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One-electron oxidative dehydrogenative annulation and cyclization reactions

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One-electron oxidation (OEO) can deeply change the structure and reactivity of organic molecules. Rings exist ubiquitously in natural products and pharmaceutical molecules. The oxidative dehydrogenative annulation/cyclization reaction has become one of the most straightforward and powerful tools to construct ring-containing molecules. This review focuses on the recent advances in OEO involved oxidative dehydrogenative annulations and cyclizations for the intermolecular and intramolecular construction of valuable ring structures.

1. Introduction

Carbon–hydrogen bonds are ubiquitous in organic molecules and the direct functionalization of C–H bonds has been identified as a promising synthetic strategy for the formation of new carbon–carbon bonds and carbon–hetero bonds.¹ Oxidative dehydrogenative coupling means a combination of one X–H bond (X: carbon or hetero-atom) with another Y–H bond (Y: carbon or hetero-atom) for the construction of a new X–Y bond directly.² Actually, this kind of transformation to construct C–C bonds could date back to the early 1960s.³ Along with the prevalence of green chemistry and sustainable chemistry, great

efforts have been devoted to explore atom-economical and step-economical strategies to achieve direct functionalizations of C–H bonds. Thus, the oxidative dehydrogenative coupling protocol was recognized by chemists again and has gained widespread attention and witnessed explosive growth in recent years.⁴

Single electron transfer (SET), as one of the simplest elemental reactions, has a deep influence on the structure and reactivity of organic molecules. One-electron oxidation (OEO) is stated to take one electron away from the substrate that undergoes further transformations.⁵ As shown in Scheme 1, there are usually two pathways to generate reactive radical intermediates or carbocation intermediates from neutral organic compounds through OEO processes. *Pathway 1*: substrates lose one electron first to form radical cation intermediates. Then a deprotonation process occurs to deliver radical species. Or a dehydrogenation process occurs to deliver the corresponding carbocation species. *Pathway 2*: substrates lose one proton first to generate carbanion intermediates. Then an

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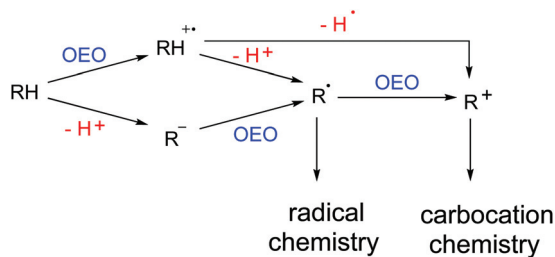
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Scheme 1

OEO process occurs to deliver radical species. One more OEO process of the radical species could occur to deliver the corresponding carbocation species (Scheme 1). When organic molecules are one-electron oxidized to their radical cations, the dissociation energies of their α -C-H bonds are remarkably weakened and the acidity of their α -C-H bonds is amazingly enhanced.⁶ Therefore, OEO processes are really beneficial for C-H bond activation. OEO involved oxidative dehydrogenative C-H functionalization has become one of the most appealing synthetic strategies in recent years.⁷

Rings are the most privileged scaffolds existing ubiquitously in natural products and pharmaceutical molecules, which exhibit attractive physiological and biological activities. They are also indispensable chemical building blocks and transition-metal ligands.⁸ Hence, the development of simple and efficient synthetic methodologies for cyclic compounds attracts intense attention all the time.⁹ The oxidative dehydrogenative annulation/cyclization reaction has become one of the most straightforward and powerful tools to construct ring-containing molecules. This review will mainly focus on the recent advances in OEO involved oxidative dehydrogenative annulations and cyclizations for the intermolecular and intramolecular construction of valuable ring structures.

2. Intermolecular oxidative dehydrogenative annulation

2.1. Construction of five-membered rings

2.1.1. Oxidative dehydrogenative [2 + 3]-annulation. Five-membered heterocycles are highly important structural motifs, which widely exist in natural products, pharmaceuticals and fundamental materials. Therefore, great efforts have been devoted to the construction of these heterocycles from readily available substrates. Among these methods, intermolecular [3 + 2]-annulation is one of the most straightforward approaches to construct five-membered heterocycles.

In 2014, the Rueping group reported a visible-light mediated oxidative [3 + 2]-cycloaddition of *N*-substituted hydroxylamines with alkenes for the construction of isoxazolines. The aerobic oxidation of hydroxylamines to nitrones can be achieved through photoredox catalysis under oxidant-free conditions. The proposed mechanism involved single electron transfer and the following deprotonation of *N*-substituted hydroxylamines to afford nitronone intermediates, which are immediately blocked by alkenes yielding [3 + 2]-cycloaddition products (Scheme 2).¹⁰

In 2014, the Xie group developed a biomimetic strategy for the synthesis of pyrrole derivatives from commercially available amino acid esters through multiple dehydrogenations, deamination, and oxidative cyclization promoted by a co-catalyst system of Cu(II) and Mn(III) (Scheme 3).¹¹ In addition, this biomimetic strategy has made a valuable contribution to the total synthesis of lycogarubin C and CPA.

In 2014, the Xiao group developed a visible-light induced aerobic oxidation/[2 + 3]-cycloaddition/aromatization cascade reaction between glycine esters and isocyanides to construct diverse 1,5-disubstituted imidazoles.¹² The reaction proceeded through a photocatalytic oxidative dehydrogenation of glycine



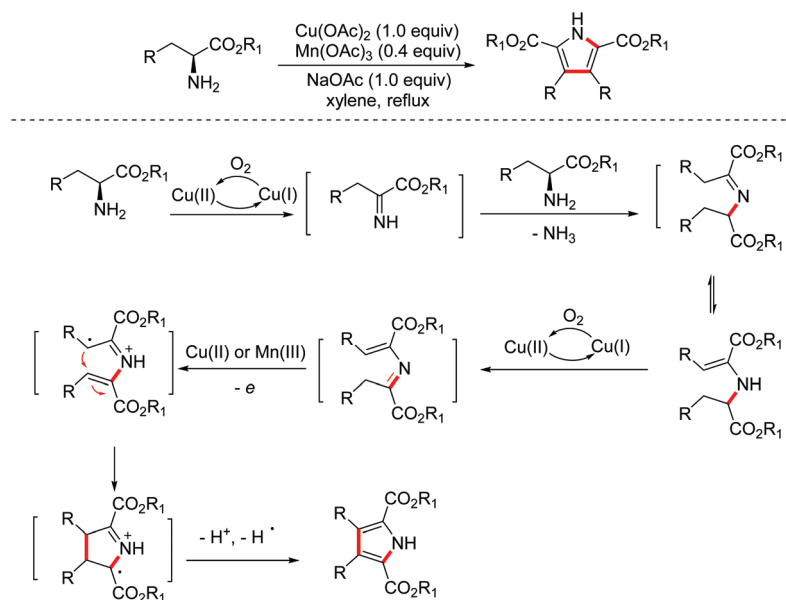
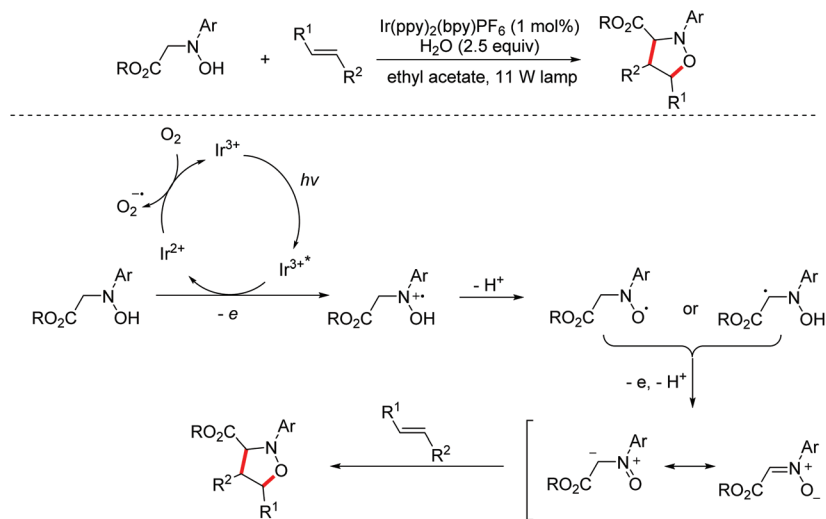
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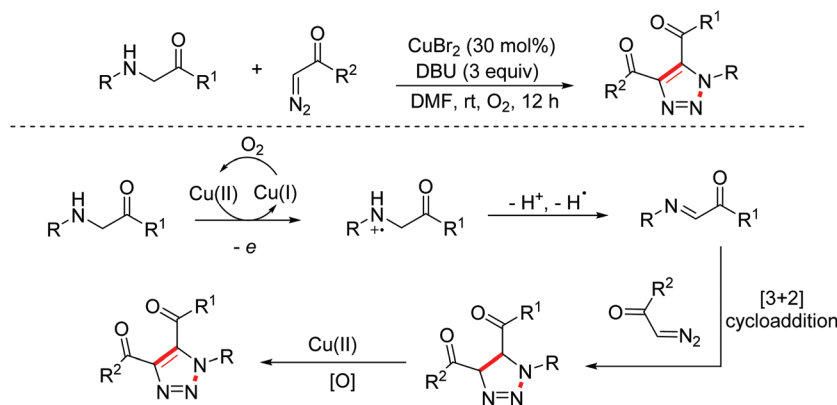
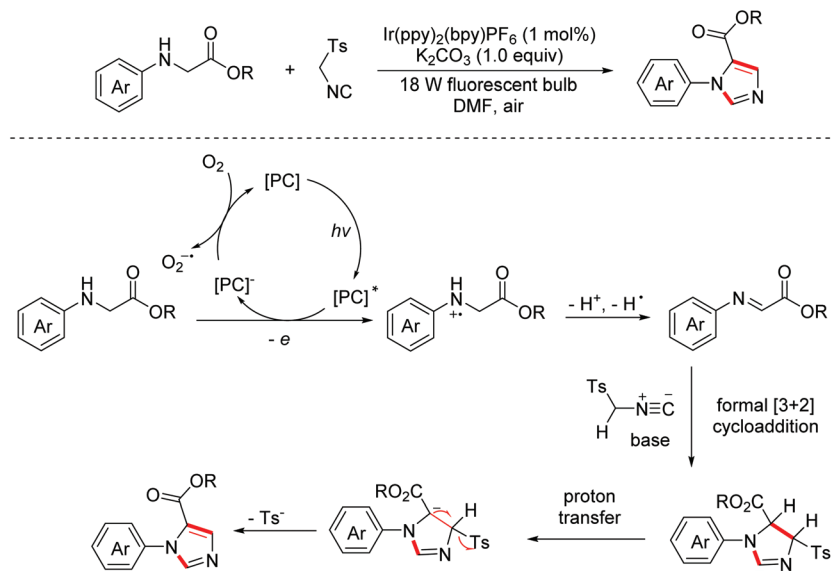
esters to generate imine intermediates, which were then captured by isocyanides *via* a formal [2 + 3]-cycloaddition with subsequent proton transfer/aromatization to produce the desired products (Scheme 4).

In 2015, the Liu group disclosed a copper-catalyzed sequential aerobic oxidation/[2 + 3]-cycloaddition/oxidative aromatization cascade reaction of glycine esters with α -diazo compounds through imine intermediates to construct 1,2,3-triazoles (Scheme 5).¹³

In 2015, the Huo group developed a copper-catalyzed aerobic oxidative dehydrogenative formal [2 + 3]-annulation of glycine derivatives with α -angelicalactone for the construction of biologically significant multi-substituted pyrrolidone deriva-

tives.¹⁴ The proposed mechanism for this process is presented in Scheme 6. Firstly, electrophilic iminium ion intermediates were formed under copper-catalyzed aerobic conditions, which then underwent nucleophilic addition with nucleophilic α -angelicalactone. Then, intramolecular nucleophilic substitution and deprotonation occurred to produce pyrrolidone derivatives. Afterward, a visible light-induced version of this transformation was reported by the Zhang group in 2018.¹⁵

The fully substituted 4,5-biscarbonyl imidazole moiety is an important core of some natural products due to its widespread biological and pharmacological activities. In 2017, the Wang group reported a copper-catalyzed aerobic oxidative reaction between glycine derivatives and 5-alkoxyoxazoles for accessing



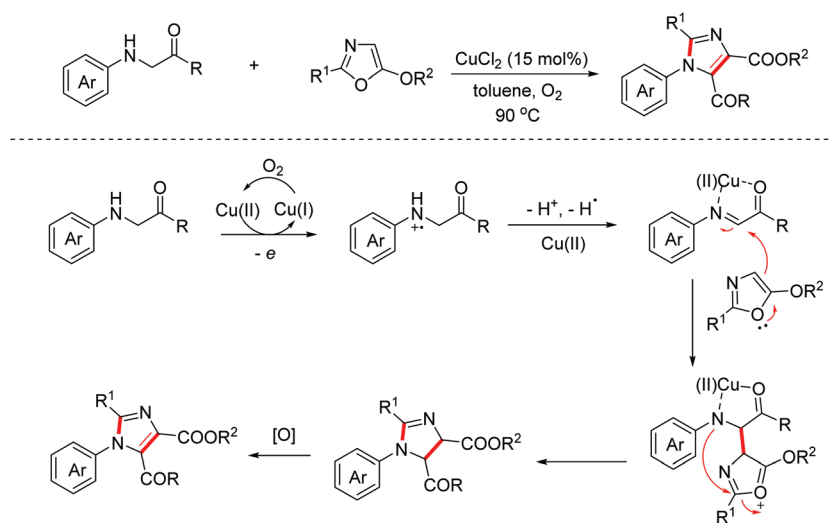
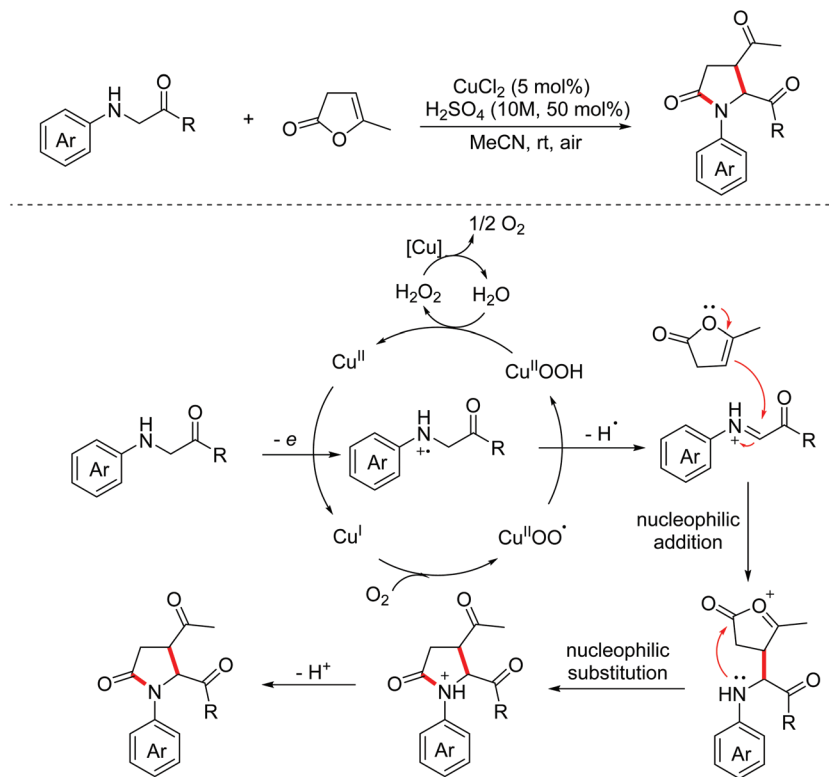
tetra-substituted 4,5-biscarbonyl imidazoles *via* the [2 + 3]-annulation/aromatization cascade annulation process.¹⁶ The process featured a similar oxidative cyclization mechanism (Scheme 7).

Enols are useful building blocks in organic synthetic chemistry and they can be *in situ* generated from the corresponding ketones. In 2019, the Baidya group disclosed the synthesis of clausenamides from *N*-arylglycine derivatives with α -keto esters *via* oxidative cross-dehydrogenative [2 + 3]-annulation.¹⁷ The mechanistic investigation proposed that the reaction proceeded through a nucleophilic addition of electrophilic imines (generated from *N*-arylglycines *via* Cu(II)-catalyzed oxidation) with nucleophilic enols (generated from ketones under base catalysis). Then a cyclization process occurred to yield pyrrolones (Scheme 8).

