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Review

Advances in the Application of Acetonitrile in Organic Synthesis since 2018

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Abstract: Acetonitrile is commonly used as an organic solvent and can also be used as an important intermediate in organic synthesis. Its widespread use has led to the development of new methods for the synthesis of a variety of important compounds. In the past decades, the conversion reactions of acetonitrile as a building block have become one of the most-attractive fields in organic synthesis. Especially in the field of electrochemical conversions involving acetonitrile, due to its good conductivity and environmentally friendly features, it has become a powerful and compelling tool to afford nitrogen-containing compounds or nitrile-containing compounds. In this review, we mainly discuss the research progress involving acetonitrile in the past five years, covering both conventional synthesis methods and electrochemical synthesis. Besides, a detailed discussion of the substrate scope and mechanistic pathways is provided.

Keywords: acetonitrile; cyanomethylation; tetrasubstituted olefins; heterocyclic; amidation

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1. Introduction

Acetonitrile as a small polar molecule and has a high relative permittivity (ε_r = 36), which is conducive to the dissociation of ion pairs into free ions [1]. The bond dissociation energy D (H-CH_2CN) equals 4.03 ± 0.09 eV, and D (CH_3-CN) equals 5.36 ± 0.03 eV [2,3]. Furthermore, the methyl proton of acetonitrile is faintly acidic with p*K*a = 31.3 in DMSO. This means that acetonitrile can be deprotonated to form nucleophile, and the nitrogen with lone pair electrons can also act as a nucleophile. Additionally, the cleavage of the H_3C-CN bond or H-CH_2CN in CH_3CN generates $^{\bullet}CN$ or $^{\bullet}CH_2CN$ radicals. Therefore, acetonitrile can be used as an important synthon in many types of organic reactions.

Because of its enrichment, low price, and excellent solvent properties, acetonitrile has been widely applied as a common solvent in organic synthesis [4–8]. Acetonitrile is also an important synthetic intermediate and often used as a source of nitrogen for the preparation of typical nitrogen-containing compounds. For example, nitrile-containing compounds are widely used in medicines [9] and materials [10]. Acetonitrile has been reported as a reliable source of cyanide in chemical compounds [11–14]. On the other hand, heterocyclic structures are widely present in various natural products or synthetic compounds and are used in organic synthesis, agriculture, animal husbandry, and other fields. Some heterocyclic compounds are also used in medicine due to their biological activity [15,16]. Acetonitrile can also be utilized in the construction of a variety of heterocyclic compounds. Examples include the synthesis of pyridine, oxazole, and tetrazole [17–20].

Acetonitrile as a building block typically provides three active sites: two carbons and one nitrogen. Up to now, scientists have developed a variety of methodologies with regard to the transformation of acetonitrile, for example cyanomethylation, the Ritter reaction, cyanation, the cyclization reaction, etc. In 2018, Hoff's group [21] comprehensively reviewed

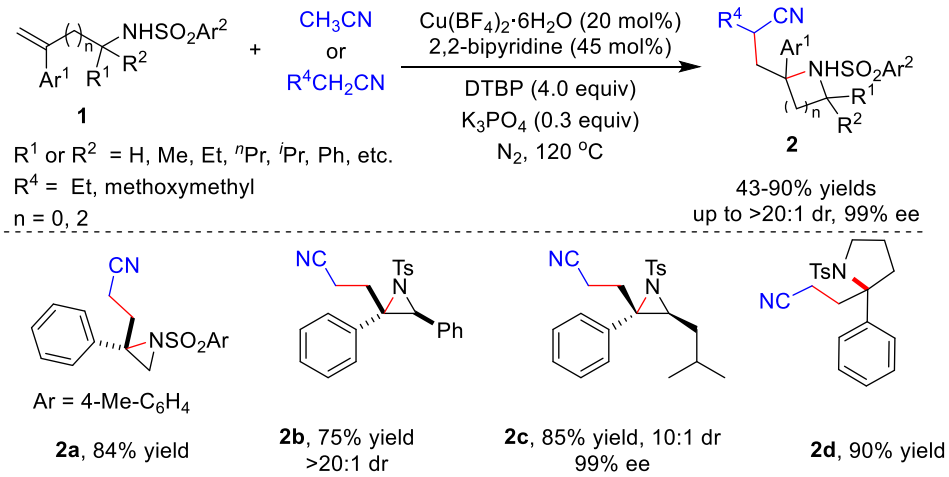
the multifarious reactions using acetonitrile before 2018, including classical approaches and modern strategies. Subsequently, Sawant and colleagues [22] showed that various reaction solvents, such as DMF, DMSO, DMA, MeCN, $CHCl_3$, and DCM, all can serve as a polyfunctional building block for the organic synthesis reaction, which mainly covers work prior to 2019. Although these reviews have been reported, a comprehensive summary of the reaction development, scope, and mechanism of electrochemical transformations involving acetonitrile is still absent. Moreover, in the past five years, many great advances have been developed in this field, especially in electrochemical synthesis. Therefore, this review summarizes the research progress of acetonitrile as a reagent, including cyanomethylation, the electrochemical oxidative cross-coupling reaction, the heterocyclic reaction, and amidation since 2018. We mainly focused on recent reports (2018 onwards), and previous reports were not included here.

2. Cyanomethylation Reaction

Cyanomethylation is very useful in organic synthesis because the cyano groups can be hydrolyzed to carboxylic acids and reduced to amines, from which other functional groups can be derived [23–26]. In addition, the cyano group is the structural unit of many drugs, such as piritramide, diphenozlate, and gallopamil [27], while acetonitrile is an ideal source of the cyanomethyl functional group due to the difficulty in breaking the C-CN bond.

2.1. Metal-Catalyzed Cyanomethylation

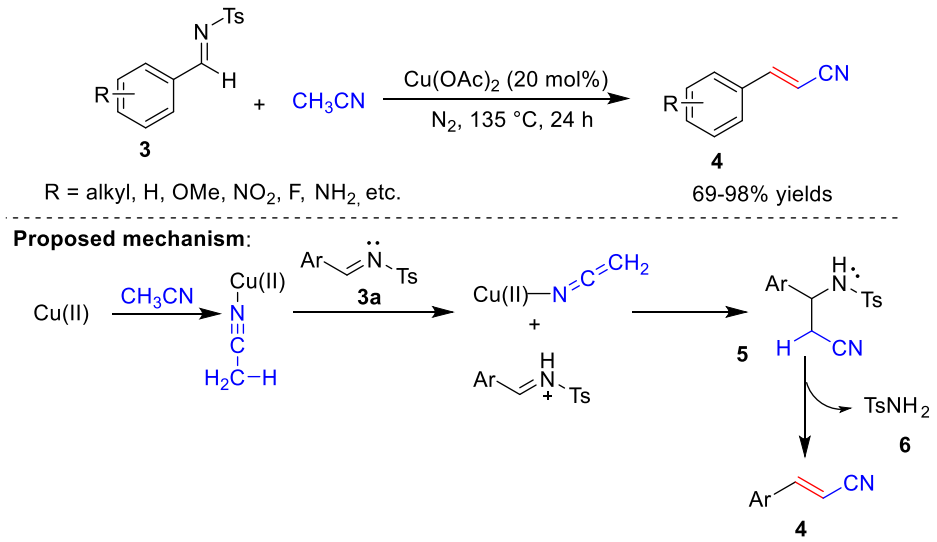
Transition metal catalysts have been widely used in various reactions. In 2020, Zhu's group developed the cyanoalkylative aziridination of *N*-sulfonyl allylamines **1** with alkyl nitriles using Cu catalysts and 2,2′-bipyridine (Scheme 1) [28]. Many *N*-sulfonyl allylamine derivatives **1** and alkyl nitriles derivative were tolerated, affording the corresponding products **2** in 43–86% yields. Furthermore, enantioenriched *N*-tosyl-allylamines could also be utilized as substrates, giving the enantioenriched aziridines in moderate to good diastereoselectivity. Five-membered heterocycles including isoindoline and pyrrolidine **2d** could be synthetized in yields of 85% and 90%, respectively.



Scheme 1. Cu-catalyzed cyanoalkylative aziridination of *N*-sulfonyl allylamines.

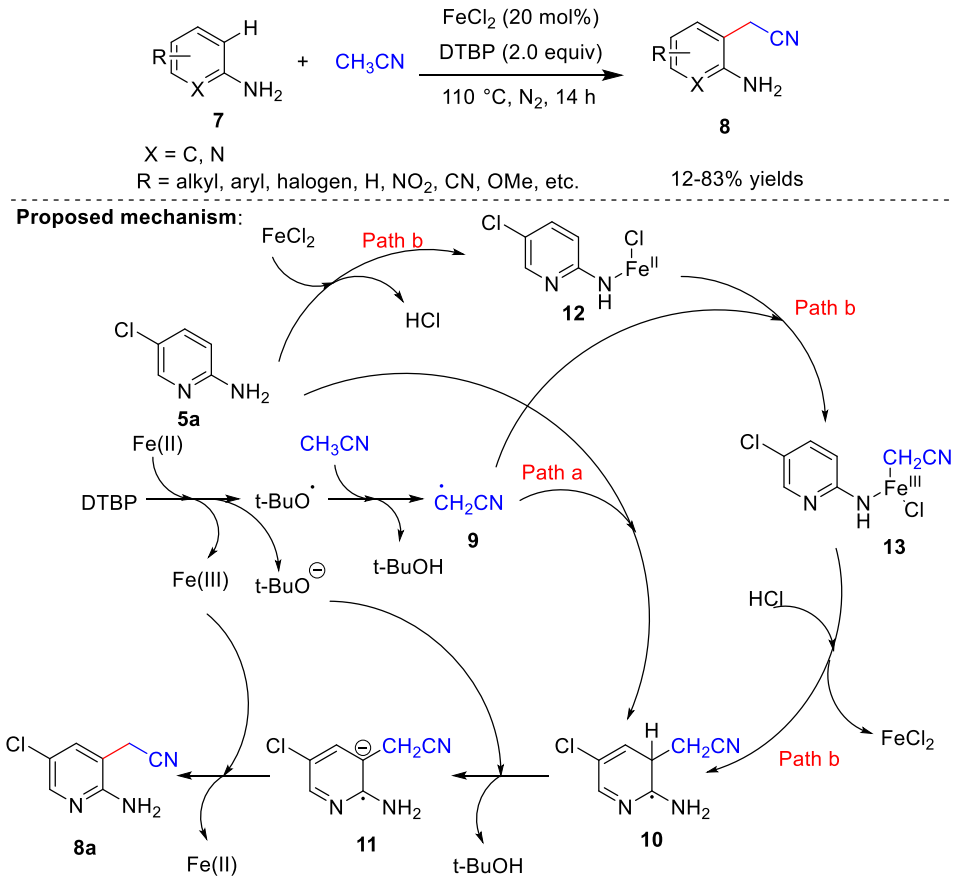
In 2021, Ahmad et al. [29] reported the Cu-catalyzed cyanomethylation of various imines **3** with acetonitrile (Scheme 2). In this process, $Cu(OAc)_2$ is used as the catalyst, and acetonitrile is used as the solvent and the CN source to synthesize arylacrylonitriles **4**. The reaction conditions can tolerate a variety of substrates, including electron-donating groups, strong electron-withdrawing groups, and sterically bulky groups. However, the reaction conditions are harsh, requiring high temperatures and long reaction times. In addition, under conditions where CuCl acts as a catalyst and K_2CO_3 acts as a base, styrene

derivatives can react with haloacetonitrile to form β,γ-unsaturated nitriles in 70–94% yields. Ahmad et al. also proposed a possible reaction mechanism (Scheme 2). First, the cyanide group of acetonitrile coordinates with copper. The complex is then attacked by (*E*)-*N*-benzylidene-4-Methylbenzenesulfonamide **3a** to give intermediate **5**. Elimination of methylbenzenesulfonamide **6** from **5** gives phenylacrylonitrile **4**.



