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Innovative approaches to the synthesis of five-membered heteroaromatics with emerging synthetic methodologies

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According to statistics, more than 70% of drugs that are available on the market contain heterocyclic units. Among them, five-membered heteroaromatics bearing nitrogen, oxygen, and sulfur have served as the most important structural motifs found in diverse pharmaceuticals. Emerging toolboxes, such as photocatalysis, biocatalysis, electrocatalysis and skeletal editing have showcased unprecedented avenues to access them. In fact, >300 publications on the topic of synthesis of five-membered heteroaromatics by using emerging toolboxes have been recorded in the last ten years, clearly indicating the significance of this field. In this study, a conceptual overview and discussions are presented to showcase the advancement of this field. Moreover, the related drugs and bioactive compounds obtained by these approaches are highlighted.

1. Introduction

Five-membered heteroaromatics bearing nitrogen, oxygen, and sulfur (including indole, pyrazole, imidazole, benzimidazole, triazole, thiazole, indazole, tetrazole, isoxazole, and thiadiazole) have emerged as highly important structural motifs in a wide range of pharmaceuticals and natural products.[1–3] The most obvious evidence is that >130 drugs containing five-membered heteroaromatics have been developed in 2013–2023, indicating their significance in the modern drug discovery.[4,5] The marketed pharmaceuticals include the following: pimobendan, a first-line

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therapy for canine chronic heart failure in veterinary cardiology; dronedarone, used for the clinical treatment of specific types of cardiac arrhythmias; raloxifene, a selective estrogen receptor modulator that improves bone mineral density while lowering the risk of certain breast cancers; and azomycin, an agent used against anaerobic bacterial infections, amoebic dysentery, and vaginal trichomoniasis. Leveraging advanced synthetic toolkits enables the efficient assembly of key intermediates for these approved drugs, thereby streamlining and expanding their synthetic accessibility.

Owing to the remarkable bioactivity of five-membered heterocycles (Fig. 1), substantial efforts have been devoted toward the development of new strategies for their synthesis.[7–9] It should be noted that traditional methods have contributed tremendously to diversify the synthesis of five-membered heterocycles through thermal conditions[10] and transition-metal catalysis.[11–13] However, there remains a pressing need to design more efficient and convenient methods to obtain these valuable compounds and expand their structural diversity. In the last decades, emerging toolboxes such as photocatalysis, biocatalysis, electrocatalysis and skeletal editing have attracted great attention due to their numerous advantages.[14–17] Photocatalysis compresses traditional multi-step synthesis into single-step light-triggered cascade reactions, providing an effective tool for constructing drug molecular skeletons under mild conditions.[18] Electrocatalysis may offer high selectivity and sustainability by tuning electrode potentials to control reaction pathways, avoiding chemical oxidants or reductants and reducing byproducts.[19] Biocatalysis excels in stereoselectivity and environmental benignity, enabling the efficient construction of complex five-membered aromatic heterocycles *via* non-natural substrates or cascade reactions.[20] In this aspect, skeletal editing is an advanced method for the

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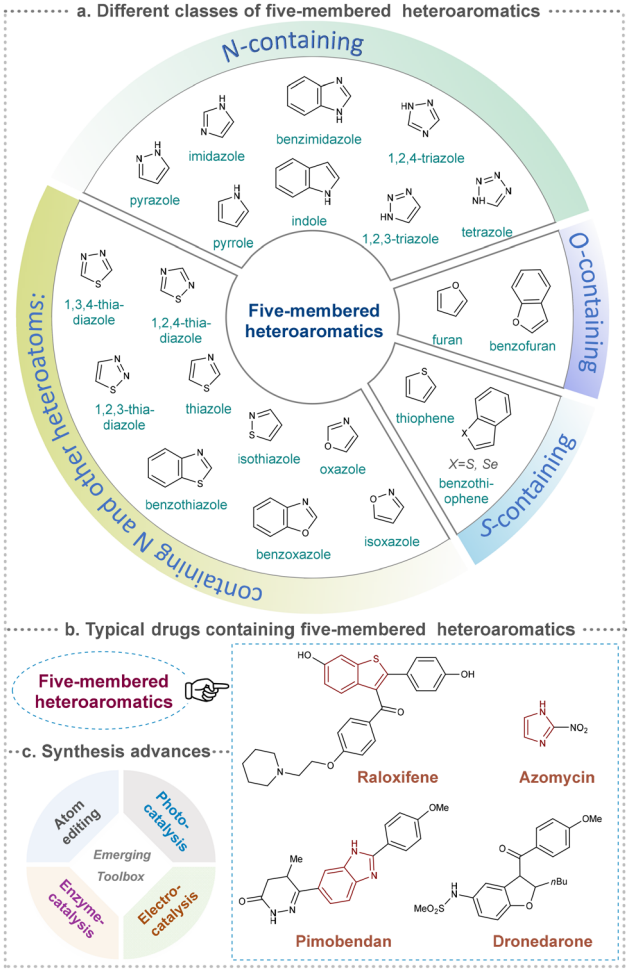


Fig. 1 Classification of different five-membered heteroaromatics and synthetic applications into drug molecules through emerging toolboxes.

diversification and transformation of known active compounds *via* the direct modification of the core structure.[21] In addition, these approaches have showcased unprecedented avenues to access five-membered heteroaromatics. Indeed, >300 recent publications on the synthesis of five-membered heteroaromatics by using emerging toolboxes have been recorded in the last ten years, which strongly indicates the significance and rapid growth of this field.[22–25] Additionally, the application of these innovative tools has successfully advanced the efficient preparation of bioactive molecules and lead compounds in drug discovery.[26–28]

Considering the significance of this research field and our deep interest in the synthesis of heterocycles through photochemical methods,[29,30] we aim to provide a critical review to mention the challenges and recent advancements in the synthesis of five-membered heteroaromatics and related drugs/bioactive molecules. This article will cover the recent advances in the application of photochemical synthesis, electrocatalysis, biocatalysis and skeletal editing to assemble five-membered heteroaromatics containing nitrogen, oxygen, sulfur, and other heteroatoms. The synthetic applications and mechanistic studies will be clearly overviewed.

2. Overview of the synthesis of five-membered heteroaromatics through emerging toolboxes

We categorized all the reported methods based on the source of heteroatoms. In the synthesis of nitrogen-containing aromatic heterocycles, a wide range of nitrogen sources such as primary amines, tertiary amines, azides and nitriles furnished the corresponding products *via* all the emerging strategies (Fig. 2a).[31–42] Among them, tertiary amines were always suitable nitrogen sources to construct five-membered heteroaromatics *via* the photochemical or biocatalysis approach.[43,44] Moreover, diazo compounds have been used for the synthesis of pyrazoles or triazoles in photo/electrochemical synthesis.[45,46] Furthermore, nitro-compounds and aziridines have been proved as feasible nitrogen sources in photocatalysis.[47,48] In addition, molecular editing has become an elegant strategy to construct five-membered heteroaromatics.[49]

For the synthesis of oxygen-containing aromatic heterocycles, phenols, alcohols, ketone derivatives and ethers have been well-established to synthesize furans and benzofurans through emerging toolboxes (Fig. 2b).[50–52] In addition, spiro-isochromene derivatives have been employed into the benzofuran synthesis *via* a photochemical approach.[53] Regarding the synthesis of sulfur/seleno-containing aromatic heterocycles, various thioethers, benzenethiol or disulfides have served as sulfur sources to obtain desirable products (Fig. 2c).[54–56] Other sulfur/seleno sources such as NH_4SCN/KSeCN have also been reported for the construction of benzoselenophenes and benzothiophenes.[57]

By designing different starting materials bearing *N*- and *O*-sources in the same molecule such as oximes, *O*-methyloximes, propargyl amides, phenolic amidines, and 2-aminophenols, the structural diversity of five-membered heteroarenes has been achieved (Fig. 2d).[58–61] To further improve the synthetic efficiency, intermolecular synthesis from separate nitrogen and oxygen sources such as by using carboxylic acids and benzyl amines as staring materials has also been developed.[62,63] Furthermore, the synthesis of *N*- and *O*-containing five-membered heteroarenes has also been developed by using starting materials bearing *N* and *O* sources such as α-azidochalcones and diazo compounds.[64,65] In addition, the intermolecular synthesis by using separate nitrogen sources and sulfur sources has been reported.[66–68]

Five-membered heteroaromatics containing *N* and *S* have been synthesized as well by using emerging toolboxes, and structural diversity has been achieved through the rational designing of various *N*- and *S*-bearing precursors, including aminothiophenols,[69] mercaptobenzonitriles,[70] and thioamide derivatives,[71] as well as intermolecular interactions between thiocyanic acid and diverse amine-containing compounds (Fig. 2e).[72,73] The utilization of unsaturated five-membered heterocycles as starting materials has also been documented.[74] Notably, innovative approaches by employing thiocyanic acid as a dual-purpose reagent to supply both *N* and *S* sources have been successfully developed for constructing high-value five-membered heteroaromatics.[75]

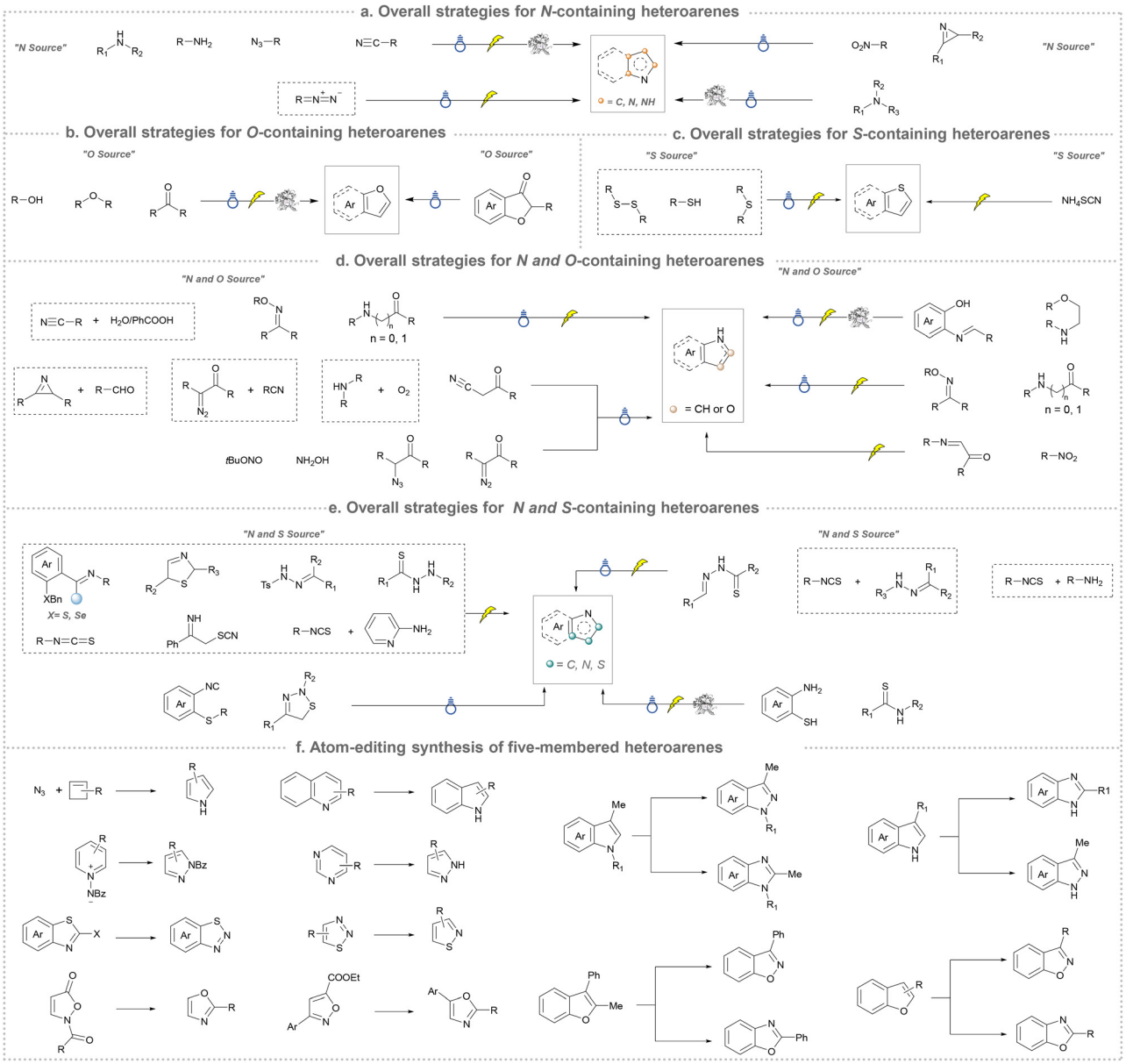


Fig. 2 Conceptual overview of synthesizing five-membered heteroaromatics *via* an emerging toolbox: (a) overall strategies for *N*-containing heteroarenes; (b) overall strategies for *O*-containing heteroarenes; (c) overall strategies for *S*-containing heteroarenes; (d) overall strategies for *N* and *O*-containing heteroarenes; (e) overall strategies for *N* and *S*-containing heteroarenes; (f) atom-editing synthesis of five-membered heteroarenes.

At last, skeletal editing is characterized by its ability to construct five-membered heteroaromatics *via* direct, atomic-level precision, eliminating the requirement of multi-step conventional synthesis.[76] We also provide a concise overview for the progress of this field (Fig. 2f). It is clear that skeletal editing provided new insight for the synthesis of five-membered aromatic heterocycles *via* elegant atom deletion, atom transfer and atom insertion. Moreover, this capability also makes it a powerful platform for late-stage functionalization and discovering new heterocyclic compounds, which will be discussed in detail in the following sections.

3. One-nitrogen-containing aromatic heterocycles

3.1 Synthesis of pyrroles

Pyrrole, a fundamental five-membered heteroaromatic characterized by a conjugated π-electron system, occupies a central role in medicinal chemistry.[77,78] Within the pharmaceutical industry, these compounds are extensively employed in the development of diverse therapeutic agents due to their multifaceted biological activities including potent antitumor efficacy *via* microtubule dynamics disruption, broad-spectrum antimicrobial action, and

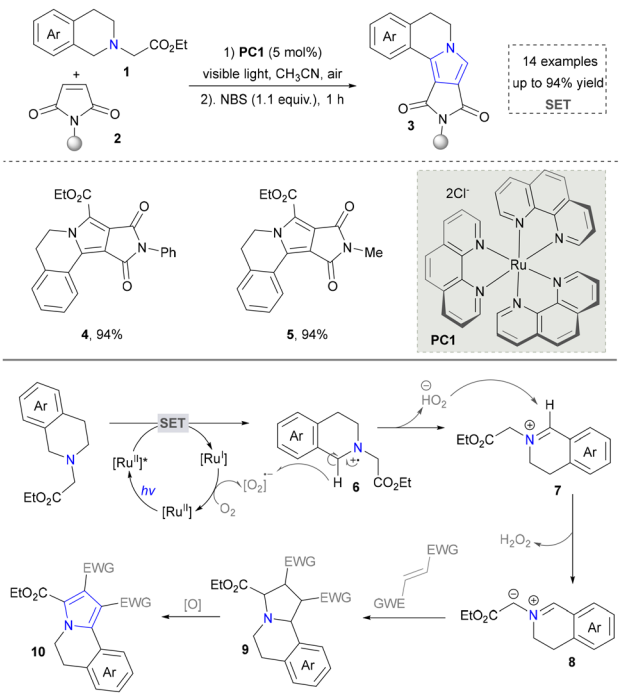
robust anti-inflammatory/analgesic properties.[79] Traditional methods for synthesizing pyrrole molecules involve condensation reactions between carbonyl compounds and amines, such as the Hantzsch pyrrole synthesis, Barton–Zard pyrrole synthesis, and Paal–Knorr reaction.[80–82] This section systematically explores the cutting-edge methodologies for the synthesis of pyrrole and its derivatives with a strong emphasis on innovative strategies.

3.1.1 Photochemical synthesis of pyrroles. As depicted in Scheme 1, the first construction of pyrroles by using photocatalytic tandem reactions was reported by Xiao's group in 2011.[83] This strategy enabled the synthesis of diverse pyrroles (**4**,**5**) starting from tertiary amines and *N*-phenylmaleimides under mild conditions. In their proposed mechanism, tertiary amine was employed as the nitrogen source, which formed imine ion (**7**) through a single electron transfer event. The imine ion further underwent a deprotonation process to form an intermediate (**8**), which was subjected to [3+2] cycloaddition and subsequent oxidative aromatization with electron-deficient components to complete the reaction. Interestingly, this is the first time that the reduction quenching mechanism of a tertiary amine on an excited photocatalyst has been applied to the series of [3+2] cycloaddition reactions. However, only highly reactive alkenes bearing EWGs were feasible in this system. Inspired by this work, heterogeneous photocatalysts have also been developed to improve the efficiency of the synthesis of pyrrole derivatives by varying tertiary amines as synthetic synthons.[84,85]

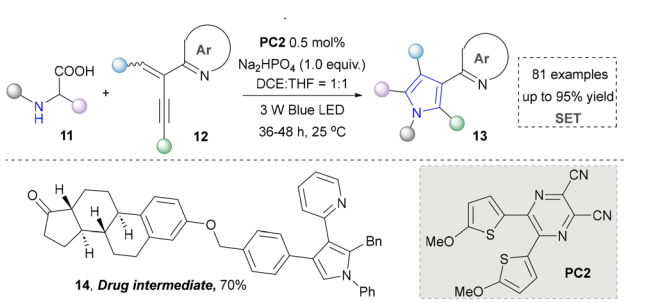
Taking advantage of the high reactivity of free radicals, a photocatalytic strategy for the construction of highly complex pyrroles was reported by Wu's group.[86] In this case, α-bromoketone was activated to form the carbon radical *via* a single electron transfer (SET) process, which further underwent the radical addition into the enamine to afford the valuable pyrroles. Compared with the traditional Hantzsch reaction, this strategy is characterized by completion within merely 2 hours under blue-light irradiation at room temperature. Later, a similar strategy of using *N*-tosylhydrazones as radical precursors *via* iodine-mediated photo-catalysis under visible light irradiation was also reported by Adimurthy's group.[87] In addition, the utilization of amino acids as nitrogen sources and the radical precursors was further developed by Jiang's group in 2021 (Scheme 2).[88] This method featured easy availability of raw materials, high synthetic efficiency and good functional group tolerance. Diverse pyrroles with tri- and tetra-substituents at the carbon positions were obtained successfully in good to excellent yields through redox-neutral radical additions, cyclisation and aerobic oxidative arylation transformations. Moreover, a drug intermediate (**14**) was successfully obtained under standard conditions, demonstrating the utility of this method for constructing pyrrole scaffolds in bioactive molecules. Nevertheless, this approach remains constrained by its dependence on N-protected α-amino acids. Additionally, the number of substrates amenable for late-stage functionalization remained limited.

In 2023, the same group extended this conceptual framework by employing TsOH as an additive to generate an electron donor–acceptor (EDA) complex with enones under visible light irradiation, thereby initiating a cascade transformation. This strategy subsequently enabled the conversion of α-amino acids into polysubstituted indole derivatives, achieving remarkable enhancement in the structural diversity of accessible indole architectures through controlled functionalization patterns.[89]

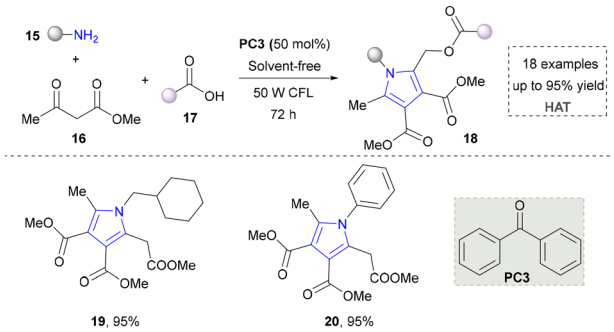
In an effort to further expand the structural diversity of pyrrole, a methodology for achieving highly substituted pyrroles using primary amines as the nitrogen source has been developed by Salles' group in 2021 (Scheme 3).[33] In this approach, a three-component reaction using various primary amines, carboxylic acids and ketones as synthetic synthons tremendously improved the structural diversity of pyrroles (**19**, **20**). Moreover, the target product was obtained under solvent-free conditions, which also showed good sustainability. Although this method advanced the synthesis of highly substituted pyrroles, it required a long reaction time (72 h). In addition, the radical pathways in the proposed mechanism still need to be further



Scheme 1 Visible-light-induced oxidation/[3+2] cycloaddition/oxidative arylation sequence to obtain pyrroles.



Scheme 2 Assembly of the azaarene-substituted pyrroles based on radical construction.

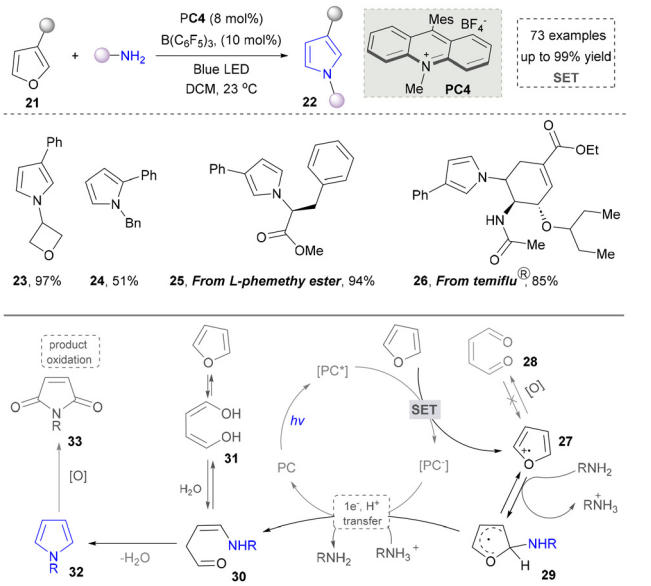


Scheme 3 Three-component reaction for complex pyrrole synthesis.

verified, especially regarding the intermediate formation and conversion process.

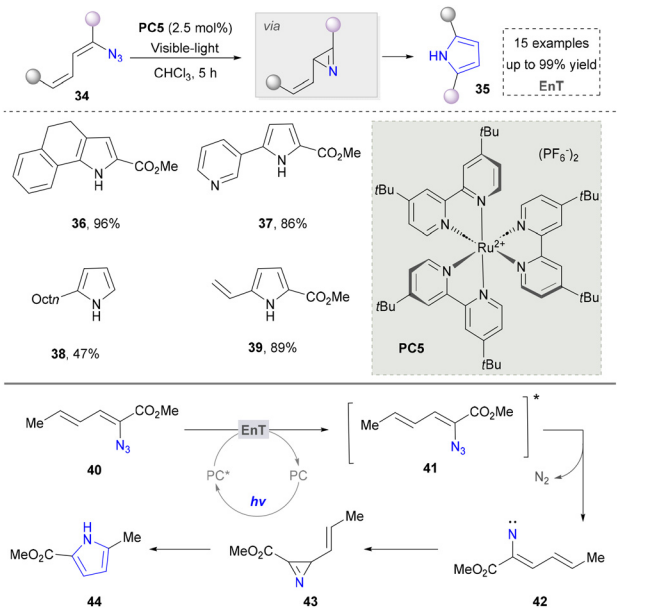
To further extend the synthesis of pyrroles through multi-component reactions, several groups persistently made significant contributions. In 2022, Tabassum's group reported a one-pot synthetic methodology for novel 6,7-bisubstituted 1*H*-pyrroles, employing substituted benzyl bromides, barbituric acid/Meldrum's acid, and aromatic amines under the irradiation of visible light, with fluorescein serving as the photocatalyst.[90] At the same year, Maheswari's group established a another three-component synthetic strategy for the synthesis of 1,2,3,4-tetrasubstituted pyrroles at ambient temperature and under photoinduced conditions, demonstrating exceptional atom economy and operational simplicity.[91] Most recently, the Heydari group devised a four-component photocatalytic assembly for functionalized pyrroles *via* the integration of amines, aldehydes, 1,3-dicarbonyl compounds, and nitromethane, which further diversified the synthesis of pyrroles through photochemical synthesis.[92]

In contrast to the most studies that focus on conventional pyrrole synthesis *via* the ring assembly, Park's group innovatively developed a molecular-editing strategy in 2024, achieving a furan-to-pyrrole conversion through single-atom exchange (Scheme 4).[93] This strategy maintained the molecular framework while altering the heteroatom type, offering a precise protocol to investigate the impact of heteroatoms on compound properties. It also broadens the raw material sources for pyrrole synthesis, providing a new route to utilize abundant furan compounds (**23**, **24**). Moreover, various furan derivatives and diverse nitrogen nucleophiles, including aliphatic amines, aromatic amines, and ammonia surrogates participated successfully in the system. Notably, this method achieved the late-stage functionalization of complex natural products and drug molecules containing a furan motif, efficiently converting them into pyrrole analogues under standard conditions. The substrate in this system tolerated ester and amide groups, enabling rapid derivatization of chiral precursors such as L-phemethy ester **25** and the *anti*-influenza drug (Tamiflu) **26**. The mechanism involved the single-electron oxidation of furan by the excited state of a photocatalyst, generating a furanic cation radical. This was followed by nucleophilic addition of an amine, C–O bond homolysis, electron transfer, and proton transfer, ultimately leading to the construction of pyrroles, which was distinct from traditional pyrrole synthesis methods.



Scheme 4 A strategy for converting furan into pyrrole through single-atom exchange.

Besides using amines/enamines as nitrogen sources, azides have emerged as a crucial alternative reagent for pyrrole synthesis due to their unique denitrification ability, photosensitising activity, and versatile intermediate generation properties.[94] In 2012, Yoon and co-workers found a photocatalytic method to activate aryl and vinyl azides directly, providing a convenient method for constructing pyrroles (Scheme 5, **36**–**39**).[95] The mechanism confirmed that the vinyl azides were activated *via* the energy transfer to form the triplet nitrene **42**. This was followed by the cyclisation of the nitrogen compartment to produce a 2*H*-azepane intermediate, which was subsequently



Scheme 5 The synthesis of pyrroles *via* visible light activation of aryl and vinyl azides.

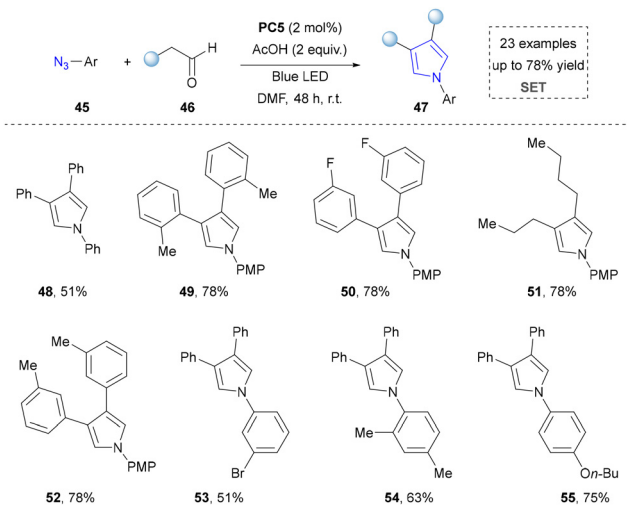
rearranged to form the pyrrole. It is well known that vinyl azides decompose into nitrile or 2*H*-azopropylline under heat and ultraviolet light and are widely used in the synthesis of various N-heterocyclic rings.[96,97]

Building on Yoon's foundational work, other groups have also explored azides as 2*H*-aziridine precursors for the synthesis of polysubstituted pyrroles. In 2019, the Maurya group reported a visible-light-driven protocol by utilizing α-azidochalcones coupled with 1- or 2-naphthols or 2-hydroxy-1,4-naphthoquinones in the presence of a ruthenium-based photocatalyst, achieving the construction of highly functionalized 2,3-fused pyrroles through a radical-mediated strategy.[98] In 2020, they further developed a catalyst-free strategy employing α-keto-vinyl azides to access structurally diverse pyrroles. This methodology demonstrated broad applicability to vinyl azides bearing a conjugated amino group.[99]

In contrast to conventional intramolecular strategies by employing azides for pyrrole synthesis, the Bandini group pioneered an intermolecular approach involving the photocatalytic condensation of aryl azides with aldehydes. (Scheme 6).[100] This methodology enabled the assembly of pyrrole scaffolds through cross-component coupling, thereby achieving a remarkable expansion in the structural diversity of pyrrole architectures compared to traditional ring-closing paradigms. Given that azides served as both nitrogen sources and oxidants, the addition of extra oxidants was not required. Moreover, this strategy was compatible with aryl, alkyl aldehydes, and multi-substituted azides, delivering corresponding pyrrole derivatives in good yields (up to 78%) under mild conditions (**48–55**).

Diverging from strategies by utilizing azides as precursors to 2*H*-aziridines, the direct employment of 2*H*-aziridines in pyrrole synthesis has been successfully established. In 2014, Xiao's group reported a photocatalytic strategy by employing 2*H*-aziridines and alkynes as starting materials to construct substituted pyrroles (**59–61**). Moreover, the utility of this approach was demonstrated by the efficient synthesis of pharmaceutical agents, HMG-CoA reductase inhibitor (**65**), showcasing its potential in drug synthesis. This strategy also featured the combination of energy transfer and redox neutral reactions, thereby facilitating the [3+2] cycloaddition of 2*H*-aziridine and alkyne and obtaining the desired products (Scheme 7).[101] The proposed mechanism showed that the one-electron oxidation reaction of 2*H*-aziridine was feasible in the presence of the excited state of the photocatalyst. Then, **69** underwent a radical addition reaction with activated alkyne group to form intermediate **71**, which subsequently underwent oxidation/intramolecular cyclization/aromatization to complete the reaction. This work accomplished the first metal-free photocascade catalysis that synergistically merges energy transfer and redox pathways, thereby affording novel tetra-substituted pyrroles. Based on this work, several research groups continuously worked on the photocatalytic synthesis of pyrroles by using 2*H*-azirines as direct building blocks. In 2019, Rastogi's group introduced nitro alkenes as new reaction partners, expanding the reaction types and product diversity of 2*H*-azirines.[102] The same group also developed a redox-neutral 1,3-dipolar cycloaddition reaction to construct tetrasubstituted pyrroles.[103] Furthermore, in 2022, Xia's team developed a single-step synthesis of pyrroles *via* visible-light-induced [3+2] aerobic oxidative cyclization of quinones and 2*H*-azirines.[104]

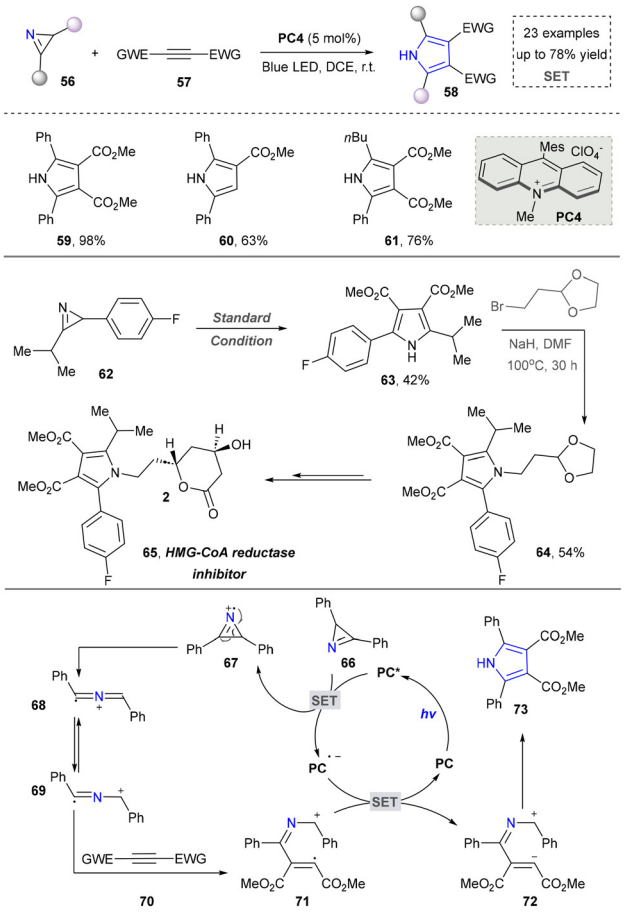
Overall, using divergent nitrogen sources, including amines, enamines, amino acids, azides and 2*H*-azirines, to construct pyrroles has been successfully achieved through different photochemical syntheses. Moreover, photocatalytic molecular editing has been a potential method to construct unprecedent pyrroles from other heteroarenes. However, despite these obvious advancements, there are only a few drugs and bioactive compounds that have been synthesized using these emerging approaches. A major constraint lies in the limited compatibility of sensitive functional groups, commonly present in active pharmaceutical ingredients, under photochemical conditions. Therefore, translating these strategies into practical routes for pharmaceuticals and natural product synthesis represents a compelling and underexplored frontier, holding considerable potential for future development.



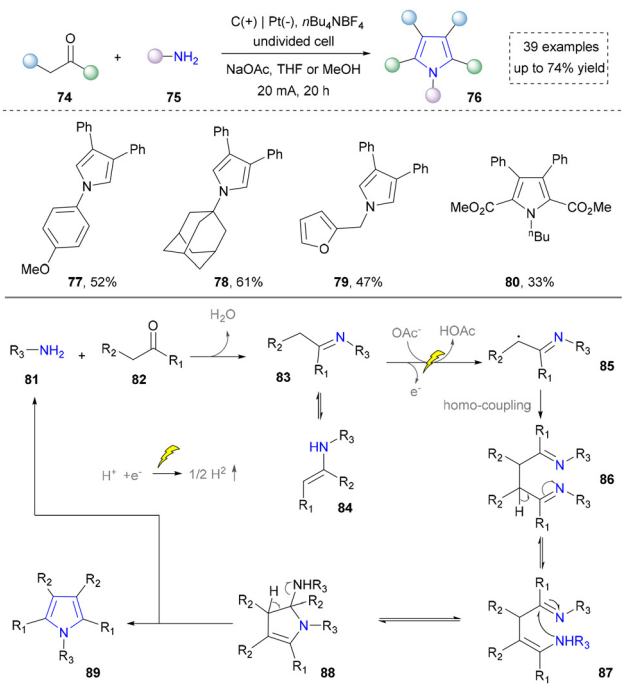
Scheme 6 Synthesis of 1,3,4-trisubstituted pyrroles from aryl azides.

3.1.2 Electrochemical synthesis of pyrroles. The Lei group pioneered a general electrooxidative annulation method in 2019 for synthesizing multi-substituted pyrroles (Scheme 8).[105] This protocol exhibited exceptional substrate adaptability across various aromatic and aliphatic amines, as well as diverse carbonyl compounds, including traditionally challenging substrates bearing multiple functional groups (**77–80**). Despite the wide range of substrates, there is still some room for improvement in reactivity and yield. The mechanistic pathway involved initial electrochemical generation of imine intermediates, followed by an anodic SET event to produce phenyl radicals. Subsequent radical addition to activated alkynes and intramolecular cyclization ultimately afforded final products.

Afterwards, primary amines have been consistently proposed as starting materials for the electrochemical synthesis of pyrroles. In 2021, the Chen group reported the use of aniline with dimethyl acetylenedicarboxylate to obtain the final product through consecutive condensation, single-electron-transfer (SET), ring closure and subsequent proton-eliminating aromatisation.[106]



Scheme 7 Visible-light-induced [3+2] cycloaddition for the synthesis of pyrroles.

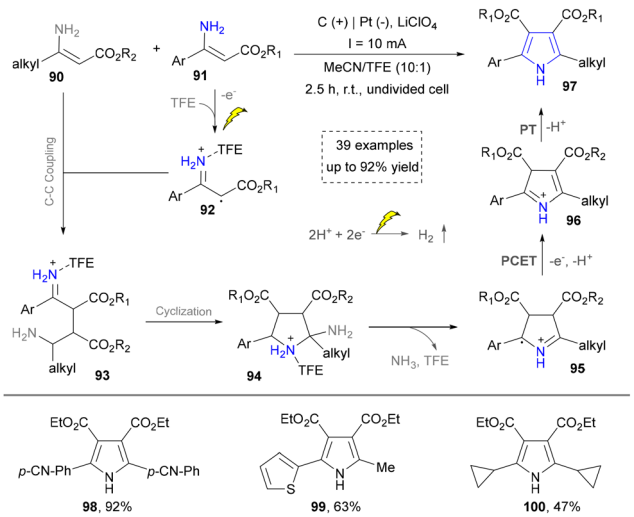


Scheme 8 Electrochemical oxidative annulation of amines and aldehydes/ketones for the synthesis of pyrroles.

Subsequently, the Yuan group disclosed that acetyl acetone was activated by iodine to form β-enamino ketone as the key intermediate. This three-component strategy significantly improved the structural diversity of pyrrole and its derivatives.[107]

Building upon these foundations, the Sarkar group has developed an effective electrochemical strategy for the hetero-coupling of aryl- and alkyl-substituted amines to synthesize tetrasubstituted aminopyrroles in 2021 (Scheme 9).[31] His approach leveraged trifluoroethanol to finely tune electrochemical parameters, achieving desired chemoselectivity through the oxidative cross-coupling of two structurally distinct enamines to construct NH-pyrroles (**98–100**). The mechanism involved the following challenging steps: (1) oxidation of the aryl-substituted enamine **91** to generate radical intermediate **92**; (2) coupling of **92** with the alkyl-substituted enamine **90** to form radical intermediate **93**. Subsequently, cyclization and oxidative aromatization yield the targeted asymmetric pyrrole product **97**. This metal-free methodology expands the substrate scope for pyrrole synthesis from systems traditionally dominated by aryl groups to aryl–alkyl hybrid systems, while exhibiting broad functional group tolerance, thereby offering a highly adaptable platform for constructing complex pyrrole building blocks in medicinal chemistry. On the basis of this work, some electrochemical methods have been reported by using different enamines as building blocks, which further diversified the pyrrole synthesis.[34,108,109]

With the ongoing exploration of the nitrogen sources required for pyrrole synthesis, Liu *et al.* reported an innovative electrochemical ring contraction strategy by utilizing Hantzsch esters in 2021, expanding the synthetic toolbox for pyrrole preparation (Scheme 10).[49] This methodology capitalized on the cathodic reduction of pyridine derivatives to generate radical anions **107**, which underwent sequential intramolecular Michael addition and ring contraction processes. This transformation efficiently converted Hantzsch ester derivatives into polysubstituted pyrroles through acetate extrusion and rearomatization



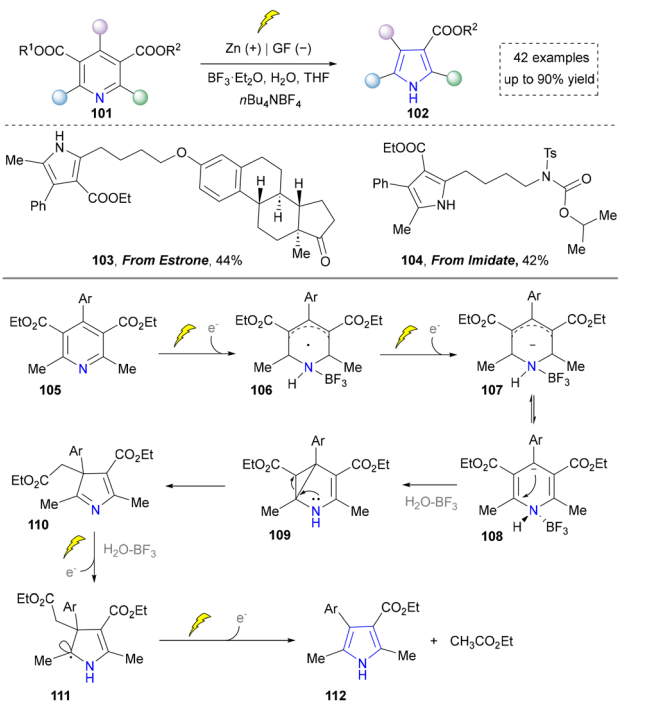
Scheme 9 Synthesis of the asymmetrically substituted NH-pyrroles by electrooxidation.

sequences, demonstrating exceptional atom economy and functional group diversity. In this case, estrone derivatives (**103**) and imidate (**104**) remained stable under strong reducing and Lewis acid conditions, indicating its significance in modifying steroid-based pharmaceuticals. Given that this also constitutes an atom-editing strategy through carbon deletion, we have not allocated an independent section for its discussion.

