Trends in organic electrosynthesis

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Dedicated to Professor Dr Hans J. Schäfer on the occasion of his 60th birthday.

Electrochemistry is a clean and convenient method for the generation on a preparative scale of many reactive intermediates (radical-ions, radicals, carbanions, carbocations, quinodimethanes). This forms the basis of organic electrosynthesis and conditions have been devised for selective and useful chemical conversions. Particularly useful and versatile are carbon–carbon bond forming reactions such as those involving the Kolbe reaction, electrohydrodimerisations and N-acyliminium cations. The *in situ* electrogeneration and regeneration of redox reagents in non-stoichiometric amounts, and the related redox catalysis, is proving to be an attractive, indirect, electrosynthetic approach. And mechanistic insight into useful preparative reactions is now at an advanced stage.

1 Introduction

Electrochemical conversions of organic compounds have much in common with photochemical conversions. Electrochemical activation to produce reactive intermediates is, like photochemical activation, non-thermal. Furthermore, organic compounds which are candidates for electrochemical conversion must have electroactive functionality (an electrophore) which is the analogue of the chromophores necessary for photochemical activation. Molecules are activated by the addition or removal of electrons at an electrode. This must involve addition to a LUMO (reduction at a cathode) and removal from a HOMO (oxidation at an anode); it is relatively easy qualitatively to identify which compounds are likely to be reducible or oxidisable. In practice, the limits coincide with the most powerfully reducing and oxidising conditions available by conventional chemistry [*ca.* +3 and -3V (*vs.* SCE)]. Benzene can thus be oxidised to benzoquinone and reduced to 1,4-dihy-

drobenzene. Many relevant books and reviews are available[1] which cover these and other basic aspects.

The most important reactive intermediates formed by electrochemical reduction and oxidation are radical-ions, radicals, carbocations and carbanions; radical-ions are usually the first-formed species but fragmentation can lead typically to radicals which may be further reduced or oxidised (Fig. 1).
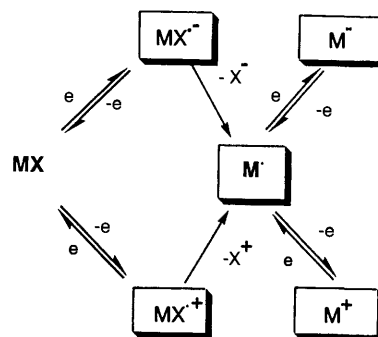

Fig. 1 Common species formed electrochemically

Electron transfer brings about *umpolung*, electron-rich compounds are oxidised to electron-deficient species (electrophiles) and reduction of electron-poor compounds gives nucleophiles. The chemical reactivity of these species is as expected; radical-anions may be nucleophilic and basic, radical-cations may be electrophilic, and both may react as radicals, *e.g.* to give coupling reactions. Much is now understood about the structural features which determine selectivity between these potentially competing pathways and it is the purpose of this review to demonstrate this understanding rather than to give a comprehensive survey of all types of useful electrosynthetic reaction. Here, we concentrate on recent examples although they are mostly based on electrosynthetic reactions which have become well-established during the past 30 years or more.

Many advances in electrosynthesis have depended on advances made in unravelling mechanisms of electroorganic reactions. Furthermore, the techniques which have been used to study mechanism, mainly electroanalytical, have also been powerful in the characterisation of short-lived intermediates and in the study of such fundamental processes as proton transfer and single electron transfer (SET). The study of electroorganic chemistry has had a considerable impact on organic and physical-organic chemistry in general.

Electrochemical conversions are clean. Either no reagent is employed, other than the electron, or electrochemistry is deployed to generate and regenerate chemical reagents in sealed systems, in non-stoichiometric amounts and possibly in benign solvents. An example is the production of adiponitrile by cathodic hydrodimerisation of acrylonitrile (the Monsanto process) which is operated by BASF in the UK at *ca.* 90000 tonnes p.a. and essentially in aqueous conditions. Other 'clean technology' aspects will become apparent.

Jim Utley is Professor of Organic Chemistry at Queen Mary and Westfield College (University of London). His early career was in physical-organic chemistry [with N. B. Chapman, J. Shorter (Hull), B. M. Wepster (Delft) and J. H. Ridd (UCL)] but, under the influence of the natural products chemist B. C. L. Weedon (QMC) and later L. Eberson (Lund), he turned seriously to synthetic, mechanistic and stereochemical aspects of organic electrochemistry in ca. 1970 and was awarded the DSc of London University in 1980. He has worked on most aspects of the subject, often in collaboration with major groups in Europe and the USA, and has been a guest Professor at the Universities of Aarhus, Münster, Texas (at Austin) and the Ecole Normale Supérieure (Paris).

2 Practical matters

Electrochemical conversions may be carried out directly at an electrode (*direct electrolysis*) or by using the electrode reaction to electrogenerate a chemical reagent (*indirect electrolysis*) or an electron transfer reagent (*mediated electrolysis*). In each of these cases the reactors are electrochemical cells which come in many designs and sizes; they are usually simple to construct and are well-described.[1,2] They may have cathode and anode compartments separated by membranes or microporous materials such as sintered glass (*divided cells*), or be single compartment (*undivided cells*). The electrode materials are usually chosen to be inert at the reducing or oxidising conditions being used and the potential at the *working electrode* may be controlled with respect to a *reference electrode* (*potentiostatic electrolysis*). Alternatively, the reactions may be run at controlled (constant) current (*galvanostatic electrolysis*). In most cases, for an electrosynthetic conversion to compete with a chemical alternative the reaction conditions should be developed to run galvanostatically in undivided cells. The reactions are also usually run in solutions containing ionic salts (*supporting electrolytes*) which must be inert at the reducing or oxidising potentials involved. Their role, in combination with the polar solvents required, is to carry the main part of the current passing between the electrodes; the (usually) neutral organic substrates are transported by convection (stirring or flowing) or diffusion.

3 Common electrochemical conversions

3.1 Carbon–carbon bond formation

Kolbe electrolysis and electrohydrodimerisation are well-established electrosynthetic processes which operate under relatively simple conditions and which give one-step carbon–carbon bond formation in a manner difficult to match by other routes (Fig. 2). These reactions, and to a lesser extent the anodic
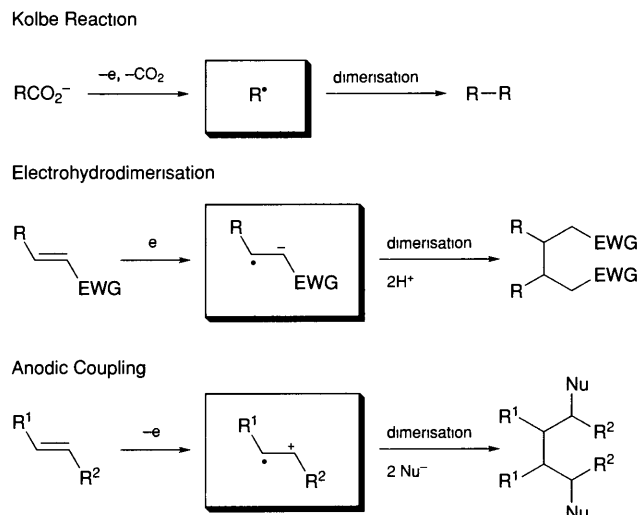
Kolbe Reaction

Electrohydrodimerisation

Anodic Coupling

Fig. 2 Coupling of electrogenerated radicals and radical-ions

coupling of alkenes, have been prominent in recent electrosynthetic developments. They have been cleverly exploited with regard to interesting target compounds, stereoselectivity and the development of intramolecular variants, *e.g.* for cyclisations.

The carbon radicals produced by anodic oxidation of carboxylate anions are known to be 'free' but, probably because of the high local concentrations formed at the electrode, coupling is the dominant reaction. Similar radicals produced homogeneously do not couple with useful yields and there is only one example[3] of a metal-based oxidant ($OsCl_6{}^-$) which gives comparable coupling. Carbon-centred radicals generated by Kolbe electrolysis are highly reactive; different radicals may be generated by co-electrolysis and they combine randomly (the

Brown–Walker reaction). They will also add to double bonds either inter- or intra-molecularly. These aspects, applied to useful synthetic conversions, are displayed in Fig. 3.

