

Recent advances in electrooxidative radical transformations of alkynes

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During the past few years, electrochemical oxidative reactions through radical intermediates have emerged as an environmentally-benign, powerful platform for the facile formation of C–E (E = C, N, S, Se, O and Hal) bonds through single-electron-transfer (SET) processes at the electrodes. Functionalized unsaturated molecules and unusual structural motifs can, for instance, be directly constructed under exceedingly mild reaction conditions through initial radical attack onto alkynes. This minireview highlights the recent advances in electrooxidation in radical reactions until June 2022, with a particular focus on radical additions onto alkynes.

electrosynthesis, electrooxidation, radicals, alkynes, additions, difunctionalization**Citation:** Zhang Y, Cai Z, Warratz S, Ma C, Ackermann L. Recent advances in electrooxidative radical transformations of alkynes. *Sci China Chem*, 2023, 66: 703–724, <https://doi.org/10.1007/s11426-022-1438-0>

1 Introduction

Alkynes are of major importance in various compounds of relevance to *inter alia* material sciences and chemical biology, while frequently being used as key intermediates in molecular syntheses [1–10]. The direct difunctionalization of alkynes represents an attractive approach for syntheses of multi-substituted alkenes, themselves representing important structural skeletons frequently found in natural products and biologically active molecules [11–13]. For the past two decades, the design of novel radical addition reactions onto unsaturated bonds has emerged as an increasingly powerful strategy to construct valuable molecular motifs [14–26], as this approach generally features mild reaction conditions, high functional group tolerance and allows for the use of a

diverse set of viable radical precursors. Among the reported procedures, visible light-promoted difunctionalization of alkenes or alkynes has been reviewed independently by Koike *et al.* [27], Lu *et al.* [28], and Gao *et al.* [29]. In contrast, Lin *et al.* [30], Varghese *et al.* [31] and Han *et al.* [32] summarized studies that focus on the electrochemical difunctionalization of alkenes. In contrast to radical addition onto alkenes, the use of alkynes continues to be underdeveloped and often challenging.

During the past decade, organic electrochemistry has been identified as a uniquely-effective tool for the generation of reactive radicals by electron and proton transfer taking place at the electrodes [33–43]. The robustness of the electrode material and modularity of the electrochemical approach set the stage for innovative redox reactions. Soluble redox mediators can be beneficial in case of inefficient direct electrolysis to enable a more efficient transfer of electrons between the electrode and the substrate (Figure 1) [44–49].

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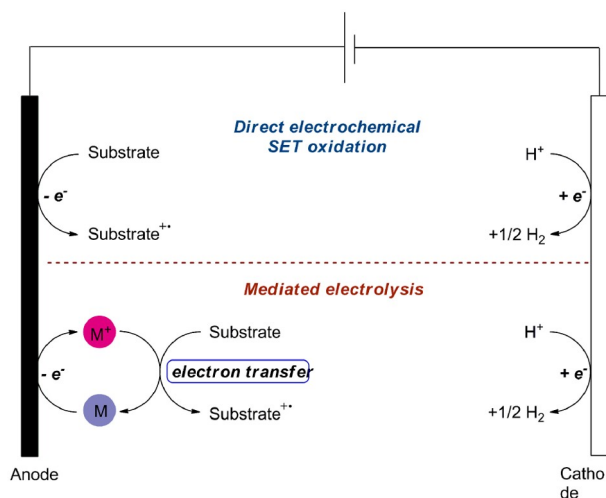


Figure 1 General representation for substrate SET anodic oxidation through direct or mediated electrolysis (color online).

In general, species with an oxidation potential lower than the applied potential, $E_{\text{ox}} < E_{\text{applied}}$, along with a suitable overpotential, will be oxidized in an anodic reaction. Meanwhile, species whose reduction potential is higher compared with the applied potential, $E_{\text{red}} > E_{\text{applied}}$, can thus be reduced in a cathodic reaction [44]. For clarity, the anode and cathode are depicted black and white, respectively within this review. The applied potential will, furthermore, determine the ratio of the reduced and oxidized form of a species in a reversible redox process. In case of constant current electrolysis (CCE) conditions, the concentration of oxidized species increases when the applied potential increases. The right amount of applied current is crucial to create the right concentration of reactive intermediates, otherwise undesired side reactions or no reactivity could be resulting [46]. While electrosynthesis offers huge potential for an ideal resource economy [50–52], key challenges remain. The occasional use of hazardous electrolytes as additives to improve conductivity as well as non-sustainable, toxic solvents inherently reduces the overall sustainability. Despite recent success [53,54] in this regard, thus far, many electrochemical syntheses continue to rely on solvents and additives which are classified as substances of high concern. Further improvement is often required regarding the selectivity of the radical formation, for instance, preventing the produced radical to undergo a second single-electron transfer (SET) at the electrode interface, thus generating the corresponding ionic species. Addressing these challenges for electrochemical radical reactions is required to unleash the full potential towards truly resource-economic, sustainable methods for environmentally-friendly industrial processes [49,55].

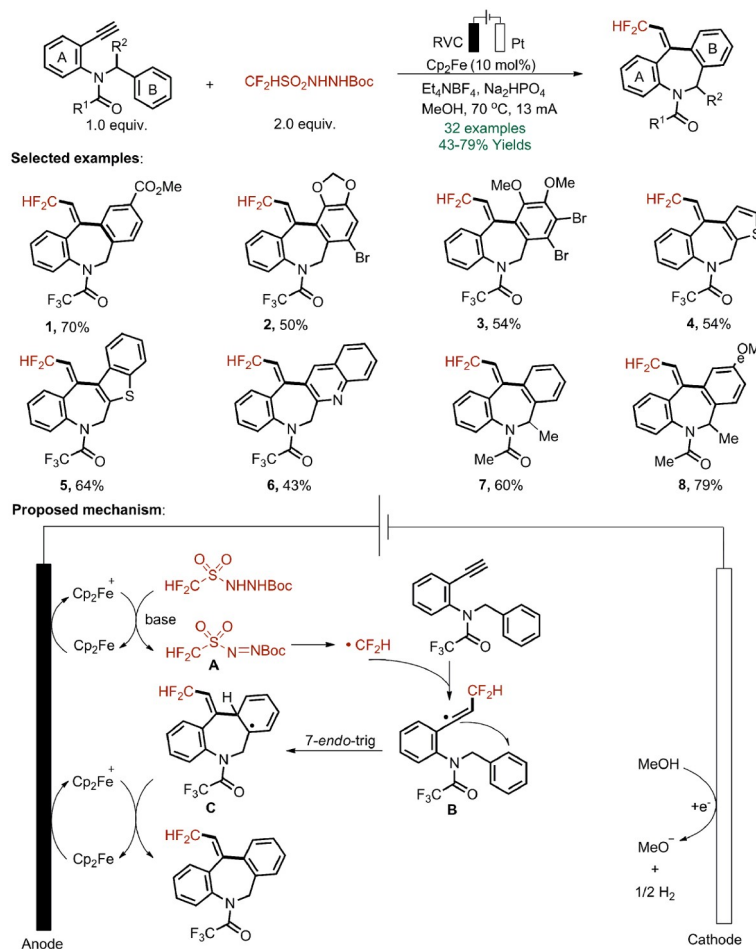
We, herein, provide an overview of recent oxidative electrochemical radical addition reactions onto alkynes, in which useful free radical intermediates are generated at the electrode materials through a SET process. While the di-

functionalization of alkynes through electroreductive [56,57] and electrooxidations *via* SET of alkynes [58] are beyond the scope of this review, we herein focus on recent electrooxidative alkyne difunctionalizations. Earlier examples have been summarized elsewhere [59]. The reactions are mainly categorized into four types according to the different chemical environment of the radical addition to the C–C triple bond: (1) intermolecular radical additions onto terminal alkynes; (2) intermolecular additions onto internal alkynes; (3) intramolecular additions onto alkynes; and (4) intramolecular radical ene-yne cascade reactions.

2 Electrochemical intermolecular radical addition onto terminal alkynes

Anodic oxidation reactions have been proven to be an efficient approach for exploring and developing novel synthetic transformations through the formation of reactive radical species to construct new chemical bonds [60–67]. In a recent example, Xu *et al.* [68] reported on the electrochemical difluoromethylation of alkynes (Scheme 1). Key to success was the difluoromethylation reagent, $\text{CF}_2\text{HSO}_2\text{NHNHBoc}$. This air-stable, solid reagent can be prepared in one step from the commercially available reagents $\text{CF}_2\text{HSO}_2\text{Cl}$ and NH_2NHBoc . Based on their studies about ferrocene-mediated electrochemical N–H activation to generate amidyl radicals [69], ferrocene was exploited as redox mediator. Thus, ferrocene proved to be an efficient mediator and promoted the oxidation and subsequent alkyne functionalization of this difluoromethylation reagent in an undivided cell equipped with a reticulated vitreous carbon (RVC) anode and a Pt cathode. The electrolytic process begins with the anodic oxidation of Cp_2Fe (Cp = cyclopentadienyl) that gives Cp_2Fe^+ . In the meanwhile, MeOH is deprotonated and H^+ reduced at the cathode to generate H_2 and MeO^- . $\text{CF}_2\text{H}\cdot$ is generated from the decomposition of **A** which is generated by Cp_2Fe^+ oxidation of the conjugate base of $\text{CF}_2\text{HSO}_2\text{NHNHBoc}$ through proton-coupled electron transfer (PCET). An amide substrate bearing a terminal alkyne moiety reacts with $\text{CF}_2\text{H}\cdot$ to furnish the vinyl radical **B**, which participates in a challenging 7-membered ring-forming step to form the radical intermediate **C**. Finally, rearomatization of **C** through PCET affords the dibenzazepine product. The reaction tolerated a variety of substituents with diverse electronic properties at all positions of ring B (**1-1-1-3**), which could also be an aromatic heterocycle, such as thiophene, pyridine and quinoline (**1-4-1-6**), while a substituted phenyl or pyridine ring proved suitable for ring A (**1-7** and **1-8**).

In 2020, Huang *et al.* [70] disclosed an electrochemical oxidative oxydihalogenation protocol using CHCl_3 , CH_2Cl_2 , $\text{ClCH}_2\text{CH}_2\text{Cl}$, and CH_2Br_2 as the halogen source to access α ,



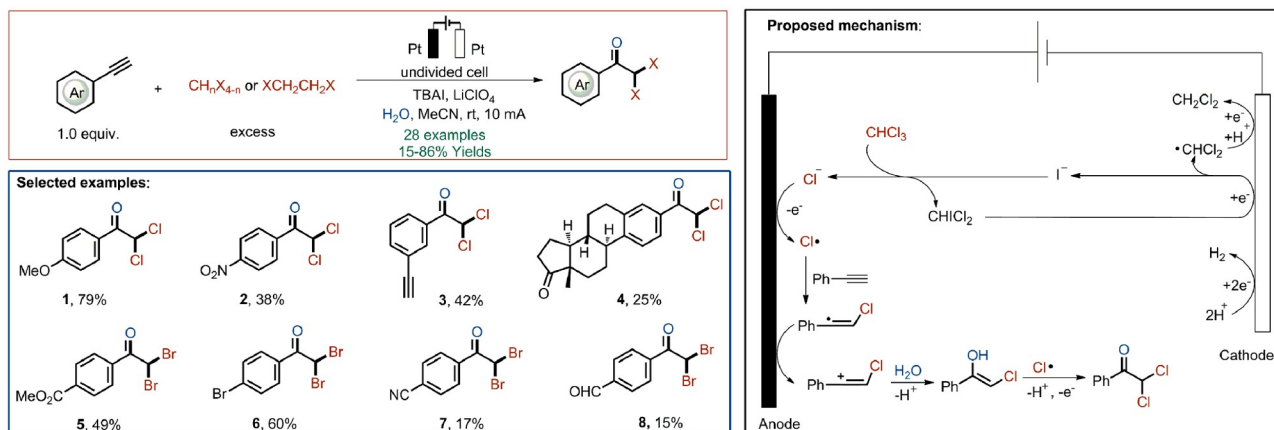
Scheme 1 Electrochemical difluoromethylarylation of alkynes [68] (color online).

α -dihaloketones at ambient temperature (Scheme 2). The reaction was conducted under constant current electrolysis at 10 mA in the presence of a terminal alkyne (0.3 mmol, 1.0 equiv.), tetrabutylammonium iodide (TBAI, 0.8 equiv.), LiClO_4 (1.0 equiv.), and H_2O (2.0 equiv.), in $\text{MeCN}/\text{CH}_2\text{X}_{4-n}$ (9.2 mL/0.8 mL) at ambient temperature. Generally, alkynes with electron-rich arenes exhibited a higher reactivity (2.1) than electron-deficient substrates (2.2 and 2.7). Moreover, internal alkynes were also found as suitable candidates for the oxydichlorination and gave the expected α,α -dichloroketones in somewhat lower yields. Radical trapping reactions indicate that radical intermediates are likely involved in this oxydichlorination process. Cyclic voltammetry (CV) studies unravelled a reduction peak of CHCl_3 at -0.94 V (vs. Ag/AgCl). However, a lower reduction potential at -0.75 V (vs. Ag/AgCl) was observed in the presence of TBAI and CHCl_3 . The authors assumed that the $\text{S}_{\text{N}}2$ iodination of CHCl_3 with TBAI forms ICHCl_2 , which was subsequently reduced at the cathode to generate iodide and $\cdot\text{CHCl}_2$. Therefore, the mechanism was proposed to commence with nucleophilic substitution of CHCl_3 with iodide, generating a chloride ion. This chloride ion is subsequently

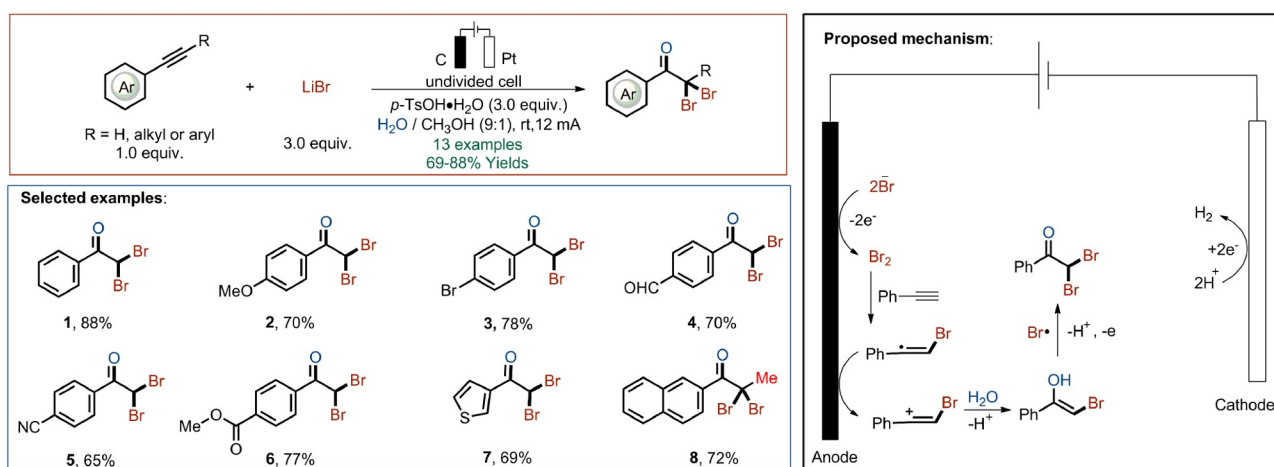
oxidized at the anode to give a chlorine radical, which participates in the addition reaction to alkynes.

