VNIVERSITAT DE VALÈNCIA

New Synthetic Methodologies to Functionalize 3,4-Dihydroquinoxalin-2-ones and 3,4-Dihydro-1,4-benzoxazin-2-ones using Visible-Light Photocatalysis

Tesi Doctoral

Jaume Rostoll Berenguer

Programa de Doctorat en Química (RD 99/2011)

Directors:

Carlos Vila Descals i José Ramón Pedro Llinares

Departament de Química Orgànica

Facultat de Química

Octubre del 2022

Declaration

Carlos Vila Descals, investigador *Ramón y Cajal* de la Universitat de València i **José Ramón Pedro Llinares**, Catedràtic d'Universitat de la Universitat de València

CERTIFIQUEN:

Que aquesta Tesi Doctoral, que porta per títol ***New Synthetic Methodologies to Functionalize 3,4-dihydroquinoxalin-2-ones and 3,4-dihydro-1,4-benzoxazin-2-ones using Visible-Light Photocatalysis*** ha sigut realitzada sota la seua supervisió en el Departament de Química Orgànica de la Universitat de València pel Graduat en Química i Màster en Química Orgànica **Jaume Rostoll Berenguer**, i per tant autoritzen la seua presentació perquè puga ser qualificada com a Tesi Doctoral amb Menció Internacional.

València, Octubre de 2022.

Dr. Carlos Vila Descals **Prof. Dr. José Ramón Pedro Llinares**

> Interesseu-vos, us conjure, per aquestes estances sagrades que designem amb l'expressiu nom de laboratoris. Demaneu que es multipliquen i s'equipen: ells són els temples del futur, de la riquesa i del benestar. És en ells on la humanitat s'engrandeix, s'enforteix i millora. Allí s'aprén a llegir en les obres de la naturalesa, obres de progrés i d'harmonia universal, mentre que les obres humanes es caracteritzen sovint per la barbàrie, el fanatisme i la destrucció.

LOUIS PASTEUR (1822-1895), al·legat a favor del finançament públic dels laboratoris a França.

> *«Prenez intérèt, je vous en conjure, à ces demeures sacrées que l'on désigne du nom expressif de laboratoires. Demandez qu'on les multiplie et qu'on les orne: ce sont les temples de l'avenir, de la richesse et du bien-être. C'est là que l'humanité grandit, se fortifie et devient meilleure. Elle y apprend à lire dans les oeuvres de la nature, oeuvres de progrès et d'harmonie universelle, tandis que ses oeuvres à elle sont trop souvent celles de la barbarie, du fanatisme et de la destruction.»*

Agraïments

Sempre m'ha voltat pel cap què posar ací. Pot sonar una mica naïf, però m'és molt complicat agrair a totes les persones que, d'una manera o d'una altra, han contribuït a que aquests quatre anys i escaig acaben en bon port.

Com no, començar pels meus directors. Gràcies a José Ramón, qui em va captivar amb la seua passió per la química orgànica des d'una aula allà pel 2015, i que després m'ha continuat transmetent la seua devoció per la recerca. Ara la cosa ja es complica més, perquè no crec que trobe les paraules precises per definir què ha significat per a la meua carrera personal i professional el fet de creuar-me amb Carlos. Des d'aquell estiu de 2015 no ja ens hem separat, i ja són més de 7 anys en què d'una manera o altra hem estat lligats amb el denominador comú de la química orgànica. Has sigut amb qui m'he emmirallat i m'ha fet estimar allò que fem tots els dies, com tindre eixos cuquets a l'estómac simplement per veure una TLC que tenia bona pinta. També, en el plànol més personal has sigut un puntal on agafar-se, especialment en temes burocràtics. Acabe aquesta etapa conscient que a banda d'un excel·lent mentor, també m'emporte un amic. Moltes gràcies també a la resta de membres del grup: Gonçal, Isabel, Mari Llum i Amparo. També al Ministeri d'Universitats la concessió d'un contracte predoctoral FPU (FPU17/00688).

Sé que no cal escriure-ho, però és per a mi molt important donar el valor que els meus pares es mereixen en tot aquest procés. Soc coneixedor del mantra sobre els fills únics, i he de reconéixer que en el meu cas és descaradament veritat. No se m'acut com haguera pogut estar més estimat pels meus pares. Eixe vincle entre tots tres no és descriptible en paraules, eixes abraçades després de setmanes a *la capital*, eixes converses d'ànims malgrat no saber ben bé què és el que faig al laboratori. A banda d'ells, a tota la meua família d'Altea, perquè funcionem com una autèntica *famiglia* italiana, tots units. A tu especialment, Joanet, que eres el (cosí) germà que ha arribat a mi després de 19 anys.

Des que estic a València, Altea ha sigut per a mi un refugi de desconnexió, un lloc on sempre soc feliç gràcies als meus amics, que estem estimant-nos i aguantant-nos des dels quatre anys: Mari Àngels, Toni, Dani, Joan, Alba, Tània, Inma, Lucia, Anna, Marina i Pere. I com no, a Mar, que més que una amiga, eres una germana. Vos estime molt.

També agrair als meus companys de laboratori Adrián, Ricardo, Álvaro i Pablo pels

bons moments que m'heu fet passar i per totes les converses motivadores i esperançadores que practiquem. Com no, agrair de manera contundent a tots aquells TFGs i TFMs que heu passat pel laboratori i heu deixat la vostra empremta en aquesta tesi: Dani, Murta, María, Fran i Víctor. Als meus companys de màster, pel grandíssim any que vam passar, especialment als que van fer el TFM al mateix grup: Dani, Jorge i David. Aquelles estones dins i fora del laboratori no es poden descriure en paraules. Als meus amics de la carrera Borja, Carles i Héctor, que qui ens anava a dir que acabaríem endinsant-nos en aquest món que desconeixíem, i que potser ara coneixem massa.

I would also like to thank Dr. Pep Cornellà for giving me the opportunity to join his research group at the Max-Planck-Institut für Kohlenforschung (Mülheim an der Ruhr, Germany). During those three months, I had the pleausure to meet such amazing people and to spend a great deal of wonderful time there in Mülheim. Specially, I would like to mention Jenni, Uri, Mire, Rakan, Marc, Franck, Clément, Xiuxiu, Edu and Sergio. Thank you all for making my stay there really fruitful and funny.

I finalment, a Laura, per tot el que no cap en aquestes pàgines. Mai li agrairé prou a la química el fet d'haver-nos creuat en el camí.

A Laura i als meus pares

Notes for the reader

- This *thesis* has been divided in three **parts**.
  - In **Part I**, the general introduction and the main objectives of this *thesis* is presented.
  - In **Part II** are accommodated *chapters* 1, 2, 3 and 4, regarding the **nucleophilic** functionalization of 3,4-dihydro-1,4-benzoxazin-2-ones and 3,4-dihydroquinoxalin-2-ones.
  - In **Part III**, *chapters* 5, 6, 7 and 8 about the **electrophilic** functionalization of the same substrates are presented and discussed.
- Numbering of all organic compounds has the form **m.n**, where **m** is the *chapter* number and **n** is the internal reference of that *chapter*.
- In all reaction schemes of *chapters* 1, 3, 4, 5, 6, 7 and 8, the newly-formed bond is highlighted with a wider line, but it does not have any stereochemical significance. On the contrary, wedged bonds in *chapter* 2 do represent the absolute configuration of the corresponding stereocenter(s).
- The reader can find an annex (page 431) with the structures of all the species that have been used as photocatalysts. Additionally, on page 432 the different photochemical setups that have been used along the *thesis* are presented.
- At the end of this document (page 435) there is a complete list of the publications that have arisen from the *thesis*.

Index

Symbols and Abbreviations

Å	Angstrom
Acr	Acridinium
AIBN	Azobisisobutyronitrile
API	Active Pharmacological Ingredient
aq.	Aqueous
$[\alpha]_D^{20}$	Specific rotation at 20 °C
Boc	*tert*-Butyloxycarbonyl
BOX	Bisoxazoline
bpy	2,2'-Bipyridine
bpz	2,2'-Bipyrazine
c	Speed of light
CAM	Ceric Ammonium Molybdate
Cbz	Benzyloxycarbonyl
CFB	Compact Fluorescent Bulb
CFL	Compact Fluorescent Light
conPET	Consecutive Proton-Coupled Electron Transfer
Cz	Carbazole
DABCO	1,4-Diazabicyclo[2.2.2]octane
DAST	Diethylaminosulfur trifluoride

DCE	1,2-Dichloroethane
DCM	Dichloromethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DEPT	Distortionless Enhancement by Polarization Transfer
DIAD	Diisopropyl azodicarboxylate
DIPEA	*N*,N-*D*iisopropylethylamine
DMAP	4-Dimethylaminopyridine
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethyl sulfoxide
DPP	Diphenylphosphoric acid
dr	Diastereomeric ratio
dtbbpy	4,4-Di-*tert*-butyl-2,2-dipyridine
δ	Chemical shift
E	Energy
E_{ea}	Electron affinity
E_I	Ionization energy
E_{red}	Reduction potential
EDA	Electron Donor-Acceptor
EDG	Electron-Donating Group
ee	Enantiomeric excess
equiv.	Equivalents
Eosin Y	Eosin Yellowish
ESI	Electrospray Ionization
EWG	Electron-Withdrawing Group
h	Planck constant

HAT	Hydrogen Atom Transfer
HE	Hantzsch ester
HP Single LED	High-Power Single Light-Emitting Diode
HPLC	High Performance Liquid Chromatography
HRMS	High Resolution Mass Spectrometry
I	Emission Intensity
IPN	Isophthalonitrile
k_n	Rate constant for process n
K_{SV}	Stern-Volmer constant
LED	Light-Emitting Diode
l:b	Linear:branched
λ	Wavelength
MeCN	Acetonitrile
Mes	Mesityl
MLCT	Metal-to-ligand charge transfer
Mp	Melting point
MS	Molecular Sieve
NFSI	*N*-Fluorobenzenesulfonimide
NMP	*N*-Methyl-2-pyrrolidone
NMR	Nuclear Magnetic Resonance
ν	Frequency
OAc	Acetate
o/n	Overnight
OTf	Trifluoromethanesulfonate (triflate)
PBQ	1,4-Benzoquinone

PC	Photocatalyst
PCET	Proton-Coupled Electron Transfer
phen	1,10-Phenanthroline
PMB	*p*-Methoxybenzyl
PMP	*p*-Methoxyphenyl
ppy	2-Phenylpyridine
PT	Proton Transfer
PTSA	*para*-Toluenesulfonic acid
pyBOX	Pyridine Bisoxazoline
Φ	Quantum yield
Q-TOF	Quadrupole Time of Flight Mass Spectrometer
rt	Room temperature
rr	Regioisomeric ratio
sat.	Saturated
SCE	Saturated Calomel Electrode
SDGs	Sustainable Development Goals
SET	Single Electron Transfer
S_n	Singlet electronic state *n*
T_n	Triplet electronic state *n*
t_r	Retention time
TBHP	*tert*-Butyl hydroperoxide
TBS	Tributylsilyl
TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran

TLC	Thin Layer Chromatography
TMS	Trimethylsilyl
Troc	2,2,2-Trichloroethoxycarbonyl
τ	Mean lifetime
UV	Ultraviolet

Part I

Introduction and Objectives

Introduction

0.1 Historical Background of Photochemistry

According to the IUPAC, photochemistry is the field of chemistry which studies the interaction between electromagnetic radiation (commonly referred as *light*) and matter.[1] Therefore, a photochemical reaction is a chemical transformation initiated upon the absorption of light. In this introductory section it will be shown the early observations that took place before the development of Quantum Theory, and how this theory was able to provide photochemistry a strong mathematical background and explain these initial phenomenons.

0.1.1 Photochemistry before the Quantum Theory

The first light-matter interactions reported were detected visually. For example, in 1556 some alchemists realized that the mineral horn silver (also known as *chlorargyrite*), which is entirely composed by silver chloride, turned black under the irradiation of the Sun. This early observation constitutes an important landmark for the development of modern photography.

Almost 200 years later, in 1777, the Swedish chemist Carl W. Scheele also attributed to light the ability of darkening silver chloride crystals, and concluded that violet light was the most capable one of promoting it. Shortly after, Theodor von Grotthuss was who, in 1817, formulated the first general principle of photochemistry: *"Only the light which is absorbed can be effective in producing photochemical changes"*. This statement was reformulated in 1841 by John W. Draper under the name of *Grotthuss-Draper Law*.

In early 1900s, the German physicists Max Planck and Albert Einstein laid the foundation of quantum mechanics with the explanation about the black-body radiation and the photoelectric effect, respectively. Afterwards, in 1920s, Erwin Schrödinger, Werner Heisenberg and Max Born among others endowed the early quantum theory with deep mathematical formalisms, as for example, the Schrödinger equation.

This new approach that was able to explain the microscopic world shook the basic con-

ceptions of several fields, among which is chemistry. Shortly after, new quantum-based chemical theories appeared, providing more accurate explanations to certain central affairs in chemistry, such as the atomic model,[2] the valence bond theory[3] and the molecular orbital theory.[4]

Regarding photochemistry, by means of quantum theory, Albert Einstein established that the light is composed by elementary particles called *photons*. The energy of a photon depends only on its frequency (ν) or on its wavelength (λ) (Equation 1).

$$E = h\nu = \frac{hc}{\lambda} \tag{1}$$

0.1.2 Modern Photochemistry

Pre-quantum concepts were updated and fully integrated in this theory, as for example the phenomenon of absorption, which was introduced in the *Grotthuss-Draper Law*. Now, within the quantum theory, the absorption process is viewed as the capture of a photon by an atom or a molecule. In this context, Johannes Stark and Albert Einstein were independently capable to formulate that *every photon absorbed will cause a chemical or physical reaction*, which constitutes the second principle of photochemistry, also known as *Stark-Einstein law* or *the photochemical equivalence law*. The concept of quantum yield (Φ) was also incorporated, providing a relationship between the number of absorbed photons and the molecules or atoms that suffer a certain photochemical process *i* (Equation 2).

$$\Phi_i = \frac{\text{n}^\text{o} \text{ of molecules that suffer the process } i}{\text{n}^\text{o} \text{ of absorbed photons}} \tag{2}$$

and according to *Stark-Einstein law* the summation of all these processes has to be 1 (Equation 3).

$$\sum_{i=1}^{i=n} \Phi_i = 1 \tag{3}$$

However, this second principle was experimentally refused when a summation of individual quantum yields greater than the unity was obtained, as for example in chain mechanisms. The fact that absorption of a photon can be followed by multiple processes made necessary a reformulation of this second statement by introducing the concept of primary and secondary processes. Thus, each light-triggered process will be considered a *photochemical primary process*, while any subsequent step will be treated as a *photochemical secondary process*. More specifically, photochemical primary processes involve electronically excited molecules and their deactivation mechanisms. Otherwise, a photochemical secondary process occurs from any intermediate formed in a primary process.

The absorption of a photon by an atom or a molecule is a necessary condition to

cause a photochemical reaction, but the absorbed light may be used for other primary process, such as the emission of light and/or heat. These last processes are considered *photophysical*, because they do not trigger any chemical change in the molecule.

In the late XX century, after the development of more accurate theories and techniques, photochemistry revolutionized several research fields, as for example supramolecular chemistry, organic chemistry, organometallic chemistry and molecular information processing, among others. As a consequence, photochemistry was clearly differentiated as a separated part of chemistry, in part because it involves novel chemical entities: the *electronically excited states*.

0.2 Formation and Fate of Excited States

When a specie absorbs a photon of suitable energy it produces a change in its electronic distribution. The result of this light-matter interaction is the formation of what is commonly known as excited state. Due to a different electronic distribution, **ground** and **excited** states differ substantially in terms of reactivity and shape. In this section it will be provided a short and comprehensive discussion about how excited states are formed through the absorption of a photon and how they evolve either

- through **photophysical processes**, which deactivate and regenerate the ground state accompanied by the emission of a photon or the emission of heat or
- through **photochemical processes**, which induce a chemical reaction yielding a photoproduct and sometimes the ground state is regenerated (Figure 1).

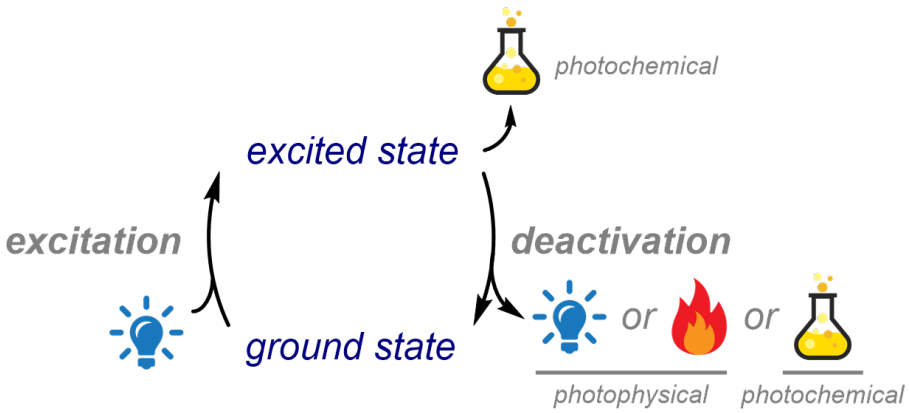


Figure 1: The formation of an excited state upon the absorption of light and its deactivation to the ground state or the induction of a chemical reaction.

0.2.1 Photophysical Processes

The term photophysical processes encompasses the formation of the excited state of a molecule and their subsequent deactivation events, which can be nonradiative or radiative and they cannot produce chemical modifications on the molecule. The latter are called photochemical processes.

The Jablonski Diagram

The best qualitative way to address all the **photophysical processes** that take place is the well-known **Jablonski diagram** (Figure 2), in which electronic states (thick horizontal lines) with either singlet (S_0, S_1 and S_2) or triplet (T_1 and T_2) multiplicity as well as their corresponding vibrational states (thin horizontal lines) are depicted.

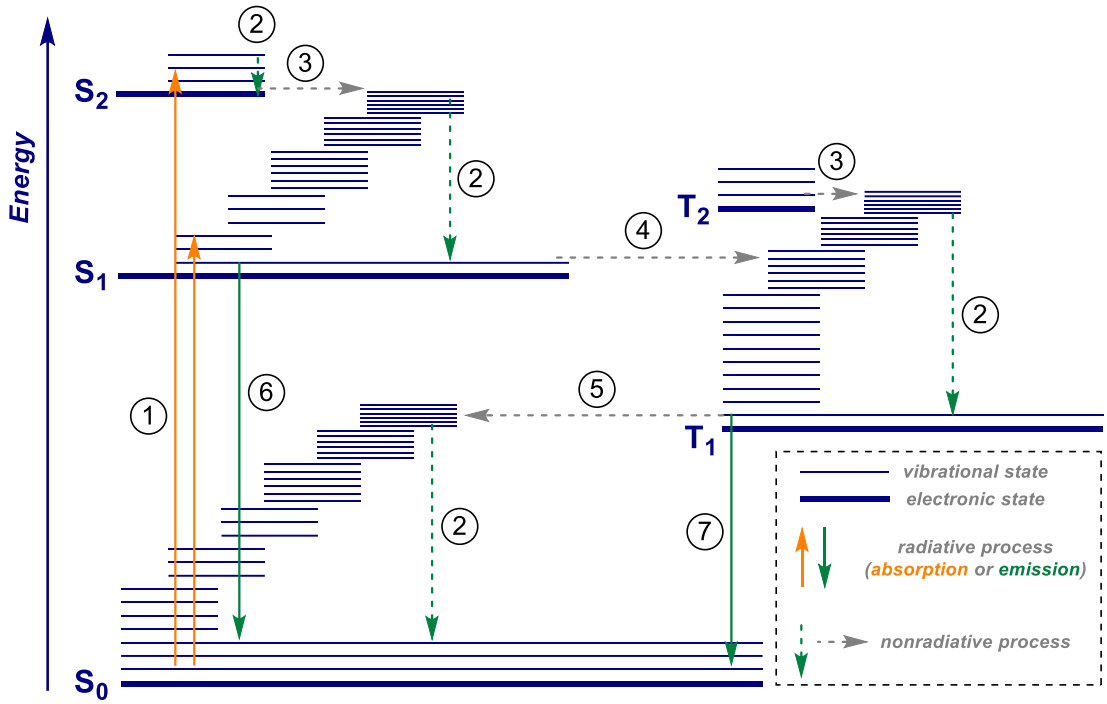


Figure 2: Jablonski diagram for the photophysical processes involving S_0, S_1, S_2, T_1, T_2 and their respective vibrational states.

Photophysical processes can be split in **radiative transitions**, when they involve the absorption or emission of a photon (Figure 2, straight arrows), or **nonradiative transitions**, when the change does not modify the energy or does release energy in form of heat (Figure 2, dotted arrows).

Nonradiative Transitions

According to the Jablonski diagram in Figure 2, after the absorption of a photon ($k_{abs} \approx 10^{16}$, ①), the ground state is promoted to an electronically excited state (S_1 or S_2) in a high vibrational level. This excess of vibrational energy is quickly dissipated to the medium through a mechanism known as **vibrational relaxation** (②), which is the fastest transition that occurs in the excited state ($k_{vr} > 10^{12}$ s).

When the lowest vibrational level of a given electronic state of any multiplicity is reached, two different isoenergetic transitions can happen

- if the transition occurs between two isoenergetic states of the **same multiplicity**, the process is known as **internal conversion** (Figure 2, ③) ($k_{ic} \approx 10^{12}$ s). For example, $S_2 \rightarrow S_1$ or
- if the transition occurs between two isoenergetic states of **different multiplicity**, the process is known as **intersystem crossing** (Figure 2, ④ and ⑤) ($k_{isc} \approx 10^{9}$ s). For example, $S_1 \rightarrow T_1$.

It is important to note that both internal conversion and intersystem crossing are irreversible processes, mainly due to fast vibrational relaxation that occurs once any of them happens.

Radiative Transitions

Radiative Transitions are those process where the molecule changes its electronic state accompanied by the emission of a photon rather than heat. Normally, the final electronic state is S_0 and, as a result, depending on the multiplicity of the excited electronic state the process is called

- **Fluorescence** if the transition is from the **singlet** state S_1 (Figure, Figure 2, ⑥) ($k_f \approx 10^{9}$ s) or
- **Phosphorescence** if the transition is from the **triplet** state T_1 (Figure 2, ⑦) ($k_p \approx 10^{0}$ s).

0.2.2 Photochemical Processes

All the unimolecular processes described beforehand are classified as photophysical because they do not trigger any change in the chemical integrity of the molecule. Nevertheless, once the excited state of a molecule is reached, it may suffer several **photochemical processes** leading to the same ground-state specie or even to the formation of a new ground-state molecule, as pictured in Figure 1.

However, it is important to note that, contrary to what one may expect, the enhanced reactivity of excited states do not arise from its excess of energy but from its **different electronic distribution**, being able to participate in chemical processes that cannot be reached under thermal conditions.

In this section, some photochemical processes regarding the scope of this *thesis* will be presented and discussed. Thus, **electron transfer** and **energy transfer** processes will be described, whereas other photochemical processes like proton transfer, photoisomerizations, thermally-forbidden pericyclic reactions, photooxidations and photoreductions among others will be omitted.

Electron Transfer

Due to the formation of an excited state, the electronic distribution of the parent molecule changes and, as a consequence, the ability to lose or to gain an electron are quite a bit different in the excited state compared to the ground state. Figure 3 exemplifies in a qualitative manner photoinduced electron transfer from the excited state of molecules.

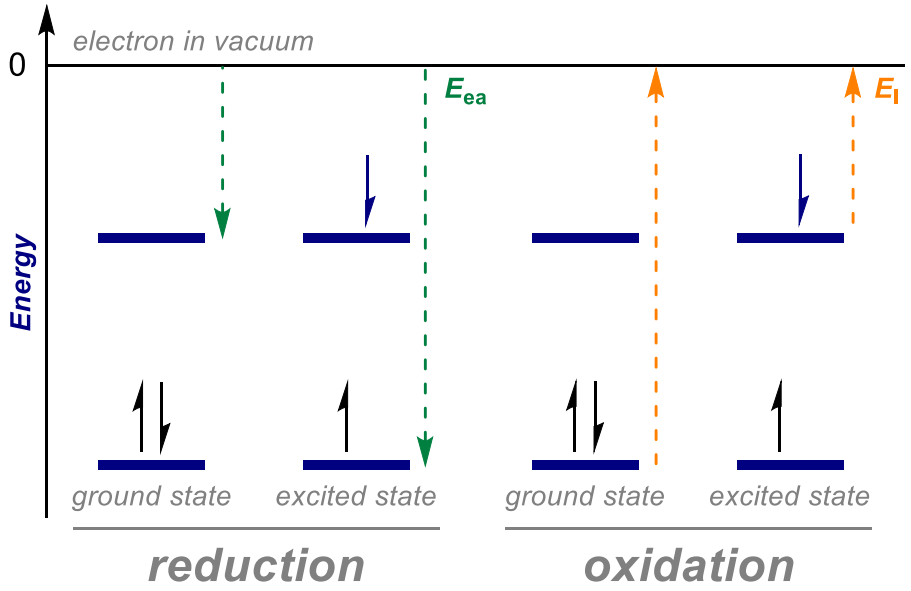


Figure 3: The compared redox behaviour between the ground and the excited state of a molecule.

In this sense, a molecule in its excited state is more prone to **reduction** because it has a low-lying vacancy, which is able to accept an electron. The associated thermodynamic process is the **electron affinity** (the amount of energy released when an electron is captured), and it is higher in the excited state. On the other hand, since an electron has been promoted to a higher energy orbital, the ability to expel an electron has been enhanced in the excited state, meaning that it is more prone to **oxidation**. Here, the thermodynamic

process is called **ionization energy** (the amount of energy required to remove an electron) and, according to Figure 3, it is lower in the excited state.

In a more practical point of view of this bimolecular photochemical process, when a molecule **M** is excited to **M*** it can suffer either a reduction or an oxidation depending on the reaction conditions. If a proper electron donor (**D**) is present (Figure 4, *left*) the result is the reduction of **M** and the oxidation of **D**, whereas if there is an electron acceptor (**A**) then the process that take place is the oxidation of **M** and the reduction of **A** (Figure 4, *right*).

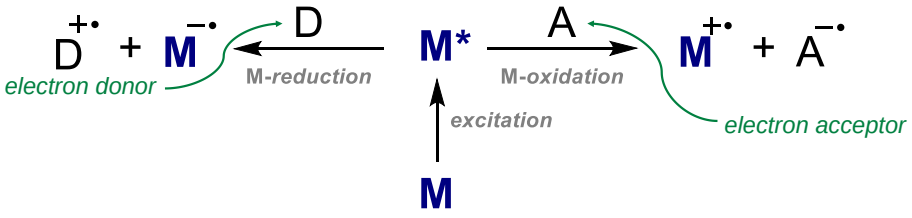


Figure 4: The potential electron transfer events that **M** can suffer upon excitation in the presence of either an electron donor (**D**) or an electron acceptor (**A**).

The ability of either **D** or **A** to interact and extract the excess energy of **M*** is commonly known as ***quenching***. *Quenching* is not exclusive for photoinduced electron transfer events but it is for any kind of deactivation of an excited state in a bimolecular way. It will be extensively explained in Section 0.2.3.

Energy Transfer

Once the excited state is reached, it can interact with a ground-state molecule transferring excess energy to it. This phenomenon is known as photoinduced **energy transfer** and it constitutes one of the most important photochemical processes, specially in nature. An unambiguous example is *photosynthesis*, where energy absorbed by the antenna (which contain chlorophyll) is transferred to the reactive center.

Energy transfer process can be represented in a simple way as shown in Figure 5. In it one can see how the excited state of **M** is able to transfer its energy to an acceptor (**A**), finally yielding the ground state of **M** and the excited state of **A**. It is trivial to deduct that for it to be a successful transfer the energy of **A*** has to be lower than the energy of **M*** (Figure 5, *right*). Energy transfer is isoenergetic, which means that the energy lost by the donor is gained by the acceptor. As shown in Figure 5-*right*, the excess energy in higher vibrational states of **A*** is quickly dissipated through vibrational relaxation to the medium.

As commented previously, the deactivation of the excited state of **M** by the action (in

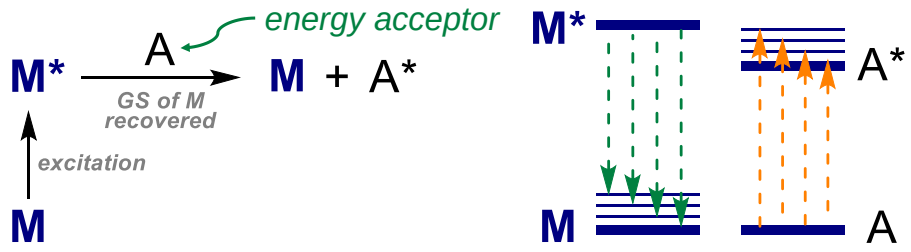


Figure 5: The energy transfer events that **M** can suffer upon excitation in the presence of either an energy donor acceptor (**A**) (*left*) and the detailed process between **M*** and **A** regarding vibrational states (*right*).

this case) of an energy acceptor (**A**) is also called ***quenching***, a bimolecular process that will be explained in Section 0.2.3.

0.2.3 Bimolecular Quenching of Excited States

In Section 0.2.1, the deactivation mechanisms by which a molecule in its excited state can be brought back to its ground state intramolecularly (namely unimolecular) have been described. However, there are some other processes where the excited state interacts with another species and, in these cases, the deactivation occurs intermolecularly, namely in a **bimolecular** manner. Electron transfer and energy transfer are, in fact, bimolecular processes because they require the assistance of a second ground-state molecule. As has been said before, this process is commonly known as ***quenching***, and it takes this name because these processes compete directly with the intermolecular deactivation events and, in some cases, they can *quench* the fluorescence as well as other deactivation pathways. Therefore, species **A** and **B** in Figure 4 and Figure 5 are, in fact, *quenchers* of the excited state of **M**.

Stern-Volmer Equation

To conceptualize all the processes (inter- and intramolecularly) that a given excited-state molecule can suffer, a more quantitative consideration should be done. For instance, in Figure 6, excited-state **M*** can be deactivated through radiative processes (fluorescence or phosphorescence), nonradiative processes (vibrational relaxation, internal conversion and intersystem crossing) or through a direct photochemical process. But, intermolecular deactivation (namely *quenching*) has to be considered as well.

Considering all the above-mentioned deactivation processes, the decrease of the concentration of **M*** through both inter- and intramolecular mechanisms can be expressed as shown in Equation (4) where the first addend obeys a first-order kinetic law (unimolecular processes) whereas the second one, which corresponds to the *quenching* event, obeys a

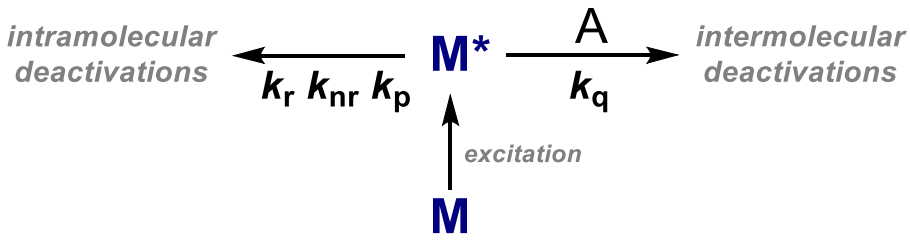


Figure 6: The inter- and intramolecular processes that a given molecule **M** in its excited state can suffer and their rate constants (k). r and nr encompasses all the radiative and nonradiative events respectively. p represents a direct photochemical process that **M*** may suffer.

second-order law (bimolecular process):

$$-\frac{d[\mathrm{M}^*]}{dt} = (k_r + k_{nr} + k_p)[\mathrm{M}^*] + k_q[\mathrm{M}^*][\mathrm{A}] \tag{4}$$

Equation (4) can be reorganized to obtain Equation (5):

$$-\frac{d[\mathrm{M}^*]}{dt} = \left(k_r + k_{nr} + k_p + k_q[\mathrm{A}]\right)[\mathrm{M}^*] \tag{5}$$

Integration of Equation 5 renders Equation 6

$$[\mathrm{M}^*] = [\mathrm{M}^*]_0 \exp\left[-\left(k_r + k_p + k_{nr} + k_q[\mathrm{A}]\right)t\right] \tag{6}$$

Lifetime of **M*** without the presence of quencher **A** can be expressed as the inverse of rate constants. Thus, for intermolecular processes, lifetime of **M*** (τ_0) is

$$\tau_0 = \frac{1}{k_r + k_{nr} + k_p} \tag{7}$$

whereas the lifetime of **M*** in the presence of **A** can be extracted from Equation (6) as

$$\tau = \frac{1}{k_r + k_{nr} + k_p + k_q[\mathrm{A}]} \tag{8}$$

Finally, the quotient between τ_0 and τ gives the so called **Stern-Volmer equation**:

$$\frac{\tau_0}{\tau} = 1 + \tau_0 \cdot k_q[\mathrm{A}] \tag{9}$$

The Stern-Volmer equation is a straightforward tool to estimate the ability of a given specie to *quench* the excited state of a molecule by just measuring its lifetime in the presence of different concentrations of *quencher*. If several experimental parameters are taken into account, lifetimes of **M** can be replaced in Equation (9) by the emission intensity I

or I^0 at a fixed wavelength:

$$\frac{I^0}{I} = 1 + \tau_0 \cdot k_q[\mathrm{A}] \tag{10}$$

Additionally, lifetime of **M** in the absence of **B** (τ_0) and the rate constant for the quenching process (k_q) can be combined in the so called **Stern-Volmer constant** (K_{SV}):

$$\frac{I^0}{I} = 1 + K_{SV} \cdot [\mathrm{A}] \tag{11}$$

All in all, the experimental evaluation of the Stern-Volmer equation depicted in Equation (11) gives valuable information in determining **photocatalytic mechanisms** or pathways.

0.3 Organic Photochemistry and Photocatalysis

In this Section, the most important aspects and landmarks of the beginnings of synthetic organic photochemistry will be presented. Afterwards, more contemporary synthetic strategies towards the preparations of organic compounds using photochemistry will be discussed. Finally, the concept of photocatalysis will be introduced and all the technology and recent developments of the field will be presented as well.

0.3.1 Early Observations

Since the early observation made by Joseph Priestley in 1790, where some vials of nitric acid turned reddish upon exposure to sunlight presumably due to the formation of NO_2, the interest in synthetic photochemistry has been increasing and this finding sets its starting point.[5]

After several decades, in 1867, Carl Julius Fritzsche observed how small crystals appeared when an anthracene solution was exposed to sunlight.[6] Although this German scientist did not determine the molecular structure of those crystals, they corresponded to the anthracene dimer through a light-enabled [4+4]-cycloaddition. This observation is considered the first organic transformation promoted by light.

0.3.2 Modern Organic Photochemistry

As mentioned earlier, the formation of excited states of molecules unlocks mechanistic pathways mainly due to a different electronic distribution compared to the ground state. These new synthetic paradigms, which are not accessible by thermal methods, have been exploited by the synthetic community to build molecular complexity, especially in natural

product synthesis.[7] In this Section, several synthetic problems which have been addressed using photochemistry will be shown.

In 1986, Crimmins took advantage of an intramolecular light-enabled alkene [2+2] cycloaddition reaction towards the synthesis of *rac-silphinene*[8] (Figure 7). The corresponding [2+2] cycloaddition took place between one electron-poor alkene and an aliphatic alkene under the irradiation of UV light (366 nm) in hexane with excellent stereocontrol, mainly due to the rigidity of the system. Finally, the obtained tetracyclic skeleton was subjected to five additional steps to yield *rac-silphinene*.

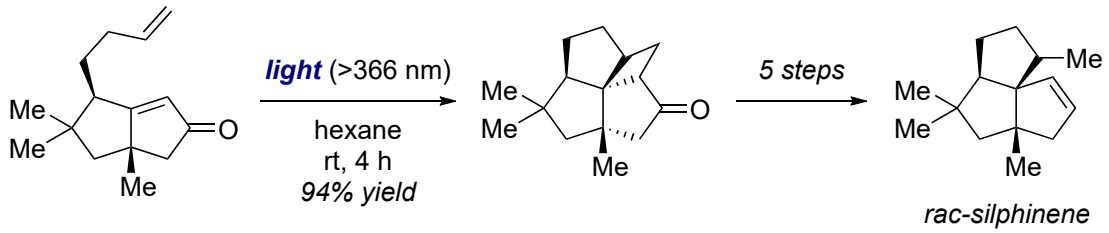


Figure 7: Synthesis of an intermediate towards *rac-silphinene* through a photoinduced [2+2] cycloaddition reaction (Crimmins).

In 1988, Winkler and collaborators pursued the synthesis of *mesembrine*.[9] To do so, they prepared a vinylogous amide and it was subjected to intramolecular alkene [2+2] cycloaddition when exposed to UV light. The other alkene counterpart was an α-substituted styrene installed in the same molecule. The product of this initial photoreaction was a fused cyclobutane-pyrrolidine bicycle, which spontaneously underwent a retro-Mannich reaction to yield the corresponding 3,4-dihydropyrrole and an aliphatic ketone. Finally, *N*-methylation and subsequent intramolecular diastereoselective aza-aldol reaction afforded *mesembrine* (Figure 8).

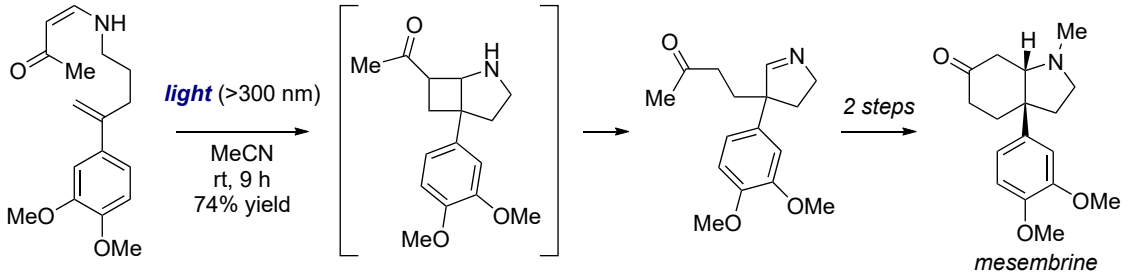


Figure 8: Synthesis of an intermediate towards *mesembrine* through a [2+2] photoinduced cycloaddition reaction (Winkler).

In 2000, the laboratory of Bach proposed a Paternò-Büchi reaction to furnish a fused oxetane-pyrrole bicycle en route to (+)-*preussin* using a chiral dihydropyrrole and ben-

zaldehyde under the irradiation of UV light[10] (Figure 9). The reaction yielded the desired product as a single enantiomer, which after two steps was derivatized to (+)-*preussin*.

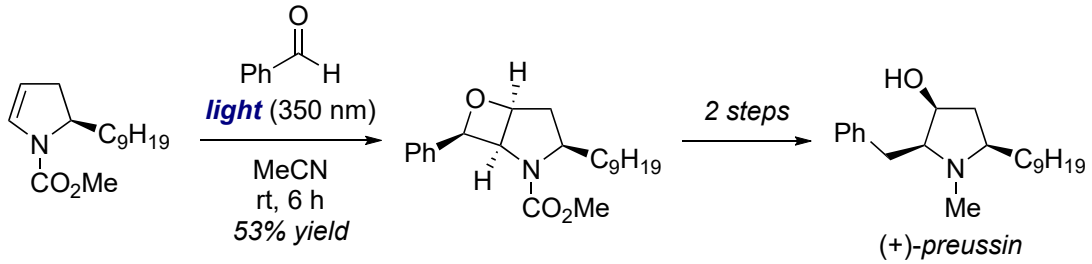


Figure 9: Synthesis of an intermediate towards (+)-*preussin* through a Paternò-Büchi reaction (Bach).

0.3.3 Photocatalysis

The word photocatalysis is made up of two parts. The first one, *photo*, is the Greek word to designate *light*, and the second one, *catalysis*, introduces a very important chemical field which exploits the effect of substoichiometric quantities of a specie capable of promoting a given chemical transformation. Hence, **photocatalysis**, in a general sense, encompasses the use of species able to absorb light and trigger a subsequent chemical event.

Photocatalysis has many implications in a fair number of chemical processes such as paper production[11] and water disinfection[12] among others. In these processes, ZnO and TiO_2 are competent heterogeneous photocatalysists but they fall out the scope of this *thesis*. In organic synthesis, photocatalysis usually takes place in an homogeneous phase, and the development of homogeneous photocatalytic organic transformations has gone hand in hand with the development of **visible-light photocatalysis**, which will be discussed in Section 0.4.

Photocatalytic Cycles

According to what has been discussed in Section 0.2.2, a given specie in its excited state can participate in several photochemical processes. But, from the point of view of **catalysis**, a photochemical reaction that arises from the direct excitation of the substrate shall not be considered in this Section. Thus, only **electron** and **energy** transfer events should be scrutinized from the perspective of regenerating the **photocatalyst** since other processes may lead to its decomposition. Therefore, three different photocatalytic cycles can be proposed as depicted in Figure 10.

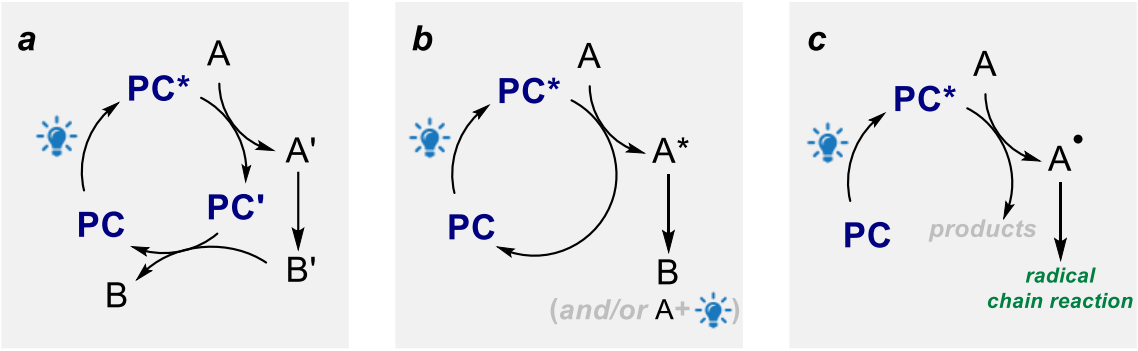


Figure 10: Three different photocatalytic cycles for photocatalyst **PC**.

- Photocatalytic cycle ***a***: the generation of the excited state **PC*** allows an electron transfer process with specie **A** yielding intermediate **A'** and the form of the photocatalyst **PC'**. Intermediate **A'** suffers a chemical change to yield **B'**, which interacts with **PC'** and furnishes the neutral final product **B** and regenerates the photocatalyst **PC** as well. This kind of photocatalytic cycle is commonly known as **photoredox catalysis**.

- Photocatalytic cycle ***b***: the generation of the excited state **PC*** triggers the energy transfer process in the present of a suitable substrate **A** to form **A*** and the ground state form of the photocatalyst. Then, excited state **A*** can suffer a chemical transformation to yield **B**, or can deactivate to its ground state through any photophysical process, such as fluorescence. This process is widely known as **energy-transfer photosensitization**.

- Photocatalytic cycle ***c***: the excited state **PC*** can react with substrate **A** to form a radical which propagates a chain mechanism. However, the photochemical interaction between **PC*** and **A** leads to decomposition of **PC**. In this case, **PC** is more considered as a **photolabile radical initiator** rather than a photocatalyst. Although **PC** is used in substoichiometric amounts, since the photocatalyst is not regenerated after a catalytic cycle, this cannot be considered a canonical photocatalytic cycle but a **photoinduced chain reaction**.

0.4 Visible-Light Photocatalysis in Organic Synthesis

In this pivotal Section, the development of visible-light photocatalysis and its application to organic synthesis will be presented. The journey from the beginnings of synthetic photochemistry, where organic substrates have to be excited directly by highly-energetic UV light, to the most modern strategies in which less-energetic **visible-light** is employed

in combinations with catalytic amounts of light-absorbing molecules capable of promoting electron transfer and/or energy transfer processes among others.

0.4.1 Why Visible Light?

The development of safer and low-environmental-impact chemical procedures has been a general thought since the early industrial developments. Indeed, in 1912, Italian chemist **Giacomo Ciamician** ensured that environmental sustainability would come from the use of **sunlight** (visible light) as the energy source for large-scale chemical processes.[13]

Besides, from a modern laboratory point of view, the use of visible light is more convenient regarding the equipment that is needed. To conduct organic transformations using UV light, it is required to use low-, medium-, or high-pressure Hg lamps or Na lamps, for example. Additionally, since common glassware is not transparent to UV lights, it is mandatory to employ quartz-based reaction vessels if high-energy light (<250 nm) has to be used. There are also some medical hazards associated with the use of UV light such as cell, eye and skin damage. On the other hand, visible-light irradiation can be easily implemented in conventional organic chemistry laboratories just by using household bulb lights or, more recently, **light-emitting diodes** (LEDs). In fact, LEDs are an excellent tool for visible-light photocatalysis as they are available in a great assortment of wavelengths.[14]

Additionally, in 1998, Paul Anastas and John C. Warner introduced the precepts of **green chemistry**, in which the scientific community is committed to develop less hazardous synthesis (*point 3*), to design procedures that ensure energy efficiency (*point 6*) and to use renewable feedstocks (*point 7*).[15] In this current of thought, in 2015 the United Nations introduced 17 **Sustainable Development Goals** (SDGs) as part of its Agenda 2030 portfolio. Among all these 17 global goals, there are some that should be modestly addressed by developing low-impact chemical processes.[16] Therefore, the use of visible light is in accordance to more sustainable chemical processes.

0.4.2 Visible-Light Photocatalysts

As shown in Figure 10, the implementation of visible-light-triggered organic transformations requires the use of a photocatalyst. A suitable photocatalyst should have the following features:[17]

- The photocatalyst must have an **absorption** spectrum in the **visible region** so that a visible-light source could excite it. Preferably, it has to absorb light in a wavelength region where the other reaction partners do not.

- The **quantum yield** in which the reactive excited state is generated must be high and that excited state should be **persistent** enough to interact with the desired substrate.

- The **redox potentials** of its excited state should match with those from the substrate, in the case of a photocatalytic cycle that involves electron transfer events (photoredox catalysis). Additionally, photocatalyst should exhibit **reversible redox behaviour** to assure catalyst turnover.

- The photocatalyst should be stable in solution, synthetically readily **available** and their properties should be easily **tunable** by synthetic modifications.

After enumerating all these characteristics that an ideal photocatalyst should posses, it is not surprising that, since the beginning of visible-light photocatalysis, polypyridyl complexes of Ru(II) and Ir(III) have been extensively used. In the next Section, an awful lot of photocatalysts will be presented, starting from the most studied one, $Ru(bpy)_3^{2+}$, as well as other metal-based ones. Then, moving towards diminishing the use os precious metals in organic synthesis, several purely organic photocatalysts will be shown.

$\mathbf{Ru(bpy)_3^{2+}}$

The complex between Ru(II) and 2,2'-bipyridine, $\mathbf{Ru(bpy)_3^{2+}}$, or even *rubipy* (Figure 13, *first row*, *left*), is the most studied photocatalyst from both the photophysical and the photochemical point of view. Like many other colored metal complexes, $Ru(bpy)_3^{2+}$ was initially employed in solar energy conversion strategies[18,19] or carbon dioxide reduction[20] and its first reported use as **photocatalyst** was in 1978 in the laboratory led by Kellog.[21] In this report, the authors observed how the reduction of phenacyl sulfonium salts using 1,4-dihydropyridines was accelerated when a catalytic amount of $Ru(bpy)_3^{2+}$, as well as visible light, was employed.

In the visible region, $Ru(bpy)_3^{2+}$ has its maximum of absorption at 452 nm, an electronic transition that corresponds to a **metal-to-ligand charge transfer** (MLCT). As an approximation, it can be considered that, when $Ru(bpy)_3^{2+}$ is irradiated by visible light, an electron from a predominantly metal-centered molecular orbital is promoted to a predominantly ligand-based molecular orbital. Thus, formally, the metal center has been **oxidized** whereas one of its 2,2'-bipyridine ligands has been **reduced**. This different electronic distribution as a consequence of the MLCT makes $Ru(bpy)_3^{2+}$ a good oxidant as well as a good reductant in its excited state, similarly to what is depicted in Figure 3 (Figure 11).

This enhanced excited-state reactive towards electron transfer events made $Ru(bpy)_3^{2+}$ a versatile photoredox catalyst, and also served as starting point for the development of new metallic complexes for similar purposes. Hence, lots of methodologies taking advantage

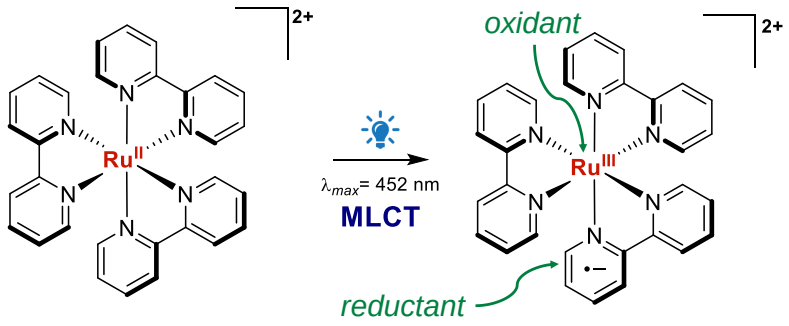


Figure 11: The excitation of $Ru(bpy)_3^{2+}$ through a MLCT by the action of visible light and the qualitative representation of its excited state.

of either the reductive or the oxidative abilities of $Ru(bpy)_3^{2+}$ have been reported. In fact, if the excited state of $Ru(bpy)_3^{2+}$ gets reduced through a **Single Electron Transfer** (SET), it is said that the reaction is controlled by a **reductive *quenching* cycle** (Figure 12, *left side*). Similarly, if in the first process the excited state of $Ru(bpy)_3^{2+}$ suffers an oxidation then the reaction is governed by an **oxidative *quenching* cycle** (Figure 12, *right side*).

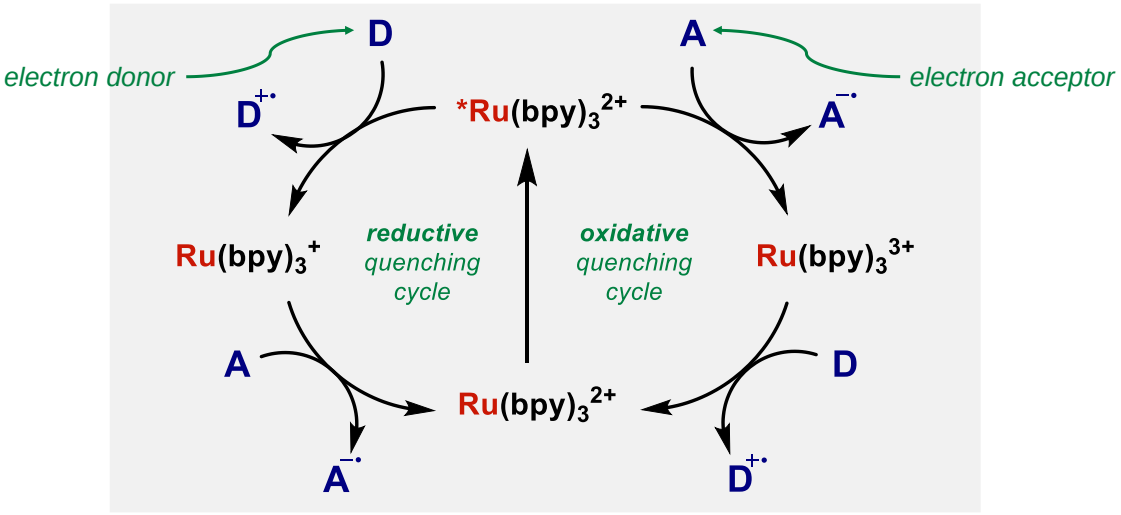


Figure 12: Reductive and oxidative quenching cycles for the $Ru(bpy)_3^{2+}$ photoredox catalyst.

Other Metal-Based Photocatalysts and Organophotocatalysts

An array of metal-based photocatalysts has been developed since the commencement of visible-light photocatalysis for organic synthesis purposes. These metal complexes are mainly based on **Ru(II)** and **Ir(III)** with different bidentate organic ligands (Figure 13), but more recently first-row metals such as **Fe**[22] or **Cu**[23,24] have proved competence to build suitable photocatalysts.

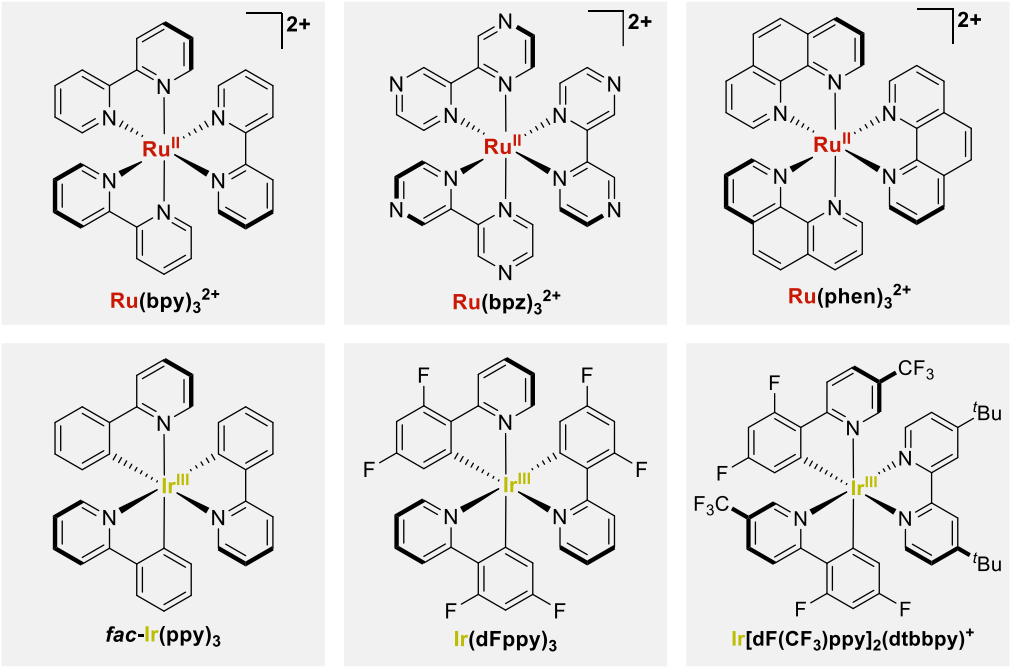


Figure 13: The most employed Ru- and Ir-based photocatalysts.

