Recent Advances in Photocatalytic Functionalization of Quinoxalin-2-ones

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Abstract: Visible-light-mediated chemical reactions have become enormously popular within the last ten years. This review covers the recent developments in visible-light photofunctionalization of quinoxalin-2-one derivatives. Reaction types have been categorized depending on the kind of bond formed: C-C, C-O, C-N, C-S, C-P and C-X, with representative examples and discussion on the catalyst used providing insightful mechanistic details. Moreover, their applications to the synthesis of biologically active compounds has also been discussed.

1. Introduction

Nitrogen heterocycles[1] are essential in chemistry and have received the attention of the synthetic community for many decades, because of their wide range of applications in pharmaceutical, medicinal and agrochemical chemistry as well as in material science. In this context, quinoxalin-2(1*H*)-one units have been identified as a privileged class of nitrogen heterocyclic scaffold present in several bioactive natural products and pharmaceutical compounds.[2] In particular, C3-substituted quinoxalin-2(1*H*)-one derivatives represent one of the most important scaffolds, due to the broad range of biological activities that they have shown (Figure 1). For example, Quinohemanine, a natural product isolated from *Streptomyces sp.* CPCC 200497, has shown moderate cytotoxicity against cancer cell line HepG2,[3] Caroverine has shown muscle relaxant activity,[4] and other derivatives have shown different pharmaceutical properties. Several quinoxalin-2-ones have been reported as antitumor agents,[5] antimicrobial compound,[6] angiotensin II receptor antagonist,[7] aldolase reductase inhibitor,[8] cannabinoid CB2 receptor agonist,[9] histamine-4 receptor antagonist,[10] epsteine-Barr virus inhibitor[11] among others.[12] Additionally, 3-arylquinoxalin-2-(1*H*)one derived polymers have been described as semiconductors having applications for material science.[13]

The traditional methods for the synthesis of 3-substituted quinoxalin-2-one derivatives consists in the condensation of 1,2-diaminobenzene derivatives with two-carbon unit donors such as α-keto esters, α-keto acids, α-aldehyde esters or α-aldehyde acids.[14] These common methods suffer several drawbacks such as prefunctionalization and multi-step procedure. Over the past years, substantial efforts have been made for the development of more efficient synthetic methodologies to access 3-substituted-quinoxalin-2-ones. In this context, the direct C-H functionalization[15] at the C3 position of quinoxalin-2(1H)-one derivatives are the most convenient method to increase their structural diversity leading a rapid way to obtain diverse derivatives, highly important for medicinal chemistry. Nevertheless, most of these strategies involve high reaction temperature and the use of an excess of strong oxidants or metal catalysts. With the growing demand for developing green, sustainable and environmentally friendly synthetic methodologies, visible-light photoredox catalysis has been proven to be a versatile and powerful tool for organic synthesis.[16] Visible-light photocatalysis has attracted extensive attention form the synthetic chemists, due to the several advantages such as high efficiency, mild conditions, energy-saving and operation simplicity. In the last years, the reports using visible-light photoredox catalysis regarding the C-H functionalization of quinoxalin-2(1H)-one has grown exponentially, which include alkylation, arylation, acylation, trifluoromethylation, alcoxylation, amidation, phosphorylation among others. Herein, we summarize the different photocatalytic C-H functionalization of quinoxalin-2-ones classifying these reactions on the nature of the bonds formed.

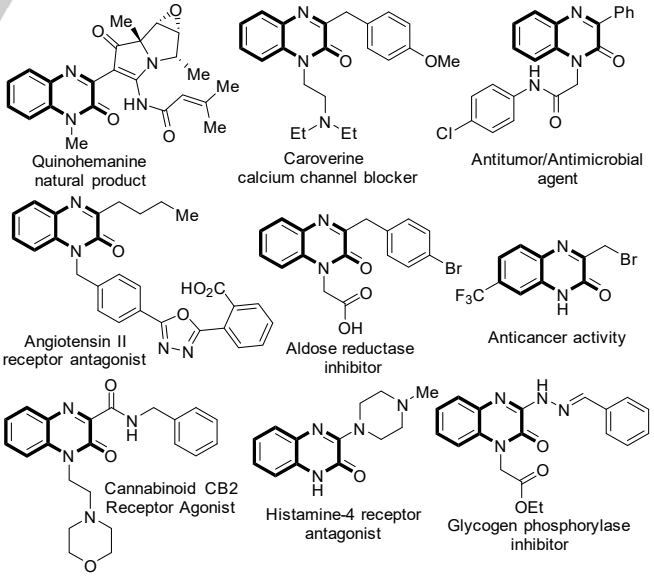
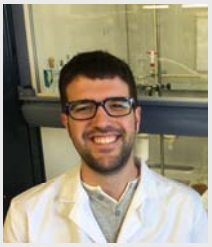


Figure 1. Representative biologically active 3-substituted quinoxalin-2(1H)-one derivatives.

Jaume Rostoll-Berenguer graduated in chemistry (2017) and received his Master's degree in Organic Chemistry (2018), both from the University of València. Since 2018, he is developing his PhD studies focused on the functionalization of amines using visible-light photocatalysis in the same University under the supervision of Dr. Carlos Vila and Prof. Dr. José Ramón Pedro.



Gonzalo Blay received his degree in chemistry (1987) and his Ph.D. (1992) from the University of València. He has been a Marie Curie postdoctoral fellow at the Agricultural University of Wageningen, The Netherlands, with Professor A. de Groot (1993–94) and visiting researcher at Aarhus University, Denmark, with Professor K. A. Jørgensen (2005). In 1996, he became Associate Professor at the Department of Organic Chemistry of the University of Valencia and was appointed Full Professor in 2012. His research interest includes organic synthesis and the development of catalytic methodologies, in particular asymmetric catalysis.

José R. Pedro graduated in chemistry from the University of València in 1974. He obtained his Ph.D. from the same university in 1977, and in the same year he became Assistant Professor, starting his independent research on natural product synthesis. In 1985, he was promoted to Associate Professor, and in 1998 to Full Professor in Organic Chemistry at Valencia University. His current research interests are in the field of asymmetric catalysis. He is the Director of the Research Group on asymmetric catalysis with metal complexes and organocatalysts at the University of València (AsymCat, GIUV13).

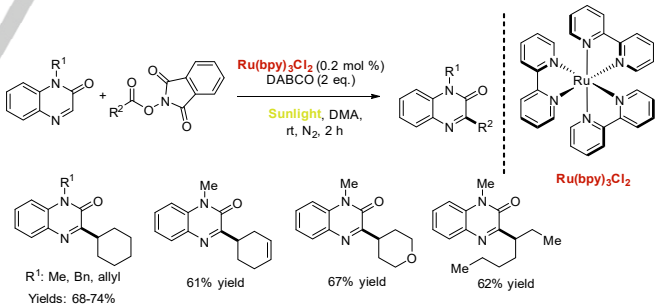
Carlos Vila received his degree in chemistry (2005) and his Ph.D. (2010) from the University of València. In 2010, he joined the group of Prof. Rueping at RWTH Aachen University, Germany, for two years as a postdoctoral researcher where he focused on photoredox catalysis. In 2012, he commenced a two-year postdoctoral stay with Prof. Feringa at Groningen University as a Marie Curie Fellow, working on cross-coupling reactions with organolithium reagents and asymmetric catalysis. In 2018, he was appointed as a 'Ramón y Cajal' researcher at the Organic Chemistry Department, Valencia University. His current research interests are asymmetric catalysis and photocatalysis.

2. C-C bond formation

The development of methodologies to achieve the formation of C-C bonds plays a central role in synthetic organic chemistry.[17] In this challenging task, photoredox catalysis represents a unique drawer in the synthetic chemist toolbox, as can be proved with the numerous procedures reported to form C-C bonds driven by visible-light in the last years. Specially, the formation of C-C bonds in quinoxalin-2-ones using photoredox catalysis has become an important research niche in the functionalization of this kind of nitrogen heterocycle, and numerous methodologies for the alkylation, fluoroalkylation, arylation and acylation have been reported recently.

2.1. Alkylation reactions

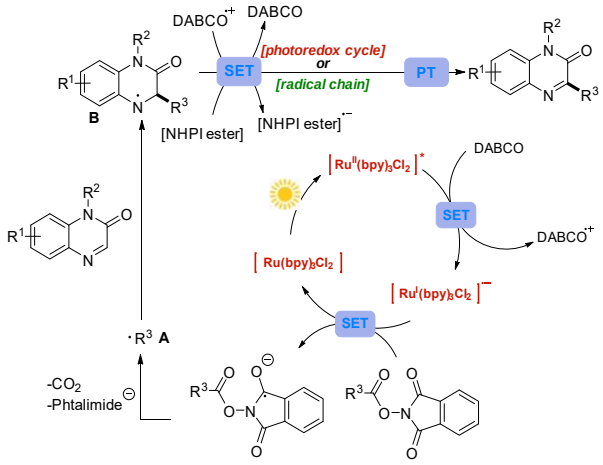
Focusing on the alkylation reaction, several strategies have been developed in order to generate carbon-centered radicals that could react with the electron-poor C=N double bond of quinoxalin-2-ones. One possibility is the utilization of the so-called redox active esters: an ester moiety containing the desired alkyl group and a platform capable of suffering Single Electron Transfer (SET) processes.[18] This strategy was employed by three independent research teams in the late 2019. First, the research group of Dong and Zhou designed a *N*-hydroxyphthalimide (NHPI) ester as the synthetic equivalent of an aliphatic *C*-centered radical.[19] Indeed, using these carboxylic acid derivatives in combination with $Ru(bpy)_3Cl_2$[20] and DABCO under sun-light, they could obtain a small collection of C-3 alkylated quinoxalin-2-ones among other related heterocycles such as coumarins, quinolones and chromenones (Scheme 1). The corresponding quinoxalin-2-ones bearing alkyl and cycloalkyl residues were obtained in moderate yields (61-74%). Additionally, they performed a 13 mmol-scale reaction generating the NHPI ester previously to the photochemical transformation in a *one-pot* procedure.



Scheme 1. C-3 alkylation of quinoxalin-2-ones using NHPI esters under photoredox conditions (Dong and Zhou, 2019).

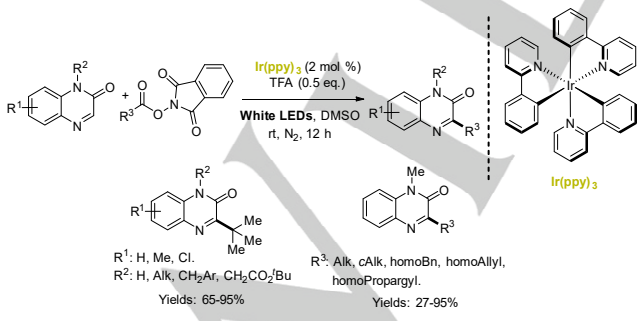
Dong *et al.* determined that a radical chain mechanism may operate along with a photoredox process, given that a value of quantum yield of 2.06 is quite low to consider a unique chain reaction mechanism.[21] Based in these considerations, they proposed a catalytic cycle in which the excited Ru(II) photocatalyst is reductively quenched by DABCO to Ru(I). After that, taking advantage of the reductant character of Ru(I), an electron transfer from this species to the NHPI ester occurs generating a radical anion, which collapses losing CO_2 and the phthalimide moiety to finally generate the *C*-centered radical **A**.

This radical can be added to the quinoxalin-2-one C=N double bond, an event that generates a *N*-centered radical (**B**). According to the researchers, after this initiation step, a chain reaction mechanism may operate at this point if this *N*-centered radical is single-electron oxidized by another molecule of NHPI ester, also providing more alkyl radical that could propagate the radical chain. Instead, the *N*-centered radical can also be oxidized by DABCO$^+$, completing the photoredox catalytic cycle (Scheme 2).



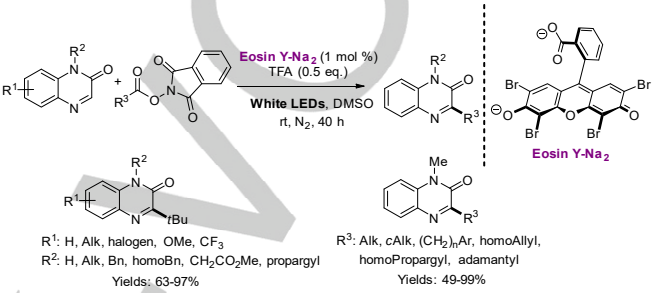
Scheme 2. Mechanism for the C-3 alkylation of quinoxalin-2-ones under photoredox/radical chain conditions.

Shortly after, the group of Wanmei Li reported a similar methodology also based in NHPI esters as *C*-centered radicals equivalents.[22] In this report, *fac*-Ir(ppy)$_3$[23] was the photocatalyst used in combination with 0.5 equivalents of TFA and DMSO as solvent. With these reaction conditions, they could report a broad family of differently substituted *C*-3-alkylated quinoxalin-2-ones (39 examples) with a great assortment of NHPI esters derivatives (Scheme 3). This catalytic system tolerates efficiently the presence of many substituents at the amidic nitrogen and is also capable of promoting the generation of several *C*-centered radicals from NHPI esters, although it failed with adamantyl and diphenylmethane-derived ones.



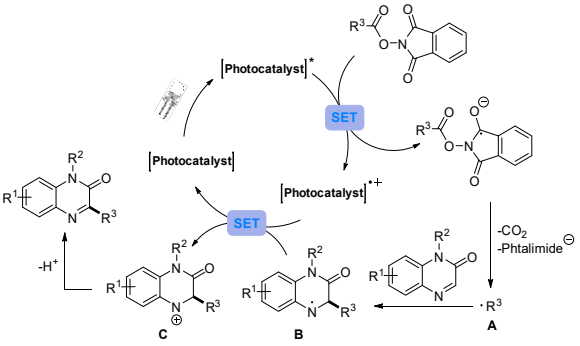
Scheme 3. Direct C-3 alkylation of quinoxalin-2-ones with NHPI esters under photoredox conditions (Li, 2019).

Finally, the team of Jin[24] reported the same abovementioned transformation but using an organophotocatalyst, the Eosin Y,[25] instead of the Ru or Ir metal complexes. From the point of view of sustainable and green chemistry, the use of organic molecules as photocatalyst is highly desirable, in order to avoid metal traces in the reaction products. This organophotocatalyst-based protocol, which also employs TFA as an additive, allowed the researchers to obtain a battery of thirty alkylquinoxalin-2-ones (Scheme 4). This methodology efficiently tolerates the substitution at both amidic group and aromatic ring and was also competent in the generation of a miscellany of challenging alkyl radicals from NHPI esters, including the adamantyl-derived one. The authors also applied their optimal reaction conditions to conduct a 10 mmol-scale batch reaction, obtaining the desired product in 87% yield, and prepared a precursor of an aldolase reductase inhibitor.[8]



Scheme 4. Eosin Y-Na$_2$-catalyzed alkylation of quinoxalin-2-ones with NHPI esters (Jin, 2019).

According to the two last proposed mechanisms, the excited state of the photocatalyst is deactivated through an oxidative quenching with the NHPI ester which, after decarboxylation and loss of the phthalimide moiety, generates the *C*-centered aliphatic radical **A**. This carbon radical is nucleophilic enough to react with the quinoxalin-2-one generating a *N*-centered radical **B**, that undergoes a Single Electron Transfer with the oxidized form of the photocatalyst. This last event induces the formation of the cation **C**, which after deprotonation expels the desired compound (Scheme 5). To fully confirm this mechanistic hypothesis, a study comparing the quenching ability of quinoxalin-2-one and the NHPI esters should have been done, because of a reductive photoredox cycle can also be operative under the reaction conditions.



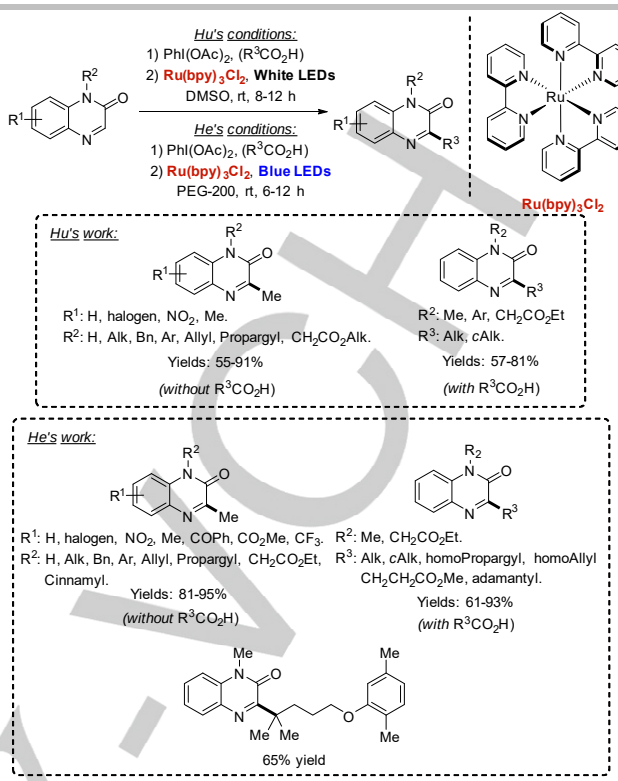
Scheme 5. Mechanistic proposal for the direct C-3 alkylation of quinoxalin-2-ones with NHPI esters under photoredox catalysis.

