

Electroorganic Chemistry

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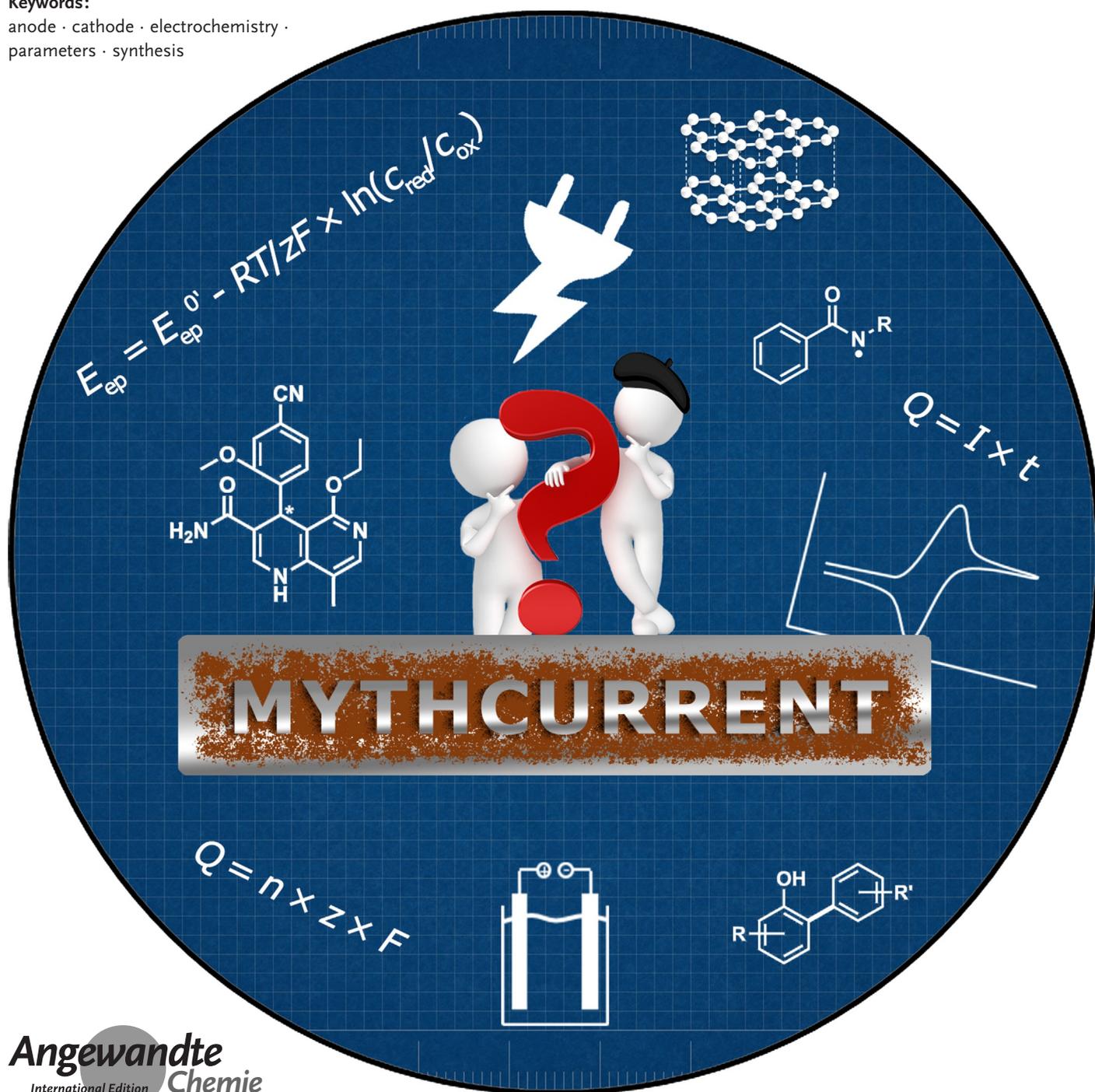
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# Reproducibility in Electroorganic Synthesis—Myths and Misunderstandings

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anode · cathode · electrochemistry · parameters · synthesis



*The use of electric current as a traceless activator and reagent is experiencing a renaissance. This sustainable synthetic method is evolving into a hot topic in contemporary organic chemistry. Since researchers with various scientific backgrounds are entering this interdisciplinary field, different parameters and methods are reported to describe the experiments. The variation in the reported parameters can lead to problems with the reproducibility of the reported electroorganic syntheses. As an example, parameters such as current density or electrode distance are in some cases more significant than often anticipated. This Minireview provides guidelines on reporting electro-synthetic data and dispels myths about this technique, thereby streamlining the experimental parameters to facilitate reproducibility.*

