C-3 FUNCTIONALIZATION OF QUINOXALIN-2-ONES AND DIHYDROQUINOXALIN-2-ONES

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Abstract. *Quinoxalin-2-ones and dihydroquinoxalin-2-ones are remarkable N-heterocycles that recently have attracted the attention of the pharmaceutical industry and synthetic organic chemists due to the biological activities that these N-heterocycles have shown. Recently, several examples of C-3 functionalization of these N-heterocycles have been described in the literature using oxidative, photochemical or electrochemical approaches. In this book chapter, we will discuss about these reactions paying attention to their synthetic utility from the point of view of the sustainability and efficiency.*

Contents

1. Introduction

Nitrogen containing heterocycles[1] are essential in general chemistry. For many decades the synthesis and functionalization of *N*-heterocycles have received the attention of the synthetic organic chemists, because of their wide range of applications in pharmaceutical, medicinal and agrochemical chemistry as well as in material science. In this context, quinoxalin-2-one[2] and dihydroquinoxalin-2-one[3] derivatives have been identified as a privileged class of nitrogen heterocyclic scaffolds present in several pharmaceutical drugs, biological active compounds and natural products. Therefore, their synthesis and functionalization have become a research topic for heterocyclic chemistry. In particular, C3-substituted (dihydro)quinoxalin-2-one derivatives represent one of the most important synthetic targets, due to the broad range of biological activities that these compounds have shown (Figure 1). Examples of biologically active quinoxalin-2-ones with alkyl (Csp^3) substituents at C-3 are **I** (caroverine) that is a calcium channel blocker that have been used as a muscle-relaxing drug,[4] **II** that is an aldolase reductase inhibitor[5] or **III** that is an angiotensin receptor antagonist.[6] Moreover, quinoxalin-2-ones with Csp^2-substituents also have been reported as an antitumor and

antimicrobial agent **IV**,[7] a cystic fibrosis transmembrane conductance regulator (CFTR) activator **V**[8] or a cannabinoid CB2 receptor agonist **VI**.[9] Furthermore, quinohemanine **VII**, a natural product isolated from *Streptomyces sp. CPCC 200497*, has shown moderate cytotoxicity against cancer cell line HepG2.[10] 3-Aminoquinoxalin-2-ones are also an important class of these nitrogen heterocycles present in histamine-4 receptor antagonist **VIII**[11] or the glycogen phosphorylase inhibitor **IX**.[12] Finally, 3-substituted-dihydroquinoxalin-2-one scaffolds have been found in biological and pharmacologically active molecules such as the antivirals **X**[13] and **XI**,[14] the anticancer **XII**[15] or the antidepressant **XIII**.[16]

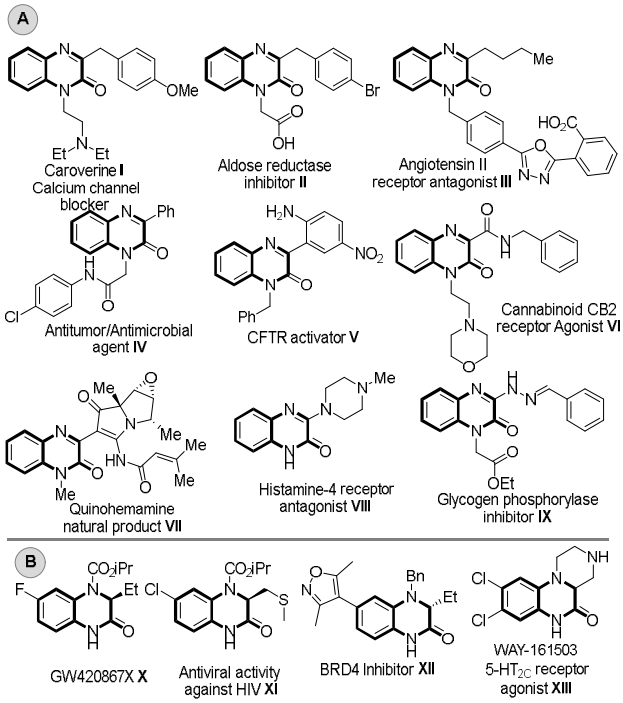


Figure 1. Representative biologically active 3-substituted quinoxalin-2-one A and dihydroquinoxalin-2-one B derivatives.

The traditional methods for the synthesis of 3-substituted quinoxalin-2-one derivatives lies in the condensation of 1,2-diaminobenzene derivatives with α-ketoacids, α-ketoesters, α-aldehyde acids or α-aldehyde esters.[17] However, these conventional methods suffer several drawbacks such as pre-functionalization of the starting materials and multi-step procedures. Consequently, over the last years, substantial efforts have been dedicated to the development of more efficient synthetic approaches to access quinoxalin-2-ones and dihydroquinoxalin-2-ones. In this context, the direct C–H functionalization[18] at the C3 position of quinoxalin-2-one derivatives is one of the most convenient method to increase their structural diversity leading a rapid way to gain different derivatives, very significant for medicinal chemistry. This chapter will focus in the description of the reactions reported for the C3-selective functionalization of these *N*-heterocycles, focusing our attention on the sustainability and availability of the methodologies, as well as the application to the synthesis of the target molecules.

2. C-3 Functionalization of quinoxalin-2-ones

2.1. C–C Bond formation

The development of methodologies to achieve the selective formation of C–C bonds plays a central role in synthetic organic chemistry. In this challenging task, several strategies can be used such as metal catalysis,

photocatalysis or electrochemical methods. In the last years, numerous procedures have been reported to form C–C bonds at C-3 position of quinoxalin-2-ones such as alkylation, fluoroalkylation, arylation or acylation reactions. We have divided the different methodologies depending of the reaction class and we have also discussed the availability, convenience and sustainability of the different approaches described in the literature.

2.1.1. Alkylation reactions

The alkylation reaction is the most studied method to functionalize the C-3 position of quinoxalin-2-ones. Therefore, we have first focused our attention in this reaction and several strategies have been described in the literature to form C–C bond. One of the most convenient methods is based in the use of non-prefunctionalized substrates. In 2018, Qu and co-workers described the C-3 benzylation of quinoxalin-2-ones using CuCl (20 mol%) as catalyst and *t*-butyl peroxybenzoate (TBPB) as oxidant under microwave irradiation at 100 ºC (entry 1, Table 1).[19] This methodology is simple and uses methylarenes as the benzylation reagents, a cheap and non-toxic copper catalyst and TBDP, one of the safest organic peroxides in handling, as oxidant. However, this method has some drawbacks such as, the metal catalysts loading is relatively high (20 mol%) and use an excess of peroxide. Moreover, *N*-unprotected quinoxalin-2-ones did not work under the optimized reaction conditions. The authors carried out a mechanistic study of the benzylation establishing the radical nature of the reaction and demonstrate the synthetic utility of their protocol describing the synthesis of an aldose reductase inhibitor.[5] Remarkably in 2021, the group of Roy (entry 2, Table 1) described the alkylation of quinoxalin-2-one with a broad class of reagents, such as cycloalkanes, cyclic ethers and alkyl arenes, using di-*t*-butyl peroxide (DTBP) as an alkoxyl radical mediator for the hydrogen atom transfer (HAT) process.[20] This dehydrogenative coupling approach has a nice scope, with 27 examples, but uses an excess of DTBP (3 equivalents) and a chlorinated solvent (dichloroethane) at 130 ºC. The authors were able to apply their methodology to a gram scale reaction with satisfactory yield (75%) and they also synthesized several important pharmaceutical agents, and demonstrate that the reaction occurs through a radical mechanism.

Another way that has been used to generate carbon-centered radicals that react with the electron-poor C=N double bond of quinoxalin-2-ones, is the use of redox active esters (R-CO_2NPhth). This class of reagents are compounds with an ester moiety containing the desired alkyl group and a platform capable of suffering Single Electron Transfer (SET) processes.[21] This strategy was employed by five independent research teams using photochemical or electrochemical protocols. Regarding to the photochemical reports, Dong,[22] Li[23] and Jin[24] (entries 3, 4 and 5, Table 1), described three methods using different photocatalysts under N_2 atmosphere. The research group of Dong used *N*-hydroxyphthalimide esters, as the synthetic equivalent of an aliphatic C-centered radical in combination with Ru(bpy)$_3$Cl$_2$ and DABCO under sun-light irradiation.[22] They described the preparation of a small collection of C-3 alkylated quinoxalin-2-ones (6 examples) among other related heterocycles such as coumarins, quinolones and chromenones. The same year, Li and co-workers reported a similar methodology also based on *N*-hydroxyphthalimide esters as C-centered radical equivalents.[23] In this report, the metal photocatalysts used was *fac*-Ir(ppy)$_3$ in combination with 0.5 equivalents of TFA and DMSO as solvent under white LEDs irradiation. Although the iridium photocatalyst is much more expensive than the ruthenium, they could report a vast scope of *C*-3-alkylated quinoxalin-2-ones (26 examples). Lastly, the team of Jin[24] reported the use of the same radical precursors in combination with an organophotocatalyst, Eosin Y, 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 more desirable, in order to avoid metal traces in the reaction products. This organophotocatalyst-based method, which also employs TFA as an additive and white LEDs as source of light, allowed the researchers to obtain 31 products, showing some examples with challenging alkyl radicals from NHPI esters, including the adamantyl-derived one. Moreover, they applied their optimized reaction conditions to conduct a 10 mmol-scale batch reaction, and prepared a precursor of an aldolase reductase inhibitor.[5]With regard to electrochemical methods using redox active esters, two very similar methods have been described. Zeng, Xu and co-workers used $NiCl_2$ as catalyst (10 mol%), graphite as anode and Ni foam as cathode in an undivided cell at 60 ºC (entry 6, Table 1).[25] With these conditions they described 29 examples. While the team of Wang[26] described also an electrochemical method using an undivided cell with two graphitic electrodes only at room temperature (entry 7, Table 1). From the point of sustainable chemistry, the last electrochemical method is superior as no metal catalyst is needed and the reaction does not require heating.

Moreover, the scope of the reaction of Wang is higher (34 examples) and a gram-scale synthesis is also reported.

One of the drawbacks of the use of redox active esters is that they need to be prepared from carboxylic acids prior to use. Therefore, from the perspective of atom economy and synthetic efficiency, the development of methodologies involving the direct use of carboxylic acids could be more convenient. Two groups, independently, described very similar methodologies involving the use of carboxylic acids. Hu's group[27] and He's group[28] reported the use of phenyl iodide(III) diacetate (PIDA) in combination with different carboxylic acids and $Ru(bpy)_3Cl_2$ (entry 8 and 9, Table 1). In the case of Hu's work, the solvent is DMSO and the source of irradiation is White LEDs, while in He's work the solvent used is PEG-200 and Blue LEDs. In the last one, the use of PEG-200 allowed that the ruthenium(II) catalytic system could be successfully recycled five times without significant decrease of its efficiency and showing better sustainability than the method described by Hu. The scope in both cases was large, with more than 30 examples from primary, secondary and tertiary carboxylic acids, but in both cases the use of a large excess of PIDA is a disadvantage. The group of Chen has also described the photochemical C-3 alkylation of quinoxalin-2-ones using PIDA in combination with alkyl carboxylic acids using $CeCl_3$ (10 mol%) as photocatalyst under blue LEDs irradiation (entry 10, Table 1).[29] In the way to simplify the methodology, a report by Qin and Li shows how carboxylic acids can be used (after decarboxylation) as useful alkyl equivalents to functionalize the C-3 of quinoxalin-2-ones (entry 11, Table 1).[30] Compared with previously reviewed methodologies, these researchers employ non-prefunctionalized aliphatic carboxylic acids (primary, secondary and tertiary) in combination with $(Ir[dF(CF_3)ppy]_2(dtbbpy))PF_6$ (2 mol%) as photoredox catalyst, $K_2S_2O_8$ as stoichiometric oxidant and lithium carbonate as base. In these conditions, the researchers accessed to a collection of 36 alkylated quinoxalin-2-ones in moderate to good yields. The major drawback of this methodology is the use of an expensive iridium photocatalyst. Another example of the use of non-prefunctionalized carboxylic acids was described by Wang and co-workers in 2021 (entry 12, Table 1).[31] They described the photoelectrochemical decarboxylative alkylation of quinoxalin-2-ones at C-3 position. The protocol involves the use of secondary or tertiary carboxylic acids, an iron salt (an earth-abundant metal that catalyze the decarboxylation *via* ligand-to-metal charge transfer) and use an undivided cell with two graphite electrodes under Blue LEDs irradiation. The authors could also apply their method to a gram scale synthesis. Moreover, with this methodology they could use secondary and tertiary alcohols as a source of alkyl radicals by preparing the corresponding alkyl oxalate (entry 13, Table 1). This intermediate product could be prepared *in situ* from the corresponding alcohol by reaction with oxalyl chloride (an inexpensive reagent). The last example using simply alkyl (secondary and tertiary) carboxylic acids as precursors for alkyl radicals to react with quinoxalin-2-ones, was described by the group of Xie (entry 14, Table 1).[32] They describe an interesting photochemical protocol, where the alkylation proceeded in the absence of metal-catalyst, acid or basic additives, or external photosensitizer. As oxidant the authors use $(NH_4)_2S_2O_8$ and DMSO as a solvent. Therefore, this protocol can be considered one of the most sustainable and environmentally friendly.

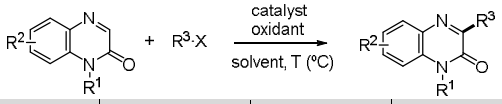
Other reagents that have been used as alkyl radical precursors for the alkylation of quinoxalin-2-ones are aldehydes (entry 15, Table 1).[33] In 2021, Lin, Yao and co-workers, reported the direct alkylation using alkyl (primary and secondary) aldehydes and di-*t*-butyl peroxide (DTBP, 3 eq., as precursor for the *t*-butoxyl radical) heating at 100 ºC in chorobenzene. The drawbacks of this methodology is the use of a large amount of a peroxide and the chlorinated solvent.

Alkyl boronic acids have also been used as radical precursors to achieve the C-3 alkylation of quinoxalin-2-ones. Two examples have been described in 2021. Wang's group described the electrochemical alkylation using alkyl (primary, secondary and tertiary) boronic acids in an undivided cell with two graphite electrodes using DMF as solvent at room temperature (entry 16, Table 1).[34] While Li, Wang, Liu and co-workers described the photochemical version using as photocatalyst $Ru(bpy)_3Cl_2$ in DMF under Blue LEDs irradiation (entry 17, Table 1), but in this case the protocol only allowed the use of secondary and tertiary alkyl boronic acids.[35]

A photochemical protocol for the alkylation of quinoxalin-2-ones using alkyl iodides as alkylation agents have been described by Zhang in 2021 (entry 18, Table 1).[36] The alkylation reaction occurs under metal- and photocatalyst-free conditions using 1-methyl-1,3,4,6,7,8-hexahydro-2*H*-pyrimido[1,2-*a*]pyrimidine as a base in DMSO and blue LEDs irradiation. The protocol allowed the use of primary, secondary and tertiary alkyl

iodides showing 34 examples. Therefore, this method could be considered quite sustainable. Finally, Xuan's group described the C-3 alkylation of quinoxalin-2-ones using 4-alkyl-1,4-dihydropyridines as alkyl radical precursors and acetoxybenziodoxole (Bi-OAc) as an electron-acceptor under blue LEDs irradiation (entry 19, Table 1).[37] Although the scope of the reaction is great (36 examples), comparing this protocol to the others, the atom economy in this case is much lower, and the solvent used is $CHCl_3$.

Table 1. Alkylation reactions at the C-3 position of quinoxalin-2-ones using alkyl radicals.