Imidazolidines represent an important class of five-membered nitrogen-containing heterocycles with a broad spectrum of biological activities. Aziridines are important synthetic syn-

thons, which can serve as masked 1,3-dipoles to participate in formal [3 + 2]-annulation with dipolarophiles. In 2017, the Punniyamurthy group reported a stereospecific Cu(II)/TBHP catalyzed one-pot reaction of *N*-alkylanilines with aziridines for the construction of 1,3-imidazolidines.¹⁸ The proposed mechanism for this process is presented in Scheme 9. Initially, the S_N2 reaction of aziridines and *N*-alkylanilines took place to deliver the pivotal intermediates, which then underwent the OEO process and the following intramolecular nucleophilic cyclization *via* the Cu(II)/TBHP catalytic cycle to yield the desired 1,3-imidazolidines.

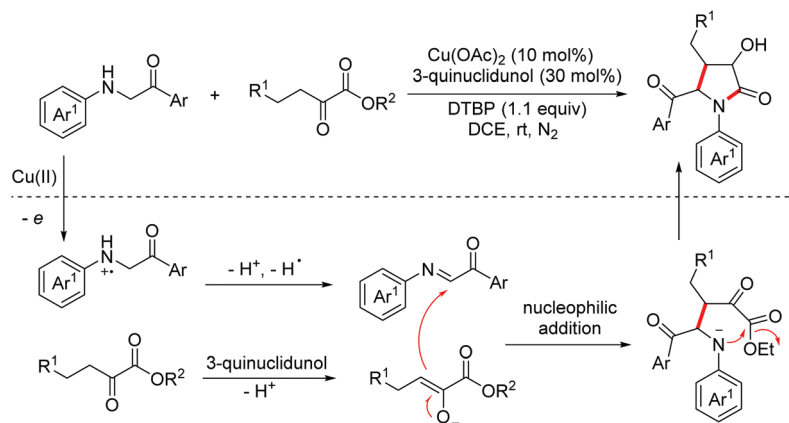
In 2018, the Huo group developed an aerobic oxidative dehydrogenative formal [2 + 3]-annulation of glycine derivatives with aziridines to produce highly functionalized imidazolidine derivatives.¹⁹ The reaction also began with the S_N2 ring-opening step. However, the authors found that the subsequent cyclization did not proceed through the classical copper induced aerobic oxidative dehydrogenative catalytic cycle after



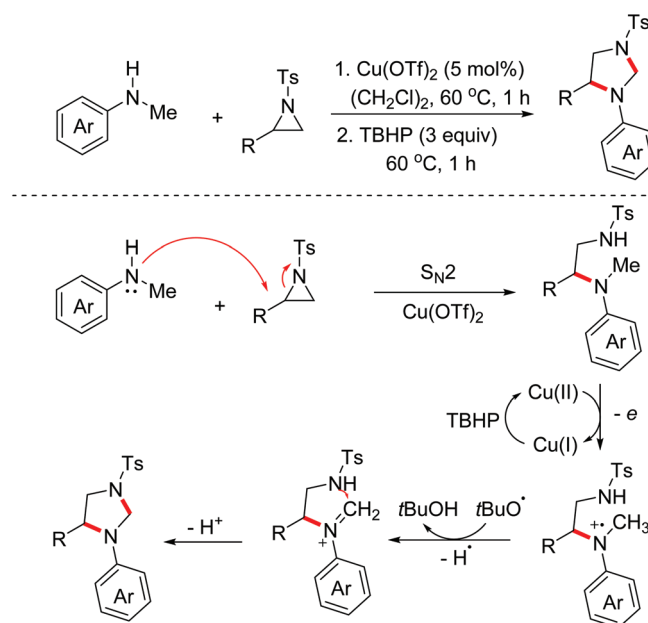
careful mechanism studies. An auto-oxidation involved mechanism with the following Brønsted acid promoted intramolecular S_N1 type nucleophilic process was proposed (Scheme 10).

In 2020, a visible-light-induced aerobic oxidative [2 + 3]-cycloaddition between glycine derivatives and styrene oxides for the construction of 1,3-oxazolidines was reported by the Zhang group.²⁰ The process involved a photo-active EDA

complex and no external photoredox catalyst was needed. A series of control and UV-Vis absorption spectroscopy experiments proved that glycine esters first interacted with benzyl iodides, which were *in situ* generated from styrene oxides in the presence of HI, to form the corresponding EDA complexes. Then, the key intermediates with charge separation were formed under visible-light irradiation with oxidation of the EDA complex. Finally, the nucleophilic addition/intra-



Scheme 8



Scheme 9

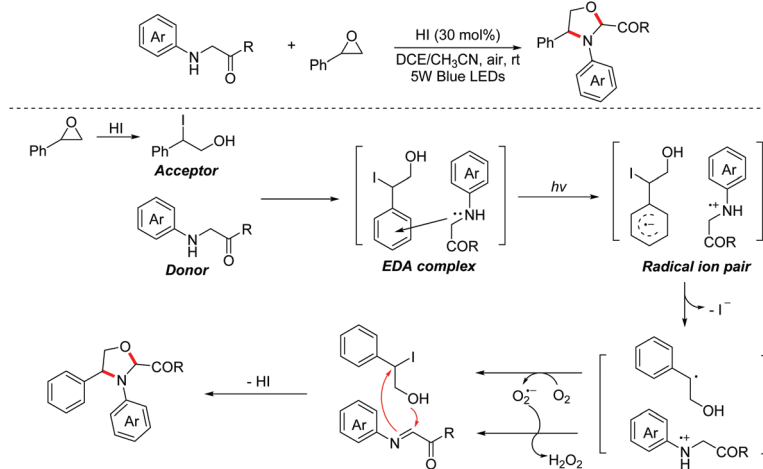
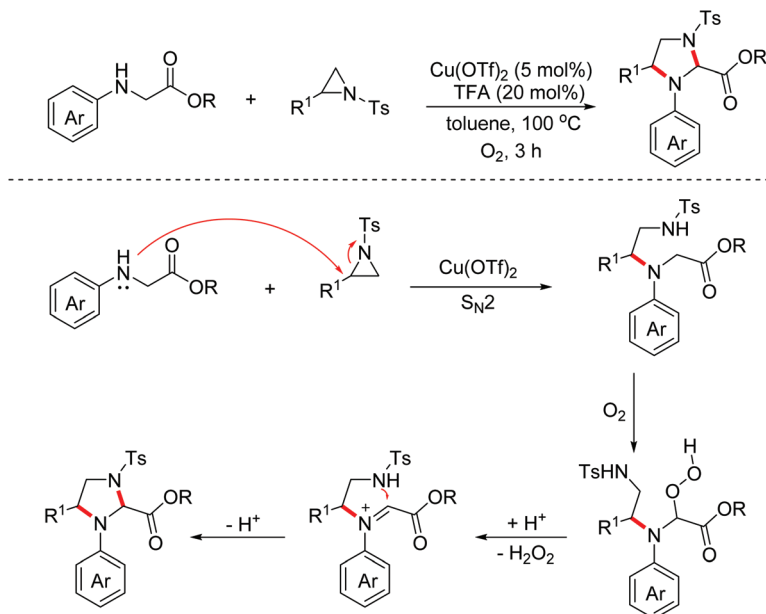
molecular nucleophilic substitution/deprotonation process occurred to give 1,3-oxazolidines (Scheme 11).

In 2020, Miao and Yang *et al.* reported a copper-catalyzed annulation of oxime acetates with α -amino acid ester derivatives for the synthesis of 4-pyrrolin-2-one derivatives. Oxime acetates act as internal oxidants and 1,3-dinucleophilic species simultaneously in this reaction.²¹ The key imine intermediates were generated by one-electron oxidation and enamino-copper intermediates were delivered by one-electron reduction. Then the transformation proceeded through nucleophilic addition, intramolecular cyclization and oxidation process between *in situ* generated enamino-copper and imine intermediates to give the desired heterocyclic products (Scheme 12).

Pyrazoles are kinds of crucial bioactive motifs, which are widely present in synthetic medicines and natural products. In

2019, the Huang group explored a Cu(I)-catalyzed oxidative formal [3 + 2]-annulation of ketoxime acetates with tetrahydroisoquinolines to construct isoquinoline-fused pyrazoles (Scheme 13).²²

Benzoheterocycle motifs exist in some important bioactive natural products and are associated with widespread bioactivity. In 2017, the Lei group developed an electro-oxidative [3 + 2]-annulation between phenols and *N*-acetylindoles under undivided electrolytic conditions to synthesize benzofuroindolines.²³ The two substrates were evenly oxidized by an anode to yield the relevant oxidized intermediates first. Then the two intermediates underwent direct cross-coupling with the following intramolecular cyclization/deprotonation to form benzofuroindolines. The chemical oxidants were avoided and H₂ was the only by-product (Scheme 14). In 2020, Zhang and Wang *et al.* also reported an electro-oxidative annulation of phenols



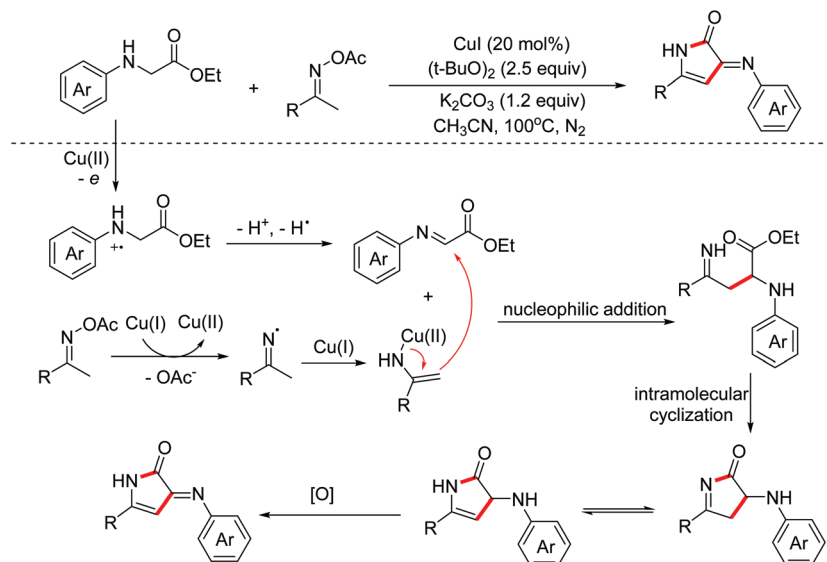
with electron-deficient alkenes to achieve 2,3-dihydrobenzofuran skeletons.²⁴

In 2020, a synthetic method of 2-diarylaminoindolo[2,3-*b*]indoles *via* a copper-catalyzed [3 + 2]-annulation reaction of diarylamines with indoles was reported by the Zhang group.²⁵ The possible mechanism is illustrated in Scheme 15. The dimerization of diphenylamine occurred first through a one-electron oxidation involved process. Then the dimers were one-electron oxidized again to generate radical cation intermediates. Subsequently, with the following reaction steps, polycyclic products were achieved (Scheme 15).

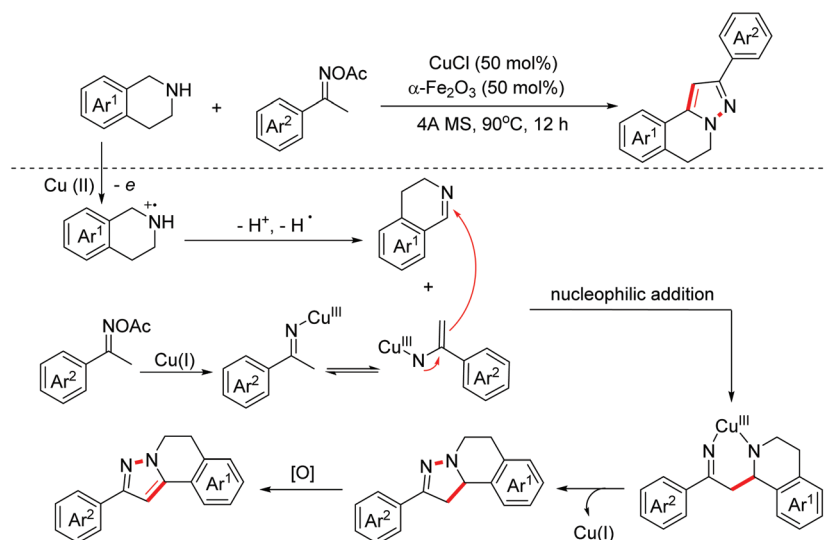
Benzothiophenes are important sulfur-containing heterocycles with promising pharmacological activity. In 2018, the Huo group realized an auto-oxidation mediated intermolecular

oxidative [3 + 2]-annulation reaction of thiophenols with alkynes to construct complex benzothiophene derivatives.²⁶ Several control experiments indicated that sulfur-centered radicals were involved as the key intermediates in the process and the following radical annulation occurred to deliver the targeted benzothiophenes (Scheme 16).

2.1.2. Oxidative dehydrogenative [2 + 2 + 1]-annulation. Nitrogen/oxygen-containing heterocyclic moieties, such as oxazoles and pyrroles, are universal skeletons in natural products which possess significant and extensive biological activities. The synthesis of these compounds is a hot topic in organic synthesis. In 2012, the Jiao group demonstrated a Cu(II)-mediated aerobic oxidative dehydrogenative [2 + 2 + 1]-annulation of aldehydes, amines and molecular oxygen to synthesize



Scheme 12



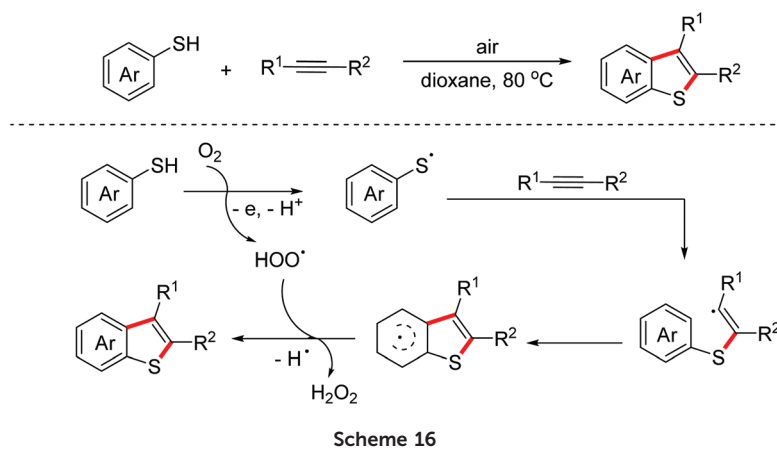
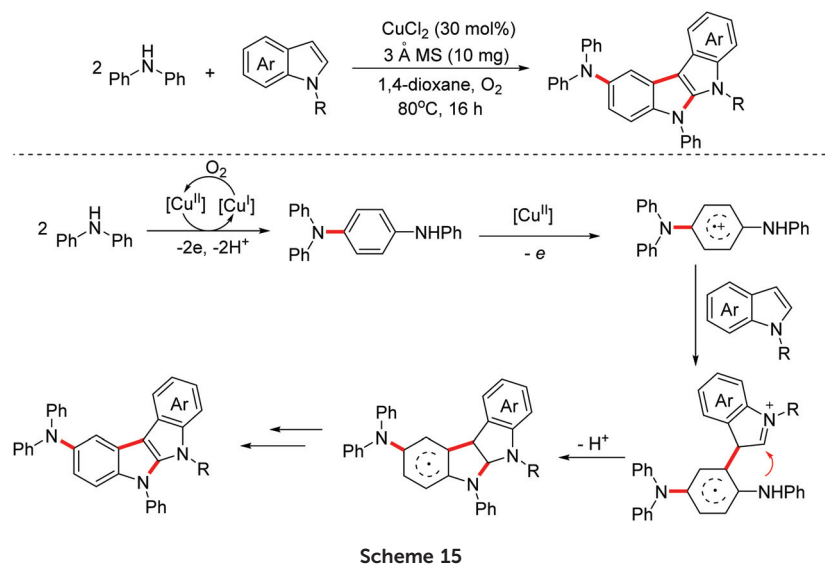
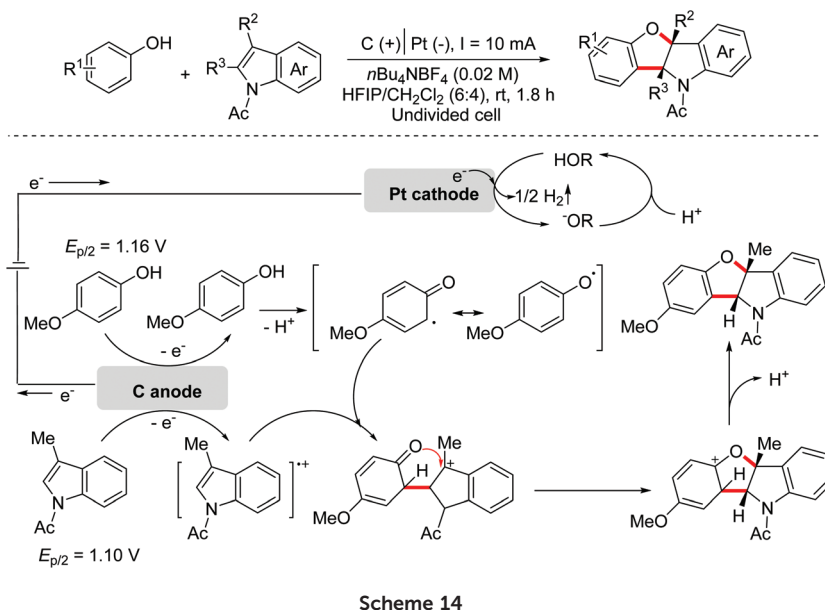
Scheme 13

