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ARTICLE

Organic Electrosynthesis: From Academia to Industry

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The growing impetus to develop greener and more cost-efficient synthetic methods has prompted Chemists to look for new ways to activate small organic molecules. Among them, electrosynthesis is one of the greenest and cheapest since it is possible to perform redox reactions without the need for any chemical reagents. Even though electrosynthesis is on the verge of a resurgence, it is far from being a new discipline. In fact, organic electrosynthesis was popularised by Manual Baizer in the early 60s while working at Monsanto. In this article, we will review the major, as well as the most recent, achievements in industrial organic electrosynthesis.

1. Introduction

The uptake of organic electrosynthesis in academic and industrial laboratories worldwide has increased substantially in recent years, owing to an ever-growing push towards more efficient, economical, and greener synthetic methods. With its rich and diverse history,^{1–3} it is perhaps surprising that the development of readily-accessible and standardised electrosynthesis equipment has only recently been realised, thus allowing it to become a useful tool for synthetic chemists. While it has been possible to improve upon previously reported methods, for example through an increase in yield, selectivity, or by reducing the amount of waste formed, the advent of new procedures that were previously impossible using conventional methodologies has also been achieved.^{4–6}

Organic electrosynthesis has been shown to exhibit a diverse range of applications including direct anodic conversion,⁷ methoxymethylation,^{8–11} chemoselective cathodic reduction,^{7,12} decarboxylative etherification,¹³ and catalytic hydrogenation.¹⁴ Indeed, some of these transformations have also shown promise at an industrial scale,^{15,16} which has helped demonstrate the green ideology of industrial electrosynthesis.¹⁷

Why is electrosynthesis a green methodology?

The majority of chemical syntheses within the manufacturing industry are conducted either under thermochemical conditions or utilise hetero- or homogeneous catalysts in order to overcome high activation barriers.¹⁸ These conditions are energy intensive, and the reagents used are often hazardous.^{17,18}

Organic electrosynthesis embodies the synthetic community's desire to move towards greener and more efficient methodologies, as it utilises the cheapest and most versatile redox agent available on the market; electricity itself. If

combined with a green source of energy (e.g. solar or wind power) then the possibility of a carbon-neutral chemical manufacturing process becomes reality.¹⁷

In addition to this, the flexibility of electrons as redox agents can reduce or even eliminate our reliance on standard, often toxic and environmentally harmful metal-derived oxidising agents such as osmium(VIII) oxide, samarium(II) iodide, and lead(IV) acetate.¹⁷ While metal electrodes, such as platinum, are often used (as discussed later in Section 4), their ability to be removed intact at the end of the synthesis reduces the need for subsequent purification in order to remove metal-containing compounds which often form under conventional reaction conditions (e.g. palladium nanoparticles from cross-coupling reactions).¹⁷ However, it should be noted that under some conditions, this is not always the case due to electrode decomposition, thereby resulting in the need for subsequent purification.¹⁹

Review scope

Currently, the field of organic electrosynthesis is experiencing renewed interest within both the academic and industrial communities as they strive to use more efficient and environmentally friendly methodologies. As a result, several reviews have been published discussing the various aspects of the field within either an academic or an industrial setting.^{7,15,17,20}

This work provides an inclusive review of the two main branches of organic electrosynthesis, in addition to a summary of the commonly encountered methods and experimental setups. The environmental advantages of electrosynthesis, and the use of electrosynthesis in academic and industrial settings will also be explored. Key examples demonstrating the versatility of electrosynthesis towards the large-scale synthesis of commodity chemicals will be presented, alongside the obstacles encountered upon scale-up.

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2. Organic electrosynthesis

Basic principles

The electrosynthesis of organic compounds can be achieved by either the addition or removal of electrons from a compound, which forms a reactive intermediate, which can then go on to form the desired product via numerous available pathways (Figure 1).^{17,21} At an anode, oxidation occurs, resulting in the removal of one or more electrons from the HOMO, forming a radical cation ($R^{+\bullet}$), whereas at a cathode, reduction results in the addition of electrons into the LUMO, forming a radical anion ($R^{-\bullet}$).

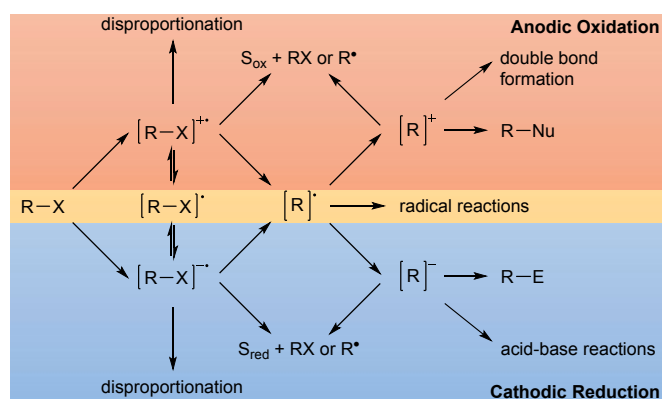


Figure 1. Possible pathways for reactivity after a single-electron transfer. X = leaving group²¹

The interaction between the electrode and reactant can be direct or mediated by redox species. In the first case the electrolysis is defined *direct*, while in the other it is defined as *indirect*.

Direct Electrosynthesis

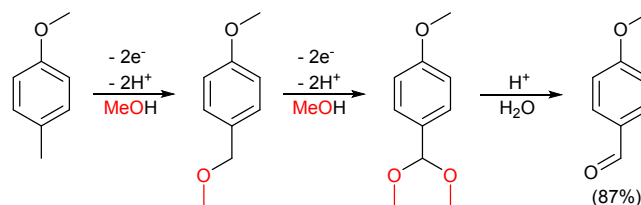
As the name suggests, direct electrosynthesis arises from direct electron transfer between the electrode and compound in solution.⁷ These processes can be separated into two categories, namely those occurring at the anode (oxidation), and those occurring at the cathode (reduction).

