



Electrochemical Construction of C–S Bond: A Green Approach for Preparing Sulfur-Containing Scaffolds

Ruonan Zou¹ Jingbo Yu² Ping Ying^{1*}

¹ College of Ecology, Lishui University, Lishui, People's Republic of China

² Key Laboratory for Green Pharmaceutical Technologies and Related Equipment of Ministry of Education and Key Laboratory of Pharmaceutical Engineering of Zhejiang Province, Collaborative Innovation Center of Yangtze River Delta Region Green Pharmaceuticals, Zhejiang University of Technology, Hangzhou, People's Republic of China

Address for correspondence Ping Ying, PhD, College of Ecology, Lishui University, 1 Xueyuan Road, Lishui 323000, People's Republic of China (e-mail: ping@lsu.edu.cn).

Pharmaceut Fronts 2024;6:e9–e19.

Abstract

The organosulfur frameworks containing C–S bonds are important structural motifs in various biologically active molecules and functional materials. In this regard, transition-metal catalysis using chemical oxidants to prime reactions has emerged as the most common method, however, is prone to several side reactions such as dimerization and overoxidation. In recent years, organic electrosynthesis has become a hot topic due to its eco-friendly and mild process in which costly catalysts and toxic oxidants could be replaced by electrons. This perspective summarized the recently developed C–S bond electrosynthesis protocols, discussing and highlighting reaction features, substrate scope, as well as its application in pharmaceuticals, and the underlying reaction mechanisms. The study helps the development of electrochemical process-enabled C–S bond construction reactions in the future.

Keywords

- ▶ electrochemical
- ▶ sulfur-containing compounds
- ▶ C–S bond

Introduction

Organosulfur compounds are considered extremely relevant building blocks in organic synthesis since it is found in a wide variety of natural products,^{1,2} pharmaceuticals,³ catalysts,⁴ as well as essential amino acids and peptides. Of note, Sulfur-containing compounds bearing C–S,⁵ N–S,⁶ and O–S bonds⁷ often show different biological activities and serve important functions in the pharmaceutical industry (▶ **Fig. 1**),⁸ including various valence states of S (II, IV, and VI), which can be sulfur-containing heterocycles, aromatic or nonaromatic. In this review, we focused on the green synthesis of the C–S bond.

Over the past decades, sustainable efforts have been devoted to the development of efficient methods for the

formation of C–S bonds.^{5,9} Transition metal-catalyzed cross-coupling reactions between aryl halides/triflates and thiols/thiolates are one of the most commonly used conventional pathways,^{10,11} however, prone to over-oxidation under traditional harsh chemical oxidation conditions.^{12–14} In addition, catalyst poisoning is inevitable, which leads to the deactivation of the metal catalyst.¹⁵

Organic electrosynthesis straightforwardly translates electrons as a “traceless” reagent in place of the generally used reactive oxidants/reductants to achieve the redox process, which has aroused much attention for its desirability to achieve sustainable synthesis.^{16–18} Fine control for oxidative abilities, which is one of the most important characterizations of electrosynthesis, provides a good option for C–S bond

received
July 29, 2023

accepted
January 30, 2024
article published online
March 11, 2024

DOI <https://doi.org/10.1055/s-0044-1780505>.
ISSN 2628-5088.

© 2024. The Author(s).

This is an open access article published by Thieme under the terms of the Creative Commons Attribution License, permitting unrestricted use, distribution, and reproduction so long as the original work is properly cited. (<https://creativecommons.org/licenses/by/4.0/>)
Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

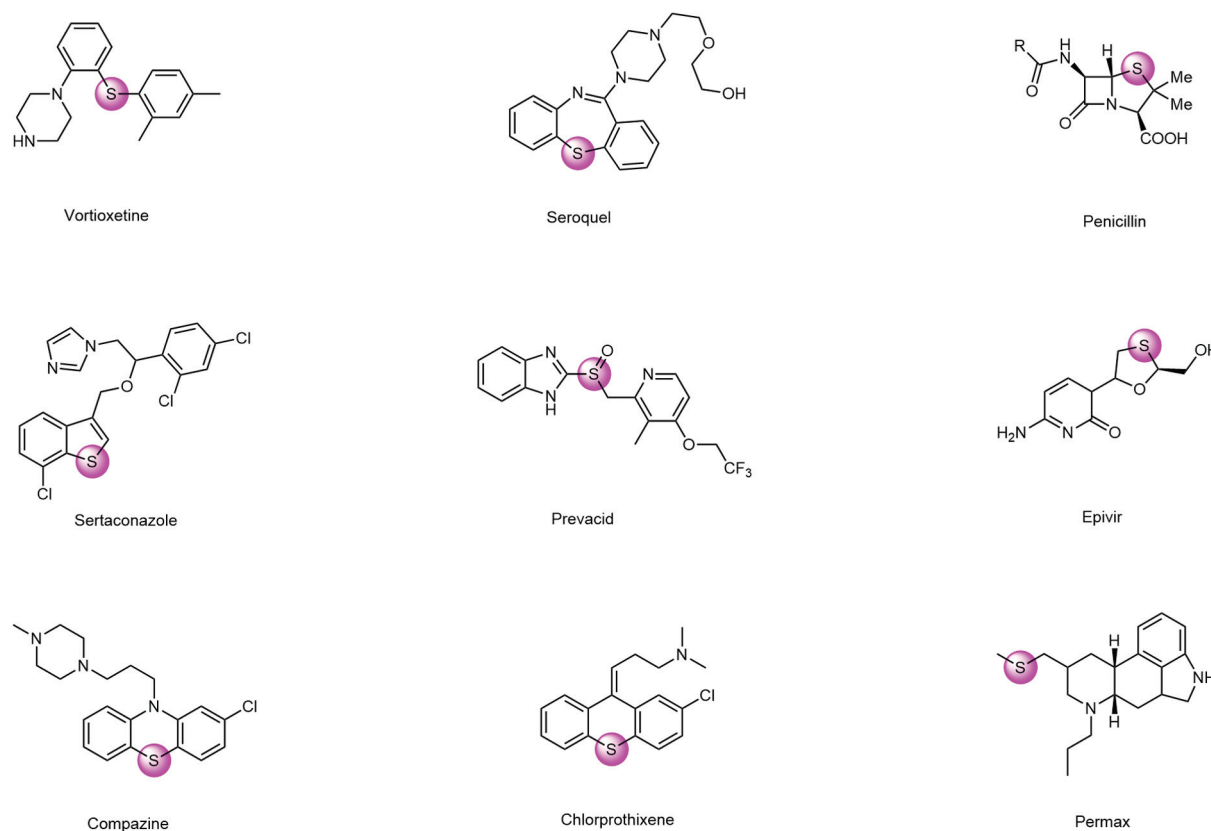
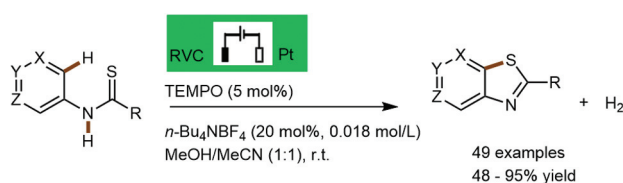


Fig. 1 Representative sulfur-containing scaffolds in natural products and pharmaceuticals.

establishment.¹⁹ The past decade has witnessed the development of electroynthesis of C–S bonds using a variety of substrates and sulfur surrogates under electrochemical conditions.^{20,21} Our research group has been actively working in the area of green and sustainable chemistry.^{22–24} In this perspective, herein, we reviewed the recent progress of electroynthesis of the C–S bond, emphasizing their basic scopes and limitations, applications in the construction of pharmaceutical molecules, and the plausible reaction mechanisms.

Electrosynthesis of C–S Bond

In 2017, Xu's group reported a metal- and reagent-free method via 2,2,6,6-tetramethylpiperidine-*N*-oxyl radical (TEMPO)-catalyzed electrolytic C–H thiolation, furnishing the benzothiazoles and thiazolopyridines in good yields (►Fig. 2).²⁵ This approach employs *n*-Bu₄NBF₄ in MeCN/MeOH (1:1) as an



X, Y, Z = C, N
R = alkyl (1°, 2°, 3°), aryl, alkenyl

Fig. 2 TEMPO-catalyzed electrolytic C–H thiolation. TEMPO, 2,2,6,6-tetramethylpiperidine-*N*-oxyl radical.

electrolyte solution, in an undivided cell with a reticulated vitreous carbon (RVC) anode and Pt plate cathode under a constant current of 10 mA. Various substituents on the *N*-aryl group are well tolerated under standard conditions. Notably, this reaction provides an efficient method to access the thiazolo[4,5-*c*]quinoline in three steps from commercially available 3-quinolinamine involving acylation, thiolation, and electrochemical cyclization, which is an intermediate for the preparation of CL075, a toll-like receptor (TRL8) agonist.²⁶ Mechanistic investigations revealed that the reaction of anode-generated TEMPO⁺ and a thioamidyl radical was involved.

