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Visible Light Photocatalysis-Controlled Reactions of N-Radicals

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Visible light photoredox-controlled reactions of N-radicals and radical ions

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Radicals are an important class of versatile and highly reactive species. Compared with the wide applications of various C-centred radicals, however, the N-radical species including N-centred radicals and radical ions, remain largely unexplored due to the lack of convenient methods for their generation. In recent years, visible light photoredox catalysis has emerged as a powerful platform for generation of various N-radical species and methodology development towards synthesis of diverse N-containing compounds. In this *tutorial review*, we highlight the recent advances in this rapidly delveloping area with particular emphases put on the working models and new reaction design.

Key learning points

- The visible light photoredox catalysis provides a powerful access to various versatile N-radical species.
- Advances in the photoredox catalytic generation of neutral N-centred radicals and reaction development.
- Advances in the photoredox catalytic generation of N-centred radical ions and reaction design.
- The current challenges and the future directions in the photochemistry of N-radical species.

Introduction

Free radical reactions represent a powerful class of chemical transformations and have attracted considerable attention from synthetic community because of their high efficiency and unique reactivity.[1-2] In particular, significant progresses have been made in the chemistry of carbon radicals over past several decades. Compared with the popularity of carbon-centred radicals, however, the synthetic utilities of N-centred radical species, including N-radicals and N-radical ions remain relatively unexplored due to a lack of general and convenient methods for their generation. The N-radical species are historically generated by stoichiometric radical initiators, thermolysis or photolysis.[3] However, the requirement for some hazardous radical initiators, elevated temperature, or high-energy UV irradiation largely limits their broad applications in modern synthetic chemistry.

Over recent years, visible light photocatalysis,[4] using visible light as a renewable energy source, has been established as a powerful and mild technique to facilitate activation of organic molecules and engineer new chemical processes selectively since the seminal studies from the groups of MacMillan,[5] Yoon,[6] and Stephenson.[7] In this context, such catalytic strategy has also proven to be a mild and general tool for conversion of N-containing compounds into highly reactive N-radical species in a controlled way, thus enabling achievement of a wide variety of new chemical reactions towards synthesis of diversely functionalized N-containing molecules. Elegant examples from the most recent literature also demonstrate the significance of this fast developing area of research. To our knowledge, however, there is still no review devoted to this emerging topic so far. Therefore, a tutorial review highlighting the main advances in this area should be timely and desirable, and will attract more research interests to this field. Therefore, we will highlight the recent advances on visible light photoredox-controlled reactions of N-radical species with particular emphases put on the working models. To calibrate the reasonable scope of this survey, this review is mainly organized based on different types of N-radical species and their precursors.

1. Neutral N-centred radicals

The C-N bonds are prominent functionalities in organic molecules and it is reported that about 84% of small-molecule pharmaceuticals contain at least one C-N bond.[8] The N-centred radicals have been established as a class of powerful intermediates and have found wide utilities in C-N bond forming reactions over the past decades.[3] However, general and mild methods for generation of N-centred radicals are still limited. Known approaches to access the N-centred radicals

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are mainly based on the reductive cleavage of the relatively weak N-N, N-O, N-S and N-X (X = Cl, Br) bonds. In most cases, the use of unstable radical precursors (e.g. N-X, N-nitrosoamides), radical initiators (e.g. AIBN, Et_3B/O_2), high reaction temperature or tedious preparation procedure for pre-incorporation of activation groups at the nitrogen atom has caused some limitations in functional group compatibility, substrate scope or practical synthesis. In addition, the direct oxidation of activated N-H bonds to N-centred radicals still relies on the use of stoichiometric strong oxidants such as DMP,[9] IBX[10] and DTBP[11] at elevated temperature. In recent years, the visible light photoredox catalysis has emerged as a powerful platform for the convenient generation of N-centred radicals under mild conditions (Fig. 1). Various N-O, N-S, N-N, N-X (Cl, Br) bonds were converted into the corresponding N-centred radicals via a single electron transfer (SET)-based reductive bond scission. In contrast, the direct transformation of N-H bond into the N-centred radical has recently been achieved through a SET oxidative process. By exploiting these highly reactive N-radical species, a variety of controlled C-N bond-forming reactions have been developed for efficient construction of structurally diverse N-containing compounds. Thus, in this part, the recent representative advances will be discussed according to different N-radical precursors.

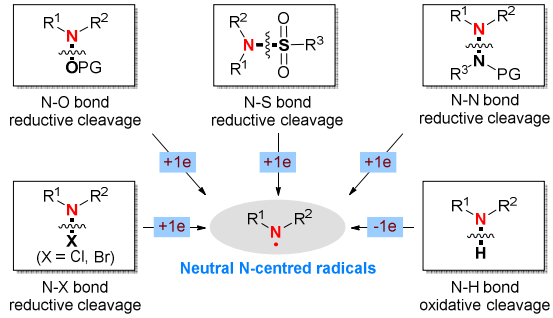
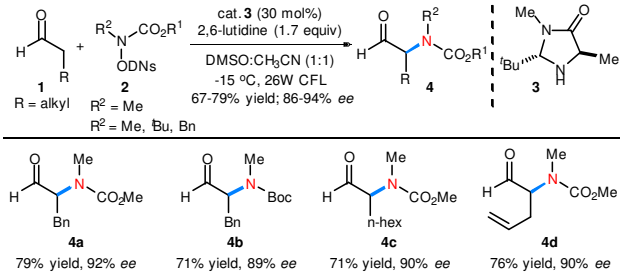


Fig. 1 Visible light photoredox catalytic generation of neutral N-centred radicals.

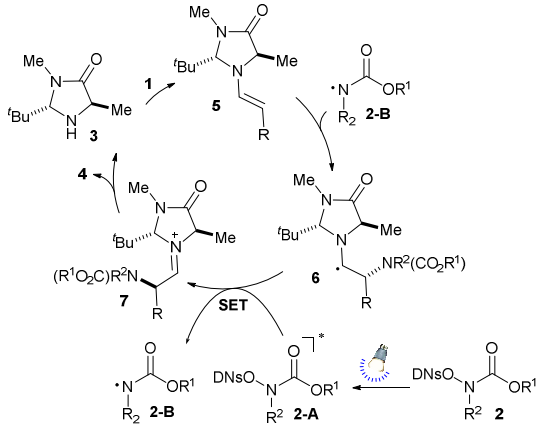
1.1 Conversion of N-O and N-S bonds into N-centred radicals

The weak N-O and N-S bonds are two highly attractive classes of N-radical precursors for the single electron transfer (SET)-based reductive generation of N-centred radicals by photocatalysis. As early as in 1990, Newcomb and co-workers reported a photoinduced conversion of the N-O bonds of N-hydroxypyridine-2-thione carbamates into N-centred radicals, which can be protonated *in situ* to produce the corresponding aminium cation radicals for subsequent intramolecular cyclization reactions under acidic conditions.[12] Inspired by this pioneering work, MacMillan and co-workers achieved a major breakthrough in this field in 2013.[13] They developed an elegant N-radical-mediated enantioselective direct α-amination of aldehydes by rationally merging visible light photocatalysis with asymmetric aminocatalysis (Scheme 1). It is found that the photolabile leaving group, dinitrophenylsulfonyloxy (ODNs), of the amine **2** is crucial to the success of this methodology, which can be selectively triggered to generate the corresponding N-centred radical upon visible light irradiation without any photocatalyst. Under the optimized conditions, various aldehydes **1** and amines **2** can be well tolerated to give the expected amination products **4** with good yields and enantioselectivities. Under this catalytic system, however, the α-dialkyl aldehydes prove ineffective probably due to their unfavourable condensation with chiral amine catalyst **3**.



Scheme 1 Enantioselective α-amination of aldehydes by combination of visible light photoredox catalysis and aminocatalysis.

