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Catalytic Nucleophilic and Electrophilic Functionalization of Dihydroquinoxalin-2-ones

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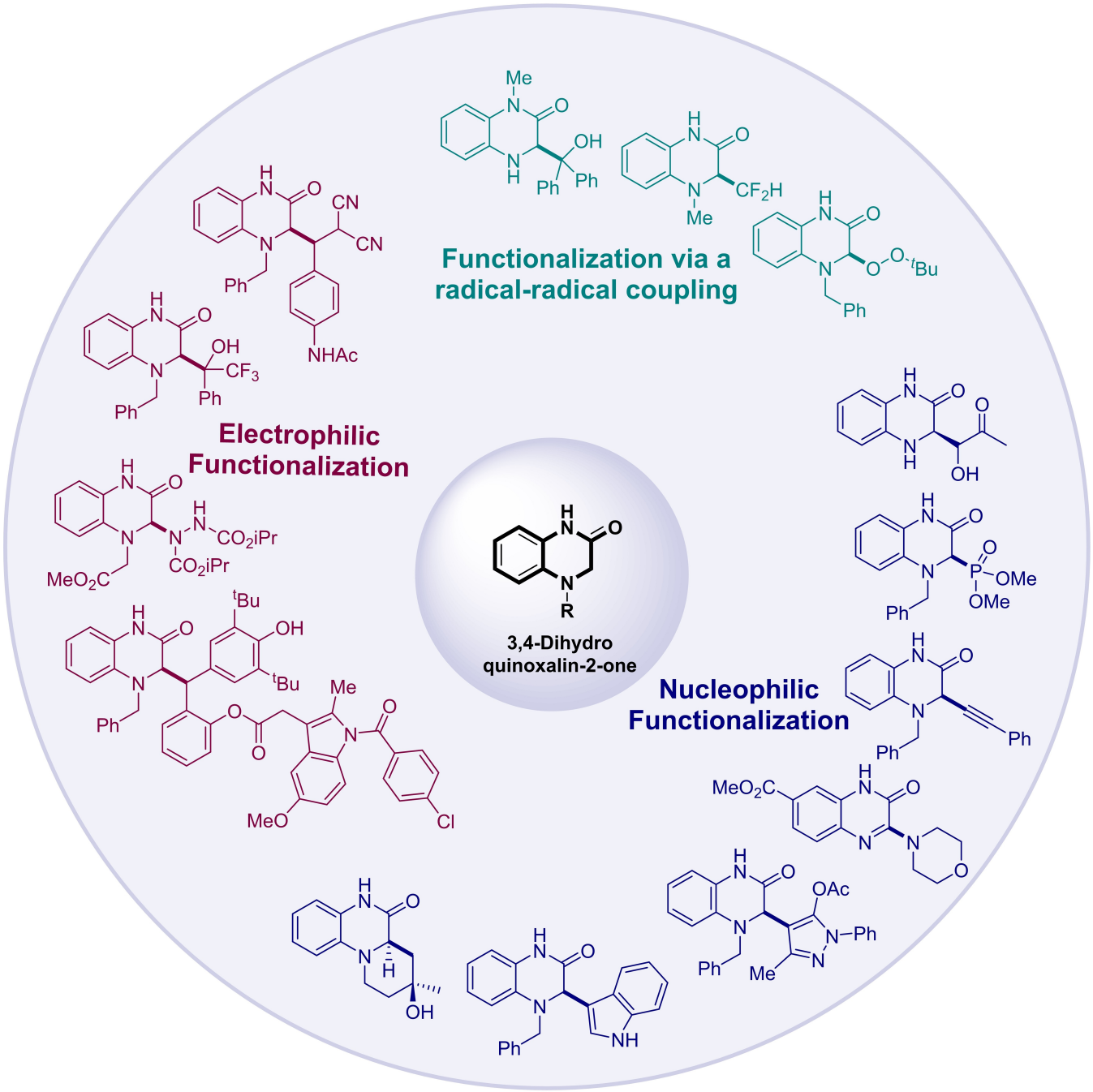

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1. Introduction

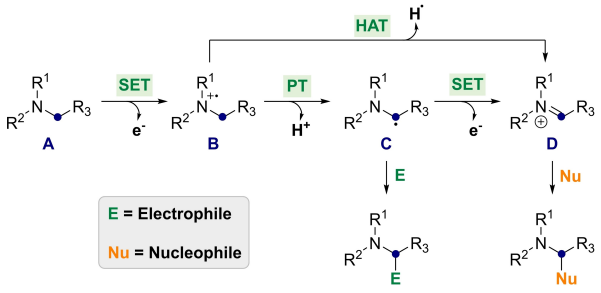
Organic amines are widely considered as key compounds in a myriad of research fields due to its ubiquitous presence in many synthetic, pharmaceutical and natural products.[1] Consequently, the scientific community has made great effort in seeking ways to prepare these compounds and how to modify them as well. In this context, the functionalization of organic amines at their α position was readily identified as a key tool, due to the fact that these substrates can participate in electron transfer events taking advantage of the electron-rich nature of the nitrogen.

Precisely, a given amine **A** can suffer a Single Electron Transfer (SET) in the presence of a proper single-electron oxidant to form the nitrogen-centered radical cation **B** (Scheme 1). Once this radical species is generated, the acidity of its α-hydrogens experience a significant increase, as demonstrated by Tilset in 1991.[2] This phenomenon makes radical cation **B** more prone to deprotonation, allowing the generation of α-amino radical **C**. This radical intermediate **C** can participate in different radical-radical coupling reactions as well as in several nucleophilic additions, given the remarkable nucleophilicity granted by the presence of the nitrogen.[3] Nevertheless, as a very reactive intermediate it can suffer another SET to yield iminium cation **D**, which exhibits electrophilicity. Alternatively, iminium cation **D** can be generated through a Hydrogen Atom Transfer (HAT) from radical cation **B**, as the dissociation energy of the α-hydrogen diminishes compared to that of amine **A**, according to a study made by Dinnocenzo.[4]

On the other hand, 3,4-dihydroquinoxalin-2-ones are a particular and interesting class of nitrogen heterocycles, that recently have focused the attention of synthetic organic chemists for developing different derivatizations due to its relevance in many areas of interest such as medicinal, pharmaceutical and material science.[5] For example, the skeleton of 3,4-dihydroquinoxalin-2-one can be found in several natural-occurring or synthetic biologically-active compounds. In fact, some studies have revealed the importance of this heterocyclic system to achieve interesting pharmacological activities.[6] Examples of biologically active 3,4-dihydroquinoxalin-2-ones can be found in Figure 1.

With the aim of boosting drug discovery, it is more convenient to expand the chemical diversity of 3,4-dihydroquinoxalin-2-one containing candidates from a common precursor, instead of procuring a desired chemical library through the *de novo* synthesis of the heterocycle. Thus, the development of different synthetic methodologies to directly functionalize the architecture of 3,4-dihydroquinoxalin-2-one is highly desirable.