Later in 2019, Mei and coworkers accomplished novel nickel-catalyzed electrochemical thiolation reactions of aryl bromides and chlorides in the absence of an external base under room temperature, using undivided electrochemical cells with a Ni foam electrode and a magnesium sheet as a sacrificial anode (►Fig. 3).²⁷ In Mei et al's work, a variety of aryl bromides and chlorides with diverse structures are successfully coupled with aryl thiols in high efficiency under constant-current electrolysis at 4.0 mA in the presence of 10 mol% NiBr₂·glyme and 4 equiv. of LiBr in *N,N*-dimethylformamide.

Oxidation of thiolates to thiyl radicals occurred on the Mg anode, as revealed by cyclic voltammetry (CV) experiment and confirmed by trapping the thiyl radical with TEMPO in 30% yield. The catalytic cycle of Ni could be accomplished through the cathodic reduction and aryl Ni(II) complex reductive elimination.

In 2018, Yuan et al revealed the difunctionalization of alkenes from the C–S and C–O/N bonds together (►Fig. 4).²⁸

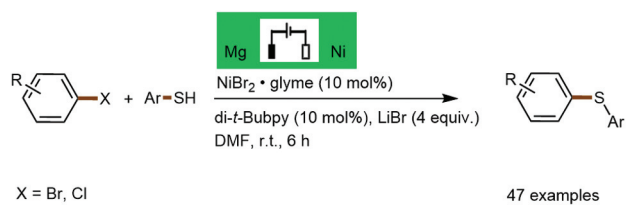


Fig. 3 Nickel-catalyzed formation of C–S bond through electrochemistry.

To overcome the inherent limitation of sensitivity to oxidants under traditional essential oxidation conditions, Yuan et al applied electrolysis to achieve the oxysulfenylation and aminosulfenylation of alkenes. Such a judicious strategy enables the simultaneous generation of C–S and C–N bonds, in an undivided cell using a two-electrode system with the graphite rod as the anode, the platinum plate as the cathode, the solution-containing *n*-Bu₄NBF₄ as the electrolyte, and CH₃CN as the solvent. Notably, this electrochemical oxidative synthetic strategy could also be applied to the hydroxysulfenylation and acyloxysulfenylation of alkenes.

In 2019, Yang et al reported the first electrochemical decarboxylative coupling reaction between cinnamic acids and NH₄SCN to provide vinyl thiocyanates in good yields.²⁹ The reaction was conducted in the presence of CH₃COONH₄ (3 equiv.) and NaHCO₃ (1 equiv.), under constant current at 5 mA in an undivided cell (►Fig. 5). It was worth noting that water was vital that no desired product was formed in the absence of water. Screening of solvent showed that mixed solvent CH₃CN/H₂O (7:1) gave the best result. While cinnamic acids bearing electron-donating or withdrawing groups were well tolerated, acrylic acid could not transform into the target products. A radical trapped experiment implied that the coupling reaction probably underwent a radical pathway and that the SCN radical intermediate might be involved in the transformation. The reaction failed to proceed when 2-methylstyrene was used instead of acrylic acid under the standard conditions, which suggested

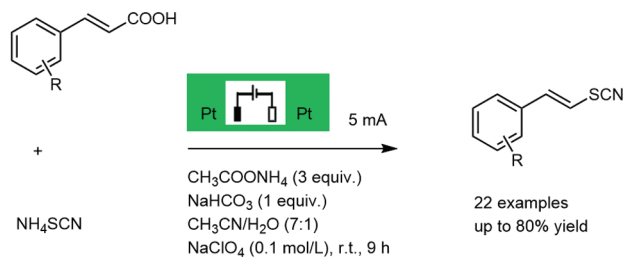


Fig. 5 Electrochemical decarboxylative coupling reactions.

2-methylstyrene was not the intermediate of this reaction. In addition, when the carboxyl group was replaced by ester, no desired product was formed, which indicated that the carboxyl group was necessary for the reaction. CV experiments showed that the oxidation of thiocyanate occurred preferentially during the reaction process, and bases could promote this reaction.

Later in 2021, Lei's group reported an unprecedented electrochemical oxidative one-carbon difunctionalization of isocyanides via the sequential addition of simple mercaptans and alcohols (►Fig. 6).³⁰ In a simple system consisting of a C (+)Pt(–) electrode, *n*-Bu₄NBF₄ electrolyte, MeCN solvent, and N₂ atmosphere under an undivided cell with 10 mA constant current at room temperature, a series of multisubstituted imine ethers were readily obtained under mild conditions, with S–C(sp²)–O bond formation. The mechanistic study showed that the sulfur radical was formed by single electron transfer (SET) oxidation of the thiophenol at the anode, which attacked the isocyanide to generate the imine radical. Further, SET of the imine radical gave the carbon cation to be captured by nucleophile MeOH and forge the desired product with hydrogen evolution. It is worth noting that the potential application of this strategy was demonstrated by the synthesis of pharmaceutical relevance moiety probenecid and ciprofibrate.

As the thiols/thiophenols (RSH) are prone to bind with transition metals and poison transition-metal catalysts which deeply hampered the development of direct C–S

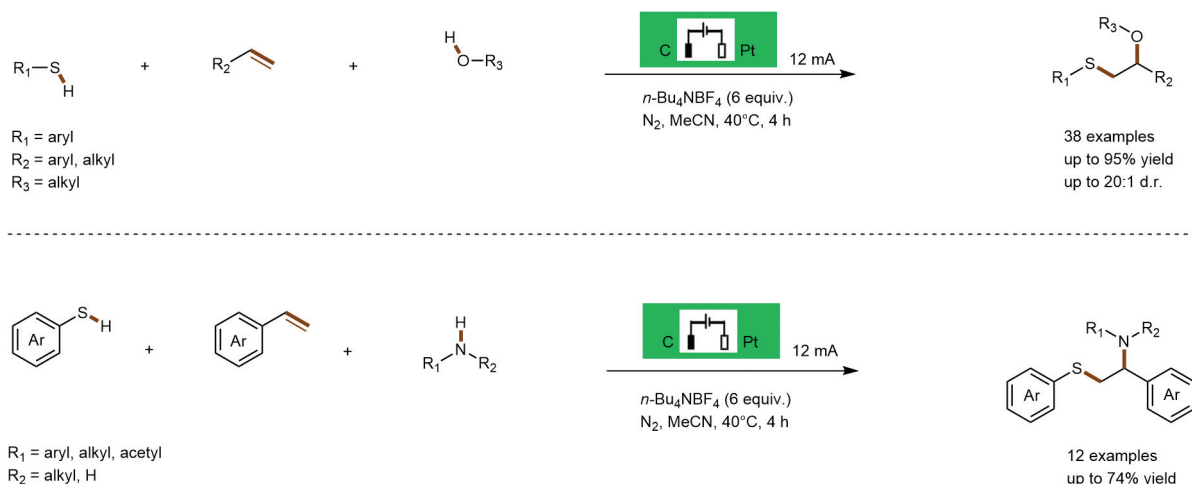


Fig. 4 Difunctionalization of alkenes by electrochemical formation of both C–S and C–O/N bonds.

