RECENT ADVANCES IN THE SYNTHESIS OF QUINOXALIN-2(1*H*)-ONE DERIVATIVES THROUGH DIRECT C3–H FUNCTIONALIZATION

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Abstract. *In this review, recent achievements on direct C3–H functionalization of quinoxalin-2(1H)-ones, including C3–H alkylation, arylation, acylation, cyanantion, alkoxylation and sulfenylation, amination and amidation, as well as phosphonation are presented. The discussion particularly emphasizes on working models and reaction mechanisms.*

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1. Introduction

Quinoxalin-2(1*H*)-ones are important bicyclic nitrogen-containing heterocycles which can be found in various natural products, pharmaceuticals, and medicinally relevant compounds.[1,2] In this heterocycle family, C3-substituted quinoxalin-2(1*H*)-ones represented one of the most important scaffolds due to their broad range of biological activities and potential applications in synthetic chemistry. Consequently, the development of novel and robust methods towards the facile construction of C3-substituted quinoxalin-2(1*H*)-ones has attracted considerable research interests. Traditionally, C3-substituted quinoxalin-2(1*H*)-ones can be accessed by the condensation reaction of 1,2-diaminobenzene with 1,2-dicarbonyl compounds or the use of cascade radical cyclization.[3-6] In the past years, tremendous interest has been paid on the direct C–H functionalization of quinoxalin-2(1*H*)-one at its C3 position which offered an alternative convenient and straightforward method to access these heterocycles.[5,6] Important achievements such as C3–H alkylation, arylation, acylation, cyanantion, alkoxylation and sulfenylation, amination and amidation, as well as phosphonation of quinoxalin-2(1*H*)-ones were sequentially investigated. Recent investigations revealed that the method can be applied not only in the synthesis of C3–H functionalized quinoxalin-2(1*H*)-one derivatives, but also in the late state modification of biologically important drug candidates and natural isolates.

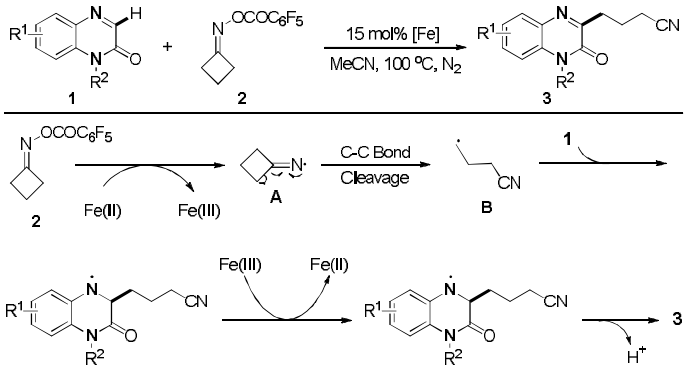
At early of 2019, Yan and Yu contributed a review article in this area which mainly focused on the reactions developed before 2019.[5] Shortly after, Pedro and Vila summarized the functionalization of quinoxalin-2-ones by using visible-light photoredox catalytic strategy.[6] Many research groups have entered the field leading to a large number of publications in the area in particular since the above two contributions.

In this chapter, we will systematically summarize recent advances in the field of C3–H functionalization of quinoxalin-2(1*H*)-ones with particular emphases put on working models and reaction mechanisms. The reactions discussed in this review mainly focused on the latest contributions published since 2020.

2. C3–H Functionalization of quinoxalin-2(1*H*)-ones

2.1. C3–H Alkylation

Cyclobutanone oxime derivatives are well known cyanoalkyl precursors which have been widely used in many important alkylation reactions.[7,8] In 2018, the Guo group reported the C3–H cyanoalkylation of quinoxalin-2(1*H*)-ones **1** with cyclobutanone oxime esters **2** by using cheap iron as catalyst (Scheme 1).[9] Apart from quinoxalin-2(1*H*)-one scaffolds **3**, the method could also be successfully applied to direct C3–H cyanoalkylation of benzothiazole and caffeine derivatives. In the reaction mechanism shown in Scheme 1, the single electron-reduction of **2** by Fe(II), followed by C–C bond cleavage would generate the key carbon-centered radical species **B**. Radical addition of **B** to quinoxain-2(1*H*)-one provided the nitrogen radical **C**, which was oxidized by Fe(III) to afford intermediate **D**. Deprotonation of **D** furnished the desired C3–H functionalization product. Shortly after, similar process was also realized under photoredox catalytic conditions,[10-14] using either a metal complex or an organic dyes as photoredox catalyst.[15-17]



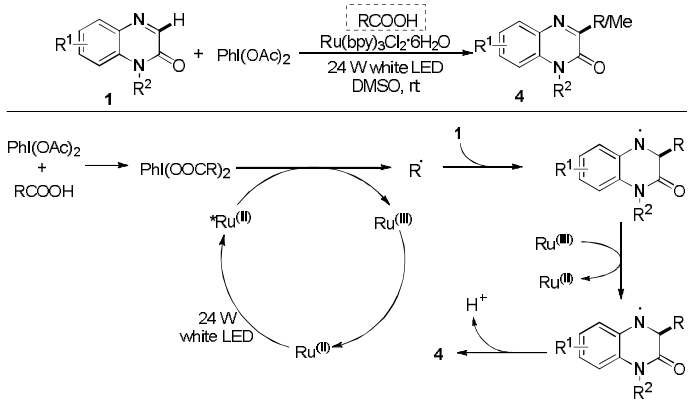
Scheme 1. Fe-catalyzed cyanoalkylation of quinoxalin-2(1*H*)-ones.

The introduction of a methyl group into a pharmacophore may dramatically improve the biological activities. Phenyliodine(III) dicarboxylates (PIDA) have proved to be effective methyl radical precursors through radical decarboxylation process.[18] In 2019, the strategy was successfully applied to C3–H methylation (or alkylation) **4** of quinoxain-2(1*H*)-ones **1** by the Hu group (Scheme 2).[19] As expected, the designed C3–H methylation reaction occurred smoothly with $PhI(OAc)_2$ as methyl radical precursor, while C3–H alkylation products could be obtained by adding aliphatic carboxylic acids into the reaction system. It was proposed that the required alkyl radical might generate through the ligand exchange of aliphatic carboxylic acids with PIDA. Almost at the same time, decarboxylative C3–H alkylation of quinoxain-2(1*H*)-ones with PIDA in recyclable ruthenium(II) catalytic system or under catalytic free reaction conditions were sequentially realized.[20,21]

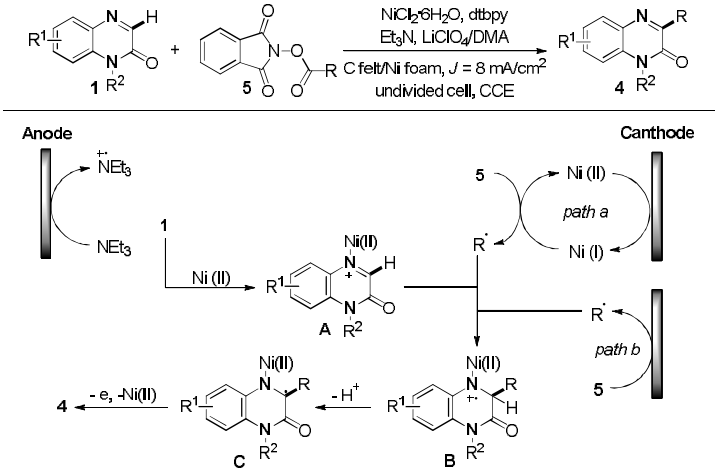
Another commonly used method to activate carboxylic acids is to convert them into *N*-hydroxyphthalimide (NHP) esters **5**.[22] In the past years, visible light-induced decarboxylation coupling of NHP esters with quinoxalin-2(1*H*)-ones **1** provided a robust synthetic route to access C3-alkylated quinoxalin-2(1*H*)-one **4** derivatives and the related reactions also well documented in form reviews.[23-25] Besides photoredox catalysis, Zeng and co-workers developed a nickel-catalyzed electrochemical alkylation

of quinoxalin-2(1*H*)-ones using NHP esters as the alkyl radical precursors (Scheme 3).[26] A range of range of NHP esters derived from primary, secondary and tertiary aliphatic carboxylic acids reacted well to give product **4** in good yield. More significantly, amino acid-derived esters also were tolerated well.