In this *Concept*, we want to collect the efforts of many researchers around the world working in the direct functionalization of 3,4-dihydroquinoxalin-2-ones at its C-3 position. Although there are many contributions in this sense since 2016, we were confident enough that the interest of the scientific community in this kind of heterocycles will grow and more elegant approaches will be developed. Throughout these lines, the existing protocols for the catalytic functionalization of 3,4-dihydroquinoxalin-2-ones will be presented and discussed. Thus, the main aim of this *Concept* is to provide a starting point



Scheme 1. General mechanisms for the α-functionalization of tertiary amines under electron-transfer events.

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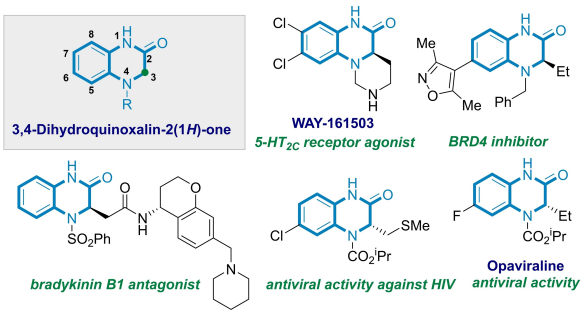
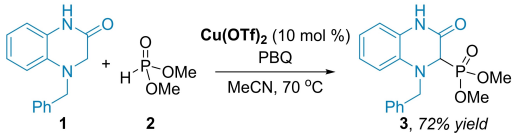


Figure 1. Biologically active 3,4-dihydroquinoxalin-2-ones.

for the development of potential synthetic methodologies for the functionalization of these nitrogen heterocycles. As posed earlier, 3,4-dihydroquinoxalin-2-ones, like many other amines, can be engaged in different single-electron events with the aim of forming a reactive intermediate.[7] Consequently, by modulating the reaction conditions, one can form the corresponding electrophilic iminium cation, which must react with a nucleophilic counterpart. On the other hand, if the intermediate generated is an α-amino radical, it can react with either an electrophile or another radical species. Henceforth, we have divided this exposition depending on the nature of the reaction counterpart in nucleophilic functionalization, electrophilic functionalization and functionalization via a radical-radical coupling.

2. Nucleophilic functionalizations

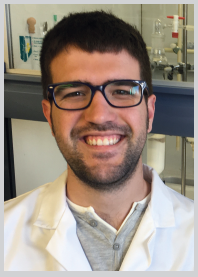
The formation of an electrophilic carbon atom at C-3 can be addressed through the oxidation of the amine to an imine (if the amine is secondary) or to an iminium cation (if the amine is tertiary). The first example of this strategy was reported by the laboratory of Huo in 2018 (Scheme 2).[8] In this case, the researchers resorted to $Cu(OTf)_2$ as single electron oxidant to generate the iminium cation of 4-benzyl-3,4-dihydroquinoxalin-2-one **1**. Cu(II) species were further recovered by the assistance of *p*-benzoquinone (PBQ) as stoichiometric oxidant. The selected nucleophile was dimethyl phosphite (**2**), obtaining just one example of phosphonylated 3,4-dihydroquinoxalin-2-one **3**



Scheme 2. Cu-catalyzed phosphonylation of 3,4-dihydroquinoxalin-2-one (Huo, 2018).

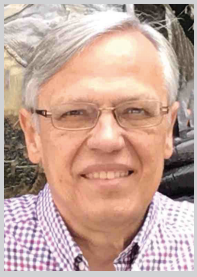
in 72% yield. Regarding the mechanism, Cu(II) salt oxidizes 3,4-dihydroquinoxalin-2-one to the corresponding radical cation, which evolves until the formation of the electrophilic iminium cation by the assistance of PBQ as oxidant to regenerate Cu(II) and as hydrogen atom acceptor and base. The nucleophilic addition of the deprotonated phosphite to the iminium cation forms the expected product.

In the same year, the laboratory of Hong used visible-light photoredox catalysis to generate the electrophilic iminium cation of 3,4-dihydroquinoxalin-2-ones **1** (Scheme 3). Specifically, they employed $Ru(bpy)_3Cl_2$ in combination with visible light (with a household 24 W compact fluorescent plug-in light (CFL) bulb) to form the abovementioned electrophile after two single electron oxidations, with the assistance of molecular oxygen from air as terminal oxidant.[9] The catalytically-generated electrophile was subjected to an *aza*-Friedel-Crafts reaction with different indoles and electron-rich phenols. Moreover, the authors were also pleased to engage different silicon



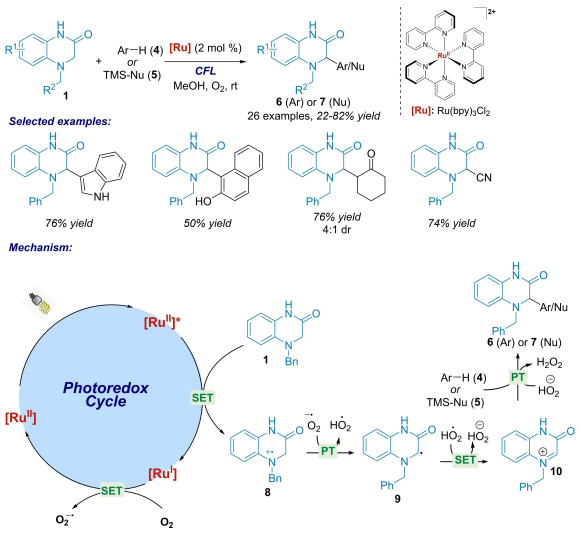
Jaume Rostoll-Berenguer graduated in chemistry (2017) and received his Master's degree in Organic Chemistry (2018), both from the University of València. In 2022, he got his PhD focused on the functionalization of amines using visible-light photocatalysis at the same University under the supervision of Dr. Carlos Vila and Prof. Dr. José Ramón Pedro. Since 2023, he is postdoctoral researcher at the University of Genève (Switzerland) in the laboratory of Prof. Clément Mazet, working in the synthesis of transition-metal complexes for organic synthesis.

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 was the Director of the Research Group on asymmetric catalysis with metal complexes and organocatalysts at the University of València (AsymCat, GIUV2013-125) until 2022. He is currently Professor Emeritus.

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, University of Valencia. His current research interests are asymmetric catalysis and photocatalysis.



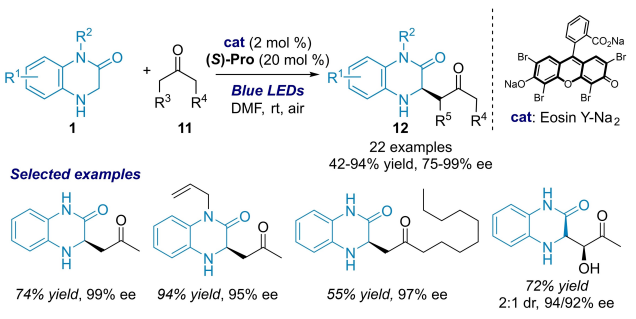
Scheme 3. Photoredox-catalyzed oxidative functionalization of 3,4-dihydroquinoxalin-2-ones with electron-rich arenes and silicon nucleophiles (Hong, 2018).

nucleophiles (such as silyl enol ether or TMS-CN) in the photoredox reaction, obtaining up to 26 examples in total. As mentioned earlier, the mechanism of this transformation involves an initial Single Electron Transfer (SET) between the excited state of $Ru(bpy)_3Cl_2$ and 3,4-dihydroquinoxalin-2-one (**1**) to generate the nitrogen-centered radical cation (**8**), which evolves until the electrophilic iminium cation **10** after a deprotonation and another SET of the α-amino radical **9**.