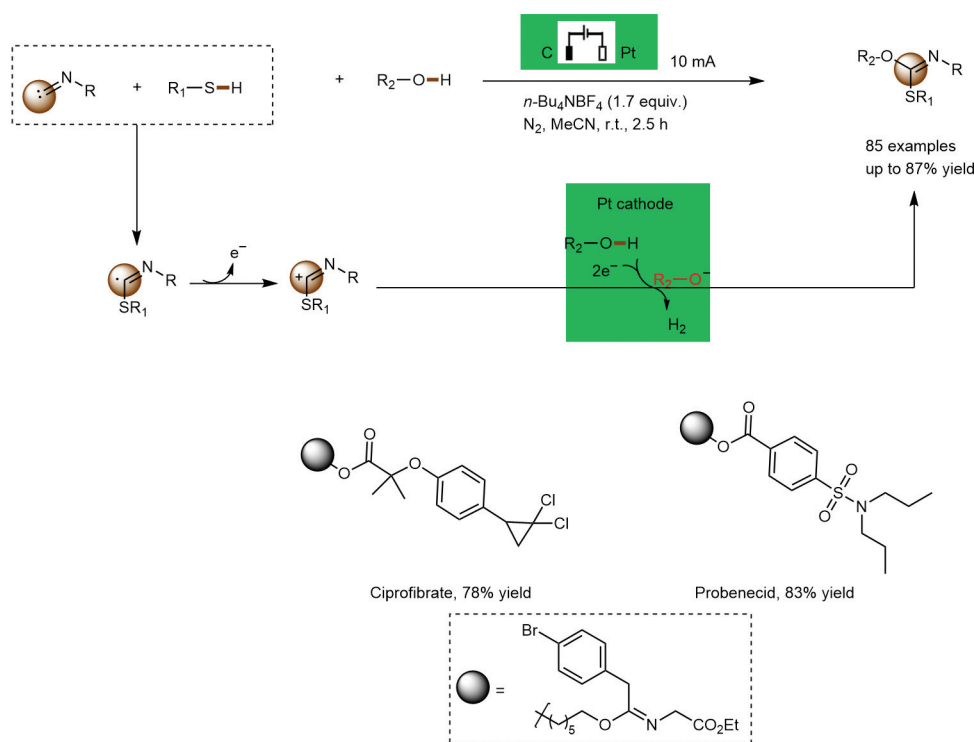


Fig. 6 Difunctionalization of isocyanides.

cross-coupling, Lei and coworkers disclosed a transition-metal catalyst and oxidant-free electrocatalytic protocol for dehydrogenative C–H/S–H cross-coupling (►Fig. 7).¹⁹ Under undivided electrolysis conditions, various aryl/heteroaryl thiols and electron-rich arenes afforded the desired products in moderate to high yield. A preliminary mechanistic study indicated that aryl radical cations are the key intermediates.

In the following year, the group achieved selective oxidative C–H sulfenylation of imidazopyridine heterocycles using hydrogen evolution as an undivided electrolytic cell (►Fig. 8).³¹ Neither transition metal catalysts nor external chemical oxidants were required to facilitate the C–S bond formation process. A broad substrate scope of thiols and imidazopyridines bearing various substituents is presented and shows good tolerance. Significantly, the scope of the thiols could be extended to aliphatic thiols. In addition, the

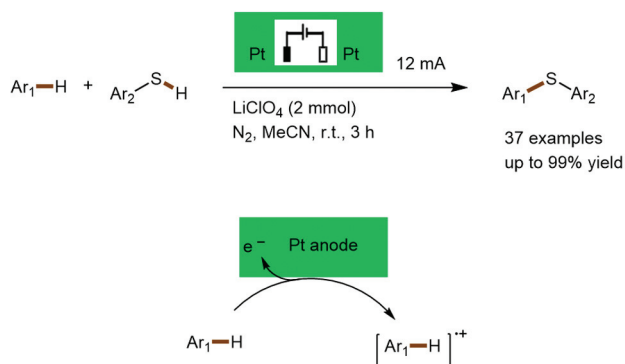


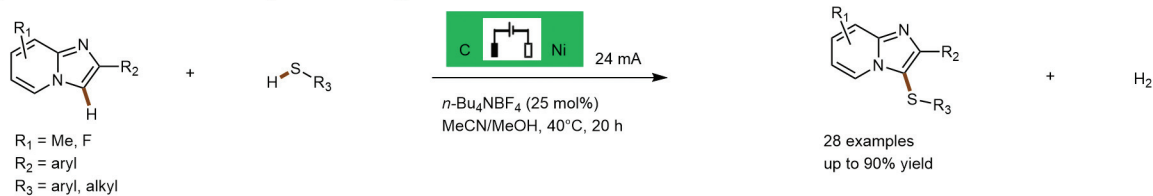
Fig. 7 Electrocatalytic oxidant-free dehydrogenative C–H/S–H cross-coupling.

scaled-up reactions in batches have also been successfully performed in 5 mmol. As disulfides were observed as side products in the reaction system, the control experiment was performed using disulfide as the starting material and the result confirmed the key intermediate role of disulfides.

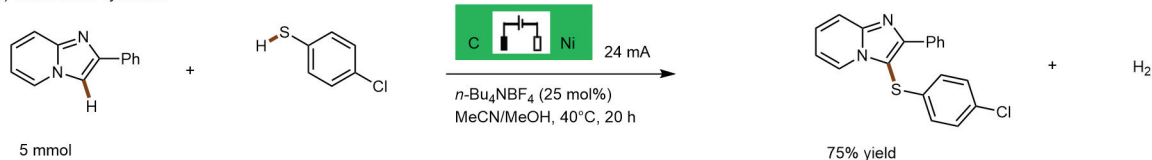
Mitsudo et al realized the metal-free dehydrogenative C–H/S–H coupling for the formation of π -expanded heteroacene derivatives (►Fig. 9).³² While only the homo-coupling product was formed without additive, the desired π -expanded cyclized products were formed in the presence of electro-generated $[\text{Br}^+]$ from $n\text{-Bu}_4\text{NBr}$. It is worth noting that the product distribution of cyclization and homo-coupling were strongly influenced by the amount of charge. Given that the amount of charge could be reduced by further stirring of the reaction mixture after electrolysis, a series of thienoacene derivatives are accommodated in good to excellent conversion yields under the standard condition of 15 minutes of additional stirring after electrolysis. Control experiments showed that the homo-coupling product is an important intermediate, CV experiments indicate that Br^- of $n\text{-Bu}_4\text{NBr}$ would be oxidized to afford $[\text{Br}^+]$, and 2-arylbenzene-1-thiol would be oxidized by $[\text{Br}^+]$ to give disulfide **D** and Br^- , which would be oxidized to $[\text{Br}^+]$ again on the anode. **D** would react with $[\text{Br}^+]$ to give the cationic species **A**. Subsequent intramolecular cyclization would give the cyclized product.

While arene activation has been well established toward the thiolation of aromatic C–H bonds over the past decades,^{33–39} Wu and coworkers disclosed a thiol activation strategy for the construction of C–S bond (►Fig. 10).⁴⁰ Mechanistic studies suggested that thiophenol was oxidized to the corresponding radical through SET on the anode. In this

a) Electrochemical oxidative C-H sulfenylation of imidazopyridines



b) Gram-scale synthesis



c) Oxidative C-H sulfenylation with disulfide

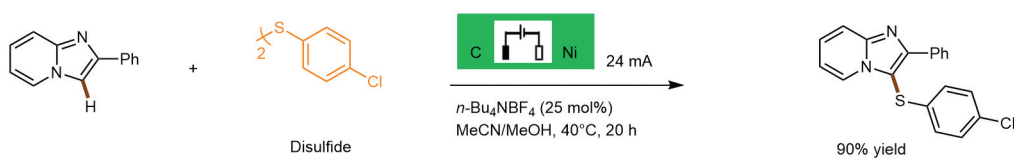


Fig. 8 Electrochemical oxidative C-H sulfenylation of imidazopyridines.

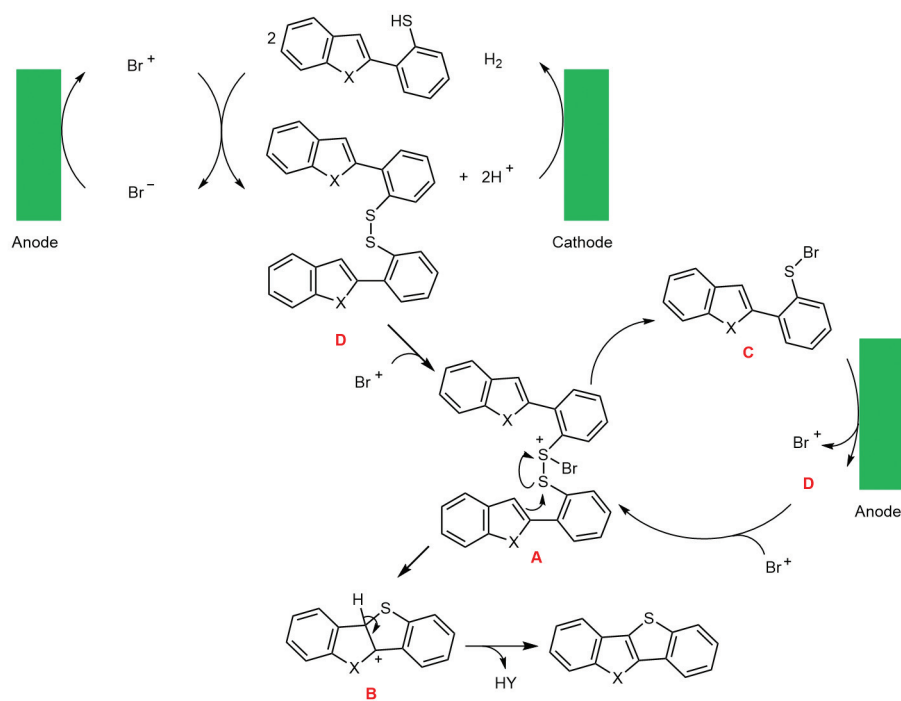


Fig. 9 Electrochemical C-H/S-H coupling for the formation of π-expanded heteroacenes.

