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Recent advances in nitro-involved radical reactions

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Nitro-containing compounds are important structural moieties in drugs, natural products, and small molecule therapeutics, and are widely used in a variety of organic transformations. During the past decades, these compounds have received considerable attention from the synthetic chemistry community, since they have been successfully applied in the preparation of amines, oximes, alkenes, nitrones and alcohols through the radical-initiated pathway. Additionally, significant progress in the chemistry of nitro radicals has been witnessed, providing efficient and rapid access to nitro-containing compounds as well as isoxazoline derivatives. Recent advances in the radical reactions involving the nitro group and various transformations have been summarized in this review.

1. Introduction

Nitro-containing compounds are important constituents of plastics, explosives, dyes, perfumes, pharmaceuticals and industrial chemicals (Fig. 1).[1] Moreover, nitro compounds have been extensively explored as valuable synthetic intermediates in various organic transformations.[2] For instance, the radical-initiated reductive coupling of nitro compounds with alkenes provides a concise way to produce amines under transition metal catalysis. On the other hand, for the traditional nitration process, a nitronium ion (NO_2^+) is generated from mixed strong acidic systems (H_2SO_4/HNO_3) which then undergoes an electrophilic substitution to deliver the nitrated products. This process often suffers from isomeric mixtures and poor functional group tolerance.[3] Therefore, the development of efficient and novel methods for the synthesis of nitro compounds has attracted great attention. To this end, a variety of nitrating reagents including $AgNO_2$, $NaNO_2$, $Fe(NO_3)_3{\cdot}9H_2O$, ^{t}BuONO, *etc*. have been well explored as sources of nitro radicals for C–N bond-forming reactions. As a result, with the rapid development of free radical chemistry, continuous efforts have been devoted to the radical reactions involving the nitro group. Despite tremendous achievements in this area, to the best of our knowledge, there is still no comprehensive review devoted to this impressive topic.

The main focus of this review is on radical reactions involving the nitro group for various transformations. Accordingly, the chemistry of the nitro radical generated from different nitrating reagents is discussed in detail, thus giving rise to nitro-containing compounds as well as isoxazoline derivatives. Additionally, we will summarize recent progress on the radical-initiated conversion of nitro compounds into amines, oximes, alkenes, nitrones and alcohols under appropriate conditions.

2. Transformations involving nitro radicals

The nitro group is a valuable building block in the preparation of pharmaceuticals, materials and dyes. Traditional methods

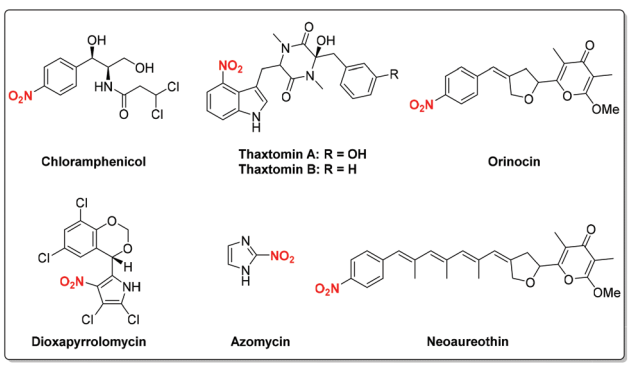

Fig. 1 Selected examples of nitro-containing compounds in natural products and bioactive molecules.

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for the synthesis of nitro compounds involving nitronium cation (NO_2^+) or nitrite anion (NO_2^-) intermediates often suffer from isomeric mixtures and poor functional group tolerance. Over the past few years, considerable efforts have been devoted to the chemistry of the nitrogen dioxide radical ($^{\bullet}NO_2$), providing an efficient and powerful strategy to access nitro compounds.

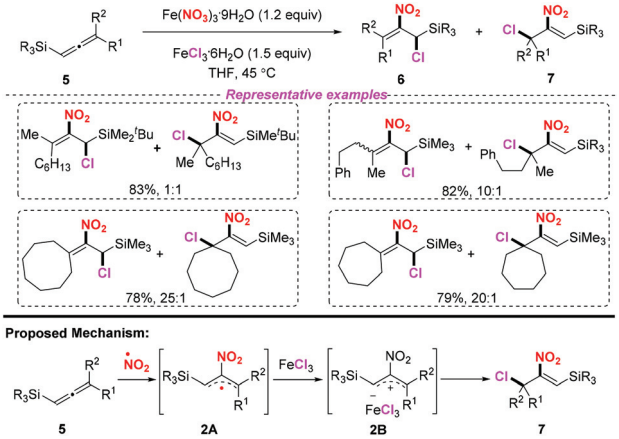
2.1. Fe-Catalyzed or mediated transformations

Iron(III) nitrate nonahydrate has been frequently used as a NO_2 radical source in radical-mediated nitration reactions. In 2010, the groups of Taniguchi[4] and Ishibashi[5] independently developed the iron-mediated halo-nitration reaction of alkenes to obtain nitro compounds (Scheme 1). Accordingly, both the reactions, involving the addition of the NO_2 radical to alkenes and the resulting terminal radicals, were trapped by a chlorine atom in the presence of a chloride salt. Both methods featured a broad substrate scope, providing a practical way to access α-chloronitroalkanes or chloro-cyclonitroalkanes in good yields. The use of iron nitrate as the nitro source in these processes further highlights its applicability, which avoids the inconvenience of using nitrogen dioxide.

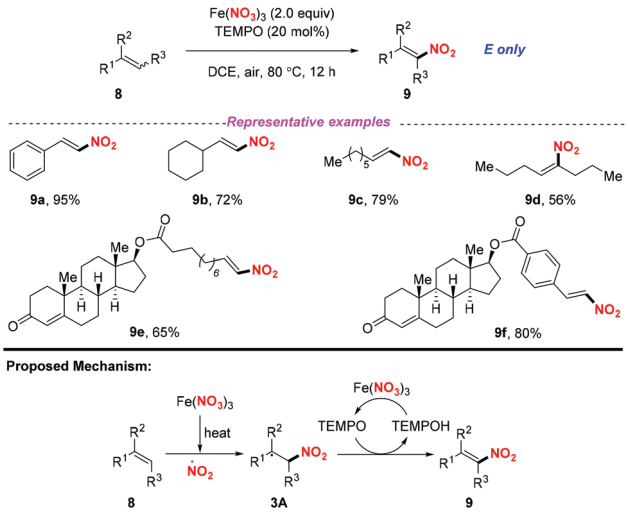
In 2013, Lee and co-workers realized an efficient nitration of silyl allenes with nitrogen dioxide radical (Scheme 2).[6] Accordingly, $Fe(NO_3)_3{\cdot}9H_2O$ was employed as the nitro radical source, providing rapid access to the formation of halo-nitroalkenes. This method exhibited a broad substrate scope, giving rise to various halo-nitroalkenes in good yields. However, in some cases, this method suffered from poor regioselectivity, which limited its further application.

At the same time, Maiti and co-workers reported a selective nitration of olefin with $Fe(NO_3)_3$ and TEMPO (Scheme 3).[7] As for the possible mechanism, the generation of the nitro radical from $Fe(NO_3)_3$ would occur under thermal conditions. Then, the addition of the nitro radical to olefin would result in a secondary or benzylic radical, followed by the reception of a hydrogen radical with TEMPO to obtain nitroalkene compounds **9**. By employing this method, a variety of aromatic, aliphatic, and heteroaromatic olefins were applicable for this transformation, providing the corresponding products in good yields with excellent *E*-selectivity. This method exhibited a broad substrate scope, which could be further applied to the late-stage functionalization of drug-like molecules.

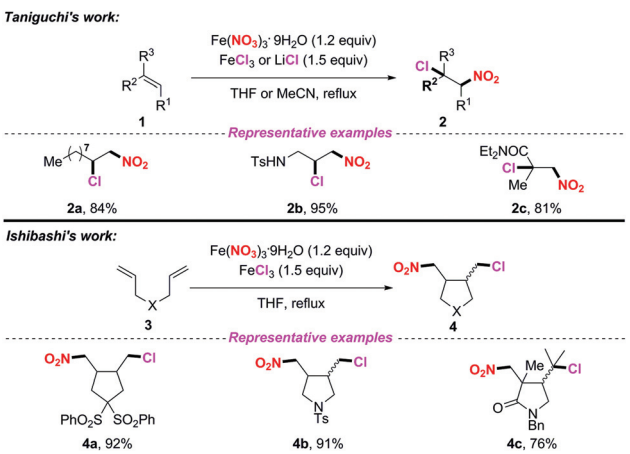
In 2016, Fan and co-workers demonstrated an efficient and regioselective remote C(5)–H nitration of 8-aminoquinoline amides by using $Fe(NO_3)_3{\cdot}9H_2O$ as a promoter and nitro source (Scheme 4).[8] Interestingly, the reaction could undergo bisnitration to afford 5,7-dinitro-8-aminoquinoline amides when $CuCl_2{\cdot}2H_2O$ was used as a catalyst. On the basis of several controlled experiments, two possible mechanisms were presented by the authors to clarify the mono- and bisnitration pathways. In the mononitration process, the coordination of **10** with Fe(III) led to a chelated intermediate **4A**, followed by the addition of a NO_2 radical at the C-5 position of the quinoline unit to form intermediate **4B**. The mononitrated product



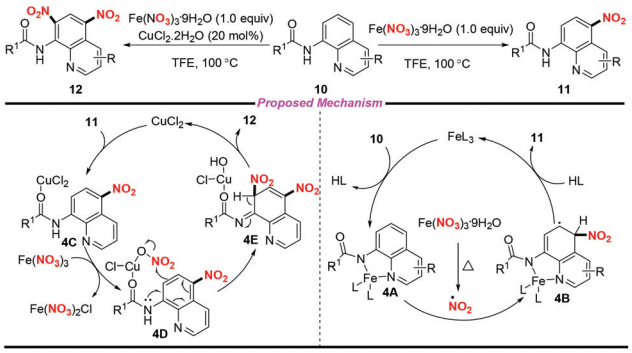
Scheme 2 Iron-mediated radical halo-nitration of silyl allenes to form halo-nitroalkenes.



Scheme 3 Iron-mediated selective nitration of olefins.



Scheme 1 Iron-mediated radical halo-nitration of alkenes and 1,6-dienes.



Scheme 4 Iron-promoted mono- and bisnitration of 8-aminoquinolinamides.

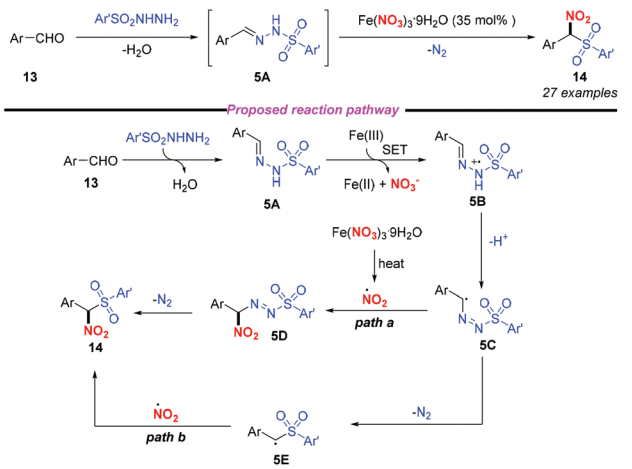
11 was obtained *via* aromatization and decomposition of **4B**. Moreover, intermediate **4D** could be generated from **11** in the presence of $CuCl_2{\cdot}2H_2O$ and $Fe(NO_3)_3{\cdot}9H_2O$, which would undergo a possible electrophilic substitution and aromatization sequence to afford the bisnitrated product **12**.

In 2015, Punniyamurthy and co-workers developed an iron (III)-mediated radical–radical coupling strategy for the generation of biarylsulfonylnitromethane to further transformations (Scheme 5).[9] This protocol featured mild reaction conditions and a broad substrate scope. Based on the mechanistic studies, the authors proposed that the condensation of aldehyde **13** combined with arylsulfonyl hydrazide could give sulfonyl hydrazine **5A**, which would undergo a single electron transfer by $Fe(NO_3)_3$ to form intermediate **5B**. The subsequent isomerization of **5B** gave the radical intermediate **5C** that could couple with the nitro radical to give **5D** and the target product **14** (path a). Alternatively, the formation of **14** could occur through the radical coupling of the nitro radical and the radical intermediate **5E** (path b). In this reaction, the simple and commercially available aldehyde and arylsulfonyl hydrazide were used as the starting materials, and water and nitrogen were produced as the only by-products, showing promising potential for further applications.

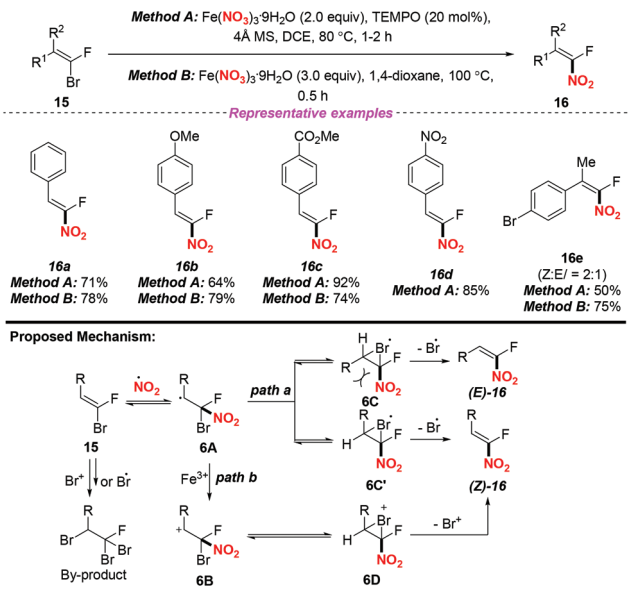
In 2017, Nenajdenko and co-workers described an efficient method for the stereoselective synthesis of β-fluoro-β-nitrostyrenes *via* a radical nitration–debromination sequence (Scheme 6).[10] The reaction proceeded readily either by employing method **A** with the use of the $Fe(NO_3)_3$/TEMPO system at 80 °C or by applying method **B** with $Fe(NO_3)_3$ in 1,4-dioxane at 100 °C, giving the corresponding α-fluoro-nitroalkenes in good yields. A possible mechanism for clarifying the stereoselectivity of the product was proposed, as shown in Scheme 6. The stereoselective formation of 1-fluoro-1-nitroolefin **15** could be explained by the formation of intermediate **6A**, which would exist preferentially in the form of closed 3-membered bromo radicals **6C** or **6C′**. Owing to the steric repulsion between its large R-group and NO_2 moiety, **6C** should be less favoured than **6C′**. Accordingly, the final products (*Z*)-**16** could be generated by the elimination of bromine from the conversion of the more stable cyclic intermediate **6C′** (path a). Besides, the elimination of Br^+ from cation **6B** and its cyclic form **6D** for accessing (*Z*)-**16** was also considered (path b).

Subsequently, Guo and co-workers demonstrated an iron-mediated nitration and cyclization of arene–alkynes, providing a practical protocol for the synthesis of 9-nitrophenathrenes (Scheme 7).[11] This methodology showed a broad substrate scope and good functional group tolerance, affording the corresponding products in good yields. According to the proposed mechanism, the reaction was initiated by the addition of the nitro radical to the alkyne moiety. Notably, $Fe(NO_3)_3{\cdot}9H_2O$ was used as both a nitro source and an oxidant in this transformation.

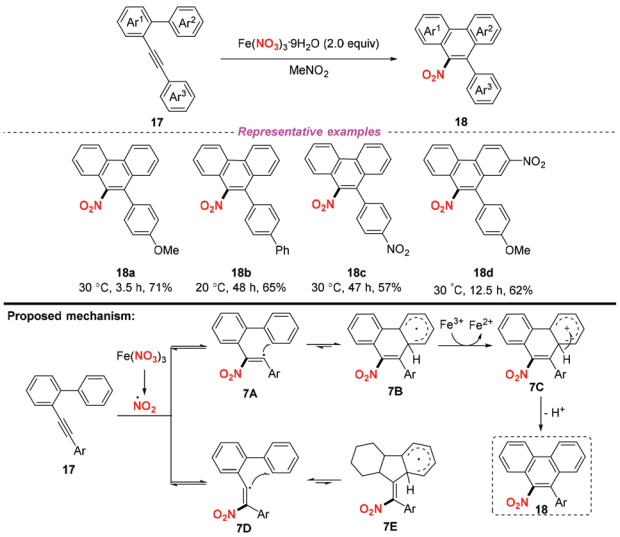
Similarly, the groups of Yan[12] and Wu[13] independently described the Fe-catalyzed or Fe-mediated tandem radical



Scheme 5 Fe(III)-Mediated radical nitration of bisarylsulfonyl hydrazones for the synthesis of biarylsulfonylnitromethane.



Scheme 6 Fe(III)-Mediated stereoselective synthesis of β-fluoro-β-nitrostyrenes *via* radical nitration debromination.



