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Direct vicinal halo-nitration of unsaturated compounds: an overview

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In this review, we spotlight the methodologies for the direct synthesis of β-halo nitroalkanes and nitroalkenes from the corresponding unsaturated hydrocarbons through vicinal halo-nitration strategies. The review is organized into two main sections: halo-nitration of alkenes and halo-nitration of alkynes. Both seminal works and recent advancements are discussed, with a particular emphasis on the mechanistic aspects of the reactions.

1 Introduction

Nitro compounds represent a crucial category of organic compounds, identified by the presence of at least one nitro group (NO_2) attached to a carbon atom. These compounds have extensive applications across diverse fields such as organic chemistry,[1] medicinal chemistry,[2] agricultural chemistry,[3] materials chemistry[4] and beyond. Moreover, they are common structural motifs found in a variety of FDA-approved drugs[5] and biologically active natural products.[6] Although nitroarenes are more commonly found in natural products and pharmaceutical agents compared to nitroalkanes and nitroalkenes, a surprisingly large number of biologically active, naturally occurring nitroalkanes and nitroalkenes have also been identified, exhibiting a wide range of properties including antimicrobial, fungicidal, and anti-inflammatory effects (Scheme 1).[7] Moreover, both nitroalkanes and nitroalkenes serve as essential building blocks, acting as either nucleophiles or electrophiles, for the formation of new carbon–carbon and carbon–heteroatom bonds.[8–12] In addition, the reduction of aliphatic and vinylic nitro compounds is a well-established and crucial method for synthesizing alkyl and vinyl amines, respectively, a process extensively applied in various industries.[13]

β-Halo nitroalkanes and nitroalkenes represent one of the most attractive and versatile classes of nitro compounds, characterized by the presence of a halogen atom adjacent to the nitro group. This unique structural feature imparts diverse reactivity to these compounds, enabling them to participate in a wide range of reaction pathways and facilitating the construction of various functionalized molecules.[14–17] Despite the significant importance of the titled compounds as building blocks in organic synthesis, general and practical methods for their preparation remain scarce. To the best of our knowledge, direct halo-nitration of unsaturated hydrocarbons is currently the only effective and straightforward synthetic strategy available (Fig. 1).

Although several noteworthy review articles covering various nitration reactions have been recently published,[18–20] despite recent advances in the synthesis of β-halo nitroalkanes and nitroalkenes through the direct difunctionalization of corresponding alkenes and alkynes, a comprehensive review on this specific topic is still lacking in the literature. In connection with our recent reviews and researches,[21] herein, we aim to summarize the available reports on the direct 1,2-halo-nitration of inexpensive and abundant feedstock alkenes and alkynes, providing an updated overview of the current state of research in this important field.

2 Halo-nitration of alkenes

This section focuses on the synthesis of β-halo nitroalkanes from the corresponding alkenes by means of the concomitant

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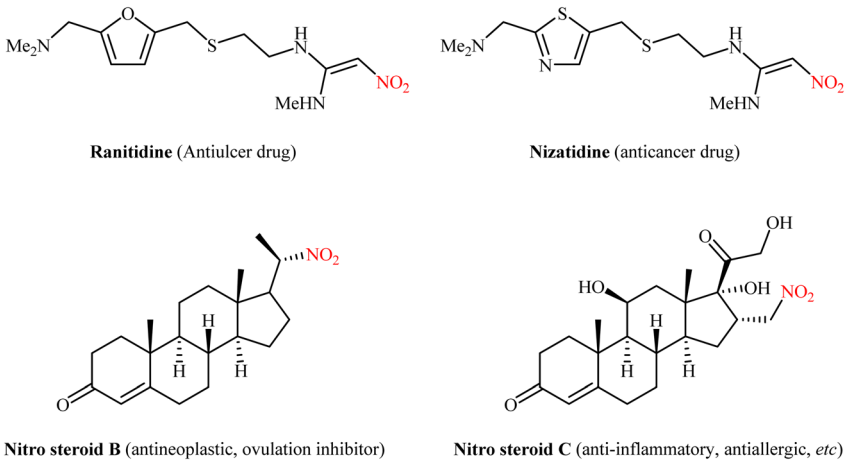


Scheme 1 Selected examples of bioactive compounds featuring a nitro-alkane or nitro-alkene unite.

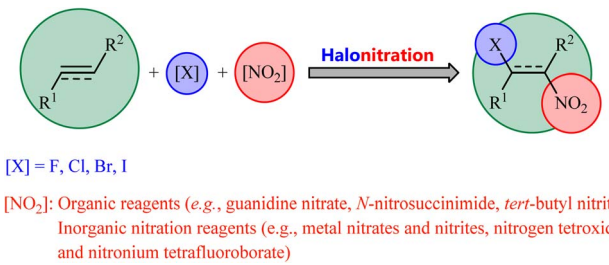


Fig. 1 Direct vicinal halo-nitration of unsaturated compounds.

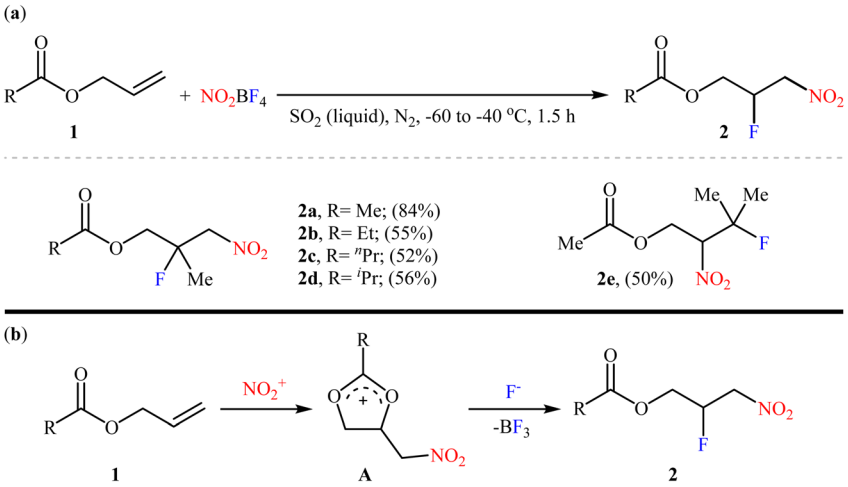
formation of C–X and C–NO_2 bonds. The section is organized into four sub-sections based on the type of C–X bond formed: (i) fluoro-nitration; (ii) chloro-nitration; (iii) bromo-nitration; and (iv) iodo-nitration.

