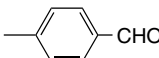
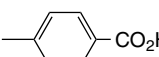
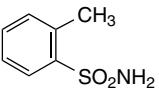
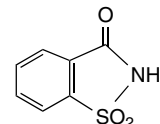
**Scheme 39** Allylic oxidation of olefins with an oxoferryl porphyrin complex.

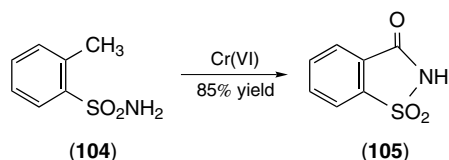
compounds (Scheme 37) [135, 136]. The electrochemically generated hydroxy radical  $[\text{OH}]^\bullet$  affords an intermediate  $[\text{ArH-OH}]^\bullet$ , which, on subsequent oxidation with  $\text{Fe}_3^+$ , gives phenol in the manner shown in Scheme 37a $\rightarrow$ d. Phenols (**99**) are obtained from benzene (**98**) and fluorobenzene by the above procedure in 64~80% yield. This method can also be used for the oxidation of side chains of alkylbenzenes. For example, methyl- and ethylbenzenes (**100**) afford benzaldehyde (**101**) ( $\text{R} = \text{H}$ ) and acetophenone (**101**) ( $\text{R} = \text{Me}$ ) in 61~83%

yields, respectively (Scheme 38) [137]. Selective allylic oxidation of olefins (**102**) has been attained to give (**103**) in aqueous buffer solutions at pH 8 with an oxoferryl porphyrin complex (Scheme 39) [138].

Alcohols have been converted into aldehydes mediated by a lipophilic  $\beta$ -cyclodextrin bearing a ferrocene moiety [139]. Efficient indirect *in situ* electroregeneration of  $\text{NAD}^+$  and  $\text{NADP}^+$  for enzymatic oxidations of butanol and 2-hexen-1-ol leading to the corresponding aldehydes using Fe bipyridine and phenanthroline complexes as redox

Tab. 4 Conditions and results in indirect electrooxidation with Cr(VI)

Substrate	Mediator	Product	Electrolysis conditions	References
$\begin{array}{c} \text{R}-\text{CH}-\text{CH}_2\text{OH} \\   \\ \text{NHOAc} \end{array}$	$\text{K}_2\text{Cr}_2\text{O}_7$	$\begin{array}{c} \text{R}-\text{CH}-\text{CO}_2\text{H} \\   \\ \text{NHOAc} \end{array}$	$\text{Cr}_2\text{O}_3 + \text{H}_2\text{SO}_4$	143
<i>p</i> -Nitrotoluene	$\text{H}_2\text{Cr}_2\text{O}_7$	<i>p</i> -Nitrobenzoic Acid	$\text{Cr}_2(\text{SO}_4)_3 + \text{H}_2\text{SO}_4$	148
<i>m</i> -Xylene	$\text{Na}_2\text{Cr}_2\text{O}_7$	<i>m</i> -Isophthalic Acid	$\text{Cr}_2\text{O}_3 + 50\% \text{H}_2\text{SO}_4 (\text{Pb})(\text{H}_3\text{PO}_4)$	144,145
<i>p</i> -Xylene	$\text{Na}_2\text{Cr}_2\text{O}_7$	Terephthalic Acid	$\text{Cr}_2\text{O}_3 + 50\% \text{H}_2\text{SO}_4 (\text{Pb})(\text{H}_3\text{PO}_4)$	144,145
	$\text{Na}_2\text{Cr}_2\text{O}_7$	Terephthalic Acid	$\text{Cr}_2\text{O}_3 + 50\% \text{H}_2\text{SO}_4 (\text{Pb})(\text{H}_3\text{PO}_4)$	144,145
	$\text{Na}_2\text{Cr}_2\text{O}_7$	Terephthalic Acid	$\text{Cr}_2\text{O}_3 + 50\% \text{H}_2\text{SO}_4 (\text{Pb})(\text{H}_3\text{PO}_4)$	144,145
<i>p</i> -Cymene	$\text{Na}_2\text{Cr}_2\text{O}_7$	Terephthalic Acid	$\text{Cr}_2\text{O}_3 + 50\% \text{H}_2\text{SO}_4 (\text{Pb})(\text{H}_3\text{PO}_4)$	144,145
	$\text{Na}_2\text{Cr}_2\text{O}_7$		$\text{Cr}_2\text{O}_3 + \text{conc. H}_2\text{SO}_4 (\text{PbO}_2-\text{Pb})$	146
Anthracene	$\text{Na}_2\text{Cr}_2\text{O}_7$	Anthraquinone	$\text{Cr}_2(\text{SO}_4)_3 + \text{H}_2\text{SO}_4$	147



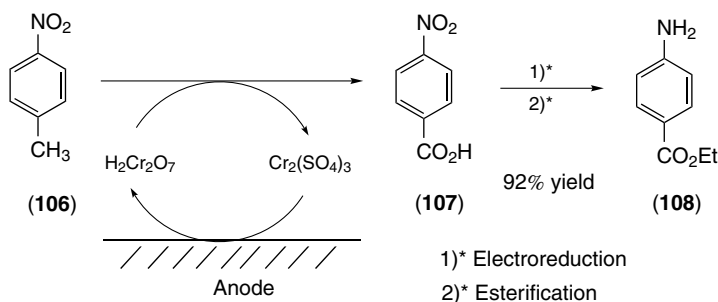
Scheme 40 Industrial saccharin synthesis with chromic acid as mediator.

catalysts have been performed [140]. Sulfonated ferrocenes have been applied as redox mediators in enzyme electrodes [141, 142].

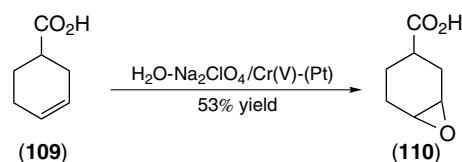
#### 15.2.4.4 Indirect Oxidation with Chromic Acid [Cr(VI)]

Chromic acid is a potential electron carrier for indirect electrooxidation. For example, *p*-xylene may be converted to terephthalic acid on treatment with Cr(VI). Similarly, methyl groups on aromatic rings

can usually be readily oxidized to carboxylic acids with Cr(VI) and selected results are shown in Table 4 [143–145]. The recovered chromium oxide is subjected to electrolysis in a strong mineral acid, that is,  $\text{H}_2\text{SO}_4$ ,  $\text{H}_3\text{PO}_4$ , by using a  $\text{PbO}_2$ -Pb electrode system to generate Cr(VI) species. The chromic acid process is used in a successful industrial indirect process for saccharin synthesis (**104**→**105**), (Scheme 40) [146]. The reaction has been applied to the commercial-scale synthesis

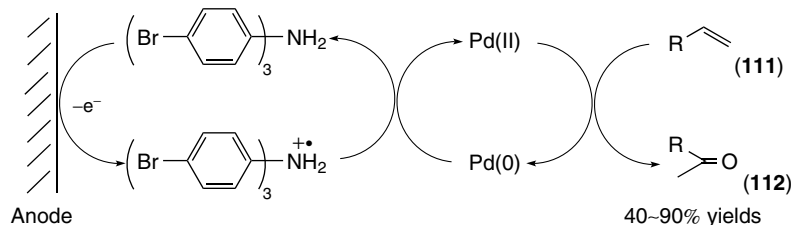


**Scheme 41** *p*-Aminobenzoate synthesis applying mediated side-chain oxidation.



Cr(V) = oxo(5,10,15,20-tetrakis(2,6-dimethyl-3-sulfonatophenyl)porphinato)chromium(V)

**Scheme 42** Epoxidation of alkenes with an Cr(V)-complex as mediator.



**Scheme 43** Electrochemical Wacker oxidation.

of anthraquinone from anthracene in Germany and the UK [147]. Synthesis of ethyl *p*-aminobenzoate benzocaine (**108**) from *p*-nitrotoluene (**106**) has been accomplished by using a two-stage electrochemical process: (1)  $\text{Cr}_2(\text{SO}_4)_3$  is electrochemically oxidized to  $\text{H}_2\text{Cr}_2\text{O}_7$ , which can react with (**106**) outside the cell to give the acid (**107**); (2) electroreduction of (**107**) with a rotating tin-plated copper cathode gives *p*-aminobenzoic acid, esterification of which provides (**108**) in 92% yield (Scheme 41) [148].

A method for preparing a  $\text{Ti}/\text{Cr}_2\text{O}_3$  electrode has been developed for the indirect electrooxidation of 2-propanol to acetone [149]. Epoxidation of alkenes has been performed using oxo[5,10,15,20-tetrakis(2,6-dimethyl-3-sulfonatophenyl)

porphinato]chromium(V) in aqueous solution. 3-Cyclohexene-1-carboxylic acid (**109**) can be converted into the corresponding epoxide (**110**) in 53% yield (Scheme 42) [150].

#### 15.2.4.5 Palladium (Pd)-assisted Oxidation

The electrochemical Wacker-type oxidation of terminal olefins (**111**) by using palladium chloride or palladium acetate in the presence of a suitable oxidant leading to 2-alkanones (**112**) has been intensively studied. As recyclable double-mediatory systems (Scheme 43), quinone, ferric chloride, copper acetate, and triphenylamine have been used as co-oxidizing agents for regeneration of the Pd(II) catalyst [151]. The palladium-catalyzed anodic oxidation of

Tab. 5a Pd(II)-mediated Wacker oxidation of olefins

Substrate	Conditions	Mediator system	Product	Yield [%]	Reference
1-Heptene	A	A	2-Heptanone	64*	118
1-Octene	A	A	2-Octanone	83*	118
<i>trans</i> -2-Octene	B	B	2-Octanone	76	153
1-Decene	B	C	2-Decanone	68	153
	A	A		91*	118
	C	C		63	119
Vinylcyclohexane	A	A	Acetylcyclohexane	33*	118
Cyclopentene	C	C	Cyclopentanone	75	119
Cyclohexene	B	B	Cyclohexanone	77	153
	A	A		29*	118
	C	C		83	119
Cycloheptene	A	A	Cycloheptenone	72*	118
Styrene	B	B	Acetophenone	61	153
	A	A		35*	118
	C	C		56	119

Note: Electrolysis conditions: A MeCN/AcOH(7/1)- $\text{NaClO}_4/\text{NaOAc}$ -(Pt);

B MeCN/ $\text{H}_2\text{O}$ (7/1)- $\text{HClO}_4/\text{Bu}_4\text{NClO}_4$ -(Pt);

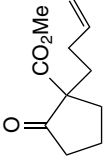
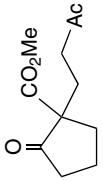
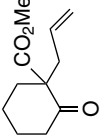
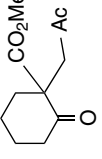
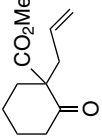
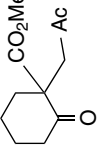
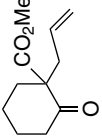
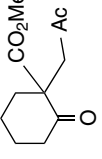
C MeCN/ $\text{H}_2\text{O}$ (7/1)- $\text{Et}_4\text{NBF}_4$ -(Pt)

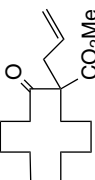
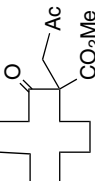
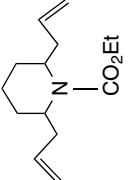
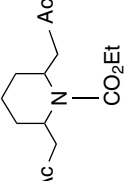
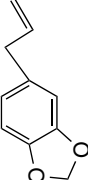
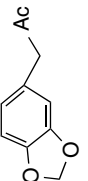
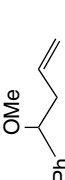
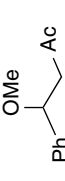
Mediator systems: A  $\text{Pd}(\text{OAc})_2/\text{Cu}(\text{OAc})_2$ ; B  $[(\text{L}_2)_2\text{MnO}_2\text{Mn}(\text{L}_2)_2](\text{ClO}_4)_4$ ;

C  $\text{Pd}(\text{OAc})_2/\text{Benzoquinone}$

\*Current efficiency.

Tab. 5b Pd(II)-mediated Wacker oxidation of olefins

Olefin	Conditions	Products	Yield [%]		Reference
			Divided cell	Undivided cell	
$\text{H}_2\text{C}=\text{CH}-(\text{CH}_2)_7-\text{CH}=\text{CH}-\text{CH}_2-\text{OAc}$	B	$\text{Ac}-(\text{CH}_2)_7-\text{CH}=\text{CH}-\text{CH}_2-\text{OAc}$	75	—	119
$\text{H}_2\text{C}=\text{CH}-(\text{CH}_2)_2-\text{CH}(\text{CO}_2\text{Me})_2$	B	$\text{Ac}-(\text{CH}_2)_2-\text{CH}(\text{CO}_2\text{Me})_2$	69	—	119
$\text{H}_2\text{C}=\text{CH}-\underset{\text{HO}}{\text{CH}}-(\text{CH}_2)_6-\text{Me}$	A	$\text{H}_2\text{C}=\text{CH}-\underset{\text{O}}{\text{C}}-(\text{CH}_2)_6-\text{Me}$	70	41	151
$\text{H}_2\text{C}=\text{CH}-\text{CH}_2-\text{O}_2\text{C}-\text{CH}=\text{CH}_2$	A	$\text{Ac}-\text{O}_2\text{C}-\text{CH}=\text{CH}_2$	64	66	151
$\text{H}_2\text{C}=\text{CH}-(\text{CH}_2)_7-\text{CHO}$	A	$\text{Ac}-(\text{CH}_2)_7-\text{CHO}$	46	74	151
	A		89	60	151
	B		76	—	119
	A		93	90	151
	B		82	—	119

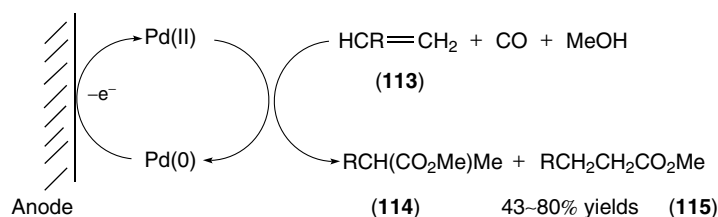
	A		79	48	151
	A		74	72	151
	A		57	85	151
	A		82	89	151

Note: Conditions: A MeCN/H<sub>2</sub>O(7/1)-Et<sub>4</sub>NOTs-(Pt/Pt);  
 B MeCN/H<sub>2</sub>O(7/1)-HClO<sub>4</sub>/Bu<sub>4</sub>NClO<sub>4</sub>-(Pt).



1-alkenes (**111**) in the presence of benzoquinone derivatives as cooxidants also affords the corresponding 2-alkanones (**112**) in good yields, depending on the type of quinone. The Wacker-type reaction of the compound in the presence of either benzoquinone or 2-methylbenzoquinone gives the ketone in over 90% yields [119, 152]. The Wacker oxidation of cyclohexene as a cyclic olefin also proceeds with good yield in an MeCN/H<sub>2</sub>O (7/1)-Bu<sub>4</sub>NClO<sub>4</sub>/Pd(OAc)<sub>2</sub>-(Pt) system [153]. Some products obtained by the Wacker-type reaction are shown in Table 5.

The methoxycarbonylation of olefins proceeds smoothly by using an electrogenerated Pd(II) to give a mixture of branched and linear esters (**114** and **115**) in good yields (Scheme 44) [154]. The Pd(II)-assisted anodic carbonylation is carried out in an MeOH-PdCl<sub>2</sub>/LiCl-(C) system by bubbling carbon monoxide in to the solution. The results are shown in Table 6. The oxidation of olefins (**116**) with the electrogenerated Pd(II) by using Pd-Pt electrodes has been shown to proceed through the formation of a Pd(II)-olefin complex, giving the carbonyl compound (**115**), (Scheme 45) [155].

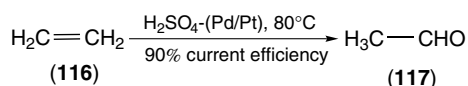


**Scheme 44** Palladium(II)-catalyzed methoxycarbonylation of olefins.

**Tab. 6** Pd(II)-mediated carbonylation of olefins [154]

Olefin		Product	Yield [%]
$R^1-CH=C \begin{matrix} R^2 \\ H \end{matrix}$		$R^1-CH_2CH_2CO_2Me$	$R^1-\overset{H}{\underset{Me}{\underset{ }{C}}}-CO_2Me$
$R^1$	$R^2$		
Me(CH <sub>2</sub> ) <sub>3</sub>	H	17	56
Me(CH <sub>2</sub> ) <sub>4</sub>	H	23	69
Me(CH <sub>2</sub> ) <sub>5</sub>	H	24	72
Me(CH <sub>2</sub> ) <sub>9</sub>	H	23	71
Me(CH <sub>2</sub> ) <sub>3</sub>	Me	12	38
$\begin{matrix} Me \\ \diagup \\ CH \\ \diagdown \\ Me \end{matrix}$	Me	11	32
$\text{---}-(CH_2)_4\text{---}$		12	38
Ph	H	23	71

*Note:* The electrochemical carbonylation is carried out in an MeOH-PdCl<sub>2</sub>/LiCl-(C) system and bubbling carbon monoxide into the solution.



**Scheme 45** Conversion of ethene to acetaldehyde at a Pd/Pt-anode.

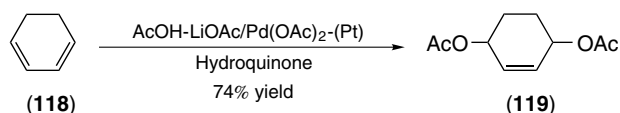
Pd-hydroquinone-mediated electrochemical 1,4-diacetoxylation of cyclohexa-1,3-diene (118), leading to 1,4-diacetoxycyclohex-2-ene (119), has been investigated (Scheme 46) [156]. Palladium-catalyzed indirect electrochemical monoacetoxylation of olefins has been attained in an MeCN/AcOH-NaClO<sub>4</sub>/AcONa/Pd(OAc)<sub>2</sub>-Cu(OAc)<sub>2</sub>-(C) system. The acetoxylation of cyclohexene produces unsaturated esters with less current efficiency, giving a 1:1 mixture of allylic and vinylic products [118].

Aromatic carbamates, precursors of isocyanates, have been electrosynthesized by

an indirect electrochemical carbonylation of aromatic amines with a palladium catalyst. The electrolysis of the amines is carried out in an MeOH-AcONa-(C) by bubbling in CO gas in the presence of Pd(OAc)<sub>2</sub> and Cu(OAc)<sub>2</sub> and the results are illustrated in Table 7 [157]. Propylene can be converted mainly to acetic and formic acids *via* acetone in an Hg(II)-HClO<sub>4</sub>-(Pt) system [158].

#### 15.2.4.6 Ruthenium (Ru)-assisted Oxidation

Instead of strong oxidants such as oxo complexes of transition metals (MnO<sub>4</sub><sup>-</sup> and



**Scheme 46** Pd-mediated diacetoxylation of cyclohexene.

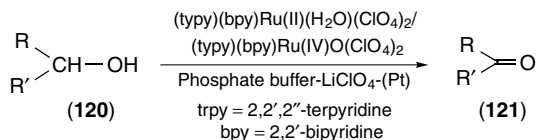
**Tab. 7** Pd(II)-catalyzed *N*-carbonylation of aromatic amines [157]

Substrate	Products	Yield [%]
C <sub>6</sub> H <sub>5</sub> NH <sub>2</sub>	C <sub>6</sub> H <sub>5</sub> NHCO <sub>2</sub> Me	99
<i>p</i> -MeC <sub>6</sub> H <sub>4</sub> NH <sub>2</sub>	<i>p</i> -MeC <sub>6</sub> H <sub>4</sub> NHCO <sub>2</sub> Me	85
<i>o</i> -MeC <sub>6</sub> H <sub>4</sub> NH <sub>2</sub>	<i>o</i> -MeC <sub>6</sub> H <sub>4</sub> NHCO <sub>2</sub> Me	84
<i>p</i> -ClC <sub>6</sub> H <sub>4</sub> NH <sub>2</sub>	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub> NHCO <sub>2</sub> Me	96
<i>p</i> -HOC <sub>6</sub> H <sub>4</sub> NH <sub>2</sub>	<i>p</i> -HOC <sub>6</sub> H <sub>4</sub> NHCO <sub>2</sub> Me	78
2,6-Me <sub>2</sub> C <sub>6</sub> H <sub>3</sub> NH <sub>2</sub>	2,6-Me <sub>2</sub> C <sub>6</sub> H <sub>3</sub> NHCO <sub>2</sub> Me	95
2,5-Me <sub>2</sub> C <sub>6</sub> H <sub>3</sub> NH <sub>2</sub>	2,5-Me <sub>2</sub> C <sub>6</sub> H <sub>3</sub> NHCO <sub>2</sub> Me	93
2,4-Me <sub>2</sub> C <sub>6</sub> H <sub>3</sub> NH <sub>2</sub>	2,4-Me <sub>2</sub> C <sub>6</sub> H <sub>3</sub> NHCO <sub>2</sub> Me	55
2,3-Me <sub>2</sub> C <sub>6</sub> H <sub>3</sub> NH <sub>2</sub>	2,3-Me <sub>2</sub> C <sub>6</sub> H <sub>3</sub> NHCO <sub>2</sub> Me	90
3,5-Me <sub>2</sub> C <sub>6</sub> H <sub>3</sub> NH <sub>2</sub>	3,5-Me <sub>2</sub> C <sub>6</sub> H <sub>3</sub> NHCO <sub>2</sub> Me	67
<i>p</i> -MeC <sub>6</sub> H <sub>4</sub> NH <sub>2</sub>	<i>p</i> -MeC <sub>6</sub> H <sub>4</sub> NHCO <sub>2</sub> Me	98

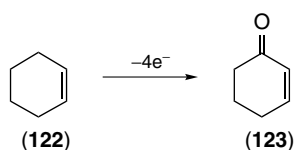
Note: Electrolysis Conditions: MeOH-AcONa/CO-(Graphite)  
Mediator System: Pd(OAc)<sub>2</sub>/Cu(OAc)<sub>2</sub>.

CrO<sub>3</sub>), a mild electrooxidation technique using Ru complexes is available for the oxidation of alcohols, aldehydes, cyclic ketones, and C–H bonds adjacent to olefinic and aromatic groups [159]. The kinetics of electrooxidation of alcohols by [(bpy)<sub>2</sub>pyRu(IV)(O)]<sup>2+</sup> has been investigated [160]. Bispyridyl, pyridyl complexes of ruthenium(IV), for example, (bpy)<sub>2</sub>pyRu(OH<sub>2</sub>)<sup>2+</sup>/(bpy)<sub>2</sub>pyRuO<sup>2+</sup> and/ or (trpy)(bpy)Ru(OH<sub>2</sub>)<sup>2+</sup>/(trpy)(bpy)RuO<sup>2+</sup> systems, proved to be good catalysts for alcohols, aldehydes, ethers, and for olefin oxidation (120→121) (Scheme 47) [161–164]. Cyclohexene (122→123) (Scheme 48) and *p*-xylene (124→125) (Scheme 49) are dissolved or dispersed in an aqueous buffer solution of the catalyst, and electrolyzed at potentials that are sufficient to cause the oxidation of Ru(II)→Ru(IV) (0.6~0.8 V vs. SCE).

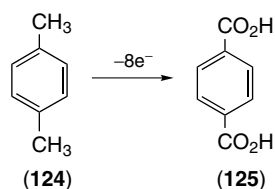
Another versatile mediatory system for various oxidative transformations (126→127) is a Ru(IV)/Ru(VIII) redox system. Ruthenium tetroxide, RuO<sub>4</sub>, generated *in situ* in aqueous sodium chloride can act as an efficient oxidant in an organic solvent for the oxidation of alcohols, aldehydes, amines, and so on (Scheme 50) [165–167]. The cleavage of cyclododecene leading to the corresponding dicarboxylic acid has been done by employing ruthenium tetroxide and cerium salt as double-mediatory systems [168]. The electrooxidation of the alcohol (128) proceeds in a CCl<sub>4</sub>-sat. aqueous NaCl-(Pt) system in the presence of a catalytic amount of RuO<sub>2</sub>·2H<sub>2</sub>O, providing (129) in 93% yield (Scheme 51); the scope of the reaction as well as the procedures are reported [169]. Benzyl alcohols can be oxidized into their corresponding benzaldehydes and benzoic



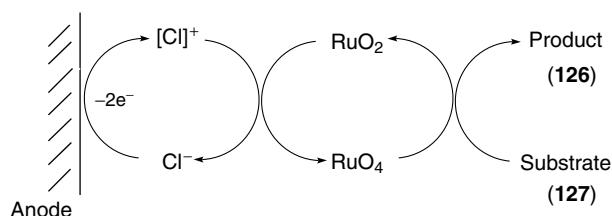
**Scheme 47** Ruthenium(IV)-complex-mediated oxidation of alcohols.



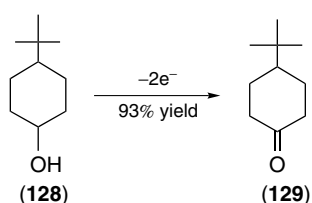
**Scheme 48** Allylic oxidation of alkene with Ru(IV)-complexes.



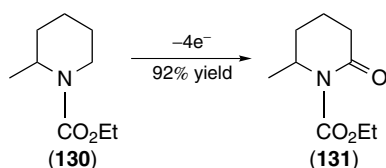
**Scheme 49** Side-chain oxidation of aromatic compounds with Ru(IV)-complexes.



**Scheme 50** Ruthenium tetroxide-mediated oxidation.



**Scheme 51** Ruthenium tetroxide-mediated oxidation of alcohols.



**Scheme 52** Ruthenium tetroxide-mediated oxidation of amines to amides.

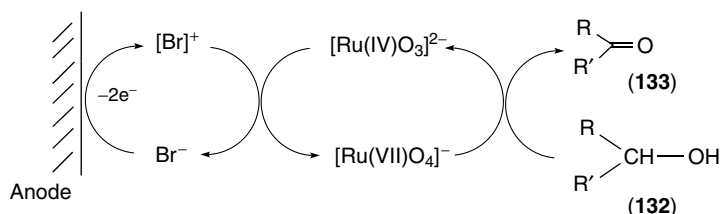
acids [170]. Similarly, the amine (**130**) can be oxidized smoothly to the amide (**131**) in good yield (Scheme 52) [166]. Various factors related to the yield and selectivity for the indirect electrooxidation of diisopropylidenglucose to ulose have been studied [171, 172]. The indirect electrosynthesis of 1,3-dichloroacetone is also well established by employing the Ru(VIII)/Ru(IV) and  $[\text{Cl}^+]/[\text{Cl}^-]$  double-mediatory system [173]. 2-Methylnaphthalene can be oxidized to vitamin K<sub>3</sub> under mild electrolysis conditions [174]. Some results are indicated in Table 8 [175–180]. The modified carbon electrode bearing functionalized polypyrrole-RuO<sub>2</sub> films can be used for benzyl alcohol oxidation [181].

A novel Ru(VII)/Ru(IV) redox system for the indirect electrooxidation of

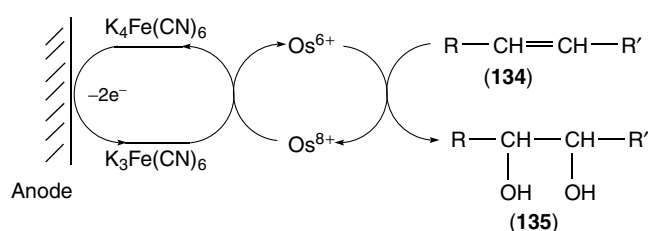
alcohols (**132**) to ketones (**133**) under basic conditions has been developed (Scheme 53) [182]. The Ru(VII) species are regenerated in either the Bu<sub>4</sub>NOH or the Bu<sub>4</sub>NOH/Br<sub>4</sub>NBr system under basic conditions.

#### 15.2.4.7 Osmium (Os)-assisted Oxidation

Osmium tetroxide is a well-known oxidizing agent for the conversion of olefins (**134**) to 1,2-diols (**135**). The indirect electrooxidation of olefins by using OsO<sub>4</sub>-K<sub>3</sub>Fe(CN)<sub>6</sub> in alkaline media as a double mediator has been reported (Scheme 54) [183]. The process consists of three reaction steps: (1) oxidation of olefins (**134**) by  $[\text{OsO}_4(\text{OH})_2]^{2-}$  in alkaline solutions; (2) regeneration of  $[\text{OsO}_4(\text{OH})_2]^{2-}$



**Scheme 53** Ruthenium(VII)-mediated oxidation of alcohols.



**Scheme 54** Osmiumtetroxide-mediated dihydroxylation of alkenes.

by the oxidation of  $[\text{OsO}_2(\text{OH})_4]^{2-}$  with ferricyanide; and (3) electro-regeneration of ferricyanide. The gaseous olefins (ethylene, propylene, and so on) are bubbled through an aqueous  $\text{KOH}/\text{K}_3\text{Fe}(\text{CN})_6/\text{OsO}_4$  solution to form glycols in 94~99% yield. A large excess of ferricyanide is effective in oxidizing  $[\text{OsO}_2(\text{OH})_4]^{2-}$  to  $[\text{OsO}_4(\text{OH})_2]^{2-}$  rapidly and quantitatively. During the overall process of olefin oxidation to the glycol, ferricyanide is converted to ferrocyanide that separates out because of its lower solubility. The regeneration of ferricyanide is performed electrochemically by using an oxygen-depolarized cathode.

Excitingly, the electrochemical Os-catalyzed asymmetric dihydroxylation of olefins with Sharpless's ligands yielding the chiral diol (138) via the chiral adduct (137) has been reported [184]. The asymmetric dihydroxylation of olefins (136) is performed by recycling a catalytic amount of potassium ferricyanide  $[\text{K}_3\text{Fe}(\text{CN})_6]$  in the presence

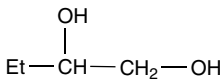
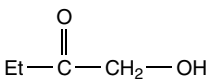
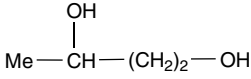
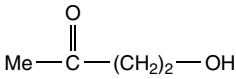
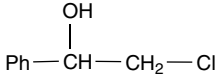
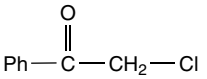
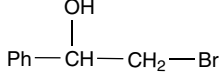
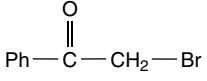
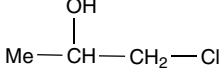
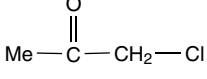
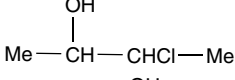
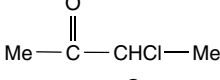
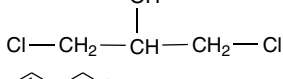
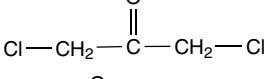
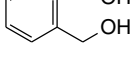
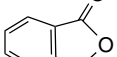
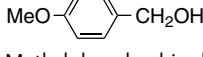
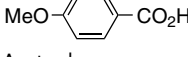
of potassium osmate  $[\text{K}_2\text{OsO}_2(\text{OH})_4]$  and a small amount of chiral ligands  $[(\text{DHQD})_2\text{PHAL}]$  (Scheme 55). Chiral induction is also found to occur in different systems such as  $\text{I}_2/\text{K}_2\text{CO}_3/\text{K}_2\text{OsO}_2(\text{OH})_2$  and  $\text{I}_2/\text{K}_3\text{PO}_4/\text{K}_2\text{HPO}_4/\text{K}_2\text{OsO}_2(\text{OH})_2$  [185, 186].

The cleavage of a double bond can be performed by employing a  $\text{K}_2\text{OsO}_2(\text{OH})_4/\text{HIO}_4$  double-mediatory system (Scheme 56) [187]. The indirect oxidative fission of the double bond of olefin (139) by the double-mediatory system proceeds in a stepwise manner involving diol (140) formation and subsequent cleavage of the C-C bond, leading to the ketone (141).

#### 15.2.4.8 Indirect Oxidation with Manganese [Mn(III)]

Alkylbenzenes can be indirectly oxidized to the corresponding aromatic aldehydes with  $\text{Mn}_2(\text{SO}_4)_3$ . Regeneration of Mn(III) is carried out by electrolysis in


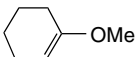

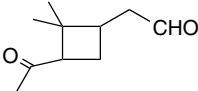
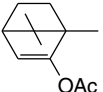
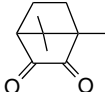
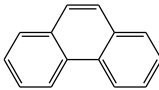
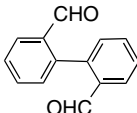
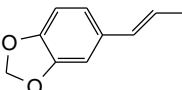
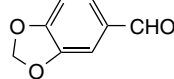
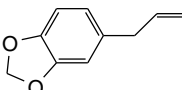
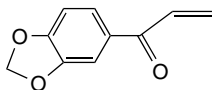
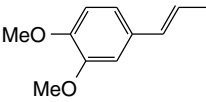
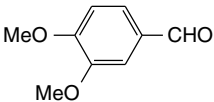
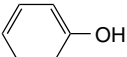
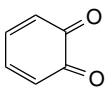

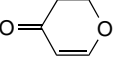
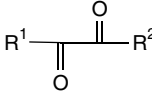
Tab. 8a Indirect electrooxidation with ruthenium mediators

Substrate	Product	Yield [%]	References
Isopropanol	Acetone	90*	165–167
Pentanol	Pentanal	41	177
Octanol	Octanal	98	177
Cyclohexanol	Cyclohexanone	77	177
Cyclododecanol	Cyclododecanone	88	169
2-Nitro-3-nonanol	2-Nitro-3-nonanone	83	169
1,1-Dichloro-2-octanol	1,1-Dichloro-2-octanone	83	169
1-Octanol	1-Octanoic Acid	68	169
1-Menthol	1-Menthone	88	169
Cyclohexylmethanol	Cyclohexanecarboxylic Acid	68	169
Allyl Alcohol	Acrylic Acid	52	177
Benzyl Alcohol	Benzoic Acid	51	177
Heptanal	Heptanoic Acid	86	169
		47	178
		41	178
HO-(CH <sub>2</sub> ) <sub>2</sub> -OH	$\gamma$ -Butyrolactone	44	178
Decane-1,5-diol	Decan-5-olide	79	169
Undecane-1,6-diol	6-Oxoundecanoic Acid	65	169
Undecane-1,10-diol	10-Oxoundecanoic Acid	89	169
		83	177
		98	177
		97	177
		98	173
		89	178
		88	177
		98	177
Methylphenylcarbinol	Acetophenone	98	177

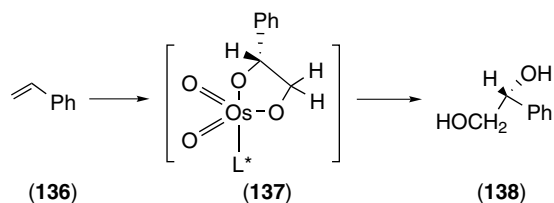
Note: Mediator System: RuO<sub>2</sub>/H<sub>2</sub>O/NaCl-NaH<sub>2</sub>PO<sub>4</sub>/Pt

\*Current efficiency.

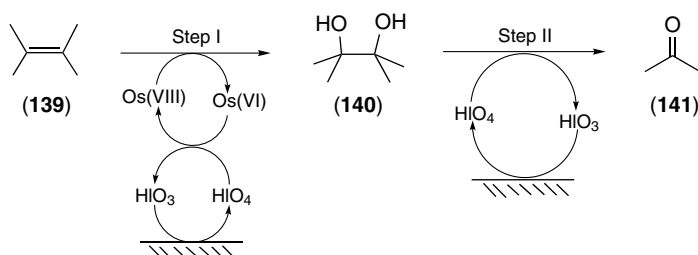
Tab. 8b Indirect electrooxidation with ruthenium mediators

Substrate	Mediator system	Product	Yield [%]	References
Cyclohexene	A		48	175
Cyclooctene	B	OHC-(CH <sub>2</sub> ) <sub>6</sub> CHO	48	180
	B	OHC-(CH <sub>2</sub> ) <sub>4</sub> CO <sub>2</sub> Me	44	180
	B		23	180
	B		57	180
Ph-COMe	A	Ph-CO <sub>2</sub> H	73	175
	B		31	180
	A		49	175
	B		68	180
	A		65	175
	B		70	180
Stilbene	B	Benzaldehyde	63~72	180
4,4'-Dimethoxystilbene	B	Anisaldehyde	82	180
	C		71	176
	C		40	176
R <sup>1</sup> ≡R <sup>2</sup>	H <sub>2</sub> O/Cl <sub>4</sub> RuO <sub>2</sub> /NaCl		69~87	179
R <sup>1</sup> = R <sup>2</sup> = alkyl, Ph				

Note: Mediator Systems: A H<sub>2</sub>O/*t*-BuOH, [(trpy)(bpy)Ru(H<sub>2</sub>O)]<sup>2+</sup>  
 B H<sub>2</sub>O/C<sub>2</sub>H<sub>4</sub>Cl<sub>2</sub>/NaIO<sub>3</sub>, (Bu<sub>4</sub>N)<sub>5</sub>(H<sub>2</sub>O)RuSiW<sub>11</sub>O<sub>39</sub>  
 C H<sub>2</sub>O/Phosphate Buffer, [(trpy)(bpy)Ru(H<sub>2</sub>O)]<sup>2+</sup>.



**Scheme 55** Electrochemical enantioselective Sharpless dihydroxylation of alkenes.



**Scheme 56** Double-bond cleavage with osmiumtetroxide/periodate.

a 55%  $\text{H}_2\text{SO}_4$ - $\text{MnSO}_4$ -( $\text{PbO}_2/\text{Pb}$ ) system, and  $\text{Mn}_2(\text{SO}_4)_3$  is regenerated in 68~78% current efficiency (or yield) [188–192]. The addition of ammonium sulfate to the electrolytic regeneration system can improve the current efficiency to 80~97% [188, 189]. Benzaldehyde has been commercially prepared from toluene by indirect electrooxidation with  $\text{Mn}_2(\text{SO}_4)_3$  by an in-cell type method [1]. Carboxylic acids may be produced when the reaction of alkylbenzenes with  $\text{Mn}_2(\text{SO}_4)_3$  is carried out at higher temperatures or at low concentration of sulfuric acid. The results obtained by oxidation with Mn(III) are summarized in Table 9.

Potassium permanganate,  $\text{KMnO}_4$ , can also be regenerated under conditions in which the electrooxidation of a suspension of tetravalent manganese oxide is carried out on 10~20 wt.% potassium hydroxide by using Ni-Fe electrodes at 80 °C in the presence of  $\text{KClO}_4$ ,  $\text{KMnO}_4$ , or  $\text{K}_3[\text{Fe}(\text{CN})_6]$ . The conversion yield of  $\text{MnO}_2$  is up to 80~97% [197]. Potassium

permanganate is also a useful electron carrier for the indirect side-chain oxidation of alkylbenzenes [198].


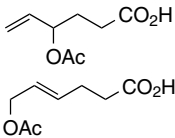
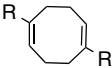
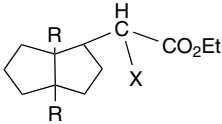
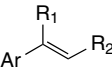
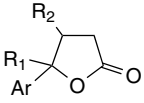
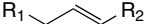
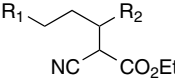
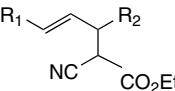
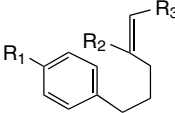
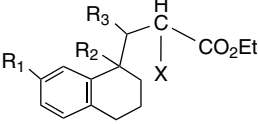
The electrooxidation of alcohols and ethers into aldehydes is successfully carried out by using the  $[(\text{L}_2)_2\text{MnO}_2\text{Mn}(\text{L}_2)_2]^{4+}/[(\text{L}_2)_2\text{MnO}_2\text{Mn}(\text{L}_2)_2]^{3+}$  system [199] and the results are indicated in Table 10 [200–204].

The electrogenerated Mn(III)-assisted coupling of various olefins with active methylene compounds proceeds by indirect electrooxidation with a small amount of  $\text{Mn}(\text{OAc})_2$  in the presence or absence of  $\text{Cu}(\text{OAc})_2$  [196]. The Mn(III)-assisted carboxymethylation of styrenes (**142**) affords  $\gamma$ -aryl- $\gamma$ -lactones (**143**) in good current yields (Scheme 57) [194, 195, 206, 207], (Table 9).

Radical addition of polyhalomethanes to olefins can be initiated by electrochemically generated Mn(III) species. The procedure offers an alternative method of a radical addition reaction with an easy control of the initiation via the current



Tab. 9 Indirect electrooxidation with manganese mediators

Olefin	Nucleophile	Product	Yield [%]	References
	$\text{Cl}_3\text{CO}_2\text{H}$		~84 (6/4)	193
	$\begin{matrix} \text{CN} \\ \text{CO}_2\text{Et} \end{matrix}$		76	194
R = H, Me	$\text{H}_2\text{C}-(\text{CO}_2\text{Et})_2$		78	195
	$\begin{matrix} \text{CN} \\ \text{CO}_2\text{Et} \end{matrix}$		~80*	195, 196
	$\begin{matrix} \text{CN} \\ \text{CO}_2\text{Et} \end{matrix}$		~60*	195, 196
R <sub>1</sub> = Propyl, Pentyl, Hexyl; R <sub>2</sub> = H R <sub>1</sub> = R <sub>2</sub> = $-(\text{CH}_2)_n$ n = 2, 3, 4, 5, 9			~55*	195, 196
	$\begin{matrix} \text{CN} \\ \text{CO}_2\text{Et} \end{matrix}$		71~79	195
R <sub>1</sub> = R <sub>2</sub> = R <sub>3</sub> = H, Me F	$\text{H}_2\text{C}-(\text{CO}_2\text{Et})_2$			

Note: Electrolysis Conditions:  $\text{AcOH}/\text{Ac}_2\text{O}-\text{AcONa}-(\text{C}/\text{C})$   
 Mediator System:  $\text{Mn}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}/\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$   
 \*Current efficiency.

density. The several results are summarized in Table 11 [208, 209].

Carbohydrates such as 6-deoxyhexoses [210] and aldopentose [211] have been oxidized electrochemically by using manganese mediators. Manganese mediators are also useful for the oxidation of  $\alpha$ -amino acids [212]. Sorbic acid precursors

are catalytically electrosynthesized on a large scale [193] (Table 9).

The effect of a surfactant such as dodecylbenzene sulfonate (DBS) has been investigated and the DBS concentration slightly influences the current efficiency [213]. The oxidation of cinnamyl alcohol to cinnamaldehyde with a solid

polymer electrolyte has been performed with high selectivity and current efficiency [214].

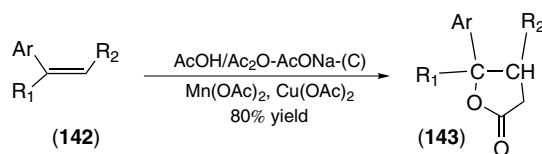
#### 15.2.4.9 Indirect Oxidation with Cerium (Ce) Complexes

Cerium(IV) ion has been widely used in the oxidation of secondary alcohols, cleavage of cycloalkanones, oxidative hydrolysis of oximes, side-chain oxidation of alkylbenzenes, quinone formation from hydroquinones, sulfoxide formation from sulfides, and functionalization of nitrogen-containing compounds [215]. The oxidation power of Ce(IV) as an oxidant increases on the order of  $\text{Ce(IV)/HClO}_4 > \text{Ce(IV)/HNO}_3 > \text{Ce(IV)/H}_2\text{SO}_4$ . For example, *p*-methoxytoluene can be oxidized with ceric ammonium nitrate,  $[\text{NH}_4]_2[\text{Ce}(\text{NO}_3)_6]$ , (abbreviated as CAN) in nitric acid even at room temperature, but with  $\text{Ce}(\text{SO}_4)_2$  in sulfuric acid elevated temperatures ( $80\sim 85^\circ\text{C}$ ) are needed. A similar oxidation of toluene with  $\text{Ce}(\text{ClO}_4)_4$  in perchloric acid readily affords benzaldehyde in 98.8% yield [28]. CAN is composed of ammonium cations and hexanitratocerate anions (144) [216] (and is very soluble in a variety of solvents [217]). When Ce(IV) in the form of CAN is reduced to Ce(III), pentanitrocerate anion

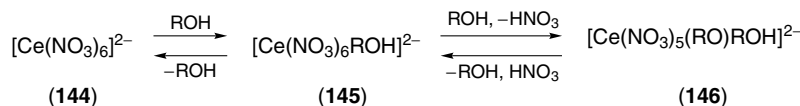
(146) is produced (Scheme 58) [216]. The electrolytic regeneration of CAN is performed in a 4 M  $\text{HNO}_3$ –(Pt/C) system in 90~98% current yield [218]. Ceric sulfate,  $\text{Ce(IV)(SO}_4)_2\cdot 4\text{H}_2\text{O}$ , is coordinated with a sulfate anion as well as water as ligands and this results in decreased oxidation power and solubility compared with CAN. Ceric sulfate is used as an electron carrier in the ex-cell method and can be regenerated in an  $\text{H}_2\text{SO}_4$ –( $\text{PbO}_2/\text{Pb}$ ) system in 70% current yield [219], and also, in a 5%  $\text{H}_2\text{SO}_4$ –(graphite) system in 70% yield [220].