Inspired by this work, Lei in collaboration with Zhang [71] published a greener method for the transformation from alkynes to α,α -dibromoaryl ketones (Scheme 3). The solvent mixture of $\text{H}_2\text{O}/\text{MeOH}$ (9:1) was hence found to be more efficient for this reaction. It is noteworthy that the addition of *p*-toluenesulfonic acid monohydrate was beneficial. Remarkably, both terminal (3-1–3-7) and internal arylalkynes (3-8) were found to be compatible with this protocol. In the reaction process, LiBr acts as both, the bromine source and as the supporting electrolyte to adjust the conductivity. A bromine radical is generated through the oxidation of bromide at the anode.

In 2020, Xu and Chen *et al.* [72] described a three-component electrochemical oxidative selenosulfonylation of alkynes for the preparation of difunctionalized alkenes (Scheme 4). Optimal conditions were identified with a constant current of 12 mA in an undivided cell using graphite (C) as the anode and Pt plate as the cathode. MeCN was found to be the ideal solvent for this transformation with Bu_4NBF_4 as the supporting electrolyte. CV studies indicated



Scheme 2 Electrochemical oxidative oxydihalogenation of alkynes [70] (color online).



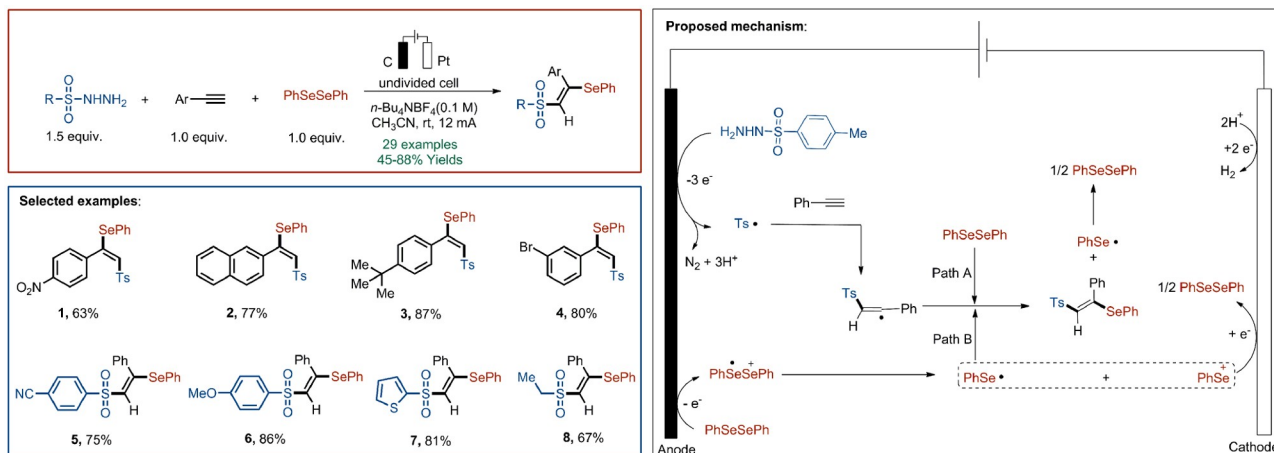
Scheme 3 Electrooxidative functionalization of alkynes for the synthesis of α,α -dibromoaryl ketones [71] (color online).

that the *p*-toluenesulfonyl hydrazide component ($E_{p/2} = 1.37$ V vs. Ag/AgCl) is easier oxidized to the corresponding radical cation than is the diphenyl diselenide ($E_{p/2} = 1.64$ V vs. Ag/AgCl). A reversible reduction peak at 0.13 V assigned to phenyl selenol radical to phenyl selenol cation was also observed, while phenylacetylene is electrochemically inert within the potential window investigated. The authors suggested that there are two possible reaction pathways for the formation of difunctionalized alkenes. While a radical cross-coupling reaction is involved in path B, the product is formed through an atom transfer reaction with diphenyl diselenide within path A.

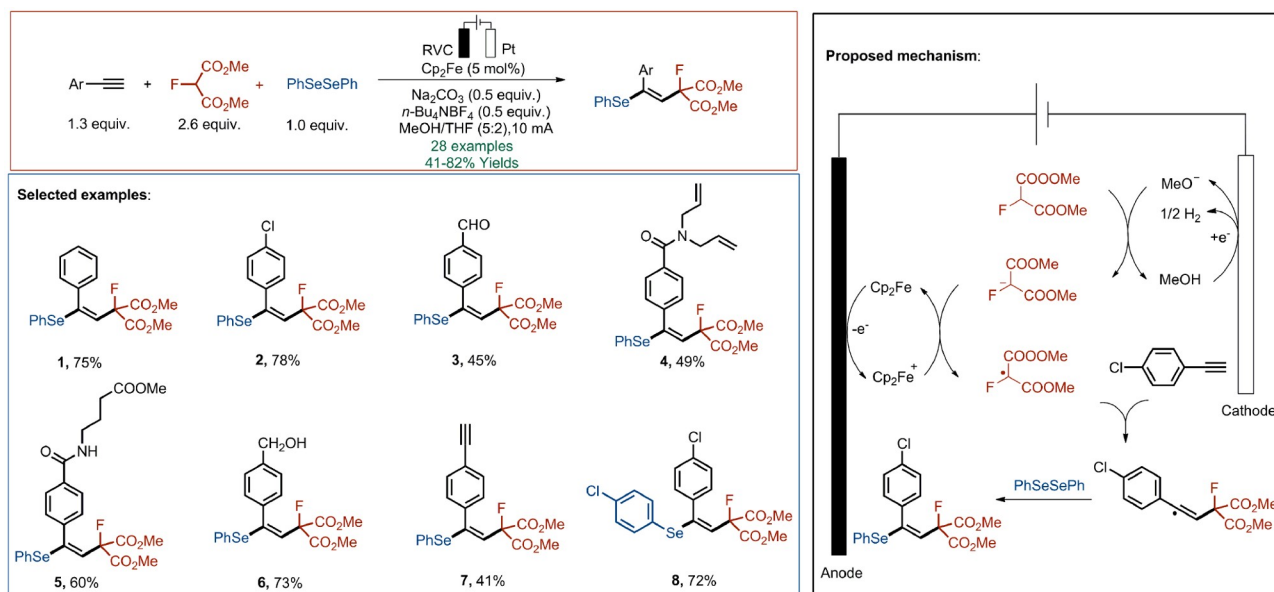
Very recently, Wang and co-workers [73] disclosed a protocol for the electrochemical seleno(monofluoro)alkylation of terminal alkynes with 1,3-dicarbonyl compounds and diselenides (Scheme 5). Optimal conditions comprise constant current electrolysis of alkynes, dimethyl 2-fluoromalonate and diphenyl diselenide in MeOH/tetrahydrofuran (THF) (5:2) in an undivided electrochemical cell equipped with an RVC anode and a Pt cathode at 65 °C

using Cp_2Fe as catalytic mediator. The authors reported 28 examples of selenomonofluoroalkylation in 41%–82% yields. Phenylacetylenes bearing various sensitive functional groups including carboxylate (5-5), terminal alkene (5-7), amide (5-4), as well as benzylalcohol (5-6) were well tolerated to give the corresponding tri-substituted alkenes. CV experiments were carried out to better understand the mechanism of this reaction [74]. These results suggested that effective PCET occurred between Cp_2Fe^+ produced through anodic oxidation of Cp_2Fe ($E_{p/2} = 0.46$ V vs. Ag/AgCl) and the conjugate base of dimethyl 2-fluoromalonate ($E_{p/2} = 0.45$ V vs. Ag/AgCl) rather than the direct oxidation ($E_{p/2} = 1.21$ V vs. Ag/AgCl), 1-chloro-4-ethynylbenzene ($E_{p/2} = 1.43$ V vs. Ag/AgCl) and diphenyldiselenide ($E_{p/2} = 1.49$ V vs. Ag/AgCl). Presumably, Cp_2Fe acts as a redox mediator in this electrochemical process with the assistance of a base for PCET. At the cathode, the reduction of protons forms H_2 .

The generation of a $C(sp^3)$ -radical by SET to β -ketoesters was exploited by the Lei group [75]. Thus, they developed an electrochemical difunctionalization of terminal alkynes to



Scheme 4 Electrooxidative difunctionalization of alkynes with sulfonyl hydrazides [72] (color online).



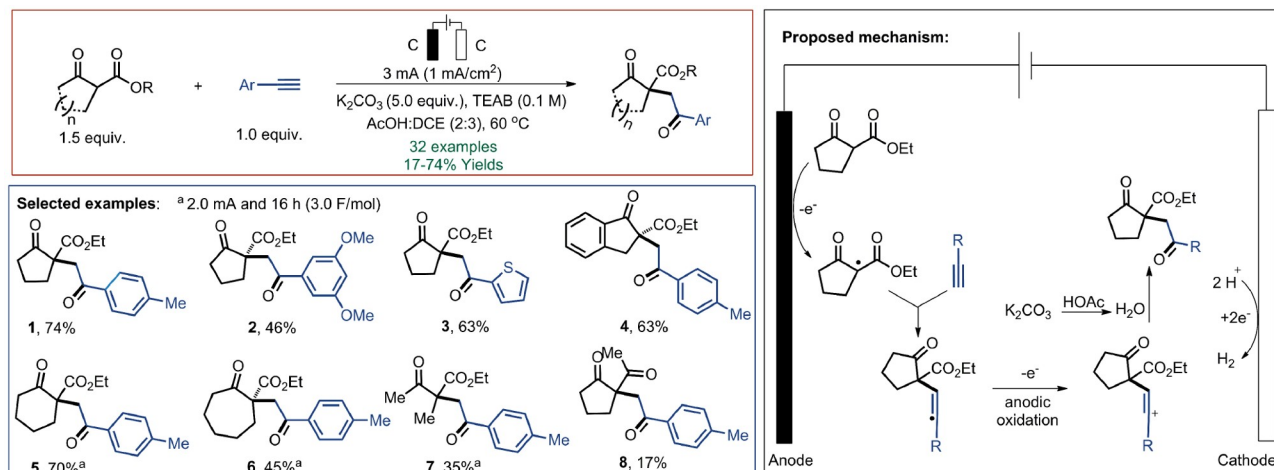
Scheme 5 Electrochemical selenoalkylation of alkynes with 1,3-dicarbonyl compounds [73] (color online).

construct 1,4-dicarbonyl compounds (Scheme 6). The generality of the difunctionalization was tested, and the oxidation-sensitive thienyl group was tolerated in this electrochemical functionalization (6-3). For cyclic β -ketoesters with a six- or seven-membered ring, moderate yields of the desired products were obtained (6-5, 6-6). However, non-cyclic β -ketoesters and 2-acetylcyclopentanone could only provide dissatisfactory yields (6-7, 6-8). CV experiments featured one oxidation peak at 1.23 V (vs. Ag/AgCl) and a broad peak at 1.24 V (vs. Ag/AgCl) for Et₄NBr (TEAB) and ethyl 2-oxocyclopentane-1-carboxylate, respectively. Mechanistic studies indicated a radical process to be operative, in which Br⁻ can promote the oxidation of β -ketoesters but is not necessarily required.

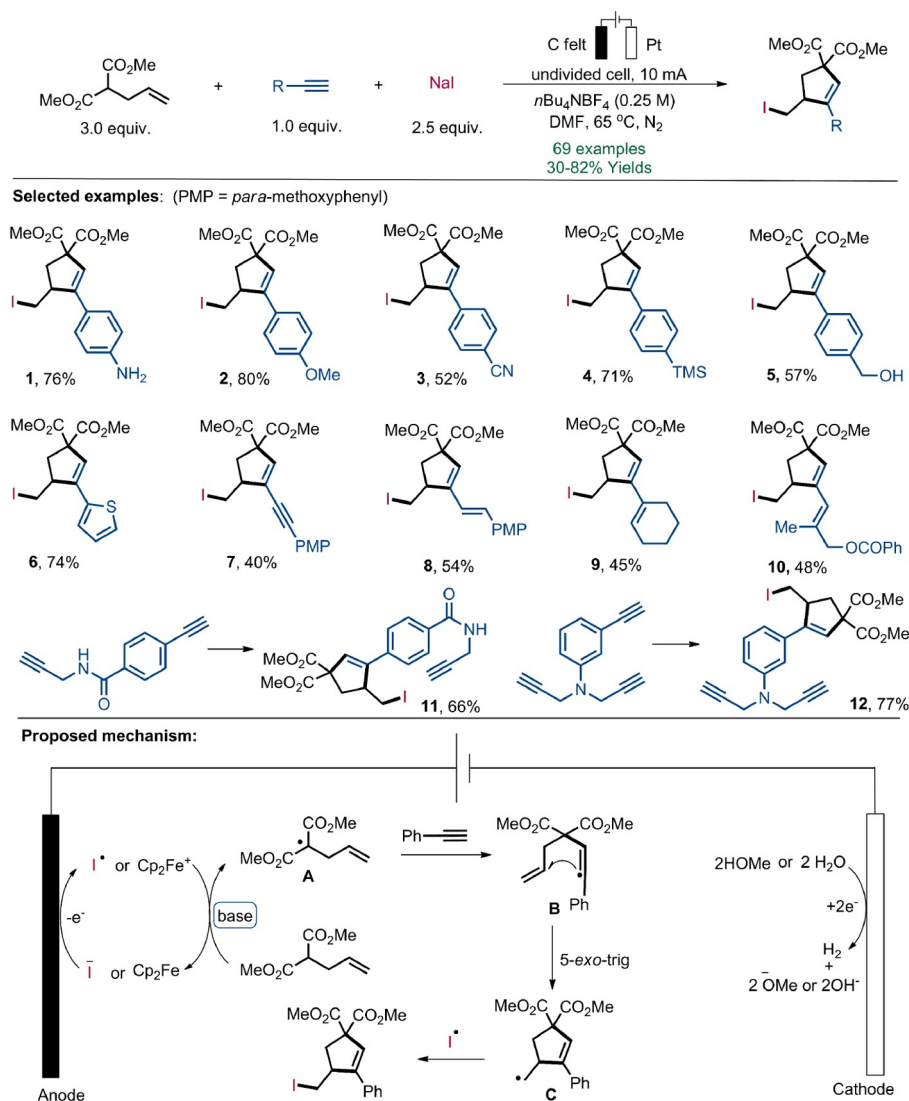
Based on this method, Lei, Huang and co-workers [76]

subsequently reported on an electrochemical mediator-induced intermolecular three component reaction to access cyclopentene derivatives (Scheme 7). In general, the reaction was not sensitive to electronic effects and steric hindrance. It is worth nothing that this electrooxidative annulation featured high site-selectivity, proceeding precisely at the aryl-alkyne sites (7-11, 7-12). A preliminary mechanistic investigation was performed, which indicated an iodine and carbon radical to be involved in the tandem reaction. Hence, the alkyl radical A, generated by anodic oxidation of dimethyl 2-allylmalonate in the presence of NaI or Cp₂Fe, is suggested as the reactive species to mediate the annulation.