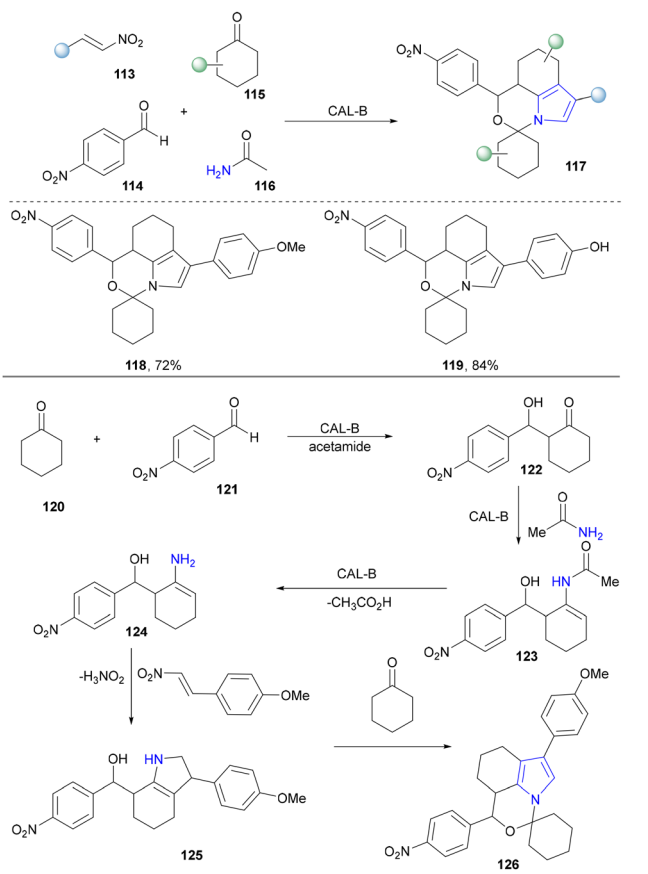
Overall, compared to traditional and photochemical approaches, electrochemical synthesis achieves direct functionalization of redox-sensitive groups, promotes reactions under mild and metal-free conditions, and exhibits superior compatibility and activation capability for low activity, high oxidation potential, or structurally unique alkene or amine precursors. This approach offers a distinct advantage for drug synthesis by avoiding stoichiometric oxidants and metal catalysts, thereby simplifying purification and reducing potential metal residues in active pharmaceutical ingredients. However, a notable limitation remains the challenge of scaling up these processes due to issues such as electrode passivation, limited reactor design for heterogeneous systems, and the need for precise control over potential and current density in complex molecular settings. In addition, while the use of amines and anilines as nitrogen sources in pyrrole synthesis has been extensively reported, the potential for employing other nitrogen sources through electrochemical methods remains largely unexplored, thus presenting ample opportunities for further development.

3.1.3 Enzymatic synthesis of pyrroles. Porphobilinogen synthase (PBGS), an ancient enzyme catalysing the first common reaction in the biosynthesis of all the tetrapyrrole pigments, such as heme, chlorophyll, and B_{12}, catalysed the formation of monopyrrole porphobilinogen from the asymmetric condensation of two molecules of 5-aminolevulinic acid (ALA).[110] In 1996, the Neier team reported that the PBGS from *Rhodobacter sphaeroides* can also catalyse the formation of a mixed pyrrole from 5-aminolevulinic acid and levulinic acid.[111] In 2023, the Zhang group established a cell-free reaction system containing 36 enzymes to produce adenosylcobalamin (AdoCbl), which is a bioactive form of vitamin B_{12}.[112]

In 2014, the Lin group established a novel lipase-initiated multicomponent reaction (MCR) catalysed by *Candida antarctica* lipase B (CALB) for the synthesis of spirooxazino derivatives (**117**).[113] Two rings containing a pyrrole ring were constructed in a single step, in one pot, utilizing commonly available nitrostyrene (**113**), aldehyde (**114**), cyclohexanone (**115**) and acetamide (**116**) substrates (Scheme 11). Throughout the reaction, CALB catalysed the initial three-step reaction, the aldol condensation of **120** and **121** to form the intermediate (**122**), the condensation of β-hydroxy ketone (**122**) and acetamide to afford the intermediate (**123**), and the hydrolysis of **123** to obtain the enamine intermediate (**124**). Subsequently, **124** underwent a Michael addition/intramolecular Nef reaction with nitroolefin to obtain the intermediate (**125**), which was eventually condensed with cyclohexanone to produce the final product spirooxazino compound (**126**). Building on this work, Wu and co-workers subsequently redesigned the lipase-initiated MCR to synthesize a broader range of spirooxazino



Scheme 10 Electrochemical strategy for the generation of pyrroles by ring contraction.

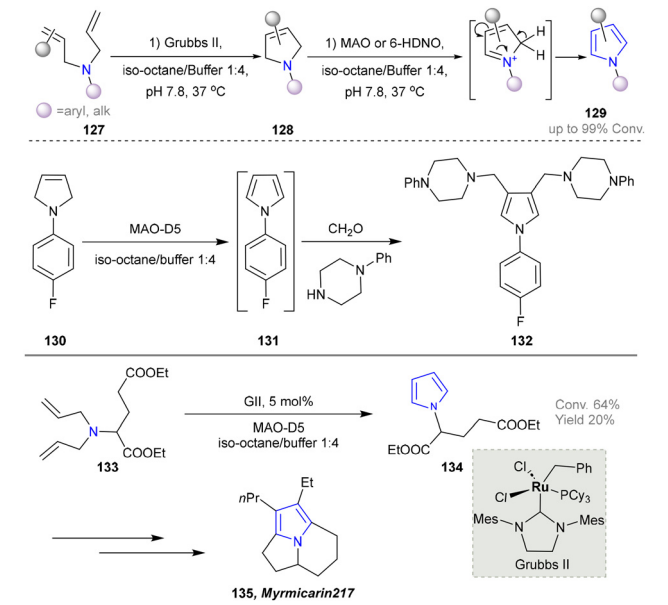


Scheme 11 Lipase-initiated synthesis of the spirooxazino derivatives.

derivatives and developed a two-enzymatic cascade MCR for the synthesis of chiral spirooxazinos.[114] Lipase from Porcine pancreas type II (PPL) catalysed asymmetric aldol reactions to generate the optically pure chemo-aldol intermediate, which was continuously employed as a starting material of CALB along with other substrates.

Monoamine oxidases (MAOs) are a class of flavin-dependent enzymes that catalyse the oxygen-driven conversion of amines to their corresponding imines.[115] The imines are then non-enzymatically hydrolysed to aldehydes, while the flavin adenine dinucleotide (FAD) cofactor is regenerated to oxidative state by molecular oxygen, producing hydrogen peroxide and ammonia formation.[116] MAO-N from *Aspergillus niger* is a highly (*S*)-selective oxidoreductase, which has widely been used in synthetic chemistry.[117,118] 6-Hydroxy-D-nicotine oxidase (6-HDNO) from *Arthrobacter nicotinovorans*, a key enzyme involved in the metabolism of nicotine, is an enantiocomplementary (*R*)-selective amine oxidase.[119]

In 2017, the Castagnolo group reported that pyrrolines can be efficiently converted into pyrroles through the aromatization activity of MAO-N or 6-HDNO whole-cell biocatalysts under mild conditions. Among them, the variant MAO-D5 catalysed the aromatization of various *N*-aryl- and *N*-alkyl-3-pyrrolines (**128**) into the corresponding pyrroles (**129**). Afterwards, a one-pot chemoenzymatic cascade process combining ring-closing metathesis (RCM) reactions with the MAO-N enzymes was established to realize the sustainable production of pyrroles from diallyl-amines/anilines (Scheme 12).[43] The MAO-Mannich chemoenzymatic methodology could be applied to synthesize the antitubercular pyrrole (**132**).[120–122] Additionally, the pyrrole precursor (**134**)[112] of the natural alkaloid Myrmicarin 217 (**135**) was obtained by the RCM-MAO chemoenzymatic cascade from the diene (**133**).[123]



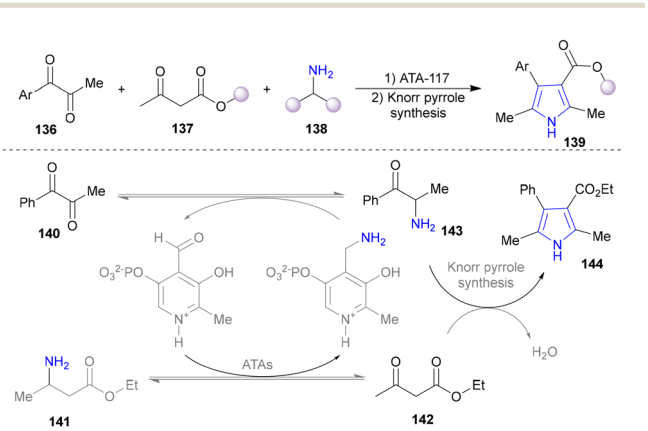
Scheme 12 Chemoenzymatic cascade process for the synthesis of pyrroles using MAO-N.

Various ketones and aldehydes can be converted into the corresponding primary amines by amine transaminases (ATAs) as biocatalysts, utilizing the reversible properties of biocatalytic amination, with a β-amino ester (**141**) functioning as both the substrate and the amine donor.[124–126] In 2018, the Turner group designed a self-sufficient strategy for the synthesis of pyrrole without external amine donors (Scheme 13).[127] The α-aminoketone (**143**), generated from α-diketones (**140**) catalysed by ATAs, condensates with β-ketone ester (**142**) *via* the Knorr pyrrole synthesis to afford substituted pyrrole (**144**). pH modification inhibited the undesired spontaneous oxidative dimerization of α-aminoketone (**143**) to produce pyrazines.

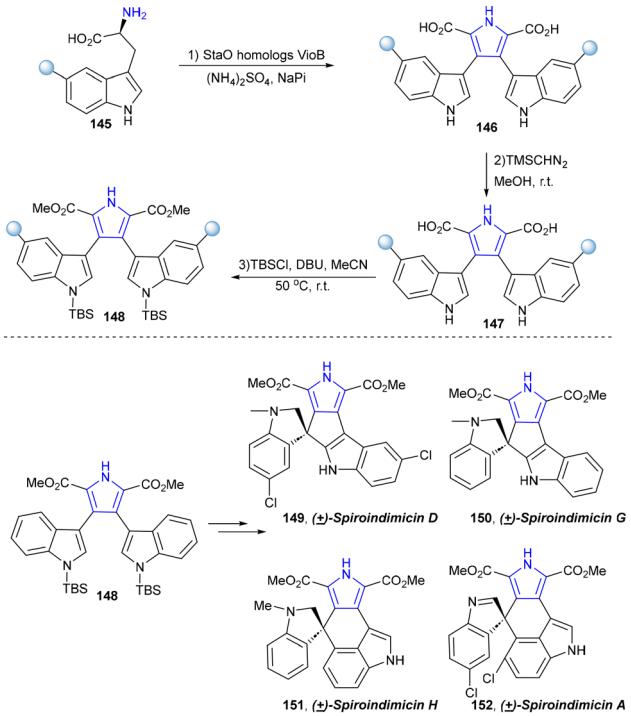
The biosynthetic pathway of violacein and indolocarbazole natural products has been fully elucidated.[128–140] In 2022, Xu's group established a chemoenzymatic pathway for the biomimetic total synthesis of the spiroindimicins (Scheme 14).[141] Two key enzymes, namely, tryptophan oxidase LaStaO and chromopyrrolic acid synthetase VioB, responsible for tryptophan dimerization in the biosynthetic pathway of bisindole alkaloids were utilized to catalyse the oxidative dimerization of (5-chloro-)L-tryptophan (**145**) in one-pot synthesis to obtain the bis-indole precursors (5,5″-dichloro-)chromopyrrolic acid (**146**), which were subsequently methylated and *N*′,*N*″-di-TBS-protected to synthesize **148**. Afterwards, two skeletally distinct spiroindimicins with the [5,5] and [5,6] spiro-ring skeleton, including (±)-spiroindimicins D (**149**) and G (**150**), and (±)-spiroindimicins H (**151**) and A (**152**), were selectively constructed *via* intramolecular oxidative coupling of C3′-C4″ and C3′-C2″, respectively.

In 2023, an environmentally benign strategy has been developed by Wang's group to synthesize pyrrole disulfides (**155**), a fusion between pyrrole and disulfide functional groups, by porcine pancreatic lipase (PPL) in ethanol at 40 °C from β-ketothioamides (KTAs) **153** and ethyl cyanoacetate (Scheme 15).[142] This strategy provided a significant improvement in the synthesis of pyrrole disulfides over the conventional synthesis methods by utilizing malodorous and toxic hydrogen sulfide gas or environmentally unfriendly reaction conditions,[143,144] contributing to the advancement of environmentally friendly biocatalysis.

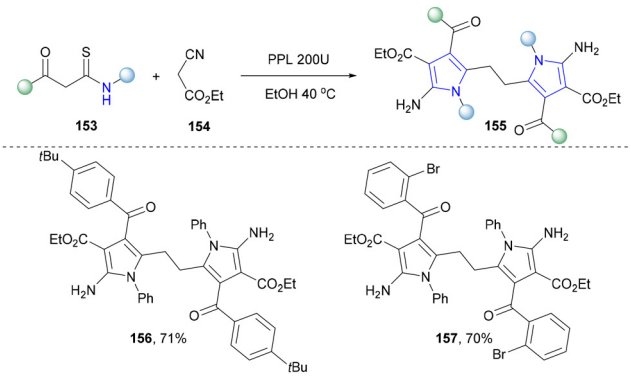
Overall, when compared to traditional synthetic methods that may require harsh conditions and metal catalysts, the



Scheme 13 Chemo-enzymatic cascades for the synthesis of pyrroles using ATA biocatalysts.



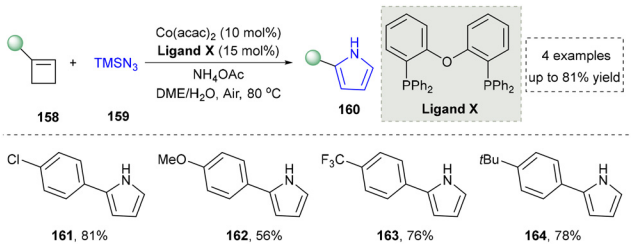
Scheme 14 Biomimetic total synthesis of the spiroindimicin family.



Scheme 15 Enzymatic synthesis of pyrrole disulfides by lipase.

enzymatic or chemoenzymatic synthesis of pyrroles can offer a more environmentally friendly and efficient alternative. There are also some enzymes catalysing the formation of pyrrole ring involved in the biosynthetic pathway of natural products,[145] such as kosinostatin[146] and coumermycin A_1,[147] but they will not be discussed here since they have not yet been applied for enzymatic synthesis. It is expected that they will provide more possibilities for the enzymatic synthesis of pyrroles in the future.

3.1.4 Atom editing for pyrrole construction. Skeletal editing has also emerged recently for the construction of pyrroles. In 2022, Wei's group disclosed the insertion of a nitrogen atom into aryl cycloalkenes through cobalt catalysis (Scheme 16).[148] This transformation enabled the direct conversion of both electron-rich and electron-deficient arylcyclobutenes (**161–164**) into the corresponding aryl-substituted pyrroles *via* direct insertion of a nitrogen



Scheme 16 Cobalt-catalyzed nitrogen-atom insertion for the pyrrole formation.

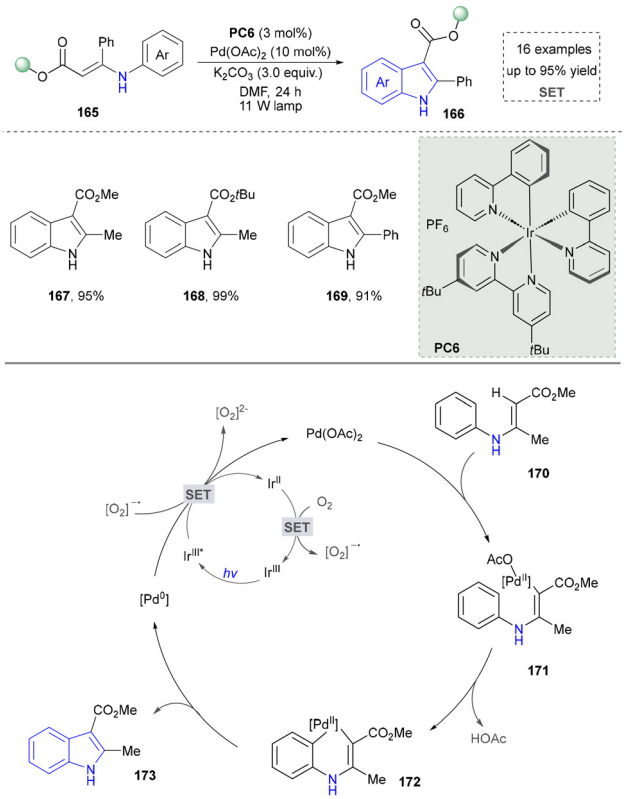
atom. Notably, the reaction proceeded under aqueous and open-air conditions, offering a simple protocol from readily available cyclobutenes. Even though the substrate scope needed further investigation, this emerging method provided a solution to access valuable pyrroles from different scaffolds.

3.2 Synthesis of indoles

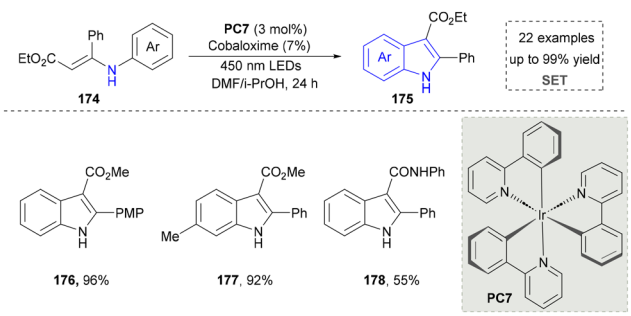
Indole represents a pivotal structural motif in organic synthesis,[149] enabling diverse functional group transformations through a wide array of chemical reactions.[150] Traditional methods include but are not limited to electrophilic halogenation, Friedel–Crafts acylation and alkylation, oxidation and reduction processes, as well as 1,2- and 1,4-addition reactions. The indole ring system is ubiquitously distributed in natural products, constituting one of the most prevalent heterocyclic frameworks in nature.[151,152] Globally, >70 synthetic indole-containing drugs have been commercialized.[153,154] Notably, the U.S. Food and Drug Administration (FDA) specifically approved 14 indole-derived pharmaceutical agents between 2015 and 2021, underscoring the continued importance of this heterocyclic system in modern drug discovery and development.[155] In this section, the synthesis of indoles through emerging approaches will be overviewed carefully.

3.2.1 Photochemical synthesis of indoles. A new strategy that combined photooxidation and a palladium-catalysed system for high-energy indole synthesis was discovered by the Rueping group in 2014 (Scheme 17).[156] 3-Phenylamino-2-crotonates with various substituents were compatible with this strategy, and the corresponding substituted indole compounds are realised in high yields (**167–169**). The mechanistic study found that the superoxide anions formed by photooxidation catalysts in the absence of oxygen or *in situ* can act as an external oxidant in the presence of aerobic and photooxidation catalysts. Since only a small amount of oxidant was produced and consumed immediately, side reactions of the substrate or product could be avoided. Therefore, this method was very suitable for substrates that were sensitive to oxidants. Even though this pioneering work still required transition metal catalysts, this dual catalytic system avoided the use of typically external oxidants by using a catalytic amount of photooxidation catalysts.

To further improve the photocatalytic synthesis of indoles from 3-phenylamino-2-crotonates as nitrogen sources, the Wu group developed a convenient strategy for the synthesis of indole under visible light irradiation through intramolecular C–C bonds in 2016 (Scheme 18).[157] By using catalytic amounts



Scheme 17 Photoredox synthesis of indoles by the palladium-catalysed C–H activation.

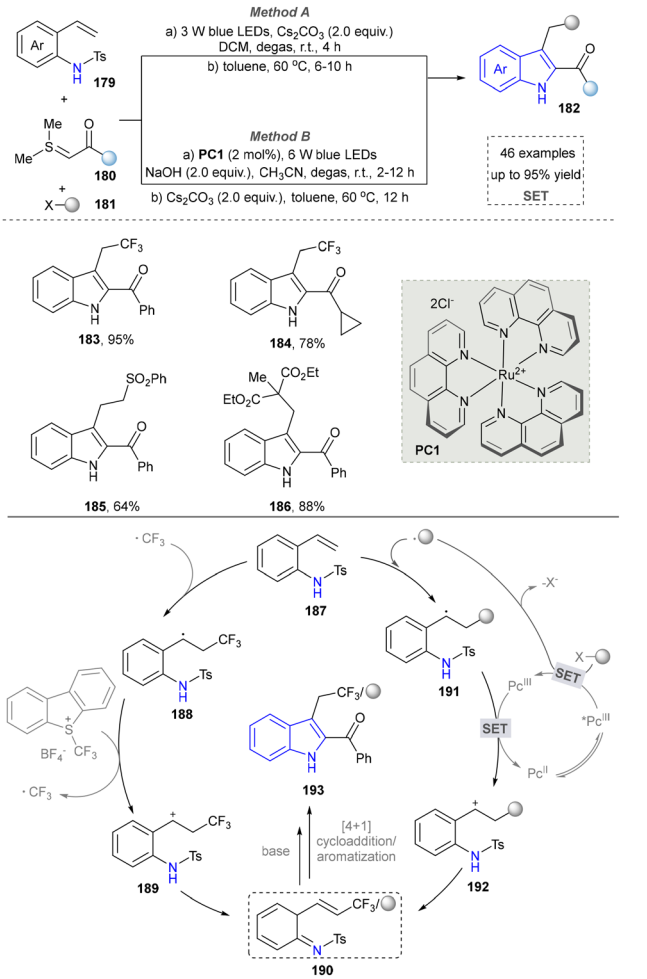


Scheme 18 Oxidant-free strategy for the synthesis of indoles under visible light irradiation.

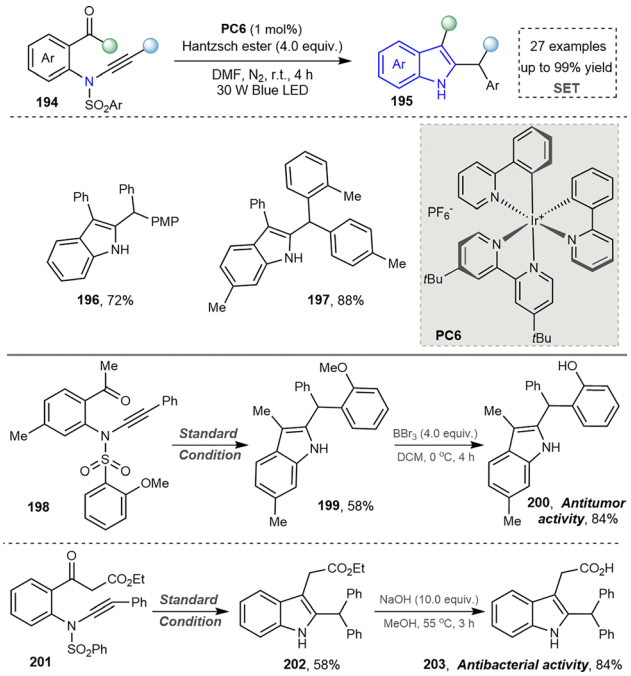
of the photosensitizer Ir(PY) and the catalyst cobalt oxime, various *N*-arylenamines were highly selectively converted to the corresponding indoles (**176–178**), with H_2 being the only by-product. Compared with the previous methods, this strategy did not require the use of oxidants and additional base, so undesirable by-products can be avoided.

In 2017, the Xiao group presented a light-driven radical-mediated strategy for the *in situ* generation of azo-o-quinone methyl esters (**190**) from alkenyl aniline (**187**) and alkyl radical precursors, followed by alkali treatment of the cyclized products for efficient and convenient synthesis of high-energy indole (Scheme 19).[158] This strategy enabled efficient multi-component reactions of alkenyl anilines, halides and thionyl groups, and showed a wide substrate range and functional group tolerance (**183–186**). Later, the Wang group found the similar method to afford indoles using radical-mediated strategy.[59] In the same year, the Kumar group also reported the synthesis of CF_3-containing indoles by using Langlois' reagent as the radical precursor.[159] This work presented a novel and practical radical Smiles rearrangement initiated by a photo-oxidation-catalysed regioselective keto-alkyne amide coupling. In 2018, Li's team developed a visible-light-induced aerobic cross-coupling of glycine derivatives with indoles for efficient BIM synthesis, featuring mild conditions and good functional group tolerance.[160]

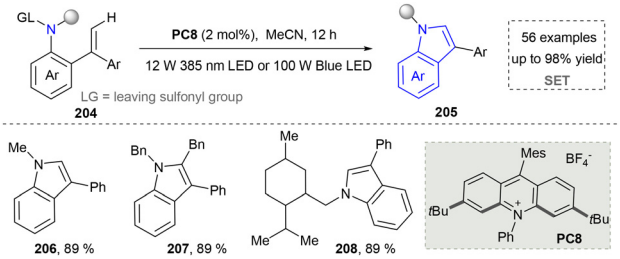
In 2015, Paixão's group pioneered a visible-light-mediated intramolecular reductive cyclization reaction of substituted 2-halobenzenesulfonamides containing terminal alkynes for indole synthesis;[161] however, this strategy suffered from a limited substrate scope. Subsequently, Xia's group developed an approach to access indoles *via* the intramolecular Mannich cyclization of *N*-vinyl-2-iodoaniline derivatives, which was successfully applied to natural product synthesis.[162] In 2020, starting from carbonyl-acetylenamide, the Ye group successfully achieved a light-facilitated Smiles rearrangement based on acetylenamides (Scheme 20) and constructed a series of 2,3-functionalized indoles



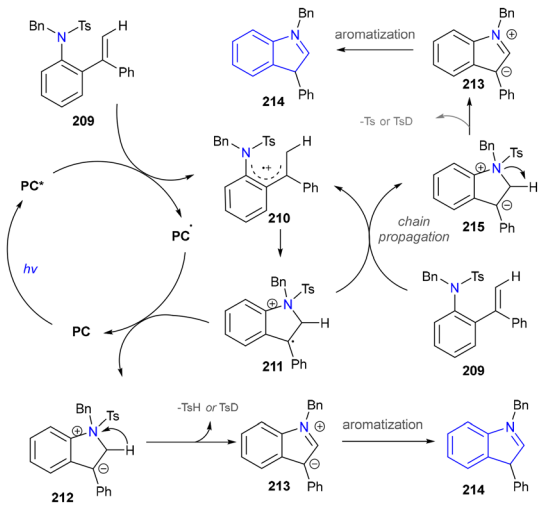
Scheme 19 Visible-light-driven aza-*ortho*-quinone methide generation.



Scheme 20 Synthesis of the functionalized indoles from the visible light-mediated keto-amide coupling.



Scheme 21 Photoinduced synthesis of indoles *via* intramolecular C–N bond formation.



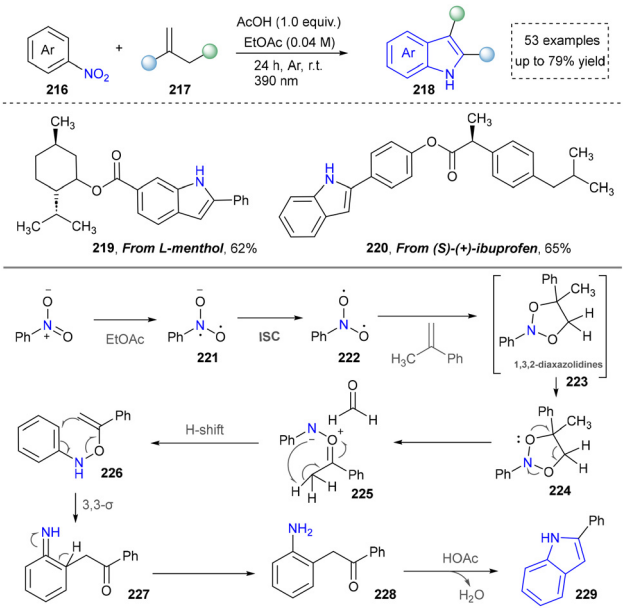
Scheme 22 Mechanism of the visible-light-induced indole synthesis through intramolecular C–N bond formation.

and 3,4-functionalized isoquinoline heterocyclic compounds (**196**, **197**). The reaction showed the following characteristics: (1) the Smiles rearrangement reaction based on acetylenamide was realized for the first time; (2) two important heterocyclic skeletons of functionalized indoles and isoquinolines were synthesized with high efficiency and selectivity, and several important bioactive molecules were further synthesized by this method (**200**, **203**). This radical Smiles rearrangement was applicable to intermolecular radical tandem reactions based on propiolamides, enabling the efficient construction of heterocyclic frameworks in a single step. The most salient feature of this strategy is its excellent compatibility with the free N–H group of indoles, allowing the product to serve directly as a building block for further functionalization.[163] On this basis, the Xia group reported a visible-light-induced, copper-catalyzed oxidative cyclization of substituted *ortho*-aminophenylpropynes for synthesizing indole derivatives, although the substrate scope was restricted to aryl compounds.[164]

In 2022, a photocatalytic method was explored by Shi's group and *N*-sulfonated aromatic derivatives served as starting materials, *N*-substituted indole products were generated efficiently through γ-fragmentation under mild conditions without any additives (Scheme 21).[165] This strategy also had a wide range of substrate scope and provided a powerful strategy for the synthesis of complex indoles (**206–208**), which promoted the further development for the synthesis of nitrogen-containing heterocycles under neutral redox conditions.

The proposed mechanism was depicted and the photoexcitation produced the highly oxidizing excited state of PC (Scheme 22). This was reductively quenched by the substrate (**209**), generating radical cationic species (**210**). The nitrogen atom in **210** then reacted with the alkene moiety intramolecularly, forming a cyclized radical cationic intermediate (**211**). A SET process between **211** and the acridine radical yielded zwitterionic intermediate (**212**) and regenerated an acridinium salt in the closed catalytic loop. The elimination of TsH or TsD from **212** formed another zwitterionic intermediate (**213**), which underwent aromatization to produce the desired indole product (**214**). Given the reaction's quantum yield of 1.77, a chain process occurred where **211** oxidized another molecule of **209** to produce **215**, ultimately yielding the final product (**214**) *via* the same intermediate (**213**).

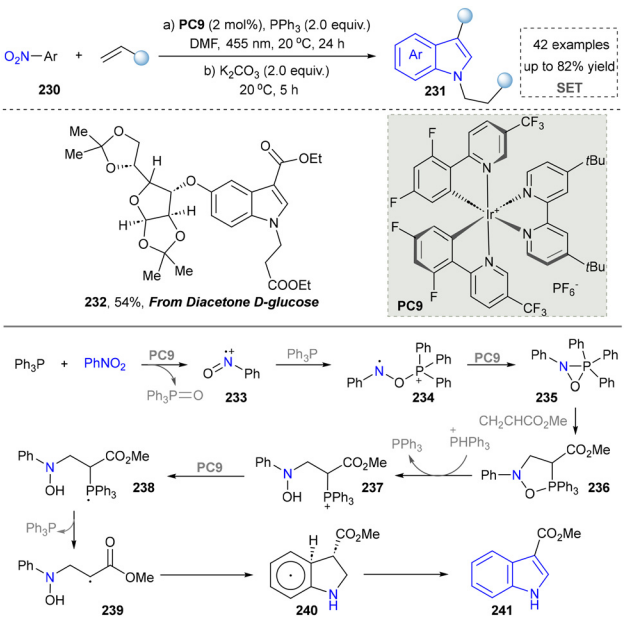
Cheap and commercially available nitroarenes have been ideal nitrogen sources for the construction of organic amines and N-containing heterocycles.[166] The Shi group developed an environmentally friendly method for the synthesis of indoles by oxidative cleavage of olefins with nitro(hetero)aromatics in 2024 (Scheme 23).[167] This strategy exploited the selective polar splitting of 1,3,2-dioxazolidine (**223**) to form carbonylimine intermediates (**225**) and N–O–C dipoles (**226**), and the novel reactivity of these dipoles, including the migration of carbonylimine to o-alkenyl hydroxylamine. Under the standard conditions, derivatives of bioactive molecules, such as L-menthol and *S*-(+)-ibuprofen (**219**, **220**), were readily converted into indole-containing drug analogues using this photoinduced method, demonstrating the potential of this method in drug-oriented



Scheme 23 Photoinduced Bartoli indole synthesis.

synthesis. This system exhibited notable tolerance toward ester and benzylic groups. However, the scope of late-stage functionalization of drug molecules remained relatively limited.

Similarly, the Studer group reported the cost-effective synthesis of indoles by photocatalysis. This strategy relied on a radical process for the activation of a nitro group and the annulation of nitroarenes and alkenes (Scheme 24).[47] Diacetone-D-glucose, a natural product-derived compound, was readily converted into the corresponding indole derivative (**232**) through late-stage functionalization. This demonstrated the good tolerance of



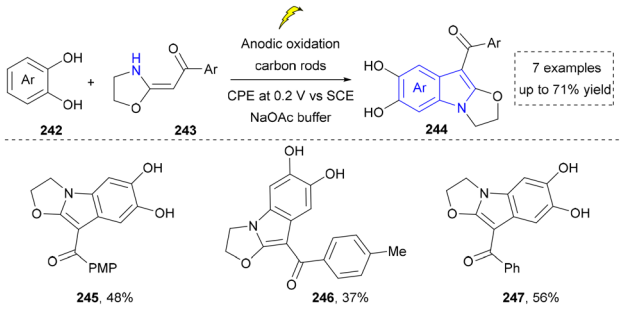
Scheme 24 Photocatalytic PPh_3-mediated synthesis of C3-functionalized indoles.

glucose compounds and acetal structures under standard conditions. Therefore, this photocatalytic system provided an efficient pathway for developing bioactive molecules containing indole skeletons. The key to success was the PPh_3-mediated radical deoxygenation of nitroarenes. With the formation of nitrosoarene radical cations (**234**), they further reacted with various alkenes with electron-absorbing groups through the double C–H bond functionalization of nitro aromatics and alkenes at room temperature, and C3-functionalized indoles were quickly obtained. This work represents a significant shift in indole synthesis strategy, moving away from traditional reliance on alkynes and transition metals towards the use of more economical and stable alkene-based electrophiles. The method maintains high yields while demonstrating broad compatibility with a wide range of sensitive functional groups and complex bioactive scaffolds, thereby providing a new and practical approach for efficient indole construction.

Other readily available compounds have also been reported as nitrogen sources for indole synthesis. For example, in 2014, Xiao's group reported a method for efficiently constructing 2-substituted indoles from styrene azides by visible-induced photocatalysis, but the substrate scope was limited.[168] In 2018, Reiser's group established a photoredox-mediated radical process for the synthesis of indoles from radical tandem cyclization of *ortho*-isocyano-α-bromo cinnamates.[41] Recently, Wang's group has developed a strategy for the synthesis of indoles, which was driven by visible-light-mediated oxidative dehydrogenation of indolines.[169]

Compared to conventional methods like Fischer indole synthesis or transition-metal-catalyzed cross-coupling, photochemical synthesis revolutionizes the substrate scope for indole compounds by eliminating the need for pre-functionalization, allowing the direct modification and construction of the indole scaffold from simple, non-activated substrates under mild and neutral conditions and enabling single-step access to traditionally challenging, sterically congested or polycyclic indole derivatives, thereby providing a vastly expanded molecular scaffold library for drug discovery. Overall, the intramolecular cyclization to furnish the indoles has been well established with different photocatalytic methods. However, it is evident that the synthesis of these starting materials often involves multiple steps, which not only complicates the process but also restricts the structural diversity of the resulting indoles. It is important to highlight that intermolecular synthesis, utilizing readily available substances, holds greater promise and deserves more attention for further exploration.

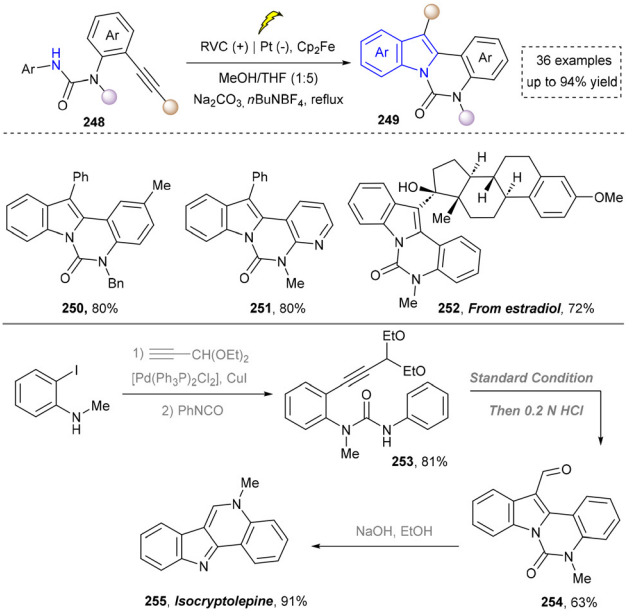
3.2.2 Electrochemical synthesis of indoles. As early as 2009, Zhong's team pioneered an electrochemical strategy for constructing fused indole derivatives through the annulation of catechol derivatives with α-oxacycloalkenone *N*,*O*-acetals (Scheme 25).[170] This groundbreaking protocol established an environmentally benign approach to access structurally complex indole architectures under mild conditions. This methodology demonstrated remarkable efficiency in simultaneously installing reactive hydroxy and carbonyl functionalities within the fused heterocyclic system, a challenging feat for



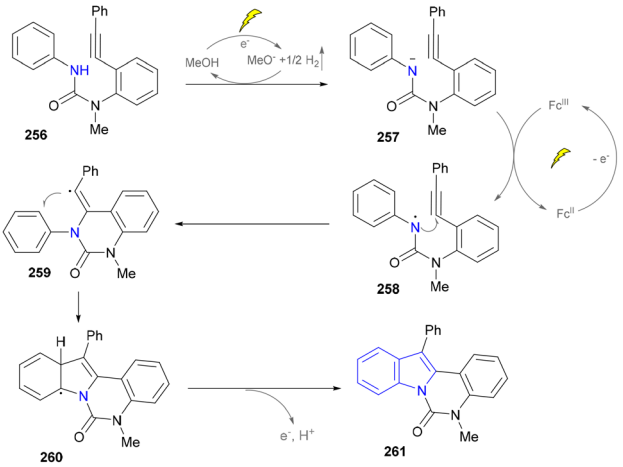
Scheme 25 Electrochemical synthesis of the fused indole derivatives.

conventional synthetic approaches (**245–247**). The key advantages of this method lied in its protection-group-free nature and mild reaction conditions (room temperature, neutral buffer), although the regioselectivity was influenced by steric effects of substrate substituents.

To further obtain diverse indoles, Xu and co-workers reported the electrochemical synthesis of highly functionalized indoles and azaindoles by C–H/N–H functionalization of (hetero)-arylamines using tethered alkynes (Scheme 26).[171] The broad functional-group tolerance of method was evidenced by the preparation of indoles bearing diverse substituents and the more challenging task of constructing complex azaindoles (**250**, **251**). This strategy was successfully applied to the late-stage modification of ethinyl estradiol derivative (**252**) under standard conditions, demonstrating the excellent compatibility with hydroxyl groups and chiral centers, underscoring the potential for the rapid synthesis of pharmaceutically active derivatives. In addition, this method required neither precious metals nor external oxidants. Finally, the utility of this method was highlighted by the concise total synthesis of isocryptolepine, which



Scheme 26 Electrochemical C–H/N–H functionalization for the synthesis of indoles.



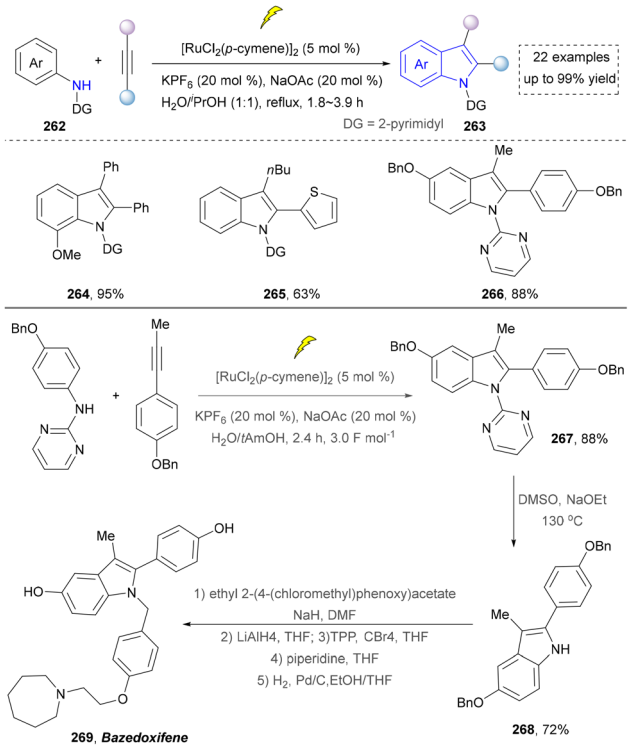
Scheme 27 (Aza)indole synthesis by C–H/N–H functionalization.

was prepared from advanced intermediate (**254**), requiring only minimal further manipulations.

