VISIBLE LIGHT-INDUCED PHOTOCATALYTIC SYNTHESIS OF FIVE-MEMBERED NITROGEN HETEROCYCLES

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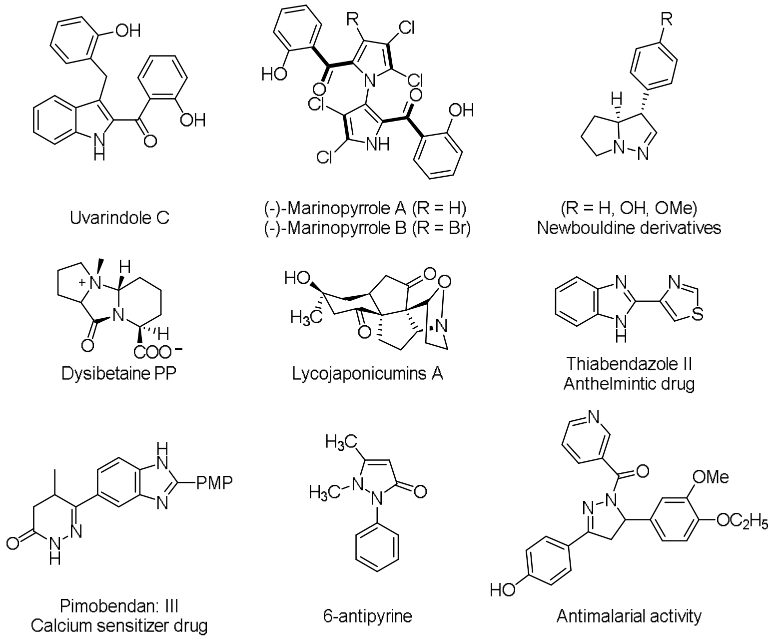
Abstract. *Five-membered nitrogen-containing heterocycles represent an important class of heterocycles widely found in many natural products and biologically active compounds. Over the past decades, great efforts have been devoted to the development of efficient catalytic methods for their synthesis. However, the development of mild and sustainable methods for the synthesis of structurally diverse nitrogen-containing heterocycles has remained an attractive but challenging topic. Recently, exploration of visible light-induced photocatalytic strategy for construction of these scaffolds has received considerable attention because of its inexhaustible, environment-friendly and efficient characteristics. Thus, this chapter will give a brief summary of recent advances in the visible light-induced synthesis of nitrogen-containing five-membered nitrogen heterocycles based on the different compound class.*

Contents

1. Introduction

Nitrogen-containing five-membered heterocycles represent an important class of heterocycles widely found in many natural products, pharmaceuticals and other biologically active compounds (Scheme 1).[1] For example, these privileged scaffolds could be found in the indole-based natural product Uvarindole C,[1a] pyrole-based Marinopyrrole A and B,[1b-1f] pyrazole-based Newbouldine derivatives,[1g] imidazole-based Dysibetaine PP,[1h] and isoxazolidine-based Lycojaponicumins A.[1i] They could also be found in numerous pharmaceuticals and other biologically active compounds, such as Thiabendazole II used as anthelmintic drug,[1j] pimobendan III,[1k] 6-antipyrine,[1l] and 1,3,5-trisubstituted pyrazolines.[1m] As a result, over the past few decades, considerable efforts have been devoted to the development of novel and efficient methods for the synthesis of these scaffolds.[2] Traditional methods for their synthesis typically depend on thermal transformations,[2a] transition-metal catalysis,[2b,2c] solid-phase synthesis[2d] and microwave acceleration.[2e-f] However, high temperature, additives or harsh conditions were often required in these processes.



Scheme 1. Selected natural products and biologically active compounds bearing five-membered nitrogen heterocycles.

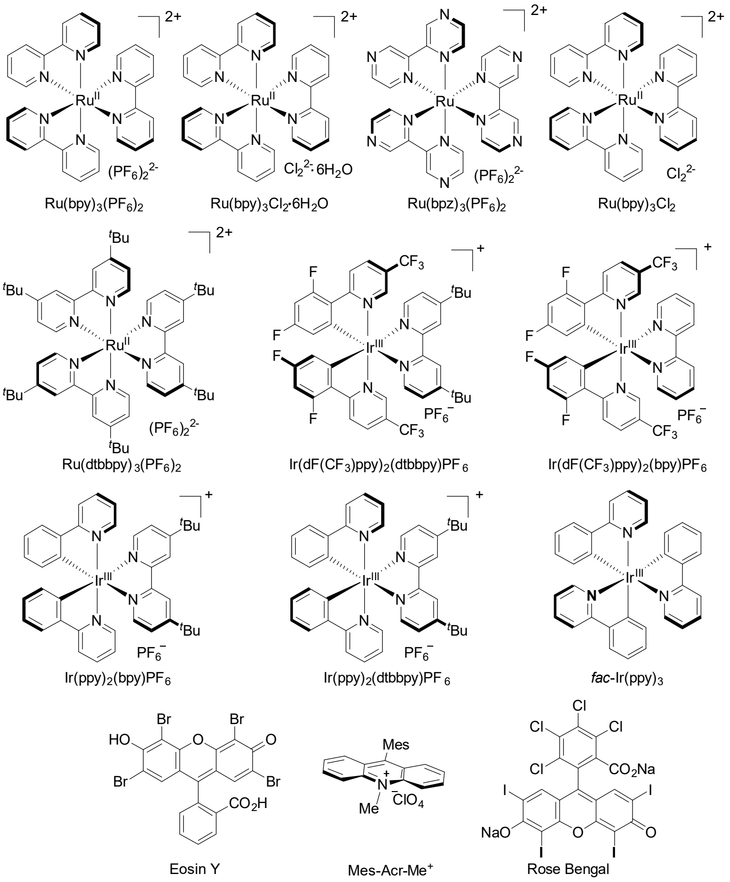
Recently, visible light-induced photocatalytic strategy has received considerable attention from the organic synthetic community because of the inexhaustible, environmentally friendly and efficient characteristics of sunlight.[3] Among most of the visible light photocatalytic reactions, the reactive species were generated relying on the synergetic effect of visible light and photocatalyst, becuase most organic molecules were easily activated by ultraviolet light rather than visible light. Thus, a variety of photocatalysts have been identified, most of which are ruthenium and iridium polypyridyl complexes, organic dyes, and inorganic semiconductors. The representative photosensitizers involved in this chapter were summarized in Scheme 2. And this chapter will give a brief summary of the recent advances on the visible light-induced photocatalytic synthesis of nitrogen-containing five-membered nitrogen heterocycles based on the different compound class.

2. Visible light-induced synthesis of pyrrole derivatives

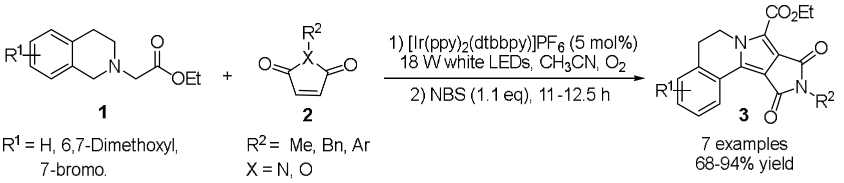
2.1. The synthesis of pyrroles

2.1.1. Visible light-induced formal [3+2] cycloaddition reaction

Visible light-induced formal [3+2] cycloaddition reaction represents a powerful approach toward synthesis of five-membered *N*-heterocycles.[4] In 2011, Xiao group reported a pioneering example of visible light-induced formal [3+2] cycloaddition of 1,3-dipole azomethine precursors **1** and dipolarophiles **2** using $[Ir(ppy)_2(dtbbpy)]PF_6$ as a photocatalyst (Scheme 3).[5] Employing this protocol, a diverse range of pyrrole scaffolds were constructed through a sequential oxidation/[3+2] cycloaddition/oxidative aromatization cascade in a one-pot manner under mild conditions, providing an efficient access to biologically important pyrrole-fused heterocyclic compounds in generally good yields (up to 94% yield). The reaction showed broad substrate scope and high functional group tolerance with respect to dihydroisoquinoline esters **1** and *N*-substituted maleimides **2**.

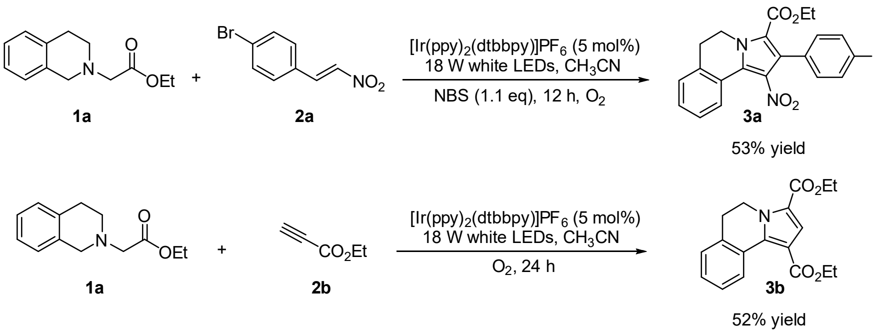


Scheme 2. Representative photosensitizers employed in visible light-induced synthesis of five-memberednitrogen heterocycles.



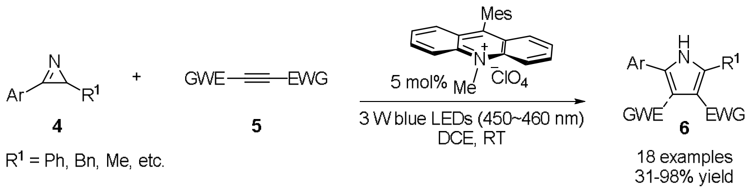
Scheme 3. Photocatalytic [3+2] cycloaddtion of dihydroisoquinoline esters and symmertrical dipolarophiles.

In addtion, the reaction with other dipolarophiles such as activated alkynes, acrylates and maleic anhydrides, could also proceed smoothly to afford the corresponding products in moderate yields. For example, when employing **2a** and **2b** as unsymmertrical dipolarophile components, the regioselectivity of the reactions was excellent and only single regioisomer was formed (Scheme 4). Interestingly, the photocatalytic system also worked well even when the oxygen was replaced by air, which greatly simplified the procedure.



Scheme 4. Photocatalytic [3+2] cycloaddtion of dihydroisoquinoline esters and unsymmertrical dipolarophiles.