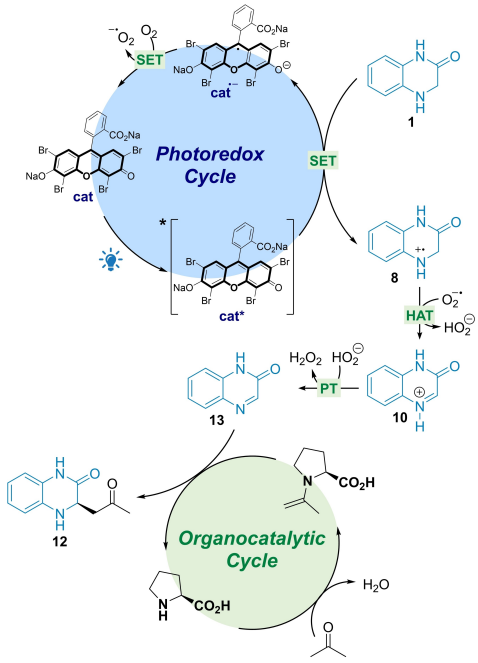
In 2019, our research group inaugurated a portfolio about the development of methodologies based on visible-light photocatalysis for the functionalization of 3,4-dihydroquinoxalin-2-ones. In this report, we were delighted to present an enantioselective organocatalytic oxidative Mannich[10] reaction between 3,4-dihydroquinoxalin-2-ones **1** and ketones **11** using Eosin yellowish as photoredox catalyst and (*S*)-Proline as organocatalyst.[11] The study of the reaction led us to perform the transformation in a sequential one-pot fashion (Scheme 4). Initially, 3,4-dihydroquinoxalin-2-one **1** was oxidized to quinoxalin-2-one by the action of Eosin Y-Na_2, molecular oxygen and Blue LEDs as energy source. Thereafter, the formed imine electrophile was trapped in an enantioselective manner by the chiral enamine formed after the condensation of (*S*)-Proline and a ketone. This strategy allowed us to generate a library of 22 3,4-dihydroquinoxalin-2-ones **12** with a chiral ketone residue at C-3 in moderate to excellent yields and excellent enantioselectivities. This reaction could be scale-up to 5 mmol using sunlight irradiation.

We also proved the actual interaction between the excited state of Eosin Y-Na_2 and 3,4-dihydroquinoxalin-2-one **1** by means of luminescence quenching experiments, showing that a photoredox cycle is feasible to generate the electrophilic quinoxalin-2-one. With this evidence in hand, we postulated a mechanism for the transformation (Scheme 5). The excited state of Eosin Y-Na_2 triggers a SET with 3,4-dihydroquinoxalin-2-one (**1**), leading to the formation of nitrogen-centered radical cation **8**. Molecular oxygen from air can mediate the regeneration of Eosin Y-Na_2 through another SET, also delivering the superoxide radical anion. Then, a Hydrogen Atom Transfer (HAT) between **8** and superoxide anion furnishes protonated quinoxalin-2-one (**10**), which was readily converted into quinoxalin-2-one (**13**) by the loss of a proton. Finally, the reaction between quinoxalin-2-one (**13**) and the chiral enamine from (*S*)-proline and the ketone yields the desired product **12** as an enantioenriched mixture.

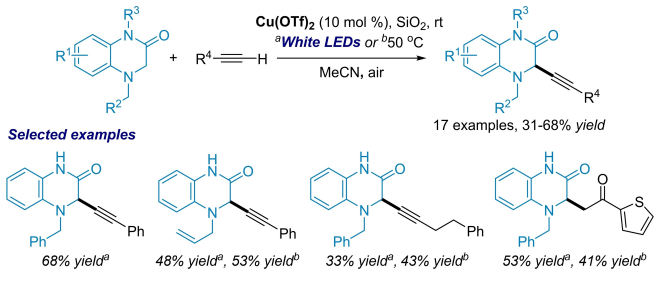
In 2020, our research group reported another strategy to functionalize 3,4-dihydroquinoxalin-2-ones at C-3 (Scheme 6).[12] This time, we resorted to Cu(II) catalysis with a twofold purpose: generate the iminium cation of 3,4-dihydroquinoxalin-2-one in the presence of oxygen and activate the terminal alkyne through its copper alkynylide in order to act as nucleophile. We confirmed that the reaction did not require the irradiation with visible light, but its performance was slightly better when this



Scheme 4. Asymmetric oxidative Mannich reaction between 3,4-dihydroquinoxalin-2-ones and ketones (Pedro and Vila, 2019).



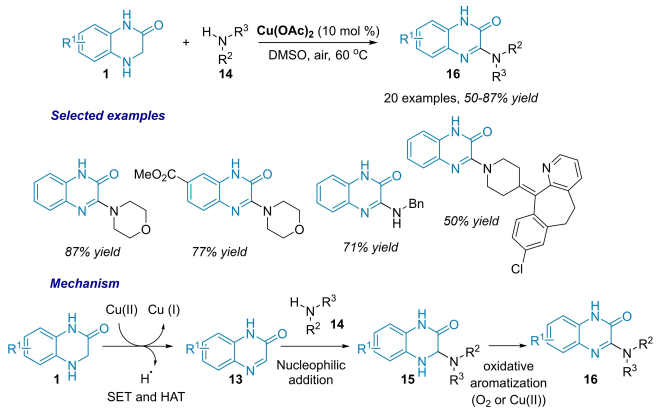
Scheme 5. Mechanism for the asymmetric oxidative Mannich reaction between 3,4-dihydroquinoxalin-2-ones and ketones.



Scheme 6. Alkynylation of 3,4-dihydroquinoxalin-2-ones with terminal alkynes under copper catalysis (Pedro and Vila, 2020).

transformation was carried out under white light. Additionally, we also proved that heating the reaction mixture to 50 °C in the dark led to the formation of the desired product in comparable outcome. With these conditions we synthesized a small library of 17C-3-alkynylated 3,4-dihydroquinoxalin-2-ones in 31 to 68% yield. Interestingly, when electron-rich terminal alkynes were employed as pronucleophiles, we did not obtain the alkynylated product but corresponding the ketone, presumably formed after the hydration of the triple bond.[13]