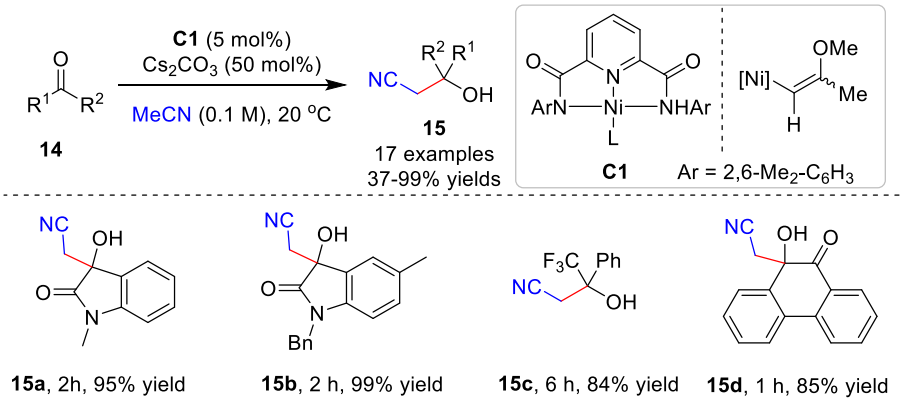
Scheme 2. Cu-catalyzed cyanomethylation.

Iron catalysts have also been used in cyanomethylation. Recently, Yao et al. [30] developed a $FeCl_2$-catalyzed method for the cyanomethylation of amino-substituted arenes **7**, using acetonitrile as the cyanomethyl source and DTBP as the oxidant (Scheme 3). Substrate adaptation studies have shown that yields are higher when substituents on the aminopyridines or anilines have an electron-withdrawing character; conversely, lower yields are obtained with electron-donating groups. In addition, the steric hindrance of the substituents greatly affects the product yields. It is noteworthy that this scheme is the amine-directed cyanomethylation reaction, and the directed amino group plays a decisive role in this reaction. When -NH_2 is replaced by other groups, the cyanomethylation reaction cannot proceed. In addition, the combinations of adjacent amino and cyanomethyl groups can synthesize some valuable nitrogen-containing heterocyclic compounds, which indicates the potential practicability of this reaction. In the control experiments, when 2,2,6,6-tetramethylpiperidine-1-oxyl and butylated hydroxytoluene were added, the corresponding cyanidation products were not generated. These results indicated that a radical process is possibly involved in the reaction. Based on controlled experiments and previous literature, the authors proposed a possible reaction mechanism (Scheme 3). First, DTBP forms a tert-butoxy radical and tert-butoxy anion in the presence of iron. A proton of acetonitrile is removed by the tert-butoxy radical to form cyanomethyl radical **9**. Next, the reaction can proceed via one of two ways: (a) **9** attacks the *ortho*-site of the amino group to afford the free radical **10**, from which a proton is subsequently abstracted by the tert-butoxy anion to give **11** and *t*-BuOH. Finally, **11** is oxidized by Fe(III) to product **8a** regenerating Fe(II). (b) $FeCl_2$ reacts with the amino group to form **12**, and **12** reacts with the cyanomethyl radical to give **13**. $FeCl_2$ is then released, and the cyanomethyl group is transferred to the aromatic ring to obtain **10**. Finally, product **8a** is formed through the same steps as Route (a).



Scheme 3. Fe-catalyzed cyanomethylation.

Ni-catalyzed cyanomethylation is also important for the construction of nitrile-containing compounds. The enantioselective cyanomethylation catalyzed by Ni(II) was developed by Shibasaki and Kumagai [31,32]. Very recently, Oudeyer and co-workers established a Ni-catalyzed cyanoalkylation of ketone derivatives **14** and acetonitrile derivatives (Scheme 4) [33]. Acetonitrile was added to various isatins or activated ketones with the Ni catalyst **C1**, affording products **15** in up to a 99% yield. Additionally, the addition of acetonitrile derivatives to ketones required the presence of $^{n}Bu_4NBF_4$ in THF to give good product yields. Preliminary mechanistic studies showed that the Tolman-type complex, Ni^{II}-complex **C1**, is the key to the cyanomethylation.

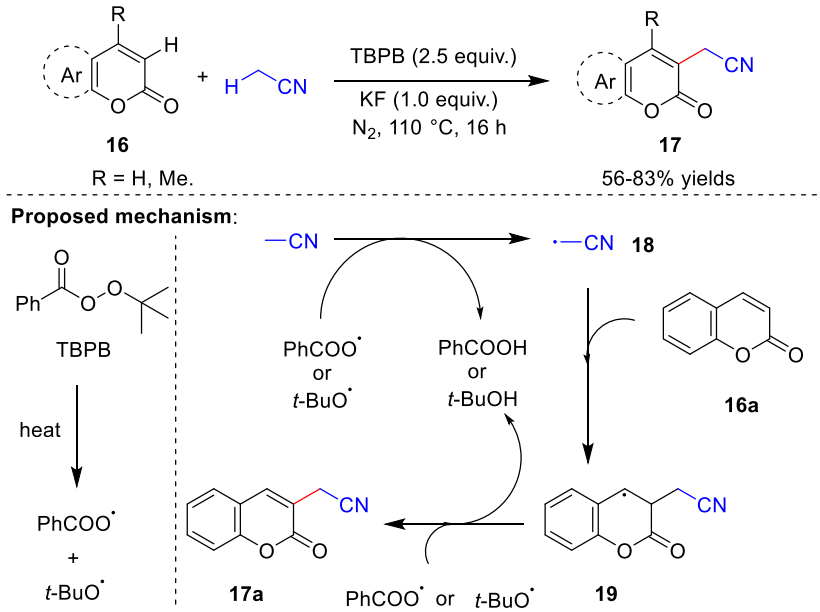


Scheme 4. Ni-catalyzed cyanomethylation.

2.2. Transition Metal-Free Cyanomethylation

Transition metal catalysts, which are widely used in organic synthesis, are usually expensive, pollute the environment, and add difficulties to post-treatment. In some areas, such as the pharmaceutical industry, even trace metals are not tolerated in the end product [34]. Developing environmentally friendly and economical synthetic methods is the trend of future development. As a result, metal-free catalyzed reactions have become a popular research topic in organic chemistry.

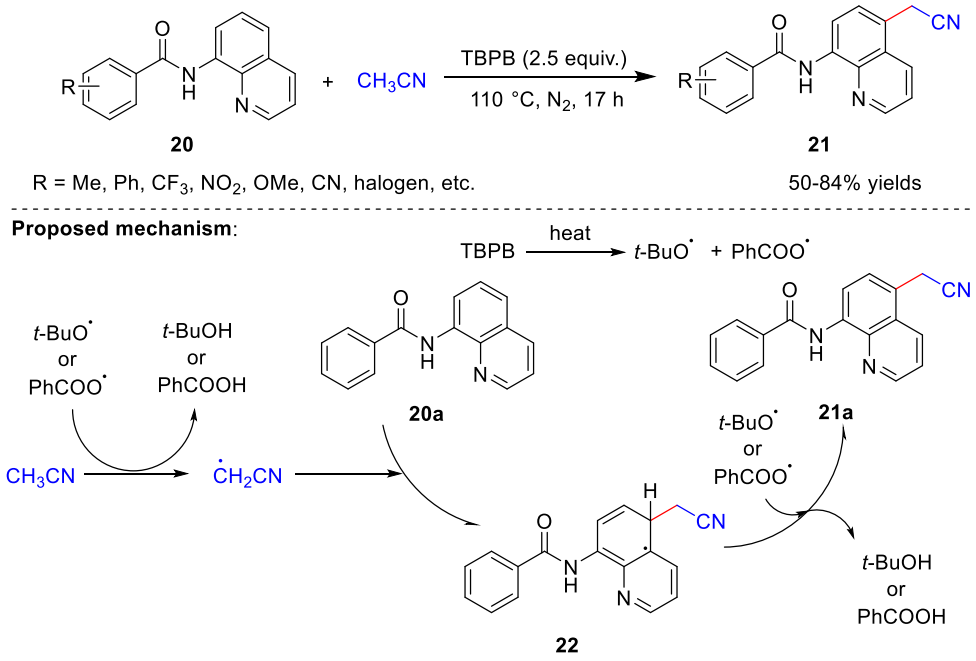
In the last few years, metal-free catalyzed direct cyanomethylation of C-H bonds, including C(sp2)-H bonds [35,36] and C(sp3)-H bonds [37], has emerged as a powerful tool in organic synthesis, which has the advantages of atom economy. In 2018, Zhang et al. [35] reported the synthesis of cyanomethylcoumarin via a cross-dehydrogenation coupling reaction between coumarin **16** and acetonitrile (Scheme 5). This reaction uses *tert*-butyl benzoperoxoate (TBPB) as the oxidant and potassium fluoride (KF) as the base over 16 h under a nitrogen atmosphere, with acetonitrile as both the reactant and solvent. The substrates for this methodology are broad, but require an excessive amount of solvent. Zhang et al. also proposed a reasonable mechanism for this reaction. Initially, TBPB is heated to form a benzoate radical and tert-butoxy radical. Next, cyanomethyl radical **18** is formed by abstraction of the acetonitrile proton from either the benzoate radical or the *tert*-butoxy radical, releasing benzoic acid or *tert*-butanol. Cyanomethyl radical **18** attacks coumarin **16a** to give intermediate **19**, which is then deprotonated to produce target product **17a**.



Scheme 5. Cyanomethylation with TBPB as the oxidant.