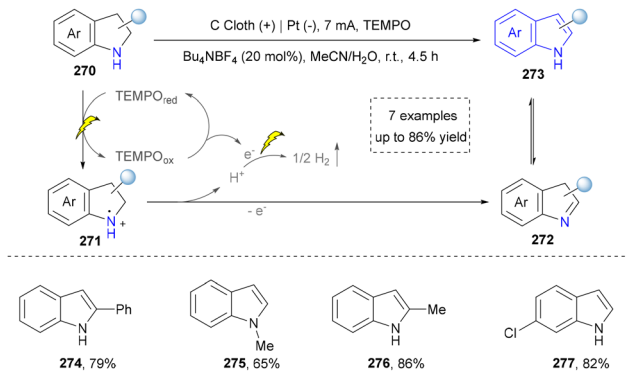
In their proposed mechanism, the electrochemical formation of (aza)indoles involved the anodic oxidation of [Cp_2Fe] to [Cp_2Fe^+] and the cathodic reduction of methanol to methoxide (MeO^-) and H_2. MeO^- deprotonated the substrate to form the corresponding anion (**257**), which underwent the single-electron transfer (SET) process with [Cp_2Fe^+] to generate nitrogen-centered radicals (**258**), which then underwent a rare 6-*exo-dig* cyclization reaction to form a vinyl radical (**259**). The further cyclization with the aryl ring produced a delocalized radical (**260**). Finally, the rearomatization of **260** *via* electron and proton elimination yielded the final product (**261**) (Scheme 27).

In 2018, the same team continuously developed the electrochemical dehydrogenative alkyne annulation to furnish indoles.[172] This method employed an undivided cell system, where a ruthenium complex catalysed the [3+2] cyclization of aniline derivatives with available alkynes to construct indole scaffolds while releasing hydrogen gas (Scheme 28). The reaction demonstrated excellent air stability in water/alcohol mixed solvents and could be performed on a gram scale. Even though the ruthenium catalyst was required, and the substrate scope (**264–266**) was expanded by intermolecular synthesis. The utility of this strategy was further demonstrated by the concise synthesis of bazedoxifene (**269**) from the key intermediate (**267**), which was readily prepared under slightly modified conditions (H_2O/*t*AmOH replace H_2O/*i*PrOH, 3.0 F mol^{-1} replace 3.2 F mol^{-1}, 2.4 h) and required further elaboration. A notable limitation, however, is the strategy's exclusive compatibility with secondary amines.

In the same year, Lei and co-workers also reported an electrochemical dehydrogenative aromatization of six- and five-membered N-heterocycles (*e.g.*, tetrahydroquinolines and indolines) using TEMPO as an organoelectrocatalyst without relying on a transition metal catalyst (Scheme 29).[173] The reaction was conducted in an undivided cell system, where anodically generated TEMPO cation mediated the stepwise dehydrogenation of N-heterocycles (with concomitant H_2 evolution), achieving yields up to 82% (**274–277**). Earlier, the same group also successfully



Scheme 28 Ruthenium-catalyzed electrochemical dehydrogenative alkyne annulation.



Scheme 29 TEMPO-promoted electrochemical receptor-free dehydrogenation of N-heterocycles.

realized the electrocatalytic reaction of the intramolecular oxidative annulation of enamines without additional oxidants. Even though the concept was known, it improved the sustainability compared with previously photocatalytic methods.[174]

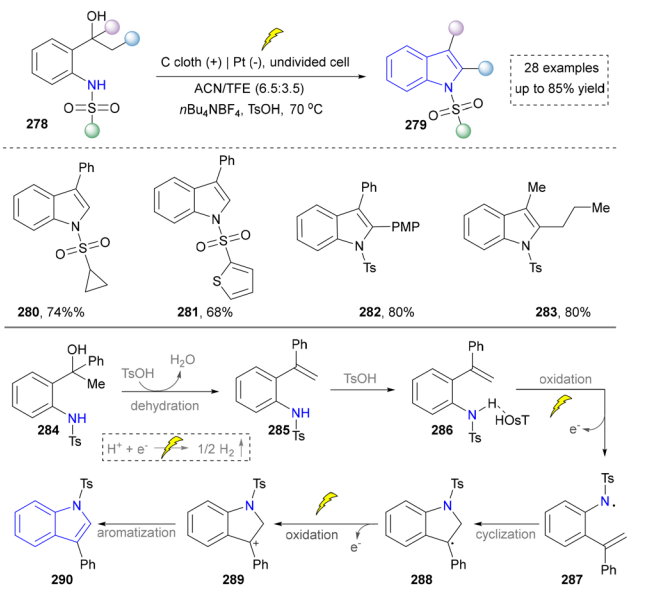
In 2023, Guo and co-workers depicted a metal- and oxidant-free electrochemical protocol for the synthesis of substituted indoles. This method involved the tandem dehydration of 1-(2-aminophenyl)alcohols followed by intramolecular dehydrogenative C–N coupling to efficiently construct an indole scaffold (Scheme 30).[175] Mechanistic investigations revealed that the transformation proceeded *via* a proton-coupled electron transfer (PCET) process to generate nitrogen-centered radicals, which subsequently underwent cyclization and oxidative aromatization. The protocol demonstrated broad functional group tolerance toward halogens, alkyl, and aryl substituents (**280–283**), while maintaining high efficiency even in the presence of water and atmospheric oxygen, highlighting its exceptional practicality and green chemistry features.

Some other methods including an electrochemical [3+2] cycloaddition approach,[176] pK_a-regulated switchable synthesis,[177] and iridium(III)-catalyzed electrochemical coupling method have been also reported based on the above-mentioned strategies.[178–180] These diverse approaches have demonstrated significant potential in green synthesis and sustainable chemistry, collectively expanding the toolbox for indole construction.

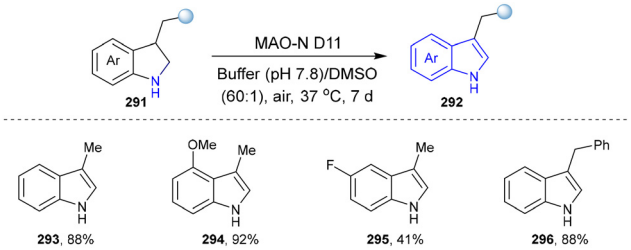
Electrosynthesis demonstrates complementary advantages over photochemical methods in substrate scope, primarily due to its direct electron-transfer mechanism. It effectively activates substrates with poor light-absorption properties or those incompatible with photosensitizers. By precise potential control, electrosynthesis enables mild and selective oxidation of electron-rich arenes or reduction of electron-deficient compounds—processes that often face challenges in photocatalysis due to undesired energy transfer or overreaction. Furthermore, it exhibits better tolerance toward substrates prone to photoinduced side reactions or in high-concentration systems where light penetration is limited.

3.2.3 Enzymatic synthesis of indoles. In 2020, Castagnolo's group reported a chemoenzymatic approach for the synthesis of various substituted indoles (Scheme 31).[36] Indoline (**291**) was first prepared by arylative dearomatization of acetyl-indoles or photocatalytic cyclization of arylaniline and then underwent aromatization, which was catalysed by MAO-N D11 to produce indole (**292**) with high selectivity but low efficiency.

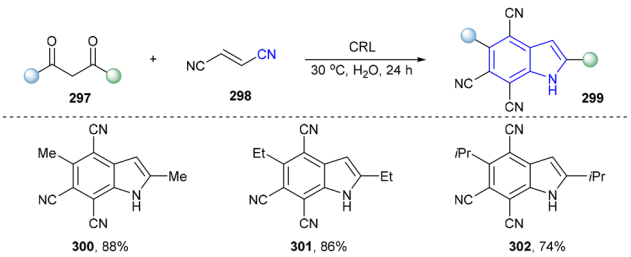
In 2021, Wang and co-workers designed a green and efficient method to synthesize indoles from 1,3-diketones with fumaronitrile utilizing *Candida rugosa* lipase (CRL) as the catalyst



Scheme 30 Electrosynthesis of the substituted indoles from 1-(2-aminophenyl) alcohols.



Scheme 31 Enzymatic synthesis of the indole derivatives catalysed by MAO.

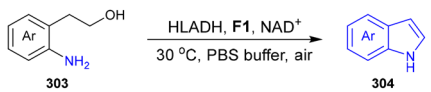


Scheme 32 Enzymatic synthesis of indoles utilizing lipase.

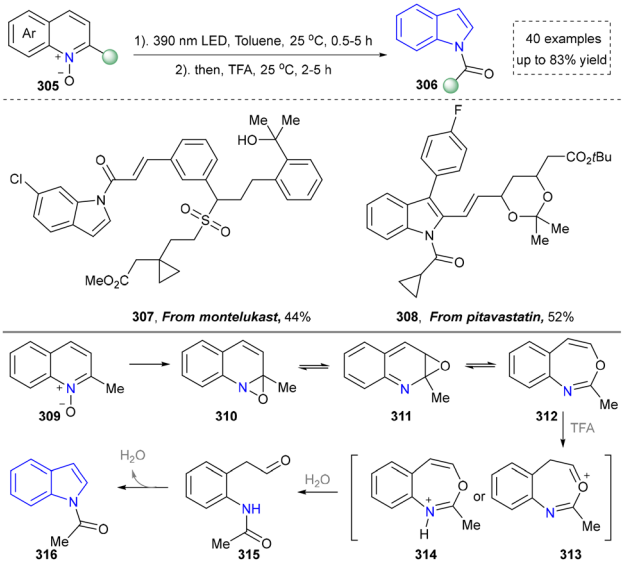
with not only satisfactory regioselectivity but also high yields (Scheme 32, **300–302**).[40]

In 2022, Zhu's group reported a sustainable two-step, one-pot cooperative chemoenzymatic system for the efficient synthesis of indoles (Scheme 33).[181] The intramolecular condensation reaction of 2-(2-aminophenyl)ethanol (**303**) was performed to obtain indoles (**304**) with 99% yield, catalysed by organocatalyst **F1** and biocatalyst HLADH (horse liver alcohol dehydrogenase). Synthetic flavinium derivative **F1**, as a bifunctional bio-mimetic organocatalyst, participated in the bioprocess for cofactor NAD^+ (nicotinamide adenine dinucleotide) regeneration and the chemo-process for oxidative cyclodehydrogenation. The cooperative chemoenzymatic process showed excellent chemoselectivity, enhanced reactivity, more efficiency, and fewer by-products, compared with those catalysed by the above-mentioned photobiocatalysts and metal manganese pincer complexes.[182]

Overall, MAO, lipase and HLADH have been used to form the indole ring with chemoselectivity, regioselectivity and specificity, though the catalytic efficiency of some enzymes needs to be further improved. Indole-containing natural products such as indigo, vinblastine,[183] and antidepressant psilocybin[184] are derived initially from l-tryptophan, which has been *de novo* synthesized in a single *Escherichia coli* with a titre of 79.4 mg L^{-1} by optimizing shakeflask fermentation without any precursor feeding. To our knowledge, enzymes involved in the formation of indole-ring are limited. Therefore, Future work should focus on mining more enzymes as biocatalysts for the synthesis of indole-containing natural products.



Scheme 33 Cooperative chemoenzymatic synthesis of indoles.



Scheme 34 Construction of indoles *via* photochemical skeletal editing.

3.2.4 Atom editing for the construction of indoles. In 2023, Levin's group has reported an atom-editing strategy by deleting carbon in azaarenes (Scheme 34).[185] This approach allowed the selective photolysis of quinoline *N*-oxides by acid-promoted rearrangement, thereby affording desirable *N*-acylindoles. This strategy demonstrated broad utility, as exemplified by the successful modification of drug molecules such as montelukast and pitavastatin derivatives. Despite the presence of sensitive functional groups (*e.g.*, hydroxy in **307** and **308**), quinoline scaffolds were directly converted into indoles under standard conditions. A key mechanistic insight was the role of added water for the *in situ* generation of acids, which facilitated the indole formation. This pathway contrasted with prior reports on the same debenzoxazepine intermediates, which typically yielded two-photon byproducts, and was unequivocally supported by ^{18}O-labeling studies. Furthermore, the obtained indoles served as versatile platforms for further diversification *via* additional atom-editing steps, leading to various nitrogen-containing molecules.

4. Two-nitrogen-containing aromatic heterocycles: pyrazoles, imidazoles, and benzimidazoles

4.1 Synthesis of pyrazoles

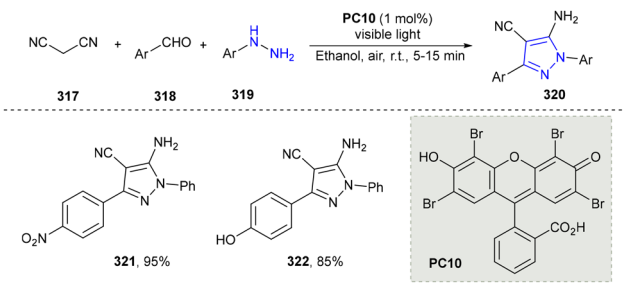
Pyrazoles and their derivatives are widely studied due to their antibacterial, anti-inflammatory, and antitumor activities, and they serve as the core structural units of many important drugs such as Celecoxib.[186–188] Additionally, pyrazoles are extensively applied in the development of pesticides, acting as precursors for the synthesis of highly efficient and low-toxicity fungicides, insecticides, and herbicides.[189,190] In materials science, pyrazole derivatives can be used to develop fluorescent probes and organic luminescent materials.[191] Their unique chemical properties also make pyrazoles important in organic synthesis,

where they can be transformed into functionalized molecules *via* various reactions.[192] Therefore, pyrazoles are not only of great significance in chemical research but also demonstrate immense potential in practical applications in pharmaceuticals, agriculture, and materials science. The cyclocondensation of hydrazine derivatives with α,β-unsaturated carbonyl compounds represents a straightforward approach to prepare polysubstituted pyrazole rings. Pyrazole formation *via* cyclization between ynones and hydrazine derivatives has been documented for over a century.[193] In this section, the synthesis of pyrazoles *via* emerging protocols will be discussed carefully.

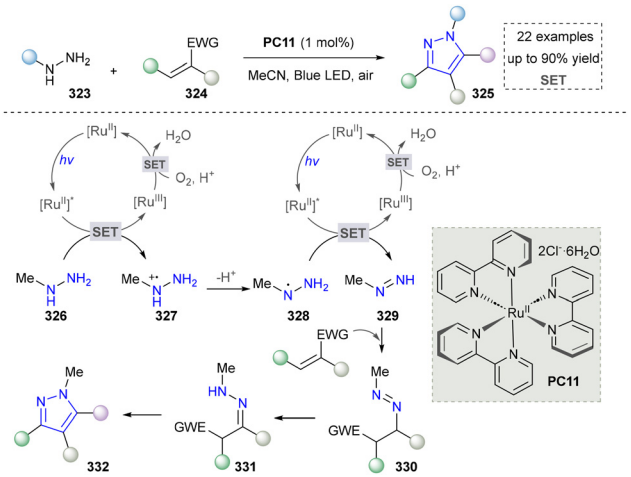
4.1.1 Photochemical synthesis of pyrazoles. In 2015, Singh's group first reported the photocatalytic synthesis of pyrazoles *via* a three-component method (Scheme 35). The aldehydes and malononitrile could form Michael acceptors, which further reacted with different hydrazines to furnish the pyrazoles efficiently (**321**, **322**), whereas the mechanism was not fully investigated. However, it is still a milestone for the rapid synthesis of pyrazoles *via* photochemical methods.[194]

In 2016, Zhu's group continuously explored the photoredox aerobic annulation for the synthesis of pyrazoles. This strategy featured the concise synthesis by using different hydrazines and Michael acceptors to furnish di/-trisubstituted pyrazoles.[195] The proposed mechanism suggested that the diazene was formed from the hydrazine *via* the SET process and oxygen worked as the electron donor. The further addition of diazene (**329**) into the Michael acceptor and the intramolecular condensation gave the final product. However, this strategy did not prove their applicability (Scheme 36). For instance, the gram-scale synthesis or synthesis of complicated pyrazoles was not investigated. In 2019, the same group extended their system by replacing Michael acceptors with an alkyne under photocatalytic conditions. Moreover, hydrazine hydrate and various hydrazines were successfully employed as nitrogen sources, demonstrating good substrate tolerance.[196]

Singha's group further extended the application of their strategy by using *in situ* formed Michael acceptors. The four-component reactions by using ethylacetoacetate, hydrazine hydrate, aromatic aldehydes and malononitrile as synthetic synthons were achieved under photoinduced conditions.[197] In 2020, hydrazines as nitrogen sources to furnish pyrazoles were further explored by the same group. They presented three-component photocatalytic methods by using coumarin units,



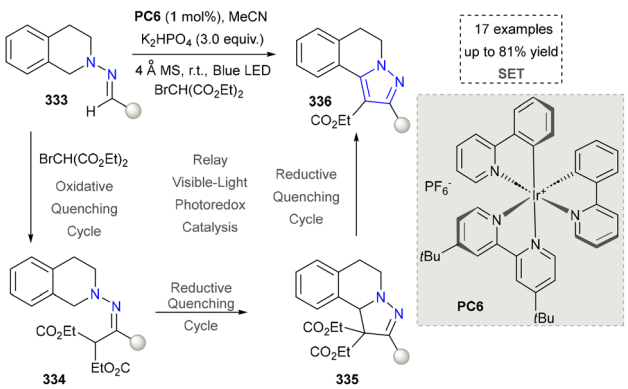
Scheme 35 Synthesis of pyrazoles from hydrazines under visible light irradiation.



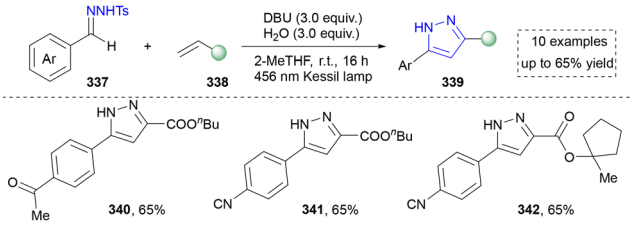
Scheme 36 Photocatalytic aerobic annulation for the green synthesis of pyrazoles.

hydrazines, and aldehydes as building blocks. The advantages of this strategy were shorter reaction time and broad substrate scope.[198] Moreover, using building blocks such as hydrazine, 1-fluoro-2-isothiocyanatobenzene, and malononitrile, Siddiqui's group described a method that further expanded the diversity of pyrazole synthesis *via* photochemical approaches.[199]

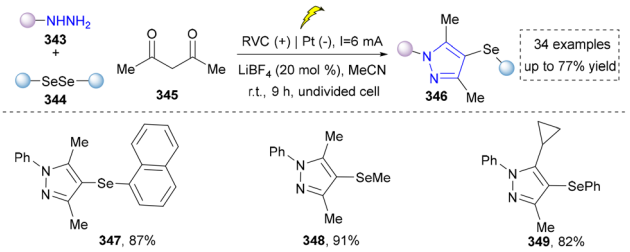
To further expand the structural diversity of pyrazoles *via* photochemical methods, the Zhu group reported a photocatalytic method to enable [4+1] annulation of hydrazones with 2-bromo-1,3-dicarbonyl compounds (Scheme 37). The key to the success was the design of three photoredox cycles, namely an oxidative quenching cycle and two reductive quenching cycles, which formed the complicated pyrazoles efficiently. However, the scope of substrate was somewhat limited due to the limitation of using 2-bromo-1,3-dicarbonyl compounds as radical precursors.[200] The direct annulation of α,β-unsaturated hydrazones under photoinduced condition was also reported by Zhu's group. This method did not require any additional photocatalyst and sunlight was applied directly to promote the synthesis of pyrazoles. It was an excellent example to activate and transform the tosylhydrazones under photoinduced conditions. However, the mechanistic



Scheme 37 Synthesis of the pyrazole derivatives *via* formal [4+1] annulation and aromatization.



Scheme 38 Visible-light-induced [3+2] cycloadditions to achieve pyrazoles.



Scheme 39 Electrochemical synthesis of 4-selanylpyrazoles.

studies in this work was not fully investigated.[201] Besides using hydrazines and hydrazones as nitrogen sources, Harrity's group described a photocatalytic method to improve the efficiency of sydnone enamine cycloaddition. In this case, the photoactivation of sydnones *via* energy transfer facilitate the [4+2] cycloaddition to form the key intermediate.[202]

Our group also contributed to the synthesis of pyrazoles *via* the photoinduced activation of *N*-tosylhydrazones (Scheme 38). Compared to traditional methods, this strategy facilitated the formation of diazo intermediate under the irradiation of visible light, which further reacted with alkenes to furnish diverse pyrazoles (**340–342**). The mechanistic studies and DFT calculations suggested the formation of a noncovalent complex, which was the key to the success. Moreover, diverse pyrazoles by using different aldehyde-derived *N*-tosylhdrazones and alkenes were obtained by using this strategy. However, only aryl-substituted *N*-tosylhdrazones were accommodated in this system.[30] Nevertheless, this method enables the straightforward synthesis of pyrazoles bearing strong electron-donating groups through the use of "donor/donor" diazo intermediates, which are typically challenging to access *via* conventional diazo chemistry. It also efficiently constructs sterically complex pyrazolines and pyrazoles featuring spiro-quaternary carbon centers.

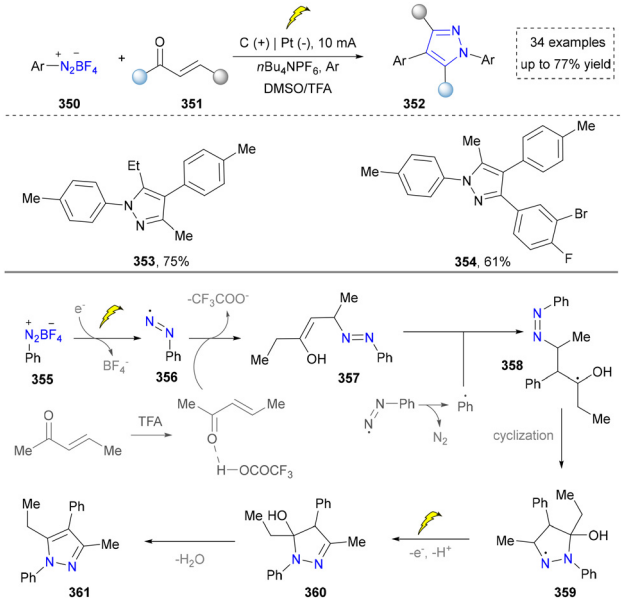
Overall, hydrazines and hydrzones as nitrogen sources have been well established to construct pyrroles. Other partners to furnish pyrroles have been also investigated including various alkenes and Michael acceptors. However, other nitrogen sources such as diazo compounds or amines were also possible to use in the photocatalytic synthesis of pyrroles. Using inactivated alkenes as substrates also needed to take some attentions which will tremendously expand the diversity of synthesized pyrroles. Moreover, selectivity control remained a significant challenge, especially for complex substrates with multiple reactive sites. Consequently, its application in large-scale production still requires complementation with established traditional methodologies. Moreover, the three-component reactions need to be investigated.

4.1.2 Electrochemical synthesis of pyrazoles. Electrocatalysis has been another emerging method to furnish the pyrazoles. In 2021, the He group reported a multicomponent approach, which constructed 4-selanylpyrazoles efficiently without the addition of catalysts and oxidants at room temperature (Scheme 39).[203] Moreover, multicomponent reactions by using phenylhydrazine, 2,4-pentanedione and diphenyl diselenide as building blocks enabled the divergent synthesis of pyrazoles (**347–349**). More importantly, gram-scale synthesis was also achieved to prove its applicability. Considering the significance of 4-selanylpyrazoles in drug discovery, this method would be highly promising in future applications. The He group further extended their strategy to synthesize 4-thiocyanato-1*H*-pyrazoles *via* electrochemical one-pot synthesis. The strategy was similar to the above work, and 1,3-diones underwent the three-component reaction using NH_4SCN and hydrazines to furnish products. In this reaction, the key to success was the formation of $(SCN)_2$ *via* the oxidation of the SCN anion and subsequent radical coupling.[204]

In 2022, the O. Terent'ev group disclosed the electrochemical intramolecular C–N coupling of α,β unsaturated hydrazones. The initial anodic two-electron oxidation of iodobenzene generated the hypervalent iodine species, which subsequently underwent nucleophilic substitution with *N*-tosylhydrazones to form the *N*-iodo intermediate.[205] At last, the electrophilic intramolecular addition and deprotonation gave the final pyrazoles. This was a typical method to activate *N*-tosylhyrazones using the formed hypervalent iodine species. In 2023, the Waldvogel group continuously disclosed the electrochemical synthesis of pyrazoles *via* [3+2] dipolar cycloaddition. The pyrazoles were obtained directly from the hydrazones and alkenes. However, this strategy was focused on the synthesis of prazolines, and the scope and reactivities of pyrazoles were relatively limited.[206] Almost at the same time, polysubstituted sulfonated pyrazoles were also obtained *via* electrochemical synthesis by Huang's group.[207]

Very recently, another nitrogen source, aryl diazonium salt, has also been reported by Tang's group (Scheme 40). In this method, aryl diazonium salts were reduced directly on the cathode, generating the aryl diazo radical intermediate, which further reacted with ketones to furnish the pyrazoles. This is the first example to from aryl radicals and aryl diazo radicals *via* the electroreduction of aryl diazonium salts. With this mild strategy, plenty of multi-substituted pyrazoles (**353**, **354**) were obtained without the addition of external catalyst and oxidants. However, they did not evaluate the potential of this method in gram-scale synthesis and drug synthesis.[45]

Overall, the developments of electrochemical synthesis provided some new insights for the synthesis of pyrroles. The nitrogen sources have been expanded to the aryl diazonium salts, which was not reported in photocatalytic methods. Moreover, several three-component methods have been developed which showed good structural diversity. Furthermore, electrons

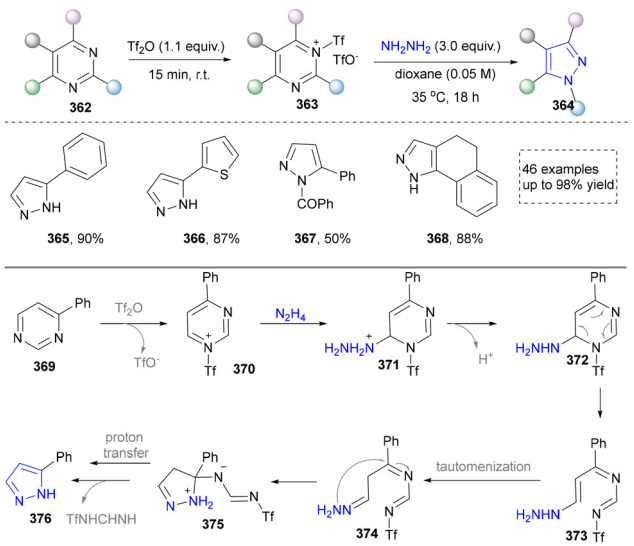


Scheme 40 Electrochemical synthesis of pyrazoles *via* a radical cyclization cascade.

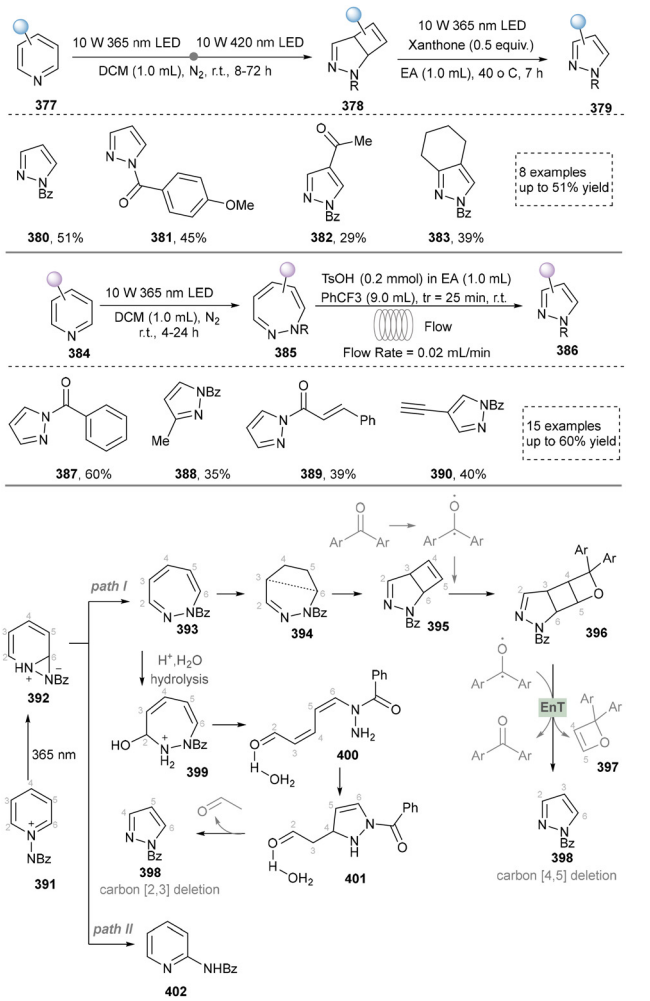
serve as a clean "reagent," reducing reagent waste and heavy metal pollution at the source, aligning with the trend toward green pharmaceutical manufacturing.

4.1.3 Atom editing for the construction of pyrazoles or indazoles. In 2022, the Sarpong group disclosed a skeletal editing strategy for converting pyrimidines into pyrazoles (Scheme 41).[208] Even though the conversion of pyrimidines into pyrazoles has previously been known, the low yields and harsh reaction conditions limited its applicability.[209,210] The key steps involve pyrimidine nitrogen triflylation followed by the addition of hydrazine, which proceeded under mild conditions to afford the target pyrazoles in high yields. This approach provided access to diverse N2-substituted pyrazoles with a broad substrate scope (**365–368**). Furthermore, the DFT and mechanistic studies proved that the triflylation of the pyrimidine core and the following hydrazine-mediated skeletal editing were the key to success.

In 2024, Zheng's group presented a metal- and catalyst-free method to access the skeletal editing of pyridines to pyrazoles (Scheme 42).[211] With the pyridinium salt as a model substrate, two-time irradiation with different light sources accomplished cyclization to achieve pyrazolines (**380–383**). Subsequent photocatalytic irradiation of this intermediate with xanthone facilitated [4,5]-carbon deletion, yielding the pyrazole product. Furthermore, 1,2-diazepine, obtained *via* irradiation under 365 nm LEDs, was converted to pyrazoles (**387–390**) selectively by deleting carbon (2,3 or 5,6) at the imine position. The synthetic application of this protocol was also demonstrated by the late-stage modifications of drugs and natural products containing pyridine units. At last, the DFT studies provided the proposed mechanism for different reaction conditions. Notably, during the revision of our manuscript, Studer's group disclosed a complementary C-to-N atom swap in indoles to access indazoles, relying on oxidative cleavage and ring closure.[212]



Scheme 41 Skeletal editing of pyrimidines to pyrazoles by formal carbon deletion.



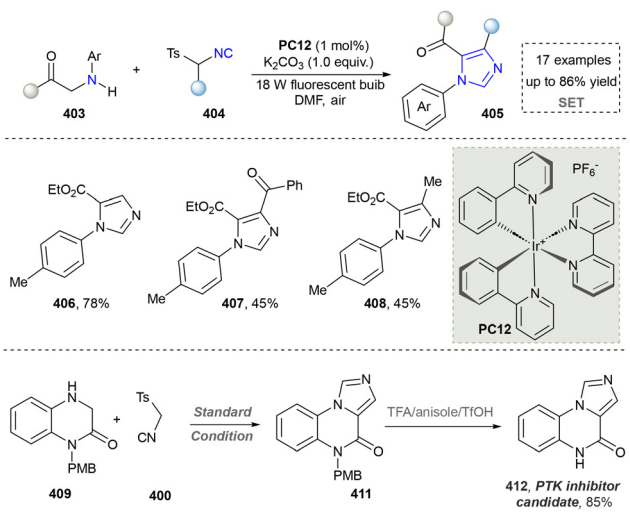
Scheme 42 Photochemical skeletal editing of pyridines to pyrazoles.

In summary, skeletal editing strategies provide a revolutionary approach for the synthesis of pyrazoles, enabling the pyrazole core by bypassing traditional lengthy *de novo* synthetic routes. However, this strategy currently faces challenges such as limited reaction generality, complexities in selectivity control, and dependence on specific activation modes or directing groups. Nevertheless, with a deep understanding of the mechanisms governing selective bond cleavage and reorganization, skeletal editing technology holds strong potential to evolve into a powerful tool for late-stage functionalization in medicinal chemistry. By allowing direct, "surgical" modification of the pyrazole ring within complex molecular frameworks, it could significantly accelerate lead compound optimization and structure–activity relationship studies, thereby opening a more direct and efficient pathway for the discovery of innovative drug molecules.

4.2 Synthesis of imidazoles

Imidazole is highly polar and readily soluble in water.[213] In biological systems, imidazole is a key component of the side chain of histidine, an amino acid found in many proteins and enzymes.[214,215] Additionally, imidazole is a common structural motif in various pharmaceuticals, including antifungal, antiprotozoal, and antihypertensive drugs.[216] Industrially, it is also used in the synthesis of certain pesticides.[217] The traditional methods to afford imidazoles relied on the Debus–Radziszewski reaction, Wallach reaction, Bredereck imidazole synthesis, and Kaiser–Johnson–Middleton dinitrile cyclization.[218] This section will introduce the progress of synthesizing imidazoles *via* three emerging protocols.

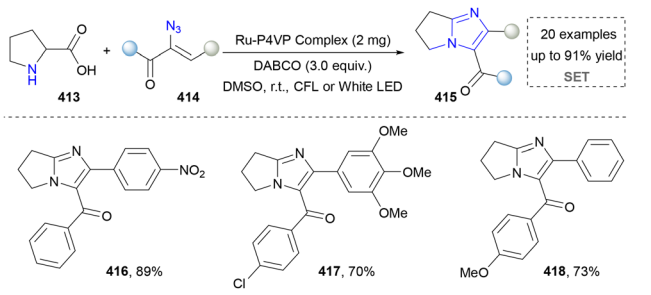
4.2.1 Photochemical synthesis of imidazoles. The first example to constructing imidazoles was reported by Xiao's group in 2014.[219] In this case, different secondary amines and isocyanides were employed into the photocatalytic cascade reaction through aerobic oxidation, [3+2] cycloaddition and aromatization (Scheme 43). Besides the synthesis of simple imidazoles (**406–408**), this strategy was extended to the preparation of key precursors (**411**) for the PTK inhibitor candidate (**412**), starting from a cyclic secondary amine under standard conditions. Despite its incompatibility with unprotected N–H substrates, the method remained a valuable tool for synthesizing drug derivatives. At the same time, the Cho group disclosed the synthesis of benzimidazoles from the phenylenediamines and benzaldehydes under visible light irradiation. This strategy did not require the involvement of a photocatalyst. The *in situ* formed imine had an obvious bathochromic shift, which promoted the cyclization and the generation of the products after the oxidation.[220]



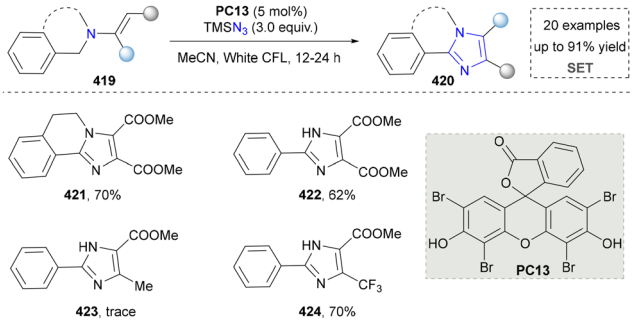
Scheme 43 Synthesis of imidazoles by photocatalytic aerobic oxidation/[3+2] cycloaddition.

Kim's group further disclosed the facile synthesis of fused imidazoles, featuring the use of readily available L-proline and α-keto vinyl azides as precursors *via* a photoinduced method (Scheme 44). The key to the success of this method was the formation of 2*H*-azirine from the α-keto vinyl azides *via* energy transfer. More importantly, the integration of this method with continuous-flow technology overcame a key barrier to scaling up purely photochemical synthesis. This combined photo-continuous flow strategy enabled the efficient synthesis of target compounds **416–418**, reducing the reaction time dramatically from 16 hours in the batch mode to only 2 minutes. The rapid construction of imidazoles indeed was helpful in organic synthesis to save time and energy. However, further in-depth investigation in application was needed since the gram-scale synthesis was not provided, which was another obvious advantage of continuous-flow chemistry.[221] Later, Maurya's group extended the photoexcitation of α-keto vinyl azides and applied into the imidazole *via* a three-component method.[222]

Afterwards, highly substituted imidazoles and dihydroisoquinoline-based imidazole derivatives were synthesized by Sharada's group (Scheme 45).[223] The advantage of this method was that no transition metal was needed under photocatalytic conditions. Moreover, $TMSN_3$ worked as a nitrogen source to induce nitrogen incorporation. Considering both imidazoles and dihydroisoquinolines as important drug motifs, this strategy shows potential to obtain some leading compounds *via* this novel skeleton assembly (**421–424**). However, the mechanistic investigation of this method was underexplored. We also noticed that some heterogeneous catalysts were designed and synthesized to facilitate the synthesis of imidazoles,[224] but they will not be discussed here since the novelty of catalysts and their efficiency are beyond the scope of this review.



Scheme 44 Photo-induced decarboxylated annulative achieve imidazoles.

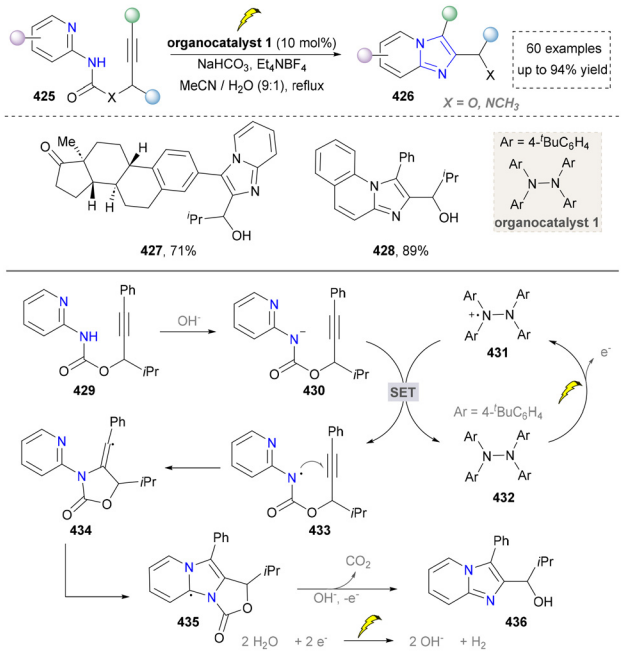


Scheme 45 Synthesis of imidazoles *via* dual C(sp^3)–H and C(sp^2)–H bond functionalization.

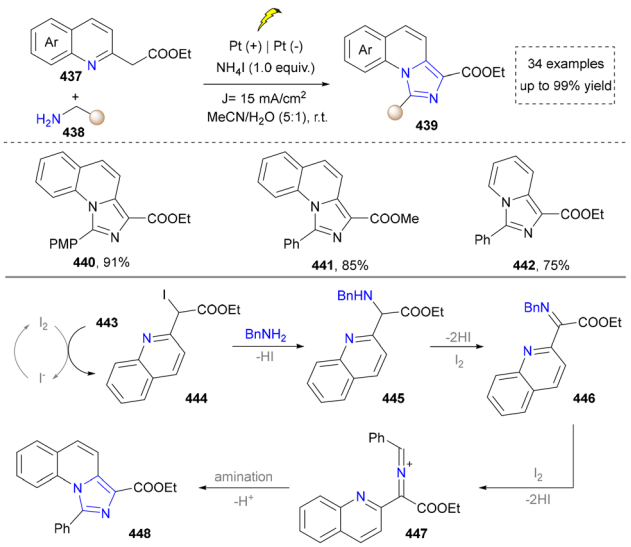
In conclusion, this section shows the obvious progress of imidazoles synthesis using photochemical methods. Different nitrogen sources including azides, $TMSN_3$, and isocyanides have been investigated to form imidazoles with amines. It was anticipated that some other convenient methods such as three-component methods, or using other readily available building blocks, would be developed in the future. Moreover, the practical application into drug synthesis and gram-scale synthesis also need to be investigated in the future.

4.2.2 Electrochemical synthesis of imidazoles. Electrocatalysis has been a robust approach to expand the synthesis of imidazoles in the last decade. There is also one review to introduce the electrochemistry for the synthesis of N-heterocycles, which was published five years ago.[225] However, there are already numerous advancements afterwards. Therefore, we will continue to update the achievement in this field. With the unique advantage of electrocatalysis, Xu's group first reported the synthesis of imidazo-fused N-heteroaromatic compounds *via* electrocatalytic C–N bond formation and [3+2] annulation in 2017 (Scheme 46).[226] The heteroarylamine (**429**) was able to generate amidyl radicals (**433**) directly through the single-electron transfer process, which underwent 5-*exo-dig* cyclization to form the vinyl radical (**434**). The vinyl radical (**434**) further reacted regioselectively with the pyridyl nitrogen to form the final product (**427**, **428**). This strategy enabled highly efficient, regioselective access to structurally complex, bioactive imidazo-fused N-heteroarenes and opened the door for the synthesis of imidazoles from the amidyl radical, which was generally challenging in other methods.