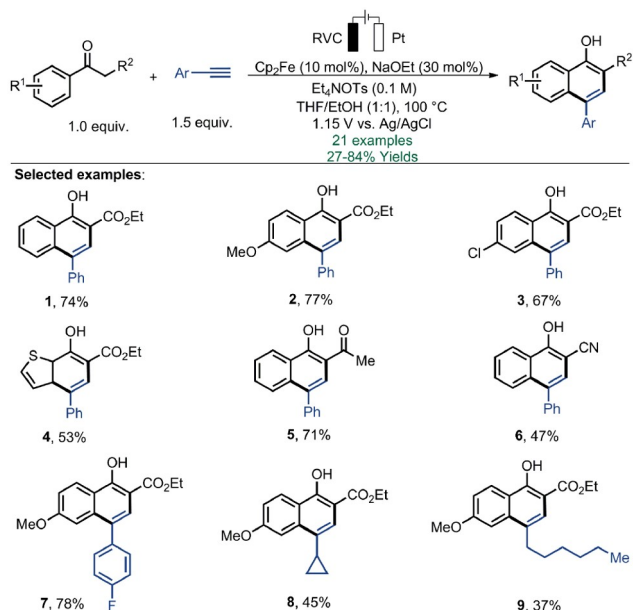
Pan and Tang developed an intermolecular [4+2] cyclization to construct 1-naphthols by means of electrolysis (Scheme 8) [77]. Key to success was the formation of the



Scheme 6 Electrooxidative difunctionalization of terminal alkynes: Access to 1,4-dicarbonyl compounds [75] (color online).



Scheme 7 Electrooxidative intermolecular [3+2] annulation for the synthesis of cyclopentene derivatives [76] (color online).



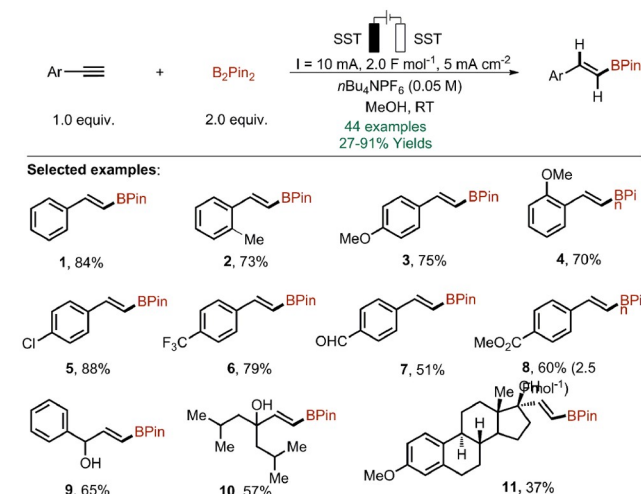
Scheme 8 Electrooxidative synthesis of 1-naphthols through intermolecular [4+2] annulation [77] (color online).

conjugate base, which was oxidized by Cp_2Fe mediation through SET. While the oxidation potential of the conjugate base of the 1,3-dicarbonyl is slightly lower than Cp_2Fe ($E_{p/2} = 0.59 \text{ V vs. Ag/AgCl}$) and therefore compatible, the oxidation potential of Cp_2Fe and 1,3-dicarbonyl compounds show a wide gap, and are, hence, difficult to react with each other ($E_{p/2} = 0.64$ and $1.27 \text{ V vs. Ag/AgCl}$, respectively). Here, ethanol is reduced at the cathode to produce an ethanolate anion and H_2 by HER. It is worth noting that alkyl-substituted alkynes were found to be amenable as well to furnish the desired products **8-8**, **8-9** in moderate yields.

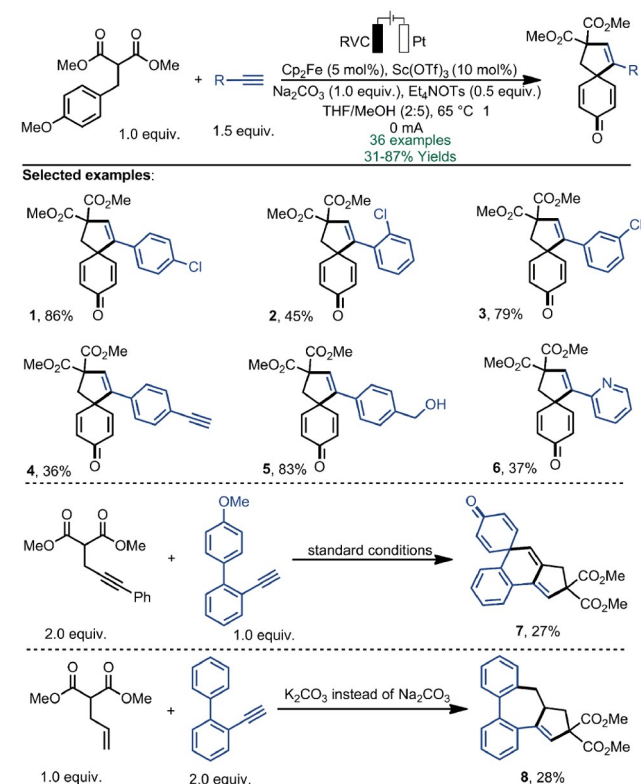
Poisson and co-workers [78] reported the electrochemical hydroboration of alkynes, exploiting B_2Pin_2 as the boron source (Scheme 9). The hydroboration relied on the electrochemical oxidation of an *in-situ* formed borate, allowing the formation of a putative boryl radical. As a model reaction, they chose phenylacetylene as the substrate and B_2Pin_2 as the boron source. Optimal conditions comprised MeOH as solvent with *n*- Bu_4NBF_4 as the electrolyte (0.05 M), stainless steel electrodes (SST) at both the cathode and anode along with a constant current of 10 mA, and a total charge of 2 F mol^{-1} under air. Thus, **9-1** was obtained in 84% yield. The authors corroborated their hypothesis that the boryl radical is formed through oxidation of an *in situ* formed borate through CV studies. Accordingly, the CV analysis of a $\text{B}_2\text{Pin}_2/\text{NaOMe}$ mixture exhibited an irreversible oxidation wave at 1.2 V vs. SCE , which was not observed on the CV measurement of sole B_2Pin_2 itself. The authors claimed that cathodic reduction of the solvent generates an alkoxide, which then donates electrons to the empty orbital of a boron atom of B_2Pin_2 and thus enables the formation of a boryl

radical through borate oxidation.

Recently, an electrochemical dearomatizing spirocyclization of alkynes with dimethyl 2-benzylmalonates was devised for the preparation of spiro[4.5]deca-trienones by Wang and Hou (Scheme 10) [79]. This approach also exploited Cp_2Fe as redox mediator in catalytic amounts to deliver a carbon-centered radical derived from the conjugate base of 1,3-dicarbonyl in a similar fashion as shown in the



Scheme 9 Electrooxidative hydroboration of alkynes [78] (color online).



Scheme 10 Electrochemical dearomatizing spirocyclization of alkynes with dimethyl 2-benzylmalonates to spiro[4.5]deca-trienones [79] (color online).

mechanism in [Scheme 7](#). Interestingly, by changing the substitution on the 1,3-dicarbonyl reagent, the authors observed that polycyclic compounds could be synthesized through intermolecular tandem cyclization (**11-7**, **11-8**).

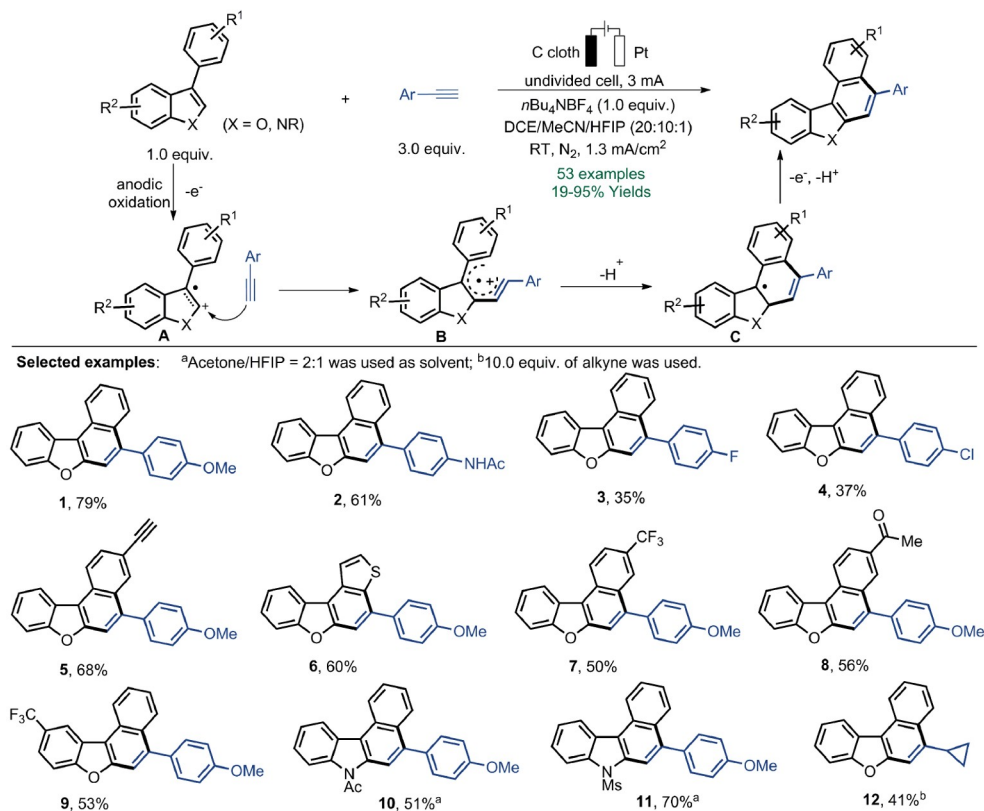
In 2020, *Lei et al.* [80] developed an electrochemical oxidative [4+2] annulation of heterobiaryl compounds with alkynes, leading to the formation of polycyclic heteroaromatic compounds ([Scheme 11](#)). Through the *in-situ* generated cationic heterobiaryl radical intermediate, various fused aromatic compounds were obtained with good yields and excellent regioselectivity. They hypothesized that the heterobiaryl radical cations (**A**) generated through single-electron oxidation of heterobiaryls can be attacked by alkynes to form the distonic radical cations **B**. Subsequent deprotonation and cyclization gave the intermediates **C**, which can furnish the final products through further oxidative aromatization. Generally speaking, the use of electron-rich alkynes as two-carbon synthons is beneficial in this annulation, probably due to their stronger nucleophilicity (**11-1–11-4**). The authors observed decreased yields for substrates with electron-deficient substituents (**11-7–11-9**).

3 Electrochemical intermolecular radical addition onto internal alkynes

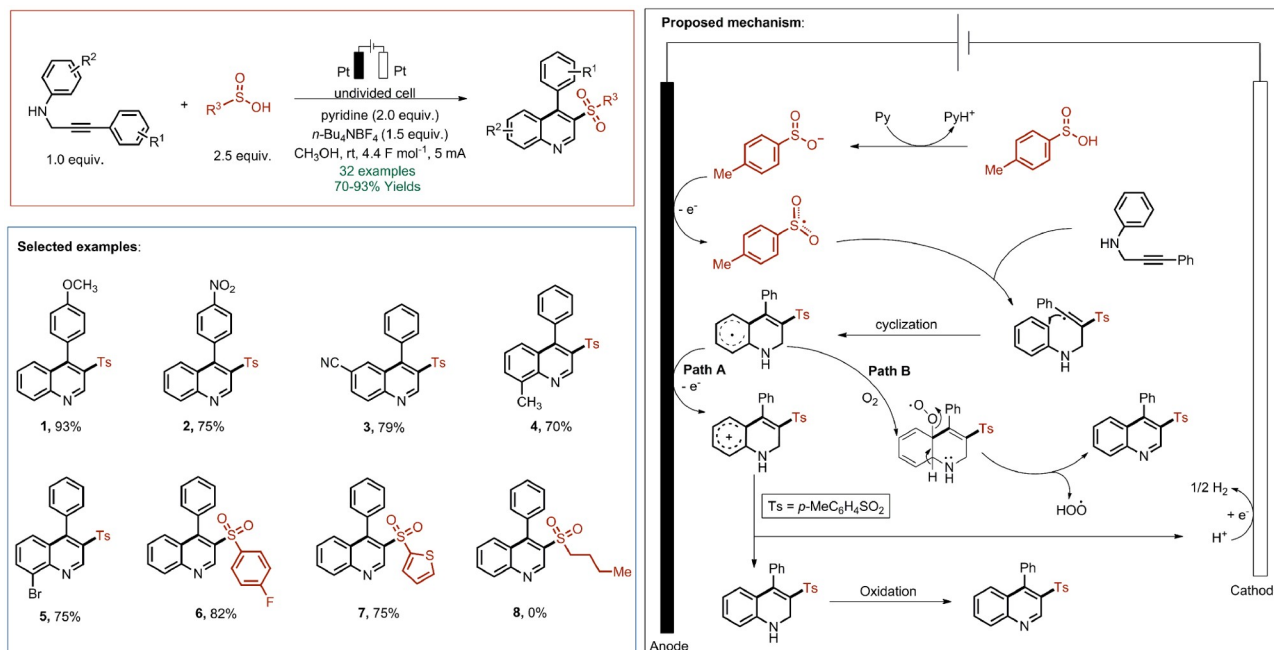
In 2021, Wang and co-workers [81] reported on an electro-

oxidative tandem cyclization of *N*-propargylanilines with sulfinic acids to provide a rapid access to 3-arylsulfonylquinoline derivatives ([Scheme 12](#)). A series of *N*-propargylanilines (0.2 mmol) and sulfinic acids (0.5 mmol, 2.5 equiv.) afforded 3-arylsulfonylquinoline products in high yields (70%–93%) and low Faradaic efficiencies (16%–21%, 56% for gram reaction) in the electrooxidation. Electrolyses were carried out in an undivided cell, using methanol and *n*-Bu₄NBF₄ as electrolyte in the presence of pyridine (0.4 mmol, 2.5 equiv.). The highest yields were obtained with the strong electron-donating methoxy group (**12-1**, as R' group), indicating that the generated sulfinyl radical is slightly electrophilic. In general, sulfinic acids with electron-donating groups gave higher yields as compared with electron-withdrawing groups. However, the reaction was limited to aryl sulfinic acids while alkyl sulfinic acids failed to deliver the corresponding products (**12-8**). CV studies indicated that the electrooxidation of sulfinic acids occurs preferentially as compared with the oxidation of substrate *N*-propargylanilines.

