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Review

Electrochemical Intramolecular Cyclization Strategies for the Synthesis of Pharmaceutically Relevant Fused *N*-Heterocycles

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Cite This: *ACS Electrochem.* 2026, 2, 845−873

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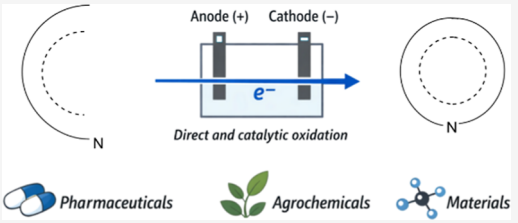
ABSTRACT: Nitrogen-containing fused aromatic heterocycles have a crucial role in the fields of pharmaceuticals, agrochemicals, and materials sciences. Electrochemical methods have increasingly emerged as powerful tools for the sustainable synthesis of these compounds. This review discusses recent progress in electrosynthetic strategies for fused systems that avoid the use of hazardous oxidants and extreme reaction conditions. There has been significant progress in the direct synthesis of various frameworks over the last few decades, specifically from 2015 to 2024. These advances are enabled by direct electrosynthetic approaches, mild redox mediators, and optimized electrolyte systems. These methodologies efficiently incorporate electron-rich and electron-deficient substrates, demonstrating broad tolerance to functional groups. Mechanistic investigations have revealed the pivotal role of radical and cationic intermediates, which are generated and controlled in situ. This facilitates regio- and chemoselective cyclization pathways. Ongoing research focuses on scalability, enhancing electrode stability, and expanding the diversity of accessible fused heterocyclic scaffolds. Innovations in this field highlight the potential of electrochemistry as a sustainable, versatile tool for synthesizing diverse nitrogen-containing fused aromatic heterocycles.



KEYWORDS: *electrosynthesis, electrocatalysis, oxidation, aromatics, fused N-heteroaromatics, sustainable synthesis*

INTRODUCTION

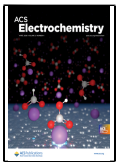
Fused heterocyclic compounds are essential to organic chemistry due to their prevalence in pharmaceuticals, agrochemicals, and functional materials. Electrochemical strategies for constructing condensed heterocycles have attracted increasing attention in response to the demand for more sustainable synthetic methodologies. This review examines the electrochemical synthesis of fused heterocycles and highlights its potential for scalable production of pharmaceutically relevant frameworks. Electrochemical methods enable the creation of complex, bioactive molecules while addressing environmental and industrial challenges. Compared with conventional synthetic methods that often rely on stoichiometric reagents and harsh conditions, electrochemical approaches provide a more sustainable alternative, although considerations regarding energy consumption and electrode material sourcing are important.

Synthetic organic electrochemistry is on the verge of a renaissance. These methods enhance selectivity and efficiency in chemical reactions, offering a promising approach to modern synthetic chemistry.[1,2] However, early pioneering research in organic electrochemistry began almost 200 years ago, when Michael Faraday prepared acetic acid by electrosynthesis in 1834.[3] A decade later, in 1847, Kolbe's decarboxylative dimerization, a C−C bond formation, became the foundation of electrochemical transformations.[4] In 1949, the Simons electrofluorination, a foundational organofluorine chemistry method, was reported.[5] In 1980, Monsanto published a study on the industrial relevance of their electrochemical hydrodimerization of acetonitrile into adiponitrile.[6] These and further industrially relevant processes indicate the potential and the revival of organic electrochemistry.[1,7−12]

Electrochemical transformations are considered environmentally benign because they use electricity as a traceless reagent, eliminating the need for harsh chemicals.[13] Electroorganic synthesis is a highly effective technique in organic synthesis, unlocking new reaction pathways and reducing the need for reagents.[14] In electrochemical organic synthesis, the applied potential drives the reaction and controls selectivity.[15,16] In direct electrolysis, selectivity is primarily governed by the electrode potential, allowing tunable control based on the substrate's redox properties. This potential-controlled regime may provide broad substrate tolerance and tunable selectivity.

Redox mediators (Figure 1) in electrochemical processes offer advantages, particularly in controlling reaction conditions and enhancing selectivity.

Received: December 6, 2025
Revised: March 1, 2026
Accepted: March 12, 2026
Published: March 21, 2026



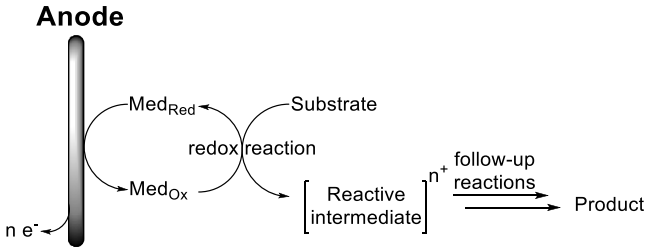


Figure 1. Redox mediator (Med) applied in electrocatalytic oxidation, illustrated with a positively charged reactive intermediate.

In mediated electrolysis, selectivity arises from the intrinsic redox properties and molecular structure of the mediator, which can enable substrate discrimination and specific reaction pathways through molecular recognition and controlled electron transfer. These mediators enable reactions at lower overpotentials, reducing energy requirements and facilitating efficient electron transfer. They also prevent undesired over-oxidation and enhance selectivity.[17,18] Thus, mediated and direct electrolysis rely on different selectivity principles, each with distinct advantages.[19−21] However, the use of redox mediators introduces complexities regarding their cost, toxicity, and recyclability, which are crucial considerations for industrial applications. Direct electrochemical methods, though potentially requiring higher potentials, offer a simpler, atom-economical approach.

A notable feature of mediated electrolysis is the formation of radical intermediates in the bulk solution, far from the electrode surface. This spatial separation minimizes electrode passivation, maintains catalytic activity, and keeps the concentration of highly reactive intermediates low.[20] Reviews by Tang and co-workers in 2020 focused on organic synthesis mediated by halogen atoms,[22] while recent work from Mei et al. highlighted advancements in electrosynthetic reactions catalyzed by transition metals, further demonstrating the expanding applications of mediated electrolysis in organic synthesis.[23] The choice between halogen-mediated and transition metal-catalyzed systems often depends on the specific substrate and desired product, each offering different advantages in terms of reactivity and selectivity.

One feature of electrochemical synthesis is its ability to invert the polarity of molecules. In traditional organic chemistry, functional groups exhibit predictable reactivity patterns. However, electrochemistry can alter the reactivity of these molecules by applying an electric current. Oxidizing or reducing a molecule at the electrode can reverse the polarity of reactive centers. This effectively "flips" nucleophilic sites so that they behave as electrophiles, or vice versa. Recently, electrochemical transformations for the modification and preparation of heterocycles have been published, including the development of the modification of non-fused nitrogen-containing organic compounds.[24−27] Electrosynthesis of heterocycles involves two mechanisms: intramolecular cyclization, where a molecule forms a ring by linking atoms within itself, and intermolecular reactions, where two substrates come together to create a cyclic structure. Intramolecular cyclization offers precise control over electron transfer, making it advantageous in electrochemistry. This precision often enhances selectivity and efficiency. Intermolecular reactions use reactive groups that form rings under electrochemical conditions, increasing the range of accessible heterocyclic structures. These structures are valuable in pharmaceutical applications and materials science.

Electrochemical oxidative ring-closing annulations involve two nucleophilic functional groups within the substrate. In a single-electron transfer, one nucleophilic group is oxidized to an electrophilic radical, and the other nucleophilic group attacks it. The cyclic radical intermediate is oxidized in a second electron transfer step, forming the cyclic product (Figure 2).[28]

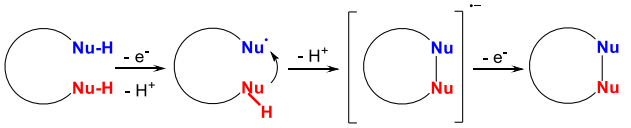


Figure 2. Intramolecular oxidative cyclization reaction in electro-organic synthesis.

Such reactions are particularly significant in electro-organic synthesis as π-conjugated systems often stabilize reactive intermediates, facilitating controlled bond formation and minimizing side reactions. These intramolecular processes play a pivotal role in creating nitrogen heterocycles. In this review, we specifically focus on intramolecular electrochemical cyclization strategies for the synthesis of fused nitrogen-containing heterocycles embedded within conjugated π-systems. In the case of preparing non-fused aromatic systems, Xu and Wu recently wrote a comprehensive summary of redox-mediated electrochemical cyclization reactions.[29] Similarly, several recent reviews have addressed broad aspects of electrochemical heterocycle synthesis, focusing on sustainability by Hashmi et al.,[30] and Devi et al.[31] carbon-heteroatom bond formation by Okumara et al.,[32] anodic construction of heterocycles by Zeng and Liang,[28] multicomponent reactions by Javahershenas et al.,[33] cascade reactions by Zhang,[34] by Elinson and colleagues[35] and specific electrochemical annulations[36] or dehydrogenations.[37]

The electro-organic synthesis of heterocycles has recently attracted greater interest, as evidenced by the reviews published by Aslam and co-workers[38] and Francke.[39] Intramolecular cyclization reactions yielding *N*-, O-, and *S*-heterocycles were comprehensively studied by Borpatra and colleagues.[40] Sbei and co-workers provided insights into the electrosynthesis of five- and six-membered nitrogen-containing heterocycles[41] followed by their review of catalytic electrosynthesis of *N*-, O-heterocycles.[42] However, these reviews generally offer broad coverage of the field and often include both fused and non-fused heterocycles, as well as intermolecular and intramolecular strategies. In contrast, the present review uniquely addresses intramolecular cyclization reactions for the construction of fused nitrogen-containing heterocycles within conjugated π-systems. By narrowing the scope to this important subclass, we aim to provide a focused and complementary resource for researchers working in electrochemical heterocycle synthesis. Recent reviews by Fersthtat et al.,[43] Swaroop,[44] Ye et al.,[45] and Yu et al.,[46] further illustrate the growing interest in electrosynthesis, but these also encompass a broader range of topics than the specific scope of our work.

Benzoxazoles are an important class of heterocyclic compounds widely incorporated into pharmaceuticals due to their potent biological activities. The benzoxazole skeleton also forms the active component in many marketed drugs, such as

https://doi.org/10.1021/acselectrochem.5c00523
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the antibiotics calcimycin, the antibacterial boxazomycin B, and the anticancer drug neosalvianen (Figure 3). Benzothiazoles are commonly used in fluorescent dyes, including cyanins, thiazole orange derivatives.[47−49]

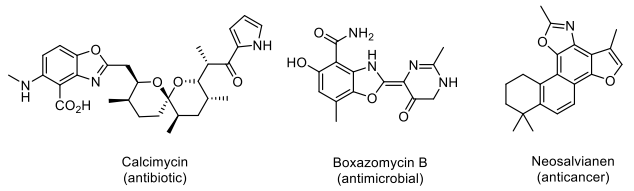
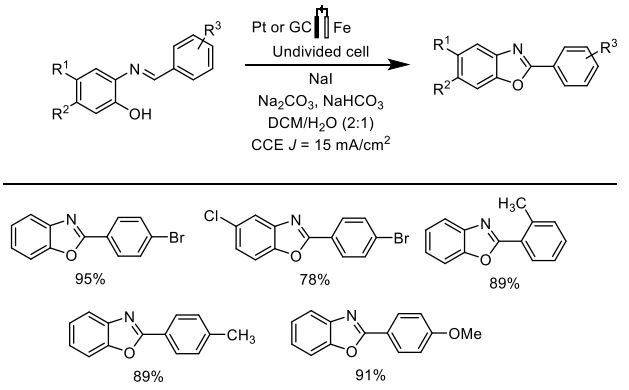


Figure 3. Selected examples of pharmacologically relevant drugs with a benzoxazole core.

The electrochemical synthesis of benzoxazoles and benzothiazoles can be achieved through several distinct strategies, including the iodine-mediated cyclization of *N*-arylimines and the bromine-mediated conversion of arylthioureas. Alternatively, benzoxazoles can be accessed directly from anilides via intramolecular C−H oxygenation. In 2013, Little's group[50] developed an effective method for the synthesis of 2-arylbenzoxazoles in an iodine-mediated electrochemical ring-closing of *N*-arylimines (Scheme 1).

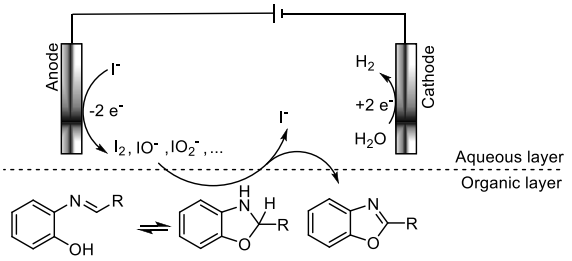
Scheme 1. Iodine-Mediated Electrosynthesis of 2-Arylbenzoxazoles[50,a]



[a]GC: glassy carbon, CCE: constant current electrolysis.

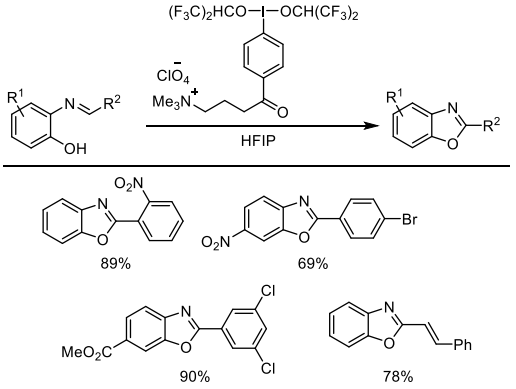
Their approach applied a mixed solvent system specifically designed to mitigate issues such as electrode passivation and the decomposition of starting materials. The reaction was conducted in a biphasic medium comprising an aqueous Na_2CO_3-DCM buffer paired with DCM as the organic phase in a 2:1 ratio. Sodium iodide served as the catalytic agent, while the electrochemical process itself was carried out in an undivided electrochemical cell. The setup utilized a glassy carbon (GC) electrode as the anode and an iron cathode, maintaining a current density of 8 mA/cm^2 without the requirement for any additional supporting electrolyte. Additionally, the method is advantageous due to its straightforward workup procedure. While they explored the substrate scope, it was found that steric factors do not affect the reaction, since the *o*-methylbenzol substituted benzoxazole gave the same yield as the *p*-methylbenzol substituted derivative (89%). Importantly, this electrochemical approach often avoids the need for stoichiometric oxidants or harsh acidic/basic conditions typically employed in traditional benzoxazole syntheses, leading to a more sustainable and milder process. The proposed mechanism involves the oxidation of benzoxazoline by hypoiodite, which is formed under basic conditions from molecular iodine generated at the anode from iodide (Scheme 2).

Scheme 2. Proposed Mechanism for the Iodine-Mediated Electrosynthesis of Benzoxazoles from Benzimines[50]



Francke and colleagues reported an alternative approach for the synthesis of benzoxazoles based on the electrochemical generation of iodine(III) mediator prior to the addition of imine (an "ex-cell" process).[51] Furthermore, the redox-active I(III) mediator possessed a quaternary ammonium moiety that served as a supporting electrolyte and facilitated the separation and reuse of the redox-active salt (Scheme 3).

Scheme 3. Application of Electro-Generated Hypervalent Iodine in the Electrosynthesis of Benzoxazoles[51,a]



[a]HFIP: 1,1,1,3,3,3-hexafluoroisopropanol.

The developed ex-cell approach did not require any additives; the oxidative formation of benzoxazoles proceeded under very mild conditions, and the method was compatible with a broad range of functional groups. The successful oxidation of the iodoaren was attributed to the choice of HFIP as the solvent for electrolysis. The solvent was selected due to its exceptional anodic stability and its ability to effectively stabilize iodine(III) species, which proved crucial for the smooth progression of the reaction.[52] Based on control experiments and DFT calculations, a novel, concerted reductive elimination pathway for benzoxazole formation has been proposed (Scheme 4).

The reaction begins with cyclization to the hemiaminal. Precoordination via hydrogen bonding between the N−H group and the Lewis basic oxygen of the HFIP ligand in the iodoarene initiates a concerted reductive elimination, yielding iodoarene and an ion pair consisting of a nitrenium cation and an HFIP anion. Finally, deprotonation yields the desired

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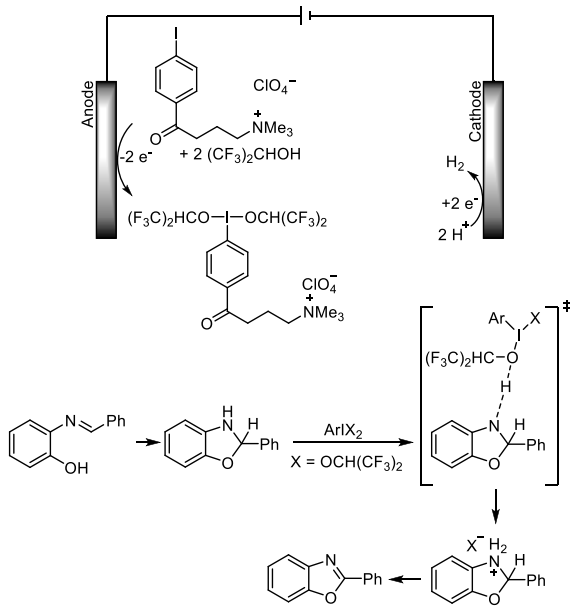
Scheme 4. Suggested Mechanism of the Electrosynthesis of the Hypervalent Iodine and Its Application in the Synthesis of 2-Phenylbenzoxazoles[52]

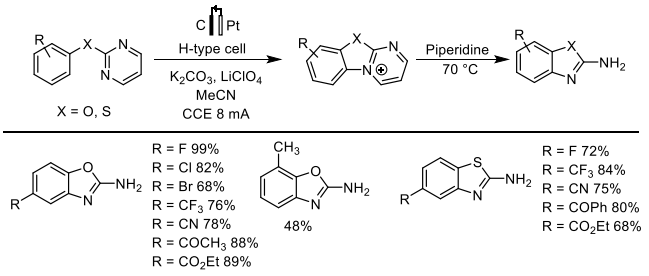


benzoxazole molecule. The "ex-cell" approach offers a significant advantage in terms of simplifying the reaction setup and reducing waste.

Yoshida and colleagues[53] developed the first synthesis of benzoxazoles and benzothiazoles from pyrimidines via C−H amination in 2015.

Electrolysis of 2-pyrimidyloxybenzenes and 2-pyrimidylthiobenzenes gave the corresponding pyrimidium, which was cleaved by piperidine, resulting in 2-aminobenzoxazole or the 2-aminobenzothiazole derivatives, respectively (Scheme 5).

Scheme 5. Electrosynthesis of Pyridinium Salts Followed by Ring Opening with Piperidine, Bearing

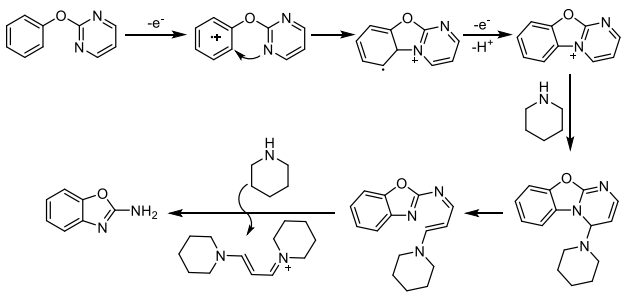


The pyrimidyl compound was oxidized in an H-type cell, employing a carbon felt anode and Pt cathode, using constant current electrolysis (8 mA) with 2.5 F, K_2CO_3 as a base, and $LiClO_4$ in acetonitrile as an electrolyte. After completing the electrolysis, the solution of the anodic chamber was treated with piperidine at 70 °C, cleaving the pyridinium to form the 2-amino derivatives. These 2-aminobenzothiazoles and 2-aminobenzoxazoles could serve as precursors for drugs as 5-HT_3 receptor agonists,[54,55] nAChR agonists[56] or inhibitors of the Leukotriene biosynthesis.[57]

2-aminobenzoxazoles or 2-aminobenzothiazoles. CCE: constant current electrolysis.[53]

The mechanism is depicted in Scheme 6. The one-electron oxidation of the substrate generates the corresponding radical

Scheme 6. Proposed Mechanism for the Intramolecular C−H Amination and Ring Opening of the Pyrimidinium Salt with Piperidine, Resulting in the 2-Aminobenzoxazoles[53]



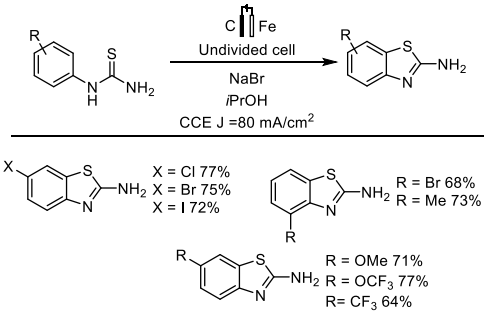
cation. This is followed by an intramolecular attack by the nitrogen atom of the pyrimidine ring, then one-electron oxidation, and finally, the loss of a proton, leading to the formation of the cyclized cationic intermediate. Then, piperidine attacks the carbon adjacent to the positively charged nitrogen atom, resulting in a ring-opening process.[53]

The formed imine is reacted with further piperidine, yielding the 2-aminobenzoxazole derivative. This method offers a unique approach utilizing pyrimidine substrates. The requirement for a separate cleavage step with piperidine adds complexity and generates additional waste.

2-Aminobenzothiazoles were also synthesized by the research group of Mollabagher[58] using NaBr as a mediator in 2022. Initially, they attempted a one-pot reaction with aniline and ammonium thiocyanate, electrolyzing the resulting thiourea. However, the yields were unsatisfactory, promoting them to optimize a two-step protocol in which the isolated thiourea was electrolyzed. They employed an undivided cell equipped with a graphite anode and an iron cathode and applied a constant current of 400 mA (80 mA/cm^2) for the electrochemical transformation of the arylthioureas. The reaction was carried out in *i*PrOH as solvent with NaBr serving as both the catalyst and electrolyte (Scheme 7).

Halogen atoms were tolerated in *ortho*- and *para*-position, and the yields varied slightly for electron-donating and withdrawing groups (64−77%), which is speculative to predict the electronic influence of the ring on the outcome of the reaction.

Scheme 7. Bromine-Catalyzed Electrosynthesis of 2-Aminobenzothiazoles[58,a]



[a]CCE: constant current electrolysis.

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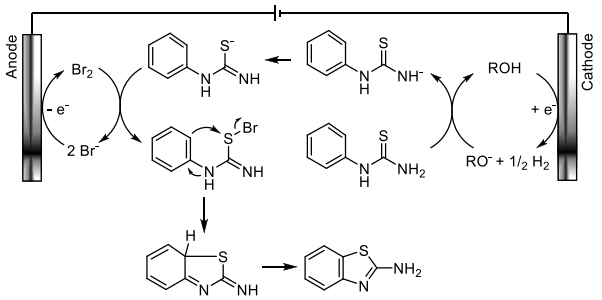
ACS Electrochem. 2026, 2, 845−873

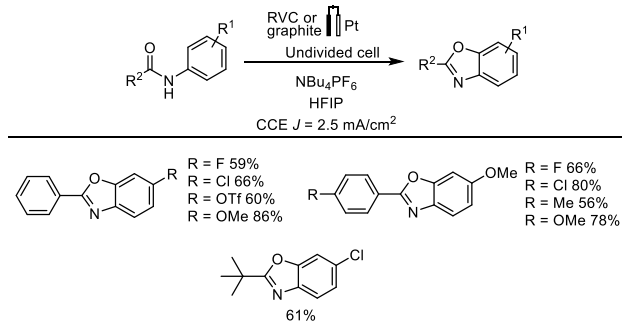
The electrogenerated base (EGB) deprotonates the phenylthiourea, and the so-formed phenylthiourea anion reacts with the molecular bromine, which is formed on the anode by oxidizing NaBr. The so-formed bromothio compound undergoes cyclization, and with the loss of a proton, the rearomatisation occurs, producing the 2-aminobenzothiazole (Scheme 8).[58]

Scheme 8. Proposed Mechanism for the Bromine-Catalyzed Electrosynthesis of 2-Aminobenzothiazoles[58]



In 2017, Waldvogel's group[59] synthesised benzoxazoles from anilides via intramolecular C−H oxygenation (Scheme 9).

Scheme 9. Electrosynthesis of Benzoxazoles from Anilides[59,a]



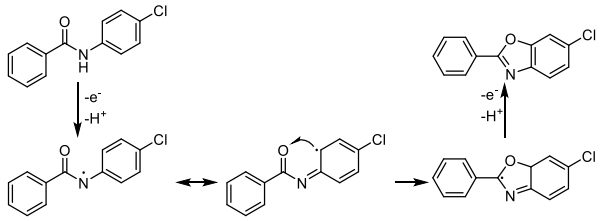
[a]RVC: reticulated vitreous carbon; HFIP: 1,1,1,3,3,3-hexafluoroisopropanol; CCE: constant current electrolysis.