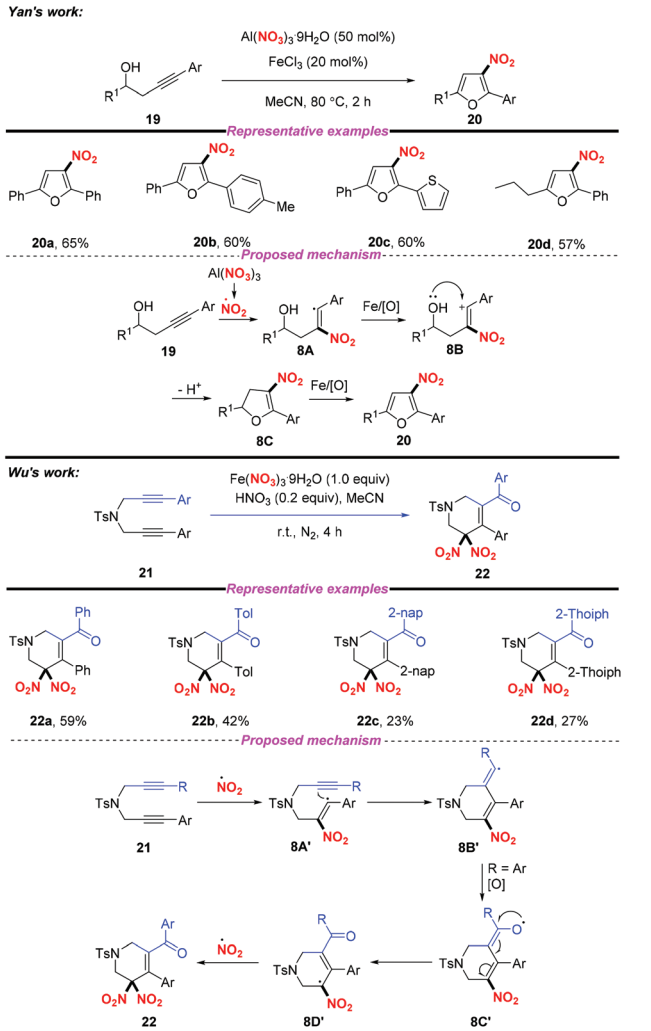
Scheme 7 Iron-mediated nitration and cyclization of arene–alkynes.

nitration/cyclization of alkynes to afford heterocyclic compounds containing a nitro group (Scheme 8). In Yan's work, they employed $Al(NO_3)_3{\cdot}9H_2O$ as a nitro radical source and the homopropargylic alcohols as receptors for the synthesis of 3-nitrofurans. Moreover, Wu and co-workers found that cyclic *gem*-dinitro compounds could be obtained through the nitration of 1,6-diynes using $Fe(NO_3)_3{\cdot}9H_2O$ as the nitro radical source. Notably, the electrophilic cyclization of alkynes could proceed in both reactions without the use of transition metals, leading to the corresponding nitro-containing heterocyclic compounds albeit with low yields.

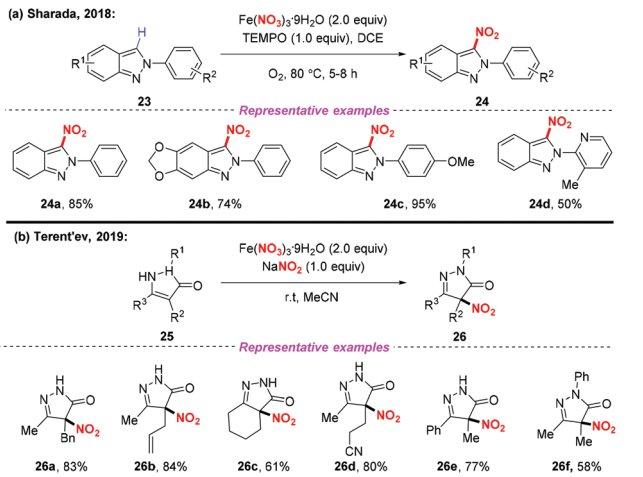
Recently, the radical nitration of heteroarenes was achieved by Sharada and co-workers, using $Fe(NO_3)_3{\cdot}9H_2O$ as the nitro radical source (Scheme 9a).[14] This strategy opened the door to the introduction of the nitro group into heteroarenes, providing the corresponding 3-nitro-2*H*-indazoles in good yields. Later, Terent'ev and co-workers also disclosed a mild nitration of pyrazolin-5-ones for the synthesis of 4-nitropyrazolin-5-ones by employing the $Fe(NO_3)_3/NaNO_2$ system. It was demonstrated that the reaction was compatible with functional groups such as *N*-phenyl and allyl groups, which are usually sensitive under nitration conditions (Scheme 9b).[15]

2.2. Cu-Catalyzed transformations

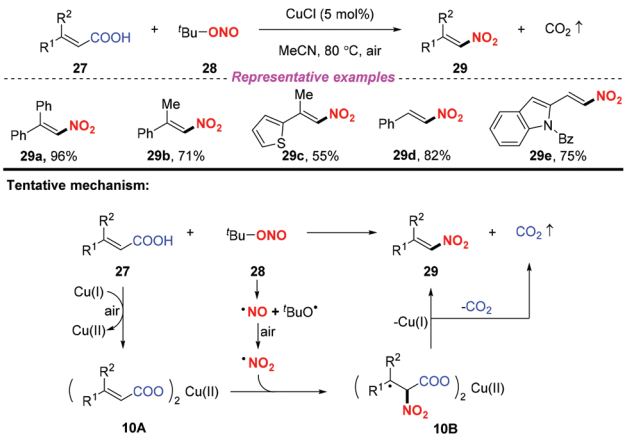
Due to its advantages of low cost, rich abundance in nature, and low toxicity, copper has received considerable attention in the development of various transformations involving nitro radicals. In 2013, Prabhu and co-workers developed a copper-catalyzed nitrodecarboxylation of unsaturated carboxylic acids for the synthesis of substituted nitroolefins (Scheme 10).[16] The protocol exhibited a broad substrate scope and good functional group tolerance and the corresponding products were obtained in moderate to good yields. Accordingly, the combination of α,β-unsaturated acid **27** with CuCl would provide the corresponding Cu(II) salt **10A**, which on further reaction with



Scheme 8 Iron-catalyzed/iron-mediated tandem cyclization *via* radical nitration.



Scheme 9 Iron(III)-mediated radical nitration of heterocyclic compounds.



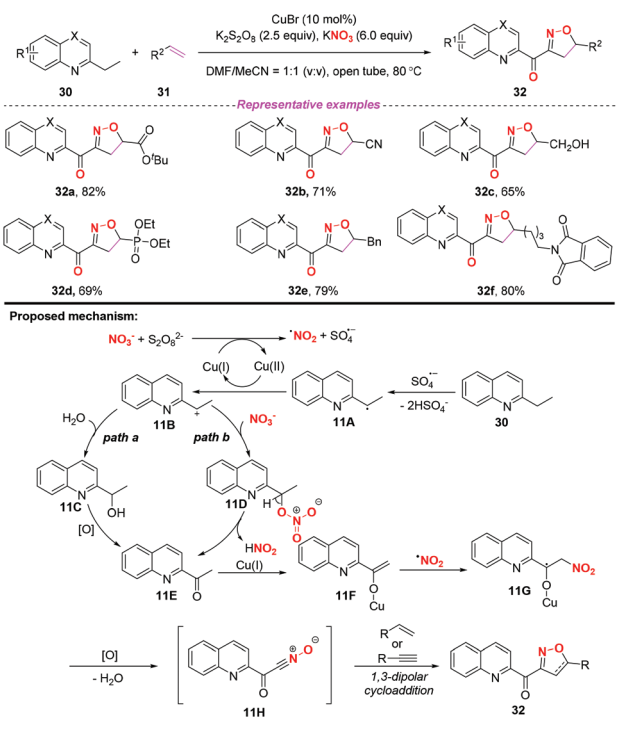
Scheme 10 Copper-catalyzed nitrodecarboxylation of unsaturated carboxylic acids for the synthesis nitroolefins.

the nitro radical formed intermediate **10B**. This intermediate **10B** would undergo decarboxylation to deliver the corresponding nitroolefin **29**.

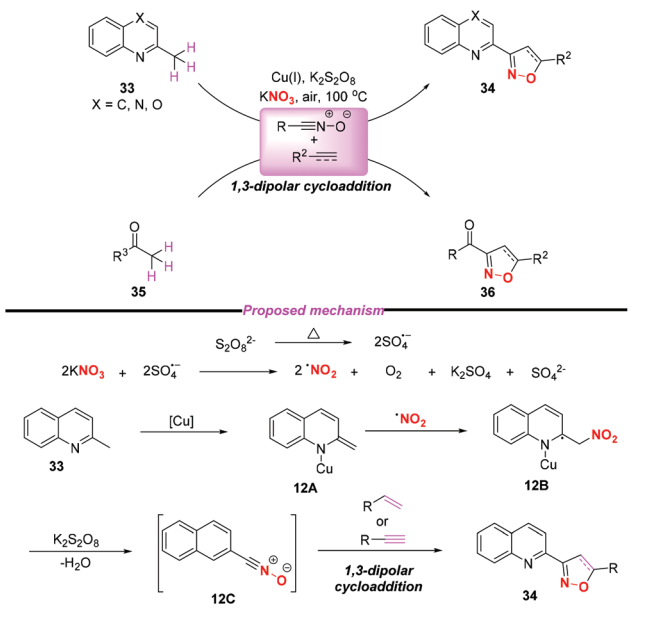
In 2015, the group of Yang developed a copper-catalyzed selective cascade sp^3 C–H bond oxidative functionalization of 2-ethylazaarenes toward the synthesis of isoxazoline derivatives (Scheme 11).[17] The scope of the copper catalyzed sp^3 C–H bond oxidative functionalization was investigated and the corresponding isoxazolines were obtained in moderate to good yields. According to the proposed mechanism, the nitro radical, sulfate anion radical and Cu(II) were initially generated through the reaction of KNO_3 with $K_2S_2O_8$ in the presence of the Cu(I) catalyst. Then, 2-ethylquinoline **30** would undergo a single electron transfer process by a sulfate anion radical to give intermediate **11A**,[18] which was oxidized by Cu(II) to produce the benzylic cation **11B**. Subsequently, the key intermediate **11E** might be generated from **11B** *via* path a or path b, followed by the conversion to active metal enol species **11F**. After the addition of the nitro radical to the reactive species **11F**, the oxidation and dehydration sequence occurred to give nitrile oxides **11H**. The formation of isoxazolines **32** would occur through intramolecular 1,3-dipolar cycloaddition of nitrile oxides **11H** with alkenes or alkynes. The potential application of isoxazolines further increased the practicality of the present method, with the combination of simple substrates and cheap catalytic systems.

Inspired by the above achievement, the same group expanded this strategy to the construction of isoxazoline derivatives using alkylazaarenes and substituted ethanones as the starting materials (Scheme 12).[19] Similarly, the mechanistic studies revealed that a nitro radical single electron transfer process might be involved as well. As important and versatile synthons, alkynes or alkenes were commercially available in large quantities, greatly increasing the scope and application of the current method.

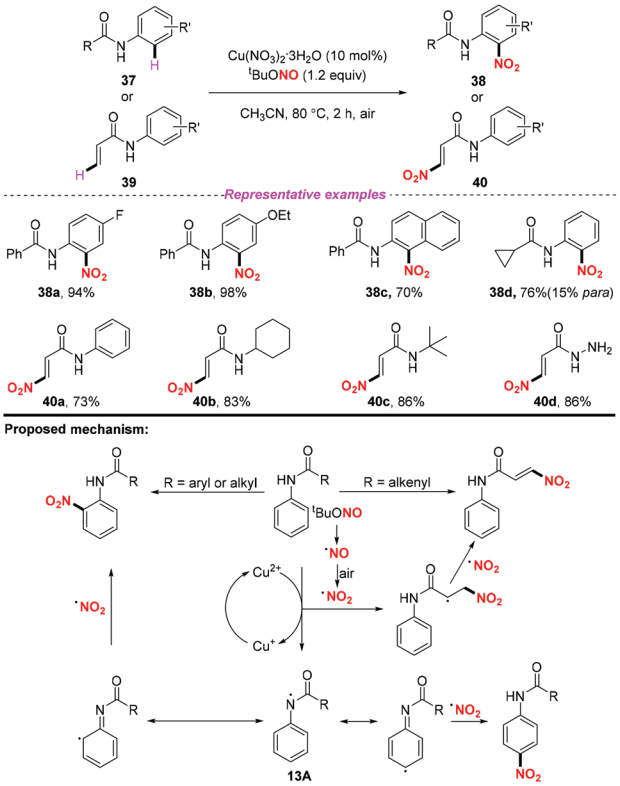
At the same time, Jiang and co-workers described a copper promoted nitration of anilides and acrylamides by using *tert*-butyl nitrite as a metal-free nitrating reagent (Scheme 13).[20] According to the putative mechanism, firstly, ^{t}BuONO underwent a thermal homolysis and oxidation sequence to form $NO_2^{\bullet}$. In the arene nitration process, a single electron oxidation of the anilide by the copper(II) salt resulted in the formation of intermediate **13A**. Then, **13A** underwent a reversible



Scheme 11 Copper-catalyzed selective cascade sp^3 C–H bond oxidative functionalization of 2-ethylazaarenes.



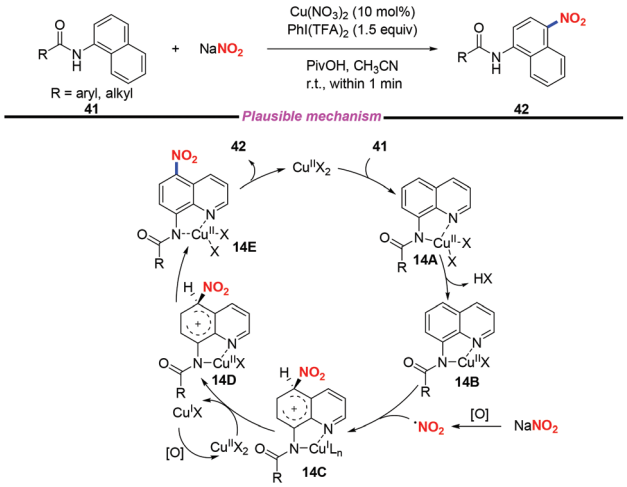
Scheme 12 Copper-catalyzed sp^3 C–H bond oxidative functionalization of alkylazaarenes.



Scheme 13 Copper-promoted nitration of anilides and acrylamides.

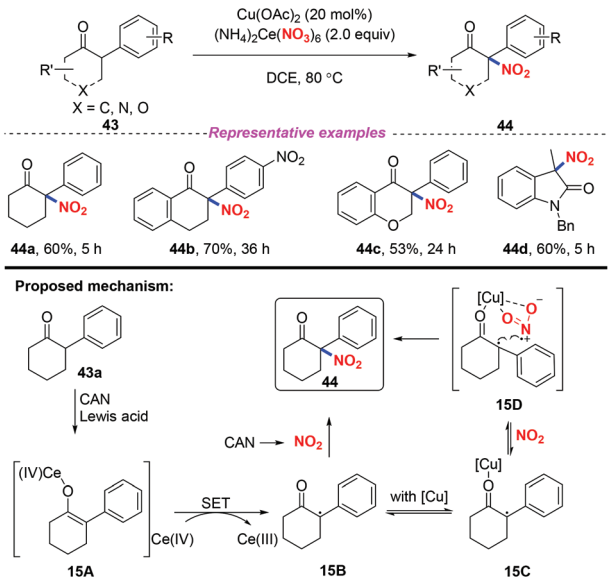
conversion followed by the coupling of the nitro radical at the *ortho*- or *para*-positions of the aromatic ring to afford the corresponding nitration products **38**. As for the olefin nitration process, the addition of the nitro radical to the alkenyl moieties followed by an *anti*-elimination in the presence of another nitro radical would give rise to the nitro substituted olefin stereoselectively. This reaction could not only realize the activation of the aryl C–H bond, but also demonstrated that the alkenyl C–H bond could be subjected to the nitration process. However, when the anilides had no substituent at the *para* position, the nitro-containing product was obtained with poor regioselectivity.

Additionally, a rapid and efficient method for copper-catalyzed highly regioselective C–H nitration of quinolines was achieved by Zhang and co-workers (Scheme 14).[21] In this transformation, by employing sodium nitrite as the nitro source, a variety of nitrated quinoline derivatives were obtained in moderate to good yields. Based on the experimental results and their previous reports, a plausible mechanism was proposed for this transformation. Initially, the chelated complex **14A** was formed through the coordination of substrate **41** with Cu(II), followed by the deprotonation of the amide group to give complex **14B**. The nitro radical was generated in the presence of $PhI(TFA)_2$ and $NaNO_2$. Then, a single electron transfer would occur between the nitro radical and complex **14B** to produce the Cu(I) intermediate **14C**, followed by oxidation, proton transfer and ligand dissociation sequence to release the desired product and regenerate the Cu(II) species.