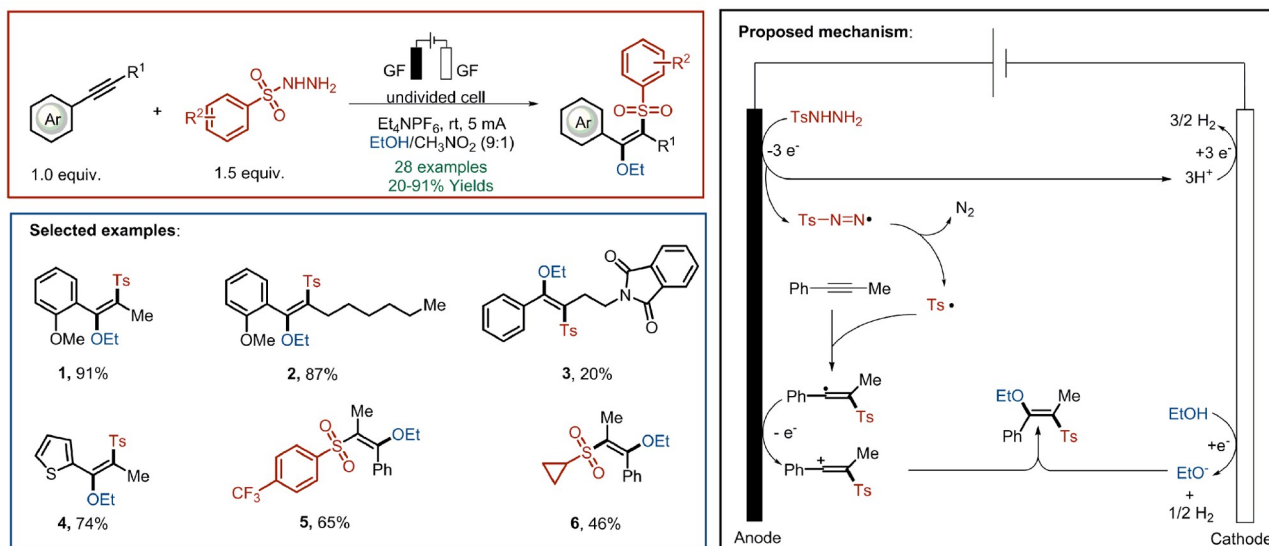
Interestingly, Zhang and Li *et al.* [82] recently developed a methodology for the electrochemical synthesis of sulfonylated enethers from internal alkynes and sulfonyl hydrazides ([Scheme 13](#)). Constant current electrolysis of the substrate mixture in an undivided cell equipped with two graphite felt (GF) electrodes gave the envisioned product using Et₄NPF₆ as supporting electrolyte in a solvent mixture of ROH/CH₃



Scheme 11 Electrooxidative [4+2] annulation of heterobiaryls with terminal alkynes [80] (color online).



Scheme 12 Electrooxidative cyclization of *N*-propargylanilines with sulfinic acid [81] (color online).



Scheme 13 Electrochemical synthesis of sulfonlated enethers from alkynes and sulfonyl hydrazides [82] (color online).

NO_2 (9:1). A total of 28 examples of ethoxysulfonylation alkenes were given with yields of 20%–91%. Excellent regio- and stereo-selectivities were observed in the electrooxidative sulfonylation of the unsymmetrical alkynes bearing an aryl and alkyl substituent. Heterocyclic oxidative-sensitive thiophene was also well-tolerated in the transformation (**13-4**). Careful CV analysis of *p*-toluenesulfonylhydrazide showed oxidation peaks at -0.17 , 0.41 , 1.62 and 2.43 V vs. Ag/AgCl in the presence of K_2CO_3 . Furthermore, the existence of sulfonyl radicals was confirmed in

radical trapping experiments. It is worth mentioning that traditional sulfonylation strategies through the addition of external oxidants such as TBAI, I_2 , FeCl_3 , cerium (IV) ammonium nitrate (CAN), pyridinium chlorochromate (PCC) and KMnO_4 failed to promote this transformation, probably due to their lower oxidation potentials (I^-/I_2 , 0.53 V; $\text{Fe}^{2+}/\text{Fe}^{3+}$, 0.77 V; $\text{Ce}^{3+}/\text{Ce}^{4+}$, 1.61 V; $\text{Ce}^{3+}/\text{Ce}^{6+}$, 1.33 V; $\text{Mn}^{7+}/\text{Mn}^{4+}$, 1.70 V).

Very recently, Zhang and Wen *et al.* [83] developed an approach for the synthesis of 2-aryl-3-sulfonyl substituted

quinolines through an electrochemical cascade annulation manifold (Scheme 14). They used *p*-toluenesulfonylhydrazide as radical precursor, and achieved the best result applying Et_4NPF_6 and ${}^t\text{Bu}_4\text{NBF}_4$ as the co-electrolytes, a mixture of hexafluoroisopropanol/dichloromethane/nitromethane (3:1:1) as solvent, 3.9 V constant voltage (cell voltage without reference electrode) under a N_2 atmosphere at ambient temperature. The reaction proceeded efficiently with fair to good yields (**14-1-14-8**), with either electron-donating or electron-withdrawing functional groups on both, the alkyne and the sulfonyl hydrazide starting material. Based on the proposed mechanism, the sulfonyl radical is formed through PCET and anodic oxidation, as well as nitrogen extrusion. Then, it reacts with the alkyne to form radical intermediate **A**. **A** is further oxidized at the anode, and the carbocation intermediate **B** is generated, which further removes a proton ion and one molecule of carbon dioxide to generate the target product.

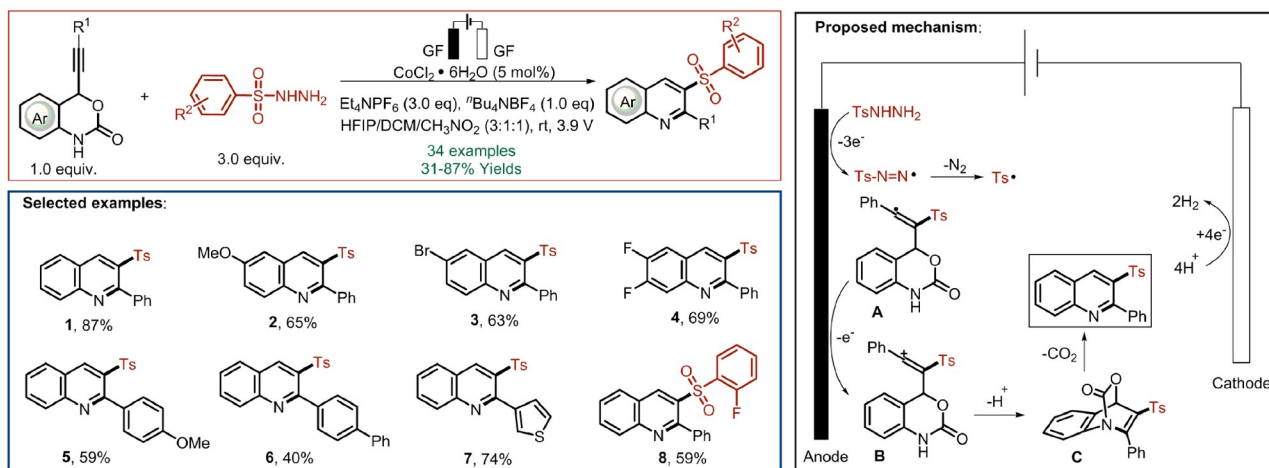
Ynones are important radical acceptors in organic synthesis, and many types of bio-relevant cyclic compounds could be obtained by cascade radical cyclization reactions. For example, the Zhang's group exploited ynones in transition-metal-mediated radical reactions to construct fluoromethylated naphthoquinones [84], indanones [85] and spiro [5.5]trienones [86]. Concurrently, Lei's group [87] used this building block in electrooxidative direct arylsulfonylation *via* a radical cyclization strategy (Scheme 15). This method provided a simple and efficient approach to prepare various sulfonylindenones in good to excellent yields. They obtained the best results by performing the reaction under a constant current electrolysis at 10 mA cm^{-2} in an undivided cell using tetrabutylammonium iodide (TBAI) as redox catalyst, LiClO_4 as electrolyte, and two platinum plates as the working electrode and cathode in $\text{CH}_3\text{CN}/\text{DCE}$ (9:1) at room temperature. Substrates with electron-donating groups in *para*-position of the aryl ring of ynone were more efficiently

converted than substrates with electron-withdrawing ones (**15-2**). Unfortunately, alkyl alkynes failed to give the corresponding products. Based on the experimental results, a plausible mechanism for radical generation is illustrated. The reaction initiates with the anodic oxidation of the iodide ion to form an $\text{I}^{\cdot+}$ species and its subsequent reaction with sulfonic acid to afford a sulfonyl radical and an iodine radical.

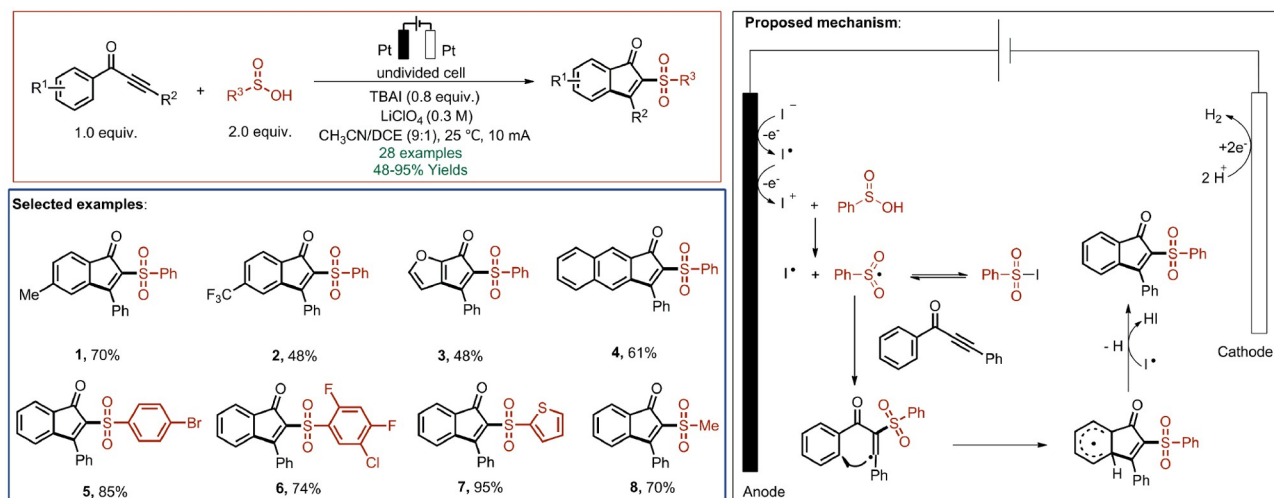
In 2021, Zhang and Ackermann *et al.* [88] reported on an electrochemical strategy for the concise synthesis of tri- and difluoromethylated spiro[5.5]trienones *via* dearomative spirocyclization of biaryl ynones (Scheme 16). Salient features of this strategy comprise (1) the first efficient dearomatization of biaryls to CF_3 -containing spiro[5.5]trienones, (2) a most user-friendly undivided cell set-up, (3) simple reaction conditions without redox mediators, (4) the absence of catalyst, and (5) high levels of regioselectivity.

The envisioned trifluoromethylation/dearomatization was accomplished with a mixed solvent system consisting of DCE and MeCN (1:1) and Et_4NClO_4 as the electrolyte using the bench-stable and inexpensive Langlois' reagent $\text{CF}_3\text{SO}_2\text{Na}$ as the $\cdot\text{CF}_3$ [89] source. A radical mechanism was proposed for this electrooxidative dearomatization reaction, which commences with the generation of the $\text{CF}_3\cdot$ from $\text{CF}_3\text{SO}_2\text{Na}$ through SET anodic oxidation. Radical addition of $\text{CF}_3\cdot$ to the C–C triple bond of ynone then affords the vinyl radical **A**, which undergoes 6-*exo*-trig cyclization to the radical species **B**. Intermediate **B** is oxidized by SET to oxocarbenium ion **C** at the anode. Finally, the corresponding product **16-1** is formed after demethylation. In addition, the reaction mixture became acidic, as pH measurements of the reaction mixture clearly revealed, which is due to the HCl generation by dehydrochlorination of the DCE cosolvent [90].

