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Highlight Review

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Electrochemical synthesis of heterocyclic compounds via carbon–heteroatom bond formation: direct and indirect electrolysis

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Seiji Suga graduated from Nagoya University under the guidance of Professor Ryoji Noyori and received his PhD in 1995. After working as a postdoctoral researcher at the University of Oxford (JSPS Postdoctoral Fellowship for Research Abroad, Prof. Sir Jack E. Baldwin), he moved to Kyoto University as an assistant professor in Prof. Jun-ichi Yoshida's research group in 1996. After being promoted to lecturer and associate professor, he was appointed as professor at Okayama University in 2008 and is currently executive director and senior vice president of the university. His research interests include the transformation of organic compounds based on electron transfer chemistry, flow chemistry, and organocatalysts.

Abstract

Electrochemical organic synthesis has attracted attention as an environmentally friendly method for constructing heterocyclic compounds via carbon–heteroatom bond formation. Herein, we describe the representative examples of electrochemical reactions to produce heterocycles and discuss them according to whether they involve direct or indirect electrolysis.

Keywords: carbon–heteroatom bond formation, electrochemical synthesis, heterocyclic compounds.

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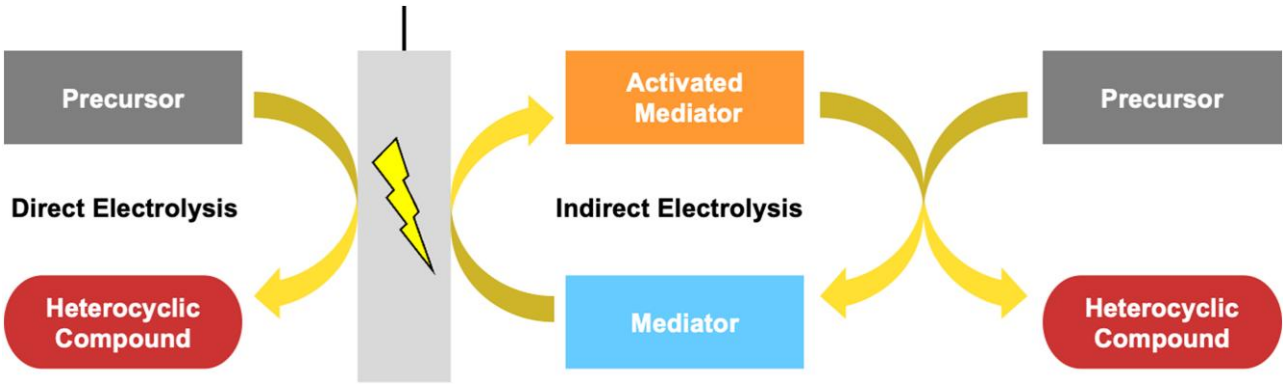
Graphical Abstract



1. Introduction

Heterocyclic compounds are significant frameworks in the field of pharmaceuticals[1–3] and material sciences.[4,5] Although many methods for the construction of heterocyclic rings have been reported, these methods often require stoichiometric amounts of chemical oxidants/reductants and harsh conditions. Therefore, the development of environmentally friendly methods for synthesizing heterocyclic compounds has been studied intensively.

Meanwhile, electrochemical organic synthesis has received considerable attention as a green method.[6]

Electrochemical synthesis can be classified as direct or indirect electrolysis. Taking anodic oxidation as an example, these two methods are depicted (Fig. 1). In direct electrolysis, the substrate is oxidized or reduced directly on an electrode. Thus, generated highly reactive intermediates give the product. In indirect electrolysis, the substrate is oxidized or reduced indirectly by redox active species generated by oxidation or reduction on an electrode. Electrochemical mediators such as halogen,[7,8] organic compounds,[9,10] and transition metals[11,12] are usually used for the indirect electrolysis. The oxidation or reduction of mediators forms active intermediates, which oxidize or reduce the substrates chemoselectively to afford the products.

Both direct and indirect electrolysis are useful and environmentally friendly methods for constructing heterocycles through carbon–heteroatom bond formation.[13–16] In this highlight review, we focus on representative reports on the electrochemical synthesis of heterocyclic compounds via carbon–heteroatom bond formation, which can be categorized as direct or indirect electrolysis.

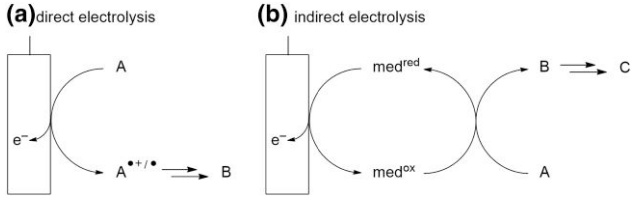


Fig. 1. a) Direct and b) indirect electrolysis (anodic oxidation).

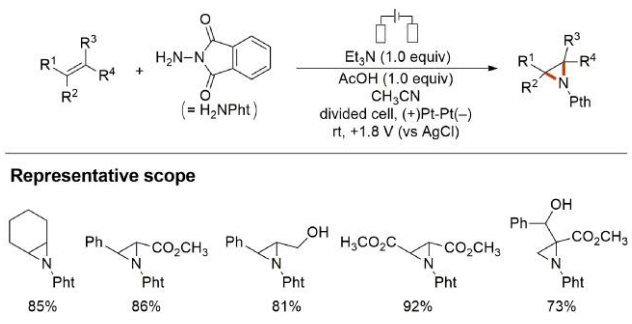
2. Synthesis of heterocyclic compounds via direct electrolysis

2.1 C–N bond formation via direct electrolysis

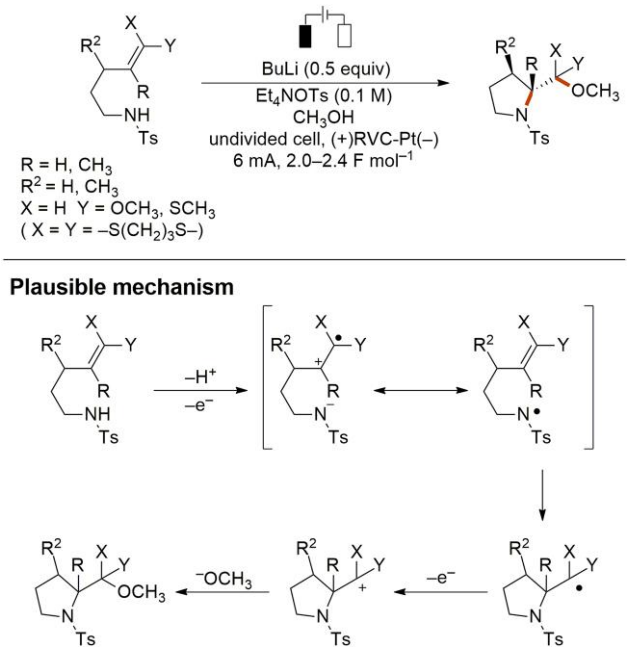
Aminyl and amidyl radicals, generated by the anodic oxidation of amines and amides, are often used as key intermediates in the synthesis of *N*-heterocyclic compounds. Yudin and Siu[17] reported the electrochemical aziridination of olefins and *N*-aminophthalimide (Scheme 1). Under constant-potential electrolysis at +1.8 V (vs AgCl), the *N*-aminophthalimide was oxidized selectively and behaved like a nitrene to produce aziridines. Remarkably, both electron-rich and electron-deficient olefins could be used in the reaction.