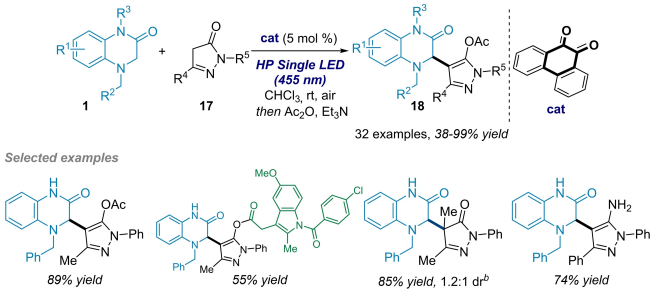
The laboratory of Huo extended its research in this field with its report on the amination of 3,4-dihydroquinoxalin-2-ones catalyzed by Cu(II) (Scheme 7).[14] In this case, the *N*-4-unprotected 3,4-dihydroquinoxalin-2-ones **1** reacted with different primary and secondary amines **14** in the presence of $Cu(OAc)_2$ under an air atmosphere. However, the formed aminated 3,4-dihydroquinoxalin-2-one **15** was reoxidized to form the expected aminated quinoxalin-2-one **16**. With these conditions, the authors were able to obtain up to 20 examples in yields between 50% and 87%. As mentioned earlier, copper can act as a redox mediator in the oxidation of 3,4-dihydroquinoxalin-2-ones in the presence of a terminal oxidant (molecular oxygen in this case). Consequently, according to the authors, 3,4-dihydroquinoxalin-2-one **1** is oxidized to the corresponding quinoxalin-2-one **13**. Now, the amine reacts with the electrophilic C=N bond to form the aminated 3,4-dihydroquinoxalin-2-one intermediate **15**, which is oxidized again to form the final C-3-aminated quinoxalin-2-one (**16**).



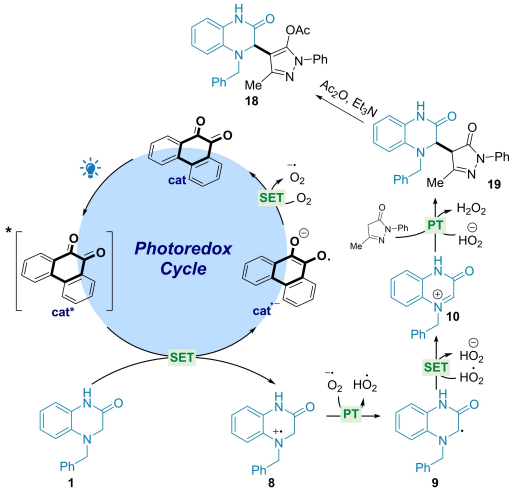
Scheme 7. Copper-catalyzed amination of 3,4-dihydroquinoxalin-2-ones leading to aminated quinoxalin-2-ones (Huo, 2021).

In 2022, our research group reported the reaction between 4-substituted-3,4-dihydroquinoxalin-2-ones **1** and pyrazol-3-ones **17** under photoredox conditions (Scheme 8).[15] After the optimization process, we realized that the best photocatalyst to conduct this transformation was 9,10-phenanthrenedione due to its high performance, its cost and the simplicity of the process.[16] To aid isolation and characterization of the product, it was crucial to perform an acetylation of the enolate using acetic anhydride once the photochemical reaction was complete. With this protocol, we prepared 32 3,4-dihydroquinoxalin-2-ones **18** bearing a pyrazole unit at C-3 in 38–99% yield. Moreover, this reaction was found to be quite a bit general since we were able to use 4-substituted-pyrazol-3-one, which in its reaction with 3,4-dihydroquinoxalin-2-one lead to the corresponding product with a quaternary carbon center. Besides, 5-aminopyrazoles were also competent substrates for our protocol.

Concerning the mechanism, 4-benzyl-3,4-dihydroquinoxalin-2-one (**1**) gets oxidized to its nitrogen-centered radical cation **8** by the action of excited 9,10-phenanthrenedione (**cat**) via a SET (Scheme 9). As usual in this kind of reactivity,



Scheme 8. Reaction between 3,4-dihydroquinoxalin-2-ones and pyrazol-3-ones under photoredox catalysis (Pedro and Vila, 2022).



Scheme 9. Mechanism for the reaction between 3,4-dihydroquinoxalin-2-ones and pyrazol-3-ones.

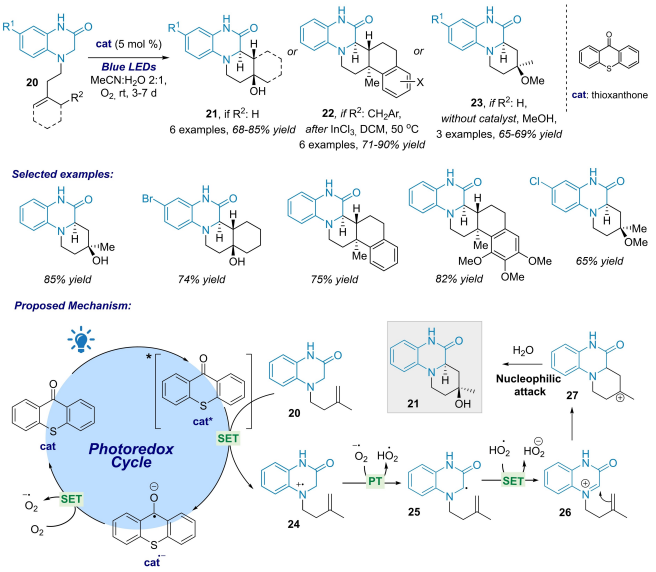
molecular oxygen regenerates 9,10-phenanthrenedione (**cat**) via another SET. Radical cation **8** evolves to iminium cation **10** via its α-amino radical **9** and after a proton transfer and another SET. The nucleophilic addition reaction between the pyrazol-3-one and the iminium cation **10** furnishes product **19**, whose enolate was captured through an acetylation to give product **18**.

To conclude the reports about the nucleophilic functionalization of 3,4-dihydroquinoxalin-2-ones, it is interesting to mention the work from the laboratory of Hong in 2022 (Scheme 10).[17] In that work, the authors built a 3,4-dihydroquinoxalin-2-one bearing an aliphatic substituent at the *N*-4 position that also have a C=C double bond. Using photoredox catalysis, they accessed the corresponding iminium cation of these sophisticated 3,4-dihydroquinoxalin-2-ones, causing the intramolecular reaction through a nucleophilic addition of the electron-rich double bond to the C=N bond using thioxanthone[18] as photocatalyst under oxygen atmosphere. Additionally, since the reaction was performed in the presence of water, a hydroxyl group was also incorporated at the γ position. Complementarily, after the cyclization, some substrates bearing a benzylic substituent experienced a further cyclization upon treatment with $InCl_3$. Moreover, in the absence of a photocatalyst, under an oxygen atmosphere, if dihydroquinoxalin-2-one derivative was irradiated in methanol for 3.5 h a polycyclic compound was obtained in good yield. In total, the authors reported 15 polycyclic 3,4-dihydroquinoxalin-2-ones with interesting molecular architecture. Regarding the mechanism to obtain the alcohols, 4-substituted-3,4-dihydroquinoxalin-2-one (**20**) gets oxidized via SET to its nitrogen-centered radical cation **24** by the action of the thioxanthone (**cat**). As usual in this kind of reactivity, molecular oxygen regenerates the photocatalyst via another SET. The iminium cation **26** is formed from the radical cation **25** through a proton transfer and another SET. The intramolecular nucleophilic addition of the C=C double bond to this iminium cation generates intermediate **27**, which can be captured by water affording product **21**. For the reaction in the absence of the photocatalyst, the authors propose that blue LED-light irradiation gradually excites the dihydroquinoxalin-2-one, which acts as a photosensitizer.