2.1 Fluoro-nitration

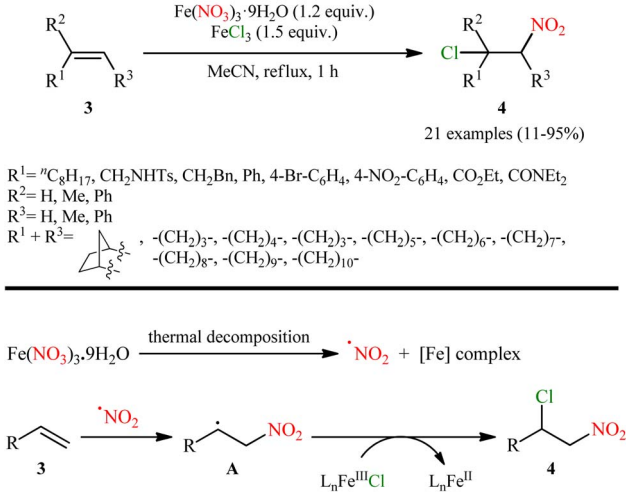
The direct vicinal fluoro-nitration of alkenes has been scarcely investigated. In fact, to the best of our knowledge, the few available reports in the literature on this chemistry date back to the early 1980s and originate exclusively from the research group of Talybov.[22–24] In their studies, nitronium tetrafluoroborate (NO_2BF_4) was demonstrated to act as a bifunctional fluoro-nitrating reagent, enabling the direct 1,2-fluoro-nitration of various activated and unactivated alkenes under catalyst- and additive-free conditions. For instance, they showed that the treatment of allylic esters **1** with 1.1 equiv. of NO_2BF_4 in liquid SO_2 at −40 °C afforded the corresponding β-fluoro nitroalkanes **2** in moderate to high yields, ranging from 50% to 84% (Scheme 2a).[23] Interestingly, the reaction exhibited a high degree of regioselectivity, in which the nitro group selectively installed on the sterically less hindered carbon atom of the double bond. Despite the high efficiency, excellent atom economy, and commercial availability of the fluoro-nitrating reagent used, this method has received little attention, and no optimized, alternative, or complementary protocols have been developed to date. Mechanistically, the reaction proceeds *via* regioselective electrophilic attack of the nitronium ion (NO_2^+) on the double bond of allylic esters **1**, leading to the formation of 1,3-dioxolan-2-ylium intermediate **A**. This is followed by nucleophilic attack by fluoride (F^-) at the carbon atom adjacent to the more substituted position of intermediate **A**, resulting in the formation of the observed β-fluoro nitro products 2 (Scheme 2b).

2.2 Chloro-nitration

Traditional methods for the direct chloro-nitration of alkenes have primarily relied on the use of nitryl chloride ($ClNO_2$)[25–28] and nitrosyl chloride (NOCl)[29–32] as bifunctional chloro-nitrating reagents, or on the combination of nitrogen dioxide (NO_2) and chlorine (Cl_2) gases as the NO_2 and Cl sources, respectively.[33] However, the significant toxicity associated with $ClNO_2$, NOCl, and Cl_2 has severely restricted the practical applicability of these methods. To circumvent the use of toxic and/or difficult to handle reagents, several alternative chloro-nitration strategies have recently been developed that operate under milder, safer, and more practical conditions. In this context, in 2010, Taniguchi and co-workers developed an iron-mediated method for the direct chloro-nitration of olefinic double bonds using readily available and commercially accessible $Fe(NO_3)_3 \cdot 9H_2O$ as a safe nitrate source and $FeCl_3$ as solid, non-toxic chlorine source.[34] The reactions were performed in refluxing acetonitrile, tolerated a broad range of alkene substrates **3** (including aromatic and aliphatic alkenes as well as α,β-unsaturated carbonyl compounds), and furnished the desired β-chloro nitroalkanes **4** in synthetically useful yields (Scheme 3). Some important information of this synthetic procedure is: (i) the reaction demonstrated an excellent level of regioselectivity, in which the nitro group was introduced at the less-hindered side of the alkene double bond; (ii) the protocol was compatible with a wide range of alkenes, including terminal, 1,1-disubstituted, 1,2-disubstituted, and 1,1,2-trisubstituted alkenes, although 1,2-diaryl alkenes were poorly reactive under the reported conditions; (iii) a variety of functional groups such as bromo, nitro, sulfonamide, amide, and ester groups were well tolerated



Scheme 2 (a) Talybov's synthesis of β-fluoro nitroalkanes **2**; (b) plausible mechanism for the formation of β-fluoro nitroalkanes **2**.

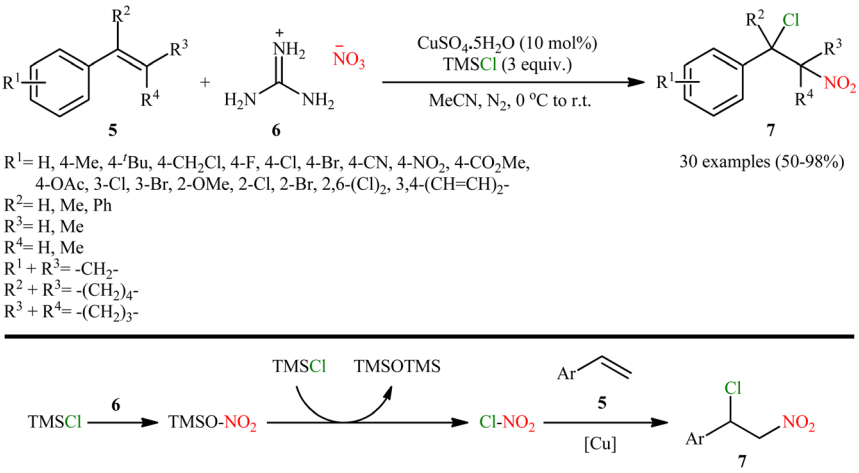


Scheme 3 Taniguchi's synthesis of β-chloro nitroalkanes **4**.

