PHOTOCATALYTIC MINISCI REACTION

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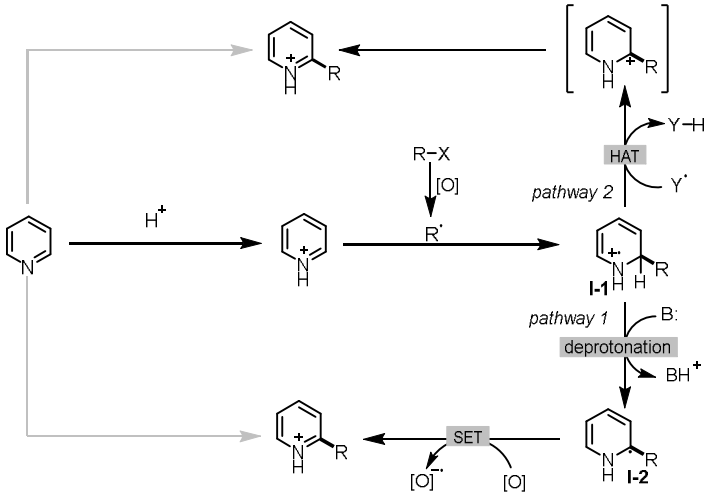
Abstract. *N-Heteroarenes are found in a wide range of natural products, small-molecule drugs, organic materials, and ligands. Consequently, methods for the selective C–H functionalization of N-heteroarenes are highly sought after, particularly for the late-stage modification of pharmaceuticals. One powerful approach for synthesizing alkyl-substituted nitrogen-containing aromatic rings is the Minisci reaction, in which a protonated N-heteroarene is attacked by an alkyl radical under oxidative and acidic conditions. Traditional Minisci reactions, however, often require an excess of oxidants, excess acid, and high temperatures, which significantly limit the substrate scope. With the rapid advancement of photocatalysis in organic synthesis, organic chemists have recently developed various photocatalytic Minisci reactions and successfully applied them to drug synthesis. In this chapter, we aim to provide a comprehensive overview of this topic, organizing the discussion by the type of radical precursor used.*

Contents

1. Introduction

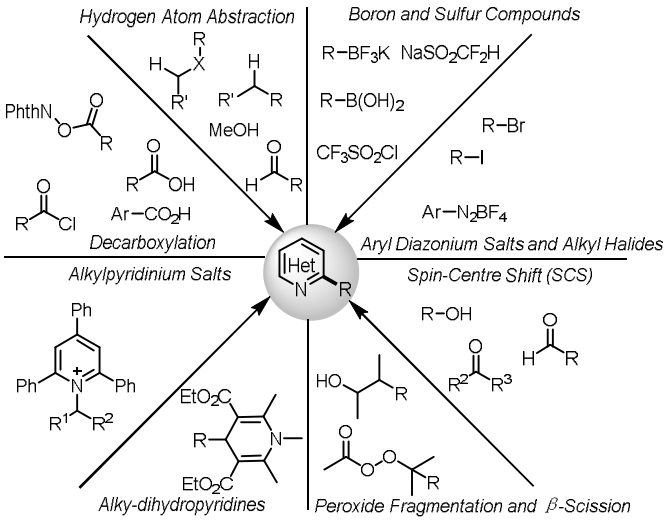
As of 2014, more than 84% of the drugs approved by the US Food and Drug Administration contained at least one nitrogen atom, and 60% contained nitrogen heterocycles. In particular, *N*-heteroarenes are among the most prevalent motifs in drugs and drug-like compounds.[1] Owing to the importance of such structures, methods for the direct C–H functionalization of unsubstituted *N*-heteroarenes are highly important for drug development.[2] One useful tool for this purpose is the Minisci reaction, in which a protonated *N*-heteroarene is attacked by an alkyl radical under oxidative conditions.[3] The Minisci reaction is complementary to Friedel-Crafts reaction. A variety of substituents, such as alkyl, aryl, trifluoromethyl, amide, hydroxymethyl, aminomethyl, and acyl, can be directly introduced into the *N*-heteroarenes.[4] In general, the Minisci reaction proceeds *via* three mechanistic steps (Scheme 1). The first step is the generation of alkyl radicals by the oxidation of the radical precursors. The second step is the addition of alkyl radical to protonated *N*-heteroarene to obtain heterocyclic aromatic radical cationic intermediates. The third step is the oxidative aromatization of the radical cationic intermediates to obtain the final product. In

the resulting radical cation **I-1**, the *a*-proton is made acidic and one possible pathway (pathway 1) involves this proton being lost in a deprotonation step, resulting in neutral radical **I-2**. Another possibility (pathway 2) is that a hydrogen atom transfer (HAT) occurs from the radical cation intermediate **I-1**.



Scheme 1. General mechanistic pathways in Minisci-type reactions.

Classic Minisci reactions often require the use of excess oxidant, excess acid, and high temperature, which may limit the scope of the substrates. Visible light reaction system generally has the advantages of high reactivity, mild conditions, and good functional group tolerance. With the rapid development of photocatalysis in organic synthesis, in recent years, organic chemists have reported a variety of photocatalytic Minisci reactions, and successfully applied to the synthesis of drugs. In this chapter, the research progress of visible light catalyzed Minisci reactions in recent years is reviewed from the perspective of the type of radical precursors (Scheme 2).

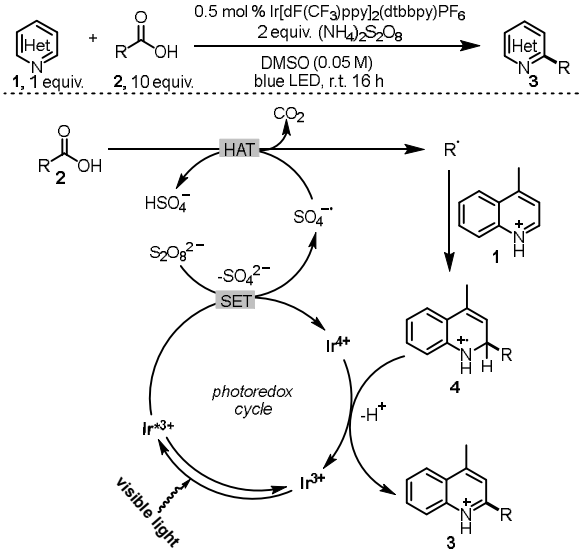


Scheme 2. Visible-light-mediated Minisci reactions.

2. Advances in radical generation *via* decarboxylation

2.1. Direct decarboxylation of carboxylic acids

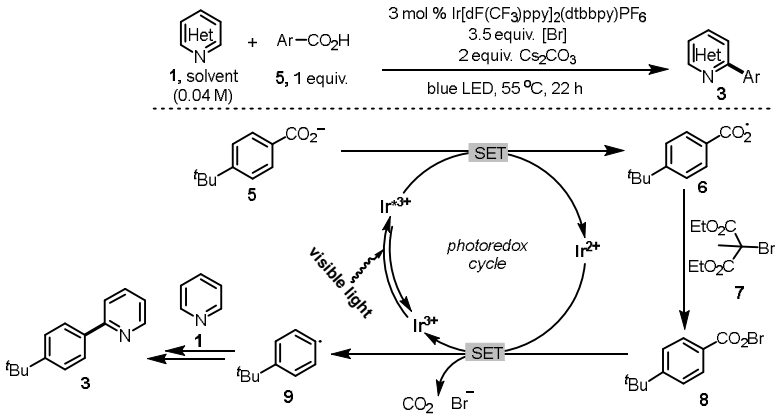
Alkyl carboxylic acids are inexpensive, stable, nontoxic, and among the most abundant, renewable feedstocks on earth, so it is of great significance to directly use alkyl carboxylic acids to achieve Minisci alkylation of *N*-heteroarenes. In 2017, Glorius et al. reported the first visible light-mediated Minisci C−H alkylation of heteroarenes using aliphatic carboxylic acids (Scheme 3).[5] In this reaction, excited state $*Ir^{III}$ photocatalyst engages in single-electron reduction with the persulfate anion ($E_{1/2}$=+1.75 V vs SCE) to afford the oxidized iridium species Ir^{IV}, the sulfate dianion, and the sulfate radical anion. The corresponding alkyl radical is then generated through hydrogen-atom-transfer (HAT) between the carboxylic acid **2** and the sulfate radical anion, followed by decarboxylation. The alkyl radical then adds to the electron-deficient heteroarene **1** to give intermediate **4** and then aromatized by Ir^{IV} complex oxidation to obtain the alkylation product **3** and complete the photocatalytic cycle. Compared with the traditional Minisci reaction, this mild reaction condition permits good functional group compatibility and a wide range of substrate scope. The reaction was successfully inhibited by the addition of radical trapping agent (TEMPO), and the product of alkyl radical trapped by TEMPO was detected by high-resolution mass spectrometry. In addition, the radical clock experiment has also proved that the reaction conducts *via* radical pathway. This reaction is suitable for five- and six-membered nitrogen heterocycles, primary, secondary and tertiary alkyl carboxylic acids, but it is not suitable for aryl carboxylic acids. Subsequently, the Chen[6] and Frenette groups[7] reported the Minisci alkylation reaction of alkyl carboxylic acid under room temperature using $Ru(bpy)_3Cl_2$ and organic photosensitive dye acridine salt as photocatalysts, respectively. In 2018, the Xia group achieved the Minisci acylation of *N*-heteroarenes using the same strategy.[8] However, the method does not require the use of photocatalyst and can be conducted under the light. The author proposed that $S_2O_8^{2-}$ can undergo homolysis to produce $SO_4^{-\bullet}$ under light excitation.



Scheme 3. Visible-light-mediated decarboxylative Minisci reaction with alkyl carboxylic acids.