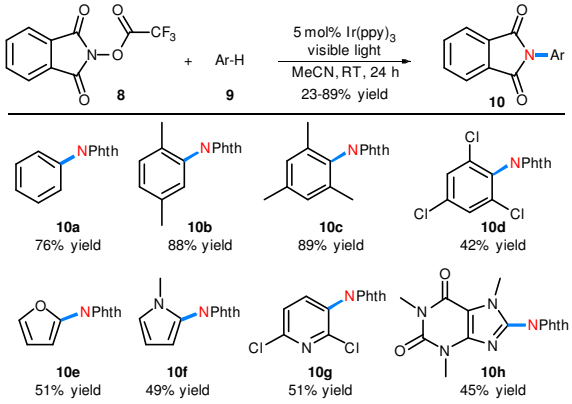
Based on the preliminary mechanistic studies, a SET-based mechanism was proposed for this reaction. As shown in Scheme 2, aldehyde **1** first reacts with the imidazolidinone catalyst **3** to form an electron-rich enamine **5**. Then, a rapid addition of an electrophilic N-centred radical **2-B** to the enamine intermediate **5** gives rise to the C-based radical **6**, which can be further oxidized to iminium ion **7** by another excited amine reagent **2-A** through a SET process. Finally, hydrolysis of iminium ion intermediate **7** delivers the desired products **4** and regenerates the chiral amine catalyst **3**.



Scheme 2 Proposed mechanism for photoredox catalytic enantioselective direct α-amination of aldehydes.

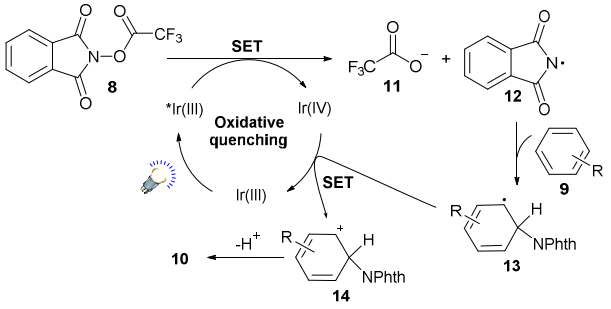
In 2014, the group of Sanford reported an interesting visible light photoredox catalytic C–H amination of arenes and heteroarenes with the use of N-acyloxyphthalimides as N-radical precursors (Scheme 3).[14] It is found that the electron-withdrawing substituents of N-acyloxyphthalimides are also vital for the generation of N-radicals by significantly enhancing the leaving ability of the carboxylate anion. The best results are obtained by employing trifluoromethylacyloxyphthalimide **8** as the N-radical precursor in the presence of 5 mol% *fac*-$Ir(ppy)_3$ as photocatalyst under visible light irradiation. Generally, high yields can be obtained in the cases of electron-rich arenes, while the arenes with electron-withdrawing

groups resulted in relatively lower yields. These observations confirmed the electrophilic nature of these N-radicals. Notably, heteroarenes such as furan, 1-methylpyrrole and pyridine can also react smoothly to give amination products in good yields.



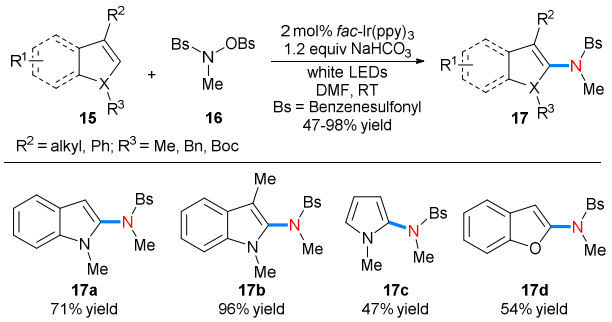
Scheme 3 Visible light photoredox catalyzed C-H amination of arenes and heteroarenes.

A possible catalytic cycle was proposed as shown in Scheme 4. First, the photoexcited *Ir(III) can be oxidatively quenched by trifluoromethylacyloxyphthalimide **8** via a SET process to generate the phthalimidyl N-radical **12**. Then, the N-radical intermediate **12** adds to the arene **9** to give the neutral radical intermediate **13**, which undergoes a sequential SET oxidation and deprotonation to deliver the expected product **10** and regenerate the ground state photocatalyst Ir(III) complex.



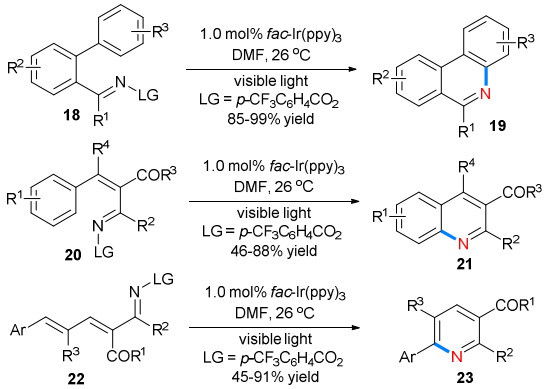
Scheme 4 Proposed mechanism for visible light photocatalyzed C-H amination of arenes and heteroarenes.

Shortly thereafter, a similar strategy was developed by the group of Yu.[15] Using the readily accessible hydroxylamine derivative **16** as a N-radical precursor, an efficient and broadly applicable visible light photocatalyzed direct C-H bond amination of various heteroarenes such as indoles, pyrroles and furans, has been achieved to produce the amination products **17** in moderate to good yields (Scheme 5). The key step of this transformation also involves a reductive cleavage of N-O bond of hydroxylamine derivative **16** to N-radical by the excited state photocatalyst *Ir(III); and the protecting group of N-radical precursors also has significant influence on this step. In accordance with Sanford's work, the electron-deficient heteroarenes did not work well either under the standard conditions.



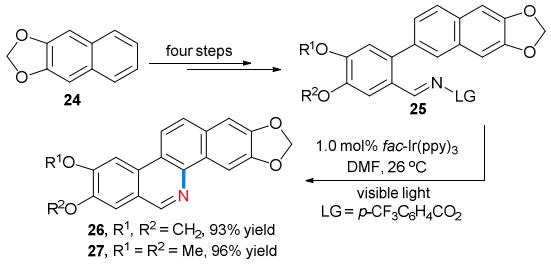
Scheme 5 Visible light photoredox catalyzed C-H amination of heteroarenes.

Historically, the cleavage of N-O bonds of acyl oximes to neutral N-radicals always requires transition-metal catalysis at elevated temperature or UV irradiation, which has caused some limitations in chemoselectivity or functional group tolerance.[3] In 2015, the Yu group reported an efficient catalytic formation of iminyl radicals from acyl oximes by visible light photoredox catalytic reductive cleavage of N-O bonds via a SET process (Scheme 6).[16] By employing these N-radical species, they achieved an intramolecular N-radical-mediated cyclization reaction of acyl oximes to produce various pyridines **19**, phenanthridines **21** and quinolines **23** with good to high yields. Notably, the authors also establish that the electron-withdrawing groups of acyl oximes are beneficial to the reaction efficiency, and *p*-trifluoromethylbenzoate was identified as the most effective leaving group.



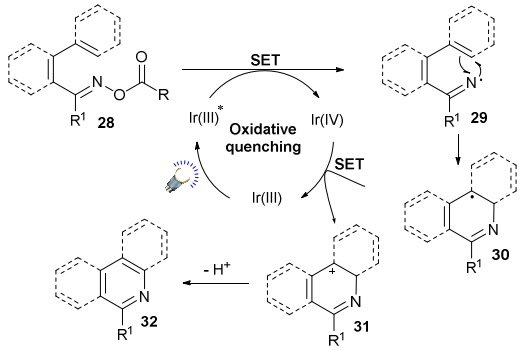
Scheme 6 Visible light photoredox catalyzed intramolecular C-H amination of heteroarenes.

Moreover, this method can be successfully applied to the concise total synthesis of biologically active benzo[c]phenanthridine alkaloids, noravicine **26** and nornitidine **27**, over five steps with good overall yields from the commercially available substrate **24** (Scheme 7).