under the reaction conditions, whereas ether functionalities were not, likely due to Lewis acidic conditions present during the transformation; (iv) in some cases, the corresponding nitroalkenes were obtained as side products, likely formed through a sequential chloro-nitration/elimination process; and (v) in reactions involving molecules bearing both electron-rich and electron-deficient alkene moieties, the nitro group was selectively added to the electron-rich alkene. According to the mechanism proposed by the authors, the reaction begins with the addition of a NO_2 radical (generated *via* thermal decomposition of $Fe(NO_3)_3 \cdot 9H_2O$) to alkene **3**, forming a carbon-centered radical intermediate **A**. This radical is subsequently trapped by a chlorine atom from the iron chloride complex, furnishing the final product **4** (Scheme 3). Shortly afterwards, the authors applied their methodology as the key strategic step in synthesis of various heterocycles having a nitromethyl group from γ- and δ-hydroxy/amino alkene derivatives through a direct chloronitration/elimination/intramolecular Michael addition sequential process.[35]

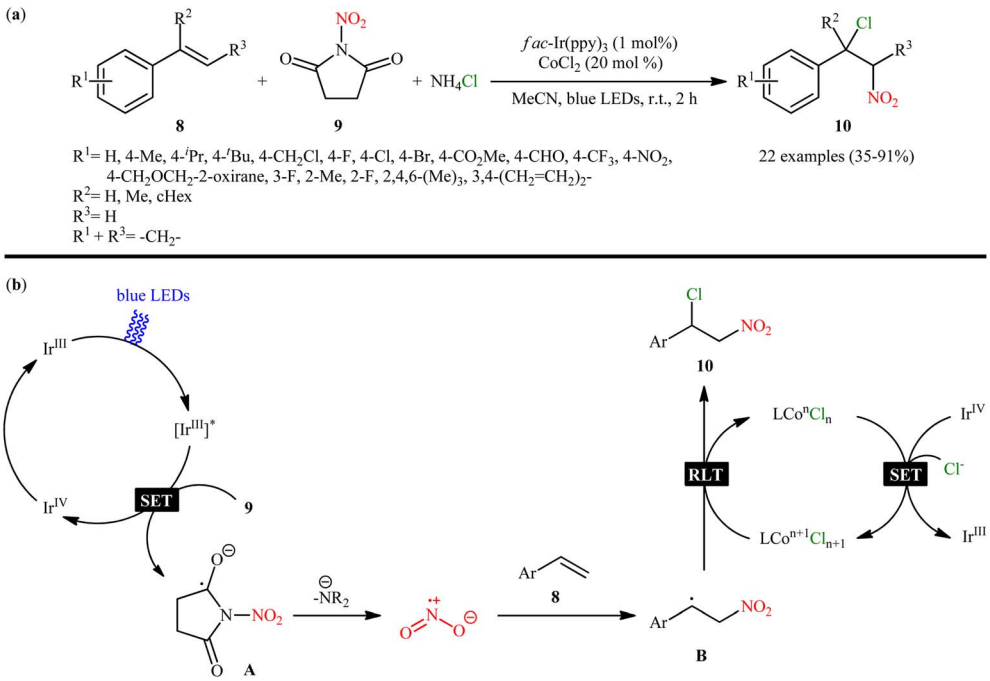
In 2020, a copper-catalyzed version of this di-functionalization reaction was reported by Deng and co-workers, who demonstrated that the treatment of styrene derivatives **5** with guanidine nitrate **6** and trimethylchlorosilane (TMSCl) in the presence of a catalytic amount of $CuSO_4$ in MeCN, afforded the corresponding (1-chloro-2-nitroethyl)arene derivatives **7** in moderate to almost quantitative yields (Scheme 4a).[36] Interestingly, the steric and electronic properties of the substituents on the aromatic units had no significant effect on the reaction efficiency. As a result, a wide range of important functional groups (*e.g.*, F, Cl, Br, CN, NO_2, CO_2Me, OCOMe, OMe) at different positions of phenyl ring of styrene derivatives were well tolerated, indicating the broad applicability of this method. A series of aliphatic alkenes and α,β-unsaturated carbonyl compounds were also subjected to this Cu-catalyzed chloro-nitration protocol, affording the expected di-functionalized products, albeit with somewhat diminished yields compared to those obtained with styrene substrates. More importantly, three scale-up experiments were performed for the chloro-nitration of simple styrene, 4-methylstyrene, and 4-(chloromethyl)styrene on 100 mmol scales to demonstrate the practicability of the method. The expected chloro-nitrated products were obtained in 92% (17.21 g), 74% (14.70 g), and 93% (21.86 g) isolated yields, respectively, demonstrating the potential of this protocol for industrial applications. While the detailed mechanistic picture remains unclear, the authors suggested that the transformation starts with the reaction between guanidine nitrate **6** and TMSCl to form $TMSONO_2$, which after reaction with another molecule of TMSCl affords highly reactive nitryl chloride. Finally, in the presence of a copper species, the *in situ* generated $ClNO_2$ reacts with styrene **5** to furnish the observed products **7** (Scheme 4b).

Following these works, in 2023, Katayev's research group devised a dual catalytic system comprised of a cobalt and an iridium-based photoredox catalyst, which enabled the direct nitrative chlorination of a wide range of aromatic alkenes **8** employing *N*-nitrosuccinimide **9** as the organic nitrating reagent and ammonium chloride as cost-effective chlorine



Scheme 4 Cu-catalyzed chloro-nitration of styrenes **5**, developed by Deng.