It is important to note that when an electrochemical reaction takes place at one electrode, another must occur at the opposite electrode in order to balance the overall charge. If designed correctly, this offers the opportunity to “pair” two processes, thus reducing time and energy consumption, and allows the generation of two desired products within one setup, which can either be isolated separately, or allowed to react with one another.¹⁷

Reactivity at the Anode

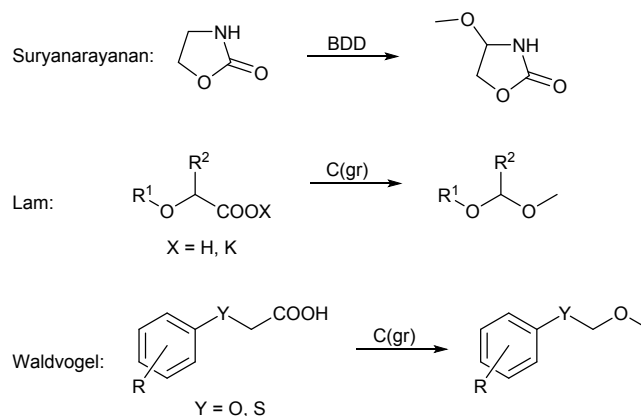
Numerous reactions can occur at the anode, the most common of which are direct oxidation, addition, substitution, and cleavage.^{7,17}

The best-known example of direct oxidation in an industrial setting is the anodic conversion of *p*-methoxytoluene into *p*-anisaldehyde by BASF (Scheme 1).⁷ This synthetic route relies upon the observation that toluene derivatives often undergo anodic acetalisation in methanol to form dimethylacetal intermediates, which can be hydrolysed to afford the corresponding aldehyde.



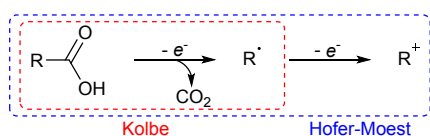
Scheme 1. The industrial electrochemical synthesis of *p*-anisaldehyde, from *p*-methoxytoluene. Conditions: bipolar graphite rings, 4–6 V, 3–5 A dm², 40–50 °C, MeOH

Though not currently used industrially, electrochemistry has shown significant promise as a method for the methoxymethylation of organic compounds.^{8,10,11} Existing routes rely on the use of toxic MOM-Cl or formaldehyde dimethyl acetal,¹⁰ however, Suryanarayanan and co-workers have shown that methoxymethyl ether functionality can be introduced into 2-oxazolidinones by means of anodic oxidation using either boron doped diamond (BDD) or carbon graphite (C_{gr}) electrodes (Scheme 2).²² This has been further complimented by work by both Waldvogel¹¹ and Lam^{8,10} who have further demonstrated the ability to introduce MOM-ether functionality into organic systems using green reagents under ambient conditions, the latter of which further showed how common problems such as the overoxidation of aromatic derivatives could be overcome through the use of flow-electrochemistry.⁸



Scheme 2. Recently reported electrochemical methoxymethylation protocols. Conditions: BDD/stainless steel, 50 mA cm⁻², H₂SO₄/MeOH (0.1 M) (top); C(gr)/C(gr), 5 mA cm⁻², MeOH (middle); C(gr)/C(gr), 20 mA cm⁻², MeOH (bottom)

The use of carboxylates in electrochemistry is well established.² Indeed, their one-electron oxidation typically results in decarboxylation to give the corresponding alkyl radical, R^\bullet , which subsequently dimerises to afford the R-R homo-dimer. This reaction is known as the Kolbe reaction. It is also possible, when using sufficiently porous electrodes (e.g. carbon graphite) to undergo a two-electron oxidation, resulting in the oxidation of the previously formed alkyl radical to the corresponding carbocation, R^+ . This reaction is known as the Hofer-Moest reaction (Scheme 3).^{23–26} Indeed, these conditions have proven useful for the synthesis of homo- and hetero-dimers alongside, more recently, phthalides,²⁷ γ -butyrolactones,²⁸ and previously inaccessible hindered alkyl ethers in high yields.¹³

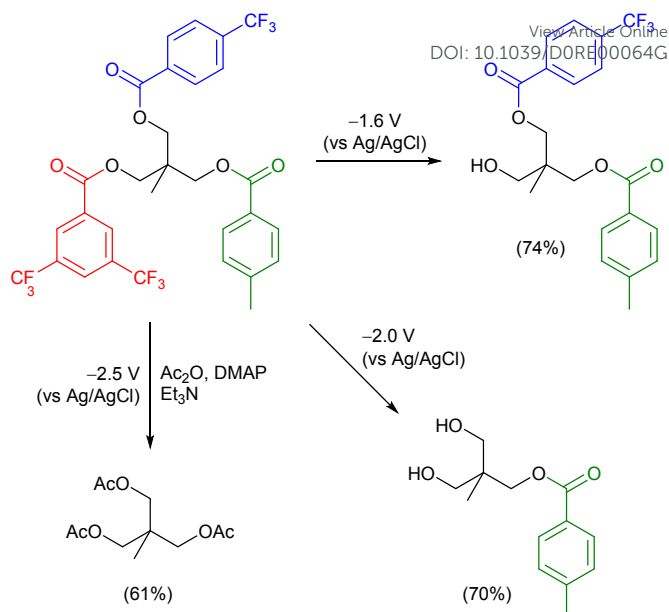


Scheme 3. General scheme demonstrating electrochemical decarboxylation and the products afforded under Kolbe (single electron transfer) and Hofer-Moest (multiple electron transfer) conditions.

Reactivity at the Cathode

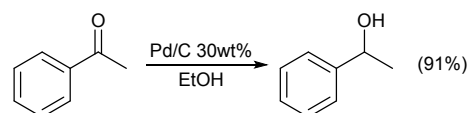
Similarly, many organic compounds can be converted into desirable products through reactions at the cathode, the most common of which is the reductive cleavage of R-X bonds (where X is an electroactive leaving group).⁷ This reaction typically results in the formation of an anion, X^- , and a radical, R^\bullet , which can either undergo reactivity or be further reduced to afford the corresponding carbanion, R^- .

The use of these electro-cleavage reactions is varied amongst the synthetic community.⁷ Significantly, Markó and co-workers have demonstrated that through subtle modification of the electroactive leaving group, it is possible to chemoselectively cleave different groups within the same molecule through control of the applied potential, a phenomenon aptly named “electrochemoselectivity” (Scheme 4).¹²



Scheme 4. Chemoselective deprotection of an alcohol under electrochemical conditions. Conditions: C(gr)/C(gr), NBu_4BF_4 /NMP-iPrOH (93:7)

If traces of water or alcohol are present in an electrochemical cell, reduction at the cathode can occur, resulting in the formation of hydrogen gas. Recently, it has been shown that this hydrogen can be utilised for the electrochemical hydrogenation of organic compounds under mild conditions.¹⁴ Sáez and co-workers have shown that, in an electrochemical cell containing Pd/C 30 wt% in ethanol, the hydrogenation of acetophenone can be achieved with relatively low current densities (10 mA cm^{-2}) via a two electron reduction (Scheme 5).¹⁴

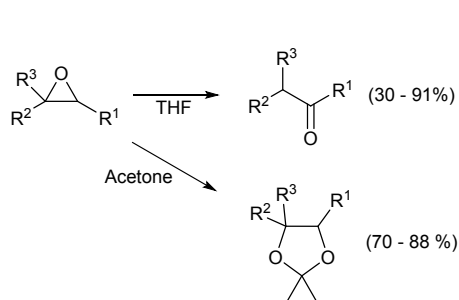


Scheme 5. Electrochemical hydrogenation of acetophenone.

