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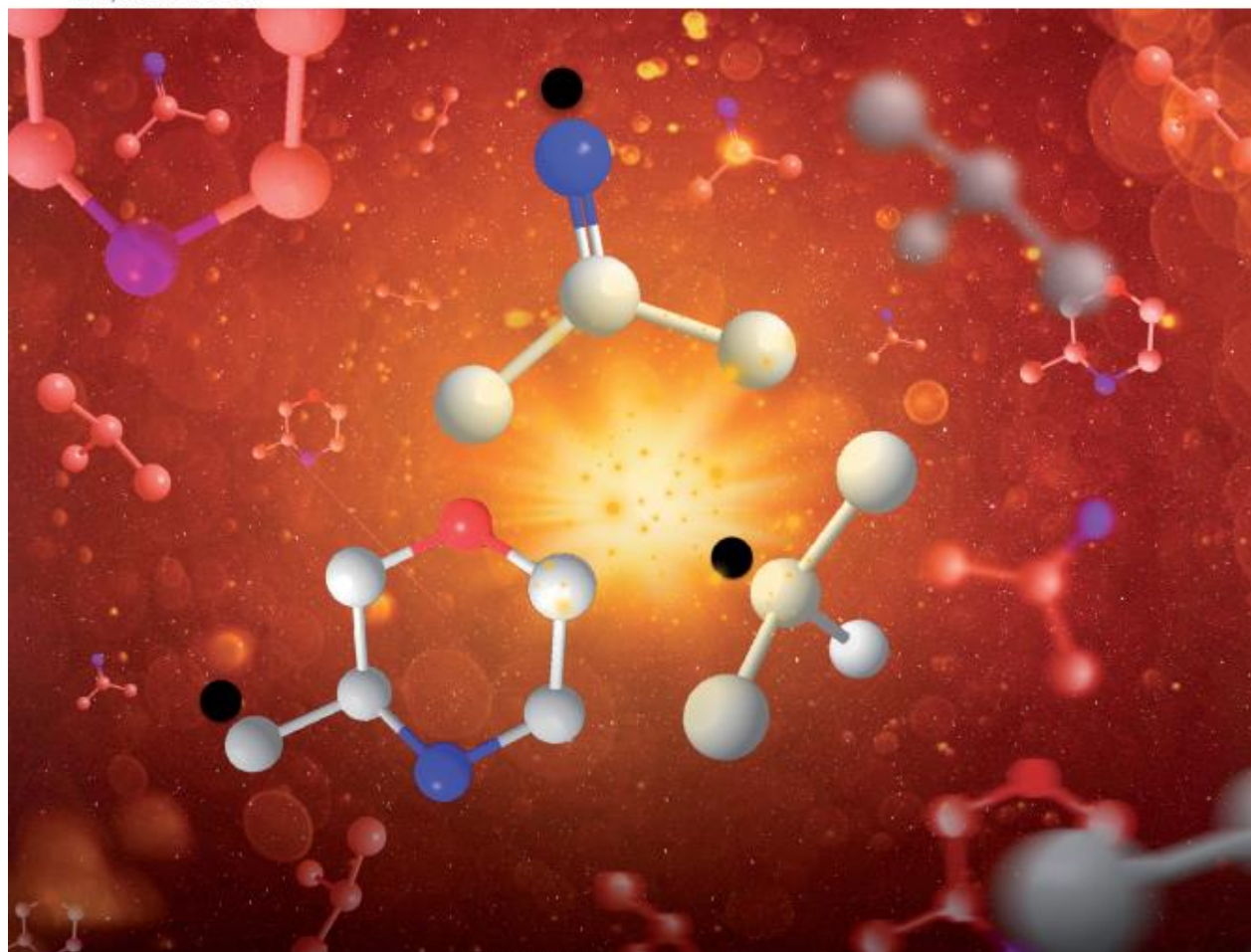
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REVIEW ARTICLE

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Photochemical radical cyclization reactions with imines,
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Photochemical Radical Cyclization Reactions with Imines, Hydrazones, Oximes and Related Compounds

Mohammed Latrache and Norbert Hoffmann*

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Abstract

Photochemical reactions are a key method to generate radical intermediates. Often under these conditions no toxic reagents are necessary. During recent years, photo-redox catalytic reactions considerably push this research domain. These reaction conditions are particularly mild and safe which enables the transformation of poly-functional substrates into complex products. The synthesis of heterocyclic compounds is particularly important since they play an important role in the research of biologically active products. In this review, photochemical radical cyclization reactions of imines and related compounds such as oximes, hydrazones and chloroimines are presented. Reaction mechanisms are discussed and the structural diversity and complexity of the products are presented. Radical intermediates are mainly generated in two ways: (1) Electronic excitation is achieved by light absorption of the substrates. (2) The application of photoredox catalysis is now systematically studied for these reactions. Recently, also excitation of charge transfer complexes have been studied in this context with many perspectives.

1 Introduction

Radical reactions are an interesting tool of synthetic organic chemistry and offer numerous alternatives to polar reactions. Thus, they contribute to extend the molecular diversity as it is highly appreciated, for instance, in the domain of pharmaceutical or agro chemistry. Due to the increased reactivity of intermediates, stable chemical bonds are formed in a convenient way.¹ Although, polar effects play an important role in radical chemistry², these reactions are carried out with a large variety of substrates. In the past, toxic reagents or activating groups have often been used to perform radical reactions in a selective way.³ For example, many of these transformations are carried out with tin reagents or selenium substituents on the starting molecules. Continuous efforts have been made to avoid the utilization of such reagents and to perform these reactions in a more sustainable way.⁴ The application of photochemical reaction conditions is a general method to generate radical species. In this context the photon is considered as a clean and traceless reagent.⁵ Since more than 10 years, photochemical reactions are again widely applied to organic synthesis.⁶ To a large extent, the recent renaissance of this research domain is based on works on photo-redox catalytic reactions and their application to organic chemistry.⁷ Meanwhile, a large variety of photoredox catalysts with different redox potentials for almost each functional group are described.

A lot of intramolecular radical reactions, especially cyclizations have been studied.⁸ They are of particular interest since a high degree of molecular complexity is generated in this way. The synthesis of

heterocycles is an important topic in domains like pharmaceutical chemistry or material science. The photochemically induced radical cyclizations and cycloadditions play an important role. To a large extent, they contribute to heterocyclic chemistry.^{9,10}

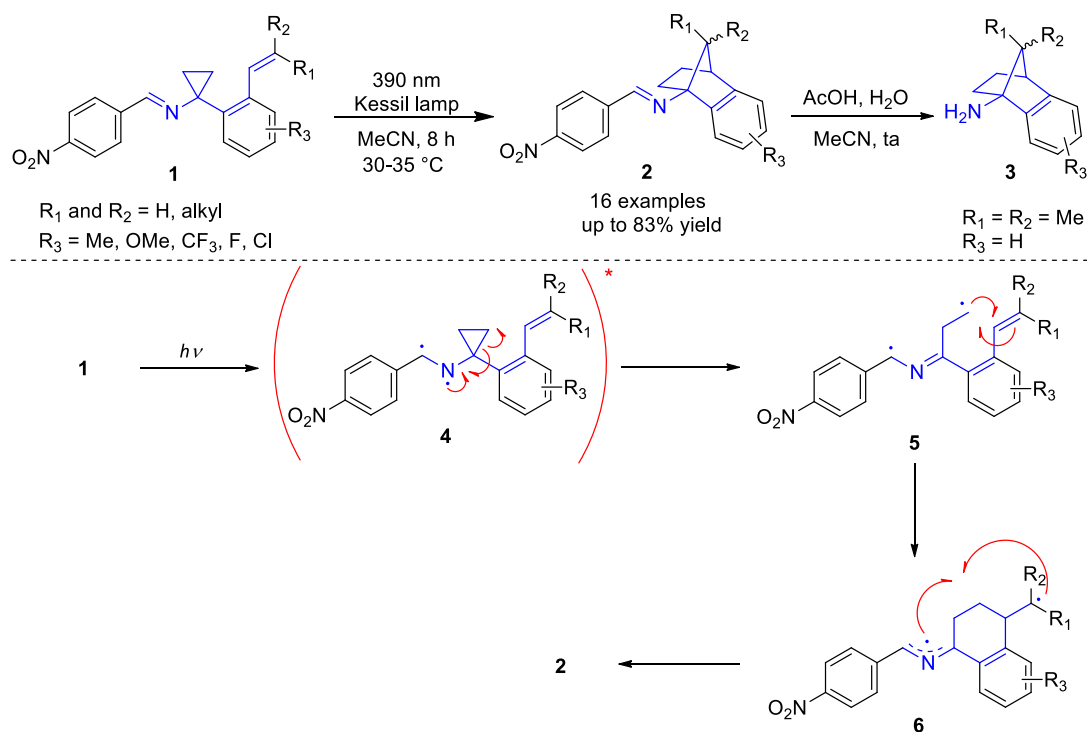
Imines possess a C=N double bond which may be easily functionalized or incorporated in heterocyclic compounds via cyclization reactions.^{11,12} Imines may be in chemical or more precisely in tautomeric equilibrium with enamines when mobile hydrogen atoms are located in the α position.¹³ Substitution of the nitrogen atom by a second nitrogen (hydrazones) or by an oxygen (oxime derivatives) reduces or inhibits tautomerization. Photochemical reactions of these derivatives have also been reported.¹⁴ In this regard, they may be compared to corresponding carbonyl compounds.¹⁵ One of the privileged photochemical processes is the fragmentation of the N-N or the N-O bond. Thus a variety of N-centered radicals are generated.

2 Imines

2.1. Generation of radical intermediates by electronic excitation of the substrates

Radical cyclisation reactions with electronically excited imines have been much less studied when compared to their carbonyl analogues. UV irradiation of imine functions provides an efficient way to access N-centered radical species which can initiate radical cyclization chemistry.^{16,17}

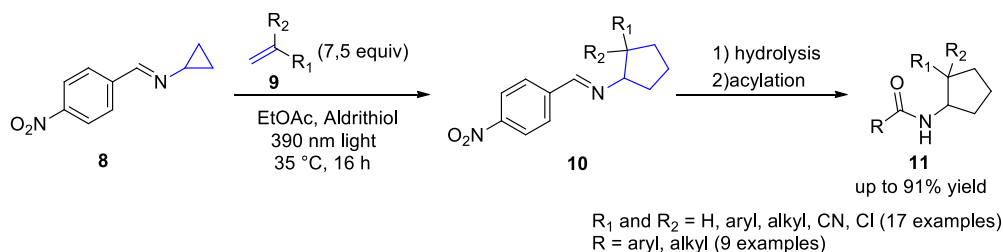
Recently, Stephenson et al. reported a masked N-centered radical strategy designed to supply 1-aminonorbornanes **3** from the Schiff bases of aminocyclopropanes **1** by initiating a multi-step radical fragmentation/ cyclization sequence forming two new C-C bonds (Scheme 1).¹⁸ The treatment of cyclopropylimine such as **1** with violet light (390 nm) results in the formation of the $S_1(n, \pi^*)$ excited state diyl **4**. The strain driven ring opening of the cyclopropane is induced by the N-centered radical. In the resulting diradical intermediate **5**, a 6-exo-trig cyclization at the alkene moiety followed by a 5-exo-trig cyclization radical combination process (**6**) occur leading to the final product **2**. It should be pointed out that the imine function is regenerated in this step. In this synthesis, the imine is both introduced (**1**) and removed (**3**) *via* simple and mild transformations.



Scheme 1: Photochemically generated masked N-centered radicals for the synthesis of 1-aminonorbornanes and the proposed mechanism.

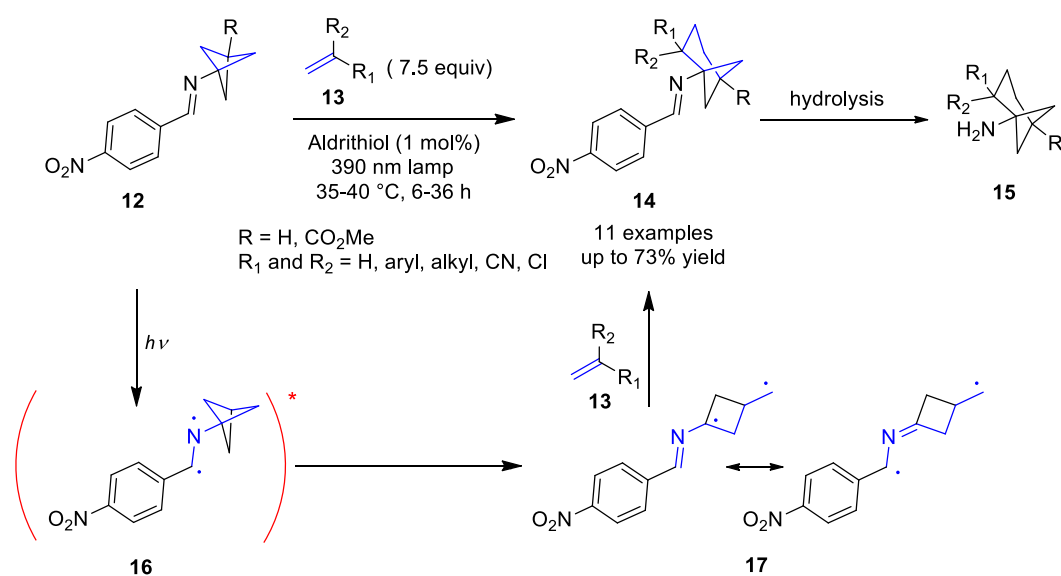
A variety of cyclopropylimines with fused aryl and heteroaryl rings has been used to access the corresponding Schiff base-protected 1-aminonorbornanes in good yields. In this reaction, the photochemical rearrangement of *N*-cyclopropylimines to 1-pyrrolines could be achieved.^{19,20} However, this reaction was not observed. In almost all cases, these transformations yield 1-aminonorbornanes **2**. Notably, it is also found that the role of the nitro motif was necessary. For example, a 3,5-bis(trifluoromethyl)benzimine system was unable to give the corresponding product upon irradiation at 390 nm or at shorter wavelengths.

The same strategy has been studied in intermolecular version *via* a formal [3+2] cycloaddition (Scheme 2).²¹ In this case, cyclopropylimines **8** and substituted alkenes **9** have been used to generate highly functionalized cyclopentylamines **11**. It should be pointed out that in this transformation a [3+2] cycloaddition, hydrolysis of the imine **10** and N-functionalization (**11**) are all carried out in a one-pot procedure.



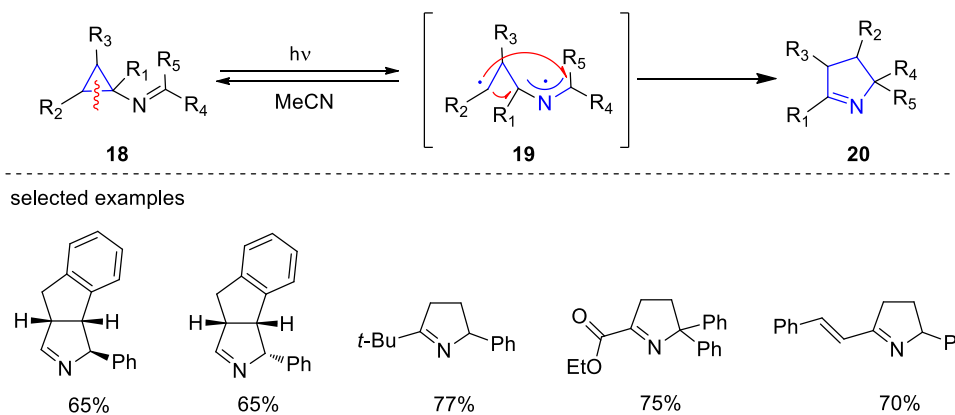
Scheme 2: Photochemically generated masked N-centered radical strategy for the synthesis of cyclopentylamines.

The ring opening of the cyclobutane was also observed under similar conditions (Scheme 3).²² Irradiation of the bicyclo [1.1.1] pentan-1-amine derived imine **12** generates the N-centered radical species **16**, which initiates cyclobutane ring cleavage generating the primary radical intermediate **17**. This nucleophilic radical reacts then with an alkene to give an inert bicyclo [3.1.1] heptan-1-imine **14**. The reaction has been performed with a variety of styrenes **13**. The imine products are easily hydrolyzed to give primary amine building blocks.



