

Towards paired and coupled electrode reactions for clean organic microreactor electrosyntheses

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Abstract

Electrosynthesis offers a powerful tool for the formation of anion and cation radical intermediates and for driving clean synthetic reactions without the need for additional chemical reagents. Recent advances in microfluidic reactor technologies triggered an opportunity for new microflow electrolysis reactions to be developed for novel and clean electrosynthetic processes. Naturally, two electrodes, anode and cathode, are required in all electrochemical processes and combining the two electrode processes into one “paired” reaction allows waste to be minimised. By decreasing the inter-electrode gap “paired” reactions may be further “coupled” by overlapping diffusion layers. The concept of “coupling” electrode processes is new and in some cases coupled processes in micro-flow cells are possible even in the absence of intentionally added electrolyte. The charged intermediates in the inter-electrode gap act as electrolyte and processes become “self-supported”. Hardly any examples of “coupled” paired electrochemical processes are known to date and both “paired” and “coupled” processes are reviewed here. Coupled electrode processes remain a challenge. In future “pairing” and “coupling” electrode processes into more complex reaction sequences will be the key to novel and clean flow-through microreactor processes and to novel chemistry.

1. Introduction

Electrosynthesis is based on adding or removing electrons with defined energy to/from a chemical process and can be employed to drive a wide range of clean chemical transformations [1, 2]. The formation of highly reactive intermediates as well as of electrogenerated acids or bases are possible [3, 4]. In several industrial processes large scale electrosynthetic processes (e.g. in the nylon-6,6 synthesis [5]) have been successfully applied and specially designed reactor systems have been developed such as filterpress systems, membrane reactors, fluidised bed reactors, or parallel-plate flow systems with down to ≈ 1 mm inter-electrode gaps [5].

In organic synthesis, over the recent years microreactor systems have gained popularity [6, 7] and they have been applied in syntheses where good reaction control, reactive intermediates, high yields, modularity, and small scale are desirable [8–10]. As will be shown in this overview, micro-flow reactor systems are also ideal

for electrosyntheses. New types of “paired” or “coupled” electrosynthetic processes could be developed in future to be conducted in micro-flow systems. However, a better understanding or how to beneficially “pair” or “couple” electrode processes is prerequisite. The main focus of this review is on reaction concepts and examples rather than on cell design and process environments.

All electrochemical reactions occur in pairs (oxidation and reduction), thus obeying the law of electroneutrality: the number of electrons added at the cathode must simultaneously be removed at the anode. Often attention is focused on only one of the reactions in a divided cell arrangement or the accompanying reaction at the counter electrode is chosen to be innocuous, not to interfere with starting materials, intermediates, or products. In “paired” electrochemical syntheses both the anodic and cathodic reactions can be matched and contribute to the formation of the final product(s) as has been emphasised and defined by Baizer [11]. Using

paired electrochemical processes to produce chemicals can result in a considerable reduction in energy consumption and by pairing electrode processes at a closely spaced anode and cathode, paired electrochemical processes can now be conducted without the need for an intentionally added supporting electrolyte [12]. The product is obtained directly by solvent removal and without laborious separation steps, which is of considerable benefit in both laboratory scale and commercial processes.

In this review a range of “paired” electrode processes are discussed and different types of processes going from “uncoupled” to “strongly coupled” are compared. The benefits and challenge of coupling electrode processes and possible applications of micro-flow reactor systems for electrosyntheses are highlighted. The future challenge of identifying new “paired” and “coupled” processes and the promise of new chemical reactions under micro-flow electrosynthesis conditions are emphasised.

2. Pairing electrosynthetic processes

Early work on “paired electrosynthesis methodology” was reported in the late 1980s particularly by Baizer and co-workers [13]. Special cells with flow-through operation and novel porous electrodes have been developed [14]. There are well-studied examples of paired electrosyntheses such as the formation of ferrocene with a sacrificial iron electrode [15] or the anodic and cathodic transformation of glucose to give gluconic acid and sorbitol [16]. This latter process may be classified as “divergent” since two products are obtained from one starting material. In addition, there are many examples for “parallel” and “convergent” processes. A methodology often employed to pair electrode processes is based on the cathodic generation of hydrogen peroxide, H_2O_2 , (or similar peroxy intermediates) from oxygen. Hydrogen peroxide as an intermediate is able to act as an oxidant despite being formed at the cathode and therefore both oxidation and reduction result in the formation of the same product (vide infra).

In commercial electrosynthetic processes, pairing electrode processes has always been important. The most prominent example of a paired electrosynthesis is the production of adiponitrile by electrohydrodimerisation of acrylonitrile, which is an industrially important intermediate used in the manufacture of nylon-6,6 [17].

The Monsanto process may be regarded as a “paired” process employing a two-phase reaction mixture and was commercialised by utilising an undivided cell consisting of a bipolar stack of carbon steel evaporated on one face with a thin layer of cadmium. Plastic spacers set the inter-electrode gap at 2 mm. From 100–200 electrodes are placed in a single stack, and the assembly installed in a pressure vessel, designed to provide a uniform, two-phase re-circulating aqueous emulsion of acrylonitrile, adiponitrile, and a bisquaternary salt/phosphate buffer system [18]. The cell stack is operated at a current density of $20 A dm^{-2}$ and 3.8 V per cell and the power usage at $2.4 kWh kg^{-1}$ is less than half that for the corresponding divided cell process ($6.0 kWh kg^{-1}$). For the recovery of the adiponitrile product, a side stream of catholyte is withdrawn from each circulating system, cooled, and counter-currently contacted with excess acrylonitrile in a multistage extraction column. A portion of the aqueous electrolyte in this traditional macroreactor process is also purged from the electrolysis circulating system to remove the organic and metal ion impurities that can adversely affect the reaction selectivity and current efficiency.

The use of the undivided cell system and two-phase conditions are the keys to high chemical and cost efficiency. The overall reaction scheme for this process, which is based on two starting materials (acrylonitrile and hydrogen) reacting at cathode and anode to give adiponitrile as a coupling product, is summarised in Figure 1 [19].

From this reaction scheme the importance of coupling anode and cathode processes is immediately apparent. For processes to be developed it is important to take into consideration the overall reaction scheme including anode and cathode reaction. It is very interesting to ask “what are the effects of bringing the two electrodes, anode and cathode, even closer together”? The recent development of new micro-reactor and micro-flow cell technology for synthetic processes [20] is now stimulating further research into electrochemical reactions which proceed in undivided cell reactions and/or under conditions where the diffusion layer of anode and cathode are made to overlap.

Inventing paired syntheses, particularly if they are going to be carried out in undivided cells, presents many intriguing challenges. The raw materials before electrolysis must be compatible. The intermediates (or products) formed at one electrode must not react irreversibly with the intermediates or products formed at the other

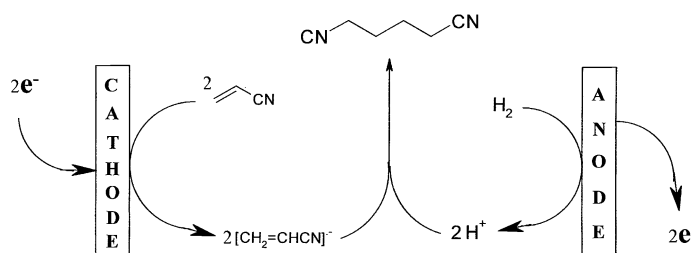


Fig. 1. Schematic presentation of the Monsanto process [19].

electrode. Above all, an intermediate must not, before reacting, return to the counter electrode and undo the electron transfer(s) that were previously accomplished. For paired electrode processes the selectivity and design of electrodes is important to avoid unwanted reactions and the development of new types of modified [21] or selective enzyme electrodes [22] will further help to improve this technology. The material used for the electrode often influences the reaction. The chemical interaction of an electroactive species generated from the substrate and the electrode is a particularly important factor in the selection of the material for the cathode or anode. Novel materials such as boron-doped diamond [23] or Ebonex [24] are now available to control electrochemical processes and many cases of specific electrode–substrate interaction exist. The interaction of graphite with formaldehyde is, for example, a promoting factor in the reductive dimerisation of formaldehyde to ethylene glycol [25]. A tin cathode has been found particularly effective for the intramolecular coupling of a carbonyl group with an aromatic ring [26]. Porous Ebonex can be beneficially employed in processes where anodic solvent decomposition is required (e.g. for the electrogeneration of acids or bases). The type of electrode material(s) is therefore critical to the selectivity of a process. When considering a paired or coupled process, each electrode may be chosen to support a particular process.