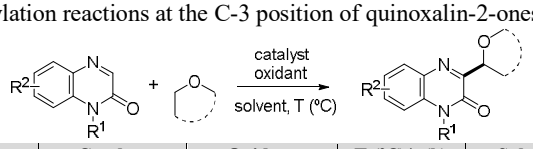
Entry	Methodology	Catalyst	Oxidant	R-X	T (ºC)/t (h)	Solvent	Scope
1[ref. 19]	-	CuCl	TBPB (2 eq.)	$ArCH_2$-H	100[a]/1	$ArCH_2$-H	30 examples
2[ref. 20]	-	-	DTBP (3 eq.)	R-H	130/4	DCE	27 examples
3[ref. 22]	Photochem.	$Ru(bpy)_3Cl_2$	-	R-CO_2NPhth	rt/2	DMA	6 examples
4[ref. 23]	Photochem.	$Ir(ppy)_3$	-	R-CO_2NPhth	rt/12	DMSO	26 examples
5[ref. 24]	Photochem.	Na_2-eosin Y	-	R-CO_2NPhth	rt/40	DMSO	31 examples
6[ref. 25]	Electrochem.	$NiCl_2$	-	R-CO_2NPhth	60/3	DMA	29 examples
7[ref. 26]	Electrochem.	-	-	R-CO_2NPhth	rt/12	DMA	34 examples
8[ref. 27]	Photochem.	$Ru(bpy)_3Cl_2$	$PhI(OAc)_2$	R-CO_2H	rt/12	DMSO	35 examples
9[ref. 28]	Photochem.	$Ru(bpy)_3Cl_2$	$PhI(OAc)_2$	R-CO_2H	rt/6	PEG-200	38 examples
10[ref. 29]	Photochem.	$CeCl_3$	$PhI(OAc)_2$	R-CO_2H	rt/12	CH_3CN	32 examples
11[ref. 30]	Photochem.	Ir(I)[b]	$K_2S_2O_8$ (2 eq.)	R-CO_2H	rt/12	DMSO/H_2O	36 examples
12[ref. 31]	Photo-electrochem.	$Fe(NH_4)_2(SO_4)_2$	-	R-CO_2H	35/16	DMSO	35 examples
13[ref. 31]	Photo-electrochem.	$Fe(NH_4)_2(SO_4)_2$	-	R-OH	35/16	DMSO	8 examples
14[ref. 32]	Photochem.	-	$(NH_4)_2S_2O_8$	R-CO_2H	rt/24	DMSO	39 examples
15[ref. 33]	-	-	DTBP (3 eq.)	R-CHO	100/12	C_6H_5Cl	30 examples
16[ref. 34]	Electrochem.	-	-	R-$B(OH)_2$	80/8	DMF	30 examples
17[ref. 35]	Photochem.	$Ru(bpy)_3Cl_2$	-	R-$B(OH)_2$	rt/12	DMF	28 examples
18[ref. 36]	Photochem.	-	-	R-I	rt/12	DMSO	34 examples
19[ref. 37]	Photochem.	-	Bi-OAc	Hantzsch ester	rt/3	$CHCl_3$	36 examples

[a]Microwave irradiation. [b.][Ir{dF(CF_3)ppy}$_2$(dtbbpy)]PF_6

To facilitate the generation of alkyl radicals by simple C–H activation, the use of molecules containing a functional group adjacent to the target sp^3 carbon, which would result in a decrease of the bond dissociation energy is a good and efficient alternative. Ethers could act as precursors for *C*-centered radicals due to the presence of the oxygen, which acts as electron-donating group for the stabilization of radicals. In this way several examples have been described using simple ethers as alkylation reagents of quinoxalin-2-ones. Yuan and co-workers[38] described the peroxide-mediated C-3 alkylation of quinoxalin-2-one derivatives with ethers using *t*-butyl hydroperoxide (TBHP) under metal-free conditions (entry 1, Table 2). In this methodology, *t*-butoxy radical generates an alkyl radical from the ether *via* C–H abstraction. The corresponding addition of the *C*-centered radical to the quinoxalin-2-one delivers the corresponding alkylated product with good yields. The solvent used is the ether itself and the reaction is run at 100ºC. Later, the group of Yuan developed a copper-catalyzed oxidative hydroxyalkylation of quinoxalin-2-one derivatives with alcohols using TBDP to generate the α-hydroxyalkyl radicals (entry 2, Table 2).[39] In this report, the authors can use primary and secondary alcohols which are the solvent as in the example above, but in this report the temperature is lower (60ºC). Additionally, two photochemical examples using ethers as precursors to generate alkyl radicals have been reported. In 2018, Wei and co-workers established a photochemical protocol for the alkylation of quinoxalin-2-ones with ethers using Rose Bengal as photocatalyst in combination with *t*-butyl hydroperoxide (TBHP) as oxidant and DABCO as a base, under the irradiation of Blue LEDs (entry 3, Table 2).[40] Later the research group of Suryavanshi reported the same transformation but using a more practical experimental setup (entry 4, Table 2).[41] They selected a similar, but cheaper, organophotoredox catalyst (Eosin Y) and were able to optimize the methodology avoiding the use of a base and employing the oxygen from air as stoichiometric

oxidant. Therefore, from the point of view of atom economy and sustainability, the last protocol was more convenient, although the authors described less examples.

Table 2. Alkylation reactions at the C-3 position of quinoxalin-2-ones using ethers.



Entry	Methodology	Catalyst	Oxidant	T (ºC)/t (h)	Solvent	Scope
1[ref. 38]	-	-	TBHP (3 eq.)	100/9	ethers	22 examples
2[ref. 39]	-	Cu_2O	TBPB (3 eq.)	60/10	alcohols	25 examples
3[ref. 40]	Photochem.	Rose Bengal	TBHP (1 eq.)	rt/24	ethers	27 examples
4[ref. 41]	Photochem.	Eosyn Y	-	25/24	ethers	17 examples

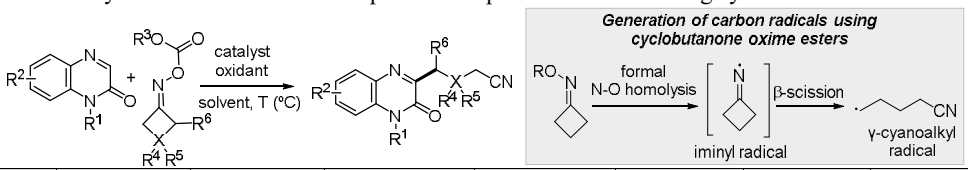
Another convenient way to generate carbon radicals is the use of cyclobutanone oxime esters.[42] These particular cyclobutanone derivatives suffer a formal N-O hemolysis to give the corresponding iminyl radical, which undergoes a β-scission to generate γ-cyanoalkyl radicals. These reagents have been used in several alkylation of quinoxalin-2-ones providing γ-cyanoalkylated product at the C-3 of the quinoxalin-2-ones. The first group that use cyclobutanone oxime esters was the laboratory of Guo (entry 1, Table 3).[43] In their protocol, $Fe(acac)_2$ catalyzed the generation of the cyanoalkyl radicals, which were added smoothly at 100 ºC to a variety of substituted quinoxalin-2-ones to afford the corresponding C3-alkylated quinoxalin-2-one derivatives (30 examples). Among the different protecting groups attached to the *O*-acyl oximes, the most suitable group was the pentafluorobenzoate. Later, different photochemical methodologies have been described. For example, in 2019 Li and co-workers established that cyclobutanone *O*-*p*-trifluoromethylbenzoyl oxime esters can act as a competent γ-cyanoalkyl radical precursors using Eosin Y as photocatalyst under the irradiation of blue LEDs describing 30 examples (entry 2, Table 3).[44] Concurrently,[45] the same research group reported an identical protocol to generate these γ-cyanoalkyl radicals but using *fac*-$Ir(ppy)_3$ instead of Eosin Y (entry 3, Table 3). Using this metal-based photocatalyst they could generate the same products. Compared with expensive transition-metal-derived photoredox catalysts, organic dyes are cheaper and offer a more sustainable choice. Shortly after, two more photochemical reports using *fac*-$Ir(ppy)_3$ and cyclobutanone oxime esters as a radical precursor were published. Xu[46] described the photochemical C-3 alkylation of quinoxalin-2-ones using perfluorobenzoyl cyclobutanone oxime as iminyl radical precursor (entry 4, Table 3), while Yang's group[47] described this alkylation using perfluoropyridin-based redox active cyclobutanone oxime (entry 5, Table 3). In this report, Yang also described the thermal generation of γ-cyanoalkyl radical by heating the reaction at 100 ºC, obtaining lower yields for the cyanoalkylated quinoxalin-2-ones (entry 6, Table 3). In terms of sustainable chemistry, the two first methods (entries 1 and 2, Table 3) are the best choice.

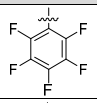
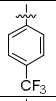
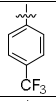
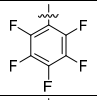
2.1.2. Fluoroalkylation reactions

In the last decades the incorporation of fluorine in chemical compounds has been proven to be a successful approach in some research fields, such as pharmaceutical, medicinal chemistry and material science.[48] Consequently, the development of methodologies to incorporate fluorine atoms in organic compounds with high efficiency is highly demanding. Due to importance of quinoxalin-2-ones in medicinal chemistry several strategies have been developed to perform fluoroalkylation reactions at this *N*-heterocycle. These strategies vary from the point of view of the fluoroalkyl radical precursors, which can be fluoroalkyl sulfinates, fluoroalkyl carboxylic acid derivatives or fluoroalkyl halides.

The most used approach to *C*-centered fluoroalkyl radicals is based in the use of fluoroalkyl-derived sulfinate salts. Compared with other trifluoromethyl sources, the advantages of these class of fluoroalkyl salts are that they are readily available, stable, easy to operate and store. These precursors have been employed by six different research teams to generate trifluoromethyl or difluoromethyl radicals in order to perform fluoroalkylation reactions of quinoxalin-2-ones at C-3 position. The first example (entry 1, Table 4) was the methodology reported by Zhao *et al.*, in which several differently substituted quinoxalin-2-ones were trifluoromethylated using CF_3SO_2Na in combination with a large amount of $PhI(OAc)_2$.[49]

Table 3. Alkylation reactions at the C-3 position of quinoxalin-2-ones using cyclobutanone oxime esters.



Entry	Methodology	Catalyst	Oxidant	R^3	T (ºC)/t (h)	Solvent	Scope
1[ref. 41]	-	$Fe(acac)_2$	-		100/18	CH_3CN	30 examples
2[ref. 42]	Photochem.	Eosin Y	-		rt/24	CH_2Cl_2	30 examples
3[ref. 45]	Photochem.	$Ir(ppy)_3$	-		rt/24	CH_2Cl_2	32 examples
4[ref. 46]	Photochem.	$Ir(ppy)_3$	-		rt/20	DMF	29 examples
5[ref. 47]	Photochem.	$Ir(ppy)_3$	-		rt/12	CH_3CN	19 examples
6[ref. 47]	-	-	-		100/12	CH_3CN	19 examples

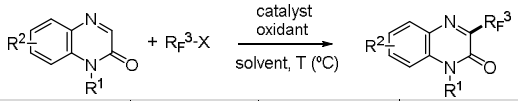
A more convenient approach was described by Jin's group, where trifluoromethylated quinoxaline-2-ones were obtained using CF_3SO_2Na under the irradiation of Blue LEDs, without the use of a photocatalyst (entry 2, Table 4).[50] The corresponding 3-trifluoromethyl-quinoxalin-2-one derivatives (26 examples) bearing a variety of substitution patterns were obtained in moderate to good yields. They performed mechanistic experiments 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. Later, Duan an coworkes, described a similar protocol for the trifluoromethylation and perfluoroalkylation of quinoxalin-2-ones using the corresponding sodium sulfinates in the presence of Eosin Y as photocatalyst and DMSO as solvent (entry 3, Table 4).[51] They described a greater scope with 43 successfully examples. In 2020, the research group of Li reported a photochemical methodology to incorporate difluoromethyl groups to quinoxalin-2-ones and other aromatic heterocycles using Rose Bengal as photocatalyst and CF_2HSO_2Na as a reagent under air atmosphere (entry 4, Table 4).[52] Later in 2021 Baishya described a protocol for the synthesis of 3-trifluoromethylquinoxalin-2-ones by using sodium triflinate in the presence of $(NH_4)_2S_2O_8$ as oxidant under air atmosphere at 55 ºC in a mixture of DMSO/water (entry 5, Table 4).[53] An electrochemical approach have also been developed by Zeng's research group using $(CF_3SO_2)_2Zn$ as fluoroalkylating agent and Et_4NBr as additive in an undivided cell equipped with a platinum net as the anode and a graphite plate as the cathode at 50 ºC in CH_3CN. In this report, the yields for the corresponding products are lower and the protocol is less efficient (entry 6, Table 4).[54]

Another reagent commonly used for trifluoromethylation reactions is $TMSCF_3$, more known as Ruppert–Prakash reagent. This particular reagent has been used by Hu and co-workers for the trifluoromethylation at the C-3 position of quinoxalin-2-ones in combination of $PhI(OAc)_2$ (2.5 eq.), KF (4 eq.) and benzoquinone (20 mol%) in CH_3CN and Ar atmosphere (entry 7, Table 4).[55] Although the $TMSCF_3$ is a commercial available reagent and is easy to use, the scope of this reaction is narrower (15 examples) and the researchers used a large amount of PIDA as oxidant.

Another strategy towards the synthesis of fluoroalkylated quinoxalin-2-ones is based in the utilization of fluoroalkyl carboxylic acid derivatives. These acid-derived species can suffer a decarboxylation to generate the desired fluoroalkyl carbon radical. It was the laboratory of Zhang who, in early 2019, developed a protocol based on the use α,α-difluoroarylacetic acids and $(NH_4)_2S_2O_8$ as oxidant under transition-metal-free conditions (entry 8, Table 4).[56] The decarboxylative fluoroalkylation reaction could take place at 60 °C and exhibited a broad substrate scope with respect to both the coupling partners (31 examples). A similar photochemical approach was developed by Wang and co-workers in 2020 (entry 9, Table 4).[57] This photocatalyst-free protocol was based on the use of sodium fluorobenzyl carboxylates and potassium persulfate as stoichiometric oxidant. The scope of the reaction was similar to the previous report.

Finally, fluoroalkyl halides constitute a readily available fluoroalkyl radical precursors through a C–X bond homolysis, which can be performed using metal catalysis or visible-light photocatalysis. Zhang and co-workers developed an efficient method for C3-difluoroalkylation of quinoxalin-2-ones with ethyl bromodifluoroacetate catalyzed by a copper catalyst at 110 ºC (entry 10, Table 4).[58] This protocol use an inexpensive and readily available copper salt as the catalyst, giving moderate to excellent yields with excellent functional group tolerance. While Jin's group developed a photochemical version of this reaction using *fac*-Ir(ppy)$_3$ as photocatalyst and DIPEA as base (entry 11, Table 4).[59] Both methods have advantages and disadvantages. Zhang's work uses as catalyst a copper salt, but the reaction is run at 110 ºC for 16 hours, whereas Jin's work is a photochemical protocol run at room temperature but using a costlier metal catalyst.

Table 4. Fluoroalkylation reactions at the C-3 position of quinoxalin-2-ones.



Entry	Methodology	Catalyst	Oxidant	R_F-X	T (ºC)/t (h)	Solvent	Scope
1[ref. 49]	-	-	$PhI(OAc)_2$	CF_3-SO_2Na	rt/12	CH_3CN	23 examples
2[ref. 50]	Photochem.	-	air	CF_3-SO_2Na	rt/12	DCE	26 examples
3[ref. 51]	Photochem.	Eosin Y	air	R_F-SO_2Na	rt/24	DMSO	43 examples
4[ref. 52]	Photochem.	Rose Bengal	air	CF_2H-SO_2Na	rt/24	DMSO	15 examples
5[ref. 53]	-	-	$(NH_4)_2S_2O_8$	CF_3-SO_2Na	55/3	DMSO/H_2O	21 examples
6[ref. 54]	Electrochem.	-	-	$(CF_3$-$SO_2)_2Zn$	50/8	CH_3CN	15 examples
7[ref. 55]	-	benzoquinone	$PhI(OAc)_2$	CF_3-$SiMe_3$	rt/4	CH_3CN	15 examples
8[ref. 56]	-	-	$(NH_4)_2S_2O_8$	RCF_2-CO_2H	60/5	DMSO	31 examples
9[ref. 57]	Photochem.	-	$K_2S_2O_8$	$ArCF_2$-CO_2Na	rt/10	H_2O	35 examples
10[ref. 58]	-	$[Cu(CH_3CN)_4]PF_6$	-	$BrCF_2CO_2Et$	110/16	CH_3CN	22 examples
11[ref. 59]	Photochem.	Ir(ppy)$_3$	-	$BrCF_2CO_2Et$	rt/12	CH_3CN	30 examples

2.1.3. Acylation reactions

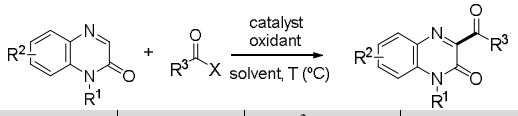
Moving to other C–C bond formation reactions, the introduction of carbonyl groups into the organic molecules is one of the most important processes in organic synthesis due to the versatility of this functional group. There are several ways to introduce an acyl group to chemical compounds. In this context, the acylation reaction *via* acyl radical precursors has become an important, direct and useful approach. The corresponding acyl radicals could be derived from α-oxocarboxylic acids, aromatic carboxylic acids, aldehydes or acyl halides.

