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Recent advances in electrocatalytic generation of indole-derived radical cations and their applications in organic synthesis

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ABSTRACT

Indole-derived radical cations, open-shell reactive species, display distinctive dual reactivity due to the carbon-centered radical and more electrophilic carbocation, which frequently appear in a variety of single electron oxidation reactions for synthesizing structurally diverse functionalized indoles and indolines. Electrocatalysis is considered as a synthetically attractive and environmentally friendly alternative for driving the single electron oxidation of indoles. Remarkable achievements in electrocatalytic indole-derived radical cation-mediated indole functionalization have been realized so far. This review comprehensively summarizes the recent progresses in the applications of electrocatalytic indole radical cations, including C(sp²)-H functionalization, dearomative 2,3-difunctionalization, and ring-opening reaction, emphasizing the vital single electron oxidation steps of indoles, the substrates scope and limitations, and the reaction mechanisms.

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1. Introduction

Indole scaffolds are prevailing and important structural motifs that frequently appear in a wide range of natural products and biologically active molecules, as well as agricultural chemicals [1–4]. Particularly, indole skeleton may be one of the most important components of heterocyclic compounds in the drug discovery [5,6]. Consequently, the development of efficient and straightforward strategies for the diverse transformation of indoles is desirable and urgent in modern synthetic chemistry [7–10]. Early works related to the functionalization of indoles mainly focused on the classics Friedel–Crafts alkylation [11,12].

Indole-derived radical cation, a synthetically useful and appealing open-shell reactive species, displays distinctive dual reactivity due to the carbon-centered radical and more electrophilic carbocation. Generally, the C3 site of the indole-derived radical cation is more nucleophilic and the C2 site is more electrophilic, which is mainly caused by the resonance structure of indole [13,14]. In addition, the radical character difference at C2 and C3 sites is also influenced by the steric effects. The low oxidation potential of indole derivatives makes them easy to be oxidized into corresponding radical cations *via* single electron oxidation process, which

provides a technically attractive platform for achieving the divergent transformation of indoles [15,16]. In the last two decades, the generation and conversion mode of indole-derived radical cations have attracted considerable interest and discussion. Numerous efficient and practical synthetic strategies for the production of indole radical cations have been reported [17–21]. Among them, the growing electrochemical technique [22–30], using traceless electron as clean and inexpensive redox reagent, provides a synthetically attractive and environmentally friendly alternative for the single electron oxidation of indoles.

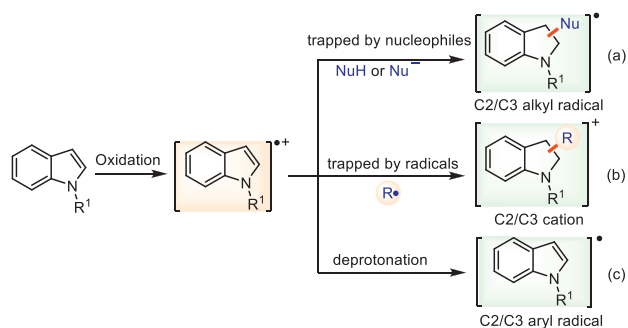
Generally, the electrochemically driven indole-derived radical cations-mediated organic transformations could undergo three different reaction modes by making the use of radical and cation centers, in which: (i) The indole radical cations are captured by various nucleophiles to deliver alkyl radical species (Scheme 1a), (ii) the indole radical cations react with external radical to form electrophilic carbocation species *via* radical-radical coupling process (Scheme 1b), and (iii) indole radical cation loses one proton to generate aryl radical species (Scheme 1c).

Recently, remarkable achievements have been made in the field of electrochemically enabled indole radical cation-initiated functionalization of indoles. Among the established chemical transformations, they can be roughly divided into two different reaction types (Scheme 2): (i) The C2–H/C3–H functionalization of indoles, and (ii) the dearomative 2,3-difunctionalization of indoles. Apart from, a small part of ring-opening reaction is also involved.

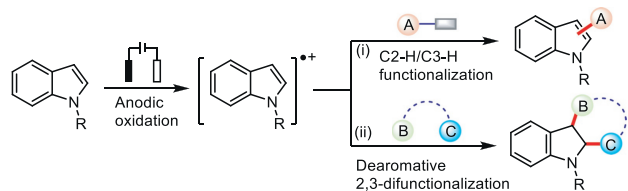
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Scheme 1. Three transformation modes of indole radical cations.



Scheme 2. Overview of electrochemical indole-derived radical cation-mediated organic transformations.

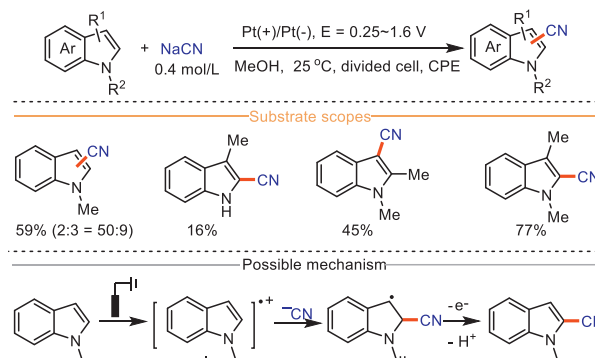
Considering the quick development of electrocatalytic indole radical cation-initiated organic transformations, and in order to stimulate the innovative synthetic modes in this growing research area, we offer herein a comprehensive survey and discussion of recent fruitful achievements in the synthetic applications of electrocatalytic indole radical cations, including the C2–H/C3–H functionalization, dearomative 2,3-difunctionalization, and ring-opening reactions. Special emphasis is placed on the formation process of indole-derived radical cations at anode, which is conducive to stimulating the interest of synthetic chemists in the development of novel transformation modes and catalytic systems. Furthermore, substrate scopes and limitations of these organic transformations are highlighted.

2. C(sp²)–H functionalization of indoles

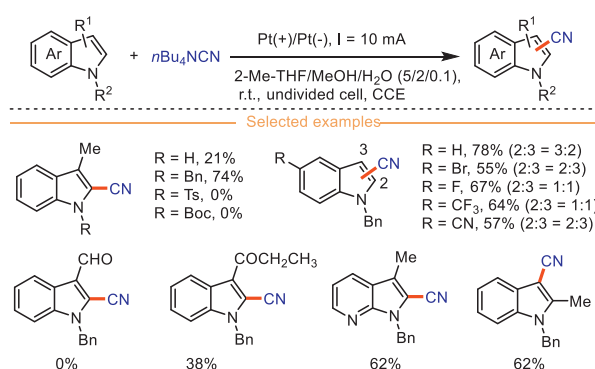
The field of catalytic C(sp²)–H functionalization of indoles, which obviates the prefunctionalization of the substrates, has garnered enormous interest and made impressive progress in the past several decades [31–42]. Catalytic strategies involving transition metals [31–33], photochemical [34], and electrochemical [35–42] catalysis systems have all been employed for the selective C–H functionalization of indoles. Considerable efforts have devoted to developing the various C2–H/C3–H functionalization of indoles based on the inherent reactivity of indoles. Among the synthetic methods developed, the direct oxidative C(sp²)–H functionalization of indoles by the generation of unique and highly reactive indole-derived radical cation intermediates with environmentally friendly electrocatalysis strategy has recently re-merged as a powerful and straightforward tool for the synthesis of diverse biologically and synthetically important functionalized indoles.

2.1. C(sp²)–H cyanation of indoles

Cyano group, a synthetically versatile and appreciated synthon in synthetic chemistry and drug discovery, can easily participate in numerous chemical transformations to build a series of structurally diverse nitrogen-containing compounds [43–45]. The electrochemical C(sp²)–H cyanation of indoles is shown to constitute a convenient and efficient synthetic alternative to traditional cyanation methods.



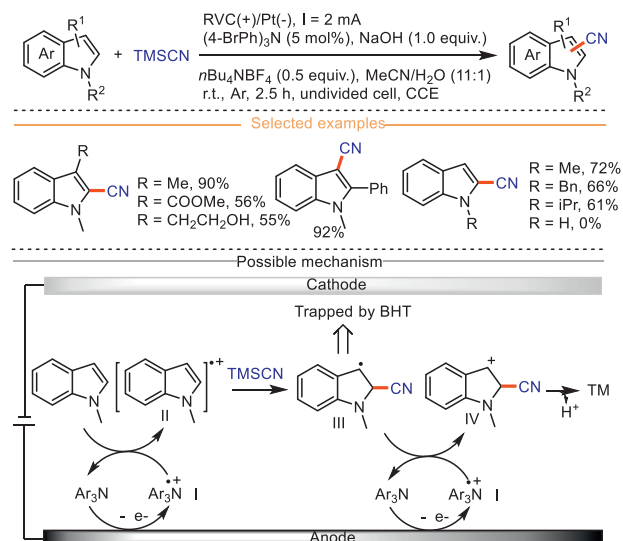
Scheme 3. Electrochemical C–H cyanation of indoles using NaCN as cyanolation reagent.



Scheme 4. Electrochemical C–H cyanation of indoles using *n*Bu₄NCN as cyanolation reagent.

As early as 1977, Yoshida *et al.* cleverly achieved the first regioselective electrochemical C(sp²)–H cyanation of indoles, in which sodium cyanide (NaCN) served as cyanide source and electrolyte for the synthesis of C2/C3-cyanated indoles in good yields (Scheme 3) [46]. Moderate regioselectivity was exhibited when 1-methylindole was used as reaction substrate in this electrochemical process, and the C-2 and C-3 cyanated indoles were obtained in 50% and 9% yields, respectively. Regrettably, only four indoles were discussed in this C–H cyanation protocol. Mechanistically, indole is preferentially oxidized at anode surface to afford radical cation intermediate **I**, which then reacts with cyanide anion to produce carbon-centered radical **II**. Finally, further anodic oxidation and the following deprotonation result in the formation of desired product cyanated indole.

Although efficient and straightforward electrochemical C–H cyanation of indoles has been established, it is hard to elude the use of large excess of highly toxic sodium cyanide, limiting its potential further implementation in synthetic chemistry. In 2022, Lecomte *et al.* illustrated a sustainable and scalable electrochemical strategy for the direct C–H cyanation of indoles using non-volatile and stable tetrabutylammonium cyanide (*n*Bu₄NCN) as cyanide source in less excess as compared to above-described method (Scheme 4) [47]. Remarkably, this reaction proceeded also smoothly for unprotected *N*-H free indole, thus broadening the scope for late-stage functionalization. Not only that, the indoles without substituents at C2- and C3-position could react with *n*Bu₄NCN with moderate regioselectivity as well. Furthermore, the practicality of this method was illustrated in a continuous-flow electrochemical reactor, thereby facilitating the potential for further synthetic applications. Unfortunately, the C(sp²)–H cyanation of *N*-Ts indole, *N*-



Scheme 5. Electrochemical C–H cyanation of indoles using TMSCN as cyanation reagent.

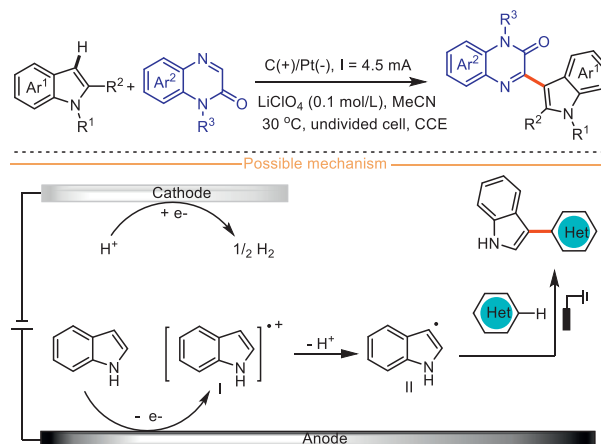
Boc indole, and indole-3-carbaldehyde remain challenging. Cyclic voltammetry analysis showed that *N*-benzyl indole had a lower oxidation potential than *n*Bu₄N⁺Cl[−], indicating that this C–H cyanation reaction began with the anodic oxidation of indole.

Efforts in developing readily accessible, controllable, and safe cyanation reagent are still highly appreciated in synthetic chemistry. Wang *et al.* employed simple and readily available trimethylsilyl cyanide (TMSCN) as cyanide source to realize the electrochemically promoted radical cation-mediated C–H cyanation of indoles, in which triarylamine served as redox medium to facilitate this reaction (Scheme 5) [48]. In this protocol, a variety of C2-cyanated indoles without substituents at 3-position were obtained with satisfactory regioselectivity. Cyclic voltammetry studies revealed that 1-phenylindole had a higher oxidation potential ($E_{p/2} = 1.27$ V vs. Ag/AgCl) compared with triarylamine ((4-BrPh)₃N) ($E_{p/2} = 1.10$ V vs. Ag/AgCl), supporting that the anodic single-electron oxidation of tris(4-bromophenyl)amine was the initial step. Additionally, the regioselectivity and yield decreased obviously in the absence of triarylamine. These observations clearly showed that tris(4-bromophenyl)amine served as redox medium to promote the formation of indole-derived radical cation and decrease reaction potential, circumventing the overoxidation of raw materials and products. Mechanistically, the redox medium triarylamine is initially oxidized into radical cation **I**, which in turn oxidizes indole into radical cation **II**. Subsequently, intermediate **II** is captured by nucleophilic TMSCN to give carbon-centered radical **III** captured by radical scavenger 2,6-di-*tert*-butyl-4-methylphenol (BHT) in control experiment. Finally, the consecutive oxidation and deprotonation affords the final C2/C3 cyanated indoles.