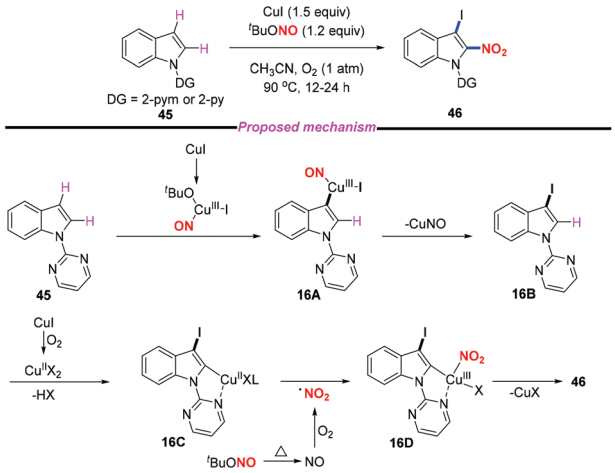


Scheme 14 Copper-catalyzed direct C–H nitration of quinolines.

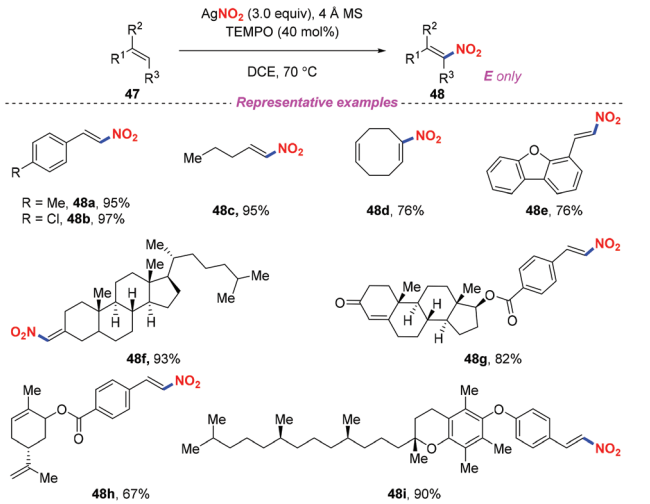
In 2017, Zhang and co-workers developed an efficient and direct copper-assisted nitrating approach for the synthesis of tertiary α-nitro-α-substituted scaffolds by using ceric ammonium nitrate as a nitrating reagent, oxidant, and Lewis acid, using copper salt as a catalyst (Scheme 15).[22] Additionally, this method was successfully applied to the efficient synthesis of commonly used clinical drug ketamine in four steps. Based on the experimental results, a possible mechanism was proposed, as shown in Scheme 15. Initially, CAN served as a Lewis acid to promote the formation of the enolized intermediate **15A**, which was oxidized by CAN to produce radical species **15B**. Then, radical **15B** was either trapped by nitrogen dioxide derived from CAN without Cu species or reacted through intermediate **15D** stabilized by Cu species to afford product **44**.



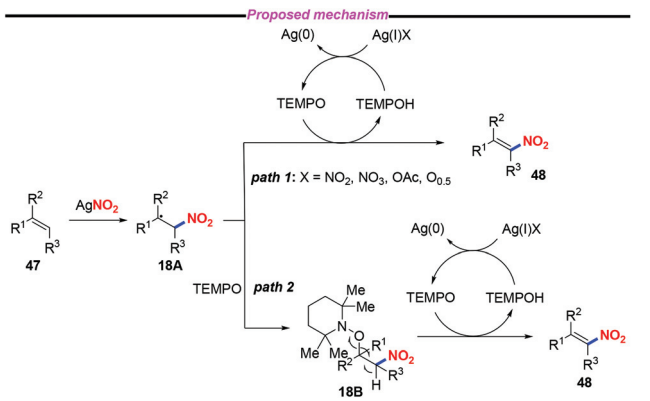
Scheme 15 Copper-assisted nitration of cyclic ketones with ceric ammonium nitrate.



Scheme 16 Copper-mediated C–H iodination and nitration of indoles.



Scheme 17 Silver-mediated efficient and stereoselective nitration of mono- and disubstituted olefins.



Scheme 18 Proposed mechanism for the nitration of olefins.

Regioselective nitration in the indole skeleton molecule remains a challenge and the development of efficient and green nitration methods under mild reaction conditions is highly desirable. In 2018, Jiang and co-workers reported an efficient copper-mediated aerobic oxidative C–H iodination and nitration of indoles through double C–H functionalization (Scheme 16).[23] This method provided rapid access to 3-iodo-2-nitroindoles in good yields with high regioselectivity under mild conditions. Moreover, the utility of this method was further demonstrated through the derivatization of the iodination and nitration products. According to the proposed mechanism, the iodination step was suggested to proceed through the electrophilic addition of a Cu(III)-iodide species to the C3 position of the indole motif. The subsequent nitration step involved C–H activation, nitro radical oxidative addition, and reductive elimination sequence. In this reaction, cuprous iodide acted both as a catalyst and an iodine source. The resulting 2-nitro-3-iodoindoles could undergo Heck, Suzuki, Negishi, Sonogashira and other coupling reactions to obtain 2-nitro-3-substituted indole compounds, which have potential biological activity.

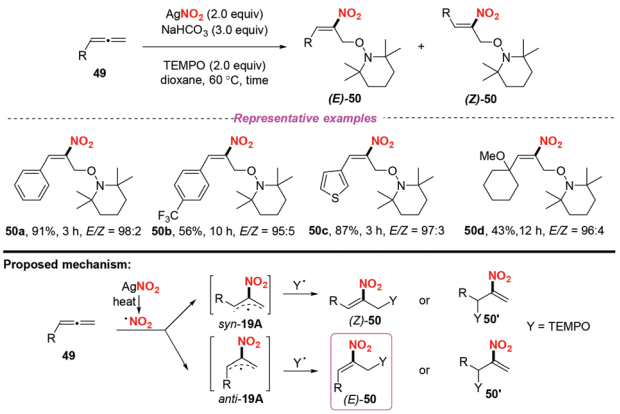
2.3. Ag-Catalyzed or mediated transformations

Nitroolefins are valuable building blocks, and have been widely applied in various carbon–carbon bond-forming transformations. Thus, the incorporation of a nitro group into the olefins has become an efficient and straightforward method to furnish nitroolefins. In 2013, Maiti and co-workers reported an efficient and stereoselective nitration of mono- and disubstituted olefins with silver nitrite and TEMPO under ambient conditions (Scheme 17).[24] This protocol featured a broad substrate scope and high stereoselectively, which could be further applied to the late-stage site-selective functionalization of complex molecule synthesis.

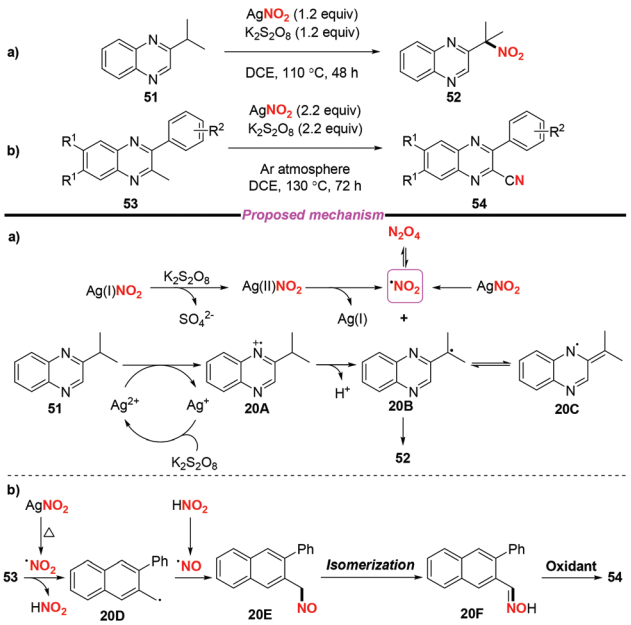
A plausible mechanism for the nitration of olefin has been outlined in Scheme 18. Initially, a nitro radical might be generated from $AgNO_2$ under thermal conditions. The addition of the nitro radical to olefin **47** would give rise to the carbon-centered radical **18A**. Subsequently, the nitroolefin product **48** could be formed *via* H-atom abstraction either from intermediate **18A** (path 1) or from intermediate **18B** (path 2).

Later, Ma and co-workers reported a highly regio- and stereoselective nitro-oxoamination reaction of mono-substituted allenes, using $AgNO_2$ as the nitro radical source (Scheme 19).[25] The reaction proceeded smoothly to access various nitroolefins **50** with good functional group compatibility. The reaction was proposed to occur through the addition of nitro radical species to allenes giving rise to the stable allylic radical intermediate *anti*-**19A** or *syn*-**19B**, which could be directly captured by a TEMPO to form C–N and C–O bonds in one step.

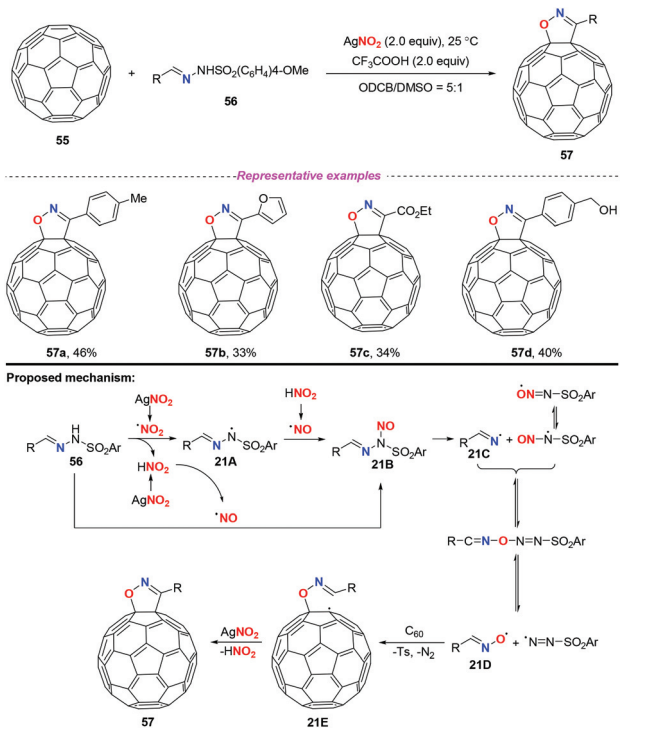
At the same time, Liu and co-workers described the $AgNO_2$-mediated nitration of the quinoxaline tertiary C–H bond and conversion of 2-methyl quinoxalines into 2-quinoxaline nitriles (Scheme 20).[26] To gain insight into the mechanism of the nitration process, the authors conducted some control experi-



Scheme 19 Silver-mediated regio- and stereoselective nitro-oxoamination reaction of mono-substituted allenes.



Scheme 20 Silver-mediated nitration of the quinoxaline benzylic C–H bond.

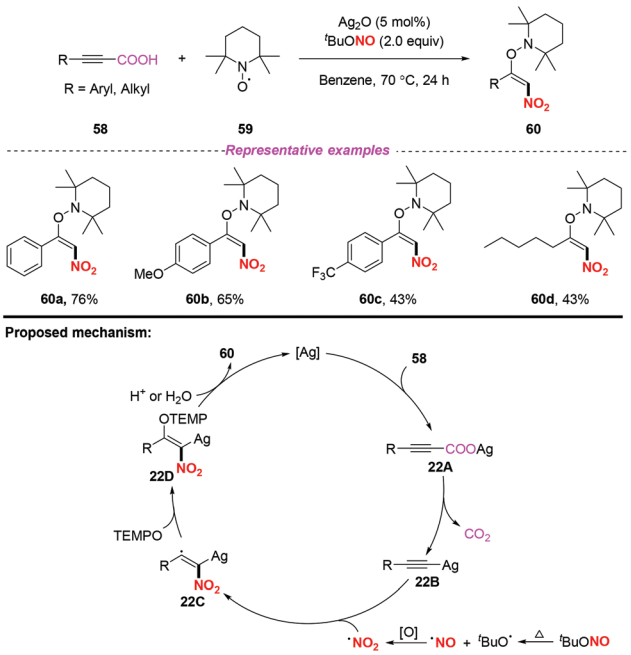


Scheme 21 Silver-mediated transformation of sulfonylhydrazones with [60]fullerene.

ments to confirm that the reaction might involve a free radical process. According to the proposed mechanism (shown in Scheme 20a) the nitro radical might be generated from $AgNO_2$ upon treatment with or without $K_2S_2O_8$. A single-electron transfer between the Ag(II) species and **51** would deliver radical intermediate **20B** (or **20C**), followed by the combination with the nitro radical to afford nitroalkane **52**. On the other hand, the direct conversion of **53** to **54** might involve the generation of nitroso intermediate **20E** and oxime **20F**, which could be further oxidized into nitrile **54**.

In 2015, Zhang and co-workers developed a novel $AgNO_2$-mediated transformation of sulfonylhydrazones with [60]fullerene to afford fulleroisoxazolines (Scheme 21).[27] It should be noted that the cleavage of the N–N bond of sulfonylhydrazones in synthetic chemistry was first disclosed. In this transformation, silver nitrite played dual roles, as a reaction initiator and as an oxygen source. Similar to previous reports, a nitro radical or a nitrosonium ion might be generated under the applied reaction conditions. Subsequently, the active species **21B** could be produced either through the coupling of the nitro radical with the nitrogen-centered radical **21A** or through the nucleophilic attack of the nitrosonium ion to sulfonylhydrazones **56**. The decomposition of the unstable species **21B** would generate the radical intermediate **21D** *via* fast equilibrium conversions. As a result, the addition of radical **21D** to [60]fullerene led to fullerenyl radical **21E**, followed by an intramolecular radical cyclization to give the final product **57**. Since the functionalization of fullerene is challenging, this work represented a rare example of free radical initiated transformation of fullerene, although the results were not satisfactory.

In the same year, Mao and co-workers developed a simple and efficient silver-catalyzed decarboxylative nitroaminoxylation of phenylpropiolic acids, resulting in the synthesis of (*E*)-β-nitroolefinic alkoxyamines with satisfactory yields (Scheme 22).[28] The mechanism for the formation of product **60** was proposed as follows: initially, the reaction of phenylpropiolic acid **58** with silver oxide would provide silver carboxylate **22A**, which could be converted into the Ag-acetylide intermediate **22B** *via* decarboxylation. Additionally, the nitro radical was generated from ^tBuONO through the oxidation of a NO radical. Subsequently, the addition of the nitro radical to the Ag-acetylide intermediate **22B** resulted in the radical intermediate **22C**,

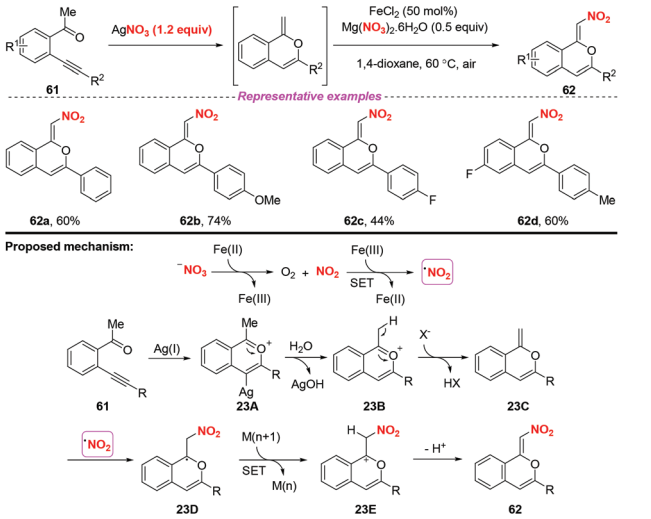


Scheme 22 Silver-catalyzed decarboxylative nitroaminoxylation reaction of phenylpropiolic acids.

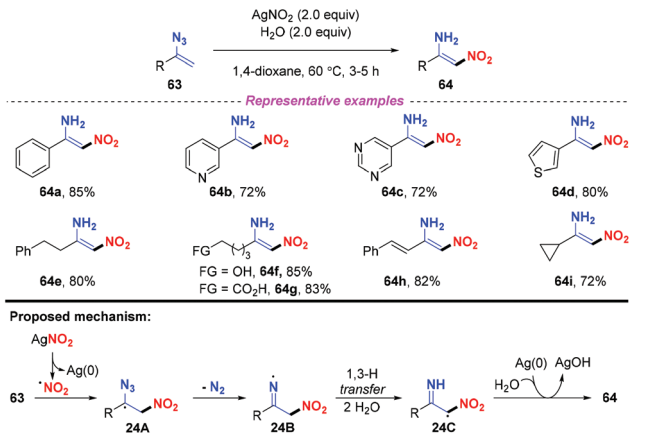
which was trapped by TEMPO to give **22D**. Finally, the protonation of **22D** would release the desired product **60** and regenerate the silver catalyst. Similar to Ma's work,[25] this reaction also illustrated the process of nitro radical addition to unsaturated bonds.