Mechanistically, Ni(I) species, generated from the cathode reduction of Ni(II), underwent single electron transfer with NHP ester to afford the key alkyl radical and Ni(II) species. Then, addition of alkyl radical to the Ni(II)-actived quinoxalin-2(1*H*)-one **A** provided radical cation intermediate **B** which subsequently deprotonated to give radical intermediate **C**. The intermediate **C** was further oxidized and released one molecule of Ni(II)) to yield the target 3-alkylquinoxalinone **4**. Note that another pathway for the generation of alkyl radical through cathode reduction of NHP ester was also possible (Scheme 3 path b).



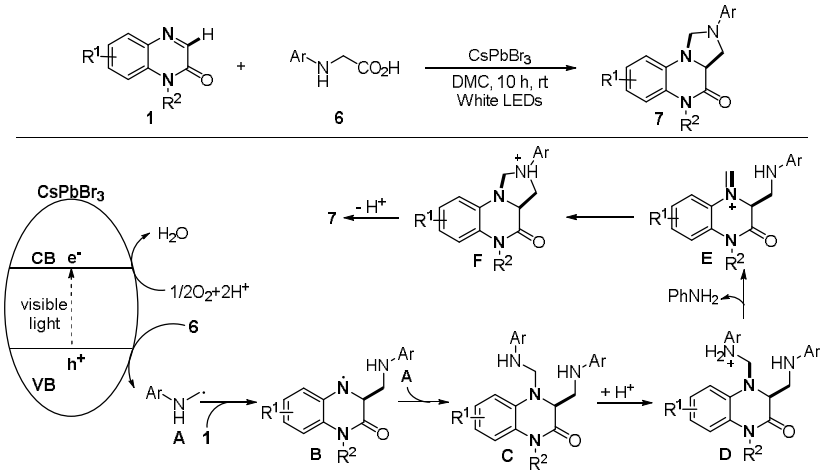
Scheme 2. C3–H methylation or alkylation of quinoxalin-2(1*H*)-ones using PIDA.



Scheme 3. Nickel-catalyzed electrochemical C3–H alkylation of quinoxalin-2(1*H*)-ones.

Very recently, a similar work about electrochemical C3–H alkylation of quinoxalin-2(1*H*)-ones by using NHP esters as alkyl radical precursors under metal- and additive-free conditions was accomplished by Wang and co-workers.[27]

In 2020, Yu, Chen *et al.* developed a visible light-induced cascade annulation reaction of quinoxalin-2(1*H*)-ones **1** with *N*-arylglycines **6** by using recyclable perovskite ($CsPbBr_3$) as photoredox catalyst (Scheme 4).[28] Different with one-step C3–H alkylation reactions mentioned above, a large variety of important poly-heterocycles, tetrahydroimidazo-[1,5-*a*]quinoxalin-4(5*H*)-ones, were obtained in moderate to good yields under the optimal reaction conditions. Control experiments revealed that the reaction occurred via a radical pathway and the key arylaminomethyl radical was generated from decarbonation of *N*-arylglycines under photocatalytic conditions, which was confirmed by EPR study. As shown in Scheme 4, trapped of the photo-generated arylaminomethyl radical by quinoxalin-2(1*H*)-ones delivered the *N*-centered radical **B**. Radical cross-coupling between **B** and **A** produced the intermediate **C**. Protonation of **C**, followed by elimination of aniline generated iminium ion **E**. Intramolecular cyclization of **E** provided **F**. Deprotonation of **F** afforded the final annulated product **7**.



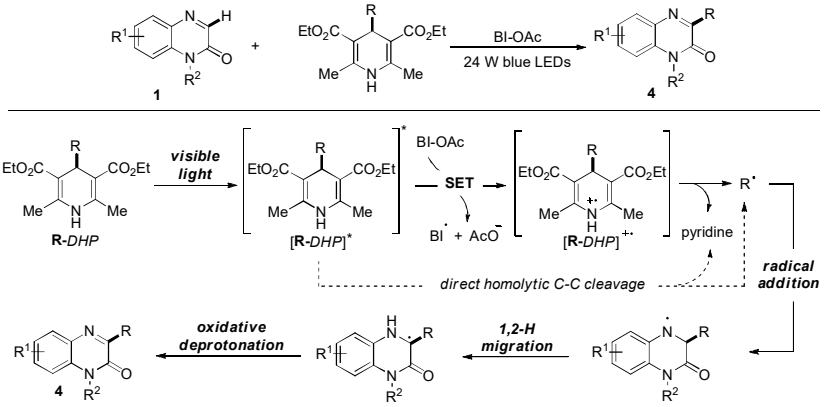
Scheme 4. Visible light-induced cascade annulation reaction of quinoxalin-2(1*H*)-ones with *N*-arylglycines.

Yu *et al.* further documented that this cascade annulation process also worked well after replacing the photoredox catalyst from perovskite ($CsPbBr_3$) with graphitic carbon nitride (g-C_3N_4).[29] It was found that the reaction solvent had a significant effect on the reaction outcome. Polycyclic heterocycle **7** could be obtained in good yield when the reaction was performed in EtOH. In contrast, the dihydroquinoxalin-2(1*H*)-ones were observed as major products upon using DMSO/H_2O as reaction media.

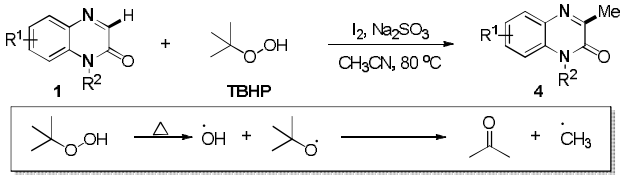
Besides PIDA, other types of hypervalent iodine reagents, such as acetoxybenziodoxole (BI-OAc) was also a good activating reagent in such alkylation processes. In 2020, our group disclosed a BI-OAc accelerated alkylation of quinoxalin-2(1*H*)-ones **1** using 4-alkyl-1,4-dihydropyridines (R-DHPs) as alkyl radical precursor (Scheme 5).[30] The reaction showed very good compatibility in the scope of both R-DHPs and quinoxalin-2(1*H*)-ones **1**, affording the functionalized heterocycles **4** in good to excellent yields. More significantly, quinoxalin-2(1*H*)-ones **1** bearing various biologically important natural isolates and drug candidates could be smoothly modified by the developed method. Mechanism investigations revealed that the reaction also proceeded via classical radical pathway and the BI-OAc served as radical acceptor to reduce the excited state [R-DHP]*. The formed $[R\text{-}DHP]^{\bullet+}$ fragmented to give the key R-alkyl radical intermediate.

At early of 2020, two metal-free C3−H methylation of quinoxain-2(1*H*)-ones **1** by directly using the

TBHP as cheap methylating reagent were simultaneously reported by the group of Yan and Xia.[31,32] In those two contributions, the key methyl radical species generated from decomposition of TBHP under thermal reaction conditions without need for external catalysts or additives (Scheme 6).

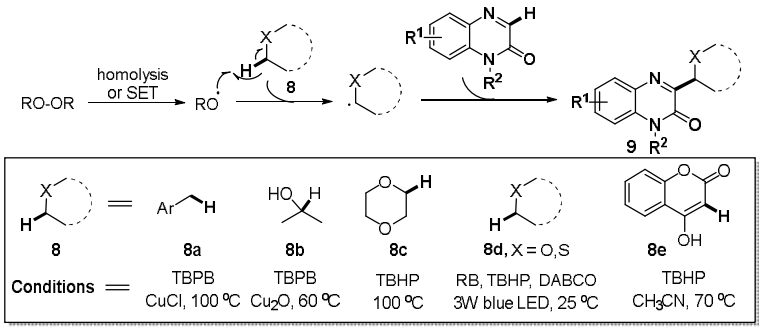


Scheme 5. C3–H alkylation of quinoxalin-2(1*H*)-ones using BI-OAc and R-DHPs.