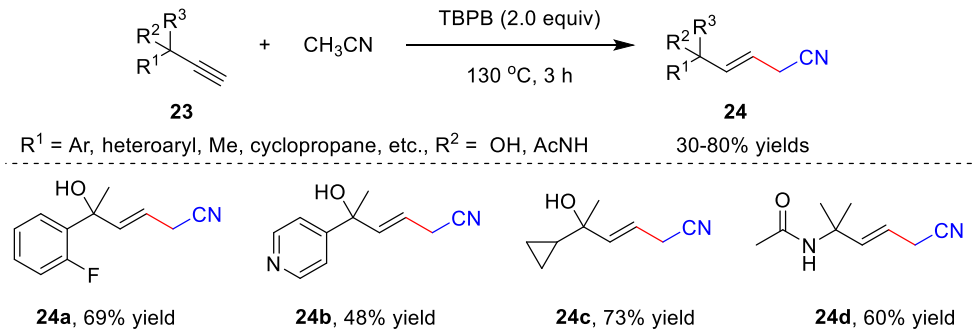
Cyanomethylation can also occur in the absence of a base. In 2021, Liu et al. [36] developed a method for the cyanomethylation of 8-aminoquinoline amides **20** (Scheme 6). This method uses only TBPB as an oxidant in the absence of metal catalysts and bases. Under these conditions, a wide range of substituents on the 8-aminoquinoline amides are tolerated, and the electronic effects and steric hindrance of the substituents have little effect on the product yields. The yields of the target products are 50–84%. It is important to note that amide's functionality is crucial to the smooth progress of the reaction. When simple quinoline or 8-amino quinoline is used in place of 8-aminoquinoline amide, the reaction does not occur smoothly. The possible reaction mechanism proposed by Liu et al. is similar to that proposed by Zhang et al. At first, the tert-butoxy radical and benzoate radical are transferred through the thermal homolytic scission of TBPB. Subsequently, the cyanomethyl

radical is generated by the hydrogen abstraction of acetonitrile by the tert-butoxy radical or benzoate radical releasing tert-butanol or benzoic acid. Thereafter, cyanomethyl radical attacks **20a** to produce intermediate **22**, which further reacts with the tert-butoxy radical or benzoate radical to produce required product **21a**. This suggests that cyanomethylation in the absence of metal catalysis may proceed via the same reaction process.



Scheme 6. Cyanomethylation with TBPB as the oxidant.

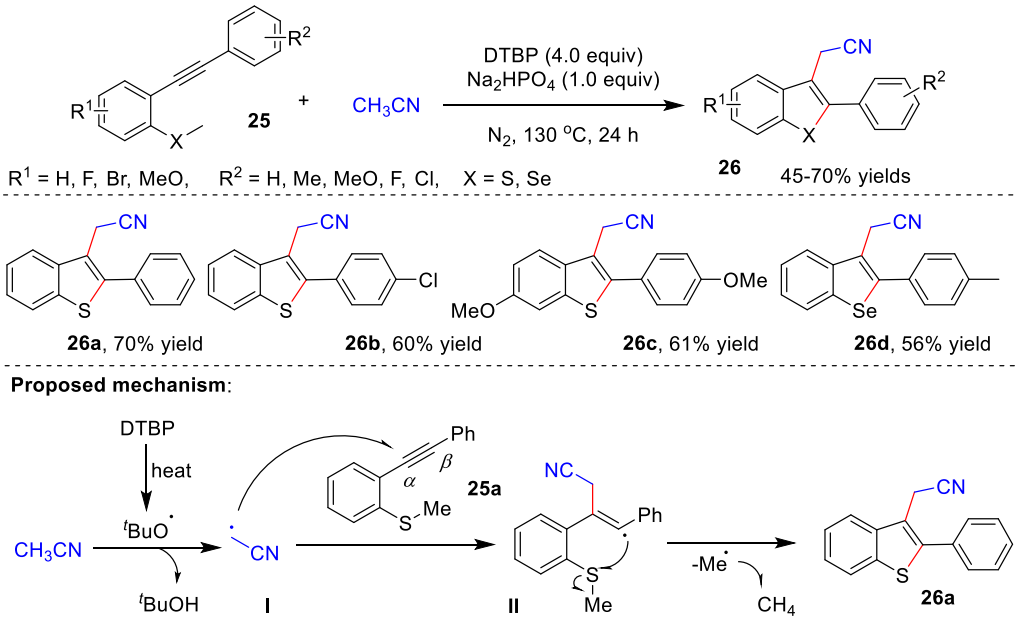
The metal-free catalyzed functionalization of unsaturated hydrocarbons involving acetonitrile is another application of cyanomethylation. Several interesting methods have been developed to provide nitrile-containing products, including the hydrofunctionalization of alkynes [38], cascade radical cyclization of alkynes [39,40], cascade radical cyclization of alkenes [41], etc. A free radical addition of acetonitrile to alkynes was developed by Liu's group in 2019 (Scheme 7) [38]. In the presence of TBPB, alkynes **23** and acetonitrile reacted in CH_3CN at 130 °C for 3 h, providing β,γ-unsaturated nitriles **24** with up to an 80% yield. The alkynes bearing aryl, alkyl, heteroaryl, cyclopropane, cyclopropane, amide, etc., units showed high compatibility with the addition reaction, affording desired products **24** in moderate to good efficiency.



Scheme 7. Addition of acetonitrile to alkynes.

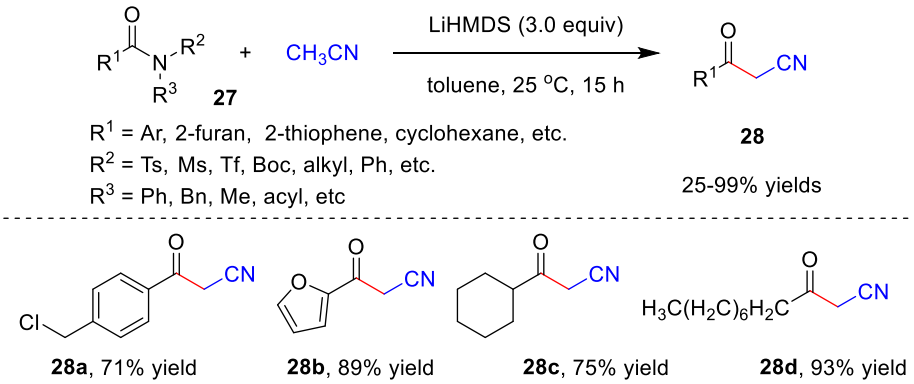
In 2020, Gao and co-workers reported an efficient cascade radical cyclization of 2-alkynylthio(seleno)anisoles **25** with acetonitrile for the construction of 3-cyanomethylated benzothio(seleno)phenes **26** (Scheme 8) [40]. Under the optimal reaction conditions, a series

of desired compounds could be achieved in 45–70% yields. The author proposed a possible reaction mechanism. The DTBP first is heated to give tert-butoxy radical, which assimilates the α-H of acetonitrile to form radical **I**. Subsequently, generated radical **I** attacks the α-position of C-C triple bond of **25a** to afford vinyl radical **II**. Finally, target product **26a** is formed through a radical 5-*exo-trig* cyclization with the sulfur atom.



Scheme 8. Cascade radical cyclization of alkynes with acetonitrile.

In addition, Lee's group recently reported an elegant metal-free catalyzed cyanomethylation of acetonitrile with both activated and unactivated amides **27** to afford diversified β-ketonitriles **28** with up to a 99% yield (Scheme 9) [42]. This reaction exhibits high functional group compatibility in the presence of LiHMDS. Benzamides **27** bearing not only electron-donating groups, but also electron-withdrawing groups could be utilized as substrates, giving corresponding β-ketonitriles **28** in moderate to excellent yields. Furthermore, heterocyclic acylamide, such as furan-2-carboxamide **27b** and thiophene-2-carboxamide, undergo the reaction smoothly, giving the desired products in an 89% yield and 80% yield, respectively. Notably, alkyl amides **27** also display good tolerance to this method. Under the optimized conditions, benzamides **27** involving various *N*-substituents react well with acetonitrile and provide corresponding **28** with 25–99% yields.

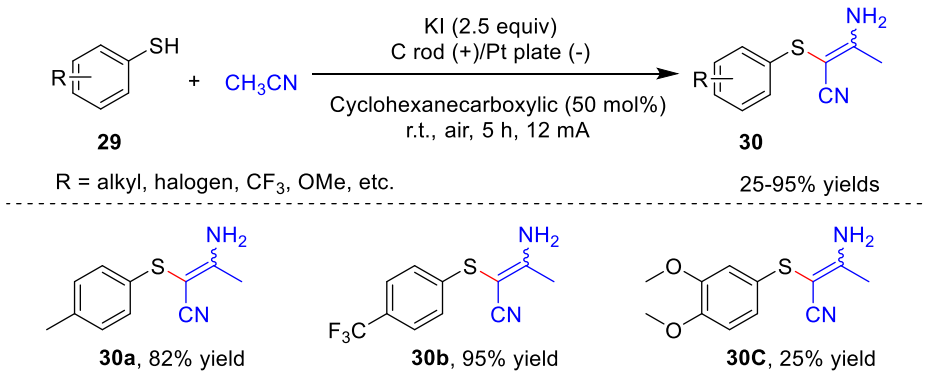


Scheme 9. Cyanomethylation of acetonitrile with amides.

3. Electrochemical Oxidative Cross-Coupling Reaction

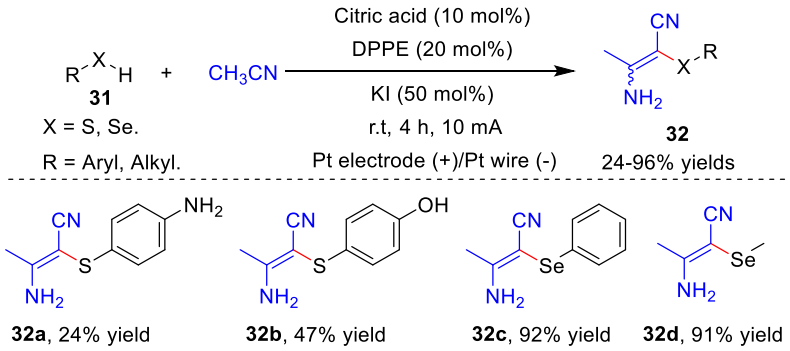
In order to activate the Csp3-H bond of acetonitrile, transition metal catalysts, oxidants, or strong bases and high reaction temperatures are usually required. The harsh reaction conditions not only inconvenience the operation, but also limit the application of the reaction. Therefore, it is urgent to develop an efficient and gentle catalyst-free method to activate the Csp^3-H bond of acetonitrile. Electrochemical synthesis has attracted the interest of scientific research workers due to its high efficiency and environmental credentials [43–48]. Tetrasubstituted olefins are not only the structural units of many drugs [49], but also important precursors for organic synthesis [50]. Therefore, the electrochemical synthesis of tetrasubstituted olefins has also become a popular topic in recent years.