In 2019, the synthesis of imidazo[1,5-*a*]quinoline was further reported by Wang's group (Scheme 47).[227] They found that iodine generated from NH_4I in the anode reacted with ethyl 2-(quinolin-2-yl)acetate (**437**) to form the iodinated intermediate (**444**), which was further substituted by the amine and oxidized in the presence of molecular iodine to yield an intermediate (**447**). At last, it underwent a tandem cyclization process to generate the final products (**440–442**). However, the structural diversity was limited since the synthesis of ethyl 2-(quinolin-2-yl)acetate was not convenient. Later, O. Terent'ev's group developed a three-component strategy, which applied pyridine-type aldehydes, amines and NH_4SCN to construct diverse CN-substituted



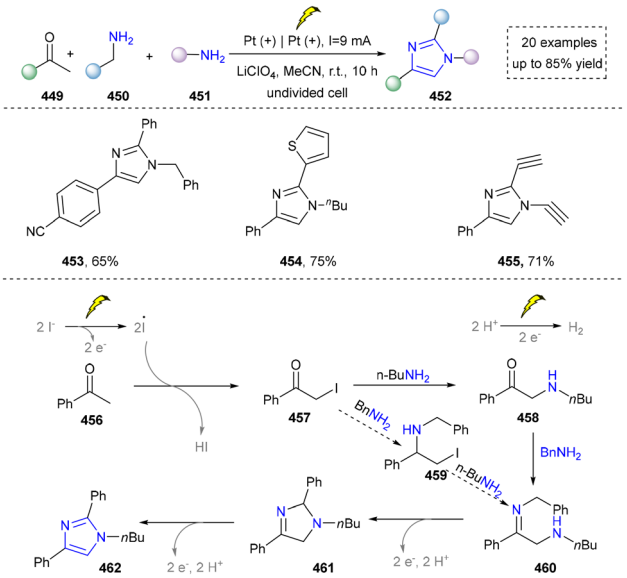
Scheme 46 Electrochemical synthesis of imidazoles through C–N bond formation.



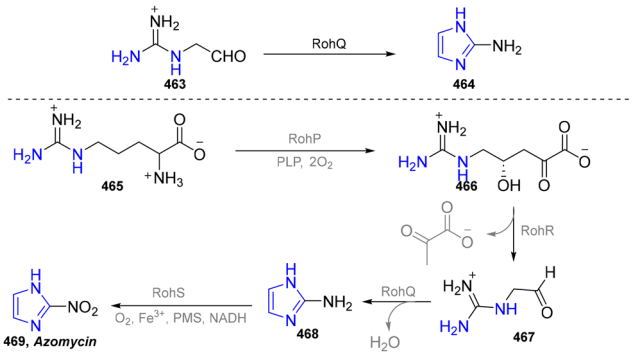
Scheme 47 Electrocatalytic synthesis of the 1,3-disubstituted imidazo[1,5-*a*]quinolines.

imidazo[1,5-*a*]pyridines, which showed a better substrate scope than Wang's work.[228,229]

In 2020, He's group described an elegant method to construct imidazoles *via* electrochemical annulation of ketones and amines. In this reaction, two different amines worked as nitrogen source, one amine reacted with *in situ* formed α-iodo ketone to generate α-amino ketone (Scheme 48).[230] The other amine was required to be a benzylic amine, as it readily condensed with the α-amino ketone to generate an imine intermediate (**460**), which further be oxidized to afford the imidazole. This



Scheme 48 Electrochemical oxidative annulation of ketones and amines used to produce imidazoles.



Scheme 49 Enzymatic synthesis of imidazoles from L-arginine.

work showed good structural diversity since the various amines could be applied to the synthesis (**453–455**). However, practical application such as synthesis of drug or bioactive molecules was not investigated. Later, Pan's group continuously reported the synthesis of sulfide imidazopyridines *via* electrochemical synthesis. In this reaction, vinyl azides, thiophenols, and pyridines reacted smoothly to form diverse imidazoles *via* a radical cyclization cascade, which further expanded the application of electrocatalysis in the imidazole synthesis.[39] Not only are the metal- and external oxidant-free conditions noteworthy, but the [2+2+1] annulation employing readily available amines also significantly broadens the structural diversity of imidazoles.

Inspired by their work, the Chen group developed the electrochemical synthesis of tetrasubstituted imidazoles from enamines and benzylamines. The advantage of this strategy is that the gram-scale synthesis of a drug analogue was reported.[231] The Chen group also developed an electrochemical tandem Michael addition to construct imidazoles efficiently, but the concept has been developed previously.[232] The Zhou group also reported the synthesis of imidazoles from ketones and amines in 2020, but this work does not explore the possibility to use two different amines.[233] In 2023, the Zhou group continuously worked in this field and reported the synthesis of imidazoles *via* electrochemical dehydrogenative amination, this work showed some advancement such as the direct C(sp^3)–H intramolecular amination.[234]

It has been witnessed that the electrocatalytic synthesis provided more possibility to diversify imidazoles. The key advantage of electrochemical pyrazole synthesis lies in its ability to directly activate various stable precursors through potential control, bypassing the reliance of traditional methods on diazo compounds and the dependence of photochemical approaches on photoactive substrates or catalysts. This enables broad compatibility with strongly electron-donating, high-oxidation-potential, heterocycle-modified, and oxidation-sensitive substrates, providing a more versatile and milder synthetic platform for constructing pyrazole frameworks. Moreover, it is clear that electrocatalysis could utilize some other nitrogen sources such as amides, which has been previously challenging in photochemical methods.

4.2.3 Enzymatic synthesis of imidazoles. Nitroimidazoles are antibiotics used for the treatment of anaerobic bacterial infections with low incidence of drug resistance.[235,236] In 2019, the Ryan group identified the biosynthetic gene cluster of azomycin in *Streptomyces cattleya* through bioinformatics analysis and analysed the biosynthetic pathway from L-arginine to azomycin by reconstructing all enzyme-catalysed reactions *in vitro*, which has paved the way for the biocatalytic synthesis of azomycin and related nitroimidazoles (Scheme 49).[237] Throughout the biosynthetic pathway, cyclodehydratase RohQ was responsible for the formation of the imidazole ring from guanidinoacetaldehyde (**463**) to produce 2-aminoimidazole (**464**), serving as a key precursor for the synthesis of azomycin (**469**).

Although imidazole compounds have important biological activities, enzymes that catalyse the formation of the imidazole ring need to be further explored. It is believed that the enzymatic synthesis of imidazole derivatives will gradually increase, with the analysis of the biosynthetic pathway of imidazole-containing natural products.

4.3 Synthesis of benzimidazoles

In light of its unique physicochemical properties and structural versatility, benzimidazole scaffold constitutes a privileged heterocyclic system in modern drug discovery and materials science.[238,239] As a bioisostere of naturally occurring purine bases, this fused bicyclic architecture demonstrates remarkable pharmacological relevance, serving as the core structure in numerous therapeutic agents including proton pump inhibitors (*e.g.*, omeprazole), antiparasitics (albendazole), and antiviral drugs.[240,241] Benzimidazole derivatives are typically prepared through the condensation of o-phenylenediamine with carbonyl compounds (aldehydes/ketones) or carboxylic acid derivatives, or *via* rearrangement of quinoxaline/triazole derivatives.[242,243] Consequently, the benzimidazole scaffold retains substantial synthetic values in contemporary research.

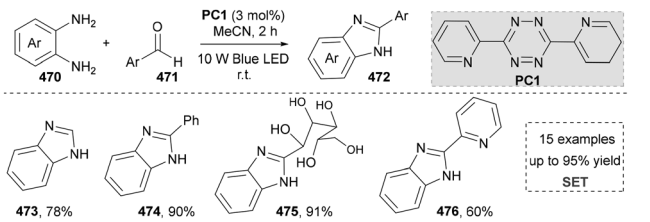
4.3.1 Photochemical synthesis of benzimidazoles. In 2013, the Biswas group disclosed that *s*-tetrazine-based molecules could work as photocatalysts to facilitate the synthesis of benzimidazole and benzothiazole (Scheme 50). This reaction showed simple operation and broad substrate scope (**473–476**) since the abundantly available aldehydes **471** and amines **470** were used as building blocks.[244] Moreover, the reaction time only took 2–3 hours, which was highly efficient. Based on this work, Chu's group further expanded this strategy and synthesised diverse benzimidazoles using fluorescein as a photocatalyst.[245] This strategy has been proved a robust and convenient way to construct the valuable benzimidazole and was further developed by several groups to improve the reactivity and efficiency *via* the design of various homogeneous and heterogenous photocatalysts.[246–252]

Besides the intermolecular cyclization, another useful strategy to afford the imidazoles *via* photocatalysis has been reported by Wang's group in 2019 (Scheme 51).[253] They used *N*-phenyl amidoxime esters (**477**) as starting materials, which formed the amidinyl radical *via* the SET process. The amidinyl radical reacted with the adjacent benzene ring to form a cyclized intermediate, which was subsequently oxidized by the photocatalyst, yielding the final product (**479–482**) after aromatization. Even though the photochemical formation of amidinyl radicals was well-established, this strategy still provided a useful method to generate 2-substituted benzimidazoles. More importantly, this method was applied to the synthesis of fungicide thiabendazole (**488**) under standard conditions, indicating the application potential of this protocol. This established the compatibility of this reaction with both aromatic and heteroaromatic aldehydes.

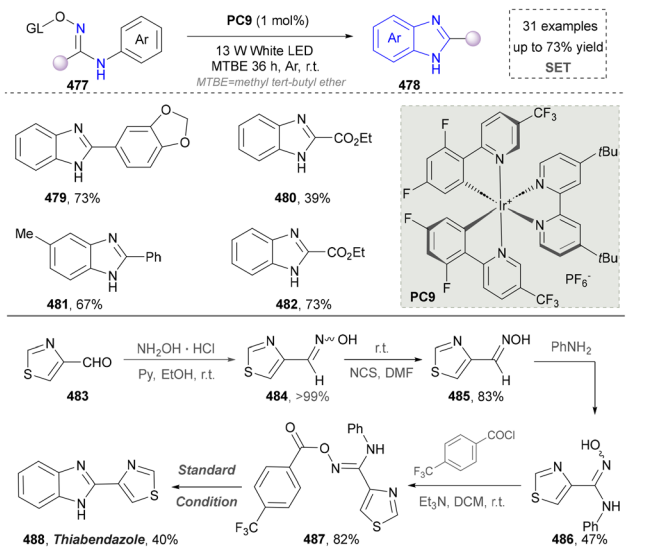
Benzimidazole synthesis has witnessed continuous methodological exploration. In 2016, Zhang's group established an efficient synthesis of polysubstituted benzimidazoles *via* a visible-light-induced intramolecular cyclization and deprotection sequence.[254] Subsequent efforts prioritized sustainability, in 2020, Ke's group developed an eosin Y-catalyzed aqueous-phase reaction of benzonitrile derivatives,[255] while Banerjee's group reported a catalyst- and solvent-free one-pot, four-component synthesis.[256] Further advancing milder strategies, Kokotos's group demonstrated a direct photochemical synthesis from diamines and aldehydes.[257] Building on this foundation, Kundu's group has recently introduced a method that merges a photocatalyst with a HAT reagent to activate ethanol for benzimidazole formation.[258]

The development of benzimidazole synthesis has been greatly accelerated by visible light photoredox catalysis. Initial work by Zhang's group on an intramolecular cyclization/deprotection sequence paved the way.[254] Subsequent research emphasized sustainability, with Ke's group (2020) reporting an eosin Y-catalyzed aqueous protocol,[255] while Banerjee's group achieved a catalyst- and solvent-free, four-component synthesis in parallel.[256] Further contributions included Kokotos's[257] milder synthesis from simple building blocks and, more recently, Kundu's innovative strategy that combines a photocatalyst with a HAT reagent, demonstrating the continued evolution in this field.[258]

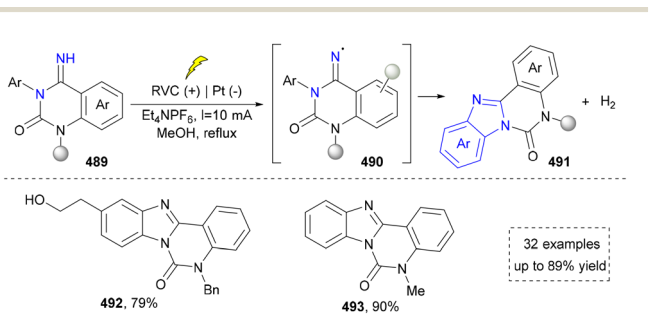
4.3.2 Electrochemical synthesis of benzimidazoles. Compared to the synthesis of different protected amines to achieve the activation under photocatalytic conditions, as early as 1982, Rogić and coworkers pioneered the electrochemical synthesis of pyrroles through a two-electron oxidative cyclodehydrogenation reaction, successfully preparing several 1,3-imidazole derivatives (Scheme 52, **492**, **493**).[259] This groundbreaking work marked the advent of electrochemical approaches in pyrrole synthesis, establishing a new paradigm in heterocyclic chemistry. Inspired by this work, Xu's group disclosed an electrocatalytic strategy, which served as a very powerful tool to access



Scheme 50 Visible-light-driven green synthesis of the 2-substituted benzimidazoles.



Scheme 51 *N*-Phenyl amidoxime esters to achieve the 2-substituted benzimidazoles.



Scheme 52 Synthesis of benzimidazoles through the anodic N–H bond cleavage.

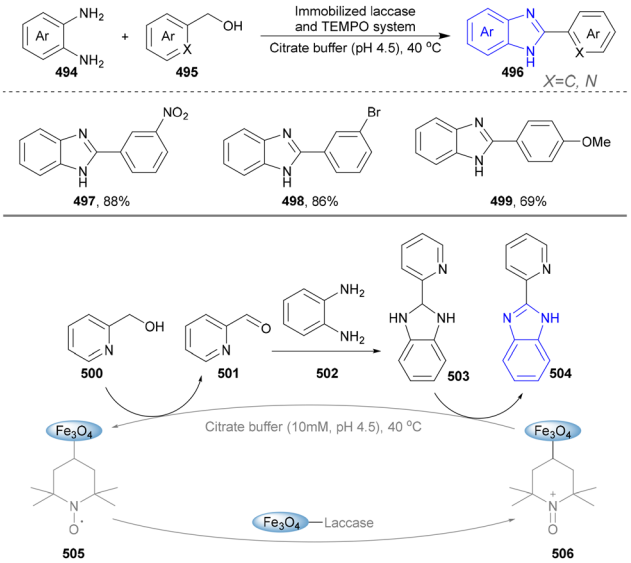
the amidinyl radical intermediate through the direct anodic cleavage of N–H bonds. This strategy was highly novel and showed good atom economy. The formed nitrogen radical reacted with the arene rings directly to furnish the different benzimidazoles. Moreover, this strategy was applied to the synthesis of a complex benzimidazole on a gram scale.[260]

Continuously, the same group further developed an electrocatalytic method to synthesize the benzimidazole through dehydrogenative cyclization of easily available *N*-aryl amidines. Compared with their first work, this protocol showed a better substrate scope. In addition, they provided the detailed mechanism to show the anodic oxidation of *N*-aryl amidine and the subsequent formation of amidinyl radical.[261] In 2023, Zhou's group also disclosed the electrocatalytic synthesis of benzimidazoles *via* intramolecular C(sp^3)–H amination as a continuous work based on their previous reports.[234]

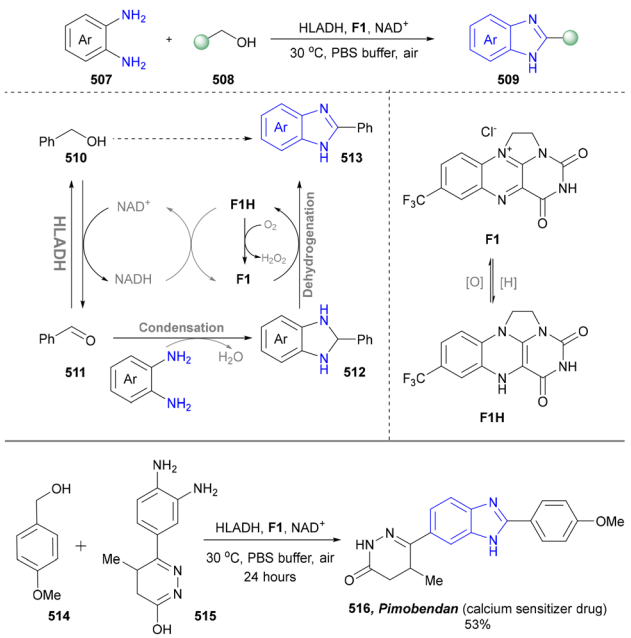
Overall, the direct electrocatalytic C–H functionalization provided some unprecedented route to construct benzimidazoles without any leading group. However, there is still some space to expand the structural diversity of benzimidazoles *via* intermolecular synthesis. The development of novel nitrogen sources in future electrochemical synthesis is poised for breakthroughs along the axes of more fundamental, greener, and smarter alternatives, thereby driving the advancement of sustainable synthetic chemistry.

4.3.3 Enzymatic synthesis of benzimidazoles. Laccases, a class of multicopper oxidases catalysing the selective oxidation of diverse substrates using oxygen as an oxidant to give water as the only by-product,[262] have demonstrated broad utility in the oxidation of alcohols to produce corresponding aldehydes or ketones.[263–265] In 2011, Beifuss' group reported that 2-substituted benzimidazole and 2,3-disubstituted benzimidazole could be synthesized by the oxidative condensation of *o*-phenylenediamine derivatives with aldehydes using oxygen as an oxidant.[266] The chemoselectivity of the reactions was influenced by optimizing the reaction conditions. A commercially available laccase from *Agaricus bisporus* catalysed *o*-phenylenediamine and benzaldehyde to afford 2-phenyl-1*H*-benzimidazole under aerobic conditions with remarkable selectivity. In 2018, Brady and colleagues reported that laccase (Novoprime Base 268) selectively catalysed the formation of 2-phenyl-substituted benzimidazoles in a mixture of acetate buffer (pH4.0) and acetonitrile.[267] To enhance the catalytic efficiency and recyclability, Faramarzi *et al.* designed a heterogeneous catalyst which was composed of immobilized laccase and TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl) on magnetic nanoparticles to synthesize 2-substituted benzimidazoles in one pot.[268] The salicyl aldehyde derivatives (**502**) produced by the oxidation of salicyl alcohol derivatives (**501**) were condensed with 2-aminoanilines (**494**) to form the benzimidazoline intermediates (**503**), which were finally aromatized to produce benzimidazoles (**504**) catalysed by the laccase/TEMPO system (Scheme 53).

The synthesis of benzimidazoles *via* intermolecular condensation was also performed through the cooperative chemoenzymatic system catalysed by an organocatalyst (**F1**) and biocatalyst HLADH reported by Zhu's group (Scheme 54).[181] In the bioprocess, HLADH converted alcohol (**510**) into aldehyde (**511**) at the



Scheme 53 Laccase-catalysed synthesis of benzimidazoles.



Scheme 54 Cooperative chemoenzymatic system for the synthesis of benzimidazoles.

cost of constantly consuming NAD^+, which was continuously regenerated *in situ* by **F1**. The resulting **F1H** was subsequently reoxidized by oxygen back to **F1**, releasing H_2O_2. In the chemoprocess, the aldehyde (**512**) underwent spontaneous condensation with diamine (**507**) to generate the corresponding imine intermediate, which was cyclized into benzimidazoline (**512**). Finally, benzimidazoline (**512**) was oxidized to obtain the corresponding benzimidazole (**513**), while **F1** was regenerated to continue the entire catalytic cycle. The transition between **F1** and **F1H** was realized *via* direct hydride transfer and C10a addition. This approach offered broad applicability for the synthesis of

diverse substituted benzimidazoles, with the cooperative effect of multiple catalysts proving more effective than their sequential application. Furthermore, the cooperative chemoenzymatic system was successfully employed to synthesize pimobendan (**516**), a calcium-sensitizing drug for the treatment of ischemic heart disease and arterial thrombotic diseases, and a moderate overall yield of 53% was obtained within 24 hours under non-optimized conditions, due to the poor aqueous solubility of the diamine in water. Furthermore, the hydroxy group was susceptible to oxidation into a carbonyl group under these reaction conditions.[269,270]

Overall, the synthesis of benzimidazole was achieved by optimizing the reaction conditions to influence the chemoselectivity of laccase or integrating HLADH with organocatalysts. Given the increasing demand for sustainable methods, the chemoselectivity and mild reaction conditions of biocatalysis are expected to drive further research and application in the synthesis of diverse benzimidazole derivatives.

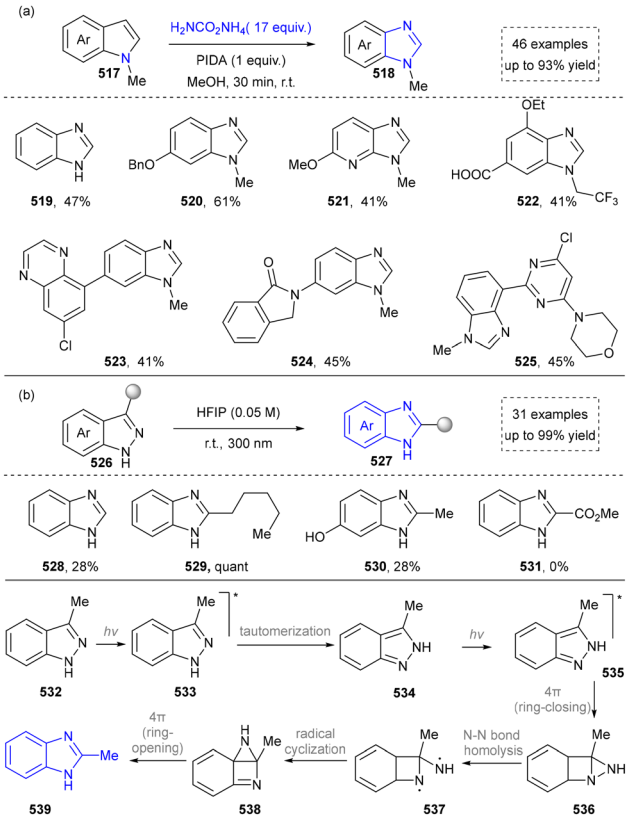
4.3.4 Atom editing for the construction of benzimidazoles. Atom editing for benzimidazole construction has gained tremendous attention recently.[271] Notably, during the preparation and revision of our manuscript, three excellent publications have been recorded for the elegant synthesis of benzimidazoles through atom editing. Morandi's group has reported the carbon-to-nitrogen atom swap that converted indoles into benzimidazoles.[272] This transformation was initiated from the oxidative cleavage step and subsequent oxidative amidation, and the Hofmann-type rearrangement and final cyclization provided the corresponding benzimidazoles (**519–525**). Leonori's group also described a photochemical method to achieve the conversion of indazoles into benzimidazoles (**528–531**). Moreover, experimental and DFT studies suggested a two-step mechanism including the excited-state tautomerization of 1H-indazoles and the subsequent photochemical rearrangement of the resulting 2*H*-isomers (Scheme 55).[273] The construction of benzimidazoles *via* atom editing has also been reported by Studer's group, which was already explained in the section of indazole synthesis.[212]

The skeletal editing strategy for constructing benzimidazole frameworks remains in its early exploratory stages, with immense room for future development. The key challenge lies in advancing this technology from "proof-of-concept" to a "practical tool." This transition depends on developing editing reactions with enhanced generality and selectivity, deepening the intelligent prediction of reaction mechanisms, and ultimately, integrating the approach with automated synthesis platforms. This integration will ultimately provide unprecedented efficiency for the construction and modification of molecules in drug discovery.

5. Three- and four-nitrogen-containing aromatic heterocycles: 1,2,3-triazoles, 1,2,4-triazoles, and tetrazoles

5.1 Synthesis of 1,2,3-triazoles

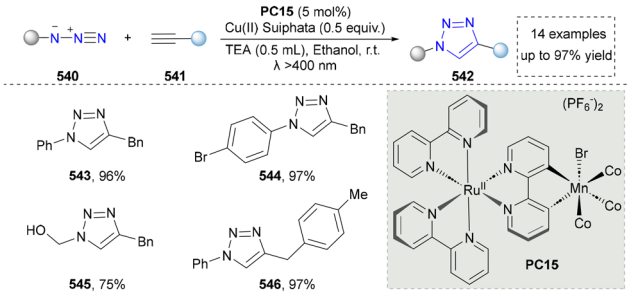
The synthesis of 1,2,3-triazoles holds profound importance in both fundamental and applied chemistry due to their unique



Scheme 55 (a) Access to benzimidazole derivatives from indoles *via* carbon-nitrogen atom exchange. (b) Photochemical conversion of indazoles into benzimidazoles.

structural and functional properties.[274] In medicinal chemistry, 1,2,3-triazole serves as a stable bioisostere for labile functional groups (*e.g.*, amides and esters), enhancing the metabolic stability while maintaining the key pharmacophoric interaction.[274,275] This is exemplified by their incorporation into clinical agents such as the antifungal drug fluconazole and the anticancer agent cabozantinib.[276] Thus, the synthesis of 1,2,3-triazole bridges fundamental research and technological innovation, driving progress across drug discovery, materials engineering, and chemical biology.[277] However, the thermal cycloaddition reaction of azides to terminal alkynes remains the most prevalent method for 1,2,3-triazole synthesis.[278] This section will focus on elucidating the pivotal role of emerging synthetic methodologies in the construction of 1,2,3-triazole scaffolds (including 1,2,3-triazole 1-oxides and 1,2,3-triazole 1-imines).

5.1.1 Photochemical synthesis of 1,2,3-triazoles. The first synthesis of 1,2,3-triazoles *via* photocatalysis has been reported by Jain's group in 2016 (Scheme 56). They constructed 1,2,3-triazoles by developing unique bimetallic complexes as photocatalysts, which facilitated efficient electron transfer to facilitate the [3+2] click reaction of azides and alkynes. This photocatalytic click reaction was performed under visible light, and showcased a good substrate scope with various alkynes and azides (**543–546**). Even though the red shift of the synthesized Ru–Mn complex as the photocatalyst was obvious, the detailed mechanism is underexplored.[279]

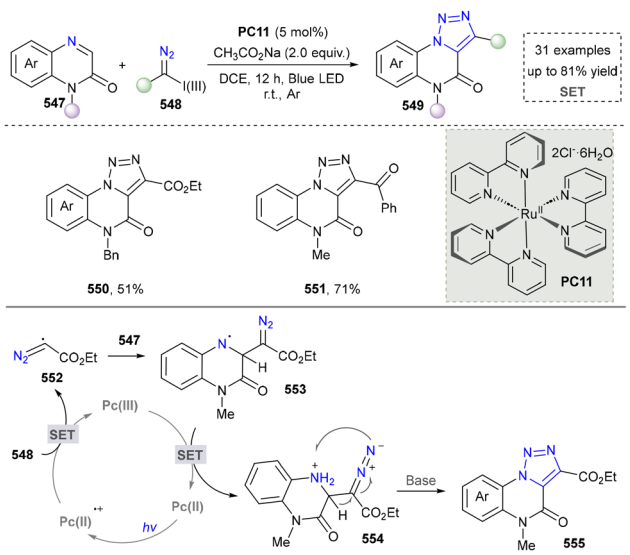


Scheme 56 Visible-light-assisted photocatalytic [3+2] reaction for the synthesis of 1,2,3-triazoles.

Later, visible-light-mediated click chemistry for the construction of diverse 1,2,3-triazoles was further developed by several research groups.[280] For instance, Pan's group developed a photocatalytic strategy under the irradiation of sunlight.[281] Moreover, some novel heterogenous catalysts were designed and prepared to facilitate the synthesis of 1,2,3-triazoles under the irradiation of visible light, which further improved the efficiency and sustainability of these reactions.[282–284]

Besides click chemistry, the synthesis of 1,2,3-triazole by using hypervalent iodine(III) diazo reagents has recently been reported (Scheme 57).[285] This unique diazo reagent has very powerful applications in organic synthesis due to their dual activities as electrophilic diazo transfer agents and oxidizing species. In this reaction, the hypervalent iodine diazo reagent (**548**) formed the radical intermediate (**552**) *via* the SET process, which reacted with *N*-Bn-quinoxalin2(1*H*)-one (**547**) and formed the final product (**550**, **551**) after [3+2] cyclization. Gratifyingly, the obtained final products had novel structures since the triazole-fused heterocycles are highly important in drug designing.[286]

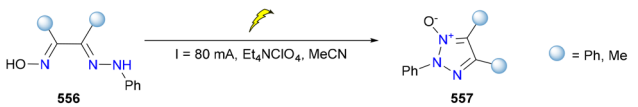
Overall, the visible-light-promoted click chemistry to afford 1,2,3-triazoles was still the mainstream in this field. However, the other methods and nitrogen sources were applied to the synthesis of 1,2,3-triazoles, except the reported diazo compounds. The successful application of alternative nitrogen sources beyond traditional diazo compounds represents a significant and promising expansion of the methodological toolkit. This trend is expected to continue, paving the way for more sustainable, efficient, and structurally novel routes to these valuable heterocycles, ultimately broadening their potential in drug discovery.



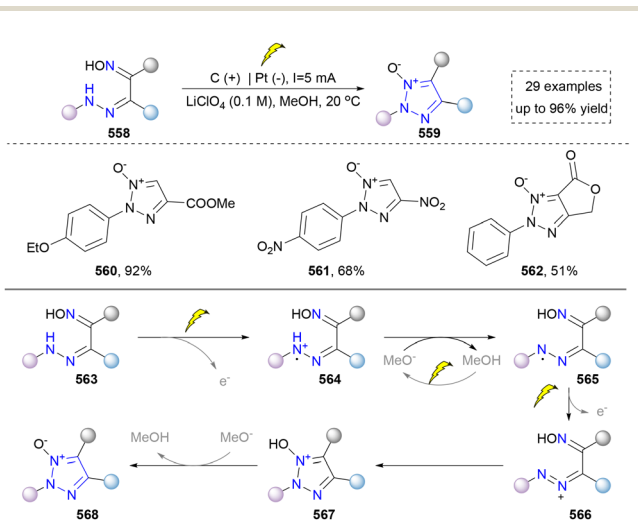
Scheme 57 Synthesis of 1,2,3-triazoles through photoredox-catalyzed [3+2] cyclization.

5.1.2 Electrochemical synthesis of 1,2,3-triazoles. Work on the construction of 1,2,3-triazoles was first reported in 1982 by Jugelt's group (Scheme 58).[287] This pioneering work showed that the oximinohydrazones (**556**) were activated, which further underwent cyclization to afford 1,2,3-triazole 1-oxides (**557**). Even though only a few products were obtained and the mechanism was not illustrated in this work, it was indeed a milestone in the electrosynthesis of 1,2,3-triazoles.

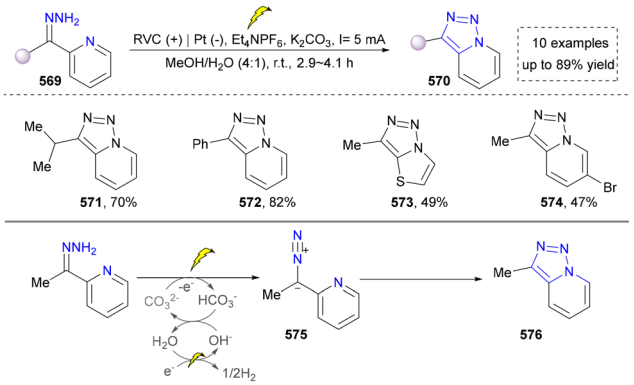
Inspired by this work, Fershtat's group also focused on the synthesis of 1,2,3-triazole 1-oxides through electrocatalysis.[288] They improved the electrochemical conditions and enhanced the atom economy compared to previous reports. Moreover, plenty of 1,2,3-triazole 1-oxides (**560–562**) were afforded by this approach, using various oximinohydrazones (**558**, Scheme 59). To elucidate the mechanism, DFT studies and cyclic voltammetry were also performed, which provided a plausible reaction mechanism as shown below. The two-time single-electron oxidation to afford diazo species (**566**) was the key to this success. In addition, the subsequent cyclization and proton elimination resulted in the formation of 1,2,3-triazole 1-oxide. The same group also described the electrosynthesis of 1,2,3-triazole 1-imines *via* a



Scheme 58 Electrochemical synthesis of 1,2,3-triazole 1-oxides.



Scheme 59 Electrochemical N–N bond forming reactions: direct access to 1,2,3-triazoles.



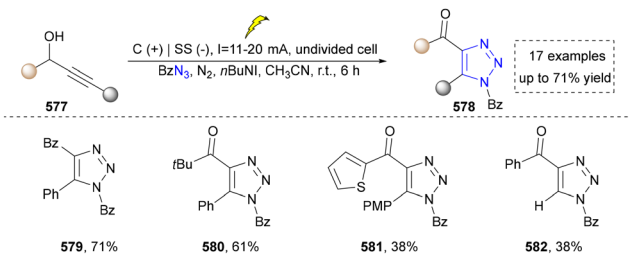
Scheme 60 Electrochemical synthesis of 1,2,3-triazoles through dehydrogenative cyclization.

similar strategy in 2024, expanding the structural diversity of 1,2,3-triazoles.[289]

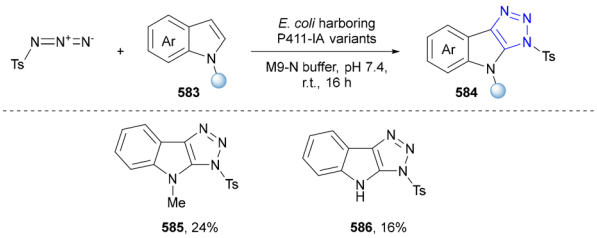
Besides the use of oximinohydrazone, Xu's group disclosed a convenient approach to synthesize [1,2,3]triazolo[1,5-*a*]pyridines *via* the electrochemical dehydrogenative cyclization of hydrazones of acylpyridines.[290] The concept was similar to the above-mentioned work. The hydrazone (**569**) underwent a two-electron oxidation with the help of carbon at the anode to generate a diazo intermediate (**575**). However, the substrate scope (**571–574**) was relatively limited due to the unavailability of the starting material (Scheme 60).

Bera's group further reported that benzoyl azides could also undergo cycloaddition with propargyl alcohols to afford 4,5-disubstituted-1,2,3-triazole scaffolds (Scheme 61, **579–582**). They also conducted the bioactivity screening *via* CLSM (confocal laser scanning microscopy) imaging, fluorescence and TCSPC (time-correlated single-photon counting) experiments, indicating the potential of these molecules in drug discovery.[291]

Oximinohydrazones and benzoyl azides have been employed in the synthesis of 1,2,3-triazole, leveraging the unique redox properties and mild conditions of electrosynthesis to potentially access diverse substitution patterns. However, to date, the development remains at an early stage, and no significant practical applications in synthesizing complex functional molecules have been documented so far. Consequently, the successful implementation of these electrochemical strategies for the practical synthesis of pharmaceutical agents or their analogues



Scheme 61 Electrochemical synthesis of the novel *N*-benzoyl-1,2,3-triazole derivatives.



Scheme 62 Enzymatic synthesis of triazoles *via* indole-azide cycloaddition.

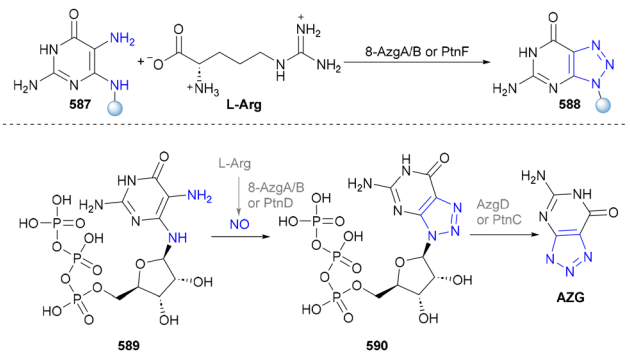
is eagerly awaited, as it would mark a critical transition from conceptual demonstration to applied synthetic utility.

5.1.3 Enzymatic synthesis of 1,2,3-triazoles. In 2019, Arnold's group described an unexpected formation of triazole (**584**) by indole-azide cycloaddition during cytochrome P450 variant-catalysed C2-amidation of 1-methylindole (**583**) with tosyl azide (TsN_3).[37] Site-saturation mutation screening of variants P-YS and P411-IA resulted in two mutants (P-YS A82S and P411-IA W82F) for improved triazole formation, which provided insights for further investigation of cytochrome P450-catalysed indole-azide cycloaddition reaction (Scheme 62).

In 2020, Du's group and Huang's group successively reported the biosynthetic pathway of triazole-bearing antimetabolite 8-azaguanine (8-AZG).[292,293] The triazolopyrimidine scaffold (**588**) could be assembled through either a non-enzymatic or an enzymatic cascade catalysed by bacterial nitric oxide synthase (NOS) ptnF or 8-AzgA/B, with nitric oxide as a building block composing the 1,2,3-triazole moiety. The final hydrolytic cleavage of ribose 5′-monophosphate moiety from the intermediate (**590**) was catalysed by 8-AzgD to yield the final product 8-AZG (Scheme 63).

Enzymes were also used to afford substrates for the chemical synthesis of triazoles.[293–295] In 2021, Yun and co-workers reported a multi-enzymatic cascade system for the synthesis of the sitagliptin intermediate, which was converted into sitagliptin *via* chemical synthesis, with benzylamine as an amino donor. The system was composed of transaminase (TA), esterase, aldehyde reductase (AHR), and formate dehydrogenase (FDH).[296]

Although relatively few reports have focused on the enzymatic synthesis of triazoles, the Arnold group's work demonstrated that the engineered P450 exhibits the potential to evolve indole-azide cycloaddition activity. Therefore, more enzymatic



Scheme 63 Enzymatic synthesis of the triazolopyrimidine scaffold.

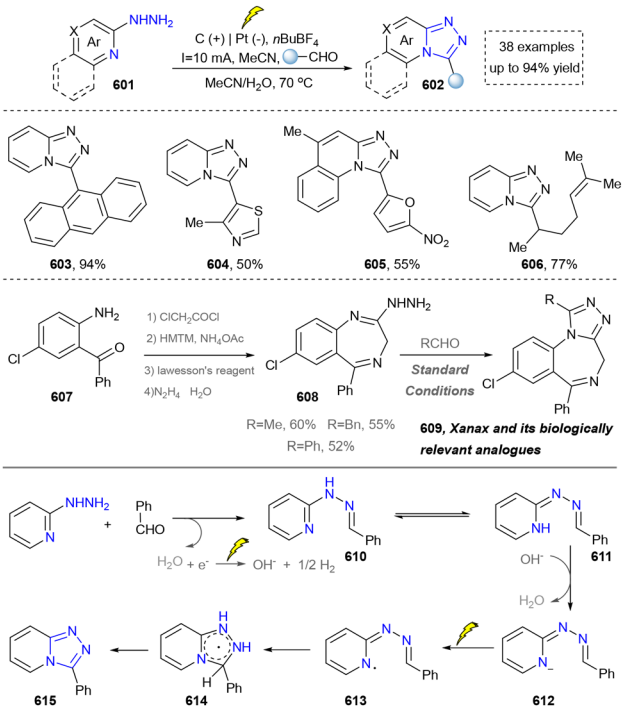
synthesis of triazoles can be realized in the future through further mining and engineering of the enzyme.

5.2 Synthesis of 1,2,4-triazoles

As a nitrogen-rich heterocyclic system, 1,2,4-triazole exhibits excellent thermal stability and the ability to form multiple hydrogen bonds, making it particularly valuable in drug designing.[297–299] This scaffold is a special structure in medicinal chemistry and plays an important role in antifungal agents (such as fluconazole derivatives), anticancer drugs and central nervous system therapeutics.[300] Classical strategies for 1,2,4-triazole derivatives involve cyclization of hydrazides/hydrazines, primary amine cyclization with nitrogen–oxygen exchange, and reactions employing guanidines, amidines, or ureas.[301] This section comprehensively discusses the synthesis of pharmacologically significant 1,2,4-triazole scaffolds by emerging synthesis methods.

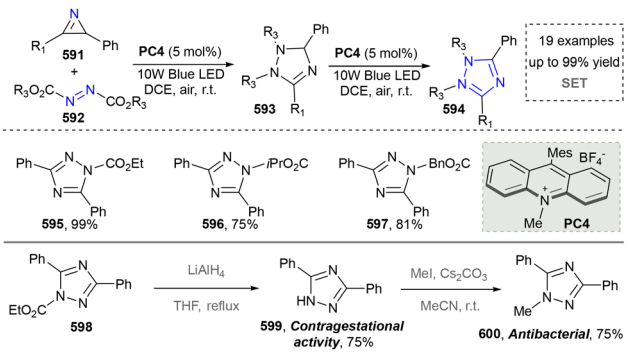
5.2.1 Photochemical synthesis of 1,2,4-triazoles. The Tang group reported a novel method to afford 1,2,4-triazoles efficiently from 2*H*-azirines and azodicarboxylates. They first achieved the synthesis of 1,2,4-triazolines under their photocatalytic reactions, which was further oxidized by the excited state of the photocatalyst to generate the desirable 1,2,4-triazoles under air condition. Besides the broad substrate scope (**595–597**), several valuable bioactive molecules (**599**, **600**) were further synthesized from the resulting 1,2,4-triazoles, which highlighted the method's utility in constructing pharmaceutically active compounds (Scheme 64).[48] Even though the synthesis of 1,2,4-triazoles by using photochemical method was still underexplored, this work provided evidence towards this direction.