In 2008, Moeller synthesized pyrrolidine derivatives by the oxidative coupling of electron-rich olefins, such as enol esters, thioenol esters, and dithioketene acetals (Scheme 2).[18] The speculated mechanism is illustrated in Scheme 2. First, the anodic oxidation of olefin with sulfonamide would generate an olefin radical cation or sulfonamidyl radical. Subsequent intermolecular cyclization of these reactive species forms a carbon-centered radical, which is then oxidized to form a cation. Finally, the cation is trapped by methoxide to afford the pyrrolidine derivative.

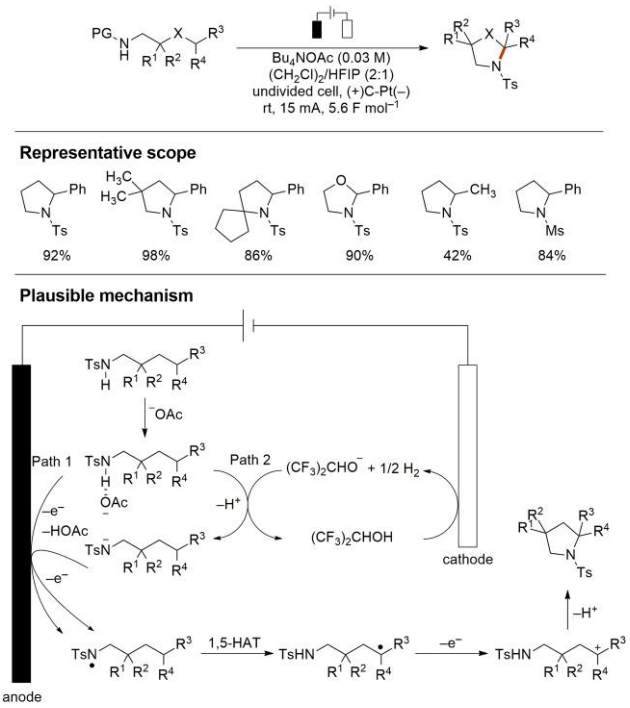
In 2018, Lei and et al.[19] reported an electrochemical oxidative intramolecular C(sp^3)–H amination of amides to give various functionalized nitrogen-containing five-membered heterocycles (Scheme 3). The use of Bu_4NOAc was essential for this reaction



Scheme 1. Electrochemical aziridination of olefins and *N*-aminophthalimide.

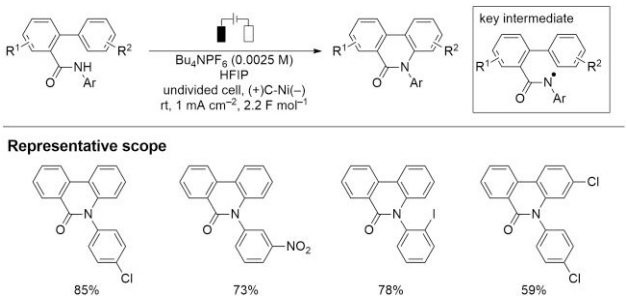


Scheme 2. Electrochemical synthesis of pyrrolidine derivatives.

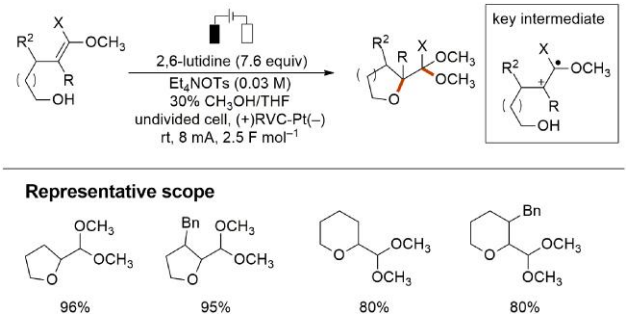


Scheme 3. Electrochemical oxidative intramolecular C(sp^3)–H amination of amides.

system since it acted not only as an electrolyte but also as a base. They proposed that the process starts with the formation of an intermolecular hydrogen-bonding complex between sulfonamide and acetate. Anodic oxidation leads to the generation of amidyl radical (Path 1). Subsequently, intramolecular 1,5-hydrogen atom transfer (1,5-HAT) of the δ C–H bond by the amidyl radical species gives a carbon-centered radical. Further oxidation of the radical forms a cationic intermediate. Next, nucleophilic attack of amide and deprotonation afford the product.



Scheme 4. Electrochemical synthesis of 5-aryl-phenanthridin-6-ones.



Scheme 5. Electrochemical synthesis of tetrahydrofurans and tetrahydropyrans.

On the cathode, the reduction of 1,1,1,3,3,3-hexafluoropropan-2-ol (HFIP) would occur to form an alkoxide and H_2 gas. The generated alkoxide would deprotonate the substrate to form *N*-anion, which would be easily oxidized to generate the amidyl radical (Path 2). In the same year, Muñiz and et al.[20] also reported an anodic benzylic C(sp^3)–H amination of amides.

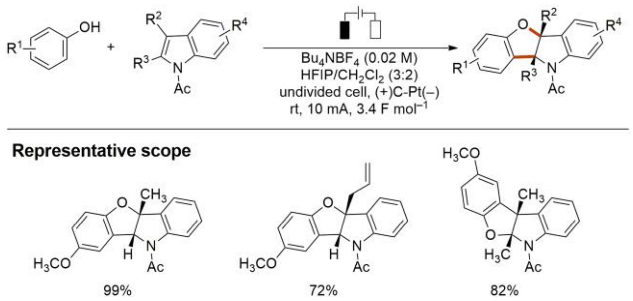
Waldvogel et al.[21] synthesized 5-aryl-phenanthridin-6-ones by direct anodic oxidation (Scheme 4). The desired products could easily be accessed by the generation of amidyl radicals that were formed by the electrooxidation of 2-biphenyl *N*-aryl amides.

2.2 C–O bond formation via direct electrolysis

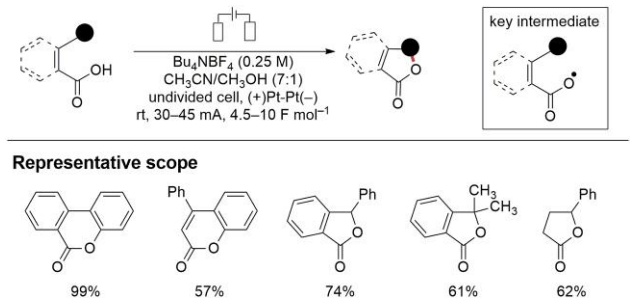
Direct oxidation is also an efficient method for constructing oxygen-containing heterocycles. In 2000, Moeller et al.[22] reported the electrochemical formation of tetrahydrofuran and tetrahydropyran rings (Scheme 5). Enol ethers would be oxidized on the anode to give radical cations, which would be trapped by the intramolecular hydroxy group. Further oxidation would give a cationic intermediate, and the addition of a solvent-derived methoxide would yield tetrahydrofurans or tetrahydropyrans.

A variety of electrooxidative reactions using phenol derivatives have been reported to construct heterocycles.[23–25] In 2017, Lei and et al.[26] developed an electrooxidative [3 + 2] annulation reaction between phenol derivatives and *N*-acetylindoles (Scheme 6). Benzofuro[3,2-*b*]indolines or benzofuro[2,3-*b*]indolines could be selectively obtained by introducing substituents at the C-3 or C-2 positions of *N*-acetylindoles. This reaction would proceed via a direct cross-coupling reaction between a phenol-based radical and a radical cation of *N*-acetylindole.