2.2. C(sp²)-H arylation of indoles

C(sp²)-C(sp²) bond is an ubiquitous chemical bond that frequently exists in both natural and synthetic molecules [49–52]. Recently, the electrochemically driven C(sp²)-H/C(sp²)-H cross-dehydrogenative coupling (CDC) reactions have been recognized as a most important and economy synthetic tool for building C(sp²)-C(sp²) bonds, which avoids the pre-functionalization of C(sp²) partners [53].

In 2022, Lou *et al.* employed the electrocatalytic indole-derived radical cation strategy to realize the C(sp²)-H arylation of indoles with quinoxalin-2(1*H*)-ones to synthesize a series of 3-(indol-2-



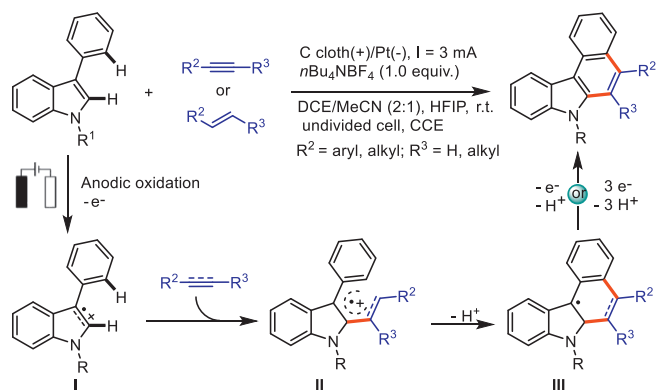
Scheme 6. Electrocatalytic indole-derived radical cation-mediated C–H arylation of indoles with quinoxalin-2(1*H*)-ones.

yl)quinoxalin-2(1*H*)-ones in a undivided cell (Scheme 6) [54]. Generally speaking, solvents have tremendous impact on the reaction outcomes. Using other solvents, such as MeOH, DMSO, DMF, H₂O or acetone instead of acetonitrile as the reaction solvent, only trace or no target product was detected. Besides, the choice of electrode material had a great influence on the reaction as well, for examples, almost no product was detected when using a graphite rod instead of platinum plate as cathode. Cyclic voltammetry results showed that indole ($E_{ox} = 1.18$ V vs. Ag/AgCl) had a lower oxidation potential than quinoxalin-2(1*H*)-one ($E_{ox} = 1.77$ V vs. Ag/AgCl), which suggested that C(sp²)-H arylation began with the oxidation of indole via a single electron transfer oxidation process on the anode surface. Differently, the anode generated indole-derived radical cation **I** loses one H⁺ preferentially to furnish indole radical intermediate **II** rather than directly reacts with quinoxalin-2(1*H*)-one. Finally, indole radical intermediate **II** attacks the quinoxalin-2(1*H*)-one, accompanied by anode oxidative deprotonation, to produce C3 arylated indoles.

2.3. C(sp²)-H alkenylation of indoles

Palladium-catalyzed alkenylation is a favored strategy for the construction of alkenylindoles [55–57]. Recently, tremendous efforts have been devoted to developing green, efficient, and metal-free synthetic methods for the alkenylation of indoles [58,59]. In 2020, Lei *et al.* reported an electrochemically driven radical cation-mediated oxidative [4 + 2] cyclization reaction of 3-arylindoles/3-arylbenzofurans with alkenes/alkynes involving a C(sp²)-H alkenylation process, allowing access to structurally valuable polycyclic heteroaromatic compounds under mild conditions (Scheme 7) [60]. This well-developed C(sp²)-H alkenylation strategy skillfully avoided the pre-functionalization of substrates, as well as the use of chemical oxidants and metal catalysts. Adding high dielectric constant fluorine-containing solvent hexafluoroisopropanol (HFIP) into this catalytic system was beneficial to stabilize the generated radical intermediates, thereby promoting the C(sp²)-H alkenylation.

Detailed cyclic voltammetry and control experimental results showed that 3-arylindole may first be oxidized into the radical cation **I** through single electron transfer (SET) at the anode surface, which then could be attacked by alkenes or alkynes to generate a new radical cation intermediate **II**. Subsequently, the consecutive deprotonation and intramolecular cyclization access to the carbon-centered radical intermediate **III**, which then undergoes further ox-



Scheme 7. Electrochemical oxidative [4+2] cyclization of 3-arylindoles/3-arylbenzofurans with alkenes/alkynes.

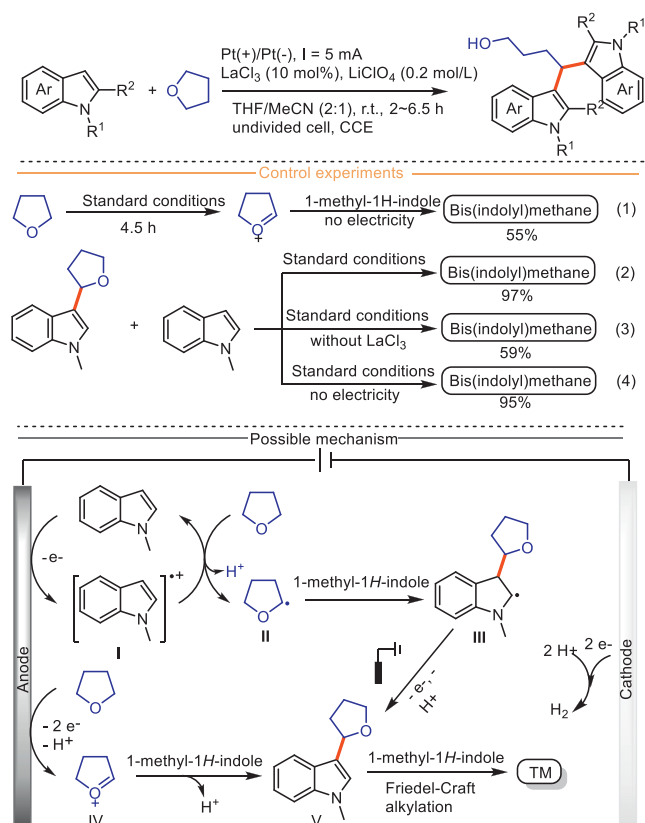
oxidative aromatization to deliver the desired polycyclic heteroaromatic compound.

2.4. C(sp²)-H alkylation of indoles

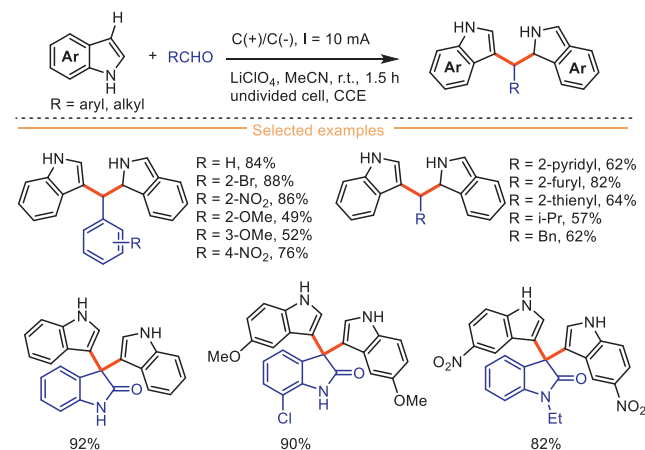
Bis(indolyl)methanes (BIMs) are privileged structural motif in many natural and synthetic molecules, and their derivatives generally display multiple biological activities, such as antibacterial, anticancer, and anti-inflammatory activities [61,62]. Although many powerful synthetic strategies for synthesizing BIMs have been developed, the challenge with these methods, however, is that they usually require external chemical oxidants, expensive catalysts, elevated temperature, and stoichiometric single-electron-transfer reagents [63–65]. Electrocatalytic strategy provides an attractive and sustainable tool for synthesizing BIMs involving dual C(sp²)-H functionalization process.

To address these limitations, in 2018, Huang *et al.* established an efficient LaCl₃-promoted electrochemical bisindolylolation of ethers for the preparation of a series of structurally diverse 3,3'-bis(indolyl)methanes *via* direct dual C(sp²)-H functionalization (Scheme 8) [66]. In this protocol, other tested electrolytes, such as NaClO₄, NH₄ClO₄, and NaBF₄, were shown to be inferior to LiClO₄ in terms of yields. To acquire insight mechanism, THF was individually electrolyzed for 4.5 h under standard conditions, followed by the addition of indole in the absence of electricity. After stirring for 1 h, bis(indolyl)methane was given in 55% yield, which supported the participation of alkoxy-carbenium ion intermediate in this project. Not only that, the effects of LaCl₃ and electricity on the reaction of C-2 indolylolation THF with indole were also studied, indicating that LaCl₃ as Lewis acid to promote the crucial Friedel–Craft alkylation process and the electricity was not necessary for this step.

The aforementioned experimental results and detailed cyclic voltammetry studies provide strong evidence for indole-derived radical cation-mediated mechanism, as shown in Scheme 8. 1-Methyl indole (*E*_{OX} = 1.46 V vs. SCE) is initially oxidized at anode into indole-derived radical cation **I**, which then in turn oxidizes tetrahydrofuran (*E*_{OX} = 1.78 V vs. SCE) into alkyl radical **II**. Subsequently, alkyl radical **II** attacks the 3-position of indole to deliver the carbon-centered radical intermediate **III**, which sequentially undergoes anodic oxidation to produce C3 alkylated intermediate **V**. It is worth mentioning that another possibility, in which alkoxy-carbenium ion **IV**, generated from the anodic oxidation of tetrahydrofuran, reacts with indole to give C-3 alkylated intermediate **V**, cannot be ruled out. Finally, classic Friedel–Craft alkylation of intermediate **V** with one molecular indole affords the desired bis(indolyl)methane.

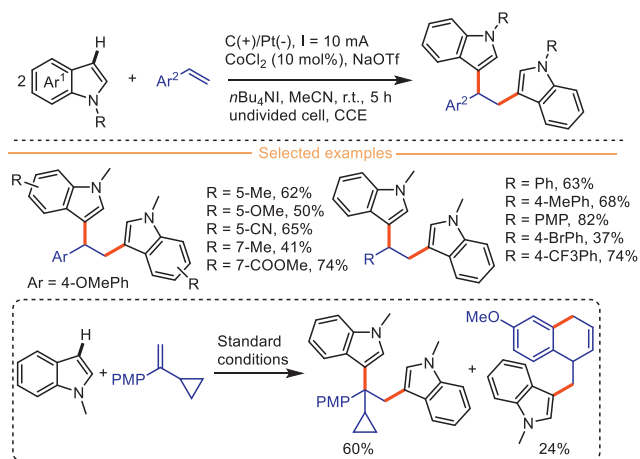


Scheme 8. LaCl₃-promoted electrochemical bisindolylolation of ethers.

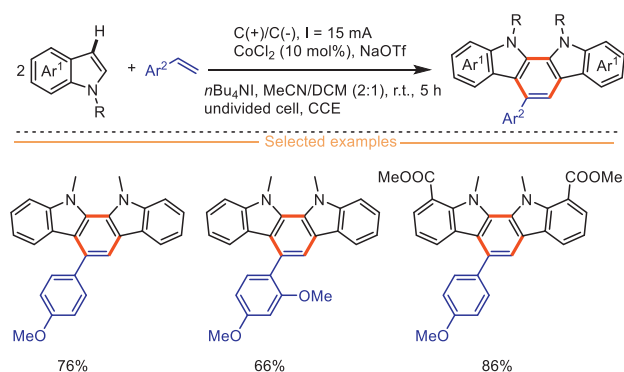


Scheme 9. Electrochemical indole-derived radical cation-mediated bisindolylolation of carbonyl compounds with indoles.

Encouraged by the success of the electrochemical preparation of bis(indolyl)methanes, Badsara *et al.* disclosed a meaningful electrochemical indole radical cation-initiated bisindolylolation of carbonyls with indoles without any metal catalysts and chemical oxidants in 2022 (Scheme 9) [67]. This strategy offers an elegant tool to synthesize structurally various bis(indolyl)methanes (BIMs) with wide substrate scope and good functional group tolerance. Pleasingly, a variety of isatin derivatives were also suitable for this bisindolylolation reaction, thereby providing a convenient and powerful synthetic approach to produce potentially valuable 3,3-di(indolyl)oxindole. Notably, the reaction almost was aborted in the presence of 2.0 equiv. radical scavenger galvinoxyl, wherein a



Scheme 10. Electrochemical diarylation of alkenes with indoles.



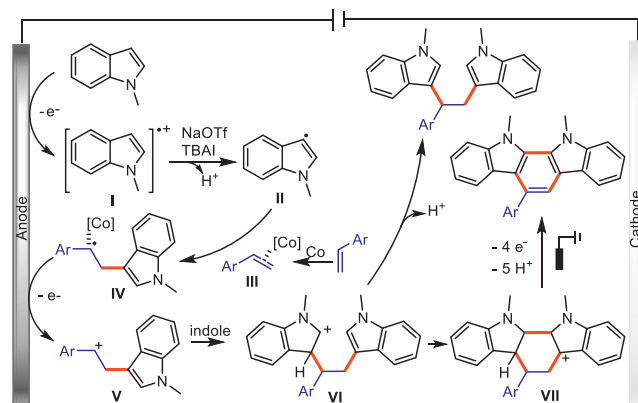
Scheme 11. Dehydrogenative [2 + 2 + 2] cyclization of alkenes with indoles.

cross-coupled product of galvinoxyl with indole was detected by HRMS, indicating the involvement of indolyl radical.