5.2.2 Electrochemical synthesis of 1,2,4-triazoles. In 2018, Zhang's group disclosed an electrocatalytic method to achieve the intramolecular dehydrogenative C–N bond formation and synthesis of 1,2,4-triazole-fused heterocycles (Scheme 65). The hydrazone formed from the benzaldehyde and hydrazine was deprotonated to generate the nitrogen ion (**612**), which further underwent the single-electron oxidation to afford the nitrogen radical species (**613**). The subsequent radical addition and anodic oxidation gave the final product. Besides the synthesis of various small molecules, the system proved to be compatible with more diverse aromatic heterocyclic amines under standard conditions, enabling the synthesis of the tricyclic-fused drug Xanax and its biologically relevant analogue (**609**).[302]

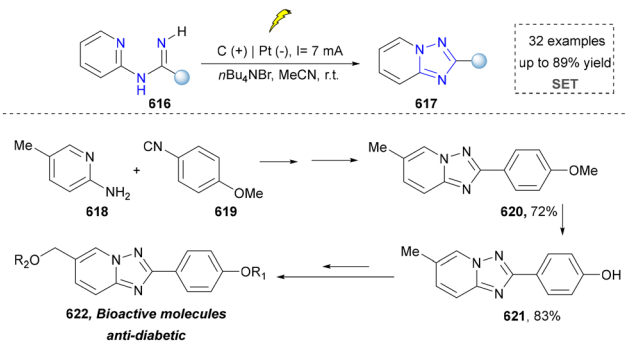


Scheme 65 Electrochemical synthesis of 1,2,4-triazole-fused heterocycles.

Later, the same group further developed their method to construct 1,2,4 triazolo[1,5-*a*]pyridines, the concept was similar to their previous work, and they used *N*-(2-pyridyl)benzamide as the starting material and the nitrogen radical was formed under the electrocatalytic condition. With this method, various 1,2,4-triazolo[1,5-*a*]pyridines were efficiently synthesized. More importantly, they also applied this strategy into the synthesis of several bioactive molecules (Scheme 66).[303] The final bioactive compound (**622**) was accessible through the synthesis of their key precursor (**620**) under their standard conditions, followed by a streamlined conversion involving only a few simple steps. However, it should be noted that the hydroxy group was not compatible within this system.



Scheme 64 Visible-light-induced cyclization reactions for the synthesis of 1,2,4-triazoles.



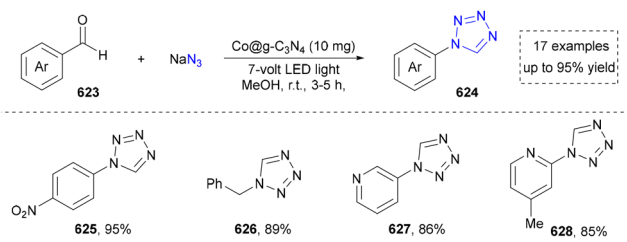
Scheme 66 Synthesis of 1,2,4-triazoles *via* intramolecular electrochemical dehydrogenation.

Overall, electrochemical synthesis has extended the scope of 1,2,4-triazoles, especially the construction of 1,2,4-triazole-fused heterocycles. Moreover, several bioactive compounds were afforded through electrochemical methods, such as Xanax and its related compounds, indicating their potential in drug synthesis. However, there is still some space to utilize other nitrogen sources or develop multi-component reactions to further diversify the 1,2,4-triazoles.

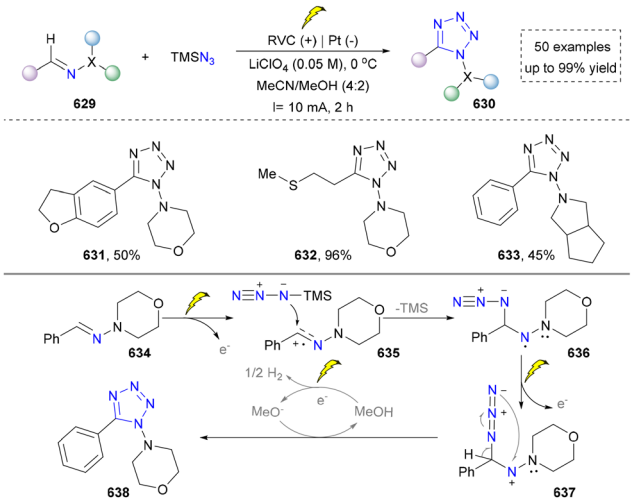
5.3 Synthesis of tetrazoles

As a nitrogen-rich heterocyclic ring (containing four nitrogen atoms), the tetrazole ring exhibits remarkable metabolic stability and can be used as a bioisosteric of carboxylic acids, significantly improving the pharmacokinetic profile of drug candidates.[304] They play an important role in several FDA-approved drugs, including antihypertensive drugs (such as losartan) and antibiotics (such as cefazolin).[305] The most common traditional approach for tetrazole synthesis involves cycloaddition reactions between azides and synthons such as nitriles, isonitriles, and imino functional groups.[306] Recent advances in green synthesis methods including photocatalysis and electrochemical methods have further enhanced the sustainability of tetrazole synthesis. The structural versatility of tetrazoles, which allows functionalization at multiple locations, continues to drive innovation in medicinal chemistry, agrochemical development, and functional material design, making them indispensable materials in modern chemical research.[307]

5.3.1 Photochemical synthesis of tetrazoles. Visible-light-driven synthesis of 1*H*-tetrazoles *via* heterogeneous photocatalysis was reported by Rai's group in 2018, which showed a very broad substrate scope (**625–628**) by using readily available aldehydes and sodium azide as starting materials.[38] In this case, NaN_3 not only worked as a nitrogen donor of the tetrazole ring but also reacted with aldehyde to generate isocyanide (Scheme 67). In particular, this work did not require the column chromatography for purification, which was highly convenient for chemists. The recyclability of the catalyst (up to five times) without any substantial change indicated the sustainability of this protocol. Moreover, this work was highlighted by the Synfacts, indicating the significance of this work.[308] This approach aims to replace traditional methods that rely on highly toxic azide reagents and harsh high-temperature/pressure conditions with milder alternatives. Efforts will focus on the replacement of toxic azide reagents by other nitrogen sources. In addition, integrating technologies like continuous flow processing could facilitate the scalable and green synthesis of tetrazoles.



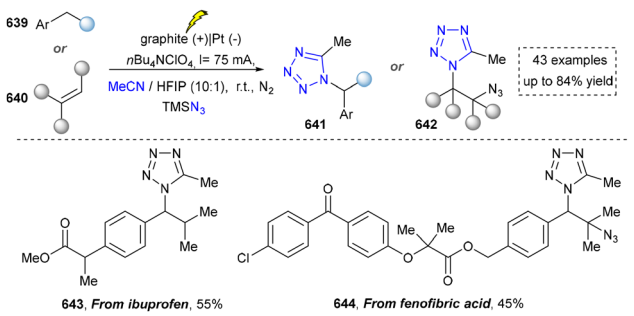
Scheme 67 Visible-light-driven synthesis of 1*H*-tetrazoles through [3+2] cycloaddition.



Scheme 68 Electrochemical synthesis of tetrazoles *via* the [3+2] cycloaddition of azides with hydrazones.

5.3.2 Electrochemical synthesis of tetrazoles. The electrochemical synthesis of tetrazoles was disclosed by Zhang's group in 2018.[309] Readily available azides and various hydrazones were employed as the starting materials to afford the tetrazoles (**631–633**) efficiently. They also provided a plausible mechanism according to the experiment studies and literature. First, the anodic oxidation of hydrazone generated the carbocation intermediate (**635**), which further reacted with azides to form the aminyl radical species (**636**) *via* C–N bond formation. The subsequent oxidation and intramolecular cyclization generated the final products (Scheme 68).

Ye's group further developed this strategy and reported a multi-component reaction (MCR) to construct tetrazoles by electrochemical synthesis (Scheme 69).[42] With the advantage of the MCR, this strategy strongly expanded the structural diversity of tetrazoles by using abundant and inexpensive chemical feedstocks. Particularly, the synthesis of tetrazoles was controlled by using alkenes or alkyls as substances. Besides the synthesis of simple molecules, this strategy was applied into the late-stage modification to afford ibuprofen and fenofibric acid analogues (**643**, **644**) under standard conditions. The electrochemical process also demonstrated excellent compatibility with a range of functional groups, including esters and



Scheme 69 Electrochemical multicomponent tetrazolation and vicinal azidotetrazolation.

ethers. These results demonstrated that this approach provided a green and sustainable synthetic methodology for the structural optimization and modification of drug molecules.

Currently, prefunctionalized organic azides remained the preferred nitrogen source for both photochemical and electrochemical synthesis. In contrast, research on the precise use of stable, readily available alternative precursors such as sulfonyl hydrazides, organic amines, or nitro compounds for reactive nitrogen species remains substantially underdeveloped. Perhaps, some novel strategies using different nitrogen sources or three- or four-component reactions can be achieved in the future.

6. One-oxygen-containing aromatic heterocycles: furans and benzofurans

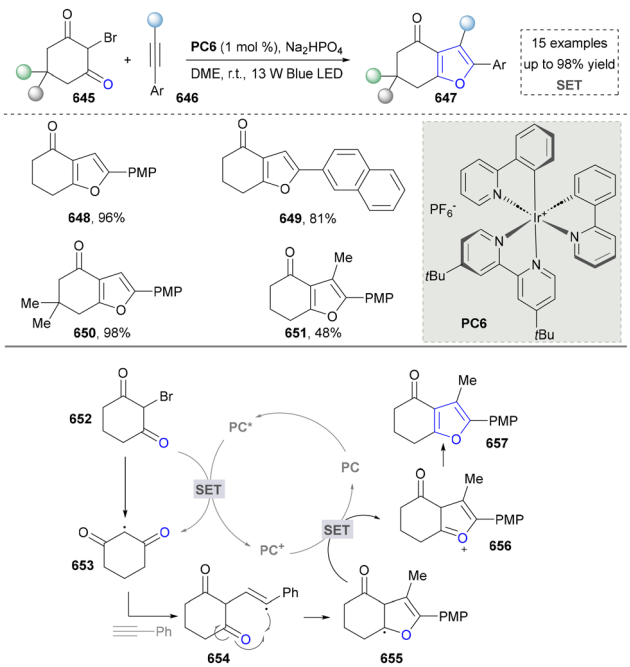
6.1 Synthesis of furans

As a privileged oxygen-containing heterocycle, the furan has been a versatile component in drug development, with many biologically active compounds containing this motif, including antiviral agents and anticancer drugs.[310] The structural versatility of furans stems from the combination of their aromatic character (6π-electronic system) with the electronic effects of the oxoheterocyclic atoms, resulting in multiple modes of functionalisation.[279] Traditional methods for the synthesis of furans include the Paal–Knorr synthesis and Feist–Bénary synthesis.[311,312] This section provides a comprehensive discussion on the synthesis of furan scaffolds of pharmacological interest through emerging synthetic approaches.

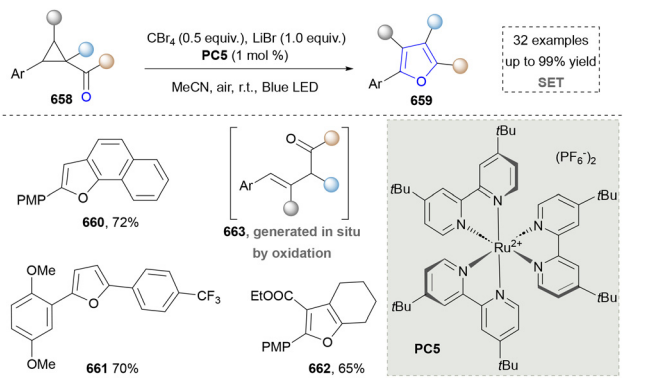
6.1.1 Photochemical synthesis of furans. The first work to synthesize furans *via* photoredox catalysis has been reported by Yu's group in 2013 (Scheme 70).[313] 2-Bromocyclohexane-1,3-dione worked as a radical precursor to form the radical species (**653**) after the SET process and further reacted with alkynes to form the corresponding vinyl radical intermediate (**654**). Subsequently, intramolecular homolytic aromatic substitution and single-electron oxidation of the cationic species occurred (**656**). At last, the deprotonation and the tautomerization yielded the final product (**648–651**).

Inspired by this work, several methods have been reported to expand the structural diversity of furans by using various radical precursors.[314–317] For instance, Wu's group disclosed that the combination of styrenes and α-alkyl ketone radicals could generate furans efficiently *via* photoredox catalysis.[318] In 2022, a double-radical-polar crossover reaction was also described, in which an α-halo ketone was used as the radical precursor, which further reacted with various allenamides to afford functionalized 2-aminofuran.[319] It should be noted that 1,3-diones without the activation of halogenation were also reported by Lei's group, and the additional persulfate salt could enable the direct hydrogen atom transfer (HAT) of the 1,3-dione.[320]

In addition, Xia and co-workers utilized cyclopropyl ketones as precursors for furan synthesis. Single-electron oxidation triggered ring opening to form a key unsaturated ketone intermediate (Scheme 71), followed by oxidative annulation to furnish diverse furans (**660–662**). However, CBr_4 as a stoichiometric oxidant was not friendly to the green synthesis. Later, the direct alkene isomerization of *in situ* formed unsaturated ketone for the synthesis of polysubstituted furans has also been reported under the irradiation of UV light.[321] In 2018, Nithyanandhan's group reported that *O*-acetylated (3′,5′-dimethylphenyl) as a starting material could be activated directly under the irradiation of light due to the good photophysical properties, but the structural diversity was very poor.[322] Similarly, the visible-light photoredox-catalysed reaction of enynones with 2,2,2-trifluoroacetamide to access polysubstituted furfuryl trifluoroacetamide derivatives under mild reaction conditions was also reported.[323] Building on previous studies, Donohoe's team utilized photoinduced alkene isomerization in 2019 to achieve efficient synthesis of polysubstituted furans under neutral conditions, thereby expanding the toolkit for the diversification of furans.[324]



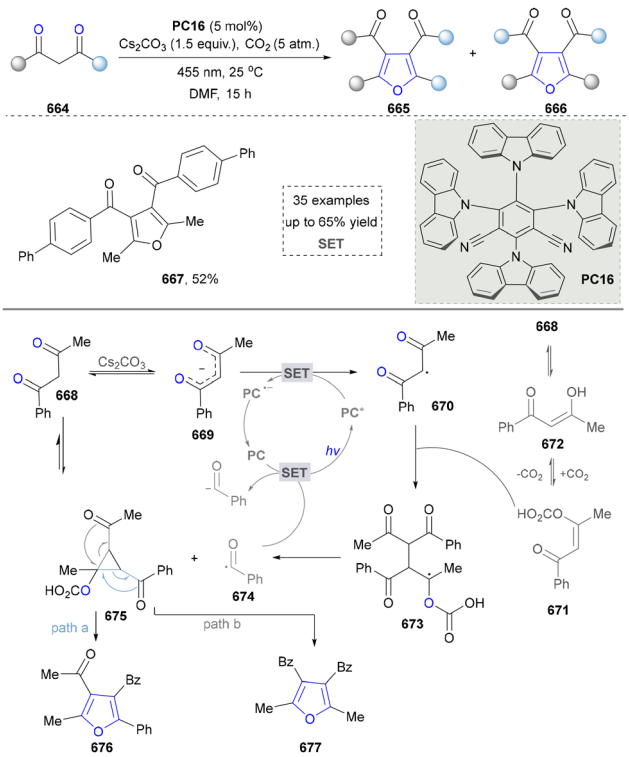
Scheme 70 Synthesis of polysubstituted furans from cyclopropyl ketones.



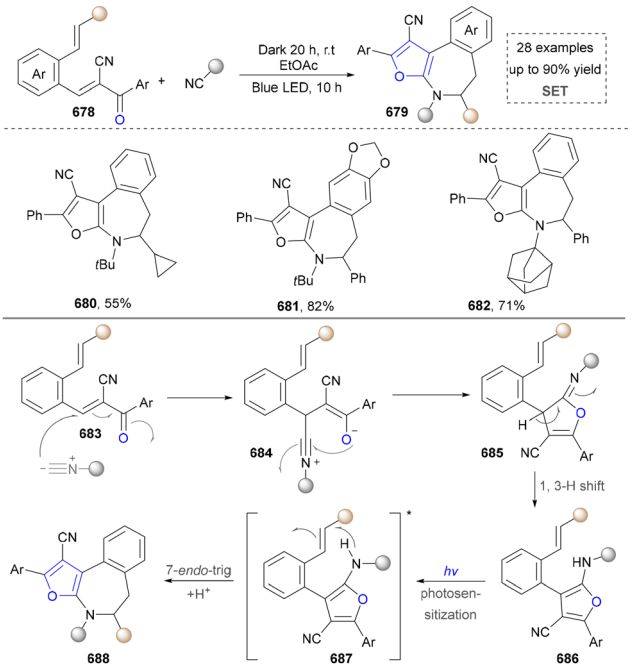
Scheme 71 Synthesis of polysubstituted furans from cyclopropyl ketones.

Later, Koenig's group significantly improved the sustainability of this strategy by the utilisation of carbon dioxide under visible light irradiation (Scheme 72). They applied 1,3-diketone as a starting material, which was deprotonated by Cs_2CO_3 to generate the corresponding enolate. After the SET process, it was oxidized to generate the radical species (**670**). 1,3-Diketone also reacted with CO_2 to obtain the intermediate (**671**), which subsequently reacted with radical species to form acylcyclopropane (**675**) as a key intermediate, which further generated the final furan product through different pathways. It was also determined that CO_2 was incorporated at the diketone enolic-OH position, which was key to success and facilitated the cleavage of a C–O bond during the rearrangement of acylcyclopropane intermediate.[325] Acceptor/acceptor diazoalkanes have been successfully employed in the photocatalytic synthesis of furans through reactions with terminal alkynes. The key to this strategy lies in the energy transfer-mediated formation of triplet carbene intermediates, which facilitates the cyclization process to construct the furan heterocycle.[326] Very recently, vinyl sulfoxonium ylides have also been proved as a suitable substrate to react with azides to form tri-substituted furans by Liu's group.[327]

Afterwards, Wang's group described an elegant strategy to construct furan-fused dihydroazepines under direct photolysis without the addition of photocatalysts and additives (Scheme 73).[328] By the design and synthesis of a substance containing conjugated dienes (**683**), the amino-substituted furan (**680–682**) was obtained directly by the cycloaddition with



Scheme 72 Photocatalytic synthesis of furans promoted by carbon dioxide.

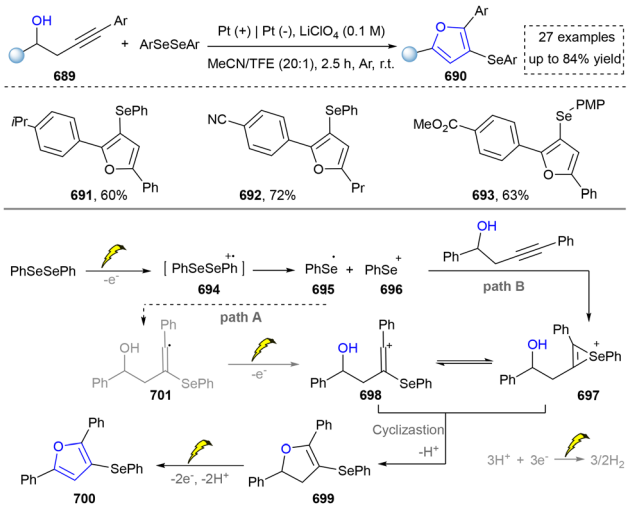


Scheme 73 Photocatalyst-free and transition-metal-free synthesis of furans.

isocyanide, which showed obvious light absorption under light irradiation. This intermediate itself worked as a photosensitizer to promote the C–N bond formation through 7-*endo-dig* cyclization to generate the complicated furan. This strategy also featured the operational simplicity and gram-scale synthesis. The late-stage applications into complex substrates were also achieved successfully, indicating the potential of this strategy in drug synthesis.

In summary, the use of ketones as oxygen sources for the synthesis of furans has been extensively and effectively explored through various methods. It is anticipated that other oxygen sources such as alcohols and molecular oxygen could also be successfully applied in this field. Moreover, photochemical synthesis of furans circumvents the use of stoichiometric hazardous oxidants while also enabling late-stage furan cyclization of complex molecules bearing acid-, base-, or heat-sensitive functional groups, thus providing a powerful tool for the rapid diversification of leading compounds.

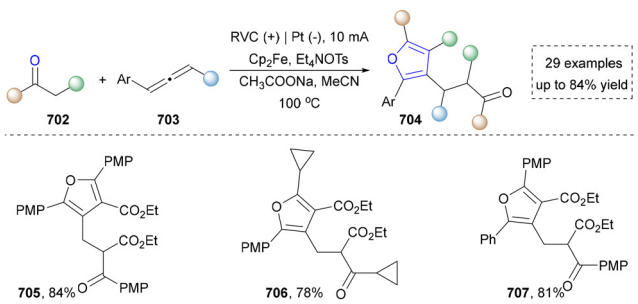
6.1.2 Electrochemical synthesis of furans. Compared to well-established methods to afford furans by photocatalysis, the electrochemical synthesis provided another pathway to access furans with more structural diversities. In 2019, Sarkar's group reported an elegant method to synthesize selenfurans (**691–693**) *via* electrocatalysis (Scheme 74). Since organoselenium compounds are highly popular in drug designing, this strategy will be of interest towards medicinal chemists. In mechanistic studies, they proved that the oxidative cyclization was the important process for the formation of the products. The oxidation of diphenyl diselenide, alkenyl radical (**701**) assisted the formation of a dihydrofuran derivative, which further underwent two-electron oxidation to generate the furans.[329]



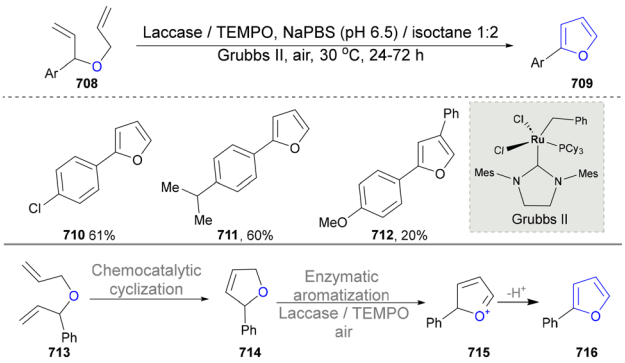
Scheme 74 Synthesis of polysubstituted furans through electrochemical selenocyclization.

Later, Tang's group also described a strategy to afford furans (**705–707**) *via* the annulation of allenes (Scheme 75). This electrochemical method avoided the traditional use of an external oxidant.[51] Similarly, Zhao's group reported the electrocatalysis approach in which 1,3-dione and alkynes were used as starting materials, a known concept, but the electrocatalysis approach avoided the use of an additional oxidant.[330]

Overall, electrochemical synthesis has emerged as a versatile and powerful platform for furan preparation, continuously pushing the boundaries of accessible structures. A key advancement lies in the innovative use of alcohols as green and atom-economical oxygen sources, enabling dehydrogenative cyclization reactions under mild conditions. Furthermore, the scope of cyclization partners has been significantly expanded beyond traditional substrates to include allenes, alkynes, and difunctionalized olefins. This diversification allows for the direct construction of highly substituted and functionalized furan cores, including complex benzo[*b*]furan scaffolds, from simple precursors, thereby greatly broadening the structural diversity and complexity achievable. Future endeavors will focus on achieving more precise oxygen-atom transfer from inert and greener oxygen sources.



Scheme 75 Electrochemically-mediated C–H functionalization to construct furans.



Scheme 76 Enzymatic synthesis of furans by *T. versicolor* laccase.

6.1.3 Enzymatic synthesis of furans. In 2019, Castagnolo's group developed a chemoenzymatic approach for the aromatization of 2,5-dihydrofuran (**714**) to furan (**716**), utilizing the *Trametes versicolor* laccase/TEMPO catalytic system under mild aqueous conditions.[331] Subsequently, a one-pot chemoenzymatic cascade process has been developed directly from diallyl ethers (**708**) to furans (**709**) through the combination of RCM reaction with the laccase/TEMPO aromatization in the same reaction medium, providing a sustainable alternative method for the industrial synthesis of furan derivatives (Scheme 76).

In 2023, Ouyang's group reported an environmentally sustainable chemoenzymatic strategy to generate *n*-butyl-5-formyl-2-furancarboxylate (*n*Bu-FFCA), the precursor of furan-2,5-dicarboxylic acid (FDCA) from commercial sodium gluconate (GA).[332] GA was catalysed by gluconate 5-dehydrogenase from *Gluconobacter oxydans* (Ga5DH) coupled with the short-chain reductase from *Pichia stipitis* (PsCR) to form 5-keto-D-gluconic acid (5KGA), which subsequently reacted to produce *n*Bu-FFC *via* dehydration and esterification.

It is attractive to convert cheap biomass into chemicals directly through furanic platform molecules. The chemo- and bio-catalytic synthesis of 2,5-bis(hydroxymethyl)furan (BHMF), a crucial building block for biobased polymers and fine chemicals, has made great progress in past decades.[333–336] In 2024, Liao *et al.*[337] established an efficient chemobiocatalytic one-pot process for converting glucose into BHMF by combining $CaCl_2$ with engineered *Saccharomyces cerevisiae* harboring MgADH1 (an HMF-resistant ADH from *Meyerozyma guilliermondii* SC1103), without the requirement of intensive 5-hydroxymethylfurfural (HMF) purification[335,338] or expensive fructose and sugar syrup.[339–343]

Although only laccase-catalysed furan ring formation has been reported, there are various enzymes involved in the formation of furan ring in natural products. For example, AteafoF from *Aspergillus terreus* catalysed the formation of furan ring in asperfuranone, an azaphilone first isolated from *A. nidulans*.[344] In the biosynthetic pathway of furanocoumarin, the formation of the furan ring involved one prenyltransferase (PT) and two cytochrome P450s.[345–347] In *Salvia miltiorrhiza* Bunge, CYP71Ds catalysed the formation of the characteristic furan ring of tanshinones,[348] then a 2-oxoglutarate-dependent dioxygenase converted dihydrofuran to furan.[349] We will not provide a detailed discussion of these examples here; however,

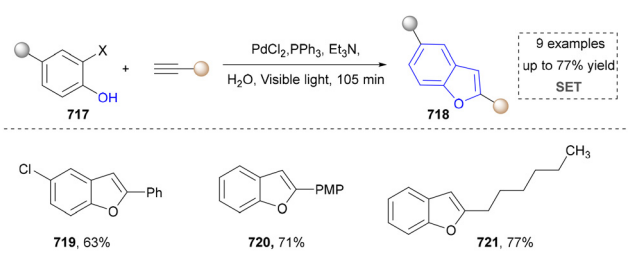
they have a great potential for enzymatic synthesis of furan, like laccase.

6.2 Synthesis of benzofurans

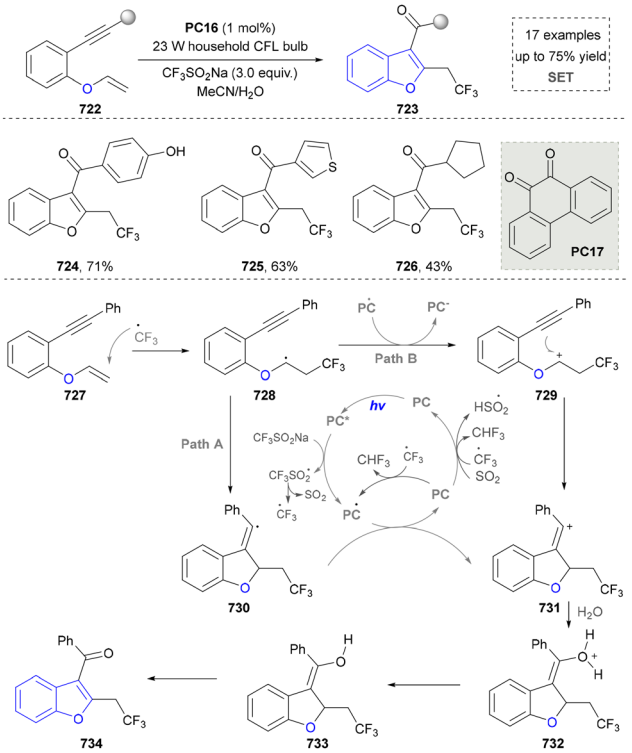
Considering that benzofurans have exceptional structural and pharmacological properties, the synthesis of benzofuran derivatives represents a critical research area in organic synthesis and medicinal chemistry.[350] Moreover, as a privileged heterocyclic scaffold, benzofuran combines the aromatic stability of benzene with the electronic diversity of the furan ring, creating unique opportunities for drug designing and material development.[351] In medicinal chemistry, benzofuran-containing compounds demonstrate broad bioactivity,[352] featuring prominently in FDA-approved drugs such as the anticoagulant dronedarone and the antipsychotic amiodarone.[353] Traditional benzofuran synthesis relies on Lewis acid-catalysed or transition metal-catalysed oxidative cyclization of substituted benzene derivatives, though the requirement for metal catalysts, ligands, and additives complicates these processes for industrial applications.[354,355] This section focuses on highlighting the groundbreaking contributions of emerging synthetic methodologies in the construction of benzofurans and related drug analogues.

6.2.1 Photochemical synthesis of benzofurans. In 2012, Ghosh's group firstly reported that visible light could stimulate the intermolecular Sonogashira coupling and cyclization reaction to generate the 2-aryl/alkylbenzofurans (Scheme 77, **719–721**). Even though the mechanism was not investigated, this pioneering work disclosed the significant role of light in the transition-metal catalysis.[356] The synthesis of naphtho[*b*]furans *via* photochemical approach was reported by Yoshimi's group in 2014. By designing the allyl 1-bromo 2-naphthyl ether as the substrate, the direct activation of the starting material and subsequent radical cyclization facilitated the formation of product. Even though the substrate scope was limited (even simple benzofuran was not successful) and lack of mechanistic studies was observed, this work still provided a novel pathway to afford the valuable naphtho[*b*]furans.[357]

To further achieve the photochemical synthesis of benzofurans, Kumar's group described an efficient method to construct benzofurans by using trifluoromethylating Langlois' reagent as a radical precursor to release the $-CF_3$ radical after single electron transfer event (Scheme 78).[159] The trifluoromethyl radical further reacted with a vinylic double bond to form the radical species (**728**) which further underwent 5-*exo*-*dig* cyclization and oxidation to form the carbocation (**729**). At last, the



Scheme 77 The formation of benzofurans by the cyclisation of *ortho*-halophenols and terminal alkynes.

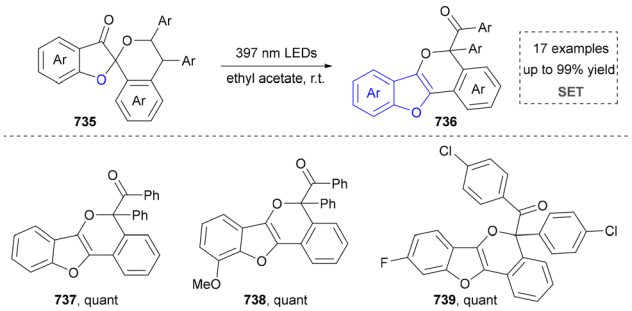


Scheme 78 Dehydrogenative cascade trifluoromethylation and oxidation.

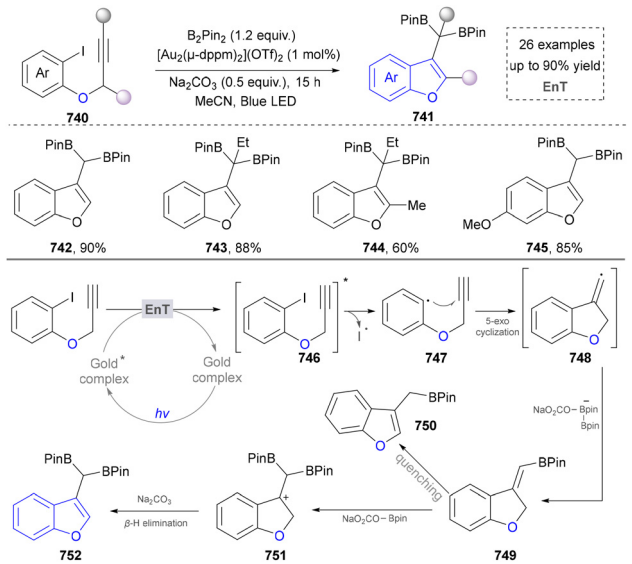
subsequent addition of water to the vinylic cation (**731**) with the elimination of hydrogen gas provided the final products (**724–726**). It should be noted that this strategy was very powerful to synthesize diverse five-membered heteroarenes including benzofurans and indoles indicating the potential of this strategy in the synthesis of drugs. In addition, various radical precursors such as arylsulfinic acids, thiosulfonates and aryldiazonium salts were applied in the synthesis of diverse benzofurans by this similar strategy.[50,358–362] α-Azidochalcones was also designed to achieve the activation of an alkene group, which further underwent the cyclization to furnish the benzofuran-2-amines.[363]

In 2019, Zhou's group designed benzofuranone-based spiroisochromenes to investigate the oxa-6π electrocyclic reaction of *cis,cis*-1,8-dioxatetraene. The targeted spiroisochromene derivatives were activated under the irradiation of 390 nm light and were transformed into the 5*H*-benzofuro[3,2-*c*]isochromene derivatives, a class of scaffolds with pronounced bioactive potential (Scheme 79, **737–739**). Interestingly, the formed product was easily turned back to the original starting material under heating conditions.[53] The direct intramolecular synthesis of dibenzofuran derivative was also reported by using 2-(2′-aminophenyl) phenol as a starting material.[364]

Hashmi's group also reported a novel method to access the diborylated benzofurans, indoles, and benzothiophenes by using photocatalysis (Scheme 80).[365] Since the geminal diboronates have attracted great attention due to their unique bioactivities, the synthesis of heteroarenes bearing five-membered rings with diboronates is highly important in medicinal chemistry. The



Scheme 79 Electrocyclic reactions of 1,8-dioxatetraene.



Scheme 80 Visible-light-induced *gem*-diborylation for the synthesis of benzofurans.

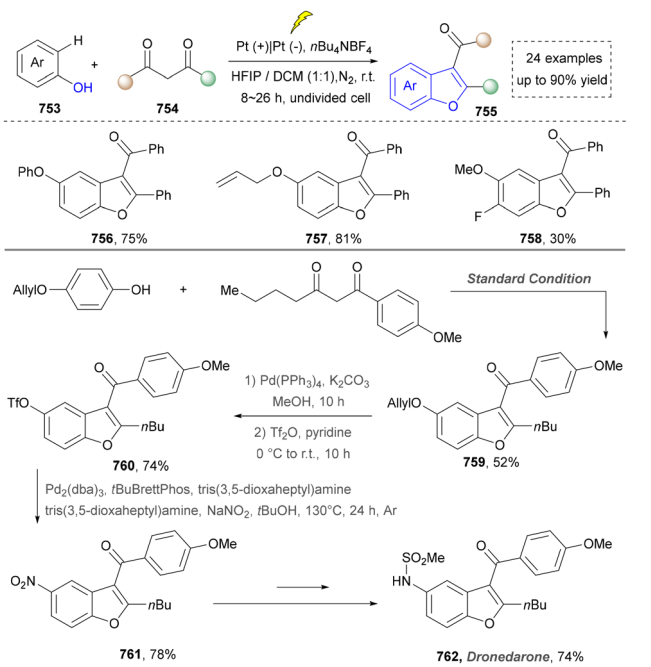
mechanistic experiments in this work proved the generation of new photosensitive gold complexes from dinuclear gold catalysts with Na_2CO_3 under blue LED illumination. With the activation of alkyne *via* energy transfer, the product (**742–745**) was formed *via* subsequent cyclization. Moreover, 10 gram-scale synthesis was also achieved, indicating the practicability of this method. This strategy pioneers the *gem*-diborylation of three core heteroaromatic scaffolds, namely benzofurans, indoles, and benzothiophenes, effectively addressing a critical synthetic gap for these biologically essential building blocks.

In summary, divergent methods through photochemical synthesis have been developed in this field. Most of the approaches focused on the radical addition of vinylic double bond and subsequent oxidation. However, some other novel protocols *via* energy transfer have also reported recently to broaden the reaction patterns. It is also promising to utilize three-component methods to further expand the photochemical synthesis of benzofurans.

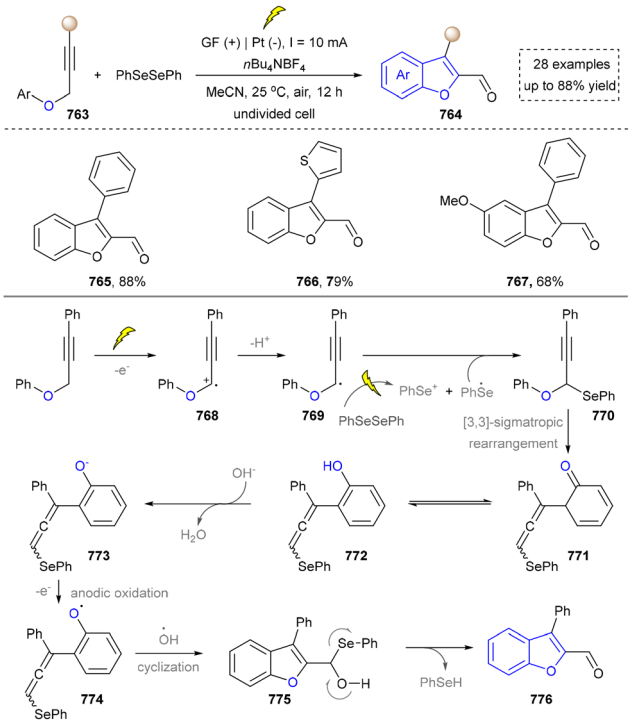
6.2.2 Electrochemical synthesis of benzofurans. Electrocatalysis provided some other pathways to obtain benzofurans compared to photocatalysis.[366] First, Shi's group reported an intermolecular cross-dehydrogenative coupling reaction using simple phenols and β-dicarbonyl compounds as starting materials (Scheme 81).[367] With this robust method, diverse benzofurans (**756–758**) have been synthesized. Furthermore, a key intermediate (**759**) for the synthesis of the marketed drug dronedarone (**762**) was efficiently prepared under standard conditions, underscoring the practical utility of this strategy. However, it also showed the limitation towards phenol bearing electron-withdrawing groups such as the nitro group.

Recently, Sun's group disclosed an elegant method to achieve the selective synthesis of benzofurans from propargylic aryl ethers in the presence of dialkyl(aryl) diselenides (Scheme 82).[368] The key to success is the single-electron oxidation of propargylic aryl ethers to generate the radical species (**769**), which further reacted with a phenyl selenium radical *via* radical-radical cross coupling to access the intermediate (**770**). The subsequent [3,3]-sigmatropic rearrangement, anodic oxidation and cyclization furnished the final benzofurans (**765–767**) under simple reaction conditions. At the same time, Cai's group also reported the synthesis of naphtho[1,2-*b*]furan-2-carbaldehyde and related derivatives *via* a similar strategy, indicating the potential of electrocatalysis upon the synthesis of benzofurans.[369]

Overall, the electrochemical synthesis of benzofurans significantly broadens the scope of applicable starting materials, which were previously challenging to use in the synthesis of benzofurans, even though current methods still predominantly rely on the built-in oxygen sources within pre-functionalized substrates. Additionally, the successful synthesis of certain drugs and intermediates through electrochemical methods highlights its promising potential in the field of pharmaceutical synthesis.



Scheme 81 Electrochemical cross-dehydrogenative coupling between phenols and β-dicarbonyl compounds.

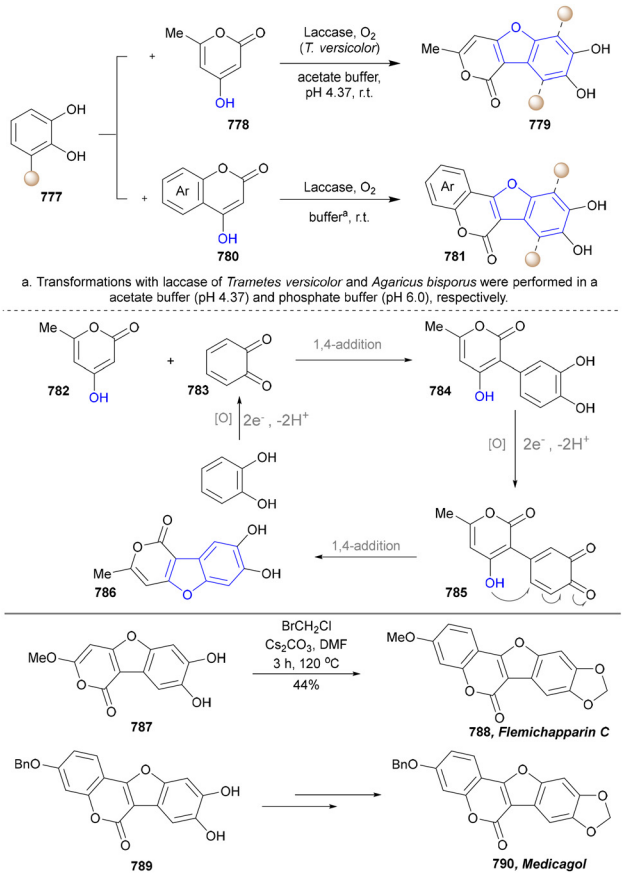


Scheme 82 Synthesis of benzofurans *via* an electrochemical cyclization reaction.

