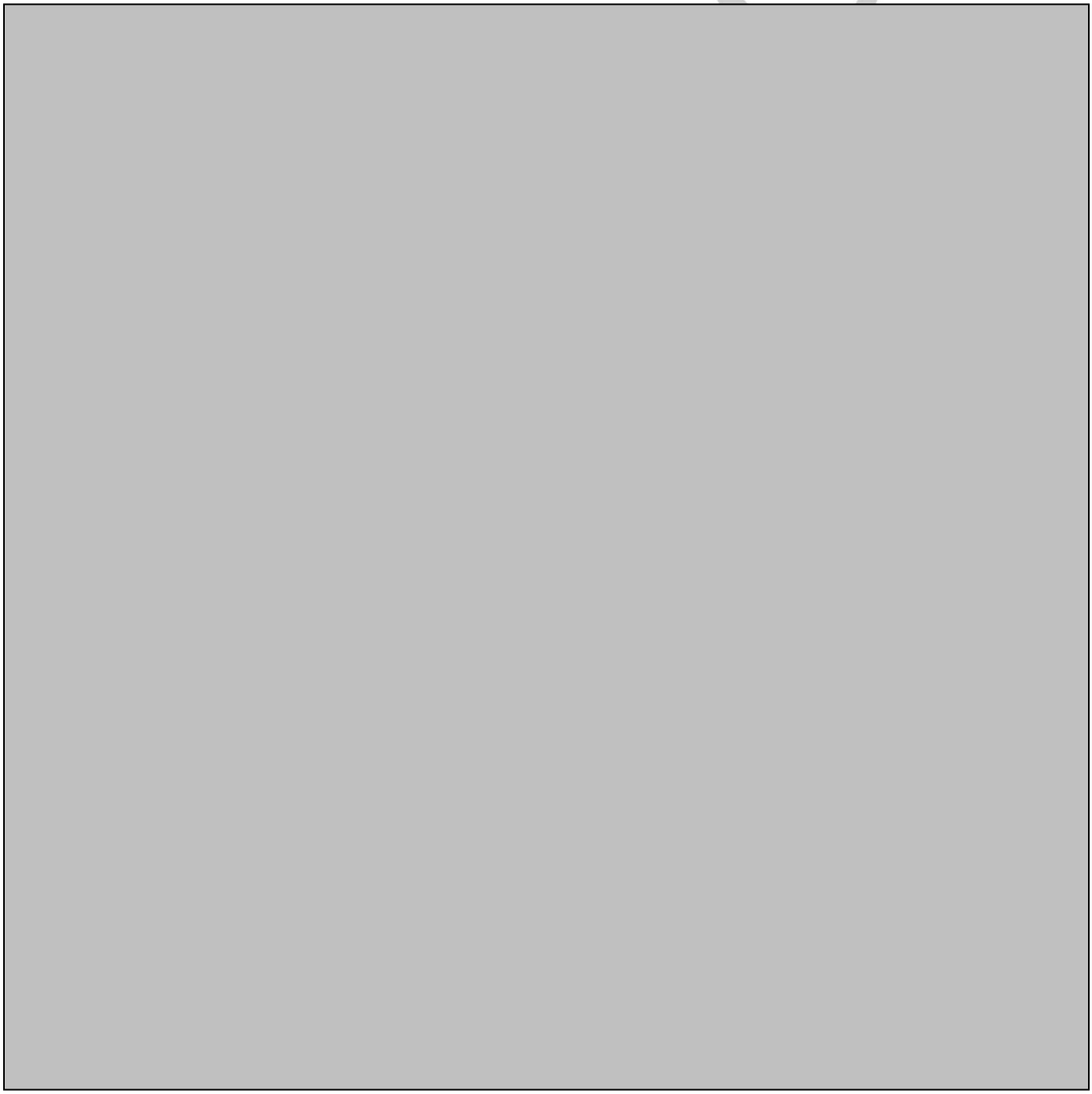
Visible Light-Mediated Reactions of β-Nitroalkenes

Dr. Sudheesh T. Sivanandan,[a]* Mukkath J. Jesline,[b] Dr. Divya K. Nair,[c]* Dr. Tarun Kumar[d]*



[a] Dr. Sudheesh T. Sivanandan*
School of Chemistry, University of Nottingham, University Park, Nottingham, UK.
E-mail: sudheesh.sivanandan@nottingham.ac.uk
[b] Mukkath J. Jesline
Department of Applied Chemistry, Cochin University of Science and Technology, Kochi 682022, Kerala, India
[c] Dr. Divya K. Nair*
Department of Chemistry, Mercy College, Palakkad, Kerala 678 006, India
E-mail: drdivyaknair@mercycollege.edu.in
[d] Dr. Tarun Kumar*
Department of Chemistry, Mohanlal Sukhadia University, Udaipur-313001, Rajasthan, India
E-mail:tarunkumar@mlsu.ac.in

Abstract: Organic transformations using visible light-mediated photoredox reactions received significant attention in the past several years. Recently, nitroalkenes have emerged as an excellent coupling partner in the visible light-mediated photoredox reactions. Due to the easy availability and diverse reactivity, several methodologies are reported on the photoredox-mediated reactions of nitroalkenes to attain different types of alkenes and heterocycles. Variety of reactions including denitrative coupling reactions, addition reactions and cycloadditions, etc are reported. However, a review that focuses entirely on this topic has not appeared yet. Considering the synthetic potential of these class of reactions, we provide a summary of various methodologies developed for the reactions of nitroalkenes under visible light photoredox catalysis.

1. Introduction

Nitro compounds are highly important in various fields such as medicinal chemistry,[1] dyes,[2,3] propellants and energetic materials,[4–13] etc. In organic synthesis, nitro compounds are used in various transformations, including functional group interconversion, substitution and elimination reactions, heterocycle preparation, Henry reaction for the synthesis of nitroalkenes, etc.[14–18] Nitroalkenes also found a variety of applications in organic synthesis due to their multiple reactive sites and reactivity pattern.[19] Nitroalkenes and their derivatives react in various ways such as Michael addition, cyclizations, denitrative couplings, Morita-Baylis-Hillman and Rauhut-Currier reactions, etc.[20–33] The diverse reactivity, easy availability, and bench-stable solid property make nitroalkene a unique motif in organic synthesis.

On the other hand, visible light-mediated photoredox reactions received considerable attention over many years.[34–43] There are several advantages for photoredox catalysis, including benign reaction conditions, controlled radical reactions, etc. It can also be used in combination with organocatalysis for asymmetric synthesis.[44] Recently, there has been an interest in the use of nitroalkenes in different types of photoredox reactions. Nitroalkene undergoes Michael addition when an anionic or neutral nucleophile is used, while the reactivity is generally inversed for the addition when the nucleophile is radical. Also, denitrogenative substitutions are extremely useful in preparing novel styrene derivatives.[45–48] These reactivities of nitroalkenes attracted many research groups to develop methodologies to use them in visible light-mediated photoredox reactions using a variety of photocatalysts (Figure 1). However, a review devoted to the visible light-mediated reactions of nitroalkenes has not appeared so far.

This review summarizes various methodologies on visible light-mediated reactions of nitroalkenes. The review is mainly divided into three sections depending on the reactivity pattern. They are (i) Substitution reactions (ii) Addition reactions and (iii) Cycloadditions/cyclizations.

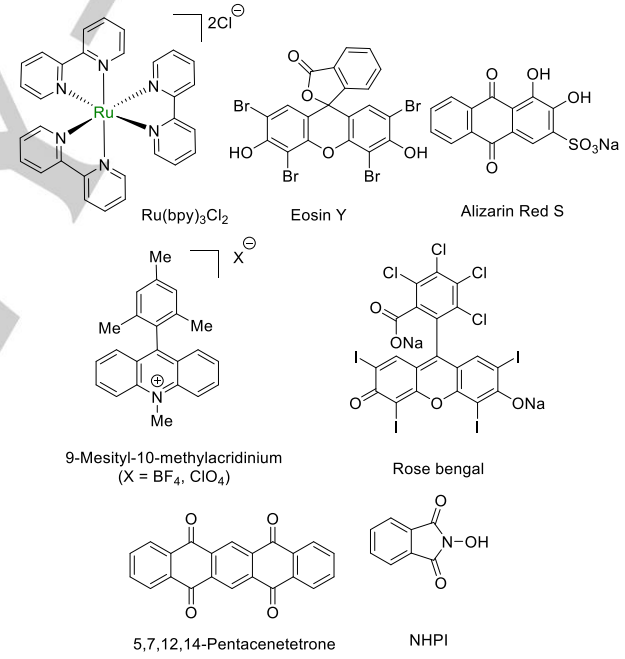


Figure 1. Photocatalysts employed in nitroalkene chemistry

Dr. Divya K. Nair received her B.Sc. and M.Sc. degrees in chemistry from the University of Calicut. She obtained her Ph.D. degree from the Indian Institute of Technology Bombay (IIT Bombay) in 2015 under the guidance of Professor I. N. N. Namboothiri. Currently, she is an assistant professor in the Department of chemistry, Mercy College (affiliated with the University of Calicut), Palakkad, Kerala. Her research interests include Michaeladdition-cyclisation reactions, photocatalysis, Morita-Baylis-Hillman reactions.