In 2021, Li *et al.* disclosed a cobalt-promoted electrocatalytic indole-derived radical cation-mediated 1,2-diarylation of olefins with indoles and other electron-rich aromatic hydrocarbons using graphite rod as anode and platinum plate as cathode in an undivided cell (Scheme 10) [68]. The key to success relied on the combination of NaOTf and *n*Bu₄NI as the electrolyte system to promote the formation of key indolyl carbon-centered radical, otherwise the reaction efficiency was extremely low or even the reaction did not proceed. This diarylation project featured broad substrate compatibility and excellent functional group tolerance under mild conditions. Specifically, the transformation of 1-methyl-1*H*-indole with 1-(1-cyclopropylvinyl)-4-methoxybenzene was performed under standard conditions, the diarylated product and ring-opening product were obtained in 60% and 24% yields, respectively, which suggested that a benzyl radical was involved in this protocol.

Generally, the electrode material has an important influence on the chemoselectivity [69]. In this project, replacing platinum plate cathode with graphite rod cathode, the chemoselectivity of this radical relay strategy shifted to the dehydrogenative [2 + 2 + 2] cyclization, albeit in low yields (Scheme 11). It was found that using the mixed solvent of MeCN and DCM can obviously improve the conversion efficiency, and various structurally complex 11,12-dihydroindolo[2,3-*a*]carbazoles were constructed in one step under mild conditions.

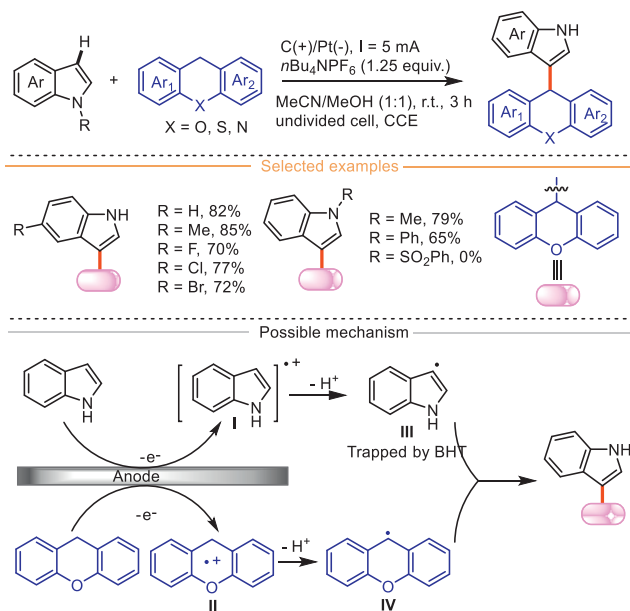
The cyclic voltammetry analysis indicated that 1-methyl indole ($E_{\text{OX}} = 0.86 \text{ V}$ vs. Ag/AgCl) had a lower oxidation potential than 4-methoxystyrene ($E_{\text{OX}} = 1.25 \text{ V}$ vs. Ag/AgCl) in the presence of



Scheme 12. Plausible mechanisms of alkene diarylation and [2 + 2 + 2] cyclization reactions.

NaOTf/*n*Bu₄NI. A persuasive catalytic mechanism of alkene diarylation and [2 + 2 + 2] cyclization reactions is outlined in Scheme 12. Anodic single electron oxidation of indole initially occurs to deliver the indole-derived radical cation intermediate **I**, which then would execute deprotonation in the presence of NaOTf/*n*Bu₄NI to generate indole carbon-centered radical **II**. Meanwhile, alkene co-ordination with the Co(II) catalyst could generate Co-alkene complex **III**. Subsequently, radical addition of the intermediate **II** across the Co-alkene complex **III** affords the benzyl radical **IV**, followed by anodic oxidation to produce the cation intermediate **V**. Finally, cation **V** reacts with one molecule of indole to offer the diarylation product through a deprotonation process using platinum plate as cathode. It is particularly noteworthy that the cation intermediate **VI** undergoes intramolecular Friedel-Crafts alkylation, followed by consecutive anodic single-electron oxidation and deprotonation to form the dehydrogenative [2 + 2 + 2] cyclization product when using graphite rod as the anode and cathode. This result is attributed to the lower redox potentials between two graphite rods, which leads to slow electron transfer and requires strong constant current.

The Minisci alkylation reaction, between electron-deficient heteroarenes with nucleophilic alkyl radical precursor, provides a straightforward and efficient tool for the quick construction of ubiquitous C(sp²)-C(sp³) bond, and is complementary to carbocation-mediated Friedel-Crafts alkylation of electron-rich arenes [70–72]. However, radical-mediated alkylation of indoles remains challenging. This dilemma appears to have been overcome by the recently popular and feasible electrochemical strategy. In 2022, Li *et al.* depicted a novel electrochemically enabled regioselectivity C(sp²)-H alkylation of electron-rich indoles using activated xanthenes as alkylating reagents in an undivided cell (Scheme 13) [73]. In this C(sp²)-H/C(sp³)-H cross-coupling reaction, various C3-alkylated indoles were constructed in moderate to good yields in the absence of any external chemical oxidants and metal catalysts. Given the electron-deficient characteristics of the radical cations, electron-deficient 1-(phenylsulfonyl)-1*H*-indole was inert in this transformation. Importantly, this C-H alkylation reaction was almost suppressed in the presence of radical scavenger BHT, wherein a cross-coupled product BHT-indole was detected by GC-MS, which indicated that the indole C(sp²) radical intermediate was involved in this transformation. Considering the inherent nature of benzyl hydrogen in xanthene, a radical-radical coupling mechanism is presented. Initially, indole and xanthene are oxidized at anode into corresponding radical cations **I** and **II**, respectively. Then, these radical cations lose one H⁺ to deliver the key carbon-centered radical **III** and **IV**. Finally, a con-



Scheme 13. Electrochemical C(sp²)–C(sp³) cross-coupling of indoles with xanthenes.

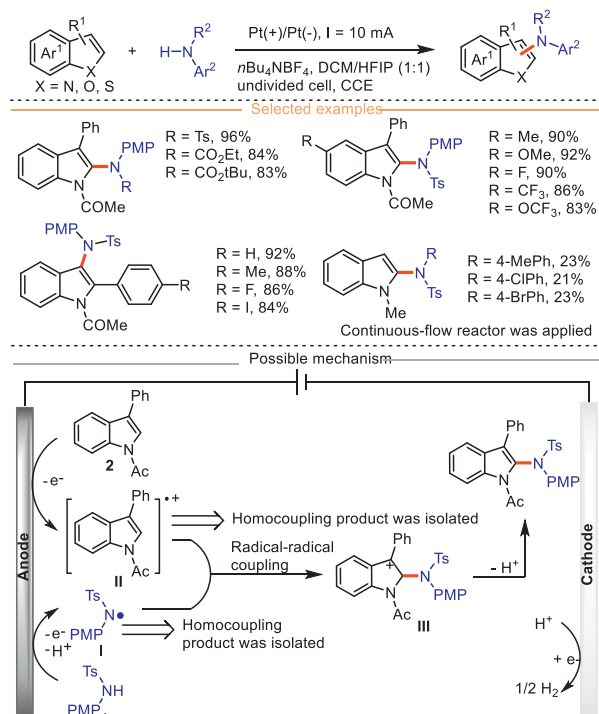
vincing radical–radical cross-coupling delivers the final product C3-alkylated indole.

2.5. C(sp²)–H amination of indoles

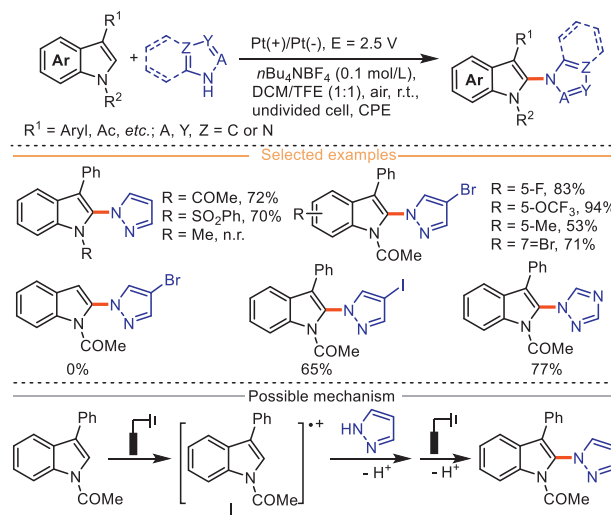
The incorporation of amino into indoles via an electrocatalytic radical cation strategy has broad application prospects. In 2021, Feng *et al.* depicted an electrochemically driven indole radical cation-mediated C–H/N–H cross-coupling of indole with aniline derivatives for constructing various C-2/C-3 aminated indoles (Scheme 14) [74]. Performing the C–H amination reaction with an electro-rich 1-methyl indole without 2/3 substituents in batch failed to isolate the corresponding coupled product due to the overoxidation of substrates. Interestingly, the C-2 aminated indoles was isolated when electro-rich 1-methylindole reacted with *N*-Ts anilines in a continuous-flow reactor, albeit with low reaction efficiency. Notably, *N*-Ts aniline **1** and indole **2** had very close oxidation potential (1.05–1.10 V vs. SCE), revealing that these two coupling partners could be oxidized simultaneously at anode surface to generate corresponding nitrogen-centered radical **I** and indole radical cation **II**, respectively. Moreover, the corresponding homocoupling products were isolated in control experiments, further suggesting that the radical–radical coupling mechanism might be involved in this transformation.

At the same year, Ackermann *et al.* also disclosed a similar electrochemical oxidative dehydrogenation C–H amination reaction of electron rich indoles with *N*-alkylsulfonamides [75]. Differently, nitrogen-centered radical is preferentially generated via anodic oxidation, which subsequently attacks the 2-position of indole to produce the thermodynamically more stable benzyl carbon-centered radical, rather than the above-mentioned radical–radical coupling mechanism.

To enhance the application of electrocatalytic indole-derived radical cation in C–N bond construction, Feng *et al.* established an efficient electrochemical strategy for synthesizing 3-substituent-2-(azol-1-yl)indole derivatives in a undivided cell (Scheme 15) [76]. Satisfactorily, synthetically useful functional group iodine was well tolerated, which should facilitate the further modification of coupled product. Unfortunately, a preliminary survey of 1-methyl-3-phenyl-1*H*-indole and other indoles without substituents at C3 position



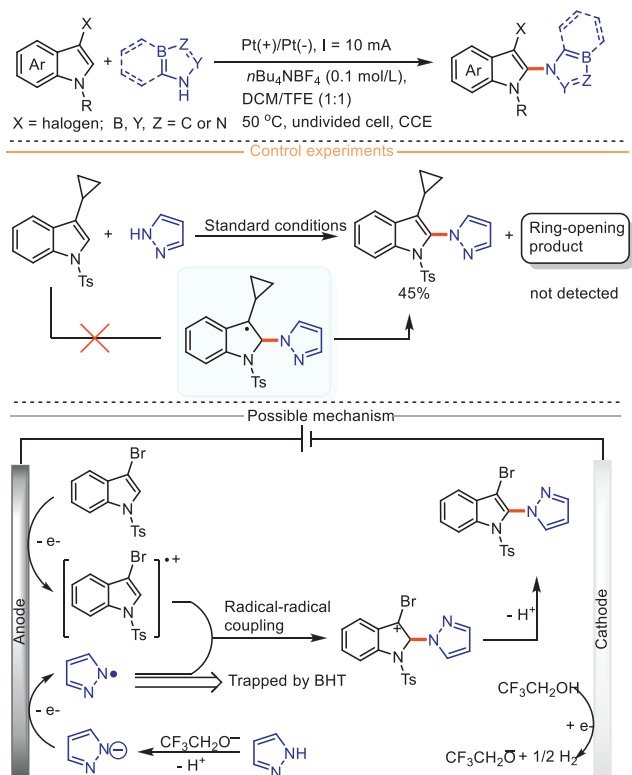
Scheme 14. Electro-oxidative C–H amination of heteroarenes with aniline derivatives.



Scheme 15. Electrochemical C(sp²)–H azolation of indoles with azoles.

sition resulted in no C–N coupled products. In this transformation process, 1-(3-phenyl-1*H*-indol-1-yl)ethan-1-one ($E_{p/2}$ = 1.35 V vs. SCE) is initially oxidized into an electrophilic indole-derived radical cation intermediate, which is easily trapped by the pyrazole ($E_{p/2}$ = 1.62 V vs. SCE), followed by deprotonation to furnish benzyl radical intermediate. The radical intermediate will undergo consecutive anodic oxidation and aromatization to yield the desired coupled product.

Usually, halogen substitutions at the C2/C3 position of indole are difficult to survive in metal-catalyzed systems. For example, the C-2 or C-3 halogenated indoles can easily participate in the formation of C–N bonds, however, the elimination of halogen atoms is hard to circumvent. To address this limitation, in 2022, Feng *et al.* designed an electrochemical radical cation strat-



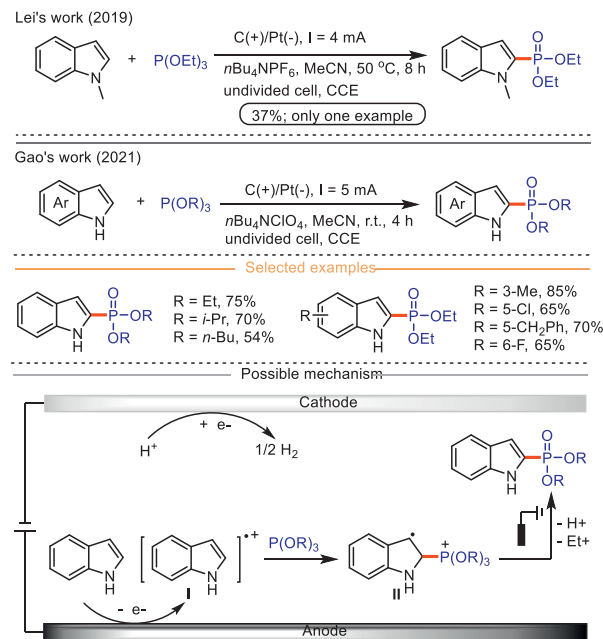
Scheme 16. Electrochemical C(sp²)-H amination of C-2 or C-3 halogenated indoles.

egy for C(sp²)-H amination of C-2/C-3 halogenated indoles with *N*-heterocycles (Scheme 16) [77]. This approach avoids the elimination of halogen atoms and provides a convenient way to construct a series of C-2/C-3 aminated halo-indoles under metal catalyst-free and chemical oxidant-free conditions. Importantly, a variety of aminated reagents, including pyrazole, triazole, benzotriazole, tetrazole and indazole were also assessed for this C(sp²)-H amination, and the relevant coupled product were produced in moderate to good yields. The C-H amination was completely suppressed when 2.0 equiv. BHT was added, wherein a cross-coupled product of BHT with pyrazole, implying that a nitrogen-centered radical was formed in this transformation. Furthermore, a ring-opening product was not detected and corresponding C-N coupled product was isolated in 45% yield, which indicated that a long live benzylic radical was not formed. Mechanism studies proved that the reaction proceeded *via* a radical-radical coupling pathway.