Reading the last three reviewed examples, one can realize how the growth in quinoxalin-2-one-functionalization has become. In less than four months, the same transformation was

independently reported by three research groups. This situation led us to compare the three catalytic protocols in terms of efficiency, scope, sustainability and more. Although the chemical reaction is the same, the way to conduct it is quite different, mainly regarding the photocatalyst used. In the two first examples, a metal-based ruthenium or iridium photocatalyst was employed. This kind of catalysts have proven their ability to promote a huge amount of chemical transformations using visible-light with high efficiency, even at low catalytic loadings. However, the chemical community must move ahead towards the development of methodologies which avoids the use of heavy and precious metals, such as Ru or Ir. This succession of these three methodologies constitutes a perfect example towards this abovementioned progression: the same transformation that can be performed using Ru or Ir, is also possible using Eosin Y-Na_2. With respect to the scope, in the two last reports a large number of alkylated quinoxalin-2-ones were obtained (27 and 30 examples respectively) compared with the first one, in which only six examples of functionalized quinoxalin-2-ones were described among other heterocycles.

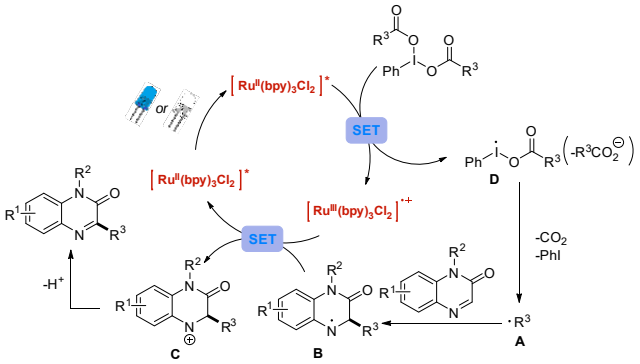
Another decarboxylative strategy to generate *C*-centered radicals under visible-light photoredox conditions has been used to access in mild conditions to C-3-alkylquinoxalin-2-ones, according to the procedures reported independently by Hu and He. They reported almost identical methodologies to generate carbon radicals from phenyliodide(III) dicarboxylates,[26] and their application to the alkylation of quinoxalin-2-ones.

Using this strategy, the Hu's laboratory could obtain a set of differently substituted C-3-alkylated quinoxalin-2-ones.[27] Their method efficiently tolerates the presence of various substituents at the amidic nitrogen and at the aromatic ring, when using phenyliodide(III) diacetate (PIDA) as the methyl radical precursor. By reacting PIDA with different carboxylic acids, they could access to several phenyliodide(III) dicarboxylates, which generated their respective *C*-centered radicals (Scheme 6). Then, these researchers applied their catalytic system to synthetize an Angiotensin II receptor antagonist precursor,[7] and they also scaled up the method to gram-scale. Meanwhile, the team of He[28] was also capable of making a collection of alkylated quinoxalin-2-ones with similar performance, including the synthesis of a precursor of a c-met kinase inhibitor[29] and the application of their protocol to several gram-scale batch reactions using either Blue LEDs or sunlight (Scheme 6). In both reports, the reaction conditions tolerate a wide range of substituted quinoxalin-2-ones bearing both electron-donating and electron-withdrawing groups, as well as a wide range of primary, secondary and tertiary carboxylic acids.



Scheme 6. Alkylation of quinoxalin-2-ones using phenyliodide(II) dicarboxylates (Hu and He, 2019).

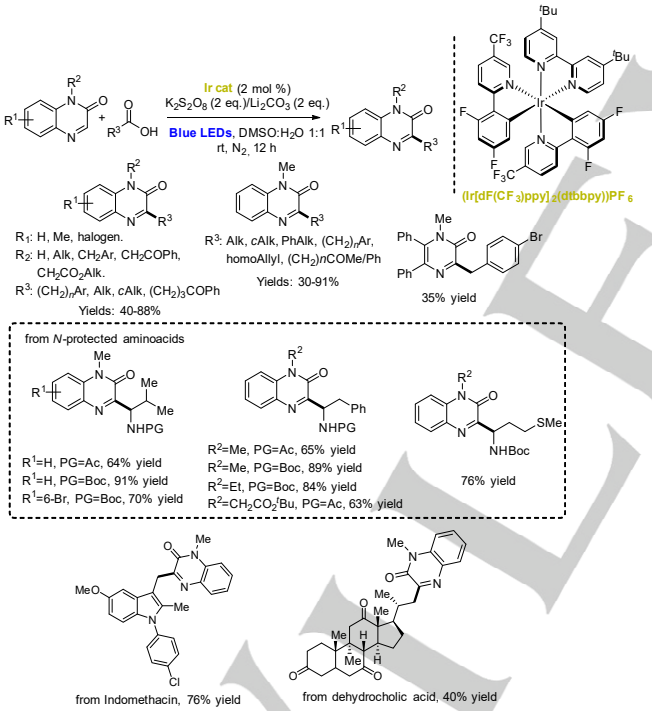
Both research groups, after doing the typical control experiments as well as some cyclic voltammetry and fluorescence emission quenching experiments, proposed a mechanism to rationalize the observed transformation. First, PIDA or other acid-derived I(III) species are one-electron reduced by the excited Ru(II). This Single Electron Transfer process results in the loss of a carboxylate anion along with the generation of the *I*-centered radical **D**, which delivers the corresponding *C*-centered radical **A** as well as phenyl iodide and CO_2. As usual, this radical can be added to the C=N double bond of the quinoxalin-2-one, a process in which the typical *N*-centered radical **B** is formed. After being oxidized by the formerly generated Ru(III), the cation **C** can be deprotonated to finally generate the corresponding C-3-alkylated quinoxalin-2-one (Scheme 7).



Scheme 7. Mechanistic hypothesis for the C-3 alkylation of quinoxalin-2-ones using phenyl iodide(III) dicarboxylates.

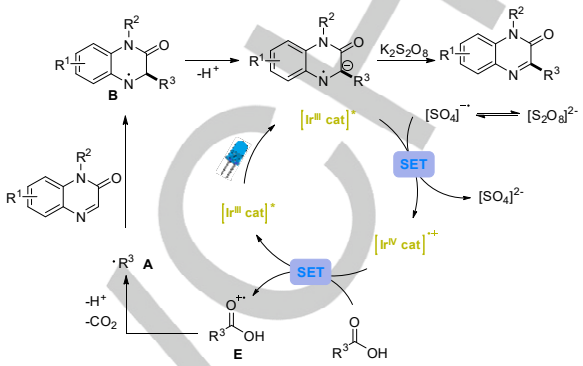
It is curious that, to the best of our knowledge, an organophotoredox catalyst-based methodology have not been described yet. As can be checked from the optimization process done by Yulai Hu, a very promising result (78%) was obtained when Eosin Y was employed as photocatalyst. This could be the starting point towards a more sustainable and cheap methodology taking advantage of these readily available *C*-centered radical precursors.

In the way to simpler alkyl equivalents, a very recent report by Qin and Li shows how carboxylic acids can be used (after decarboxylation) as useful alkyl equivalents to functionalize quinoxalin-2-ones.[30] Compared with previously reviewed methodologies, these researchers employ non-prefunctionalized aliphatic carboxylic acids in combination with $(Ir[dF(CF_3)ppy]_2(dtbbpy))PF_6$ as photoredox catalyst, $K_2S_2O_8$ as stoichiometric oxidant and lithium carbonate as base to access a collection of thirty six C-3-alkylated quinoxalin-2-ones in moderate to good yields. The scope regarding to the *C*-radical species include primary, secondary and tertiary carboxylic acids. Interestingly, this methodology is competent when *N*-protected natural amino acids were employed, as well as with the drug indomethacin and dehydrocholic acid for late-stage functionalization (Scheme 8). Moreover, they could prepare an aldolase reductase inhibitor[8] in 55% overall yield after 3 steps.



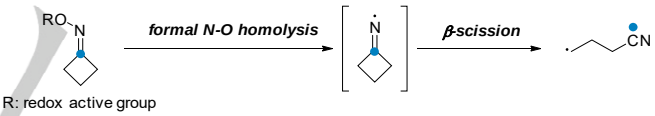
Scheme 8. C-3 Alkylation of quinoxalin-2-ones with carboxylic acids (Li, 2020).

After conducting some control experiments, these researchers proposed a mechanism explaining the pathway of this transformation. In solution, the peroxo bridge in persulfate anions can homolytically be cleaved generating sulfate radical anions,[31] that can engage a SET with the excited state form of the Ir(III) photocatalyst, releasing sulfate anion and Ir(IV). The resulting Ir(IV) is oxidant enough to promote a SET with the carboxylic acid to produce a carboxyl radical **E**, which can lose a proton and decarboxylate to finally generate the *C*-centered radical **A**. As always, this carbon radical **A** can react with C=N quinoxalin-2-one double bond and, after deprotonation of the created *N*-centered radical **B**, the desired product is obtained upon aromatization by potassium persulfate (Scheme 9).



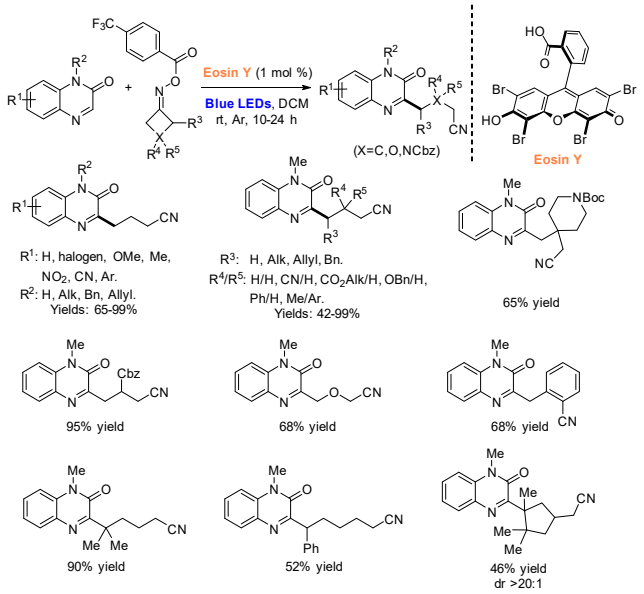
Scheme 9. Proposed mechanism for the direct C-3 alkylation of quinoxalin-2-ones with carboxylic acids.

Although the decarboxylation of NHPI or other esters constitutes an elegant strategy to obtain *C*-centered radicals in mild reaction conditions, there are other sophisticated ways to generate these odd-electron species using photocatalysis. A very surprising and outstanding route to carbon radicals is the use of cyclobutanone oxime esters.[32] These particular cyclobutanone derivatives can suffer a β-scission when the corresponding iminyl radical is generated to obtain γ-cyanoalkyl radicals (Scheme 10).



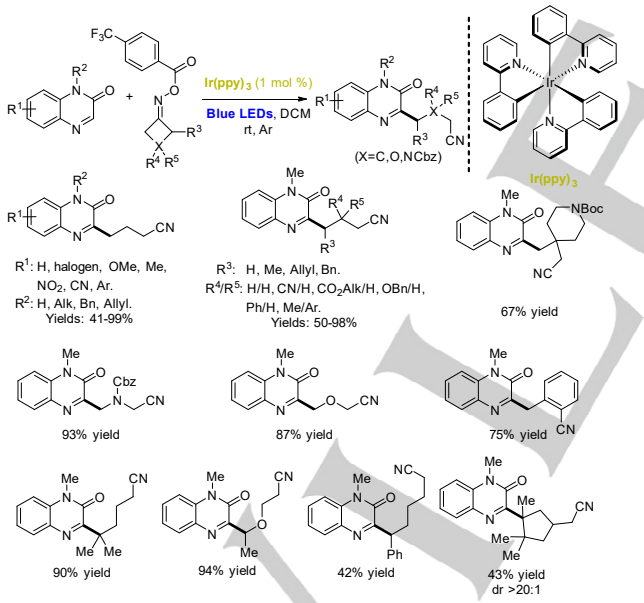
Scheme 10. Generation of γ-cyanoalkyl radicals via β-scission of iminyl cyclobutanone radicals.

As in other alkylation strategies, this mild access to γ-cyanoalkyl radicals has been exploited by several research groups on route to C-3 γ-cyanoalkylated quinoxalin-2-ones, proving once again the interest of the synthetic community towards the functionalization of this aromatic nitrogen heterocycle. Li *et al.*, in 2019, were the pioneers in using photoredox catalysis to generate these radicals to form new C-C bonds in quinoxalin-2-ones.[33] These researchers established that cyclobutanone *O*-*p*-trifluoromethylbenzoyl oxime esters can act as a competent γ-cyanoalkyl radical precursors, along with Eosin Y as photocatalyst under the irradiation of Blue LEDs. Using these conditions, the team of Li was capable of accessing to a set of thirty-three differently substituted γ-cyanoalkylated-quinoxalin-2-ones, with a broad scope of substituted quinoxalin-2-ones as well as other *O*-*p*-trifluoromethylbenzoyl oxime esters with great performance (Scheme 11). They demonstrated the versatility of the γ-cyanoalkylated-quinoxalin-2-ones prepared, by the transformation of the cyano group in a protected amine, in a primary amide, in an ethyl ester and a carboxylic acid, with good yields.



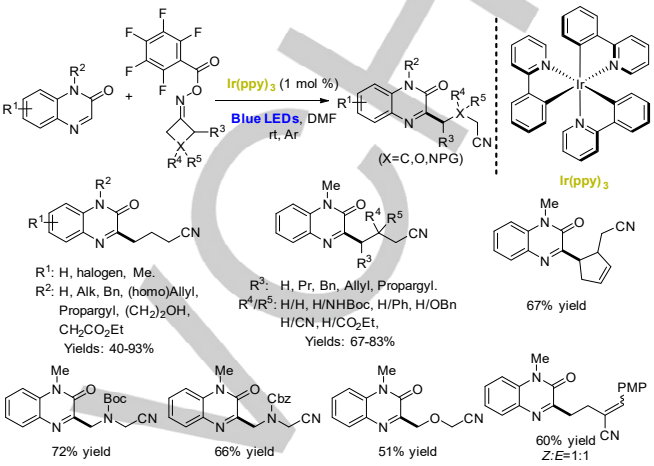
Scheme 11. γ-Cyanoalkylation of quinoxalin-2-ones using Eosin Y (Li, 2019).

Simultaneously,[34] the same laboratory reported an identical protocol to generate these γ-cyanoalkyl radicals but using *fac*-Ir(ppy)$_3$ instead of Eosin Y. Using this metal-based photocatalyst they could generate the same products, as they previously did with Eosin Y (Scheme 12).



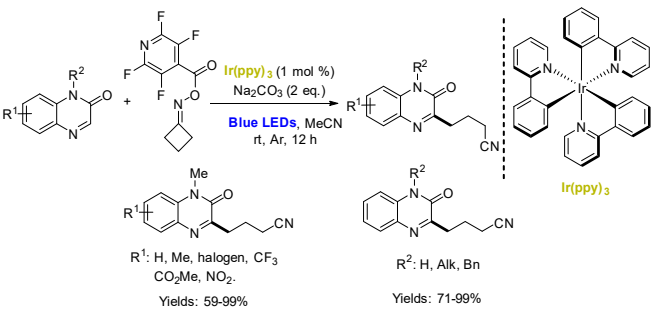
Scheme 12. γ-Cyanoalkylation of quinoxalin-2-ones using Ir(ppy)3 (Li, 2019).

Shortly after, Xu and collaborators performed the same transformation but using a perfluorobenzoyl cyclobutanone oxime as iminyl radical precursor.[35] Using this different redox active group, they could not obtain suitable results with Acridinium Dye-1 as organophotocatalyst, so they were forced to switch to *fac*-Ir(ppy)$_3$ in combination with Blue LEDs and DMF as solvent. With these optimal conditions in hand, a large family of γ-cyanoalkylated quinoxalin-2-ones (29 examples) using sophisticated cyclobutanone oximes was reported (Scheme 13). Morevover, the authors extend their methodology for the functionalization of C2-O-substituted quinoxalines with good results (66-72% yields).



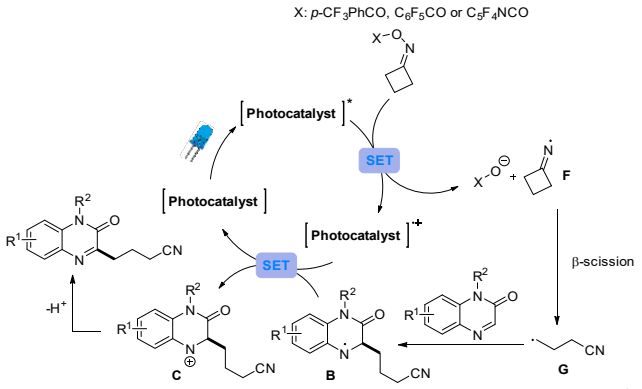
Scheme 13. γ-Alkylation of quinoxalin-2-ones using visible light photoredox catalysis (Xu, 2019).