Subsequently, Xiao and coworkers in 2014 further extended this strategy to non-tertiary amine precursors to achieve the synthesis of polysubstituted pyrroles without using metal photocatalyst.[6] As shown in Scheme 5, a veriaty of *2H*-azirines **4** and activated alkynes **5** participated in the reaction smoothly to give the desired pyrrole products **6** with generally good yields. This reaction was also tolerant of many functional groups. For example, both electron-withdrawing and electron-donating groups could be introduced to the aromatic ring of diaryl group substituted **4**, thus giving the products **6** with generally good yields. However, when introducing alkyl or vinyl groups to **4**, an obvious decrease of the yield was observed.

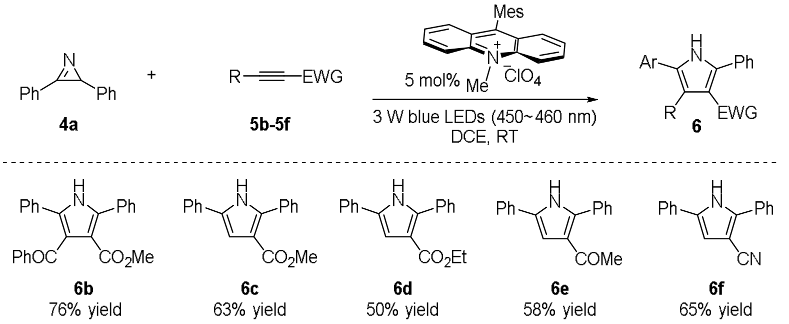


Scheme 5. Visible light-induced photocatalytic [3+2] cycloaddtion of *2H*-azirines and activated alkynes.

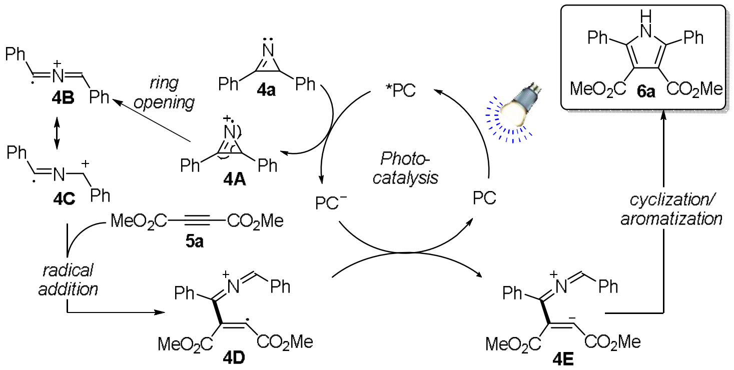
Moreover, significant variation in alkynes **5** could be tolerated even though the yields were somewhat lower. Methyl 4-oxo-4-phenylbut-2-ynoate, methyl and ethyl propiolate, but-3-yn-2-one, and propiolonitrile were all suitable dipolarophiles, providing the corresponding product in moderate yields (50-76% yield) (Scheme 6).

A plausible mechanism was proposed as shown in Scheme 7. The process of single electron oxidation of 2*H*-azirine occurred in the presence of the excited state of photocatalyst to give the radical cation intermediate **4A**. Then, the radical cation intermediate **4A** underwent a ring-opening to generate the 2-azaallenyl radical cation **4B** and its electronic isomer **4C**. Next, radical addition of **4C** to the activated alkyne **5a** delivered the intermediate **4D**, which underwent another SET oxidation to form the intermediate **4E**. Finally, a sequential intramolecular cyclization and aromatization process furnished the final polysubstituted pyrrole **6a**.

In 2015, the Glorius group developed an external-photocatalyst-free approach for the synthesis of valuable polycyclic pyrrole-based heterocycles.[7] As shown in Scheme 8, brominated pyridine **7** was treated with the bicyclic enol carbamate **8** in the presence hexamethyldisilazane (HMDS) as the base in trifluorotoluene under the irradiation of the blue LEDs. This reaction exhibits good tolerance. For example, a range of brominated pyridines with different functional groups, including halogens, cyano, eseter, aryl, alkyl, methoxy, and trifluoromethyl groups were well tolerated to give the desired products in generally moderate yields.



Scheme 6. Visible light-induced photocatalytic [3+2] cycloaddition of *2H*-azirines and unsymmertrical alkynes.

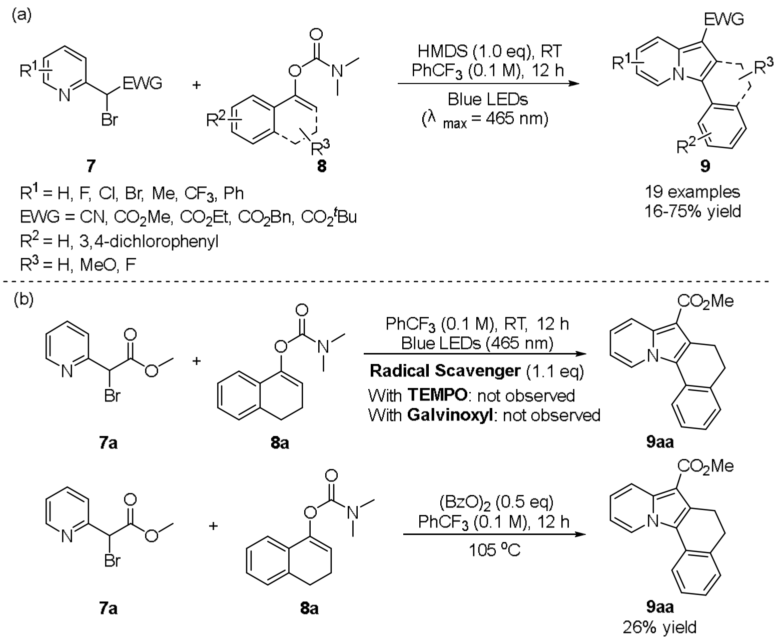


Scheme 7. The plausible reaction mechanism.

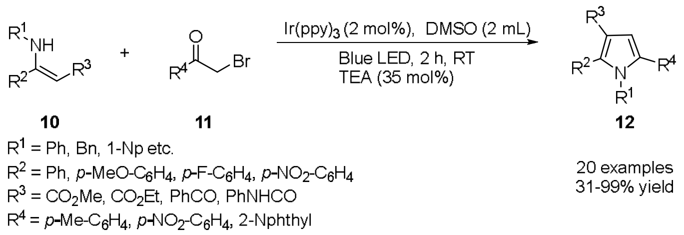
It was postulated that the mechanism may involve a radical chain process, which is supported by radical-clock experiments and the control reaction using the thermal radical initiator dibenzoylperoxide. In the radical-clock experiments, the reactions mixture were allowed to stir at rt for 12 h under irradiation of visible light from 5 W blue LEDs (λ_{max}=465 nm). The reaction mixture was analyzed by nanospray ESI mass spectrometry. In both cases, methyl 5,6-dihydrobenzo[g]pyrido[1,2-a]indole-7-carboxylate (**9aa**) was not observed. On the contrary, when adding radical initiator dibenzoyl peroxide to the reaction, a 26% yield of product **9aa** was obtained.

2.1.2. Visible light-induced Hantzsch reaction

In 1890, Hantzsch reported the synthesis of pyrrole by an equimolecular mixture of chloroacetone and acetoacetic ester under reflux in concentrated aqueous ammonia.[8] However, the Hantzsch pyrrole synthesis has received little attention form the synthetic community since its discovery. Until recently, further development of the Hantzsch pyrrole synthesis has been reported.[9] Traditionally, the Hantzsch reaction involves an S_N2 nucleophilic substitution between enamine and α-halo ketones, followed by dehydration condensation. However, high temperature, strong organic base or lewis acid are always required in these reactions. In 2016, Wu and coworkers reported a facile and efficient approach to the synthesis of polysubstituted pyrroles in a one-pot fashion by visible light photocatalysis at ambient temperature.[10] As shown in Scheme 9, the authors used 3-aryl-3-aminoacrylate **10** to react with α-bromo-1-aryl-ethanone **11** to give a range of polysubstituted pyrroles in generally good yields. This protocol represents an important advance in the Hantzsch reaction and opened a new potential way for development of a milder, greener, and more efficient process for the synthesis of 2,5-diaryl-substituted pyrroles.



Scheme 8. Visible-light-mediated external photocatalyst-free synthesis of polycyclic pyrrole-fused heterocycles.

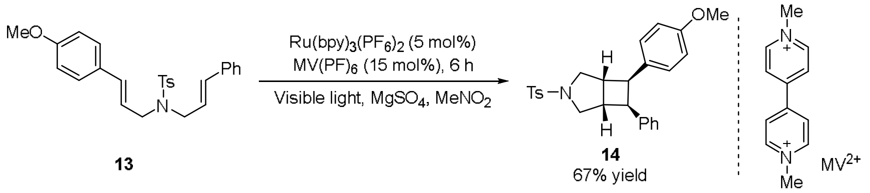


Scheme 9. Visible light-induced Hantzsch reaction for synthesis of pyrroles.

2.2. The synthesis of pyrrolidines and pyrrolines

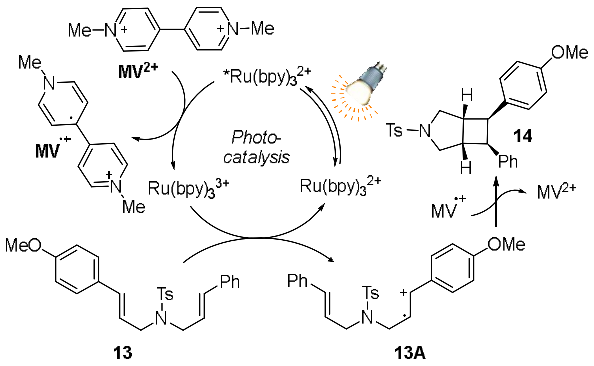
2.2.1. Visible light-induced formal [2+2] cycloaddition reaction

The [2+2] cycloaddition reaction represents a powerful method to build four-membered cyclic systems in oganic chemistry, and it can also enable construction of five-membered cyclic systems when using finely designed substrates. In 1908, the Ciamician group reported the first example of a photoinitiated [2+2] enone cycloaddition under irradiation of intense sunlight.[11] Since this pioneering work, however, the strategy of photoredox catalyzed [2+2] cycloadditon reaction initiated by visible light have developed slowly. Recently, the Yoon group reported the first example of visible light-induced intramolecular [2+2] cycloaddition of bis(enone).[12] Subsequently, several similar cycloaddition reactions were developed using similar strategy to give pyrrolidine heterocycles, which significantly extended the substrate scope. For example, in 2010, Yoon and co-workers reported that bis(styrene) **13** underwent intramolecular cycloaddition *via* a single electron transfer (SET) process upon irradiation of visible light to give pyrrolidine **14** in 67% yield using $Ru(bpy)_3(PF_6)_2$ as a photocatalyst and $MV(PF)_6$ as an oxidant (Scheme 10).[13]



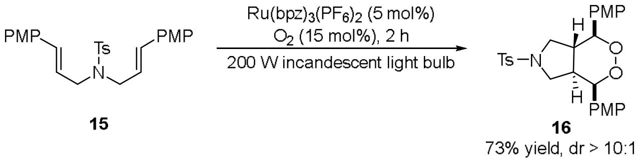
Scheme 10. Visible light-induced synthesis of pyrrolidine-fused compounds.