Although the Minisci alkylation with alkyl carboxylic acid as radical precursor has been widely developed, the Minisci arylation with aryl carboxylic acid as radical precursor is difficult to achieve. After the oxidation of aryl carboxylic acid to produce carboxylic radical, it is difficult to remove one molecule of CO_2 to produce aryl radical because of the conjugation effect of carboxyl group and aromatic ring. On the contrary, the carboxyl radical can easily abstract hydrogen atom from the solvent to obtain aryl carboxylic acid again. In 2017, the Glorius group achieved the first Minisci arylation reaction with aryl carboxylic acid

under photocatalysis (Scheme 4).[9] This method solved the problem that aryl carboxyl radical is difficult to eliminate CO_2 and more inclined to abstract hydrogen atom in the system**.** They hypothesize that the resulting carboxyl radical **6** abstracts bromine atom from **7** to obtain benzoyl hypobromate **8**, which can easily remove CO_2 under photocatalytic reduction. The authors have proved that the process of CO_2 removal is advantageous by calculation. They proposed that the excited photocatalyst $*Ir^{III}$ oxidizes the carboxylic acid **5** to obtain Ir^{II} and carboxylic radicals **6**, then the carboxylic radicals abstract the bromine atoms in the system to obtain benzoyl hypobromate **8**, which is then reduced by Ir^{II} while losing a molecule of Br^- and CO_2 to obtain the aryl radical **9**. Then the aryl radical **9** adds to the heteroarene **1** to obtain the product **3**.



Scheme 4. Visible-light-mediated Minisci reaction with aryl carboxylic acids.

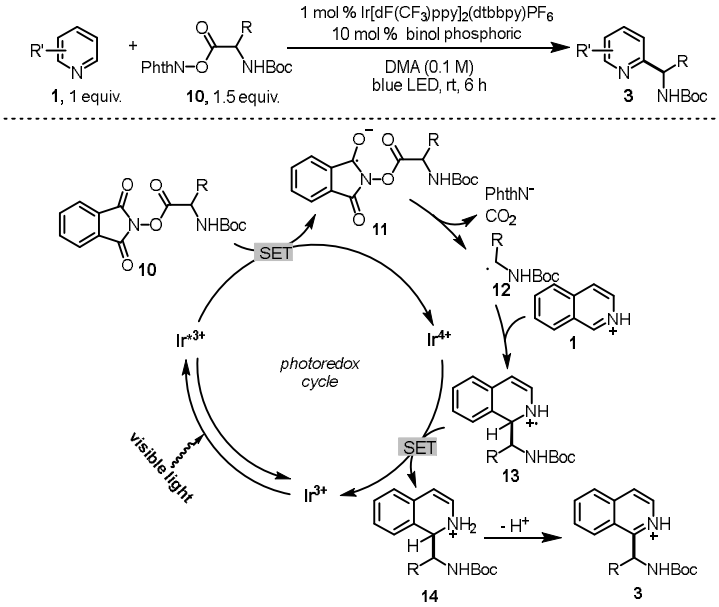
2.2. Decarboxylation of activated carboxylic acids

In the developed visible light-catalyzed decarboxylated Minisci reactions, excessive strong oxidants are usually required to achieve oxidative decarboxylation and rearomatization. However, due to the use of strong oxidants in the system, the reaction is not compatible with sensitive functional groups, and easy to generates byproducts of radical addition. Therefore, it is of great significance to realize the photocatalytic Minisci decarboxylated alkylation of *N*-heteroarenes under neutral redox conditions.

N-(Acyloxy)phthalimide can be efficiently obtained by one-step condensation of alkyl carboxylic acid and *N*-hydroxyphthalimide, and this type of active carboxylic ester has been widely used in photocatalytic halogenation and 1,4-addition reactions.[10-12] In recent years, the Baran group has realized metal-catalyzed decarboxylation coupling reactions using such active carboxylic esters as alkylation reagents.[13] In this type of reaction, the active carboxylate can be reduced by metal or photocatalyst to produce alkyl radical. Based on this process, the Fu group reported the first visible light-catalyzed Minisci reaction with amino acid-derived *N*-(acyloxy)phthalimide as a precursor of alkyl radicals in 2018 (Scheme 5).[14] The authors proposed that active carboxylate **10** oxidizes photocatalyst Ir^{II} to Ir^{III}, producing *α*-amino-alkyl radical **12** *via* intermediate **11**, which is added to *N*-heteroarene **1** to give the intermediate **13**. Then **13** was oxidized by $*Ir^{IV}$ to obtain final alkylation product **3** *via* intermediate **14**. The reaction is redox neutral and does not require additional oxidants. Subsequently, the Fu group also realized the Minisci alkylation reaction with alkyl carboxylic acids esters under neutral photocatalytic redox conditions using a catalytic amount of Lewis acid.[15] In 2020, the Wang group achieve the Minisci formylation reaction with active ester of formalic acid as the precursor of formyl radical using the same strategy.[16]

Although many of the methods discussed herein are able to form stereocenteres through the addition of prochiral radicals, controlling absolute stereochemistry at such centers has been a long-standing challenge. Based on the Minisci reaction with amino acid-derived *N*-(acyloxy)phthalimide **10** as a precursor of alkyl radicals reported by the Fu group, in 2018, Phipps and co-workers reported the use of chiral Brønsted acid **15** catalysis to induce asymmetry in the addition of prochiral, acyl-protected *a*-aminoalkyl radicals **12** to *N*-heteroarene, obtaining the final product **3** (Scheme 6).[17] Moreover, the reaction also has good

regioselectivity. For the unsubstituted quinoline substrate, the reaction can selectively obtain 2-site alkylation products. For pyridine substrates, the reaction occurs at 2 or 6 sites. In the same year, the Jiang group used organic photocatalysts to achieve stereoselective control of the Minisci reaction using the same chiral control strategy.[18]



Scheme 5. Visible-light-mediated Minisci reaction with activated esters.

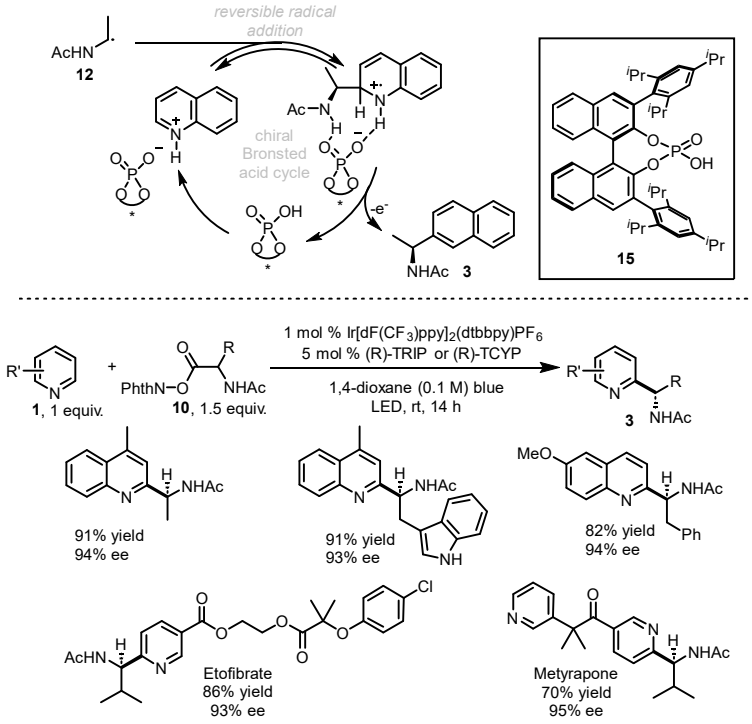
In 2019, the Wang group realized the Minisci reaction with active carboxylic ester as source of alkyl radical under neutral redox conditions using cheap copper as photocatalyst (Scheme 7).[19] In this reaction, the copper photocatalyst does not need to be prepared in advance and can be generated in the reaction system. The authors proposed that a photoactivated copper photocatalyst $*Cu^{I}$ reduces the active carboxylic ester **16** to generate intermediate **17**, which removes a molecule of phthalimide and CO_2 to produce an alkyl radical and Cu^{II}. The alkyl radical is added to the *N*-heteroarene **1** to give the intermediate **18**, which is oxidized by Cu^{II} to obtain the alkylation product **3** *via* intermediate **19**.

Minisci reactions using *N*-(acyloxy)phthalimide as an alkyl radical precursor have poor atomic economy due to the removal of a molecule of phthalimide. In order to improve the atomic economy of Minisci reaction under neutral redox condition, the Stephenson group reported the Minisci alkylation reaction using pyridine *N*-oxide **20** as the radical receptor and activated carboxylic acid reagent, and acyl chloride **21** as a precursor of alkyl radical under photocatalysis (Scheme 8).[20] Moreover, no additional oxidant is required for this reaction, and pyridine *N*-oxide **20** acts as both a precursor to *N*-heteroarene and a reagent for activating acyl chloride. First, pyridine nitrous oxide reacts with acyl chloride **21** to obtain *N*-acyloxy pyridine salts **22**, which are reduced by $*Ir^{III}$ to pyridine **1**, alkyl radicals and Ir^{IV}, and then the alkyl radicals are added to pyridine **1** and then oxidized by Ir^{IV} to obtain alkylated products **3**.