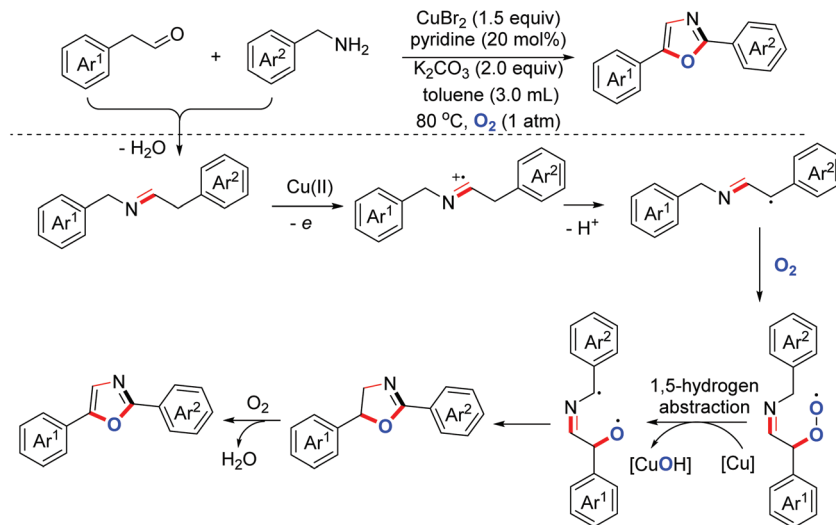
oxazole derivatives with the removal of six hydrogen atoms and the functionalization of four C(sp³)-H bonds (Scheme 17).²⁷ In 2015, the Pan group accomplished a facile synthesis of 2,5-disubstituted oxazoles *via* a copper-catalyzed cascade reaction of alkenes with azides.²⁸ Subsequently, TsOH/I₂-mediated and copper-catalyzed oxidative dehydrogenative annulations of amines and alkynes to construct substituted oxazoles were developed by the Chen and Jiao groups, in 2017 and 2018 respectively.²⁹

1*H*-Pyrrol-2(3*H*)-ones, an important class of nitrogen heterocycles, represent the key structural motifs in many valuable biologically active molecules and natural products. In 2016, Tu and Zhang *et al.* reported a CuO/TEMPO-mediated multi-step cascade process of diarylethanones and primary amines to

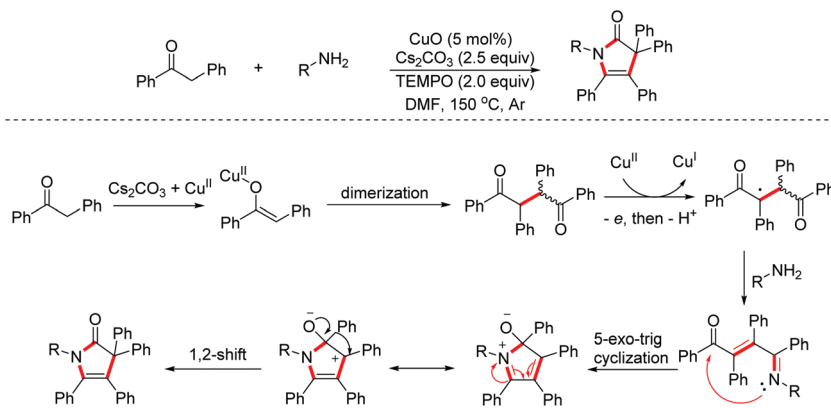
access multi-aryl 1*H*-pyrrol-2(3*H*)-ones.³⁰ Moreover, the AIE (Aggregation Induced Emission) effects of these compounds were also evaluated by the authors (Scheme 18).

Pyrroles are a vital class of aromatic heterocycle compounds, which can be found in many bioactive natural products and significantly important pharmaceuticals. In 2017, the Zhao group explored a Cu(I)-catalyzed oxidative annulation of diverse amines, alkyne esters and maleimides to synthesize fully substituted dihydropyrroles *via* the cleavage of C(sp²)-H/N-H bonds.³¹ The proposed mechanism indicated that the key radical intermediates were formed through one-electron oxidation of imine intermediates, which were derived from *in situ* generated enamines. Subsequently, intramolecular cyclization and the following oxidation occurred to yield pyrroles

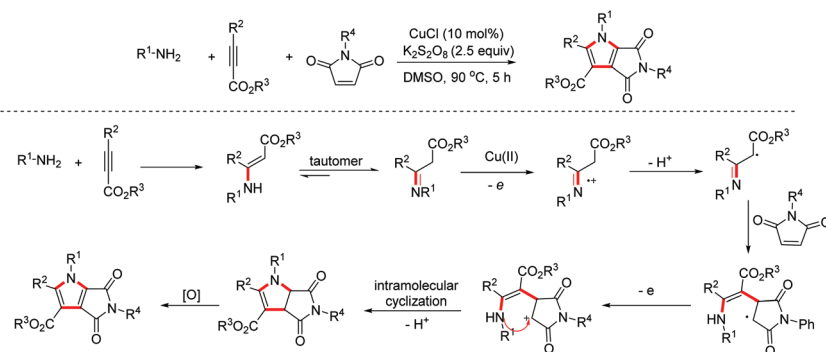




Scheme 17



Scheme 18



Scheme 19

(Scheme 19). In 2018, a similar $\text{Mn}(\text{OAc})_3$ -promoted oxidative annulation of alkenes with amines/alkyne esters or enaminone esters to deliver polysubstituted dihydropyrroles was developed by the Zhang group.³²

2.1.3. Oxidative dehydrogenative [4 + 1]-annulation. In 2018, the Xu group explored an electrochemical dehydrogenative [4 + 1]-annulation of *N*-allyl amides with 1,3-dicarbonyl compounds to obtain pyrrolidines.³³ Mechanistic experiments

suggested that carbon centered radical intermediates were obtained from malonates through deprotonation and the following OEO process in the presence of redox-active catalysts. Later, radical intermediates were added to the alkenyl moiety of *N*-allyl amides generating radical adducts, which then underwent step-wise transformations to deliver pyrrolidine derivatives (Scheme 20).

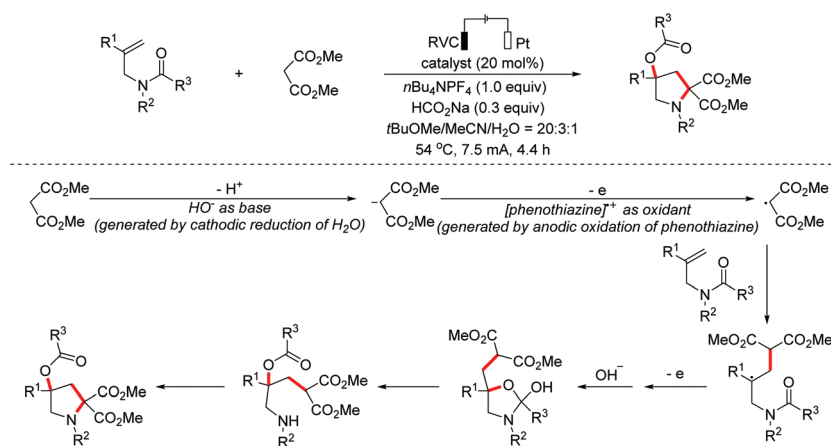
2.2. Construction of six-membered rings

2.2.1. Oxidative dehydrogenative [4 + 2]-annulation.

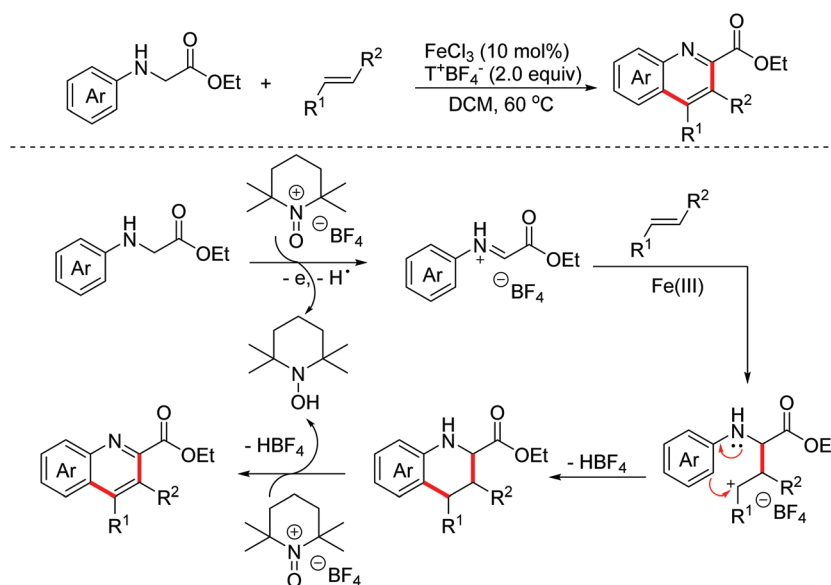
Quinoline derivatives exist in a number of natural products and synthetic pharmaceuticals possessing diverse biological activities.³⁴ Many different strategies for the synthesis of quinolines have been developed. Among them, the direct oxidative dehydrogenative [4 + 2]-annulation of various substituted

aniline derivatives with olefins is one of the most atom-economical strategies to construct decorated quinolines.

In 2011, the Mancheño group developed an oxidative Povarov/aromatization tandem reaction of glycine derivatives with alkenes to synthesize substituted quinolines employing FeCl_3 as the catalyst and the (2,2,6,6-tetramethylpiperidin-1-yl)oxy (TEMPO) oxoammonium salt as the oxidant.³⁵ The proposed mechanism is shown in Scheme 21. Firstly, iminium ions were formed *via* one-electron oxidation and the following dehydrogenation of glycine derivatives. Then, the nucleophilic attack on iminium intermediates by alkenes occurred to generate carbocationic species, which underwent a F-C reaction to afford the corresponding quinolines. In 2012, an FeCl_3 -catalyzed approach between glycine derivatives and alkynes was developed by the Hu group.³⁶ Since 2012, the Jia group realized this tandem oxidative degenerative [4 + 2]-annulation



Scheme 20



Scheme 21

process using various catalyst systems, including TBPA⁺/InCl₃/O₂, Ce(IV)/InCl₃/TBPA/O₂ and TBN/InCl₃/O₂, for the construction of substituted quinolones.³⁷

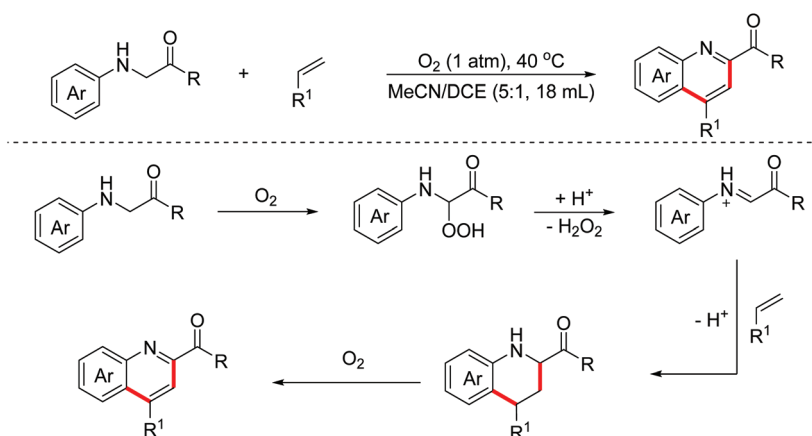
In 2014, the Huo group discovered an unprecedented auto-oxidation coupling of glycine derivatives. The reaction was performed using organic solvents under an air atmosphere in the absence of any redox-active catalyst and chemical oxidants.³⁸ The proposed mechanism implied that glycine esters were first auto-oxidized to generate hydroperoxide, which was then transformed into the iminium ion intermediate through the Brønsted acid-catalyzed S_N1-type procedure. Subsequently, the Povarov reaction and the following aromatization process proceeded to form complex quinolines (Scheme 22). In 2015, the Huo group disclosed that CBr₄ can promote this transformation more efficiently under an air atmosphere.³⁹

In 2015, the Liu group developed a K₂S₂O₈-catalyzed cross-dehydrogenative coupling of glycine derivatives with olefins.⁴⁰ In this process, the SO₄ radical anion abstracted one hydrogen

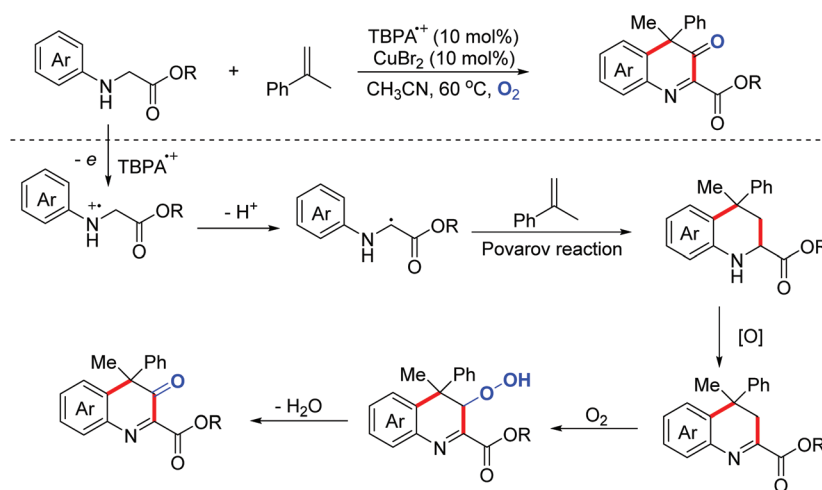
atom from glycine derivatives first to form radical intermediates, which then were one-electron oxidized by a Cu(II) salt to afford the crucial imine intermediates. In 2016, they also reported that the Cu(OTf)₂/NHPI/O₂ system is efficient for this transformation.⁴¹ In 2017, this annulation reaction using a gold-oxazoline complex as a catalyst was reported by the Feng group.⁴²

In 2016, the Zhang group accomplished a photocatalytic oxidative dehydrogenative coupling/aromatization tandem reaction of glycine esters with alkenes under an air atmosphere. It also featured the same imine pathway.⁴³ In 2017, the Wu group demonstrated a Cu(II) salt-catalyzed C–H functionalization of glycine derivatives to deliver a variety of heterocycles.⁴⁴ The process was triggered by visible light irradiation and no external photosensitizer was involved. The complexes formed *in situ* from Cu(II) salts with substrate amines or imines were identified as the key intermediates.

In 2017, the Jia group reported a radical cation salt-catalyzed tandem oxidative Povarov reaction of glycine esters and



Scheme 22



Scheme 23

α -methylstyrenes for the preparation of 3,4-dihydroquinoline-3-one derivatives (Scheme 23).⁴⁵

In 2020, the Huo group developed an auto-oxidative Povarov/aromatization tandem reaction of glycine derivatives with enamides to yield quinoline derivatives. The transformation was performed using only catalytic amounts of Brønsted acid and O₂. The acylamino group was used as both activating and leaving groups to improve the reaction efficiency (Scheme 24).⁴⁶

In 2020, the Brasholz group developed a visible-light mediated oxidative dehydrogenative [4 + 2]-annulation/aromatization reaction of glycine esters with indoles to synthesize indolo[3,2-*c*]quinolones (Scheme 25).⁴⁷

Besides glycine derivatives, *N*-benzylanilines are also suitable substrates for the preparation of quinolines *via* a similar oxidative Povarov/aromatization tandem reaction. In 2012, the Liu group developed an iron-catalyzed oxidative annulation of *N*-benzyl anilines with alkynes or alkenes for the synthesis of quinoline derivatives (Scheme 26). The process proceeded through the imine intermediate pathway.⁴⁸ After that, radical cation salt and Fe(OTf)₃/AcOH-prompted aerobic oxidative Povarov reactions of *N*-benzylanilines have also been explored by the Jia and Sun groups, in 2015 and 2018 respectively.⁴⁹

As shown above, the oxidative dehydrogenative Povarov reaction of secondary amines has been well developed. A similar tandem process using tertiary amines as the substrates was also realized. The process also involved sequential single electron transfer and dehydrogenation to generate iminium

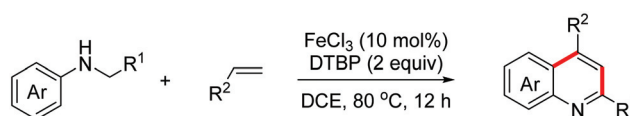
ions, and then the Povarov reaction was performed with electron-efficient alkenes to deliver the desired products.