The oxidation of toluene to benzaldehyde (max. yield 98.8%) can be performed in a  $\text{Ce}(\text{ClO}_4)_3$ – $\text{HClO}_4$ –(Pt/Ti–Cu) system by using the in-cell method in an undivided cell [28]. Indirect electrooxidations of organic compounds with Ce(IV) are listed in Table 12 [221–230]. For the electrogeneration of Ce(IV), platinized titanium or platinum oxide-on-titanium electrodes are known to be suitable for continuous oxidation of Ce(III) in perchloric acid.

An alternative redox system, other than Ce(IV), for the oxidation of toluene to benzaldehyde has been developed by utilizing the  $\text{Co(III)}\text{--H}_2\text{SO}_4$  system that has an intrinsically higher redox potential. The advantage of the latter system is that



**Scheme 57** Manganese(III)-assisted carboxymethylation of styrenes.



**Scheme 58** Ligand exchange in cerium(IV)-complexes.

Tab. 10 Indirect electrooxidation of alcohols, ethers and aromatics with manganese mediators

Substrate	Conditions	Mediator system	Product	Yield [%]	References
Ph-CH <sub>2</sub> OH	A	A	Ph-CHO	70	199
<i>p</i> -Me <sub>2</sub> CH-C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub> OH	A	A	<i>p</i> -Me <sub>2</sub> CH-C <sub>6</sub> H <sub>4</sub> -CHO	73	199
<i>p</i> -MeO-C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub> OH	A	A	<i>p</i> -MeO-C <sub>6</sub> H <sub>4</sub> -CHO	86	199
<i>o</i> -MeO-C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub> OH	A	A	<i>o</i> -MeO-C <sub>6</sub> H <sub>4</sub> -CHO	80	199
<i>o</i> , <i>p</i> -(Me) <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> -CH <sub>2</sub> OH	A	A	<i>o</i> , <i>p</i> -(Me) <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> -CHO	76	199
<i>p</i> -PhO-C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub> OH	A	A	<i>p</i> -PhO-C <sub>6</sub> H <sub>4</sub> -CHO	78	199
(Ph) <sub>2</sub> CHOH	A	A	(Ph) <sub>2</sub> C=O	90	199
<i>p</i> -PhCH <sub>2</sub> O-C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub> OH	A	A	<i>p</i> -PhCH <sub>2</sub> O-C <sub>6</sub> H <sub>4</sub> -CHO	83	199
<i>p</i> -MeO-C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub> OMe	A	A	<i>p</i> -MeO-C <sub>6</sub> H <sub>4</sub> -CHO	79	199
<i>p</i> -MeO-C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub> OC <sub>8</sub> H <sub>17</sub>	A	A	<i>p</i> -MeO-C <sub>6</sub> H <sub>4</sub> -CHO	80	199
<i>o</i> -MeO-C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub> OMe	A	A	<i>o</i> -MeO-C <sub>6</sub> H <sub>4</sub> -CHO	94	199
Ph-CH=CH-CH <sub>2</sub> -OH	B	C	Ph-CH=CH-CHO	90	199
Benzene	A	B	Benzoquinone	62~70*	199
Toluene	A	B	Benzaldehyde	80*	146, 190–192, 203, 204
<i>m</i> -Chlorotoluene	A	C	<i>m</i> -Cl-C <sub>6</sub> H <sub>4</sub> -CHO	33*	200

o-Xylene		A	35 °C	C	o-Me-C <sub>6</sub> H <sub>4</sub> -CHO	45*	201
m-Xylene		A	35~40 °C	C	m-Me-C <sub>6</sub> H <sub>3</sub> -CHO	35*	201
p-Xylene		A	25~30 °C	C	p-Me-C <sub>6</sub> H <sub>4</sub> -CHO	68~78*	201, 202, 205
p-Cymene		A		C	Resin	—	147, 200
		A		C	p-MeO-C <sub>6</sub> H <sub>4</sub> -CHO		200
		A		C			188
Naphthalene		B		B	Naphthoquinone		189
Anthracene		C		B	Anthraquinone		189

Note: Electrolysis Conditions: A MeCN-LiClO<sub>4</sub> or Et<sub>4</sub>NClO<sub>4</sub>-(Pt); B H<sub>2</sub>O/THF-H<sub>2</sub>SO<sub>4</sub>/MnO<sub>2</sub>-(Pt)/Mn<sub>2</sub>(SO<sub>4</sub>)<sub>3</sub>;  
C H<sub>2</sub>O-H<sub>2</sub>SO<sub>4</sub>-(PbO<sub>2</sub>/Pt)/Mn<sub>2</sub>(SO<sub>4</sub>)<sub>3</sub>

Mediator Systems: A [(L<sub>2</sub>)<sub>2</sub>MnO<sub>2</sub>Mn(L<sub>2</sub>)<sub>2</sub>](ClO<sub>4</sub>)<sub>4</sub>; B Mn<sub>2</sub>(SO<sub>4</sub>)<sub>3</sub>/(NH<sub>4</sub>)<sub>2</sub>SO<sub>4</sub>; C (NH<sub>4</sub>)<sub>2</sub>SO<sub>4</sub>

\* Current efficiency.

Tab. 11 Indirect electrooxidation with  $\text{Mn}(\text{OAc})_2$  Mediator [194, 195, 206, 207]

Olefin	Halide	Product	Yield [%]
	$\text{BrCCl}_3$		95
	$\text{BrCCl}_3$		83
	$\text{BrCCl}_3$		60
	$\text{CBr}_4$		60
	$\text{CBr}_4$		96
	$\text{Br}_2\text{CHCO}_2\text{Et}$		52
	$\text{Br}_2\text{C}(\text{CO}_2\text{Et})_2$		61
	$\text{Br}_2\text{CF}_2$		40
	$\text{C}_8\text{F}_{17}\text{I}$		80

Note: Conditions:  $\text{AcOH}-\text{AcOK}/\text{Mn}(\text{OAc})_2-(\text{C})$ -(Stainless steel).

the electrolysis is not dangerous in the presence of organic materials and it is inexpensive.

As a typical example of indirect electrooxidation of alkylbenzenes, the oxidation conditions and results on *p*-methoxytoluene (**147**) with CAN in acetic acid or methanol are shown in Scheme 59 [219]. The treatment of (**147**) with CAN in methanol at room temperature affords the aldehyde (**148**), exclusively. However, the oxidation of (**147**) with CAN in either aqueous 50% acetic acid

or methanol gives anisaldehyde (**148**) as the major product together with a small amount of the dimer (**149**). The oxidation of *p*-methoxybenzyl methyl ether with CAN in methanol readily affords (**148**) in 97% yields. The oxidation of *p*-*t*-butyltoluene (**150**) with CAN in methanol, however, results in only 10% yields of (**153**) along with the recovered (**150**) [219]. The desired oxidation of (**150**) is accomplished by treatment with CAN in aqueous 50% acetic acid at 85~90 °C, giving (**153**) in 90% yield (Scheme 60). The

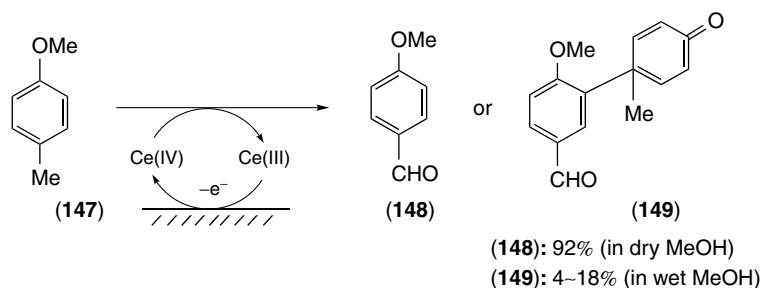
Tab. 12 Indirect electrooxidation of alkylbenzenes and hydrocarbons with cerium mediators

Substrate	Electrolysis conditions	Mediator	Product	Yield [%]	References
Toluene	A	A	Benzaldehyde	—	221–224
<i>p</i> -Chlorotoluene	A	A	<i>p</i> -Chlorobenzaldehyde	—	221
<i>o</i> -Chlorotoluene	A	B		97	225
<i>p</i> -Aminotoluene	A	B	<i>o</i> -Chlorobenzaldehyde	99	225
<i>p</i> -Xylene	A	A	<i>p</i> -Aminobenzaldehyde	—	221
	A	A	<i>p</i> -Methylbenzaldehyde	—	221–223
	H <sub>2</sub> O-H <sub>2</sub> SO <sub>4</sub> -(PbO <sub>2</sub> )	A		70*	205
<i>p</i> -Methoxytoluene	A	A	<i>p</i> -Methoxybenzaldehyde	—	221, 223
	H <sub>2</sub> O/CH <sub>2</sub> Cl <sub>2</sub> -H <sub>2</sub> SO <sub>4</sub> -(Pt)	A		94	226
	B	C		93*	219
	H <sub>2</sub> O-H <sub>2</sub> SO <sub>4</sub> -(?)	A		72*	227
<i>p</i> -Cyanotoluene	A	A	<i>p</i> -Cyanobenzaldehyde	—	221
<i>p</i> -Isopropyltoluene	C	A	<i>p</i> -Isopropylbenzaldehyde	90*	228
<i>p</i> - <i>t</i> -Butyltoluene	B	C	<i>p</i> - <i>t</i> -Butylbenzaldehyde	90*	219
3,4,5-Trimethoxytoluene	C	A	3,4,5-Trimethoxybenzaldehyde	93*	229
<i>m</i> -Phenoxytoluene	H <sub>2</sub> O-CF <sub>3</sub> CO <sub>2</sub> H-(Pt)	D	<i>m</i> -Phenoxybenzaldehyde	37	231
	H <sub>2</sub> O/MeOH-H <sub>2</sub> SO <sub>4</sub> -(Pt)	B	O=CH   HO-C-H   H-C-OH   HC-OH   H-C-CH <sub>2</sub> OH	85	230

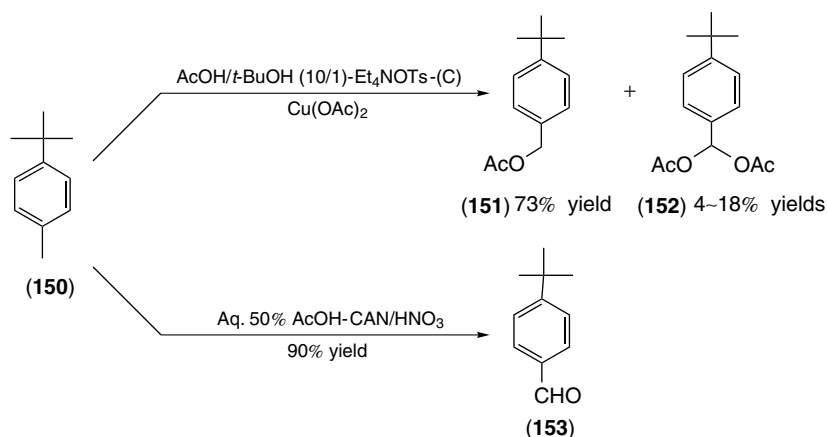
Note: Mediators: A Ce(SO<sub>4</sub>)<sub>2</sub>; B Ce(MeSO<sub>3</sub>)<sub>3</sub>; C CAN; D Ce(TFA)<sub>4</sub>.

Electrolysis Conditions: A MeCN/H<sub>2</sub>O-NaBF<sub>4</sub>/H<sub>2</sub>SO<sub>4</sub>-(Pt); B H<sub>2</sub>O/HNO<sub>3</sub>-(Pt); C H<sub>2</sub>O-H<sub>2</sub>SO<sub>4</sub>/PhH-(Pt).

\* Current efficiency.



**Scheme 59** Selective side-chain oxidation of *p*-methoxytoluene with cerium (IV) as mediator.



**Scheme 60** Selective side-chain oxidation of 4-*t*-butyltoluene with cerium (IV) as mediator.

electrooxidation of (150) in an AcOH-*t*-BuOH(10:1)-Et<sub>4</sub>NOTs-Cu(OAc)<sub>2</sub>-(C) system gives the two-electron oxidation product (151) (78% yield) together with (152) (7%) [219]. Apparently, the actual path of the reaction depends strongly on the oxidation conditions and reaction media employed. Ceric trifluoroacetate in aqueous TFA is effective for the oxidation of *m*-phenoxytoluene to *m*-phenoxybenzaldehyde [231].

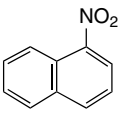
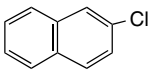
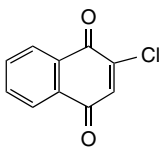
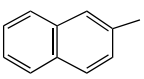
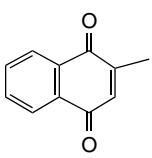
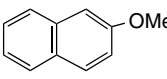
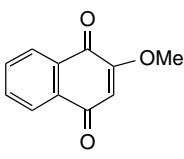
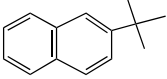
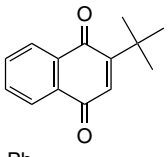
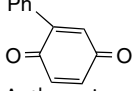
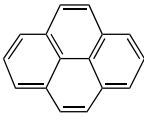
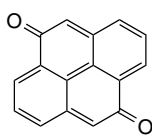
Methanesulfonic acid has been found to solubilize the Ce(IV)/Ce(III) couple. This makes Ce-mediated electrosynthesis practical for the preparation of aromatic

carbonyl compounds, that is, aldehydes, ketones, and quinones [232–235]. Ceric ion can be regenerated electrochemically at high current efficiency (95%). Results are summarized in Table 13 [235, 236]. The larger scale production of naphthoquinone has been examined in a pilot plant [238].

#### 15.2.4.10 Copper (Cu) and Silver (Ag)-assisted Oxidation

The electrocatalytic oxidation of styrene with molecular oxygen in the presence of CuCl<sub>2</sub> in an acetonitrile solution promotes the C=C double-bond cleavage reaction

Tab. 13 Indirect electrooxidation of aromatic nuclei with cerium mediators

Substrate	Electrolysis conditions	Mediator	Product	Yield [%]	Reference
Naphthalene	H <sub>2</sub> O-H <sub>2</sub> SO <sub>4</sub> -(Pb/Sb)	Ce(SO <sub>4</sub> ) <sub>3</sub>	Naphthoquinone	–	238
	H <sub>2</sub> O-HNO <sub>3</sub>	CAN/Ce(SO <sub>4</sub> ) <sub>3</sub>		70	236
1-Naphthol	H <sub>2</sub> O-H <sub>2</sub> SO <sub>4</sub> -(PbO <sub>2</sub> /Ti)	Ce(MeSO <sub>3</sub> ) <sub>2</sub>	Naphthoquinone	–	237
	H <sub>2</sub> O-H <sub>2</sub> SO <sub>4</sub> -(Pb/Sb)	Ce(MeSO <sub>3</sub> ) <sub>2</sub>	Naphthoquinone	94	232
	H <sub>2</sub> O-H <sub>2</sub> SO <sub>4</sub> -(Pb/Sb)	Ce(MeSO <sub>3</sub> ) <sub>2</sub>		99	232
	H <sub>2</sub> O-H <sub>2</sub> SO <sub>4</sub> -(Pb/Sb)	Ce(MeSO <sub>3</sub> ) <sub>2</sub>		94	232
	H <sub>2</sub> O-H <sub>2</sub> SO <sub>4</sub> -(Pb/Sb)	Ce(MeSO <sub>3</sub> ) <sub>2</sub>		93	232
	H <sub>2</sub> O-H <sub>2</sub> SO <sub>4</sub> -(Pb/Sb)	Ce(MeSO <sub>3</sub> ) <sub>2</sub>		94	232
Biphenyl	H <sub>2</sub> O-HNO <sub>3</sub>	CAN/Ce(SO <sub>4</sub> ) <sub>3</sub>		70	236
Anthracene	H <sub>2</sub> O-MeSO <sub>3</sub> H-(Pt/Nb)	Ce(MeSO <sub>3</sub> ) <sub>2</sub>	Anthraquinone	95	232
	H <sub>2</sub> O-HNO <sub>3</sub>	CAN/Ce(MeSO <sub>3</sub> ) <sub>2</sub>		90	236
	H <sub>2</sub> O-HNO <sub>3</sub>	CAN/Ce(MeSO <sub>3</sub> ) <sub>2</sub>		65	236

to form benzaldehyde. It is found that a continuous addition of Cl<sup>–</sup> is required to maintain the catalytic activity [239]. Further extensions for the air-oxidation of benzene mediated with the Cu(I)/Cu(II)

redox couple in aqueous chloride solutions have been made.

Electrochemically reduced copper (II) sulfate activates dioxygen that reacts with benzene to afford phenol (26%),



hydroquinone (56%), and *p*-benzoquinone (43%) in good Faradaic yields [240].

The epoxidation of alkenes is one of the most important oxidation methods. Electrochemical epoxidation of electron-poor olefins such as enoates (**154**→**155**) and enones has been accomplished by using silver(III)oxo bis(2,2'-bipyridine) and similar complexes (Scheme 61) [241]. (*E*)-Dimethyl glutaconate is electrolyzed in an MeCN-LiClO<sub>4</sub>/AgOAc(bpy)-(Pt) system to give the *trans*-epoxide in 90% yield.

The combination of anodic oxidation of benzene using the Ag(I)/Ag(II) mediator with cathodic oxidation of benzene using the Cu(I)/Cu(II) mediator in a single electrolytic cell produces *p*-benzoquinone selectively in both the anodic and the cathodic chambers [242]. Silver-mediator promoted electrooxidation of hydrocarbon has been attempted [243]. The kinetics of indirect oxidation of catechol and L-dopa with IrCl<sub>6</sub><sup>2-</sup> has been studied in polymer-coated glassy carbon [244].

#### 15.2.4.11 Thallic Ion [Tl(III)]-assisted Oxidation

Olefins that react with thallic ions may undergo functionalization to 1,2-diols by oxidation with electrogenerated Tl(III) to give the carbonyl compounds and 1,2-diones. For this purpose, Tl(ClO<sub>4</sub>)<sub>3</sub>, Tl<sub>2</sub>(ClO<sub>4</sub>)<sub>3</sub>, and Tl(NO<sub>3</sub>)<sub>3</sub> can be used. The regeneration of Tl(III) can be carried out in a Tl<sub>2</sub>SO<sub>4</sub>-H<sub>2</sub>SO<sub>4</sub>-(Pt) system at 3.3~3.9 V,

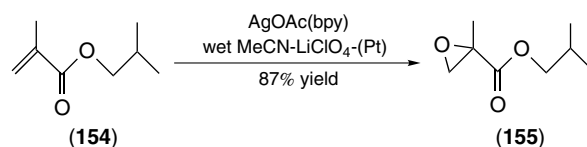
2 A/dm<sup>2</sup> at 25 °C in 69~99% current efficiency [245]. 2-Butene can be efficiently converted to 2-butanone in a two-phase system consisting of 1,3-dichloropropane and aqueous Tl<sub>2</sub>(SO<sub>4</sub>)<sub>3</sub>-H<sub>2</sub>SO<sub>4</sub>-(Pt) under vigorous stirring. Some typical results are listed in Table 14 [246–248].

### 15.3 Indirect Electroreduction

Mediators employed in electroreduction media play an important role in indirect electroorganic synthesis. Surveyed here are the reactions in which metal complexes are used as electroreductive catalysts.

Indirect electrochemical reactions usually involve a multi-electron-transfer system that consists of a set of electron transmission units (Fig. 4). Although the overall feature of an electron-transfer process in indirect electrosynthetic reactions is understandable, each step of the electron transmission has not yet been elucidated [10].

Indirect electroreductions use metal complexes, metal ions, and metal organic compounds as mediators. Their characteristic features are well documented both in monographs [8, 11, 13, 15, 17] and reviews [249–252]. This chapter reviews the potential of such mediators for electroreduction, which involve recyclable metal and nonmetal complexes, but not enzymatic systems.



**Scheme 61** Epoxidation of electron deficient olefins with silver complexes.

Tab. 14 Conditions and results in indirect electrooxidation with Tl(III)

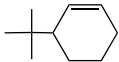
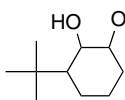
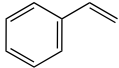
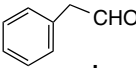
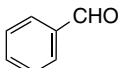
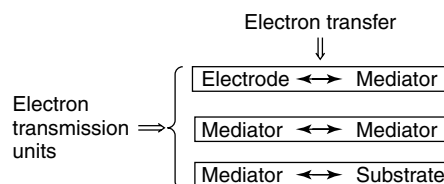
Substrate	Conditions	Mediator	Product (current efficiency, %)	Ref- erence
$\text{Me}-\text{CH}=\text{CH}_2$	$\text{TlClO}_4/\text{HClO}_4\text{-(Pt)}$	$\text{Tl}(\text{ClO}_4)_3$	$\text{Me}-\underset{\text{OH}}{\text{CH}}-\underset{\text{OH}}{\text{CH}_2}$ $\text{Me}-\underset{\text{O}}{\text{C}}-\text{Me}$	246
$\text{Me}-\text{CH}=\text{CH}-\text{Me}$	$\text{TiSO}_4/\text{H}_2\text{SO}_4\text{-(Pt)}$ $60^\circ\text{C}$	$\text{Ti}_2(\text{SO}_4)_3$	$\text{Me}-\text{CH}_2-\text{C}(\text{O})-\text{Me}$ (97)	245
Cyclohexene	$\text{TlClO}_4/\text{HClO}_4\text{-(Pt)}$	$\text{Tl}(\text{ClO}_4)_3$	Cyclopentane-1-carboxylic acid, Cyclohexanone, Cyclohexane-1,2-dione, Cyclohexane-1,2-diol	247
Cyclohexane-1,2-dione	$\text{TlClO}_4/\text{HClO}_4\text{-(Pt)}$	$\text{Tl}(\text{ClO}_4)_3$	$\text{C}_6\text{H}_8\text{O}_3$	247
	$\text{TlClO}_4/\text{HClO}_4\text{-(Pt)}$	$\text{Tl}(\text{ClO}_4)_3$		247
$\text{C}_7\text{H}_{15}-\text{CH}=\text{CH}_2$	$\text{TiSO}_4/\text{H}_2\text{SO}_4\text{-(Pt)}$ $60^\circ\text{C}$	$\text{Ti}_2(\text{SO}_4)_3$	$\text{C}_7\text{H}_{15}-\underset{\text{O}}{\text{C}}-\text{Me}$ (99)	245
	$\text{TiNO}_3 + \text{HNO}_3$ $30^\circ\text{C}$	$\text{Ti}(\text{NO}_3)_3$ ,	 , 	197

Fig. 4 Electron transfer consists of a set of electron transmission units.



Indirect electroreduction with Ni, Co, and Fe complexes has been well studied, and will be discussed first. Furthermore, the synthetic use of palladium, rhodium, and ruthenium complexes as mediators in the electroreduction of organic compounds are finding increasing applications. Metallic complexes derived from chromium, manganese, molybdenum, tungsten, and rhenium have also been used as mediators for special conversions. Recently, tin, zinc, and mercury

complexes, which are relatively difficult to recycle, have also been used as mediators.

### 15.3.1

#### Indirect Reduction with Mediators Containing Nickel, Cobalt, and Iron

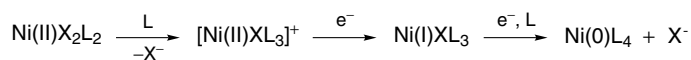
##### 15.3.1.1 Nickel (Ni) Complex Mediators

The electroreduction of Ni(II) complexes to the corresponding Ni(0) complexes has been investigated intensively. The synthetic use of the Ni(0) complex

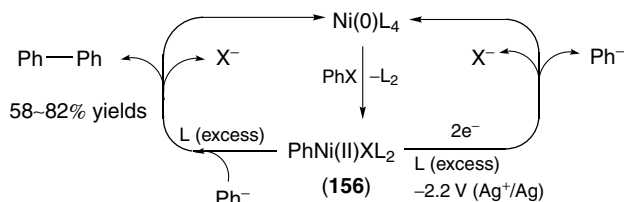
as a mediator has attracted the interest of numerous electrosynthetic chemists [253–257]. The electroreduction of  $\text{Ni(II)L}_2$  complexes [ $\text{L} = N,N'$ -ethylenebis(salicylideneiminato)] to the corresponding  $\text{Ni(I)}$  complexes at an  $\text{MeOH-(Pt)}$  system has been performed [257]. The  $\text{Ni(I)}$  complexes react rapidly with either alkyl bromides or alkyl iodides and the reaction leads to an alkyl radical, which gives a dimer and regenerates the  $\text{Ni(II)}$  complex. Controlled-potential catalytic reduction of 2-bromo- or 2-iodoethanol with electrogenerated  $\text{Ni(I)}$  salen gives rise to the formation of 1,4-butanediol in 41% yield [258].

Recently, chloro-, bromo-, and iodobenzenes have been subjected to electroreduction using  $\text{Ni(0)}$  complex mediators to yield biphenyl.  $\text{NiC}_2\text{L}_2$  and  $\text{NiBr}_2\text{L}_2$  [ $\text{L} = \text{P(Ph)}_3$ ,  $(\text{Ph})_2\text{PCH}_2\text{CH}_2\text{P(Ph)}_2$ ] have been used as catalysts [259–265]. Protic media such as alcohols, that is, methanol, ethanol or alcohol-water mixtures are found to be suitable solvents for achieving the electrosynthesis of biaryls from aryl halides according to a procedure that involves a catalytic process by nickel-2,2'-bipyridine complexes [266]. Electrochemical cross-coupling between

2-halopyridines and aryl or heteroaryl halides catalyzed by  $\text{Ni(bpy)}$  complexes proceeds smoothly to give 2-arylpyridines in good yields [267]. The electroreductive coupling of phenyl halides is carried out in a  $\text{THF/HMPA(1:1)-LiClO}_4$  system in the presence of  $\text{Ni(II)X}_2\text{L}_2$  and an excess of ligand ( $\text{L} = \text{phosphine ligand}$ ) to produce  $\text{Ni(I)XL}_3$  (Scheme 62) [264]. The electroreduction of  $[\text{Ni(I)XL}_3]^+$  occurs at  $-1.9\text{ V}$  to give  $\text{Ni(0)L}_4$  and  $\text{X}^-$  (Scheme 62). Oxidative addition of  $\text{Ni(0)L}_4$  to  $\text{PhX}$  smoothly proceeds to yield  $\text{PhNi(II)XL}_2$  complexes (**156**) when an excess of  $\text{PhX}$  is present in the electrolysis medium (Scheme 63). The unstable complex  $\text{PhNi(II)XL}_2$  (**156**) undergoes a two-electron reduction, which liberates  $\text{Ni(0)L}_4$ ,  $\text{Ph}^-$ , and  $\text{X}^-$  species. The regenerated  $\text{Ni(0)L}_4$  probably recycles the process through the subsequent oxidative addition to  $\text{PhX}$ . The desired biphenyl is produced by the reaction of the complex (**156**) with  $\text{Ph}^-$  in the presence of an excess amount of the ligand ( $\text{L}$ ) and the subsequent reductive elimination of the  $\text{Ni(0)}$  species [265]. In the absence of the ligand, an unstable low-valent  $\text{Ni}$  species can be regenerated in a  $\text{THF/HMPA (1:2)}$  solution. Electrolyses in a mercury pool leads to the following Faradaic yields of the dimer: 75% (from  $\text{PhBr}$ ), 80% (from  $\text{PhI}$ ), and



**Scheme 62** Electroreduction of nickel complexes.



**Scheme 63** Electroreductive coupling of aryl halides to biaryls.

Tab. 15 Electroreductive coupling of organic halides by using Ni complexes as mediators [268]

Substrate	Electrolysis Conditions <sup>1</sup>	Mediator <sup>2</sup>	Product	Yield [%]	References
<i>t</i> -Bu-Br	THF/Bu <sub>4</sub> NClO <sub>4</sub> /(Au) (or EtOH)	A	<i>n</i> -C <sub>8</sub> H <sub>18</sub>	15	269
PhX	A	B	Ph-Ph	82 <sup>3</sup>	270–277
	A	B	Ph-Ph	75 <sup>4</sup>	259–265, 268, 274–279
	A	A	Ph-Ph	80 <sup>5</sup>	259–265, 268, 274–279
	EtOH/Bu <sub>4</sub> NX/(Au) (or LiX)	C	Ph-Ph	5~6	274–277
	DMF/HMPT/LiClO <sub>4</sub> /(Hg)	B	Ph-Ph	80	280
PhCH <sub>2</sub> Cl	A	B	(PhCH <sub>2</sub> ) <sub>2</sub>	95	270, 278
4-MeC <sub>6</sub> H <sub>4</sub> Br	B	B	(4-HMeC <sub>6</sub> H <sub>4</sub> ) <sub>2</sub>	75	280
4-MeC <sub>6</sub> H <sub>4</sub> Cl	A	B	(4-MeC <sub>6</sub> H <sub>4</sub> ) <sub>2</sub>	57	270–273
3-MeC <sub>6</sub> H <sub>4</sub> Cl	A	B	(3-MeC <sub>6</sub> H <sub>4</sub> ) <sub>2</sub>	70	270–273
4-MeOC <sub>6</sub> H <sub>4</sub> Br	B	B	(4-MeOC <sub>6</sub> H <sub>4</sub> ) <sub>2</sub>	36	280
4-AcC <sub>6</sub> H <sub>4</sub> Br	B	B	(4-AcC <sub>6</sub> H <sub>4</sub> ) <sub>2</sub>	47	280
4-MeO <sub>2</sub> CC <sub>6</sub> H <sub>4</sub> Cl	B	B	(4-MeO <sub>2</sub> CC <sub>6</sub> H <sub>4</sub> ) <sub>2</sub>	51	280
4-PhC <sub>6</sub> H <sub>4</sub> Cl	A	B	(4-PhC <sub>6</sub> H <sub>4</sub> ) <sub>2</sub>	71	270–273

<sup>1</sup>Electrolysis Conditions: A NiBr<sub>2</sub>(PBu<sub>3</sub>)<sub>2</sub>; B NiCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>; C NiBr<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>.<sup>2</sup>Mediators: A THF/HMPT/LiClO<sub>4</sub>/(Hg); B DMF/Bu<sub>4</sub>NBr/(Pb); C NiBr<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>.<sup>3</sup>X = Cl.<sup>4</sup>X = Br.<sup>5</sup>X = I.

95% (from PhCl). However, the turnover is estimated to be less than 10 times because the Ni(II) salt is partially hydrolyzed into Ni hydroxide during the electrolysis. Addition of hydrochloric acid or perchloric acid allows the regeneration of the electroactive Ni(II) species and the electrolysis can be conducted continuously. A survey of the Ni(0) complex-assisted reductive dimerization of aryl halides is collected in Table 15 [268].

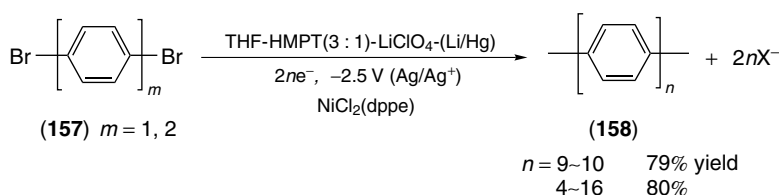
Poly(1,4-phenylene) polymers (**158**) are prepared by the electroreduction of aryl halides (**157**) in a THF/HMPA(3/1)-LiClO<sub>4</sub>(or Bu<sub>4</sub>NBF<sub>4</sub>)-(Li/Hg) system with NiCl<sub>2</sub>(dppe) complex as a catalyst (Scheme 64) [281]. The electroreduction of 1,4-dichlorobenzene (**159**) in the presence of Ni(II)(dppe) complexes in a DMSO-Bu<sub>4</sub>NBF<sub>4</sub>-(C) system proceeds to give polymers (**160**) in a high yield (Scheme 65) [270]. Poly(2,5-pyridine) films are deposited on glassy carbon, platinum, and gold electrodes by electroreduction in the presence of Ni[(PPh<sub>3</sub>)<sub>4</sub>] catalysts [282]. The dichloro(1,2-bis(di-2-propylphosphino)benzene)nickel(II) plays a role as an electrocatalyst for the reductive

coupling of any halide. Poly(*N*-ethyl-3,6-carbazolediyl) is synthesized from 3,6-dibromo-*N*-ethylcarbazole by electroreduction in a DMA-LiBF<sub>4</sub>/NiBr<sub>2</sub> (bpy)-(Mg/Hg) system at -1.3 V (SCE) [283].

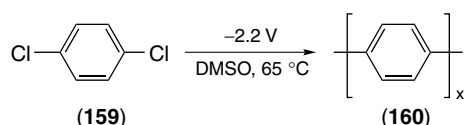
The electroreductively produced ArNi(II)XL<sub>2</sub> (**162**) can lead to the corresponding aryl-carboxylates (**163**) [284]. Electroreduction of the arylnickel complexes (**162**), formed by insertion of an electrogenerated [Ni(0)L<sub>2</sub>] into aryl halide (**161**) (X = Br, Cl) in the presence of CO<sub>2</sub> in a THF/HMPA-LiClO<sub>4</sub> (or Bu<sub>4</sub>NBF<sub>4</sub>) system, affords the carboxylate (**163**) (Scheme 66) [271–273].

The mechanism of the chain reaction, leading to benzoic acid has been investigated on the basis of a detailed kinetic analysis of the propagation of this catalytic chain and of its competition with the chain leading to biphenyl [278].

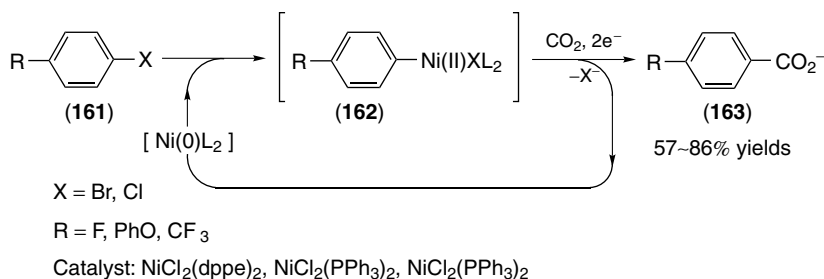
Electrocarboxylation of benzylic chlorides has been intensively investigated in the presence of a Ni(II) complex as a catalyst [274–277]. Fenoprofen (**165**), an anti-inflammatory agent, is electrosynthesized from (**164**) in a THF/HMPA-Bu<sub>4</sub>NBF<sub>4</sub>-(C/Ni) system in the presence of NiCl<sub>2</sub>(dppp) as a mediator under bubbling



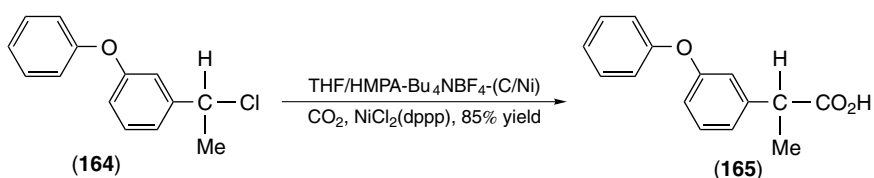
**Scheme 64** Poly(1,4-phenylene) polymers by electroreduction of aryl halides.



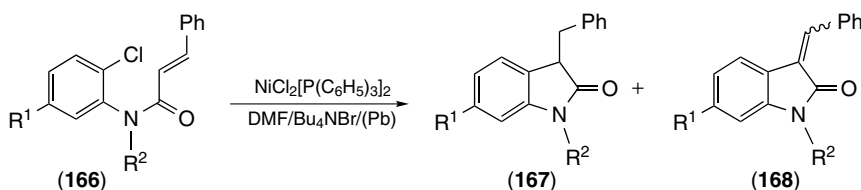
**Scheme 65** Electroreduction of 1,4-dichlorobenzene to poly(1,4-phenylene).



**Scheme 66** Nickel-catalyzed carboxylation of aryl halides.



**Scheme 67** Electrocarboxylation of benzylchlorides.



**Scheme 68** 2-Oxindol derivatives by nickel-catalyzed cyclization of aryl halides.

$\text{CO}_2$  (Scheme 67) [277]. Recently, the combination of a new electrolyzer for organic solvents and oxidation of metal powder as an alternative to sacrificial anodes has been developed [269].

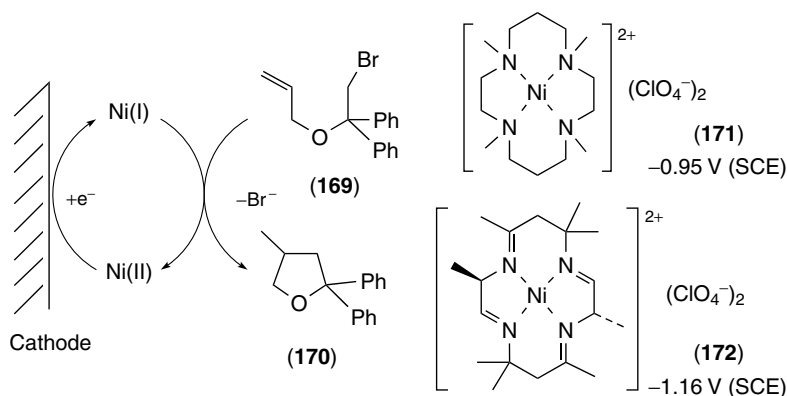
Electroreduction of benzyl bromide with Ni(I) complexes provides different products depending on the reduction potentials: potential (V vs.  $\text{Ag}/\text{Ag}^+$  in MeCN)  $-1.45$  bibenzyl 76%, toluene 2%;  $-1.80$  bibenzyl 7%, toluene 90% [280].

The synthetic utility of  $\text{Ni}(\text{II})\text{Cl}_2\text{L}_2$  [ $\text{L} = \text{P}(\text{Ph}_3)$ ] as a mediator has been shown in the preparation of 2-oxindole derivatives (167) and (168) (Scheme 68). First, the  $\text{Ni}(0)$  complex produced in a

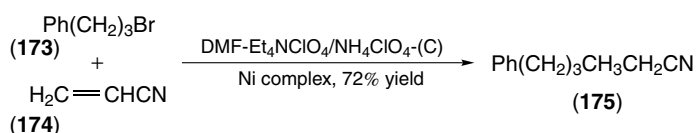
$\text{DMF-Bu}_4\text{NBr}-(\text{Pt}/\text{Pb})$  system at  $60^\circ\text{C}$  initiates the cyclization through its insertion into the  $\text{Ar}-\text{Cl}$  bond of (166). The subsequent carbometallation followed by the electroreductive elimination of the  $\text{Ni}(0)$  complex by warming up to  $70^\circ\text{C}$  gives (167) (55%) and (168) (8%) [279].

Cyclopropanation of a tandem-radical  $[2 + 1]$  cycloaddition occurs by a Ni complex-catalyzed electroreduction of 2-bromo- or 2-iodo-1,6-diene derivatives [285].

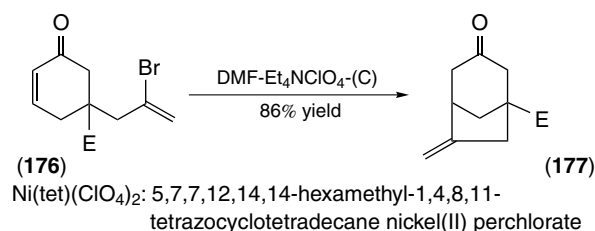
The electroreductive cyclization of the halogenated ether (169) or a halogenated ester using Ni(II) complexes (171) and (172) proceeds in the manner shown in Scheme 69 [286]. The radical



**Scheme 69** Nickel-catalyzed cathodic cyclization of unsaturated ethers.



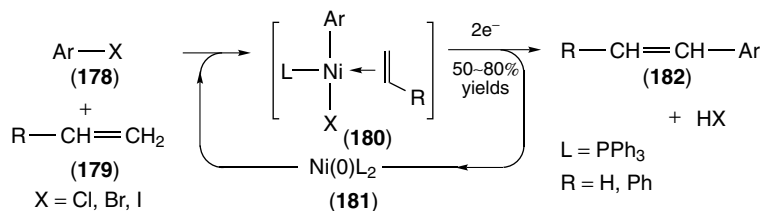
**Scheme 70** Cathodic coupling of 3-phenylpropylbromide with acrylonitrile.



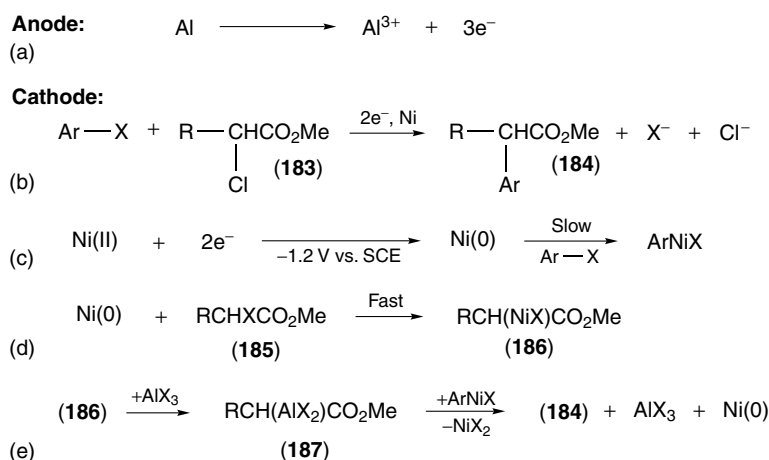
**Scheme 71** Cyclization of vinylbromide **176** to bicyclic compound **177**.

cyclization in a DMF-Et<sub>4</sub>NClO<sub>4</sub>-(C) system affords the tetrahydrofuran (**170**) in 53~58% yield. The electroreductive intermolecular addition of alkyl radicals to conjugated systems has been achieved using a Ni(II) complex as an electron-transfer catalyst [287]. The coupling reaction of 3-phenylpropyl bromide (**173**) with acrylonitrile (**174**) is carried out in a DMF-Et<sub>4</sub>NClO<sub>4</sub>/NH<sub>4</sub>ClO<sub>4</sub>-(C) system to give the adduct (**175**) in 72% yield (Scheme 70). The

electroreductive arylation of conjugated esters using a Ni salt as a catalyst takes place to yield  $\beta$ -arylpropionates in a moderate yield [288]. Intramolecular cyclization of the vinyl bromide (**176**) to the bicyclo compound (**177**) proceeds in a DMF-Et<sub>4</sub>NClO<sub>4</sub>-(C) system in the presence of a Ni(tet)(ClO<sub>4</sub>)<sub>2</sub> complex in 86% yield (Scheme 71) [289]. The *in situ* electrogenerated Ni(I) salen complex is found to be an effective catalyst for reductive



**Scheme 72** Nickel-catalyzed coupling of aryl halides and alkenes.



**Scheme 73**  $\beta, \gamma$ -Unsaturated esters by coupling of  $\alpha$ -chloroesters with vinyl or aryl halides.

intramolecular cyclization of 6-iodo- and 6-bromo-1-phenyl-hexynes to yield benzyldenecyclopentane in 84% yield [290].

The reactivity of Ni(0)(bpy) complexes toward organic halides (RX: PhI, PhCH<sub>2</sub>Cl, 4-MeOC<sub>6</sub>H<sub>4</sub>Br, C<sub>6</sub>H<sub>13</sub>Br, and so on) are shown to be dependent on the amount of the ligands present in an *N*-methylpyrrolidone solution [291].

A new catalytic coupling of aromatic halides (178) and alkenes (179) has been developed using  $\sigma$ -arylnickel complexes (180) (Scheme 72) [292]. The coupling reaction can be realized in a THF/HMPA-LiClO<sub>4</sub>-(Au) system at 25~50 °C. The  $\sigma$ -arylnickel complexes (180) obtained are stable enough to be detected (reduction at -1.3 V vs. SCE); however, they decompose

in a few minutes to give the substituted olefins (182). If triethylamine is added as a base together with the aryl halide, the yield of the cross-coupling product is almost doubled [292]. Ni(II)-catalyzed intramolecular cyclization of *o*-halogenated aromatic compounds proceeds in 30~90% yield [293].

$\beta, \gamma$ -Unsaturated esters (184) have been synthesized by a one-step electrochemical procedure from  $\alpha$ -chloroesters (183) and aryl or vinyl halides (Scheme 73b) [294, 295]. This novel electroreductive cross-coupling method is based on the use of a Ni(II)(bpy) catalyst and a sacrificial aluminum anode in a one-compartment cell (Scheme 73). The whole cathodic process progresses at -1.2 V (SCE) (Scheme 73c),

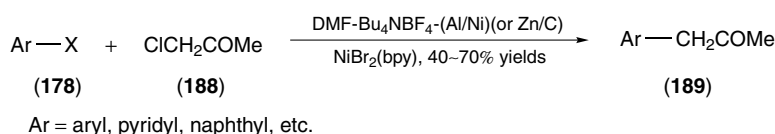


and the reaction sequence is shown in Schemes 73(c~e), including the key step (Scheme 73e) that allows the recycling of the catalyst. The electroreductive intermolecular coupling of aryl halides (178) with  $\alpha$ -chloroketones (188) has also been attained in a DMF-Bu<sub>4</sub>NBF<sub>4</sub>-(Al/Ni or Zn/C) system in the presence of a catalytic amount of a Ni complex to give the product (189) in 40~70% yield (Scheme 74) [296, 297]. Some results are shown in Table 16.