In 2019, Lu et al. [51] reported the electrochemical oxidative Csp^3-H/S-H cross-coupling reaction of acetonitrile and thiophenol **29** to form tetrasubstituted olefins **30** (Scheme 10). In this protocol, KI is used as the electrolyte and medium, cyclohexanecarboxylic is used as the additive, and a series of tetra-substituted alkenes can be obtained in 25–95% yields by reaction under a 12 mA constant current. The results of the substrate range test showed that the reactivity of the thiophenols with electron-neutral substituents (such as methyl, ethyl, isopropyl, or tertiary butyl group) and electron-withdrawing substituents (such as F, Cl, Br, or trifluoromethyl group) substituents is smooth (**20a**, 82% yield; **20b**, 95% yield), but the yields of the thiophenols with strong electron-donating substituent are significantly reduced (**20c**, 25% yield). Moreover, under standard conditions, the diphenyl disulfide and diphenyl diselenide can also generate the corresponding tetrasubstituted olefins.



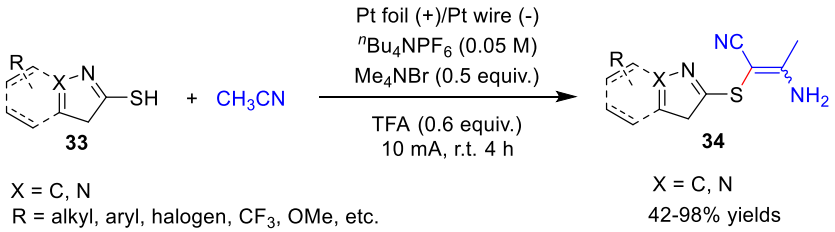
Scheme 10. Synthesis of tetrasubstituted olefins by thiophenol and acetonitrile.

In the same year, He et al. [52] also reported a method for the synthesis of tetrasubstituted olefins **32** using thiophenol **31** and acetonitrile (Scheme 11). The reaction was carried out with KI as the electrolyte and citric acid and 1,2-bis(diphenylphosphino)ethane (DPPE) as the additives at a current of 10 mA. This method has excellent substrate tolerance and can be applied to a variety of substituent phenylthiols/thiols to obtain products at moderate to high yields. Moreover, oxidatively labile functional groups such as amino (**32a**, 24% yield) and hydroxy (**32b**, 47% yield) can also tolerate this reaction and obtain the corresponding products. In addition, diphenyl diselenide (**32c**) and dimethyldiselenide (**32d**) can also be applied to this condition, and tetrasubstituted olefins can be obtained in high yields. Under this condition, the reaction at the gram-scale is also tolerated, and the product is obtained with good yields. In addition, He et al. further cyclized some of the products to obtain 4*H*-1,4-benzothiazine scaffolds, which are widely used in pharmaceutical chemistry. This result suggested that the reaction has potential applications in industry.



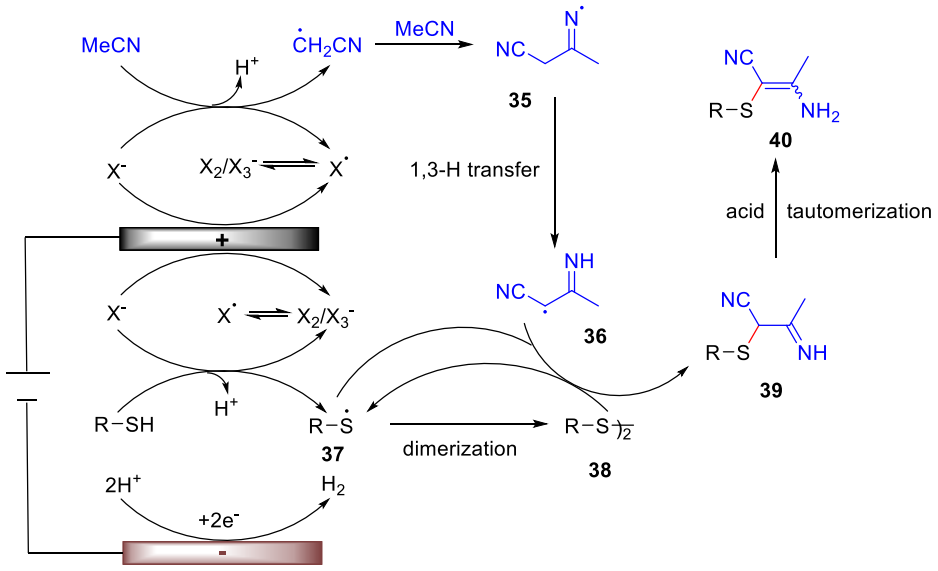
Scheme 11. Synthesis of tetrasubstituted olefins via thiophenol and acetonitrile.

Organic catalysts have also been used in electrochemical reactions. In 2022, Wan et al. [53] reported the electrochemical synthesis of tetrasubstituted olefins **34** with acetonitrile and heteroaryl thiols **33** catalyzed by a bromide salt (Scheme 12). The reaction is performed with $^{n}Bu_4NPF_6$ as the electrolyte solution, Me_4NBr as the catalyst, and trifluoroacetic acid (TFA) as the additive at a constant current of 10 mA. A series of heteroaryl vinyl sulfides **34** was synthesized using acetonitrile and 2-mercaptobenzoxazoles **33** as substrates. The results showed that the proposed method has wide adaptability. Substitution of 2-mercaptobenzoxazole derivatives by various electron-donating or electron-withdrawing substituents can obtain the corresponding products in high yields. Pyridine rings are also tolerated in this reaction. The same conditions can also be applied to converting the 1,3,4-oxadiazole moiety into heteroaryl vinyl sulfides. The corresponding products can be obtained from substrates with different substituents (electron-donating substituents and electron-withdrawing substituents) on the benzene ring on the C5-benzene ring of the 1,3,4-oxadiazole moiety. In addition, the benzene ring can also be substituted by other aromatic moieties or alkyl substituents, and tetrasubstituted olefins can also be obtained with excellent yields.



Scheme 12. Synthesis of tetrasubstituted olefins by acetonitrile and heteroaryl thiols.

The approaches presented all pass through a similar reaction path, on which we propose a possible mechanism for the synthesis of tetrasubstituted olefins **40** by electrochemical oxidation of acetonitrile and thiophenols/thiols (Scheme 13). First, halogen ions (X^-) are anodized to form radicals, which then abstract the hydrogen atoms of acetonitrile to form cyanomethyl radicals. The addition of the cyanomethyl radical to another acetonitrile produces iminoradical **35**. Intermediate **36** is then obtained by 1,3-hydrogen transfer. At the same time, the halogen radical attacks the S-H bond to produce the sulfur radical **37**, which then dimerizes to form disulfide **38**. Finally, intermediate **36** may couple with sulfur radicals **37** to afford tetrasubstituted olefins **40** or it may undergo a substitution reaction with disulfide **38** to give tetrasubstituted olefins **40**. Simultaneously, the cathode-reduced proton releases H_2.



Scheme 13. Mechanism of electrochemical synthesis of tetrasubstituted olefins from acetonitrile and thiols.

4. Cyclization Reaction

4.1. Synthesis of Oxazole

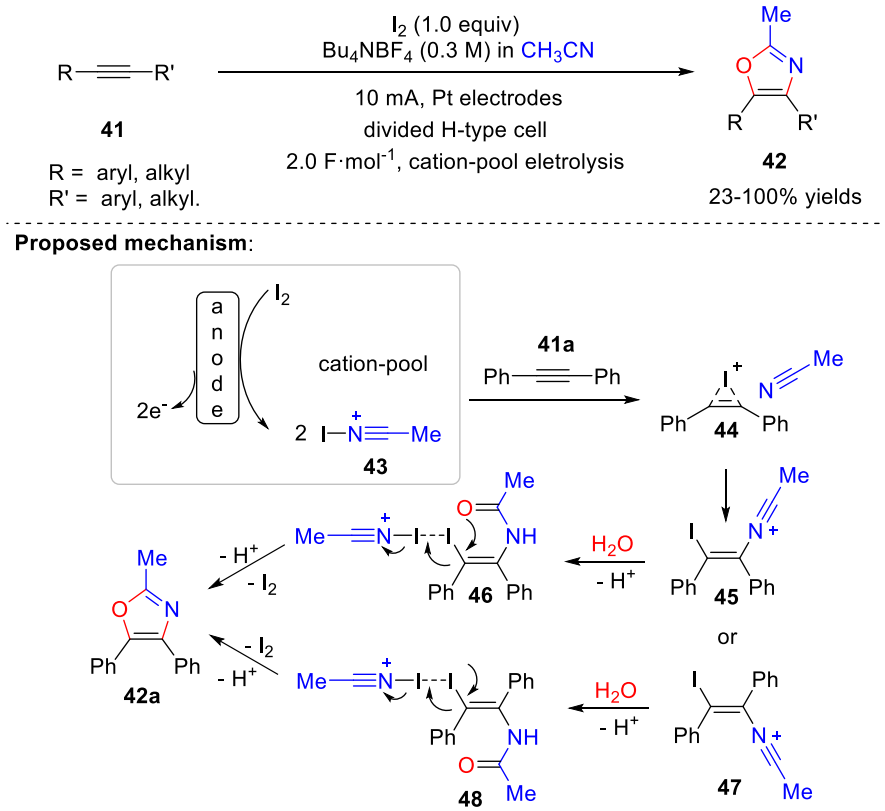
Nitrogen-heterocyclic compounds exist widely in daily life. A considerable number of materials, pesticides, and drug molecules contain nitrogen-heterocyclic structural units. As a result, the development of novel strategies for heterocycle synthesis of nitrogen has been a hot area of organic synthesis. As an ideal nitrogen source, acetonitrile has also been widely used in the synthesis of nitrogen-heterocycles [54].

Oxazole is an important nitrogen-heterocyclic compound. A large number of oxazole compounds and their derivatives are used as drugs to treat various types of diseases. In recent years, a variety of electrochemical synthesis methods of oxazole compounds have been developed. In 2021, Sattler et al. [55] reported the electrochemical synthesis of 1,3-oxazoles **42** from alkynes **41** and acetonitrile (Scheme 14). The good reactivity relies on the symmetric of the substrates. The methodology can tolerate most electron-donating and -withdrawing groups. The yields are reduced when unsymmetrical alkyl-aryl alkynes are used. When dialkyl-substituted alkynes are employed, the yields of the desired products are further lowered. This synthetic method is suitable for symmetric alkynes, but not for unsymmetrical alkyl-aryl alkynes. Sattler et al. proposed a reaction mechanism for this protocol. At the positive electrode, intermediate **43** is formed, which then attacks the Diphenylacetylene **41a** to form the nitrile ion **44**. Intermediate **45** or intermediate **47** may then be generated. Intermediate **45/47** is then deprotonated with water to give **46**/**48**, and further protons and iodine molecules are removed by **43** to obtain target product **42a**.