The examples involving the construction of partially fluorinated compounds[4] and C-glycosides[5], compounds with interesting rheological or liquid crystal properties, are derivative of Weedon's pioneering work[6] with the cross-coupling Kolbe reaction [Fig. 3(a)]. Many fatty acids were thus synthesised and their stereochemistry established, including absolute configuration. Kolbe oxidation is also a convenient method for generating the trifluoromethyl radical[7] which may substitute into aromatics or add to double bonds [Fig. 3(b)]. Addition of anodically generated radicals is clearly very fast; the hex-5-enyl radical is known to cyclise with $k = 2.9 \times 10^4$ s^{-1} which compares with a value of 10^7 s^{-1} estimated in a theoretical treatment[8] based on the ratios of the products formed competitively in tandem cyclisations such as that shown. Anodic generation of carbon radicals will initiate these radical tandem cyclisations in a practically convenient one-pot reaction and with good regio- and stereo-selectivity, as demonstrated in one of several examples [Fig. 3(d)].

Electrohydrodimerisation (EHD) is a common outcome of the cathodic reduction of alkenes activated by electron-withdrawing groups (see Fig. 2). Numerous examples are known[1] but here we will concentrate on just two recent reports which illustrate the versatility and scope of the reaction (Fig. 4). It depends on the rapid combination of delocalised anion-radicals. They must be formed under conditions which minimise competing protonation, *i.e.* hydrogenation of the double bond. Thus, alkenes activated by a variety of electron-withdrawing groups (commonly CO_2R, COR, CN, NO_2, C=NR) will undergo EHD.

The electrohydrodimerisation[9a] of dimethyl maleate [Fig. 4(a)] nicely illustrates the simplicity of conditions (constant current, graphite electrodes, MeOH-NaOAc electrolyte) which may be developed for a reaction which in the laboratory was run on a 100 g scale and later developed to pilot scale. In this case dimerisation of the radical-anions is faster than protonation, even in methanol solution, which is a consequence of the double activation by two CO_2Me groups which greatly delocalise the negative charge effectively, thus reducing the basicity of the radical-anion and enhancing its radical character. This is an important concept in designing EHD reactions. For the second example given [Fig. 4(b)], the EHD of a series of cinnamate esters, the radical-anion dimerises faster[9b] the more the charge is delocalised (resulting in a less negative E^0). A linear relationship between E^0 and log k_2 is found.

The EHD of cinnamate esters proceeds with subsequent *in situ* Dieckmann condensation to give 3,4-diarylcyclopentanones with high stereoselectivity. The all-*trans* isomer is the only detectable product. Furthermore, chiral esters reduce[9c] with a diastereoselectivity which can reach 95%. Study of this reaction has taught us much about the mechanism of EHD and it will be returned to (section 5).

3.2 Functionalisation

In a seminal review[10] of the prospects for electrosynthesis in industry, C–C bond formation and functionalisation of alkenes and aromatics were highlighted as likely to be significant. The most important examples of electrochemical functionalisation involve anodic oxidation, probably because hydrocarbon radical-cations often readily deprotonate (X = H in Fig. 1) which paves the way for subsequent functionalisation. Some examples are given in Fig. 5. The 'industrial' use is illustrated by the efficient conversion of substituted toluenes into the corresponding benzaldehydes [Fig. 5(a)]. In addition to the example given[11] it is understood that several related processes are used by BASF to produce fine chemicals for flavourings and perfumes.

The other examples[12] are recent adaptations of the reaction discovered by Ross–Eberson–Nyberg, and much exploited by Tatsuya Shono, whereby amides are oxidised to N-acyliminium cations [e.g. 1 in Fig. 5(b)]. No other route is so direct and this must be the method of choice for preparation of these versatile intermediates. Because they are usually formed in methanol solution it is the α-methoxyamides which are isolated. These are easily converted by treatment with acid into the N-acyliminium cations which can then undergo reaction with a variety of nucleophiles.

A short route[12a] to the Geissman–Waiss lactone [2, Fig. 5(b)] and its enantiomer is based on electrochemical formation of an N-acyliminium cation (1) which is functionalised under stereochemical control. More ambitious are those recently reported syntheses[12b] which involve intramolecular trapping of N-acyliminium cations; the example given [Fig. 5(c)] is a one-
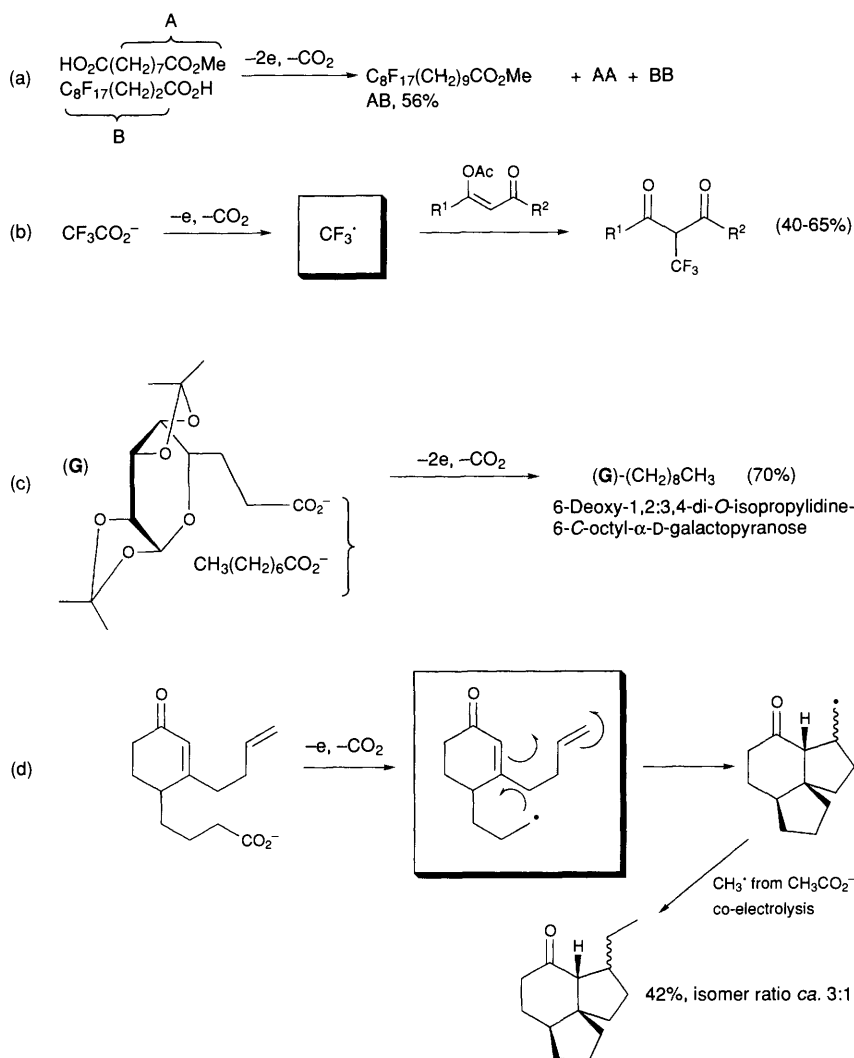

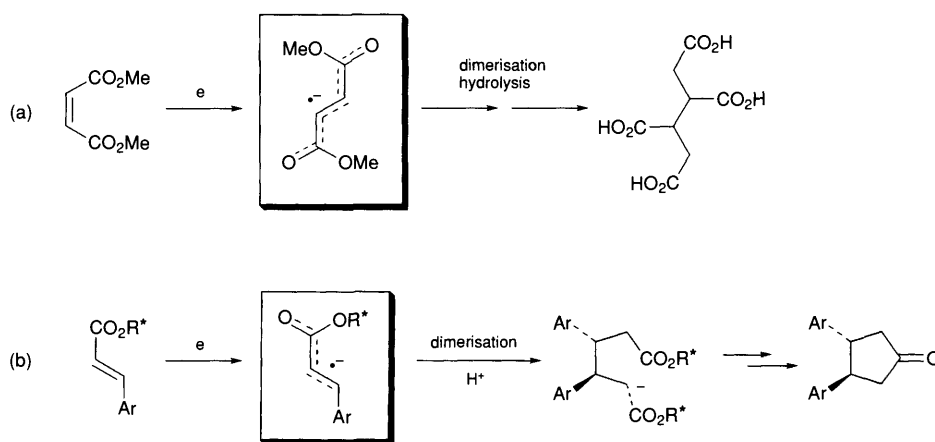Fig. 3 The Kolbe reaction revisited

Fig. 4 Electrohydrodimerisation

pot procedure. This approach has been exploited in several other similar syntheses.