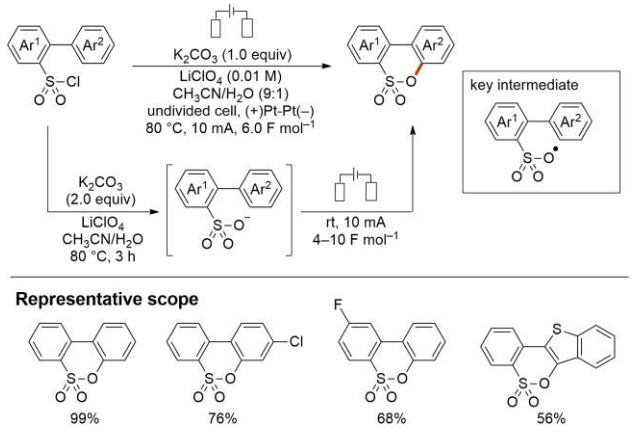
In general, carboxyl radicals generated by oxidizing carboxylates are known to be intermediates for Kolbe electrolysis.[27]



Scheme 6. Electrooxidative [3 + 2] annulation reaction between phenol derivatives and *N*-acetylindoles.



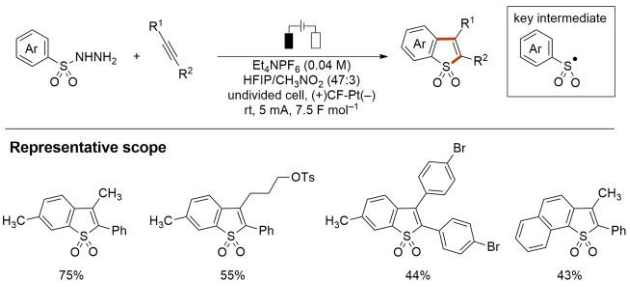
Scheme 7. Direct dehydrogenative lactonization via C(sp^2/sp^3)–O bond formation.



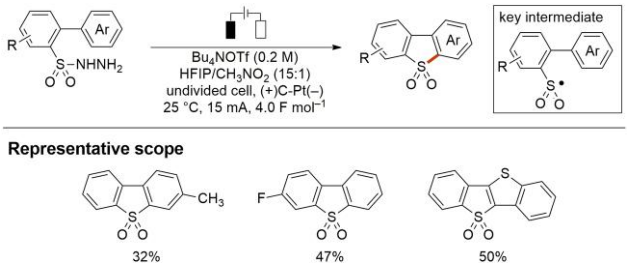
Scheme 8. Electrochemical synthesis of sultone derivatives.

Recently, carboxyl radicals have been applied to intramolecular cyclization reactions. In 2018, Zhang et al.[28] achieved direct dehydrogenative lactonization via C(sp^2/sp^3)–O bond formation (Scheme 7). Electro-generated carboxyl radicals are the key intermediates. When C(sp^2)–H/O–H coupling is carried out, 6-*endo-trig* radical cyclization and subsequent reactions give diaryl-fused lactones or coumarine derivatives. For C(sp^3)–O bond formation, 1,5-HAT occurs to form a benzyl radical by the carboxyl radical. Subsequent oxidation and a nucleophilic attack of carboxylate afford five-membered lactones. In the same year, Luo,[29] Xu,[30] and Lei[31] also reported an electrochemical synthesis of diaryl-fused lactones.

Sulfo radicals, the sulfur analogs of carboxyl radicals, could be applied to cyclization reactions. In 2023, our group reported the electrochemical synthesis of sultone derivatives via electrooxidative C–O bond formation (Scheme 8).[32]



Scheme 9. Electrochemical synthesis of benzo[*b*]thiophene dioxide with sulfonyl hydrazides and internal alkynes.



Scheme 10. Electrochemical synthesis of dibenzothiophene dioxide from biaryl sulfonyl hydrazides.

Hydrolysis of sulfonyl chlorides and electrolysis in the presence of K_2CO_3 offered a variety of sultone derivatives.

2.3 C–S bond formation via direct electrolysis

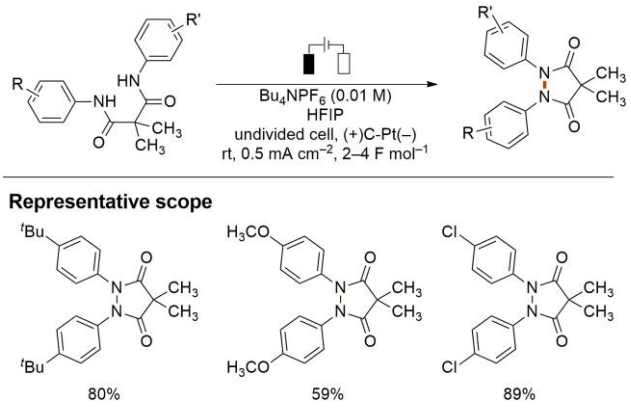
Sulfur-centered radical species, such as a thiyl radical and a sulfonyl radical, are easily generated by direct electrooxidation of their precursors. They have been used to functionalize sulfur-containing groups and to carry out radical cascade cyclizations.[33,34] In 2022, Zhang et al.[35] reported an electrochemical synthesis of benzo[*b*]thiophene dioxides via the formation of C–S and C–C bonds with sulfonyl hydrazides and internal alkynes (Scheme 9). Electrooxidation of sulfonyl hydrazides generates sulfonyl radicals via dehydrogenation and a denitrogenation. Sulfonyl radical reacts with internal alkynes to form alkenyl radicals. Subsequent intramolecular cyclization affords benzo[*b*]thiophene dioxides.

In 2023, we developed an electrochemical synthesis of dibenzothiophene dioxide via the generation of a sulfonyl radical from biaryl sulfonyl hydrazides (Scheme 10).[36]

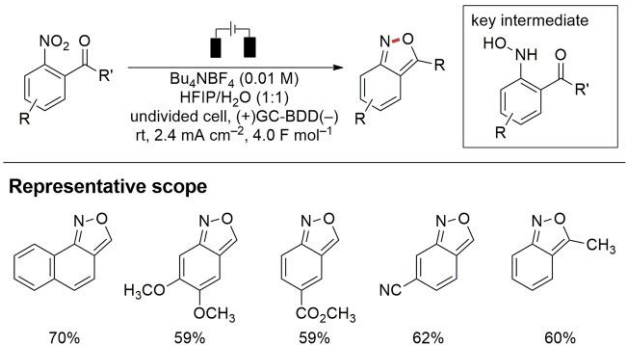
2.4 Heteroatom–heteroatom bond formation via direct electrolysis

Direct anodic oxidation is an efficient method not only for carbon–heteroatom bond formation but also for heteroatom–heteroatom bond formation. Waldvogel et al.[37] reported an electrochemical synthesis of pyrazolidin-3,5-diones via N–N bond formation (Scheme 11). Anodic oxidation of substituted 2,2-dimethylmalonic dianilides in HFIP afforded a variety of desired products. This reaction would proceed via the generation of an amidyl radical.

A few methods have been reported for the synthesis of heterocyclic compounds via bond formation with a heteroatom by electroreduction. In 2019, Waldvogel et al.[38] reported the synthesis of 2,1-benzisoxazoles via N–O bond formation



Scheme 11. Electrochemical synthesis of pyrazolidin-3,5-diones via N–N bond formation.



Scheme 12. Electroreductive synthesis of pyrazolidin-3,5-diones via N–O bond formation.