To conclude the reports on photoredox-triggered cyanopropylation of quinoxalin-2-ones using redox-active cyclobutanone oxime esters, at early 2020, Yang's research team reported a synthetic protocol.[36] In the abovementioned work, a set of γ-cyanopropylated quinoxalin-2-ones were synthetized using a perfluoropyridin-based redox active cyclobutanone oxime. Although they only described sixteen quinoxalin-2-one-derived examples (Scheme 14), they conducted a lot of experiences in order to gain insight in the reaction mechanism, as well as a comparison of the generation of the desired radical under thermal reaction conditions. This last study, along with the reaction using other radical acceptors, will not be further mentioned because it is out of the scope of this review. These researchers confirmed by means of fluorescence quenching experiments that the excited state of *fac*-Ir(ppy)$_3$ can be deactivated by the redox-active oxime. Additionally, they conducted cyclic voltammetry experiments to support their mechanistic hypothesis.



Scheme 14. γ-Cyanopropylation of quinoxalin-2-ones using perfluoropyridin-derived oxime ester (Yang, 2019).

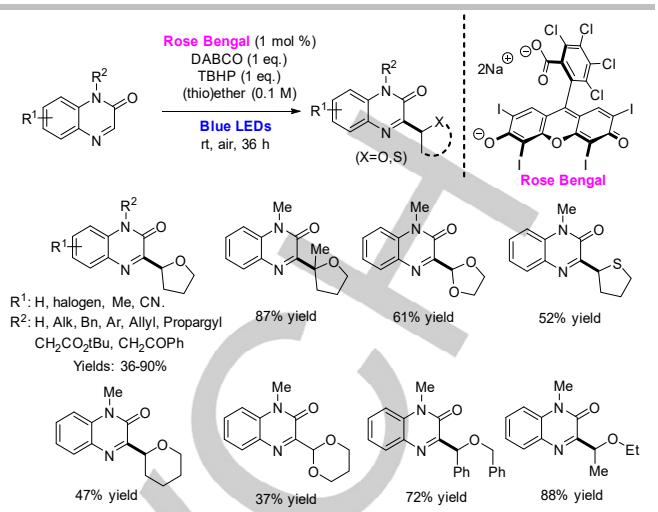
Due to the similarity of the last four reports on C-C bond forming methodologies using cyclobutanone oxime redox-active esters, a unified mechanism can be proposed. According to the control experiments performed by these research groups, as well as to further mechanistic insights, the *N-O* bond of the corresponding cyclobutanone oxime ester can be cleaved by the excited state of the photocatalyst through a SET, in which the iminyl radical **F** and the carboxylate anion are formed. Then, the radical **F** undergoes a β-scission to generate a γ-cyanopropyl radical (**G**), which can react with the electrophilic quinoxalin-2-one C=N double bond. The resulting *N*-centered radical **B** is one-electron oxidized via a SET from the oxidized form of the photocatalyst and, after deprotonation, the desired product is finally obtained (Scheme 15).



Scheme 15. Mechanistic proposal for the γ-cyanopropylation of quinoxalin-2-ones under photoredox catalysis.

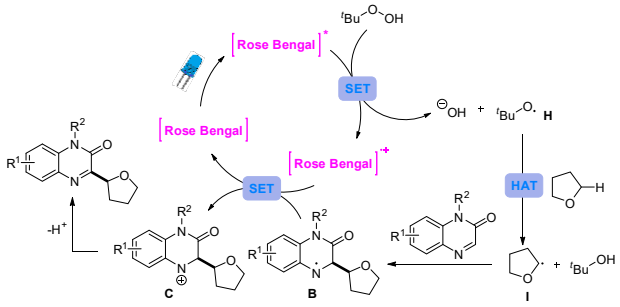
Overseeing these reports about the use of this kind of cyclobutanone oxime derivatives as synthetic equivalents of γ-cyanopropyl radicals, one can notice, again, the intense research around the photoredox-enabled alkylation of quinoxalin-2-ones. In just six months, four similar methodologies were reported and, surprisingly, the first one in the chronological line was the most sustainable, because of the use of Eosin Y as photoredox catalyst, avoiding the use of expensive and toxic metals complexes. Regarding the scope of the reaction, the two Xin Li's works showed a broad scope, particularly in the design and use of complex redox-active oximes, while the labour of Yang[36] and collaborators goes deeper into the mechanistic aspects of this transformation.

The easiest way to generate simple alkyl radicals would be by C-H activation of a hydrocarbon. In this sense, two research groups found that simple ethers could act as these *C*-centered radical equivalents due to the presence of the oxygen, that acts as electron-donating group in the stabilization of radicals. In mid-2018, the research group of Wei exploited this possibility conducting the C-C bond forming reaction between quinoxalin-2-ones and simple ethers.[37] After an exhaustive optimization process, they established that Rose Bengal,[38] in combination with *tert*-butyl hydroperoxide (TBHP) as oxidant and DABCO, under the irradiation of Blue LEDs can promote the generation of *C*-centered radicals at alpha position of the ethers, that can be engaged in an alkylation reaction with quinoxalin-2-ones. This protocol led the authors to obtain a collection of twenty-seven *C*-3-alkylated quinoxalin-2-ones with several ethers, as well as tetrahydrothiophene (Scheme 16).



Scheme 16. C-3-Alkylation of quinoxalin-2-ones with simple ethers via photoredox catalysis (Wei, 2018).

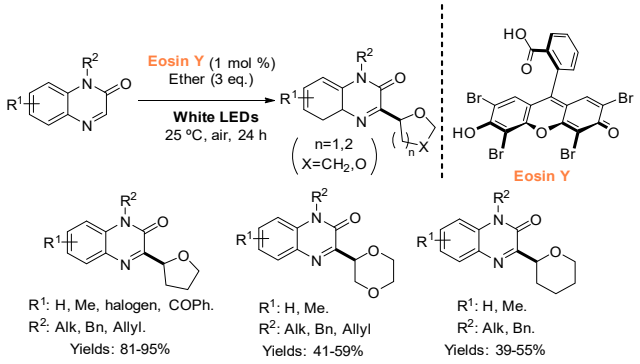
These researchers confirmed the generation of the *C*-centered radical trapping it with TEMPO and further detection by LC/MS. They also performed an irradiation on/off experience proving this way the absence of a radical chain mechanism. On the base of these experiments, a mechanism by which the reaction should proceed was given. Upon the excitation of Rose Bengal by the Blue LEDs, a reductive O-O bond cleavage of TBHP to generate the *tert*-butyloxy radical **H** occurs via a SET from the excited dye. Subsequently, the *O*-centered radical **H** is capable to abstract a hydrogen from tetrahydrofuran (or other ether) via a HAT to generate the *C*-centered radical **I.** This radical **I** is a good nucleophile due to the neighbour oxygen atom, and therefore, can be added to the electrophilic C=N double bond of que quinoxalin-2-one generating the corresponding *N*-centered radical **B.** Radical **B** can undergo a SET with the oxidized form of Rose Bengal to, after the loss of a proton, releases the final product and regenerate the photocatalyst (Scheme 17).



Scheme 17. Mechanistic proposal for the direct C-3 oxyalkylation of quinoxalin-2-ones using ethers.

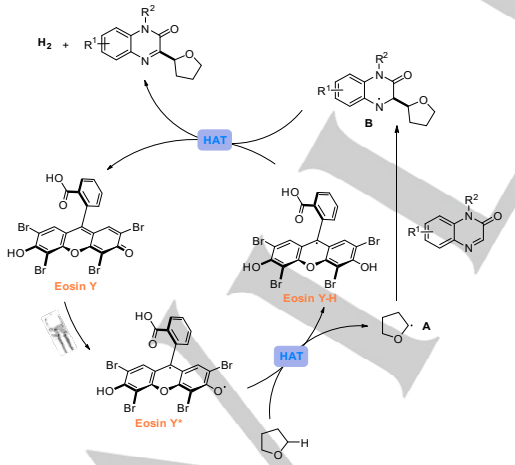
Few months later, in early 2019, the laboratory of Suryavanshi reported the same abovementioned transformation but using a more practical experimental setup.[39] Although they also selected a similar organophotoredox catalyst, they were able to develop a methodology in which the need of a base is avoided, and in which the stoichiometric oxidant is the oxygen from air. From the point

of view of sustainable and green chemistry, the use of oxygen as oxidant is an advantage. After conducting an optimization process, these researchers determined that the Eosin Y, under the irradiation of White LEDs, was the best photocatalyst to carry out the reaction. Using these optimal conditions, the authors could generate a family of seventeen examples of C-3-oxyalkylated quinoxalin-2-ones with cyclic ethers (Scheme 18).



Scheme 18. C-3 oxyalkylation of quinoxalin-2-ones with cyclic ethers using photoredox catalysis (Suryavanshi, 2019).

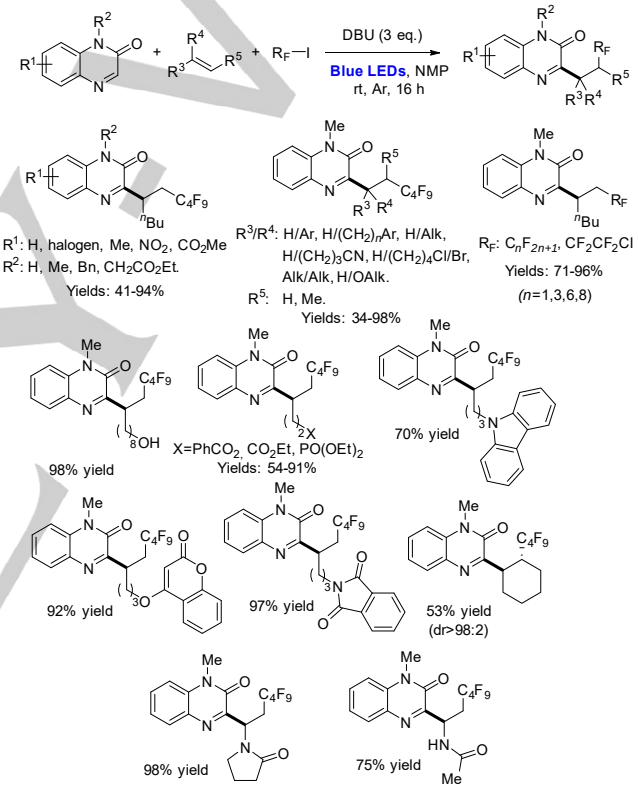
Then, the authors postulated a simple mechanism, in which the role of oxygen is not explained in the process towards the final product. Because of this, we have incorporated it tentatively. In this mechanistic hypothesis, the excited state of Eosin Y might act as a direct HAT catalyst capable of abstracting a hydrogen from THF (or other ether).[40] The resulting *C*-centered radical **A** can react with the electrophilic C=N double bond of quinoxalin-2-one to generate the usual *N*-centered radical **B**, which can suffer HAT with Eosin Y-H leading to the desired C-3-oxyalkylated quinoxalin-2-one along with hydrogen gas. (Scheme 19).



Scheme 19. Mechanistic proposal for the Eosin Y-mediated oxyalkylation of quinoxalin-2-ones.

These last two examples represent the best way to conduct the C-3 alkylation of quinoxalin-2-ones in terms of practicability and sustainability, because they can access *C*-centered radicals directly, without the need of previously-synthetized redox-active molecules such as NHPI esters or cyclobutanone oxime esters. However, that seems possible only with substrates bearing strong electron-donating groups such as ethers derivatives.

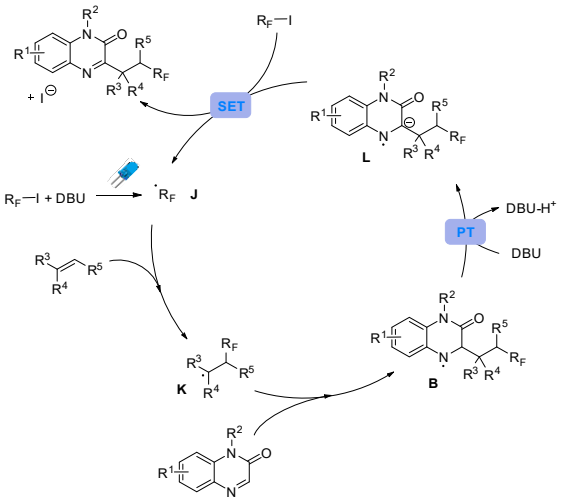
Continuing to review the photoinduced alkylation methodologies of quinoxalin-2-ones, in 2019 Armido Studer reported an elegant approach through a catalyst-free tricomponent reaction.[41] Under the irradiation of Blue LEDs, they were capable of coupling quinoxalin-2-ones with alkenes and perfluoroalkyl iodides using DBU as base. Using these conditions, they could access a library of forty four C-3 alkylated-quinoxalin-2-ones, bearing multiple and complex substitution patterns in all involved reaction products, in good to excellent yields (Scheme 20). For example, the reaction tolerates groups such as nitriles, esters, halogens, free alcohols, phosphonates, amides or complex heteroaromatic moieties. Remarkably, the reaction is completely diastereoselective, when cyclohexene was used as an alkene affording the *trans* isomer.



Scheme 20. Tricomponent reaction between quinoxalin-2-ones, alkenes and perfluoroalkyl iodides enabled by visible-light (Studer, 2019).

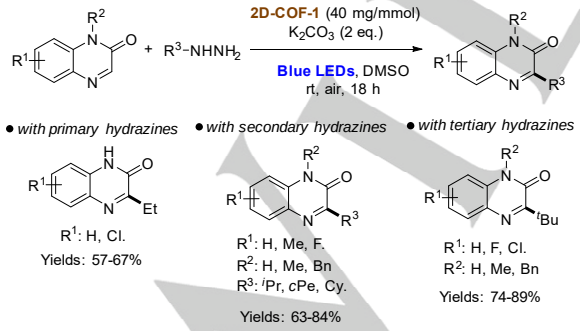
According to the authors, a radical chain mechanism is operative. Due to some radical experiments, where the authors analyse the reaction products such as the cyclopropane ring opening product and the cyclization product observed when diethyl 2,2-diallylmalonate was used. The formation of an Electron Donor-Acceptor (EDA) complex between perfluoroalkyl iodide and DBU shifts the absorption to the visible region and, upon Blue LED irradiation, the C-I bond can be homolyzed to generate the perfluoroalkyl radical **J**, which can react with an olefin to afford the most substituted radical carbon **K**. This *C*-centered radical can react with electron-deficient C=N double bond of quinoxalin-2-one to generate the *N*-centered radical **B**, that can be deprotonated by DBU towards radical anion **L**. Finally, a SET coupled with

perfluoroalkyl iodide homolysis may provide the desired product and perfluoroalkyl radical **A**, completing this way the radical chain process (Scheme 21). To support the radical chain, either quantum yield determination or on/off light experience should have been conducted.



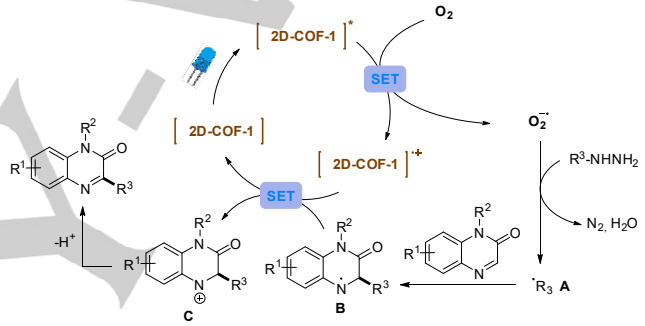
Scheme 21. Mechanistic proposal for the light-enabled tricomponent reaction.

The last example on alkylation of quinoxalin-2-ones comes from Yang's research group in early 2020.[42] These researchers employed a Covalent Organic Framework (COF),[43] more specifically hydrazone based 2D-COFs previously, reported by them.[44] Using their customized two-dimensional 2D-COF-1, they can access alkylated quinoxalin-2-ones taking aliphatic hydrazines as alkyl equivalents in combination with potassium carbonate as base under the irradiation of Blue LEDs in an aerobic heterogeneous reaction environment. The corresponding *C*-centered radicals were generated smoothly under the reaction conditions, which allowed the authors to prepare a set of C-3-alkylated quinoxalin-2-ones with good yields (57-89%) using either primary, secondary or tertiary aliphatic hydrazines (Scheme 22).



Scheme 22. C-3 Direct alkylation of quinoxalin-2-ones using 2D-COD-1 as heterogeneous photocatalyst (Yang, 2020).

These researchers also took advantage of their heterogeneous methodology to perform a gram-scale batch reaction in which the desired product was isolated through four simple operational steps: centrifugation, evaporation, washing and filtration. Moreover, from the point of view of sustainable and green chemistry, the isolation and recyclability of the heterogeneous catalyst is really important. Therefore, the authors carried out a photocatalyst recycling experiment between 1-methylquinoxalin2(1*H*)-one and cyclohexylhydrazine hydrochloride under the standard reaction conditions, observing that their COF photocatalyst maintain its photocatalytic activity even after six runs. The authors also provided a mechanistic hypothesis based on some previously performed control experiments. According to them, after being excited by the Blue LEDs, the heterogeneous photocatalyst is engaged in a SET with O_2 to provide superoxide anion, which can oxidize the corresponding hydrazine with the concomitant loss of N_2 to generate the C-centered radical **A**. This last highly reactive specie can react with the electrophilic C=N double bond of quinoxalin-2-one to afford the usual N-centered radical **B**, which becomes oxidized through a SET with 2D-COF-1+. Finally, a deprotonation of **C** (Scheme 23) finally furnishes the desired product.