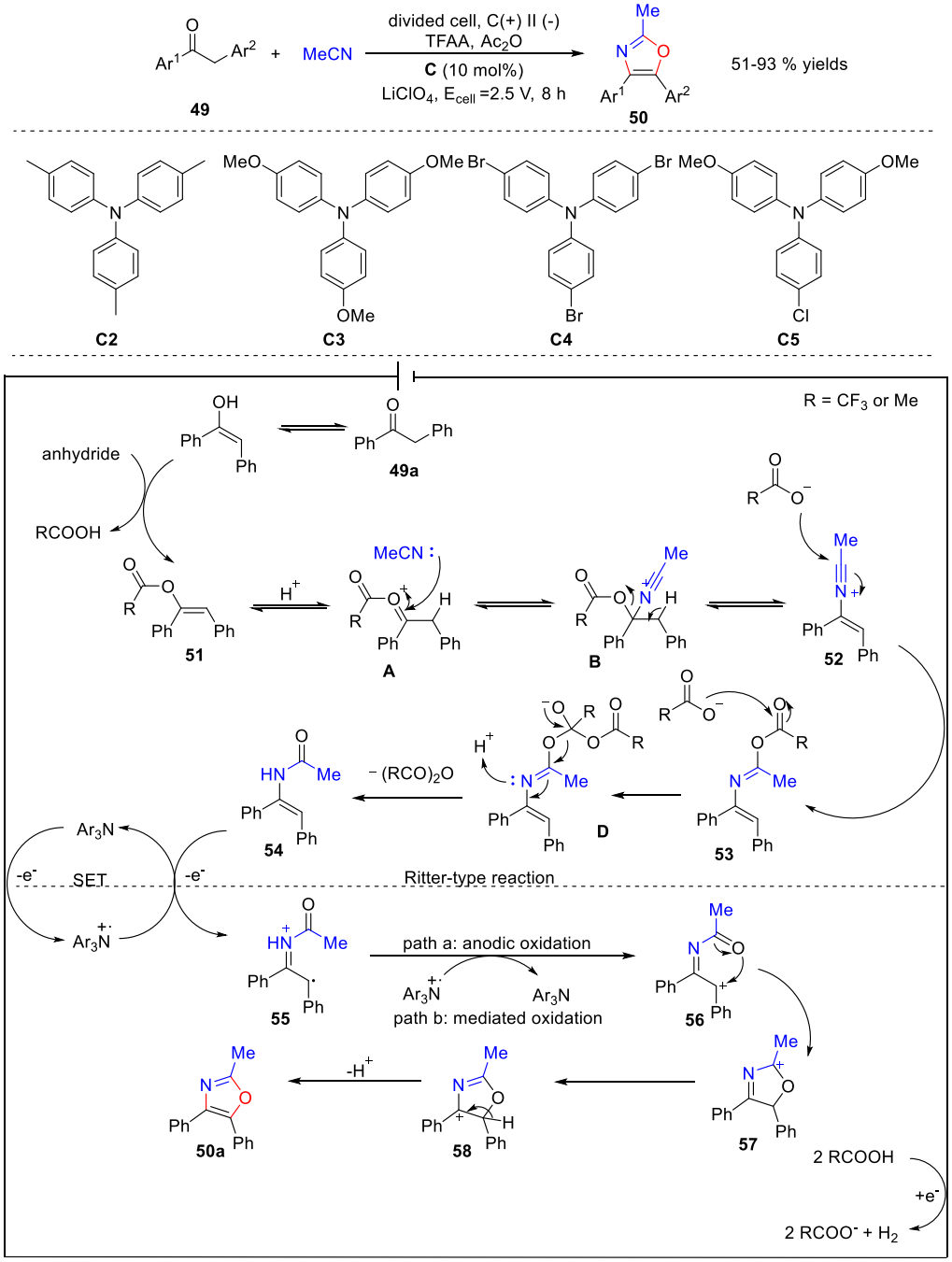
Inspired by Sattler's work, Bao et al. [56] proposed an electrochemical synthesis of poly-substituted oxazoles **50** from ketones **49** and acetonitrile in 2022. With TFAA as the ketone activator and Ar_3N as the catalyst, high yields of the desired products can be obtained and a variety of functional groups can be tolerated. Scheme 15 shows the possible mechanism of this reaction. In the presence of anhydride, ketones form vinyl ester **51**. Then acid-promoted addition to vinyl ester **A** and a subsequent Ritter-type reaction deliver intermediate **52**. Intermediate **52** is attacked by the carboxylate, and then, the anhydride is removed to afford amide **54**. The radical cation produced by Ar_3N at the anode attacks **54** through a single electron transfer (SET) process to give radical cation **55**, which is then directly oxidized (a) or undergoes mediated oxidation (b) to form cation **56**. Finally, desired product **50a** is obtained by intramolecular cyclization and deprotonation, releasing H_2 at the cathode.

4.2. Synthesize Dihydroimidazole and 2-Oxazoline

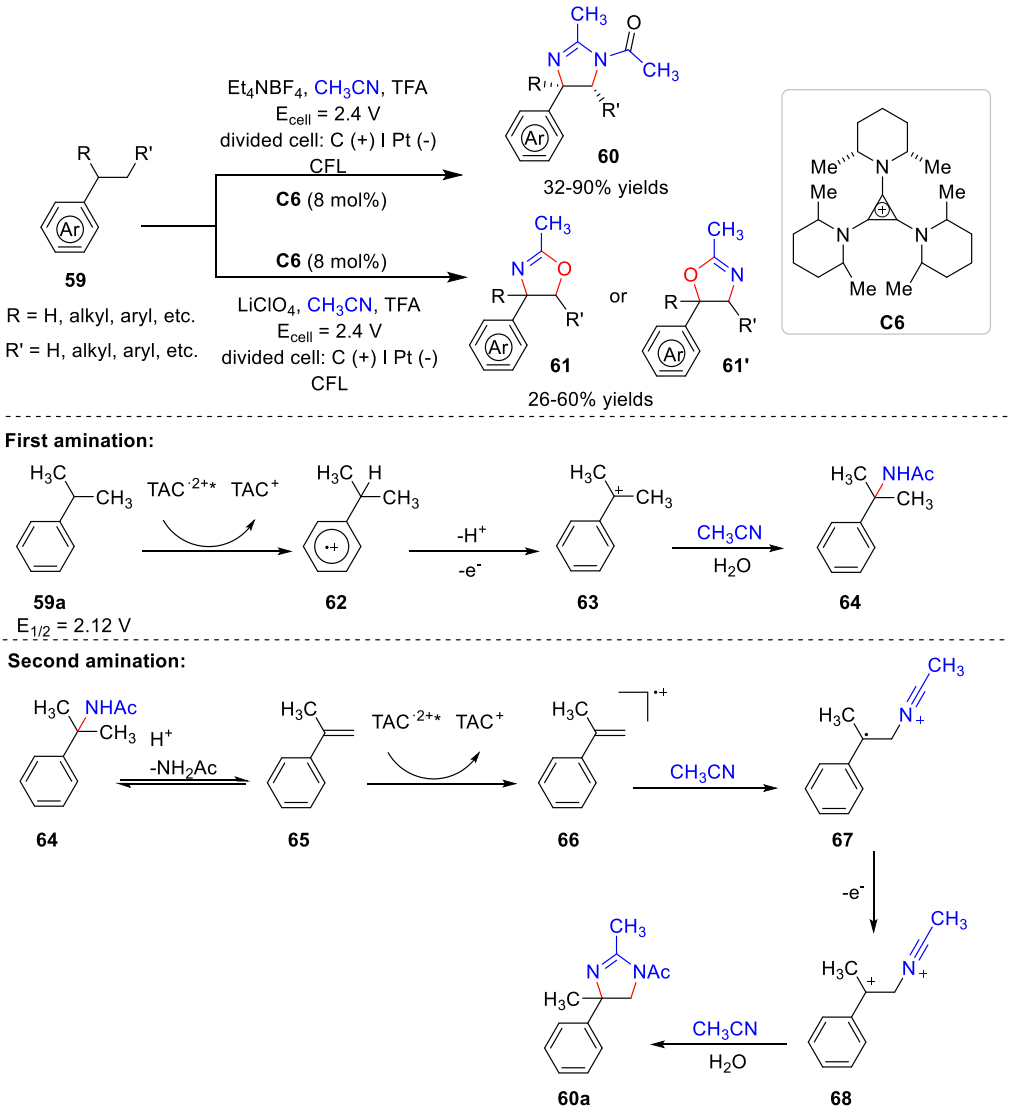
In addition to the simple photochemical reaction or electrochemical reaction, electrophotocatalysis (EPC) combining the energy of light and electrons has also been developed in recent years. In 2021, Shen et al. [57] reported the electrophotocatalytic diamination of vicinal C-H bonds (Scheme 16). Using alkyl aromatics **59** as the raw materials and acetonitrile as the solvent and nitrogen source, 1,2-diamine derivatives were synthesized via an electrophotocatalytic strategy. Depending on the electrolyte used, either 3,4-dihydroimidazole or 2-oxazoline products can be obtained, of which the yields are moderate to good. Shen et al. also successfully synthesized a series of biologically active molecules such as a 5,7-dibromoisatin analogue (**60a**, 42% yield) and a celebrex analogue (**60b**, 56% yield) with pharmacological activity using this method. In addition, this scheme can be used to obtain valuable 1,2-diamines or the free dihydroimidazole adducts after a slight modification of the reaction procedure. Shen et al. also proposed a possible mechanism for the synthesis of 3,4-dihydroimidazoles, which is shown in Scheme 11. First, the trisaminocyclopropenium (TAC) ion acts as a catalyst and undergoes radical attack of **59a**, forming radical cation **62** under illumination. Radical cation **62** is then deprotonated and oxidized to give cation **63**, which is then converted into amide **64** by the Ritter reaction. The mechanism of the formation of product **60a** from amide **64** is not clear. The authors suggested that an elimination reaction of amide **64** produces α-methylstyrene **65**, which is then converted into either 3,4-dihydroimidazole or 2-oxazoline by solvent capture and oxidation under the influence of the electrolyte.



Scheme 14. Synthesis of 1,3-oxazoles from alkynes and acetonitrile.