The reactor design is crucial for efficient electrosyntheses. Flow through systems have been proposed with channel geometry [27] or with flow through porous plug electrodes [28]. Rather than employing a flow-through system with anode and cathode placed vis-à-vis, electrode geometries such as the interdigitated electrode array can be highly effective [29] (see Figure 2a). An interdigitated electrode system (arrays of microscopic electrodes made from metal sputtered into patterns onto a substrate) system can now be produced routinely and in extremely small dimensions via advanced lithographic techniques [30]. Each electrode has a band geometry with a bandwidth of typically 0.1–100 μm and a gap between electrodes of similar size. For the interdigitated

band electrode of equally sized electrodes and gaps, the steady-state feedback current has been determined [31, 32] and the approximate (steady state) diffusion layer thickness δ can be equated in good approximation to the width of the inter-electrode gap between the electrodes, w (Equation 1).

$$\delta = w \quad (1)$$

For all common (uniformly accessible) hydrodynamic electrodes the (steady state) diffusion layer thickness can be expressed based on the Nernst diffusion layer model (Equation 2) [33].

$$\delta = n F A D C_{\text{Bulk}} / I_{\text{lim}} \quad (2)$$

In this expression, δ is the diffusion layer thickness, n the number of electrons transferred per molecule diffusing to the electrode, F the Faraday constant, D the diffusion coefficient, C_{Bulk} the bulk concentration, and I_{lim} the mass transport limited current. Forced convection will reduce the diffusion layer thickness and therefore increase the current. Typical values for the diffusion layer thickness at hydrodynamic electrodes are 10–500 μm [34] and in more forceful agitated systems, values down to 1 μm [35] and even $<0.1 \mu\text{m}$ [36] can be achieved.

With reference to Figure 2 and by comparing the above two equations it can be seen that “coupling” of paired processes will occur when the inter-electrode gap (width w for interdigitated electrodes or height $2h$ for channel electrodes) approaches approximately 2δ . For non-uniformly accessible electrode systems such as the channel electrode (Figure 2b) coupling will be increasing towards the trailing edge of the electrodes (The dotted line is indicating the approximate extend of the diffusion layer). On the other hand, increasing the rate of flow through the channel cell will decrease the diffusion layer thickness and therefore decouple the processes at anode and cathode (see Figure 3b). Similarly, flow across an interdigitated array electrode will also affect the coupling between processes and essentially decouple process at high flow rates (see Figure 3a).

There are further types of electrode systems similar to interdigitated band arrays but these are based on porous insulator separated electrodes with flow on both or on only one side of the electrode systems (see Figure 3c). These can be expected to follow similar principles except that convective flow has a smaller effect on the concentration profile within the porous insulator or membrane. Finally, in addition to the effect the diffusion layer thickness has on processes in micro flow systems, the magnitude of the reaction layer [37] provides a further important parameter for the interaction of the two electrodes and for the pathway of overall chemical processes triggered by the electrochemical process. A full understanding of “coupled” electrochemical processes will require a detailed understanding of both diffusion layer and reaction layer composition, for example based on a detailed numerical simulation.

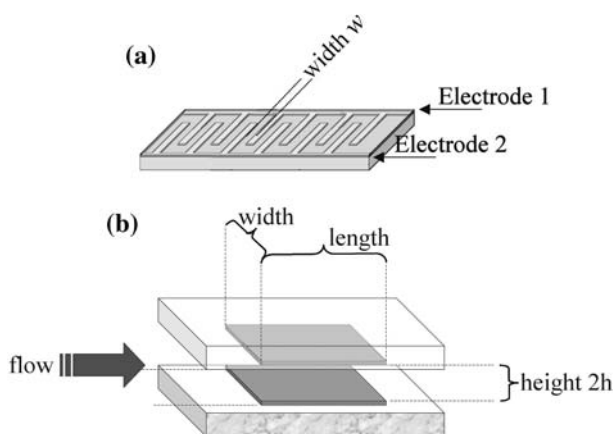


Fig. 2. Schematic drawing of (a) an interdigitated electrode system and (b) a rectangular duct micro-flow cell electrode system.

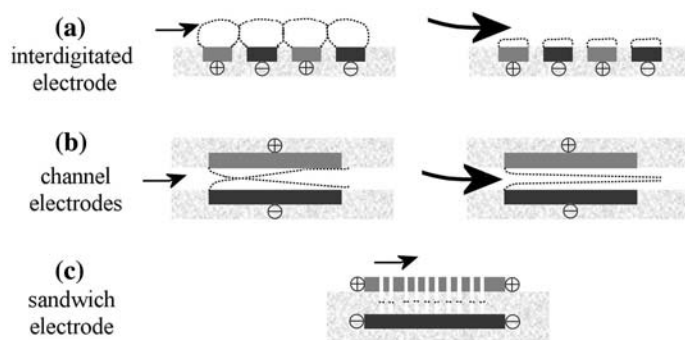


Fig. 3. Schematic drawing of the concentration profile (dotted line) in the presence of strong or weak convective flow (see arrow) for (a) interdigitated electrodes, (b) channel electrodes, and (c) a semi-open “sandwich” electrode.

3. Parallel, divergent, and convergent paired electro-organic reactions

3.1. Parallel paired electroorganic syntheses

The least complicated approach to a paired electrochemical process is to use two starting materials which are converted into two products without any chemical interaction during the electrolysis process. There is one prominent example for this type of process which is the formation of phthalide and 4-(*t*-butyl)benzaldehyde dimethylacetal.

In 1999, BASF AG introduced a parallel commercial paired electrosynthesis for the simultaneous formation of two products. Methyl phthalate is cathodically reduced to phthalide while at the anode 4-(*t*-butyl)toluene is oxidised to give 4-(*t*-butyl)benzaldehyde dimethylacetal (Figure 4) [38, 39]. In this process methanol is used both as a reagent and as a solvent. However, overall as much methanol is released from reduction of the diester as is consumed in making 4-(*t*-butyl)benzaldehyde dimethylacetal. Protons are simultaneously generated at the anode and consumed at the cathode.

3.2. Divergent paired electroorganic syntheses

The use of a single starting material can be beneficial when two distinct products are formed at cathode and anode. In this “divergent” process the overall balance of

charges is maintained and the two products have to be separated post-electrolysis. The paired oxidation of glucose to gluconate with the simultaneous reduction of glucose to sorbitol is an example of a divergent paired, industrial scale electroorganic process. The indirect oxidation by anodically generated bromine of glucose to gluconate is used commercially. The electrochemical reduction to sorbitol (and mannitol) was for some years an industrial process until a catalytic process replaced it. It was postulated that if the two could be paired into a single undivided flow cell, the economics for each would be improved and full details of this procedure have since been published [40, 41]. The reaction at the cathode involves the electrochemical hydrogenation of glucose. An indirect oxidant (Br_2) is then electrochemically generated at the anode and oxidises the reactant in the bulk solution. Hydrogen evolution is a side reaction at the cathode (Figure 5). A continuous, electrochemical tubular – stirred tank reactor was employed (see Table 1).

3.3. Convergent paired electroorganic syntheses

Processes in which two starting materials upon oxidation and reduction give the same product may be employed in a “convergent” process. Although it is unusual for oxidation/reduction processes to yield the same product, there are several examples of this type of process.

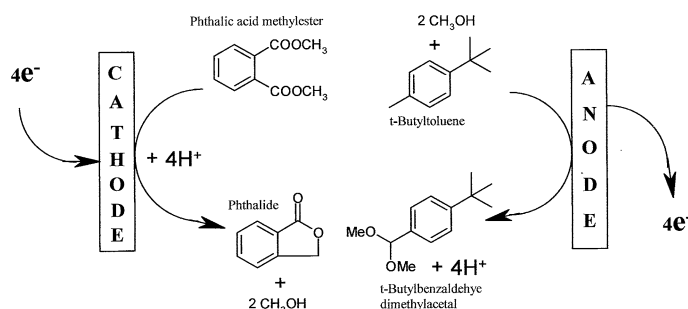


Fig. 4. Schematic presentation of an industrially applied (BASF AG) paired electrosynthesis of phthalide at the cathode and 4-(*t*-butyl)benzaldehyde dimethylacetal at the anode [38, 39].

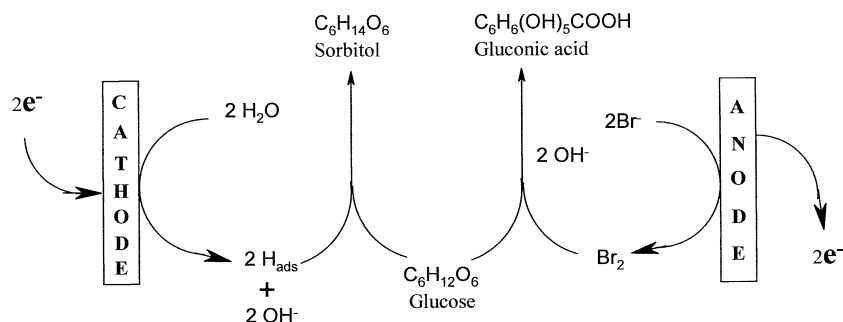


Fig. 5. Schematic presentation of the paired production of gluconic acid and sorbitol from glucose [40, 41].

3.3.1. Formation of glyoxalic acid

Through paired electrosynthesis, oxalic acid and glyoxal were separately reduced and oxidised yielding glyoxalic acid [42]. In the oxidation process, both chlorine and oxygen gas could be used as an oxidising agent for glyoxal. It was found that the percentage of transformation and selectivity was higher with chlorine gas than with oxygen gas (Figure 6). Overall, this process highlights the advantages of a paired synthesis with high percentage yield, selectivity, and purity, low waste and a 'simple' synthesis that is normally very difficult to perform by conventional chemical methods.