2.6. C(sp²)-H phosphorylation of indoles

Phosphorus-containing heterocycles are an important class of molecules, widely applied in pharmaceuticals, agrochemicals, and synthetic chemistry [78,79]. The direct C(sp²)-H phosphorylation, especially electrochemically promoted, offers an unprecedented opportunity, spurring the development of green and efficient strategy for forging ubiquitous C(sp²)-P bonds [80]. In 2019, Lei *et al.* developed an novel and scalable electrochemically enabled radical cation-mediated C(sp²)-H phosphorylation under exogenous-oxidant-free and metal catalyst-free conditions (Scheme 17) [81]. In this protocol, the C(sp²)-H phosphorylation of imidazo[1,2-*a*]pyridines was discussed emphatically, while the phosphorylation of indole was only one example.

To further explore the application of electrocatalytic indole-derived radical cation in C(sp²)-H phosphorylation of indoles, in 2021, Gao *et al.* achieved an elegant regiodivergent N-1/C-2 phos-



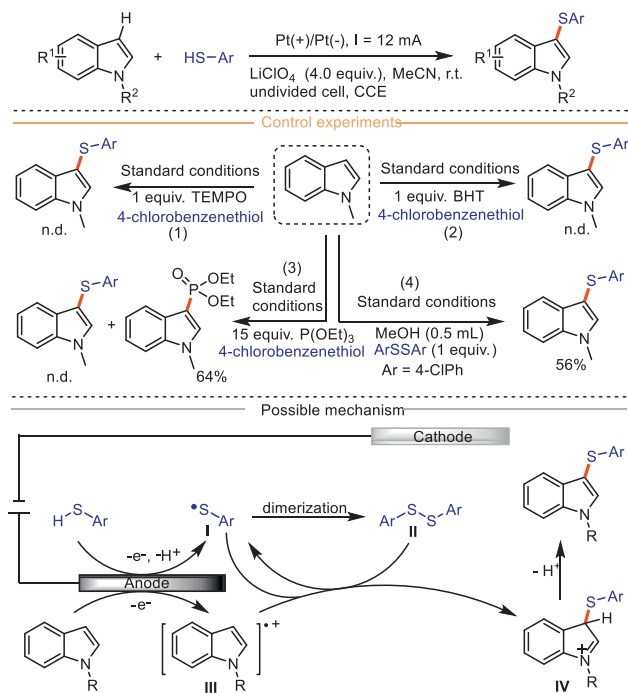
Scheme 17. Electrochemical C(sp²)-H phosphorylation of indoles.

phorylation of unprotected N-H free indoles (Scheme 17) [82]. By simply tuning the electrolyte *n*Bu₄NI to *n*Bu₄NClO₄, the C-2 phosphorylated indole was formed preferentially in good yield. It is particularly noteworthy that either electron-withdrawing or electron-donating substitutes on the N-H free indoles were suitable for this phosphorylation in satisfactory yields, which is the deficiency of many electrocatalytic C-H functionalization of indoles. Similarly, an electrocatalytic indole-derived radical cation mechanism is presented in Scheme 17, indole (a lower oxidation potential compared with P(OEt)₃) is initially oxidized into the corresponding radical cation intermediate **I**, which then reacts with nucleophilic P(OEt)₃ to deliver a new radical cation intermediate **II**. Finally, intermediate **II** undergoes consecutive anodic oxidation, deprotonation, and dealkylation to afford the desired phosphorus-containing indole.

2.7. C(sp²)-H sulfurization/sulfonylation of indoles

Sulfur-containing indoles usually exhibit multiple biological and pharmacological activities, and also serve as building blocks to construct biologically significant molecules [83,84]. Electrocatalytic C(sp²)-H sulfurization/sulfonylation of indoles offers a powerful synthetic route to access a series of structurally valuable sulfur-containing indoles.

In 2017, Lei *et al.* developed an elegant and environmentally benign electrochemical C(sp²)-H thiolation of indoles, enabling the formation of C(sp²)-S bond in the absence of any chemical oxidants and metal catalysts (Scheme 18) [85]. In this case, the scalability of this C-H thiolation was evaluated by carrying out a 5 mmol scale reaction, and the corresponding functionalized indole was obtained in 60% yield. To acquire insight into the mechanism, a series of detailed control experiments were conducted. Adding 1 equiv. of TEMPO or BHT to reaction system, this C-H thiolation was completely suppressed under standard conditions (Scheme 18, Eqs. 1 and 2). Subsequently, the C-H thiolation of indoles was performed in the presence of 15.0 equiv. triethyl phosphite (P(OEt)₃). Interestingly, no C-H thiolation product was observed, but the indole-phosphorylation product was isolated in 64% yield, thus indicating the involvement of indolyl radical (Scheme 18, Eq. 3) [86].



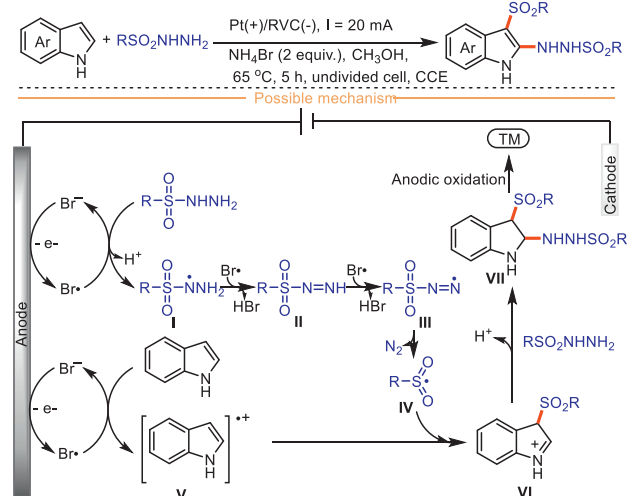
Scheme 18. Electrochemical C(sp²)-H thiolation of indoles with thiophenols.

Additionally, the reaction of diphenyl sulfide with *N*-methyl indole proceed smoothly by adding a small amount of MeOH severed as proton source under standard electrochemical conditions, and the final product was generated in 56% yield (Scheme 18, Eq. 4).

Additionally, 4-chlorobenzenethiol ($E_{\text{OX}} = 1.27\text{ V}$ vs. Ag/AgCl) and 1-methyl indole ($E_{\text{OX}} = 1.28\text{ V}$ vs. Ag/AgCl) had very close oxidation potential in acetonitrile. Mechanistically, this C(sp²)-H thiolation begins with the anode oxidative deprotonation of thiophenol to generate the sulfur radical **I**, which usually undergoes rapid dimerization to produce a disulfide **II**. At the same time, indole can also be converted to the indole-derived radical cation **III** at the anode surface via single electron oxidation process. Subsequently, the indole radical cation **III** undergoes either the radical-radical coupling with the anode generated sulfur radical **I** or radical substitution with the disulfide **II** generated from homocoupling of sulfur radical **I** to deliver a cation intermediate **IV**. Finally, the desired product is obtained through aromatization of cation intermediate **IV**.

In 2019, Pan *et al.* described a sustainable electrochemically enabled indole-derived radical cation-mediated chemoselective sulfonylation and hydrazination of C2, C3-unsubstituted indoles with arylsulfonyl hydrazide, using ammonium bromide as both electrochemical redox catalyst and electrolyte (Scheme 19) [87]. It should be particularly emphasized that the nature of halogen ions was a key factor influencing reaction outcomes, among which NH₄Br showed the optimized catalytic performance, while other redox catalysts such as NaI, NH₄I, and *n*Bu₄NBr exhibited low or even no catalytic activity. Sulfonyl hydrazine compounds have been reported to exhibit interesting biochemical activities, especially anti-tumor activities. Consequently, the anti-tumor activity of these synthetic indole-containing sulfonyl hydrazines were tested and discussed. *In vitro*, the hydrazination indoles showed excellent anti-cancer activity, which is attributed to the inhibition cell migration and tubulin aggregation by sulfonyl hydrazines in T-24 cells, thereby leading to cell apoptosis.

Mechanistically, the redox medium NH₄Br (lower oxidation potential compared with indole and sulfonyl hydrazide) is firstly oxidized into bromine radical, which then in turn oxidizes sulfonyl



Scheme 19. Electrocatalytic indole-derived radical cation-mediated sulfonylation and hydrazination.

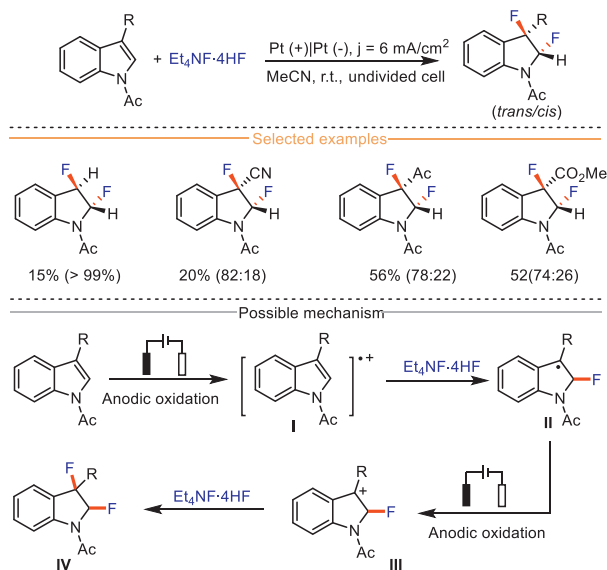
hydrazide into radical intermediate **I**. Then, the radical intermediate **I** undergoes two consecutive oxidations by bromine radicals to afford the nitrogen-centered radical **III**, which then loses one molecular nitrogen to produce sulfonyl radical **IV**. Meanwhile, indole could similarly be oxidized by the anode formed bromine radical to generate indole-derived radical cation intermediate **V**, which then reacts with sulfonyl radical **IV** to give intermediate **VI** via a radical-radical coupling process. Finally, a nucleophilic addition occurs between intermediate **VI** and sulfonyl hydrazide to furnish the intermediate **VII**, followed by quick aromatization to produce final functionalized indole.

3. Indole radical cation-mediated dearomative 2,3-difunctionalization of indoles

The dearomatization of indoles represents a straightforward and powerful synthetic approach for the synthesis of high-value-added indole-based three-dimensional molecules [88–91]. Recently, the vigorous development of the oxidative indole-derived radical cation-mediated C(sp²)-H functionalization of indoles provides an opportunity for the dearomative 2,3-difunctionalization of indoles. The recent oxidative dearomatization strategies mainly rely on stoichiometric oxidant and/or expensive catalyst, which would limit the broader application of indole radical cations in dearomatization reactions [88–94]. Electrocatalysis, a highly appealing synthetic technique, offers convenient for achieving the indole radical cation-mediated dearomative 2,3-difunctionalization of indoles. This section mainly illustrates the synthetic applications of electrocatalytic indole-derived radical cation intermediate for the dearomative 2,3-difunctionalization of indoles.

3.1. Dearomative 2,3-difunctionalization of indoles involving nucleophile capture of the indole-derived radical cation

Among the developed electrocatalytic indole-derived radical cation-mediated dearomative 2,3-difunctionalization reactions, the indole radical cations are easily attacked by structurally diverse nucleophiles to deliver carbon-centered radical species. In 2010, Fuchigami *et al.* successfully achieved an elegant electrochemical dearomative 2,3-difluorination of *N*-acetyl-3-substituted indoles using the stable and easily accessible Et₄NF·4HF as fluorinating reagent, in which various *trans*-2,3-difluoro-2,3-dihydroindoles



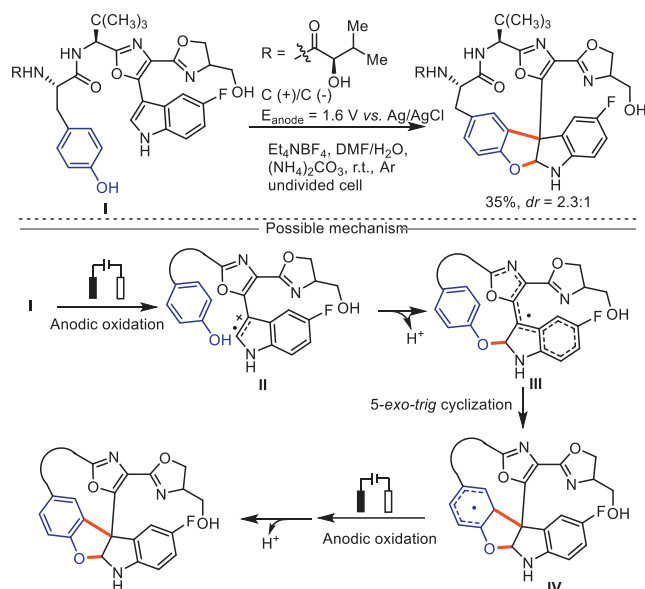
Scheme 20. Electrochemical dearomative 2,3-difluorination of indoles.

were generated exclusively or selectively (Scheme 20) [95]. Compared with the previously reported fluorination reactions of indoles, one distinct advantage with this synthetic method is that the reaction does not apply toxic gas CF_3OF , thus making it more operable.