Electrogenerated Reagents

It is possible to generate a plethora of reagents *in-situ* using electrochemistry using either the anode or the cathode. The most commonly encountered electrogenerated species are acids, bases, and superoxide.¹⁷

In most electrochemical setups, trace amounts of water in the reaction medium are oxidised at the anode to form an acidic environment, which can be used to catalyse reactions that occur near the electrode surface.¹⁷ The acidity of the medium can be controlled through careful selection of the solvent and supporting electrolyte used for the electrolyses, with one of the most acidic systems arising from a DCM/LiClO₄ mixture.²⁹ This system has been shown to be very effective at converting epoxides into ketones and acetones using a low amounts of charge ($<1 \text{ F mol}^{-1}$; Scheme 6).³⁰

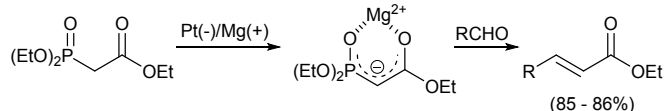


Scheme 6. Electrochemical conversion of epoxides into ketones (A) and acetonides (B). Conditions: Pt foil/Pt foil, 10 mA cm⁻²

Similarly, bases such as anions or anionic radicals can be generated at the cathode from so-called pro-bases, which can then be used either for deprotonation or to initiate base-catalysed reactions.³¹⁻³⁴ The key advantage of these bases is that they can be generated *in-situ* in aprotic solvents, thus avoiding the need to handle corrosive or potentially unstable bases. However, unlike electrogenerated acids, the requirements for the effective generation of base are somewhat more demanding, namely:¹⁷

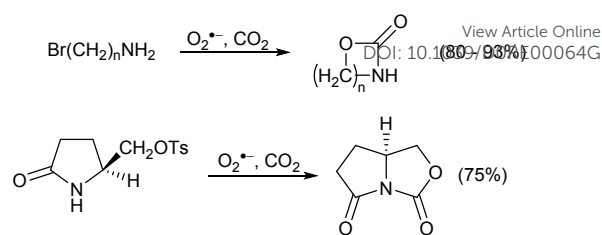
- 1) The reduction potential of the pro-base must be less negative than the other components of the solution,
- 2) The electrogenerated base must be of low nucleophilicity and a weak reducing agent.

Moreover, either a divided cell (see Section 4) or a sacrificial anode must be used if anionic products are to be isolated.¹⁷ The utility of these bases was exemplified by Frontana-Urbe and co-workers, who demonstrated the electro-reduction of triethyl phosphonoacetate in the presence of aldehydes, resulting in the synthesis of a variety of unsaturated esters via an anionic intermediate (Scheme 7).³⁵



Scheme 7. Synthesis of unsaturated esters via an anionic intermediate using a sacrificial magnesium anode. Conditions: Pt gauze/Mg rod, Et₄NBF₄/DMF (0.03 M), 2 mA cm⁻², N₂ atmosphere

Electrogenerated superoxide (O₂⁻) can also be used synthetically as a base, though it can also be used as a reducing agent or nucleophile.³⁶ The latter is best exemplified upon its generation in the presence of carbon dioxide, resulting in the formation of peroxodicarbonate, C₂O₆²⁻. Indeed, this represents a viable method of carbon capture, as the carbon dioxide can be used as a carbon feedstock for other synthetic processes, as evidenced by Moracci and Inesi through the conversion of primary and secondary amines into carbamides using electrochemically synthesised peroxodicarbonate (Scheme 8).³⁷



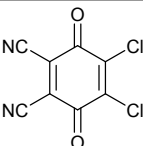
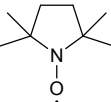
Scheme 8. Electrochemical generation and reactivity of superoxide, resulting in the formation of carbamides from primary and secondary amines. Conditions: -1.0 V vs SCE, Hg pool (cathode), Pt gauze (anode), TEAP/MeCN (0.1 M), CO₂(g) & O₂(g)³⁸

Indirect Electrosynthesis

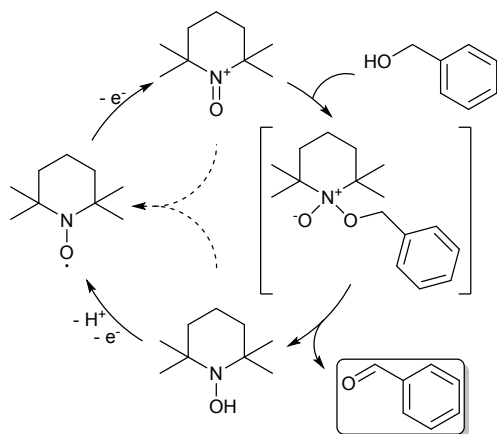
Indirect electrosynthesis requires the use of an *in-situ* generated redox catalyst, also known as a mediator or electron carrier, through which the electron transfer can occur.⁷ Several anodic reactions have been carried out using a variety of mediators, such as 2,2,6,6-tetramethylpiperidiny-1-oxyl (TEMPO) derivatives, hypervalent iodine reagents, and even ferrocene.³⁹⁻⁴³ However, in industrial processes, halide salts are typically favoured over these due to their ease of use, and the ability to easily extract them from reaction mixtures.⁷ Extensive reviews of the use of redox catalysts can be found in the literature,^{43,44} and a summary of the most commonly-encountered redox catalysts can be found in Table 1.

Table 1. Commonly encountered redox catalysts and their associated potentials vs (a) SHE; (b) Ag/AgNO₃; (c) Fc/Fc⁺

Mediator	E / V	Ref.
	0.28 ^a	45
	-0.15 ^a	46
	0.027 ^a	47
	-0.48 ^a	48
	0.52 ^a	49
	0.88 ^b	50
	1.32 ^b	51

	0.40 ^b	52
	0.25 ^c	53

Usually, these mediators are regenerated in-situ, thus allowing reactions to occur electrocatalytically, such as the oxidation of benzyl alcohol to benzaldehyde under basic conditions (Scheme 9).⁵⁴



Scheme 9. Indirect electrochemical synthesis of benzaldehyde from benzyl alcohol using TEMPO as a mediator.

In contrast, limited progress has been made regarding the synthesis and use of mediators for cathodic reductions, however, some examples such as the catalytic reduction of CFCs and dihalides are known.^{55,56}

3. Control of the electrochemical process

In electrosynthesis, factors such as temperature, pressure, solvent, current density, current efficiency, and redox potential decide the fate of the reaction. These are summarised in Table 2.

Table 2. Summary of factors taken into consideration during electrochemical reaction design.