3.3.2. Formation of 2-alkoxy-tetrahydrofurans

Ishifune et al. [43] describe the electroreduction of aliphatic esters to form 2-alkoxytetrahydrofurans using a novel electrolysis system (see Table 1). The paired electrolysis system consists of a cathodic reduction of aliphatic esters and an anodic oxidation of THF solvent forming the tetrahydrofuryl-protected form of a primary alcohol (Figure 7). Ultrasound was employed to continuously unblock the electrodes. An interesting effect of magnesium in the process was postulated. The authors suggest that magnesium ions promote the electroreduction of aliphatic esters which are hardly reduced under usual electroreductive conditions. Overall, from a synthetic viewpoint, this is a novel example of a paired electrosynthesis yielding protected alcohols directly from aliphatic esters.

3.3.3. Formation of propylene oxide

Interdigitated coplanar band electrodes were made from platinum ink printed on alumina and their application to the epoxidation of propylene investigated in both a tank cell and flow cell [44], using a convergent paired process. Bromide solutions were saturated in propylene, then the bromide oxidised to bromine at the anode, which then reacts with water to form hypobromous acid. This in turn reacts with propylene to form propylene bromohydrin. The hydroxide ions produced at the cathode were then necessary to complete the overall reaction (Figure 8).

The performances of various platinum arrays were investigated. Many factors were found to influence their results such as the flow conditions, applied voltage, cell temperature, electrolyte concentration and the inter-electrode distance. Experiments were carried out with inter-electrode distances of the different arrays varying between 250 μm and 1 mm (see Table 1).

3.3.4. Formation of benzyl – nitroalkyl adducts

Chiba and co-workers have reported [45] a benzylic nitroalkylation process, accomplished by the paired reaction of various benzyl phenyl sulfides and nitroalkanes in the presence of lithium perchlorate. Paired electrolyses were performed in an undivided cell, with divided cells actually giving the desired products in very poor yields (Figures 9 and 10). Similar reactions using a benzylphenylether gave no desired nitromethylated

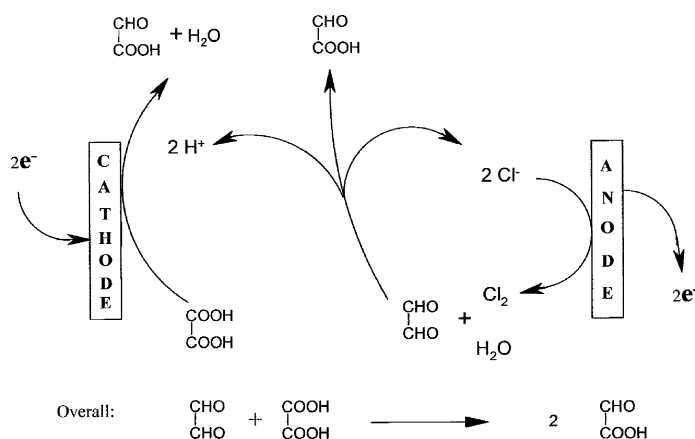


Fig. 6. Schematic presentation of the convergent glyoxalic acid electrosynthesis [42].

Table 1. Divergent and convergent paired synthetic processes

Example / Reference	Product(s)	Starting Material(s)	Current Efficiency (%)	Anode Material / Reaction	Cathode Material / Reaction
1. [40, 41]	Sorbitol Gluconate	Glucose	100% for both products	Graphite anode Glucose → gluconate via "Br ⁺ "	Raney Ni Cathode Glucose → sorbitol via electrocatalytic reduction
2. [42]	Glyoxalic acid	Oxalic acid Glyoxal	40% yields of both products	Graphite Glyoxal → glyoxalic acid via Cl ₂	Lead Plate (99.99%) ^a Oxalic acid via proton reduction
3. [43]	2-Alkoxytetra-hydrofuran	Aliphatic esters	General acetal percentage yield 87%	Platinum Formation of THF cations by anodic oxidation	Magnesium Formation of the acetal via combination between the alkoxide formed at the cathode and THF cation
4. [44]	Propyl epoxide	Propylene	68%	^b	^b
5. [45]	Various nitroalkylated compounds	Varied benzyl sulfides including benzyl dithioacetals	68–100%	Glassy carbon anode Benzyl cations generated by anodic oxidation of sulfides and then trapped by nitroalkyl anions	Platinum cathode Formation of nitroalkyl anions. ^c
6. [46]	Various nucleophilic substituted aromatics	Methoxy arenes with 1 <i>H</i> -tetrazoles	88% ^{d,e}	Radical cations of electron-rich aromatics generated at platinum anode PbO ₂	Platinum cathode Nitrogen heterocyclic anions act as nucleophiles.
7. [47]	<i>p</i> -Benzoquinone	Benzene	Total current efficiency, 94%	Benzene anodically oxidised.	PbO ₂ Benzene "cathodically oxidised" using a Cu ⁺ /O ₂ redox system
8. [48]	Protected homoallylic alcohols	Allyl bromide; benzaldehyde and <i>N,N</i> -dimethyl-formamide	50–60% ^f	Platinum Anodically generated electrophile + homoallylic alcoholate Platinum ^g	Glassy carbon Metal-free allylation of benzaldehyde by allyl bromide reduction. Platinum
9. [49]	2,6-Dimethyl-4-arylpiperidine-3,5-dicarbonitrile	Benzylthiocyanate, benzylchloride,	67%		
10. [50]	Cyanoacetic acid	<i>p</i> -methylbenzyl chloride, or toluene CO ₂ ^h	24.7% ⁱ	Platinum net or carbon plates. Generation of CH ₂ CN radicals from solvent	Platinum or lead plates. CH ₂ CN Radicals are coupled with cathodic CO ₂ -reduced species

^aTypical distance between two electrodes 10 mm. A polycarbonyl styrene cationic exchanging membrane was used to separate the anode and cathode cells.

^bInterdigitated coplanar band electrodes made from platinum ink printed on alumina.

^cPaired electrolyses were performed in 3 M lithium perchlorate and in dry nitromethane solutions.

^dTotal yield for products A and B. Product ratio 3:2, respectively.

^ePaired electrolysis performed using an undivided cell in acetonitrile solvent with tetrabutylammonium salt of the heterocyclic anion as the electrolyte.

^fElectrolyses were conducted in a quasi-divided cell at a constant current of 1.50 mA (higher current densities caused the production of several by-products); yield range reflects products A-C.

^gPlatinum electrodes in a two-compartment cell setup divided by a glass frit. Acetonitrile solvent was used in all electrolyses.

^hSynthesis of CA actually involves the solvent, acetonitrile and a tetraalkylammonium salt anion. Saturation of cells with carbon dioxide was achieved by continuous bubbling of the gas.

ⁱUnder certain experimental conditions this represented the greatest current efficiency.

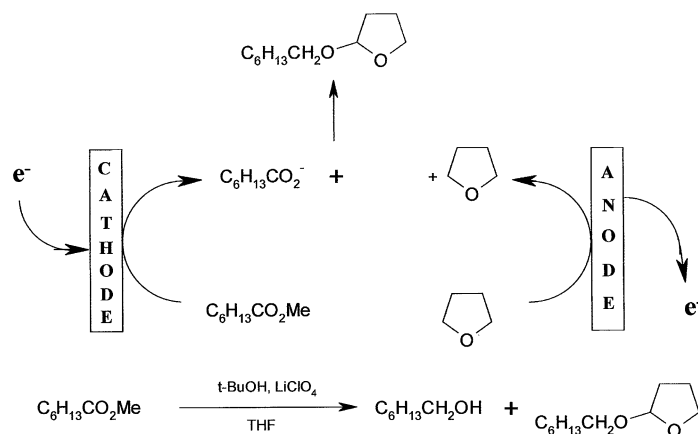


Fig. 7. Paired electrolysis system of the combination between cathodic reduction of an aliphatic ester and anodic oxidation of THF [43].

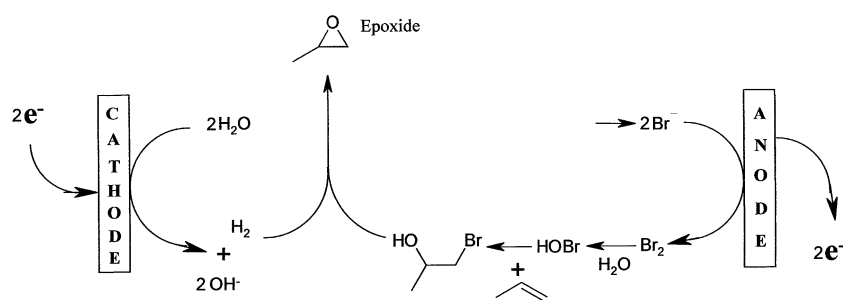


Fig. 8. Schematic presentation of propylene epoxidation process at interdigitated electrodes [44].