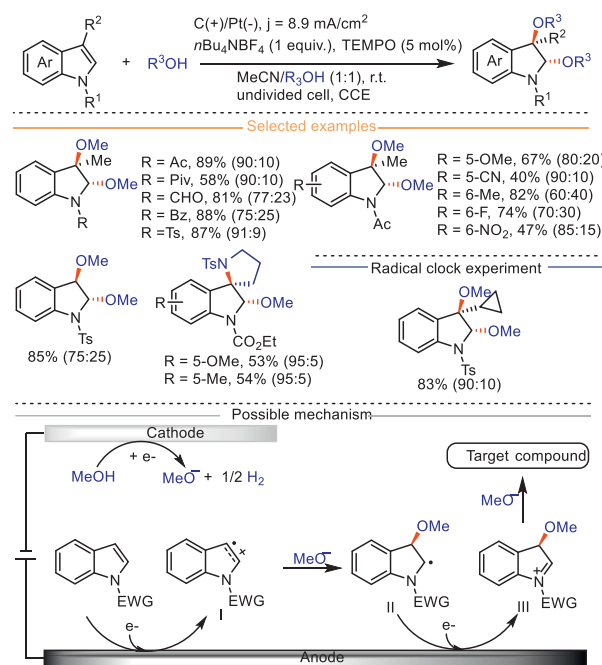
Mechanistic studies have shown that this 2,3-difluorination protocol begins with the anodic single electron oxidation of indole, resulting in indole-derived radical cation **I**. Subsequently, the nucleophilic fluoride ion selectively attacks the 2-position of indole radical cation **I** to deliver the radical intermediate **II**, which is further oxidized at anode to afford the cation **III**. Finally, nucleophilic substitution of cation **III** with fluoride ion affords the 2,3-difluoro-2,3-dihydroindoles.

In 2015, Harran *et al.* described an appealing and efficient electrocatalytic indole radical cation-mediated intramolecular dearomative macrocyclization to construct the benzofuro[2,3-*b*]indoline core moiety of DZ-2384, a highly potent anticancer agent (Scheme 21) [96]. It is worth noting that the phenol moiety as nucleophile to participate this transformation. In this case, the substrate **I** containing indole and phenol skeleton undergoes anodic single electron oxidation to generate the key radical cation intermediate **II**, and then the phenolic hydroxyl group in the substrate attacks the C-2 position of indole radical cation to produce the radical intermediate **III** owing to the driving force of intramolecular cyclization in the presence of 5 equivalents of ammonium carbonate ($(\text{NH}_4)_2\text{CO}_3$). Finally, the anode oxidative deprotonation of radical intermediate **III** affords the target macrocyclic compound.

In 2019, Vincent *et al.* developed a similar electrochemical approach for TEMPO-promoted dearomative 2,3-dialkoxylation of indoles with alcohols, providing a simple and straightforward route to produce the structurally diverse *trans*-2,3-dialkoxy-2,3-dihydroindoles with good to excellent selectivity under external-oxidant-free and transition-metal-free conditions (Scheme 22) [97]. This protocol features simple operation, broad substrate scope, and excellent functional group tolerance. It is particularly emphasized that when 2,3-disubstituted indoles were employed as substrates, the resulting dimethoxylated indolines would spontaneously convert into α -methoxy indoles *via* elimination of methanol. Adding 5 mol% of 2,2,6,6-tetramethylpiperidinyl-1-oxyl (TEMPO) could improve the reaction efficiency and avoid the decomposition of indoles. In constant current electrolysis conditions, the anodic re-



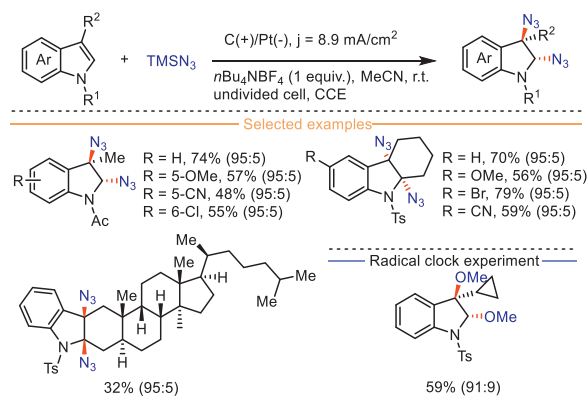
Scheme 21. Electrochemical indole-derived radical cation-mediated macrocyclizations.



Scheme 22. Electrochemical dearomative 2,3-dialkoxylation of indoles.

action potentials of each reaction were above 2 V (vs. Ag/AgCl), higher than the oxidation potential of indole and TEMPO. These observations proved that the direct electrolysis of indole is usually present, and TEMPO could be used as a sacrificial reagent in this project. In addition, the ring-opening product was not detected in the dimethoxylation reaction of 3-cyclopropyl indole, offering an important clue for further mechanistic studies.

Differently with above-described mechanism by Fuchigami's group, the methoxy anion (MeO^-) preferentially attacks the C3-position of indole-derived radical cation **I** generated from the anodic oxidation of indole rather than the C2-position. Then, the resulting C2-centered radical **II** could be oxidized into iminium ion



Scheme 23. Electrochemical dearomative 2,3-diazidation of indoles.

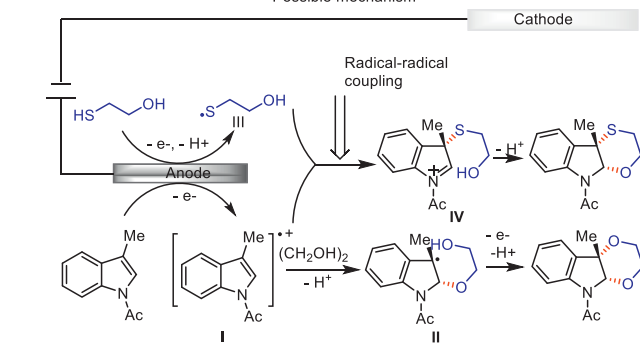
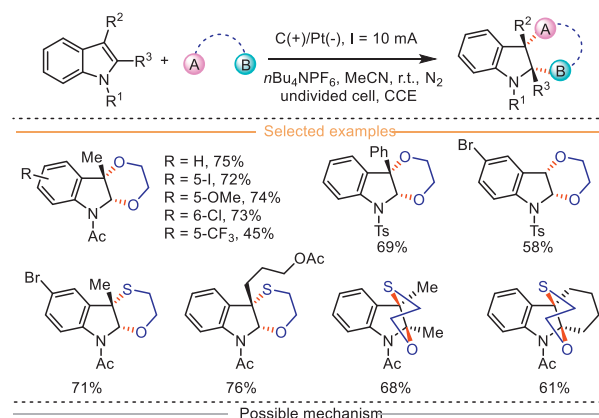
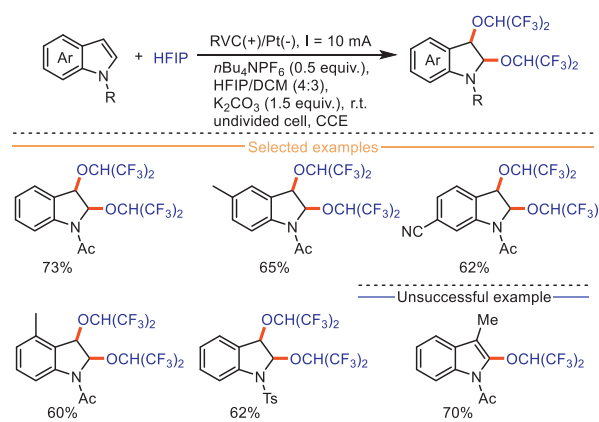
III, which then undergoes nucleophilic substitution with MeO^- to eventually deliver 2,3-dialkoxylation product.

Almost simultaneously, Xu and co-workers employed a direct electrocatalytic technology to realize the dearomative 2,3-dimethoxylation of the 2,3-unsubstituted *N*-acetyl indole in 46% yield [98]. Unfortunately, one example of oxidative dearomative 2,3-dimethoxylation of indole was reported.

Stimulating by the recent developments in electrochemical diazidation of olefins [99–101], the commonly used nucleophilic azidotrimethylsilane (TMSN_3) were also assessed for this electrochemical transformation. As anticipated, a series of *N*-acetyl indoles were successfully converted to the corresponding 2,3-diazide-2,3-dihydroindoles with excellent *trans*-diastereoselectivity (Scheme 23). Impressively, the successful synthesis of 2,3-diazide indoles through dearomatization of steroid-derived indole proved the versatility of this developed tool for complex substrates bearing multiple C-H bonds prone to oxidation. Similar to the above-described dialkoxylation reaction, the diazotization of 3-cyclopropyl indole proceed smoothly, and the ring-opening products also was not observed.

Fascinated by the unique reactivity of indole-derived radical cation, Lei *et al.* realized an attractive electrochemically driven dearomative $[n+2]$ cyclization reaction of indoles with various bis-nucleophiles, providing a convenient synthetic route for the construction of biologically valuable five to eight-membered heterocycle-2,3-fused indolines with excellent regio- and stereo-selectivity in an undivided cell (Scheme 24) [102]. A brief survey indicated that solvent had a tremendous influence on reaction outcomes, and replacing MeCN with DCM did not favor this dearomative $[n+2]$ cyclization and most indole was decomposed after electrolysis. Most importantly, a variety of bis-nucleophiles containing O-, N-, and S-nucleophilic groups could participate in this oxidative dearomative cyclization reaction.

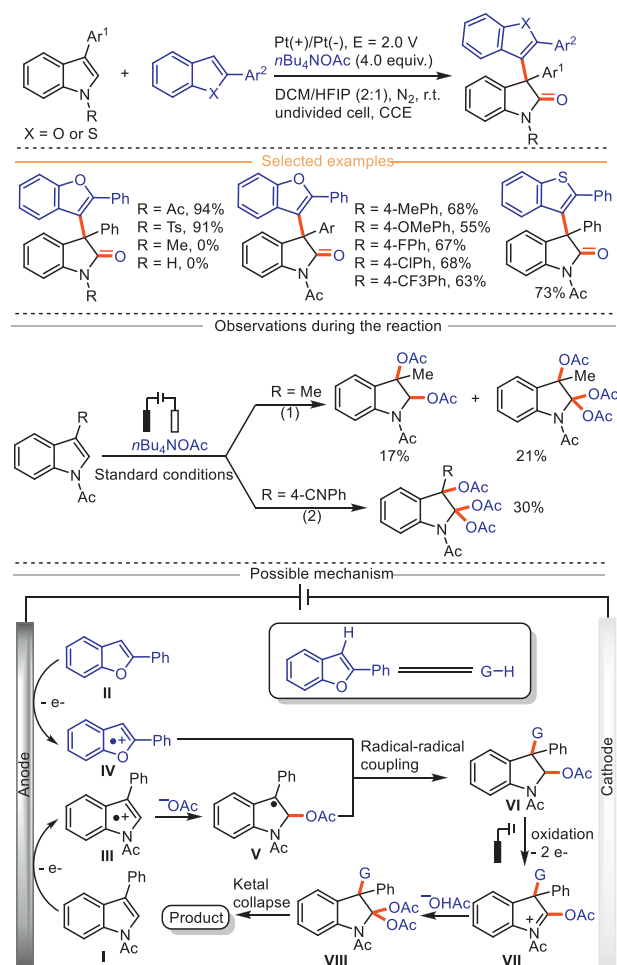
Mechanistically, the fast anodic single electron oxidation of indole delivers the radical cation **I**, in which C3 position shows more remarkable radical character affected by phenyl stabilization, and C2 position exhibits more electrophilic character. Then, the indole-derived radical cation **I** generally undergoes two different reaction pathways by utilizing its distinctive properties. One case is that the bis-nucleophile diol preferentially attacks the C2 position of radical cation **I** and loses one H^+ to form carbon-centered radical **II**, followed by consecutive anodic oxidation, intramolecular nucleophilic cyclization and deprotonation process to furnish the dearomative 2,3-dialkoxylation product. Apart from this, two different anodic oxidation events occur, including the oxidation of indole and 2-mercaptoethan-1-ol. Subsequently, radical-radical coupling between indole-derived radical cation **I** and sulfur radical **III** access

Scheme 24. Electrochemically driven dearomative $[n+2]$ cyclization reaction of indoles with various bis-nucleophiles.

Scheme 25. Electrochemical 2,3-dialkoxylation of indoles with HFIP.

to cation intermediate **IV**. Followed by intramolecular nucleophilic cyclization to produce the desired dearomative product.