Factors	Options		
Method	Galvanostatic	Potentiostatic	
Solvent	Aqueous		Organic
Additives	Supporting electrolyte	Liquid ions	No additives
Reaction Conditions	Mild		

There are two main operational modes to perform electrolytic conversions, potentiostatic (constant voltage) and galvanostatic (constant current). Potentiostatic electrolysis typically results in

more selective reactions, since the electrolysis potential matches that of the substrate, however, the need for a more costly three-electrode arrangement makes it more costly, and therefore it is not always suitable for larger-scale cells.⁵⁷

Electrolyses conducted in galvanostatic mode are technically simple, since they only require an inexpensive two-electrode setup.⁵⁷ However, in order to reduce the formation of side products, a clear difference of potential between the desired and undesired products is required. Despite this, galvanostatic mode is the most utilised within an industrial setting, both in batch- and flow-chemistry techniques.

Current density, which describes the concentration of reactive intermediates formed and determines the reaction pathway, represents another key parameter which must be carefully considered.⁵⁷ Generally, low current densities favour the intended electro-organic reaction, while a higher current density may be economically advantageous, as it increases the rate of electrolysis, thus facilitating a higher synthetic throughput.⁵⁷

The current efficiency, the fraction of transferred charge consumed to generate a specific product, is another decisive factor that must be taken into account when designing industrial electrosynthesis equipment.³ Through careful regulation the current efficiency, greater control of the charge consumption and therefore of the degree of transformation is possible.

As with most chemical reactions, the outcome of an electrolytic process is highly dependent on the nature of the solvent. In particular, its conductivity is crucial to ensure an efficient charge transport throughout the solution. At first glance, water may be regarded as the best and greenest candidate, however, its use is limited by the low solubility of organic reactants and the presence of multiple reaction pathways that lead to undesired by-products.

Electron transfer in organic media is challenging but not impossible. The use of methanol, acetic acid, dioxane/water and even DMF, as well as aprotic solvents (e.g. acetonitrile, dimethylformamide, propylene carbonate) is well described in literature.¹⁷ In cases of negligible conductivity of the medium, as often encountered with organic solvents, the use of a supporting electrolyte becomes essential.³ Quaternary ammonium or alkaline-metal cations in combination with weakly coordinating anions (e.g. hexafluorophosphate, *closo*-borate derivatives, perchlorate, etc) represent the most common example of supporting electrolyte. However, the need to separate them after electrolysis, their relative cost, and their incompatibility with modern wastewater treatments tends to limit their uptake within an industrial setting.¹⁵ Recently, these issues have been circumvented through the advent of room temperature ionic liquids (RTIL or IL).^{58,59} Ionic liquids are organic salts that exist in a liquid form at room temperature. Their high ionic conductivity, low-volatility, low flammability,

and high recyclability make them ideal candidates for industrial electrochemistry.¹⁷

Nevertheless, some limitations still remain, such as their associated risks of ecological harm when improperly disposed of, their high synthesis costs, and their low diffusion coefficients, the latter of which necessitates the use of large and therefore expensive electrode areas.²⁰ Other possible approaches such as solid polymer electrolyte technology (SPE),¹⁸ electrochemical microreactors (ECMRs)⁵⁷ and microemulsions (μE)¹⁷ are currently under scrutiny both academically and commercially.

In common chemical transformations, high temperatures and pressures may be required. Electrochemical processes typically take place under mild conditions, thus proving to be a cheaper, greener and safer alternatives to classical synthetic methodologies. In some circumstances increasing the temperature at an industrial level may be required to speed up the reaction or decrease the viscosity of the medium and therefore enhance the mass transport rates, which is easily achieved through the use of modified reactors.¹⁵

4. Cell design in electrosynthesis

An electrolysis cell, either on a laboratory scale or industrial scale can, for all intents and purposes, be considered as a chemical reactor.¹⁵ Table 3 summarizes some of the decisions that must be made in the process of cell design.

Table 3. Summary of the differences between typical undivided and divided industrial electrochemical setups

	Cell Design	
	Undivided	Divided
Operation Mode	Batch or Continuous	
Pair of Electrodes	Single	Multiple
Electrode Material	Noble metals, carbon, steel, nickel	
Electrode Connection	Monopolar	Bipolar
Electrode Geometry	2D	3D
Electrode Movement	Static	Dynamic
Interelectrode Gap	Narrow	Capillary

In some instances, the success of an electrolysis may be hindered by an unavoidable reaction at the counter electrode resulting in, for example, a drastic drop in yield or contamination of the desired product. Consequently, the type of electrochemical cell used for the reaction must be considered.

A divided cell with two distinct compartments is commonly used to overcome this limitation. For laboratory scale applications, a simple divided H-cell is employed (Figure 2, A), where porous materials such as a sintered-glass frit or ion-exchange membrane are used to separate the two compartments.¹⁷ These membranes are characterized by a functionalised polymer backbone which selectively transports either cations (CEMs, cation exchange membranes) or anions (AEMs, anion exchange membranes), and reduces charge transport resistance. Perfluorinated sulfonic acid membranes (Nafion®) are among the most frequently employed CEMs followed by other sulfonated polymers such as styrenes, polyimides, and arylene ethers, although with less remarkable performances.

On the other hand, polyketones, poly(arylene)s or polyolefins linked to alkyltrimethylammonium, cyclic ammonium, multi-substituted imidazolium, cobaltocenium, and tetrakisaminophosphonium cations are considered to be the most common AEMs.⁶⁰

Using a divided cell gives users a more independent choice of anode/anolyte or cathode/catholyte while maintain current efficiency, helping to isolate electrode products, and preventing the formation of explosive or toxic mixtures (e.g. H_2/O_2 or H_2/Cl_2).¹⁵ Despite these advantages, divided cells lead to additional costs, additional seals and possible maintenance problems. In particular, both CEMs and AEMs seem to suffer from degradation when exposed to organic molecules, resulting in significant losses in ion conductivity.⁶¹ This limitation represents the main challenge in the design of divided systems in the upcoming years.

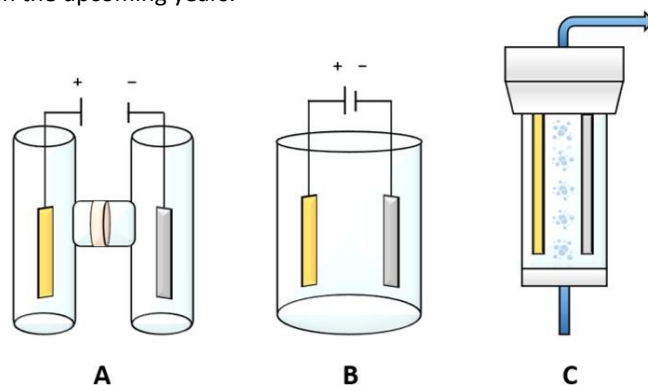


Figure 2. Schematic of an undivided cell (A), divided cell (B), and undivided flow-cell (C)

For this reason, undivided cells are generally preferred and more widely used. In the “undivided” configuration (Figure 2, B) the anolyte and catholyte are held within the same compartment without any physical barrier between them.⁵⁷ This type of cell has cost benefits, not only due to its simpler design but also because of its lower internal resistance and longer lifetime.