Additionally, **visible-light-absorbing organic molecules** have recently centered the attention as they can also participate in photochemical events in the same way as metal-based ones.[25] In fact, they are not merely metal-free alternatives but also can offer a wide variety of transformations and, in some cases, the tunability of their excited-state properties is easier. Figure 14 shows the most important families of **organophotocatalysts**: xanthenes,[26] pyrylium salts,[27] acridinium salts,[28–30] thiazines,[31] quinones[32] and cyanoarenes.[28,33]

0.4.3 Applications in Organic Synthesis

Although the first reported example of a visible-light photocatalytic reaction dates from 1978,[21] the starting point of modern visible-light photocatalysis is 2008 with two publications from the research groups of MacMillan[34] and Yoon.[35] Since then, visible-light photocatalysis has been growing year by year and a great number of elegant and sophisticated applications have been published. In this Section, the seminal studies of MacMillan and Yoon will be presented. Thereafter, a short selection of contemporary works from the groups of Knowles, Nicewicz and Schindler will be discussed.

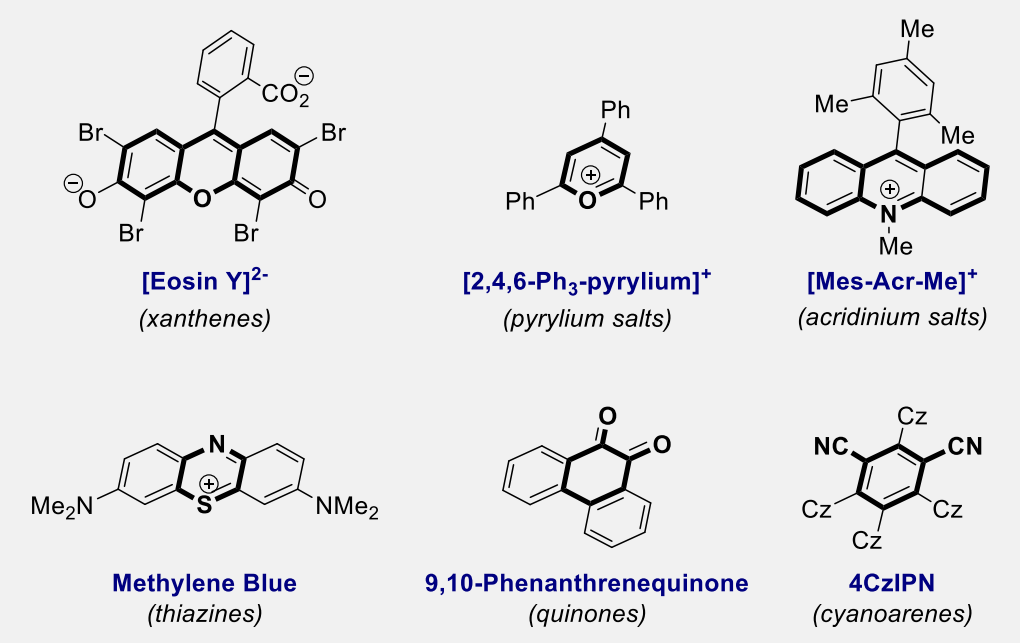


Figure 14: The most important families of organophotocatalysts. The parent structure of each family is marked with a tick line. Cz: Carbazole.

Seminal Studies

In 2008, the research group of MacMillan reported the enantioselective α-alkylation of aldehydes with bromomalonates and related electrophiles using a combination of photoredox catalysis and organocatalysis (Figure 15).[34] Specifically, they employed the above mentioned $Ru(bpy)_3^{2+}$ as photoredox catalyst and a chiral imidazolidinone, which had already been developed by themselves,[36] as asymmetric inductor. The irradiation of the reaction mixture with a compact fluorescent light (CFL) allowed them to obtain the corresponding alkylated products in good to excellent yields and with high enantioselectivities.

In the same year, the laboratory of Yoon developed a diastereoselective intramolecular alkene formal [2+2] cycloaddition reaction enabled by photoredox catalysis (Figure 16).[35] Similarly, they also required the use of $Ru(bpy)_3^{2+}$ as photoredox catalyst and DIPEA as sacrificial electron donor. Using these conditions they were pleased to obtain an assortment of fused tetrasubstituted cyclobutanes in high yields and excellent diastereocontrol.

Selected Examples

The first selected example comes from the laboratory of Knowles, in which they are interested in a synthetic strategy known as **Proton-Coupled Electron Transfer** (PCET).[37] The interest of that process arises from the ability of some substrates to undergo an electron and a proton transfer process in a concerted way. Specifically, in 2016, they envi-

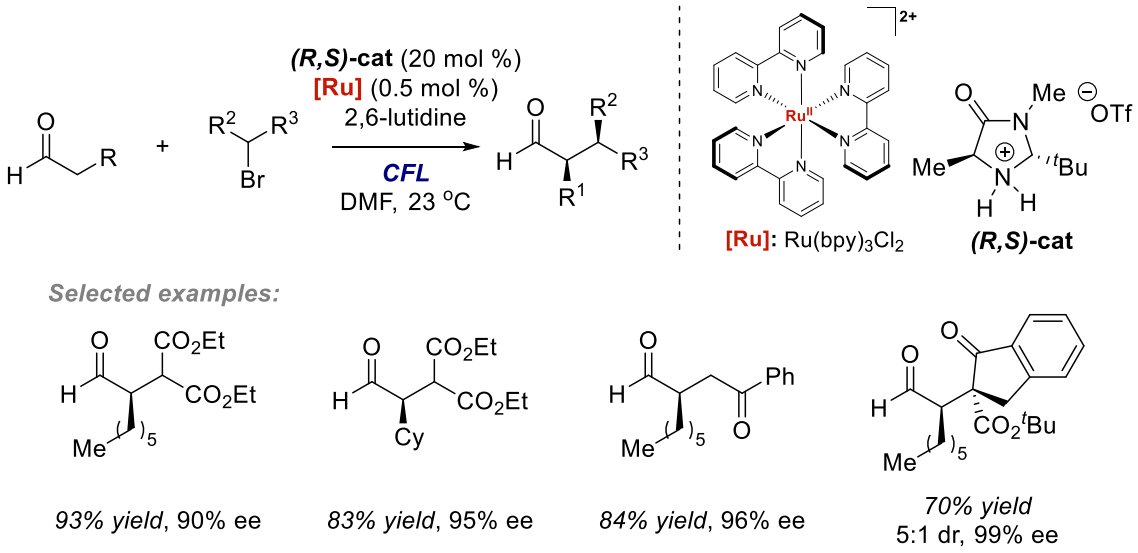


Figure 15: Enantioselective α-alkylation of aldehydes through a combination of photoredox catalysis and organocatalysis (MacMillan).

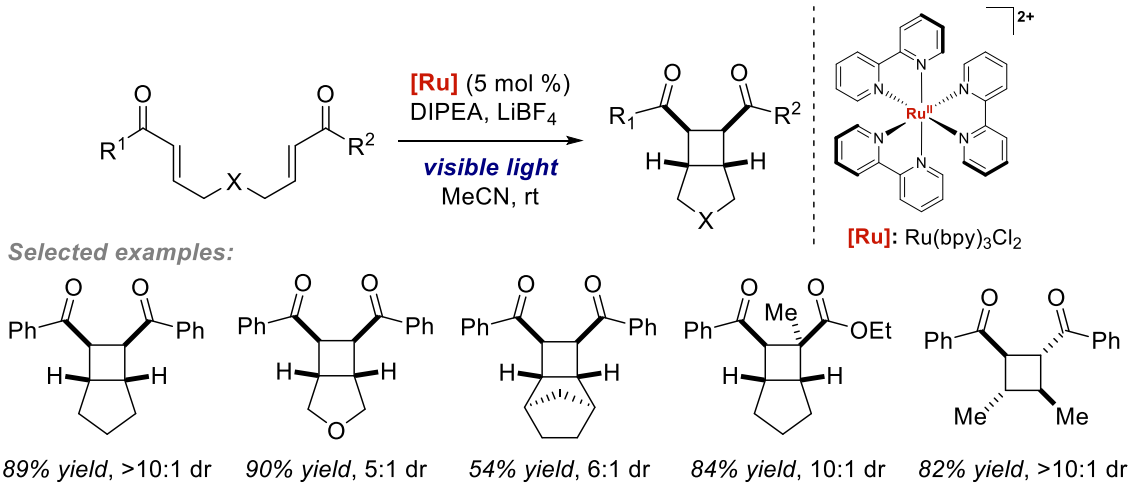


Figure 16: Diastereoselective intramolecular [2+2] cycloaddition of dienones enabled by photoredox catalysis (Yoon).

sioned that a *N*-alkyl secondary amide could participate in a PCET through its N−H bond in the presence of both an oxidant photocatalyst and a Brønsted base. PCET would allow the formal homolysis of that N−H bond to generate the corresponding amidyl radical, which could trigger an intramolecular 1,5-Hydrogen Atom Transfer (HAT) from a distal aliphatic C−H bond yielding, in a selective way, a remote alkyl radical. Finally, this alkyl radical can react with an electron-poor alkene through a Giese-type reaction (Figure 17).[38]

In 2020, Nicewicz and collaborators, as part of their research interests in acridinium photocatalysis, reported a strategy to achieve redox potentials as low as -3.36 V vs SCE, compared to that of elemental lithium. They observed that the reduced acridinium cata-

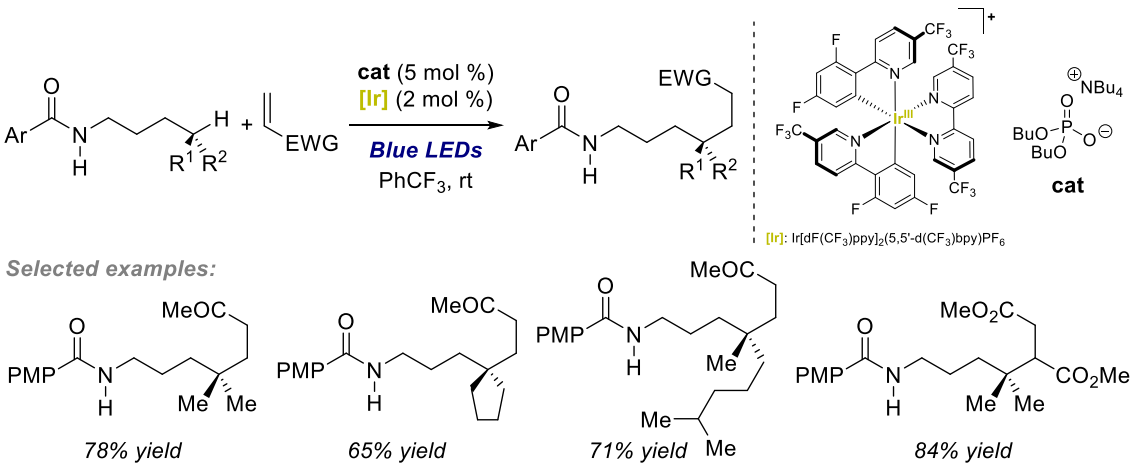


Figure 17: Remote C−H bond functionalization enabled by PCET (Knowles).

lyst (generated after a SET with DIPEA) can be promoted to an excited-state in which it becomes a highly reductant specie. In their report, a complete electrochemical, spectroscopical and theoretical characterization is shown. Besides, they were pleased to apply this feature, known as **consecutive Photoinduced Electron Transfer** (conPET), to the reduction of challenging substrates such as electron rich aryl chlorides and bromides, as well as the desulfonylation of amines (Figure 18).[30]

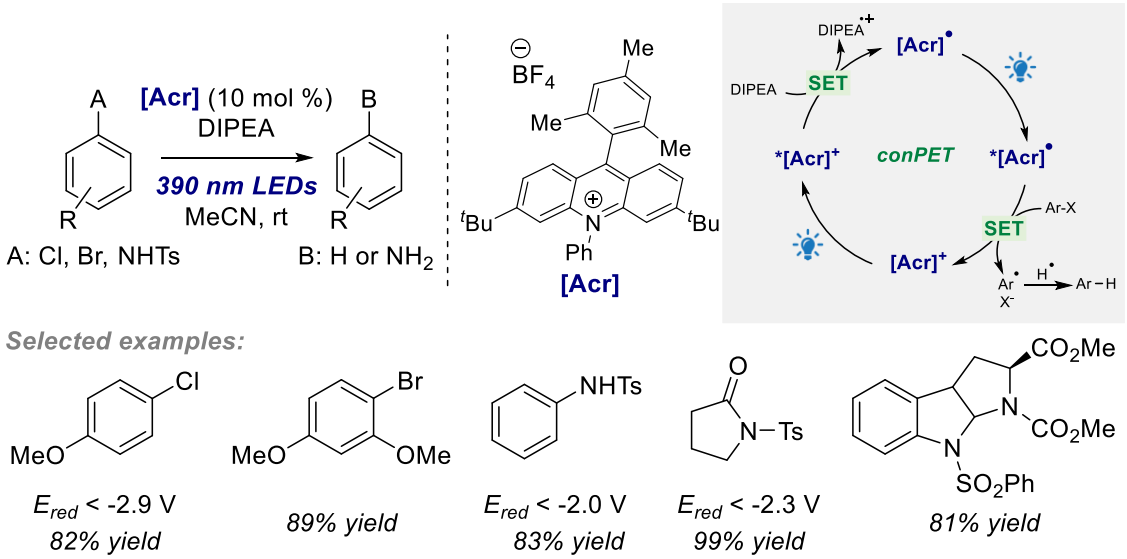


Figure 18: Dehalogenation and desulfonylation of highly strong bonds enabled by conPET.

The last example is from the research group of Schindler, who in 2020 described an elegant synthesis of highly functionalized azetidines through an intermolecular aza-Paternò-Büchi reaction enabled by visible-light **energy transfer photocatalysis**. The choice of electron-rich rigid 2-isoxazolines allowed the reaction with a great amount of

unactivated alkenes under energy transfer conditions (Figure 19).[39]

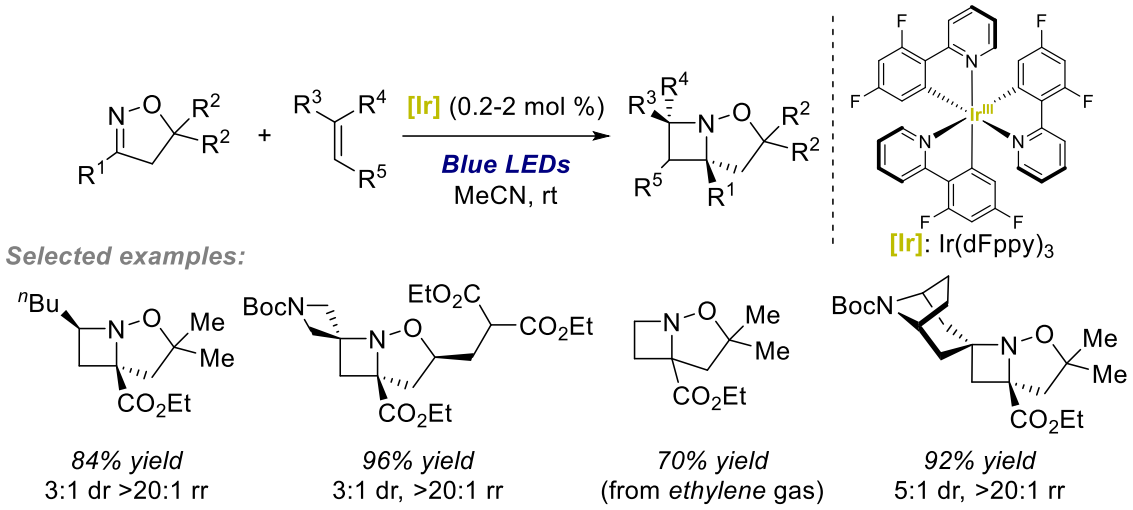


Figure 19: Synthesis of highly functionalized azetidines through visible-light photocatalysis (Schindler).

0.5 Organic Amines in Photoredox Catalysis

In this Section, the particular relationship between organic amines and visible-light photocatalysis will be presented. Since this *thesis* covers the use of **photoredox catalysis**, from this point onwards only that kind of photocatalysis (Figure 10, ***a***) will be considered. Specifically, the α-functionalization of amines using photoredox catalysis with either nucleophiles or electrophiles will be exposed. Later on, the two flagships of this *thesis*, the **3,4-dihydro-1,4-benzoxazin-2-one** and the **3,4-dihydroquinoxalin-2-one**, will be introduced, and the previous methodologies for its functionalization will be reviewed.

0.5.1 α-Functionalization of Amines

As has been noticed in the seminal works of MacMillan[34] and Yoon,[35] the electron-rich character of tertiary amines makes them suitable substrates to be engaged in electron transfer processes in the context of photoredox catalysis. This behaviour has been exploited by several research groups to functionalize tertiary amines rather than utilizing them as merely sacrificial electron donors.

In particular, tertiary amines bearing a methylene group at its α position can be enrolled in distinct photoredox events that enable its selective α-functionalization (Figure 20). Tertiary amine **A** can suffer a SET to generate the corresponding radical cation **B**. Once this radical cation **B** is generated, the acidity of the α-H increases significantly, as

suggested by Tilset in 1991.[40] This phenomenon makes radical cation **B** prone to deprotonation and it generates α-amino radical **C**, which has nucleophilic character.[41] However, if a second oxidation event takes place, α-amino radical **C** can be converted to iminium cation **D**, which exhibits electrophilic character. Alternatively, iminium cation **D** can be generated through a HAT from radical cation **B**, as the dissociation energy of the α-H diminishes compared to that of **A**, according to a study performed by Dinnocenzo.[42]

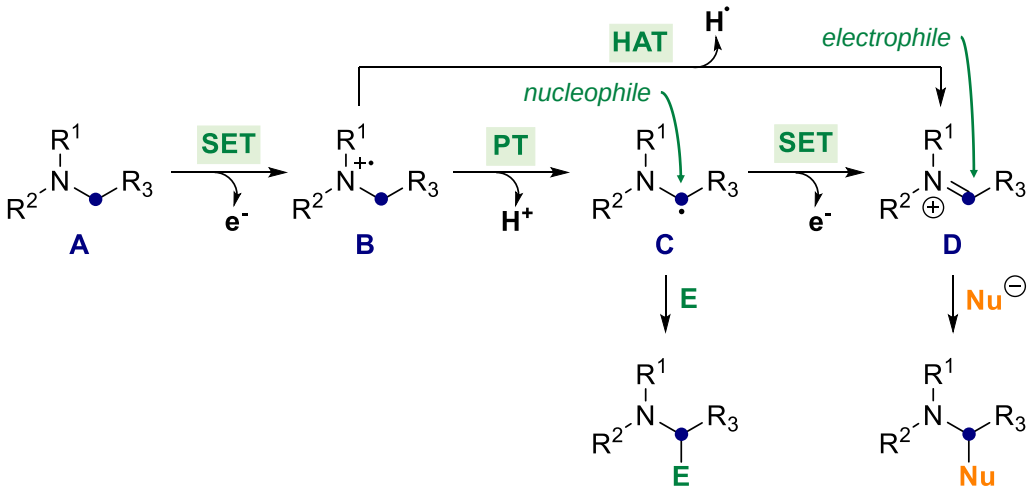


Figure 20: General mechanisms for the α-functionalization of tertiary amines under photoredox catalysis.

As evidenced in Figure 20, depending on the reaction conditions one can **modulate** the stage in which the oxidation process stops. Therefore, tertiary amines bearing an α-methylene moiety can be functionalized with either **nucleophiles** or **electrophiles**, just as will be shown thereafter.

Nucleophilic α-Functionalization of Amines

Iminium cations (Figure 20, **D**) can be nucleophilically attacked to form a new C−C or C−X bond. The tertary amines which have been extensively used for developing this kind of transformations are ***N*-aryl tetrahydroisoquinolines**,[43,44] due to the fact that the iminium cation is formed through the abstraction of a benzylic hydrogen and the resulting double bond gets conjugated with the aromatic system.

The first example of nucleophilic functionalization of *N*-aryl tetrahydroisoquinolines under photoredox catalysis is from the research group of Stephenson, who in 2010 reported the aza-Henry reaction with those amines and nitroalkanes.[45] In this case, the Ir photocatalyst is capable of generating the corresponding iminium cation in combination with molecular oxygen (Figure 21).

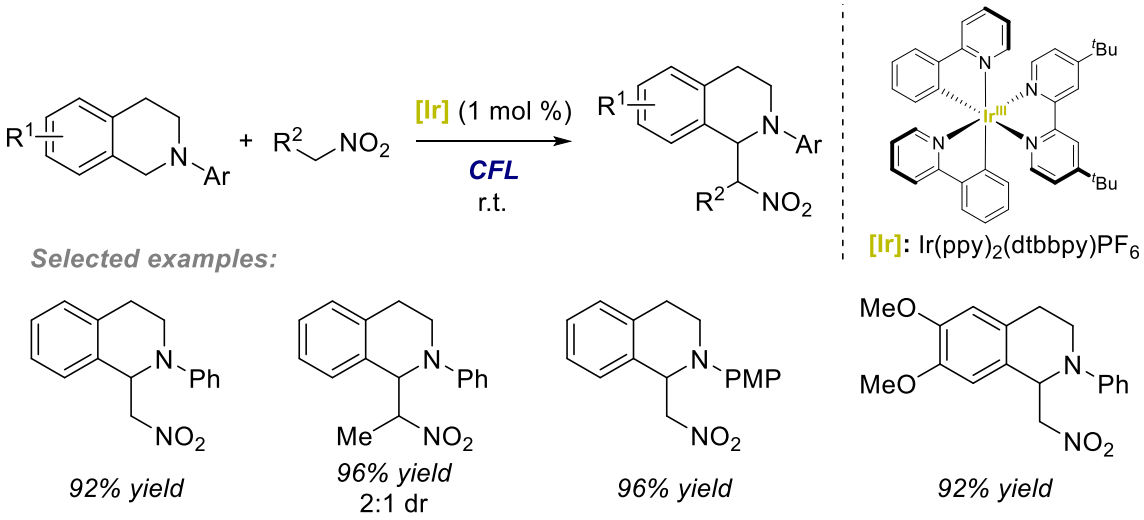


Figure 21: Functionalization of *N*-aryl tetrahydroisoquinolines with nitroalkanes through photoredox catalysis (Stephenson).

Besides, ***N*,*N*-dialkylanilines** have also demonstrate their capability to undertake α-functionalization via iminium cation using photoredox catalysis. Indeed, the research group of Rueping developed a three-component reaction between *N*,*N*-dialkylanilines, isocyanides and water or carboxylic acids.[46] This Ugi-type reaction[47] was promoted by an Ir complex as photoredox catalysis and molecular oxygen as terminal oxidant (Figure 22).

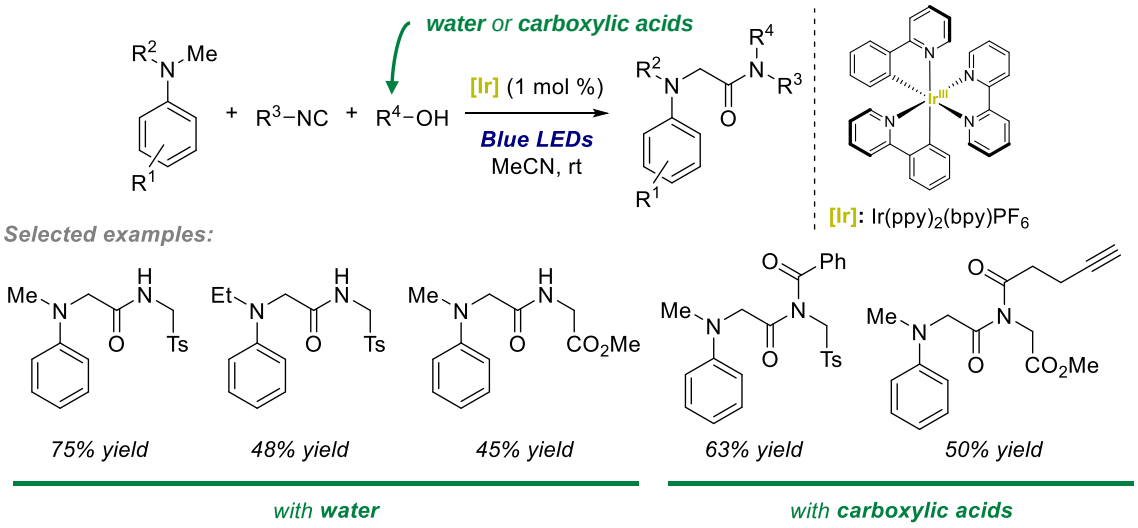


Figure 22: Three-component Ugi-type reaction between *N*,*N*-dialkylanilines, isocyanides and water/carboxylics acids promoted by photoredox catalysis (Rueping).

Apart from tertiary amines, some secondary analogues can be engaged in photoredox catalysis. However, assuming an equivalent mechanism to that shown in Figure 20, the electrophilic product should be an imine rather than an iminium cation. In this sense,

***N*-aryl glycines** have been exploited by several research groups. As an example, in 2021 the laboratory of Wang developed a dual catalytic methodology formed by an iridium complex as photoredox catalyst and a chiral phosphoric acid as organocatalyst for the enantioselective α-alkylation of *N*-aryl glycines with α-bromo ketones (Figure 23).[48] Both tertiary and quaternary α-bromo ketones were used, obtaining the corresponding products in high yields with excellent diastereoselectivities and enantioselectivities.

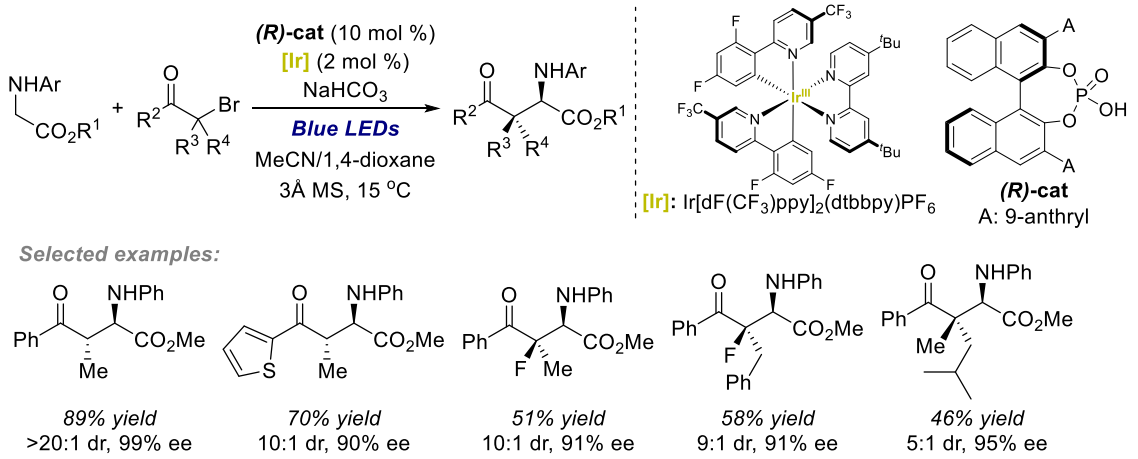


Figure 23: Enantioselective functionalization of *N*-aryl glycines with α-bromo ketones enabled by photoredox catalysis (Wang).

Electrophilic α-Functionalization of Amines

Whereas two consecutive single-electron oxidation of tertiary amines leads to the formation of the corresponding iminium cation (Figure 20, **A** to **D**), if the process is stopped after the first SET, α-amino radical (Figure 20, **C**) intermediate can be also exploited in synthetic chemistry taking advantage of its nucleophilic character.

Again, ***N*-aryl tetrahydroisoquinolines** have also been subjected to electrophilic functionalization through photoredox catalysis. The pioneer work comes from the laboratory of Reiser in 2012, who were capable of generating the corresponding α-amino radical of *N*-aryl tetrahydroisoquinolines using $Ru(bpy)_3Cl_2$ under an inert atmosphere, which reacted with electron-poor alkenes to obtain the expected products in moderate yields.[49] Besides, they developed an intramolecular version leading to interesting fused indoles, although in low yield (Figure 24).

In 2018, the research group of Phipps reported an elegant enantioselective Minisci-type reaction of quinolines or pyridines with redox-active esters derived from aminoacids. To achieve the transformation, the authors used a combination of an Ir complex as photoredox catalyst and a chiral phosphoric acid as organocatalyst. However, the generation

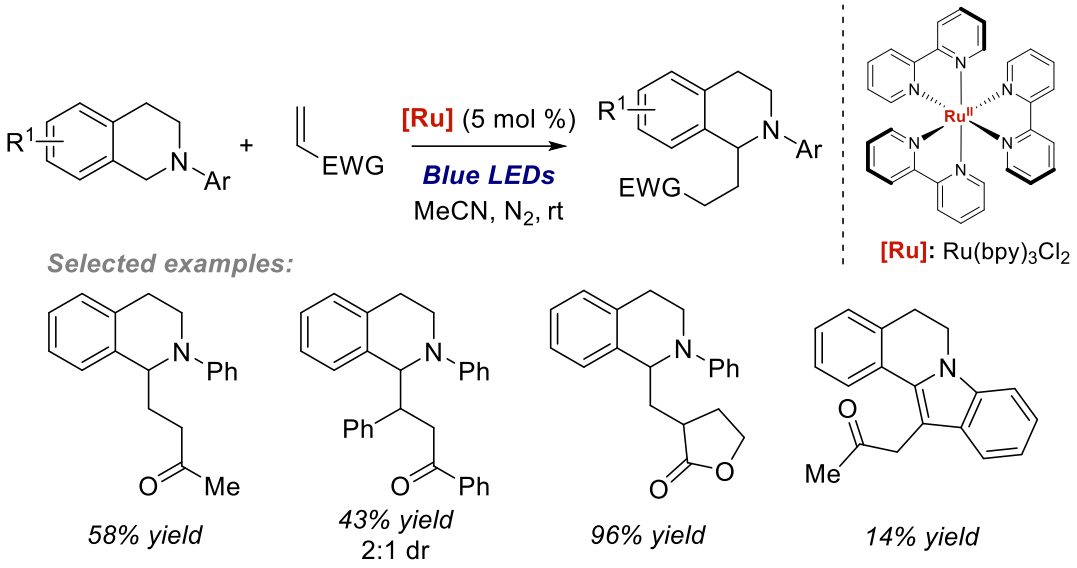


Figure 24: Electrophilic functionalization of *N*-aryl tetrahydroisoquinolines with electron-poor alkenes (Reiser).

of the corresponding α-amino radical goes through a different pathway to that depicted in Figure 20. The presence of the phthalimide moiety in the so-called redox-active ester allows single-electron reduction rather than oxidation of amine electrons. In fact, redox-active esters have been extensively used in redox organic transformations.[50,51] All in all, the generated α-amino radical reacted with the proper quinoline or pyridine in an asymmetric fashion to yield the corresponding Minisci products in high to excellent yields with generally excellent enantioselectivities (Figure 25).

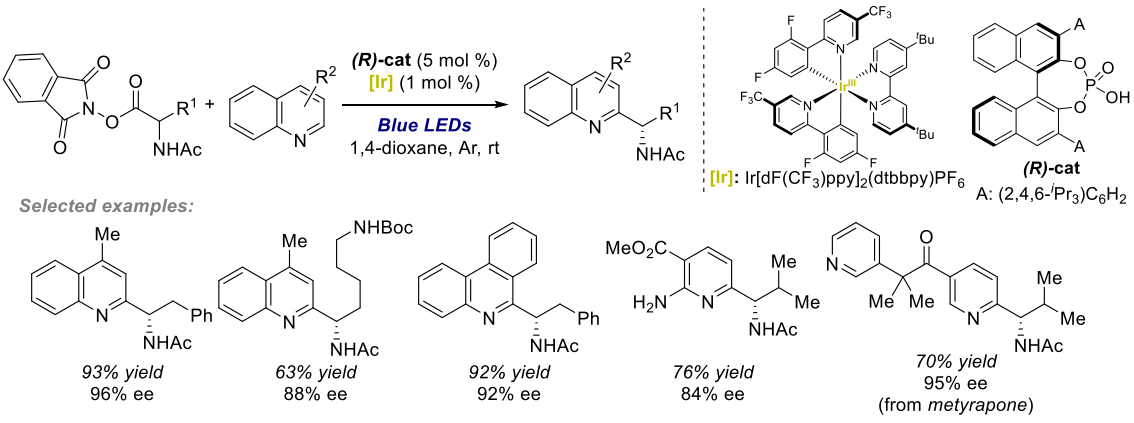


Figure 25: Photoredox-enabled enantioselective Minisci-type reaction (Phipps).

0.5.2 3,4-Dihydro-1,4-benzoxazin-2-ones and 3,4-Dihydroquinoxalin-2-ones

In this *thesis*, 3,4-dihydro-1,4-benzoxazin-2-ones and 3,4-dihydroquinoxalin-2-ones have been selected as substrates to carry out synthetic transformations using visible-light photoredox catalysis (Figure 26). The selection of these reasonably similar cyclic amines was not by chance, but for the scarce existence of functionalization protocols given the biological importance of these heterocycles.[52]

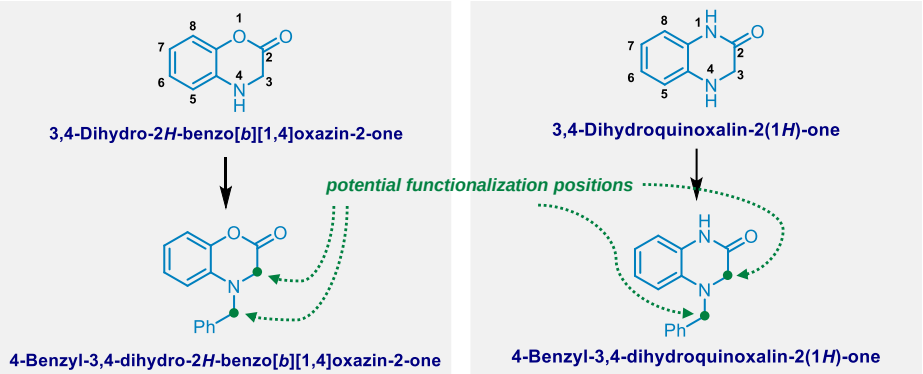


Figure 26: Parent structures of 3,4-dihydro-1,4-benzoxazin-2-one and 3,4-dihydroquinoxalin-2-one and their benzylic alkylation products at N-4.

Parent 3,4-dihydro-1,4-benzoxazin-2-one and 3,4-dihydroquinoxalin-2-one skeleton (Figure 26, *top*) have a secondary aminic nitrogen at their *4* position. Besides, the installation of a benzylic substituent at the N-4 position generates a tertiary amine, which is more electron-rich than the secondary one, allowing these structures to be engaged in synthetic transformations based on electron-transfer events (Figure 26, *bottom*). Nevertheless, some regioselectivity issues may arise as there are two methylene groups in α to the N-4. Still, the rigidity of the cyclic system should allow the potential functionalization to happen through the C-3 position.

Importance of 3,4-dihydro-1,4-benzoxazin-2-ones and 3,4-dihydroquinoxalin-2-ones

3,4-Dihydro-1,4-benzoxazin-2-ones[53–61] and 3,4-Dihydroquinoxalin-2-ones[61–69] are prevailing scaffolds that can be found either in several natural-occurring or synthetic biologically-active compounds. In fact, some studies have revealed the importance of these heterocyclic systems to achieve interesting pharmacological activities. Examples of biologically active 3,4-dihydro-1,4-benzoxazin-2-ones and 3,4-dihydroquinoxalin-2-ones are shown in Figure 27.

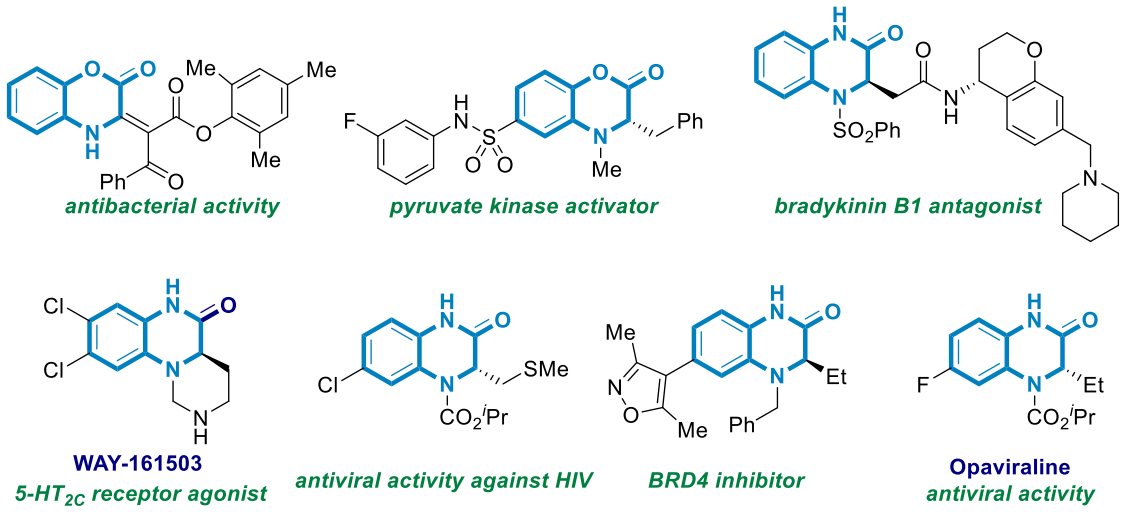


Figure 27: Different biologically-active 3,4-dihydro-1,4-benzoxazin-2-ones and 3,4-dihydroquinoxalin-2-ones.

C-3 Functionalization of 3,4-dihydro-1,4-benzoxazin-2-ones and 3,4-dihydroquinoxalin-2-ones

Traditionally, the preparation of complex 3,4-dihydro-1,4-benzoxazin-2-ones and 3,4-dihydroquinoxalin-2-ones such as those shown in Figure 27 has relied on the *de novo* synthesis from commercially available starting materials.[70,71] However, from a **diversity-oriented synthesis** point of view, it is interesting to develop direct functionalization methodologies in order to generate straightaway a library of potential candidates for drug discovery.[72] In this Section, all the reports regarding the C-3 functionalization of 3,4-dihydro-1,4-benzoxazin-2-ones and 3,4-dihydroquinoxalin-2-ones will be presented in chronological order.

The first example of 3,4-dihydroquinoxalin-2-one C-3 functionalization comes from the laboratory of Xiao in 2016. In their report, the authors shown how to functionalize several *N*-aryl glycines or other α-TMS-derived amines with ketones in the presence of $Ir(ppy)_3$ as photoredox catalyst and $LiBF_4$ as stoichiometric Lewis acid.[73] Among all these products, the authors were able to generate the α-amino radical of two 3,4-dihydroquinoxalin-2-ones, bearing two different protecting groups at N-1, and to react them with benzophenone, obtaining the corresponding carbinols in good yield. (Figure 28).

In 2016 the research group of Huo cut the ribbon of 3,4-dihydro-1,4-benzoxazin-2-one C-3 functionalization with their report on Fe-catalyzed aza-Friedel-Crafts reaction between these kind of cyclic amines and indoles.[74] In this case, the corresponding iminium cation was generated using catalytic $FeCl_2$ and *tert*-butyl hydroperoxide (TBHP) as termi-

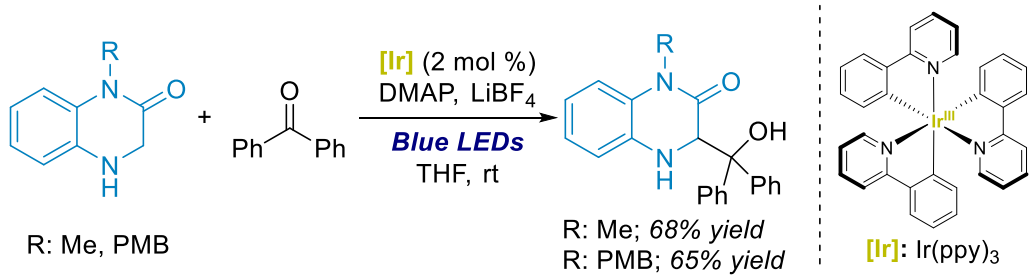


Figure 28: C-3 alkylation of 3,4-dihydroquinoxalin-2-ones with benzophenone using photoredox catalysis (Xiao).

nal oxidant. The authors were pleased to obtain a library of 33 C-3 arylated 3,4-dihydro-1,4-benzoxazin-2-ones (Figure 29).

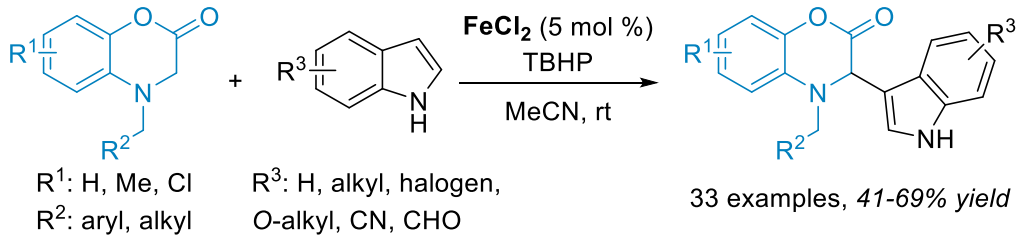


Figure 29: Fe-catalyzed aza-Friedel-Crafts reaction between 3,4-dihydro-1,4-benzoxazin-2-ones and indoles (Huo).

It was the same research group who, in 2017, reported the C-3 alkylation of 3,4-dihydro-1,4-benzoxazin-2-ones with dialkyl malonates, generating this time the iminium cation using $Fe(OTf)_3$ and DDQ as terminal oxidant.[75] Additionally, the authors rapidly adapted the reaction conditions to employ several ketones as nucleophilic counterparts (Figure 30).

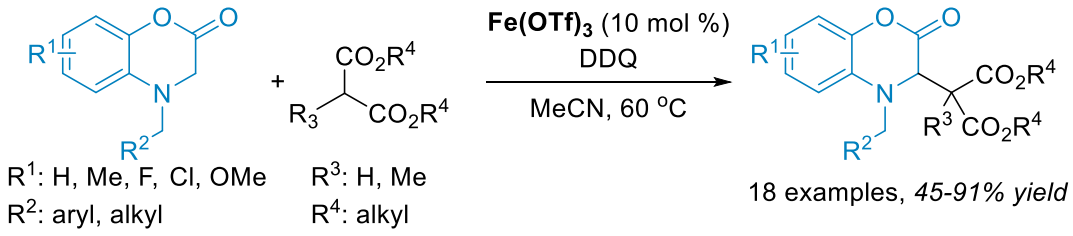


Figure 30: Fe-catalyzed alkylation of 3,4-dihydro-1,4-benzoxazin-2-ones with bromomalonates (Huo).

It was also the laboratory of Huo the responsible of developing, in 2018, the Cu-catalyzed the phosphonation of 3,4-dihydro-1,4-benzoxazin-2-ones through their iminium

cations using organic phosphites as nucleophiles and PBQ as terminal oxidant.[76] Using these conditions, they were able to forge C−P bonds in several 3,4-dihydro-1,4-benzoxazin-2-ones and phosphites, resulting in a collection of 24 differently substituted adducts. Moreover, they applied the methodology to the C-3 functionalization of 4-benzyl-3,4-dihydroquinoxalin-2-one with dimethyl phosphite, obtaining the corresponding product in 72% yield (Figure 31).

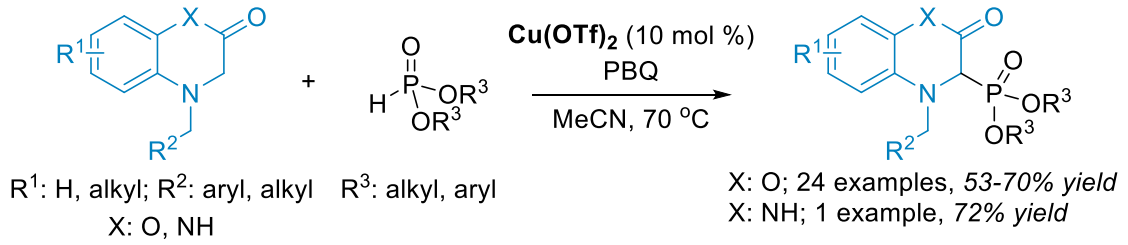


Figure 31: Cu-catalyzed phosphonation of 3,4-dihydro-1,4-benzoxazin-2-ones (Huo).

In 2018, He and collaborators were the first ones to apply visible-light photoredox catalysis to the generation of the iminium cation of 3,4-dihydroquinoxalin-2-ones. In their work, they reported the aerobic functionalization of 3,4-dihydro-1,4-benzoxazin-2-ones with indoles by means of photoredox catalysis using $Ru(bpy)_3Cl_2$ as photoredox catalyst.[77] However, the expected 18 products were obtained in generally low yields (Figure 32).

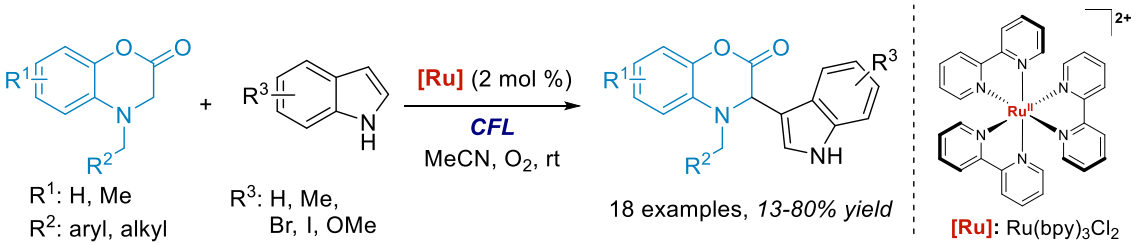


Figure 32: Aza-Friedel-Crafts reaction between 3,4-dihydro-1,4-benzoxazin-2-ones and indoles enabled by visible-light photoredox catalysis (He).

Additionally, in the same year, the research group of Hong[78] employed the usual $Ru(bpy)_3Cl_2$ photocatalyst, CFL as light source and oxygen from air as terminal oxidant to functionalize 3,4-dihydroquinoxalin-2-ones via iminium cation. The selected nucleophiles were indoles, other electron-rich arenes and also some silicon nucleophiles. The reaction was also performed in the absence of photocatalyst but leading to the products in lower yields. Besides, the reaction was also tested with one 3,4-dihydro-1,4-benzoxazin-2-one (Figure 33).

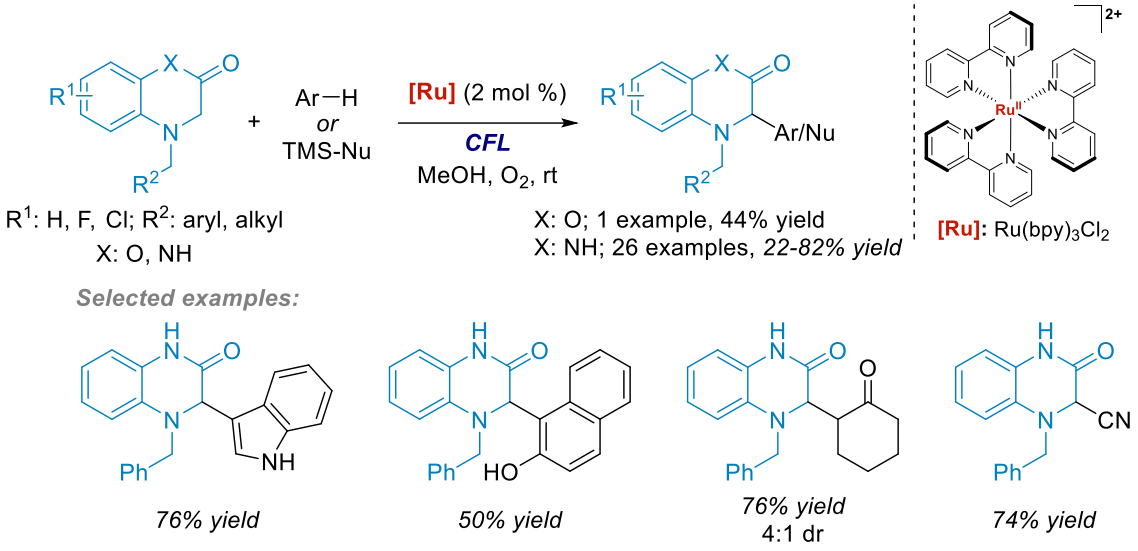


Figure 33: Photoredox-catalyzed oxidative functionalization of 3,4-dihydroquinoxalin-2-ones with electron-rich arenes and silicon nucleophiles (Hong).

In 2020, the laboratory of Huo went back to the field with their thermal peroxidation of mainly 3,4-dihydro-1,4-benzoxazin-2-ones using TBHP and other analogue.[79] The corresponding internal peroxides were obtained in moderate to high yields. 3,4-Dihydroquinoxalin-2-ones were also suitable substrates for peroxidation, allowing the authors to obtain 4 examples in high yields (Figure 34). Interestingly, the authors shown how the obtained peroxides could serve as starting materials for further derivatizations. Hence, they were pleased to make them react with dimethyl malonate, phenylacetylene and *N*,*N*-dimethylaniline (Friedel-Crafts reaction) among others.

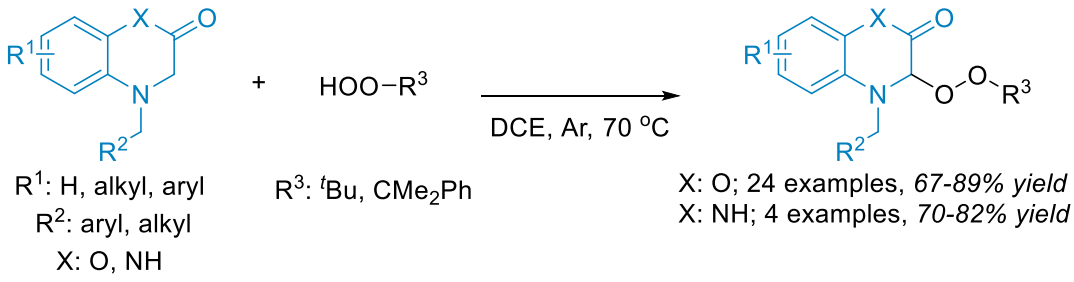


Figure 34: Peroxidation od 3,4-dihydro-1,4-benzoxazin-2-ones with alkyl hydroperoxides (Huo).

The last report of the research group of Huo appeared in 2021, where they reported the N-4-unprotected amination of 3,4-dihydroquinoxalin-2-ones with primary and secondary aliphatic amines using Cu catalysis under an aerobic atmosphere.[80] In this case, the nucleophile which is generated through copper catalysis is not an iminium cation but an imine. Additionally, once the addition of a given amine to the imine takes place, the formed sec-

ondary amine suffers another oxidation process yielding the corresponding C-3-aminated quinoxalin-2-one (Figure 35).

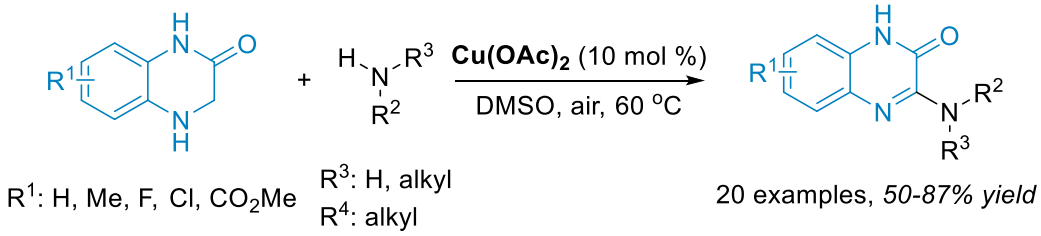


Figure 35: Cu-catalized aerobic oxidative amination of 3,4-dihydroquinoxalin-2-oes (Huo).

In 2022, the group of Liu developed a protocol to introduce the difluoromethyl moiety at the C-3 position of 3,4-dihydroquinoxalin-2-ones.[81] To do this, they employed *S*-difluoromethyl diaryl sulfonium salts developed by themselves as difluoromethyl radical precursors, and an organophotoredox catalyst derived from 1,4-diaminonaphthalene. When unprotected 3,4-dihydroquinoxalin-2-ones at N-4 were employed, they obtained a mixture of C-3 difluoromethylated 3,4-dihydroquinoxalin-2-ones and the corresponding difluoromethylated quinoxalin-2-one. However, by using DDQ they could force the oxidation process and generate exclusively the corresponding quinoxalin-2-one (Figure 36).