3.3 Other cyclisation reactions

The intramolecular reactions of electrogenerated radical-ions, radicals, cations or carbanions are well-established and have featured recently in useful preparative procedures. Three fairly typical examples are shown in Fig. 6. The first [Fig. 6(a)] comes[13] from the work of Little et al; it serves to emphasise an important point concerning mechanism. The relevant reaction centres should not only be proximate but also predictions concerning successful cyclisation demand a mechanistic hypothesis and knowledge of Baldwin's rules! In this case there is a clear difference in reducibility of the two reactive groups and the first electron transfer is to the activated alkene function. But from that point there are several possibilities: (i) the first-formed radical-anion could add to carbonyl as a radical or nucleophile; (ii) protonation could give a radical as the attacking species; or (iii) further electron transfer could give a carbanion as the key nucleophile. Little et al have summarised[13] the electrochemical and chemical arguments and their preferred mechanism is given in Fig. 6.

However, each case must be considered on its merits! The coupling involving anodic oxidation of enol ethers [Fig. 6(b)] has two identical electroactive centres and the coupling is likely to be either via two radical-cations combining (radical-ion/radical-ion coupling) or one radical-cation centre attacking a neighbouring enol ether function (radical-ion/substrate coupling). All that we know about analogous cathodic couplings, involving radical-anions, suggests that radical-ion/substrate routes are rare and radical-ion/radical-ion routes common (see section 5). But the final example [Fig. 6(c)] is best explained in

terms of electrophilic (or radical) attack by the radical-cation from the enol ether adding to the furan ring. There are many similar ring closure reactions old and new,[14] typically involving closure onto electron-rich aromatics, e.g. phenols and phenol ethers.

3.4 Polymerisation via electrogenerated intermediates

Anodic oxidation of electron-rich aromatics produces radical-cations in a sea of the nucleophilic starting materials and electrophilic addition can induce stepwise polymerisation. The mechanism is similar to that of acid-catalysed polymerisation and early examples[15] of such anodic polymerisation were the formation of polypyrroles, polythiophenes and polyanilines [Fig. 7(a) and (b). In these cases the polymers are formed as a film on a solid anode, often platinum, and they may be further oxidised (doped) to produce conducting films; the charge carriers are radical-cation centres (polarons).

Although soluble polymers may be made anodically, by appropriate substitution with lipophilic groups, they are mostly obtained as intractable films. In contrast, the cathodic formation of some polymers can be carried out at a mercury cathode and stirring prevents film formation. This approach has led to a particularly versatile method for the cathodic preparation of poly-p-xylylenes (PPXs)[16] and poly-(p-phenylenevinylenes) (PPVs)[17]—see Fig. 7(c). The key intermediates, as highlighted, are quinodimethanes. The parent p-quinodimethane (xylylene) polymerises rapidly when formed cathodically, although not so rapidly as to preclude its detection by fast sweep cyclic voltammetry. Combination of the quinodimethanes (QDMs) is unselective and an unsymmetrical QDM gave the statistical ratio of possible linkages [ref. 17 and Fig. 7(d)]. This means that cross-coupling of different QDMs, produced by co-electrolysis
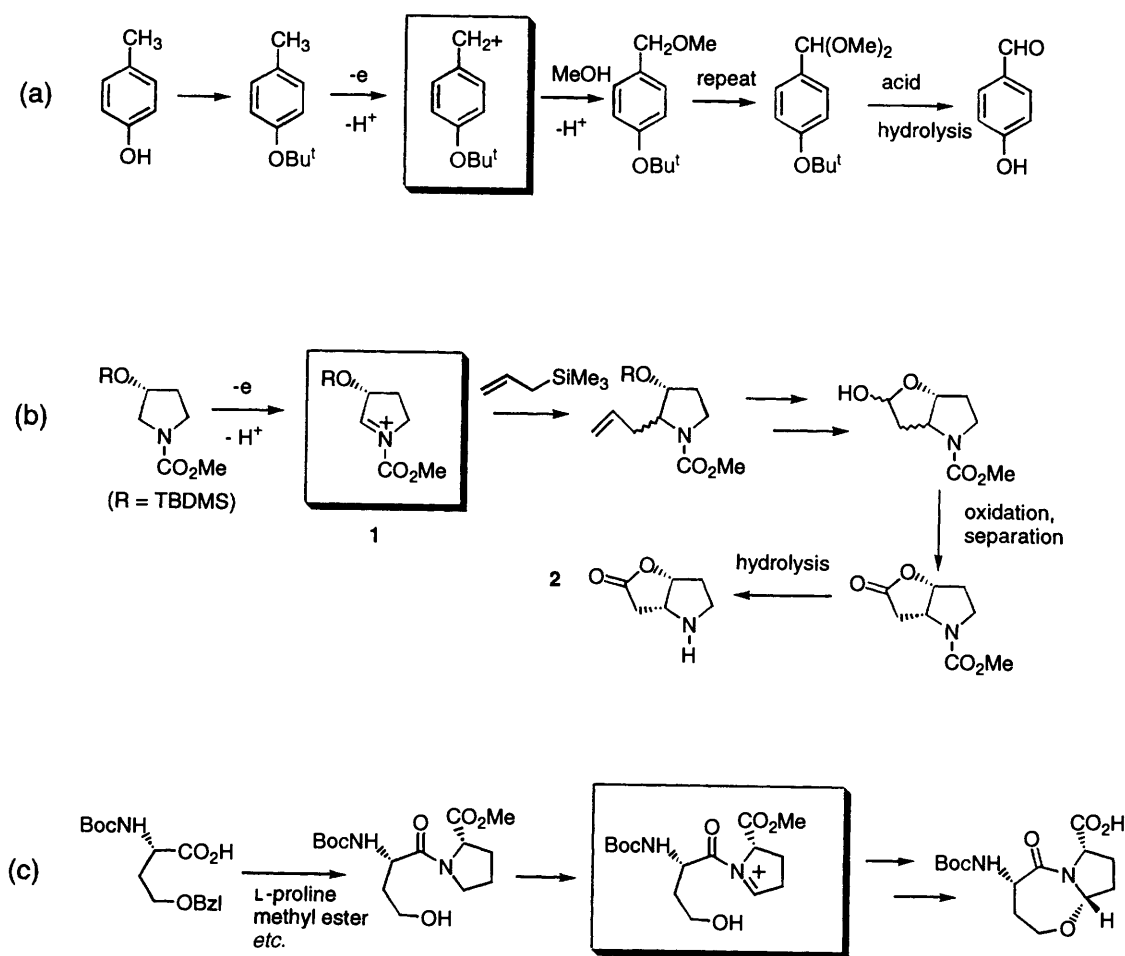

Fig. 5 Anodically generated cations

of different bis-(halomethyl)arenes, leads to random co-polymers, cf. the random coupling in the Kolbe reaction. Furthermore, a considerable range of functionality is tolerated in the cathodic method and by careful choice of functionality and electrolysis conditions it is possible electrochemically to produce PPXs and PPVs which are soluble in organic solvents. This also allows their formation at solid cathodes.