(Scheme 12). Four-electron reduction of nitroarenes gave hydroxylamines via the generation of nitrosoarenes, and subsequent intramolecular reactions afforded the desired products in moderate yields. By applying this strategy, which is an electroreduction of nitroarenes, their group has reported several syntheses of heterocyclic compounds.[39,40]

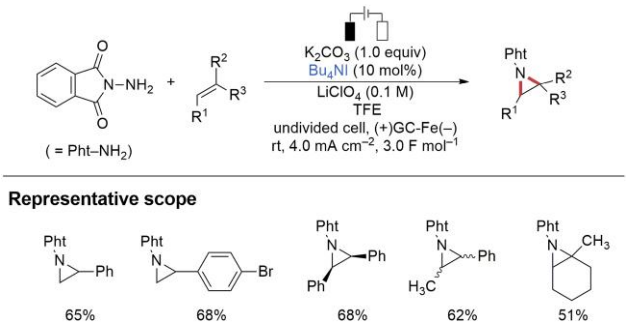
3. Synthesis of heterocyclic compounds via indirect electrolysis

3.1 Synthesis of heterocyclic compounds using halogen mediators

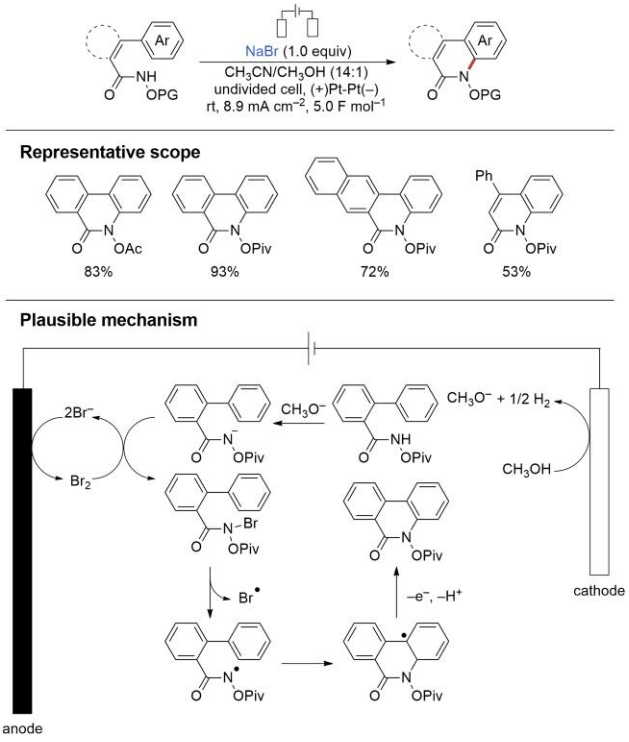
3.1.1 C–N bond formation using halogen mediators. Indirect electrolysis using halogen mediators, such as bromides and iodides, is also an efficient method for constructing heterocycles. Electrochemical oxidation of halides offers a reactive cationic species, which are used in a variety of chemical reactions.[8]

In 2015, Little et al.[41] reported the efficient electrocatalytic aziridination of alkenes with Bu_4NI (Scheme 13). Compared with Yudin's work, the use of iodide enables an easy procedure that uses an undivided cell in constant-current electrolysis. This aziridination is proposed via a radical mechanism that includes an iodine radical and an amidyl radical.

In 2018, Zeng et al.[42] reported the electrochemical synthesis of lactams using NaBr as a mediator (Scheme 14). A key reagent of this reaction system was not only NaBr but also methanol. The proposed mechanism is shown in Scheme 14.



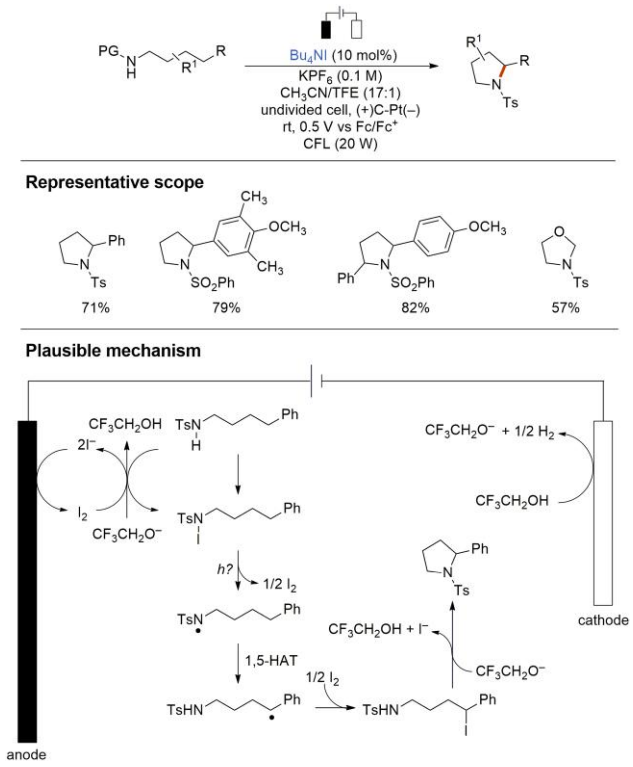
Scheme 13. Electrocatalytic aziridination with iodide as the mediator.



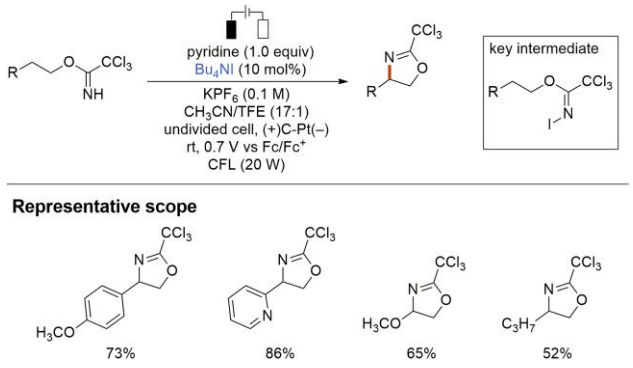
Scheme 14. Electrochemical synthesis of lactams using NaBr as a mediator.

On the cathode, reduction of methanol occurs to generate methoxide, which deprotonates the amide. On the anode, bromide is oxidized to form bromine. The deprotonated substrate reacts with bromine to afford an intermediate bearing a N–Br bond. Next, homolytic cleavage of the N–Br bond gives *N*-acetoxyl amidyl radical. Subsequent radical cyclization and rearomatization yields the lactam.

In 2019, Stahl and Wang[43] reported the electrochemical synthesis of pyrrolidine derivatives using Bu_4NI as a mediator with photoirradiation (Scheme 15). The presence of both Bu_4NI and photoirradiation was essential for this reaction, and a pyrrolidine was not obtained in the absence of Bu_4NI. The plausible mechanism is illustrated in Scheme 15. On the anode, iodide is oxidized to form I_2. I_2 reacts with the substrate in the presence of an electro-generated base to give the reactive intermediate bearing a N–I bond. Photolysis contributes to homolysis of the N–I bond to form an amidyl radical, which undergoes 1,5-HAT to afford a carbon-centered radical. Subsequent trapping of the radical with I_2 gives alkyl



Scheme 15. Electrochemical synthesis of pyrrolidine derivatives using Bu_4NI as an electrochemical mediator.