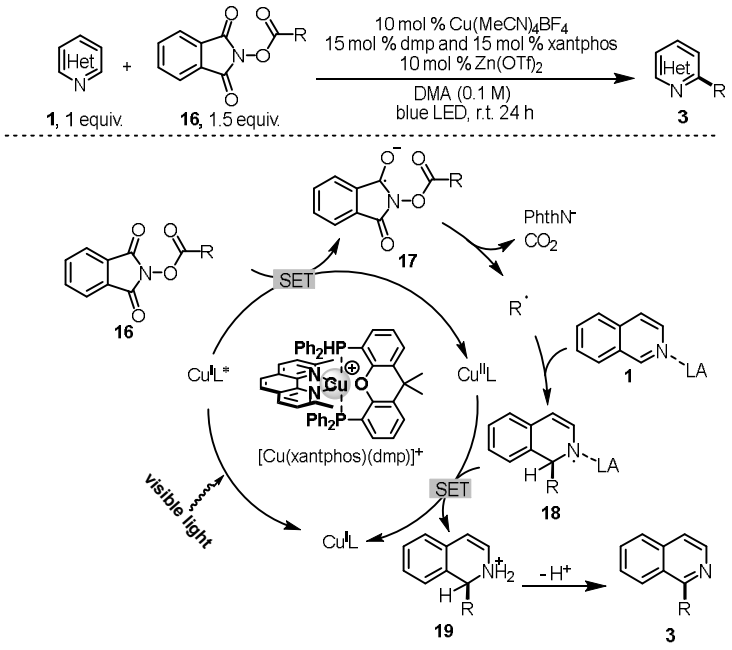
3. Advances in radical generation *via* hydrogen atom abstraction

3.1. Minisci reactions *via* intermolecular hydrogen atom abstraction

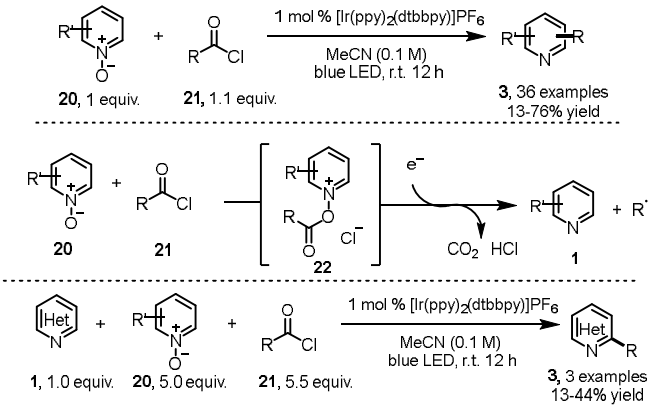
In general, direct transformations of C–H bonds are highly desirable, particularly with regard to atom economy and synthesis of starting materials. It follows therefore, that if two C–H bonds could be formally converted a new C–C bond, this would be a highly desirable process.



Scheme 6. Visible-light-mediated enantioselective Minisci reaction with activated esters.



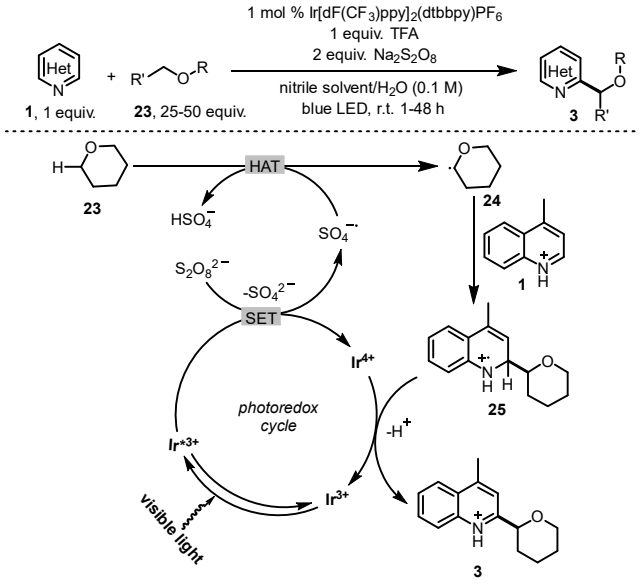
Scheme 7. Cu-catalyzed Minisci reaction with activated esters.



Scheme 8. Visible-light-mediated Minisci reaction with acyl chloride.

Minisci-type reactions provide a valuable opportunity to perform this type of coupling if the radical nucleophile can be generated from abstraction of a hydrogen atom (HAT, hydrogen atom transfer). In general, HAT most commonly occurs *via* intermolecular hydrogen atom abstraction or intramolecular hydrogen atom abstraction and advances in these areas will be covered in the following two subsections.

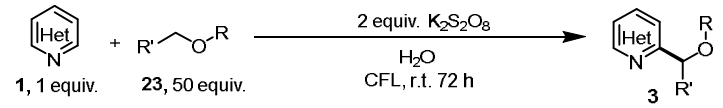
In 2015, the MacMillan group reported the first Minisci reaction with ether compounds *via* HAT process under photocatalysis (Scheme 9).[21] The mechanism of this reaction is similar to that of Minisci reaction reported by the Glorius group for decarboxylation of alkyl carboxylic acid under photocatalysis. The photocatalyst $*Ir^{III}$ in the excited state was oxidized by persulfate to produce Ir^{IV} and a molecule of $SO_4^{-\bullet}$. Then the $SO_4^{-\bullet}$ acts as HAT reagent to abstract hydrogen atom from the C–H bonds of *a*-oxygen **23** and obtain alkyl radical **24**. The alkyl radical **24** is added to the *N*-heteroarene **1** to give the intermediate **25,** which is oxidized by Ir^{IV} to obtain the product **3**.



Scheme 9. Visible-light-mediated Minisci reaction with ethers.

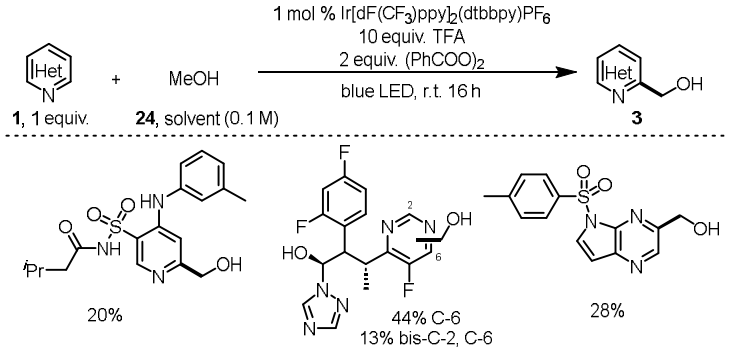
This reaction is the first Minisci reaction to undergo *via* HAT process under photocatalysis, which avoids the traditional high temperature reaction conditions, makes the reaction have good functional group tolerance and a wide range of substrate scope, which further demonstrated the superiority of photocatalysis.

Subsequently, the Shah group reported the Minisci alkylation reaction of ether compounds **23** without photocatalyst under light conditions. In this reaction, the authors proposed that *N*-heteroarene **1** and persulfate formed EDA (electron-donor-acceptor) complex, which produced $SO_4^{-\bullet}$ under light conditions, and then abstracted hydrogen atoms from the C–H bonds of *a*-oxygen to produce alkyl radicals. Then the aryl radical adds to the heteroarene **1** to give the product **3** (Scheme 10).[22]



Scheme 10. Visible-light-mediated Minisci reaction with ethers under photocatalyst-free conditions.

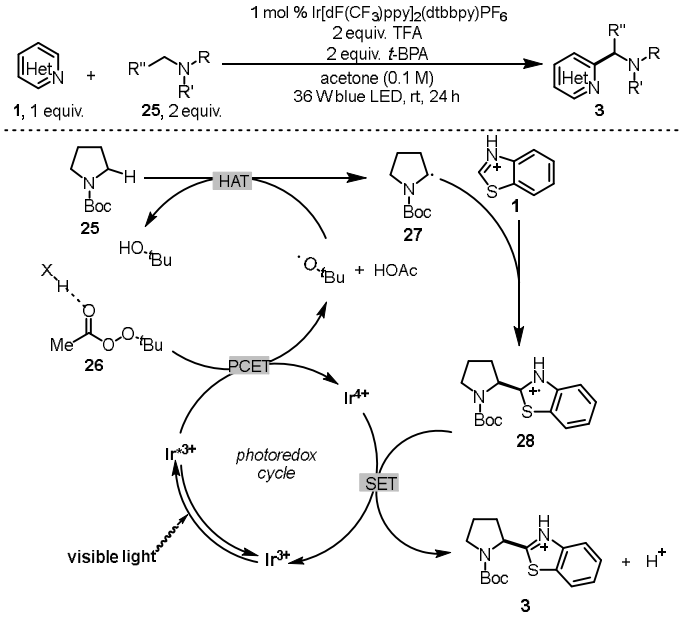
Inspired by the Minisci reaction of ether compounds under photocatalysis reported by the MacMillan group, in 2016, the Di Rocco group achieved photocatalyzed hydroxymethylation of *N*-heteroarene **1** using peroxide as the oxidant and methanol **24** as the solvent, obtaining product **3** (Scheme 11).[23] This mild reaction condition has a good functional group compatibility, especially for some functional groups that are easy to be oxidized. The mild reaction conditions make the reaction suitable for the late hydroxymethylation modification of complex *N*-heteroarenes, which is very useful for the discovery of bioactive molecules.



Scheme 11. Visible-light-mediated Minisci reaction with methanol.