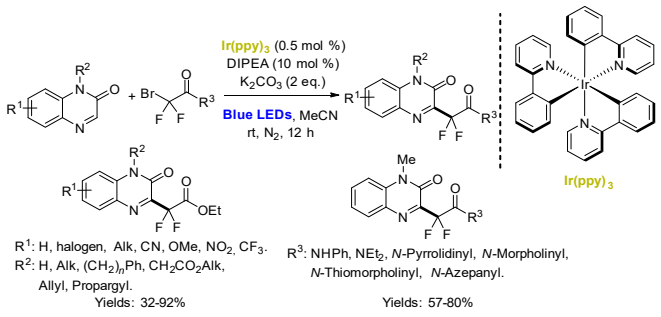
Scheme 23. Mechanistic proposal for the heterogeneous photocatalyzed C-3-allylation of quinoxalin-2-ones.

2.2. Fluoroalkylation reactions

The incorporation of fluorine into certain molecular entities has been proven to be a fruitful strategy in some research fields, such as pharmaceutical and medicinal chemistry.[45] Thus, the development of methodologies to incorporate this special halogen atom with high efficiency is demanding. Due to the highly interest of quinoxalin-2-ones in medicinal chemistry and taking advantage of the operational simplicity of visible light photoredox catalysis, several strategies have been developed to merge fluoroalkylated carbon chains in this nitrogen heterocycle. These strategies vary from the point of view of the fluoroalkyl radical precursor, which can be fluoroalkyl halides, fluoroalkyl carboxylates or fluoroalkyl sulfinates.

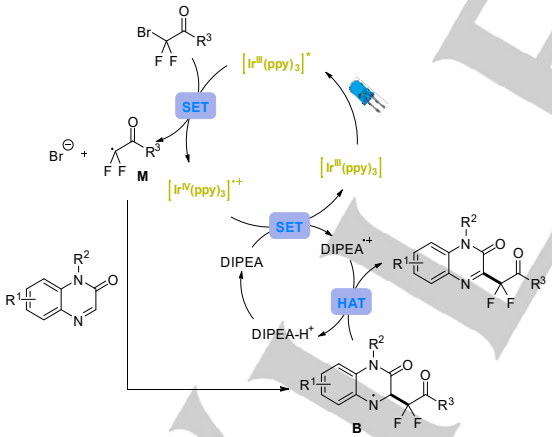
Fluoroalkyl halides constitute a readily available fluoroalkyl radical precursors through a C-X bond homolysis, which can be performed using visible-light photocatalysis, as the Jin research group reported.[46] These researchers, in 2019, developed a methodology based on the use of *fac*-Ir(ppy)$_3$ and DIPEA to fluoroalkylated quinoxalin-2-ones using fluoroalkyl bromides under the irradiation of Blue LEDs. Using their methodology, they can access a collection of differently substituted quinoxalin-2-ones bearing a fluoroalkyl moiety at C-3 position (Scheme 24). Different electron-donating (*t*Bu, Me or MeO) or electron-withdrawing (F, Cl, Br, CF_3, CN or NO_2), were tolerated at the

aromatic ring of the quinoxalinones as well as different *N*-protecting alkyl groups at the amide. Moreover, the authors extend their methodology to series of 2-bromo-2,2-difluoroamides with good results. Furthermore, they were also capable of scaling up their methodology to obtain more than one gram of the desired product.



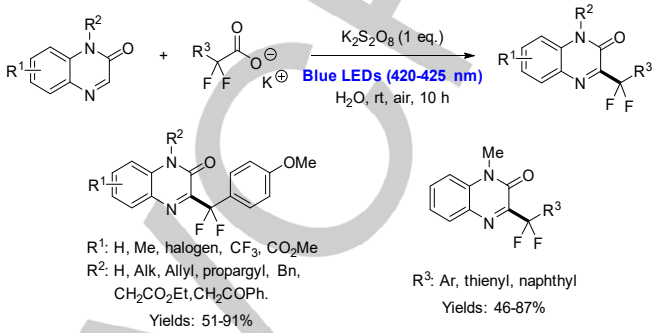
Scheme 24. C-3 fluoroalkylation of quinoxalin-2-ones using fluoroalkyl bromides (Jin, 2019).

These researchers also postulated a mechanism in which both photoredox (*fac*-Ir(ppy)$_3$) and tertiary amine (DIPEA) catalytic systems merge to afford the desired product. First, upon the irradiation of Blue LEDs, a SET coupled with C-Br bond homolysis occurs by the action of excited state Ir(III) photocatalyst, which can be regenerated via another SET with DIPEA. The resulting *C*-centered fluoroalkyl radical **M** can react with quinoxalin-2-one's C=N double bond to generate a *N*-centered radical **B**, which can undergo a HAT with DIPEA$^{+\cdot}$ to finally afford C-3-fluoroalkylated quinoxalin-2-one (Scheme 25).



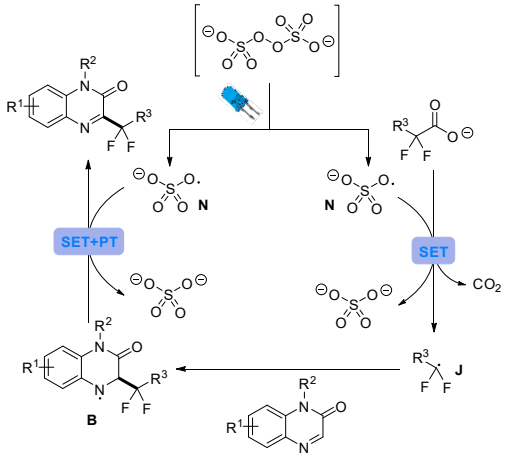
Scheme 25. Mechanistic proposal for the fluoroalkylation of quinoxalin-2-ones using visible-light photoredox catalysis.

The second strategy towards fluoroalkylated quinoxalin-2-ones is based in the utilization of fluoroalkyl carboxylates. These acid-derived species can suffer a photochemical-triggered decarboxylation to generate the desired fluoroalkyl carbon radical. It was the laboratory of Lei Wang who, in early 2020, developed a photocatalyst-free protocol based on these carboxylates to fluoroalkylate quinoxalin-2-ones using potassium persulfate as stoichiometric oxidant.[47] They could synthetize a large family differently substituted fluoroalkyl quinoxalin-2-ones using several fluorobenzyl carboxylates (Scheme 26). As in the previous reports, the reaction tolerates a wide range of groups in the aromatic ring of the quinoxalinones as well as *N*-protecting alkyl groups of the amide. Regarding the fluoroalkyl reagent, several *para-, meta-, ortho-* and disubstituted potassium α,α-difluoroarylacetates were used obtaining, in general, good yields.



Scheme 26. Fluoroalkylation of quinoxalin-2-ones with fluoroalkyl carboxylates (Wang, 2020).

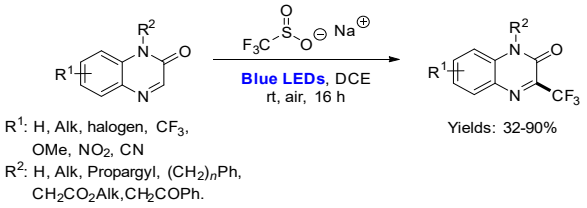
After detecting the formation of *C*-centered fluoroalkyl radical with TEMPO by HRMS, the researchers postulated a mechanism by which the reaction may proceed. First, peroxo bond in persulfate anion is homolyzed by the assistance of Blue LEDs to generate sulfate radical anions **N**, which can be engaged in a SET-coupled decarboxylation of fluorocarboxylate **J**. The lately formed *C*-centered benzylic fluoroalkyl radical can react with the electrophilic C=N double bond of quinoxalin-2-one to afford the characteristic *N*-centered radical **B**. Finally, after deprotonation and SET with a sulfate radical anion, the final product is generated (Scheme 27).



Scheme 27. Mechanistic proposal for the visible light-triggered fluoroalkylation of quinoxalin-2-ones with fluoroalkyl carboxylates.

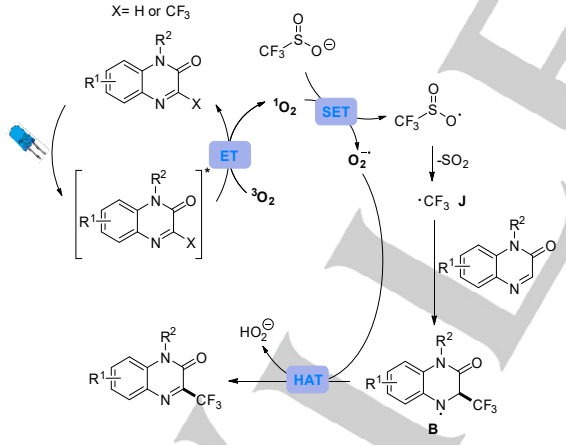
The third and last approach to *C*-centered fluoroalkyl radicals is based in the use of fluoroalkyl-derived sulfinate salts.[48] These precursors have been employed by four research teams to generate trifluoromethyl or difluoromethyl radicals in order to

fluoroalkylate quinoxalin-2-ones using visible-light photocatalysis. The first example was the methodology reported by Jin *et al.*, in which several differently substituted quinoxalin-2-ones were trifluoromethylated using CF_3SO_2Na under the irradiation of Blue LEDs, without the use of a photocatalyst.[49] The corresponding 3-trifluoromethyl-quinoxalin-2(1*H*)-one derivatives bearing a variety of substitution patterns were obtained in moderate to good yields (Scheme 28).



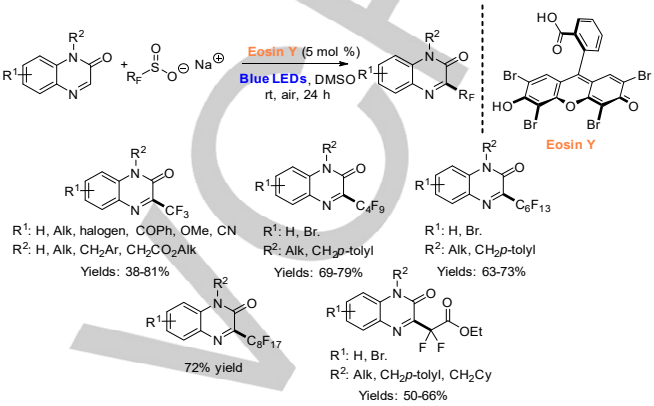
Scheme 28. Trifluoromethylation of quinoxalin-2-ones under photocatalyst-free conditions (Jin, 2019).

Additionally, they performed enough experiences to ensure that both starting quinoxalin-2-one and 3-trifluoromethylquinoxalin-2-one might act as photosensitisers to generate singlet oxygen upon the irradiation of Blue LEDs through an Energy Transfer (ET) process. Singlet oxygen can be engaged in a SET with sodium trifluoromethyl sulfinate and, after the release of SO_2, trifluoromethyl radical (**J**) is afforded. As usual, this kind of radicals can act as nucleophile and, therefore, is able to react with C=N quinoxalin-2-one double bond. The *N*-centered radical **B** that is formed in the previous step can undergo a HAT with superoxide anion to finally provide the desired product (Scheme 29).



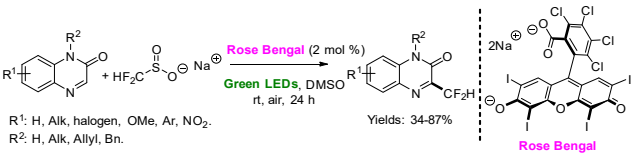
Scheme 29. Mechanistic proposal for the trifluoromethylation of quinoxalin-2-ones using sulfinates.

Two months later, the research group of Duan developed a protocol in which quinoxalin-2-ones could be trifluoromethylated and perfluoroalkylated using sodium sulfinates along with Eosin Y as photocatalyst and DMSO as solvent.[50] Applying these conditions, the authors could access a collection of forty differently substituted quinoxalin-2-ones with diverse perfluoroalkyl sodium sulfinates in good yields (Scheme 30). The reaction tolerates the presence of several functional groups at the aromatic ring as well as at the amidic nitrogen. The authors extend their methodology to other heterocyclic compounds such coumarin, benzoxazin-2-one and xanthine derivatives. To show the scalability of their photocatalytic perfluoroalkylation protocol, four different gram-scale reactions were performed, affording the corresponding products with good yields (59-70%). A plausible mechanistic hypothesis is given in Scheme 32.



Scheme 30. Eosin Y-photocatalyzed perfluoroalkylation of quinoxalin-2-ones with sulfinates (Duan, 2019).

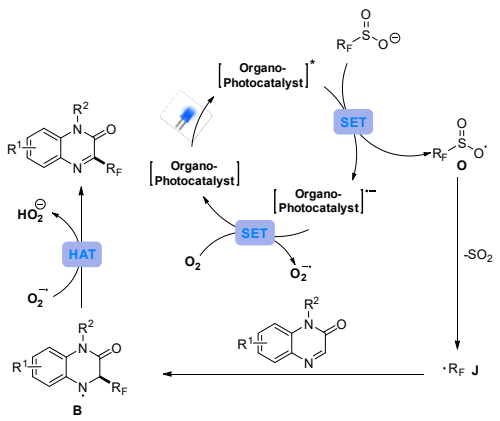
In early 2020, Li and collaborators reported a methodology to incorporate difluoromethyl groups to quinoxalin-2-ones and other aromatic heterocycles.[51] The CF_2H group is an important fluorinated functional group that, recently, have received huge attention in medicinal chemistry and pharmaceutical industry. This fluorinated group has been used as a lipophilic hydrogen bond donor, and as isostere of a thiol, a hydroxyl, and an amide, bringing new opportunities for drug development.[52] The approach described by Li is based in the use of Rose Bengal as photoredox catalyst and sodium difluoromethyl sulfinate as a fluorinating agent (Hu's reagent),[53] under the irradiation of Green LEDs in air atmosphere. By using these conditions, the researchers could generate a set of difluoromethylated quinoxalin-2-ones in moderate to good yields (34-87%). Additionally, they could extend its methodology to other (hetero)aromatic systems as well as to several bioactive molecules (Scheme 31).



Scheme 31. Difluoromethylation of quinoxalin-2-ones using Eosin Y (Li, 2020).

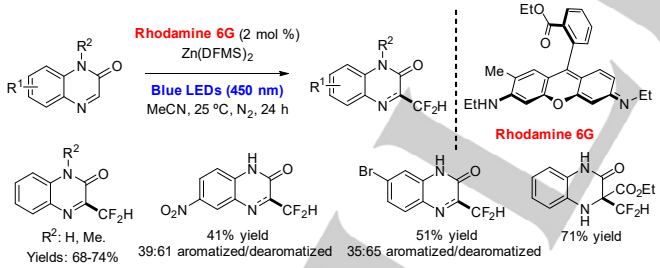
Due to the similarity of the last two reviewed methodologies, a unified mechanism is given. After a SET between the light-excited photocatalyst and the proper sulfinate, *O*-centered **O** radical is formed, which experiences a spontaneous loss of SO_2 to generate fluoromethyl radical **J**. As usual, this *C*-centered radical can react with C=N double bond of quinoxalin-2-one to furnish a

N-centered radical **B**, which can experiment a HAT with superoxide anion to release the desired product (Scheme 32).



Scheme 32. Mechanistic hypothesis for the organophotocatalyzed-fluoroalkylation of quinoxalin-2-ones with sodium sulfinates.

To conclude the review of photochemical-enabled fluoroalkylation methods of quinoxalin-2-ones, a very recent report from the research team of Alemán is detailed.[54] These researchers developed a protocol for the direct C=N difluoromethylation of imines based on the generation of the corresponding difluoromethyl radical from zinc difluoromethyl sulfinate,[55] along with Rhodamine 6G as photocatalyst.[56] Among the imines which they used, there are five quinoxalin-2-ones, and the corresponding difluoromethylated products were obtained in moderate yields, obtaining in some cases a mixture of aromatized and dearomatized products (Scheme 33). In this protocol, the reaction is conducted under nitrogen atmosphere, in contrary to the previous examples where the reaction was performed under air.



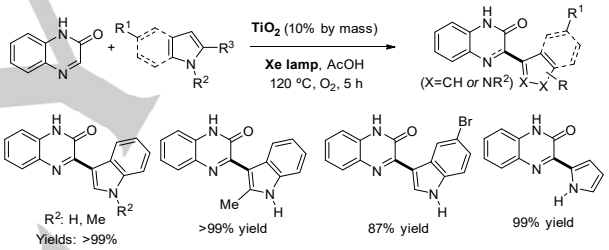
Scheme 33. Difluoromethylation of quinoxalin-2-ones with Zn(DFMS)2 under photoredox conditions (Alemán, 2020).

