RECENT ADVANCES IN ELECTROCHEMICAL SYNTHESIS OF DIVERSIFIED FUNCTIONALIZED SPIRO[N.5]ENONE DERIVATIVES

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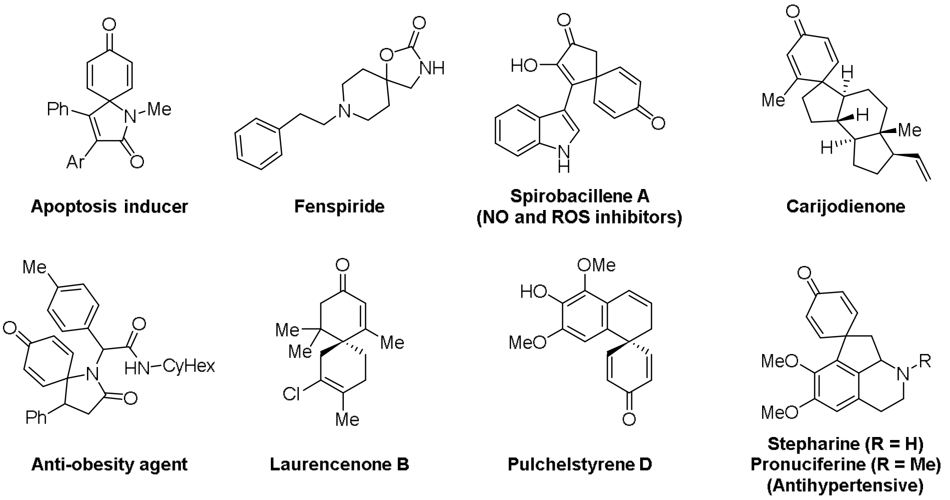
Abstract. *Spirocyclic [n.5]enone derivatives exhibit a wide range of biological activities and are commonly found in natural products, and can serve as key synthetic intermediates in organic synthesis. Developing an efficient and environmentally friendly method for the synthesis of functionalized spiro[n.5]enone derivatives is important for expanding the diversity of these compounds, which is of significant importance in drug discovery. Electrochemical synthesis has recently emerged as a green, versatile, and powerful tool for the construction of functionalized spiro[n.5]enone derivatives through the dearomative spirocyclization process driven by the electrochemically formed radical or radical cation species under environmentally benign conditions. In this review, we highlight the recent progress made in the electrochemical synthesis of diversified functionalized spiro[n.5]enone derivatives in the past decade.*

Contents

1. Introduction

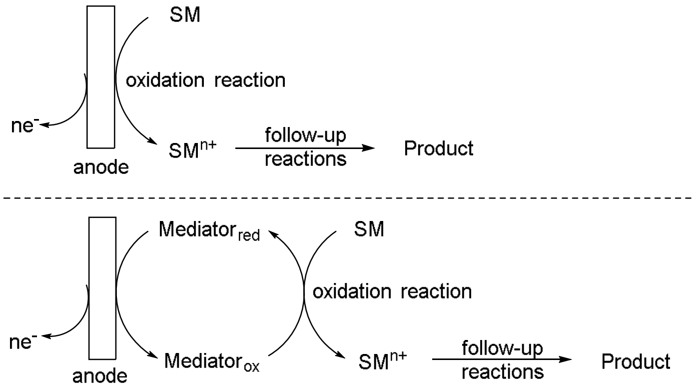
Spiro heterocycles appear as pivotal core units, which have wide prevalence in biological activities and natural products and broad application prospects in organic catalysis. The tetrahedral configuration of the carbon atom being shared leads to conformational constraints and structural intricacy, which could contribute to the enhanced diversity of biological activity and pharmacological properties.[1] Among them, spiro[n.5]enone frameworks are widely prevalent in chiral ligands, natural products, approved drugs, and drug candidates such as Spirobacillene A, Carijodienone, antimalarial drug candidate, apoptosis inducer, anti-obesity agent, Laurencenone B and so on (Scheme 1).[2] Introducing different functional groups into spiro[n.5]enone frameworks could enhance the diversity of molecular libraries and provide a series of drug candidates, which is of high importance in drug discovery. In recent years, considerable efforts have been devoted to the synthesis of diversified functionalized spiro[n.5]enone derivatives.[3] Although some elegant and remarkable achievements have been achieved in the past several decades, a general and green protocol access to a range of functionalized spiro[n.5]enones are still of great importance.

Radical-induced dearomatization process has attracted significant attention from synthetic chemists as it enables the transformation of easily available arene moieties into the desired spiro[n.5]enone skeletons bearing a stereogenic center in a straightforward manner.[4] Remarkably, diversified functionalization of spiro[n.5]enone derivatives, including alkylation, trifluoromethylation, phosphorylation, nitration, selenolation, and so on, can be achieved by this strategy under conventional conditions. However, the use of stoichiometric amounts of oxidants and transition-metal salts was required to generate either the radicals from the precursors, or the radical cations species from the substrates in most cases. In this context, electrochemical synthesis has emerged as a green, versatile, and efficient tool to access highly reactive radical and radical ion intermediates under external oxidation-free conditions, as electrons are utilized as traceless redox agents to activate various substrates, which could avoid unwanted side reactions and tedious work-up procedures.[5] On the other hand, owing to the development of electrochemical theory and apparatus, electrochemical synthesis has been applied to some bulk chemical productions over the past decades.[6] For example, bleached montan wax can be produced in 11000 tons per year by using electrogenerated chromic acid in Clariant company, which was technically applied by several companies.[7] Noteworthy, the synthetic scalability of electrosynthesis has well been illustrated in those cases, making it highly appealing for industrial production.



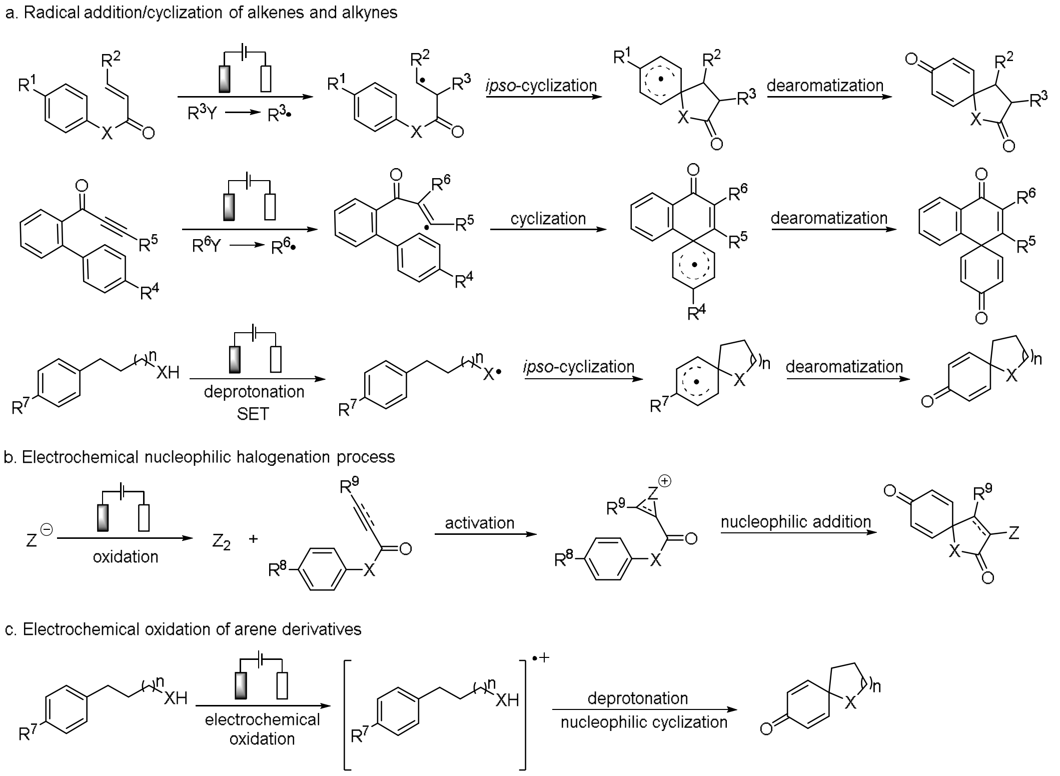
Scheme 1. Selected examples of biologically active spiro[n.5]enones and natural products.

From a mechanistic perspective, electrochemical oxidation can be classified into two types: direct electrolytic oxidation and indirect oxidation. In the first case, reactants could lose electrons directly at the surface of anode in a heterogeneous electron transfer process, resulting in the formation of activated species *in situ*. These activated species can then undergo further transformations to yield the final product. On the other hand, indirect oxidation has been driven by the redox mediator, which could be activated on the surface of the anode. Then the reactants could be converted to the key intermediates in the presence of the mediator in a homogeneous electron transfer process. Remarkably, indirect oxidation could circumvent the hindrance in the kinetics of heterogeneous electron transfer between the electrode and substrates, which means that overpotentials could be avoided. Moreover, different and higher selectivity could be obtained by indirect oxidation process in some cases (Scheme 2).[8]



Scheme 2. Electrochemical direct oxidation and indirect oxidation.