Organic amine compounds also exist widely in nature and are easy to obtain. As alkylating agents, organic amines are of great significance in the alkylation of *N*-heteroarenes, which can easily obtain arylbenzylamines. Although Minisci alkylation with ether compounds has been widely reported, it is very difficult to achieve Minisci alkylation with organic amines. The reason is that organic amines are more easily oxidized than ethers, and the *α*-amino radical intermediates produced by the HAT process are easily oxidized to imines under high temperature and oxidation conditions. However, mild photocatalytic reaction conditions provide an effective way to solve this problem. In 2018, the Wang group reported a photocatalyzed Mnisci reaction with amine as the radical precursor (Scheme 12).[24] This mild reaction has a broad substrate scope and offers the first general method for synthesis of aminoalkylated *N*-heteroarenes without need for substrate prefunctionalization, and is scalable to the gram level. Furthermore, the reaction was found to be applicable to other hydrogen donors besides amines (*i.e.* ethers, an aldehyde, a formamide, *p*-xylene, and alkanes), thus enabling the preparation of *N*-heteroarenes bearing various types of substituents. For the mechanism of the reaction, the reduction of *t*-BPA **26** (E^0=−1.56V vs SCE) by $^*Ir^{III}$ ($E_{1/2}^{IV/*III}$=−0.89 V vs SCE) *via* proton-coupled electron transfer under acidic conditions affords an oxidized iridium species (Ir^{IV}), acetic acid, and a *t*-butoxy radical. *α*-Aminoalkyl radical **27** is then generated by means of HAT between the *N*-protected amine **25** and the *t*-butoxy radical. *α*-Aminoalkyl radical **27** then adds to the

protonated electron-deficient heteroarene **1** *via* a Minisci-type pathway to afford radical cation **28**. Single-electron oxidation of this intermediate by Ir^{IV} ($E_{1/2}^{IV/III}$=+1.70 V vs SCE in MeCN/H_2O=2:1) and deprotonation gives the final *α*-aminoalkylated product **3** and closes the photoredox cycle. Subsequently, the Berthelot group[25] and the Johnson group[26] reported two similar Minisci reactions with amines, respectively.



Scheme 12. Visible-light-mediated Minisci reaction with amines.

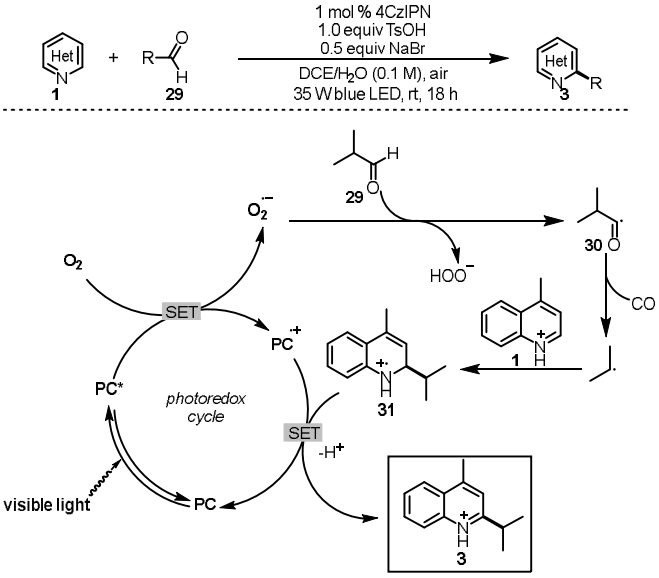
In 2019, the Huang group achieved the Minisci alkylation reaction with aldehydes *via* decarbonylation under photocatalytic conditions using oxygen as the oxidant (Scheme 13).[27] They proposed that $O_2^{-\bullet}$ can abstract acyl hydrogen atoms of aldehydes **29** to produce acyl radical **30**, which removes one molecule of CO to obtain alkyl radical, and then alkyl radical is added to *N*-heteroarene **1** to give intermediate **31**, which was oxidized by photocatalyst to obtain alkylation product **3**.

In Minisci reactions that produce alkyl radical through the HAT process, the reaction site is often at the *α*-position of the heteroatom for activated hydrocarbons. However, for unactivated alkanes, there are often multiple reaction sites due to the small differences in C–H bonds at each site, which makes the reaction confusing and difficult to separate products. In 2018, the Chen group reported a Minisci alkylation reaction with high methylene selectivity (Scheme 14).[28] The authors proposed that perfluorinated hydroxybenziodoxole (PFB-OH) **33** is reduced by excited photocatalyst $*Ru^{II}$ to obtain a strong electrophilic carboxyl radical **34**, which is highly selective to abstract the hydrogen from the methylene **32** and produce alkyl radical **35**. The authors proposed that the selectivity of the reaction lies in the PFB-OH used, and the introduction of four fluorine atoms in the aromatic ring is crucial. The authors proved that the sub-methyl site is easily oxidized to carbocation after generating free radicals, which explains the reason why the sub-methyl site does not react. This mild condition has a wide range of substrate scope and also a high methylene selectivity for natural product molecules.

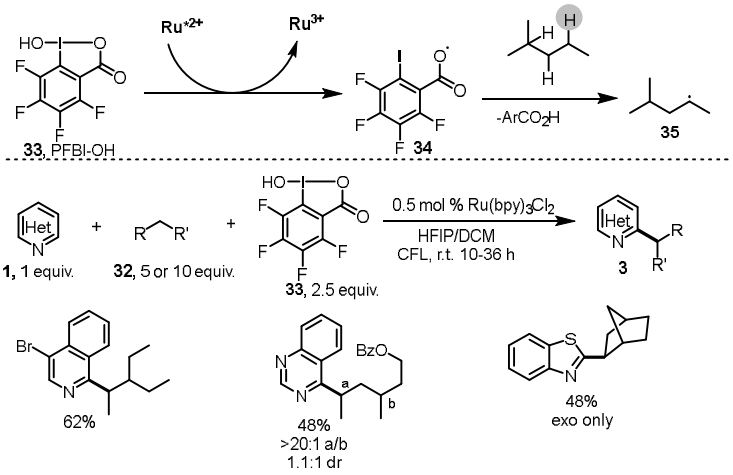
3.2. Minisci reactions *via* intramolecular 1,5-hydrogen migration

In 2018, the Zhu group realized the Minisci alkylation of the distant C–H bond of alcohols **36** using the strategy of oxygen radical 1,5-hydrogen migration (Scheme 15).[29] [29] The mixture of **36** and phenyliodine bis(trifluoroacetate) (PIFA) **37** results in the dialkoxyiodobenzene **38**. Homolysis of **38** induced by visible-light irradiation leads to the alkoxy radical **39**. The alkoxy radical **39** can undergo 1,5-hydrogen

migration within the molecule to obtain the alkyl radical **40**, which is added to the *N*-heteroarene **1** to give the intermediate **41**. Then **41** is oxidized by PIFA to obtain the product **3**. Subsequently, the Chen group achieved a similar Minisci alkylation reaction of the distant C–H bond of alcohols using $Ru(bpy)_3Cl_2$ as the photocatalyst and PFBI-OH as the oxidizing agent.[30]



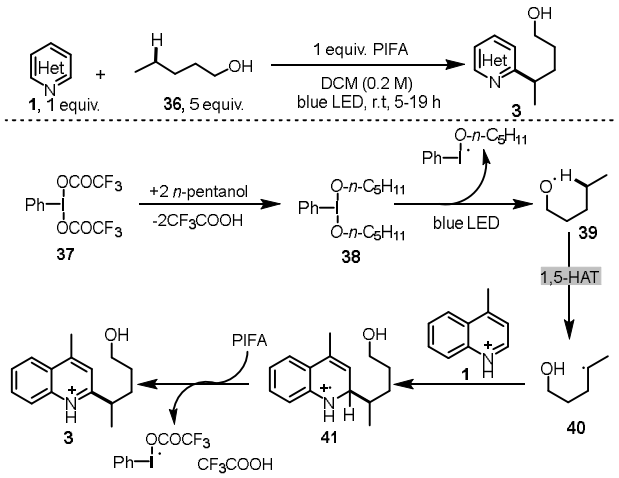
Scheme 13. Visible-light-mediated Minisci reaction with aldehydes using O_2 as the oxidant.



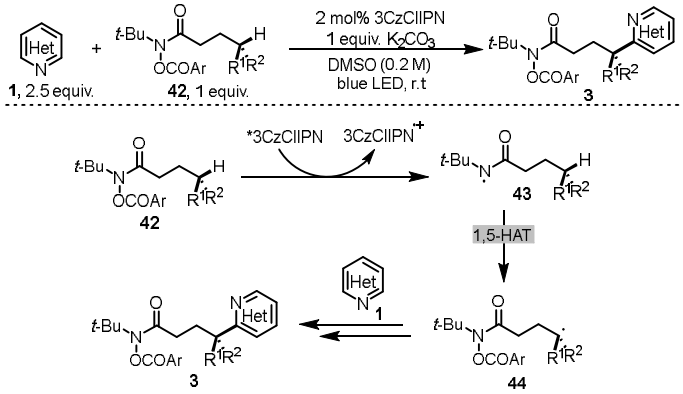
Scheme 14 Visible-light-mediated Minisci reaction with high selectivity of methylene.

Inspired by the intramolecular 1,5-hydrogen migration of alcohols, in 2019, the Yu group found that amides can also undergo intramolecular 1,5-hydrogen migration to achieve the Minisci alkylation of the amides' distant C–H bonds (Scheme 16).[31] In this reaction, the photocatalyst reduces the amide substrate **42** to obtain nitrogen radical **43**, which occurs intramolecular 1,5-hydrogen migration to produce alkyl radical **44**. Then the alkyl radical **44** adds to the heteroarene **1** to give the product **3**. Similarly, the Chen group

achieved a similar Minisci alkylation reaction of the distal C–H bond of sulfonyl protected amine molecules using $Ru(bpy)_3Cl_2$ as the photocatalyst and BI-OAc as the oxidizing agent.[32]



Scheme 15. Visible-light-mediated Minisci reaction with alcohols *via* 1,5-hydrogen-atom-transfer.