A plausible mechanism was outlined in Scheme 11. Firstly, upon irradiation of visible light, the photocatalyst $Ru(bpy)_3^{2+}$ was excited to give its excited state $^*Ru(bpy)_3^{2+}$, which was oxidated by oxidant **MV**$^{2+}$ *via* an oxidative quenching process to give radical cation intermediate **MV**$^{+}$ with release of the oxidative state $Ru(bpy)_3^{3+}$. Then, bis(styrene) **13** was oxidized to give radical cation intermediate **13A** by the $Ru(bpy)_3^{3+}$, completing the photocatalytic cycle. At the same time, the cation intermediate **13A** underwent intramolecular cycloaddition and SET reduction to give the desired product **14**.



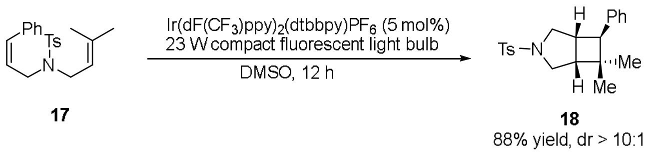
Scheme 11. The proposed mechanism.

In 2012, Yoon group employed molecular oxygen as oxidant and $Ru(bpz)_3(PF_6)_2$ as photosensitizer to achieve an aerobic [2+2+2] cycloaddition of bis(styrene) of type **15**, providing an efficient access to the synthesis of novle pyrrolidine-fused endoperoxide **16** (Scheme 12).[14]



Scheme 12. Visible light-induced [2+2+2] cycloaddition for synthesis of pyrrolidine-fused endoperoxide.

As shown in Schemes 10-12, the nature of the photoinduced SET processes resulted in that generation of the radical ion intermediates is limited to the electron-rich substrates. In contrast, the catalytic strategy of visible light-induced energy transfer provides an efficient complementary method. In 2012, the Yoon group described an interesting [2+2] cycloaddition of styrene **17** promoted by a photoinduced electron transfer process, wherein the electron donating group is not required; and the corresponding pyrrolidine-fused cyclobutane **18** was obtained in 88% yield (Scheme 13).[15]



17

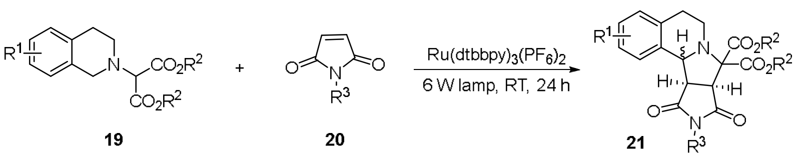
18

88% yield, dr > 10:1

Scheme 13. Visible light-induced [2+2] cycloadditin reaction for synthesis of pyrrolidine-fused cyclobutane.

2.2.2. Visible light-induced 1,3-dipolar cycloaddition reaction

1,3-Dipolar cycloadditions of azomethine ylides reprensent a versatile platform for the synthesis of synthetically and biologically important nitrogen-containing five-membered heterocycles. In 2011, the group of Rueping used *N*-alkyl tetrahydroisoquinolines (THIQ) **19** as the precursors of azomethine ylides to react with dipolarophile maleimides for synthesis of a class of fused pyrrolidine compounds **21** (Scheme 14).[16] Changing the electronic properties of the THIQ ring by introducing various electron-donating or electron-withdrawing groups has no obvious effect on reaction efficiency and selectivity. Interestingly, when one or two methoxy substituents were present in the aromatic ring， the reaction proceeded smoothly with slightly improved diastereoselectivities (up to 5:1 d.r.). In sharp contrast to the Xiao's methods for the synthesis of pyrroles,[5] this process of oxidative aromatization did not occur. As a result, extra oxidants were not necessary.



19

R^1 = H, F, Br, MeO, 6,7-(OMe)$_2$

R^2 = Me, Et

20

R^3 = Me, Ph

21

10 examples

56-67% yield

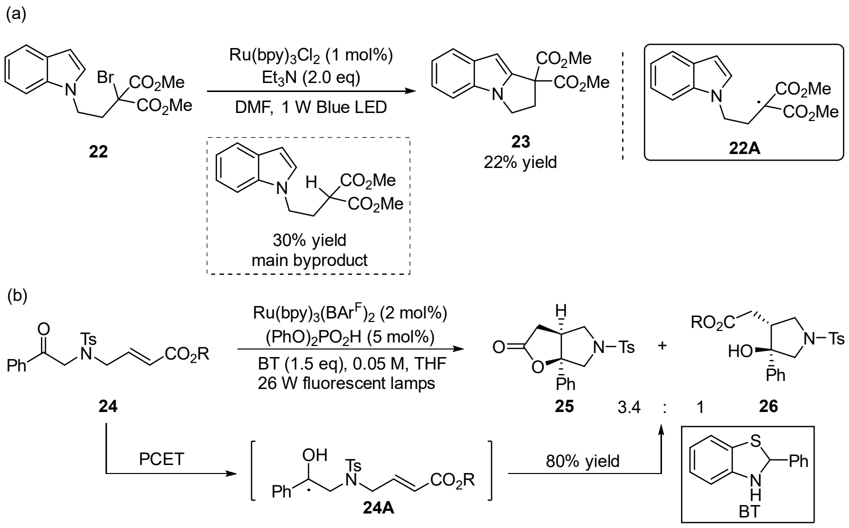
Scheme 14. Visbile light-induced 1,3-dipolar cycloaddtion of azomethine ylides and maleimides.

2.2.3. Visible light-induced radical cyclization reaction

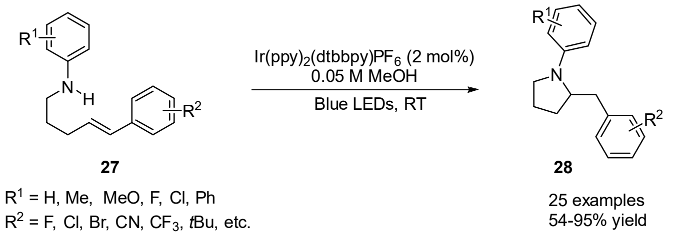
Radical and radical cation intermediates produced by visible light-induced photoredox catalysis are a useful class of reactive species and could participate in a wide range of radical addition reactions. In 2010, the Stephenson group developed a 5-*exo*-trig radical cyclization of indole derivative **22** by photoredox catalytic reductive dehalogenation reaction for the synthesis indole-fused pyrrolidines (Scheme 15a). In this reaction, the cyclized product **23** was obtained in 22% yield because of the preferential reductive dehalogenation.[17a] In 2013, Knowles reported an interesting visible light-induced intramolecular ketyl-olefin coupling of ketones **24** *via* carbon radical 5-*exo*-trig cyclization (Scheme 15b).[17b] In this reaction, substrate **24** cyclized smoothly to give products **25** and **26** in a combined 80% isolated yield as a 3.4:1 mixture of diastereomers when using 2-phenyl-dihydrobenzothaizoline (BT) as a H-atom source.

Shortly after, Knowles achieved an intramolecular olefin hydroamination *via* nitrogen radical-based cation 5-*exo*-trig cyclization reaction of simple amines **27** to synthesize *N*-aryl pyrrolidines **28** (Scheme 16).[18] Employing Ir(ppy)$_2$(dtbbpy)PF$_6$ as a photocatalyst, a variety of substituted aniline substrates of type **27** bearing electron withdrawing or donating groups such as H, Me, MeO, F, Cl, Ph were all well tolerated to give the corresponding products **28** with up to 95% yield. Meanwhile, the scope of styrenyl acceptors was also extensively evaluated. Changing the electronic properties or modifing the steric hindrance of the styrenyl acceptors did not have any obvious effect on the reaction efficiency.

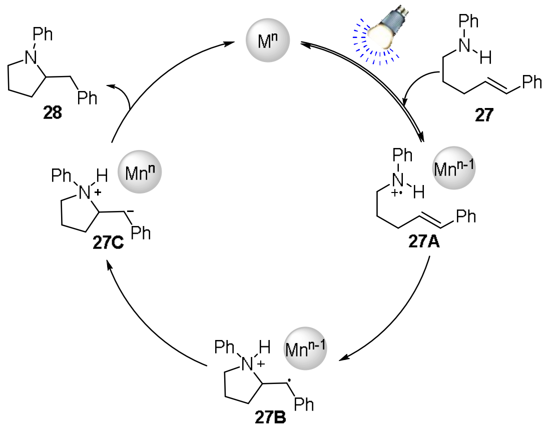
The mechanism was proposed as depicted in Scheme 17. Initially, aminium radical cation **27A** could be generated from the process of single electron oxidation upon the irradiation of visible light. Then, the aminium radical cation **27A** underwent intramolecular olefin addition to form C-N bond and carbon radical **27B**, which was in turn reduced by the reduced form of photocatalyst to give carbanion **27C**. At last, a favorable proton transfer process occurred to result in the desired hydroamination product **28**.



Scheme 15. Visible light-induced carbon radical cyclization reactions.

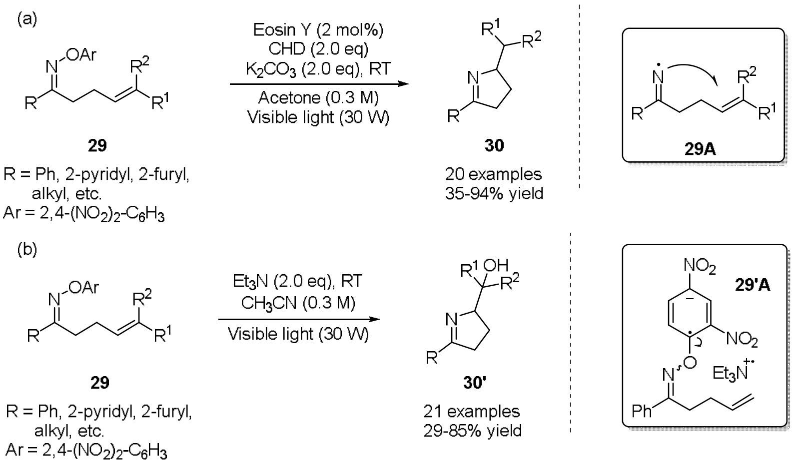


Scheme 16. Visible light-induced nitrogen radical cation-based 5-*exo*-trig cyclization reaction.