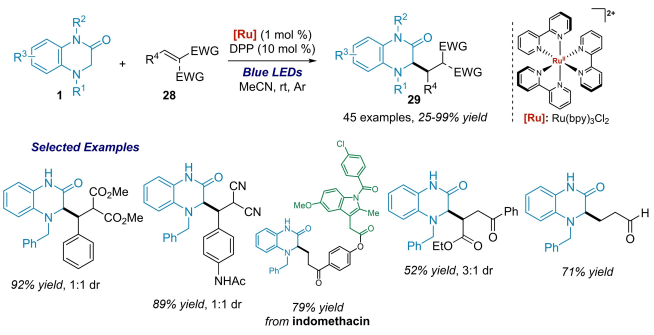
3. Electrophilic functionalizations

The generation of a nucleophilic position at C-3 often requires the formation of a carbon-centered radical (Scheme 11). In the specific case of 3,4-dihydroquinoxalin-2-ones, this potential organic radical has both an electron-donating group (the tertiary amine) as well as an electron-withdrawing group (the carbonyl) at the adjacent positions, conferring a superior stability and reactivity to this open shell intermediate. In 2020, our research group decided to embark on the generation of this particular α-amino radical of 3,4-dihydroquinoxalin-2-one **1** using photoredox catalysis for the 1,4-radical addition to electron poor olefins **28**.[19,20] We selected benzylidene malonates as competent electrophiles to react with the potential carbon-centered radical. After the optimization of the reaction conditions, we realized that the reaction needed the cooperative participation of $Ru(bpy)_3Cl_2$ as photoredox catalyst and diphenyl phosphoric acid (DPP) as cocatalyst. Using these reaction conditions, we were able to generate a broad library of 45 C-3-alkylated 3,4-dihydroquinoxalin-2-ones (**29**) in 29–99% yield, including two relevant examples with substrates bearing biologically relevant scaffolds, such as oleic acid and indomethacin. Furthermore, we could scale-up to a gram scale reaction using sunlight irradiation.

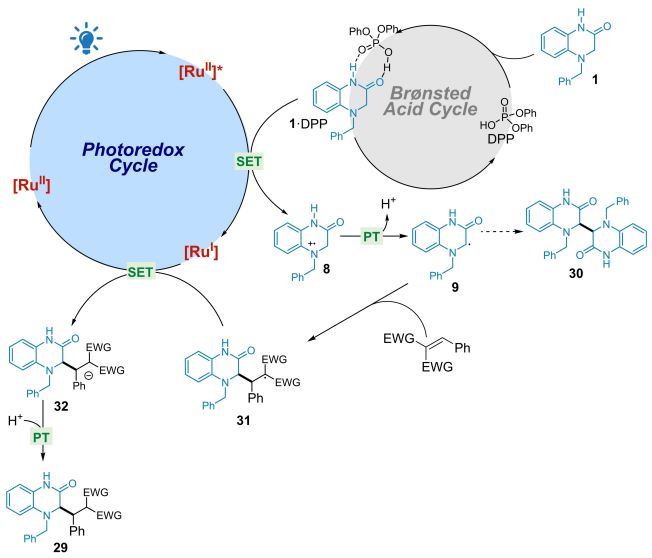
The mechanism of this transformation was deeply studied using different techniques, especially steady-state luminescence quenching, cyclic voltammetry and nuclear magnetic resonance (Scheme 12). Our investigations led us to prove that 4-benzyl-3,4-dihydroquinoxalin-2-one **1** is not able to quench the excited state of $Ru(bpy)_3Cl_2$ by itself, requiring the presence of the DPP to reach the redox potential of $Ru(bpy)_3Cl_2$. Therefore, we postulated that the formation of a cyclic adduct with DPP (**1**·DPP) through two hydrogen bonds is the responsible for



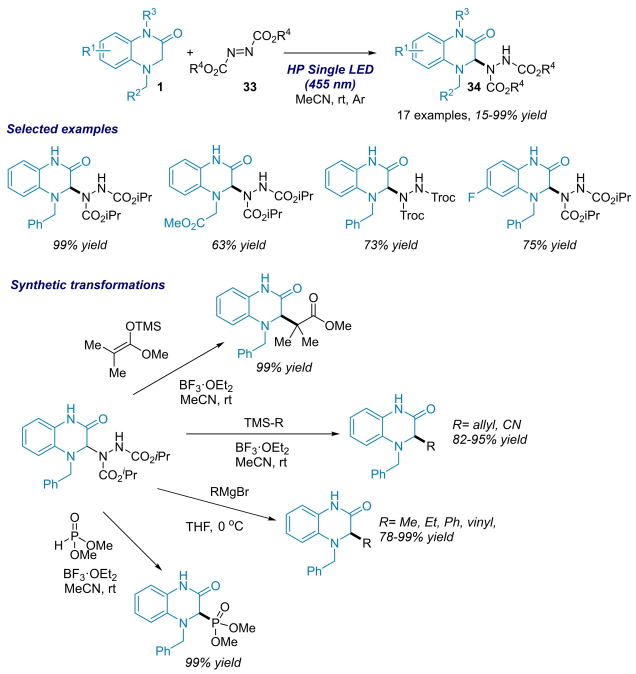
Scheme 10. Construction of polycyclic 3,4-dihydroquinoxalin-2-ones through visible-light photoredox catalysis (Hong, 2022).



Scheme 11. Photochemical Giese reaction between 3,4-dihydroquinoxalin-2-ones and electron-poor alkenes (Pedro and Vila, 2020).



Scheme 12. Mechanism for the Giese reaction between 3,4-dihydroquinoxalin-2-ones and electron-poor alkenes.

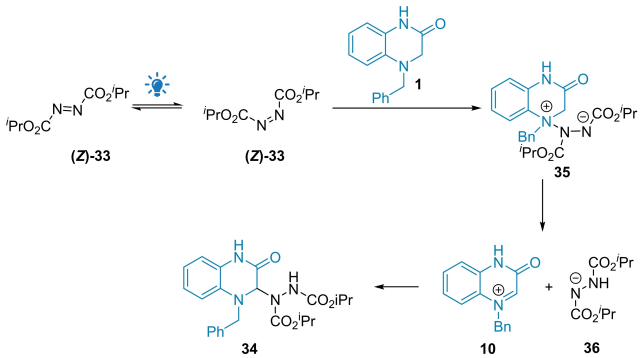


Scheme 13. Amination of 3,4-dihydroquinoxalin-2-ones with dialkyl azodicarboxylates and nucleophilic derivatizations of C-3-aminated 3,4-dihydroquinoxalin-2-one under different reaction conditions. (Pedro and Vila, 2020).

quenching the excited state of the photocatalyst. After the formation of the radical cation **8**, the loss of a proton generates the desired α-amino radical **9**, whose formation was further confirmed by the isolation of dimeric 3,4-dihydroquinoxalin-2-one **30** through C-3. However, the productive pathway includes the nucleophilic conjugate addition to the corresponding electron-poor alkene, leading to the formation of a highly stabilized radical **31**. A final SET with the Ru(I) form of the catalyst and a protonation of the enolate **32** furnished the desired Giese product **29**.