Two distinct methodologies were developed. It is noteworthy that both methods utilise hexafluoroisopropanol as a solvent, a crucial component for the efficacy of the reaction. The initial method is constant current electrolysis (8.4 mA), which employs a reticulated vitreous carbon (RVC) anode and a platinum cathode, positioned angularly relative to each other. The second method is also a constant current electrolysis (2.5 mA/cm^2), but it uses beaker-type cell with a flat isostatically graphited anode and a platinum plate cathode, which are placed parallel to each other.

Substituents that donate electrons to either the amide or anilide moiety of the substrate improve the reaction. Furthermore, common leaving group functionalities are also compatible with this reaction. Aromatic systems and quaternary alkyl groups are tolerated on the amide part of the substrate, while hydrogen atoms lead to non-selective degradation products.

The proposed mechanism is outlined in Scheme 10. It is suggested that oxidation of the substrate generates an amidyl radical, which is stabilized by resonance with the adjacent aromatic ring. This initial oxidation step may be facilitated by

Scheme 10. Proposed Mechanism of the Electrochemical Benzoxazole Synthesis Through an Amidyl Radical Route[59]

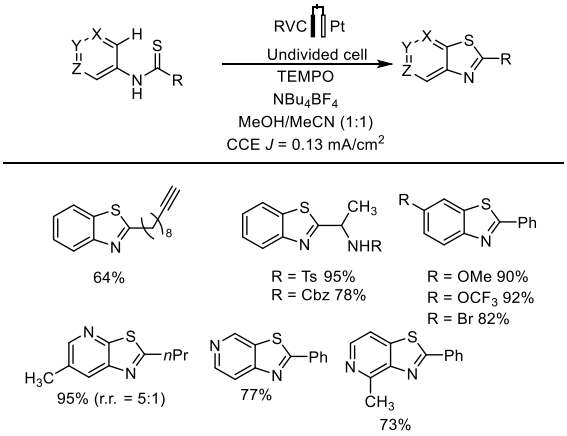


deprotonation of the amide, which is enhanced by alcoholate anions produced from HFIP at the cathode.

Bond formation between the amidic oxygen and the ortho carbon of the aromatic ring results in the formation of a heterocyclic radical. A second oxidation, followed by proton loss, completes the product formation.[59] An aryl radical is likely to engage in considerable coupling reactions at the position para to the amidyl group. This is indeed observed, and the presence of a substituent at the para-position of the *N*-substituted aryl ring is necessary to prevent side reactions at this site. Emphasizing this in other reactions like carbazoles by Waldvogel. Electron-donating substituents on the ring facilitate the reaction by stabilizing the intermediate radical. If a substituent blocks the ortho position on the substrate, no product is formed.

Xu and his colleagues developed a method for synthesizing benzothiazoles and thiazolopyridines via intramolecular C−H thiolation, catalyzed by 2,2,6,6-tetramethylpiperidine-*N*-oxyl radical (TEMPO) in 2017.[60] Reaction conditions and relevant examples of the 49 synthesized compounds are shown in Scheme 11.

Scheme 11. Electrosynthesis of Benzothiazoles and Thiazolopyrdines[60,a]



[a]r.r.: ratio of regioisomers; CCE: constant current electrolysis.

The reaction was carried out in an undivided cell with NBu_4BF_4 electrolyte, TEMPO as a mediator with constant current electrolysis (10 mA, 0.13 mA/cm^2) in a mixed solvent system (MeCN/MeOH, 1:1). The reaction was performed under an inert atmosphere, but can be carried out under air with a decreased yield. For the synthesis of the benzothiazoles, at the para position of the substrate, electron-donating and -withdrawing substituents, halogens (F, Br), and fluorine-containing functionalities were all tolerated, except the nitro group, which leads to substrate decomposition. Both ortho and

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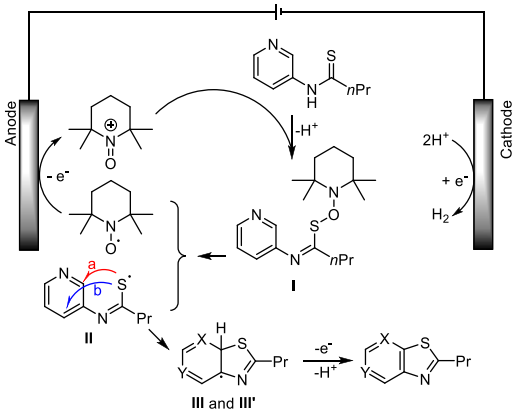
para-substituted thioamides formed the desired benzothiazole, although two regioisomers were obtained using the meta-derivate. Besides the production of benzothiazoles, the electrolytic C−H thiolation reaction could also be utilized for the synthesis of thiazolopyridines, which present greater synthetic challenges. The 3-aminopyridine-based substrates reacted regioselectively at the α-position of the pyridyl ring to afford thiazolo[5,4,*b*]pyridines. To highlight its synthetic utility, the electrosynthetic method was employed as a key step in preparing 2-propyl-substituted thiazolo[4,5-*c*]quinoline, an intermediate used in the synthesis of CL075, a toll-like receptor 8 (TLR8) agonist.[61]

The proposed inner-sphere mechanism is outlined in Scheme 12. TEMPO is initially oxidized at the anode to

Scheme 12. Proposed Mechanism for the TEMPO-Catalyzed Electrosynthesis of Benzothiazoles and Thiazolopyridines[60]



form TEMPO+, which then reacts with thioamide to produce intermediate **I** after a proton is lost. The weak S−O bond in **I** subsequently undergoes homolytic cleavage, generating the thioamidyl radical **II** and simultaneously regenerating TEMPO. The oxidation via inner-sphere electron transfer enables *N*-arylthioamides with various electronic properties to efficiently participate in the electrochemical reaction. Furthermore, the formation of **I** reduces the concentration of the thioamidyl radical, thereby minimizing the likelihood of radical dimerization. In the next step, radical cyclization of **II** at the α-position (path a) or γ-position (path b) of the pyridyl ring leads to the formation of azacyclohexadienyl radicals **III** and **III′**, both of which can rearomatize through the loss of an electron and a proton to produce the corresponding thiazolopyrdine.[60] The use of a stable nitroxide radical as a mediator is a significant advantage, as it allows for catalytic turnover. However, the long-term stability and potential for decomposition of TEMPO under prolonged electrolysis conditions should be considered.

The summarized reaction parameters of the described benzoxazole and benzothiazole synthesis are shown in Tables 1 and 2.

Preparation of Benzisoxazoles by Electrochemical Methods

Benzisoxazoles are nitrogen- and oxygen-containing heterocyclic compounds with significant traction in medicinal chemistry. Their structural motif is featured in several clinically important drugs, including the atypical antipsychotics risperidone and paliperidone, as well as the anti-epileptic agent zonisamide (Figure 4).[62] Such versatility in biological activity, combined with the capacity for fine-tuning potency and selectivity, makes benzisoxazoles attractive starting points in drug development.

Benzisoxazoles can be synthesized via direct electrolysis of 2-nitrobenzaldehydes or 2-nitroacylbenzenes, utilizing electrochemical activation to promote ring closure.[63] Alternatively, selenium-catalyzed cyclization of 2-nitrophenylacetylenes provides an efficient route to these heterocycles under milder conditions.

Waldvogel's group[64] developed the first electrosynthesis using an undivided cell for synthesizing benzisoxazoles in 2019. They performed a constant current electrolysis (2.4 mA/cm^2) on 2-nitrobenzaldehydes in an undivided cell with GC anode and boron-doped diamond (BDD) cathode and NBu_4BF_4 as an electrolyte in a mixed solvent, 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) water (1:1) (Scheme 13).

The reaction went smoothly with electron-donating and electron-withdrawing groups, which is a novelty since the previous electrochemical efforts did not broaden the scope of benzisoxazoles with EWGs. See therefore the work of Hyo Kim[65] and Peters;[66] both developed potentiostatic methods for synthesizing benzisoxazoles. Most approaches for the electrosynthesis of *N*-heterocycles involve oxidation reactions; therefore, the anode serves as the working electrode. In this manner, this reaction is unique because it involves a reduction, utilizing the BDD cathode as the working electrode.

In 2024, Waldvogel's research group[67] published a sustainable, general, and scalable electrochemical protocol for direct access to 2,1-benzisoxazoles from 2-nitroacylbenzenes, performing a reductive cyclization. They applied a constant current electrolysis (3.7 mA/cm^2) in an undivided cell with sulfuric acid serving both as an electrolyte and as a proton donor, catalyzing the cyclo-condensation in MeOH/H_2O/acetone (Scheme 14).[67]

This work used inexpensive and readily reusable carbon-based electrodes and employs environmentally benign reaction conditions, representing a significant step towards sustainable synthesis. The method's broad substrate scope, demonstrated by moderate to high isolated yields (up to 81%), coupled with its facile scalability—evidenced by successful 50-fold scale-up electrolysis—underscores its practical relevance for accessing 2,1-benzisoxazole building blocks for medicinal chemistry and related investigations. Importantly, this electrochemical

Table 1. Reaction Conditions of Benzoxazole Synthesis

ref	substrate	anode/cathode	mediator	electrolyte/solvent	current density [mA/cm^2]
Little[50]	imine	Pt or GC/Fe	NaI	Na_2CO_3/DCM -H_2O	15
Francke[51]	imine	GC/Pt	iodine(III)	$ArMe_3NClO_4$/HFIP	15
Yoshida[53]	pyrimidine	C/Pt	none	$LiClO_4$/MeCN	(8 mA)
Waldvogel[59]	anilide	RVC or graphite/Pt	none	NBu_4PF_6/HFIP	2.5

https://doi.org/10.1021/acselectrochem.5c00523
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Table 2. Reaction Conditions of Benzthiazole Synthesis

	substrate	anode/cathode	mediator	electrolyte/solvent	current density [mA/cm^2]
Yoshida[53]	pyrimidine	C/Pt	none	$LiClO_4$/MeCN	(8 mA)
Molla-bagher[58]	thiourea	C/Pt	NaBr	NaBr/*i*PrOH	80
Xu[60]	thioamide	RVC/Pt	TEMPO	NBu_4BF_4/MeOH − MeCN	0.13

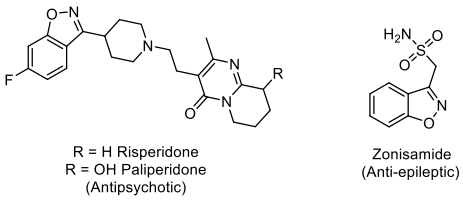
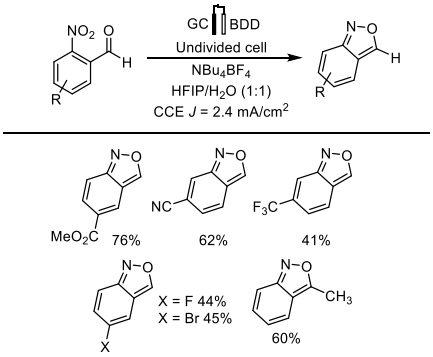


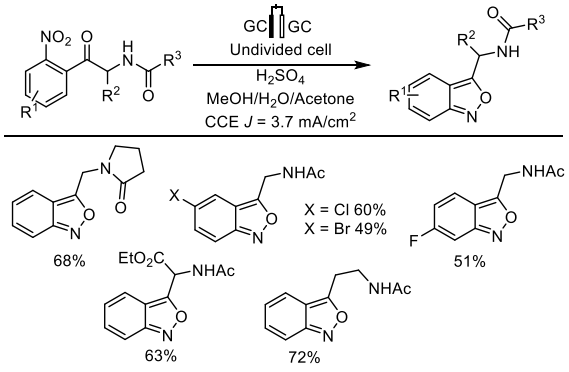
Figure 4. Some widely used benzisoxazole-based drugs.

Scheme 13. Electrosynthesis of Benzisoxazoles by Waldvogel[64,a]



[a]BDD: boron-doped diamond; HIFP: 1,1,1,3,3,3-hexafluoroisopropanol.

Scheme 14. Intramolecular Benzisoxazole Synthesis from 2-Nitroacylbenzenes[67,a]

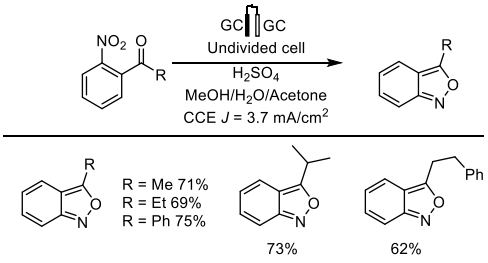


[a]GC: glassy carbon, CCE: constant current electrolysis.

approach offers a milder and more sustainable alternative to many traditional benzotriazole syntheses, which often rely on harsh conditions and potentially hazardous reagents. The emphasis on sustainable materials and scalable processes positions this work as a promising advancement for potential industrial implementation.

The method allowed variation on the aryl ring, the α-position, and on the acyl motif. The acyl motif tolerated electron-deficient (CF_2H) and sterically demanding groups (*t*Bu) and also alkene and alkyne substituents. The aryl ring allowed diversification with electron-donating (Me, OMe) and withdrawing groups (F, Br, Cl, CF_3). It is important to note that halogens are usually not tolerated in cathodic reductions due to electrochemical dehalogenation,[68,69] which highlights the mildness of this method. Moreover, additional substituents could be introduced in the α-position (alkyl and ester), and the elongation of the chain was also possible, giving rise to a substituted tryptamine derivative. The method could be applied for the synthesis of 3-alkyl substituted benzisoxazoles (Scheme 15).[67]

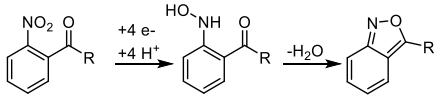
Scheme 15. One-step Electrosynthesis of 3-Alkyl Substituted Benzisoxazoles[67,a]



[a]GC: glassy carbon, CCE: constant current electrolysis.

The mechanism is shown in Scheme 16. First, the nitro group is reduced to the hydroxylamine at the cathode, which then undergoes intramolecular condensation to form the benzisoxazole.

Scheme 16. Proposed Mechanism of the Reductive Cyclization of 2-Nitroacylbenzenes to Benzisoxazoles[67]



Pan and his colleagues[70] synthesized benzisoxazoles from *ortho*-nitrophenylacetylenes using diphenyl diselenide as a catalyst in 2021 (Scheme 17). They performed constant potential electrolysis (1.6 V vs. Ag/AgCl) in an undivided cell but obtained a slightly lower yield (72%) with constant current electrolysis (5 mA, 0.4 F/mol). Pt served as the anode, graphite rod as the cathode and the catalyst was diphenyl diselenide. They used MeCN as solvent and Et_4NPF_6 as electrolyte, while both turned out to be sensitive parameters of the reaction and the yields decreased dramatically when changing the electrolyte to NBu_4I or NBu_4BF_6 or the solvent to DMSO or DMF. A variety of nitroalkynes with different aromatic groups at the alkyne position, including electron-withdrawing groups and electron-donating groups, reacted effectively, resulting in the desired products with moderate to medium yields (51−78%). A noteworthy observation is that the *ortho*-chloro derivative required a longer reaction time but yielded a better result compared to the other products (89%). It was found that terminal alkynes are unsuitable for the reaction. No corresponding products were detected for either

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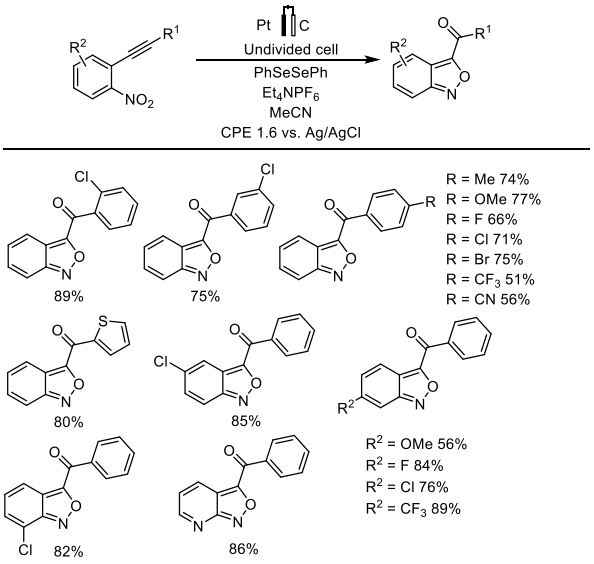
Scheme 17. Selenium-Catalyzed Electrosynthesis of Benzisoxazoles[70,a]



[a]CPE: constant potential electrolysis.

unsubstituted terminal alkynes or TMS-substituted alkynes, as reactions with these substrates led to the formation of multiple byproducts.[70]

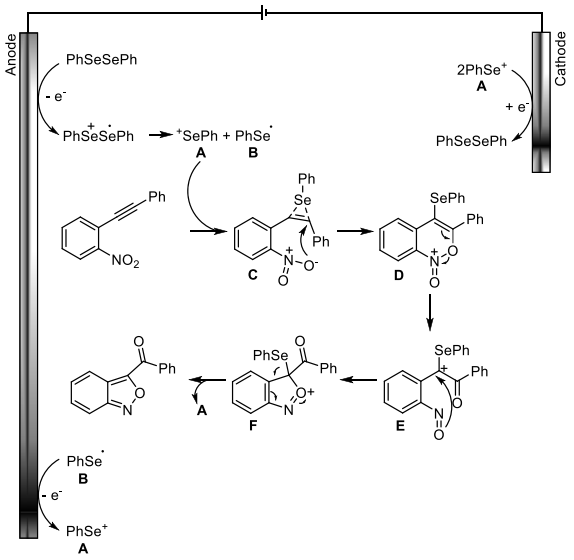
The functional group tolerance on the benzene ring attached to the nitro group was also investigated. Among them, the electronic effect of R^2 had a minimal impact on the reaction, with both showing medium to good yields (56−89%). The yield for electron-withdrawing groups was higher than for electron-donating ones. Additionally, the electron-poor 2-nitro-3-(phenylethynyl)pyridine produced the target product in a good yield (86%).

This reaction initiates with the formation of selenium cation **A** and phenyl selenium radical **B**, generated by the activation of diphenyl diselenide during anodization. Phenylselenium radical **B** can also regenerate selenium cation **A** by single electron transfer at the anode. The addition of **A** to the alkyne results in the formation of intermediate **C**. Subsequently, the oxygen of the nitro group in intermediate **C** undergoes an intramolecular nucleophilic cyclization, attacking the alkyne activated by selenium cation to form intermediate **D**. The cleavage of the N−O bond produces intermediate **E**, which releases a selenium cation after the cyclization, yielding the final product (Scheme 18). Control experiments using 1,1-diphenylethylene, a radical scavenger, confirmed that radicals are not involved in the mechanism.

Electrochemical Synthesis of Benzimidazoles and Pyridoimidazoles

Benzimidazoles are versatile heterocyclic compounds that play a pivotal role in medicinal chemistry due to their broad range of biological activities. They serve as essential scaffolds in numerous clinically significant drugs. For instance, omeprazole, a benzimidazole-derived proton pump inhibitor, revolutionized the treatment of gastric acid-related disorders and remains a cornerstone therapy today. Albendazole, another well-known benzimidazole, is used globally to combat parasitic infections, thus improving public health. Enviradine, an experimental non-nucleoside reverse transcriptase inhibitor, highlights the antiviral potential of this class. The structural diversity and

Scheme 18. Proposed Mechanism for the Selenium-Catalyzed Benzisoxazole Synthesis[70]



biological relevance of benzimidazoles ensure their continued importance in drug discovery (Figure 5).[71]

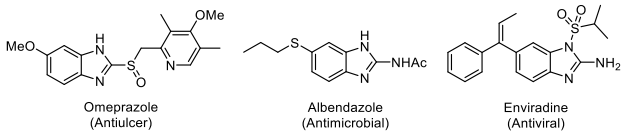


Figure 5. Some active pharmaceutical agents with benzimidazole skeleton.

Benzimidazoles can be synthesized via direct electrolysis through intramolecular C−H amination of imines, a strategy that can also be applied to the formation of pyridomidazoles. Additionally, 1,2-disubstituted benzimidazoles can be obtained by electrolysis of benzylic alkylamine.

Xu and his colleagues[72] synthesized benzimidazoles by intramolecular C−H amination in 2017. They used a constant current electrolysis (10 mA, 0.13 mA/cm^2) in an undivided cell using an RVC anode and Pt cathode with refluxing MeOH (Scheme 19). Increasing the current to 20 mA decreased the yield, suggesting that a relatively low current density is important for optimizing the reaction. NEt_4PF_6 served as an electrolyte, but NEt_4BF_4 or NEt_4OTs can also be employed. Changing the solvent to MeCN or performing the reaction at room temperature decreased the yield. While the reaction was carried out under an argon atmosphere, it can also be performed under air with only a slightly decreased yield.

Various polar functionalities, including alcohol, ester, carbamate, sulfonamide, and Boc-protected amine or amino-ester groups, were found to be well tolerated. The reaction showed excellent compatibility with amidine reactants containing various substituents at the *para* or *meta* position of the phenyl ring. All *meta*-substituted amidines produced a 1:1 mixture of regioisomers, while the cyclization of *para*, *meta*-disubstituted ones resulted in benzimidazoles as single regioisomers. The reaction of a 2-naphthylamines also displayed clear regioselectivity. The aromatic ring at the amidine moiety also tolerated halogen atoms and a methyl group and even a nitrogen atom (Scheme 19). While

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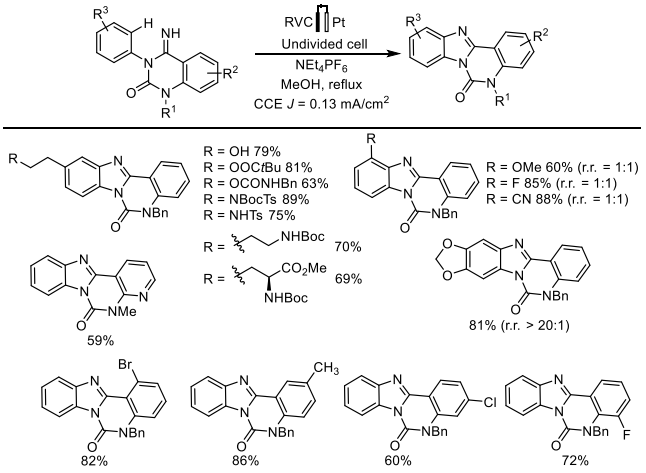
Scheme 19. Electrosynthesis of Benzimidazoles by Xu[72,a]



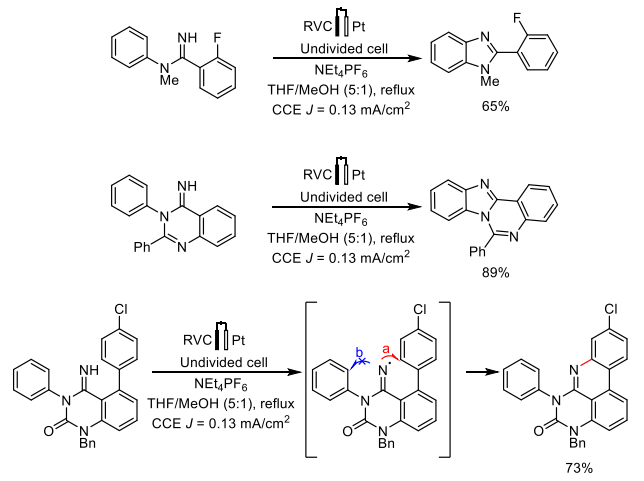
[a]RVC: reticulated vitreous carbon; r.r.: ratio of regioisomers; CCE: constant current electrolysis.

demonstrating broad functional group compatibility, this method's reliance on relatively high current density and the potential for overoxidation need to be considered for larger-scale applications. The formation of regioisomers in some cases may also necessitate purification steps.

The electrochemical cross-coupling reaction can also be applied to the synthesis of other heterocycles with medicinal significance, such as a 1,2-disubstituted benzimidazole,[73] benzo[4,5]imidazo[1,2-*c*]quinazoline,[74] and a phenanthridine,[75] starting from readily accessible amidines. Notably, the preferred formation of a six-membered ring was the key factor driving the regioselective generation of the phenanthridine. Density functional theory (DFT) calculations indicated that the 6-*endo*-trig cyclization (path a) of the NCR intermediate to form a six-membered ring was preferred in terms of both kinetics and thermodynamics, compared to the alternative five-membered ring formation (path b, Scheme 20).[72]

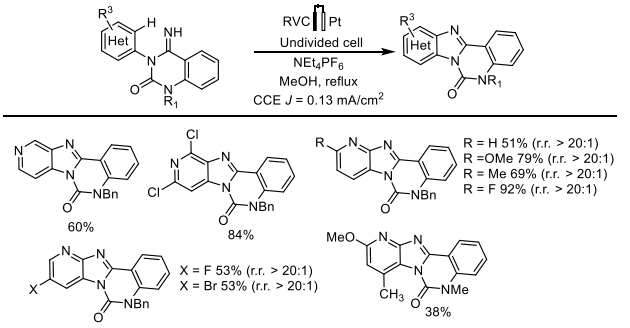
In the same publication, hardly accessible functionalized pyridoimidazoles were also prepared using the same method (Scheme 21).