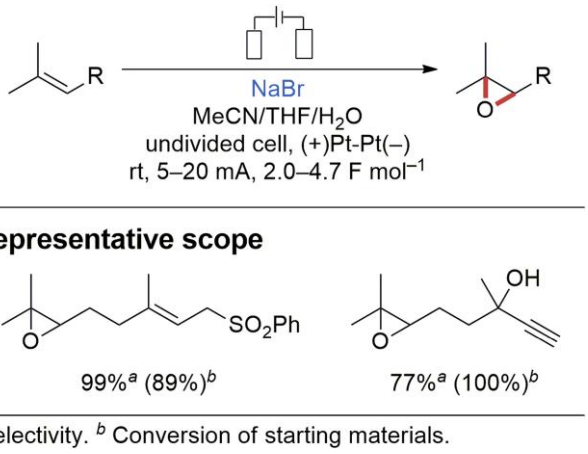
Scheme 16. Electrochemical synthesis of oxazoline derivatives using Bu_4NI as an electrochemical mediator.

iodide. Next, an electro-generated base promotes nucleophilic substitution to yield a pyrrolidine. With the same photoelectrochemical protocol, they achieved the synthesis of oxazoline derivatives from imidate substrates via cleavage of the electro-generated N–I bond (Scheme 16).

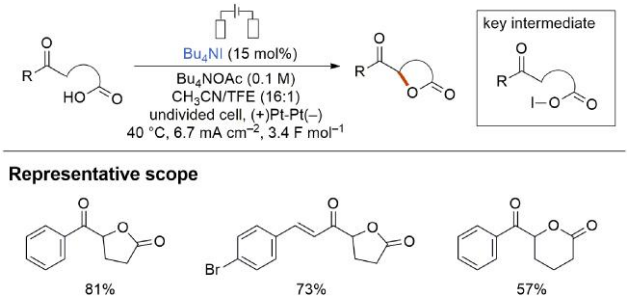
3.1.2 C–O bond formation using halogen mediators.

Indirect electrolysis using halides can be applied to the construction of O-heterocycles. In 1979, Torii et al.[44] reported that olefin epoxidation by NaBr promoted electrochemical oxidation (Scheme 17). In a MeCN/THF/H_2O mixed solvent, bromide would be oxidized to form [Br^+].[45] Next, [Br^+] would react with several olefins to yield epoxides in high selectivity.

In 2017, Xu et al.[46] reported the electrochemical lactonization with Bu_4NI as a mediator (Scheme 18). On the anode, electrooxidation of iodide would occur to give an iodine. The iodine would react with in situ-generated carboxylate to



Scheme 17. Olefin epoxidation by NaBr-promoted electrochemical oxidation.



Scheme 18. Electrochemical lactonization with Bu_4NI as the mediator.

form a key intermediate bearing an O–I bond. Next, homolytic cleavage of the O–I bond would afford the carboxyl radical, and subsequent reactions would yield lactams. Kolbe decarboxylation did not occur in this reaction system.

3.1.3 C–S bond formation using halogen mediators.

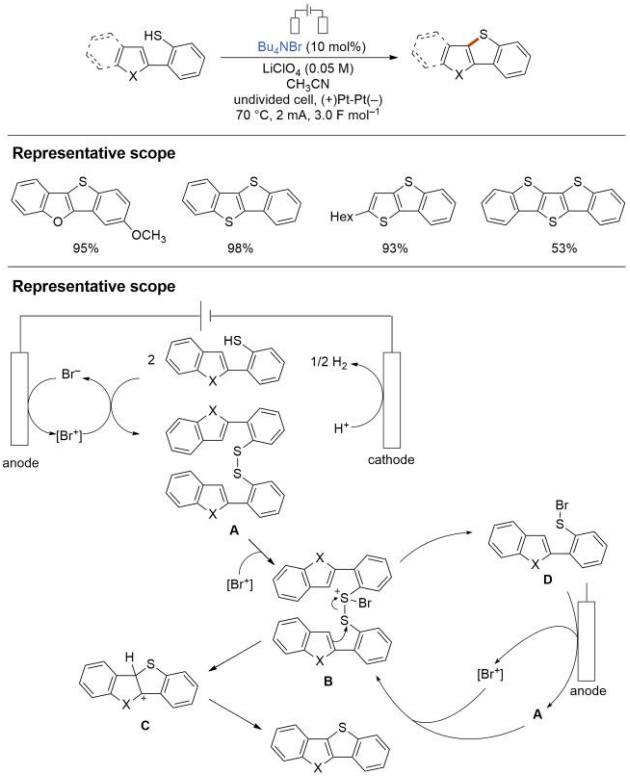
Indirect electrolysis using halogen mediators is one of the most powerful methods for forming a C–S bond. In 2020, our group reported the electrochemical synthesis of thienoacene derivatives by a dehydrogenative C–H/S–H coupling reaction with Bu_4NBr as a mediator (Scheme 19).[47] The desired product was not obtained without the use of Bu_4NBr. Therefore, Bu_4NBr was essential in this reaction. A plausible mechanism is illustrated in Scheme 19. First, Br^- would be oxidized to afford [Br^+], which would react with a thiol to give a disulfide **A**. **A** would be oxidized by [Br^+] to form cationic intermediate **B** bearing a S–Br bond. Subsequent intermolecular cyclization would give the intermediate **C** and arylthiobromide **D**. Deprotonation of **C** would yield the desired product. **D** would be oxidized to give disulfide **A**.

With a similar strategy, we developed an electrochemical synthesis of dibenzothiophene derivatives from bis(biaryl) disulfide (Scheme 20).[48] Without Bu_4NBr, this desired reaction did not proceed at all. Under the electrochemical conditions with Bu_4NBr, several dibenzothiophene derivatives, in particular electron-rich ones, were obtained efficiently.

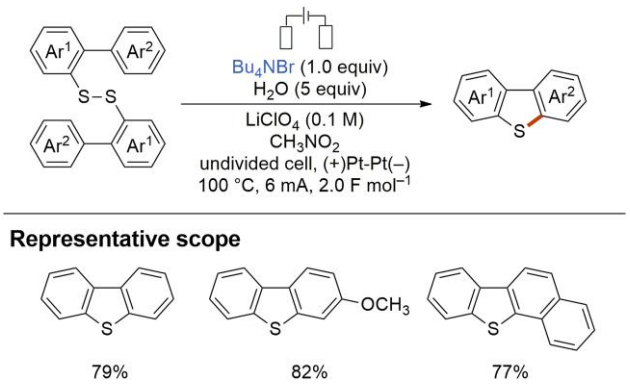
3.2 Synthesis of heterocyclic compounds using organic mediators

3.2.1 C–N bond formation using organic mediators.

Recently, there have been rapid developments in the synthesis

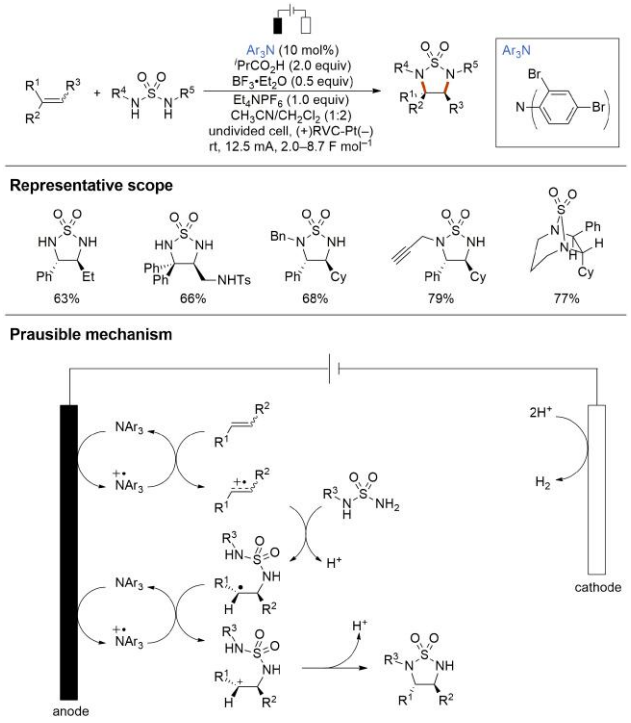


Scheme 19. Electrochemical synthesis of thienoacene derivatives by a dehydrogenative C–H/S–H coupling reaction with Bu_4NBr as a mediator.