One year later, after developing a practical approach to the generation of the α-amino radical of 3,4-dihydroquinoxalin-2-ones, we decided to extend the scope of this nucleophile with other interesting electrophiles. Consequently, we focused our attention on dialkyl azodicarboxylates (**33**): a particular azo derivatives bearing electrophilic nitrogen atoms due to the presence of two ester groups.[21] The use of these reagents would allow us to form C–N bonds in a very straightforward way. Nonetheless, after conducting the optimization of the reaction conditions, we realized that this reaction did not require the assistance of neither a photoredox catalyst nor DPP. Even though, the irradiation of the reaction mixture with blue light only speeded up the transformation, but it can also proceed in the dark. This simple methodology allowed us to generate a collection of 17 aminated 3,4-dihydroquinoxalin-2-ones (**34**) in 15–99% yield (Scheme 13).[22] Additionally, we took advantage of the lability of this C–N bond under certain reaction conditions to derivatize these aminals with several nucleophiles. Specifically, in the presence of $BF_3{\cdot}OEt_2$, aminated 3,4-dihydroquinoxalin-2-one **35** experienced the nucleophilic addition of different silicon nucleophiles such as a silyl enol ether, TMS-CN and allyl-TMS. Besides, stronger nucleophiles such as Grignard reagents, did not require the presence of $BF_3{\cdot}OEt_2$ to participate in the nucleophilic reaction, allowing us to obtain four additional dihydroquinoxaline derivatives using either MeMgBr, EtMgBr, vinyl-MgBr or PhMgBr. Finally, dimethyl phosphite was also engaged in this derivatization using, again, $BF_3{\cdot}OEt_2$, delivering the expected product bearing a new C–P bond.

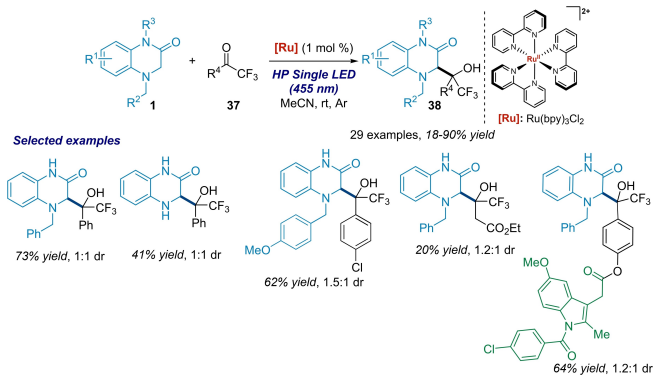
As noted by the reaction conditions, the mechanism of this transformation must be diametrically opposed to that of the Giese reaction (Scheme 14). Since light does not trigger the reaction but increases the rate of the transformation, we attributed this observation to the *E-Z* isomerization of the azo group in (***E***)-**33**, generating the more reactive derivative (***Z***)-**33**. Then a nucleophilic addition of the tertiary amine in 3,4-dihydroquinoxalin-2-one **1** to the electrophilic azo compound (***Z***)-**33** results in the formation of the zwitterionic intermediate



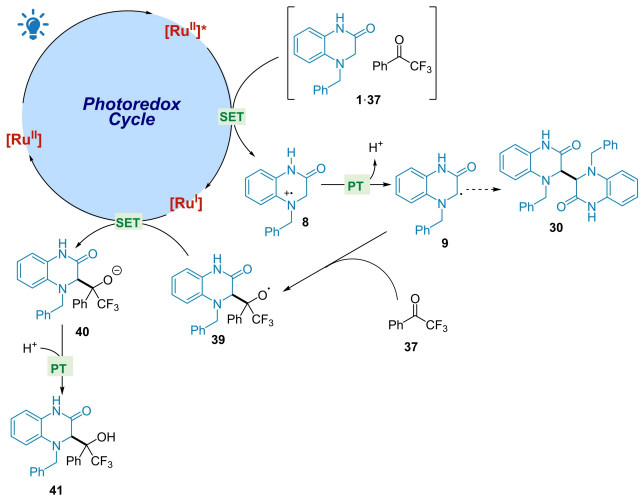
Scheme 14. Mechanism for the C-3 amination of 3,4-dihydroquinoxalin-2-ones with dialkyl azodicarboxylates.

35, which evolves to the formation of iminium cation **10** and deprotonated hydrazine **36**. Finally, a nucleophilic addition of **36** to the electrophilic iminium cation **10** delivered the observed product **34**.

In 2022, after having studied the reaction of 3,4-dihydroquinoxalin-2-ones with 1,4-electrophiles, we decided to step forward and to develop a methodology using 1,2-electrophiles. Instinctively, we focus our attention on trifluoromethyl ketones (**37**), since they have been extensively used in a myriad of polar transformations as electrophiles. However, its use in the context of radical reactions was limited.[23] We confronted 3,4-dihydroquinoxalin-2-one **1** and trifluoroacetophenone **37** under photoredox conditions and, after the optimization process, we selected $Ru(bpy)_3Cl_2$ as the best photocatalyst.[24] With these conditions in hand we investigated the generality of the transformation, resulting in the generation of up to 29 3,4-dihydroquinoxalin-2-ones (**38**) bearing a trifluoromethyl carbinol moiety in 18–90% yield (Scheme 15). In addition, the reaction can be scaled up to 1 mmol using HP Single LED (455 nm) as well as sunlight irradiation.



Scheme 15. Reaction between 3,4-dihydroquinoxalin-2-ones and trifluoromethyl ketones under photoredox conditions (Pedro and Vila, 2022).



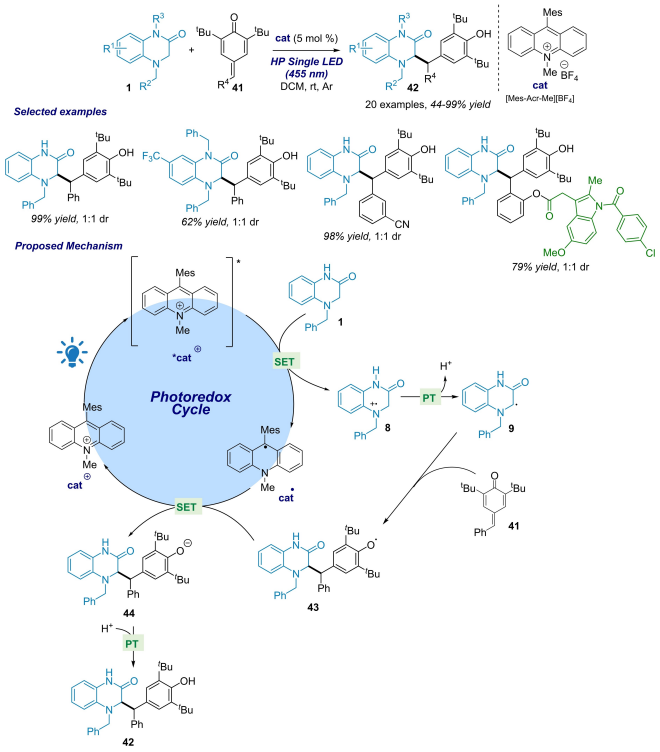
Scheme 16. Mechanism for the radical addition of 3,4-dihydroquinoxalin-2-ones to trifluoromethyl ketones under photoredox catalysis.