Scheme 20. Electrosynthesis of Medically Important *N*-Heterocyclic Compounds[72,a]



[a]RVC: reticulated vitreous carbon, CCE: constant current electrolysis.

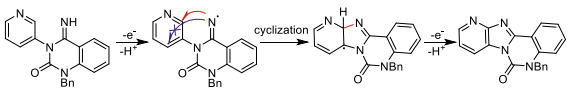
Scheme 21. Electrosynthesis of Pyridoimidazoles[72,a]



[a]RVC: reticulated vitreous carbon; CCE: constant current electrolysis; r.r.: ratio of regioisomers.

Pyridoimidazoles could be readily synthesized via electrolysis of 4- and 3-aminopyridine-derived substrates. Notably, the products obtained from the latter were formed with excellent regioselectivity. In contrast, a previously reported non-electrochemical cyclization of iminyl radicals resulted in low selectivity.[76] In this reaction, the EGB deprotonates the substrate, which then loses an electron to the anode and forms the iminyl radical **I**. The cyclization of the nucleophilic NCR **I** onto the attached pyridyl ring forms the cyclohexadienyl radical **II**, which then rearomatizes through electron and proton elimination to yield azabenzimidazole (Scheme 22).

Scheme 22. Proposed Mechanism for the Electrosynthesis of (aza)benzimidazoles[72]



DFT-based calculations indicated that the cyclization of the amidyl radical at the α-position of the pyridyl ring was favored both thermodynamically and kinetically over the alternative γ-position, which accounts for the experimental observation that this compound was the only regioisomer detected. The reliance on DFT calculations to rationalize regioselectivity is a strength, but experimental confirmation of the proposed mechanism would further solidify the understanding of this reaction.

A direct electrosynthesis method for 1,2-disubstituted benzimidazoles was published in 2023. The reactions were in an undivided cell using constant current (10 mA, 10 mA/cm^2), NBu_4PF_6 as an electrolyte in DMAc/HFIP (2:1) with Pt electrodes without inert conditions (Scheme 23).[77]

Benzylic amines bearing either electron-donating or electron-withdrawing substituents on the benzene ring participated readily in the reaction. However, compounds with substituents in the meta position exhibited lower yields, likely due to steric hindrance. Asymmetric dibenzylamines yielded separable isomers but did not exhibit measurable chemoselectivity. Substitution of the aniline ring has also left room for diversification. Substituents like Me, OMe, Br, Cl, CF_3, and the strongly electron-withdrawing CN were also tolerated in different positions on this part of the molecule. The substituent in *ortho* position to the benzylamine decreased product formation. The high performance of this method is hampered by the requirement of DMAc/HFIP mixtures, posing potential environmental and cost concerns. Finding

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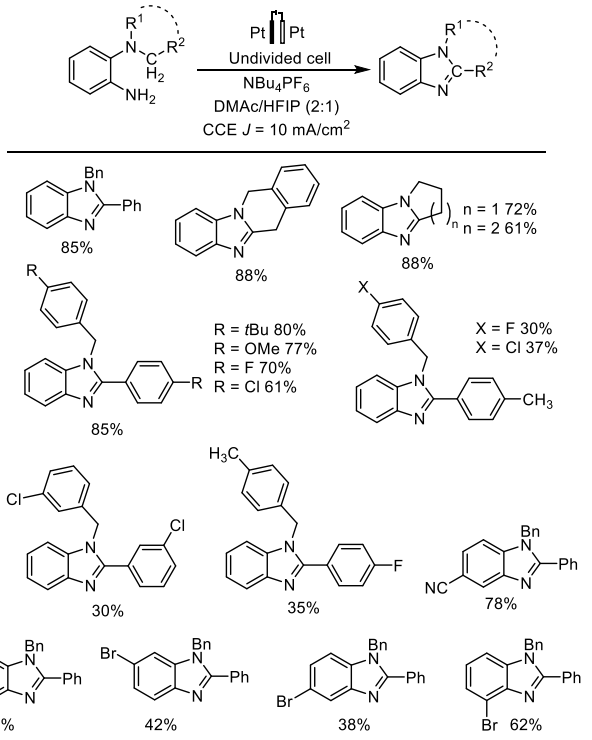
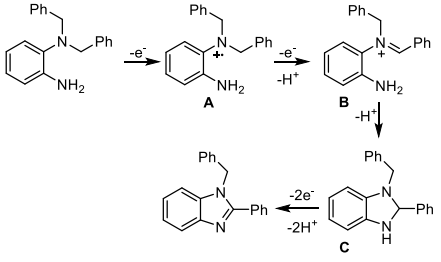
Scheme 23. Intramolecular Electrosynthesis of Benzimidazoles[77,a]



[a]DMAc: *N*,*N*-dimethylacetamide, HFIP: hexafluoroisopropanol, CCE: constant current electrolysis.

greener solvent alternatives would be a key step toward improving its sustainability. In this reaction, initially, dibenzyl benzenediamine undergoes electron loss, generating a free radical intermediate **A**, which participates in a single electron transfer (SET) process at the anode. Following this, intermediate **A** undergoes deprotonation, forming iminium ion **B**, which rapidly undergoes cyclization to yield intermediate **C**. Ultimately, intermediate **C** loses two electrons and protons, forming the product (Scheme 24).[77]

Scheme 24. Proposed Mechanism for the Oxidative Electrochemical Benzimidazole Synthesis[77]



Intramolecular Electrosynthesis of Fused Quinolines

Quinolines serve as both key motifs and valuable precursors in medicinal chemistry,[78] and in chemosensors.[79−81] They also function as remarkably versatile intermediates in organic synthesis (Figure 6).[82] Several APIs contain a quinoline core, such as anticancer agents (e.g., Camptothecin),[83] compounds with antimalarial (e.g., Chloroquine),[84] or antibacterial (e.g., Ciprofloxacin)[85] effects.

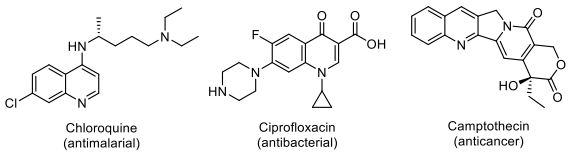
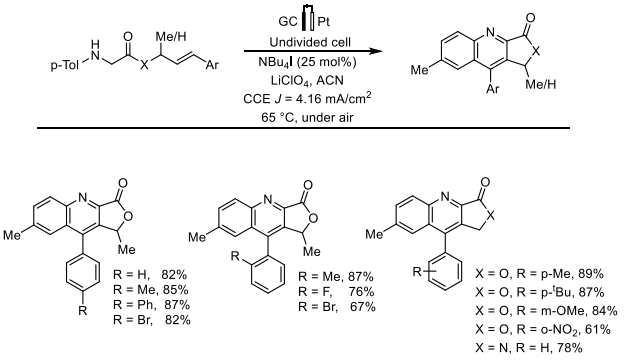


Figure 6. Selected examples of pharmacologically relevant quinoline-based drugs.

Ghosh and co-workers[86] developed an efficient electrocatalytic cycloaddition approach for the construction of a lactone- or lactam-fused quinolines. Diverse arrays of functionalities are well-compatible under this metal-free, mild, and scalable electro-redox protocol under air (Scheme 25). In this method, an undivided cell with graphite and platinum electrodes were applied, using constant current (4.16 mA/cm^2) in a NBu_4I−$LiClO_4$ electrolyte in acetonitrile.[86]

Scheme 25. Electrochemical Synthesis of Fused Quinolines in a Metal-free Electrocatalytic [4 + 2] Annulation[86,a]



[a]CCE: constant current electrolysis.

Mechanistic studies indicate that an iodide-mediated electrooxidation of secondary amines leads to the formation of their corresponding imines and a subsequent [4 + 2] cycloaddition, resulting in the fabrication of C−C bonds. This process is followed by aromatization, yielding a six-membered conjugated core structure (Scheme 26).

Quinoline *N*-Oxides by Electrochemical Transformations

Quinoline *N*-oxides serve as both key motifs and valuable precursors in medicinal chemistry,[87] and, owing to their 1,2-dipolar N−O bond, they also function as remarkably versatile intermediates in organic synthesis.[88]

Waldvogel's group[64] introduced the synthesis of quinoline *N*-oxides from 2-nitrocinnamaldehydes (Scheme 29). They used a constant current electrolysis (2.4 mA/cm^2) with a GC anode, a Pt cathode, with Et_4NBF_4 as electrolyte and HFIP/H_2O (1:1) as solvent (Scheme 27).

The presence of electron-withdrawing and electron-donating groups had no significant impact on the yields, and electrochemically sensitive substituents, like CN and halogens, were also well-tolerated without notably reducing the yield. Scaling up the reaction to 5 mmol of non-substituted substrate yielded a similar result to the small-scale procedure, but more charge was needed. Furthermore, these quinoline *N*-oxides can be transformed into the corresponding quinolines under electrochemical conditions.

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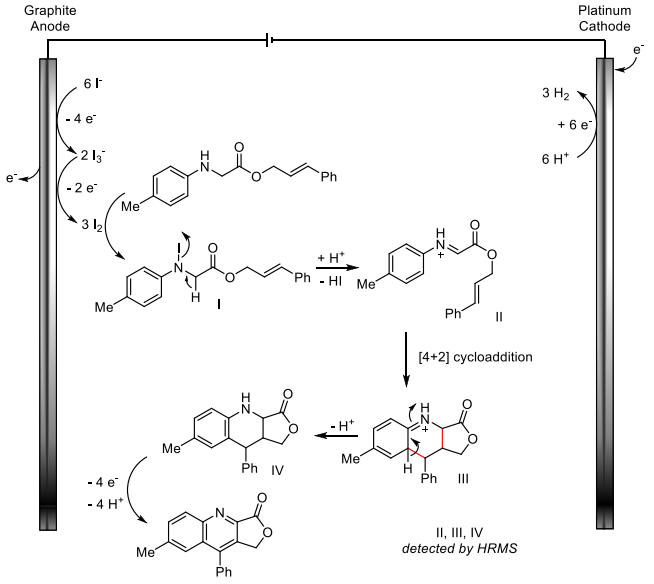
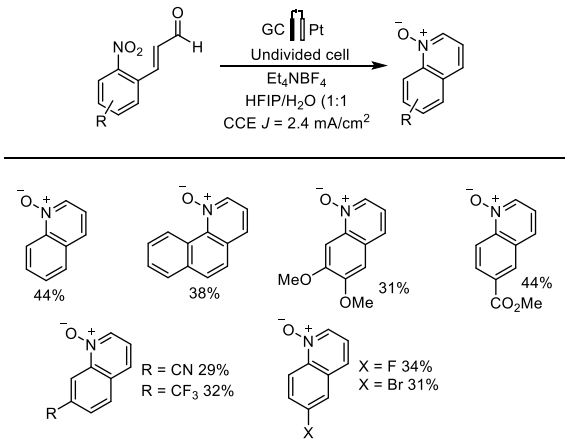
Scheme 26. Proposed Mechanism for Iodine-Mediated Oxidative Electrochemical Quinoline Skeleton Synthesis[86]



Scheme 27. Synthesis of Quinoline *N*-Oxides From 2-Nitrocinnamaldehydes by Waldvogel[64,a]



[a]HFIP: 1,1,1,3,3,3-hexafluoroisopropanol, CCE: constant current electrolysis.

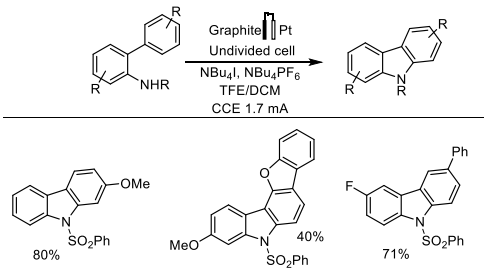
Carbazole Synthesis Using Electrochemical Methods

Carbazole is a widely encountered structural motif present in numerous natural and synthetic compounds. It has been associated with a variety of biological activities, including anti-Alzheimer,[89] antitubercular,[90] fungicidal[91] properties. In addition, carbazoles are frequently employed as electronic materials—such as photoconductive polymers and organic optoelectronic materials—due to their excellent photophysical characteristics.[92] As a result, the exploration of new synthetic strategies for carbazole frameworks offers substantial value in both biological and materials research.

In the best of our knowledge, four different methods were published for the synthesis of carbazoles in 2020 and 2021. Carbazoles can be prepared through several electrochemical methods, including the dehydrogenative C−H amination of arylsulfonamides and the direct electrolysis of biaryl-amides without the need for any catalyst.

Carbazoles were synthesized from arlysulfonamides via dehydrogenative C−H amination by Chen and colleagues[93] in 2020 (Scheme 28). The electrochemical reaction was

Scheme 28. Electrochemical Carbazole Synthesis[93,a]



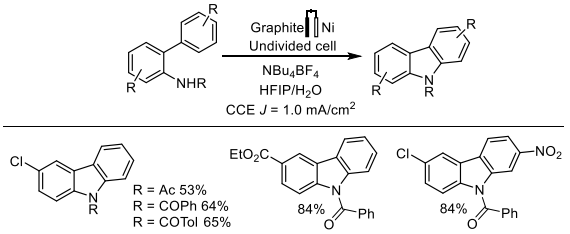
[a]TFE: trifluoroethanol, CCE: constant current electrolysis.

performed in an undivided cell using constant current electrolysis (1.7 mA) with a graphite rod anode and Pt cathode, NBu_4I as a catalyst, and NBu_4PF_6 as an electrolyte in a trifluoroethanol and dichloromethane (1:1) mixture under a nitrogen atmosphere. Product formation with a decreased yield was still observed even in the absence of the catalyst.[93] Compared to traditional metal-catalyzed cross-coupling reactions used for carbazole synthesis, this electrochemical method offers the potential to reduce metal waste and avoid the use of potentially toxic ligands.

Initially, they investigated 2-amidobiaryls with various substituents on the benzene ring attached to the aniline moiety. The results showed that several 2-amidobiaryls were compatible with the reaction, producing carbazoles in moderate to good yields (20−85%), regardless of the presence of electron-donating substituents (methyl, *t*-butyl, methoxy, methylenedioxy) or electron-withdrawing substituents (chloro, fluoro). In this developed protocol, variation of the protecting group revealed that sulfonamide was more effective than amide. To showcase the method's practical application, the authors employed it to synthesize the alkaloids Clausine C, H, L, and Glycozoline.

Also in 2020, Waldvogel's group[94] developed a method for synthesizing carbazoles from biaryl-amides by direct electrolysis without using any catalyst (Scheme 29). They performed constant current electrolysis (1.5 mA, 1 mA/cm^2) in an undivided cell with an isostatic graphite anode and a nickel cathode in HFIP containing 15% water. Higher or lower amounts of water decreased the yield significantly. It was found that NBu_4BF_4 provided superior conversion compared to NBu_4PF_6.

Scheme 29. Carbazole Synthesis by Electrochemical Ring Closure[94,a]



[a]HFIP: 1,1,1,3,3,3-hexafluoroisopropanol, CCE: constant current electrolysis.

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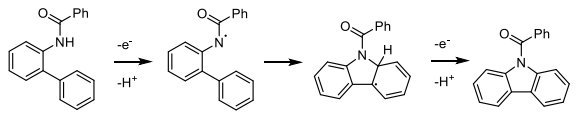
The transformation proceeds mechanistically, most likely via a radical pathway. Deprotonation of the amide by the EGB, followed by anodic oxidation, leads to the amidyl radical, which then undergoes cyclization. A second deprotonation and oxidation lead to aromatization and the formation of the carbazole (Scheme 30).[94]

Scheme 30. Suggested Mechanism of the Carbazole Synthesis by Waldvogel[94]

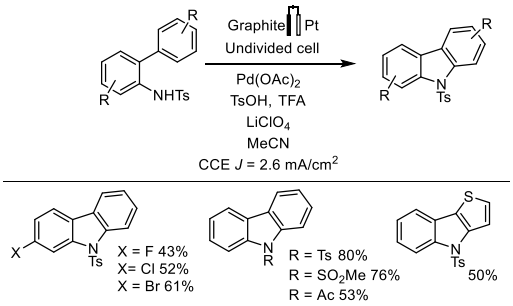


Compared to Chen's method, where substrate scope was restricted to compounds containing sulfonamide protecting groups, Waldvogel demonstrated that, apart from benzoyl protecting groups, 4-methyl-substituted benzoyl and acetyl groups are also compatible protecting groups for this transformation. The benzoyl groups afforded a slightly higher yield compared to the acetyl-protected derivative. Waldvogel showed that both aryl moieties can contain different substitution patterns. Electron-withdrawing groups such as halogens, esters, or cyano, which allow subsequent reactions, are tolerated. The moderate yields of the compounds without any substituent at the para position, and the *N*-protected natural product glycozoline, can be explained by the well-known fact, established through studies by this research group, that a free para-position or benzylic-position on the anilide moiety significantly increases the likelihood of side reactions.[95−97] Compounds with electron-donating groups showed moderate performance due to incomplete conversion of the starting material. Increasing the amount of charge only decreased the yield. In some instances, the addition of 15% water was detrimental, leading to very low conversion of the starting material. In these cases, excluding water resulted in improved conversion. Substrates with the highly electron-withdrawing pyridinyl moiety, which exhibit good oxidation resistance, could not be obtained by this method. To highlight the practical applicability of this method, the group synthesized a protected Carprofen in good yields, which could be easily deprotected with NaOH in MeOH/H_2O at 80 °C. Both methods offer valuable routes to carbazoles, but the reliance on potentially problematic solvents like HFIP and the sensitivity to reaction conditions (water content, protecting groups) should be considered. The differing substrate scopes highlight the importance of selecting the most appropriate method based on the specific target molecule.

Lei and co-workers[98] synthesized carbazoles using Pd as catalyst in 2020 (Scheme 31). They performed a constant current electrolysis (6 mA) in an undivided cell with $LiClO_4$ as electrolyte and $Pd(OAc)_2$ as catalyst in MeCN with a graphite rod anode and Pt cathode and TsOH and TFA as additives under nitrogen atmosphere.

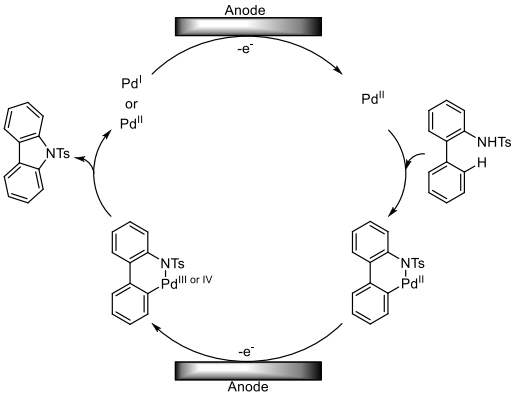
In the first step, the coordination of the amido group of **1** to $Pd(OAc)_2$ promotes cyclopalladation, resulting in the formation of the six-membered palladacycle **2**. This palladacycle can then be oxidized to a Pd(III) or Pd(IV) complex (complex **3**). Next, palladium complex **3** undergoes a reductive elimination to yield the desired product **2b** and Pd(I) or Pd(II). Pd(I) can then be oxidized at the anode to regenerate Pd(II), completing the catalytic cycle (Scheme 32).[98]

Scheme 31. Palladium Acetate-Mediated Electrosynthesis of Carbazoles[98,a]



[a]CCE: constant current electrolysis.

Scheme 32. Proposed Mechanism of the Pd-Catalyzed Electrosynthesis of Carbazoles[98]

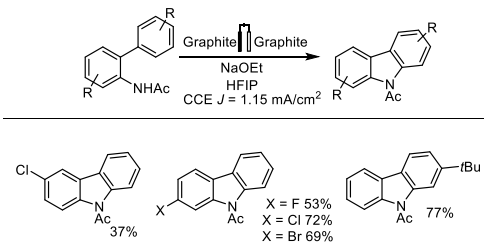


The yield decreased dramatically when the mixture was exposed to air. This reaction tolerated halogens, alkyl, and alkoxy groups, and a thiophene-annulated carbazole could also be synthesized. The C4 substituted carbazoles with electron-donating groups performed better than the electron-withdrawing ones. The protecting group at the nitrogen atom could also be varied: sulfonamides and amides performed with moderate yields (53−76%).

Antonchick and his colleagues[99] synthesized carbazoles without the use of any metals in 2021 (Scheme 33).

The reaction was carried out in an undivided cell under constant current electrolysis (5 mA, 1.15 mA/cm^2) using graphite electrodes with NaOEt or KO*t*Bu as the base in HFIP. During the optimization of the reaction conditions, they

Scheme 33. Electrochemical Carbazole Synthesis by Antonchick[99,a]



[a]HFIP: 1,1,1,3,3,3-hexafluoroisopropanol, CCE: constant current electrolysis.

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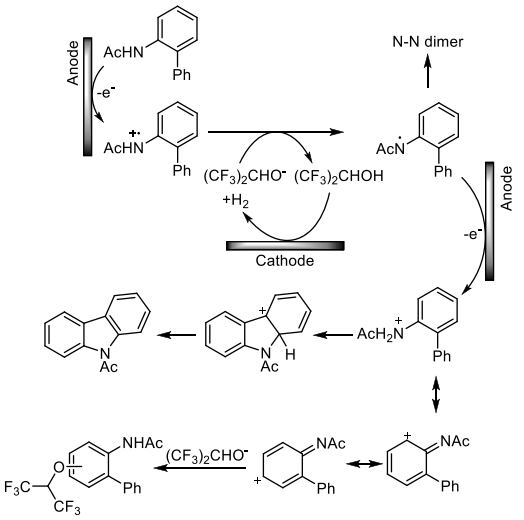
continuously observed the formation of the HIFP-substituted benzamides as side products.

Anodic oxidation of the anilide forms a highly acidic cation radical **A**. Proton abstraction by the EGB results in *N*-acyl radical intermediate **B** formation, which undergoes a second oxidation with the formation of nitrenium ion **C**. The rearomatization of the intermediate **D** formed by nucleophilic attack of the aryl ring to the nitrenium ion **C** affords the desired carbazole,[99] as depicted in Scheme 34.

Scheme 34. Proposed Mechanism of the Carbazole Synthesis and the HFIP-Substituted Side Product Formation[99]



Substitutions at various positions on both rings were tolerated. In particular, various substitutions at the 4-position of the aniline ring, as well as electron-neutral and electron-donating substituents at the para position of the phenyl ring, showed good compatibility under the reaction conditions. Notably, for the first time, an *N*-formyl-2-aminobiphenyl substrate was successfully converted into the corresponding carbazole derivative, without the formation of a six-membered ring phenanthridin-6-one, as observed in previous studies.[100]

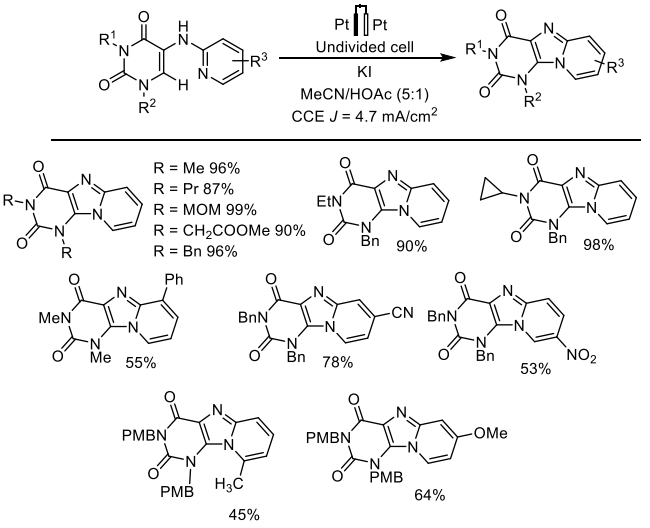
The summarized reaction parameters of the described carbazole electrosynthesis are summarized in Table 3.