## 1. Introduction

Electroorganic synthesis has experienced a renaissance over the last years, even though it almost vanished during the second half of the 20th century. Most recently, the diversity of modern electrosynthesis, as an emerging tool in organic chemistry, was highlighted by multiple groups—for a selection of reviews see Refs. [1,2]. A variety of organic transformations have been facilitated by the use of electricity as a reagent. Nevertheless, based on the origin of electrochemistry as a subfield of physical chemistry, the appearance and understanding of electronic signals has remained the focus. The signals are crucially important in battery research, but have less synthetic utility in organic electrochemistry. Besides all the existing procedures for laboratory-scale preparative electrolysis, a comprehensive guide on the technical aspects can be found in the book *Organic Electrochemistry*.<sup>[3]</sup>

The heterogeneous scientific backgrounds of the many research groups who have entered the field of organic electrosynthesis have caused a variety of inconsistencies in the reproducibility of synthetic procedures, since no common ground or laboratory best practice has been established. Minor changes of reaction parameters can significantly influence the outcome of an electrolysis, which hampers the applicability of electroorganic techniques. Additionally, the unawareness of important facts in electroorganic synthesis is increasing the obstacles for newcomers to this area. The concept of electrons passing from the electrode into the electrolyte or vice versa poses initial challenges for experimentalists. The success of an electrosynthesis depends on the surface and local currents, which are interconnected with mass transport and other vital parameters. To support the community in obtaining reproducible conversions, we provide a survey with recommendations and give a detailed description of common myths and misunderstanding in electroorganic synthesis.

Finally, an improved understanding of advantages and pitfalls will provide the user with easily reproducible electroorganic procedures on a laboratory scale. The success of a ground-breaking development in technology strongly depends on its reliability in terms of application scenarios. In addition, knowledge about the critical parameters in electro-

synthesis should pave the way for a better acceptance of this emerging technique in common synthetic laboratories and its application in complex synthesis procedures.

## 2. General Myths in Electroorganic Synthesis

Although many chemists are well-aware of the advantages of electroorganic synthesis and use this technique, they still remain a minority. This is likely caused by the misunderstanding that a novel concept needs to be employed, even though in redox reactions

electrons instead of conventional stoichiometric reagents are used. In this context, comprehensive guidelines have been published recently to assist beginners.<sup>[4,5]</sup> However, several myths need to be emphasized and brought into perspective for the broader community.

### 2.1. Can Electroorganic Chemistry Always Be Considered as Synthetic Chemistry?

In principle, this technique uses electric current as a traceless activator and driver for organic transformations. However, a precise definition of different aims is crucial. Electroorganic analytical chemists investigate organic molecules with regards to their electrochemical properties and demonstrate feasible transformations at a fundamental level. The isolation of products in high yields is commonly not anticipated. In contrast, an electroorganic synthetic chemist is keen to access products on a preparative scale by using electricity instead of conventional reagents for the transformations. Electrosynthesis on a very small scale is more advanced, since electroconversion is conducted at low concentrations. As the local component concentrations at the electrode are low, this crucial parameter for the cell potential can cause failure. This aspect is often faced in medicinal chemistry, but can be circumvented with large quantities of mediator.

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### 2.2. Is Electroorganic Synthesis Always Sustainable?

This claim of it being a highly sustainable technique is used by many chemists involved in electroorganic synthesis—but is it true? Considering all the evidence stated in the recent literature, there are certainly advantages over conventional transformations, such as inherent safety, limited reagent waste, and electrical current from renewable resources, following the principles of “Green Chemistry”.<sup>[6]</sup> However, rapidly emerging techniques and processes are increasingly distancing themselves from those principles by employing large quantities of supporting electrolytes to facilitate conductivity in organic solvents. In some cases, those widely used additives are hazardous, harmful, or even toxic, such as the potentially explosive perchlorates. Moreover, organic electrocatalysis is gaining increasing attention by demonstrating the ease of effecting several challenging transformations. However, the necessity for additional reagents and thus waste generation diminishes the sustainability of those procedures, as do transformations which require the excessive use of supporting electrolytes.<sup>[7]</sup> When designing novel electroorganic techniques, sustainable conversion issues need thorough consideration, such as using lower quantities of supporting electrolyte and mediators, as well as the absence of separators and many more factors. In addition to the Faradaic efficiency, the terminal voltage is important, as the product determines the electric efficiency, which is directly associated with the costs for the required electricity and downstream processing.<sup>[8]</sup>

### 2.3. Should Electroorganic Transformations Be Preferred?

As in any kind of decision, the advantages and disadvantages of several methods should be evaluated prior to an experiment. In this respect, electroorganic chemistry is commonly highly favorable in terms of sustainability and economic benefits. However, time-consuming electrolysis at low potentials or microscale electrolysis, which demonstrates the possibility of a transformation without further scale-up evaluations, hampers acceptance of the method in synthetic organic laboratories. A broad range of applications, such as for total synthesis, are envisioned. Moreover, once the equipment for electrosynthesis is at hand, the barrier for a researcher to get started decreases. The full benefit of electroorganic synthesis is becoming apparent in process development, wherein the avoidance of scarce elements, better overall efficiency, and metal-free operations are crucial.