Scheme 6. C3−H methylation of quinoxalin-2(1*H*)-ones using TBHP as methylating reagent.

Another method for C3−H alkylation of quinoxalin-2(1*H*)-ones **1** is based on the use of C−H/C−H cross-dehydrogenative-coupling strategy. As shown in the general reaction mechanism depicted in Scheme 7, homolysis or single electron reduction of peroxides afforded alkyloxy radical species, which then underwent hydrogen abstraction from suitable alkyl radical precursors affording the required alkyl radical species.



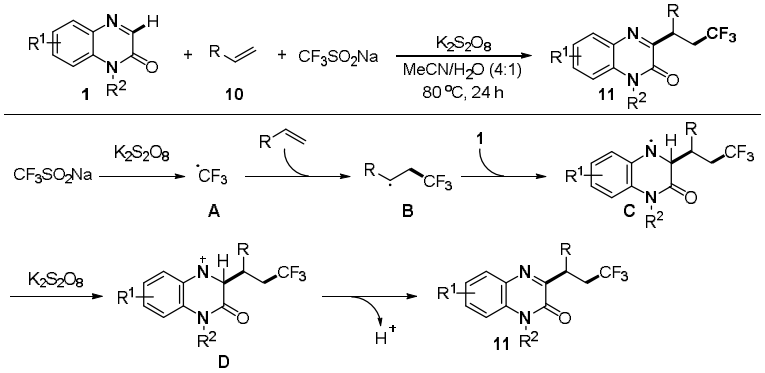
Scheme 7. C3−H alkylation of quinoxalin-2(1*H*)-ones through C−H/C−H cross-dehydrogenative-coupling.

By using this strategy, the Qu group realized the C3−H benzylation and hydroxyalkylation of

quinoxalin-2(1*H*)-ones **1** under copper catalytic conditions.[33,34] Besides methylarenes **8a** and alcohols **8b**, cyclic ethers **8c**, **8d** and 4-hydroxycoumarins **8e** also proved to be suitable substrates in this C−H/C−H cross-dehydrogenative-coupling process.[35-38] Note that, most of those functionalization processes occurred under mild reaction conditions, affording the corresponding heterocycles **9** in good yields and excellent functional group tolerance.

Because of the unique effect of fluorine atom on physical and biological properties, the introduction of a perfluoroalkyl group into an organic framework finds wide applications in medicinal chemistry and materials science. There is no doubt that the development of C3−H perfluoroalkylation of quinoxalin-2(1*H*)-ones have attracted considerable attentions. Some commonly used perfluoroalkyl reagents, including sodium perfluoroalkanesulfinates,[39-42] perfluoroalkyl halides,[43,44] fluoro-containing aliphatic carboxylic acids,[45-47] and $TMSCF_3$[48] were sequentially involved in the synthesis of perfluoroalkylquinoxalin-2(1*H*)-ones through the C3−H functionalization strategy.

Based on previous works on the synthesis of C3-alkylated quinoxalin-2(1*H*)-ones through three component reactions,[49,50] Wei and co-workers recently developed a three-component reaction of quinoxalin-2(1*H*)-ones **1**, un-activated alkenes **10** and CF_3SO_2Na under oxidative reaction conditions (Scheme 8).[42] Optimization of reaction conditions revealed that $K_2S_2O_8$ action as oxidant was the best choice and the addition of water in the system could increase the reaction yield. As the reaction mechanism depicted in Scheme 8, under the oxidative conditions, Langlois' reagent provided CF_3 radical along with the release of SO_2. Then, selectively addition of radical **A** to un-activated alkenes **10** afforded radical intermediate **B**. The addition of B to quinoxalin-2(1*H*)-ones produced nitrogen-centered radical species **C**, which was subsequently oxidized to cation **D** with the assistance of $K_2S_2O_8$. Finally, deprotonation of **D** furnished the final perfluoroalkyl functionalized quinoxalin-2(1*H*)-one **11**.

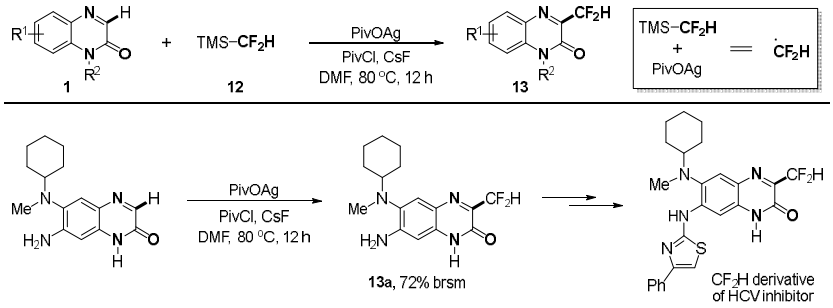


Scheme 8. C3−H trifluoroalkylation of quinoxalin-2(1*H*)-ones through three component reactions.

Wei and co-workers further realized a visible-light promoted three component reaction of quinoxalin-2(1*H*)-ones, un-activated alkenes and CF_3SO_2Na.[51] The reaction occurred under very mild conditions with catalytic amount of 4CzIPN (1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene) as photoredox catalyst and air as the green terminal oxidant.

In 2021, the Chu group developed a silver-catalyzed radical difluoromethylation of quinoxalin-2(1*H*)-ones **1** utilizing commercially available $TMSCF_2H$ **12** as radical CF_2H agent to give **13** (Scheme 9).[52] It is important to mention that the development method could be applied as key step for the facile construction of CF_2H derivative of HCV inhibitor. Apart from quinoxalin-2(1*H*)-ones **1**, other types of

radical trapping agents, *e.g.* vinyl carboxylic acids, alkenes, dienes, and isonitriles also suitable substrates to react with the generated CF_2H radical to create new C−CF_2H bonds.

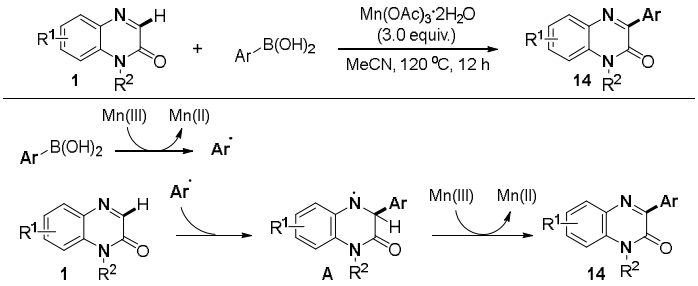


Scheme 9. Silver-catalyzed C3−H difluoromethylation of quinoxalin-2(1*H*)-ones.