There are several synthetic methodologies that have been described for the introduction of an acyl group at the C-3 position of quinoxalin-2-ones (Table 5). The α-oxocarboxylic acids has been the most used acylation reagents and five protocols have been reported. In 2017, Hu and co-workers[60] described the successfully decarboxylative acylation of quinoxalin-2-ones with α-oxocarboxylic acids employing a catalytic amount of $AgNO_3$ (10 mol%) and an $K_2S_2O_8$ as oxidant at 100 ºC in a CH_3CN/H_2O mixture (Table 5, entry 1). The scope is quite large with 26 examples. The majority of the examples are related to aromatic α-oxocarboxylic acids obtaining good yields, though aliphatic α-oxocarboxylic acids provide the products with much lower yields. In 2020, the research group of Wei developed a better protocol using Acridine Red as photocatalyst under the irradiation of Blue LEDs (entry 2, Table 5).[61] Using these optimized reaction conditions, they could synthesize a library of 28 differently substituted 3-acyl-quinoxalin-2-ones with moderate to good yields. In this report,

aromatic, heteroaromatic and aliphatic α-oxocarboxylic acids were all suitable for this transformation, affording the corresponding functionalized quinoxalinones with good yields. Later, He's group developed a similar methodology to incorporate an acyl group at the C-3 position of quinoxalin-2-ones, without the need of a photocatalyst but using a more energetic light source (400 nm).[62] Using a mixture of DCE and water as solvent and the oxygen from air as oxidant, they could obtain a set of 3-acylquinoxalin-2-ones in moderate to good yields. In this report, aliphatic α-oxocarboxylic acids were not suitable giving low yields of 3-acyl-quinoxalin-2-ones. Finally, two other protocols using α-oxocarboxylic acids have been reported, but in these cases in combination with PIDA, and therefore less efficient taking in account the atom economy of the processes. In 2020, Xuan, Xu and co-workers described a photochemical method in aqueous phase under photocatalyst free conditions (entry 4, Table 5).[63] Again when aliphatic α-oxocarboxylic acids were used the corresponding product were obtained with low yields. Zhao's group reported a very similar process, but in this case the reaction was heated to 80 ºC in CH_3CN, obtaining similar results in only 0.5 h but with lower sustainability (entry 5, Table 5).[64]

Although 2-oxocarboxylic acids 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. In fact, several examples using aldehydes as acyl radical precursors for the C-3 acylation of quinoxalin-2-ones have been described. In 2018, Qu and co-workers described the acylation of quinoxalin-2-ones using aromatic aldehydes and a large amount of *t*-butyl hydroperoxide TBHP at 80 ºC in DCE as a solvent (entry 6, Table 5).[65] The advantages of this reaction compared to the previous works are the metal-free and mild conditions, inexpensive and readily available starting materials, with broad range of substrates (36 examples) and excellent functional group tolerance. Aliphatic aldehydes could also react but affording the corresponding products with moderate yield. Moreover, the reaction could be scale-up to 1 gram. Finally, two photochemical approaches using aldehydes have been described by Ni's research group. First they described the C-3 acylation reaction using aldehydes in combination with Eosin Y as photocatalyst and $(NH_4)_2S_2O_8$ as oxidant in CH_3CN under blue LEDs irradiation (entry 6, Table 5).[66] Later, they described a similar approach, but without the use of a photocatalyst. They described the acylation with aldehydes in combination with PIFA under blue LEDs irradiation.[67] Although the last method did not require the use of a photocatalyst, PIFA is more expensive than $(NH_4)_2S_2O_8$ and CH_2Cl_2 is a less convenient solvent compared to CH_3CN. In both reports, the reaction did not tolerate aliphatic aldehydes.

Table 5. Acylation reactions at the C-3 position of quinoxalin-2-ones.



Ref.	Methodology	Catalyst	Oxidant	R^3CO-X	T (ºC)/t (h)	Solvent	Scope
1[ref. 60]	-	$AgNO_3$	$K_2S_2O_8$	RCO-CO_2H	100/3	CH_3CN/H_2O	26 examples
2[ref. 61]	Photochem.	Acridine Red	air	RCO-CO_2H	rt/8	DCE	28 examples
3[ref. 62]	Photochem.	-	air	RCO-CO_2H	rt/4	DCE/H_2O	32 examples
4[ref. 63]	Photochem.	-	PIDA	RCO-CO_2H	rt/24	H_2O	32 examples
5[ref. 64]	-	-	PIDA	RCO-CO_2H	80/0.5	CH_3CN	20 examples
6[ref. 65]	-	-	TBHP	RCO-H	80/5	DCE	36 examples
7[ref. 66]	Photochem.	Eosin Y	$(NH_4)_2S_2O_8$	RCO-H	40/16	CH_3CN	14 examples
8[ref. 67]	Photochem.	-	PIFA	RCO-H	rt/3	CH_2Cl_2	26 examples

2.1.4. Arylation reactions

Moving 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 *N*-heterocycle allows the extension of the conjugated π system. The arylation of quinoxalin-2-ones has been also extensively studied with multitude of synthetic approaches to prepare 3-aryl-quinoxalin-2-ones. The first approach described was based in the use of aryl boronic acids. Arylboronic acids represent versatile building blocks in organic synthesis. They are fundamental reagents in transition metal-catalyzed cross-coupling reactions and we start the description of the arylation reactions of quinoxalin-2-ones using this kind of reagents.[68] In 2013, the group of Alami reported the palladium-catalyzed oxidative C3-arylation of quinoxalin-2-ones with arylboronic acids under an O_2

atmosphere (entry 1, Table 6).[69] The scope of the reaction was quite broad (20 examples) for both quinoxalin-2-ones and arylboronic acids and gave in general excellent yields. In this reaction, the catalyst loading of palladium is relatively low (5 mol%), and molecular oxygen is the terminal oxidant, however the reaction is carried out at 100 ºC. In 2018, Reddy and collaborators, described an interesting arylation of quinoxalin-2-ones with aryl boronic acids promoted by $Mn(OAc)_3 \cdot 2H_2O$ that provides the corresponding arylated products with good yields.[70] This method is remarkable because the authors avoid the use of a palladium catalyst, although the amount of the manganese salt is large (3 equiv.). In 2021, the research group of Li reported the use of arylboronic acids for the arylation of quinoxalin-2-ones under photochemical conditions (entry 3, Table 6). Their protocol is based in the use of Eosin Y as organophotocatalyst and $K_2S_2O_8$ as oxidant in water as solvent under air atmosphere and blue LEDs irradiation.[71] Although the yields are lower than the previous reports (up to 63%), this protocol has more advantages from the point of view of sustainable chemistry such as the mild reaction conditions, water as a solvent and avoid the use of metals.

Aryl trialkylsilanes have been also used as reagents for palladium cross-coupling reactions. Wu and co-workers described the Hiyama coupling of quinoxalin-2-ones with aryl alkylsilanes catalyzed by palladium acetate (10 mol%) in water under O_2 atmosphere at 80 ºC (entry 4, Table 6).[72] The corresponding 3-aryl-quinoxalinones (27 examples) were obtained with good yields, but the method did not tolerate *N*-unsubstituted quinoxalin-2-ones.

The Pd-catalyzed direct functionalization of C–H bonds has been demonstrated as an important cross-coupling strategy for the formation of a range of C–C bonds owing to its atom- and step-economical nature. Lee's group described a arylation strategy using simple arenes, $Pd(TFA)_2$ (10 mol%) as catalyst and Ag_2O (1.5 equiv.) as oxidant at 110 ºC (entry 5, Table 6).[73] Although this method does not require pre-functionalization of the arylation reagents the use of stoichiometric silver salts is a drawback.

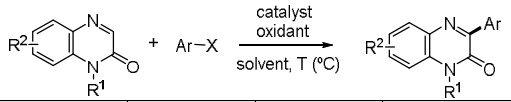
Another convenient arylation reagents that have been also employed for the preparation of 3-aryl-quinoxalin-2-ones are aryl hydrazines. Lee *et al.*[74] reported the iodosobenzene-mediated direct oxidative C3 arylation of quinoxalin-2-ones using aryl hydrazine as the aryl radical source under aerobic conditions (entry 6, Table 6). This method has been studied extensively with more than 25 examples under mild reaction conditions. In 2020, Yang's laboratory described a photochemical arylation of quinoxalin-2-ones with aryl hidrazines employing a Covalent Organic Framework (COF).[75] They could access to a collection of arylated quinoxalin-2-ones (23 examples), using their customized two-dimensional 2D-COF-1, in combination with K_2CO_3 as base under the irradiation of Blue LEDs in DMSO and air atmosphere at room temperature. They also extended their methodology to alkyl hydrazines. This methodology has several advantages such as mild reaction conditions, the use of metal-free heterogeneous catalyst and the scale up of the reaction. Moreover, the authors carried out photocatalyst recycling experiments, observing that their COF photocatalyst maintained its photocatalytic activity even after six runs. In 2020, Baishya and co-workers, described a C-3 arylation of quinoxalines using aryl hidrazines mediated by $K_2S_2O_8$ under metal-, photocatallyst and light-free conditions (entry 7, Table 6).[76] The authors had to carry out the reaction at 50 ºC in CH_3CN for 9 hours in order to obtain good yields. In this report, they also used as arylating agent boronic acids.

Aryl diazonium salts are frequently employed for nucleophilic aromatic substitutions (Sandmeyer's reaction), where the N_2 molecule acts as a leaving group. But this class of reagents can also be used as aryl radical precursors. In fact, Kim's group stablished the C-3 arylation of quinoxalin-2-ones using aryldiazonium salts as aryl radical precursors in the presence of Eosin Y as the organophotocatalyst, DMSO as solvent under the irradiation of blue LEDs (entry 9, Table 6).[77] Using these conditions, they carried out 31 examples obtaining the corresponding 3-arylquinoxalin-2-ones in moderate to good yields. Moreover, the authors could scale up the reaction to obtaining the 1-methyl-3-(4-methylphenyl)quinoxalin-2-one in 1.13 grams (90% yield). Interestingly, a mechanochemical methodology for the arylation of quinoxalin-2-ones using aryldiazonium salts have been described by Xia, Li and co-workers in 2022 (entry 10, Table 6).[78] The corresponding products were obtained with good yields although the scope of the reaction is narrower than the previous one (15 examples). In these reports, aryl diazonium salts have to be prepared previously. However, there are two examples that described the arylation reaction at C-3 of quinoxalin-2-ones using aryl diazonium salts prepared *in situ* by the reaction of anilines and *t*-butyl nitrite. In principle, these approaches are more convenient because of its experimental facility. In 2017, Yuan described the arylation of quinoxalin-2-ones

with arylamines using *t*-butyl nitrite in acetone at room temperature (entry 11, Table 6).[79] This report highlight a metal-free procedure using an environmentally friendly solvent, with a good substrate scope (30 examples). To further demonstrate the synthetic utility of this protocol, the authors applied their protocol to the synthesis of the antitumor and antimicrobial agent **IV**.[7] In 2018, Zhang described the same reaction but using CH_3CN as a solvent (entry 12, Table 6).[80]

Finally, diaryliodonium salts have been also used as aryl radical precursors for the arylation of quinoxalin-2-ones (entry 13, Table 6).[81] Zhang's research group stablished a metal-free procedure for the synthesis of 3-arylquinoxalin-2-ones (31 examples) using diaryliodonium tetrafluoroborates under mild conditions (room temperature and CH_3CN as solvent), although the reaction times are long (3 days) and the atom economy is low because only one of the aryl groups of the reagents is incorporated to the final product.

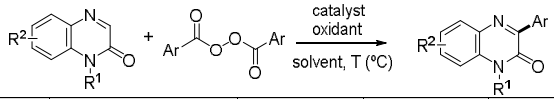
Table 6. Arylation reactions at the C-3 position of quinoxalin-2-ones.



Entry	Methodology	Catalyst	Oxidant	R^3CO-X	T (ºC)/t (h)	Solvent	Scope
1[ref. 69]	-	$Pd(OAc)_2$	O_2	Ar-$B(OH)_2$	100/20	DMF	20 examples
2[ref. 70]	-	-	$Mn(OAc)_3$	Ar-$B(OH)_2$	120/12	CH_3CN	14 examples
3[ref. 71]	Photochem.	Eosin Y	$K_2S_2O_8$	Ar-$B(OH)_2$	rt/12	H_2O	26 examples
4[ref. 72]	-	$Pd(OAc)_2$	O_2	Ar-$SiMe_3$	80/9	H_2O	27 examples
5[ref. 73]	-	$Pd(TFA)_2$	Ag_2O	Ar-H	110/20	Ar-H	34 examples
6[ref. 74]	-	-	PhIO	Ar-NH_2NH_2	rt / 9	CH_3CN	27 examples
7[ref. 75]	Photochem.	2D-COF-1	air	Ar-NH_2NH_2	rt/24	DMSO	23 examples
8[ref. 76]	-	-	$K_2S_2O_8$	Ar-NH_2NH_2	50/9	CH_3CN	27 examples
9[ref. 77]	Photochem.	Eosin Y	-	Ar-N_2BF_4	rt/2	DMSO	31 examples
10[ref. 78]	Mechanochem.		$BaTiO_3$[a]	Ar-N_2BF_4	rt / 4	CH_3CN	15 examples
11[ref. 79]	-	-	*t*BuONO	Ar-NH_2	rt/1.5	Acetone	30 examples
12[ref. 80]	-	-	*t*BuONO	Ar-NH_2	rt/48	CH_3CN	32 examples
13[ref. 81]	-	-	-	Ar_2-IBF_4	rt/72	CH_3CN	31 examples

Aryl acyl peroxides are relatively cheap and readily from available carboxylic acid derivatives, and can generate easily *O*-centered radicals (acyloxyl radicals) or *C*-centered radicals (aryl radicals) *via* decarboxylation under different reaction conditions. In 2020, these reagents were used in four reports for the C-3 arylation of quinoxalin-2-ones under photochemical or thermal conditions (Table 7). The research groups of Li[82] and He[83] reported independently the same photocatalyst-, metal and additive-free protocol for the arylation of quinoxalin-2-ones using aryl acyl peroxides under the irradiation of 420 nm LEDs. The only differences of these two report are the solvent (Li used acetone while He ethyl acetate) and the scope of the reaction: Li reported 40 examples, while He only described 13 examples. In both articles, they explored the scalability of the reaction to gram-scale and the synthesis of the same antitumor agent.[7] The same year, Wei[84] and Chen[85] independently described the same protocol, but thermal conditions were used instead of photochemical conditions. In both cases, they heat the reaction at 80 ºC, but again the solvent is different. Wei used ethyl acetate, whereas Chen used acetone as solvent.

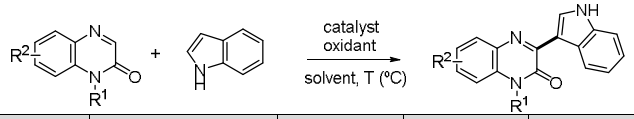
Table 7. Arylation reactions at the C-3 position of quinoxalin-2-ones using diaroyl peroxides.