Once again, the intense research around functionalization of quinoxalin-2-one has favoured the appearance of four works that incised on fluoroalkylation of these nitrogen heterocycles. Remarkably, in these protocols an organic-based photocatalyst plays the central role, and even one of them does not need it. This constitutes a great move through more sustainable metal-free photochemical methodologies. It has been proved that metal sulfinates can act as efficient precursors of fluoroalkyl carbon radicals, which can undergo radical addition to quinoxalin-2-one C=N double bond.

2.3. Arylation reactions

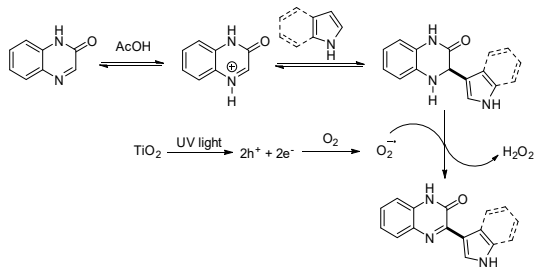
Moving on to other C-C bond forming reactions, it is important to consider the incorporation of an aromatic moiety into quinoxalin-2-ones. The arylation of the C-3 position of this heterocycle allows the extension of the conjugated π system. The direct reaction of quinoxalin-2-ones with (hetero)arenes is only conceivable when highly nucleophilic arene derivatives are selected. However, the incorporation of unfunctionalized aryl groups is also possible by the use of several reactive derivatives. There are just three reported examples on the photochemical-enabled C-3 arylation of quinoxalin-2-ones.

The first of them comes from Chupakhin's laboratory in 2015, who employed titanium dioxide (TiO_2) as photocatalyst.[57] This heterogeneous photocatalyst has been employed usually in light-enabled synthetic chemistry as well as in photodegradation of some dangerous species.[58] TiO_2 has its maximum of absorption in the UV region, thus the authors used a Xe lamp (5000 K, 35 W) as energy source, along with acetic acid as solvent in an aerobic setup. Using these harsh conditions, the researchers could directly arylate quinoxalin-2-ones (among other nitrogen heterocycles) with indoles and pyrrole, that are out of the scope of this review. The corresponding heteroaryl quinoxalin-2-ones were obtained in excellent yields after 5 h (Scheme 34).



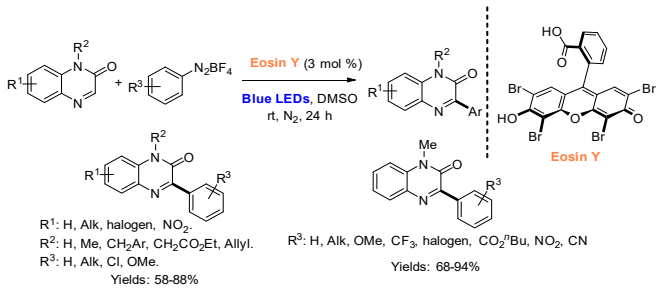
Scheme 34. C-3 direct arylation of quinoxalin-2-ones with indoles and pyrrole (Chupakhin, 2015).

These researchers also proposed a mechanism by which this transformation might proceed. First of all, the Friedel-Crafts reaction between the corresponding nucleophilic nitrogen heterocycle and the *N*-protonated quinoxalin-2-one takes place. The product of this aminoalkylation reaction can be oxidized by the superoxide anion, which is released upon the TiO_2 excitation under UV light in combination with O_2 (Scheme 35). When the energy of the band gap is provided, electrons in TiO_2 promote to the conduction band while leaving positive holes (h^+) in the valence band.



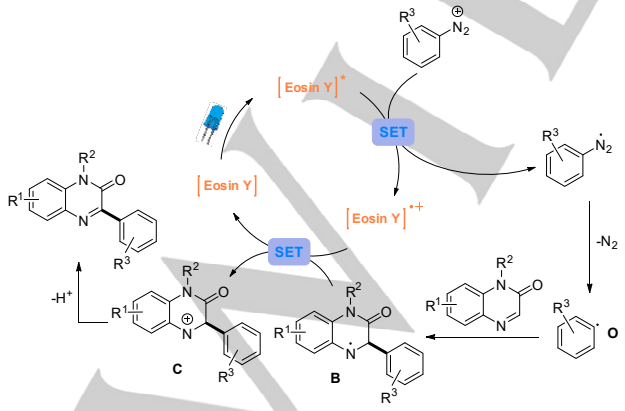
Scheme 35. Plausible mechanism for the heteroarylation of quinoxalin-2-ones using TiO_2.

When the incorporation of a non-nucleophilic arene derivative in quinoxalin-2-ones is desired, another strategy should be used. The researchers in the group of Kim realized that aryldiazonium salts could act as aryl radical precursors in photoredox conditions.[59] Aryl diazonium salts are commonly employed for nucleophilic aromatic substitutions (Sandmeyer's reaction), where the nitrogen molecule acts as a leaving group. The authors established Eosin Y as the best photocatalyst, in combination with DMSO as solvent under the irradiation of Blue LEDs.[60] Using these conditions, they could generate thirty one examples of C-3-aryl quinoxalin-2-ones in moderate to good yields (Scheme 36). A variety of aryldiazonium salts bearing electron-donating and electron-withdrawing substituents in the aryl groups were compatible with the protocol, obtaining good yields. Moreover, the authors could scale up the reaction to obtaing the C-3-aryl quinoxalin-2-one in 1.13 grams.



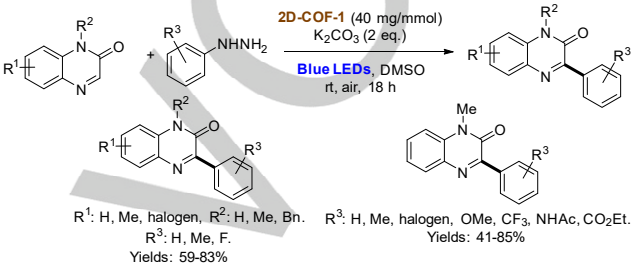
Scheme 36. Light-enabled arylation of quinoxalin-2-ones with aryldiazonium salts (Kim, 2018).

Regarding the mechanism, the authors performed the typical control experiments and then they provided a plausible mechanistic hypothesis (Scheme 37). The aromatic radical **O** is generated through a SET with the excited state of Eosin Y, with the concomitant loss of N_2. This *C*-centered radical can react with the C=N double bond of quinoxalin-2-one yielding the corresponding *N*-centered radical **B**. After another SET with the oxidized form of Eosin Y, the *N*-centered radical **B** is single-electron oxidized to cation **C**, which undergoes a deprotonation to finally generate the desired product.



Scheme 37. Mechanistic proposal for the arylation of quinoxalin-2-ones with aryldiazonium salts using Eosin Y.

The last approach towards C-3 arylated quinoxalin-2-ones comes from the already mentioned work of Yang on the utilization of hydrazines as *C*-centered radical precursors.[42] In the section referred to alkylation procedures, we showed how the team of Yang used a heterogeneous system based on a COF to generate alkyl radicals from hydrazines. They were also able to extend their methodology to aromatic hydrazines in order to obtain 3-aryl-quinoxalin-2-ones in moderate to good yields (Scheme 38). The mechanism by which the authors rationalize this transformation can be found in Scheme 23. but considering that, in this case, an aromatic hydrazine is used and therefore an aromatic radical is generated.



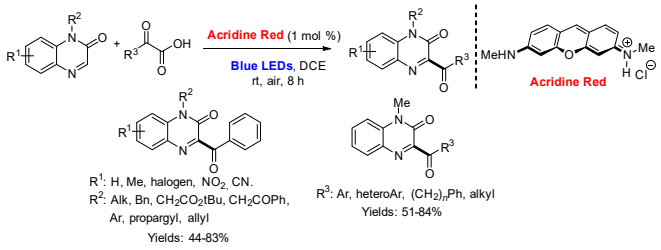
Scheme 38. C-3 arylation of quinoxaline-2-ones using aromatic hydrazines (Yang, 2020).

These last three reviewed methodologies on the C-3 arylation of quinoxalin-2-ones represent different approaches to the desired transformation. The first one explores the highly nucleophilic character of indoles and pyrroles and the acidic conditions to favour an aza-Friedel-Crafts reaction, while the two last ones take advantage of two different nitrogen-substituted aromatic compounds as aryl radical precursors. It is also interesting the utilization of titanium dioxide for synthetic purposes as an electron source after UV irradiation. Along with the use of COFs or other related species, the construction of photochemical methods based on heterogeneous catalysts is beneficial from the point of view of industry and sustainable chemistry. Heterogeneous catalysis offers the advantage that products are readily separated from the catalyst, and the heterogeneous catalysts are often more stable and degrade much slower than homogeneous catalysts and can be reused.

2.3. Acylation reactions

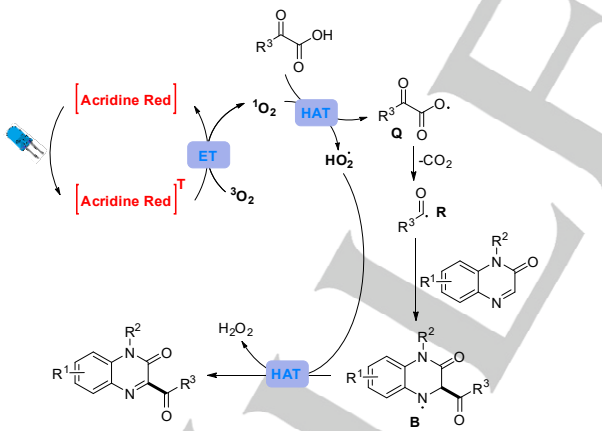
To finish the journey through the reactions involving the formation of C-C bonds in quinoxalin-2-ones, we must mention the three existing methodologies for the acylation at the C-3 position of this aromatic heterocycle using aliphatic and aromatic glyoxylic acids as acyl radical synthetic equivalent. In early 2020, the research group of Wei developed a protocol based on the Acridine Red ability for sensitizing triplet oxygen under the irradiation of Blue LEDs.[61] Using these optimal reaction conditions, they could synthetize a library of twenty eight differently substituted 3-acyl-quinoxalin-2-ones in moderate to good yields (Scheme 39). A series of aryl α-oxocarboxylic acids with electron-donating (Me or MeO) and electron-withdrawing (F, Cl, Br, and CF_3) groups attached to the phenyl ring, heterocyclic α-oxocarboxylic acids as well as aliphatic α-oxocarboxylic acids were all suitable for this

transformation, affording the corresponding functionalized quinoxalinones with good yields.



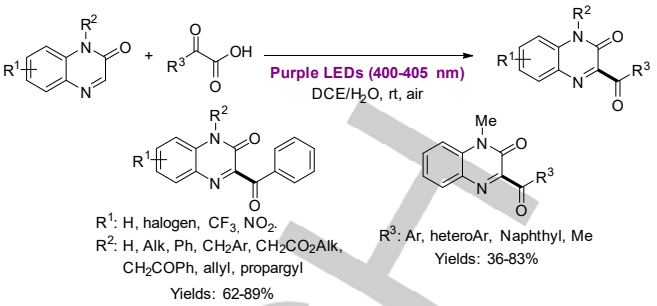
Scheme 39. C-3 acylation of quinoxalin-2-ones with glyoxylic acids using Acridine Red (Wei, 2020).

To gain insight into the reaction mechanism, the researchers conducted several control experiments such as performing the reaction under N_2 atmosphere, using 2,6-bis(1,1-dimethylethyl)-4-methylphenol (BHT) or using 1 equivalent of DABCO (strong $^1O_2$ physical quencher), observing a suppression and inhibition of the formation of product. Therefore, they established that the organic dye might act as a photosensitizer of triplet oxygen through an energy transfer (ET) process. Then, singlet oxygen can be engaged in a HAT with the proper glyoxylic acid to afford the *O*-centered radical **P**, which undergoes a spontaneous decarboxylation to form acyl radical **Q**. This *C*-centered radical **Q** can react with quinoxalin-2-one's C=N double bond and therefore the *N*-centered radical **B** is furnished. Finally, *N*-centered radical **B** can suffer a HAT with the hydroperoxide radical to generate the corresponding 3-acylated-quinoxalin-2-one (Scheme 40).



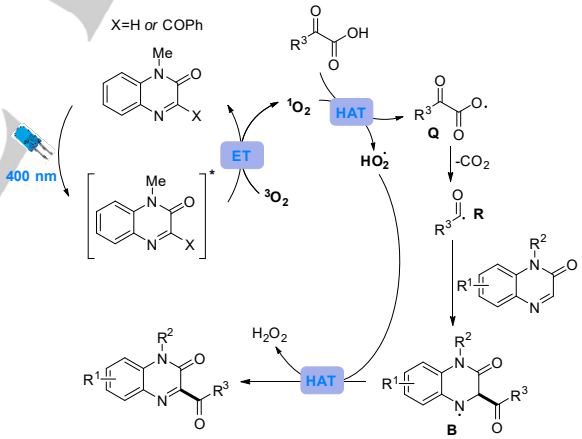
Scheme 40. Mechanistic hypothesis for the Acridine Red-catalysed acylation of quinoxalin-2-ones.

One month later, He and coworkers reported a similar methodology to incorporate an acyl group in the C-3 position of quinoxalin-2-ones.[62] Using a more energetic light source (400 nm), the authors could develop a photocatalyst-free version for the acylation of quinoxalin-2-ones. Using a mixture of DCE and water as solvent and the oxygen from air as oxidant, they could obtain a set of quinoxalin-2-ones acylated in the C-3 position in moderate to good yields (Scheme 41).



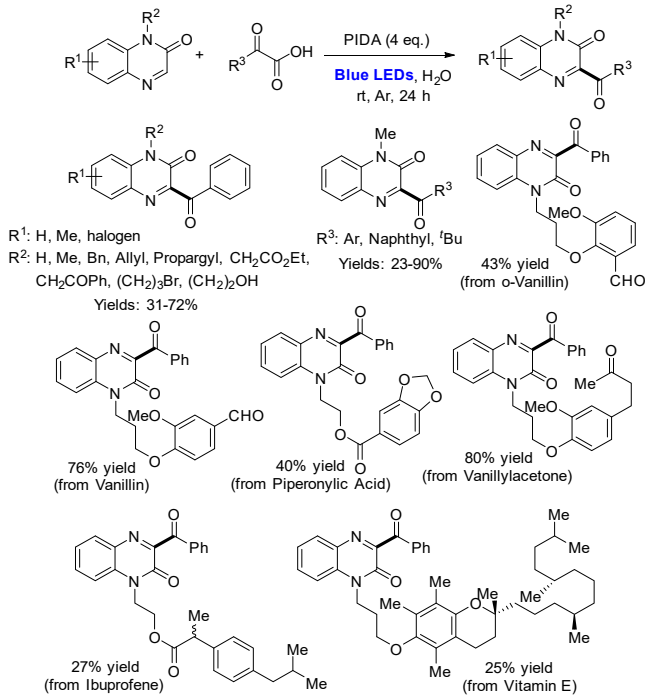
Scheme 41. Catalyst-free acylation of quinoxalin-2-ones with glyoxylic acid (He, 2020).

To prove the practicability of the methodology, the researchers carried out a gram-scale reaction, furnishing 1.11 g (84% yield) of the desired product. In order to prove the implication of singlet oxygen in the reaction pathway, they conducted several O_2-trapping experiences with 9,10-dimethylanthracene, obtaining the expected [4+2] cycloaddition products. Additionally, their results on UV-Vis spectroscopy revealed that either quinoxalin-2-one or the final product could act as triplet oxygen photosensitizers under 400 nm-light irradiation. Based on these experiences, they were able to propose a similar mechanistic pathway than the one in Scheme 40. But, in this case the photosensitizer was quinoxalin-2-one (or the reaction product) instead of Acridine Red (Scheme 42).



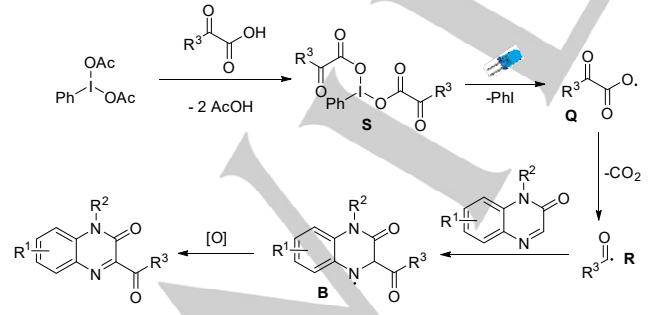
Scheme 42. Mechanistic pathway for the catalyst-free acylation of quinoxalin-2-ones with glyoxylic acids.

Finally, also in early 2020, the laboratory of Xuan described the same transformation as the two previous ones but using this time phenyliodine(III)diacetate (PIDA)[63] in combination with Blue LED irradiation.[64] This photocatalyst-free protocol led the authors to obtain a large amount of 3-acylquinoxalin-2-ones in low to moderate yields. They were also able to conduct the reaction with quinoxalin-2-ones derived from natural molecules and pharmaceutically relevant compounds (Scheme 43).



Scheme 43. C-3 acylation of quinoxalin-2-ones with glyoxylic acids (Xuan, 2020).