In 2017, Jiang and co-workers established a silver-mediated C(sp^3)–H functionalization and 6-*endo-dig* oxo-cyclization of conjugated β-alkynyl ketones under oxidative conditions (Scheme 23).[29] By employing $AgNO_3$ as a nitrating reagent, this method enabled the synthesis of nitro-branched (*Z*)-isochromenes in moderate to good yields. On the basis of radical trapping studies and previous reports, a possible mechanism involving the formation of the nitro radical by the SET process between Fe(II) salts and activated NO_3^- was proposed. The subsequent transformation steps, Ag-catalyzed 6-*endo-dig* oxo-cyclization/H-transfer/SET/radical addition afforded isochromenes **62**. This reaction showed that not only the nitrite group but also the nitrate group could be used as the source of nitro radicals for accessing nitro-containing products.

The nitrification of vinyl azides into *N*-unprotected enamines was achieved by Bi and co-workers (Scheme 24).[30] In general, various (hetero)arenes or alkanes were compatible in this reaction, furnishing the corresponding products **64** in good yields. Notably, by employing this strategy, alkyl vinyl azides bearing OH and COOH groups were well-tolerated to furnish the functionalized nitroenamine products. On the basis of experimental results and DFT calculations, a plausible mechanism was proposed, as depicted in Scheme 24. The nitro radical, which was firstly generated from $AgNO_2$ with the release of Ag(0), would attack the terminal carbon of vinyl azide **63**, leading to intermediate **24A**. The iminyl radical **24B**



Scheme 23 Silver-catalyzed C(sp^3)–H nitration of β-alkynyl ketones for accessing functionalized isochromenes.

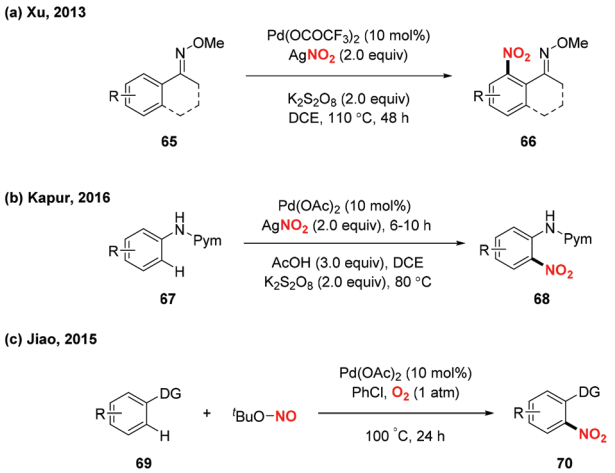


Scheme 24 Silver-mediated nitrification of vinyl azides into nitroenamines.

was subsequently formed by releasing N_2 from **24A**, which would undergo a 1,3-H transfer with the assistance of water to give intermediate **24C**. Finally, the resulting radical **24C** could be converted to **64** by the transfer of an H atom from water to the iminyl *N*-site.

2.4. Pd-Catalyzed transformations

Over the past decades, palladium-catalyzed C–H functionalizations of organic compounds have been widely applied in synthetic organic chemistry. In 2013, Liu and co-workers developed a novel palladium-catalyzed chelation-assisted site-regiospecific nitration of aromatic C–H bonds, using $AgNO_2$ as a nitro radical source (Scheme 25a).[31] This protocol exhibited excellent mononitration selectivity, broad functional group and substrate tolerance, providing the corresponding nitroarenes in good yields. Later, Kapur and co-workers described a palladium-catalyzed regioselective C–H nitration of anilines

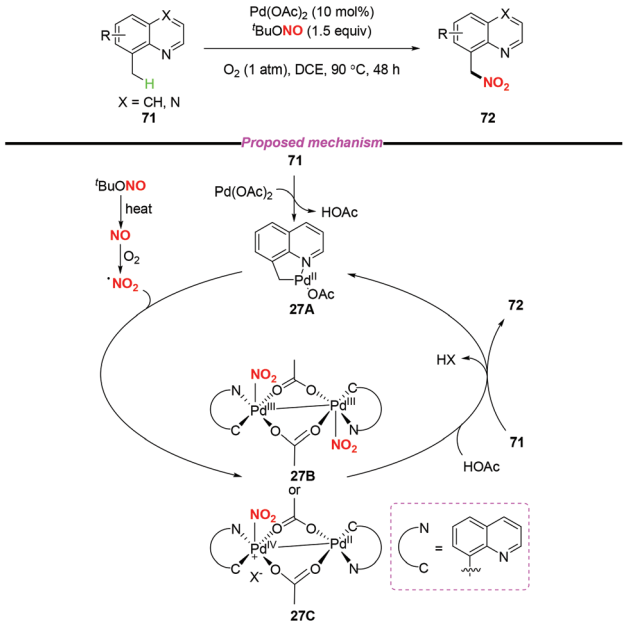


Scheme 25 Palladium-catalyzed nitration of aromatic C–H bonds (Xu, Kapur and Jiao).

using pyrimidine as a removable directing group (Scheme 25b).[32] Additionally, Jiao and co-workers demonstrated Pd-catalyzed aerobic oxidative C–H nitration of arenes with *tert*-butyl nitrite (TBN) as the radical precursor. In this reaction, molecular oxygen was employed as the terminal oxidant and oxygen source to initiate the active radical reactants (Scheme 25c).[33]

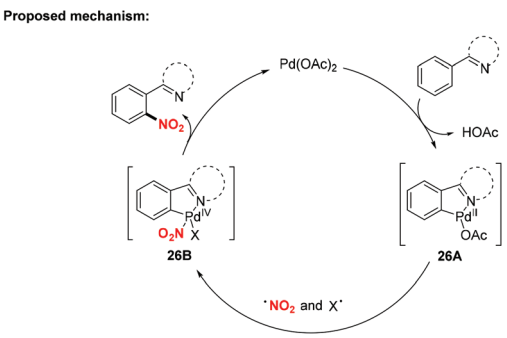
According to the mechanism proposed by Jiao and co-workers, the palladacycle intermediate **26A** was firstly formed by directing group assisted *ortho*-selective cyclometallation on the benzene. Then, oxidative addition of active radicals (such as NO_2, ^tBuO) to **26A** provided Pd(IV) intermediate **26B**, which would undergo reductive elimination to afford the corresponding products (Scheme 26).

In 2015, Liu and co-workers described a novel palladium-catalyzed sp^3 C–H nitration of 8-methylquinolines, which produces 8-(nitromethyl)quinolines in moderate to excellent yields (Scheme 27).[34] During the reaction process, ^{t}BuONO was used as a NO_2 radical source under mild conditions. To gain insight into the mechanism of the sp^3 C–H nitration, the authors carried out several mechanistic experiments, and proposed a possible mechanism to clarify the reaction pathway. Firstly, palladacycle intermediate **27A** was formed through a reaction of $Pd(OAc)_2$ with 8-methylquinoline, and the NO_2 radical was generated from *tert*-butyl nitrite *via* a NO radical intermediate. Then, the addition of the NO_2 radical to the palladium center of **27A** delivered Pd(III)–Pd(III) species **27B** or Pd(IV)–Pd(II) species **27C**. Finally, the reductive elimination of **27B** or **27C** in the presence of another molecule of **71** would release the desired product **72** and regenerate **27A**.



Scheme 27 Palladium-catalyzed sp^3 C–H nitration of 8-methylquinolines.

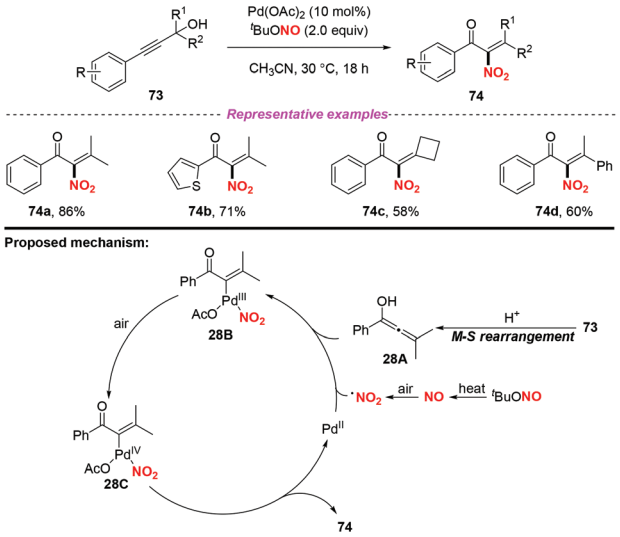
A palladium-catalyzed Meyer–Schuster/nitration of propargylic alcohols to access α-nitroenones under aerobic conditions was developed by Song and co-workers in 2016 (Scheme 28).[35] Similarly, the NO_2 radical was generated from ^{t}BuONO (TBN) *via* the NO radical intermediate. On the basis of several control experiments, a tentative reaction mechanism is depicted in Scheme 28. Firstly, propargylic alcohol **73** was converted into the allenol intermediate **28A** *via* the Meyer–Schuster rearrangement. The addition of the NO_2 radical to intermediate **28A** led to the formation of intermediate **28B** in the presence of $Pd(OAc)_2$, which was further oxidized into intermediate **28C**. Finally, the desired product **74** was formed *via* reductive elimination along with the regeneration of the palladium catalyst. When α-nitroenone was subjected to the subsequent hydrogenation reduction, α-amino alcohol was obtained, which could be used as a raw material to synthesize various oxazoline ligands.



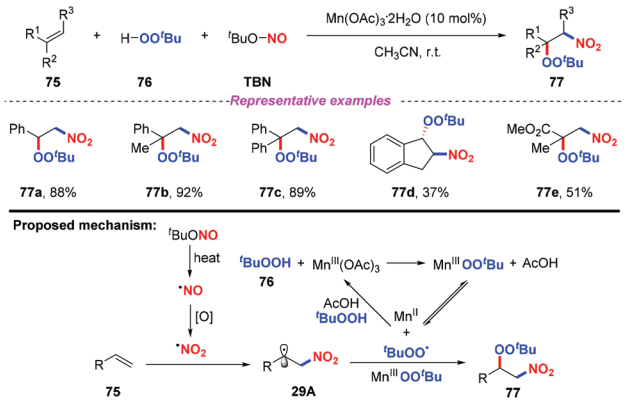
Scheme 26 Proposed mechanism for the palladium-catalyzed nitration of aromatic C–H bonds.

2.5. Mn-Catalyzed transformations

Recently, Li and co-workers reported a novel and selective three-component nitration–peroxidation of alkenes with ^{t}BuONO (TBN) and ^{t}BuOOH (TBHP) to afford β-peroxy nitro compounds in moderate to good yields (Scheme 29).[36] The



Scheme 28 Palladium-catalyzed nitration of Meyer–Schuster intermediates with TBN as a nitrogen source at ambient temperature.

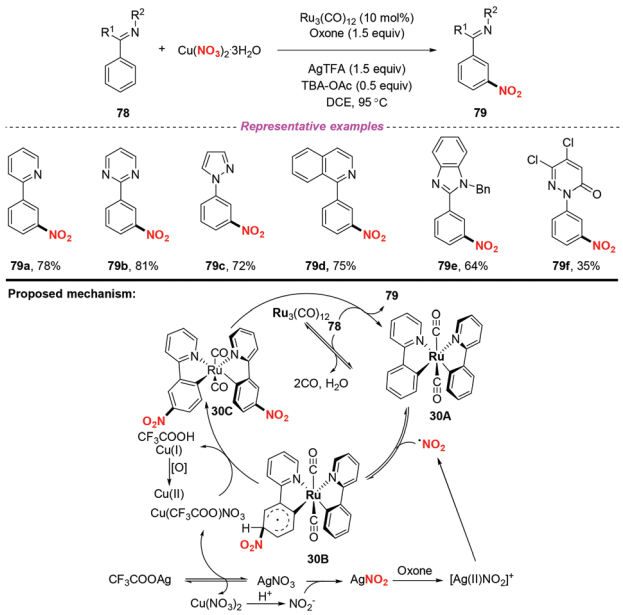


Scheme 29 Manganese-catalyzed nitration peroxidation of alkenes.

reaction proceeded readily at room temperature by employing $Mn(OAc)_3{\cdot}2H_2O$ as the catalyst. Based on the experimental results, a possible mechanism for the nitration–peroxidation of alkenes was proposed, as shown in Scheme 29. Initially, the nitro radical and peroxyl radical ($^{\bullet}OO^tBu$ or Mn-OO^tBu) were generated from TBN and ^{t}BuOOH, respectively. Then, the addition of the nitro radical to alkene **75** would result in the formation of key intermediate **29A**, followed by the radical cross-coupling with a peroxyl radical ($^{\bullet}OO^tBu$ or Mn-OO^tBu) to give the final product 77.

2.6. Ru-Catalyzed transformations

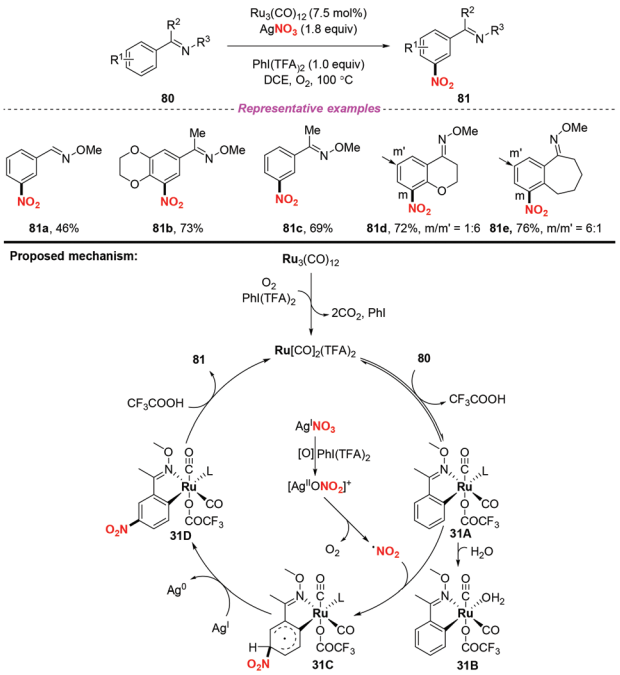
Over the past few years, significant progress in Ru-catalyzed *meta*-C_{Ar}–H functionalization has been achieved by using the *ortho*-metalation strategy. In 2016, Zhang and co-workers reported the first example of Ru-catalyzed *meta*-selective C_{Ar}–H nitration of 2-aryl *N*-aromatics using $Cu(NO_3)_2{\cdot}3H_2O$ as the nitro radical source (Scheme 30).[37] Moreover, by using the



Scheme 30 Ruthenium-catalyzed *meta*-selective C_{Ar}–H nitration of 2-aryl *N*-aromatics.

nitration products as the starting materials, this methodology was further applied to the synthesis of pharmaceutical intermediates, clinical candidates and marketed drugs. On the basis of the detailed mechanistic investigation, a plausible catalytic cycle is depicted in Scheme 30. Firstly, the active Ru complex **30A** was formed through the C_{Ar}–H activation of substrate **78** with $Ru_3(CO)_{12}$, which was confirmed by X-ray diffraction analysis. Subsequently, electrophilic addition of the nitrogen dioxide radical to the *para*-carbon of the Ru–C_{Ar} σ-bond would deliver species **30B**, followed by deprotonation to give a more stable intermediate **30C** with the assistance of a new copper(II) salt, $Cu(CF_3COO)NO_3$. In this process, the new copper(II) salt was derived from an anion exchange between $Cu(NO_3)_2$ and AgTFA. Finally, ligand exchange of complex **30C** with **78** would provide the nitration product **79**, and regenerate complex **30A**.

The same group later developed an oxime-directed *meta*-C_{Ar}–H nitration of arenes by using $AgNO_3$ as the nitro radical source (Scheme 31).[38] Mechanistic studies revealed that a new *ortho*-ruthenated monomeric octahedral complex was involved. On the basis of the experimental results, a possible mechanism for the *meta*-C_{Ar}–H nitration process was proposed, as shown in Scheme 46. Initially, the active Ru(II) catalyst was formed through the oxidation of the Ru(0) precatalyst using $PhI(TFA)_2$ and O_2 as the oxidant. Then, the *ortho*-C–H bond cleavage of **80** led to Ru(II) complex **31A**, which would further undergo a water-ligand exchange to give complex **31B**. On the other hand, $AgNO_3$ was oxidized by $PhI(TFA)_2$ to yield a Ag(II) salt, followed by the release of the nitrogen dioxide radical. The resulting nitrogen dioxide radical would attack the *para* position of the C–Ru bond to afford Ru^{II} species **31C**. The reductive deprotonation of **31C** would result in the formation



Scheme 31 Ruthenium-catalyzed oxime-directed *meta*-C_{Ar}–H nitration of arenes.