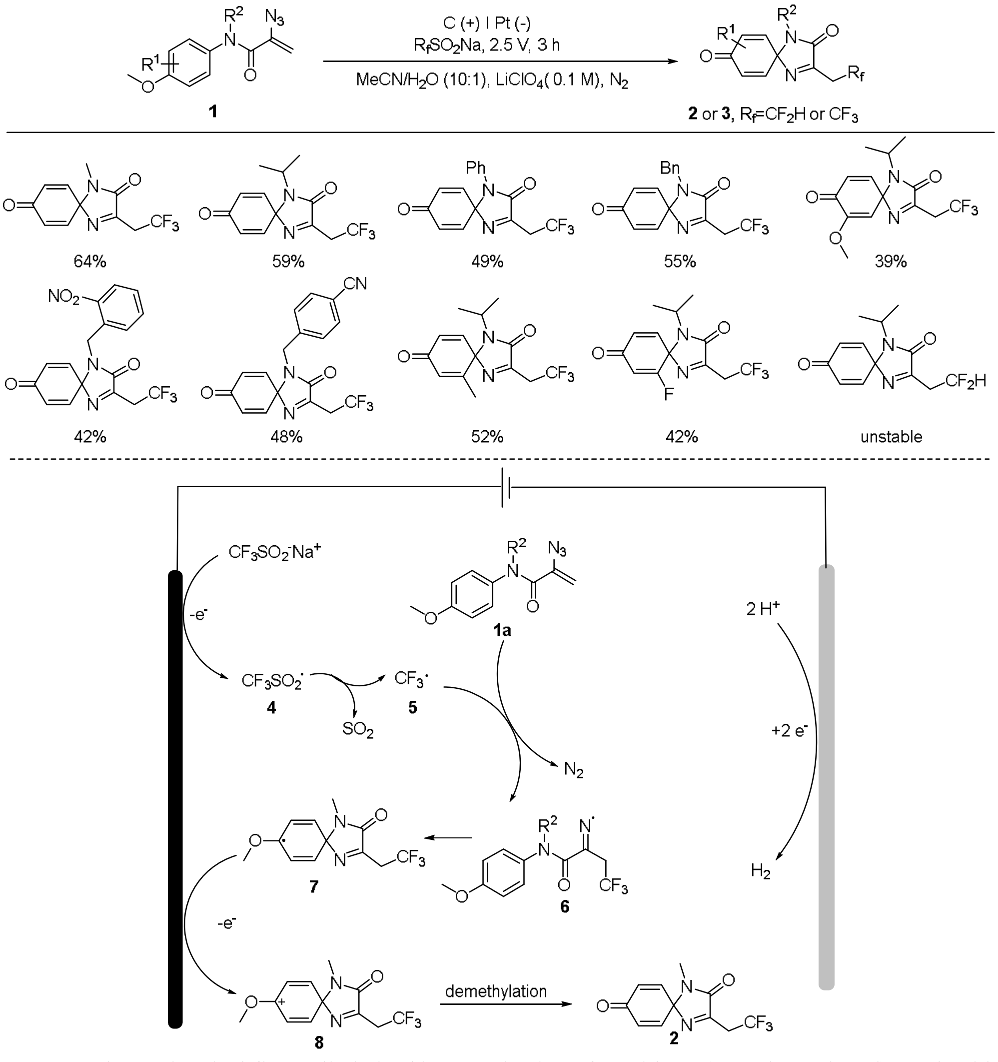
In recent years, electrochemical synthesis of functionalized spiro[n.5]enone derivatives have drawn increasing attention.[9] In contrast to the conventional synthesis, electrochemical protocol can simplify the difficulty of workup, improve the functional group tolerance in the absence of external bases, oxidants, and metal salts, which could be of great importance in the scalability and sustainability. On the other hand, electrochemical synthesis requires a suitable apparatus to be performed. Remarkably, a range of functionalized spiro[n.5]enones can be isolated in moderate to good yields on a gram scale in most electrochemical cases. In general, there are three pathways for the synthesis of functionalized spiro[n.5]enones (Scheme 3). First, the corresponding radical species could be formed from the precursors *via* either electrochemical direct oxidation or indirect oxidation, the key radical intermediate could be obtained by the following radical addition to alkene or alkyne moiety of substrates. The final dearomative product could be furnished through the subsequent radical cyclization and oxidation process. Second, alkene and alkyne moiety could be activated by bromine, formed by electrochemical oxidation at the surface of the anode, to give the key bromonium ion species. the halogenated spiro-cyclization product could be formed by nucleophilic addition process in the presence of base. Third, electron-rich arene derivatives could be converted to the corresponding radical cation species through electrochemical oxidation, which could be trapped by the nucleophilic side chain to give the formation of functionalized spiro[n.5]enones. In this review, we will focus on electrochemical synthesis of diversified functionalized spiro[n.5]enones over the past decade, which can be classified into three main categories: i) electrochemical synthesis of functionalized spiro[4.5]dienone derivatives; ii) electrochemical synthesis of functionalized spiro[4.5]trienone derivatives; iii) electrochemical synthesis of functionalized spiro[5.5]trienone derivatives.



Scheme 3. General pathways for electrochemical synthesis of functionalized spiro[n.5]enones.

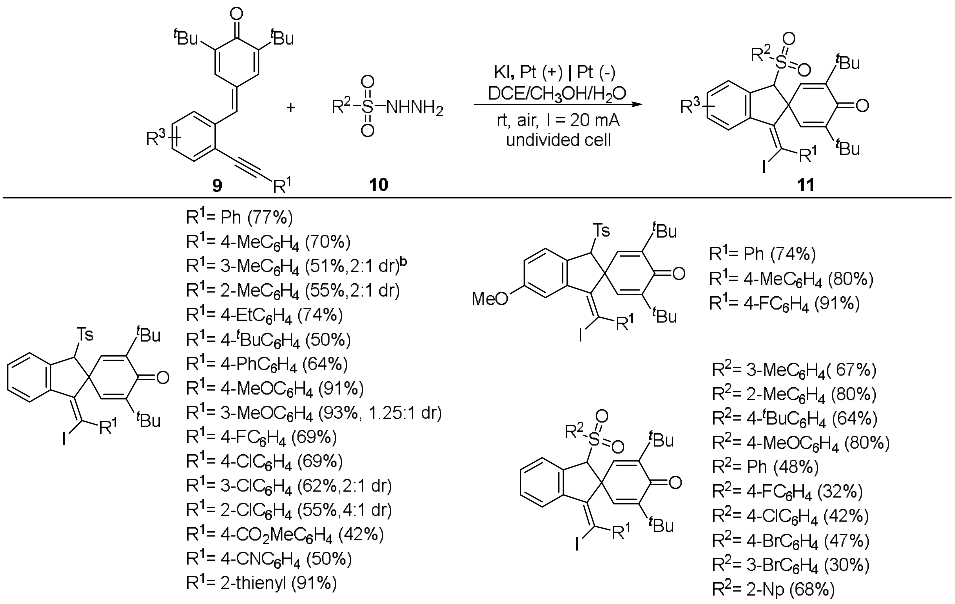
2. Electrochemical synthesis of functionalized spiro[4.5]dienone derivatives

In 2020, the Xu group developed an electrochemical fluoroalkylation-dearomatization of 2-azido-*N*-(4-methoxyphenyl) acrylamide **1**, leading to a range of trifluoromethylative aze-spiro[4.5]dienone derivatives **2** through the intermediates **4**, **5**, **6**, **7**, **8**. The reactions were performed in an undivided cell, equipped Pt plate as the anode and carbon plate as the cathode in constant voltage mode in the presence of CF_3SO_2Na, as an inexpensive and bench-stable fluorine source. Besides the synthesis of trifluoromethylative aze-spiro[4.5]dienone derivatives, this strategy has been proven suitable to give the formation of trifluoromethylative phenanthridines when biaryl vinyl azides were employed as the substrates under the same conditions. Moreover, difluoroethylated *N*-heterocycles **3** were also obtained when CF_2HSO_2Na was subjected to the same electrochemical conditions (Scheme 4).[10] To shed light on the mechanism, some cyclic voltammetry experiments were carried out by the authors, which suggested that CF_3SO_2Na was more likely to be oxidized first. Likely, the aza-spiro[4.5]dienones formed through radical addition/dearomatization manner.



Scheme 4. Electrochemical fluoroalkylation/dearomatization of 2-azido-*N*-(4-methoxyphenyl) acrylamides.

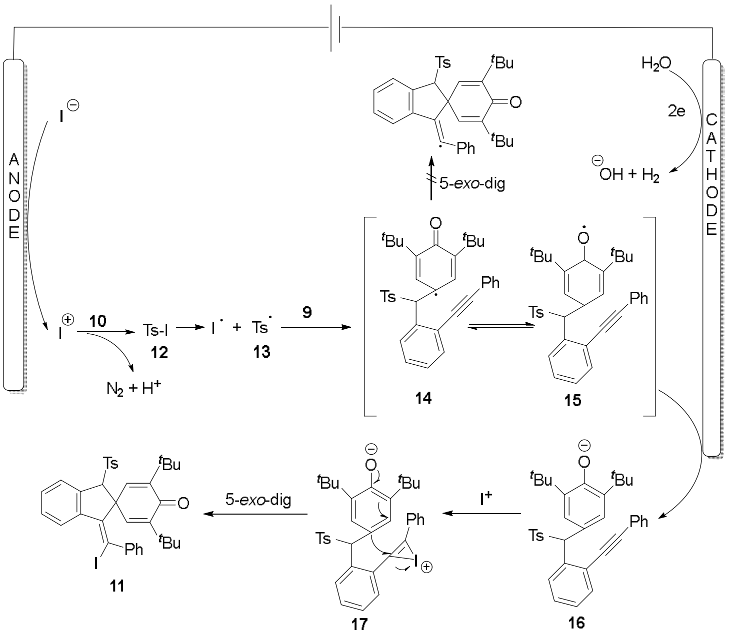
In 2020, the Jiang group released the electrochemical synthesis of spirocyclohexadienone-containing (*E*)-indenes **11** through annulation/iodosulfonylation of 1,5-enyne-containing *para*-quinone methides **9** (Scheme 5).[11] The reactions were performed by using available arylsulfonyl hydrazides **10** and potassium iodide in an undivided cell in constant current mode, without any additional catalyst or oxidant. Interestingly, potassium iodide was thought to act as the triple role of an electrolyte, a redox catalyst, and an iodination reagent. Moreover, the authors found that the current density was crucial to achieving high efficiency, as the weak current only can give the formation of the 1,6-addition product, which has been identified as the key intermediate in the following control experiment. Noteworthy, this electrochemical protocol could be easily amplified on 2.0 mmol scale under standard conditions.