As stated earlier, the successful generation of the α-amino radical of 3,4-dihydroquinoxalin-2-one using $Ru(bpy)_3Cl_2$ as photoredox catalyst requires the presence of a Bronsted acid cocatalyst.[20] In this case, the reaction was found to proceed with just $Ru(bpy)_3Cl_2$, revealing another mechanistic pathway to that shown in Scheme 11. After conducting several luminescence quenching experiments, we discovered that an adduct of 4-benzyl-3,4-dihydroquinoxalin-2-one **1** and trifluoroacetophenone **37**, whose structure could not be determined, was the responsible of the quenching of the excited state of $Ru(bpy)_3Cl_2$ (Scheme 16). From here, the evolution of the radical cation **8** to the α-amino radical **9** is known. The radical 1,2-addition to trifluoroacetophenone **37** causes the formation of the corresponding oxygen-centered radical **39**, which was reduced by the Ru(I) form of the catalyst to form the expected alkoxide **40**. Finally, the protonation of this anion yields the expected trifluoromethyl carbinol **38**.

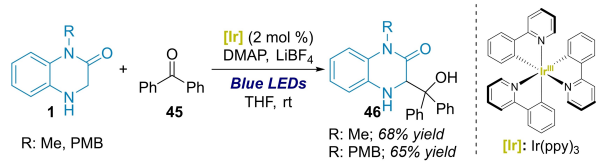
Finally, in early 2023 our research group made the last contribution in the functionalization of 3,4-dihydroquinoxalin-2-ones using photocatalysis. After developing two 1,4-additions and one 1,2-additions, we interrogated the possibility to develop a 1,6-addition of 3,4-dihydroquinoxalin-2-one. Immediately, we identified that *p*-quinone methides (**41**) could be used for this purpose. *p*-Quinone methides can be viewed as α,β,γ,δ-diunsaturated ketones, which are formally accessed by the change of a carbonyl group in *p*-benzoquinone for a trigonal carbon group. The presence of the remaining carbonyl group enables the *p*-quinone methide to exhibit electrophilicity at its δ position, thus permitting 1,6-type nucleophilic addition.[25] However, to prevent easier 1,2- or 1,4-additions, *p*-quinone methides are usually decorated with bulky groups at both α positions. Pleasingly, after the optimization of the reaction conditions we could select [Mes-Acr-Me][BF_4] (the Fukuzumi's catalyst)[26] as the best photocatalyst in terms of efficiency. Using these conditions, we could synthesize 20 products (**42**) bearing a 1,1-diaryl moiety in 44–99% yield (Scheme 17).[27] Regarding the reaction mechanism, the interaction of the excited state form of [Mes-Acr-Me][BF_4] with 4-benzyl-3,4-dihydroquinoxalin-2-one **1** was proven by luminescence quenching experiments, suggesting that the first SET may occur between these two species (Scheme 17). Then, the resulting nitrogen-centered radical cation **8** experiments a deprotonation to generate α-amino radical **9**, which is able to react with *p*-quinone methide (**41**) in a 1,6-fashion to form the expected oxygen-centered radical **43**. As usual, another SET from the reduced photocatalyst provokes the formation of alkoxide **44**, which protonation finally furnishes the observed product **42**.

4. Functionalizations via a radical-radical coupling

An α-amino radical can also participate in radical-radical coupling transformations instead of acting as nucleophile. The first example where this reactivity was proposed comes from the laboratory of Xiao in 2016 (Scheme 18). In their report, the



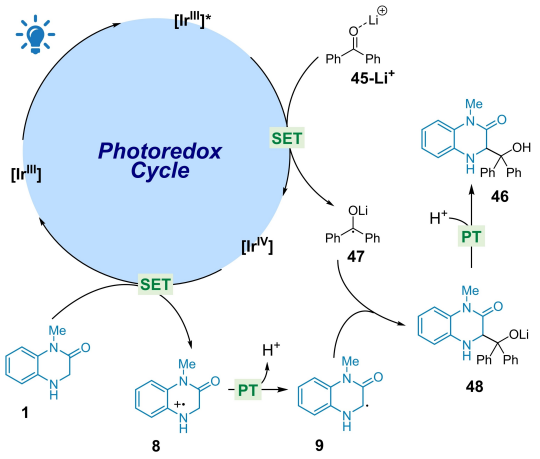
Scheme 17. Reaction and proposed mechanism between 3,4-dihydroquinoxalin-2-ones and *p*-quinone methides under photoredox conditions (Pedro and Vila, 2023).



Scheme 18. Radical-radical coupling between 3,4-dihydroquinoxalin-2-one and benzophenone under photoredox catalysis (Xiao, 2016).

authors employed $Ir(ppy)_3$ as photoredox catalysis to generate both the α-amino radical (via an oxidation) and the corresponding ketyl radical of benzophenone (via a reduction) upon coordination with $LiBF_4$.[28] Finally, a radical-radical coupling furnishes the expected product of this redox-neutral transformation. Although the researchers developed this methodology for several amines, only two examples can be found where 3,4-dihydroquinoxalin-2-ones was employed as radical precursor.

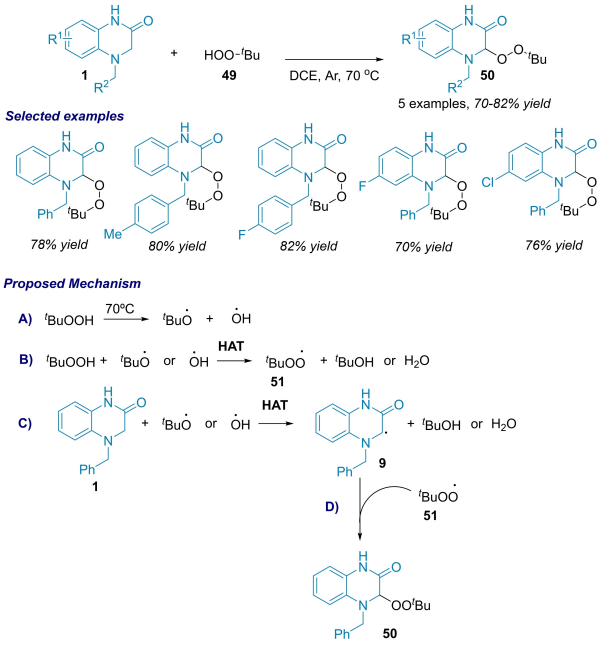
As mentioned earlier, the mechanism proposed by the authors involves the separate generation of the two radical counterparts (Scheme 19). Initially, excited state of $Ir(ppy)_3$ triggers a SET with lithium-coordinated benzophenone **45-Li$^+$** to generate the corresponding ketyl radical **47**. On the other hand, the Ir(IV) form of the photocatalyst is oxidant enough to generate radical cation **8** from 3,4-dihydroquinoxalin-2-one **1**. Then, radical cation **8** experiments loss of a proton to form the α-amino radical **9**. Finally, a radical-radical coupling between



Scheme 19. Mechanism for the radical-radical coupling between 3,4-dihydroquinoxalin-2-one and benzophenone.

the two radicals delivers the expected lithium alkoxide **48**, whose protonation generates the desired product **46**.