2.2. C3−H Arylation

The traditional methods for direct C3−H arylation of quinoxalin-2(1*H*)-ones consisted in the palladium-mediated coupling reaction. For instance, Alami and Messaoudi realized the Pd(II)-catalyzed C3−H arylation of quinoxalin-2(1*H*)-ones with arylboronic acids as coupling reagent.[53,54] Lee and co-workers developed a $Pd(TFA)_2$-mediated coupling of quinoxalin-2(1*H*)-ones with arenes which needed not use of pre-functionalized arylating reagents.[55]

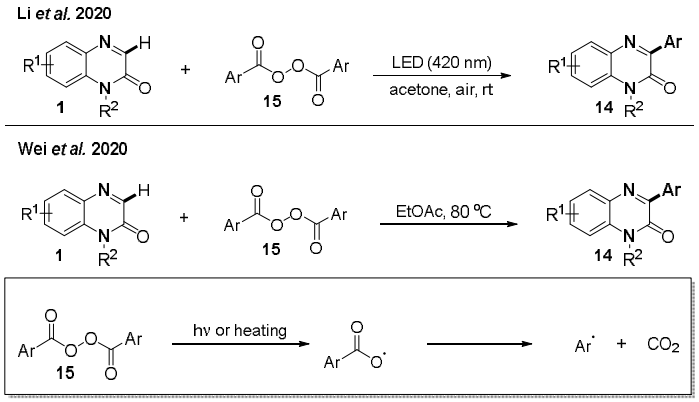
To avoid the use of palladium catalyst, radical oxidative-coupling offered an alternative route to access C3−H arylated quinoxalin-2(1*H*)-ones. Early work by the Reddy group showed that besides coordinating with metal complex, arylboronic acids could also be employed as aryl radical precursors (Scheme 10).[56] In the presence of $Mn(OAc)_3{\cdot}2H_2O$, various boronic acids could smoothly react with quinoxalin-2(1*H*)-ones **1** to provide the desired C3–H arylated product **14** in good to excellent yield. It was proposed that arylboronic acid could be oxidized by Mn(III) to provide the aryl radical, which further added to quinoxalinone to afford the nitrogen centered radical **A**. Oxidative deprotonation of **A** afforded the C3–H arylquinoxalin-2(1*H*)-one **14**.



Scheme 10. Mn (III)-mediated direct C3−H arylation of quinoxalin-2(1*H*)-ones.

By using the similar radical oxidative-coupling strategy, other types of aryl radical precursors, such as diaryliodonium salts,[57] aryldiazonium salts,[58-60] arylhydrazines [61-63] were successfully applied towards the synthesis of C3−H arylquinoxalin-2(1*H*)-ones. These reactions generally occurred under mild reaction conditions without the need of transition-metals.

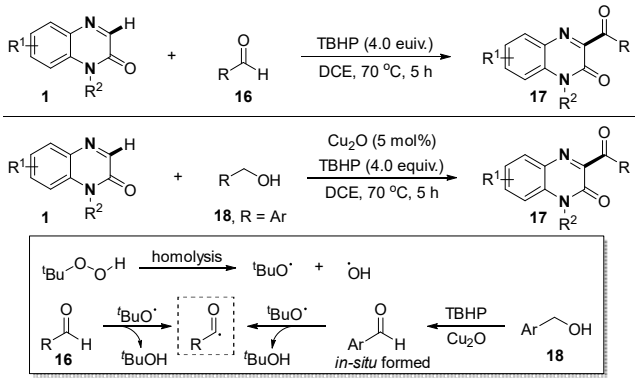
In a recent contribution, Li and co-workers reported a visible light-induced C3−H arylation of quinoxalin-2(1*H*)-ones **1** with aryl acyl peroxides **15** (BPO).[64] The reaction smoothly occurred under 420 nm LED irradiation without the use of additional photoredox catalyst, metals, or additives. Mechanism investigation shown that quinoxalin-2(1*H*)-one **1** served as photocatalyst and underwent an energy transfer (ET) process with BPO. At the same time, Wei *et al.* realized the same process under thermal reaction conditions.[65] In both cases, aryl radical generated from homolysis/decarboxylation of BPO **15** under visible light irradiation or thermal conditions was proposed as key intermediate for the formation of final C3−H arylated heterocycle **14** (Scheme 11).



Scheme 11. C3−H arylation of quinoxalin-2(1*H*)-ones using BPO.

2.3. C3−H Acylation

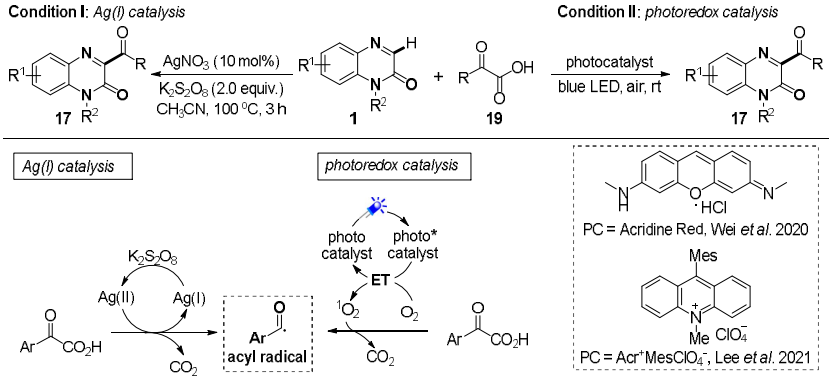
Aldehydes are one of the most important acylating agents in C3–H acylation of quinoxalin-2(1*H*)-ones. In 2018, Yuan and Qu disclosed an oxidative cross-dehydrogenative coupling of quinoxalin-2(1*H*)-ones **1** with aldehydes **16** (Scheme 12).[66] The reaction occurred under metal-free conditions with the use of *tert*-butyl hydroperoxide (TBHP) as oxidant. Both aromatic aldehydes and alkylic aldehydes reacted well, affording the C3−H acylated quinoxalin-2(1*H*)-ones **17** in moderate to good yields. Interestingly, benzyl alcohols **18** also could serve as acylated reagents which might because benzyl alcohols were *in-situ* oxidized to aldehydes during the reaction with the assistance of TBHP and Cu_2O.



Scheme 12. C3−H acylation of quinoxalin-2(1*H*)-ones involving aldehydes as acylating agents.

In 2020, Zhao *et al.* realized a similar coupling reaction of quinoxalin-2(1*H*)-ones with aldehydes by employing Eosin Y as organic photoredox catalyst and hydrogen-atom transfer reagent.[67] Note that the method could be successfully scaled up to 6 mmol scale under batch conditions without affecting the reaction yield.

Decarboxylative acylation of α-oxo-carboxylic acids with quinoxalin-2(1*H*)-ones is another commonly used strategy to access C3-arylated quinoxalin-2(1*H*)-ones. In 2017, Hu and co-workers developed the Ag-catalyzed acylation of quinoxalin-2(1*H*)-ones **1** with α-oxo-carboxylic acids **19** in the presence of stoichiometric $K_2S_2O_8$ as terminal oxidant (Scheme 13, left).[68] Both aryl and alkyl substituted α-oxo-carboxylic acids were used as acylating reagents to introduce into the skeleton of quinoxalin-2(1*H*)-ones. To avoid the use of excess amount of peroxide oxidants, Wei and co-workers found single-state oxygen ($^1O_2$) could oxidize α-oxo-carboxylic acids **19** to provide acyl radical with release of CO_2 under photoreox catalytic conditions (Scheme 13, right side).[69] Under the irradiation of 3 W blue LED, photocatalyst Acridine Red reached its photo-excited state. Then, transfers energy between excited Acridine Red with O_2 afforded singlet oxygen $^1O_2$ and the ground state Acridine Red. The formed $^1O_2$ reacted with α-oxo-carboxylic acids **19** gave the key acyl radical, along with the release of CO_2. Finally, after a general radical addition/oxidative furnished the target acylated products **17**.

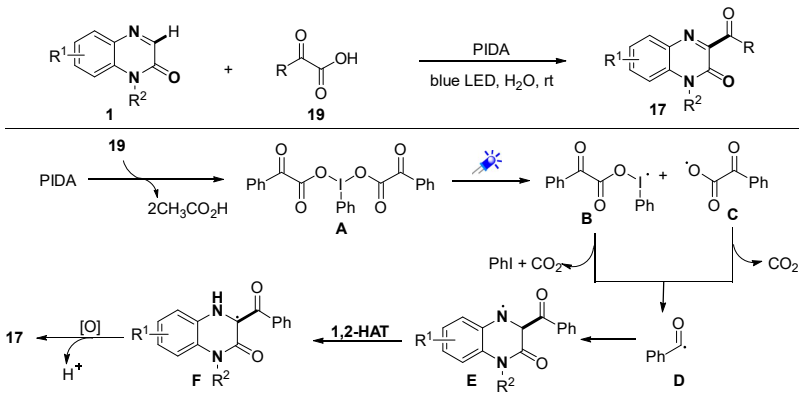


Scheme 13. C3−H acylation of quinoxalin-2(1*H*)-ones involving α-oxo-carboxylic acids as acylating agents.