In 2014, the Seidel group reported copper(I) catalyzed oxidative [4 + 2]-cycloaddition reactions of *N*-aryl tetrahydroisoquinolines with 1-vinylpyrrolidin-2-one for the synthesis of polycyclic amines *via* dual functionalization of both a C(sp³)-H bond and a C(sp²)-H bond (Scheme 27).⁵⁰

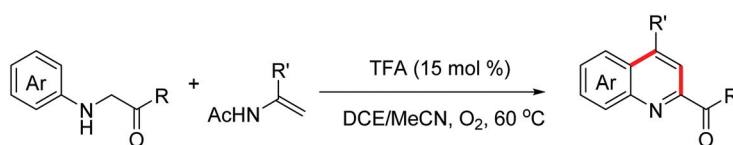
In 2016, the Huo group demonstrated a cobalt-catalyzed aerobic oxidative dehydrogenative formal [4 + 2]-annulation reaction of *N,N*-dimethylanilines with dihydrofuran to obtain hexahydrofuroquinoline motifs (Scheme 28).⁵¹

In 2016, the Guan group reported an iron-catalyzed dehydrogenative [4 + 2]-cycloaddition reaction of tertiary anilines and enamides for the synthesis of tetrahydroquinolines with amido-substituted quaternary carbon centers (Scheme 29).⁵² In 2018, the Lei group also developed an electrochemical oxidative [4 + 2]-annulation of tertiary anilines with enamides to generate tetrahydroquinolines.⁵³

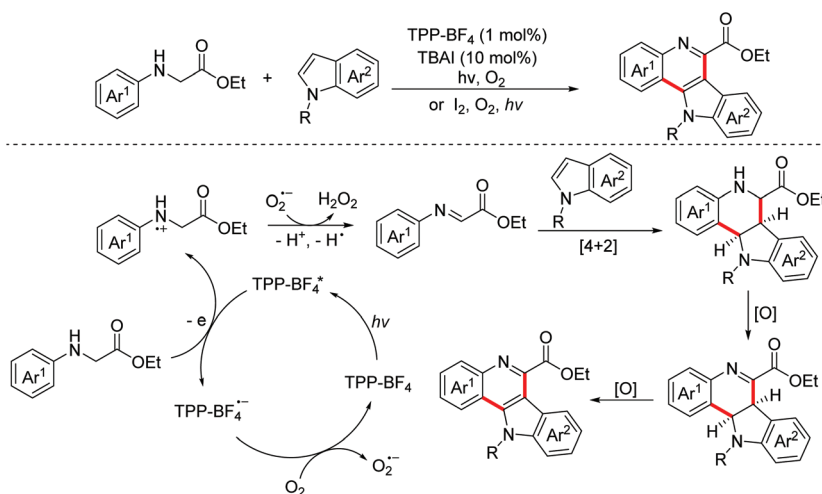
Electron-deficient alkenes, such as maleimides, can also be used as building blocks in the oxidative dehydrogenation



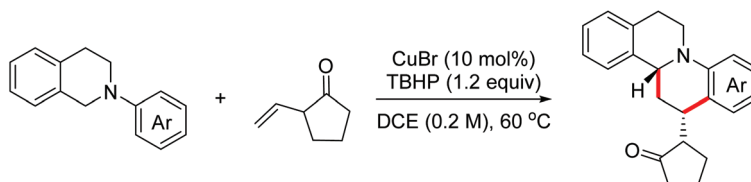
Scheme 26



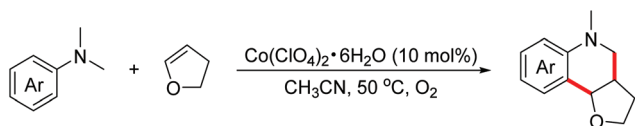
Scheme 24



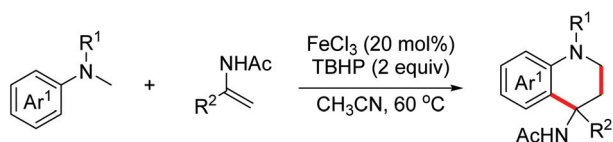
Scheme 25



Scheme 27



Scheme 28

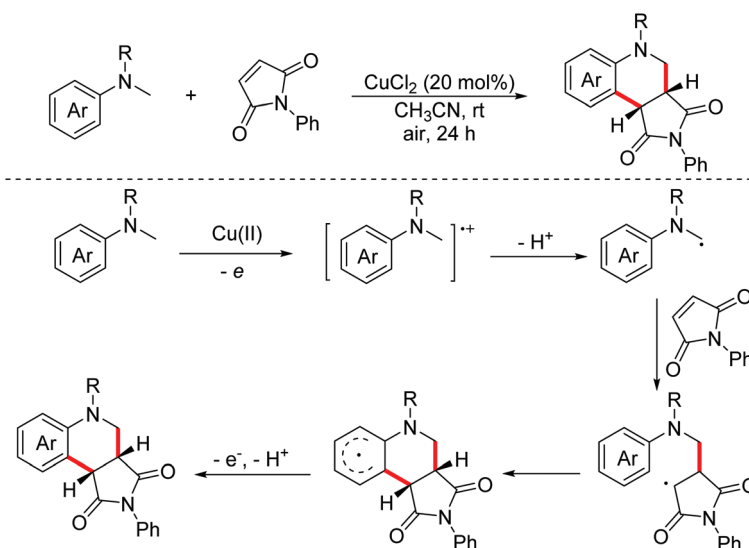


Scheme 29

cross-coupling cascade of *N,N*-dimethylanilines. The transformation involved a single electron transfer followed by deprotonation to give α -amino alkyl radicals from tertiary amines. Subsequently, electrophilic radicals were added to the electron-deficient double bond with subsequent free-radical cyclization to generate the corresponding cyclohexadienyl radicals, which were then readily rearomatized by a second electron transfer/proton elimination leading to the final products.

In 2011, Miura and Hirano developed a copper-catalyzed oxidative annulation of *N*-methylanilines with electron-deficient olefins involving maleimides and benzylidene malonitriles to obtain the corresponding tetrahydroquinolines through the C(sp³)-H and C(sp²)-H bond functionalization procedure (Scheme 30).⁵⁴ In 2016, the Bissemer group explored a direct functionalization of α -amino C-H bonds of *N*-methylanilines under copper(i) photocatalysis with Brønsted acids as co-catalysts.⁵⁵ Various catalytic systems were developed to achieve the transformation.⁵⁶ In 2018, the Wu group developed a photo-catalyzed oxidative annulation of tertiary anilines with maleimides to synthesize tetrahydroquinolines using Ru(bpy)₃²⁺ and cobaloxime as co-catalysts under redox-neutral conditions.⁵⁷ In 2018, the Sundén group reported an EDA-mediated photochemical oxidative annulation reaction for the synthesis of tetrahydroquinolines from dialkylanilines and maleimides using molecular oxygen as the terminal oxidant.⁵⁸ The mechanism investigation revealed that α -aminoalkyl radicals were generated *via* an electron donor-acceptor (EDA) complex.

In 2018, the Lei group reported a photoinduced oxidative [4 + 2]-annulation of imines with alkenes for accessing multi-substituted 3,4-dihydroisoquinoline derivatives with high regioselectivity and *trans*-diastereoselectivity utilizing a dual photo-redox/cobaloxime catalytic system.⁵⁹ Initially, alkene radical



Scheme 30

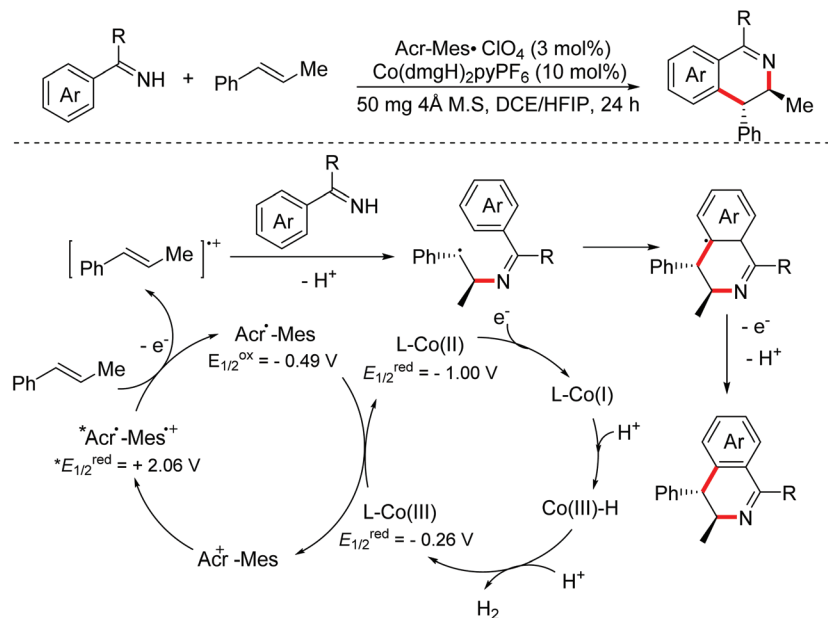
cation intermediates were delivered through one-electron oxidation of substrate alkenes by the excited photosensitizer. Then radical addition with imines occurred to generate relatively stable benzyl radicals, which underwent radical cyclization leading to the final isoquinoline derivatives (Scheme 31).

In 2020, Weng, Chiang and Lei *et al.* developed an electrochemical oxidative dehydrogenative [4 + 2]-annulation of indole derivatives to construct polycyclic indoline derivatives (Scheme 32).⁶⁰

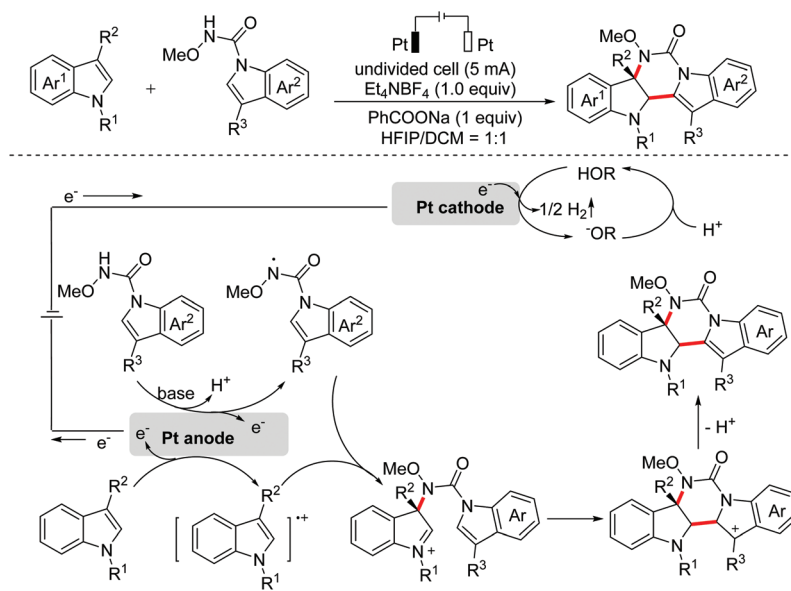
In 2020, Tang and Pan *et al.* reported an electrochemical catalyzed [4 + 2]-annulation of alkynes with 1,3-dicarbonyl

compounds to synthesize 1-naphthol derivatives *via* the C-centered radical-mediated intramolecular cyclization process (Scheme 33).⁶¹

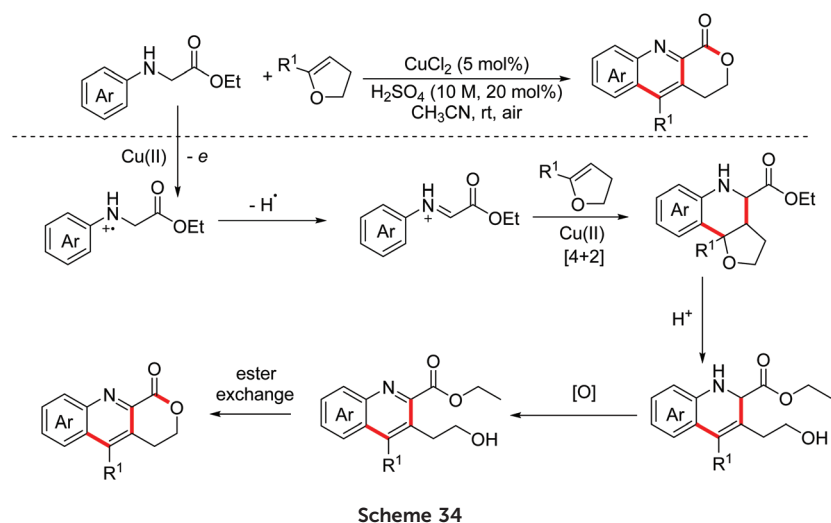
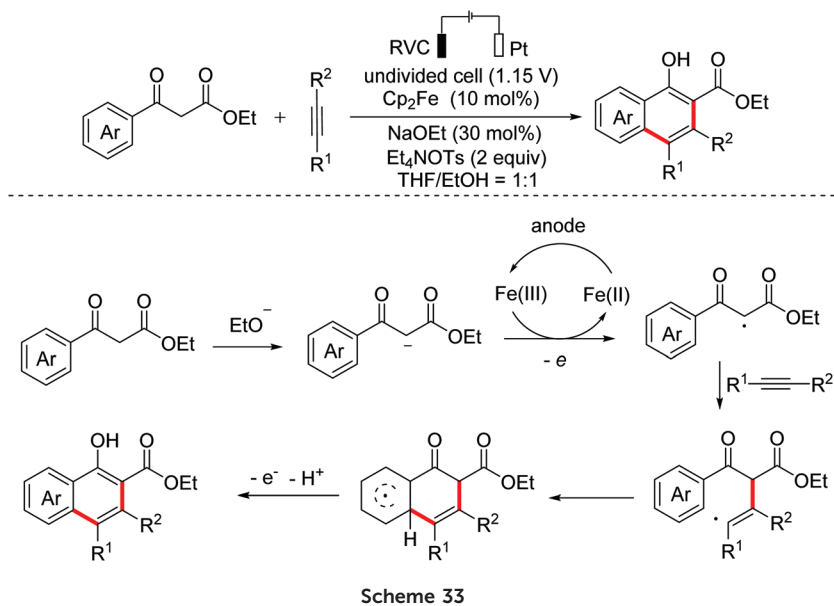
Quinoline-fused lactones are important subunits in a lot of bioactive natural and synthetic products. In 2015, the Huo group accomplished an oxidative dehydrogenative coupling of glycine derivatives with 2,3-dihydrofuran using the dual catalyst system $\text{CuCl}_2\text{-H}_2\text{SO}_4$ (Scheme 34).⁶² This methodology could achieve the synthesis of the analogue of bioactive luotonin A. Afterwards, similar tandem processes, using the TBPA^+/O_2 and photoredox catalyst systems, were



Scheme 31



Scheme 32



achieved by the Jia and Li groups in 2016 and 2018, respectively.⁶³

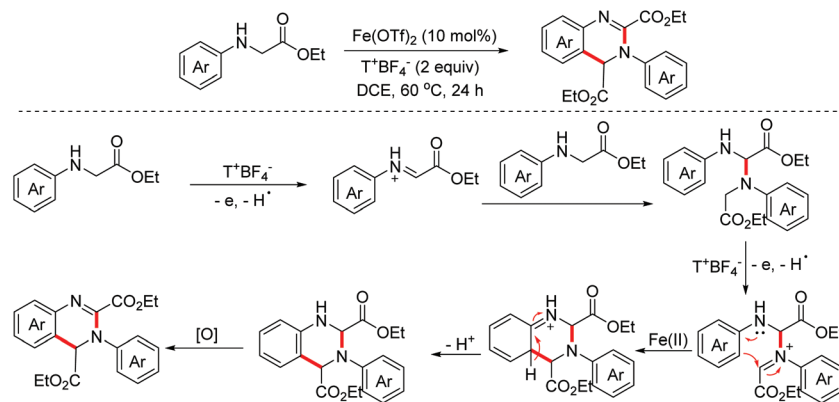
In 2013, the Mancheño group reported an iron-catalyzed homo-condensation of glycine esters to construct dihydroquinazolines using the TEMPO oxoammonium salt as the oxidant.⁶⁴ The mechanistic study confirmed that an iminium ion was formed first, which was then trapped by another glycine ester molecule (Scheme 35). A radical cation salt-induced homo-condensation of glycine derivatives was also developed by the Jia group in 2016.⁶⁵

In 2017, the Jia group achieved a radical cation salt-triggered dual removable activating group enabled Povarov homo-condensation reaction of *N*-aryl amino esters to deliver the desired quinoline-4-carboxylate esters.⁶⁶ Control experiments revealed that a radical-mediated process was involved (Scheme 36).