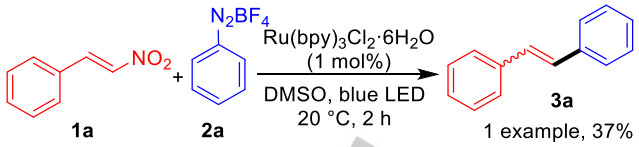
Mukkath J. Jesline was born in 1994 in Kerala, India. She pursued her Batchelor of Science in Chemistry from St. Albert's College, Kerala, and received her Master of Science in Chemistry from Kochin University of Science and Technology, Kochi, India. She carried out her master's research project at the Indian Institute of Technology Bombay under the supervision of Prof. Irishi N. N. Namboothiri. Currently, she is working as a Scientist at Sygnature Discovery Ltd, UK.

Dr. Sudheesh T. Sivanandan pursued his Integrated Masters in Science at IIRBS, Mahatma Gandhi University, Kerala (India), under the guidance of Prof. Ibrahim. Ibnusaud. After working for a year in Johnson Matthey Chemicals Pvt. Ltd, Mumbai as a development officer in Dr. Thomas Colacot's group, he moved to the Indian Institute of Technology Bombay (IIT Bombay), where he pursued his Ph.D. under the guidance of Prof. Irishi N. N. Namboothiri. Currently, he is carrying out his post-doctoral research in the University of Nottingham, UK.

Dr. Tarun Kumar received his M.Sc. degree in chemistry from the University of Rajasthan, Jaipur, in 2010 and his Ph.D. from the Indian Institute of Technology Bombay (IIT Bombay) in 2016 under the supervision of Professor I. N. N. Namboothiri. He completed his post-doctoral studies at the University of Reims, France, with Dr. Florian Jaroschik. Currently, he is an assistant professor in the Department of Chemistry, Mohanlal Sukhadia University Udaipur. His research interests include activation of carbon-fluorine bond, development of new research methodologies for the synthesis of biologically important heterocycles and carbocyles.

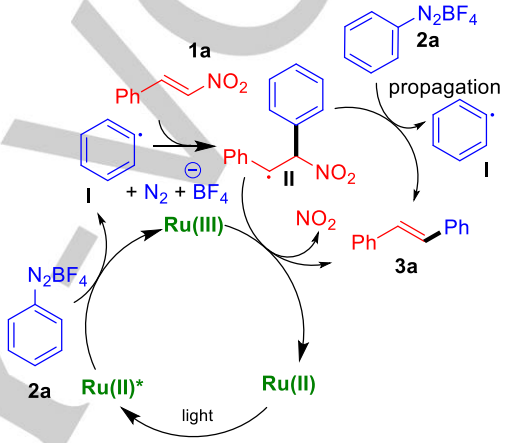
2. Substitution reactions

In 2012, König *et al.* reported the arylation of unsaturated compounds such as alkenes, alkynes and enones, using aryl diazonium salts **2** under visible light photoredox catalysis (Scheme 1).[49] Ruthenium based photocatalyst was used for the transformation along with blue LED irradiation. High yields, low catalyst loadings and mild conditions were the highlights of the reaction. They demonstrated the scope of the reaction using a variety of unsaturated compounds, including one example of nitroalkene **1a**. Interestingly, direct sunlight was sufficient to carry out the reaction, and the yields were comparable to those of laboratory conditions.



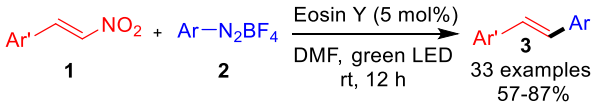
Scheme 1. Reaction of nitroalkenes with aryl diazonium salts (König, 2012)

A plausible mechanism is outlined in Scheme 2. Photoexcited ruthenium catalyst facilitated the generation of aryl radical **I***via* elimination of dinitrogen from the diazonium salt **2a**. The aryl radical **I** was then added to nitrostyrene **1a** to make another radical intermediate **II**. The benzylic radical intermediate **II** can be converted to the cation *via* radical propagation by transferring an electron to another aryl diazonium compound **2a** or to the catalyst to complete the catalytic cycle. Further denitration affords the alkene**3a**.



Scheme 2. Mechanism for the reaction of nitroalkenes with aryl diazonium salts

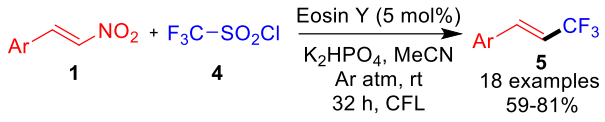
In 2016, Wang and co-workers reported a similar synthesis of stilbene derivatives **3** from nitroalkenes **1** and aryl diazonium salts **2** using eosin Y as the photocatalyst in the presence of green LED (Scheme 3).[50] A wide variety of nitroalkenes **1** and aryl diazonium salts **2** were used, and the products **3** were formed in very good yields with exclusive (*E*) selectivity. Control experiments suggest a radical pathway that is similar to Scheme 2.



Scheme 3. Reaction of nitroalkenes with aryl diazonium salts (Wang, 2016)

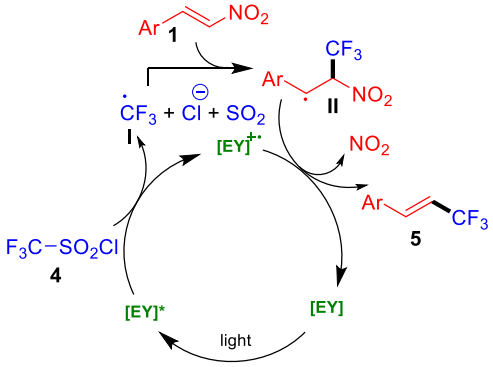
The trifluoromethyl group is an important fragment in the pharmaceutical and material field.[51–53] Owing to its importance, Balaraman *et al.* in 2017, reported a metal-free trifluoromethylation of nitroalkenes **1**u sing visible-light photoredoxcatalysis (Scheme 4).[54] Eosin Y was used as the photocatalyst along with CFL irradiation. Cheap and easily available trifluoromethanesulfonyl chloride**4** was used as the CF_3 source, and the (*E*)-isomer of the product **5** was exclusively formed in the reaction. An aromatic group was necessary for the nitroalkene substrates **1** as the reaction failed when alkyl substrates were used. Also, competitive experiments with electronically different substrates suggested

that an aryl ring with an electron-withdrawing group facilitated the reaction.



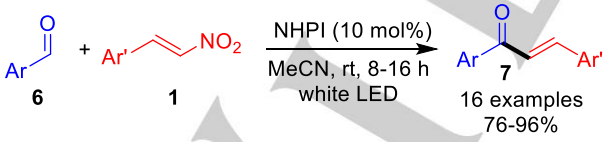
Scheme 4. Trifluoromethylation of nitroalkene (Balaraman, 2017)

Experiments with radical scavengers led to the conclusion that the reaction follows a radical pathway. The photoexcited catalyst undergoes a single electron transfer (SET) with triflyl chloride **4**, forming trifluoromethyl radical **I** with the release of sulfur dioxide and chloride anion. The addition of trifluoromethyl radical **I** to the nitroalkene **1** generates the benzyl radical **II**, which further undergoes oxidation with eosin-Y radical cation and nitro group elimination forms the alkene **5** (Scheme 5).



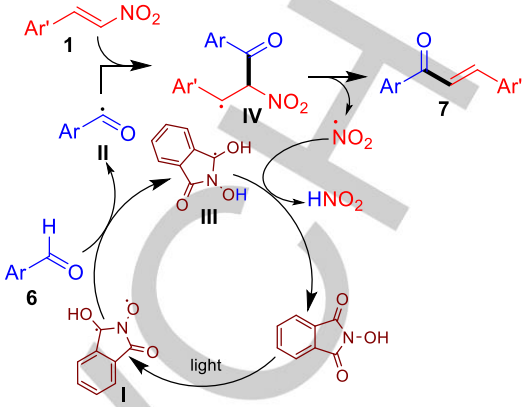
Scheme 5. Mechanism for the trifluoromethylation of nitroalkene.