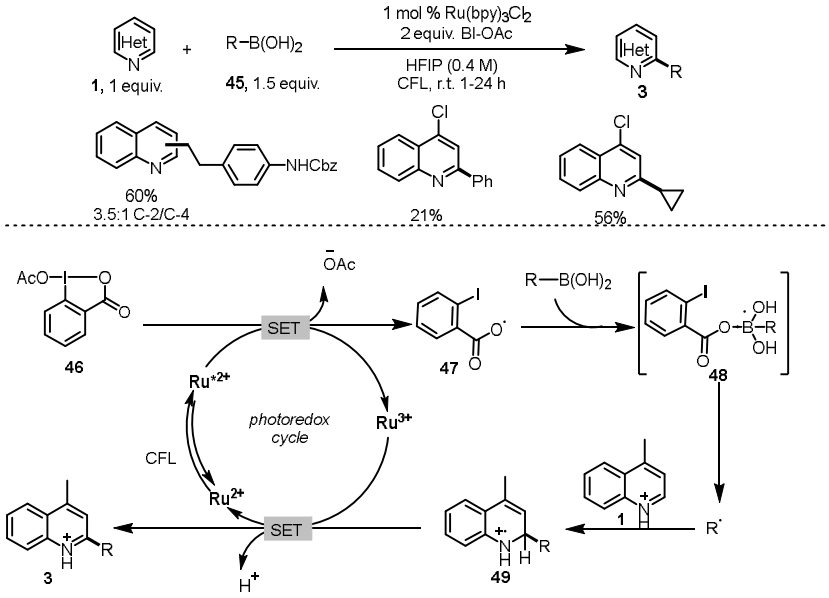
Scheme 16. Visible-light-mediated Minisci reaction with amides *via* 1, 5-hydrogen-atom-transfer.

4. Advances in radical generation from boron compounds

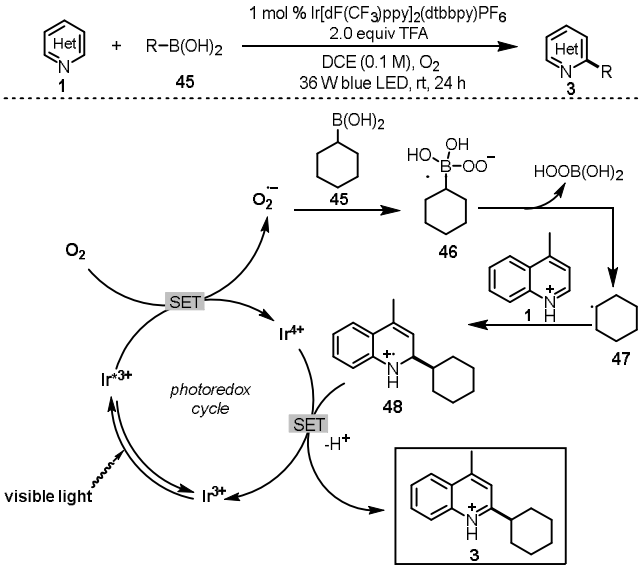
In 2016, the Chen group reported the Minisci reaction with alkyl boric acid **45** as the radical precursor under photocatalysis (Scheme 17).[33] The reaction uses hypervalent iodine-based benziodoxole-derived oxidant BI-OAc **46** as oxidant. The authors suggested that the carboxyl radical **47** produced by the reduction of BI-OAc by photocatalyst $*Ru^{II}$ is added to alkyl boric acid **45** to activate the carbon-boron bond and produce alkyl radical *via* intermediate **48**. The alkyl radical is added to the *N*-heteroarene **1** to give the intermediate **49**, which is oxidized by Ru^{III} to obtain the product **3**. This mild reaction condition has a good functional group compatibility and a wide range of substrate scope. Moreover, this reaction can be used in the late functionalization of drug molecules and natural products. It is worth mentioning that the reaction is also applicable to arylboric acid.

In 2020, the Wang group also realized Minisci alkylation reaction of alkyl boric acid using oxygen as oxidant under photocatalysis (Scheme 18).[34] This mild protocol uses an inexpensive, green oxidant; permits efficient functionalization of various *N*-heteroarenes with a broad range of primary and secondary alkyl boronic acids; and is scalable to the gram level. The authors demonstrated the practicality and sustainability

of the protocol by preparing or functionalizing several pharmaceuticals and natural products. As for the mechanism of the reaction, they proposed that the excited photocatalyst $*Ir^{III}$ was quenched with O_2 to form a superoxide radical anion ($O_2^{\bullet-}$), along with a highly oxidized iridium species Ir^{IV}. The superoxide radical anion reacts with the boronic acid **45** to form alkyl radical **47** *via* intermediate **46**, which then adds to the protonated electron-deficient heteroarene **1** *via* a Minisci-type pathway to afford radical cation **48**. Single-electron oxidation of radical cation **48** by Ir^{IV} ($E_{1/2}^{IV/III}$=+1.70 V vs SCE in 2:1 MeCN/H_2O) and subsequent deprotonation to give alkylated product **3** and complete the photoredox cycle.

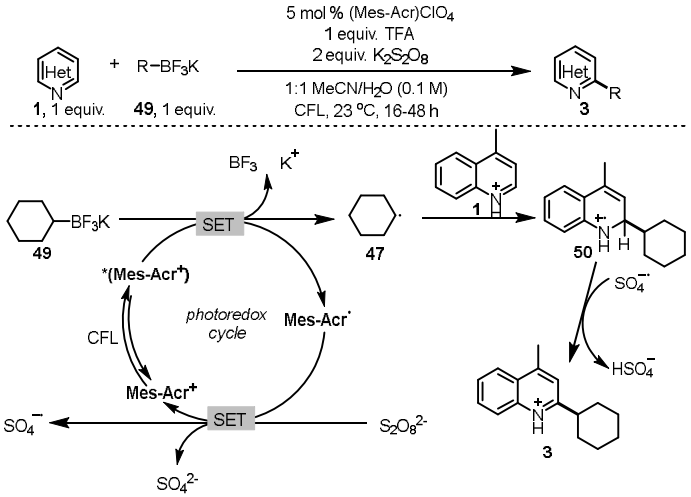


Scheme 17. Visible-light-mediated Minisci reaction with alkyl boronic acids.



Scheme 18 Visible-light-mediated Minisci reaction with alkyl boronic acids using O_2 as the oxidant.

In 2017, the Molander group realized the Minisci reaction with potassium alkyl trifluoroborate as a precursor of alkyl radical under photocatalysis (Scheme 19).[35] Based on the strong oxidizing properties of acridine photocatalyst,[36] the author proposed that acridine photocatalyst can directly oxidize alkyl potassium trifluoroborate **49** to produce alkyl radical **47**, which adds to the protonated electron-deficient heteroarene **1** *via* a Minisci-type pathway to afford radical cation **50**. Single-electron oxidation of this radical cation **50** by $SO_4^{-\bullet}$ give the alkylated product **3**. Based on this strategy, the Molander group then realized the heteroarylation of the 2 sites of dihydropyranoids, which was difficult to achieve with other methods.[37]



Scheme 19. Visible-light-mediated Minisci reaction with alkyl trifluoroborate salts.

5. Advances in radical generation from sulfur compounds

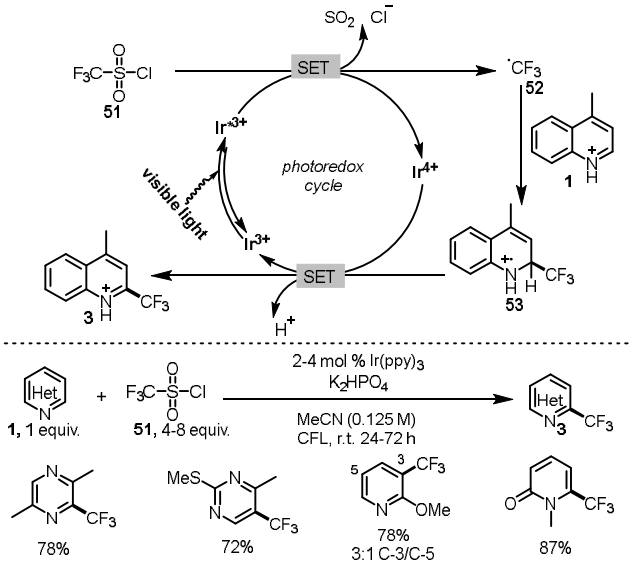
In 2011, the MacMillan group reported a photocatalyzed Minisci reaction with trifluoromethane sulfonyl chloride to achieve trifluoromethylation of *N*-heteroarenes (Scheme 20).[38] In this reaction an excited photocatalyst $*Ir^{III}$ reduced trifluoromethane sulfonyl chloride **51** to Ir^{IV} and trifluoromethyl radicals **52**, and then the trifluoromethyl radicals were added to *N*-heteroarenes **1** to give the intermediate **53**, which was oxidized by Ir^{IV} to produce trifluoromethyl products **3**. In this reaction, because the trifluoromethyl radical is an electrophilic radical, it selectively adds to the relatively electron-rich site of the *N*-heteroarenes, which is opposite to the selectivity of the traditional Minisci reaction.

In 2020, the Li group achieved difluoromethylation of *N*-heteroarenes using oxygen as an oxidant under visible light catalysis (Scheme 21).[39] In this reaction, the authors proposed that sodium difluoromethanesulfonic acid **54** can be oxidized by excited state photocatalyst to obtain difluoromethyl radical **55**, then added to *N*-heteroarene **1** to obtain heterocyclic aromatic radical intermediate **56**. Oxygen oxidizes the low-state photocatalyst to complete the photocatalytic cycle and obtain $O_2^{-\cdot}$.The $O_2^{-\cdot}$oxidized the aromatic radical intermediate **56** to obtain difluoromethylation product **3**. This mild reaction is suitable for the late difluoromethylation modification of complex drug molecules, and provides an efficient and practical method for the research and development of difluoromethylate drugs.