Entry	Methodology	Catalyst	Oxidant	T (ºC)/t (h)	Solvent	Scope
1[ref. 82]	Photochem.	-	air	rt/2	Acetone	40 examples
2[ref. 83]	Photochem.	-	air	rt/3	EtOAc	13 examples
3[ref. 84]	-	-	air	80/24	EtOAc	24 examples
4[ref. 85]	-	-	air	80/12	Acetone	25 examples

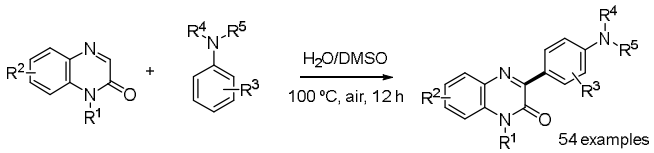
One easy way to introduce aryl moieties into organic molecules is employing the Friedel-Crafts reaction. In this case, the reactions are favored when electron-rich aromatic compounds are used as reagents. In this regard, indoles represent perfect nucleophiles to perform Friedel-Crafts reactions. Moreover, indole is one of the most important *N*-heteroaromatic scaffolds because of its ubiquitous presence in biologically active molecules and natural occurring compounds.[86] Indole has been used as nucleophile for the C-3 arylation of quinoxalin-2-ones (Table 8). The first report was described by the group of Yuan in 2010 (entry 1, Table 8).[87] They described a one pot synthetic procedure for the preparation of 3-(indol-3-yl)quinoxalin-2-ones using TfOH as Brønsted acid and air as oxidant in DMF at 80 ºC. The drawback of this methodology is the use of a strong Brønsted acid. Later, Chupakhin's laboratory described a synthetic protocol using titanium dioxide (TiO_2) as photocatalyst, along with acetic acid as solvent at 120 ºC under O_2 atmosphere and irradiation of a Xe lamp.[88] Using these harsh conditions, the researchers could directly arylate quinoxalin-2-ones with indoles with good yields, but the scope of the reaction is very narrow with only 4 examples. Finally, a more suitable and practical synthetic method was described by Yotphan in 2018 (entry 3, Table 8).[89] In his report, iodine-catalyzed reaction of quinoxalin-2-ones with indoles in methanol was developed, without the requirement of acids, heating or oxidants others than air. This protocol represents a more sustainable and convenient synthetic methodology with a good substrate scope (25 examples) and functional group compatibility. Additionally, the scalability of the reaction to 10 mmol was performed with excellent results.

Table 8. Friedel-Crafts reactions of indoles with quinoxalin-2-ones.



Entry	Methodology	Catalyst	Oxidant	T (ºC)/t (h)	Solvent	Scope
1[ref 87]	-	TfOH	air	80/1-28	DMF	21 examples
2[ref 88]	Photochem.	TiO_2	O_2	120/5	AcOH	4 examples
3[ref 89]	-	I_2	air	rt/8	MeOH	25 examples

Finally, another arylation using quinoxalin-2-ones as electrophiles was reported by Li and co-workers using anilines as a coupling partners (Scheme 1).[90] The reaction takes place selectively at *p*-position to the amine group and is performed in mixture of H_2O/DMSO at 100 ºC using air as sole oxidant. This reaction is an efficient and green methodology, with perfect atom economy and without the requirement of any kind of catalyst. The authors described a superb scope with 54 examples and they also carried out several mechanistic studies that demonstrate a radical pathway. Moreover, they study the recyclability and reusability of their system. The H_2O/DMSO was recycled trough vacuum distillation and was reused for other reactions, obtaining comparable yields for 5 reaction cycles showing a great sustainability.



Scheme 1. Arylation reactions at the C-3 position of quinoxalin-2-ones with anilines.

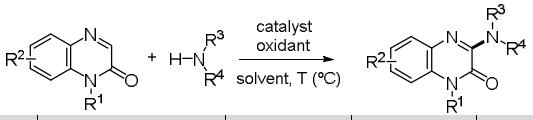
2.2. C–N Bond formation

The formation of a C–N bond represents a crucial endeavor in organic synthesis, due to the importance, the synthetic usefulness and biological importance of nitrogen atom in multitude of molecules. For example, nitrogen is the fourth element by mass in the human body as it is part of the DNA and proteins. Therefore, the incorporation of this atom to organic molecules is pivotal for chemical synthesis. The direct C–H amination allows the construction of C–N bonds and leads to the rapid incorporation of nitrogen atoms into molecules, which offers a potentially highly atom economical synthesis of nitrogen derived compounds with minimal

environmental impact. Several examples have been described for the direct C-3 amination, amidation and sulfoximination of quinoxalin-2-ones, that we will disclose in the next lines.

The first oxidative amination of quinoxalin-2-ones was reported by Gulevskaya in 2008.[91] They used $AgPy_2MnO_4$ or $KMnO_4$ as oxidants and the corresponding aliphatic amines (primary and secondary) were used as solvent. The scope of the methodology was narrow (7 and 6 examples), and the yields of the corresponding products were moderate. Later, in 2016 Cui and co-workers developed a more efficient method for the C-3 amination of quinoxalin-2-ones using aliphatic primary and secondary amines catalyzed by $Cu(OAc)_2$ (5 mol%) using air as oxidant (entry 3, Table 9).[92] The reaction conditions are mild and a better scope of the reaction (24 examples) was accomplished. From the point of view of sustainable chemistry, the recycling of the catalyst is an important issue that in heterogeneous catalysis is a fundamental characteristic. In 2017, the group of Phan described the amination of quinoxalin-2-ones at C3 with secondary and primary alkyl amines using a copper-organic framework (Cu-CPO-27) as heterogeneous catalyst obtaining a collection (15 examples) of 3-aminoalkylated quinoxalin-2-ones with good yields (entry 4, Table 9).[93] The authors showed that the Cu-MOF catalyst can be reused over 5 consecutive runs, obtaining similar conversion for each run. In 2017, Jain's group developed a I_2-catalyzed C-3 amination of quinoxalin-2-ones using TBHP as terminal oxidant (entry 5, Table 9).[94] The protocol exhibited a wide substrate scope (32 examples) with primary and secondary aliphatic amines (1 example with an aromatic amine) and good functional group tolerance, obtaining the corresponding aminated quinoxalin-2-ones with good to excellent yields under metal free conditions. They also showed the synthetic utility of their methodology, by showing the preparation of an aldose reductase inhibitor, that possess antidiabetic activity.[5b] A more sustainable method to functionalize the C-3 position with nitrogen nucleophiles was achieved by the research group of Wei in 2018.[95] They described a organophotoredox method, based on the use of Eosin Y as organophotocatalyst that catalyzed the reaction of quinoxalin-2-ones with an assortment of primary and secondary aliphatic amines under the irradiation of blue LEDs (entry 5, Table 9) being the oxidant the oxygen from air. Finally, an electrochemical complementary methodology has also been described for the amination of quinoxalin-2-ones with secondary and primary aliphatic amines (entry 6, Table 9).[96] Zeng and co-workers described this reaction using an undivided cell, at room temperature, with a graphite as an anode and a platinum net as a cathode. Interestingly, they could perform the reaction using imidazole and benzotriazole as nitrogen source obtaining the corresponding products with good yields. The practicability of the protocol was demonstrated by a scale-up reaction to 10 mmol (59% yield).

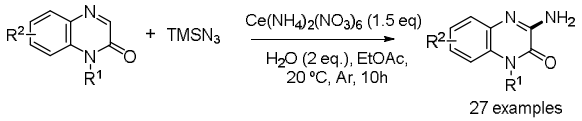
Table 9. Amination reactions at the C-3 position of quinoxalin-2-ones.



Entry	Methodology	Catalyst	Oxidant	T (ºC)/t (h)	Solvent	Scope
1[ref. 91]	-	-	$AgPy_2MnO_4$	rt/6	Amine	7 examples
2[ref. 91]	-	-	$KMnO_4$	rt/24	Amine	6 examples
3[ref. 92]	-	$Cu(OAc)_2$	air	100/12	DMSO	24 examples
4[ref. 93]	-	Cu-CPO-27	O_2	80/16	DMA	15 examples
4[ref. 94]	-	I_2	TBHP	rt/16	dioxane	32 examples
5[ref. 95]	Photochem.	Eosin Y	air	rt/24	THF	30 examples
6[ref. 96]	Electrochem.	-	-	rt/6	DMF	21 examples

The introduction of a simple NH_2 moiety into organic molecules is not an easy task. Recently, Zhang and co-workers described an efficient, simple and mild amination of quinoxalin-2-ones with $TMSN_3$ in the presence of ceric ammonium nitrate as oxidant, that provides 3-aminoquinoxalin-2-ones with good yields (Scheme 2).[97] They could apply their method to a gram scale reaction with good results (74 % yield). The drawback of this protocol is the use of overstoichiometric amounts of a cerium salt.

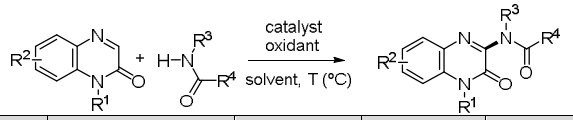
Amide represent an important class of nitrogen containing chemical group, which is found in numerous natural products, pharmaceuticals, and functional materials.



Scheme 2. Amination at the C-3 position of quinoxalin-2-ones with $TMSN_3$.

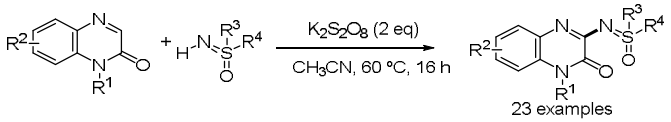
However, the C–N bond formation using amides as nitrogen nucleophiles is challenging, because amides are less nucleophilic than amines due to the delocalization of the lone pair to the neighbor carbonyl group. Several methods have been developed for the functionalization of quinoxalin-2-ones at the C-3 with amides moieties (Table 10). The research group of Yuan described a palladium-catalyzed oxidative amidation of quinoxalin-2-ones with acetonitrile (entry 1, Table 10).[98] A series of 3-acetamido quinoxalin-2-one derivatives (23 examples) were prepared with good yields using acetonitrile as an amidation reagent, $Pd(OAc)_2$ (10 mol%) as catalyst and $K_2S_2O_8$ as oxidant. Disappointedly, when *N*-unprotected quinoxalin-2-one was tested, the desired amidation product was not observed. After that, the same group further extended the methodology to prepare other 3-amidated quinoxalines. They reported a copper-catalyzed amidation using a wide range of amides and employing $K_2S_2O_8$ as oxidant under microwave irradiation (entry 2, Table 10).[99] The reaction tolerates primary and secondary aliphatic amides as well as primary and secondary aromatic amides. Interestingly, this method is ligand- and base-free. However, the reaction needed *N*-substituted quinoxalin-2-ones to obtain good conversions. Later, in 2019 the same group reported a more sustainable approach for the C3-amidation of quinoxalin-2-ones by developing a transition-metal free protocol using Selectfluor as a mild oxidant (entry 3, Table 10).[100] The scope of the reaction is similar to the previously reported methods, but in this case when the reaction was carried out with the *N*-unprotected quinoxalin-2-one the corresponding amidation product was obtained with moderate yield. They showed the robustness of their methodology by performing a gram-scale reaction. The same year, Wei-Min He and collaborators stablished a more sustainable methodology for the amidation of quinoxalin-2-ones (entry 4, Table 10).[101] They described the photochemical cross-dehydrogenative coupling of quinoxalin-2-ones and simple amides using Rhodamine B as organophotoredox catalyst, ambient air as simple oxidant at room temperature under the irradiation of Blue LEDs. The corresponding products (32 examples) are obtained with good yields. One drawback of this method is that the reaction only tolerates primary aliphatic/aromatic amides. An interesting amidation of quinoxalin-2-ones was stablished by Zhang in 2019 (entry 5, Table 10).[102] This group reported a $Cu(OAc)_2$-catalyzed direct cross-dehydrogenative coupling of quinoxalin-2-ones with diverse *N*-unprotected quinoxalin-2-ones and quinolin-2-ones. The scope of the reaction was broad, 26 examples, and they observed a good functional group tolerance.

Table 10. Amidation reactions at the C-3 position of quinoxalin-2-ones.



Entry	Methodology	Catalyst	Oxidant	T (°C)/t (h)	Solvent	Scope
1[ref. 98]	-	$Pd(OAc)_2$	$K_2S_2O_8$	100/12	CH_3CN	23 examples
2[ref. 99]	-	CuBr	$K_2S_2O_8$	80/0.5	CH_3CN	38 examples
3[ref. 100]	-	-	Selectfluor	60/4	CH_3CN	31 examples
4[ref. 101]	Photochem.	Rhodamine B	air	rt/24	$ClCH_2CH_2Cl$	32 examples
5[ref. 102]	-	$Cu(OAc)_2$	air	120/8	DMAc	26 examples

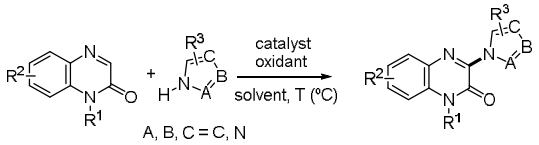
Ongoing with the formation of C–N bonds, another interesting example was described by Yotphan and co-workers (Scheme 3).[103] They performed a metal-free protocol for the direct coupling of sulfoximines to quinoxalin-2-one derivatives under oxidative conditions using $K_2S_2O_8$ as oxidant. Sulfoximine represents an intriguing functionality with high chemical stability and potent biological activities, however their use as reagent is less studied. Under optimized conditions, a broad range of quinoxalinone and sulfoximine substrates were compatible with this transformation, which could provide the corresponding products (23 examples) with moderate to excellent yields.



Scheme 3. Sulfoximation at the C-3 position of quinoxalin-2-ones with sulfoximes.

Azoles are an important class of compounds that are broadly found in pharmaceutical agents, natural products and functional materials.[104] Therefore, the development of synthetic methodologies for the direct functionalization of such compounds is pivotal for synthetic organic chemistry, especially the direct oxidative coupling to form C–N bonds to provide more efficient and concise synthesis of azoles. Some protocols have been developed for the C-3 functionalization of quinoxalin-2-ones with azoles, especially with pyrazoles. Wang, Li and co-workers were the first that described this reaction using a photochemical protocol without an external photosensitizer and air as terminal oxidant under the irradiation of a 390-395 nm LEDs (entry 1, Table 11).[105] The corresponding quinoxalin-2-one derivatives (32 examples) were obtained with moderate to good yields, and the reaction tolerates the use of pyrazoles, triazoles, 1*H*-indazole, 1*H*-1,2,4-benzotriazole and 1*H*-benzimidazole. Later, Xia's research group reported a strategy for the oxidative functionalization of quinoxalin-2-ones with pyrazoles using PIFA as oxidant (entry 2, Table 11).[106] The reaction takes place in only 1 hour in EtOAc under mild reaction conditions. The scope of the reaction is very broad (47 examples), and in general the yields are higher than the previously reported. They also extend the methodology to benzimidazole, 1*H*-indazole, 1*H*,2,4-triazole, 1*H*-benzotriazole and 1*H*-tetrazole derivatives with good results. Lastly, an electrochemical approach has also been described (entry 3, Table 11).[107] In 2021, Wang described the electro-oxidative C-3 functionalization of quinoxalin-2-ones with pyrazoles using an undivided cell with two graphite electrodes at room temperature for 8 h. The scope of the reaction is narrower than the other methods (29 examples) and they could also use as azoles 1*H*,2,3-triazole and 1*H*-benzotriazole.

Table 11. Amination reactions at the C-3 position of quinoxalin-2-ones with azoles.



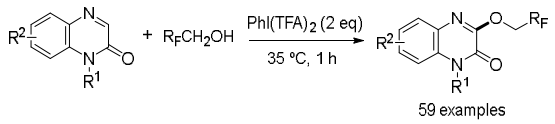
Entry	Methodology	Catalyst	Oxidant	T (ºC)/t (h)	Solvent	Scope
1[ref. 105]	Photochem.	-	air	rt/20	CH_3CN	32 examples
2[ref. 106]	-	-	$PhI(TFA)_2$	rt/1	EtOAc	47 examples
3[ref. 107]	Electrochem.	-	-	rt/8	CH_3CN	29 examples

2.3. C–O Bond formation

The C–O bond formation reactions using the nucleophilic character of alcohols or alkoxides are pivotal for organic synthesis. In this sense, the reaction between an alkoxide and an organic halide, the Williamson's synthesis of ethers,[108] constitutes an important milestone in the formation of C–O bonds. In the context of C-3 functionalization of quinoxalin-2-ones, some protocols have been developed for the formation of C-O at this position.

