ELECTROCHEMICAL SYNTHESIS OF HETEROCYCLIC COMPOUNDS

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Guilherme M. Martins,[a]* Guilherme B. Simoso,[a] Pedro P. de Castro[b]*
[a]*Department of Chemistry, Federal University of São Carlos, São Carlos, São Paulo, 13565-905, Brazil*
[b]*Department of Pharmacy, Federal University of Juiz de Fora, Minas Gerais, 35010-177, Brazil*
(e-mail: guilherme.martins@ufscar.br)

Abstract. *Herein, we present a comprehensive overview of recent advancements in the electrochemical synthesis of heterocyclic compounds. This chapter emphasizes the role of organic electrosynthesis in the efficient and sustainable formation of heterocycles. It highlights significant progress in reaction mechanisms, electrode materials, and electrochemical conditions that enhance the selectivity and yield of heterocyclic compounds. Additionally, emerging trends and future directions are discussed, providing insights into ongoing research and potential applications.*

Contents

1. Introduction

Organic electrosynthesis is a versatile and convenient method for performing organic reactions, using electrical energy to drive chemical transformations of organic compounds, which has gained notable attention in recent years due to its environmental benefits and synthetic efficiency.[1–5] The mild reaction conditions are advantageous, allowing for the handling of sensitive functional groups in a diversity of substrates. By applying electrochemical principles, it enables the construction of complex molecules with high selectivity and atom economy,[6] therefore promoting environmentally friendly and sustainable synthesis.[7]

Electrosynthesis offers precise control over organic reactions by adjusting the current and electrode potential, reducing energy consumption, and making it both environmentally friendly and cost-effective. This method can generate redox reagents directly from readily available materials or with the assistance of mediators, eliminating the need for complex pre-modifications. Unlike traditional methods that rely on expensive pre-formed reagents, electrosynthesis provides greater reaction flexibility and facilitates chemical transformations. Additional benefits include reduced waste production, high selectivity, reproducibility, and the possibility of scale-up,[8] which align with the principles of green chemistry.[9,10]

Over time, several review articles have emphasized the significance of electrosynthesis, highlighting key transformations such as electrochemical annulation,[11] alkene[12] and alkyne functionalization,[13] electrohalogenation,[14] electrochalcogenation,[15] phosphorylation,[16] mono-, di- and trifluoromethylation,[17] and metalla-electrocatalysis,[18] among others. Additionally, there has been a growing focus on studies discussing the electrosynthesis of heterocycles.[19,20]

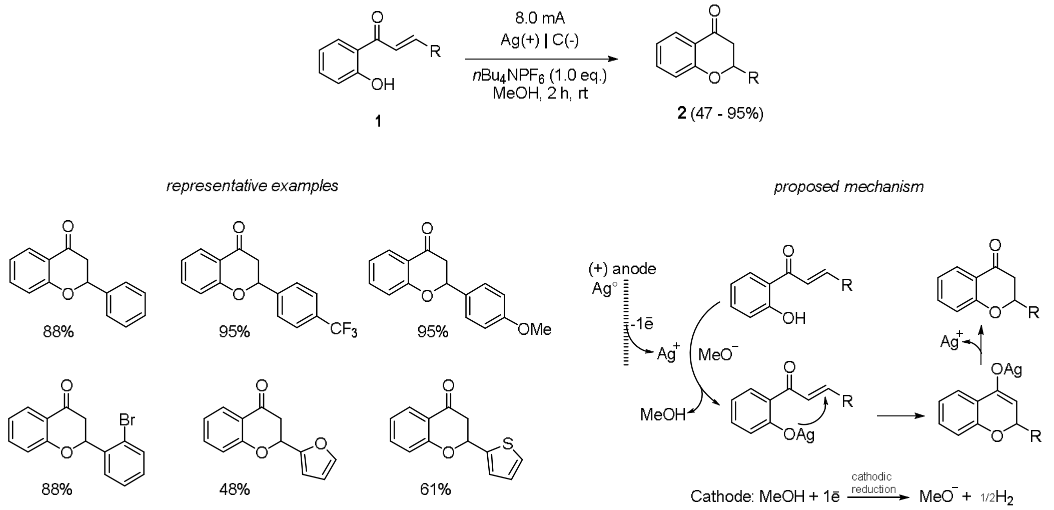
The electrochemical synthesis of heterocyclic compounds is a significant advancement in organic chemistry, enhancing and expanding possibilities for new synthetic strategies. The importance of integrating new technologies in heterocyclic synthesis is evident as it enables the exploration of unconventional reaction pathways, facilitating the creation of complex heterocyclic structures that were previously challenging to synthesize using traditional methods. This is particularly relevant in drug discovery and materials science, where heterocyclic compounds contribute significantly to the development of pharmaceuticals, agrochemicals, fine chemicals, and advanced intermediated compounds.[21-23]

In this chapter, a comprehensive overview of recent advancements in the electrochemical synthesis of heterocyclic compounds is provided, including significant progress in reaction mechanisms, electrode materials, and electrochemical conditions that enhance selectivity and yield in the preparation of heterocyclic compounds. For better comprehension, the chapter is categorized based on the different types of bonds formed and includes a miscellaneous section covering other relevant topics.

2. C–O Bond formation

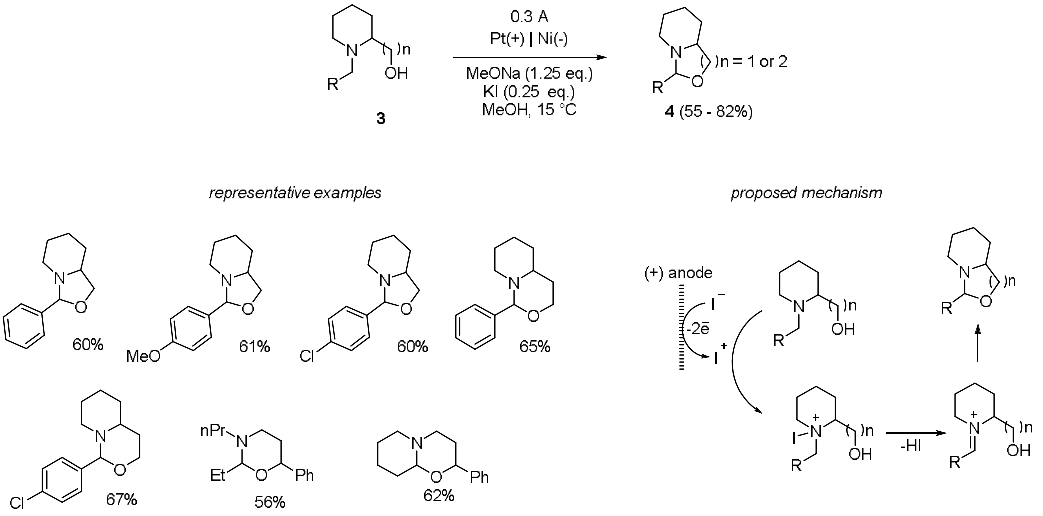
Oxygen-containing heterocycles represent a significant class of bioactive molecules. Due to their abundant occurrence in nature and diverse range of biological activities, these compounds play crucial roles in numerous biological processes and are essential in the development of new pharmaceuticals.[24]

In 2023, Martins, Mendes, and co-workers introduced an innovative electrochemical method for the synthesis of flavanones **2** *via* the intramolecular oxa-Michael addition of hydroxychalcones **1**, employing a sacrificial silver electrode (Scheme 1),[25] affording flavanones in up to 95% yield. The reaction setup consisted of silver (Ag) electrodes at the anode, graphite (C) at the cathode, tetrabutylammonium hexafluorophosphate ($n\mathrm{Bu_4NPF_6}$) as the electrolyte, and methanol (MeOH) as the solvent. A plausible reaction mechanism was proposed based on control reactions, cyclic voltammetry and theoretical investigations. In this transformation, methanol underwent cathodic reduction, generating methoxide anion and hydrogen gas. Simultaneously, the anodic generation of silver(I) species played a crucial role in maintaining the reaction charge balance. The subsequent 6-*endo-trig* cyclization, followed by solvent-mediated proton transfer, afforded the formation of the desired flavanone product. This methodology demonstrated promising potential for silver-catalyzed transformations, presenting sacrificial electrodes as an alternative to costly metal catalysts, thereby enhancing convenience while minimizing toxicity and eliminating by-products.