### 2.4. Is Electrosynthesis with Graphite Electrodes Metal-Free?

The synthesis of natural products and active pharmaceutical ingredients (APIs) is highly valued in organic synthesis. However, metal impurities are not tolerated for the subsequent medicinal use.<sup>[9]</sup> This is why carbon-based electrodes are often employed in electrosynthesis. However, graphite is not entirely metal-free, as traces of metal ashes are enclosed



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in the carbon material.<sup>[10]</sup> These metals can influence the properties and reactivity of graphite electrodes. This is why alternatives, such as boron-doped diamond (BDD) on a silicon support, have been developed.<sup>[11,12]</sup> Despite the low costs of isostatic graphite, the alternatives have several advantages, such as enabling metal-free synthesis and redox windows beyond common electrode materials.

### 2.5. Is Electrosynthesis beyond Common Equipment in Organic Synthesis Laboratories and Requires Specialized Setups?

The opposite is in fact true. It was demonstrated that conventional 6 V batteries can be used as power sources connected to three-necked round-bottom flasks for electrolysis with graphite rods.<sup>[13]</sup> Nevertheless, the reproducibility of the experiments might suffer in these home-made setups, as several electrolysis parameters might be sensitive to minor changes. Therefore, commercially available setups are recommended for beginners. Such plug-and-play solutions are available from several providers, for example, IKA<sup>®</sup>.<sup>[14–16]</sup>

### 3. Look at Your Electrolytic Cell

Considering that the concept of the working and counter electrode under galvanostatic (constant current) conditions is known, or can be recalled,<sup>[4]</sup> we highlight parameters of the electrolytic cell which should be focused on much more—namely, electrode geometry and surface features, membranes, tilt angle between electrodes, stirring, and the distance between the electrodes.

#### 3.1. Electrode and Electrolyte Always Act as a Couple

Before considering the concept of the electrolytic cell, a rather general assumption is required. In many cases, a separate discussion of the individual electrolysis parameters is performed. This is simply not accurate, as each parameter influences each other, most dominantly the interaction between electrodes and the electrolyte. The redox performance of the cell is precisely adjusted by the choice of electrode material plus the composition of the electrolyte, which consists of solvent and a supporting electrolyte. The latter can be a salt, acid, or base.<sup>[17]</sup> This liaison enables the user to shift the electrochemical window quite extensively.

#### 3.2. Active Electrode Surface

The working electrode, which can be either the anode or cathode, is the working horse of the process. Not only the type of material, but also the 3D geometry of the electrode is crucial, which was shown, among others, by Peters et al. in the electroorganic reduction of arenes (Figure 1 a).<sup>[18]</sup> Variations in size or shape, such as with wire, mesh, or foam electrodes, as well as rough surfaces may result in larger active electrode surfaces or higher local current densities.<sup>[19]</sup> Zinc was employed as the cathode material, but these plates were only compatible at very low temperatures ( $-78^{\circ}\text{C}$ ). Shrinking the size to a thin galvanized wire led to the reactivity being maintained even at room temperature and the reduced product could be obtained in a similar yield. By increasing the size of the active electrode by laser-grafting of the anode, Beil et al. could show that dehydrogenative coupling reactions of veratrole derivatives can be improved on a preparative scale.<sup>[20]</sup> In addition, in both reports, the cleaning of the electrodes was critical. By using sandpaper or by polishing the electrodes, the active layer formed during electrolysis could be removed and a plain and clean electrode could be recovered.<sup>[18,20]</sup> Only by this cleaning procedure could a reliable and reproducible procedure be guaranteed. A similar purification routine was applied in our laboratory when cleaning boron-doped diamond electrodes with sulfuric acid. It was not sufficient to only rinse these electrodes with solvents to acquire consistent yields, an additional cleaning by high current density electrolysis in dilute sulfuric acid was essential.<sup>[12,21]</sup> A comparable observation regarding surface treatment was seen by Tian et al., with platinum cathodes needing to be purified in concentrated nitric acid (65 %) for 15 min prior to use.<sup>[22]</sup> This finding demonstrates that the