Electrochemical Synthesis of Fluorescent N9-Fused Tricyclic Xanthines

Xanthine derivatives, particularly those featuring chemically modified tri- or tetracyclic fused structures, are well-documented adenosine receptor antagonists or phosphodiesterase inhibitors.[101−103] These compounds exhibit promising therapeutic potential across a range of diseases, including cancer,[104] Parkinson's disease,[105] Alzheimer's disease[106] and asthma.[107] Xanthines thus stand as significant pharmacophores with broad applicability in medicinal chemistry and therapeutic development.

Guo's group[108] synthesized fluorescent N9-fused tricyclic xanthines via electrochemical intramolecular C−H amination catalyzed by iodine in the year 2021 (Scheme 35).

Scheme 35. Iodine-Catalyzed Electrosynthesis of Fluorescent N9 Fused Tricyclic Xanthines by Guo[108,a]



[a]CCE: constant current electrolysis, PMB: *para*-methoxybenzyl group.

They performed a constant current electrolysis (7 mA, 4.66 mA/cm^2) in an undivided cell using Pt anode and Pt cathode with KI as a catalyst in MeCN/AcOH 5:1. The screening of various halide-containing salts demonstrated that chloride and bromide do not work as redox catalysts. The reaction was performed under air and MeOH or MeCN/H_2O 5:1 can also be used as a solvent, but not pure MeCN. Graphite felt anode is also suitable as a working electrode. The variation in the uracil moiety, alongside the *N*-methyl group, involved a range of *N*-alkyl groups, including ethyl-, propyl-, butyl-, cyclopentyl-, methoxymethyl-, methoxyethoxymethyl-, allyl-, alkyl ester-, and benzyl. Additionally, uracils with two different alkyl substituents on the N1 and N3 atoms were also viable substrates, producing the corresponding products in acceptable yields. The reaction demonstrated wide compatibility with various functional groups on the pyridine ring, including alkyl, methoxy, aryl, halogen, trifluoromethyl, ester, cyanide, and the oxidation-sensitive nitro, producing the expected cyclo-amination products in yields from 53% to 95%. Strong electron-withdrawing groups generally harmed the reaction efficiencies. Additionally, the pyridine motif with two different substituents at the *ortho*, *meta*, and *para* positions successfully underwent the reaction, yielding the desired products in 95%, 93%, and 65% yields, respectively.

Table 3. Reaction Conditions of the Described Carazole Electrosynthesis

ref	substrate	anode/cathode	mediator	electrolyte/solvent	current density [mA/cm^2]
Chen[93]	arlysulfonamides	graphite/Pt	NBu_4I	NBu_4PF_6/TFE-DCM	(1.7 mA)
Waldvogel[94]	biaryl-amide	graphite/Ni	none	NBu_4BF_4/HFIP−H_2O	1
Lei[98]	arlysulfonamides	graphite/Pt	$Pd(OAc)_2$	$LiClO_4$/MeCN	2.6
Antonchick[99]	biaryl-amide	graphite/graphite	none	NaOEt/HFIP	1.15

https://doi.org/10.1021/acselectrochem.5c00523
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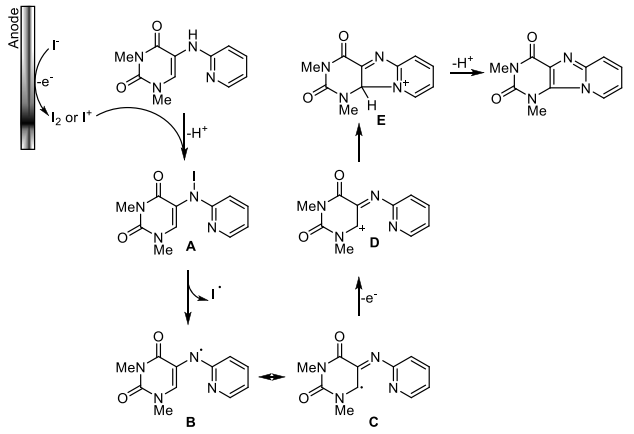
The 2-aminopyridine moiety also showed tolerance to variation. Other medicinally relevant heterocycles, including 2-aminopyrimidine, 2-aminopyrazine, 1-aminoisoquinoline, and 2-aminquinoline-derived substrates, were compatible, and their corresponding tricyclic compounds were obtained in yields ranging from 37% to 91%. The distinct advantages of this methodology were demonstrated through a direct comparison with substrates previously tested under iron catalysis. The electrochemical conditions presented here outperformed those reported in the literature, providing access to compounds that could not be obtained through Fe-catalyzed procedures.[109]

Purine-fused tricyclic derivatives have demonstrated notable physicochemical properties, making them valuable tools for applications in chemical biology.[110,111] Therefore, the photophysical properties of selected N9-fused tricyclic xanthines were examined. Most of the tricyclic xanthine derivatives displayed strong photoluminescence, featuring long fluorescence lifetimes and high fluorescence quantum yields. In the first step of this reaction, iodine gets oxidized at the anode to form molecular iodine or hypervalent iodine species I^+ which are attacked nucleophilic by the amine nitrogen atom. The N−I bond then undergoes easy homolytic cleavage to form the *N*-centered radical **B**, which has a resonance structure **C**. As a result, the heterogeneous oxidation of **C** at the anode generates the cation species **D**. Following this, an intramolecular nucleophilic attack forms cyclic intermediate **E**. Finally, deprotonation assisted by an electrogenerated acetate anion leads to the formation of the final product (Scheme 36).[108]

Scheme 36. Suggested Mechanism of the Iodine-Catalyzed Electrosynthesis of the N9 Annulated Xanthines[108]



Imidazo-Fused *N*-Heteroaromatic Compound by Electrosynthesis

Imidazo-fused heteroaromatic compounds are valuable scaffolds, appearing in numerous bioactive molecules, including the marketed pharmaceuticals against insomnia, cardiotonic Olprinone, and antibacterials (Figure 7).[112]

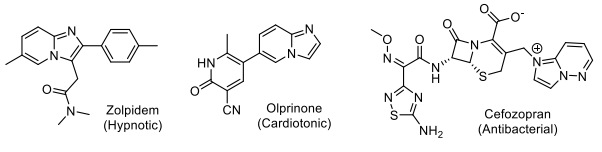
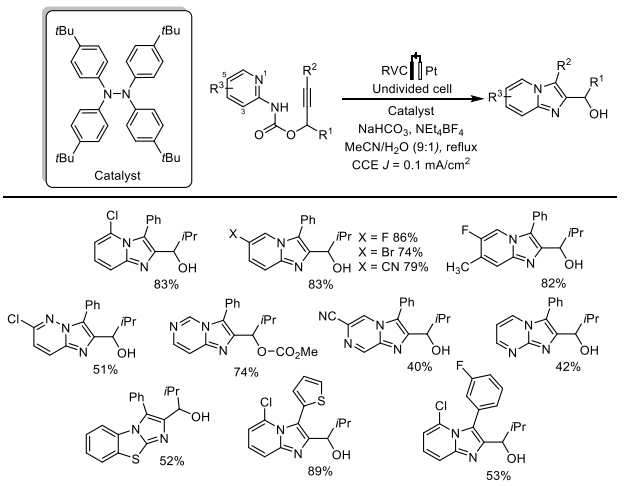


Figure 7. Some imidazole-fused drugs.

Xu and colleagues[113] synthesized imidazole-fused *N*-heteroaromatic compounds through regiospecific electrochemical (3 + 2) annulation reaction of heteroaryl amines with tethered internal alkynes in 2018 (Scheme 37). The

Scheme 37. Arylhidrazine-Catalyzed Imidazole-Fused *N*-Heterocycle Synthesis[113,a]



[a]CCE: constant current electrolysis.

electrosynthesis employs a novel tetraarylhydrazine as the catalyst, $NaHCO_3$ as a base, Et_4NBF_4 as an electrolyte in $MeCN/H_2O$ (9:1) as solvent under reflux temperature. RVC served as an anode, Pt as a cathode and the reaction was performed in an undivided cell using a constant current (7.5 mA, 0.1 mA/cm^2). Performing the reaction under atmospheric conditions only slightly reduced the yield.

It is the first time that hydrazine is used as an electrocatalyst.[17] Other tetraarylhydrazines with similar or higher oxidation potentials, triarylamines, and ferrocene showed poor catalytic performance during reaction optimization.

The annulation of a 2-aminopyridine derivative exhibited broad tolerance for diverse substituents at the C6, C5, and C4 positions of the pyridyl ring, though substitution at the C3 position was not observed. This direct C−H functionalization strategy eliminates the need for pre-functionalized starting materials, offering a significant step economy compared to conventional methods that often require multi-step syntheses of complex precursors.

The 2-aminopyridine moiety could be successfully replaced with various aminodiazine structures. The reaction proceeded efficiently in all cases, irrespective of the nitrogen atom positions, resulting in the formation of imidazo[1,2-*b*]-pyridazines, an imidazo[1,2-*c*]pyrimidine, imidazo[1,2-*a*]-pyrazines, and an imidazo[1,2-*a*]pyrimidine. The electrolytic method also enabled the preparation of medicinally significant imidazo[2,1-*b*]benzothiazoles. The novelty of using a hydrazine as an electrocatalyst is significant. However, the potential toxicity and cost of hydrazine derivatives should be considered for large-scale applications.

Variation of the propargyl group was also possible. The benzene ring at the alkyne terminus could be functionalized with a wide range of substituents exhibiting diverse electronic and steric properties. The introduction of an alkyl group in R^2 failed to produce the corresponding imidazopyridine product in $MeCN/H_2O$. Instead, when the reaction was carried out in

https://doi.org/10.1021/acselectrochem.5c00523
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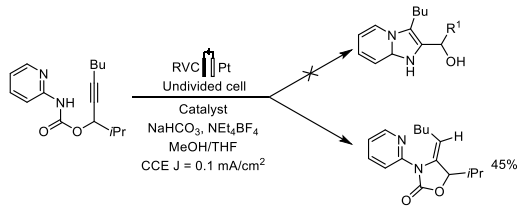
MeOH/THF, a solvent system with enhanced hydrogen-atom donating capacity, the hydroamidation product was obtained (Scheme 38).[113]

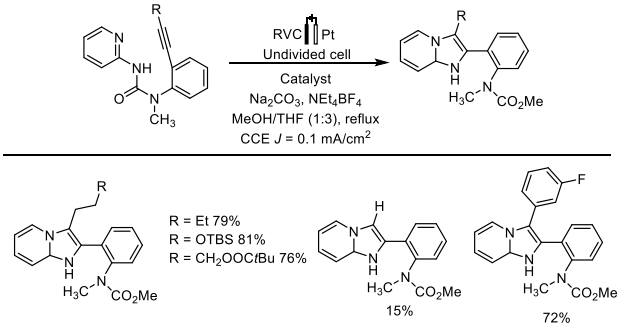
Scheme 38. Hydroamination in the Electrosynthesis of Imidazo-Fused *N*-Heterocycles, if the Alkyne Moiety is Linked to an Alkyl Chain[113,a]



[a]CCE: constant current electrolysis.

They speculated that the terminal alkyl substituent caused the intermediate vinyl radical to favor H-atom abstraction from the solvent over the azaphilic cyclization. To tackle this issue, they took inspiration from their recent findings, which revealed that forming a six-membered ring in the initial step of the amidyl radical cyclization cascade can significantly enhance the subsequent construction of the five-membered ring.[114] Indeed, the urea-linked substrates, especially those carrying an alkyl-capped alkyne, exhibited significantly improved reaction compatibility and furnished imidazopyridines even with lower amounts of the arylhidrazine catalyst (Scheme 39).

Scheme 39. Scope of the Imidazo-Fused Cyclic Compounds to Alkynes[113,a]



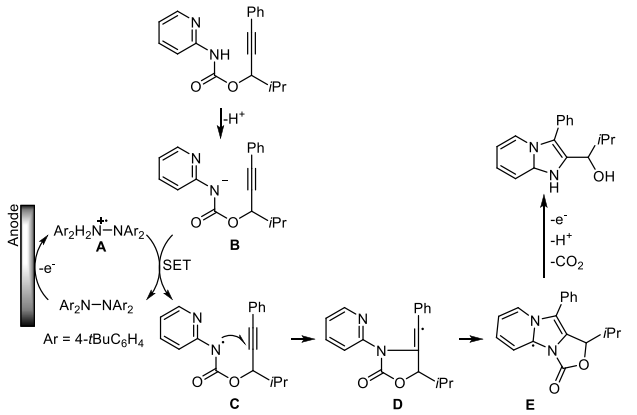
[a]CCE: constant current electrolysis.

The mechanism is outlined in Scheme 40. The process begins with anodic oxidation of the catalyst and deprotonation of the amide by the EGB. A single electron transfer occurs from **B** to **A**, which results in the formation of amidyl radical **C** and the regeneration of the catalyst. The 5-*exo*-dig cyclization of **C** produces the vinyl radical **D**, which undergoes a regioselective reaction with the pyridyl nitrogen to form the tricyclic radical intermediate **E**. Subsequent one-electron oxidation of **E**, followed by hydrolysis of its carbonyl linker, leads to the formation of the imidazopyridine product **3**.[113]

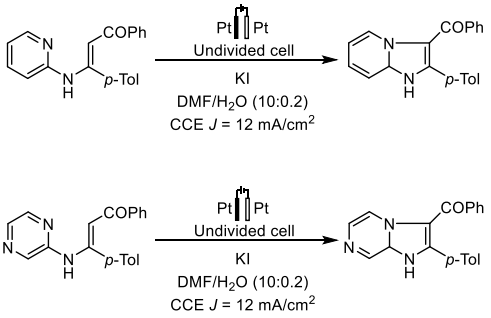
Imidazo[1,2-*a*]pyridine and imidazo[1,2-*a*]pyrazine Synthesis

Lei and co-workers[115] synthesized a series of indoles (see chapter Indoles) in the year 2017. During this research, they broadened the substrate scope and synthesized an imidazo[1,2-*a*]pyridine and an imidazo[1,2-*a*]pyrazine (Scheme 41).[115] They performed constant current electrolysis (7 mA, 12 mA/cm^2) in an undivided cell with Pt electrodes, using KI as an electrocatalyst and electrolyte in DMF/H_2O (10:0.2). The mechanism is outlined in Scheme 56, in the chapter of indole synthesis.

Scheme 40. Proposed Mechanism of the Arylhydrazine Catalysed Electrosynthesis of Imidazo Fused *N*-Heterocycles[113]



Scheme 41. Synthesis of imidazo[1,2-*a*]Pyridine and imidazo[1,2-*a*]Pyrazine[115,a]



[a]CCE: constant current electrolysis.

Pyrido[1,2-*a*]benzimidazoles Prepared by Electrosynthesis

Pyrido[1,2-*a*]benzimidazole serves as a central structural motif in medicinal chemistry, appearing prominently in a range of bioactive molecules, including antimalarial,[116] anticancer,[117] and antiviral agents[118] (Figure 8).

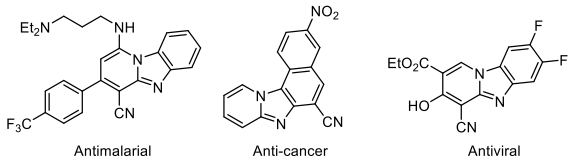


Figure 8. Bioactive pyrido[1,2-*a*]benzimidazoles.

Lei and colleagues[119] synthesized a range of pyrido[1,2-*a*]benzimidazoles (Scheme 42) in 2020. The reaction was performed in an undivided cell using constant current electrolysis (2 mA, 4 mA/cm^2) with $Pd(PPh_3)_2(OAc)_2$ as a catalyst, LiClO4 as electrolyte, a carbon cloth anode and iron as the cathode in MeCN/HCOOH (1:1) under inert atmosphere. Changing the current to higher or lower values led to decreasing yields.[119]

The reaction tolerated electron-donating groups such as alkyl and OMe substituents and electron-withdrawing groups

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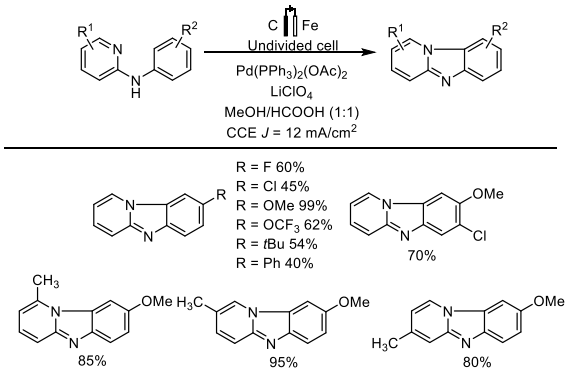
Scheme 42. Pd-Catalyzed Electrosynthesis of pyridio[1,2-*a*]Benzimidazoles[119,a]

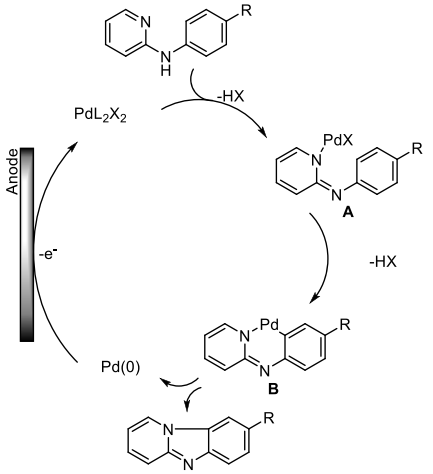


[a]CCE: constant current electrolysis.

such as CF_3 and halogens on the benzene ring. Nitro and CN derivatives were not discussed. Substrates with electron-donating groups performed better, yielding up to 99%. Regioisomers were observed when substrates with *meta* substituents on the benzene ring were reacted. This was not the case when the electron-donating OMe group was also introduced in the *para* position.

Diversification of the pyridine ring went smoothly with alkyl substituents and the CF_3 group. However, the pyrido[1,2-*a*]benzimidazoles with the electron-withdrawing CF_3 at the pyridine ring showed a decreased yield. Initially, Pd(II) coordinates with a substrate, followed by a two-step electrophilic deprotonation process assisted by $^-$OAc or $HCOO^-$, leading to the formation of the Pd arylation complex **B**. Complex **B** then undergoes reductive elimination, yielding the desired product and Pd(0). The Pd(0) species is subsequently reoxidized at the anode, regenerating Pd(II) (Scheme 43).[119]

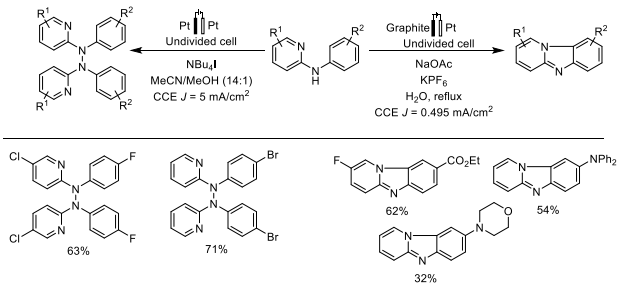
Scheme 43. Proposed Mechanism of the Pd-Catalyzed Electrosynthesis of pyrido[1,2-*a*]Benzimidazoles[119]



While this palladium-catalyzed method provides high yields and broad substrate scope, the electrochemical approach offers a sustainable advantage through in situ catalyst regeneration, potentially minimizing both catalyst loading and metal contamination compared to stoichiometric palladium-mediated reactions. Addressing the cost and environmental concerns associated with palladium, through effective recovery and recycling strategies, remains crucial for broader implementation.

Pyrido[1,2-*a*]benzimidazoles were also synthesized by Chen and colleagues[120] in 2020. They performed direct electrolysis (0.495 mA/cm^2) on biaryl amines in refluxing water, using KPF_6 as the electrolyte and NaOAc $\cdot$ 3 H_2O as the base, with a constant current in an undivided cell equipped with a graphite anode and a Pt cathode. By changing the anode to Pt, the electrolyte to NBu_4I and the current density to 5 mA/cm^2, intermolecular N−N coupling could be achieved instead of the intramolecular C−H amination (Scheme 44). The C−H

Scheme 44. Electrosynthesis of pyrido[1,2-*a*]Benzimidazoles and Hydazines from Biaryl Amines[120,a]

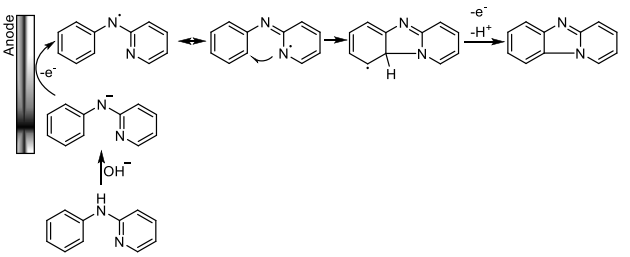


[a]CCE: constant current electrolysis.

amination was exemplified on 32 compounds. The cyclization reaction tolerated a broad spectrum of functional groups, including alkyls, ethers, thioethers, halogens, amines, aldehydes, and ketones.[120]

The mechanism is proposed to proceed via a nitrogen-centered radical (Scheme 45). First, the amine gets

Scheme 45. Proposed Mechanism of the Direct Electrosynthesis of pyrido[1,2-*a*]Benzimidazoles[120]



deprotonated by the EGB. The formed anion gets oxidized on the anode, forming the radical, which then undergoes intramolecular cyclization. Second oxidation and deprotonation form the desired pyrido[1,2-*a*]benzimidazole.[120]

Electrosynthesis of Benzotriazoles

Benzotriazoles, characterized by their distinctive fused five-membered heterocyclic structure, have broad applications spanning pharmaceuticals,[121] functionalized materials,[122] and organic synthesis.[123−125] In particular, 2-aryl-2H-benzotriazoles are especially noteworthy due to their pivotal roles in various drugs,[126,127] organic electronic devices,[128] and UV stabilizers[129] (Figure 9).

Li and his colleagues[130] synthesized benzotriazoles through intramolecular N−N coupling of *o*-aminyl azobenzenes in 2024 (Scheme 46). They performed a constant current electrolysis (16 mA) under air, using a carbon rod anode

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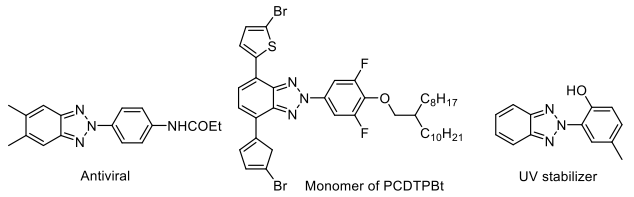
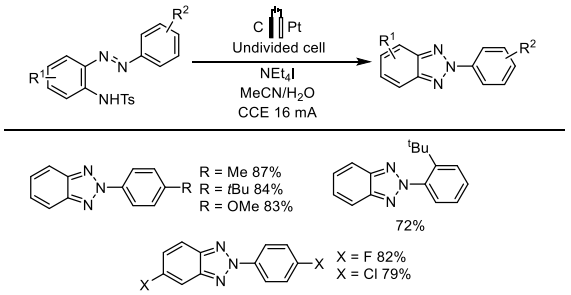


Figure 9. Important 2-aryl-2H-benzotriazoles.

Scheme 46. Electrosynthesis of Benzotriazoles by Li[130,a]



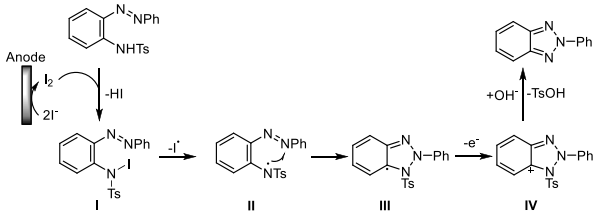
[a]CCE: constant current electrolysis.

and a Pt cathode with Et4NI as an electrolyte in MeCN with 2 equiv of water. Higher or lower amounts of water only decreased the yield. Switching to solvents, such as HFIP, DCE, DME, DMSO, and NMP, failed to accelerate the radical cyclization.[130]

Substrate scope was investigated with alkyl groups, OMe, OCF_3 and halogens on one side of the molecule. The methyl ester derivative could not be obtained. Substances with electron-withdrawing groups performed less well than those bearing electron-donating groups. Introducing substituents in the *meta* position gave the corresponding products in moderate yields, and a decreased yield was observed with substituents in the *ortho* position, indicating that bulky groups at this position cause steric hindrance during the cyclization process. Testing the protective group of the amine showed that the reaction works best with the Ts group, and decreased yields were observed with Ac or Mes. The yield decreased dramatically when the amine was unprotected. The reliance on iodine chemistry and the generation of HI as a byproduct remain significant sustainability concerns. The relatively limited substrate scope and the need for a specific protecting group (Ts) also restrict the broad applicability of this method.