Encouraged by the pioneering works aforementioned about electrocatalytic indole-derived radical cations, in 2020, Pan *et al.* established a practical electrochemically enabled dearomative 2,3-difunctionalization of indoles with HFIP in an undivided cell (Scheme 25) [103]. Using a reticulated vitreous carbon (RVC) as anode and platinum plate as cathode, a series of structurally complex dihydroindoles with potential antitumor activity were produced in good to excellent yields. Notably, when the anode material was replaced with a platinum plate electrode, no target product was observed. Meanwhile, K_2CO_3 played an integral role in this reaction, otherwise the protocol could not proceed. Furthermore, 3-methylindole could react with HFIP under standard conditions to give the 2-alkoxylation indole instead of the expected 2,3-

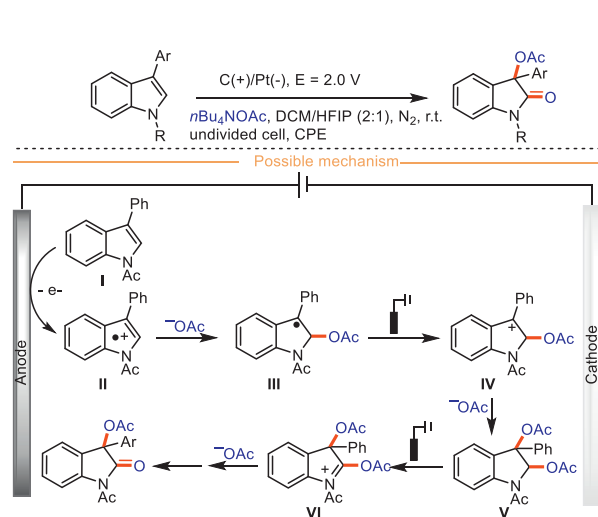


Scheme 26. Electrochemically promoted dearomatization of 3-aryl indoles to synthesize 3,3-diaryl-2-oxindoles.

dialkoxylated indole. Mechanistically, HFIP preferentially attacks the C3-position of indole-derived radical cation rather than the C2-position.

In 2022, Feng *et al.* described a powerful and scalable electrocatalytic strategy for achieving the selective dearomative 2,3-difunctionalization of indoles with electron-rich aromatic hydrocarbons, including benzofurans and benzothiophenes in an undivided cell (Scheme 26) [104]. Using platinum plate as anode and cathode, and $n\text{Bu}_4\text{NOAc}$ as electrolyte, a wide variety of synthetically useful oxindoles were synthesized with good to excellent yields in the absence of any chemical oxidants and transition-metal catalysts. It is worth noting that the choice of mixed solvents (DCE/HFIP) was crucial, among which a single solvent could not effectively facilitate this electrochemical protocol. Furthermore, electrolyte $n\text{Bu}_4\text{NOAc}$ was indispensable, and the reaction could not occur without the electrolyte containing OAc^- . This reaction featured easily operation, broad substrate scope, and good functional group compatibility. Unsatisfactory, replacing the electron-withdrawing groups at the N-1 position of indole with methyl group or a free N-H, these substrates did not react under optimized conditions.

Interestingly, using 1-(3-methyl-1*H*-indol-1-yl)ethan-1-one as reaction partner to react with benzofuran, the anticipated product was not detected, wherein the di-OAc and tri-OAc functionalized indolines were isolated in 17% and 21% yields, respectively. Similarly, the tri-OAc functionalized indoline was obtained when us-

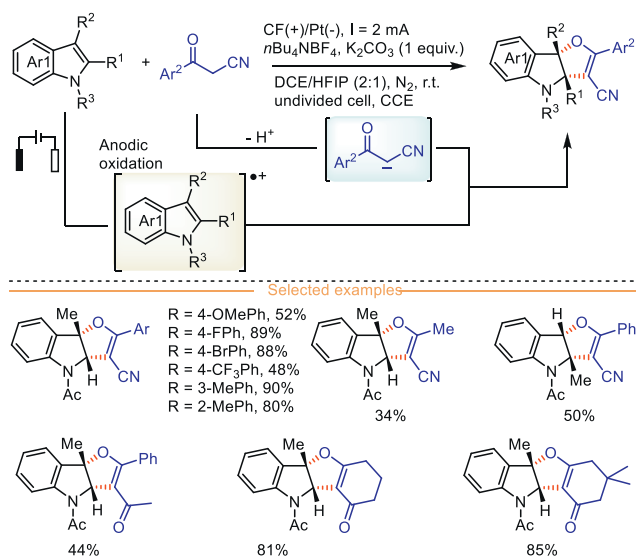


Scheme 27. Electrochemically promoted dearomatization of 3-aryl indoles for the synthesis of 3-aryl-3-hydroxyl-2-oxindoles.

ing 4-(1-acetyl-1*H*-indol-3-yl)benzonitrile as substrate. These observations supported that $n\text{Bu}_4\text{NOAc}$ played dual role in this protocol, including acting as electrolyte and carbonyl oxygen atom source. Besides, the phosphorylated indole and benzofuran were detected by HRMS in control experiments, which indicated that the corresponding indole-derived and benzofuran-derived radical cation might be formed simultaneously at the anode surface. Cyclic voltammetry results indicated that the reaction substrates indole and benzofuran had a similar oxidation potential, supporting that the simultaneous oxidation of both components was reasonable in this protocol. Based on these experimental results and cyclic voltammetry studies, a possible mechanism for dearomatization of 3-aryl indoles is outlined in Scheme 26. Initially, the partners indole **I** and benzofuran **II** are simultaneously oxidized into the corresponding radical cation **III** and **IV** at anode surface, respectively. Subsequently, the acetate ion derived from $n\text{Bu}_4\text{NOAc}$ selectively attacks the C2-position of indole radical cation **III** to form benzyl radical intermediate **V**, which then reacts with radical cation **III** to give intermediate **VI** via a radical-radical coupling process. Followed by anodic oxidation and nucleophilic substitution affords the unstable di-OAc functionalized species **VIII**, which then undergoes hydrolysis to yield the desired product.

By simply switching the platinum anode to carbon anode, the coupling partner benzofurans did not participate this reaction, and the 3-aryl indoles were selectively converted into 3-aryl-3-hydroxyl-2-oxindoles in moderate yields (Scheme 27). Either the electron-donating or electron-withdrawing group on the indole ring could access to the corresponding products in moderate yields. This electrochemical protocol also begins with the anodic oxidation of 3-aryl indole to furnish the radical cation **II**, which then reacts with acetate ion to generate radical intermediate **III**. Followed by consecutive anodic oxidation and nucleophilic substitution to produce the intermediate **V**. Finally, the target product 3-aryl-3-hydroxyl-2-oxindole is obtained similar to the aforementioned reaction process in Scheme 26.

Despite important progress has been made in the field of electrochemically enabled dearomative 2,3-difunctionalization of indoles involving nucleophile capture of the indole-derived radical cation, many unresolved problems remain. These strategies tend to excessively rely on the heteroatom-centered nucleophiles, therefore carbon-centered nucleophiles remain challenging. In 2022, Lei *et al.* illustrated an unparalleled electrocatalytic dearomative [3 + 2] cyclization of indoles, using simple and easily accessible benzo-



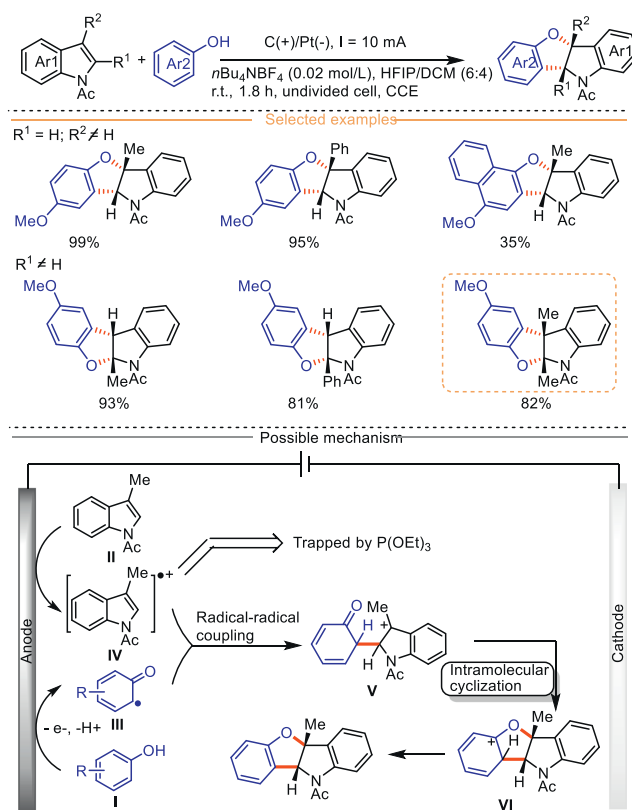
Scheme 28. Electrooxidative annulation of β -ketonitriles and indole derivatives.

lactonitriles as carbon-centered nucleophiles for the construction of a series of polycyclic fused heterocyclic compounds (Scheme 28) [105]. Mechanistically, benzoylacetone nitrile is converted to corresponding carbanion assisted by base K_2CO_3 , which then selectively attacks C-2 position of indole-derived radical cation generated from indole at anode. Interestingly, the commonly used 1,3-dicarbonyl compounds containing α -H were also tested to evaluate the versatility of this protocol, the desired dearomatic [3 + 2] cyclization products were furnished in moderate yields.

3.2. Dearomatic 2,3-difunctionalization of indoles involving radical capture of the indole-derived radical cation

Given the unique reaction reactivity of indole-derived radical cation, it also can be preferentially captured by radical species. Benzofuroindoline structural skeletons frequently exist in some important bioactive natural and synthetic molecules [106,107]. The direct oxidative [3 + 2] cyclization of indoles with phenols provides a convenient, atom and step economic method for the synthesis of benzofuroindolines. In 2012, Vincent *et al.* depicted a novel oxidative [3 + 2] radical cyclization reaction of phenols with *N*-acetyl indoles for the construction of benzofuro[3,2-*b*]indolines in one step, however, the excess amount of $FeCl_3$ and 2,3-dicyano-5,6-dichlorobenzoquinone (DDQ) were hard to circumvent in this project [108].

Developing efficient and sustainable electrochemical method may provide potential solutions to address these limitations above-mentioned. In 2017, Lei *et al.* skillfully developed an environmentally benign electrocatalytic indole radical cation-mediated [3 + 2] cyclization of indoles with phenols for producing a series of structurally rich benzofuro[3,2-*b*]indolines without any chemical oxidants and metal catalysts in an undivided cell (Scheme 29) [109]. The key to success was not only the application of electrocatalytic strategy, but also the addition of co-solvent hexafluoroisopropanol (HFIP). Strong electron-rich phenols were usually required, for example, 4-methylphenol was not reactive in this case. Pleasingly, the indole partners bearing various C-3 substituents such as alkyl, allyl, and phenyl groups were all suitable for this [3 + 2] cyclization project, affording expected benzofuro[3,2-*b*]indolines in good to excellent yields. Differently, a variety of C-2 substituted indoles were converted to benzofuro[2,3-*b*]indolines with opposite regioselectivity. Moreover, 2,3-disubstituted indoles could react smoothly with 4-methoxyphenol to produce benzofuro[2,3-*b*]indolines with

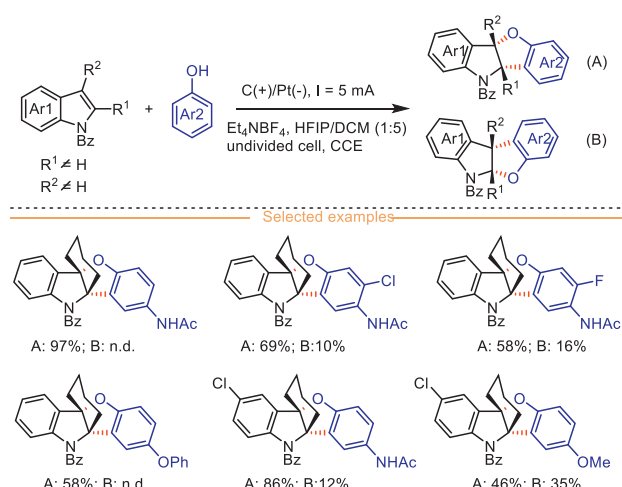


Scheme 29. Electrochemical dearomatic [3 + 2] cyclization of phenols with indoles to construct benzofuro[3,2-*b*]indolines.

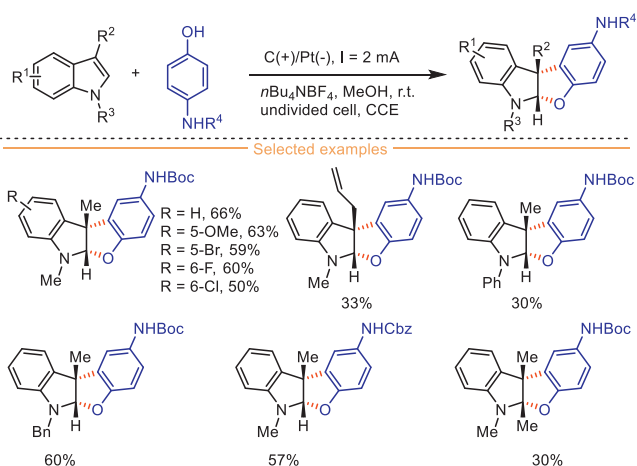
regioselectivity consistent with the C-2 substituted indoles. Regrettably, changing the classic polarity of C2 and C3 positions on indoles by coordination of Lewis acid with *N*-acetyl indole failed, the reaction regioselectivity of C-2 substituted *N*-acetyl indoles could not be tuned to benzofuro[3,2-*b*]indolines.

Detailed cyclic voltammetry experimental results revealed that the model reaction partners (3-methyl-*N*-acetylindole and 4-methoxyphenol) had quite close oxidation potentials, which suggested that it was possible for the simultaneous oxidation of both substrates at the anode surface. Firstly, the single electron oxidation of 4-methoxyphenol I occurs accompanied by the deprotonation process to deliver a C-centered radical III isomerized from the generated O-centered radical. Meanwhile, *N*-acetylindole II is oxidized at anode into indole-derived radical cation intermediate IV, which then reacts with the generated radical III to give the cation intermediate V via a radical-radical coupling process. Finally, intramolecular cyclization occurs to give the intermediate VI, which then loses one H^+ to deliver the target dearomatization product.

