Review

EMERGING TRENDS OF ORGANIC ELECTROSYNTHESIS IN BRAZIL

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This review provides an overview of the recent progress in organic electrosynthesis in Brazil, ranging from 2013 to 2023. By highlighting the principles, applications, and limitations of various electrosynthetic methodologies, this article aims to contribute to the understanding of basic principles and stimulate research in this field in Brazil. Moreover, the limitations and challenges associated with organic electrosynthesis are covered. Factors such as electrode material selection, solvent effects, and reaction optimization are discussed, highlighting the need for further research and development to overcome these obstacles. Finally, future prospects are outlined.

Keywords: electrochemistry; organic electrosynthesis in Brazil; electrolysis; green chemistry; organic synthesis.

INTRODUCTION

Electrosynthesis research and industrial developments have been established over the years, dating back almost two centuries.[1] Research in organic electrosynthesis has produced a vast literature, and several researchers have stood out in this area.[2-7]

In the beginning, electrochemical studies in Brazil focused on fundamental areas such as electrochemical kinetics and reaction mechanisms. Over time, the studies have turned to materials science, such as corrosion and protection, electrocatalysis, water treatment, electrolysis, and organic electrosynthesis.[8-13] We highlight that nowadays significant advances in the field of organic electrosynthesis have been observed in Brazil, concurrently with the increasing of this scientific pursuit worldwide (Figure 1).

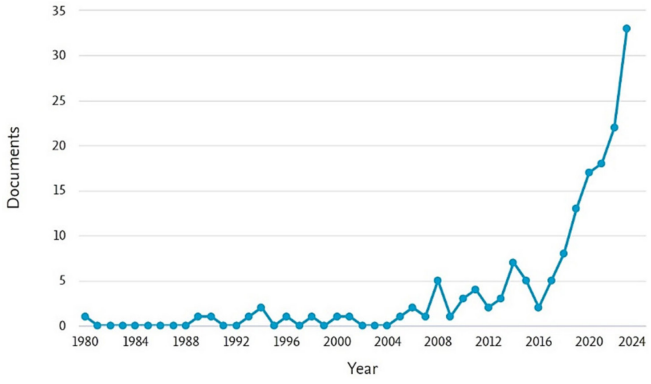

Figure 1. *Worldwide publications of scientific articles on organic electrosynthesis between the 1980s and 2023 (source: Scopus)*

As a matter of fact, we are facing an era of scarce resources, excessive use of fossil energy, and a high level of pollution, which encourages researchers to seek the development and use of clean energy sources, including in the area of synthetic organic chemistry.[14,15] As a consequence, there was a growing worldwide interest for the development of milder synthetic methods, such as the use of organic electrosynthesis to obtain organic molecules.

Organic electrosynthesis is a powerful and sustainable method of conducting organic reactions, which has gained significant attention in recent years for its environmental benefits and synthetic efficiency.[16-18] This innovative technique involves the use of electrical energy to drive chemical transformations of organic compounds. The mild reaction conditions are beneficial, allowing for easier handling of delicate functional groups and a broader range of substrates. By harnessing the principles of electrochemistry, it enables the construction of complex molecules with high selectivity and atom economy, paving the way for green and sustainable synthesis. Electrosynthesis allowed precise control of the reactions by adjusting the current and electrode potential, leading to the desired product with high accuracy. Moreover, it reduces energy requirements, making it environmentally friendly and cost-effective. Organic electrosynthesis can generate redox reagents on the spot from readily available materials, eliminating the need for complex pre-modifications. Unlike traditional methods that depend on costly pre-formed reagents, this approach provides enhanced reaction flexibility, facilitating chemical transformations in an efficient manner, enabling chemical transformations in an efficient pathway, often eliminating complex pre-modifications. Another advantages are the minimal waste produced, the selectivity, reproducibility, scalability under continuous flow conditions,[19,20] and much more, aligning with many green chemistry principles.[21]

Organic reactions often involve the transfer of electrons between different species, which are referred to as redox processes. In a redox reaction, one species undergoes oxidation, losing electrons, while another species undergoes reduction, receiving electrons. Electrons are transferred from the species being oxidized (the reducing agent) to the species being reduced (the oxidizing agent). Reactions performed under electrochemical conditions are enabled by the application of an electric potential which allows a non-spontaneous electron-flow always using an electrochemical cell. Reaction mechanisms can occur in an electrochemical cell similar to reactions in conventional systems. However, in an electrochemical cell, electricity is used to boost reactions by applying a potential difference (electrical voltage) between two electrodes, an anode and a cathode. These reactions are by definition voltage-controlled and very specifically promoted. After the formation of oxidized or reduced intermediates via single electron transfer (SET), which can encompass a variety of species including radicals or formally charged molecules, different reaction pathways can be favored, promoting different transformations, such as functionalization, substitution, elimination, rearrangement, additions, or coupling reactions, among others (Scheme 1a). In general, there are two main types of reactions: direct reactions and

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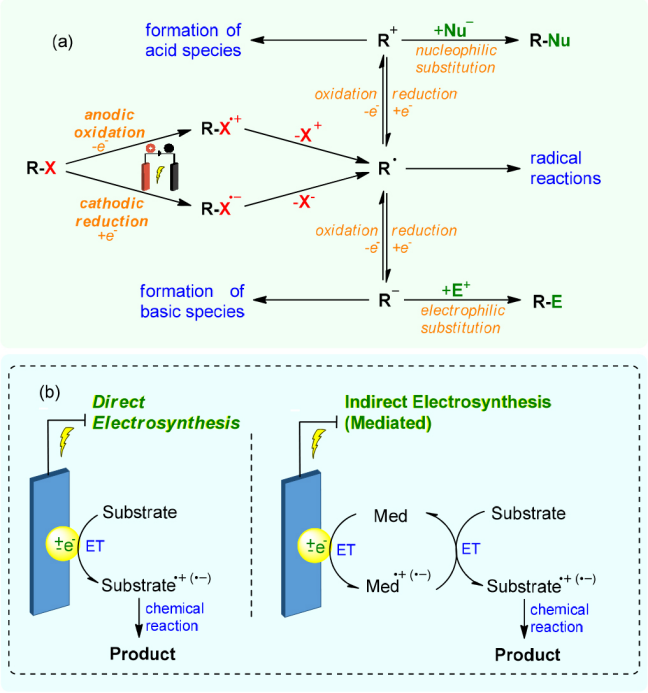
mediated reactions (Scheme 1b). In direct reactions, the electron transfer occurs directly between the electrode and the organic substrate. The organic reagent itself accepts or donates electrons directly to the electrode. This is common in electrosynthesis when the organic substrate is easily oxidable or reduced. On the other hand, in mediated reactions, the electron transfer occurs through a redox mediator, which is a compound that accepts or donates electrons between the electrode and the organic reagent. The mediator acts as an intermediary in the electron transfer, allowing the reaction to proceed more efficiently. This is useful when the organic substrate is not directly electroactive.[22-24]



Scheme 1. *General possible mechanisms for the electron transfer (a) and principle of redox mediation (b)*

Experimentally, in an electrochemical cell, two electrodes are immersed in an electrolyte solution containing the reactants. The electrode in which the oxidation occurs is known as the anode, and the electrode at which reduction occurs is the cathode. When an electric potential is applied across the electrodes, electrons flow from the anode to the cathode through the external circuit (potential application), while ions migrate through the electrolyte to maintain overall charge balance.[15] The electrolysis setup can be assembled using either a potentiostatic or galvanostatic cell. In potentiostatic cells, a constant potential (voltage) is applied between the working electrode and the reference electrode. The potential is maintained at a fixed value throughout the reaction, and as the reaction proceeds, the current flows between the working and counter electrodes. On the other hand, in galvanostatic cells, a constant current (ampere) is applied between the working and counter electrodes. As the reaction progresses, the potential between the working electrode and the reference electrode is continuously measured to be monitored and stabilized by the variation of the potential. The reference electrode provides a stable potential, essential for accurately measuring the potential of the working electrode. This is valuable in controlling the potential of the electrochemical cell and studying the kinetics of electrochemical reactions. On the other hand, when the goal is to observe just a reaction transformation, electrical current can be applied to the electrochemical cell without the reference electrode, and the products generated can be analyzed using techniques such as spectroscopy or chromatography without the need for rigorous potential control.[25,26] Both have their unique advantages and applications, and researchers should choose the most suitable configuration based on the objectives of their electrochemical reactions.