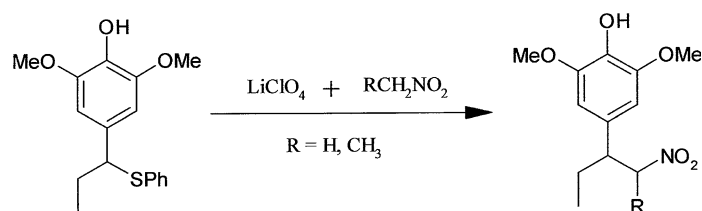


Fig. 9. Overall reaction scheme for the paired benzylic nitroalkylation employing a nitroalkane and a benzylphenylsulfide as starting materials [45].

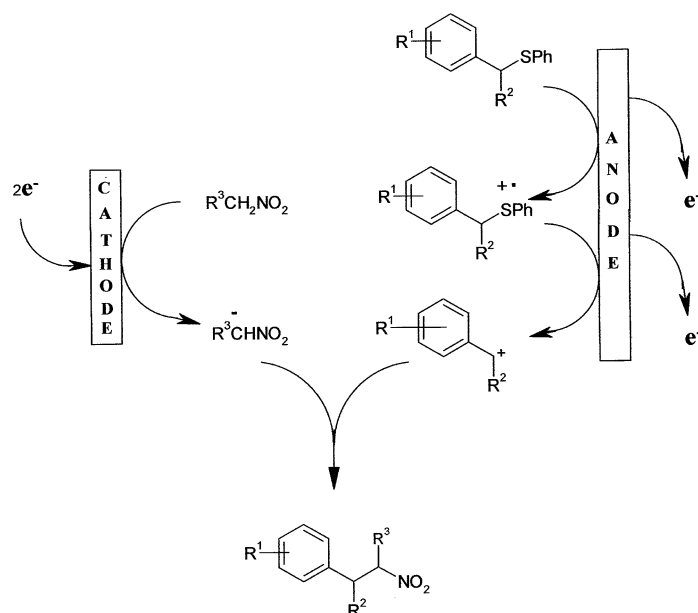


Fig. 10. Schematic presentation of the proposed reaction mechanism of the benzylic nitroalkylation by paired electrolysis [45].

products. The result showed that the benzylic phenylsulfanyl group was essential for the electrochemical generation of the corresponding benzyl cation. Additionally, it was reported that the perchlorate electrolyte was presumed to assist the oxidative fission of the carbon–sulfur bond. In conclusion, paired electrolysis of benzyl sulfides and dithioacetals in lithium perchlorate and nitroalkane solution efficiently accomplished the electrooxidative generation of the corresponding benzyl cations at the anode with the simultaneous electroreductive generation of a nitroalkyl anion at the cathode. In Figure 10 the formation of oxidised forms of thiophenol and hydrogen as side products are omitted.

3.3.5. Formation of tetrazole anion – methoxyarene cation adducts

Evans and co-workers [46] performed coupling reactions with methoxy arenes and 1*H*-tetrazoles. Although the mechanism behind the reaction is not fully explained, the direct coupling of cations produced at the anode and anions produced at the cathode was intended. A convergent paired electrosynthesis is developed in which anions of nitrogen heterocycles are generated at the cathode, and radical cations of electron-rich aromatics

are produced at the anode. Reaction between these two electrogenerated species leads to products via nucleophilic substitution at the aromatic substrate (Figure 11). Interestingly, attempts to achieve similar substitution reactions on 1,4-dimethoxybenzene using other types of anions (benzoate, trifluoroacetate, acetate, 2,4-dinitrophenolate, and the anion of diethyl nitromalonate) did not produce satisfactory yields.

3.3.6. Formation of *p*-benzoquinone and hydroquinone from benzene

Ito et al. [47] reported the oxidation of aromatics using a paired process (Figure 12). Historically, this is the first reported example of the production of the same product from the same starting material both in the anode and cathode chambers, i.e. a convergent synthesis. A single H-type electrolytic cell with $\text{Cu}^+/\text{Cu}^{2+}$ mediator is required in this procedure and oxygen in contact with the Cu^+ intermediate is the actual cathodic oxidising reagent.

3.3.7. Formation of homoallylic alcohols

The allylation of an aldehyde in a convergent paired electrolysis under indium-free conditions was performed

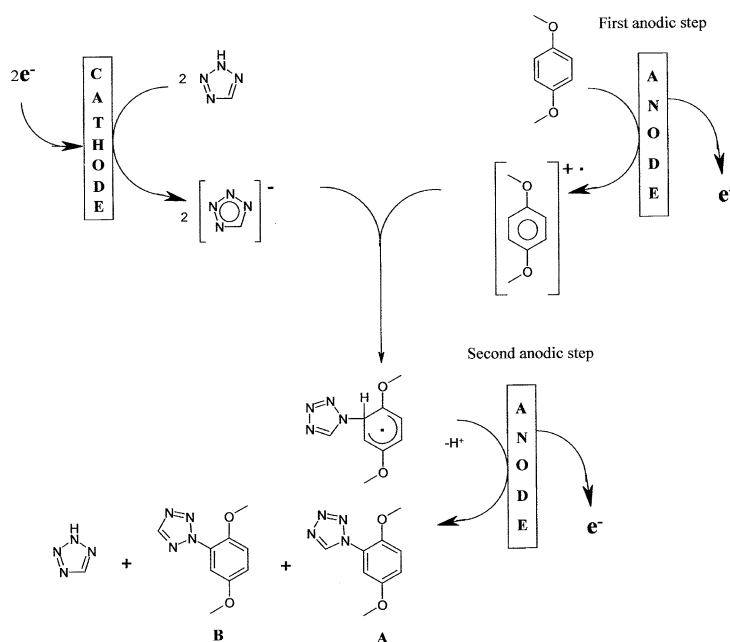


Fig. 11. Schematic presentation of a paired coupling process employing anodically generated radical cations and cathodically generated heterocyclic anions [46].

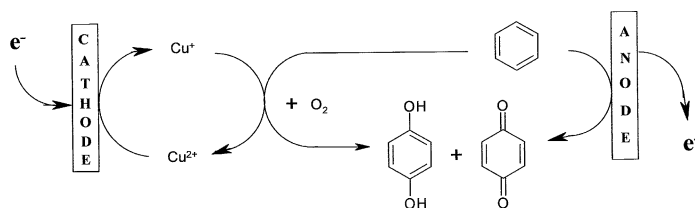


Fig. 12. Schematic presentation of the convergent synthesis of *p*-benzoquinone and hydroquinone via simultaneous anodic and cathodic oxidation of benzene [47].

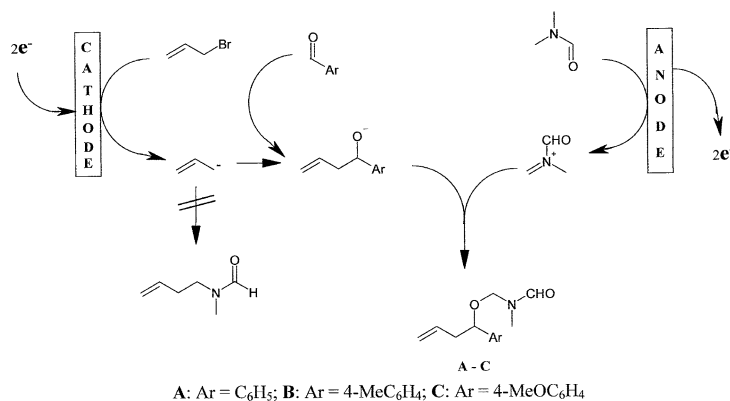


Fig. 13. Schematic presentation of the paired electrocatalysis of formamide-protected homoallylic alcohols [48].

in *N,N*-dimethylformamide (DMF), and the formation of the corresponding three-component product was observed [48] (Figure 13). Experimentally, it was observed that the best results for the paired electrolysis for the formation of such formamide-protected homoallylic alcohols were obtained when the allyl bromide/aldehyde ratio was 2:1. It was suggested that an excess of allylbromide is required for formation of the allylic anion, which then reacts with the protons produced in the anodic oxidation of the DMF to yield propene. The coupling product *N*-but-3-enyl-*N*-methylformamide, which reportedly should be obtained by the reaction of cathodically generated allylic anion with the anodically generated formyl iminium ion was not detected in significant amounts even in the absence of aldehydes. One potential problem is the conversion of aldehydes containing electrochemically sensitive functional groups such as cyano, nitro, dimethylamino group or halide functionalities which reportedly lead to side reactions and to several by-products.

3.3.8. Formation of 2,6-dimethyl-4-arylpyridine-3,5-dicarbonitriles

Batanero et al. [49] report the formation of 2,6-dimethyl-4-arylpyridine-3,5-dicarbonitrile as the major product from a wide range of aromatic precursors in acetonitrile. It is assumed that the 3-aminocrotonitrile anion generated initially (Figure 14) passes through a glass frit diaphragm to the anodic compartment resulting in the formation of the final product, **A** (Figure 15). Two concurrent pathways are proposed to explain the formation of **A**. An alternative mechanism has been postulated for the oxidation of toluene to the corresponding 2,6-dimethyl-4-arylpyridine-3,5-dicarbonitriles (Figure 16). Overall the process is complex and has not

been optimised as a paired or coupled electrocatalytic reaction.