Very recently, Lee *at al.* developed a visible light promoted decarboxylative coupling of α-oxo-carboxylic acids with quinoxalin-2(1*H*)-ones with $Acr^+MesClO_4^-$ as photoredox catalyst.[70] Condition optimization revealed that the reaction outcomes were based on the reaction atmosphere used. The C3−H acylated quinoxalin-2(1*H*)-ones were obtained in good yields when the reaction was performed in air. In contrast, only the α-hydroxylalkylaed quinoxalin-2(1*H*)-ones were isolated as major products in argon atmosphere.

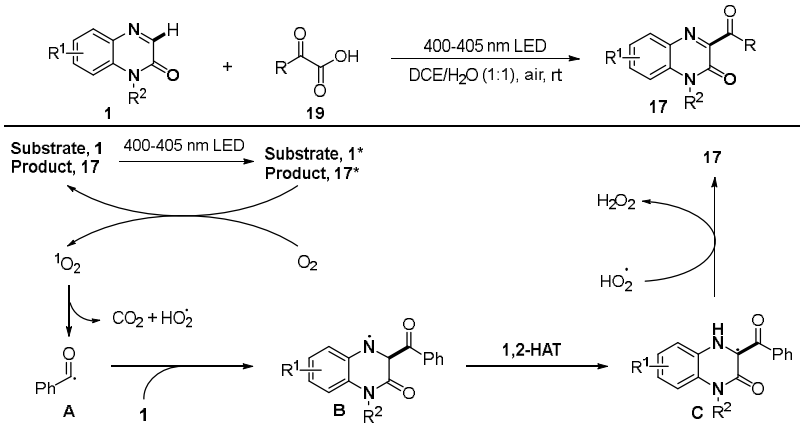
In 2020, our group realized a visible light-promoted decarboxylative acylation of α-oxo-carboxylic acids **19** with quinoxalin-2(1*H*)-ones **1** under photoredox catalyst free conditions (Scheme 14).[71] It was found that the reaction could be directly applied by using water as the green solvent. Quinoxalin-2(1*H*)-ones **1** bearing natural isolates or pharmacology molecule fragments, such as *o*-Vanillin, Vanillin, Piperronylic acid, Vanillylacetone, Ibuprofen and Vitamin E, all reacted well to provide acylated products **17** in good yields. Mechanistically, α-oxo-carboxylic acids **19** first reacted with phenyliodine(III) diacetate (PIDA) to give the ligand exchanged intermediate **A**, which underwent I−O bond homolytic cleavage to afford I-centered radical **B** and O-centered radical **C** under blue light irradiation. The fragmentation of **B** and **C**

provided the required acyl radical species to finish the desired acylation process. In same year, the Zhao group reported a similar work about PIDA-promoted C3−H acylation of quinoxalin-2(1*H*)-ones with high temperature as driving force.[72]



Scheme 14. Visible light-promoted C3−H acylation of quinoxalin-2(1*H*)-ones in water.

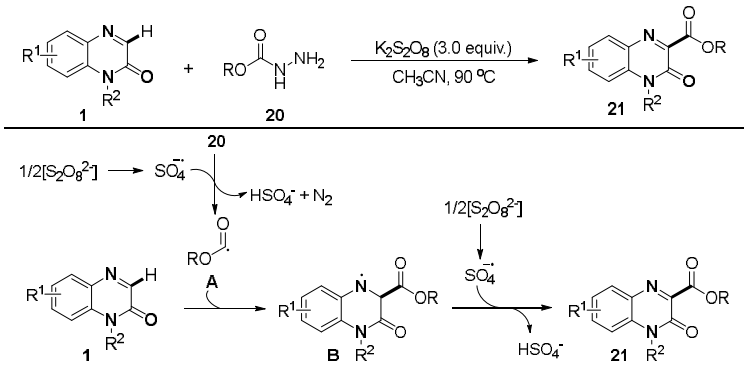
Further investigation by the He group revealed that the above visible light promoted C3−H acylation process could efficiently occurred under metal-, strong oxidant- and external photocatalyst-free conditions (Scheme 15).[73] The reaction took advantage of oxygen as terminal oxidant, ultimately avoiding the generation of waste. Ultraviolet-visible absorption experiment showed that quinoxalin-2(1*H*)-one structure (either starting materials **1** or products **17**) could absorb 400-405 nm light well, which might as photocatalyst to activate the oxygen in air.



Scheme 15. Visible light-promoted C3−H acylation of quinoxalin-2(1*H*)-ones under metal-, strong oxidant- and external photocatalyst-free conditions.

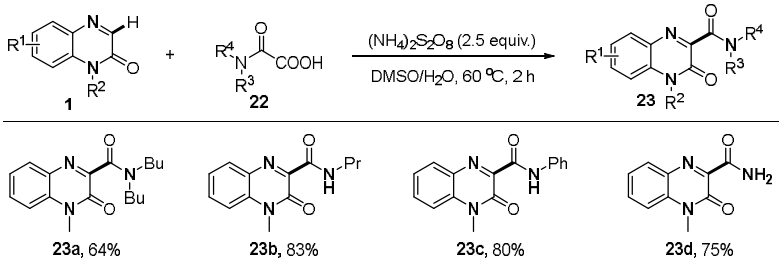
In 2019, the He group reported an alkoxycarbonylation of quinoxalin-2(1*H*)-ones **1** with carbazates **20** as ester sources (Scheme 16).[74] Apart from carbazates **20**, the developed acylation process could also smoothly occur using acyl hydrazines as acylating reagents. Note that, only the decarboxylation alkylation

product was observed when *tert*-butyl derived carbazate was employed in this transformation. As depicted in Scheme 16, hydrogen atom transfer of sulfate radical anion with methyl carbazate provided alkoxycarbonyl radical intermediate **A**, together with HSO_4^- species. Then, quinoxalin-2(1*H*)-ones **1** captured the alkoxycarbonyl radical **A** to give nitrogen-centered radical intermediate **B**. Hydrogen atom transfer of **B** with sulfate radical anion afforded the final C3−H alkoxycarbonylated quinoxalin-2(1*H*)-one **21**.



Scheme 16. Metal-free C3−H alkoxycarbonylation of quinoxalin-2(1*H*)-ones.

Then, a similar strategy was applied to realize the C3−H carbamoylation of quinoxalin-2(1*H*)-ones **1** using oxamic acids **22** as efficient carbamoyl radicals (Scheme 17).[75] Different types of *N*-substituted oxamic acids **22** worked well to give the functionalized products **23** in good yield with the assistance of 2.5 equivalents of $(NH_4)_2S_2O_8$ as oxidant. More significantly, *N*-unsubstituted oxamic acid, such as 2-amino-2-oxoacetic acid, were also suitable carbamoyl radical precursor, and gave product **23d** in 75% yield. At the same time, Ma and co-workers realized a copper-mediated C3−H carbamoylation of quinoxalin-2(1*H*)-ones utilizing hydrazinecarboxamides as carbamoyl radical reagents.[76]



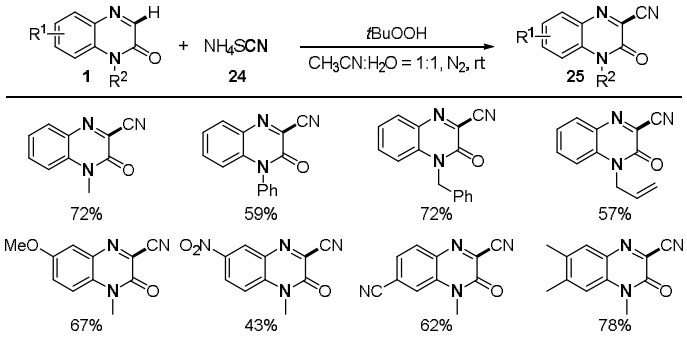
Scheme 17. Metal free C3−H carbamoylation of quinoxalin-2(1*H*)-ones.