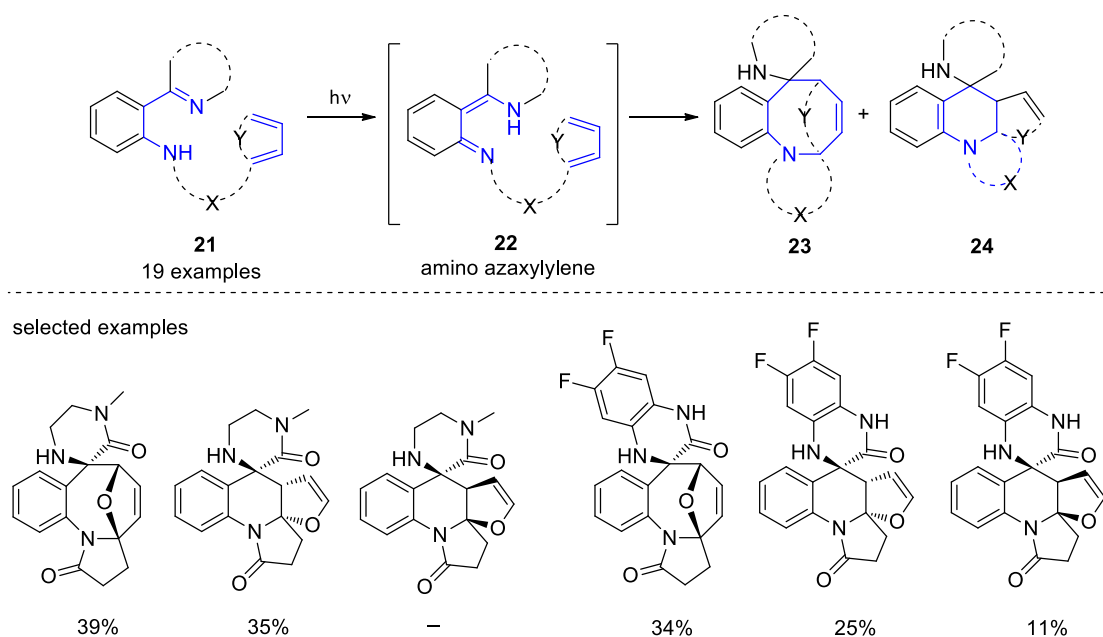
Scheme 3: Photochemical synthesis of bicyclo[3.1.1]heptan-1-amines.

The photochemical cyclopropylimine-pyrroline rearrangement has been reported for the first time in 2001.¹⁹ In 2005, a thorough study of the mechanism, regiochemistry and stereochemistry of the reaction has been published. It was found that electronically excited nonequilibrated diradicals are involved in the mechanism as transients. Their decay leads to pyrrolines and cyclopropylimine isomers. The regiochemistry of the reaction is related to the ability of different groups to stabilize the radical formed during the reaction. The stereochemistry of reaction depends on the irradiation time and the substitution of the imine. Simple and complex substitution pattern of the cyclopropane ring and in the iminic position of the *N*-cyclopropylimine structure have been used to synthesize the corresponding 1-pyrrolines (Scheme 4).²⁰



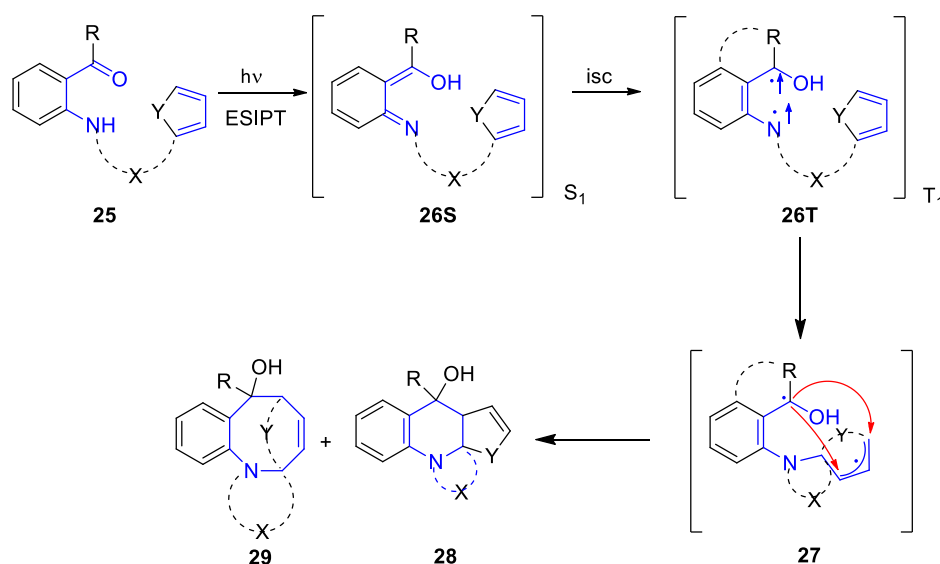
Scheme 4: The N-Cyclopropylimine-1-pyrroline photorearrangement.

In 2015, Kutateladze et al. reported an imine-based photoassisted intramolecular cycloaddition to synthesize complex nitrogen poly-heterocycles (Scheme 5). Irradiation of imines containing *o*-amido groups **21** produces reactive amino azaxylylenes intermediates **22**. They are photogenerated *via* excited state intramolecular proton transfer (ESIPT), which undergo intramolecular [4 + 2] (**23**) and [4 + 4] (**24**) cycloadditions to yield complex N,O-heterocycles with a spiro-connected nitrogen heterocyclic moiety.²³ A variety of cyclic imines containing *o*-amido groups with tethered furan and pyrrole-based unsaturated pendants have been used to access the corresponding [4 + 2] and [4 + 4] formal cycloadditions products in good yields.



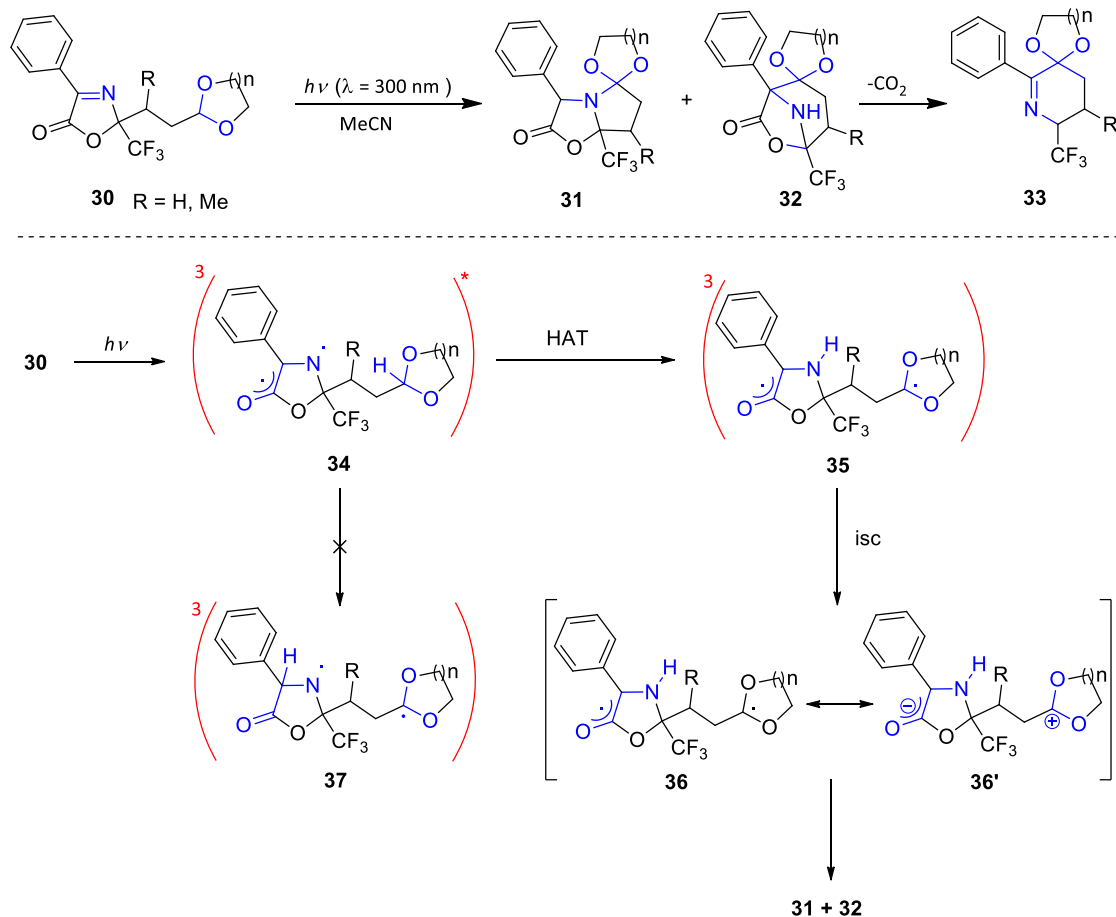
Scheme 5: Photogeneration of amino azaxylylenes and their intramolecular photocyclizations.

The mechanism of such reactions has previously been experimentally and computationally studied with azaxylylenes photogenerated by ESIPT in aromatic *o*-amido ketones and aldehydes bearing unsaturated functionalities (Scheme 6).²⁴ Amides of aromatic *o*-ketones and aldehydes **25** undergo fast and efficient ESIPT leading to their tautomeric form, azaxylylene **26S**. Intersystem crossing yields the triplet azaxylylene diradicaloid species **26T**. In a first step, the nitrogen centered radical adds to a double bond to form the diradical intermediate **27**. Radical combination leads to both **28** and **29**.



Scheme 6: The proposed mechanism of the intramolecular [4 + 2] and [4 + 4] formal cycloadditions.

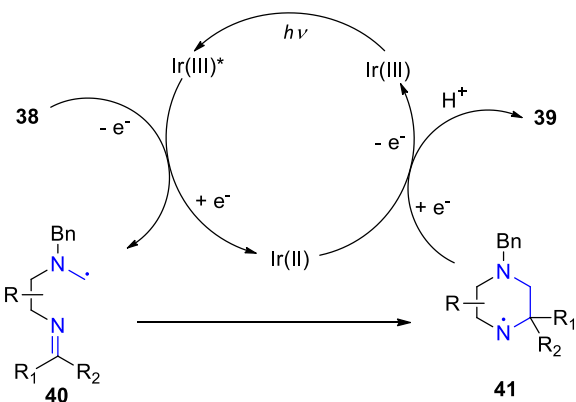
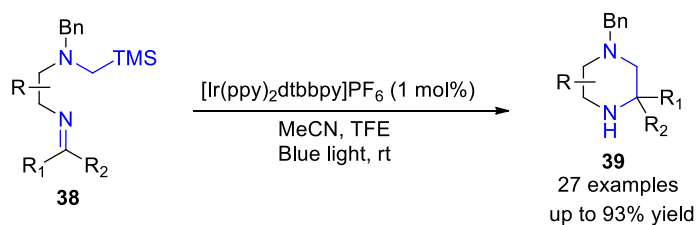
Hydrogen atom transfer, induced by light absorption, generates high energy radical species that can rearrange or react with other species to form complex structures. Hoffmann et al. reported a photochemically induced intramolecular hydrogen atom transfer in cyclic imines followed by a cyclization leading to two compound families resulting either from the formation of a C–C bond or a C–N bond (Scheme 7).²⁵ A mechanism supported by a computational study is suggested. After electronic excitation of imine function **30** which generates the triplet excited state diyl **34**, an intramolecular hydrogen atom transfer occurs from the acetal moiety to the imine nitrogen atom in one-step process (the proton and the electron are simultaneously transferred). Single electron transfer from acetal functions is very difficult²⁶ which excludes a two-step HAT process (the electron is transferred first, and the proton follows).²⁷ The hydrogen abstraction at the carbon atom of the imine function is energetically less favored. The resulting diradical **35** undergoes intersystem crossing to give singlet state intermediate **36** or **36'**. C-C Coupling reaction yields the bicyclo[3.2.1]-octane derivative **32** and the N-C coupling produces the bicyclo[3.3.0]octane derivative **31**. Similar reactions have been carried out with α,β -unsaturated furanones.²⁸



Scheme 7: Photoinduced intramolecular radical cyclisation *via* 1,5-HAT with imines.

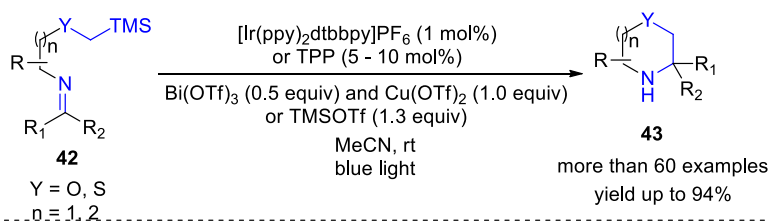
2.2 Generation of radical intermediates by photoredox catalysis.

Numerous reports of radical additions to imines under visible light photocatalysis for the synthesis of saturated N-heterocycles have been reported. In 2016, Bode's group described a photocatalytic synthesis of piperazines from silicon amine protocol (SLAP) reagents with an imine moiety using $[\text{Ir}(\text{ppy})_2\text{dtbbpy}]\text{PF}_6$ as the catalyst (Scheme 8).²⁹ Single-electron oxidation of the α -silyl amine **38** by photoexcited $\text{Ir}(\text{III})^*$ complex and desilylation generate the $\text{Ir}(\text{II})$ species and the nitrogen stabilized carbon-centered radical **40**. This latter species adds to iminic carbon giving the cyclized N-centered radical **41**. A single-electron-transfer reduction followed by protonation affords the piperazine product **39** and regenerates the $\text{Ir}(\text{III})$ catalyst. This reaction tolerates a wide range of heteroaromatic, aromatic, and aliphatic SLAP reagents.

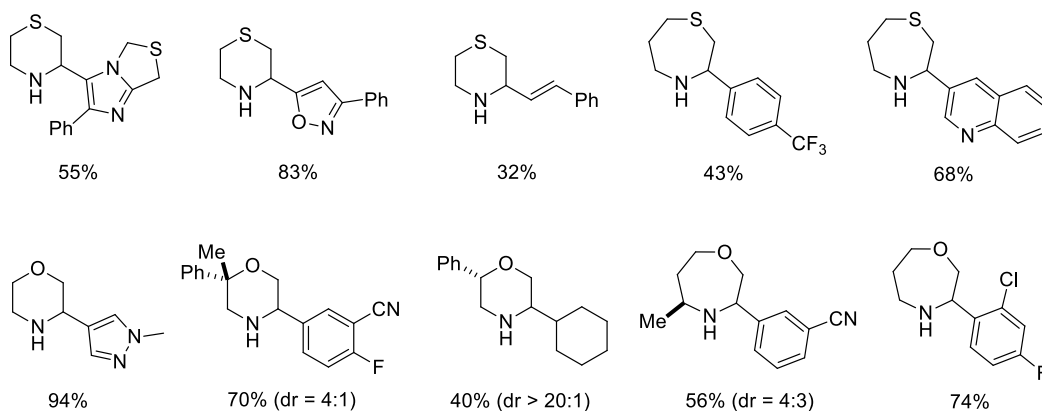


Scheme 8: Photoredox catalytic synthesis of piperazines using SLAP reagents and the proposed mechanism.

The synthesis of substituted morpholines, oxazepanes, thiomorpholines, and thiazepanes (**43**) has also been reported (Scheme 9).³⁰ The key point in this transformation is the use of a Lewis acid to activate the imine **42** which induces an alternative photocatalytic cycle with an initial Lewis acid-assisted single-electron reduction of the imine.