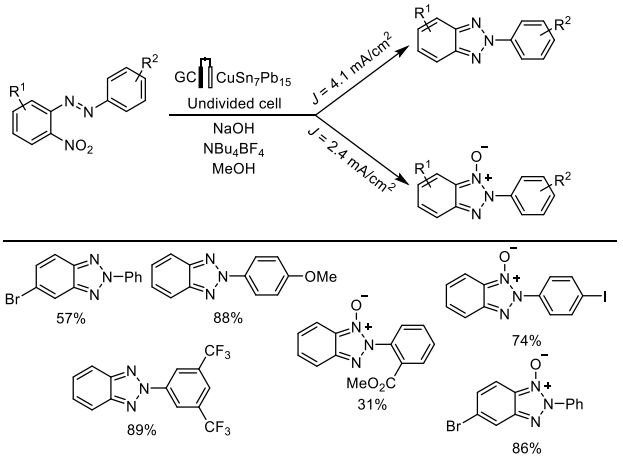
The mechanism is outlined in Scheme 47. Initially, I is oxidized to I_2 at the anode, which subsequently reacts with the substrate to form **I** through the creation of an N−I bond and the release of HI. The homolytic cleavage of intermediate **II** then leads to an intramolecular cyclization that generates **III** by attacking the N═ N bond. Anodic oxidation of intermediate **III** yields the cationic species **IV**. At the same time, water is reduced at the cathode, producing hydrogen gas and OH^- ions. Finally, cationic **IV** undergoes deprotonation and Ts-group removal, facilitated by OH^-, to afford the final product.[130]

Scheme 47. Suggested Mechanism of the Iodine-Catalyzed Electrosynthesis of Benziotriazoles[130]



Also in 2024, Waldvogel and colleagues[131] synthesized benzotriazoles and their *N*-oxides by direct electrolysis of 2-nitroazobenzenes (Scheme 48).

Scheme 48. Electrosynthesis of 2H-2-(Aryl)benzo[d]-1,2,3-Triazoles and Their *N*-Oxides Starting from 2-Nitroazobenzenes[131,a]



[a]GC: glassy carbon.

The formation of benzotriazoles is a 4-electron reduction, and by reducing the current density from 4.1 mA/cm^2 to 2.4 mA/cm^2, the 2-electron reduction, bearing *N*-oxides, becomes accessible. The research group used NaOH as a base, NBu_4BF_4 as an electrolyte, and MeOH as a solvent for both syntheses. Six cathodes were screened, and $CuSn_7Pb_{15}$ gave the best results when glassy carbon was used as the anode. The reaction went smoothly not only with electron-withdrawing groups but also with electron-donating groups.

The reaction begins with the reduction of the starting material to the nitroso compound at the cathode (Scheme 49), either by the addition of $2e^-/2H^+$ or by $4e^-/4H^+$, which generates the hydroxylamine first. This compound is then further reversibly oxidized at the anode, resulting in a loss of $2e^-/2H^+$. Next 5-atom 6π-electrocyclization converts the intermediate to the benzotriazole *N*-oxide, which can be further reduced to the benzotriazole.

1,2,4-Triazole-fused Heterocycles Prepared by Electrochemical Reactions

Triazolopyridines and related triazole-fused polyaromatic frameworks serve as privileged scaffolds in numerous biologically active compounds and functional materials.[132] These core structures have been linked to a broad spectrum of biological activities, including antipsychotic,[133] antibacterial,[134] and antiproliferative[135] effects (Figure 10).

Zhang and his colleagues[136] synthesized 1,2,4-triazolo[4,3-*a*]pyridines via intramolecular dehydrogenative C−N cross-coupling in 2018 (Scheme 50). The electrosynthesis was performed under constant current conditions (10 mA) in an undivided cell, equipped with a graphite rod anode and a Pt plate cathode, with NBu_4BF_4 as an electrolyte in MeCN/H_2O (9:1) at 70 °C under air. First, they obtained the triazole by

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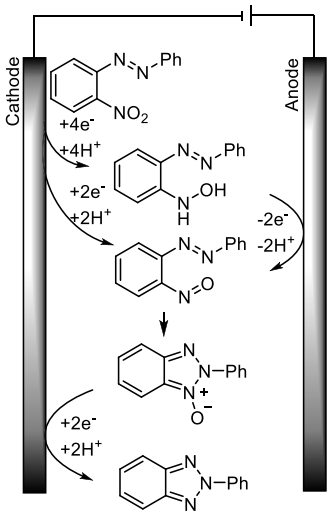
Scheme 49. Mechanism of the Reduction of 2-Nitroazobenzenes to Benzotriazole and Their *N*-Oxides[131]



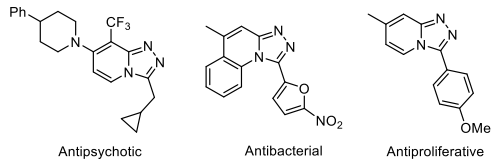
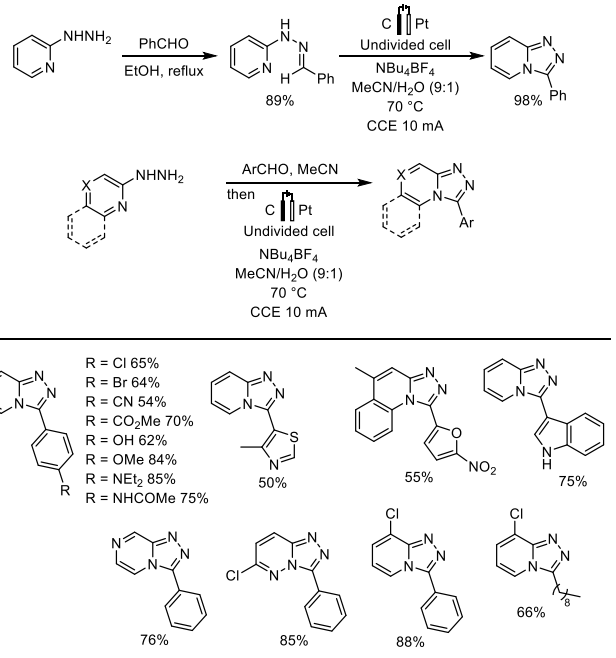


Figure 10. Important triazole-fused heterocycles.

Scheme 50. Electrosynthesis of 1,2,4-Benzotriazoles by Zhang[136,a]



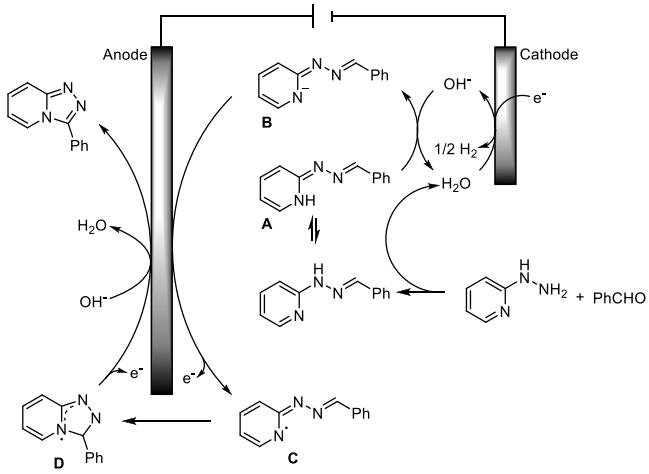
[a]CCE: constant current electrolysis.

cyclization of the isolated hydrazone, then they developed a one-pot reaction, condensing the aromatic aldehyde and the hydrazone, followed by electrolysis without isolating the imine. Under the optimized conditions, substituted 2-hydrazinopyridine reacted with various aromatic aldehydes to efficiently produce a range of 3-aryl[1,2,4]-triazolo[4,3-*a*]pyridines and related heterocyclic derivatives.

2-Hydrazinopyridines reacted with various aromatic aldehydes to efficiently produce a range of 3-aryl[1,2,4]-triazolo-[4,3-*a*]pyridines and related heterocyclic derivatives. (Hetero)-aromatic aldehydes have proven to be viable substrates, generating useful compounds. The benzothiazole-substituted molecule can be used as OLED material,[137] and the nitrofuran-substituted one shows good inhibitory activity against several bacterial strains.[134] The reaction conditions tolerated various functional groups, including halogens, alcohols, and electron-donating or -withdrawing groups, allowing further transformations. This broad functional group tolerance distinguishes this method from many classical triazole syntheses that often require extensive protecting group strategies to avoid unwanted side reactions and achieve acceptable yields.

The C−N cross-coupling reaction also demonstrated a wide substrate scope, accommodating both aliphatic and unsaturated aldehydes. The scalability of the synthesis was evaluated on several compounds. Using 10 mmol starting material and 100 mA current furnished the cyclized products in good yields. The condensation of 2-hydrazinopyridine with benzaldehyde yields the hydrazone, which exists in equilibrium with its tautomer **A** (Scheme 51). The use of relatively high current

Scheme 51. Suggested Mechanism of the Electrosynthesis of 1,2,4-Benzotriazoles[136,a]



[a]CCE: constant current electrolysis.

density might require careful optimization for larger-scale reactions. While the one-pot procedure is advantageous, the potential for side reactions during the hydrazone formation and subsequent cyclization needs to be considered.[136]

Subsequent deprotonation by hydroxide ions—generated through the cathodic reduction of water—produces a nitrogen ion intermediate **B**. Oxidation of **B** by the anode, via a single-electron transfer (SET) process, likely generates a nitrogen radical intermediate **C**. Intramolecular radical addition, followed by anodic oxidation and deprotonation, then leads to the final product through the formation of intermediate **D**. Concurrently, the cathodic reduction of water releases hydrogen gas as a byproduct.

The one-pot synthesis of 1,2,4-triazolo[1,5-*a*]pyridin-5(4H)-one derivatives from simple alkyl carboxylic acids was developed by Ye and his colleagues, applying an electrochemical rearrangement strategy (Scheme 52). The reaction

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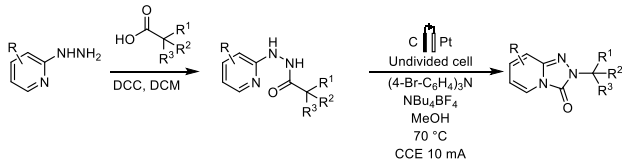
Scheme 52. Electrocatalytic Method for 1,2,4-Benzotriazole Derivatives by Zhang[138,a]



[a]DCC: dicyclohexylcarbodiimide, CCE: constant current electrolysis.

was carried out in an undivided cell using a graphite rod anode and a platinum plate cathode, under constant current conditions (10 mA/cm^2) at 70 °C. Bu_4NBF_4 was employed as the supporting electrolyte in methanol, and tris(4-bromophenyl)amine (10 mol %) redox mediator was used. The reaction enabled the efficient and sustainable preparation of over 60 functionalized triazolopyridinones under mild conditions. The electrochemical method was successfully scaled up to a 10 gram scale, providing not only racemic but enantiomerically pure triazolopyridinones. Late-stage functionalization of complex molecules, including natural products, amino acids, and pharmaceutical compounds, was also demonstrated.[138]

Mechanistic studies suggested that the transformation proceeds via intramolecular cyclization followed by 1,2-carbon migration. First, the hydrazide is proposed to undergo two consecutive anodic oxidations, either directly at the anode or mediated by the anodically generated tris(*p*-bromophenyl)-amine radical cation ($(4-Br-C_6H_4)_3N^{+\bullet}$). Subsequent deprotonation by the cathodically generated methoxide anion yields a *trans*-diazo intermediate, which isomerizes to the more reactive *cis*-diazo species. This is then subjected to an intramolecular nucleophilic attack of the carbonyl group by the pyridine nitrogen, followed by a concerted 1,2-alkyl migration from carbon to nitrogen, resulting in the formation of the rearranged product (Scheme 53).[138]

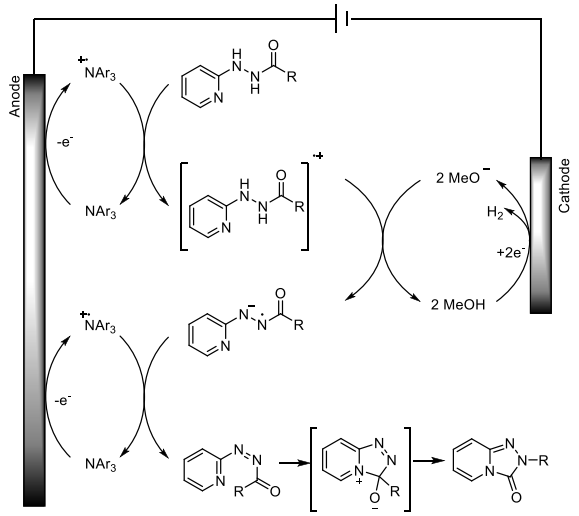
Electrosynthesis of Indoles

Indoles rank among the most important structural motifs, appearing in numerous natural products, pharmaceuticals, and agrochemicals.[139,140] Indole derivatives are also key building blocks in fluorescent cyanine-based chemosensors,[48] labeling reagents,[141] photosensitizing polymers.[142] Electro-organic synthesis of indoles and their electrochemical functionalization has been reviewed in 2020 by Yu and colleagues.[46] In this review, we picked out five examples constituting the indole ring for indoles or polycyclic aromatic compounds with the indole moiety.

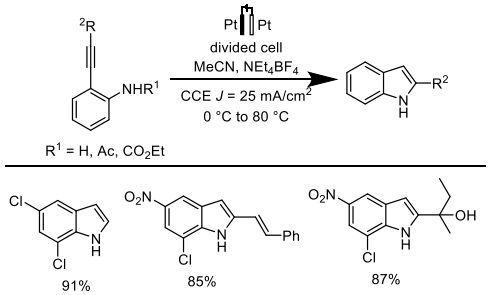
Indoles can be synthesized through various electrochemical approaches, including the reaction of cathodically generated cyanomethyl anions with alkynylanilines, and the ferrocene-catalyzed cyclization of arylamines, which can also be applied to azaindoles. Indoles can also be obtained from 2-vinylanilides using phenothiazine mediator.

Rossi and colleagues[143] synthesized indoles in 2008 by reacting the cathodically formed cyanomethyl anion with alkynylanilines in a divided cell (Scheme 54). They performed

Scheme 53. Proposed Mechanism of the Electrocatalytic 1,2,4-Benzotriazole Synthesis[138]



Scheme 54. Electrosynthesis of Indoles by Rossi[143,a]



[a]CCE: constant current electrolysis.

a constant current electrolysis (25 mA/cm^2) with Pt electrodes in MeCN with Et_4NBF_4 as electrolyte at 0 °C and added the alkine to the cathode chamber after the cyanomethyl anion was formed, then heated up the mixture to 80 °C to shorten the reaction time, although cyclization can occur at room temperature. Under these reaction conditions, it can be hypothesized that the acyl-protecting group on the nitrogen atom is removed through hydrolysis of the amide functionality, catalyzed by the residual water present in the reaction medium.[143] While this method provides access to indoles, the requirement for a divided cell and cryogenic temperatures adds complexity and energy consumption, potentially hindering scalability.

Xu and colleagues[114] synthesized indoles and azaindoles from arylamines with ferrocene as a redox catalyst in 2016 (Scheme 55). They carried out a constant current electrolysis (5 mA, 4.16 mA/cm^2) using RVC as anode and Pt as cathode, with NBu4BF4 as electrolyte and Cp_2Fe as a mediator in refluxing THF/H_2O (5:1) under argon atmosphere. The reaction carried out under air did not impact the yield significantly.

The electrolysis showed excellent compatibility with diverse electron-donating and electron-withdrawing groups at various positions. *Meta-substituted* substances generated two separable regioisomers without high selectivity (1.7:1 isomer ratio). 4- and 3-aminopyridines reacted efficiently under the standard reaction conditions, offering a novel approach to 5-, 4-, and 6-azaindoles. As in earlier indole synthesis, the cyclization was largely insensitive to the electronic and steric features of the pyridine ring and alkyne. The method enabled the synthesis of isocryptolepine and allowed late-stage modification of ethinyl estradiol to yield an indole-functionalized derivative, further

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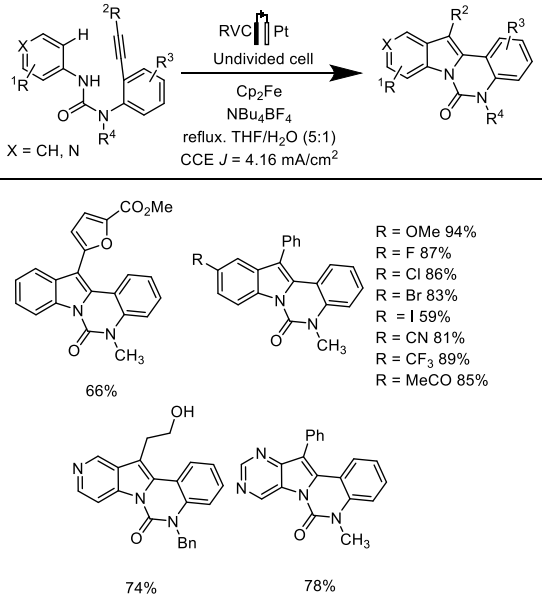
Scheme 55. Electrosynthesis of Indoles by Xu[114,a]

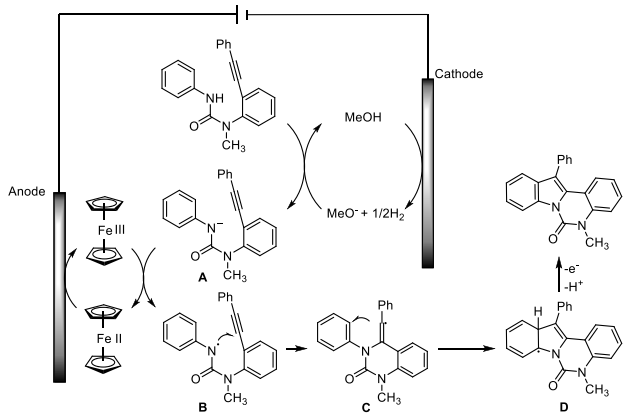


[a]RVC: reticulated vitreous carbon, CCE: constant current electrolysis.

demonstrating its synthetic utility.[144] The process begins with anodic oxidation of ferrocene to ferrocenium ion.

The EGB formed on the cathode deprotonates the substrate to furnish the anion **A**. SET between **A** and ferrocenium ion affords the nitrogen-centered radical **B** and regenerates ferrocene. Next, **B** undergoes a rare 6-*exo*-dig cyclization, forming the vinyl radical **C**, which then engages in a second cyclization with the aryl ring to produce the delocalized radical **D**. Finally, the rearomatization of **D** through electron and proton elimination yields the final product (Scheme 56).[114]

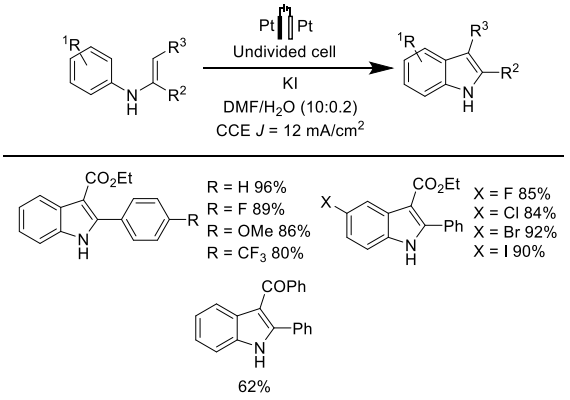
Scheme 56. Proposed Mechanism of the Ferrocene-Catalyzed Indole Synthesis[114]



The use of ferrocene as a mediator is advantageous for its ability to facilitate electron transfer. The formation of regioisomers in some cases also requires further optimization.

Lei's group[115] synthesized indoles from *N*-aryl enamines in 2017 (Scheme 57) and, as discussed before, an imidazo[1,2-*a*]pyridine and an imidazo[1,2-*a*]pyrazine (Scheme 43). They carried out a constant current electrolysis (7 mA, 12 mA/cm^2) in an undivided cell with Pt electrodes, using KI as an electrocatalyst and electrolyte in DMF/H_2O (10:0.2). Substituting the carboxylic ester with a ketone resulted in

Scheme 57. Electrosynthesis of Indoles by Lei[115,a]

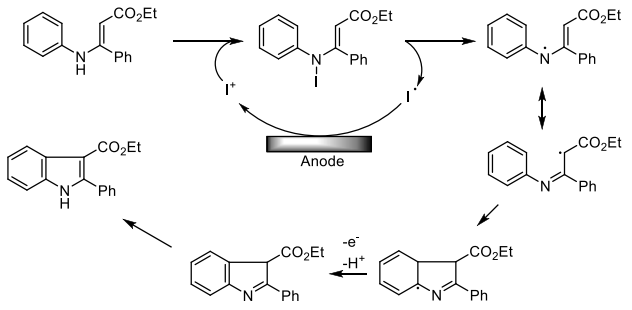


[a]CCE: constant current electrolysis.

reduced reaction efficiency. Initially, anodic oxidation of iodide ions occurs twice to produce a hyperiodide intermediate (I^+). The in situ generated I^+ then reacts with the *N*-aryl enamine, yielding an *N*-iodo intermediate. Homolytic cleavage of the N−I bond initiates the cyclization process. Intramolecular radical addition, followed by oxidation and deprotonation, subsequently leads to the formation of the indole.[115]

Meanwhile, the iodine radical formed during this process is re-oxidized at the anode to regenerate the hyperiodide intermediate. In parallel, the cathodic reduction of water releases hydrogen gas, completing the electrochemical cycle (Scheme 58).[115] The use of iodine as a catalyst, while effective,

Scheme 58. Proposed Mechanism of the Iodine-Catalyzed Electrosynthesis of Indoles[115]



raises environmental concerns related to halogenated waste. Optimizing the catalyst loading and exploring strategies for iodine recovery would be crucial for improving the sustainability of this process.

Xu and co-workers synthesized indoles from 2-vinylanilides using phenothiazine as a molecular catalyst in 2021 (Scheme 59).[145] The reaction was carried out in an undivided cell, employing constant current electrolysis (7.5 mA, 6.25 mA/cm^2) with NBu_4PF_6 as electrolyte and a phenothiazine as a molecular catalyst in MeCN/H_2O (2:1) at 55 °C using an RVC anode and a Pt cathode under argon atmosphere. Changing the solvent to pure MeCN or MeCN/H_2O 1:1 diminished the yield. Also, raising the current to 10 mA or changing the mediator to ferrocene reduced the outcome of product formation.

The scope of the indole electrosynthesis was explored by varying the substituents on both the alkene and the benzene ring. The benzene ring accommodated substituents with a

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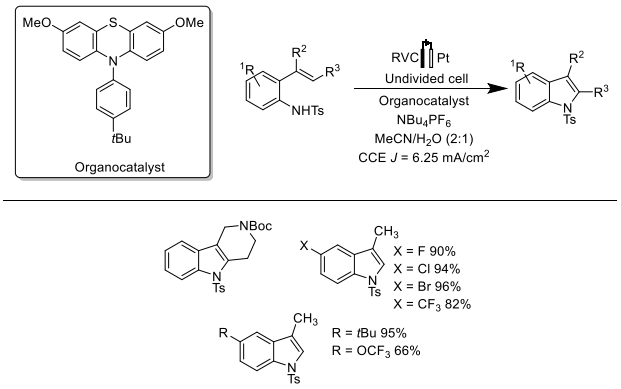
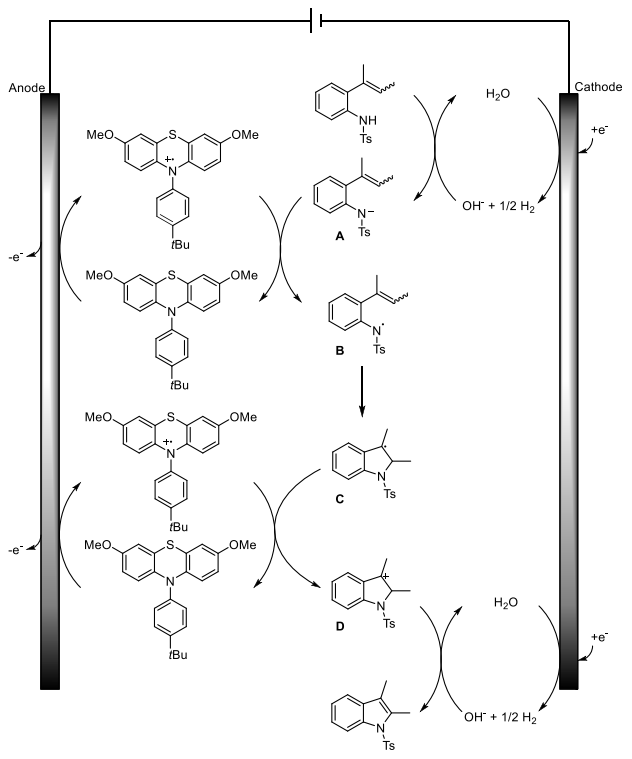
Scheme 59. Electrosynthesis of Indoles by Xu[145,a]



[a]RVC: Reticulated vitreous carbon, CCE: constant current electrolysis.

range of electronic properties, including alkyl groups, halides, OCF_3, and CF_3. Unsubstituted indoles and the Boc and Ac-protected indoles could not be obtained by this method. The proposed mechanism is outlined in Scheme 60. The electro-

Scheme 60. Suggested Mechanism of the Phenothiazine-Catalysed Electrosynthesis of Indoles[145]



chemical process begins with the anodic oxidation of the catalyst, thereby generating its radical cation. The EGB deprotonates the anilide to its conjugate base **A**, which is then oxidized by the radical cation to the nitrogen-centered radical **B**. The cyclisation of **B**, followed by further oxidation by the radical cation and subsequent deprotonation, yields the final indole. It is hypothesized that the failure to form the unsubstituted indole was due to the more challenging radical cyclisation process required to form a secondary carbon radical.[145]

Parameters of the described indole electrosynthesis are summarized in Table 4.