4 The indirect approach

The examples dealt with so far involve the reactions of intermediates produced directly at the electrode by hete-rogeneous electron transfer. Disadvantages of this approach can include the inhibition of the electrode reaction by formation of non-conducting films (not all polymer formation is as welcome as that of pyrrole etc.) and for a given conversion the electrode overpotential required may be significantly greater than that expected from theory. This leads to lack of selectivity and unwanted competition from side reactions such as oxidation or reduction of solvent. Much attention has been paid in recent years to electrosynthetic conversions which are indirect, i.e. the electrode reaction is used to generate and regenerate a reagent. Typically, these are generated at potentials which are less cathodic or anodic than those required for the corresponding direct electron transfer. The reagents may be formed in situ (at less than stoichiometric concentration) or ex situ. A special situation arises when the electrogenerated reagent is an electron-transfer reagent, often called a mediator. In many cases the mediator is formed reversibly at the electrode and, after diffusion into the bulk solution, is involved in electron transfer with the target substrate. This may be in an unfavourable equilibrium which is driven forward by a rapid and chemically irreversible follow-up reaction. This situation is illustrated for reductive cleavage in Fig. 8. The practical consequence is that the target substrate is converted at a potential up to ca. 0.5 V less

than indicated by its formal potential. And because the mediator is constantly and rapidly regenerated the term redox catalysis is often applied (see later).

4.1 Electrogenerated reagents

In the simplest applications of this approach quite common reagents are generated electrochemically, normally in situ. Chlorine can conveniently be introduced into a reaction mixture by anodic oxidation of chloride; thus methyl hypochlorite[18] is the effective reagent in the practically convenient conversion of 3 into 4 by anodic oxidation of a mixture of starting material and sodium chloride in methanol solution. Similarly, the anodic generation of bromine in NaOAc–HOAc is superior to direct electrolysis for the allylic acetoxylation[19] of β-ionone to give 5. Direct anodic conversion of the less easily oxidised α-ionone in NaOAc–HOAc gives many products but clean allylic acetox-ylation to 6 is achieved by the in situ generation[19] of Co^{III} acetate from the Co^{II} salt which is present at ca. 10 mol%. Cathodic reduction is probably the method of choice for preparation[20a] of solutions of Cr^{II} and this method has recently been used[20b] to induce free radical cyclisations, e.g. in the high yielding conversion of 7 into 8.

The examples described above, and collected in Fig. 9, are merely recent representatives of many successful applications of this approach. The success of this approach is not surprising considering that the manufacture of most highly oxidising and reducing species is electrolytic (Li, Na, Al, F$_2$, S$_2$O$_8^{2-}$, Ce^{IV}, Cr^{VI} and many more)! A process[21] for the large-scale production of naphthaquinone, as an intermediate in a route to anthraquinone, depends on the generation and regeneration of non-stoichiometric amounts of Ce^{IV}.

Rather less common electrogenerated reagents include the hypervalent iodobenzene difluorides, e.g. 4-O$_2$NC$_6$H$_4$IF$_2$, pre-pared by anodic oxidation[22] of the corresponding iodobenzene
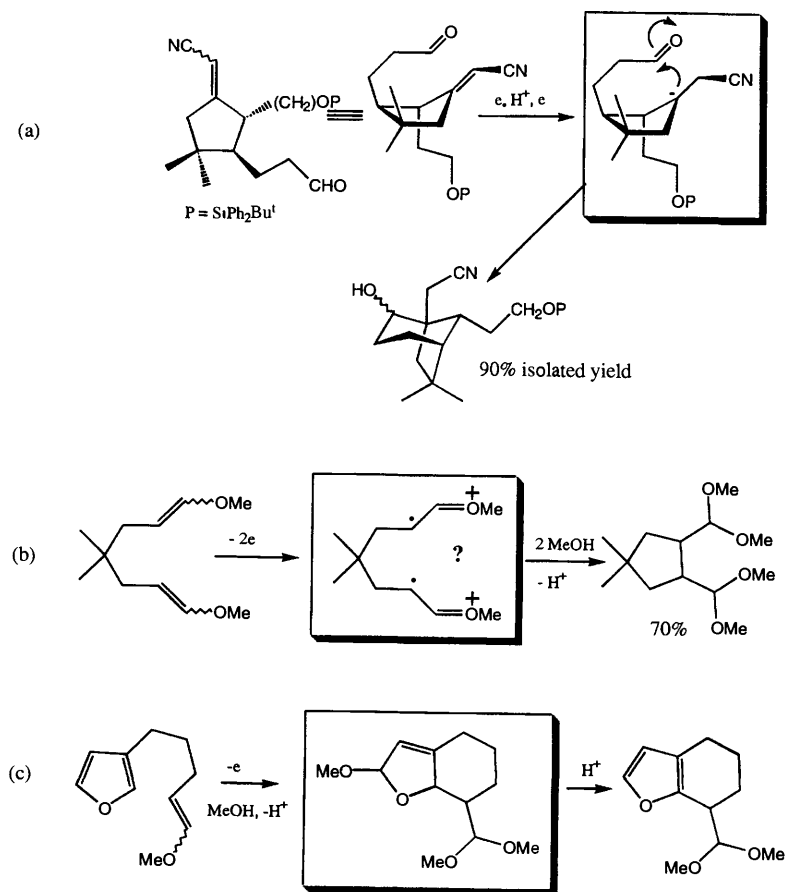
(a)

P = SiPh$_2$Bu^t

90% isolated yield

(b)

70%

(c)

Fig. 6 Other intramolecular cyclisation

in the presence of Et₃N·3HF. This reagent has been used,[22] *ex situ*, for the conversion of **9** into **10**. And a convenient and inexpensive method for the preparation of Ruppert's reagent (CF₃SiMe₃) has been developed.[23] This reagent is commonly used to introduce the trifluoromethyl group *via* a number of addition or coupling routes. Ruppert's reagent may now be prepared in high yields by simple constant current reduction of CF₃Br at a nickel cathode in the presence of Me₃SiCl. The correct choice of anode material is crucial to the success of this reduction! A sacrificial Al anode is used—*i.e.* one which dissolves to give Al³⁺ in step with the cathodic reaction.

Perhaps the most significant recent development concerning the electrogeneration of reagents at low or catalytic concentrations is an electrochemical variant[24] of the Sharpless asymmetric dihydroxylation of alkenes using Osᵛᴵᴵᴵ in the presence of a chiral ligand. This has been developed by researchers[24a] at Engelhard Ltd to the point where it could be used on a commercial scale. Double mediation is used in this reaction

[Fig. 10(a)]. The original Sharpless method uses stoichiometric amounts of ferricyanide to oxidise Osᵛᴵ to maintain the required concentration of Osᵛᴵᴵᴵ; in the electrochemical version a lower concentration of ferricyanide is used and its level is maintained by anodic oxidation. Thus the ferricyanide acts as the second mediator causing the Osᵛᴵᴵᴵ concentration to be maintained electrochemically but indirectly. The point of this is that the process is run in a two-phase system (cyclohexane–water) and the Osᵛᴵᴵᴵ/chiral ligand complex reacts with the alkene in the organic phase but can be regenerated with ferricyanide at the interface. An alternative to ferricyanide is iodine in a mixture in which iodide is recycled anodically[24b] to iodine.