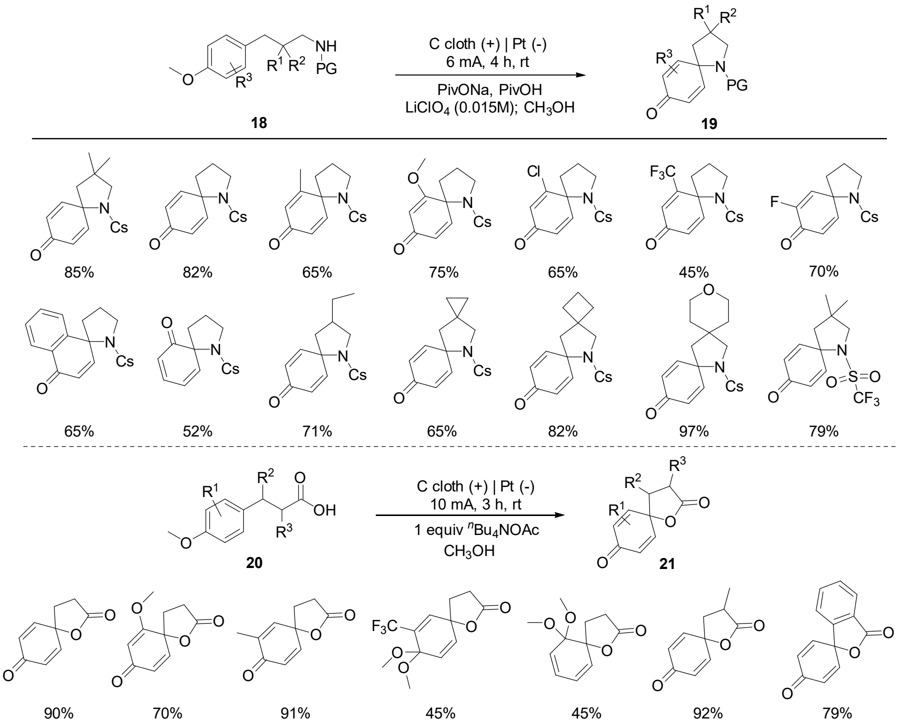
Scheme 5. Electrosynthesis of spirocyclohexadienone-containing (*E*)-indenes.

Given these results of cyclic voltammetry experiments, the authors found that KI was more likely to be oxidized than the substrate **9** and $TsNHNH_2$ under electrochemical conditions, leading to the formation of iodonium I^+, which can react with *p*-tosylsulfonyl hydrazide to generate the arylsulfonyl iodide intermediates **12**. Subsequently, the key arylsulfonyl radical species **13** could be formed through homolysis. Followed by radical addition to the 1,5-enyne-containing *p*-quinone methide **9**, the corresponding cyclohexadienone radical **14** could be obtained, which could be converted to the phenol anion spices **15**. Finally, the activation of the triple bond of **16** by iodonium I^+ could give the highly reactive intermediate and **17**, which was thought to furnish the desired product **11** through intramolecular *ipso*-cyclization (Scheme 6).[11]

In 2022, the Lei group developed an electrochemical oxidation spiroamination of anisole derivatives **18**, which led to a series of spiropyrrolidines **19** with diverse functional groups in moderate to excellent yields (Scheme 7).[12] The reactions were performed in an undivided cell in constant current mode. Interestingly, the authors found that the base was crucial in this process, and the extra addition of PivOH in the presence of PivONa could improve the selectivity toward **19**. Noteworthy, the Cs group, a more electron-withdrawing group than the Ts group, has been proven more efficient, which has been attributed to suppressing the oxidation of the amino moiety. Moreover, the corresponding spirolactones **21** could be obtained in good yields under slightly modified conditions when *para*-methoxyphenylpropioinc acids **20** were used as the starting materials. Additionally, the potential application of this protocol was demonstrated by the synthesis of **19** and **20** on the gram scale in an electrochemical flow cell.



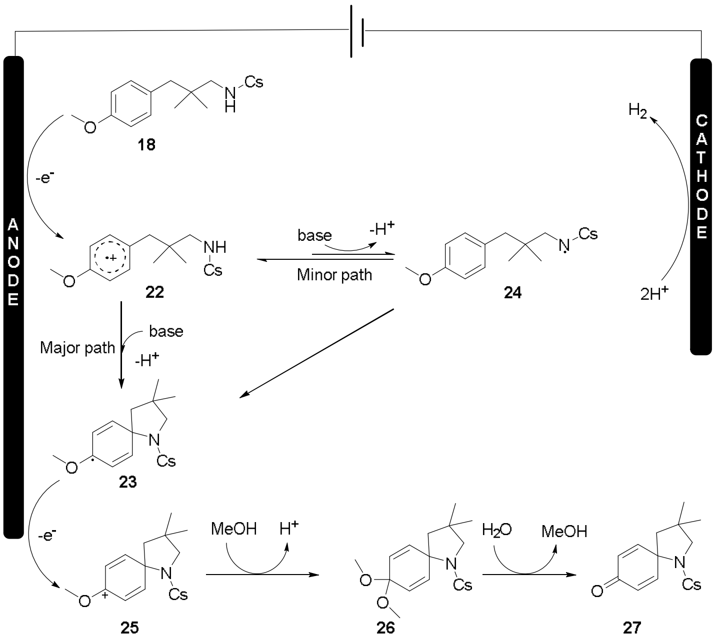
Scheme 6. Proposed mechanism for electrosynthesis of spirocyclohexadienone-containing (*E*)-indene.



Scheme 7. Electrochemical synthesis of spiropyrrolidines and spirolactones.

To determine whether the aromatic core or the amino group was more easily oxidized, the oxidation potential of *p*-propylanisole, *n*-PrNHCs, and **18** were studied by cyclic voltammetry experiments. They suggested that the aromatic moiety was involved in the initial oxidation.

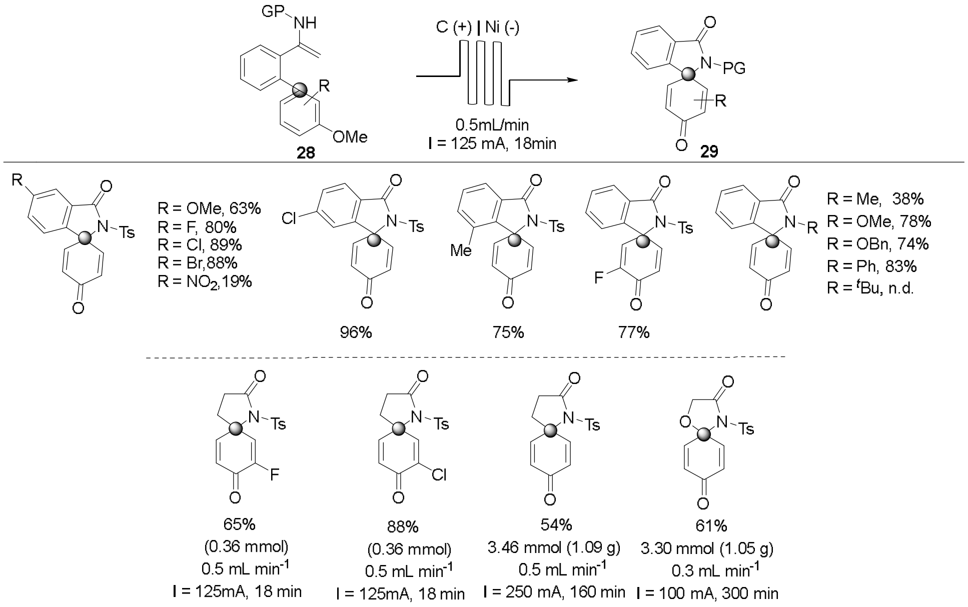
The effect of the base was tested by ^{1}H NMR experiments, which indicated that the N-H bond of **18** could be activated in the presence of the base. Based on these results and literature reports, a plausible mechanism is illustrated in Scheme 8. First, the radical cation **22** could be formed through the direct oxidation of the substrate. In the presence of base, the intermediate could be converted to the radical intermediate **23**. Followed by further oxidation, the carbon cation **25** could be furnished, which was thought to be trapped by methanol to give the diol intermediate **26**, the desired product could be formed through the hydrolysis of **26** to give **27**. However, the formation of the radical intermediate **23** could also be driven by adding the nitrogen-centered radical intermediate **24** to the aromatic core.[12]



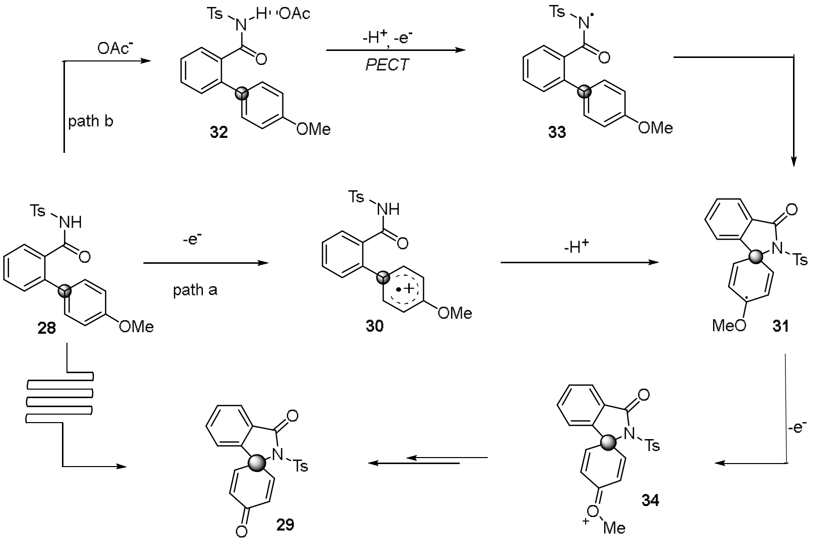
Scheme 8. Proposed mechanism for electrochemical synthesis of spiropyrrolidines.