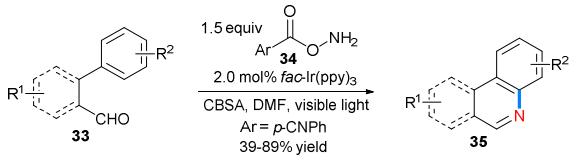
Scheme 7 Total synthesis of noravicine and nornitidine.

As shown in Scheme 8, the postulated catalytic cycle begins with the generation of excited state photocatalyst *Ir(III) upon irradiation by a 5W white LEDs. Then, it is oxidatively quenched by acyl oximes **28** through SET to give rise to oxidizing Ir(IV) complex and key iminyl radicals **29**, which further undergoes an intramolecular radical cyclization to form new neutral radical intermediates **30**. Another SET oxidation of **30** by the oxidizing Ir(IV) complex gives cationic intermediates **31** and regenerates the ground state photocatalyst. A final deprotonation of **31** gives rise to the expected aromatization product **32**.



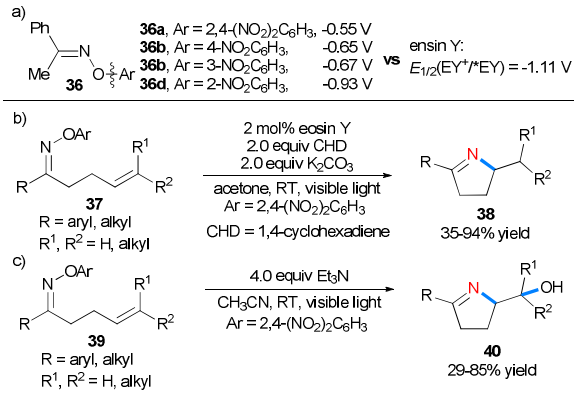
Scheme 8 Proposed mechanism for visible light photocatalyzed iminyl radical-mediated intramolecular cyclization.

Shortly thereafter, the Yu group expanded this visible light photoredox catalytic protocol to a one-pot process for practical synthesis of phenanthridines and quinolines **35** from simple biaryl aldehydes or cinnamaldehydes **33** and O-acyl hydroxylamines **34** in the presence of *p*-Cl-benzenesulfonic acid (CBSA) as an additive (Scheme 9).[17] At the same time, Yu and co-workers also recently disclosed a visible light-induced iminyl radical-mediated intramolecular cyclization reactions of readily available 2-(N-arylcarbamoyl)-2-chloroiminoacetates via N-Cl cleavage with or without photocatalyst, affording valuable quinoxalin-2(1*H*)-one derivatives in good yields.[18]



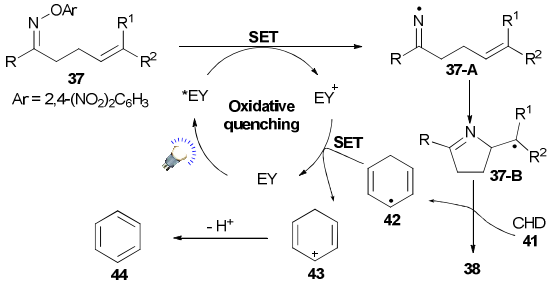
Scheme 9 Visible light photocatalyzed one-pot synthesis of phenanthridines and quinolines.

Quite recently, Leonori and co-workers reported analogous visible light-induced iminyl radical-mediated intramolecular hydroimination and iminohydroxylation of O-aryl oximes by using organic dye eosin Y as the photoredox catalyst (Scheme 10).[19] They investigated the reduction potential profiles of oximes **36** carefully by electrochemical studies to identify suitable activating groups. The results of Scheme 10a showed that all of the oximes **36a**-**36d** bearing nitro group on the phenyl ring can be reduced by the excited state photocatalyst eosin Y ($E_{1/2}(EY^+/^*EY)$ = -1.11 V) and **36a** appears to be more favorable owing to its relatively higher reduction potential (-0.55 V). Indeed, by using 2.0 equiv of 1,4-cyclohexadiene (CHD) as the hydrogen source in the presence of stoichiometric K_2CO_3 as base, a broad range of O-aryl oximes **37** undergo radical hydroimination smoothly to give pyrroline derivatives **38** in moderate to good yields (Scheme 10b). Notably, it is also found that an unprecedented visible light-induced radical iminohydroxylation cyclization of 2,4-dinitro-substituted oximes can also be achieved by combination Et_3N and CH_3CN without any photocatalyst (Scheme 10c). Control experiments and analysis of reaction mixture indicate that the oxygen atom in final product comes from the nitro group of 2,4-dinitro-substituted *O*-aryl oximes**.** During this transformation, an interesting reversible formation of electron donor-acceptor (EDA) complex of Et_3N/O-aryl oxime is postulated to be the key to the visible light-induced SET process and iminyl radical generation.



Scheme 10 Visible light photoredox catalyzed radical hydroimination and iminohydroxylation of O-aryl oximes.

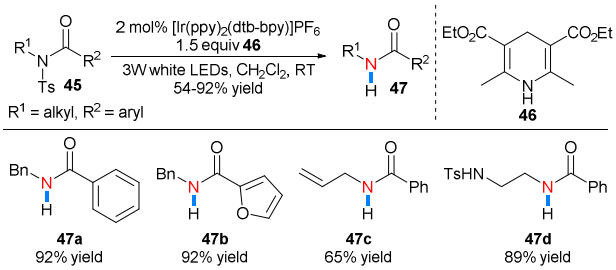
As shown in Scheme 11, it is postulated that O-aryl oximes **37** is initially transformed into iminyl radical **37-A** via a SET process, followed by a 5-*exo*-radical cyclization to give the C-centred radical **37-B** (Scheme 11). Then, the C-radical intermediate **37-B** abstracts a H-atom from CHD to deliver the product **38** with the generation of radical **42**. Finally, the radical **42** undergoes another SET oxidation to regenerate the ground state photocatalyst eosin Y.



Scheme 11 Proposed mechanism for photoredox hydroimination cyclization of O-aryl oximes.

The reductive cleavage of N-S bonds also provides a possible access to N-radicals. In 2013, Xiao and co-workers reported the first example of visible light-induced desulfonylation reaction of tosyl amides **45** by SET reductive cleavage of N-S bonds with the use of Hantzsch ester **46** as H-atom donor (Scheme 12).[20] The mild reaction conditions proves to be tolerant of various functional groups to give the corresponding desulfonylation products **47** in good yields. It is noteworthy that this protocol shows high chemoselectivity for desulfonylation of tosyl amides. For instance, the Ts group of

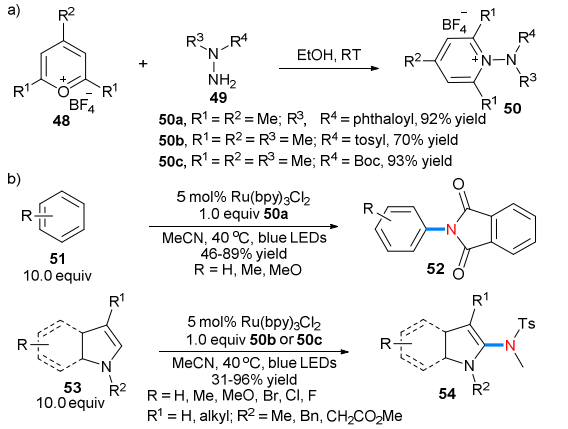
amides can be selectively removed to give the desired product **47d** in 89% yield, while the simple unactivated N-Ts group remains intact. Thus, this methodology provides a mild and practical alternative to traditional reductive desulfonylation of tosyl amides.



Scheme 12 Visible light photoredox catalyzed desulfonylation of tosyl amides.