2.4. C3−H Cyanation

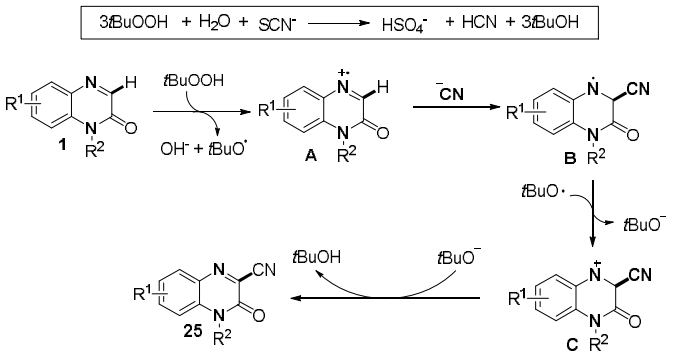
In 2019, Jin and co-workers firstly realized the direct C3−H cyanation of quinoxalin-2(1*H*)-ones **1** *via* ^{t}BuOOH-mediated radical oxidative coupling reaction (Scheme 18).[77] With ammonium thiocyanate **24** as the CN source, a wide range of functional groups, like F, Cl, Br, CF_3, CN, NO_2, alkyl, acyl, ester, benzyl, alkenyl, alkynyl could be well tolerated. Note that the target 3-cyanoquinoxalin-2(1*H*)-one **25** could effectively be transformed into quinoxalinone-3-carboxamides under palladium and lanthanum dual-catalytic system.

A plausible mechanism was proposed in Scheme 19 to explain the formation of

3-cyanoquinoxalin-2(1*H*)-one **25**. Initially, cyanide ion was formed under oxidative reaction conditions from SCN^-. Single electron oxidation of quinoxalin-2(1*H*)-one **1** by ^{t}BuOOH gave nitrogen centered radical cation **A**, which was regioselectively trapped by cyanide ion to give radical intermediate **B**. Oxidation of **B**, followed by deprotonation provided the final product **25**.



Scheme 18. TBHP-mediated direct C3−H cyanation of quinoxalin-2(1*H*)-ones.



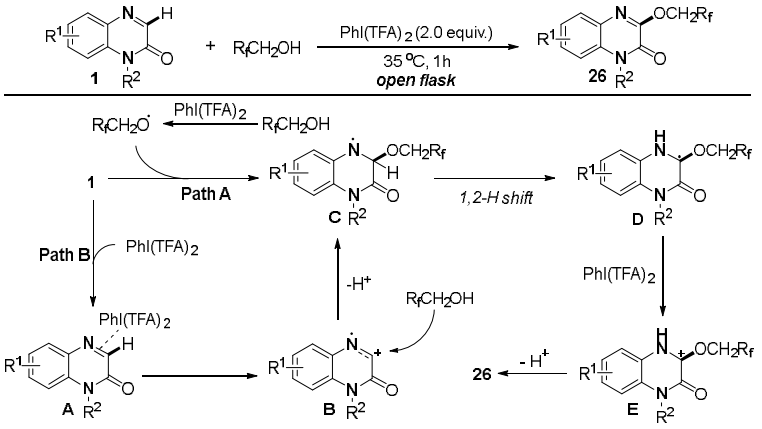
Scheme 19. Plausible reaction mechanism.

2.5. C3–H Alkoxylation and sulfenylation

Fluoroalkoxyl aryl ethers are widely found in many physicochemical, agricultural agents and materials due to their unique biological properties. In 2019, the Zhang group demonstrated an oxidative fluoroalkoxylation of quinoxalin-2(1*H*)-ones **1** with fluoroalkyl alcohols *via* the cross-dehydrogenation coupling (CDC) strategy under transition-metal and solvent-free conditions (Scheme 20).[78,79] The reaction showed quite air stable and could directly proceeded in an open flask. A wide range of *N*-protecting groups including alkyl, ester and allyl groups were compatible in this transformation, affording C3−H fluoroalkoxylated quinoxalin-2(1*H*)-ones **26** in good yields. More significant, a two-step synthesis of histamine-4 receptor antagonist was achieved using the developed method as key step.

According to mechanism investigations, a plausible reaction pathway was proposed in Scheme 20. Firstly, fluoroalkoxyl radical was generated from fluoroalkyl alcohols in the presence of $PhI(TFA)_2$ as oxidant. Then, selective addition of fluoroalkoxyl radical to quinoxalin-2(1*H*)-ones **1** afforded nitrogen centered radical species **C**. An alternative process for the formation of **C** was also possible, which could not be excluded at the current stage. As shown in path B, coordination of quinoxalin-2(1*H*)-one **1** with

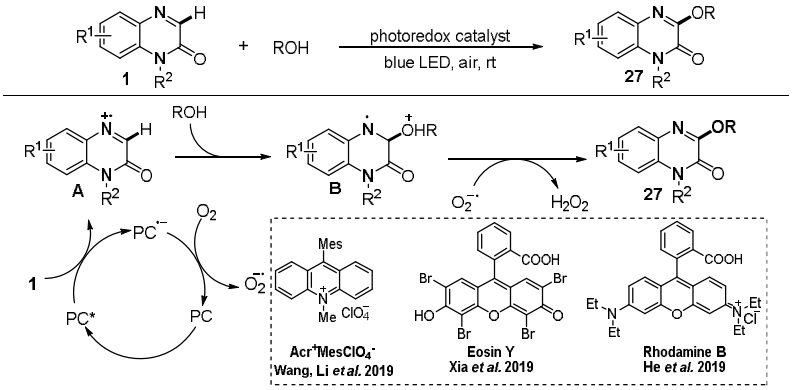
$PhI(TFA)_2$ provided intermediate **A**, which subsequently underwent single electron transfer to give radical cation **B**. Nucleophilic tapping of **B** by fluoroalkyl alcohols delivered the desired intermediate **C**. The final functionalized heterocycle **26** was formed via 1,2-*H* shift/oxidative deprotonation sequence from **C**.



Scheme 20. PIFA-mediated C3–H fluoroalkoxylation of quinoxalin-2(1*H*)-ones.

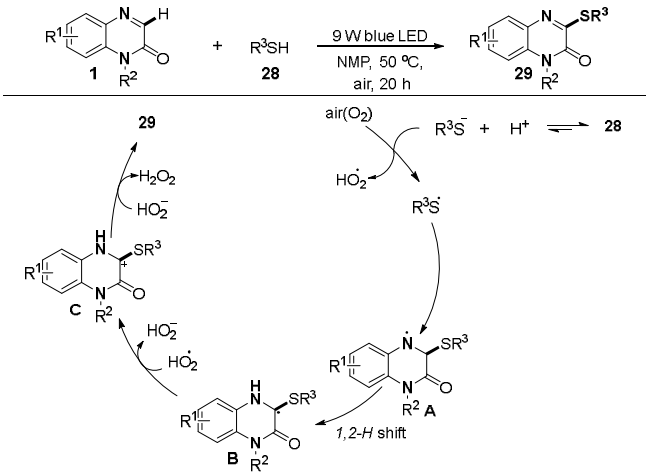
Shortly after this work, with hexafluoroisopropanol as fluoroalkoxyl reagents, Qiang and Huang realized a similar process involving the use of CuBr as catalyst.[80] Interestingly, Shen and co-workers utilized similar strategy accomplished the C3−H d_3-alkoxylation of quinoxalin-2(1*H*)-ones by using deuterated alcohol as alkoxy radical donor.[81]

Visible light-promoted C3−H alkoxylation of quinoxalin-2(1*H*)-ones **1** has also attracted considerable attention (Scheme 21).[82-85] This reaction generally proceeded in air atmosphere with an organic dye as the green photoredox catalyst. It should be pointed out that phenols did not react at the current photo-catalytic reaction conditions. Different with previously reported C3−H alkoxylations with the formation of alkoxyl radicals as the key intermediates, direct nucleophilic addition of alcohols to photo-generated radical cation **A** was proposed to explain the formation of the target heterocycles **27**.