Most recently, a third type of cell (Figure 2, C), the flow-through cell,³ has become popular in both academic and industrial

laboratories. Electrosynthesis in flow cells is usually associated with large scale operations, since scale-up can be achieved with ease by increasing the number of flow electrolyzing devices. On the one hand, using flow cells for electro-conversion usually requires more electrical equipment (e.g. pumps, or bespoke flow setups), thus increasing setup costs, however, continuous synthesis under well-defined and standardised conditions can be easily achieved. In comparison with classical flask/batch chemistry, flow chemistry offers the possibility of reducing amounts of solvents and substrates, thus reducing reagent costs and the quantity of waste produced, alongside straightforward control of possible gas evolution, and simplification of the optimisation process.

The operation mode must also be taken into consideration during electrolysis. It is possible to operate under batch conditions, where the electrolysis cell is charged with reactants, ideally without any gradient of concentration (though use of a back-mix reactor, or stirred-tank reactor),¹⁵ which are left to react for a certain period before the resulting mixture is worked-up to extract the product. The great advantage of this design is the simplicity of construction and the wide range of materials that can be used. It is, however, limited in terms of space-time yield (due to the physically large footprint of the reactors) and is not suitable when mass transfer control is necessary.

Alternatively, it is possible to operate in continuous flow (e.g. a plug-flow reactor) by feeding a continuous stream into the electrolytic cell that circulates for a certain time and then exits before total conversion.³ In this case the reaction is completed after a determinate number of cycles.

Another important differentiation among cell designs relies in the type of electrode used. Ideal electrode materials require an adequate electronic conductivity, corrosion stability, and a selective electrocatalytic activity that promotes the desired reaction while, at the same time, discouraging undesired reactions. On a laboratory scale, platinum or thin layers of noble metals on a less expensive carrier (such as copper, or titanium) are typically used for single-electron transformations whilst carbon (graphite, glassy, etc), due to its higher surface area and increased porosity which promotes substrate adsorption, is used for multiple-electron transfers.³

Due to its inexpensiveness and availability, carbon is widely used in industrial organic electrolyses, mostly as an anode. Common inexpensive alternatives to carbon are represented by nickel or titanium. Other exotic alternatives to carbon are also used such as conductive ceramics like Ebonex,³ which is known for its resistance to corrosion and high overpotentials or more recently, boron doped diamond (BDD). For the cathode, steel, stainless steel, and nickel tend to be the most suitable and highly used candidates in electrochemical industries.

Especially on large scale reactions, it is common to find multiple cathodes and anodes in the same cell. Depending on the

electrical connection, the cell may be monopolar (Figure 2, A), if the voltage is applied between each cathode and anode, or bipolar (Figure 2, B), if there are only two external electrical contacts at the two end electrodes.¹⁵ The bipolar cell, in addition to the simplicity of electrical connection, has the advantage of requiring less power to produce the equivalent amount of product of monopolar cells. However, in bipolar cells another problem may arise, known as the electrical leakage current, which is an additional current between electrodes in neighbouring cells that causes loss in current efficiency and corrosion.¹⁵

The plate and frame and parallel-plate geometry with the two-dimensional electrodes in horizontal or, more commonly, vertical position are the most popular configurations in industrial setups.¹⁵ Electrode movement (rotating electrodes) may enhance mass transport or facilitate the mixing of reactants, albeit with additional maintenance needs.¹⁵ The option of rotating the electrode has led to well characterized cell designs such as the pump cell and the rotating cylinder, both of which are commonly used in industry. Three dimensional porous electrodes provide higher areas of reaction, and so they enhance mass transfer and improve gas disengagement but may lead to problems of potential and current distribution.

Finally, the inter-electrode gap must be considered. Narrow-gap or even capillary-gap (1 mm) and thin electrolyte films are particularly necessary in the processing of poorly conductive electrolytes. The need to maintain a uniform capillary gap over large electrodes or multiple electrode stacks, however, requires precise engineering, particularly in the case of rotating electrodes or divided cells. In the energy-intensive processes, such as chlor-alkali production and water electrolysis, the trend is towards the so-called zero gap cells where the electrodes contact the membrane.

It is evident that there are benefits and drawbacks for every possible variable and thus, depending on the reaction of interest, a good compromise between all of these parameters must be found.

5. Industrial electrosynthesis

In 1988 some semiquantitative success criteria for electrochemical process parameters were described by D. Degner,⁶² but in 1990s these conditions became much stricter and have since become even tougher. The conditions for the successful realisation of an electrochemical process differ greatly depending on the product capacity.^{3,63} Not to be forgotten, the uptake of electrosynthesis in an industrial setting is also dependent on four key factors: high levels of safety, high quality and reliability, high selectivity and yield, and low energy and atom consumption. If one of these key principles is not met, the likelihood of adoption of the process is practically zero. A summary of the various commercial and pilot electrochemical processes currently used within the chemical industry can be found in Table 4.⁷ One of the most famous electrochemical

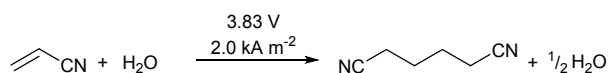
process is the synthesis of adiponitrile (Figure 3).^{64,65} Adiponitrile is used to make polyamides such as nylon-6,6. Mosanto's Baizer process currently affords over 300,000 tons per year worldwide *via* a cathodic hydrocoupling with the use of water and release of oxygen.⁶³ However, the process is still under investigations for further optimisation.^{1661039/D0RE00064G}

Table 4. A summary of current industrial electrochemical syntheses. Modified with permission from Table 2 in Sequeira, C and Santos, D, Electrochemical Routes for Industrial Synthesis, *J. Braz. Chem. Soc.*²⁰