1.2 Conversion of N-N bonds into N-centred radicals

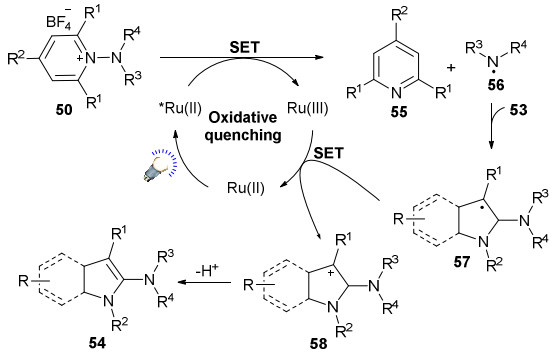
The rupture of the N-N bonds also provides an efficient to access N-centred radical species. Over the past decades, the N-containing precursors with relatively weak N-N bonds such as N-nitrosoamides, thiosemicarbazones, N-benzotriazolylimines, N-acyltriazenes and dihydropyridines, have been successfully applied to generation of the various N-radicals by thermolysis, UV irradiation or chemical initiation.[3] Despite the wide applications of these methods in organic synthesis, some limitations in generality still remain owing to the use of toxic, unstable reagents, or harsh reaction conditions. As a result, the search for more mild and efficient methods for conversion of N-N bonds into N-radicals is still highly desirable.



Scheme 13 Visible light photoredox catalyzed direct C-H amidation of arenes and heteroarenes.

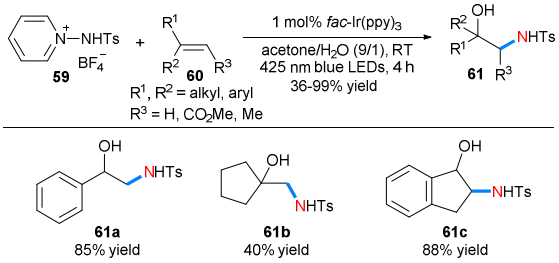
In 2015, the Studer group disclosed an elegant visible light-induced direct amidation of arenes **51** and heteroarenes **53** by using N-aminopyridinium salts **50** as the N-radical precursors under mild conditions (Scheme 13b).[21] Notably, these N-aminopyridinium salts **50a**-**50c** can be easily prepared on large scale by one-step reaction from commercial pyrylium salts **48** (Scheme 13a). These pyrylium salts are very stable and can be stored for months at room temperture. Using 5 mol% of $Ru(bpy)_3Cl_2$ as photocatalyst under visible light irradiation from blue LEDs, a wide range of amidation products of electron-rich arenes and heteroarenes can be obtained with good yields and complete regiocontrol. The N-Ac and N-Boc-protected indoles are not suitable for this reaction probably due to their lower activity toward the electrophilic N-radicals species.

A possible mechanism for this reaction is depicted in Scheme 14. An initial oxidative quenching of the photoexcited photocatalyst *Ru(II) complex by N-aminopyridinium salts **50** delivers the neutral N-centred radical intermediate **56** after cleavage of N-N bond and strongly oxidizing Ru(III) species. Then, an addition of N-radical **56** to heteroarene **53** delivers the C-centred radical **57**. Ultimately, another SET oxidation of **57** by the oxidizing Ru(III) and deprotonation of the resultant intermediate **58** gives rise to the final product **54** and closes the catalytic cycle.



Scheme 14 Proposed mechanism for direct C-H amidation of arenes and heteroarenes.

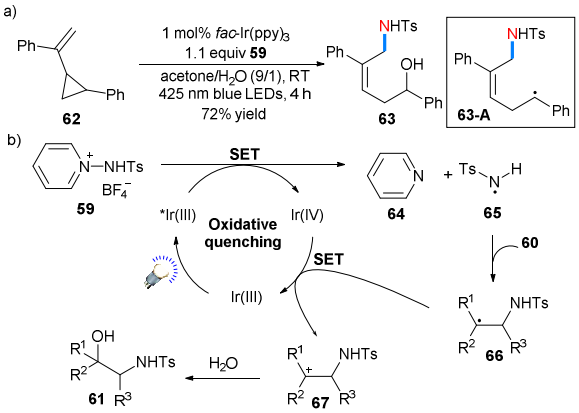
The group of Koike and Akita also recently identified a similar class of N-radical precursors and developed a photoredox catalytic aminohydroxylation of olefins for synthesis of vicinal aminoalcohol derivatives (Scheme 15).[22] It is also found that the amidyl radical source is critical to this transformation, and the N-Ts-protected 1-aminopyridinium salt **59** has proven to be the best of choice. Various styrenes and their derivatives **60** bearing electron-donating or -withdrawing substituents on the phenyl ring react smoothly in presence of 1 mol% of *fac*-Ir(ppy)$_3$ in a mixed solvent system (acetone/H_2O = 9/1) under visible light irradiation, furnishing the corresponding aminoalcohols **61** in good yields. In contrast, the aliphatic alkenes lead to less satisfactory results. Importantly, this methodology is also suitable for a gram scale reaction without apparent loss of reaction efficiency.



Scheme 15 Photoredox catalytic intermolecular aminohydroxylation of olefins.

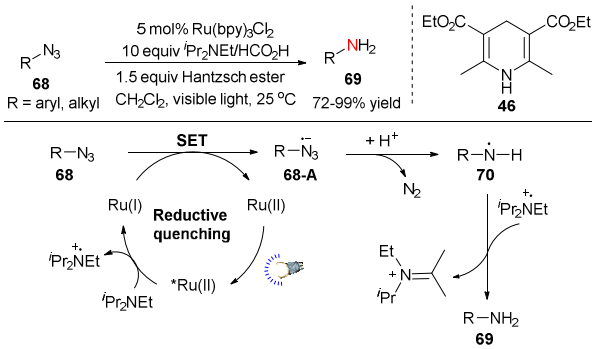
To further investigate the mechanism, a ring-opening radical clock reaction with 1-phenyl-2-(1-phenylethenyl)cyclopropane

62 has been conducted (Scheme 16a). Under the standard condition, the reaction also works well to afford the expected ring-opening product **63** with 72% yield, which suggested the involvement of radical intermediate **63-A** and radical nature of this process. As a result, a visible light photoredox catalytic SET-based radical mechanism was also postulated for this reaction. As shown in Scheme 16b, a SET oxidative quenching of the excited state *Ir(III) complex by 1-aminopyridinium salt **59** delivers the pyridine **64** and amidyl radical **65**. Then, the amidyl radical **65** undergoes a radical addition to alkene **60** to give a C-radical intermediate **66.** The C-radical **66** can be further oxidized by oxidizing Ir(IV) through another SET process to form cationic intermediate **67**, followed by nucleophilic attack of H_2O to give the final product **61** and close the photoredox catalytic cycle.



Scheme 16 Mechanistic study and proposed mechanism for photoredox catalytic aminohydroxylation of olefins.

Organic azides represent a class of versatile synthetic building blocks with wide applications in N-radical-mediated reactions for synthesis of diverse N-containing compounds.[23] Recently, the visible light-induced activation of organic azides and reaction design has attracted considerable attention from the synthetic community. In 2011, the Liu group reported an efficient visible light photoredox catalytic reduction of organic azides **68** using a combination of tertiary ammonium salt and Hantzsch ester as a hydrogen donor (Scheme 17).[24] The catalytic system proves to be tolerant of various functional groups, giving the corresponding primary amines **69** with good chemoselectivities and yields in organic or aqueous media. Notably, this mild protocol can be successfully applied to reduction of azide-containing biomolecules, such as DNA oligonucleotide and flavanone disaccharide-derived azides.

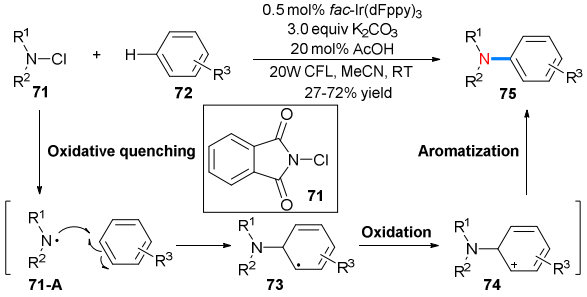


Scheme 17 Visible light photoredox catalytic reduction of organic azides and postulated mechanism.