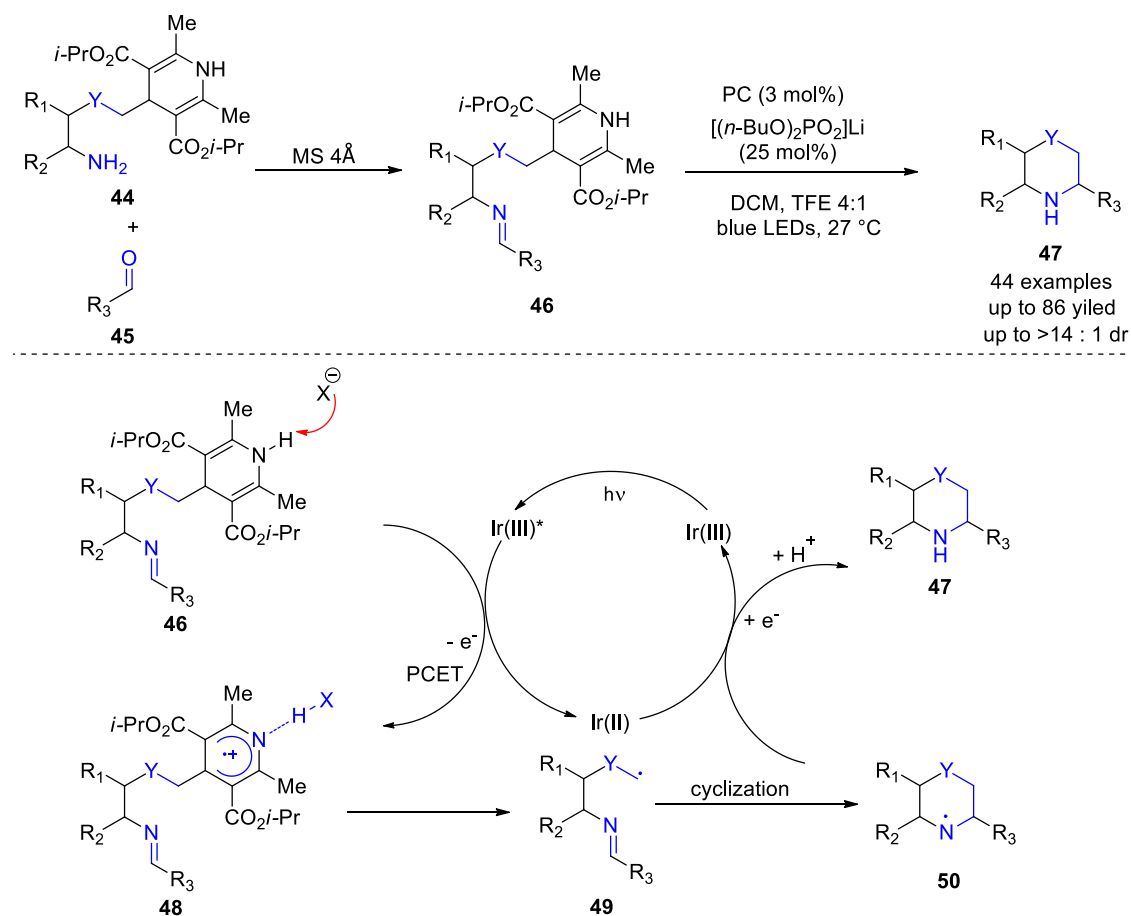


Selected examples



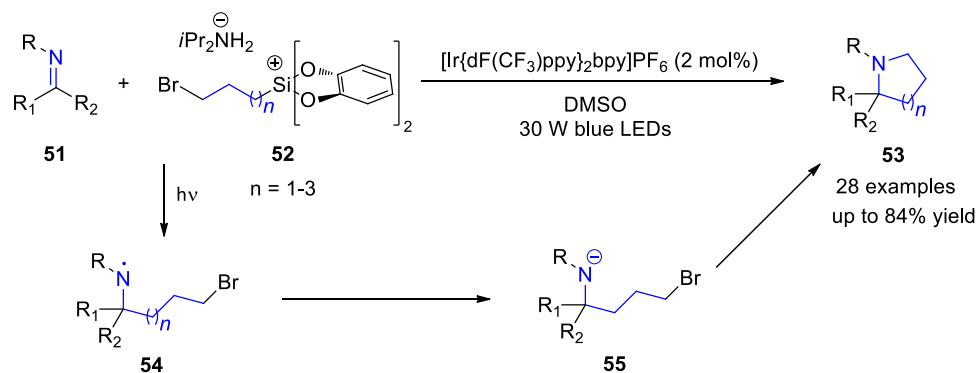
Scheme 9: Photoredox catalytic synthesis of saturated N-heterocycles using SLAP reagents.

Shortly thereafter, Romanov-Michailidis et al. also developed an efficient approach for the synthesis of saturated nitrogen containing heterocycles using a dual-catalyst system composed of an iridium photocatalyst and a lithium phosphate base (Scheme 10).³¹ Condensation of complex amino-dihydropyridine (DHP) reagents **44** with heteroaromatic, aromatic, and aliphatic aldehydes **45** give imino-tethered DHP intermediates **46** that undergo photoredox catalytic cyclization with visible light irradiation to afford corresponding cyclization products **47** in high yields (54–86%) and with excellent levels of diastereocontrol (up to >14 : 1 dr). The mechanism begins with a proton coupled electron transfer (PCET) quenching of the photoexcited Ir(III)* species by imino-DHP **46** with help from the Brønsted-basic phosphate anion (X⁻)³² to give radical-cationic intermediate **48** which then undergoes β-cleavage to afford α-heteroatom stabilized C-centered radical **49**. The latter adds to the iminic carbon via 6-endo-trig cyclization to give N-centered radical **50**. Single-electron-transfer reduction followed by proton transfer leads to the product and regenerates Ir(III) photocatalyst.



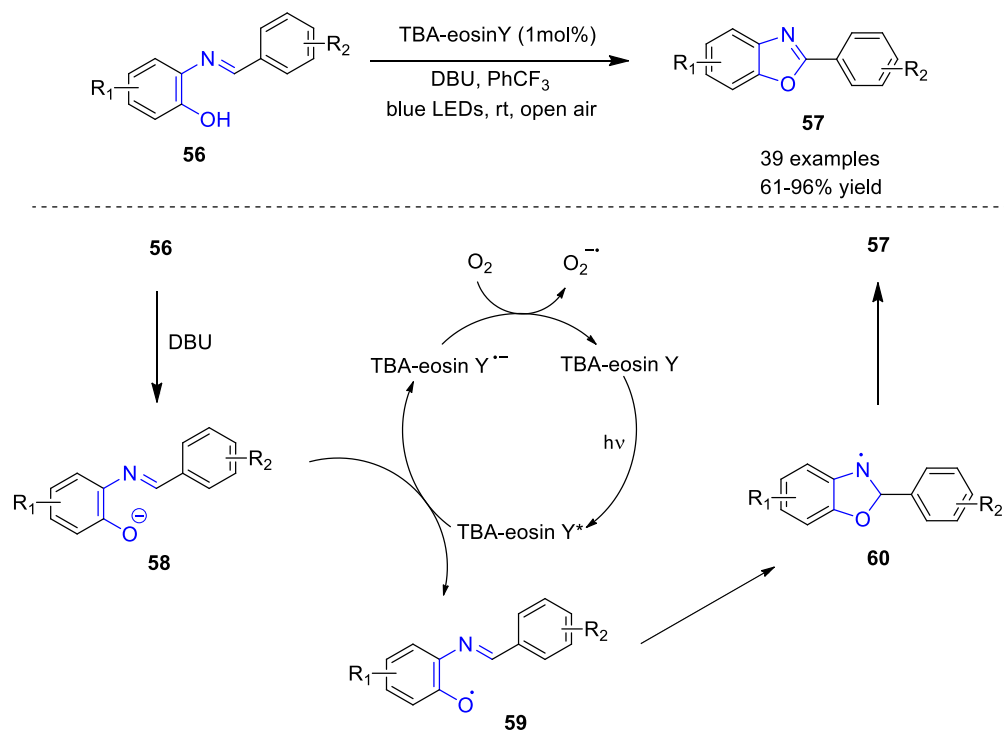
Scheme 10: Synthesis of saturated N-heterocycles by photoredox cyclization of imino-tethered dihydropyridines and the proposed mechanism.

Radical alkylation and subsequent cyclization in photoredox-mediated radical/polar crossover (RPC) process leading to saturated N-heterocycles has been reported (Scheme 11).³³ Under visible light irradiation conditions, alkyl radicals possessing pendant leaving groups (e.g. bromide) generated from corresponding alkyl silicates leads to C–C bond formation with imines. Subsequent reduction of the resulting nitrogen-centered radical **54** furnishes an amide anion **55** that engage the leaving group in an intramolecular nucleophilic substitution. The substituted pyrrolidines, piperidines, and azepanes were obtained in yields up to 84%. Further examples of radical reactions with silicates have been published.³⁴



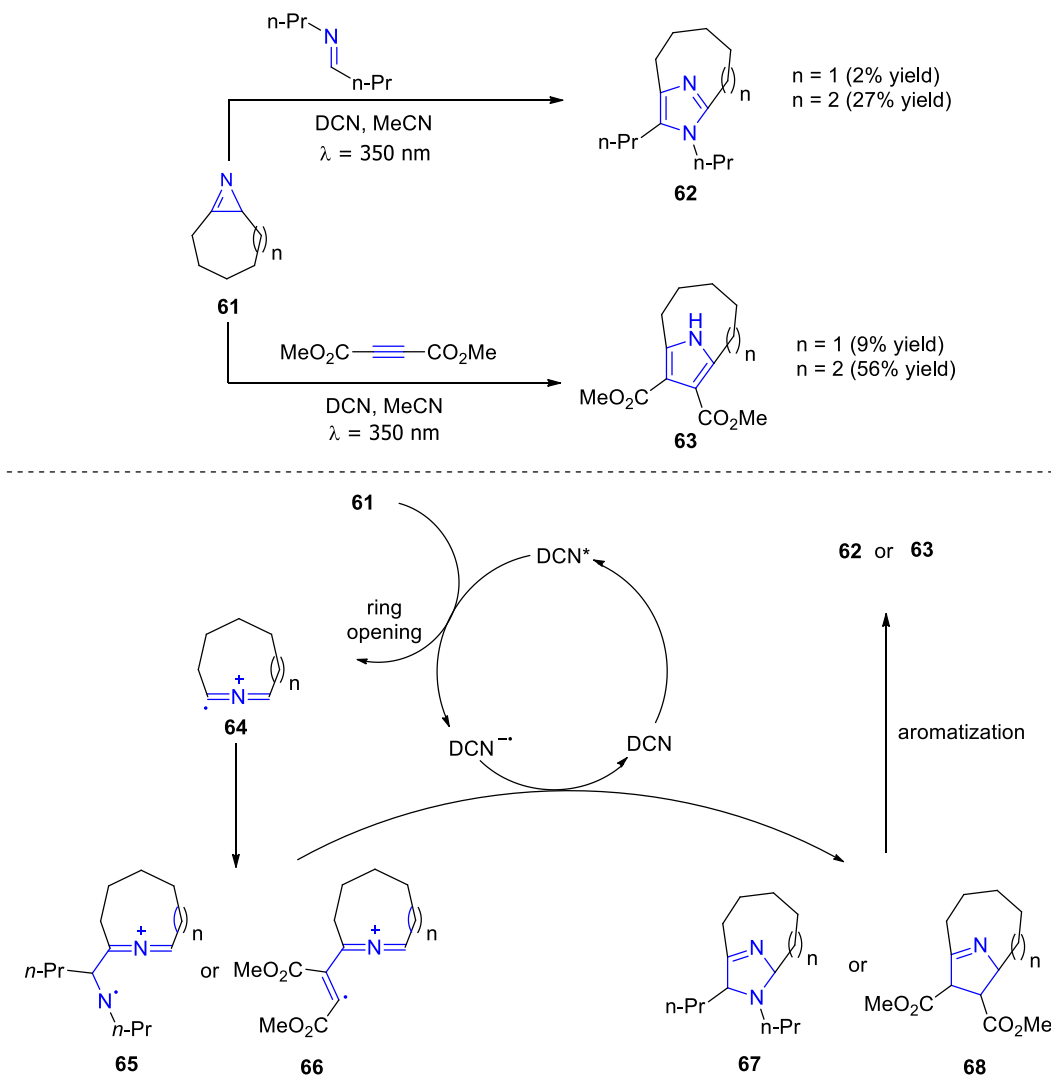
Scheme 11: Photoredox-mediated radical/polar crossover (RPC) process for the synthesis of saturated N-heterocycles.

In 2014, the group of Wu and Liu developed a visible-light supported method for aerobic catalytic oxidative cyclization of phenol-2-imines **56** (Scheme 12).³⁵ By combining bis(tetrabutylammonium salt) (TBA)-eosin Y and molecular oxygen as oxidant in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as a base, 39 examples of phenol-2-imines (**56**) were readily transformed with excellent yield into 2-substituted benzoxazoles **57**. The suggested photocatalytic aerobic dehydrogenation mechanism is depicted in Scheme 12.³⁶ The phenol moiety can be easily deprotonated to the corresponding phenolate anion **58**, a much stronger electron donor, in the presence of DBU. The efficient electron transfer from phenolate anion to the excited TBA-eosin Y generates the phenoxyl radical **59**. The photocatalyst is regenerated by oxidation of the TBA-eosin Y radical ion by molecular oxygen. The phenoxyl radical **59** undergoes intramolecular 5-endo cycloaddition to the imine carbon atom to form the corresponding aminyl radical **60** which can react with the photocatalyst or superoxide radical anions to afford the dehydrogenated product **57** selectively.



Scheme 12: Visible-light supported aerobic catalytic oxidative cyclization of 2-substituted phenolic imines and the proposed mechanism.

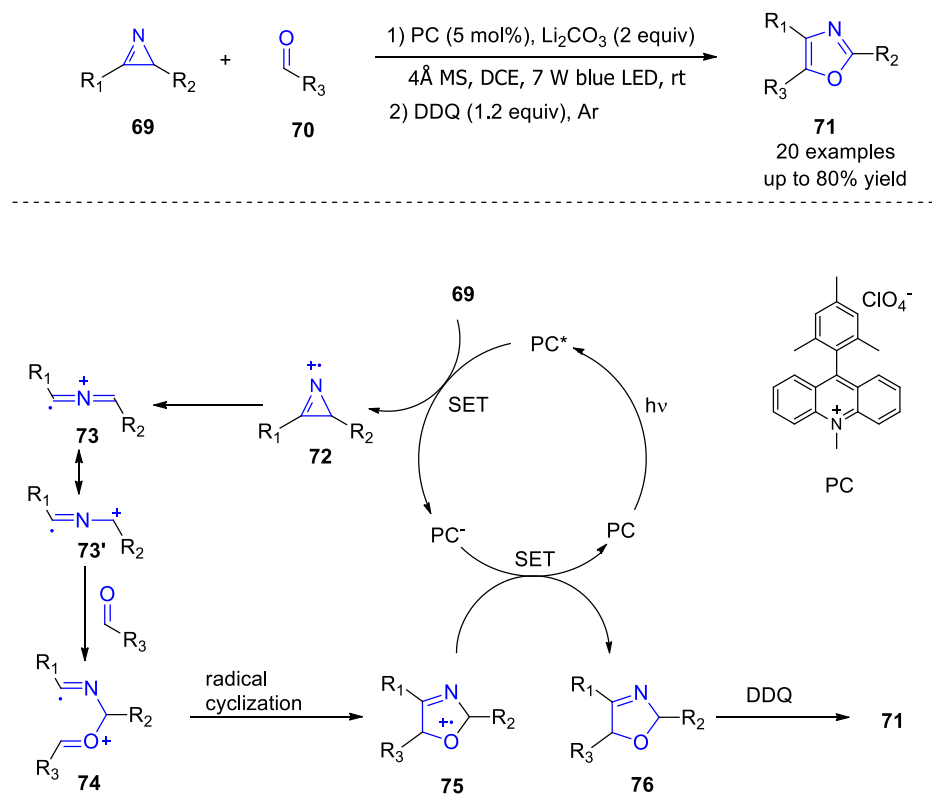
The photocycloaddition reaction of 2*H*-azirines, known for a long time, is an extremely versatile and important process for the synthesis of aza-heterocycles. Remarkable achievements have been made toward understanding the factors which determine the photochemical behavior in a given system.³⁷ In 1991, Müller and Mattay reported the synthesis of imidazolophanes **62** and pyrrolophanes **63** by means of photoinduced electron transfer (PET) using 1, 4-naphthalenedicarbonitrile (DCN) as the photocatalyst (Scheme 13).³⁸ Under these conditions, the electron acceptor is excited by irradiation with light at $\lambda=350$ nm in the presence of azirine **61**, leading to the DCN radical anion and a reactive azirine radical cation. This latter species opens to the linear 2-azaallenyl radical cation **64**. In a two-step process, radical addition of **64** to activated alkynes or imine double bond leads to intermediates **65**, **66** which subsequently undergo a reduction/cyclization sequence (**67**, **68**) followed by aromatization to give corresponding imidazolophanes **62** and pyrrolophanes **63**.



Scheme 13: The synthesis of imidazolophanes and pyrrolophanes.