Scheme 17. The proposed mechanism.

In addition to the wide use of the nitrogen radical cations towards nitrogen-containing heterocycles, there was emerging research interest about the exploration of neutral nitrogen radicals because of its wide applications in the synthesis of *N*-containing molecules.[19] For example, Leonori described a novel visible light-induced divergent hydroimination and iminohydroxylation cyclization by using finely designed *O*-aryl oximes substrates (Scheme 18).[20] Employing organic photocatalyst Eosin Y under visible light-irradiation, oximes **29** could undergo *N*-radical cyclization smoothly in the presence of cyclohexadiene (CHD) as H-atom source and K_2CO_3 as the base, giving pyrrolines **30** in good to excellent yields. Changing the electronic properties *via* modifing the substituents on phenyl ring did not have any obvious effect on the reaction efficiency. Moreover, oximes bearing 2-pyridyl, 2-furyl, 2-naphthyl were also well tolerated in this reaction. In addition, the substrate scope could be extended to a series of aliphatic group-substituted oximes. It was postulated that the mechanism mainly involved the photocatalytic generation of iminyl radical **29A** as the key intermediate *via* a SET reduction, which underwent an intramolecular 5-*exo*-trig radical cyclization to give the desired pyrroline compounds **30**. Considering the low reduction potential and LUMO energy of the 2,4-dinitro-substituted aryl oximes **29**, Leonori and co-workers develped a complementary activation mode for generation nitrogen radical (Scheme 18b). In this process, visible light-irradiation of oxime **29** in the presence of stoichiometric Et_3N led to formation of an electron donor–acceptor complex **29A**, which also then generated iminyl radical to allow for a 5-*exo*-trig radical cyclizaion and oxidation sequence for synthesis of iminoalcohols **30'** in good to high yields.



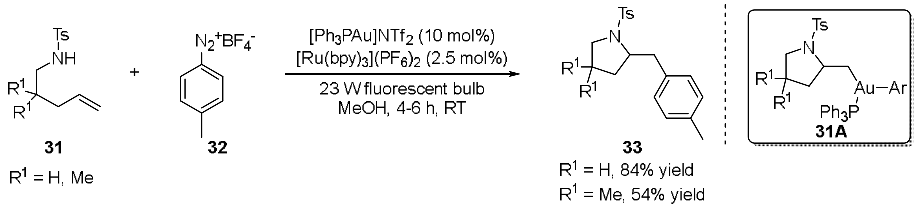
Scheme 18. Visible light-induced 5-*exo*-trig radical cyclization of iminyl radicals.

2.2.4. Visible light-induced nucleophilic cyclization reaction

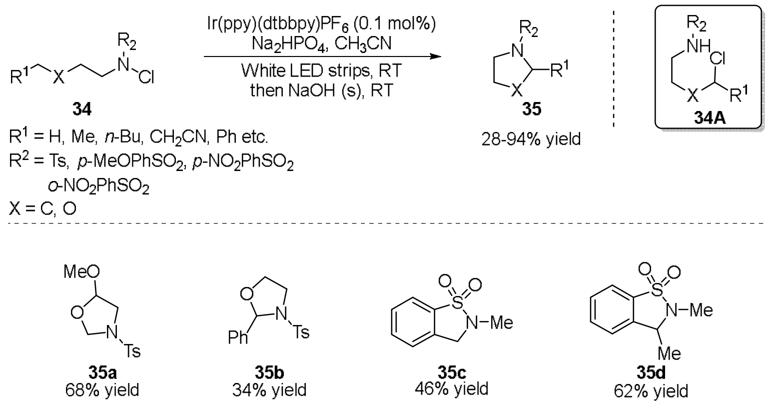
In addition to the direct radical cyclization of *N*-radical and radical ions, visible light-induced radical-mediated nucleophilic cyclization of amines represents another approach for the construction of C-N bond or synthesis of heterocycle compounds. In 2013, Glorius reported two examples of aryl radical-mediated intramolecular cyclization of **31** toward synthesis of pyrrolidines **33** by combining gold and photoredox catalysis (Scheme 19).[21a] In this reaction, the cataionic Au(I) catalyst initially activated the alkene moiety to form alkylgold(I) complex in an *anti*-selective cyclization manner, which then reacted with photogenerated aryl radical to form the key intermediate Au(III) species **31A**. A final reductive elimination of **31A** resulted in the formation of product. Shortly after, employing this strategy, an intermolecualr multicomponent oxyarylation of alkenes was also reported by the same research group.[22] At the same time, Nicewicz and coworkers have also reported the synthesis of several pyrrolidines under metal-free condition using internal alkenes substrates.[21b]

Moreover, visible light-induced single photocatalyst-catalyzed nucleophilic cyclization could also provide an efficient method for the synthesis of heterocycle compound. In 2015, the Yu group reported a visible light-promoted $C(sp^3)$-H bond amidation of *N*-chlorosulfonamides **34** (Scheme 20).[23] In this reaction, it was postulated that the key intermediate **34A** was initially formed *via* photoredox catalyzed sequential *N*-radical generation/1,5-HAT/chlorination process, and could be further transformed into the desired products

35 under the basic conditions. Notably, the protecting group sulfonyl is critical to the reaction, since the Boc or the alkyl group did not resulted in any desired product in this reaction system. Interestingly, changing the atom X into oxygen atom provided the oxazoline products **35a** and **35b** in moderate yields. In addition, cyclic benzosulfonamides **35c** and **35d** could also be synthesized.



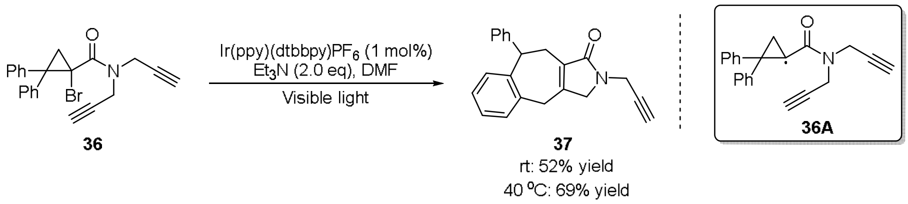
Scheme 19. Visible light-induced radical addition/nucleophilic cyclization cascade by synergistic gold and photoredox catalysis.



Scheme 20. Visible light-induced C(sp^3)-H amidation of *N*-chlorosulfonamides.

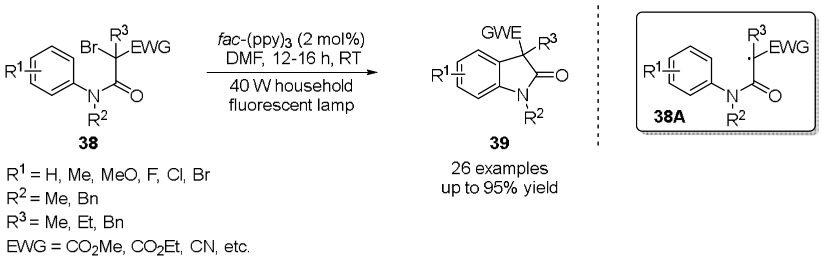
2.3. The synthesis of pyrrolidin-2-ones

Tandem radical cyclization provides an efficient method for the synthesis of complex carbocycles and heterocycles. With the development of photoredox catalysis, tandem radical cyclization has also enjoyed impressive advances.[24] In 2011, Stephenson reported an interesting visible-light-mediated tandem radical cyclization toward the synthesis of tricyclic pyrrolidinones.[25] As shown in Scheme 21, bromocyclopropane substrate **36** could be transformed into the tricyclic pyrrolidinnone **37** *via* the key radical intermediate **36A** in the presence of Et$_3$N under visible light-irradiation. Notably, the temperature was an important parameter. When improving the temperature from 25 °C to 40 °C, the reaction could work smoothly and furnish the product **37** in 69% yield.



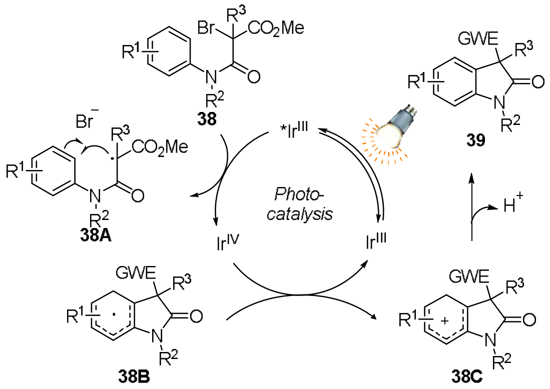
Scheme 21. Visible light-induced tandem radical cyclization of bromocyclopropane.

Shortly after, Yu and co-workers reported that 2-electron-withdrawing group-substituted 2-bromoanilides **38** could be converted to valuable 3,3-disubstituted pyrrolidin-2-one compounds **39** *via* the addition of photogenerated carbon radicals to the phenyl ring (Scheme 22).[26] This protocol was tolerant of various substrates containing electron-donating groups (2-Me, 4-Me, 3-Me, 4-MeO) or electron-withdrawing groups (4-F, 2-Cl, 4-Cl, 4-Br) on phenyl ring. Remarkably, the stoichiometric hydrogen bromide produced as byproduct did not hinder the catalytic process. Notably, the R^3 moiety needs to be alkyl groups such as methyl and benzyl.



Scheme 22. Visible light-induced tandem radical cyclization of bromocyclopropanes.