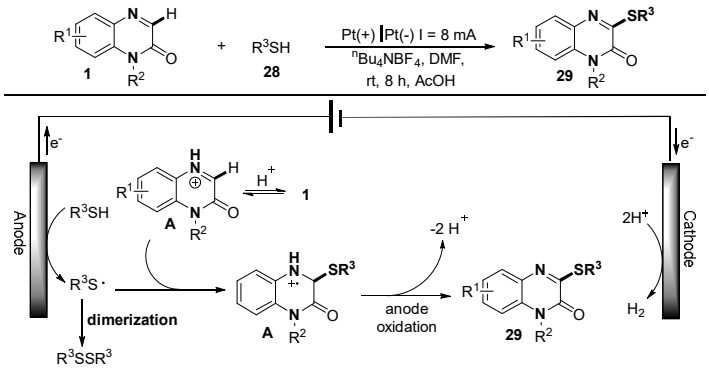
Scheme 21. Visible light-promoted C3−H alkoxylation of quinoxalin-2(1*H*)-ones.

In 2019, Pan and co-workers reported the first example of direct C3−H sulfenylation of quinoxalin-2(1*H*)-ones **1** with thiols **28** under visible light irradiation using O_2 as green oxidant (Scheme 22).[86] Both aromatic and aliphatic thiols worked well. In contrast, only 20% yield of the corresponding C3–H sulfenylation product was obtained when heterocyclic thiol was involved. The successful scale-up reaction and facile synthesis of biologically active 2-(3-(4-chlorothiophenoxy)-2-oxoquinoxalin-1(2*H*)-yl)acetic acid (CTPOQA) further documented the method attractive and valuable. The author proposed that thiols could partially convert to thiol anion, which subsequently oxidized to S-centered radical by oxygen under blue LED irradiation. Then, selective addition of S-centered radical to electron-deficient C=N bond of quinoxalin-2(1*H*)-ones gave N-centered radical **A**. 1,2-H shift of **A** afforded **B**. Oxidative deprotonation of **B** provided the final product **29**.



Scheme 22. Catalyst free, visible light-promoted C3−H sulfenylation of quinoxalin-2(1*H*)-ones.

In 2020, the Li group reported an electrochemical C3−H sulfenylation of quinoxalin-2(1*H*)-ones **1** with thiols **28** (Scheme 23).[87] Importantly, oxidants and catalysts were not required to run the process.



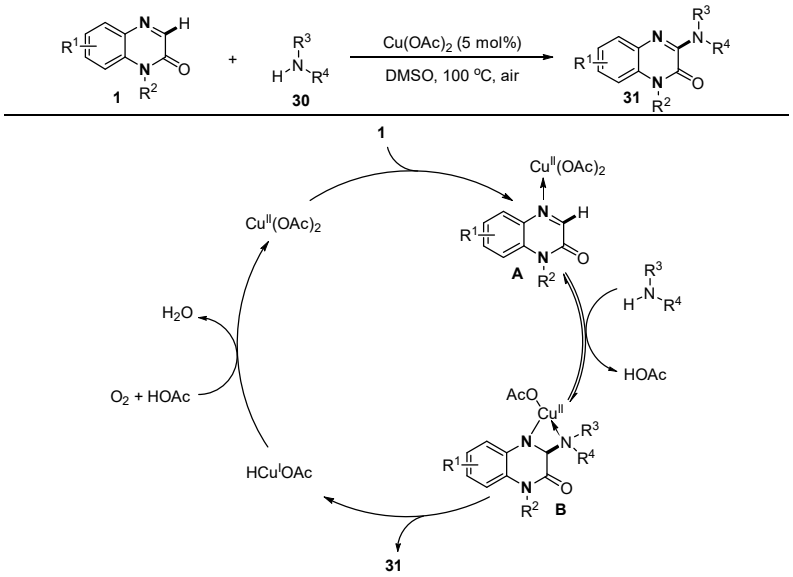
Scheme 23. Electrochemically C3−H sulfenylation of quinoxalin-2(1*H*)-ones

Sulfenyl group derived from various primary, secondary, and tertiary thiols **28** could be easily introduced to C3 position of quinoxalin-2(1*H*)-ones **1** to give the final product **29**. Condition optimization showed that the addition of 2.0 equiv. of CH_3COOH as additive dramatically increased the reaction yield. As revealed in Scheme 23, the acid additive could help the formation of protonated quinoxaline-2(1*H*)-one intermediate **A**, which accelerated the reaction rate of sulfur radical addition step.

2.6. C3−H Amination and amidation

In 2008, the Gulevskaya group demonstrated the first example of C3−H alkylamination of quinoxalin-2(1*H*)-ones **1** with $AgPy_2MnO_4$ (1.2 equiv.) or $KMnO_4$ (2.0 equiv.) as oxidants.[88] Despite the reaction tolerated well with primary and secondary alkyl amines, the general low reaction yields and the need of excessive oxidants limited its further application. To overcome those shortages, many novel and efficient C3−H alkylamination reactions has been developed in the last years.[89-92] For instance, the Cui group disclosed the oxidative amination of quinoxalin-2(1*H*)-ones **1** with aliphatic amines **30** in the presence of catalytic amount of cheap $Cu(OAc)_2$ (5 mol%) as catalyst (Scheme 24).[89] Under the standard conditions, various 3-amino quinoxalin-2(1*H*)-ones **31** could be obtained in good to excellent isolated yields. Interestingly, oxygen was utilized as terminal oxidants which greatly reduced the waste formation.

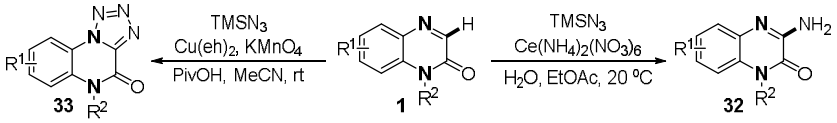
According to the experimental results and literature reports, a possible mechanism was proposed. Initially, coordination of Cu(II) species with imine moiety of quinoxalin-2(1*H*)-one **1** to form the activated intermediate **A**. Then, nucleophilic addition of amine to intermediate **A** afforded intermediate **B** with the release of HOAc. β-Hydrogen elimination of **B** afforded the final 3-amino quinoxalin-2(1*H*)-ones **31** along with the Cu(I) species. Oxidation of Cu(I) with green O_2 as oxidant completed the catalytic cycle.



Scheme 24. Copper-catalyzed C3−H amination of quinoxalin-2(1*H*)-ones.

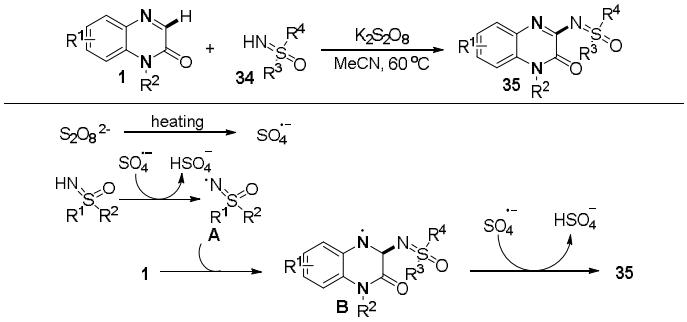
Apart from the above C3−H amination of quinoxalin-2(1*H*)-ones **1** *via* ionic reaction pathway, another commonly method is radical functionalization. Early work developed by Zhang and co-workers showed that $TMSN_3$ could be easily oxidized to N_3 radical under oxidative reaction conditions (Scheme 25).[93,94] It was

found that the oxidant selection had a significant effect on the reaction outcomes. A wide range of 3-aminoquinoxalin-2(1*H*)-one **32** were obtained in the presence of 1.5 equiv. of ceric ammonium nitrate (CAN) as oxidant. By contrast, a formal [3+2]-cycloaddition product, tetrazolo[1,5-*a*]quinoxalin-4(5*H*)-ones **33**, was isolated as major product with copper bis(2-ethylhexanoate) [$Cu(eh)_2$] as catalyst and $KMnO_4$ as oxidant.