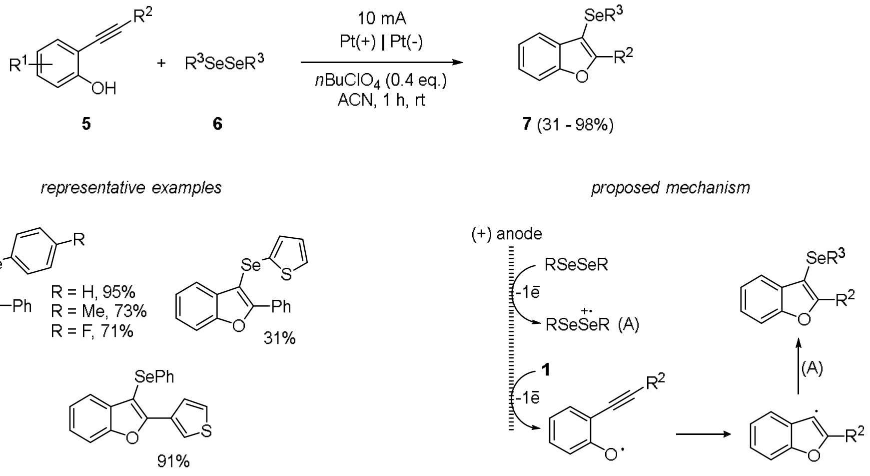
Scheme 1. Electrosynthesis of flavanones *via* oxa-Michael addition.

Okimoto and co-workers developed an electrooxidation methodology for the synthesis of oxazinane and oxazolidine derivatives **4** through the cyclization of *N*-benzyl-2-piperidine alcohols and 3-dialkyl amino-1-phenylpropanol **3** (Scheme 2).[26] The reactions were carried out in an undivided cell at a constant current of 0.3 A, using platinum as the anode and nickel as the cathode electrodes, with MeOH as the solvent at a temperature of 15 °C. In the reaction mechanism, the iodide ion from KI loses two electrons at the anode to form an iodonium ion, which is then attacked by the nitrogen atom to form an iminium ion. The hydroxyl group attacks the C=N bond, leading to the formation of the cyclic derivatives **4**. The study revealed that intramolecular attack by the hydroxyl group can occur both at benzyl and alkyl carbon atoms, indicating that a benzylic carbon atom is not mandatory for cyclization.



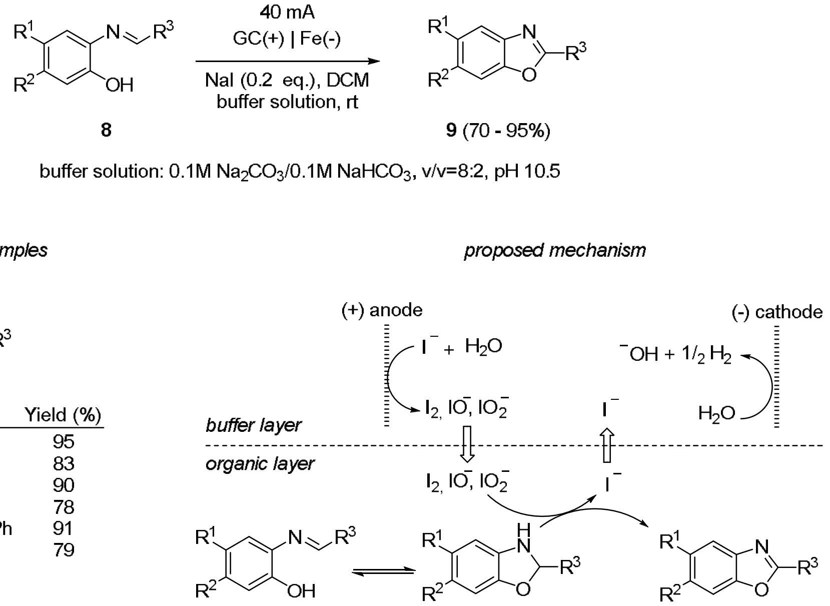
Scheme 2. Electrooxidative cyclization of aminoalcohols.

Martins, Braga, and co-workers described a regioselective electrochemical method to synthesize selenylbenzo[*b*]furan derivatives **7** by cyclization of 2-alkynylphenols **5** in the presence of *bis*-selenylated derivatives **6** (Scheme 3).[27] Galvanostatic electrolysis using platinum (Pt) electrodes in an undivided cell, at room temperature, and in an open system without oxidants, bases, or transition metals, led to the desired derivatives in up to 98% yield. The gram-scale synthesis produced 45% of the product after 20 h in a model example. The low yield was attributed to the similar oxidation potentials of the products and starting materials, which led to product degradation when exposed for a prolonged period in the electrochemical cell. Interestingly, using 2-[(trimethylsilyl)ethynyl]phenol as substrate, a *bis*-selenylated derivative was successfully prepared. Control experiments suggest that the reaction mechanism probably involves a radical pathway, although a phenyl selenium cation mechanism could not be ruled out.



Scheme 3. Electrochemical synthesis of selenylbenzo[*b*]furans *via* 2-alkynylphenol cyclization.

Zeng and co-workers developed an electrochemical strategy for the synthesis of 2-substituted benzoxazoles **9** through the indirect anodic oxidation of a Schiff base **8** (Scheme 4).[28] Initially, the authors found problems involving electrode passivation due to material deposition. However, using a two-phase system consisting of an aqueous carbonate buffer and dichloromethane (DCM), this issue was prevented, and the desired benzoxazole adduct **9** was obtained without any degradation. The process was carried out under constant current conditions at 40 mA in an undivided cell, employing GC (glassy carbon) as the anode and Fe as the cathode electrodes, and a buffer solution of 0.1M Na_2CO_3/0.1M $NaHCO_3$, v/v=8:2, (pH 10.5). A catalytic amount of NaI was applied as a redox catalyst in a two-phase system comprising buffer and CH_2Cl_2 as the solvent, resulting in the desired products in up to 95% yield. Replacing the carbonate buffer solution with water resulted in a lower yield, highlighting the significance of pH in the reaction. Using the buffer, the pH value remained stable throughout the electrolysis process. The electrochemical oxidation of iodide in the buffer layer leads to the formation of I_2, which can be converted to HIO, which then disproportionates into IO^- (hypoiodite) and IO_2^- (iodite). In the organic layer, simultaneous intramolecular cyclization establishes an equilibrium between the Schiff base and benzoxazoline, with each iodine-containing species serving as an oxidizing agent toward benzoxazoline and resulting in the formation of benzoxazole products. One notable advantage of this method is its independence from additional supporting electrolytes or oxidants, as sodium iodide effectively fulfills both roles.



8

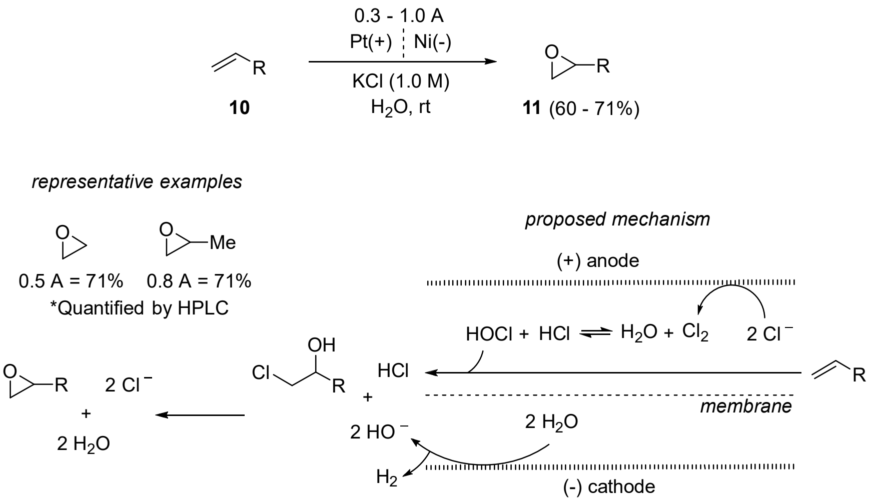
9 (70 - 95%)

buffer solution: 0.1M Na_2CO_3/0.1M $NaHCO_3$, v/v=8:2, pH 10.5

R^1	R^2	R^3	Yield (%)
H	H	4-BrPh	95
CH_3	H	4-BrPh	83
H	CH_3	4-BrPh	90
Cl	H	4-BrPh	78
H	H	4-OMePh	91
H	H	Ph	79

Scheme 4. Electrochemical synthesis of 2-substituted benzoxazoles.