Two main types of electrochemical cells are commonly employed: undivided cells or divided cells (Figure 2).[24] Undivided cells do not have a physical barrier between the anode and cathode compartments, allowing the electrolyte solution and reactants to freely mix between the two electrodes. These cells offer simplicity and high current efficiency due to the unrestricted movement of reactants, enabling a variety of paths for electron transfer. However, are susceptible to the unwanted mixture of the electrolyte solution with the reactants between the two electrodes, and may result in non-desirable chemical reactions. On the other hand, divided cells incorporate a physical barrier (a glass frit, a porous ceramic, a porous polymer sheet, or an ion-selective membrane), which separates the anode and cathode compartments. Each compartment contains its own electrode and electrolyte solution, ensuring that the electrochemically formed intermediate at each electrode remains isolated and cannot be mixed. This enhances product selectivity and control over reactions, as it reduces cross-contamination and allows better results. However, divided cells generally require a more complex setup and may experience reduced current efficiency due to increased resistance caused by the presence of the barrier. The choice between undivided and divided cells depends on the specific requirements of the organic electrosynthesis reaction. For simpler setups and higher current efficiency, undivided cells may be the best choice. Conversely, when enhanced selectivity and controlled reactions are essential, divided cells become more advantageous.[22,23]

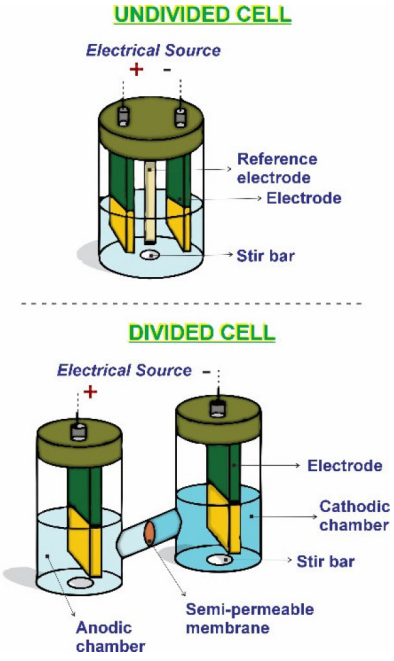


Figure 2. *Undivided cell (top). Divided cell (bottom). Reprinted with permission from Lodh et al.[24] (copyright (2023) permission from Frontiers Media SA, all rights reserved)*

In organic electrosynthesis, the choice of electrode materials plays a crucial role in determining the success and efficiency of the electrochemical reactions. The two primary types of electrodes applied are inert electrodes or sacrificial electrodes. Inert electrodes, such as graphite, platinum, and glassy carbon, are widely employed

due to their chemical stability. These electrodes do not participate in the redox reactions themselves and act as mere electron transfer mediators. Their inherent stability ensures minimal contamination, making them suitable for a broad range of electrosynthetic applications. Moreover, inert electrodes offer excellent reproducibility and can endure extended operation periods, making them desirable choices for long-term processes. On the other hand, the sacrifice electrodes are typically composed of metals with low oxidation potentials, and are utilized to release metal ions into the solution during the electrochemical process. These metal ions serve as active species, playing crucial roles as catalysts and coordinators in synthetic organic reactions, and examples of this electrodes are made of zinc, magnesium, aluminum, silver, etc. Furthermore, the choice of electrode material can directly impact the selectivity and yield of the desired products. Certain materials may promote side reactions or generate undesired by-products, while others may offer enhanced control over the chemical reaction.

The choice of an electrode material plays a significant role in the redox potential window for electrosynthesis reactions. The redox potential window refers to the range of electrical potentials within which a specific electrochemical reaction can occur. This choice influences the conditions under which the reaction can take place and can impact the efficiency, selectivity, and yield of the process. These potentials determine at which electrical potentials a species can be reduced or oxidized at the electrode's surface. Besides the redox potential window, the electrode material can also affect the reaction kinetics, including electron transfer rates, polarization, among other factors. The material should not only exhibit suitable electrical conductivity but also possess chemical stability and compatibility with the reaction medium. Additionally, the electrode's surface area and porosity can significantly influence the reaction kinetics and mass transfer, thereby affecting the overall efficiency of the electrosynthetic process.[27,28]

In electrochemical synthesis, both batch reactions and flow reactions are widely applied techniques. Each approach has its own set of characteristics, advantages, and disadvantages that should be considered when planning and executing electrochemical transformations. Batch reactions involve conducting the entire electrochemical synthesis in a single vessel or cell. The reactants are combined in the cell, and the reaction proceeds until completion. Characteristics of batch reactions include simplicity and ease of setup, making them accessible for both beginners and expert chemists. On the other hand, a continuous flow electrochemistry involves the continuous flow of reactants through an electrochemical cell, wherein the reactions occur as the reagents pass through the cell (Figure 3).[29] Flow reactors in electrochemistry offers several unique advantages over batch reactors conditions, such as improving mixing, fast heat exchange, multistep reaction sequences, smaller amount of electrolyte, reliable scale-up, among others.[19] Flow reactions also facilitate the optimization of reaction conditions through rapid screening of different parameters. This accelerates the identification of the optimal reaction conditions and saves valuable time and resources. However, flow reactions may require specialized equipment and expertise in flow chemistry techniques, which can be a barrier for some researchers. Recently, Cantillo and co-workers[30] reported an organic chemist's guide for translating batch electrochemistry to single-pass continuous flow conditions, and can be useful for those who want to go deeper into the subject. The choice between the two approaches depends on the specific requirements of the synthesis, the available resources, and the expertise of the researcher.

Considering the current advancements and the significant importance of electrosynthesis in organic chemistry, this short-review article highlights the recent advances in the field of organic electrosynthesis in Brazil, focusing on the period from 2013 to 2023. We discuss the main concepts, practical applications, and also the limitations of electrosynthesis methods, aiming to contribute to a better understanding and progress in this field. Factors such as electrode material selection, solvent effects, and reaction scope will be discussed. Additionally, we evaluate the challenges that organic electrosynthesis faces in Brazil. Finally, we outline some ideas for the future and potential advances of organic electrosynthesis in Brazil.

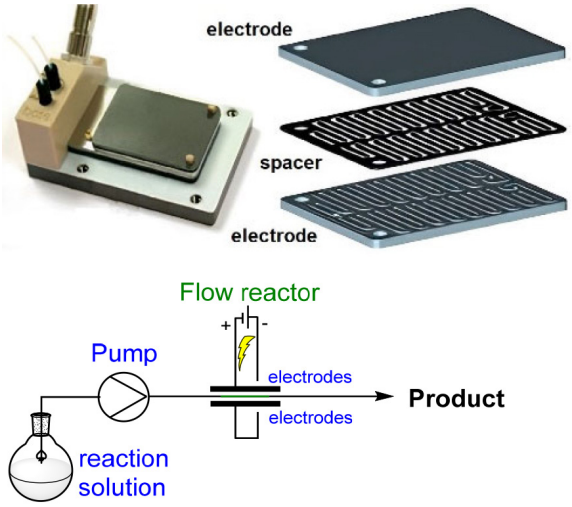


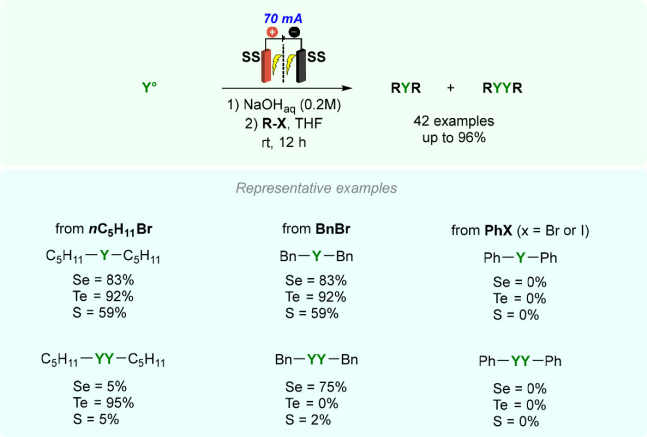
Figure 3. *Syrris® electroflow microflow cell and its components (top) and a generic flow cell in electrosynthesis (bottom). Reprinted with permission from Green et al.[31] (copyright (2015) permission from Springer, all rights reserved)*

ORGANIC ELECTROSYNTHESIS IN BRAZIL

Inert electrodes

Over the years, numerous review articles have highlighted the importance of electrosynthesis, discussing important transformations such as electrohalogenation,[32] electrochemical annulation,[33] phosphorylation,[34] alkene difunctionalization,[35] alkynes functionalization,[36] electrochemical chalcogenation,[37] mono-, di-, and trifluoromethylation,[38] and metalla-electrocatalysis,[39] among others.