3.3.9. Formation of cyanoacetic acid

Recently, Batanero and Barba [50] have described the paired synthesis of cyanoacetic acid. The conventional synthesis of cyanoacetic acid is usually carried out by the reaction of chloroacetic acid and alkaline cyanides, thus a potentially dangerous and environmentally problematic process. Cyanoacetic acid was synthesised using a novel 'green' process with CO₂ and acetonitrile starting materials and based on a methodology similar to the previous paired electrocatalysis of 2,6-dimethyl-4-arylpyridine-3,5-dicarbonitrile (Figure 17). The proposed reaction scheme depicts a rather simplified overview of the process and it was acknowledged that further study is required for a full mechanistic understanding.

4. The use of peroxo-intermediates in paired electroorganic reactions

The use of hydrogen peroxide as an intermediate in electroorganic processes is important. Hydrogen peroxide is a versatile and cheap reagent which is readily formed *in situ* by reduction of oxygen. It has become popular in paired electrocatalysis where extensive work has been carried out by Nonaka and coworkers [51–54]. Hydrogen peroxide was employed in the paired formation of sulfones, aminoiminomethane-sulfonic acids and nitrones. Often a WO₄²⁻/WO₅²⁻ redox mediator is used and hydrogen peroxide is formed at the cathode. The ability of hydrogen peroxide although being formed cathodically to act as a strong oxidising reagent allows

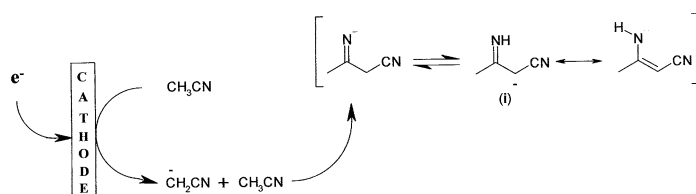


Fig. 14. Schematic presentation of the cathodic formation of the 3-aminocrotonitrile anion intermediate (i) [49].

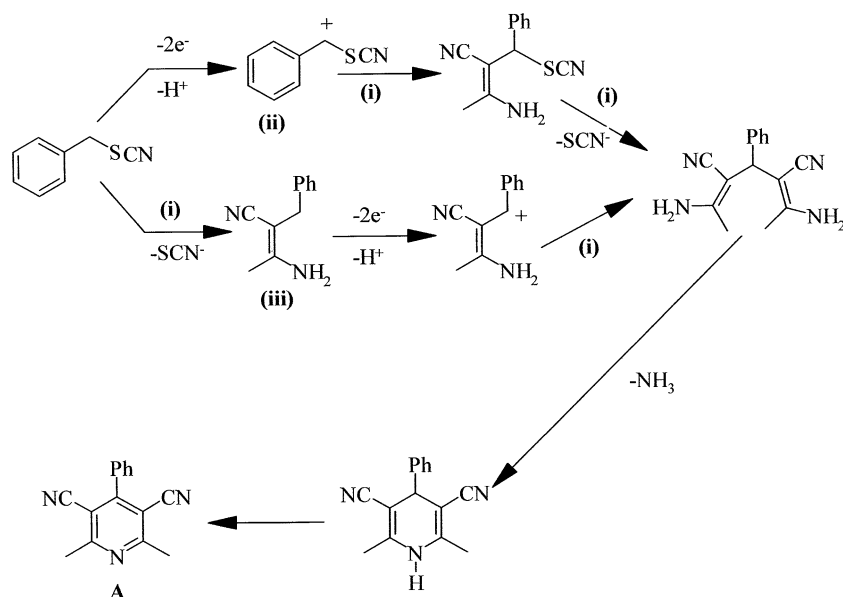


Fig. 15. Schematic presentation of the proposed mechanistic pathway for the formation of 2,6-dimethyl-4-arylpyridine-3,5-dicarbonitriles A [49].

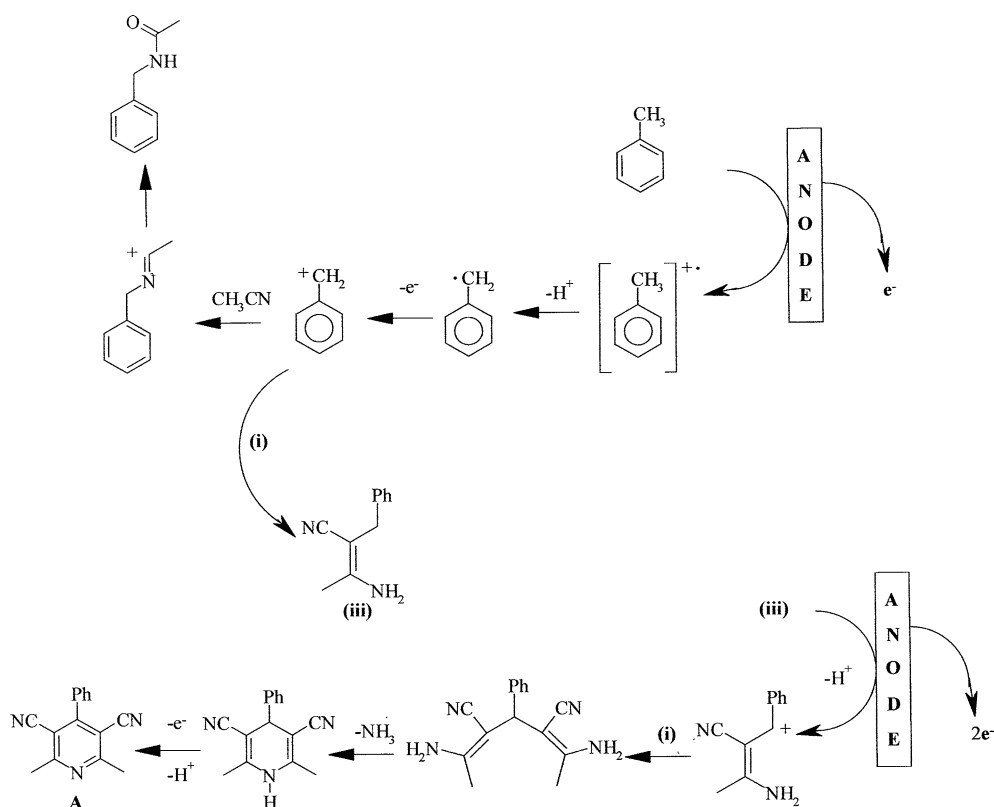


Fig. 16. Schematic presentation of the proposed alternative mechanistic pathway for the formation of 2,6-dimethyl-4-arylpyridine-3,5-dicarbonitriles A during the anodic oxidation of toluene [49].

“paired” processes to be designed where an oxidation occurs at both cathode and anode. In these processes oxygen is consumed and converted to water.

4.1. Formation of sulfones

Pairing the indirect cathodic and anodic oxidations of sulfides with tungstate/pertungstate and Os(VIII)/

Os(VI) redox mediators, respectively, a paired electro-synthesis of the corresponding sulfone was proposed [51] (Figure 18).

4.2. Formation of nitrones

The paired electro-synthesis of nitrones via the cathodic and anodic indirect oxidations of *N*-hydroxylamines was

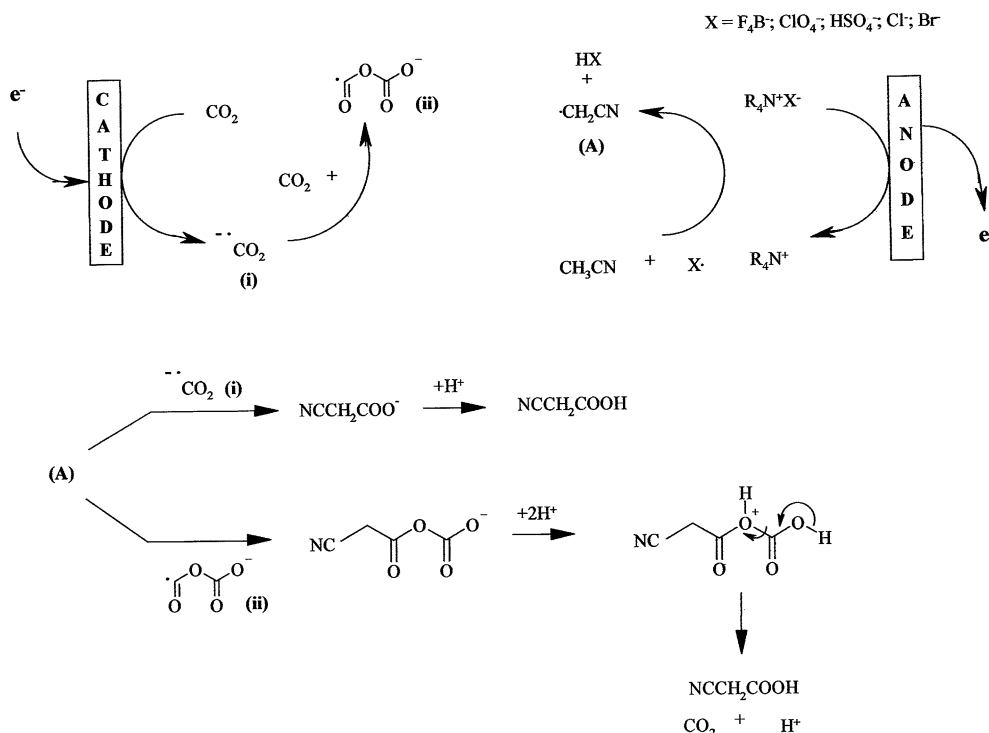


Fig. 17. Schematic presentation of the paired synthesis of cyanoacetic acid from CO₂ and acetonitrile [50].