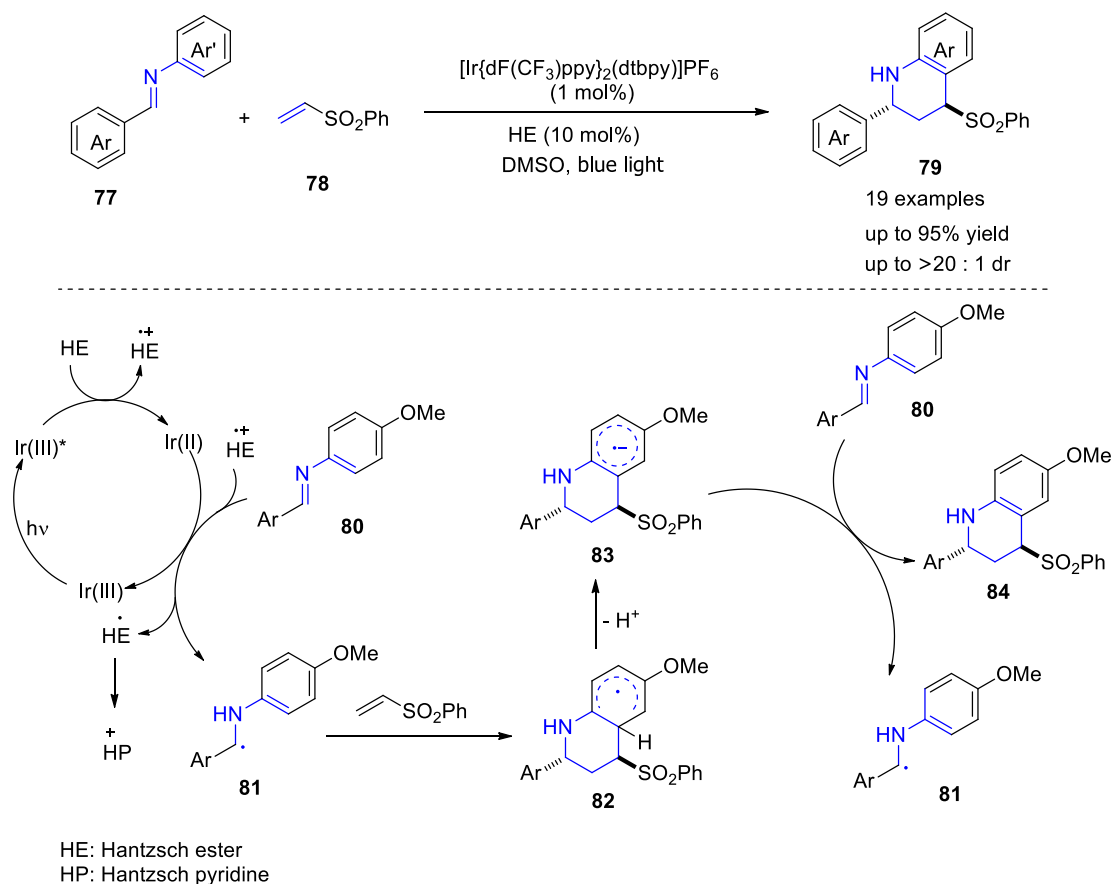
Recently, Xiao and Lu et al. reported a visible light photoredox-catalyzed [3 + 2] cycloaddition/oxidative aromatization sequence of 2*H*-azirines **69** and aldehydes **70** using 9-mesityl-10-methylacridinium perchlorate as a photocatalyst and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) as an oxidizing agent (Scheme 14).³⁹ This catalytic system provides an efficient access to highly functionalized oxazoles **71** from easily accessible 2*H*-Azirine **69** by a single-electron-transfer process to give radical cation **72** which then undergoes homolytic cleavage of the C–C bond to generate the 2-azaallenyl radical cation **73**. Nucleophilic attack of benzaldehyde on **73** delivers the intermediate **74**, which subsequently undergoes an intramolecular radical cyclization to afford the new radical cation **75**. After that, this transient species **75** undergoes another single-electron-transfer reduction by the reducing photocatalyst to afford the cycloadduct **76** with the concomitant regeneration of photocatalyst. Finally, the oxidative aromatization of 2,5-

dihydrooxazole **76** yields the desired oxazole product **71**. Under similar conditions, electro-deficient alkynes react with 2*H*-azirines to yield polysubstituted pyrroles.⁴⁰



Scheme 14: Visible light photoredox-catalyzed [3 + 2] cycloaddition/oxidative aromatization sequence of 2*H*-azirines and aldehydes.

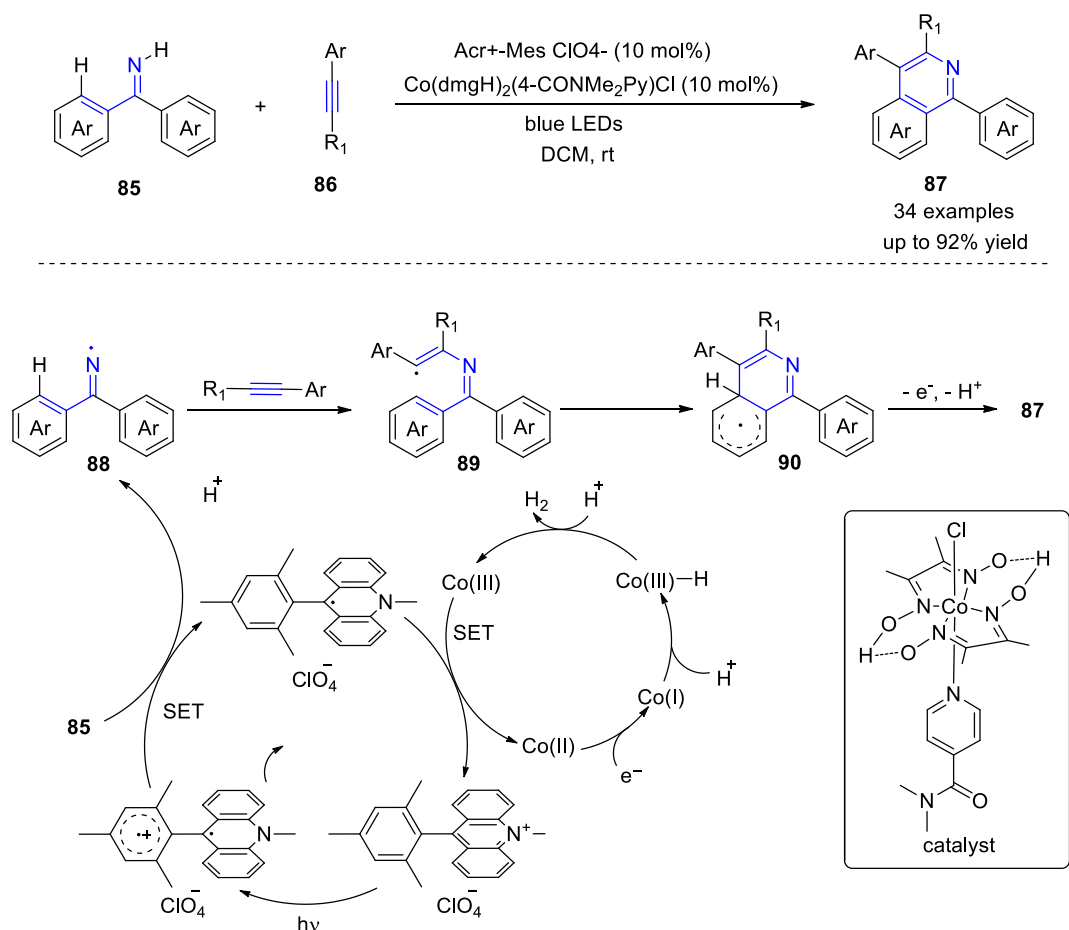
Further studies of consecutive radical addition cyclization reactions leading to *N*-polyheterocyclic compounds have been reported. In 2018, Dixon's group described a visible light photocatalyzed polarity reversed Povarov reaction of aryl imines **77** and electron deficient alkenes. Using [Ir{dF(CF₃)ppy}₂(dtbpy)]PF₆ as photocatalyst and the commercial Hantzsch ester as a stoichiometric reductant, a range of substituted tetrahydroquinoline **79** were obtained in high yields and with typically good to excellent diastereoselectivity in favor of the *trans* diastereoisomer (Scheme 15).⁴¹ A proton coupled electron transfer (PCET) based mechanism is proposed. After photochemical excitation of the photo-catalyst, electron transfer occurs from the Hantzsch ester (HE) derivative to the catalyst yields the Ir(II) species. Electron transfer from this Ir(II) species coupled to a proton transfer from the Hantzsch ester radical cation to the imine function leads to the α -amino radical **81** which then reacts with the phenyl vinyl sulfone in a step-wise radical cyclization to give the stabilized Povarov radical intermediate **82**. In a base assisted homolytic aromatic substitution-type mechanism, this intermediate **82** loses a proton to form strongly reducing radical anion intermediate **83** which can reduce fresh imine substrate **80** with concomitant protonation to lead to the product **84** and regenerates the key α -amino radical in a radical chain process.



Scheme 15: The photocatalytic polarity reversed Povarov reaction and the postulated mechanism.

Another consecutive radical addition cyclization reaction leading to various isoquinolines and related polyaromatics has been reported (Scheme 16).⁴² In a photoredox catalytic process, an iminyl radical intermediate **88** is generated by N–H cleavage. The latter initiates a cascade C–N/C–C bonds formation in the presence of alkynes to give the cyclization products **87** in good yields up to 92%. It should be noted that the photocatalyst is regenerated in a cobalt co-catalytic cycle. In these steps the intermediate **90** is transformed into the final product **87** (rearomatization) via electron and proton transfer to the Co(II) species.

Using a dual photoredox/cobaloxime catalytic system, oxidative [4+2] annulation of NH imines and alkenes for the synthesis of multisubstituted 3,4-dihydroisoquinolines has been described.⁴³

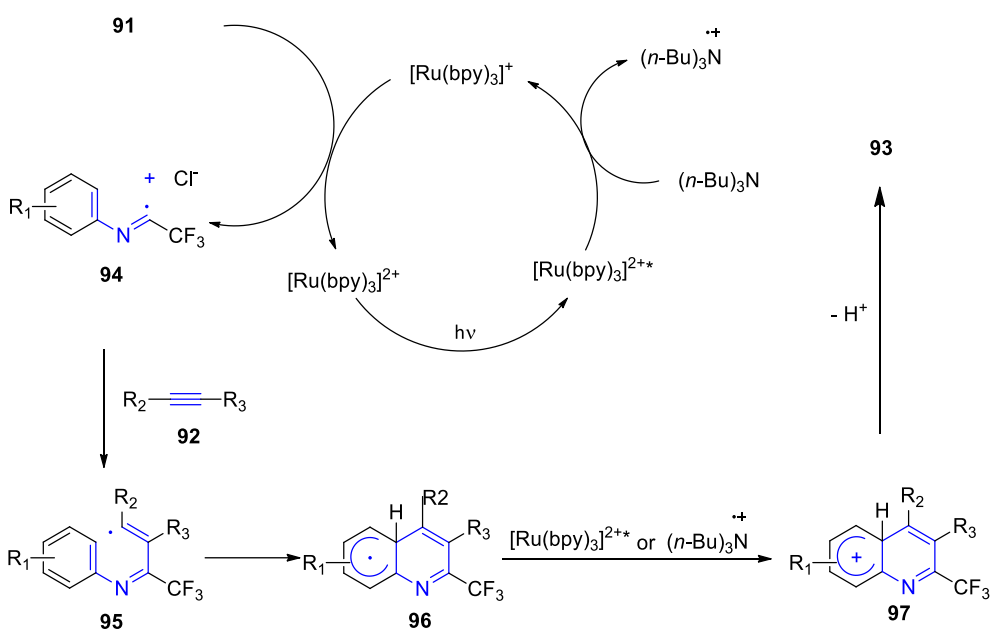
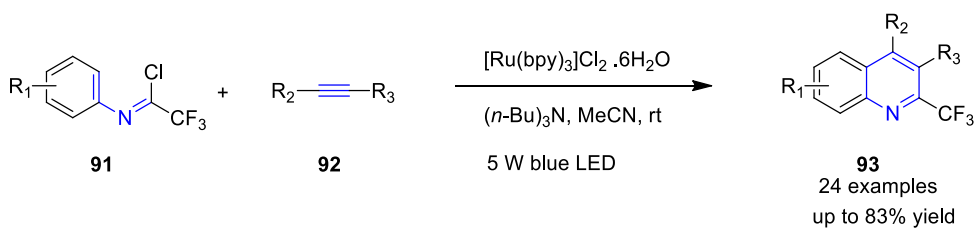


Scheme 16: Visible-light synthesis of isoquinolines and related polyaromatics.

3 imidoyl chlorides

Activation of C–heteroatom bond on the imine carbon is useful for the generation of imidoyl radicals by photoredox catalysis. This attractive intermediate has been used as key intermediate in the synthesis of various nitrogen-containing heterocycles. Intra- and intermolecular additions of imidoyl radicals to triple carbon-carbon and carbon-nitrogen bonds, as well as cyclizations onto aromatic rings under visible-light irradiation were reported.⁴⁴ In 2013, Zhou et al. reported a visible-light-mediated radical addition cyclization of trifluoroacetimidoyl chlorides **91** with alkynes **92** for the synthesis of 2-trifluoromethyl quinolines **93** using imidoyl radicals as a key intermediate (Scheme 17).⁴⁵ The reaction is initiated by photochemical excitation of $[\text{Ru}(\text{bpy})_3]^{2+}$. Single-electron-transfer from electron donor ($n\text{-Bu}$)₃N to excited $[\text{Ru}(\text{bpy})_3]^{2+*}$ generates $[\text{Ru}(\text{bpy})_3]^+$ and the radical cation of tributylamine. The imidoyl chloride is reduced and a chloride ion is released. The resulting radical intermediate **94** undergoes radical addition (**95**) cyclization with the alkyne **92**. The bicyclic radical intermediate **96** is oxidized by either the photoexcited $[\text{Ru}(\text{bpy})_3]^{2+*}$ catalyst or the radical cation ($n\text{-Bu}$)₃N⁺ yielding the cation intermediate **97**. After deprotonation (rearomatization), the final product **93** is obtained.

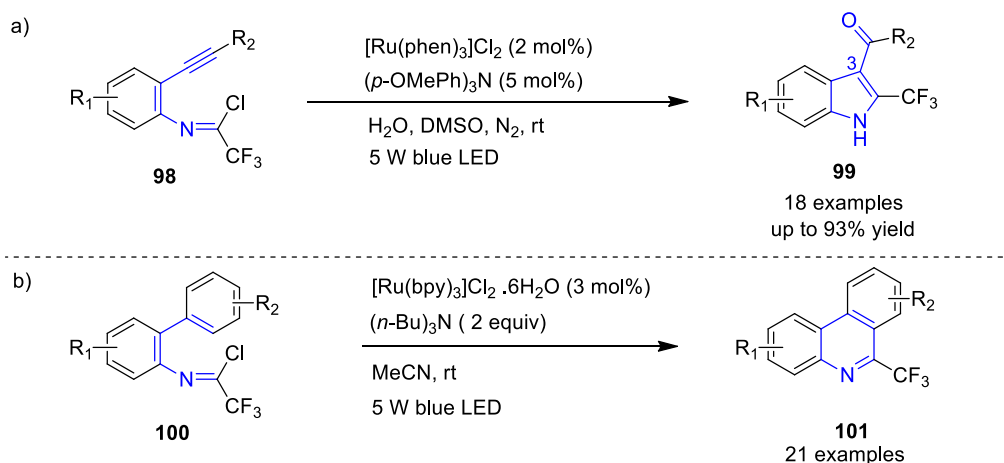
Various functional groups including methoxy, ester, and ketone present in alkyne, and a variety of para, meta, ortho-substituted phenylacetylenes all worked well to afford the 2-trifluoromethyl quinolines in good yields.



Scheme 17: The synthesis of 2-trifluoromethyl quinolines and the proposed mechanism.

Under similar conditions, the intramolecular cyclization version was also described. In this case, N-[2-(alkynyl)phenyl]trifluoroacetimidoyl chlorides **98** were used to synthesize 2-trifluoromethyl indoles **99** carrying acyl groups in position 3 (Scheme 18a). A large variety of functional groups can tolerate these mild reaction conditions.⁴⁶

A similar reaction was carried out by Fu et al. for the synthesis of 6-trifluoromethyl phenanthridines **101** through photoredox-catalyzed intramolecular radical cyclization of trifluoroacetimidoyl chlorides **100** (Scheme 18b).⁴⁷

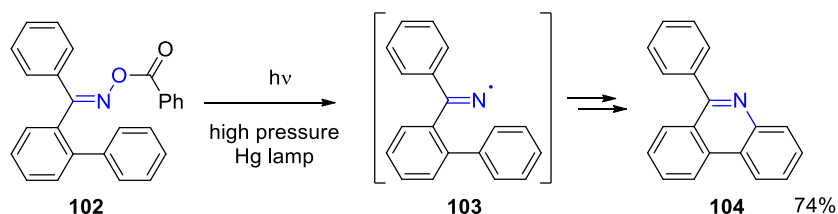


Scheme 18: Light-promoted imidoyl radical cyclization.