Significant advances in the synthesis of organochalcogenides have been observed,[40,41] and they have been increasingly recognized by their diverse biological and medicinal properties, encompassing antiviral, antimicrobial, antitumor, and antioxidant activities.[42] Considering this, the investigation of environmentally friendly methodologies for the synthesis of chalcogenides compounds has gained significant scientific interest. In 2016, Navarro and co-workers[43] developed an electrochemical synthesis of organochalcogenides using NaOH aqueous solution employing a divided-cell (Scheme 2, Figure 4). Employing a two-step approach, monochalcogenides were obtained as the major products. Selenide (Se^{2-}), telluride (Te^{2-}), and sulfide (S^{2-}) anions were produced employing a two-compartment electrochemical cell with a Nafion® membrane separation, equipped with stainless steel electrodes. The corresponding chalcogenides (Se, Te or S, 0.5 mmol) were electrochemically reduced in a 0.2 M NaOH solution (pH 13), applying a constant current of 70 mA under an inert atmosphere. Subsequently, the respective organic halide (R–X, 1.0 mmol) in tetrahydrofuran (THF) (5 mL) was added and the mixture was stirred at 25 °C for 12 h, delivering products in yields of up to 96%. Significant yields were obtained when employing benzyl and primary alkyl halides as reaction substrates. Whereas lower yields were obtained with secondary halides and no products were observed applying adamantyl or aryl halides. This suggests that the reaction follows an S_N2 mechanism,[44] as proposed by the authors.



Scheme 2. *Electrochemical synthesis of organochalcogenides*

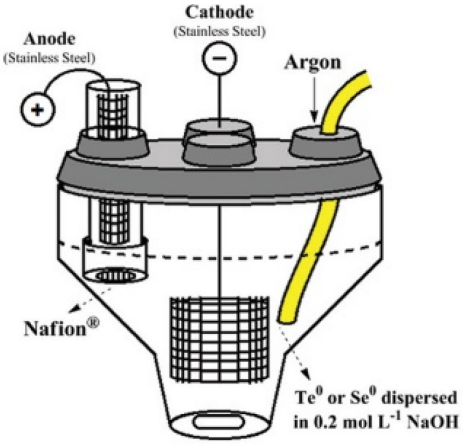
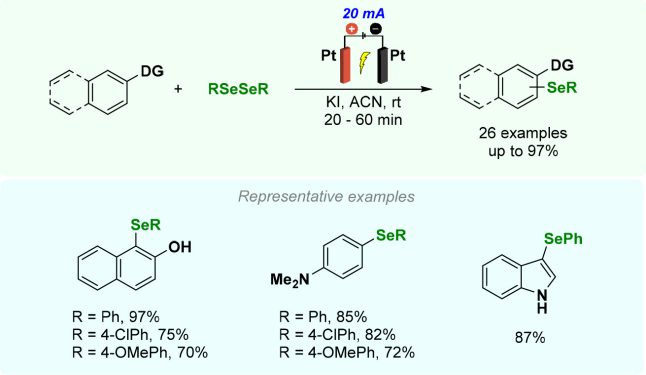


Figure 4. *Two compartment electrochemical cell separated by a Nafion® membrane applied for the electrochemical synthesis of organochalcogenides. Reprinted with permission from Navarro and co-workers[43] (copyright (2016) permission from Royal Society of Chemistry (RSC), all rights reserved)*

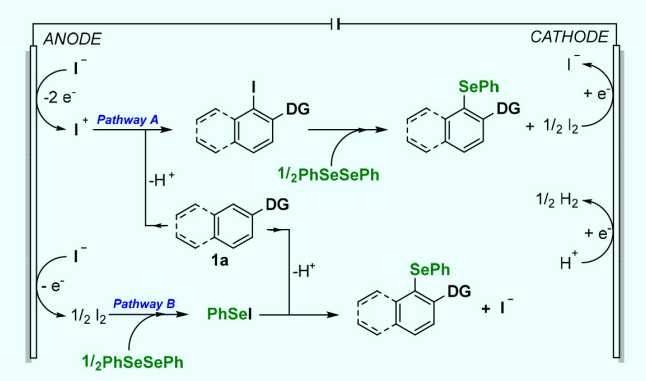
Introducing fluorine atoms into molecules holds great importance due to the exceptional properties. Performing fluorinations in organic molecules is quite challenging due to fluorine's high reactivity and the difficulty in achieving selectivity. The reaction conditions frequently involve harsh conditions, and certain fluorinated reagents can be costly. Additionally, environmental concerns are significant, as the traditional synthetic procedure usually need the use of excessive fluorine reagents. However, with technological advances, we are finding better ways to address these challenges. In the last years, Waldvogel and co-workers,[45] Fuchigami and co-workers,[46,47] and Wirth and co-workers[48] have conducted an electrochemical fluorocyclization of *N*-allylcarboxamides, fluoro-desulfurization of dithioacetals, and fluorination of α-dicarbonyl compounds utilizing (difluoroiodo)arene (a hypervalent iodine) as fluorine source. Additionally, Lennox and co-workers[49] conducted an electrochemical vicinal difluorination of alkenes.

The use of iodine salts as mediators has been widely studied to promote the synthesis of new compounds. Miller and Watkins[50] pioneered the utilization of electrolytically generated I^+ for iodination reactions in aromatic species, and an extensive mechanistic investigation was carried out. Their findings revealed that the electrochemical oxidation of iodine (I_2) in acetonitrile resulted in the production of $MeCNI^+$ as an equivalent species to I^+, facilitating subsequent electrochemical reactions with aromatic compounds. In 2006, Yoshida and co-workers[51] performed a comprehensive study employing CSI-MS, which demonstrated that $(MeCN)_2I^+$ serves as the primary species generated through the anodic oxidation of I_2 in MeCN, effectively identifying the precise equivalent species of I^+. The application of iodine salts as mediators has been widely studied to promote the synthesis of new compounds.[52,53] Considering this, in 2019, Mendes and co-workers[54] reported a synthesis of selenylated arenes through electrochemically oxidative C(sp_2)–H bond selenylation mediated by iodine salt (Scheme 3). This regioselective reaction offers good yields using Pt electrodes and KI as an electrolyte and mediator. The method is scalable, operates under atmospheric conditions, and utilizes non-toxic and easily handleable reagents. The electrochemical selenylation of 2-naphthol, *N,N*-dimethylaniline, and 1*H*-indole derivatives resulted in yields of up to 97%. However, experiments involving 1,3,5-trimethoxybenzene and 5,6,7,8-tetrahydronaphthalen-2-ol derivatives were less efficient, yielding products in 41 and 44%, respectively. Additionally, naphthylamine derivatives were completely suppressed.