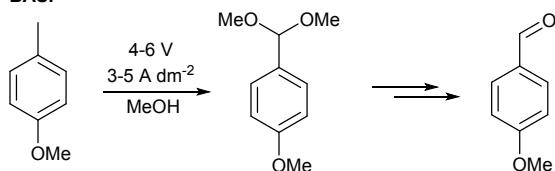
Product	Raw Material	Company
Acetoin	Butanone	BASF
Acetylenedicarboxylic acid	1,4-Butynediol	BASF
Adipoin dimethyl acetal	Cyclohexanone	BASF
Adiponitrile	Acrylonitrile	BASF, Monsanto
4-Aminomethylpyridine	4-Cyanopyridine	Reilly Tar
Anthraquinone	Anthracene	L. B. Holliday, ECRC
Azobenzene	Nitrobenzene	Johnson Matthey Co.
Bleached montan wax	Raw montan wax	Clariant
Calcium gluconate	Glucose	Sandoz, India
Calcium lactobionate	Lactose	Sandoz, India
S-Carbomethoxy methylcysteine	Cysteine + chloroacetic acid	Spain
L-Cysteine	L-Cystine	Wacker Chemie AG
Diacetone-2-ketogulonic acid	Diacetone-L-sorbose	Hoffman- La Roche
Dialdehyde starch	Starch	CECRI
1,4-Dihydronaphthalene	Naphthalene	Clariant
2,5-Dimethoxy- 2,5-dihydrofuran	Furan	BASF
2,5-Dimethoxy-2,5-dihydrofuryl-1-ethanol	Furfuryl-1-ethanol	Otsuka
Dimethylsebacate	Monomethyladipate	Asahi Chemical
Gluconic acid	Glucose	Sandoz, India
Hexafluoropropylene oxide	Hexafluoropropylene	Clariant
m-Hydroxybenzyl alcohol	m-Hydroxybenzoic acid	Otsuka
p-Anisaldehyde	p-Methoxytoluene	BASF
Perfluorinated hydrocarbons	Alkyl substrates	3M, Bayer, Clariant
Polysilanes	Chlorosilanes	Osaka Gas
Salicylic aldehyde	o-Hydroxybenzoic acid	India
Succinic acid	Maleic acid	CERCI, India
3,4,5-Trimethoxy benzaldehyde	3,4,5-Trimethoxy toluene	Otsuka Chemical
3,4,5-Trimethoxytolyl alcohol	3,4,5-Trimethoxy toluene	Otsuka Chemical

The anodic methoxylation of substituted toluenes is a well-developed topic (Figure 3). Currently, BASF is producing over 10,000 tons per year of *p*-tolualdehyde, which is used as a building block for the synthesis of the fragrance lysmeral.¹⁵ BASF is more well-known for their large-scale synthesis of *p*-anisaldehyde. The anodic methoxylation of *p*-methoxytoluene has been achieved using a capillary gap cell since the 1960s, with over 3,500 tons produced per year.⁶³ More elegantly, this compound is also produced in paired electrolysis, where a cathodic hydrogenation of dimethyl phthalate is associated with the anodic methoxylation of the *p*-toluene.⁶⁷ This process allows BASF to synthesise 4000 tons per year of each product. Additionally, other substituted toluene derivatives have undergone anodic methoxylation at Otsuka, BASF, and Hydro Quebec, affording over 1,000 tons per year.

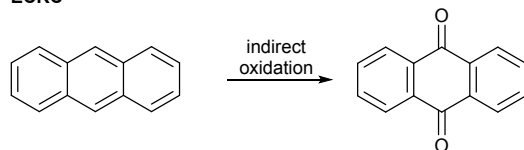
Baizer Process



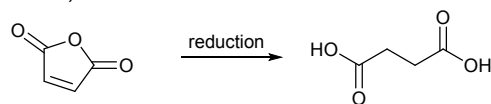
BASF



ECRC



CERCI, India



Otsuka

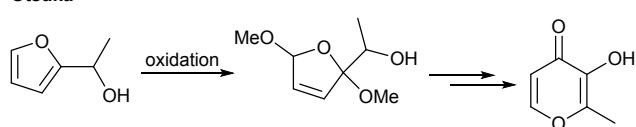


Figure 3. Summary of established industrial electrochemical syntheses

A similar process has been utilised by ECRC and Hydro Quebec to facilitate the transformation of anthracene (Figure 3) or a naphthalene/butadiene mixture respectively into anthraquinone, with ECRC reporting the production of over 1000 tons per annum.⁶³

Among other processes, the electrochemical production of succinic acid has facilitated its wide applications in the food, cosmetics, and drug industries, in addition to its use as a raw material for synthesis. The electroreduction of maleic anhydride has been undertaken for at least 80 years, leading to the synthesis of over 30 tons per year by CERCI (Figure 3).⁶³ It is a

preferred method compared to the commonly used fermentation processes, as the electroreduction is the greener option since, for every ton of succinic acid synthesised using the fermentation method, 10 tons of waste water are produced. Remarkably, the reactor used also facilitates the production of succinic acid as part of a paired electrolysis, with the iodide ions oxidised at the anode.⁶⁸

Furthermore, anodic methoxylation is used by Otsuka in the production of the flavour enhancer maltol, with 150 tons produced per annum. The oxidation of 2-hydroxy-ethylfuran provides an intermediate which undergoes a rearrangement to provide the desired maltol (Figure 3).¹⁵

Carbon dioxide as a raw material in electrochemistry

In 2019, it was shown that industrial electroreduction of CO₂ conjointly used with other biotechnologies is an area of prolific interest in Europe, with several companies investigating its use to synthesise commodity chemicals such as formic acid, lactate, acetone and alcohols.^{69,70} The electrochemical reduction of CO₂ into synthesised commodity chemicals represents a powerful and environmentally friendly challenge.⁶⁹ Giving the numerous products and valuable intermediates that can be made, the market potential for the commercialization of reduced CO₂ product can rise to a multi-billion-dollar market. It is noteworthy that the electrolysis of CO₂, in conjunction with the electroreduction of water, is currently being investigated for its potential as a large-scale, green manufacturing method of methanol.^{69,71}

The production of gases such as methane, propane, ethylene, isobutene, carbon monoxide, is another potential profitable segment market. Gases are used in different industries as fuel (methane), fruit-ripening agents (ethylene), and as a reducing agent in chemical processes (carbon monoxide). Thus, the onsite generation of these gases from CO₂ rather than buying it could reduce the overall process cost. The reduction of CO₂ has also shown promise in the area of solar fuels however, this lies beyond the scope of this review.⁷²

At an industrial scale, the main obstacles to the uptake of the electroreduction of CO₂ are the cost, scalability, selectivity, activity, and stability. These key criteria are fundamental and need to be enhanced in synergy to implement competitive CO₂ technologies. Significant investigations have shown that the nature of the cathode can, in aqueous, organic, and ionic liquid media, directly alter the outcome of the electrolyses, similar to the changes induced through the use of a catalyst.^{70,73} Moreover, the electrolyte composition, the opposite anodic reaction, and the potential membrane used are different adjustable parameters that need to be kept in mind. Finally, emphasizing the design of the reactor would lead to enhancing the mass transport, the robustness of the catalyst and the electrodes structures. This difficult challenge means that only a

few large-scale CO₂ technologies exist, which are only in precommercial stages.⁵³

Anodic methoxylation of 2-methylfuran

The natural product 2-methyl-3-mercaptofuran is used as a flavouring agent in the food industry, where it confers a meaty and juicy taste in products.⁷⁴ Its synthesis involves a key intermediate, 2-methyl-2,5-dimethoxyfuran, which is produced electrochemically from 2-methylfuran (Scheme 10).