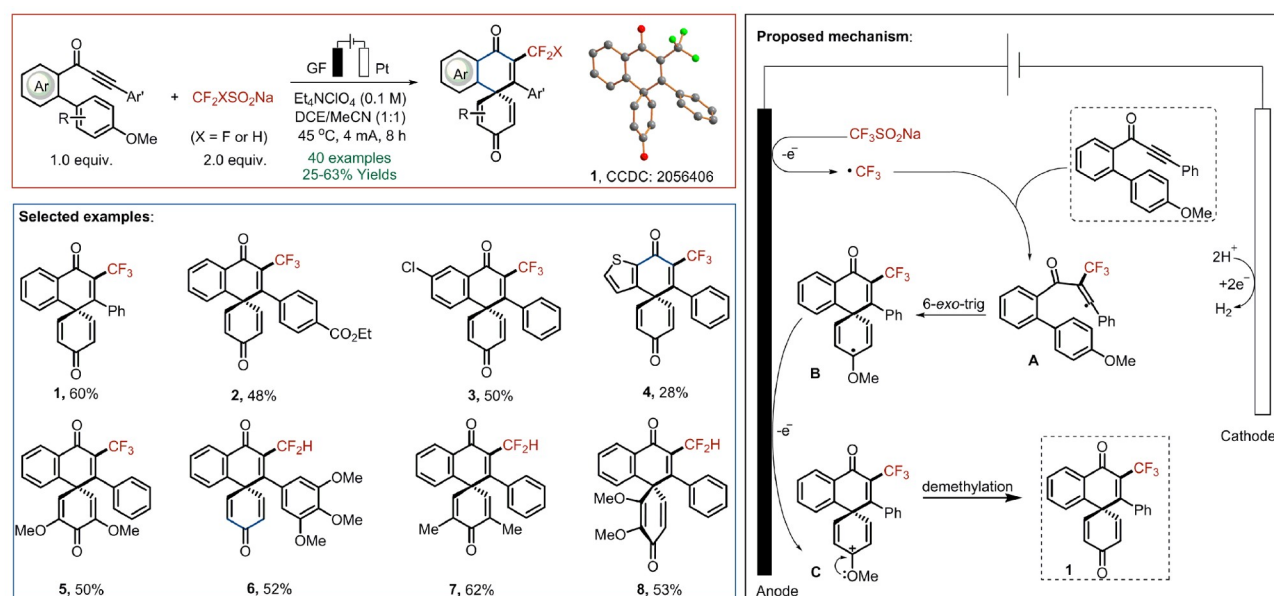
Interestingly, an electrooxidative radical cyclization of biaryl ynones with various carbon- and heteroatom-centered radical precursors was later found to occur *via* a sequential



Scheme 14 Electrochemical cascade annulation for the synthesis of 2,3-disubstituted quinolines [83] (color online).



Scheme 15 Electrooxidative cyclization of ynones with sulfinic acids [87] (color online).



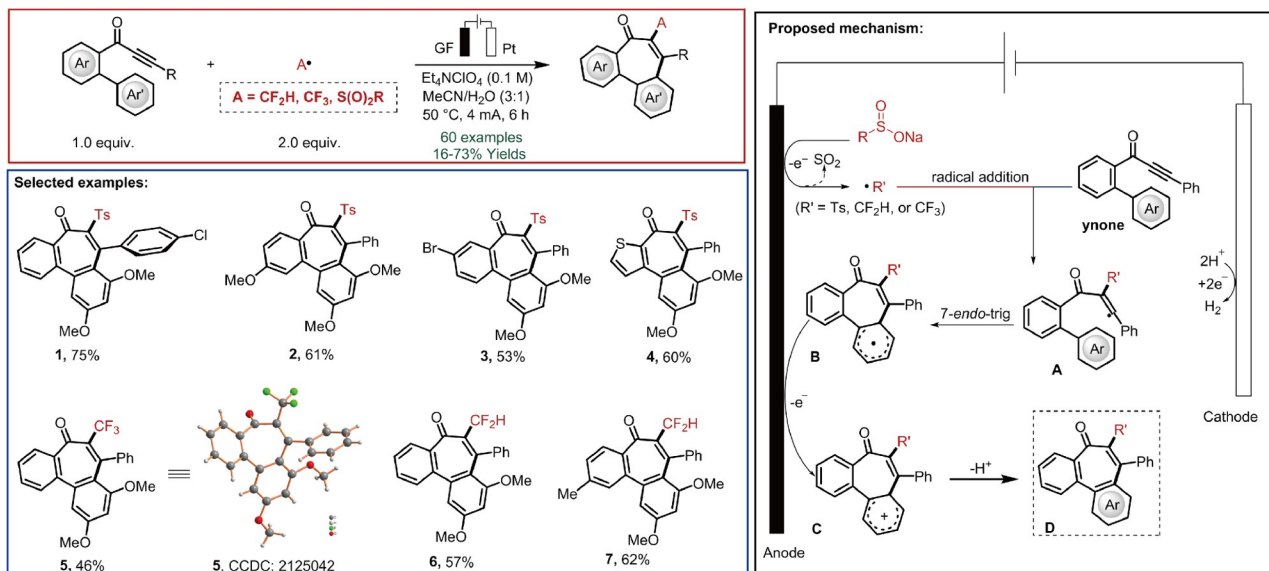
Scheme 16 Electrooxidative dearomatization of biaryls access to fluoromethylated spiro[5.5]trienones [88] (color online).

radical addition/7-endo-trig/radical cyclization domino [91] reaction (Scheme 17) [92]. This approach provided a step-economical and strategically novel disconnection for the facile assembly of a wide range of carbocyclic 6-7-6 fused ring systems (17-1–17-7), which is the core scaffold of the natural product allocolchicine and its analogues. Remarkably, the sulfonyl group on the products could be easily removed by photoredox catalysis at ambient temperature. The synthetic utility of the developed domino strategy was further reflected by the preparation of bioactive NSC 51046 analogues (Scheme 18, left).

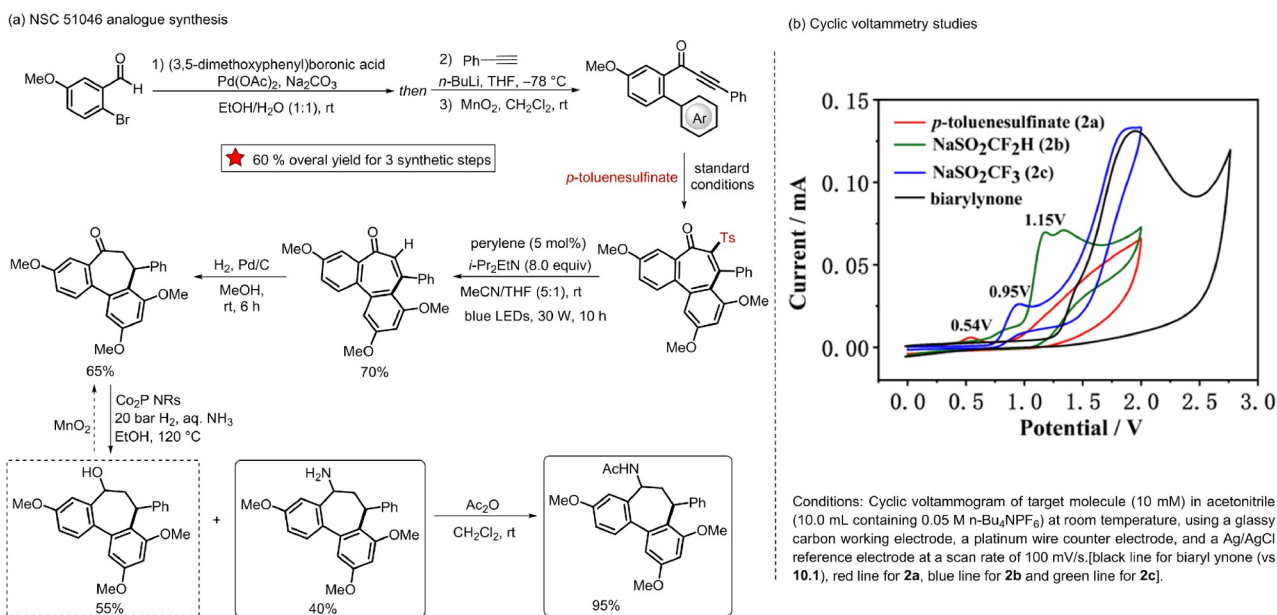
In addition, the oxidation potentials of the different radical sources were determined in order to understand the reaction mechanism. Reactants 18-2a, 18-2b and 18-2c exhibit ox-

idation peaks at 0.54, 0.95 and 1.15 V vs. Ag/AgCl, respectively, indicating that these radical precursors are preferentially oxidized by anodic oxidation. Based on the experimental results, a radical mechanism is proposed for this electrooxidative radical reaction as depicted in Scheme 17 (right). First, the radical species, a sulfonyl, CF_3 or CF_2H radical is generated through anodic oxidation. Selective radical addition of $\text{R}'\cdot$ to the C–C triple bond of ynone affords vinyl radical **A**, which undergoes 7-endo-trig cyclization to intermediate **B**. Then, further SET oxidation occurs with intermediate **B** and deprotonation to form the desired product.

Inspired by this approach, the group of Wang *et al.* [93] disclosed a dearomatization of activated alkynes (Scheme



Scheme 17 Electrooxidative construction of tricyclic 6-7-6-system by radical addition of biarylynes [92] (color online).

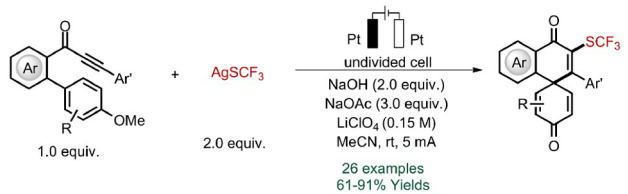


Scheme 18 (a) NSC 51046 analogue synthesis (Ar = 3,5-dimethoxyphenyl); (b) CV studies [92] (color online).

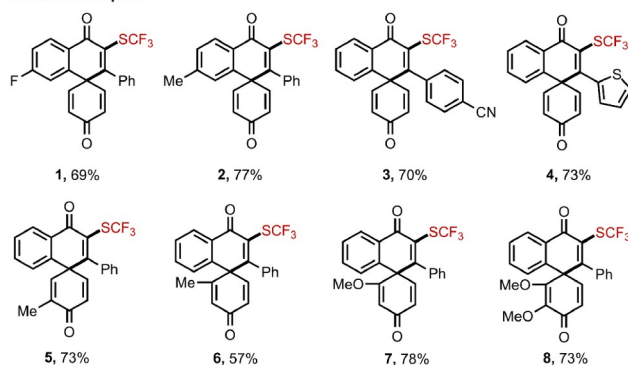
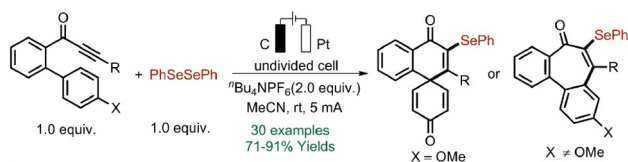
19). They developed an electrochemical trifluoromethylthiolation and spirocyclization for the synthesis of SCF₃-containing spiro[5.5]trienones from biaryl ynone with AgSCF₃ as the trifluoromethylthiolation reagent. CV analysis of AgSCF₃ using a Pt/Pt electrode as the working electrode reveals a lower oxidation potential ($E_{p/2} = 0.38 \text{ V}$, vs. Ag/AgCl) compared with the potential using a glassy carbon/Pt wire as the counter electrode ($E_{p/2} = 1.85 \text{ V}$, vs. Ag/AgCl), indicating the higher efficacy with a Pt/Pt electrode set-up. CV analysis also revealed that AgSCF₃ could be oxidized at a

lower potential ($E = 1.85 \text{ V}$ vs. Ag/AgCl) than the ynone substrate ($E > 2.25 \text{ V}$ vs. Ag/AgCl) under otherwise identical conditions, showing that a direct oxidation of AgSCF₃ to its corresponding free radical intermediate is most likely preferred.

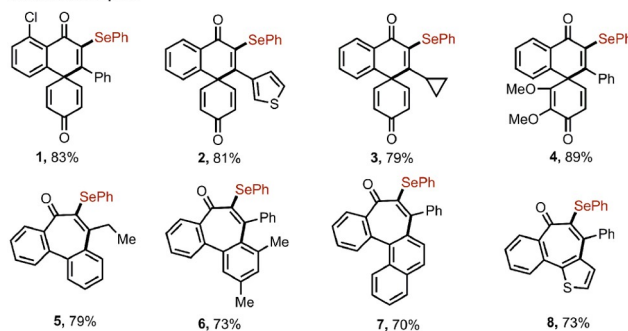
Concurrently, Reddy *et al.* [94] disclosed an electrochemical selenylative carbannulation of biaryl ynone (Scheme 20). The reaction proceeded efficiently using constant current electrolysis of ynone and diphenyl diselenide in MeCN solution in an undivided electrochemical cell set-



Selected examples:

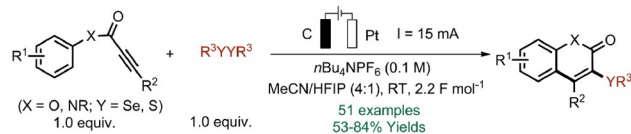
**Scheme 19** Electrochemical trifluoromethylthiolation/spirocyclization of alkynes [93] (color online).

Selected examples:

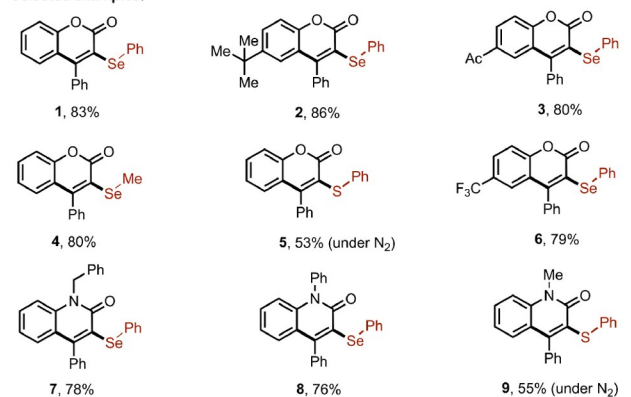
**Scheme 20** Electrochemical selenylative carbannulation of biaryl ynones [94] (color online).

up equipped with a graphite electrode anode and a Pt cathode at ambient temperature employing *n*-Bu₄NPF₆ as a supporting electrolyte. While the biaryl ynones having a 4-methoxy group on the distal phenyl ring furnished selenyl spiro[5.5]trienones through dearomative spirocyclization, other substrates provided selenodibenzocycloheptan-5-ones in terms of *ortho*-cyclization. CV studies showed a lower oxidation potential for PhSeSePh compared with the ynones. Thus, the diphenyl diselenide is oxidized first.

In 2019, the Guo group [95] developed a direct electrochemical oxidative cyclization of alkynoates and alkynamides with diselenides or disulfides for the synthesis of coumarins and quinolinones (Scheme 21). CV studies re-



Selected examples:

**Scheme 21** Cyclization of alkynes with diselenides or disulfides provides access to coumarins and quinolinones [95] (color online).

vealed that diphenyl diselenide and diphenyl disulfide are oxidized preferentially at the anode to form the cationic radical intermediate, which then yields a radical and a cationic species. This transformation displayed ample substrate scope and good yields.