Scheme 3. *Electrochemical oxidative C(sp_2)–H bond selenylation of activated arenes*

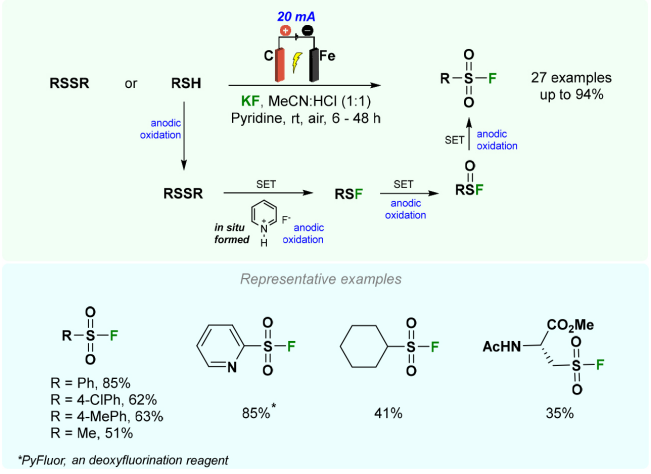
Two reaction pathways were considered (Scheme 4). In pathway A, the reaction initiates with the anodic oxidation of the iodide ion, resulting in the formation of the iodonium ion. Subsequently, electrophilic substitution occurs, which is quickly captured by the diselenide, leading to the formation of the final product and iodine. In pathway B, the reaction begins with the anodic oxidation of the iodide ion, giving rise to the iodine mediator. The diselenide undergoes oxidation, forming RSeI, which then attacks the activated arenes to generate the final product followed by the elimination of a proton and iodide ion.



Scheme 4. *Proposed mechanism for selenation of (hetero)arenes*

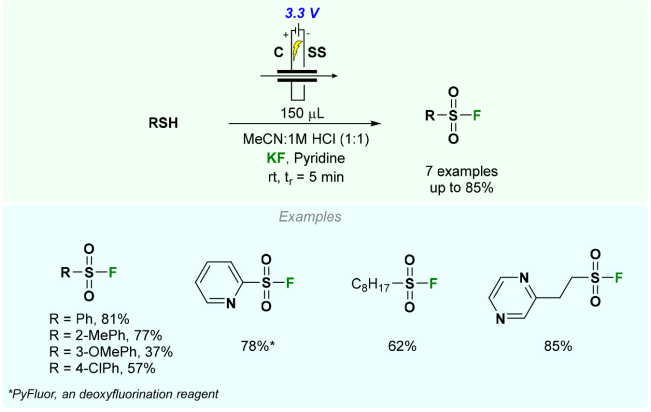
In 2019, Noël and co-workers[55] developed an electrochemical method for synthesizing sulfonyl fluorides. The method involved the use of thiols or disulfides and utilized KF as the source of fluoride (Scheme 5). This protocol eliminates the need for external oxidants or

catalysts, and the reaction was suitable in a wide range of substrates, encompassing alkyl, benzyl, aryl, and heteroaryl thiols or disulfides. Kinetic experiments were conducted to investigate the anodic oxidation of 4-(trifluoromethyl)thiophenol and its conversion to the corresponding disulfide. Upon the formation of the disulfide, it was immediately consumed, leading to the subsequent formation of the corresponding sulfonyl fluoride. The use of KF as a fluoride source ensures a safe and cost-effective transformation, thereby increasing the economic viability of the process and reducing potential hazards.



Scheme 5. *Synthesis of sulfonyl fluoride through electrochemical oxidative coupling of thiols and potassium fluoride*

In the following year, Noël and co-workers[56] made a further progress with the previously discussed methodology by proposing a continuous-flow procedure for achieving the electrochemical oxidative coupling of thiols and KF to synthesize sulfonyl fluorides (Scheme 6). This flow method significantly reduced reaction times to 5 min, compared to 6-36 h in batch, and demonstrated scalability for this approach (2.0 to 10 mmol scale). They achieved yields of up to 85% by applying 0.1 M of thiol, 0.6 M of pyridine, 0.5 M of KF, 3.30 V, 1 M of HCl/MeCN (1:1 v/v), at a total flow rate of 150 μL min^{-1} and a residence time of 5 min, using graphite and stainless steel as electrodes. Furthermore, the flow-based sulfonyl fluoride synthesis was applied for telescoping without the need for interim purification.



Scheme 6. *Continuous-flow procedure for the electrochemical oxidative coupling of thiols and KF to synthesize sulfonyl fluorides*

The authors emphasize that the experiments were conducted in a homemade electrochemical flow reactor, as shown in Figure 5. Furthermore, the synthesis of sulfonyl fluoride in a continuous flow system can easily be telescoped and integrated into a subsequent

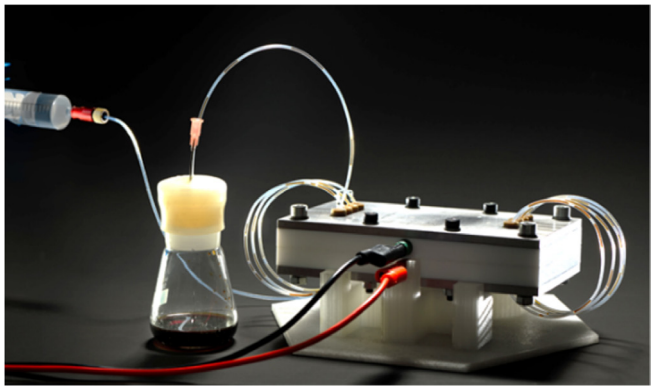
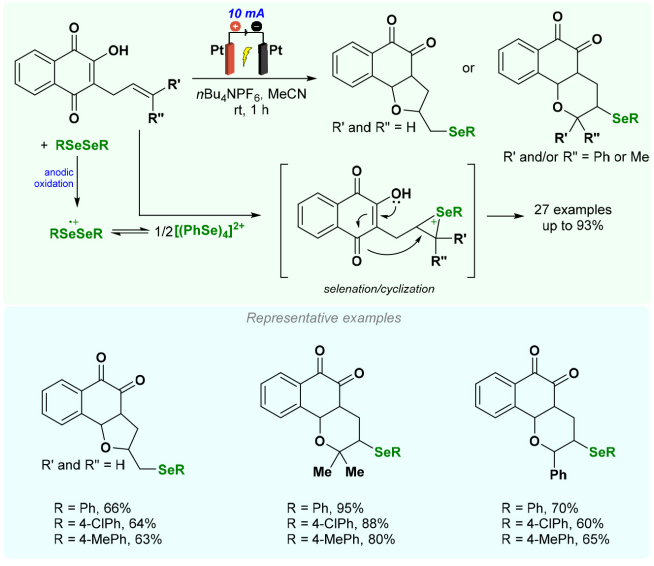


Figure 5. *Homemade electrochemical flow reactor used for the sulfonyl fluoride synthesis through oxidative coupling of thiols and potassium fluoride. Reprinted with permission from Noël and co-workers[58] (copyright (2018) permission from Springer, all rights reserved)*

SuFEx reaction (sulfur fluoride exchange),[57] eliminating the necessity for intermediate purification.

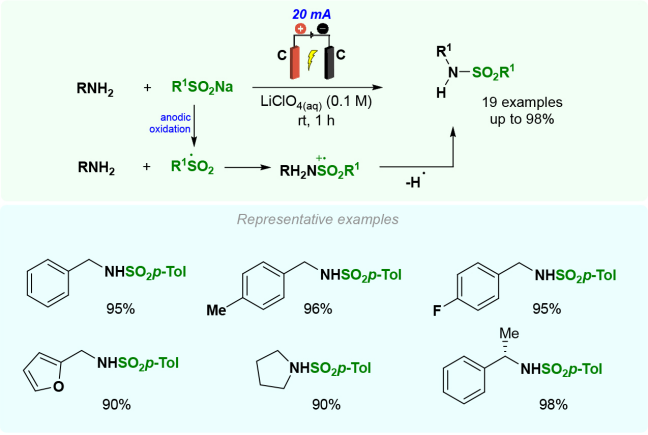
In 2020, da Silva Júnior and co-workers[59] described an electrochemical approach to introduce selenium into naphthoquinone compounds through an anodic oxidative selenation/cyclization process (Scheme 7). Several quinone-hybrid molecules were obtained using an undivided cell, platinum electrodes, nBu$_4$NPF$_6$ as electrolite and MeCN as solvent, at room temperature. These quinone-hybrid molecules exhibited interesting biological activity against five different cancer cell lines and *Trypanosoma cruzi*, the causative agent of Chagas disease. For the investigation of the reaction mechanism, the authors relied on the literature and analyses of cyclic voltammetry. The results suggested that the $[(PhSe)_2]^+$ radical cation generated (probably a dicationic tetramer)[60-62] undergoes a carbophilic reaction of the selenium dication with lapachol, forming a cationic intermediate, which undergoes nucleophilic cyclization, delivering products. In 2023, da Silva Júnior and co-workers[63] reported a variation of the previous method, applying disulfides to sulphenylation/cyclization of quinones, obtaining yields up to 93% under the same reaction conditions.