The Mnᴵᴵᴵ-mediated electrosynthesis of sorbic acid precursors is another, exceptionally well-described,[25] process which was developed to operate in a flow cell on a multi-kilogram scale [Fig. 10(b)]. The reaction is catalytic in Mnᴵᴵ and its success depends on the additional role of Cuᴵᴵ in promoting the oxidation of an allylic radical to the corresponding cation.
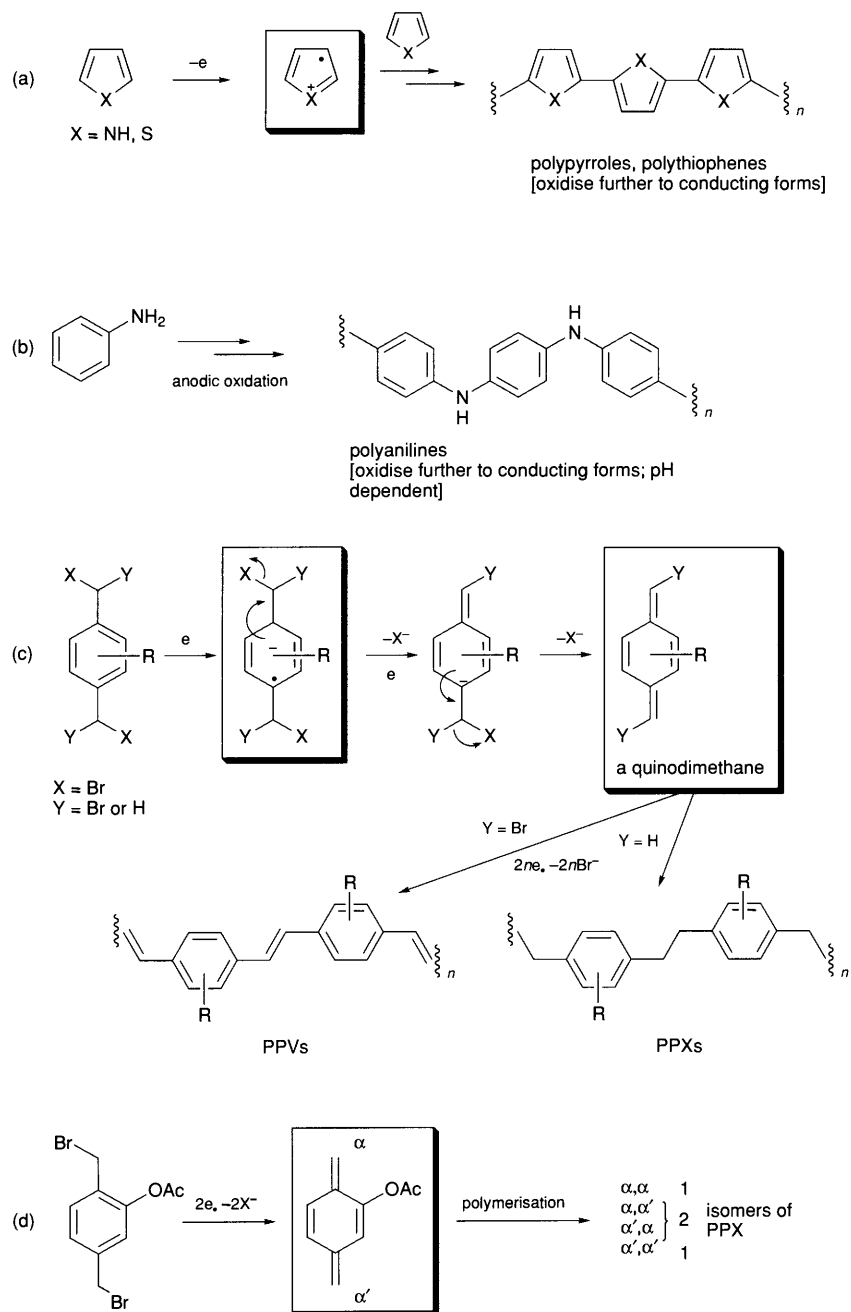

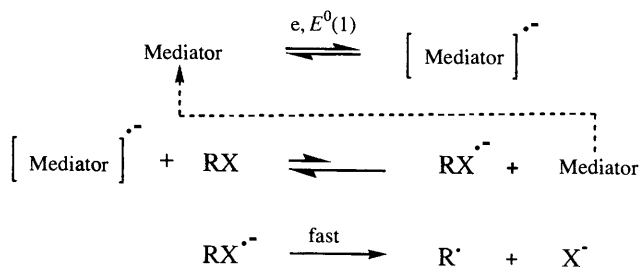Fig. 7 Polymers from electrogenerated intermediates

e, E^0(1)

Mediator ⇌ [Mediator]⁻˙

[Mediator]⁻˙ + RX ⇌ RX⁻˙ + Mediator

RX⁻˙ →fast→ R˙ + X⁻

And: E^0(1) positive to E^0(2) where E^0(2) refers to:
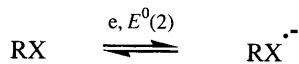
e, E^0(2)

RX ⇌ RX⁻˙

Fig. 8 Mediated electrolysis (redox catalysis)

4.2 Redox catalysis

A scheme for the redox-catalysed cleavage of an organic halide has been set out in Fig. 8. It is the clearest case, in which the mediator acts as a single electron transfer (SET) reagent and the follow-up reaction, for alkyl halides at least, is very fast, perhaps even concerted with electron transfer. It is the coupled chemistry which allows direct or indirect reactions, cathodic in these cases, to proceed at more positive potentials. Some recent, preparatively useful, examples are given in Fig. 11. Each of these may in some sense be described as redox catalysis but where catalytic amounts of transition metal complexes are the mediators it is not always clear whether SET is involved (outer-sphere electron transfer) or whether intermediate complexes are formed (inner-sphere electron transfer).

ortho-Quinodimethanes are much used as synthons in cycloaddition reactions; they are produced by a variety of routes and several of these involve 1,4-elimination. Recently, it was discovered[26] that co-electrolysis of 1,2-bis(bromo-methylarenes) and dienophiles (maleic anhydride or quinone based) gave the Diels–Alder adduct expected for reaction involving the o-QDM derived from the dihalide [Fig. 11(a)].
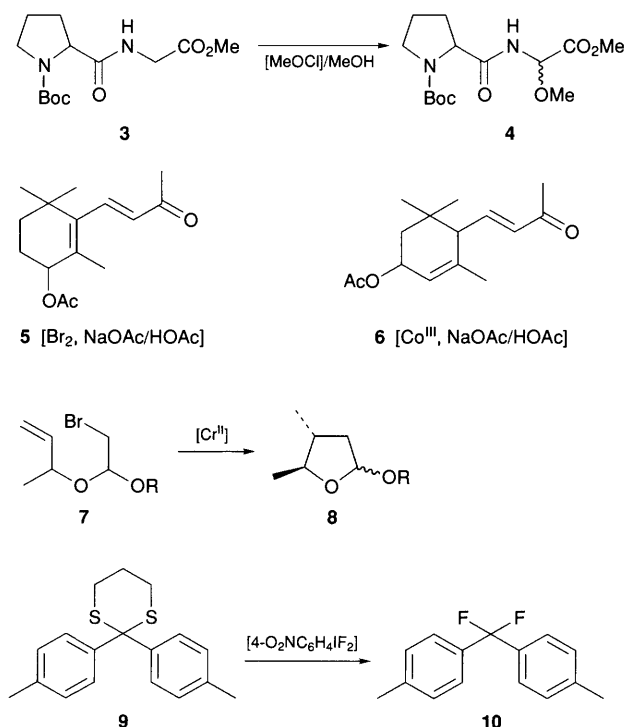
3 → [MeOCl]/MeOH → **4**

5 [Br₂, NaOAc/HOAc]

6 [Co^{III}, NaOAc/HOAc]

7 → [Cr^{II}] → **8**

9 → [4-O₂NC₆H₄IF₂] → **10**

Fig. 9 Conversions with electrogenerated reagents

(a) Electrolyte: C₆H₁₂/H₂O

L = hydroquinidine
4-chlorobenzoate

90% yield, >90% ee

[Os⁸⁺/L]   [Os⁶⁺/L]

[Fe(CN)₆³⁻]   (maintained by anodic oxidation)

(b)
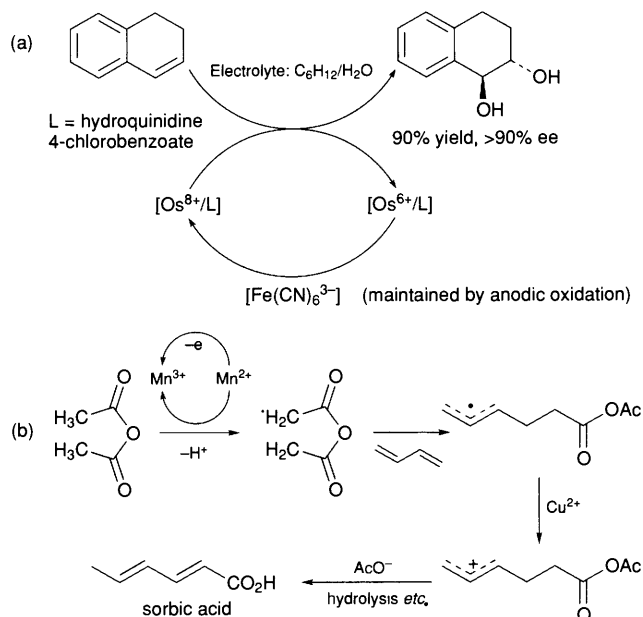
sorbic acid   AcO⁻ / hydrolysis etc.