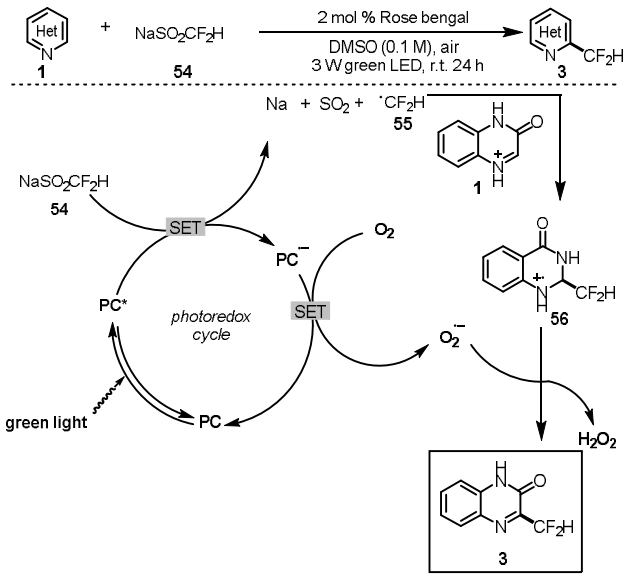
6. Advances in radical generation from alkyl halides

In 2017, the Fadeyi group reported a Minisci alkylation reaction with alkyl iodides catalyzed by $Mn_2(CO)_{10}$ under photocatalysis (Scheme 22).[40] As a new photocatalyst, $Mn_2(CO)_{10}$ can be excited by visible light to obtain $[Mn(CO)_5]$ radical.[41] $[Mn(CO)_5]$ radical can abstract the iodine atom from alkyl iodide **57** to obtain alkyl radical **47** and $Mn(CO)_5I$. This process is different from the single-electron redox process of other photocatalysts, and the iodine atom abstract process is not affected by the redox potential of the substrate. The resulting alkyl radical **47** is added to the *N*-heteroarene **1** to give the intermediate **58**, which is oxidized by $Mn(CO)_5I$ to obtain the product **3** and $[Mn(CO)_5]$ active catalyst. This reaction is the first

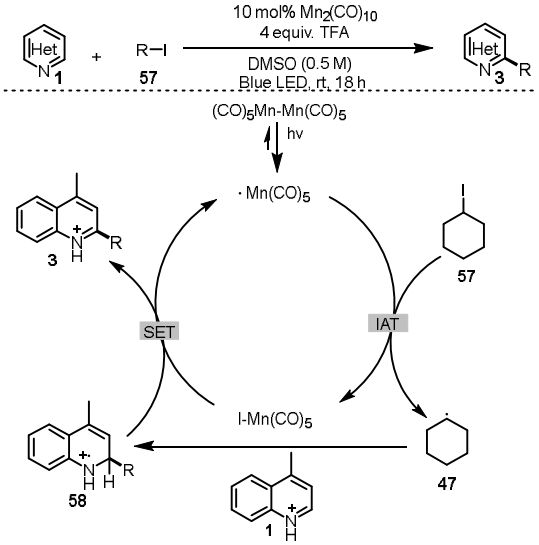
Minisci reaction with alkyl iodides catalyzed under visible light, which does not require high temperature and additional oxidant. Primary, secondary and tertiary alkyl radicals were all accessible with this method and the scope of heterocycles was broad, including examples of late-stage functionalization. This mild reaction provides a good method for the late alkylation modification of drugs and natural products containing *N*-heteroarene.



Scheme 20. Visible-light-mediated Minisci reaction with trifluoromethane sulfonyl chloride.

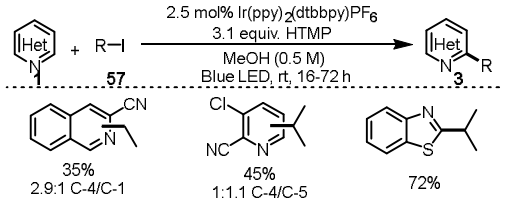


Scheme 21. Visible-light-mediated Minisci reaction with sodium difluoromethane sulfonate using O_2 as the oxidant.



Scheme 22. $Mn_2(CO)_{10}$-Catalyzed Minisci reaction with alkyl iodides.

In 2018, the Nuhant group reported a Minisci alkylation reaction of alkyl iodides under photocatalysis (Scheme 23).[42] In this reaction, 2,2,6,6-tetramethylpiperidine (HTMP) is used as a reducing agent to reduce the photocatalyst excited state $*Ir^{III}$ to obtain Ir^{II} with strong reducing ability, which reduces alkyl iodide **57** to produce alkyl radicals, which adds to the heteroarene **1** to give the product **3**. The scope is broad with respect to heteroarenes, and a variety of primary, secondary and tertiary fragments can be coupled.

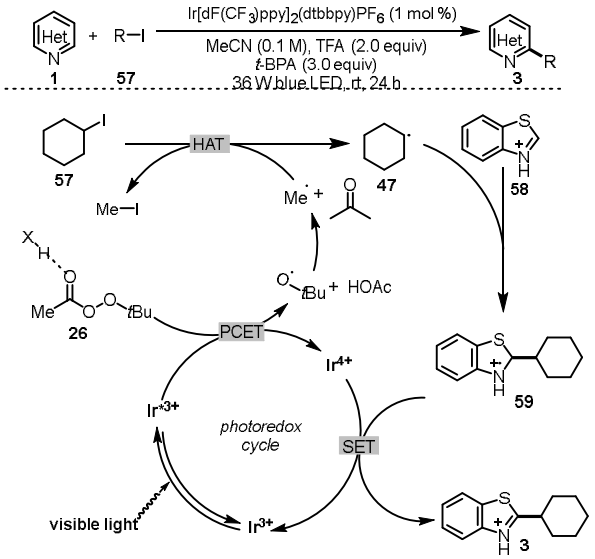


Scheme 23 Visible-light-mediated Minisci reaction with alkyl iodides.

In 2019, the Wang group reported the Minisci alkylation reaction with alkyl iodides using *t*-butyl peroxide acetate (*t*-BPA) as an oxidant under photocatalysis (Scheme 24).[43] In this reaction, *t*-BPA **26** oxidized the excited photocatalyst $*Ir^{III}$ by means of PCET to obtain *t*-butoxy radical and Ir^{IV}. The *t*-butoxy radical was *β*-cleaved to produce methyl radical, and the methyl radical abstracted the iodine atom from alkyl iodide **57** to obtain alkyl radical **47**, which was added to *N*-heteroarene **58** to give the intermediate **59**. Then **59** is oxidized by Ir^{IV} to obtain the product **3** and complete the photocatalytic cycle.

In 2019, the Wang group reported a visible-light-mediated Minisci C–H alkylation of heteroarene with unactivated alkyl halides using molecular oxygen as an oxidant at room temperature (Scheme 25).[44] This mild protocol is compatible with a wide array of sensitive functional groups and has a broad substrate scope. Notably, functionalization of (iso)quinolines, pyridines, phenanthrolines, quinazoline, and other heterocyclic compounds with unactivated primary, secondary, and tertiary alkyl halides proceeds smoothly under the standard conditions. The robustness of this protocol is further demonstrated by the late-stage functionalization of complex nitrogen-containing natural products and drugs. The authors propose that alkyl bromide **57** may produce tiny amounts of bromide under irradiation of light, oxidation of bromide by the photocatalyst generates an electrophilic bromine radical, which can abstract the hydrogen from $(Me_3Si)_3SiH$

60, generating a silyl radical species [$(Me_3Si)_3Si^{\cdot}$] **61**. Subsequent halogen abstraction from alkyl bromide **57** provides nucleophilic alkyl radical **47** and the bromosilane byproduct. This abstraction step is effectively irreversible owing to the difference in bond dissociation energy between the Si–Br bond of Me_3Si–Br (96 kcal/mol) and the Csp^3–Br bond of bromoethane (69 kcal/mol). Alkyl radical **47** then adds to the protonated electron-deficient heteroarene **1** *via* a Minisci-type pathway to afford radical cation intermediate **62**. Single-electron oxidation of Ir^{2+} by O_2 forms the superoxide radical anion ($O_2^{-\cdot}$) and completes the photoredox cycle. $O_2^{-\cdot}$ can abstract a hydrogen atom from radical cation intermediate **62** to form the final alkylated product **3**.



Scheme 24. Visible-light-mediated Minisci reaction with alkyl iodides using *t*-BPA as the oxidant.

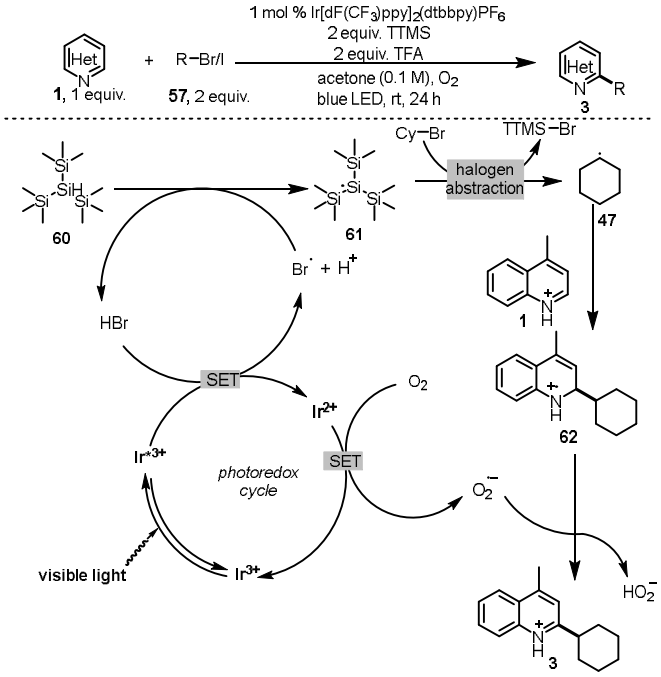
7. Minisci reactions *via* spin center shift (SCS)

It is known that deoxyribonucleoside diphosphates, the monomeric precursors of DNA, are formed by radical deoxygenation of ribonucleoside diphosphates catalysed by RNRs in all organisms. This enzymatic process involves a crucial (3,2)-spin-centre shift (SCS) from **63** to **64** that leads to both *β*-C–O bond cleavage and elimination of water (Scheme 26).[45]