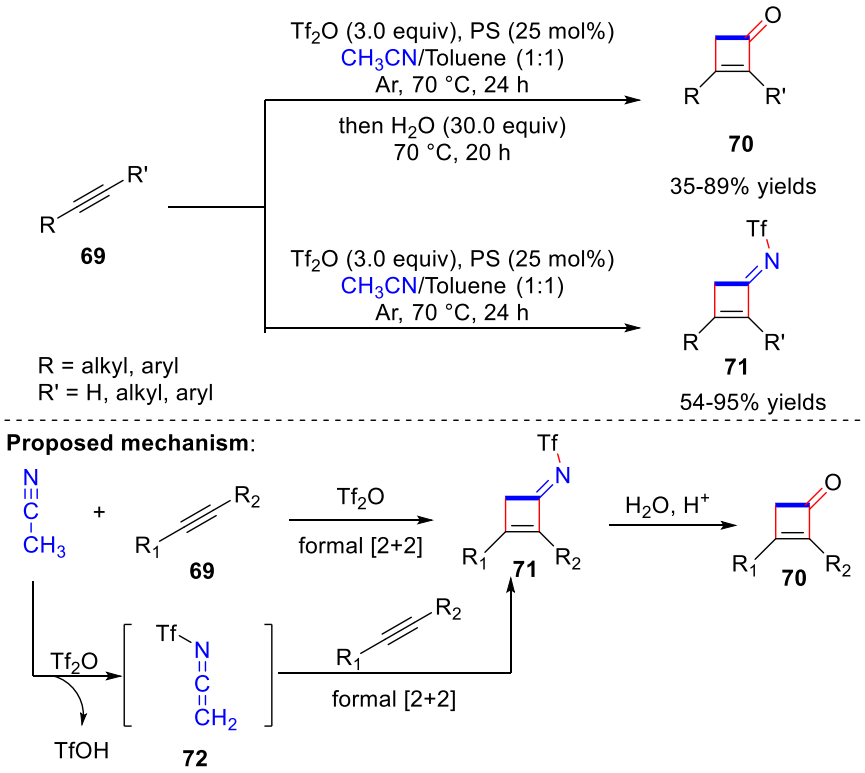
Scheme 15. Synthesis of 1,3-oxazoles from ketones and acetonitrile.



Scheme 16. Synthesis of dihydroimidazoles and 2-oxazolines.

4.3. Synthesis of Cyclobutenone

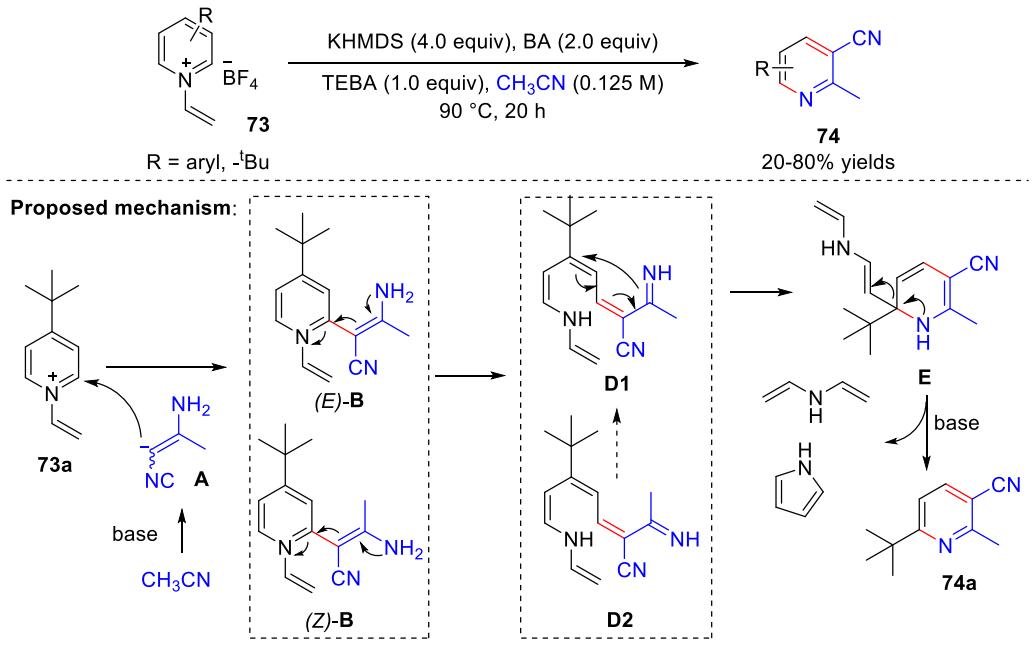
In 2021, Qin et al. [58] reported the first synthesis of cyclobutenone **70** by [2+2] cyclization using acetonitrile as a raw material for C2 cyclization (Scheme 17). The first step of the reaction uses acetonitrile as the raw material and solvent and a proton sponge (PS) as the base, in the presence of catalytic triflic anhydride (Tf_2O); the reaction with an alkyne **69** affords cyclobutene amines **71**. Subsequently, H_2O was added to the reaction mixture in order to form cyclobutenone **70**. This method is capable of tolerating alkyl- and aryl-substituted alkynes. However, terminal alkynes are not amenable to the reaction conditions. The reaction with enyne substrates proceeds normally without being affected by the C=C bond. A mechanism for this reaction has also been proposed. First, acetonitrile is activated by Tf_2O to form intermediate **72**, then **72** is converted to cyclobutene **71** by a [2+2] cyclization reaction. Finally, cyclobutene **71** is hydrolyzed to cyclobutenyl ketone **70**.



Scheme 17. Synthesis of cyclobutenone.

4.4. Synthesis of 3-Cyanopyridine

3-Cyanopyridines are ubiquitous motifs in pharmaceuticals, natural products, and bioactive molecules. Acetonitrile is a common and abundant precursor for the synthesis of 3-cyanopyridines. In 2019, Doyle and colleagues used α-peroxy-γ,γ-dichloropropanes as the substrate and acetonitrile as the nitrogen source in the presence of KO^{t}Bu to give 3-cyanopyridines in 54–69% yields [59]. Subsequently, Trofimov reported the cyclization of available acylethynylpyrroles with acetonitrile to provide a series of pyrrolyl-pyridines in 63–87% yields [60]. In 2022, Duan et al. reported a new strategy for the synthesis of 2-methylnicotinonitriles **74** through the degenerate ring transformation of *N*-substituted pyridinium salts **73** (Scheme 18) [61]. The reaction was carried out using potassium hexamethyldisilazide (KHMDS), benzoic acid (BA), and benzyl triethyl ammonium chloride (TEBA) as additives in acetonitrile at 90 °C for 20 h. This reaction is applicable to various phenyl-substituted 4-phenyl-1-vinylpyridin-1-ium tetrafluoroborates and 3-aryl pyridinium salts, while 4-alkyl-substituted pyridinium salts are limited. This strategy may react through the following pathways: First, acetonitrile forms the 3-ACN anion in situ under the action of the base and then conducts nucleophilic attack on the *ortho*-carbon of pyridinium salt to obtain intermediates (*E*)-**B** and (*Z*)-**B**. Then, the ring opening of adduct B is triggered by electron transfer to give azapolyenes **D1** and **D2**. Subsequently, dihydropyridine intermediate **E** is formed via a 6π-aza electrocyclization with the assistance of the CN group. Finally, intermediate **E** is aromatized to corresponding product **74a**.

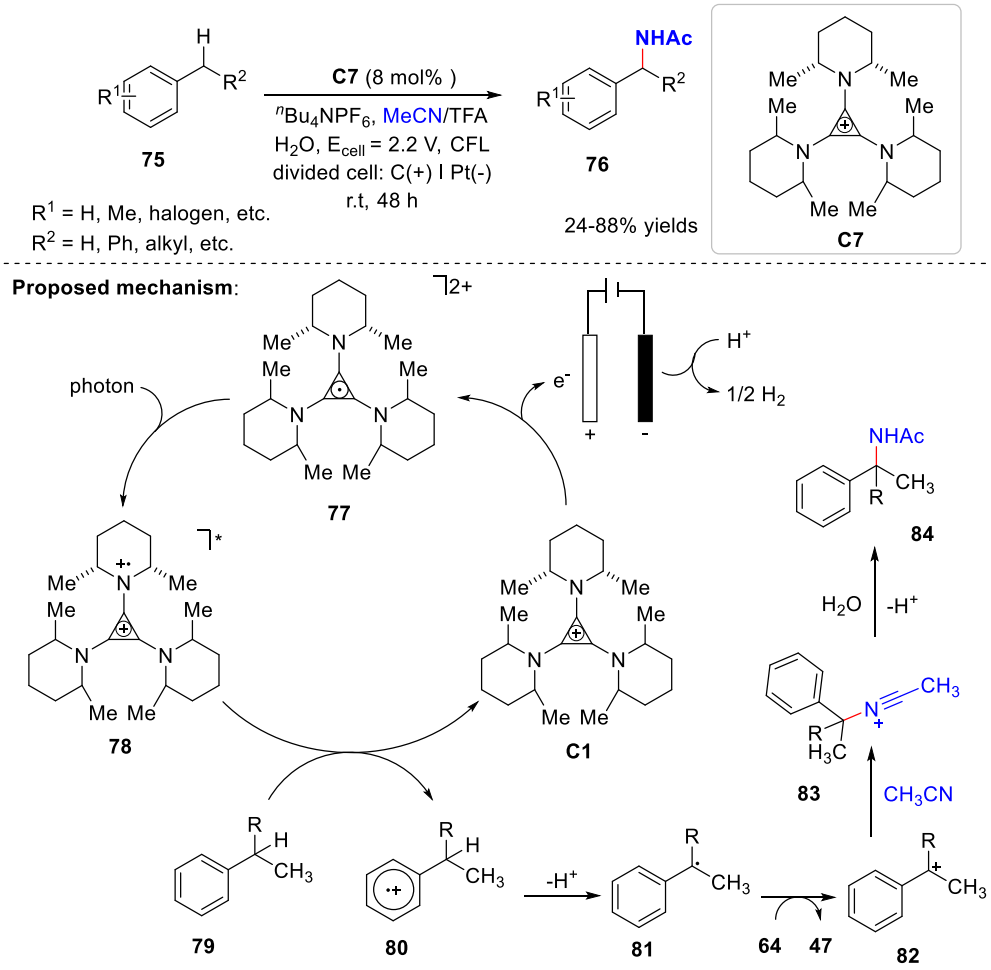


Scheme 18. Synthesis of 3-cyanopyridine.