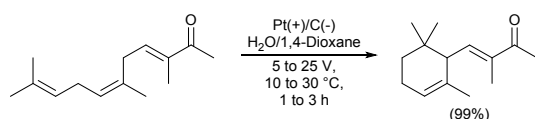


Scheme 10. Electrochemical synthesis of 2-methyl-2,5-dimethoxyfuran from 2-methylfuran.

In 2017, Tengzhou Tianshui Biological Technology Co., Ltd. has developed an anodic methoxylation process which is simple, safe, reliable and low in energy consumption.⁷⁵ In fact, the process uses a catalytic amount of sodium chloride thus avoiding the requirement of chlorine gas or liquid bromine treatment. In a 3000 L reactor containing 165 kg of 2-methylfuran and 430 kg of methanol, the reaction can be carried out at 10 °C over a 25-hour period using a current of 4000 A. Performing this reaction under more dilute conditions with the same current allows the reaction to be carried out at 20 °C, however, longer reactions times (ca. 30 hours) are required. Once the conversion of the starting material has reached over 99.5 % the electrolyte is subjected to desolvation and further modification to afford the compound of interest.

Cathodic diterpene cyclisation.

The methyl ionone is a homolog of ionone: its properties such as good stability, elegant fragrance, and a better taste than ionone makes it a compound of high interest. Among the six different isomers the α -iso-methyl ionone has the purest and most pleasant aroma. To date processes are facing problems such as poor selectivity, complicated purification procedures, complex process and high equipment costs.⁷⁶ An elegant process has been developed which affords the α -iso-methyl ionone via a cathodic diterpene cyclisation (Scheme 11).



Scheme 11. Cathode-mediated diterpene cyclisation

Wanhua Chemical Group Co.,Ltd. has developed a cathodic cyclisation of diterpene which affords the α -iso-methyl ionone with a high selectivity, purity and yield.⁷⁷ The process consists of loading the raw material in an electrolytic cell with 1,4-dioxane and water as the electrolyte, performing the electrolysis, followed by a desolvation and separation of the final product. The reaction is carried out in an 800 L electrolytic cell using a platinum anode and a carbon cathode. Once the

product is isolated, the dioxane aqueous solution recovered can be reused for further electrolyses after solvent volume adjustment. Up to 150 kg of raw material can be used each time, which yields more than 500 kg of α -iso-methyl ionone with a selectivity over 99.1%, a yield over 99% and a purity over 98.9%. In addition to this example, the process has been applied to two specific diterpenes to afford new ionones such as difluoro and cyclopropyl ionone derivatives (Figure 4). Their synthesis has been performed on a 1 kg scale, which affords the corresponding ionones with a good selectivity above 69.5%, in high yields and purity.

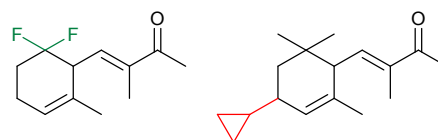
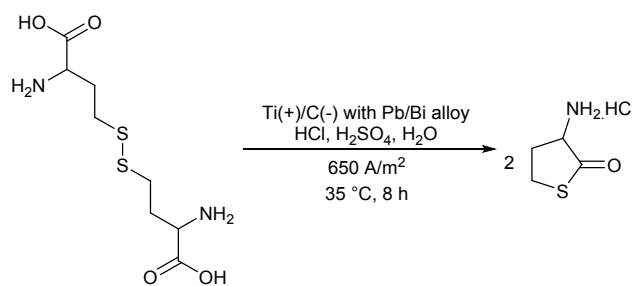


Figure 4. Ionone derivatives synthesised electrochemically on large (1 Kg) scale

Cathodic reduction of DL-homocystine.

DL-homocystine thiolactone hydrochloride is a biochemical reagent and a pharmaceutical building block used in the preparation of the drugs Citalone and Ersteine.⁷⁸ The compound of interest has already been synthesised on a large scale by the reduction of the DL-homocystine with a Zinc/H⁺ treatment. This synthetic route has two disadvantages: firstly, there is a high environmental impact as large quantities of zinc salts are produced and secondly, the method is hazardous as the process itself is exothermic and hydrogen is formed thus requiring rigorous safety measures. In 2019, Wuhan BJM Pharm Inc. developed an electrochemical reduction process on a 200 kg scale which overcomes the preceding environmental and safety issues (Scheme 12).⁷⁹



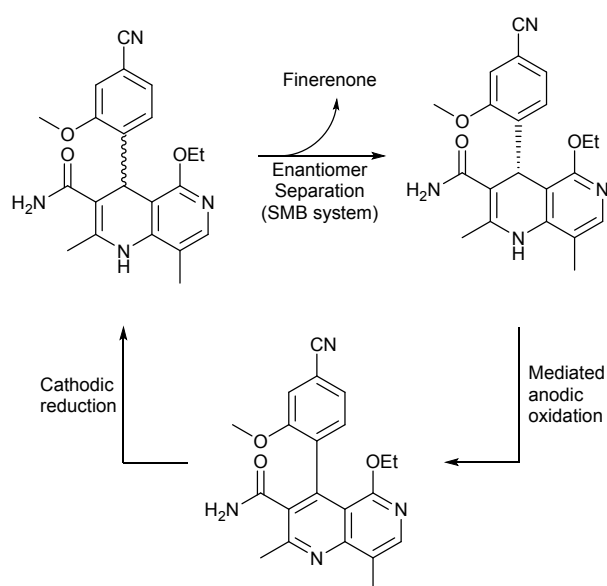
Scheme 12. Electrochemical synthesis of DL-Homocystine thiolactone hydrochloride from DL-Homocystine

Interestingly the cathode used is a carbon electrode covered by a lead bismuth alloy. They noticed that the modification of the cathode material and structure improved its mechanical strength and significantly prolonged its service life. In addition, as the cost of DL-homocystine is greater than that of DL-methionine, a new method for the synthesis of DL-homocystine from DL-methionine was devised, thus further reducing the cost of synthesising the thiolactone. The use of a nickel-based catalyst and high pressure in the generation of the DL-

homocystine has reduced the reaction time from 12 hours to 7 hours and improved the yield from 45.2% to 72.7%. This first stage preparation appears to be the limiting step and could be subject to further optimisation.