Among the most produced chemicals in the world is ethylene oxide. It is widely used in the production of plastics, detergents, solvents, and other products, with an annual production exceeding millions of tons. Taking this into consideration, in 2020, Sargent and co-workers developed an electrochemical methodology for the synthesis of epoxides **11** from the corresponding olefins **10** (Scheme 5).[29] The reactions were carried out in a divided flow electrochemical cell, with a platinum foil (1 cm^2) on palladium (Pd) as the anode, nickel (Ni) foam as the cathode, and an Ag/AgCl reference electrode. An anion exchange membrane was used to separate the anodic and cathodic chambers, a 1.0 M potassium chloride (KCl) solution was used as the electrolyte, and water played a dual role as a solvent and a reagent. As part of the study, the current density was varied between 0.3 A/cm^2, 0.5 A/cm^2, 0.8 A/cm^2, and 1.0 A/cm^2, since current densities above 0.3 A/cm^2 are industrially relevant. Compared to the current production of ethylene oxide, this method does not release CO_2 into the atmosphere. The chloride added as the electrolyte mediates the reaction, oxidizing to chlorine gas (Cl_2), which, in equilibrium with water, produces hypochlorous acid (HOCl) and HCl. The olefin then reacts with the produced HOCl to form the corresponding chlorohydrin. The water reduced at the cathode releases H_2 and produces the hydroxide anion, which reacts with the chlorohydrin and HCl to form the final product.



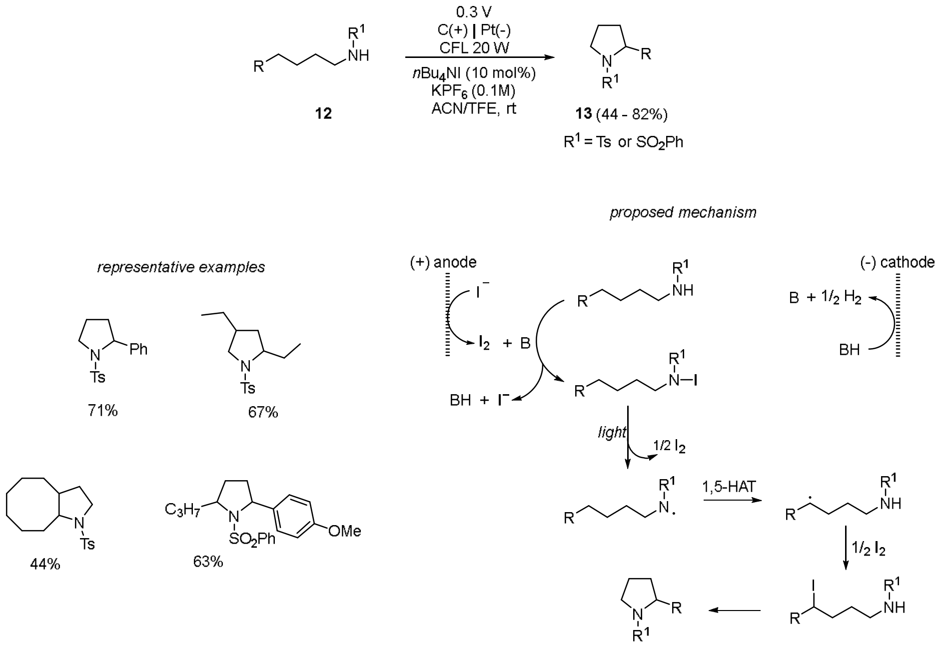
Scheme 5. Chloride-mediated selective electrosynthesis of olefins oxides.

3. C–N Bond formation

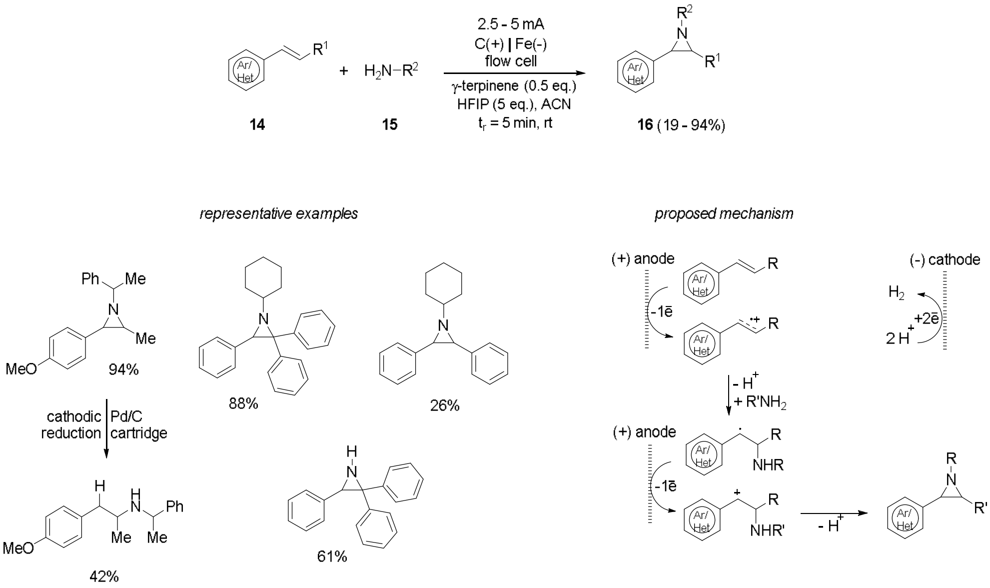
Direct amination of Csp^3–H bonds is of great interest in the field of C–H functionalization since nitrogen heterocycles and amines are commonly found in many pharmaceuticals and natural products. Additionally, The Hofmann-Löffler reaction is a significant chemical process that allows the modification of Csp^3–H bonds by creating a distant intramolecular free radical intermediate. This reaction results in the formation of cyclic amines from *N*-halogenated amines and typically requires strong acids, heat, or light to proceed.[30]

Stahl and co-workers developed a combined electrochemical/photochemical method for the dehydrogenative Csp^3–H/N–H coupling using various *N*-alkyl sulfonamide substrates **12**, demonstrating good reactivity with both sp^2 and sp^3 N–H bonds to form the corresponding pyrrolidine **13** (Scheme 6).[31] Iodide acts as an electrochemical mediator and involves light-induced cleavage of the intermediate N–I bond, allowing the electrochemical process to occur at low electrode potentials and significantly enhancing the functional-group compatibility of electrochemical C–H amination. Functional-group tolerance is achieved through the synergistic use of a low-potential mediator (I^-/I_2) along with photochemical activation of the N–I intermediate formed under reaction conditions. The anodic potential required for the regeneration of I_2 at the electrode (0.3-0.7 V *vs.* Fc/Fc^+) is significantly lower than the redox potential of electron-rich arenes and other substituents, avoiding degradations.

Electrochemical aziridination of internal alkenes is a modern method for efficiently synthesizing valuable aziridine derivatives, offering precise control over regioselectivity under mild conditions. Considering this, in 2021, Noël and co-workers developed an electrochemical aziridination of internal alkenes with primary amines (Scheme 7).[32] The reaction, conducted in a homemade electrochemical flow reactor, was applied in 28 examples, achieving yields of up to 94%, with a residence time of only 5 min. The reaction employed alkene **14**, amine **15**, 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP), γ-terpinene, MeCN as solvent, a carbon anode, and an iron cathode, with a current density between 2.5 and 5 mA. The cathode generated hydrogen gas, which could be employed in a subsequent reactor to reduce the aziridine to the desired hydroaminated product using Pd/C (cartridge). Mechanistic investigations and theoretical calculations (DFT) suggested that the alkene undergoes anodic oxidation before coupling with the amine. This method proved effective in the direct conversion of olefins and primary amines into aziridines **16**. The addition of a hydrogen and electron donor can reduce overoxidation.