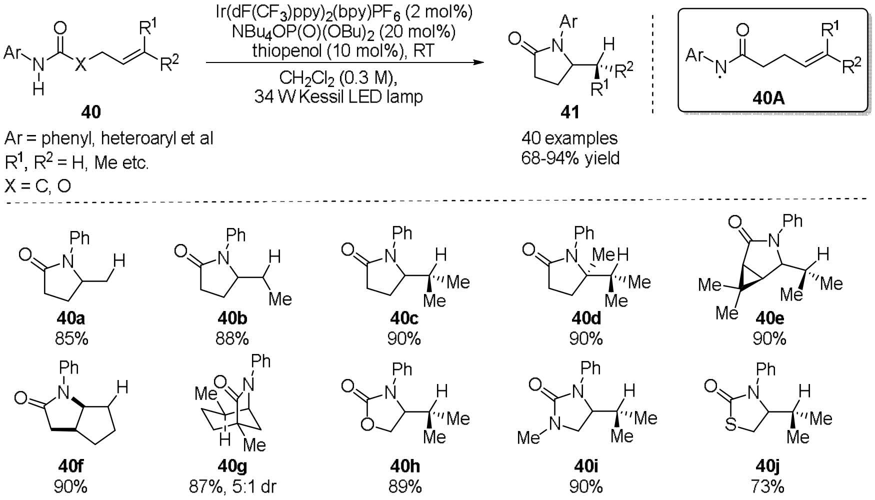
A possible mechanism was proposed as shown in Scheme 23. Upon irradiation of visible light, the Ir^{III} photocatalyst was initially converted to its excited state $^*\text{Ir}^{\text{III}}$. Then, the excited state $^*\text{Ir}^{\text{III}}$ was oxidized to the Ir^{IV} species, and the substrate **38** was reduced *via* a process of single electron transfer to generate the radical intermediate **38A**. Subsequently, the intermediate **38A** underwent an intramolecular radical addition to the phenyl ring to afford the radical species **38B**. This radical species was liable to be oxidized into the cation intermediate **38C** and undergo a proton transfer to give the aromatization product **39**.



Scheme 23. The proposed mechanism.

Since then, some analogous molecular scaffolds such as the biologically important pyrrolidin-2-one have drawn extensive attention from the organic community. In this regard, *N*-arylacrylamides were the most widely used. In 2015, Xiao and Chen summarized the representative advances in this field of tandem radical cyclization reaction of *N*-arylacrylamides according to different types of radical sources, including carbon, phosphorus, sulphur, and nitrogen radicals.[24a] Quite recently, the groups of Xia, Cheng and others also developed a series of tandem radical cyclization reactions of *N*-arylacrylamides using carbon or phosphorus radical source, which significanlty extended the scope of this strategy.[27a-d] Notably, Xiao and Wu extended this strategy to sulfur ylides to synthesize a variety of 3-acetyl oxindoles.[27e]

More recently, Knowles and co-workers reported a mild and efficient intramolecular hydroamidation of unactivated olefins *via* proton-coupled electron transfer (PCET), wherein amidyl radical was involved as the key reactive species.[28] This protocol exhibited good tolerance with respect to the phenyl moiety, and anilides that have electron-deficient or electron-rich substituents all cyclized smmothly. With respect to the olefin component, a variety of di-, tri-, and tetrasubstituted olefins were successfully accommodated, as shown in the synthesis of products **40a-d**. In addtion, a number of bicyclic products **40e-g** could be synthesized in excellent yields with good diastereoselectivity. It was worth mentioning that carbamates, ureas and thiolcarbamates could run smoothly under standard conditions to give corresponding products **40h-j** in excellent yield (73-90%). In this reaction, **40A** was the key radical intermediate, which was generated *via* a visible light-induced PCET process (Scheme 24).



Scheme 24. Visible light-induced intramolecular radical hydroamidation.

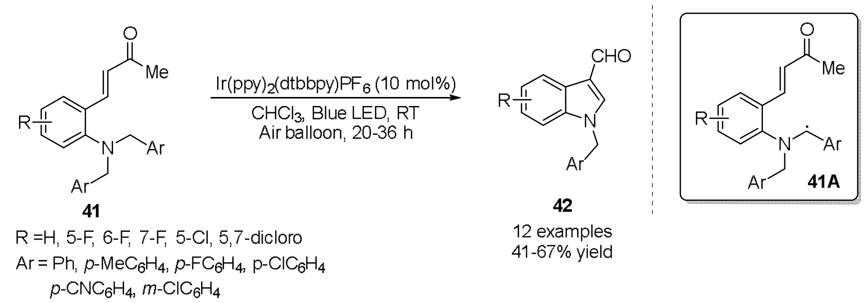
3. Visible light-induced synthesis of indole derivatives

3.1. The synthesis of indoles and its derivatives *via* tandem radical cyclization

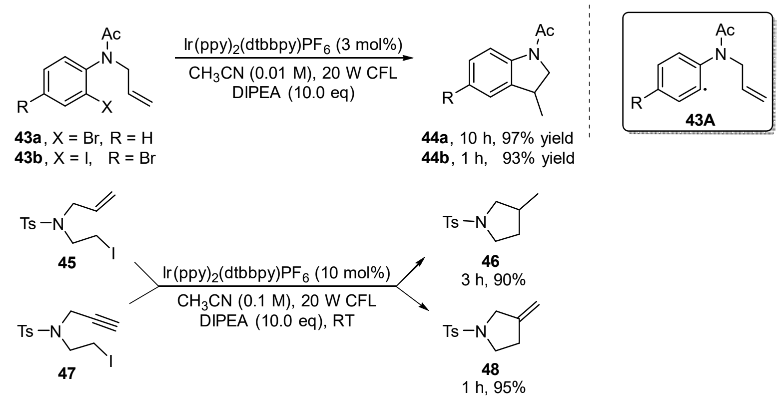
The indole and indoline motifs represent a privileged class of five-membered *N*-heterocycles, which widely exist in natural products, pharmaceuticals, agrochemicals, and material sciences. In addition to the classical Fischer indole synthesis, a wide variety of synthetic methods for construction of indoles have also been well established over the past decades. Recently, visible light-induced indole synthesis has aroused great interests among organic chemists because of the potential sustainable property and mild conditions. Particularly, photoredox catalytic tandem radical cyclization provided a reliable method for the indole and indoline synthesis.

In 2012, Oliver, Pandey and co-workers reported an interesting intramolecular α-amino radical cyclization reaction for synthesis of 5,6-dihydroindolo[2,1-*a*]-tetrahydroisoquinolines by visible light photoredox catalysis.[29] Shortly thereafter, Rueping and co-workers developed a novel intramolecular α-amino radical cyclization reaction of tertiary amines **41** to afford the indole-3-carbaldehydes **42** *via* the radical intermediate **41A** (Scheme 25).[30] A variety of substituents on phenyl ring were well tolerated. Both of the position of substitent and electric property did not have any obvious effect on reaction efficiency, affording the products with modrate to good yields.

In 2012, Lee and co-workers developed an intramolecular phenyl radical cyclization reaction of aryl halides **43** to give a class of indoline products **44** *via* the aryl radical intermediate **43A**.[31] In this reaction, both ary bromide and aryl iodide worked well to afford the products **44** in excellent yields. Interestingly, this protocol could also be applied to synthesis of the indolines **46** and **48** from alkyl iodides **45** and **47**, which greatly extended the synthetic potential of this methodology (Scheme 26). However, 10 equivalents of di-isopropyl-ethylamine (DIPEA) needed to be used as a sacrificial reductant. In the same year, Stephenson disclosed a similar intramolecualr reductive cyclization of aryl iodides with this strategy using Hantzsch ester as reductant instead of DIPEA, providing an efficient access to indolines and pyrrolines.[32]

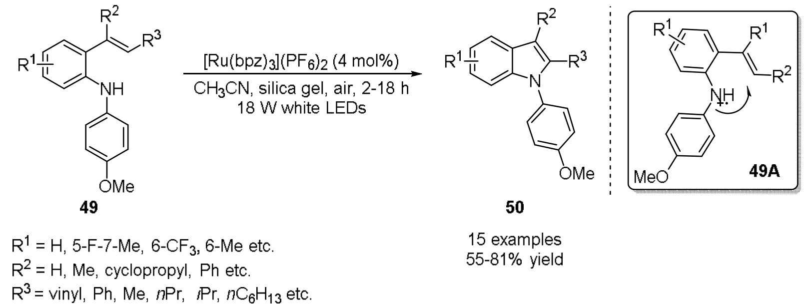


Scheme 25. Visible light-induced tandem radical cyclization of tertiary amines.



Scheme 26. Visible light-induced reductive intramolecular cyclization of aryl and alkyl halides.

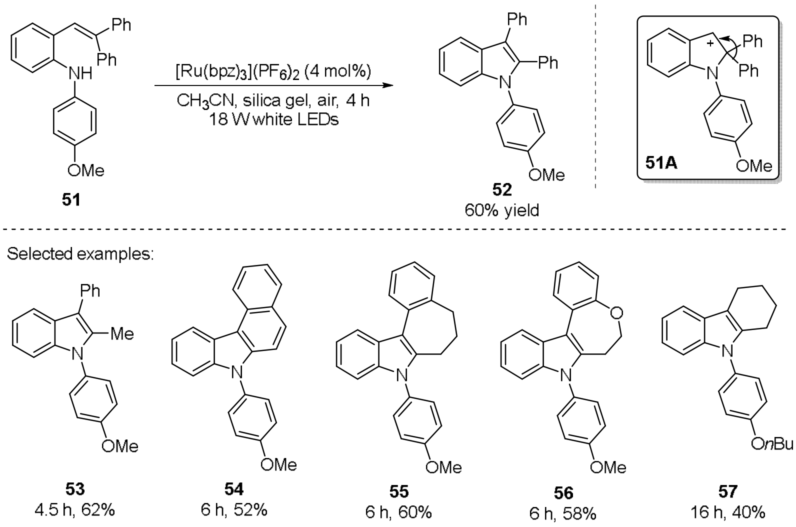
In 2012, Zheng and co-workers developed an oxidative C-N bond formation/aromatization cascade of styryl anilines **49** *via* nitrogen radical cation intermediate **49A**.[33] As depicted in Scheme 27, both the electron-rich and electron-deficient substituents on phenyl ring of styryl anilines could be tolerated well. On the contrary, the scope of protecting groups on styryl aniline was very narrow, and the electron-rich *p*-methoxyphenyl group was critical to the reaction. With the respect to olefin moiety, the electron property and the stereric hinderance did not have obvious effect on the reaction efficiency. In addtion, the reaction could be performed in the open air and oxygen might serve as the terminal oxidant.



Scheme 27. Visible light-induced tandem radical cyclization of styryl anilines.

Considering this fact, authors employed silica gel to improve the absorption of oxygen, thus leading to significantly improved yield.