Enantiomeric enrichment using electrosynthesis.

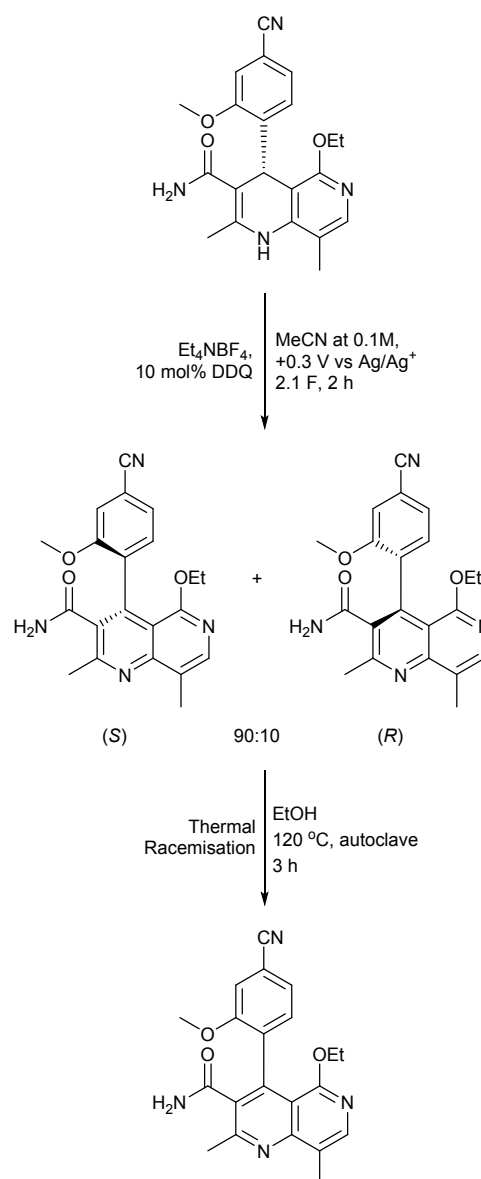
Finerenone is a nonsteroidal antimineralocorticoid and a potential drug candidate for the treatment of chronic heart failure.⁸⁰ The original synthesis was unsuitable for large-scale production due to its high solvent consumption owing to highly dilute reaction conditions, the need for several chromatographic purifications, the use of an excess of reagent, and a low overall yield. Recently, Bayer Pharma developed a larger-scale process synthesis to synthesise Finerenone. Indeed, the last enantiomer purification of 500 kg of the racemic using simulated moving bed plant afforded 48% yield of pure Finerenone. For economic reason there was a need to not destroy the other enantiomer and instead create a process which enables the conversion of the non-interesting enantiomer in the racemate, which could then undergo another enantiomer separation. This enantiomeric enrichment has been achieved by the means of a cycle: 1) oxidation 2) electrochemical reduction 3) enantiomer purification (Scheme 13).



Scheme 13. Electrochemical racemisation of Finerenone, followed by enantiomeric separation

The first step oxidises the dihydropyridine moiety into its pyridine analogue. The reaction of the undesired enantiomer with different chemical oxidants such as [TEMPO][BF₄], DDQ, CAN, NHPT, PCC, Chloranil, MnO₂, KMnO₄, Mn(III)OAc, RuCl₃, Bi(NO₃)₃, I₂, HNO₃, ⁿBu₄IO₄ and NaIO₄ was investigated. While yields between 42 and 98% were achieved, all of the methodologies required the use of stoichiometric or superstoichiometric amounts of oxidising agents, thus a different approach using mediated electrochemical oxidation

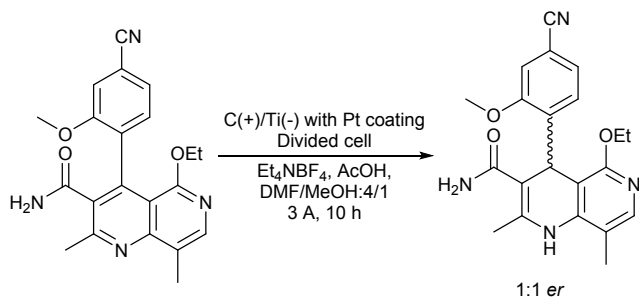
was utilised (Scheme 14). These specific conditions led to a mixture of atropisomers with a yield of 94% and a ratio of 9:1 which could be racemised thermally.



Scheme 14. Possible synthetic pathway for the racemisation of Finerenone

Once the oxidation had been achieved, the reduction conditions needed to be non-enantioselective in order to afford a racemic mixture that could be subjected to another enantiomer separation by means of SMB. An electrochemical reduction of the pyridine moiety was developed (Scheme 15). The electroreduction is possible *in flow* within a micro-flow cell with a 10 cm² area, and in a multipurpose cell with a 100 cm² active electrode cross-sectional area. The ideal current density applied was determined to be within the range of 10 to 30 mA/cm². When the electrolysis is conducted in pure methanol, yields greater than 97% in batch cells were achieved, however, the use

of a mixture of methanol and DMF improved the power efficiency when the reaction was conducted *in flow*.



Scheme 15. Electrochemical reduction carried out under flow conditions during the racemisation of Finerenone

The oxidation/reduction method described here can be conducted several times in succession with the possibility of a quasi-continuous mode production. At the end 200 kg of the pure enantiomer Finerenone were prepared from the mixed enantiomers for clinical trials.

6. Concluding remarks

Organic electrochemistry and its applicability to both academic and industrial problems is receiving ever increasing interest as we continue to seek more efficient and environmentally friendly chemical syntheses.

The overall productivity of an electrochemical reaction can be fine-tuned through thoughtful selection of the cell-type (divided vs undivided vs flow), supporting electrolyte, electrode material, and electrochemical mode. However, upon moving from laboratory to industrial scale, other factors such as the electrode geometry and the separation between them must be taken into consideration.

Not only can direct oxidation and reduction be induced at the anode and cathode respectively, but the synthesis of highly reactive intermediates can afford a wide variety of reactions ranging from methoxymethylation to catalytic hydrogenation. Indeed, through the use of rigorous design processes, numerous chemical manufacturers have started to incorporate organic electrochemistry into their procedures, in order to reduce cost and increase both yield and reaction selectivity. Moreover, advances have been made with the electrochemical conversion of carbon dioxide into more useful synthetic building blocks, which represents a major step towards reducing greenhouse gas emissions of the chemical industry. When coupled with a renewable source of electricity, organic electrochemistry truly represents a viable, sustainable, and versatile methodology for future synthesis of organic compounds.

Conflicts of interest

There are no conflicts to declare.

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