Scheme 7. *Synthesis of selenil-naphthoquinone compounds through an anodic oxidative selenation/cyclization process*

Recently, Menezes and co-workers[64] proposed an intriguing methodology for a solvent-free electrochemical synthesis of

sulfonamides using a graphite powder macroelectrode (Scheme 8). An electrolytic cell was developed (Figure 6), and the electro-oxidation was conducted on the graphite powder macroelectrode utilizing an aqueous electrolyte within a cavity cell. The active electrode (300 mg of graphite powder) was meticulously measured, combined with sodium *p*-toluenesulfinate (1.0 mmol), and introduced into the cavity created by the graphite stick and Teflon® base. A correspondingly-sized aluminum rod was then positioned atop the mixture, and a weight of 2.5 kg was applied for 10 min. Subsequently, benzylamine (0.5 mmol) was incrementally added (with an automatic pipette) to the compressed graphite powder and *p*-toluenesulfinate. To prevent any potential dispersion of the compacted substance into the electrolytic solution, a filter paper with small holes was added above the compressed material. The electrolysis was carried out in a constant current of 20 mA for 1 h. Aqueous solution of $LiClO_4$ (0.1 M) was used as the supporting electrolyte. As a mechanistic pathway, electro-synthetic conditions favor the oxidation of sulfinate (with an oxidation potential of 1.04 V). The resulting radical reacts with the amino group, forming an intermediate that undergoes hydrogen loss, delivering the final product.



Scheme 8. *Solvent-free electrochemical synthesis of sulfonamides*

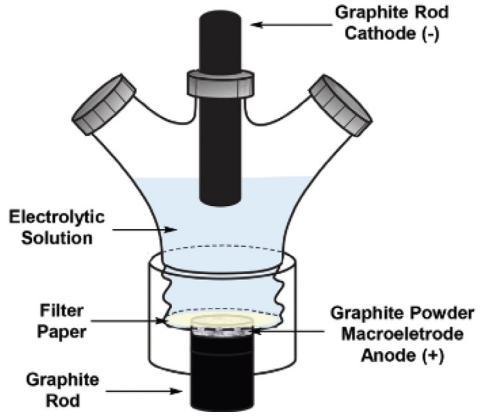
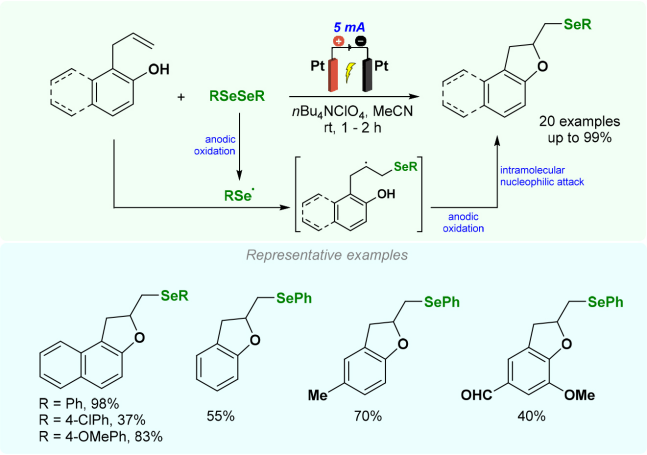


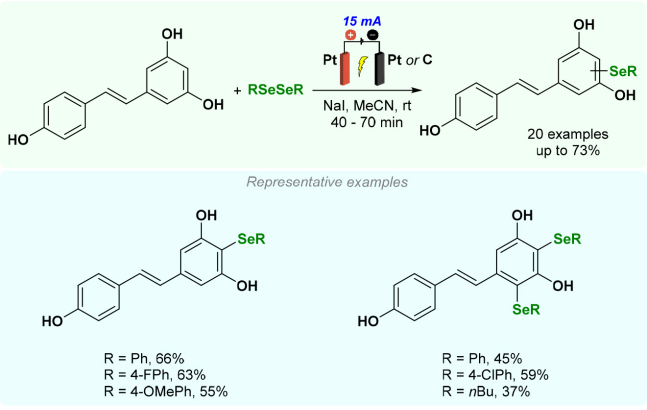
Figure 6. *Representative illustration of an electrochemical cavity cell. Reprinted with permission from Menezes and co-workers[64] (copyright (2020) permission from Royal Society of Chemistry (RSC), all rights reserved)*

Although existing literature for synthesizing selenide compounds through oxidative C–Se bond formation *via* $C(sp_2)$–H bond activation in arenes, many of these methods involve the use of external oxidants or catalysts.[65-72] In 2020, Braga and co-workers[73] proposed an intramolecular electrochemical oxidative oxyseleno-cyclization of allylnaphthol and allylphenol derivatives without external oxidants (Scheme 9). This method demonstrates remarkable compatibility with diverse functional groups, resulting in the synthesis of a range of dihydrofurans containing organoselenium moieties. The successful conduction of a large-scale experiment was achieved, and a scope with total of 20 selenyl-dihydrofurans derivatives were obtained with yields of up to 99% using 0.2 equiv. of nBu_4NClO_4 as an electrolyte, MeCN as a solvent, and Pt working electrodes in an undivided cell. Interestingly, the reaction failed to deliver products when performed with KI salts. Considering the results of the control reactions, such as the complete inhibition of transformation with a radical scavenger 2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO), the authors believe that the reaction mechanism follows a radical pathway, albeit not ruling out a route involving the phenyl selenium cation. Additionally, several selenylated products have demonstrated comparable inhibitory activity against the enzyme acetylcholinesterase (AChE) using galanthamine as model, a commercially available drug applied as Alzheimer's disease treatment.



Scheme 9. *Selenofunctionalization of allylnaphthol/phenol derivatives*

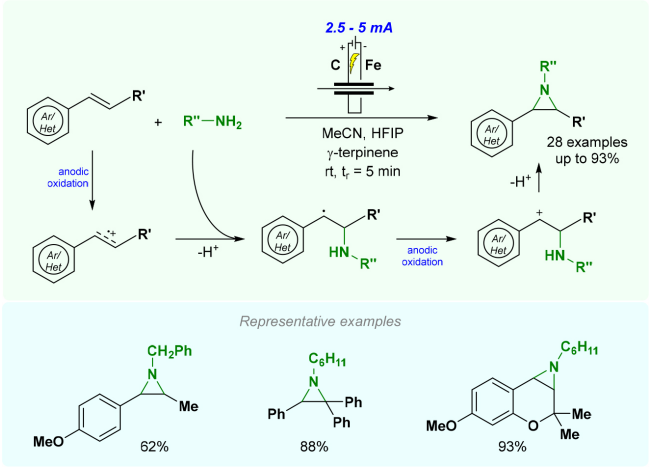
In 2021, Mendes and co-workers[74] reported a protocol to achieve a regioselective electrochemical oxidative $C(sp_2)$–H selenylation of resveratrol (Scheme 10), leading to the formation of unprecedented mono- and bisselenylated compounds involving a galvanostatic electrolysis utilizing platinum and graphite electrodes in an undivided cell. The method exhibited high efficiency under oxidant-free, base-free, and transition metal-free conditions, all performed in an open system at ambient temperature. Notably, this strategy required a sub-stoichiometric quantity of NaI, serving as both an electrolyte and mediator. The method demonstrated good functional group compatibility and proved effective for allylic diselenide derivatives,



Scheme 10. *Electrochemical oxidative $C(sp_2)$–H bond selenylation of resveratrol*

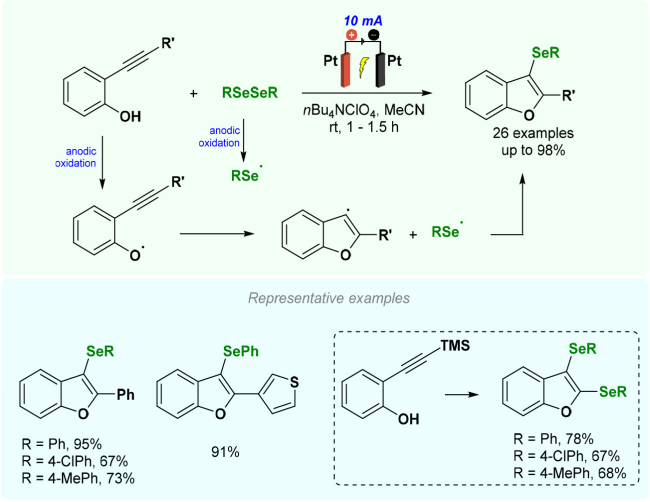
usually problematic substrates in this type of transformation, delivering products in yields of up to 73%.