In 2022, the Ye group reported an electrochemical dearomative spirocyclization of arenol derivatives **28** for the synthesis of spirodienones **29** in flow (Scheme 9).[13] Compared to conventional batch synthesis, continuous flow electrosynthesis is greener and more sustainable, as can be electrolyte-free owing to the very close distance between two electrodes. Interestingly, the authors found that HFIP played a crucial role in this process, which has been attributed to its unique capability in stabilizing the electrochemically generated radical and radical cation intermediates. Additionally, the precious platinum electrode can be replaced by a much more economical nickel cathode in the electrochemical flow reactor. Remarkably, this electrochemical dearomative strategy is not only suitable to biphenyl skeletons, but also to the substrates with the all-carbon or oxygenated tethers between the methoxyphenyl and amide moieties.

Given the significant gap in the oxidation potential between *N*-tosylbenzamide and 4-methoxy-1,1'-biphenyl, the authors thought the first electrochemical single-electron oxidation occurs at the methoxyphenyl moiety of the substrate **28**, which could give the key radical cation intermediate **30**. On the other hand, the amidyl radical **33** could be obtained through the proton-coupled electron transfer process of **32** in the presence of the acetate ion, the key radical intermediate **31** could be generated by the follow-up radical spirocyclization. Finally, the desired product **29** could be afforded from the cyclohexadienyl oxonium species **34**, which was thought to form in a second anodic single-electron oxidation (Scheme 10).[13]

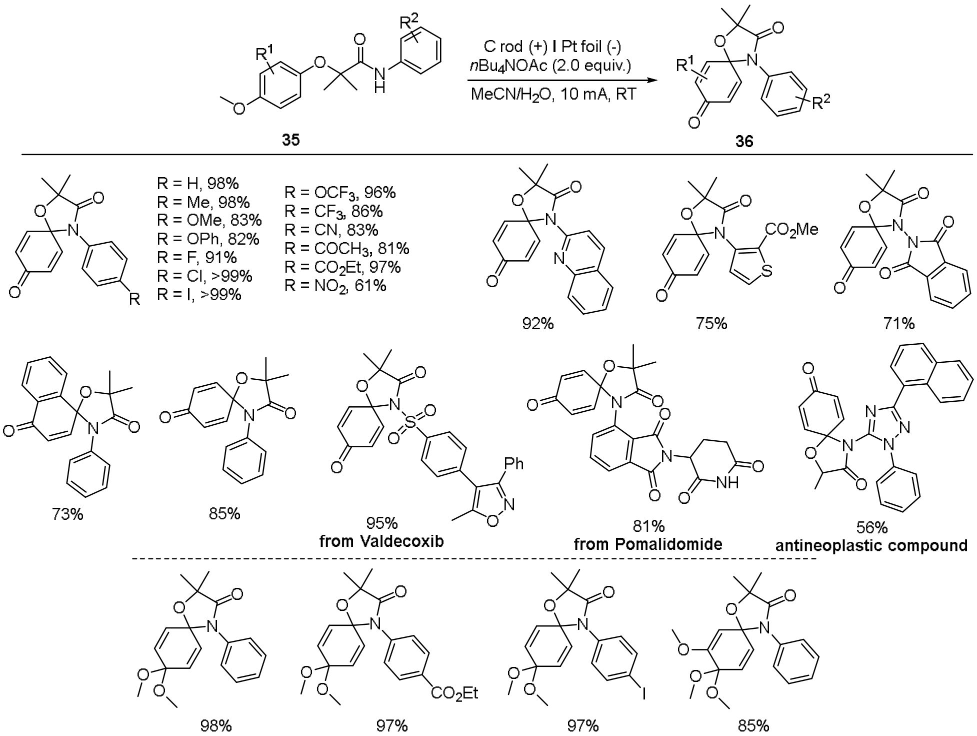


Scheme 9. Electrochemical synthesis of spirodienones in flow.



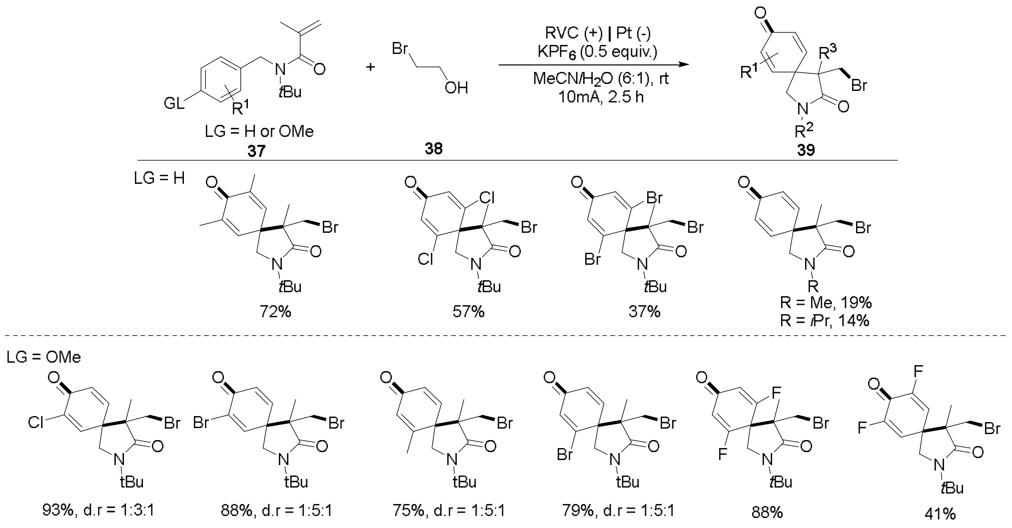
Scheme 10. Proposed mechanism for electrochemical synthesis of spirodienones in flow.

In 2023, the Huang group reported an electrochemical synthesis of spirooxazolidinones **36** through dearomative amination of phenol derivatives **35** in the absence of metal catalysts and external chemical oxidations (Scheme 11).[14] The reactions were carried out in an undivided cell equipped with a carbon rod anode and a platinum foil cathode at room temperature in constant current mode, and presented a broad substrate scope and diverse functional group compatibility. The presence of water has been proven crucial in this process and the ratio of MeCN/H_2O had a dramatic effect on the efficiency. Interestingly, the deprotection of the *para*-methoxyphenyl (PMP) group of the substrates could be achieved under slightly modified electrochemical conditions. Based on the cyclic voltammetry studies and control experiments, a plausible mechanism driven by the electrochemical oxidation of *p*-methoxybenzene moiety in the substrate was proposed by the authors, which is in line with Ye's work.

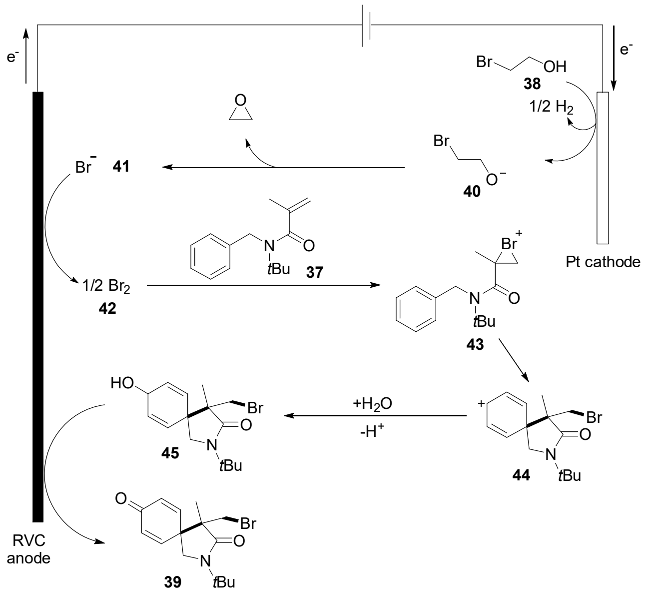


Scheme 11. Electrochemical synthesis of spirooxazolidinones.

In the same year, the Wang group released an electrochemical synthesis of brominated 2-azaspiro[4.5]decances **39** through electrophilic bromination/spirocyclization of *N*-benzyl-acrylamides **37** in the presence of **38** (Scheme 12).[15] After the extensive screening of bromides sources, 2-bromoethan-1-ol has been proven efficient in this process. Moreover, the authors found that the proportion of water in the mixed solvent has a significant effect on the reaction efficiency. Interestingly, different *para*-substituents on the benzyl moiety of substrates were tested, *N*-(4-alkoxybenzyl)-, *N*-(4-Fluorobenzyl)acrylamide could be converted to the desired products in moderate to good yields. Noteworthy, the steric hindrance of the protecting groups on nitrogen proved to be crucial in this transformation. Unfortunately, *N*-(4-unsubstituted-benzyl)-acrylamide was not compatible to give the formation of the same product. Additionally, a range of cyclohepta[*c*]pyrrole-1,6-diones were furnished in good yields when different nitrogen-containing heterocycles served as the nucleophiles to attack the brominated 2-azaspiro[4.5]decanes in the presence of base. To shed light on the mechanism, some control experiments were carried out by the authors. The reaction proceeded smoothly in the presence of Br_2 without electricity, which suggested that Br_2 could be involved in this process. Given the result of the ^{18}O-labelling experiment, the newly formed oxygen in the product was thought to be derived from H_2O. Based on these results, a plausible mechanism is illustrated in Scheme 13.[15] First, an alkoxy anion **40** could be reduced from 2-bromoethan-1-ol at the surface of cathode, which was thought to give the Br^- **41** by the intramolecular cyclization. Subsequently, the key species Br_2 **42** could be obtained by anodic oxidation, which could react with **37** to generate the bromonium ion intermediate **43** through the electrophilic addition/cyclization manner, then the cationic intermediate **44** could be trapped by H_2O. Finally, the second oxidation of **45** could give the final product.