However, the above-described dearomatic [3 + 2] cyclization method does not meet the requirements of synthetic chemists, for example, the regioselective cyclization of 2,3-disubstituted indoles for the synthesis of benzofuro[3,2-*b*]indolines remains incredibly problematic. A bulky benzyloxy group on N1-position of 2,3-disubstituted indoles is generally beneficial to the selective construction of benzofuro[3,2-*b*]indolines. In 2020, Jia *et al.* achieved a sustainable electrochemical enabled indole-derived radical cation-mediated regioselective [3 + 2] cyclization of 2,3-disubstituted *N*-benzyloxyindoles with phenols, affording a variety of structurally rich benzofuro[3,2-*b*]indolines in good to excellent yields (Scheme 30) [110]. By increasing the bulk of *N*-substituents, this developed electrochemical method showed better results in regioselectivity compared to the similar strategy reported by Lei's



Scheme 30. Electrochemical regioselective [3 + 2] cyclization reaction of indoles with phenols.

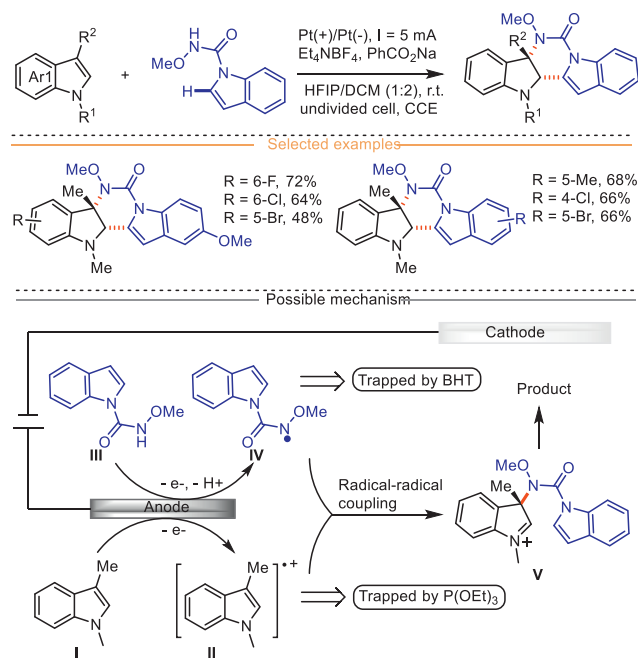


Scheme 31. Electrochemical dearomative [3 + 2] cyclization of phenols with indoles to construct benzofuro[2,3-*b*]indolines.

group [109], although a few substrates showed deteriorating regioselectivity.

However, the inherent influencing factors and underlying mechanisms of these electrochemically driven regioselective [3 + 2] cyclization reactions between indoles with phenols remain unclear, and the speculation of key indole-derived radical cation intermediate lacks powerful and direct evidence. Supported by detailed DFT calculation and experimental results, Lei *et al.* proved that C2 and C3 positions in the *N*-acetyl indole-derived radical cation have a similar radical character, the regioselectivity was controlled by the steric effects at C2 and C3 positions rather than the electronic effect (Scheme 31) [105]. The C3 position of the indole-derived radical cation showed more remarkable radical property when *N*-acetyl was replaced by *N*-methyl group, which further promoting the generation of benzofuro[2,3-*b*]indolines with high regioselectivities. Similar to the previous methods, the reaction substrates *N*-methyl indole and *N*-Boc-4-aminophenol can be oxidized simultaneously into the corresponding radical cation and radical intermediates, respectively.

In 2020, Lei *et al.* employed an electrocatalytic strategy to realize the indole-derived radical cation-mediated dearomative [4 + 2] cyclization between different indoles, providing a straight-



Scheme 32. Electrooxidation enables selective dearomative [4 + 2] cyclization between indole derivatives.

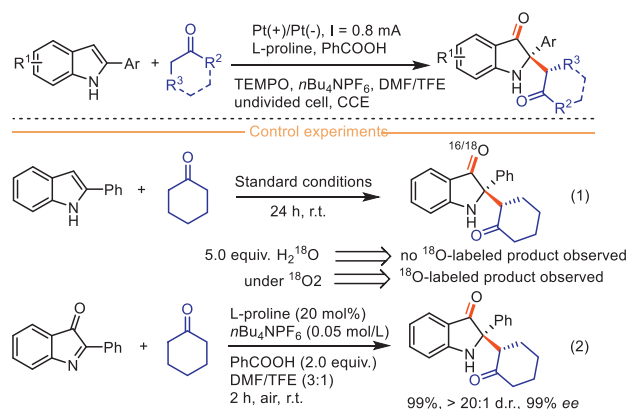
forward synthetic route for the rapid preparation of highly functionalized and biologically important pyrimido[5,4-*b*]indoles under mild conditions (Scheme 32) [111]. Notably, the dearomative [4 + 2] cyclization reaction did not occur in the absence of HFIP or PhCOONa. In this case, 3-substituted indoles and indoles bearing amide group served as radical cation and nitrogen-centered radical donors, respectively, to achieve this dearomative [4 + 2] cyclization reaction. Importantly, this protocol featured a broad substrate scope, meaning that a variety of 3-substituted indoles were successfully transferred to the expected polycyclic compounds with good to excellent regio- and stereoselectivity.

A believable mechanism is presented in Scheme 32. This protocol begins with the anodic oxidation of 1,3-dimethylindole **I** ($E_{\text{OX}} = 0.6\text{ V}$ vs. Ag/AgCl) to form the indole-derived radical intermediate **II**, which could be trapped by $\text{P}(\text{OEt})_3$ in a control experiment. At the same time, another reaction partner *N*-methoxy-1*H*-indole-1-carboxamide **III** ($E_{\text{OX}} = 1.1\text{ V}$ vs. Ag/AgCl, and a new oxidation peak was observed at 0.6 V in the presence of 1 equiv. PhCOONa) also undergoes anode oxidative deprotonation assisted by the base PhCO_2Na to furnish the *N*-centered radical intermediate **IV** captured by radical scavenger BHT. Then, radical-radical cross-coupling between indole radical cation **II** and *N*-centered radical **IV** affords the cation intermediate **V**, followed by intramolecular nucleophilic cyclization and deprotonation process to produce the final dearomative product with excellent regioselectivity.

3.3. Others dearomative 2,3-difunctionalization of indoles

C2-Quaternary indolin-3-ones are highly valuable structural skeletons in many natural and synthetic molecules that possess a wide diversity of important biological activities [102–115]. The oxidative dearomatization of 2-arylindole with external reagent provides a simple and straightforward method for the rapid construction of C2-quaternary indolin-3-ones [116–118]. Recently, efforts to develop green and practical synthetic strategies for synthesizing various 2,2-disubstituted indol-3-ones are still highly appreciated.

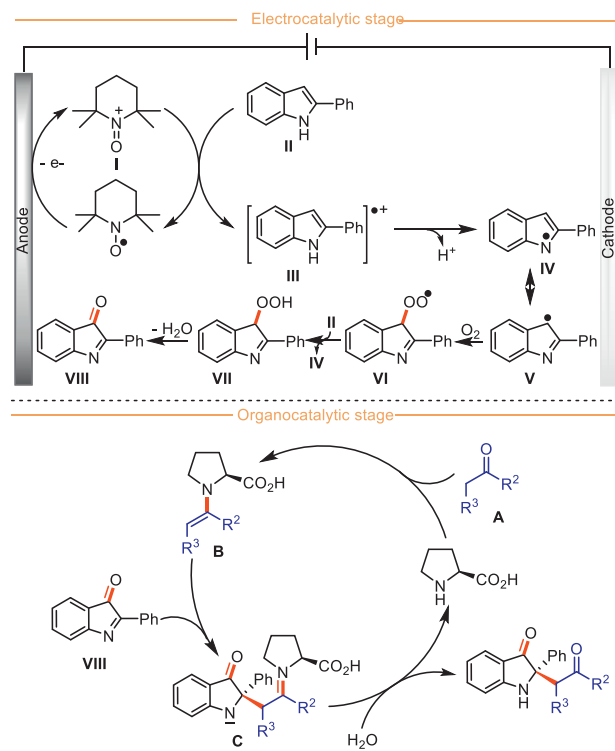
In 2020, He *et al.* described a highly attractive and creative TEMPO-mediated enantioselective dearomatization of 2-arylindoles



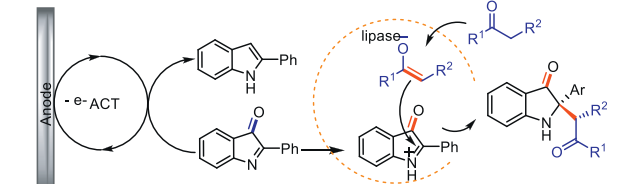
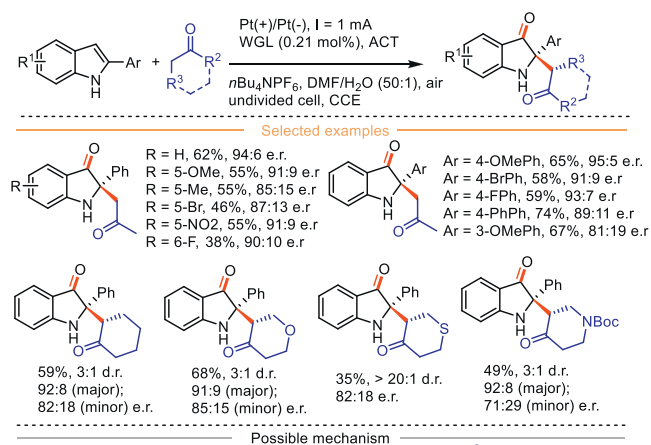
Scheme 33. Highly enantioselective electrosynthesis of C2-quaternary indolin-3-ones.

with ketones by merging electrocatalysis with organic proline-catalysis (Scheme 33) [119]. This protocol provided an efficient strategy for producing structurally rich and changeable C2-quaternary indolin-3-ones with high enantioselectivity when using L-proline as the chiral catalyst in an undivided cell. In this case, the addition of benzoic acid was beneficial to suppress the side reactions without obviously affecting the enantioselectivity, which might be attributed to the favorable formation of the key imine intermediate. The detailed survey on the substrate scopes of 2-arylindoles bearing electron withdrawing and electron donating groups revealed that the electronic effects exhibited only slight influence on the diastereo- and enantioselectivities of the transformations. A series of detailed isotope-labeling experiments were conducted to investigate the reasonable reaction mechanism. Upon subjecting 2-phenylindole and cyclohexanone to this system in the presence of 5.0 equiv. H_2^{18}O , no ^{18}O -labeled product was observed. Meanwhile, the model reaction was performed in the $^{18}\text{O}_2$ atmosphere, and it was found that the oxygen atom in the product was labeled by ^{18}O (Scheme 33, Eq. 1). These results supported that O-atom of the carbonyl is derived from molecular O_2 , not H_2O . In previous reports, the single electron oxidation of 2-phenylindole can usually form the key intermediate 2-phenyl-3H-indol-3-one in the presence of O_2 [120]. As anticipated, the synthetic 2-phenyl-3H-indol-3-one was quantitatively converted to the corresponding C2-quaternary indolin-3-ones with excellent enantioselectivity under standard conditions without electricity, which demonstrated that 2-phenyl-3H-indol-3-one was a key intermediate, and the followed transformation does not require the participation of electricity (Scheme 33, Eq. 2).

Based on the above-mentioned control experimental results, a logical mechanism is outlined in Scheme 34. Initially, TEMPO ($E_{\text{OX}} = 0.78 \text{ V}$ vs. Ag/AgCl) is oxidized into the TEMPO^+ I at the anode, which then in turn oxidizes 2-phenylindole II ($E_{\text{OX}} = 1.02 \text{ V}$ vs. Ag/AgCl) to produce the key indole-derived radical cation III. Subsequently, the radical cation III loses one H^+ to generate carbon-centered radical V (trapped by BHT), which is rapidly captured by molecular O_2 to access radical intermediate VI. Followed by hydrogen atom transfer between substrate 2-phenylindole with radical VI to afford intermediate VII, which loses one molecule of H_2O to give the key intermediate 2-phenyl-3H-indol-3-one VIII. Notably, the above-described control experiments indicated that the subsequent transformation of intermediate VIII does not involve electro-redox processes. In the organic catalytic cycle, the electron-rich enamine B, generated by condensation of ketone with L-proline, undergoes a nucleophilic addition to intermediate VIII to deliver the intermediate C, followed by the hydrolysis process to give the final product.

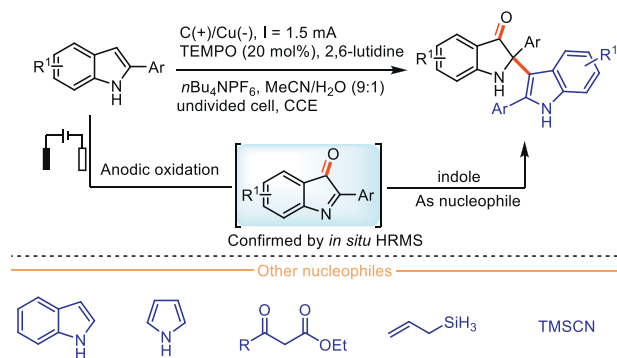


Scheme 34. Possible mechanism.



Scheme 35. Enantioselective dearomatization of 2-arylindoles by merging the enzymatic catalysis with electrocatalysis.