As for the mechanism, it is postulated that the visible light photoexcited *Ru(II) complex is first reduced by DIPEA via a SET process to give the reduced form of the photocatalyst Ru(I) (Scheme 17). Then, azide **68** can be reduced by the reducing Ru(I) complex to form the azide radical anion **68-A**, which undergoes further N_2-extrusion and protonation to give the neutral aminyl radical **70**. Finally, the intermediate **70** abstracts a H-atom to give the final product **69**.

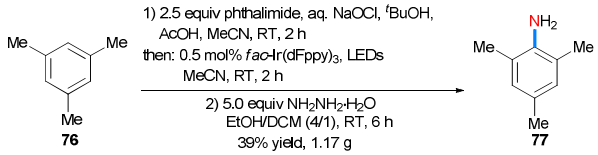
1.3 Conversion of N-X bonds into N-centred radicals

As a powerful alternative to access N-radicals, N-halo compounds, especially N-Cl bond, have also been often used to generate N-radicals owing to their easy preparation and high stability compared to its N-Br or N-I analogues. In 2014, Lee and co-workers reported an interesting visible light photocatalyzed generation of N-centred radicals from N-chlorophthalimide **71** for sp^2 C-H imidation of arenes and heteroarenes without introduction of any site-directing group (Scheme 18).[25] The mechanism begins with the oxidative quenching of photoexcited *Ir(III) complex by **71** to generate N-centred radical **71-A**, followed by radical addition/oxidation/aromatization sequence to give the amination products **75**. This reaction shows high functional group tolerance and broad substrate scope. Importantly, unlike the classical electrophilic amination of arenes, this protocol enables imidation of both electron-rich and electron-deficient arenes to give the corresponding products in moderate to good yields, albeit with moderate chemoselectivity.



Scheme 18 Visible light photocatalyzed amination of arenes and heteroarenes.

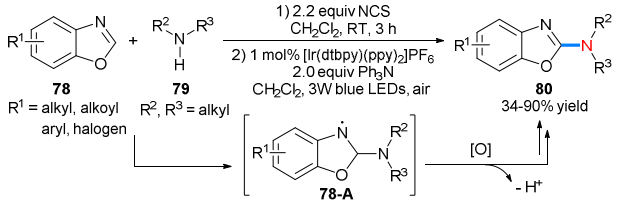
Notably, a gram scale reaction involving one-pot sequential N-chlorination/imidation/deprotection also proceeded well to give aminomesitylene **77** in 39% overall yield starting from simple phthalimide (Scheme 19).



Scheme 19 Gram-scale one-pot process for amination of mesitylene.

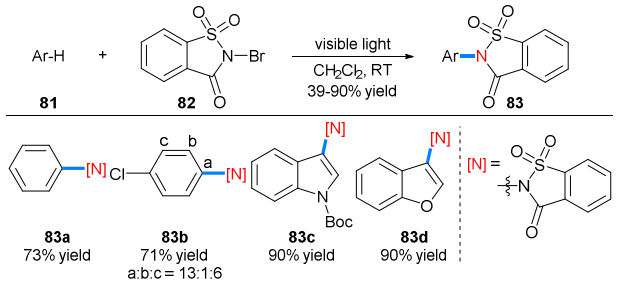
The Xue group also independently developed a similar photoredox catalytic two-step, one-pot reaction for amination of benzoxazoles using various cyclic and acyclic secondary

amines (Scheme 20).[26] In this reaction, the secondary amines are directly used as N-radical precursors, which can be initially transformed into the N-Cl compounds in the presence of stoichiometric NCS. The high functional group tolerance and broad scope with respect to both reaction partners render this strategy a practical access to biologically important 2-aminobenzoxazoles. On the contrary to Lee's work, a Ph_3N-mediated reductive quenching cycle is proposed for this reaction. And, the reduced photocatalyst Ir(II) undergoes a SET-reduction of the N-Cl bond to give the corresponding N-centred radical. Then, an addition of the N-centred radical to benzoxazole **79** gives the radical intermediate **78-A**, which could undergo a sequential SET-oxidation by oxygen or other existed oxidants and deprotonation to furnish the final aromatization product **80**.



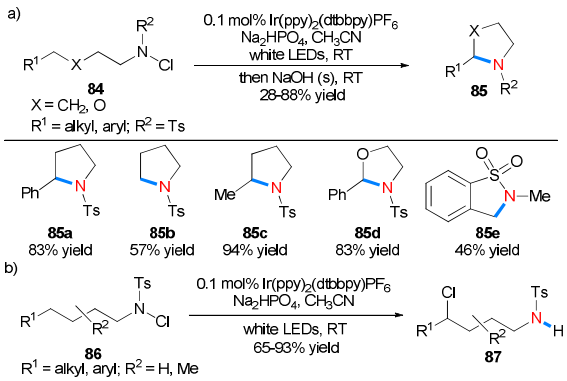
Scheme 20 Visible light photocatalyzed two-step, one-pot amination of benzoxazoles.

Interestingly, the Luo group recently disclosed a photoredox catalyst-free imidation of arenes and heteroarenes **81**, wherein the generation of N-centred radical was enabled by visible light-induced homolytic cleavage of the readily available and bench stable N-bromosaccharin (NBSA) **82** (Scheme 21).[27] It is also found that N-radical precursors are vital for this reaction. On the basis of DFT calculation and experimental results, NBSA **82** was finally identified to be superior as amine reagent over N-bromosuccimide (NBS) and N-bromophthalimide (PNBS). Under optimized conditions, a wide variety of electron-rich and electron-poor arenes and heteroarenes can be well tolerated to afford the expected amination products **83** with good yields and regioselectivity. However, some highly electron-rich aromatic rings, such as phenols and anilines failed to give the corresponding products.



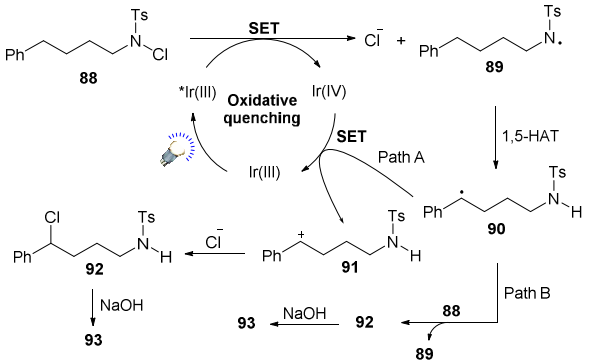
Scheme 21 Visible light photoredox catalytic imidation of arenes and heteroarenes.

Despite the impressive advances in the field of visible light photocatalyzed C(sp^2)-H amination/amidation, the variant of inert C(sp^3)-H bonds by photocatalysis remains largely unexplored. In 2015, the Yu group developed a visible light photoredox-mediated Hofmann-Löffler-Freytag (HLF) reaction[28] of N-chlorosulfonamides **84** under weak basic conditions at room temperature.[29] Interestingly, it is found that a lower photocatalyst loading leads to significantly increased yield by reducing the amount of dechlorination by-product. Under the standard conditions, a range of diversely functionalized pyrrolidines, oxazolidines and cyclic benzosulfonamides **85** were obtained in moderate to good yields (Scheme 22a). More importantly, without addition of NaOH (s), the initially chlorinated products **87** can be isolated in good yields (Scheme 22b), indicating that such chlorination products might be the key intermediates in cyclization reaction. Notably, this methodology can be also successfully applied to late-stage modification of biologically important N-containing compounds, (−)-*cis*-myrtanylamine and (+)-dehydroabietylamine.



Scheme 22 Visible light photocatalyzed remote C(sp^3)–H amidation and chlorination of N-chlorosulfonamides.