source to form the corresponding β-chlorinated nitro compounds **10** in modest to excellent yields within 2 h (Scheme 5a).[37] Aliphatic alkenes such as allylbenzene, (2-methylallyl) benzene, and but-3-en-1-ylbenzene also provided the corresponding difunctionalized products under identical conditions, albeit only moderate yields. However, α,β-unsaturated carbonyl compounds proved largely incompatible with this scenario, as they afforded poor yields or, in some cases, no desired product at all, likely due to decomposition and/or spontaneous elimination of HCl. Notably, the authors further demonstrated the synthetic utility of their methodology through the late-stage functionalization of alkenes architecturally complex bioactive molecules such as indometacin, esteron, and (S)-ibuprofen. Interestingly, a similar principle was also successfully applied to the nitrative bromination of a library of aryl substituted olefins by simply replacing NH_4Cl with NH_4Br and $CoBr_2$ with $CoBr_2$. According to the authors, this chloro-nitration reaction proceeds *via* the following mechanistic pathways, as illustrated in Scheme 5b: at first, the ground state photocatalyst Ir^{III} undergoes photoexcitation under visible-light irradiation to generate the excited state $[Ir^{III}]^*$. This excited species then reduces *N*-nitrosuccinimide **9** *via* a single-electron transfer (SET) process to afford the radical ion intermediate **A**, which subsequently undergoes mesolytic N–N bond cleavage to generate a nitryl radical. Next, the resulting nitryl radical selectively adds to the β-position of styrene **8** to form the stabilized benzyl radical intermediate **B**. Afterwards, radical intermediate **B** undergoes a cobalt-assisted radical ligand transfer (RLT) process, leading to the formation of the observed product **10** and concurrent regeneration of the low-valent cobalt



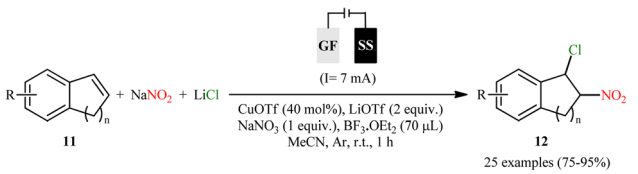
Scheme 5 (a) Katayev's synthesis of β-chloro nitroalkanes **10**; (b) proposed mechanism for the formation of β-chlorinated nitro compounds **10**.

catalyst. Instantaneously, the low-valence cobalt intermediate undergoes thermodynamically favorable one-electron oxidation by the oxidized form of the photocatalyst Ir^{IV} in the presence of an external Cl^- to regenerate the ground-state Ir^{III} and the high-valence cobalt salt, thus completing both the photoredox and cobalt catalytic cycles.

Very recently, in an attractive contribution in this field, Liu and Li along with their co-workers disclosed an interesting copper-catalyzed electrochemical 1,2-chloro-nitration of styrene derivatives **11** employing inexpensive $NaNO_2$ and LiCl as sources of NO_2^- and Cl^- ions, respectively.[38] The reactions were conducted in an undivided cell assembled with a graphite felt (GF) anode and a stainless steel (SS) cathode using CuOTf as the catalyst, LiOTf as the supporting electrolyte, and BF_3 OEt_2 as the Lewis acid under constant-current of 7 mA at room temperature and provided the desired chloro-nitrated products **12** in good to excellent yields, ranging from 75% to 95% yield (Scheme 6). Although styrenes bearing either electron-donating (*e.g.*, Me, ^{t}Bu) or electron-withdrawing (*e.g.*, F, Cl, Br, CF_3, CN, NO_2, CHO) functional groups were well tolerated under the reaction conditions, substrates containing phenylsulfonyl or ferrocene moieties failed to participate in the reaction (Scheme 7). Moreover, the applicability of aliphatic alkenes as starting materials was unfortunately not explored in this study. Based on a series of control experiments and previous reports, the authors proposed a tentative mechanism for this electrocatalytic reaction, as depicted in Scheme 8.

2.3 Bromo-nitration

In 1963, Meinwald and co-workers reported one of the earliest examples of direct bromo-nitration of alkenes, employing nitrosyl bromide (NOBr) as a bifunctional bromo-nitrating reagent.[39] Although the study was limited to norbornene as the sole substrate, it could be an inspiration for further researchers. Almost half a century later, in the same paper describing iron-mediated direct chloro-nitration of alkenes using the combination of $Fe(NO_3)_3 \cdot 9H_2O$ with $FeCl_3$,[34] Taniguchi's research group also reported a single example of bromination version of the same reaction using CBr_4 as a bromine source. Thus, in refluxing MeCN, the reaction of cyclooctene (an unactivated cyclic alkene) with excess $Fe(NO_3)_3 \cdot 9H_2O$ and carbon tetrabromide (CBr_4) furnished 1-bromo-2-nitrocyclooctane in a moderate yield (56%). Recently, with the objective of designing a general and practical method



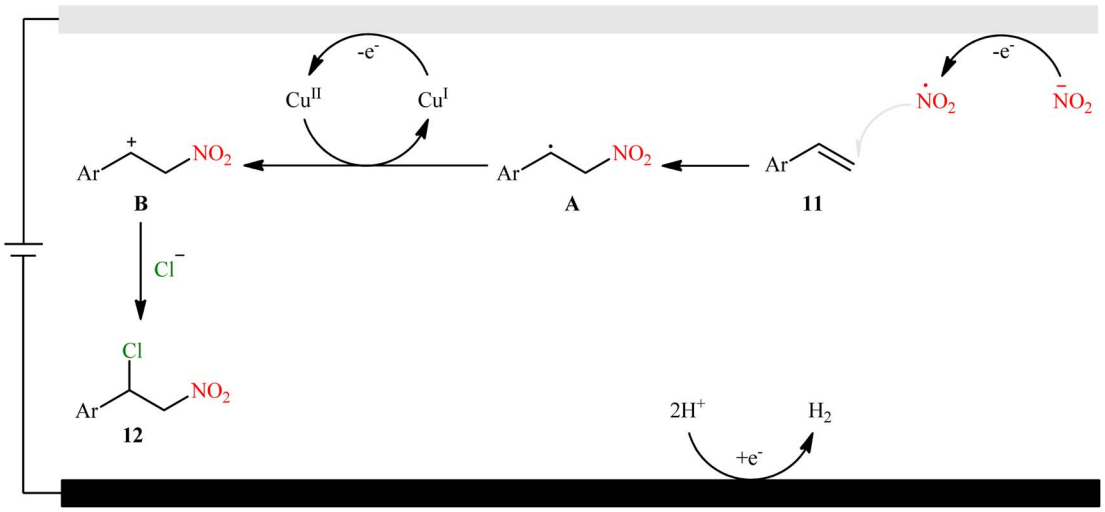
Scheme 6 Electrochemical chloro-nitration of aromatic alkenes **11**, reported by Liu-Li.