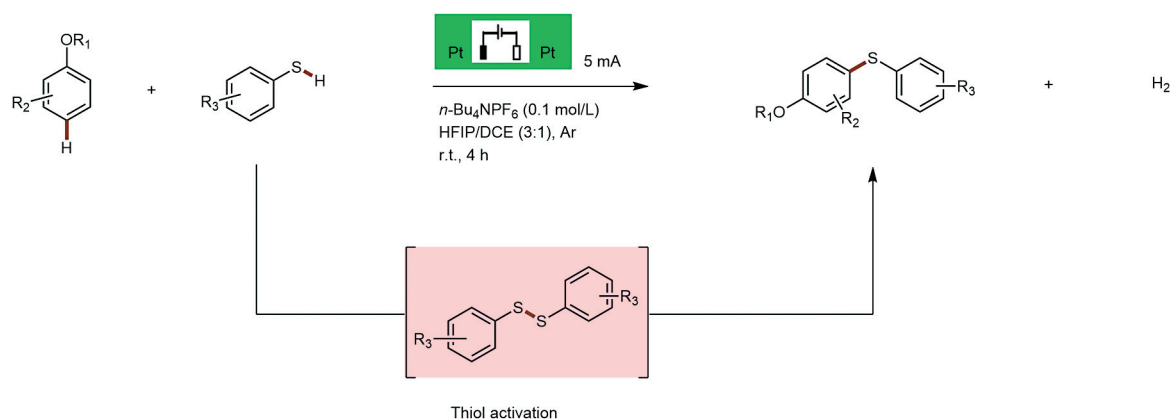


Fig. 10 The construction of the C–S bond via an electrochemical thiol activation strategy.

pathway, two platinum plates were used as electrodes, $n\text{-Bu}_4\text{NPF}_6$ as electrolytes, and hexafluoroisopropanol as a solvent or a co-solvent for the stabilization of the radical cation intermediate.

Besides the coupling between sp^2 C–H of arenes and S–H, electrochemical oxidative C–H/S–H cross-coupling between sp^2 C–H of enamines and thiophenols with H_2 evolution was also developed,⁴¹ and biologically important vinyl sulfides could be formed without external oxidant, transition-metal catalyst, and higher reaction temperature. The optimized conditions consist of the solvent (CH_3CN), the electrolyte ($n\text{-Bu}_4\text{NBF}_4$), the electrodes ($\text{C}(\text{close})(+)|\text{Fe}(-)$) and the atmosphere (N_2), all of which are essential to achieve a smooth reaction with satisfactory yield (►Fig. 11). This protocol is compatible with halogen-substituted substrates but does not tolerate 2-mercaptobenzothiazole due to poor solubility. In addition, when mercaptans were used as substrates, either no or a trace amount of products was detected.

Inspired by Lei and coworker's work, Li et al explored the disulfide arylation of terminal olefins for the synthesis of gem-bisarylthio enamines from vinyl azides and thiophenols under electrochemical conditions (►Fig. 12).⁴² An undivided cell with two platinum plates as electrodes, KI (1 equiv.) as the electrolyte, and MeCN as the solvent was used in the reaction. When the reaction is conducted at room temperature with a constant current of 10 mA, the target product was obtained in up to 97% yield. It is worth noting that a nitrogen atmosphere is not required as the reaction can proceed in the air. A series of mechanistic control experiments showed that

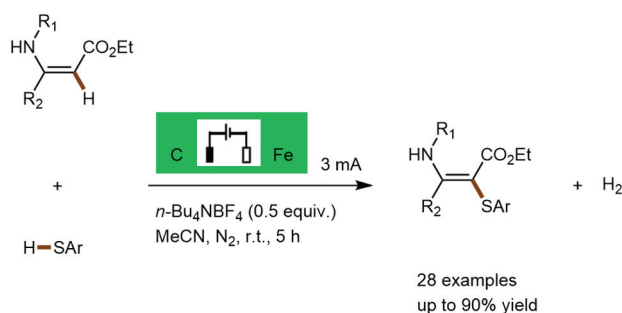


Fig. 11 Electrochemical coupling between sp^2 C–H of arenes and S–H.

I_2 was not directly involved in the reaction, but the iodine atom was responsible for the oxidative coupling. Different from the common mechanism in C–S bond formation which involves disulfanes, the replacement of thiophenol with disulfane failed to obtain the desired product, indicating that disulfanes were not the key intermediate in this transformation. Additionally, an electrochemical study was conducted at the glassy carbon electrode, and the results showed that thiophenol readily reacts with iodine radicals, and vinyl azides can further help the overall electrochemical cross-coupling reaction.

Besides, vinyl azides can be coupled with sodium azide and benzenesulfonyl hydrazides for environmentally benign electrochemical synthesis of phenanthridines and β -ketosulfones. Exogenous oxidants, metal catalysts, or expensive photoredox are considered to be indispensable for the preparation of phenanthridine and its derivatives via tandem radical addition/cyclization. In 2020, Li et al reported an efficient metal-free oxidative cyclization of biaryl vinyl azide with readily available sodium azide and benzenesulfonyl hydrazide as radical precursors. In this method, diverse phenanthridines and β -ketosulfones were prepared at room temperature in moderate to high yield (►Fig. 13).⁴³ The optimized reaction condition was obtained in $\text{MeCN}:\text{H}_2\text{O}$ (10:1) using LiClO_4 (0.1 mol/L) as the supporting electrolyte and $\text{C}(+)/\text{Pt}(-)$ as the electrodes at a constant potential of 2.3 V for 2 hours. Control experiments indicated that the reaction proceeds through a radical process, and sulfonyl

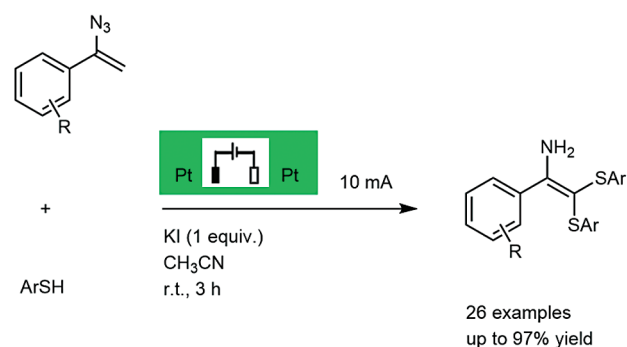


Fig. 12 Electrochemical oxidative cross-coupling between vinyl azides and thiophenols.

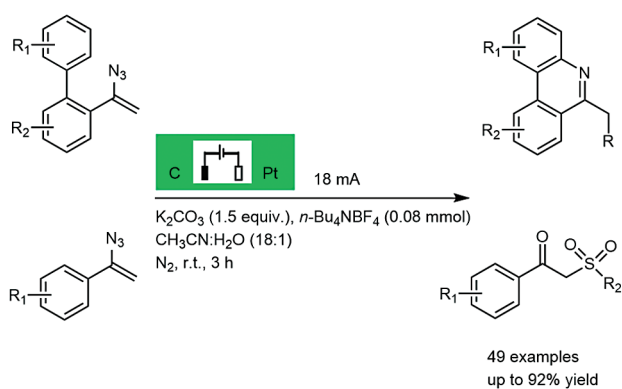


Fig. 13 Electrochemical coupling of vinyl azides.

radicals come from electro-oxidation of sulfonyl hydrazide. Cyclic voltammogram studies showed that the oxidation of sulfonyl hydrazide undergoes a coupling reaction with biaryl vinyl azide.