Then, they proposed a pathway by which the reaction should proceed. First, the phenyliodide(III) diacetate can suffer a ligand exchange with glyoxylic acid to yield phenyliodide(III) diglyoxylate (**S**). This intermediate can suffer a light-assisted I-O bond homolysis to generate *O*-centered radical **Q** along with phenyl iodide. After losing CO_2, *O*-centered radical is transformed into acyl radical **R**, which can undergo a radical addition with the C=N double bond of quinoxalin-2-one to furnish *N*-centered radical **B**. Finally, the *N*-centered radical should be oxidized to be transformed in the desired product but, unfortunately, the authors do not provide any explanation about the way by which this last step might occur. Probably, excess of PIDA (as it is a I(III) specie) could act as the required final oxidant (Scheme 44).



Scheme 44. Mechanistic proposal for the C-3 acylation of quinoxalin-2-ones with PIDA.

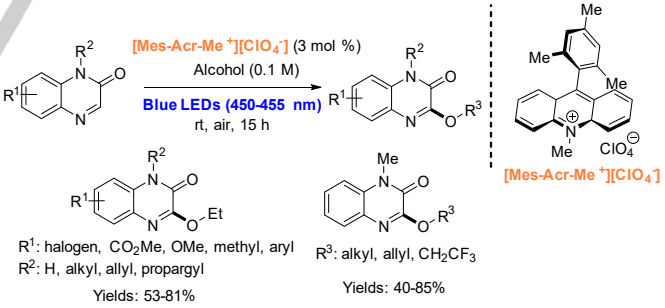
These three acylation approaches lie in the use of the same acyl radical precursor: glyoxylic acid. Although this 2-oxoacids are readily available, the overall reaction could be more atom economical if the acyl radical could be generated directly from an aldehyde through a HAT. This paradigm has been exploited under photoredox catalysis for many transformations but, to the best of our knowledge, it has not been applied to quinoxalin-2-ones.

3. C-O and C-S bond formation

The formation of C-O bonds using the nucleophilic character of alcohols or alkoxides has been used for a long time. The reaction between an alkoxide and an organic halide, the Williamson's synthesis of ethers,[65] constitutes an important landmark in the formation of C-O bonds. Due to the polar character of the C=N bond in quinoxalin-2-ones, the use of alcohols or related species to generate a C-O new bond in the C-3 position have attracted the attention of several researchers.

The field of photochemistry has also exploited this possibility using the visible-light in combination with a photocatalyst to activate such an inert substrate, as the quinoxalin-2-one is. The single-electron oxidation of azomethinic nitrogen by an excited-state photocatalyst could generate a radical cation more prone to undergo a nucleophilic addition. This strategy has been exploited by three research groups independently using different organophotoredox catalysts to achieve the formation of a C-O bond in the C-3 position using alcohols as nucleophiles.

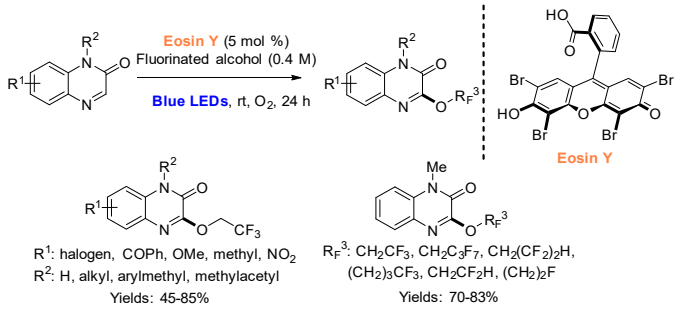
First, in 2019, Li and coworkers[66] selected the [Mes-Acr-Me^+][ClO_4^-] photocatalyst[67] (also known as Fukuzimi's catalyst) as the suitable catalytic species to conduct this transformation in combination with Blue LEDs and ethanol (or other aliphatic alcohol), that serves as nucleophile and as solvent. This catalytic system allows the authors to obtain a collection of twenty-seven differently substituted quinoxalin-2-ones with a C-O bond at the C-3 position. The reaction conditions tolerate the presence of multiple substitution patterns in the amidic nitrogen (alkyl, allyl or propargyl) as well as in the aromatic ring (electron-donating as well as electron-withdrawing groups) (Scheme 45).



Scheme 45. C-O bond forming reaction of quinoxalin-2-ones and alcohols using [Mes-Acr-Me^+][ClO_4^-] as photocatalyst (Li, 2019).

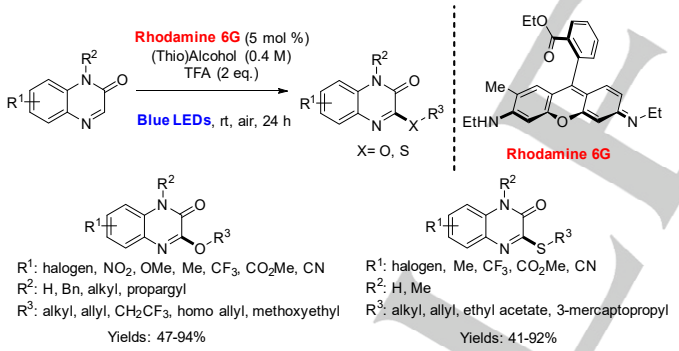
Then, another example of the C-3 photoredox alkoxylation of quinoxalin-2-ones comes from the Hao laboratory in early 2020.[68] These researchers were interested in introducing a fluorinated scaffold in quinoxalin-2-ones at the C-3 position along with the formation of a new C-O bond. The authors described an approach using Eosin Y as photocatalyst, 2,2,2-trifluoroethanol (and other aliphatic fluorinated alcohols) as nucleophile/solvent and Blue LEDs as energy source. Using this protocol, they could obtain a battery of forty C-3-alcoxifluorinated quinoxalin-2-ones (Scheme 46). They demonstrate the applicability of the reaction,

performing a gram-scale reaction (72% yield, 1.86 grams) and the synthesis of histamine-4 receptor antagonist through the C–H trifuoroethoxylation, followed by a nucleophilic substitution with 1-methylpiperazine.



Scheme 46. Photochemical fluoroalcoxylation of quinoxalin-2-ones enabled by Eosin Y (Hao, 2020).

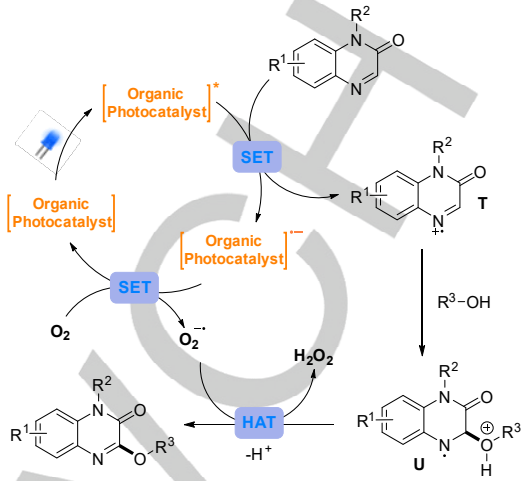
In 2019, the research group of Li reported the same transformation but using Rhodamine 6G as photocatalyst and adding also trifluoroacetic acid as an additive under the irradiation of Blue LEDs.[69] This alternative catalytic system could provide thirty-four examples of differently substituted alkoxylated quinoxalin-2-ones with aliphatic alcohols. Additionally, the authors could extend the scope of this catalytic protocol to the formation of C-S bond using aliphatic thiols as nucleophiles, obtaining a set of twenty examples of 3-substituted thioalkoxylated quinoxalin-2-ones (Scheme 47).



Scheme 47. C-O and C-S forming reaction protocol using Rhodamine 6G and TFA (Li, 2019).

The incorporation of sulfur taking advantage of the nucleophilicity of the sulfides is another interesting transformation given that sulfur-containing substrates have attracted the interest of several research fields such as materials or pharmaceutical chemistry.[70] The direct incorporation of sulfur through a Cross Dehydrogenative Coupling (CDC) between quinoxalin-2-ones and sulfides under photoredox conditions (as these researchers did) avoids the use of strenuous reaction conditions that may result in the oxidation of sulfides to sulfoxides or sulfones.

While keeping the same (or almost the same) nucleophiles, the last three methodologies differ in the photocatalyst that they employed. Due to the similarity of the catalysts, it is plausible to assess a common mechanistic hypothesis to rationalize this kind of transformation based on photochemical-enabled single-electron transfer events, as is depicted in Scheme 48.

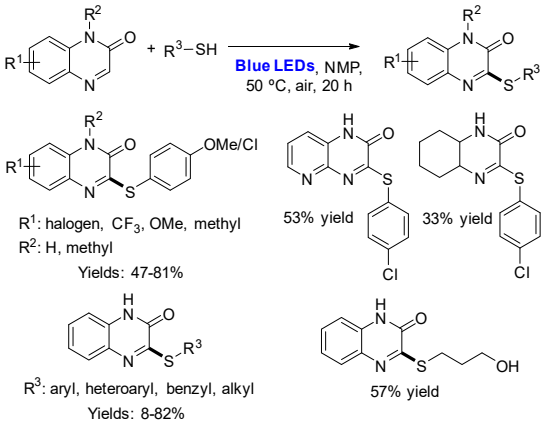


Scheme 48. Mechanistic hypothesis for the photoredox-catalyzed alkoxylation of quinoxalin-2-ones.

First of all, the corresponding organic dye ([Mes-Acr-Me]$^+$, Rhodamine 6G or Eosin Y) is promoted to its excited state by the action of Blue LEDs irradiation. This electronically excited specie can participate in a Single Electron Transfer (SET) process in which the organic dye accepts an electron from the azomethinic nitrogen of the quinoxalin-2-one to generate the reduced form of the catalyst and the radical cation of the quinoxalin-2-one (**T**). Upon another SET event, the native form of the dye is recovered by the action of molecular oxygen. In this process the superoxide anion is also generated. This oxidized form of the quinoxalin-2-one is more electrophilic than the neutral one and, owing to this, the proper oxygenated nucleophile can be added to the electrophilic double bond and generate the radical cation **U**. This charged radical can transfer a proton to the superoxide anion to provide the hydroperoxide radical and, finally, this last specie can abstract a hydrogen atom (Hydrogen Atom Transfer, HAT) to regenerate the carbon-nitrogen double bond. This last step can also be viewed as the single-electron oxidation (SET) of deprotonated-**U** by the hydroperoxide radical to generate the *N*-centered cation and hydroperoxide anion. The final stage would be another deprotonation and the subsequent generation of the double bond. This mechanistic hypothesis is also supported by the canonical control experiments and other experiences, such as radical trapping and HRMS detection of intermediates among them.

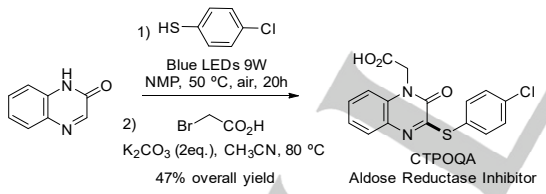
Regarding the direct formation of C-S bonds, in late 2019, Pan and collaborators reported a visible-light-enabled photocatalyst-free protocol for the sulfenylation of quinoxalin-2-ones with thiols.[71] After screening some photocatalysts, they realized that the reaction could proceed without photocatalyst. Therefore, the researchers optimized the reaction conditions between quinoxalin-2-one and *p*-mercaptoanisole under catalyst-free conditions, and they found out that conducting the transformation in NMP at 50 °C under the irradiation of Blue LEDs allows them to obtain the desired product in 76% yield while diminishing the amount of *p*-mercaptoanisole dimer formation. They also applied these optimal conditions to other quinoxalin-2-ones and sulfides

in order to build a library of C-3 sulfenylated quinoxalin-2-ones (Scheme 49). This methodology is particularly interesting from the point of view of sustainable chemistry as no photocatalyst is used and the final oxidant is oxygen, although is necessary to increase the reaction temperature to obtain good conversions to the final products.



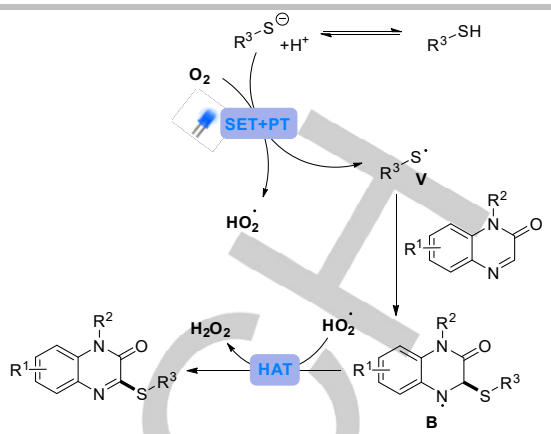
Scheme 49. Visible-light-enabled sulfenylation of quinoxalin-2-ones (Pan, 2019).

Among the whole collection of sulfenyl-derivatives obtained, there are two that do not fit into the family of sulfenylquinoxalin-2-ones, but they are also interesting substrates: the sulfenyl-pyridopyrazin-2-one and the sulfenyl-hexahydroquinoxalin-2-one. Despite the low yield in which these two challenging products were obtained, they broadened the scope of the present methodology. The authors reported also a gram scale reaction (1.11 gr) and the synthesis of 2-(3-(4-chlorothiophenoxy)-2-oxoquinoxalin-1(2H)-yl)acetic acid (CTPOQA), which showed aldose reductase inhibitor activity,[72] in 47% yield after 2 steps (Scheme 50).



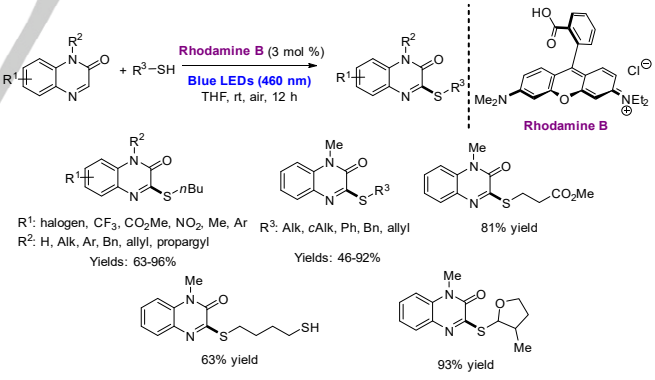
Scheme 50. Synthesis of an aldose reductase inhibitor (CTPOQA).

Concerning the mechanism of the reaction, the authors postulated a radical process in which a partially deprotonated *p*-mercaptoanisole can engage a single-electron oxidation assisted by the Blue LEDs to form the corresponding thiyl radical along with hydroperoxide radical. This *S*-centered radical **V** can dimerize towards the disulfine (it was also isolated) and can also undergo a radical addition to the electron-poor C=N double bond of the quinoxalin-2-one. The formed *N*-centered radical can finally suffer a Hydrogen Atom Transfer (globally, a PT and a SET) from the hydroperoxide radical to generate the desired product (Scheme 51).



Scheme 51. Proposed reaction mechanism (Pan, 2019).

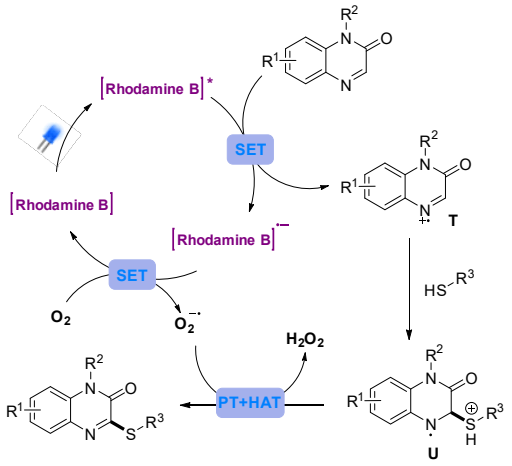
Finally, shortly after, a very similar methodology developed by the Wei-Min He laboratory was published.[73] These researchers stablished that the direct C-3 sulfenylation of quinoxalin-2-ones using thiols could be achieved using Rhodamine B as photocatalyst using THF as solvent. Surprisingly, they reported that this transformation does not proceed without photocatalyst, as opposed to the Pan work.[71] The researchers applied the optimized reaction conditions to other differently substituted quinoxalin-2-ones and distinct thiols, with forty examples including a variety of aliphatic thiols and quinoxalinones bearing electron-donating (Me) and electron-withdrawing groups (F, Cl, CO_2Me, CF_3, NO_2) (Scheme 52). The applicability of the thioetherification protocol was confirmed on a gram scale under the irradiation of a blue LED or sunlight (89%, 1.77 g and 83% yield, 1.64 g, respectively).



Scheme 52. Rhodamine B-catalyzed C-3 sulfenylation of quinoxalin-2-ones with thiols (He, 2019).

This methodology worked exquisitely for almost all aliphatic thiols even with the more challenging ones, but when benzenethiol was employed, the yield of the reaction dropped to 46%. A plausible mechanism by which this transformation should proceed was also proposed by the authors, being the key step the addition of the sulfide to the monooxidized form of quinoxalin-2-one **T** by the photoredox catalyst after being excited by the Blue LEDs (Scheme 53). After that, a PT and a HAT should happen to **U** to

finally form the desired product, releasing hydrogen peroxide too. The final oxidant of the reaction is, again the oxygen from the air.