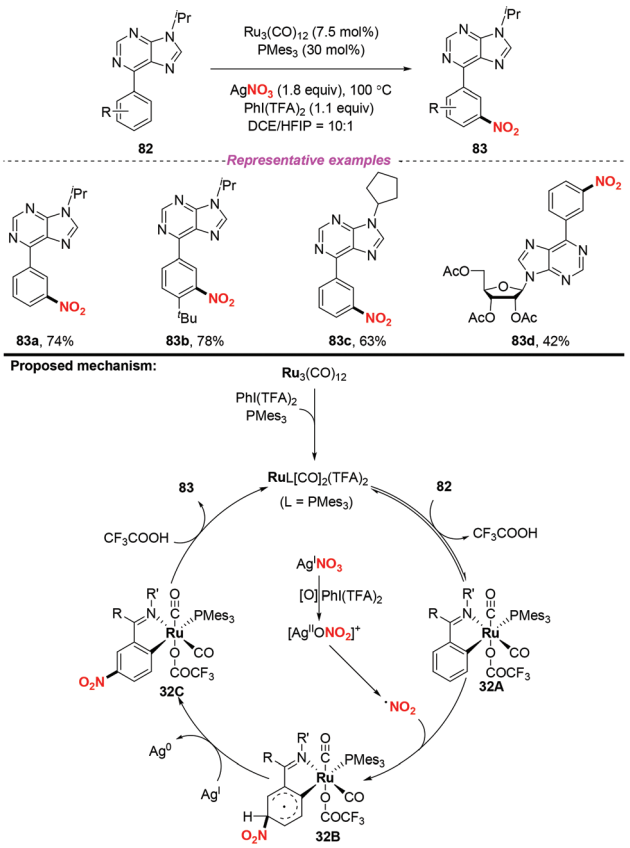
of intermediate **31D**. Finally, ligand exchange of **31D** with CF_3COOH would release the *meta*-nitrated product **81** and regenerate the active Ru(II) catalyst.

In 2018, the same group extended the above strategy to the ruthenium-catalyzed tertiary phosphine ligand promoted *meta*-C–H nitration of 6-arylpurines and nucleosides (Scheme 32).[39] The authors found that the sterically hindered phosphine ligand played a crucial role in catalytic efficiency. By employing this method, a series of *meta* nitrated products were obtained in good yields, showing a broad substrate scope and high functional group tolerance. The possible reaction pathway was similar to the previous reports, and is shown in Scheme 32.

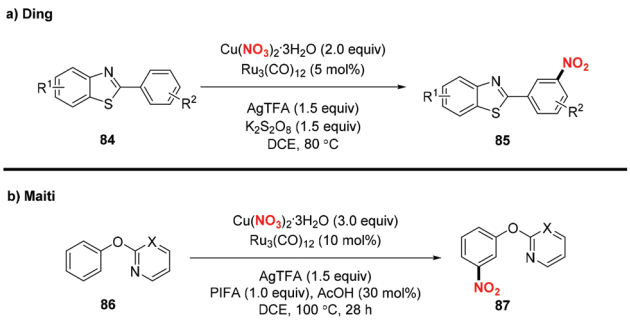
Recently, the group of Ding developed an efficient method for the synthesis of *meta*-nitrated 2-arylbenzothiazole **85** through the ruthenium-catalyzed *meta*-selective C–H nitration pathway (Scheme 33a). Similarly, Maiti and co-workers also developed a directing group assisted ruthenium catalyzed approach to produce *meta*-nitrated phenols **86** (Scheme 33b).[40b] Both the reactions featured a broad substrate scope and gave rise to *meta*-nitrated benzothiazole and phenol derivatives with structural complexity that could not be readily prepared by other methods.

2.7. Under transition metal free conditions

2.7.1 TBN as a nitro radical source. Except for the above-mentioned approaches employing nitro radicals under transition metal catalysis, the development of a metal-free nitration process is promising for the formation of nitro compounds through a radical process. For instance, in 2013, Maiti

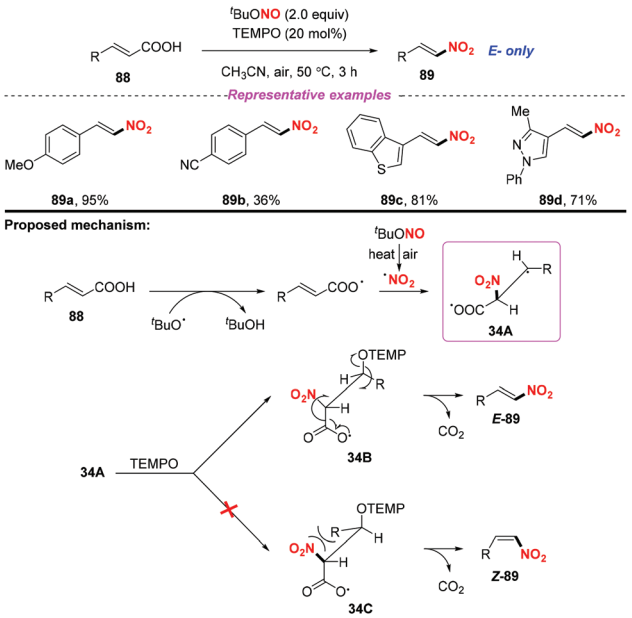


Scheme 32 Ruthenium-catalyzed $PMes_3$-promoted *meta*-C–H nitration of arenes.



Scheme 33 Ruthenium-catalyzed *meta*-C–H nitration of arylbenzothiazole.

and co-workers developed a mild, metal-free decarboxylative nitration protocol for the synthesis of nitroolefins from α,β-unsaturated carboxylic acids using ^{t}BuONO and TEMPO under aerobic conditions (Scheme 34).[41] The substrate scope of this reaction was quite broad, and α,β-unsaturated carboxylic acids bearing aromatic and heterocyclic groups were well-tolerated. According to the proposed mechanism, the nitro radical was generated from TBN *via* the homolytic cleavage of O–NO bonds and subsequent oxidation, which would attack the double bond of olefins to form the benzylic radical



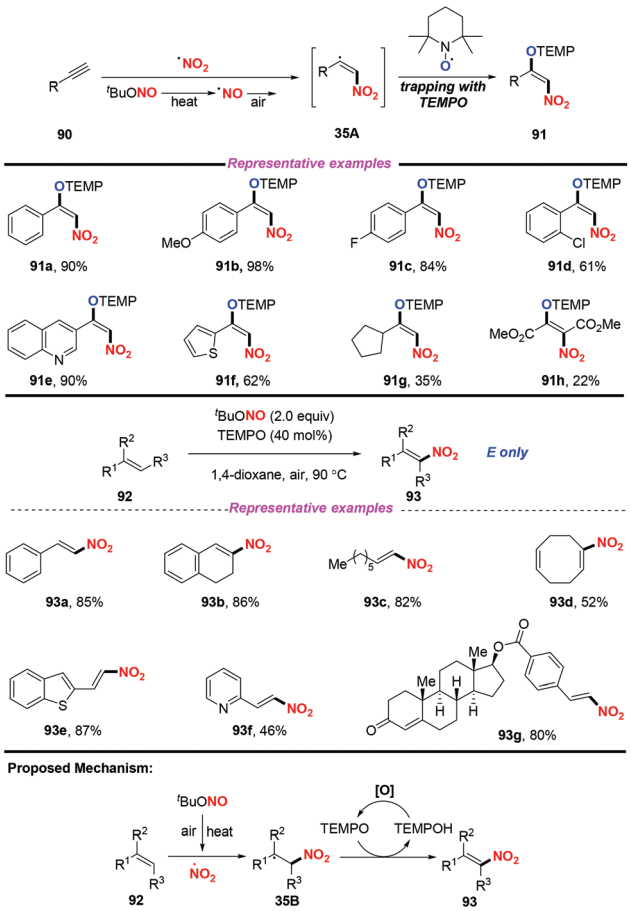
Scheme 34 Synthesis of (*E*)-nitroolefins *via* decarboxylative nitration using TBN and TEMPO.

34A. Then, the radical coupling of intermediate **34A** with TEMPO would lead to the preferential formation of energetically more favorable intermediate **34B** over **34C**, followed by *anti*-elimination to afford *E*-nitroolefins.

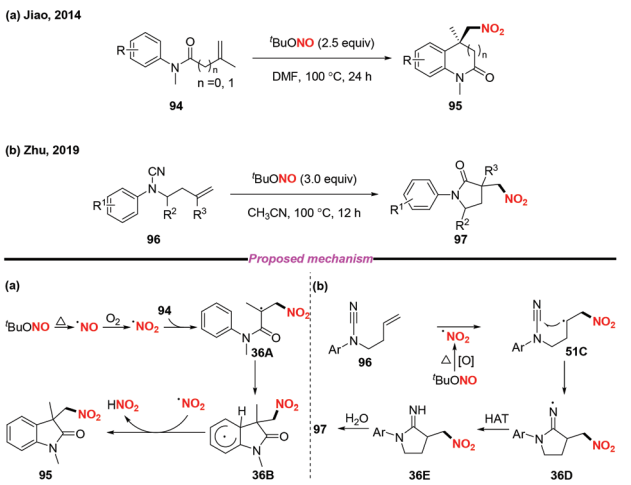
Additionally, the same group also extended this strategy for the stereoselective nitro-aminoxylation of alkynes with TBN and TEMPO (Scheme 35a).[42a] The reaction featured a wide substrate scope and good functional group tolerance, leading to (*E*)-β-nitroolefinic alkoxyamines in high yields. Meanwhile, by employing the TBN and TEMPO system, the authors found that alkenes were suitable for the stereoselective nitration process, providing direct access to nitroolefins with excellent *E*-selectivity (Scheme 35b).[42b]

In 2014, the group of Jiao reported a highly efficient metal-free nitro-carbocyclization of activated alkenes, giving rise to various nitro-containing oxindoles *via* tandem C–N and C–C bond formation (Scheme 36a).[43] Additionally, Zhu and co-workers recently developed a novel method for the preparation of γ-lactams through radical-mediated nitration–aminocarbonylation of unactivated olefins under metal-free conditions (Scheme 36b).[44] Notably, the nitro radical was generated from the homolysis of *tert*-butyl nitrite in both reactions for further transformations.

In 2015, Liang and co-workers demonstrated a novel and convenient metal-free nitration and cyclization of 1,6-enynes (Scheme 37).[45] This transformation exhibited good functional-group tolerance and was amenable to scale up. Mechanistic investigations revealed that the reaction was initiated *via* the addition of the nitro radical to the C–C triple bond of the 1,6-enynes **98** to generate intermediate **37A**, which subsequently underwent intramolecular carbocyclization to give radical intermediate **37B**. Finally, the desired product **99** was formed

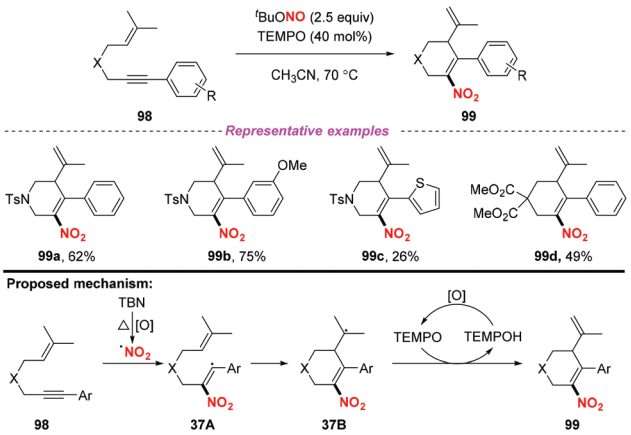


Scheme 35 Aerobic oxynitration of alkynes and alkenes with TBN and TEMPO.



Scheme 36 Synthesis of nitro-containing oxindoles and γ-lactams under metal-free conditions.

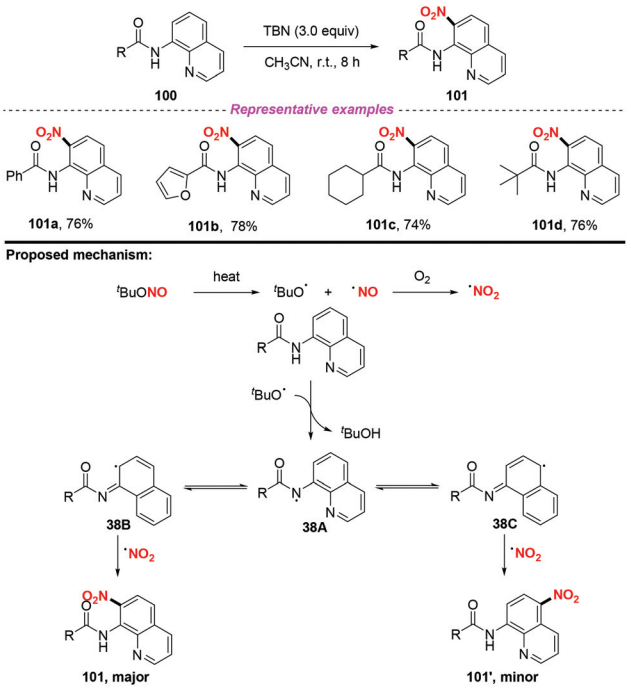
through the oxidative dehydrogenation of intermediate **37B** with TEMPO. In contrast to the traditional enyne ring-closing reaction using precious transition metal catalysts such as rhodium, gold and platinum, this reaction proceeded



Scheme 37 Metal-free nitro-carbocyclization of 1,6-enynes with TBN and TEMPO.

smoothly under metal-free conditions, affording six-membered (hetero)cyclic compounds containing nitro groups in moderate to good yields.

Furthermore, the group of Hajra developed a regioselective nitration at the C-7 position of quinoline compounds using TBN under metal-free conditions in 2018 (Scheme 38).[46] Preliminary mechanistic studies involved the radical trapping experiments, according to which a radical pathway was involved in this transformation. Firstly, TBN would undergo thermal homolysis to generate an alkoxy radical and nitric oxide, followed by oxidation to form a nitro radical in the presence of molecular oxygen. Then, carboxamide would undergo

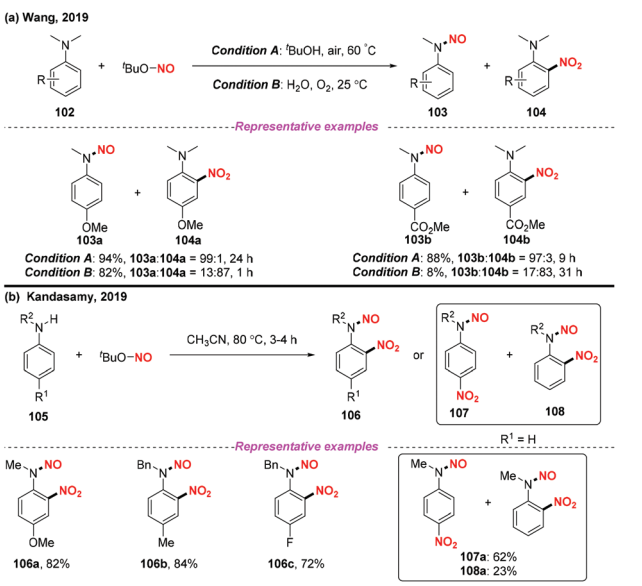


Scheme 38 Metal-free selective nitration at the C-7 position of quinoline compounds using TBN.

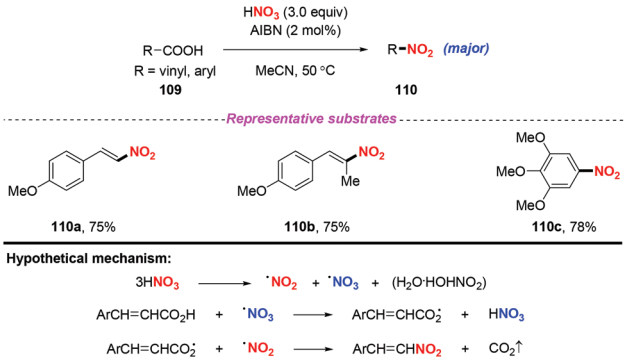
an alkoxy radical mediated intermolecular hydrogen atom transfer process to give nitrogen-centered radical **38A**, which would isomerise to quinoline radical **38B** or **38C**. Finally, the major product **101** was delivered *via* the coupling of the nitro radical with quinoline radical **38B**, accompanied by the formation of a minor amount of the C-5 nitrated product **101′**.