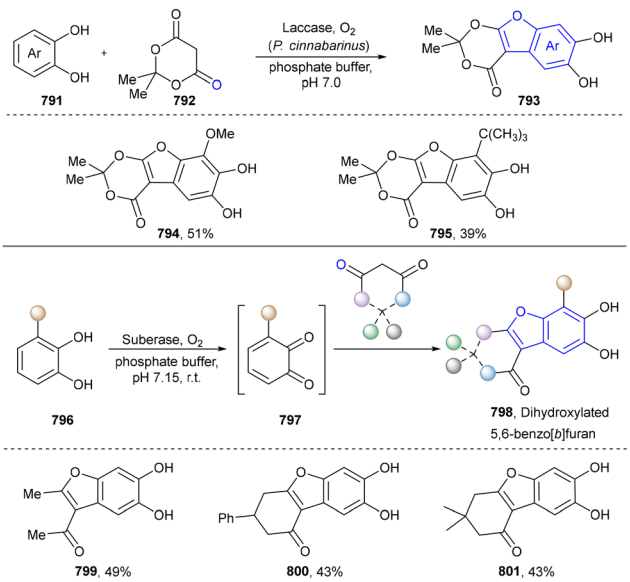
6.2.3 Enzymatic synthesis of benzofurans. As early as 2005, Beifuss and co-workers reported the laccase-catalysed domino reactions for the first time, since then laccase has been used in the synthesis of five-membered heteroaromatics.[370] Commercially available laccase from *T. versicolor* or *A. bisporus* catalyses domino reactions of **778** or **780** and catechols (777) to form coumestans and derivatives. The entire domino process included two oxidations and two 1,4-additions (Scheme 83). More importantly, excellent functional group tolerance was demonstrated by the system toward 1,2-dihydroxybenzene containing carbonyl and ether moieties. This allowed the preparation of benzofuran scaffolds (**787**, **789**) under standard conditions, which were conveniently elaborated into natural products, flumequaparin C (**788**) and the medicagol (**790**), further validating the significance of this strategy in natural product synthesis. 3,4-Dihydro-7,8-dihydroxy-2*H*-dibenzofuran-1-ones could be synthesized from cyclohexane-1,3-diones and catechols catalysed by laccase from *A. bisporus* without by-products.[371]

More benzofuran derivatives such as coumestans had been obtained *via* the oxidation–Michael addition reactions between catechols and various 1,3-dicarbonyl compounds in the presence of *Pycnoporus cinnabarinus* laccase[372] and *Myceliophthora thermophila* laccase Suberase®, which exhibited non-stereoselectivity but high regioselectivity (Scheme 84).[373,374]

Overall, laccase-catalysed domino reactions exhibited great potential for the synthesis of benzofurans from catechols and various substrates. These studies highlighted the versatility of the laccase-initiated cascade reactions as a green pathway for the synthesis of organic compounds. As described above, the selectivity of natural laccases was not ideal; therefore, further research should focus on laccase engineering and optimization of reaction conditions to improve the selectivity.



Scheme 83 Enzymatic synthesis of benzofurans by laccase.



Scheme 84 Enzymatic synthesis of the benzofuran derivatives by laccase.

7. One-sulfur-containing aromatic heterocycles: thiophenes and benzothiophenes

7.1 Synthesis of thiophenes

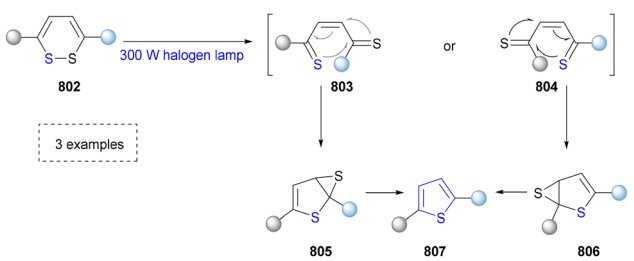
Thiophene is a key heterocyclic scaffold, which is widely found in pharmaceutical preparations, dyes and natural products, and is an important intermediate in pharmaceuticals.[375,376] Representative examples include cephalosporin antibiotics (*e.g.*, cefalotin, cefaloridine, and cefoxitin), exhibiting broad-spectrum antibacterial activity.[377] Emerging strategies including light-mediated and electrochemical annulation are attracting significant attention for their ability to streamline the construction of complex thiophene-containing architectures while enhancing structural diversity and pharmacological potential. Conventional approaches for thiophene synthesis typically utilize the Gewald and Fiesselmann methods.[378]

7.1.1 Photochemical synthesis of thiophenes. As early as 1999, Towers and colleagues pioneered a photochemical strategy by utilizing the photosensitivity of thiarubrines, wherein visible light irradiation generated photosulfurized intermediates (**803** and **804**) that underwent rapid desulfurization to yield thiophene derivatives **807** (Scheme 85).[379] However, due to the limited substrate scope, they did not further explore the broader applicability or mechanistic intricacies of this methodology in subsequent studies. Moreover, the light sources were also energy-consuming, which was also needed to improve.

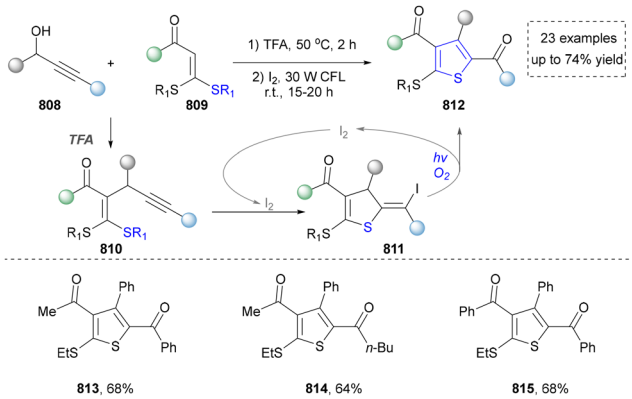
In 2012, Wu and co-workers reported a facile visible-light-driven protocol for synthesizing 3,4-diarylthiophenes from 3,4-diaryl-2,5-dihydrothiophenes, utilizing a platinum(II) terpyridyl complex as a photocatalyst and acetonitrile as the solvent.[380] This strategy achieved yields, which were comparable to conventional thermal synthesis under visible light irradiation, demonstrating the viability of photoredox catalysis in thiophene synthesis.

Advancing this field, Luo's group disclosed a relay catalytic approach in 2020, integrating chemical catalysis and photocatalysis to streamline the synthesis of complex thiophenes (**813–815**) from simple precursors (Scheme 86).[56] Their one-pot protocol first employed chemical catalysis to assemble dihydrothiophene intermediates (**811**), followed by visible-light-mediated iodocyclization/deiodinative transformation of alkyne thioether intermediates using substoichiometric iodine.

Afterwards, Pan's group developed a similar method for constructing polysubstituted thiophenes through [3+2] cyclization of



Scheme 85 Photoinduced synthesis of thiophenes.



Scheme 86 Synthesis of 2,4-diacyl thiophenes from α-oxo-ketene dithioacetals and propargylic alcohols.

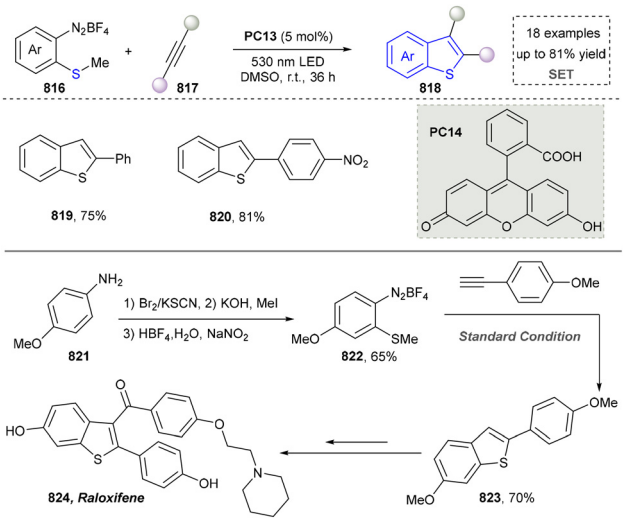
alkynes with easily available ketene dithioacetals, further expanding the synthetic toolbox for modular thiophene functionalization.[381]

Overall, light-driven technologies in thiophene synthesis remain in their infancy. Complicated starting materials are required to prepare to furnish the thiophene synthesis. Furthermore, systematic investigations into key scientific questions such as photosensitizer design and energy transfer mechanisms remain underexplored. Notably, electrochemical synthesis routes of thiophenes have not been reported to date. This gap may stem from challenges such as redox potential matching and electrode interface modulation. The development of novel photo-/electro-responsive catalysts to overcome the energy barrier limitations of conventional pathways remains a valuable research direction for providing innovative strategies toward the green synthesis of thiophene derivatives.

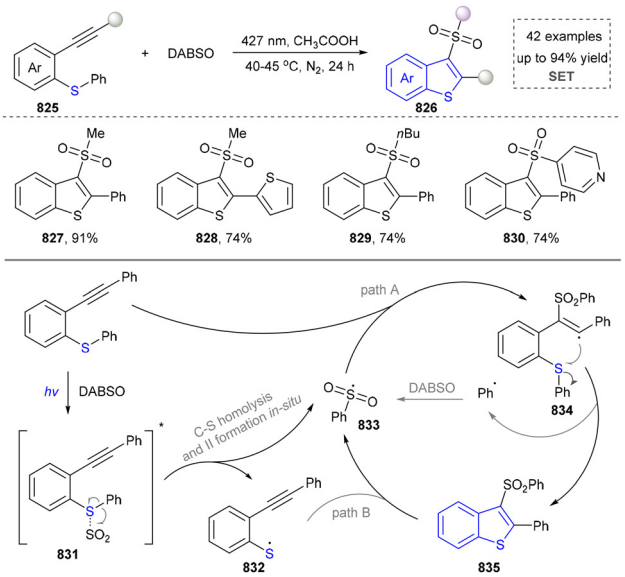
7.2 Synthesis of benzothiophenes (benzoselenophenes)

The benzothiophene scaffold represents a privileged heterocyclic system. Within medicinal chemistry, benzothiophene-containing compounds demonstrate remarkable pharmacological diversity, as exemplified by clinically significant agents such as raloxifene (a selective estrogen receptor modulator with anticancer applications) and numerous other therapeutic candidates, exhibiting potent antimicrobial and anti-inflammatory activities.[382,383] Benzothiophenes are conventionally synthesized *via* intramolecular electrophilic cyclization of *O*-alkynyl aryl thioethers or transition metal (Pd/Cu/Au)-catalysed intramolecular C–S bond formation. Alternative approaches include Cu/Pd-catalysed intermolecular C–S coupling and intramolecular Heck reactions.[384] However, the green and efficient synthesis of benzothiophene remains a focus of interest.

7.2.1 Photochemical synthesis of benzothiophenes (benzoselenophenes). König's group first reported the photocatalytic synthesis of benzothiophenes under the irradiation of visible light in 2012 (Scheme 87).[385] They applied the diazonium salt as the staring material, which was reduced by the excited state of the photocatalyst to form the aryl radical. Then the addition to the alkyne yielded a vinyl radical, which underwent cyclization and follow-up oxidation to provide the final products (**819**, **820**). Finally, this methodology provided a metal-free route to



Scheme 87 Photocatalytic synthesis of benzothiophenes.



Scheme 88 Photo-induced synthesis of 3-(alkyl/arylsulfonyl) benzothiophenes.

afford the drug raloxifene (**824**) by efficient synthesis of the key intermediate (**823**) under standard conditions. This was achieved by reacting the amine-derived compound (**822**) with the alkyne under standard photoredox conditions, thus furnishing **823** in 70% isolated yield. However, it also indicated that the hydroxy group was not tolerable in this system, and using demethylation of a methoxy group can solve the aforementioned problem.

Inspired by this work, Luna's group also reported a similar method to construct the benzothiophenes from diazonium salts and alkynes, but this method relied on the precious gold catalysis.[386] Moreover, several continuous reports focused on the photocatalytic synthesis of benzothiophenes from alkynes and various radical precursors.[387–393] For example, Zhu's group reported the synthesis of benzothiophenes and benzoselenophenes through the photocatalytic annulation of available thiophenols or 1,2-diphenyldiselane with alkynes.[394] Wu's group reported the synthesis of benzothiophenes using sodium metabisulfite as a radical precursor, which further reacted with 2-alkynylthioanisoles.[395] With all of these methods, the divergent synthesis of benzothiophenes has been achieved. In addition, Kitamura's group disclosed the irradiation of the iodinated benzo[*b*]thiophenes with a Hg lamp (>290 nm) and afforded [1]benzothieno[3,2-*b*][1]benzothiophene derivatives (BTBTs) successfully.[396]

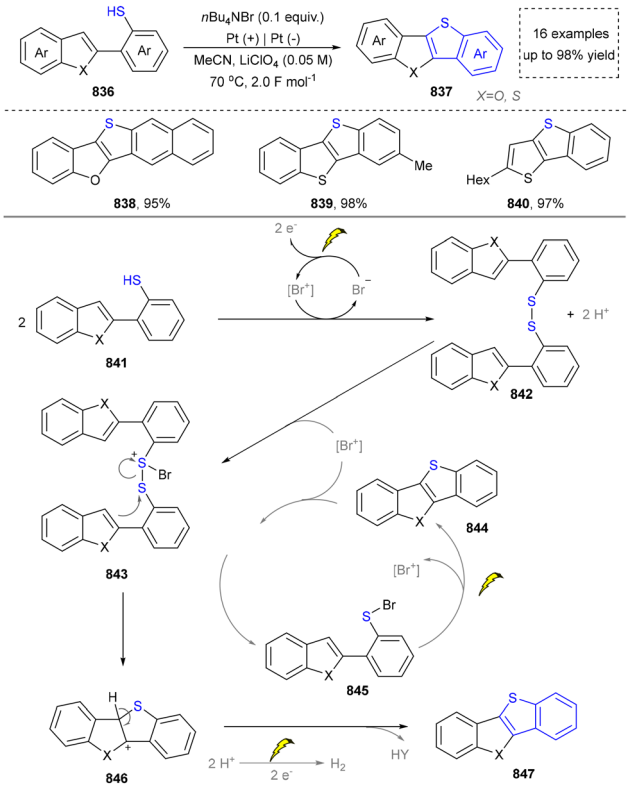
In 2024, Li's group further developed this method. The synthesis of 3-(alkyl/arylsulfonyl)benzothiophenes and benzoselenophenes was achieved *via* the photoinduced tandem cyclization of 2-alkynylthioanisoles or-selenoanisoles with DABSO as radical precursors (Scheme 88, **827–830**). Moreover, this reaction proceeded smoothly without any external photocatalyst, improving the sustainability of benzothiophene synthesis.[397] Benzenethiol-linked 1,6-enynes were also applied to the synthesis of benzothiophenes, whereas this strategy has been well-established in the synthesis of benzofurans.[398]

Overall, the synthesis of benzothiophenes from photochemical approaches has been well explored. The thiol source was mostly from thioethers, which reacted with different alkynes to obtain benzofurans through the photoredox catalysis. However, the starting material in these cases was relatively difficult to prepare. The radical precursors had to be introduced into the starting material in most of the cases, which limited the practical use of this protocol.

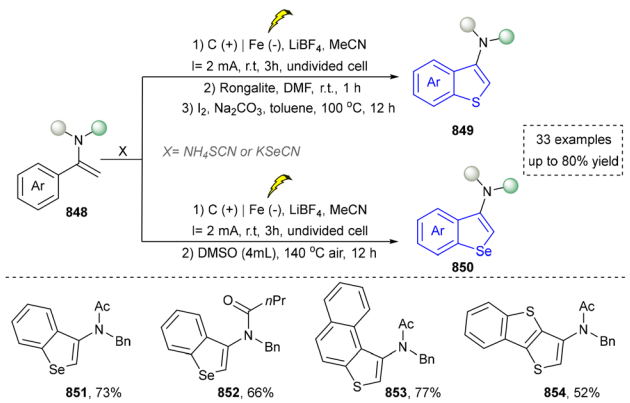
7.2.2 Electrochemical synthesis of benzothiophenes. With the development of electrocatalysis, the synthesis of benzothiophenes was also achieved by this strategy. Suga's group first disclosed the electrochemical synthesis of thienoacene derivatives (Scheme 89).[55] With 2-(benzo[b]furan-2-yl)benzenethiol as the starting material, the electro-oxidative dehydrogenative cyclization was achieved with the assistance of nBu$_4$NBr. The formed [Br$^+$] oxidized the starting material to give the disulfide, which further reacted with [Br$^+$] to obtain the cationic species. After the subsequent intramolecular cyclization and deprotonation, the final product (**838–840**) was generated. Based on this work, the same group further developed the synthesis of dibenzothiophenes *via* the electrocatalytic activation of bis(biaryl) disulfides.[399] Park's group also further expanded the application of disulfides to the synthesis of benzothiophenes.[54] Wang's group also disclosed the electrocatalysis of sulfonated benzothiophenes by using 2-alkynylthioanisoles and sodium sulfonates.[400]

The synthesis of benzoselenophenes and benzothiophenes *via* electrochemical oxidative method has also been disclosed by Zeng's group (Scheme 90). The enamide underwent oxidative electrochemical selenocyanation with KSeCN/NH$_4$SCN to afford radical species as the key intermediate, which further underwent cyclization to furnish the final products (**851–854**).[401]

Overall, the electrochemical synthesis of benzothiophenes has contributed to the utilization of different starting materials such as thiols and disulfides. There are also some methods, which are very similar to photochemical methods; however,



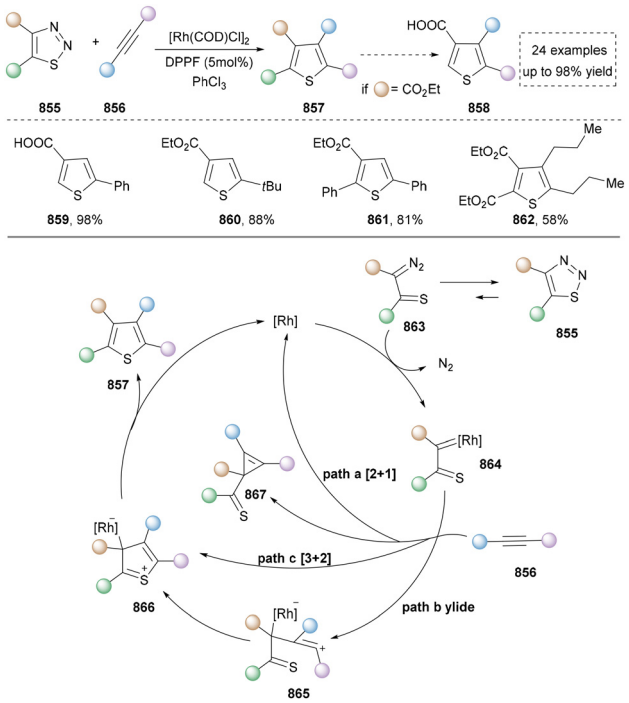
Scheme 89 Electrochemical synthesis of the thienoacene derivatives.



Scheme 90 Electrocatalytic synthesis of benzoselenophenes and benzothiophenes.

concise reactions by using simple synthetic synthons should be the future target. Another future integrated photo-electro system holds promise. Here, photocatalysis would generate key sulfur radicals, while electrochemical control of electrode potential would facilitate the cyclization and aromatization. This synergy could offer unprecedented command over reaction pathways and selectivity, presenting a new approach to overcome current selectivity challenges.

7.2.3 Atom editing for the construction of benzothiophenes. In 2016, Gevorgyan's group described a method for the modular synthesis of multisubstituted thiophenes from



Scheme 91 Modular synthesis of polysubstituted thiophenes from 1,2,3-thiadiazoles.

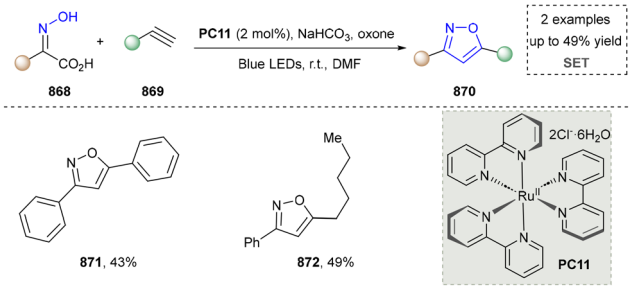
1,2,3-thiadiazoles (Scheme 91)[402] The key to success for this atom-editing strategy was the formation of rhodium thiavinyl carbenes, which further reacted with alkynes efficiently to form the desirable thiophenes. However, the substrate scope was also broad including diverse alkynes and substituted 1,2,3-thiadiazoles (**859–862**).

8. Aromatic heterocycles containing hybrid heteroatoms: isoxazoles, oxazoles, benzoxazoles, isothiazoles, thiazoles, and benzothiazoles

8.1 Synthesis of isoxazoles

As a privileged heterocyclic scaffold containing adjacent nitrogen and oxygen atoms, the isoxazole ring exhibits remarkable metabolic stability and serves as a bioisostere for various carboxylic acid derivatives and other heterocycles, which significantly enhance the pharmacokinetic profiles of bioactive molecules.[403,404] This structural motif features prominently in numerous pharmaceuticals, including COX-2 inhibitors (*e.g.*, valdecoxib), antibacterial agents, and CNS-active compounds.[405,406] Isoxazole rings are traditionally constructed through [3+2] cycloaddition of *N*-chlorosuccinimide-chlorinated hydroxylamines with alkynes, or *via* 1,3-dipolar cycloaddition of oxidized nitriles with terminal alkynes.[407] This section provides a comprehensive discussion on emerging eco-friendly methodologies that have significantly enhanced the efficient synthesis of isoxazoles.

8.1.1 Photochemical synthesis of isoxazoles. In 2016, Leonori's group disclosed the photocatalytic synthesis of isoxazolines



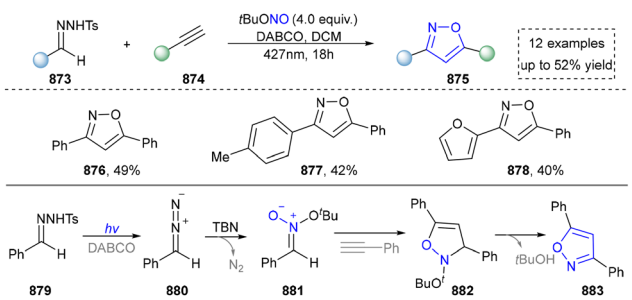
Scheme 92 Visible light promoted the synthesis of isoxazoles.

and isoxazoles *via* the *in situ* generation of nitrile oxides from readily available hydroxyamino acid (Scheme 92). The nitrile further reacted with alkynes to furnish isoxazoles; however, the scope was not investigated in detail (only two examples: **871** and **872**).[68]

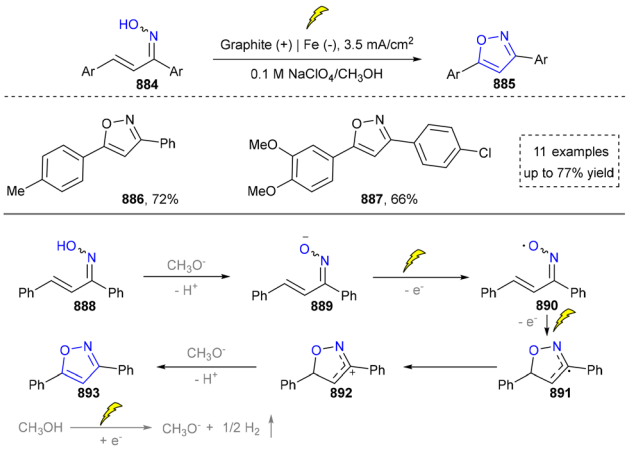
Recently, our group has also disclosed the synthesis of isoxazoles *via* a photoinduced three-component strategy. In this case, the *N*-tosylhydrazones (**879**) were activated under the irradiation of light to generate *in situ* diazo compounds (**880**), which further reacted with *tert*-butyl nitrite to form the intermediate nitronate **881**.[29] The nitronate underwent the [3+2] cycloadditions with different alkynes to furnish the final isoxazoles (**876–878**). The isoxazolines was also afforded by using alkene as a starting material. More importantly, two antitrypanosomal agents were synthesized efficiently by using this strategy (Scheme 93).

Overall, the photochemical synthesis of isoxazoles was underexplored, and the reported cases demonstrated certain advantages over traditional thermal conditions or transition metal catalysis. Although the concept is not entirely novel, there is still significant room for further exploration. In particular, it is worth noting that the investigation of different nitrogen sources, beyond the commonly studied oximes and hydrazones, is also highly warranted.

8.1.2 Electrochemical synthesis of isoxazoles. In 2014, Little's group reported the first example to obtain 3,5-disubstituted isoxazoles *via* electrochemical synthesis (Scheme 94). Chalcone oximes were applied directly as substrates, which were deprotonated and subsequently oxidized to generate the aminoxyl radical (**890**). Afterwards, an intramolecular radical addition to the alkene generated the cyclized intermediate (**891**), which underwent



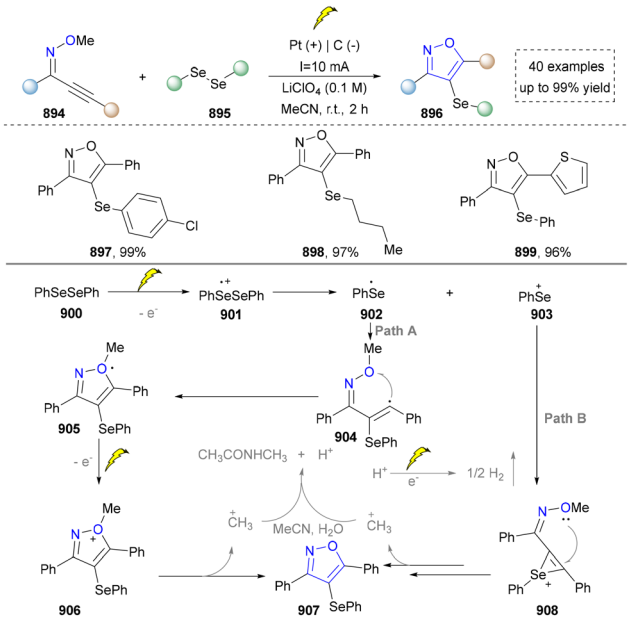
Scheme 93 Visible-light-mediated strategy for the synthesis of Isoxazoles.



Scheme 94 Electrochemical synthesis of the 3,5-disubstituted isoxazoles.

oxidation and follow-up deprotonation again to afford isoxazoles. Even though only a few substrates (**886**, **887**) were evaluated in this system, it is still a pioneering work in the electrochemical synthesis of isoxazoles.[408] Moreover, using oximes and alkynes as starting materials to synthesize isoxazoles has been disclosed *via* intermolecular cycloadditions.[409] Except the use of oximes, cathodic reduction of the nitro substance and subsequent intramolecular cyclization also generated isoxazoles, which was reported by Waldvogel and Peters' group independently.[410,411]

To further expand the structural diversity of isoxazoles, the synthesis of organoselenyl isoxazoles has been disclosed by Hu's group in 2024 (Scheme 95).[412] In this method, diverse organoselenyl isoxazoles were afforded under electrocatalytic conditions. In their proposed mechanism, the phenyl selenium radical generated from diorganyl diselenides reacted with

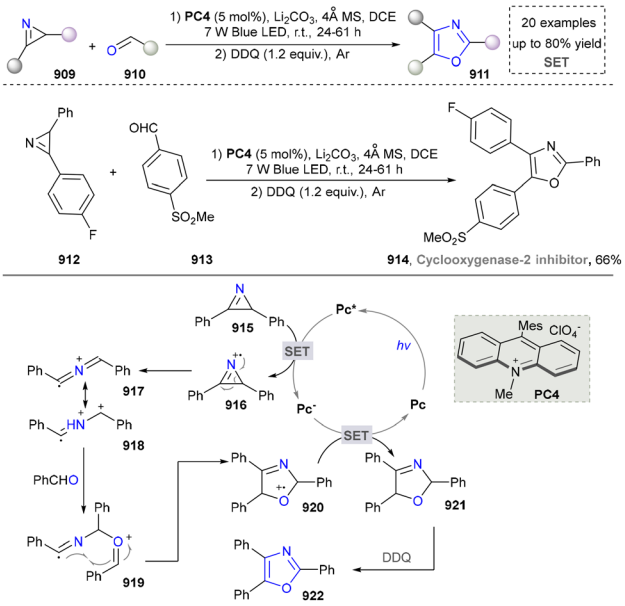


Scheme 95 Electrochemically promoted synthesis of organoselenyl isoxazoles.

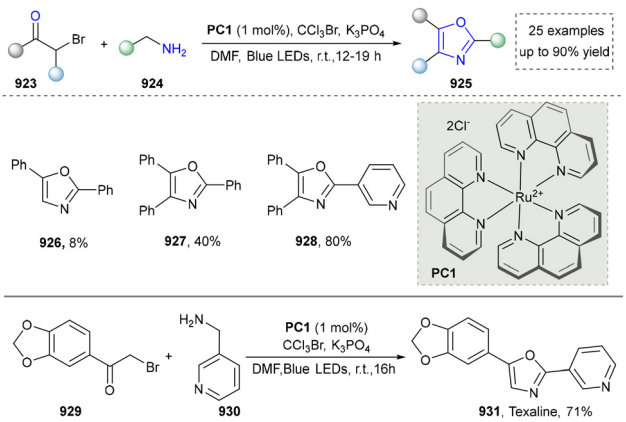
2-alkyn-1-one *O*-methyloximes to generate the vinyl radical (**904**), which further underwent an intramolecular radical cyclization to form the cyclized intermediate (**905**). Follow-up oxidation at the anode afforded the corresponding pentacyclic cation intermediate (**906**), which further dropped the methyl cation to form the product.

In summary, the synthesis of isoxazoles *via* electrochemical methods has been well established, especially the application of oximes as a nitrogen source. Moreover, nitrogen sources were extended to the nitro substance, which further diversified the synthesis of isoxazoles. Therefore, the substrate scope of isoxazole synthesis was strongly extended compared with traditional or photochemical methods such as the generation of organoselenyl isoxazoles. Therefore, there is still some space to explore other nitrogen sources and reaction reagents to construct novel isoxazoles.

8.1.3 Atom editing strategies for the construction of isoxazoles. Besides the C-to-N atom swapping in indoles to afford indazoles and benzimidazoles, Studer's group realized the skeletal editing in benzofurans to access isoxazoles efficiently.[212] The strategy was similar to the cleavage of the indoles. It should be noted that this method was successfully applied to the modification of the benzofuran-containing drugs, indicating the potential of atom editing in drug design and modifications. The generality of this strategy for synthesizing a range of five-membered heteroaromatics has prompted the consolidation of their representative examples into a unified scheme, with specifics provided in Scheme 111.



Scheme 96 [3+2] cycloaddition/oxidative aromatization sequence to afford oxazoles.



Scheme 97 Synthesis of substituted oxazoles by photocatalysis.

8.2 Synthesis of oxazoles

Oxazole, a distinctive heterocyclic scaffold incorporating both nitrogen and oxygen atoms represents a privileged structural motif, which is extensively distributed in natural products and pharmaceutical agents.[413] As evidenced by its presence in FDA-approved therapeutics such as the antibacterial drug linezolid and the antiviral agent pleconaril, this scaffold maintains persistent research interest and occupies a pivotal position in both organic synthesis and medicinal chemistry.[414–416] Oxazole synthesis methodologies include the Robinson–Gabriel synthesis, Fischer oxazole synthesis (using cyanohydrins and aldehydes), and Bredereck reaction.[417] This section will critically examine the transformative role of environmentally benign strategies in constructing this pharmacologically significant heterocyclic framework.

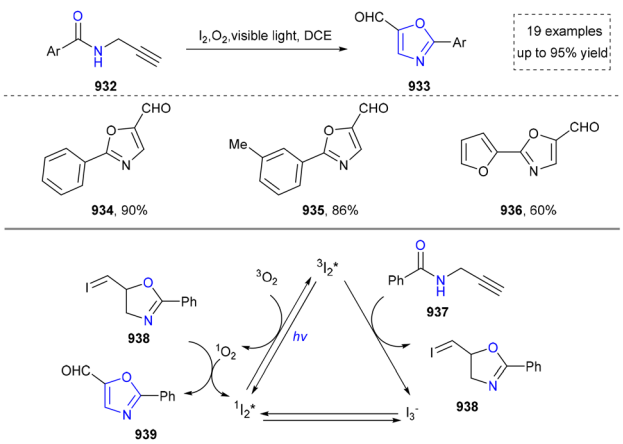
8.2.1 Photochemical synthesis of oxazoles. Compared with synthesis of isoxazoles, oxazoles have been well explored *via* using different nitrogen sources. The first case was reported by Xiao's group in 2015, and one-pot synthesis of oxazoles efficiently from azirines and aldehydes has been achieved under photocatalytic conditions (Scheme 96).[66] The potential of this method was further highlighted by the single-pot synthesis of cyclooxygenase-2 inhibitor **914** under standard conditions, which was obtained efficiently in 66% yield. This result indicated that the presence of strong electron-withdrawing groups (EWGs), such as the sulfonyl group, on the benzaldehyde substrates was compatible with the reaction conditions. In normal cases, azirines were oxidized to 2-azaallenyl radical cations through single-electron oxidation, and subsequent ring opening provided the intermediate (**917**), which further reacted with an aldehyde to furnish another intermediate (**919**). Afterwards, the radical addition and single-electron reduction generated 2,5-dihydrooxazole (**921**). At last, the oxidative aromatization provided the oxazole product (**922**). It should be noted that this photochemical method could utilize commercially available aldehydes to furnish oxazoles, thereby strongly expanding the structural diversity. Inspired by this work, Wang's group also disclosed the three-component reaction of 2*H*-azirines, alkynyl bromides, and molecular oxygen to furnish oxazoles by following similar concepts.[418]

α-Bromoketones were also applied to the synthesis of oxazoles by Cho's group (Scheme 97).[419] In this case, α-bromoketones reacted with benzylamines to give diverse oxazoles (**926–928**) under

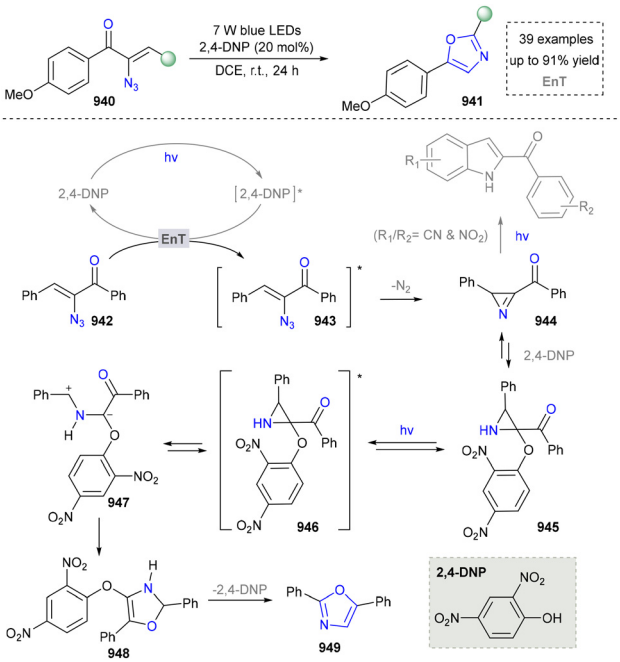
photocatalytic conditions. Furthermore, the methodology enabled the efficient synthesis of the natural product Texaline (**931**), which was obtained in 71% yield from **929** and **930**, under optimized conditions (**PC** 1 mol%, CCl_3Br 1.5 equiv., K_3PO_4 3.0 equiv., DMF 0.1 M, Blue LEDs 7 W, 16 h). The successful incorporation of a pyridine-based substrate (**930**) as the starting material confirmed the compatibility of the pyridine moiety with the reaction conditions. Moreover, this natural product was produced on a gram scale, highlighting the applicability of this method. Later, CO_2-pomoted cyclization of α—bromo ketones and amines to construct substituted oxazoles has also been reported by Li's group, which improved the sustainability of this method.[420] In 2023, Srivastava's group found that using benzil and benzyl amine could also form the oxazoles *via* photocatalysis.[63] The concept was similar to the above work and both of them relied on the synthesis of imine as an intermediate.

To further expand the structural diversity of oxazoles *via* photochemical synthesis, Wang's group employed the readily available propargyl amide as a starting material, which underwent cyclization to generate a valuable oxazole (Scheme 98).[59] In the mechanistic studies, they proved that linked I_2/visible light activated the C–C triple bond efficiently, which was followed by nucleophilic addition by electron-donating amide groups, providing the final products (**934–936**). Inspired by this pioneering work, several groups continuously utilized the propargyl amides to synthesize oxazoles under photocatalytic conditions.[421,422] For example, Mal's group further developed this method by using charge-transfer complexes as semi-heterogeneous photocatalysts.[423] Selenium-π-acid catalysis has also been reported by Liu's group to facilitate the activation of propargyl amide, thereby forming the oxazoles under photocatalytic conditions.[424]

Later, the photoannulation of α-azidochalcones into 2,5-diaryloxazoles was reported by Maurya's group in 2022 (Scheme 99). They also proposed the mechanism as shown below. The α-azidochalcones (**942**) were activated *via* energy transfer to form the excited-state of the substrate (**943**), which further released N_2 to afford 2*H*-azirine (**944**) as a key intermediate. 2*H*-Azirine either further reacted with 2,4-dinitrophenol to form 2,5-diaryloxazoles (**946**) *via* the photoexcitation again or formed indole directly after



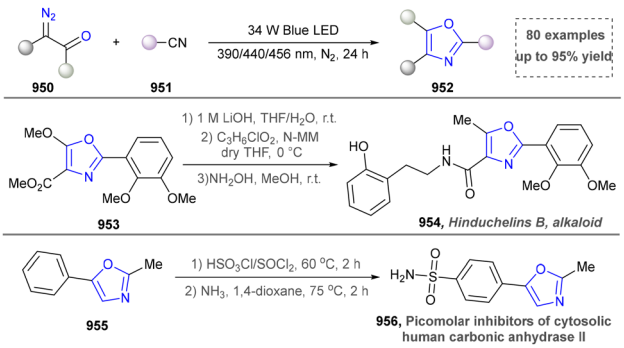
Scheme 98 Photocatalytic activation of alkynes for cyclization reactions.



Scheme 99 Visible light promoted the conversion of α-azidochalcones into 2,5-diaryloxazoles.

the rearrangement by replacing the photocatalyst to $Ru(bpy)_3(PF_6)_2$.[65] Enaminone was also reported as a nitrogen source to afford oxazoles by Baell and Liu's group, repectively.[67,425]

Besides the use of azide as the nitrogen source, the diazo compounds were applied for the synthesis of oxazoles in 2023. Maiti's group disclosed the initial photolysis of the diazo compound to afford singlet carbenes, which were tapped by nitriles and underwent [3+2] cycloaddition to form substituted oxazoles (Scheme 100). Compatible with diverse diazo compounds and nitriles, it efficiently builds complex oxazole scaffolds, including drug intermediates and isotope-labelled derivatives. Its integration with continuous-flow technology successfully addresses the scalability challenge in photochemistry, offering a practical and sustainable synthetic route. This method further enabled a concise two- to three-step synthesis of bioactive oxazoles from **953** and **955**, providing efficient access to compounds such as hinduchelins B



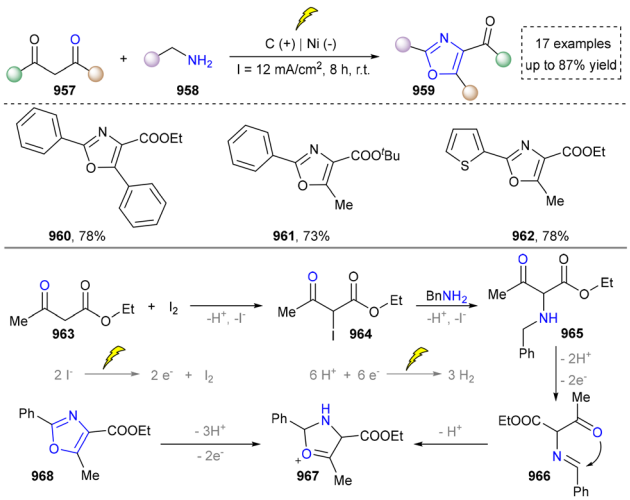
Scheme 100 Photoinduced [3+2] cycloaddition for the synthesis of oxazoles.