4 Oximes

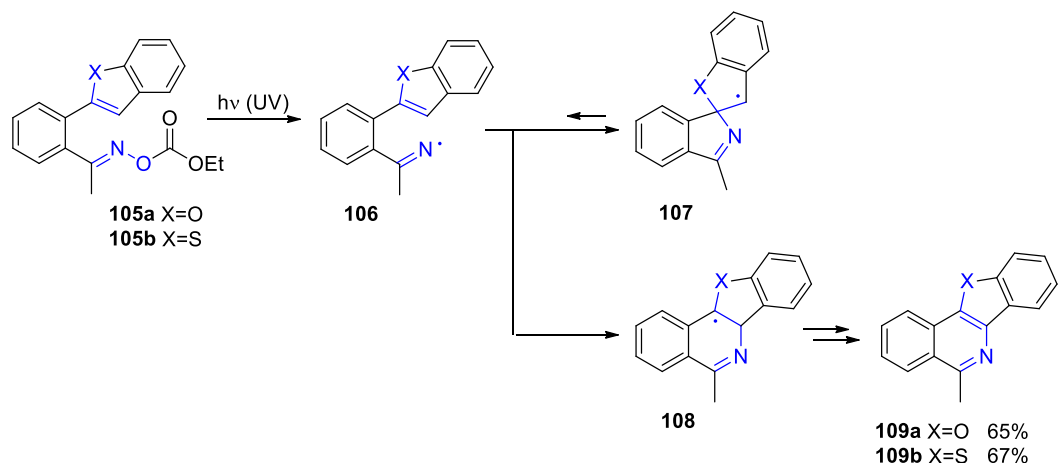
4.1. Generation of radical intermediates by electronic excitation of the substrates

In photochemical or microwave induced reactions, oximes are suitable precursors for nitrogen centered radicals.⁴⁸ A variety of nitrogen containing heterocycles are obtained in this way. A typical example is depicted in Scheme 19. Irradiation of the oxime derivative **102** leads to homolytic fragmentation of the N-O bond (**103**).⁴⁹ Concomitantly formed acyloxy radicals or phenyl radicals (resulting from decarboxylation) preferentially react with the solvent. Cyclization of intermediate **103** yields the phenanthridine **104**. This reaction is frequently observed. For example, it plays a key role in the photochemical stability of pesticides containing this functional group.⁵⁰ In this context, a profound theoretical investigation has been carried out on the competition between the bond fragmentation and E/Z isomerization of the oxime function. A series of phenanthridine have been synthesized using sensitization with dicyanoanthracene.⁵¹ In this case mechanistic studies based on the Hammett plots were carried out.



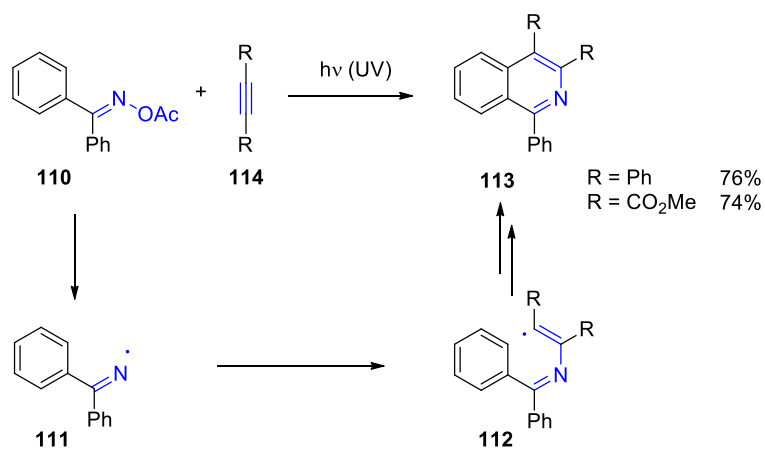
Scheme 19. Photochemically induced radical cyclization via formation of nitrogen centered radical leading to phenanthridine.

The same reaction was carried out with benzofuran **105a** and benzothiophene derivatives **105b** (Scheme 20).⁵² In this case, the oxime was used with a carbonate protecting group. The iminyl radical intermediate **106** was generated by UV irradiation. EPR spectroscopy has been carried out. DFT calculations revealed that spirocyclization (**107**) is kinetically favored, especially at low temperatures, while ortho cyclisation (**108**) is thermodynamically favored. The corresponding phenanthridines **109a,b** have been isolated in good yields. The synthesis strategy can be further extended in heterocyclic chemistry, for example to the preparation of corresponding pyrrolizidine derivatives.⁵³



Scheme 20. Synthesis of phenanthridines with benzofuran and benzothiophene substituted oxime derivatives.

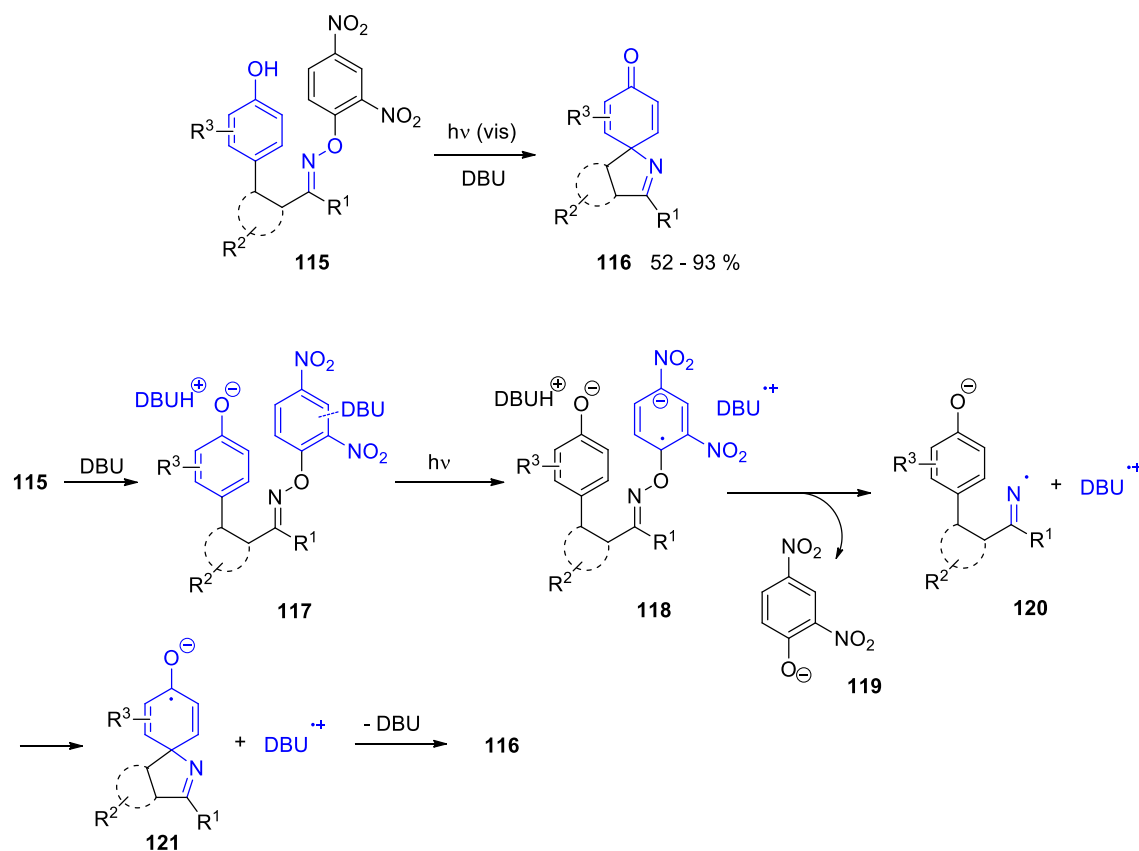
Addition cyclization reactions were carried out. In such an example, a nitrogen centered radical intermediate **111** is generated from a corresponding oxime **110** (Scheme 21).⁵⁴ After addition of an alkyne **114**, a vinyl radical **112** is formed. The final isoquinoline derivative **113** is then obtained in a cyclization step.



Scheme 21. Radical addition cyclization applied to the synthesis of isoquinoline derivatives.

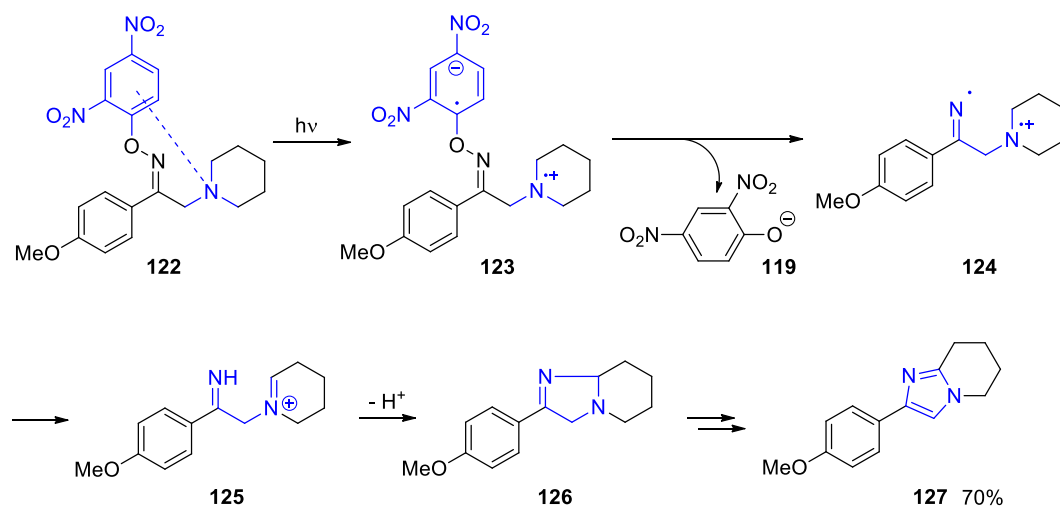
4.2. Generation of radical intermediates by irradiation of charge transfer complexes

Excitation of a ground state charge transfer complex is now applied to the formation of radical intermediates. Such a reaction was carried out with visible light irradiation (Scheme 22).⁵⁵ In this case, the oxime function in **115** carries a dinitrophenyl substituent as leaving group. The intramolecular radical addition takes place on a phenol substituent. The resulting spiropyrroline derivatives **116** were obtained in yields up to 93%. In the present paper 27 examples have been published. It is a typical example of a dearomatization reaction. Such transformations are often used to increase structural complexity. Visible light irradiation is also recommended since the dienone moiety in **116** undergoes photochemical rearrangements under UV irradiation. Furthermore, the reaction has been carried out in the presence of DBU. It has been shown that DBU deprotonates the phenol moiety and generate a charge transfer complex with dinitrophenyl substituent on the oxime function (**117**). Both the phenolate and the charge transfer complex significantly increase the light absorption in the visible domain (450 – 600 nm). After photochemical excitation, electron transfer takes place in the charge transfer moiety leading to a radical ion pair **118**.^{56,57} The cleavage of the N-O bond of the oxime and the release of dinitrophenolate **119** yields the nitrogen centered radical intermediate **120**. The latter undergoes cyclization (**121**) and after transfer of an electron to the radical cation of DBU, the final product **116** is formed.



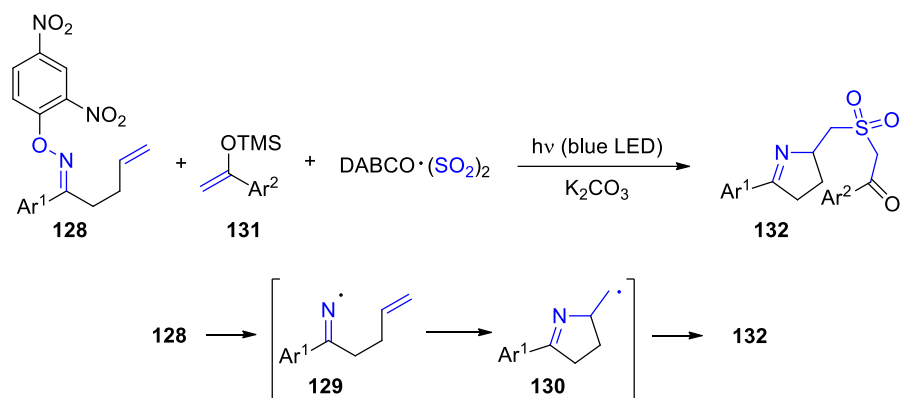
Scheme 22. Synthesis of spiropyrrolines. The cleavage of the N-O bond is induced by visible light absorption of a charge transfer complex **117**.

A similar reaction with an intramolecular charge transfer interaction between tertiary amines and the 2,4-dinitrophenyl protecting group has also been reported. A typical example is presented in Scheme 23.⁵⁸ After light absorption of the charge transfer complex **122**, an intramolecular electron transfer takes place leading to the intramolecular radical ion pair **123**. N-O Bond fragmentation occurs and 2,4-dinitrophenolate **119** is released. In the resulting iminyl radical intermediate **124**, an intramolecular hydrogen transfer leads to imine iminium species **125**. Nucleophilic addition and deprotonation yield the dihydroimidazole **126**. Under the reaction conditions, oxidation takes place and the imidazole **127** is isolated in good yield. This convenient imidazole synthesis was carried out with 27 substrates leading to the corresponding imidazole derivatives with yields up to 85%. If a corresponding pyrrolidine substrate was used instead of a piperidine, no oxidation in the final step was observed. The resulting dihydroimidazoles were isolated in good yields.



Scheme 23. Synthesis of imidazoles using excitation of an intramolecular charge transfer complex of a tertiary amine and a dinitrophenyl moiety.

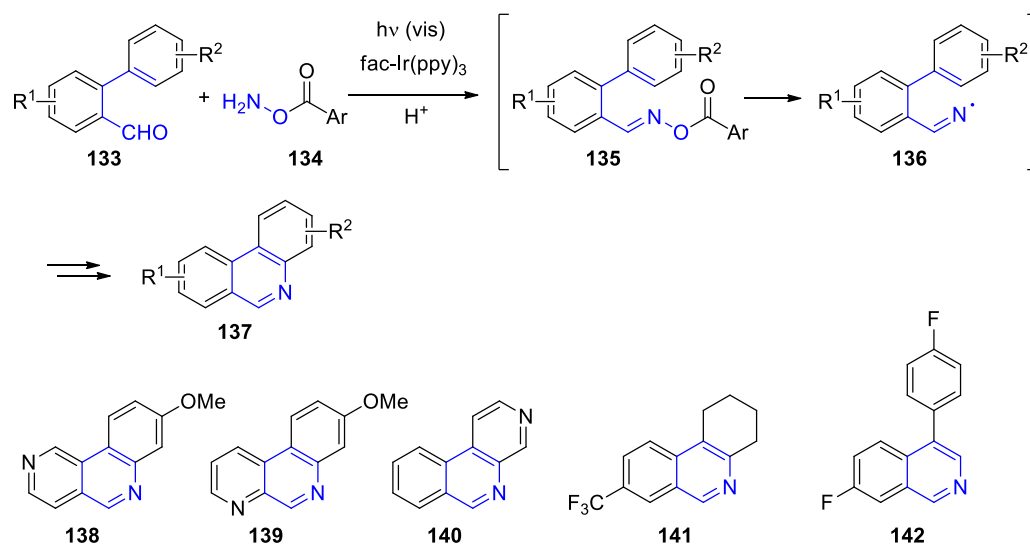
Using the above-mentioned activation by light absorption of an intermolecular charge transfer complex with a dinitrophenyl substituted oxime function (**128**), the radical intermediate **129** is generated by the release of dinitrophenolate (Scheme 24).⁵⁹ Cyclization yields the intermediate **130**. This intermediate is trapped by SO_2 and various silyl enol ethers **131** leading to the final product **132**. A variety of aromatic substrates have been successfully transformed. Also, heteroaromatic compounds ($Ar^1 = 2\text{-furyl}$) can be obtained. In the present report, 20 different derivatives have been transformed with yields up to 92%.



Scheme 24. Synthesis of pyrrolines using radical trapping with SO₂ and silyl enol ethers.