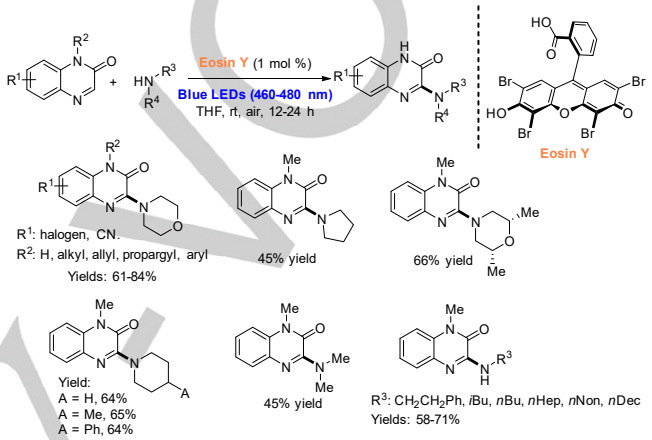
Scheme 53. A plausible mechanism for the C-3 sulfenylation of quinoxalin-2-ones under photoredox catalysis.

Comparing these last two methodologies, one can realize that the catalyst-free protocol of Pan[71] worked efficiently with both aliphatic and aromatic thiols (although with moderate yields) and the Wei-Hin Me[73] approach worked very well with aliphatic thiols but was quite unsuccessful with the aromatic derivatives. Despite the similarity in the reported transformation, the catalytic system is substantially distinct, and it should be the reason for the different performance. Pan proposed that the thiol may suffer a light-promoted formal homolysis to generate the corresponding *S*-centered radical, process that would trigger the next steps of the mechanism. The observed better performance of aromatic sulfides in catalyst-free conditions should arise from the stability of the aromatic radical, as the lone electron can be delocalized through the π system and, therefore, it can be generated more easily. In contrast, the methodology reported by Wei-Hin Me uses Rhodamine B to generate the *N*-centered radical cation of the quinoxalin-2-one. After this, the next step is the addition of the thiol and, as can be expected, the aliphatic derivatives are more nucleophilic than the aromatic thiols, and they can provide the expected products in better yields than the last ones. The same feature that conferred the required stability to the aromatic sulfur radicals for their performance in the first case, is the one that worsens the reactivity of aromatic thiols as nucleophiles in the second case.

4. C-N and C-P bond formation

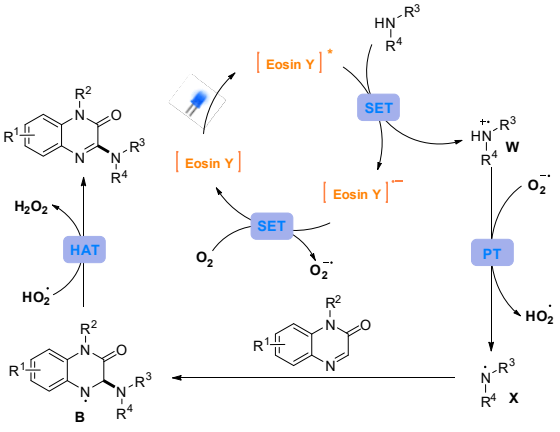
The nitrogen is the fourth element by mass in the human body as it is part of the DNA and proteins. Thus, the direct incorporation of nitrogen to molecules is crucial in several research fields such as medicinal and pharmaceutical chemistry. The direct formation of C-N bonds represents the easiest way to integrate nitrogen due to its ability to act as a nucleophile and, additionally, the lone pair located on the nitrogen might participate in photochemical-enabled electron transfer processes.

Regarding the quinoxalin-2-one scaffold, the direct functionalization of the C-3 position under photoredox conditions with nitrogen nucleophiles could be achieved as the research group of Wei Wei reported in 2018.[74] They were capable of designing a catalytic system based on Eosin Y to smoothly access a library of thirty-one compounds containing new C-N bonds by combining quinoxalin-2-ones with an assortment of primary and secondary aliphatic amines under the irradiation of Blue LEDs (Scheme 54). The scope of secondary amines includes important pharmaceutical scaffolds such as morpholine, pyrrolidine or piperidine derivatives.



Scheme 54. Photoredox-catalyzed C-3 amination of quinoxalin-2-ones using primary and secondary amines (Wang, 2018).

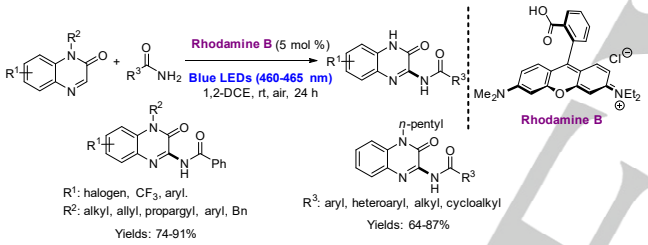
To gain insight into the mechanism of the reaction, the authors performed a sequence of control experiments. They concluded that the reaction was completely inhibited in the dark or in absence of Eosin Y and, in the presence of TEMPO or DMPO the reaction does not proceed too. Moreover, an interesting experience based on radical trapping by DMPO and subsequent detection by Electronic Paramagnetic Resonance (EPR) was performed at different irradiation periods. Using this approach, they were capable of detect the trapped radical. Based on these experiences, the researchers conjectured the reaction mechanism depicted in Scheme 55.



Scheme 55. Plausible reaction mechanism for the photoamination of quinoxalin-2-ones with amines.

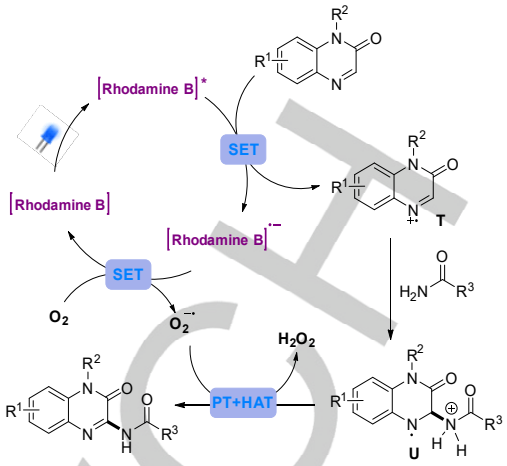
According to the authors, upon the excitation of Eosin Y by the Blue LEDs irradiation an electron transfer from this excited form of the catalyst to the aliphatic amine occurs, generating the *N*-centered radical cation **W** and the reduced form of the organic dye, which is reoxidized by the action of O_2. The superoxide anion generated in the last SET event could participate in a Proton Transfer (PT) with the aminoradical cation **W** to produce the neutral *N*-centered radical **X** that can undergo a radical addition to the electrophilic C=N bond of the quinoxalin-2-one. Finally, this *N*-centered radical **B** could suffer a Hydrogen Atom Transfer (HAT) promoted by the hydroperoxide radical to finally yield the C-3-aminated quinoxalin-2-one.

Later, in 2019, Wei-Min He and collaborators reported a more challenging C-N bond formation in quinoxalin-2-ones using amides as nitrogen nucleophiles.[75] Amides are less nucleophilic than amines due to the delocalization of the lone pair to the neighbour carbonyl group. However, these researchers developed a methodology to achieve this transformation using photoredox catalysis in mild conditions. They selected Rhodamine B as the best photocatalyst to conduct the transformation, along with 1,2-DCE as solvent and Blue LEDs. Using these conditions, they could access a set of amidoquinoxalin-2-ones in good to excellent yields (Scheme 56). The reaction tolerates (hetero)aryl and aliphatic primary amides, as well as different protecting groups such as alkyl, allyl, benzyl and aryl substituents at the nitrogen of the quinoxalin-2-ones.



Scheme 56. C-3 functionalization of quinoxalin-2-ones using amides as nucleophiles under photoredox catalysis (He, 2019).

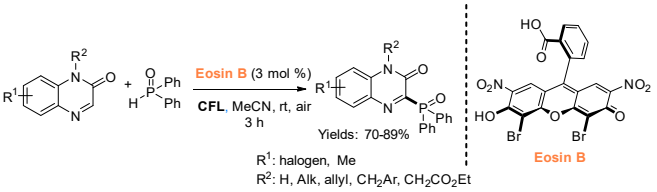
These authors also showed how this transformation could be scaled up to gram-range while maintaining the yield (83%, 1.39 g). Finally, they conducted several control experiments to gain some insights about the reaction mechanism. The reaction was completely inhibited in the presence of radical scavengers such as BHT, TEMPO and 1,1-diphenylethylene, as well as when the reaction was conducted under N_2 atmosphere. The proposed mechanism was along the same lines as previously described ones for C-O forming transformations (Scheme 57).



Scheme 57. Mechanistic proposal for the photoredox-catalyzed C-3 amidation of quinoxalin-2-ones.

Upon excitation of Rhodamine B by the Blue LEDs, the single-electron oxidation of quinoxalin-2-one to its radical cation **T** occurs. Then, the amide adds to **T** to generate the radical cation **U**, which after a Proton Transfer and an Hydrogen Atom Transfer (both with superoxide radical generated after the reoxidation of [Rhodamine B]$^{\bullet-}$ by molecular oxygen) finally provides the desired product.

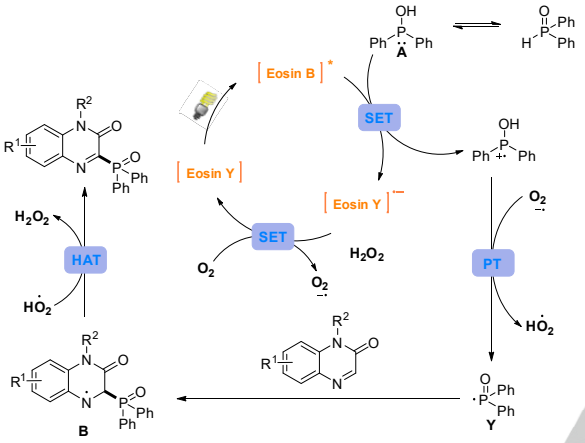
Finally, going down through the family of pnictogens, one can realize that, following the reasoning for the oxygen, sulfur and nitrogen nucleophiles, the inherent nucleophilicity of phosphorous-containing molecules should be used to form C-P bonds in quinoxalin-2-ones under photochemical conditions. However, in fact, there is only one example of direct C-P bond formation between quinoxalin-2-ones and phosphorous nucleophiles, that comes from the Dae Young Kim research group in 2018.[76] These researchers observed that Eosin B was the best photocatalyst for the C-3 phosphorylation of several quinoxalin-2-ones with diphenylphosphine oxide under the irradiation of a 20 W compact fluorescence lamp (Scheme 58). They also reported a gram scale reaction obtaining 3-(diphenylphosphoryl)-1-methylquinoxalin-2(1*H*)-one in 80% yield.



Scheme 58. Direct C-P bond formation in quinoxalin-2-ones under photoredox catalysis (Kim, 2018).

Despite the good yields in which the corresponding products were obtained, the researchers could not extend the protocol to other secondary phosphine oxides. Additionally, they proposed a tentative mechanism for this transformation based on previous studies on radical addition of this kind on P(V)-nucleophiles to several substrates (Scheme 59), such as the addition of these phosphine oxides to non-activated alkenes.[77] According to this report, upon the excitation of the photocatalyst by the light, a SET

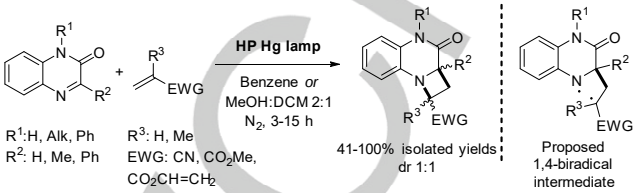
between the catalyst and the phosphine oxide occurs in order to generate (after deprotonation) the phosphinoyl radical **Y**. These mechanistic events were implemented by the authors but, according to previous reports on C-X bond formation in quinoxalin-2-ones, they should have considered the possibility of a different pathway, based on the single-electron oxidation of quinoxalin-2-one and the subsequent generation of the corresponding radical cation, that could suffer the nucleophilic addition of the phosphine oxide. A Stern-Volmer fluorescence emission quenching experience should have been done to determine the magnitude in which each one of them (phosphine oxide and quinoxalin-2-one) can deactivate the excited state of Eosin B.



Scheme 59. Mechanistic proposal for the direct C-3 phosphinylation of quinoxalin-2-ones using visible-light.

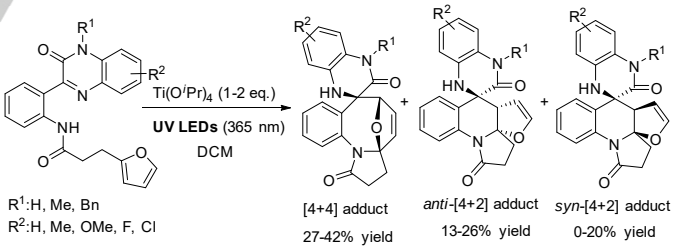
5. Photocycloadditions of quinoxalin-2-ones

Photocycloaddition reactions enable a versatile and straightforward access to carbocyclic or heterocyclic organic compounds.[78] In this context, the photochemical reactions of compounds containing the C=N double bond have been extensively investigated. However, there are very few reports of photocycloadditions using quinoxalin-2(1*H*)-one derivatives and require highly energetic UV light. Nishio, in 1984, described an interesting [2+2] photocycloaddition of a series quinoxalin-2(1H)-ones with five electron-deficient olefins (acrylonitrile, methacrylonitrile, methyl acrylate, methyl methacrylate and vinyl acrylate).[79] The irradiation of quinoxalines at 300 nm (High Pressure Hg lamp) in the presence of the electron-poor olefins using benzene or a mixture of MeOH:DCM as solvent, depending on the solubility of the substrates, affords the corresponding [2+2] cycloadducts with good yields 41-100%, excellent regioselectivity but poor diastereoselectivity (dr 1:1) (Scheme 60). The author tested different reaction conditions in order to study the mechanism. For example, the formation of the cycloadducts decreased in the presence of O_2 and was completely suppressed in the presence of *trans*-stilbene (a triplet quencher). Moreover, the isolated yields of the products were constant when the reaction was conducted in the presence of a series of triplet sensitizers such as acetone and 1-(3-methoxyphenyl)ethan-1-one. These experiments suggest that this [2+2] photocycloaddition may take place from the excited state of quinoxalin-2-one. While the author explains the excellent regioselectivity and the poor diastereoselectivity, by the interaction of the triplet of the quinoxalin-2-one with the electron poor olefin, affording a 1,4-biradical intermediate, which cyclizes to give the final cylcoadducts. In 1987, he also described the photocycloadditions of quinoxalin-2-ones with aryl alkenes, obtaining the corresponding azetidines with low to good yields *via* [2+2]cycloaddition of the carbon-nitrogen double bond and the alkene double bond.[80]



Scheme 60. [2+2] cycloaddition of quinoxalin-2-ones with electron-poor olefins enabled by UV light (Nishio, 1984.

In 2015, Kutateladze and coworkers, reported an intramolecular photocycloaddition using 3-substituted-quinoxalin-2-one to prepare complex spiro-polyheterocycles bearing a quinoxalin-2-one moiety under UV LEDs irradiation (365 nm).[81] In this case, the reaction is not very selective and [4+4], *anti*-[4+2] and *syn*-[4+2] adducts are observed in the majority of the cases (Scheme 61), however the complexity of the molecules is impressive. The authors observed that the photocyclization was accelerated in the presence of 1-2 equivalents of $Ti(O^iPr)_4$ as Lewis acid. In some cases, the authors did not report the *syn*-[4+2] adducts due to the difficulty of their isolation. Although this photoreaction is not very selective, affords highly complex *N,O*-heterocycles with two spiro-connected nitrogen heterocyclic moieties, making this methodology significant for developing very complex three-dimensional molecular architectures in only one reaction step.

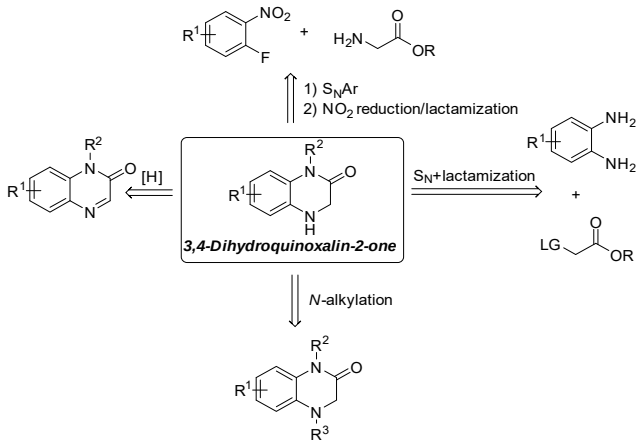


Scheme 61. Intramolecular photochemical-enabled cycloadditions of quinoxalin-2-one-related molecules (Kutateladze, 2015).