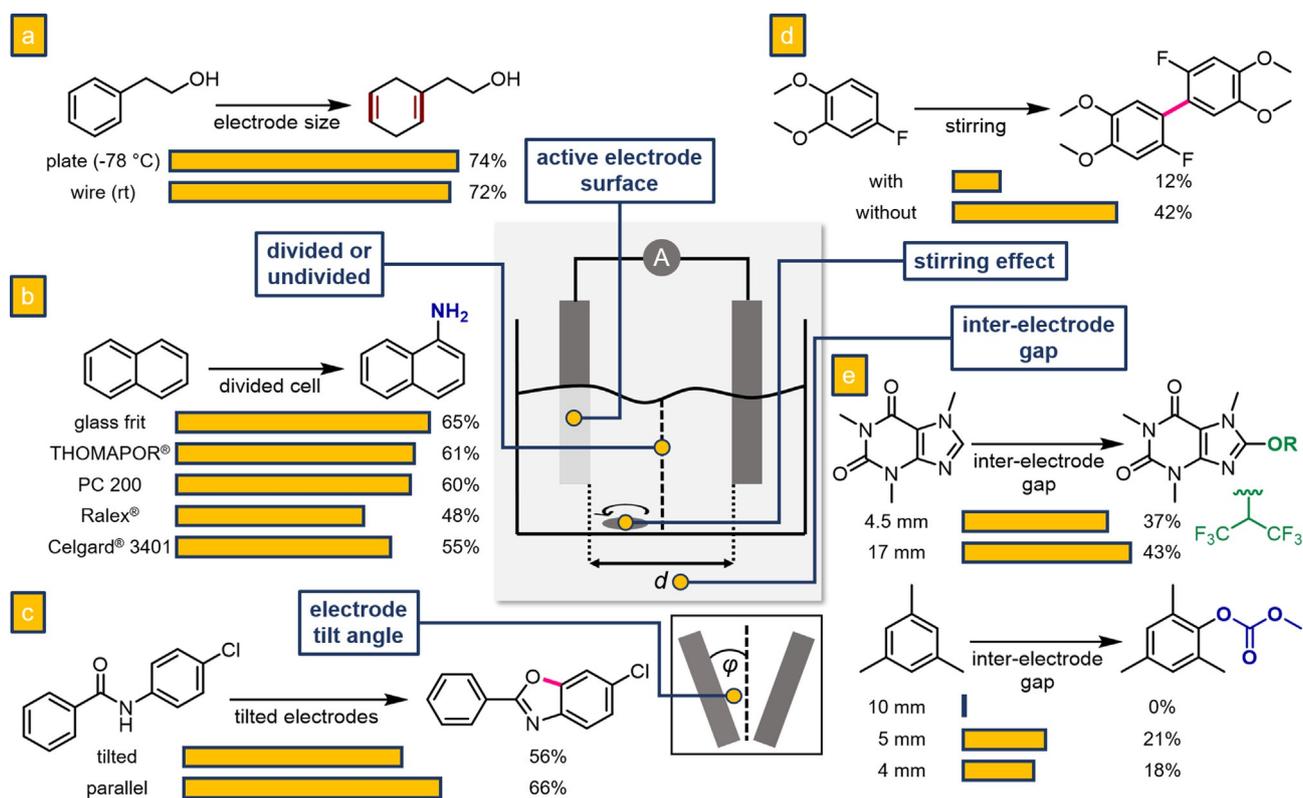
electrode surface can be highly susceptible to electrode fouling from promoted side reactions, for example, over-oxidations to form polymers. These tend to adsorb on the electrode and limit the active electrode surface. Therefore, thorough cleaning is required, as stated above.<sup>[23]</sup> It is noteworthy that electrode fouling can also lead to enhanced performance and selectivity.<sup>[24]</sup>

#### 3.3. Separator for Divided Electrolysis

In the case of a divided electrolysis cell, a crucial parameter is the choice of the separator. Its function is not only to separate the anodic and cathodic compartment, but also to prevent the migration of ions, substrate, intermediates, or products and thus avoid undesired reactions from taking place. The effect of ion migration was shown by Möhle et al., who compared a glass frit with different anion-exchange membranes and discovered very different outcomes (Figure 1 b).<sup>[25]</sup> Namely, the efficiency of aromatic amination was up to 20 % superior with glass frits compared to anion-exchange membranes such as Ralex®. It is highly recommended to immerse the separator in the electrolyte 24 h prior to application in the electrolysis to allow sufficient swelling, soaking of the pores, and thus sufficient conductivity. If tetraalkylammonium salts are employed, the purification of such multiple-use membranes has to be performed carefully as these ions tend to adsorb on the membranes.<sup>[8\*]</sup>

#### 3.4. Electrode Arrangement

In many cases reported in the literature, self-made electrolysis cells are utilized, but reveal a poor reproducibility in different laboratories. Often round-bottom flasks, vials, or Schlenk tubes are found equipped with electrodes, which can be difficult to replicate by other groups.<sup>[26]</sup> This is also the case regarding the application of electricity by using conventional batteries instead of precisely controllable power sources.<sup>[13,27]</sup> Therefore, the observed reactivity is likely to be observed exclusively in the authors laboratory. The use of standardized equipment is recommended, which can be purchased by suppliers such as IKA®.<sup>[14,15]</sup> The crucial difference between a self-made and a commercialized set-up was shown by Gieshoff et al., who could demonstrate that the angle between the electrodes in a round-bottom flask has a significant effect on the reaction outcome of intramolecular C–N coupling reactions (Figure 1 c).<sup>[28]</sup> The yield of the formed benzoxazole could be varied between 56 % and 66 % simply by moving from a  $40^{\circ}$  tilt of the electrodes to a parallel arrangement. This effect originates from there being a much more homogeneous electric field with parallel electrodes.<sup>[3]</sup> Therefore, local hot spots in the electric field can be avoided, which would promote side reactions. In particular, carbonization can easily occur at the wrinkles of platinum foil anodes