In 2020, Huo and collaborators came back to the field with their report about the peroxidation of 3,4-dihydroquinoxalin-2-ones at the C-3 position using *tert*-butyl hydroperoxide (TBHP, **49**) (Scheme 20).[29] Although the main substrate of their scope was 3,4-dihydro-1,4-benzoxazin-2-one, they also included five examples of their peroxidation protocol using 3,4-dihydroquinoxalin-2-ones. Their thermal protocol was very simple. Just by mixing the desired 3,4-dihydroquinoxalin-2-one with TBHP in 1,2-dichloroethane (DCE) at 70 °C, the transformation proceeds smoothly to form the expected peroxidated product in 70–82 % yield. Regarding the mechanism, the authors propose a thermal

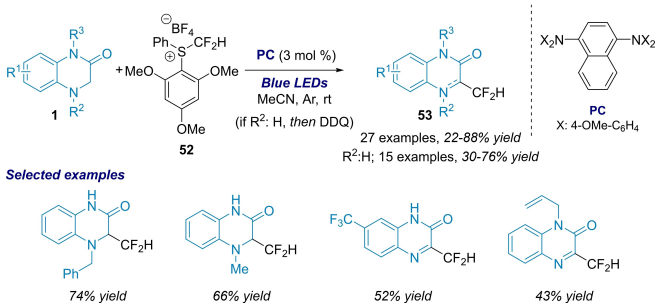


Scheme 20. Thermal C-3 peroxidation of 3,4-dihydroquinoxalin-2-ones with TBHP (Huo, 2020).

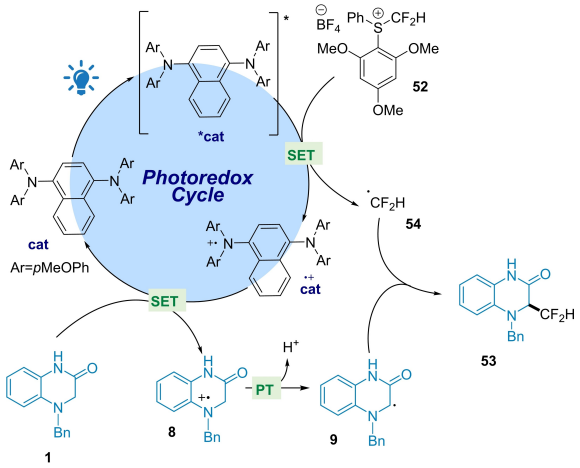
homolysis of the O–O bond in TBHP, resulting in the formation of the hydroxyl radical as well as the *tert*-butoxyl radical (**51**). Any of these radicals can participate in a HAT with 3,4-dihydroquinoxalin-2-one to generate the corresponding α-amino radical (**9**). Additionally, these radicals can also abstract a hydrogen atom to TBHP to generate *tert*-butyl peroxy radical (**51**), which is able to react with the α-amino radical via a radical-radical coupling and deliver the expected product **50**.

Finally, in 2022, the laboratory of Liu reported a radical difluoromethylation of 3,4-dihydroquinoxalin-2-ones.[30] To do this, they employed *S*-difluoromethyl diaryl sulfonium salts developed by themselves as difluoromethyl radical precursors,[31] and an organophotoredox catalyst derived from 1,4-diaminonaphthalene (Scheme 21). They reported 27 examples with low to good yields (22-82%). When unprotected 3,4-dihydroquinoxalin-2-ones at N-4 were employed, they obtained a mixture of C-3 difluoromethylated 3,4-dihydroquinoxalin-2-ones and the corresponding difluoromethylated quinoxalin-2-one. However, by using DDQ (2,3-dichloro-5,6-dicyanobenzoquinone) they could force the oxidation process and generate exclusively the difluoromethylated quinoxalin-2-one (15 examples) with moderate yields

The authors proposed the mechanism represented in Scheme 22, where a radical-radical coupling is suggested



Scheme 21. Photocatalytic difluoromethylation of 3,4-dihydroquinoxalin-2-ones (Liu, 2022).



Scheme 22. Mechanism for the radical-radical coupling between 3,4-dihydroquinoxalin-2-one and *S*-(difluoromethyl) sulfonium salt.

involving the generation of the two radical counterparts by photoredox catalysis. Initially, the *S*-(difluoromethyl)diarylsulfonium salt **52** is reduced by the excited state of the diamine photocatalyst to generate the $^{\bullet}CF_2H$ radical (**54**) along with the radical cation photocatalyst ($cat^{+\cdot}$). After, the radical cation of the photocatalyst generates the radical cation **8** from 4-benzyl-3,4-dihydroquinoxalin-2-one **1**. This radical cation **8** forms the α-amino radical **9** through a proton transfer event. Finally, the radical-radical coupling between the two radicals affords the fluorinated dihydroquinoxalin-2-one **53**.

5. Conclusions and perspectives

As summarized in this review, we have shown that the highly interesting nitrogen heterocycles such as 3,4-dihydroquinoxalin-2-ones can be functionalized through oxidative conditions. Several successful electrophilic and nucleophilic catalytic functionalization methodologies for the synthesis of these nitrogen heterocycles have been described in the literature over the last few years. In these reports, the reaction conditions are crucial in order to generate the corresponding iminium cation or the α-amino radical from the dihydroquinoxalinone. Most of the reports use the assistance of photoredox catalysis in order to generate the reaction intermediates. Generally, the examples reported are regarding the nucleophilic additions to the corresponding reactive iminium ions, however the number of nucleophiles is still narrow (indoles, silicon nucleophiles, ketones, pyrazolones, alkynes, amines, phosphites have been used). Additionally, only four examples have been described concerning electrophilic functionalizations, where electron-poor alkenes, azodicarboxilates, trifluoromethyl ketones, *p*-quinone methides have been used. Moreover, three radical-radical coupling reactions have been developed to synthesize C-3-functionalizated quinoxalinones. Therefore, there is still room for the development of new functionalization reactions using other nucleophiles or electrophiles, as well as radicals intermediates with these cyclic amines. For example, the formation of C–S, C–Se or C–X bonds at the C3 position of dihydroquinoxalin-2-ones have not been developed. Additionally, the development of enantioselective versions of the functionalization reactions is also highly desirable, because only one example has been described involving an organocatalytic Mannich reaction.

Conflict of Interests

The authors declare no conflict of interest.

Keywords: dihydroquinoxalin-2-ones · nitrogen heterocycles · catalytic nucleophilic functionalization · catalytic electrophilic functionalization · photocatalysis

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