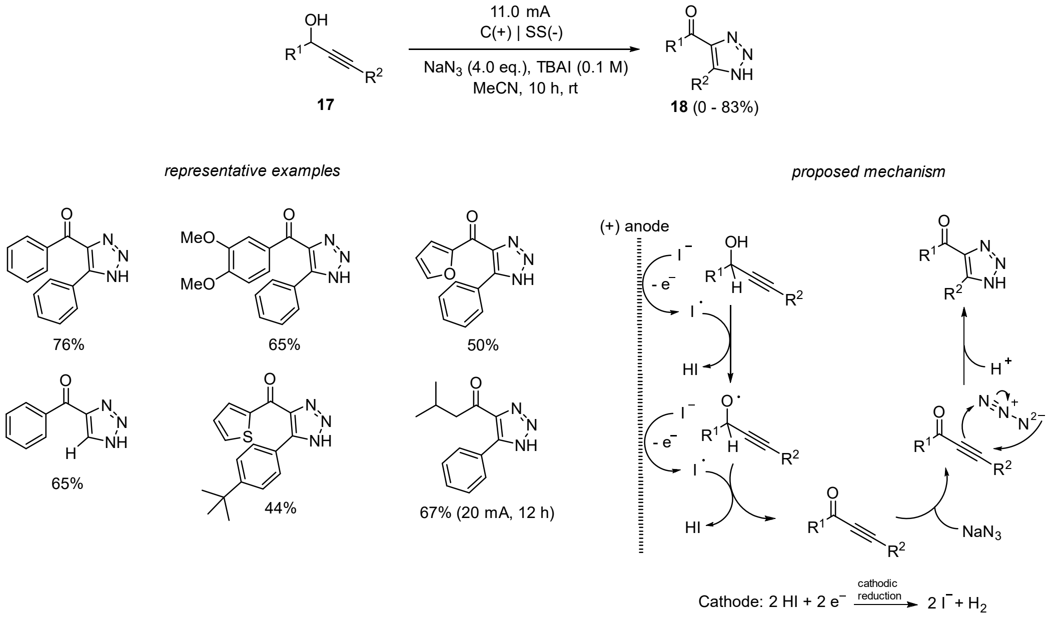
Scheme 6. Electrochemical/photochemical Hofmann-Löffler reaction.



Scheme 7. Electrochemical synthesis of 2-substituted benzoxazoles.

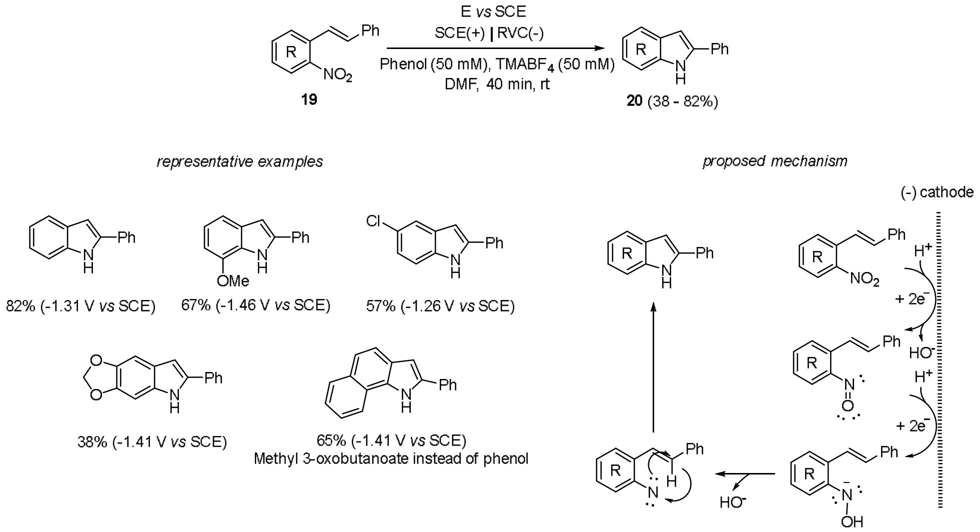
The use of 0.5 equivalent of 1,4-cyclohexadiene (1,4-CHD) resulted in a significant reduction in imine formation. However, γ-terpinene, being an economical and non-toxic alternative compared to 1,4-CHD, was effective in preventing alkene overoxidation (Scheme 7).

In 2022, the Nobel Prize in Chemistry was awarded to three scientists for their notable contributions to the advancement of click chemistry and bioorthogonal chemistry.[33-35] Since their discovery, these areas of chemistry have gained widespread recognition and have been extensively studied, and has led to numerous investigations into the 1,2,3-triazole core. This heterocycle is found in drugs and natural products, with significant biological activities.[36,37] Taking advantage of this opportunity, in 2023, Bera and co-workers developed an electrochemical methodology for the synthesis of 4,5-disubstituted triazole derivatives **18** from secondary propargylic alcohols **17** and sodium azide (Scheme 8).[38] The reactions were carried out in an undivided electrochemical cell under constant current, using carbon as the anode and stainless steel (SS) as the cathode, at room temperature. Acetonitrile was used as the solvent, and tetrabutylammonium iodide (TBAI) as the electrolyte. In the proposed mechanism, the iodide anion acts as a redox mediator, being oxidized at the anode to form radical iodine, which in two subsequent steps oxidizes the propargylic alcohol **17** to a carbonyl derivative. Subsequently, a [3+2]-cycloaddition with the azide occurs, yielding the 4,5-disubstituted triazole derivatives **18**. To confirm the mechanism, control reactions and density functional theory calculations were performed.



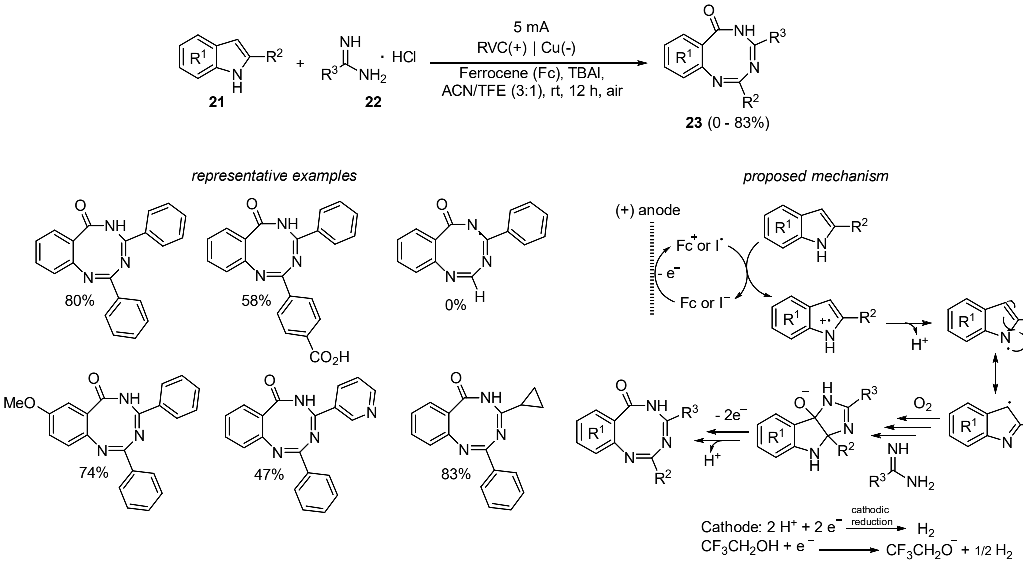
Scheme 8. Synthesis of 1,2,3-triazole derivatives *via* electrochemical oxidation and click chemistry.

Indole derivatives are valued for their diverse biological properties, playing a crucial role in pharmaceutical research by showing significant antioxidant, antimicrobial, and anticancer activities, thereby making it pivotal in the development of new drugs and bioactive compounds.[39,40] Peters and co-workers developed an electrosynthetic methodology to produce 1*H*-indole derivatives **20** by reduction of *o*-nitrostyrene **19** (Scheme 9).[41] The reactions were carried out in an undivided cell with a constant potential relative to the saturated calomel electrode (SCE), which acted as the anode, reticulated vitreous carbon (RVC) as the cathode, and the real reference electrode consisted of a mercury amalgam saturated with cadmium in contact with DMF saturated with both cadmium chloride and sodium chloride (this electrode has a potential of -0.76 V relative to the saturated calomel electrode at 25 °C). Dimethylformamide was used as the solvent, tetramethylammonium tetrafluoroborate ($TMABF_4$) as the electrolyte, phenol as the H^+ source, and the reaction was conducted at room temperature for 40 minutes. The mechanism was proposed in another article by the same group,[42] and involves the double reduction of *o*-nitrostyrene derivatives **19** in a slightly acidic medium, followed by the formation of a nitrene intermediate. Next, after an intramolecular cyclization, the desired 1*H*-indole derivative **20** is formed. Cyclic voltammetry was conducted to determine the ideal potential for the reduction of each molecule in the examples.