Recently, Wang and co-workers presented a solvent-controlled chemoselective *N*-dealkylation-*N*-nitrosation or nitration of *N*-alkyl anilines utilizing TBN as a nitro radical source (Scheme 39a).[47] Similarly, the Kandasamy group developed a practical protocol for the regioselective nitration of *N*-alkyl anilines using TBN under metal free conditions (Scheme 39b).[48] In both reactions, the nitro radical was generated from the homolysis of *tert*-butyl nitrite for the synthesis of *N*-nitrosoanilines, nitroanilines and *N*-nitroso-nitroanilines. It was interesting that three different products could be generated from *N*-alkyl anilines under different reaction conditions.

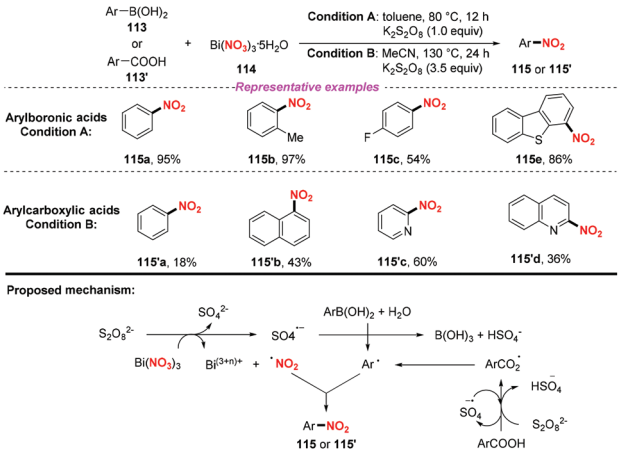
2.7.2. Other nitro radical sources. In 2002, Roy and co-workers found that nitric acid could be employed as the nitro radical source for the nitrodecarboxylation of alkenyl and aryl carboxylic acids, giving rise to nitrostyrenes and nitroarenes (Scheme 40).[49] In this transformation, AIBN played a dual role as both a free radical initiator and a catalyst. A proposed mechanism for this transformation is depicted in Scheme 40. Initially, HNO_3 could undergo thermal homolysis to generate $NO_2^{\bullet}$, $NO_3^{\bullet}$, and $H_2O{\cdot}HONO_2$. Then, the combination of the nitro radical with the acyloxy radical followed by subsequent nitrodecarboxylation would furnish the desired product. Interestingly, in this reaction, the cheap and commercially available nitric acid was employed as the source of the nitro radical. It should be noted that the reaction could only tolerate electron-rich alkenyl and aryl carboxylic acids, resulting in limited substrate scopes.



Scheme 39 Metal-free nitration of *N*-alkyl anilines.



Scheme 40 AIBN-catalyzed nitrodecarboxylation of aromatic α,β-unsaturated carboxylic acids and ring-activated benzoic acids.

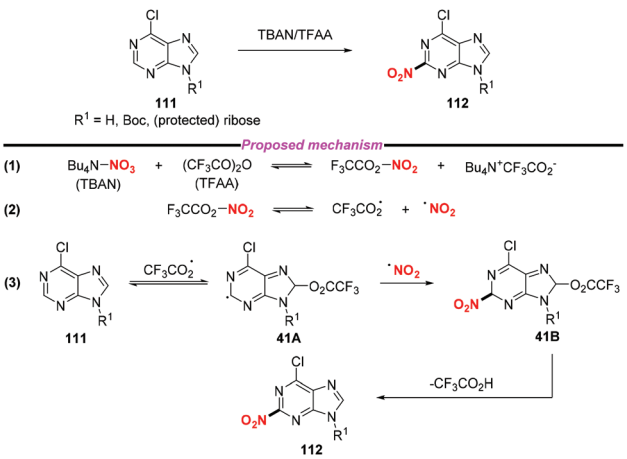


Scheme 42 Metal-free *ipso*-nitration of arylboronic acids and aromatic carboxylic acids.

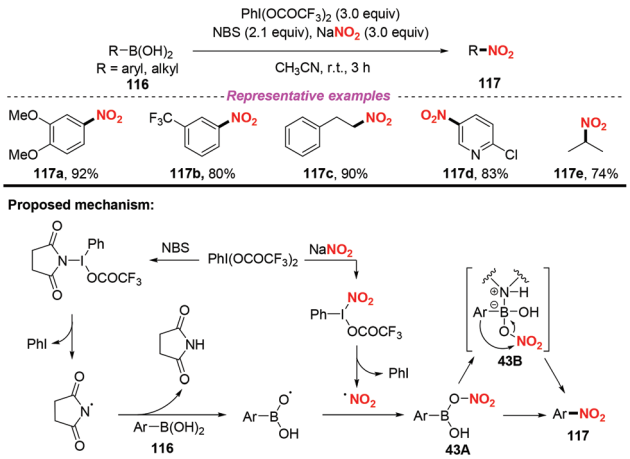
In the same year, the Koomen group developed an efficient and selective nitration of purine at the C-2 position using a mixture of tetrabutylammonium nitrate (TBAN) and trifluoroacetic anhydride (TFAA).[50] In 2005, the same group presented an extensive NMR study to demonstrate that the reaction occurred in a three-step process (Scheme 41).[51] Initially, the homolytic cleavage of $CF_3CO_2NO_2$ generated the trifluoroacetoxyl radical and nitro radical. The subsequent addition of the reactive $CF_3CO_2^{\bullet}$ to purine **111** at the C-8 position would form a highly delocalized radical **41A**. Then the combination of **41A** with the nitro radical would give rise to intermediate **41B** followed by the elimination of CF_3CO_2H, leading to the nitrated product **112**.

In 2015, the Maiti group disclosed a novel and one pot synthetic method of *ipso*-nitration of arylboronic acids by using bismuth nitrate as a nitro radical source.[52a] In the conversion of arylboronic acid, this protocol exhibited a broad substrate scope and good functional group tolerance, affording various nitroarenes in good to excellent yields. In 2019, the same group demonstrated that aromatic carboxylic acids could be converted into nitroarenes by using $Bi(NO_3)_3/K_2S_2O_8$ under acid-free conditions.[52b] However, compared to their previous work, this method suffered from high temperature, narrow substrate scope and poor yield. On the basis of the control experiments, a radical–radical coupling pathway was proposed to be involved in both reactions (Scheme 42).

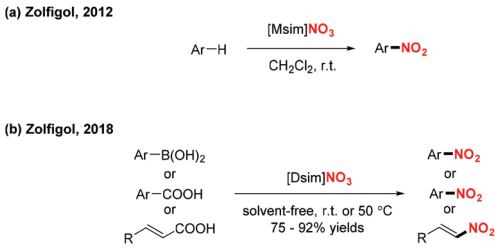
In 2015, Goswami and co-workers developed a novel transition metal free method for the oxidative *ipso*-nitration of organoboronic acids, which was the complement of Maiti's work (Scheme 43).[53] In this transformation, a combination of PIFA-NBS and sodium nitrite was used as the nitro source. Based on the control experimental results, oxygen-centred radicals could be generated from organoboronic acids in the presence of NBS and PIFA. On the other hand, the nitro radical was released through one electron oxidation of $NaNO_2$ by PIFA, which reacted with the oxygen-centred radical to form the stable species **43A**. Finally, nitro transfer to the aryl group *via* 1,3-aryl migration would enable the coordinated species **43B** to afford nitroarenes **117**. This reaction featured good to



Scheme 41 Metal-free selective purine C2 nitration reaction using a mixture of TBAN and TFAA.



Scheme 43 Metal-free oxidative *ipso*-nitration of diversely functionalized organoboronic acids.



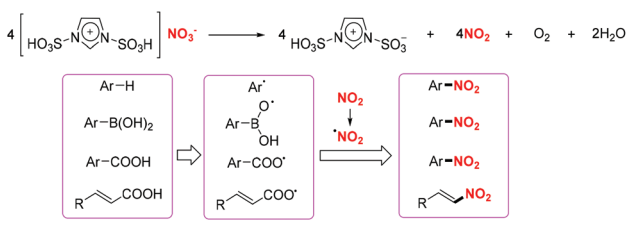
Scheme 44 Ionic liquid as nitrating reagent for the nitration of arylboronic acids, α,β-unsaturated acids and benzoic acid derivatives.

excellent yields and broad substrate scope, which could realize the nitration of arylboronic acids, alkenylboronic acids and alkylboronic acids.

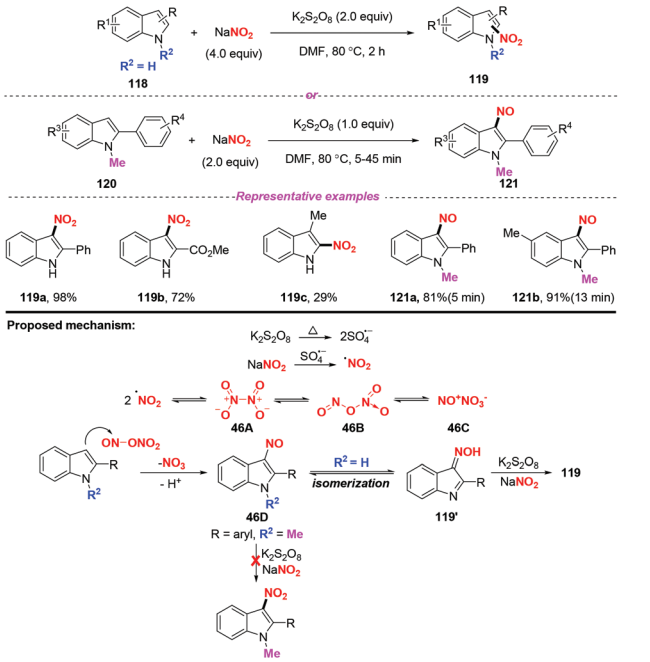
In 2012 and 2018, the group of Zolfigol designed two novel Brønsted imidazolium nitrates ([Msim]-NO_3 and [Dsim]-NO_3), which served as an ionic liquid and a nitrating agent for the efficient nitration of aromatic compounds, arylboronic acids, α,β-unsaturated acids and benzoic acid derivatives, respectively (Scheme 44).[54] These transformations exhibited a broad substrate scope and good functional group tolerance, affording various nitro-containing products in good to excellent yields.

A plausible mechanism for these transformations involving the release of nitrogen dioxide from [Msim]NO_3 was proposed. According to this, the combination of aryl radicals or oxygen-centred radicals with nitro radicals leads to the synthesis of nitro-containing compounds (Scheme 45).

In 2019, Zou and co-workers developed a mild and selective radical nitration/nitrosation of indoles with $NaNO_2$ using $K_2S_2O_8$ as an oxidant (Scheme 46).[55] The reaction worked well under thermal conditions to provide 3-nitro- or 3-nitrosoindoles, showing broad substrate scope compatibility and operational simplicity. A possible mechanism was depicted in Scheme 46. Under thermal conditions, sulphate radical anions were generated from $K_2S_2O_8$ *via* homolytic decomposition, which subsequently reacted with $NaNO_2$ to produce a nitro radical. The nitro radical generated might exist in the dimeric forms **46A**, **46B** and **46C**. The nitrosyl N-atom of **46B** or **46C** would be attacked by the nucleophilic indole to give the nitroso compound **46D**. The 3-nitrosoindole **46D** was remarkably stable when the 2-phenyl substituted indole substrate was protected by a methyl group. Nevertheless, if the indole was not protected, **46D** would be further oxidized to the 3-nitroindoles **119** *via* oxime **119′**.

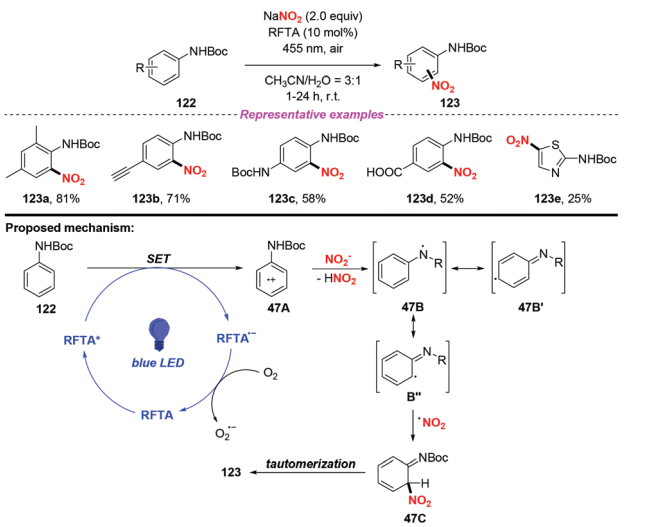


Scheme 45 Proposed mechanism for the synthesis of nitroolefins and nitroarenes.

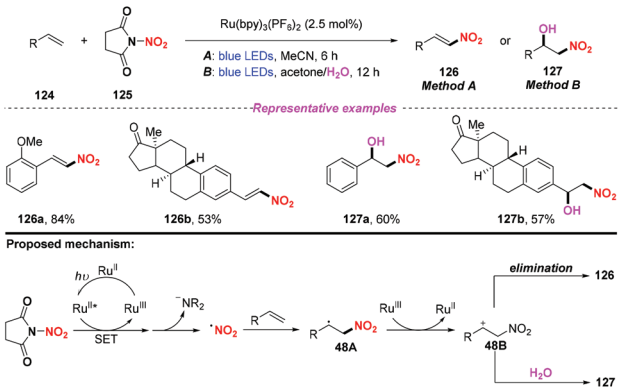


Scheme 46 Radical nitration or nitrosation of indoles by the $NaNO_2$/$K_2S_2O_8$ system.

The photocatalytic nitration of protected anilines by using riboflavin tetraacetate as an organic photoredox catalyst was achieved by König and co-workers (Scheme 47).[56] In this reaction, $NaNO_2$ was utilized as the nitro radical source under ambient conditions, providing various nitroanilines in moderate to high yields without the need for acid or stoichiometric oxidation agents. A possible mechanism of the photonitration was proposed as follows: initially, the radical cation **47A** was generated from aniline **122** *via* a single-electron transfer of the photoexcited catalyst, followed by the loss of a proton to form stabilized radical **47B″**. Then, the nitro radical could react with



Scheme 47 Visible-light-mediated nitration of protected anilines.

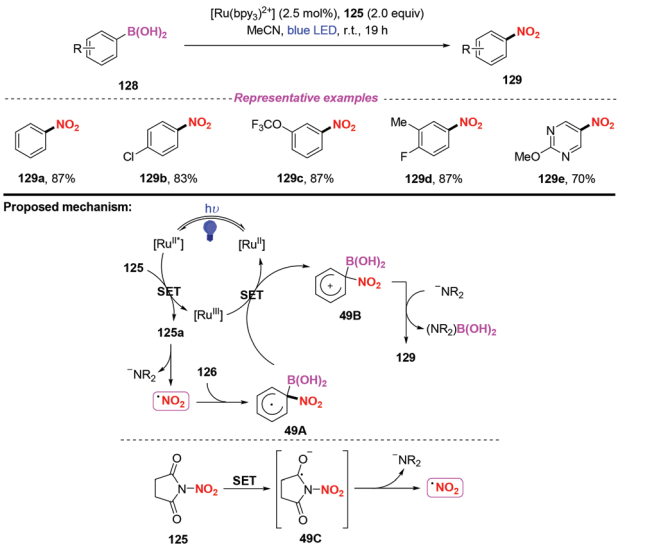


Scheme 48 Visible-light-mediated nitration of olefins.

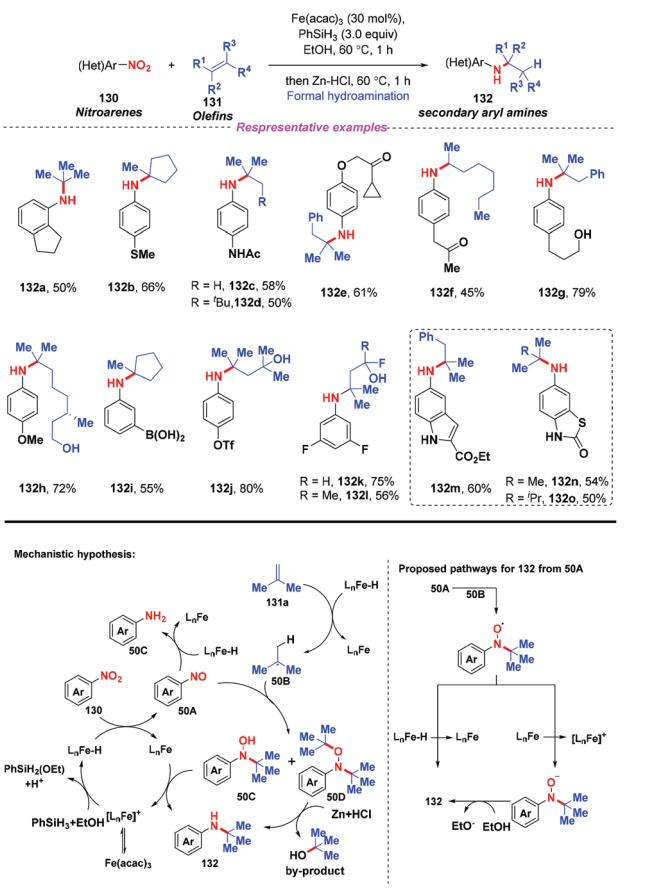
47B″ to give **47C**, which underwent rearomatization to afford the *para*- and *ortho*-regioisomeric substitution product **123**. This protocol exhibited mild reaction conditions, broad substrate scope and good functional group compatibility, affording various nitroaromatic in good yields. However, when the aromatic ring was replaced by the heterocyclic ring, such as thiazole, the reaction efficiency was remarkably decreased.