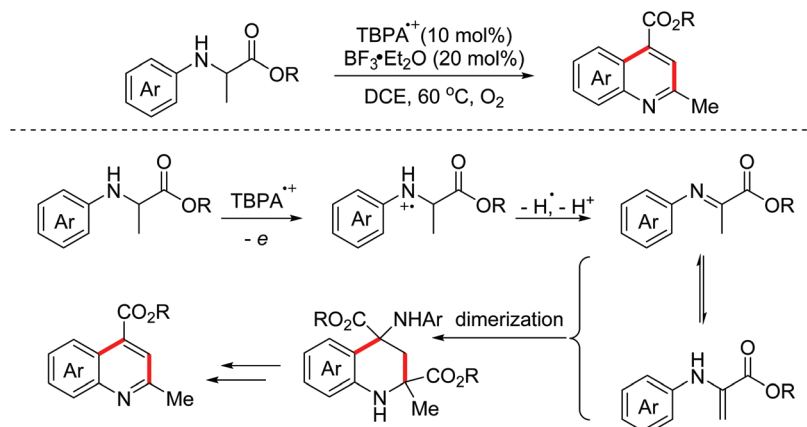
Pyrimidinethiones are the core structure of numerous natural products and possess promising pharmacological properties. In 2014, the Sun group developed a photo-assisted metal-free multi-component dehydrogenative condensation of aryl aldehydes, thioureas and THF (or THP, 1,4-dioxane) to afford the corresponding pyrimidinethiones.⁶⁷ In this transformation, dihydrofuran was first formed by dehydrogenative oxidation of THF, which could undergo a nucleophilic addition/annulation with the *in situ* formed imine derivatives to deliver pyrimidinethiones (Scheme 37).

In 2018, the Chen group reported an FePc-catalyzed biomimetic oxidative coupling annulation of tetrahydrocarbolines enabling the rapid construction of isochromanoindolenines (Scheme 38).⁶⁸

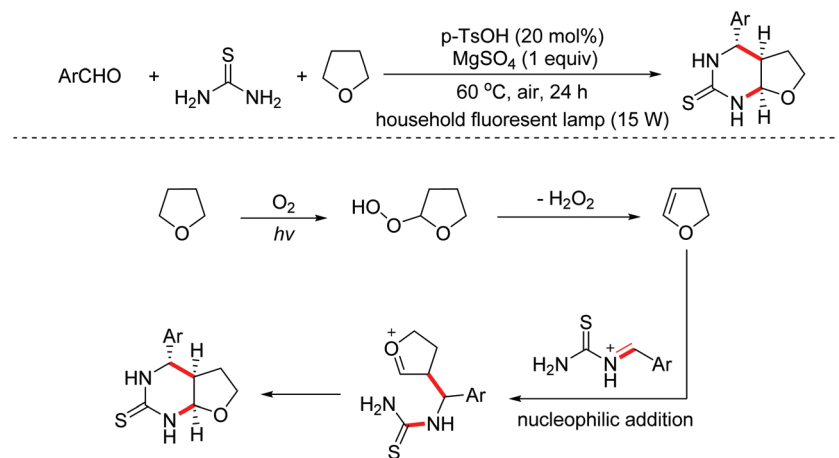
In 2015, the Liu group reported a copper-catalyzed oxidative Povarov reaction between *N*-alkyl *N*-methylanilines and satu-



Scheme 35



Scheme 36

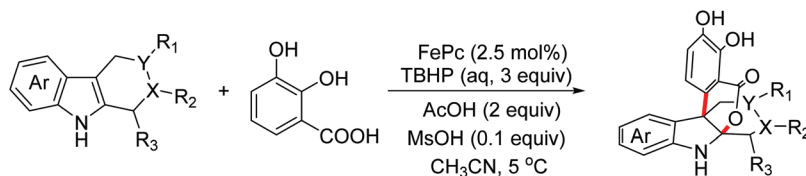


Scheme 37

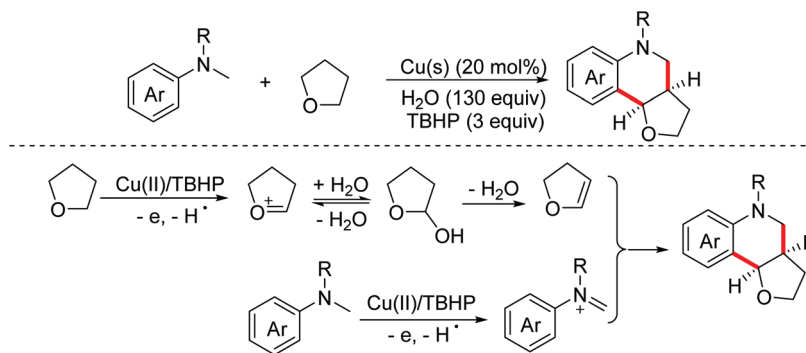
rated oxa- and thiacyclic compounds to achieve the preparation of tetrahydroquinoline derivatives *via* activating inert sp^3 C–H bonds.⁶⁹ In this process, saturated tetrahydrofurans were oxidized by $\text{Cu}(\text{II})/\text{TBHP}$ to form dihydrofurans. In the meantime,

N-alkylanilines underwent one-electron oxidation and dehydrogenation to deliver imine intermediates (Scheme 39).

Recently, the Huo group put forward the concept of the dual oxidative-dehydrogenative (DOD) annulation strategy.



Scheme 38



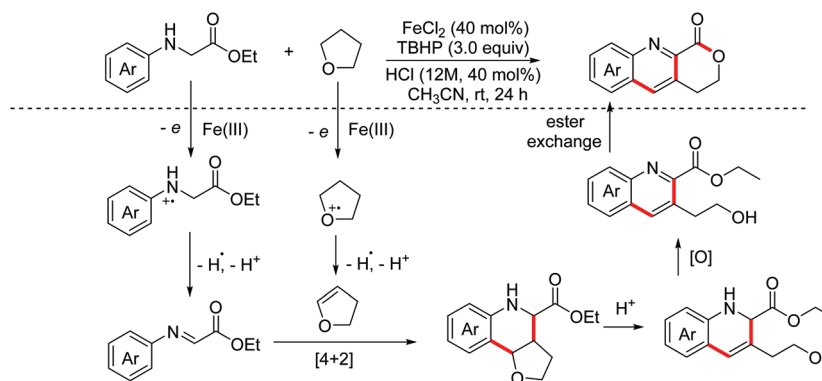
Scheme 39

Compared with the cross-dehydrogenative coupling (CDC) reaction, the DOD annulation reaction activates four C–H bonds in substrates simultaneously. In 2015, the Huo group developed an iron-catalyzed DOD [4 + 2] tandem annulation of glycine derivatives with tetrahydrofurans for the synthesis of highly valuable quinoline fused lactones (Scheme 40).⁷⁰

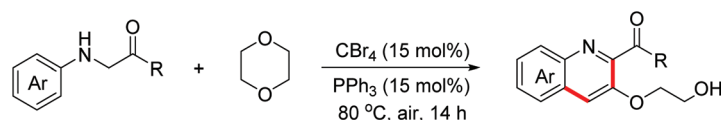
In 2016, the Huo group disclosed a CBr_4 -promoted DOD reaction of glycine derivatives with dioxane for the synthesis of

complex quinoline motifs (Scheme 41). This work proved again that CBr_4 can be an efficient reagent to initiate radical reactions under mild reaction conditions. The key imine and dioxene intermediates were formed *via* the oxidation of glycine esters and dioxane by a bromine radical.⁷¹

The utility of the DOD strategy was further established by the Huo group. They successfully exploited a $\text{Cu(II)}/\text{DDQ}/\text{O}_2$ system-catalyzed DOD tandem reaction of readily available



Scheme 40



Scheme 41

glycine derivatives and ethylbenzenes in 2018.⁷² The mechanism study revealed that the active imines and styrenes were obtained through the oxidation of Cu(II)/O₂ and DDQ respectively. Then the Cu(II)-promoted [4 + 2] Povarov reaction and the following oxidative aromatization occurred to achieve the quinolone derivatives (Scheme 42).

Quinoline derivatives bearing a quaternary carbon center exhibit excellent bioactivities. In 2019, the Huo group disclosed a Cu(II)/DDQ/O₂-catalyzed cascade reaction of *N*-arylglycine derivatives with cumene derivatives for the synthesis of substituted 3,4-dihydroquinoline-3-one derivatives (Scheme 43).⁷³

2.2.2. Oxidative dehydrogenative [3 + 3]-annulation. The oxidative dehydrogenative [3 + 3]-annulation is another promising strategy for the construction of six-membered heterocyclic compounds. In 2016, the Han group developed a Cu(II)/TEMPO system catalyzed [3 + 3]-annulation of commercially available amidines and saturated ketones for the synthesis of pyrimidines.⁷⁴ The proposed mechanism showed that saturated ketones were oxidized to enones *via* oxidative dehydrogenation first, which then underwent intermolecular conjugate addition with amidines followed by intramolecular condensation and finally aromatization to produce the desired pyrimidines (Scheme 44).

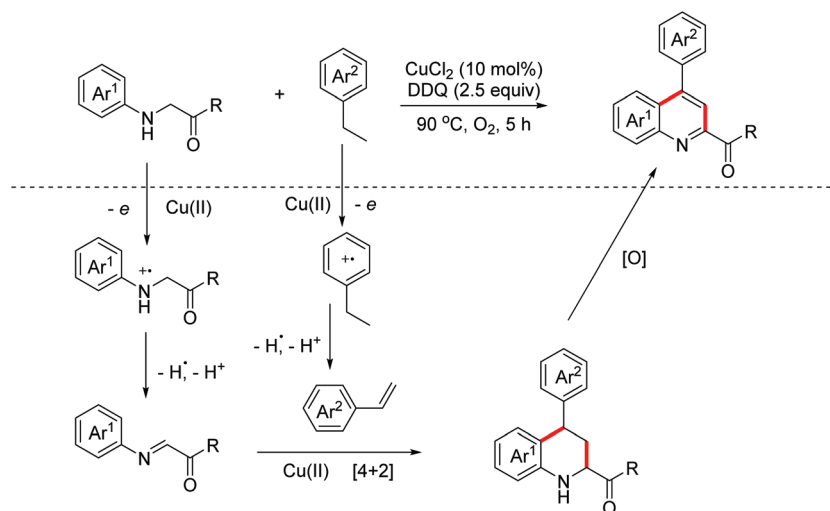
In 2017, the Fan group presented a Cu(II)-catalyzed one-pot cascade reaction of saturated ketones with electron-deficient

enamines for the synthesis of functionalized pyridines under an air atmosphere.⁷⁵ The oxidation of saturated ketones and the following Michael addition were involved in this transformation (Scheme 45).

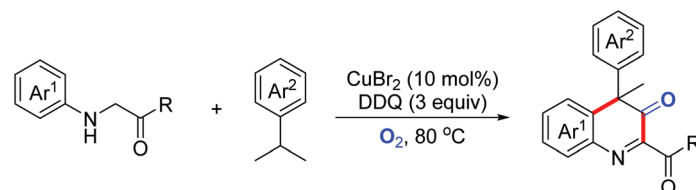
The oxidative dehydrogenative functionalization of C(sp³)-H for the construction C-C bonds is mainly focused on C(sp³)-H adjacent to heteroatoms other than C(sp²)-H bonds. In 2017, the Yan group employed 1,3-diarypropenes as substrates to achieve the syntheses of bio-active pyranonaphthoquinones through DDQ-promoted C(sp³)-H and C(sp²)-H functionalization.⁷⁶ In the key step, 1,3-diarypropenes were oxidized by DDQ through SET followed by dehydrogenation to generate allylic cations, which were then attacked by nucleophilic lawsones (Scheme 46).

In 2019, the Huo group developed an oxidative dehydrogenative formal [3 + 3]-annulation of benzylhydrazines with aziridines for the synthesis of highly functionalized tetrahydrotriazines.⁷⁷ The plausible mechanism is shown in Scheme 47. In the presence of Cu(OAc)₂ and O₂, benzylhydrazines were oxidized to deliver nucleophilic hydrazones. Subsequently, nucleophilic ring opening of aziridines with hydrazones occurred. Finally, intramolecular oxidative amination occurred to deliver the desired triazines (Scheme 47).

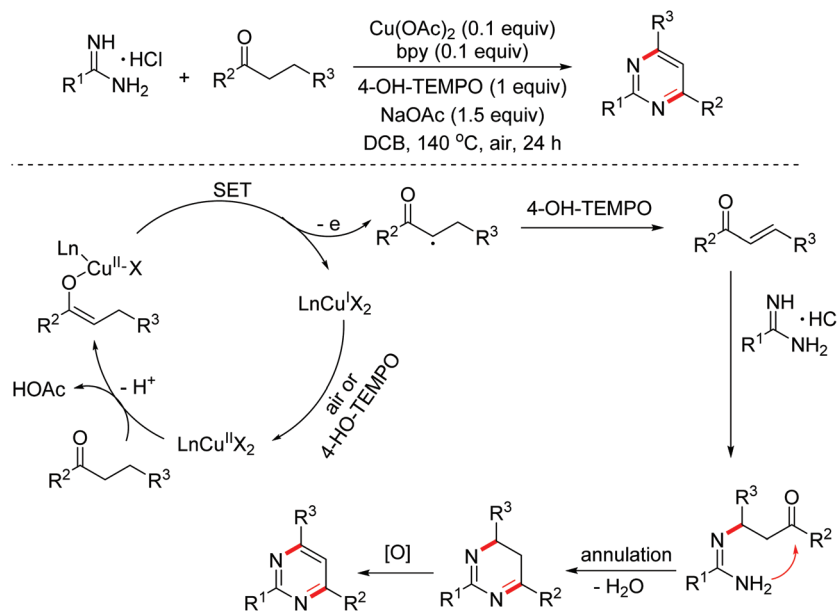
2.2.3. Other examples. Hantzsch esters, 1,4-dihydropyridine derivatives, are one of the most important heterocycles in biologically active and naturally occurring molecules. In 2014,



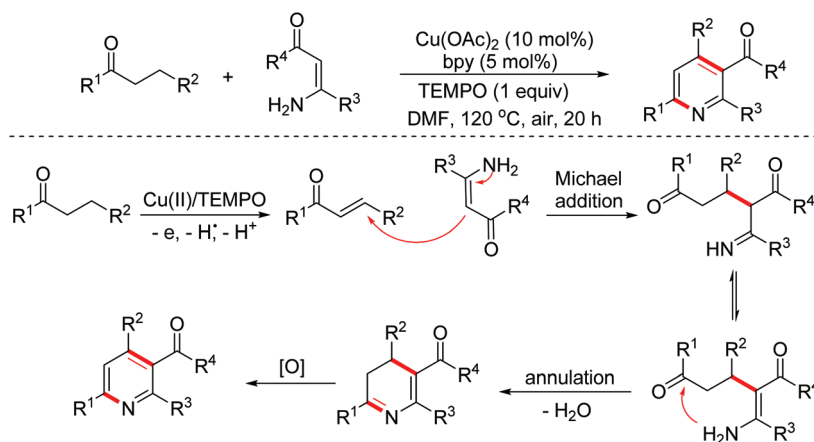
Scheme 42



Scheme 43



Scheme 44



Scheme 45

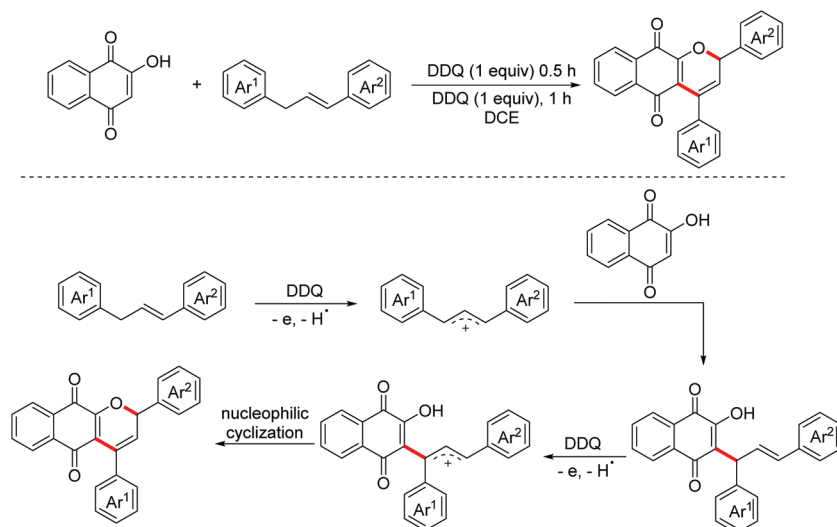
the Jia group reported a radical cation salt prompted cascade reaction between glycine derivatives and β -ketoesters for the construction of 1,4-dihydropyridines using the fragment-reassembly strategy (Scheme 48).⁷⁸ A radical pathway was proposed for this transformation. In 2016, the Le group reported a similar approach to access 1,4-dihydropyridine derivatives by a copper-catalyzed aerobic cascade oxidative coupling/cyclization.⁷⁹ Different from Jia's work, iminium intermediates were proposed as the key intermediates.