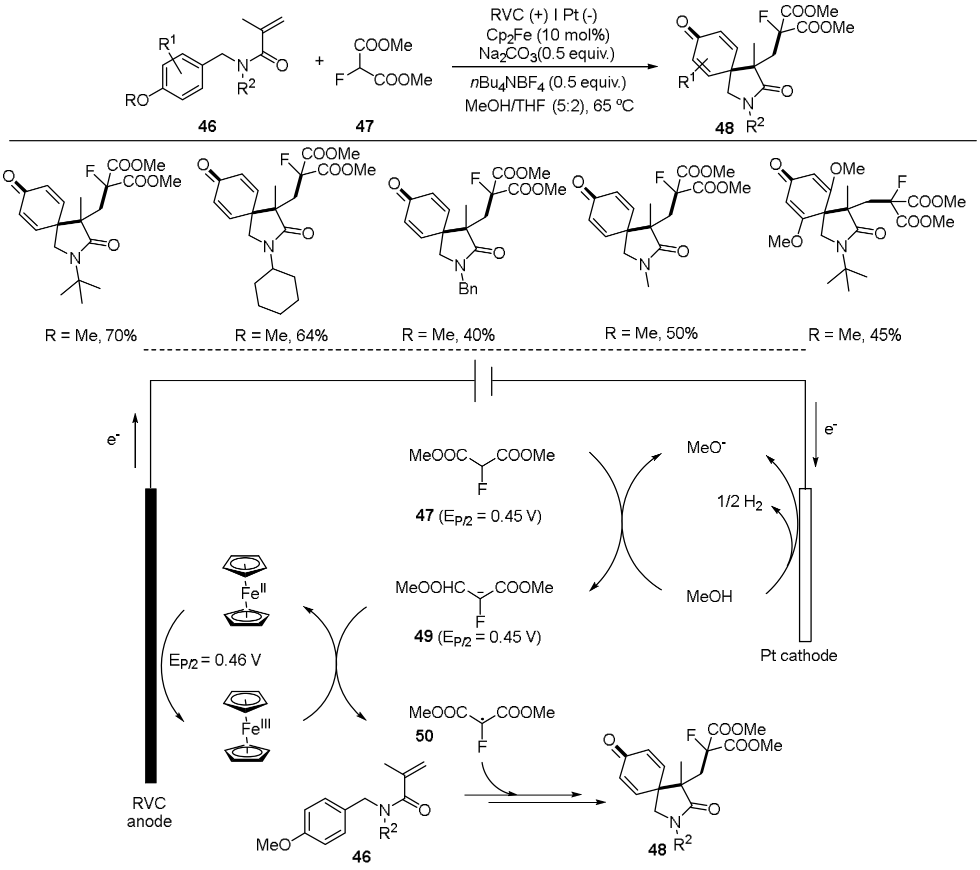


Scheme 12. Electrochemical synthesis of brominated 2-azaspiro[4.5]decanes.



Scheme 13. Proposed mechanism for electrochemical synthesis of brominated 2-azaspiro[4.5]decanes.

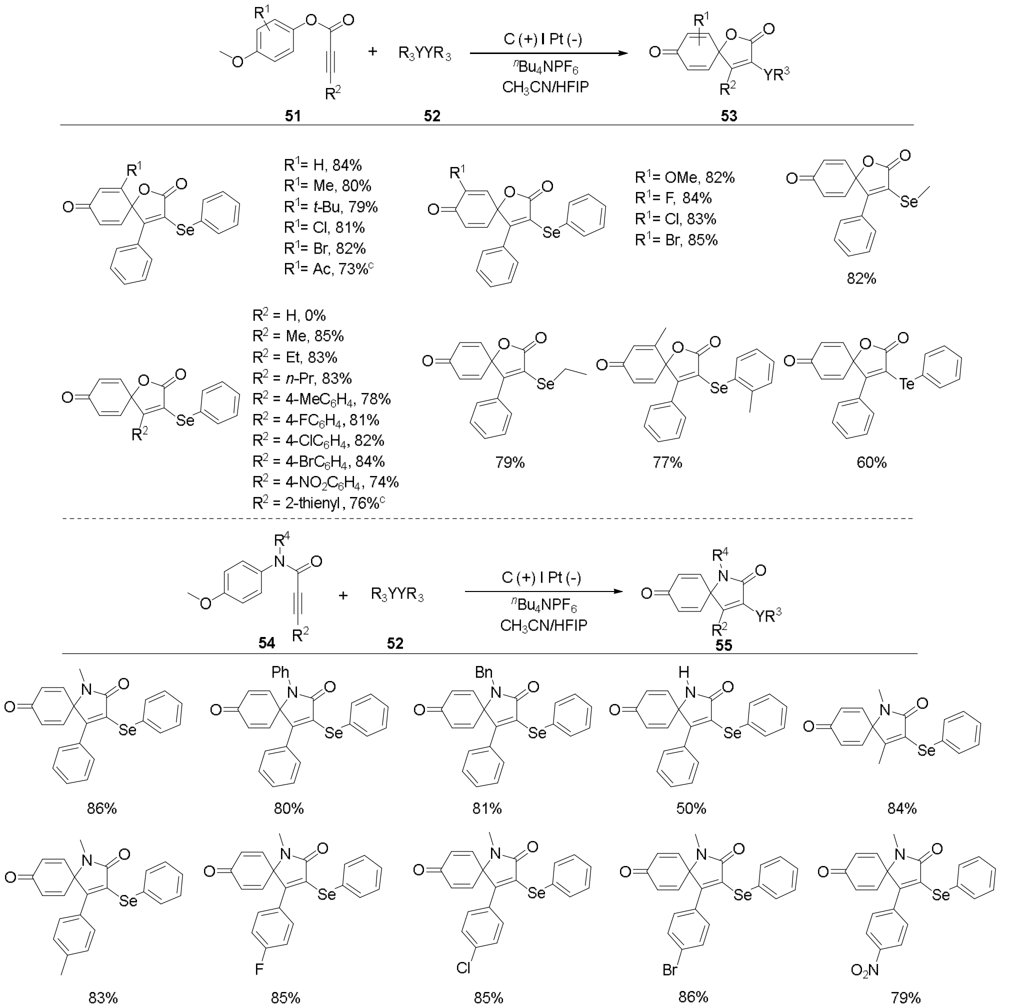
In 2023, the same group developed an electrochemical synthesis of monofluoroalkylative 2-azaspiro[4.5]decanes **48** through the spirocyclization of *N*-(4-alkoxybenzyl)acrylamides **46** with fluorodimethyl malonate **47**, which can lead to a range of dearomative products in moderate yields under the mild conditions (Scheme 14).[16] Noteworthy, the same strategy has been proven efficient in the preparation of monofluorinated 2-oxindoles, and indole[2,1-a]isoquinolines. Importantly, the authors found that Cp_2Fe and Na_2CO_3 played crucial roles in this transformation, since the reaction failed to give the desired product in the absence of either Cp_2Fe or Na_2CO_3. In contrast to the previous work, this dearomatization process was thought to be driven by the electrochemically formed monofluoroalkyl radical. Firstly, Cp_2Fe could be oxidized to form Cp_2Fe^+ at the surface of the anode, which could react with the carbanion intermediate formed through the deprotonation of **49** to generate the monofluoroalkyl radical species **50**. Followed by radical addition and *ipso*-cyclization process, the final dearomative product could be obtained.



Scheme 14. Electrochemical synthesis of monofluorinated 2-azaspiro[4.5]decanes.

3. Electrochemical synthesis of functionalized spiro[4.5]trienone derivatives

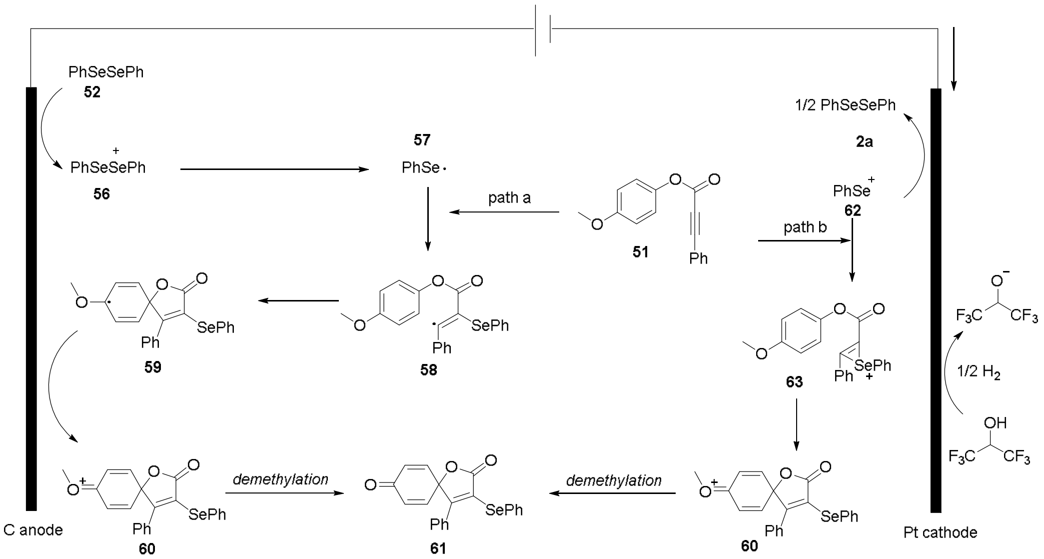
In 2020, the Guo group released an electrochemical synthesis of spiro[4.5]trienones **53** through radical cascade reaction of alkynoates **51** with diselenides **52** as selenium radical precursors. A broad substrate scope and good functional group tolerance were demonstrated (Scheme 15).[17] The reactions were performed in an undivided cell equipped with graphite rod anode and platinum plate cathode in constant current mode at room temperature. HFIP was proven crucial to the reaction efficiency, which resulted from its low-nucleophilicity and protic nature. Interestingly, the substitute group on the oxygen atom of the substrate can be expanded to *t*-butyl, or benzyl group, the same product can be isolated in good yield. Moreover, the tellurium-substituted spiro[4.5]trienones can be obtained when diphenyl ditelluride was subjected to the same conditions. Besides alkynoates, alkynamides **54** have been proven suitable to give the corresponding spirocyclization products **55** in reasonable yields. Remarkably, electrochemical continuous flow system has been applied to the scale-up reaction, which is superior to the batch reactor.