Yadav *et al*. in 2018 reported a denitrative benzoylation of nitroalkenes **1** in the presence of white LED for the synthesis of chalcones **7** (Scheme 6).[55] Considering avoiding precious metal-based catalysts, *N*-hydroxyphthalimide was used as the organophotocatalyst in this reaction. Various aldehydes **6** were used as benzoyl radical precursors. Nitroalkenes **1** and aldehydes **6** with both electron-donating and electron-withdrawing groups attached to the aromatic ring participated well in the reaction. However, aliphatic nitroalkenes and aldehydes failed to deliver the products.



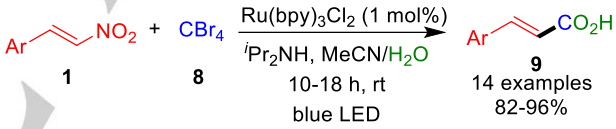
Scheme 6. Benzoylation of nitroalkenes (Yadav, 2018)

A variety of control experiments were conducted to demonstrate the reaction pathway. Traditional radical scavenger experiments and electron paramagnetic resonance (EPR) experiments suggested the involvement of radical intermediates. An intermolecular competing kinetic isotope effect (KIE) experiment showed that the rate-determining step is the activation of the aldehydic C-H bond. The reaction does not occur in a radical chain pathway, as evident from the light on/off experiment. Based on these observations, the mechanism is proposed in Scheme 7. Light-activated NHPI forms reactive *O*-radical intermediate **I** that abstracts the hydrogen atom from the aldehyde **6**, forming acyl radical **II**. The acyl radical intermediate **II** further adds to the nitroalkene **1** forming a benzyl radical intermediate **IV**. Denitration of this intermediate **IV** delivers the chalcone **7**, and the NHPI catalyst regenerates by converting nitronate radical into nitrous acid.



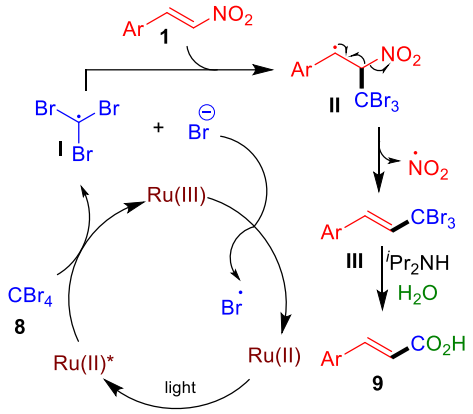
Scheme 7. Mechanism for the benzoylation of nitroalkenes

Yadav *et al*. in 2018 reported another photoredox application of nitroalkenes **1** by synthesizing cinnamic acids **9** (Scheme 8).[56] The reaction involved a one-pot denitrative tribromomethylation-hydrolysis in forming *trans*-cinnamic acids **9** in high yields. Tetrabromomethane **8** is used as the precursor for tribromomethyl radical, which then replaces the nitro group in the alkene **1**. Further hydrolysis of tribromomethyl styrene gives the cinnamic acid derivatives **9**. Notably, CCl_4 did not react under these conditions, probably due to its less easily reducing nature compared to CBr_4.



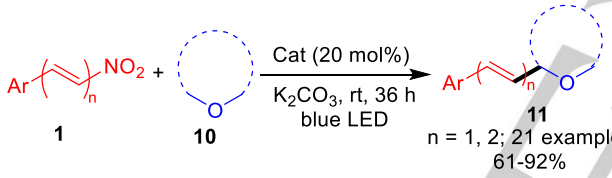
Scheme 8. Denitrative carboxylation of nitroalkenes (Yadav, 2018)

Control experiments with TEMPO and light on/off experiment suggested that the reaction requires continuous light and the mechanism involves radical species. Photoexcited ruthenium catalyst generates bromonium ion and CBr_3 radical **I** from CBr_4 **8**. The bromonium ion reduces Ru(III) to Ru(II) to complete the catalytic cycle, and the resulting bromine radical dimerizes to form Br_2. The CBr_3 radical **I** is further added to the nitroalkene **1** to form a benzyl radical **II**. Denitration of benzyl radical **II** generates the tribromomethyl styrene intermediate **III**,followed by hydrolysis of CBr_3 group forms cinnamic acid **9**. The intermediate tribromomethyl styrene **III** was also isolated without hydrolysis to support the proposed pathway. (Scheme 9).



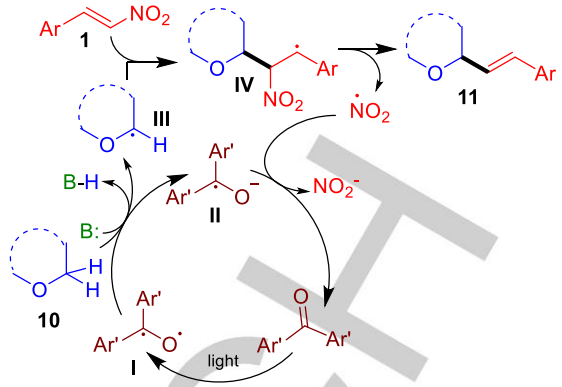
Scheme 9. Mechanism for the denitrative carboxylation

In 2019, Li and co-workers reported a photocatalytic C(sp^3)-H alkenylation of cyclic and acyclic ethers **10** using nitroalkenes **1** *via* a proton-coupled electron transfer (Scheme 10).[57] The reaction was highly selective towards *E*-isomer, affording the products **11** in very good yields. Among different ketone-based photocatalysts screened, 5,7,12,14-pentacenetetrone was superior to others in catalyzing the reaction. Using K_2CO_3, along with the catalyst, increased the yield of the products **11** drastically. Various nitroalkenes **1** possessing aromatic and hetero aromatic rings tolerated the reaction conditions. Aromatic rings with *ortho* substituents as well as electron-withdrawing groups afforded in lower yield compared to para-substituted as well as electronically rich and neutral substituents.



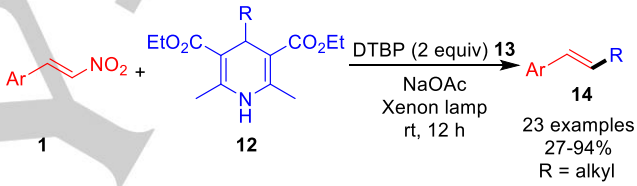
Scheme 10. Allyl ether synthesis from nitroalkenes (Li, 2019)

Several control experiments were carried out to gain insights into the reaction mechanism. Experiment with TEMPO indicated the SET pathway as the reaction was inhibited under these conditions, and the TEMPO-ether adduct was isolated. The light on/off experiment suggested that the reaction does not proceed *via* a radical chain pathway. There was no reaction observed in the absence of photocatalyst. Based on these observations, a plausible mechanism is proposed. Photoexcited catalyst **I** oxidize the ether **10**, and in the presence of a base, the alkyl radical intermediate **III** is generated. This alkyl radical **III** adds to the nitroalkene **1**, forming benzyl radical intermediate **IV**. Further elimination of nitronate radical deliver the alkenylated ether **11**, and the nitronate radical is reduced by the catalyst intermediate **II** to form nitronate and regenerating photocatalyst (Scheme 11).



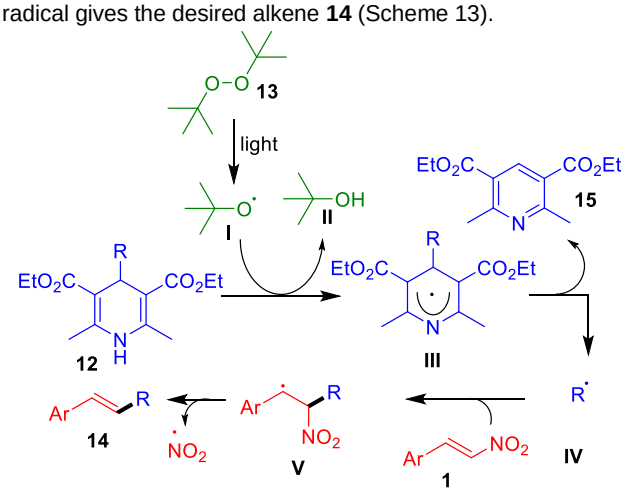
Scheme 11. Mechanism for the Allyl ether synthesis

Li and co-workers in 2020 reported a photocatalyst-free denitroalkylation of nitroalkenes **1** with Hantzsch ester **12** under xenon lamp irradiation (Scheme 12).[58] The reaction was highly stereoselective, affording *trans* isomer of the product **14** exclusively with broad substrate scope and good yields. Control experiments demonstrated the necessity of light and oxidant as no product was formed without them. The addition of TEMPO inhibited the reaction, and the alkyl-TEMPO adduct was detected by mass spectrometry, suggesting a radical pathway.