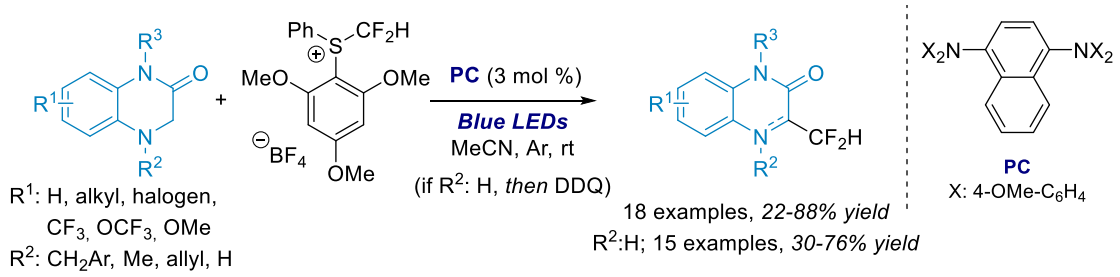


Figure 36: Difluoromethylation of 3,4-dihydroquinoxalin-2-ones through visible-light photoredox catalysis (Liu).

Finally, also in 2022, Hong and collaborators described such an elegant methodology to build complex polycyclic systems bearing a 3,4-dihydroquinoxalin-2-one moiety using visible-light organophotocatalysis.[82] Using thioxanthone and an aerobic atmosphere they were able to obtain 12 different polycyclic structures with complete diastereoselectivity in high yields (Figure 37).

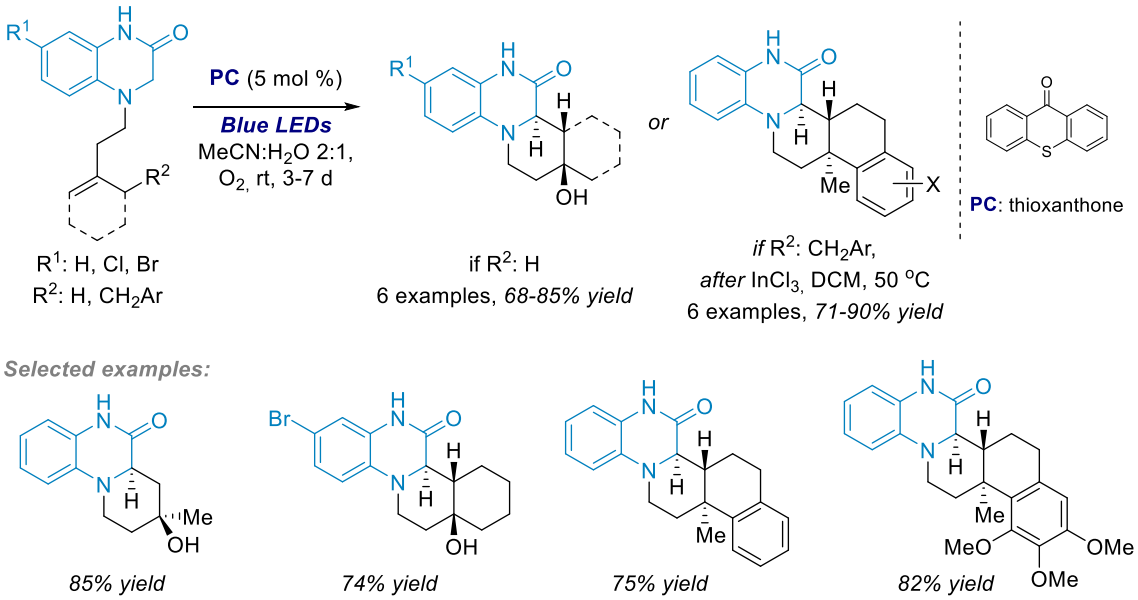
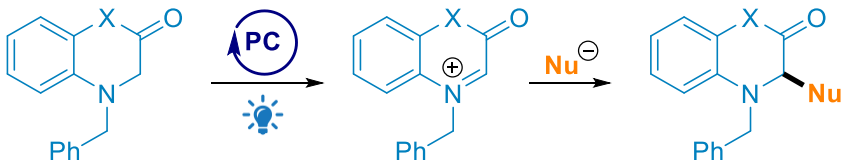


Figure 37: Construction of polycyclic 3,4-dihydroquinoxalin-2-ones thorough visible-light photoredox catalysis (Hong).

General Objectives

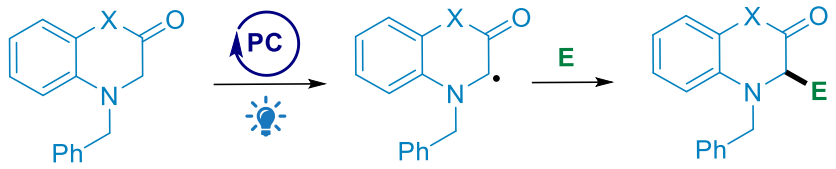
Having disclosed several theoretical aspects of photochemistry, specially visible-light photoredox catalysis, and after introducing the motivation and the needs of developing C-3 functionalization of **3,4-dihydro-1,4-benzoxazin-2-ones** and **3,4-dihydroquinoxalin-2-ones** methodologies (**Part I**), the present *thesis* states the following main **objectives**:

- **Part II**: Nucleophilic functionalization of 3,4-dihydro-1,4-benzoxazin-2-ones and 3,4-dihydroquinoxalin-2-ones.



  - In *Chapter 1*, a methodology to functionalize 3,4-dihydro-1,4-benzoxazin-2-ones with **indoles** and other electron-rich arenes using an organophotoredox catalyst is presented.
  - In *Chapter 2*, a fruitful combination of photoredox catalysis and organocatalysis for the enantioselective Mannich-type reaction between 3,4-dihydroquinoxalin-2-ones and **ketones** is shown.
  - In *Chapter 3*, the C-3 functionalization of 3,4-dihydroquinoxalin-2-ones using **pyrazolones** as nucleophiles and an organophotoredox catalyst is explained.
  - In *Chapter 4*, the alkynylation of 3,4-dihydroquinoxalin-2-ones with **terminal alkynes** using both copper catalysis and visible light is exposed.

- **Part III**: Electrophilic functionalization of 3,4-dihydro-1,4-benzoxazin-2-ones and 3,4-dihydroquinoxalin-2-ones.



  - In *Chapter 5*, the reaction between 3,4-dihydroquinoxalin-2-ones and **electron-poor alkenes** using a dual catalytic system is presented.
  - In *Chapter 6*, **dialkyl azodicarboxylates** were employed as electrophiles to functionalize both 3,4-dihydro-1,4-benzoxazin-2-ones and 3,4-dihydroquinoxalin-2-ones.
  - In *Chapter 7*, the 1,2-addition reaction of 3,4-dihydroquinoxalin-2-ones to **trifluoromethyl ketones** by means of photoredox catalysis is exposed.
  - In *Chapter 8*, the 1,6-addition of 3,4-dihydroquinoxalin-2-ones to ***p*-quinone methides** is developed and posed.

Part II

Nucleophilic Functionalization of 3,4-dihydro-1,4-benzoxazin-2-ones and 3,4-dihydroquinoxalin-2-ones

Chapter 1

Functionalization of 3,4-Dihydro-1,4-Benzoxazin-2-ones with Indoles and Electron-Rich Arenes under Visible-Light Organophotoredox Catalysis

1.1 Introduction and state of the art

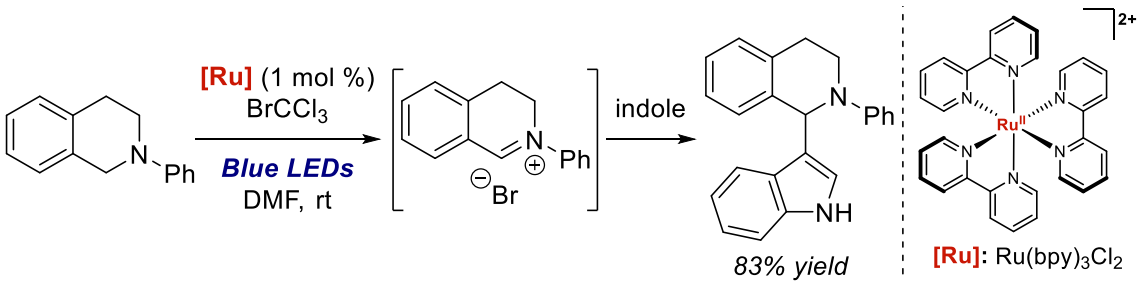
Indoles have been extensively used in organic synthesis due to the high nucleophilicity of its C-3 position[83,84] through one of the cornerstones of organic chemistry: the **Friedel-Crafts reaction**,[85,86] which is one of the most straightforward way to form C−C bonds.

In addition, there are a myriad of indole-containing interesting molecules from the point of view of medicinal chemistry,[87–89] agrochemistry[90] and materials science[91] among other fields. Thus, the development of methodologies that allow the selective accommodation of this aromatic heterocycle is of high interest. Indeed, our research group has much experience in the use of indole as nucleophile, specially in enantioselective synthesis.[92–95]

There are also a lot of visible-light photoredox catalysis methodologies where indoles serve as nucleophiles. Specially, they have been broadly implemented in α-functionalization of *N*-aryl tetrahydroisoquinolines[96–102] and *N*-aryl glycines.[103–106]

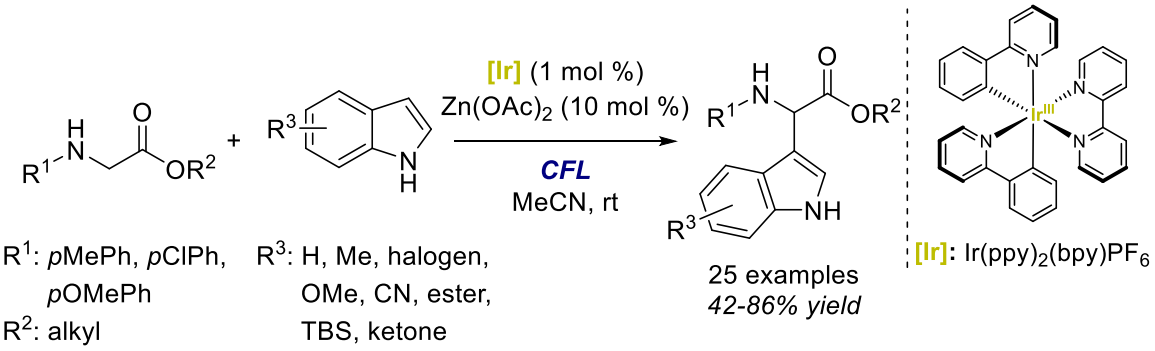
It is worth highlighting the work of the group of Stephenson, who in 2012 reported a general methodology to functionalize *N*-aryl tetrahydroisoquinolines with several nucleophiles, being one of them indole, using visible-light photoredox catalysis.[107] In this case, the authors developed a step-by-step protocol in which the iminium cation of *N*-aryl tetrahydroisoquinolines was generated in the presence of $Ru(bpy)_3Cl_2$ and $BrCCl_3$ as sto-

ichiometric oxidant. Thereafter, the iminium cation was trapped with, for example, indole yielding the corresponding aza-Friedel-Crafts product in 83% (Scheme 1.1).



Scheme 1.1: Aza-Friedel-Crafts reaction between *N*-aryl tetrahydroisoquinolines and indole under visible-light photoredox catalysis (Stephenson).

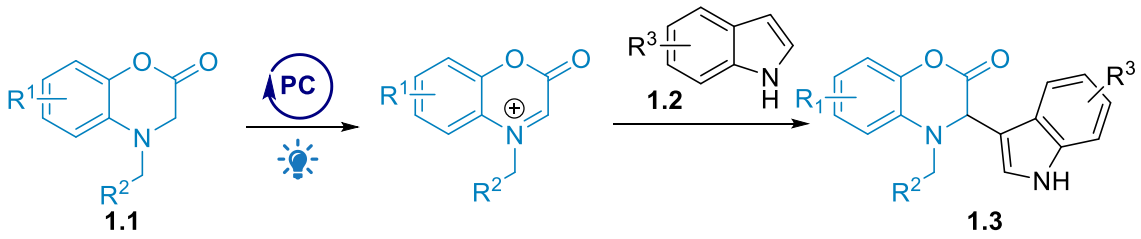
Complementarily, in 2012 the research group of Rueping pioneered with their work on α-functionalization of *N*-aryl glycine esters with indoles by means of a dual catalytic system formed by $Ir(ppy)_2(bpy)PF_6$ as photoredox catalyst and $Zn(OAc)_2$ as Lewis acid.[108] According to the authors, the Lewis acid catalyzes the imine formation once the photochemical oxidation of the aminic nitrogen takes place. Besides, the coordination of Zn(II) to the imine increases its electrophilicity (Scheme 1.2).



Scheme 1.2: Aza-Friedel-Crafts reaction between *N*-aryl glycines and indoles under visible-light photoredox catalysis and Lewis acid catalysis (Rueping).

1.2 Objectives

The main objective for this *chapter* is to develop a methodology to functionalize 3,4-dihydro-1,4-benzoxazin-2-ones (**1.1**) with indoles (**1.2**) employing visible-light photoredox catalysis. To achieve this objective, several partial objectives are postulated:



1. Synthesis of 3,4-dihydro-1,4-benzoxazin-2-ones (**1.1**) bearing substituents with different electronic and steric properties.

2. Optimization of the reaction conditions between 3,4-dihydro-1,4-benzoxazin-2-one **1.1a** and indole (**1.2a**) to obtain the corresponding Friedel-Craft product **1.3aa** with the highest yield.

3. Study of the scope of the reaction between different 3,4-dihydro-1,4-benzoxazin-2-ones (**1.1**) and indoles (**1.2**). It will try to extend the scope to other tertiary amines and other electron-rich arenes as well.

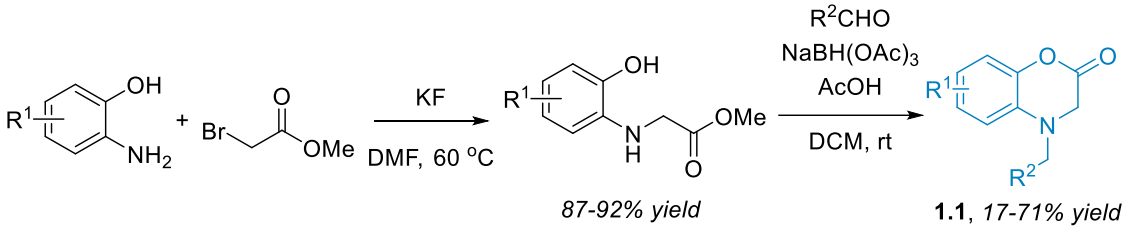
4. Synthetic transformations over the reaction products **1.3**. Synthesis of structurally-related *Cephalandole A*.

5. Mechanistic investigations and proposal of a reaction mechanism.

1.3 Results and Discussion

1.3.1 Synthesis of 3,4-dihydro-1,4-benzoxazin-2-ones

The synthesis of 3,4-dihydro-1,4-benzoxazin-2-ones **1.1** was accomplished following a two-step methodology reported by Kikelj in 2008 (Scheme 1.3).[109]



Scheme 1.3: General synthetic methodology to prepare 3,4-dihydro-1,4-benzoxazin-2-ones **1.1**.

In the first step, the corresponding *o*-aminophenol reacts with methyl bromoacetate in the presence of potassium fluoride through a S_N2 reaction to obtain the expected aryl glycinates in high yields (Figure 1.1). In this case, unsubstituted *o*-aminophenol as well as its 3- and 4-methyl regioisomers were subjected to this transformation.

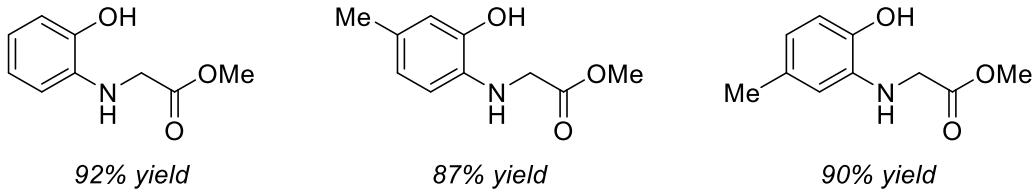
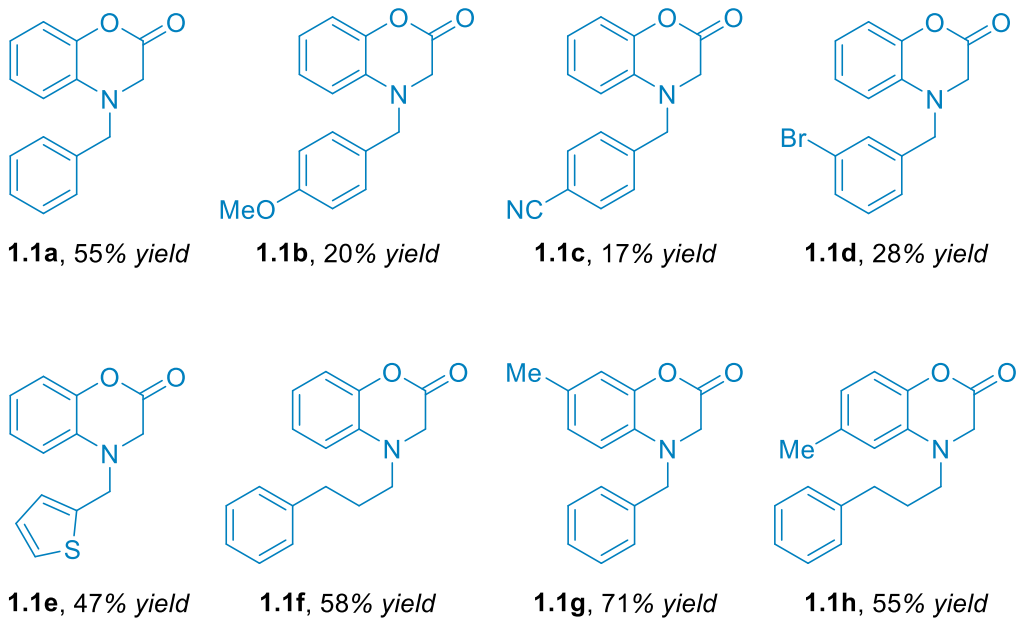


Figure 1.1: Synthesis of three different aryl glycinates.

The second and last step of this synthetic sequence corresponds to the tandem reductive amination over the secondary amine group of each aryl glycinate, and the subsequent lactonization (transesterification) fo finally furnish 3,4-dihydro-1,4-benzoxazin-2-ones **1.1**. The reductive amination was carried out using $NaBH(OAc)_3$, which reduces the incipient iminium cation formed after the condensation between the aryl glycinate and the proper aldehyde. Once the tertiary amine is generated, the presence of acetic acid facilitates the lactonization reaction to finally yield the desired 3,4-dihydro-1,4-benzoxazin-2-ones **1.1a**-**1.1h** in low to moderate yields (Figure 1.2).



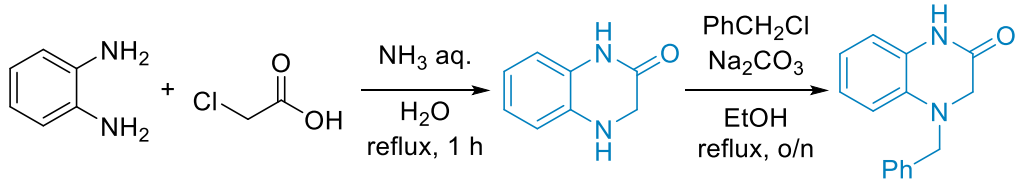
1.1a, 55% *yield* **1.1b**, 20% *yield* **1.1c**, 17% *yield* **1.1d**, 28% *yield*

1.1e, 47% *yield* **1.1f**, 58% *yield* **1.1g**, 71% *yield* **1.1h**, 55% *yield*

Figure 1.2: Synthesis of eight different 3,4-dihydro-1,4-benzoxazin-2-ones **1.1a**-**1.1h** from aryl glycinates.

1.3.2 Synthesis of 3,4-dihydroquinoxalin-2-one 1.4 and 1.5

The structural analogues 3,4-dihydroquinoxalin-2-one **1.4** and **1.5** were synthesised according to a reported methodology.[110] Initially, *o*-phenylenediamine was reacted with chloroacetic acid in the presence of aqueous ammonia at reflux temperature for 1 hour, obtaining 3,4-dihydroquinoxalin-2-one **1.4** in 55% yield (Scheme 1.4). Afterwards, quinoxaline **1.4** was subjected to *N*-alkylation with benzyl chloride in the presence of Na_2CO_3 to obtain 4-benzyl-3,4-dihydroquinoxalin-2-one **1.5** in 90% yield (Scheme 1.4).



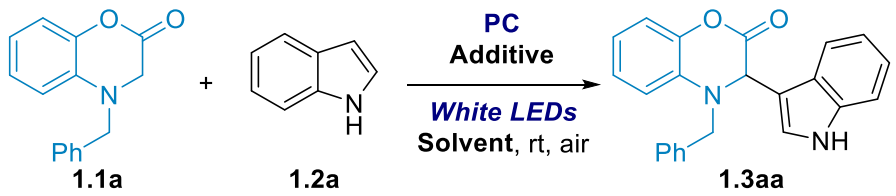
1.4, *55% yield* **1.5**, *90% yield*

Scheme 1.4: Synthetic methodology to prepare 3,4-dihydroquinoxalin-2-one **1.4** and **1.5**.

1.3.3 Optimization of the Reaction Conditions

To study the photoredox-catalyzed aza-Friedel-Crafts reaction between 3,4-dihydro-1,4-benzozazin-2-ones (**1.1**) and indoles (**1.2**), compounds **1.1a** and **1.2a** were selected as

model substrates to optimize the reaction conditions (Scheme 1.5).

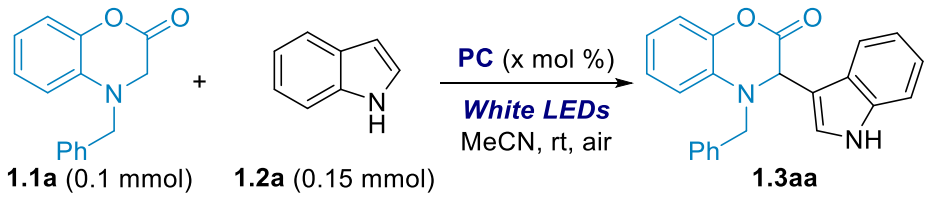


Scheme 1.5: Overview of the model reaction to carry out the optimization of the reaction conditions.

First of all, the evaluation of the photoredox catalyst will be carried out, followed by the assessment of the best molar ratio between substrates that ensures that the reaction proceeds with the maximum yield of **1.3aa**. Besides, the effect of several acid additives over the outcome of the reaction will be evaluated. Finally, the choice of the best solvent to perform the reaction will be studied.

Evaluation of the Photoredox Catalyst

The photoredox catalyst is the key element that ensures the formation of the iminium cation in substrates **1.1**. Therefore, the precise selection of it constitutes the most important part of the optimization process. A great assortment of photoredox catalysts were available in our laboratory, being them either metal-based photocatalysts or organophotoredox catalysts. As preliminary reaction conditions, MeCN was chosen as solvent and 0.1 mmol of **1.1a** and 0.15 mmol of **1.2a** were used (Scheme 1.6). Table 1.1 shows the yield in which product **1.3aa** is obtained in the presence of each photocatalyst.



Scheme 1.6: Evaluation of the photoredox catalyst in the reaction between **1.1a** and **1.2a**. Reaction overview.

To our delight, when the omnipresent $Ru(bpy)_3Cl_2$ (**A**) photocatalyst is employed, the expected product **1.3aa** was delivered in 28% yield (Table 1.1, Entry 1) showing that the iminium cation of **1.1a** could be generated under aerobic photoredox conditions. This preliminary result led us to further explore other photocatalyst families. TiO_2 (**B**) was tested as photocatalyst in an attempt to develop a more user-friendly heterogeneous methodology, but the desired product was obtained in only 11% yield (Table 1.1, Entry 2). In situ-

Table 1.1: Evaluation of the photoredox catalyst in the reaction between **1.1a** and **1.2a**. Yield of **1.3aa** in each case.

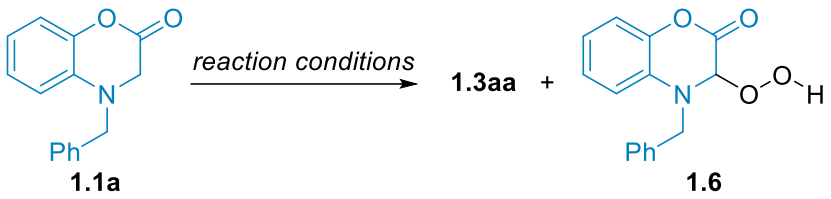
Entry[a]	**PC (x mol %)**	**t (h)**	**Yield 1.3aa (%)**[b]
1	$Ru(bpy)_3Cl_2$ (**A**) (1)	18	28
2	TiO_2 (100) (**B**)	72	11
3	$Fe(bpy)_3SO_4$ (**C**) (5)	72	NR
4	Rose Bengal (**D**) (5)	28	38
5	Eosin-Y-Na_2 (**E**) (5)	25	27
6	Methylene Blue (**F**) (5)	24	29
7	[2,4,6-Ph_3-pyrillium][BF_4] (**G**) (5)	48	13
8	[Mes-Acr-Me][BF_4] (**H**) (5)	23	35
9	DDQ (**I**) (10)	24	20
10	9,10-Phenanthrenequinone (**J**) (10)	24	33

[a]Reaction conditions: **1.1a** (0.1 mmol), **1.2a** (0.15 mmol), photoredox catalyst (**PC**, x mol %), MeCN (1 mL), under air atmosphere and under white LEDs irradiation.
[b]Yield determined after purification by column chromatography.

generated $Fe(bpy)_3SO_4$ (**C**) was also engaged in this transformation, but with no product observation after 72 hours of reaction (Table 1.1, Entry 3). Within the family of purely organic photocatalysts, a wide array of them were tested under the reaction conditions. Rose Bengal (**D**), Eosin Y-Na_2 (**E**) and Methylene Blue (**F**) granted compound **1.3aa** in 38, 27 and 29% yield respectively (Table 1.1, Entries 4-6), whereas the more sophisticated [2,4,6-Ph_3-pyrillium][BF_4] (**G**) and [Mes-Acr-Me][BF_4] (**H**) were able to generate the desired product in 13 and 35% yield respectively (Table 1.1, Entries 7 and 8). Finally, as representatives of the quinone family, DDQ (**I**) and 9,10-phenanthrenequinone (**J**) were employed, delivering the expected compound **1.3aa** in 20 and 33% yield respectively (Table 1.1, Entries 9 and 10).

In most of the above-mentioned cases, 3,4-dihydro-1,4-benzoxazin-2-one **1.1a** is fully consumed under the reaction conditions, but the yields in which **1.3aa** is obtained are significantly lower compared to what would be expected. After a conscientious examination of the reaction mixture, a by-product could be isolated by column chromatography. This product derives from the 3,4-dihydro-1,4-benzoxazin-2-one skeleton in which an oxygen molecule has been incorporated, forming the corresponding hydroperoxide **1.6** (Scheme 1.7). The chemical entity of this secondary product was elucidated by means of

^{1}H-NMR, ^{13}C-NMR and HRMS.



Scheme 1.7: Hydroperoxide secondary product **1.6**, which is obtained in several cases during the reaction.

Evalutation of the Molar Ratio

Having realized that there were al least one secondary reaction that converts 3,4-dihydro-1,4-benzoxazin-2-one **1.1a** in an undesirable product, the reactions in which the photoredox catalyst provided a good result were repeated but using now 0.15 mmol of **1.1a** and 0.1 mmol of **1.2a** (Table 1.2). Moreover, *fac*-Ir(ppy)$_3$ (**K**) became available in our laboratory at this stage.

Table 1.2: Evaluation of the photoredox catalyst in the reaction between **1.1a** and **1.2a** changing the molar ratio. Yield of **1.3aa** in each case.

Entry[a]	PC (x mol %)	t (h)	Yield 1.3aa (%)[b]
1	$Ru(bpy)_3Cl_2$ (**A**) (1)	18	48
2	*fac*-Ir(ppy)$_3$ (**K**) (1)	48	7
3	Rose Bengal (**D**) (5)	24	53
4	[Mes-Acr-Me][BF_4] (**H**) (5)	36	27
5	9,10-Phenanthrenequinone (**J**) (10)	24	53
6	Benzyl (**L**) (10)	48	15

[a]Reaction conditions: **1.1a** (0.15 mmol), **1.2a** (0.1 mmol), photoredox catalyst (**PC**, x mol %), MeCN (1 mL), under air atmosphere and under white LEDs irradiation.
[b]Yield determined after purification by column chromatography.

In most of the cases, the yield was significantly improved using this molar ratio between **1.1a** and **1.2a**. Specifically, with $Ru(bpy)_3Cl_2$ (**A**) the yield in which **1.3aa** is generated varied from 28 to 48% (Table 1.2, Entry 1). Unfortunately, *fac*-Ir(ppy)$_3$ (**K**) mismatched the reaction conditions, obtaining the desired product in a very low 7% yield (Table 1.2, Entry 2). Within the family of organophotocatalysts, the use of this new molar

ratio in combination with either Rose Bengal (**D**) or 9,10-phenanthrenequinone (**J**) improved the yield of **1.3aa** until 53% in both cases (Table 1.2, Entries 3 and 5) putting into account that this molar ratio between **1.1a** and **1.2a** was more convenient to get a better yield of **1.3aa**.

At this point, we were gratingly surprised about the competence of 9,10-phenanthrenequinone (**J**) in this transformation. There were few precedents that use this very simple molecule as photocatalyst. Specifically, just the group of Kumar employed it in 2018 in a photoredox trifluoromethylation/cyclization of 1,6-enynes en route to 2,3-disubstituted benzofurans.[111] Contrary to its isomer anthraquinone, 9,10-phenanthrenequinone absorbs light in the visible region so in principle it is a suitable candidate in visible-light photoredox catalysis. To test the necessity of the existence of a tricyclic rigid scaffold in 9,10-phenanthrenequinone, the aza-Friedel-Crafts reaction was also conducted using benzyl (**L**), which is an analogue that exhibits free rotation along some C−C bonds (Table 1.2, Entry 6). In this case, the expected product **1.3aa** was obtained in just a 7% yield, revealing the imperious requirement of that cyclic system.

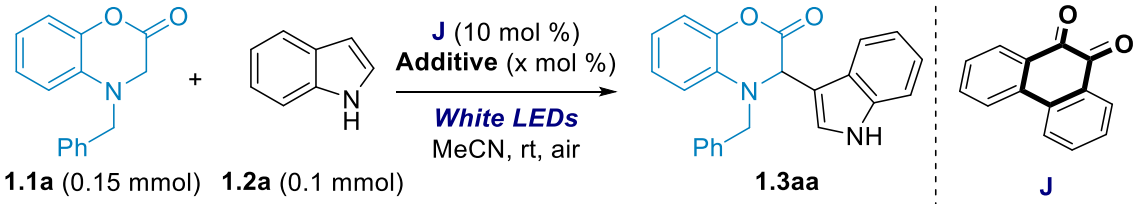
After we realized that both Rose Bengal (**D**) and 9,10-phenanthrenequinone (**J**) provided the same yield of **1.3aa**, we decided to continue the optimization process using the last one. The reasons behind this decision rely in essence on the price and the molecular weight. According to Merck (Sigma Aldrich), Rose Bengal has a price of 81,41 €/mmol whereas 9,10-phenanthrenequinone can be purchased just by 0.78 €/mmol[†]. Besides, in alignment with the development of more sustainable chemical processes, the molecular weight of Rose Bengal (**D**) and 9,10-phenanthrenequinone (**J**) is 1017.64 and 208.21 g/mol respectively, so using a low-molecular-weight photocatalyst allowed us to use less mass of catalyst. Correspondingly, 9,10-phenanthrenequinone (**J**) was chosen as the best photocatalyst to continue the optimization process.

Effect of Acid Additives

In the route to improve the yield in which product **1.3aa** is formed, we wanted to study the effect of some either Brønsted or Lewis acids over the reaction outcome. To do so, a 10 mol % catalytic loading of several acids were tested using 0.15 mmol of **1.1a**, 0.1 mmol of **1.2a**, 9,10-phenanthrenequinone (**J**) as photocatalyst and MeCN as solvent (Scheme 1.8). Among all the possibilities, benzoic acid and acetic acid were chosen from the family of Brønsted acids, whereas Zn(II) salts were selected from the Lewis acids family (Table 1.3).

The use of benzoic acid or acetic acid as additive lead to a diminished yield of 36 and 26% respectively (Table 1.3, Entries 2 and 3). Indeed, the addition of these acids may

[†]Checked on Merck (Sigma-Aldrich) on 02/09/2022.



Scheme 1.8: Effect of acid additives in the reaction between **1.1a** and **1.2a** using **J** as photocatalyst.

Table 1.3: Evaluation of acid additives in the reaction between **1.1a** and **1.2a** using **J** as photocatalyst. Yield of **1.3aa** in each case.

Entry[a]	Additive (x mol %)	Yield 1.3aa (%)[b]
1	-	53
2	$PhCO_2H$ (10)	36
3	AcOH (10)	26
4	$Zn(OAc)_2$ (10)	26
5	$Zn(OTf)_2$ (10)	43
6[c]	$Zn(OTf)_2$ (10)	76 (83)[d]
7[c]	$Zn(OTf)_2$ (5)	74

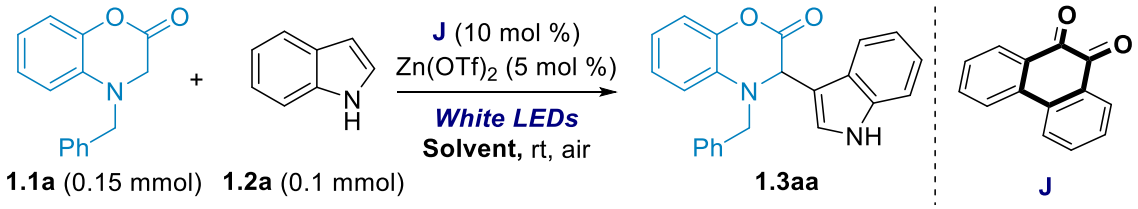
[a]Reaction conditions: **1.1a** (0.15 mmol), **1.2a** (0.1 mmol), **J** (10 mol %), Additive (x mol %), MeCN (1 mL), under air atmosphere and under white LEDs irradiation. Reaction time: 24 h.
[b]Yield determined after purification by column chromatography.
[c]Reaction time was 9 h.
[d]Yield determined by ^{1}H-NMR using *p*-methoxyacetophenone as internal standard.

cause the partial protonation of the N-4 in the starting material **1.1a** and, as a consequence, the interaction with the excited state of the photoredox catalyst is more difficult. In this sense, the use of Lewis acids instead of Brønsted acids avoids the protonation of this aminic nitrogen. $Zn(OAc)_2$ and $Zn(OTf)_2$, which are moderately soft acids, were tested as acid additives under our conditions. When the reaction was performed using $Zn(OAc)_2$, product **1.3aa** was isolated in 26% yield (Table 1.3, Entry 4). Thereafter, when the effect of $Zn(OTf)_2$ was practiced, the expected product **1.3aa** was isolated in only 43% yield (Table 1.3, Entry 5). This last result resulted confusing because indole **1.2a** was fully consumed as shown by TLC. This meant that product **1.3aa** was not stable enough under these reaction conditions and, once it is formed, it experiments a decomposition pathway. To address this issue, the reaction was repeated but the irradiation time was diminished from 24 to 9 hours. Then, the crude reaction mixture was analyzed by ^{1}H-NMR using

p-methoxyacetopheone as internal standard. To our delight, product **1.3aa** was found to be formed in 83% yield, which became 76% after isolation by column chromatography (Table 1.3, Entry 6). Finally, a decrease in the catalytic loading of $Zn(OTf)_2$ until 5 mol % resulted in a comparable yield of 74% (Table 1.3, Entry 7).

Evaluation of the Solvent

Once the use of 5 mol % of $Zn(OTf)_2$ resulted beneficial for the reaction performance, the effect of the solvent was examined. Acetonitrile is one of the most employed solvents in photochemistry, mainly due to its transparency in the visible region and most of the ultraviolet region. Moreover, its high relative permittivity allows acetonitrile to be a suitable medium for electron-transfer and energy-transfer processes. For all these reasons, acetonitrile is often set as starting solvent for a reaction optimization process. However, some other solvents were tested under our potential optimal conditions (Scheme 1.9).



Scheme 1.9: Effect of the solvent in the reaction between **1.1a** and **1.2a** using **J** as photocatalyst and $Zn(OTf)_2$ as additive.

An assortment of solvents from different families was chosen. From the group of aromatic solvents, toluene was tested as model but, unfortunately, product **1.3aa** was only generated in 40% yield (Table 1.4, Entry 2). Polar aprotic solvents were also tested, being the chosen one *N*,*N*-dimethylformamide (DMF). Lamentably, the use of this solvent requires a water extraction workup after the reaction and, presumably, product **1.3aa** is not stable under this conditions, given the low yield in which it was isolated (Table 1.4, Entry 3). From the family of ethers THF was selected, but it was only capable of generating the corresponding product in 34% yield (Table 1.4, Entry 4). Two chlorinated solvents, DCM and $CHCl_3$, were also tried under these reaction conditions but, again, obtaining the desired product in a lower yield compared to MeCN (Table 1.4, Entries 5 and 6).

Once we determined that MeCN seemed to be the best solvent to conduct the aza-Friedel-Crafts reaction, the presence of a significant amount of water was examined. Thus, the reaction was done using a MeCN:H_2O 9:1 mixture but, in this case, product **1.3aa** was only formed in 35% yield (Table 1.4, Entry 7). Hence, according to these essays, the best solvent to perform the reaction is MeCN (Table 1.4, Entry 1).

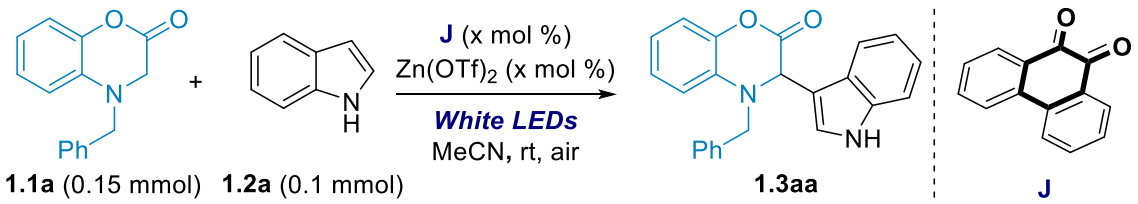
Table 1.4: Evaluation of the solvent in the reaction between **1.1a** and **1.2a** using **J** as photocatalyst and $Zn(OTf)_2$ as additive. Yield of **1.3aa** in each case.

Entry[a]	Additive (x mol %)	Yield 1.3aa (%)[b]
1	MeCN	74
2	Toluene	40
3	DMF	12
4	THF	34
5	DCM	30
6	$CHCl_3$	31
7	MeCN:H_2O 9:1	35

[a]Reaction conditions: **1.1a** (0.15 mmol), **1.2a** (0.1 mmol), **J** (10 mol %), $Zn(OTf)_2$ (5 mol %), Solvent (1 mL), under air atmosphere and under white LEDs irradiation. Reaction time: 9 h.
[b]Yield determined after purification by column chromatography.

Final Adjustments in the Optimal Conditions

Having determined the main optimal conditions to carry out the aza-Friedel-Crafts reaction between **1.1a** and **1.2a**, several minor adjustments were done, mainly regarding the loading of the two catalytic species (Scheme 1.10).



Scheme 1.10: Final adjustments in conditions in the reaction between **1.1a** and **1.2a** using **J** as photocatalyst, $Zn(OTf)_2$ as additive and MeCN as solvent.

To test if the photocatalyst loading could be diminished, the reaction was tested under the optimal reaction conditions but using a 5 mol % of **J**. To our pleasure, the expected product **1.3aa** was obtained in the same yield than when a 10 mol % of **J** is employed (Table 1.5, Entry 2). For experimental commodity, we decided not to further decrease the catalytic loading of **J**. However, there was still limit to reduce the amount of $Zn(OTf)_2$ and, correspondingly, the reaction was set using a 2.5 mol % of $Zn(OTf)_2$, fortunately obtaining the desired product in a comparable yield of 75% (Table 1.5, Entry 3).

Finally, in an effort of employing a less excess of amine **1.1a** over indole **1.2a** than the original conditions, the reaction was done using 0.12 mmol of **1.1a** and 0.1 mmol of **1.2a**,

Table 1.5: Final adjustments in conditions in the reaction between **1.1a** and **1.2a** using **J** as photocatalyst, $Zn(OTf)_2$ as additive and MeCN as solvent. Yield of **1.3aa** in each case.

Entry[a]	**J (x mol %)**	**$Zn(OTf)_2$ (x mol %)**	**Yield 1.3aa (%)**[b]
1	10	5	74
2	5	5	74
3	5	2.5	75
4[c]	5	2.5	45

[a]Reaction conditions: **1.1a** (0.15 mmol), **1.2a** (0.1 mmol), **J** (x mol %), $Zn(OTf)_2$ (x mol %), MeCN (1 mL), under air atmosphere and under white LEDs irradiation. Reaction time: 9 h.
[b]Yield determined after purification by column chromatography.
[c]0.12 mmol of **1.1a** instead of 0.15 mmol were used.

but the yield in which product **1.3aa** is generated dropped from 75 to 45% (Table 1.5, Entry 4).

1.3.4 Scope of the Reaction

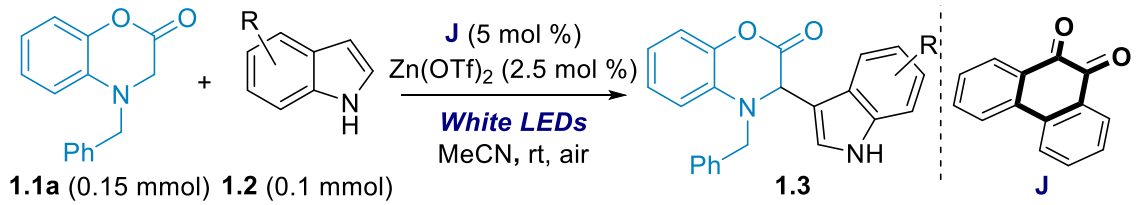
Once the optimal conditions for the reaction had been established, the next part of this study encompassed how different substituents in either 3,4-dihydro-1,4-benzoxazin-2-ones **1.1** or indoles **1.2** can affect the yield. According to the last section, the optimal conditions to set this transformation involves the use of 0.15 mmol of **1.1**, 0.1 mmol of **1.2**, 5 mol % of **J**, 2.5 mol % of $Zn(OTf)_2$, 1 mL of MeCN and under air atmosphere.

In this section, a wide exploration on how different substitution patterns, regarding both electronic and steric features, affect the yield will be presented. Firstly, the substitution on all the positions of the indole **1.2** moiety will be explored. Thereafter, the synthesized 3,4-dihydro-1,4-benzoxazin-2-ones **1.1** will be employed. Complementary, the scope of this methodology will be extended to other electron-rich arenes as well.

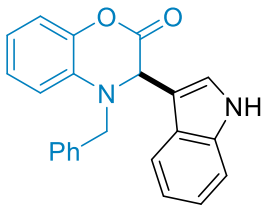
Scope of the Reaction with Different Indoles

All the indoles **1.2** that were required to conduct this study were commercially available and they were at our disposal in our laboratory (Scheme 1.11).

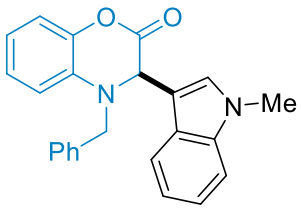
First of all, the effect of a methyl substituent at the azole ring of the indole is examined. When that methyl group is placed in N-1 or C-2 positions of the indole, the reaction outcome is comparable with the model one (**1.3ab** and **1.3ac**). However, the reaction did not proceed when skatole (3-methylindole) was used, presumably due to the less nucleophilicity of the C-2 position.



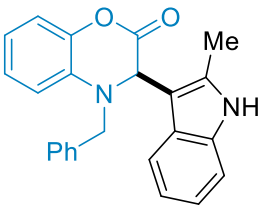
1.1a (0.15 mmol) **1.2** (0.1 mmol) **1.3** **J**



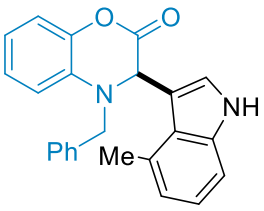
1.3aa, 9h, *75% yield*



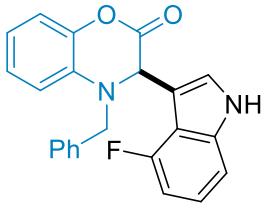
1.3ba, 15h, *58% yield*



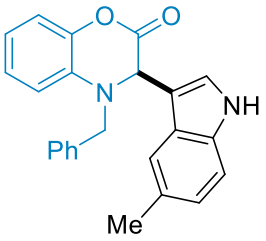
1.3ca, 11h, *58% yield*



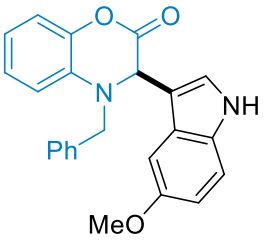
1.3da, 12h, *64% yield*



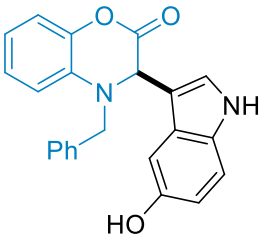
1.3ea, 14h, *79% yield*



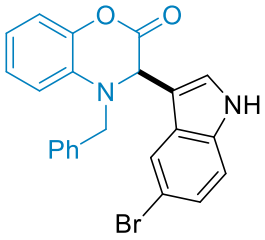
1.3fa, 11h, *63% yield*



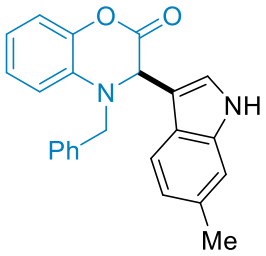
1.3ga, 11h, *68% yield*



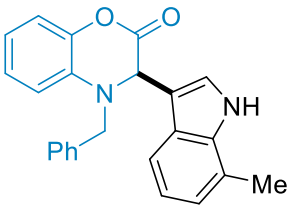
1.3ha, 11h, *66% yield*



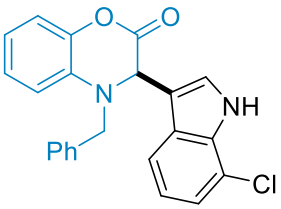
1.3ia, 14h, *54% yield*



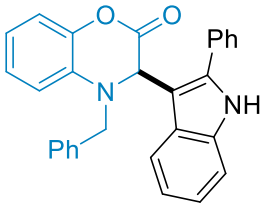
1.3ja, 14h, *77% yield*



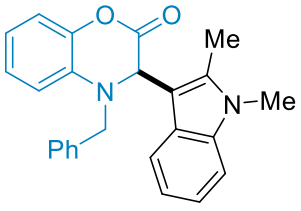
1.3ka, 14h, *71% yield*



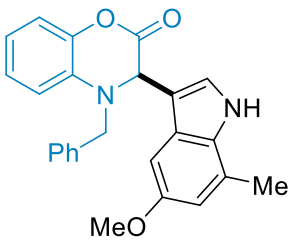
1.3la, 16h, *59% yield*



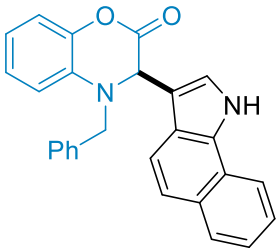
1.3ma, 14h, *80% yield*



1.3na, 12h, *70% yield*



1.3oa, 11h, *70% yield*



1.3pa, 14h, *77% yield*

Scheme 1.11: Scope of the reaction using amine **1.1a** and different indoles **1.2**[a]

[a]Reaction conditions: **1.1a** (0.15 mmol), **1.2** (0.1 mmol), **J** (5 mol %), $Zn(OTf)_2$ (2.5 mol %), MeCN (1 mL), under air atmosphere and under white LEDs irradiation for the indicated time. Yield determined after purification by column chromatography.

Substitution at the C-4 position was also investigated. Hence, 4-methylindole (**1.2d**) and 4-fluoroindole (**1.2e**) were subjected to the optimal reaction conditions, obtaining the corresponding products **1.3ad** and **1.3ae** in 64 and 79% yield respectively. These results shown how the reactivity is not considerably affected when either an electro-donating or an electro-withdrawing group are placed in C-4.

Different substitution at C-5 of the indole with electro-donating groups (−OMe or −OH) lead to the expected products in good yield (**1.3ag** and **1.3ah**), whereas when a bromine atom was present at this position, a significant drop in the yield was obtained (**1.3ai**). The same effect was observed when a chlorine atom was placed at the C-7 position (**1.3al**). Moreover, a methyl group at either C-6 or C-7 positions was efficiently tolerated, obtaining the expected products in 77 and 71% yield.

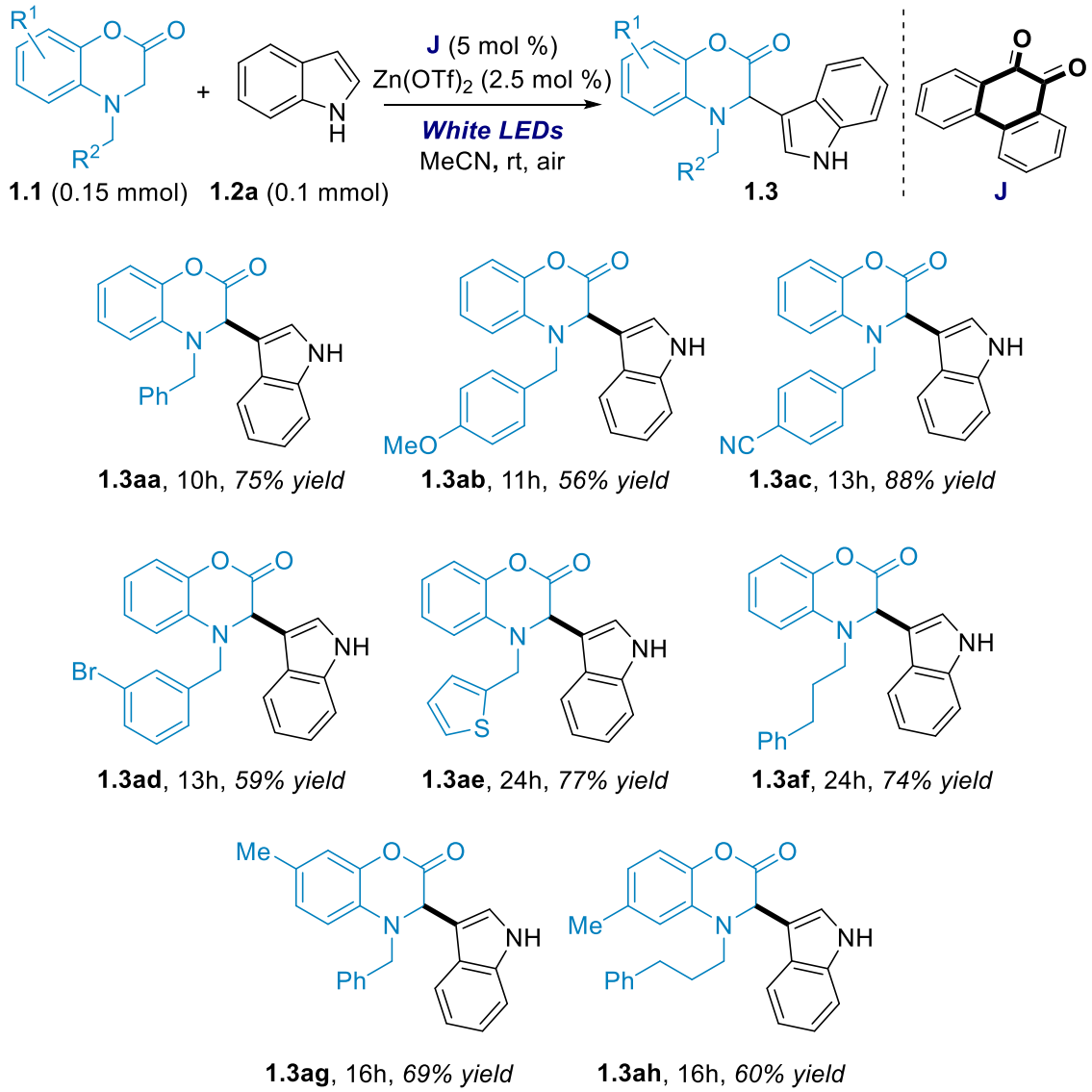
Further substitution in the heterocyclic ring of the indole was explored. 2-phenylindole (**1.2m**) and even the disubstituted 1,2-dimethylindole (**1.2n**) fit the reaction conditions to deliver the products in 80% and 70% yield respectively (**1.3am** and **1.3an**). Surprisingly, the electro-donating character of both indoles surpasses the steric congestion that is generated near the reactive centre.

Finally, two more complex indole scaffolds were tested, such as 5-methoxy-7-methylindole (**1.2o**) and benzo[*g*]indole (**1.2p**). To our delight, the corresponding products **1.3ao** and **1.3ap** were obtained in 70% and 77% yield, respectively.

Scope of the Reaction with Different 3,4-Dihydro-1,4-benzoxazin-2-ones

Once the scope of the indoles had been studied, the next step was to focus on the generality of the reaction regarding the substitution at 3,4-dihydro-1,4-benzoxazin-2-ones (**1.1**) derivatives. To address this goal, the already-prepared 3,4-dihydro-1,4-benzoxazin-2-ones **1.1b**-**1.1h** led us to study the effect of the substitution at either the aminic nitrogen (N-4) or the parent aromatic ring of 1,4-benzoxazin-2-one (Scheme 1.12).