Interestingly, *gem*-diphenyl styryl aniline **51** could be converted into 2,3-diphenyl indole **52** under the standard conditions (Scheme 28). In this reaction, the key intermediate **51A** may undergo a 1,2-phenyl shift to give the corresponding product. Thus, a series of *gem*-diphenyl styryl anilines were evaluated under the standard conditions, leading to formation of a range of structurally disverse indole derivatives **53-57** with good yields. Notably, the 1,2-carbon shift is not limited to aryl groups, alkyl groups could also undergo 1,2-carbon shift.



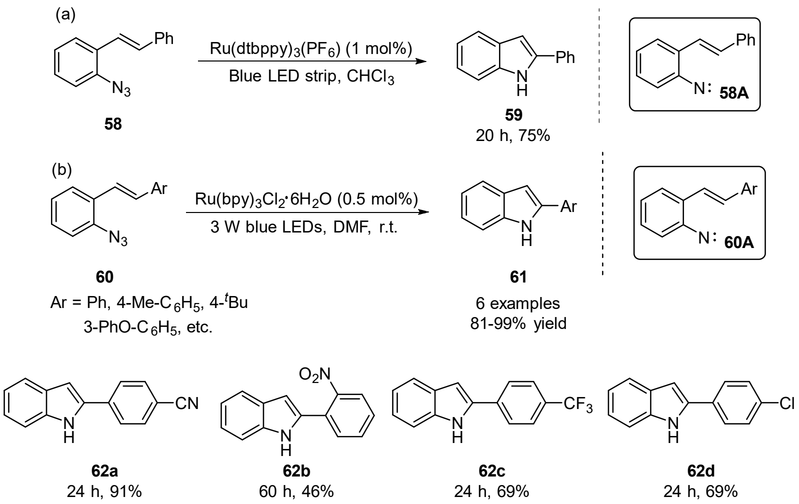
Scheme 28. Visible light-induced radical cyclization/1,2-carbon shift cascade of styryl anilines.

Nitrenes are a versatile synthons for the synthesis of aziridines, indoles and pyrroles.[34] The generation of nitrene *via* visible light photocatalytic activation was an attractive stragegy since dinitrogen was the only byproduct. Recently, Yoon reported one example of indole synthesis *via* nitrene intermediate catalyzed by visible light photocatalysis.[35] As shown in Scheme 29a, styryl azide **58** could be transformed into indole product **59** *via* photogenerated intermediate **58A** generated from the styryl azide **58** *via* an energy transfer process. Notably, this protocol was also employed as an efficient method for the synthesis of pyrroles. At almost the same time, the group of Xiao and Chen developed a similar reaction of aryl-substituted styryl azides **60** (Scheme 29b).[36] Remarkably, incorporation of various electron-donating groups at the meta- or para-position of the benzene ring could be well tolerated to give indoles **61** with 81-99% yield. However, as shown in the synthesis of **62b**, incorporation of a group to *ortho*-position resulted in an obvious decrease of yield, presumably due to the steric hindrance.

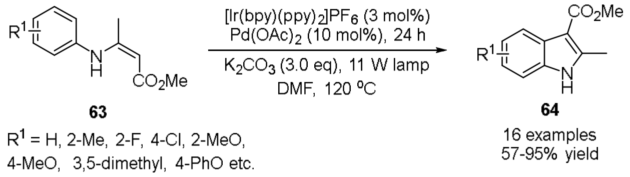
3.2. The synthesis of indole derivatives *via* dual catalysis

Recently, the strategy of visible light-induced dual catalysis has been developed as a powerful method to develop novel photochemical syntheses that are otherwise inaccessible when using single catalytic entity.[37] In 2014, the Rueping group reported a palladium-catalyzed C-H activation induced by photoredox catalysis for the indole synthesis (Scheme 30).[38] This protocol used $[Ir(bpy)(ppy)_2]PF_6$ as a photocatalyst to facilitate the reoxidation of reduced palladium catalyst, which avoided the use of equivalent external oxidant. Irrespective of the electron property and the position of the substitents on phenyl ring, a wide range of aromatic enamines **63** could be transformed into indoles **64** in moderate to excellent yields.

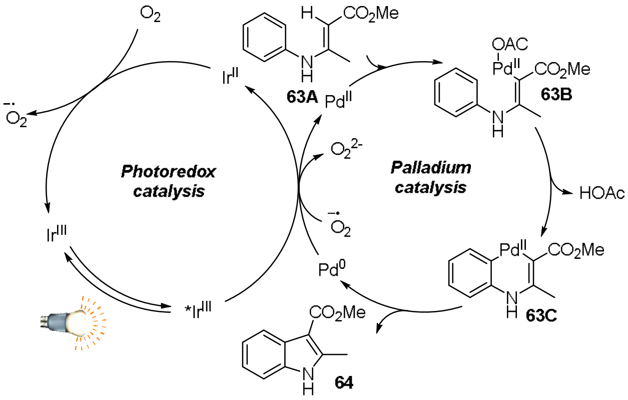
The proposed mechanism was as described in Scheme 31. Initially, a Pd^{II}-catalyzed aryl C-H activation of the substrate **63A** occurred to give an intermediate **63C**, which underwent a reductive elimination to form indole **64** with release of the Pd^0 species. Then, the Pd^0 species could be oxidized by either the photoredox catalysis or the superoxide anion to regenerate the Pd^{II} complex. Despite of the advanteges of this protocol, however, high temperature was necessary. Thus, how to achieve the reaction under mild conditions was still a challenge.



Scheme 29. Visible light-induced indole synthesis *via* energy transfer.

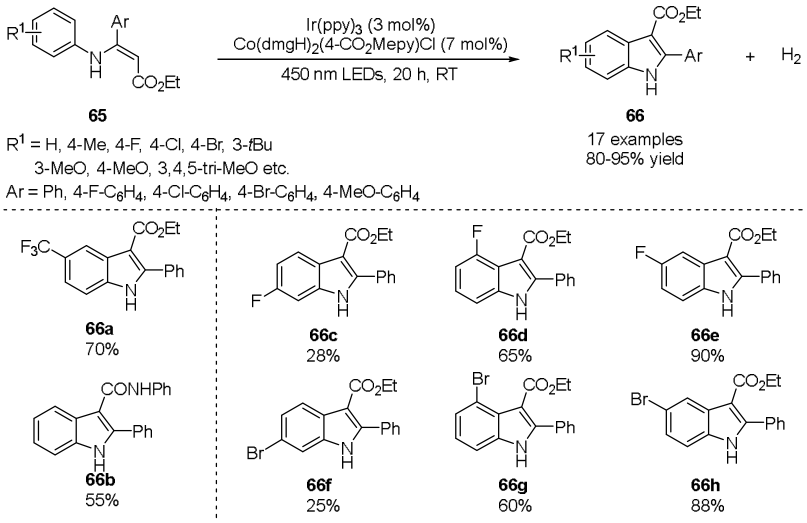


Scheme 30. Visible light-induced synthesis of indoles by a combined palladium catalysis and photoredox catalysis.



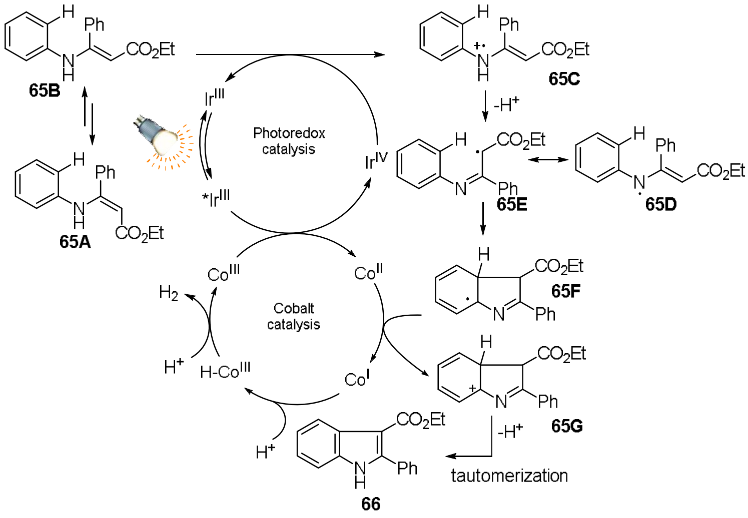
Scheme 31. The proposed mechanism.

Shortly after, the combination of cobalt catalysis and photoredox catalysis has emerged as another efficient strategy. For instance, in 2016, Wu and co-workers reported an oxidant-free method for indole synthesis starting from a range of *N*-aryl enamines.[39] As described in Scheme 32, a variety of *N*-aryl enamines **65** with electron-dificient or electron-rich groups on the aromatic ring were well tolerated, and all of them proceeded smoothly to give the corresponding indole products **66** in high yields (80-95%) under standard conditions. However, in the case of enamines bearing strong electron-withdrawing trifluoromethyl group, the yield declined to 70% (**66a**). As demonstrated in synthesis of indole **66b**, replacement of the carboxylic ester by amide resulted in an obvious decrease in the yield.



Scheme 32. Visible light-induced synthesis of indoles by combining photoredox catalysis and cobalt catalysis.

The proposed mechanism was shown in Scheme 33.



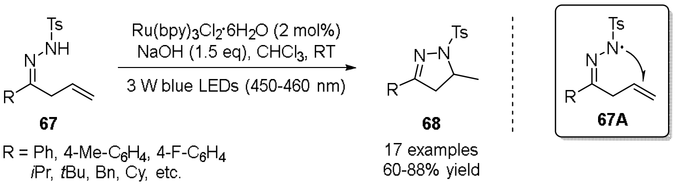
Scheme 33. The proposed mechanism.

Initially, photocatalyst Ir(ppy)$_3$ was excited to its excited state Ir(ppy)$_3$*, which was oxidized by Co^{II} to give Ir^{IV} *via* the process of single electron transfer. The oxidative Ir^{IV} species further abstracted one electron from enmine **65B** to produce radical cation intermediate **65C** and regenerate ground state photocatalyst Ir(ppy)$_3$, closing the photocatalytic cycle. Then, the resulting cation intermediate **65C** lose one proton to form radical intermediate **65D**, which was in resonance with **65E**. Next, intermediate **65E** underwent an intramolecular radical addition to give rise to the adduct **65F**, which was subsequently oxidized by Co^{II} to form **65G** with release of Co^{I} catalyst. Eventually, deprotonation of **65G** followed by tautomerization would afford the desired product indole **66**. The reduced Co^{I} species reacted with proton to form Co^{III}-H hydride, which could react with another proton to produce H$_2$ and Co^{III}.