The conjugated addition of aryl bromides to activated olefins has

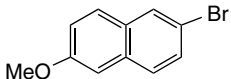
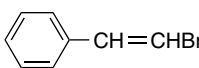
been accomplished in ethanol by the use of Ni(II)(bpy) complexes as a catalyst [298]. 2- or 3-bromothiophenes are efficiently coupled with activated alkyl chlorides ( $\alpha$ -chloroesters,  $\alpha$ -chloroketones,  $\alpha$ -chloronitriles), benzyl chloride or vinyl halides, in a one-step electrochemical reaction, using a sacrificial anode and Ni(II)(bpy) complexes [299, 300].

The electrosynthesis of homoallyl alcohols (193) or  $\beta$ -hydroxy esters (196) has been carried out by the reaction of methallyl chloride (190) (Scheme 75) or



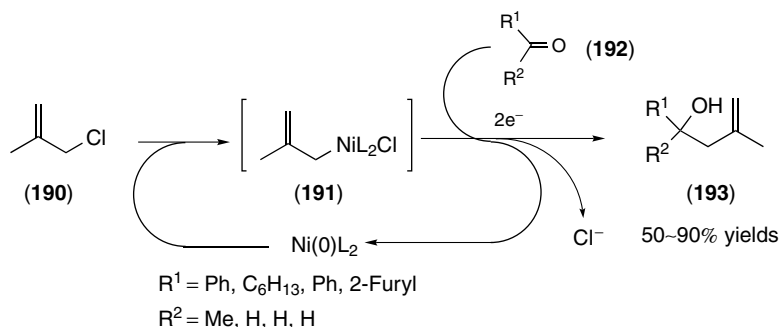
**Scheme 74** Coupling of aryl halides with  $\alpha$ -chloroketones.

**Tab. 16** Nickel-catalyzed electroreductive coupling of  $\alpha$ -chloroesters with aryl and vinyl halides<sup>1</sup> [294]

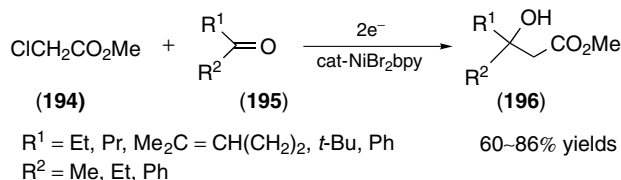
ArX	Chloroester	Coupling product <sup>2</sup> yield [%]
Bromobenzene	MeCHClCO <sub>2</sub> Me (50)	40
Iodobenzene	ClCH <sub>2</sub> CO <sub>2</sub> Me (20)	70
<i>p</i> -Methoxyiodobenzene	MeCHClCO <sub>2</sub> Me (20)	85
4-Bromotrifluoromethylbenzene	MeCHClCO <sub>2</sub> Me (20)	66
4-Bromocyanobenzene	ClCH <sub>2</sub> CO <sub>2</sub> Me (20)	60
	MeCHClCO <sub>2</sub> Me (20)	70
1-Methylnaphthalene	MeCHClCO <sub>2</sub> Me (20)	80
1-Bromonaphthalene	MeCHClCO <sub>2</sub> Me (20)	40
	MeCHClCO <sub>2</sub> Me (20)	45
2-Bromothiophene	MeCHClCO <sub>2</sub> Me (20)	40
	ClCH <sub>2</sub> CO <sub>2</sub> Me (20)	55
	MeCHClCO <sub>2</sub> Me (20)	60

<sup>1</sup> Carried out in a DMF-Bu<sub>4</sub>NBr/NiBr<sub>2</sub>/2,2-Bipyridine-(Al/C) system.

<sup>2</sup> Based on initial ArX.



**Scheme 75** Homooallyl alcohol by nickel-catalyzed addition of methallyl chloride to carbonyl compounds.



**Scheme 76** β-Hydroxyester by nickel-catalyzed addition of methyl chloroacetate to carbonyl compounds.

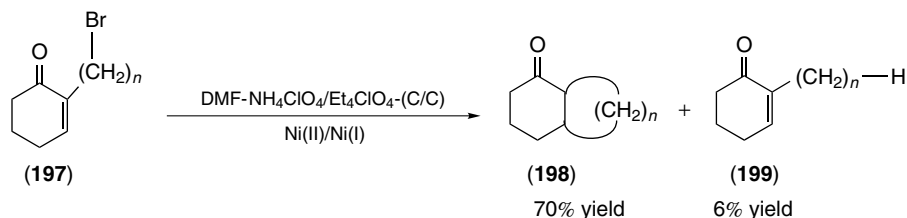
methyl chloroacetate (194) (Scheme 76) with carbonyl compounds (195) in a DMF-Bu<sub>4</sub>NBr-(Zn/C) system in the presence of the Ni(II)Br<sub>2</sub>(bpy) complex as a mediator [301, 302]. An electrochemical, Ni(0)-catalyzed Reformatsky reaction of methyl chlorodifluoroacetate and carbonyl compounds has been performed in a one-compartment cell using a zinc anode to give 2,2-difluoro-3-hydroxyesters in 45–77% yields [303]. Allylation of benzoic anhydride with alkyl bromide is performed in an HMPA-Bu<sub>4</sub>NClO<sub>4</sub>-(Pt) using 10 mol% of NiBr<sub>2</sub>-(bpy) [304].

It is known that the [Ni(I)(OEiBC)]<sup>-</sup> complex mediates electrocatalytic reductions of alkyl halides and methyl *p*-toluenesulfonate [305]. The nucleophilicity of the Ni(I) complex is comparable to that of the “supernucleophile” vitamin B<sub>12</sub>. Recently, the formation of

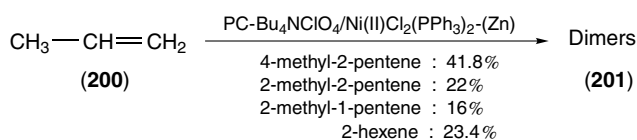
transient alkyl-Ni(III) complexes has been reported in the electrochemical reduction of Br(CH<sub>2</sub>)<sub>4</sub>CN mediated by the Ni(II) macrocycle, (R,R,S,S)-Ni(tmc) [306], of methyl iodide with Ni(I)(OEiBC) [305], of butyl bromides [280], and of alkyl bromides with a cyclic tetraamine complex of Ni(II) [307].

The electrosynthesis of bicyclic ketones (198) has been performed by the reduction of bromoalkylcyclohexenones using Ni(II) complexes as mediators. The electrochemical Michael-type addition (197)→(198) can be attained in a DMF-NH<sub>4</sub>ClO<sub>4</sub>/Et<sub>4</sub>NClO<sub>4</sub>-(C/C) system in the presence of Ni(cyclam)(ClO<sub>4</sub>)<sub>2</sub> as a redox mediator at -1.8 V (SCE) (Scheme 77) [308].

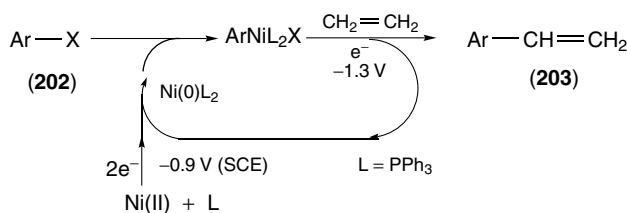
Olefin dimerization (200→201) catalyzed by electrogenerated Ni(I) complexes is performed in a PC-Bu<sub>4</sub>NClO<sub>4</sub>-(Zn) system in the presence of an Ni(II)Cl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>



**Scheme 77** Intramolecular cathodic Michael-type addition.



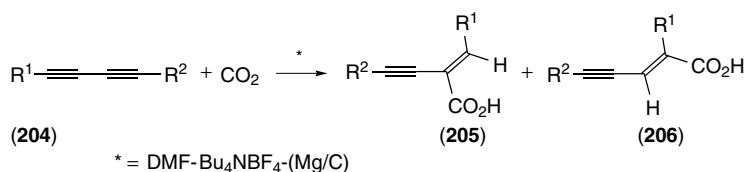
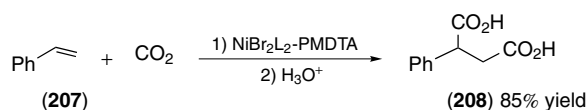
**Scheme 78** Nickel-catalyzed cathodic olefin dimerization.



**Scheme 79** Addition of nickel(0)-complexes to ethylene.

complex (Scheme 78) [309]. The electrolysis is carried out in a one-compartment cell with a sacrificial anode (Zn, Cd, Al, and so on). The oxidative addition of the electrogenerated Ni(0) complexes to aryl halides (202) yields (203); the reaction is influenced by the concentrations of the ligands triphenylphosphine, halide ion, and triethylamine (Scheme 79) [310]. The electrochemical behavior of Ni(II)X<sub>2</sub>L<sub>2</sub> (X = Cl, Br, I; L = PPh<sub>3</sub>) in *N*-methylpyrrolidinone is affected by halide salts (X<sup>−</sup>), by the concentration of the ligand, and the presence of olefin [311]. The electroreduction of the Ni(II) species can lead to soluble Ni(0) complexes only when the Ni(II) reagent is complexed by both PPh<sub>3</sub> and X<sup>−</sup>. In

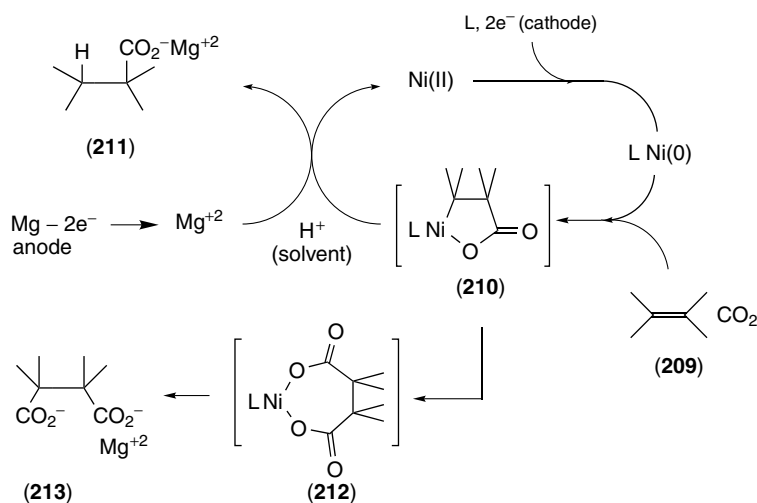
the absence of an olefin, the electroreduction of Ni(II) successively gives Ni(I) and then Ni(0) of the type Ni(0)L<sub>3</sub>, whereas, in the presence of an olefin, for example, ethylene, the total reduction of Ni(II)X<sub>2</sub>L<sub>2</sub> can be attained in the absence of added L, leading directly to the Ni(0) species such as Ni(0)L<sub>2</sub>C<sub>2</sub>H<sub>4</sub>. These zero-valent complexes probably exist as an anionic form Ni(0)L<sub>3</sub>X<sup>−</sup> and Ni(0)L<sub>2</sub>C<sub>2</sub>H<sub>4</sub>X<sup>−</sup> depending on the nature and concentration of X<sup>−</sup> [311]. The electrogenerated cationic Ni(I) complexes may act as an isomerization catalyst for alkenylbenzene. The [Ni(I)(PPh<sub>3</sub>)<sub>4</sub>]<sup>+</sup> complex is prepared directly by one-electron reduction of the parent Ni(II) perchlorate in an MeCN-Bu<sub>4</sub>NClO<sub>4</sub>-(C/C) system [312].

**Scheme 80** Electrocarboxylation of diynes.**Scheme 81** Cathodic biscalboxylation of styrenes.

Ni(II) associated with PMDTA (2,5,8-trimethyl-2,5,8-triazanonane) is found to be a catalyst precursor for the incorporation of CO<sub>2</sub> into alkynes in an electrolysis using a dissolving Mg anode [313, 314]. Different carboxylic acids are formed depending on the nature of the auxiliary ligand [315]. The incorporation of CO<sub>2</sub> into alkynes catalyzed by electrogenerated Ni(bpy) complexes using a sacrificial Mg anode gives  $\alpha,\beta$ -unsaturated acids in moderate to good yields [316]. Recently, the first example of direct CO<sub>2</sub> incorporation into conjugated 1,3-diynes has been reported. The electrosynthesis of 2-vinylidene-3-yne carboxylic acids (205) and (206) from CO<sub>2</sub> and substituted 1,3-diynes (204) is attained in a DMF-Bu<sub>4</sub>NBF<sub>4</sub>-(Mg/C) system by using a nickel-triamine complex as the catalyst and results in a regio- and stereoselective addition to one triple bond (Scheme 80) [317, 318]. The simultaneous activation of CO<sub>2</sub> and diynes by electrogenerated Ni(0)(bpy) complexes enables the selective incorporation of one molecule of CO<sub>2</sub> into unsaturated systems and the preparative-scale electrosynthesis of carboxylic acids [319]. The electrogenerated Ni(0)(bpy) complexes can also be used for the electrochemical incorporation of CO<sub>2</sub> into C–C double bonds. Olefins (207) are

carboxylated to give mono- or dicarboxylic acid derivatives (208) in 85% yield, depending on the alkene structures (Scheme 81). The proposed catalytic cycle for the nickel-catalyzed electrocarboxylation of alkenes (209) is shown in Scheme (82) [320]. The electrolysis is performed in a DMF-Bu<sub>4</sub>NBF<sub>4</sub>/Ni(bpy)<sub>3</sub>(BF<sub>4</sub>)<sub>2</sub>-(Mg/C) system in an undivided cell under a CO<sub>2</sub> atmosphere (1 atm). In the presence of Mg(II), the intermediates (210) and (212) are converted to magnesium carboxylates (211) and (213) together with Ni(II). These carboxylates, which accumulate during the course of the reaction, are a stable species. A tandem cyclization–carboxylation of unsaturated haloaryl ethers has been investigated by electrogenerated Ni complexes [321]. 2-Bromomethyl-1,4-dibromo-2-butene undergoes electroreductive carboxylation under CO<sub>2</sub> atmosphere in a DMF-Bu<sub>4</sub>NI-(Ni)-(Pt) system to afford 3-methylene-4-pentenoic acid in 57% yield [322]. The electrocarboxylation of vinyl bromides under CO<sub>2</sub> has been performed in a DMF-BU<sub>4</sub>NBF<sub>4</sub>-(Mg)-(Pt) system, giving the corresponding acids in good yields [323].

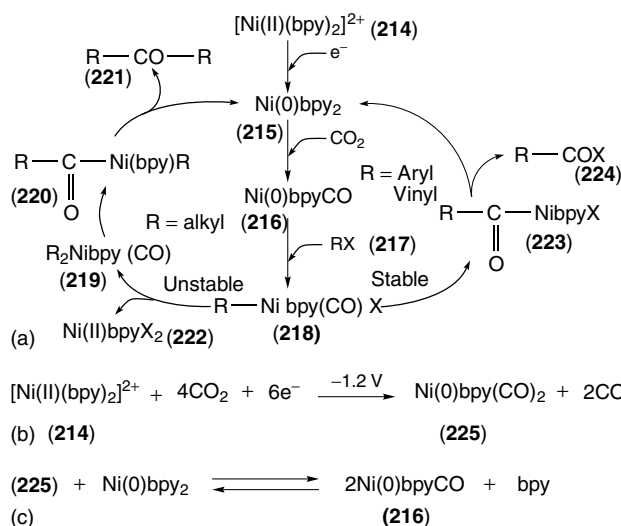
Raney nickel(W-2) covering the Ni electrode has been found to be an effective catalyst under normal pressure and



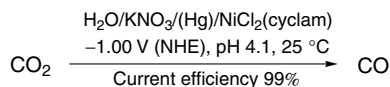
**Scheme 82** Catalytic cycle of carboxylation of alkenes.

at room temperature for the electrocatalytic reduction of unsaturated functional groups such as C=O, C=N, C≡N, C=C, C≡C, and N=O bonds [324]. The reduction is carried out in an MeOH-MeONa system and the discharge potential of this system is  $-1.0$  V (SCE) in contrast to the potential of  $-1.5$  V at a nickel-plated cathode. The use of transition-metal complexes as electrocatalysts, however, can shift this negative potential toward the positive side. The electroreduction of an Ni(bpy) complex, in the presence of CO<sub>2</sub> in *N*-methylpyrrolidone (NMP) or DMF as a solvent gives the corresponding Ni(0) complex (225) associated with two molecules of CO (Scheme 83b). Symproportionation with (215) leads to (216) (Scheme 83c). Oxidative addition of an alkyl halide to (216), followed by an internal CO shift and reductive elimination, leads to the formation of Ni(II) and the symmetrical ketone (221) in high yield (Scheme 83a). The Ni(0) species is electrochemically regenerated, thus giving rise to an efficient

catalytic process [325]. The Ni(0)(bpy)<sub>2</sub> complex (225) formed at  $-1.2$  V (SCE) reacts stoichiometrically with CO<sub>2</sub> to yield the stable Ni(0)(bpy)(CO<sub>2</sub>) complex (225) (Scheme 83b). The concentration of the Ni(0) species (225) and (216) is determined by the Scheme (83c). The various steps of the Ni(II)bpyX<sub>2</sub> (214)-catalyzed electrosynthesis of ketones (221) from halides (217) and CO<sub>2</sub> are summarized in Scheme (83a). Ketones can also be readily obtained by the electroreduction of an organic halide in the presence of metal carbonyls and NiBr<sub>2</sub>(bpy) complexes in DMF [326]. Catalytic CO<sub>2</sub> incorporation into epoxides has been realized by the use of Ni(II)(cyclam) [327]. The dissolution of a stainless steel anode provides catalytic Ni species that enable the efficient synthesis of ketones by electrolysis of organic halides in DMF in the presence of bipyridine and CO [328]. Electro-assisted synthesis of 2-chlorobenzal bromide has been conducted in a DMF-Bu<sub>4</sub>NBr-(Cu/Ni) system in the presence of 1,2-dibromoethane and 1,10-phenanthroline monohydrate in an



**Scheme 83** Nickel-catalyzed formation of ketones and acid halides from carbon dioxide and aryl or vinyl halides.



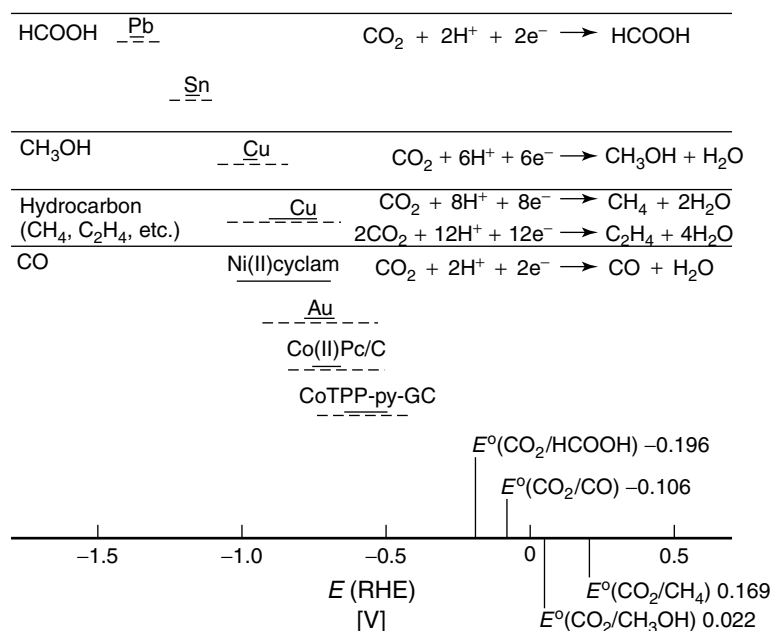
**Scheme 84** Cathodic reduction of carbon dioxide to carbon monoxide.

undivided cell, yielding the desired product in 90% yield [329].

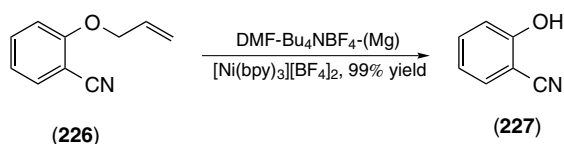
The electrocatalytic reduction of  $\text{CO}_2$  is important not only for alternative fuel sources but also for the storage of electric energy. The direct electroreduction of  $\text{CO}_2$  to  $\text{CO}$  requires a large negative potential (e.g. in DMF,  $-2.21\text{ V}$  and in MeCN,  $-2.10\text{ V}$  vs. SCE) [330]. Many efforts have been made in search of significant metal-complex (or cluster) catalysts for the reduction of  $\text{CO}_2$ . Nickel, Co, Fe, Re, Ru, and Rh-metallic complexes have all been used for this purpose. Among them,  $\text{NiCl}_2(\text{cyclam})$  (Scheme 84) [331–335],  $[\text{Fe}_4\text{S}_4(\text{SR})_4]^{2-}$  [336],  $\text{Re}(\text{bpy})(\text{CO})_3\text{Cl}$  [337], and  $\text{Ru}(\text{trpy})(\text{dppe})\text{Cl}^+$  [338] complexes turn out to be efficient homogeneous catalysts for the selective reduction of  $\text{CO}_2$  to  $\text{CO}$

at relatively low potentials. However, the current yield and turnover numbers need to be improved. Metal phthalocyanines are also used as electrocatalysts [339]. The direct conversion of  $\text{CO}_2$  to methane, using Ru complexes as electrocatalysts, is also a very interesting research subject [340]. A comparison of the  $\text{CO}_2$  reduction potential observed on different electrodes together with thermodynamic potentials,  $E_0$ , is given in Fig. 5 [341]. Some results obtained by electroreduction of  $\text{CO}_2$  in the presence of Ni complexes together with other mediators are presented in Table 17 [342–344].

The electrocatalytic reduction of nitrous oxide to dinitrogen has been achieved at a mercury electrode using Ni(II) complexes of macrocyclic polyamines [355].



**Fig. 5** Comparison of carbon dioxide reduction potentials observed on different electrodes together with thermodynamic potentials,  $E^\circ$ .



**Scheme 85** Cleavage of an aryl allyl ether for deprotection of a phenol.

Nickel-catalyzed electroreductive cleavage of the carbon–oxygen bond of allyl ethers has been reported [356]. The influence of the nature of the ligands associated to the Ni center tends to determine the chemoselectivity of the above reaction [357].

The cationic complex  $[\text{Ni}(\text{bpy})_3](\text{BF}_4)_2$  is a good catalyst for the electroreductive cleavage of the C–O (allyl) bond of allyl ethers, affording parent alcohols or phenols. The Ni(II)-catalyzed electroreductive deprotection of allyl ethers is found to proceed in a DMF– $\text{Bu}_4\text{NBF}_4$ –(Mg) system. For

example, the electrolysis of 2-cyanophenyl allyl ether (**226**) has been electrochemically deprotected in the presence of a Ni catalyst,  $\text{Ni}(\text{bpy})_3(\text{BF}_4)_3$  to give the phenol (**227**) in quantitative yield (Scheme 85) [358].

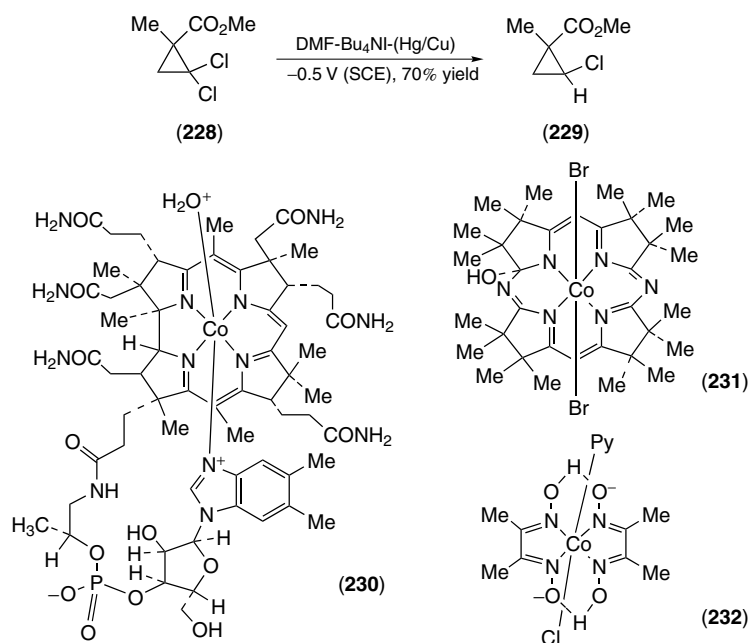
The electroreductive dehalogenation of *gem*-dichlorocyclopropane derivatives (**228**) to the monochloride (**229**) has been performed by electrolysis in a DMF– $\text{Bu}_4\text{Ni}$ –(Hg/Cu) system at  $-0.5$  V (SCE) in the presence of  $\text{Ni}(\text{II})(\text{BF}_4)_2 \cdot 6\text{H}_2\text{O}$  (or  $\text{Co}(\text{II})(\text{BF}_4)_2 \cdot 6\text{H}_2\text{O}$ ) and anthracene (Scheme 86) [359]. An intramolecular propargyl transfer reaction has been

Tab. 17 Electroreduction of carbon dioxide with mediators

Electrolysis conditions	Mediator	Current efficiency [%] (product ratio)	Turnover No./h	Reference
H <sub>2</sub> O/KNO <sub>3</sub> /(Hg) –1.0 V vs. NHE	NiCl <sub>2</sub> (cyclam) <sup>a</sup>	99 (CO)	32	332
H <sub>2</sub> O/NaClO <sub>4</sub> /(Hg) –1.4 V vs. SCE	Ni(II) (cyclam) <sup>a</sup>	... (CO)	...	342
H <sub>2</sub> O/MeCN(2 : 1)/LiClO <sub>4</sub> /(Hg) –1.6 V vs. SCE	Ni(tamc) <sup>b</sup>	98 (CO/H <sub>2</sub> , 2 : 1)	6	335
TMU/Bu <sub>4</sub> NBF <sub>4</sub> /(C/Ni) <sup>c</sup> Zn(powder) or Mg(turnings)	NiCl(dppp)	85 ~ 96 (R-CO <sub>2</sub> <sup>-</sup> )	...	269
MeCN H <sub>2</sub> O/Bu <sub>4</sub> NClO <sub>4</sub> /(Pt) –0.8 ~ 1.3 V vs. SCE	[(Me <sub>6</sub> [14]ane N <sub>4</sub> )Ni(II)] <sup>2+</sup>	95 ~ 100 (CO)	...	343
H <sub>2</sub> O/Clarks-Lubs buffer/(Hg/Pt) –1.2 V vs. SCE	Co(tsp) <sup>d</sup> or Ni(tsp)	...	...	333
H <sub>2</sub> O/MeCN(2 : 1)/KNO <sub>3</sub> /(Hg) –1.6 V vs. SCE	Co(tamc) <sup>b</sup>	90 ~ 93 (CO/H <sub>2</sub> , 1 : 1)	78	335
H <sub>2</sub> O/Clark-Lubs buffer/(Hg) 1.1 ~ 1.5 V vs. SCE	Co(tcpp) <sup>e</sup>	... (formate)	...	344
DMF/Bu <sub>4</sub> NBF <sub>4</sub> /(Hg) –2.0 V vs. SCE	[Fe <sub>4</sub> S <sub>4</sub> (SR) <sub>4</sub> ] <sup>2-</sup> (R = Ph, PhCH <sub>2</sub> )	93 (formate)	...	336 345
H <sub>2</sub> O/KCl/(Pt) –0.6 V vs. SCE	K <sub>2</sub> Fe(II)[Fe(II)(CN) <sub>6</sub> ]	100 (CO → MeOH)	...	346
DMF/H <sub>2</sub> O(9 : 1)/Et <sub>4</sub> NCl/(C) –1.2 vs. NHE	Re(bipy) <sub>3</sub> Cl	98 (CO)	300	337
MeCN/Bu <sub>4</sub> NPF <sub>6</sub> /(Pt) –1.4 V vs. SCE	Ru(trpy) <sub>3</sub> <sup>f</sup> (appene)Cl <sup>h,g</sup>	... (CO)	...	338
H <sub>2</sub> O/DMF/NaOH/H <sub>3</sub> PO <sub>4</sub> –1.50 V vs. SCE	[Ru(bpy) <sub>2</sub> (CO) <sub>2</sub> ] <sup>2+</sup>	(pH 6: CO, formate)	...	347 348 349
H <sub>2</sub> O/Na <sub>2</sub> SO <sub>4</sub> /KHCO <sub>3</sub> –0.9 V vs. Hg <sub>2</sub> SO <sub>4</sub> , pH 4	RuO <sub>2</sub> /TiO <sub>2</sub> (35/65) (electrode)	76 (MeOH)	–	350
MeCN/Bu <sub>4</sub> NClO <sub>4</sub> /Me <sub>2</sub> NH/Me <sub>2</sub> NHCl/(Hg) –1.30 V vs. SCE	[Ru(bpy) <sub>2</sub> (CO) <sub>2</sub> ] <sup>2+</sup>	75.7 (formate)	21.4 (DMF)	351
MeCN/Bu <sub>4</sub> NPF <sub>6</sub> /(Pt) –1.55 V vs. SSCE	cis-Rh(bpy) <sub>2</sub> <sup>h</sup> (CF <sub>3</sub> SO <sub>3</sub> ) <sub>2</sub>	64 (formate)	–	338
H <sub>2</sub> O/Et <sub>4</sub> NClO <sub>4</sub> /(C) –0.8 V vs. Ag/Ag <sup>+</sup>	Rh(bpy) <sub>3</sub> Cl <sub>3</sub>	25 (formate)	–	347
CH <sub>2</sub> Cl <sub>2</sub> /Bu <sub>4</sub> NBF <sub>4</sub> /(Pt) –1.50 ~ –1.65 V (Ag/Ag <sup>+</sup> )	Pd(oep) <sup>i</sup>	– (oxalate)	–	352
MeCN/Bu <sub>4</sub> NClO <sub>4</sub> /(Pt) –1.55 V vs. SSCE	poly-Re(vbpy) (CO) <sub>3</sub> Cl	92.8 (CO)	516	353
MeCN/Bu <sub>4</sub> NPF <sub>6</sub> /(Pt) –1.50 ~ –1.55 V vs. SCE	fac-Re(bpy) (CO) <sub>3</sub> Cl <sup>h</sup>	85 (CO)	20~30	354

<sup>a</sup> cyclam: 1,4,8,11-tetraazacyclotetradecane<sup>b</sup> tamc: tetraazamacrocyclic complexes<sup>c</sup> TMU: tetramethylurea<sup>d</sup> tsp: 4,4',4'',4'''-tetrasulfonated Phthalocyanine<sup>e</sup> tcpp: mesotetracarboxyphenylporphine<sup>f</sup> trpy: 2,2',2''-terpyridine<sup>g</sup> appene: cis 1,2-bis(diphenylphosphino)ethylene<sup>h</sup> bpy: 2,2'-bipyridine<sup>i</sup> oep: 2,3,7,8,12,13,17,18-octaethylporphyrin.





**Scheme 86** Dehalogenation of *gem*-dichlorocyclopropane derivatives.

attained by Ni complexes [360]. Cyclic sulfides have been synthesized by the Ni complex-catalyzed electroreduction of unsaturated thioacetates and thiosulfonates [361].

The hydrogenation of styrene into ethylbenzene using a two-compartment cell separated by a hydrogen-permeable sheet prepared from  $\text{LaNi}_5$  has been investigated [362]. Electrocatalytic hydrogenation of conjugated enones to the corresponding carbonyl compounds has been achieved in aqueous methanol at nickel bromide, fractal nickel, and Raney nickel electrodes made of the compressed powders in good yields [363]. The hydrogenation of acetone has been studied in basic aqueous solutions with a dispersed Raney nickel electrode [364]. The electrocatalytic hydrogenation of carvone and limonene at a Raney nickel cathode was investigated in an aqueous solution containing a

non-micelle-forming surfactant to give the corresponding alcohols as major products [365]. Palladium on Ni in methanol is found to be a very effective and highly selective cathode for the electrocatalytic hydrogenation of nitrobenzenes to anilines [366].

#### 15.3.1.2 Cobalt (Co) Complex Mediators

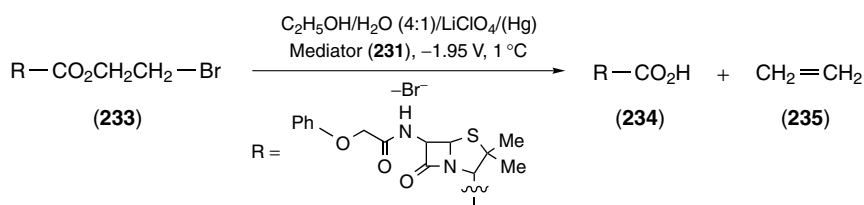
Vitamin  $\text{B}_{12}$  derivatives and their model compounds have recently been used as recyclable electrocatalysts for the reduction of alkyl halides since low-valent Co species are good nucleophiles toward organic substrates [367–369]. Examples of such electrocatalysts are the vitamin  $\text{B}_{12}$  derivatives aquocobalamin (230), dibromo[l-hydroxy-2,2,3,3,7,7,8,8,12,12,13,13,17,17,18,18-hexadecamethyl-10,20-diazaoctahydroporphinato]cobalt(III) (231), and cobaloxim (232). The above Co(I) complexes can be

used for the reductive cleavage of the C–X (halogen) bond through the formation of alkylcobalt(III) complexes, bearing a Co–C covalent bond with a subsequent two-electron reduction to regenerate the Co(I) species. For example, the  $\beta$ -haloethyl protecting group of the ester (233) can be readily removed by reductive elimination of ethylene (235) to liberate the free acid (234) (Scheme 87) [370–372].

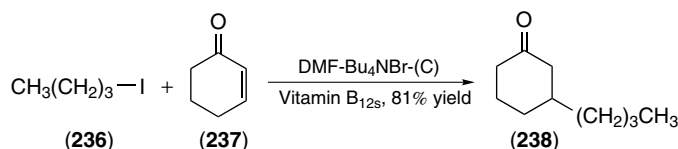
Intermolecular addition of butyl iodides (236) to cyclohexenone (237) has been

achieved in a DMF–Bu<sub>4</sub>NBr–(C) system by the Co(I)L complex vitamin B<sub>12</sub> generated at carbon cloth electrodes, giving (238) (Scheme 88) [373].

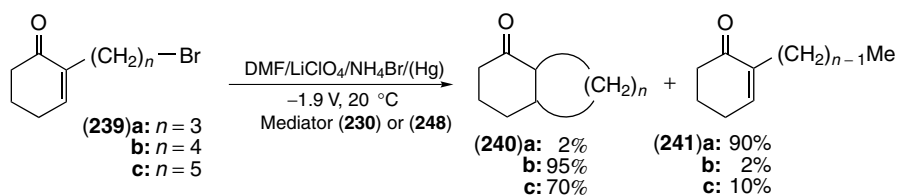
A novel Michael-type addition of alkyl halides to  $\alpha,\beta$ -enones (239) has been realized using either aquocobalamin (232) or dibromo[l-hydroxy-8H-HDP]cobalt(III) (248) [374]. The electrolysis of (239) in a DMF–LiClO<sub>4</sub>/NH<sub>4</sub>Br–(Hg) system involves competition between two paths that may lead either to bicyclic ketones (240)



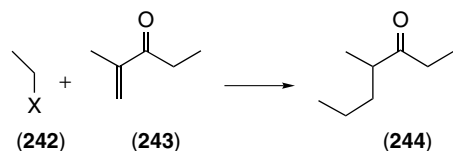
**Scheme 87** Cathodic elimination for deprotection of a carboxylic acid.



**Scheme 88** Cathodic vitamin B<sub>12</sub>-catalyzed addition of butyl iodide to cyclohexenone.



**Scheme 89** Cathodic cyclization of bromoalkylenones.

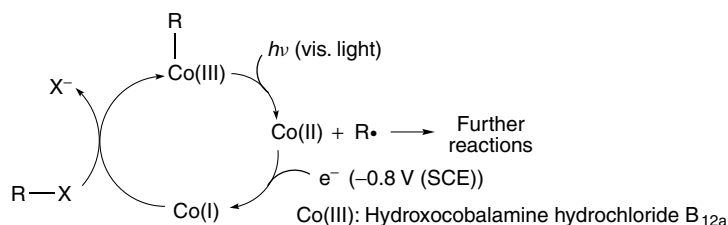


**Scheme 90** Cathodic addition of ethyl bromide to 2-methyl-1-penten-3-one.

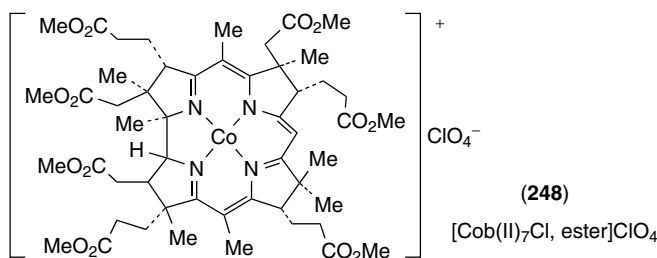
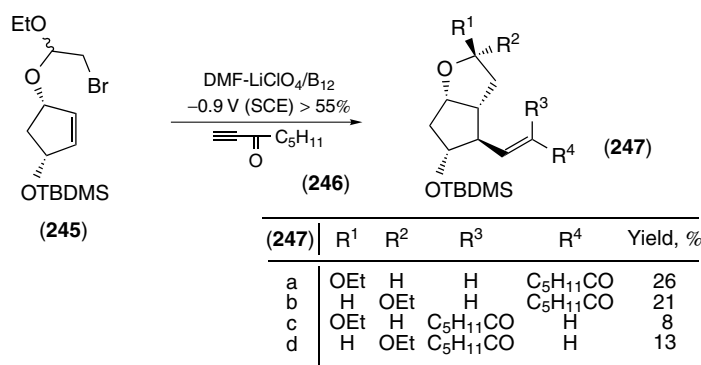
through C–C bond formation, or open-chain products (**241**) *via* substitution of bromine by hydrogen (Scheme 89) [374]. A device for the Michael-type addition of ethyl bromide (**242**) to 2-methyl-1-penten-3-one (**243**), a precursor of the pheromone, (*dl*)-4-methyl-3-heptanone (**244**), has been made by means of the photocatalytic electroreduction of vitamin B<sub>12</sub> in combination with solar power (Scheme 90) [375].

Radical reactions mediated by organocobalt complexes (**248**) have been proven

to be useful in the construction of carbon and hetero-ring systems [376, 377]. A prostaglandin F<sub>2</sub> $\alpha$  precursor (**247**) containing all the structural elements for the C<sub>6</sub> to C<sub>20</sub> segments with 8R, 9S, 11R, and 12R configurations has been electrosynthesized in a one-step operation by sequential two-C–C bond formations. For example, a B<sub>12</sub>-catalyzed radical cyclization–addition sequence is operative for the binding of chiral cyclopentene bromoacetal (**245**) and 1-octyn-3-one (**246**)



**Scheme 91** Generation of carbon-centered free radicals by vitamin B<sub>12</sub>-photoelectrocatalysis.



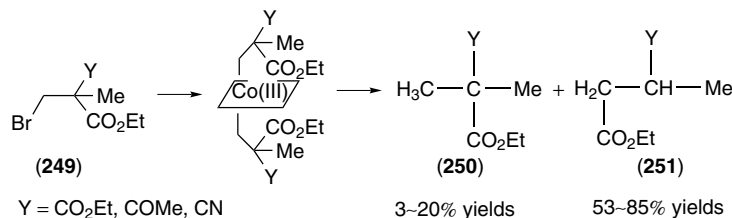
**Scheme 92** Synthesis of a prostaglandin F<sub>2</sub> $\alpha$ -precursor.

(Scheme 92) [378]. A general mode of action for carbon-centered free radicals by B<sub>12</sub>-photoelectrocatalysis is depicted in Scheme 91.

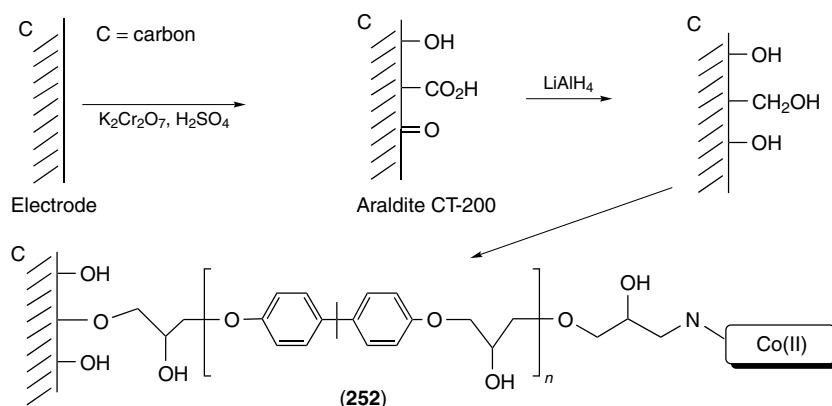
Carbon-skeleton rearrangements have been catalyzed by heptamethyl-cobyrinate perchlorate, [Cob(II)<sub>7</sub>Cl, ester]ClO<sub>4</sub>, under electrolysis conditions [379–383]. Electrochemical rearrangements are performed by the electrolysis of 2-substituted 1-bromo-2-ethoxycarbonylpropane (**249**) in a DMF-Bu<sub>4</sub>NBF<sub>4</sub>/Co(III) complex-(Pt/Pt) system using the Co(III) complex in an undivided cell containing imidazole (Scheme 93). The trivalent Co complex is electrochemically reduced to the monovalent Co complex, and the resulting species reacts with alkyl bromide to give the monoalkylated complex. The subsequent one-electron reduction leads to a

radical intermediate, which then disproportionates to the dialkylated complex and the monovalent Co species. The dialkylated complex is converted into the products (**250**) and (**251**) through electrooxidation on the anode [384, 385]. The cobaloxim-mediated 1,2-acyl migration of 2-(bromomethyl)cycloalkanones can lead to the formation of ring-enlarged compounds as the major products [386]. The electrolysis is carried out in a MeOH-Et<sub>4</sub>NOTs-KOH-(Pt) system at a current density of 20 mA cm<sup>-2</sup>.

The electroreductive dehalogenation of  $\alpha$ -haloacetic acids has been achieved with cobalamin [387]. The hydrophobic vitamin B<sub>12</sub> Co complex immobilized on a glassy carbon electrode (**252**) may catalyze the electrochemical carbon-skeleton rearrangements of



**Scheme 93** Electrochemical rearrangement of 2-substituted 1-bromo-2-ethoxycarbonylpropane.



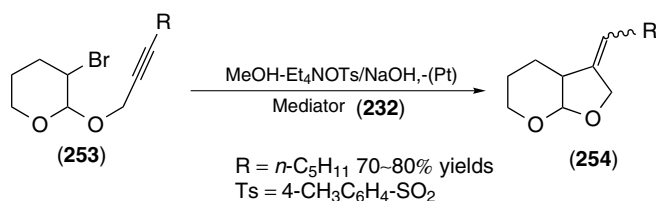
**Scheme 94** Cathodic dehalogenation with immobilized vitamin B<sub>12</sub>.

alkyl halides bearing electron-withdrawing groups (Scheme 94) [388]. The electrode surface is coated with a polymeric monomer, Araldite CT-200, bearing vitamin B<sub>12</sub>. Vitamin B<sub>12</sub> may induce the formation of surfactant aggregates in a water-in-oil microemulsion offering the possibility of selecting a suitable microenvironment for the reactant as a means of controlling kinetics and reactivity [389].

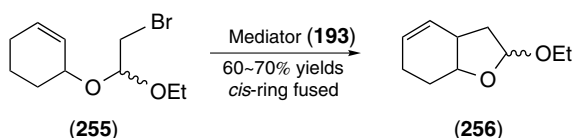
Cobaloxime(I), electrochemically regenerated from chloro(pyridine)-cobaloxime (III) (232), has been employed as a mediator in the reductive cleavage of the C–Br bond of 2-bromoalkyl 2-alkynyl ethers (253), giving (254) through radical trapping of the internal olefin (Scheme 95) [390]. An interesting feature of the radical cyclization (253)→(254) is the reaction in methanol, unlike the trialkyltin hydride-promoted radical reactions that need an aprotic non-polar solvent. An improved procedure for the electroreductive radical cyclization of (253) has been attained by the combined use of cobaloxime(III) (232) and a zinc plate as a sacrificial anode in an undivided cell [391]. The procedure is advantageous in terms of the turnover of the catalyst and the convenience of the operation.

The treatment of the bromoacetal (255) with catalytic amounts (~10%) of a Co(I) species, generated by the electroreduction of cobaloxime (232) in an MeOH–LiClO<sub>4</sub> system at –1.8 V, produces the cis-fused adduct (256) in 60 ~ 70% yield (Scheme 96) [392]. Cathodic reduction is used for the synthesis of a [Co(CO)3PBu<sub>3</sub>]<sup>–</sup> complex in a methanol-methyl formate medium, which catalyzes the alkoxycarbonylation of dichloromethane to dimethyl malonate in up to 75% yield [393]. The Co(II) complexes are found to be effective for the homogeneous reduction of *gem*-dichlorocyclopropanes in the presence of anthracene [394]. The formation of the C–C double bond of (258) may be ascribed to the α-elimination of the Co–H species. Thus, benzalchloride (257) can be converted to a mixture consisting primarily of *cis*- and *trans*-stilbenes (258) by the action of electrogenerated Co(I)(salen) (Scheme 97) [395–398].