The aminic nitrogen of 3,4-dihydro-1,4-benzoxazin-2-ones plays a pivotal role in this kind of transformation, as the generation of the corresponding iminium cation initially relies on the single electron oxidation of this nitrogen. Hence, the electronic environment of this nitrogen is expected to affect sharply in the outcome of the reaction. To test this hypothesis, amine **1.1b** and **1.1c**, which bear either a −OMe or a −CN group respectively, were tested as iminium cations precursors. Surprisingly, the most electron-rich amine **1.1b** provided the product in worse yield (**1.3ba**) than the most electron-poor amine **1.1c** (product **1.3ca**). Nevertheless, these results can be explained in terms of secondary or decomposition pathways. In other words, amine **1.2b** is more prone to oxidation so the formation of the iminium cation is faster and thus, the probability to suffer a secondary reaction is higher. Likewise, product **1.3ba** could also experience decomposition mecha-



Scheme 1.12: Scope of the reaction using different amines **1.1** and indole **1.2a**[a]

[a]Reaction conditions: **1.1** (0.15 mmol), **1.2a** (0.1 mmol), **J** (5 mol %), $Zn(OTf)_2$ (2.5 mol %), MeCN (1 mL), under air atmosphere and under white LEDs irradiation for the indicated time. Yield determined after purification by column chromatography.

nisms due to this more electron-rich tertiary nitrogen.

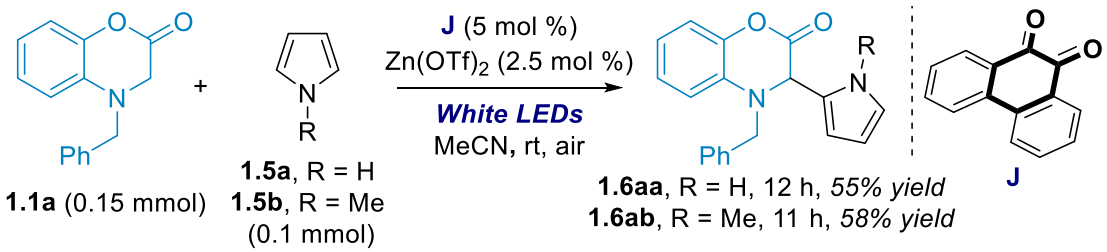
Other benzylic substituents at N-4 were also tested. Specifically, *m*-bromine derivative **1.1d** delivered the expected product in 59% yield, whereas amine **1.1e**, which bears a 2-thiophene unit, produced the aza-Friedel-Crafts product in 77% yield. On the other hand, a longer saturated chain over N-4 could also fit, as product **1.3fa** was generated in 74% yield.

Finally, substituted 3,4-dihydro-1,4-benzoxazin-2-ones at the parent aromatic ring with a methyl substituent were subjected to study. In fact, 3,4-dihydro-1,4-benzoxazin-

2-one **1.1g** bearing a methyl substituent at C-7 provided the expected product **1.3ga** in 69% yield. Moreover, a more sophisticated 3,4-dihydro-1,4-benzoxazin-2-ones with both a methyl in C-6 and a C_3 aliphatic chain at N-4 was also tested. Pleasingly, product **1.3ha** was obtained in 60% yield.

Scope of the Reaction with other Electron-Rich Arenes

To extend the practicability of our dual catalytic system, we decided to try other Friedel-Crafts-type nucleophiles. Initially, both *N*-H pyrrole (**1.7a**) and *N*-Me pyrrole (**1.7b**) were subjected under the reaction conditions, obtaining the expected C-2 alkylated products **1.8aa** and **1.8ab** in 55 and 58% yield respectively (Scheme 1.13).



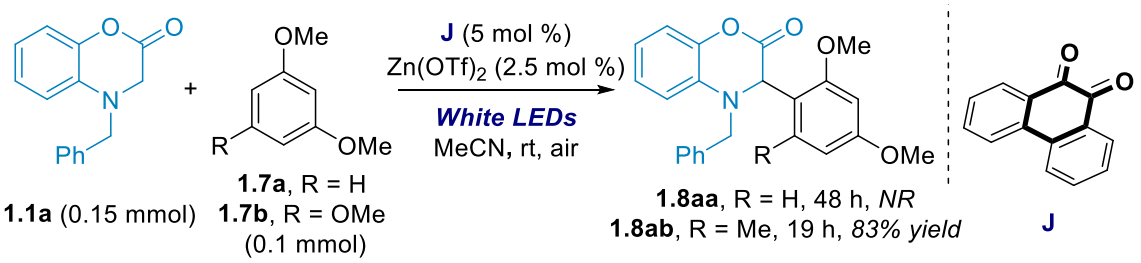
Scheme 1.13: Scope of the reaction using amine **1.1a** and different pyrroles **1.7**[a]

[a]Reaction conditions: **1.1a** (0.15 mmol), **1.7** (0.1 mmol), **J** (5 mol %), $Zn(OTf)_2$ (2.5 mol %), MeCN (1 mL), under air atmosphere and under white LEDs irradiation for the indicated time. Yield determined after purification by column chromatography.

Additionally, we thought that electron-rich benzene derivatives could eventually be suitable for our photocatalytic reaction. To explore this field, our methodology was tested with 1,3-dimethoxybenzene (**1.9a**) and 1,3,5-trimethoxybenzene (**1.9b**). However, the less electron-rich 1,3-dimethoxybenzene was not nucleophilic enough to participate in the aza-Friedel-Crafts reaction but, its trisubstituted analogue delivered the expected product **1.10ab** in 83% yield (Scheme 1.14).

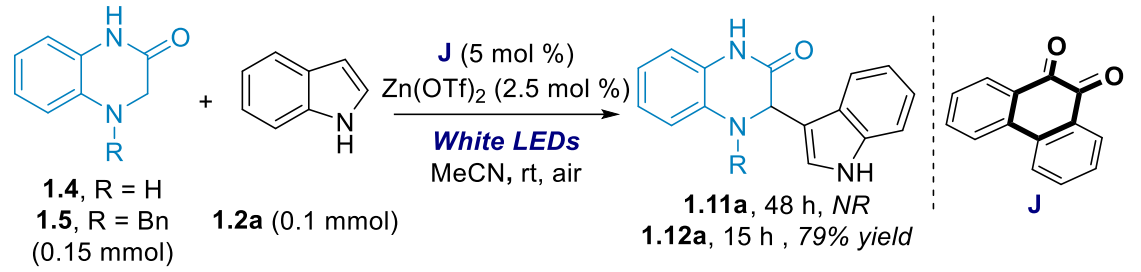
Scope of the Reaction with 3,4-dihydroquinoxalin-2-ones 1.4 and 1.5

Given the structural similarity, the photocatalytic aza-Friedel-Crafts reaction was also tried using quinoxalines **1.4** and **1.5**. The N-4-unprotected quinoxaline **1.4** failed in providing the desired product, probably because the nitrogen center is not enough electron rich and therefore the oxidation could not take place with photocatalyst **J**. However, the more electron-rich quinoxaline **1.5**, in the presence of indole **1.2a**, was able to generate the expected product **1.11b** in 79% yield (Scheme 1.15).



Scheme 1.14: Scope of the reaction using amine **1.1a** and electron-rich benzene derivatives **1.9**[a]

[a]Reaction conditions: **1.1a** (0.15 mmol), **1.9** (0.1 mmol), **J** (5 mol %), $Zn(OTf)_2$ (2.5 mol %), MeCN (1 mL), under air atmosphere and under white LEDs irradiation for the indicated time. Yield determined after purification by column chromatography.



Scheme 1.15: Scope of the reaction using quinoxalines **1.4** or **1.5** and indole **1.2a**[a]

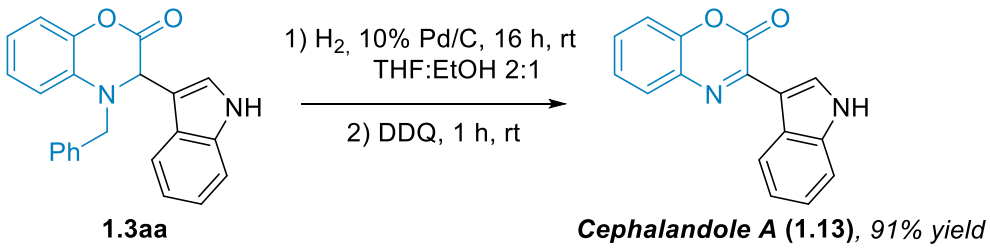
[a]Reaction conditions: **1.4/1.5** (0.15 mmol), **1.2a** (0.1 mmol), **J** (5 mol %), $Zn(OTf)_2$ (2.5 mol %), MeCN (1 mL), under air atmosphere and under white LEDs irradiation for the indicated time. Yield determined after purification by column chromatography.

1.3.5 Synthetic Transformations. Synthesis of *Cephalandole A*

With all the library of indole-containing 3,4-dihydro-1,4-benzoxazin-2-ones **1.3**, we wanted to expand the interest of our transformation by applying several synthetic modifications over some of them.

At some point, we realized the structural resemblance between product **1.3aa** and *Cephalandole A*: a natural product which has been isolated from Taiwanese orchid (*Cephalanceropsis gracilis*), although its precise structure is known for a few years.[112,113] We were confident enough about accessing *Cephalandole A* from **1.3aa** after few transformations (Scheme 1.16). Compound **1.3aa** was subjected to a hydrogenolysis reaction to remove the benzyl protecting group at N-4 position using H_2 and palladium over carbon as catalyst. Afterwards, the newly formed secondary amine was oxidized to the corresponding imine by the action of DDQ, leading to desired *Cephalandole A* (**1.13**) in 91% yield after two steps.

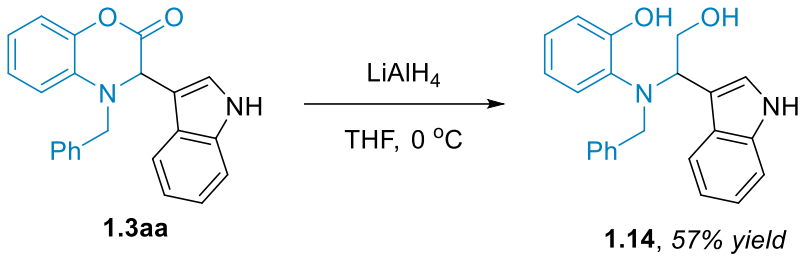
Moreover, product **1.3aa** could be transformed into a tryptophol derivative **1.14** just by reduction of the lactone moiety. In fact, some tryptophols have been isolated from



Scheme 1.16: Synthesis of *Cephalandole A* (**1.13**) from compound **1.3aa**[a]

[a]Reaction conditions: 1) **1.3aa** (0.085 mmol), 10% Pd/C (0.017 mmol), H_2 (1 atm), THF (2 mL) and EtOH (1 mL); 2) DDQ (0.085 mmol). Two-step yield determined after purification by column chromatography.

natural sources and have proven their ability to exhibit interesting biological activities.[114] Hence, when **1.3aa** is treated with $LiAlH_4$ in THF, tryptophol analogue **1.14** was obtained in 57% yield (Scheme 1.17).



Scheme 1.17: Synthesis of a tryptophol derivative **1.14** from compound **1.3aa**[a]

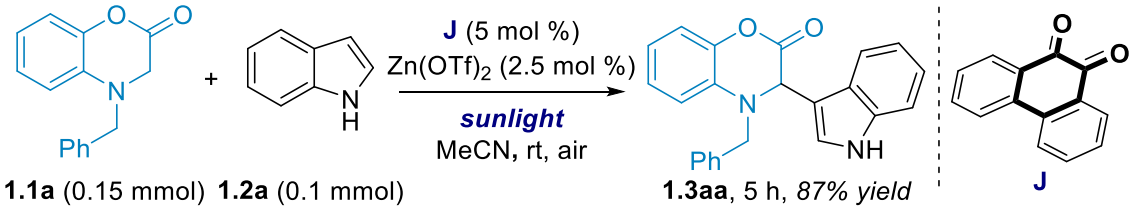
[a]Reaction conditions: **1.3aa** (0.044 mmol), $LiAlH_4$ (1 M in THF, 0.087 mmol) and THF (1 mL). Yield determined after purification by column chromatography.

1.3.6 Mechanistic Investigations

Mechanistic Experiments

After the synthetic part of this *Chapter*, we focused our attention in determining the reaction mechanism. First of all, we wanted to know the relationship between light power and the performance over the reaction. Thus, the aza-Friedel-Crafts reaction between **1.1a** and **1.2a** in the presence of **J** and $Zn(OTf)_2$ was done under sunlight irradiation. Delightfully, we observed how product **1.3aa** was generated in 87% after only 5 hours of irradiation (Scheme 1.18 and Table 1.6, Entry 2).

This result was in concordance with what we expected. In fact, all the optimization and the scope of this chapter was done using white LEDs with a power of 5 W. Instead,



Scheme 1.18: Reaction between **1.1a** and **1.2a** using sunlight as energy source[a]

[a]Reaction conditions: **1.1a** (0.15 mmol), **1.2a** (0.1 mmol), **J** (5 mol %), $Zn(OTf)_2$ (2.5 mol %), MeCN (1 mL), under air atmosphere and under sunlight irradiation for 5 h. Yield determined after purification by column chromatography.

the power of sunlight irradiation vary from 1321 and 1413 W so a higher performance is expected given the superior power of sunlight. In fact, when the same reaction was tried in the darkness, only a trace amount of **1.3aa** could be detected by ^{1}H-NMR (Table 1.6, Entry 3).

Table 1.6: Control experiments for the Friedel-Crafts reaction between **1.1a** and **1.2a**.

Entry[a]	Deviation	1.3aa (%)[b]
1	*none*	75
2	sunlight irradiation	87
3	darkness	trace
4	without **J**	<5% conversion
5	with TEMPO (1.5 equiv.)	no conversion
6	Ar atmosphere	12% conversion

[a]Reaction conditions: **1.1a** (0.15 mmol), **1.2a** (0.1 mmol), **J** (5 mol %), $Zn(OTf)_2$ (2.5 mol %), MeCN (1 mL), under air atmosphere and under white LEDs irradiation. Note deviations for each case. Reaction time: 9 h.

[b]Conversion of compound **1.2a** to product **1.3aa** determined by ^{1}H-NMR.

Having determined the necessity of visible light, our attention was focused on the role of 9,10-phenanthrenequinone (**J**) in this transformation. Indeed, when the reaction was done without photocatalyst **J**, the conversion of **1.2a** to product **1.3aa** was lower than 5%, as determined by ^{1}H-NMR (Table 1.6, Entry 4).

As depicted in Figure 20 of the *Introduction*, this kind of transformations rely on the generation of the iminium cation through the existence of several radical species. A straightforward experiment to prove the existence of radical species is to perform the reaction but also adding a radical scavenger such as TEMPO. Indeed, once we tried the

reaction in the presence of 1.5 equivalents of TEMPO, we did not observe product **1.3aa** in the reaction mixture (Table 1.6, Entry 5).

Apart from that, all the photochemical reactions done in this chapter have been done under an air atmosphere. This was not only for practical experimental reasons but for the necessity to hold the terminal oxidant of the reaction: molecular oxygen. According to Figure 20 in *Introduction*, the generation of the iminium cation from a tertiary amine requires two single-electron oxidations. One of them may arise from the excited state of the photocatalyst through a SET, but there must be a specie capable of reoxidizing the reduced form of the photocatalyst. There are a lot of chemical entities that can act as terminal oxidants (TBHP, $BrCCl_3$, DDQ...) but the most convenient one from several points of view, including environmental issues and low-waste generation, is molecular oxygen. In this sense, when the aza-Friedel-Crafts reaction between **1.1a** and **1.2a** was repeated but having changed the regular air atmosphere for an argon one, just a 12% conversion from **1.2a** to **1.3aa** was observed (Table 1.6, Entry 6). In fact, this slightly high conversion may come from an inefficient air exclusion from the reaction vessel or/and 9,10-phenanthrenequinone (**J**) acting as terminal oxidant.

Unfortunately, it is important to note that 9,10-phenanthrenequinone (**J**) is not a fluorescent compound so it was not possible to perform luminiscence quenching experiments to find out accurately the interaction between the substrates and the excited state form of the photocatalyst.

Proposed Mechanism

With all this information in hand, we were able to postulate a tentative mechanism by which our photochemical aza-Friedel-Crafts reaction may proceed (Figure 1.3).

Once **J** is excited by the action of visible-light to **J***, a SET between it and amine **1.1a** occurs to generate amine radical cation **1.I** as well as the reduced form of the photocatalyst $\mathbf{J}^{-\bullet}$. Molecular oxygen is the responsible of reoxidizing $\mathbf{J}^{-\bullet}$ to its initial form **J** via a SET, a process that also generates the superoxide radical anion $O_2^{-\bullet}$.

As shown in the *Introduction*, the α-H in a radical cation is more acidic than in its neutral form.[40,42] Hence, superoxide anion can abstract a proton from radical cation **1.I** to yield neutral α-amino radical **1.II** and hydroperoxide radical. Here, hydroperoxide radical may act now as oxidant to finally generate electrophilic iminium cation **1.III** and hydroperoxide anion. At this point, it is noteworthy to mention that hydroperoxide anion can react with the recently formed iminium cation to generate product **1.6**, as shown in Scheme 1.7. However, iminium cation **1.III** is electrophilic enough to react via a aza-Friedel-Crafts reaction with indole **1.2a** and ultimately generate product **1.3aa**.

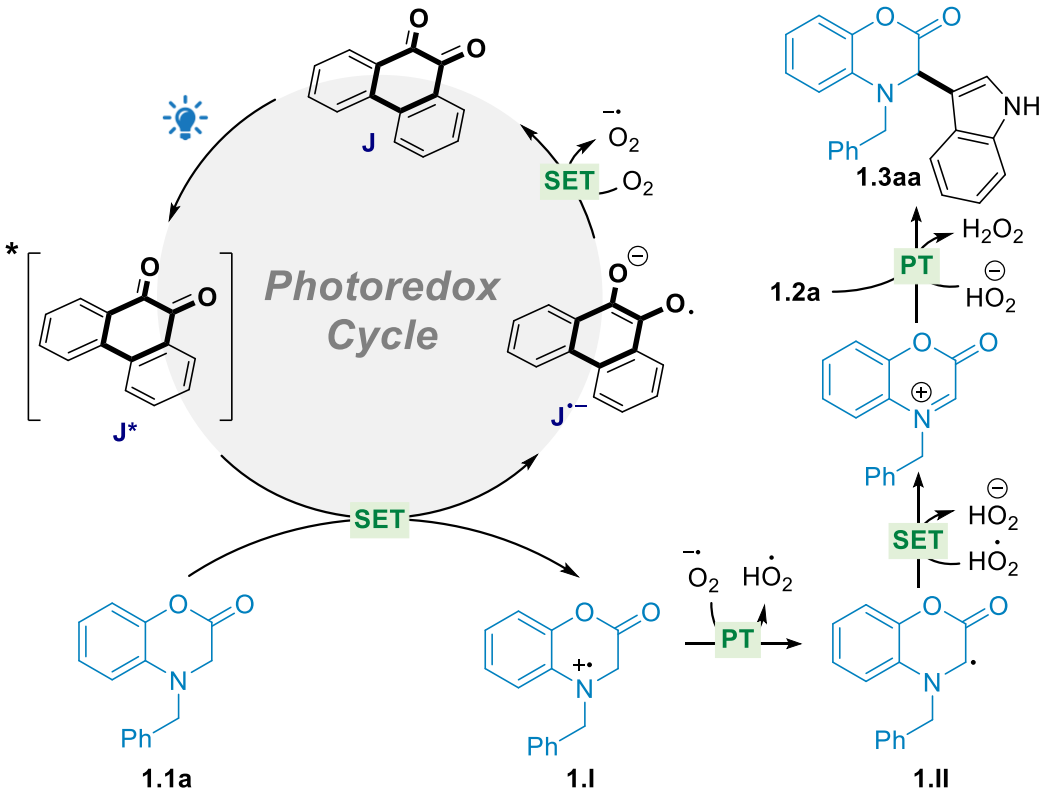


Figure 1.3: Mechanism for the photocatalytic aza-Friedel-Crafts reaction between **1.1a** and **1.2a**.

1.4 Experimental Section

1.4.1 General Methods

Reaction Flasks, Reagents and Substrates

- Photocatalytic reactions were carried out in 5 mL vials under air unless otherwise indicated.
- Commercial reagents were used as purchased.
- All photocatalysts, acids, indoles and related arenes were commercially available.
- 3,4-dihydro-1,4-benzoxazin-2-ones **1.1a**, **1.1b** and **1.1c** were synthesized according to a procedure published in the literature, and the spectroscopic data (^{1}H-NMR and ^{13}C-NMR) match with those reported.[109] 3,4-dihydro-benzoxazin-2-ones derivatives **1.1d**, **1.1e**, **1.1f**, **1.1g** and **1.1h** were synthesized according to the same procedure and were characterized by ^{1}H-NMR, ^{13}C-NMR and HRMS.
- Quinoxalines **1.4** and **1.5** were prepared according to a reported procedure, and the spectroscopic data (^{1}H-NMR and ^{13}C-NMR) match with those reported.[110]

Melting Points

- The melting point has been determined with a Büchi Melting Point M-560 apparatus, using capillary tubes. Melting points have not been corrected.

Chromatographic Methods

- Reactions were monitored by TLC analysis using Merck Silica Gel 60 F-254 thin layer plates and these are visualized using both a UV lamp (254 nm) and then a CAM solution (10 g of $Ce(SO_4)_2$, 25 g of phosphomolybdic acid and 80 mL of concentrated H_2SO_4, then diluted until 1 L with deionized water).
- Flash column chromatography was performed on Merck Silica Gel 60, 0.040-0.063 mm as stationary phase.
- Mobile phases were prepared by mixing solvents (hexanes, EtOAc, DCM), which have technical quality or higher.

Nuclear Magnetic Resonance (NMR)

- NMR spectra were run in a Bruker Avance 300 DPX at 300 MHz for ^{1}H, 282 MHz for ^{19}F and 75 MHz for ^{13}C using residual nondeuterated solvent as internal standard ($CHCl_3$: δ 7.26 and δ 77.00 ppm respectively, MeOH: δ 3.34 ppm and δ 49.87 ppm respectively, acetone-d_6): δ 2.05 ppm and δ 29.84 ppm respectively, DMSO-d_6: δ 2.5 and δ 39.52 ppm respectively).
- Chemical shifts (δ) are given in ppm and coupling constants (J) in Hz.
- The carbon multiplicity was established by DEPT experiments.

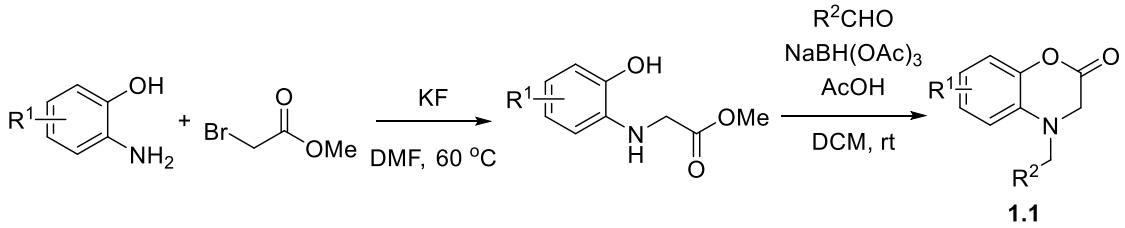
High Resolution Mass Spectrometry (HRMS)

- High resolution mass spectra (HRMS-ESI) were recorded on an AB SCIEX Triple TOFTM spectrometer equipped with an electrospray source with a capillary voltage of 4.5 kV (ESI).

1.4.2 Synthetic Procedures and Characterization

Synthesis of 3,4-dihydro-1,4-benzoxazin-2-ones 1.1

3,4-dihydro-1,4-benzoxazin-2-ones **1.1** were prepared following a reported two-step procedure with some modifications.[109]

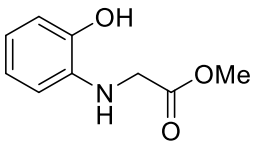


1.1

In a 100 mL round bottomed flask, the corresponding *o*-aminophenol (20 mmol, 1 equiv.), KF (2.9 g, 50 mmol, 2.5 equiv.) and DMF (20 mL) were sequentially added under regular atmosphere. To this suspension, methyl bromoacetate (1.9 mL, 20 mmol, 1 equiv.) was added and the mixture was stirred at 60 °C until complete consumption of the *o*-aminophenol as judged by TLC (approximately 4 hours). Thereafter, DMF was removed via vacuum distillation and the obtained residue was dissolved in EtOAc (30 mL) and it was washed with saturated aqueous $NaHCO_3$ (25 mL), water (25 mL) and brine (25 mL). The resulting organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure to obtain the crude *N*-aryl methyl glycinate, which was used in the next step without further purification.

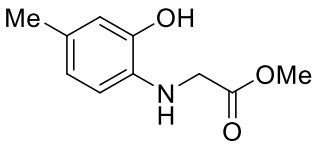
In a 100 mL round bottomed flask, the crude *N*-aryl methyl glycinate (20 mmol) was dissolved in DCM (30 mL). To this solution, the corresponding aldehyde (24 mmol, 1.2 equiv.) was added and the resulting solution was cooled down to 0 °C. Then, glacial AcOH (1.7 mL, 30 mmol, 1.5 equiv.) was added, and the mixture was stirred at 0 °C for 30 minutes. After this period of time, $NaBH(OAc)_3$ (6.4 g, 30 mmol, 1.5 equiv.) was added in portions and the mixture was gradually warmed to room temperature and stirred at that temperature overnight. Then, the reaction mixture was diluted with DCM (10 mL) and the organic phase was washed with saturated aqueous $NaHCO_3$ (15 mL), water (15 mL) and brine (15 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure to obtain a residue, which was purified by column chromatography using hexane:EtOAc mixtures to obtain the corresponding 3,4-dihydro-1,4-benzoxazin-2-one **1.1**.

Methyl (2-hydroxyphenyl)glycinate



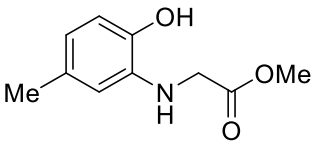
Brown solid; 91% yield; **Mp** 92-94 °C; **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 6.90 – 6.78 (m, 1H), 6.75 (dd, J = 7.8, 1.7 Hz, 1H), 6.74 – 6.62 (m, 1H), 6.60 (dd, J = 7.8, 1.5 Hz, 1H), 3.94 (s, 2H), 3.79 (s, 3H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 172.2 (C), 144.4 (C), 135.9 (C), 121.5 (CH), 119.2 (CH), 114.9 (CH), 113.3 (CH), 52.3 (CH_3), 46.5 (CH_2). Physical and spectroscopic data match with those reported in the bibliography.[109]

Methyl (2-hydroxy-4-methylphenyl)glycinate



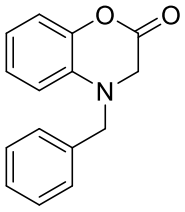
Brown solid; 87% yield; **Mp** 115-117 °C; **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 6.61 (d, J = 7.9 Hz, 1H), 6.51 (s, 1H), 6.48 (d, J = 8.0 Hz, 1H), 3.92 (s, 2H), 3.77 (s, 3H), 2.17 (s, 3H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 172.7 (C), 144.6 (C), 133.2 (C), 128.8 (C), 121.1 (CH), 115.8 (CH), 112.8 (CH), 52.2 (CH_3), 46.4 (CH_2), 20.4 (CH_3). Physical and spectroscopic data match with those reported in the bibliography.[109]

Methyl (2-hydroxy-5-methylphenyl)glycinate



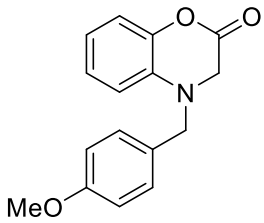
Brown solid; 90% yield; **Mp** 124-126 °C; **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 6.64 (d, J = 7.9Hz, 1H), 6.47 (d, J = 7.9Hz, 1H), 6.40 (s, 1H), 3.93 (s, 2H), 3.78 (s, 3H), 2.24 (s, 3H). Physical and spectroscopic data match with those reported in the bibliography.[109]

4-Benzyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-one (1.1a)



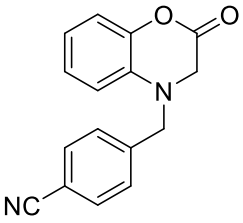
White solid; **Mp** 54-56 °C; **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 7.42 – 7.28 (m, 5H), 7.14 – 7.03 (m, 2H), 6.95 – 6.83 (m, 2H), 4.38 (s, 2H), 3.79 (s, 2H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 164.9 (C), 141.7 (C), 135.6 (C), 134.8 (C), 128.9 (CH), 127.9 (CH), 127.8 (CH), 125.3 (CH), 120.1 (CH), 117.0 (CH), 113.2 (CH), 53.5 (CH_2), 49.8 (CH_2). Physical and spectroscopic data match with those reported in the bibliography.[109]

4-(4-Methoxybenzyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-one (1.1b)



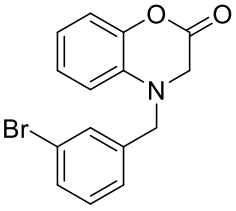
White solid; **Mp** 250-252 °C; **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 7.28 – 7.20 (m, 2H), 7.11 – 7.02 (m, 2H), 6.94 – 6.84 (m, 4H), 4.31 (s, 2H), 3.81 (s, 3H), 3.74 (s, 2H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 165.0 (C), 159.3 (C), 141.8 (C), 135.0 (C), 129.2 (CH), 127.3 (C), 125.2 (CH), 120.0 (CH), 117.0 (CH), 114.3 (CH), 113.2 (C), 55.3 (CH_3), 52.9 (CH_2), 49.5 (CH_2). Physical and spectroscopic data match with those reported in the bibliography.[109]

4-(4-Cyanobenzyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-one (1.1c)



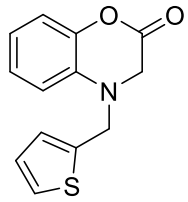
White solid; **Mp** 128-130 °C; **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 7.66 (d, J = 8.5 Hz, 2H), 7.45 (dd, J = 7.9, 0.7 Hz, 2H), 7.11 (dd, J = 7.9, 1.5 Hz, 1H), 7.03 (ddd, J = 8.0, 7.5, 1.6 Hz, 1H), 6.91 (td, J = 7.7, 1.5 Hz, 1H), 6.69 (dd, J = 8.0, 1.5 Hz, 1H), 4.44 (s, 2H), 3.86 (s, 2H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 164.3 (C), 141.8 (C), 141.5 (C), 134.1 (C), 132.8 (CH), 128.0 (CH), 125.3 (CH), 120.9 (CH), 118.4 (C), 117.3 (CH), 113.3 (CH), 111.9 (C), 53.5 (CH_2), 50.7 (CH_2). Physical and spectroscopic data match with those reported in the bibliography.[109]

4-(3-Bromobenzyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-one (1.1d)



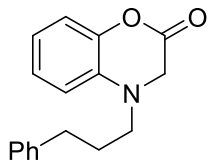
Colorless oil; **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 7.51 – 7.39 (m, 2H), 7.29 – 7.19 (m, 2H), 7.14 – 7.00 (m, 2H), 6.89 (td, J = 7.7, 1.4 Hz, 1H), 6.79 (dd, J = 8.0, 1.5 Hz, 1H), 4.34 (s, 2H), 3.81 (s, 2H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 164.6 (C), 141.8 (C), 138.2 (C), 134.4 (C), 131.1 (CH), 130.7 (CH), 130.5 (CH), 126.2 (CH), 125.3 (CH), 123.1 (C), 120.5 (CH), 117.2 (CH), 113.2 (CH), 53.1 (CH_2), 50.2 (CH_2).

4-(Thiophen-2-ylmethyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-one (1.1e)



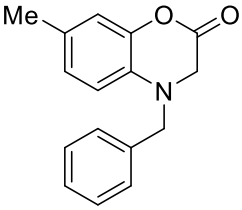
White solid; **Mp** 73-74 °C; **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 7.27 (dd, *J* = 5.1, 1.3 Hz, 1H), 7.13 – 7.05 (m, 2H), 7.05 – 6.96 (m, 3H), 6.89 (ddd, *J* = 8.2, 7.2, 1.5 Hz, 1H), 4.58 (s, 2H), 3.80 (s, 2H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 164.8 (C), 141.9 (C), 137.6 (C), 133.9 (C), 127.2 (CH), 127.0 (CH), 126.0 (CH), 125.2 (CH), 120.4 (CH), 117.1 (CH), 113.2 (CH), 49.3 (CH_2), 48.2 (CH_2).

4-(3-Phenylpropyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-one (1.1f)



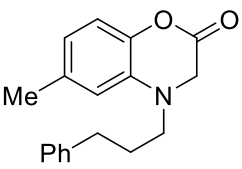
Greenish oil; **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 7.21 – 7.13 (m, 2H), 7.11 – 7.02 (m, 3H), 6.93 – 6.85 (m, 2H), 6.70 – 6.62 (m, 1H), 6.51 (dd, *J* = 8.4, 1.5 Hz, 1H), 3.62 (s, 2H), 3.08 – 2.97 (m, 2H), 2.54 (t, *J* = 7.5 Hz, 2H), 1.78 (dq, *J* = 9.1, 7.5 Hz, 2H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 164.6 (C), 141.5 (C), 140.8 (C), 134.2 (C), 128.3 (CH), 128.2 (CH), 126.0 (CH), 125.0 (CH), 119.1 (CH), 116.7 (CH), 112.4 (CH), 49.7 (CH_2), 48.2 (CH_2), 32.7 (CH_2), 26.4 (CH_2).

4-Benzyl-7-methyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-one (1.1g)



Colorless oil; **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 7.42 – 7.28 (m, 5H), 6.91 (d, *J* = 1.7 Hz, 1H), 6.86 (ddd, *J* = 8.2, 1.9, 0.7 Hz, 1H), 6.75 (d, *J* = 8.2 Hz, 1H), 4.33 (s, 2H), 3.74 (s, 2H), 2.29 (s, 3H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 165.2 (C), 141.8 (C), 135.8 (C), 132.5 (C), 130.2 (C), 129.0 (CH), 127.9 (CH), 127.9 (CH), 125.6 (CH), 117.5 (CH), 113.2 (C), 53.8 (CH_2), 50.1 (CH_2), 20.4 (CH_3). Physical and spectroscopic data match with those reported in the bibliography.[75]

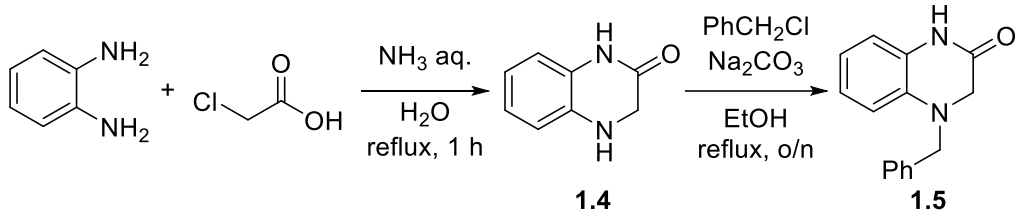
6-Methyl-4-(3-phenylpropyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-one (1.1h)



Colorless oil; **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 7.36 – 7.28 (m, 2H), 7.24 – 7.19 (m, 3H), 6.92 (d, *J* = 8.1 Hz, 1H), 6.61 (ddd, *J* = 8.1, 1.9, 0.7 Hz, 1H), 6.40 (d, *J* = 1.5 Hz, 1H), 3.80 (s, 2H), 3.19 (dd, *J* = 8.3, 6.7 Hz, 2H), 2.71 (t, *J* = 7.4 Hz, 2H), 2.26 (s, 3H), 2.02 – 1.90 (m, 2H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 165.0 (C), 141.0 (C), 139.8 (C), 135.0 (C), 134.0 (C), 128.6 (CH), 128.4 (CH), 126.2 (CH), 120.0 (CH), 116.7 (CH), 113.2 (CH), 50.1 (CH_2), 48.4 (CH_2), 32.9 (CH_2), 26.6 (CH_2), 21.3 (CH_3).

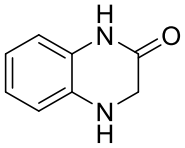
Synthesis of 3,4-dihydroquinoxalin-2-ones 1.4 and 1.5

3,4-dihydroquinoxalin-2-ones **1.4** and **1.5** were prepared following a reported procedure with some modifications.[110]



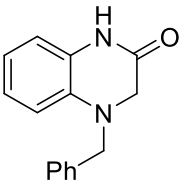
1.4 **1.5**

In a 250 mL round bottommed flask, *o*-phenylenediamine (10.8 g, 100 mmol, 1 equiv.), chloroacetic acid (9.5 mg, 100 mmol, 1 equiv.), H_2O (80 mL), and aqueous NH_3 (33%, 10 mL) were added. The resulting suspension was heated to reflux temperature for 1 h. The mixture was then cooled in an ice-water bath and the resulting precipitate was vacuum filtered. The crude 3,4-dihydroquinoxalin-2-one (**1.4**, 8.2 g, 55 mmol, 55% yield) was used in the next step without any further purification.



^{1}H-NMR (300 MHz, DMSO-d$_6$) δ 10.19 (s, 1H), 6.77 – 6.72 (m, 1H), 6.73 – 6.67 (m, 1H), 6.64 (ddt, J = 7.7, 1.4, 0.6 Hz, 1H), 6.57 (ddd, J = 7.9, 7.1, 1.5 Hz, 1H), 5.92 (s, 1H), 3.70 (d, J = 1.8 Hz, 2H). **^{13}C{^{1}H}-NMR (75 MHz, DMSO-d$_6$)** δ 166.0 (C), 134.8 (C), 126.1 (C), 122.7 (CH), 117.7 (CH), 114.9 (CH), 113.3 (CH), 46.4 (CH_2). Physical and spectroscopic data match with those reported in the bibliography.[110]

To a 100 mL round bottomed flask, 3,4-dihydroquinoxalin-2-one (**1.4**, 1.48 g, 10 mmol, 1 equiv.) and sodium carbonate (2.12 g, 20 mmol, 2 equiv.) were added. Then, 96% EtOH (30 mL) was added followed by benzyl chloride (1.4 mL, 12 mmol, 1.2 equiv.). The reaction mixture was stirred at reflux temperature for 16 h. After this period of time, EtOH was removed by rotary evaporation and the residue was dissolved with EtOAc (100 mL). The organic phase was washed with water (2x50 mL) and the combined aqueous phases were extracted with AcOEt (50 mL). The combined organic phases were dried over $MgSO_4$, filtered and evaporated. The dark brown residue was crystallized from EtOH to obtain 4-benzyl-3,4-dihydroquinoxalin-2-one **1.5** (1.8 g, 7.5 mmol, 75% yield) as slightly brown crystals.



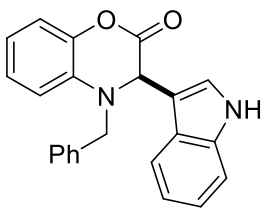
^{1}H-NMR (300 MHz, CDCl$_3$) δ 9.44 (bs, 1H), 7.31 – 7.17 (m, 5H), 6.87 (ddd, J = 8.3, 7.3, 1.7 Hz, 1H), 6.77 (dd, J = 7.9, 1.7 Hz, 1H), 6.73 – 6.66 (m, 2H), 4.35 (s, 2H), 3.76 (s, 2H); **^{13}C{^{1}H}-NMR (75 MHz, CDCl$_3$)** δ 67.5 (C), 136.3 (C), 135.2 (C), 128.8 (CH), 127.6 (CH), 127.5 (CH), 126.1 (C), 124.2 (CH), 119.0 (CH), 115.8 (CH),

112.1 (CH), 53.5 (CH_2), 52.1 (CH_2). Physical and spectroscopic data match with those reported in the bibliography.[78]

General Procedure for the Photocatalytic aza-Friedel-Crafts Reaction between 3,4-dihydro-1,4-benzoxazin-2-ones 1.1 and indoles 1.2

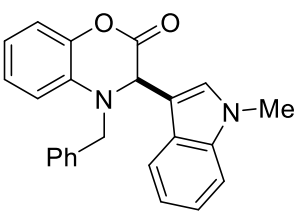
In a 5 mL borosilicate vial, the corresponding 3,4-dihydro-1,4-benzoxazin-2-one (**1.1**, 0.15 mmol, 1.5 equiv.), the corresponding indole (**1.2**, 0.1 mmol, 1 equiv.), 9,10-phenanthrenequinone (**J**, 1.0 mg, 0.005 mmol, 5 mol %) and $Zn(OTf)_2$ (0.9 mg, 0.0025 mmol, 2.5 mol %) were placed. Then, MeCN (1 mL) was added and the reaction mixture was placed 2 cm away from white LEDs (see page 432 for further details about the photochemical setup). The conversion of the starting materials was traced regularly by TLC, and it was stopped when indole **1.2** was consumed. The resultant reaction mixture was purified by column chromatography using hexane:EtOAc mixtures (from 95:5 to 85:15) to obtain the expected pure compound **1.3**.

4-Benzyl-3-(1*H*-indol-3-yl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-one (1.3aa)



Using 4-benzyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-one (**1.1a**, 35.8 mg, 0.15 mmol) and indole (**1.2a**, 11.7 mg, 0.1 mmol), according to General Procedure, compound **1.3aa** (26.6 mg, 0.075 mmol, 75% yield) was obtained after 10 h as a white solid; **Mp** 66-68 ^{o}C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.12 (bs, 1H), 7.51 (d, J = 7.9 Hz, 1H), 7.38 – 7.27 (m, 5H), 7.24 – 7.17 (m, 1H), 7.16 – 7.04 (m, 3H), 6.91 (td, J = 7.7, 1.4 Hz, 1H), 6.82 (dd, J = 8.0, 1.2 Hz, 1H), 6.72 (d, J = 2.6 Hz, 1H), 5.41 (s, 1H), 4.62 (d, J = 14.9 Hz, 1H), 4.15 (d, J = 14.8 Hz, 1H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 164.6 (C), 141.8 (C), 136.1 (C), 135.8 (C), 134.1 (C), 128.8 (CH), 127.8 (CH), 126.1 (C), 125.4 (CH), 122.9 (CH), 122.8 (CH), 120.4 (CH), 119.9 (CH), 119.1 (CH), 116.5 (CH), 113.9 (CH), 111.3 (CH), 108.7 (C), 55.9 (CH), 51.6 (CH_2). Physical and spectroscopic data match with those reported in the bibliography.[75]

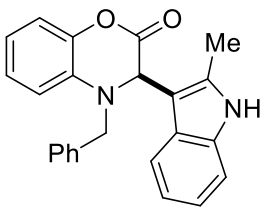
4-Benzyl-3-(1-methyl-indol-3-yl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-one (1.3ab)



Using 4-benzyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-one (**1.1a**, 35.8 mg, 0.15 mmol) and *N*-methylindole (**1.2b**, 13.1 mg, 0.1 mmol), according to General Procedure, compound **1.3ab** (21.2 mg, 0.058 mmol, 58% yield) was obtained after 15 h as a brown solid. **Mp** 193-196 ^{o}C; **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 7.48 (dt, J = 8.0, 1.0 Hz, 1H), 7.38 – 7.21 (m, 7H), 7.16 – 7.10 (m, 2H),

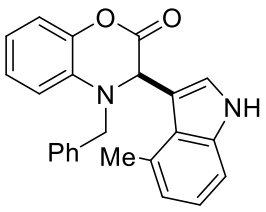
7.10 – 7.04 (m, 1H), 6.92 (td, *J* = 7.7, 1.5 Hz, 1H), 6.82 (dd, *J* = 8.0, 1.4 Hz, 1H), 6.59 (d, *J* = 0.6 Hz, 1H), 5.40 (d, *J* = 0.6 Hz, 1H), 4.61 (d, *J* = 14.9 Hz, 1H), 4.16 (d, *J* = 14.9 Hz, 1H), 3.64 (s, 3H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 164.5 (C), 141.8 (C), 136.7 (C), 136.2 (C), 134.1 (C), 128.8 (CH), 127.8 (CH), 127.7 (CH), 127.2 (CH), 126.7 (C), 125.3 (CH), 122.4 (CH), 120.0 (CH), 119.8 (CH), 119.2 (CH), 116.6 (CH), 113.8 (CH), 109.4 (CH), 107.1 (C), 55.8 (CH), 51.5 (CH_2), 32.9 (CH_3). Physical and spectroscopic data match with those reported in the bibliography.[75]

4-Benzyl-3-(2-methyl-1*H*-indol-3-yl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-one (1.3ac)



Using 4-benzyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-one (**1.1a**, 35.8 mg, 0.15 mmol) and 2-methylindole (**1.2c**, 13.1 mg, 0.1 mmol), according to General Procedure, compound **1.3ac** (21.2 mg, 0.058 mmol, 58% yield) was obtained after 11 h as a brown solid. **Mp** 200-204 °C; **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 7.98 (bs, 1H), 7.29 – 7.22 (m, 4H), 7.18 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.16 – 7.03 (m, 5H), 6.95 (ddd, *J* = 8.1, 6.9, 1.1 Hz, 1H), 6.89 (td, *J* = 7.7, 1.4 Hz, 1H), 6.80 (dd, *J* = 8.1, 1.4 Hz, 1H), 5.34 (s, 1H), 4.59 (d, *J* = 16.1 Hz, 1H), 3.98 (d, *J* = 16.1 Hz, 1H), 2.02 (s, 3H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 166.0 (C), 140.7 (C), 136.6 (C), 135.4 (C), 135.2 (C), 134.6 (C), 128.7 (CH), 127.3 (CH), 127.2 (CH), 126.5 (C), 125.5 (CH), 121.7 (CH), 120.2 (CH), 119.1 (CH), 118.7 (CH), 117.0 (CH), 113.2 (CH), 110.5 (CH), 106.0 (C), 55.8 (CH), 49.9 (CH_2), 11.6 (CH_3). Physical and spectroscopic data match with those reported in the bibliography.[75]

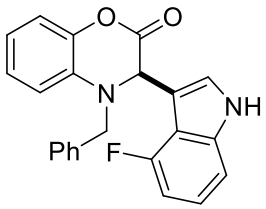
4-Benzyl-3-(4-methyl-1H-indol-3-yl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-one (1.3ad)



Using 4-benzyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-one (**1.1a**, 35.8 mg, 0.15 mmol) and 4-methylindole (**1.2d**, 13.1 mg, 0.1 mmol), according to General Procedure, compound **1.3ad** (23.6 mg, 0.064 mmol, 64% yield) was obtained after 12 h as a brown solid. **Mp** 70-74 °C; **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 8.07 (bs, 1H), 7.34 – 7.29 (m, 3H), 7.21 (dd, *J* = 6.6, 3.0 Hz, 2H), 7.19 – 7.04 (m, 4H), 6.97 – 6.83 (m, 3H), 6.64 (d, *J* = 2.5 Hz, 1H), 5.70 (s, 1H), 4.63 (d, *J* = 14.4 Hz, 1H), 4.07 (d, *J* = 14.4 Hz, 1H), 2.48 (s, 3H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 164.8 (C), 141.5 (C), 136.0 (C), 135.7 (C), 134.6 (C), 130.8 (C), 128.8 (CH), 128.1 (CH), 127.8 (CH), 125.4 (CH), 124.8 (C), 122.7 (CH), 122.6 (C), 122.4 (CH), 119.7 (CH), 116.5 (CH), 113.4 (CH), 110.2 (C), 109.2 (CH), 55.3 (CH), 51.0 (CH_2), 20.5 (CH_3). Physical

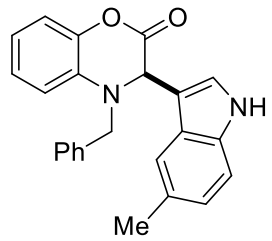
and spectroscopic data match with those reported in the bibliography.[75]

4-Benzyl-3-(4-fluoro-1*H*-indol-3-yl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-one (1.3ae)



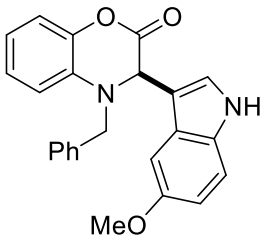
Using 4-benzyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-one (**1.1a**, 35.8 mg, 0.15 mmol) and 4-fluoroindole (**1.2e**, 13.5 mg, 0.1 mmol), according to General Procedure, compound **1.3ae** (22.9 mg, 0.059 mmol, 59% yield) was obtained after 14 h as a colorless oil. **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 8.28 (bs, 1H), 7.14 (dd, J = 7.9, 1.6 Hz, 1H), 7.11 – 7.08 (m, 2H), 7.00 (td, J = 7.7, 1.6 Hz, 1H), 6.89 (td, J = 7.7, 1.5 Hz, 1H), 6.85 – 6.77 (m, 1H), 6.74 – 6.63 (m, 2H), 5.71 (s, 1H), 4.46 (d, J = 15.5 Hz, 1H), 4.35 (d, J = 15.5 Hz, 1H); **^{19}F{^{1}H}-NMR (282 MHz, $CDCl_3$)** δ -121.20 (s); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 164.9 (C), 156.6 (d, J_{C-F} = 246.6 Hz, C), 141.8 (C), 138.2 (d, J_{C-F} = 10.9 Hz, C), 136.5 (C), 133.7 (C), 128.7 (CH), 127.4 (CH), 127.2 (CH), 125.3 (CH), 123.3 (d, J_{C-F} = 7.9 Hz, CH), 123.1 (CH), 119.8 (CH), 116.4 (CH), 115.2 (d, J_{C-F} = 19.4 Hz, C), 114.7 (CH), 107.7 (d, J_{C-F} = 3.9 Hz, C), 107.6 (d, J_{C-F} = 3.8 Hz, CH), 105.8 (d, J_{C-F} = 19.6 Hz, CH), 56.8 (d, J_{C-F} = 3.2 Hz, CH), 51.7 (d, J_{C-F} = 1.5 Hz, CH_2); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{23}H_{18}FN_2O_2$ 373.1347, found 373.1342.

4-Benzyl-3-(5-methyl-1*H*-indol-3-yl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-one (1.3af)



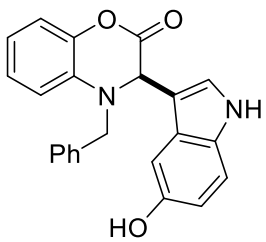
Using 4-benzyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-one (**1.1a**, 35.8 mg, 0.15 mmol) and 5-methylindole (**1.2f**, 13.1 mg, 0.1 mmol), according to General Procedure, compound **1.3af** (23.2 mg, 0.063 mmol, 63% yield) was obtained after 11 h as a brown solid. **Mp** 68-70 °C; **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 8.01 (bs, 1H), 7.37 – 7.27 (m, 5H), 7.24 (dd, J = 1.6, 0.8 Hz, 1H), 7.20 (dd, J = 8.3, 0.7 Hz, 1H), 7.12 (dd, J = 7.9, 1.5 Hz, 1H), 7.04 (ddd, J = 9.4, 8.0, 1.6 Hz, 2H), 6.92 (td, J = 7.7, 1.5 Hz, 1H), 6.82 (dd, J = 8.0, 1.4 Hz, 1H), 6.67 (d, J = 2.5 Hz, 1H), 5.37 (d, J = 0.7 Hz, 1H), 4.61 (d, J = 14.8 Hz, 1H), 4.12 (d, J = 14.8 Hz, 1H), 2.41 (s, 2H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 164.6 (C), 141.9(C), 136.1 (C), 134.3 (C), 134.1 (C), 129.7 (C), 128.8 (CH), 127.9 (CH), 127.8 (CH), 126.4 (C), 125.3 (CH), 124.4 (CH), 122.9 (CH), 119.8 (CH), 118.7 (CH), 116.5 (CH), 113.9 (CH), 110.9 (CH), 108.2 (C), 55.8 (CH), 51.5 (CH_2), 21.4 (CH_3). Physical and spectroscopic data match with those reported in the bibliography.[75]

4-Benzyl-3-(5-methoxy-1*H*-indol-3-yl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-one (1.3ag)



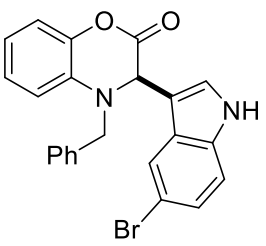
Using 4-benzyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-one (**1.1a**, 35.8 mg, 0.15 mmol) and 5-methoxyindole (**1.2g**, 14.7 mg, 0.1 mmol), according to General Procedure, compound **1.3ag** (26.1 mg, 0.068 mmol, 68% yield) was obtained after 11 h as a white solid; **Mp** 150-154 °C; **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 8.05 (bs, 1H), 7.40 – 7.27 (m, 5H), 7.19 (dd, *J* = 8.8, 0.7 Hz, 1H), 7.13 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.08 (ddd, *J* = 8.0, 7.5, 1.5 Hz, 1H), 6.91 (ddd, *J* = 7.5, 1.5 Hz, 1H), 6.88 – 6.79 (m, 3H), 6.72 (dd, *J* = 2.6, 0.6 Hz, 1H), 5.34 (d, J = 0.6 Hz, 1H), 4.62 (dd, *J* = 14.7, 0.8 Hz, 1H), 4.10 (d, *J* = 14.7 Hz, 1H), 3.72 (s, 3H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 164.7 (C), 154.6 (C), 141.8 (C), 136.1 (C), 134.3 (C), 130.8 (C), 128.8 (CH), 127.9 (CH), 127.8 (CH), 126.4 (C), 125.5 (CH), 123.7 (CH), 119.8 (CH), 116.6 (CH), 113.7 (CH), 113.6 (CH), 112.1 (CH), 108.7 (C), 100.3 (CH), 55.8 (CH), 55.7 (CH_3), 51.3 (CH_2). Physical and spectroscopic data match with those reported in the bibliography.[75]

4-Benzyl-3-(5-hydroxy-1*H*-indol-3-yl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-one (1.3ah)



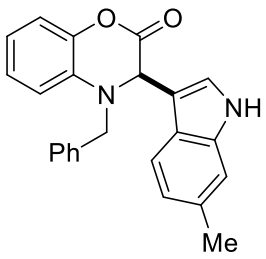
Using 4-benzyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-one (**1.1a**, 35.8 mg, 0.15 mmol) and 5-hydroxyindole (**1.2h**, 13.3 mg, 0.1 mmol), according to General Procedure, compound **1.3ah** (24.4 mg, 0.066 mmol, 66% yield) was obtained after 11 h as a colorless oil. **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 8.05 (bs, 1H), 7.38 – 7.23 (m, 5H), 7.13 (d, *J* = 8.7 Hz, 1H), 7.11 – 7.02 (m, 2H), 6.89 (td, *J* = 7.7, 1.4 Hz, 1H), 6.86 – 6.79 (m, 2H), 6.76 (dd, *J* = 8.7, 2.3 Hz, 1H), 6.67 (d, *J* = 2.5 Hz, 1H), 5.28 (s, 1H), 4.60 (d, *J* = 14.9 Hz, 1H), 4.12 (d, *J* = 14.9 Hz, 1H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 164.7 (C), 150.1 (C), 141.7 (C), 136.1 (C), 134.1 (C), 131.0 (C), 128.8 (CH), 127.8 (CH), 126.7 (C), 125.4 (CH), 123.8 (CH), 119.8 (CH), 116.6 (CH), 113.9 (CH), 112.8 (CH), 112.0 (C), 108.0 (C), 103.6 (CH), 56.0 (CH), 51.6 (CH_2); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{23}H_{19}N_2O_3$ 371.1390, found 371.1393.