Fig. 10 Electrochemical 'Sharpless' dihydroxylation and radical addition route to sorbic acid

Direct reduction of the dihalides is known[16] to give o-QDMs and in the absence of a dienophile they polymerise. However, the co-electrolyses are carried out at the reduction potential of the dienophile which is several hundreds of millivolts less negative than that required for direct reduction of the dihalide. Furthermore, cyclic voltammetric experiments (Fig. 12) show nicely the characteristic behaviour of redox-catalysed systems. In the absence of dihalide the dienophile/mediator shows chemically reversible reduction with the radical-anion having a significant lifetime. The radical-anion can transfer an electron to the added dihalide which rapidly loses bromide anion (cf. Fig. 8); eventually the o-QDM is formed which can react, probably relatively slowly, with the regenerated mediator [Fig. 11(a)]. On the cyclic voltammetric timescale the re-generated mediator is rapidly reduced and it is this process which is responsible for the loss of reversibility and the more than doubling of the peak current (the *catalytic current*) seen in Fig. 12.

The second example[27] [Fig. 11(b)] nicely illustrates several issues. It is undoubtedly a preparatively useful electrosynthetic reaction but although it is plausibly portrayed as involving radical cyclisation on to a double bond the mechanism is far from established. The best yields are obtained for closure on to double bonds activated by CO₂Me. This raises the question of whether it is the nickel catalyst which is reduced or the conversion of the substrate electrophore into radical-anion followed by intramolecular displacement of bromide. No voltammetric data is presented and the choice of reference electrode (Ag/AgCl) makes it difficult to be certain that Ni^I is involved although there is good precedent for this. Furthermore, the mediator, and electrolyte system (NH₄ClO₄, DMF, Et₄N-ClO₄) is highly hazardous. The use of perchlorate electrolytes is banned in many electrochemical laboratories and usually tetraalkylammonium tetrafluoroborates are adequate alternatives.

In contrast, much more is known about the nickel complex catalysed reductive cross-coupling[28] of alkyl and aryl halides (Fig. 11(c)]. The reactions are carried out at constant current but at potentials (ca. −1.2 V vs. SCE) at which Ni⁰ formation occurs. Organic halides are well-known to react with Ni⁰ complexes by oxidative addition. Instances of this have been established[29] for the electrochemical formation of poly-(p-phenylene) from 1,4-dibromobenzene and of poly-p-xylylene from 1,4-bis-(chloromethylbenzene); both processes are catalysed by nickel complexes. The reaction given

[Fig. 11(c)] fits well into this picture; apart from the case displayed similar cross-coupling reactions have been demonstrated[29] between aryl halides and a variety of other organic halides and allylic compounds.

4.3 The $S_{RN}1$ reaction

One other type of mediated electrosynthetic reaction must be mentioned. Under the special reaction conditions pertaining in liquid ammonia (H-atom abstraction precluded) and the use of a magnesium 'sacrificial' anode to deliver a stoichiometric amount of Mg^{2+} cations, it is possible reductively to cleave aryl halides to aryl σ-radicals and force *in situ* reaction with organic nucleophiles. The outcome is a reaction sequence in which the mediator radical-anion is regenerated, effectively by electron transfer from the nucleophile. Thus, in principle the reaction is only initiated electrochemically; in practice a small charge is consumed. The reaction scheme, and just one preparative example from many,[30] are displayed in Fig. 13.

4.4 Electroenzymatic synthesis

The use of redox enzymes as mediators, with the prospect of harnessing their catalytic activity and selectivity, has long been a goal of organic electrochemists. But the practical problems are formidable and a major obstacle is the slowness of electron transfer between electrodes and redox proteins. For analytical purposes electrodes modified with other redox functions (*e.g.* ferrocene) have been developed; in these cases the modified electrode promotes indirect electron transfer between the electrode and redox protein. The kinetics of the various steps involved (reaction between enzyme and substrate, rate of electron transfer between mediator and cofactor) have to be

carefully balanced. Even so, such modified electrodes lack long-term stability and are not suitable for larger-scale synthesis.

More promising is the application of bulk solution redox mediators combined with the design of special reactors. These approaches have been well reviewed,[31] and the reviewer (E. Steckhan) has been responsible for most of the recent

Cyclic voltammetry of:
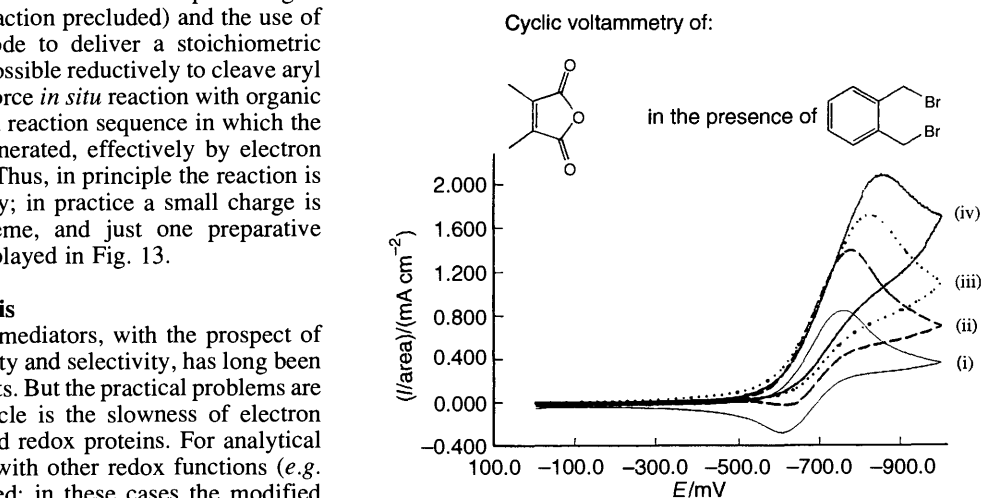
Fig. 12 Characteristic cyclic voltammetric behaviour for redox catalysis Conditions: Hg bead cathode, DMF–Et_4NBr (0.1M), 0.3 V s^{-1}, V vs. Ag/AgBr: (i) anhydride only, (ii) 0.5 equiv. dibromide, (iii) 1.0 equiv. dibromide, (iv) 2.0 equiv. dibromide
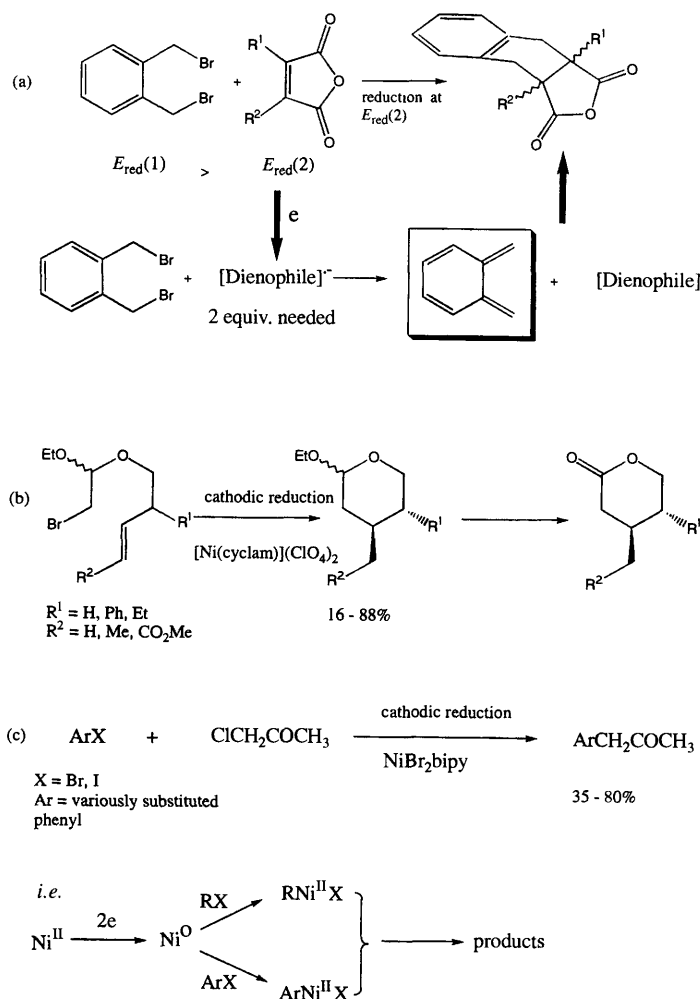
Fig. 11 Some redox catalysed reactions