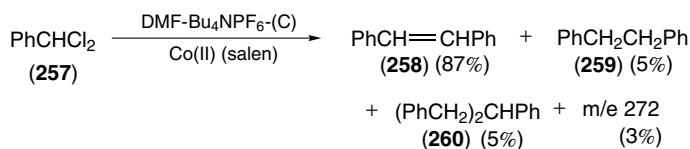
A microemulsion made from dodecane, water, and didodecyldimethylammonium bromide has proven to be a good medium for the catalytic reduction of *trans*-1,2-dibromocyclohexane and for S<sub>N</sub>2 reactions



**Scheme 95** Cyclization of bromoalkyl alkynyl ethers.



**Scheme 96** Cyclization of bromoalkyl alkenyl ethers.



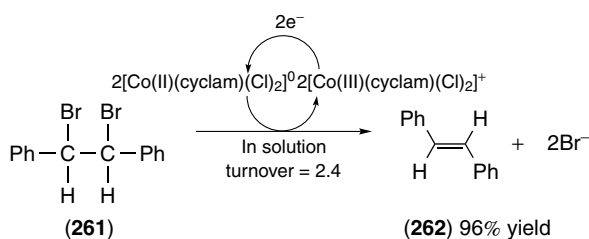
**Scheme 97** Stilbene from benzalchloride via an  $\alpha$ -elimination at cobalt catalysts.

of alkyl bromides with electrogenerated Co(I) complexes [399].

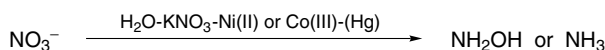
The Co(III) complexes with the 1,4,8,11-tetraazacyclotetradecane (cyclam) ligand are found to behave as redox mediators for the indirect electroreduction of *meso*-1,2-dibromo-1,2-diphenylethane (**261**) leading to *trans*-stilbene (**262**) in a DMF-Bu<sub>4</sub>NClO<sub>4</sub>-(Pt) system (Scheme 98) [400].

The use of the Co(I) porphyrin for the homogeneous electroreduction of dioxygen in DMF-Bu<sub>4</sub>NClO<sub>4</sub>-(C) system in the presence of benzoic anhydride has been developed [401]. The reduction of [(TMpyP)Co(II)]<sup>4+</sup> (where TMpyP = *meso*-tetrakis(1-methylpyridinium-4-yl)

porphyrin) at  $-0.49$  V (SCE) leads to the formation of [(TMpyP)Co(I)]<sup>3+</sup>. The addition of cyclohexene to this mixture affords cyclohexene oxide. The integration of the current–time curves for the reduction of [(TMpyP)Co(II)]<sup>4+</sup> under a dioxygen atmosphere gives a turnover number up to 15 during the first 15 min of bulk electrolysis. Electropolymerized films of [Co(v-terpy)<sub>2</sub>]<sup>2+</sup> (v-terpy = vinylterpyridinyl) exhibit reactivity patterns, especially with regard to ligand exchange, which differ from those exhibited by [Co(terpy)<sub>2</sub>]<sup>2+</sup> in solution [402]. The films are active in the catalytic electroreduction of CO<sub>2</sub> to CO.



**Scheme 98** Cathodic elimination at *vic*-dibromides to stilbenes.



Catalyst	NH <sub>2</sub> OH (current yield, %)	NH <sub>3</sub>
Co(III)(cyclam)	88	2
Ni(II)(cyclam)	68	2

**Scheme 99** Electrocatalytic reduction of nitrates.

Electrocatalytic reduction of  $\text{NO}_3^-$  takes place efficiently in the presence of a catalytic amount of  $\text{Co(III)(cyclam)}$  or  $\text{Ni(II)(cyclam)}$  in aqueous media at a mercury cathode (Scheme 99) [403].

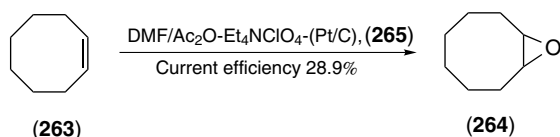
A polypyrrole film electrochemically deposited on gold electrodes from an  $\text{MeCN-LiClO}_4/\text{Co(OAc)}_2$  solution shows electrocatalytic activity in dioxygen reduction [404]. The catalytic electroreduction of dithio dipropionic acid (PSSP) with the water-soluble cobalt(III)tetrakis(4-trimethyl-ammonium phenyl) porphyrin (CoTMAP) has been studied. The Co catalyst adsorbed on the glassy carbon electrode plays a major role in the electroreductive cleavage of the S–S bond [405].

#### 15.3.1.3 Iron (Fe) Complex Mediators

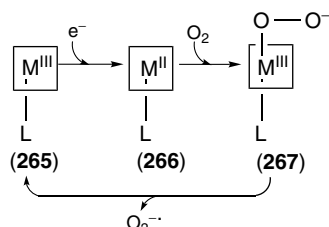
The use of Fe, indium, and zinc as sacrificial anodes in the electrochemically assisted Reformatsky reaction of ethyl 2-bromoalkanoates with succinic anhydride is found to be effective, giving 1-ethyl-3-oxohexanedioates in 49~80%

yields [406]. Catalytic epoxidation of cyclooctene (**263**), leading to the epoxide (**264**), has been performed by using electrogenerated metalloporphyrin oxo complexes prepared from [5,10,15,20-tetrakis-(pentafluorophenyl)porphinato]iron(III)chloride (**265**) by electroreduction in a  $\text{DMF}/\text{Ac}_2\text{O-Et}_4\text{NClO}_4\text{-(Pt/C)}$  system (Scheme 100) [407]. The reduced form (**266**) of the catalyst (**265**) tends to transfer electrons to a dioxygen to generate a superoxide ion *via* (**267**) (Scheme 101). For example, the catalyst (**265**) reacts with acetic anhydride to yield metal oxo porphyrin complexes (**268**) *via* (**269**) that are used in epoxidizing cyclooctene (**263**), leading to (**264**) (Scheme 102).

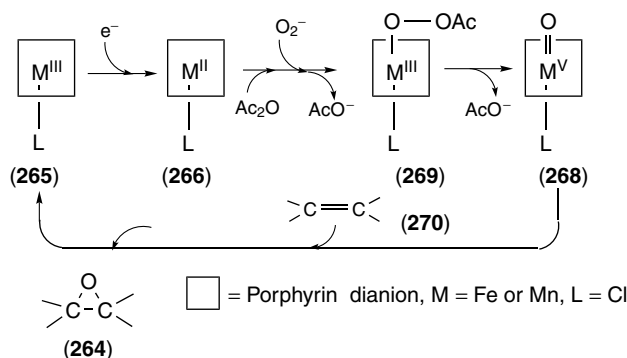
Carbon dioxide has been reduced to methanol with the Everitt's salt (ES)-mediated electrode in the presence of 1,2-dihydroxybenzene-3,5-disulphonato(iron) ferrate(III) complex (Scheme 103) [408, 409]. The reduction proceeds as follows: a weak coordination bond is first formed between the central metal of ES and ethanol, then the subsequent insertion of  $\text{CO}_2$  onto



**Scheme 100** Electrocatalytic epoxidation of cyclooctene.



**Scheme 101** Reduction of oxygen to superoxide anion.



**Scheme 102** Catalytic cycle for the epoxidation of alkenes with iron or manganese complexes.



ES = Everitt's salt,  $\text{K}_2\text{Fe(II)[Fe(II)(CN)}_6]$

PB = Prussian blue,  $\text{KFe(III)[Fe(II)(CN)}_6]$

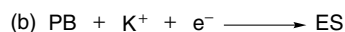
**Scheme 103** Catalytic reduction of carbon dioxide to methanol.

the metal complex proceeds to form an intermediate Fe(III)-iron-ethyl formate complex, which is finally reduced by ES with the consumption of protons in solution to form methanol and the starting metal complex (Scheme 103a). This reaction may proceed continuously when the produced PB is electrochemically reduced to ES (Scheme 103b). A large-scale regeneration of ferricyanide from ferrocyanide produced in the preparation of 3,4,5-trimethoxybenzaldehyde from the hydrazide using a ferri/ferrocyanide redox system has been attained in 70~75% current efficiency [410].

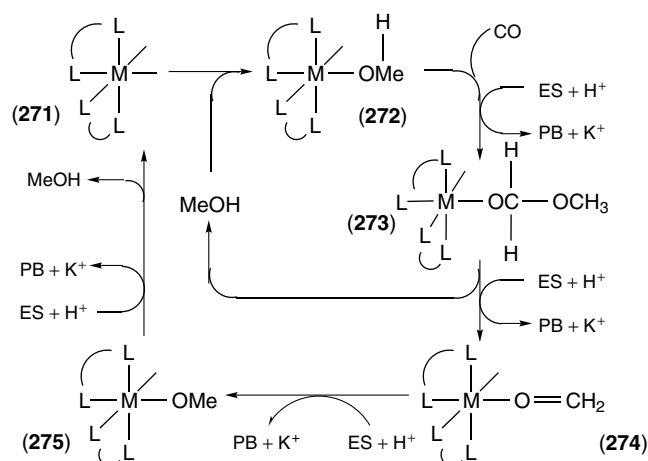
Electrochemical carboxylation of acetophenone with  $\text{CO}_2$  coupled with nitrite reduction proceeds by the controlled-potential electrolysis of  $\text{CO}_2$ -saturated acetonitrile containing  $[\text{Fe}_4\text{S}_4(\text{SPh})_4]^{2-}$ ,  $\text{NO}_2^-$ ,  $\text{PhCOCH}_3$ , and a dehydration

agent at  $-1.25\text{ V}$  (SCE) giving 78% current efficiency for the formation of  $\text{PhCOCH}_2\text{CO}_2^-$  [411]. The electroreduction of CO into methanol is also performed by using the ES-coated platinum electrode as a mediator in the presence of sodium aquapentacyanoferrate(II),  $\text{Na}_3[\text{Fe}(\text{CN})_5(\text{H}_2\text{O})]$ , as homogeneous catalysts at a three-phase(electrode/solution/gas) interface (Scheme 104) [412–414]. The mediated electroreduction of CO and  $\text{CO}_2$  to methanol (see 271→275) has been achieved by the use of surface-confined metal complexes (271), for example, aquapentacyanoferrate(II), aquopentafluoroferrate(III), and 4,5-dihydroxybenzene-1,3-disulphonatoferrate(III) (Scheme 105) [346]. The general feature of the metal complex capable of operating as a catalyst in the reduction of CO and  $\text{CO}_2$  is that it should have at least one labile





**Scheme 104** Electroreduction of carbon monoxide to methanol.

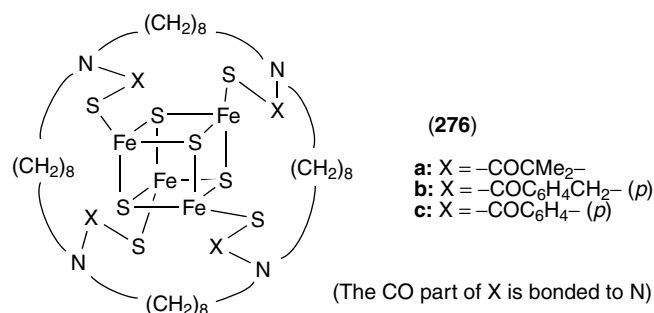


**Scheme 105** Catalytic cycle for the reduction of carbon monoxide to methanol.

ligand in its coordination shell, which can be replaced by a new ligand in the course of the reaction.

Electroreductive fixation of CO<sub>2</sub> into formate can be efficiently performed by using Fe<sub>4</sub>S<sub>4</sub> cubane clusters (276) bearing a 36-membered methylene backbone in a DMF-Bu<sub>4</sub>NBF<sub>4</sub>-(Pt/Hg) system

(Scheme 106) [415]. The reductive fixation of CO<sub>2</sub> to thioesters catalyzed by [Mo<sub>2</sub>Fe<sub>6</sub>S<sub>8</sub>(SEt)<sub>9</sub>]<sup>3-</sup>, leading to α-keto acid, has also been investigated [416]. Similarly, electroreduction of CO<sub>2</sub> using Fe-S clusters (276) is carried out in a DMF-Bu<sub>4</sub>NBF<sub>4</sub>/[Fe<sub>4</sub>S<sub>4</sub>(SCH<sub>2</sub>Ph)<sub>4</sub>]<sup>2-</sup>-(Pt/Hg) system under CO<sub>2</sub> at −2.0 V (SCE)



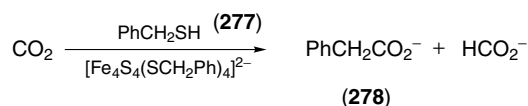
**Scheme 106** Fe<sub>4</sub>S<sub>4</sub> cubane cluster for the cathodic fixation of carbon dioxide.

in the presence of benzylthiol (**277**) to give phenylacetate (**278**) and a formate (Scheme 107) [345].

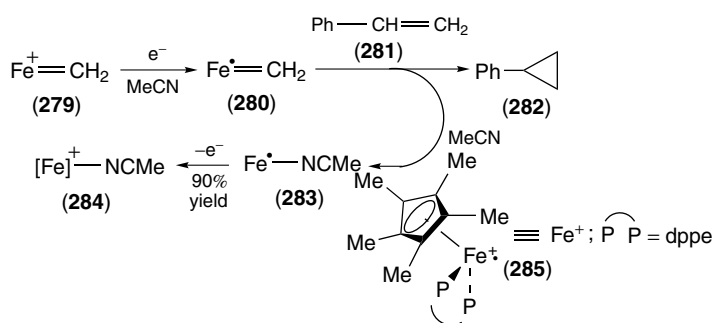
Methylene addition to the C–C double bond of styrene (**281**) with  $[\text{Fe}(\text{C}_5\text{Me}_5)(\text{dppe})(=\text{CH}_2)]^+ \text{BF}_4^-$  (**279**) leading to phenylcyclopropane (**282**) proceeds in a  $\text{CH}_2\text{Cl}_2/\text{MeCN}-\text{Bu}_4\text{NPF}_6\text{-Pt}$  system at a potential of  $-0.6\text{ V}$  (SCE) via a radical intermediate (**280**) (Scheme 108) [417].

Ligand exchange is completed within 2 min at  $20^\circ\text{C}$  (1 mmol scale). The compound  $[\text{Fe}(\text{C}_5\text{Me}_5)(\text{dppe})\text{MeCN}]^+ \text{BF}_4^-$  (**284**) is isolated in 90% yield.

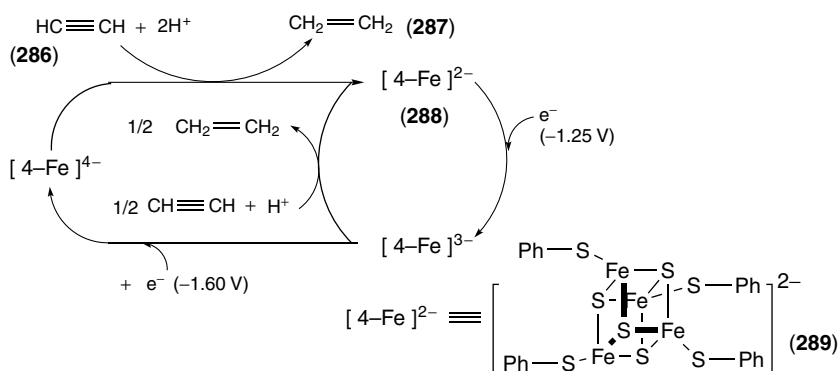
Reduction of acetylene (**286**) to ethylene (**287**) is catalyzed by nitrogenase-like catalysts,  $[\text{Fe}_4\text{S}_4(\text{SPh})_4]^{3-}$  (**289**) or  $[\text{Mo}_2\text{Fe}_6\text{S}_9(\text{SPh})_8]^{3-}$  ( $[\text{Mo-Fe}]^{3-}$ ), which are electrosynthesized in a  $\text{CH}_3\text{OH}/\text{THF}-\text{LiCl}(\text{Hg})$  system from  $[\text{4-Fe}]^{3-}$  (**288**) or



**Scheme 107** Cathodic reduction of carbon dioxide to formate.



**Scheme 108** Cathodic cyclopropanation with an iron-methylene complex.



**Scheme 109** Catalytic cycle for the iron-complex-mediated reduction of ethyne to ethene.

$[\text{Mo-Fe}]^{3-}$  tetrabutylammonium salts. The reduced species of (288) or  $[\text{Mo-Fe}]^{3-}$  are capable of reducing acetylene to ethylene (Scheme 109) [418].

The water-soluble Fe porphyrin,  $3\text{Na}^+ [\text{Fe(III)(TPPS)}]^{3-} \cdot 12\text{H}_2\text{O}$  [ $\text{H}_2\text{TPPS}_4^-$  = tetra-anionic form of *meso*-tetrakis( $\pi$ -sulfonatophenyl)porphine], has recently been shown to be an effective catalyst for the electroreduction of nitrite to ammonia [419]. The Fe *meso*-tetrakis(*N*-methyl-4-pyridyl)porphyrin and/or the Fe *meso*-tetrakis( $\pi$ -sulfophenyl)porphyrin complex shows a catalytic activity for the reduction of dioxygen in aqueous solutions, leading to hydrogen peroxide [420].

The reductive behavior of iron-carbene porphyrins has been investigated. A  $2e^- + \text{H}^+$  reduction of thiocarbonyl complexes can lead to the corresponding thioformyl complexes in a reversible system [421].

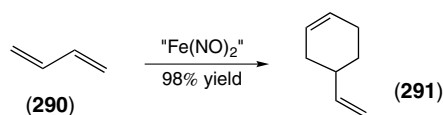
A preparative method using a ferrous hyponitrite complex,  $[\text{Fe(NO)}_2\text{Cl}]^{2+}$ , as an active electrocatalyst for selective cyclodimerization has been investigated. The active catalyst  $\text{Fe(NO)}_2$  can be prepared

by the electroreduction of  $[\text{Fe(NO)}_2\text{Cl}]^{2+}$  in a propylene carbonate/(Pt/Fe) system and the catalyst is used *in situ* for the cyclodimerization of butadiene (290) to yield 4-vinylcyclohexene (291) in 98% yield (Scheme 110) [422]. The superiority of inner-sphere catalysts such as the Fe(III) porphyrin complex for the indirect electroreduction of vicinal dibromoalkanes has been pointed out in terms of rate constants and selectivity [423].

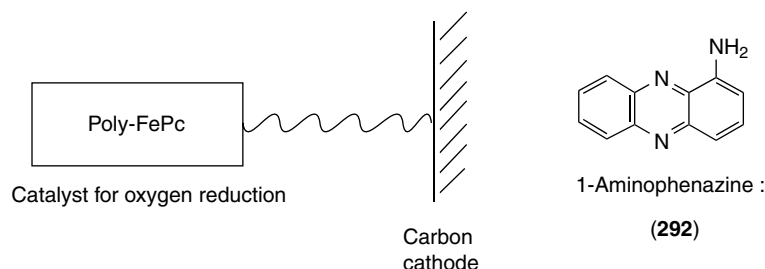
Hemoglobin, myoglobin, cytochrome C, and cytochrome oxidase are all electrochemically reduced in the presence of quinoxaline. Quinoxaline is preferentially reduced to the anion radical that can release its electron. Metalloproteins can serve as the electron acceptors in which the metal ion is reduced [424].

Electrosynthesis of 5-nitroguaiacol from 4-nitroanisole has been performed by the electroreduction of Fenton's reagent in an  $\text{MeCN}/\text{H}_2\text{O}(1:1)\text{-Fe}_2(\text{SO}_4)_2/\text{HClO}_4\text{-(Pt/SUS)}$  (SUS = Stainless Steel) system [425].

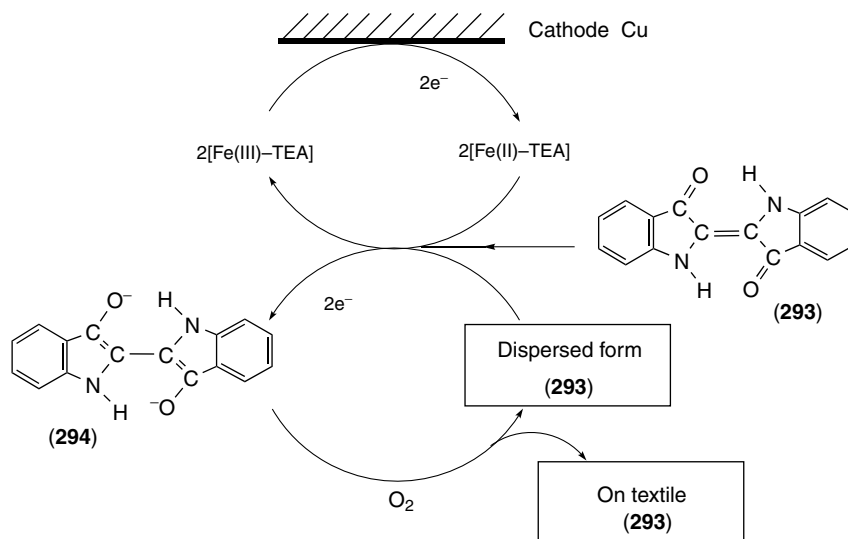
Polymeric Fe phthalocyanine (poly-FePc) is known to be a better catalyst



**Scheme 110** Cyclodimerization of butadiene via cathodically prepared  $\text{Fe(NO)}_2$ .



**Scheme 111** Cathodic reduction of oxygen at low overvoltage.



**Scheme 112** Cathodic reduction of indigo to leuco-indigo with iron complexes.

for dioxygen reduction than monomeric FePc. The polymeric Fe phthalocyanine-coated electrode is prepared via the “melt-synthesis” method. It shows the lowest polarization and maintains the most positive potential at a  $10 \text{ mA cm}^{-2}$  discharge (Scheme 111) [426].

A glassy carbon electrode coated with an anodically formed polymer of 1-aminophenazine (**292**) mediates the reduction of Fe(III), which occurs in the region of the potential in which the reduction of (**292**) takes place [427].

The reduction of indigo (**293**), which is insoluble in water and alkaline solutions, to the disodium salt of leuco-indigo (**294**), which is soluble in alkaline solutions, is crucial to the application of (**293**) as a textile dye. Recently, a procedure for indirect electroreduction of a dispersed (**293**) dye with coordination compounds of Fe(II) and Fe(III) salts, and triethanolamine has been developed as a mediatory system (Scheme 112) [428, 429]. With this reversible redox system as a

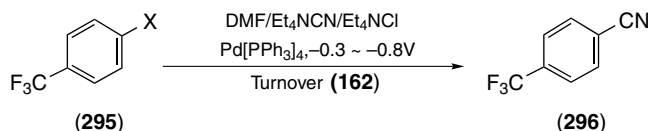
mediator, the finely dispersed indigo dye (**293**) can be reduced under the following conditions: the catholyte is prepared by mixing  $\text{Fe}_2(\text{SO}_4)_3$ ,  $\text{H}_2\text{O}$ , triethanolamine, and  $\text{NaOH}$ , and then adding water. Indigo is added to the catholyte solution and a dispersion agent (naphthalenesulfonic acid condensation product), and the mixture is electrolyzed at a Cu cathode at  $-1.05 \sim -1.10 \text{ V (Ag/AgCl)}$ . Electrocatalytic reduction of nitrite to ammonia has been demonstrated using a water-soluble ion porphyrin as the catalyst [430].

### 15.3.2

#### Indirect Reduction with Mediators Containing Palladium, Rhodium, Iridium, and Platinum

##### 15.3.2.1 Palladium (Pd) Complex Mediators

A catalytic electrode for the reduction of aqueous bicarbonate ( $\text{CO}_3\text{H}^-$ ) leading to a formate ( $\text{HCO}_2^-$ ) has been



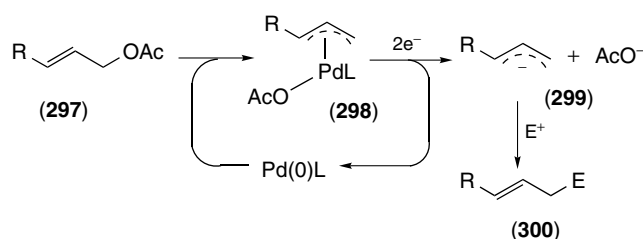
**Scheme 113** Cathodic cyanation of aryl chlorides.

devised. A Pd-impregnated polymer on a metallic electrode is shown to catalyze the reaction of hydrogen with  $\text{CO}_3\text{H}^-$  to form  $\text{HCO}_2^-$  [431]. A Pd(II)-metalloporphyrin complex has been used as a novel homogeneous catalyst for the electroreduction of  $\text{CO}_2$  leading to an oxalate (see Table 17) [352]. The Pd(triphos)L( $\text{BF}_4$ ) complexes (L = MeCN,  $\text{P}(\text{OMe})_3$ ,  $\text{PEt}_3$ ,  $\text{P}(\text{CH}_2\text{OH})_3$ , and  $\text{PPh}_3$ ) are able to catalyze the electroreduction of  $\text{CO}_2$  to CO in acidic acetonitrile solutions [432]. The analogous Ni and Pt complexes do not catalyze the  $\text{CO}_2$  reduction under similar conditions.

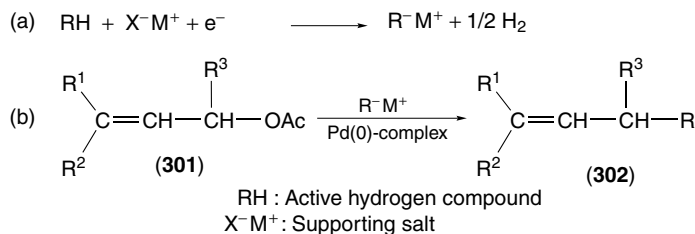
Long-lived homogeneous Pd(0) $\text{L}_4$  [L =  $\text{P}(\text{Ph})_3$ ] catalysts for the cyanation of aryl chlorides (295) (X = Cl) have been developed, which are activated by cathodic reduction (Scheme 113) [433]. A high temperature,  $130^\circ\text{C}$ , and a high-boiling solvent, dimethylformamide, are required because Pd does not insert into the aryl C–Cl bond at lower temperatures. Catalytically inactive metal species formed in undesirable side reactions with cyanide are electrochemically restored to a catalytically

active state. In the case of electrocyanation, (295) is converted to (296); the number of turnovers of Pd-complex catalysts can be improved from 8 to 162 by the passage of a small amount of electricity. In addition, Ni(0) $\text{L}_4$  complexes can be used in place of Pd(0) $\text{L}_4$  complexes as electrocatalysts for the cyanation of acyl chlorides.

The Pd(0)-catalyzed displacement of allylic acetates (297) with various nucleophiles *via* the allylic Pd(II) complex (298) is a well-established procedure (Scheme 114). Through attack of electrons ( $+2e^-$ ) in place of nucleophiles, (298) is expected to undergo a reductive cleavage providing allylic carbanions (299) and the acetate anion along with Pd(0) complexes. The latter can then be captured by various electrophiles (polarity inversion, Scheme 114) leading to (300) [434]. This procedure is useful for the deprotection of allyl esters under neutral conditions. Recently, a mechanistic study of the Pd-catalyzed reaction of allylic acetate (297), using carbonyl compounds as an electrophile, has been reported [435].



**Scheme 114** Pd(0)-catalyzed nucleophilic substitution of allylic acetates.



**Scheme 115** Pd(0)-catalyzed substitution of allylic acetates with electrogenerated carbanions.

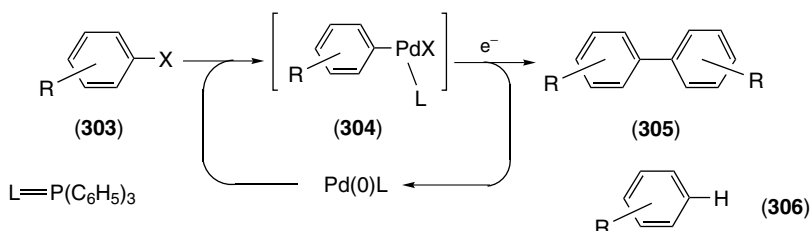
The Pd(0)-catalyzed electrophilic reaction of allyl acetates (**301**) with electrochemically induced carbanions leading to (**302**) has been performed (Scheme 115) [436]. The electrolysis is carried out in a DMF- $\text{Et}_4\text{NClO}_4$ -(Pt) system in the presence of the active hydrogen compound,  $\text{Ph}_3\text{P}$ , and  $\text{Pd(II)(PhCN)}_2\text{Cl}_2$  at a current density of  $0.26 \text{ A dm}^{-2}$  and the allyl acetate (**301**).

The Pd-catalyzed electro-cleavage of the C–O bond of allyl aryl ether proceeds smoothly in a DMF- $\text{Bu}_4\text{NBF}_4$ -(Mg)-(Stainless Steel) system, giving deprotected products in 73~99% yield [437]. The sp–sp intermolecular coupling reaction with the Pd water-soluble catalyst prepared *in situ* from Pd(II) acetate and sulfonated triphenylphosphine in an MeCN- $\text{H}_2\text{O}$  system yields diynes in 45~65% yields [438]. Similarly, the  $\text{sp}^2$ – $\text{sp}$  coupling of 2-iodophenols or 2-iodoanilines and terminal alkynes followed by intramolecular cyclization gives indol and furan

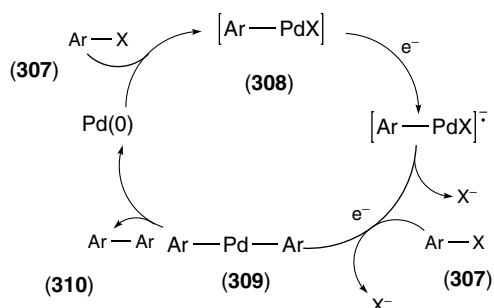
derivatives in 60~99% yield [438]. Electrocatalytic dechlorination of chloroaromatics on a palladium-loaded carbon felt cathode in an aqueous medium has been attained in good yields [439].

The Pd(0)-catalyzed electroreductive coupling of aryl halides (**303**) is a currently relevant topic. In the electroreduction of aryl halides (**307**) the replacement of the halogen atom by hydrogen predominantly takes place giving (**306**). Difficulties are encountered, however, when aryl–aryl coupling products (**305**) *via* (**304**) are wanted (Scheme 116). An efficient electroreductive coupling of aryl bromides (**307**) ( $\text{X} = \text{Br}$ ) and iodides (**307**) ( $\text{X} = \text{I}$ ) into biaryls (**310**) has been shown to occur in a DMF/ $\text{Et}_4\text{NOTs}$ /(Pb cathode) system in the presence of Pd(0) and/or Pd(II) catalysts (Scheme 117) [440].

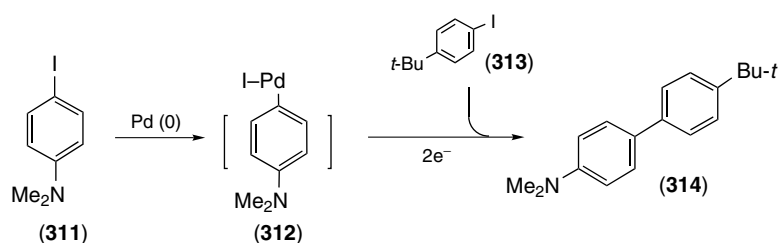
The cross-coupling between two different aryl iodides (**311**) and (**313**), leading to (**314**), can be achieved by using stoichiometric amounts of Pd(0) complexes in the



**Scheme 116** Cathodic coupling of aryl halides.



**Scheme 117** Catalytic cycle for cathodic coupling of aryl halides.

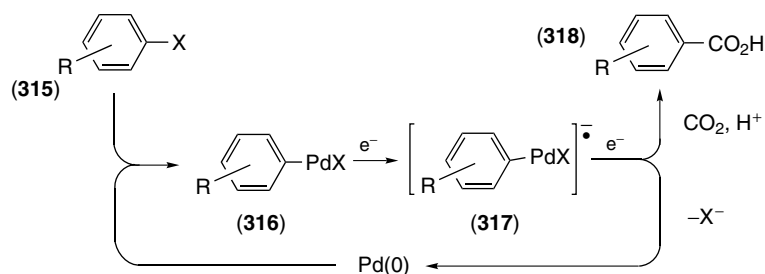


**Scheme 118** Cross coupling of aryl iodides.

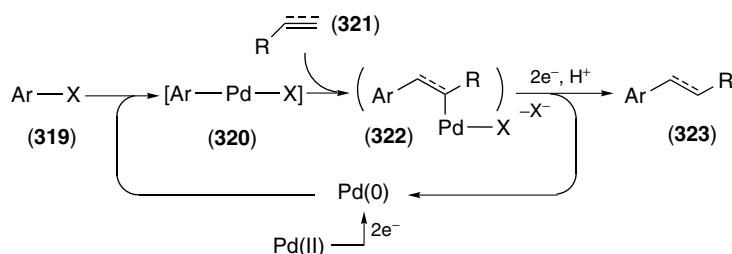
electrolysis media (Scheme 118) [440]. On the basis of kinetic results, the transient species is thought to be an anionic penta-coordinated bisarylpalladium(II) complex, which undergoes rapid loss of the halide ligand to yield a neutral bisarylpalladium(II) species [441–446].

Electroreductive carboxylation of aryl halides,  $\beta$ -bromostyrene, and allyl acetates

has been shown to occur in an aprotic solvent saturated with  $\text{CO}_2$  in the presence of electrocatalysts such as  $\text{PdCl}_2\text{L}_2$  or  $\text{PdL}_4$  [ $\text{L} = \text{P}(\text{Ph})_3$ ]. For example, the electrolysis of 4-*t*-butyliodobenzene (315) ( $\text{R} = t\text{-Bu}$ ;  $\text{X} = \text{I}$ ) in a DMF- $\text{Et}_4\text{NOTs}$ -( $\text{Pt}/\text{Pb}$ ) system in the presence of a catalytic amount of  $\text{Pd}(\text{II})\text{Cl}_2[\text{P}(\text{Ph})_3]_2$  and triphenylphosphine gives 4-*t*-butylbenzoic acid



**Scheme 119** Catalytic cycle for carboxylation of aryl iodides.



**Scheme 120** Cross coupling of aryl halides and alkynes or alkenes.

(318) ( $R = t\text{-Bu}$ , 81%) and  $t$ -butylbenzene (5%) (Scheme 119) [447]. Similarly, the Pd(II) complex catalyzes the electrosynthesis of aromatic carboxylic acids under  $\text{CO}_2$  atmosphere [448]. The electrocarboxylation of vinyl triflates is performed with  $\text{CO}_2$  and a catalytic amount of  $\text{PdCl}_2(\text{PPh}_3)_2$  to give  $\alpha,\beta$ -unsaturated carboxylic acids [449].

Electroreductive hydrocoupling of aryl halides (319) with olefins (321) and acetylenes (321) also proceeds with  $\text{PdCl}_2[\text{P}(\text{Ph})_3]_2$  as the electrocatalyst in a DMF- $\text{Et}_4\text{NOTs}$ -(Pt/Pb) system. Electrochemical cross-coupling of 4- $t$ -butyliodobenzene (319) ( $\text{Ar} = 4\text{-}t\text{-BuC}_6\text{H}_4$ ,  $\text{X} = \text{I}$ ) with styrene affords the corresponding coupling product (323) ( $\text{Ar} = 4\text{-}t\text{-BuC}_6\text{H}_4$ ,  $\text{R} = \text{Ph}$ ) in 85% yield (Scheme 120) [450]. A polymer-supported 1,2-bis(diisopropylphosphino)benzene Pd(II) complex is found to show a better catalytic activity than the structurally analogous monomeric Pd(II) complex in the Heck arylation of methyl acrylate by iodobenzene [451].

#### 15.3.2.2 Platinum (Pt) Complex Mediators

The adsorption of  $\text{CO}_2$  on Pt electrodes has been intensively studied and the chemisorbed particles are known to be tightly bound to the surface and not to be desorbed by rinsing. Recently, the mechanism for the reductive adsorption

of  $\text{CO}_2$  on Pt metals has been studied [451]. Chemisorbed particles are found to have formed only on Pt and Rh. The electroreduction of  $\text{CO}_2$  on these metals proceeds as a result of the interaction of  $\text{CO}_2$  molecules, activated in the course of adsorption on the metal surface, with chemisorbed hydrogen. However, the further reduction of these chemisorbed intermediates proceeds very slowly because of their very strong adsorption. Neither reductive chemisorption of  $\text{CO}_2$  nor interactions of  $\text{CO}_2$  with adsorbed hydrogen have been observed with Ir, Pd, Os or Ru [452].

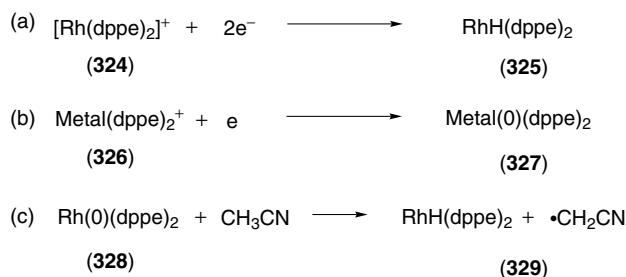
A poly- $\pi$ -nitrostyrene coated Pt electrode has been used for the electrocatalytic reduction of 1,2-dibromo-1,2-diphenylethane to stilbene in a  $\text{CH}_3\text{CN}-\text{R}_4\text{NBF}_4$  system. The turnover number for catalyst sites is estimated to be 10 000 [453].

#### 15.3.2.3 Rhodium and Iridium Complex Mediators

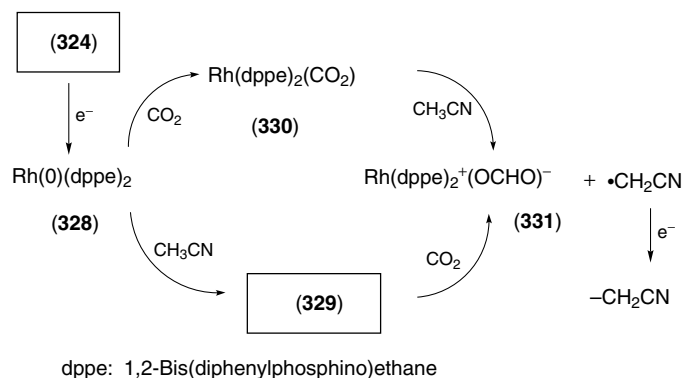
Recently,  $\text{Rh}(\text{dppe})_2\text{Cl}$  ( $\text{dppe} = 1,2\text{-bis}(\text{diphenylphosphino})\text{ethane}$ ) has been shown to catalyze the electroreduction of  $\text{CO}_2$  in an acetonitrile solution. The Rh complex can be electrochemically reduced to the corresponding rhodium hydride.

The electroreduction of  $[\text{Rh}(\text{dppe})_2]^+$  (324) and analogous Ir complexes leads to a neutral species  $\text{HRh(0)(dppe)}_2$





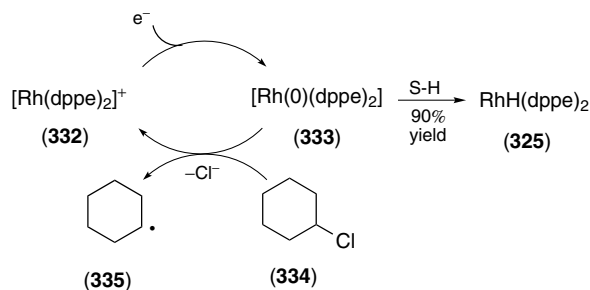
**Scheme 121** Reduction of rhodium(I) and reaction of rhodium(0) species.



**Scheme 122** Reduction of carbon dioxide by electrogenerated rhodium(0).

(325) (Scheme 121a) in the initial step. The neutral species  $\text{Rh(0)}(\text{dppe})_2$  (328) may occasionally react with acetonitrile to afford  $\text{RhH}(\text{dppe})_2$  (329) (a slow reaction) (Scheme 121c). Electrogenerated (328) may react with  $\text{CO}_2$  to generate the ionic metalloformate  $\text{Rh}(\text{dppe})_2^+(\text{OCHO})^-$  (331) via two

pathways (Scheme 122) [454, 455]. The current efficiencies for the formation of the formate anion vary between 42% and 22%, depending on the electrolysis periods. The electrocatalytic reduction of  $\text{CO}_2$  to either CO or the formate ion, in an  $\text{MeCN-Bu}_4\text{NPF}_6\text{-(Pt)}$  system using  $[\text{cis-M}(\text{bpy})_2(\text{O}_3\text{SCF}_3)]^{2+}$  ( $\text{M} = \text{Rh} - 1.5 \text{ V}$ ;



**Scheme 123** Reduction of cyclohexyl chloride to cyclohexyl radicals by rhodium(0).

Ir  $-1.59$  V vs. SCE), has been reported [338].

Constant-potential electrolysis of the  $[\text{Rh}(\text{dppe})_2]\text{Cl}$  in an  $\text{MeCN-Bu}_4\text{NClO}_4\text{-(Hg)}$  system gives  $\text{RhH}(\text{dppe})_2$  (**325**) in ca. 90% yield. When cyclohexyl chloride (**334**) is added to the  $[\text{Rh}(\text{dppe})_2]^+$  (**332**) electrolysis solution, the radical intermediate (**335**) together with  $\text{Cl}^-$  is produced as shown in Scheme (123) [456]. The cyclohexyl radical (**335**) generated in this manner has several channels for product formation.

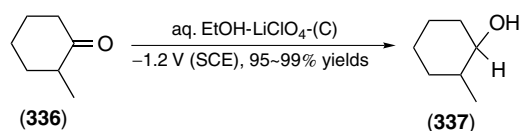
The  $\text{Rh}(\text{III})(\text{bpy})_3\text{Cl}_3$  complex catalyzes the electroreduction of  $\text{CO}_2$  to a formate in an  $\text{H}_2\text{O-Et}_4\text{NClO}_4\text{-(C/Pt)}$  system (See Table 17) [347].

Recently, it was found that the asymmetric hydroformylation of styrene by  $\text{Rh}_4(\text{CO})_{12}\text{L}_2$  via electroreduction in the presence of CO and hydrogen provides regio- and enantioselective products (e.g. >30%) when chiral ligands, ( $\text{L} = (1\text{R}, 2\text{S})\text{-Ph}_2\text{PNMeCHMeCHPhOPPh}_2$  and  $\text{Me}_2\text{C}(\text{NMePPh}_2)\text{-CH}_2\text{OPPh}_2$ ), are used [457]. Electroreduction of Rh and Pt complexes can be applied to the synthesis of active

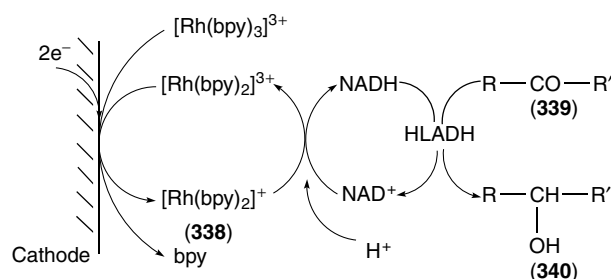
species useful for regio- and enantioselective olefin hydroformylation [458].

Electrocatalytic hydrogenation of carbonyl groups has been carried out by electrolysis of the ketone (**336**) in an aqueous  $\text{EtOH-LiClO}_4\text{-(C)}$  system in the presence of Rh complexes to yield the alcohol (**337**) in 95 ~ 99% yields (Scheme 124) [459, 460].

Electroreduction of  $\text{CO}_2$  catalyzed by a rhodium complex,  $[(\text{RhCp}^*)_3(\mu_3\text{-S})_2]^{2+}$  in an  $\text{MeCN-Bu}_4\text{NBF}_4\text{-(C)}$  system produces formate and oxalate in 60% current efficiency [461]. The direct electroreduction of  $\text{NAD}^+$  at  $-1.1$  V (SCE) leads to inactive dimers and even at  $-1.8$  V, active NADH is formed in only 50% yield. Recently, the use of the  $[\text{Rh}(\text{bpy})_2]^+$  complex (**338**) as an efficient electron-transfer agent for the regeneration of NADH from  $\text{NAD}^+$  has been reported [462]. The electroreduction of  $\text{NAD}^+$  to NADH using the agent (**338**) produced cathodically from  $[\text{Rh}(\text{bpy})_3]^{3+}$  proceeds well in the tris-HCl Buffer-(Pt/C) system (Scheme 125). The regenerated NADH is oxidized by ketone (**339**) giving alcohol (**340**) under catalysis of horse liver alcohol-dehydrogenase (HLAD). A



**Scheme 124** Electrocatalytic hydrogenation of carbonyl compounds.



**Scheme 125** NADH-regeneration in an electroenzymatic reduction.



**Scheme 126** Electrocatalytic NAD(P)H regeneration with formate as a hydride donor.

Scheme (126) [463].