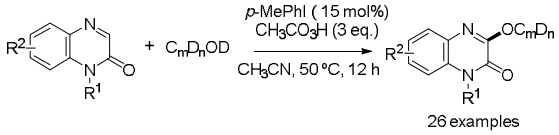
Zhang and co-workers[109] described the first report on the oxidative C–H fluoroalkoxylation of quinoxalin-2-ones with fluoroalkyl alcohols. The use of fluoroalkyl alcohols offers the added advantage of introducing highly lipophilic fluorine moieties into the target compound. In this communication, $PhI(TFA)_2$ was employed as an oxidant under solvent and metal free conditions (Scheme 4). The authors showed a wide scope obtaining the corresponding quinoxalin-2-one derivatives with good yields. Besides trifluoroethanol, other fluoroalkyl alcohols were also effective obtaining the corresponding product with good yields. Moreover, the trifluoroethoxyl group could also be used as an available leaving group in S_NAr reactions. So, the authors investigated the reactivity of trifluoroethyl ethers derivatives toward nucleophilic substitution with morpholine obtaining the corresponding aminated products which are histamine-4 receptor antagonists.[11] The

authors study the mechanism of the reaction by performing several experiments which revealed radical intermediates.



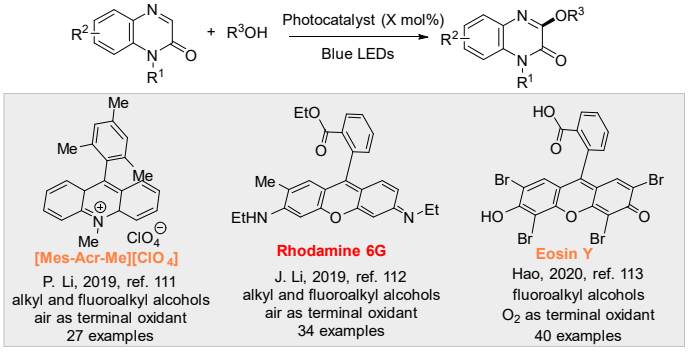
Scheme 4. Fluoroalcoxylation at the C-3 position of quinoxalin-2-ones with fluoroalkyl alcohols.

Another example of metal-free alkoxylation of quinoxalin-2-ones with deuterated alcohols was described by Shen's group using *p*-iodomethylbenzene as catalyst, peroxyacetic acid as oxidant at 50 ºC in CH_3CN (Scheme 5).[110] The corresponding deuterated quinoxalin-2-one derivatives were obtained with moderated to good yields. As in the previous example, control experiments verify that a radical pathway is involved in the reaction.



Scheme 5. Trideuteroalcoxylation at the C-3 position of quinoxalin-2-ones with deuterated alcohols.

The field of photochemistry has also been explored to carry out the C-3 functionalization of quinoxalin-2-ones with alcohols and fluoroalkyl alcohols. Three methods have been described using different organophotoredox catalysts (Scheme 6). In 2019, Pinhua Li and co-workers described the first etherification of quinoxalinones under visible-light photoredox catalysis using as catalyst the Fukuzimi's photocatalyst, the alcohol as solvent at room temperature under air atmosphere and Blue LEDs irradiation.[111] 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), and several alcohols can be used as reagents (primary and secondary). However, the reaction did not proceed using phenols or tertiary alcohols as reagents. The same year, Jianjun Li and collaborators described the same transformation but using Rhodamine 6G as organophotocatalyst and adding trifluoroacetic acid as an additive under the irradiation of Blue LEDs.[112] Their methodology has a good substrate scope (34 examples), but did not work when tertiary alcohols or phenols are used. Finally, the last example of etherification of quinoxalin-2-ones using a photochemical protocol was reported by Hao in 2020.[113] This group described the fluoroalcoxylation of quinoxalin-2-ones using Eosin Y as photocatalyst under O_2 atmosphere at room temperature under irradiation of Blue LEDs.



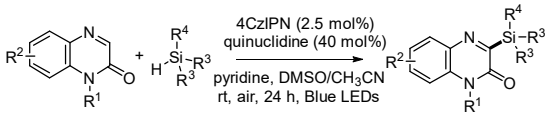
Scheme 6. Alcoxylation at the C-3 position of quinoxalin-2-ones using photochemical methods.

They demonstrate the applicability of the reaction, performing a gram-scale reaction (72 % yield, 1.86 grams) and the synthesis of a histamine-4 receptor antagonist[11] through the C–H trifuoroethoxylation, followed by a nucleophilic substitution with 1-methylpiperazine.

Finally, an electrochemical complementary methodology has also been described for the C3 alcoxylation of quinoxalin-2-ones with primary and secondary aliphatic alcohols.[114] Yu, Li and co-workers described the etherification reaction using an undivided cell, at room temperature, with a graphite as an anode and a platinum plate as a cathode. The substrate scope was extensive (30 examples), but when secondary alcohols were used as reagents the corresponding products were obtained with moderate yields.

2.4. C–Si Bond formation

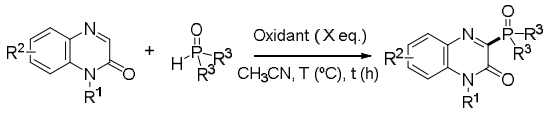
Organosilanes have gained increased attention from synthetic organic chemists due to their high lipophilicity which allows studies to evaluate their biological activity. They are also very important for materials science.[115] Therefore, the direct introduction of silicon motifs in biological active compounds is very interesting for medicinal chemistry. Only one example has been reported by Sun and collaborators for the photoredox C-3 silylation of quinoxalin-2-ones with *t*-butyldimethylsilane using 4-CzIPN as organophotocatalyst in air at room temperature under Blue LEDs irradiation (Scheme 7).[116] They could apply these conditions to several substituted quinoxalin-2-ones (23 examples), as well as other silanes such triethylsilane and triisopropylsilanes. Moreover, they could scale up the reaction to 6 mmol with good results (63% yield).



Scheme 7. Silylation at the C-3 position of quinoxalin-2-ones with trialkylsilanes.

2.5. C–P Bond formation

Phosphorous containing molecules are important for organic chemistry because these compounds have found wide applications as pharmaceuticals, agrochemicals, functional materials, and so on.[117] Moreover, they are also important intermediates in organic synthesis. Therefore, it is of great importance in synthetic organic chemistry develop methodologies for the construction of the C–P bond. In this context, several methodologies have been described for the cross-dehydrogenative coupling reaction between quinoxalin-2-ones and phosphorous reagents. In 2016, Cui and co-workers reported the first direct C3-phosphonation of quinoxalin-2-ones with H-phosphonates, H-phosphinates or H-phosphine oxides under transition-metal free conditions (Scheme 8).[118] The methodology uses as oxidant $K_2S_2O_8$ (3 equivalents) in CH_3CN at 100 ºC. Under these conditions, the authors reported a good substrate scope (20 examples) with good yields. Moreover, the authors performed some control experiments suggesting that the reaction involved a radical pathway. In 2019, Yuan's research group described a milder protocol for the direct phosphonation of quinoxalin-2-ones under transition-metal free conditions.[119] They described an efficient and convenient protocol for the C–P bond formation at C-3 position of quinoxalin-2-ones using H-phosphonates, H-phosphinates or H-phosphine oxides. In their method, the oxidant used is Selectfluor (1.5 eq.) in CH_3CN at 40 ºC. Moreover, they reported more examples (25), and a gram-scale reaction. As in the previous example, the authors claim that this transformation proceed *via* radical mechanism after the analysis of control experiments.

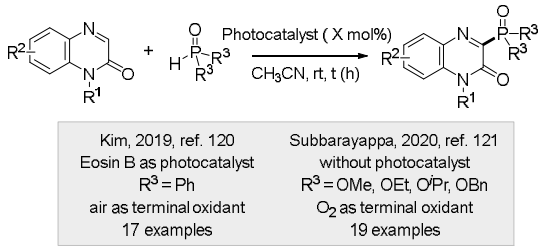


Cui et al: $K_2S_2O_8$ (3 eq.) as oxidant at 100 °C, 7 h (20 examples)

Yuan et al: Selectfluor (1.5 eq.) as oxidant at 40 °C, 3 h (25 examples)

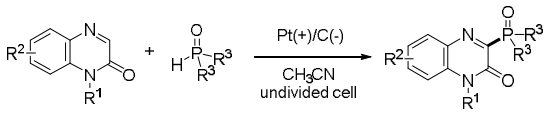
Scheme 8. Phosphonylation at the C-3 position of quinoxalin-2-ones.

Two photochemical approaches have been also developed for the functionalization of quinoxalinones with phosphorous reagents. In 2018, Kim and co-workers developed the visible light photoredox-catalyzed C3-phosphorylation of quinoxalin-2-ones with diphenylphosphine oxide in ambient air at room temperature under the irradiation of a 20 W compact fluorescence lamp (Scheme 9).[120] The reaction worked well with inexpensive and readily available Eosin B as an organophotoredox catalyst without any metal, oxidant, or additive. The final oxidant is the oxygen from air. A wide range of functional groups were compatible with this transformation and the authors showed 17 examples and a gram scale reaction (80% yield). However, the authors only performed the reaction with diphenylphosphine oxide. In 2020, Subbarayappa established an interesting phosphonation of quinoxalin-2-ones using only oxygen as oxidant under the irradiation of 40 W incandescent lamp.[121] This method is very convenient for the functionalization with alkyl phosphonates due to the mild reaction conditions without the use of any photocatalyst.



Scheme 9. P-Functionalization at the C-3 position of quinoxalin-2-ones.

Lastly, two electrochemical complementary methodologies have also been established for the C3 phosphorous functionalization of quinoxalin-2-ones (Scheme 10). Wang's research group described the oxidative coupling reaction of diaryl phosphine oxides using an undivided cell, at 50 ºC, with a graphite as an anode and a platinum plate as a cathode.[122] With this conditions the authors presented 21 examples with moderate to good yields and a 5 mmol scale reaction (84% yield). While Zeng's group described the C-3 functionalization of quinoxalin-2-ones using diaryl phosphine oxide as well as dialkyl phosphonates (23 examples).[123] They also use an undivided cell with a graphite anode and a platinium net as cathode and the temperature of the reaction was 40 ºC in CH_3CN.

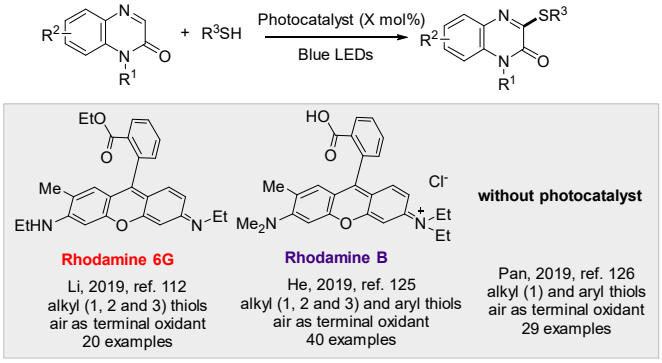


Scheme 10. Electrochemical phosphorylation at the C-3 position of quinoxalin-2-ones.

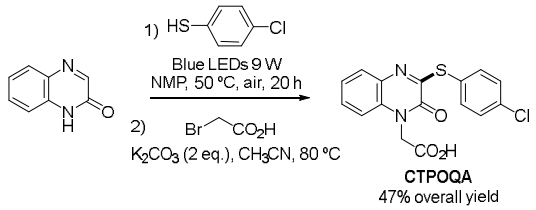
2.6. C–S Bond formation

Sulfur containing molecules have attracted great interest of chemists because of their prevalence in various materials and pharmaceutically relevant drugs.[124] Consequently, numerous efforts have been devoted to establish direct, efficient and reliable methods for the formation of C–S bonds. However, cross dehydrogenative C–S coupling reaction to construct sulfur containing compounds still remains a challenge because thiols can be easily over-oxidized to sulfoxides and sulfones. Therefore, the development of new methods under mild reaction conditions is essential to incorporate sulfenyl groups into molecules. In this context, several methodologies have been described for the tioetherification of quinoxalin-2-ones. In 2019, three different groups have described photochemical approaches to accomplish the functionalization of quinoxalin-2-ones with thiols (Scheme 11). In 2019, Li research group described in the same article for the etherification of quinoxalin-2-ones, the extension of the scope of his catalytic protocol to the formation of C–S bond using aliphatic thiols as nucleophiles. Rhodamine 6G as used as organophotocatalyst and trifluoroacetic acid as an additive under the irradiation of Blue LEDs.[112] Under these conditions, the authors obtained a set of 20 examples of 3-substituted thioalkoxylated quinoxalin-2-ones with good yields. Shortly

after, a very similar protocol established by the Wei-Min He laboratory was published.[125] They reported the direct C-3 sulfenylation of quinoxalin-2-ones with thiols using Rhodamine B as photocatalyst and THF as solvent under the irradiation of Blue LEDs. The authors applied the optimized reaction conditions to a variety of substituted quinoxalin-2-ones and distinct aliphatic (primary, secondary and tertiary) thiols, obtaining a total of 40 structures. Moreover, benzene thiol could be used, although the yield of the corresponding reaction product was moderate. Interestingly, the applicability of the thioalcoxylation method 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). From the point of view of atom economy and sustainable chemistry, Pan and co-workers described a more convenient method. They developed a visible-light-enabled photocatalyst-free protocol for the sulfenylation of quinoxalin-2-ones with thiols under the irradiation of Blue LEDs.[126] They conducted the reaction at 50 ºC in *N*-methyl-2-pyrrolidone (NMP) obtaining good yields with a good substrate scope (29 examples). The examples using aryl thiols are remarkable, due to that in the previous reports aryl thiols were not suitable. However, they only described 3 examples using primary aliphatic thiols with moderate yields. In addition, the authors reported also a gram scale reaction to synthesize 2-(3-(4-chlorothiophenoxy)-2-oxoquinoxalin-1(2H)-yl)acetic acid (CTPOQA) in 47 % overall yield after 2 steps, which had showed aldose reductase inhibitor activity[127] (Scheme 12).



Scheme 11. Sulfenylation at the C-3 position of quinoxalin-2-ones using photochemical methods.



Scheme 12. Synthesis of CTPOQA, an aldolase reductase inhibitor.

Finally, an electrochemical method has also been established for the C3 thioalcoxylation of quinoxalin-2-ones. In 2020, Jianjun Li described the electrochemical cross-dehydrogenative coupling between quinoxalin-2-ones and thiols using an undivided cell with platinum electrodes for both the cathode and the anode in DMF at room temperature.[128] Under these conditions, several examples of quinoxalin-2-ones functionalized at C-3 position with sulfide groups were obtained with moderate to good yields (31 examples). The reaction tolerates efficiently primary, secondary and tertiary alkyl thiols, although when they used aryl thiols the corresponding products were obtained with low yields.

3. C-3 Functionalization of dihydroquinoxalin-2-ones

The functionalization at the C-3 position of 3,4-dihydroquinoxalin-2-ones has been studied by several research groups using diverse nucleophiles. However, the interest about the functionalization of these

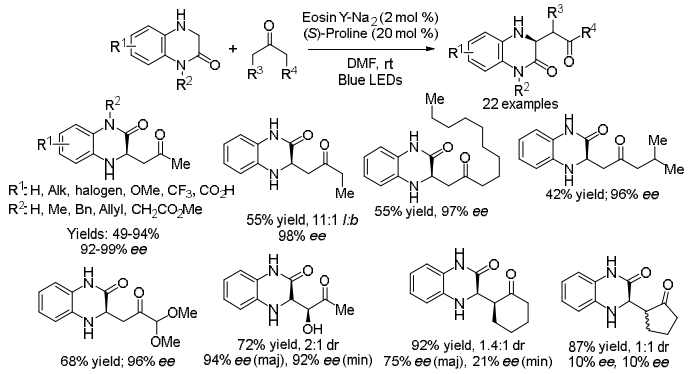
derivatives has emerged very recently and, due to that, only few examples can be found in the literature. This section is divided into four subsections. In the first one, the examples regarding the functionalization of 3.4-dihydroquinoxalin-2-ones with carbon nucleophiles are presented. Then, in the second subsection the efforts on the formation of C–N bonds are discussed. Finally, in the two last subsections the functionalization of 3,4-dihydroquinoxalin-2-ones with either oxygen nucleophiles or phosphorous nucleophiles is presented.

3.1. C–C Bond formation

The formation of C–C bonds is one of the most important flagships in organic chemistry. As a result, a great effort is being done for the C-3 functionalization of 3,4-dihydroquinoxalin-2-ones with carbon nucleophiles using different approaches.