4-Benzyl-3-(5-bromo-1*H*-indol-3-yl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-one (1.3ai)



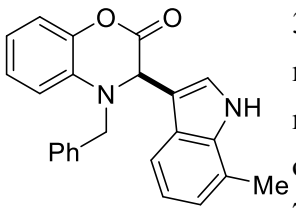
Using 4-benzyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-one (**1.1a**, 35.8 mg, 0.15 mmol) and 5-bromoindole (**1.2i**, 19.6 mg, 0.1 mmol), according to General Procedure, compound **1.3ai** (23.4 mg, 0.054 mmol, 54% yield) was obtained after 14 h as a white solid; **Mp** 152-154 ^{o}C; **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 8.21 (bs, 1H), 7.54 (d, J = 1.8 Hz, 1H), 7.40 – 7.32 (m, 3H), 7.32 – 7.24 (m, 3H), 7.17 (d, J = 8.6 Hz, 1H), 7.15 – 7.05 (m, 2H), 6.93 (td, J = 7.7, 1.4 Hz, 1H), 6.84 (dd, J = 8.0, 1.3 Hz, 1H), 6.71 (d, J = 2.6 Hz, 1H), 5.29 (s, 1H), 4.62 (d, J = 14.6 Hz, 1H), 4.06 (d, J = 14.6 Hz, 1H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 164.5 (C), 141.8 (C), 135.7 (C), 134.4 (C), 134.0 (C), 128.9 (CH), 128.0 (CH), 127.7 (CH), 126.5 (C), 125.8 (CH), 125.5 (CH), 124.0 (CH), 121.8 (CH), 120.2 (CH), 116.6 (CH), 114.1 (CH), 113.8 (C), 112.7 (CH), 108.4 (C), 55.3 (CH), 51.5 (CH_2). Physical and spectroscopic data match with those reported in the bibliography.[75]

4-Benzyl-3-(6-methyl-1*H*-indol-3-yl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-one (1.3aj)



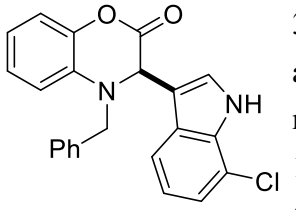
Using 4-benzyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-one (**1.1a**, 35.8 mg, 0.15 mmol) and 6-methylindole (**1.2j**, 13.1 mg, 0.1 mmol), according to General Procedure, compound **1.3aj** (28.3 mg, 0.077 mmol, 77% yield) was obtained after 14 h as a brown solid. **Mp** 70-74 ^{o}C; **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 7.98 (bs, 1H), 7.43 – 7.26 (m, 6H), 7.16 – 7.07 (m, 2H), 7.06 (td, J = 7.7, 1.6 Hz, 1H), 6.96 (dd, J = 8.2, 1.4 Hz, 1H), 6.91 (td, J = 7.7, 1.5 Hz, 1H), 6.81 (dd, J = 8.0, 1.4 Hz, 1H), 6.66 (d, J = 2.5 Hz, 1H), 5.37 (d, J = 0.7 Hz, 1H), 4.61 (d, J = 14.8 Hz, 1H), 4.15 (d, J = 14.8 Hz, 1H), 2.44 (s, 3H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 164.6 (C), 141.9 (C), 136.3 (C), 136.1 (C), 134.2 (C), 132.7 (C), 128.8 (CH), 127.8 (CH), 127.7 (CH), 125.3 (CH), 123.9 (C), 122.3 (CH), 122.2 (CH), 119.8 (CH), 118.7 (CH), 116.5 (CH), 113.8 (C), 111.2 (CH), 108.6 (C), 56.0 (CH), 51.5 (CH_2), 21.6 (CH_3). Les dades físiques and espectroscòpiques coincideixen amb les que es troben descrites en la bibliografia.[75]

4-Benzyl-3-(7-methyl-1*H*-indol-3-yl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-one (1.3ak)



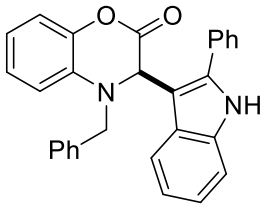
Using 4-benzyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-one (**1.1a**, 35.8 mg, 0.15 mmol) and 7-methylindole (**1.2k**, 13.1 mg, 0.1 mmol), according to General Procedure, compound **1.3ak** (26.1 mg, 0.071 mmol, 71% yield) was obtained after 14 h as a colorless oil. **Mp** 75-77 °C; **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 8.03 (s, 1H), 7.33 (m, 6H), 7.12 (dd, J = 7.9, 1.5 Hz, 1H), 7.10 – 7.03 (m, 2H), 7.01 (ddd, J = 7.2, 1.6, 0.8 Hz, 1H), 6.91 (td, J = 7.7, 1.4 Hz, 1H), 6.81 (dd, J = 8.1, 1.4 Hz, 1H), 6.73 (d, J = 2.6 Hz, 1H), 5.39 (d, J = 0.7 Hz, 1H), 4.61 (d, J = 14.9 Hz, 1H), 4.16 (d, J = 14.9 Hz, 1H), 2.42 (s, 3H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 164.5 (C), 141.9 (C), 136.1 (C), 135.4 (C), 134.2 (C), 128.8 (CH), 127.8 (CH), 127.8 (CH), 125.7 (C), 125.3 (CH), 123.3 (CH), 122.6 (CH), 120.7 (CH), 120.5 (C), 119.8 (CH), 116.8 (CH), 116.5(CH), 113.9 (CH), 109.2 (C), 56.0 (CH), 51.6 (CH_2), 16.4 (CH_3). Physical and spectroscopic data match with those reported in the bibliography.[75]

4-Benzyl-3-(7-chloro-1*H*-indol-3-yl)-3,4-dihydro-2H-benzo[*b*][1,4]oxazin-2-one (1.3al)



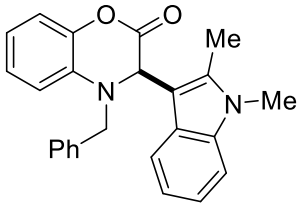
Using 4-benzyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-one (**1.1a**, 35.8 mg, 0.15 mmol) and 7-cloroindole (**1.2l**, 15.2 mg, 0.1 mmol), according to General Procedure, compound **1.3al** (22.9 mg, 0.059 mmol, 59% yield) was obtained after 16 h as a white solid; **Mp** 148-150 °C; **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 8.29 (bs, 1H), 7.39 (d, J = 8.0 Hz, 1H), 7.36 – 7.24 (m, 5H), 7.21 (dd, J = 7.6, 0.7 Hz, 1H), 7.15 – 7.02 (m, 3H), 6.92 (td, J = 7.7, 1.4 Hz, 1H), 6.85 (dd, J = 8.0, 1.3 Hz, 1H), 6.80 (d, J = 2.6 Hz, 1H), 5.35 (s, 1H), 4.64 (d, J = 14.7 Hz, 1H), 4.12 (d, J = 14.7 Hz, 1H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 164.2 (C), 141.8 (C), 135.8 (C), 134.0 (C), 133.2 (C), 128.9 (CH), 127.9 (CH), 127.5 (C), 125.5 (CH), 123.4 (CH), 122.2 (CH), 121.3 (CH), 120.1 (CH), 117.9 (CH), 116.8 (C), 116.6 (CH), 113.9 (CH), 110.0 (C), 55.7 (CH), 51.6 (CH_2). Physical and spectroscopic data match with those reported in the bibliography.[75]

4-Benzyl-3-(2-phenyl-1*H*-indol-3-yl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-one (1.3am)



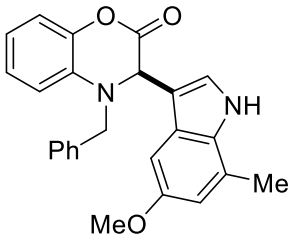
Using 4-benzyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-one (**1.1a**, 35.8 mg, 0.15 mmol) and 2-phenylindole (**1.2m**, 19.3 mg, 0.1 mmol), according to General Procedure, compound **1.3am** (34.4 mg, 0.080 mmol, 80% yield) was obtained after 14 h as a brown solid. **Mp** 88-90 °C; **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 8.27 (bs, 1H), 7.54 – 7.46 (m, 2H), 7.42 – 7.32 (m, 4H), 7.22 – 7.14 (m, 3H), 7.11 – 7.05 (m, 3H), 7.04 – 6.96 (m, 2H), 6.96 – 6.91 (m, 2H), 6.90 – 6.82 (m, 1H), 6.69 (dd, J = 8.1, 1.4 Hz, 1H), 5.57 (s, 1H), 4.42 (d, J = 16.2 Hz, 1H), 3.87 (d, J = 16.3 Hz, 1H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 166.2 (C), 140.5 (C), 139.4 (C), 136.4 (C), 135.9 (C), 134.2 (C), 131.3 (C), 129.0 (CH), 128.9 (CH), 128.7 (CH), 128.4 (CH), 127.0 (CH), 126.9 (CH), 126.3 (C), 125.5 (CH), 122.9 (CH), 120.7 (CH), 120.0 (CH), 118.9 (CH), 116.9 (CH), 113.1 (CH), 111.1 (CH), 107.6 (C), 56.1 (CH), 50.0 (CH_2). Physical and spectroscopic data match with those reported in the bibliography.[75]

4-Benzyl-3-(1,2-dimethyl-1*H*-indol-3-yl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-one (1.3an)



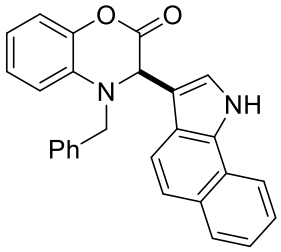
Using 4-benzyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-one (**1.1a**, 35.8 mg, 0.15 mmol) and 1,2-dimethylindole (**1.2n**, 14.5 mg, 0.1 mmol), according to General Procedure, compound **1.3an** (26.7 mg, 0.070 mmol, 70% yield) was obtained after 12 h as a brown solid. **Mp** 195-199 °C; **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 7.31 – 7.22 (m, 4H), 7.19 – 7.14 (m, 3H), 7.14 – 7.08 (m, 2H), 7.05 (ddd, J = 8.1, 7.4, 1.6 Hz, 1H), 6.96 (ddd, J = 8.0, 6.9, 1.1 Hz, 1H), 6.88 (ddd, J = 7.9, 7.5, 1.4 Hz, 1H), 6.78 (dd, J = 8.1, 1.4 Hz, 1H), 5.38 (d, J = 0.5 Hz, 1H), 4.57 (d, J = 16.2 Hz, 1H), 3.99 (d, J = 16.2 Hz, 1H), 3.63 (s, 3H), 2.12 (s, 3H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 166.1 (C), 140.9 (C), 140.7 (C), 137.0 (C), 136.8 (C), 134.6 (C), 128.7 (CH), 127.2 (CH), 127.1 (CH), 125.8 (C), 125.5 (CH), 121.3 (CH), 120.0 (CH), 119.0 (CH), 118.6 (CH), 117.0 (CH), 113.2 (CH), 109.0 (CH), 105.3 (C), 56.2 (CH), 49.9 (CH_2), 29.6 (CH_3), 10.3 (CH_3). Physical and spectroscopic data match with those reported in the bibliography.[75]

4-Benzyl-3-(5-methoxy-7-methyl-1*H*-indol-3-yl)-3,4-dihydro-2H-benzo[*b*][1,4]oxazin-2-one (1.3ao)



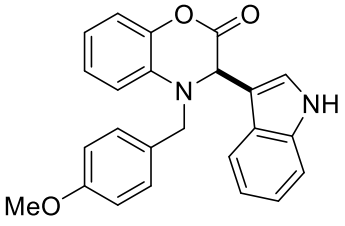
Using 4-benzyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-one (**1.1a**, 35.8 mg, 0.15 mmol) and 5-metoxi-7-methylindole (**1.2o**, 16.1 mg, 0.1 mmol), according to General Procedure, compound **1.3ao** (27.9 mg, 0.070 mmol, 70% yield) was obtained after 11 h as a white solid; **Mp** 150-152 °C; **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 7.98 (bs, 1H), 7.40 – 7.27 (m, 5H), 7.13 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.07 (td, *J* = 7.7, 1.5 Hz, 1H), 6.91 (td, *J* = 7.7, 1.4 Hz, 1H), 6.82 (dd, *J* = 8.1, 1.3 Hz, 1H), 6.74 – 6.62 (m, 3H), 5.33 (s, 1H), 4.61 (d, *J* = 14.8 Hz, 1H), 4.10 (d, *J* = 14.7 Hz, 1H), 3.71 (s, 3H), 2.36 (s, 3H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 164.7 (C), 154.7 (C), 141.8 (C), 136.1 (C), 134.3 (C), 130.6 (C), 128.8 (CH), 127.9 (CH), 127.8 (CH), 125.8 (C), 125.4 (CH), 123.3 (CH), 121.6 (C), 119.8 (CH), 116.5 (CH), 114.1 (CH), 113.8 (CH), 109.1 (C), 97.8 (CH), 55.8 (CH), 55.6 (CH_3), 51.2 (CH_2), 16.4 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{25}H_{23}N_2O_3$ 399.1703, found 399.1708.

3-(1*H*-Benzo[*g*]indol-3-yl)-4-benzyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-one (1.3ap)



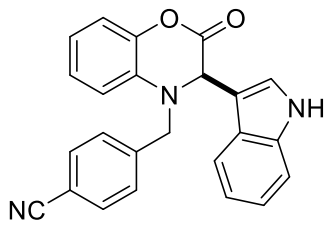
Using 4-benzyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-one (**1.1a**, 35.8 mg, 0.15 mmol) and benzo[*g*]indole (**1.2p**, 16.7 mg, 0.1 mmol), according to General Procedure, compound **1.3ap** (31.0 mg, 0.077 mmol, 77% yield) was obtained after 14 h as a brown solid. **Mp** 196-200 °C; **^{1}H-NMR (300 MHz, acetone-d_6)** δ 11.25 (bs, 1H), 8.27 (d, *J* = 8.2 Hz, 1H), 7.94 (d, *J* = 8.0 Hz, 1H), 7.69 (d, *J* = 8.8 Hz, 1H), 7.58 – 7.29 (m, 8H), 7.18 – 7.02 (m, 2H), 6.99 – 6.87 (m, 3H), 5.68 (d, *J* = 0.6 Hz, 1H), 4.68 (d, *J* = 15.1 Hz, 1H), 4.40 (d, *J* = 15.1 Hz, 1H); **^{13}C{^{1}H}-NMR (75 MHz, acetone-d_6)** δ 165.0 (C), 143.0 (C), 138.0 (C), 135.2 (C), 131.9 (C), 131.5 (C), 129.5 (CH), 129.4 (CH), 128.6 (CH), 128.3 (CH), 126.5 (CH), 126.1 (CH), 125.0 (CH), 123.1 (C), 123.0 (C), 122.2 (CH), 121.6 (CH), 121.1 (CH), 120.6 (CH), 119.7 (CH), 117.0 (CH), 115.4 (CH), 111.0 (C), 57.4 (CH), 52.5 (CH_2); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{27}H_{21}N_2O_2$ 405.1598, found 405.1592.

3-(1*H*-Indol-3-yl)-4-(4-methoxybenzyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-one (1.3ba)



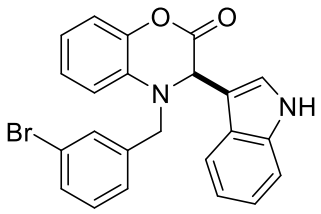
Using 4-(4-methoxybenzyl)-3,4-dihydro-2*H*-benzo[*b*][1,4] oxazin-2-one (**1.1b**, 40,4 mg, 0.15 mmol), and indole (**1.2a**, 11.7 mg, 0.1 mmol), according to General Procedure, compound **1.3ca** (21,5 mg, 0.056 mmol, 56% yield) was obtained after 10 h as a colorless oil. **Mp** 52-54 °C; **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 8.09 (bs, 1H), 7.50 (d, J = 7.9 Hz, 1H), 7.35 – 7.30 (m, 1H), 7.24 – 7.16 (m, 3H), 7.16 – 7.04 (m, 3H), 6.92 (dd, J = 7.7, 1.4 Hz, 1H), 6.90 – 6.83 (m, 3H), 6.71 (d, J = 2.4 Hz, 1H), 5.37 (d, J = 0.4 Hz, 1H), 4.57 (d, J = 14.4 Hz, 1H), 4.07 (d, J = 14.3 Hz, 1H), 3.82 (s, 3H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 164.5 (C), 159.2 (C), 141.9 (C), 135.8 (C), 134.3 (C), 129.2 (CH), 127.8 (C), 126.1 (C), 125.3 (CH), 122.79 (CH), 122.76 (CH), 120.4 (CH), 119.8 (CH), 119.2 (CH), 116.5 (CH), 114.2 (CH), 113.9 (CH), 111.2 (CH), 108.8 (C), 55.30 (CH) 55.28 (CH_3), 50.9 (CH_2). Les dades físiques and espectroscòpiques coincideixen amb les que es troben descrites en la bibliografia.[75]

3-(1*H*-Indol-3-yl)-4-(4-cyanobenzyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-one (1.3ca)



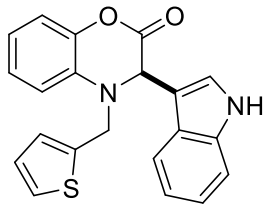
Using 4-(4-cyanobenzyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-one benzonitril (**1.1c**, 39,6 mg, 0.15 mmol) and indole (**1.2a**, 11.7 mg, 0.1 mmol), according to General Procedure, compound **1.3ba** (33,4 mg, 0.088 mmol, 88% yield) was obtained after 13 h as a colorless oil. **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 8.15 (bs, 1H), 7.66 – 7.59 (m, 2H), 7.52 (d, J = 7.9 Hz, 1H), 7.41 (d, J = 8.5 Hz, 2H), 7.35 (d, J = 8.1 Hz, 1H), 7.26 – 7.19 (m, 1H), 7.18 – 7.11 (m, 2H), 7.04 (td, J = 7.7, 1.6 Hz, 1H), 6.94 (td, J = 7.7, 1.5 Hz, 1H), 6.76 (d, J = 2.5 Hz, 1H), 6.65 (dd, J = 8.0, 1.4 Hz, 1H), 5.39 (s, 1H), 4.60 (d, J = 16.0 Hz, 1H), 4.27 (d, J = 16.0 Hz, 1H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 164.1 (C), 142.1 (C), 141.9 (C), 135.8 (C), 133.4 (C), 132.7 (CH), 128.1 (CH), 126.0 (C), 125.4 (CH), 123.1 (CH), 122.9 (CH), 120.7 (CH), 120.6 (CH), 118.9 (CH), 118.6 (C), 116.8 (CH), 113.9 (CH), 111.6 (C), 111.4 (CH), 108.5 (C), 57.0 (CH), 51.7 (CH_2); **HRMS (ESI/Q-TOF)** m/z $[M + H]^+$ calcd for $C_{24}H_{18}N_3O_2$ 380.1394, found 380.1398.

4-(3-Bromobenzyl)-3-(1*H*-indol-3-yl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-one (1.3da)



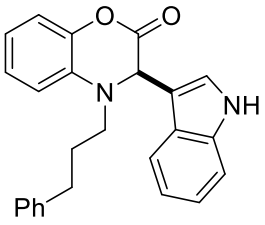
Using 4-(3-bromobenzyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-one (**1.1d**, 47,7 mg, 0.15 mmol), and indole (**1.2a**, 11.7 mg, 0.1 mmol), according to General Procedure, compound **1.3da** (25,5 mg, 0.059 mmol, 59% yield) was obtained after 13 h as a colorless oil. **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 8.13 (s, 1H), 7.54 – 7.49 (m, 1H), 7.46 – 7.41 (m, 2H), 7.35 – 7.31 (m, 1H), 7.25 – 7.18 (m, 3H), 7.17 – 7.11 (m, 2H), 7.05 (dd, *J* = 7.9, 1.6 Hz, 1H), 6.93 (td, *J* = 7.7, 1.4 Hz, 1H), 6.81 – 6.69 (m, 2H), 5.39 (d, *J* = 0.5 Hz, 1H), 4.54 (d, *J* = 15.2 Hz, 1H), 4.12 (d, *J* = 15.3 Hz, 1H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 164.4 (C), 141.9 (C), 138.7 (C), 135.8 (C), 133.7 (C), 130.9 (CH), 130.7 (CH), 130.4 (CH), 126.2 (CH), 126.0 (C), 125.4 (CH), 122.9 (C), 122.9 (CH), 122.9 (CH), 120.6 (CH), 120.2 (CH), 119.0 (CH), 116.7 (CH), 113.9 (CH), 111.3 (CH), 108.6 (C), 56.3 (CH), 51.2 (CH_2); **HRMS (ESI/Q-TOF)** *m/z* [M + H]$^+$ calcd for $C_{23}H_{18}BrN_2O_2$ 433.0546, found 433.0539.

3-(1*H*-Indol-3-yl)-4-(thiophen-2-ylmethyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2- one (1.3ea)



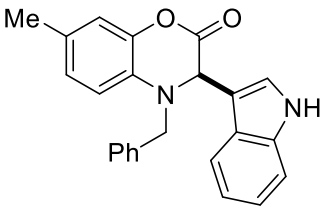
Using 4-(thiophen-2-ylmethyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-one (**1.1e**, 36,8 mg, 0.15 mmol), and indole (**1.2a**, 11.7 mg, 0.1 mmol), according to General Procedure, compound **1.3ea** (27,8 mg, 0.077 mmol, 77% yield) was obtained after 24 h as a colorless oil. **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 8.13 (bs, 1H), 7.56 (d, *J* = 7.9 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 1H), 7.27 (dd, *J* = 5.0, 1.0 Hz, 1H), 7.25 – 7.17 (m, 1H), 7.17 – 7.06 (m, 3H), 6.99 – 6.90 (m, 4H), 6.74 (d, *J* = 2.4 Hz, 1H), 5.45 (s, 1H), 4.77 (d, *J* = 15.1 Hz, 1H), 4.35 (d, *J* = 15.4 Hz, 1H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 164.6 (C), 142.0 (C), 139.3 (C), 135.8 (C), 133.7 (C), 126.9 (CH), 126.6 (CH), 126.0 (C), 125.7 (CH), 125.4 (CH), 123.2 (CH), 122.8 (CH), 120.4 (CH), 120.3 (CH), 119.1 (CH), 116.7 (CH), 114.0 (CH), 111.3 (CH), 108.5 (C), 55.5 (CH), 46.7 (CH_2); **HRMS (ESI/Q-TOF)** *m/z* [M + H]$^+$ calcd for $C_{21}H_{17}N_2O_2S$ 361.1005, found 361.1008.

3-(1*H*-Indol-3-yl)-4-(3-phenylpropyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-oae (1.3fa)



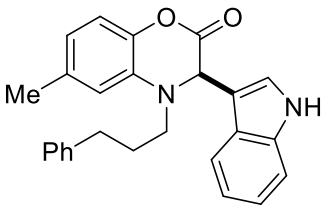
Using 4-(3-phenylpropyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-one (**1.1f**, 40,1 mg, 0.15 mmol), and indole (**1.2a**, 11.7 mg, 0.1 mmol), according to General Procedure, compound **1.3fa** (28,3 mg, 0.074 mmol, 74% yield) was obtained after 24 h as a colorless oil. **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 8.07 (bs, 1H), 7.66 (dd, J = 7.7, 0.5 Hz, 1H), 7.33 – 7.25 (m, 3H), 7.25 – 7.11 (m, 5H), 7.11 – 7.04 (m, 2H), 6.86 (ddd, J = 8.1, 7.4, 1.4 Hz, 1H), 6.75 (dd, J = 8.0, 1.3 Hz, 1H), 6.69 (d, J = 2.2 Hz, 1H), 5.40 (d, J = 0.7 Hz, 1H), 3.50 – 3.36 (m, 1H), 3.16 – 3.00 (m, 1H), 2.68 (t, J = 7.4 Hz, 2H), 2.09 – 1.94 (m, 2H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 164.3 (C), 141.6 (C), 141.1 (C), 135.9 (C), 133.8 (C), 128.5 (CH), 128.4 (CH), 126.1 (CH), 125.9 (C), 125.3 (CH), 122.8 (CH), 122.8 (CH), 120.5 (CH), 119.1 (CH), 119.1 (CH), 116.6 (CH), 112.9 (CH), 111.3 (CH), 109.4 (C), 56.8 (CH), 47.3 (CH_2), 32.9 (CH_2), 28.3 (CH_2); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{25}H_{23}N_2O_2$ 383.1754., found 383.1759.

4-Benzyl-3-(1*H*-indol-3-yl)-7-methyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-one (1.3ga)



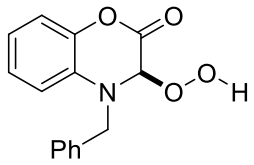
Using 4-benzyl-7-methyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-one (**1.1g**, 38,0 mg, 0.15 mmol), and indole (**1.2a**, 11.7 mg, 0.1 mmol), according to General Procedure, compound **1.3ga** (25,4 mg, 0.069 mmol, 69% yield) was obtained after 16 h as a white solid; **Mp** 175-177 °C; **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 8.11 (bs, 1H), 7.52 (d, J = 7.9 Hz, 1H), 7.38 – 7.26 (m, 6H), 7.24 – 7.17 (m, 1H), 7.16 – 7.10 (m, 1H), 6.93 (d, J = 1.4 Hz, 1H), 6.86 (ddd, J = 8.1, 1.9, 0.6 Hz, 1H), 6.73 (d, J = 2.5 Hz, 1H), 6.70 (d, J = 8.2 Hz, 1H), 5.37 (d, J = 0.4 Hz, 1H), 4.56 (d, J = 14.8 Hz, 1H), 4.12 (d, J = 14.8 Hz, 1H), 2.31 (s, 3H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 164.8 (C), 141.9 (C), 136.3 (C), 135.8 (C), 131.7 (C), 129.9 (C), 128.8 (CH), 127.8 (CH), 127.7 (CH), 126.2 (C), 125.7 (CH), 122.8 (CH), 122.8 (CH), 120.4 (CH), 119.2 (CH), 117.1 (CH), 114.0 (CH), 111.2 (CH), 108.8 (C), 56.0 (CH), 51.8 (CH_2), 20.5 (CH_3). Physical and spectroscopic data match with those reported in the bibliography.[75]

3-(1*H*-Indol-3-yl)-6-methyl-4-(3-phenylpropyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-one (1.3ha)



Using 6-methyl-4-(3-phenylpropyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-one (**1.1h**, 38,0 mg, 0.15 mmol), and indole (**1.2a**, 11.7 mg, 0.1 mmol), according to General Procedure, compound **1.3ha** (23,8 mg, 0.060 mmol, 60% yield) was obtained after 16 h as a colorless oil. **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 8.08 (bs, 1H), 7.71 – 7.61 (m, 1H), 7.39 – 7.25 (m, 3H), 7.24 – 7.09 (m, 5H), 6.93 (d, J = 8.1 Hz, 1H), 6.72 (d, J = 2.3 Hz, 1H), 6.64 (ddd, J = 8.1, 1.8, 0.6 Hz, 1H), 6.50 (d, J = 1.5 Hz, 1H), 5.37 (d, J = 0.6 Hz, 1H), 3.41 (ddd, J = 13.9, 8.0, 5.8 Hz, 1H), 3.13 – 2.98 (m, 1H), 2.68 (td, J = 7.4, 3.1 Hz, 2H), 2.30 (s, 3H), 2.10 – 1.88 (m, 2H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 164.4 (C), 141.1 (C), 139.6 (C), 135.9 (C), 135.0 (C), 133.4 (C), 128.5 (CH), 128.4 (CH), 126.1 (CH), 126.0 (C), 122.9 (CH), 122.7 (CH), 120.4 (CH), 119.6 (CH), 119.1 (CH), 116.2 (CH), 113.5 (CH), 111.3 (CH), 109.5 (C), 56.9 (CH), 47.2 (CH_2), 32.9 (CH_2), 28.3 (CH_2), 21.4 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{26}H_{25}N_2O_2$ 397.1911, found 397.1918.

4-Benzyl-3-hydroperoxi-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-one (1.6)



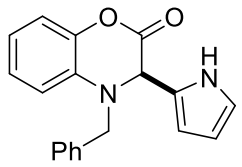
Obtained several times in varying amounts as a brown solid; **Mp** 143-146 °C; **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 7.38 – 7.21 (m, 5H), 7.10 (dd, *J* = 4.1, 3.4 Hz, 1H), 7.07 – 6.92 (m, 3H), 5.73 (s, 1H), 5.28 (d, *J* = 16.1 Hz, 1H), 5.09 (d, *J* = 16.1 Hz, 1H), 4.35 (bs, 1H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 162.9 (C), 142.0 (C), 135.4 (C), 129.0 (CH), 128.0 (C), 127.6 (CH), 126.5 (CH), 124.5 (CH), 123.4 (CH), 118.2 (CH), 115.8 (CH), 90.6 (CH), 45.6 (CH_2).

Specific Procedure A for the Photocatalytic aza-Friedel-Crafts Reaction between 3,4-dihydro-1,4-benzoxazin-2-ones 1.1 and pyrroles 1.7

In a 5 mL borosilicate vial, the corresponding 3,4-dihydro-1,4-benzoxazin-2-one (**1.1**, 0.15 mmol, 1.5 equiv.), the corresponding pyrrole (**1.7**, 0.1 mmol, 1 equiv.), 9,10-phenanthrenequinone (**J**, 1.0 mg, 0.005 mmol, 5 mol %) and $Zn(OTf)_2$ (0.9 mg, 0.0025 mmol, 2.5 mol %) were placed. Then, MeCN (1 mL) was added and the reaction mixture was placed 2 cm away from white LEDs (455 nm) (see page 432 for further details about the photochemical setup). The conversion of the starting materials is traced regularly by TLC, and it is stopped when pyrrole **1.7** is consumed. The resultant reaction mixture is purified by column chromatography using hexane:EtOAc mixtures (from 95:5 to 85:15) to obtain

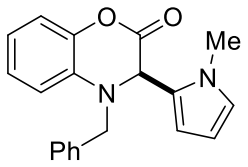
the expected pure compound **1.8**.

4-Benzyl-3-(1*H*-pyrrole-2-yl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-one (1.8aa)



Using 4-benzyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-one (**1.1a** 35.8 mg, 0.15 mmol), and pyrrole (**1.7a**, 6.9 μL, 0.1 mmol), according to Specific Procedure A, compound **1.8aa** (16.7 mg, 0.055 mmol, 55% yield) was obtained after 12 h as a brown solid. **Mp.** 127-130 ^{o}C; **^{1}H RMN (300 MHz, $CDCl_3$)** δ 7.95 (bs, 1H), 7.45 – 7.27 (m, 5H), 7.15 – 7.07 (m, 2H), 6.97 – 6.87 (m, 2H), 6.67 (td, J = 2.7, 1.5 Hz, 1H), 6.06 (dd, J = 6.1, 2.7 Hz, 1H), 5.92 – 5.83 (m, 1H), 5.03 (s, 1H), 4.65 (d, J = 14.3 Hz, 1H), 4.08 (d, J = 14.3 Hz, 1H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 164.2 (C), 141.4 (C), 135.6 (C), 133.7 (C), 129.0 (CH), 128.1 (CH), 128.0 (CH), 127.7 (CH), 125.7 (CH), 123.1 (C), 120.3 (CH), 119.1 (CH), 116.8 (CH), 113.9 (CH), 108.9 (CH), 56.9 (CH), 51.6 (CH_2). Physical and spectroscopic data match with those reported in the bibliography.[75]

4-Benzyl-3-(1-methyl-1*H*-pyrrole-2-yl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-one (1.8ab)



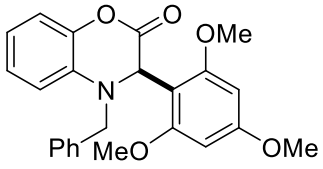
Using 4-benzyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-one (**1.1a** 35.8 mg, 0.15 mmol), and *N*-methylpyrrole (**1.7b**, 8.9 μL, 0.1 mmol), according to Specific Procedure A, compound **1.8ab** (18.4 mg, 0.058 mmol, 58% yield) was obtained after 11 h as a yellow oil. **^{1}H RMN (300 MHz, $CDCl_3$)** δ 7.37 – 7.30 (m, 5H), 7.10 (dd, J = 7.9, 1.5 Hz, 1H), 7.06 – 7.00 (m, 1H), 6.89 (dd, J = 7.7, 1.5 Hz, 1H), 6.76 (dd, J = 8.0, 1.3 Hz, 1H), 6.42 (t, J = 2.5 Hz, 1H), 6.31 (t, J = 2.0 Hz, 1H), 5.75 (dd, J = 2.6, 1.9 Hz, 1H), 4.93 (s, 1H), 4.55 (d, J = 14.5 Hz, 1H), 4.07 (d, J = 14.5 Hz, 1H), 3.53 (s, 3H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 165.6 (C), 141.9 (C), 136.3 (C), 134.2 (C), 128.8 (CH), 128.0 (CH), 127.7 (CH), 125.2 (CH), 122.3 (CH), 120.6 (CH), 119.7 (CH), 116.4 (CH), 115.7 (C), 113.8 (CH), 107.8 (CH), 56.9 (CH), 51.2 (CH_2), 36.2 (CH_3). Physical and spectroscopic data match with those reported in the bibliography.[75]

Specific Procedure B for the Photocatalytic aza-Friedel-Crafts Reaction between 3,4-dihydro-1,4-benzoxazin-2-ones 1.1 and electron-rich benzene derivatives 1.9

In a 5 mL borosilicate vial, the corresponding 3,4-dihydro-1,4-benzoxazin-2-one (**1.1**, 0.15 mmol, 1.5 equiv.), the corresponding electron-rich benzene derivative (**1.9**, 0.1 mmol, 1 equiv.), 9,10-phenanthrenequinone (**J**, 1.0 mg, 0.005 mmol, 5 mol %) and $Zn(OTf)_2$ (0.9 mg, 0.0025 mmol, 2.5 mol %) were placed. Then, MeCN (1 mL) was added and the re-

action mixture was placed 2 cm away from white LEDs (see page 432 for further details about the photochemical setup). The conversion of the starting materials is traced regularly by TLC, and it is stopped when the electron-rich benzene derivative **1.9** is consumed. The resultant reaction mixture is purified by column chromatography using hexane:EtOAc mixtures (from 95:5 to 85:15) to obtain the expected pure compound **1.10**.

4-Benzyl-3-(2,4,6-trimethoxyphenyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-one (1.10ab)

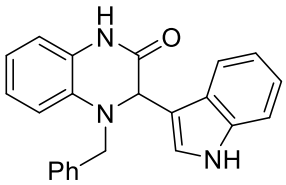


Using 4-benzyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-one (**1.1a**, 35.8 mg, 0.15 mmol), and 1,3,5-trimethoxybenzene (**1.9b**, 16.8 mg, 0.1 mmol), according to Specific Procedure B, compound **1.10ab** (33.6 mg, 0.083 mmol, 83% yield) was obtained after 19 h as a yellow solid. **Mp.** 124-128 ^{o}C; **^{1}H RMN (400 MHz, $CDCl_3$)** δ 7.25 – 7.21 (m, 2H), 7.21 – 7.15 (m, 3H), 7.04 (dd, J = 7.9, 1.5 Hz, 1H), 6.88 (ddd, J = 8.0, 7.6, 1.5 Hz, 1H), 6.70 (td, J = 7.7, 1.4 Hz, 1H), 6.50 (dd, J = 8.1, 1.3 Hz, 1H), 6.04 (s, 2H), 5.87 (s, 1H), 4.37 (d, J = 16.6 Hz, 1H), 4.22 (d, J = 16.6 Hz, 1H), 3.77 (s,31H), 3.59 (s, 6H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 67.5 (C), 161.8 (C), 159.3 (C), 141.0 (C), 137.9 (C), 133.9 (C), 128.4 (CH), 126.8 (CH), 126.5 (CH), 124.6 (CH), 117.4 (CH), 115.7 (CH), 111.8 (CH), 106.7 (C), 90.7 (CH), 55.5 (CH_3), 55.3 (CH), 53.9 (CH_3), 50.7 (CH_2). Physical and spectroscopic data match with those reported in the bibliography.[75]

Specific Procedure C for the Photocatalytic aza-Friedel-Crafts Reaction between 3,4-dihydroquinoxalin-2-ones 1.4 or 1.5 and indole 1.2a

In a 5 mL borosilicate vial, the corresponding 3,4-dihydroquinoxalin-2-one (**1.4** or **1.5**, 0.15 mmol, 1.5 equiv.), indole (**1.2a**, 0.1 mmol, 1 equiv.), 9,10-phenanthrenequinone (**J**, 1.0 mg, 0.005 mmol, 5 mol %) and $Zn(OTf)_2$ (0.9 mg, 0.0025 mmol, 2.5 mol %) were placed. Then, MeCN (1 mL) was added and the reaction mixture was placed 2 cm away from white LEDs (see page 432 for further details about the photochemical setup). The conversion of the starting materials is traced regularly by TLC, and it is stopped when indole **1.2a** is consumed. The resultant reaction mixture is purified by column chromatography using hexane:EtOAc mixtures (from 95:5 to 85:15) to obtain the expected pure compound **1.11a** or **1.12a**.

4-Benzyl-3-(1*H*-indol-3-yl)-3,4-dihydroquinoxalin-2(1*H*)-one (1.12a)

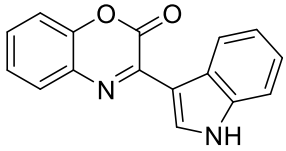


Using 4-benzyl-3,4-dihydroquinoxalin-2(1*H*)-one (**1.5**, 35.8 mg, 0.15 mmol, 1.5 equiv.), and indole (**1.2a**, 11.7 mg, 0.1 mmol, 1 equiv.), according to Specific Procedure C, compound **1.12a** (27.9 mg, 0.079 mmol, 79% yield) was obtained after 15 h as a yellow solid. **Mp** 174-176 °C; **^{1}H-NMR (300 MHz, acetone-d$_6$)** δ 10.17 (bs, 1H), 9.58 (bs, 1H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.41 – 7.23 (m, 6H), 7.14 – 7.06 (m, 1H), 7.03 – 6.94 (m, 3H), 6.92 – 6.85 (m, 1H), 6.82 – 6.74 (m, 2H), 5.28 (s, 1H), 4.66 (d, *J* = 15.3 Hz, 1H), 4.33 (d, *J* = 15.4 Hz, 1H);**^{13}C{^{1}H}-NMR (75 MHz, acetone-d$_6$)** δ 166.9 (C), 138.8 (C), 137.5 (C), 135.8 (C), 129.4 (CH), 128.6 (C), 128.5 (CH), 128.0 (CH), 127.5 (C), 124.1 (CH), 124.0 (CH), 122.6 (CH), 120.4 (CH), 120.1 (CH), 119.6 (CH), 115.8 (CH), 113.9 (CH), 112.2 (CH), 112.0 (C), 60.0 (CH), 52.6 (CH_2). Physical and spectroscopic data match with those reported in the bibliography.[78]

Specific Procedure D for the synthesis of *Cephalandole A* (1.13)

In a 25 mL round-bottom flask, compound **1.3aa** (30 mg, 0.085 mmol, 1 equiv.) and Pd/C 10% w/w (18.1 mg, 0.017 mmol, 20 mol %) are introduced. THF (2 mL) and EtOH (1 mL) are then added and the resulting suspension is bubbled with H_2 and allowed to stir for 16 h with a H_2 balloon. The reaction is monitored by TLC, and when product **1.3aa** is consumed, DDQ (19.3 mg, 0.085 mmol, 1 equiv.) is added directly to the reaction mixture. After 1 hour, the reaction mixture is filtered through Celite, the solvents are evaporated under reduced pressure and the crude is purified by column chromatography using hexane:EtOAc 95:5 to obtain *Cephalandole A* (**1.13**, 20.3 mg, 0.077 mmol, 92% Rdt.) as a crystalline yellow solid.

3-(1*H*-Indol-3-yl)-2*H*-benzo[*b*][1,4]oxazin-2-one, *Cephalandole A* (1.13)

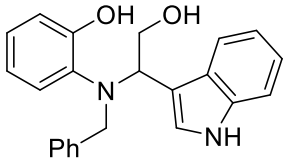


Mp 250-255 °C; **^{1}H RMN (300 MHz, acetone-d$_6$)** δ 11.04 (bs, 1H), 8.88 – 8.82 (m, 1H), 8.78 (t, J = 1.5 Hz, 1H), 7.87 – 7.83 (m, 1H), 7.57 – 7.49 (m, 1H), 7.49 – 7.35 (m, 2H), 7.35 – 7.28 (m, 1H), 7.28 – 7.21 (m, 2H); **^{13}C{^{1}H}-NMR (75 MHz, acetone-d$_6$)** δ 153.0 (C), 149.1 (C), 146.2 (C), 137.9 (C), 134.6 (CH), 133.2 (C), 129.6 (CH), 128.9 (CH), 127.4 (C), 126.1 (CH), 124.2 (CH), 124.1 (CH), 122.5 (CH), 116.8 (CH), 112.8 (CH), 112.4 (C). Physical and spectroscopic data match with those reported in the bibliography.[75]

Specific Procedure E for the synthesis of tryptophol derivative 1.14

Compound **1.3aa** (15.5 mg, 0.044 mmol, 1 equiv.) is introduced into a 10 mL round bottomed flask and purged with N_2. Anhydrous THF (1 mL) is then added via syringe and the resulting solution is cooled down to 0 ^oC. After 5 min, $LiAlH_4$ (0.08 mL, 1 M in THF, 0.087 mmol, 2 equiv.) is added via syringe and the reaction mixture is stirred for 1.5 h at 0 ^{o} C. After this time, the reaction is stopped with aqueous saturated NH_4Cl (1 mL) and with aqueous saturated Rochelle salt (5 mL). The resulting solution is extracted with EtOAc (3x10 mL), and the combined organic phases are washed with brine (10 mL) and dried over anhydrous $MgSO_4$. After filtering, the solvent is removed under reduced pressure and the resulting residue is purified by column chromatography using hexane:EtOAc mixtures (from 90:10 to 60:40) to obtain product **1.14** (9.0 mg, 0.025 mmol, 57% Rdt.) as a brown oil.

2-(Benzyl(2-hydroxy-1-(1*H*-indol-3-yl)ethyl)amino)phenol (1.14)



^{1}H RMN (300 MHz, acetone-d$_6$) δ 8.59 (bs, 1H), 7.42 (d, *J* = 8.0 Hz, 1H), 7.36 – 7.27 (m, 5H), 7.25 – 7.20 (m, 1H), 7.11 (t, *J* = 7.6 Hz, 2H), 7.03 – 6.95 (m, 2H), 6.70 (d, *J* = 7.8 Hz, 2H), 6.55 (d, *J* = 7.9 Hz, 1H), 4.29 – 4.21 (m, 3H), 4.12 (dd, *J* = 10.8, 6.1 Hz, 1H), 4.01 (dd, *J* = 10.8, 7.7 Hz, 1H); **^{13}C{^{1}H}-NMR (75 MHz, acetone-d$_6$)** δ 144.4 (C), 139.0 (C), 136.3 (C), 128.5 (CH), 127.7 (CH), 127.2 (CH), 126.9 (C), 121.9 (CH), 121.8 (CH), 120.2 (CH), 119.3 (CH), 119.1 (CH), 116.2 (C), 116.1 (C), 114.2 (CH), 112.2 (CH), 111.1 (CH), 111.0 (CH), 66.2 (CH_2), 48.8 (CH_2), 44.6 (CH); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{23}H_{23}N_2O_2$ 359.1754, found 359.1757.

Chapter 2

Asymmetric Oxidative Mannich Reactions between 3,4-Dihydroquinoxalin-2-ones and Ketones through a combination of Organophotoredox Catalysis and Organocatalysis

2.1 Introduction and state of the art

2.1.1 Enantioselective Synthesis

Early Developments

The development of new synthetic methodologies in order to generate enantiomerically-enriched molecules is nowadays one of the most important goals in modern organic chemistry.[115–117] Throughout the course of history, the strategy to obtain optically-active molecules has evolved. Initially, it was based on the resolution of racemic mixtures and the use of enantiomerically-pure starting materials (chiral pool). Thereafter, the development of chiral reagents[118] and chiral auxiliaries[119] permitted the development of asymmetric reactions using achiral starting materials.

However, the most important breakthrough in this field came in the 1960s, where several enantiocontroled reactions were developed using substoichiometric amounts of chiral information. Specifically, the use of chiral metal complexes in a catalytic amount was the first well-established approach to develop a great assortment of methodologies to obtain enantiomerically-enriched molecules.[120,121] The pinnacle of the metal-catalyzed

asymmetric catalysis was the recognition of the works of Sharpless,[122,123] Knowles[124] and Noyori[115] with the Nobel Prize in Chemistry in 2001.

In fact, the use of chiral metal complexes is nowadays one of the most robust and reliable synthetic strategy.[125] Hence, a fair number of industrial procedures have implemented this complexes for the synthesis of relevant molecules,[120] specially using an asymmetric catalytic alkene hydrogenation reaction.[126,127]

Organocatalysis

Although most of the advances in asymmetric catalysis must be allocated to chiral metal complexes, in the recent years the organic chemistry community has put a lot of effort in developing asymmetric transformations using purely organic molecules as catalysts. This branch of organic chemistry, organocatalysis, has grown exponentially since the beginning of this century.[128] However, one of the very first successful example of asymmetric organocatalyzed reaction was reported in 1974, where Hajos and Parrish were capable of synthesizing a biclyclic cetol through an intramolecular aldol reaction.[129] In this case, (*S*)-proline worked as organocatalyst, but its mode of action was not fully understood until 2000.[130]

The use catalytic amounts of small organic molecules to promote enantioselective transformations offers several advantages in contrast to chiral metal complexes. Specifically, organocatalysis offers a low cost and easy experimental setup, while avoiding the generation of metal-containing waste. The culmination of organocatalysis occurred last year, when Benjamin List and David W. C. MacMillan were awarded the Nobel Prize in chemistry "*for the development of asymmetric organocatalysis*".

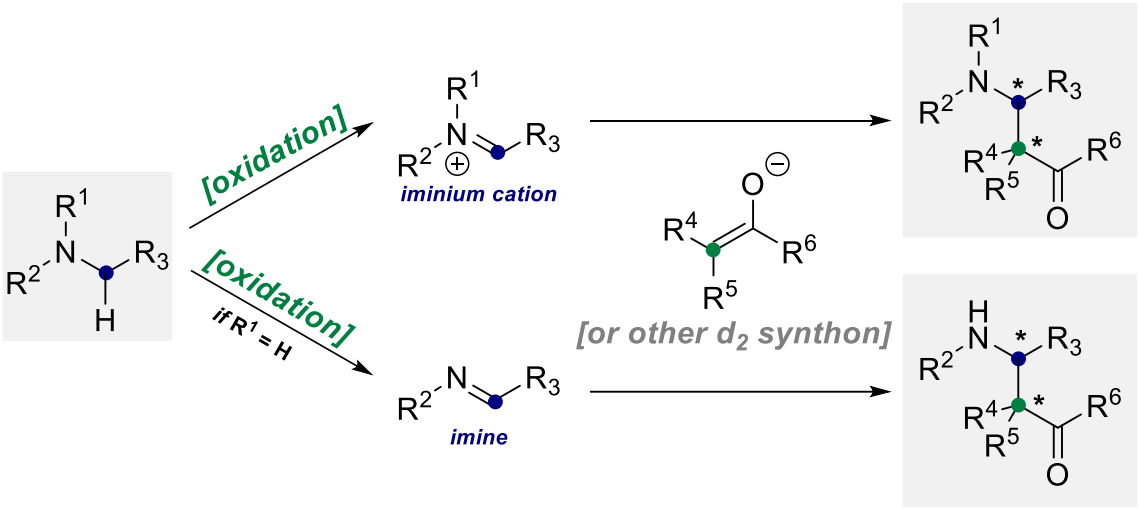
Hitherto, a vast number of organocatalysts which their particular mode of action have been developed. In this *chapter*, the development of a Mannich-type reaction will be discussed. Hence, the use of ketones as nucleophiles in organocatalysis requires the formation of a chiral enamine through a condensation with a chiral secondary amine, such as proline.[131] Although this would not be the unique approach, the asymmetric Mannich reaction promoted by proline has been widely studied.[132]

2.1.2 Asymmetric Oxidative Mannich Reactions

The Concept

The enantioselective addition of enolates to an electrophilic C=N double bond, the well-known Mannich reaction, is a widely-used and straightforward approach to chiral amines. Nevertheless, a large number of imines are unstable under regular reaction conditions or even they are governed by an equilibrium that favours the non-electrophilic

enamine form. To tackle this issue, the pre-synthesis of electrophilic C=N bonds is circumvented by the in-situ oxidation of secondary or tertiary amines that bear an α-H (Scheme 2.1). Logically, if a tertiary amine is oxidized, the product would be an iminium cation, whereas if the amine is secondary, the result would be an imine. In both cases, if there is an enolate (or other d_2 synthon) in the medium, as well as a proper catalyst to induce asymmetry, an enantioselective Mannich reaction can take place.



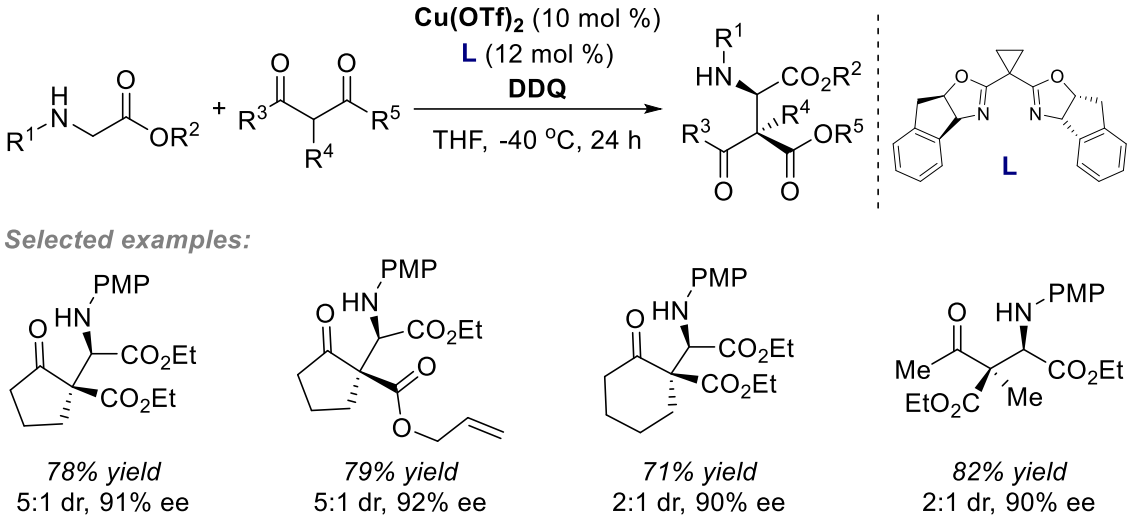
Scheme 2.1: General overview of the asymmetric oxidative Mannich reaction.

This strategy was rapidly recognized as a powerful tool, and several methodologies can be found in the bibliography. In fact, in 2021 we reviewed the asymmetric oxidative Mannich reactions.[133] Among all reports, four examples have been selected to exemplify this stereoselective methodology.