Benzothiazole is one of the most important frameworks in the field of pharmaceuticals due to its bioactivities including antiviral, antitumor, and antiseptic agents as well as tracers for β -amyloid plaques in Alzheimer's disease.^{44,45} While the traditional intramolecular dehydrogenative C–S cross-coupling of *N*-aryl thioureas or *N*-aryl thioamides using external chemical oxidants are prone to over-oxidation to afford ureas or amides, electro-synthesis avoids the over-oxidation by controlling the operating voltage and current. Wang et al developed external oxidant-free intramolecular dehydrogenative C–S cross-coupling reactions under undivided electrolytic conditions (–**Fig. 14**).⁴⁶ Thiourea **E** was generated during the reaction and the intramolecular dehydrogenative C–S cross-coupling could be performed in the presence of sodium benzoate (2 equiv.) as a base. Mechanistic experiments showed that SET was preferred with a sulfur anion

intermediate generated *in situ* from the acid–base equilibrium rather than with *N*-phenylbenzothioamide **F**. Notably, this reaction could be conducted on a gram scale in 5 mmol, which is important for further application.

As the collaborative analysis of continuous-flow and electrochemistry, flow electrochemistry provides advantages over traditional batch reactors including a large ratio of electrode surface to reactor volume, a shorter reaction time, a more efficient mass transfer enabled by the shorter distance between electrodes, lower concentrations or even obviate of supporting electrolyte.^{47–50} In 2018, Xu's group and Wirth collaborated to achieve a novel catalyst- and supporting electrolyte-free method for the electro-synthesis of benzothiazoles and thiazolopyridines in continuous flow (–**Fig. 15**).⁵¹ Especially, thiazolo[4,5-*c*]quinolone **G**, an important intermediate in the synthesis of TLR8 receptor agonist CL075, could be obtained in 97% isolated yield, by employing platinum as the cathode and graphite as the anode.

After these findings, in 2019, Xu's group further extended the modular flow electrolysis cell to the synthesis of benzofused six-membered *S*-heterocycles by intramolecular dehydrogenative C–S coupling (–**Fig. 16**).⁵² The reaction was equipped with a Pt cathode and a carbon-filled polyvinylidene fluoride (C/PVDF) anode. Given the ease of oxidative desulfurization of thioamides, the addition of trifluoroacetic acid and $\text{Sc}(\text{OTf})_3$ was important for the success of this reaction, which helped avoid overoxidation of the heterocyclic product and promoted the oxidation of the thioamide substrate. It is worth mentioning that in contrast to the reaction in flow, electrolysis of **H** in a batch reactor afforded a mixture of **I** and **J**, indicating the great importance of the flow cell.

In 2022, de Souza et al developed an electrochemical sulfonylation protocol for the synthesis of α -sulfonylated ketones in both batch and continuous-flow regimes,

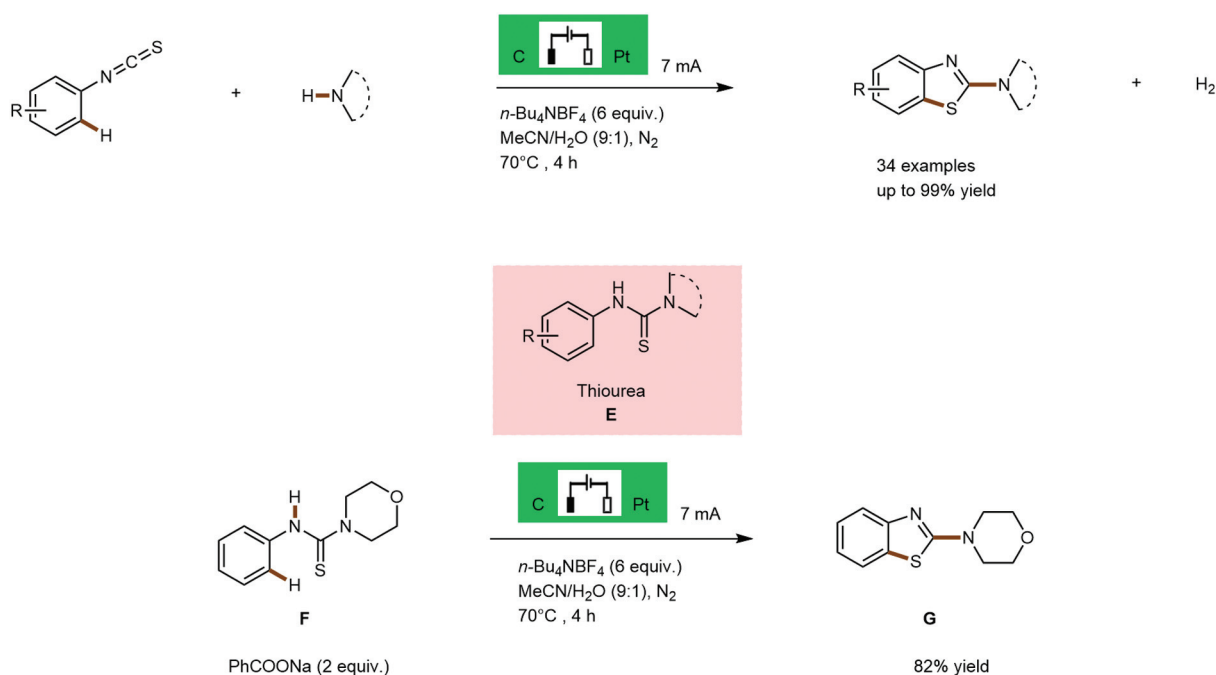


Fig. 14 Electrochemical intramolecular dehydrogenative C–S cross-coupling reactions.

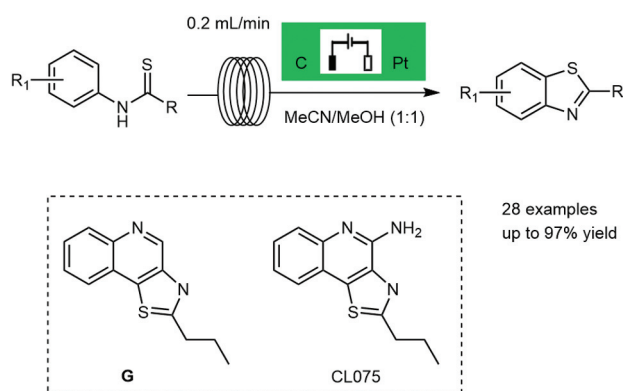


Fig. 15 Flow electrochemical synthesis of benzothiazoles and thiazolopyridines.

involving thiophenols/thiols and enol-acetates (**Fig. 17**).⁵³ In the batch conditions, α -sulfenylated ketones were obtained in high yields in the absence of additional oxidant and metallic catalysts. Notably, the Boc-cysteine proved to be extremely tolerant, which opened up the possibilities of synthesizing new building blocks from amino acids and peptides or functionalizing them at a later stage. Although $n\text{-Bu}_4\text{NBF}_4$ was screened as the ideal electrolyte in batch conditions with an undivided cell using ACN:H₂O as the solvent, the translation of batch protocol to continuous flow is an obstacle because the reaction mixture can clog up in the microchip regardless of monophasic reaction for pumping or use two different channels for pumping each of the reagents. To address this limitation, $\text{HBF}_4\cdot\text{Py}$ was used as an electrolyte which is completely miscible in ACN:H₂O. After the screening of reaction conditions, the optimal continuous-flow conditions were established as two different channels for pumping (substrates **K** and **L** and ACN were pumped in channel 1, and the mixture of $\text{HBF}_4\cdot\text{Py}$ and H₂O was pumped in channel 2), resulting the desired product in 83% yield in a 7.5-minute residence time.

He et al developed a C–S and C–O bond construction protocol via an electrochemical carbenoid insertion reaction of diazo compounds (**Fig. 18**).⁵⁴ The S–H insertion reaction was performed at room temperature under 5 mA constant current in an undivided electrolytic cell equipped with a graphite anode and a graphite cathode using TBAB as the electrolyte and DCE as the solvent. A variety of thiols underwent S–H insertion reactions with diazo esters, giving the desired product in moderate to high yields. The robustness of this transformation was further demonstrated by the O–H insertion reaction. In contrast to S–H insertion reactions, O–H insertion results in poor efficiency besides the synthesis of analgesic drug salicylic acid; however, the substituents in the phenyl were tolerated well in the process. When TBAI was used as the electrolyte for the optimization of reaction conditions, various C–O bond products were obtained in a yield of 22 to 73%.