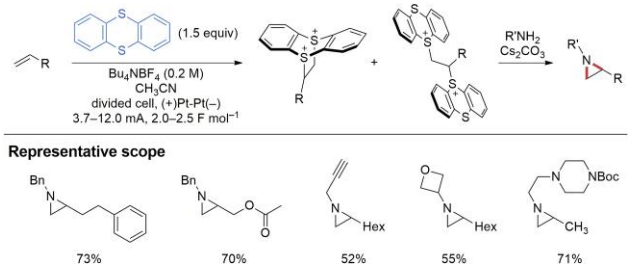


Scheme 20. Electrochemical synthesis of dibenzothiophene derivatives from bis(biaryl) disulfides.

of heterocyclic compounds using organic mediators by electrochemical techniques. In 2019, Xu et al.[49] reported a diastereoselective electrocatalytic 1,2-diamination reaction of di- and tri-substituted alkenes by forming sulfamides using tris(2,4-dibromophenyl)amine as an organic mediator (Scheme 21). Although the desired reaction proceeded without the organic mediator, the reactions proceeded more efficiently with the mediator since side reactions were prevented. A catalytic current was observed in the cyclic voltammogram with an alkene and the mediator. This suggests that single electron transfer (SET) occurred between alkenes and the mediator. The proposed mechanism is illustrated in Scheme 21. Triarylamine is oxidized to form a stable triarylamine radical cation. SET occurs between the radical cation and an alkene, forming an alkene radical cation intermediate with regeneration of the



Scheme 21. Diastereoselective electrocatalytic 1,2-diamination reaction of di- and tri-substituted alkenes.



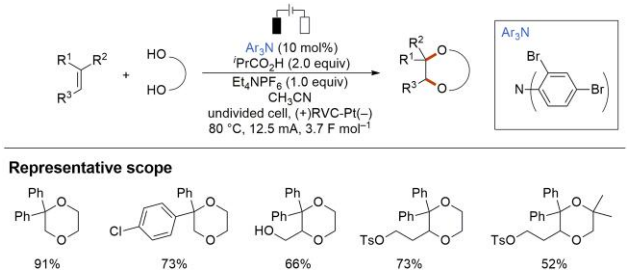
Scheme 22. Aziridination by coupling amines and alkenes via an electro-generated dication.

triarylamine. This intermediate is trapped by a sulfamide to afford a carbon radical. Subsequently, oxidation of the radical on the anode or SET between it and the triaryl amine radical cation occurs to give a carbocation. Next, the carbocation undergoes intramolecular cyclization to yield cyclic sulfamide.

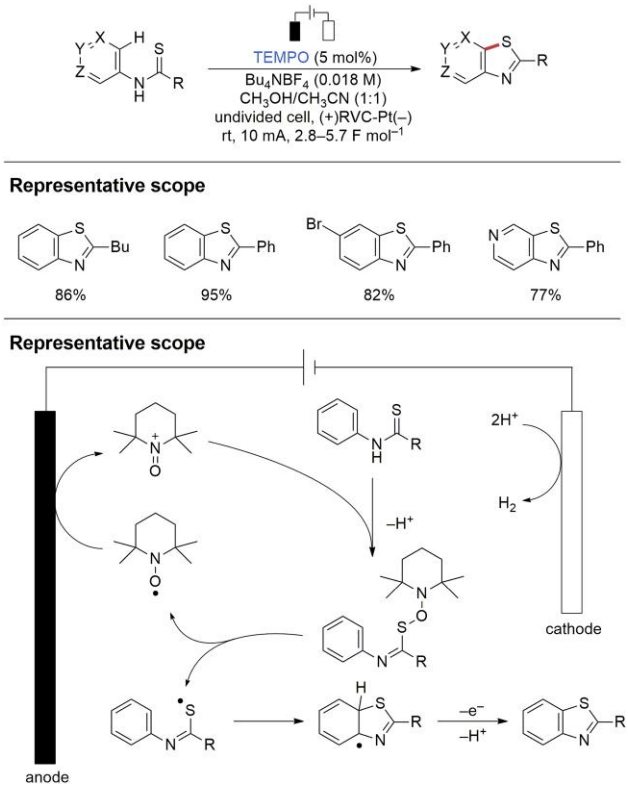
In 2021, Wickens et al.[50] reported aziridination by coupling amines and alkenes via an electro-generated dication with a thianthrene as the dication source (Scheme 22). First, anodic oxidation of thianthrene affords thianthrene radical cation, which reacts with an alkene to form a mono- or bis-adducted dication. These electro-generated dications are pooled until full conversion and then undergo an efficient reaction with amines to give a variety of aziridines.

3.2.2 C–O bond formation using organic mediators.

Indirect electrolysis using organic mediators is also helpful for the synthesis of *O*-heterocyclic compounds. In 2018, Xu and Cai[51] reported the electrochemical annulation of alkenes with diols using triarylamine as a mediator (Scheme 23). SET occurs between alkenes and triarylamine radical cation,



Scheme 23. Electrochemical annulation of alkenes with diols using triarylamine.

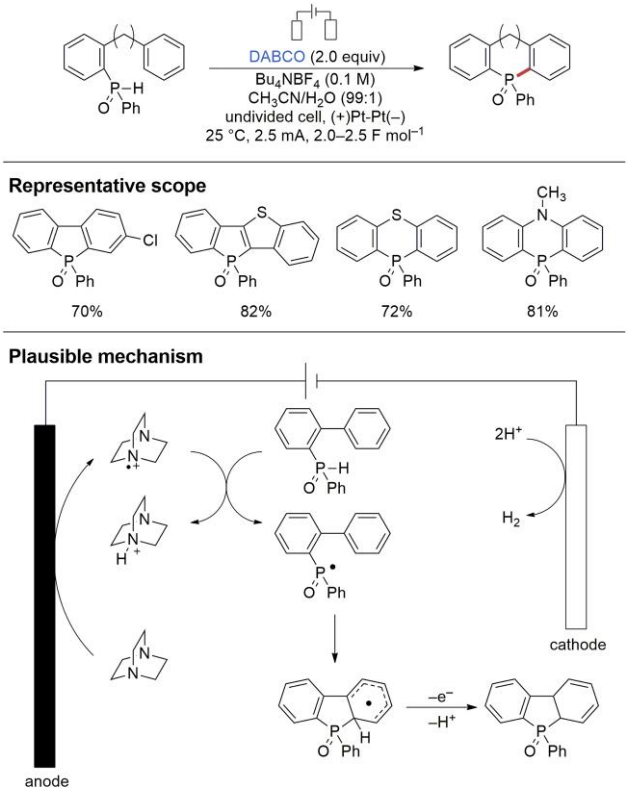


Scheme 24. Electrochemical synthesis of benzothiazoles and thiazolopyridines with TEMPO.

which is formed by the oxidation of triarylamine to form alkene radical cations. Diols trap these radicals to afford functionalized 1,4-dioxanes and 1,4-dioxepanes with diverse substitution patterns.