(**954**) and picomolar inhibitors of cytosolic human carbonic anhydrase II (**956**).[68] This group continuously unveiled that the combination of photoelectro-chemical (PEC) reaction to facilitate the synthesis of oxazoles and imide-fused pyrroles *via* the formation of a carbene radical anion.[64] Moreover, arylazo sulfones were applied as an arylating agent to furnish the oxazoles *via* the formation of diazenyl radicals.[426] Xia's group also described a similar strategy to afford oxazoles at almost the same time.[427]

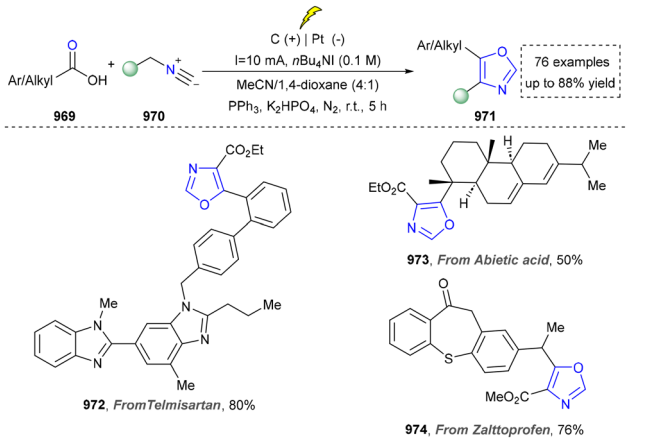
Overall, various nitrogen sources have been applied to the synthesis of oxazoles through photochemical methods. Moreover, photochemical strategies for synthesizing oxazoles demonstrate excellent compatibility with heterocyclic substituents. They also enable the retention of sensitive functional groups such as aldehyde groups on the skeleton that conventional methods seldom achieve. In addition, several drugs and natural products were synthesized successfully from these approaches. Therefore, it is highly possible that other heteroarenes also have possibilities to be afforded by photochemical methods.

8.2.2 Electrochemical synthesis of oxazoles. In 2014, Yuan's group first found that readily available β-diketone derivatives could achieve the synthesis of oxazoles (**960–962**) directly under the electrocatalytic conditions (Scheme 101).[428] In this method, molecular I_2 was electrogenerated *in situ* at the anode, and electrochemical oxidation played a key role in the generation of oxazoles.[429] Electrochemical synthesis enables the efficient construction of highly congested, fully substituted oxazole skeletons from simple precursors, whereas such transformations are notoriously challenging for traditional methods. He's group also described a similar work based on the above-mentioned concept.[430]

Xia's group also described an elegant method to afford oxazoles by using abundant and inexpensive carboxylic acids and benzyl amines as starting materials (Scheme 102). Besides typical advantages of electrochemical synthesis such as free of oxidants, this method was successfully employed for the late-stage modification of drugs, and several drug analogues bearing oxazoles were efficiently afforded under standard conditions (**972–974**).[62] The system demonstrated excellent functional group tolerance, accommodating stable unsaturated bonds, benzylic group and other heteroaromatics. Furthermore, its applicability was underscored by a successful gram-scale synthesis.



Scheme 101 Electrochemically promoted synthesis of polysubstituted oxazoles.



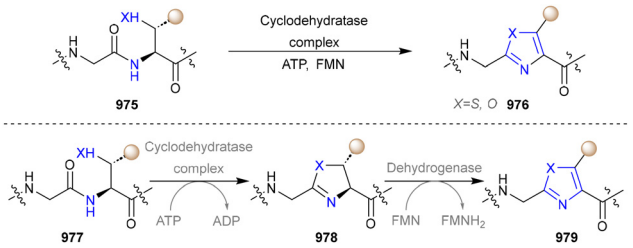
Scheme 102 Electrochemical synthesis of oxazoles *via* [3+2] cycloaddition.

Almost at the same time, MeCN worked simultaneously as a solvent and as a nitrogen source, which has been achieved by several groups.[430–433] With this method, polysubstituted oxazoles were synthesized from readily available ketones/alkynes and acetonitrile under electrocatalytic conditions. Inspired by this work, Li's group also reported a convenient method to construct the oxazole by using MeCN as a nitrogen source. This four-component reaction by using terminal alkynes, (thio)xanthenes, nitriles, and water as starting materials has been developed in the absence of any catalyst and external oxidant with excellent structural diversity.[434] The *N*,*N*,*N*,*N*-tetramethyl ethylenediamine (TMEDA) has also been applied as a nitrogen source for the synthesis of oxazoles by Cho's group.[435] Moreover, TMEDA played the role of a mediator in this system to facilitate the reaction. In addition, intramolecular electro-oxidative addition of *N*-propargyl benzamides has been reported.[436,437]

Compared to the photochemical synthesis of oxazoles, electrochemical synthesis provided novel routes to expand the diversity of the oxazoles. For instance, new nitrogen sources including MeCN to construct oxazoles have been reported, which showed unique advantage of the electrosynthesis.

8.2.3 Enzymatic synthesis of oxazoles. In 2014, Mitchell and co-workers reported that azole heterocycles in thiazole/oxazole-modified microcin (TOMM) natural products were biosynthesized through the sequential action of cyclodehydratase complex (composed of homologous protein of E1 ubiquitin-activating enzymes and YcaO superfamily) and flavin mononucleotide (FMN)-dependent dehydrogenase (Scheme 103).[58]

The studies remain on the discovery of the enzyme, responsible for azoline biogenesis in thiazole/oxazole-modified microcin (TOMM) natural products. Therefore, further research should focus on the application of enzymes in the synthesis of thiazoles and oxazoles.

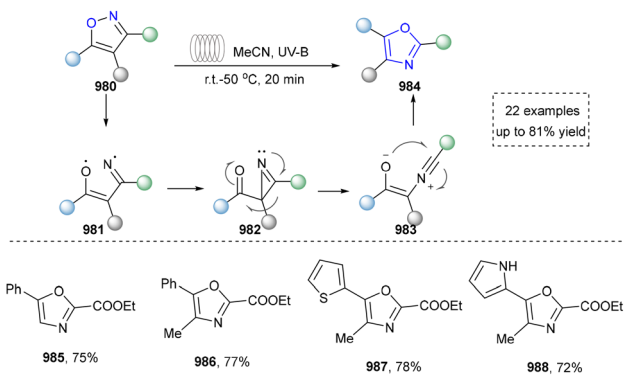


Scheme 103 Enzymatic synthesis of thiazole/oxazole-modified microcin.

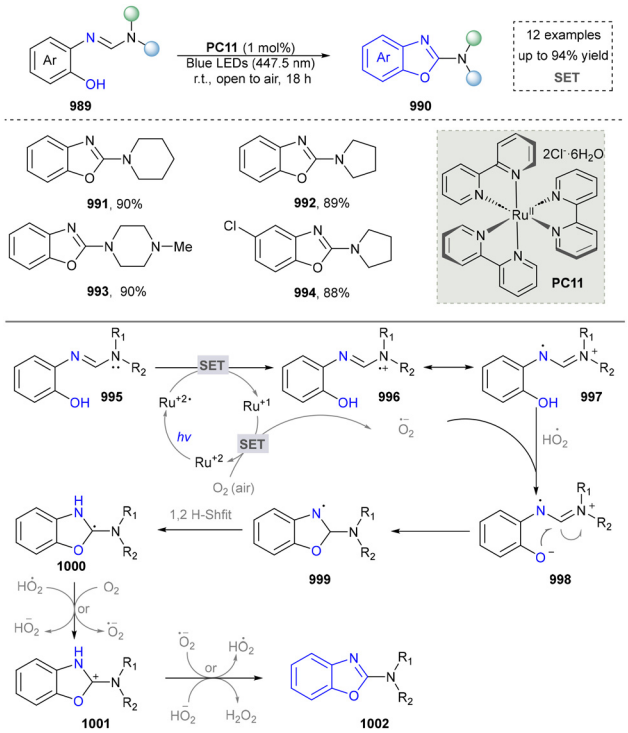
8.2.4 Atom editing strategies for the construction of oxazoles. The conversion of isoxazoles into oxazoles (**985–988**) has been recently reported by Baumann's group. The direct irradiation of isoxazoles under UV light achieved this transformation *via* a photochemical transposition reaction (Scheme 104).[438] Furthermore, the integration of continuous flow enabled the completion of this reaction within 20 minutes, demonstrating the successful coupling of skeletal editing with flow processes, thereby offering an effective solution for the scalable synthesis *via* atom-editing strategies. However, the substrate scope was relatively limited. Despite its early stage, atom-editing synthesis of oxazoles offers transformative potential through unparalleled step economy and late-stage modification. This approach is rapidly establishing itself as a critical strategy to address long-standing synthetic challenges and unlock novel chemical landscapes for medicinal chemistry.

8.3 Synthesis of benzoxazoles

The synthesis of benzoxazoles is particularly valuable as it combines synthetic accessibility with exceptional drug-like properties.[439,440] Numerous benzoxazole derivatives have demonstrated broad-spectrum pharmacological potential, encompassing antifungal, anti-inflammatory, antimalarial, anti-trypanosomal, and anticancer properties, as well as ectoparasitic, antipneumococcal, and antituberculosis activities, among other pharmacological effects.[441–444] Benzoxazoles are classically prepared by reacting *o*-aminophenols with carboxylic acid derivatives, aldehydes, or alcohols.[445] This section provides a comprehensive discussion on emerging synthetic strategies for benzoxazole derivatives, highlighting their significance in contemporary medicinal chemistry.



Scheme 104 Access to diverse oxazoles from isoxazoles enabled by continuous-flow photoisomerization.

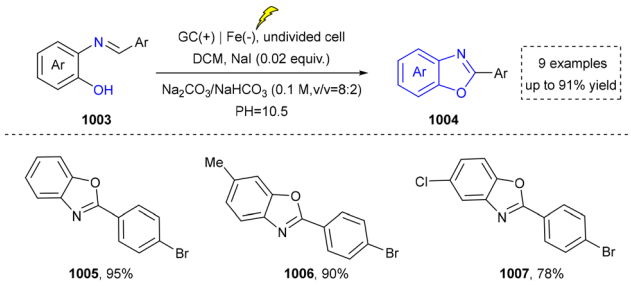


Scheme 105 Visible-light-triggered oxidation for the synthesis of 2-aminobenzoxazoles.

8.3.1 Photochemical synthesis of benzoxazoles. Yadav's group first reported the synthesis of benzoxazoles *via* a photocatalytic method (Scheme 105).[446] The phenolic amidines (**995**) as a starting material generated the nitrogen-centered distonic amidinium radical cation (**996**) after the single electron oxidation, which further reacted with an oxygen radical anion to furnish the phenol anion (**998**) *via* proton abstraction. Afterwards, the cyclization formed the aminyl radical species (**999**), which subsequently underwent the oxidation and aromatization to give the final products (**991–994**). This method provides an efficient tool for the rapid construction of a 2-benzoxazole compound library, featuring diverse cyclic or acyclic alkylamino groups. Similarly, Liu's group achieved the synthesis of benzoxazoles by using eosin Y bis(tetrabutyl ammonium salt) as an organic photocatalyst to improve the sustainability of this method.[447] Tran's group extended this method by forming imines *in situ* by reacting 2-substituted anilines with aldehydes.[448] Le's group further reported the synthesis of benzoxazole from glycine derivatives; however, the formation of imine intermediate was still the key to success.[449]

Overall, the synthesis of imines has been a crucial step in constructing benzoxazoles, using directly either as a starting material or as an intermediate. However, considering the potential drawbacks and limitations associated with the use of imines, such as their instability or the complexity of their synthesis, it will be highly innovative and valuable to explore alternative synthetic strategies that bypass the requirement of imines.

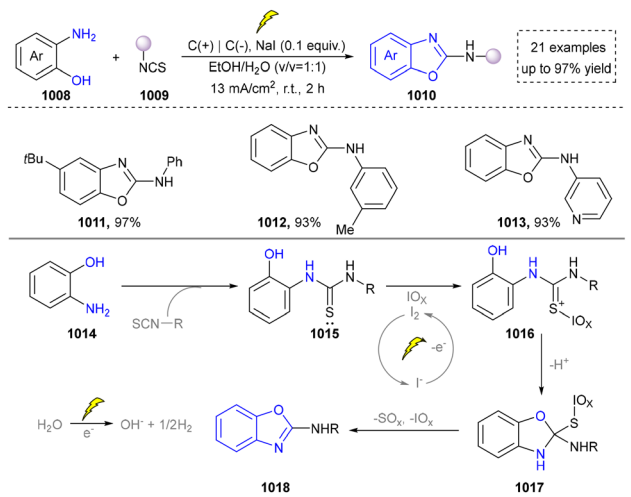
8.3.2 Electrochemical synthesis of benzoxazoles. The first work to achieve the anodic oxidation of Schiff base was discovered in 1982 by Solomun's group.[450] Little's group further



Scheme 106 Electrochemical synthesis of the 2-substituted benzoxazoles.

developed the electrochemical synthesis of 2-substituted benzoxazoles in 2014 (Scheme 106).[451] In this case, catalytic amount of NaI was used as a redox catalyst, which facilitated the oxidation of *in situ* formed benzoxazoline to generate the final products (**1005–1007**). Advantageously, this method required a two-phase buffer system, which was highly convenient to use. Moreover, special Schiff bases were prepared as staring materials, which led to a limited substrate scope.[452] To improve the efficiency and the sustainability of this method, Vaccaro's group disclosed that the use of the solid ammonium salt as a recyclable electrolyte did not require any additional supporting electrolyte or mediator.[453] Glycine derivatives were also applied in the synthesis of benzoxazoles *via* the *in situ* formation of Schiff bases under electrocatalytic conditions.[454] Moreover, Yoshida's group reported the electrochemical oxidation of 2-pyrimidyloxybenzenes and the subsequent dearomatization of pyrimidinium ions by adding piperidine to obtain 2-amino benzoxazoles.[455]

To avoid the preparation of Schiff bases from aminophenols and aldehydes, direct use of aminophenols became an ideal protocol to access benzoxazoles, which have been developed recently.[456–459] Among the related studies, Wacharasindhu's work developed an electrochemical method, which achieved the direct synthesis of 2-aminobenzoxazoles from 2-aminophenols and isothiocyanates (Scheme 107).[460] This method showcased a decent



Scheme 107 Electrochemical NaI/NaCl-mediated synthesis of 2-aminobenzoxazoles.

substrate scope (**1011–1013**) and demonstrated good compatibility with various starting materials. Furthermore, Wang's group developed an electrochemical approach by using simple nitrogen sources such as NH_4^+ and formamide, which avoided the synthesis of aminophenols and further expanded the diversity of synthesized benzoxazoles.[461]

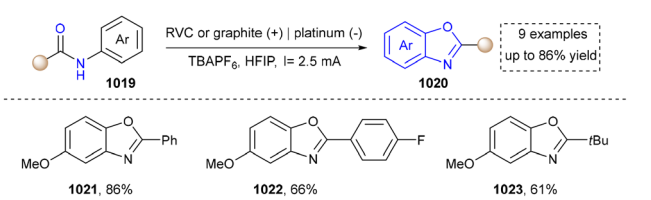
Besides using aminophenols or related analogues to synthesize benzoxazoles, electrochemical synthesis of benzoxazoles from anilides has been disclosed by Waldvogel's group (Scheme 108).[462] The key to success was the direct N–H activation to an amidyl radical through the anodic oxidation, which was stabilized by the adjacent aromatic ring. The subsequent cyclization and oxidation provided the final products (**1021–1023**). To further gain insights into the mechanism, the same group further conducted a series of mechanistic studies including potential dependence in CV data, substituent effect-induced changes in product selectivity, and solvent trapping experiments supporting the presence of cations to validate their proposed mechanism.[463]

Therefore, it is clear that the electrosynthesis approaches have already overcome some limitations of photocatalysis methods such as the feasibility of other nitrogen sources besides imines. Electrosynthesis has also expanded the scope of nitrogen sources to include available amines and anilides, which not only broadens the synthetic pathways but also provides valuable clues for further development. However, although the diversity of starting materials and sustainability has increased, there is no significant improvement in the structural diversity of the final products compared to traditional methods.

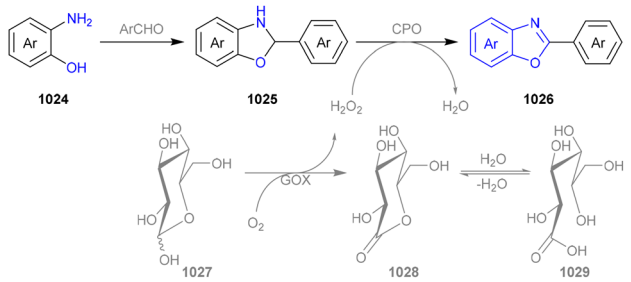
8.3.3 Enzymatic synthesis of benzoxazoles. In 2010, the Maurya group reported a bienzymatic approach to synthesize 2-arylbenzoxazoles catalysed by a glucose oxidase (GOX)–chloroperoxidase (CPO) system in an aqueous medium. Benzoxazoline (**1025**) was first formed *via* the condensation of aromatic aldehydes with 2-aminophenol (**1024**).[464] H_2O_2 *in situ*-generated by GOX was utilized by CPO for the oxidation of benzoxazoline (**1025**) to synthesize heteroaromatic products in excellent yields, which effectively avoided the low operational stability of CPO caused by the facile oxidative degradation of the porphyrin ring (Scheme 109).

The above-mentioned immobilized laccase and TEMPO system could also be utilized to synthesize 2-substituted benzoxazoles.[268] The one-pot enzymatic cascade included the generation of salicylaldehyde derivatives, the condensation of salicylaldehyde derivatives with 2-hydroxy-anilines and the biocatalytic dehydrogenation.

In 2019, Wang's group employed hemoglobin from *Vitreoscilla* (VHb) as a biocatalyst for the oxidative cyclization to



Scheme 108 Electrochemical synthesis of benzoxazoles from anilides.

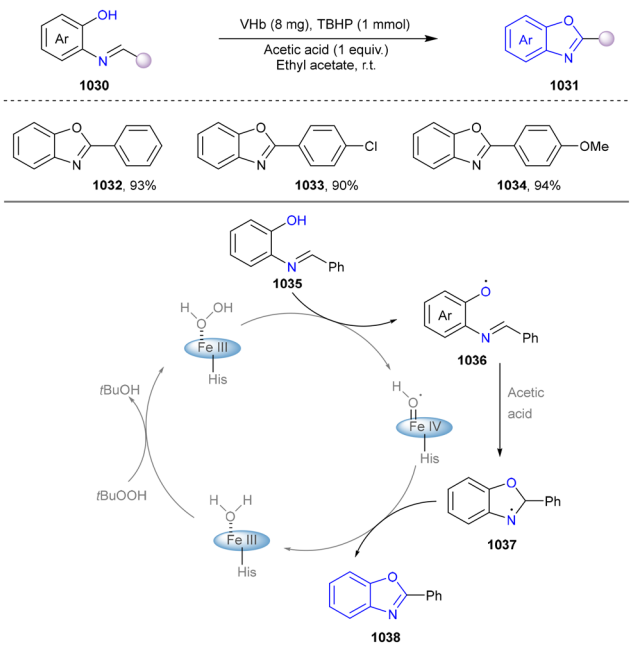


Scheme 109 Enzymatic synthesis of 2-substituted benzoxazoles *via* the GOX-CPO system.

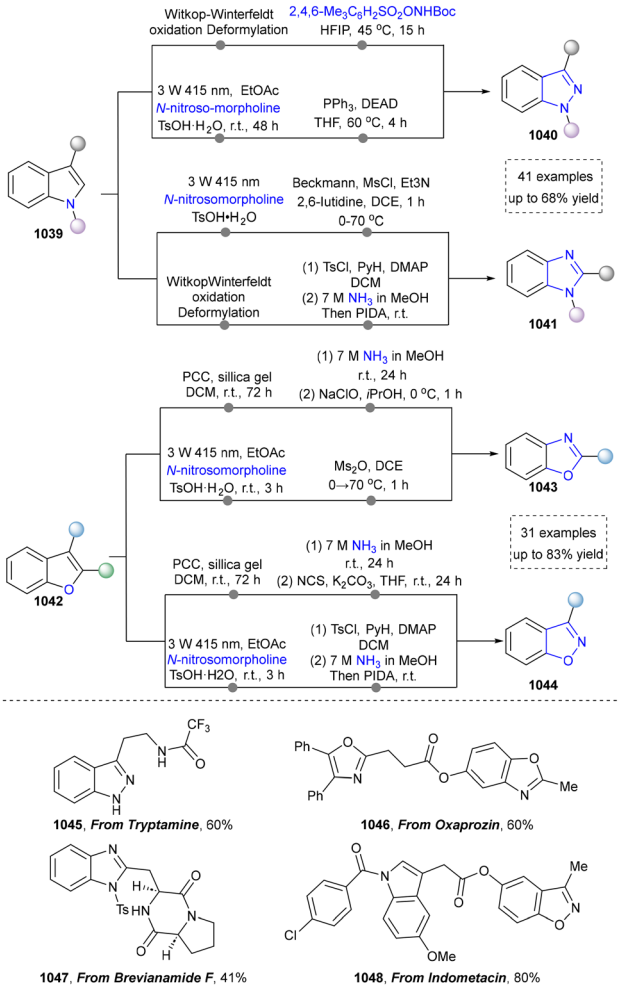
synthesize 2-substituted benzoxazoles with satisfactory yields (84–97%) (Scheme 110).[465]

In this subsection, three examples of enzymatic syntheses of benzoxazoles were described. Nevertheless, the biosynthetic pathway of bioactive benzoxazoles with *meta*- and *ortho*-substituted heterocycles has been gradually elucidated, such as cytotoxic benzoxazole nataxazole,[466] antibiotics A33853,[467] antibiotic caboxamycin,[468] and closoxazole A and B,[469] providing new insight for further enzymatic synthesis of benzoxazole moiety.

8.3.4 Atom editing strategies for the construction of benzoxazoles. Efficient synthesis of benzoxazole from benzofuran was also reported by Studer's group, which provided an elegant strategy for the C-to-N atom swapping and skeletal editing of diverse indoles (Scheme 111) and benzofurans. This strategy enabled selective access to diverse products (**1043**, **1044**) from a common starting material without the need for *de novo* synthesis. Remarkably, the protocol was widely applicable to complex drug-derived substrates (**1045–1048**) and was capable of effecting selective transformations. Other five-membered heteroarenes including



Scheme 110 Enzymatic synthesis of 2-substituted benzoxazoles *via* oxidative cyclization.



Scheme 111 Carbon-to-nitrogen atom exchange of indoles and benzofurans to form aromatic heterocycles.

indazoles, benzisoxazoles, and benzimidazoles have been discussed in the above sections. Overall, this method featured the strong tolerance for editing the five-member heteroarenes and also proved its applicability in the medication of different natural products and pharmaceuticals.[212] Therefore, the obtained benzoxazoles were more complex and contained a wider variety of substituents, which significantly expanded the structural diversity of this class of compounds.

In summary, although the atom editing synthesis of benzoxazoles is still in its early stages, the direct-editing paradigm it represents is providing medicinal chemists with a powerful and unprecedented tool, holding significant potential to greatly accelerate the processes of lead discovery and optimization. Future efforts will probably expand directly toward developing traceless editing strategies that avoid the introduction of or need for additional protecting groups.

8.4 Synthesis of thiazoles and isothiazoles

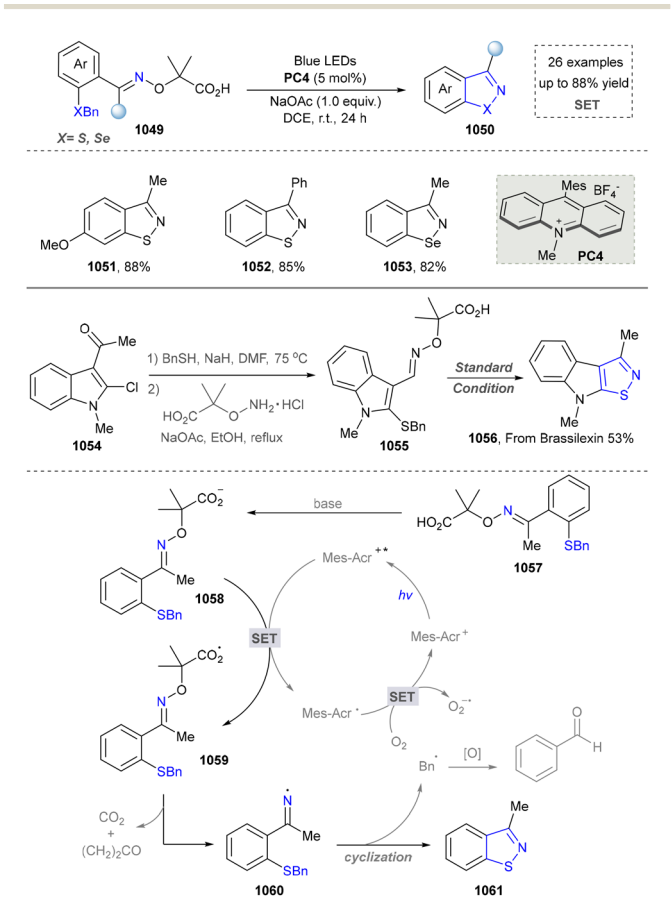
The isothiazole scaffold represents a structurally unique heterocyclic system of growing importance in medicinal chemistry.[470] Isoxazole derivatives offer diverse bioactive scaffolds that remain

at the forefront of modern drug discovery, exemplified by marketed antiviral (denotivir), antibacterial (sulfafurazole), and antipsychotic (ziprasidone) agents, along with numerous investigational agents in anticancer, antidiabetic, antifungal, and neuroprotective categories.[471,472] Conventional isothiazole synthesis depends on condensation reactions followed by coupling/alkylations.[470] However, the green and efficient synthesis of isoxazoles continues to represent a high-value research endeavour in contemporary medicinal chemistry.

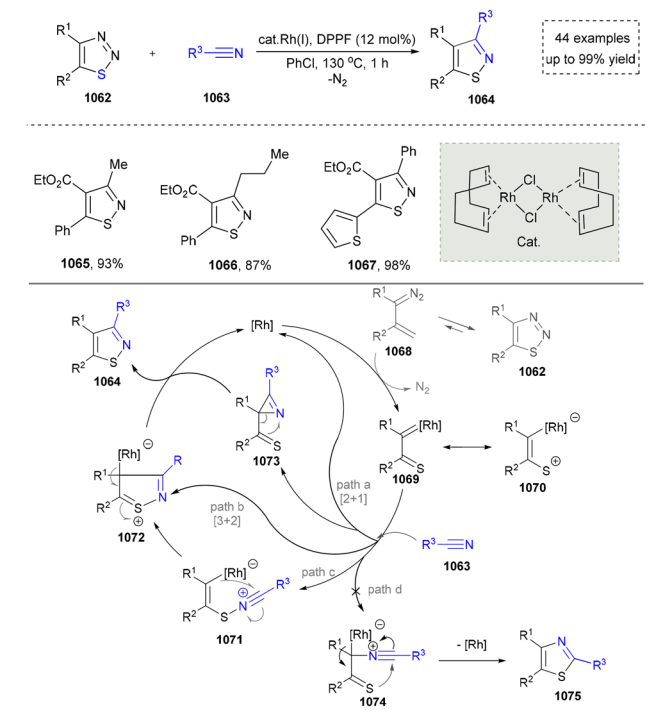
8.4.1 Photochemical synthesis of isothiazoles. The synthesis of isothiazoles *via* a photochemical approach remained underexplored until reported by Alemán's group (Scheme 112). They applied the α-amino-oxy acid (**1058**) as the starting material to form the imine radical (**1060**) *via* single electron oxidation. The subsequent intramolecular cyclization gave the final products. This method was also feasible to construct thiazoles with different heteroarenes, indicating its strong substrate scope (**1051–1053**).[473] Furthermore, the valuable molecule, brassilexin analogue (**1056**), was synthesized in only three steps from 3-acetyl-2-chloro-1-methyl-1*H*-indole (**1054**) through this methodology, achieving a 53% total yield. This result also indicated that the indole-derived α-amino-oxy acid was compatible with the system and served as a viable substrate for constructing tricyclic isothiazoles. This was the only example for the photochemical synthesis of isothiazoles. Moreover, the electrochemical methods have not been explored so far, suggesting that there is considerable room for exploration in this field.

8.4.2 Atom editing strategies for the construction of isothiazoles. In 2016, Lee's group reported a method to achieve the skeletal editing in 1,2,3-thiadiazoles to access diverse isothiazoles (Scheme 113).[474] The key to success of this strategy is the generation of α-thiavinyl Rh-carbenoid intermediate **1069**, which further reacted with nitriles to afford various isothiazoles (**1065–1067**). Even though this method was a pioneering work for skeletal editing of 1,2,3-thiadiazoles, the synthetic complications of the starting material limited the application of this protocol. In 2024, the photochemical permutation of thiazoles to afford isothiazoles has been reported by Leonori's group.[475] This novel strategy highlighted the potential of photoexcitation upon atom editing. In this case, the photoexcitation allowed thiazoles to access their π,π* singlet excited states, which further underwent a series of structural rearrangements to achieve the final transformation of the cyclic system. They also found that this method was feasible to other azole compounds, including benzo[*d*] isothiazole, indazole, pyrazole and isoxazole, indicating the strong tolerance of this method.

In 2025, Sarpong's group reported a cheminformatics platform designed to identify which skeletal editing maximized the exploration of new chemical space.[476] This work introduced a framework for quantifying the impact of core-atom transformations in heteroaromatic compounds and highlighted specific skeletal editing that most significantly enabled accessing unexplored chemical regions. Furthermore, it called for the development of new synthetic methodologies to achieve these prioritized core-atom modifications.



Scheme 112 Visible light-promoted N–S bond formation for the synthesis of isothiazoles.



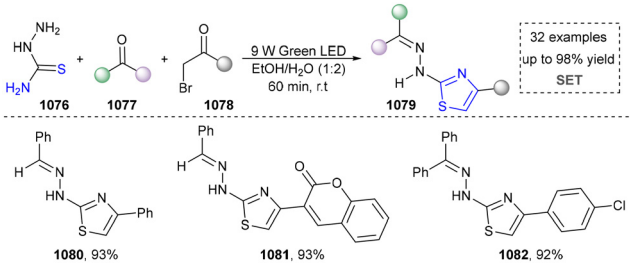
Scheme 113 Synthesis of isothiazoles *via* ring transformation of 1,2,3-thiadiazoles using nitriles.

In the context of drug discovery, photochemical, electrochemical and enzymatic synthesis holds a distinct advantage for the rapid exploration of a new chemical substrate scope from scratch. Conversely, when the objective shifts to the precise skeletal modification of existing complex drug molecules, atom editing emerges as a more promising and cutting-edge direction.

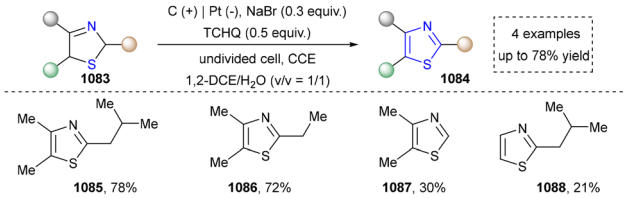
8.5 Synthesis of thiazoles

The thiazole motif is a pharmacologically indispensable heterocycle, valued for its unique electronic properties and broad-spectrum of bioactivity.[477] It is also crucial in medicinal chemistry, in fact, thiazole derivatives exhibit versatile bioactivities through interactions with multiple enzymatic and receptor targets in biological systems, demonstrating therapeutic relevance across nearly all medical domains.[478] Thiazole derivatives exhibited promising therapeutic potential across antibacterial, antifungal, antitubercular, anticancer, antiviral, anti-inflammatory/analgesic, hypoglycemic, antiepileptic, antiparasitic, and antioxidant applications.[479–482] Thiazole derivatives are typically synthesized through multi-step functional group transformations, exemplified by the Cook–Heilbron thiazole synthesis and Hantzsch method.[483,484] It remains a highly active area of research, and this section will provide a comprehensive overview of the implementation of emerging green technologies in the synthesis of thiazole compounds.

8.5.1 Photochemical synthesis of thiazoles. The efficient synthesis of thiazoles through the photochemical method has been disclosed by Hossain's group (Scheme 114). This method applied readily available thioacylhydrazone (**1076**), carbonyl (**1077**), and phenacyl bromide (**1078**) as starting materials to synthesize thiazoles without the addition of a photocatalyst. After the successful syntheses of valuable thiazoles (**1080–1082**), all the synthesized compounds demonstrated potential antioxidant activity, which was proved by the IC_{50} values of the DPPH radical scavenging experiment.[485] The relative scarcity of reports on the photochemical *de novo* synthesis of thiazoles stems from the combined effects of the high efficiency and maturity of classical methods, alongside the intrinsic complexity of photochemical routes. As a complementary tool, photochemical strategies are uniquely suited for constructing highly challenging thiazole molecules that are difficult to access *via* traditional means, particularly those with unique substitution patterns or exceptionally high functional group density. Additionally, chemists are encouraged to further evaluate the bioactivities of these compounds.



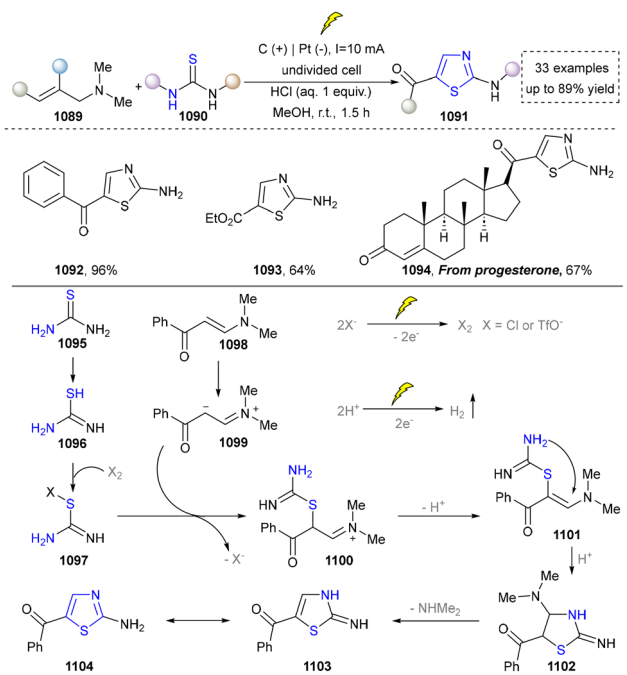
Scheme 114 Visible-light-induced synthesis of the 2-(2-hydrazinyl)-thiazole derivatives.



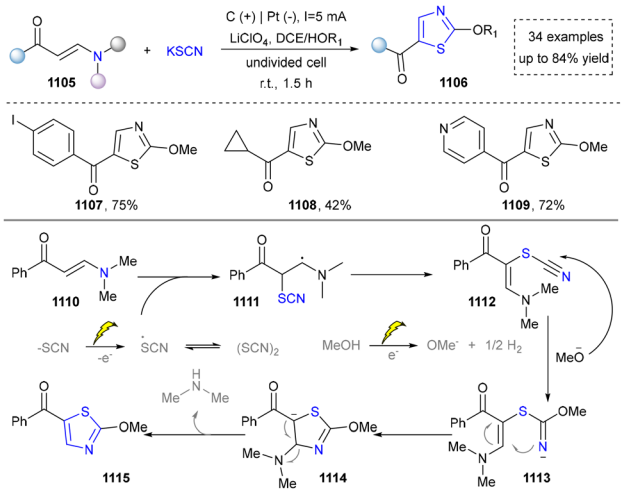
Scheme 115 Electrochemical synthesis of thiazoles.

8.5.2 Electrochemical synthesis of thiazoles. In 2020, Zeng's group reported the electrochemical synthesis of thiazoles from 2,5-dihydrothiazolines (Scheme 115).[486] They proved that halide ions and tetrachlorohydroquinone (TCHQ) were able to serve as redox catalysts to facilitate the oxidation of 2,5-dihydrothiazoles, enabling the synthesis of thiazoles efficiently (**1085–1088**). However, the construction of 2,5-dihydrothiazoles was not convenient, thereby limiting the application of this method. The same group also found that the reaction of active methylene ketones with thioureas could generate 2-aminothiazoles with the assistance of DL-alanine by using NH_4I as a redox mediator.[487,488] Inspired by this work, the synthesis of 2-aminothiazoles from ketones and NH_4SCN was described instead of using thioureas.[489]

In 2022, an electrochemical approach for the construction of 2-aminothiazoles by using readily accessible enaminones and thioureas has been reported by Wan's group (Scheme 116), which thoroughly explored the chemical space of aminothiazoles (**1092**, **1093**) by using diverse starting materials. Furthermore, this strategy was successfully employed in the synthesis of chiral steroids, including a progesterone derivative (**1094**) under slightly modified conditions (stirred for 3 h, 3.7 F mol^{-1}),



Scheme 116 Electrochemical C–H thiolation/C–N amination for thiazole synthesis.



Scheme 117 An electrochemical-enabled cascaded cyclization to obtain 2-alkoxythiazoles.

which confirmed that the cyclic enone was tolerable in this system. Moreover, detail mechanistic studies have been performed which showed that cascade enamine α-C–H thiolation (**1110**) and C–N bond amination (**1102**) were the key to success. Moreover, hydrochloric acid worked as both the electrolyte and the acid promoter in this reaction.[490]

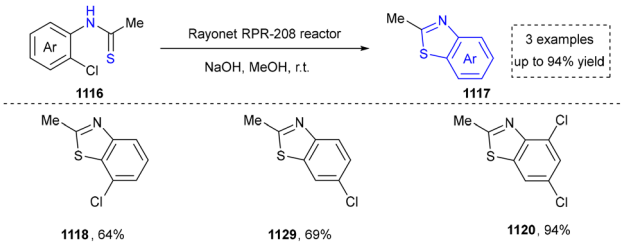
In 2024, Wan's group further developed their method and the electrochemical oxidative cyclization of enaminones with thioamides to achieve the thiazoles without using any catalyst and oxidants, improving the sustainability of this method.[71]

To further expand the structural diversity of thiazoles by using enaminones as the nitrogen source, Wen's group developed the cascade three-component cyclization of enaminones with potassium thiocyanate and alcohols (Scheme 117).[75] The reaction proceeded smoothly *via* the oxidative C–H thiolation and nucleophilic tandem cyclization to construct the C–O, C–S, and C–N bonds, and the subsequent cleavage of C–N bond generated various 2-alkoxythiazoles (**1107–1109**).

Overall, electrochemical synthesis offers an efficient route to thiazole skeletons with varying degrees of substitution, bypassing the need for elaborate synthetic sequences. Moreover, the successful use of enaminones as a nitrogen source demonstrates its promising potential for expanding the scope of suitable starting materials. This progress not only highlighted the versatility of electrochemical methods but also suggested that numerous other possibilities awaited exploration in the future.

8.6 Synthesis of benzothiazoles

The benzothiazole scaffold represents a privileged heterocyclic system in medicinal chemistry due to its versatile pharmacological profile and structural adaptability.[491] Its synthesis is pivotal for developing bioactive molecules, as the core structure confers enhanced binding affinity and metabolic stability.[492] In fact, benzothiazole derivatives exhibit diverse therapeutic properties, including anticancer (*e.g.*, tasisulam), antimicrobial (*e.g.*, ethoxzolamide), and neuroprotective (*e.g.*, riluzole) activities.[6,493] The

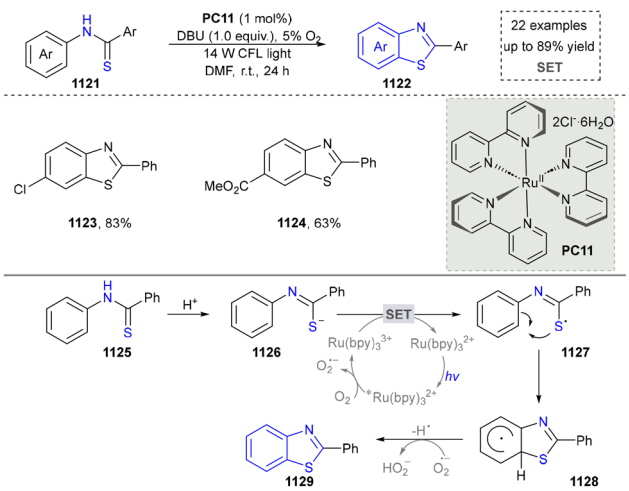


Scheme 118 Photochemical synthesis of 2-methylbenzothiazoles.

advancement of benzothiazole-based medicinal chemistry has emerged as a rapidly evolving and highly dynamic research frontier.[494] In clinical practice, numerous benzothiazole-derived compounds have been successfully implemented as therapeutic agents, demonstrating high therapeutic efficacy against diverse disease pathologies.[495] Benzothiazoles are traditionally prepared *via* the Phillips method or Jacobson synthesis.[496] Emerging methods of benzothiazole synthesis are discussed in this section.