2.3. Construction of small rings

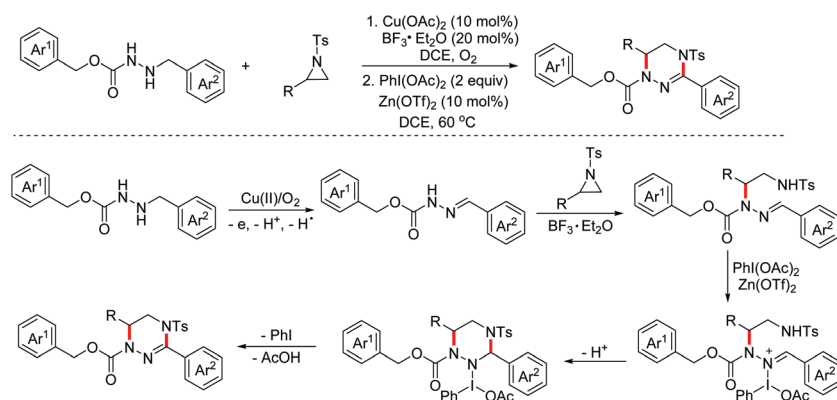
Cyclopropanes are useful building blocks that can undergo a variety of transformations for the preparation of pharmaceuticals and functional materials. The synthesis of this synthon

has evoked considerable interest and resulted in the development of different synthetic strategies. In 2015, the Antonchick group developed a copper-catalyzed direct oxidative cyclopropanation of electron-deficient alkenes with acetophenone derivatives (Scheme 49).⁸⁰

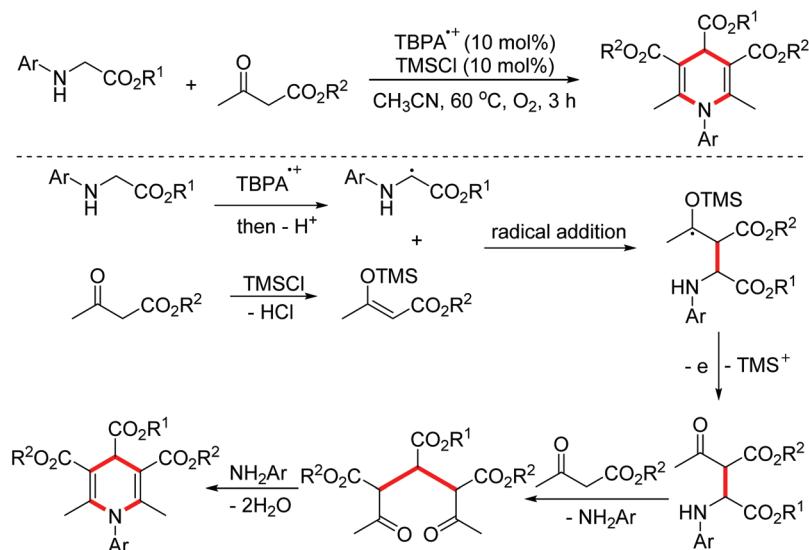
In 2018, the Li group developed an aziridination of substituted alkenes through electrochemical catalytic oxidation employing hexafluoroisopropanol sulfamate as the nucleophilic nitrogen source.⁸¹ A proposed mechanism for this reaction is shown in Scheme 50. The alkenes were oxidized by the anode to their radical cations first, which were then attacked by nucleophilic HfsNH_2 . The adducts underwent second anodic oxidation/intramolecular nucleophilic ring closure leading to the final products (Scheme 50).



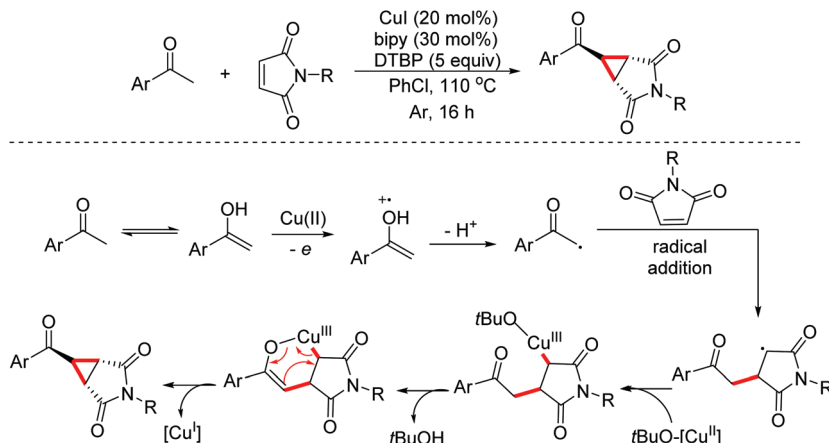
Scheme 46



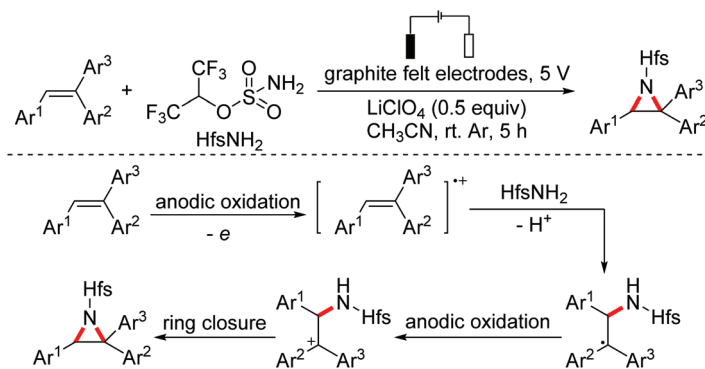
Scheme 47



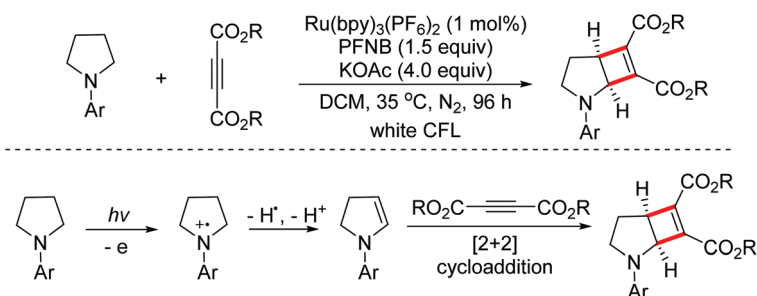
Scheme 48



Scheme 49



Scheme 50



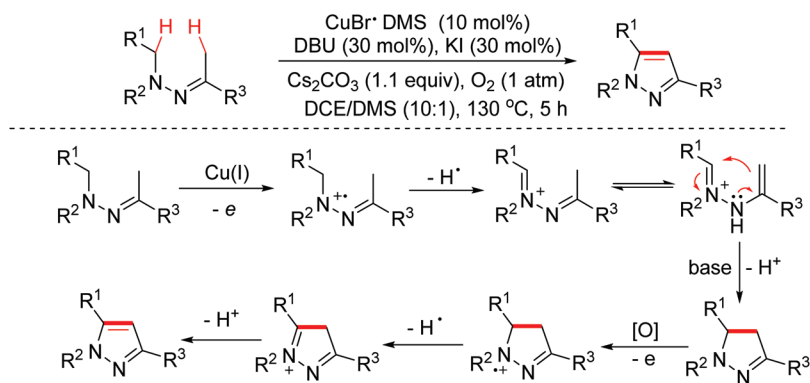
Scheme 51

In 2018, the Xu group developed a visible-light induced dehydrogenation/[2 + 2] cycloaddition sequence for the dual functionalization of two $\text{C}(\text{sp}^3)\text{-H}$ bonds to construct small strained cyclobutene skeletons.⁸² The mechanistic study proved that the elusive cyclic enamine intermediates were formed under these mild reaction conditions (Scheme 51).

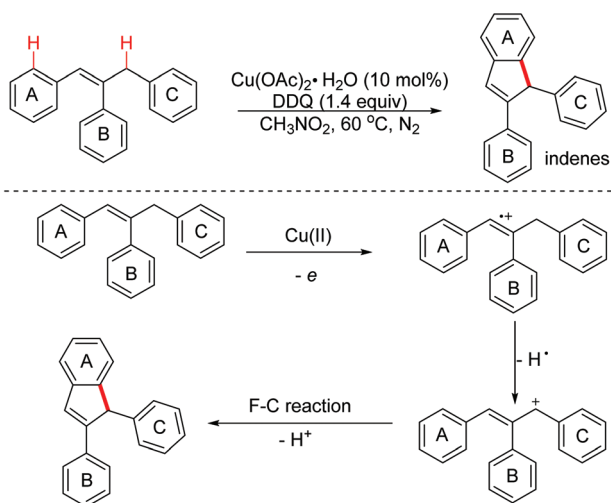
3. Intramolecular oxidative dehydrogenative cyclization

3.1. Construction of five-membered rings

3.1.1. C–C bond formation. Intermolecular one-electron oxidative dehydrogenative annulation has been extensively dis-



Scheme 52



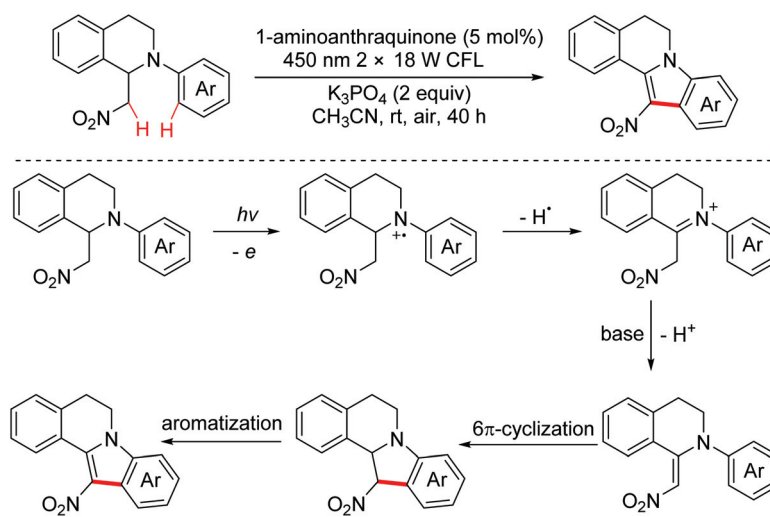
Scheme 53

cussed as mentioned above. Compared with intermolecular cases, the development of new methodologies for the formation of new C–C bonds in an intramolecular manner has also been realized recently.

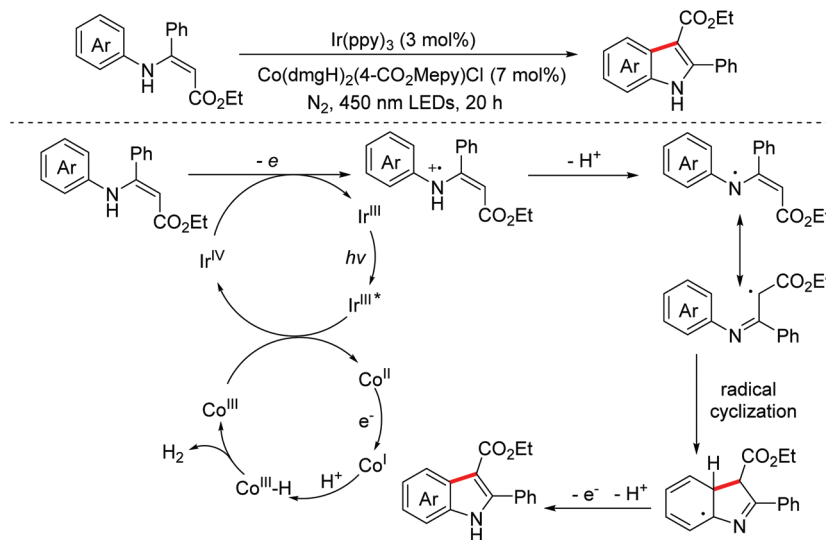
In 2013, the Ge group developed a copper-catalyzed aerobic intramolecular dehydrogenative cyclization reaction of *N,N*-disubstituted hydrazones through $\text{C}(\text{sp}^3)\text{--H}$ functionalization.⁸³ A possible mechanism was proposed that hydrazines were first oxidized to form iminium ions, which then underwent tautomerization to generate the corresponding enamines. Subsequently, intramolecular cyclization/aromatization occurred to deliver the pyrazole products (Scheme 52).

In 2014, the Deng group reported a $\text{Cu}(\text{II})/\text{DDQ}$ -promoted dehydrogenative intramolecular cyclization for the straightforward synthesis of indene derivatives from (*Z*)-1,2,3-triaryl propenes *via* OEO involved benzylic/allylic $\text{C}(\text{sp}^3)\text{--H}$ bond activation (Scheme 53).⁸⁴

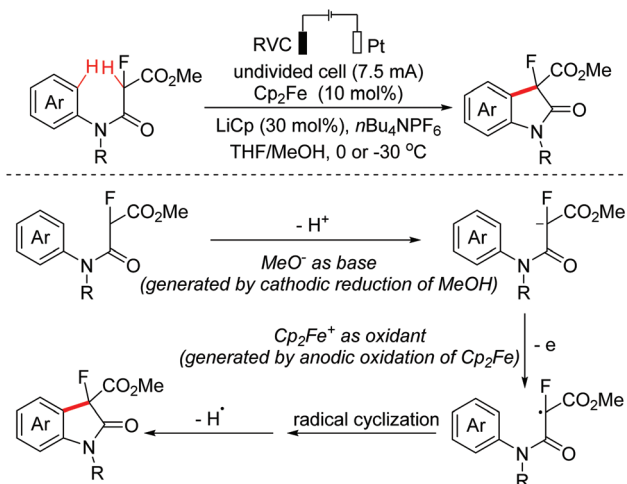
In 2015, the Brasholz group explored a visible light induced intramolecular dehydrogenative oxidation/ 6π -cyclization/oxidation cascade reaction to synthesize 12-nitroindoloisoquinolines from 2-aryltetrahydroisoquinolines (Scheme 54).⁸⁵



Scheme 54



Scheme 55



Scheme 56

In 2016, the Wu group described a synthetic strategy for the synthesis of highly substituted indoles *via* visible-light induced intramolecular C(sp²)-C(sp²) bond coupling of *N*-aryl enamines.⁸⁶ The transformation involved one-electron oxidation and the following deprotonation to generate the key radical intermediates (Scheme 55). In 2017, an electrocatalytic dehydrogenative annulation of *N*-aryl enamines was developed by the Lei group.⁸⁷

Oxindoles are omnipresent backbones for chemical and biological applications. In 2017, the Xu group developed an electrochemical intramolecular cross-coupling reaction of C(sp³)-H and C(sp²)-H bonds from malonate amides for the straightforward construction of C3-fluorinated oxindoles using Cp₂Fe as the redox catalyst.⁸⁸ Mechanism research showed that *in situ* generated MeO⁻ abstracted a proton of substrates

to deliver their conjugated bases, which then underwent the OEO process to form the key radical intermediates (Scheme 56). Afterwards, the group employed a similar method to achieve intramolecular C(sp³)-H/C(sp²)-H cross-coupling of 1,3-dicarbonyl compounds.⁸⁹