3.2.3 C–S bond formation using organic mediators.

Indirect electrolysis using organic mediators can be applied to the construction of *S*-heterocycles. In 2017, Xu et al.[52] reported the electrochemical synthesis of benzothiazoles and thiazolopyridines from thioamides with 2,2,6,6-tetramethylpiperidine-*N*-oxyl radical (TEMPO) as an organic mediator (Scheme 24). TEMPO is oxidized on the anode to give $TEMPO^+$, which reacts with thioamide to form TEMPO-adduct intermediate bearing a S–O bond. Subsequently, the weak S–O bond (bond dissociation energy [BDE] = 12.5 kcal mol^{-1}) of the intermediate undergoes homolytic cleavage to give thioamidyl radical and regenerate TEMPO. Intramolecular cyclization of thioamidyl radical and rearomatization afford the desired product. In 2018, Xu et al.[53] applied the method for synthesizing benzothiazoles and thiazolopyridines in continuous flow.



Scheme 25. Electrosynthesis of phosphacycles using DABCO.

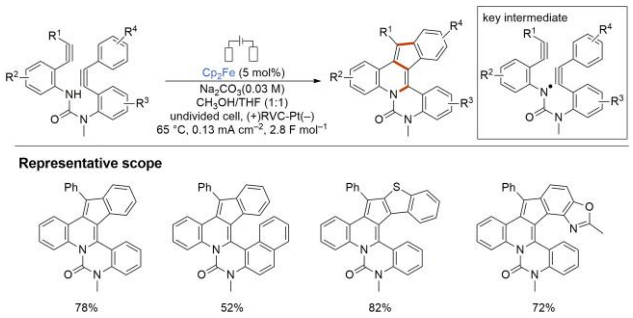
3.2.4 C–P bond formation using organic mediators.

Indirect electrolysis using organic mediators is one of the most powerful ways to form a C–P bond. In 2021, our group reported the electrosynthesis of phosphacycles via dehydrogenative C–P bond formation using 1,4-diazabicyclo[2,2,2]octane (DABCO) as a mediator (Scheme 25).[54] The use of DABCO as a HAT mediator was essential. The plausible mechanism is illustrated in Scheme 25. The oxidation of DABCO affords DABCO radical cation. HAT between DABCO radical cation and phosphine oxide occurs to form phosphinyl radical and $DABCOH^+$. Intramolecular cyclization of P-centered radical gives radical intermediate, which is oxidized and deprotonated to yield the desired product.

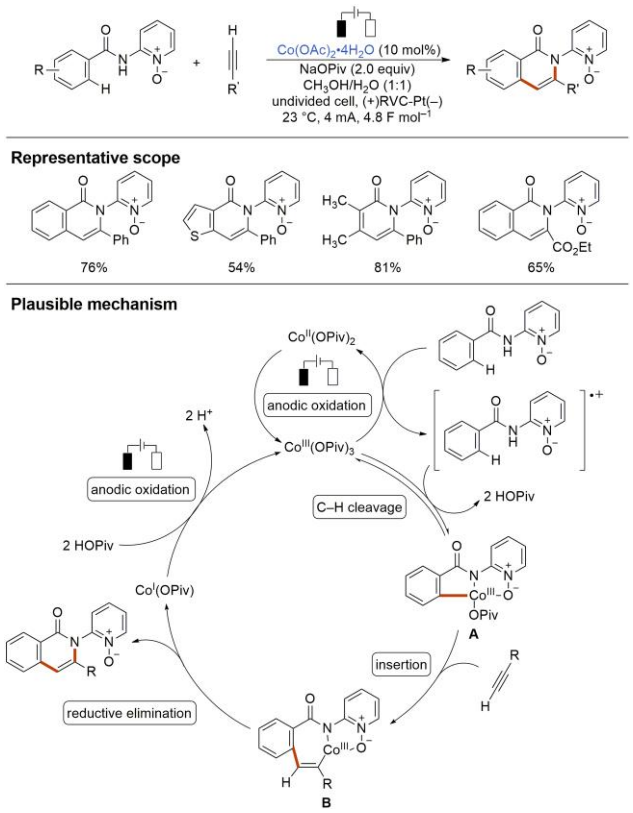
3.3 Synthesis of heterocyclic compounds using transition metal mediators

3.3.1 C–N bond formation using transition metal mediators.

Indirect electrolysis using transition metal mediators is one of the most efficient methods for synthesizing heterocyclic compounds, especially when two or more bonds form. In 2017, Xu et al. reported an electrochemical synthesis of polycyclic *N*-heteroaromatics with ferrocene as a mediator. The oxidation of ferrocene(II) on the anode affords ferrocene(III) (Scheme 26).[55] SET between ferrocene(III) and the amide anion gives the amidyl radical. Three subsequent radical cyclizations yield the desired compound. Only ferrocene is oxidized on the anode, preventing overoxidation of the target materials.

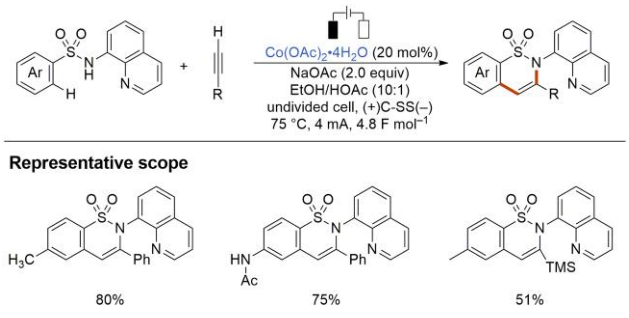


Scheme 26. Electrochemical synthesis of polycyclic *N*-heteroaromatics with ferrocene.

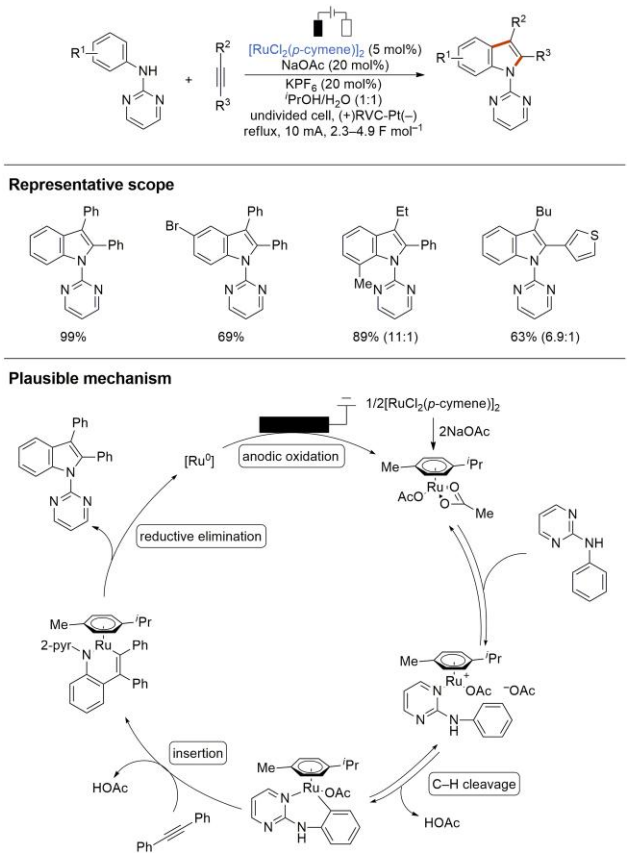


Scheme 27. Electrochemical synthesis of lactam derivatives by cobalt catalysis.