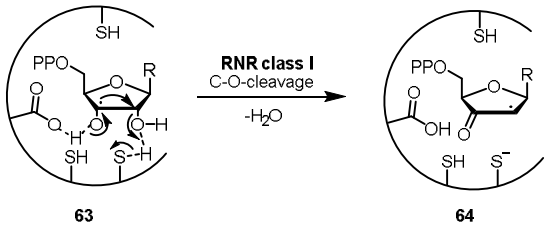
Due to its being a feedstock chemical, the employment of MeOH as a surrogate for a methyl radical, through a formal C–O functionalization, is very attractive. In 2015, the MacMillan group achieved the Minisci reaction of alcohols **65** as precursors of alkyl radicals using SCS as a key step under photocatalysis (Scheme 27).[46] The system relies on dual photoredox and HAT catalytic systems and exploits a SCS elimination event from key radical intermediate **68** (see mechanistic rationale). After addition of the *α*-hydroxyalkyl radical **66** to the heteroarene **1** to give the intermediate **67** and subsequent deprotonation, undergoes an SCS elimination of water. With this, the radical migrates from the C2-carbon to the benzylic position, resulting in benzyl radical intermediate **69**. This is then reduced and protonated, furnishing the final alkyl product **3**. This reaction is only suitable for primary alcohols, and is not suitable for secondary and tertiary alcohols, probably because of the steric hindrance of secondary and tertiary alcohols, and it is difficult for thiol radicals to abstract the hydrogen atoms of the hydroxyl group. This reaction can also be applied to cyclic ether compounds, and the alkylation products of ether ring-opening can be obtained through the SCS process.

Since carbonyl compounds widely exist in nature, it is of great significance to deoxidize carbonyl compounds to produce alkyl radicals for Minisci reaction. However, carbonyl compounds generally act as electrophilic alkyl groups and are therefore difficult to couple to *N*-heteroarenes owing to polarity

mismatch.[47,48] The Wang group reported the first Minisci reaction with carbonyl compounds as the precursor of alkyl radicals (Scheme 28).[49] The PCET process is combined with SCS process in this reaction. The authors proposed that excited *Ir^{III} photocatalyst is reduced by trimethylsilane **60** to obtain Ir^{II}, which is more reductive. With the help of an acid, Ir^{II} underwent PCET process with carbonyl compounds **70** to obtain ketyl radical **71** and complete the photocatalytic cycle. Ketyl radical **71** then was added to the *N*-heteroarene **1** to give intermediate **72**, which underwent the 1,2-H transfer to give intermediate **73**. Then intermediate **73** underwent SCS to obtain benzyl radical **74**. This benzyl radical then abstracted hydrogen atoms from the system to produce alkylation products **3**. This alkylation strategy represents a general use of abundant commercially available ketones and aldehydes as latent alkyl radical equivalents.



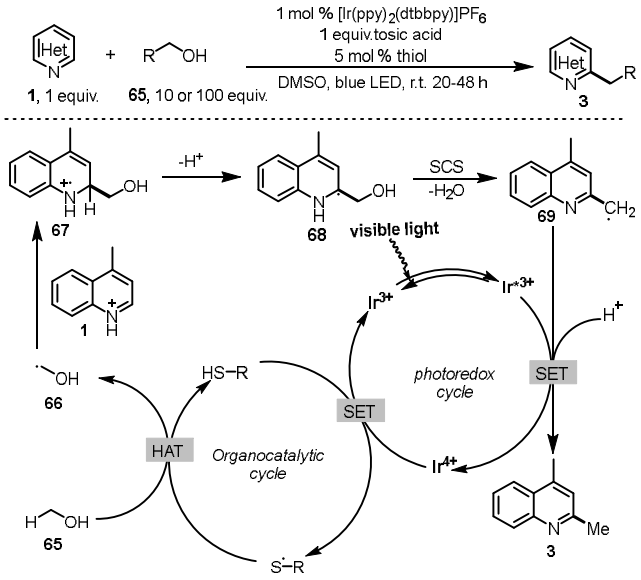
Scheme 25. Visible-light-mediated Minisci reaction *via* halogen atom transfer.



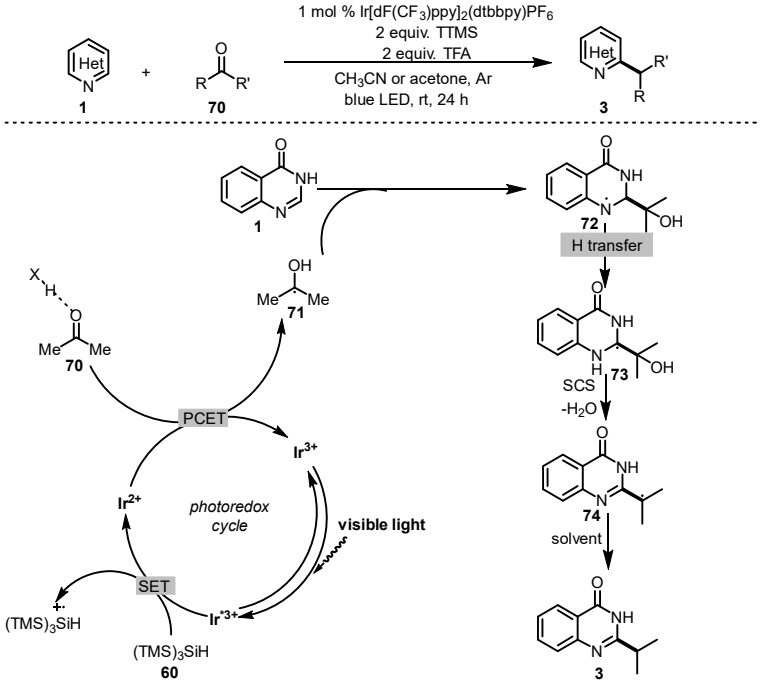
Scheme 26. The spin-centre shift (SCS) process in organism.

In 2020, the Huang group also realized the Minisci hydroxylalkylation reaction with aldehyde using SCS as a key step under photocatalysis (Scheme 29).[50] The authors propose that the bromine anion can be oxidized by excited photocatalyst to obtain bromine radical, which can abstract acyl hydrogen atoms of aldehydes **75** to obtain acyl radical **76**. Then, the radical addition of acyl radical **76** to the *N*-heterocycle **1** to give the intermediate **77**, deprotonation, and a SCS process occurred sequentially to generate the hydroalkyl

radical **79** *via* intermediate **78**, which is reduced by low-state photocatalyst and then combined with a proton to obtain hydroxyl alkyl product **3**.

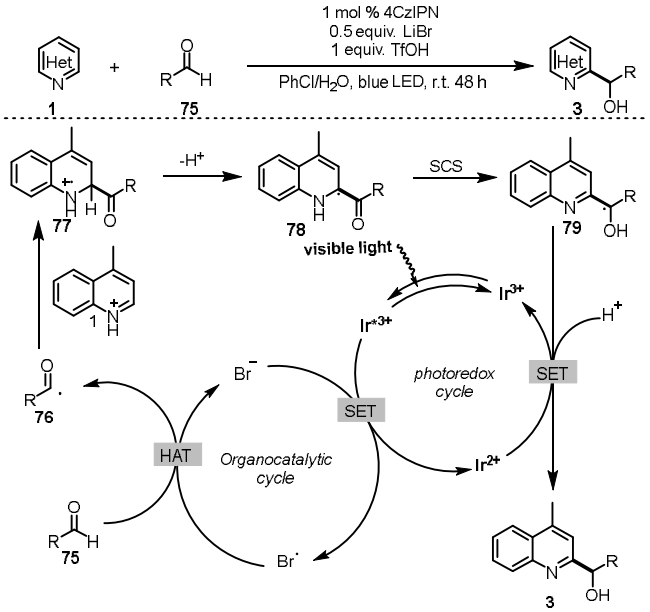


Scheme 27. Visible-light-mediated Minisci reaction with primary alcohols *via* SCS process.



Scheme 28 Visible-light-mediated deoxygenation Minisci reaction with carbonyl compounds *via* SCS process.

The present mild photoredox neutral protocol provides an important alternative, especially for the challenging Minisci hydroalkylations, as well as a promising approach for atom-economical Minisci reactions with broader *N*-heterocycle scope.



Scheme 29. Visible-light-mediated Minisci hydroxyalkylation with aldehydes *via* SCS process.

8. Advances in radical generation from C–C fragmentation

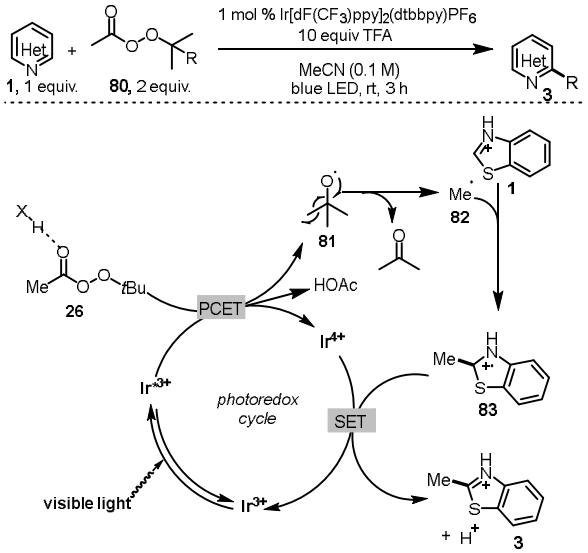
In 2014, the Di Rocco group reported the Minisci alkylation reaction with peroxides **80** as precursors of alkyl radicals under photocatalysis (Scheme 30).[51] The reaction mechanism is similar to the photocatalyzed Minisci alkylation of alkyl iodides reported by the Wang group. In this reaction, *t*-butyl peroxyacetate **26** oxidizes the excited photocatalyst $*Ir^{III}$ *via* PCET to obtain *t*-butoxy radical **81** and Ir^{IV}. *t*-Butoxy radical undergo *β*-cleavage to produce methyl radical **82** which added to the *N*-heteroarene **1** to give intermediate **83**, which is oxidized by Ir^{IV} to obtain methylated product **3**. The "magic methyl" effect denotes the ability of a small alkyl substituent, in particular a methyl group, to modulate the biological and physical properties. Given the streamlined approach of late-stage functionalization, methods for the installation of small alkyl groups into complex scaffolds is therefore a desirable prospect.