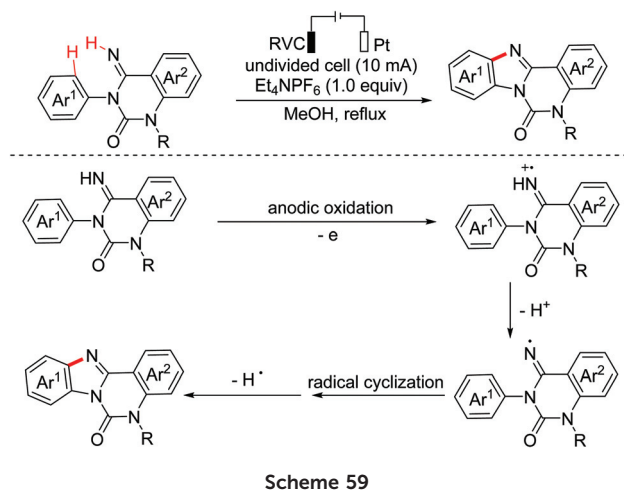
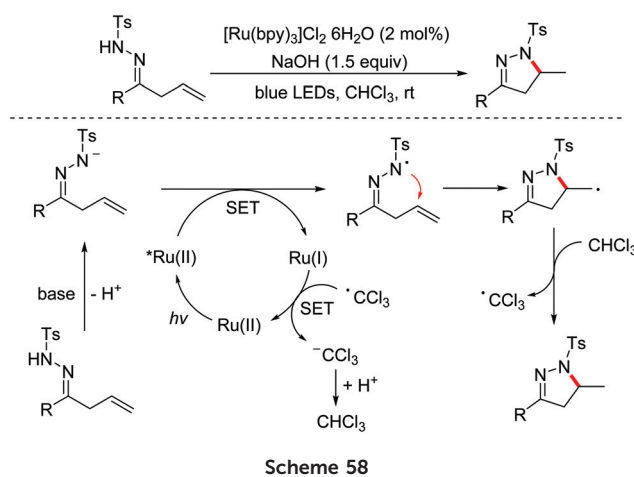
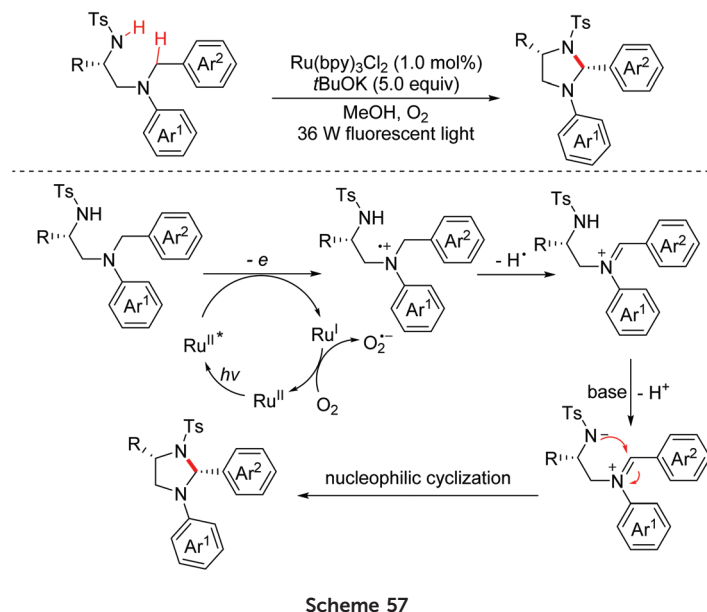
3.1.2. C-N bond formation. Construction of the C-N bond is always a powerful tool in organic synthetic chemistry. It is a straightforward way to synthesize nitrogen-containing compounds, which are ubiquitous motifs in medicinal and biological chemistry. Using *N*-centered radicals generated from *N*-H bond cleavage to directly form C-N bonds is an attractive approach in the synthetic community. In 2011, the Xiao group described an efficient strategy for the synthesis of highly substituted tetrahydroimidazole derivatives by means of visible-light induced intramolecular cyclization reactions of diamines.⁹⁰ In this process, iminium ions were formed under visible-light promoted aerobic conditions. Then an intramolecular nucleophilic cyclization occurred to deliver tetrahydroimidazoles (Scheme 57).

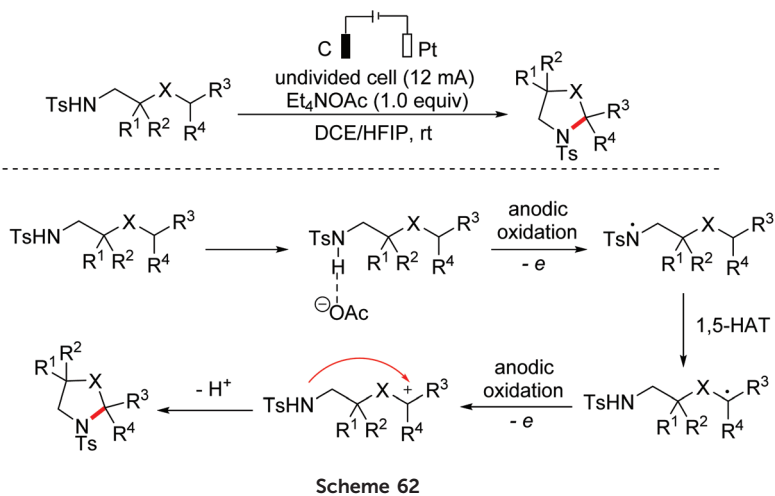
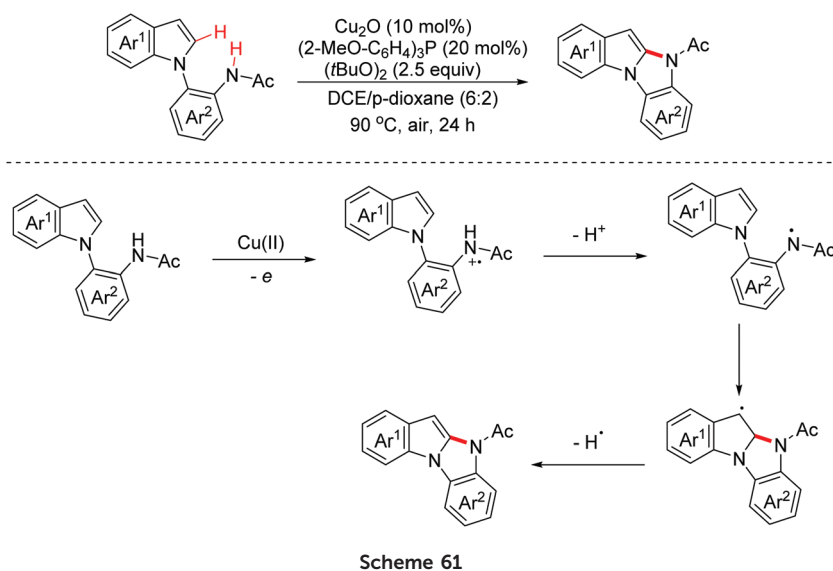
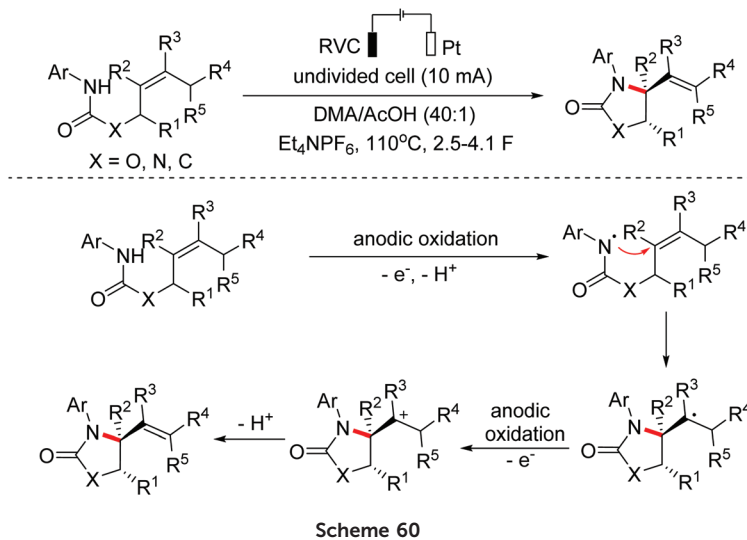
In 2014, the Xiao group disclosed a visible-light-catalyzed intramolecular cyclization of β,γ-unsaturated hydrazones to synthesize 4,5-dihydropyrazoles (Scheme 58).⁹¹

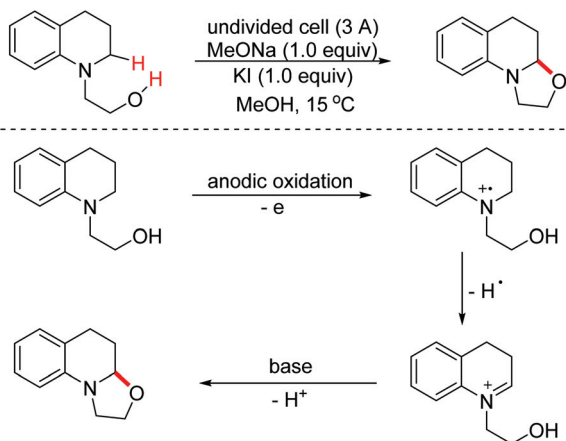
In 2017, the Xu group demonstrated an electrochemical oxidative cleavage of *N*-H bonds to generate amidinyl radicals, which then underwent intramolecular cyclization to afford a host of polycyclic benzimidazoles and pyridoimidazoles (Scheme 59).⁹²

In the same year, the Xu group also disclosed an electrochemical intramolecular oxidative amination reaction of tri- or tetrasubstituted alkenes to provide cyclic carbamates, ureas and lactams.⁹³ The mechanistic study revealed that a nitrogen-centered radical-initiated cyclization process was involved in the transformation (Scheme 60).

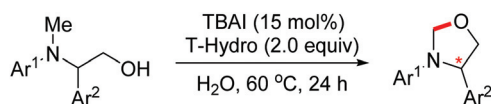
In 2017, the Rao group explored a copper-catalyzed intramolecular C-N coupling reaction for benzoimidazo[1,2-*a*]







Scheme 63



Scheme 64

indole formation. A one-electron oxidation initiated anilidyl radical pathway was proposed (Scheme 61).⁹⁴

In 2018, the Lei group reported an intramolecular electrooxidative cross-coupling reaction of the C(sp³)-H bond and the N-H bond of amides for the construction of pyrrolidines (Scheme 62).⁹⁵

3.1.3. C-O bond formation. Oxazolidines, relatively stable cyclic *N,O*-acetals, widely exist in many active natural products and possess widespread biological and pharmaceutical activities. Therefore, many synthetic methodologies have been explored to forge these ubiquitous scaffolds. Among them, the

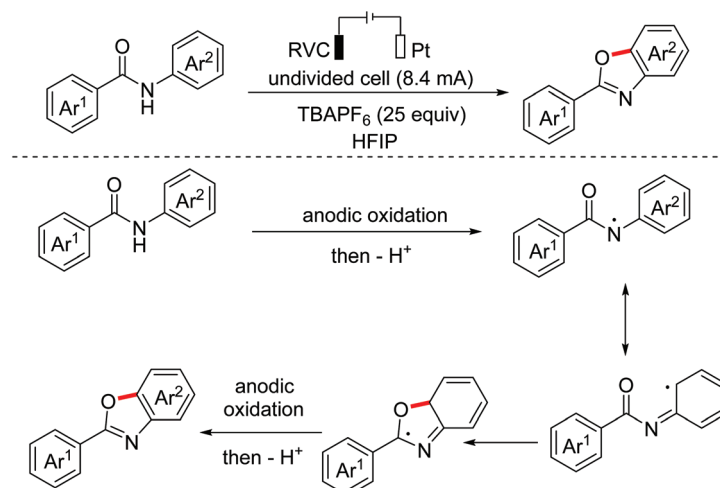
direct oxidative functionalization of a C(sp³)-H bond next to nitrogen with alkyl O-H to construct a new C-O bond is a straightforward route. In 2006, the Okimoto group developed an electrochemical oxidative intramolecular C-H/O-H cyclization reaction of hydroquinolyl/hydroisoquinolyl alcohols toward the synthesis of fused oxazolidine derivatives.⁹⁶ The key imine intermediates were formed first by one-electron oxidation and the following dehydrogenation, which were then attacked by the intramolecular hydroxyl group to complete the process (Scheme 63).

In 2016, the Punniyamurthy group described a TBAI/T-Hydro promoted oxidative cross-coupling reaction of *N*-alkyl C-H bonds with alkyl O-H and N-H bonds for the construction of functionalized oxazolidines and imidazolidines with high optical purity (Scheme 64).⁹⁷

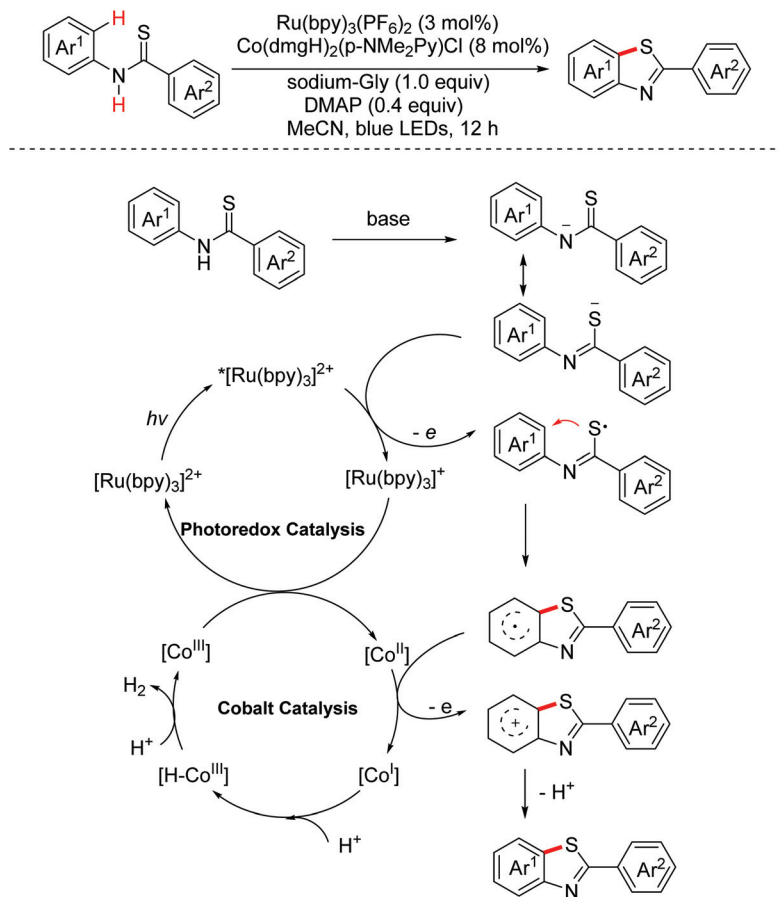
In 2017, the Waldvogel group developed an electrochemical intramolecular coupling of anilides for the synthesis of benzoxazoles *via* the key amidyl radical intermediates (Scheme 65).⁹⁸

3.1.4. C-S bond formation. As one of the most important carbon-heteroatom bonds in organic chemistry, C-S bonds ubiquitously exist in a large number of bioactive natural products with an extensive spectrum of pharmaceutical and biological activity. In 2015, Wu and Lei *et al.* developed a photoredox cobalt-catalyzed C-H functionalization/C-S bond formation reaction for the construction of benzothiazoles under external oxidant-free conditions.⁹⁹ The proposed mechanism involves the formation of the key sulfur-centered radical intermediates (Scheme 66).