3.1.1. Alkylation reactions

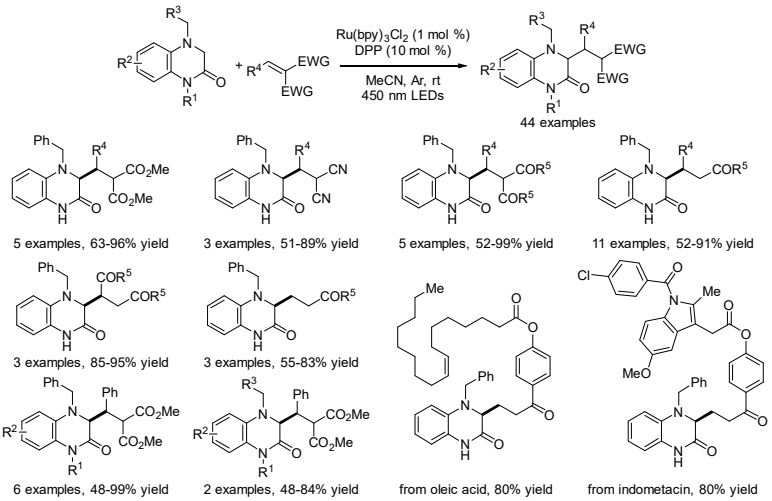
Two examples can be found in the literature regarding the alkylation of 3,4-dihydroquinoxalin-2-ones at the C-3 position. The first one was described by our research group in 2019 (Scheme 13).[129] We envisioned that the 3,4-dihydroquinoxalin-2-one could be photochemically oxidized in the presence of Eosin Y to quinoxalin-2-one, which might be trapped by the chiral enamine formed from a linear ketone and (*S*)-proline. This combined oxidation-asymmetric Mannich reaction protocol allowed us to obtain a library of 20 enantiomerically enriched 3-substituted 3,4-dihydroquinoxalin-2-ones in good to excellent yields (49-94%) and with excellent stereocontrol (75-99% *ee*). Our protocol was quite tolerant regarding the substitution at both the amidic nitrogen and the aromatic ring with different electron-donating and electron-withdrawing groups. It is important to note that the presence of different redox-active moieties, such as -NCH_2CO_2Me as well as the allyl group, are completely tolerated, obtaining only the desired product. With respect to the nucleophile, the reaction worked well with acetone, but the performance was lower when larger ketones were employed. However, those products were also generated with excellent enantioinduction and an excellent linear:branch selectivity. Interestingly, our reaction could be scaled-up to 5 mmol using sunlight as the irradiation source, obtaining the desired chiral product in 67% yield and 99% *ee*.



Scheme 13. Enantioselective alkylation of 3,4-dihydroquinoxalin-2-ones with ketones.

The second methodology about the alkylation of 3,4-dihydroquinoxalin-2-ones was also described by us (Scheme 14).[130] In this case, we were interested in the generation of an α-amino radical at the C-3 position. The formation of this nucleophilic radical (namely a captodative radical) was envisioned because the presence of both electron-donating group (the aminic nitrogen) and the electron-withdrawing group (the amide) is crucial for its stability and for its enhanced nucleophilicity. To our surprise, we had to employ a photocatalyst ($Ru(bpy)_3Cl_2$) in combination with a Brønsted acid (diphenyl phosphoric acid, DPP) to trigger the reaction between the 3,4-dihydroquinoxalin-2-one and dimethyl benzylidenemalonate. Besides, the reaction needs to be carried out under argon atmosphere in order to avoid overoxidation of the α-amino radical. Having stablished the optimized reaction conditions, the robustness of our protocol was subjected to investigation. A myriad of electron-poor alkenes were found to be competent in our methodology, namely arylidene malonates

(5 examples, 63-96% yield), arylidene malononitriles (3 examples, 51-89% yield), Knoevenagel adducts derived from 1,3-diketones (5 examples, 52-99% yield), α,β-unsaturated ketones (11 examples, 52-91% yield), endiones (3 examples, 83-95% yield) and several interesting substrates such as cyclohexenone (97% yield), acrolein (71% yield), methyl vinyl ketone (83% yield) and two attractive electron-poor alkenes derived from oleic acid (80% yield) or indometacin (79% yield). The scope regarding the substitution of the 3,4-dihydroquinoxalin-2-one moiety was also studied. The reaction was quite tolerant to different electron-donating and electron-withdrawing groups at the aromatic ring (5 examples, 66-99% yield). Additionally, two different 3,4-dihydroquinoxalin-2-ones bearing benzylic substituents with either a CH_3O or a CF_3 group were also tested (2 examples, 48-84% yield).



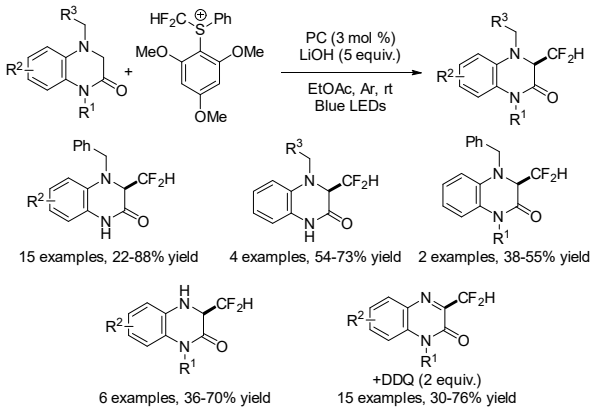
Scheme 14. Alkylation of 3,4-dihydroquinoxalin-2-one using electron-poor alkenes.

The practicability of our methodology was demonstrated by conducting the alkylation of 4-benzyl-3,4-dihydroquinoxalin-2-one with *trans*-1,4-diphenylbut-2-ene-1,4-dione at gram-scale using sunlight as energy source, obtaining the corresponding product in 97% yield (1.15 g) after 3 h. Several synthetic derivatizations of the products were also carried out. Namely, the 1,4-diketone moiety was transformed into two (*N*-H and *N*-allyl) pyrrole-containing derivatives. Additionally, one 1,3-diketone derivative reacted with methylhydrazine to yield the expected pyrazole core. Finally, to overcome the disadvantage that α,β-unsaturated monoesters are not suitable in this protocol, the diester derivative was selectively decarboxylated by means of Krapcho decarboxylation. In order to find out the mechanism by which the reaction may proceed, several experiments were carried out. After the determination of the quantum yield, voltammetry studies, luminiscence quenching experiments among others, we proposed that a complex between DPP and the corresponding 3,4-dihydroquinoxalin-2-one is the responsible of the quenching of the excited state of $Ru(bpy)_3Cl_2$. To the best of our knowledge, this activation of a tertiary amine towards single electron transfer is unprecedented.

3.1.2. Fluoroalkylation reactions

Just one example about the fluoroalkylation of 3,4-dihydroquinoxalin-2-ones can be found in the literature. It was developed in 2022 by the research group of Guo Kai-Liu using their own-developed *S*-(difluoromethyl) diarylsulfonium salts as bench-stable precursors of difluoromethyl radical (Scheme 15).[131] Their findings led them to select a naphthalene-1,4-diamine as photocatalyst, LiOH as additive, EtOAc as solvent and Blue LEDs as energy source. With these optimized conditions in hand, they were able to explore the generality of the transformation by testing differently substituted 3,4-dihydroquinoxalin-2-ones. First, they engaged variously substituted 4-alkyl-3,4-dihydroquinoxalin-2-ones under their optimal conditions, obtaining

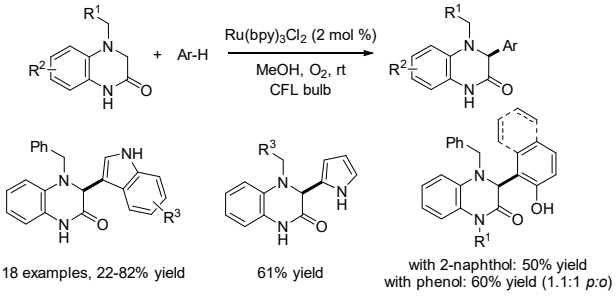
a library of 21 difluoromethylated 3,4-dihydroquinoxalin-2-ones in moderate to good yields (22-82%). Moreover, they applied their photocatalytic conditions to N-H unprotected 3,4-dihydroquinoxalin-2-ones. These secondary amines reacted smoothly with the difluoromethyl radical precursor to furnish the expected products in moderate yields (6 examples, 36-70% yield). In some cases, they found trifluoromethylated quinoxalin-2-ones, which could come from overoxidation of the parent 3,4-dihydroquinoxalin-2-ones derivatives. The authors took advantage of this fact adding a second oxidation step using DDQ. With this sequence, they were capable of obtaining 15 difluoromethylated quinoxalin-2-ones in moderate to good yield (30-74%). The authors also carried out several mechanistic studies that shown that the reaction occurs through a radical pathway.



Scheme 15. Fluoroalkylation of 3,4-dihydroquinoxalin-2-one using *S*-(difluoromethyl) diarylsulfonium salts.

3.1.3. Arylation reactions

There is only an example regarding the arylation of 3,4-dihydroquinoxalin-2-ones, which has been described by the laboratory of Hong in 2018 (Scheme 16).[132] In this work, the authors were able to oxidize the tertiary amine moiety of 3,4-dihydroquinoxalin-2-one to the iminium cation, which could be trapped by an indole through a Friedel-Crafts reaction. Although the reaction can proceed without the need of a photocatalyst, the yield is higher when $Ru(bpy)_3Cl_2$ is employed. In order to reach the iminium cation of 3,4-dihydroquinoxalin-2-one, the reaction should be conducted under O_2 atmosphere, using MeOH as solvent and CFL bulb as the source of radiation. The scope reaction was studied using indoles bearing either electron-donating or electron-withdrawing groups, obtaining the expected products in 22-82% yield (17 examples). Interestingly, the generality of the reaction could be further extended to other electron-rich arenes such as 2-naphthol (50% yield), phenol (60% yield, 1.1:1 *p*:*o*) as well as pyrrole (61% yield).



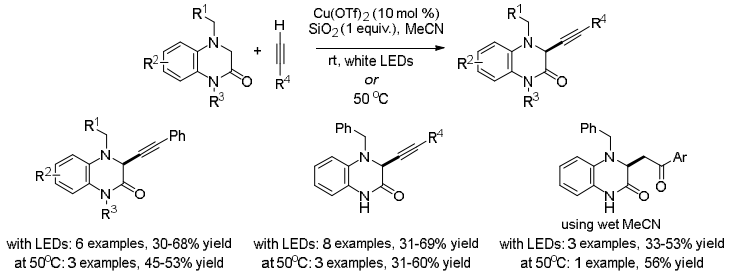
Scheme 16. Arylation of 3,4-dihydroquinoxalin-2-ones with indoles and other electron-rich arenes through a Friedel-Crafts reaction.

The robustness of the reaction was also studied using different 3,4-dihydroquinoxalin-2-ones, obtaining the desired products in moderate to good yields (5 examples, 49-75%). Most of the examples were also reported without $Ru(bpy)_3Cl_2$, but the products were obtained in significant lower yield. Several experiments were carried out to find out the mechanism of the reaction, showing a radical mechanism where the visible-light irradiation is necessary.

3.1.4. Alkynylation reactions

To the best of our knowledge, the only alkynylation reaction of 3,4-dihydroquinoxalin-2-ones was described by our research group in 2020.[133] On one hand, as in many alkynylation reactions, a metal ion is needed to activate the terminal alkyne through the formation of the metal alkynylide. On the other hand, oxidation of tertiary amines until the iminium cation can be accomplished using a catalytic metal under an aerobic atmosphere. In our case, the best metal capable of participating efficiently in this double role was copper (II) triflate. Additionally, we found out that the irradiation of the reaction mixture with white light was beneficial for the outcome of the reaction, as well as the use of silica (SiO_2) as additive (Scheme 17).

Once stablished the optimized conditions, the scope of the reaction was examined (16 examples). First, the substitution at the 3,4-dihydroquinoxalin-2-one skeleton was subjected to study. The reaction tolerated the presence of different substituents at the aminic nitrogen (3 examples, 45-53% yield), as well as at the aromatic ring (3 examples, 31-60% yield). Then, several differently substituted aromatic terminal alkynes were tested in our protocol, obtaining the desired products in moderate to good yield (6 examples, 44-68%). Besides, two aliphatic terminal alkynes bearing either a cyclopropane ring (31% yield) or a 1-phenylethane group (33% yield). Interestingly, when the reaction was carried out with electron-rich terminal alkynes using wet MeCN, the alkyne moiety was hydrated and the ketone-derived product was obtained (3 examples, 33-53% yield).



Scheme 17. Alkynylation of 3,4-dihydroquinoxalin-2-ones with terminal alkynes.

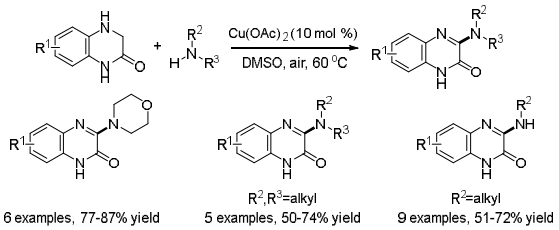
Then, to showcase the versatility of our alkynylated 3,4-dihydroquinoxalin-2-ones, three hydrogenation protocols were applied. *Z*-alkene could be obtained in the presence of Lindlar's catalyst (95% yield), whereas complete hydrogenation was achieved with catalytic $Pd/CaCO_3$ (99% yield) Besides, both complete hydrogenation and hydrogenolysis of the benzyl protecting group was accomplished with regular Pd/C (10%) catalyst (99% yield). Finally, to gain insight into the reaction mechanism, a series of simple experiments were conducted. The reaction did not proceed in the presence of TEMPO or under argon atmosphere, showing that a radical pathway is likely but molecular oxygen is crucial for the outcome of the reaction. As expected, the reaction without copper (II) triflate did not generate the desired product, indicating that this metal probably acts as both a redox catalyst for the oxidation of 3,4-dihydroquinoxalin-2-one and as an activating agent for terminal alkynes.

3.2. C–N Bond formation

The direct formation of a C–N bond at the C-3 position of 3,4-dihydroquinoxalin-2-ones has been reported by the group of Huo[134] and by us[135] in 2021. Regardless of the final aminated product, the approach that both research laboratories have described is quite a few different. While the research group of Huo employed amines as nucleophiles once the iminium cation of 3,4-dihydroquinoxalin-2-one is generated, the strategy followed by us took advantage of the electrophilicity of dialkyl azodicarboxylates as aminating agents.

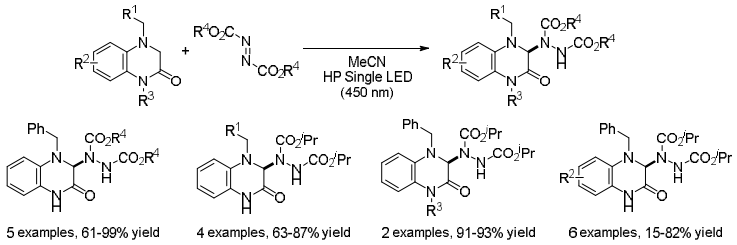
From an electronic point of view, in the first case the authors developed a nucleophilic amination whereas we reported an electrophilic one (Scheme 18).

In the work of Huo, 3,4-dihydroquinoxalin-2-ones, which are unprotected at the aminic nitrogen, could be oxidized to quinoxalin-2-ones assisted by $Cu(OAc)_2$ under an aerobic atmosphere. Once the oxidation occurs, the electrophilic C=N bond reacts with several primary and secondary amines but their protocol failed with anilines. As expected, when the amination takes place, the product is reoxidized under the reaction conditions to achieve aromatic 3-aminated-quinoxalin-2-ones in moderate to high yield (20 examples, 50-87% yield) bearing different patterns of substitution at both the aromatic ring and the amino nucleophile. They were also able to scale-up the reaction to obtain 1.34 g (68% yield) of morpholine-derived quinoxalin-2-one. The mechanism proposed by the authors was the one stablished for this kind of oxidative functionalization of amines in which copper acts as a redox catalyst in the oxidation of 3,4-dihydroquinoxalin-2-one with molecular oxygen.