In 2019, the Chen group realized the Minisci alkylation reaction *via β*-cleavage of alcohols (Scheme 31).[52] In this reaction, alcohols **84** produce oxygen radicals **85**, because there is no 1,5-hydrogen migration site, oxygen radicals undergo *β*-cleavage to give aldehydes **86** and alkyl radical **87**. In other words, the 1,5-hydrogen migration Minisci reaction and the *β*-cleavage Minisci reaction of alcohols are determined by the alcohol substrates. When there are hydrogen atoms at the 1,5-hydrogen migration site, the 1,5-hydrogen migration Minisci reaction products are obtained, and when there are no hydrogen atoms at the 1,5-hydrogen migration site, the *β*-cleavage Minisci reaction products are obtained.

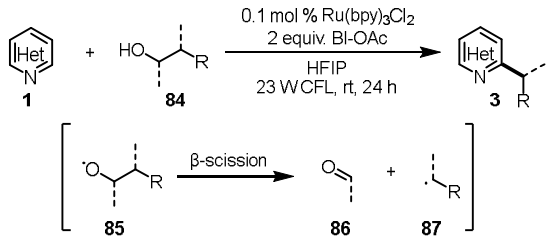
9. Advances in radical generation from diazonium salts

As a common aryl radical precursor, the addition of aryl diazonium salts to *N*-heteroarenes is well known. However, until recently aryl diazonium salts have not been used extensively in Minisci-type reactions due to typically low yields and formation of byproducts.[53] In 2014, the Xue group reported a photocatalyzed Minisci reaction with aryl diazonium salts as aryl radical precursors (Scheme 32).[54] Due to the oxidative nature of diazonium salts **88**, the reaction is redox-neutral and utilizes $Ru(bpy)_3Cl_2$ as a

photoredox catalyst under aqueous conditions. The HCl salts of the heteroarenes **1** are used as substrates and the scope is broad, with a range of arylated heterocycles **3**. Although pyridine gives a mixture of regioisomers under Xue's conditions, interestingly quinoline is arylated exclusively at the 2-position. More complex heterocycles are also smoothly arylated, including aminopyrazine and caffeine, based on a 5-membered ring.



Scheme 30. Visible-light-mediated Minisci reaction *via* peroxide fragmentation.

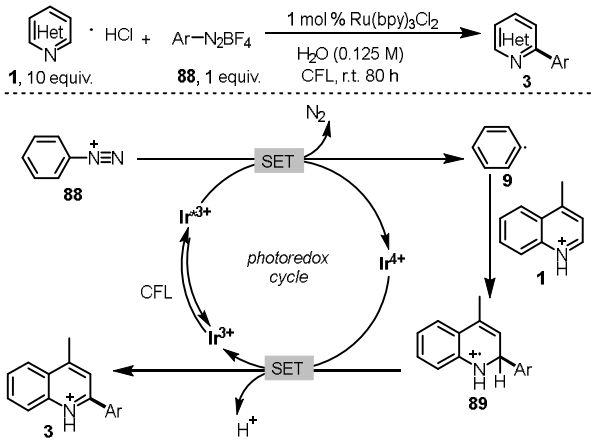


Scheme 31. Visible-light-mediated Minisci reaction with alcohols *via* β-scission.

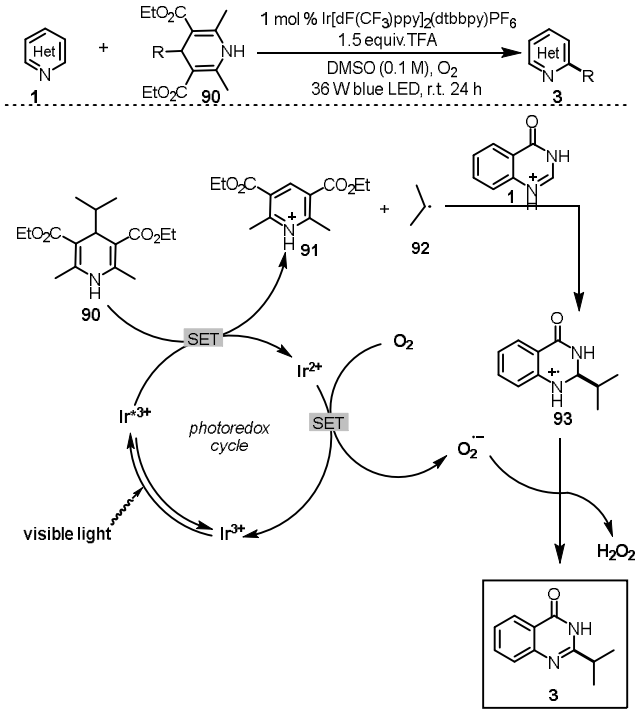
10. Advances in radical generation from dihydropyridines

Aldehydes have been employed not only as precursors of acyl radicals generated by means of hydrogen atom transfer but also, to a lesser extent, as sources of alkyl radicals generated by decarbonylation of acyl radicals. However, even though aldehydes are convenient precursors for alkyl radicals, the existing decarbonylative protocols tend to give mixtures of alkylated and acylated products resulting from incomplete decarbonylation. In order to solve this problem, in 2017, the Molander group synthesized a series of 1,4-dihydropyridine (DHPs) derivatives from alkyl aldehydes in one step,[55] which could produce alkyl radicals by means of oxidative homolysis of alkyl dihydropyridine to achieve the alkylation reaction of benzoquinone and *N*-heteroarenes.[56] In this reaction, alkylation is realized without acylation byproducts. In 2020, the Wang group also realized Minisci alkylation of alkyl dihydropyridine using oxygen as oxidant under photocatalysis (Scheme 33).[57] In this reaction, the authors proposed that an excited photocatalyst $^*Ir^{III}$ directly oxidize alkyl dihydropyridine **89** to obtain pyridine **90** and alkyl radical **91**, which then adds to the protonated electron-deficient heteroarene **1** to afford radical cation intermediate **92**. Single-electron oxidation of Ir^{2+} by O_2 forms the superoxide radical anion (O_2^{-}) and completes the photoredox cycle.

$O_2^{-\cdot}$ can abstract a hydrogen atom from radical cation intermediate **92** to form the final alkylated product **3**. This mild protocol uses an inexpensive, green oxidant and is suitable for late-stage C–H alkylation of complex nitrogen-containing molecules.



Scheme 32. Visible-light-mediated Minisci reaction with aryl diazonium salts.

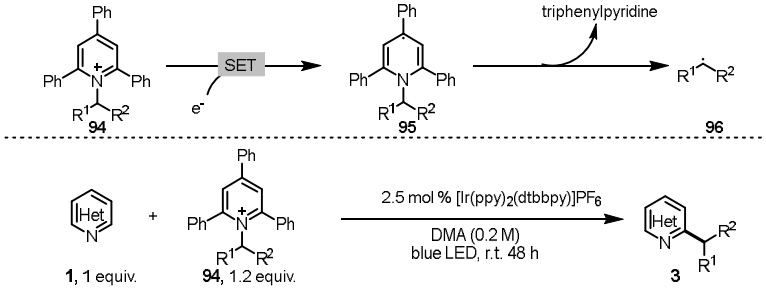


Scheme 33. Visible-light-mediated Minisci reaction with alky-dihydropyridines.

11. Radicals from alkylpyridinium salts

Organic amines are widely found in nature, the Minisci alkylation of amines through the HAT process of *ortho* C–H bond of nitrogen atoms is described in the previous chapter. Given the ready availability of

alkyl amines, cleavage of C–N bonds in alkyl amine-derivatives represents an attractive option for the generation of carbon-centered radical fragments. The Glorius group recently reported a Minisci-type protocol that uses such an approach (Scheme 34).[58] In the field of photochemistry, the generation of alkyl radical through the break of carbon-nitrogen bond is not common, which provides a new way for organic amine molecules to participate in Minisci reaction. The authors proposed that photocatalyst reduced alkyl pyridine salts **93** to produce alkyl radicals **95** *via* intermediate **94**, which makes the reaction without the need for additional oxidants.



Scheme 34. Visible-light-mediated Minisci reaction with alkylpyridinium salts.

12. Conclusions

In this chapter, visible light catalyzed Minisci reactions of carboxylic acid, activated ester, activated and unactivated alkanes, boric acid, trifluoroborate, trifluoromethane sulfonyl chloride, halogenated hydrocarbons, alcohols, aldehydes, ketones, aryl diazonium salts, alkyl dihydropyridine and alkyl pyridine salts are described from the perspective of radical producing precursor compounds. It can be seen that visible light catalyzed Minisci reaction has made great progress in recent years. Among them, *N*-heteroarenes, such as quinoline, isoquinoline, pyridine and pyrimidine, which are most suitable for Minisci reaction, are also the most widely studied skeleton structures in pharmaceutical chemistry, which means that we need to further improve and develop Minisci reaction. This includes the use of inexpensive and readily available radical precursors, milder reaction conditions, better stereoselectivity and regional selectivity, and avoidance of the use of precious metal photocatalysts. As more and more synthetic chemists develop new methods of radical production, further breakthroughs will be made in the Minisci reaction in the future.

Acknowledgements

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