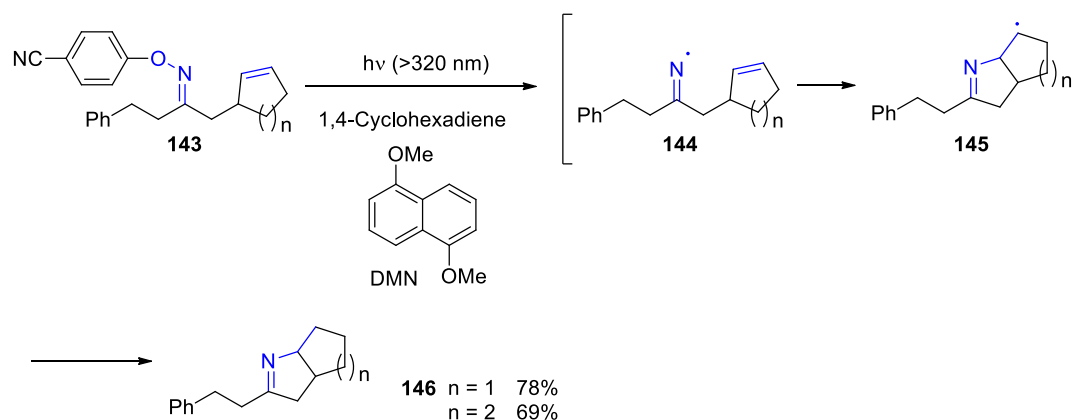
4.3. Generation of radical intermediates by photoredox catalysis.

Using photoredox catalysis with an iridium complex, a one pot procedure for the synthesis of phenanthridines has been realized (Scheme 25).⁶⁰ In the first acid catalyzed step, the oxime derivative **135** is formed by condensation of **133** and **134**. In the photochemical step, the nitrogen centered radical **136** is generated. Cyclization leads to the final product **137**. Under these mild reaction conditions, also benzonaphthyridines such as **138**, **139** or **140** have been synthesized. Starting from corresponding precursors, a variety of quinoline derivatives such as **141** and **142** are accessible. In the present report, the preparation of 28 derivatives with yields up to 89% has been described. The reaction sequence was also applied to the synthesis of benzophenanthridine alkaloids and pyridines.⁶¹



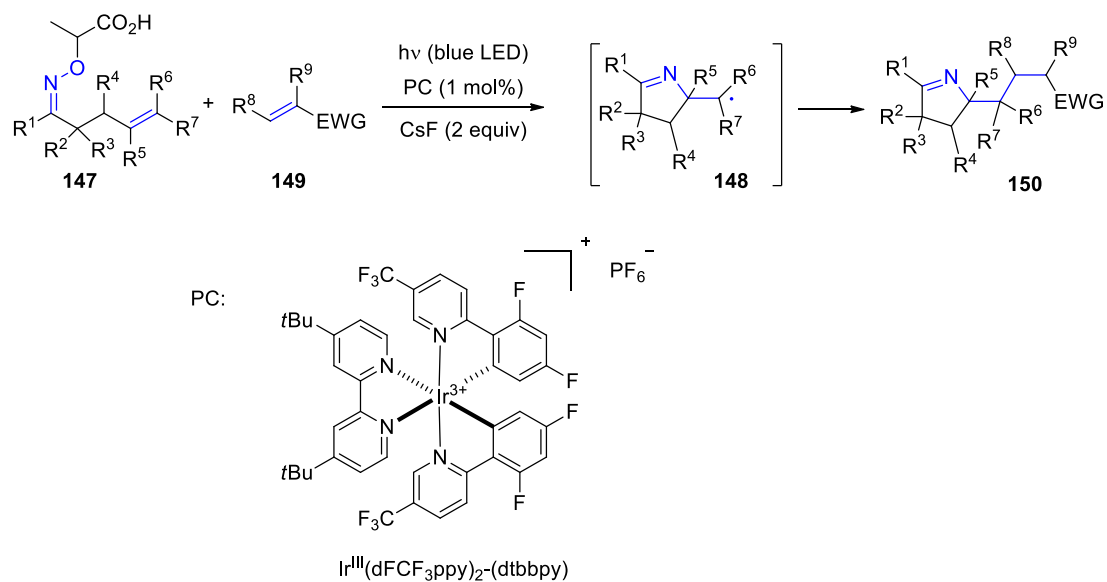
Scheme 25. Photoredox catalytic synthesis of phenanthridines and quinoline derivatives.

The oxime function can also be protected with phenyl substituents. In this case, the cleavage of the N-O bond is accompanied with the release of phenol or phenolate. In the photochemical transformation of **143** in the presence of 1,5-dimethoxynaphthalene (DMN), a photochemical electron transfer from this donor molecule to **143** is involved (Scheme 26).⁶² The nitrogen centered radical **144** is thus generated. Cyclization leads to the bicyclic radical **145**. After hydrogen abstraction from 1,4-cyclohexadiene, the final products **146** are obtained. Recently, similar reactions have been carried out using photoredox catalysis with visible light.⁵⁶ In this case also simple ketones such as chloroanthraquinone can be used as sensitizer or photocatalyst.⁶³ Detailed theoretical and physicochemical studies of such reactions have been carried out.⁶⁴



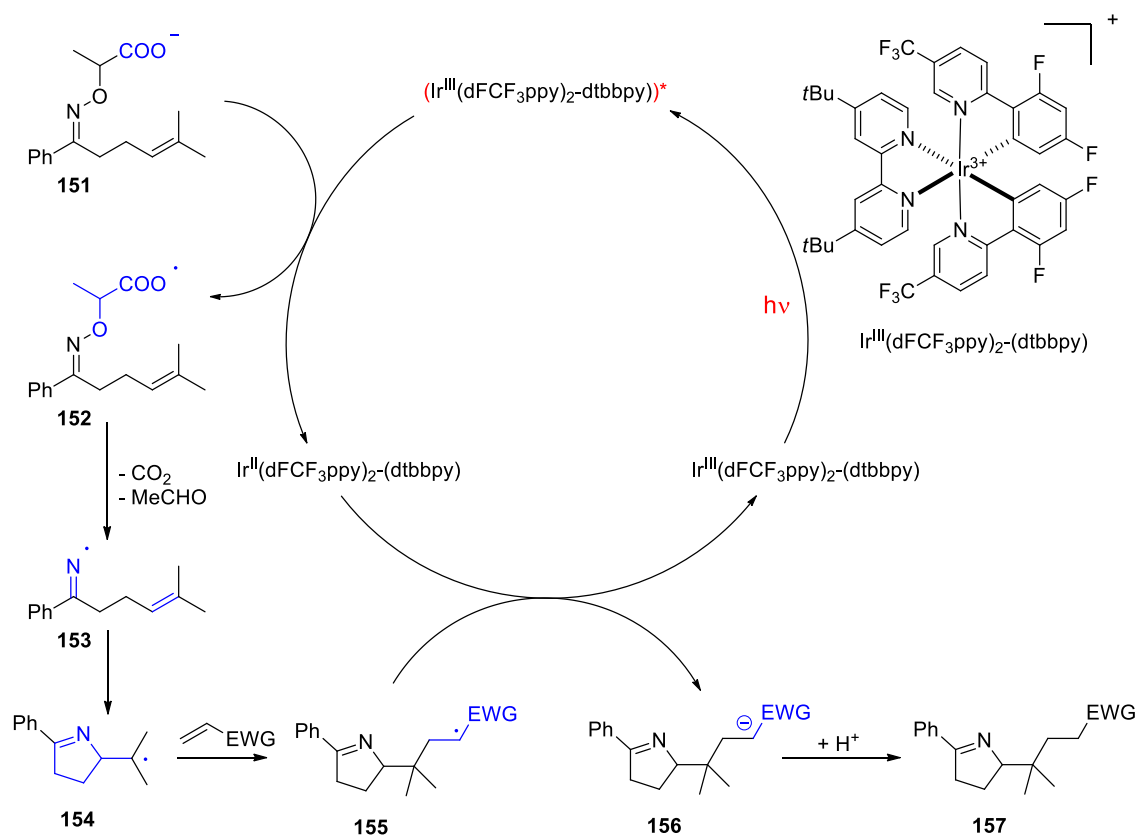
Scheme 26. Photoredox catalyzed synthesis of hexahydrocyclopenta[b]pyrroles and hexahydroindoles.

Radical species which result from a cyclization step can be trapped by various reagents. This leads to a further increase of molecular complexity and diversity. A large variety of pyrrolines have been synthesized starting from **147** in which the oxime group is O-alkylated by lactic acid (Scheme 27).⁶⁵ During the reaction, pyrroline radical intermediates **148** are formed. Several electron deficient alkenes **149** are added which leads to the final products **150**. More than 30 compounds **150** have been reported in the present investigation. The products were isolated with yields up to 91%. Various carboxylic acid derivatives have been used as leaving groups such as oxalic acid⁶⁶ or groups enabling Barton decarboxylation.⁶⁷



Scheme 27. Synthesis of a large variety of pyrrolines starting from oximes. Photoredox catalysis is involved.

The following photoredox catalysis mechanism has been suggested (Scheme 28). After photochemical excitation of the Ir(III) complex, the carboxylate function in **151** is oxidized. An Ir(II) species is formed. The resulting neutral radical **152** immediately undergoes fragmentation; carbon dioxide and acetaldehyde are released. Cyclization of the resulting iminyl radical **153** yields the alkyl radical **154**. Addition of the electron deficient alkene leads to the electrophilic radical **155**. The latter is reduced by the Ir(II) species. In this step, the photoredox catalyst is regenerated. Protonation of the anion intermediate **156** yields the final product **157**.



Scheme 28. Proposed mechanism for formation of pyrrolines in the photo-redoxcatalytic transformation of oximes with electron-deficient alkenes.

Very similar reactions have been carried out with silylenolethers as trapping reagent. In such an investigation, also a large variety of pyrrolines have been synthesized.⁶⁸ About 35 examples are reported. The products are obtained with yields up to 83%. Also, styryl borates have been successfully used as trapping reagent.⁶⁹

Various trapping reagents enables the introduction of a large number of functional groups. A selection of pyrroline derivatives from one particular investigation is depicted in Figure 1.⁷⁰ The reactions have been carried out using photo redox catalysis with N-methyl mesitylacridinium perchlorate. The usefulness of this synthetic approach is also demonstrated in the modification of natural products (Scheme 29).⁷¹ The morphine derivative **158** was readily transformed into the corresponding dihydropyrroline compounds **160**, **161** and **162**. The nitrogen centered radical **159** is the key intermediate in these reactions.

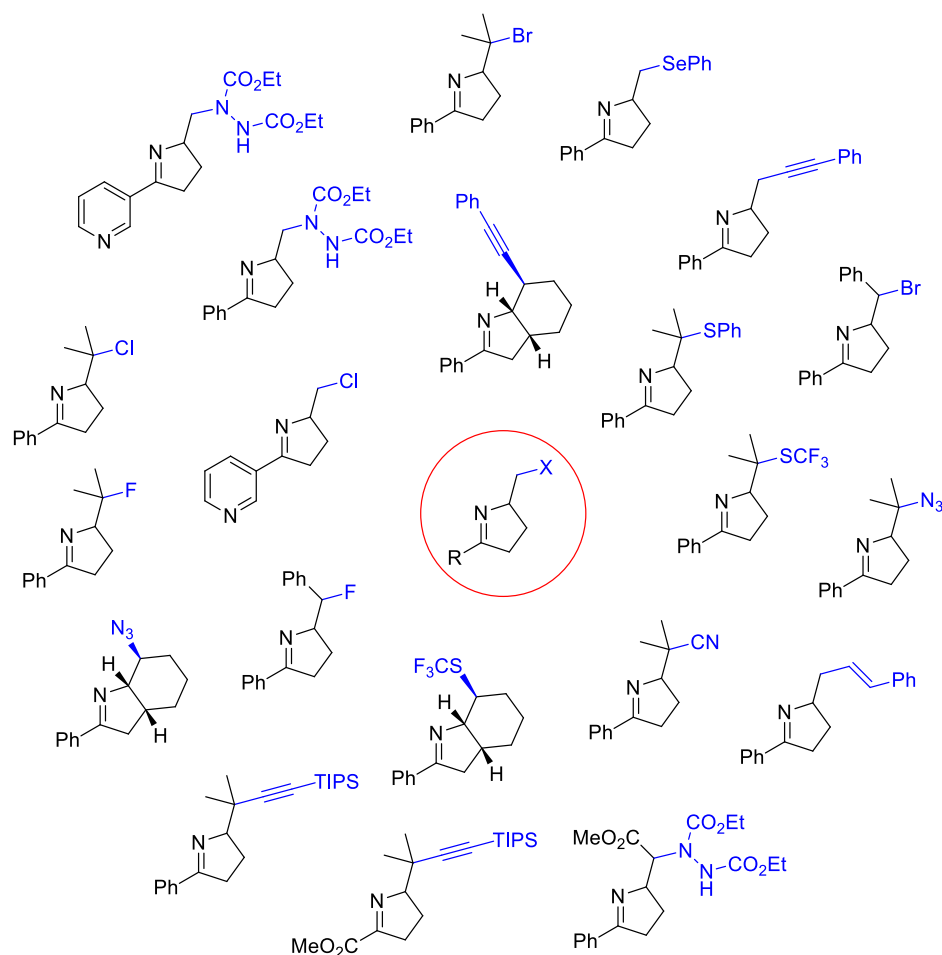
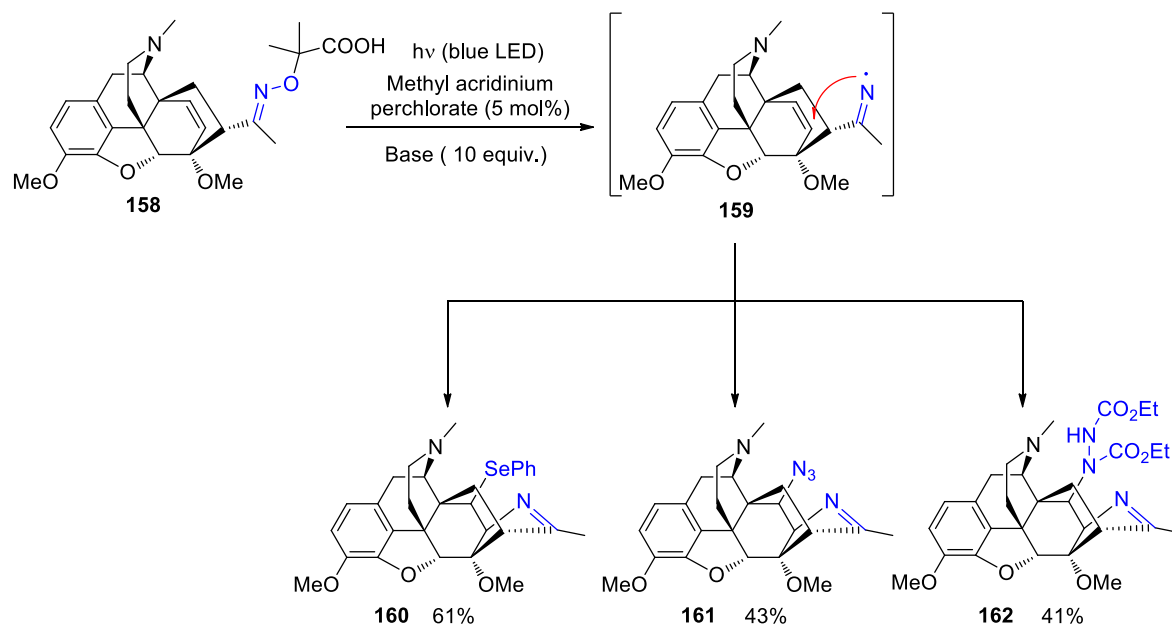
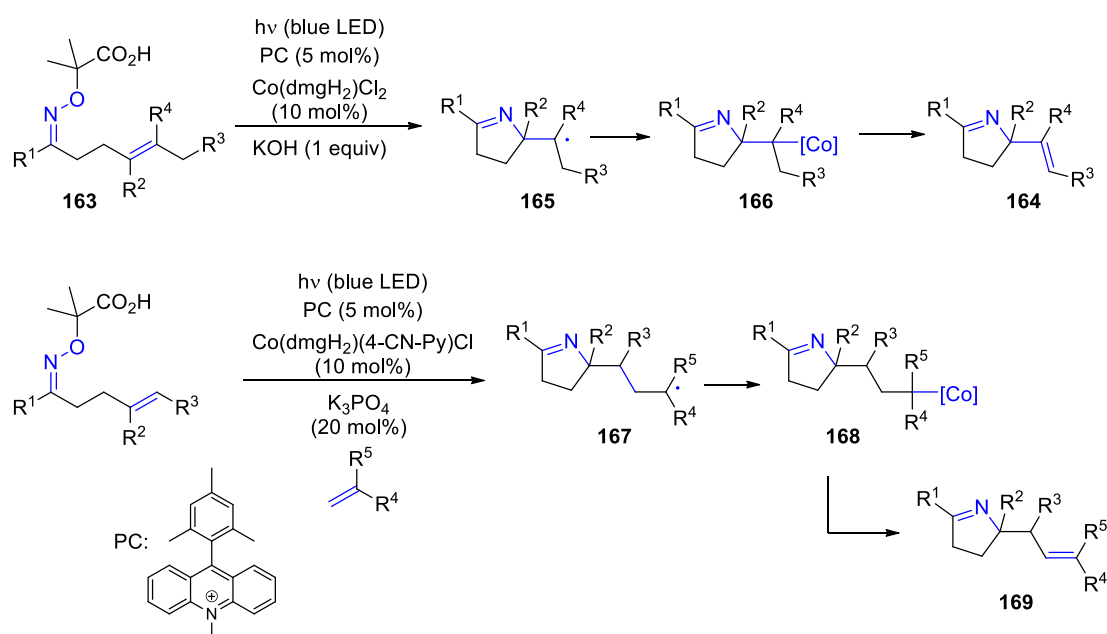


Figure 1. Structural diversity in a pyrroline family is generated by variation of the trapping reagent.