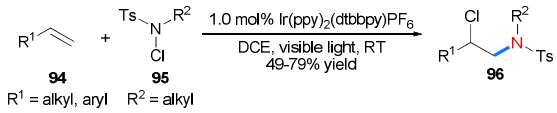
Based on the TEMPO trapping and radical clock experiments, a SET-based radical mechanism is also proposed (Scheme 23). The photoexcited *Ir(III) complex is first oxidatively quenched by N-chlorosulfonamide **88** to deliver the N-radical intermediate **89** and oxidizing Ir(IV) complex. Then, N-radical **89** undergoes an intramolecular hydrogen atom transfer (HAT) to give C-radical **90**, which is subsequently oxidized by Ir(IV) to generate cation **91** (path A). Finally, the intermediate **91** can be quickly trapped by chloride to give the chlorination products **92**, which can be easily further transformed into the cyclic products **93** upon subsequent addition of NaOH. At this stage, the radical chain propagation pathway might also be possible for the formation of **92** directly from C-radical intermediate **90** (path B).[30]



Scheme 23 Proposed mechanism for visible light photocatalyzed C(sp^3)–H amidation of N-chlorosulfonamides.

Recently, the group of Yu further expanded this strategy to a photoredox catalytic intermolecular chloramination of olefins **94** by employing N-chlorosulfonamides **95** as both N-radical

precursor and chlorine source (Scheme 24).[31] The reaction is also initiated by cleavage of the N-Cl bond of N-chlorosulfonamides **95** and terminated by a chlorine atom transfer or chloride anion addition process. A wide variety of styrene derivatives and aliphatic olefins **94** have proven to be suitable for this reaction, giving the corresponding chloramination products **96** in satisfactory yields.

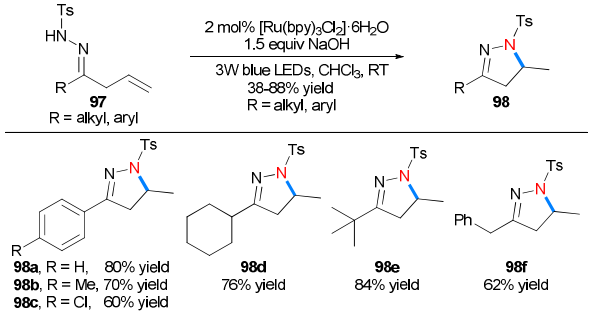


Scheme 24 Visible light photoredox catalytic regioselective chloramination of olefins.

1.4 Conversion of N-H bonds into N-centred radicals

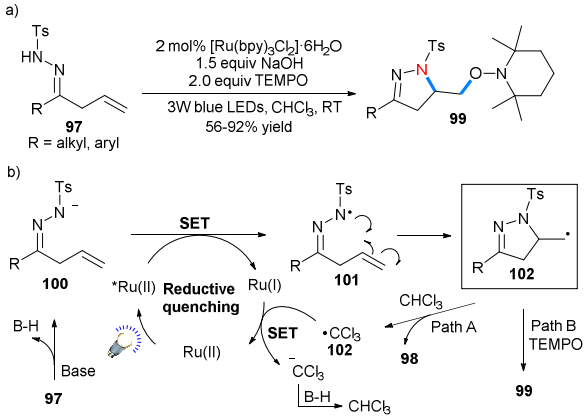
Over the past several years, remarkable advances have been achieved in the field of reductive scission of weak N-O, N-S, N-N, and N-halo (Cl or Br) bonds into N-radicals by photocatalysis as discussed above. Despite these impressive achievements, however, the development of more mild methods for direct conversion of strong N-H bonds into the N-centred radicals is still an attractive but challenging task for organic chemists. Classically, most of the known protocols for direct transformation of various N-H bonds into the corresponding N-centred radicals require harsh reaction conditions or use of sthoichiometric strong oxidants.[3]

Inspired by the pioneering works of Nicolaou,[9] Han,[32] Chiba,[33] Lei,[11] and Li[34] on direct generation of N-radicals from N-H bonds by use of strong stoichiometric oxidants, Xiao, Chen and co-workers in 2014 developed the first visible light-induced catalytic conversion of reluctant N-H bonds of β,γ-unsaturated hydrazones **97** into N-centred radicals under irradiation by 3W blue LEDs at room temperature (Scheme 25).[35] This protocol allows efficient intramolecular addition of hydrazonyl radical to the terminal alkenes, affording the corresponding hydroamination products, 4,5-dihydropyrazoles **98**, in good yields. The readily available of substrates, high functional group tolerance and mild reaction conditions are particularly attractive.



Scheme 25 Visible light photoredox catalytic N-radical-mediated hydroamination of β,γ-unsaturated hydrazones.

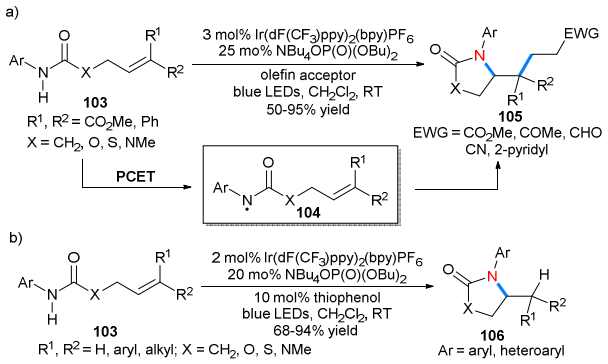
Interestingly, upon addition of TEMPO as radical trapping reagent, a synthetically useful radical oxyamination reaction of β,γ-unsaturated hydrazones **97** can be also achieved to give the corresponding oxyamination products **99** in moderate to high yields (Scheme 26a). These results also suggested the involvement of C-radical **102** in this process, which should be formed after addition of N-radicals to alkene. Based on a series of control experimental results involving deuterium-labeling, Stern–Volmer luminescence-quenching and on-off light, an N-centred radical-mediated mechanism is postulated for these reactions (Scheme 26b). An initial deprotonation of β,γ-unsaturated hydrazone **97** gives anionic intermediate **100** under basic condition, which can be easily oxidized to the key N-centred radical **101** by the photoexcited *Ru(II) complex via a SET process. Then, the intermediate **101** undergoes a 5-*exo*-radical cyclization to deliver the terminal C-radical intermediate **102**, which might proceed through two different pathways depending on the presence or absence of TEMPO. Without addition of TEMPO, intermediate **102** can abstract a H-atom from $CHCl_3$ to give the hydroamination products **98** (Scheme 26b, Path A) with generation of trichloromethyl radical **102**, which can regenerate the ground state photocatalyst Ru(II) via another SET oxidation process and close the photoredox catalytic cycle. In the presence of stoichiometric amount of TEMPO, the radical intermediates **102** can be trapped by TEMPO instead to afford the oxyamination products **99** (Scheme 26b, Path B).



Scheme 26 Visible light photoredox catalytic oxyamination of β,γ-unsaturated hydrazones and proposed mechanism.

Recently, the group of Knowles developed an elegant dual catalytic system for photoredox catalytic carboamination of alkenes by rational combination of photocatalyst and Brønsted base catalyst at room temperature (Scheme 27a).[36] It was established that the concerted oxidative proton-coupled electron transfer (PCET) activation allowed homolytic cleavage of the strong amide N-H bonds of olefin-containing amides **103** for generation of key amidyl radicals **104** without any strong stoichiometric oxidants. It is found that the Brønsted base is vital for the PCET process by modulating the oxidation potential of N-aryl amides through a H-bond interaction. The phosphate base, $NBu_4OP(O)(OBu)_2$, is identified to be superior to lutidine, DMAP or NBu_4OBz. Under the optimal conditions, the amidyl radical-mediated carboamination of various olefins **103** proceeded smoothly to furnish the corresponding heterocycles **105** in good yields. It should be noted that this dual catalytic strategy provides a new potential platform for direct activation of inert N-H bonds. Based on this work, the Knowles group further achieved an N-radical-mediated hydroamidation of substrates **103** by combination of a concerted photocatalyst/phosphate base-mediated PCET activation and a thiolphenol cocatalyst as H-atom donor

(Scheme 27b).[37] This strategy can also be applied to modification of bioactive molecules, progesterone and gibberellic acid-derived carbamates.