Scheme 15. Electrochemical synthesis of spiro[4.5]trienones from alkynes and diselenides.

Based on the results of the control experiments and the previous works, the authors thought that diphenyl diselenide is more likely to be oxidized to give the cationic radical intermediate **56**, which could be converted to the phenylselenium radical **57**. Followed by the radical addition to alkyne moiety, the key vinyl radical **58** could be obtained, which was thought to give the formation of oxygenium cation species **60** through the intramolecular spirocyclization of **58** and the second anodic oxidation of **59**. Finally, the desired compound **61** could be formed through the demethylation of **60**. On the other hand, the pathway involved by the phenyl selenium cation **63**, derived by reaction of alkynoates **51** with phenyl selenium cation **62**, could not be ruled out by the authors (Scheme 16).[17]

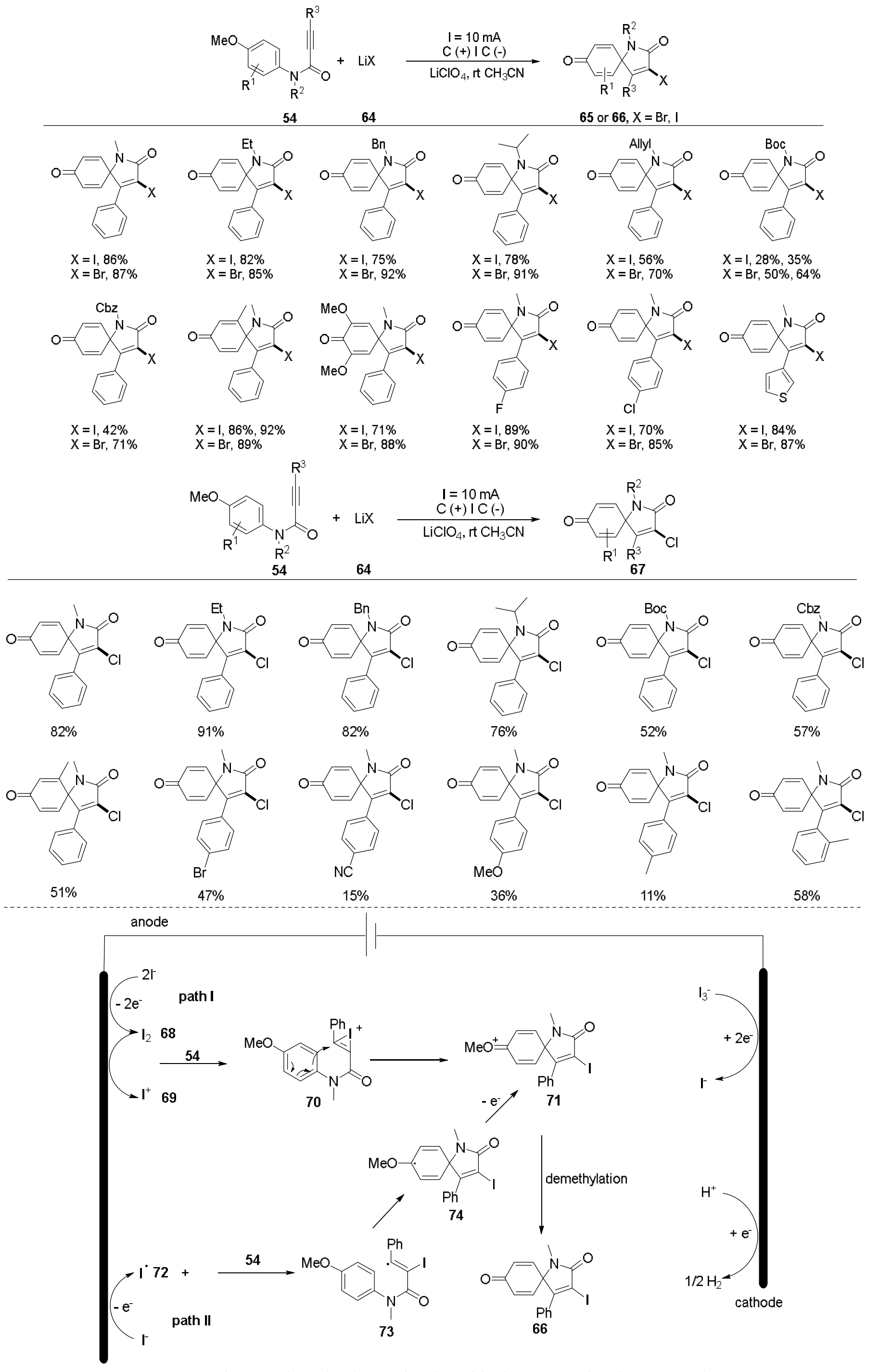
In 2020, the Xu group developed an electrochemical synthesis of halogenated spiro[4.5]trienones through oxidative dearomatization of *N*-aryl alkynamides **54**. A broad substrate scope and functional group tolerance have been demonstrated (Scheme 17).[18] The reactions were carried out in an undivided cell by using readily available LiCl, LiBr, and LiI **64** as the halogen source under metal-catalyst- and exogenous-oxidant-free conditions at room temperature to give the relevant bromo/iodo derivatives **65** and **66**. In contrast to the previous works, the author proposed that the oxygen atom of the ketone group could derive from the methoxy group of the substrate, as the reaction underwent smoothly under nitrogen atmosphere. Besides the iodination and bromination of *N*-aryl alkynamides, the dearomative chlorination to **67** could also be achieved when LiCl served as the chlorine source. Furthermore, the potential applicability of this electrochemical protocol was well illustrated by a scale-up experiment. Based on the results of cyclic voltammetry experiments, the anodic oxidation of LiI was thought to occur first, which could give the formation of iodine cation **69** from **68**. Then the cyclic iodonium **70** could be generated from **54** through the activation of the C≡C triple bond to give **71**, which could be converted to the final product **66** in a thermodynamically controlled *ipso*-electrophilic spirocyclization manner. Remarkably, the other pathway driven by the iodine radical **72**, formed by the anodic oxidation, could not be excluded by means of **73** and **74** intermediates.



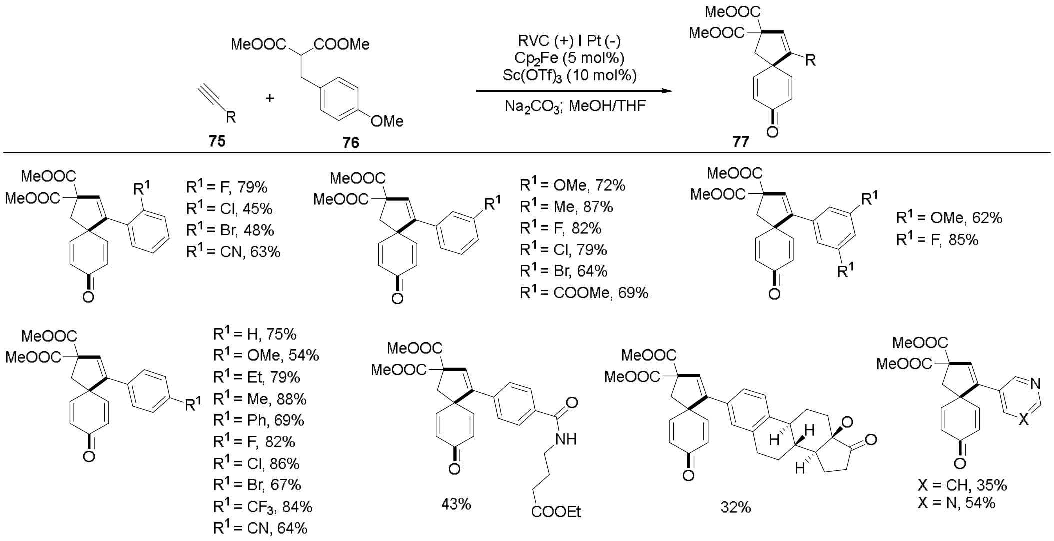
Scheme 16. Proposed mechanism for electrochemical synthesis of spiro[4.5]trienones from alkynes and diselenides.

In 2022, the Chen group reported an electrochemical synthesis of 3-halogenated spiro[4.5]trienones through the same strategy using NaX (Br, I) as the halogen source. Noteworthy, the substrate scope could be expanded to *N*-(alkynoyl)-6-methoxytetrahydro-quinolines, which could furnish a series of halogenated pyrrolo-[2,1-j] quinolones under the same electrochemical conditions. Moreover, the authors proposed a plausible mechanism, which is in line with the previous work.[19]

In 2022, the Wang group developed an electrochemical synthesis of spiro[4.5]deca-trienones **77** through dearomative spirocyclization of alkynes **75** with dimethyl 2-benzylmalonates **76** (Scheme 18).[20] The reactions were carried out in the presence of the catalytic amount of Cp_2Fe, which served as an electrocatalyst, in an undivided cell, leading to a series of spiro[4.5]deca-trienones with excellent yields from alkynes and dimethyl 2-benzylmalonates. The authors found that $Sc(OTf)_3$ played an important role in this reaction, which was thought to facilitate the conversion of ketals to ketones. Moreover, the type and amount of base and reaction temperature had a dramatic effect on the reaction efficiency. Noteworthy, this electrochemical dearomatization strategy was compatible with a series of sensitive functional groups such as alcohols, amides, amino acids, and biologically active molecules. The use of noble-metal reagents and C–Br-based malonates can be avoided.