significant advances in the field. The flavour of this work is indicated in Fig. 14, which illustrates a model oxidation reaction in which the refreshment of NAD+ is achieved with anodically regenerated ruthenium complex. In this instance, carried out in a phosphate buffer solution, 10 mmol of substrate was converted at a rate of 28 turnovers per hour in the presence of 5 mol% mediator and NADH. The components of such reactions are all in solution which can therefore be carried out in a flow reactor. The key feature of these so-called *electrochemical enzyme membrane reactors* is a separator equipped with an ultrafiltration membrane; this permits the low molecular mass product to pass out of the reactor but retains the higher molecular mass mediator and redox enzyme. Model oxidations of alcohol to ketone and the reverse reductions have been achieved with good turnover and the high enantioselectivity expected for enzyme reactions.

5 Selected mechanistic aspects

Modern software-driven electroanalytical equipment allows deceptively precise measurements to be made. Such measurements have long been the province of specialist groups, skilled in the art of performing high scan rate voltammetry and related amperometric experiments. Furthermore, the relevant theory is well-described in standard textbooks. Now, commercially available computer simulation software apparently allows one to measure, say, a series of cyclic voltammograms at various sweep speeds and by fitting redox peak shifts and peak shapes
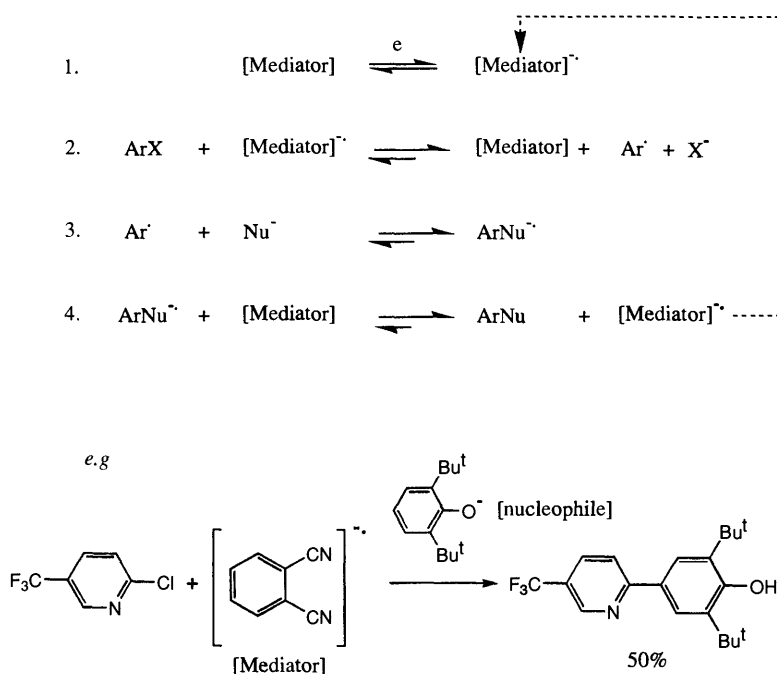

Fig. 13 The S_{RN}^1 reaction

HLADH   =   horse liver alcohol dehydrogenase
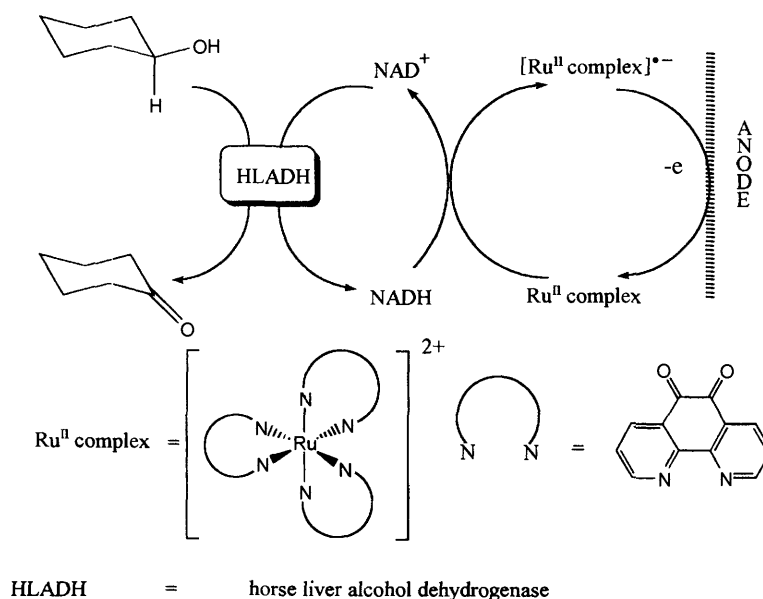
Fig. 14 Indirect electro-regeneration of NAD+

by simulation propose a 'mechanism'. There are dangers in this approach. However sophisticated the electrochemical work-stations the value and precision of the measurements are usually crucially dependent on the design of cells, the preparation and size of electrodes, and the 'know-how' associated with detecting and eliminating disturbing effects, *e.g.* from adsorption. And data may be collected and processed without appreciation of the assumptions made in deriving the controlling theory! For example in linear sweep voltammetry (LSV) mechanistic conclusions and associated rate constants can be derived from shifts in measured peak potentials (E_p), for a chemically irreversible system, with scan rate (v). The slope of the linear plot of logv *vs.* E_p is different for different mechanistic possibilities. But reliable conclusions can only be drawn if the peak potentials are measured carefully and, crucially, the rate of the irreversible chemical follow-up reaction after initial electron transfer must be quite fast, *i.e.* the reaction must be completely under kinetic control. To be convincing about mechanistic suggestions it is wise to seek evidence from a variety of methods and determine not only kinetics of follow-up reactions but also reaction orders, coulometry and, where possible, energies of activation. And above all it is essential to characterise all products thoroughly and achieve good material balance. Against this background it is perhaps useful to indicate, very selectively, those types of measurements which give information concerning the mechanisms of electrosynthetic reactions and in some cases data of considerable general interest.

Because electrohydrodimerisation is such an important electrosynthetic process (*cf.* section 3.1) much attention has been paid to elucidating the mechanism of key examples. Plausible possibilities are given in Fig. 15. The list is not
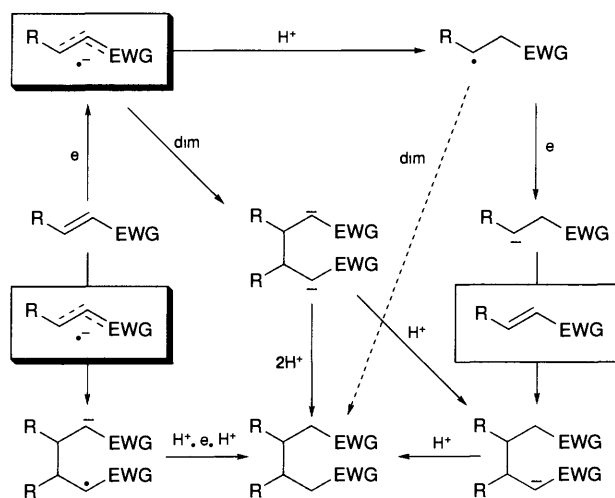

Fig. 15 Major potential routes for electrohydrodimerisation

exhaustive but 'paper' mechanisms also have to be viewed in the light of general mechanistic common sense. The routes given divide into the radical dimerisation routes (of radical-anion or radical) and the intermediate–substrate routes (addition of radical-anion or carbanion to neutral starting material). It is not easy to distinguish between these possibilities using purely electroanalytical methods; the LSV approach works only for those cases demonstrably under kinetic control (very fast follow-up reaction) and both radical–radical and radical–substrate routes give second-order kinetics. Furthermore, there is always the possibility that the low concentration, non-steady state, regimes used for voltammetric studies give results not relevant to the high concentration, steady state, conditions of preparative electrolysis.