### 15.3.3

## Indirect Reduction with Mediators Containing Ruthenium and Osmium

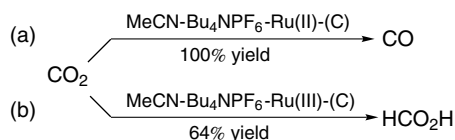
#### 15.3.3.1 Ruthenium (Ru) Complex Mediators

The catalytic reduction of CO<sub>2</sub> with Ru complexes under electroreduction conditions has been documented [464–467].

The electroreduction of CO<sub>2</sub> in an aqueous DMF(9:1)-[Ru(bpy)<sub>2</sub>(CO)<sub>2</sub>]<sup>2+</sup> (**346**) or [Ru(bpy)<sub>2</sub>(CO)Cl)]-(Hg) system at -1.50 V (SCE) at pH 6 produces CO and molecular hydrogen (H<sub>2</sub>) [348, 468]. A similar electrolysis at pH 9.5 affords not only CO and H<sub>2</sub> but also the formate anion, HCO<sub>2</sub><sup>-</sup> [349]. The [Ru(bpy)<sub>2</sub>(CO)<sub>2</sub>]<sup>2+</sup> (**346**) is electroreduced by two electrons to afford [Ru(bpy)<sub>2</sub>(CO)] (**343**) with CO elimination. The compound (**343**) reacts with CO<sub>2</sub> to give the complex [Ru(bpy)<sub>2</sub>(CO)(CO<sub>2</sub><sup>-</sup>)]<sup>+</sup> (**344**), which is protonated to afford [Ru(bpy)<sub>2</sub>(CO){C(O)OH}]<sup>+</sup> (**345**) and



**Scheme 127** Catalytic cycle for the electroreduction of carbon dioxide to carbon monoxide and formate.

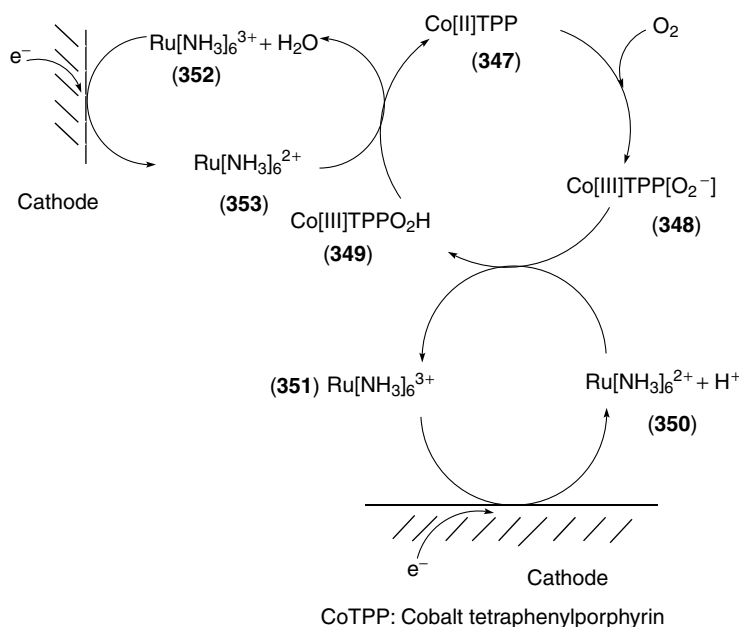


**Scheme 128** Electroreduction of carbon dioxide to carbon monoxide and formate.

$[\text{Ru}(\text{bpy})_2(\text{CO})_2]^{2+}$ . The former is reduced to provide  $\text{HCO}_2^-$  (Scheme 127). Product-selective electroreduction of  $\text{CO}_2$  to either CO or formate in an  $\text{MeCN-Bu}_4\text{NPF}_6\text{-(Pt)}$  system has been shown to occur using precursor complexes such as  $[\text{Ru}(\text{trpy})(\text{dppe})\text{Cl}]^+$  or  $[\text{cis-Rh}(\text{bpy})_2(\text{TFMS})_2]^+$  ( $\text{trpy} = 2,2',2''$ -tripyridine;  $\text{TFMS} = \text{trifluoromethanesulfonyl anion}$ ) [338]. The Ru(II) complex is found to be a good  $\text{CO}_2$  reduction catalyst at a potential of  $-1.4 \text{ V (SCE)}$  and the electrolysis results in the exclusive formation of CO (Scheme 128a). In contrast, the electroreduction of  $\text{CO}_2$

with the Rh(III) complex yields a mixture of formate and molecular hydrogen in 64% (12% current efficiency) (Scheme 128b). Electroreduction of  $\text{CO}_2$  using a  $[\text{Ru}(\text{bpy})_2(\text{CO})_2]^{2+}$  (**346**) catalyst in an  $\text{MeCN-Bu}_4\text{NClO}_4\text{-(Hg)}$  system in the presence of  $\text{Me}_2\text{NH}$  and  $\text{Me}_2\text{NHHCl}$  affords a formate and DMF with current efficiencies 75.7% and 21.4% [351].

Recently, C–C bond formation has been found to a certain extent in the electroreduction of  $\text{CO}_2$  catalyzed by a Ru complex  $[\text{Ru}(\text{bpy})(\text{trpy})(\text{CO})](\text{PF}_6)_2$  [469]. Further investigations reveal that the selective formation of  $\text{HCO}_2^-$  and  $\text{C}_2\text{O}_4^{2-}$



**Scheme 129** Catalytic cycle of ruthenium(III) reduction with (Co(II)TPP) immobilized in Nafion.

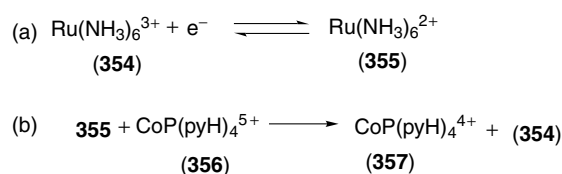
has been attained in the electroreduction of CO<sub>2</sub> catalyzed by mono- and dinuclear Ru complexes that are prepared by the reaction of [Ru(bpy)<sub>2</sub>Cl<sub>2</sub>] with dmbbbpy (2,2'-bis(1-methylbenzimidazol-2-yl)-4,4'-bipyridine) [470]. The electroreductive conversion of CO<sub>2</sub> into methanol has been performed using a Ru-modified glassy carbon electrode prepared by electropolymerization of mercaptohydroquinone [471]. Ru-modified electrodes possess excellent functions in the selective reduction of CO<sub>2</sub> to methanol with almost 100% current efficiency in the potential range −0.6 to −0.8 V (SCE). Electrodes composed of RuO<sub>2</sub> + TiO<sub>2</sub> (35/65 mol%) and RuO<sub>2</sub> + Co<sub>3</sub>O<sub>4</sub> + SnO<sub>2</sub> + TiO<sub>2</sub> (20/10/8/62 mol%) show high current efficiencies for methanol production from CO<sub>2</sub> [350]. Some results are presented in Table 17.

Cobalt tetraphenylporphyrin (Co(II) TPP) (347) is immobilized in Nafion works for the electroreduction of a dioxygen when [Ru(NH<sub>3</sub>)<sub>6</sub>]<sup>2+</sup> (350) ions are present in the

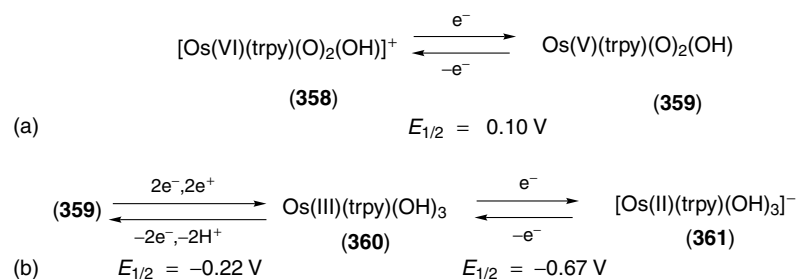
coating [472]. The electrons are transferred from the electrode to the almost immobile catalyst sites by (350) ions incorporated in the coating. Scheme (129) provides a schematic depiction of the catalytic cycles (350)→(351) and (347)→(348)→(349), which proceed within the Nafion coatings on the electrodes [472]. The [CoP(pyRu(NH<sub>3</sub>)<sub>5</sub>)<sub>4</sub>]<sup>8+</sup> complex prepared from the reaction of Ru(NH<sub>3</sub>)<sub>5</sub>OH<sub>2</sub><sup>2+</sup> (355) with [CoP(pyH)<sub>4</sub>]<sup>4+</sup> [cobalt *meso*-tetrakis(4-pyridyl)porphyrin] (357) within Nafion coatings on graphite electrodes acts as a catalyst in the four-electron reduction of the dioxygen (Scheme 130) [473]. A Ru-cofacial diporphyrin is effective as a dinitrogen electroreduction catalyst [474].

### 15.3.3.2 Osmium (Os) Complex Mediators

Recent work on the use of polypyridyl-aquo [Os(VI)(trpy)(O)<sub>2</sub>(OH)]<sup>+</sup> complexes (358) has shown that the reduction may proceed stepwise through a series of oxidation states [(358)→(359)→(361)] with



**Scheme 130** Reduction of [CoP(pyH)<sub>4</sub>]<sup>4+</sup> with ruthenium(II) in the oxygen reduction.



**Scheme 131** Reversible three-electron redox couple of Os(VI)/Os(III).

the retention of a common coordination number. A reversible three-electron redox couple based on Os(VI)/Os(III) has been reported [475]. Because of the differences in the pH dependence of the couples involved, Os(V) (**359**) becomes a stable oxidation state from pH = 11 to pH = 13.3. The redox couples are shown in Scheme (131).

A suitable comparison of the Os(VI)/Os(III) couple is the well-studied three-electron oxidant  $\text{HCrO}_4^-$ , where the intermediate oxidation states Cr(V)/Cr(IV) appear to be unstable with respect to disproportionation. However, the Os system shows a dramatically enhanced electrochemical reversibility compared to Cr(IV). This feature may play an important role in the ability of related systems that act as redox catalysts.

Recently, effective chiral ligands for the enantioselective dihydroxylation of olefins have been intensively investigated. Among the reported asymmetric dihydroxylation systems, the superiority of an  $\text{H}_2\text{O}/t\text{-BuOH-K}_3\text{Fe}(\text{CN})_6/\text{K}_2\text{CO}_3$  system with chiral ligands, that is, dihydroquinidine (DHQD) and/or a dihydroquinine (DHQ) derivative, has been mentioned (see Sect. 15.2.4.7) [476].

#### 15.3.4

##### **Indirect Reduction with Mediators Containing Chromium, Molybdenum, and Tungsten**

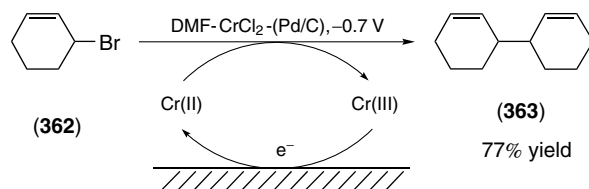
###### **15.3.4.1 Chromium (Cr) Complex Mediators**

Chromium(II) salts are widely used in organic synthesis. However, the high sensitivity to air and the low solubility of Cr(III) salts in anhydrous solvents prevent their synthetic use as electrocatalysts. The electroreduction of both  $\text{CO}_2$  and CO to methanol has been achieved by the

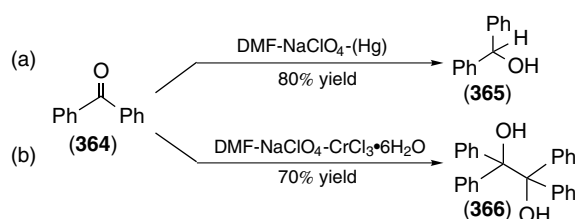
use of surface-confined metal complexes like a diaquobis(oxalato)chromate(III) and aquopentachlorochromate(III) as mediators [346]. The general feature of metal complexes, capable of operating as catalysts in the reduction of both  $\text{CO}_2$  and CO, is the requirement of at least one labile ligand in their coordination shell, which can be replaced by a new ligand in the course of the reaction.

Recently, the reductive C–C coupling of benzyl and allyl halides, for example, (**362**)  $\rightarrow$  (**363**), has been developed by electrochemically regenerating Cr(II) complexes. The electroreduction of Cr(III) to Cr(II) complexes takes place in a DMF-(Pt/C) system at  $-0.4\text{ V}$  (SCE) (Scheme 132) [477]. 2-Arylpyrimidines and 2-arylpyrazines are electrosynthesized in 61~79% yields in a DMF/Py-NiBr<sub>2</sub>(bpy)-(Fe/Ni)-system by the reaction of 2-chloropyrimidine and/or 2-chloropyrazine with aryl halides [478]. Electrochemical alkenylation of aldehydes using an Al sacrificial anode in the presence of Cr(II)/Ni(II) catalysts affords the corresponding allyl-alcohol derivatives in good yield [479]. Electrochemical arylation of aromatic aldehydes with aryl halides using a stainless steel sacrificial anode catalyst, in the presence of NiBr<sub>2</sub>(bpy), leads to the corresponding arylated secondary alcohols in good yield [480]. The major advantages of the procedure are: (1) the use of a catalytic amount of Cr complexes; (2) facile product isolation by extraction with cyclohexane; and (3) operation as a continuous process.

Pinacol formation from ketones and aldehydes by cathodic reduction has been enhanced in the presence of Cr(II) complexes. Electrolysis of a mixture of benzophenone (**364**) and chromium chloride hexahydrate in a DMF- $\text{NaClO}_4$  system



**Scheme 132** Cathodic coupling of cyclohexenyl bromide with chromium(III) as mediator.



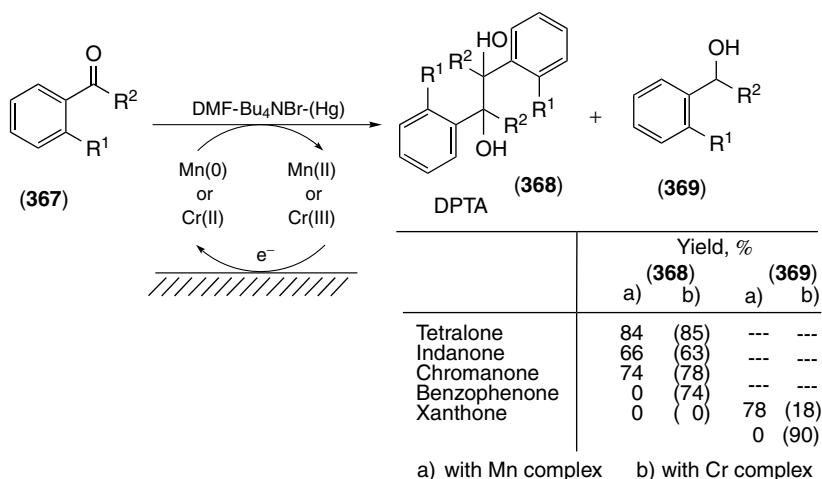
**Scheme 133** Cathodic coupling of benzophenone (pinacolization) with chromium(III) as mediator.

at  $-0.65$  V in a divided cell under nitrogen gives the pinacol (**366**) (70%) (Scheme 133) [481–483]. An important requirement for obtaining good yields of the pinacol is the presence of a catholyte that is preelectrolyzed at ca.  $-0.6$  V ( $\text{Ag}/\text{Ag}^+$ ) for ca.  $0.3 \text{ F mol}^{-1}$ , prior to the addition of carbonyl compounds. Under these conditions,  $\beta$ -ionone,  $\beta$ -ionylideneacetaldehyde, and retinal can lead to the corresponding pinacols in 75%, 60%, and 25% yields, respectively [483]. Absence of the Cr complex causes the formation of the benzhydrol (**365**) (Scheme 133).

The electroreductive coupling of the hindered aromatic ketones (**367**) has been achieved in a  $\text{DMF-Bu}_4\text{NBr-(Hg)}$  system by the aid of  $\text{CrCl}_3$  or  $\text{MnCl}_2$  as the electrocatalyst (Scheme 134) [484, 485]. The reductive coupling proceeds at a less negative potential [ $E_{1/2} - 1.44 \sim -1.53$  V (SCE)] than the reduction of the ketone ( $-1.63 \sim -2.01$  V). In some cases, Mn electrocatalysts favor the reduction to the carbinol (**369**), whereas a Cr catalyst promotes the formation of the pinacol (**368**).

The one-electron reduction of carbenium ions to the corresponding radicals has been performed using Cr(II) complexes as electrocatalysts. Hexamethyltropylium cations can be electrochemically reduced in a  $\text{CH}_2\text{Cl}_2\text{-Bu}_4\text{NClO}_4\text{-(Pt)}$  system to give a mixture of hexamethylcycloheptatriene (ca. 40%) and its dimer (ca. 20%) [486]. Alkylation of methyl phenylacetate occurs by electrolysis of a  $\eta^6$ -tricarbonylchromium complex in an  $\text{MeCN-Et}_4\text{NBr-(Mg)-(Pt)}$  system in the presence of alkyl bromide [487]. A free-radical cyclization of  $\alpha$ -bromoacetals to 2-alkoxy-tetrahydrofurans induced by the activated Cr(II) acetate has been reported. The electrolysis is carried out in a  $\text{DMF-LiClO}_4/\text{Cr}_2(\text{OAc})_4(\text{H}_2\text{O})_2\text{-(C)}$  system in the presence of ethylenediamine, and the acetal is added to this solution [488].

Secondary trichloromethyl carbinols and their corresponding esters can be reduced with the electrogenerated Cr(II) $\text{Cl}_2$  complex to form dichlorovinylidene compounds *via* a 1,2-elimination in one step. In-cell electroreduction of



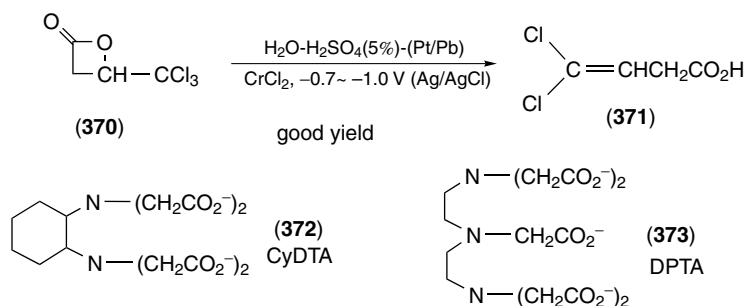
**Scheme 134** Cathodic coupling of arylketones with chromium(III) as mediator.

3-trichloromethyloxetan-2-one (**370**) in an aqueous  $\text{H}_2\text{SO}_4$  (5%)/ $\text{CrCl}_2$ -(Pt/Pb) system affords dichlorovinylacetic acid (**371**) in good yield (Scheme 135) [489]. After extraction of the product (**371**) with dichloromethane, the catholyte can be used again for the next electrolysis. Recyclable  $\text{Cr(III)}/\text{Cr(II)}$  redox couples have been used as reduction catalysts in different electrolytes [490]. The electroreductive preparation of  $\text{Cr(II)CyDTA}$  and  $\text{Cr(II)DPTA}$  complexes is carried out in an aqueous  $\text{AcONa}$ -electrolyte in the presence of  $\text{Cr(III)L}$  ( $\text{L} = \text{CyDTA}$  (**372**),

$\text{DPTA}$  (**373**)) at  $\text{pH} = 6$ . The  $\text{Cr(II)L}$  complexes are strong reducing agents for triple bonds as well as the nitro group [490].

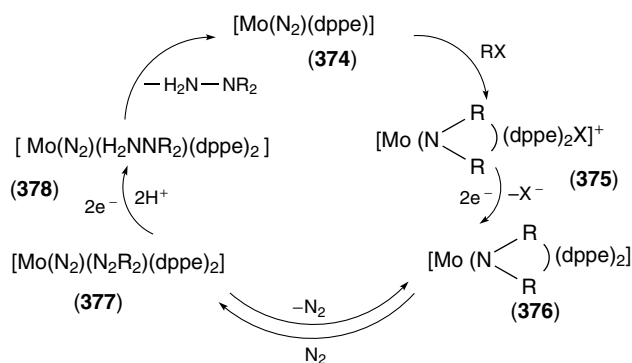
#### 15.3.4.2 Molybdenum (Mo) Complex Mediators

Dinitrogen-coordinated complexes of Ti, Zr, Mo, and W have been studied as potent mediators in electrolysis media [491–495]. Preliminary results from the electroreduction of  $[\text{Mo}(\text{N}_2\text{RR}')(\text{S}_2\text{C-NMe}_2)_3]^+$  reveal that the two-electron reduction of the cation leads to electroactivation of the



**Scheme 135** Reductive elimination with chromium(III).



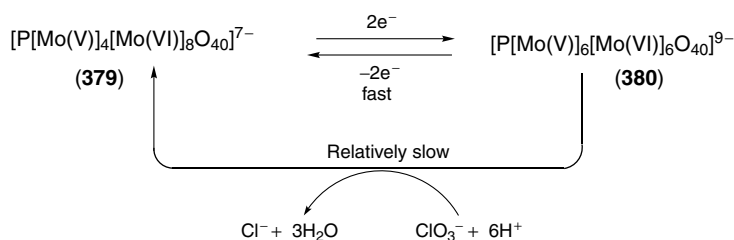


**Scheme 136** Catalytic cycle for the cathodic conversion of dinitrogen into 1,1-dialkylhydrazine.

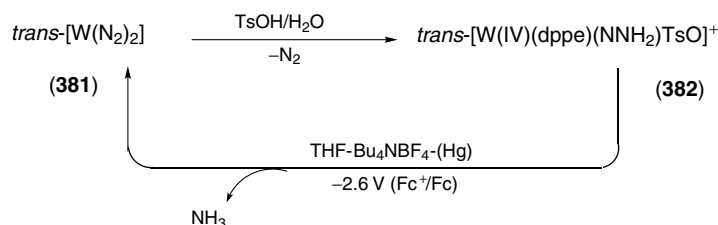
$\text{N}_2\text{RR}'$  ligand towards attack by electrophiles and that the subsequent reduction/protonation are shown to liberate the free hydrazine in good yield [494].

Combining the electroreduction of the hydrazido Mo complex (377) and the regeneration of the dinitrogen Mo complex (374) opens up the possibility of an electrochemical

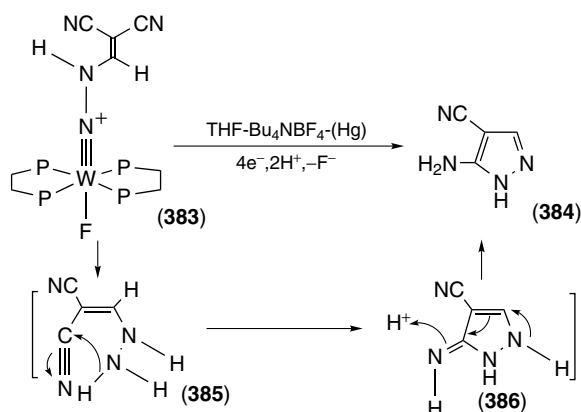
cycle (374)  $\rightarrow$  (375)  $\rightarrow$  (376)  $\rightarrow$  (377)  $\rightarrow$  (378) to produce organohydrazines,  $\text{H}_2\text{N-NR}_2$ , from dinitrogen (Scheme 136) [495]. Constant current electrolysis of  $[\text{Mo}(\text{NNR}_2)(\text{dppe})_2\text{X}]^+$  (375) under nitrogen in a THF- $\text{Bu}_4\text{NBF}_4$ -(Pt or Hg) system at  $-1.8 \text{ V}$  (SCE) leads to the rapid formation of  $[\text{Mo}(0)(\text{NNR}_2)(\text{dppe})_2]$  (376) after the capture of two electrons. Further



**Scheme 137** Cycle for the molybdenum-catalyzed reduction of chlorate to chloride.



**Scheme 138** Reduction of a tungsten-hydrazine complex to ammonia.



**Scheme 139** Reduction of a 1-hydrazino-2,2-dicyanoethylene-tungsten complex to a 5-amino-4-cyanopyrazole.

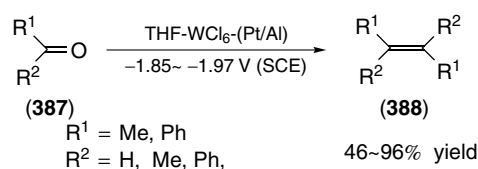
reduction takes place at a much slower rate and at the end of the electrolysis up to 45% of  $[\text{Mo}(\text{N}_2)_2(\text{dppe})_2]$  (374) and 60%~70% of hydrazine are isolated. The results suggest a successful electrochemical cycle for nitrogen-atom fixation as shown in Scheme (136) [495]. Electroreductively produced 12-molybdophosphate (379) behaves as a reducing agent for chlorate ions leading to chloride ions (Scheme 137) [496].

#### 15.3.4.3 Tungsten (W) Complex Mediators

Electrosynthesis of ammonia has been achieved using a  $\text{W}(\text{dppe})_2$  complex. Controlled potential electrolysis of *trans*- $[\text{W}(\text{NNH}_2)(\text{dppe})_2\text{TsO}]^+$  (382) (Scheme 138) in a  $\text{THF-Bu}_4\text{BF}_4\text{-(Hg)}$  system generates free  $\text{NH}_3$  and  $\text{N}_2\text{H}_4$  along with

the revived parent dinitrogen complex (381) [497]. Electrolysis on a Pt cathode gives substantially lower yields of *trans*- $[\text{W}(\text{N}_2)_2]$  (381). Electroreductive cleavage of the W–N bond of the  $[\text{WNH-CH}=\text{C}(\text{CN})_2(\text{dppe})\text{F}]^+$  complex (383) has been shown to give 5-amino-4-cyanopyrazole (384) in yields of up to 50% via the processes (383)→(385)→(386)→(384), which are beneficial to the recovery of  $[\text{W}(\text{N}_2)_2(\text{dppe})_2]$  complexes (Scheme 139) [498, 499].

Recently, the C–C bond formation through an electroreduction of a diazoalkane group, incorporated as a ligand into W complexes, has been reported. One-electron reduction of *trans*- $[\text{W}(\text{N}_2\text{CH}_2)_2\text{L}_2\text{F}]^+$  in an  $\text{MeCN-Bu}_4\text{NBF}_4\text{-(Hg)}$  system affords  $\text{W}(\text{N}_2\text{CH}_2\text{CH}_2\text{N}_2)\text{L}_2\text{F}$  (L = dppe) in 55% yield [500].



**Scheme 140** Tungsten-catalyzed reductive dimerization of carbonyl compounds to alkenes.

Electrochemically reduced W species tend to transform carbonyl compounds into olefins after dimerization. For example, benzaldehyde (**387**) can be quantitatively converted into stilbene (**388**) by electroreduction in a THF-Bu<sub>4</sub>NClO<sub>4</sub>/WCl<sub>6</sub>-(Al/Pt) system at a potential of -1.9 V (SCE) (Scheme 140) [501].

The electrogeneration of alkene metathesis catalysts from WCl<sub>6</sub> has been studied intensively. The reduction of WCl<sub>6</sub> in CH<sub>2</sub>Cl<sub>2</sub> (or ClCH<sub>2</sub>CH<sub>2</sub>Cl)-Bu<sub>4</sub>NPF<sub>6</sub>-(Al/Pt) under a controlled potential of -1.2 V (SCE) gives the *in situ* active catalyst species (**389**). A metal-carbene-initiated process similar to that for olefin metathesis with conventional catalysts has been proposed. 2-Pentene (**390**) can be converted to 3-hexene (**391**→**392**→**393**) and 2-butene (**394**→**395**→**396**) via alkene metathesis in a CH<sub>2</sub>Cl<sub>2</sub>-WCl<sub>6</sub>/Al/e<sup>-</sup> system (Scheme 141). In place of WCl<sub>6</sub>, MoCl<sub>5</sub> salts can be used in the same manner [502, 503]. The electroreduction of dioxygen to hydrogen peroxide, which oxidizes tungstate to pertungstate in the solution, brings about the oxidation of

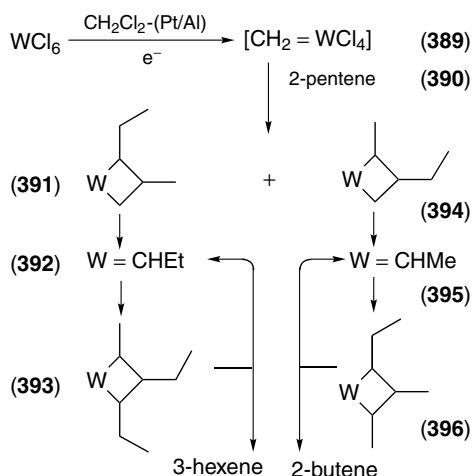
sulfoxides to the corresponding sulfones in high efficiency [504].

### 15.3.5

#### Indirect Reduction with Mediators Containing Manganese and Rhenium

##### 15.3.5.1 Manganese (Mn) Complex Mediators

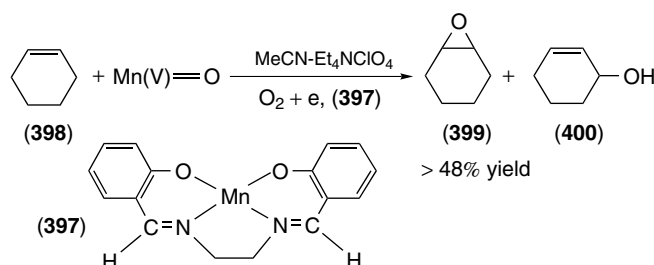
The combination of the cathode with a catalyst for the electroreduction of dioxygen has attracted great interest. In particular, metal porphyrins and phthalocyanines are proposed as potential catalysts [505]. Recently, the catalytic electroreduction of dioxygen using [5,10,15,20-tetrakis-(1-methylpyridinium-4-yl)porphinato]manganese has been performed in H<sub>2</sub>O-KH<sub>2</sub>PO<sub>4</sub>/NaOH (pH = 7)-(C) [506]. It is widely recognized that the porphyrin in a high-spin divalent state plays the role of an active species. The electrochemically activated dioxygen enables olefin epoxidation through electroreduction. The catalytic reaction sequence is of particular



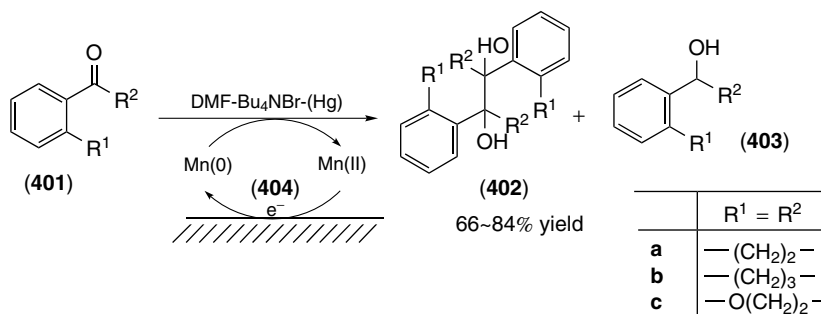
**Scheme 141** Electrogenated metathesis catalyst and reaction with 2-pentene.

interest since it involves the essential elements of the cytochrome P-450 catalytic cycle. The electrolytic epoxidation proceeds in a  $\text{CH}_2\text{Cl}_2\text{-Bu}_4\text{NClO}_4\text{-(C)}$  system containing an axial base (1-methylimidazole), olefin, and benzoic anhydride in the presence of Mn(III) tetraphenylporphyrin chloride [507]. Very recently, electrochemical olefin epoxidation with a Mn *meso*-tetraphenylporphyrin (TPP) catalyst has been carried out with hydrogen peroxide generated at polymer-coated electrodes [508]. The glassy carbon electrode is coated with a film of poly- $[\text{Ru}(\text{bpy})_3]^{2+}$ , having high permeability to dioxygen and very low permeability to porphyrin. The polymer film prevents electroreduction of the high-valent metal oxo porphyrin  $[\text{Mn}(=\text{O})\text{TPP}]$ . Hydrogen peroxide is electrogenerated by reduction of dioxygen in methylene chloride

containing benzoic acid as a proton source,  $[\text{Mn}(\text{TPP})\text{Cl}]$  as a catalyst, 1-methylimidazole as the axial base, and the olefin as a substrate. The electroreduction of an  $[\text{Mn}(\text{III})(\text{salen})]^+$  [ $\text{salen} = N,N'$ -ethylenebis(salicylaldiminato))] complex (397) in an  $\text{MeCN-Et}_4\text{NClO}_4(\text{AcO})_2\text{O/O}_2\text{-(C)}$  system in the presence of 1-methylimidazole and olefin (398) yields the corresponding epoxide (399) in over 48% yield, based on the electrochemical charge passed, together with allylic oxidation products (400) (Scheme 142) [509]. Electrocatalytic epoxidation of cyclohexene by a Mn(III) porphyrin complex using an electron mediator in the presence of methylene blue has been reported [510]. Hindered aromatic ketones (401) can be converted electrochemically to either the corresponding pinacols (402) or to benzylic alcohols (403) using a



**Scheme 142** Cathodic epoxidation with Mn(III)-complex and oxygen.

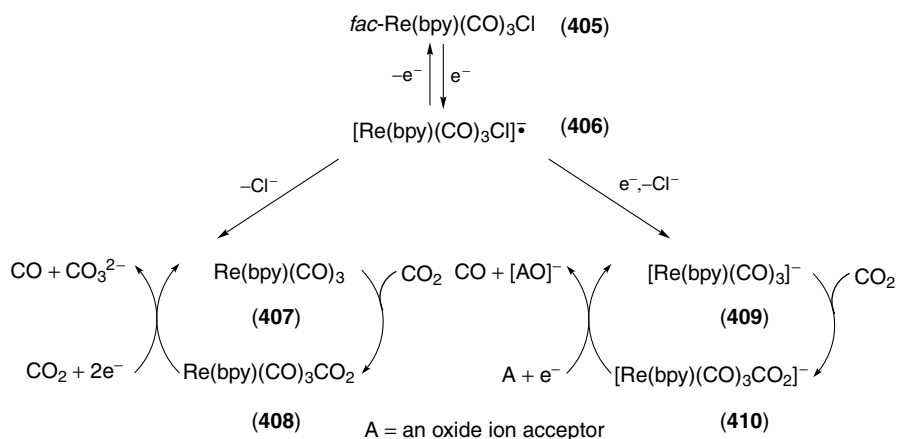


**Scheme 143** Manganese-mediated pinacolization and hydrogenation of aryl ketones.

Mn(II)/Mn(0) (404) couple as a mediator (see Scheme 143) [485].

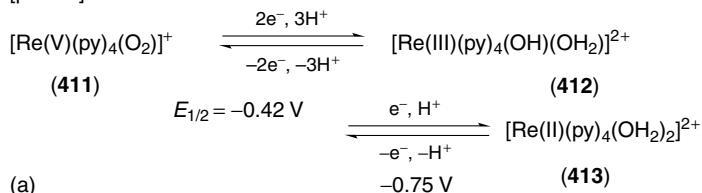
**15.3.5.2 Rhenium (Re) Complex Mediators**  
Current interest in formylrhenium complexes stems from their potential in the

industrial catalytic reduction of CO. In this connection, the electrochemical conversion of formylrhenium to hydridorhenium complexes has been investigated. The electroreduction of *cis*-[(CO)<sub>5</sub>ReRe(CHO)(CO)<sub>4</sub>]<sup>−</sup> in an MeCN-Et<sub>4</sub>NClO<sub>4</sub> system by

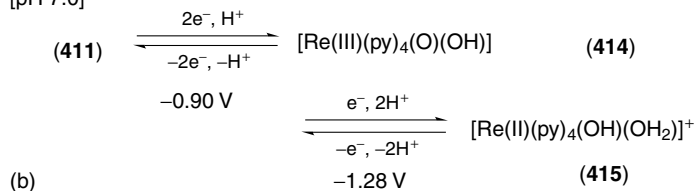


**Scheme 144** Catalytic cycle of cathodic carbon dioxide reduction with rhenium complexes to carbon monoxide.

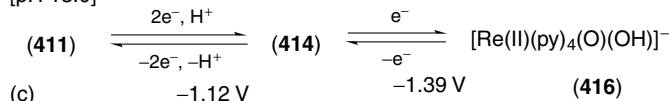
[pH 1.0]



[pH 7.0]



[pH 13.0]



**Scheme 145** pH-dependent redox couples of rhenium(V)-complexes.

the passage of  $0.035 \text{ F mol}^{-1}$  of electricity (turnover ca. 30) quantitatively yields *cis*- $[(\text{CO})_5\text{ReRe}(\text{H})(\text{CO})_4]^-$  [511]. The cyclic voltammetry of *fac*- $\text{Re}(\text{bpy})(\text{CO})_3\text{Cl}$  (**405**) in the reduction of  $\text{CO}_2$  to CO in an  $\text{MeCN-Bu}_4\text{NPF}_6$ -(Pt) system is indicative of two different electrocatalytic pathways as follows: (**406**) $\rightarrow$ (**407**) $\rightarrow$ (**408**); (**406**) $\rightarrow$ (**409**) $\rightarrow$ (**410**) (Scheme 144) [354]. The electrolysis of  $[\text{fac-Re}(\text{bpy})(\text{CO})_3]_2$  in  $\text{CO}_2$ -saturated DMF- $\text{Bu}_4\text{NPF}_6$  at  $-1.8 \text{ V}$  results in the production of CO with current efficiencies over 85%. The complex  $\text{Re}(\text{vbpy})(\text{CO})_3\text{Cl}$  (vbpy = 4-vinyl-4'-methyl-2,2'-bipyridine) coated with a polymeric film on a Pt electrode, electrochemically reduces  $\text{CO}_2$  to CO [353]. The turnover numbers attained using the modified electrode greatly exceed those observed for the analogous electrocatalytic reduction of  $\text{CO}_2$  by  $\text{Re}(\text{bpy})(\text{CO})_3\text{Cl}$  in a homogeneous solution (bpy = 2,2'-bipyridine) (See Table 17). The *trans*- $[\text{Re}(\text{V})(\text{py})_4(\text{O})_2]^{+3}$  complex is known to be in a stable oxidation state and reduction leads to strong reducing aqua complexes with a potential use as electrocatalytic reductants [512]. The electroreduction is carried out in an  $\text{H}_2\text{O-CF}_3\text{SO}_3\text{H}(\text{C})$  system in the presence of the  $\text{Re}(\text{V})$  complex, and the potentials for the  $\text{Re}(\text{V}/\text{III})$  and  $\text{Re}(\text{III}/\text{II})$  redox couples are pH-dependent due to the acidic character of the aqua

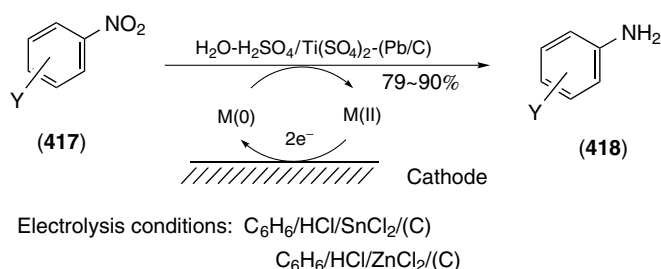
ligands in these three oxidation states. Reduction potentials and dominant proton compositions are given for pH = 1.0 (**411** $\rightarrow$ **412** $\rightarrow$ **413**) (Scheme 145a), 7.0 (**411** $\rightarrow$ **414** $\rightarrow$ **415**) (Scheme 145b), and 13.0 (**411** $\rightarrow$ **414** $\rightarrow$ **416**) (Scheme 145c). Reduction at potentials more negative than that of the  $\text{Re}(\text{III}/\text{II})$  couple gives the  $\text{Re}(\text{II})$  complex, which is a good electrocatalyst for the reduction of water to hydrogen over the pH range of 0.5–13.

### 15.3.6

#### Indirect Reduction with Mediators Containing Titanium, Tin, and Lead

##### 15.3.6.1 Titanium (Ti) Complex Mediators

Titanium ions can also be used as redox catalysts for the indirect cathodic reduction of nitro compounds (**417**). The electroreduction is carried out in an  $\text{H}_2\text{O-H}_2\text{SO}_4/\text{Ti}(\text{SO}_4)_2$ -(Pb/Cu) system at  $45\sim 80^\circ\text{C}$  under  $5\sim 20 \text{ A m}^{-2}$ . Nitrobenzene, dinitrobenzene, nitrotoluene, 2,4-dinitrotoluene, 2-nitro-*m*-xylene, nitrophenol, 2,4-dinitrophenol, nitrophenetole, *o*-nitroanisole, 4-nitrochlorotoluene, nitrobenzenesulfonic acid, and 4,4'-dinitrostilbene-2,2'-disulfonic acid can all be reduced by this procedure to the corresponding amino compounds (**418**) in good yields (Scheme 146) [513–516]. Tin



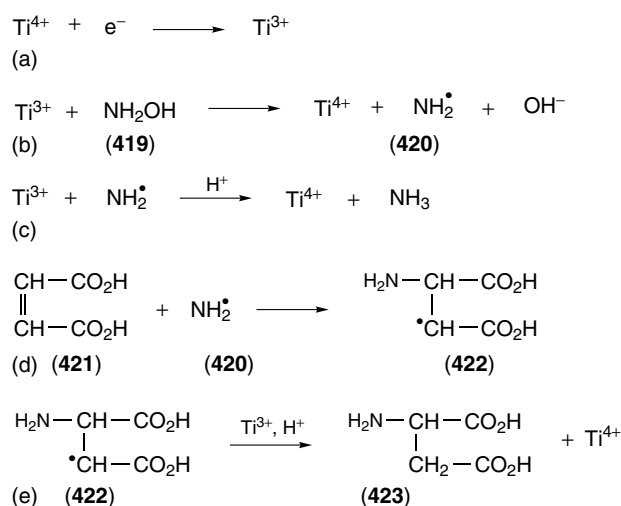
**Scheme 146** Titanium(III)-mediated reduction of substituted nitrobenzenes.

and zinc powders formed in an acidic aqueous solution by electrolysis at high current density ( $0.5 \text{ A cm}^{-2}$ ) can be used for the reduction of nitro compounds to the corresponding amines [517–521]. The conversion and current yields can exceed 90%. Pilot-scale productions of aniline and *p*-aminophenol have been realized [514].

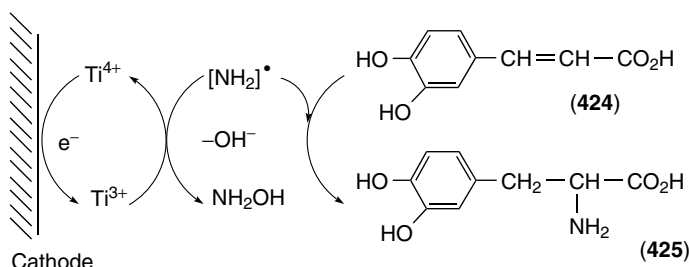
The catalytic reduction of *o*-nitrophenol by the surface of a Ti(IV)/Ti(III) redox system on a Ti/TiO<sub>2</sub> electrode has been used in a preparative-scale operation [522]. 5-Nitro-salicylic acid [523] and

*p*-nitroaniline [524] can also be reduced at a Ti/TiO<sub>2</sub> electrode. An excess of electrons will accumulate on TiO<sub>2</sub> particles, which may improve the rate of dioxygen reduction [525]. An electrochemically generated low-valent Ti complex acts as a reducing agent for the conversion of 1-nitroalkenes to the corresponding nitriles [526]. During the electroreduction of the nitroalkene, the yellow color of the Ti(IV) chloride-DMF complex changes to deep violet.

Electrochemical amination of enoic acids has been performed using an electro-generated Ti<sup>3+</sup> species as a homogeneous



**Scheme 147** Reductive amination of maleic acid.



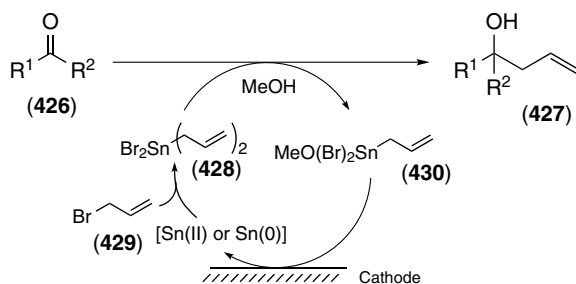
**Scheme 148** Synthesis of *d,l*-dopa by a reductive amination.

catalyst. The amination of maleic acid (421) with (419) gives aspartic acid (423) *via* radicals (420) and (422) in high yield (Scheme 147) [527]. *dl*-Dopa (425) is electrosynthesized by the amination of (424) in an aqueous  $\text{H}_2\text{SO}_4\text{-Ti}^{4+}\text{-(Hg)}$  system in the presence of hydroxylamine sulfate (Scheme 148) [528].