Scheme 12. Denitrative alkylation of nitroalkenes (Li, 2020)

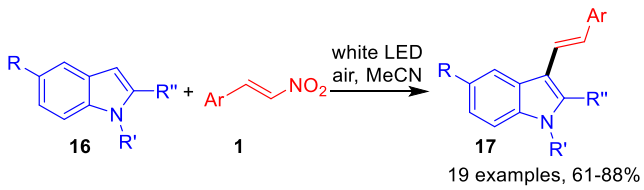
Upon irradiation, DTBP **13** forms the tertiary butoxy radical **I** that abstracts hydrogen atom from Hantzsch ester **12** to form intermediate **III**. The intermediate **III** is then fragmented into the radical intermediate **IV** and pyridine derivative **15**. The addition of radical **IV** to the nitroalkene **1** forms another benzyl radical intermediate **V,** which upon elimination of nitrogen dioxide radical gives the desired alkene **14** (Scheme 13).



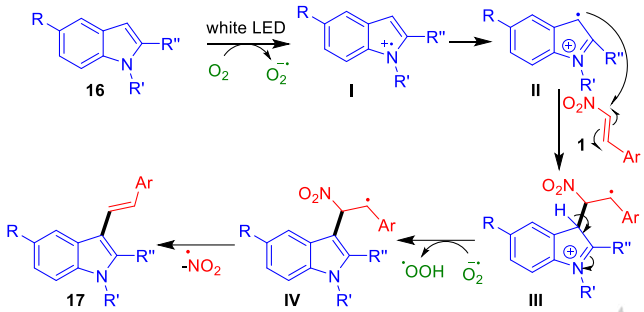
Scheme 13. Mechanism for the denitrative alkylation of nitroalkenes

In 2020, Chawla *et al.* developed a visible light mediated coupling of indoles **16** to *β*-nitrostyrenes **1** in moderate to good yields without any catalyst and external oxidant (Scheme

14).[59] Various nitrostyrenes **1** with diverse substitution are found to be efficient for this reaction. The alkenylation of indoles **16** were proposed to occur in a radical pathway (Scheme 15). The indolyl radical **I** formed upon light irradiation in the presence of air-oxygen, underwent conjugate addition with nitroalkene, formed a Michael adduct radical **III**, which then eliminates perhydroxy radical (·OH_2) to form **IV**, followed by NO_2 radical afforded the C3-alkenylated indoles **17**.

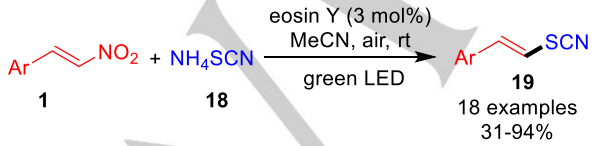


Scheme 14. Alkenylation of indoles with nitroalkenes (Chawla, 2020)



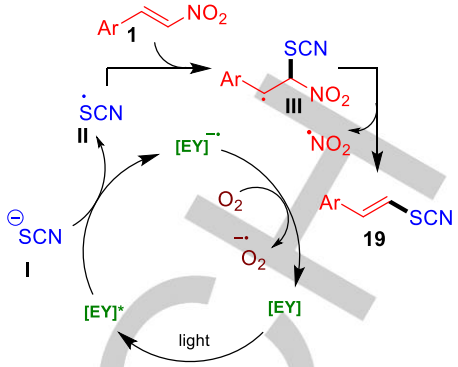
Scheme 15. Mechanism for the alkenylation of indoles with nitroalkenes

In 2020, Yadav and co-workers reported the synthesis of vinyl thiocyanates **19** from nitroalkenes **1** *via* denitrative thiocyanation reaction catalyzed by photo-induced eosin Y (Scheme 16).[60] The reaction was performed in acetonitrile solvent in presence of aerobic oxygen. The reaction conditions were thoroughly stabilized and a variety of nitroalkenes **1** were screened under optimized conditions. The thiocyanation reaction worked well with electron rich nitrostyrenes **1** and delivered the products **19** in good to excellent yields, whereas nitroalkenes **1** with strong electron withdrawing substituents and heteroaryl group delivered the vinyl thiocyanates **19** in lower yields. However, this method did not work with aliphatic nitroalkenes. This may be attributed to the formation of more stabilized radical intermediate in case of aromatic nitroalkenes **1**, its contrary in aliphatic nitroalkenes radical intermediate is comparatively less stable.



Scheme 16. Synthesis of vinyl thiocyanates from nitroalkenes (Yadav, 2020)

The proposed mechanism for the formation of vinyl thiocyanates **19** involves a radical pathway. Initially, the photo-excited eosin Y oxidizes thiocyanate anion **I** into a thiocyanate radical *via* SET. This thiocyanate radical adds to nitroalkene double bond forming another radical XX, which on loss of nitro group converted into vinyl thiocyanate **19**. The role of aerobic oxygen in the process was suggested to complete the catalytic cycle by oxidizing the eosin Y anionic radical into ground state (Scheme 17).

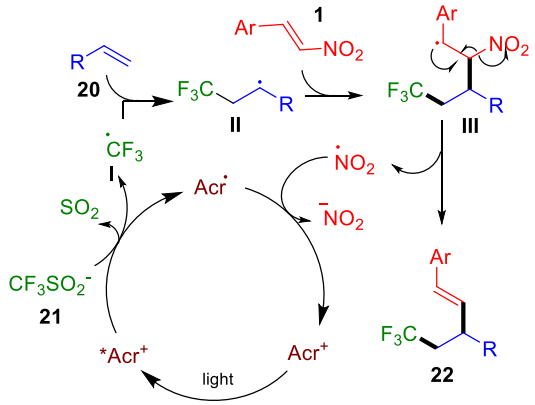


Scheme 17. Mechanism for the synthesis of vinyl thiocyanates

Owing to the importance of difunctionalization of alkenes and CF_3-compounds in various fields, Akondi and co-workers in 2021 reported a visible light-mediated three-component trifluoromethyl-alkenylation in the presence of organophotocatalyst (Scheme 18).[61] Langlois reagent **21** was used as the trifluoromethyl radical source to react with different alkenes **20** and nitrostyrenes **1**. 9-Mesityl-10-methylacridinium perchlorate was used as the photocatalyst with blue LED irradiation, and the products **22** were isolated in very good yields. Differently substituted nitroalkenes **1** participated in the reaction giving the products **22** in good yields, except alkyl and heteroatom substituted nitroalkenes. A wide variety of alkenes **20** were also used in the reaction, including late-stage functionalization of biologically important estrone and clonixin.

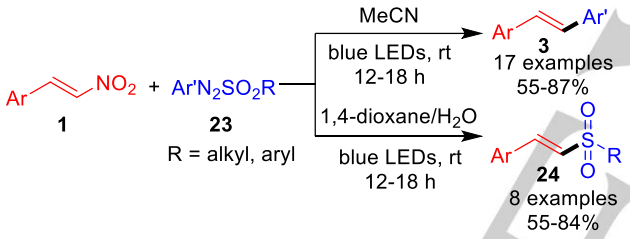
Scheme 18. Three-component trifluoromethyl-alkenylation (Akondi, 2021)

Different control experiments, such as reaction in the presence of radical scavengers and a radical clock experiment, were performed and concluded that the reaction proceeds *via* a radical pathway. Reductive quenching of the catalyst with Langlois reagent **21** forms the trifluoromethyl radical **I**. Adding this radical **I** to the alkene **20** affords another radical **II** that adds to nitroalkene **1** to form benzyl radical intermediate **III**. Further elimination of nitro radical forms the difunctionalized alkene **22** (Scheme 19).