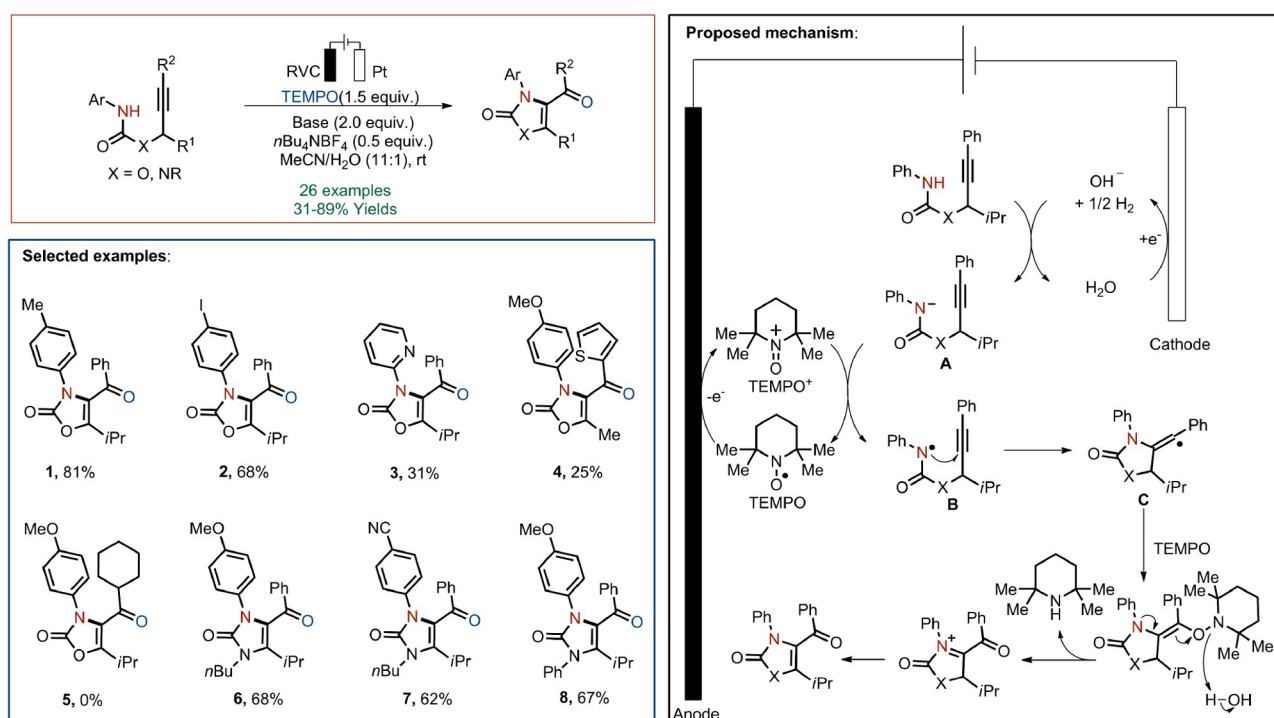
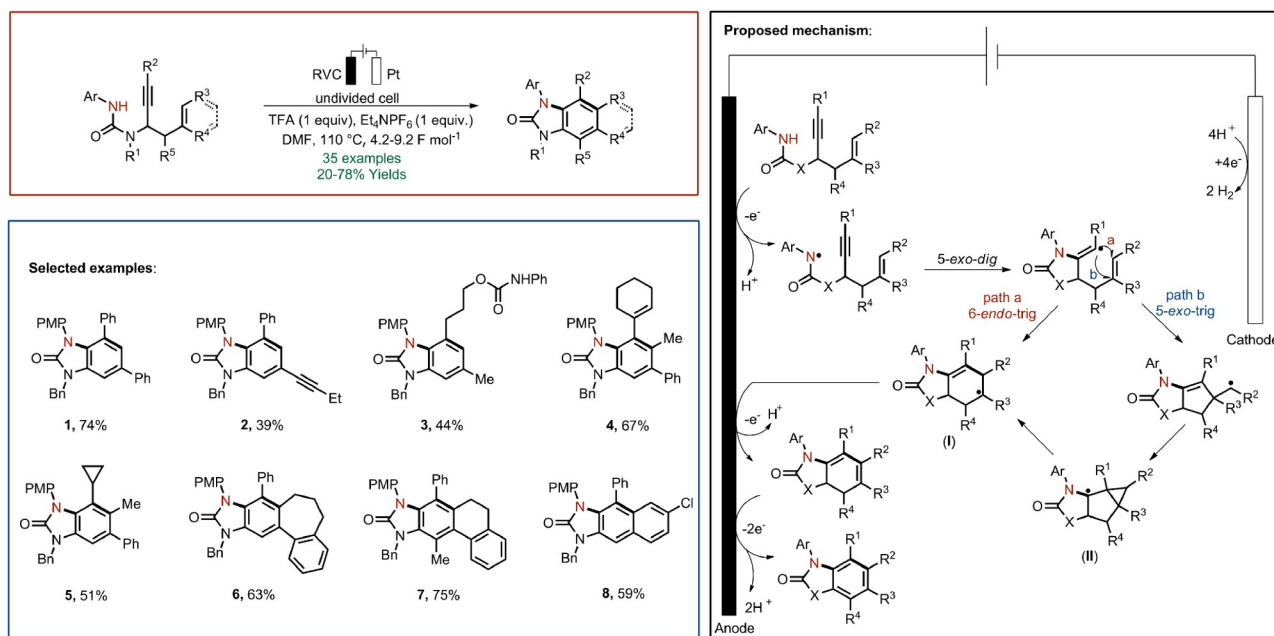
4 Electrochemical intramolecular radical direct addition to alkynes

Benzimidazolone and benzoxazolone scaffolds can be found in a variety of pharmaceutical molecules. Traditionally, they were prepared from a benzene derivative through the construction of an additional five membered heterocyclic ring. In contrast, in 2019, Xu *et al.* [96] reported on an efficient procedure that enables the synthesis of both of these important scaffolds through an electrochemical dehydrogenative cyclization cascade (Scheme 22). With the designed urea substrate in hand, they obtained the target benzimidazolone product in high yield after electrolysis at 100 °C and a constant current of 10 mA with a RVC anode, a platinum plate cathode in DMF in the presence of 1 equiv. of trifluoroacetic acid (TFA) as acid additive. The oxidation potential of the product ($E_{p/2} = 1.26$ V vs. SCE) is significantly higher than the one of the urea starting material ($E_{p/2} = 0.96$ V vs. SCE), which prevents oxidative decomposition of the product during the electrolysis. According to the proposed mechanism, the arylamine motif in the starting material is anodically oxidized and deprotonated to furnish an amidyl radical, which then undergoes 5-*exo*-dig cyclization to generate the vinyl radical. Intramolecular 6-*endo*-trig cyclization of the vinyl radical results in the formation of the cyclic carbon radical I. Alternatively, the vinyl radical can

undergo 5-*exo*-trig cyclization to generate an exocyclic C-centered radical, which can subsequently be converted into **I** via a tricyclic radical intermediate **II**.

The same group later reported on an electrochemically-enabled intramolecular aminoxygenation of alkynes via amidyl radical cyclization derived from ureas (Scheme 23) [97]. A series of functionalized oxazol-2-ones and imidazol-

2-ones were thereby prepared through oxidative cyclization of propargylic carbamates and ureas. The electrochemistry relies indeed on the dual function of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) as a redox mediator for the amidyl radical formation as well as the oxygen atom donor. Mechanistic experiments revealed the crucial role of a base, which needs to be sufficiently strong to deprotonate the



Scheme 23 Electrochemically enabled intramolecular aminoxygenation of alkynes [97] (color online).

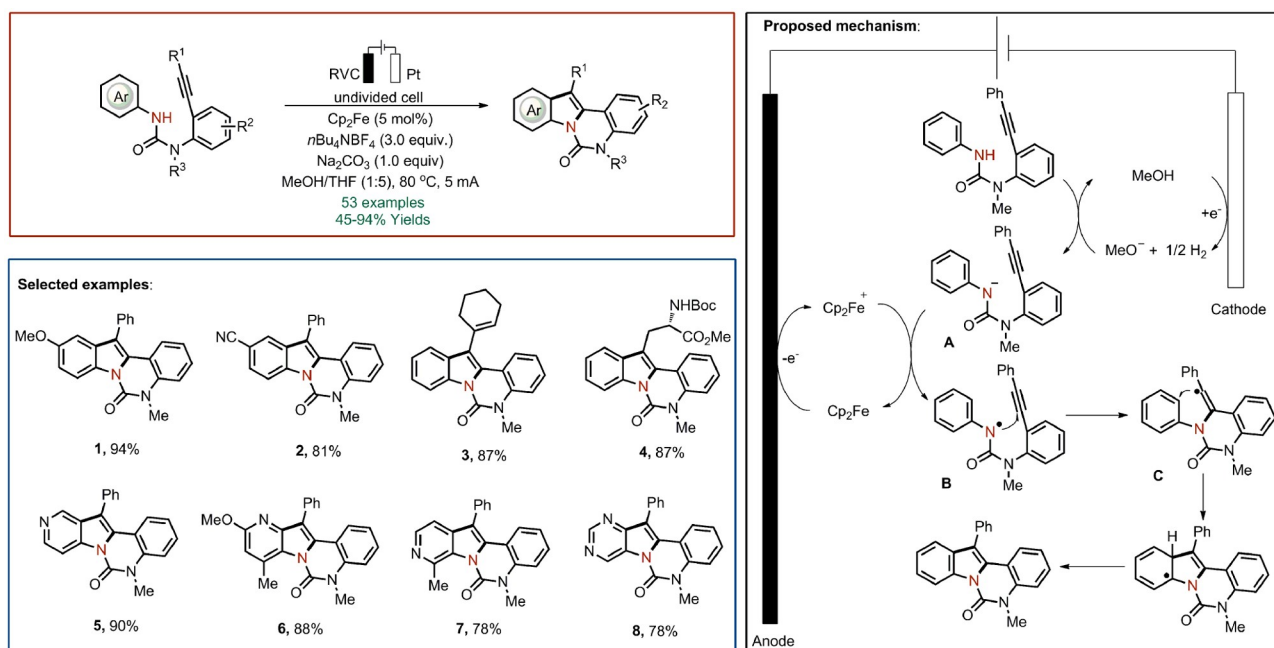
carbamate for enabling the aminooxygenation.

Indeed, the Xu group [98] initially used this strategy in 2016 to synthesize the popular heterocycles indoles and azaindoles (Scheme 24). As to the reaction mechanism, first anodic oxidation of $[\text{Cp}_2\text{Fe}]$ to $[\text{Cp}_2\text{Fe}]^+$ and concomitant cathodic reduction of the protons from methanol form methoxide (MeO^-) and H_2 . Second, MeO^- deprotonates the urea to furnish the anion **A**, which is a much better electron-donor than the neutral precursor. Hence, SET from **A** to $[\text{Cp}_2\text{Fe}]^+$ affords *via* overall PCET the electron-deficient nitrogen-centered radical **B**, and regenerates $[\text{Cp}_2\text{Fe}]$. This efficient SET is favoured over the cathodic reduction of $[\text{Cp}_2\text{Fe}]^+$, thus allowing the electrolysis to be carried out in an undivided cell. Subsequently, amidyl radical **B** participates in a rare 6-*exo*-dig cyclization to give the vinyl radical **C**, which then undergoes a second cyclization with the aryl ring to afford the delocalized radical. Finally, rearomatization by electron and proton elimination generates the final product. The cyclization was largely unaffected by the electronic or steric properties of the aryl ring and the alkyne substituent. It is noteworthy that a wide range of substituents R^1 including aryl groups, heterocyclic rings as well as alkenyl and alkyl groups were well tolerated on the alkyne moiety.

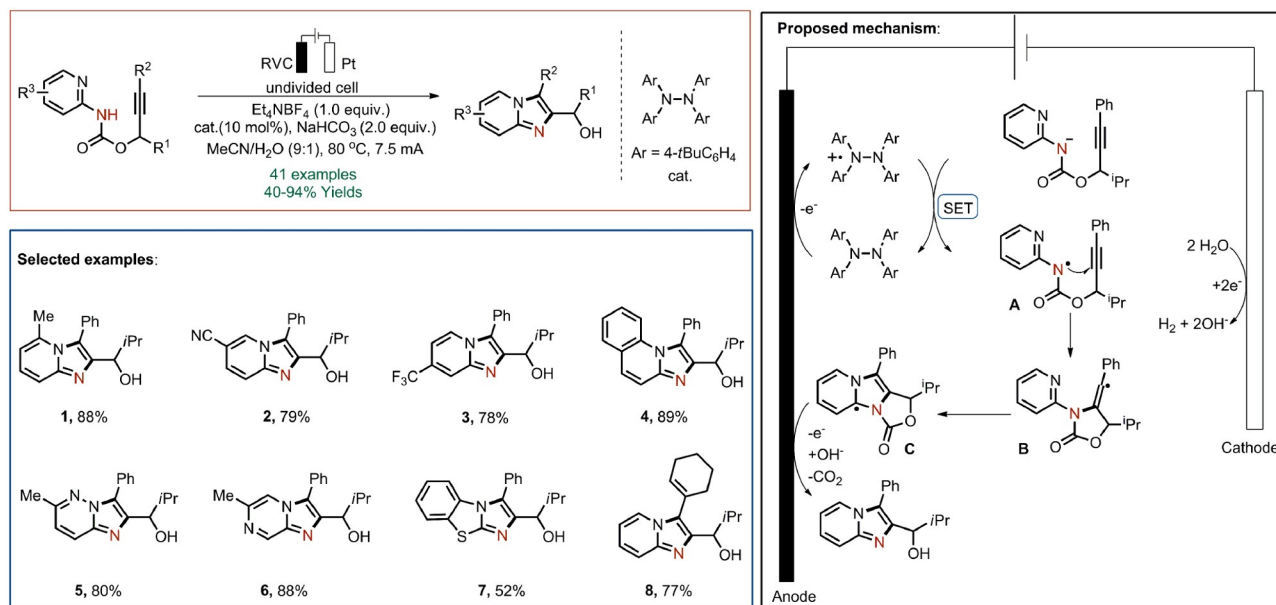
By changing the substrate to carbamate and using tetra-arylhydrazine instead of Cp_2Fe as the redox mediator, the Xu group [99] developed a strategy for preparing a variety of imidazo-fused *N*-heteroaromatic compounds through electrochemical [3+2] annulation reaction of heteroarylamines with tethered internal alkynes (Scheme 25). The optimal results were obtained when carbamate was electrolyzed with

a constant current of 7.5 mA in a mixture of $\text{MeCN}/\text{H}_2\text{O}$ (9:1) under 80°C in the presence of 10 mol% tetra-arylhydrazine employing an undivided cell equipped with a RVC anode and a platinum cathode. According to the proposed mechanism, the reaction begins with the anodic oxidation of the mediator ($E_{\text{p}/2} = 0.68\text{ V vs. SCE}$), which generates the stable radical-cation intermediate M^+ . Contemporaneously, hydroxide is generated from the heterolytic cleavage and reduction of H_2O at the cathode. It deprotonates carbamate to afford its conjugate base, which possess a significantly lower oxidation potential than carbamate ($E_{\text{p}/2} = 1.76\text{ V}$ for carbamate, 0.66 V for its conjugate base, *vs.* SCE). Then, SET occurs, which results in the formation of amidyl radical **A** and the regeneration of the redox catalyst. The 5-*exo*-dig cyclization of **A** affords vinyl radical **B**, which then regio-selectively reacts with the pyridyl nitrogen to generate the tricyclic radical intermediate **C**. The ensuing one-electron oxidation of **C**, followed by the hydrolysis of its carbonyl linker, forms the imidazopyridine product ($E_{\text{p}/2} = 1.20\text{ V vs. SCE}$). The use of a redox mediator allows to perform the reaction under significantly milder conditions, and protects the desired product from decomposition by overoxidation.