Selected Examples

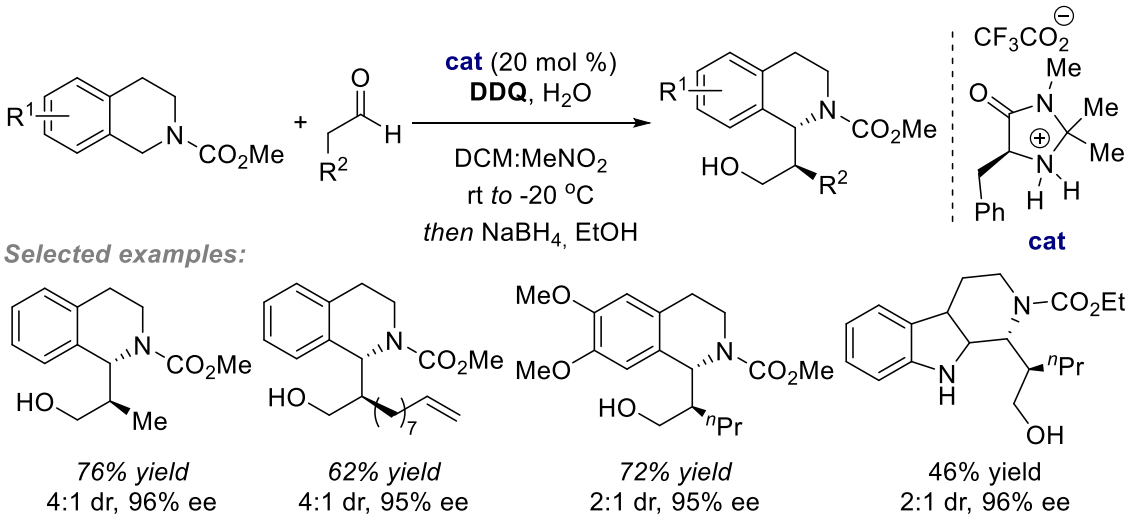
Although the enantioinduction is provided in all cases by a chiral catalyst, the oxidation step may occur through either a catalytic oxidation or a stoichiometric oxidation. In the first two examples, the amine is oxidized through the direct action of a stoichiometric oxidant.

In 2011, the research group of Wang reported an oxidative asymmetric Mannich reaction between *N*-aryl glycine esters and β-ketoesters using DDQ as stoichiometric oxidant.[134] In this case, the asymmetric induction came from a copper complex with a chiral oxazoline ligand. Here, the first step is the oxidation of the *N*-aryl glycine ester to the corresponding imine. Thereafter, the chiral Lewis acid induces the asymmetric addition of the enolate to the electrophilic C=N double bond (Scheme 2.2).



Scheme 2.2: Asymmetric oxidative Mannich reaction between *N*-aryl glycine esters and β-ketoesters using DDQ as oxidant (Wang).

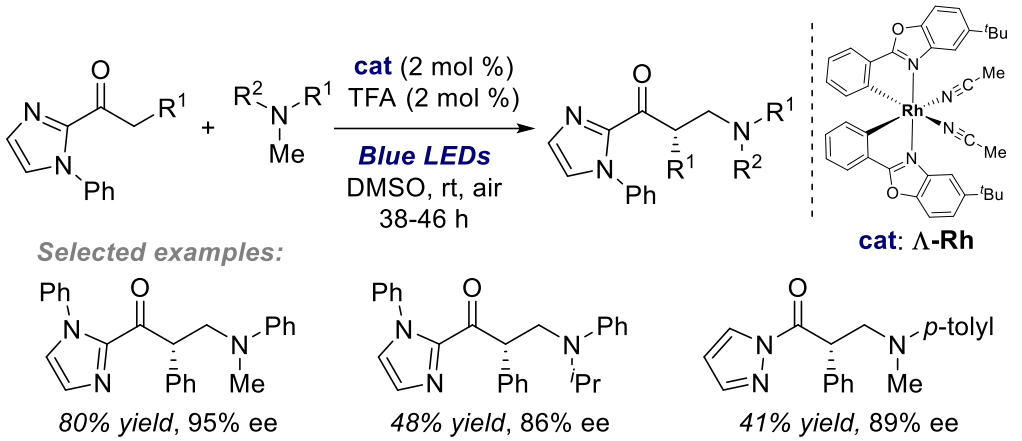
Rather than a secondary amine, in 2016 the group of Liu employed tetrahydroisoquinoline methyl carbamates as iminium ion precursors.[135] Again, DDQ served as direct stoichiometric oxidant to generate the corresponding iminium cation, which experimented a nucleophilic addition of the chiral enamine formed after a condensation between an aldehyde and the chiral imidazolidinone (also known as MacMillan organocatalyst). A final carbonyl reduction allowed an easier isolation and characterization of the Mannich products (Scheme 2.3).



Scheme 2.3: Enantioselective oxidative Mannich reaction between tetrahydroisoquinoline carbamates and aldehydes (Liu).

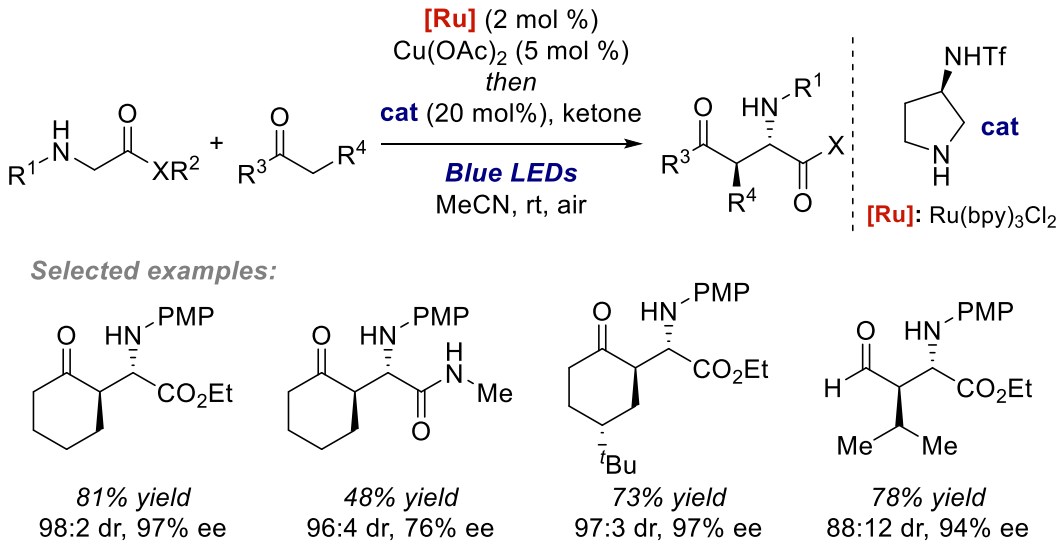
On the other hand, the last two examples rely on the catalytic oxidation of the amine,

specifically through photoredox catalysis, which is the central topic of this *thesis*. In 2015, Meggers' laboratory used a chiral-at-rhodium complex which developed themselves to facilitate an asymmetric oxidative Mannich reaction between acyl imidazoles and *N*,*N*-dialkylanilines.[136] In this case, the behaviour of the chiral Rh complex is dual, since it catalyzes the photoredox aerobic oxidation of the tertiary amine under the irradiation of blue LEDs, and it also acts as chiral Lewis acid to promote the enantioselective addition of the corresponding enolate to the iminium cation (Scheme 2.4).



Scheme 2.4: Enantioselective oxidative Mannich reaction acyl imidazoles and *N*,*N*-dialkylanilines (Meggers).

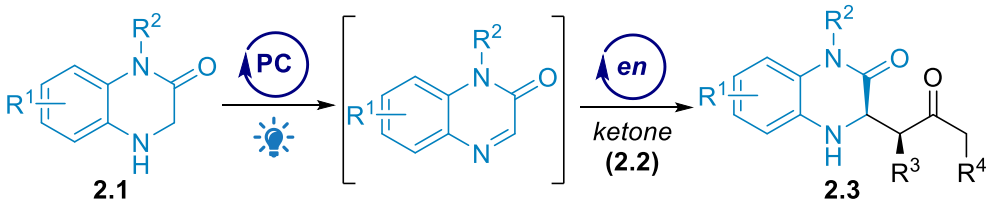
Finally, in 2020 Zhang and collaborators reported the asymmetric oxidative Mannich reaction between *N*-aryl glycine esters or amides and aldehydes or ketones.[137] In this case, the authors developed a dual catalytic system that consisted in the merged action of $Ru(bpy)_3Cl_2$ as photoredox catalyst and a chiral pyrrolidine as enamine-forming organocatalyst. Initially, the *N*-aryl glycine ester gets oxidized to the corresponding imine by the excited state of $Ru(bpy)_3Cl_2$, whose turnover was assured by molecular oxygen as terminal oxidant. Thereafter, the aldehyde or ketone reacts with the imine via a chiral enamine (Scheme 2.5). The role of Cu(II) in this transformation should be to stabilize the imine intermediate and increase its electrophilic character.



Scheme 2.5: Asymmetric Mannich reaction between *N*-aryl glycine esters or amides and aldehydes or ketones (Zhang).

2.2 Objectives

The main objective for this *chapter* is to develop a methodology to functionalize 3,4-dihydroquinoxalin-2-ones (**2.1**) with ketones (**2.2**), employing visible-light photoredox catalysis and organocatalysis. To achieve this objective, several partial objectives are postulated:



1. Synthesis of 3,4-dihydroquinoxalin-2-ones (**2.1**) bearing substituents with different electronic and steric properties.

2. Optimization of the reaction conditions between 3,4-dihydroquinoxalin-2-one **2.1a** and acetone (**2.2a**) to obtain the corresponding Mannich product **2.3aa** with the highest yield and the highest enantioselectivity.

3. Study of the scope of the reaction between different 3,4-dihydroquinoxalin-2-ones (**2.1**) and ketones (**2.2**).

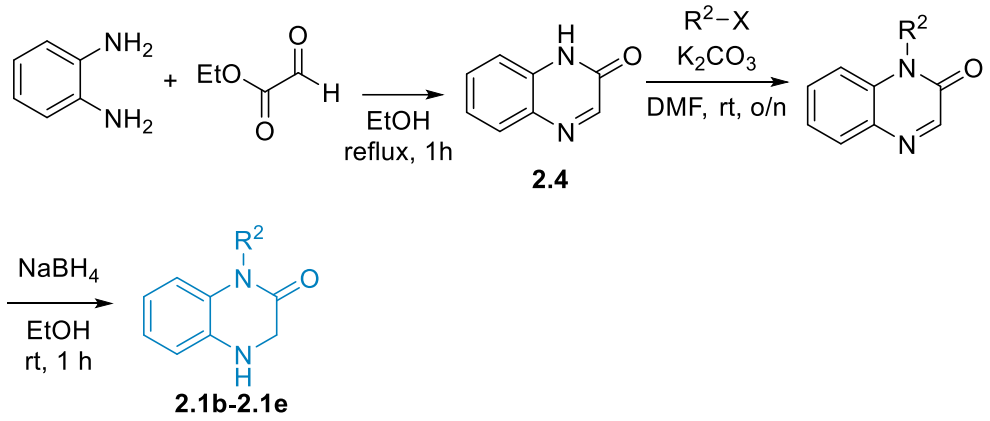
4. Synthetic transformations of the reaction products **2.3**..

5. Mechanistic investigations and proposal of a reaction mechanism.

2.3 Results and Discussion

2.3.1 Synthesis of 3,4-dihydroquinoxalin-2-ones 2.1

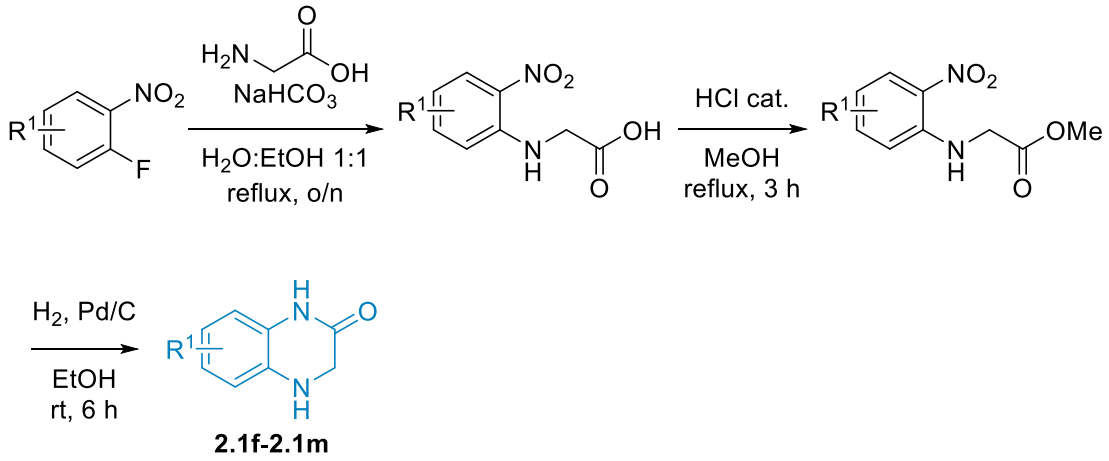
The synthesis of 3,4-dihydroquinoxalin-2-ones **2.1** was accomplished using different procedures depending on the substituents that they bear. 3,4-Dihydroquinoxalin-2-one **2.1a** was already prepared (see *Chapter 1*). 3,4-Dihydroquinoxalin-2-ones **2.1b**-**2.1e** were synthesized through a three-step procedure, in which the first step is the condensation/amidation of *o*-phenylenediamine with ethyl glyoxylate to yield quinoxalin-2-one **2.4**. Thereafter the N-1 amidic nitrogen is alkylated with the proper alkyl halide in the presence of K_2CO_3 as base. Finally, the N-1-alkylated quinoxalin-2-ones are treated with $NaBH_4$ in EtOH to access 3,4-dihydroquinoxalin-2-ones **2.1b**-**2.1e** (Scheme 2.6)



Scheme 2.6: Overview of the synthetic sequence to obtain 3,4-dihydroquinoxalin-2-ones **2.1b**-**2.1e**.

3,4-Dihydroquinoxalin-2-ones **2.1f**-**2.1m** were prepared following a three-step procedure from commercially available 2-fluoronitrobenzenes (Scheme 2.7). The first step involves a nucleophilic aromatic substitution between the activated fluorobenzene and glycine to generate the corresponding *o*-nitroanilines. Thereafter, the pendant carboxylic acid is methylated through a Fischer esterification reaction with methanol in the presence of a catalytic amount of hydrochloric acid. Finally, the treatment of the corresponding nitroesters with H_2 in the presence of Pd/C triggers the nitro group reduction and the subsequent spontaneous lactamization to yield the desired 3,4-dihydroquinoxalin-2-ones **2.1f**-**2.1m**.

Finally, 3,4-dihydroquinoxalin-2-ones **2.1n** and **2.1o** were prepared using the same procedure that the one followed for **2.1a** in *Chapter 1*. Figure 2.1 summarizes all the synthesized 3,4-dihydroquinoxalin-2-ones that will be used in this *Chapter*.



Scheme 2.7: Overview of the synthetic sequence to obtain 3,4-dihydroquinoxalin-2-ones **2.1f**-**2.1m**.

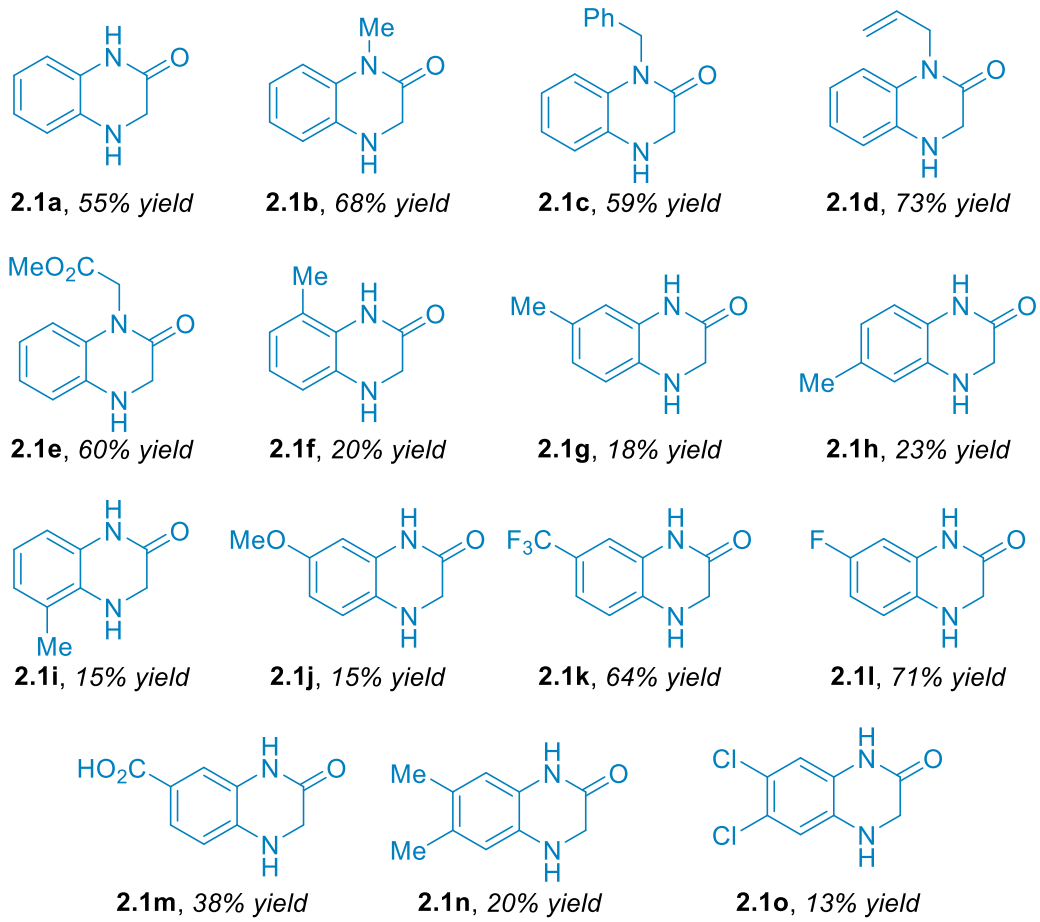
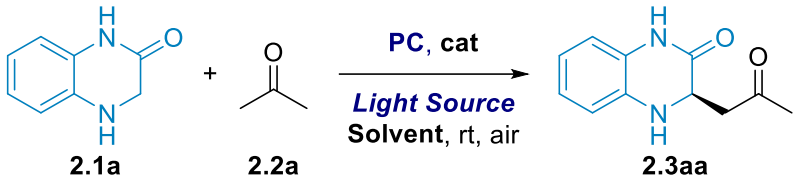


Figure 2.1: Summary of all 3,4-dihydroquinoxalin-2-ones **2.1a**-**2.1o** that were synthesized.

2.3.2 Optimization of the Reaction Conditions

In the aim of developing a protocol to C-3 functionalize 3,4-dihydroquinoxalin-2-ones **2.1** with ketones **2.2** in an enantioselective manner, the reaction between **2.1a** and **2.2a** to

form **2.3aa** was selected as model to perform the optimization process (Scheme 2.8).

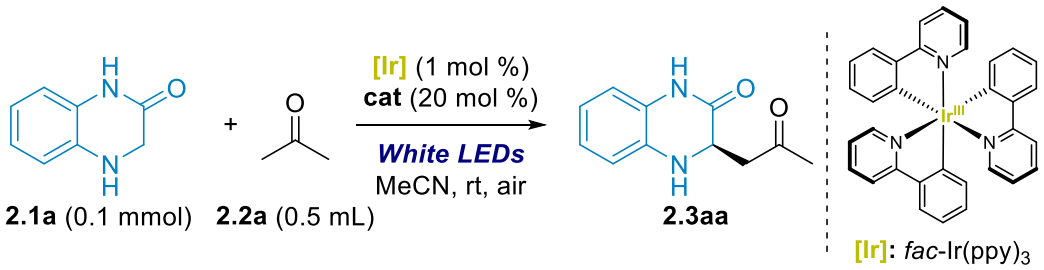


Scheme 2.8: Overview of the model reaction to carry out the optimization of the reaction conditions.

Among the parameters that will be adjusted to obtain product **2.3aa** in high yield and high enantioselectivity, the first one will be the chiral secondary amine that serves as organocatalyst. Thereafter, both the light source and the photoredox catalyst will be evaluated. Finally, the selection of the best solvent to run the reaction will be conducted.

Evaluation of the Organocatalyst

The secondary amine organocatalyst is responsible for the induction of the enantioselectivity of the reaction. Specifically, this kind of catalysts undergoes a condensation reaction with a ketone or aldehyde to form a chiral enamine, which reacts with the corresponding electrophilic C=N bond to yield the Mannich product. In this sense, proline has become one of the most studied and prevalent organocatalyst in this field. Moreover, proline-derived aminoalcohols (for example the Hayashi-Jørgensen catalyst) have shown promising activity in this kind of transformations. Hence, several chiral secondary amine organocatalysts will be engaged in the asymmetric oxidative Mannich reaction between **2.1a** and **2.2a**. To perform this study, $Ir(ppy)_3$ (**K**) was selected as potential photocatalyst, MeCN as solvent and white LEDs was light source (Scheme 2.9).

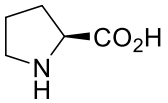
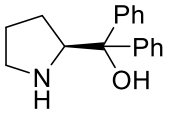
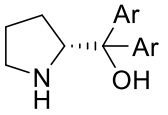
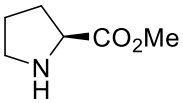
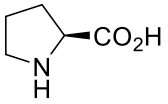
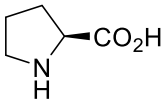


Scheme 2.9: Evaluation of the organocatalyst in the reaction between **2.1a** and **2.2a**. Reaction overview.

To our delight, when (*S*)-proline (**I**) and $Ir(ppy)_3$ (**K**) were combined, the corresponding product was obtained in 33% yield with complete enantioselectivity (99% ee) after 26

hours (Table 2.1, Entry 1). However, neither the chiral prolinol **II** nor the **III** (Hayashi-Jørgensen catalyst) were able to produce compound **2.3aa** (Table 2.1, Entries 2 and 3). Similarly, when (*S*)-proline methyl ester was used, the reaction proceeded in 20% yield and 98% ee but it required 80 hours (Table 2.1, Entry 4). Having determined that (*S*)-proline was the best organocatalyst in terms of both the yield and the enantiomeric excess, it was selected as the optimal catalyst. Finally, the reaction was repeated at 0.2 mmol scale, obtaining the same results (Table 2.1, Entry, 5).

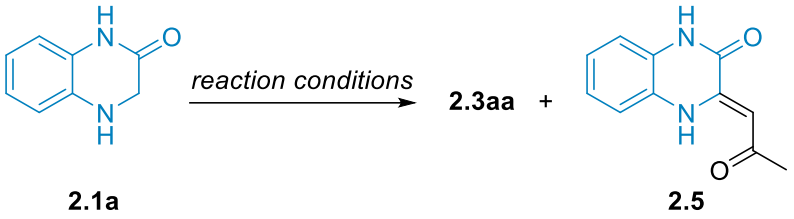
Table 2.1: Evaluation of the organocatalyst in the reaction between **2.1a** and **2.2a**.

Entry[a]	cat (20 mol %)		t (h)	Yield 2.3aa (%)[b]	ee (%)[c]
1		(**I**)	26	33	99
2		(**II**)	–	–	–
3	 Ar: 3,5-$(CF_3)_2C_6H_3$	(**III**)	–	–	–
4		(**IV**)	80	20	98
5[d]		(**I**)	75	34	99
6[de]		(**I**)	48 + 80	77	99

[a]Reaction conditions: **2.1a** (0.1 mmol), **2.2a** (0.5 mL), $Ir(ppy)_3$ (1 mol %), cat (20 mol %), MeCN (0.5 mL), under air atmosphere and under white LEDs irradiation.
[b]Yield determined after purification by column chromatography.
[c]Enantiomeric excess determined by chiral HPLC analysis.
[d]0.2 mmol of **2.1a**, 1 mL of **2.2a** and 1 mL of MeCN were used.
[e]Yield determined after purification by column chromatography using Et_3N-deactivated silica gel.

However, during the progress of this optimization we realized that, when the reaction was exposed to large periods under light irradiation, a sub-product appeared (Scheme 2.10). The structural entity of this compound was established by NMR techniques, and it was attributed to overoxidation of product **2.3aa**. In fact, after finishing this project, a methodology to prepare these oxidized products was reported by Li and Zhang.[138] To avoid the formation of **2.5**, we decided to perform the reaction in two one-pot steps. Initially, 3,4-dihydroquinoxalin-2-one **2.1a** was treated with $Ir(ppy)_3$ (**K**) under air and the irradiation

of white LEDs, and then the light source was disconnected and acetone (**2.2a**) and (*S*)-proline (**I**) were added. Using this strategy we could generate product **2.3aa** in 77% yield and 99% ee after 48 hours of oxidation (under irradiation) and 80 hours of Mannich reaction (Table 2.1, Entry 6).



Scheme 2.10: Secondary product formed during the reaction from **2.3aa** oxidation.

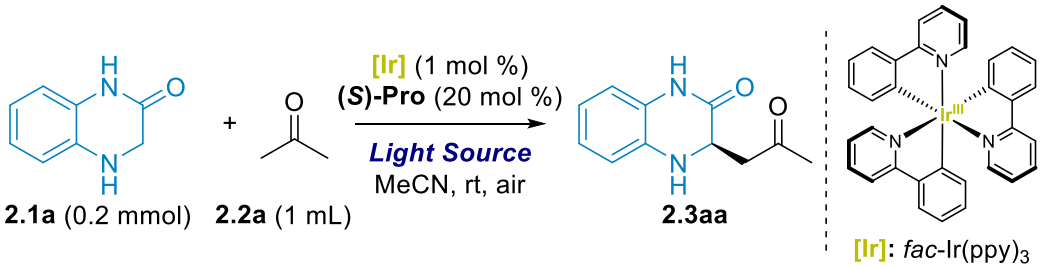
Indeed, during the purification of product **2.3aa** by column chromatography, partial formation of this byproduct **2.5** was observed. To avoid it, we decided to assay different purification conditions. In this sense, we tried to elute product **2.3aa** from the chromatographic column faster, but it lead to unsatisfactory separation and still to partial decomposition. Then we decided to diminish the acidity of the silica gel used as stationary phase. Specifically, we added 1% (v/v) of Et_3N to the mobile phase but, although we could prevent decomposition of **2.3aa** largely, it was not adequate enough for us. Finally, we prepared deactivated silica gel by suspending this stationary phase in DCM and adding Et_3N afterwards. Evaporation to dryness of this suspension generated again a fine powder. Pleasingly, the use of this stationary phase resulted in complete prevention of product **2.3aa** decomposition, as it was isolated in 77% yield (Table 2.1, Entry 6).

In light of these results, we decided to continue the optimization process using this one-pot procedure and Et_3N-deactivated silica gel for the purification.

Evaluation of the Light Source

The results shown in *Chapter 1* as well as in the optimization of the organocatalyst in this *Chapter* were conducted using white LEDs. Nevertheless, at this time other light sources become available in our laboratory, specifically a compact fluorescent light (CFL) and a blue LED strip, which was placed surrounding a crystallizing dish. As can be noted from *Chapter 1*, the power of the light source is relevant to the reaction rate. To test the effect of light source over the reaction success, we performed it using these new light sources (Scheme 2.11).

When the reaction was done under the irradiation of CFL, the time required for the oxidation of 3,4-dihydroquinoxalin-2-one **2.1a** decreased from 48 to 24 hours, albeit the yield od **2.3aa** dropped from 77 to 66% (Table 2.2, Entry 2). In the same line, when the



Scheme 2.11: Evaluation of the light source in the reaction between **2.1a** and **2.2a**. Reaction overview.

reaction was carried out using blue LEDs, product **2.3aa** was generated in 59% yield but the oxidation step only required 4 hours (Table 2.2, Entry 3). It is important to note that, as the light source only affects the oxidation step, the enantioselective addition of acetone to oxidized **2.1a** delivered product **2.3aa** in 99% ee in all cases.

Table 2.2: Evaluation of the light source in the reaction between **2.1a** and **2.2a**.

Entry[a]	Light Source	t_1 (h)	t_2 (h)	Yield 2.3aa (%)[b]	ee (%)[c]
1	White LEDs	48	80	77	99
2	CFL	24	79	66	99
3	Blue LEDs	4	68	59	99

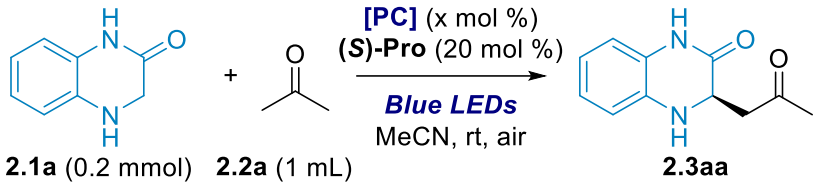
[a]Reaction conditions: **2.1a** (0.2 mmol), **2.2a** (1 mL), $Ir(ppy)_3$ (1 mol %), (*S*)-proline (20 mol %), MeCN (1 mL), under air atmosphere and under light source irradiation.
[b]Yield determined after purification by column chromatography.
[c]Enantiomeric excess determined by chiral HPLC analysis.

Hence, the use of blue LEDs was, from our point of view, beneficial for the reaction practicability so we decided to continue the optimization process using this source of light.

Evaluation of the Photoredox Catalyst

In this two-step procedure, the photoredox catalyst is the responsible of generating the electrophilic C=N bond from **2.1a**, in combination with molecular oxygen as terminal oxidant. Thus, the exhaustive determination of the best photocatalyst to perform this oxidation is crucial for the success of the optimization process (Scheme 2.12).

First of all, $Ru(bpy)_3Cl_2$ (**A**) was engaged in the asymmetric oxidative Mannich reaction as photoredox catalyst, yielding the desired product in 66% after 5.5 hours of oxidation (Table 2.3, Entry 2). In order to avoid the use of precious metals in catalysis,



Scheme 2.12: Evaluation of the photoredox catalyst in the reaction between **2.1a** and **2.2a**. Reaction overview.

we decided to test some organophotoredox catalysts, such as [Mes-Acr-Me][BF_4] (**H**), Rose Bengal (**D**), 9,10-phenanthrenequinone (**J**) and Eosin-Y-Na_2 (**E**). Pleasingly, when acridinium **H** was used, product **2.3aa** could be isolated in 82% yield after 8.5 hours of irradiation (Table 2.3, Entry 3). However, a drop in the enantiomeric excess was observed (from 99 to 97% ee). On the other hand, Eosin-Y-Na_2 (**E**) also exhibited a good performance in promoting the oxidation of **2.1a** in 9 hours, isolating the desired product in 63% yield and 99% ee (Table 2.3, Entry 6).

Table 2.3: Evaluation of the photoredox catalyst in the reaction between **2.1a** and **2.2a**.

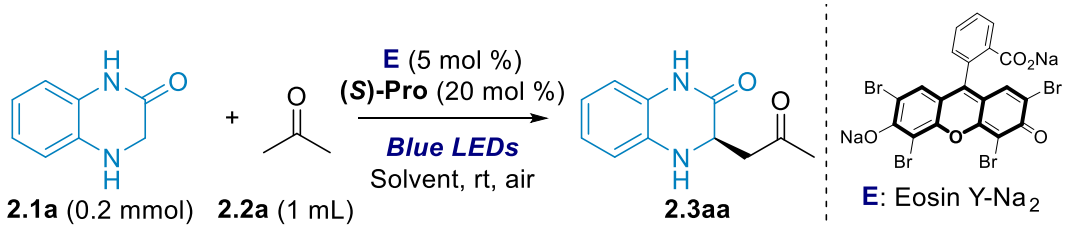
Entry[a]	**PC (x mol %)**	**t_1 (h)**	**t_2 (h)**	**Yield (%)**[b]	**ee (%)**[c]
1	$Ir(ppy)_3$ (**K**) (1)	4	68	59	99
2	$Ru(bpy)_3Cl_2$ (**A**) (1)	5.5	70	66	99
3	[Mes-Acr-Me][BF_4] (**H**) (5)	8.5	70	82	97
4	Rose Bengal (**D**) (5)	16	74	22	99
5	9,10-Phenanthrenequinone (**J**) (10)	180	72	65	93
6	Eosin-Y-Na_2 (**E**) (5)	9	86	63	98

[a]Reaction conditions: **2.1a** (0.2 mmol), **2.2a** (1 mL), **PC** (x mol %), (*S*)-proline (20 mol %), MeCN (1 mL), under air atmosphere and under blue LEDs irradiation.
[b]Yield determined after purification by column chromatography.
[c]Enantiomeric excess determined by chiral HPLC analysis.

Thus, with the intention to develop a more cost-effective process, we decided at this point to select Eosin-Y-Na_2 (**E**) as the optimal photoredox catalyst to continue the optimization process.

Evaluation of the Solvent

Although MeCN is widely employed in photoredox catalysis, we decided to check the performance of other solvents in our asymmetric oxidative Mannich reaction (Scheme 2.13).



Scheme 2.13: Evaluation of the solvent in the reaction between **2.1a** and **2.2a**. Reaction overview.

When DMF was employed as solvent, we could reduce the oxidation time (t_1) from 9 to 8 hours, as well as the time for the Mannich reaction (t_2) from 68 to 46 hours, obtaining product **2.3aa** in 75% yield and 99% ee (Table 2.4, Entry 2). Following this result, we decided to try another polar aprotic solvent such as DMSO, but in this case the expected product was obtained in 63% yield and 84% ee, even requiring longer reaction times (Table 2.4, Entry 3). Thereafter, toluene was tested as solvent, but the low solubility of Eosin-Y-Na_2 (**E**) in that solvent hampered the success of the reaction because 78 hours were required for **2.1a** oxidation (Table 2.4, Entry 4). Finally, the reaction was tried with $CHCl_3$ and, although the product was obtained in 86% yield, the oxidation step took 78 hours to happen (Table 2.4, Entry 5).

Table 2.4: Evaluation of the solvent in the reaction between **2.1a** and **2.2a**.

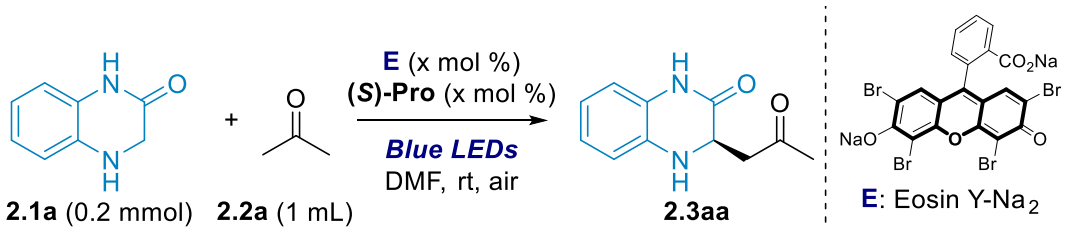
Entry[a]	Solvent	t_1 (h)	t_2 (h)	Yield (%)[b]	ee (%)[c]
1	MeCN	9	68	63	98
2	DMF	8	46	75	98
3	DMSO	9	86	63	84
4	Toluene	78	72	33	92
5	$CHCl_3$	78	72	86	98

[a]Reaction conditions: **2.1a** (0.2 mmol), **2.2a** (1 mL), **E** (5 mol %), (*S*)-proline (20 mol %), solvent (1 mL), under air atmosphere and under blue LEDs irradiation.
[b]Yield determined after purification by column chromatography.
[c]Enantiomeric excess determined by chiral HPLC analysis.

After realizing that using DMF as solvent the reaction offered its best performance from a balanced point of view (reaction times, yield and ee), it was selected as the optimal solvent. However, it is important to note that the use of DMF as solvent requires a later work-up to remove it, but even in this case we thought that it was worth it.

Evalutation of the Catalytic Loadings and other Adjustments

The last stage in the optimization process was to adjust the catalytic loading of both Eosin-Y-Na_2 (**E**) and (*S*)-proline (**I**) (Scheme 2.14).



Scheme 2.14: Evaluation of the catalytic loading in the reaction between **2.1a** and **2.2a**. Reaction overview.

Pleasingly, when the catalytic loading of Eosin-Y-Na_2 (**E**) was decreased from 5 to 2 mol %, the results in which **2.3aa** were obtained did not change, and surprisingly the Mannich reaction was completed in just 21 hours (Table 2.5, Entry 2). Nevertheless, if the catalyst loading of (*S*)-proline was reduced until 10 mol % the rate of the Mannich reaction decreased, and 81 hours were needed to complete it (Table 2.5, Entry 3).

Moreover, to identify reaction conditions for the use of more sophisticated ketones **2.2** rather than acetone, the asymmetric oxidative Mannich reaction was performed using just 10 equivalents of acetone (**2.2a**), obtaining the corresponding product in 82% yield and 96% ee after an increased reaction time of 65 hours (Table 2.5, Entry 4). Although, the reaction proceeded much slower, here it has been proved that the use of more expensive ketones is, at least, possible.

To conclude the optimization process we tested the reaction using green LEDs, which became available at this point in our laboratory. However, although the maximum of absorption of Eosin-Y-Na_2 (**E**) is in the range of green light, compound **2.1a** lasts 73 hours to be oxidized (and not completely) and thus product **2.3aa** was only obtained in 38% yield (Table 2.5, Entry 5). This surprising result may arise from the less power of these green LEDs, compared to that of blue LEDs.

2.3.3 Scope of the Reaction

With the optimal conditions in hand (Table 2.5, Entry 2), the next step was to establish the generality of the asymmetric oxidative Mannich reaction between 3,4-dihydroquinoxalin-2-ones (**2.1**) and ketones (**2.2**). For this purpose, the differently substituted 3,4-dihydroquinoxalin-2-ones (**2.1**) that were previously prepared (Figure 2.1) as well as several commercial ketones (**2.2**) were subjected to the optimal reaction conditions.

Table 2.5: Evaluation of the catalytic loading and other adjustments in the reaction between **2.1a** and **2.2a**.

Entry[a]	E (x mol %)	(*S*)-Pro (x mol %)	t_1 (h)	t_2 (h)	Yield (%)[b]	ee (%)[c]
1	5	20	8	46	75	98
2	2	20	6.5	21	74	99
3	2	10	9,5	81	78	98
4[d]	2	20	6.5	65	82	96
5[e]	2	20	73	23	38	98

[a]Reaction conditions: **2.1a** (0.2 mmol), **2.2a** (1 mL), **E** (x mol %), (*S*)-proline (x mol %), DMF (1 mL), under air atmosphere and blue LEDs irradiation.
[b]Yield determined after purification by column chromatography.
[c]Enantiomeric excess determined by chiral HPLC analysis.
[d]10 equiv. of **2.2a** were used.
[e]Green LEDs were used.

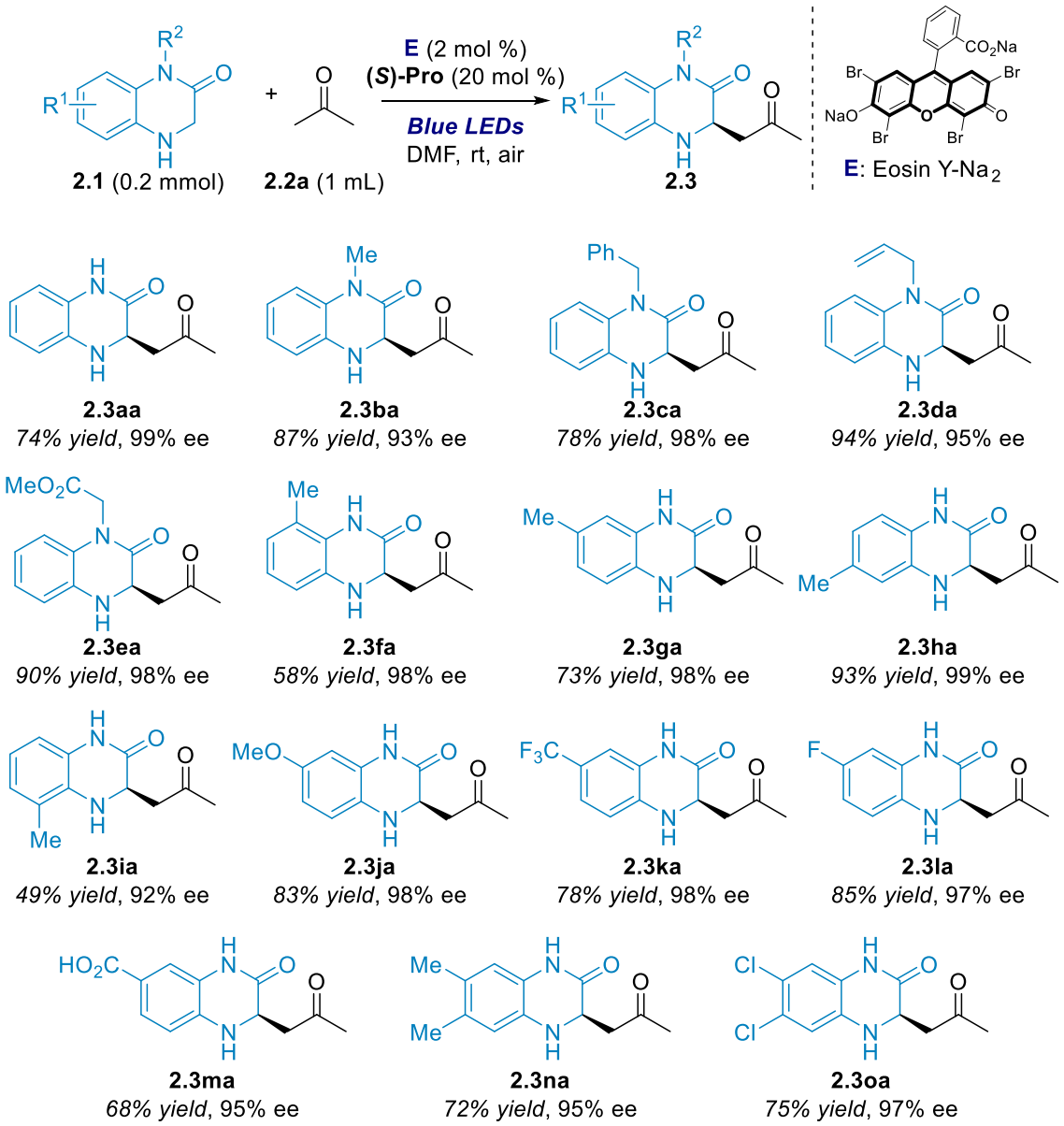
Specifically, these optimal reaction conditions involve the use of 0.2 mmol of **2.1** and a 2 mol % of Eosin-Y-Na_2 (**E**) to obtain the corresponding imine intermediate upon oxidation with molecular oxygen, under the irradiation of blue LEDs. Thereafter, the electrophilic C=N double bond reacts with 1 mL of acetone (or 10 equiv. of a given ketone **2.2**) in the presence of (*S*)-proline to deliver the corresponding Mannich product **2.3**.

Scope of the Reaction with 3,4-dihydroquinoxalin-2-ones 2.1

In this *Section*, the effect of several substitution patterns over the system of 3,4-dihydroquinoxalin-2-one (**2.1**) in its competence as electrophile in the asymmetric oxidative Mannich reaction will be studied (Scheme 2.15).

First of all, the substitution on the amidic nitrogen (N-1) will be interrogated by using 3,4-dihydroquinoxalin-2-ones **2.1a**-**2.1e**. When a methyl substituent was placed at N-1, the corresponding product **2.3ba** was obtained in 87% yield but with a lower enantiomeric excess of 93% ee. However, when a benzyl or a CH_2CO_2Me functionality is set in the same position, the corresponding products (**2.3ca** and **2.3ea**) were generated in high yield without any erosion in the enantioselectivity. In fact, the presence of an additional methylene group in α position of the activating group (benzyl, CH_2CO_2Me) and a nitrogen atom could have generated regioselective issues in the photoredox oxidation, but in our case the oxidation only took place through the secondary amine. Besides, the reaction tolerates the presence of an allyl group also at N-1, as product **2.3da** is delivered

in excellent yield but with slightly lower enantiomeric excess. It is important to note here that alkenes can act as radical acceptors and, since the oxidation mechanism is thought to involve radical intermediates, the survival of the allyl moiety is notable.



Scheme 2.15: Scope of the reaction using different 3,4-dihydroquinoxalin-2-ones **2.1** and acetone (**2.2a**)[a].

[a]Reaction conditions: **2.1** (0.2 mmol), **2.2a** (1 mL), **E** (2 mol %), (*S*)-proline (20 mol %), DMF (1 mL), under air atmosphere and blue LEDs irradiation.

Next, the effect of either electron-donating or electron-withdrawing groups in the parent aromatic ring of 3,4-dihydroquinoxalin-2-one was subjected to consideration. First of all, the consequence of a methyl group in each position of the parent aromatic ring of

3,4-dihydroquinoxalin-2-one was studied. In fact, when a methyl is placed in either C-6 or C-7 (**2.1g** and **2.1h**) the expected products **2.3ga** and **2.3ha** were generated in high to excellent yields (73 and 93%) and excellent enantioselectivities (98 and 99% ee). However, the substitution at C-5 and C-8 positions considerably affected the performance of the reaction, since products **2.3fa** and **2.3ia** were obtained in moderate yields (58 and 49%) and with a slightly decrease in the enantioselectivity for **2.3ia** (92% ee), probably due to the proximity of that substituent to the reactive center.

The substitution at C-7 was further examined by using 3,4-dihydroquinoxalin-2-ones bearing either electron-donating or electron-withdrawing groups at that position. On one hand, an $-$OMe functionality was efficiently tolerated, obtaining the corresponding product **2.3ja** in 83% yield and 98% ee. On the other hand, 3,4-dihydroquinoxalin-2-ones that are substituted with $-CF_3$, $-$F or $-CO_2H$ groups at C-7 were conveniently converted into the desired products **2.3ka**, **2.3la** and **2.3ma** in high yields and with excellent enantioinduction. It is important to point out that product **2.3ma** required an extra treatment with trimethylsilyldiazomethane ($TMSCHN_2$) to transform it into the corresponding methyl ester in order to facilitate the determination of its enantiomeric excess by HPLC.

Finally, 6,7-disubstituted-3,4-dihydroquinoxalin-2-ones bearing either methyl groups (**2.1n**) or chlorine atoms (**2.1o**) were employed as pre-electrophiles in this asymmetric oxidative Mannich reaction, showing in both cases a good performance in terms of yield (72 and 75%) and excellent in terms of enantioselectivity (**2.3na** and **2.3oa**).

Scope of the Reaction with ketones 2.2

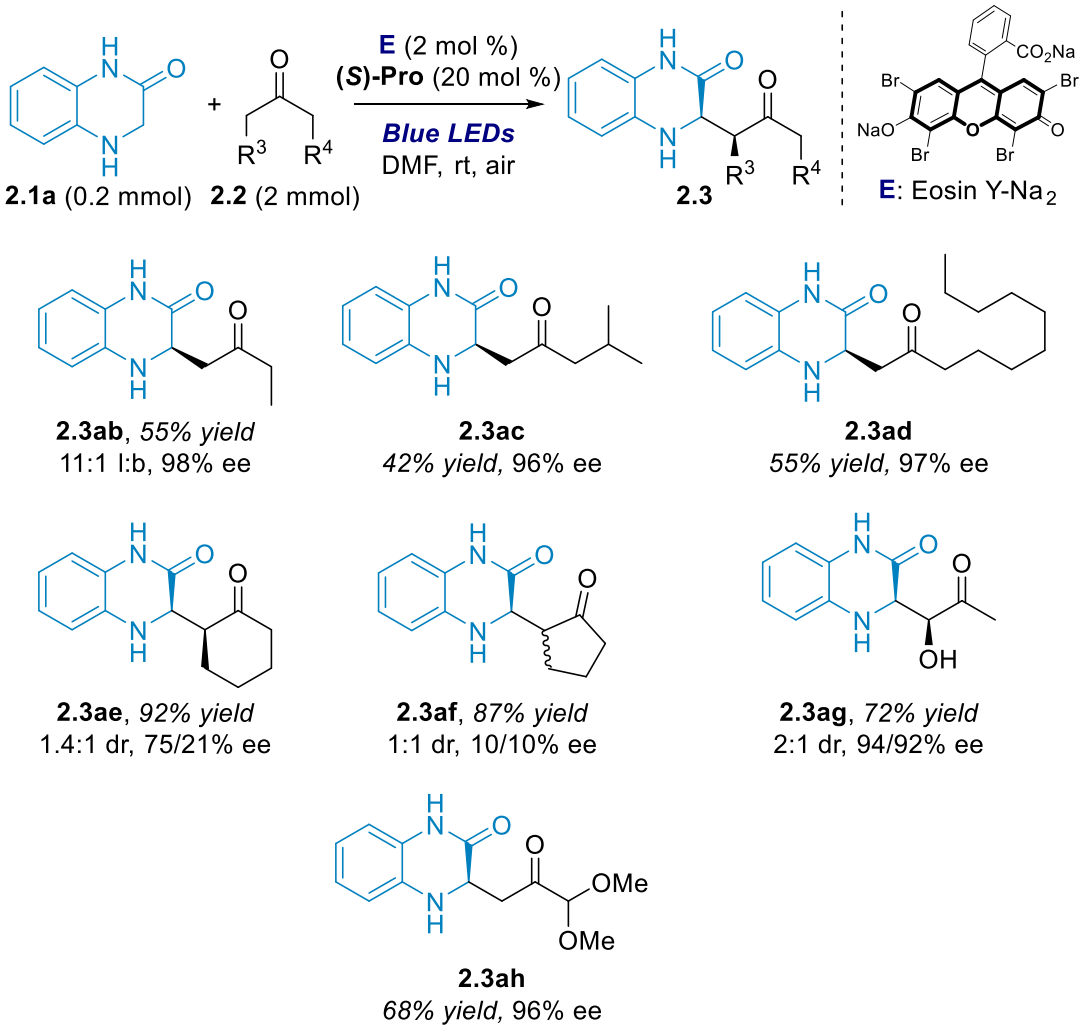
Additionally, the robustness of our catalytic protocol was subjected to other ketones rather than acetone (**2.2a**). In general terms, the operability of our methodology to accommodate more complex ketones was found to be worse, in comparison with 3,4-dihydroquinoxalin-2-ones, but some interesting results were obtained.

Methyl ethyl ketone (**2.2b**) provided product **2.3ab** in moderate yield (55%) but in excellent enantiomeric excess (98% ee), also showing an exquisite regioselectivity towards the less substituted carbon atom (linear:branched 11:1). With the increase of the aliphatic carbon chain, the results were similar. Indeed, when isobutyl methyl ketone was used, product **2.3ac** was obtained in 42% yield and 96% ee as a single regioisomer. In the same vain, 2-undecanone (**2.2d**) was also accommodated, obtaining the expected product **2.3ad** in 55% yield and 97% ee.

At this point, we decided to extend the scope to cyclic ketones. When cyclohexanone (**2.1e**) was tested as nucleophile, the corresponding product **2.3ae** was obtained in excellent yield, but with low diastereoselectivity and enantioselectivity. Unfortunately, when cyclopentenone (**2.2f**) was used, the corresponding product (**2.3af**) was again obtained in

high yield but with no diastereo discrimination and nearly as a racemic mixture. Additionally, when cycloheptanone was employed, the reacction resulted very slow, with almost no product formation after seven days.

Additionally, pyruvic aldehyde dimethyl acetal (**2.1h**) reacted smoothly with oxidized **2.1a** to give the corresponding product **2.3ah** in 68% yield and 96% ee.



Scheme 2.16: Scope of the reaction using 3,4-dihydroquinoxalin-2-one **2.1a** and different ketones (**2.2**)[a].

[a]Reaction conditions: **2.1a** (0.2 mmol), **2.2** (2 mmol), **E** (2 mol %), (*S*)-proline (20 mol %), DMF (1 mL), under air atmosphere and blue LEDs irradiation.

Besides, when hydroxyacetone (**2.2g**) was subjected to the asymmetric oxidative Mannich reaction, product **2.3ag** was obtained in 72% yield, 2:1 dr and 94% and 92% ee for the major and the minor diastereomer respectively. Interestingly, in this case only the branched isomer was formed, in contrast to when other methyl ketones were used. The preferential branched product, as well as the relative stereochemistry between the two

chiral centers, can be explained with theoretical models Figure 2.2. First of all, the exclusive formation of the branched product is illustrated by the preferential formation of the corresponding (*E*)-enamine between (*S*)-proline and hydroxyacetone (**2.2g**). (*Z*)-enamine is less favoured due to steric hindrance, and the least substituted one is excluded in favour of the most substituted for orbitalic reasons, as has been proved computationally.[139,140] Hence, in the chair-like Zimmerman-Traxler transition state that is widely accepted for these processes, OH is placed in an equatorial position. However, due to the *cis* stereochemistry of the imine, the group A has to be axial, whereas B has to be equatorial. According to these theoretical models, this transition state should be the one with lowest energy and thus, the one that is responsible for the preferential formation of the major diastereomer of product **2.3ag**. On the other hand, the not-negligible formation of the other diastereomer may arise from the more energetic boat-like transition state.[141]

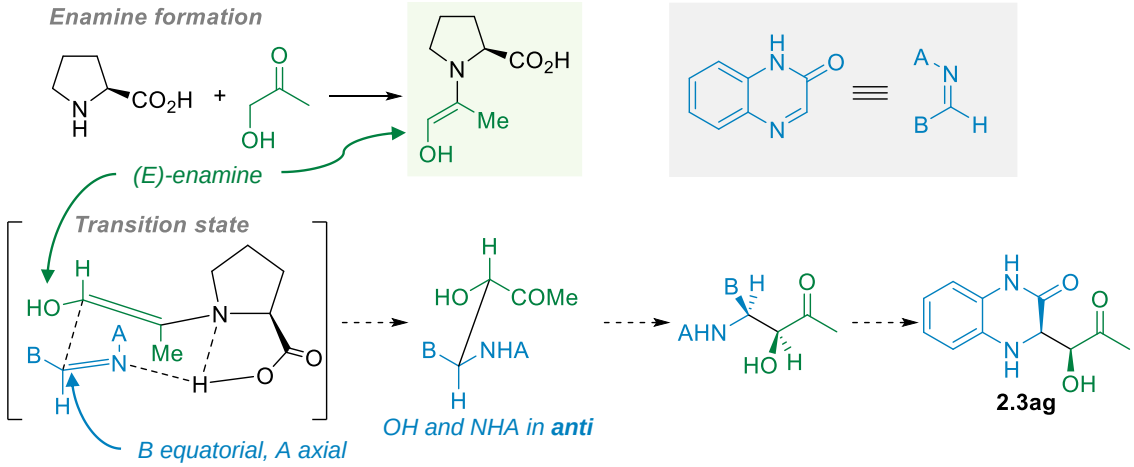
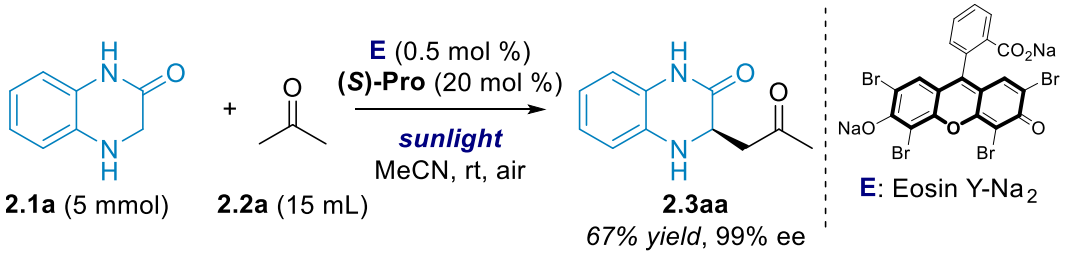


Figure 2.2: Stereochemical model to explain the relative stereochemistry in product **2.3ag**.