Recently, the group of Katayev designed and developed a practical and bench-stable succinimide-derived nitrating reagent for C–NO_2 bond formation in the presence of a photocatalyst under visible light (Scheme 48).[57] This protocol not only enabled the direct nitration of the sp^2 C–H bond of alkenes, but also provided rapid access to valuable nitrohydrin building blocks and functionalized isoxazole-motifs in one-step. According to the proposed mechanism, the generation of the nitro radical through photoinduced single-electron transfer and subsequent N–N bond fragmentation of the reagent were the key to promote the reaction.

After this, the same group further developed a photocatalytic and metal-free *ipso*-nitration of aryl- and heteroarylboronic acids **128** by using this newly nitrating reagent (Scheme 49).[58] The reaction featured operational simplicity, mild conditions, and excellent functional group compatibility, delivering nitro(hetero)aromatic compounds **129** in good yields. Similar to their previous report, the *ipso*-nitration process included the formation of the NO_2 radical, radical addition, single-electron transfer oxidation and deboronylation.



Scheme 49 Visible-light-mediated nitration of heteroarylboronic acids.



Scheme 50 Iron-mediated olefin hydroamination of nitroarenes.

3. Nitro group participated in radical reactions

3.1. Fe-Catalyzed or mediated transformations

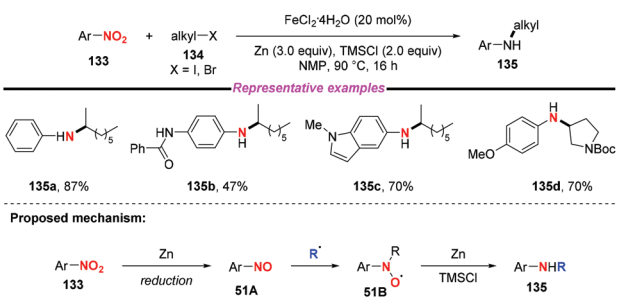
Given the prevalence of amines in pharmaceutical chemistry and some limitations of the current method for amine synthesis, Baran and co-workers[59] developed a practical method for direct C–N bond formation between nitro(hetero)arenes and simple olefins in 2015 (Scheme 50). In this pioneering report, the authors employed aliphatic olefins as coupling-partners, nitroarenes as radical pro-receptors, cheap silane and zinc metals as reducing agents and abundant iron salts as catalysts, furnishing various secondary amines in moderate to good yields. A possible mechanism for the formation of hydro-

amine products was described as follows: in accordance with previous studies,[60] iron hydride species was initially formed *in situ* and it reacted with olefin **131** to give the alkyl radical **50B**. Additionally, the iron hydride species would reduce the nitroarenes to the corresponding nitrosoarenes, which could either undergo further reduction to the aniline side product **50C**, or coupling with either one or two equivalents of alkyl radical **50B** to afford intermediate **50C** or **50D**, respectively. Finally, the reduction of hydroxylamine **50C** by the L_nFe species would release the desired secondary amine **132** and regenerate the iron catalyst. The desired product **132** might also be generated by the reduction of intermediate **50D** in the presence of Zn and HCl.

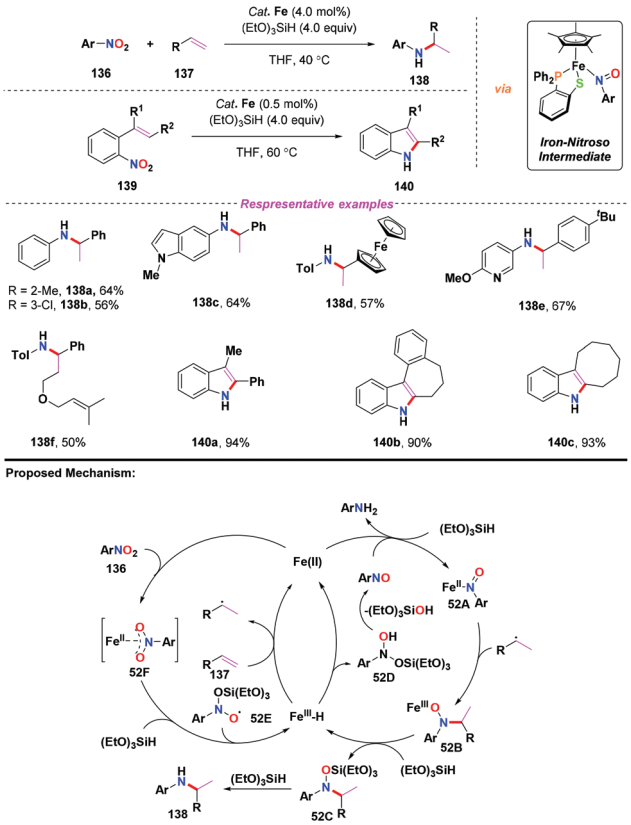
Subsequently, Hu and co-workers developed an iron-catalyzed reductive coupling of nitro(hetero)arenes with alkyl halides to synthesize (hetero)aryl amines using a $FeCl_2{\cdot}4H_2O$/TMSCl system (Scheme 51).[61] This approach tolerated various functional groups. Remarkably, primary, secondary and tertiary alkyl halides could be coupled, showing broad substrate scope compatibility. On the basis of mechanistic studies, it was suggested that the addition of alkyl radicals to nitrosoarene was the major reaction pathway.

Recently, Wang and co-workers further applied the iron(II)/$(EtO)_3SiH$ system for the reductive coupling of nitroarenes with olefins *via* an iron-nitroso intermediate (Scheme 52).[62] By employing a single half-sandwich iron(II) compound as the catalyst, a variety of branched amines and indole derivatives were obtained in moderate to good yields under mild conditions. To gain more insights into the mechanism, several control experiments were carried out to confirm the formation of radical intermediates. Accordingly, similar to Baran's work, a radical mechanism was proposed for the C–N bond coupling (Scheme 52). Compared with Baran's work, this reaction worked well *via* the intramolecular reductive coupling process to enable the synthesis of indoles in excellent yields.

In 2015, Cui and co-workers developed an iron-catalyzed reductive coupling of unactivated alkenes with nitroalkenes (Scheme 53).[63] According to the proposed mechanism, initially, the Fe(III)-catalyst was converted into Fe hydride species **53A** in the presence of silane and alcohol. Then, the addition of **53A** to alkene **142** would produce intermediate **53B**, followed by disintegration to give Fe(II) species **53C** and alkyl radical **53D**. The resulting alkyl radical **53D** was captured



Scheme 51 Iron-catalyzed reductive coupling of nitro(hetero)arenes with alkyl halides.



Scheme 52 Iron-catalyzed olefin hydroamination of nitroarenes.

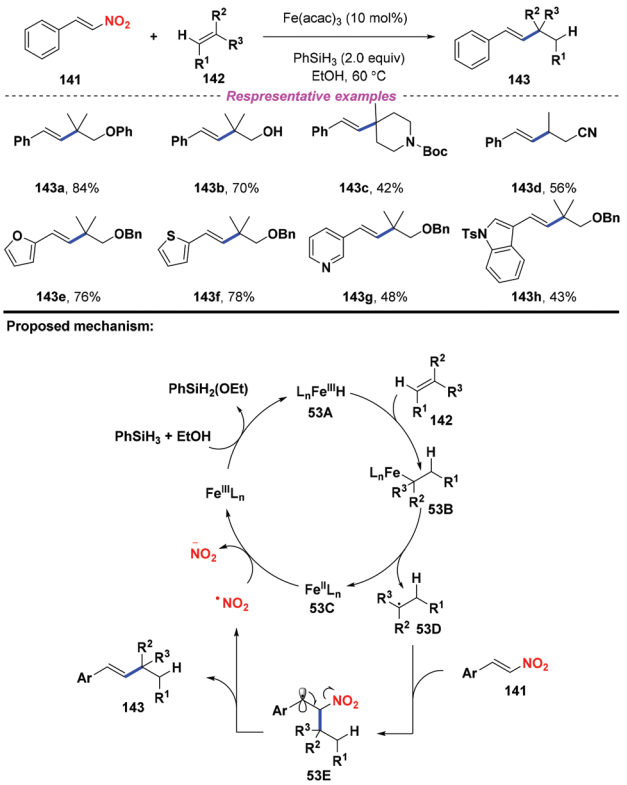
by nitroalkene **141** to generate the β-nitro radical **53E**. Finally, the continuous elimination of **53E** would furnish the alkylated styrene product **143** with the release of a nitro radical, which would undergo reduction by Fe(II) species **53C** to complete the catalytic cycle. This reaction exhibited good functional group compatibility, and many sensitive groups such as hydroxyl, cyano, ether, and heterocycle groups were compatible in this transformation.

3.2. Ni-Catalyzed transformations

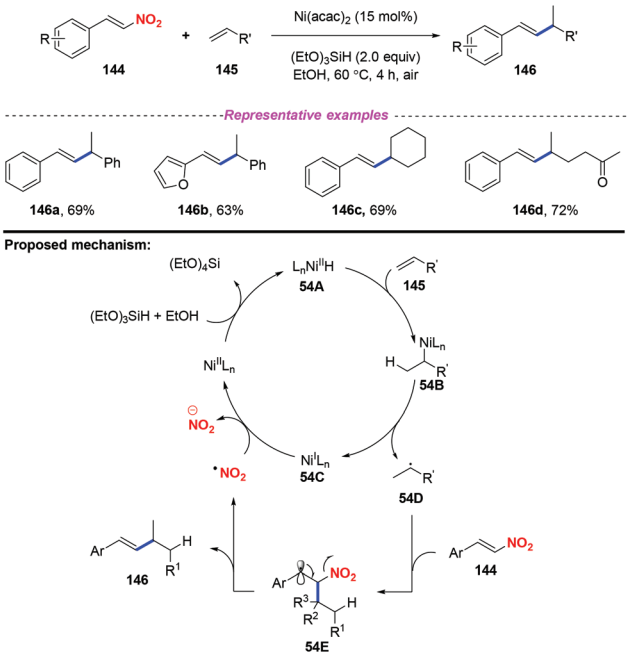
Given the importance of alkylated styrenes in natural products and pharmaceuticals, the group of Wang developed a nickel-catalyzed denitrated coupling reaction of nitroalkenes with aliphatic and aromatic alkenes in 2016 (Scheme 54).[64] On the basis of mechanistic investigations and previous reports, a plausible mechanism for this reaction was proposed, as depicted in Scheme 54. Initially, Ni hydride **54A** was formed from Ni(II) and $(EtO)_3SiH$, which was regioselectively added to alkene **145** and resulted in intermediate **54B**. The dissociation of **54B** delivered Ni(I) species **54C** and alkyl radical **54D**, which were trapped by nitroalkene **144** to form the radical **54E**. Subsequently, the elimination of **54E** would give the alkylated styrene product **146** along with the release of a nitro radical.

3.3. Ag- or Mn-Catalyzed transformations

Vinyl sulfones are valuable building blocks in synthetic organic chemistry, and have been widely used in Michael

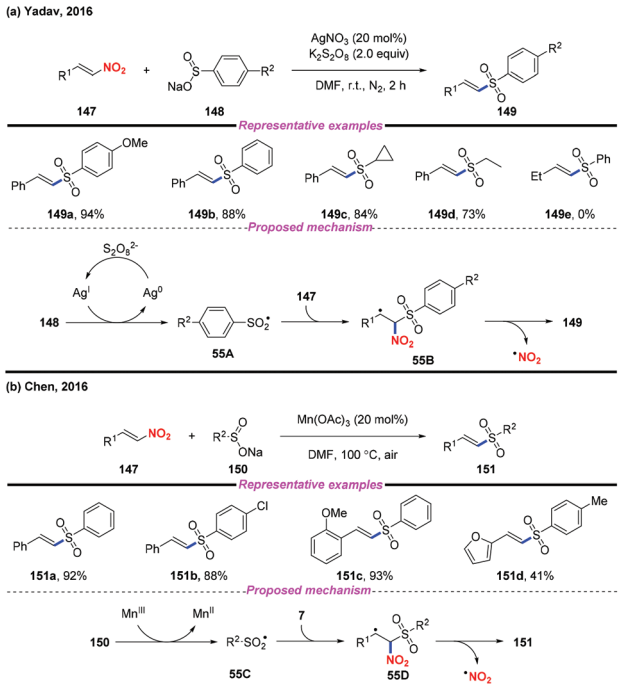


Scheme 53 Fe-Catalyzed reductive coupling of unactivated alkenes with nitroalkenes.



Scheme 54 Nickel-catalyzed denitrated coupling reaction of nitroalkenes with aliphatic and aromatic alkenes.

addition and cycloaddition reactions. In 2016, Yadav and co-workers reported a silver-catalyzed approach for the highly stereoselective synthesis of (*E*)-vinyl sulfones by denitrative



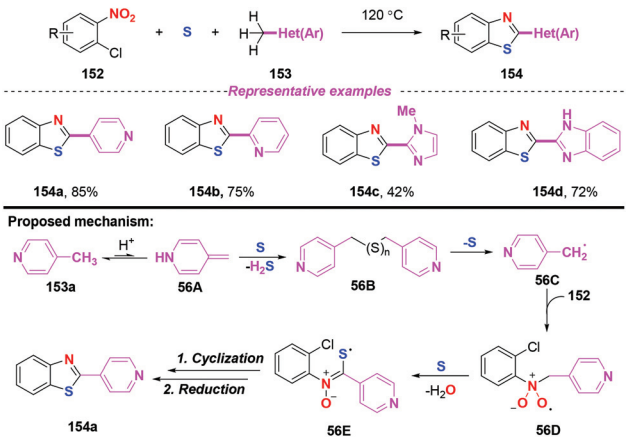
Scheme 55 Silver-catalyzed coupling reaction of nitroolefins with sodium sulifinates.

coupling of nitroolefins and sodium sulfinates in the presence of $K_2S_2O_8$ (Scheme 55a).[65] Additionally, Chen and co-workers described a Mn(III)-mediated regioselective synthesis of (*E*)-vinyl sulfones from nitroolefins and sodium sulfinates at the same time (Scheme 55b).[66] According to the mechanism proposed by both groups, a sulfonyl radical was initially generated from sodium sulfonate, followed by radical addition and elimination sequence to give the desired product.

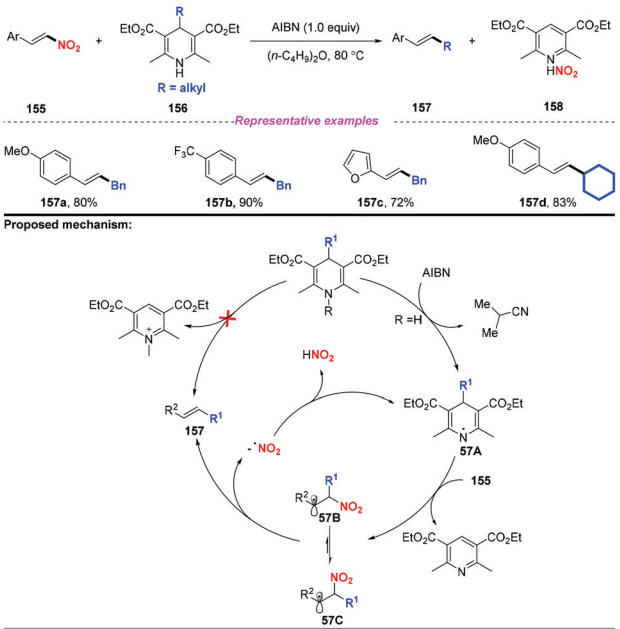
3.4. Under transition metal free conditions

In 2013, a straightforward and atom economical approach to 2-hetarylbenzothiazoles starting from 2-halonitroarenes, methylhetarenes, and elemental sulfur was achieved by Nguyen and co-workers (Scheme 56).[67] By the combination of 4-picoline and sulfur, benzyl radicals were generated under mild conditions without the need for additional radical initiators. As disclosed by their previous work, the mechanism for the outcome involved single electron transfer, radical addition and cyclization. In particular, sulfur-centered radical **56E** was generated from nitro radical species **56D** and elemental sulfur *via* a single electron transfer process.