Interestingly, the same group observed different products when using a MeOH/THF (1:3) solvent mixture (Scheme 26) [100]. In terms of the reaction mechanism, the difference of this report is represented by the methanolysis of the cationic intermediate formed from radical species **C** (Scheme 25), which affords the imidazopyridine. It is worth noting that the basic additive Na_2CO_3 plays a crucial role in this transformation, which supposedly assists the substrate oxidation



Scheme 24 Electrochemical C-H-N-H functionalization for the synthesis of functionalized (aza)indoles [98] (color online).



Scheme 25 Electrochemical synthesis of imidazo-fused *N*-heteroaromatic compounds [99] (color online).

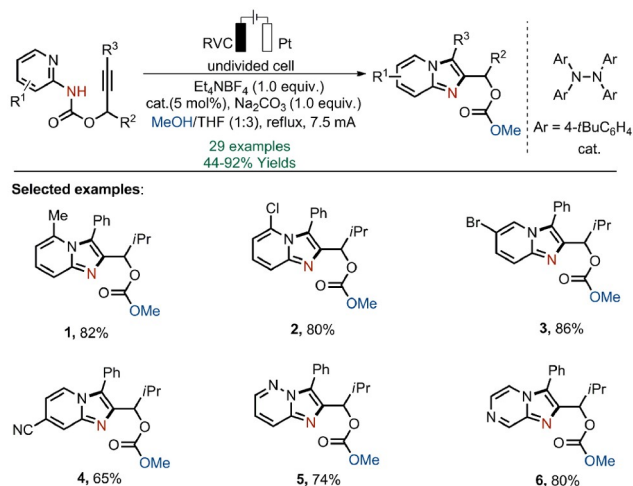
through direct deprotonation of the substrate or increasing the concentration of MeO⁻ in the solution.

Interestingly, Xu *et al.* [101] also designed urea-tethered diynes as reaction substrates (Scheme 27), which can be transformed into polycyclic *N*-heteroaromatics through PCET-based electrochemical cascade radical cyclization. The employment of ferrocene as a mild and selective redox catalyst allowed for a versatile access to a variety of electron-rich polycyclic aromatic hydrocarbons including helicene-like structures, without any overoxidation. The electro-synthesis involves an unprecedented amidyl radical cascade cyclization process to form three rings in a single operation. After optimizing a range of reaction conditions, the best results were obtained when the electrolysis was conducted

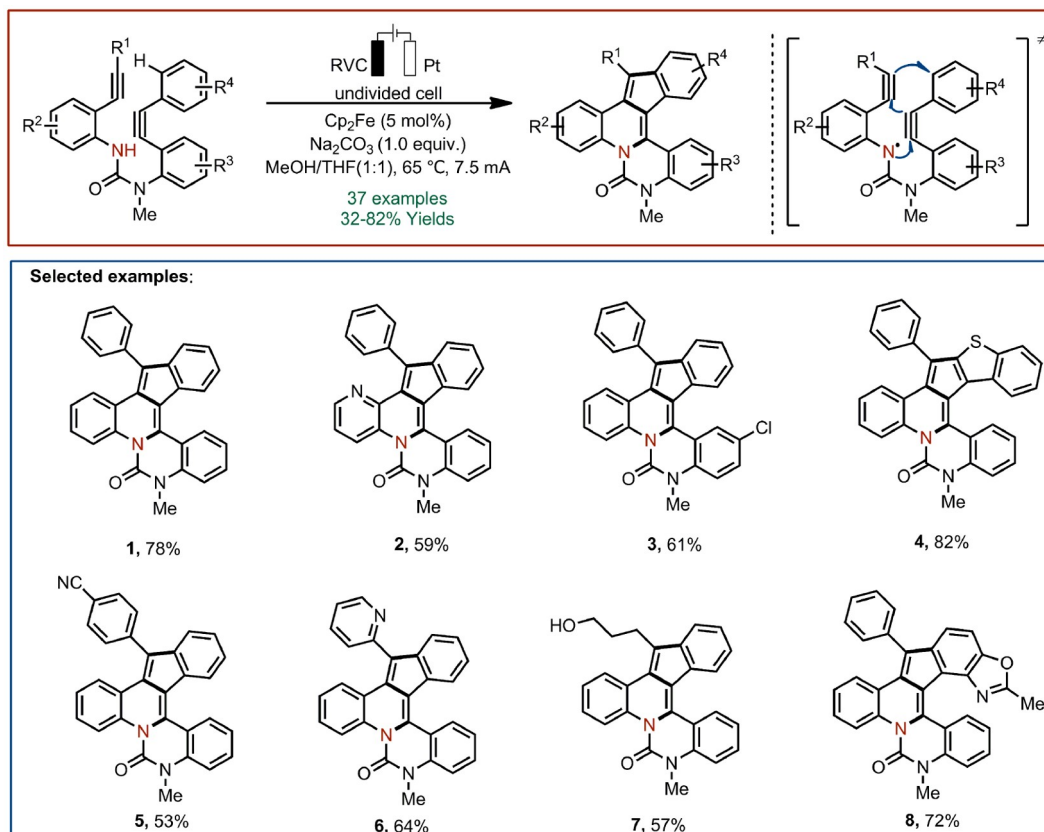
under a constant current of 7.5 mA in an undivided cell equipped with an RVC anode and a Pt plate cathode, with the aid of 5 mol% of Cp₂Fe (*E*_{p/2} = 0.45 V vs. SCE in 1:1 THF/MeOH) as a redox catalyst, Na₂CO₃ as an additive, and *n*Bu₄NBF₄ as supporting electrolyte in THF/MeOH (1:1) at 65 °C.

In 2020, Li and Wen *et al.* [102] published the electrochemical intramolecular C–H/N–H functionalization for the assembly of isoxazolidine-fused isoquinoline-1(2*H*)-ones. They identified the optimal conditions with constant current electrolysis at 2 mA for 4 h. *n*Bu₄NBF₄ as supportive electrolyte in ethanol at 80 °C turned out to give high yield using an undivided cell set-up (Scheme 28). Benzamides functionalities at the *para*-position with electron-withdrawing and electron-donating properties were well tolerated in the transformation. For *meta*-substituted benzamides, the reaction predominantly took place at the less hindered position of the aromatic ring with good site-selectivities. Generally, substrates with electron-withdrawing groups at the phenyl ring of the alkyne moieties outperformed the ones with electron-donating substituents (28-5 and 28-6). Through CV studies, the authors observed that the oxidation potential of amide is about 0.8 V vs. SCE, which is much lower than that of ethanol (1.5 V vs. SCE).

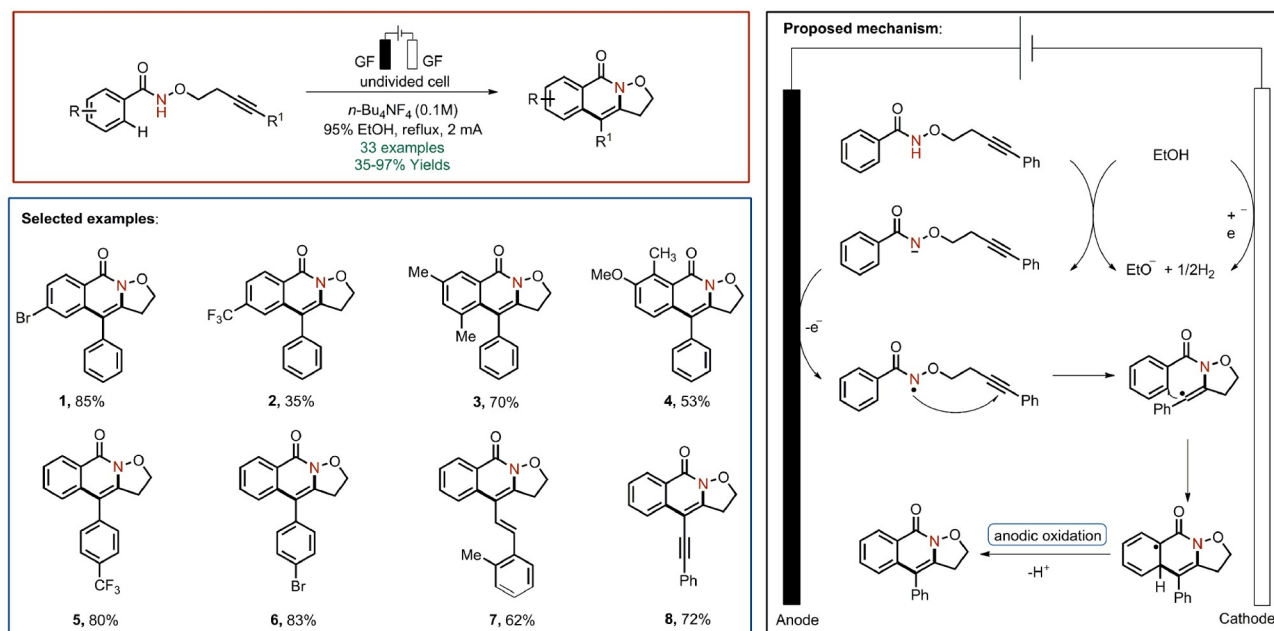
Recently, Guo and Liu *et al.* [103] disclosed an electro-synthesis of azaheterocycles through anodic oxidative cyclization of 1,6-enynes (Scheme 29). The desired reaction was achieved when the electrolysis was carried out in an undivided cell equipped with a carbon cloth anode and a platinum plate cathode using 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) as solvent and a constant current of 10 mA in the presence of *n*Bu₄NOAc and room temperature. The



Scheme 26 Electrooxidative synthesis of *N*-heteroarenes through [3+2] annulation [100] (color online).



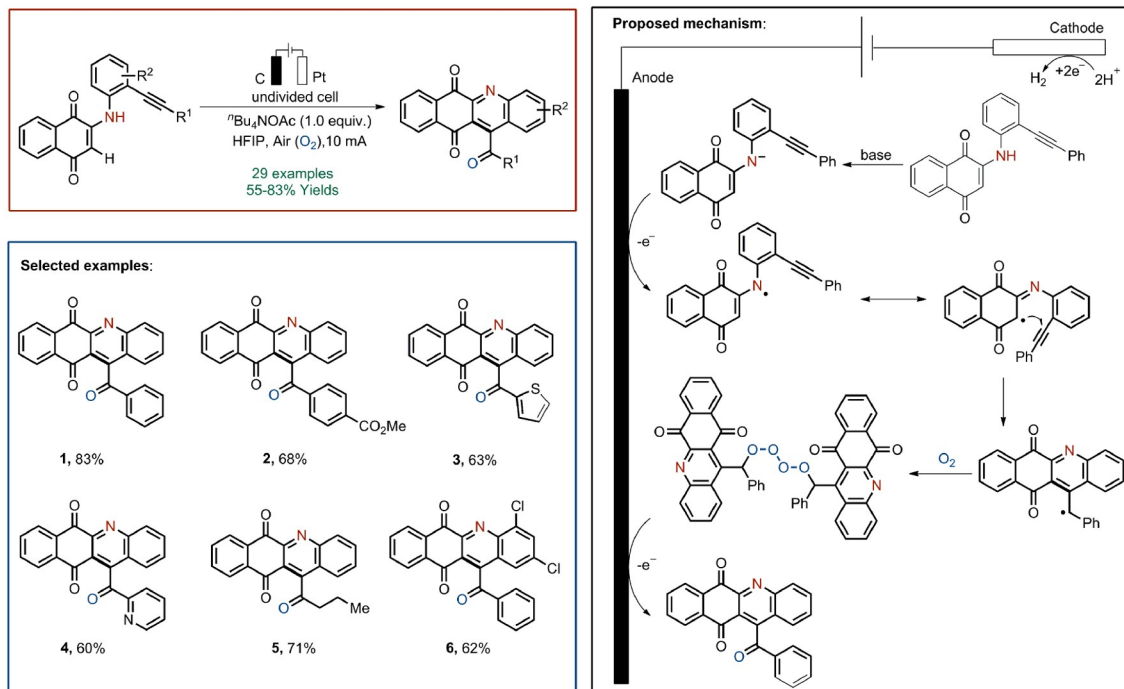
Scheme 27 Electrochemical synthesis of polycyclic *N*-heteroarenes [101] (color online).



Scheme 28 Intramolecular C-H/N-H functionalization access to isoquinolinones [102] (color online).

findings showed that the electronic effect of the substituents on the arene of the alkyne did not have a significant effect on the reaction's efficiency. It is noteworthy that the reaction

proceeded smoothly when the benzene ring was replaced by a thiophene, pyridine or alkanes (**29-3–29-5**). CV studies demonstrated a rise of the current between 1.5 and 2.0 V (*vs.*



Scheme 29 Electrooxidative cyclization of 1,6-enynes access to azaheterocycles [103] (color online).

Ag/AgCl) due to the electrooxidation of the substrate. Therefore, the authors proposed the formation of the key N-centered radical by anodic oxidation of the conjugate base of the substrate by PCET. The absence of an indole byproduct suggests that the alkyl radical is more stable. Then, intramolecular radical addition of the alkyl radical with the alkyne moiety occurs.