for the synthesis of β-bromo nitroalkanes *via* direct 1,2-bromo-nitration of the respective alkenes, Katayev and co-workers were able to demonstrated that a diverse array of β-bromo nitroalkanes **14** could be efficiently obtained in modest to excellent yields by treating the corresponding alkenes **13** with $Fe(NO_3)_3 \cdot 9H_2O$ and LiBr in an undivided cell assembled with GF and SS electrodes under a constant current of 15 mA (Scheme 8a).[40] A broad range of alkenes, including aliphatic (both cyclic and acyclic), aromatic (electron-rich and electron-poor), α,β-unsaturated carbonyl compounds, and (vinylsulfonyl)arenes, were employed to establish the general applicability of this synthetic process. In addition, the protocol was successfully applied to the late-stage functionalization of structurally complex natural products, highlighting its potential utility in the synthesis of advanced intermediates and bioactive compounds. Moreover, to further demonstrate the operational simplicity and scalability of the protocol, the process was successfully applied on a decagram scale to three selected alkene substrates. Mechanistically, based on a series of control experiments, it was confirmed that this bromo-nitration reaction most likely proceeds *via* a radical pathway, as illustrated in Scheme 8b.

In a related investigation, the same research group demonstrated the utility of inexpensive and readily available NH_4Br as a brominating agent for the direct bromo-nitration of alkenes, using *N*-nitrosuccinimide **9** as the source of nitryl radicals.[37] Thus, a library of β-bromo nitroalkanes **16** were synthesized in moderate to good yields *via fac*-$Ir(ppy)_3/CoBr_2$-catalyzed bromo-nitration of styrene derivatives **15** with NH_4Br and *N*-nitrosuccinimide **9** in MeCN under blue LED irradiation. As shown in Scheme 9, both electron-rich and electron-poor styrene derivatives were compatible with this reaction. However, the applicability of α-substituted and β-substituted styrenes, as well as aliphatic alkenes, was not explored within this synthetic strategy. The authors proposed mechanism for this reaction is analogous to the one depicted for chloro-nitration of alkenes in Scheme 5b.

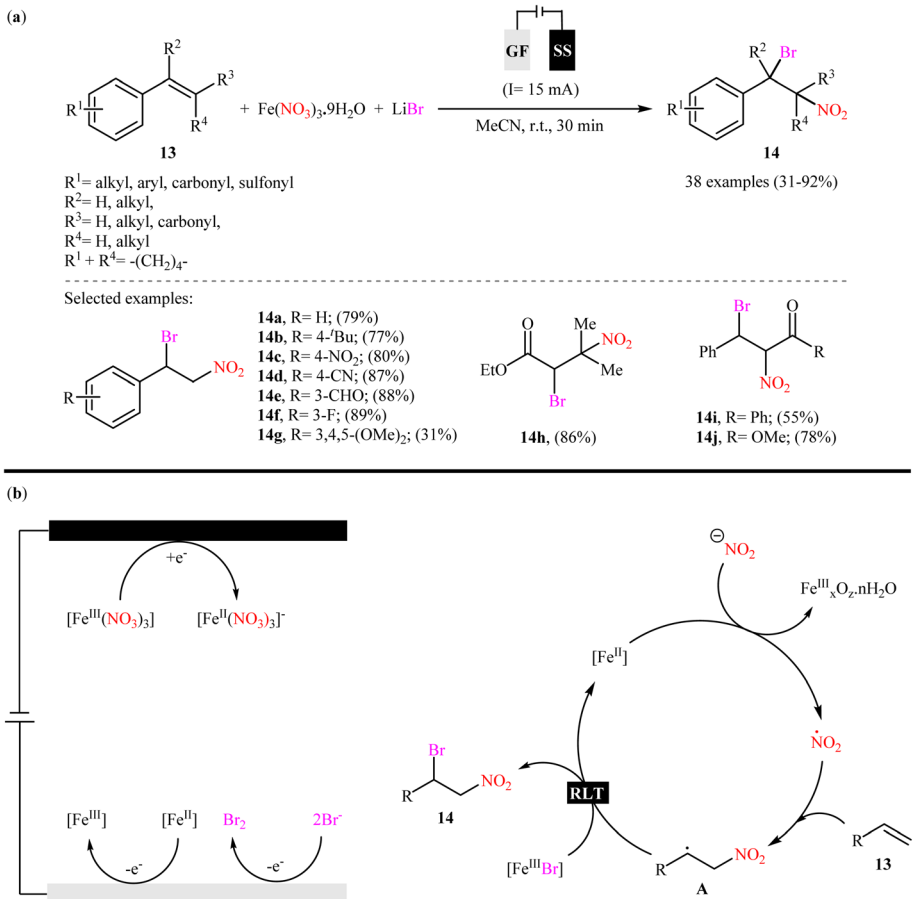
2.4 Iodo-nitration

The first example on direct vicinal iodo-nitration of alkenes has been reported by Stevenasn and Emmons in 1957,[41] when a small series of alkenes **17** underwent regioselective nitrative iodination in the presence of a combination of dinitrogen tetroxide (N_2O_4) and molecular iodine (I_2) in dry ether to form the corresponding β-iodo nitroalkanes **18** in moderate to excellent yields (Scheme 10). However, since then, the synthesis of β-iodo nitroalkanes has received little attention for nearly 60 years, probably due to the inherent instability of these compounds and their tendency to undergo spontaneous elimination of hydrogen iodide (HI).[42,43] Drawing inspiration from the pioneering work of Stevens and Emmons, in 2016, the research group of Majee developed an efficient one-pot protocol for the synthesis of vicinal diiodo carbonyl compounds from α,β-unsaturated carbonyl substrates, employing a combination of NH_2OH HCl and $NaIO_4$ as both the oxidizing agent and the *in situ* source of nitrosyl iodide (NOI).[44] According to the mechanism proposed by the authors, this diiodination reaction

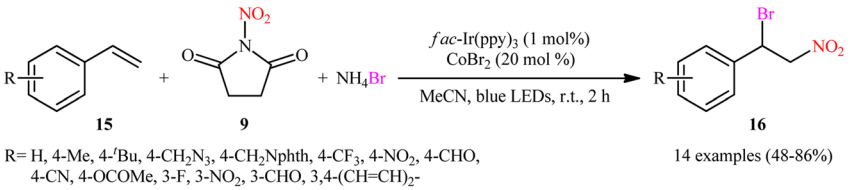


Scheme 7 Presumable pathway of the reaction in Scheme 6.