5. Amidation Reaction

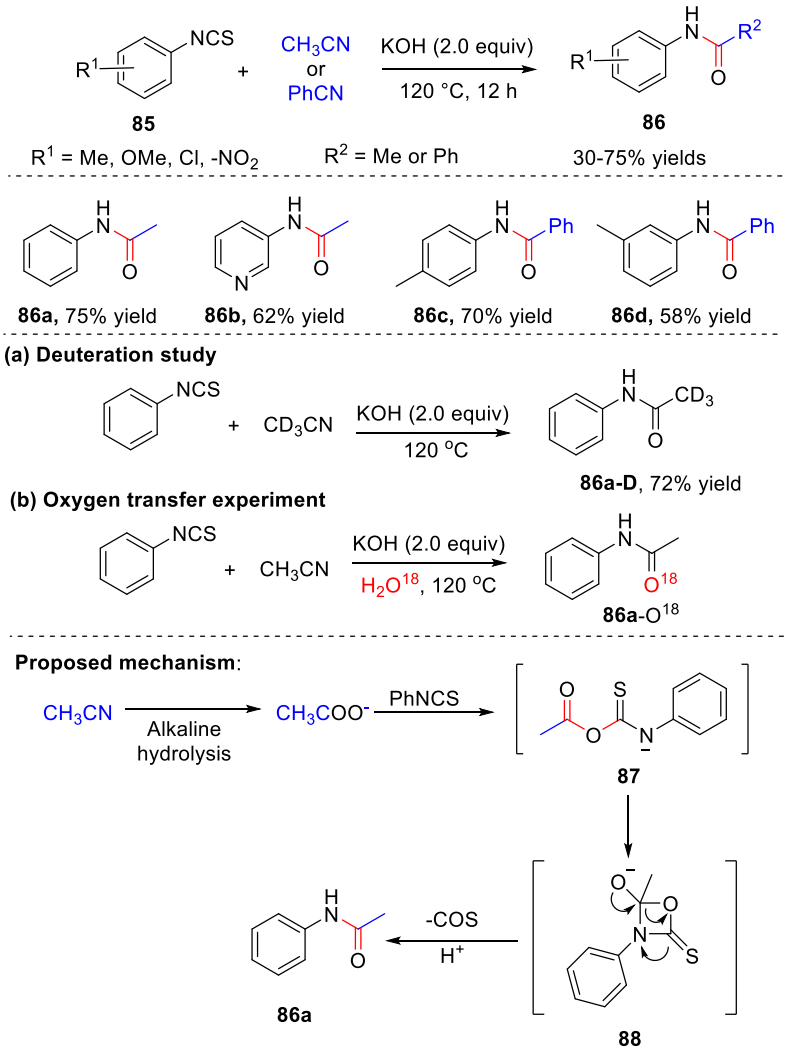
Amide bonds are the structural units of many bioactive molecules and play a crucial role not only in maintaining the life activity of various organisms, but are also widely present in pharmacologically active compounds and organic materials. According to the statistics, about 25% of drugs on the market contain amide bonds, and the construction of amide bonds has become an important link in drug development [62–66].

In recent years, the method of constructing the C-N bond to synthesize amide from acetonitrile by the Ritter reaction has also been developed. In 2021, Shen et al. [67] reported a method for C-H amination via an electrophotocatalytic Ritter-type reaction (Scheme 19). Using trisaminocyclopropenium **C7** as a catalyst, acetonitrile was used to attack the benzyl C-H bond of **75**, giving corresponding acetamide **76** following irradiation with a compact fluorescent light (CFL) and a 2.2 V current. The yields of the desired products range from 36–88%. Additionally, the reaction can be used to modify complex molecules. For example, sertraline derivatives can be obtained in a 40% yield, and retinoic acid receptor agonist derivatives can be obtained in a 63% yield. In addition, compound **76** was also synthesized on a gram-scale with a yield of 50%. This result further demonstrated the potential use of this reaction in industry. The process of this reaction involves oxidation of **C7** to radical **77**, which is then irradiated to form intermediate **78**. This intermediate attacks the aromatics to form radical cation **80**, which is subsequently deprotonated and oxidized to form carbocation **82**. Dehydration leads to the formation of an amide through a Ritter-type reaction.



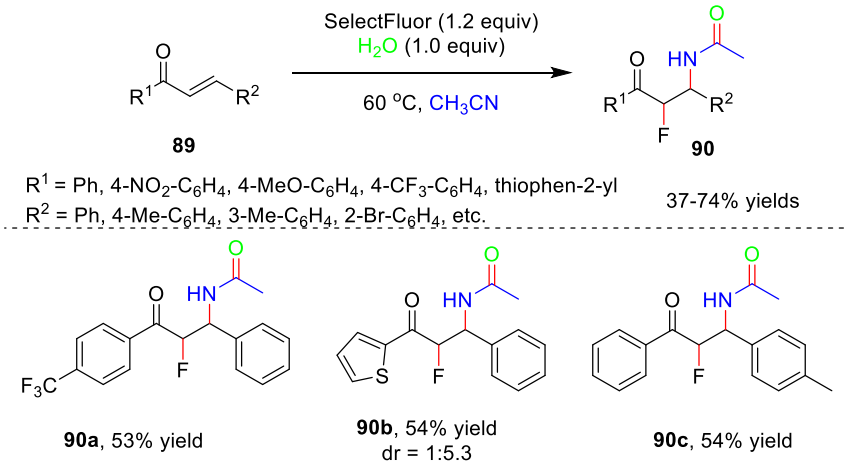
Scheme 19. Synthesis of amide by electrophotocatalytic reaction.

In 2022, our group reported a reaction of aryl isothiocyanate with acetonitrile to form amides **86** (Scheme 20) [68]. This method uses acetonitrile as the raw material and solvent and KOH as the base. The reaction with phenyl isothiocyanate **85** at 120 °C provides a series of acetamides **86** without additional additives. When an aryl isothiocyanate bearing an electron-donating group is used, the yields of the corresponding products are 51–75%. This scheme also tolerates the substitution of aryl isothiocyanates with halogen atoms, but the yields are lower. In addition, when benzonitrile is used instead of acetonitrile, the corresponding amides can also be obtained. For example, *N*-(4-methylphenyl)benzamide **86c** was easily prepared from benzonitrile in a 70% yield. In order to explore the reaction mechanism, a series of control tests was completed. First, deuterated acetonitrile is also suitable for this method to obtain the product deuterated acetanilide (Scheme 20a), which indicates that acetonitrile is involved in this reaction. It also provides a convenient way to synthesize deuterated acetanilide. Second, model reactions of MeCN/H_2O^{18} also demonstrate that the carbonyl oxygen atoms may originate from H_2O (Scheme 20b). Through a series of controlled experiments, we proposed possible mechanisms for this reaction (Scheme 20). Acetonitrile is hydrolyzed to the carboxylic acid under basic conditions. Then, the carboxylic acid is added to the phenyl isothiocyanate to form intermediate **87**. Next, generated intermediate **87** undergoes the loss of carbonyl sulfide (COS) to give final product **86a**.



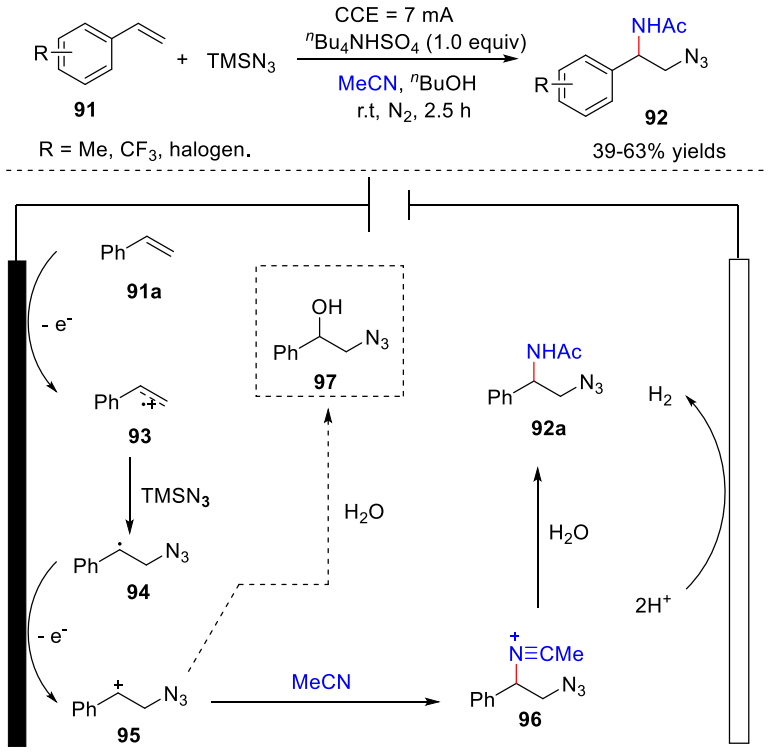
Scheme 20. Synthesis of amide by acetonitrile and isothiocyanate.

The difunctionalization of alkenes involving acetonitrile can synchronously form two new chemical bonds. This strategy usually starts with the addition of a radical to an alkene, which then undergo a single electron transfer, affording the carbocation. Finally, the Ritter-type amination of the carbocation and acetonitrile gives the desired difunctionalization product. As far as we know, a variety of reaction systems have been developed in recent years, including Selectfluor and benzoyl peroxide (BPO) as a radical initiator [69–71], photocatalysts [72], and electrochemistry [73]. The regioselective aminofluorination of α,β-unsaturated ketones was developed by Li's group in 2019 (Scheme 21) [69]. Selectfluor as the oxidant and fluorine source could work well in CH_3CN/H_2O to give α-fluoroamides **90** in 37–74% yields. The reaction has a relatively wide substrate scope, and most products have been synthesized without diastereomers. In addition, when the loading of Selectfluor was increased from 1.2 equivalent to 3.0 equivalent, the α-difluoro-β-amidation was obtained in a 55% yield. In 2022, Zhang et al. reported a tandem fluorination/Ritter reaction of α-diazo 2*H*-benzopyran-4-one compounds using Selectfluor as the fluoride source in MeCN to synthesize β-fluoramides with moderate yields [74].