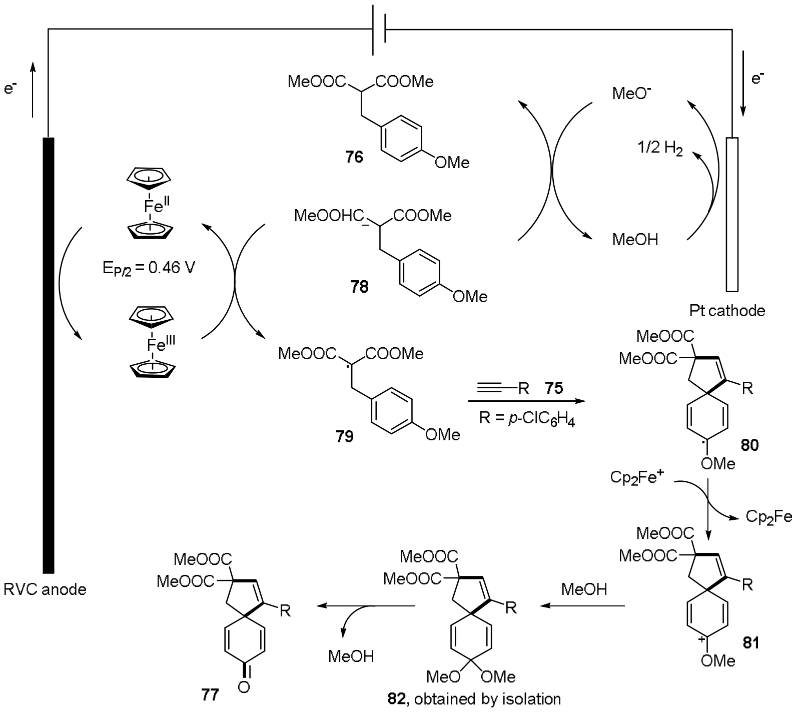


Scheme 17. Electrochemical synthesis of halogenated spiro[4.5]trienones.



Scheme 18. Electrochemical synthesis of spiro[4.5]deca-trienones.

Interestingly, 8,8-dimethoxyspiro[4.5]triene **82** could be obtained in an acceptable yield, when the same substrates were subjected to the same conditions for 2 h, and **82** could be converted to the desired compound **77** in an 85% yield in the absence of electricity. This suggested that **82** was the likely key intermediate. Given the results of control experiments, a plausible mechanism is illustrated in Scheme 19.[20]



Scheme 19. Proposed mechanism for electrochemical synthesis of spiro[4.5]deca-trienones.

Initially, the carbanion intermediate **78** formed through the deprotonation of **76** in the presence of MeO^-, is oxidized by the ferrocene cation to give the carbon-centered radical species **79**. Subsequently, the radical intermediate **80** could be generated by the radical addition cyclization of **75**, which could lead to the construction of the ketal **82** through the following oxidation and nucleophilic addition of **81**. Finally, the ketal could generate the spiro product in a $Sc(OTf)_3$-mediated hydrolysis (Scheme 19).

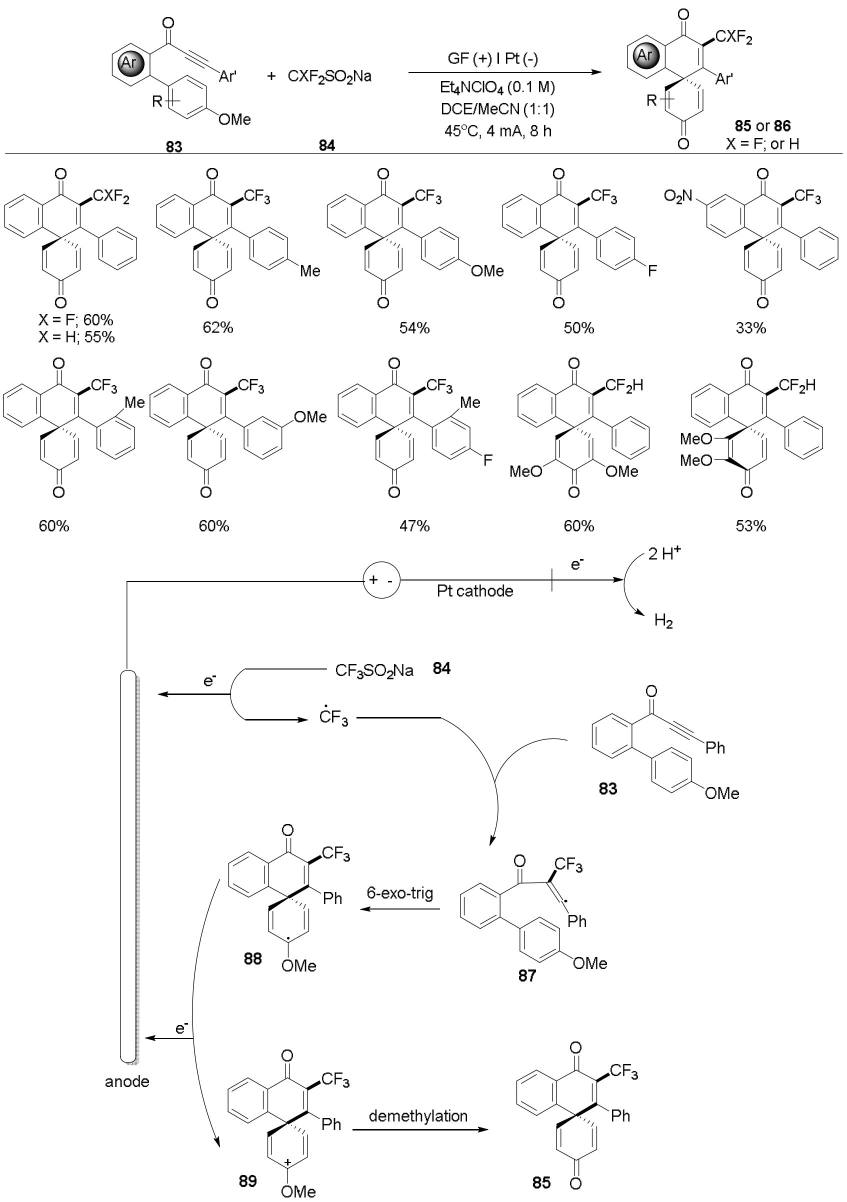
4. Electrochemical synthesis of functionalized spiro[5.5]trienone derivatives

In 2021, the Ackermann group developed an electrochemical synthesis of tri- and difluoromethylated spiro[5.5] trienones **85** and **86** through radical spirocyclization of biaryls **83** in an undivided cell and under a constant current mode (Scheme 20).[21] In contrast to previous works, this protocol could proceed smoothly in the absence of the catalytic redox mediator, in which CF_3 radical was thought to derive from $NaSO_2CF_3$ **84** through anodic oxidation. Moreover, the synthesis of difluoromethylated spiro[5.5]trienones **86** was achieved by using $NaSO_2CF_2H$ as the fluorine source under the same conditions. Noteworthy, the trifluoromethylated spiro[5.5] trienones could be readily converted to a range of more value-added scaffolds in one step. Based on the results of the control experiments, a plausible mechanism was provided by the authors. Initially, radical addition of CF_3 radical, formed through anodic oxidation from $NaSO_2CF_3$ **84**, to alkyne moiety of **83** gave the key intermediate **87**, which could be converted to the radical species **88** through 6-*exo*-trig cyclization. By the second oxidation, the oxocarbenium ion **89** could be obtained, which could be transformed into the final product by the subsequent demethylation.

In 2021, the Reddy group reported an electrochemical synthesis of selenylated spiro[5.5]trienones **90** through the spirocyclic dearomatization of biaryl ynones **83** under metal-free and chemical oxidant-free conditions (Scheme 21).[22] The reactions were carried out in an undivided cell equipped with graphite plate as the anode and platinum plate as the cathode in constant current mode. Noteworthy, the products could be tuned to the seleno-dibenzocycloheptenones in an intramolecular *ortho*-annulation manner, when the *para*-substitute of the substrates is not the methoxy group. Furthermore, the spirocyclization product could be obtained when 4-ethoxy biaryl ynone was subjected to the electrochemical conditions. The oxidation potential of diphenyl diselenide is lower than that of the substrate **83**, which suggested that diphenyl diselenide could be oxidized preferentially at the surface of the anode to generate the radical intermediate **91**. Followed by the radical addition and *ipso*-annulation process, the key radical intermediates **92** and **93** were obtained. Finally, the selenylated spiro product **90** was believed to form by the following dearomatization process of **94**.

In the same year, the Wang group released the electrochemical synthesis of SCF_3-containing spiro[5.5]trienones **96** by the trifluoromethylthiolative spirocycliztion of activated alkynes **83** with stable and readily available $AgSCF_3$ **95** (Scheme 22).[23] The reactions were carried out in an undivided cell equipped with two platinum plates as the anode and cathode in a constant current mode. Importantly, the authors found that the oxidation potential of $AgSCF_3$ was notably lower when utilizing a platinum plate rather than a glassy carbon as the working electrode, which was thought to be helpful for the reaction efficiency. Remarkably, the addition of NaCl was important to improve the reaction yield, which could be attributed to the slow reduction of silver anion at the surface of the cathode. Moreover, good functional group tolerance and good regioselectivity have been demonstrated in this electrochemical protocol.