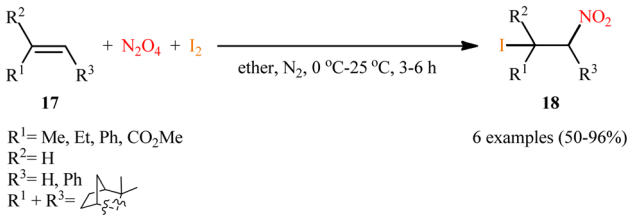
proceeds *via* two sequential steps: an initial iodo-nitration of the α,β-unsaturated carbonyl compounds with *in situ* generated nitrosyl iodide (NOI), followed by a denitrative iodination of the resulting β-iodo nitroalkanes in the presence of excess $NaIO_4$. Needless to say, the lack of general and practical methods for the direct 1,2-iodo-nitration of alkenes highlights the need for further research to develop efficient, mild, and broadly applicable strategies for accessing this valuable transformation.



Scheme 8 (a) Katayev's synthesis of β-bromo nitroalkanes **14**; (b) a proposed pathway for the formation of β-bromo nitroalkanes **14**.



Scheme 9 Ir/Co-catalyzed bromo-nitration of styrenes **15** with NH_4Br and *N*-nitrosuccinimide **9**.



Scheme 10 Stevenasn–Emmons's synthesis of β-iodo nitroalkanes **18**.

3 Halo-nitration of alkynes

In this section, we focus on the direct introduction of halogen and nitro groups into alkynes. Due to the lack of reported methods for the direct fluoro-nitration and bromo-nitration of alkynes, the discussion is divided into two main subsections: chloro-nitration and iodo-nitration.

3.1 Fluoro-nitration

To the best of our knowledge, thus far, no reporting guideline exists for the direct fluoro-nitration of alkynes, indicating a significant gap in the existing synthetic toolkit and presenting an opportunity for future development in this area.

3.2 Chloro-nitration

In 2016, Gao and Xu reported one of the earliest examples of the direct chloro-nitration of alkynes employing $Cu(NO_3)_2 \cdot 3H_2O$ as the nitro source and $SnCl_2 \cdot 2H_2O$ as the chlorine source.[45] The reaction was carried out in MeCN under an inert atmosphere, tolerated various terminal and internal alkynes **19**, and generally provided the corresponding α-chloro-β-nitroalkenes **20** as mixtures of E/Z isomers in moderate to excellent yields (Scheme 11a). Overall, the relative reaction rates of substrates in this transformation followed the order: terminal aryl alkynes > internal aryl–aryl alkynes ≈ internal aryl-alkyl alkynes > terminal alkyl alkynes > silyl protected alkynes. Interestingly, the electronic and steric effects of the substituents on the phenyl ring periphery of aromatic alkynes had no significant influence on the outcome of the reaction. Therefore, substrates bearing either electron-donating (*e.g.*, Me, OMe) or electron-withdrawing (*e.g.*, F, Cl, Br, Ac, CN) group in the *ortho*-, *meta*-, or *para*-position of the aryl ring were all suitable for this reaction. More importantly, a scale-up experiment was also successfully performed under the standard reaction conditions (1.50 g, 76% yield), demonstrating the practicability of the method. Based on a series of control experiments, the authors proposed two possible pathways for this nitrative difunctionalization, as illustrated in Scheme 11b. Initially, copper nitrate coordinates to the C≡C bond of alkyne **19** to form complex **A**. In the first pathway (path A), the *in situ* generated Cl ion from $SnCl_2$ attacks the activated C≡C bond of complex **A** to give the intermediate (E)-**B**, which subsequently undergoes a nitro group[1,3]-shift to afford alkene (E)-**20** as the major product. Notably, in the case of terminal alkynes, intermediate (E)-**B** may be further stabilized through a six-membered intramolecular hydrogen–bonding interaction. In the second pathway (path B), which is favored for substrates bearing strong electron-donating groups, a ligand exchange between chloride and nitrate ions leads to the formation of complex **C**. Next, this complex undergoes a *cis*-insertion to generate the complexed adduct (Z)-**B**, which subsequently affords (Z)-**20** as the major product.