2.3.4 Gram-Scale Reaction and Synthetic Transformations

Having studied the scope of the asymmetric oxidative Mannich reaction, we decided to scale-up the process to 5 mmol scale, also switching blue LEDs for sunlight in the first oxidation step (Scheme 2.17). To our delight, the oxidation of **2.1a** took place in 6 hours and, after the Mannich reaction with **2.2a** in the presence of (*S*)-proline, 689 mg of product **2.3aa** (67% yield) in 99% ee were obtained. In this case, the reaction could take place using just 0.5 mol % of photocatalyst **E**.

Afterwards, we thought to perform several synthetic modifications over product **2.3aa**. During the course of these derivatizations, we realized that compound **2.3aa** was quite unstable under certain reaction conditions, leading to the formation of oxidized product **2.5** (Scheme 2.10). Hence, the potential diversification of the ketone functional group was

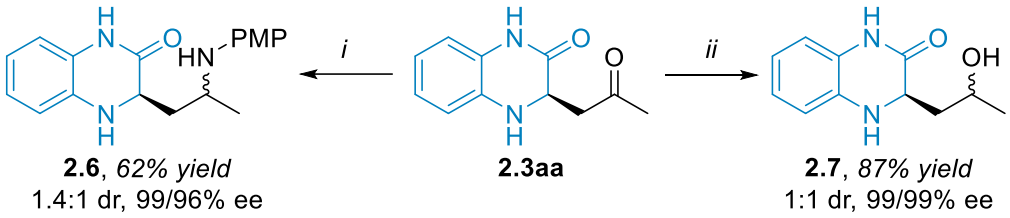


Scheme 2.17: Gram-scale reaction using 3,4-dihydroquinoxalin-2-one **2.1a**, acetone (**2.2a**) and sunlight as energy source[a].

[a]Reaction conditions: **2.1a** (5 mmol), **2.2a** (15 mL), **E** (0.5 mol %), (*S*)-proline (20 mol %), DMF (15 mL), under air atmosphere and sunlight irradiation.

partially masked by this drawback. Nevertheless, we could engage compound **2.3aa** in a reductive amination reaction with *p*-anisidine in the presence of $NaBH(OAc)_3$ to form compound **2.6** in 62% yield, 1.4:1 dr and 99 and 96% ee for the major and the minor diastereomer respectively (Scheme 2.18, *left*).

Additionally, we decided to reduce the ketone moiety in **2.3aa** diastereoselectively. To do so, we conducted the desired reaction at -78 °C using Luche reduction conditions but, unfortunately, that lead to the formation of the corresponding aminoalcohol **2.7** in 1:1 dr. For practicality, we finally did the reduction using standard conditions with $NaBH_4$ at 0 °C, obtaining the desired product **2.7** in 87% yield, 1:1 dr and 99 and 99% ee for the major and the minor diastereomer respectively (Scheme 2.18, *right*).



Scheme 2.18: Synthetic transformations over product **2.3aa**[a].

[a]Reaction conditions: *i*) **2.3aa** (0.15 mmol), AcOH (0.3 mmol,) *p*-anisidine (0.225 mmol), $NaBH(OAc)_3$ (0.3 mmol), DCM (1.5 mL), from 0 °C to rt for 48 h; *ii*) **2.3aa** (0.15 mmol), $NaBH_4$ (0.3 mmol), MeOH (1.5 mL), at 0 °C for 1 h.

2.3.5 Mechanistic Investigations

After all the synthetic part of the work, we wanted to find out the mechanism behind our transformation. Since our reaction involves two independent steps, they will be treated separately.

Photochemical Oxidation of 3,4-dihydroquinoxalin-2-ones

The first step of our protocol is the oxidation of a C−N to a C=N bond. This step is necessary because it provides the electrophilic imine that will react enantioselectively with the proper ketone **2.2**. As discussed earlier, this oxidation is achieved using Eosin-Y-Na_2 (**E**) in the presence of molecular oxygen and under the irradiation of blue LEDs. Therefore, the aim of this section is to prove the necessity of each reaction parameter for an efficient outcome.

First of all, the canonical control experiments for a given photochemical reaction were done (Table 2.6). Initially, the photochemical oxidation of **2.1a** was conducted in the dark and, after 24 hours, just a trace amount of oxidized **2.4** was detected, showing that the action of blue LEDs is necessary (Table 2.6, Entry 2). Then, the need to use Eosin-Y-Na_2 (**E**) as photocatalyst is investigated. In fact, when the oxidation was done without Eosin-Y-Na_2 (**E**), the conversion of amine **2.1a** to the expected imine **2.4** was as high as 83%, but it required 102 hours (Table 2.6, Entry 3). This observation implies that there is an operative photocatalytic cycle in the oxidation of **2.1a** to **2.4**, but in the absence of photocatalyst this reaction may take place, presumably thorough direct excitation of amine **2.1a**. On the other hand, the existence of radical intermediates in the reaction mechanism was proved by using TEMPO, as the oxidation reaction did not proceed in the presence of this radical scavenger (Table 2.6, Entry 4). Finally, the need of molecular oxygen as terminal oxidant was demonstrated using an argon atmosphere. In this case, after 24 hours of irradiation, the corresponding imine **2.4** was only detected in trace amount by ^{1}H-NMR (Table 2.6, Entry 5). Additionally, H_2O_2 has been detected in the reaction media using the iodine-starch test. This finding confirms the implication of O_2 in the oxidation process, as H_2O_2 is the product of O_2 reduction.

Table 2.6: Control reactions in the photochemical oxidation of **2.1a**.

Entry[a]	Deviation	Conversion to 2.4 (%)[b]
1	*none*	90
2	darkness	trace
3	without **J**	83% after 102 h
4	with TEMPO (1.5 equiv.)	no conversion
5	Ar atmosphere	trace

[a]Reaction conditions: **2.1a** (0.2 mmol), **E** (2 mol %), DMF (1 mL), under air atmosphere and blue LEDs irradiation. Note deviations for each case. Reaction time: 24 h

[b]Conversion of compound **2.2a** to product **2.4** determined by ^{1}H-NMR.

Moreover, to prove the interaction between the excited state of Eosin-Y-Na_2 (**E**) and the 3,4-dihydroquinoxalin-2-one **2.1a**, we performed Stern-Volmer luminescence quenching experiments. For this purpose, an array of five solutions containing 0.1 mM of Eosin-Y-Na_2 (**E**) and increasing amounts of **2.1a** (from 0 to 20 mM) were prepared. Thereafter, the emission spectrum of each solution was recorded, having set 400 nm as excitation wavelength. The luminescence intensity was collected at its maximum (566 nm) (Table 2.7).

Table 2.7: Concentration of **2.1a** and Eosin-Y-Na_2 (**E**) in each solution, and their luminescence intensity at 566 nm.

Solution	**2.1a (mM)**	**E (mM)**	I	I^0/I
1	0	0.1	537.3	1
2	5	0.1	376.2	1.428
3	10	0.1	293.9	1.828
4	15	0.1	239.8	2.241
5	20	0.1	208.8	2.573

In consistence with a *quenching* process, the higher the concentration of **2.1a**, the lower the luminescence intensity of Eosin-Y-Na_2 (**E**) (Figure 2.3). According to the Stern-

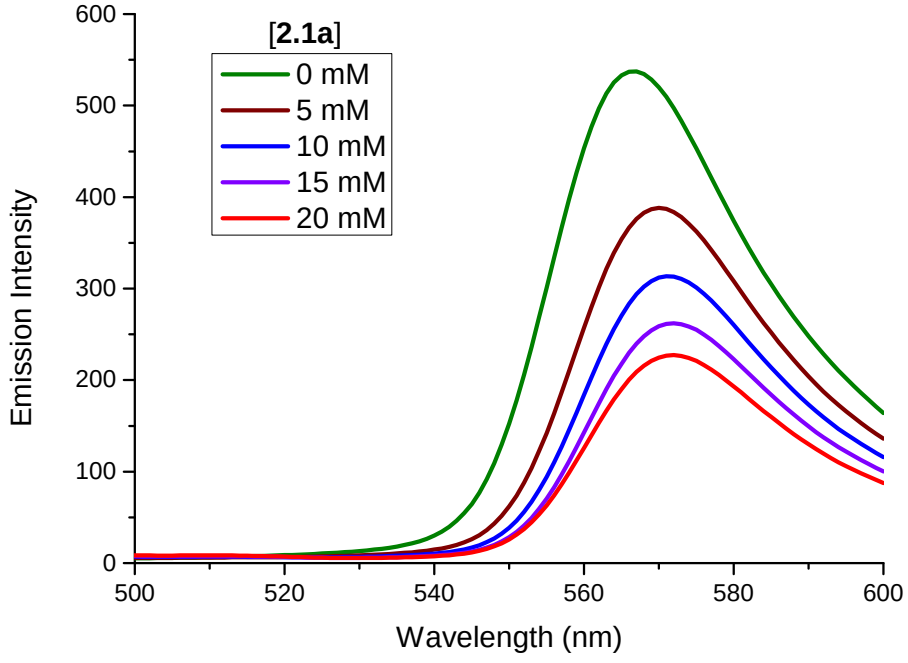


Figure 2.3: Superimposed emission spectra for each solution of Table 2.7.

Volmer relationship shown in Equation (11) (page 12), the quotient I^0/I, where I^0/I is the emission intensity of the solution without **8.1a** and I is the emission intensity of each solution, has to be directly proportional to the concentration of the quencher (**2.1a** in this case). Hence, from the plot of I^0/I versus the concentration of **2.1a**, it is possible to extract the Stern-Volmer constant (K_{SV}) for the photocatalytic process (Figure 2.4). In this case, K_{SV} has a value of 79 M^{-1}.

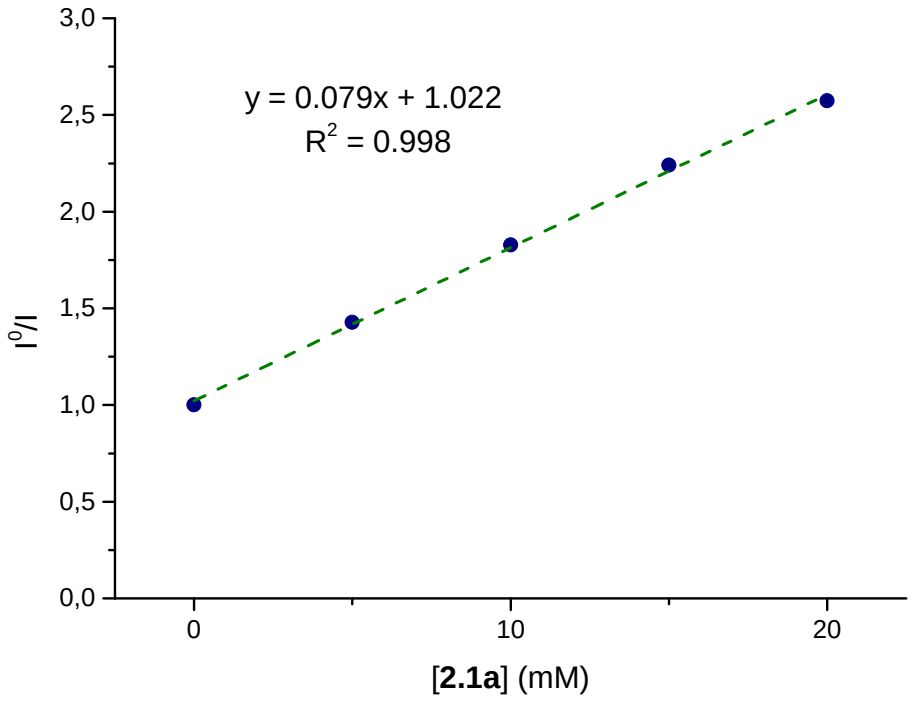


Figure 2.4: Stern-Volmer plot of I^0/I vs [**2.2a**]. Determination of K_{SV} through linear regression.

To sum up, after these experiments it has been proved that the photocatalytic oxidation requires light irradiation, the presence of Eosin-Y-Na_2 (**E**) as photocatalyst and the use of an oxygen atmosphere. Moreover, through Stern-Volmer analysis, the interaction between the excited state of Eosin-Y-Na_2 (**E**) and 3,4-dihydroquinoxalin-2-one **2.1a** has been demonstrated.

Asymmetric Mannich Reaction

The stereochemical course of the proline-catalyzed enantioselective aldol reaction has been widely studied, and it is strongly established.[142] Moreover, the Mannich reaction, as a particular case of the aldol reaction, is equally well-founded.[143]

Thus, according to the stereochemical model, the enamine formed through a condensation reaction between (*S*)-proline and acetone (**2.2a**) forms a chair-like transition state with the imine **2.4**. Due to the cis configuration of the imine **2.4**, group B has to be

equatorial and A has to be axial. The attack of the chiral enamine to the *Re* face of the imine generates product **2.3aa** with a absolute *R* configuration of its stereogenic center (Figure 2.5).

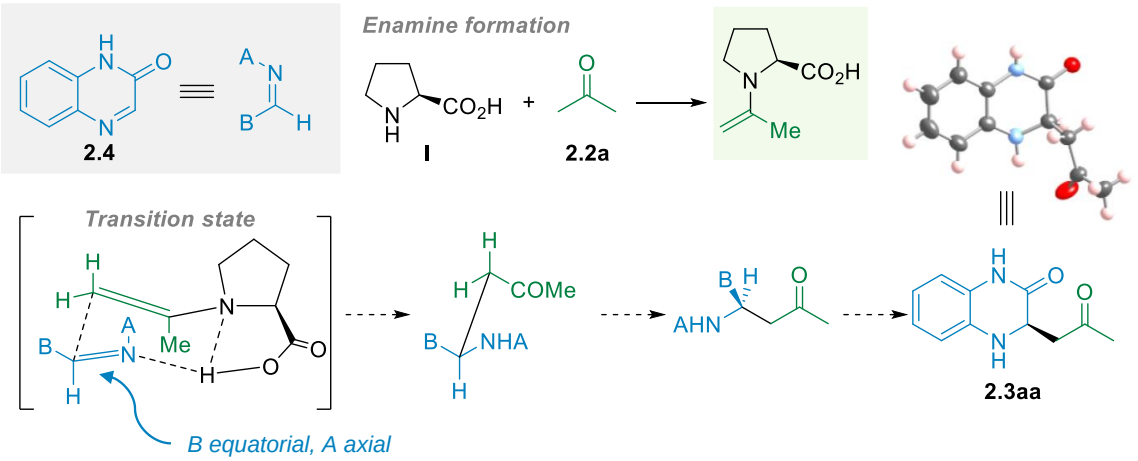


Figure 2.5: Stereochemical model for the enantioselective Mannich reaction between imine **2.4** and acetone (**2.2a**).

Additionally, by means of X-Ray single-crystal diffraction the absolute configuration od product **2.3aa** has been confirmed as *R*. In addition, the configuration of all the asymmetric oxidative Mannich products **2.3** has been established by correlation as *R*.

Proposed Mechanism

With all this information in hand, we were able to postulate a mechanism by which our two-step asymmetric oxidative Mannich reaction may proceed (Figure 2.6).

Upon excitation of Eosin-Y-Na_2 (**E**) by blue LEDs, a SET event between **E*** and 3,4-dihydroquinoxalin-2-one **2.1a** occurs. This process leads to the formation of radical cation **2.I** and the reduced form of the photocatalyst $\mathbf{E}^{-\bullet}$. Thereafter, $\mathbf{E}^{-\bullet}$ gets reoxidized by O_2 to its initial form **E** through another SET, along with the formation of superoxide radical anion $O_2^{-\bullet}$.

This last reactive oxygen specie triggers a HAT with radical cation **2.I** to generate protonated quinoxalin-2-one **2.II** and the hydroperoxide anion, that after deprotonation of **2.II** forms H_2O_2. Finally, quinoxalin-2-one **2.4** reacts in an enantioselective manner with the chiral enamine formed after the condensation of acetone (**2.2a**) and (*S*)-proline to yield enantioenriched product **2.3aa**.

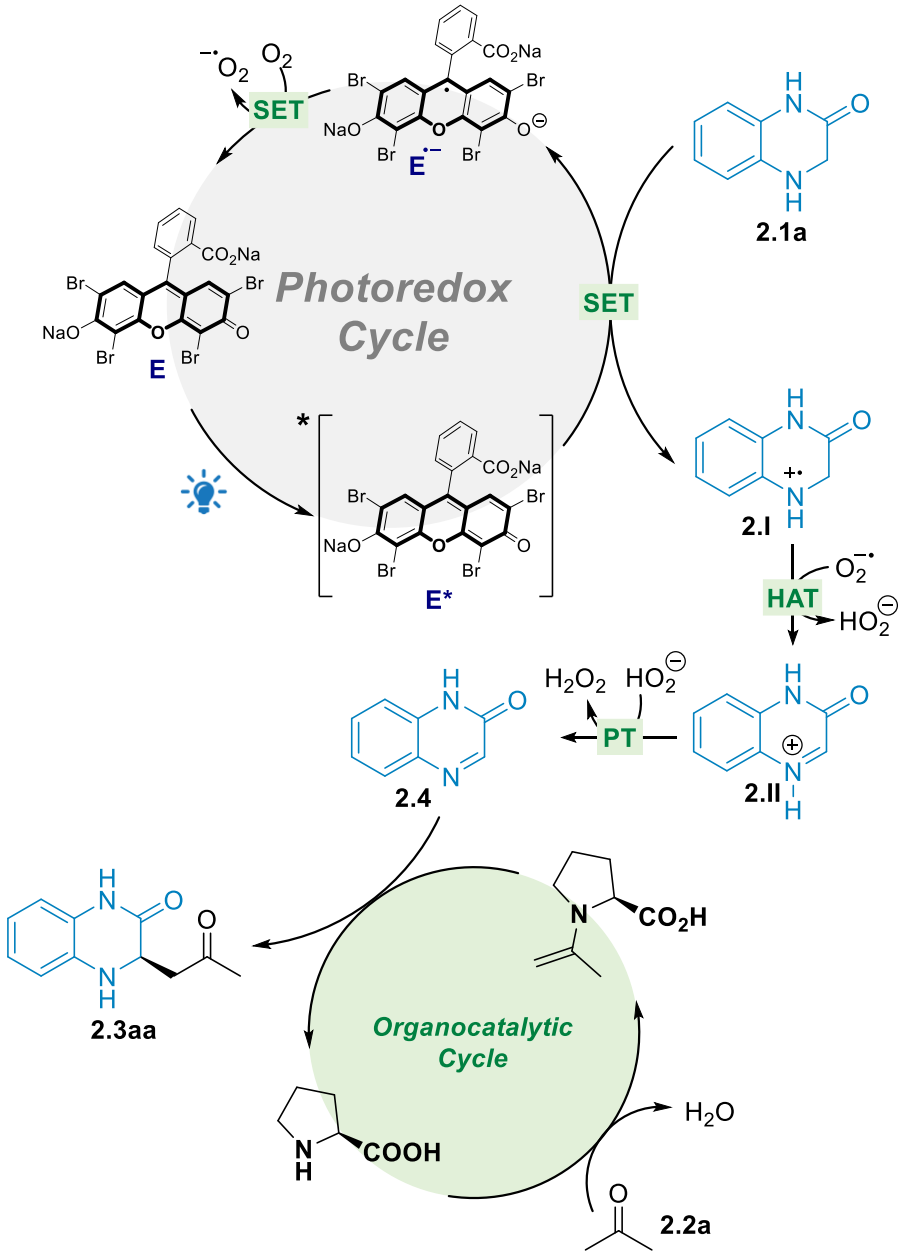


Figure 2.6: General mechanism for the asymmetric oxidative Mannich reaction between **2.1a** and **2.2a**.

2.4 Experimental Section

2.4.1 General Methods

Experimental methods regarding, **Chromatographic Methods**, **Nuclear Magnetic Resonance (NMR)** and **High Resolution Mass Spectrometry (HRMS)** can be found in Section 1.4.1 of *Chapter 1* (page 62).

Reaction Flasks, Reagents and Substrates

- Photocatalytic reactions were carried out in 10 mL round bottomed flasks under air unless otherwise indicated.
- Commercial reagents were used as purchased.
- All photocatalysts and ketones were commercially available.
- 3,4-Dihydroquinoxalin-2-ones **2.1a**, **2.1n** and **2.1o** were prepared according to a reported procedure.[110] 3,4-Dihydroquinoxalin-2-ones **2.1b**-**2.1e** were prepared adapting a published procedure.[144] 3,4-Dihydroquinoxalin-2-ones **2.1f**-**2.1m** were synthesized adapting a reported procedure.[145]

Fluorescence Spectroscopy

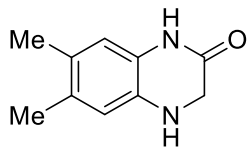
- All the emission spectra were obtained using a Jasco FP-750 Spectrofluorometer.

2.4.2 Synthetic Procedures and Characterization

Synthesis of 3,4-dihydroquinoxalin-2-ones 2.1a, 2.1n and 2.1o

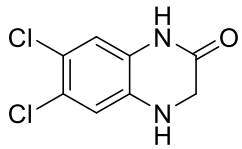
The procedure for the synthesis of 3,4-dihydroquinoxalin-2-one **2.1a** is described in *Section 1.4.2* of *Chapter 1* (page 67). 3,4-Dihydroquinoxalin-2-ones **2.1n** and **2.1o** were prepared using the same methodology.

6,7-Dimethyl-3,4-dihydroquinoxalin-2(1*H*)-one (2.1n)



^{1}H-NMR (300 MHz, DMSO-d$_6$) δ 10.05 (s, 1H), 6.49 (s, 1H), 6.44 (s, 1H), 5.64 (s, 1H), 3.62 (d, J = 1.9 Hz, 2H), 2.05 (s, 3H), 2.04 (s, 3H); **^{13}C{^{1}H}-NMR (75 MHz, DMSO-d$_6$)** δ 168.7 (C), 137.2 (C), 132.4 (C), 123.8 (C), 121.7 (CH), 118.9 (C), 113.2 (CH), 32.1 (CH_2), 18.7 (CH_3), 18.5 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{10}H_{13}N_2O^+$ 177.1022, found 177.1026.

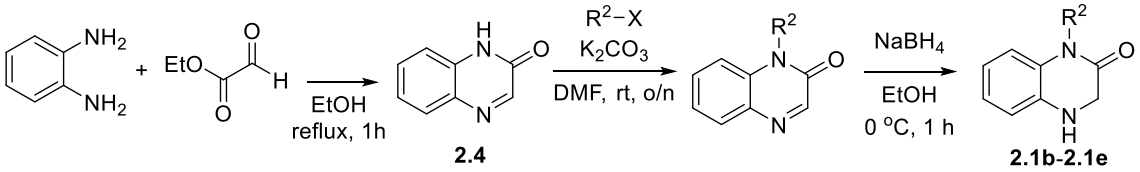
6,7-Dichloro-3,4-dihydroquinoxalin-2(1*H*)-one (2.1o)



^{1}H-NMR (300 MHz, DMSO-d$_6$) δ 10.43 (s, 1H), 6.84 (s, 1H), 6.80 (s, 1H), 6.35 (s, 1H), 3.78 (d, J = 1.7 Hz, 2H); **^{13}C{^{1}H}-NMR (75 MHz, DMSO-d$_6$)** δ 165.7 (C), 136.4 (C), 127.2 (C), 124.1 (C), 118.8 (C), 115.5 (CH), 112.3 (CH), 52.8 (CH_2); **HRMS (ESI/Q-TOF)** *m/z* [M + H]$^+$ calcd for $C_8H_7Cl_2N_2O^+$ 216.9930, found 216.9935.

Synthesis of 3,4-dihydroquinoxalin-2-ones 2.1b-2.1e

3,4-Dihydroquinoxalin-2-ones **2.1b**-**2.1e** were prepared adapting a published procedure.[144]

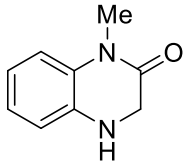


To a suspension of *o*-phenylenediamine (1.08 g, 10 mmol, 1 equiv.) in EtOH (10 mL) was added ethyl-2-oxoacetate (11 mmol, 1.1 equiv., 50% in toluene) dropwise. The mixture was stirred at reflux for 1h, then at room temperature overnight. Thereafter, the solid was filtered, washed with EtOH and finally dried under vacuum to give quinoxalin-2-one **2.4**, which was used in the next step without further purification.

Then, to a stirred suspension of quinoxalin-2-one **2.4** (0.73 g, 5 mmol, 1 equiv.) in DMF (10 mL) potassium carbonate (0.83 g, 6 mmol, 1.2 equiv.), and the corresponding alkyl halide (8 mmol, 1.6 equiv.) was added. The mixture was stirred at room temperature overnight. EtOAc (20 mL) and water (20 mL) were added, and the aqueous layer was extracted with EtOAc (2x15 mL). The combined organic layers were washed with sat. aq. NH_4Cl (15 mL) and brine (15 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. The residue was purified by flash chromatography using hexane:EtOAc mixtures (from 99:1 to 97:3) to afford N-1 alkylated quinoxalin-2-ones.

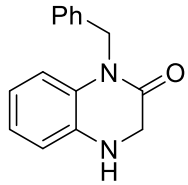
Finally, N-1 alkylated quinoxalin-2-ones (5 mmol, 1 equiv.) were dissolved in EtOH (10 mL) and the solution was cooled down to 0 °C. Thereafter, $NaBH_4$ (5.5 mmol, 1.1 equiv.) was added to the reaction mixture in portions. The mixture was stirred at 0 °C until the starting material disappeared as shown by TLC (approximately 1 hour). Then, the reaction mixture was filtered through a pad of silica using EtOAc as eluent. The solvent was removed under reduced pressure to obtain pure N-1 alkylated 3,4-dihydroquinoxalin-2-one **2.1b**-**2.1e**.

1-Methyl-3,4-dihydroquinoxalin-2(1*H*)-one (2.1b)



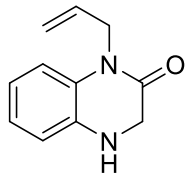
^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.01 – 6.78 (m, 3H), 6.71 (dd, J = 7.9, 1.5 Hz, 1H), 3.97 (s, 2H), 3.37 (s, 3H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 163.6 (C), 135.8 (C), 132.33 (C), 125.7 (CH), 120.5 (CH), 118.2 (CH), 117.7 (CH), 39.4 (CH_2), 31.0 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_9H_{11}N_2O^+$ 163.0871, found 163.0876.

1-Benzyl-3,4-dihydroquinoxalin-2(1*H*)-one (2.1c)



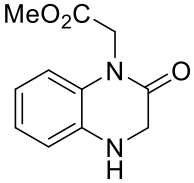
^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.34 – 7.15 (m, 5H), 6.91 – 6.76 (m, 2H), 6.75 – 6.63 (m, 2H), 5.15 (s, 2H), 4.05 (s, 2H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 162.0 (C), 137.0 (C), 137.0 (C), 130.9 (C), 128.8 (CH), 128.5 (CH), 128.0 (CH), 126.2 (CH), 120.2 (CH), 119.7 (CH), 117.8 (CH), 48.9 (CH_2), 40.2 (CH_2); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{15}H_{15}N_2O^+$ 239.1184, found 239.1180.

1-Allyl-3,4-dihydroquinoxalin-2(1*H*)-one (2.1d)



^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.97 – 6.88 (m, 2H), 6.86 – 6.79 (m, 1H), 6.72 (ddd, J = 7.3, 1.5, 0.5 Hz, 1H), 5.93 (ddt, J = 17.2, 10.3, 5.1 Hz, 1H), 5.28 (dtd, J = 10.4, 1.6, 0.8 Hz, 1H), 5.16 (dtd, J = 17.2, 1.8, 0.8 Hz, 1H), 4.90 (dt, J = 5.1, 1.7 Hz, 2H), 3.98 (s, 2H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 165.4 (C), 135.6 (C), 132.1 (C), 128.4 (CH), 123.6 (CH), 119.8 (CH), 116.7 (CH_2), 115.5 (CH), 114.3 (CH), 47.7 (CH_2), 44.4 (CH_2); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{11}H_{13}N_2O^+$ 189.1028, found 189.1032.

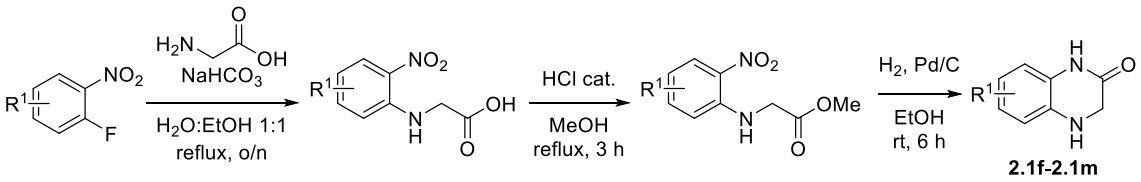
Methyl 2-(2-oxo-3,4-dihydroquinoxalin-1(2*H*)-yl) acetate (2.1e)



^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.94 (td, J = 7.6, 1.3 Hz, 1H), 6.84 (td, J = 7.8, 1.3 Hz, 1H), 6.76 (dd, J = 7.7, 1.3 Hz, 1H), 6.70 (dd, J = 8.0, 1.2 Hz, 1H), 4.67 (s, 2H), 4.03 (s, 2H), 3.78 (s, 3H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 175.0 (C), 167.4 (C), 149.9 (CH), 131.3 (CH), 130.9 (C), 124.1 (CH), 124.0 (C), 113.2 (CH), 52.9 (CH_3), 47.5 (CH_2), 43.0 (CH_2); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{11}H_{13}N_2O_3^+$ 221.0926, found 221.0929.

Synthesis of 3,4-dihydroquinoxalin-2-ones 2.1f-2.1m

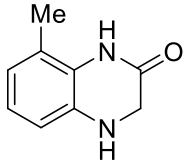
3,4-Dihydroquinoxalin-2-ones **2.1f**-**2.1m** were synthesized adapting a reported procedure.[145]



In a 100 mL round bottom flask, glycine (0.38 g, 5 mmol, 1 equiv.), $NaHCO_3$ (0.84 g, 10 mmol, 2 equiv.), H_2O (10 mL), and EtOH (10 mL) were placed. Subsequently, the corresponding 2-fluoronitrobenzene (5 mmol, 1 equiv.) was added. The reaction mixture was heated at reflux temperature overnight. After this time, the reaction was acidified with 6M HCl and it was extracted with EtOAc (3 x 30 mL), dried over $MgSO_4$ and filtered. The solvent was then evaporated under reduced pressure, to obtain crude *N*-aryl glycine as an orange solid. The crude *N*-aryl glycine was dissolved in MeOH (20 mL) and two drops of concentrated HCl were added. It was allowed to react at reflux for 3 h. Afterwards, the solvent was evaporated under reduced pressure and the residue was purified by column chromatography using hexane:EtOAc mixtures to obtain the corresponding *N*-aryl glycine methyl ester.

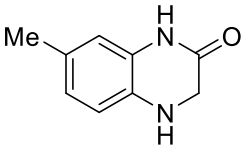
In a round bottomed flask, the proper *N*-aryl glycine methyl ester (3 mmol, 1 equiv.) was suspended in EtOH (10 mL). Then, Pd/C (10% w/w, 90 mg) was added in one portion and the resulting mixture was stirred at rt overnight with a H_2-filled balloon. When the starting material disappeared, the solution was filtered through a pad of Celite (eluting with EtOAc) and concentrated. If necessary, the crude product was washed with hexane:DCM 1:1 mixture several times to afford the corresponding 3,4-dihydroquinoxalin-2-one **2.1b**-**2.1e**.

8-Methyl-3,4-dihydroquinoxalin-2(1*H*)-one (2.1f)



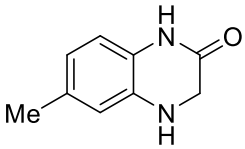
^{1}H-NMR (300 MHz, acetone-d$_6$) δ 8.68 (bs, 1H), 6.72 (t, J = 7.6 Hz, 1H), 6.61 (d, J = 7.2 Hz, 1H), 6.56 (ddd, J = 7.4, 1.4, 0.7 Hz, 1H), 5.22 (bs, 1H), 3.76 (s, 2H), 2.28 (s, 3H); **^{13}C{^{1}H}-NMR (75 MHz, acetone-d$_6$)** δ 150.8 (C), 131.8 (C), 127.2 (C), 123.3 (C), 122.6 (CH), 120.4 (CH), 111.8 (CH), 46.8 (CH_2), 16.0 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_9H_{11}N_2O^+$ 163.0871, found 163.0875.

7-Methyl-3,4-dihydroquinoxalin-2(1*H*)-one (2.1g)



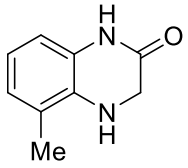
^{1}H-NMR (300 MHz, DMSO-d$_6$) δ 10.15 (bs, 1H), 6.82 – 6.26 (m, 3H), 5.74 (bs, 1H), 3.65 (s, 2H), 2.13 (s, 3H); **^{13}C{^{1}H}-NMR (75 MHz, DMSO-d$_6$)** δ 166.3 (C), 132.5 (C), 126.5 (C), 126.3 (C), 123.0 (CH), 115.5 (CH), 113.4 (CH), 46.6 (CH_2), 20.3 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_9H_{11}N_2O^+$ 163.0871, found 163.0868.

6-Methyl-3,4-dihydroquinoxalin-2(1*H*)-one (2.1h)



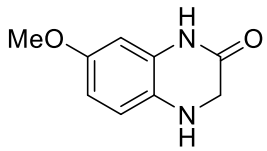
^{1}H-NMR (300 MHz, CDCl$_3$) δ 8.31 (bs, 1H), 6.63 (d, J = 7.9 Hz, 1H), 6.56 (ddd, J = 7.9, 1.7, 0.7 Hz, 1H), 6.51 (s, 1H), 3.96 (s, 2H), 2.24 (s, 3H); **^{13}C{^{1}H}-NMR (75 MHz, CDCl$_3$)** δ 166.7 (C), 150.4 (C), 132.5 (C), 123.1 (C), 120.3 (CH), 115.5 (CH), 114.9 (CH), 47.1 (CH_2), 20.9 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_9H_{11}N_2O^+$ 163.0871, found 163.0870.

5-Methyl-3,4-dihydroquinoxalin-2(1*H*)-one (2.1i)



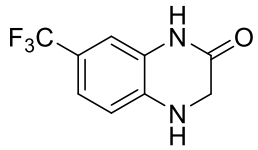
^{1}H-NMR (300 MHz, DMSO-d$_6$) δ 10.16 (bs, 1H), 6.69 – 6.57 (m, 2H), 6.57 – 6.46 (m, 1H), 5.39 (bs, 1H), 3.72 (d, J = 2.1 Hz, 2H), 2.07 (s, 3H); **^{13}C{^{1}H}-NMR (75 MHz, DMSO-d$_6$)** δ 165.9, 132.6 (C), 125.8, 124.2 (CH), 121.3 (C), 117.3 (CH), 113.1 (CH), 46.6 (CH_2), 16.9 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_9H_{11}N_2O^+$ 163.0871, found 163.0867.

7-Methoxy-3,4-dihydroquinoxalin-2(1*H*)-one (2.1j)



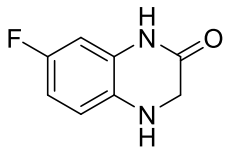
^{1}H-NMR (300 MHz, acetone-d$_6$) δ 9.11 (bs, 1H), 6.74 (d, J = 8.5 Hz, 1H), 6.35 (d, J = 2.6 Hz, 1H), 6.24 (dd, J = 8.5, 2.6 Hz, 1H), 5.28 (bs, 1H), 3.78 (d, J = 1.9 Hz, 2H), 3.69 (s, 3H); **^{13}C{^{1}H}-NMR (75 MHz, acetone-d$_6$)** δ 165.3 (C), 156.3 (C), 136.0 (C), 120.3 (C), 115.5 (CH), 103.2 (CH), 100.0 (CH), 54.6 (CH_3), 46.7 (CH_2); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_9H_{11}N_2O_2^+$ 179.0821, found 179.0818.

7-(Trifluoromethyl)-3,4-dihydroquinoxalin-2(1*H*)-one (2.1k)



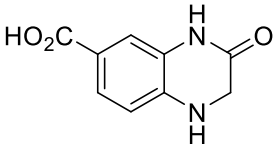
^{1}H-NMR (300 MHz, acetone-d$_6$) δ 9.47 (bs, 1H), 7.26 – 6.96 (m, 2H), 6.85 (d, J = 8.6 Hz, 1H), 5.89 (bs, 1H), 3.95 (d, J = 1.6 Hz, 2H); **^{19}F{^{1}H}-NMR (282 MHz, acetone-d$_6$)** δ -61.59; **^{13}C{^{1}H}-NMR (75 MHz, acetone-d$_6$)** δ 165.0 (C), 138.0 (C), 126.2 (C), 125.4 (C, q, J_{C-F} = 134.8 Hz), 123.2 (CH), 120.1 (CH, q, J_{C-F} = 4.0 Hz), 118.9 (C, q, J_{C-F} = 65.4 Hz), 112.9 (CH), 111.6 (CH, q, J_{C-F} = 3.9 Hz), 46.0 (CH_2); **HRMS (ESI/Q-TOF)** *m/z* [M + H]$^+$ calcd for $C_9H_8F_3N_2O^+$ 217.0589, found 217.0584.

7-Fluoro-3,4-dihydroquinoxalin-2(1*H*)-one (2.1l)



^{1}H-NMR (300 MHz, acetone-d$_6$) δ 6.78 (dd, J = 8.6, 5.2 Hz, 1H), 6.68 (dd, J = 9.5, 2.7 Hz, 1H), 6.59 (td, J = 8.7, 2.8 Hz, 1H), 3.79 (s, 2H); **^{19}F{^{1}H}-NMR (282 MHz, acetone-d$_6$)** δ -121.34; **^{13}C{^{1}H}-NMR (75 MHz, acetone-d$_6$)** δ 163.0 (C), 155.6 (C, d, J_{C-F} = 262.2 Hz), 130.8 (C, d, J_{C-F} = 4.0 Hz), 129.5 (C, d, J_{C-F} = 7.4 Hz), 118.3 (CH, d, J_{C-F} = 6.9 Hz), 112.5 (CH, d, J_{C-F} = 26.9 Hz), 106.9 (CH, d, J_{C-F} = 26.9 Hz), 41.6 (CH_2); **HRMS (ESI/Q-TOF)** *m/z* [M + H]$^+$ calcd for $C_8H_8FN_2O^+$ 167.0621, found 167.0616.

3-Oxo-1,2,3,4-tetrahydroquinoxaline-6-carboxylic acid (2.1m)



^{1}H-NMR (300 MHz, DMSO-d$_6$) δ 12.14 (bs, 1H), 10.39 (bs, 1H), 7.38 (dd, J = 8.2, 1.8 Hz, 1H), 7.32 (d, J = 1.7 Hz, 1H), 6.66 (bs, 1H), 6.63 (d, J = 8.3 Hz, 1H), 3.85 (s, 2H); **^{13}C{^{1}H}-NMR (75 MHz, DMSO-d$_6$)** δ 167.7 (C), 165.4 (C), 139.2 (C), 125.7 (CH), 125.3 (C), 119.4 (C), 116.4 (CH), 112.4 (CH), 46.0 (CH_2); **HRMS (ESI/Q-TOF)** *m/z* [M + H]$^+$ calcd for $C_9H_9N_2O_3^+$ 193.0613, found 193.0608.

General Procedure for the non-enantioselective asymmetric oxidative Mannich reaction between 3,4-dihydroquinoxalin-2-ones 2.1 and ketones 2.2

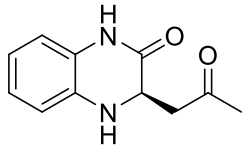
In a 10 mL round bottom flask Eosin-Y-Na$_2$ (**E**, 2.8 mg, 0.004 mmol, 2 mol %), the proper 3,4-dihydroquinoxalin-2-one (**2.1**, 0.2 mmol) and DMF (1 mL) were added. The mixture was stirred under blue LEDs irradiation (see page 432 for further details about the photochemical setup) until the starting material was consumed (as showed by TLC) (432). Then, *rac*-Pro (4.6 mg, 0.4 mmol, 20 mol %) and the proper ketone (**2.2**, 1 mL for acetone or 10 equiv. for other ketones) were added and the mixture was stirred at

room temperature in the dark. When completed (TLC), the reaction mixture was diluted with EtOAc (25 mL) and DMF was extracted with water (3 x 5 mL) and brine (5 mL). The organic phase was dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography using Et_3N-deactivated silica gel as stationary phase and DCM:acetone mixtures (from 100:1 to 100:3) as eluent to afford product **2.3** as a racemic mixture.

General Procedure for the enantioselective asymmetric oxidative Mannich reaction between 3,4-dihydroquinoxalin-2-ones 2.1 and ketones 2.2

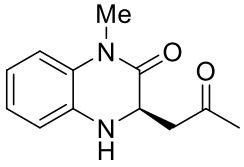
In a 10 mL round bottom flask Eosin-Y-Na_2 (**E**, 2.8 mg, 0.004 mmol, 2 mol %), the proper 3,4-dihydroquinoxalin-2-one (**2.1**, 0.2 mmol) and DMF (1 mL) were added. The mixture was stirred under blue LEDs irradiation (see page 432 for further details about the photochemical setup) until the starting material was consumed (as showed by TLC) (432). Then, (*S*)-Pro (4.6 mg, 0.4 mmol, 20 mol %) and the proper ketone (**2.2**, 1 mL for acetone or 10 equiv. for other ketones) were added and the mixture was stirred at room temperature in the dark. When completed (TLC), the reaction mixture was diluted with EtOAc (25 mL) and DMF was extracted with water (3 x 5 mL) and brine (5 mL). The organic phase was dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography using Et_3N-deactivated silica gel as stationary phase and DCM:acetone mixtures (from 100:1 to 100:3) as eluent to afford product **2.3** as an enantioenriched mixture.

(*R*)-3-(2-Oxopropyl)-3,4-dihydroquinoxalin-2(1*H*)-one (2.3aa)



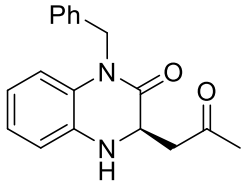
Using 3,4-dihydroquinoxalin-2(1*H*)-one (**2.1a**, 29.6 mg, 0.2 mmol) and acetone (**2.2a**, 1 mL), in accordance with General Procedure, product **2.3aa** (30.2 mg, 0.148 mmol, 74% yield) was obtained as a yellow solid. Enantiomeric excess (99%) was determined by chiral HPLC (Chiralcel OD-H), hexane:*i*-PrOH 80:20, 1 mL/min, major enantiomer t_r = 10.63 min, minor enantiomer t_r = 13.96 min. $[\alpha]_D^{20}$ +148.1 (c 0.5, $CHCl_3$) (99% ee); **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 8.86 (bs, 1H), 6.89 (ddd, *J* = 7.8, 5.9, 3.0 Hz, 1H), 6.79 – 6. 71 (m, 2H), 6.67 (d, *J* = 7.5 Hz, 1H), 4.69 (bs, 1H), 4.37 (dd, *J* = 10.3, 2.3 Hz, 1H), 3.34 (dd, *J* = 18.6, 2.3 Hz, 1H), 2.86 (dd, *J* = 18.6, 10.3 Hz, 1H), 2.23 (s, 3H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 207.6 (C), 168.1 (C), 133.1 (C), 124.9 (C), 124.0 (CH), 119.5 (CH), 115.4 (CH), 114.4 (CH), 52.2 (CH), 44.9 (CH_2), 30.3 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{11}H_{12}N_2O_2^+$ 205.0972, found 205.0967.

(*R*)-1-Methyl-3-(2-oxopropyl)-3,4-dihydroquinoxalin-2(1*H*)-one (2.3ba)



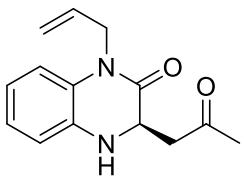
Using 1-methyl-3,4-dihydroquinoxalin-2(1*H*)-one (**2.1b**, 32.4 mg, 0.2 mmol) and acetone (**2.2a**, 1 mL), in accordance with General Procedure, product **2.3ba** (38.0 mg, 0.174 mmol, 87% yield) was obtained as a yellow oil. Enantiomeric excess (93%) was determined by chiral HPLC (Chiralpak IC), hexane:*i*-PrOH 90:10, 1 mL/min, major enantiomer t_r = 40.27 min, minor enantiomer t_r = 45.74 min. $[\alpha]_D^{20}$ +88.4 (c 0.5, $CHCl_3$) (93% ee) ; **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 6.98 – 6.80 (m, 3H), 6.75 – 6.68 (m, 1H), 4.69 (s, 1H), 4.28 (dt, *J* = 10.3, 2.3 Hz, 1H), 3.40 – 3.26 (m, 4H), 2.80 (dd, *J* = 18.6, 10.3 Hz, 1H), 2.21 (s, 3H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 207.7 (C), 166.8 (C), 134.6 (C), 128.6 (C), 123.7 (CH), 119.7 (CH), 114.6 (CH), 114.6 (CH), 52.5 (CH), 44.8 (CH_2), 30.4 (CH_3), 29.1 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{12}H_{15}N_2O_2^+$ 219.1134, found 219.1130.

(*R*)-1-Benzyl-3-(2-oxopropyl)-3,4-dihydroquinoxalin-2(1*H*)-one (2.3ca)



Using 1-benzyl-3,4-dihydroquinoxalin-2(1*H*)-one (**2.1c**, 47.7 mg, 0.2 mmol) and acetone (**2.2a**, 1 mL), in accordance with General Procedure, product **2.3ca** (45.9 mg, 0.156 mmol, 78% yield) was obtained as a yellow oil. Enantiomeric excess (98%) was determined by chiral HPLC (Chiralpak AD-H), hexane:*i*-PrOH 80:20, 1 mL/min, major enantiomer t_r = 15.18 min, minor enantiomer t_r = 13.29 min. $[\alpha]_D^{20}$ +74.8 (c 0.3, $CHCl_3$) (98% ee); **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 7.37 – 7.16 (m, 5H), 6.96 – 6.85 (m, 1H), 6.85 – 6.78 (m, 1H), 6.76 – 6.66 (m, 2H), 5.22 (d, *J* = 16.2 Hz, 1H), 5.09 (d, *J* = 16.2 Hz, 1H), 4.75 (bs, 1H), 4.42 (dt, *J* = 10.2, 2.4 Hz, 1H), 3.38 (dd, *J* = 18.5, 2.5 Hz, 1H), 2.89 (dd, *J* = 18.5, 10.2 Hz, 1H), 2.24 (s, 3H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 207.6 (C), 166.9 (C), 136.4 (C), 134.8 (C), 128.8 (CH), 127.8 (C), 127.2 (CH), 126.3 (CH), 123.9 (CH), 119.8 (CH), 115.5 (CH), 114.8 (CH), 52.6 (CH), 45.9 (CH_2), 44.5 (CH_2), 30.4 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{12}H_{15}N_2O_2^+$ 295.1447, found 295.1442.

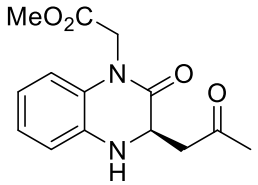
(*R*)-1-Allyl-3-(2-oxopropyl)-3,4-dihydroquinoxalin-2(1*H*)-one (2.3da)



Using 1-allyl-3,4-dihydroquinoxalin-2(1*H*)-one (**2.1d**, 37.6 mg, 0.2 mmol) and acetone (**2.2a**, 1 mL), in accordance with General Procedure, product **2.3da** (45.9 mg, 0.188 mmol, 94% yield) was obtained as a yellow oil. Enantiomeric excess (95%) was determined by chiral HPLC (Chiralpak IC), hexane:*i*-PrOH 90:10, 1

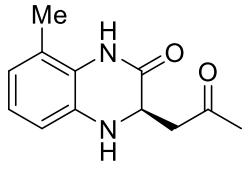
mL/min, major enantiomer t_r = 29.00 min, minor enantiomer t_r = 36.21 min. $[\alpha]_D^{20}$ +72.7 (c 0.5, $CHCl_3$) (95% ee) ; **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 6.96 – 6.86 (m, 2H), 6.80 (ddd, *J* = 7.1, 6.6, 1.5 Hz, 1H), 6.73 – 6.68 (m, 1H), 5.87 (ddt, *J* = 17.2, 10.5, 4.8 Hz, 1H), 5.23 – 5.12 (m, 2H), 4.70 (bs, 1H), 4.60 (ddt, *J* = 16.7, 4.5, 1.8 Hz, 1H), 4.46 (ddt, *J* = 16.7, 4.8, 1.8 Hz, 1H), 4.31 (dt, *J* = 10.2, 2.4 Hz, 1H), 3.31 (dd, *J* = 18.5, 2.5 Hz, 1H), 2.81 (dd, *J* = 18.5, 10.2 Hz, 1H), 2.21 (s, 3H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 207.6 (C), 166.4 (C), 134.7 (C), 131.9 (CH), 127.7 (C), 123.7 (CH), 119.7 (CH), 116.5 (CH_2), 115.2 (CH), 114.8 (CH), 52.5 (CH), 44.6 (CH_2), 44.4 (CH_2), 30.3 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{14}H_{17}N_2O_2^+$ 245.1290, found 245.1284.

(*R*)-Methyl 2-(2-oxo-3-(2-oxopropyl)-3,4-dihydroquinoxalin-1(2*H*)-yl)acetate (2.3ea)



Using methyl 2-(2-oxo-3,4-dihydroquinoxalin-1(2*H*)-yl)acetate (**2.1e**, 44.0 mg, 0.2 mmol) and acetone (**2.2a**, 1 mL), in accordance with General Procedure, product **2.3ea** (49.7 mg, 0.180 mmol, 90% yield) was obtained as a yellow oil. Enantiomeric excess (98%) was determined by chiral HPLC (Chiralcel AD-H), hexane:*i*-PrOH 80:20, 1 mL/min, major enantiomer t_r = 15.54 min, minor enantiomer t_r = 12.35 min. $[\alpha]_D^{20}$ +77.6 (c 0.3, $CHCl_3$) (98% ee) ; **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 6.92 (td, *J* = 7.6, 1.3 Hz, 1H), 6.81 (td, *J* = 7.7, 1.4 Hz, 1H), 6.72 (dd, *J* = 7.7, 1.4 Hz, 1H), 6.65 (d, *J* = 7.8 Hz, 1H), 4.73 (bs, 1H), 4.64 (s, 2H), 4.36 (dt, *J* = 10.3, 2.4 Hz, 1H), 3.77 (s, 3H), 3.23 (dd, *J* = 18.6, 2.4 Hz, 1H), 2.84 (dd, *J* = 18.6, 10.3 Hz, 1H), 2.19 (s, 3H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 207.5 (C), 168.7 (C), 167.2 (C), 134.3 (C), 127.5 (C), 124.1 (CH), 119.9 (CH), 115.1 (CH), 114.0 (CH), 52.5 (CH_3), 52.4 (CH), 44.1 (CH_2), 43.7 (CH_2), 30.3 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{14}H_{17}N_2O_4^+$ 277.1188, found 277.1184.