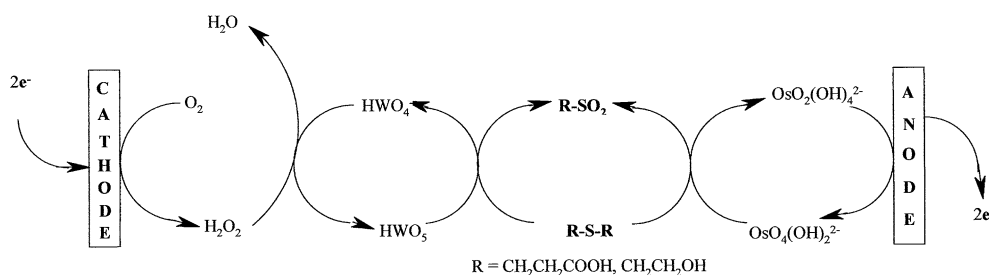


Fig. 18. Schematic presentation of the paired electro-synthesis of di(2-carboxyethyl)sulfone and di(2-hydroxyethyl)sulfone (R-SO₂-R) from the corresponding sulfides (R-S-R) [51].

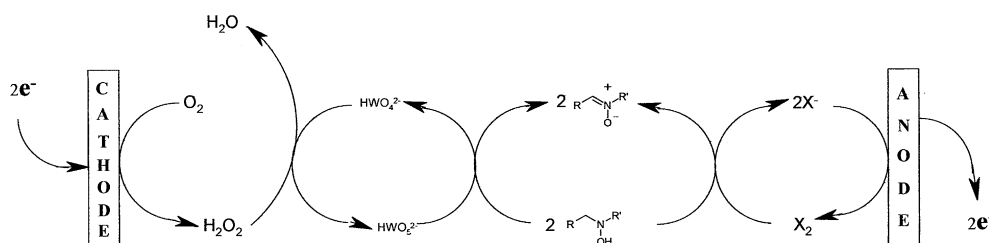


Fig. 19. Schematic presentation of the paired synthesis of nitrones from hydroxylamines with X = Br or I [51, 52].

also developed using a similar procedure to that for sulfones [51] (Figure 19). One advantage of this route is the replacement of the osmium mediator that was required in the production of sulfones. In this case, an anodic oxidation involving an X₂/X⁻ (X = Br, I) redox mediator was paired with the cathodic peroxide process.

4.3. Formation of aminoiminomethane-sulfonic acids

In further work by Nonaka and Chou et al. [51] the paired electro-synthesis of aminoiminomethane-sulfonic acids from the corresponding thioureas was investigated. The procedure is a mediator driven process

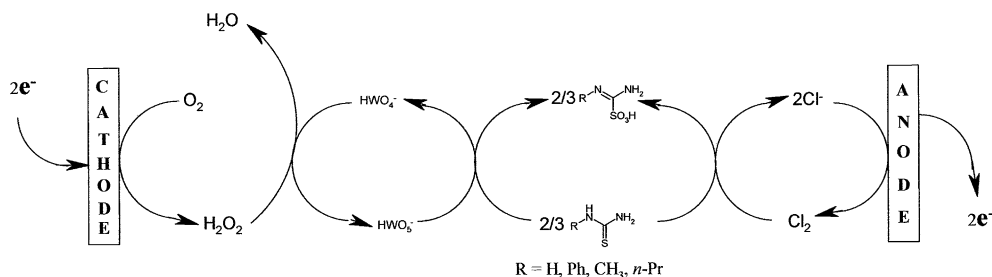


Fig. 20. Schematic presentation of the paired electro-synthesis of aminoiminomethane-sulfonic acid derivatives from thioureas [51, 53].

(Figure 20). It was reported that both the individual and total current efficiencies in the flow-type divided cell seemed to be a “little higher” than those in the H-type cell. It was suggested that this was due to the rapid promotion of the O₂ reduction at the cathode and rapid diffusion of Cl₂ into the anodic solution bulk in the former cell (Table 2).

4.4. Formation of epoxides and 1,2-dibromides

Nonaka and coworkers [54] have extended the electro-organic synthesis range with the development of a paired process for the simultaneous production of epoxides and 1,2-dibromides using concurrent cathodic and anodic oxidation processes (Figure 21). If desired, the dibromides may be further converted to the epoxides. A [VO(acac)₂] / [VO(acac)₂OOH] redox mediator was used for the cathodic oxidation of olefinic compounds to the corresponding epoxides. The oxidation process consists of a multi-step sequence involving (i) the cathodic reduction of dioxygen to hydrogen peroxide, (ii) the chemical oxidation of [VO(acac)₂] to [VO(acac)₂OOH] with the resulting hydrogen peroxide, (iii) the chemical epoxidation of olefins with [VO(acac)₂OOH], and (iv) the regeneration of [VO(acac)₂]. Simultaneously, the olefinic starting materials were indirectly oxidised (brominated) with a Br⁻/Br⁺ mediator to give the corresponding 1,2-dibromides.

4.5. Formation of arabinose

Chou and coworkers [51] have also proposed a convergent – paired electrooxidative method developed to synthesise D-arabinose using a mediator driven process and cathodic hydrogen peroxide generation (Figure 22).

4.6. Formation of 2,5-dimethoxy-2,5-dihydrofuran

An example of a convergent process in contrast to the earlier direct anodic methoxylation of furans [56] is an indirect multi-mediated system was employed (Figure 23). The formation of hydrogen peroxide is catalysed by using either a water-soluble cobalt porphyrin or an *N*-methylated phenanthroline dione (PDMe_{on}), which is cathodically reduced to the hydroquinone

(PDMe_{oi}). The hydroquinone generates hydrogen peroxide by reaction with oxygen from air. The hydrogen peroxide is then used to oxidise bromide to bromine. At the anode, bromide is directly oxidised to give bromine. Thus, at both electrodes bromine is formed as an oxidant, and it is this that is used in the formation of 2,5-dimethoxy-2,5-dihydrofuran from furan, regenerating the bromide. Hence, two electrodes generate two molecules of a two-electron oxidation product, formally a 200% – process [56].

5. Paired and self-supported electroorganic reactions in micro-flow reactors

5.1. The reduction of activated olefins with and without supporting electrolyte

Paddon et al. [12] reported the use of a simple thin layer flow cell geometry with working and auxiliary electrodes directly facing each other, allowing electro-synthetic processes to be conducted in flow-through mode. It was shown that at a sufficiently small cell height, the two diffusion layers of the working and auxiliary electrodes overlap (or “couple”). Initially experiments with the ferrocene/ferricinium redox system in organic solvents were employed to determine the degree of diffusion layer coupling. Increases in current due to the diffusion of ferrocene across the inter-electrode gap were shown to be flow rate dependent. The oxidation of ferrocene in ethanol was observed in the absence of supporting electrolyte.

The two-electron two-proton reduction of the activated olefin tetraethyl-ethylenetetracarboxylate to tetraethyl-ethantetracarboxylate was investigated (Figure 24). Experiments were conducted using nickel and platinum working electrodes and the former resulted in considerably better results. High product yields were obtained (approaching 90%) when the electrode length was increased and the volume flow rate decreased. Higher yields were obtained for low flow rates and the highest yield was obtained without intentionally added electrolyte. Under these conditions the olefin was dissolved in ethanol, passed through the cell, and the product isolated by evaporation of the solvent. Although the versatility of this hydrogenation

Table 2. Application of mediators in paired processes

Example	Product(s)	Starting material(s)	Current efficiency	Anode material/Reaction	Cathode material/Reaction
1. [51]	Sulfones	Sulfides	166% ^a	Platinum Os(VIII)/Os(VI) mediator	Graphite plate HWO ₄ /HWO ₅ mediator.
2. [51, 52]	Nitrones	<i>N</i> -Hydroxyl-amines	185% ^b	DSA (Dimensionally Stable Anode; RuO ₂ /Ti) Anodic oxidation with X ₂ /X ⁻ (X: Br, I) redox mediator.	Graphite Indirect oxidation with WO ₄ ⁻ /WO ₃ ⁻ mediator and H ₂ O ₂ formed via O ₂ reduction ^c .
3. [51, 53]	Aminoimino-methane – sulfonic acids	Thioureas	136% 142% ^d	DSA or platinum plate. Indirect oxidation using Cl ₂ /Cl ⁻ redox mediator.	Graphite plate. Indirect oxidation of thioureas with WO ₄ ⁻ /WO ₃ ⁻ mediator. Cathodic process driven by H ₂ O ₂ electrogeneration from O ₂ .
4. [54]	Epoxides and 1,2-dibromides	Olefins	~ 190% ^e	DSA Br ⁻ /Br ⁺ mediated indirect oxidation of olefins	Graphite [VO(acac) ₂]/[VO(acac) ₂ OOH] redox mediator for the indirect cathodic oxidation of olefins to form epoxides.
5. [55]	D-arabinose	Sodium gluconate (C ₆ H ₁₁ O ₇ Na)	88.37% ^f 39.12% ^f	Graphite Sodium gluconate oxidised via Fe ²⁺ /Fe ³⁺ and Cl ⁻ /ClO ⁻ mediators.	Graphite Fe ²⁺ /Fe ³⁺ and V ⁴⁺ /V ⁵⁺ mediators in addition to hydroxyl radicals indirectly oxidise sodium gluconate.
6. [56]	2,5-Dimethoxy-2,5-dihydro- furan	Fran, Methanol	185–190% current efficiency	Direct Oxidation of Br ⁻	Indirect oxidation of Br ⁻ via <i>N</i> -methylated phenanthroline and H ₂ O ₂ phenanthroline dione and H ₂ O ₂ exchanging membrane.