In 2022, the same research team disclosed an unprecedented 4-acetamido-2,2,6,6-tetramethyl-1-piperidineoxy (ACT) initiated enantioselective dearomatization of 2-arylindoles with ketones by merging the enzymatic catalysis with electrocatalysis, resulting in the synthesis of structurally diverse 2,2-disubstituted indolin-3-ones with good enantio- and diastereo-selectivities (Scheme 35) [121]. Usually, only oxidoreductases can be used for

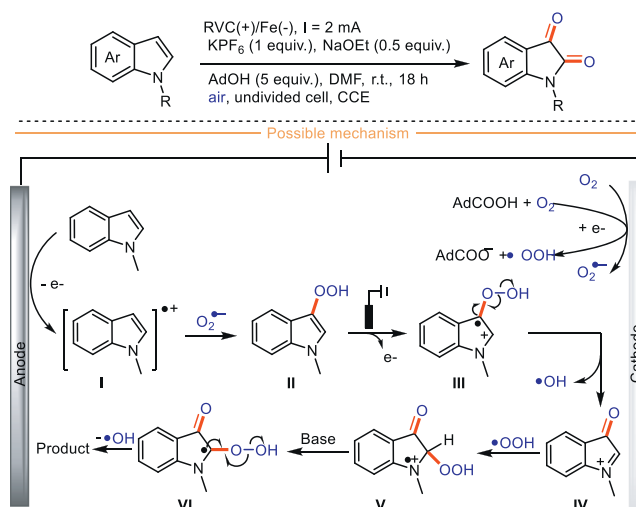


Scheme 36. Electrochemical oxidative dearomatization of 2-arylindoles.

electron transfer between electrodes and molecules, and the cofactors are often required in the active sites of oxidoreductases. One of the main roles of electrochemistry is to regenerate the cofactor. In this protocol, wheat germ lipase (WGL), an abundant and readily available hydrolase that general exhibits good stability, high catalytic efficiency, and wide substrate scope, was used to realize this enantioselective electrochemical transformation. Both the electricity and wheat germ lipase played vital roles in this dearomatization reaction; and this transformation does not occur upon the omission of either. Similar to the previously work reported by the same group in 2020 [119], the key intermediate 2-phenyl-3*H*-indol-3-one is firstly generated in the presence of molecular oxygen under electrochemical conditions. Subsequently, the target product 2,2-disubstituted indolin-3-one is furnished with good enantio- and diastereoselectivities under enzymatic conditions.

Despite the significant progress has been achieved in the field of indole-derived radical cation-mediated dearomatization of 2-arylindoles for the synthesis of C2-quaternary indolin-3-ones by merging electrocatalysis with other catalysis, developing a more general and sustainable method that could overcome the limitation of nucleophiles is still necessary. In 2022, Kumar *et al.* reported a scalable electrochemically promoted dearomatization dimerization of 2-arylindoles to build structurally complex C2-quaternary indolin-3-one derivatives (Scheme 36) [122]. In this conversion, TEMPO served as an electrocatalytic redox agent to facilitate the anodic single electron oxidation of 2-arylindole to generate the key indole-derived radical cation, otherwise a trace amount of product was observed. It should be highlighted that some other nucleophiles, including indoles, 1,3-dicarbonyls, pyrroles, allylsilane, and TMSCN, were suitable for this protocol, thereby providing a highly competent method to access synthetically valuable C2-quaternary indolin-3-ones. Meanwhile, the practicality of this developed strategy has been effectively demonstrated through the construction of a highly valuable metagenediindole A and other late-stage valuable synthetic transformations. Mechanistically, similar to the previously well-established dearomatization of 2-arylindole [119–121], the intermediate 2-phenylindole-3-one is formed under electrochemical conditions.

The synthesis of functionalized isatins has particularly attracted considerable attention from synthetic chemists [123]. In 2022, Kumar *et al.* reported a scalable electrocatalytic indole-derived radical cation-mediated aerobic oxidation of indoles in an undivided cell (Scheme 37) [124]. This synthetic protocol presented an efficient and straightforward method for the assembly of structurally useful isatins in moderate to good yields. Detailed experimental outcomes proved that the acid AdCO_2H , electricity, and oxygen were all indispensable, without one of these factors the reaction did not happen. Besides, the effect of electrode materials on the reaction



Scheme 37. Electrocatalytic indole-derived radical cation-mediated aerobic oxidation of indoles.

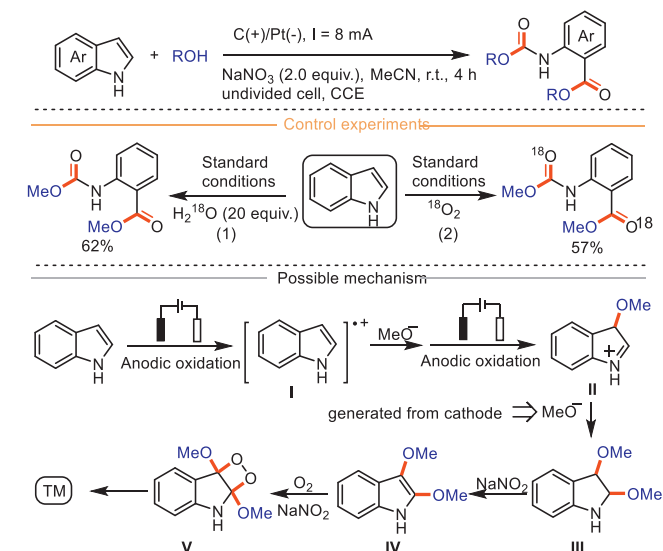
was also particularly critical, only trace amounts of products were detected when using platinum or graphite felt electrode instead of RVC, which might attribute to the high surface area of RVC electrode [69]. Unsatisfactorily, indoles bearing electron-withdrawing groups at N1-position, such as Ac and Boc, failed to furnish the corresponding isatins.

An indole radical cation-mediated aerobic oxidation mechanism supported by DFT calculations is presented in Scheme 37. Firstly, the anode single electron oxidation of *N*-methyl indole ($E_{\text{ox}} = 1.27 \text{ V}$, a calculated oxidation potential vs. SCE) furnishes the indole-derived radical cation intermediate **I**, which subsequently reacts with the cathode reduction generated superoxide anion $\text{O}_2^{\bullet-}$ to produce intermediate **II** via a radical-radical coupling process. Followed by further anodic oxidation of intermediate **II** gives a new radical cation **III**, which then undergoes the homolytic cleavage of the oxygen–oxygen bond to generate cation **IV** and radical $\bullet\text{OH}$. Cation **IV** would be attacked by radical $\bullet\text{OOH}$, which is originated from O_2 and AdCO_2H at cathode surface, and loses one proton assisted by base, to form intermediate **VI**. Finally, a homolytic cleavage of intermediate **VI** affords the desired isatin.

4. Other indole-derived radical cation-mediated organic transformation

Not limited to the synthetic applications outlined above, the electrocatalytic indole-derived radical cations can also be applied to synthesize other various structurally and synthetically valuable organic frameworks. Unarguable, the direct oxidative cleavage of $\text{C}2=\text{C}3$ double bond of indoles, reported in 1951 by Witkop [125], provides a powerful and atom-economical tool for the preparation of a variety of 2-ketoacetanilide derivatives, which are important synthetic intermediates in organic chemistry and drug discovery [126–128]. The emerging electrochemical technology offers an extremely attractive alternative for oxidative cleavage of $\text{C}2=\text{C}3$ double bond of indoles mediated by indole-derived radical, avoiding the involvement of chemical oxidants.

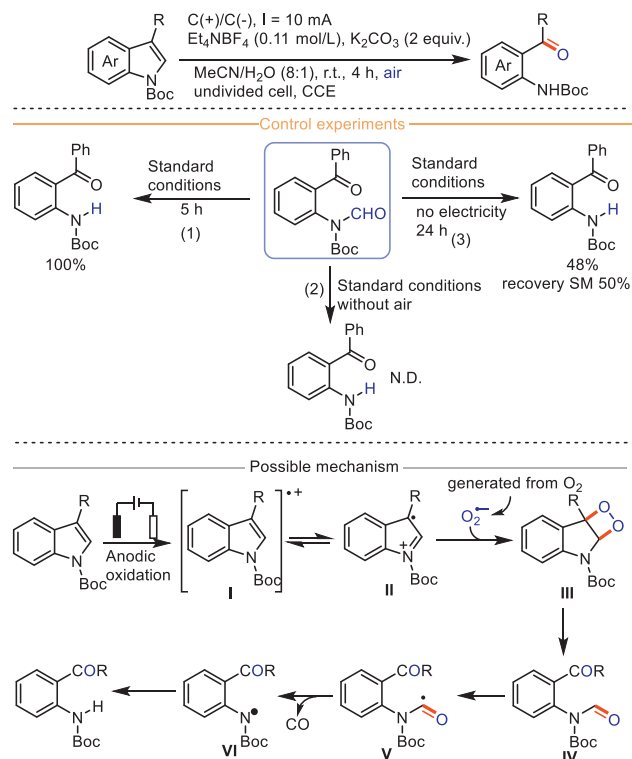
In 2021, Fang *et al.* developed an interesting electrochemical oxidative cleavage of $\text{C}2=\text{C}3$ double bond of indoles with alcohols, which offered a convenient and simple route to access structurally rich and synthetically important *o*-amidobenzoate building blocks (Scheme 38) [129]. Predictably, indoles bearing substituents (e.g., CH_3 or Ph) on the 2-/3-position could not be converted to intended ring-opening product, offering a valuable clue for investigating the reaction mechanism. Isotope-labeling experiments dis-



Scheme 38. Electrochemical oxidative cleavage of C2=C3 double bond of indoles with alcohols.

closed that the two carbonyl oxygen atoms all originated from O₂, not H₂O. Detailed cyclic voltammetry studies showed that MeOH had no obvious oxidation peak in the range of 0–2.5 V. In contrast, an obvious oxidation peak of indole was observed at this region. Essential to the success of this oxidative ring-opening reaction is the anodic single electron oxidation of indole to generate corresponding radical cation intermediate **I**, which subsequently reacts with cathode formed MeO[−], followed by anodic oxidation to produce iminium ion intermediate **II**. Afterward, the resulting iminium ion **II** is poised to be captured by MeO[−] to deliver the dimethoxylated intermediate **III**, which then undergoes a rapid oxidation to afford dimethoxylated indole **IV** due to instability of *N*-unprotected indole. Finally, four-membered ring intermediate **V**, generated from intermediate **IV** with molecular O₂, undergoes fragmentation to produce the desired product.

In the above-mentioned oxidative ring-opening reaction, the indoles without substituents on 3-position are required. In 2022, Liu *et al.* developed an unparalleled electrochemically driven aerobic cleavage of C(2)=C(3)/C(2)-N bonds of indoles under an air atmosphere, in which molecular oxygen as carbonyl oxygen atom (Scheme 39) [130]. This ring-opening protocol provided a green and efficient approach for producing structurally useful *ortho*-amino aryl ketones in an operationally simple undivided cell. Interestingly, a *N*-formylated product was obtained when benzofuran was used as electrochemical oxidation substrate, offering a powerful clue for subsequent mechanism studies. Indeed, the synthetic *N*-formyl substrate can be converted to corresponding *ortho*-amino aryl ketones in quantitative yield under the standard conditions (Scheme 39, Eq. 1). In contrast, the reaction could not proceed without oxygen (Scheme 39, Eq. 2). Furthermore, only 48% yield of ring-opening product was isolated without electricity, indicating that electricity was not a necessary condition for this deformylation reaction, but it could obviously facilitate this transformation (Scheme 39, Eq. 3). Mechanistically, *N*-Boc-3-phenyl indole (*E*_{ox} = 1.6 V vs. SCE) is first oxidized at the anode to form indole-derived radical cation **I** and the resonance structure **II**, which then is quickly trapped by the cathode generated superoxide radical anion (O₂^{•−}) to afford a four-membered peroxide **III**. Subsequently, fragmentation of peroxide **III** affords a ring-opening intermediate **IV**, followed by single electron oxidation to deliver acyl radical intermediate **V**. Finally, acyl radical **V** would release CO assisted by



Scheme 39. Electrochemically driven aerobic cleavage of C(2)=C(3)/C(2)-N bonds of indoles.

electricity to produce nitrogen-centered radical **VI**, which then abstracts a hydrogen atom to furnish the desired product.

5. Conclusions and outlook

Considering the unique dual reactivity of open-shell indole-derived radical cation species, it has attracted considerable attention in the field of constructing functionalized indoles and indolines in the past few decades. In this presented review, we have comprehensively summarized the current state of the art in electrochemically driven indole-derived radical cation-mediated functionalization of indoles, including C2-H/C3-H selective functionalization, dearomative 2,3-difunctionalization, and few ring-opening reaction. Meanwhile, the generation and conversion modes of indole-derived radical cation were discussed emphatically. In comparison with the developed traditional synthetic strategies, these electrochemical approaches are highly appealing and popular on account of their environmentally friendly and sustainable innate characters. Although tremendous achievements have been realized, the challenges as well as opportunities still remain in the future for synthetic chemistry and drug discovery. The inherent influencing factors and underlying mechanisms of electrochemically driven C(sp²)-H functionalization reaction remain unclear, leading to the lack of powerful tools to achieve a single regioselectivity control. In addition, the limited availability of nucleophiles restricts the further application of electrochemically driven dearomative 2,3-difunctionalization of indoles in synthetic chemistry, as does achieving the orderly transformation of indole-derived radical cation.

Future efforts in this research field may focus on developing novel electrocatalytic systems to address the limited availability of nucleophiles. Therefore, conceptually novel electrocatalytic strategies, including the use of electrochemical redox catalysts, and more

specific methods that merging with photocatalysis, metal catalysis, and/or Lewis acid catalysis, are required. Generally, catalyst control is a useful strategy for tuning the regioselectivity. Hence, the development of new catalysts is conducive for the realization of regioselectivity control. At the same time, we hope that this review of electrocatalytic indole-derived radical cation-mediated indoles functionalization will provide some insights into this emerging study field and spur continued interest in the organic community for discovering more innovative strategies and novel transformation modes.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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