Lactones are significant subunits in numerous natural products, bioactive molecules, and pharmaceuticals. However, the general procedures of synthesizing such compounds involve the use of toxic and expensive transition metal catalysts, as well as photocatalysts with exogenous oxidants, high temperatures, and long reaction times. To address those issues, Yang et al developed the first electrochemical cascade sulfonylation and lactonization process of alkenes using sulfonyl hydrazines as an arylsulfonylation reagent (**Fig. 19**).⁶ The reaction was conducted in a N₂ atmosphere using C (+)/Pt (–) as electrodes, CH₃CN/H₂O (10/1) as a solvent, LiClO₄ as an electrolyte, and AcOH as an additive, and γ -sulfonylated phthalides with broad and excellent substrate tolerance were achieved. The CVs of substrates indicated that sulfonyl hydrazines were more susceptible to being electrochemically oxidized and forming the benzenesulfonyl radical.

Electrochemical reactors play an important role in achieving satisfactory reaction results. Most electrochemical reactors used to establish C–S bonds consist of easily available

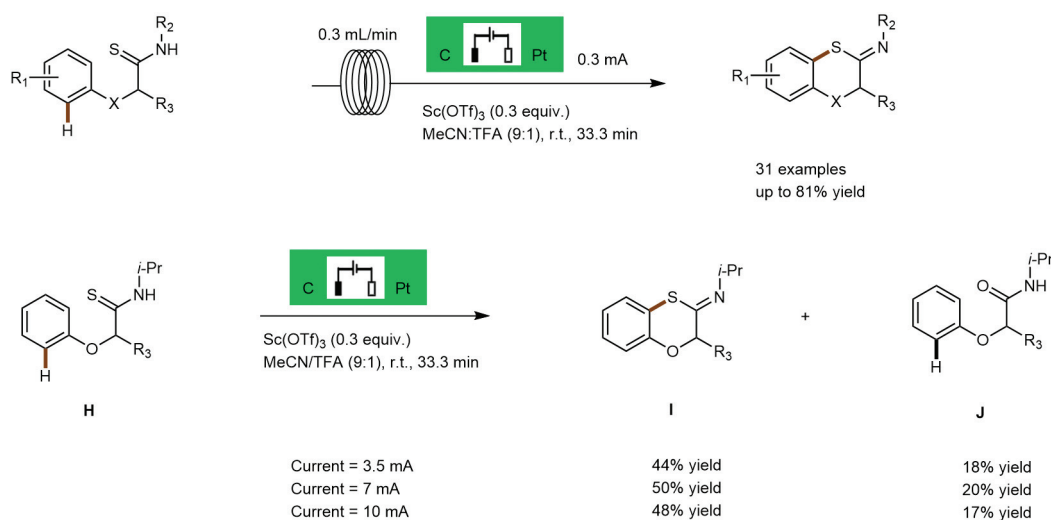


Fig. 16 Flow electrochemical synthesis of benzofused six-membered S-heterocycles.

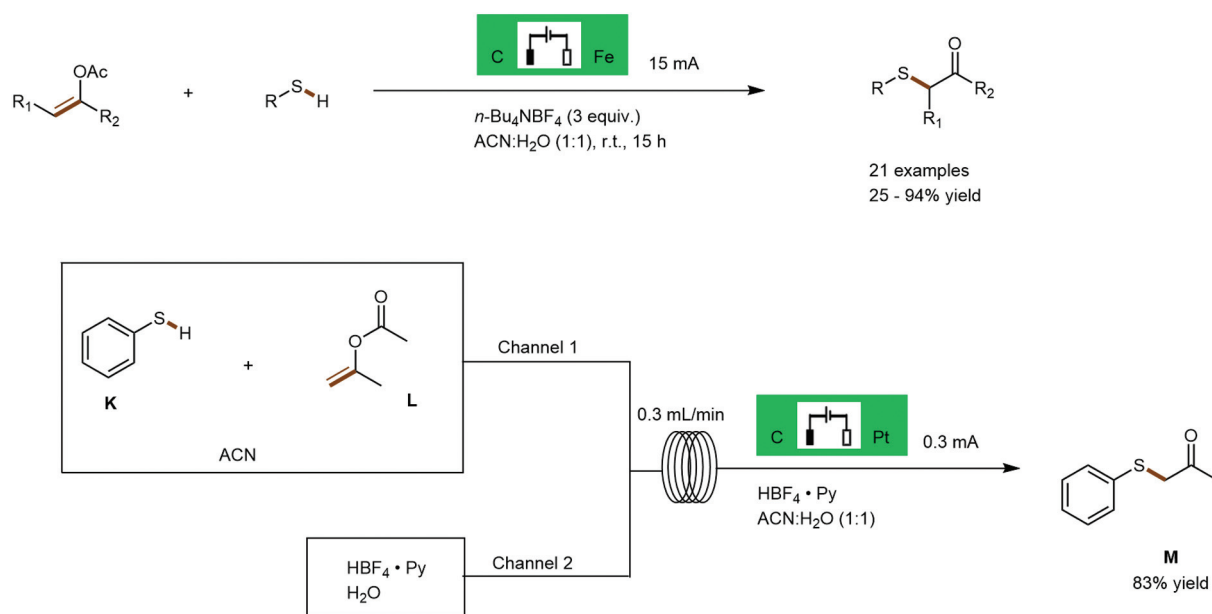


Fig. 17 Electrochemical synthesis of α -sulfonylated ketones.

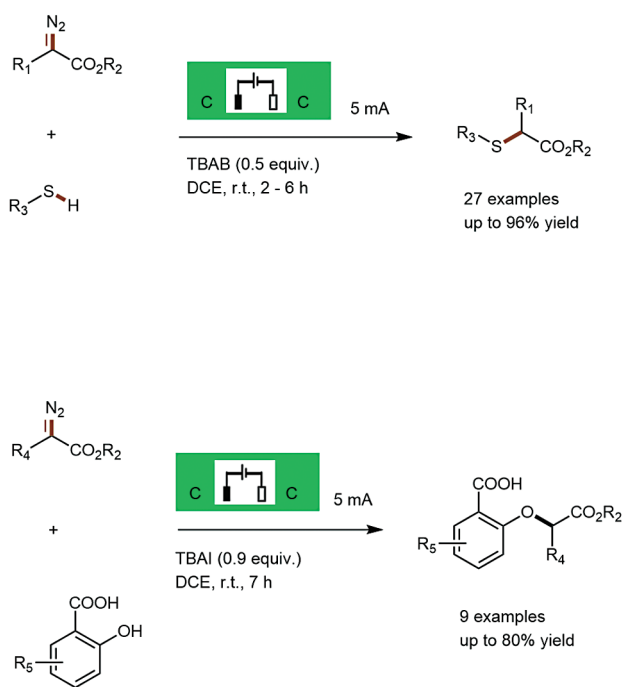


Fig. 18 Electrochemical carbenoid insertion reaction of diazo compounds.

setups including undivided cells and common electrodes like RVC, Pt, Fe, and carbon rods. In recent years, with the popularity of flow electrochemistry, researchers have begun to design flow electrochemistry reactors independently to improve the efficiency of the reaction. Huang et al designed an easy-to-machine flow electrolysis cell assembled from two aluminum bodies with a groove (**Fig. 20A**).⁵² The two aluminum bodies (① and ⑤) and the cathode (④) which consists of a piece of platinum foil were fixed on a stainless steel base for the avoidance of deformation. The anode (②) is made of carbon-filled polyvinylidene fluoride and insulated from the aluminum body by PTFE or silicone film. The anode and cathode are held apart by a fluorinated ethylene propylene (FEP) foil (③) of 125 μm thickness. A rectangular reaction channel with a total length of 313 mm and a width of 3.2 mm is cut in the FEP foil to give an overall channel volume of 125 μL . The whole device is held together by steel screws and wing nuts. The reaction mixture flows in and out through the inlet and outlet (⑥ and ⑦). Wirth et al designed the micro-flow electrochemical reactor made out of two bodies (**Fig. 20B**)⁵¹ with two parts of the reactor held apart by one FEP foil, into which a reaction channel is cut, giving different reaction volumes depending on the design of the flow path (**Fig. 20C**). The electrodes were placed in the

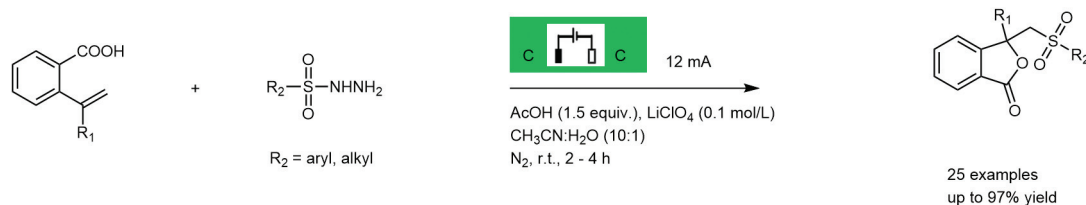


Fig. 19 Electrochemical sulfonylation-induced lactonization of alkenes.