Subsequently, Tang and co-workers disclosed an efficient alkyl transfer reaction that enabled the formation of C–C bonds through C–C bond cleavage (Scheme 57).[68] The scope of this reaction was quite broad, and a range of alkyl substituted Hantzsch esters were applied as alkylation reagents to afford nitroolefins in good yields. The proposed mechanism for this transformation was considered to proceed through a free radical-chain pathway. Initially, the H radical is extracted from dihydropyridine **156** to generate the DHP radical **57A**, followed



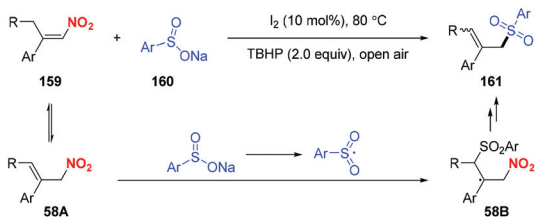
Scheme 56 Synthesis of 2-hetarylbenzothiazoles from 2-halonitroarenes, methylhetarenes, and elemental sulfur.



Scheme 57 AIBN-mediated coupling of nitroolefins with Hantzsch esters.

by fragmentation to provide the alkyl radical. Subsequently, the alkyl radical was added to the nitroolefin, resulting in the formation of radical **57B** or **57C** interconverted by internal rotation. Finally, the resulting radical would undergo β-elimination to give the thermodynamically controlled product with the release of a nitro radical.

In 2018, Chen and co-workers reported a metal-free sulfonylation of nitroalkenes to furnish β,β-disubstituted nitroalkenes (Scheme 58).[69] Accordingly, the putative mechanism revealed that the Lewis base-promoted equilibrium between nitroalkenes and allylic nitro compounds was the key to complete the process.

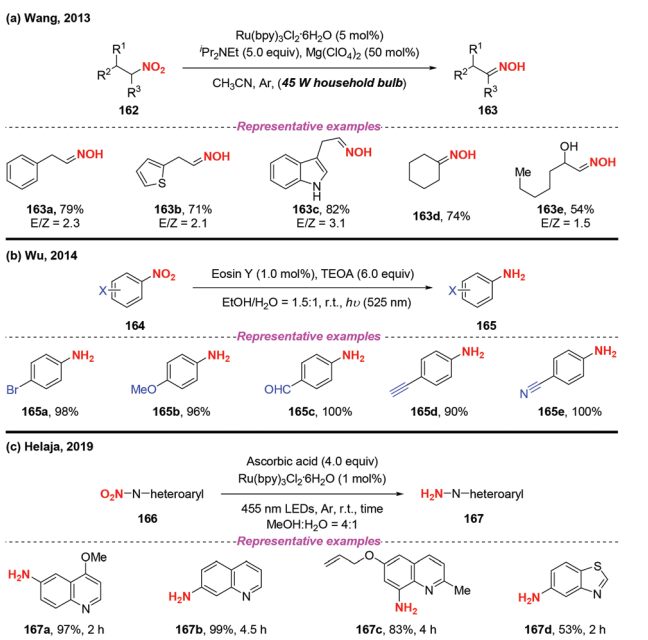


Scheme 58 I_2-Catalyzed sulfonylation of nitroalkenes for the synthesis of allyl sulfones.

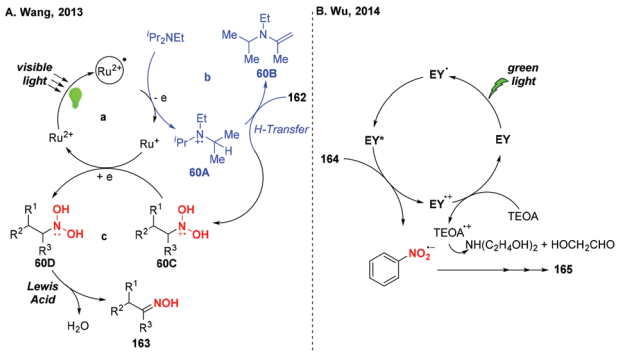
3.5. Under photocatalysis

Over the past few years, visible-light-promoted organic transformations have made impressive progress in synthetic chemistry with the advantages of operational simplicity and mild conditions. In this case, the visible-light photocatalyzed reduction of nitro compounds has been independently developed by the groups of Wang[70] (Scheme 59a), Wu[71] (Scheme 59b) and Helaja[72] (Scheme 59c). For instance, Wang and co-workers found that nitroalkanes could be smoothly reduced to the corresponding oximes under the synergistic effects of visible light irradiation. Moreover, Wu and co-workers employed visible light in nitroarene photoreduction using eosin Y as a photosensitizer and triethanolamine (TEOA) as a reductant. To address the issue that the eosin Y/TEOA photoreduction protocol was incompatible with nitroquinolines, Helaja and co-workers recently utilized a chemoselective strategy for reduction of nitro N-heteroaryls by employing ascorbic acid ($AscH_2$) as hydrogen source.

According to the mechanism proposed by Wang and co-workers, the amine radical cation **60A** was initially formed *via* a single-electron transfer oxidation by the excited Ru(II)* and



Scheme 59 Photoinduced reduction of nitro-containing compounds.

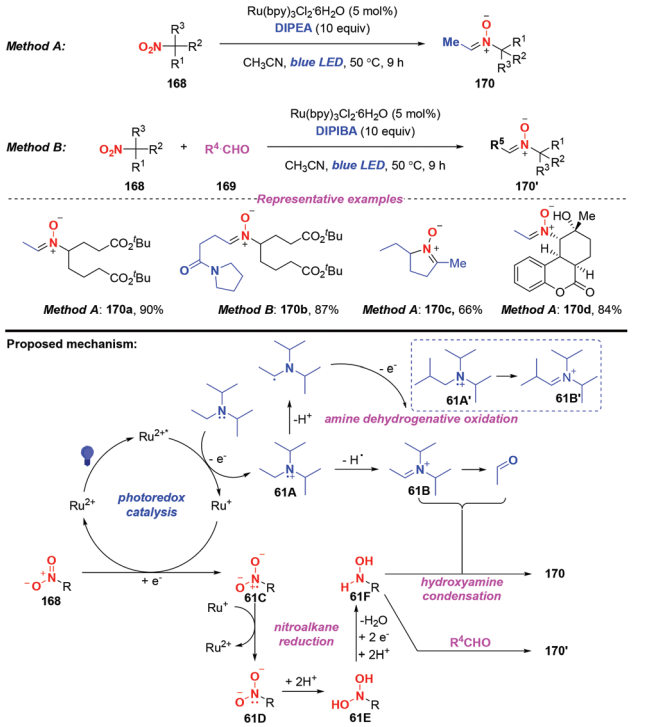


Scheme 60 Possible mechanism for the photoinduced reduction of nitroalkanes and nitroarenes.

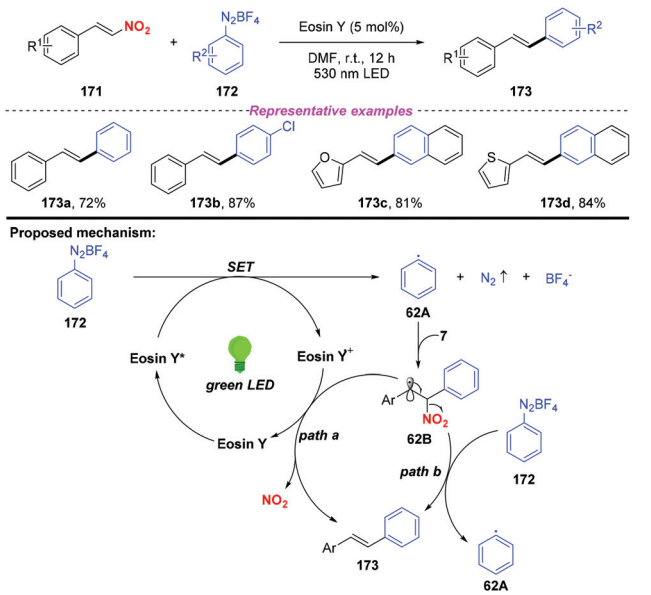
then underwent a hydrogen atom transfer process with substrate **162** to give a reduced cationic intermediate **60C** (Scheme 60). Subsequently, **60C** would proceed through a single-electron reduction by Ru(I) to produce intermediate **60D**, which would undergo Lewis acid promoted dehydration to give oxime **163**. In Wu's protocol, they suggested that the nitro group has much greater ability of accepting electrons than the other reducible groups, resulting in the selective reduction of nitrobenzenes under visible light.

Nitrones are considered as versatile intermediates for the synthesis of naturally occurring compounds and bioactive molecules. In 2015, the group of Hong presented a concise visible-light-induced photocatalytic transformation of nitroalkanes to nitrones in good yields (Scheme 61).[73] On the basis of the experimental results, a possible mechanism was proposed for this transformation. Initially, the excited $Ru(bpy)_3^{2+}$* was quenched by DIPEA *via* a single-electron transfer oxidation to generate the radical cation of DIPEA. The radical cation **61A** would be subsequently converted into iminium species **61B** or acetaldehyde either through the release of a hydrogen radical or a proton. Alternatively, nitroalkane **168** would undergo a single-electron transfer reduction by Ru^+ to afford **61C** and **61D**, respectively. The subsequent protonation of **11D** would afford the dihydroxyamine **61E** and the hydroxylamine species **61F**. Finally, the alkylnitrone product **170** was produced through the condensation of the hydroxylamine species **61F** with iminium species **61B** or acetaldehyde. On the other hand, the hydroxylamine **61F** would react with the external alkylaldehyde when DIPEA was replaced by DIPIBA, giving rise to the cross alkylated nitrone **170′** in good yield.

In 2016, Wang and co-workers reported a visible-light-induced cross-coupling of aryl diazonium salts with nitroalkenes for the synthesis of stilbene derivatives (Scheme 62).[74] This reaction features high stereoselectivity, providing various (*E*)-stilbene compounds in good yields. To gain insight into the reaction mechanism, several mechanistic investigations have been conducted. According to the proposed mechanism, the aryl radical **62A** was produced by a single electron transfer between the excited state of Eosin Y and aryl diazonium salt **172**, which was trapped by nitroalkene **171** to give the β-nitro



Scheme 61 Visible-light-promoted reduction of nitroalkanes to access nitrones.



Scheme 62 Photoinduced synthesis of stilbene derivatives *via* cross-coupling of aryl diazonium salts with nitroalkenes.

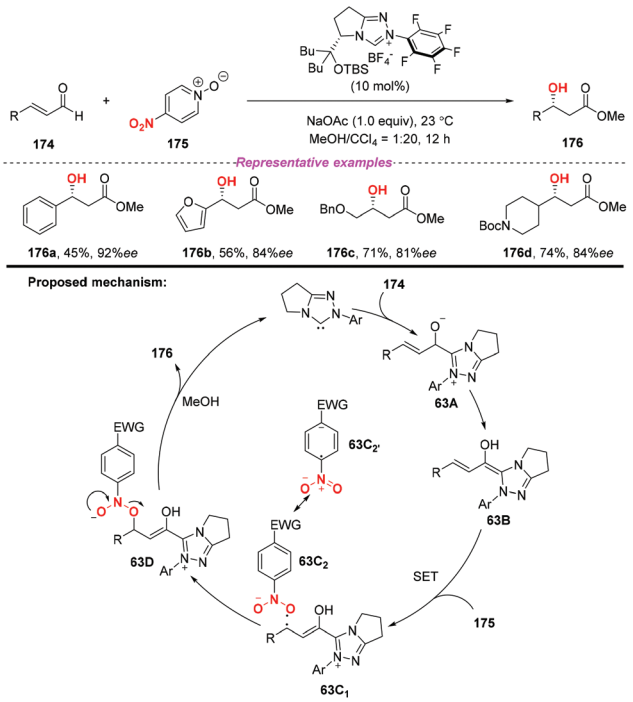
radical **62B**. Subsequently, the radical intermediate **62B** could be converted into coupling product **173** either through a single-electron oxidation by the Eosin Y radical cation or a radical chain-transfer process by the aryl diazonium salt **172** along with the elimination of the nitro group.

3.6. NHC-catalyzed transformations

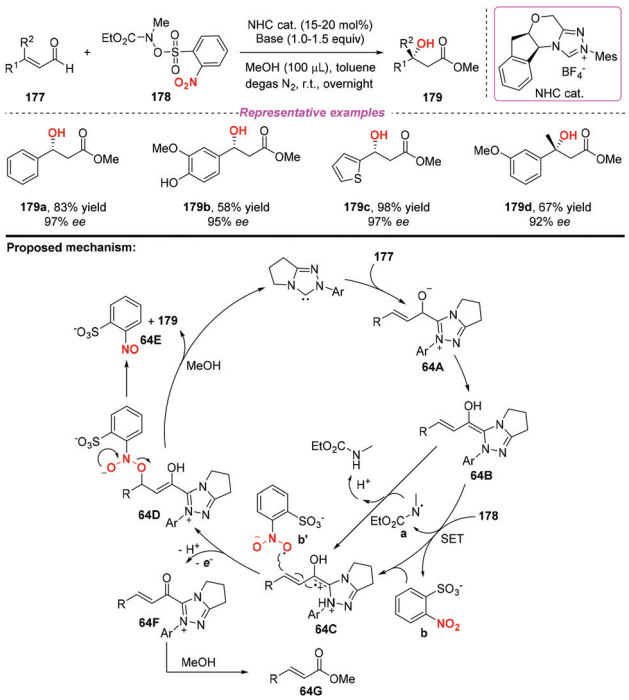
During the past two decades, N-heterocyclic carbene (NHC)-catalyzed reactions have achieved considerable progress in organic synthesis. In particular, it has been proved that NHCs could be applied to the development of single electron transfer (SET) reactions. In 2014, Rovis and co-workers developed the first example of the NHC-catalyzed oxidation reaction using electron-deficient nitrobenzenes as an oxidant (Scheme 63).[75] A proposed mechanism for the reaction has been shown in Scheme 63. Initially, the combination of substrate **174** with a catalyst would give intermediate **63A**, which subsequently underwent a single-electron oxidation by the nitrobenzene to afford Breslow-centered radical cation $\mathbf{63C_1}$ and nitrobenzene-derived radical anion $\mathbf{63C_2}$. After this, the cross-coupling of a homoenolate-centered radical and an O-centered radical led to species **63D**. Finally, NHC-bound alkoxide **63D** would react with MeOH to deliver the product **176** and release the catalyst.

At almost the same time, the group of Chi also reported a similar N-heterocyclic carbene-catalyzed β-hydroxylation of enals by using nitrobenzenesulfonic carbamate **178** as the oxidant (Scheme 64).[76] This oxidative single-electron-transfer reaction provided highly enantioselective access to β-hydroxyl esters in good to excellent yields. Similar to Rovis's work, the authors presented a plausible mechanism including the formation of Breslow intermediate **64A**, radical coupling, single electron oxidation and deprotonation processes.

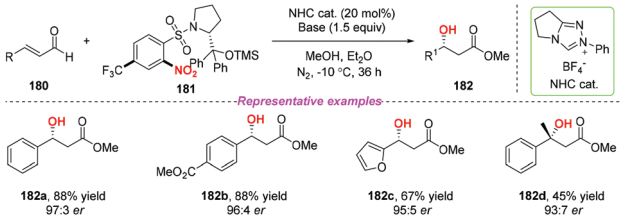
In addition, the same group developed a new class of chiral nitroarenes as enantioselective single-electron-transfer oxidants for carbene-catalyzed radical reactions in 2019 (Scheme 65).[77] Notably, the high enantioselectivity control in carbene-catalyzed β-hydroxylation of enals was realized by chiral transfer from the oxidants to the substrates. By using this method, a variety of chiral β-hydroxyl esters were obtained in moderate to good yields with high enantioselectivities.



Scheme 63 NHC-catalyzed β-hydroxylation of enals using nitroarenes as an oxidant.



Scheme 64 Chiral NHC-catalyzed β-hydroxylation of enals using nitroarenes as an oxidant.



Scheme 65 NHC-catalyzed β-hydroxylation of enals using chiral nitroarenes as an oxidant.

4. Conclusion and outlook

In conclusion, this review summarizes the recent advances in radical reactions involving the nitro group. Overall, approaches for the synthesis of amines, oximes, alkenes, nitrones and alcohols through the radical-initiated pathway have been developed. Besides, a variety of readily available nitrating reagents including $AgNO_2$, $NaNO_2$, $Fe(NO_3)_3{\cdot}9H_2O$, ^tBuONO, *etc.* have been well explored as the source of the nitro radical. Usually, the nitro radical can be readily generated in the presence of a transition metal catalyst or under photocatalysis for further

transformations. The transformations usually feature a broad substrate scope and good functional group tolerance under mild conditions.

Despite the remarkable achievements in the radical chemistry of the nitro group, there are still many issues that need to be addressed. It is anticipated that the asymmetric conversion of functionalized nitro compounds into optically pure molecules will be continually developed, since only a few examples have been reported so far. Furthermore, the discovery of new reactivities with the nitro radical through sustainable processes based on electrochemistry or flow chemistry can be expected in the near future.

Conflicts of interest

There are no conflicts to declare.

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