Scheme 9. Electrosynthesis of substituted 1*H*-indoles from *o*-nitrostyrenes.

In 2024, Huang and co-workers proposed an electrosynthetic methodology for the formation of eight-membered benzo[1,3,5]triazocin-6(5*H*)-ones **23** through the electrochemical oxygenation and annulation of indole derivatives **21** in the presence of amidines **22** (Scheme 10).[43]



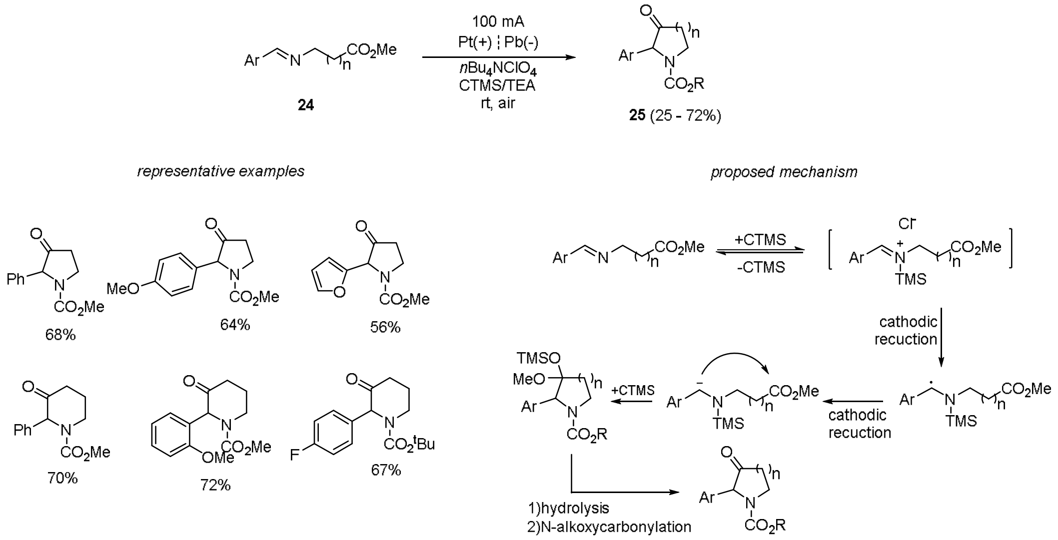
Scheme 10. Electrochemical oxygenation and annulation of indole derivatives.

This core is similar to benzotriazocines, known for their anesthetic and sedative activities.[44] The reactions were carried out in an undivided cell under constant current electrolysis, using reticulated vitreous carbon (RVC) as the anode and copper as the cathode. Acetonitrile and trifluoroethanol (TFE) were employed as solvent mixtures, tetrabutylammonium iodide as the electrolyte, and ferrocene as a mediator. The reactions proceeded over 12 h at room temperature in the presence of air. In the proposed mechanism, both ferrocene and iodide can act as mediators to oxidize the indole derivatives **21**. Following H$^+$ loss, the resonance-stabilized intermediate undergoes a series of transformations to yield the derivatives **23** (Scheme 10).

4. C–C Bond formation

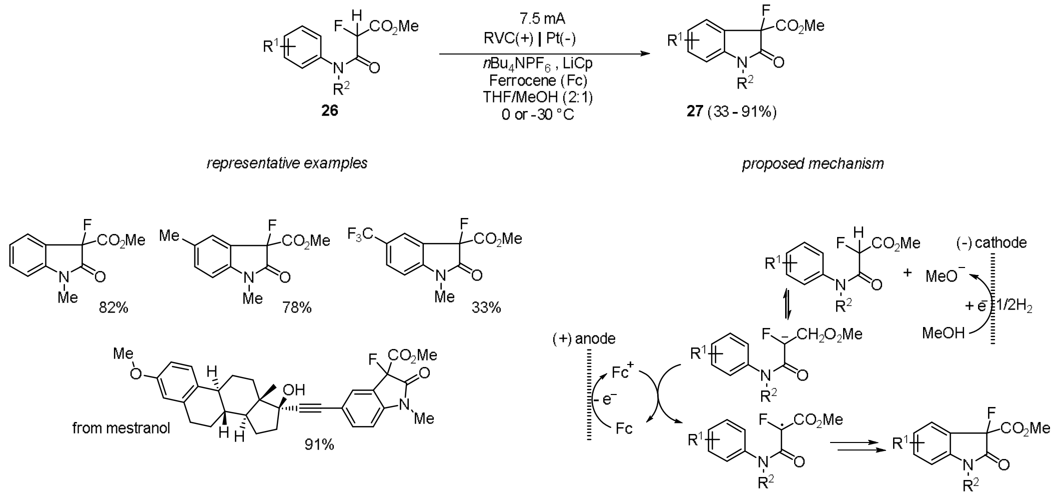
Electrosynthesis has emerged as a powerful strategy in the synthesis of heterocycles through C–C bond formation. This approach applies electrical current to initiate controlled oxidation and reduction reactions, enabling the *in-situ* generation of reactive intermediates and the selective coupling of functional groups.

Kise and co-workers investigated the electroreduction of aromatic β- and γ-imino esters **24** derived from β-alanine and GABA (Scheme 11).[45] In the presence of chlorotrimethylsilane (CTMS), followed by *N*-alkoxycarbonylation, the resulting cyclic five- and six-membered amines afforded mixed ketals of pyrrolidin-3-ones and piperidin-3-ones derivatives **25**. The electroreductive intramolecular coupling was achieved using $n\text{Bu}_4\text{NClO}_4$ as a supporting electrolyte, CTMS and triethylamine (TEA) as additives, in a divided cell equipped with a lead cathode, a platinum anode, and a ceramic diaphragm, applying a constant current of 100 mA at room temperature. Subsequent acid hydrolysis of the mixed ketals delivered *N*-alkoxycarbonyl-2-aryl pyrrolidin-3-ones and 2-aryl piperidin-3-ones in up to 72% yield. The proposed mechanism involves an initial one-electron transfer to the CTMS complex, followed by *N*-silylation and an additional one-electron transfer to the resulting radical intermediate, generating an anion after cathodic reduction. Intramolecular attack of the carbanion on the ester group forms an *O*-anion, which is then *O*-silylated. During the workup, *N*-desilylation results in the final ketals, which were hydrolyzed to ketones by treatment with 1 M HCl.



Scheme 11. Electroreductive intramolecular coupling of aromatic β- and γ-imino esters.