Scheme 27 Visible light photoredox catalytic alkene carboamination and hydroamidation.

2. N-Radical ions

N-Radical ions, especially N-centred radical cations, represent another versatile family of reactive radical species and have also found wide applications in C-N bond forming reactions over the past years.[3] Recently, the visible light photocatalysis has also been established as a mild tool for facile generation of these reactive species. In this context, depending on the properties of substrates, four main reactivity modes of N-radical cations have recently been disclosed (Fig. 2), including: further conversion into α-amino radicals **107** (Path A) or iminium ions **108** (Path B) upon release of a proton or H-atom, respectively; direct addition to electron-rich olefins for C-N bond formation (Path C); and conversion into new C-based radicals **110** through a ring-opening process (Path D). The first two reaction modes of N-radical cations have recently been summarized by MacMillan,[4] Xia,[38] Zheng,[39] and Lei.[40] Thus, in this part, we will highlight the recent advances about the last two reaction models of N-centred radical cations.

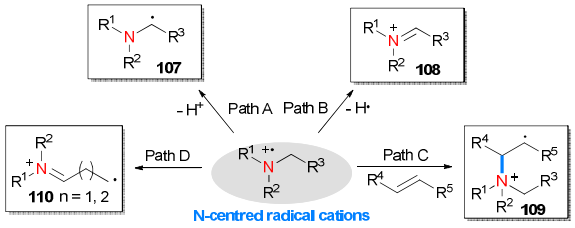
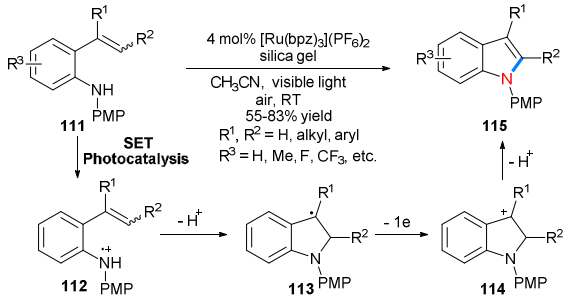


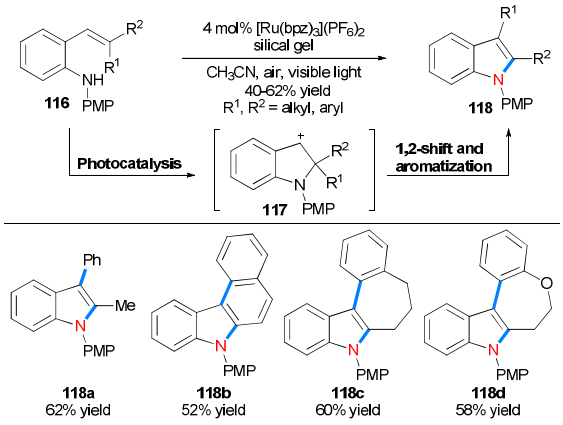
Fig. 2 Visible light photoredox catalytic generation of N-radical ions and reaction development.

2.1 Addition of N-centred radical cations to alkenes

In 2012, the group of Zheng reported the first example of photoredox catalytic generation of N-centred radical cations and application to the synthesis of N-arylindole derivatives from styrenyl anilines in the open air and under 18W white light LEDs irradiation (Scheme 28).[41] In this reaction, the N-*p*-methoxyphenylanilines **111** can be easily oxidized to their N-radical cations **112** by the photoexcited strongly oxidizing $Ru(bpz)_3^{2+}$ complex. Then, the intermediate **112** undergoes a sequential intramolecular cyclization/aromatization process to deliver the N-arylindole products **115** through intermediates **113** and **114**. A key feature of this protocol is the requirement for silica gel to significantly accelerate the reaction and improve the yields of the desired products. A range of electron-rich and electron-poor arylamines can participate in the reaction smoothly to give indole derivatives in good yields. More importantly, this methodology can also be extended to the synthesis of 2,3-disubstituted N-arylindoles from gem-disubstituted styryl anilines via a 1,2-carbon shift of the benzylic carboncation intermediate **117** (Scheme 29).

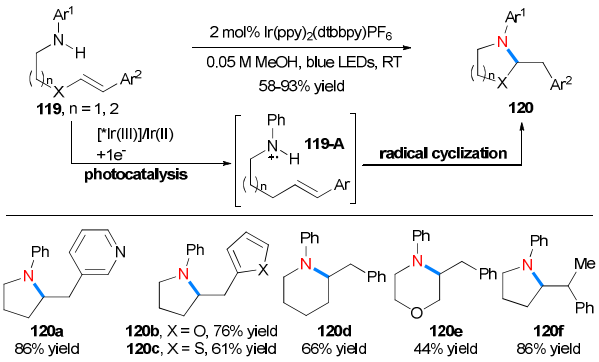


Scheme 28 Visible light photoredox catalytic N-centred radical cation-mediated C-N bond formation/aromatization reaction.



Scheme 29 Photoredox catalytic N-centred radical cation-mediated C-N bond formation/1,2-carbon shift/aromatization cascade.

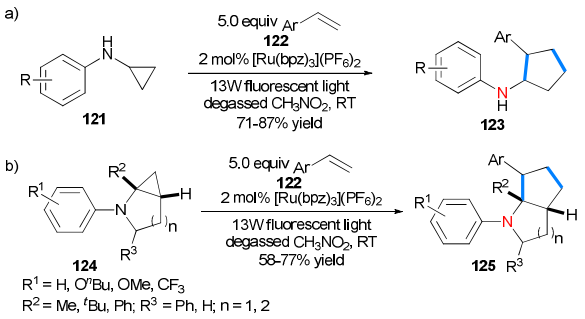
The development of aminium radical cation-mediated olefin amination in a catalytic fashion remains largely unexplored. In this context, the Knowles group recently reported the first example of visible light photoredox catalytic direct conversion of simple secondary amine **119** into aminium radicals **119-A**, and achieved an efficient intramolecular *anti*-Markovnikov hydroamination of olefins with these species (Scheme 30).[42] In contrast to the classic transition-metal-catalyzed olefin hydroamination, this strategy features mild reaction conditions, good functional group tolerance and operational simplicity. A wide range of structurally diverse N-heterocycles **120** have been obtained in generally good yields. Notably, the overall process is redox-netrual and obviates the use of any external oxidant.



Scheme 30 Visible light photoredox catalytic aminium radical cation-mediated olefin hydroamination.

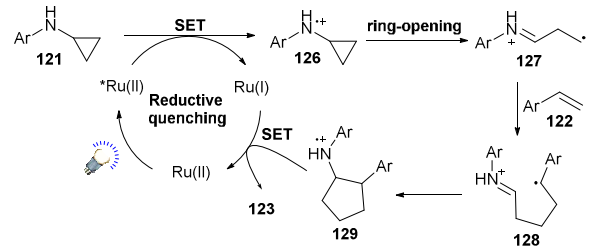
2.2 N-Centred radical cation-mediated cycloaddition

It has been well documented that cyclopropylamines can undergo irreversible opening of the cyclopropyl ring to *in situ* generate highly reactive species when they are oxidated to the N-radical cations. However, the generation of these nitrogen radical cations always require high-energy UV light irradiation or use of strong stoichiometric oxidants. In 2012, Zheng and co-workers reported an interesting photoredox catalytic N-radical cation-mediated intermolecular formal [3+2] cycloaddition of cyclopropylamines **121** and **124** with olefins under the mild conditions (Scheme 31).[43] Both of monocyclic and bicyclic cyclopropylamines were well tolerated to give the corresponding carbocycles **123** and heterocycles **125** with good regioselectivities and yields. However, the monocyclic tertiary amines proved to be not suitable for this reaction probably due to the slow rate of ring-opening step. As for the olefin partners, only substituted terminal styrenes worked well, while the internal olefins failed to deliver the desired products. Despite some limitations, this work opened a potential way for design of new catalytic cycloaddition modes with these N-centred radical cations. Shortly thereafter, the Zheng group further extended this strategy to an intermolecular [3+2] annulation of cyclopropylanilines with aryl- and heteroaryl substituted terminal alkynes.[44-45]



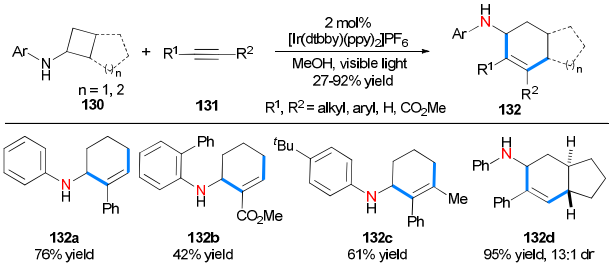
Scheme 31 Visible light photoredox catalytic N-radical cation-mediated [3+2] annulation of cyclopropylamines with alkenes.