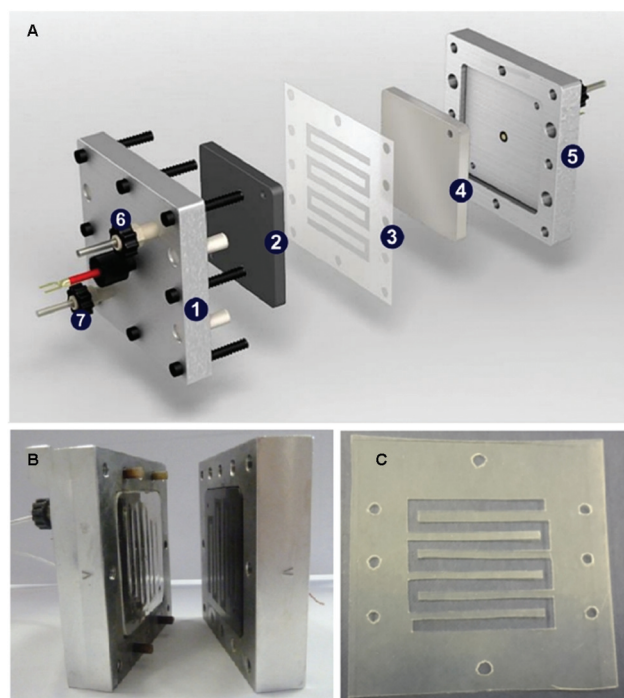


Fig. 20 (A) Design of flow electrolysis cell. ① and ⑤, aluminum bodies; ②, anode; ③, a fluorinated ethylene propylene foil; ④, cathode; ⑥ and ⑦, the inlet and outlet, respectively. (B) Design of micro-flow electrochemical reactor. (C) Flow path. (Reproduced with permission from Huang C, Qian XY, Xu HC. Continuous-flow electro-synthesis of benzofused S-heterocycles by dehydrogenative C–S cross-coupling. *Angew Chem Int Ed* 2019;58:6650–6653.⁵²)

square center of the body and connected by a copper plate attached to a wire and connected to the power supply.

Summary

The ubiquity of sulfur-containing molecules in biologically active natural products and pharmaceuticals has long attracted synthetic chemists to develop efficient strategies for their synthesis. Traditional methods usually require the use of chemical oxidants like carbon tetrabromide (CBr_4), di-*tert*-butyl peroxide (DTBP), potassium persulfate ($\text{K}_2\text{S}_2\text{O}_8$), etc., which were prone to over-oxidation; however, compared with the conventional methods, electro-synthesis, employing the electron as a potent, controllable, yet traceless redox reagent, has emerged as a mild and eco-friendly method for chemical transformation. Herein, we summarized the recent important developments in C–S bond formation in terms of various electro-synthesis ways, especially, for the synthesis of pharmaceutical molecules. In addition, the scope, limitations, and mechanisms are described and discussed, detailing the fundamental aspects and benefits of electrochemistry for the construction of the C–S bond.

The content of this review demonstrates that it is possible to provide new synthetic routes and to improve the existing methodologies, to obtain processes more in line with current environmental protection aims. However, the electro-synthesis construction of C–S bonds involving enantioselectivities is still

challenging, and more attention from the electrochemical community is anticipated to focus on the development of more efficient, sustainable, and practical electro-strategies to address the current challenges in chemical selectivity and enantioselectivity.

Funding

We are grateful to the Key R&D Plan Projects of Lishui (Grant No. 2023zdyf11), Zhejiang Provincial Key R&D Project (Grant Nos. 2020C03006 & 2019-ZJ-JS-03), and the Zhejiang Provincial College Student Science and Technology Innovation Activity Plan and New Talent Plan (Grant No. 2022R434A016) for financial support.

Conflict of Interest

None declared.

References

- Nicolaou KC, Li R, Lu Z, et al. Streamlined total synthesis of shishijimicin A and its application to the design, synthesis, and biological evaluation of analogues thereof and practical syntheses of PhthNSSMe and related sulfonylating reagents. *J Am Chem Soc* 2018;140(38):12120–12136
- Nicolaou KC, Totokotsopoulos S, Giguère D, Sun YP, Sarlah D. Total synthesis of epicoccin G. *J Am Chem Soc* 2011;133(21):8150–8153
- Feng M, Tang B, Liang SH, Jiang X. Sulfur containing scaffolds in drugs: synthesis and application in medicinal chemistry. *Curr Top Med Chem* 2016;16(11):1200–1216
- Ke Z, Tan CK, Chen F, Yeung YY. Catalytic asymmetric bromoetherification and desymmetrization of olefinic 1,3-diols with C2-symmetric sulfides. *J Am Chem Soc* 2014;136(15):5627–5630
- Dong B, Shen J, Xie L. Recent developments on 1,2-difunctionalization and hydrofunctionalization of unactivated alkenes and alkynes involving C–S bond formation. *Org Chem Front* 2023;10:1322
- Yang J, Li G, Yu K, Xu B, Chen Q. Electrochemical sulfonylation-induced lactonization of alkenes: synthesis of sulfonyl phthalides. *J Org Chem* 2022;87(02):1208–1217
- Du J, Du Y, Gui Q. Progress in S–X bond formation by halogen-mediated electrochemical reactions. *Synthesis* 2023;55:2799–2816
- Rance DJ. Sulfur-containing drugs and related organic compounds. In: Damani LA, ed. *Chemistry, Biochemistry, and Toxicology*. Chichester: Ellis Horwood, Ltd.; 1989:217–268
- Chen ZW, Bai R, Annamalai P, et al. The journey of C–S bond formation from metal catalysis to electrocatalysis. *New J Chem* 2022;46:15–38
- Beletskaya IP, Ananikov VP. Transition-metal-catalyzed C–S, C–Se, and C–Te bond formation via cross-coupling and atom-economic addition reactions. *Chem Rev* 2011;111(03):1596–1636
- Lee CF, Liu YC, Badsara SS. Transition-metal-catalyzed C–S bond coupling reaction. *Chem Asian J* 2014;9(03):706–722
- Shen C, Zhang P, Sun Q, Bai S, Hor TS, Liu X. Recent advances in C–S bond formation via C–H bond functionalization and decarboxylation. *Chem Soc Rev* 2015;44(01):291–314
- Gensch T, Klauk FJR, Glorius F. Cobalt-catalyzed C–H thiolation through dehydrogenative cross-coupling. *Angew Chem Int Ed Engl* 2016;55(37):11287–11291
- Wang H, Lu Q, Qian C, et al. Solvent-enabled radical selectivities: controlled syntheses of sulfoxides and sulfides. *Angew Chem Int Ed Engl* 2016;55(03):1094–1097
- Chang JR, Chang SL, Lin TB. γ -Alumina-supported Pt catalysts for aromatics reduction: a structural investigation of sulfur poisoning catalyst deactivation. *J Catal* 1997;169:338–346
- Saueremann N, Meyer TH, Qiu Y, et al. Electrocatalytic C–H activation. *ACS Catal* 2018;8:7086–7103