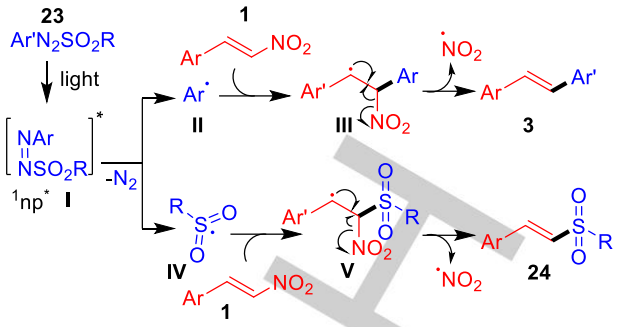
Scheme 19. Mechanism for the three-component trifluoromethyl-alkenylation

In 2021, Chawla and co-workers reported the solvent selective denitrative coupling of nitroalkenes **1** and aryl diazosulfones **23** for the synthesis of stilbenes **3** and vinylsulfones **24** (Scheme 20).[62] The reaction was carried out with blue LED irradiation without any photocatalysts. Upon irradiation, the aryl diazosulfones **23** served as the aryl and sulfonylradical precursors in acetonitrile and dioxane/water mixture, respectively. Presumably, the selectivity arises by the trapping of the aryl radical by water forming phenol in the presence of air. The reaction was also highly stereoselective, affording the *trans* isomer of the products **3/24** exclusively.



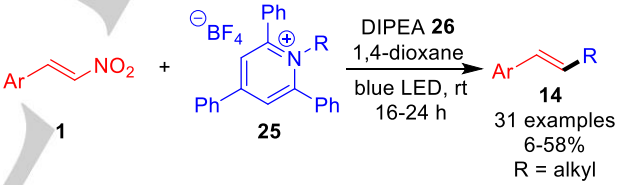
Scheme 20. Denitrative arylation/sulfonylation of nitroalkenes (Chawla, 2021)

There was no product detected in the absence of light and while using radical scavengers, suggesting a radical pathway for the reaction mechanism. Also, the formation of aryl-TEMPO adduct was detected by GC-MS. Based on these observations, a plausible mechanism is proposed. Upon irradiation with light, excitation of aryl diazosulfone **23** occur and further elimination of nitrogen gas releases the aryl radical **II** and sulfonyl radical **IV**. These radical then adds to the nitroalkene **1** to form benzyl radical intermediates **III/V** and subsequent elimination of nitrogen dioxide radical delivers the products **3/24** (Scheme 21).



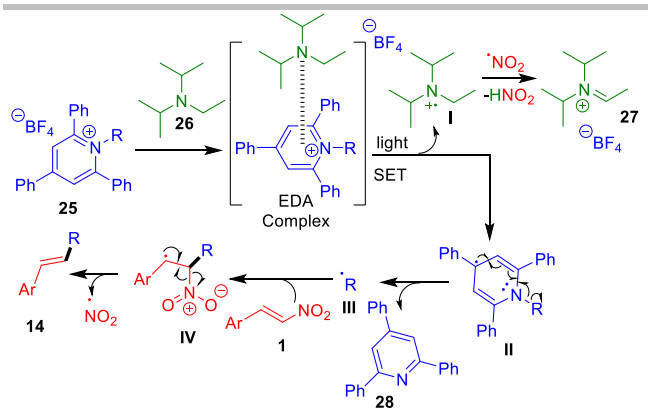
Scheme 21. Mechanism for the denitrative arylation/sulfonylation

In 2021, Jakubec *et al*. reported the denitrative alkylation of nitroalkenes **1** using *N*-alkylpyridinium salts **25** for the synthesis of functionalized alkenes **14** (Scheme 22).[63] The reaction worked well under photocatalyst-free conditions with blue LED irradiation at room temperature to afford the products **14** in moderate to good yields. Apart from varying electronically different substrates, a variety of *N*-alkylpyridinium salts **25** derived from biologically interesting compounds, including natural amino acids and Mexiletine (an antiarrhythmic drug), were also used in the reaction. Different functional groups were tolerated, such as primary benzylic, primary and secondary alcohol, etc. However, even at elevated temperatures, primary alkyl substrates could not couple with nitroalkenes **1**. The nitroalkenes **1** having substituents on the *α*- or *β*-*β*-di positions and those derived from alkyl substrates did not work well under the optimized conditions.



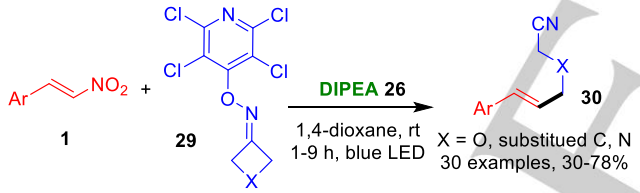
Scheme 22. Denitrative alkylation of nitroalkenes using *N*-alkylpyridinium salts

Reactions carried out using TEMPO as the radical scavenger led to the isolation of benzylated TEMPO adduct, suggesting the radical mechanism. Initially, the formation of the EDA complex with electron-rich DIPEA **26** and electron-poor *N*-alkyl pyridinium salt **25** followed by light irradiation forms the radical intermediates **I** and **II**. The radical intermediate **II** breaks into triphenyl pyridine **28** and radical **III**. The addition of this radical intermediate **III** to nitroalkenes **1** forms a benzylic radical **IV**, and further elimination of nitrogen dioxide radical delivers the coupling product **14** (Scheme 23).



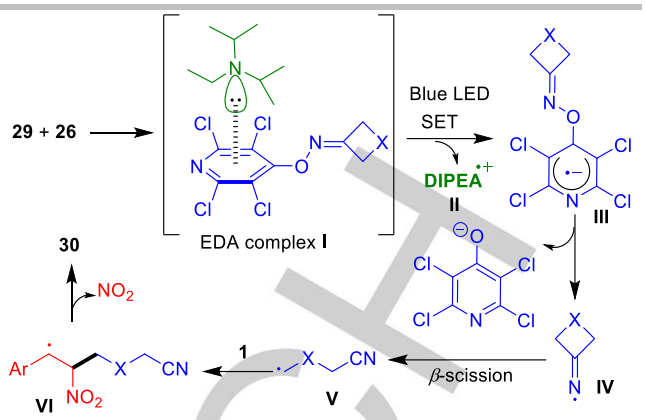
Scheme 23. Mechanism for the denitrative alkylation of nitroalkenes

Recently, in 2022 Yang *et al.* reported a photoinduced, photocatalyst-free cyanoalkylation of nitroalkenes **1** for the synthesis of cyanoalkylated alkenes **30** in appreciable yields (Scheme 24).[64] The Cyanoalkylation of nitroalkenes **1** was facilitated by the EDA complex, which involved a denitrative cross-coupling of *O*-aryl oximes **29** with nitroalkens **1**. The methodology was successfully explored over a variety of nitroalkenes **1** and *O*-aryl oximes **29**. The possibility of the formation of the EDA complex between DIPEA **26** and *O*-aryl oxime **29** was supported by UV−vis absorption experiments. To confirm the involvement of radical intermediates in the reaction, many controlled experiments were performed. Introduction of TEMPO greatly prevented the reaction, further the formation of radical scavenger and iminyl radical or cyanoalkyl radical adduct was detected by ESI-HRMS, which supported the radical pathway of the reaction.



Scheme 24. Denitrative cyanoalkylation of nitroalkenes (Yang, 2022)

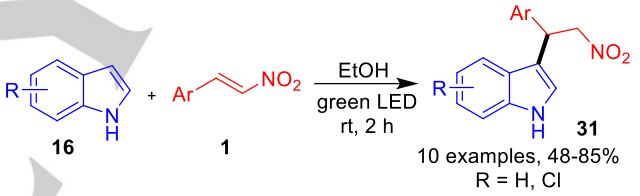
The proposed mechanism involved the formation of EDA-complex **I** between DIPEA **26** and *O*-aryl oxime **29**, which on photoexcitation generates radicals **II** and **III** *via* SET mechanism. The radical **III** delivered the iminyl radical **IV** *via* homolytic cleavage of the N−O bond. Then, the iminyl radical **IV** was converted to cyanoalkyl radical **V** by a *β*-scission. The regioselective addition of cyanoalkyl radical **V** to nitroalkene **1** delivered another intermediate **VI**, which delivers the product **30** after the elimination of the nitro group (Scheme 25).