Scheme 18. Nucleophilic amination of 3,4-dihydroquinoxalin-2-ones with secondary and primary aliphatic amines.

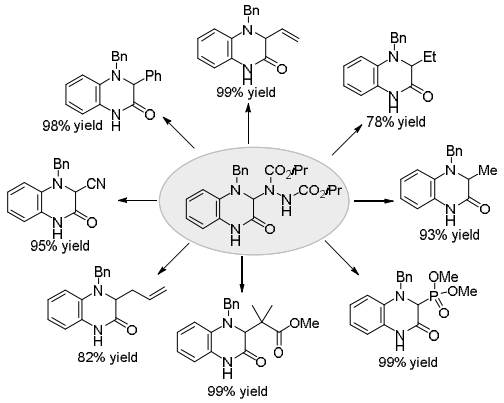
As previously noted, our research group employed a different approach towards aminated 3,4-dihydroquinoxalin-2-ones. We used dialkyl azodicarboxylates as aminating agent, and we found out that the reaction with 4-benzyl-3,4-dihydroquinoxalin-2-one was feasible, obtaining the desired product in 91% yield after 24 h in CH_3CN at rt. Nevertheless, when we conducted the reaction under the irradiation of High Power (HP) Single LED (450 nm) the expected product was also obtained but the reaction time was shortened to 2 h. With this very simple protocol in hand, the generality of the reaction was studied, obtaining a library of C-3 aminated 3,4-dihydroquinoxalin-2-ones with different dialkyl azodicarboxylates (5, examples, 61-99% yield). Then, the substitution pattern was explored regarding the 3,4-dihydroquinoxalin-2-one scaffold, being able to generate several 3,4-dihydroquinoxalin-2-one with different substitution features in 15-93% yield (12 examples) (Scheme 19).



Scheme 19. Electrophilic amination of 3,4-dihydroquinoxalin-2-ones with dialkyl azodicarboxylates.

In order to test some synthetic modifications on the reaction products, the methodology was scaled-up to 6.6 mmol scale, using either sunlight or a blue LED strip (450 nm) as radiation source, obtaining the aminated 3,4-dihydroquinoxalin-2-one with diisopropyl azodicarboxylate in 83-90% yield. Interestingly, we found that the aminated product could be further derivatized taking advantage of the dicarbamate moiety ability as leaving group under certain conditions (Scheme 20). Precisely, C–C bond forming reactions could be carried out on aminated 3,4-dihydroquinoxalin-2-one with either a Grignard reagent or a silicon nucleophile

(also adding $BF_3 \cdot OEt_2$), obtaining the corresponding alkylation products in excellent yield (99% for most of the cases). Besides, C–P bond forming reaction could also take place using dimethyl phosphite in the presence of $BF_3 \cdot OEt_2$.

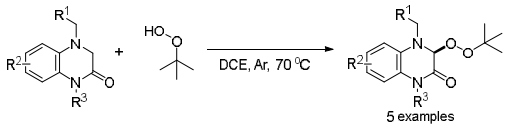


Scheme 20. Synthetic diversification of the aminated products obtained from 3,4-dihydroquinoxalin-2-ones and dialkyl azodicarboxylates.

Additionally, in order to shed light on the reaction mechanism, canonical control experiments were done. The reaction in the presence of either TEMPO as radical scavenger or under an aerobic atmosphere furnished the expected product in high yield, showing that a radical pathway is unlikely for the reaction. The rate-increasing phenomenon observed when the reaction was irradiated could come from the *E*-*Z* isomerization of the azo group, making it more electrophilic.

3.3. C-O Bond formation

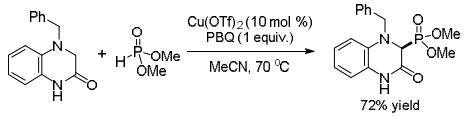
The C–O bond forming reactions involving the C-3 position of 3,4-dihydroquinoxalin-2-ones are scarce and just a few reactions can be found in a work of Huo in 2020 (Scheme 21).[136] In that report, the authors developed a protocol for the peroxidation of 3,4-dihydro-1,4-benzoxazin-2-ones using *t*-butyl hydroperoxide (TBHP). The scope of the reaction was narrow with only five examples, although the yields of the corresponding products were good (70-82%).



Scheme 21. Peroxidation of 3,4-dihydroquinoxalin-2-ones using TBHP.

3.4. C–P Bond formation

Regarding the development of methodologies for C–P bond formation at the C-3 position of 3,4-dihydroquinoxalin-2-ones, there is only one example from the laboratory of Huo, which appeared in the literature in 2018 (Scheme 22).[137]



Scheme 22. Phosphonation of 4-benzyl-3,4-dihydroquinoxalin-2-one using dimethyl phosphite.

That report is about the phosphonation of 3,4-dihydro-1,4-benzoxazin-2-ones with organic phosphites, but the authors also tested the reaction using 4-benzyl-3,4-dihydroquinoxalin-2-one and dimethyl phosphite, obtaining the desired product in 72% yield by the joint action of $Cu(OTf)_2$ and *p*-benzoquinone (PBQ).

4. Conclusions

As summarized in this chapter, the C-3 functionalization of quinoxalin-2-ones and dihydroquinoxalin-2-ones is a hot topic in organic synthesis. It is shown that a variety of functional groups can be readily incorporated at the C3 position of these *N*-heterocycles using several methodologies (metal, electrochemical and photochemical) attesting to the potential of these approaches in the synthesis of highly biologically active heterocycles. Many of the methodologies discussed above can be described as a green and sustainable. Some of them completely avoid the use of any transition metals, while others use visible-light as an energy source. Despite these achievements, more challenges remain to be addressed, such as tolerance of functional groups, extend the substrate scope, the real application for the synthesis of target molecules, the formation of C–X or C–Se bonds or the development of more robust catalytic systems. Moreover, the functionalization of dihydroquinoxalin-2-ones is underdeveloped compared with the synthetic repertoire to functionalize quinoxalin-2-ones.

Acknowledgements

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References

1. Moody, C. J. in: *Advances in Nitrogen Heterocycles*, AI Press LTD., London, **1999**.
2. a) Carta, A.; Piras, S.; Loriga, G.; Paglietti, G. *Mini-Rev. Med. Chem*. **2006**, *6*, 1179-1200; b) Shi, L.; Hu, W.; Wu, J.; Zhou, H.; Zhou, H.; Li, X. *Mini-Rev. Med. Chem*. **2018**, *18*, 392-413.
3. Shi, L.; Zhou, H.; Wu, J.; Li, X. *Mini-Rev. Org. Chem.* **2014**, *12*, 96-112.
4. Kudo, Y.; Shibata, S., *Br. J. Pharmacol*, **1984**, *83*, 813-820.
5. a) Wu, B.; Yang, Y.; Qin, X.; Zhang, S.; Jing, C.; Zhu, C.; Ma, B. *ChemMedChem* **2013**, *8*, 1913-1917. b) Hussain, S.; Parveen, S.; Hao, X.; Zhang, S.; Wang, W.; Qin, X.; Yang, Y.; Chen, X.; Zhu, S.; Zhu, C.; Ma, B. *Eur. J. Med. Chem*. **2014**, *80*, 383-392.
6. Meyer, E.; Joussef, A. C.; de Souza, L. D. B. P. *Synth. Commun*. **2006**, *36*, 729-741.
7. Sanna, P.; Carta, A.; Loriga, M.; Zanetti, S.; Sechi, L.*Il Farmaco* **1999**, *54*, 169-177.
8. Cil, O.; Phuan, P.-W.; Lee, S.; Tan, J.; Haggie, P. M.; Levin, M. H.; Sun, L.; Thiagarajah, J. R.; Ma, T.; Verkman, A. S. *Cell. Mol. Gastroenterol. Hepatol.* **2016**, *2*, 317-327.
9. Cowden, W. B.; March, D. R.; Robertson, A.; Jenkins, N. WO 2005021547 A2 20050310, **2005**.
10. Jiang, B.; Zhao, W.; Li, S.; Liu, H.; Yu, L.; Niu, W.; He, H.; Wu, L. *J. Antibiot*, **2018**, *71*, 965-967.
11. Smits, R. A.; Lim, H. D.; Hanzer, A.; Zuiderveld, O. P.; Guaita, E.; Adami, M.; Coruzzi, G.; Leurs, R.; de Esch, I. J. P. *J. Med. Chem.* **2008**, *51*, 2457-2467.
12. Galal, S. A.; Abdelsamie, A. S.; Tokuda, H.; Suzuki, N.; Lida, A.; El-Hefnawi, M. M.; Ramadan, R. A.; Atta, M. H. E.; El Diwani, H. I. *Eur. J. Med. Chem*. **2011**, *46*, 327-340.
13. a) Ren, J.; Nichols, C. E.; Chamberlain, P. P.; Weaver, K. L.; Short, S. A.; Chan, J. H.; Kleim, J.-P.; Stammers, D. K. *J. Med. Chem.* **2007**, *50*, 2301-2309. b) Cass, L. M.; Moore, K. H. P.; Dallow, N. S.; Jones, A. E.; Sisson, J. R.; Prince, W. T. *J. Clin. Pharmacol*. **2001**, *41*, 528-535.
14. Rösner, M.; Billhardt-Troughton, U.-M.; Kirsh, R.; Kleim, J.-P.; Meichsner, C.; Riess, G.; Winkler, I. U.S. Patent 5,723, 461, **1998**.
15. Yang, Y.; Zhao, L.; Xu, B.; Yang, L.; Zhang, J.; Zhang, H.; Zhou, J. *Bioorg. Chem.* **2016**, *68*, 236-244.
16. Hayes, D. J.; Mosher, T. M.; Greenshaw, A. J. *Behav. Brain Res.* **2009**, *197*, 323-330.
17. a) Mamedov, V. A.; Zhukova, N. A. *Prog. Heterocycl. Chem*. **2012**, *24*, 55-88; b) Shi, L.; Zhou, H.; Wu, J.; Li, X. *Mini-Rev. Org. Chem*. **2015**, *12*, 96-112.

18. a) Monika, M.; Selvakumar, S. *Synthesis* **2019**, *51*, 4113-4136; b) Ke, Q.; Yan, G.; Wu, X. *Org. Biomol. Chem*. **2019**, *17*, 5863-5881; c) Rostoll-Berenguer, J.; Blay, G.; Pedro, J. R.; Vila, C. *Eur. J. Org. Chem*. **2020**, *2020*, 6148-6172.
19. Hu, L.; Yuan, Y.; Fu, J.; Zhang, T.; Gao, L.; Xiao, Y.; Mao, P.; Qu, L. *Eur. J. Org. Chem*. **2018**, *2018*, 4113-4120.
20. Singh, S.; Dagar, N.; Roy, S. R. *Org. Biomol. Chem*. **2021**, *19*, 5383-5394.
21. Murarka, S. *Adv. Synth. Catal.* **2018**, *360*, 1735-1753.
22. Liu, L.; Pan, N.; Sheng, W.; Su, L.; Liu, L.; Dong, J.; Zhou, Y.; Yi, S.-F. *Adv. Synth. Catal*. **2019**, *361*, 4126-4132.
23. Zhang, H.; Xu, J.; Zhou, M.; Zhao, J.; Zhang, P.; Li, W.; *Org. Biomol. Chem*. **2019**, *17*, 10201-10208.
24. Yan, Z.; Sun, B.; Zhang, X.; Zhuang, X.; Yang, J.; Su, W.; Jin, C. *Chem. Asian J.* **2019**, *14*, 3344-3349.
25. Lian, F.; Xu, K.; Meng, W.; Zhang, H.; Tan, Z.; Zeng, C. *Chem. Commun.* **2019**, *55*, 14685-14688.
26. Niu, K.; Song, L.; Hao, Y.; Liu, Y.; Wang, Q. *Chem. Commun.* **2020**, *56*, 11673-11676.
27. Xue, W.; Su, Y.; Wang, K.-H.; Zhang, R.; Feng, Y.; Cao, L.; Huang, D.; Hu, Y. *Org. Biomol. Chem.* **2019**, *17*, 6654-6661.
28. Xie, L.-Y.; Jiang, L.-L.; Tan, J.-X.; Wang, Y.; Xu, X.-Q.; Zhang, B.; Cao, Z.; He, W.-M. *ACS Sustainable Chem. Eng.* **2019**, *7*, 14153-14160.
29. Zhang, L.; He, J.; Zhang, P.; Zheng, K.; Shen, C. *Mol. Cat.* **2022**, *519*, 112145.
30. Shao, M.; Liang, H.; Liu, Y.-L.; Qin, W.; Li, Z. *Asian J. Org. Chem.* **2020**, *9*, 782-787.
31. Niu, K.; Zhou, P.; Ding, L.; Hao, Y.; Liu, Y.; Song, H.; Wang, Q. *ACS Sustainable Chem. Eng*. **2021**, *9*, 16820-16828.
32. Hong, Y.-Y.; Peng, Z.; Ma, H.; Zhu, Q.; Xu, X.-Q.; Yang, L.-H.; Xie, L.-Y. *Tetrahedron Lett.* **2022**, *89*, 153595.
33. Wang, BY.; Yao, H.; Zhong, X.; Yan, Z.; Lin, S. *Tetrahedron Lett.* **2021**, *64*, 152720.
34. Niu, K.; Hao, Y.; Song, L.; Liu, Y.; Wang, Q. *Green Chem*. **2021**, *23*, 302.
35. Yao, L.; Zhu, D.; Wang, L.; Liu, J.; Zhang, Y.; Li, P. *Chin. Chem. Lett*. **2021**, *32*, 4033-4037.
36. Sun, J.; Yang, H.; Zhang, B.; *Green Chem*. **2022**, *24*, 858-863.
37. He, X.-K.; Lu, J.; Zhang, A.-J.; Zhang, Q.-Q.; Xu, G.-Y.; Xuan, J. *Org. Lett*. **2020**, *22*, 5984-5989.
38. Yuan, J.; Fu, J.; Yin, J.; Dong, Z.; Xiao, Y.; Mao, P.; Qu, L. *Org. Chem. Front.* **2018**, *5*, 2820-2828.
39. Fu, J.; Yuan, J.; Zhang, Y.; Xiao, Y.; Mao, P.; Diao, X.; Qu, L. *Org. Chem. Front*. **2018**, *5*, 3382-3390.
40. Wei, W.; Wang, L.; Yue, H.-L.; Bao, P.; Liu, W.; Hu, C.; Yang, D.; Wang, H. *ACS Sustainable Chem. Eng.* **2018**, *6*, 17252-17257.
41. Mane, K. D.; Kamble, R. B.; Suryavanshi, G. *New J. Chem*. **2019**, *43*, 7403-7408.
42. a) Zard, S. Z. *Chem. Soc. Rev.* **2008**, *37*, 1603-1618. b) Morcillo, S. P. *Angew. Chem. Int. Ed.* **2019**, *58*, 14044-14054.
43. Yang, L.; Gao, P.; Duan, X.-H.; Gu, Y.-R.; Guo, L.-N. *Org. Lett*. **2018**, *20*, 1034-1037.
44. Zhang, W.; Pan, Y.-L.; Yang, C.; Chen, L.; Li, X.; Cheng, J.-P. *J. Org. Chem.* **2019**, *84*, 7786-7795.
45. Zhang, W.; Pan, Y.-L.; Yang, C.; Li, X.; Wang, B. *Org. Chem. Front*. **2019**, *6*, 2765-2770.
46. Zhao, B.; Kong, X.; Xu, B. *Tetrahedron Lett.* **2019**, *60*, 2063-2066.
47. Xia, P.-J.; Hu, Y.-Z.; Ye, Z.-P.; Li, X.-J.; Xiang, H.-Y.; Yang, H. *J. Org. Chem.* **2020**, *85*, 3538-3547.
48. a) Krisch, P. *Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications*; Wiley-VCH: Weinheim, **2004**. b) *Fluorine in Medicinal Chemistry and Chemical Biology*; Ojima, I., Ed.; Wiley-Blackwell: Chichester, **2009**.
49. Wang, L.; Zhang, Y.; Li, F.; Hao, X.; Zhang, H.-Y.; Zhao, J. *Adv. Synth. Catal.* **2018**, *360*, 3969-3977.
50. Wang, J.; Sun, B.; Zhang, L.; Xu, T.; Xie, Y.; Jin, C. *Asian J. Org. Chem.* **2019**, *8*, 1942-1948.
51. Wei, Z.; Qi, S.; Xu, Y.; Liu, H.; Wu, J.; Li, H.; Xia, C.; Dua, G. *Adv. Synth. Catal.* **2019**, *361*, 5490-5498.
52. Zhang, W.; Xiang, X.-X.; Chen, J.; Yang, C.; Pan, Y.-L.; Cheng, J.-P.; Meng, Q.; Li, X. *Nat. Commun.* **2020**, *11*, 638.
53. Dutta, N. B.; Bori, J.; Gogoi, P.; Baishya, G. *ChemistrySelect* **2021**, *6*, 1471-1477.
54. Jiang, Y. Y.; Xu, K.; Zeng, C.-C. *Org. Chem. Front.* **2019**, *6*, 2392-2397.