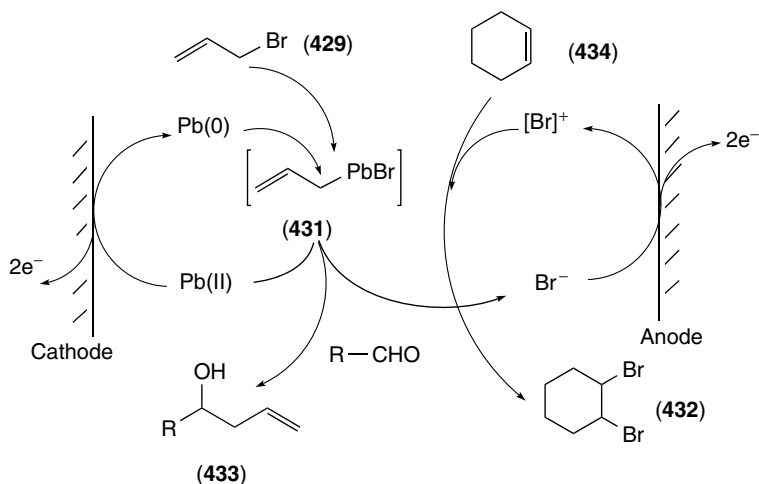
It is known that the Ti complex acts as a reversible carrier of electrons from the cathode to the catalytically active Mo(III) complex in a Ti-Mo-pyrocatechol system for the electroreduction of CO on a mercury cathode [529].

### 15.3.6.2 Tin (Sn) Complex Mediators

Recently, the electrochemical recycling of allyltin reagents has been realized for the first time in protic solvents. Difficulties in the recycling of metallic allyl reagents *in situ* are due to the fact that reaction conditions that allow (1) generation of the organotin reagents; (2) allylation of carbonyl compounds; and (3) reductive regeneration of zero or low-valent metal complexes, in a single cell at the same time, have to be found. The Grignard-type allylation of carbonyl compounds has been performed in an



**Scheme 149** Tin-mediated reductive allylation of carbonyl compounds.



**Scheme 150** Barbier-type allylation of carbonyl compounds with electrogenerated lead(0).

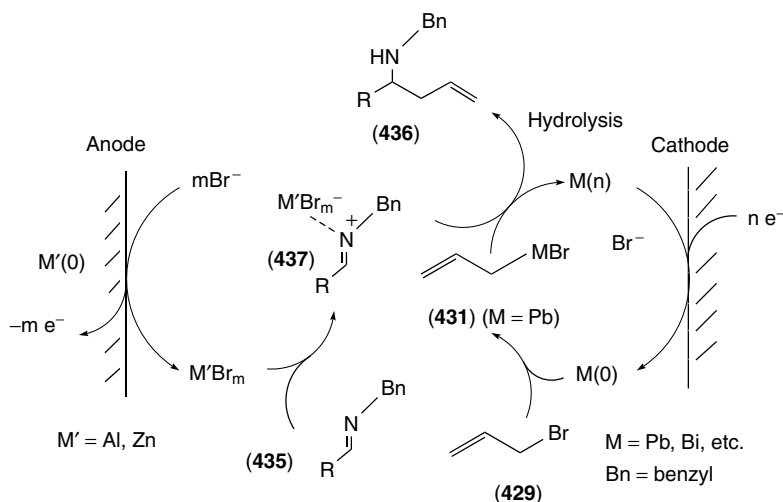


MeOH/AcOH-(Allyl)<sub>2</sub>SnBr<sub>2</sub>-(Pt) system at 50~55 °C. As illustrated in Scheme 149 [530], diallyltin dibromide (428) produced from metallic Sn and allyl bromide in methanol reacts with carbonyl compounds (426) to give the allylated products (427) together with allyldibromotin monomethoxide (430). The latter compound (430) may be reduced at the cathode to di- or zero-valent Sn, which reacts smoothly with allyl bromide to regenerate diallyltin dibromide (428).

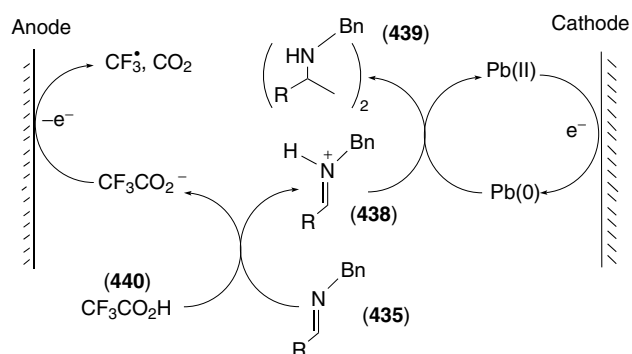
The dimethylpyrrolidinium-Sn mediated reduction of aryl bromides, bearing electron-withdrawing and electron-donating groups to give the corresponding debrominated products, has been described [531].

### 15.3.6.3 Lead (Pb) Complex Mediators

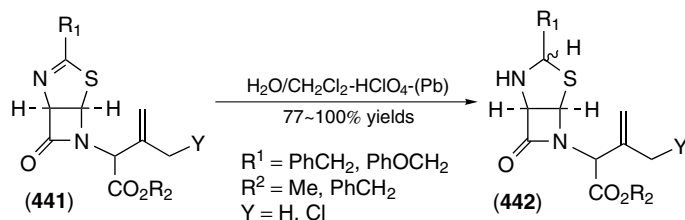
Barbier-type allylation (429→433) of carbonyl compounds with allyl bromide (429) has been achieved through recycling



**Scheme 151** Barbier-type allylation of imines with electrogenerated lead(0).



**Scheme 152** Lead(0) catalyzed cathodic hydrodimerization of imines.



**Scheme 153** Cathodic hydrogenation of a thiazoline ring.

of the *in situ* generated allyllead complex (431) in a DMF/AcOH-PbBr<sub>2</sub>-(Pt) system in the presence of cyclohexene (434) as a bromine-trapping agent (Scheme 150) [532].

An electroreductive Barbier-type allylation of imines (434) with allyl bromide (429) also occurs in a THF-PbBr<sub>2</sub>/Bu<sub>4</sub>NBr-(Al/Pt) system to give homoallyl amine (436) (Scheme 151) [533]. The combination of Pb(II)/Pb(0) redox and a sacrificial metal anode in the electrolysis system plays a role as a mediator for both cathodic and anodic electron-transfer processes. The metals used in the anode must have a less positive anodic dissolution potential than the oxidation potentials of the organic materials in order to be present or to be formed *in situ*. In addition, the metal ion plays the role of a Lewis acid to form the iminium ion (437) by associating with imine (435) (Scheme 151).

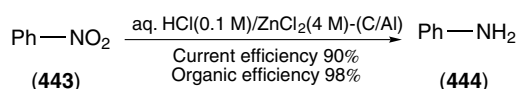
Electroreductive hydrodimerization (435→439) of the imine (435) has been performed in a THF-CF<sub>3</sub>CO<sub>2</sub>H(TFA)/PbBr<sub>2</sub>-(Pt) system using an undivided cell (Scheme 152) [534]. For the conversion, both TFA and PbBr<sub>2</sub> are indispensable, since the lack of either of the

additives results in the formation of a complex mixture. Probably, the imine (435) associates with TFA to afford the iminium ion (438) that undergoes a one-electron reduction with cathodically generated Pb(0) to form the 1,2-diamine (439) (Scheme 152). Electroreductive hydrogenation of the C=N double bond of thiazoline-azetidinone derivatives (441) has been performed in an H<sub>2</sub>O/CH<sub>2</sub>Cl<sub>2</sub>-HClO<sub>4</sub>-(Pb) system to afford (442) in 77~100% yield (Scheme 153) [535]. A Pb cathode, together with the change of the electrode polarity using a commutator, is essential for the conversion.

#### 15.3.7

##### Indirect Reduction with Mediators Containing Zinc (Zn), Mercury (Hg), and Cadmium (Cd)

The use of Zn powder in a multiphase system is a way to solve many of the difficulties involved in the operation of electroorganic processes under a low maximum current density [513–516]. A three-phase system, water/organic, substrate/metal powder can be used for the reduction of halides and nitro compounds under a high



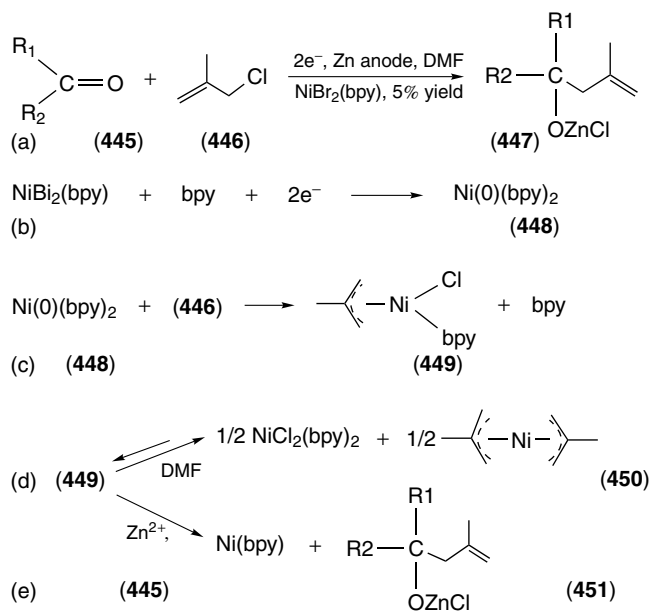
**Scheme 154** Zinc-mediated reduction of nitroaryl compounds to amines.

current density ( $>0.5 \text{ A cm}^{-2}$ ). Electroreductive dechlorination of polychlorinated biphenyls has been performed using zinc phthalocyanine as a mediator in an  $\text{H}_2\text{O}-\text{HClO}_4\text{-(C)}$  suspension system, leading to biphenyl in quantitative yield [536].

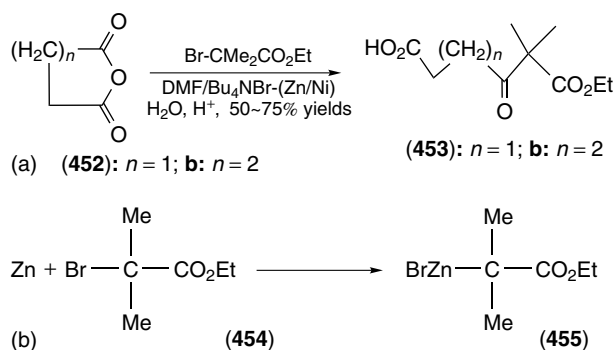
The preparative electroreduction of nitrobenzene (**443**) is performed in an aqueous HCl/ZnCl<sub>2</sub>-(C/Al) system with

the substrate dissolved in a second phase to give aniline (**444**) in 98% yield (Scheme 154) [515]. Zinc and tin are the best metals for the high current-density reduction in which chemical and current yields can exceed 90% [516].

Electrochemical activation of the Zn species has been attained in a DMF-Et<sub>4</sub>NClO<sub>4</sub>-(Zn/Pt) system [537, 538]. The



**Scheme 155** Nickel-zinc-mediated cathodic allylation of carbonyl compounds.



**Scheme 156** Nickel-zinc-mediated cathodic Reformatsky reaction with anhydrides.

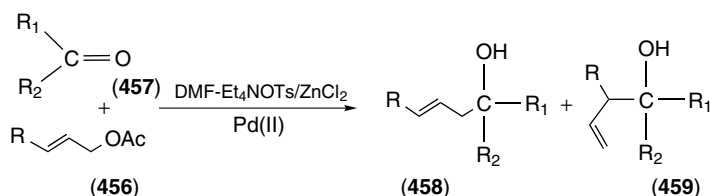
reactivity of ultrafine Zn powders, produced by the use of ultrasound, has been evaluated for the Reformatsky reaction, Barbier allylation, alkyne reduction, reductive dehalogenation, and so on [539]. The combination of a sacrificial Zn anode and an  $\text{NiBr}_2(\text{bpy})$  complex realizes an efficient electrosynthesis of homoallylic alcohols (**447**) from allylic chlorides (**446**) (or acetates) and carbonyl compounds (**445**) (Scheme 155) [302]. The electroreductive allylation of the carbonyl compounds (**445**) using a Ni catalyst together with the Zn(II) species is carried out in a DMF- $\text{Bu}_4\text{NBr}/\text{NiBr}_2\cdot(\text{Zn}/\text{C})$  system. The Ni bipyridine complex is readily reduced at  $-1.2$  V (SCE) (Scheme 155b). The zero-valent Ni species, which reacts very rapidly with an allylic chloride ( $k > 200 \text{ M}^{-1} \text{ s}^{-1}$ ), may afford the ( $\pi$ -allyl)nickel chloride (**449**) (Scheme 155c). However, disproportionation of the Ni complex is observed in DMF in contrast to acetonitrile as shown in Scheme 155d. The zinc anode may provide the Zn(II) species that avoid side reactions involving the carbonyl compounds and minimize the reduction of allylic chlorides.

The mechanism of the  $\text{ZnBr}_2$ -assisted, nickel-catalyzed Reformatsky reaction has been discussed [540]. The reaction involves the electroreduction of a Ni(II) complex to a Ni(0) complex, oxidative addition of the  $\alpha$ -chloroester to the Ni(0) complex, and Zn(II)/Ni(II) transmetallation, leading to an organozinc Reformatsky reagent. Most recently, the Reformatsky reaction

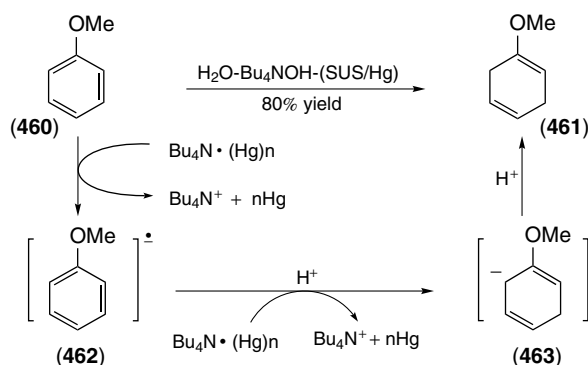
of ethyl 2-bromoalkanoates with succinic anhydride (**452**) ( $n = 1$ ) has been performed successfully in the absence of any Ni(II) species (Scheme 156a). The electrolysis of the anhydrides (**452**) and the bromide is carried out in a DMF- $\text{Bu}_4\text{NBr}$ -(Zn/Ni) system in an undivided cell to give 3-oxoalkanedioates (**453**) [541]. Anodically generated Zn cations probably react with the anions derived from the electroreduction of the bromide (**454**) to form the Reformatsky reagent  $\text{BrZnCM}_2\text{CO}_2\text{Et}$  (**455**) (Scheme 156b).

The mechanism of the Zn chloride-assisted, palladium-catalyzed reaction of allyl acetate (**456**) with carbonyl compounds (**457**) has been proposed [434]. The reaction involves electroreduction of a Pd(II) complex to a Pd(0) complex, oxidative addition of the allyl acetate to the Pd(0) complex, and Zn(II)/Pd(II) transmetallation leading to an allylzinc reagent, which would react with (**457**) to give homoallyl alcohols (**458**) and (**459**) (Scheme 157). Substituted  $\beta$ -lactones are electrosynthesized by the Reformatsky reaction of ketones and ethyl  $\alpha$ -bromobutyrate, using a sacrificial Zn anode in 35~92% yield [542]. The effect of cathode materials involving Zn, C, Pt, Ni, and so on, has been investigated for the electrochemical allylation of acetone [543].

Electroreduction of  $\text{CO}_2$  on a Zn electrode is performed in an aqueous  $\text{K}_2\text{SO}_4$ -(Pt/Zn) system. Faradaic efficiency for the formation of CO (80%), formate (10%),



**Scheme 157** Palladium-zinc-mediated cathodic addition of allyl acetate to carbonyl compounds.



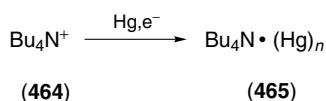
**Scheme 158** Mercury-catalyzed Birch reduction of anisole.

and dihydrogen (10%) has been attained at the potential of  $-1.6$  V (Ag/AgCl) [544].

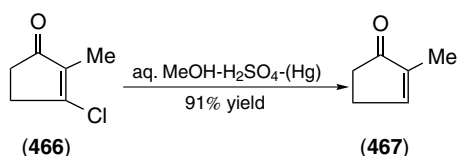
The reaction of 2-bromomethyl-1,4-dibromo-2-butene with aldehydes or ketones in the presence of the electrogenerated reactive zinc in DMF at  $0^\circ\text{C}$  gives the corresponding isoprenylated alcohols in good yields [545]. The electroreduction of a catalytic amount of  $\text{ZnBr}_2$  in an  $\text{MeCN-ZnBr}_2\text{-(Zn)}$  system, which provides active zinc, catalyzes the reductive coupling of allyl bromides and chlorides with carbonyl compounds with high regioselectivity [546]. 2-Arylpyridines (40~60% yields) are prepared by electroreductive coupling of 2-halopyridines and aryl or heteroaryl

halides catalyzed by  $\text{NiBr}_2(\text{bpy})$  complexes in a  $\text{DMF-ZnBr}_2\text{-(Zn)}$  system [547].

The Birch-type electrochemical reduction (460)→(461) has been shown to proceed through the action of tetrabutylammonium amalgam in the steps (460)→(462)→(463), in contrast to a direct electron transfer from the electrode to the aromatics (Scheme 158) [548]. The preparative-scale reduction of anisole, of 1,2,3,4-tetrahydro-6-methoxynaphthalene, and several aromatic steroids is performed in an  $\text{H}_2\text{O-Bu}_4\text{NOH-(Hg)}$  system. The unique aspect of the reduction is the proposed formation of a tetrabutylammonium amalgam complex,  $\text{Bu}_4\text{N(Hg)}_n$  (465)



**Scheme 159** Generation of tetrabutylammonium amalgam.



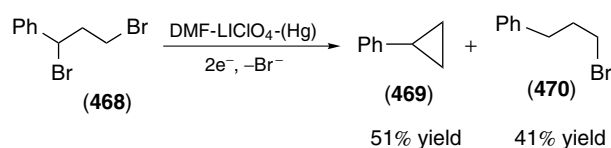
**Scheme 160** Cathodic removal of a vinylic chlorine atom.

(Scheme 159) [549, 550]. Temperature and electrolyte concentration are found to have a profound effect on the reaction rate. The  $\text{Bu}_4\text{N}(\text{Hg})_n$  can be used for the reduction of  $\beta$ -estradiol 3-methyl ether and the reaction has been shown to be more selective than the conversion methods based on alkali metal-ammonia reduction [551].

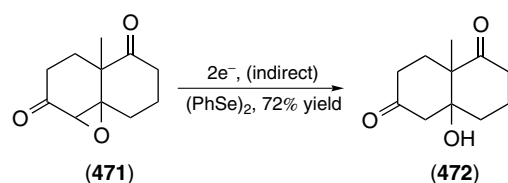
Electroreductive removal of the chlorine atom from 2-methyl-3-chlorocyclopenten-1-one (**466**) has been performed in an aqueous  $\text{MeOH-H}_2\text{SO}_4\text{-(Hg)}$  system at  $-0.80$  to  $-0.85$  V (SCE) (Scheme 160) [552]. In the course of the reaction, an Hg compound is produced in a dimeric form, which undergoes further reduction to yield

the desired product (**467**) in 91% yield. The Hg cathode plays the role of a reducing catalyst. Electrochemical reduction of 8-bromobornan-2-one in an  $\text{HMPA-Bu}_4\text{NBr-(Pt/Hg)}$  system also suggests the formation of an organomercurial intermediate that leads to the formation of dihydrocarvone as the major product [553].

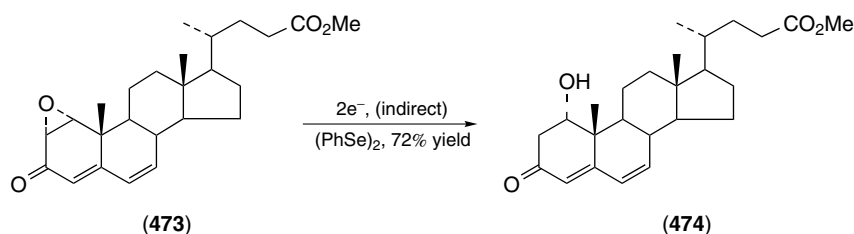
Indirect electroreduction of allyl alcohols leading to the corresponding unsaturated hydrocarbons is attained using a mercury electrode in a strongly acidic medium containing an iodide salt [554]. The reaction involves transformation of the alcohol into the iodide, the reaction of the iodide with mercury, the protonation of the



**Scheme 161** Cyclopropane formation by cathodic  $\gamma$ -elimination of a 1,3-dibromide.



**Scheme 162**  $\beta$ -Hydroxyketones by reductive ring opening of  $\alpha,\beta$ -epoxyketones with diphenyldiselenide.



**Scheme 163**  $\beta$ -Hydroxyketosteroid by reductive ring opening of  $\alpha,\beta$ -epoxyketosteroid with diphenyldiselenide.

organomercury compound, and the reduction of the Hg salt to hydrocarbon and Hg. Benzyl alcohols are similarly reduced to the corresponding hydrocarbons.

The electroreductive preparation of highly strained small-ring compounds is a useful general synthetic method [555–557]. The electroreduction of 1,3-dibromide (468), leading to the cyclopropane derivative (469) has been achieved *via* an organo Hg species, which involves sequential one-electron reductions with the intervention of organo Hg(I) radicals and dimeric Hg(I) species (Scheme 161) [558–560].

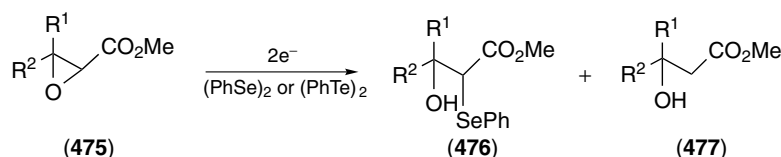
Removal of the iodine atom from aryl iodides proceeds smoothly in a DMF-Bu<sub>4</sub>NClO<sub>4</sub>-(Hg) system [561, 562]. A Cd-modified electrode-assisted allylation of aldehydes and ketones has been attained in a DMF-Et<sub>4</sub>NClO<sub>4</sub> system, in which the

allylation occurs using either a Pt cathode along with a Cd anode or a Pt cathode and a Cd-modified Pt anode [563].

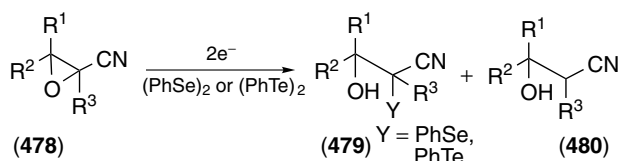
### 15.3.8

#### Indirect Reduction with Mediators Containing Selenides (Se) or Tellurides (Te)

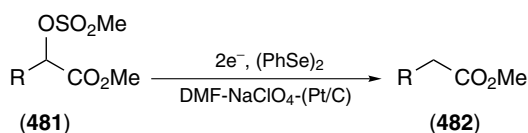
Electroreductively generated PhSeSePh and PhTeTePh anions work as mediators for the ring-opening of  $\alpha,\beta$ -epoxy carbonyl compounds (471) and (473) leading to the corresponding  $\beta$ -hydroxy compounds (472) and (474) (Schemes 162 and 163) [564]. For example, the electrolysis of (473) in an MeOH-NaClO<sub>4</sub>-(Pt) system in the presence of PhSeSePh and dimethyl malonate affords the ring-opening product (474) in 72% yield (Scheme 163). The direct electroreduction of epoxy ketones



**Scheme 164**  $\beta$ -Hydroxyesters by reductive ring opening of  $\alpha,\beta$ -epoxyesters with diphenydiselenide.



**Scheme 165**  $\beta$ -Hydroxynitriles by reductive ring opening of  $\alpha,\beta$ -epoxynitriles with diphenydiselenide.



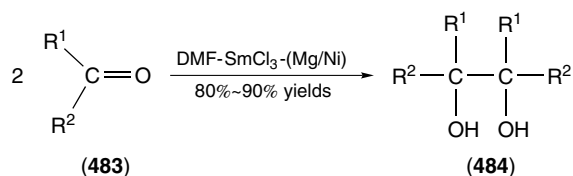
**Scheme 166** Desoxygenation of  $\alpha$ -hydroxyesters via reduction of the methanesulfonates with diphenydiselenide as mediator.

provides the  $\beta$ -hydroxy ketones (ca. 30% yield) together with dehydration and pinacolization products [565, 566]. The novel mediator-associated ring-opening reactions of epoxy compounds can be used for the preparation of  $\beta$ -hydroxy ketones,  $\beta$ -hydroxy esters, and nitriles from their corresponding  $\alpha,\beta$ -epoxy compounds. The ring-opening is carried out in a THF/H<sub>2</sub>O(9/1)-Bu<sub>4</sub>NBF<sub>4</sub>-(C) or DMF-Et<sub>4</sub>NOTs-(C) system in the presence of dimethyl malonate as a proton source.

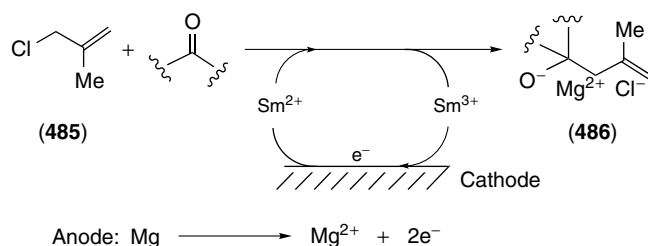
The electroreductive ring-opening of  $\alpha,\beta$ -epoxy esters (475) and nitriles (478) proceeds stepwise as shown in Schemes (164 and 165). In both cases, the intermediates (476) and (479) can be isolated when the mediator-assisted reductions are carried out at room temperature. The whole reduction can be completed at 50 °C. For example, the electrolysis of a phenylglycidic ester (475) ( $R^1 = \text{Ph}$ ,  $R^2 = \text{H}$ ) in an MeOH-NaClO<sub>4</sub>-(Pt) system in the presence of PhSeSePh at room temperature gives

(476) in 68% yield, while at 50 °C (477) is formed in 75% yield (Scheme 164). Interestingly, the use of PhTeTePh at room temperature affords (477) directly. The PhSe<sup>−</sup> or PhTe<sup>−</sup> assisted electroreduction of  $\alpha,\beta$ -epoxy nitrile (478) at room temperature produces  $\alpha$ -(phenylseleno)- or  $\alpha$ -(phenyltelluro)- $\beta$ -hydroxy nitriles (479) ( $Y = \text{Te}$ ) (Scheme 165). The direct conversion of (478) to (480) can be achieved *via* electrolysis at 50 °C.

The methanesulfonates (481) of  $\alpha$ -hydroxy esters can be converted to the deoxygenated esters (482) in 70~88% yields by indirect electrolysis with PhSeSePh as a recyclable reagent in a divided cell (Scheme 166). The procedure involves the formation of  $\alpha$ -phenylselenoester by substitution of the  $\alpha$ -methylsulfonyloxy group with the PhSe<sup>−</sup> followed by displacement of the  $\alpha$ -phenylseleno group with PhSe<sup>−</sup>. The electrolysis is performed in a DMF-NaClO<sub>4</sub>-(Pt/C) system in the presence of PhSeSePh and ethyl malonate at 50 °C [567].



**Scheme 167** Samarium-mediated cathodic hydrodimerization of carbonyl compounds.



**Scheme 168** Samarium-mediated Barbier-type reaction of carbonyl compounds with allyl halides.



## 15.3.9

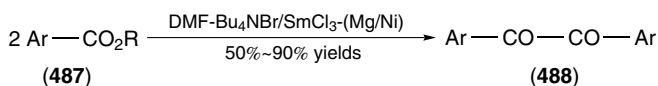
**Indirect Reduction with Mediators  
Containing Miscellaneous Metal  
Complexes****15.3.9.1 Samarium (Sm) and Indium (In)  
Complex Mediators**

The potential of lanthanide compounds as reagents in organic synthesis has attracted much attention from electroorganic chemists. In particular, low-valent lanthanides are used as reagents for various coupling reactions of carbonyl compounds and/or organic halides. Sm(II) derivatives play the role of one-electron transfer agents in the C–C bond forming reaction. The first use of the active Sm(II) species as mediator in an electrolysis is attained by the coupling of carbonyl compounds (483) leading to the corresponding 1,2-diols (484) (Scheme 167) [568]. The electrolysis is carried out in DMF or *N*-methyl 2-pyrrolidone in the presence of 5~10% of SmCl<sub>3</sub> by the use of sacrificial

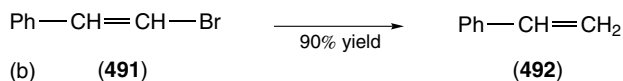
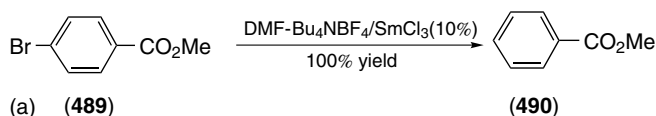
anodes (Mg or Al) in an undivided cell [568].

The Barbier-type reaction of aldehydes and ketones with allyl halides (485) in the presence of SmI<sub>2</sub>, leading to homoallyl alcohols (486), has received recent interest as a one-step alternative to the Grignard reaction. However, the reactions require the use of stoichiometric amounts of the reducing Sm(III) species. Recently, the electroreductive Barbier-type allylation of carbonyl compounds in an SmI<sub>2</sub>-mediated reaction has been developed [569]. The electrolysis of (485) is carried out in a DMF-SmCl<sub>3</sub>-(Mg/Ni) system in an undivided cell to give the adduct (486) in 50~85% yields (Scheme 168) [569]. Electrosynthesis of  $\gamma$ -butyrolactones has been achieved by the reductive coupling of ethyl 3-chloropropionate with carbonyl compounds in the presence of a catalytic amount of SmCl<sub>3</sub> [570].

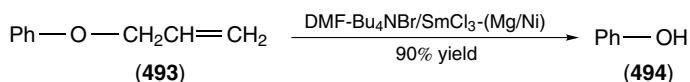
The Sm-catalyzed synthesis of  $\alpha$ -diketones from aromatic esters [571], the



**Scheme 169** Samarium-catalyzed synthesis of diketones from aromatic esters.



**Scheme 170** Samarium-catalyzed cathodic debromination of aryl bromides.



**Scheme 171** Samarium-catalyzed cleavage of allyl phenyl ethers.

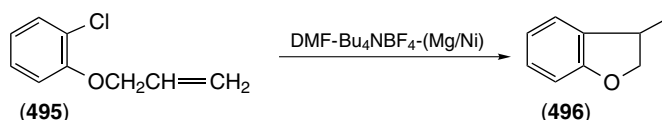
reductive cleavage of C–X bonds [572], and the deprotection of the allyl moiety from alkyl and aryl allyl ethers [573] have all been performed effectively. The electrochemically supported Reformatsky reaction of ketones with  $\beta$ -lactones has been performed by the use of In complexes to yield  $\beta$ -hydroxy esters in 80% yield [574].

The Sm-assisted reductive dimerization of aromatic esters (**487**), leading to diketones (**488**) is carried out in a DMF-Bu<sub>4</sub>NBr-(Mg/Ni) system in the presence of SmCl<sub>3</sub> as a mediatory catalyst (Scheme 169) [571].

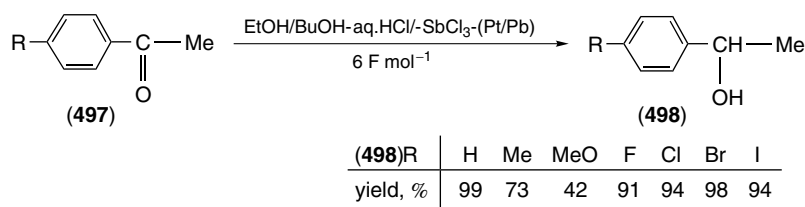
The electroreductive dehalogenation of aromatic halides (**489**) and (**491**) with

an SmCl<sub>3</sub> catalyst can be attained in a DMF-Bu<sub>4</sub>NBF<sub>4</sub>/SmCl<sub>3</sub>(10%)-(Mg/Ni) system, giving (**490**) and (**492**) in good yields (Scheme 170). The use of the electrogenerated Sm species is also effective in the electroreduction of aromatic chlorides and fluorides [572].

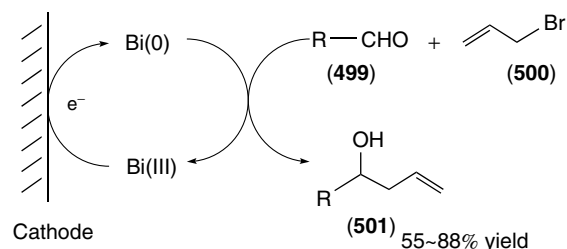
The SmCl<sub>3</sub>-catalyzed electroreductive cleavage of allyl ethers (**493**) leading to (**494**) has been performed in a DMF-Bu<sub>4</sub>NBr-(Mg/Ni) system in the presence of SmCl<sub>3</sub> (10 mol%) in an undivided cell (Scheme 171) [573]. A similar ether cleavage does not proceed in the cases of *o*-chlorophenyl or *o*-bromophenyl allyl ethers (**495**) and the reduction of the Ar–Cl



**Scheme 172** Cathodic cyclization of *o*-allyloxy-chlorobenzene.



**Scheme 173** Antimony-mediated cathodic hydrogenation of aryl ketones.



R = *p*-Cl–C<sub>6</sub>H<sub>4</sub>, Cyclohexyl, *n*-C<sub>8</sub>H<sub>17</sub>, Ph-CH = CMe

**Scheme 174** Bismuth-catalyzed cathodic allylation of aldehydes.

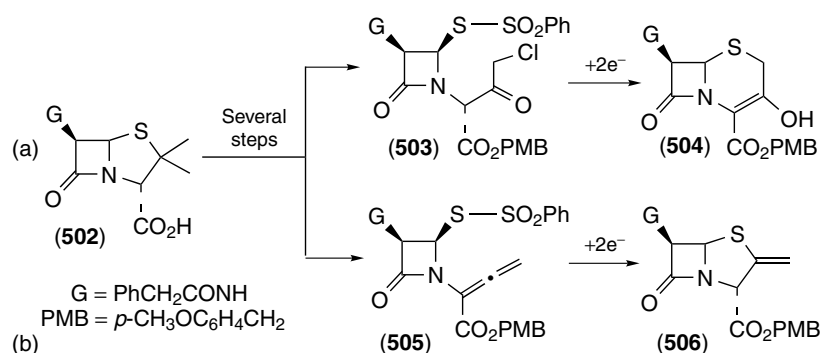
or Ar–Br bond takes place instead, giving the cyclized product (**496**) (Scheme 172). Aliphatic aldehydes can be electrochemically reduced faster than aryl allyl ethers to give the corresponding pinacols [573].

### 15.3.9.2 Antimony (Sb) and Bismuth (Bi) Complex Mediators

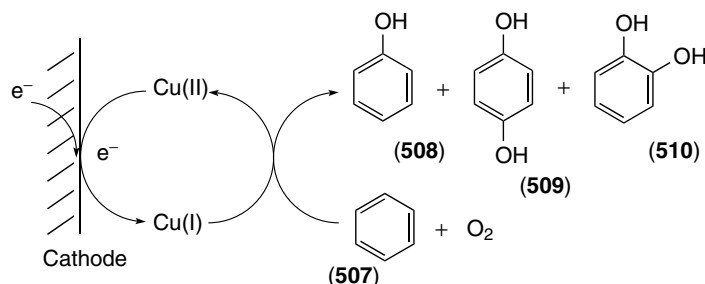
Antimony(III) trichloride can be used as a catalytic mediator in the electroreduction of carbonyl compounds. The advantage of the procedure is illustrated by the selective reduction of acetophenones (**497**), leading to the corresponding benzylic alcohols (**498**) (Scheme 173) [575]. The electroreduction is performed in an EtOH/BuOH(1/1.5)-aq.HCl-(Pt/Pb) system in the presence

of SbCl<sub>3</sub> (ca. 4.0 mol%) with passage of 6 F mol<sup>-1</sup> of electricity. A possible mechanism that accounts for the formation of antimony hydride through the reduction of Sb deposited on the electrode surface by active hydrogen atoms has been proposed [576].

Because of lack of catalytic processes for metals such as Sb and Bi (except for a few cases) [530, 532], recycling of the metals in multimediatory redox systems is of current interest. Recently, allylation of aldehydes (**499**) with (**500**) has been performed in an aqueous CH<sub>2</sub>Cl<sub>2</sub>-BiCl<sub>3</sub>-(Pt) two-phase system. Although the reaction (**499**→**501**) can proceed in neutral solution, the best result is obtained in acidic media (Scheme 174) [577].



**Scheme 175** Bismuth/tin-catalyzed cyclization of azetidin-2-one derivatives.



**Scheme 176** Cathodic production of phenol by copper(I)-catalyzed oxygenation of benzene.

A new electrolysis system comprising two metal redox couples, Bi(0)/Bi(III) and Al(0)/Al(III), has been shown to be effective for electroreductive Barbier-type allylation of imines [533]. The electrode surface structure has been correlated with the activity towards the electroreduction of hydrogen peroxide for Bi monolayers on Au(III) [578]. Electroreductive cyclization of the 4-(phenylsulfonylthio)azetidin-2-one derivative (**502**) as well as the allenecarboxylate (**505**) leading to the corresponding cyclized compounds (**504**) and (**506**) has been achieved with the aid of bimetallic metal salt/metal redox systems, for example, BiCl<sub>3</sub>/Sn and BiCl<sub>3</sub>/Zn (Scheme 175) [579]. The electrolysis of (**502**) is carried out in a DMF-BiCl<sub>3</sub>/Py-(Sn/Sn) system in an undivided cell by changing the current direction every 30 s, giving the product (**504**) in 67% yield.

#### 15.3.9.3 Copper (Cu) Complex Mediators

Since the catalytic effect of Cu<sup>2+</sup> ions with Fenton's reagent has been recognized, continuing interest has been focused on the role of the Cu species in oxidizing systems. The electrochemical alkyltransfer reaction of trialkylboranes to carbonyl compounds has been performed in an undivided cell by using the sacrificial Cu anode in a DMF-Bu<sub>4</sub>NI system, giving the alkylated products in 62~77% yields [580].

Phenol (**508**) is found to be produced continuously from benzene (**507**) by aerial oxidation in aqueous sulfuric acid when a Cu(I)/Cu(II) redox couple is used as a mediator (Scheme 176) [581]. The Cu(I)-mediated electroreduction of oxygen in the presence of chloride is found to be effective for toluene oxidation, leading to benzaldehyde and benzyl chloride [582]. Recently, benzene has also been oxidized

with dioxygen in the presence of Cu<sup>+</sup> ions. The reaction can be operated continuously when the active Cu<sup>+</sup> ions are regenerated electrochemically [583]. The electrolysis is carried out in an aq. MeCN/H<sub>2</sub>SO<sub>4</sub>(0.1N)[1:9(v/v)] system in the presence of copper sulfate in a divided cell. The reaction is highly pH-dependent, and pH control during electrolysis is essential.

The electroreduction of CO<sub>2</sub> using a Cu cathode leads preferentially to methane and ethane [584, 585]. The selectivity is dependent on the cationic species as well as on the HCO<sub>3</sub><sup>−</sup> concentration [586]. Hydrogen evolution prevails over CO<sub>2</sub> reduction in a Li<sup>+</sup> electrolyte, whereas CO<sub>2</sub> reduction proceeds favorably in Na<sup>+</sup>, K<sup>+</sup>, and Cs<sup>+</sup> solutions [587–589].

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## 16 Conducting Polymers

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## 16.1

### Introduction

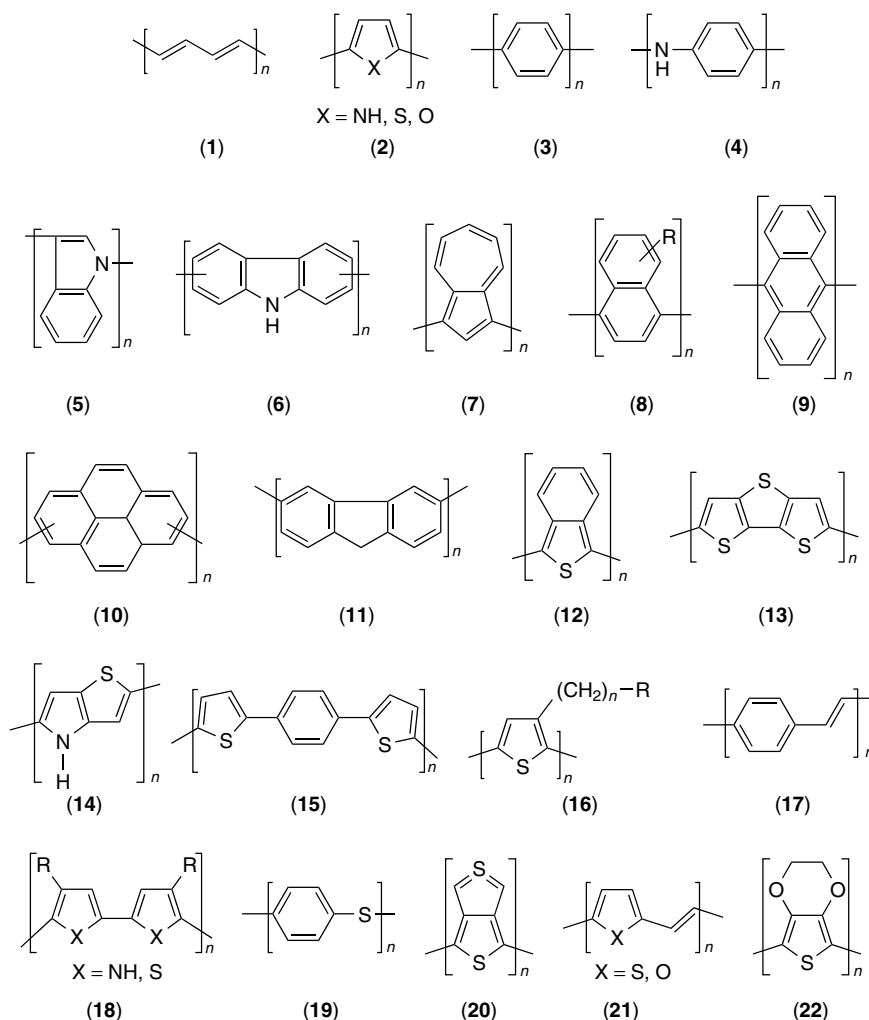
In 1977, the American scientists Heeger, MacDiarmid, and their Japanese colleague Shirakawa discovered that doping polyacetylene (PA) with iodine endowed the polymer with metallic properties, including an increase in conductivity of 10 orders of magnitude [1]. The successful doping of PA – the equivalent of oxidation or reduction in electrochemical terminology – encouraged the same scientists to test PA as a rechargeable active battery electrode [2]. Their promising results stimulated worldwide efforts to find additional applications. In the course of these studies, conducting polymers with properties similar to PA were discovered, such as polyphenylene (PP) and polyphenylenevinylenes, as pure hydrocarbons, on the one hand, and polypyrrole (PPy) polythiophene (PTh), and polyaniline (PANI) on the other. Nowadays, a great number of different monomers that form conducting polymers upon chemical or electrochemical preparation techniques are known (Fig. 1).

In 2000, Heeger, MacDiarmid, and Shirakawa were awarded the Nobel Prize for their pioneering work in this new field of polymer science. Therefore, it is not surprising that the interest in these

materials has gained a new stimulation and worldwide many groups are eager to synthesize specially tailored novel compounds, for example, for the generation of light-emitting materials.

Electrochemistry is one of the most promising areas in the research of conducting polymers. Thus, the method of choice for preparing conducting polymers, with the exception of PA, is the anodic oxidation of suitable monomeric species such as pyrrole [3], thiophene [4], or aniline [5]. Several aspects of electrosynthesis are of relevance for electrochemists. First, there is the deposition process of the polymers at the electrode surface, which involves nucleation-and-growth steps [6]. Second, to analyze these phenomena correctly, one has to know the mechanism of electropolymerization [7, 8]. And thirdly, there is the problem of the optimization of the mechanical, electrical, and optical material properties produced by the special parameters of electropolymerization.

A central point of research is still the analysis of the electrochemical reaction occurring during charging, which are also known under the term “doping process”. Even in the earliest stage of research it was clear that these processes were not comparable with the classic doping of typical semiconductors. Rather, they correspond to oxidation in the case of *p*-doping or



**Fig. 1** Building units of conducting polymers, (1): polyacetylene (PA); (2): polypyrrole (PPy), polythiophene (PTh), polyfuran (PFu); (3): polyphenylene (PP); (4): polyaniline (PANI); 5: polyindole (PIND); (6): polycarbazole (PCaz); (7): polyazulene (Paz); (8): polynaphthalene (PNa); (9): polyanthracene (PAnth); (10): polypyrene (PPyr); (11): polyfluorene (PFlu); (12): poly(isothionaphthalene) (PITN); (13): poly(dithienothiophene); (14): poly(thienopyrrole); (15): poly(dithienylbenzene); (16): poly(3-alkylthiophene); (17): poly(phenylene vinylene); (18): poly(bipyrrole) (PBPy), poly(bithiophene) (PBT); (19): poly(phenylenesulfide); (20): 4-poly(thienothiophene); (21): poly(thienyl vinylene), poly(furan vinylene); (22): poly(ethylenedioxythiophene) (PEDOT).

reduction in the case of *n*-doping. Thus, in electrochemical terminology, the doping process corresponds to a redox reaction. Especially for applications, it is important

to know the phenomenological details of such redox reactions, for example, in which potential range the charging occurs and what is the maximum level of oxidation

before the material starts degrading. Moreover, from the viewpoint of fundamental research, one would like to know the molecular details of the charge storage process; in recent years, a lot of work has gone into explaining this phenomenon [9].