Scheme 25. Mechanism for the Denitrative cyanoalkylation

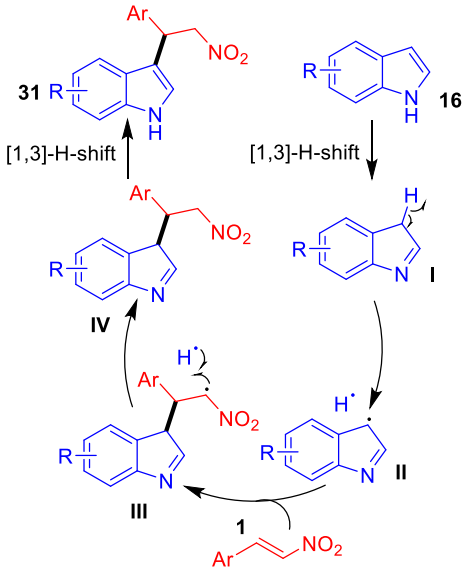
3. Addition reactions

Singh *et al.* in 2016 reported a green LED mediated Friedel-Crafts alkylation of indoles **16** with nitroalkenes **1** (Scheme 26).[65] The reaction proceeded smoothly in ethanol without any photocatalyst, and the products **31** were isolated in good yields. The reaction was highly regioselective, affording substitution at the 3-position of indole. Control experiments in the dark as well as in the presence of TEMPO demonstrated that the reaction goes through a photochemical-radical pathway.



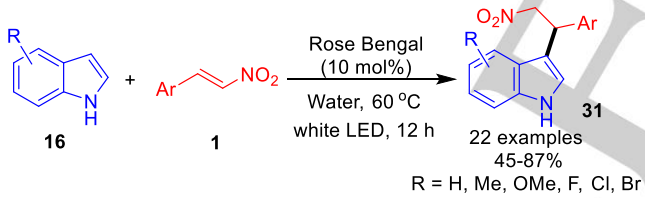
Scheme 26. Friedel-Crafts alkylation of indoles with nitroalkenes without photocatalyst (Singh, 2016)

The mechanism proposes that, in the presence of light irradiation, indole **16** undergoes a [1,3]-hydrogen shift followed by hydrogen atom removal to form the intermediate **II**. This radical intermediate **II** is then adds to the nitroalkene **1** in a Michael fashion to form nitronate radical intermediate **III**, which combines with the hydrogen atom to form intermediate **IV**. Further [1,3]-hydrogen shift affords the Friedel-Crafts alkylated adduct **31** (Scheme 27).



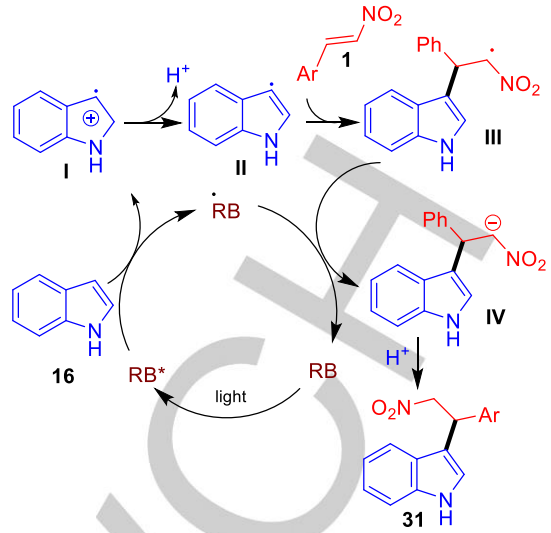
Scheme 27. Mechanism for the Friedel-Crafts alkylation of indoles in the absence of photocatalyst

In 2020, Meng *et al.* also reported a Friedel-Crafts alkylation of indoles **16** with nitroalkenes **1**. Rose bengal was used as the photocatalyst under visible light irradiation (Scheme 28).[66] Notably, the reaction was carried out in water affording the products **31** in moderate to good yields. However, a higher temperature (60 °C) was necessary to obtain the products **31** in good yields. The control experiments showed that the reaction proceeds through a radical pathway and does not require any oxygen atmosphere. The cyclic voltammetry experiments also found that the reaction between rose bengal and indole **16** was spontaneous.



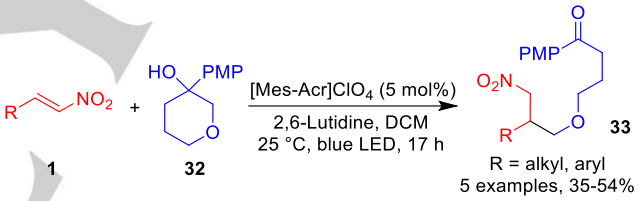
Scheme 28. Friedel-Crafts alkylation of indoles in the presence of photocatalyst (Meng, 2020)

Based on the control experiments conducted, a plausible mechanism is proposed in Scheme 29. Initially, rose bengal oxidizes the indole **16**, forming a radical cation **I**. Further deprotonation gives alkenyl radical **II**, which adds to the nitroalkene **1** forming a nitronate radical intermediate **III**. This intermediate **III** was oxidized by the rose bengal radical to form nitronate **IV**, and the catalyst was regenerated. Nitronate **IV** is then protonated to afford the alkylated indole **31**.



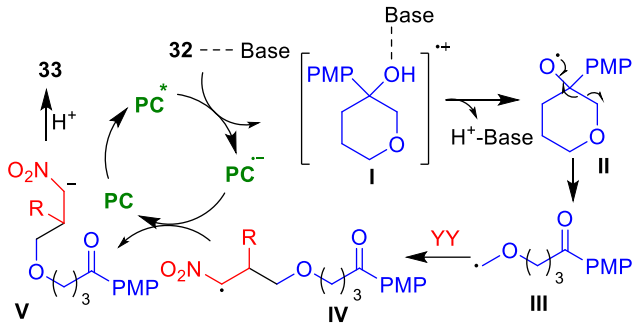
Scheme 29. Mechanism for the Friedel-Crafts alkylation of indoles in the presence of photocatalyst

Recently, in 2022 Alemán *et al.* reported the introduction of stabilized α-alkoxy radicals generated in the remote position of ketones into the *β*-position of nitroalkenes **1** (Scheme 30).[67] Activated cycloalkanols **32** were used as the precursor of alkyl/alkoxy radicals. Functionalization of nitroalkenes **1** proceeded smoothly using this methodology, albeit with moderate yields.



Scheme 30. Addition of α-alkoxy radical to nitroalkenes (Alemán, 2022)

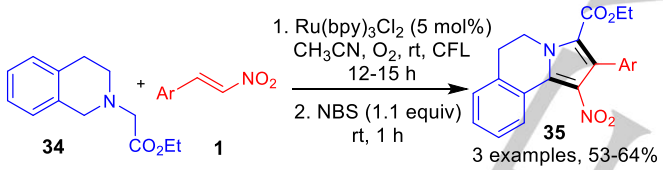
Plausible mechanism was proposed after a series of control experiments. The reported mechanism involves the oxidation of the *p*-methoxyphenyl ring in compound **32** by the photoexcited catalyst and delivering the radical cation intermediate **I**. Deprotonation of intermediate **I** by the base and concerted electron transfer leads to the formation of alkoxy radical **II**. Then the alkoxy radical **II** is converted to the alkyl radical **III** by a *β*-C-C bond cleavage, which on reaction with nitroalkene**1** forms another radical intermediate **IV**. Reduction of radical intermediate **IV** by the photocatalyst forming the anionic intermediate **V**, which on protonation delivered the product **33** (Scheme 31).



Scheme 31. Mechanism for the addition of α-alkoxy radical to nitroalkenes

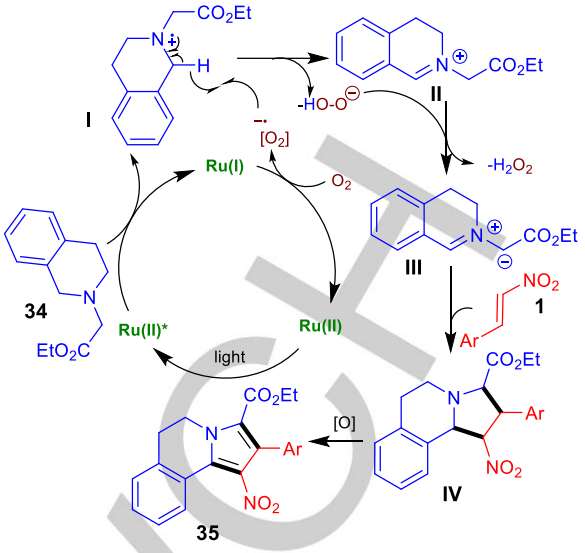
4. Cycloadditions/Cyclizations

In 2011, Xiao and co-workers reported a visible light-mediated oxidative cycloaddition-aromatization sequence of dihydroisoquinolines **34** with a wide variety of electron-deficient alkenes (Scheme 32).[68] Among other alkenes, different nitroalkenes **1** were also used in this reaction for the efficient synthesis of biologically important pyrrolo[2,1-*a*]isoquinolines **35**. The reaction was carried out in the presence of $Ru(bpy)_3Cl_2$ and molecular oxygen with CFL irradiation. Notably, adding NBS to the reaction mixture after consuming the starting material improved the yield and reaction time. The reaction was highly regiospecific, and only one regioisomer was observed.