Electrosynthesis of Cinnoline Derivatives

Cinnoline derivatives have a wide range of biological activities, including anticancer, antimicrobial, anti-inflammatory, antiparasitic, and herbicidal properties (Figure 11).[146] Despite their

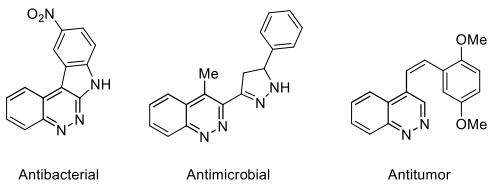


Figure 11. Selected biologically important cinnolines.

importance, broadly applicable methods for synthesizing cinnolines are still scarce, as traditional ways have a narrow scope, harsh conditions, and require multiple steps.[147] This highlights the value of electrosynthetic ways, offering a modular and efficient route to cinnolines.

Recently, Cai et al.[148] developed a one-pot, two-step electrochemical synthesis of cinnolines from *ortho*-alkynyl acetophenones and sulfonyl hydrazides, utilizing an organocatalytic cascade radical cyclization and migration strategy. This method stands out for its mild conditions, excellent yields, and high substrate scopes and high regioselectivity (Scheme 61).

Mechanistic investigations—including isotope labeling, radical trapping, singlet oxygen and superoxide radical anion inhibition studies, cyclic voltammetry, etc.—support a proposed electrochemically induced cascade radical cyclization and migration pathway (Scheme 62).[148]

Electrosynthesis of Indole-Fused Polycyclic Compounds

Huang's group[149] synthesized indole-fused polycyclic compounds by electrochemical decarboxylation of α-imino-oxy acids catalyzed by NBu_4Br in 2021 (Scheme 63). The reaction was carried out in an undivided cell using constant current electrolysis (3 mA, 3 mA/cm^2) with an RVC anode, Pt cathode, NBu_4Br as mediator and NBu_4BF_4 as electrolyte, Cs_2CO_3 as base in HFIP/TFE (4:1).

Using a higher amount of NBu_4Br and employing it also as electrolyte, in the absence of NBu_4BF_4 resulted in diminished yields. Other halogen-containing catalysts, like KI, NaI, NBu_4I, and NaBr reduced the product formation. No product was detected when using TEMPO or ferrocene mediator. The

Table 4. Reaction Conditions of the Described Indole Electrosynthesis

ref	substrate	anode/cathode	mediator	electrolyte/solvent	current density [mA/cm^2]
Rossi[143]	alkynylaniline	Pt/Pt	NBu_4I	Et_4NBF_4/MeCN	25
Xu[114]	arylamine	RVC/Pt	none	Et_4NBF_4/THF -H_2O	4.16
Lei[115]	n-aryl enamine	Pt/Pt	$Pd(OAc)_2$	KI/DMF − H_2O	12
Xu[145]	2-vinylanilide	RVC/Pt	none	NBu_4PF_6/MeCN−H_2O	6.25

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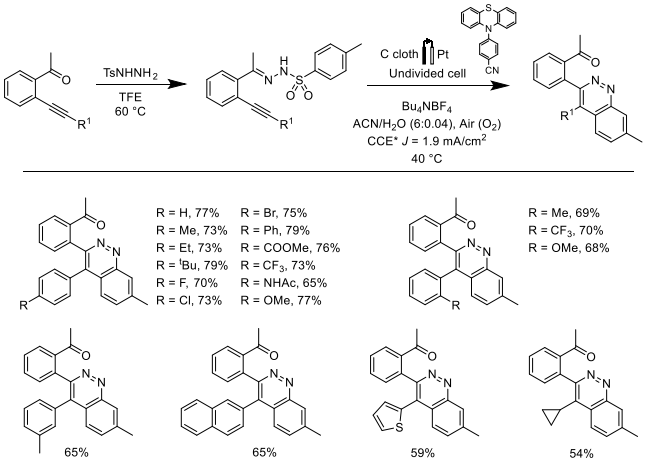
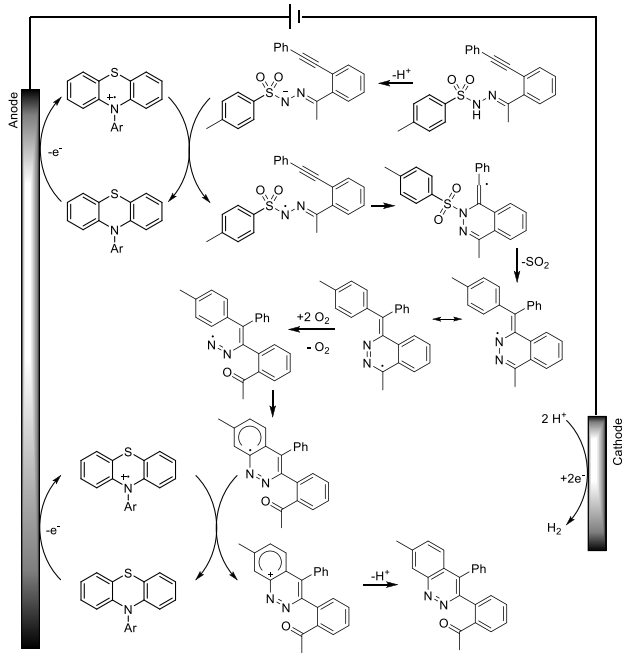
Scheme 61. A One-Pot Electrosynthesis of Cinnolines from *ortho*-Alkynyl Acetophenones and Sulfonyl Hydrazides[148,a]



[a]*Carbon cloth anode (35 mm × 15 mm), platinum plate cathode (10 mm × 10 mm × 0.1 mm); 10 mA, CCE: constant current electrolysis, isolated yields for the two steps.

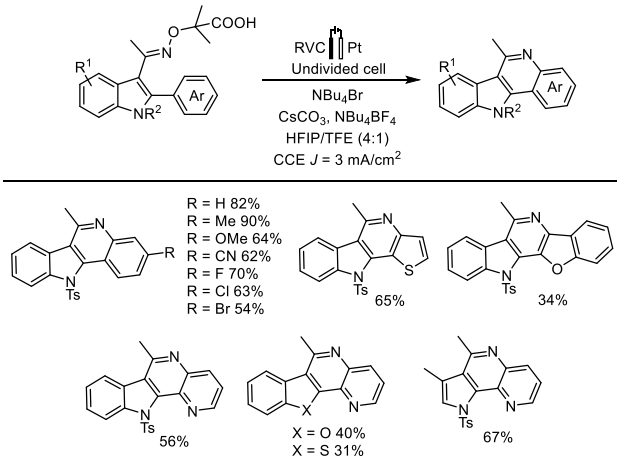
Scheme 62. Proposed Mechanism for the Electrosynthesis of Cinnoline Skeleton[148]



mixed solvent system was essential for the reaction's success, as omitting either component significantly reduced the yield. Furthermore, the HFIP/TFE ratio played a crucial role in determining the overall efficiency.

A variety of intriguing *N*-heterocyclic products featuring the indole scaffold have been successfully synthesized. The aromatic ring of the starting substrate could be functionalized with a wide variety of substituents exhibiting diverse electronic properties at the *para*, *ortho*, or *meta* positions. The OMe-substituted substrate in the meta position yielded two regioisomers with a 1:1.1 ratio. Changing the Ts protecting group of the nitrogen to Me, Bn, or Boc reduced the yield of the product (41−59%). The aromatic ring can be substituted with other (hetero)aromatic moieties, including 2-naphthalene,

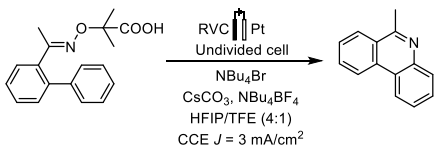
Scheme 63. Electrosynthesis of Indole-Fused Polycycles by Huang[149,a]



[a]RVC: Reticulated vitreous carbon, CCE: constant current electrolysis, HIFP: 1,1,1,3,3,3-hexafluoroisopropanol, TFE: 2,2,2-trifluoroethanol.

2-thiophene, 2-benzofuran, 2-pyridine, or 4-pyridine groups. Notably, this method is not restricted to indoles only. Substrates derived from benzofuran, benzothiophene, and pyrrole also successfully yielded the corresponding products. This approach proved to be effective in synthesizing 6-methylphenanthridine (Scheme 64). Phenantridines and phenantridiniums are recognized as chromophores with excellent optical properties.[150,151]

Scheme 64. Electrochemical Synthesis of 6-Methylphenantridine[149,a]



[a]RVC: Reticulated vitreous carbon, CCE: constant current electrolysis.

A plausible mechanism, as the anodic oxidation of Br^- produces Br^+, a mixture of Br_2, Br_3^-, and Br^+. Carboxylic acid is deprotonated by the base and oxidized by the active species Br^+ to form radical **B** (Scheme 65). The intermediate **B** can also be generated by direct anodic oxidation. Intermediate **B** undergoes sequential fragmentation of CO_2 and acetone, resulting in the key iminyl radical **C**, which undergoes intramolecular homolytic aromatic substitution, leading to radical intermediate **D**. Finally, the oxidation of **D** by the anode or Br^+, followed by deprotonation, yields the product.

Electrochemical Synthesis of Polycyclic *N*-Heteroaromatics

Polycyclic aromatic hydrocarbons (PAHs), composed of multiple fused aromatic rings, play a pivotal role in material science due to their unique optoelectronic properties and structural tunability.[152,153] These features enable their use in organic semiconductors, photovoltaic cells, and organic light-emitting diodes, where subtle modifications to their molecular framework can fine-tune charge transport, absorption spectra, and emission profiles. Polycyclic aromatic hydrocarbons and their derivatives have also been used as chemosensors and

https://doi.org/10.1021/acselectrochem.5c00523
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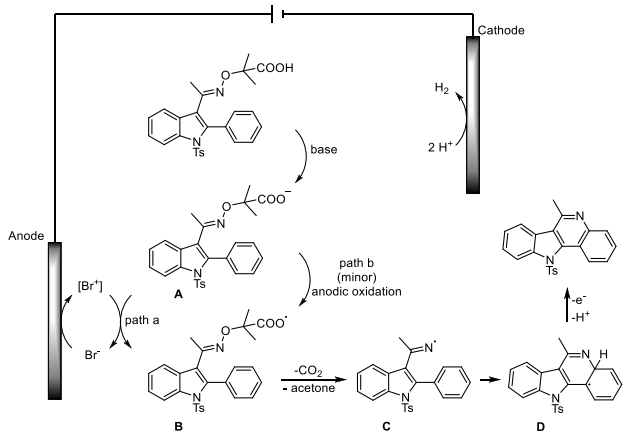
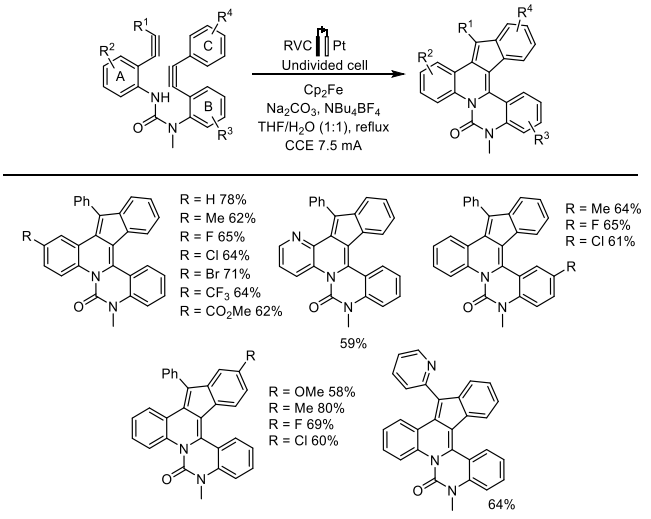
Scheme 65. Proposed Mechanism for the Bromine-Catalyzed Electrosynthesis of Indole-Fused Polycycles[149]



fluorescent dyes.[80,154,155] As a result, PAHs remain a cornerstone in designing advanced, high-performance materials for emerging technologies. Xu and co-workers[156] developed a ferrocene-catalyzed method for the synthesis of nitrogen-doped polycyclic aromatic hydrocarbons (PAHs) from easily available urea-tethered diynes in 2017 (Scheme 66). The

Scheme 66. Ferrocene-Catalyzed Electrosynthesis of Nitrogen-Doped PAHs[156,a]

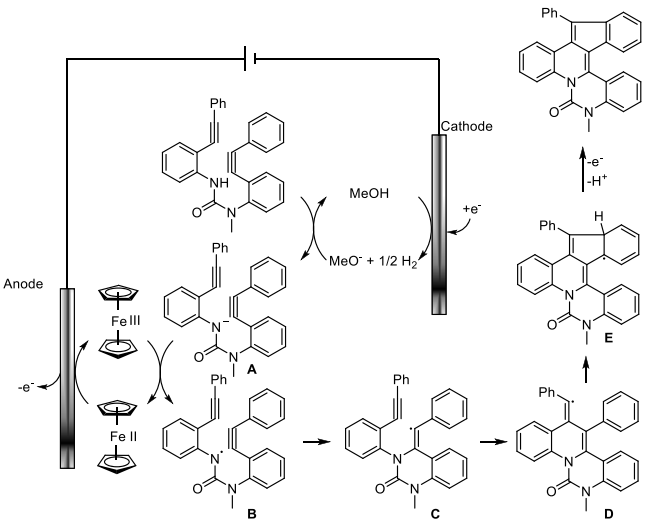


[a]RVC: Reticulated vitreous carbon, CCE: constant current electrolysis, Cp_2Fe: ferrocene.

developed method involves constant current electrolysis (7.5 mA) performed in an undivided cell equipped with an RVC anode and a Pt cathode, using Cp_2Fe as a catalyst, Bu_4BF_4 as an electrolyte, Na_2CO_3 as an additive in a refluxing THF/MeOH (1:1) mixture.

Raising the current to 10 mA had a more pronounced negative impact on reaction efficiency compared to lowering it to 5 mA. At 10 mA, the redox catalyst may fail to cycle quickly enough to support the increased current, potentially resulting in competitive oxidation of the product and a subsequent decrease in yield. Although diynes are susceptible to base-promoted hydroamidation and their products are prone to overoxidation, the use of ferrocene as a mild redox catalyst, combined with the continuous generation of the required base at the cathode, enables efficient synthesis of a variety of electron-rich PAHs, including helical structures. Exploring the substrate scope, diversification was made on all three rings, A, B, C, and the terminal alkyne R^1. The reaction was compatible with various diynes, in which alkyl substituents, halogens, and an ester group were tolerated. Changing the phenyl ring A to a pyridyl ring was also feasible. The terminal phenyl ring C could be functionalized with OMe, Me, F, or Cl. However, substitution with the strongly electron-withdrawing CN group resulted in base-promoted alkyne hydroamidation, leading to monocyclization instead. The mechanism is outlined in Scheme 67. In the first step, the EGB deprotonates the

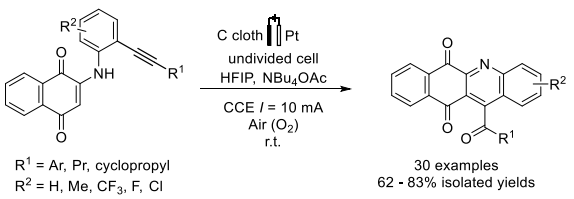
Scheme 67. Proposed Mechanism of the Ferrocene-Catalyzed Electrosynthesis of *N*-Doped PAHs[156]



amide to form the amidyl anion **A**, which then undergoes a SET with the $Cp^2Fe(III)$, which is formed at the anode, to produce the amidyl radical **B**. Intermediate **B** then undergoes a series of cyclization reactions and in the final step, oxidation and deprotonation give rise to the PAH.[156]

In 2023, Guo reported an electrochemical intramolecular oxidative cyclization of 1,6-enyne substrates to furnish a broad array of azaheterocycles under remarkably mild, metal-free conditions (Scheme 68).[157] The transformation was performed in an undivided cell under an open-air atmosphere, employing constant current electrolysis (10 mA) with a carbon-cloth anode and Pt cathode, Bu_4NOAc as the supporting electrolyte, and HFIP as the solvent. Notably, no external catalyst or chemical oxidant was required. The optimized conditions proved highly robust, as varying the electrolyte or modifying

Scheme 68. One-step Intramolecular Electrochemical Synthesis of Nitrogen-Doped PAHs[157,a]



[a]HIFP: 1,1,1,3,3,3-hexafluoroisopropanol CCE: constant current electrolysis.

https://doi.org/10.1021/acselectrochem.5c00523
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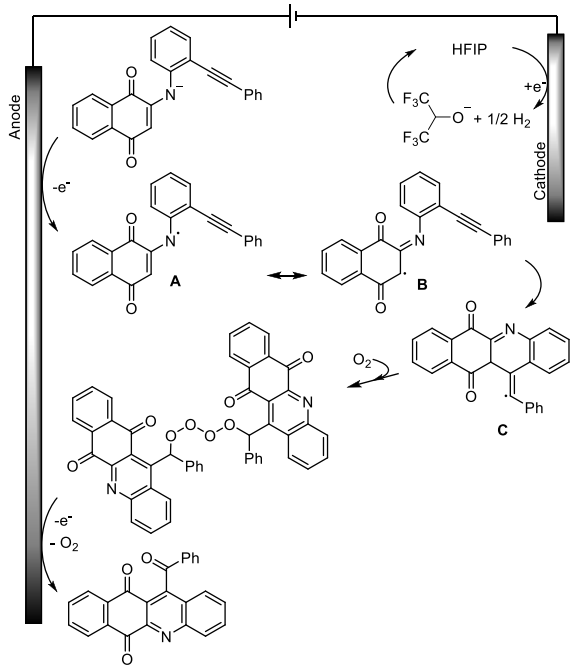
the solvent system significantly decreased efficiency, thereby underscoring the essential role of HFIP in promoting the oxidative cyclization. A wide substrate scope was demonstrated on 30 derivatives, establishing excellent tolerance toward diverse functional groups, as well as electronically and sterically differentiated substitution patterns on both the alkyne and amine components. The reaction accommodated electron-rich and electron-poor aromatic groups, heteroarenes, and variously substituted enynes without noticeable loss in reactivity. Importantly, the method is scalable, as demonstrated by a gram-scale electrolysis that delivered the desired azaheterocycle in comparable yield.

Mechanistic investigations, including isotope-labeling experiments, support the formation of an *N*-centered radical as the key reactive intermediate (Scheme 69). The process is initiated

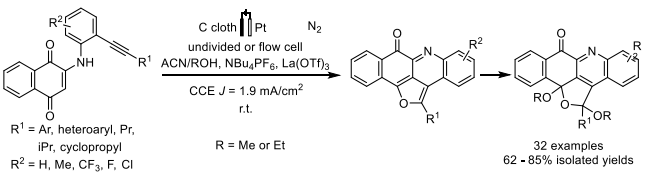
Scheme 69. Suggested Mechanism of the Intramolecular Electrochemical Synthesis of Nitrogen-Doped PAHs[157]



by anodic oxidation of the deprotonated substrate, which is generated in situ under the basic conditions arising from the cathodic reduction of HFIP. This results in the *N*-centered radical (**A**). Resonance stabilization facilitates the equilibrium of A with the corresponding C-centered radical (**B**), whose enhanced stability is responsible for the absence of indole-type byproducts. The intramolecular addition of B to the alkyne forms a benzyl-type radical (**C**) in a 6-*exo*-dig cyclization. Under aerobic conditions, **C** undergoes radical−radical coupling with molecular oxygen, producing a transient peroxide that undergoes O−O bond cleavage followed by oxidation to furnish the azaheterocyclic product with concurrent regeneration of O_2. In an alternative pathway, **C** may undergo oxidation to form a carbocation, which is then intercepted by water to yield an alcohol intermediate that ultimately produces the same product after further oxidation. Consistent with labeling studies, the oxygen-trapping way appears to be the predominant route.[157] This metal-free approach is a significant step towards greener electrosynthesis. However, the continued reliance on HFIP as a solvent remains a concern, limiting its overall sustainability.

In 2023, Chen and co-workers[158] reported an electrochemical dehydrogenative cascade cyclization-alkoxylation for synthesizing pyridine-fused PAHs (Scheme 70). The reaction

Scheme 70. Electrochemical Synthesis of 6-Methylphenantridine[158,a]



[a]CCE: constant current electrolysis.

was carried out in an undivided cell under a nitrogen atmosphere, employing constant-current electrolysis (J = 1.9 mA cm^{-2}) with a carbon cloth anode, Pt cathode, and NBu_4PF_6 as an electrolyte in an ACN/MeOH solvent mixture. The incorporation of the supporting electrolyte $La(OTf)_3$ proved essential, and its absence drastically reduced the reaction efficiency. The optimized conditions facilitated the seamless formation of the desired polycyclic *N*-doped PAHs. The investigation revealed broad functional group tolerance and compatibility with a variety of substrates, including those that are electronically and sterically diverse.[158] A notable advantage of this methodology is its excellent scalability up to the multigram scale. Transition to a continuous-flow electrolysis setup enabled large-scale production by extending the electrolysis time.

The electrochemical process, as described in Scheme 69, initiates with the formation of the C benzylic radical. In the presence of $La(OTf)_3$, this radical is converted into a tight ion-pair intermediate, which rapidly cyclizes via intramolecular anion−cation coupling to give a furan intermediate (Scheme 70, middle). Finally, alkoxylation, enabled by alkoxy radicals formed through anodic oxidation of methoxide, affords the pyridine-fused dialkoxy *N*-heteroaromatic product. The use of a lanthanide salt ($La(OTf)_3$) as a Lewis acid raises concerns about the environmental impact and cost of the process. Exploring alternative, more sustainable additives would be beneficial.

CONCLUSION

The electrochemical synthesis of fused nitrogen-containing aromatic heterocycles is a versatile strategy in modern organic synthesis. A review of the methods employed reveals a broad substrate scope, demonstrating tolerance toward diverse functional groups and compatibility with diverse electronic and steric properties. Significant advances have been made in the efficient utilization of anodic oxidation, radical cascades, and selective cyclization pathways for constructing complex heterocyclic frameworks. These include benzoxazoles, benzothiazoles, isoxazoles, carbazoles, xanthines, imidazopyridines, pyridobenzimidazoles, benzotriazoles, indoles, azaindoles, phenanthridines, and other polycyclic compounds. Furthermore, innovative approaches using mixed solvent systems, pioneering electroredox catalysts, and fine-tuned electrochemical conditions have effectively addressed challenges such as overoxidation and competing side reactions, thereby enabling high yields and excellent product specificity.

https://doi.org/10.1021/acselectrochem.5c00523
ACS Electrochem. 2026, 2, 845−873

Collectively, these advances facilitate the efficient synthesis of structurally complex *N*-heterocycles with significant relevance in pharmaceutical and materials science applications.

However, challenges such as the scalability of electrochemical processes, electrode stability, and the development of universal conditions for broader heterocycles require attention. Addressing these limitations will require further research into flow chemistry to enhance process control and productivity, the design of robust and passivation-resistant electrode materials, and efficient strategies for mediator recovery and recycling. Progress in these areas is expected to further expand the industrial applicability of electrochemical annulation strategies.

In conclusion, advances in electrosynthesis demonstrate its potential as a sustainable, efficient and powerful tool for the synthesis of nitrogen-containing aromatic heterocycles. Future developments will likely focus on integrating scalable reactor technologies, improving material durability, and advancing sustainable catalyst and mediator systems, including the use of earth-abundant electrode materials and recyclable redox mediators.

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The manuscript was written through the contributions of all authors. All authors have given approval to the final version of the manuscript.

Funding

This work was supported by the National Research, Development and Innovation Office, Hungary (K135946).

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

The Bolyai János Research Scholarship of the Hungarian Academy of Sciences (BO/85/24/7) for E.K. is also acknowledged.