The development of conducting polymers is naturally related to hopes of feasible technical applications. Thus, conducting polymers are discussed as active battery electrodes [10], electrochromic displays (ECD) [11], anticorrosives [12], sensors [13], electrocatalysts [14], antistatic materials [15], or light-emitting materials (OLED) [16].

A basic property of all conducting polymers is the conjugation of the chain-linked electroactive monomeric units, that is, the monomers interact via a  $\pi$ -electron system. In this respect, they are fundamentally different from redox polymers. Although redox polymers also contain electroactive groups, the polymer backbone is not conjugated and the interaction between the "isolated" redox centers is weak. Consequently, redox polymers are nonconductors [17]. They will not be discussed in this context.

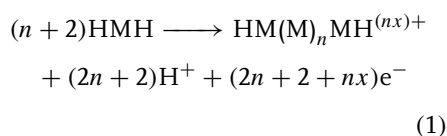
## 16.2 Mechanism of Electrochemical Polymerization

### 16.2.1 Reactions in Solution

Electropolymerization of conducting polymers differs markedly from other polymerization reactions. In the normal electrochemically induced polymerization reactions, the electrode catalytically triggers chain growth and, consequently, the process requires little electricity [18]. By contrast, the anodic oxidation leading

to conducting polymers involves a reaction sequence in which each coupling step has to be activated by two species. It has an electrochemical stoichiometry of 2.07 to 2.6 farad  $\text{mol}^{-1}$  of reacting monomer [7, 19]. It has been deduced from numerous measurements that the film-forming process needs only 2 farad  $\text{mol}^{-1}$ , that is, 2 electrons/molecule, and the additional charge serves the partial reversible oxidation (doping) of the polymer film. As the potential needed for monomeric oxidation is always significantly higher than the charging of the existing polymer, the two processes – film formation and its oxidation – occur simultaneously.

Taking this stoichiometry into account, the complete reaction equation for the polymerization of a suitable monomer HMH (e.g. pyrrole) is



$(2n+2)$  electrons are used for the polymerization reaction itself, while the additional charging of the polymer film requires  $nx$  electrons. In general,  $x$  lies between 0.25 and 0.4. This means that every third to fourth monomeric subunit in the film is charged.

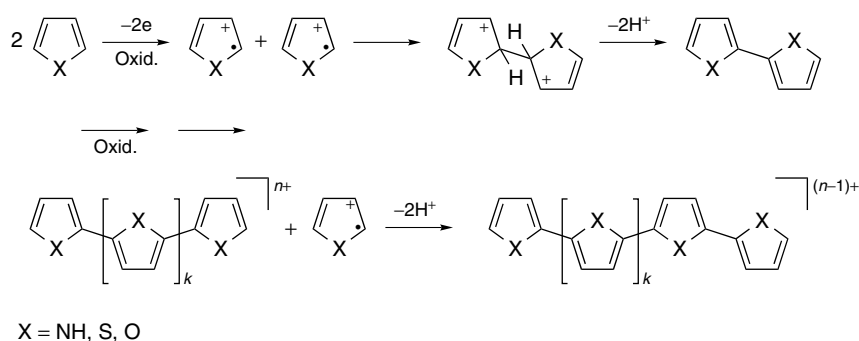
The mechanism of electropolymerization is still not fully understood. The one certainty is that in the very first step the neutral monomer is oxidized to a radical cation. It must have an oxidation potential that is accessible via a suitable solvent–electrolyte system and should react more quickly with identical species than with nucleophiles in the electrolyte solution. Therefore, as a general rule, polymerization without defects becomes less successful with increasing oxidation potential of the starting monomer, for example, in

the order pyrrole < thiophene < benzene. As the nucleophilicity of the solvents commonly used in electropolymerization rises in the order  $\text{HF} < \text{CF}_3\text{COOH} < \text{SO}_2 < \text{CH}_3\text{NO}_2 < \text{CH}_2\text{Cl}_2 < \text{PC} < \text{CH}_3\text{CN} < \text{H}_2\text{O}$ , only monomers with low oxidation potentials such as pyrrole or ethylenedioxythiophene can be polymerized in water [20]. Even in the case of thiophene, small amounts of water are sufficient for nucleophilic addition to block further growth of the oligomer chain [21]. By contrast, benzene can be only partially polymerized in  $\text{CH}_3\text{CN}$  or PC, as the newly formed oligomers react with the solvent more readily than with the cations of the oligomeric intermediates. In dry  $\text{SO}_2$ , conductive polyparaphenylene films are formed in high yield [22].

The very first mechanistic concept for the formation of conducting polymers was presented by Diaz [7] in 1981. He suggested, by analogy to the long-known coupling reactions of radical cations in aromatic compounds, that in the polymerization of pyrrole the monomers dimerize at the  $\alpha$ -position after oxidation at the electrode, and that protons are eliminated from the doubly charged dihydrodimer, forming a dimeric neutral species. As the dimer, on account of its greater conjugation, is more

easily oxidized than the monomer under the given experimental conditions, it is immediately oxidized to the cation. Chain growth should be accompanied by the addition of new cations of the monomeric pyrrole to the already charged oligomers. This, in turn, is followed by another proton elimination and the oxidation of the propagated oligomeric unit to a cation (Scheme 1).

This classic chain-propagation mechanism is still widely accepted in the literature [23]. However, recent studies using the so-called *oligomer approach* [24] have shown that this mechanistic view is by far too simple. Thus, the rate constants of the coupling reactions between the growing chain and the monomeric cation should not change during the propagation process. However, all experimental data clearly show that the rate constants for the dimerization of monomeric cations are high but decrease considerably for reactions between a chain of increasing length and monomeric cations. This rules out a chain-propagation process. Obviously, after the formation of a dimer, a sequence of subsequent “dimerization” steps leads to the formation of soluble oligomers with chain lengths normally ranging between four to eight units [25, 26]. All these reactions preferably occur in



**Scheme 1** Classical formation mechanism of conducting polymers [7].

solution without or with only small precipitation on the electrode. Subsequently, deposition and growth processes set in, triggered by nucleation reactions. They are strongly influenced by the concentration of the starting monomer, the temperature, and relevant electrochemical parameters such as the formation potential. Especially, at high concentrations of monomer, the deposition may begin at a shorter chain length.

Quantitative investigations of the kinetics of these  $\alpha$ -coupling steps suffered because rate constants were beyond the timescale of normal voltammetric experiments until ultramicroelectrodes and improved electrochemical equipment made possible a new transient method called *fast scan voltammetry* [27]. With this technique, cyclic voltammetric experiments up to scan rates of  $1 \text{ MV s}^{-1}$  are possible, and species with lifetimes in the nanosecond scale can be observed. Using this technique, P. Hapiot et al. [28] were the first to obtain data on the lifetimes of the electrogenerated pyrrole radical cation and substituted derivatives. The resulting rate constants for the dimerization of such monomers lie in the order of  $10^9 \text{ M}^{-1} \text{ s}^{-1}$ . The same authors were also able to show that the radical cation of the pyrrole tetramer, by contrast, is rather stable [28c]. The data indicated that the rate constant of dimerization is lower than  $10^4 \text{ M}^{-1} \text{ s}^{-1}$ . This tendency of decreasing reactivity as a function of chain length is a general property of all chainlike conjugated oligomers [29]. Thus, in the series of unsubstituted thiophenes, the radical cations of monomeric thiophene dimerize with a rate constant greater than  $10^9 \text{ M}^{-1} \text{ s}^{-1}$ , while the lifetimes of oligomer cation radicals increase with chain length [30]. For example, the rate constant for the dimerization of the unsubstituted thiophene tetramer is about

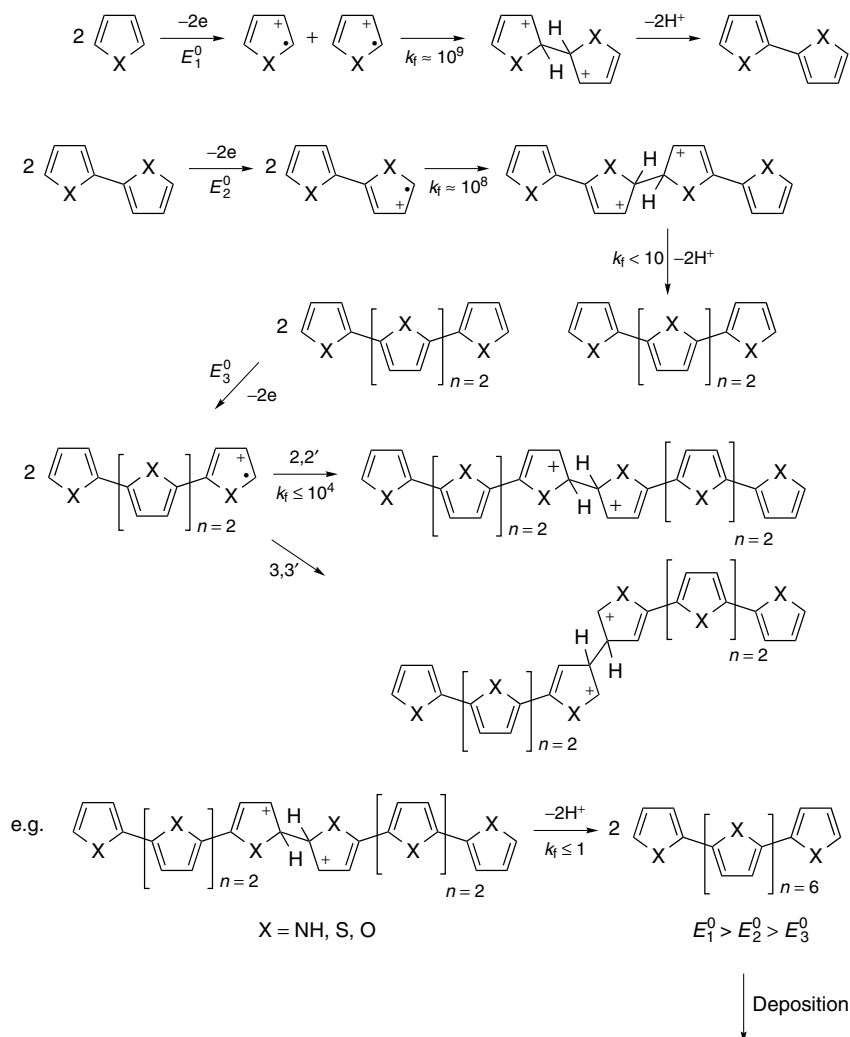
$10^5 \text{ M}^{-1} \text{ s}^{-1}$  [30a, 31], that of the pentamer is below  $10^4 \text{ M}^{-1} \text{ s}^{-1}$  [32].

From all these measurements, it is clear that the rate constants of the dimerization of chainlike conjugated oligomers, and of their coupling steps with the original monomer, decrease with increasing chain length. In addition, the rates of all these second-order reactions are a function of the concentrations of the reacting species. Therefore, as can be shown by simulations, a monomeric reactive radical cation as starting species, which is highly concentrated, is far more likely to couple with monomeric radical cations than with radical cations of higher oligomers (Scheme 2).

Studies by Heinze et al. on donor-substituted thiophenes or pyrroles [33] such as methylthio (= methylsulfonyl) or methoxy-substituted derivatives provide further clear evidence for this reaction pathway. They found, for instance, that 3-methylthiothiophene or 3-methoxythiophene (**2**) undergo a fast coupling reaction. However, deposition processes or insoluble film formation could not be detected in usual experiments with these compounds, even at high concentrations. Similarly, the corresponding 3,3'-disubstituted bithiophenes (**2a**) do not polymerize, but the anodic oxidation of 4,4'-disubstituted bithiophenes (**2c**) produces excellent yields of conducting polymers.

A careful analysis based on these experimental results excluded a chain-propagation process [33a]. On account of the 3-position of the methylthio or methoxy substituent in the thiophene or pyrrole rings, three isomeric dimers may be formed. The main reaction path can be deduced from the mesomeric forms of the radical cations (**2**)<sup>+</sup>. The two most important mesomeric structures are those with the unpaired electron in

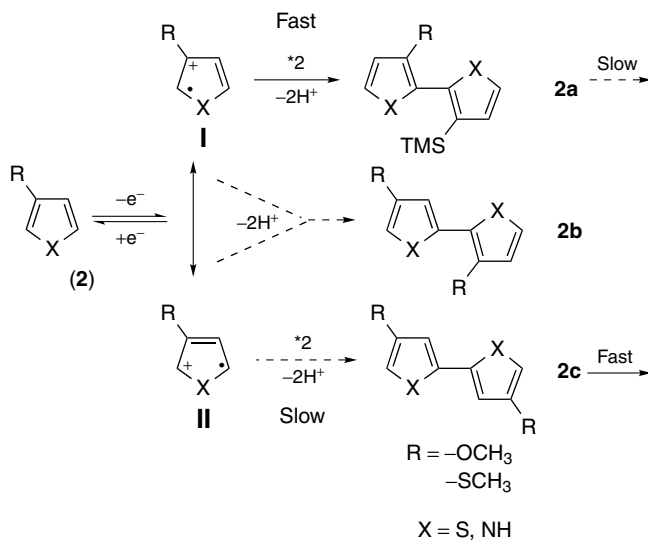




**Scheme 2** “Dimerization” steps during oligomerization in solution as deduced from the *oligomer approach*.

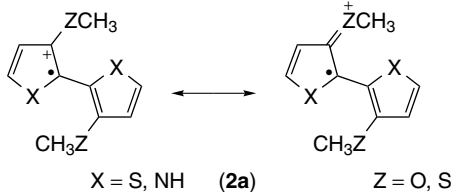
an  $\alpha$ -position (**I**, **II**). Structure **I**, with the positive charge next to the donor substituent, is preferred, because of the stabilizing +M-effect of the methoxy or methylthio substituents. Therefore, the 3,3'-disubstituted-2,2'-dimers (**2a**) are the essential products of the radical–radical coupling process. Dimers (**2b**) and (**2c**) are minor side products (Scheme 3).

The main products initially formed, dimers (**2a**), will undergo further slow coupling steps. At the given potentials, dimers (**2a**) will immediately be oxidized to the corresponding monoradical cations. Again, the monoradical cations can be found in different mesomeric structures. The most reasonable notation has the positive charge next to the donor



**Scheme 3** First coupling steps after the oxidation of 3-methylthio- or 3-methoxythiophene (pyrrole) (2).

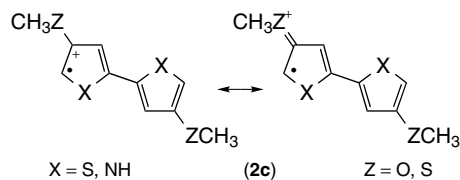
substituent and the unpaired electron at the blocked inner  $\alpha$ -position as shown below in the important mesomeric structures of the radical cations of (2a).



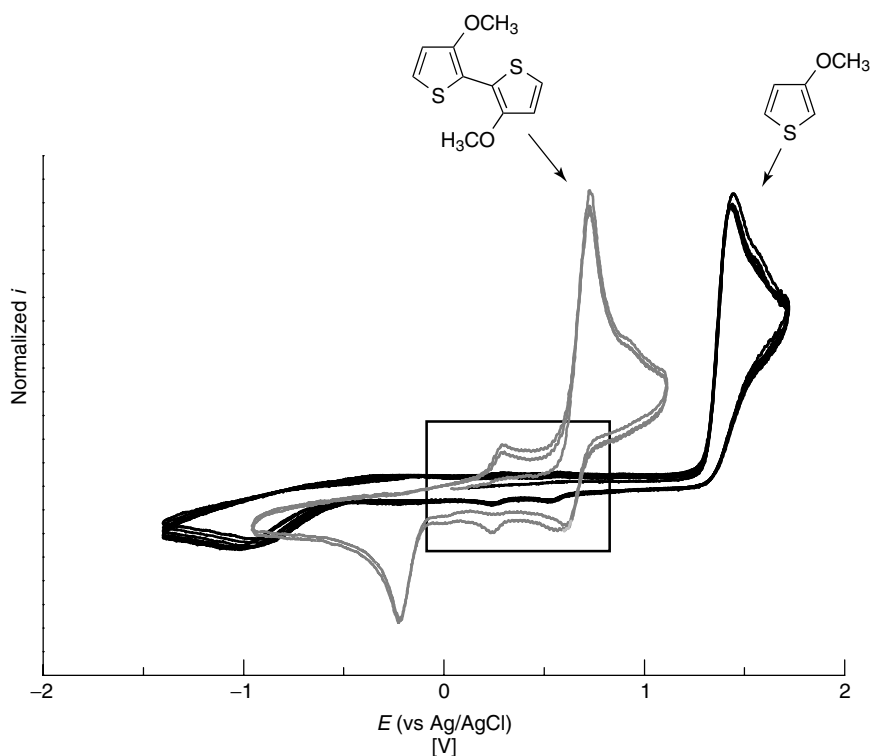
Therefore, the reactivity of these cationic species, similar to that of all other 3,3'-substituted bithiophenes or bipyrroles, is low, probably resulting in a rate constant for the dimerization of  $\leq 10^4 \text{ M}^{-1}\text{s}^{-1}$  [33d]. The tetrameric products of the subsequent coupling are even more stable than the dimers, which means that the "polymerization" process stops at this level, or becomes very slow. This reaction pattern is shown in Fig. 2, where the resulting species of

the oxidation of 3-methoxythiophene (2) and 3,3'-dimethoxybithiophene (2a) are identified as a tetrathiophene derivative.

By contrast, the high polymerization tendency of dimers (2c) is a result of the fact that the most important mesomeric structures (see below) have the unpaired electron at a nonblocked site. The coupling of the radicals is very fast, and the products of the coupling steps in turn have substituents in "outer"  $\beta$ -positions of the oligomer, which makes it reactive [33].



All these findings prove that the electropolymerization mechanism of donor-substituted thiophenes and pyrroles does not involve a chain-propagation



**Fig. 2** Cyclic voltammetry for the oxidation of 3-methoxythiophene (**2**),  $c = 6 \times 10^{-4}$  in acetonitrile + 0.1 M TBAPF<sub>6</sub>,  $\nu = 0.1 \text{ V s}^{-1}$  and 3,3'-dimethoxy-bithiophene (**2a**),  $\nu = 0.1 \text{ V s}^{-1}$ . The resulting oligomer after the oxidation of both (**2**) and (**2a**) is a tetrathiophene derivative, which can be reversibly oxidized up to a dication (see square).

process with successive coupling steps of the starting radical cation. By contrast, it must be concluded that oligomerization in solution preferably occurs via consecutive “dimerization” steps leading from a dimer to a tetramer and then to an octamer. In the case of a hypothetical chain growth reaction, the extremely high reactivity of (**2**)<sup>+</sup> should trigger an almost perfect formation of a polymeric chain. However, this has never been observed.

It would be an oversimplification to assume that these simple coupling and electron-transfer reactions reflect all the steps occurring in front of the electrode. In addition, parallel reactions

such as homogeneous symproportionations ( $\text{D}^{2+} + \text{M} \rightleftharpoons \text{M}^{+\bullet} + \text{D}^{+\bullet}$ ) autocatalytically produce radical cations of the lower oligomers [34]. Other possible side reactions are, for example, (reversible) dimerization without elimination of protons or  $\beta$ -linkage reactions. Thus, Cava et al. could show that during oligomerization in solution branched  $\beta$ - $\beta$ -coupling steps compete with the linear  $\alpha$ - $\alpha$ -coupling [35]. In addition, their results reveal that the elimination of protons after the coupling of the radical cations may be slow. In this case, a charged  $\sigma$ -complex exists as a short-lived intermediate. In the case of the

pyrrole oligomerization (dimer–tetramer), the deprotonation step is significantly slower than the radical–radical coupling step [28d], indicating that the stability of the  $\sigma$ -dimer increases as a function of chain length.

The importance of the proton elimination has been overlooked for a long time. Originally, it was assumed that proton elimination is always a fast reaction the driving force of which is the rearomatization of the system and that rate-determining steps during electropolymerization are related to coupling reactions between cationic species. The new findings clarify details of the polymerization reaction, which have not been understood up to now. Obviously, the rates of proton elimination from “dimeric” coupling intermediates diminish so drastically that charged  $\sigma$ -dimers with more than four units in one conjugated chain segment are fairly stable in the charged state. Proton elimination from such species takes place only when  $\sigma$ -intermediates are oxidized to a higher charging level, which increases the reactivity of the system. Thus, the charged  $\sigma$ -dimer of the thiophene octamer does not undergo a deprotonation step as long as the electrode potential does not exceed the oxidation potential of the octathiophene trication [36]. The reason for this effect is that the acidity of proton containing coupled  $\sigma$ -intermediates decreases as a function of chain length and the number of electron-donating groups within the oligomer. The positive charges are stabilized in dependence on electronic factors and the extent of the conjugated system. Thus, “ $\sigma$ -dimers” of pyrrole oligomers are more stable than the corresponding thiophene oligomers; and the chain length criterion proves greater stability – that means a lower tendency for proton release – of such intermediates for an increasing chain

length. An important consequence of this behavior is that oligomeric chains cannot grow via the coupling of a monomeric species with an oligomeric chain because the resulting intermediates do not eliminate protons.

An essential prerequisite for successful oligomerization and polymerization is a sufficiently “strong” base in solution to accept the protons from the  $\sigma$ -intermediates. In the case of protonated pyrroles, the  $pK_a$  value lies in the range between 4 and  $-4$ , whereas the  $pK_a$  value of acetonitrile is about  $-10$ . Therefore, the oligomerization of pyrrole in pure acetonitrile may already stop at the level of  $\sigma$ -intermediates of bi- or more likely of tetrapyrrole. Acetonitrile is a weaker base than the  $\sigma$ -intermediates. Consequently, a stronger base must be used to initiate the elimination of protons. Water fulfills this condition. Pyrrole can be polymerized in acetonitrile in the presence of 1% water [6, 37]. A similar effect results from the application of a sterically hindered base such as 2,6-di-*tert*-butylpyridine [38]. However, the concentration should be kept low because, at high concentrations proton, abstraction from the monomeric radical cation may occur, thus forming a neutral radical [28d]. The “base” effect can be also observed in the case of thiophenes. For example, the rate of oligomerization and polymerization increases when 2,6-di-*tert*-butylpyridine is added to a solution of bithiophene. However, in the case of monomeric thiophene, the high oxidation potential of the starting species between ( $>1.6$  V versus Ag/AgCl) prevents any formation of conducting polymeric material. The reason is that under these conditions nucleophilic substitution reactions between the respective base and the highly reactive cations take place or the formation

of neutral radicals leads to unknown side products [21, 28d, 39].

Recently, the discussion about the formation of  $\pi$ - or  $\sigma$ -dimers as intermediates of the oligomerization has intensified. Thus, on the basis of concentration and temperature-dependent UV-vis and ESR data, Miller et al. have suggested that the radical cations of substituted oligothiophenes may form  $\pi$ -dimers [40]. Other authors have subsequently reached similar conclusions [41]. In all cases, voltammetric analysis indicates the reversible formation of radical cations without chemical follow-up steps. Accordingly, it has been concluded that weakly interacting  $\pi$ -mers form rapidly and also decay relatively quickly in the experimental timescale. Very recent cyclic voltammetric studies of the oxidation of diphenylpolyenes, oligophenylenevinyls, and oligothiophenes have indicated strong changes of the voltammetric response as a function of temperature, concentration, and scan rate. A detailed evaluation of all data gave clear evidence that the formation of the radical ions is followed by rapid reversible dimerization between oligomer chains, accompanied by the formation of a  $\sigma$ -bond [42]. Moreover, applying NMR measurements, A. Merz et al. could show that the radical cations of 5,5'-diphenyl-3,3',4,4'-tetramethoxy-2,2'-bipyrrole reversibly dimerize and form a  $\sigma$ -dimer in solution, the equilibrium constant of which is temperature-dependent [43]. Similarly, by oxidizing 1,3,5 tripyrrolidinobenzene, Effenberger et al. succeeded in isolating a dimeric  $\sigma$ -complex and, by using X-ray structure analysis, were able to unequivocally prove the existence of the  $\sigma$ -bond in the solid state [44]. Using cyclic voltammetry and spectroscopic techniques, Heinze et al. [45] could show that the dimerization

of these species takes place between the radical cations (RR coupling). It is also noteworthy that the dimerization step is, in principle, chemically reversible. After the reduction of the dimer, the starting species is regenerated. Moreover, no protons are eliminated from the dicationic dimer. Owing to the electron-donating amino nitrogens, the acidity of the dimer is so weak that rearomatization from the dicationic  $\sigma$ -dimer to the neutral biphenyl cannot take place and can be achieved only after the addition of a strong base. A similar tendency can be observed in the formation of conducting oligomers and polymers. The stability of the " $\sigma$ -dimers" increases with the length of the growing chain.

In the past, some authors [46] have questioned the radical-radical coupling (RR) mechanism on the ground that the strong coulomb repulsion between small cation radicals renders a direct dimerization of such particles improbable. Instead, they postulated a radical-substrate coupling (RS). An electrophilic attack by the radical cation on the neutral monomer or oligomer produces the single-charged coupling product, which eliminates its protons only after a further charge transfer, becoming a neutral oligomer. However, the principal objection to the RR path – the strong Coulombic repulsion between charged particles – is not convincing for reactions in solution. Using the Debye-Smoluchovski theory [47], it has been shown that even small ionic molecules that are equally charged are able to dimerize at a diffusion-controlled rate [48]. Recently, applying the oligomer approach, several authors have demonstrated that the "dimerization" reactions of heterocyclic monomers and oligomers involve coupling between two electrogenerated cation radicals rather than with the starting molecule [28, 32, 33, 42, 43, 45].

Careful quantitative kinetic studies of the coupling steps of oligomeric pyrroles and thiophenes have confirmed this mechanistic pattern [49]. In addition, quantum chemical studies reveal that the dimerization of two radical cations becomes perfectly feasible when solvent effects are included [50].

### 16.2.2

#### Solid-state Processes

Despite the vast quantity of data on electropolymerization, relatively little is known about the processes involved in the deposition of oligomers (polymers) on the electrode, that is, the heterogeneous phase transition. Research – voltammetric, potential, and current step experiments – has concentrated largely on the induction stage of film formation of PPy [6, 51], PTh [21, 52], and PANI [53]. In all these studies, it has been overlooked that electropolymerization is not comparable with the electrocrystallization of inorganic metallic phases and oxide films [54]. Thus, two- or three-dimensional growth mechanisms have been postulated on the basis that the initial deposition steps involve one- or two-electron transfers of a soluted species and the subsequent formation of ad-molecules at the electrode surface, which may form clusters and nuclei through surface diffusion. These phenomena are still unresolved.

Electropolymerization begins with the formation of oligomers in solution. Above a critical chain length, insoluble oligomers form, which deposit themselves on the electrode surface [55]. Two additional findings support this thesis. In potential step experiments, optical signals indicating the deposition of oligomers on the electrode only change when the current on the  $i$ - $t$  curve starts to rise again after

the typical  $t^{-1/2}$  drop. In potentiodynamic experiments, the observed oxidation currents, as well as the visible changes on the electrode surface, are dependent on the scan rate. The slower the scan rate, the more visible the electrode coating and the greater the rise in the oxidation current [56]. The electrodeposition process can be also monitored by spectroelectrochemical in situ techniques [57]. Especially useful are ellipsometric studies [58] combined with time-resolved UV-vis spectroscopy [59, 60]. Measurements of the deposition of oligothiophenes reveal that during the starting period of electrolysis only species in the solution phase are generated and that the growth of the nuclei is not a simple three-dimensional deposition process but a fairly complex one.

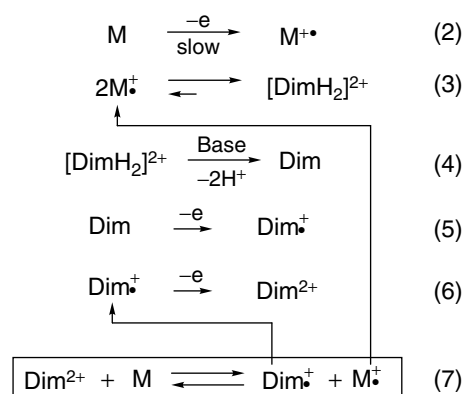
The literature contains descriptions of trace-crossings or nucleation loops that normally appear on the reverse sweeps of the first cycle in all voltammograms, provided the scan reversal lies close to the peak potential [51a]. This has been interpreted as the start of the nucleation process of the corresponding polymer. A strong argument for this assumption has been that this effect always appears in voltammetric experiments with freshly polished electrodes and only in the reverse sweep of the first cycle [6, 51, 61]. Such behavior is similar in this respect to the electrochemical deposition of metal on a foreign substrate, in which an overpotential is required for nucleation, after which further growth of the metallic layer occurs at the characteristic redox potential of the metal, leading to a trace-crossing in the reverse sweep. However, recent voltammetric studies have shown that such trace-crossings still appear even if deposition processes or insoluble film formation cannot be detected

under any conditions, even at high concentrations [33a]. Moreover, the potentiodynamic electropolymerization of pyrrole or substituted derivatives at high concentrations produces the trace-crossing, even after the electrode has become polymer-coated [62]. This is inconsistent with an interpretation based on the nucleation-and-growth mechanism. Normally, during multisweep experiments trace-crossing disappears because of the fact that the growing polymer layer produces a significant cathodic current in the reverse voltammetric sweep.

By contrast, experimental data support the view that the additional anodic current observed in the reverse sweep results from slow follow-up or symproportionation reactions occurring in the diffusion layer in front of the electrode. In the early 1970s, Feldberg [63] demonstrated the theoretical possibility of trace-crossing in ECE reactions (electrochemical, chemical, electrochemical) involving slow rate constants for the chemical step. This is one process that may take place during the oligomerization of the monomeric starting species in solution. Trace-crossing results from the slow formation of a neutral tetramer or octamer ( $k \approx 10^4 \text{ M}^{-1} \text{ s}^{-1}$ ) in the diffusion layer and its subsequent oxidation to its mono- or dication. The rate-determining step is the slow elimination of protons from charged  $\sigma$ -intermediates.

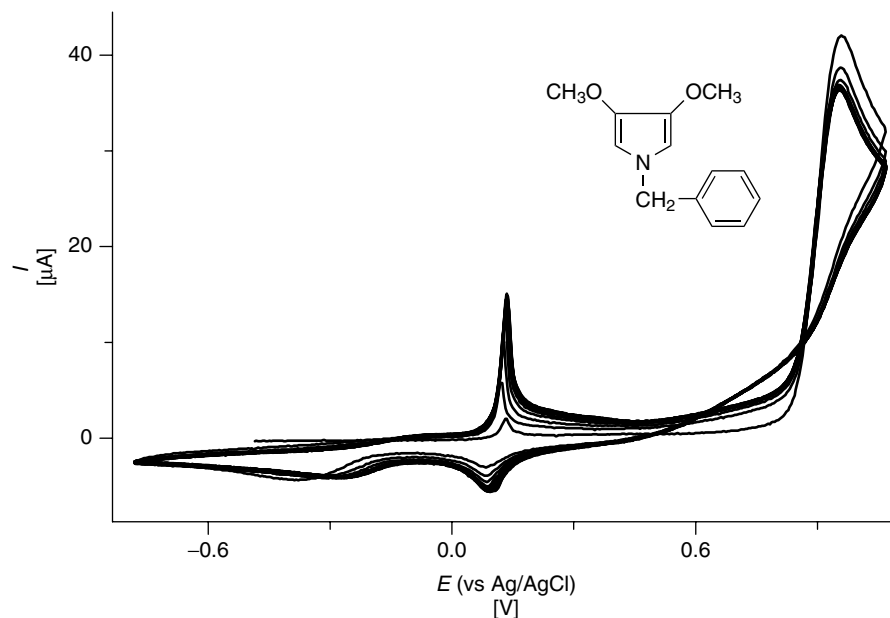
The fact that extensive trace-crossing is also observed during generation and deposition of oligomers has stimulated further explanations [64]. A very realistic mechanism that is in excellent agreement with experimental data is based on the assumption of homogeneous symproportionation reactions (Eq. 7) taking place after the generation and oxidation of dimers that are formed by the coupling of monomeric

radical cations such as pyrrole or thiophene (see Scheme 2, Eqs. 2–7).



Symproportionation reactions occur between dications of the dimer and the neutral monomeric starting species. Although the thermodynamic equilibrium lies on the left side, the fast coupling reaction of  $\text{M}^{\bullet+}$  shifts the reaction to the right side and generates an additional flux of oxidizable species which results in a strong trace-crossing (Fig. 3). Simulations which have been carried out for a vast number of different rate parameters and mechanistic variants show that both symproportionation reactions and slow eliminations of protons from the dihydridimer explain the trace-crossing [33a, 64, 65]. Up to now, all available results indicate that the so-called *nucleation loop* in cyclic voltammetry is not the result of a nucleation step but of homogeneous follow-up reactions of soluble oligomers in the diffusion layer.

Galvanostatic, potentiostatic, or potentiodynamic techniques can be used to electropolymerize suitable monomeric species and form the corresponding film on the electrode. The potentiodynamic experiment, in particular, provides useful information on the growth rate of conducting polymers. The increase in current with



**Fig. 3** Multisweep cyclic voltammogram (6 scans): trace-crossing effect during potentiodynamic polymerization of N-benzyl-3,4-dimethoxy-pyrrole in acetonitrile, 0.1 M TBAPF<sub>6</sub>, +1% H<sub>2</sub>O,  $\nu = 200 \text{ mV s}^{-1}$ ,  $T = 298 \text{ K}$ .

each cycle of a multisweep cyclic voltammogram (CV) is a direct measure of the increase in the surface of the redoxactive polymer and, hence, a measure of relative growth rates (Fig. 4).

The relative growth rate per cycle  $\nu$  is calculated from the anodic peak current of the respective polymer oxidation using Eq. (8)

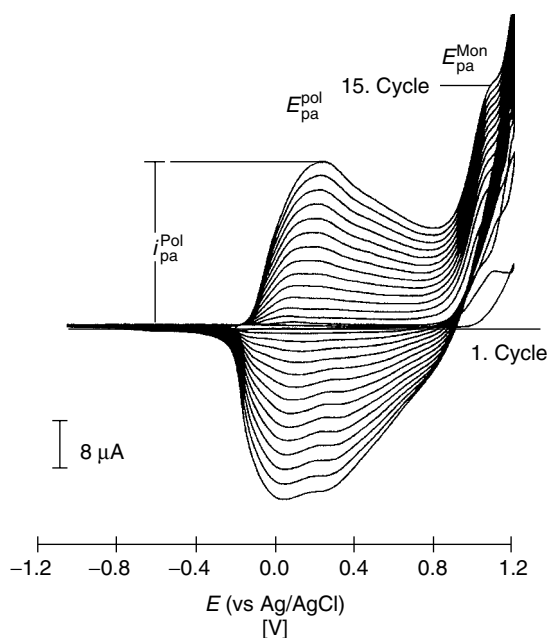
$$\nu = \frac{k \cdot i_{\text{pa}}^{\text{pol}}}{(n - 1)} \quad (8)$$

where  $k$  is a proportionality constant. The parameter  $\nu$  is by its nature a function of the conditions of polymerization and, thus, must be standardized to  $\nu_0$ , in relation to which only one growth parameter may be changed [38]. Quartz microbalance measurements reveal that deposition occurs preferably in the potential range where

the monomer and short oligomers are oxidized (Fig. 5). In general, no deposition is observed outside of this range. Surprisingly, lowering the temperature raises the efficiency of deposition owing to the fact that the solubility of the soluble oligomers decreases [66].

However, despite all these observations, it is still unclear which additional coupling steps take place after the nucleation of an oligomeric layer on the electrode. In the literature, experimental data have been presented to support the view that, with the formation of an oxidized “prefilm”, the process gradually transforms into one in which the chain growth can take place on the surface immediately by coupling of the monomer cation radical and the oxidized chain in the film [67]. However, the assumption of heterogeneous coupling of monomers





**Fig. 4** Potentiodynamic growth of a polypyrrole film in acetonitrile (+1% H<sub>2</sub>O),  $\nu = 0.1 \text{ V s}^{-1}$ ,  $T = 298 \text{ K}$ , number of cycles  $n = 15$ ,  $E_{pa}^{mon} = 1.0 \text{ V}$  versus Ag/AgCl,  $E_{pa}^{pol} = 0.31 \text{ V}$  versus Ag/AgCl.

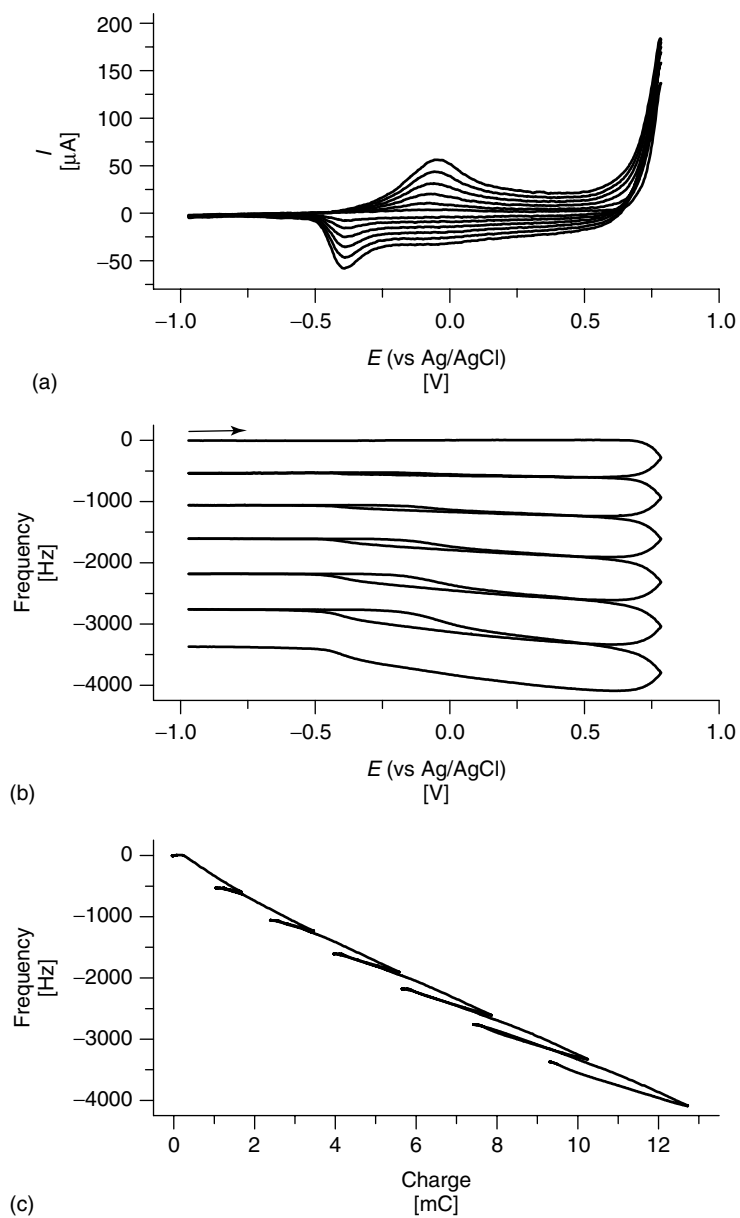
or dimers with the existing layer of oligomers seems rather improbable, as the oligomers in the film are not highly reactive and the rate constants for the dimerization of monomers or dimers are very high.

A few years ago, solid-state voltammetric measurements on sexiphenylene layers revealed for the first time that the material “polymerizes” upon *p*-doping in the solid state on the electrode [68]. It was shown that sexiphenylene dimerizes at low oxidation potentials, while at high potentials long chains are produced and cross-linking steps become more and more predominant [69]. Since then, further solid-state experiments with monodisperse oligothiophenes have confirmed these early results and provided new insights into the general polymerization mechanism of conducting polymers [36].

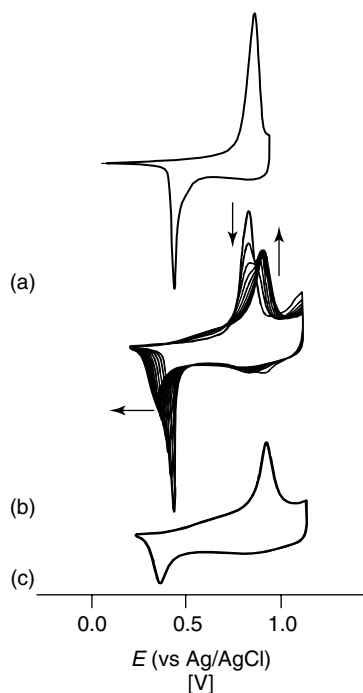
The application of low-temperature voltammetry to octathiophene (H-T<sub>8</sub>-H),

for instance, allows the reversible generation of trications or even tetracations. This stability disappears when the temperature is raised. If, in the case of H-T<sub>8</sub>-H, the switching potential is set in the ascent of the anodic trication wave at 1.25 V, two new waves appear – one in the anodic, the second one in the cathodic scan – and gradually increase, while the original signals for redox processes of the starting material decrease (Fig. 6).

The resulting isopotential point confirms that H-T<sub>8</sub>-H reacts to produce a new electroactive species without side reactions. The optical absorption of the electrochemically generated product is red-shifted and its cathodic peak potentials upon discharging (reduction) lie negative to those of the educt, indicating that the product consists of larger molecules with a more extended redox system. If experiments are carried out at higher sweep rates ( $\nu > 100 \text{ m V s}^{-1}$ ), broad waves are



**Fig. 5** Quartz crystal microbalance measurements during potentiodynamic polymerization of 4,4'-dimethoxy-bithiophene in  $\text{CH}_2\text{Cl}_2$ , 0.1 M TBAPF<sub>6</sub>,  $\nu = 0.01 \text{ V s}^{-1}$ : (a) cyclic voltammetry; (b) frequency-potential plot showing mass changes as a function of the applied potential; (c) frequency charge plot showing mass changes as a function of charge consumed during potentiodynamic cycling.



**Fig. 6** Potentiodynamically generated solid-state coupling of octathiophene: (a) cyclic voltammogram of H-T<sub>8</sub>-H,  $E_{\lambda} = 1.07$  V; (b) cyclic voltammetry during coupling,  $E_{\lambda} = 1.25$  V; (c) cyclic voltammogram of H-T<sub>16</sub>-H,  $E_{\lambda} = 1.25$  V. The resulting sexidecithiophene forms a stable  $\sigma$ -“dimer” after oxidation. Experimental conditions: CH<sub>2</sub>Cl<sub>2</sub>/TBAPF<sub>6</sub>,  $T = 268$  K. [From Ref. [36].]

observed during the cathodic reverse scan at potentials around 0 V. This is typical for the discharging of protons formed during the process. The coulometric analysis of the voltammograms shows that one charge is lost per molecule (by proton cleavage) in the condensation reaction. The average functionality of a monomer unit,  $f$ , has been calculated from coulometric data. The resulting values of  $f < 2$ , together with all other observations, give clear evidence that the short-chain H-T<sub>8</sub>-H dimerizes quantitatively in this solid-state reaction, forming an isomer of sexidecithiophene. This product may be  $\alpha, \alpha'$ -,  $\alpha, \beta'$ -, or  $\beta, \beta'$ -coupled. In any case, the hysteresis between the charging and discharging steps is characteristic of the formation of  $\sigma$ -intermediates during the polymerization process. Analogous reactions have been observed for other

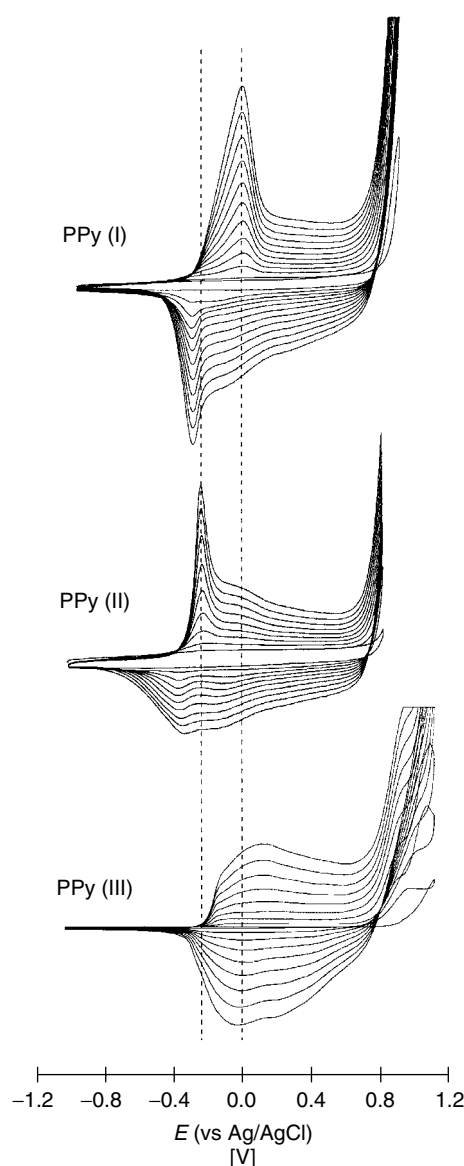
short-chain oligomers, such as sexithiophene or sexideciphenylene, leading to dodecathiophene and -phenylene. All these materials can be polymerized further at higher formation potentials. The number of coupling steps depends strongly on the applied potential. At the end of such processes, the voltammograms have the typical shape of those of conducting polymers in general, that is, they exhibit the characteristic current plateau and high current waves at different potentials at the onset of charging and the end of discharging. Under these conditions, the average functionality may be larger than the limiting value for infinite chains ( $f = 2$ ). From this, however, it must be concluded that chain-lengthening steps as well as coupling reactions between the chains take place, leading to a network with  $\sigma$ -interchain bonds ( $sp^3-sp^3$ ) and regular bonds between  $sp^2-sp^2$  centers. All these experiments give no indication of a polymer of infinite length. On the basis of IR data, Furukawa et al. concluded from studies of thiophene oxidation that the degree of polymerization is rather low, ranging from 10 to 35 [70]. For the conjugation length of PTh, a number of ca. 11 has been estimated [71].