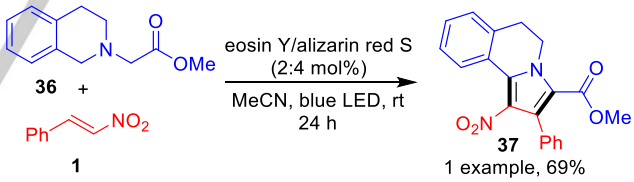
Scheme 32. [3+2] Cycloaddition of nitroalkenes (Xiao, 2011)

No product formation was observed in the absence of a photocatalyst, visible light or oxygen, which showed the role of photoredox catalysis. Photoexcited Ru (II) catalyst oxidizes the dihydroisoquinoline **34** to form the iminium ion **II**. Ru (II) was regenerated in the catalytic cycle using molecular oxygen. Deprotonation of the iminium ion generates the azomethine ylide **III**, which underwent a [3+2] cycloaddition with nitroalkenes **1**. Oxidative aromatization of the adduct **IV** affords the pyrrolo[2,1-*a*]isoquinolines **35** (Scheme 33).

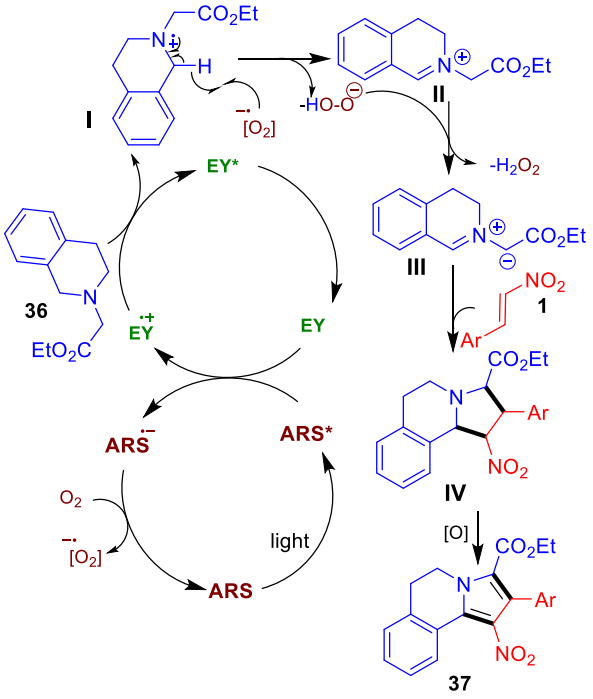


Scheme 33. Mechanism for the [3+2] Cycloaddition of nitroalkenes

Hosseini-Sarvari and co-workers employed β-nitrostyrene and tetrahydroisoquinoline ester for the construction of pyrrolo[2,1-a] isoquinoline frame work in one pot through a visible light mediated reaction (Scheme 34).[69] They used a combination of two organic dyes, as photocatalysts, for the cascade [3+2]-cycloaddition reaction. The Alizarin red S (ARS) and eosin Y (EY) combination was efficient to drastically improve the yield of the reaction rather than using them alone. The ARS got excited to ARS* by irradiation and a oxidative/reductive quenching between ARS* and EY afforded $EY^{\bullet+}$, which then transformed the tetrahydroisoquinoline into a radical cation. Deprotonation of this intermediate into an ylide which then underwent [3+2]-cycloaddition with *β*-nitrostyrene followed by oxidative aromatisation afforded the pyrrolo[2,1-a] isoquinoline.

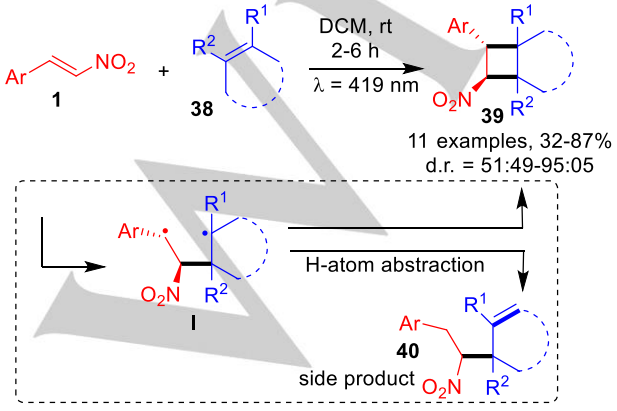


Scheme 34. [3+2] Cycloaddition of nitroalkenes (Hosseini-Sarvari, 2021)



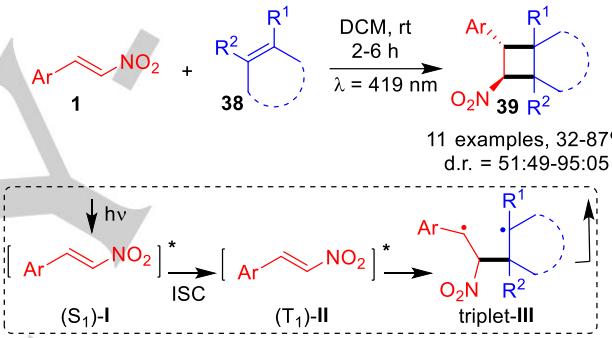
Scheme 35. Mechanism for the [3+2] Cycloaddition of nitroalkenes

Nitroalkenes are potential substrate for (2+2) photocycloaddition reactions, however their (2+2) photocycloaddition reaction with olefin is very less explored and most of the intermolecular (2+2) photocycloadditions were performed under short wave length irradiation.[70-71] In 2017, Bach and co-worker reported a (2+2) photocycloaddition reaction of nitrostyrenes with olefins irradiated by a longer wavelength light (λ = 419 nm) and the cyclobutane derivatives were isolated in moderate to good yields in a diastereoselective manner (Scheme 36).[72] This reaction is proposed to proceed via 1,4-diradical intermediate which is formed by photo excited addition of olefin to nitrostyrene. This 1,4-diradical readily transformed to cyclobutanes. The intermediacy of diradical was supported by the characterization of a side product XX (Scheme XX), formation of which can be explain from the 1,4-diradical intermediate. The formation of 1,4-diradical indicate that the reaction involves a triplet reaction pathway which was further supported by an experiment in which the reaction rate was accelerated on addition of triplet sensitizer 9H-thioxanthen-9-one.



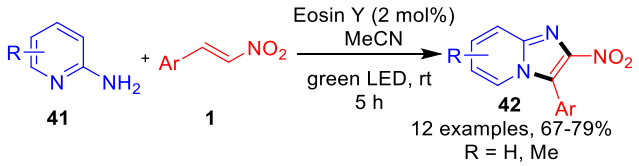
Scheme 36. [2+2] Cycloaddition of nitroalkenes (Bach, 2017)

In continuation to their previous work on intermolecular (2+2) photocycloaddition reaction of nitrostyrenes with olefins, in 2019, Bach *et. al.* reported the same (2+2) photocycloaddition reaction with improved reaction conditions, larger substrate scope and more mechanistic insights (Scheme 37).[73] The synthesis of cyclobutane derivatives from (2+2) photocycloaddition reaction of nitrostyrenes with olefins were reported under three different conditions *viz.* (i) at λ_{max} = 419 nm, ambient temperature, (ii) λ_{max} = 424 nm, ambient temperature and (iii) λ_{max} = 424 nm, -78 °C. The reactivity of differently substituted nitroalkenes and olefins were studied for the reaction and the cyclobutanes were isolated in moderated to good yields in most cases, however the nitroalkenes with electron withdrawing groups were found to be less reactive and the electron deficient olefins did not react under the optimized conditions. Detailed mechanistic studies were performed by the group in which the experimental evidences were provided to further support the involvement of 1,4-diradical intermediate and a triplet reaction pathway. When 1,1-dicyclopropylethylene was reacted with nitrostyrene along with normal cyclobutane derivative formation of a minor tricyclic product XX was observed. The formation of this side product was proposed from 1,4-diradical intermediate (Scheme XX).