A possible mechanism was also proposed for this reaction (Scheme 32). The photoexcited *Ru(II) complex first oxidizes the cyclopropylaniline **121** by a SET process to give the N-centred radical cation **126**. Because of the inherent cyclopropyl ring strain, an irreversible ring opening of **126** occurs to afford the β-carbon radical iminium ion **127**. Then, the intermediate **127** undergoes a sequential radical addition to terminal olefins and intramolecular cyclization to generate N-radical cation **129**. Finally, another SET reduction of **129** by the reducing Ru(I) complex gives rise to the product **123** with the concomitant regeneration of photocatalyst.



Scheme 32 Catalytic cycle for visible light photoredox catalytic [3+2] cycloaddition of cyclopropylamines with alkenes.

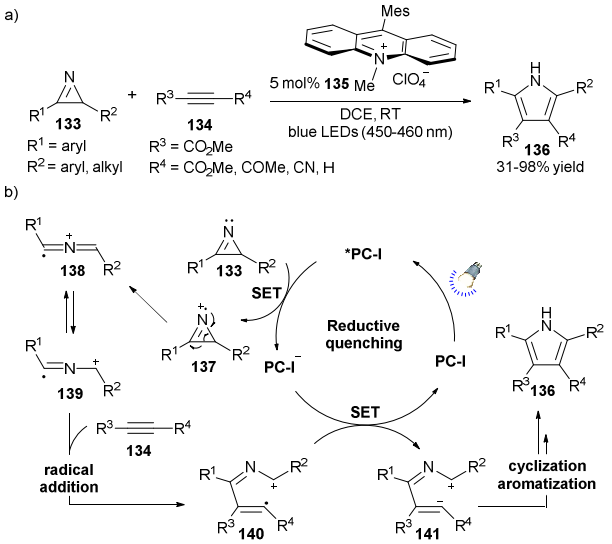
It is documented that the ring opening of cyclobutanes is typically much slower than that of cyclopropanes, while the strain energy of cyclobutane ring is similar to that of cyclopropane. It is the same case regarding cyclobutylcarbinyl radicals and cyclopropylcarbinyl radicals. As a result, development of N-radical cation-mediated cyclizations of cyclobutylanilines remains largely unexplored and a challenging task for chemists. Recently, the group of Zheng reported the first example of visible light photoredox catalytic formal [4+2] annulation of cyclobutylanilines **130** and alkynes **131**, wherein the cyclobutylaniline radical cations were also involved as the key intermediate (Scheme 33).[46] In this reaction, both terminal alkynes and internal alkynes reacted well with various electron-poor and -rich cyclobutylanilines to furnish the amine-substituted cyclohexene derivatives **132** in moderate to good yields. In addition, a range of bicyclic cyclobutylanilines also reacted well with alkynes to deliver the highly functionalized hydrindans and decalins with diastereoselectivities and good yields.



Scheme 33 Visible light photocatalyzed [4+2] cycloaddition of cyclobutylanilines with alkynes.

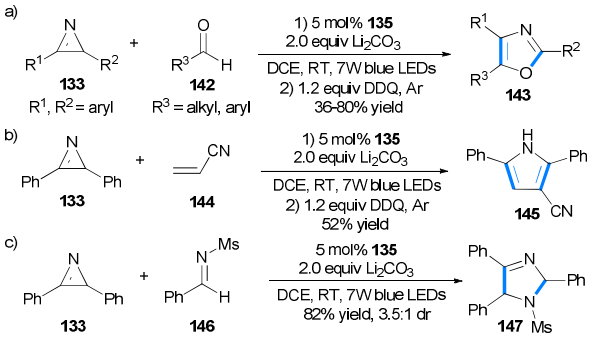
Since their first report by Neber and Burgard in 1932,[47] 2*H*-azirines have been widely used as valuable building blocks for synthesis of N-heterocycles by transition-metal catalysis or UV irradiation. In 2014, Xiao, Lu and co-workers developed a visible light photoredox catalytic formal [3+2] cycloaddition of 2*H*-azirines **133** with various electron-poor alkynes for high-yielding synthesis of densely functionalized pyrroles **136** using 9-mesityl-10-methyl-acridinium perchlorate as a photocatalyst (Scheme 34a).[48] It is worthwhile that this metal-free protocol can be successfully applied as the key step to the formal synthesis of HMG-CoA reductase inhibitor. Mechanistic studies indicated a reductive quenching cycle for this reaction. As shown in Scheme 34b, a SET reduction of the excited state

photocatalyst **135** by 2*H*-azirines **133** delivers the N-radical cation **137**, which undergoes a ring-opening to give the intermediate **138**. Then, a radical addition of **139** to alkynes **134** generates intermediate **140**. Ultimately, the intermediate **140** undergoes another SET oxidation by the reducing photocatalyst and intramolecular cyclization/aromatization to give the final product **136**.



Scheme 34 Visible light photoredox catalyzed [3+2] cycloaddition of 2*H*-azirines and possible mechanism.

Based on this work, the group of Xiao and Lu recently extended this strategy to a photoredox catalytic [3+2] cycloaddition/oxidative aromatization sequence of 2*H*-azirines and aldehydes for assembly of biologically important oxazoles (Scheme 35).[49] A series of aromatic and aliphatic aldehydes **142** are found to react well with 2*H*-azirines **133** to give the corresponding oxazoles **143** in moderate to good yields. More importantly, both of electron-deficient alkenes such as acrylonitrile **144** and N-Ms imine **146** also proved to be suitable for this reaction, producing pyrrole **145** and 2,5-dihydroimidazole **147** in 52% and 82% yield, respectively.



Scheme 35 Visible light photocatalyzed [3+2] cycloaddition of 2*H*-azirines with aldehydes, alkene and imine.

Conclusions and future prospects

In recent years, the visible light photoredox catalysis has been well established as a powerful tool for activation of N-containing compounds. A range of N-N, N-O, N-S, N-X (Cl, Br) and even strong N-H bonds can be easily transformed into the corresponding N-radicals and N-radical ions by photoredox catalytic reductive or oxidative cleavage. Employing these reactive species, a wide range of photoredox catalytic C-N bond forming reactions have been developed for synthesis of diversely functionalized nitrogen compounds.

Despite these advances, however, challenges still remain as follows: (1) the activation of other more challenging N-H bonds and exploration of new reaction modes; (2) the asymmetric variants of N-radical and radical ion-mediated reactions. We believe that the development of dual catalytic system by combination of the visible light photoredox catalysis with other catalytic strategies such as organocatalysis or transition-metal catalysis or use of chiral photocatalysts would provide potential solutions to those challenging problems.[50] More importantly, exploration of nitrogen compounds under these catalytic systems might lead to discovery of their novel reactivity or reaction modes, which are not accessible by using either single catalyst. Considering the relative youth of this emerging field, the development of many more impressive dual catalytic systems for the visible light photoredox catalysis-controlled reactions of N-radicals and radical ions can be envisaged in the near future.

Acknowledgements

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