6. Functionalization of dihydroquinoxalin-2-ones

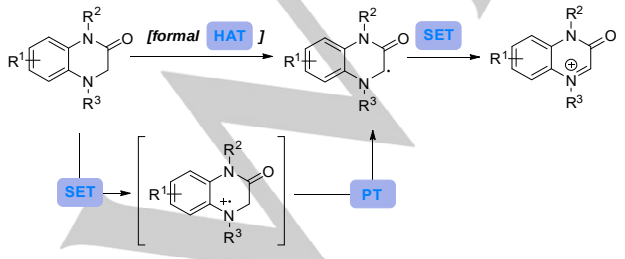
Among the possibilities of derivatization of quinoxalin-2-ones, the reduction of the C=N double bond leading to 3,4-dihydroquinoxalin-2-ones launches a new opportunity paradigm in photochemical-enabled chemical transformations. There are more synthetic aproaches towards 3,4-dihydroquinoxalin-2-ones (Scheme 62), for example the two-step route based on a nucleophilic aromatic substitution of the corresponding 2-fluoronitrobenzene with an alkyl glycinate derivative and a successive nitro reduction followed by a spontaneous

lactamization. The last main strategy en route to 3,4-dihydroquinoxalin-2-ones is the direct nucleophilic substitution/lactamization of 1,2-benzenediamines with alkyl acetates bearing a leaving group in its α position. This approach is only convenient when symmetric 1,2-benzenediamines are employed. Additionally, 3,4-dihydroquinoxalin-2-ones can in turn be derivatized through *N*-alkylation of the anilinic nitrogen with alkyl halides (or other alkylating agents) or with aldehydes under reductive amination conditions.



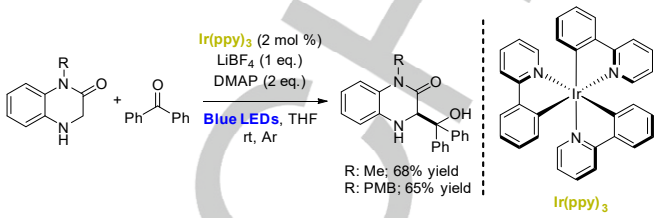
Scheme 62. The three main synthetic approaches to 3,4-dihydroquinoxalin-2-ones and further derivatization of them.

As previously mentioned, 3,4-dihydroquinoxalin-2-ones offer new opportunities in photocatalysis, manly at the methylene group. The electron transfer processes involving electron-rich amines by means of visible-light photocatalysis have been intensely studied since the last decade.[82] In this context, 3,4-dihydroquinoxalin-2-ones could be suitable substrates to be engaged in this kind of light-assisted transformations. According to reported studies, the synthetic abilities of these amines can be tuned depending on the reaction conditions. Specifically, Single-Electron Oxidation of 3,4-dihydroquinoxalin-2-one may lead to the formation of the corresponding α-amino radical through a SET and a PT (formally a HAT). This highly reactive specie can react as a nucleophile but generally, if an oxidant is present, another Single-Electron Oxidation may take place to form a more stable C=N double bond (imine if the starting amine was secondary or an iminium cation if the starting amine was tertiary) due to its conjugation with both the carbonyl and the aromatic ring, that can now react as an electrophile (Scheme 63).



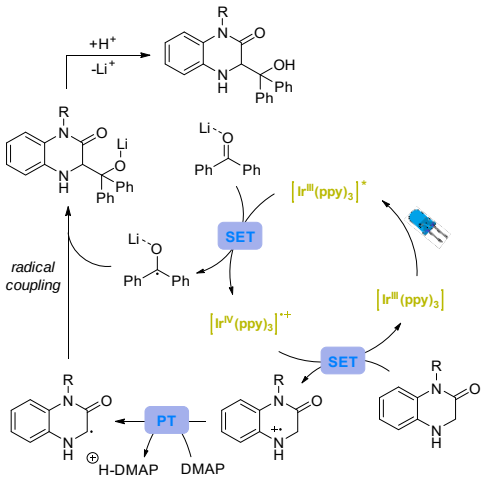
Scheme 63. Electron Transfer events in 3,4-dihydroquinoxalin-2-ones.

In 2016, the researchers from the group of Xiao were able to generate the α-amino radical of 3,4-dihydroquinoxalin-2-one (among other amines) using *fac*-Ir(ppy)$_3$ as photocatalyst.[83] They reported just two examples in which this radical was coupled with benzophenone through its lithium-bonded ketyl radical (Scheme 64).



Scheme 64. 3,4-Dihydroquinoxalin-2-one radical coupling with benzophenone under visible-light photoredox catalysis (Xiao, 2016).

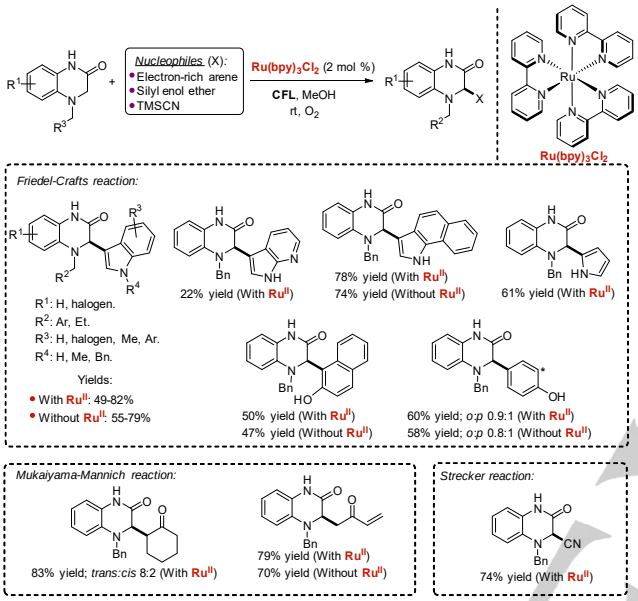
These researchers were also capable of proposing a mechanistic pathway by which its developed reaction should proceed. However, they performed all the mechanistic investigations using ethyl *N*-*p*-tolyl glycinate as model substrate, and its behaviour compared to 3,4-dihydroquinoxalin-2-one could be different. Considering the strong fluorescence emission quenching of *fac*-Ir(ppy)$_3$ by benzophenone, upon coordination of Li(I), the ketone suffers a SET with the excited state of *fac*-Ir(ppy)$_3$, enabling the formation of the corresponding lithium-bonded ketyl radical, along with Ir(IV). This highly oxidant form of the photocatalyst can abstract an electron from the aminic nitrogen of 3,4-dihydroquinoxalin-2-one through a SET, which after deprotonation gives the corresponding α-amino *C*-centered radical. Finally, the coupling between the two *C*-centered radicals furnishes the desired product (Scheme 65).



Scheme 65. Mechanistic proposal for the radical coupling between 3,4-dihydroquinoxalin-2-one and benzophenone..

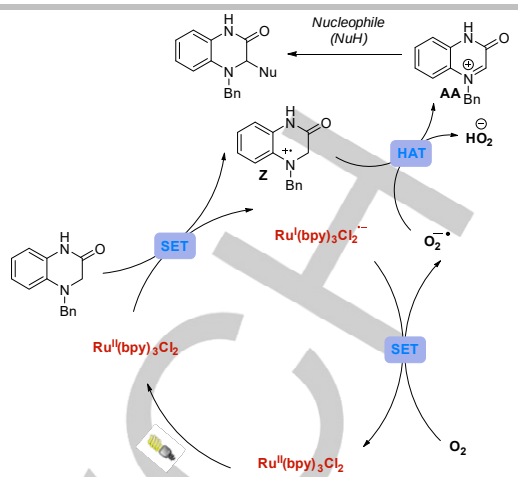
Two years later, Hong and collaborators developed a protocol in which 4-alkyl-3,4-dihydroquinoxalin-2-ones were two-electron oxidized to iminium cation.[84] This highly reactive intermediate was efficiently trapped by a large number of carbon nucleophiles, that can be classified in electron-rich arenes (Friedel-Craft

reaction), silyl enol ethers (Mukaiyama-Mannich reaction) and TMSCN (Strecker reaction). They realized that the reaction could proceed without the need of a photocatalyst, albeit with lower performance than with $Ru(bpy)_3Cl_2$. In fact, they observed that, when they mixed 4-benzyl-3,4-dihydroquinoxalin-2-one with indole, an absorption band around 400 nm appeared, suggesting the formation of a visible-light-absorption complex. They could obtain a broad collection of C-3 functionalized 3,4-dihydroquinoxalin-2-ones bearing multiple substitution patterns in moderate to good yields. In some cases, the photocatalytic methodology was compared with the reaction without $Ru(bpy)_3Cl_2$ (Scheme 66).



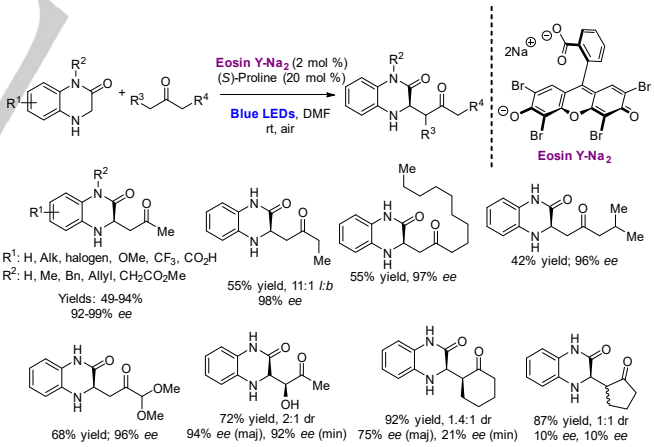
Scheme 66. C-3 functionalization of 3,4-dihydroquinoxalin-2-ones with several nucleophiles enabled by visible light (Hong, 2018).

According to the authors, the Ru^{II}-based photocatalyst is promoted to its excited state through the absorption on visible-light. Then, this highly oxidant specie can abstract an electron from the tertiary nitrogen of 3,4-dihydroquinoxalin-2-one through a SET to afford radical cation **Z**, which can be further oxidized by the action of superoxide radical anion (formed by O_2 oxidation of Ru^{I}) to finally produce the iminium cation **AA**. The last step would be the trap of this electrophilic intermediate **AA** by an electron-rich arene, a silyl enol ether or TMSCN (Scheme 67). The photocatalyst-free mechanism is not showed in Scheme 67 but, according to the authors, it is enabled by the photosensitization of triplet O_2, that is facilitated by either the starting 3,4-dihydroquinoxalin-2-one or the final product upon the absorption of visible-light.



Scheme 67. Possible mechanistic pathway for the functionalization of 3,4-dihydroquinoxalin-2-ones with several nucleophiles under photoredox conditions.

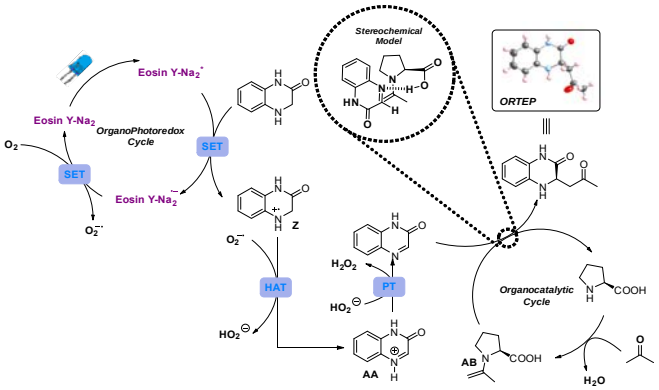
In 2019, our research group developed a *one-pot* methodology for the enantioselective Mannich reaction between 3,4-dihydroquinoxalin-2-ones and ketones by combining organophotoredox catalysis and organocatalysis.[85] After the optimization process, we realized that Eosin Y-Na_2 and (*S*)-Proline were the best photocatalyst and organocatalyst, respectively. Using this couple of catalysts, along with DMF as solvent, we could prepare twenty-two differently substituted 3,4-dihydroquinoxalin-2-ones with several ketones in good to high yields and excellent enantioselectivities (up to 99% ee) (Scheme 68).



Scheme 68. Asymmetric Mannich reaction of 3,4-dihydroquinoxalin-2-ones with ketones under photoredox/organocatalysis (Pedro and Vila, 2019).

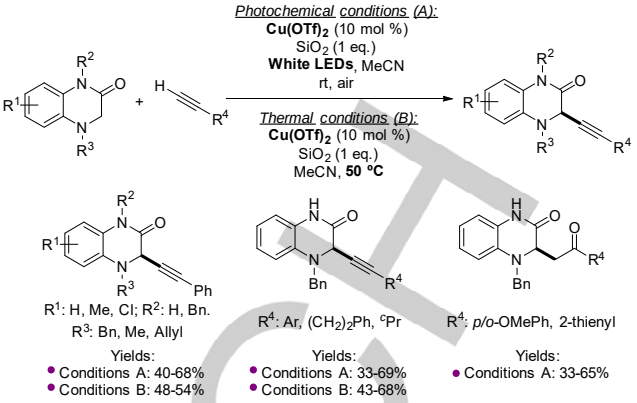
After conducting the canonical control experiments, and based on the strong fluorescence emission quenching of Eosin Y in the presence of 3,4-dihydroquinoxalin-2-one, we postulated that the excited state of Eosin Y must be deactivated by 3,4-dihydroquinoxalin-2-one through a SET. The resulting radical cation **Z** must be converted to protonated quinoxalin-2-one (**AA**) via a HAT with superoxide anion. After deprotonation, quinoxalin-2-one can be alkylated in an enantioselective manner by the chiral

enamine **AB**, that is formed through a condensation between acetone (or the corresponding ketone) and (*S*)-Proline. The stereogenic assignation of the chiral center was established by means of X-Ray Crystallography as well as by theoretical models (Scheme 69).



Scheme 69. Mechanistic proposal for the asymmetric Mannich reaction of 3,4-dihydroquinoxalin-2-ones with ketones.

In early 2020, our research team also reported the alkynylation of 3,4-dihydroquinoxalin-2-ones enabled by copper catalysis.[86] In this work, a comparison between thermal and photochemical conditions in the performance of the alkynylation reaction was carried out. The ability of copper species to activate terminal alkynes through the formation of the corresponding copper alkynylide is well known. Additionally, amines can also be oxidized towards the iminium cation by the action of copper, in combination with a stochiometric oxidant. Regarding the studied transformation, our experiences showed a noticeable increase in the yield (from 51% to 68%) of the desired product when the reaction mixture was also irradiated with White LEDs, but the role of visible-light was not established. However, we were able to obtain a family of 3-ethynyl-3,4-dihydroquinoxalin-2-ones in moderate to good yields using several terminal alkynes, $Cu(OTf)_2$ as catalyst and SiO_2 as an additive (Scheme 70). In this transformation, Cu^{II} plays a dual role: it can activate the terminal alkyne and is also capable of acting as a redox mediator between 3,4-dihydroquinoxalin-2-one and O_2 towards the electrophilic 3,4-dihydroquinoxalin-2-one iminium cation. Considering that the role of the visible-light is not fully understood and that the key feature of the reaction pathway is the Cu^{II}/Cu^{I} redox system, the mechanism of this transformation is out of the scope of this review.



Scheme 70. Copper catalyzed alkynylation of 3,4-dihydroquinoxalin-2-ones with terminal alkynes (Pedro and Vila, 2020).

7. Conclusions

In summary, in this review we have presented an overview of the direct visible-light photoredox functionalization of quinoxalin-2(1*H*)-one derivatives that have been reported in the last years. Several successful photoredox catalytic methodologies have been described using very mild conditions, including alkylation, trifluoroalkylation, arylation, acylation, etherification, thioetherification, amination and phosphinylation, using simple molecular oxygen as a final oxidant. Different chemical procedures using photoredox catalysts such as polypyridyl metal complexes, organophotocatalyst, heterogeneous photocatalyst, and even catalyst-free have been detailed. These new methodologies have provided a powerful tool for the incorporation of different functional groups at the C3 position of quinoxalin-2(1*H*)-ones broadening the versatility of these *N*-heterocycles, particularly important in the areas of pharmaceutical and medicinal chemistry. However, the visible-light photocatalytic formation of C–Se or C-X bonds at the C3 position of quinoxalin-2(1*H*)-ones have not been described, although developing these protocols will extend the synthetic possibilities for the functionalization of these nitrogen heterocycles. We hope that this review will serve as a handy reference for synthetic chemists interested in developing new protocols for the functionalization of quinoxalin-2-one heterocycles using visible-light photoredox catalysis.

Acknowledgements ((optional))

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Keywords: quinoxalin-2-ones • visible-light photocatalysis • radicals • synthetic methods • photoredox catalysis

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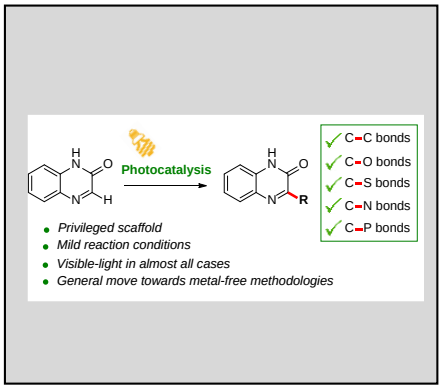

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Quinoxalin-2(1*H*)-one is an important class of nitrogen heterocycle in medicinal and pharmaceutical industry that in recent years have become a synthetic target in organic chemistry. This review covers the recent advances in the functionalization of this particular nitrogen heterocycle through photocatalysis.

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