Aziridines find a versatile application in pharmaceutical, agrochemical, and material sciences due to their unique three-membered ring structure.[75,76] The most common approach involves the ring expansion of epoxides using nucleophilic attack by amines under the influence of Lewis acids or metal catalysts.[77] Noteworthy advances have been made in electrochemical synthesis methodologies. For instance, Siu and Yudin[78] developed an electrochemical aziridination using *N*-amino-phthalimide as the source of electrophilic nitrogen, applying a divided-cell. A variant of this protocol was achieved by Little and co-workers[79] through an iodide-mediated electrocatalytic approach. Additionally, Cheng and co-workers[80] presented an electrochemical strategy utilizing trifluoromethylated sulfamates as coupling partners. Recently, Wickens and co-workers[81] proposed an aziridine synthesis by coupling amines and alkenes *via* an electrogenerated dication. In 2021, Noël and co-workers[82] developed an electrochemical aziridination of internal alkenes with primary amines (Scheme 11). This reaction was conducted in a homemade electrochemical flow reactor (Figure 5), and a wide reaction scope was evaluated (28 examples), affording products in yields of up to 93%, in a residence time of 5 min. The reaction was conducted applying alkene (1.0 mmol), amine (5.0 equiv.), 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP, 5.0 equiv), γ-terpinene (0.5 equiv.), MeCN as solvent (0.1 M), a C anode and Fe cathode, and a current density between 2.5 and 5.0 mA. The cathode played a crucial role in generating hydrogen gas, which could be employed in a subsequent reactor to facilitate the reduction of aziridine, leading to the desired hydroaminated product. Through mechanistic investigations and theoretical calculations using density functional theory (DFT), a reaction mechanism was proposed, suggesting that the alkene undergoes anodic oxidation before to follow for a coupling reaction with the amine. This approach demonstrated the possibility of directly converting olefins and primary alkyl amines into aziridines, as evidenced by the broad applicability demonstrated in 28 different examples.



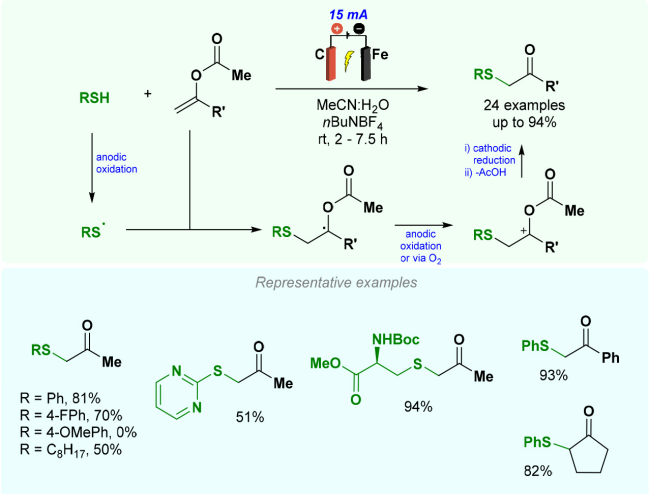
Scheme 11. *Continuous-flow procedure for the electrochemical aziridination of internal alkenes with primary amines*

Braga and co-workers[83] also developed a regioselective electrochemical synthesis of selenylbenzo[*b*]furan derivatives *via* cyclization of 2-alkynylphenols (Scheme 12). By a galvanostatic electrolysis, platinum electrodes in an undivided cell under oxidant-free, base-free, and transition metal-free conditions in an open system at ambient temperature delivered products in up to 98% yield. A gram-scale synthesis was achieved through cyclization of 2-(phenylethynyl)phenol with diphenyl diselenide. The reaction was conducted for 20 h, resulting in a 45% yield of the desired product. Interestingly, the use of 2-[(trimethylsilyl)ethynyl]phenol afforded the bis-selenylated product. According to control reactions, the reaction mechanism suggests a radical pathway, similarly as proposed above.



Scheme 12. *Synthesis of selenylbenzo[b]furan derivatives through the cyclization of 2-alkynylphenols*

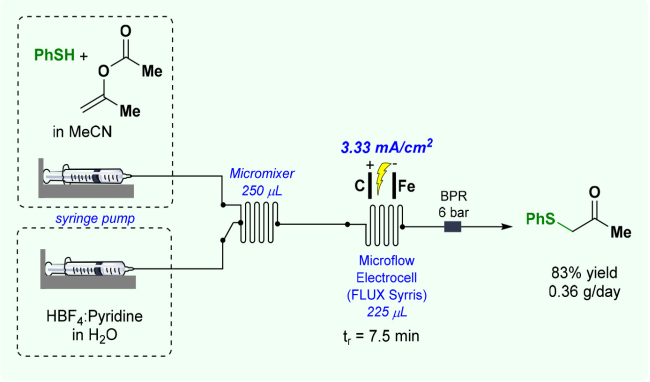
In 2022, de Oliveira and co-workers[84] investigated an electrochemical synthesis of α-sulfenylated ketones using both batch and continuous flow systems (Schemes 13 and 14). By employing thiophenols/thiols and enol-acetates, and nBu$_4$NBF$_4$ as electrolyte, the authors successfully obtained α-sulfenylated ketone derivatives without requiring additional oxidants or catalysts. The authors emphasized the remarkable tolerance of the Boc-cysteine substrate, significantly enhancing its practical applicability. The potential scalability of the methodology was successfully demonstrated in both batch and continuous flow conditions. Mechanistic insights were also reported while the TEMPO radical scavenger trapped the thiyl radical, and the transformation was completely inhibited when subjected to standard conditions. Similarly, through gas chromatography–mass spectrometry (GC-MS) analysis, the presence of the corresponding disulfide formed via cathodic reduction was observed. The process begins with the formation of the thiyl radical through the electrochemical anodic oxidation of thiol. This radical is then captured by the enol-acetate. Following this initial step,



Scheme 13. *Electrochemical synthesis of α-sulfenylated ketones*

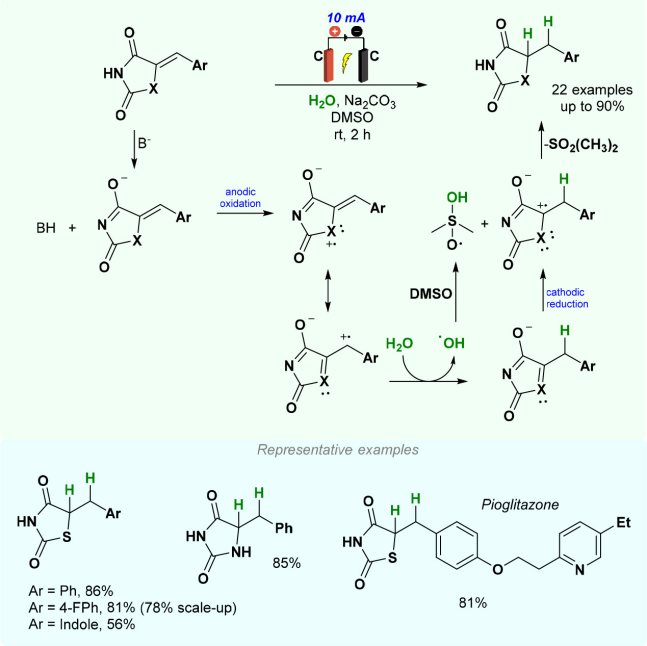
the desired α-sulfenylated ketone is obtained through the cathodic reduction and hydrolysis of the intermediate.