**Figure 1.** Overview of crucial, but under-explored parameters (electrode geometry, membrane, electrode tilt angle, stirring, gap between electrodes) with regards to the use of constant-current electrolysis cells.

and black deposits are forming through decomposition processes.<sup>[29]</sup> In contrast, these hot spots are beneficial for the degradation of organic molecules in waste water, as local high currents favor the degradation reactions.<sup>[30]</sup>

### 3.5. Effect of Stirring in Batch Electrolysis

Another rather unexpected electrolysis parameter is mechanical stirring. Since the heterogeneous reaction takes place at the electrode surface, mass transfer by stirring comes into play much later, if intermediates are sufficiently stable. Although dehydromerization reactions between activated arenes on an active molybdenum anode were successfully reported by Beil et al.,<sup>[20]</sup> some substrates gave low conversion. By excluding stirring, the yield of the fluoroveratrole substrate could be approximately tripled up to 42% (Figure 1d).<sup>[31]</sup> More surprisingly, under these conditions the homocoupling reaction required a non-stirred electrolyte, whereas cross-coupling of activated benzyl nitriles was only possible with stirring. This strong influence of mechanical stirring on the outcome of a batch-type electrolysis was also observed by Broese et al. in the electrocatalytic Newman-Kwart rearrangement of *O*-aryl thiocarbamates.<sup>[32]</sup>

### 3.6. Inter-electrode Gap

Although the distance between the electrodes can be expected to have an effect, it has been rather poorly investigated. Although mentioned earlier by the Baran group,<sup>[18]</sup> more recently Dörr and co-workers provided a comprehensive survey of electrolysis cell parameters through a design of experiment (DoE) strategy.<sup>[33]</sup> This approach allows the parameters to be screened and correlated simultaneously through software analysis. The authors considered typical parameters such as temperature or concentration, but more importantly the speed of stirring and the distance between the electrodes (Figure 1e). After several optimization cycles of the electrode distance, a reproducible increase in the yield of 8-alkoxycaffeine from 37% to 43% was observed. The influence of the electrode distance on an electroorganic transformation was also demonstrated by Gieshoff et al. during the anodic generation of organic carbonates. In this case, a precise electrode distance had to be employed to ensure conversion. Smaller distances around 5 mm resulted in diminished yields, whereas a larger electrode distance did not lead to the desired product at all.<sup>[34]</sup> Narrow-gap flow cells exhibit tremendous benefits over batch electrolysis cells due to their continuous processing. Extremely small inter-electrode distances of a few 100 micrometers can be achieved, which enables a dramatic decrease in the concentration of the supporting electrolyte. In some cases, operation without supporting electrolyte is feasible. This approach was used for the successful synthesis of important

building blocks as well as pharmaceutically relevant targets.<sup>[35,36]</sup>

### 3.7. Ohmic Heating

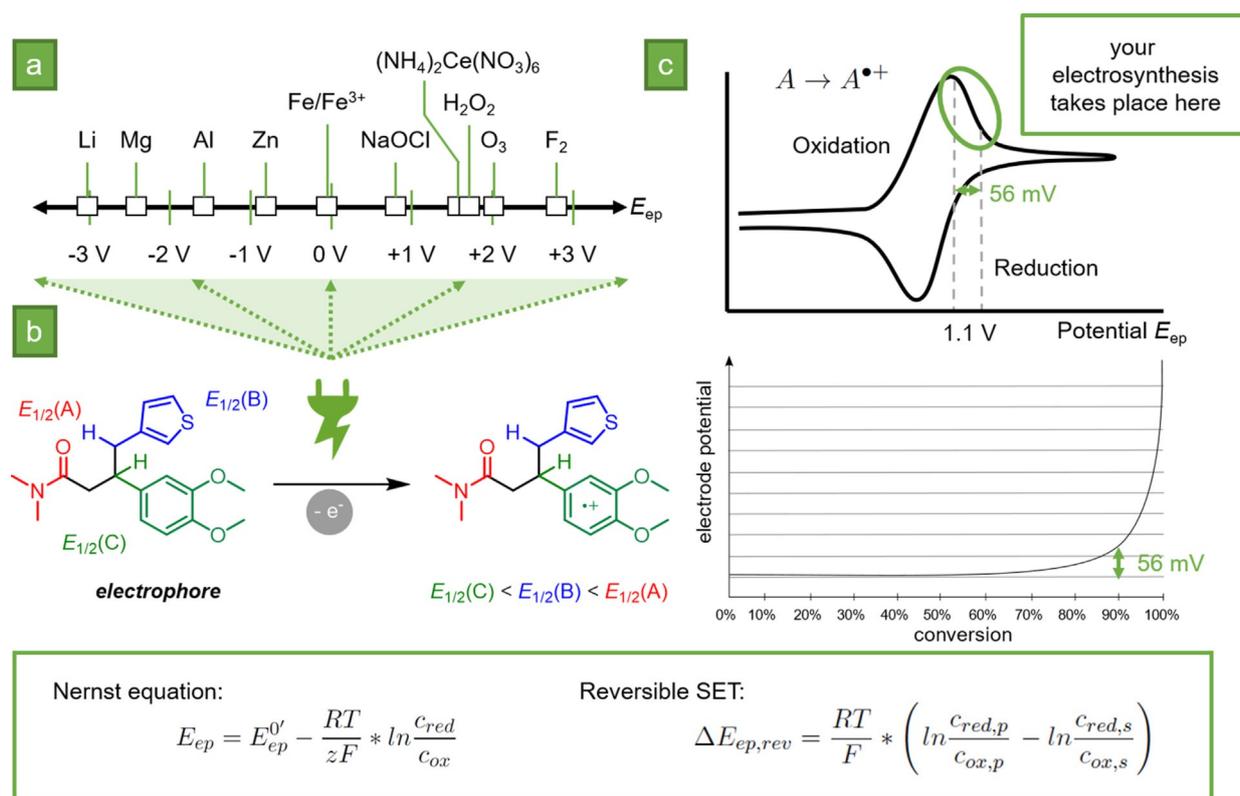
The electrolysis temperature generally has a minor effect on the conversions, which allows batch reactions to be carried out without precise temperature control. In many examples, the elevated temperatures result in better ionic conductivity and better mass transport, which is beneficial for the electroorganic synthesis.<sup>[37]</sup> However, at higher current densities Ohmic heating needs to be considered and external cooling applied. Recently, Selt et al. observed this phenomenon during the process optimization of the synthesis of 3,3',5,5'-tetramethyl-2,2'-biphenol in a flow electrolysis cell.<sup>[36]</sup> At current densities as high as 60 mA cm<sup>-2</sup>, the internal heating required compensation with a cooling jacket.