Scheme 37. [2+2] Cycloaddition of nitroalkenes (Bach, 2019)

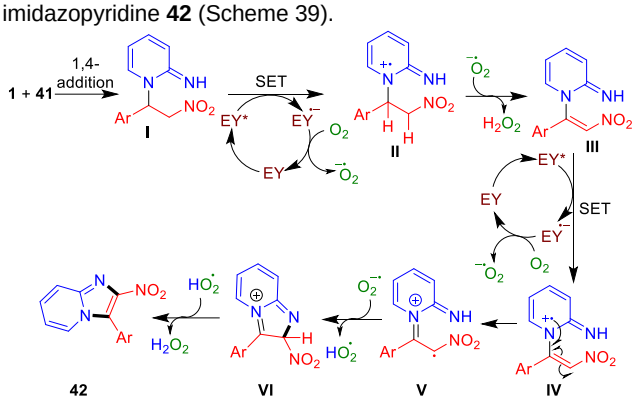
In 2016, Singh *et al.* reported the photoredox reactions of nitroalkenes **1** towards the synthesis of imidazopyridines **42** (Scheme 38).[65] 2-Aminopyridines **41** were reacted with nitroalkenes **1** in the presence of eosin-Y photocatalyst under green light irradiation to form imidazopyridines **42** in moderate to good yields with high regioselectivity. The presence of oxygen was necessary for the reaction as there was no reaction in its absence. Experiment with radical scavenger TEMPO clearly indicated that the reaction follows a radical pathway.



Scheme 38. Reaction of 2-aminopyridines with nitroalkenes (Singh, 2016)

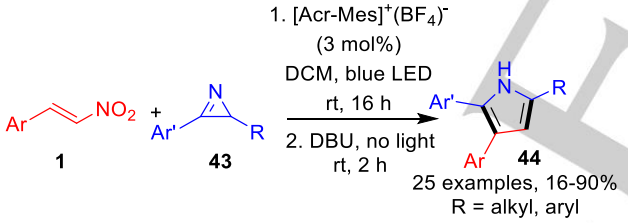
Initially, the 2-aminopyridine **41** undergoes a Michael addition with nitroalkene **1**, which further undergoes an oxidative quenching with photoexcited eosin Y to form a radical intermediate **II**. Eosin Y radical anion is then regenerated by molecular oxygen, forming a superoxide radical anion. The superoxide radical anion converts to the hydrogen peroxide by abstracting two hydrogen atoms from the intermediate

II,generating nitroalkene **III**. The nitroalkene **III** then undergoes another SET with photoexcited eosin Y to form radical intermediate **IV**, which further cyclizes intramolecularly, followed by hydrogen atom transfer delivers the imidazopyridine **42** (Scheme 39).



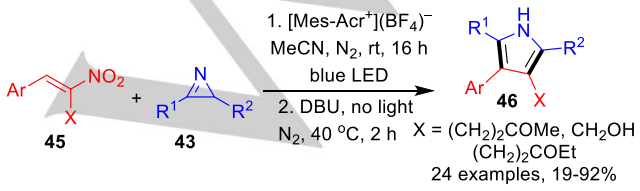
Scheme 39. Mechanism for the reaction of 2-aminopyridines with nitroalkenes

Rastogi *et al.* in 2019 reported a formal [3+2] cycloaddition of 2*H*-azirines **43** and nitroalkenes **1** in the presence of visible light for the synthesis of trisubstituted pyrroles **44** (Scheme 40).[74] Under metal catalysis, C-N bond cleavage of 2*H*-azirines **43** occurs,[75] while under photochemical conditions, C-C bond cleavage is found to be the pathway that leads to the formation of substituted pyrroles **44** after reacting with nitroalkene **1**. The reaction performed well in the presence of organicdye 9-mesityl-10-methylacridinium tetrafluoroborate with blue light irradiation. After the initial cycloaddition, the light source is removed, and the aromatization was achieved with DBU as the base.

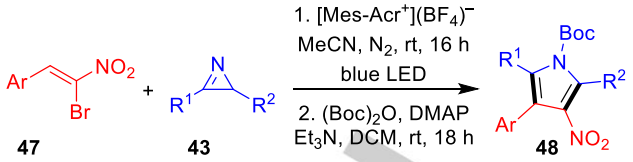


Scheme 40. [3+2] Cycloaddition of 2*H*-azirines and nitroalkenes (Rastogi, 2019)

Rastogi and co-workers later developed another photocatalytic [3+2] cycloaddition of *2H*-azirines with α-substituted nitroalkenes for the synthesis of highly substituted pyrroles by employing 9-Mesityl-10-methylacridinium tetrafluoroborate (Mes-Acr$^+$BF$_4^-$) as photocatalyst (Scheme 41 & 42).[76] The reaction of *2H*-azirines and nitroalkenes alcohol, ketone and ester groups at *α*-position yielded tetrasubstituted pyrroles upon [3+2] cycloaddition followed by the elimination of nitro group (Scheme 41), whereas, *α*-bromonitroalkenes afforded the debrominated pyrroles (Scheme 42).

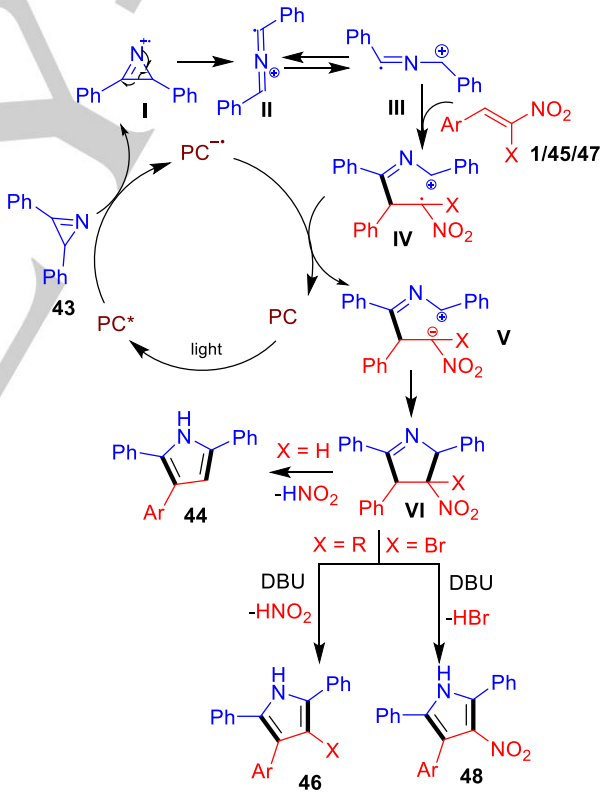


Scheme 41. [3+2] Cycloaddition of 2*H*-azirines and MBH adducts of nitroalkenes (Rastogi, 2012)



Scheme 42. [3+2] Cycloaddition of 2*H*-azirines and α-bromonitroalkenes (Rastogi, 2012)

There was no product formation in the absence of light or photocatalyst. Also, the involvement of 2-azaallenyl radical **II** was confirmed using a radical trapping reagent. Oxidative quenching of the azirine **43** with photoexcited catalyst forming azirine radical cation **I**. The ring opening of azirine radical cation **I** by a C-C bond cleavage gives 2-azaallenyl radical cation **II/III**. The radical cation **II/III** adds to the nitroalkene **1/45/47**, forming another intermediate **IV**, and further ring closure after reduction with photocatalyst gives the cyclic intermediate **VI**. While simple nitroalkene **1** deliver trisubstituted pyrrole **44** after elimination of nitro group, a-bromonitroalkene **47** follows the elimination of bromide to form tetrasubstituted pyrrole **48**. MBH adducts of nitroalkenes **45** also undergo the elimination of nitro group forming tetrasubstituted pyrrole **46** (Scheme 43).



Scheme 43. Mechanism for the [3+2] cycloaddition of 2*H*-azirines and nitroalkene derivatives

5. Conclusions and outlook

In conclusion, various synthetic methodologies have been developed for the reactions of nitrostyrenes under visible light

photoredox catalysis. Several reaction partners were employed in the reaction to achieve synthetically challenging and biologically important molecules. Despite the noteworthy advancement in the visible light-mediated reactions of nitrostyrenes, several challenging opportunities remain. They include the development of different photocatalysts, use of challenging coupling partners, advances in asymmetric reactions, and synthesis of natural products, drug molecules and active pharmaceutical ingredients.

Keywords: Catalysis • Cycloaddition • Nitroalkene • Photoredox • Visible-light

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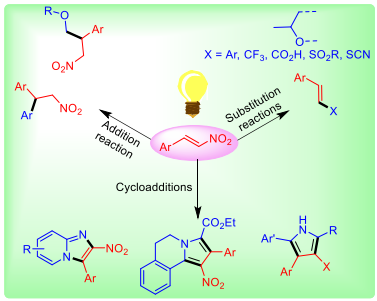

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