In very recent publications, it was shown that the quality of the polymerization process and the structure of the resulting polymers strongly depend on the

formation potential applied during the electrochemical experiments [26, 37, 62, 72]. Thus, in the case of polypyrrole, two variants showing well-shaped voltammograms can be clearly distinguished. PPy (I), which is the dominant component of polypyrrole, normally prepared under mild conditions at a formation potential of 0.9 V versus Ag/AgCl, has an oxidation wave at 0.0 V and a reduction wave at  $-0.28$  V. (Fig. 7) It turned out that the material obtained is weakly cross-linked and contains  $\sigma$ -interchain bonds and regular bonds between the chains. PPy (II) which is generated at very low formation potentials of  $+0.75$  V or less has a sharper wave at ca.  $-0.23$  V and a fairly broad much weaker reduction wave at  $-0.37$  V. PPy (II) is a material which contains linear chain sequences with eight units and is cross-linked via  $\sigma$ -bonds. This establishes unconventional properties of the polymers such as a cation exchange mechanism during charging and discharging. A third variant is PPy (III). It is a partially conjugated polymer with both saturated pyrrolidine and unsaturated rings in a polymeric network. The acid catalyzed trimerization of pyrrole and the follow-up electrochemical and chemical reactions [73] play a crucial role in the

formation of PPy (III). In highly acidic solutions at low formation potentials, a passivating film is generated (PPy (IV)).

PPy was the first conducting polymer to be structurally analyzed. The discovery that  $\alpha, \alpha'$ -disubstituted pyrrole did not polymerize led to the conclusion that the



**Fig. 7** PPy variants generated by galvanostatic or potentiodynamic techniques. PPy (I) is formed in acetonitrile with 1% water. The average conjugation length is about 30 units. The material is weakly cross-linked. PPy (II) is formed at low oxidation potentials ( $\leq 0.75$  V versus Ag/AgCl) or low current densities ( $6 \mu\text{A cm}^{-2}$ ). It consists of short chains with  $\sigma$ -dimers in the charged state. PPy (III) showing symmetric voltammograms during charging and discharging cycles is a strongly cross-linked material. [From Ref. [73].]

pyrrole units in PPy are  $\alpha$ -linked [74]. Magic angle spinning  $^{13}\text{C}$ -NMR data supported the view that the pyrrole units are linked chiefly in the  $\alpha, \alpha'$ -position, although  $\alpha, \beta$  bondings are also found [75]. On the other hand, already in 1984, XPS measurements of PPy revealed that a full one-third of the pyrrole rings in a chain are irregularly bonded [76].

Similarly, a chain structure with predominantly  $\alpha, \alpha'$ -coupling between the monomer units was postulated for polythiophene (PTh) on the basis of spectroscopic findings and mechanistic studies. IR measurements of uncharged, chemically produced examples, in particular, clearly revealed that  $\alpha, \alpha'$ -bonding predominated in the polymers produced from  $\alpha, \alpha'$ -dibromothiophene, 2,2'-bithiophene, or 3-methylthiophene [4, 77]. The IR data correlated very well with  $^{13}\text{C}$ -NMR measurements, which similarly confirm the dominance of  $\alpha, \alpha'$ -bonding in P3-MeTh [78]. In agreement with these findings, the electrochemical oxidation of 3,3';5,5'-tetramethyl-2,2'-bithiophene unambiguously demonstrated that the non-blocked outer  $\beta$ -position is nonreactive [42c]. However, it should be noted that the coupling steps of thiophene oligomers may involve interchain reactions leading to a polymeric network. The reactivity of such oligomers depends on their respective charging level.

All these data show that only small changes of the polymerization parameters may lead to characteristic differences in the resulting structures of conducting polymers. Structural properties – for example, regularity and homogeneity of chain structures, but also chain length play an important role in our understanding of the properties of such materials. Spectroscopic methods have proved particularly

suitable for characterizing structural properties. These comprise surface techniques, such as XPS, AES (Auger electron spectroscopy), or ATR (attenuated total reflection [IR] spectroscopy), on the one hand, and the usual methods of structural analysis, such as NMR, ESR, and X-ray diffraction techniques, on the other [79].

During the 1980s, the chain length criterion was the most important factor related to the structural characterization of conducting polymers. The importance of this parameter lies in the considerable influence of the electric as well as the electrochemical properties of conducting polymers. However, the molecular weight techniques normally used in polymer chemistry cannot be employed on account of extreme insolubility of the materials. A comparison between spectroscopic findings (XPS, UPS, EES) for PPy and model calculations has led some researchers to conclude that 10 is the minimum number of monomeric units in a PPy chain, with the maximum within one order of magnitude higher [76, 80]. By electropolymerizing  $\alpha, \alpha'$ -tritium labeled  $\beta, \beta'$ -dimethylpyrrole and comparing the tritium activity in the monomer and the polymer, Nazzari and Street obtained molecular weights which indicate chain lengths of between 100 and 1000 pyrrole units [81]. By contrast, the *oligomer approach* has shown that oligomerization in solution produces soluble oligomers with chain lengths between 8 to 12 units. During solid-state polymerization in dependence on the applied electrode potential, linear chains up to 30 units as well as cross-linked networks are generated [25, 69]. Thus, the real chain length is still unclear but cross-linking effects may contribute to high molecular weights.

### 16.3 Redox Processes in Conducting Polymers

Conducting polymers, provided they are chemically produced, are initially insulators. Their metallike properties, that is, their high conductivity and optic reflectivity, only become obvious after “doping”. Even in the earliest stages of research on these materials, it was clear that these processes were not comparable with the classic doping of inorganic semiconductors. Rather, they correspond to oxidation in the case of *p*-doping or reduction in the case of *n*-doping. Suitable redox reagents are either chemical electron acceptors, such as iodine, or electron donors, such as potassium naphthalide; or the process may be electrochemically induced via an electrochemical cell. Because of the redox reaction, the polymer chain is negatively charged in the case of reduction and positively charged in the case of oxidation. To maintain electroneutrality, the appropriate counterions diffuse into the polymer during charging and out of the polymer during discharging.

The knowledge that conducting polymers can be charged, that is, oxidized and reduced, raised the question of possible applications, such as the construction of a polymer battery, at an early stage [82]. But basic research was long unable to explain the charge storage mechanism. Theoretical concepts that describe the voltammetric response during charging and discharging of redoxactive films were developed more than two decades ago [83]. In the ideal case, reversible cyclic voltammograms (CVs) should show completely symmetrical and mirror-image cathodic and anodic waves

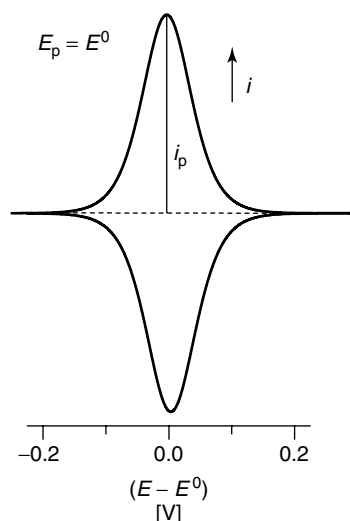
with identical peak potentials and current levels (Fig. 8).

The current in the reversible case is then

$$i = \frac{n^2 F^2 A \Gamma_T v \cdot \exp \Theta}{RT(1 + \exp \Theta)^2}, \quad (9)$$

where  $\Theta = (nF/RT)(E - E^0)$ , and  $\Gamma_T = \Gamma_0 + \Gamma_R$  correspond to the total surface covered with reduced and oxidized sites. The other parameters have their usual meanings. Apart from the mirror symmetry of the waves, it is also characteristic that, in contrast to measurements obtained with soluble redox systems, current *i* and the scan rate *v* are directly proportional to each other.

The above statements are valid for monomolecular layers only. In the case of polymer films with layer thickness into the  $\mu$ -range, as are usually produced by electropolymerization, it must be taken into account that charge transport is dependent on both the electron exchange reactions between neighboring oxidized and reduced sites and the flux of counterions in keeping with the principle of electroneutrality [84, 85]. Although the



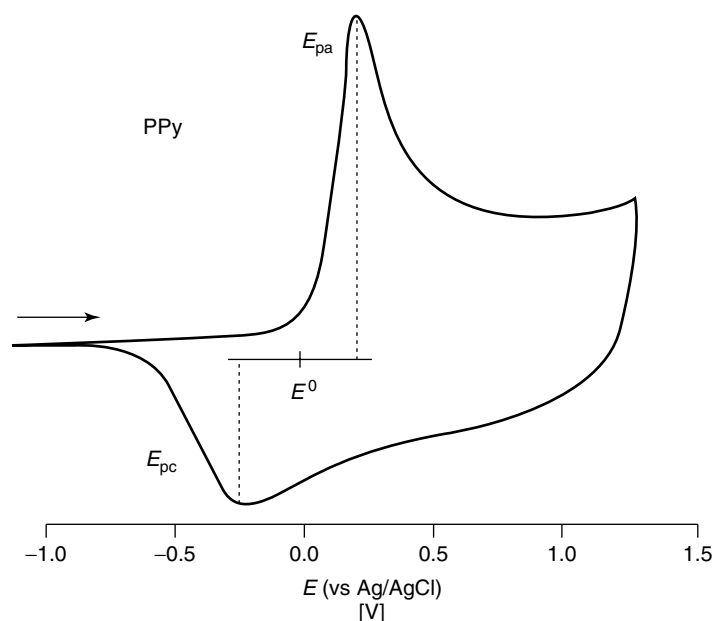
**Fig. 8** Theoretical cyclic voltammogram for a redoxactive film with noninteracting sites.

molecular mechanisms of these processes are not yet understood in all their detail, their phenomenology can be adequately described by the laws of diffusion. All variants of the diffusion mass transport are possible from the finite limiting case to semi-infinite diffusion, depending on film thickness, the values of the formal diffusion coefficients, and the experimental timescales used. For voltammetric experiments, this implies that as the sweep rate increases there must be a shift from mirror symmetrical CV diagrams with  $i$  proportional to  $v$  to the classic, asymmetrical voltammograms with  $i$  proportional  $v^{1/2}$ .

Although the potentiodynamic charging and discharging of conducting polymers produces voltammograms of very different shape depending on type and polymerization conditions, one frequently finds CV diagrams (Figs. 7, 9) with a very similar shape. This is particularly the case

when polymeric films are produced under mild conditions at low formation potentials [4, 5, 11c, 19, 34, 74]. Characteristic features of these systems are, in the case of the  $p$ -doping, a steep anodic wave at the start of charging, followed by a broad flat plateau as potential increases. In the reverse scan, a potential-shifted cathodic wave appears at the negative end of the capacity-like plateau.

The conspicuous separation between the cathodic and anodic peak potentials (hysteresis) was initially interpreted in terms of the simple theory of redox polymers as a kinetic effect of slow heterogeneous charge transfer; the thermodynamic redox potential of the whole system was calculated from the mean value between  $E_{pa}$  and  $E_{pc}$  [5, 7a, 86]. As a simplification, it was assumed that the interaction between the charged oligomeric segments was negligible. These redox data correlate



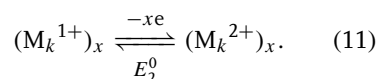
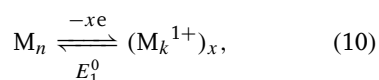
**Fig. 9** Cyclic voltammogram for the oxidation of polypyrrole,  $v = 0.5 \text{ mV s}^{-1}$ ,  $T = 298 \text{ K}$ .

well with potential values obtained by extrapolation from quantum mechanical calculations [87] and redox potential measurements [29, 88, 89] on oligomers of defined chain length. As expected, with increasing conjugation length, the respective oxidation and reduction potentials shift towards lower energy values. However, the small discrepancy between the measured and the extrapolated  $E_{pa}$  values gave rise to the opinion that the conjugation length of the neutral polymer covered only 5 to 10 monomeric units [88].

Furthermore, from quantum mechanical findings, it was concluded that the onset potentials measured in the polymers reflected only the initial ionization of such systems and that further ionization steps had to be linked to structural changes in the system [87]. Substitution effects, too, influence the position of the oxidation potentials of the polymers. Whereas electron-donating substituents lower oxidation potentials just as they do in the monomers, the electron-withdrawing substituents raise them. The fact that in the majority of cases there is a linear relation between the oxidation potentials for the monomers and the polymers shows that the substituents' effects are primarily of an electronic nature [79, 90, 91]. Feldberg and Rubinstein [92] offered another explanation for the typical separation between anodic and cathodic peak potentials of conducting polymers. In their opinion, the hysteresis is not due to a classic square scheme involving a heterogeneous and homogeneous kinetics but due to N-shaped free energy curves as a consequence of phase transitions in the polymer. Later on, Gottesfeld et al. presented a model in which they explained the hysteresis by consideration of resistive effects in the polymer film. They suggested that the electrochemistry is reversible and that the film

resistivity is inversely related to the amount of (oxidizing) charge [93]. In a neutral polymer, the initial resistivity may be large enough to produce a significant  $iR$  drop thereby delaying the onset of oxidation. A small amount of oxidation can cause a reduction in resistivity and the charge will flow at some later stages of the scan.

Another concept has been developed on a refined model based on two-step redox systems typical for organic compounds [94]. This concept treats a polymer chain with the degree of polymerization  $n$  as  $x$  weakly interacting segments containing  $k$  monomeric units, each of which can be charged up to a diionic state in two redox steps with different potentials ( $1 < k \ll n$ ,  $x * k = n$ ).



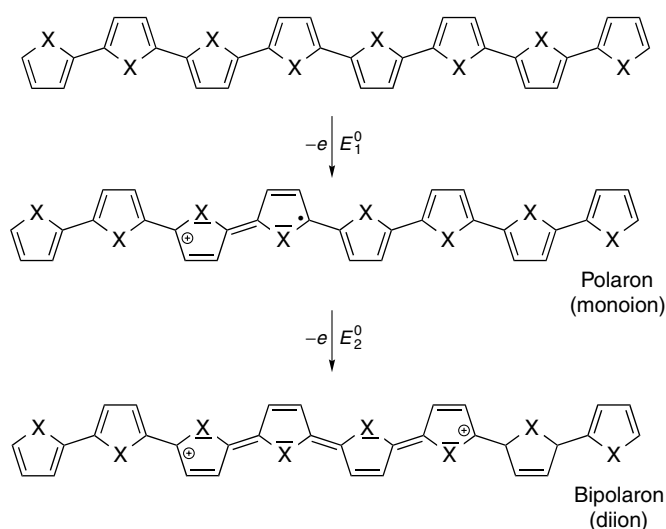
This concept implies negligible interaction energies between the segments; consequently, the essential determinant of the position of the redox potentials must be the structure of the so-called effectively conjugated segments (ECS) [95].

These ideas developed by chemists resemble the bipolaron model, which presents the solid-state physicist's view of the electronic properties of doped conducting polymers [96]. The model was originally constructed to characterize defects in inorganic solids. In chemical terminology, bipolarons are equivalent to diionic states of a system ( $S = 0$ ) after oxidation or reduction from the neutral state. The transition from the neutral state to the bipolaron takes place via the polaron state (= monoion,  $S = 1/2$ ,



ESR signal) and, thus, corresponds sequentially as well to redox transitions observed in two-step redox systems. In contrast to normal redox processes, however, additional local distortions occur in the chain during the charging of the polymer. Already in the first step, the formation of polarons, there is a gain of relaxation energy  $E_{\text{rel.}}$ . This is released by structural relaxation after ionization, for which a vertical Franck–Condon-like ionization energy  $E_{\text{IP-v}}$  is necessary.  $E_{\text{rel.}}$  corresponds to the bonding energy of the polaron [96]. The structural relaxation causes a local distortion of the chain in the vicinity of the charge, whereby the twisted benzoid-like structure of the affected segments transforms into a quinoid-like structure in which the single bonds between the monomeric units shorten and assume double-bonding character.

Removing a second electron from the polymer segment results not in two polarons, but in the bipolaron, which is predicted to be energetically more favored than the polaron. The reason for this lies in the respective structural relaxations: that for the bipolaron is considerably greater than that for the polaron. The ionization energy required to remove a second electron decreases, or the electron affinity for taking up a second electron increases. In addition, it is assumed that the locally distorted bipolaron state comprises only four or five units of a chain segment (Fig. 10). The energy gain of the bipolaron compared with two polarons is said to be about 0.45 eV in the case of polypyrrole [97] and 0.35 eV in the case of polyparaphenylene [96a]. In terms of redox energies, this means that the redox potentials  $E_2^0$  for bipolaron formation should be much lower than the potential  $E_1^0$  for polaron



**Fig. 10** Formation of the bipolaron (= diion) state in PPY or PTh upon oxidation. In the model, it is assumed that the ionized states are stabilized by a local geometrical distortion from a benzoid-like to a quinoid-like structure. Hereby, one bipolaron should thermodynamically become more stable than two polarons despite the Coulombic repulsion between two similar charges.

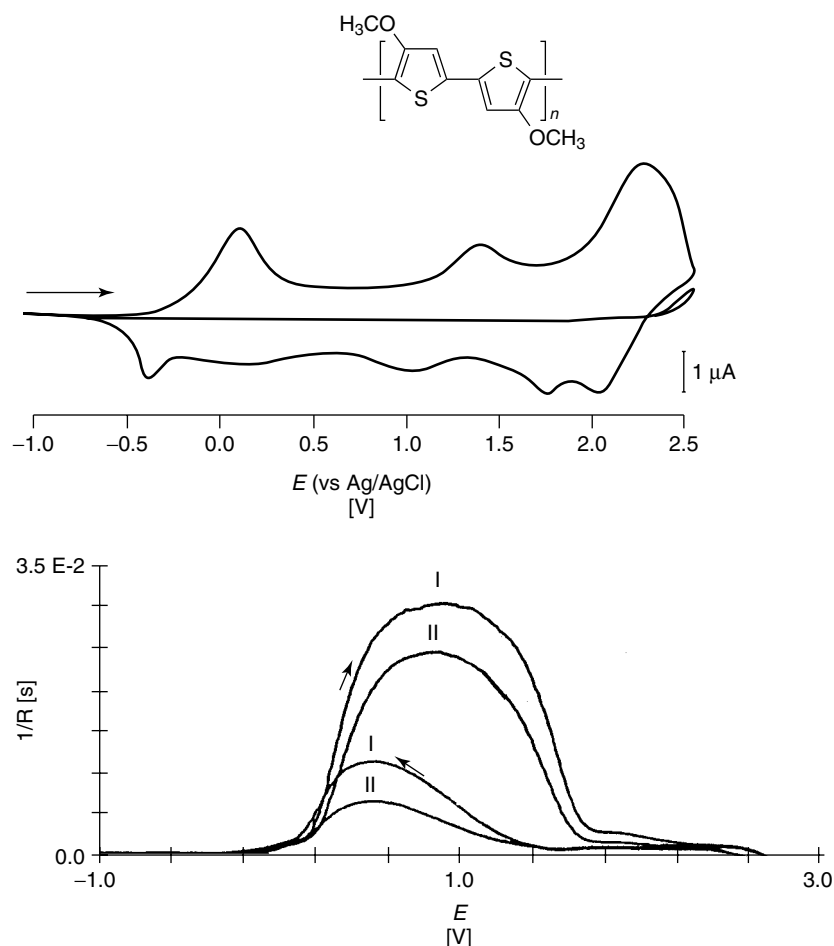
formation. The model is based on the ideal assumption that the chain length of the linear polymer is infinite, which results, as far as electronic properties are concerned, in a band structure. During charging, polaron and bipolaron states develop in the bandgap region, which leads to characteristic optical transitions.

Whereas the intermediate existence of polarons (= radical ions) has been unequivocally proved by ESR measurements and optical absorption spectra, up to now the existence of bipolarons has been only indirectly deduced from the absence of the ESR signal and the disappearance of the visible polaron band from the optical absorption spectra [98, 99]. On the other hand, spinfree – diionic charge – states in aromatics, whose optical properties bear a remarkably resemblance to the predictions of the bipolaron model, have long been known [100]. Theoretical calculations of optical transitions in conjugated (chain-like) systems show that transitions of radical ions or diions are in principle similar to those predicted by the bipolaron model [101]. A strong argument against the validity of the bipolaron model is the fact that conductivity in highly doped polymers decreases drastically [102]. (Fig. 11) According to the predictions of the model, the conductivity should increase at a higher doping level, owing to better overlap between the bipolaron and the valence band [96c]. So far, electrochemical measurements have not provided any direct proof for the formation of a bipolaron state in conjugated oligomers and polymers. Similarly, electrochemical and ESR spectroscopic studies by Nechtschein et al. indicate that the bipolaron state is not much more stable than the polaron state [103]. Additional strong arguments against the validity of the bipolaron model are resulting from optical UV–vis spectra of

oligomers and polymers. Thus, the spectra of short oligomers of thiophenes are very similar to those of polymers [104]. The long-wavelength transitions of oligomers are continuously shifted to lower energies as a function of chainlength. Only the intensities of the band increases because of the fact that the transition moment is polarized parallel to the chain, the band shapes do not change on going from oligomers to polymers. Consequently, there is no necessity to apply the band model (bipolaron model) instead of well-established “molecule” models. Finally, the fact that the chain lengths of conducting polymers do not exceed numbers of 30 to 50 supports the view that these materials should be handled as molecular systems [70, 71, 104d, 105].

A major barrier to a conclusive interpretation of voltammetric data on conjugated conducting polymers was the lack of measurements for well-defined model systems. A very important step was the measurement of charging/discharging behavior of oligomers of the phenylene-vinylene type [89a, 106] as well as of conjugated oligomers in different chain-like series [5, 24, 107]. All these data clearly demonstrate that the redox behavior of such oligomers and polymers depend on the chain length of the systems (Fig. 10). They complement theoretical and experimental results already presented in the older literature [87, 88, 108].

The following trends have been established as a function of increasing chain length. Firstly, redox states of identical charge (e.g., mono- or diion) shift towards lower energies. Obviously, the redox energies of different states gradually approach a common convergence limit with increasing chain length. Secondly, adding successive monomeric subunits in the molecular chain enlarges the number of



**Fig. 11** Cyclic voltammetry and in situ conductivity measurements of poly-(4,4'-dimethoxy-bithiophene) in  $\text{CH}_2\text{Cl}_2$ , 0.1 M TBAPF<sub>6</sub>,  $\nu = 5 \text{ mV s}^{-1}$ ,  $T = 273 \text{ K}$ : (a) cyclic voltammogram containing a background curve without polymer; (b) conductance as function of potential, measured during potentiodynamic cycling.

accessible redox states, and thirdly, the energy gap widens considerably between the lowest and the highest charged states. This is a consequence of the Coulombic repulsion created by every new excess charge introduced into the system and contradicts the predictions of the bipolaron model. Moreover, in experiments in solution, the stabilization of diionic states does not increase relative to monoionic

states. All experimental data reveal – in excellent agreement with quantum mechanical calculations – that the generation of higher redox states essentially requires more or at least the same energy (in the case of long conjugated chains with  $n \geq 8$ ) than the formation of the monoionic (polaron) state.

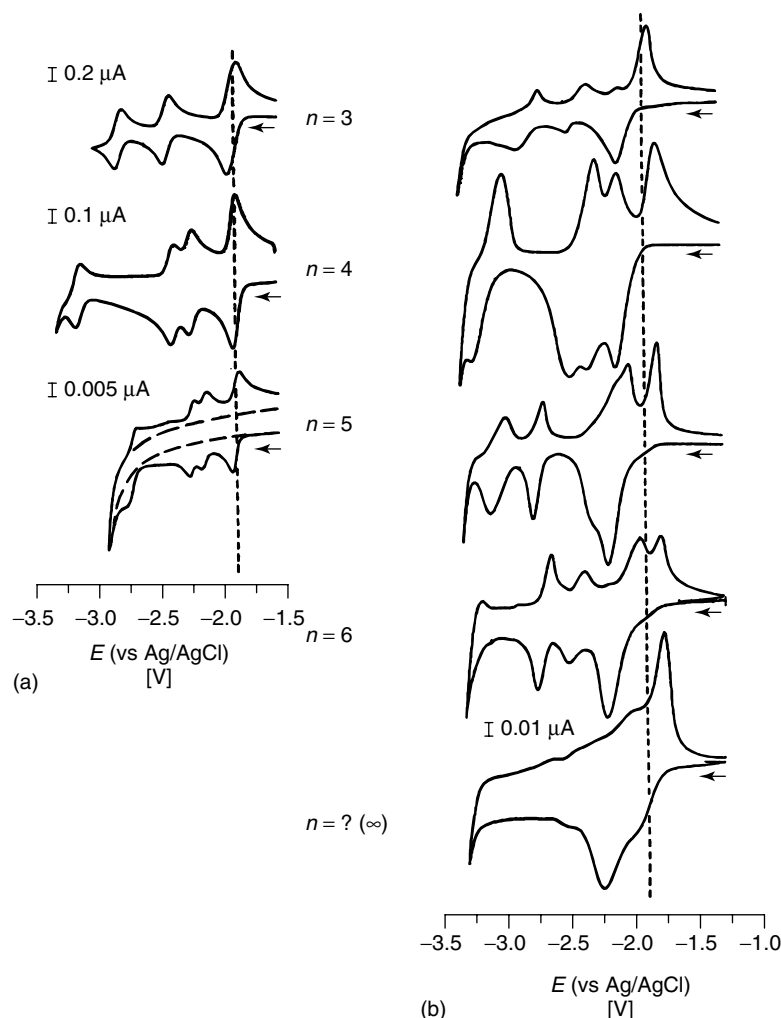
For real polymer systems – characterized by a more or less broad distribution

of molecular weight and, depending on the conditions of formation, various structural defects – this means that at the start of charging there is a high density of virtually degenerated redox states, which generates the peak-shaped anodic wave. As potential increases, the density of the redox states decreases but remains finite within the experimentally accessible potential range. This explains the broad plateaulike waves that are so often characteristic of the potential range following the peaklike main wave in voltammetric experiments. Unequivocal experimental evidence for this interpretation has been obtained from voltammetric measurements carried out under solid-state conditions on a series of oligophenylenevinylenes [89b]. The voltammograms clearly show that with increasing chain length the waves of succeeding redox steps superimpose and finally yield peak-shaped voltammograms involving the broad current plateau at higher charging levels (Fig. 12).

It is interesting to note that all the solid-state voltammograms in this experiment, both of the monodisperse oligomers and the polymer, again show the same hysteresis as has been observed for many polymers such as PPy or PTh (see Fig. 9). Originally, these phenomena were interpreted as redox-related structural changes within the solid film. It was assumed that during charging the polymeric chains stabilized through transition from a benzoid into a quinoid-like structure and become planar and that, therefore, the discharging process occurs at a considerably lower potential. Obviously, this seemed to be the missing link in the evidence of the bipolaron model [68, 5, 107b,c, 109].

However, quite another picture results from recent studies of soluble oligomers, which clearly show that their oxidized

species reversibly dimerize and form energetically stabilized  $\sigma$ -intermediates [42, 43]. Depending on the structure of the at least doubly charged  $\sigma$ -“dimers”, their discharging occurs at considerably lower potentials than oxidation (or reduction) of the neutral starting compound, producing a strong hysteresis between charging and discharging of the respective oligomers. During the discharging process, the  $\sigma$ -bonds between the chains break, and the system relaxes into its aromatic ground state. Even for small equilibrium constants between dimer and monomer ( $K < 100$ ) under solid-state conditions, a predominant amount of the charged species is transformed into the “dimeric” state, because of the high surface concentrations of the oligomers or polymers. Therefore, voltammetric solid-state experiments very often show the characteristic hysteresis between charging and discharging. A critical evaluation of all relevant data gives evidence that  $\sigma$ -dimers are formed in the equilibrium state, not  $\pi$ -dimers, as postulated in the literature some years ago [41, 110]. They are the key intermediates of the radical–radical coupling mechanism (see Scheme 2). In the past, it was assumed that the deprotonation of such intermediates is fast, leading to a rearomatized coupling product. All recent measurements carried out with linear thiophene oligomers reveal that the deprotonation rate constants become considerably smaller than the coupling rate constants as the chain length of the oligomer increases [111]. Thus, the hexathiophene, and even more so, the octathiophene, coupling products are stable as long as the oligomers are only weakly charged ( $y \sim 0.1$ ). Besides the hysteresis, these new findings explain all important electrochemical, electronic, and optical properties of conducting polymers. They



**Fig. 12** Reduction of oligophenylenevinylene (OPV) (a) in solution THF, 0.1 M TBAPF<sub>6</sub> and (b) in the solid-state DMA, 0.1 M TBABr  $T = 208$  K,  $\nu = 0.1$  V s<sup>-1</sup>. The vertical dashed line indicates the convergence limit of  $E_1^0$  for the OPVs in solution. The number of redox states increases as a function of chain length. For OPV with  $n = 6$ , a hepta-anion formation is observed. [From Ref. [80b].]

overcome the massive, and frequently criticized, inconsistencies of the bipolaron model [40, 5, 112–114]. A major advantage of this new view on the properties of conducting polymers is its excellent agreement with findings in (physical) organic chemistry, without reference to

models correlated with periodic lattice properties as applied in the case of crystalline solids. It should be kept in mind that conducting polymers are amorphous materials.

Closely connected with the problems of the charge storage mechanism is the

question to what extent one must and can distinguish between faradaic and capacitive processes during charging and discharging [7a, 33c, 115–117]. Feldberg, in particular, holds that it is hardly possible to draw such a distinction, and that the capacitive charge portion is proportional to the amount of the oxidized polymer [118]. He concludes from a comparison with optical data that the faradaic oxidation processes in CV experiments are essentially limited to the range of the “peak-shaped” anodic wave, whereas the adjoining broad anodic tail represents the large double-layer capacity of the system. The solid-state experiments just mentioned provide strong evidence that the current plateau is due to faradaic processes [89b]. Similar conclusions must be drawn from charging/discharging experiments with poly(4,4'-dimethoxybithiophene), in which, at the end of the anodic charging in the plateaulike region, the current drops to almost zero (Fig. 11) [33c].

A further characteristic for charge storage in conducting polymers is the amount of doping and insertion. This gives the mole fraction of the corresponding monomers, whose charge is compensated by incorporated counterions; in the case of *p*-doping (oxidation), the counterions are anions. The doping level is determined either by elementary analysis or by coulometric measurements. However, these measuring techniques may produce different results, as the elementary analysis cannot distinguish an additional solvent portion or organic coions, such as tetraalkylammonium ions, and coulometry also includes the capacitive charging. The optimum doping level for PPy or PTh is about 0.33, but can have very much lower values. This depends, inter alia, on structure and the applied charging potential,

but is also influenced by environmental parameters such as the solvent or supporting electrolyte [119–123].

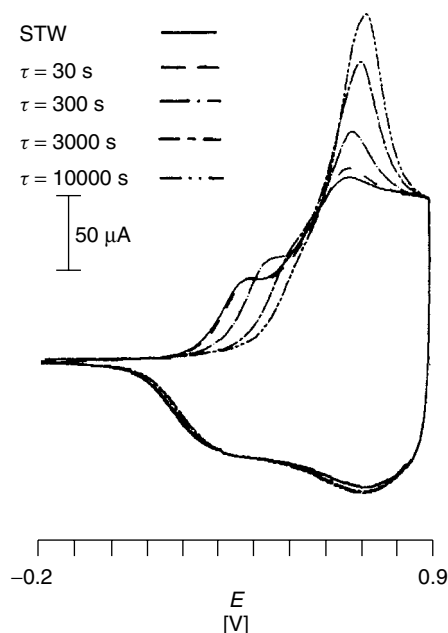
From the respective doping levels one can deduce that, on the oxidation of PPy, and often on that of PTh as well, every third or fourth heterocycle is charged, whereas in the case of PPP (poly-*p*-phenylene) provided that the experiments take place in common solvents such as propylene carbonate, only every sixth monomeric unit is charged [121]. In contrast, if one uses SO<sub>2</sub>, a solvent with low nucleophilicity, PPP can be reversibly oxidized to a doping level of 0.24, which corresponds formally to a charge on every fourth monomer unit [124]. The differences in chargeability of PPP and PPy are explained by the high oxidation potential of PPP. This significantly increases the reactivity of this system towards the solution and other nucleophilic impurities. One should note that polymers such as PA and PPP can be more highly charged by reduction (*n*-doping) than by oxidation.

Moving to a higher doping level, for example, 0.5, forces a charge in every second monomeric subunit, which, of course, induces a coulombic repulsion. Therefore, to achieve this, a higher electrode potential must be applied. And this, normally, results in overoxidation effects [125]. Through the overoxidation process, a degradation of the polymer occurs, often induced by nucleophilic solvents such as water or nitriles. Therefore, overoxidized materials can be discharged only to a limited extent, which is a serious drawback for applications. In principle, a doping level of 1 should be possible. That means that every monomeric unit bears a positive charge after doping. Up to now, only the very stable poly(4,4-dimethoxybithiophene) system has been charged up to this doping level [33c]. A characteristic

feature of such a perfectly charged system is that the faradaic current drops to zero after passing the highest available redox state. (Fig. 11)

A very important electrochemical phenomenon, which is not well understood, is the so-called *memory effect*. This means that the charging/discharging response of a conducting polymer film depends on the history of previous electrochemical events. Thus, the first voltammetric cycle obtained after the electroactive film has been held in its neutral state differs markedly in shape and peak position from subsequent ones [126]. Obviously, the waiting time in the neutral state of the system is the main factor determining the extent of a relaxation process. During this waiting time, which extends over several decades of time ( $1-10^5$  s), the polymer slowly relaxes into an equilibrium state. (Fig. 13) After relaxation, the first oxidation wave of the polymer appears at more

positive potentials than those observed in the steady state within a voltammetric multisweep experiment. Memory effects have been observed in different materials, for example, polypyrrole, polythiophene, and PANI. It is a very general property of conducting polymers. In the literature, different explanations have been presented. Heinze et al. [107b] suggested a relaxation from a twisted to a planar form during charging and vice versa during discharging. Zotti et al. discussed an expulsion of solvent leading to a shrinkage of the polymeric matrix [127] and Baudoin attributed the relaxation to the ion pair content of the film [128]. In a subsequent study, Nechtschein and Odin showed that the ion pair formation is inconsistent with data obtained in different electrolytes [129]. In addition, they found that the relaxation does not depend on whether the potential is imposed or left free during the relaxation. In a similar model, Otero and coworkers modified these interpretations and suggested that when a polymer film is oxidized, electrons are extracted from the polymeric chain generating polarons and bipolarons, reorganizing double bonds and angles between monomeric units given rise to conformational movements. Free volume is generated and counterions and solvent penetrate by diffusion control from the solution: the polymer swells. If the oxidized polymer is reduced by a potential sweep, opposite processes take place and the polymer shrinks; meanwhile, counterions move toward the solution by

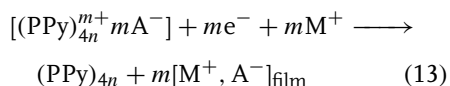
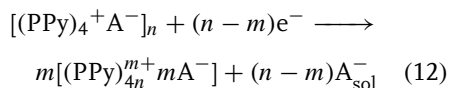


**Fig. 13** Memory effect in cyclic voltammetry: poly(3-methylthiophene) in  $\text{CH}_3\text{CN}/0.1 \text{ M TBAPF}_6$ ,  $\nu = 20 \text{ mV s}^{-1}$ . The solid line corresponds to the steady state. The broken lines show the voltammetric response after different relaxation (waiting) times  $\tau$  at a potential of  $-0.200 \text{ mV}$ . [From Ref. [128].]

diffusion control [130]. In a very recent paper, Heinze et al. [131] presented experimental details, which support the view that  $\sigma$ -intermediates formed during the charging process are the cause for the slow relaxation processes during discharging. It is well known that  $\sigma$ -intermediates are formed during charging of conducting polymers with high rates because of the fact that the concentration of the charged species lies between 1 and 10 M<sup>-1</sup>. On the other hand, the stability of  $\sigma$ -dimers increases as a function of chain length. Their decay under solid-state conditions during discharging may be a very slow process.

As already mentioned, the principle of electroneutrality must be fulfilled in charged polymers. Consequently, in freshly prepared *p*-doped polymers, anions must compensate the positive charges within the polymeric chains. However, spectroelectrochemical studies [132], electrochemical quartz crystal microbalance (EQCM) measurements [133], and SIMS and XPS measurements [134] on the mechanism of ion transport during charging and discharging of conducting polymers prove that discharging involves not only the expulsion of anions but also the incorporation of cations. In the case of small anions, this cation exchange mechanism is surprising. Recent results on structural peculiarities of PPy during charging [62, 72] indicate that PPy chains "dimerize" upon oxidation of the neutral chains, forming  $\sigma$ -bonds between the chains, and that, therefore, immobile localized charges are generated, which, in turn, prevent any movement of the anionic counterions [135]. In consequence, during the first discharging process, mobile anions slowly diffuse out of the film; in the second step, cations are incorporated into the polymer, forming ion pairs with

the immobile anions, (Eqs. 12 – 13).



Using polymeric or large anions during electropolymerization, a pure cation transport generally results upon anodic charging and discharging [136]. This has been confirmed by in situ monitoring of the mass change during electrochemical switching using a quartz crystal microbalance [137].

Electrochemical measurements of PANI produce a picture of the charge storage mechanism that differs fundamentally from that obtained using PPy or PTh. In the cyclic voltammetric experiment, one observes two reversible waves in the potential range between -0.2 and +1.2 V versus SCE. Above +1.0 V, the current decreases to zero. Capacitive currents and overoxidation effects, as in the case of PPy or PTh, do not occur [138]. The striking changes in the charge, characteristic of PANI compared with PPy and PTh, are largely explained by the nitrogen atoms capturing a considerable part of the coulombic interaction between the charged centers.

PANI is usually produced by the anodic oxidation of aniline in acidic aqueous solution [5, 139], but can also be produced by chemical oxidation [138b, 140]. Hence, it is not surprising that the oxidation of PANI is pH-dependent and that, therefore, in addition to electron-transfer processes, proton-transfer reactions occur during charging. Although it is usually assumed that PANI has a chain structure (emeraldine) with head-tail connections



between the aniline units [141], the existence of cyclic structures has also been postulated in the literature [142]. However, the synthesis and the characterization of monodisperse aniline oligomers support the view of a linear chain in the nonoxidized state [141]. It is generally accepted that there are different, possibly coexisting forms of PANI, including benzoid and quinoid rings, free amines (NH), imines, and protonated amines and imines [143]. Depending on the pH-value of the solution, different protonated structures are formed. In the simplest case, it is assumed that polycationic states are formed in the first step [144]. In the second step, which correlates with the second oxidation peak in the CV-diagram, protons are eliminated and additional electrons are abstracted (Scheme 4). This corresponds with MacDiarmid's observations, which show that the second redox step is strongly pH-dependent [138b]. Shacklette et al. [145] showed in a very thorough study of the phenyl-end-capped tetramer of oligoaniline that the first oxidation step involves a 2e-transfer step, leading to the emeraldine salt form in which 50% of the nitrogens are oxidized. The second oxidation wave also indicates a 2e-step and varies with pH at a rate of approximately 120 mV/pH, which suggests a deprotonation of four protons. In this case, the resulting species should be the pure imine form.

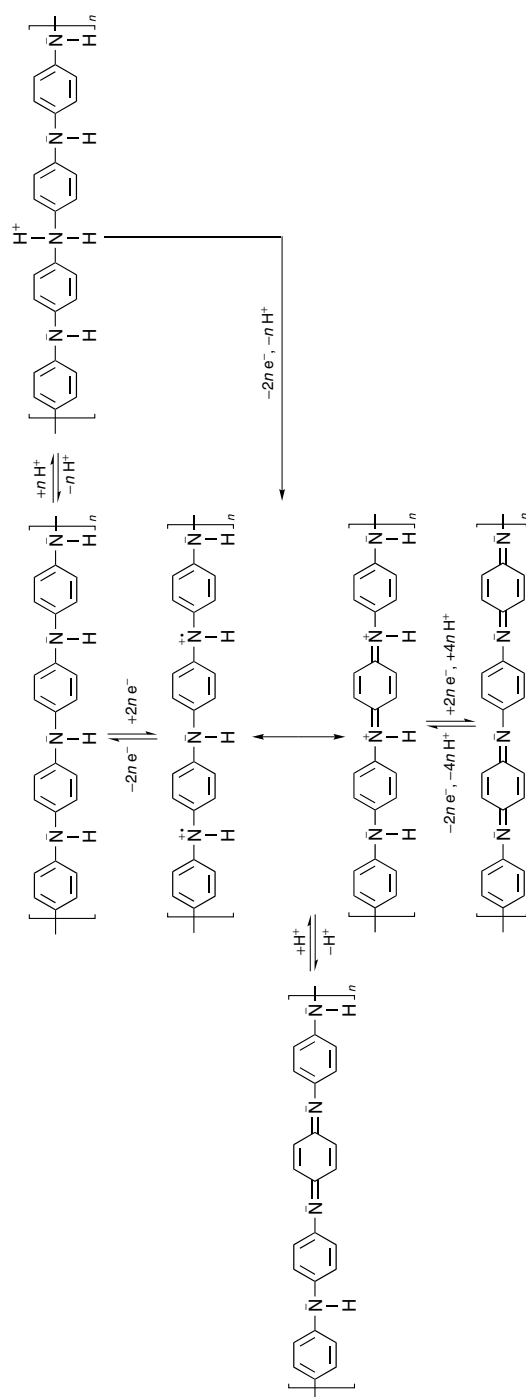
#### 16.4 Applications

The starting point for applications was the discovery that PA can function as an active electrode [2] in a rechargeable polymer battery. Since then, the prospects of

technical applications have grown considerably. Apart from the battery electrode, conducting polymers are discussed as potential ECD, antistatic materials, anticorrosives, electrocatalysts, and light-emitting materials. The most advanced developments are the battery [82, 146], antistatic materials [147, 20d], and light-emitting devices [148].

The attraction in the development of a rechargeable polymer battery lies in the specific weight of polymers, which is considerably lower than that of ordinary inorganic materials, as well as the potential environmental benefit. At the beginning of the battery research, the PA cell was most extensively studied [2, 10]. However, owing to its chemical instability, it has virtually no commercial prospects. A promising candidate for a polymer battery that does not possess the typical disadvantages of PA is PPy [119b, 149]. Its open circuit voltage lies near 3.5 V versus  $\text{Li}^+/\text{Li}$ . Charge capacity is about 70 to 85 A h  $\text{kg}^{-1}$ , and the effective energy density reaches values of 40 to 60 W h  $\text{kg}^{-1}$ . A crucial disadvantage of PPy is that during discharging cations are incorporated into the polymeric layer, which leads to consumption of the electrolyte and stops the charging /discharging process in thin layer cells. The reason for this phenomenon lies in structural peculiarities of PPy, which forms  $\sigma$ -dimers during charging, producing immobile positive charges correlated with immobile anions [133c, 150].

An important problem encountered with polymer electrodes is that of overoxidation. It occurs after reversible charging of an electrode with high oxidation potentials and leads to the degradation of the polymer. The results of thorough studies [125, 151] show that such degenerative mechanisms are promoted by the nucleophilicity of the solvent.



**Scheme 4** Redox steps during charging/discharging of PANI.

Apart from polymer batteries, applied research on conducting polymers has reached an advanced stage in the fields of ECD [11, 152], antistatic layers [147], and light-emitting devices [148]. Electrochromic displays are based on an electrochemical reaction of a material that displays a visual charge upon changing its redox state. The advantages of using ECD are their ease of preparation and the uniformity of the prepared films. Furthermore, ECDs have no limited visual angle, but continue to exhibit a memory function even after the driving voltage has been removed. Erasing and rewriting can be performed almost at will. The suitability of PPy, PTh, and PANI as ECD has been intensively studied. PANI appears to be particularly promising, as its color changes during oxidation range from yellow through green, blue, and violet to brown [139c, 153].

Baytron<sup>®</sup>, a conducting polymer [154] derived from 3,4-ethylenedioxythiophene, is a commercially available product that can be used as an antistatic or electrostatic coating of plastics and glass. Moreover, it has successfully been applied as counterelectrode in capacitors and as a hole-injection layer in organic light-emitting diodes [155].

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