In conclusion, there is much more to optimize in regard to electrolysis cells and none of the possible parameters should be underestimated. In addition, all readers and authors are encouraged to report a full optimization table (in the Supporting Information) with all parameters covered, not only an extract of the successful ones, which are briefly highlighted in the manuscripts!

## 4. Control Your Potential—Dial in Your Reactivity

### 4.1. Dialing-In the Desired Redox Potential

The enhanced performance of electrical current as a safe and highly efficient redox reagent can be realized by highlighting the driving force of electrochemical transformations: the electric potential  $E_{ep}$ . Conventional oxidizers, electrochemical mediators, and photoredox catalysts have a specific redox potential, whereas the electric current can be adjusted over a broad range of potentials depending on the electrode and electrolyte (Figure 2a).<sup>[38]</sup> Novel materials have shown unique reactivity; for example, the stability of boron-doped diamond (BDD) combined with 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) over a large potential range was impressively demonstrated by the Waldvogel group during the synthesis of various biaryls.<sup>[39]</sup> Manipulation of the redox window offers numerous possibilities for highly selective transformations which have not been possible using conventional reagents, for example, the synthesis of the natural product dixiamycin B or polycycles from phenols.<sup>[40]</sup> Moreover, in recent studies, several sophisticated structures, including natural products, have been successfully constructed in electroorganic transformations, which impressively demonstrates that almost any reaction can be dialed-in using electricity as a reagent.<sup>[2]</sup> If



**Figure 2.** Potential as a driving force in electroorganic synthesis: a) Dialing-in the reactivity by potential control offers numerous possibilities over conventional redox reagents. b) Analogous to chromophores, molecules have several electrophores and the one with the lowest oxidation potential will be oxidized first. c) Cyclic voltammogram of a general substrate A with the highlighted potential window for electro-synthesis. The increase in the electrode potential with conversion is small compared to the electrochemical window, as determined with the Nernst equation and diffusion parts. Half-cell potential  $E_{ep}$ , standard half-cell potential  $E_{ep}^{0'}$ , number of electrons transferred per half-cell reaction  $z$ , temperature  $T$ , gas constant  $R$ , Faraday constant  $F$ , and concentrations of the reduced ( $c_{red}$ ) and oxidized ( $c_{ox}$ ) species of product P and substrate S.

more sophisticated substrates are required in the electrosynthesis, the electrophore with the lowest redox potential will undergo the initial oxidation (Figure 2b).<sup>[3]</sup> In contrast, constant potential electrolysis allows a specific subunit of a substrate to be addressed and, thus gives high additional value. This can be intensified by consideration of the increased potential during an electrolysis.