ABBREVIATIONS

BDD	boron-doped diamond
CCE	constant current electrolysis (galvanostatic)
CPE	constant potential electrolysis (potentiostatic)
Cp_2Fe	ferrocene
DCE	1,2-dichloroethane - in the synthesis of benzotriazoles
EGB	electro-generated base
GC	glassy carbon
HFIP	1,1,1,3,3,3-hexafluoroisopropanol
NCR	nitrogen-centered radical
PAH	polycyclic aromatic hydrocarbon
PMB	p-methoxybenzyl (at N9 fused xanthines)
TFE	3,3,3,-trifluorethanol
RVC	reticulated vitreous carbon
SET	single electron transfer

REFERENCES

(1) Yan, M.; Kawamata, Y.; Baran, P. S. Synthetic Organic Electrochemical Methods Since 2000: On the Verge of a Renaissance. *Chem. Rev.* **2017**, *117* (21), 13230−13319.

(2) Bayannavar, P. K.; Nayak, M. R.; Kamble, R. R. Electrosynthesis of Organic Compounds. In *Electrochemistry of Organic and Organometallic Compounds; Inamuddin*; Altalhi, T., Neves Cruz, J., Mazumder, M. A. J., Eds.; Elsevier, 2025; pp 267−294. DOI: 10.1016/B978-0-443-30124-7.00010-4.

(3) Faraday, M. Fünfte Reihe von Experimental - Untersuchungen Über Elektricität. *Ann. Phys.* **1834**, *108* (26−30), 401−453.

(4) Kolbe, H. Beobachtungen Über Die Oxydirende Wirkung Des Sauerstoffs, Wenn Derselbe Mit Hülfe Einer Elektrischen Säule Entwickelt Wird. *J. für Prakt. Chemie* **1847**, *41* (1), 137−139.

(5) Simons, J. H. Production of Fluorocarbons: I. The Generalized Procedure and Its Use with Nitrogen Compounds. *J. Electrochem. Soc.* **1949**, *95* (2), 47.

(6) Baizer, M. M. The Electrochemical Route to Adiponitrile. *Chem. Tech.* **1980**, *10* (3), 161−164.

(7) Sequeira, C. A. C.; Santos, D. M. F. Electrochemical Routes for Industrial Synthesis. *J. Braz. Chem. Soc.* **2009**, *20* (3), 387−406.

(8) Kovács-Kószó, E.; Kosztolányi, J.; Setiadi, D.; Csizmadia, I. G. Climate Change Indicates That a Balanced Environment Is a Historic Requirement. *Int. J. Environ. Stud.* **2022**, *79* (6), 955−980.

(9) Liang, R.; Zheng, S.; Wang, K.; Yuan, Z. Cost-Aware Bayesian Optimization for Self-Driven Condition Screening of Flow Electrosynthesis. *ACS Electrochem.* **2025**, *1* (3), 360−368.

(10) Wagenknecht, J. H. Industrial Organic Electrosynthesis. *J. Chem. Educ.* **1983**, *60* (4), 271.

(11) Cardoso, D. S. P.; Šljukić, B.; Santos, D. M. F.; Sequeira, C. A. C. Organic Electrosynthesis: From Laboratorial Practice to Industrial Applications. *Org. Process Res. Dev.* **2017**, *21* (9), 1213−1226.

(12) Brachi, M.; El Housseini, W.; Beaver, K.; Jadhav, R.; Dantanarayana, A.; Boucher, D. G.; Minteer, S. D. Advanced Electroanalysis for Electrosynthesis. *ACS Org. Inorg. Au* **2024**, *4* (2), 141−187.

(13) Frontana-Uribe, B. A.; Little, R. D.; Ibanez, J. G.; Palma, A.; Vasquez-Medrano, R. Organic Electrosynthesis: A Promising Green Methodology in Organic Chemistry. *Green Chem.* **2010**, *12* (12), 2099−2119.

(14) Pollok, D.; Waldvogel, S. R. Electro-Organic Synthesis − a 21st Century Technique. *Chem. Sci.* **2020**, *11* (46), 12386−12400.

(15) Bard, A. J.; Faulkner, L. R.; White, H. S. *Electrochemical Methods: Fundamentals and Applications*, 3rd ed.; Wiley, 2022.

(16) Moeller, K. D. Synthetic Applications of Anodic Electrochemistry. *Tetrahedron* **2000**, *56* (49), 9527−9554.

(17) Francke, R.; Little, R. D. Redox Catalysis in Organic Electrosynthesis: Basic Principles and Recent Developments. *Chem. Soc. Rev.* **2014**, *43* (8), 2492−2521.

(18) Wang, F.; Stahl, S. S. Electrochemical Oxidation of Organic Molecules at Lower Overpotential: Accessing Broader Functional Group Compatibility with Electron−Proton Transfer Mediators. *Acc. Chem. Res.* **2020**, *53* (3), 561−574.

(19) Nutting, J. E.; Rafiee, M.; Stahl, S. S. Tetramethylpiperidine N-Oxyl (TEMPO), Phthalimide N-Oxyl (PINO), and Related N-Oxyl Species: Electrochemical Properties and Their Use in Electrocatalytic Reactions. *Chem. Rev.* **2018**, *118* (9), 4834−4885.

(20) Chen, N.; Xu, H.-C. Electrochemically Driven Radical Reactions: From Direct Electrolysis to Molecular Catalysis. *Chem. Rec.* **2021**, *21* (9), 2306−2319.

(21) Novaes, L. F. T.; Liu, J.; Shen, Y.; Lu, L.; Meinhardt, J. M.; Lin, S. Electrocatalysis as an Enabling Technology for Organic Synthesis. *Chem. Soc. Rev.* **2021**, *50* (14), 7941−8002.
(22) Tang, H.-T.; Jia, J.-S.; Pan, Y.-M. Halogen-Mediated Electrochemical Organic Synthesis. *Org. Biomol. Chem.* **2020**, *18* (28), 5315−5333.
(23) Ma, C.; Fang, P.; Liu, Z.-R.; Xu, S.-S.; Xu, K.; Cheng, X.; Lei, A.; Xu, H.-C.; Zeng, C.; Mei, T.-S. Recent Advances in Organic Electrosynthesis Employing Transition Metal Complexes as Electrocatalysts. *Sci. Bull.* **2021**, *66* (23), 2412−2429.
(24) Mousa, M. O.; Adly, M. E.; Mahmoud, A. M.; El-Nassan, H. B. Synthesis of Tetrahydro-*β*-Carboline Derivatives under Electrochemical Conditions in Deep Eutectic Solvents. *ACS Omega* **2024**, *9* (12), 14198−14209.
(25) Kaboudin, B.; Behroozi, M.; Sadighi, S. Recent Advances in the Electrochemical Reactions of Nitrogen-Containing Organic Compounds. *RSC Adv.* **2022**, *12* (47), 30466−30479.
(26) Shono, T.; Matsumura, Y.; Inoue, K. Indirect Electrooxidation of Amines to Nitriles Using Halogen Ions as Mediators. *J. Am. Chem. Soc.* **1984**, *106* (20), 6075−6076.
(27) Xu, Z.; Kovács, E. Beyond Traditional Synthesis: Electrochemical Approaches to Amine Oxidation for Nitriles and Imines. *ACS Org. Inorg. Au* **2024**, *4* (5), 471−484.
(28) Liang, S.; Zeng, C.-C. Organic Electrochemistry: Anodic Construction of Heterocyclic Structures. *Curr. Opin. Electrochem.* **2020**, *24*, 31−43.
(29) Wu, Z.-J.; Xu, H.-C. Redox-Mediated Electrochemical Cyclization Reactions. In *Sustainable and Functional Redox Chemistry*; Inagi, S., Ed.; The Royal Society of Chemistry, 2022; p 29. DOI: 10.1039/9781839164828-00001.
(30) Hashmi, S. Z.; Bareth, D.; Dwivedi, J.; Kishore, D.; Alvi, P. A. Green Advancements towards the Electrochemical Synthesis of Heterocycles. *RSC Adv.* **2024**, *14* (26), 18192−18246.
(31) Devi, S.; Jyoti; Kiran; Wadhwa, D.; Wadhwa, D.; Sindhu, J. Electro-Organic Synthesis: An Environmentally Benign Alternative for Heterocycle Synthesis. *Org. Biomol. Chem.* **2022**, *20* (26), 5163−5229.
(32) Okumura, Y.; Sato, E.; Mitsudo, K.; Suga, S. Electrochemical Synthesis of Heterocyclic Compounds via Carbon−Heteroatom Bond Formation: Direct and Indirect Electrolysis. *Chem. Lett.* **2024**, *53* (8), upae146.
(33) Imeni, S.; Makarem, A.; Javahershenas, R. Recent Advances in Multicomponent Electro-Organic (Electrochemical) Synthesis of Heterocycles. *Asian J. Org. Chem.* **2023**, *12* (8), No. e202300303.
(34) Zhang, C.; Chen, D.; Wan, J. P.; Liu, Y. Recent Advances in Electrochemical Cascade Cyclization Reactions. *Synthesis (Stuttg)* **2023**, *55* (18), 2911−2925.
(35) Elinson, M. N.; Vereshchagin, A. N.; Ryzkov, V. F. Electrochemical Synthesis of Heterocycles via Cascade Reactions. *Curr. Org. Chem.* **2017**, *21* (15), 1427−1439.
(36) Martins, G. M.; Zimmer, G. C.; Mendes, S. R.; Ahmed, N. Electrifying Green Synthesis: Recent Advances in Electrochemical Annulation Reactions. *Green Chem.* **2020**, *22* (15), 4849−4870.
(37) Ye, Z.; Zhang, F. Recent Advances in Constructing Nitrogen-Containing Heterocycles via Electrochemical Dehydrogenation. *Chin. J. Chem.* **2019**, *37* (5), 513−528.
(38) Aslam, S.; Sbei, N.; Rani, S.; Saad, M.; Fatima, A.; Ahmed, N. Heterocyclic Electrochemistry: Renewable Electricity in the Construction of Heterocycles. *ACS Omega* **2023**, *8* (7), 6175−6217.
(39) Francke, R. Recent Advances in the Electrochemical Construction of Heterocycles. *Beilstein J. Org. Chem.* **2014**, *10*, 2858−2873.
(40) Borpatra, P. J.; Deka, B.; Deb, M. L.; Baruah, P. K. Recent Advances in Intramolecular C−O/C−N/C−S Bond Formation via C−H Functionalization. *Org. Chem. Front.* **2019**, *6* (20), 3445−3489.
(41) Sbei, N.; Listratova, A. V.; Titov, A. A.; Voskressensky, L. G. Recent Advances in Electrochemistry for the Synthesis of N-Heterocycles. *Synthesis (Stuttg)* **2019**, *51* (12), 2455−2473.
(42) Listratova, A. V.; Sbei, N.; Voskressensky, L. G. Catalytic Electrosynthesis of N,O-Heterocycles − Recent Advances. *Eur. J. Org. Chem.* **2020**, *2020* (14), 2012−2027.
(43) Titenkova, K.; Chaplygin, D. A.; Fershtat, L. L. Electrochemical Generation of Nitrogen-Centered Radicals and Its Application for the Green Synthesis of Heterocycles. *ChemElectroChem* **2024**, *11* (17), No. e202400395.
(44) Swaroop, T. R.; Shivaprasad, C. M.; Preetham, R.; Sadashiva, M. P.; Rangappa, K. S. Developments in the Electrochemical Synthesis of Thia-Heterocycles. *Phosphorus. Sulfur. Silicon Relat. Elem.* **2022**, *197* (9), 891−898.
(45) Ye, Z.; Zhang, X.; Ma, W.; Zhang, F. Advances in S−N Bond Formation via Electrochemistry: A Green Route Utilizing Diverse Sulfur and Nitrogen Sources. *Green Chem.* **2023**, *25* (7), 2524−2540.
(46) Yu, Y.; Zhong, J.-S.; Xu, K.; Yuan, Y.; Ye, K.-Y. Recent Advances in the Electrochemical Synthesis and Functionalization of Indole Derivatives. *Adv. Synth. Catal.* **2020**, *362* (11), 2102−2119.
(47) Domahidy, F.; Kovács, B.; Cseri, L.; Katona, G.; Rózsa, B.; Mucsi, Z.; Kovács, E. Comprehensive Study of Thiazole-Orange-Based DNA Dyes. *ChemPhotoChem* **2024**, *8* (10), No. e202400080.
(48) Szepesi Kovács, D.; Kontra, B.; Chiovini, B.; Muller, D.; Toth, E. Z.; Ábrányi-Balogh, P.; Wittner, L.; Varady, G.; Turczel, G.; Farkas, Ö.; Owen, M.; Katona, G.; Gyorffy, B.; Keserű, G. M.; Mucsi, Z.; Rózsa, B.; Kovács, E. Effective Synthesis, Development and Application of a Highly Fluorescent Cyanine Dye for Antibody Conjugation and Microscopy Imaging. *Org. Biomol. Chem.* **2023**, *21* (44), 8829−8836.
(49) Mishra, A.; Behera, R. K.; Behera, P. K.; Mishra, B. K.; Behera, G. B. Cyanines during the 1990s: A Review. *Chem. Rev.* **2000**, *100* (6), 1973−2012.
(50) Li, W.-C.; Zeng, C.-C.; Hu, L.-M.; Tian, H.-Y.; Little, R. D. Efficient Indirect Electrochemical Synthesis of 2-Substituted Benzoxazoles Using Sodium Iodide as Mediator. *Adv. Synth. Catal.* **2013**, *355* (14−15), 2884−2890.
(51) Koleda, O.; Broese, T.; Noetzel, J.; Roemelt, M.; Suna, E.; Francke, R. Synthesis of Benzoxazoles Using Electrochemically Generated Hypervalent Iodine. *J. Org. Chem.* **2017**, *82* (22), 11669−11681.
(52) Broese, T.; Francke, R. Electrosynthesis Using a Recyclable Mediator−Electrolyte System Based on Ionically Tagged Phenyl Iodide and 1,1,1,3,3,3-Hexafluoroisopropanol. *Org. Lett.* **2016**, *18* (22), 5896−5899.
(53) Morofuji, T.; Shimizu, A.; Yoshida, J. Electrochemical Intramolecular C-H Amination: Synthesis of Benzoxazoles and Benzothiazoles. *Chem.—A Eur. J.* **2015**, *21* (8), 3211−3214.
(54) Sato, Y.; Yamada, M.; Yoshida, S.; Soneda, T.; Ishikawa, M.; Nizato, T.; Suzuki, K.; Konno, F. Benzoxazole Derivatives as Novel 5-HT3 Receptor Partial Agonists in the Gut. *J. Med. Chem.* **1998**, *41* (16), 3015−3021.
(55) Yoshida, S.; Shiokawa, S.; Kawano, K.; Ito, T.; Murakami, H.; Suzuki, H.; Sato, Y. Orally Active Benzoxazole Derivative as 5-HT3 Receptor Partial Agonist for Treatment of Diarrhea-Predominant Irritable Bowel Syndrome. *J. Med. Chem.* **2005**, *48* (22), 7075−7079.
(56) O'Donnell, C. J.; Rogers, B. N.; Bronk, B. S.; Bryce, D. K.; Coe, J. W.; Cook, K. K.; Duplantier, A. J.; Evrard, E.; Hajós, M.; Hoffmann, W. E.; Hurst, R. S.; Maklad, N.; Mather, R. J.; McLean, S.; Nedza, F. M.; O'Neill, B. T.; Peng, L.; Qian, W.; Rottas, M. M.; Sands, S. B.; Schmidt, A. W.; Shrikhande, A. V.; Spracklin, D. K.; Wong, D. F.; Zhang, A.; Zhang, L. Discovery of 4-(5-Methyloxazolo[4,5-b]Pyridin-2-Yl)-1,4-Diazabicyclo[3.2.2]Nonane (CP-810,123), a Novel A7 Nicotinic Acetylcholine Receptor Agonist for the Treatment of Cognitive Disorders in Schizophrenia: Synthesis, SAR Development, and in Vivo Efficacy. *J. Med. Chem.* **2010**, *53* (3), 1222−1237.
(57) Lazer, E. S.; Miao, C. K.; Wong, H.-C.; Sorcek, R.; Spero, D. M.; Gilman, A.; Pal, K.; Behnke, M.; Graham, A. G. Benzoxazolamines and Benzothiazolamines: Potent, Enantioselective Inhibitors of Leukotriene Biosynthesis with a Novel Mechanism of Action. *J. Med. Chem.* **1994**, *37* (7), 913−923.

https://doi.org/10.1021/acselectrochem.5c00523
ACS Electrochem. 2026, 2, 845−873

(58) Ahdenov, R.; Mohammadi, A. A.; Makarem, S.; Taheri, S.; Mollabagher, H. Eelectrosynthesis of Benzothiazole Derivatives via C−H Thiolation. *Heterocycl. Commun.* **2022**, *28* (1), 67−74.
(59) Gieshoff, T.; Kehl, A.; Schollmeyer, D.; Moeller, K. D.; Waldvogel, S. R. Electrochemical Synthesis of Benzoxazoles from Anilides − a New Approach to Employ Amidyl Radical Intermediates. *Chem. Commun.* **2017**, *53* (20), 2974−2977.
(60) Qian, X.-Y.; Li, S.-Q.; Song, J.; Xu, H.-C. TEMPO-Catalyzed Electrochemical C−H Thiolation: Synthesis of Benzothiazoles and Thiazolopyridines from Thioamides. *ACS Catal.* **2017**, *7* (4), 2730−2734.
(61) Kokatla, H. P.; Yoo, E.; Salunke, D. B.; Sil, D.; Ng, C. F.; Balakrishna, R.; Malladi, S. S.; Fox, L. M.; David, S. A. Toll-like Receptor-8 Agonistic Activities in C2, C4, and C8Modified Thiazolo[4,5-c]Quinolines. *Org. Biomol. Chem.* **2013**, *11* (7), 1179−1198.
(62) Uto, Y. 1,2-Benzisoxazole Compounds: A Patent Review (2009 − 2014). *Expert Opin. Ther. Pat.* **2015**, *25* (6), 643−662.
(63) Simonetti, S. O.; Beil, S. B.; Waldvogel, S. R. Nitro Substrates in Reductive Electrosynthesis: A Review. *ACS Electrochem.* **2025**, *1* (6), 805−818.
(64) Rodrigo, E.; Baunis, H.; Suna, E.; Waldvogel, S. R. Simple and Scalable Electrochemical Synthesis of 2,1-Benzisoxazoles and Quinoline N-Oxides. *Chem. Commun.* **2019**, *55* (81), 12255−12258.
(65) Hyo Kim, B.; Moo Jun, Y.; Rack Choi, Y.; Byung Lee, D.; Baik, W. Electrochemical Synthesis of 2,1-Benzisoxazoles by Controlled Potential Cathodic Electrolysis. *Heterocycles* **1998**, *48* (4), 749−754.
(66) Hosseini, S.; Bawel, S. A.; Mubarak, M. S.; Peters, D. G. Rapid and High-Yield Electrosynthesis of Benzisoxazole and Some Derivatives. *ChemElectroChem* **2019**, *6* (16), 4318−4324.
(67) Lenhard, M. S.; Winter, J.; Sandvoß, A.; Gálvez-Vázquez, M. D. J.; Schollmeyer, D.; Waldvogel, S. R. Simple and Versatile Electrochemical Synthesis of Highly Substituted 2,1-Benzisoxazoles. *Org. Biomol. Chem.* **2025**, *23* (10), 2391−2399.
(68) Lei, C.; Liang, F.; Li, J.; Chen, W.; Huang, B. Electrochemical Reductive Dechlorination of Chlorinated Volatile Organic Compounds (Cl-VOCs): Effects of Molecular Structure on the Dehalogenation Reactivity and Mechanisms. *Chem. Eng. J.* **2019**, *358*, 1054−1064.
(69) Gütz, C.; Bänziger, M.; Bucher, C.; Galvão, T. R.; Waldvogel, S. R. Development and Scale-Up of the Electrochemical Dehalogenation for the Synthesis of a Key Intermediate for NS5A Inhibitors. *Org. Process Res. Dev.* **2015**, *19* (10), 1428−1433.
(70) Wang, L.-W.; Feng, Y.-F.; Lin, H.-M.; Tang, H.-T.; Pan, Y.-M. Electrochemically Enabled Selenium Catalytic Synthesis of 2,1-Benzoxazoles from o-Nitrophenylacetylenes. *J. Org. Chem.* **2021**, *86* (22), 16121−16127.
(71) Bansal, Y.; Silakari, O. The Therapeutic Journey of Benzimidazoles: A Review. *Bioorg. Med. Chem.* **2012**, *20* (21), 6208−6236.
(72) Zhao, H.-B.; Hou, Z.-W.; Liu, Z.-J.; Zhou, Z.-F.; Song, J.; Xu, H.-C. Amidinyl Radical Formation through Anodic N−H Bond Cleavage and Its Application in Aromatic C−H Bond Functionalization. *Angew. Chem., Int. Ed.* **2017**, *56* (2), 587−590.
(73) Carvalho, L. C. R.; Fernandes, E.; Marques, M. M. B. Developments Towards Regioselective Synthesis of 1,2-Disubstituted Benzimidazoles. *Chem.—A Eur. J.* **2011**, *17* (45), 12544−12555.
(74) Lyakhova, E. A.; Gusyeva, Y. A.; Nekhoroshkova, J. V.; Shafran, L. M.; Lyakhov, S. A. Synthesis and Affinity to DNA of Phenylbenzoimidazoles and Benzoimidazo[1,2-c]Quinazolines. *Eur. J. Med. Chem.* **2009**, *44* (8), 3305−3312.
(75) Zhang, B.; Studer, A. Recent Advances in the Synthesis of Nitrogen Heterocycles via Radical Cascade Reactions Using Isonitriles as Radical Acceptors. *Chem. Soc. Rev.* **2015**, *44* (11), 3505−3521.
(76) Beaume, A.; Courillon, C.; Derat, E.; Malacria, M. Unprecedented Aromatic Homolytic Substitutions and Cyclization of Amide. Iminyl Radicals: Experimental and Theoretical Study. *Chem. − A Eur. J.* **2008**, *14* (4), 1238−1252.
(77) Li, A.; Li, C.; Yang, T.; Yang, Z.; Liu, Y.; Li, L.; Tang, K.; Zhou, C. Electrochemical Synthesis of Benzo[d]Imidazole via Intramolecular C(Sp3)−H Amination. *J. Org. Chem.* **2023**, *88* (4), 1928−1935.
(78) Yadav, P.; Shah, K. Quinolines, a Perpetual, Multipurpose Scaffold in Medicinal Chemistry. *Bioorg. Chem.* **2021**, *109*, 104639.
(79) Udhayakumari, D. A Comprehensive Anthology of Literature Based on Quinoline Chemosensors from 2006 to 2022. *J. Mol. Struct.* **2023**, *1287*, 135715.
(80) Csomos, A.; Kovács, E.; Madarász, M.; Fedor, F. Z.; Fülöp, A.; Katona, G.; Rózsa, B.; Mucsi, Z. Two-Photon Fluorescent Chemosensors Based on the GFP-Chromophore for the Detection of Zn2+ in Biological Samples − From Design to Application. *Sensor. Actuator. B Chem.* **2024**, *398*, 134753.
(81) Domahidy, F.; Cseri, L.; Turczel, G.; Huszár, B.; Rózsa, B. J.; Mucsi, Z.; Kovács, E. Cryptocyanine-Based Fluorescent Probes for DNA Detection: Controlling Solubility and Aggregation Through Side Chain Design. *Adv. Sens. Res.* **2026**, *5* (1), No. e00139.
(82) Ferreira, L. M.; García-García, P.; García, P. A.; Castro, M. Á. A Review on Quinolines: New Green Synthetic Methods and Bioactive Potential. *Eur. J. Pharm. Sci.* **2025**, *209*, 107097.
(83) Sharma, V.; Mehta, D. K.; Das, R. Synthetic Methods of Quinoline Derivatives as Potent Anticancer Agents. *Mini-Rev. Med. Chem.* **2017**, *17*, 1557−1572.
(84) Das, R. R.; Jaiswal, N.; Dev, N.; Jaiswal, N.; Naik, S. S.; Sankar, J. Efficacy and Safety of Anti-Malarial Drugs (Chloroquine and Hydroxy-Chloroquine) in Treatment of COVID-19 Infection: A Systematic Review and Meta-Analysis. *Front. Med.* **2020**, *7*, 482.
(85) Vidyavathi, M.; Srividya, G. A Review on Ciprofloxacin: Dosage Form Perspective. *Int. J. Appl. Pharm.* **2018**, *10* (4), 6−10.
(86) Ghosh, S.; Mallick, S.; Karolly, D.; De Sarkar, S. Easy Access to Fused Tricyclic Quinoline Derivatives through Metal-Free Electrocatalytic [4 + 2] Annulation. *ACS Org. Inorg. Au* **2024**, *4* (5), 492−497.
(87) Mfuh, A. M.; Larionov, O. V. Heterocyclic N-Oxides - An Emerging Class of Therapeutic Agents. *Curr. Med. Chem.* **2015**, *22*, 2819−2857.
(88) Wang, Y.; Liming, Z. Recent Developments in the Chemistry of Heteroaromatic N-Oxides. *Synthesis (Stuttg).* **2015**, *47* (03), 289−305.
(89) Thiratmatrakul, S.; Yenjai, C.; Waiwut, P.; Vajragupta, O.; Reubroycharoen, P.; Tohda, M.; Boonyarat, C. Synthesis, Biological Evaluation and Molecular Modeling Study of Novel Tacrine−Carbazole Hybrids as Potential Multifunctional Agents for the Treatment of Alzheimer's Disease. *Eur. J. Med. Chem.* **2014**, *75*, 21−30.
(90) Sellamuthu, S.; Gutti, G.; Kumar, D.; Kumar Singh, S. Carbazole: A Potent Scaffold for Antitubercular Drugs. *Mini. Rev. Org. Chem.* **2018**, *15* (6), 498−507.
(91) Saravanabhavan, M.; Sathya, K.; Puranik, V. G.; Sekar, M. Synthesis, Spectroscopic Characterization and Structural Investigations of New Adduct Compound of Carbazole with Picric Acid: DNA Binding and Antimicrobial Studies. *Spectrochim. Acta, Part A* **2014**, *118*, 399−406.
(92) Hsu, C.-S. Organic Light-Emitting Devices. Synthesis, Properties and Applications. In *Organic Process Research & Development*; Müllen, K.; Scherf, U., Eds.; Wiley, 2006, Vol. *45*(43), pp 7115−7116. DOI: 10.1002/anie.200685411.
(93) Zhang, P.; Li, B.; Niu, L.; Wang, L.; Zhang, G.; Jia, X.; Zhang, G.; Liu, S.; Ma, L.; Gao, W.; Qin, D.; Chen, J. Scalable Electrochemical Transition-Metal-Free Dehydrogenative Cross-Coupling Amination Enabled Alkaloid Clausines Synthesis. *Adv. Synth. Catal.* **2020**, *362* (12), 2342−2347.
(94) Kehl, A.; Schupp, N.; Breising, V. M.; Schollmeyer, D.; Waldvogel, S. R. Electrochemical Synthesis of Carbazoles by Dehydrogenative Coupling Reaction. *Chem.—A Eur. J.* **2020**, *26* (68), 15847−15851.
(95) Kehl, A.; Gieshoff, T.; Schollmeyer, D.; Waldvogel, S. R. Electrochemical Conversion of Phthaldianilides to Phthalazin-1,4-