8.6.1 Photochemical synthesis of benzothiazoles. The first pioneering work to produce benzothiazoles under photochemical conditions was reported by Ramakrishnan's group in 1979 (Scheme 118).[497] In this reaction, *ortho*-halogenothioacetanilide was activated under the direct irradiation of light to furnish the benzothiazoles (**1118–1120**). Although a powerful light setup was required, it was still a milestone for the photoinduced synthesis of benzothiazoles. In 2021, Li's group employed this reaction under the irradiation of visible light, sunlight or blue LED, which further improved the energy efficiency of this strategy. However, halogen-substituted thioamides were still required, which limited the substrate scope in this reaction.[498]

To avoid halogen-substituted thioamides, Li's group further developed a photocatalytic method to construct the 2-substituted benzothiazoles in 2012 (Scheme 119).[499] With the assistance of photocatalyst, this reaction was finalized under the irradiation of visible light with diverse thioamides as substrates. The mechanism suggested that the thioamide was first deprotonated to

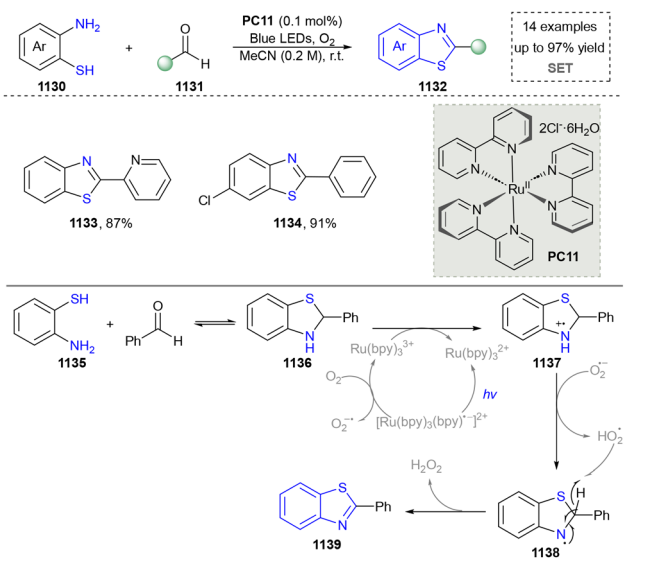


Scheme 119 Visible light photoredox radicals for the synthesis of the 2-substituted benzothiazoles.

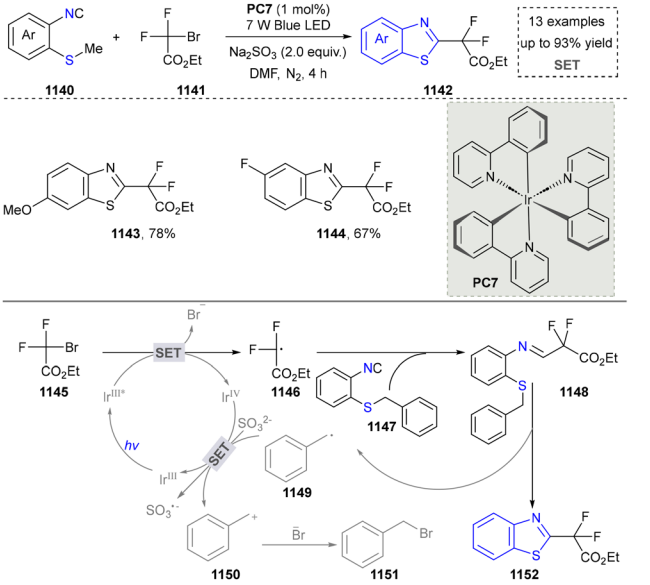
generate the anion intermediate (**1126**), which was oxidized by the excited state of photocatalyst to generate radical species (**1127**). The radical intermediate further reacted with the benzene ring, which further underwent the oxidation to provide the final products (**1123**, **1124**). In 2015, Lei's group further found that a dual catalytic system *via* photoredox cobalt-catalysis could obviate the use of the oxidant, providing a novel strategy to construct the C–S bonds.[500] A study by Gustafson and others also expanded the application of this method.[501,502] Some heterogeneous photocatalysts have also been applied to the synthesis of benzothiazoles from thioamides.[503]

Besides the use of thioamides, 2-aminothiophenols and various aldehydes as synthetic synthons have been disclosed by Cho's group (Scheme 120). Considering the ready availability of aldehydes and the convenience to prepare the 2-aminothiophenols, this strategy was highly convenient and provided diverse benzothiazoles (**1133**, **1134**). In this reaction, benzothiazoline (**1136**) was the key intermediate from the starting materials, which was oxidized by the excited state of the photocatalyst through an SET process. Afterwards, oxygen was involved in facilitating the deprotonation of radical species and finally completed the reaction.[504] The same group further reported that *in situ*-generated photosensitizing disulfides from 2-aminothiophenols could also promote the synthesis of benzothiazoles.[505] Biswas' group also found a similar strategy to construct the benzothiazoles with different photocatalysts.[244] Some heterogeneous photocatalysts have also been applied to the synthesis of benzothiazoles from aminothiophenols.[506–508]

In 2019, Zhang's group also reported a photocatalytic method by using the 2-isocyanoaryl thioethers as the starting material (Scheme 121). With ethyl 2-bromo-2,2-difluoroacetate and 5-(trifluoromethyl)-5*H* dibenzo[*b*,*d*]thiophen-5-ium trifluoromethanesulfonate (**1146**) as radical precursors, 2-CF_2/CF_3-containing benzothiazoles (**1143**, **1144**) have been successfully obtained in good to excellent yields *via* radical cascade cyclization.[509]



Scheme 120 Synthesis of the 2-substituted benzothiazoles *via* visible light-driven photoredox.

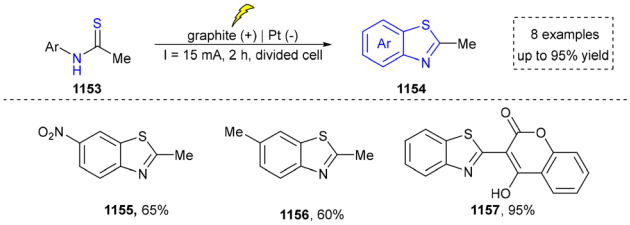


Scheme 121 Photocatalytic cyclization for the synthesis of 2-CF_2/CF_3-containing benzothiazoles.

Overall, the development of photochemical synthesis has significantly advanced the construction of benzothiazoles. In addition, it is possible to use simple starting materials such as 2-aminothiophenols to construct benzothiazoles. The intermolecular cyclization also improved the structural diversity. Hopefully, more synthetic synthons and convenient methods, such as multicomponent reactions (MCRs), can be developed to further expand the scope and efficiency of benzothiazole synthesis.

8.6.2 Electrochemical synthesis of benzothiazoles. In 1979, the electrochemical synthesis of benzothiazoles was reported, which showcased the potential of electrocatalysis. However, the mechanistic studies and substrate scope (**1155–1157**) was poorly described (Scheme 122).[510] Electrochemical strategies demonstrate excellent compatibility with functional groups prone to oxidation (*e.g.*, hydroxyl), prone to hydrolysis (*e.g.*, ester), or sensitive to acids or bases. This is a key advantage over traditional synthetic methods that rely on harsh conditions such as strong oxidants, strong acids, or high temperatures.

In 2017, Lei's group found that 2-aminobenzothiazoles could be synthesized *via* electrochemical synthesis (Scheme 123). Compared to traditional methods, this work utilized aryl isothiocyanates and various amines as starting materials, which strongly expanded the structural diversity of benzothiazoles (**1161–1163**). The thiourea generated from nucleophilic addition

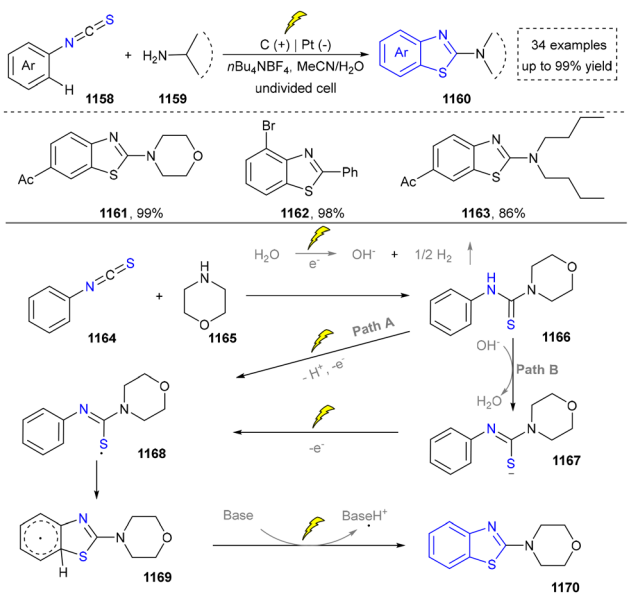


Scheme 122 Electrochemical synthesis of benzothiazole derivatives.

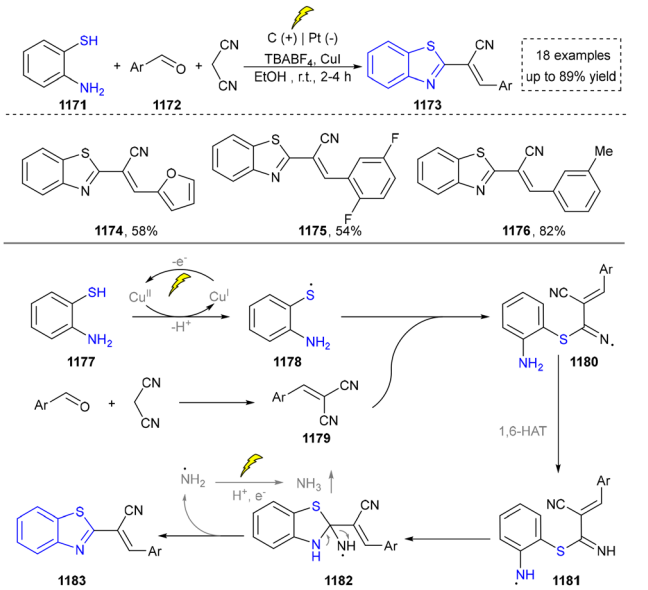
of amine to isothiocyanates (**1066**) was the key intermediate, which underwent anodic oxidation twice to complete the synthesis of benzothiazoles.[70] This approach allows for the efficient preparation of benzothiazole derivatives that are challenging to obtain through conventional oxidative methods due to the presence of sensitive functional groups, notably halogenated compounds and those bearing strong electron-withdrawing substituents. It thus offers a robust tool for the optimization of drug lead candidates. Wirth's group further expanded the electrocatalytic activation of thioamides and afforded valuable thiazolopyridines.[511] Liu's group also developed a three-component method, but the concept was similar to Lei's work.[512]

2-Aminothiophenols as nitrogen sources to construct benzothiazoles *via* electrochemical synthesis have also been established. In 2022, Luo's group reported an efficient Fe-catalysed electrochemical approach to synthesize benzothiazoles by using different 2-aminothiophenols and ethers as starting materials. In this case, *in situ* formation of aldehydes from ethers was the key to success.[457] To further expand the use of electrochemical synthesis, Du's group disclosed a three-component strategy to construct benzothiazoles (Scheme 124). The structural diversity was strongly expanded by using various 2-aminothiophenols, aldehydes and malononitrile. In their proposed mechanism, a Knoevenagel condensation between malononitrile and benzaldehyde generated the intermediate (**1179**), the thiol radical from Cu-catalysis reacted with **1179** to give the radical species (**1180**), which further underwent 1,6-HAT and intramolecular cyclization to afford **1182**. The subsequent release of -NH_2 radicals completed the reaction.[69] The intermolecular cyclization of isocyanides with thiols or diselenides has also been reported recently by He's group.[513]

In summary, the synthesis of benzothiazoles by using electrochemical methods was extended to other nitrogen sources



Scheme 123 Electrochemical dehydrogenation for the synthesis of benzothiazoles.



Scheme 124 Cu-catalyzed electron-relayed synthesis of 2-alkenylbenzothiazoles.

including isothiocyanates, which have been previously challenging to use. Moreover, three-component reactions including simple aldehydes and different 2-aminothiophenols as starting materials have also been developed, which strongly extended the structural diversity of obtained benzothiazoles such as the construction of 2-alkenylbenzothiazoles. However, the practical application of these methods is still in its early stage and warrants further exploration.

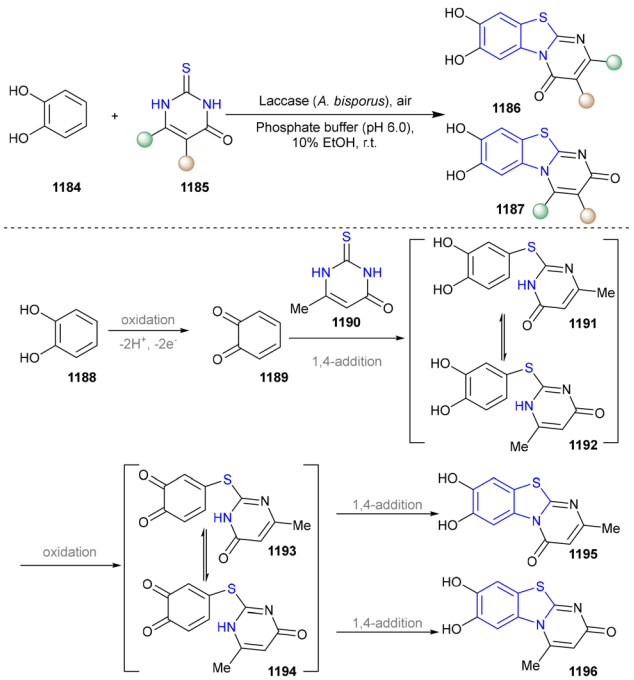
8.6.3 Enzymatic synthesis of benzothiazoles. In 2010, the GOX–CPO catalytic system reported by Maurya's group could also be used to prepare benzothiazoline in excellent yields by the condensation of aldehydes with 2-aminothiophenol, indicating the utility of the GOX-CPO system in the aromatization of benzoazoline and benzothiazoline.[492]

In 2017, Beifuss's group utilized a commercial laccase from *A. bisporus* to catalyse the synthesis of novel pyrimidobenzothiazoles without regio-selectivity from **1185** and catechol **1184** (Scheme 125).[514] 2-Phenylbenzothiazole was also obtained by the condensation of aldehydes and 2-aminothiophenol, which was catalysed by Novoprime Base 268 or the laccase (*T. versicolor*)/DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) catalytic system.[32,515]

As described above, the enzymatic synthesis of benzothiazole and benzoxazoles was catalysed by laccase and the GOX-CPO system. Therefore, further engineering of these enzymes, which can be applied to the synthesis of both benzothiazoles and benzoxazoles, is highly desirable.

8.7 Synthesis of 1,2,3-thiadiazoles

1,2,3-Thiadiazoles represent crucial nitrogen–sulfur heterocyclic scaffolds extensively present in natural products and pharmaceutical molecules.[516] Numerous bioactive compounds containing this framework exhibit significant therapeutic effects including antiviral, anticancer, and antifungal activities.[517] Additionally,

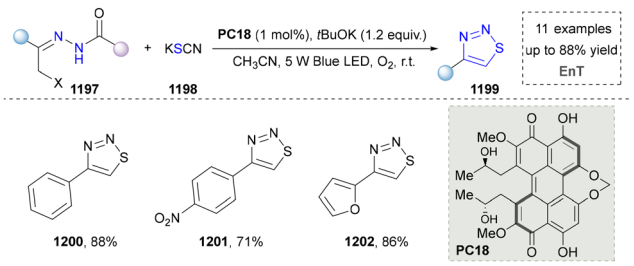


Scheme 125 Laccase-catalysed synthesis of pyrimidobenzothiazoles.

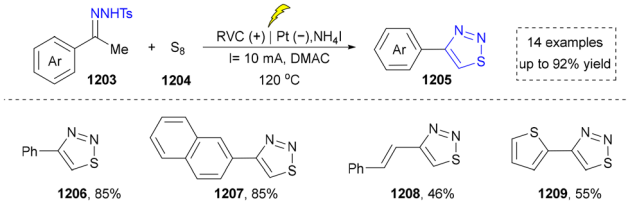
1,2,3-thiadiazoles serve as versatile synthetic intermediates in organic synthesis.[518] While traditional synthetic methodologies such as the Hurd-Mori,[519] Wolff,[520,521] and Pechmann syntheses[522] have been established, this section will emphasize the emerging synthetic strategies that demonstrate enhanced values in constructing 1,2,3-thiadiazole derivatives.

In 2019, Rao's group reported a photocatalytic method to afford 1,2,3-thiadiazoles efficiently (Scheme 126).[72] This strategy relied on the [4+1] annulations of α-bromo-*N*-benzoyl-hydrazone **1203** and potassiumthiocyanate **1198** to furnish the key intermediate **1203**, which was further oxidized by singlet oxygen to give the final products (**1200–1202**). However, the preparation of the starting material was complicated, which limited the application of this method. Moreover, no progress has been made toward significantly expanding the structural diversity of 1,2,3-thiadiazoles.

8.7.1 Electrochemical synthesis of 1,2,3-thiadiazoles. 1,2,3-Thiadiazoles were also synthesized using the electrochemical methods by Tang's group.[523] This method enabled the insertion of element sulfur into *N*-tosylhydrazones, thereby forming



Scheme 126 Photocatalytic method to afford the 1,2,3-thiadiazole derivatives.



Scheme 127 Electrosynthesis of 1,2,3-thiadiazoles.

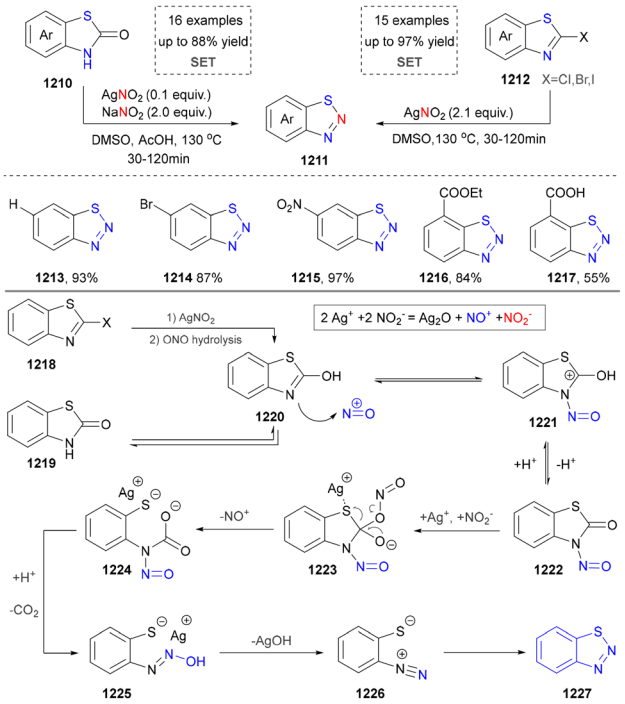
valuable 1,2,3-thiadiazoles (**1206–1209**). Diverse *N*-tosylhydrazones from acetophenones were suitable in this system (Scheme 127). However, it should also be noted that other tosylhydrazones from aliphatic ketones or aryl ketones bearing an alkyl chain were not feasible to this strategy. Furthermore, this strategy avoided the use of bromo-activated hydrazones, which improved the synthetic convenience.

Overall, the synthesis of 1,2,3-thiadiazoles *via* emerging methods remains underexplored. Only the hydrazones and related derivatives were reported as the nitrogen sources to construct 1,2,3-thiadiazoles. Compared to privileged scaffolds like benzothiazole and benzoxazole, which are prevalent in pharmaceuticals, the 1,2,3-thiadiazole core is relatively uncommon in marketed drugs. This has, to some extent, reduced the urgency for intensive exploration of new synthetic methods targeting it. Despite the challenges, the successful development of an electrochemical synthesis would represent the precise electrochemical construction of N–N and C–S bonds under mild conditions. Its underlying mechanism could potentially inspire the synthesis of other unstable heterocycles.

8.7.2 Atom editing strategies for the construction of benzo[1,2,3]thiadiazoles. In 2024, Hrobárik and co-workers found that benzothiazol-2(3*H*)-ones and 2-halogen-substituted benzothiazoles could undergo skeletal editing to access benzo[1,2,3]thiadiazoles (**1213–1217**) *via* a facile silver-catalysed reaction (Scheme 128).[524] The reaction exhibited broad functional group compatibility (*e.g.*, nitro, ester, bromo, and carboxylic acid). Furthermore, mechanistic studies verified that the additional nitrogen atom of benzo[1,2,3]thiadiazoles was incorporated from additive $AgNO_2$ or $NaNO_2$. Atom editing necessitates a stable precursor scaffold for precise modification, yet a synthetically tractable precursor for direct conversion *via* single-atom operations is lacking, making controlled editing highly challenging. Furthermore, weaker market demand compared to classic pharmacophores has limited research impetus. Future efforts may therefore focus on developing catalytic single-atom editing systems to convert stable precursors directly into this valuable heterocycle.

8.8 Synthesis of 1,2,4-thiadiazoles

1,2,4-Thiadiazoles constitute another important class of heterocyclic compounds with distinctive biological properties, frequently incorporated into bioactive molecules.[525,526] Notably, the commercial antibiotic cefozopran, containing this scaffold, exhibits remarkable antibacterial activity.[527] Conventional synthetic routes typically require stoichiometric oxidants,[528] whereas

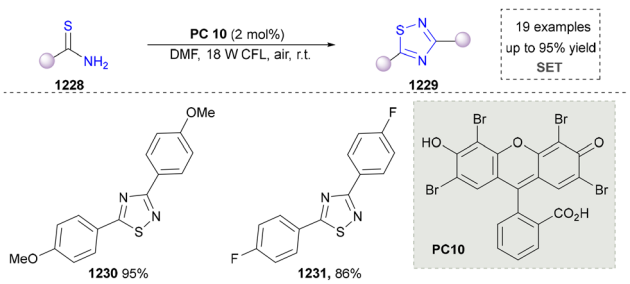


Scheme 128 Benzo[1,2,3]thiadiazole synthesis from benzothiazol-2(3*H*)-ones and 2-halobenzothiazoles by single-step skeletal editing.

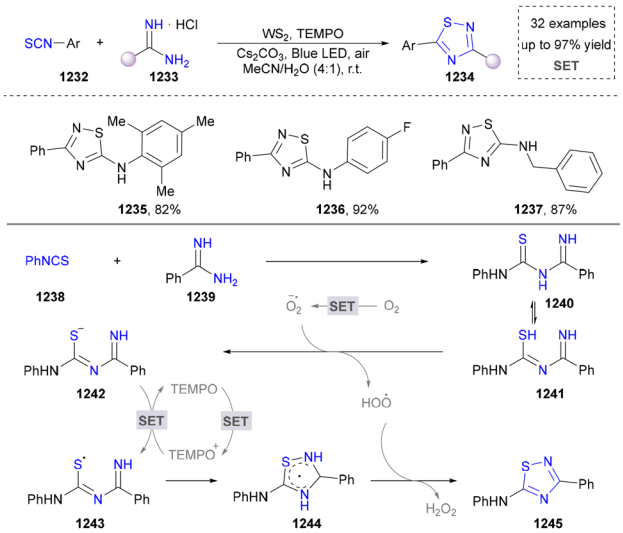
this section will highlight the advantages of modern synthetic approaches in constructing 1,2,4-thiadiazoles systems.

8.8.1 Photochemical synthesis of 1,2,4-thiadiazoles. In 2013, Yadav's group found a new approach to obtain 1,2,4-thiadiazoles from primary thioamides under photocatalytic conditions (Scheme 129). Not only aromatic thioamides, but also aliphatic thioamides were accommodated in this system to furnish the desirable products (**1230**, **1231**). This strategy relied on the photoredox activation of thioamides and oxygen as the electron donor and oxidation. The proposed mechanism was presented, but the mechanistic studies was not well investigated. Moreover, the poor diversity of thioamides limited the scope of thioamides.[529]

To further improve the synthetic efficiency, the He group disclosed that WS_2 served as the semiconductor photocatalyst to achieve the synthesis of 1,2,4-thiadiazoles (**1235–1237**) efficiently with TEMPO and O_2 (in air) as the redox catalysts. This



Scheme 129 Visible-light-driven aerobic oxidative cyclization to afford 1,2,4-thiadiazoles.

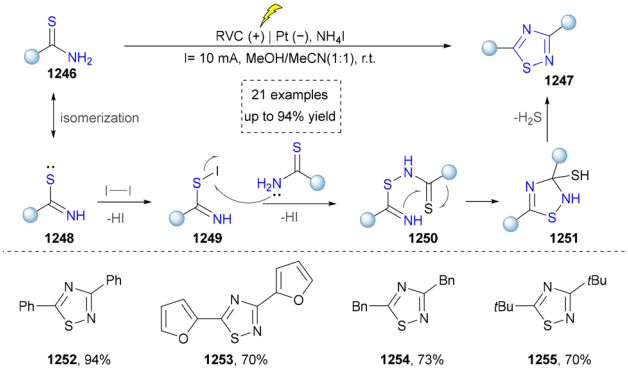


Scheme 130 Semi-heterogeneous photosynthesis of 5-amino-1,2,4-thiadiazoles.

strategy featured the more structural diversity using phenyl isothiocyanate and benzimidamide hydrochloride as substrates. Importantly, the large-scale synthesis was also applied to prove its applicability. The catalyst was also recyclable up to five times, which further improved the sustainability of this strategy (Scheme 130).[530] Photochemical synthesis provides an effective method for preparing aliphatic 1,2,4-thiadiazoles, which are challenging to obtain through conventional approaches and allow for lipophilicity adjustment. The retained N–H bond in these high-yield products facilitates subsequent functionalization.

8.8.2 Electrochemical synthesis of 1,2,4-thiadiazoles. Inspired by the photocatalytic synthesis of 1,2,4-thiadiazoles from thioamides, the Pan group also reported an elegant method to complete this reaction *via* electrocatalytic synthesis (Scheme 131, **1252–1255**). The advantage of this method was the use of inexpensive NH_4I as the electrolyte and catalyst. Moreover, the additional oxidants were not required.[531]

Later, the Liu group also extended the electrocatalytic synthesis of 1,2,4-thiadiazoles from phenyl isothiocyanates and 2-aminopyridines.[73] In 2020, the amino 1,2,4-thiadiazoles were

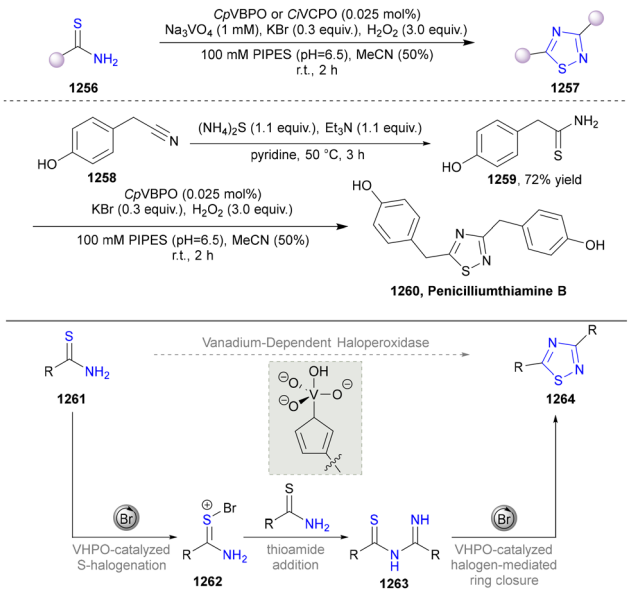


Scheme 131 Electrochemical synthesis of 3,5-disubstituted-1,2,4-thiadiazoles.

also achieved by using imidoyl thiourea as the starting material under electrocatalytic conditions.[532] Recently, the Wan group has also found that the electrocatalytic protocol furnished the oxidative cyclization of enaminones with thioamides.[71]

Overall, the synthesis of 1,2,4-thiadiazoles *via* an electrocatalytic method gives some new insights to broaden the substrate scope. The structural diversity was further improved using some other substances such as 2-aminopyridines and enaminones, which were previously challenging for photochemical synthesis. Hopefully other reagents can be further explored in this field.

8.8.3 Enzymatic synthesis of 1,2,4-thiadiazoles. Recently, Biegasiewicz and Davis's team[533] has established an enzymatic halide recycling strategy for intermolecular halogenation-mediated bond formation catalysed by vanadium-dependent haloperoxidase (VHPO), achieving the intermolecular oxidative dimerization of thioamides **1261** to generate 1,2,4-thiadiazole compounds **1264**, relying on two distinct *S*-bromination events that enable heterocycle formation. VHPO was the repetitive halide oxidation using H_2O_2 as the stoichiometric oxidant to produce electrophilic halogens in the form of hypohalous acid (HOX). *S*-Bromothioamide, produced by VHPO-catalysed *S*-bromination of the thioamide, is activated by the addition of another equivalent of the thioamide to produce iminobenzathiamide, which finally undergoes VHPO-catalysed halogen-mediated ring closure and tautomerization to form the 1,2,4-thiadiazole. This enzyme-mediated strategy has wide substrate applicability to a variety of thioamide substrates, such as aromatic, heterocyclic and aliphatic thioamides. More importantly, this method was successfully applied to the chemoenzymatic synthesis of penicilliumthiamine B (**1260**), an anticancer natural product, from commercially available materials, demonstrating its practical value in pharmaceutical synthesis (Scheme 132). This successful application also proved that the unprotected phenol group was tolerable in this system.



Scheme 132 1,2,4-Thiadiazole synthesis by vanadium-dependent haloperoxidases.

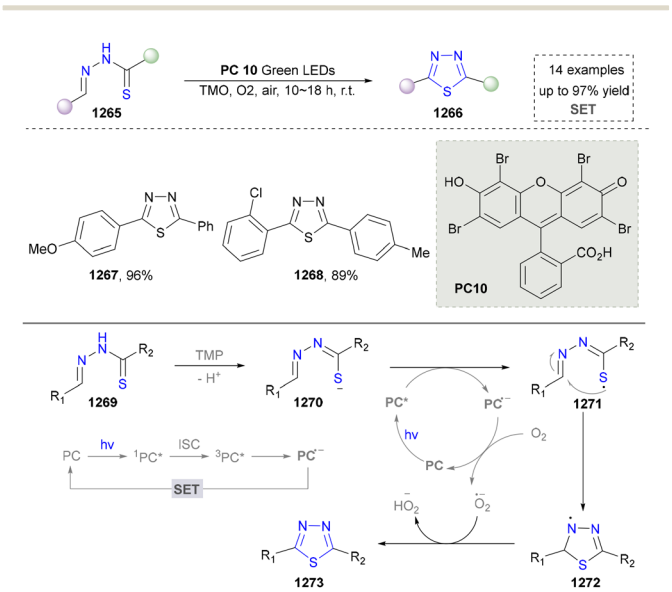
8.9 Synthesis of 1,3,4-thiadiazoles

As a significant member of azole heterocycles, thiadiazoles demonstrate diverse biological and pharmacological activities.[534] Their unique aromatic structure containing two nitrogen atoms and one sulfur atom enables chemical modifications to develop highly bioactive derivatives, making the synthesis and bioactivity exploration of thiadiazole derivatives a research focus. Representative drugs include sulfamethizole (a sulfonamide antibiotic with a 1,3,4-thiadiazole moiety for bacterial infections) and acetazolamide (a carbonic anhydrase inhibitor for treating edema, epilepsy, and glaucoma).[535] Although dehydration cyclization and direct cyclization remain common methods for 1,3,4-thiadiazole synthesis,[536–539] this section will discuss the substantial contributions of innovative synthetic methodologies in this field.

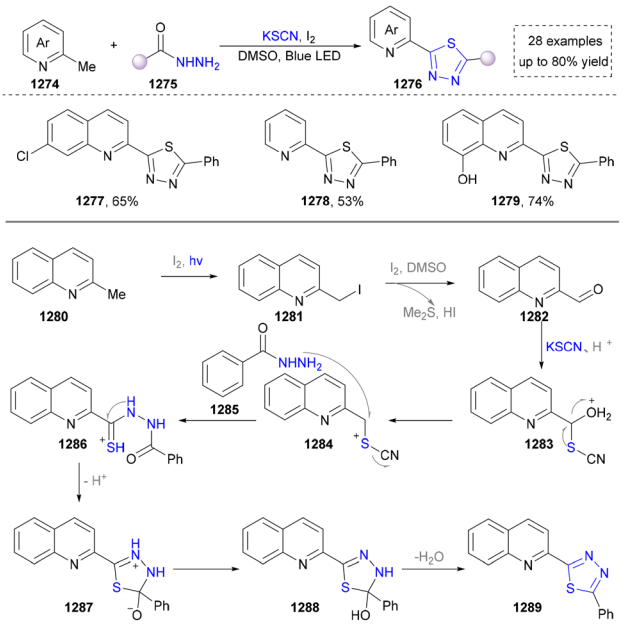
8.9.1 Photochemical synthesis of 1,3,4-thiadiazoles. Besides the synthesis of 1,2,4-thiadiazoles, 1,3,4-thiadiazoles have been obtained using photochemical synthesis. The Singh group first disclosed the photocatalytic synthesis of 1,3,4-thiadiazoles (**1267**, **1268**) through the cyclization of hydrazones. The one-pot method has also been achieved using aldehydes and hydrazines directly *via* the *in situ* formation of hydrazones (Scheme 133).[540]

Thiadiazoles (**1277–1279**) and selenadiazoles have also been achieved using the light-assisted method. In this case, benzoylhydrazines **1285** and 2-methylquinolines **1280** worked as starting materials and the products were formed through subsequent photocatalysis-induced iodine substitution, oxydic aldehyde formation, and nucleophilic addition. Importantly, the synthesized products showed attractive fluorescence properties for cell imaging, indicating their potential (Scheme 134).[541] Therefore, intermolecular synthesis of 1,3,4-thiadiazoles using different nitrogen sources and sulfur sources provided an efficient method, which also showed good structural diversity.

8.9.2 Electrochemical synthesis of 1,3,4-thiadiazoles. The electrochemical method has also been applied to the synthesis of 1,3,4-thiadiazoles by Li's group. In this reaction, efficient synthesis



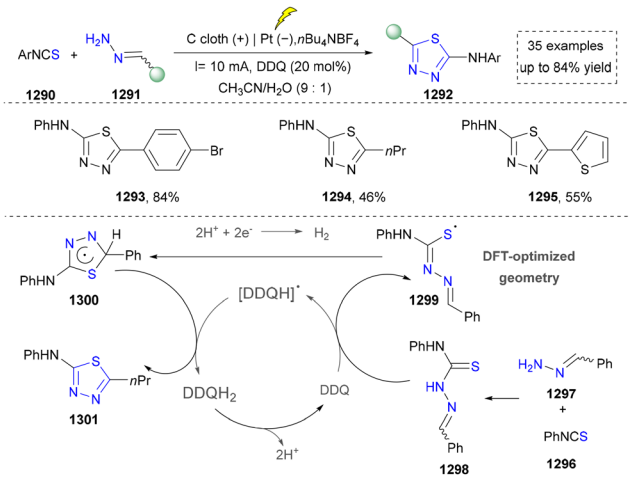
Scheme 133 Visible-light-promoted synthesis of 1,3,4-thiadiazoles.



Scheme 134 Photoinduced construction of thiadiazole derivatives.

of 2-amino-1,3,4-thiadiazoles (**1293–1295**) from various isothiocyanates and hydrazones was presented (Scheme 135). The mechanistic studies proved that the *in situ*-formed thioacylhydrazone **1298** was the key intermediate. Moreover, the hydrogenated DDQ was necessary, which was oxidized at the anode and further activated the thioacylhydrazone to furnish the final product **1301**.[542] The Fan group also reported the electrocatalytic [4+1] cyclization to afford 1,3,4-thiadiazoles with alcohols as the C1 synthons.[543] Moreover, *N*,*N*-dimethylhydrazinecarbothioamide was used as the thiol source. However, the substrate scope was not fully investigated. Therefore, the methods to construct 1,3,4-thiadiazoles were still underexplored and only hydrazones were applied to the synthesis of 1,3,4-thiadiazoles *via* photochemical or electrochemical strategies.

Electrochemical synthesis of 1,3,4-thiadiazoles overcomes the inherent limitations of traditional methods in handling sensitive



Scheme 135 Electrochemical oxidative synthesis of 1,3,4-thiadiazoles.

functional groups such as naked N–H bonds, eliminating the need for multi-step protection/deprotection procedures. This strategy enables the direct utilization of inexpensive starting materials containing sensitive motifs, allowing for the straightforward and efficient modification of complex molecular frameworks. Concurrently, applying this powerful tool to the direct modification of complex bioactive molecules represents a promising frontier.

Conclusions

Over the past decade, the advent of emerging approaches such as photochemical, electrochemical, biocatalysis and atom editing has revolutionized the construction of five-membered heteroarenes. These innovative approaches have not only provided new methods but also made the synthesis of previously challenging five-membered ring heteroarenes more feasible and efficient. Compared to traditional methods, photochemistry and electrochemistry always offer mild, eco-friendly conditions to avoid using additional additives or stoichiometric oxidants. More importantly, they could also create some unique pathways to activate inert bonds and precisely functionalize substrates, significantly broadening accessible substrate scopes. Enzymatic catalysis operates with biocompatible media and high selectivity, ideal for modifying complex bio-derived molecules and expanding natural substrate libraries. Atomic editing performs atom-precise modifications directly constructing novel heterocycles beyond conventional reach, always providing novel structural motifs. It is also important to acknowledge that these strategies come with their own inherent limitations. For example, photochemistry is constrained by limited light penetration depth and challenges in scale-up, with strategies employing photosensitizers in conjunction with continuous-flow systems being adopted to enhance the photon utilization efficiency.[544,545] Furthermore, electrochemistry suffers from limitations such as mass transport constraints at the electrode interface and competing side reactions, which can be effectively mitigated through the modification of the electrode interface.[546] The limitations of enzyme chemistry primarily stem from its narrow substrate specificity and instability under non-physiological conditions, making rational design and directed evolution *via* protein engineering key to expanding its application scope, even though such technologies have not yet been applied to the synthesis of five-membered aromatic heterocycles.[547] Meanwhile, molecular editing, an emerging strategy, is progressively evolving towards greater refinement.

In addition to integrating emerging technologies with continuous-flow synthesis to address scalability challenges, the development of integrated and hybrid catalytic systems has emerged as a pivotal strategic direction. For instance, continuous flow reactors are promising platforms for electrochemical synthesis, as they allow for the rapid refreshment of reagents at the electrode surface.[548] The incorporation of artificial intelligence and machine learning is poised to enable the predictive modelling and rational design of complex hybrid catalytic networks, shifting the discovery paradigm from empirical screening to informed design.[549,550] Another highly significant trend is the convergence

and synergy among these four strategies. For example, the combination of enzymatic stereocontrol with photoredox-mediated bond activation within catalytic cascades promises to transcend the boundaries of singular methodologies, creating novel and sustainable pathways to complex heterocycles from basic feedstocks.[551] In addition, photoenzyme catalysis and electroenzyme catalysis have emerged as cutting-edge areas in chiral biocatalysis.[552,553] There is no doubt that the future impact of these hybrid technologies on the synthesis of five-membered heteroarenes will be impossible to ignore.

The application to natural product and drug synthesis has also been achieved, even though the related findings are still very poorly compared with the quantities of marked drugs and natural products baring these scaffolds. Furthermore, these methods enabled the late-stage modification of natural products and drugs. Moving forward, it is also necessary to develop synthetic methods that utilize more drug candidates without active group protection, with the long-term goal of applying these strategies to the total synthesis of natural products. We have also noticed that the direct application of these emerging toolboxes in drug discovery and lead modification remains largely underexplored. Hence, it is highly encouraging for medicinal chemists to apply these approaches more widely.

It is also worth noting that the synthesis of some of the five-membered heteroarenes using these emerging toolboxes remains underexplored, thus leaving ample room for further investigation. For instance, syntheses of thiophenes and isothiazoles by electrochemical synthesis have remained unexplored. The synthesis of pyrazoles, 1,2,4-triazoles, tetrazoles, thiophenes, benzothiophenes, isoxazoles, and isothiazoles *via* biocatalysis was also unexplored. Moreover, some five-membered heteroarenes have only a few reports, indicating that more concerted efforts are needed to fully explore their potential. The growing field of atom editing has also attracted considerable interest for its ability to diversify five-membered heteroarenes from other core structures. Overall, we are convinced that these emerging toolboxes will continue to yield more significant findings and applications in this field. Looking ahead, medicinal chemistry is also poised to greatly benefit from these innovative approaches.

In summary, each of these methods has its own distinct advantages in the synthesis of five-membered heteroaromatics. It is precisely through their complementary strengths that they have collectively driven the field forward at a remarkable pace.

Author contributions

Y. Z., W. D. Z, and S. D. conceived the project. Z. H. and Q. L. conducted the literature survey. Y. Z., Z. H., Z. L and Q. L. wrote the manuscript. W. D. Z and S. D. guided and reviewed the manuscript. All authors have given approval to the final version of the manuscript.

Conflicts of interest

There are no conflicts to declare.

Data availability

No primary research results, software or code have been included, and no new data were generated or analysed as part of this review.

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