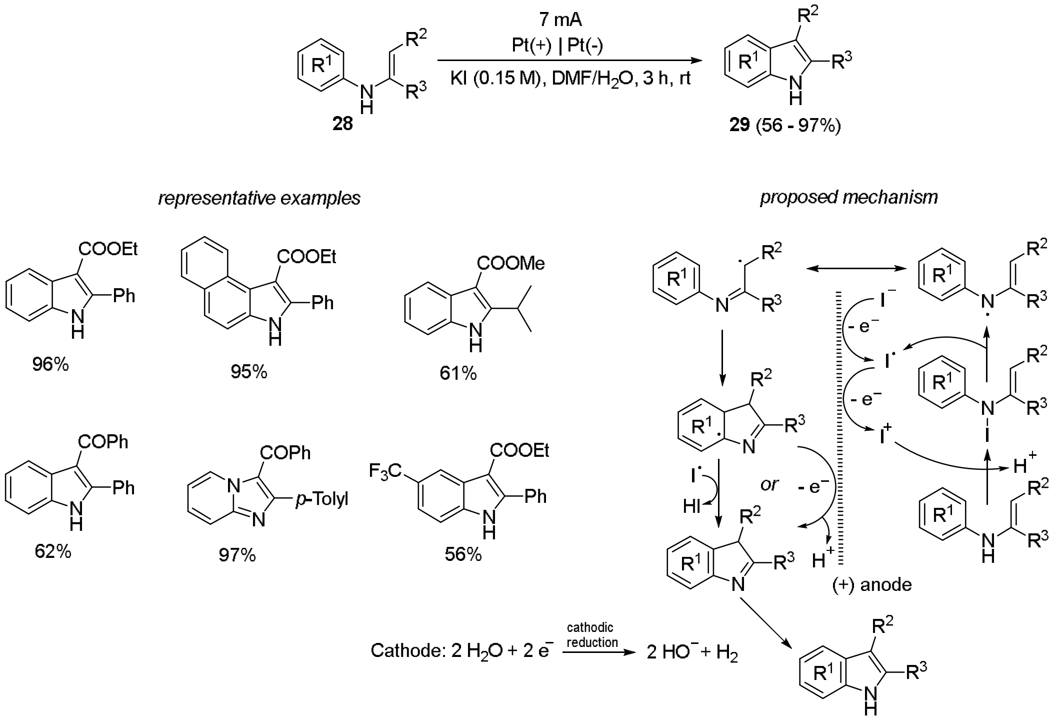
In 2017, Xu and Wu have developed a chemoselective electrochemical cross-coupling reaction of Csp^3–H and Csp^2–H bonds from malonate amides **26**. By using Cp_2Fe (ferrocene) as the redox catalyst, and continuously generating oxidant and base *in situ* at low temperature, the synthesis of heat-sensitive fluorinated oxindoles **27** was described (Scheme 12).[46] The anode material played a crucial role in this transformation. However, using platinum or graphite plates as the anode resulted in only trace of product, likely due to the specific potential window that each electrode offers during the transformation. This approach also highlighted that electrochemical oxidation using redox catalysis can produce functionalized monofluoroalkyl radicals through C–H bond activation. The substrate scope tolerated a diversity of substituents with different electronic properties on the *N*-aryl group of the amide substrate. By applying a potential difference across the electrolysis cell, the anodic oxidation of Cp_2Fe and the cathodic reduction of MeOH are initiated. This generates MeO^-, which abstracts the malonyl proton to form an enolate intermediate. Next, electron transfer from this intermediate to Cp_2Fe^+ afford a key radical intermediate, regenerating Cp_2Fe. Radical cyclization, followed by rearomatization afford the final oxindole product.



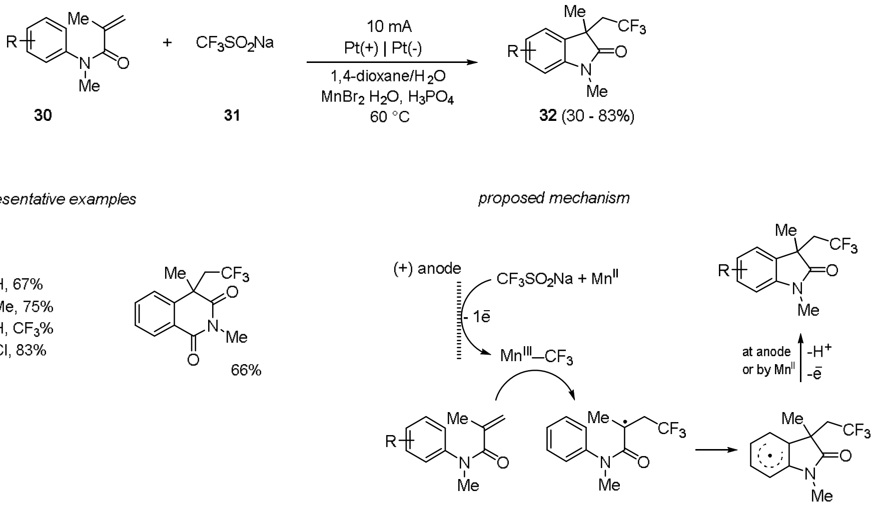
Scheme 12. Electrochemical cross-coupling reaction of Csp^3–H and Csp^2–H bonds.

Due to the importance of the indole core, Lei and co-workers conducted the synthesis of these derivatives **29** through an electrosynthetic methodology involving the annulation of *N*-aryl enamines **28** mediated by iodides (Scheme 13).[47] The reactions were carried out in an undivided cell under constant current, using platinum as both anode and cathode for 3 h at room temperature. Potassium iodide was used as the electrolyte, and a mixture of dimethylformamide and water was used as the solvent. Literature data[48] and control reactions using iodine, *N*-iodosuccinimide (NIS), and the radical scavengers 2,2,6,6-tetramethylpiperidin-1-yl-oxyl (TEMPO) and butylated hydroxytoluene (BHT) were carried out to propose a plausible reaction mechanism. Initially, the hyperiodide intermediate (I^+) is generated from the anodic double oxidation of the iodide ion. Then, the *N*-aryl enamine **28** reacts with the *in situ* generated I^+ to form an *N*-iodo intermediate. The hemolytic cleavage of the N–I bond initiates the radical propagation process. Intramolecular radical addition, and deprotonation lead to the formation of indole derivatives **29**. Meanwhile, the generated iodine radical can be oxidized by the anode to regenerate the hyperiodide intermediate. At the same time, the cathodic reduction of water balances the charges and releases hydrogen gas.

Additionally, Mo and co-workers introduced an electrochemical approach mediated by manganese for trifluoromethylation/Csp^2–H functionalization of *N*-arylmethacrylamide derivatives **30** using sodium trifluoromethanesulfinate **31** (Langlois reagent) as the CF_3 source (Scheme 14).[49] This method afforded trifluoromethyl-containing oxindoles **32** in up to 83% yield. The setup employed $MnBr_2$ as a mediator, Pt electrodes with a constant current of 10 mA, over 6 h. While H_3PO_4 (2 equiv.) was initially required as a sacrificial oxidizer, its substitution by AcOH afforded similar results without the need of an electrolyte. The Mn(III)–CF_3 species formed *via* anodic oxidation of Mn(II) in the presence of Langlois reagent facilitates the addition of CF_3 radicals to the olefins. Next, this intermediate can undergo intramolecular cyclization, followed by oxidation (by Mn(II) species or at the anode), and aromarization, to afford the final product.

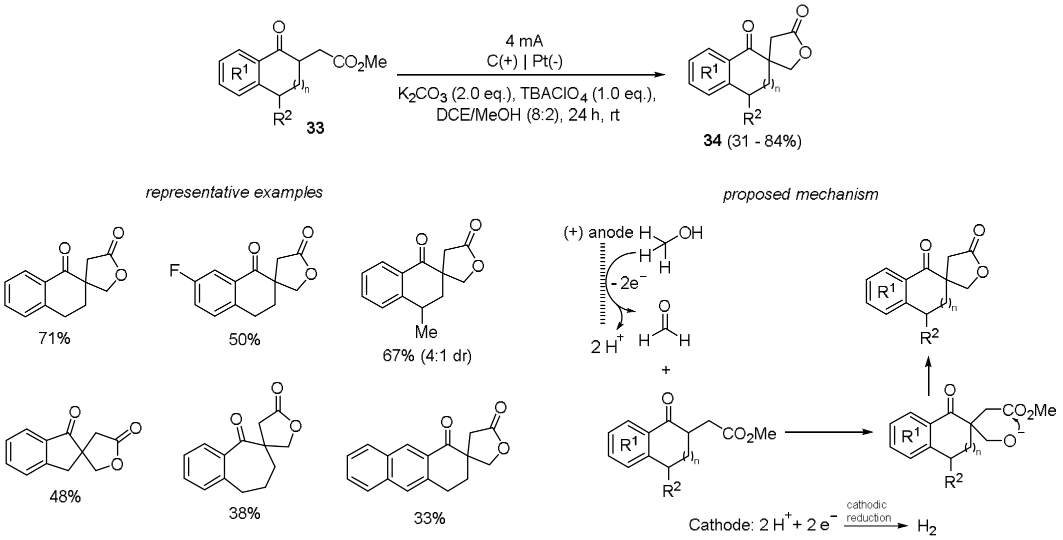


Scheme 13. Electrocatalytic annulation of *N*-aryl enamines to substituted indoles.



Scheme 14. Oxindoles and related heterocycles synthesis by trifluoromethylation/C*sp*^{2}–H functionalization.