#### 4.2. Increased Potential with Ongoing Conversion in Constant-Current Electrosynthesis

Potentiostatic electrolyses are prolonged due to the lowered current with ongoing conversion, whereas galvanostatic electrolysis facilitates rapid transformation with possibilities for scale-up. However, in galvanostatic electrolysis the potential control is only maintained by the lowest oxidation/reduction potential of the substrate, electrolyte, or additive present at each time.<sup>[3]</sup> Less-selective processes can result, which can be described to a first approximation by the Nernst equation and a diffusion part (Figure 2, bottom box).<sup>[3]</sup> This initial approximation lacks the fact that no current is present, and over-potentials for hydrogen and substrate are not sufficiently considered. A more precise physical description of the involved processes of exchange current is given by the Butler–Vollmer equation (see chapter 7 in *Organic Electrochemistry* and chapter 1–2.2 in *Analytical Electrochemistry*),<sup>[3,41]</sup> but is not included here, as the focus is on its application in synthesis. Clearly, the potential increases drastically at very high conversions beyond 95%. Below this conversion, only negligible changes occur to the potential. This can either lead to undesired over-reactions or addressing undesired functionalities in the molecule, if more sophisticated substrates are employed. Moreover, if an irreversible electron transfer occurs, the value is even higher due to follow-up reactions. Although potential changes occur, compared to the potential window, the changes are only diminutive deviations from the starting value, in the range of a few mVs. As the electrosynthesis takes place in the green highlighted part of the potential window in Figure 2c, which is in the range of changes of a couple of hundred mVs, it often does not drastically influence the desired conversion and the desired process can be driven to high yields. However, processes can be established which are robust towards this increased potential and remain selective.<sup>[42]</sup> This would enable dialing-in reactivities and fast transformations to be performed that can be easily scaled-up.

#### 5. Watch your Carbon Electrode—Graphite Is Not Graphite

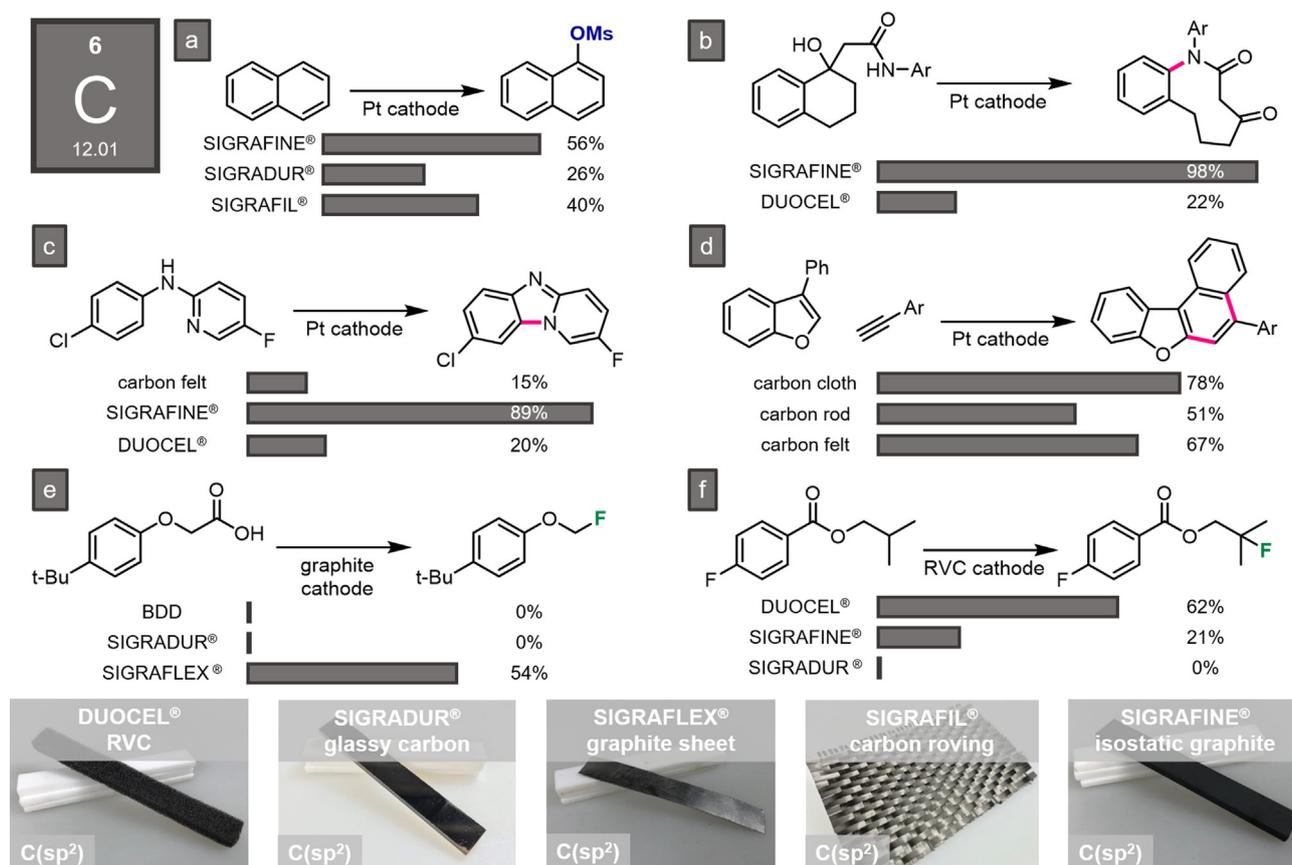
In many reported cases, carbon-based electrodes are inexpensive alternatives and reveal good mechanical stability and high chemical reactivity. Nevertheless, carbon is not equal to carbon, since the morphology, the  $sp^2/sp^3$  ratio of the carbon, and the preparation process of the conductive carbon material largely determines its reactivity. These processes could also introduce impurities, such as trace metals, which