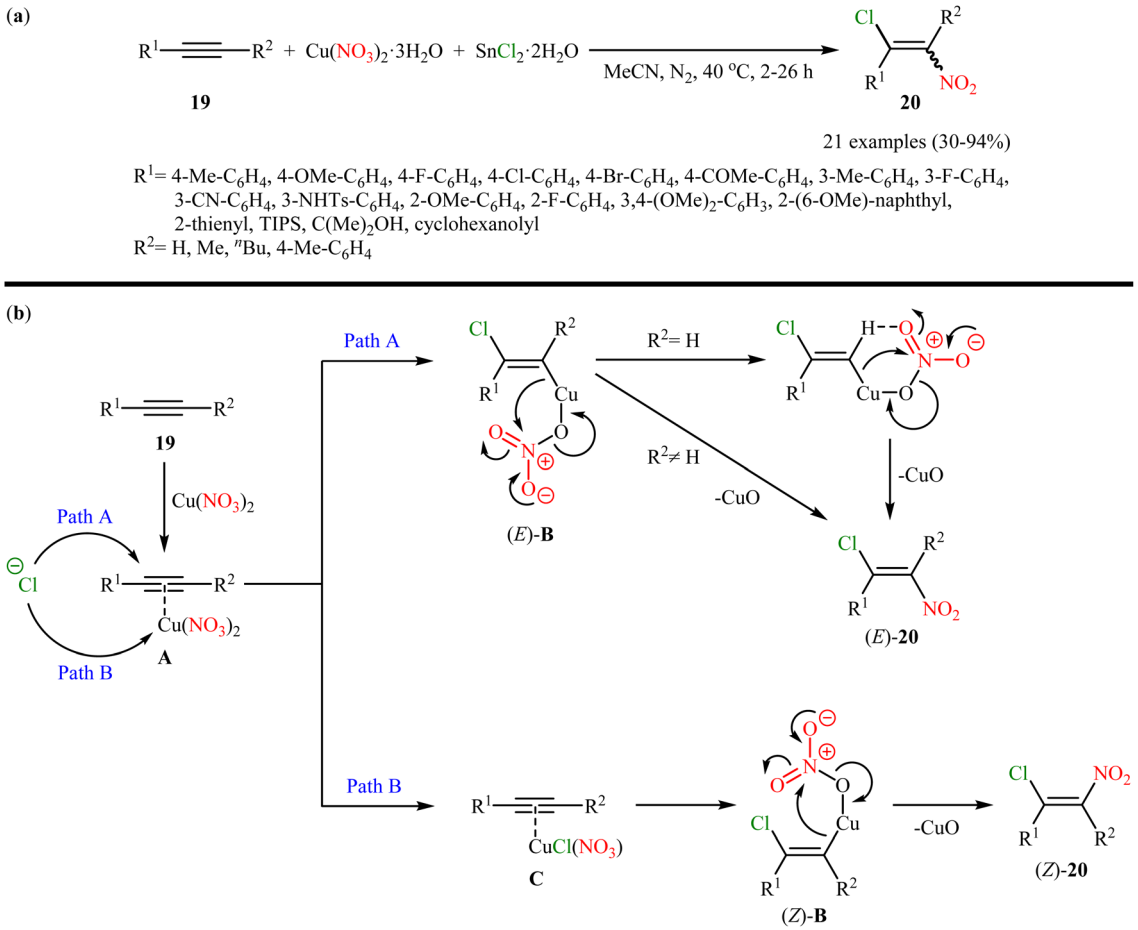
Along this line, in 2020, Deng's research group developed a mild and efficient method for synthesizing α-chloro-β-nitroalkenes *via* the reaction of alkynes with guanidine nitrate **6** and TMSCl in the presence of a catalytic amount of $CuSO_4$ in MeCN at room temperature.[36] A small series of terminal aromatic alkenes **21** suitably participated in this reaction, delivering moderate yield of the desired nitro chlorinated products **22** (Scheme 12). However, the applicability of aliphatic alkenes was not investigated in this study. Although the detailed reaction pathway has not been fully elucidated, the authors proposed a plausible preliminary mechanism, as shown in Scheme 12a. The sequence begins with the reaction of TMSCl with guanidine nitrate **6**, generating $TMSONO_2$ *in situ*. This intermediate then reacts with a second equivalent of TMSCl to produce nitryl chloride ($ClNO_2$), a highly electrophilic nitrating species. In the final step, nitryl chloride engages in a copper-catalyzed reaction with alkenes **21**, furnishing the desired product **22**.

3.3 Bromo-nitration

To the best of our awareness, the direct bromo-nitration of alkynes has not yet been reported in the literature, similar to the case of fluoro-nitration.

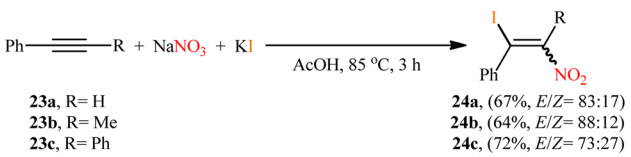
3.4 Iodo-nitration

After pioneering work by Stevenasn and Emmons on direct 1,2-iodo-nitration of tolane and phenylacetylene using N_2O_4 and I_2 as sources of nitro and iodo groups, respectively,[41] first practical report on the direct synthesis of α-iodo-β-nitroalkenes from the

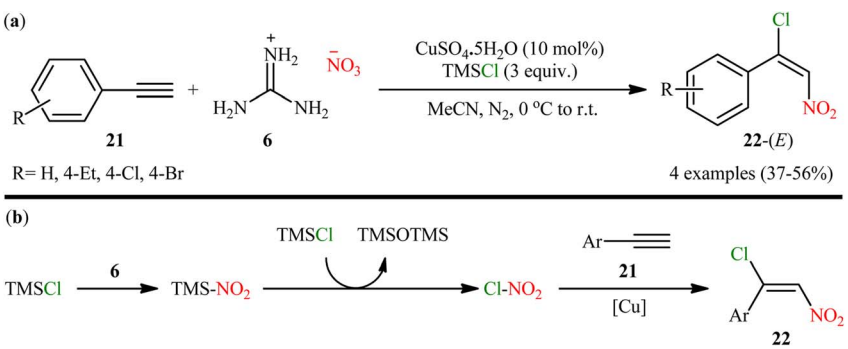


Scheme 11 (a) Gao-Xu's synthesis of α-chloro-β-nitroalkenes **20**; (b) proposed reaction mechanism for the formation of α-chloro-β-nitroalkenes **20**.

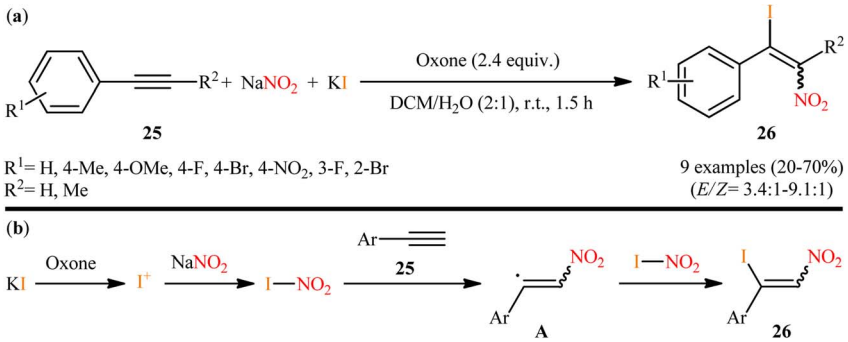
respective alkynes was published in 1998, by Yusubov *et al.*[46] In this report they demonstrated that treatment of phenylacetylene derivatives **23** with sodium nitrate ($NaNO_3$) and potassium iodide (KI) under additive-free conditions in acetic acid at 85 °C afforded the corresponding α-iodo-β-nitrostyrenes **24** in moderate to good yields (Scheme 13). The reaction displayed a high degree of regioselectivity, with the iodo group predominantly installed on the carbon adjacent to the aryl group, and showed moderate stereoselectivity, favoring the formation of (E)-isomers over (Z)-isomers. Notably, oct-4-yne did not work well in the reaction and as a result, no other aliphatic alkynes were examined in the protocol. Moreover, when 1-phenyl-2-(trimethylsilyl)acetylene was used as the



Scheme 13 Yusubov's synthesis of -iodo-β-nitrostyrenes **24**.