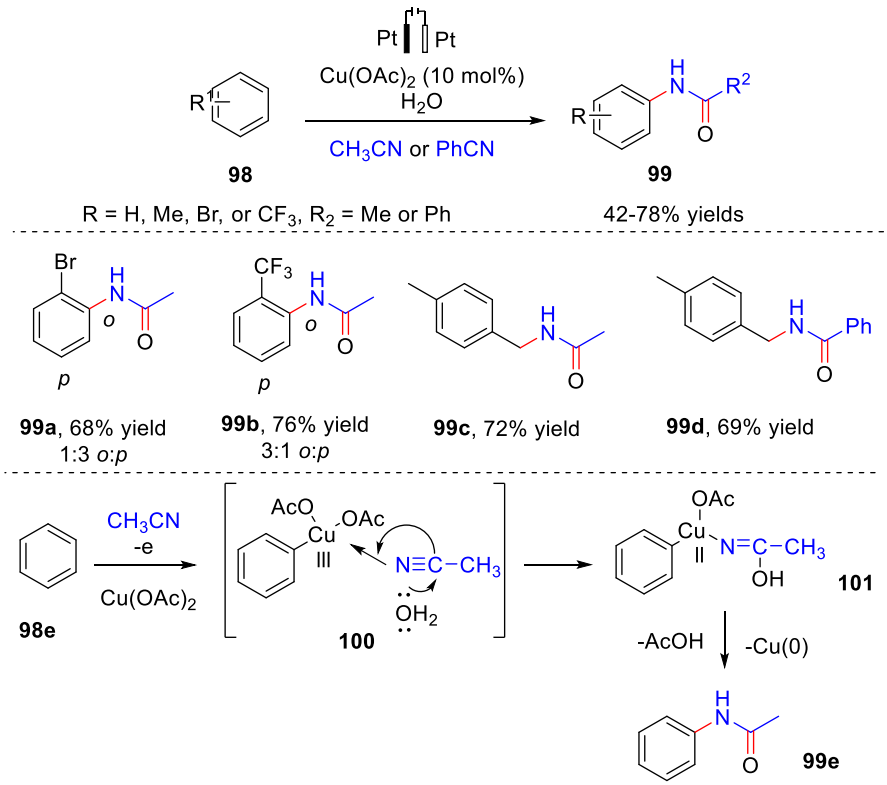
Scheme 21. Aminofluorination of α,β-unsaturated ketones.

In 2023, Yu et al. [73] reported the electrochemical synthesis of vicinal azidoacetamides **92** (Scheme 22). The reaction uses substituted styrenes/tetrasubstituted alkenes **91** and $TMSN_3$ as raw materials. In the MeCN/^{n}BuOH system, the amides can be obtained in 35–63% yields using constant-current electrolysis with $^n Bu_4NHSO_4$ as the electrolyte. This approach can tolerate both electron-donating and electron-withdrawing group substitutions of styrene. In addition to acetonitrile, azide amides can also be obtained by this method from other aliphatic nitriles. Possible mechanisms for this reaction have been proposed. Styrene **91a** is first oxidized at the anode to form intermediate **93**, which is then trapped by $TMSN_3$ to form radical **94**. Radical **94** is then further oxidized at the anode to form benzyl cationic intermediate **95**, which undergoes nucleophilic addition with acetonitrile to yield intermediate **96**. Finally, **96** is hydrolyzed to form vicinal azidoacetamides **92a**. Additionally, benzyl cation **95** can also be trapped by water to generate undesired azidohydroxylation product **97**.



Scheme 22. Electrochemical synthesis of vicinal azidoacetamides.

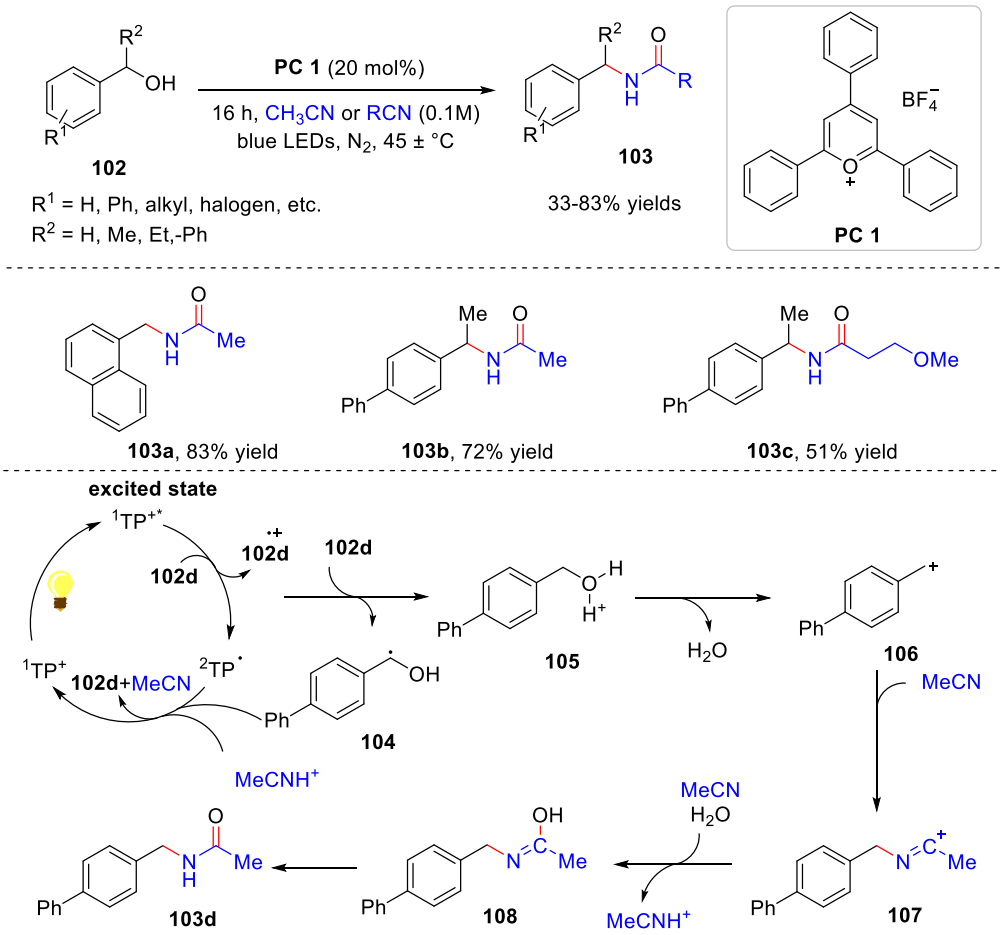
Amination between C-H bond activation on the benzene ring has also been realized. Strekalova et al. [75] reported the synthesis of *N*-phenylacetamide **99** by electrochemical oxidation of aromatic compounds **98** under the catalysis of copper salts (Scheme 23). This method uses $Cu(OAc)_2$ as the catalyst, with no other additives, and reacts for 2–4 h at an 80 mA current to obtain the amides. However, this reaction requires large amounts of acetonitrile as the solvent and reactant (40 mL). The presence of a substituent on the benzene ring will lead to the production of the isomeric amide. When bromobenzene is used, the product is predominantly *N*-(4-bromophenyl)acetamide (**99a**), while using trifluoromethylbenzene as the substrate causes *N*-(2-(triuoromethyl)phenyl)acetamide to be the main product (**99b**). When the aromatic ring contains a methyl group, the reaction takes place on the methyl fragment. Even if the aromatic ring is substituted by multiple methyl groups (xylene, mesitylene), amidation will also occur on one of the methyl groups, and amidation products with one substituted methyl group are obtained as the main product (**85c**). Moreover, when benzonitrile is used instead of acetonitrile, the corresponding benzamides can also be obtained with moderate yields (up to 69% yield). The author proposed the possible reaction mechanism of the amidation of benzene (Scheme 16). In addition, according to the nature of the substrate (aromatic or heteroaromatic, presence of methyl or other substituents) and the oxidation potential of the aromatic, the reaction is carried out in different ways under the same conditions. The presence of a methyl substituent on the benzene ring leads to selective amidation of the benzyl fragment, and the reaction has been carried out through the oxidation of the methyl group. However, in the process of the electrooxidation of heteroarenes (e.g., 2-phenylpyridine), dimers are formed instead of acetylamides because heteroarenes can coordinate with metals. Similar to Strekalova's work, Song's group developed an electrophilic amidomethylation of the aromatic C-H bond. This strategy using acetonitrile as the NHAc source and DMSO as the CH_2 source could provide various *N*-benzylic amide derivatives in 31–82% yields [76].



Scheme 23. Electrochemical synthesis of amides catalyzed by copper.

The photocatalytic amidation reaction has also been reported. In 2023, Bao et al. [77] developed a photocatalytic dehydration of alcohol **102** to synthesize amides **103** (Scheme 24).

The reaction uses 2,4,6-triphenylpyrylium tetrafluoroborate (**PC1**) as a catalyst, and benzyl alcohol and acetonitrile can produce amide after 16 h of blue light irradiation in a nitrogen atmosphere. Benzyl alcohols containing electron-donating groups respond well, with yields ranging from 50 to 63%. Substituting benzyl alcohol with an electron-withdrawing group yields a lower-yielding amide. *Ortho-*, *meta-*, and, polysubstituted groups in the phenyl ring of benzyl alcohols also react smoothly. Naphthyl methanol can provide amide with a higher yield (**103a**, 83% yield). The amide can also be obtained from secondary alcohols by this method (**103b**, 72% yield). This method is also applicable to other alkyl nitriles (**103c**, 51% yield), but increasing the alkyl chain reduces the activity of the nitriles, resulting in lower yields. Through control experiments and DFT calculations, Bao et al. proposed the possible mechanism of the reaction. The photocatalyst is first excited under light to the excited state (^{1}**TP**$^+$). The SET process between **102d** and ^{1}**TP**$^+$ then takes place. The resultant **102d**$^+$ can be used as a Brønsted acid to protonate another **102d** to obtain protonated benzyl alcohol **105** and α-hydroxybenzyl radical **104**. Subsequently, the protonated **105** undergoes dehydration to obtain the benzyl carbocation (**106**). Then, the nucleophilic attack of MeCN on **106** occurs, producing iminium carbocation **107**. After the generation of **107**, the following steps are similar to those of the conventional Ritter reaction. First, H_2O produced from the dehydration step attacks **107** with the support of solvent molecules (MeCN). Finally, obtained imide alcohol intermediate **108** gives rise to product **103d** by tautomerism. The intermediates, **104** and $MeCNH^+$, participate in the catalytic regeneration of **PC1** from ^{2}**TP**$^\bullet$ and are converted to **102d** and MeCN.



Scheme 24. Photocatalytic synthesis of amide.

6. Conclusions

Acetonitrile has been widely used in organic synthesis and is an important organic substance. This review described the recent synthesis of cyanides, tetrasubstituted olefins, heterocyclic compounds, and amides from acetonitrile, with methodologies involving conventional metal catalysis and electrochemical reactions. It is worth noting that the conditions for the amidation reaction involving acetonitrile are generally applicable to other nitriles. However, some of the new methods require the consumption of large amounts of acetonitrile, which undoubtedly increases the cost of the reaction and also causes a waste of resources. If this problem can be solved, these new methods will be more practical. It is worth noting that electrochemical reactions have the advantage of being mild, having short reaction times, and being more environmentally benign compared with conventional metal catalysis and oxidation reactions. Acetonitrile is well suited for use as a solvent and reactant in electrochemical reactions due to its unique properties. Therefore, more applications that utilize acetonitrile in electrochemistry are worth developing.

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Conflicts of Interest: The authors declare no conflict of interest.

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