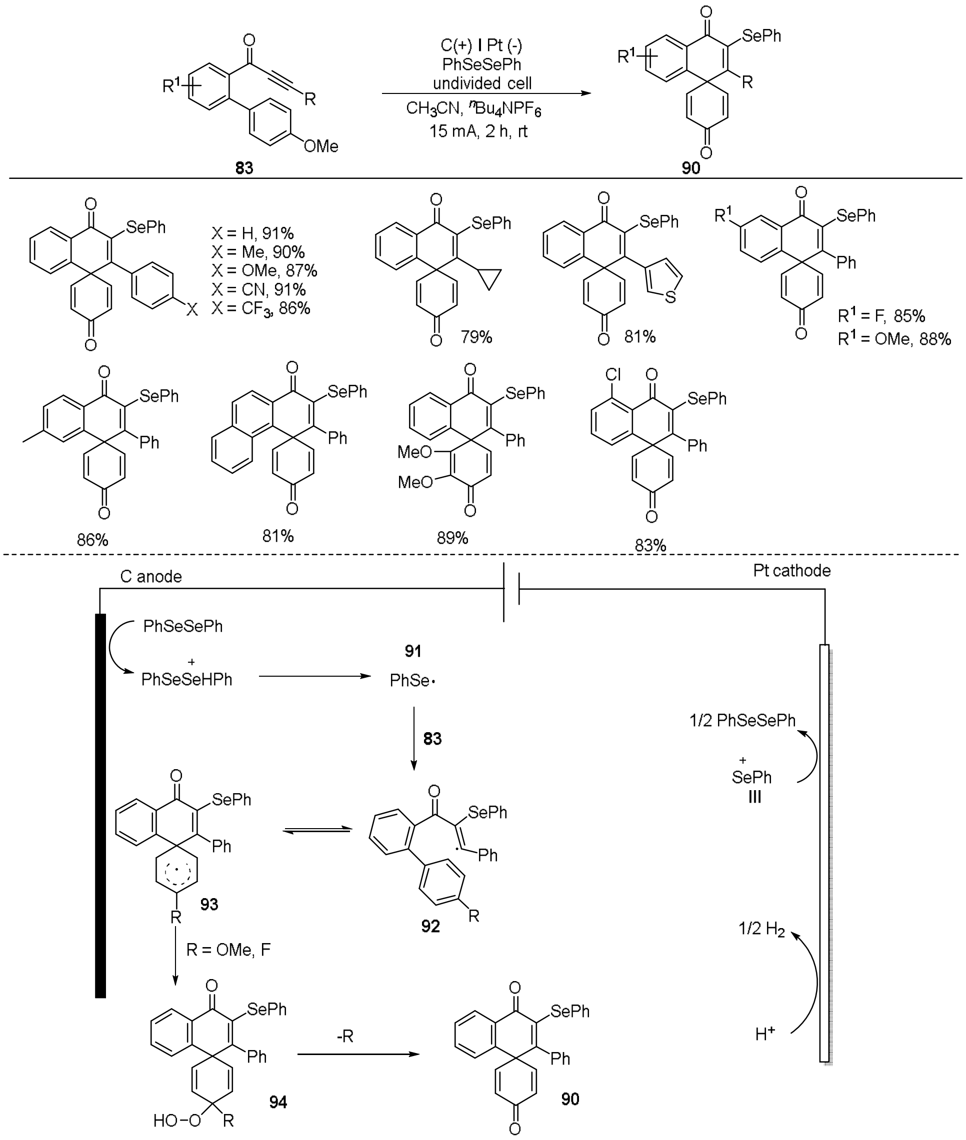
Based on the results of cyclic voltammetry analysis, $AgSCF_3$ **95** was proposed to be oxidized first with respect the substrate **83**, since a lower oxidation potential of $AgSCF_3$ was detected. The authors also performed the same reaction under anhydrous conditions, which gave the same dearomative product **96** in a slightly lower yield. This suggested that the main source of the newly formed oxygen was not from water. Based on these results and literature reports, a proposed mechanism is illustrated in Scheme 23.[23] The anodic oxidation of $AgSCF_3$ led to the formation of SCF_3 radical **97**, which could react with the alkyne moiety of the substrate **83** to access the key vinyl radical species **98**. Subsequently, **98** could be converted into the radical intermediate **99** *via* an intramolecular radical *ipso* cyclization. Finally, the spiro product **100** could be obtained through the following oxidation process, which could be converted to the final product **96** through the demethylation process.



Scheme 20. Electrochemical synthesis of tri- and difluoromethylated spiro[5.5]trienones.

5. Conclusion

Over the past ten years, significant advancements have occurred in the electrochemical synthesis of functionalized spiro[n.5]enone derivatives. This progress has led to the emergence of exciting methodologies for constructing spiro[n.5]enone frameworks under electrochemical conditions. To date, electrochemical synthesis has been applied to the preparation of halogenated, aminated, fluoroalkylated, trifluoromethylthiolated, selenolated spiro[n.5]enones, with the formation of new C−X, C−N, C−CF_3, C−SCF_3, C−Se bonds into the spiro-di/trienones skeletons. Significantly, the majority of these electrochemical transformations involve oxidative reactions without the need for stoichiometric sacrificial chemical oxidants, which could provide a green and sustainable pathway to diversified functionalized spiro[n.5]enones. Moreover, the good scalability of electrochemical synthesis has been well illustrated by the combination of electrochemistry and flow chemistry in some cases, which could be of high importance in the rapid preparation of diverse spirocyclic scaffolds.



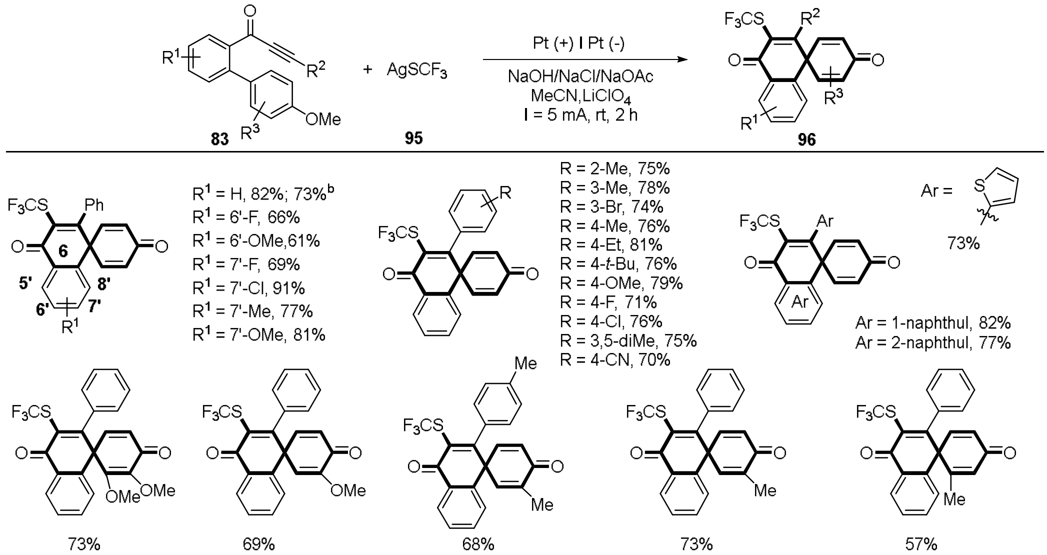
Scheme 21. Electrochemical synthesis of selenylated spiro[5.5]trienones.

Despite the aforementioned advancements, some challenges still persist in the electrosynthesis of spiro[n.5]enones. From the perspective of this review, we would like to list them as follow:

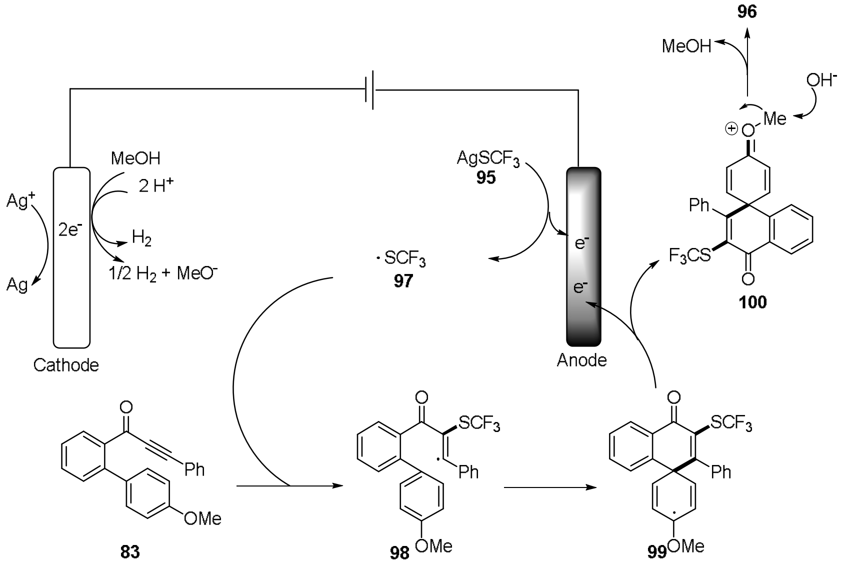
1) design novel electrochemical activation methods for arene derivatives to unlock new reactivity;

2) enriching the compound library by incorporating other functional groups into spiro[n.5]enones;
3) development of enantioselective synthesis of functionalized spiro[n.5]enones;
4) bioactivity study of spiro[n.5]enones to discover the potential drug candidate;

In conclusion, electrochemical synthesis of spiro[n.5]enones can offer a sustainable, efficient, and environmentally benign strategy to enrich the diversity of functionalized spiro-heterocycles, which could be highly important in drug discovery.



Scheme 22. Electrochemical synthesis of SCF$_3$-containing spiro[5.5]trienones.



Scheme 23. Proposed mechanism for electrochemical synthesis of SCF$_3$-containing spiro[5.5]trienones.

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