Scheme 29. Transformation of morphine derivative into corresponding dihydropyrrole compounds.

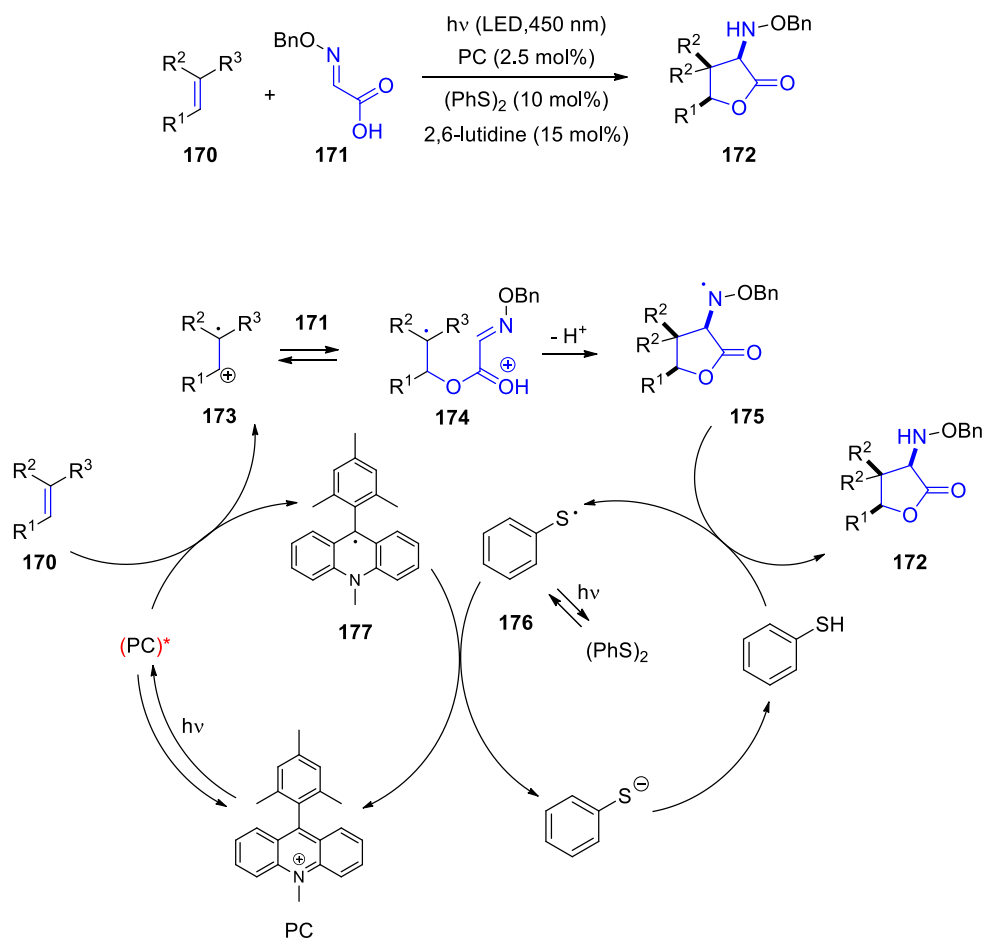
Photoredox catalysis is often combined with organometallic catalysis.⁷¹ In such a reaction, oximes like **163** have been transformed into dihydropyrroles **164** (Scheme 30).⁷² As previously discussed, a dihydropyrrole radical intermediate **165** is generated in a photoredox catalytic process. It is trapped by a cobalt complex (**166**) and elimination of a cobalt species ($[\text{Co}]\text{H}$) leads to the final product **164**. Under similar conditions and in the presence of alkenes the latter are added leading to corresponding radicals **167** which are then trapped by a cobalt complex (**168**). Elimination of a cobalt species leads to the final products **169**. Around 60 examples are reported in the present study. The products have been isolated in yields up to 95% for simple cyclizations and yields up to 77% for cyclization with subsequent addition to alkenes.



Scheme 30. Photoredox-organometallic dual catalysis applied to the synthesis of dihydropyrroles from oxime derivatives.

Radical addition may also occur at the carbon atom of the oxime function. In a photoredox catalytic reaction, styrene derivatives **170** have been added to oximes from α -keto or glyoxylic acid **171** yielding butyrolacton compounds **172** (Scheme 31).⁷³ In the present report 21 different butyrolactones have been synthesized with yields up to 88%. The products can easily be reduced to the corresponding α -amino lactones. The reaction starts with the excitation of the acridinium photo catalyst PC. At the excited state, it is capable of oxidizing the alkene **170** and radical cation **173** is generated. The latter reacts with the glyoxylic acid oxime **171** leading to the intermediate **174**. Deprotonation by an amine base and radical cyclization yields intermediate **175**. Hydrogen from thiophenolate is transferred and the final product **172** is obtained. The concomitantly generated phenylthiyl radical **176** oxidizes the reduced species **177** of

the acridinium photocatalyst which is thus regenerated. Phenylthiyl radicals **176** are also generated by photochemical fragmentation of diphenyl disulfide. Thiyl radicals play a key role as mediators in many radical reactions.⁷⁴



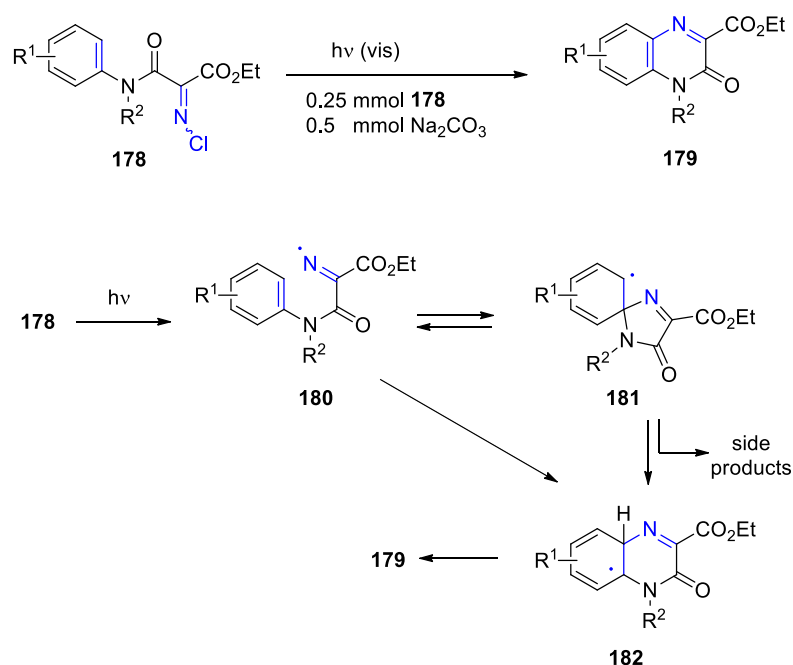
Scheme 31. Photo redox catalytic synthesis of butyrolactones from alkenes and glyoxylic acid oximes.

5 Chloroimino derivatives

5.1. Generation of radical intermediates by electronic excitation of the substrates

The acyl substituents of the oxime function can be replaced by other leaving groups such as halogens. For example, chloroimino derivatives like **178** undergo photochemically induced radical cyclization leading to quinoxalinones **179** (Scheme 32).⁷⁵ The reaction was carried out with visible light in the presence or the absence of a ruthenium base photoredox catalyst. Depending on the substitution pattern either the first or the second variant was more efficient. The reaction has been carried out with 20 different substrates. The quinoxalinones **179** have been isolated with yields up to 97%. As previously explained, the iminyl radicals **180** are generated. Radical cyclization may occur either in the ipso position

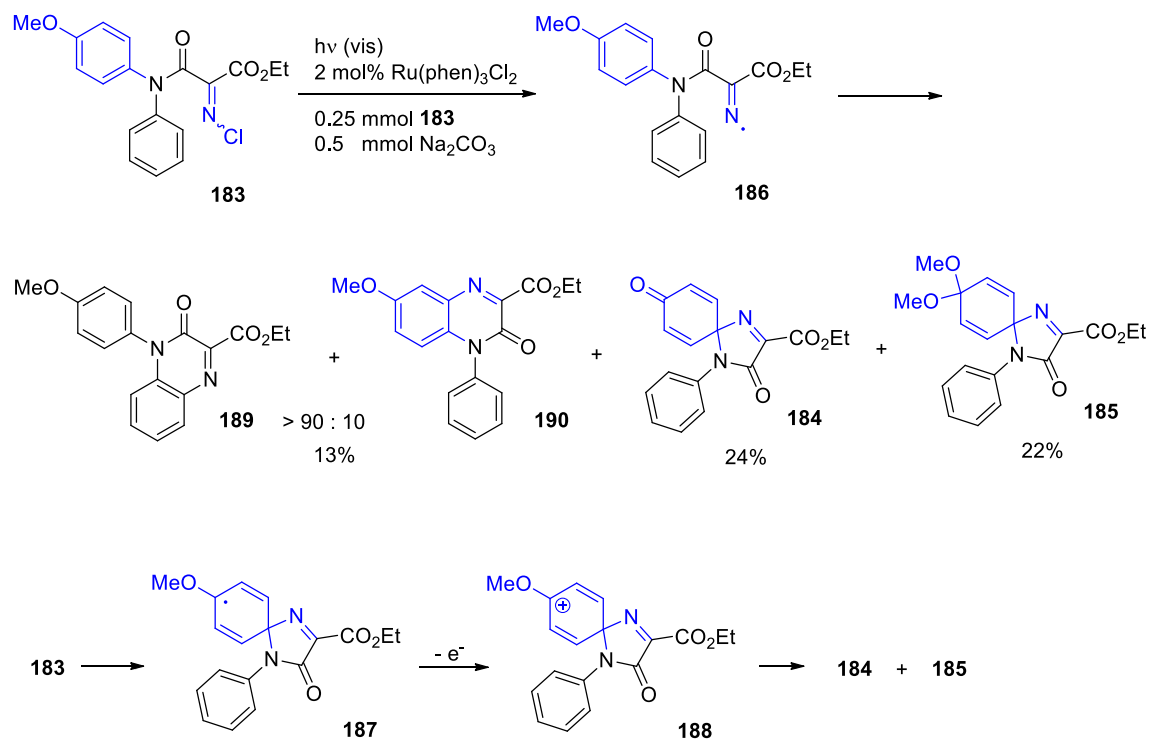
(**181**) or the ortho position (**182**) of the aromatic ring. The first reaction mode is kinetically favored but reversible. Furthermore, a rearrangement of **181** into **182** was discussed. Thus generally, the final products **179** result from ortho cyclization.



Scheme 32. Synthesis of quinoxalinones using radical cyclization with chloroimino derivatives.

5.2. Generation of radical intermediates by photoredox catalysis.

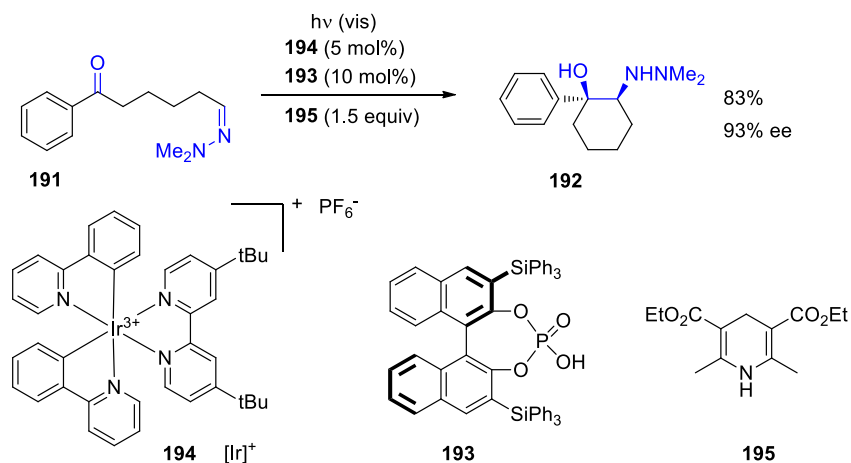
An interesting observation was made for the transformation of compound **183** (Scheme 33).⁷⁶ When the reaction was carried out in the presence of the photoredox catalyst $\text{Ru}(\text{phen})_3\text{Cl}_2$, mainly compounds **184** and **185** resulting from spiro cyclization at the p-methoxyphenyl substituent were isolated. Addition of the electrophilic nitrogen centered radical **186** with the electron richer aryl substituent is indeed favored since polar effects have an influence on radical reactions.² Under photoredox catalytic conditions, the resulting radical intermediate **187** is oxidized and the cation intermediate **188** leads to **184** and **185**. Radical cyclization at the phenyl ring leads to minor amounts of the quinoxalinone **189**. Only traces of the corresponding quinoxalinone **190** resulting from ortho cyclization at the p-methoxyphenyl substituent were obtained. It should be mentioned that in the absence of a photoredox catalyst, the spirocyclic intermediate **187** cannot be oxidized. In this case, only the quinoxalinones **189** and **190** were formed in comparable amounts owing to the reversible formation of the intermediate **187** or **181** (Scheme 32).



Scheme 33. Competitive formation of spiro cyclic products **184** and **185** in the radical cyclization with chloroimino derivatives.

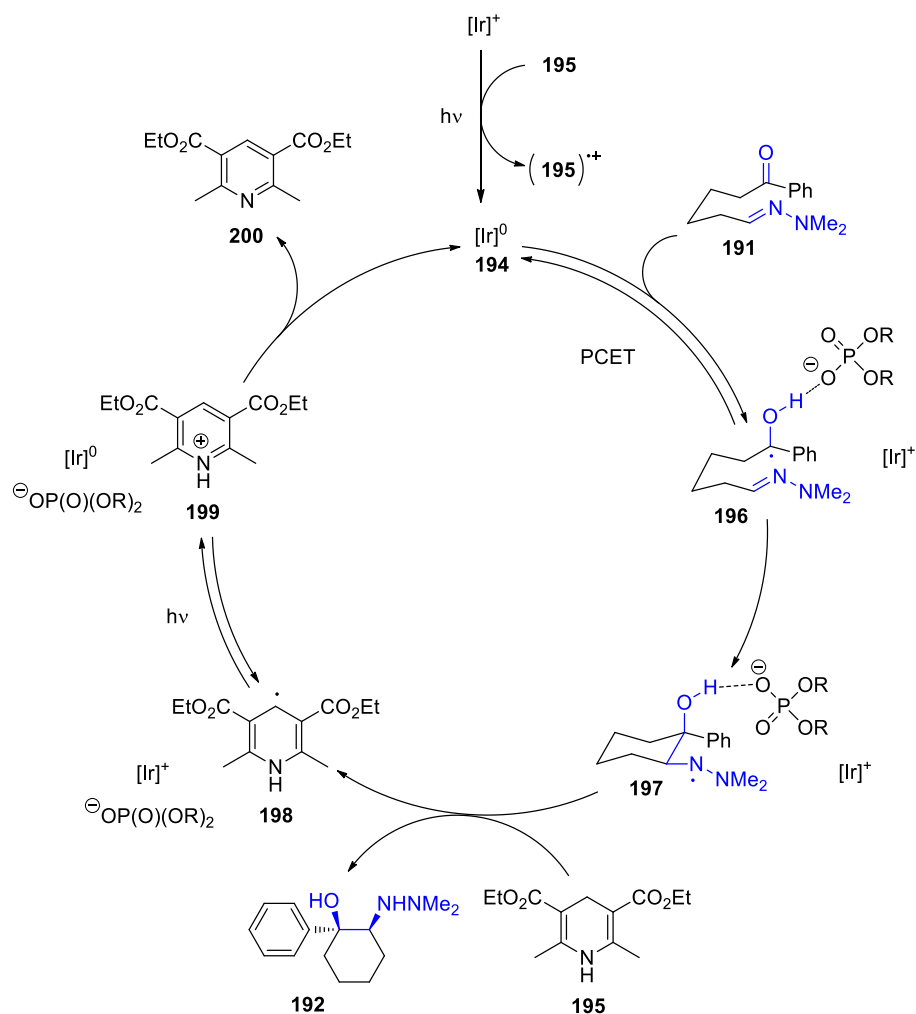
6 Hydrazones

In the case of hydrazone derivatives, radical reactions can be carried out at the carbon atom or at the nitrogen atoms, which provide numerous perspectives for applications to the synthesis of heterocycles.⁷⁶ A remarkable radical cyclization has been reported for the keto hydrazone **191** (Scheme 34).⁷⁷ The reaction is carried out in the presence of the chiral phosphoric acid derivative **193** involving photoredox catalysis with the iridium complex **194**. The Hantzsch ester **195** is used as hydrogen donor. The hydroxyl hydrazine product **192** was obtained in high yield and almost complete enantioselectivity.