^aElectrolyses were carried out in a H-type and flow type (filter-press type) divided cells. Cathodic and anodic chambers separated with a NafionTM cation exchanging membrane.

^bElectrolysis performed in H-type divided and beaker-type undivided cells.

^cCathodic (indirect substrate) oxidations typically involve the following set of reactions: O₂ + 2e⁻ + 2H₂O → 2OH⁻ + H₂O₂ + 2OH⁻ → 2HO₂⁻ + H₂O/WO₃⁻ + Substrate → WO₄⁻ + Product.

^dMaximum current efficiencies reflect H-type divided and flow type divided cells, respectively.

^eElectrolyses performed galvanostatically in H-type cells with cathodic and anodic chambers separated with a NafionTM exchange membrane.

^fCurrent efficiencies represent D-arabinose production in anolyte and catholyte chambers, respectively. Total current efficiency: 127.49% (obtained using a divided cell).

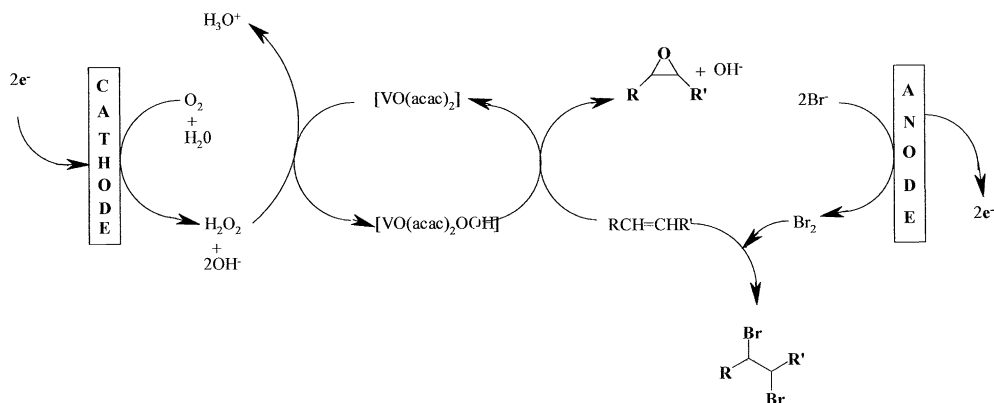


Fig. 21. Schematic presentation of the paired electrocatalysis of epoxides and 1,2-dibromides from olefinic starting materials [54].

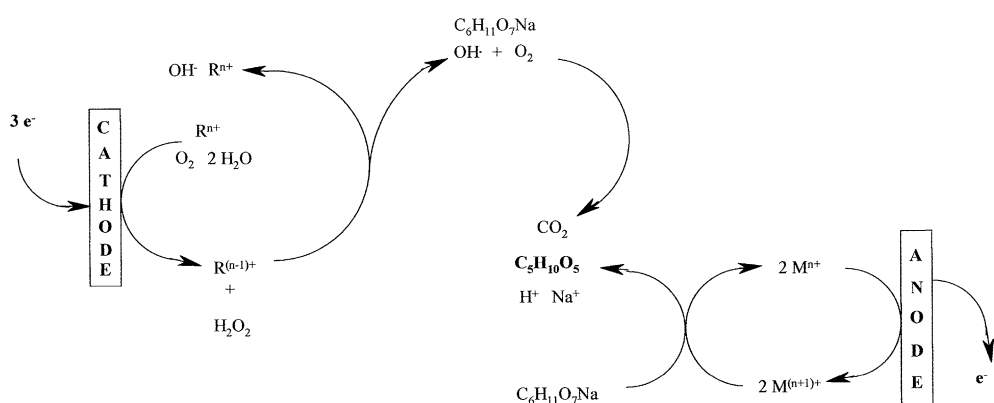


Fig. 22. Schematic presentation of the paired electrooxidation of gluconate to arabinose [55].

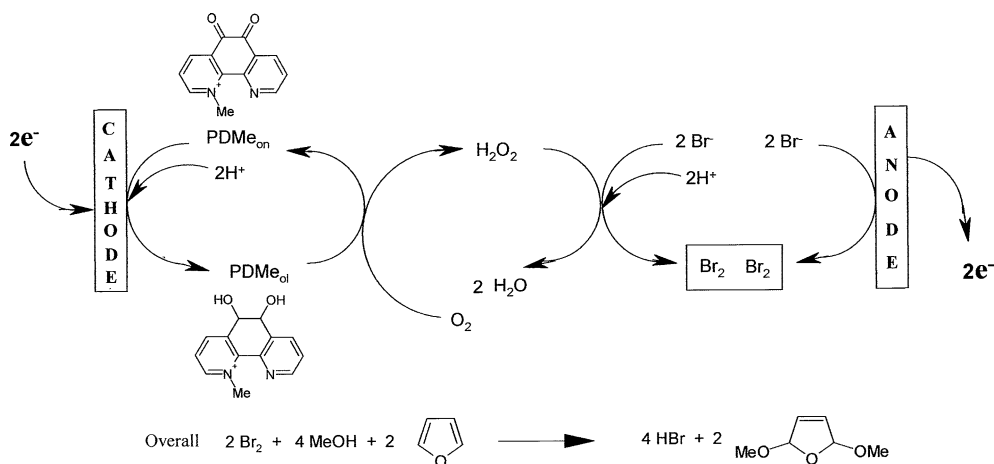


Fig. 23. Schematic presentation of the paired electrocatalysis producing two equivalents of bromine for the methoxylation of furan to 2,5-dimethoxy-2,5-dihydrofuran [56].

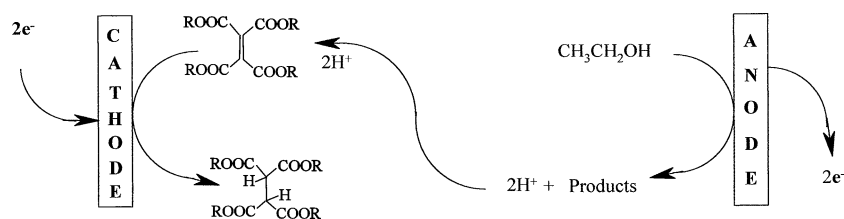


Fig. 24. Schematic presentation of the paired hydrogenation of activated olefins in ethanol in a nickel working electrode platinum counter electrode flow through cell in the absence of supporting electrolyte [12].

approach is currently limited (the olefin, tetraethyl-ethylenetetracarboxylate is known to undergo no side reactions during reduction) the process may be regarded as a proof-of-principle for high yield self-supported electro-synthesis.

5.2. Formation of benzyl methoxylation products with and without intentionally added supporting electrolyte

Yoshida and coworkers [28] have demonstrated the use of a micro-flow cell consisting of porous anode and cathode which are separated with a porous Teflon spacer (see Figure 25). The flow of reagent in this system is from the anode through the spaces and then through the cathode. The system was employed for the methoxylation of *p*-methoxytoluene, *N*-methoxycarbonylpyrrolidone, and acenaphthylene. For the oxidation of *p*-methoxytoluene in methanol the di-methoxylated product (see Figure 26) was isolated in ca. 70% yield. The design of the flow through reactor allowed process to be conducted in the absence of intentionally added

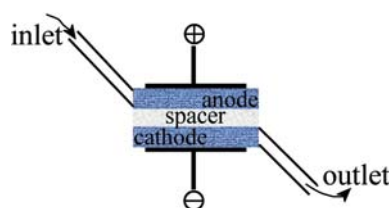


Fig. 25. Schematic drawing of a methoxylation microelectrolysis cell with inlet through a porous carbon electrode, a porous PTFE spacer, and an outlet through a porous carbon cathode [28].