4. Visible light-induced synthesis of pyrazole derivatives

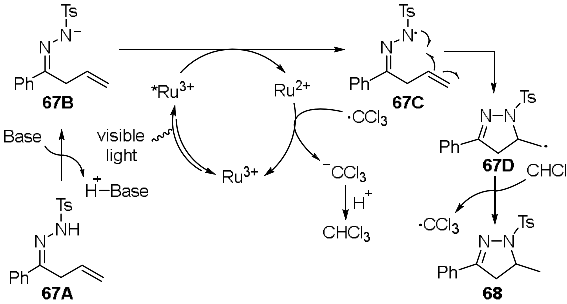
4.1. The synthesis of pyrazoles and its derivatives *via* nitrogen radical cyclization

Although various carbon radicals have been widely used in catalytic radical cyclization reactions,[40] nitrogen-centered radicals were more reactive intermediates, but have been largely unexplored in organic synthesis probably due to limited mild methods for their generation. Traditional methods for their generation typically required the use of nitrogen-functionalized precursors or various stoichiometric toxic, potentially explosive or unstable radical initiators.[19,41] In 2014, Xiao and Chen developed an oxidative deprotonation electron transfer (ODET) strategy for the photoredox catalytic generation of hydrazonyl radicals of type **67A** from ketone hydrazones **67**, which could undergo intramolecular radical cyclization reaction to give pyrazole derivatives **68** (Scheme 34).[42] Notably, the protecting group on the nitrogen atom of β,γ-unsaturated hydrazone was essential for the generation of the hydrazonyl radicals. This protocol was tolerant of a variety of aryl or alkyl substituted β,γ-unsaturated hydrazones and enabled assembly of a variety of 4,5-dihydropyrazoles in modrate to good yields. This work opened a new atom-economical and mild way to develop visible light-induced N-H bond activation and *N*-radical-mediated reactions.



Scheme 34. Visible light-induced hydrazonyl radical 5-*exo*-trig cyclization for the synthesis of pyrazolines.

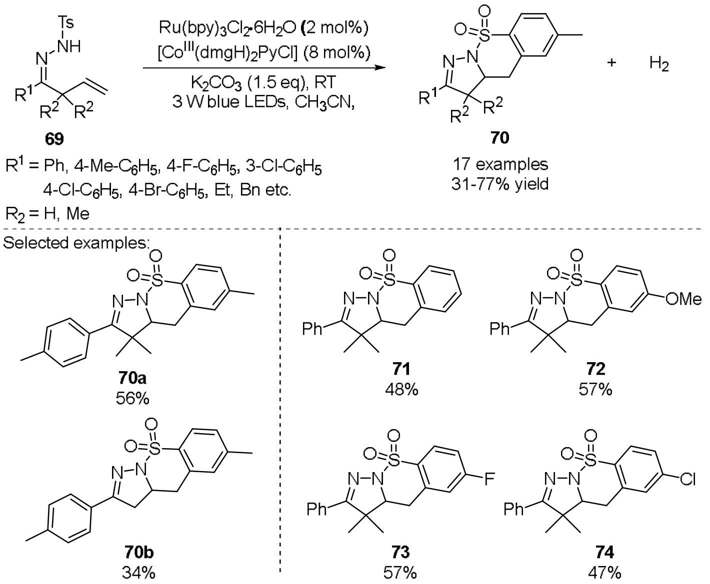
On the basis of a series mechanistic studeis, a possible mechanism was proposed as shown in Scheme 35. Initially, deprotonation of β,γ-unsaturated hydrazone **67A** occurred in the presence of base to give the nitrogen anion intermediate **67B**. Then, intermediate **67B** was oxidized into nitrogen radical intermediate **67C** *via* a single electron transfer with release of the reductive photocatalyst Ru^{2+}. Ultimately, neutral nitrogen radical **67C** underwent a 5-*exo*-trig radical cyclization to give a terminal carbon radical **67D**, which abstracted the hydrogen atom from the chloroform to afford the final product **68**.



Scheme 35. The proposed mechanism.

The reduced photocatalyst Ru^{2+} was oxidized to its ground state Ru^{3+} by trichloromethyl radical, thus closing the photocatalytic cycle.

Shortly after, the group of Xiao and Chen have further developed visible light-induced olefin aerobic oxyamination and carboamination of β,γ-unsaturated hydrazones, which further extended the synthetic applicability of this strategy.[43] Moreover, in 2016, Xiao and co-workers developed an external oxiant-free radical cyclization reaction of β,γ-unsaturated hydrazones by a combination of photoredox catalysis and cobalt catalysis (Scheme 36).[44] In this reaction, a wide range of β,γ-unsaturated hydrazones **69** bearing electron-dificient or electron-rich group on the phenyl ring could react smoothly and provided the dihydropyrazole-fused benzosultams **70** in moderate to good yields. The reaction with geminally disubstituted β,γ-unsaturated hydrazones gave rise to better yields (**70a**). Meanwhile, as shown in the synthesis of compounds **72-74**, changing the electron property of the substituents on the tosyl group has no obvious effect on the reaction efficiency.



Scheme 36. Visible light-induced dual catalysis for the synthesis of dihydropyrazole-fused benzosultams.

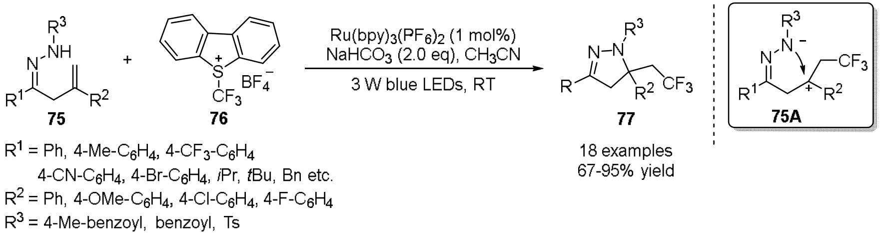
4.2. The synthesis of pyrazole derivatives *via* nucleophilic cyclization

With development of visible light photocatalysis, radical-mediated nucleophilic cyclization has rencently been established as another powerful method for the pyrazoles synthesis. In 2015, the Chen group reported a practical and efficient CF_3 radical-mediated nucleophilic cyclization of β,γ-unsaturated hydrazones **75** for synthesis of CF_3–containing pyrazolines **77** through **75A** as the key intermediate (Scheme 37).[45] In this reaction, a variety of functional groups on the phenyl ring were well accommodated to give the expected products with generally good yields. Interesting, the β,γ-unsaturated hydrazones with benzoyl or 4-Me-benzoyl group rather than Ts group could also work well, and give the desired products in moderate yields. Notably, this protocol could also be tolerant of a range of β,γ-unsaturated oximes to allow for synthesis of biologically interesting CF_3–containing isoxazolines.

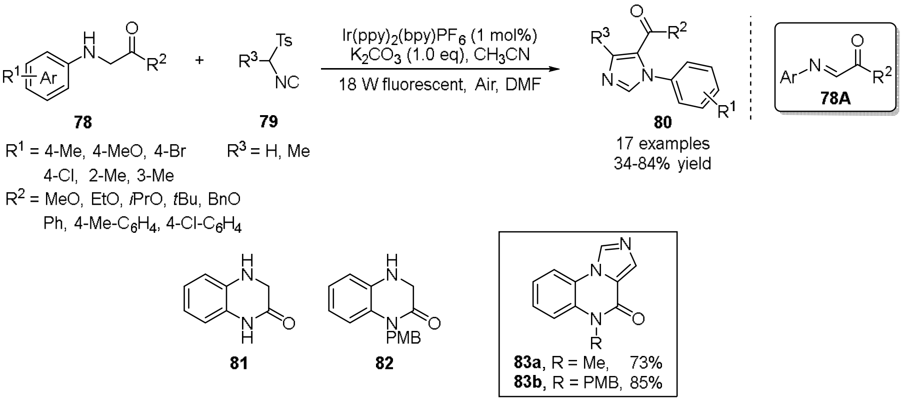
5. Visible light-induced synthesis of imidazole derivatives

5.1. The synthesis of imidazoles derivatives *via* formal [3+2] cyclization

In analogous to the visible light-induced pyrrole synthesis,[5] photoredox catalytic [3+2] cycloaddtion of isocyanides could also provide a direct route to the synthesis of imidazoles. For instance, in 2014, the Xiao group employed imines **78A** formed *in situ* from glycine derivatives **78** by the photoredox catalysis as two-atom fragment to react with isocyanides **79** as a three-atom fragment in a formal [3+2] cyclization manner, leading to synthesis of a novel class of multiply substituted imidazoles **80** (Scheme 38).[46] In this work, a variety of glycine derivatives were tested and most of them could be transformed into the desired products in moderate to high yields. Notably, both cyclic glycine derivatives **81** and **82** could also participate in the reaction smoothly to furnish the corresponding biologically useful imimidazole-fused heterocyclic compounds **83** in 73% and 85% yields, respectively.



Scheme 37. Visible light photocatalytic synthesis of CF_3–containing pyrazolines by radical trifluoromethylation/cyclization cascade.

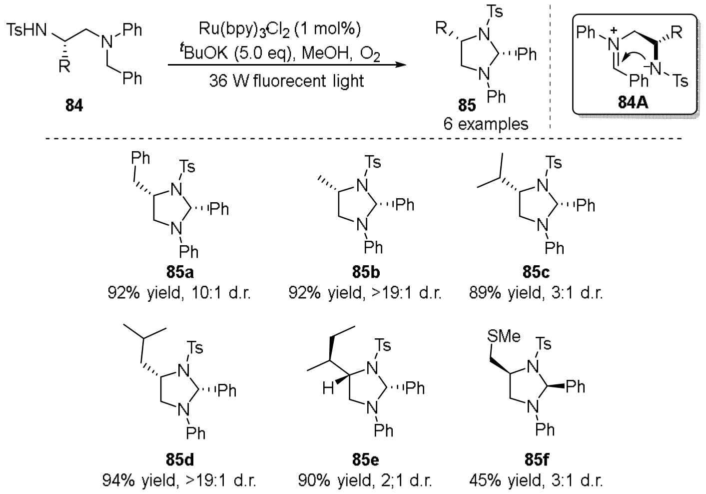


Scheme 38. Visible light-induced photocatalytic formal [3+2] cycloaddtion of glycine derivatives and isocyanides for the synthesis of imidazoles.