The transformation under continuous flow conditions was carried out using the commercially available electrochemical system from Syrris® (Flux Asia) with a microflow electrocell (9 cm^2 surface area, 225 µL volume reactor). The optimal reaction condition was achieved at a residence time of 7.5 min, delivering 1-(phenylthio) propan-2-one in a 83% yield and a productivity of 0.36 g *per* day (Scheme 14). Overall, the authors described a direct protocol to obtain α-sulfenylated ketones by electrosynthesis using thiols or thiophenols and enol-acetates. With this approach it is possible to obtain significant yields (up to 94%), a broad scope, and scalability.



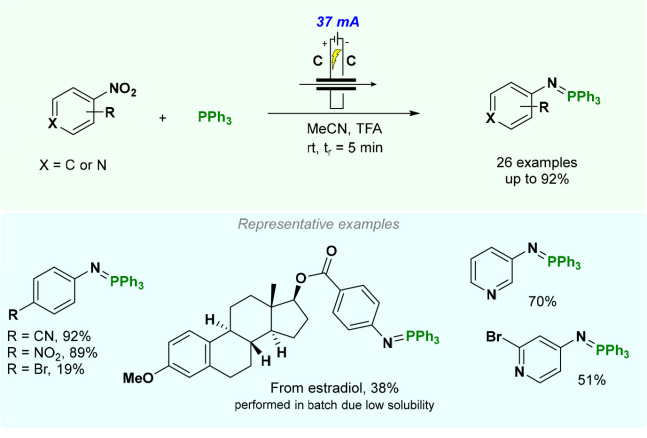
Scheme 14. *Electrochemical synthesis of α-sulfenylated ketones in flow conditions*

Thiazolidine-2,4-diones are a relevant class of heterocycles due to their diverse range of biological activities, particularly in the context of developing novel anti-diabetic agents, such as pioglitazone, ciglitazone, lobeglitazone, rosiglitazone, and troglitazone.[85,86] The synthesis of these derivatives typically involves a condensation reaction between thiazolidine-2,4-dione and aldehydes, followed by a hydrogenation step using either H_2/Pd under pressure or an excess of $NaBH_4$.[87] However, a significant limitation in many of these synthetic routes is the need of transition metal catalysis, which can represent a problematic issue in the context of the synthesis of active pharmaceutical ingredients (API). Therefore, there is a growing interest in the development of alternative methodologies that are more sustainable, efficient, and environmentally friendly for the synthesis of these crucial compounds.[88] The pursuit of transition-metal free protocols, applying greener hydrogen sources and innovative reaction conditions, holds great promise in addressing these challenges and advancing the field of organic synthesis in the context of drug development. In 2023, de Oliveira and co-workers[89] have introduced a novel transition-metal free methodology designed for the chemoselective reduction of benzylidene thiazolidine-2,4-diones and analogous heterocycles (Scheme 15). The approach enables the synthesis of a diverse range of reduced derivatives, affording yields of up to 90%. Additionally, the scaled-up reaction (0.5 to 6 mmol) displayed comparable reactivity, yielding 78% for the synthesis of 5-(4-fluorobenzyl)thiazolidine-2,4-dione. One of the highlights of this methodology is its simplicity and safety, as it relies on water as the hydrogen source, making it an attractive and practical option for chemical transformations. In order to demonstrate the practical application and potential of this method, the authors successfully synthesized the antidiabetic API pioglitazone with a notable 81% yield. This is the first hydride and transition-metal free protocol for the synthesis of pioglitazone. The proposed mechanism was supported by control experiments and cyclic voltammetry, providing a basis for the elucidation of the reaction pathway. The reaction begins with the deprotonation of thiazolidine-2,4-dione by sodium carbonate, affording the corresponding anion. This anion undergoes anodic oxidation, generating a radical cation that subsequently reacts with a water molecule, abstracting a hydrogen atom. Next, this intermediate receives an electron at the cathode electrode and, following to second hydrogen abstraction, deliver the desired product.



Scheme 15. *Electrochemical reduction of 5-benzylidene thiazolidine-2,4-diones derivatives*

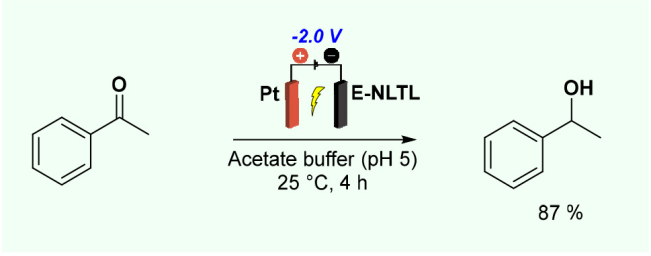
Recently, Noël and co-workers[90] developed a novel electrochemical technique for the synthesis of aryliminophosphoranes. The key innovation of this method is its utilization in a continuous-flow system, which enhances efficiency and convenience (Scheme 16). A mixture of trifluoroacetic acid (TFA) (50 mol%), PPh_3 (3.5 equiv.), nitro(hetero)arenes (1.0 equiv.), and MeCN (0.05 M) as the solvent provided products with yields of up to 92%. The method allowed the synthesis of aryliminophosphoranes without the need for additional supporting electrolytes. The transformation was conducted in a flow electrochemical reactor equipped with two graphite electrodes operated in a galvanostatic cell in a residence time of 5 min, and exhibited tolerance towards functional groups, especially electron-deficient nitroarenes. The experiment was scaled-up over 15.2 h, resulting in



Scheme 16. *Continuous-flow procedure for the synthesis of aryliminophosphoranes*

4.1 g of product (79% yield - productivity rate of 6.45 g *per* day). In addition, the versatility of the aryliminophosphoranes is demonstrated as intermediaries to synthesize anilines, amines and amides. From respective aryliminophosphorane, a telescoped-flow method has been developed applying a tube-in-tube reactor charged with CO_2 for *in situ* production of isocyanate. The isocyanate was then transformed into amide through the coupling with TFA. In contrast to literature, this methodology notably eliminates the need for potentially hazardous reagents, such as azides and molecular bromine, even when conducted at room temperature. Furthermore, it enabled a scale-up reaction without the need for additional electrolyte.

In 2023, Brondani and co-workers[91] combined electrochemistry and biocatalysis for the electroreduction of acetophenone by applying lipase stabilization to obtain 1-phenylethanol (Scheme 17). A Sn/Pb electrode (63 and 37% m/m) was polished and covered with a Nafion film modified using lipase from *Thermomyces lanuginosus*, an applied potential of –2.0 V using an acetate buffer at pH 5.0 for 4 h, delivering 1-phenylethanol in 87% without forming the corresponding pinacol dimer. The 1-phenylethanol was favored in the presence of lipases from *Candida antarctica B* (Novozym 435), *Rhizomucor miehei* (Lipozima RM-IM), and *Burkholderia cepacia* (PS-D Amano I), but the best results were obtained using *Thermomyces lanuginosus* (immobilized on methylcyclopentadienyl manganese tricarbonyl (MMT), silica gel and Lipolase 100T). The method stood out for enzyme stability, reproducibility, and the possibility of storing and reusing the modified electrode.



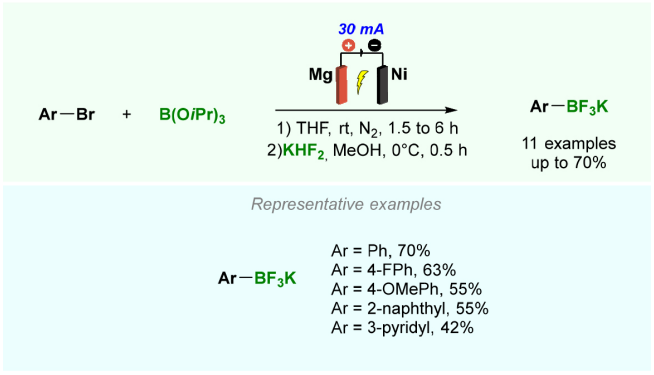
Scheme 17. *Electroreduction of acetophenone by applying lipases*

Sacrificial electrodes

Among various electrochemical techniques, the use of sacrificial electrodes in organic electrosynthesis have gained increasing interest. These electrodes, typically composed of metals with low oxidation potentials, are employed to release metal ions into the solution during the electrochemical process. These metal ions can act as active species, playing fundamental roles as catalysts and coordinators in synthetic organic reactions. Magnesium, copper, zinc, aluminum, iron, and silver are among the frequently metals employed as sacrificial electrodes in electro-organic transformations. One notable disadvantage of employing sacrificial metals is that the electrode becomes non-recyclable as a result of metal salt formation. However, the benefits of this approach can overcome these disadvantages, as these metals in solution could suppress the overoxidation of substrates, active intermediates, or final products, and can replace a catalyst.