In electrosynthesis with transition metal mediators, anodic oxidation is often used to reoxidize transition metals. In 2018, Ackermann et al.[56] reported the electrochemical synthesis of lactam derivatives via C–H/N–H activation by water-tolerant cobalt catalysis (Scheme 27). This reaction did not proceed at all without the use of $Co(OAc)_2•4H_2O$. The substrate of substituted pyridine *N*-oxide was very important for the formation of the *N*,*O*-bidentate coordination mode for C–H/N–H activation. A plausible catalytic cycle is shown in Scheme 27. Cobalt(III) carboxylate is generated by an anodic oxidation of cobalt(II) carboxylate. Next, carboxylate-assisted C–H activation affords cobalt(III) cycle **A**, and migratory insertion of a terminal alkyne gives cobalt(III) cycle **B**. Either *β*-hydride elimination or reductive elimination yields lactam derivatives and cobalt(I) carboxylate. Finally, cobalt(I) carboxylate is oxidized to regenerate cobalt(III) carboxylate.



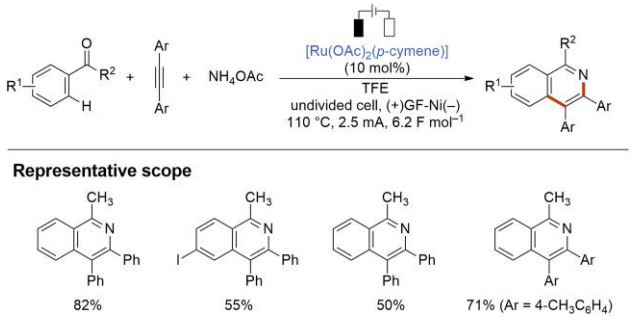
Scheme 28. Cobalt-catalyzed electrochemical annulation for the synthesis of sultams.



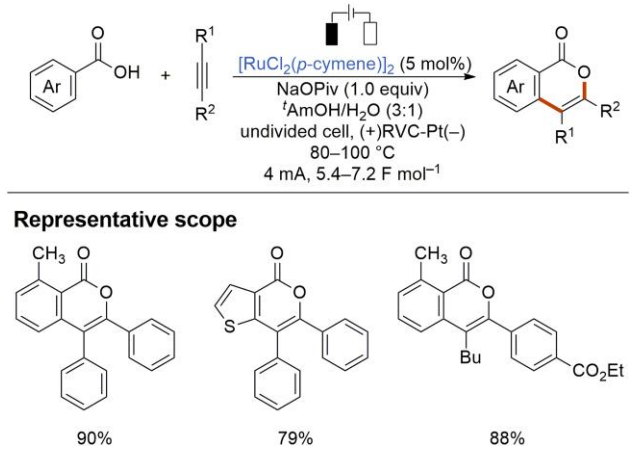
Scheme 29. Ruthenium-catalyzed electrochemical synthesis of indoles.

In 2020, Lei et al.[57] reported a cobalt-catalyzed electrochemical annulation to synthesize sultams (Scheme 28). Sultams were not obtained without the cobalt catalyst and electricity. Co(I) and Co(III) are generated under cobalt-catalyzed electrochemical conditions.

In 2018, Xu et al.[58] reported ruthenium-catalyzed electrochemical synthesis of indoles from aniline derivatives and internal alkynes (Scheme 29). In the presence of NaOAc, $[RuCl_2(p\text{-cymene})]_2$ is converted to ruthenium diacetate complex, which reacts with the *N*-2-pyrimidyl group of the substrate to form an *N*-coordinate complex. Reversible C–H activation of the complex occurs to give a six-membered ruthenacycle. Acetate ligand is displaced by an internal alkyne. Next, irreversible migratory insertion into the Ru–C bond



Scheme 30. Electrochemical synthesis of isoquinoline derivatives using [Ru(OAc)$_2$(*p*-cymene)] as a transition metal mediator.



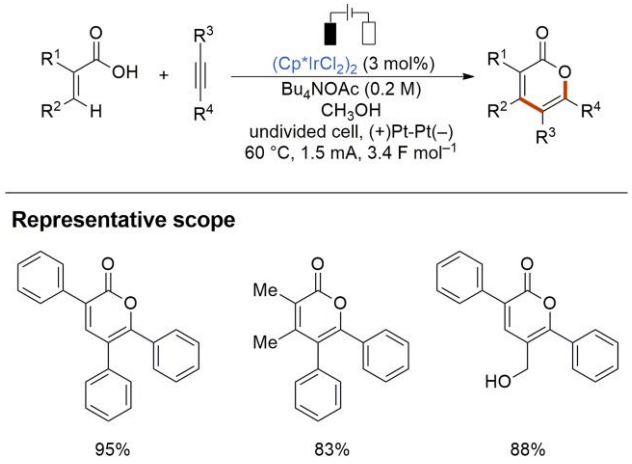
Scheme 31. Electrochemical synthesis of lactone derivatives using [RuCl$_2$(*p*-cymene)] as a mediator.

and reductive elimination afford indoles and Ru(0). Ru(0) is oxidized on the anode to regenerate Ru(II) complex.

In 2021, Ackermann et al.[59] reported the electrosynthesis of isoquinoline derivatives using [Ru(OAc)$_2$(*p*-cymene)] as a transition metal mediator (Scheme 30). Ruthenium-catalyzed electrooxidative three-component annulation of acetophenone derivatives, internal alkynes, and NH_4OAc afforded several isoquinoline derivatives. Experimental results and computational studies supported rapid C–H activation and a ruthenium(II/III) manifold.

3.3.2 C–O bond formation using transition metal mediators. Transition metal-catalyzed electrosynthesis can be used to construct *O*-heterocyclic compounds via C–O bond formation. In 2018, Ackermann et al.[60] reported an electrochemical synthesis of lactone derivatives using [RuCl$_2$(*p*-cymene)] as a mediator (Scheme 31). This report was the first electrocatalytic organometallic C–H activation with weak *O*-coordination by benzoic acids. This reaction would proceed via a ruthenium (0/II) catalytic cycle.

In 2019, Mei et al.[61] developed the iridium-catalyzed electrochemical synthesis of α-pyrones from vinyl carboxylic acids and internal alkynes via C–H/O–H functionalization (Scheme 32). Without electricity or Ir catalyst, the desired product was not obtained. Therefore, electricity and the Ir catalyst were essential in this reaction. Various kinds of α-pyrones were obtained under the reaction conditions.



Scheme 32. Electrochemical synthesis of α-pyrones from vinyl carboxylic acids and internal alkynes via C–H/O–H functionalization.

4. Conclusion

In this highlight review, we summarize representative electrochemical reactions to construct heterocyclic rings via carbon–heteroatom bond formation. Direct anodic oxidation not only generates olefin radical cation species but also gives heteroatom-centered radical species, which could be applied to cyclization reactions. Synthesis of heterocyclic compounds using halogen mediator can lead to the formation of a heteroatom (N, O, S)–halogen bond by electro-generated halogen species. Halogen mediators are also useful and gaining attention in the field of photoelectrocatalytic reactions. Organic mediators, such as triarylamine and thianthrene, enable novel electrochemical cyclization reactions. Transition metal-free mediated systems also have the advantage of being able to perform late-stage functionalization without the risk of contamination. Reaction systems using transition metals as mediators are effective for very challenging reactions such as intermolecular cyclization with alkynes by making good use of their characteristics. The electrochemical synthesis of heterocyclic compounds should become increasingly important as we strive to achieve a sustainable society.

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