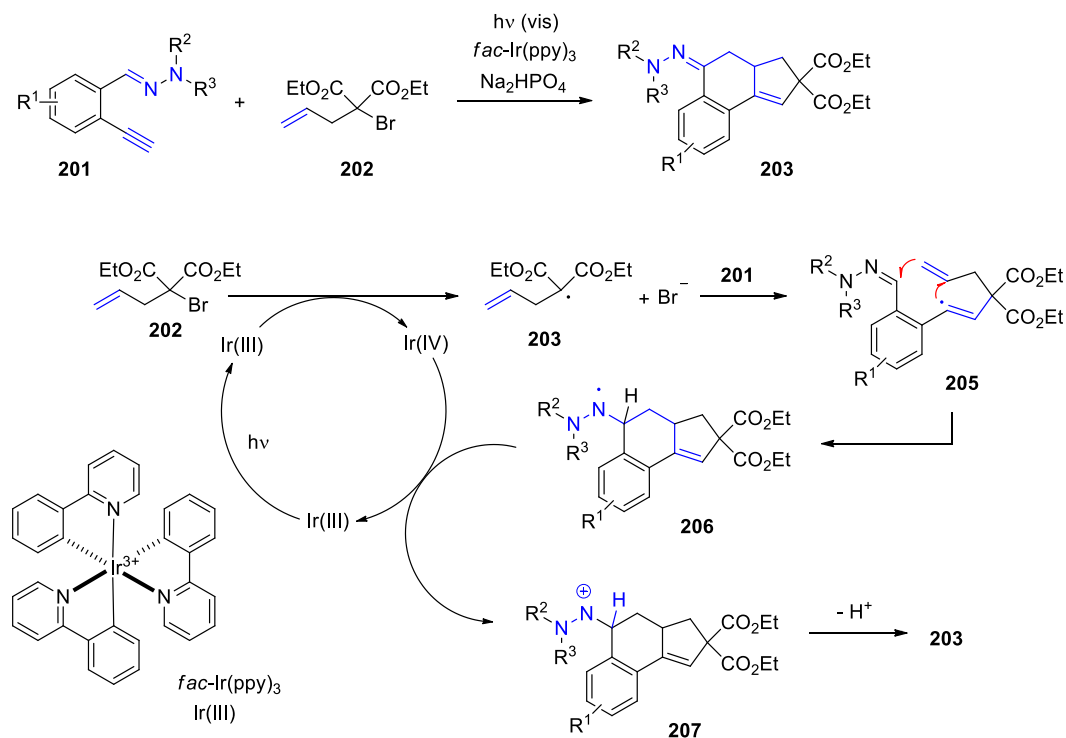
Scheme 34. Enantioselective photopinacolization like reaction of a ketohydrazone.

The following mechanism has been discussed. After Photochemical excitation of the photo-catalyst, electron transfer occurs from the Hantzsch ester derivative to the catalyst leading to the $[\text{Ir}]^0$ species (Scheme 35). This step initiates the catalytic cycle. Electron transfer from the $[\text{Ir}]^0$ species to the ketone function leads to the intermediate **196**. It must be pointed out that this transfer is coupled to a proton transfer from the phosphoric acid derivative **194**. Aside many chemical processes, such proton coupled electron transfer (PCET) processes are now widely reported in photoredox catalytic reactions.³² In the present case, this step is exergonic by 5.2 kcal/mol as it was determined by calculations. C-C bond formation leads to the intermediate **197** with a tertiary alcohol function and a nitrogen centered radical. During this step, the phosphoric acid derivative **193** remain complexed to the intermediates in the way that efficient chiral induction occurs. The final product **192** is formed by hydrogen atom transfer from the Hantzsch ester **195**. In an additional photochemical process, involving electron and proton transfer steps, the pyridine derivative **200** is formed via intermediates **198** and **199** and the catalytically active species $[\text{Ir}]^0$ is generated.



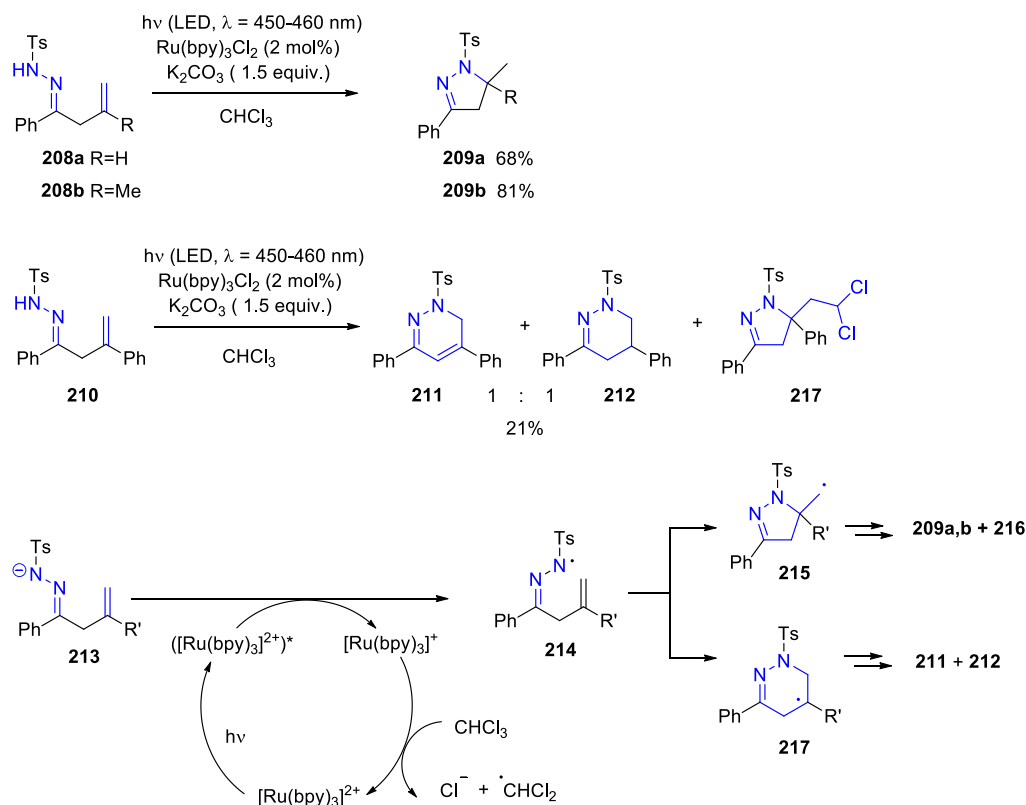
Scheme 35. Suggested mechanism of the enantioselective photo-redox catalytic mixed pinacolization analogue cyclization (Scheme 34).

Consecutive radical addition cyclization reactions lead to complex polycyclic compounds. In a photoredox catalytic reaction, the hydrazone derivative **201** carrying an alkyne substituent was transformed with the malonic ester derivative **202** (Scheme 36).⁷⁸ Two rings are formed in this reaction (**203**). The products were obtained in yields up to 92%. The synthesis of 20 different products by this method has been reported. The reaction has been carried out on gram scale. It can also be used for the preparation of polycyclic pyridine derivatives. The reaction starts with the excitation of the iridium photocatalyst which is now capable of reducing the malonic ester bromide **202**. The radical intermediate **204** is generated by release of bromide. Addition of this radical to the alkyne function (**205**) and double cyclization yields the nitrogen centered radical **206**. Oxidation of the latter leads to the corresponding cation **207**. After deprotonation, the final product **203** is obtained.



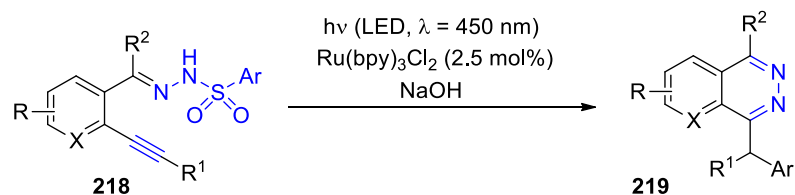
Scheme 36. Radical addition cyclization reaction leading to cyclohexylidenehydrazine-fused polycycles.

Cyclization reactions are also observed at the amine nitrogen of a hydrazone function.⁷⁹ Hydrazone derivatives such as **208a,b** or **210** (Scheme 37) undergo radical cyclization leading to dihydropyrazoles such as **209a,b** or to dihydropyridazine such as **211** or tetrahydropyrazines **212**.⁸⁰ Photoredox catalysis with $\text{Ru(bpy)}_3\text{Cl}_2$ was applied to generate the nitrogen centered radicals **214** from the **213**. In the case of **208a,b**, only exocyclization was observed leading to the radical intermediates **215** and the final products **209a,b** were isolated. In the case of **210**, both exo and endo cyclization were observed. Thus products **211**, **212** and **216** are formed. It should be pointed out that **216** is formed by trapping of the primary radical **215** by a dichloromethyl radical. Calculations revealed that exo cyclization is kinetically favored and thermodynamically disfavored in the case of **208a,b**. The reaction conditions have further been optimized. In the presence of TEMPO, radical intermediates **215** are trapped. Elimination of TEMPO-H then yields dihydropyrazoles.⁸¹ Various trapping reagents favors the formation of corresponding dihydropyrazoles or tetrahydropyrazoles.⁸²



Scheme 37. Formation of dihydropyrazoles, dihydropyridazines or tetrahydropyridazines from hydrazones.

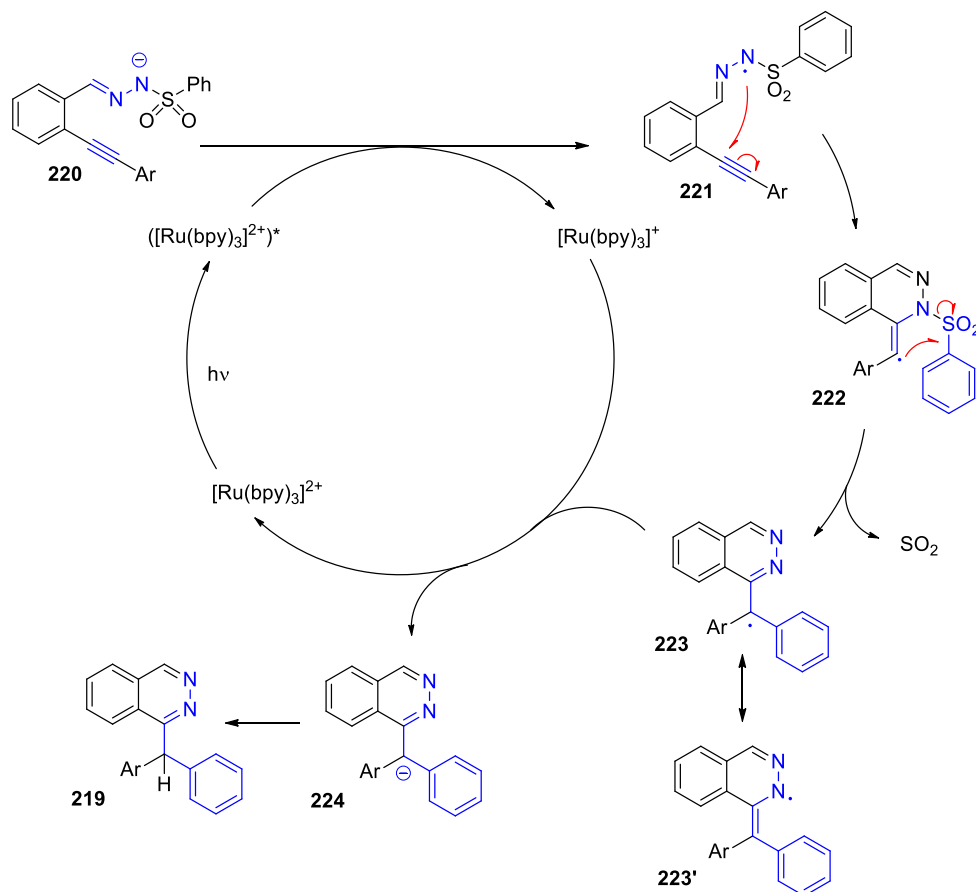
In similar reactions carried out in a basic medium, aromatic compounds **218** carrying an alkyne function and a hydrazinyl aryl sulfone group are transformed into phthalazines **219** (Scheme 38).⁸³ In the present paper, 25 derivatives have been successfully transformed and the products have been isolated with yields up to 83%. This compound family is interesting due to their pharmaceutical properties such as bactericidal or antitumor activities.



Scheme 38. Photoredox catalytic synthesis of phthalazines.

Again, a nitrogen centered radical **221** is generated by oxidation of the corresponding anion **220** using photoredox catalysis with $\text{Ru(bpy)}_3\text{Cl}_2$ (Scheme 39). In a first cyclization, the racial intermediate **222** is

generated. In a Smiles rearrangement, SO_2 is eliminated, and a second cyclization takes place which leads to the radical **223** or **223'**. The latter intermediate is reduced by electron transfer from the Ru(I) species generated in the photoredox catalytic cycle (**224**). Protonation occurs in the diarylmethyl position of **224** and not at the nitrogen atom of the phthalazine ring. Deuterium labeling experiences showed that a proton or a deuterium is transferred from the solvent. Similar reactions have been recently reported.⁸⁴



Scheme 39. Mechanism of Photoredox catalytic synthesis of phthalazines involving a Smiles rearrangement.

7 Conclusion

Imines and related compounds with a C=N double bond such as oximes or hydrazones play a key role in the synthesis of numerous heterocycles. The synthesis methodology is considerably enriched by radical reactions. It is well established that photochemical reactions give access to a large variety of radical intermediates. Thus toxic reagents, typically used in many ground state radical reactions are avoided. In this way, radical chemistry becomes more and more sustainable. Since about 15 years in academic research and for some years now in chemical industry, photochemical reactions experience a renaissance in the field of organic synthesis. This impact originates mainly from numerous research activities in the domain of photoredox catalysis, especially with visible light. More recently, systematic studies on the excitation of charge transfer complexes to generate reactive intermediates have been

carried out. These developments also push radical chemistry so that it will significantly gain importance in organic synthesis.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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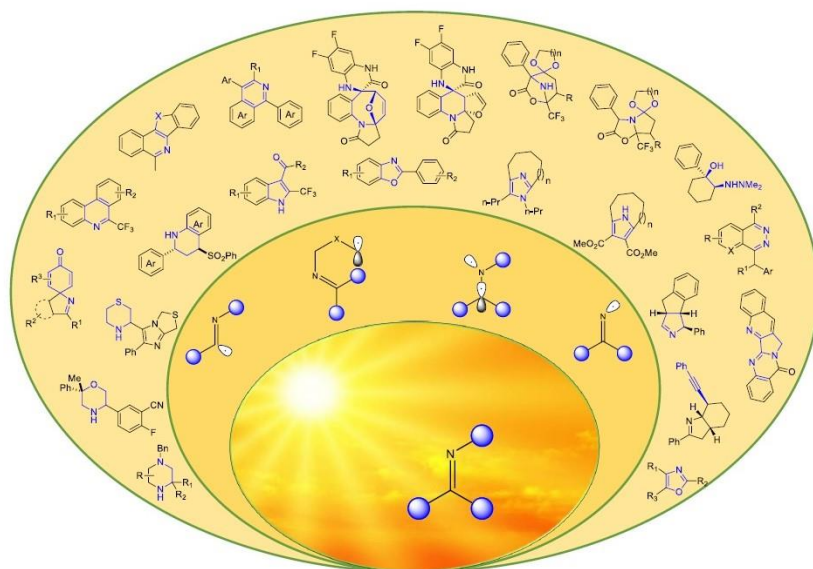
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Photochemical reactions of imines, hydrazones, oximes and related Compounds provides an efficient access to radical intermediates in the synthesis of heterocycles.