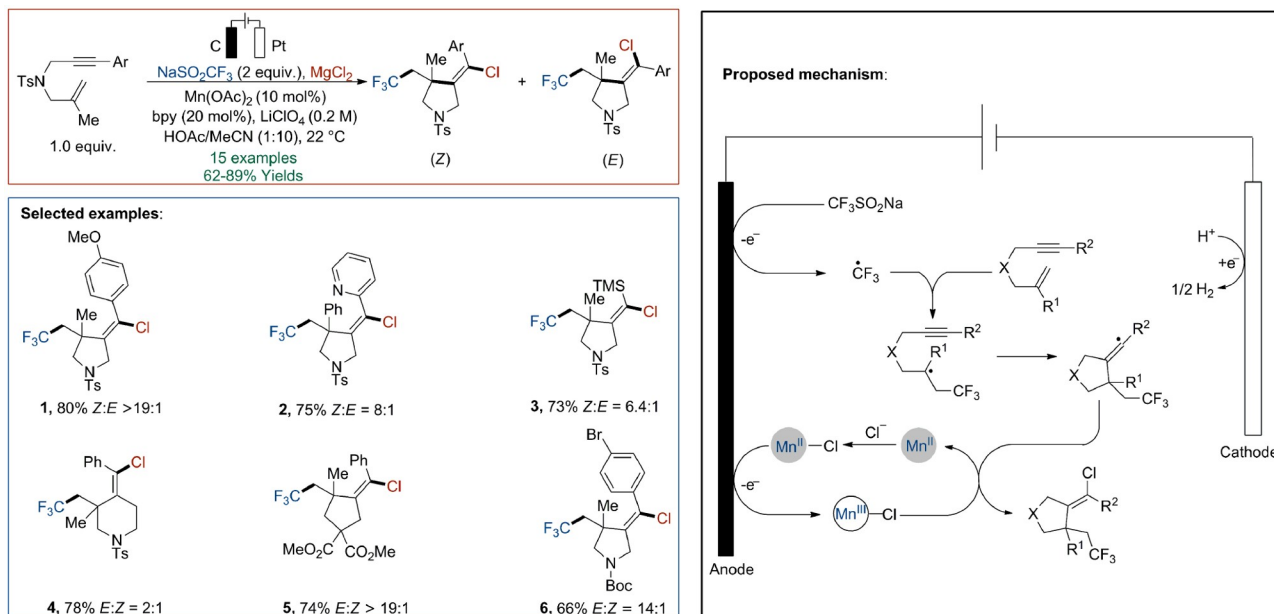
5 Electrochemical intramolecular radical ene-yne cascade reaction

In 2018, the Lin group [104] developed a manganese-catalyzed chlorotrifluoromethylation of alkenes (Scheme 30). Commercially available Langlois reagent $\text{CF}_3\text{SO}_2\text{Na}$ and MgCl_2 were used as the transfer agents to generate the $\text{CF}_3\cdot$ and $\text{Cl}\cdot$ radicals, respectively, *via* electrochemical oxidation, and the subsequent reaction of these radicals with the 1,6-enyne substrate was controlled by a redox-active manganese catalyst. The reduction potentials of $\text{CF}_3\text{SO}_2\text{Na}$ and $[\text{Mn}^{\text{II}}]\text{-Cl}$ are 0.81 and 0.75 V *vs.* Ag/AgCl, respectively.

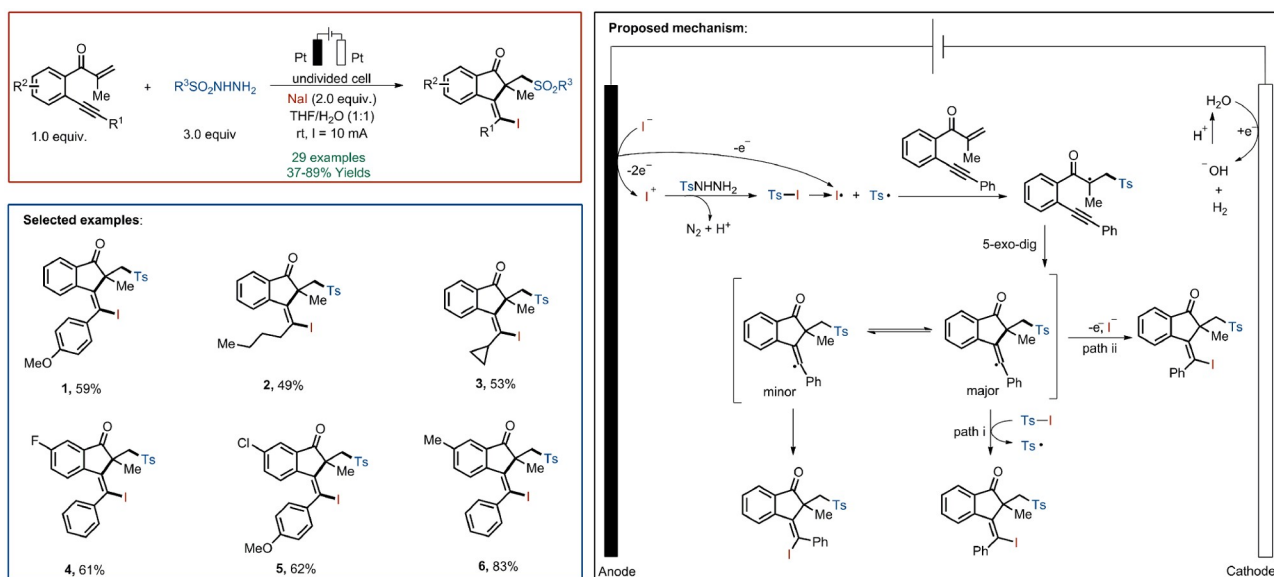
It seems that both species could be oxidized on the electrode surface. However, $[\text{Mn}^{\text{II}}]\text{-Cl}$ is persistent in the reaction, as indicated by the reversible behaviour observed in the CV studies. The addition of the $\text{CF}_3\cdot$ radical to the alkene takes place preferentially, owing to the higher reactivity of $\text{CF}_3\cdot$ compared with the one of $[\text{Mn}^{\text{II}}]\text{-Cl}$ and the higher reactivity of an alkene relative to an alkyne. Finally, the highly reactive carbon-centered radical generated by a 5-*exo*-

dig cyclization is converted to an alkenyl chloride *via* radical atom transfer in the presence of $[\text{Mn}^{\text{III}}]\text{-Cl}$ [105]. A set of 1,6-enynes with electron-rich, electron-deficient, and electron-neutral aryl groups on the alkyne were identified as amenable substrates, providing the chlorotrifluoromethylated pyrrolidines in high yield and with excellent stereoselectivity (30-1-30-6). The scope of this radical cyclization reaction can be extended to piperidine formation using a 1,7-enyne substrate. Furthermore, the introduction of a chelating ligand allowed for the ene-yne cyclization to take place with high stereochemical control over the geometry of the alkene group in the pyrrolidine product.

In 2020, Jiang and Tu *et al.* [106] reported on an electrochemically induced three-component cascade annulation reaction of 1,6-enynes towards 1-indanones (Scheme 31). This electrochemical halosulfonylation employed sodium halides as both halogen sources and electrolytes. The reaction was carried out with 1,6-enynes and *p*-toluene sulfonyl hydrazide in an undivided cell with two platinum plates as the electrodes under constant current electrolysis at 10 mA. The reaction in the presence of NaI in a THF/water (1:1) mixture worked efficiently at room temperature. When *p*-toluene sulfonyl hydrazide was used in the reactions of different 1,6-enynes to investigate the impact of substituents on the arylalkyne, all substrates efficiently participated in the electrocatalytic cyclization with good efficiency. Notably, substrates with cyclopropyl and *n*-butyl groups at the alkyne instead of the aryl moiety were also suitable for this trans-



Scheme 30 Synthesis of chlorotrifluoromethylated pyrrolidines by radical ene-yne cyclization [104] (color online).

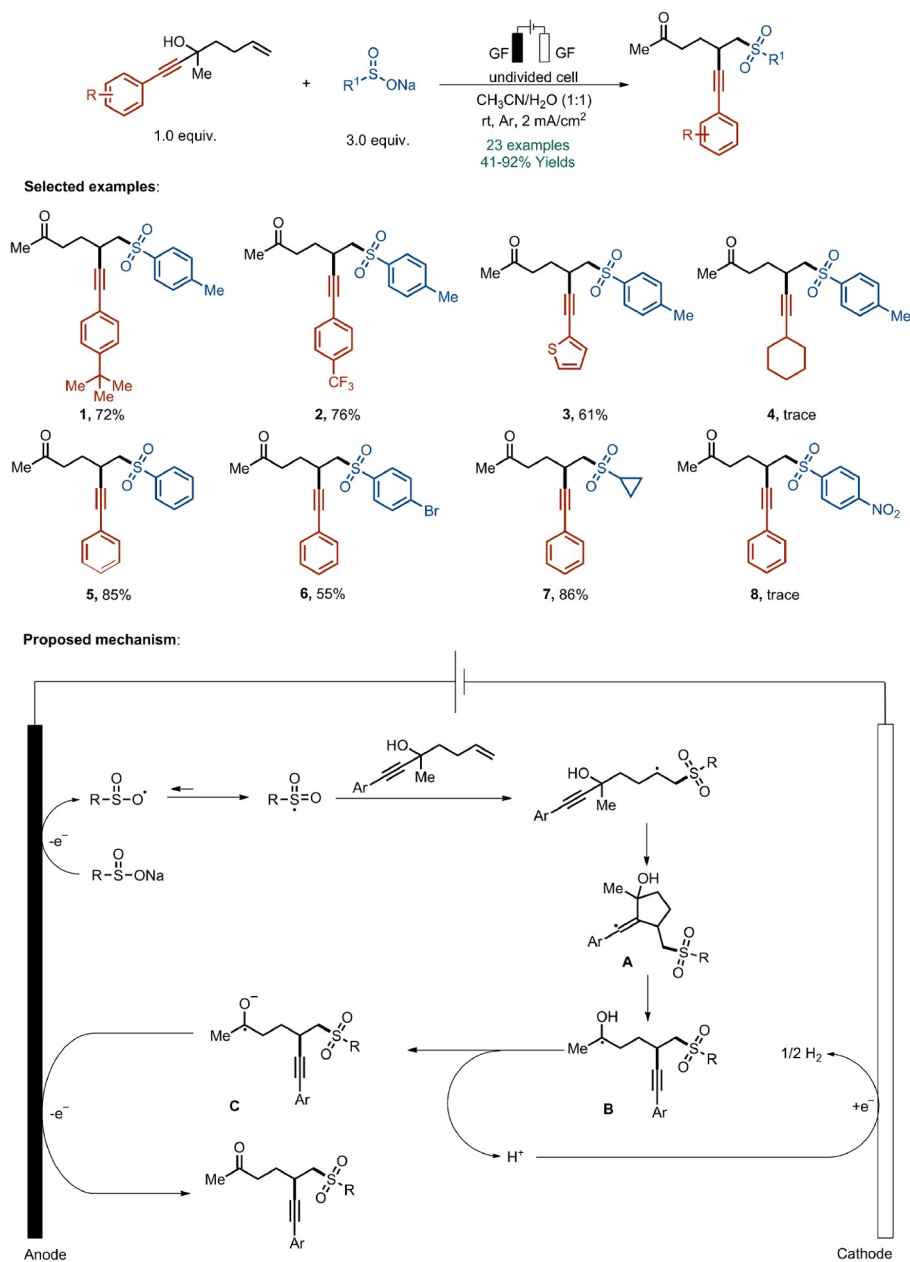


Scheme 31 Electrocatalytic annulation-halosulfonation of 1,6-enynes toward 1-indanones [106] (color online).

formation (**31-2** and **31-3**). In addition, control experiments indicated that *p*-tolylsulfonyl iodide is a key intermediate which is formed from arylsulfonyl hydrazide and NaI under electrocatalytic conditions. In detail, anodic oxidation of the iodide ion generates iodonium I^+ . The iodonium species subsequently reacts with arylsulfonyl hydrazide to give an arylsulfonyl iodide intermediate, followed by homolysis to yield an arylsulfonyl radical and an iodine radical. The later can be converted into I^+ by oxidation.

In 2018, the Pan group [107] reported on an elegant electrochemical alkynyl migration for the radical difunctio-

nalization of alkenes (**Scheme 32**). In comparison with the previously reported photocatalytic radical trifluoromethylative alkylation of olefins developed by Zhu *et al.* [108] in 2017, this electrochemical reaction proceeds smoothly without the use of any metal catalyst or additive, thereby representing a new and ecofriendly strategy for the difunctionalization of non-activated olefins. It is worth mentioning that the difunctionalization represents the first example of an electrochemical distal radical migration reaction. The key step during the reaction process is the formation of the vinyl radical **A** after 1,5-radical cyclization,



Scheme 32 Electrochemical alkynyl migration for the radical difunctionalization of alkenes [107] (color online).

which further undergoes the regioselective C–C bond cleavage to generate the radical **B**. Then, dehydrogenation of **B** will deliver the ketyl radical **C**, which is oxidized at the anode to afford the final product. Thus far, the reaction is however limited to aryl alkynes (**32-4**).

6 Conclusions and perspectives

The merger of electrochemical strategies with molecular organic synthesis has greatly facilitated the formation of various radicals by electron transfer, which arguably represents the easiest and most sustainable manner to generate

radical species. For the past several years, electrooxidative radical reactions have hence emerged as a powerful platform in molecular synthesis, often proceeding through PCET with electricity as the sole oxidant. In select cases catalytic amounts of a redox mediator are required. The use of stoichiometric amounts of chemical oxidants or usually expensive visible light photocatalysts is thereby avoided.

Herein, we have summarized the major recent advances in electrochemical radical addition reactions onto challenging alkynes, particularly for the direct construction of C(sp²)–CF₂H bonds by rare difluoroalkyl radical addition to alkynes. Despite of indisputable progress, these methods are often restricted to specific types of radical precursors. In addition,

compared with the extensive study of electrochemical oxidative radical reactions, less examples on electrochemical reductive radical reactions have reported thus far [109–116]. In order to develop more efficient and greener electrochemical radical reactions, the design of new reagents and the understanding of mechanisms that can be cleaved into diverse radicals by oxidation or reduction of electrodes, such as phosphoryl, aroyl, non-allylic alkyl, boron and alkoxy radicals, are required in order to expand the toolbox of electrochemical radical reactions.

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Conflict of interest The authors declare no conflict of interest.

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