Spirolactones are important components in medications and bioactive natural products used against heart failure, kidney problems, and cancer.[50,51] In 2024, Shengqing and co-workers conducted the electrosynthesis of spirolactones **34** from α-tetralone derivatives **33** (Scheme 15).[52] The reactions were carried out in an undivided cell under constant current, using carbon as the anode and platinum as the cathode, for 24 h at room temperature. Potassium carbonate was used as the base, tetrabutylammonium perchlorate (TBAClO$_4$) as the electrolyte, dichloroethane (DCE) as the solvent, and methanol as the co-solvent and reagent. For the proposal of a plausible mechanism, control reactions were performed, and previous literature reports were studied.[53] First, methanol is oxidized in the anode to formaldehyde with the loss of two electrons; this step also requires the presence of K_2CO_3, which is crucial to facilitate the oxidation process. Next, an aldol reaction occurs between formaldehyde and α-tetralone derivatives **33**. The lactonization of the formed intermediate generates the desired spirolactones **34**. The cathodic reduction of H^+ balances the reaction.

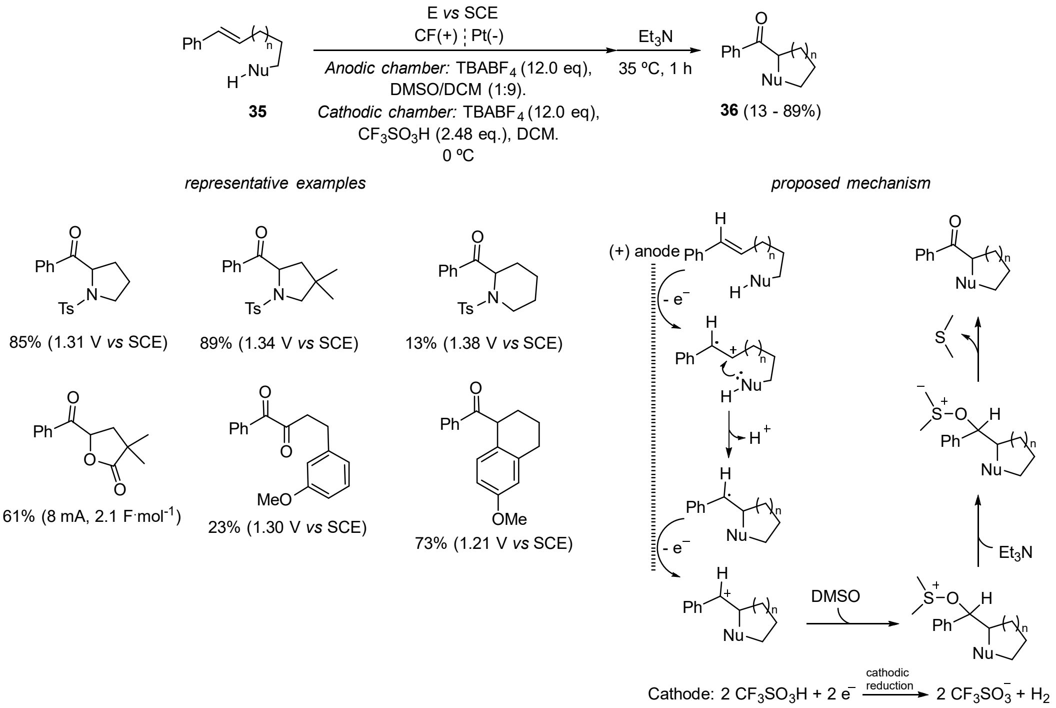


Scheme 15. Electrochemical synthesis of spirolactones from α-tetralone derivatives.

5. Miscellaneous

Chemical transformations involving the formation of multiple and different bond types are often classified as "miscellaneous" due to their diversity. These reactions are essential in modern chemistry, enabling the formation and cleavage of multiple covalent bonds between different atoms like carbon, oxygen, nitrogen, and sulfur.

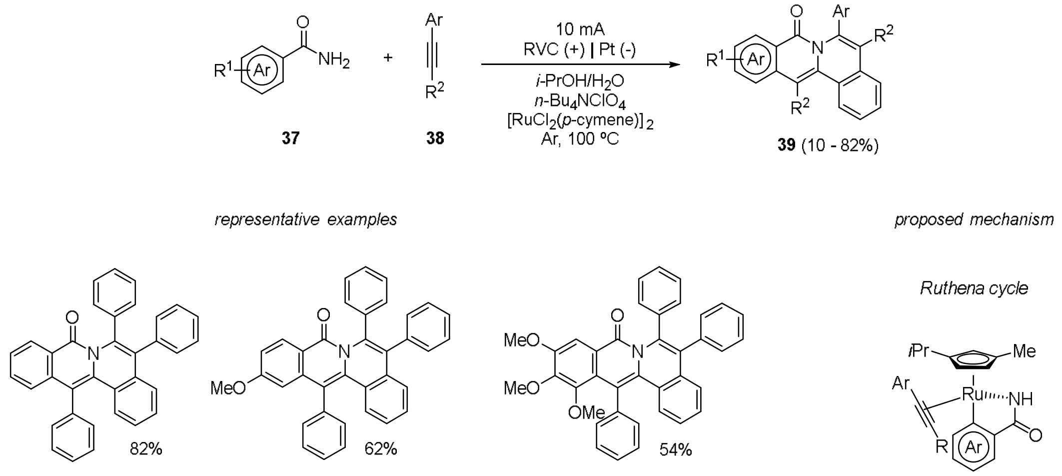
Additionally, vicinal difunctionalization of alkenes, involving reactions with nucleophiles and/or electrophiles at adjacent sp^2 carbons, is an effective method in organic synthesis to increase molecular complexity, being particularly useful for constructing cyclic structures, including those containing exocyclic ketones, which are common in natural products and biologically active compounds.[59] Yoshida and co-workers developed an electrosynthetic methodology for the synthesis of exocyclic ketones **36** *via* difunctionalization of alkenes **35** (Scheme 16).[60] The reactions were carried out in an H-type divided cell, using carbon felt (CF) as the anode and platinum as the cathode. The anodic chamber was charged with alkene **35**, tetrabutylammonium tetrafluoroborate (TBABF$_4$), and a mixture of dimethyl sulfoxide and dichloromethane (DCM). The cathodic chamber contained tetrabutylammonium tetrafluoroborate (TBABF$_4$), triflic acid, and dichloromethane (DCM). Following control experiments, a mechanism was proposed. Initially, anodic oxidation of **35** produces the radical cation. An intramolecular nucleophilic attack, followed by deprotonation, forms a cyclic benzylic radical, which is further oxidized to generate the benzylic cation. Attack by DMSO forms the cyclic alkoxysulfonium ion. After treatment with triethylamine, a sulfur ylide is formed, and an intramolecular proton transfer followed by the elimination of dimethyl sulfide generates the exocyclic ketone **36**. The cathodic reduction of triflic acid produces hydrogen and balances the charges.



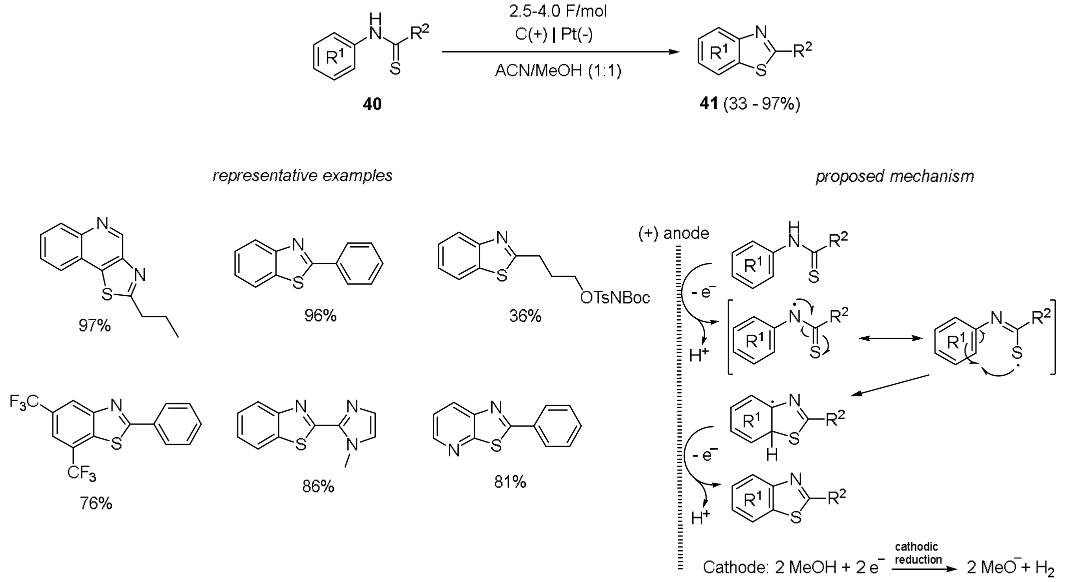
Scheme 16. Electrosynthesis of exocyclic ketones *via* alkoxysulfonium ions.