Scheme 12 (a) Deng's synthesis of α-chloro-β-nitroalkenes **22**; (b) possible mechanism for the formation of α-chloro-β-nitroalkenes **22**.

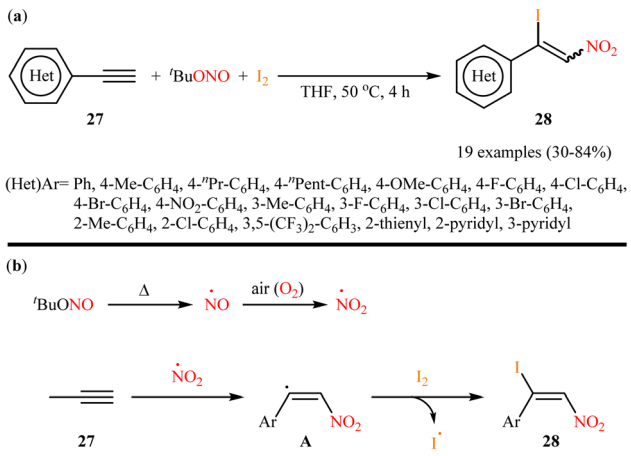


Scheme 14 (a) Oxone-mediated iodo-nitration of alkynes **25** with $NaNO_2$ and KI; (b) mechanistic proposal for the formation of α-iodo-β-nitrostyrenes **26**.

substrate, the major product was 1,2-diiodo-2-nitro-1-phenylethene (39%), while the expected α-iodo-β-nitrostyrene was obtained in low yield (19%), indicating that silyl-protected arylacetylenes are incompatible with the reaction conditions. Subsequently, the same authors demonstrated a similar system for this transformation, using a combination of KI and $Mg(NO_3)_2$ in HNO_3, albeit with lower efficiency.[47] Recently, Xu and co-workers applied this reaction as the key strategic step in synthesis of isoxazoles from alkynes.[48]

Following these works, the group of Kuhakarn demonstrated that a range of α-iodo-β-nitrostyrenes **26** could be obtained in synthetically useful yields and high (E)-selectivity from the reaction of arylacetylenes **25** with $NaNO_2$ and KI employing oxone as a benign oxidant in a DCM/H_2O solvent mixture at room temperature (Scheme 14a).[43] The examples showed that both terminal and internal alkynes were compatible with this methodology. Notably, substrates bearing strongly electron-donating (*e.g.*, OMe) or strongly electron-withdrawing groups (*e.g.*, NO_2) gave the poorest results among the compounds tested. This was attributed to the formation of a competing 1,2-diiodinated side product, promoted by the enhanced reactivity of the OMe group toward iodination reaction, and the strong deactivating effect of the NO_2 group, respectively. Although the detailed mechanism remains unclear, the authors propose that the reaction likely proceeds *via* a radical pathway, as depicted in Scheme 14b.

In 2017, Xu and colleagues investigated the applicability of ^{t}BuONO as the nitro source in iodo-nitration reactions of alkyne substrates.[49] THF was found to be the best solvent for the reaction and, among several solvents tested, dioxane, toluene, DMF, DMSO, MeOH, and ^{i}PrOH were found to be completely ineffective. Apparently, the outcome of the reaction was highly dependent on the selected iodinating agents. Consequently, a small series of iodine source (*i.e.*, I_2, KI, NaI) were screened in THF, the best results being those with I_2. Under optimized conditions, the reactions tolerated various terminal aromatic and heteroaromatic alkynes **27** and gave corresponding iodo-nitrated products **28** in fair to high yields (Scheme 15a) However, the extension of this interesting acid-/additive-free iodo-nitration reaction to aliphatic and internal alkynes was not explored. It is interesting to note that compared with the iodonitration reported by Kuhakarn, the current protocol provided both better yields and higher stereoselectivities of the products. Mechanistically, the authors proposed that this di-functionalization reaction most likely proceeds *via* a radical pathway as depicted in Scheme 15b.



Scheme 15 (a) Xu's synthesis of β-iodonitro alkenes **28**; (b) proposed mechanistic pathway for the formation of β-iodonitro alkenes **28**.

4 Conclusion

The direct vicinal nitrative difunctionalization of readily available alkenes and alkynes has emerged as a highly effective strategy for the rapid and efficient synthesis of β-functionalized nitro compounds from simple and easily accessible starting materials within a single click. In this context, the direct halo-nitration of unsaturated hydrocarbons offers an attractive approach for accessing synthetically valuable β-halo nitroalkanes and nitroalkenes from simple and ubiquitous feedstock materials, with high atom, step, and pot economy. Although this page of β-halo nitroalkane/nitroalkene synthesis has been known for over half a century, it did not attract the attention of chemists for several decades due to the reliance on toxic and/or difficult-to-handle nitrating and halogenating reagents. Recently, however, with the development of non-toxic and user-friendly reagents, this area has regained significant attention

and emerged as a hot topic in synthetic organic chemistry. Although significant progress has been made, this field remains nascent and requires further research to reach maturity. For example, no reporting guidelines have been established for the direct fluoro- and bromo-nitration of alkynes. This absence in the literature highlights a significant gap in the field and underscores the need for further investigation in this domain. Additionally, while a range of organic (*e.g.*, guanidine nitrate, *N*-nitrosuccinimide, *tert*-butyl nitrite) and inorganic (*e.g.*, metal nitrates and nitrites, nitrogen tetroxide, nitronium tetrafluoroborate) nitro transfer reagents have been employed in these transformations, many suffer from issues of toxicity and/or explosiveness. Future efforts are expected to focus on developing safer, milder, and more sustainable nitrating reagents to broaden the scope and practical utility of these strategies.

Conflicts of interest

There are no conflicts to declare.

Data availability

No new results or data were generated in the preparation of this review article.

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