Diones by Dehydrogenative N−N Bond Formation. *Chem.—A Eur. J.* **2018**, *24* (3), 590−593.
(96) Gieshoff, T.; Kehl, A.; Schollmeyer, D.; Moeller, K. D.; Waldvogel, S. R. Insights into the Mechanism of Anodic N−N Bond Formation by Dehydrogenative Coupling. *J. Am. Chem. Soc.* **2017**, *139* (35), 12317−12324.
(97) Kehl, A.; Breising, V. M.; Schollmeyer, D.; Waldvogel, S. R. Electrochemical Synthesis of 5-Aryl-Phenanthridin-6-One by Dehydrogenative N,C Bond Formation. *Chem. − A Eur. J.* **2018**, *24* (65), 17230−17233.
(98) Wang, Q.; Zhang, X.; Wang, P.; Gao, X.; Zhang, H.; Lei, A. Electrochemical Palladium-Catalyzed Intramolecular C—H Amination of 2-Amidobiaryls for Synthesis of Carbazoles. *Chin. J. Chem.* **2021**, *39* (1), 143−148.
(99) Puthanveedu, M.; Khamraev, V.; Brieger, L.; Strohmann, C.; Antonchick, A. P. Electrochemical Dehydrogenative C(Sp2)−H Amination. *Chem.—A Eur. J.* **2021**, *27* (30), 8008−8012.
(100) Bao, H.; Hu, X.; Zhang, J.; Liu, Y. Cu(0)/Selectfluor System-Catalyzed Intramolecular Csp2-H/Csp2-H Cross-Dehydrogenative Coupling (CDC). *Tetrahedron* **2019**, *75* (42), 130533.
(101) Chrysant, S. G. The Impact of Coffee Consumption on Blood Pressure, Cardiovascular Disease and Diabetes Mellitus. *Expert Rev. Cardiovasc. Ther.* **2017**, *15* (3), 151−156.
(102) Monteiro, J. P.; Alves, M. G.; Oliveira, P. F.; Silva, B. M. Structure-Bioactivity Relationships of Methylxanthines: Trying to Make Sense of All the Promises and the Drawbacks. *Molecules* **2016**, *21*, 974.
(103) Cushnie, T. P. T.; Cushnie, B.; Lamb, A. J. Alkaloids: An Overview of Their Antibacterial, Antibiotic-Enhancing and Antivirulence Activities. *Int. J. Antimicrob. Agents* **2014**, *44* (5), 377−386.
(104) Lu, Y.-P.; Lou, Y.-R.; Xie, J.-G.; Peng, Q.-Y.; Zhou, S.; Lin, Y.; Shih, W. J.; Conney, A. H. Caffeine and Caffeine Sodium Benzoate Have a Sunscreen Effect, Enhance UVB-Induced Apoptosis, and Inhibit UVB-Induced Skin Carcinogenesis in SKH-1 Mice. *Carcinogenesis* **2007**, *28* (1), 199−206.
(105) Drabczyńska, A.; Müller, C. E.; Schiedel, A.; Schumacher, B.; Karolak-Wojciechowska, J.; Fruziński, A.; Zobnina, W.; Yuzlenko, O.; Kieć-Kononowicz, K. Phenylethyl-Substituted Pyrimido[2,1-f]-Purinediones and Related Compounds: Structure−Activity Relationships as Adenosine A1 and A2A Receptor Ligands. *Bioorg. Med. Chem.* **2007**, *15* (22), 6956−6974.
(106) Prasanthi, J. R. P.; Dasari, B.; Marwarha, G.; Larson, T.; Chen, X.; Geiger, J. D.; Ghribi, O. Caffeine Protects against Oxidative Stress and Alzheimer's Disease-like Pathology in Rabbit Hippocampus Induced by Cholesterol-Enriched Diet. *Free Radic. Biol. Med.* **2010**, *49* (7), 1212−1220.
(107) Hasegawa, T.; Nadai, M.; Apichartpichean, R.; Muraoka, I.; Nabeshima, T.; Takagi, K. Pharmacokinetic Characteristics of N7-Substituted Theophylline Derivatives and Their Interaction with Quinolone in Rats. *J. Pharm. Sci.* **1991**, *80* (10), 962−965.
(108) Yang, Q.-L.; Li, Y.-Y.; Liu, Y.; Ren, T.-X.; Guo, L.-C.; Wang, D.-C.; Xie, M.-S.; Qu, G.-R.; Guo, H.-M. Electrochemically Facilitated Oxidative C−H Amination Enables Access to Fluorescent N9-Fused Tricyclic Xanthines. *Org. Chem. Front.* **2021**, *8* (19), 5410−5417.
(109) Maes, J.; Rauws, T. R. M.; Maes, B. U. W. Synthesis of C8. N9 Annulated Purines by Iron-Catalyzed C. H Amination. *Chem. − A Eur. J.* **2013**, *19* (28), 9137−9141.
(110) Kusmierek, J. T.; Jensen, D. E.; Spengler, S. J.; Stolarski, R.; Singer, B. Synthesis and Properties of N2,3-Ethenoguanosine and N2,3-Ethenoguanosine 5'-Diphosphate. *J. Org. Chem.* **1987**, *52* (12), 2374−2378.
(111) Secrist, J. A.; Barrio, J. R.; Leonard, N. J.; Villar-Palasi, C.; Gilman, A. G. Fluorescent Modification of Adenosine 3′,5′-Monophosphate: Spectroscopic Properties and Activity in Enzyme Systems. *Science (80-)* **1972**, *177* (4045), 279−280.
(112) Bagdi, A. K.; Santra, S.; Monir, K.; Hajra, A. Synthesis of Imidazo[1{,}2-a]Pyridines: A Decade Update. *Chem. Commun.* **2015**, *51* (9), 1555−1575.
(113) Hou, Z.-W.; Mao, Z.-Y.; Melcamu, Y. Y.; Lu, X.; Xu, H.-C. Electrochemical Synthesis of Imidazo-Fused N-Heteroaromatic Compounds through a C−N Bond-Forming Radical Cascade. *Angew. Chem., Int. Ed.* **2018**, *57* (6), 1636−1639.
(114) Hou, Z.-W.; Mao, Z.-Y.; Zhao, H.-B.; Melcamu, Y. Y.; Lu, X.; Song, J.; Xu, H.-C. Electrochemical C−H/N−H Functionalization for the Synthesis of Highly Functionalized (Aza)Indoles. *Angew. Chem., Int. Ed.* **2016**, *55* (32), 9168−9172.
(115) Tang, S.; Gao, X.; Lei, A. Electrocatalytic Intramolecular Oxidative Annulation of N-Aryl Enamines into Substituted Indoles Mediated by Iodides. *Chem. Commun.* **2017**, *53* (23), 3354−3356.
(116) Singh, K.; Okombo, J.; Brunschwig, C.; Ndubi, F.; Barnard, L.; Wilkinson, C.; Njogu, P. M.; Njoroge, M.; Laing, L.; Machado, M.; Prudêncio, M.; Reader, J.; Botha, M.; Nondaba, S.; Birkholtz, L.-M.; Lauterbach, S.; Churchyard, A.; Coetzer, T. L.; Burrows, J. N.; Yeates, C.; Denti, P.; Wiesner, L.; Egan, T. J.; Wittlin, S.; Chibale, K. Antimalarial Pyrido[1,2-a]Benzimidazoles: Lead Optimization, Parasite Life Cycle Stage Profile, Mechanistic Evaluation, Killing Kinetics, and in Vivo Oral Efficacy in a Mouse Model. *J. Med. Chem.* **2017**, *60* (4), 1432−1448.
(117) Perin, N.; Nhili, R.; Ester, K.; Laine, W.; Karminski-Zamola, G.; Kralj, M.; David-Cordonnier, M.-H.; Hranjec, M. Synthesis, Antiproliferative Activity and DNA Binding Properties of Novel 5-Aminobenzimidazo[1,2-a]Quinoline-6-Carbonitriles. *Eur. J. Med. Chem.* **2014**, *80*, 218−227.
(118) Kotovskaya, S. K.; Baskakova, Z. M.; Charushin, V. N.; Chupakhin, O. N.; Belanov, E. F.; Bormotov, N. I.; Balakhnin, S. M.; Serova, O. A. Synthesis and Antiviral Activity of Fluorinated Pyrido[1,2-a]Benzimidazoles. *Pharm. Chem. J.* **2005**, *39* (11), 574−578.
(119) Duan, Z.; Zhang, L.; Zhang, W.; Lu, L.; Zeng, L.; Shi, R.; Lei, A. Palladium-Catalyzed Electro-Oxidative C−H Amination toward the Synthesis of Pyrido[1,2-a]Benzimidazoles with Hydrogen Evolution. *ACS Catal.* **2020**, *10* (6), 3828−3831.
(120) Lv, S.; Han, X.; Wang, J.-Y.; Zhou, M.; Wu, Y.; Ma, L.; Niu, L.; Gao, W.; Zhou, J.; Hu, W.; Cui, Y.; Chen, J. Tunable Electrochemical C−N versus N−N Bond Formation of Nitrogen-Centered Radicals Enabled by Dehydrogenative Dearomatization: Biological Applications. *Angew. Chem., Int. Ed.* **2020**, *59* (28), 11583−11590.
(121) Al-Soud, Y. A.; Al-Masoudi, N. A.; Ferwanah, A. E.-R. S. Synthesis and Properties of New Substituted 1,2,4-Triazoles: Potential Antitumor Agents. *Bioorg. Med. Chem.* **2003**, *11* (8), 1701−1708.
(122) Novak, I.; Abu-Izneid, T.; Kovač, B.; Klasinc, L. Electronic Structure and Stability of Benzotriazoles. *J. Phys. Chem. A* **2009**, *113* (35), 9751−9756.
(123) Katritzky, A. R.; Rachwal, S. Synthesis of Heterocycles Mediated by Benzotriazole. 1. Monocyclic Systems. *Chem. Rev.* **2010**, *110* (3), 1564−1610.
(124) Booker-Milburn, K. I.; Wood, P. M.; Dainty, R. F.; Urquhart, M. W.; White, A. J.; Lyon, H. J.; Charmant, J. P. H. Photochemistry of Benzotriazole: An Unprecedented Tautomer-Selective Intermolecular [2+2] Photocycloaddition. *Org. Lett.* **2002**, *4* (9), 1487−1489.
(125) Li, H.-C.; Gao, W.-X.; Huang, X.-B.; Zhou, Y.-B.; Liu, M.-C.; Wu, H.-Y. Cu(I)/KOH-Promoted Condensation between o-Arylenediamines and Nitroarenes to Access 2-Aryl-2H-Benzotriazoles. *Adv. Synth. Catal.* **2020**, *362* (14), 2847−2851.
(126) De Moor, O.; Dorgan, C. R.; Johnson, P. D.; Lambert, A. G.; Lecci, C.; Maillol, C.; Nugent, G.; Poignant, S. D.; Price, P. D.; Pye, R. J.; Storer, R.; Tinsley, J. M.; Vickers, R.; Wilkes, F. J.; Wilson, F. X.; Wren, S. P.; Wynne, G. M. Discovery and SAR of 2-Arylbenzotriazoles and 2-Arylindazoles as Potential Treatments for Duchenne Muscular Dystrophy. *Bioorg. Med. Chem. Lett.* **2011**, *21* (16), 4828−4831.
(127) Briguglio, I.; Piras, S.; Corona, P.; Gavini, E.; Nieddu, M.; Boatto, G.; Carta, A. Benzotriazole: An Overview on Its Versatile Biological Behavior. *Eur. J. Med. Chem.* **2015**, *97*, 612−648.
(128) Klein, M. F. G.; Pasker, F. M.; Kowarik, S.; Landerer, D.; Pfaff, M.; Isen, M.; Gerthsen, D.; Lemmer, U.; Höger, S.; Colsmann, A.

https://doi.org/10.1021/acselectrochem.5c00523
ACS Electrochem. 2026, 2, 845−873

Carbazole−Phenylbenzotriazole Copolymers as Absorber Material in Organic Solar Cells. *Macromolecules* **2013**, *46* (10), 3870−3878.
(129) Catalán, J.; de Paz, J.; Torres, M. R.; Tornero, J. D. Molecular Structure of a Unique UV Stabilizer: Tinuvin P. *J. Chem. Soc., Faraday Trans.* **1997**, *93* (9), 1691−1696.
(130) Gao, A.; Chen, K.; Ma, F.; Li, A.; Li, H. Electrochemical N-Centered Radical-Triggered Intramolecular N−N Coupling for the Cyclization of o-Aminyl Azobenzenes. *Eur. J. Org. Chem.* **2024**, *27* (46), No. e202400854.
(131) Wirtanen, T.; Rodrigo, E.; Waldvogel, S. R. Selective and Scalable Electrosynthesis of 2H-2-(Aryl)-Benzo[d]-1,2,3-Triazoles and Their N-Oxides by Using Leaded Bronze Cathodes. *Chem. − A Eur. J.* **2020**, *26* (25), 5552.
(132) Balaban, A. T.; Oniciu, D. C.; Katritzky, A. R. Aromaticity as a Cornerstone of Heterocyclic Chemistry. *Chem. Rev.* **2004**, *104* (5), 2777−2812.
(133) Cid, J. M.; Tresadern, G.; Vega, J. A.; de Lucas, A. I.; Matesanz, E.; Iturrino, L.; Linares, M. L.; Garcia, A.; Andrés, J. I.; Macdonald, G. J.; Oehlrich, D.; Lavreysen, H.; Megens, A.; Ahnaou, A.; Drinkenburg, W.; Mackie, C.; Pype, S.; Gallacher, D.; Trabanco, A. A. Discovery of 3-Cyclopropylmethyl-7-(4-Phenylpiperidin-1-Yl)-8-Trifluoromethyl[1,2,4]Triazolo[4,3-a]Pyridine (JNJ-42153605): A Positive Allosteric Modulator of the Metabotropic Glutamate 2 Receptor. *J. Med. Chem.* **2012**, *55* (20), 8770−8789.
(134) Sadana, A. K.; Mirza, Y.; Aneja, K. R.; Prakash, O. Hypervalent Iodine Mediated Synthesis of 1-Aryl/Hetryl-1,2,4-Triazolo[4,3-a] Pyridines and 1-Aryl/Hetryl 5-Methyl-1,2,4-Triazolo[4,3-a]-Quinolines as Antibacterial Agents. *Eur. J. Med. Chem.* **2003**, *38* (5), 533−536.
(135) Zheng, H.; Wang, K.; Zhang, W.; Liu, R. Selenium Dioxide−Mediated Synthesis of Fused 1,2,4-Triazoles as Cytotoxic Agents. *Synth. Commun.* **2015**, *45* (24), 2849−2856.
(136) Ye, Z.; Ding, M.; Wu, Y.; Li, Y.; Hua, W.; Zhang, F. Electrochemical Synthesis of 1,2,4-Triazole-Fused Heterocycles. *Green Chem.* **2018**, *20* (8), 1732−1737.
(137) Wu, J.; You, Q.; Lan, J.; Guo, Q.; Li, X.; Xue, Y.; You, J. Cu-Catalysed Direct C−H (Hetero)Arylation of [1,2,4]Triazolo[4,3-a]Pyridine to Construct Deep-Blue-Emitting Luminophores. *Org. Biomol. Chem.* **2015**, *13* (19), 5372−5375.
(138) Ye, Z.; Wu, Y.; Chen, N.; Zhang, H.; Zhu, K.; Ding, M.; Liu, M.; Li, Y.; Zhang, F. Enantiospecific Electrochemical Rearrangement for the Synthesis of Hindered Triazolopyridinone Derivatives. *Nat. Commun.* **2020**, *11* (1), 3628.
(139) Andreani, A.; Rambaldi, M. Indole Derivatives as Agrochemicals. *J. Heterocycl. Chem.* **1988**, *25* (5), 1519−1523.
(140) Kochanowska-Karamyan, A. J.; Hamann, M. T. Marine Indole Alkaloids: Potential New Drug Leads for the Control of Depression and Anxiety. *Chem. Rev.* **2010**, *110* (8), 4489−4497.
(141) Mujumdar, S. R.; Mujumdar, R. B.; Grant, C. M.; Waggoner, A. S. Cyanine-Labeling Reagents: Sulfobenzindocyanine Succinimidyl Esters. *Bioconjugate Chem.* **1996**, *7* (3), 356−362.
(142) Chen, P.; Hu, G.; Nakashima, Y.; Xu, Z.; Watanabe, T.; Kondo, S.; Kovács, E.; Cabral, H. Optoregulated MRNA Delivery Controls Pleiotropic Immune Signaling for Tumor-Targeted Therapy. *Angew. Chem., Int. Ed.* **2025**, *64* (43), No. e202513610.
(143) Arcadi, A.; Bianchi, G.; Inesi, A.; Marinelli, F.; Rossi, L. Electrochemical-Mediated Cyclization of 2-Alkynylanilines: A Clean and Safe Synthesis of Indole Derivatives. *Eur. J. Org. Chem.* **2008**, *2008* (5), 783−787.
(144) Whittell, L. R.; Batty, K. T.; Wong, R. P. M.; Bolitho, E. M.; Fox, S. A.; Davis, T. M. E.; Murray, P. E. Synthesis and Antimalarial Evaluation of Novel Isocryptolepine Derivatives. *Bioorg. Med. Chem.* **2011**, *19* (24), 7519−7525.
(145) Zheng, Y.-T.; Song, J.; Xu, H.-C. Electrocatalytic Dehydrogenative Cyclization of 2-Vinylanilides for the Synthesis of Indoles. *J. Org. Chem.* **2021**, *86* (22), 16001−16007.
(146) Lewgowd, W.; Stanczak, A. Cinnoline Derivatives with Biological Activity. *Arch. Pharm. (Weinheim)* **2007**, *340* (2), 65−80.
(147) Tan, Q.; Xu, B. C-H Bond Activation as a Powerful Tool in the Construction of Biologically Active Nitrogen-Containing Heterocycles. In *Studies in Natural Products Chemistry*; Elsevier, 2016; Vol. *50*; pp 299−340. DOI: 10.1016/B978-0-444-63749-9.00009-8.
(148) Cai, C.; Lu, Y.; Yuan, C.; Fang, Z.; Yang, X.; Liu, C.; Guo, K. Organocatalytic Electrosynthesis of Cinnolines through Cascade Radical Cyclization and Migration. *ACS Sustain. Chem. Eng.* **2021**, *9* (50), 16989−16996.
(149) Wan, J.-L.; Cui, J.-F.; Zhong, W.-Q.; Huang, J.-M. Iminyl-Radicals by Electrochemical Decarboxylation of α-Imino-Oxy Acids: Construction of Indole-Fused Polycyclics. *Chem. Commun.* **2021**, *57* (79), 10242−10245.
(150) Prunkl, C.; Pichlmaier, M.; Winter, R.; Kharlanov, V.; Rettig, W.; Wagenknecht, H.-A. Optical, Redox, and DNA-Binding Properties of Phenanthridinium Chromophores: Elucidating the Role of the Phenyl Substituent for Fluorescence Enhancement of Ethidium in the Presence of DNA. *Chem.—A Eur. J.* **2010**, *16* (11), 3392−3402.
(151) Zhang, J.; Lakowicz, J. R. Enhanced Luminescence of Phenyl-Phenanthridine Dye on Aggregated Small Silver Nanoparticles. *J. Phys. Chem. B* **2005**, *109* (18), 8701−8706.
(152) Seyler, H.; Purushothaman, B.; Jones, D. J.; Holmes, A. B.; Wong, W. W. H. Hexa-Peri-Hexabenzocoronene in Organic Electronics. *Pure Appl. Chem.* **2012**, *84* (4), 1047−1067.
(153) Wagner, J.; Kumar, D.; Kochman, M. A.; Gryber, T.; Grzelak, M.; Kubas, A.; Data, P.; Lindner, M. Facile Functionalization of Ambipolar, Nitrogen-Doped PAHs toward Highly Efficient TADF OLED Emitters. *ACS Appl. Mater. Interfaces* **2023**, *15* (31), 37728−37740.
(154) Nagy, M.; Rácz, D.; Nagy, Z. L.; Fehér, P. P.; Kovács, S. L.; Bankó, C.; Bacsó, Z.; Kiss, A.; Zsuga, M.; Kéki, S. Amino-Isocyanoacridines: Novel, Tunable Solvatochromic Fluorophores as Physiological PH Probes. *Sci. Rep.* **2019**, *9* (1), 8250.
(155) Bankó, C.; Nagy, Z. L.; Nagy, M.; Szemán-Nagy, G. G.; Rebenku, I.; Imre, L.; Tiba, A.; Hajdu, A.; Szöllősi, J.; Kéki, S.; Bacso, Z. Isocyanide Substitution in Acridine Orange Shifts DNA Damage-Mediated Phototoxicity to Permeabilization of the Lysosomal Membrane in Cancer Cells. *Cancers (Basel)* **2021**, *13* (22), 5652.
(156) Hou, Z.-W.; Mao, Z.-Y.; Song, J.; Xu, H.-C. Electrochemical Synthesis of Polycyclic N-Heteroaromatics through Cascade Radical Cyclization of Diynes. *ACS Catal.* **2017**, *7* (9), 5810−5813.
(157) Cai, C.; Lu, Y.; Yuan, C.; Fang, Z.; Yang, X.; Liu, C.; Guo, K. Metal-Free C−C Cross Coupling: Electrosynthesis of Azaheterocycles through Anodic Oxidation Cyclization of 1,6-Enynes. *ACS Sustain. Chem. Eng.* **2022**, *10* (10), 3288−3294.
(158) Chen, J.; Qiao, Y.; Guan, W.; Yuan, C.; Yao, Y.; Fang, Z.; Zhao, Y.; Liu, C.; Guo, K. Electrosynthesis of Highly Functionalized Polycyclic N-Heteroaromatics through Cascade Radical Cyclization and Alkoxylation in Batch and Continuous-Flow. *ACS Sustain. Chem. Eng.* **2023**, *11* (50), 17728−17738.