Protected amides undergo reactions with alkynes, leading to the formation of simple isoquinolones catalyzed by metals like Ni, Ru, Rh, and Co.[63–67] Tang and co-workers introduced a novel double-electrocatalytic organometallic C–H activation using amides **37** and alkynes **38** to synthesize polycyclic isoquinolinones **39** (Scheme 17).[68] This method employed $[RuCl_2(p\text{-cymene})]_2$ (5 mol%), NaOPiv (1.0 equiv), $n\text{-}Bu_4NClO_4$ (1.0 equiv), and a 10 mA current, achieving the desired analogues in up to 82% yield, without external oxidants after 14 h. Electron-rich and electron-deficient substituents in both alkynes and benzoylamides were well-tolerated, although an increase in methoxy substituents in benzoylamides reduced reaction efficiency. The electric current serves to oxidize Ru(0) to Ru(II) at the anode, which is required for catalyst regeneration, distinguishing this method from those relying on strong oxidizers and enabling efficient derivative synthesis under mild electrical conditions and free of protective groups.

The benzothiazole core is present in various bioactive compounds, including antiviral, antitumor, and antiseptic agents, as well as compounds targeting Alzheimer's disease.[54] The synthesis of substituted benzothiazoles continues to present challenges, despite advancements with photoredox processes and the use of ruthenium and cobalt catalysts.[55] However, the complete removal of metal traces remains a significant obstacle for large-scale processes.[56,57] Influenced by these factors, Wirth and co-workers reported the electrosynthesis of benzothiazoles **41** from *N*-(hetero)aryl-thioamides **40,** without the use of electrolytes and catalysts (Scheme 18).[58] The reactions were carried out in an undivided continuous flow electrochemical cell with constant current (although the total charge used varied with the substrate), using carbon as the anode and platinum as the cathode. A solvent mixture containing acetonitrile (ACN) and methanol was employed, and depending on the solubility of the substrate, a small amount of water was added. In the proposed mechanism, the *N*-(hetero)aryl-thioamides **40** undergo anodic oxidation to form a thioamidyl radical intermediate. After intramolecular cyclization and an additional anodic oxidation, the benzothiazole derivatives **41** are obtained. The authors also reported the formation of dimers, and studies using TEMPO, a radical scavenger, were conducted.

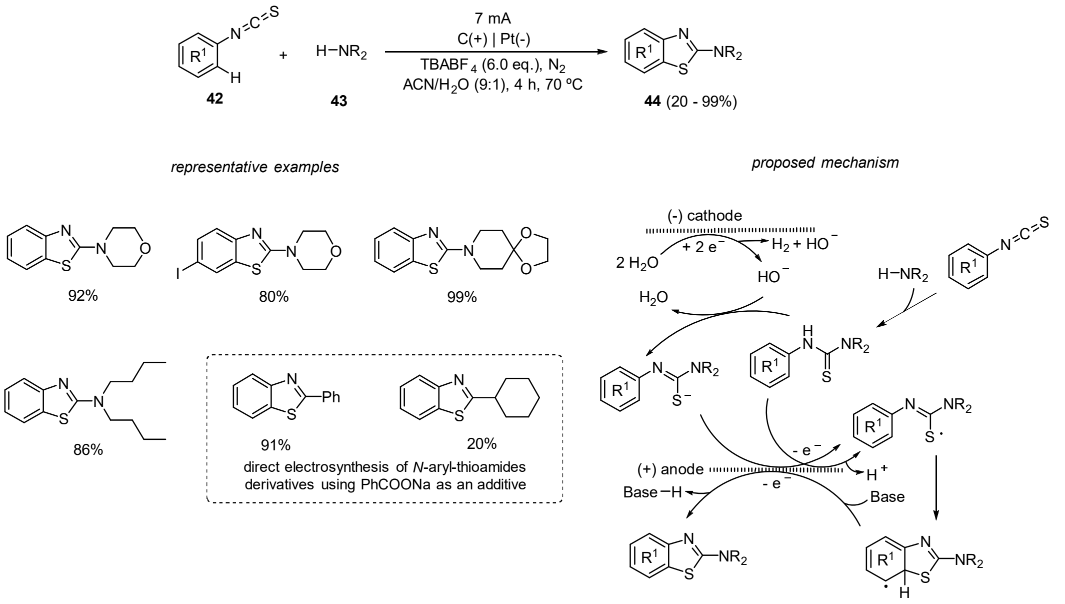


Scheme 17. Electrosynthesis of polycyclic isoquinolinones.



Scheme 18. Electrosynthesis of benzothiazoles and thiazolopyridines in continuous flow.

The electrosynthesis of 2-aminobenzothiazole derivatives **44** using amines **43** and aryl isothiocyanates **42** was reported by Lei and co-workers (Scheme 19).[61] The reactions were carried out in an undivided cell under constant current using carbon as the anode and platinum as the cathode at 70 °C for 4 h in an inert nitrogen atmosphere. The electrolyte used was tetrabutylammonium tetrafluoroborate (TBABF4), and the solvent was a mixture of acetonitrile (ACN) and water. The proposed mechanism was based on control reactions and literature reports.[55,62] Initially, the *in situ* nucleophilic addition of amines **43** to aryl isothiocyanates **42** generates thiourea derivatives. Subsequent deprotonation by hydroxide, generated from the cathodic reduction of water, produces an intermediate with a negative charge on the sulfur atom. Anodic oxidation leads to the formation of a thiyl radical. Alternatively, the radical can also be generated directly from the anodic oxidation of thiourea derivatives. The sulfur radical then undergoes cyclization, generating a radical on the benzene ring. Subsequent anodic oxidation and deprotonation by a base furnish the final product **44**. Simultaneously, the cathodic reduction of water releases hydrogen gas during the reaction. The authors also performed the direct anodic oxidation of *N*-aryl-thioamide derivatives using sodium benzoate (PhCOONa) as an additive.



Scheme 19. Electrosynthesis of benzothiazoles.

6. Emerging trends and future perspectives

In recent years, there have been significant advancements in the electrochemical synthesis of heterocyclic compounds, offering innovative synthetic approaches. One key trend that stands out is the growing emphasis on sustainability and eco-friendly practices. Researchers are working towards reducing waste, using renewable energy sources, and adopting greener methods, all aiming to make heterocyclic synthesis more environmentally friendly. Additionally, there is interest in exploring new materials, electrolytes, and reaction conditions to further improve these synthesis methods.

Another notable aspect is the adoption of advanced electrochemical methods, including flow electrochemistry, photoelectrochemistry, and electrocatalysis. These methods provide better control over reactions, enhancing reactivity and selectivity. The future is promising, with efforts directed towards refining and integrating these methods into efficient protocols for synthesizing heterocyclic compounds. Furthermore, researchers are actively designing new redox mediators, exploring novel reaction mechanisms, and customizing electrode surfaces to achieve higher levels of control and efficiency. Collaboration among academia, industry, and research institutions will be pivotal in addressing these challenges and advancing the field of electrochemical synthesis of heterocyclic compounds towards new discoveries.

7. Conclusions

This chapter summarized significant advancements in the electrochemical synthesis of heterocyclic compounds, emphasizing reaction mechanisms, electrode materials, and optimized electrochemical conditions to enhance both selectivity and yield. Detailed discussions covered the synthesis of key heterocyclic groups such as those involving C–O, C–N, C–C, and miscellaneous bond formations, providing a comprehensive analysis of their synthetic pathways. The use of mediators was observed to enable the achievement of milder reaction conditions, contributing to the broader applicability and efficiency of electrochemical methods in heterocyclic synthesis. Furthermore, electrochemical synthesis synergistically integrates with other technologies such as photochemical reactions and continuous flow processes, further enhancing synthetic efficiency and scope. This overview highlighted the pivotal role of electrochemistry in advancing the field of heterocyclic chemistry, promising continued progress in pharmaceuticals, materials science, and related fields.

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