In the early 1990s, review articles already discussed the use of sacrificial electrodes. For example, Chaussard *et al.*[92] described a paper focusing on "The Use of Sacrificial Anodes in Electrochemical Functionalization of Organic Halides." More recently, several studies have reported different electrosynthesis methods utilizing sacrificial electrodes. These include obtaining silver acetylides from acetylenes using Ag^0 as the sacrificial electrode,[93] electrochemically synthesizing copper(I) acetylides with Cu^0 as the electrode,[94,95] employing a sacrificial Cu^0 electrode to synthesize copper-*N*-heterocyclic carbene complexes using a flow reactor,[96] the using of Mg^0 or Al^0 anodes for an electrochemical Birch reduction,[97] and the electroreducing of triphenylphosphine oxide (TPPO) to triphenylphosphine (TPP).[98] In 2023, Guo and co-workers[99] have highlighted this growing interest of the scientific community in a review article entitled "A Guide to Organic Electroreduction Using sacrificial Anodes."

Several methods for obtaining organoboron compounds are described in the literature. However, expensive and toxic catalysts are often employed, such as palladium, copper, nickel, iron, iridium salts, etc.[100-104] In 2014, Menezes and co-workers[105] proposed an electrochemical synthesis of potassium aryltrifluoroborates from the corresponding aryl halides (1.0 equiv.), triisopropyl borate (2.0 equiv.), using THF as the solvent within an inert atmosphere at temperatures ranging from 0 to 25 °C, applying Mg^0 as the sacrificial anodic electrode (Scheme 18). The methodology was developed with demonstration of a broad group tolerance, while the electronic effects of substituents in the aromatic bromide minimally affect the transformation, delivering products in yields of up to 70%. An undivided cell was employed, utilizing sacrificial Mg^0 as the anode and nickel foam as the cathode. A 30 mA constant current was applied until the full consumption of the starting material (1.5 to 6 h).

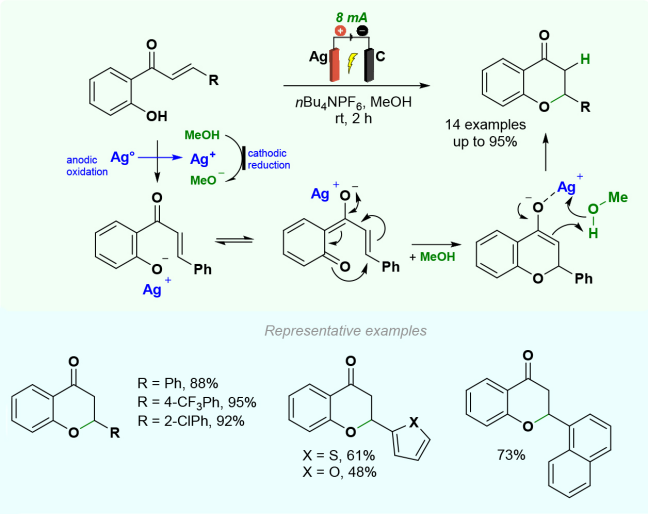


Scheme 18. *Electrochemical synthesis of potassium aryltrifluoroborates using Mg^0 as sacrificial electrode*

In 2023, Mendes and co-workers[106] developed an electrochemical synthesis of flavanones through the intramolecular oxa-Michael addition of hydroxychalcones, applying a sacrificial silver electrode (Scheme 19). The corresponding flavanones were obtained in up to 95% yield by using silver electrodes at the anode, graphite at the cathode, nBu$_4$NPF$_6$ (1.0 equiv.) as the electrolyte, and methanol as the solvent. Cyclic voltammetry and theoretical studies guided the authors to propose a plausible mechanism. The reaction involves the cathodic reduction of methanol, providing a methoxide anion and hydrogen gas. Concurrently, the anodic formation of silver(I) played a vital role in maintaining reaction charge balance. After a 6-*endo*-trig cyclization, the solvent-mediated proton transfers lead to the desired product. The method demonstrated promising prospects for silver-catalyzed transformations. Additionally, this methodology revealed new synthetic possibilities, raising intriguing questions about the possibility of replacing expensive metal catalysts with sacrifice electrodes. This could make chemical transformations more convenient and environmentally friendly due to the reduction of toxicity and elimination of by-products.

PERSPECTIVES OF ORGANIC ELECTROSYNTHESIS IN BRAZIL

Organic electrosynthesis has gained worldwide prominence as an alternative to conventional synthetic methods. In recent years,



Scheme 19. *Electrosynthesis of flavanones via oxa-Michael addition using Ag^0 as sacrificial electrode*

there has been a growing interest and adoption of this innovative approach by researchers and the chemical industry. In this context, various future perspectives emerge, pointing towards a promising and transformative landscape in the field of organic synthesis.

One of the most notable perspectives is the growing emphasis on environmental sustainability. Organic electrosynthesis offers numerous advantages in terms of toxic waste reduction and lower environmental impact. When operating in softer reaction conditions and using electrodes such as catalysts, this approach aligns perfectly with the worldwide sustainable development goals. With the increasing pressure for more environmentally friendly and responsible practices, it is expected that electrosynthesis finds wide application in various sectors of the national chemical industry. Brazil has a robust scientific and technological community, capable of exploiting and improving efficiency in organic reactions. The search for new reaction conditions as well as the development of different electrodes, reactors and reaction cells promises to open new horizons in terms of selectivity and reaction paths in electrochemical reactions, enabling the synthesis of valuable products.

A critical factor for the consolidation of electrosynthesis here in Brazil is the investment in the formation of specialized human resources. Training scientists and students in organic electrochemistry is crucial to promote research and innovation in this field. The creation of postgraduate programs and the update of courses focused on this subject is fundamental for the development of specific expertise and the strengthening of this research line in Brazilian universities and research institutions.

In addition, it is important to highlight the fundamental role of international collaborations. Knowledge exchange with researchers from other countries can provide access to advanced technologies, resources and innovative perspectives. The establishment of partnerships with world renowned research groups can catalyze the fast advance of electrosynthesis in Brazil, providing technical knowledge and accelerating the incorporation of new technologies.

CONCLUSIONS

It has become evident that exploring the field of organic electrosynthesis in Brazil is essential to follow the global advances in this domain. The utilization of electrochemical methods for organic synthesis presents several advantages over traditional synthetic approaches. Notably, the eco-friendly and sustainable nature of electrosynthesis offers a promising alternative to conventional methods, reducing the reliance on toxic reagents and minimizing the generation of harmful waste. Furthermore, the ability to conduct reactions under milder conditions enhances the overall green and sustainable character of electrosynthesis, making it an attractive prospect for modern chemical synthesis.

Given the highlighted advantages and potential benefits, it is imperative for Brazil to continue exploring and investing in the field of organic electrosynthesis to remain at the forefront of scientific development. By addressing the challenges and limitations identified in this review, researchers can pave the way for further improvements and breakthroughs in this area. Additionally, identifying future prospects and potential directions outlined in this review will provide a valuable tutorial for guiding research efforts and driving innovation in organic electrosynthesis within the Brazilian scientific community. Ultimately, promoting advances in this field will not only contribute to the nation's scientific progress but also contribute to sustainable and environmentally conscious chemical synthesis practices on a global scale.

At the end, this review has shown that we still have a relatively small number of scientific publications in this area compared to other countries around the world. Given the promising potential and advantages of electrosynthesis in relation to traditional synthetic methods, it is crucial to invest in this research field to strengthen our presence in the global scientific scenario. By expanding our efforts and resources, we can boost not only Brazilian science and technology, but also contribute significantly to the search for more sustainable and efficient chemistry solutions. We are convinced that by encouraging and supporting our researchers, we can accelerate the evolution of electrosynthesis in our country and consolidate our role as protagonists in the advancement of this important scientific area.

ACKNOWLEDGMENTS

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