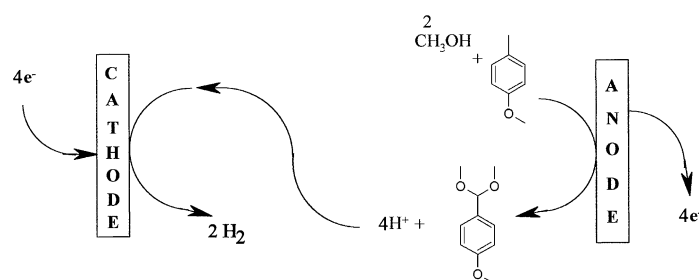


Fig. 26. Schematic presentation of the paired electro-synthetic methoxylation of methoxytoluene in the absence of intentionally added electrolyte [28].

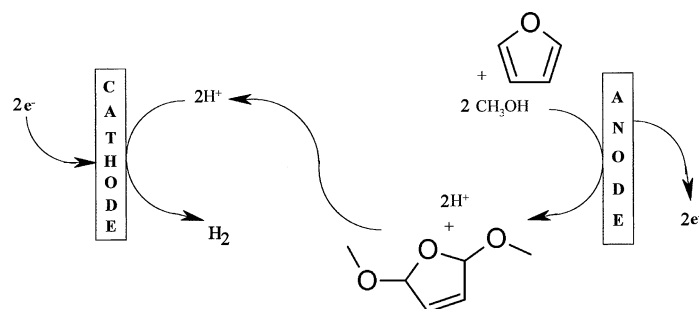


Fig. 27. Schematic presentation of the paired and coupled anodic methoxylation of furan in a micro flow cell [27].

electrolyte. Protons generated at the anode are likely to reduce the resistance in the inter-electrode gap. It was pointed out that the scale-up of this type of reactor system would be relatively easy and clean bulk electrolysis processes could be possible for a wider range of chemical systems.

5.3. Formation of furan methoxylation products with and without intentionally added supporting electrolyte

The methoxylation of furan [57] is conducted anodically in methanolic solution and can be readily conducted as a paired electrochemical process. In a micro-flow cell with a carbon anode and platinum cathode this process is also possible under coupled diffusion layer conditions. Horii et al. [27] have demonstrated that quantitative conversion of furan to 2,5-dimethoxy-2,5-dihydrofuran is possible even in the absence of added supporting electrolyte (Figure 27). An inter-electrode gap of 80 μm was employed and the flow rate optimised. The importance of the choice of electrode material was pointed out.

5.4. Formation of benzyl dimers with and without intentionally added supporting electrolyte

Ping He and coworkers [58] have demonstrated a further type of highly efficient and self-supported electro-synthetic reaction. A thin layer flow cell (see Figure 2b) was employed and the reduction of 4-nitrobenzylbromide in dimethylformamide (DMF) investigated. In this process reduction of 4-nitrobenzylbromide leads to the formation of a short lived radical anion intermediate which

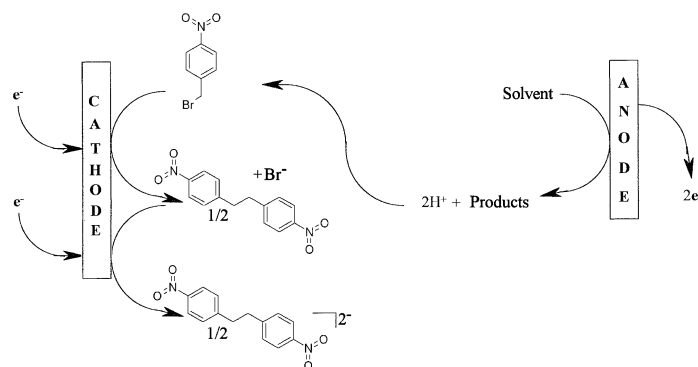


Fig. 28. Schematic presentation of the paired and coupled electrocatalysis of di-(4-nitrobenzyl) from 4-nitrobenzylbromide in DMF and in the absence of intentionally added supporting electrolyte [57].

undergoes C–Br bond cleavage. The resulting 4-nitrobenzyl radical rapidly dimerises in DMF solution and the resulting dimer is further reduced to the dimer dianion (see Figure 28).

Overall, this process produces side products due to the formation of bromide and due to the uncontrolled anode process. However, when optimised, excellent yields of the product di(4-nitrobenzyl) were obtained even in the absence of intentionally added electrolyte. The success of the process was explained based on a propagation mechanism in which the dimer dianion produced at the cathode is able to cause the reduction of two further 4-nitrobenzylbromide molecules which leads to the formation of a second dimer molecule in the solution phase without contact to the electrode. This process may be regarded as “paired” but “coupling” appears not to be essential. Next, processes are considered where “coupling” is essential.

6. Coupled paired electrochemical reactions

Although there are many “paired” electrochemical processes, it is very difficult to find examples for

“coupled” electrochemical processes. This is perhaps surprising given the importance and conceptually simple nature of this problem. It appears possible that both the complexity of coupled electrode processes and the lack of studies in this field are the main reasons for the absence of more published work. The development of micro-flow reactor system will stimulate further developments and possibly lead to entirely new chemical processes based on “coupled” and “paired” electrode processes. The following example indicates how a fundamental study (here with an array of microband electrodes) can help in identifying new processes and help optimising conditions for coupled electrode processes.

Amatore and Brown [59] describe the use of a pair of closely spaced microband electrodes, which for the reaction discussed below leads to the definition of a volume where the diffusion layers of the two electrodes overlap. The experimental set-up is effectively a ‘microreactor’ of only several femolitres volume, the bulk serving solely as a stream of reagents and products. They outlined the oxidation of anthracene coupled with the simultaneous reduction of dioxygen in acetonitrile to yield the anthracene radical cation and the superoxide anion (see Figure 29). The latter react quickly to form

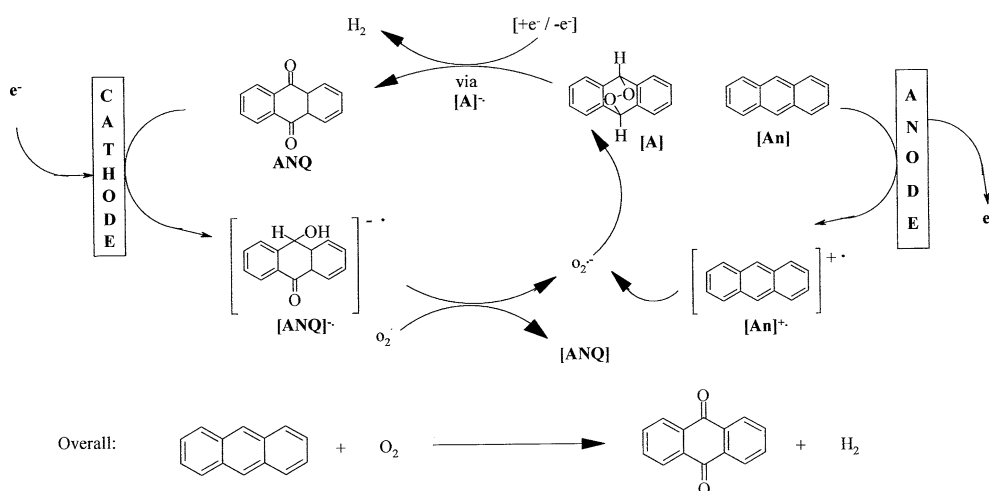


Fig. 29. Schematic presentation of the paired and coupled electrocatalysis of 9,10-anthracenedione from anthracene and oxygen [58].

initially 9,10-dihydro-9,10-epidioxyanthracene, which rearranges into the product 9,10-anthracenedione. The simultaneous formation of dihydrogen has been proposed.

The double band array used in the study was constructed using a 'sandwich' of window glass, platinum and gold foil, and a second layer of glass. The cell then consisted of a platinum anode and a gold cathode, each of 5 μm thickness, separated by 2.5 μm over a total length of 4 mm. Surprisingly high yields of approximately 90% were reported. The small dimensions of the femtolitre reactor allow reactive intermediates such as the superoxide anions to exist and to react within a defined reaction volume and timescale, which under conventional electrosynthesis conditions would not be possible.

7. Conclusion and future trends

There are many examples of "paired" electrochemical processes and the importance of pairing processes for clean electrosynthetic processes has been highlighted. In contrast, to date there are hardly any "coupled" electrode processes where the diffusion layer of anode and cathode overlap to give the desired product. There are clear benefits from coupling electrode processes such as the elimination of supporting electrolyte as a potential problem during product purification. In future, more chemical systems need to be studied under coupled diffusion layer conditions in order to identify useful processes and beneficial effects. A wider range of processes including C–C coupling, epoxidation, and protective group transformations will be possible under microflow conditions. In addition to one phase flow, two phase liquid–liquid flow systems may provide additional benefits. There will be novel electrosynthetic processes and novel chemistry under conditions where (i) the anode and the cathode are brought into close contact and (ii) electrodes are designed to allow only selective transformations to occur. In future, more work will be necessary and both new experimental and simulation tools will be required to extend the list of paired and coupled electrosynthetic processes for clean electrosynthetic transformations.

Acknowledgements

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