55. Xue, W.; Su, Y.; Wang, K.-H.; Cao, L.; Feng, Y.; Zhang, W.; Huang, D.; Hu, Y. *Asian J. Org. Chem.* **2019**, *8*, 887-892.
56. Hong, G.; Yuan, J.; Pan, G.; Wang, Z.; Yang, L.; Xiao, Y.; Mao, P.; Zhang, X. *Org. Chem. Front.* **2019**, *6*, 1173-1182.
57. Gao, Y.; Zhao, L.; Xiang, T.; Li, P.; Wang, L. *RSC Adv.* **2020**, *10*, 10559-10568.
58. Wang, L.; Liu, H.; Li, F.; Zhao, J.; Zhang, H.-Y.; Zhang, Y. *Adv. Synth. Catal.* **2019**, *361*, 2354-2359.
59. Jin, C.; Zhuang, X.; Sun, B.; Li, D.; Zhu, R. *Asian J. Org. Chem.* **2019**, *8*, 1490-1494.
60. Zeng, X.; Liu, C.; Wang, X.; Zhang, J.; Wang, X.; Hu, Y. *Org. Biomol. Chem.* **2017**, *15*, 8929-8935.
61. Bao, P.; Liu, F.; Lv, Y.; Yue, H.; Li, J.-S.; Wei, W. *Org. Chem. Front*. **2020**, *7*, 492-498.
62. Xie, L.-Y.; Bai, Y.-S.; Xu, X.-Q.; Peng, X.; Tang, H.-S.; Huang, Y.; Lin, Y.-W.; Cao, Z.; He, W.-M. *Green Chem.* **2020**, *22*, 1720-1725.
63. Lu, J.; He, X.-K.; Cheng, X.; Zhang, A.-J.; Xu, G.-Y.; Xu, J. *Adv. Synth. Catal.* **2020**, *18*, 6558-6563.
64. Ni, H.; Shi, X.; Li, Y.; Zhang, X.; Zhao, J.; Zhao, F. *Org. Biomol. Chem*. **2020**, *18*, 6558-6563.
65. Yuan, J.-W.; Fu, J.-H.; Liu, S.-N.; Xiao, Y.-M.; Mao, P.; Qu, L.-B. *Org. Biomol. Chem.* **2018**, *16*, 3203-3212.
66. Ni, H.; Li, Y.; Shi, X.; Pang, Y.; Jin, C.; Zhao, F. *Tetrahedron Lett*. **2021**, *68*, 152915.
67. Ni, H.; Li, Y.; Deng, J.; Shi, X.; Pan, Q. *New J. Chem*. **2021**, *45*, 22432-22436.
68. Hall, D. G. *Boronic Acids: Preparation and Applications in Organic Synthesis, Medicine and Materials*; Wiley-VCH: Weinheim, **2011**.
69. Carrër, A.; Brion, J.-D.; Messaoudi, S.; Alami, M. *Org. Lett.* **2013**, *15*, 5606-5609.
70. Ramesh, B.; Reddy, C. R.; Kumar, G. R.; Reddy, B. V. S. *Tetrahedron Lett*. **2018**, *59*, 628-631.
71. Bao, H.; Lin, Z.; Jin, M.; Zhang, H.; Xu, J.; Chen, B.; Li, W. *Tetrahedron Lett*. **2021**, *66*, 152841.
72. Liu, X.; Liu, Z.; Xue, Y.; Li, J.; Zou, D.; Wu, Y.; Wu, Y. *Tetrahedron Lett*. **2020**, *61*, 152612.
73. Paul, S.; Khanal, H. D.; Clinton, C. D.; Kim, S. H.; Lee, Y. R. *Org. Chem. Front*. **2019**, *6*, 231-235.
74. Paul, S.; Ha, J. H.; Park, G. E.; Lee, Y. R. *Adv. Synth. Catal*. **2017**, *359*, 1515-1521.
75. Tian, M.; Liu, S.; Bu, X.; Yu, J.; Yang, X. *Chem. Eur. J*. **2020**, *26,* 369-373.
76. Dutta, N. B.; Bhuyan, M.; Baishya, G. *RSC Advances* **2020**, *10*, 3615-3624.
77. Kwon, S. J.; Jung, H. I.; Kim, D. Y. *ChemistrySelect* **2018**, *3*, 5824-5827.
78. Liu, Fu, Chen, L.-N.; Chen, A.-M.; Ye, Z.-P.; Wang, Z.-W.; Liu, Z.-L.; He, X.-C.; Li, S.-H.; Xia, P.-J. *Adv. Synth. Catal*. **2022**, *364*, 1080-1084.
79. Yuan, J.; Liu, S.; Qu, L. *Adv. Synth. Catal*. **2017**, *359*, 4197-4207.
80. Zhang, R.; Yin, K. *Synlett*, **2018**, *29*, 597-602.
81. Yin, K.; Zhang, R. *Org. Lett.* **2017**, *19*, 1530-1533.
82. Xu, J.; Zhang, H.; Zhao, J.; Ni, Z.; Zhang, P.; Shi, B.-F.; Li, W. *Org. Chem. Front*. **2020**, *7*, 4031-4042.
83. Xie, L.-Y.; Peng, S.; Yang, L.-H.; Peng, C.; Lin, Y.-W.; Yu, X.; Cao, Z.; Peng, Y.-Y.; He, W.-M. *Green Chem*. **2021**, *23*, 374-378.
84. Lv, Y.; Bao, P.; Yue, H.; Wei, W. *Tetrahedron Lett.* **2020**, *61*, 152559.
85. Chen, B.; Wang, S.; Song, J.; Wang, X.; Yu, B.; Yang, X. *Tetrahedron Lett.* **2021**, *62*, 152681.
86. Sundberg, R. J., Ed. *Indoles,* Academic Press: San Diego, **1996**.
87. Han, Y.-Y.; Wu, Z.-J.; Zhang, X.-M.; Yuan, W.-C. *Tetrahedron Lett.* **2010**, *51*, 2023-2028.
88. Utepova, I. A.; Trestsova, M. A.; Chupakhin, O. N.; Charushina, V. N.; Rempel, A. A. *Green Chem.* **2015**, *17*, 4401-4410.
89. Moikham, M.; Kittkool, T.; Yotphan, S. *Synthesis* **2018**, *50*, 2337-2346.
90. Xu, J.; Huang, L.; He, L.; Liang, C.; Ouyang, Y.; Shen, J.; Jiang, M.; Li, W. *Green Chem*. **2021**, *23*, 6632-6638.
91. Gulevskaya, A. V.; Burov, O. N.; Pozharskii, A. F.; Kletskii, M. E.; Korbukova, I. N. *Tetrahedron* **2008**, *64*, 696-707.
92. Li, Y.; Gao, M.; Wang, L.; Cui, X. *Org. Biomol. Chem*. **2016**, *14*, 8428-8432.
93. Hoang, T. T.; To, T. A.; Cao, V. T. T.; Nguyen, A. T.; Nguyen, T. T.; Phan, N. T. S. *Catal. Commun*. **2017**, *101*, 20-25.
94. Gupta, A.; Deshmukh, M. S.; Jain, N. *J. Org. Chem.* **2017**, *82*, 4784-4792.

95. Wei, W.; Wang, L.; Bao, P.; Shao, Y.; Yue, H.; Yang, D.; Yang, X.; Zhao, X.; Wang, H. *Org. Lett.* **2018**, *20*, 7125-7130.
96. Li, K.-J.; Xu, K.; Liu, Y.-G.; Zeng, C.-C.; Sun, B.-G. *Adv. Synth. Catal*. **2019**, *361*, 1033-1041.
97. Yang, Q.; Yang, Z.; Tan, Y.; Zhao, J.; Sun, Q.; Zhang, H.; Zhang, Y. *Adv. Synth. Catal.* **2019**, *361*, 1662-1667.
98. Yuan, J.; Liu, S.; Xiao, Y.; Mao, P.; Yang, L.; Qu, L. *Org. Biomol. Chem*. **2019**, *17*, 876-884.
99. Yuan, J.; Zhu, J.; Fu, J.; Yang, L.; Xiao, Y.; Mao, P.; Dua, X.; Qu, L. *Org. Chem. Front*. **2019**, *6*, 925-935.
100. Yuan, J.; Zhu, J.-L.; Li, B.; Yang, L.-Y.; Mao, P.; Zhang, S.-R.; Li, Y.-C.; Qu, L.-B. *Org. Biomol. Chem*. **2019**, *17*, 10178-10187.
101. Xie, L.-Y.; Hu, J.-L.; Song, Y.-X.; Jia, G.-K.; Lin, Y.-W.; He, J.-Y.; Cao, Z.; He, W.-M. *ACS Sustainable Chem. Eng*. **2019**, *7*, 19993-19999.
102. Guo, T.; Wang, C.-C.; Fu, X.-H.; Liu, Y.; Zhang, P.-K. *Org. Biomol. Chem*. **2019**, *17*, 3333-3337.
103. Sumunnee, L.; Pimpasri, C.; Noikham, M.; Yotphan, S. *Org. Biomol. Chem*. **2018**, *16*, 2697-2704.
104. a) Rossello, A.; Bertini, S.; Lapucci, A.; Macchia, M.; Martinelli, A.; Rapposelli, S.; Herreros, E.; Macchia, B. *J. Med. Chem.* **2002**, *45*, 4903-4912. b) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893-930.
105. Sun, M.; Wang, L.; Zhao, L.; Wang, Z.; Li, P. *ChemCatChem* **2020**, *12,* 5261-5268.
106. Guo, J.; Zhang, L.; Du, X.; Zhang, L.; Cai, Y.; Xia, Q. *Eur. J. Org. Chem*. **2021**, 2230-2238.
107. Niu, K.; Ding, L.; Zhou, P.; Hao, Y.; Liu, Y.; Song, H.; Wang, Q. *Green Chem*. **2021**, *23*, 3246-3249.
108. Wang, Z. *Williamson Ether Synthesis*. In *Comprehensive Organic Name Reactions and Reagents*, Ed. Z. Wang, **2010**, 3026-3030.
109. Xu, J.; Yang, H.; Cai, H.; Bao, H.; Li, W.; Zhang, P. *Org. Lett*. **2019**, *21*, 4698-4702.
110. Jin, J.; Tong, J.; Yu, W.; Qiao, J.; Shen, C. *Catal. Commun*. **2020**, *141*, 106008.
111. Zhao, L.; Wang, L.; Gao, Y.; Wang, Z.; Li, P. *Adv. Synth. Catal.* **2019**, *361*, 5363-5370.
112. Zhou, J.; Zhou, P.; Zhao, T.; Ren, Q.; Li, J. *Adv. Synth. Catal.* **2019**, *361*, 5371-5382.
113. Xu, X.; Xia, C.; Li, X.; Sun, J.; Hao, L. *RSC Adv.* **2020**, *10*, 2016-2026.
114. Jiang, X.; Yang, L.; Ye, Z.; Du, X.; Fang, L.; Zhu, Y.; Chen, K.; Li, J.; Yu, C. *Eur. J. Org. Chem*. **2020**, *2020*, 1687-1694.
115. Pooni, P. K.; Showell, G. A.; *Mini-Rev. Med. Chem*. **2006**, *6*, 1169-1177.
116. Dai, C.; Zhan, Y.; Liu, P.; Sun, P. *Green Chem*. **2021**, *23*, 314-319.
117. a) Khan, Q. A.; Lu, J.; Hecht, S. M. *J. Nat. Prod.* **2009**, *72*, 438-442. b) Duan, Z. F.; Li, X.; Huang, H. X.; Yuan, W.; Zheng, S. L.; Liu, X. Z.; Zhang, Z.; Choy, E.; Harmon, D.; Mankin, H.; Hornicek, F.; *J. Med. Chem.* **2012**, *55*, 311-3121. c) Bayne, J. M.; Stephan, D. W.*Chem. Soc. Rev.* **2016**, *45*, 765-774.
118. Gao, M.; Xie, Y.; Chauvin, R.; Cui, X. *Chem. Commun*. **2016**, *52*, 2846-2849.
119. Mai, W.-P.; Yuan, J.-W.; Zhu, J.-L.; Li, Q.-Q.; Yang, L.-R.; Xiao, Y.-M.; Mao, P.; Qu, L.-B. *ChemistrySelect*, **2019**, *4*, 11066-11070.
120. Kim, Y.; Kim, D. Y. *Tetrahedron Lett*. **2018**, *59*, 2443-2446.
121. Rawat, D.; Kumar, R.; Subbarayappa, A. *Green Chem*. **2020**, *22*, 6170-6175.
122. Hu, C.; Hong, G.; Zhou, C.; Tang, Z.-C.; Han, J.-W.; Wang, L.-M. *Asian J. Org. Chem.* **2019**, *8*, 2092-2096.
123. Li, K.-J.; Jiang, Y.-Y.; Xu, K.; Zeng, C.-C.; Sun, B.-G. *Green Chem*. **2019**, *21*, 4412-4421.
124. Feng, M.; Tang, B.; Liang, S. H.; Jiang, X. *Curr. Top. Med. Chem.* **2016**, *16*, 1200-1216.
125. Xie, L.-Y.; Chen, Y.-L.; Qin, L.; Wen, Y.; Xie, J.-W.; Tan, J.-X.; Huang, Y.; Cao, Z.; He, W.-M. *Org. Chem. Front.* **2019**, *6*, 3950-3955.
126. Teng, Q.-H.; Yao, Y.; Wei, W.-X.; Tang, H.-T.; Li, J.-R.; Pan, Y.-M. *Green Chem.* **2019**, *21*, 6241-6245.
127. Qin, X. Y.; Hao, X.; Han, H.; Zhu, S. J.; Yang, Y. C.; Wu, B. B.; Hussain, S.; Parveen, S.; Jing, C. J.; Ma, B.; Zhu, C. J. *J. Med. Chem.* **2015**, *58*, 1254-1267.
128. Zhou, J.; Li, Z.; Sun. Z.; Ren, Q.; Zhang, Q.; Li, H.; Li, J. *J. Org. Chem*. **2020**, *85*, 4365-4372.
129. Rostoll-Berenguer, J.; Blay, G.; Muñoz, M. C.; Pedro, J. R.; Vila, C. *Org. Lett.* **2019**, *21*, 6011-6015.
130. Rostoll-Berenguer, J.; Blay, G.; Pedro, J. R.; Vila, C. *Org. Lett.* **2020**, *22*, 8012-8017.

131. Xiong, W.; Qin, W-B.; Zhao, Y-S.; Fu, K-Z.; Liu, G-K. *Org. Chem. Front.* **2022**, *9*, 2141-2148.
132. Akula, P. S.; Hong, B-C.; Lee, G-H. *RSC Adv.* **2018**, *8*, 19580.
133. Rostoll-Berenguer, J.; Blay, G.; Pedro, J. R.; Vila, C. *Synthesis* **2020**, *52,* 544-552.
134. Wan, S.; Wang, J.; Huo, C. *Tetrahedron Letters* **2021,** *78*, 153271.
135. Rostoll-Berenguer, J.; Capella-Argente, M.; Blay, G.; Pedro, J. R.; Vila, C. *Org. Biomol. Chem.* **2021,** *19*, 6250-6255.
136. Wang, J.; Bao, X.; Wang, J.; Huo, C. *Chem. Commun.* **2020**, *56*, 3895-3898.
137. Wang, J.; Li, J.; Wei, Y.; Yang, J.; Huo, C. *Org. Chem. Front.* **2018**, *5*, 3534-3537.