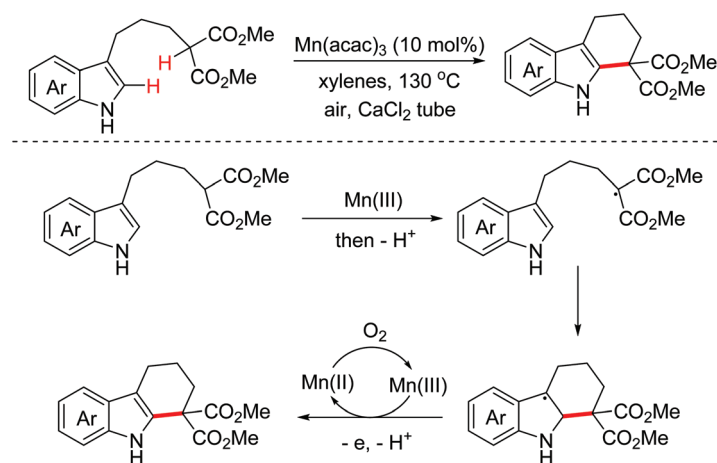
In 2017, Song and Xu *et al.* disclosed a TEMPO-catalyzed electrochemical C-H thiolation reaction for the synthesis of benzothiazoles and thiazolopyridines *via* the thioamidyl radical intermediate pathway.¹⁰⁰ In 2018, Wirth and Xu *et al.* explored the electrochemical dehydrogenative C-S bond formation in the continuous-flow method to produce thiazolopyridines *via* a similar procedure.¹⁰¹



Scheme 65



Scheme 66



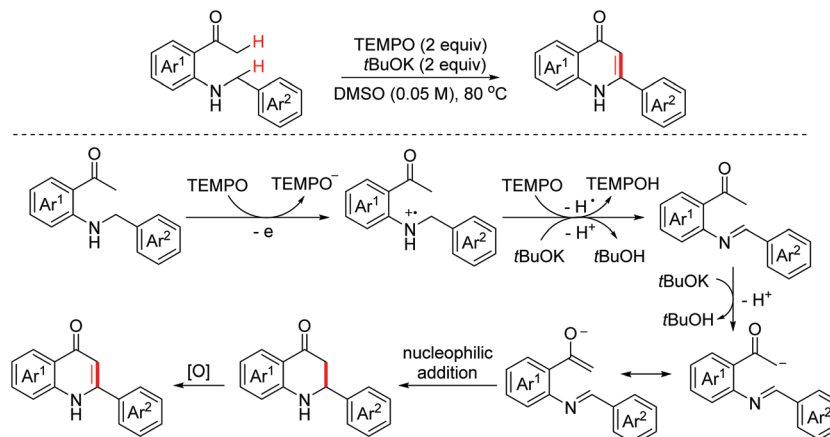
Scheme 67

3.2. Construction of six-membered rings

3.2.1. C–C bond formation. Dehydrogenative C–C bond formation by converting two C–H bonds to a C–C bond is an ideal process to construct six-membered heterocyclic skeletons. Indole alkaloids are prime substructures in bioactive natural

and medicinal products. The Kanai group developed a manganese(III)-catalyzed aerobic dehydrogenative intramolecular cyclization to produce ring-fused indole skeletons in 2013 (Scheme 67).¹⁰²

4-Quinolone scaffolds exist in numerous marketed drug molecules. In 2015, the Long group disclosed an oxidative



Scheme 68

intramolecular Mannich reaction of secondary amines with unmodified ketones through C(sp³)-H/C(sp³)-H coupling to form valuable 4-quinolones employing TEMPO as the oxidant and *t*BuOK as the base (Scheme 68).¹⁰³

In 2017, a CBr₄ promoted intramolecular aerobic oxidative dehydrogenative arylation of aldehydes for the synthesis of xanthenes and fluorenones was explored by the Huo group.¹⁰⁴ The reaction proceeded through a radical pathway (Scheme 69).

It is worth mentioning that the activation of a C-H bond next to an oxygen atom is more difficult than the activation of a C-H bond adjacent to a nitrogen atom owing to its relatively higher oxidation potential. In 2018, the Scheidt group reported a chiral Lewis acid-catalyzed enantioselective intramolecular cross-dehydrogenative coupling to access valuable tetrahydropyrans from unfunctionalized ethers (Scheme 70).¹⁰⁵

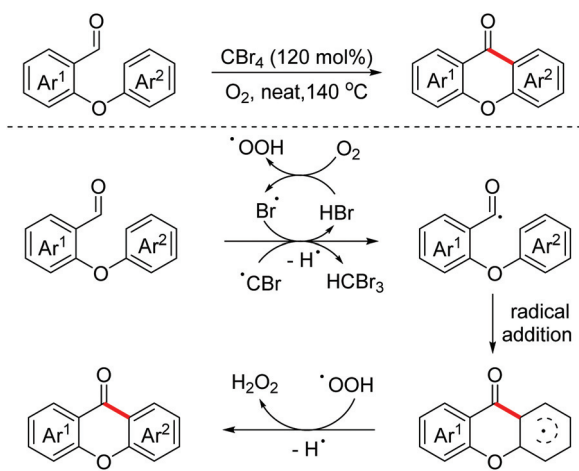
3.2.2. C-N bond formation. Ring-fused tetrahydroquinolines are structurally important units in various natural products. In 2013, the Toste group reported a chiral phosphate anion catalyzed enantioselective C-N bond forming reaction to

produce fused tetrahydroisoquinolines *via* intramolecular oxidative dehydrogenative coupling.¹⁰⁶ The formation of a tight chiral ion-pair of chiral phosphate anions and the cationic oxidant with the substrates is pivotal in the transformation (Scheme 71).

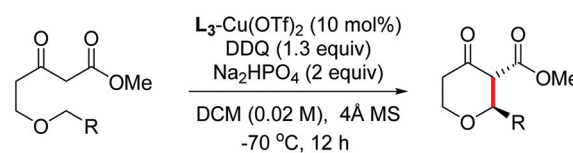
In 2014, the Huo group demonstrated a stable radical cation salt promoted intramolecular dehydrogenative coupling reaction to deliver ring-fused tetrahydroquinoline derivatives under mild conditions.¹⁰⁷ The OEO process was involved in the generation of the active iminium ion species (Scheme 72).

In 2017, the Xu group developed an electrochemical catalyzed C(sp²)-H/N-H cross-coupling of biaryl aldehydes to regioselectively synthesize fused pyridines employing NH₃ as a nitrogen donor.¹⁰⁸ A plausible mechanism proposed that aldimines were formed *in situ* from aldehyde substrates and NH₃, which then underwent anodic oxidation to generate the key aryl radical cation intermediates (Scheme 73).

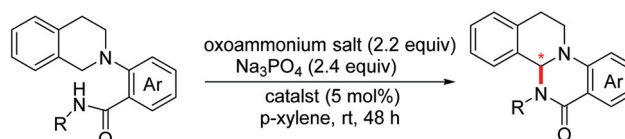
3.2.3. C-O bond formation. Oxygen-containing heterocycles are widely prevalent motifs in natural products and bioactive compounds, and therefore the development of efficient synthetic methods to construct them is highly desirable. Intramolecular electrochemical oxidative C-O bond formation



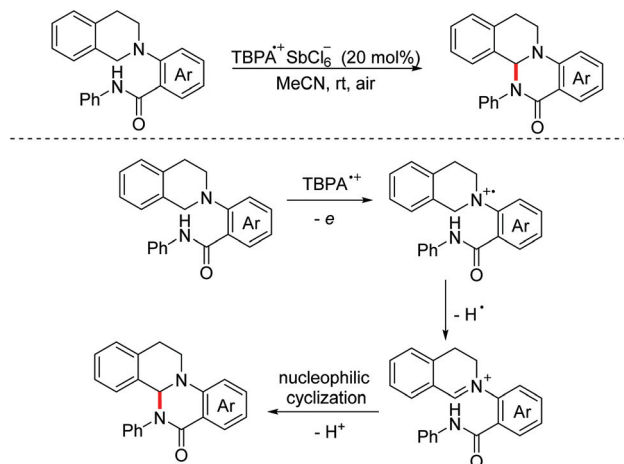
Scheme 69



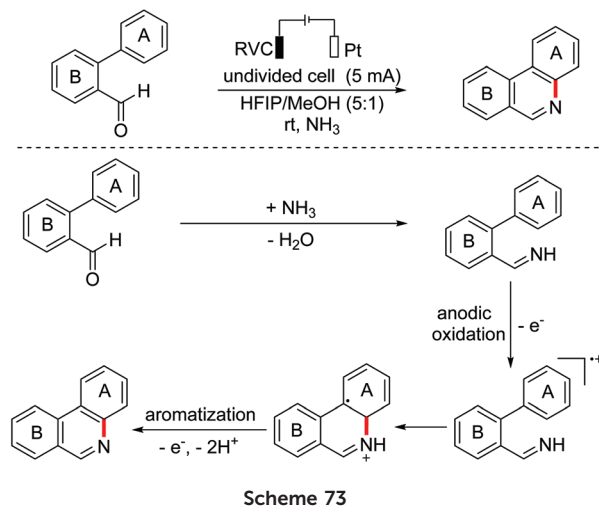
Scheme 70



Scheme 71



Scheme 72



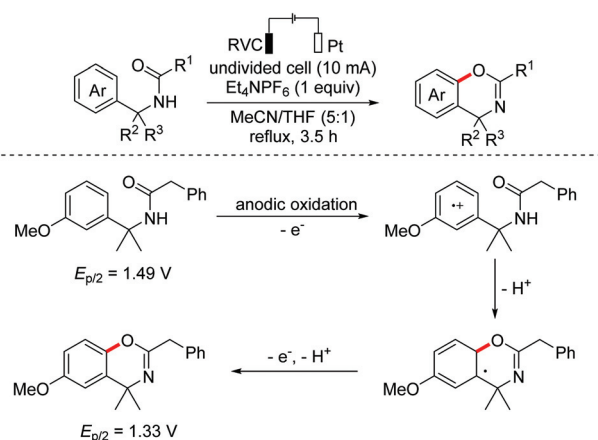
Scheme 73

has become a powerful tool nowadays. In 2017, the Xu group developed an intramolecular anodic dehydrogenative coupling of aromatic C–H bonds with amide groups for the synthesis of benzoxazines (Scheme 74).¹⁰⁹

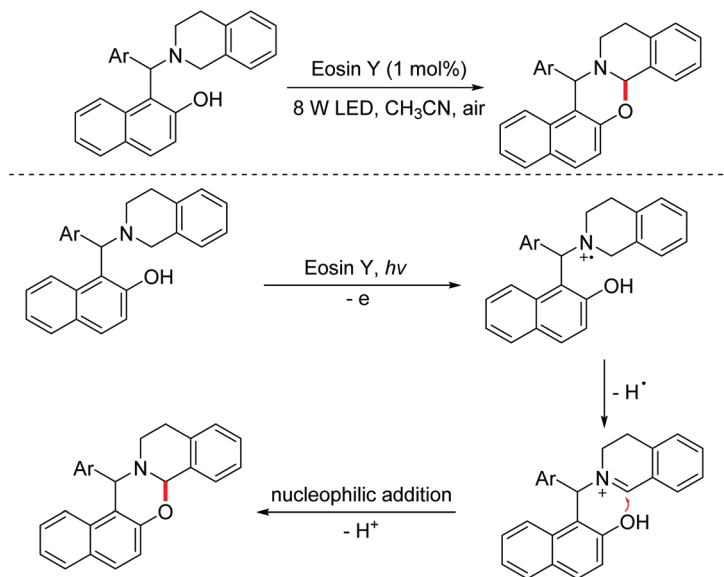
In 2017, the Baruah group disclosed a visible-light induced intramolecular cross-dehydrogenative coupling of 1-aminoalkyl-2-naphthols for the construction of 1,3-oxazines.¹¹⁰ Imine intermediates were involved in the transformation (Scheme 75).

In 2017, Gu and Wang *et al.* reported an I₂-catalyzed intramolecular dehydrogenative C(sp³)–H and O/N–H coupling reaction for the synthesis of substituted benzoxazinones (Scheme 76).¹¹¹

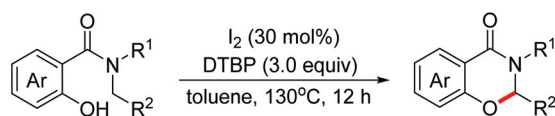
In 2018, an intramolecular anodic Kolbe oxidative/cyclization procedure of aryl phosphonic acid monoesters for the synthesis of ethoxy dibenzooxaphosphorin oxides was developed by the Mo group.¹¹² In the key step, aryl phosphonic acids underwent Kolbe oxidation through anodic oxidation to gene-



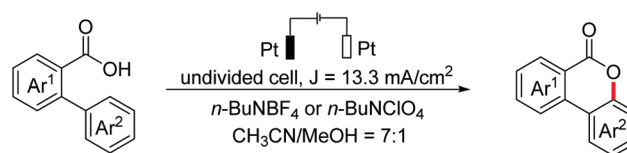
Scheme 74



Scheme 75



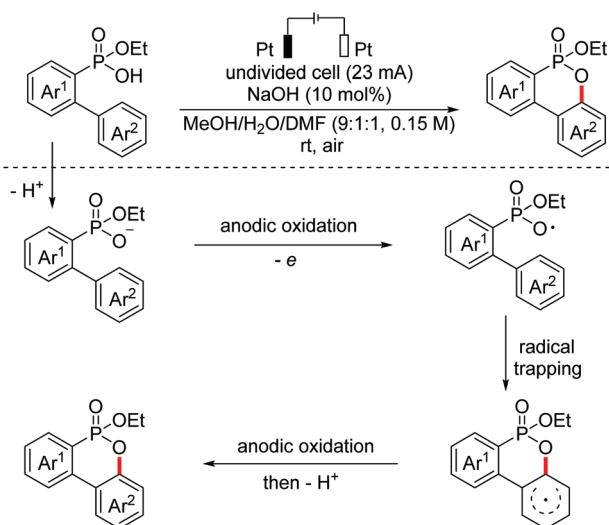
Scheme 76



Scheme 78

rate phosphonic acid radicals, which were then trapped by the intramolecular aromatic ring (Scheme 77). In the same year, the same research group reported a similar C(sp²)-H functionalization/C-O bond formation reaction to afford dibenzopyranones.¹¹³

In 2018, an electrochemical dehydrogenative lactonization reaction of 2-aryl carboxylic acids to construct benzo-3,4-coumarins was developed by the Zeng, Luo and Lei groups independently (Scheme 78).¹¹⁴ In 2020, the Yatham group reported a photocatalyzed version of this transformation.¹¹⁵

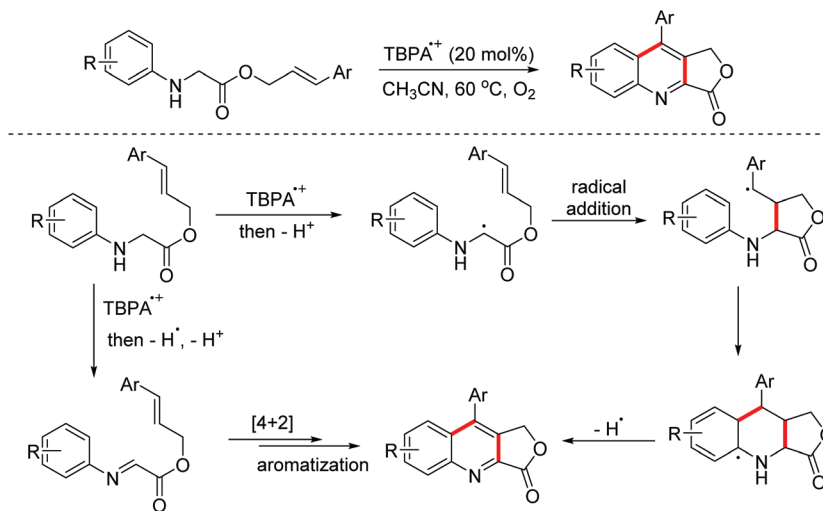


Scheme 77

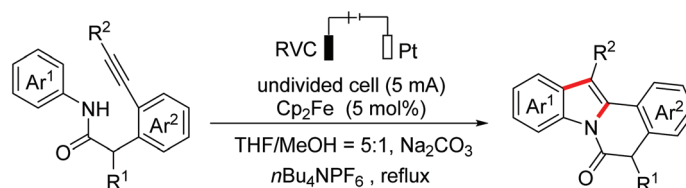
3.3. Construction of multiple rings

Polyheterocyclic compounds widely exist in natural and synthetic compounds. In 2015, the Jia group developed a radical cation salt promoted intramolecular C(sp³)-H bond oxidation of *N*-aryl glycine esters with amides for the construction of lactones and lactams (Scheme 79).¹¹⁶ In 2019, the Jia group employed the same strategy to achieve the synthesis of polyheterocycles containing dihydroquinoline skeletons.¹¹⁷

In 2016, Lu and Xu *et al.* developed an electrochemical cascade cyclization to synthesize indoles and azaindoles.¹¹⁸ The possible mechanism is presented in Scheme 80. The *in situ* generated MeO⁻ *via* cathodic reduction of methanol acted as a base to generate substrate anions, which then underwent the OEO process to afford nitrogen-centered radicals. Subsequently, cascade radical cyclization and the following aromatization occurred to complete the transformation. More applications of this cascade cyclization strategy were disclosed by the Xu group in 2017 and 2018.¹¹⁹



Scheme 79



Scheme 80

4. Conclusion

The OEO process involved cross-dehydrogenative coupling has emerged as a concise and straightforward synthetic methodology for the construction of new C–C/C–X bonds. As one of the important puzzles, remarkable and instructive advances have been made in the construction of useful ring compounds through one-electron oxidative dehydrogenative annulation and cyclization reactions. In this review, we outlined the recent exciting progress in this area.

Despite many oxidative dehydrogenative annulation and cyclization processes being achieved by OEO approaches, this area still includes great challenges. It is still highly desirable to explore new catalytic systems and new substrates to expand the scope of the OEO cross-dehydrogenative coupling process. The synthesis of heterocycles has been intensively studied recently in this area. However, the synthetic method of carbocyclic compounds is relatively rare. Considering the requirement of green and sustainable chemistry, the development of electricity or visible-light induced OEO processes might be desirable. Asymmetric catalysis has not been well studied in oxidative dehydrogenative annulation and cyclization reactions.

Conflicts of interest

There are no conflicts to declare.

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