require consideration (see Section 2.4). Common plate materials are isostatic graphite (SIGRAFINE<sup>®</sup>), graphite sheets (SIGRAFLEX<sup>®</sup>), or glassy carbon (SIGRADUR<sup>®</sup>). If larger electrode surfaces are favored, carbon-roving (SIGRAFIL<sup>®</sup>), reticulated vitreous carbon (RVC, DUOCEL<sup>®</sup>), or other carbon fibers can be utilized. The outcome of electrolyses with these materials can range from comparable to very different. Even in the simplest case of graphite, one can consider that some types of graphite have a high porosity while some are more compact. It is, therefore, crucial to state the type of carbon materials employed as precisely as possible.

The C–H activation of naphthalene was extensively studied by the Waldvogel group and was shown to not only depend on the membrane, but also on the carbon anode. The selective mesylation of naphthalene at the 1-position was best when using isostatic graphite, while glassy carbon or carbon-roving gave much lower yields (Figure 3a). Only a carbon-felt electrode could approach the best yield of 56% found for the SIGRAFINE<sup>®</sup> case. The mono-amination of the same position was much less sensitive towards the choice of anode material, but rather to the choice of membrane (see Section 3.3). Nevertheless, the yield varied by up to 20% with the different carbon materials, with glassy carbon and graphite sheets giving moderate yields, while higher performances of up to 70% were observed for carbon fibers, carbon-roving, and isostatic graphite.<sup>[25]</sup>

The use of carbon-based electrodes appears to be quite powerful for effecting C–C or C–N bond-forming reactions, as observed by various groups over the last few years.<sup>[43]</sup> The ring-expansion reaction of benzylic alcohols into nine-membered lactams was studied by Xu et al. on different carbon anodes (Figure 3b).<sup>[44]</sup> Remarkably, the reaction worked best with isostatic graphite, whereas RVC and platinum gave diminished conversions for the described transformation. As recently described by the Chen group, the intramolecular formation of C–N bonds proceeds moderately with carbon felt, carbon cloth, or RVC, which all exhibit a large surface, but exceptionally high yields of 89% were obtained when using isostatic graphite (Figure 3c).<sup>[45]</sup> The intramolecular cycloaddition reaction of phenylbenzofurans with aromatic alkynes exhibited a significant dependence on the applied carbon anode, as described by Hu et al. (Figure 3d).<sup>[46]</sup> Carbon cloth resulted in a yield as high as 78%, whereas carbon rods and felt resulted in diminished amounts of the product of 51% and 67%, respectively.

In recent studies on the fluoro-decarboxylation of aryl-oxyacetic acids it was observed that commonly employed isostatic graphite suffered from corrosion in the highly reactive fluoride-containing electrolyte. Berger et al. found that the application of SIGRAFLEX<sup>®</sup> led to enhanced performance and facilitated higher conversions (Figure 3e).<sup>[47]</sup> Similar differences as in the cycloaddition reactions were observed by Takahira et al., who studied electrochemical fluorination reactions (Figure 3f).<sup>[48]</sup> Very smooth surfaces such as glassy carbon gave no conversion at all, whereas isostatic graphite gave low yields of 21%. Only the high-performance material RVC with its large surface area gave yields as high as 62%.



**Figure 3.** Commonly used carbon materials as anodes. They all provide distinct reactivity and facilitate precise chemistry, but they all behave very differently when applied as anode materials.

The anodic dehydrogenative C(sp<sup>3</sup>)–H amination investigated by Nikolaienko et al. revealed that the use of several carbon allotropes as anode material resulted in different reactivity and performance. Besides graphite, the authors used glassy carbon and RVC to obtain their desired cyclic products from the Hofmann-Löffler-Freytag reaction. The products were obtained in different yields and the authors thoroughly investigated the intermediates by cyclic voltammetry measurements.<sup>[49]</sup>

The use of different carbon morphologies should, therefore, not be underappreciated, the carbon-type well-documented, and a variety of them should be tested in all cases of interest.

## 6. Conclusions

Apart from refuting the common misunderstandings in electroorganic synthesis, many pitfalls can be avoided by familiarizing chemists in early stages of education to this novel technique. A uniform description of the parameter set used for electroorganic processes is essential to facilitate high standards with respect to the reproducibility of experiments. More reliable procedures will lead to a rapid increase in developments and, thus, the establishment of sustainable synthesis procedures for natural products or active pharma-

ceutical ingredients (APIs), as electroorganic synthesis possesses many hidden treasures. The precise control of electrolysis parameters and dialing-in the desired reactivity will provide novel pathways in synthetic organic chemistry.

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## Conflict of interest

The authors declare no conflict of interest.

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