The application of a relatively new technique to these issues has been especially helpful. Scanning electrochemical microscopy[32] is a method whereby a species generated electrochem-

ically at an electrode (diameter *ca.* 60 μm) may be collected at the tip of an ultramicroelectrode (*ca.* 5 μm) in close but variable proximity. The current measured is a function of the amount of electrogenerated species which survives the journey between the electrodes and the journey time may be varied by varying the interelectrode distance. The theory for these experiments has been established[32] and application to the electrohydrodimerisation of acrylonitrile, the 'parent' EHD reaction, shows[33] unambiguously that the reaction is second-order in radical-anion and that the radical-anions dimerise rapidly following initial electron transfer [$k_2 = (6 \pm 3) \times 10^7$ dm^3 mol^{-1} s^{-1}]. The speed of this reaction makes it difficult to maintain one argument used against the radical-anion/radical-anion routes, *i.e.* that coulombic repulsion would be prohibitively severe.

The same conclusion has been reached[9b] for the much slower EHD of esters of cinnamic acid; in DMF solution the radical-anion of methyl cinnamate undergoes second-order reaction at $k_2 = (7.8 \pm 0.7) \times 10^2$ dm^3 mol^{-1} s^{-1}. Valid LSV experiments give values for the slopes of logv *vs.* E_p plots consistent with the radical-anion/radical-anion route. This analysis is supported[9b] by measurements on the reduction of the *trans*-cyclohexane-1,2-diol diester of cinnamic acid which has adjacent activated alkene groups. Cyclic voltammetry shows the two electron transfers to be sequential and for intramolecular reaction both units need to be converted into radical-anions. At the radical-anion/substrate stage no intramolecular reaction is observed at modest sweep speeds despite the favourable disposition of the potentially reactive centres. The question now arises as to whether, in EHD, any clear example of radical–substrate has ever been established.

Intramolecular reductive cyclisation has recently been analysed[34] in detail with emphasis on the conversion of ω-keto-α,β-unsaturated esters (Fig. 16). The results of LSV measure-
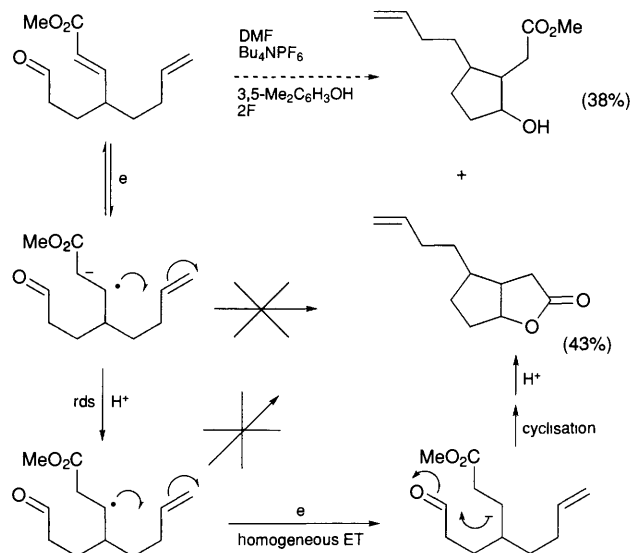

Fig. 16 Reductive cyclisation of ω-keto-α,β-unsaturated esters

ments and chemical arguments were used to reduce the plausible mechanistic possibilities to a handful and the product from the 'designer' reaction shown in Fig. 16 strongly indicated the key intermediate to be the carbanion. It was confidently assumed that the intermediate hex-5-enyl radical would have cyclised rapidly to an alternative product had it not been rapidly reduced, presumably by the first-formed radical-anion. It is rare that second electron transfers are heterogeneous (at the electrode) and in most cases initially-formed intermediates diffuse away from the electrode and react in bulk solution; in this case the slow step (protonation) is believed to occur in bulk solution. In this report[34] the authors recommend adoption of a common mechanistic language based on lower-case letters for elementary steps with upper-case reserved for rate determining

steps Thus, in the Little–Fry description the reaction in Fig 16 would be an e-P-d-c-p reaction (e = ET at the electrode, d = ET in solution, c = cyclisation, P/p = protonation) Time will tell

Finally, an important spin-off of much earlier synthetic work which engendered a need to know more about the redox potentials (E^0) of electrogenerated radicals has led to a relatively simple and powerful method for making such measurements This is now well-reviewed [35] The method is based on measuring relative amounts of products from the competing reactions following cathodic generation of aromatic radical-anions (with a known E^0) in the presence of alkyl halides (Fig 17) Depending on the reduction potential of the
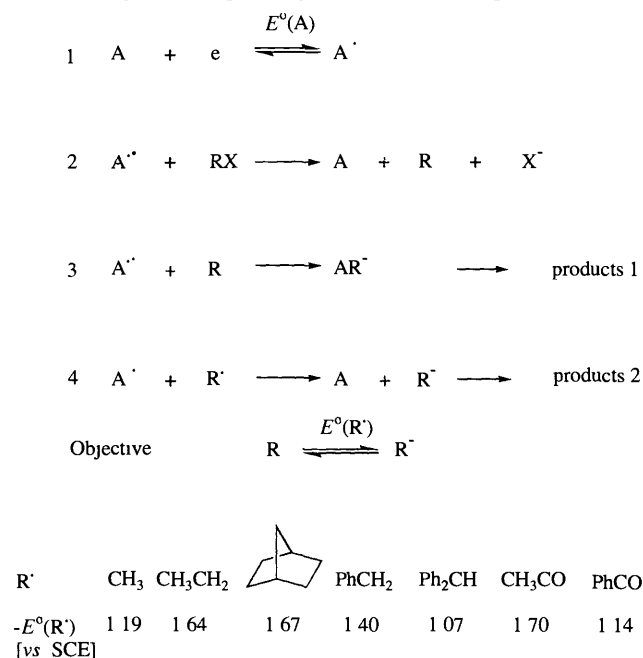
$$E^0(A)$$
$$1 \quad A \ + \ e \ \rightleftharpoons \ A^{\cdot -}$$

$$2 \quad A^{\cdot -} \ + \ RX \ \longrightarrow \ A \ + \ R^{\cdot} \ + \ X^-$$

$$3 \quad A^{\cdot -} \ + \ R^{\cdot} \ \longrightarrow \ AR^- \ \longrightarrow \ \text{products 1}$$

$$4 \quad A^{\cdot -} \ + \ R^{\cdot} \ \longrightarrow \ A \ + \ R^- \ \longrightarrow \ \text{products 2}$$

$$E^0(R^{\cdot})$$
Objective $\quad R^{\cdot} \ \rightleftharpoons \ R^-$

R$^{\cdot}$	CH$_3$	CH$_3$CH$_2$	(norbornyl)	PhCH$_2$	Ph$_2$CH	CH$_3$CO	PhCO
-E^0(R$^{\cdot}$) [vs SCE]	1 19	1 64	1 67	1 40	1 07	1 70	1 14

Fig. 17 Measurement of standard potentials for electrogenerated radicals

alkyl radical (R$^{\cdot}$) it will either be reduced by the aromatic radical-anion (k_4) or couple with it (k_3) There is much evidence to support the necessary assumption that the coupling is fast, ca 10^9 dm^3 mol^{-1} In these circumstances the measurable product ratios give a 'competition parameter', q, defined as $q = k_4/(k_4 + k_3)$ Plots of q vs the E^0 values for aromatic radical-anion formation are S-shaped and it can be shown that the mid-point of such curves gives a reduction potential of the radical from which the corresponding E^0 value can be calculated Thus, the standard potentials for many carbon-centred radicals have been measured, examples, some of which are given in Fig 17, include aliphatic, allyl, benzyl and acyl radicals

6 Dedication

This review is dedicated to Professor Dr Hans J Schafer (University of Munster), a pioneer in the field, on the occasion of his 60th birthday

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