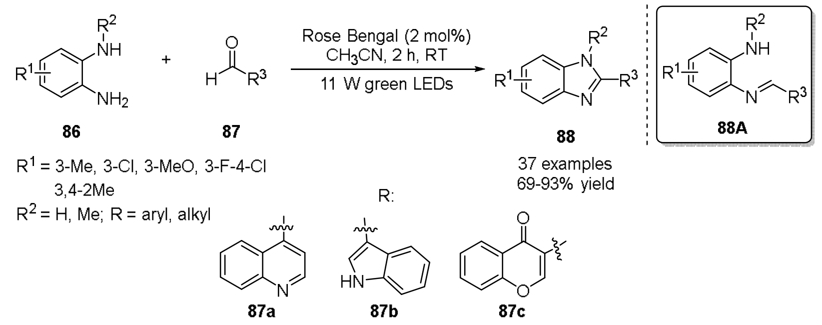
5.2. The synthesis of imidazole derivatives *via* nucleophilic cyclization

Visible light-induced photoredox catalyzed nucleophilic cyclization represents another reliable method for the synthesis of imidazole derivatives. In 2011, the Xiao group reported a practical and visible light-induced protocol for synthesis of tetrahydroimidazoles **85** from the diamines **84** *via* the intermediates **84A** under mild conditions (Scheme 39).[47] The diamines derived from L-alanine and L-leucine could be transformed into the desired products **85b** and **85d** with excellent yields and diastereoselectivities (92%, >19:1 and 94%, >19:1). Similarly, the starting materials prepared from L-valine and L-isoleucine also could react well to give the product **85c** and **85e** in 89% and 90% yields, respectively. This protocol provides a mild, efficient and ecomomic approach to the synthesis of chiral tetrahydroimidazoles.

Quite recently, the group of Srivastava and Kamal developed an efficient and metal-free method for the synthesis of biologically important 2-substituted benzimidazoles of type **88** *via* the imine intermediates **88A** using *o*-phenylenediamines **86** and aldehydes **87** as the starting materials (Scheme 40).[48] In this protocol, a variety of differently substituted *o*-phenylenediamines and aldehydes were examined and most of them could generate the expected products in good yields. Particularly, heteroaromatic aldehydes **87a-c** also proved to be suitable substrates to react with *o*-phenylenediamine to afford the corresponding biologically interesting benzimidazoles.



Scheme 39. Photocatalytic oxidative nucleophilic cyclization of chiral diamines for synthesis of tetrahydroimidazoles.



Scheme 40. Visible light photocatalytic nucleophilic cyclization for the synthesis of 2-substituted benzimidazoles.

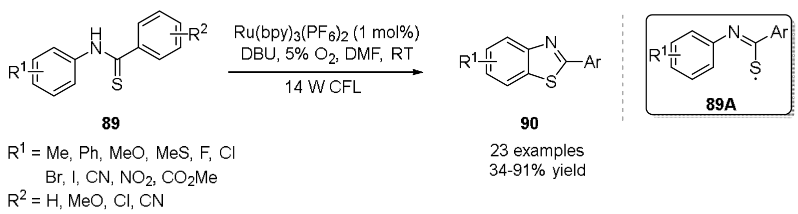
6. Miscellaneous

6.1. Visible light-induced synthesis of thiazole derivatives

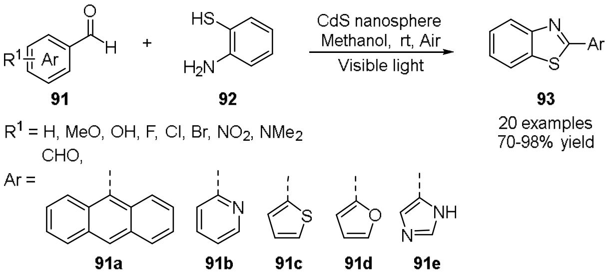
In addition to the aforementioned nitrogen-containing five-membered heterocycles, other types of biologically important heterocyclic scaffolds such as thiazoles, isoxazoles and their derivatives were also widely found in many natural products or medicinal reagents.

In 2012, the Li group reported a mild approach for the synthesis of 2-substituted benzothiazoles **90** from thioamides **89** *via* aerobic visible light-inducd photoredox catalysis (Scheme 41).[49a] In this reaction, the oxygen (5%) was used as the terminal oxidant and the water was the only byproduct. In contrast, Lei and Wu also developed an external oxidant-free oxidative cross-coupling reaction of thioamides **89** for construction of benzothiazoles using their previously developed visible light-induced photoredox and cobalt catalysis.[49b]

Shortly after, Biswas reported an alternative method for synthesis of 2-substituted benzothiazoles **93** using CdS nanosphere as a heterogenous recyclable photocatalyst (Scheme 42).[49c] In this reaction, a series of aromatic aldehydes of type **91** with diverse electron-deficient or electron-rich groups on the aromatic ring could react well with **92** to afford the products **93** in generally good yields. Notably, the heteroaromatic aldehydes such as **91b-e** could be well tolerated.

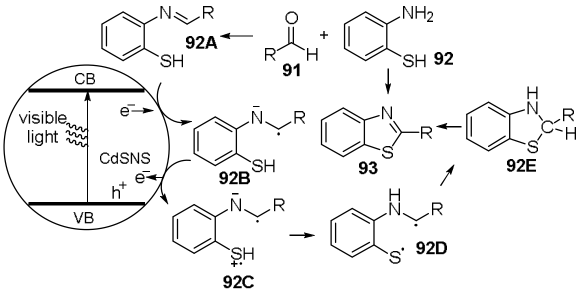


Scheme 41. Visible light-induced photocatalytic aerobic synthesis of benzothiazoles.



Scheme 42. Visible light-induced synthesis of benzothiazoles using CdS nanosphere as recyclable photocatalyst.

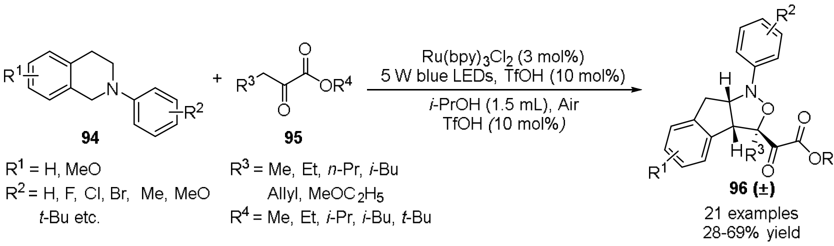
A proposed mechanism was shown in Scheme 43. Initially, imines **92A** were formed *in situ* from aldehydes **91** and aniline **92**. At the same time, an electron transfered from valence band (**VB**) of CDSNS, leaving behind a hole ($\mathbf{h^+}$) in the conduction band (**CB**) upon irradiation of visible light. Then, the imine **92A** was reduced *via* a SET process to give radical anion intermediate **92B**, which underwent another SET oxidition to form intermediate **92C**. A subsequent proton transfer of **92C** occurred to afford the biradical intemediate **92D**, which underwent a radical coupling to furnish intermediate **92E**. A final oxidative aromatization of **92E** led to the products **93**. Remarkably, CdS was used as a heterogeneous recyclable photocatalyst, which could be easily removed from the reaction system.



Scheme 43. Visible light-induced synthesis of benzothiazoles catalyzed by CdS nanosphere.

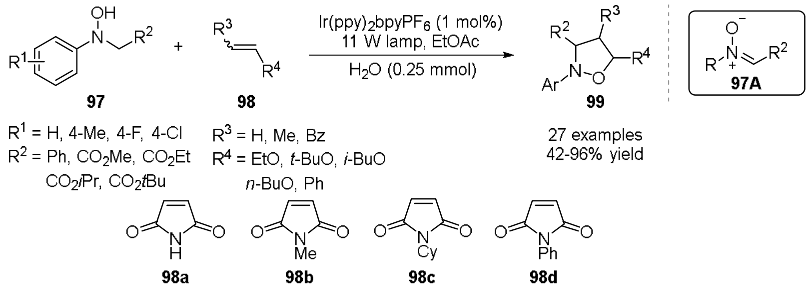
6.2. Visible light-induced synthesis of isoxazole derivatives

The isoxazolidine and bicyclic isoxazolidine scaffolds are not widely found in natural alkaloids, but also extensively employed as versatile intermediates for the synthesis of pharmaceutically active compounds. Thus, development of novel and efficient methods for the synthesis of isoxazole derivatives is of great importance. In 2013, the Zhu group reported a mild and concise method for synthesis of isoxazolidine skeletons by visible light-induced oxidative tandem reactions (Scheme 44).[50] As for the substrate scope of *N*-aryltetrahydroisoquinolines **94**, the catalytic system showed high functional group tolerance with respect to R^1 and R^2 groups. Moreover, a wide range of functionalized α-ketoesters **95** also proved to be suitable for the reaction, giving the desired products in moderate to good yields. Considering the high diastereoselectivity, recation efficiency and operational simplicity, this protocol should be attractive approach to the synthesis of dactylicapnosinine derivatives.



Scheme 44. Visible light-induced photoredox catalytic synthesis of polycyclic isoxazole derivatives.

Shortly after, the Rueping group employed hydroxylamine substrates **97** as the precursors of nitrones to react with alkenes as dipolarophiles towards synthesis of isoxazolidines **99** (Scheme 45).[51] In this protocol, photogenerated nitrones intermediate **97A** from **97** was postulated to be the key intermediates, which then reacted with electron-rich alkene **98** *via* a [3+2] cycloaddition manner. Under the optimal conditions, a wide range of substituted hydroxylamines **97** and alkenes **98** were well tolerated, furnishing the desired isoxazolidine products **99** in good yields. Notably, all of the products could be obtained with excellent diastereoselectivity (>99:1), when using alkenes **98a-d**. Thus, this protocol provides a mild and attractive access for the synthesis of valuable isoxazolidines.



Scheme 45. Visible light-induced photoredox catalytic synthesis of isoxazole derivatives.

7. Conclusions

In conclusion, during the past several years, a great of efforts have been devoted to the development of visible light-induced photocatalytic methods for synthesis of various biologically important and synthetically useful five-membered nitrogen heterocycles. The combination of visible light photocatalysis with other catalytic modes also enabled development of novel synthetic methodologies capable of allowing construction of complex heterocyclic compounds. Because of the safe, cheap and renewable source of sun light, visible light photocatalytic heterocycle synthesis will continue to receive extensive interest from the synthetic community.[52]

Despite these impressive advances described in this section, however, much more endeavors should be further devoted to this field, particularly with respect to the development of enantioselective photochemical transformations. Development of novel bifunctional photocatalyst[53] or combination of photocatalysts with other types of chiral catalysts will provide a potentially powerful platform towards this target.[54] We hope that this chapter will stimulate more research endeavors in this area.

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