Scheme 25. Selective reaction of $TMSN_3$ with quinoxalin-2(1*H*)-ones.

Due to their high chemical stability and biological activities, sulfoximine have been widely used in pharmacophores, agrochemistry and materials science. In 2018, Yotphan and co-workers developed a $K_2S_2O_8$-mediated radical oxidative coupling of quinoxalin-2(1*H*)-ones **1** with NH-sulfoximines **34** (Scheme 26).[95] The reaction showed good substrate scopes with respect to both quinoxalin-2(1*H*)-one **1** and NH-sulfoximine components **34**. A series of 3-sulfoximidoyl quinoxalinones **35** could be obtained in good yields under optimal conditions. Mechanistic investigation revealed that nitrogen-centered radical species **A**, generated from NH-sulfoximine **34** under oxidative reaction condition was indeed formed as the key intermediate. Inspired by this method, oxidative radical coupling of quinoxalin-2(1*H*)-ones with other amide radical precursors, such as amidates,[96,97] acetonitrile[98] and NH-sulfoximines,[99] were sequentially realized.

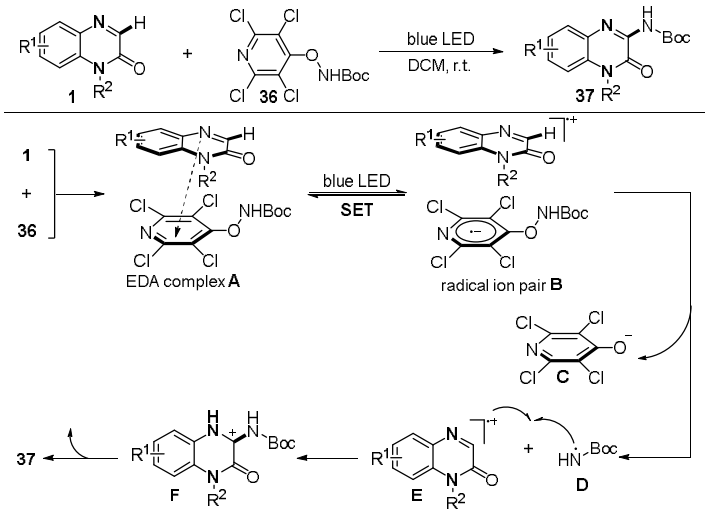


Scheme 26. $K_2S_2O_8$-promoted C3−H amidation of quinoxalin-2(1*H*)-ones with NH-sulfoximines.

Visible light-promoted C3−H amination or amidation of quinoxalin-2(1*H*)-ones generally required the use of photoredox catalysts.[100-102] In a recent contribution, Yang and co-workers developed an electron donor-acceptor complex (EDA) enabled direct C3−H amination of quinoxalin-2(1*H*)-ones **1** under visible light irradiation without the need of any additive or photoredox catalysts. (Scheme 27).[103] The easy-to-prepared *O*-perhalopyridin-4-yl hydroxylamines **36** were utilized as shelf-stable and versatile amidyl-radical precursors. Apart from quinoxalin-2(1*H*)-ones **1**, the method could be further applied to the C−H amination of other important heterocyclic analogues, such as 2*H*-benzo[*b*][1,4]oxazin-2-one and coumarins.

Mechanistically, the two starting materials initially led to the formation of EDA complex **A** which was confirmed by UV-vis absorption and ^{19}F NMR experiment. Under blue LED irradiation, a single electron transfer (SET) process occurred within the EDA complex **A** to give the radical ion pair intermediate **B**.

Fragment of **B** provided radical cation species **E** and amidyl radical **D**, which subsequently underwent radical coupling to deliver **F**. Finally, deprotonation of cation **F** gave the C3−H aminated quinoxalin-2(1*H*)-one **37**.

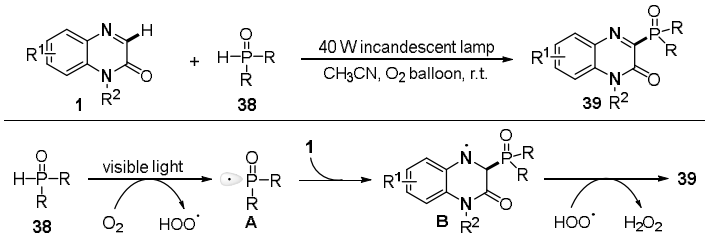


Scheme 27. EDA complex enabled C3−H amination of quinoxalin-2(1*H*)-ones.

2.7. C3−H Phosphonation

The development of facile and efficient methods for the formation of C−P bonds is one of the central tasks in modern organic chemistry due to the wide application of organophosphorus compounds. In general, direct C3−H phosphonation of quinoxalin-2(1*H*)-ones are largely relied on radical strategy. In the reported processes, P-centered radicals could be generated either in the presence of stoichiometric oxidants, such as $K_2S_2O_8$,[104] Selectfluor,[105] or under photoredox catalytic conditions[106] and electrochemically conditions.[107,108]

Very recently, Subbarayappa and co-workers realized a catalyst-free, visible-light induced C3−H phosphonation of quinoxalin-2(1*H*)-ones **1** with phosphonates or phosphine oxides **38** (Scheme 28).[109] Under 40 W incandescent lamp irradiation, a wide range of C3−H phosphonated quinoxalin-2(1*H*)-ones **39** could be obtained in good yields by using aerobic oxygen as green oxidant. Mechanistic studies showed that the reaction was completely shuttled down under inert atmosphere (N_2). No desired product was observed by adding radical scavengers, TEMPO or BHT, which confirmed the radical feature of current reaction.



Scheme 28. Catalyst free, visible light-promoted C3–H phosphonation of quinoxalin-2(1*H*)-ones.

As proposed by authors, phosphonates or phosphine oxides initially transferred to the P-centered radical species **A** under the irradiation of visible light at O_2 atmosphere. Selective radical addition of **A** to quinoxalin-2(1*H*)-one **1** provided nitrogen-centered radical intermediate **B**. Oxidative deprotonation of **B** with the assistance of hydro peroxy radical delivered the C−P bond formation product **39**.

3. Conclusion

In this chapter, we have summarized recent advances in the field of direct C3–H functionalization of quinoxalin-2(1*H*)-ones. A wide range of C3–H functionalization reactions, including C3–H alkylation, arylation, acylation, cyanantion, alkoxylation and sulfenylation, amination and amidation, as well as phosphonation of quinoxalin-2(1*H*)-ones have been described. Recent investigations revealed that the method can be applied not only in facile synthesis of C3–H functionalized quinoxalin-2(1*H*)-one derivatives, but also in the late state modification of biologically important drug candidates and natural isolates. It is clear that development of additional novel direct C3–H functionalization of quinoxalin-2(1*H*)-one reactions will continue. Despite some important progresses have been made in this fast-developing research area, some challenges still remain. Firstly, most of the reported functionalization processes focused on the generation of radicals as key intermediates which always required the use of strong oxidants or photoredox catalyst as radical initiations. Thus, one future goal would be the design oxidants or catalysts free radical functionalization processes, *e.g.* the formation of an EDA complex. On the other hand, continuous investigation less reported C–X, X–Si, C–Se bond formation reactions to further extend the substrates scope would constitute another important direction.

Acknowledgement

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