- 17 Huang B, Sun Z, Sun G. Recent progress in cathodic reduction-enabled organic electrosynthesis: trends, challenges, and opportunities. *Science* 2022;243(02):243–277
- 18 Wang Y, Tang S, Yang G, Wang S, Ma D, Qiu Y. Electrocarboxylation of aryl epoxides with CO₂ for the facile and selective synthesis of β -hydroxy acids. *Angew Chem Int Ed Engl* 2022;61(38):e202207746
- 19 Wang P, Tang S, Huang P, Lei A. Electrocatalytic oxidant-free dehydrogenative C-H/S-H cross-coupling. *Angew Chem Int Ed Engl* 2017;56(11):3009–3013
- 20 Tang S, Liu Y, Lei A. Electrochemical oxidative cross-coupling with hydrogen evolution: a green and sustainable way for bond formation. *Chem* 2018;4:27–45
- 21 Li J, Al-Mahayni H, Chartrand D, et al. Electrochemical formation of C-S bonds from CO₂ and small molecule sulfur species. *Nat Synth* 2023;2:757–765
- 22 Guo SZ, Yu ZQ, Su WK. Continuous-flow processes for the production of floxacillin intermediates: efficient C–C bond formation through a rapid and strong activation of carboxylic acids. *Pharmaceutical Fronts* 2020;2(03):e128–e132
- 23 Yu J, Ying P, Wang H, et al. Mechanochemical asymmetric cross-dehydrogenative coupling reaction: liquid-assisted grinding enables reaction acceleration and enantioselectivity control. *Adv Synth Catal* 2020;362:893–902
- 24 Xiang K, Ying P, Ying T, et al. α -C-H functionalization of glycine derivatives under mechanochemical accelerated aging en route to the synthesis of 1,4-dihydropyridines and α -substituted glycine esters. *Green Chem* 2023;25:2853–2862
- 25 Qian XY, Li SQ, Song JS, Xu HC. TEMPO-catalyzed electrochemical C-H thiolation: synthesis of benzothiazoles and thiazolopyridines from thioamides. *ACS Catal* 2017;7(04):2730–2734
- 26 Kokatla HP, Yoo E, Salunke DB, et al. Toll-like receptor-8 agonistic activities in C2, C4, and C8 modified thiazolo[4,5-c]quinolines. *Org Biomol Chem* 2013;11(07):1179–1198
- 27 Liu D, Ma HX, Fang P, Mei TS. Nickel-catalyzed thiolation of aryl halides and heteroaryl halides through electrochemistry. *Angew Chem Int Ed Engl* 2019;58(15):5033–5037
- 28 Yuan Y, Chen Y, Tang S, Huang Z, Lei A. Electrochemical oxidative oxysulfenylation and aminosulfenylation of alkenes with hydrogen evolution. *Sci Adv* 2018;4(08):eaat5312
- 29 Yang SM, He TJ, Lin DZ, Huang JM. Electrosynthesis of (*E*)-vinyl thiocyanates from cinnamic acids via decarboxylative coupling reaction. *Org Lett* 2019;21(07):1958–1962
- 30 Guan Z, Zhu S, Wang S, et al. Electrochemical oxidative carbon-atom difunctionalization: towards multisubstituted imino sulfide ethers. *Angew Chem Int Ed Engl* 2021;60(03):1573–1577
- 31 Yuan Y, Cao Y, Qiao J, et al. Electrochemical oxidative C-H sulfenylation of imidazopyridines with hydrogen evolution. *Chin J Chem* 2019;37:49–52
- 32 Mitsudo K, Matsuo R, Yonezawa T, Inoue H, Mandai H, Suga S. Electrochemical synthesis of thienoacene derivatives: transition metal-free dehydrogenative C-S coupling promoted by a halogen mediator. *Angew Chem Int Ed Engl* 2020;59(20):7803–7807
- 33 Alvaro E, Hartwig JF. Resting state and elementary steps of the coupling of aryl halides with thiols catalyzed by alkylbisphosphine complexes of palladium. *J Am Chem Soc* 2009;131(22):7858–7868
- 34 Uyeda C, Tan Y, Fu GC, Peters JC. A new family of nucleophiles for photoinduced, copper-catalyzed cross-couplings via single-electron transfer: reactions of thiols with aryl halides under mild conditions (0 °C). *J Am Chem Soc* 2013;135(25):9548–9552
- 35 Wang Y, Deng L, Wang X, et al. Electrochemically promoted nickel-catalyzed carbon-sulfur bond formation. *ACS Catal* 2019;9:1630–1634
- 36 Yan SY, Liu YJ, Liu B, Liu YH, Shi BF. Nickel-catalyzed thiolation of unactivated aryl C-H bonds: efficient access to diverse aryl sulfides. *Chem Commun (Camb)* 2015;51(19):4069–4072
- 37 Iwasaki M, Miki N, Tsuchiya Y, Nakajima K, Nishihara Y. Synthesis of benzoisosenazolone derivatives by Nickel-catalyzed dehydrogenative direct selenation of C(sp²)-H bonds with elemental selenium in air. *Org Lett* 2017;19(05):1092–1095
- 38 Iwasaki M, Kaneshika W, Tsuchiya Y, Nakajima K, Nishihara Y. Palladium-catalyzed peri-selective chalcogenation of naphthylamines with diaryl disulfides and diselenides via C-H bond cleavage. *J Org Chem* 2014;79(23):11330–11338
- 39 Choudhuri K, Maiti S, Mal P. Iodine(III) enabled dehydrogenative aryl C–S coupling by *in situ* generated sulfenium ion. *Adv Synth Catal* 2019;361:1092–1101
- 40 Wang JH, Lei T, Wu HL, et al. Thiol activation toward selective thiolation of aromatic C-H bond. *Org Lett* 2020;22(10):3804–3809
- 41 Li D, Li S, Peng C, et al. Electrochemical oxidative C-H/S-H cross-coupling between enamines and thiophenols with H₂ evolution. *Chem Sci (Camb)* 2019;10(09):2791–2795
- 42 Li G, Yu K, Yang J, Xu B, Chen Q. Electrochemical oxidative cross-coupling between vinyl azides and thiophenols: synthesis of gem-bisarylthio enamines. *J Org Chem* 2021;86(22):15946–15952
- 43 Li G, Kong X, Liang Q, et al. Metal-free electrochemical coupling of vinyl azides: synthesis of phenanthridines and β -ketosulfones. *Eur J Org Chem* 2020:6135–6145
- 44 Kok SHL, Gambari R, Chui CH, et al. Synthesis and anti-cancer activity of benzothiazole containing phthalimide on human carcinoma cell lines. *Bioorg Med Chem* 2008;16(07):3626–3631
- 45 Liu C, Lin J, Pitt S, et al. Benzothiazole based inhibitors of p38 α MAP kinase. *Bioorg Med Chem Lett* 2008;18(06):1874–1879
- 46 Wang P, Tang S, Lei A. Electrochemical intramolecular dehydrogenative C-S bond formation for the synthesis of benzothiazoles. *Green Chem* 2017;19:2092–2095
- 47 Atobe M, Tateno H, Matsumura Y. Applications of flow microreactors in electrosynthetic processes. *Chem Rev* 2018;118(09):4541–4572
- 48 Pletcher D, Green RA, Brown RCD. Flow electrolysis cells for the synthetic organic chemistry laboratory. *Chem Rev* 2018;118(09):4573–4591
- 49 Folgueiras-Amador AA, Philipps K, Guilbaud S, Poelakker J, Wirth T. An easy-to-machine electrochemical flow microreactor: efficient synthesis of isoindolinone and flow functionalization. *Angew Chem Int Ed Engl* 2017;56(48):15446–15450
- 50 Arai K, Wirth T. Rapid electrochemical deprotection of the isonicotinylloxycarbonyl group from carbonates and thiocarbonates in a microfluidic reactor. *Org Process Res Dev* 2014;18:1377–1381
- 51 Folgueiras-Amador AA, Qian XY, Xu HC, Wirth T. Catalyst- and supporting-electrolyte-free electrosynthesis of benzothiazoles and thiazolopyridines in continuous flow. *Chemistry* 2018;24(02):487–491
- 52 Huang C, Qian XY, Xu HC. Continuous-flow electrosynthesis of benzofused S-heterocycles by dehydrogenative C-S cross-coupling. *Angew Chem Int Ed Engl* 2019;58(20):6650–6653
- 53 de Souza AAN, Bartolomeu AA, Brocksom TJ, Noël T, de Oliveira KT. Direct synthesis of α -sulfenylated ketones under electrochemical conditions. *J Org Chem* 2022;87(09):5856–5865
- 54 He Z, Zhao W, Li Y, Yu Y, Huang F. Electrochemical S-H and O-H insertion reactions from thiols or salicylic acids with diazo esters. *Org Biomol Chem* 2022;20(41):8078–8082