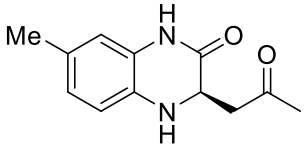
(*R*)-8-Methyl-3-(2-oxopropyl)-3,4-dihydroquinoxalin-2(1*H*)-one (2.3fa)



Using 8-methyl-3,4-dihydroquinoxalin-2(1*H*)-one (**2.1f**, 32.4 mg, 0.2 mmol) and acetone (**2.2a**, 1 mL), in accordance with General Procedure, product **2.3fa** (25.3 mg, 0.116 mmol, 58% yield) was obtained as a yellow solid. Enantiomeric excess (98%) was determined by chiral HPLC (Chiralpak AY-H), hexane:*i*-PrOH 80:20, 1 mL/min, major enantiomer t_r = 22.01 min, minor enantiomer t_r = 16.10 min. $[\alpha]_D^{20}$ +108.8 (c 0.3, $CHCl_3$) (98% ee); **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 7.88 (bs, 1H), 6.81 (t, *J* = 7.7 Hz, 1H), 6.63 (d, *J* = 7.1 Hz, 1H), 6.56 (d, *J* = 7.8 Hz, 1H), 4.65 (bs, 1H), 4.31 (dt, *J* = 10.2, 2.4 Hz, 1H), 3.33 (dd, *J* = 18.6, 2.4 Hz, 1H), 2.84 (dd, *J* = 18.6, 10.3 Hz, 1H), 2.23 (s, 3H), 2.22 (s, 3H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 207.5 (C),

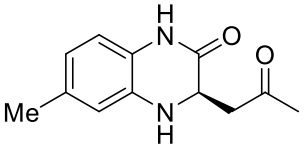
167.6 (C), 133.2 (C), 123.5 (CH), 123.3 (C), 123.05 (C), 121.4 (CH), 112.6 (CH), 52.0 (CH), 44.7 (CH_2), 30.3 (CH_3), 16.4 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{12}H_{15}N_2O_2^+$ 219.1134, found 219.1130.

(*R*)-7-Methyl-3-(2-oxopropyl)-3,4-dihydroquinoxalin-2(1*H*)-one (2.3ga)



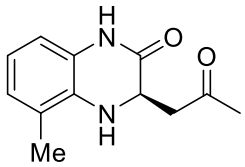
Using 7-methyl-3,4-dihydroquinoxalin-2(1*H*)-one (**2.1g**, 32.4 mg, 0.2 mmol) and acetone (**2.2a**, 1 mL), in accordance with General Procedure, product **2.3ga** (31.9 mg, 0.146 mmol, 73% yield) was obtained as a yellow solid. Enantiomeric excess (98%) was determined by chiral HPLC (Chiralpak AY-H), hexane:*i*-PrOH 80:20, 1 mL/min, major enantiomer t_r = 24.80 min, minor enantiomer t_r = 18.93 min. $[\alpha]_D^{20}$ +92.5 (c 0.5, $CHCl_3$) (98% ee); **^{1}H-NMR (400 MHz, $CDCl_3$)** δ 8.68 (bs, 1H), 6.70 (dd, *J* = 7.9, 1.0 Hz, 1H), 6.58 (d, *J* = 7.9 Hz, 1H), 6.55 (d, *J* = 1.0 Hz, 1H), 4.56 (bs, 1H), 4.32 (dd, *J* = 10.3, 2.2 Hz, 1H), 3.32 (dd, *J* = 18.6, 2.3 Hz, 1H), 2.85 (dd, *J* = 18.6, 10.3 Hz, 1H), 2.24 (s, 3H), 2.22 (s, 3H); **^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$)** δ 207.6 (C), 168.3 (C), 130.7 (C), 129.3 (C), 125.0 (C), 124.5 (CH), 115.9 (CH), 114.4 (CH), 52.4 (CH), 44.7 (CH_2), 30.34 (CH_3), 20.5 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{12}H_{15}N_2O_2^+$ 219.1134, found 219.1137.

(*R*)-6-Methyl-3-(2-oxopropyl)-3,4-dihydroquinoxalin-2(1*H*)-one (2.3ha)



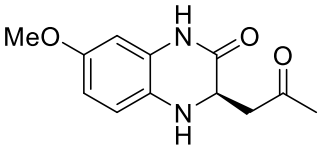
Using 6-methyl-3,4-dihydroquinoxalin-2(1*H*)-one (**2.1h**, 32.4 mg, 0.2 mmol) and acetone (**2.2a**, 1 mL), in accordance with General Procedure, product **2.3ha** (40.6 mg, 0.186 mmol, 93% yield) was obtained as a yellow solid. Enantiomeric excess (99%) was determined by chiral HPLC (Chiralcel IC), hexane:*i*-PrOH 85:15, 1 mL/min, major enantiomer t_r = 24.64 min, minor enantiomer t_r = 23.26 min. $[\alpha]_D^{20}$ +96.8 (c 0.4, $CHCl_3$) (99% ee) ; **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 8.59 (bs, 1H), 6.61 (d, *J* = 7.9 Hz, 1H), 6.58 – 6.53 (m, 1H), 6.50 (s, 1H), 4.61 (bs, 1H), 4.33 (dd, *J* = 10.3, 2.1 Hz, 1H), 3.31 (dd, *J* = 18.6, 2.3 Hz, 1H), 2.85 (dd, *J* = 18.6, 10.4 Hz, 1H), 2.23 (s, 3H), 2.22 (s, 3H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 207.6 (C), 167.9 (C), 133.9 (C), 133.0 (C), 122.5 (C), 120.1 (CH), 115.2 (CH), 115.1 (CH), 52.2 (CH), 44.8 (CH_2), 30.3 (CH_3), 20.9 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{12}H_{15}N_2O_2^+$ 219.1134, found 219.1127.

(*R*)-5-Methyl-3-(2-oxopropyl)-3,4-dihydroquinoxalin-2(1*H*)-one (2.3ia)



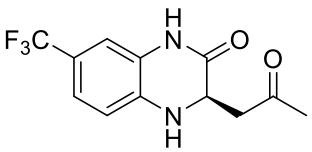
Using 5-methyl-3,4-dihydroquinoxalin-2(1*H*)-one (**2.1i**, 32.4 mg, 0.2 mmol) and acetone (**2.2a**, 1 mL), in accordance with General Procedure, product **2.3fa** (21.4 mg, 0.098 mmol, 49% yield) was obtained as a yellow solid. Enantiomeric excess (92%) was determined by chiral HPLC (Chiralpak AY-H), hexane:*i*-PrOH 80:20, 1 mL/min, major enantiomer t_r = 16.84 min, minor enantiomer t_r = 14.29 min. $[\alpha]_D^{20}$ +101.5 (c 0.3, $CHCl_3$) (92% ee); **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 8.64 (bs, 1H), 6.79 (ddd, *J* = 7.4, 1.5, 0.7 Hz, 1H), 6.68 (t, *J* = 7.6 Hz, 1H), 6.62 (dd, *J* = 7.8, 1.5 Hz, 1H), 4.73 (bs, 1H), 4.36 (dt, *J* = 10.4, 2.4 Hz, 1H), 3.34 (dd, *J* = 18.6, 2.3 Hz, 1H), 2.87 (dd, *J* = 18.6, 10.5 Hz, 1H), 2.24 (s, 3H), 2.16 (s, 3H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 207.9 (C), 167.9 (C), 131.3 (C), 125.6 (CH), 124.5 (C), 122.5 (C), 119.0 (CH), 113.4 (CH), 52.2 (CH), 44.7 (CH_2), 30.4 (CH_3), 16.5 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{12}H_{15}N_2O_2^+$ 219.1134, found 219.1129.

(*R*)-7-Methoxy-3-(2-oxopropyl)-3,4-dihydroquinoxalin-2(1*H*)-one (2.3ja)



Using 7-methoxy-3,4-dihydroquinoxalin-2(1*H*)-one (**2.1j**, 35.6 mg, 0.2 mmol) and acetone (**2.2a**, 1 mL), in accordance with General Procedure, product **2.3ja** (38.9 mg, 0.166 mmol, 83% yield) was obtained as a yellow solid. Enantiomeric excess (98%) was determined by chiral HPLC (Chiralcel IC), hexane:*i*-PrOH 80:20, 1 mL/min, major enantiomer t_r = 34.19 min, minor enantiomer t_r = 25.01 min. $[\alpha]_D^{20}$ +116.6 (c 0.3, $CHCl_3$) (98% ee); **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 8.67 (bs, 1H), 6.63 (d, *J* = 8.4 Hz, 1H), 6.30 (dd, *J* = 8.5, 2.6 Hz, 1H), 6.25 (d, *J* = 2.5 Hz, 1H), 4.69 (bs, 1H), 4.33 (dt, *J* = 10.4, 2.3 Hz, 1H), 3.73 (s, 3H), 3.31 (dd, *J* = 18.6, 2.3 Hz, 1H), 2.84 (dd, *J* = 18.6, 10.4 Hz, 1H), 2.22 (s, 3H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 207.7 (C), 167.4 (C), 156.7 (C), 134.1 (C), 118.7 (C), 116.0 (CH), 104.5 (CH), 100.6 (CH), 55.5 (CH_3), 52.1 (CH), 44.9 (CH_2), 30.3 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{12}H_{15}N_2O_3^+$ 235.1083, found 235.1078.

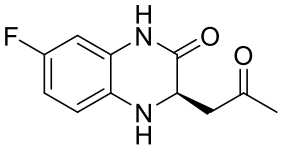
(*R*)-3-(2-Oxopropyl)-7-(trifluoromethyl)-3,4-dihydroquinoxalin-2(1*H*)-one (2.3ka)



Using 7-(trifluoromethyl)-3,4-dihydroquinoxalin-2(1*H*)-one (**2.1k**, 43.2 mg, 0.2 mmol) and acetone (**2.2a**, 1 mL), in accordance with General Procedure, product **2.3ka** (42.5 mg, 0.156 mmol, 78% yield) was obtained as a white solid. Enantiomeric excess (98%) was determined by chiral HPLC (Chiralcel IC), hex-

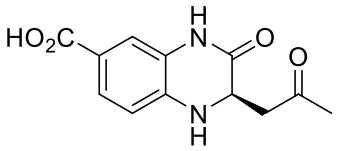
ane:*i*-PrOH 90:10, 1 mL/min, major enantiomer t_r = 14.09 min, minor enantiomer t_r = 28.62 min. $[\alpha]_D^{20}$ +77.6 (c 0.5, THF) (98% ee); **^{1}H-NMR (300 MHz, DMSO-d$_6$)** δ 10.51 (s, 1H), 7.07 (ddd, J = 8.3, 2.0, 0.7 Hz, 1H), 6.98 (d, J = 1.8 Hz, 1H), 6.78 (d, J = 8.3 Hz, 1H), 6.56 (s, 1H), 4.32 – 4.26 (m, 1H), 2.98 (dd, J = 17.2, 4.7 Hz, 1H), 2.80 (dd, J = 17.2, 6.9 Hz, 1H), 2.15 (s, 3H); **^{19}F{^{1}H}-NMR (282 MHz, DMSO-d$_6$)** δ -59.41 (s); **^{13}C{^{1}H}-NMR (75 MHz, DMSO-d$_6$)** δ 205.7 (C), 166.4 (C), 137.4 (C), 125.5 (C), 124.9 (C, q, J_{C-F} = 270.3 Hz), 120.0 (CH, q, J_{C-F} = 4.1 Hz), 117.3 (C, q, J_{C-F} = 31.9 Hz), 112.8 (CH), 111.1 (CH, q, J_{C-F} = 3.9 Hz), 51.2 (CH), 45.3 (CH_2), 30.3 (CH_3); **HRMS (ESI/Q-TOF)** m/z [M + H]$^+$ calcd for $C_{12}H_{12}F_3N_2O_2^+$ 273.0851, found 273.0856.

(*R*)-7-Fluoro-3-(2-oxopropyl)-3,4-dihydroquinoxalin-2(1*H*)-one (2.3la)



Using 7-fluoro-3,4-dihydroquinoxalin-2(1*H*)-one (**2.1l**, 33.2 mg, 0.2 mmol) and acetone (**2.2a**, 1 mL), in accordance with General Procedure, product **2.3la** (37.8 mg, 0.170 mmol, 85% yield) was obtained as a yellow solid. Enantiomeric excess (97%) was determined by chiral HPLC (Chiralcel IC), hexane:*i*-PrOH 85:15, 1 mL/min, major enantiomer t_r = 14.06 min, minor enantiomer t_r = 20.37 min. $[\alpha]_D^{20}$ +118.2 (c 0.5, $CHCl_3$) (97% ee) ; **^{1}H-NMR (300 MHz, CDCl$_3$)** δ 9.05 (bs, 1H), 6.65 – 6.57 (m, 2H), 6.53 (d, J = 8.7 Hz, 1H), 4.61 (bs, 1H), 4.30 (dt, J = 10.3, 2.4 Hz, 1H), 3.34 (dd, J = 18.6, 2.3 Hz, 1H), 2.84 (dd, J = 18.6, 10.3 Hz, 1H), 2.24 (s, 3H); 19F NMR (282 MHz, CDCl3) δ -124.0 (s); **^{13}C{^{1}H}-NMR (75 MHz, CDCl$_3$)** δ 207.6 (C), 168.5 (C), 156.8 (C, d, J_{C-F} = 237.3 Hz), 129.4 (C, d, J_{C-F} = 2.2 Hz), 125.9 (C, d, J_{C-F} = 10.4 Hz), 115.0 (CH. d, J_{C-F} = 8.7 Hz), 110.0 (CH, d, J_{C-F} = 22.5 Hz), 103.0 (CH, d, J_{C-F} = 26.9 Hz), 52.2 (CH), 44.6 (CH_2), 30.4 (CH_3); **HRMS (ESI/Q-TOF)** m/z [M + H]$^+$ calcd for $C_{11}H_{12}FN_2O_2^+$ 223.0883, found 223.0878.

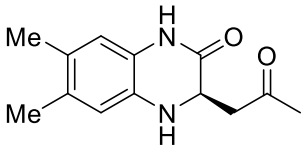
(*R*)-3-Oxo-2-(2-oxopropyl)-1,2,3,4-tetrahydroquinoxaline-6-carboxylic acid (2.3ma)



Using 3-oxo-1,2,3,4-tetrahydroquinoxaline-6-carboxylic acid (**2.1m**, 38.4 mg, 0.2 mmol) and acetone (**2.2a**, 1 mL), in accordance with General Procedure, product **2.3ma** (33.8 mg, 0.136 mmol, 68% yield) was obtained as a yellow solid. To determine the enantiomeric excess the carboxylic acid moiety was derivatized to the corresponding methyl ester using diazomethyltrimethylsilane (2 equiv.) in dry toluene (2 mL) at rt. Enantiomeric excess of **2.3ma**-methyl ester (95%) was determined by chiral HPLC (Chiralpak AD-H), hexane:*i*-PrOH 80:20, 1 mL/min, major enantiomer t_r = 25.93 min, minor enantiomer t_r = 21.85 min. $[\alpha]_D^{20}$ +42.0 (c 0.2, DMSO) (95% ee); **^{1}H-NMR (400 MHz, DMSO-d$_6$)** δ 10.44 (bs, 1H), 7.37 (dd, J = 8.2, 1.9 Hz,

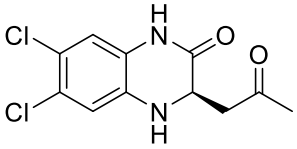
1H), 7.33 (d, *J* = 1.9 Hz, 1H), 6.68 (d, *J* = 8.3 Hz, 1H), 6.59 (bs, 1H), 4.28 (ddd, *J* = 6.6, 4.7, 1.6 Hz, 1H), 2.98 (dd, *J* = 17.1, 4.8 Hz, 1H), 2.79 (dd, *J* = 17.1, 6.9 Hz, 1H), 2.15 (s, 3H); **^{13}C{^{1}H}-NMR (101 MHz, DMSO-d$_6$)** δ 205.7 (C), 167.2 (C), 166.2 (C), 138.2 (C), 125.2 (CH), 124.8 (C), 119.2 (C), 115.9 (CH), 112.2 (CH), 51.3 (CH), 45.4 (CH_2), 30.3 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* [M + H]$^+$ calcd for $C_{12}H_{13}N_2O_4^+$ 249.0870, found 249.0872.

(*R*)-6,7-Dimethyl-3-(2-oxopropyl)-3,4-dihydroquinoxalin-2(1*H*)-one (2.3na)



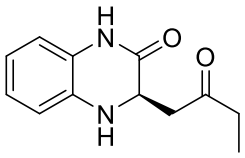
Using 6,7-dimethyl-3,4-dihydroquinoxalin-2(1*H*)-one (**2.1n**, 35.2 mg, 0.2 mmol) and acetone (**2.2a**, 1 mL), in accordance with General Procedure, product **2.3na** (33.4 mg, 0.144 mmol, 72% yield) was obtained as a yellow solid. Enantiomeric excess (95%) was determined by chiral HPLC (Chiralpak AD-H), hexane:*i*-PrOH 80:20, 1 mL/min, major enantiomer t_r = 13.09 min, minor enantiomer t_r = 10.16 min. $[\alpha]_D^{20}$ +8.6 (c 0.4, $CHCl_3$) (95% ee) ; **^{1}H-NMR (300 MHz, CDCl$_3$)** δ 8.77 (bs, 1H), 6.52 (s, 1H), 6.48 (s, 1H), 4.51 (bs, 1H), 4.30 (dd, *J* = 10.3, 2.3 Hz, 1H), 3.29 (dd, *J* = 18.5, 2.3 Hz, 1H), 2.85 (dd, *J* = 18.5, 10.3 Hz, 1H), 2.22 (s, 3H), 2.14 (s, 6H); **^{13}C{^{1}H}-NMR (75 MHz, CDCl$_3$)** δ 207.6 (C), 168.2 (C), 132.1 (C), 130.8 (C), 127.7 (C), 122.8 (C), 116.6 (CH), 115.9 (CH), 52.4 (CH), 44.6 (CH_2), 30.4 (CH_3), 19.3 (CH_3), 18.8 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* [M + H]$^+$ calcd for $C_{13}H_{16}N_2O_2^+$ 233.1285, found 233.1280.

(*R*)-6,7-Dichloro-3-(2-oxopropyl)-3,4-dihydroquinoxalin-2(1*H*)-one (2.3oa)



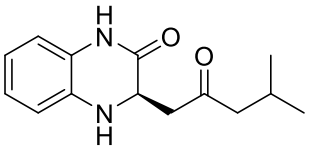
Using 6, 7-dichloro-3,4-dihydroquinoxalin-2(1*H*)-one (**2.1o**, 43.4 mg, 0.2 mmol) and acetone (**2.2a**, 1 mL), in accordance with General Procedure, product **2.3oa** (40.97 mg, 0.150 mmol, 75% yield) was obtained as a white solid. Enantiomeric excess (97%) was determined by chiral HPLC (Chiralpak AD-H), hexane:*i*-PrOH 80:20, 1 mL/min, major enantiomer t_r = 9.59 min, minor enantiomer t_r = 8.35 min. $[\alpha]_D^{20}$ +119.2 (c 1.0, THF) (97% ee) ; **^{1}H-NMR (300 MHz, DMSO-d$_6$)** δ 10.50 (bs, 1H), 6.88 (s, 1H), 6.85 (s, 1H), 6.30 (bs, 1H), 4.21 (ddd, *J* = 4.5, 3.8, 1.7 Hz, 1H), 2.96 (dd, *J* = 17.3, 4.6 Hz, 1H), 2.77 (dd, *J* = 17.3, 7.3 Hz, 1H), 2.14 (s, 3H); **^{13}C{^{1}H}-NMR (75 MHz, DMSO-d$_6$)** δ 205.7 (C), 166.5 (C), 134.3 (C), 126.1 (C), 118.2 (C), 115.4 (CH), 113.9 (CH), 51.2 (CH), 45.1 (CH_2), 30.2 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* [M + H]$^+$ calcd for $C_{11}H_{10}Cl_2N_2O_2^+$ 273.0192, found 273.0201.

(*R*)-3-(2-Oxobutyl)-3,4-dihydroquinoxalin-2(1*H*)-one (2.3ab)



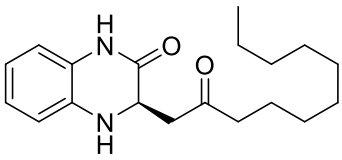
Using 3,4-dihydroquinoxalin-2(1*H*)-one (**2.1a**, 29.6 mg, 0.2 mmol) and butanone (**2.2b**, 179 μL, 2 mmol, 10 eq.), in accordance with General Procedure, product **2.3ab** (24.0 mg, 0.110 mmol, 55% yield) was obtained as a yellow solid as an inseparable mixture of linear and branched regioisomers. Linear:branched regioisomeric ratio (11:1) was determined by ^{1}H-NMR. Enantiomeric excess of the linear product (98%) was determined by chiral HPLC (Chiralpak AY-H), hexane:*i*-PrOH 80:20, 1 mL/min, major enantiomer t_r = 28.26 min, minor enantiomer t_r = 25.25 min. $[\alpha]_D^{20}$ +99.3 (c 0.7, $CHCl_3$) (98% ee) ; **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 8.67 (bs, 1H), 6.89 (ddd, *J* = 7.8, 6.7, 2.2 Hz, 1H), 6.81 – 6.63 (m, 3H), 4.72 (bs, 1H), 4.37 (dt, *J* = 10.4, 2.3 Hz, 1H), 3.32 (dd, *J* = 18.4, 2.3 Hz, 1H), 2.83 (dd, *J* = 18.4, 10.4 Hz, 1H), 2.63 – 2.41 (m, 2H), 1.10 (t, *J* = 7.3 Hz, 3H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 210.5 (C), 168.1 (C), 133.2 (C), 124.9 (C), 124.1 (CH), 119.5 (CH), 115.3 (CH), 114.4 (CH), 52.3 (CH), 43.6 (CH_2), 36.3 (CH_2), 7.6 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{12}H_{15}N_2O_2^+$ 219.1134, found 219.1130.

(*R*)-3-(4-Methyl-2-oxopentyl)-3,4-dihydroquinoxalin-2(1*H*)-one (2.3ac)



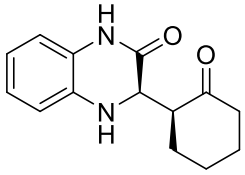
Using 3,4-dihydroquinoxalin-2(1*H*)-one (**2.1a**, 29.6 mg, 0.2 mmol) and methyl isobutyl ketone (**2.2c**, 250 μL, 2 mmol, 10 eq.) in accordance with General Procedure, product **2.3ac** (20.7 mg, 0.084 mmol, 42% yield) was obtained as a yellow solid as a single regioisomer. Enantiomeric excess (96%) was determined by chiral HPLC (Chiralcel OD-H), hexane:*i*-PrOH 80:20, 1 mL/min, major enantiomer t_r = 7.74 min, minor enantiomer t_r = 10.47 min. $[\alpha]_D^{20}$ +82.9 (c 0.3, $CHCl_3$) (96% ee) ; **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 8.69 (bs, 1H), 6.89 (ddd, *J* = 7.8, 6.6, 2.4 Hz, 1H), 6.80 – 6.72 (m, 2H), 6.68 (d, *J* = 7.8 Hz, 1H), 4.72 (bs, 1H), 4.36 (d, *J* = 10.4 Hz, 1H), 3.28 (dd, *J* = 18.5, 2.3 Hz, 1H), 2.81 (dd, *J* = 18.5, 10.4 Hz, 1H), 2.36 (d, *J* = 1.5 Hz, 1H), 2.34 (s, 1H), 2.25 – 2.09 (m, 1H), 0.93 (d, *J* = 6.6 Hz, 6H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 209.9 (C), 168.2 (C), 133.2 (C), 124.9 (C), 124.1 (CH), 119.5 (CH), 115.4 (CH), 114.4 (CH), 52.2 (CH), 52.1 (CH_2), 44.5 (CH_2), 24.7 (CH), 22.5 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{14}H_{19}N_2O_2^+$ 247.1447, found 247.1442.

(*R*)-3-(2-Oxoundecyl)-3,4-dihydroquinoxalin-2(1*H*)-one (2.3ad)



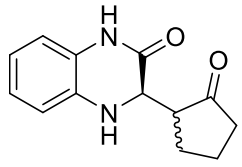
Using 3,4-dihydroquinoxalin-2(1*H*)-one (**2.1a**, 29.6 mg, 0.2 mmol) and undecan-2-one (**2.2d**, 410 µL, 2 mmol, 10 eq.) in accordance with General Procedure, product **2.3ad** (34.8 mg, 0.110 mmol, 55% yield) was obtained as a yellow solid as a single regioisomer. Enantiomeric excess (96%) was determined by chiral HPLC (Chiralcel OD-H), hexane:*i*-PrOH 80:20, 1 mL/min, major enantiomer t_r = 7.74 min, minor enantiomer t_r = 10.47 min. $[\alpha]_D^{20}$ +70.8 (c 0.3, $CHCl_3$) (97% ee); **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 8.38 (bs, 1H), 6.92 – 6.86 (m, 1H), 6.79 – 6.73 (m, 1H), 6.73 – 6.65 (m, 2H), 4.72 (bs, 1H), 4.36 (dt, *J* = 10.4, 2.3 Hz, 1H), 3.30 (dd, *J* = 18.4, 2.3 Hz, 1H), 2.82 (dd, *J* = 18.5, 10.4 Hz, 1H), 2.54 – 2.34 (m, 2H), 1.32 – 1.14 (m, 14H), 0.88 (t, *J* = 6.6 Hz, 3H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 210.3 (C), 168.0 (C), 133.2 (C), 124.9 (C), 124.1 (CH), 119.5 (CH), 115.3 (CH), 114.4 (CH), 52.2 (CH), 43.9 (CH_2), 43.2 (CH_2), 31.8 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 29.1 (CH_2), 23.7 (CH_2), 22.6 (CH_2), 14.1 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{19}H_{28}N_2O_2^+$ 317.2224, found 317.2217.

(3*R*)-3-(2-oxocyclohexyl)-3,4-dihydroquinoxalin-2(1*H*)-one (2.3ae)



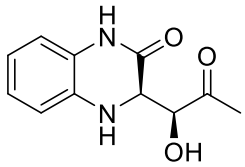
Using 3,4-dihydroquinoxalin-2(1*H*)-one (**2.1a**, 29.6 mg, 0.2 mmol) and ciclohexanone (**2.2e**, 207 µL, 2 mmol, 10 eq.) in accordance with General Procedure, product **2.3ae** (45.0 mg, 0.184 mmol, 92% yield) was obtained as a yellow solid as an inseparable mixture of diastereomers. Diastereomeric ratio (1.4:1) was determined by ^{1}H-NMR. Enantiomeric excess (75% maj, 21% min) was determined by chiral HPLC (Chiralpak IC), hexane:*i*-PrOH 90:10, 1 mL/min, major diastereomer (major enantiomer t_r = 61.43 min, minor enantiomer t_r = 51.37 min) and minor diastereomer (major enantiomer t_r = 24.44 min, minor enantiomer t_r = 26.79 min). $[\alpha]_D^{20}$ +14.9 (c 0.3, $CHCl_3$) (75% ee/21% ee); Minor diastereomer labelled with an asterisk. **^{1}H-NMR (400 MHz, $CDCl_3$)** δ 9.63 – 9.01 (m, H+H*), 6.98 – 6.80 (m, 1H+1H*), 6.80 – 6.55 (m, 3H+3H*), 4.80 (d, *J* = 1.9 Hz, 1H), 4.70 (dd, *J* = 5.2, 3.0 Hz, 1H*), 4.48 (d, *J* = 2.3 Hz, 1H*), 4.18 (dd, *J* = 9.3, 1.8 Hz, 1H), 3.30 (dt, *J* = 10.5, 5.2 Hz, 1H*), 2.80 – 2.63 (m, 1H), 2.57 – 1.50 (m, 8H+8H*); **^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$)** δ 212.9 (C*), 212.2 (C), 168.1 (C*), 166.4 (C), 133.6 (C*), 132.6 (C), 124.9 (C), 124.1 (CH*), 124.0 (CH), 123.7 (C*), 119.2 (CH), 118.3 (CH*), 115.5 (CH), 115.2 (CH*), 114.5 (CH), 113.2 (CH*), 56.8 (CH), 55.1 (CH*), 53.5 (CH*), 50.1 (CH), 42.7 (CH_2), 42.3 (CH2*), 30.8 (CH_2), 27.7 (CH_2), 27.7 (CH2*), 27.6 (CH2*), 24.7 (CH2*), 24.7 (CH_2); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{14}H_{17}N_2O_2^+$ 245.1290, found 245.1295.

(3*R*)-3-(2-Oxocyclopentyl)-3,4-dihydroquinoxalin-2(1*H*)-one (3af)



Using 3,4-dihydroquinoxalin-2(1*H*)-one (**2.1a**, 29.6 mg, 0.2 mmol) and ciclopentanone (**2.2f**, 177 μL, 2 mmol, 10 equiv.) in accordance with General Procedure, product **2.3af** (40.1 mg, 0.174 mmol, 87% yield) was obtained as a yellow solid as an inseparable mixture of diastereomers. Diastereomeric ratio (1:1) was determined by ^{1}H-NMR. Enantiomeric excess (10% maj, 10% min) was determined by chiral HPLC (Chiralpak ODH), hexane:*i*-PrOH 95:15, 1 mL/min, major diastereomer (major enantiomer t_r = 14.99 min, minor enantiomer t_r = 10.90 min) and minor diastereomer (major enantiomer t_r = 18.84 min, minor enantiomer t_r = 16.24 min); **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 8.97 (bs, 1H+1H), 6.94– 6.80 (m, 1H+1H), 6.78– 6.71 (m, 2H+1H), 6.71– 6.66 (m, 1H+1H), 6.61– 6.54 (m, 1H), 4.98 (bs, 1H), 4.71 (d, *J* = 2.7 Hz, 1H), 4.14 (d, *J* = 7.9 Hz, 1H), 3.93 (bs, 1H), 3.18– 2.88 (m, 1H), 2.61– 1.58 (m, 7H+6H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 219.9 (C), 219.8 (C), 167.7 (C), 166.5 (C), 133.1 (C), 133.0 (C), 125.1 (C), 124.2 (C), 124.1 (CH), 119.7 (CH), 118.9 (CH), 115.5 (CH), 115.3 (CH), 114.8 (CH), 113.6 (CH), 57.7 (CH), 54.4 (CH), 53.7 (CH), 48.5 (CH), 38.4 (CH_2), 38.3 (CH_2), 26.6 (CH_2), 23.4 (CH_2), 20.5 (CH_2), 20.0 (CH_2); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{13}H_{15}N_2O_2^+$ 231.1134, found 231.1128.

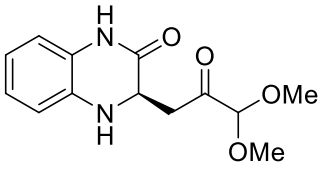
(3*R*)-3-(1-hydroxy-2-oxopropyl)-3,4-dihydroquinoxalin-2(1*H*)-one (2.3ag)



Using 3,4-dihydroquinoxalin-2(1*H*)-one (**2.1a**, 29.6 mg, 0.2 mmol) and hydroxyacetone (**2.2g**, 140 μL, 2 mmol, 10 eq.) in accordance with General Procedure, product **2.3ag** (31.7 mg, 0.144 mmol, 72% yield) was obtained as a yellow solid as an inseparable mixture of diastereomers of the branched regioisomer. Diastereomeric ratio (2:1) was determined by ^{1}H-NMR. Enantiomeric excess (94% maj, 92% min) was determined by chiral HPLC (Chiralpak AS-H), hexane:*i*-PrOH 80:20, 1 mL/min, major diastereomer (major enantiomer t_r = 79.77 min, minor enantiomer t_r = 62.93 min) and minor diastereomer (major enantiomer t_r = 90.88 min, minor enantiomer t_r = 111.46 min). $[\alpha]_D^{20}$ +11.1 (c 0.4, THF) (94% ee/92% ee); Minor diastereomer labelled with an asterisk. **^{1}H-NMR (300 MHz, DMSO-d_6)** δ 10.34 (bs, 1H*), 10.26 (bs, 1H), 6.76 – 6.43 (m, 4H+4H*), 6.16 (d, *J* = 1.5 Hz, 1H), 5.90 (d, *J* = 2.1 Hz, 1H*), 5.74 (d, *J* = 5.7 Hz, 1H*), 5.70 (d, *J* = 5.0 Hz, 1H), 4.34 (t, *J* = 2.2 Hz, 1H), 4.23 (dd, *J* = 4.0, 2.4 Hz, 1H*), 4.18 (dd, *J* = 5.8, 4.2 Hz, 1H*), 4.12 (dd, *J* = 5.2, 2.6 Hz, 1H), 2.18 (s, 3H*), 2.12 (s, 3H); **^{13}C{^{1}H}-NMR (75 MHz, DMSO-d_6)** δ 209.9 (C*), 209.4 (C), 165.0 (C*), 164.6 (C), 133.8 (C), 133.6 (C*), 125.9 (C*), 124.7 (C), 122.7 (CH*), 122.7 (CH), 117.0 (CH*), 116.6 (CH), 114.5 (CH*), 114.4 (CH), 113.2 (CH*), 112.4 (CH), 79.6 (CH), 78.1 (CH*),

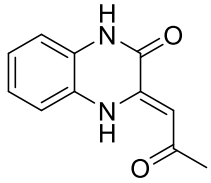
60.2 (CH), 58.7 (CH*), 26.9 (CH_3), 26.8 (CH3*); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{11}H_{12}N_2O_3^+$ 221.0921, found 221.0916.

(*R*)-3-(3,3-dimethoxy-2-oxopropyl)-3,4-dihydroquinoxalin-2(1*H*)-one (2.3ah)



Using 3,4-dihydroquinoxalin-2(1*H*)-one (**2.1a**, 29.6 mg, 0.2 mmol) and 1,1-dimethoxyacetone (**2.2h**, 242 µL, 2 mmol, 10 eq.) in accordance with General Procedure, product **2.3ah** (35.94 mg, 0.136 mmol, 68% yield) was obtained as a yellow solid as a single regioisomer. Enantiomeric excess (96%) was determined by chiral HPLC (Chiralcel AD-H), hexane:*i*-PrOH 80:20, 1 mL/min, major enantiomer t_r = 20.06 min, minor enantiomer t_r = 16.15 min. $[\alpha]_D^{20}$ +70.9 (c 0.4, $CHCl_3$) (96% ee) ; **^{1}H-NMR (400 MHz, $CDCl_3$)** δ 8.63 (bs, 1H), 6.89 (ddd, *J* = 7.8, 7.0, 1.9 Hz, 1H), 6.79 – 6.71 (m, 2H), 6.66 (d, *J* = 7.8 Hz, 1H), 4.54 (bs, 1H), 4.53 (s, 1H), 4.39 (dt, *J* = 10.2, 2.4 Hz, 1H), 3.46 – 3.39 (m, 7H), 2.98 (dd, *J* = 19.0, 10.2 Hz, 1H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 204.9 (C), 167.7 (C), 132.9 (C), 124.9 (C), 124.1 (CH), 119.6 (CH), 115.4 (CH), 114.4 (CH), 103.7 (CH), 54.9 (CH_3), 54.9 (CH_3), 52.0 (CH), 39.8 (CH_2); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{13}H_{17}N_2O_4^+$ 265.1183, found 265.1186.

(*Z*)-3-(2-Oxopropylidene)-3,4-dihydroquinoxalin-2(1*H*)-one (2.5)



Yellow solid; **^{1}H-NMR (300 MHz, DMSO-d_6)** δ 12.95 (bs, 1H), 11.86 (bs, 1H), 7.50 – 7.25 (m, 1H), 7.19 – 6.93 (m, 3H), 6.05 (s, 1H), 2.18 (s, 3H); **^{13}C{^{1}H}-NMR (75 MHz, DMSO-d_6)** δ 197.3 (C), 155.7 (C), 143.2 (C), 126.2 (C), 124.2 (C), 123.6 (CH), 123.4 (CH), 116.0 (CH), 115.3 (CH), 93.2 (CH), 29.8 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for 203.0827, $C_{11}H_{11}N_2O_2^+$, found 203.0821.

Specific Procedure A for the 5 mmol-scale enantioselective asymmetric oxidative Mannich reaction using sunlight as visible-light source:

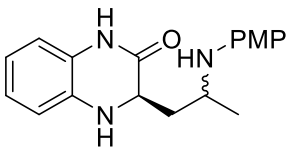
In a 250 mL round bottomed flask 3,4-dihydroquinoxalin-2-one (**2.1a**, 740 mg, 5 mmol), Eosin-Y-Na_2 (**E**, 17.3 mg, 0.025 mmol, 0.5 mol %) and DMF (15 mL) were placed. The reaction mixture was placed at the upper part of the building in sunny hours under vigorous stirring for 6 h (see page 434 for further details about the photochemical setup). Then, (*S*)-Pro (**I**, 115 mg, 1 mmol, 20 mol %) and acetone (**2.2a**, 15 mL) were added and the resulting mixture was stirred for 10 h in the darkness. Thereafter, excess of acetone was removed under reduced pressure. Then, the reaction mixture was diluted with EtOAc (50 mL) and most of the DMF was extracted with water (5x20 mL) and brine (20

mL). The organic layer was dried over anhydrous $MgSO_4$ and the solvent was evaporated under reduced pressure. The obtained residue was purified by column chromatography using DCM:acetone mixture (100:2) as eluent to afford product **3aa** (689 mg, 3.37 mmol, 67% yield) as a yellow solid. Spectroscopic data match with those obtained for the same product at 0.2 mmol-scale. Enantiomeric excess (99%) was determined by chiral HPLC (Chiralcel OD-H), hexane:*i*-PrOH 80:20, 1 mL/min, major enantiomer t_r = 10.66 min, minor enantiomer t_r = 14.20 min.

Specific Procedure B for the synthesis of compound 2.6

In an oven-dried 25 mL round bottomed flask compound **2.3aa** (30.6 mg, 0.15 mmol) and a magnetic stir bar were placed. The flask was purged with N_2 and then, DCM (1.5 mL) was added. The solution was cooled down to 0 °C and AcOH (8.6 μL, 0.15 mmol, 1 equiv.), *p*-anisidine (27.7 mg, 0.225 mmol, 1.5 equiv.) and $NaBH(OAc)_3$ (63.6 mg, 0.3 mmol, 2 equiv) were added successively and the reaction mixture was stirred at rt for 48 h. Then, aq. sat. NH_4Cl (10 mL) was added and the solution was stirred for 10 min. Once the evolution of gas ceased, the mixture was diluted with DCM (10 mL) and the layers were separated. The aqueous layer was extracted with DCM (2x10 mL) and the combined organic layers were dried over $MgSO_4$. After the evaporation of the solvent, the residue was purified by column chromatography using DCM:acetone mixtures (from 100:1 to 100:3) as eluent to afford compound **2.6** (29.0 mg, 0.093 mmol, 62% yield) as a pale yellow oil. The diasteromeric ratio (1.4:1) was determined by ^{1}H-NMR and the enantiomeric excess (99% maj; 96% min) was determined by chiral HPLC (Phenomenex Amylose-1), hexane:*i*-PrOH 80:20, 1 mL/min, Major diastereoisomer (major enantiomer t_r = 36.10 min, minor enantiomer t_r = 22.47 min) Minor diastereosomer (major enantiomer t_r = 29.00 min, minor enantiomer t_r = 20.34 min).

3-(2-((4-Methoxyphenyl)amino)propyl)-3,4-dihydroquinoxalin-2(1*H*)-one (2.6)



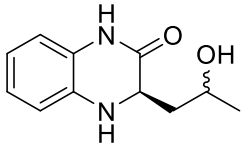
$[\alpha]_D^{20}$ +30.9 (c 0.5, $CHCl_3$) (99% ee/96% ee); Minor diastereoisomer labelled with an asterisk. **^{1}H-NMR (500 MHz, $CDCl_3$)** δ 8.63 (bs, 1H), 8.54 (bs, 1H*), 6.92 – 6.38 (m, 7H+7H*), 5.09 (bs, 1H*), 4.11 (dd, *J* = 7.3, 6.2 Hz, 1H), 4.02 (dd, *J* = 9.2, 2.9 Hz, 1H*), 3.68 (s, 3H+3H*), 3.63 – 3.51 (m, 1H+1H*), 2.17 (dt, *J* = 14.4, 3.1 Hz, 1H*), 1.94 (m, 2H), 1.72 (dt, *J* = 14.5, 9.6 Hz, 1H*), 1.14 (d, *J* = 6.3 Hz, 3H), 1.11 (d, *J* = 6.3 Hz, 3H*); **^{13}C{^{1}H}-NMR (126 MHz, $CDCl_3$)** δ 169.5 (C), 168.9 (C*), 152.9 (C*), 152.4 (C), 141.2 (C), 140.9 (C*), 133.6 (C*), 132.8 (C), 125.4 (C*), 125.3 (C), 123.9 (CH), 123.9 (CH*), 119.4 (CH), 119.3 (CH*), 116.3 (CH, CH*), 115.3 (CH*), 115.1 (CH), 115.0 (CH), 115.0 (CH*), 114.4 (CH), 114.3 (CH*),

56.8 (CH*), 55.8 (CH_3), 55.7 (CH_3*), 53.3 (CH), 51.2 (CH*), 46.1 (CH), 38.2 (CH_2), 38.1 (CH_2*), 21.7 (CH_3*), 21.1 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for 312.1707, $C_{18}H_{22}N_3O_2^+$, found 312.1721.

Specific Procedure B for the synthesis of aminoalcohol 2.7

In an oven-dried 25 mL round bottomed flask was placed compound **2.3aa** (30.6 mg, 0.15 mmol) and a magnetic stir bar. The flask was purged with N_2 and then, MeOH (1.5 mL) was added. The solution was cooled down to 0 °C and, after 5 minutes, $NaBH_4$ (11.3 mg, 0.3 mmol, 2 equiv.) was added in one portion. The mixture was stirred at 0 °C until the starting material was consumed. Then, the reaction was stopped with aq. sat. NH_4Cl (5 mL) and the aqueous phase was extracted with DCM (3x10 mL). The combined organic phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was filtered through a pad of silica eluting with EtOAc to afford compound **2.7** (26.9 mg, 0.131 mmol, 87% yield) as a yellowish oil. The diastereomeric ratio (1:1) was determined by ^{1}H-NMR and the enantiomeric excess was determined by chiral HPLC (Chiralcel IC), hexane:*i*-PrOH 80:20, 1 mL/min, major enantiomer 1 t_r = 12.56 min, minor enantiomer 1 t_r = 8.45 min, , major enantiomer 2 t_r = 15.25 min, minor enantiomer 2 t_r = 10.62 min.

3-(2-hydroxypropyl)-3,4-dihydroquinoxalin-2(1*H*)-one (2.7)



$[\alpha]_D^{20}$ +42.6 (c 0.3, $CHCl_3$) (96% ee/99% ee); Minor diastereoisomer labelled with an asterisk. **^{1}H-NMR (400 MHz, $CDCl_3$)** δ 9.19 (bs, 1H), 9.06 (bs, 1H*), 7.05 – 6.62 (m, 4H+4H*), 4.89 (bs, 1H*), 4.52 (bs, 1H), 4.21 (dd, *J* = 7.8, 4.9 Hz, 1H*), 4.16 – 4.04 (m, 2H+H*), 3.35 (bs, 1H), 2.63 (bs, 1H*), 2.22 (ddd, *J* = 14.4, 4.2, 2.6 Hz, 1H*), 2.04 (ddd, *J* = 13.7, 6.8, 3.2 Hz, 1H), 1.93 (ddd, *J* = 14.4, 7.8, 3.0 Hz, 1H), 1.77 (ddd, *J* = 14.5, 10.2, 8.4 Hz, 1H*), 1.29 (d, *J* = 1.5 Hz, 3H*), 1.27 (d, *J* = 1.5 Hz, 3H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 170.0 (C*), 169.2 (C), 133.7 (C), 133.26 (C*), 125.4 (C*), 125.4 (C), 124.1 (CH*), 124.0 (CH), 119.7 (CH*), 119.4 (CH), 115.6 (CH*), 115.5 (CH), 114.5 (CH), 114.6 (CH*), 68.3 (CH), 65.1 (CH*), 56.2 (CH), 54.2 (CH*), 40.0 (CH_2*), 39.7 (CH_2), 24.7 (CH_3), 23.7 (CH_3*);**HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for 207.1134, $C_{11}H_{15}N_2O_2^+$, found 207.1141.

Chapter 3

Functionalization of 3,4-Dihydroquinoxalin-2-ones with Pyrazolones under Visible-Light Photoredox Catalysis

3.1 Introduction and state of the art

Pyzazol-3-one is a nitrogen-containing heterocycle that derives from pyrazole, and therefore it bears two consecutive nitrogen atoms and a carbonyl group at its C-3 position (Figure 3.1). As many other heterocycles of this kind, pyrazol-3-one suffers from the exixtence of several tautomeric equilibriums and, consequently, it has distinct nucleophilic positions (Figure 3.1).

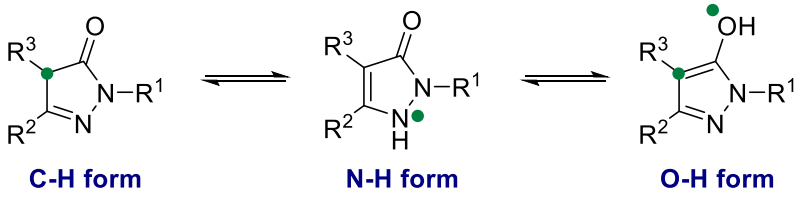


Figure 3.1: Tautomeric forms in pyrazol-3-one. Nucleophilic positions are marked with a green circle.

The skeleton of pyrazol-3-one can be found in several compounds that have a myriad of applications in many fields, such as the agrochemical industry or as active pharmaceutical ingredients (API).[146,147] It is important to highlight some of them, such as edaravone,[148] a neuroprotective agent (Figure 3.2, *left*), metamizole,[149,150] the most powerful antipyretic, which is the API of Nolotil (Figure 3.2, *center*) and tartrazine,[151,152] a synthetic lemon yellow azo dye primarily used as a food coloring (Figure 3.2, *right*)

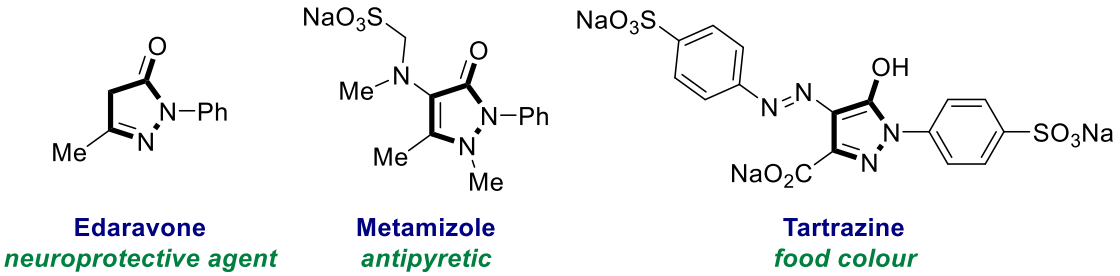
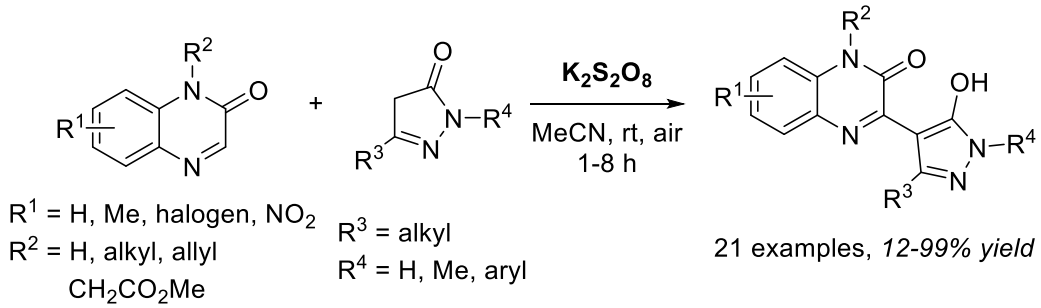


Figure 3.2: Relevant pyrazol-3-one derivatives.

In organic chemistry, pyrazol-3-ones have been extensively used as nucleophiles in a great assortment of methodologies, especially in enantioselective processes.[147,153] In fact, our research group has wide experience in the asymmetric functionalization of these heterocyles with several electrophiles.[154–156] However, to the best of our knowledge, there are not reports about the use of such heterocycles in visible-light mediated processes.

Moreover, there is just one report about the C-3 functionalization of quinoxalin-2-ones with pyrazol-3-ones, and it came from the laboratory of Yotphan in 2018.[157] In this case, the authors employed thermal oxidation conditions with stoichiometric $K_2S_2O_8$ (Scheme 3.1).

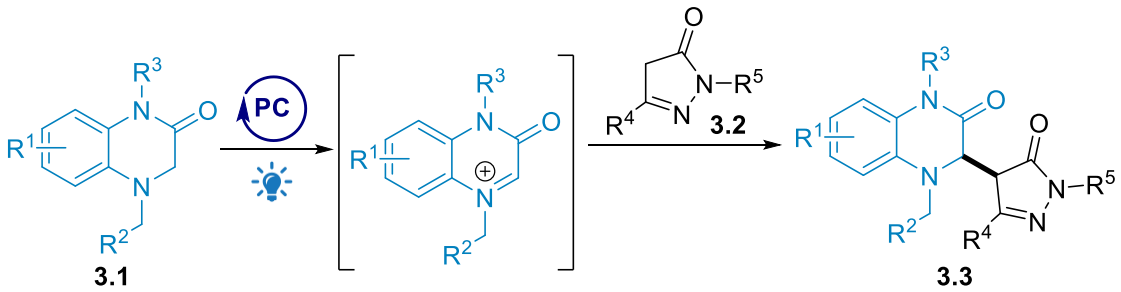


Scheme 3.1: Functionalization of quinoxalin-2-ones with pyrazol-3-ones under thermal oxidation conditions (Yotphan).

In light of this precedents, we thought that it would be of interest the development of a protocol for the C-3 functionalization of 3,4-dihydroquinoxalin-2-ones (**3.1**) with pyrazol-3-ones (**3.2**) using visible-light photoredox catalysis. Our approach consists in the generation of the iminium cation of the more electron-rich 4-alkyl-3,4-dihydroquinoxalin -2-ones through aerobic photocatalysis, and the subsequent trapping of this electrophile with pyrazol-3-ones.

3.2 Objectives

The main objective for this *Chapter* is to develop a methodology to functionalize 3,4-dihydroquinoxalin-2-ones (**3.1**) through the iminium cation, with pyrazol-3-ones (**3.2**) employing visible-light photoredox catalysis. To achieve this objective, several partial objectives are postulated:



1. Synthesis of 4-alkyl-3,4-dihydroquinoxalin-2-ones (**3.1**) bearing substituents with different electronic and steric properties.

2. Optimization of the reaction conditions between 4-benzyl-3,4-dihydroquinoxalin-2-one **3.1a** and 5-methyl-2-phenylpyrazol-3-one (edaravone, **3.2a**) to obtain the corresponding product **3.3aa** with the highest yield.

3. Study of the scope of the reaction between different 4-alkyl-3,4-dihydroquinoxalin-2-ones (**3.1**) and different pyrazol-3-ones (**3.2**).

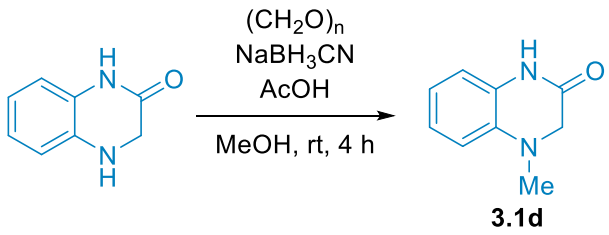
4. Mechanistic investigations and proposal of a reaction mechanism.

3.3 Results and Discussion

3.3.1 Synthesis of 4-alkyl-3,4-dihydroquinoxalin-2-ones 3.1

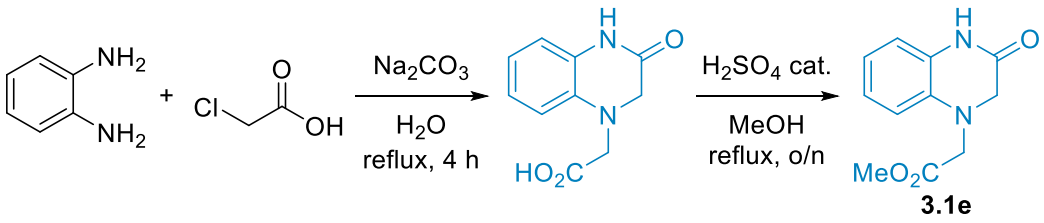
The required 4-alkyl-3,4-dihydroquinoxalin-2-ones **3.1a**-**3.1c** and **3.1f**-**3.1l** were prepared from its N-4 unprotected analogues of *Chapter 2* (pages 113 and 115). The subsequent alkylation of N-4 with the corresponding alkyl chloride was done following the same procedure that was used for the synthesis of **1.5** in *Chapter 1* (page 67).

4-methyl-3,4-dihydroquinoxalin-2-one **3.1d** was prepared from its N-4-unprotected analogue following a reported procedure,[158] in which N-4 is methylated using a reductive amination with paraformaldehyde in the presence of $NaBH_3CN$ (Scheme 3.2).



Scheme 3.2: Synthesis of 3,4-dihydroquinoxalin-2-one **3.1d**.

Besides, 3,4-dihydroquinoxalin-2-one **3.1e** was prepared following a two-step procedure. In the first step, the reaction between *o*-phenylenediamine and two equivalents of chloroacetic acid gives 3,4-dihydroquinoxalin-2-one with a CH_2CO_2H group at N-4.[159] The subsequent methylation of the carboxylic acid through a Fischer esterification delivers ester **3.1e** (Scheme 3.3).



Scheme 3.3: Synthesis of 3,4-dihydroquinoxalin-2-one **3.1e**.

Figure 3.3 shows all 3,4-dihydroquinoxalin-2-ones **3.1** that have been synthesized and will be used in this *Chapter*.

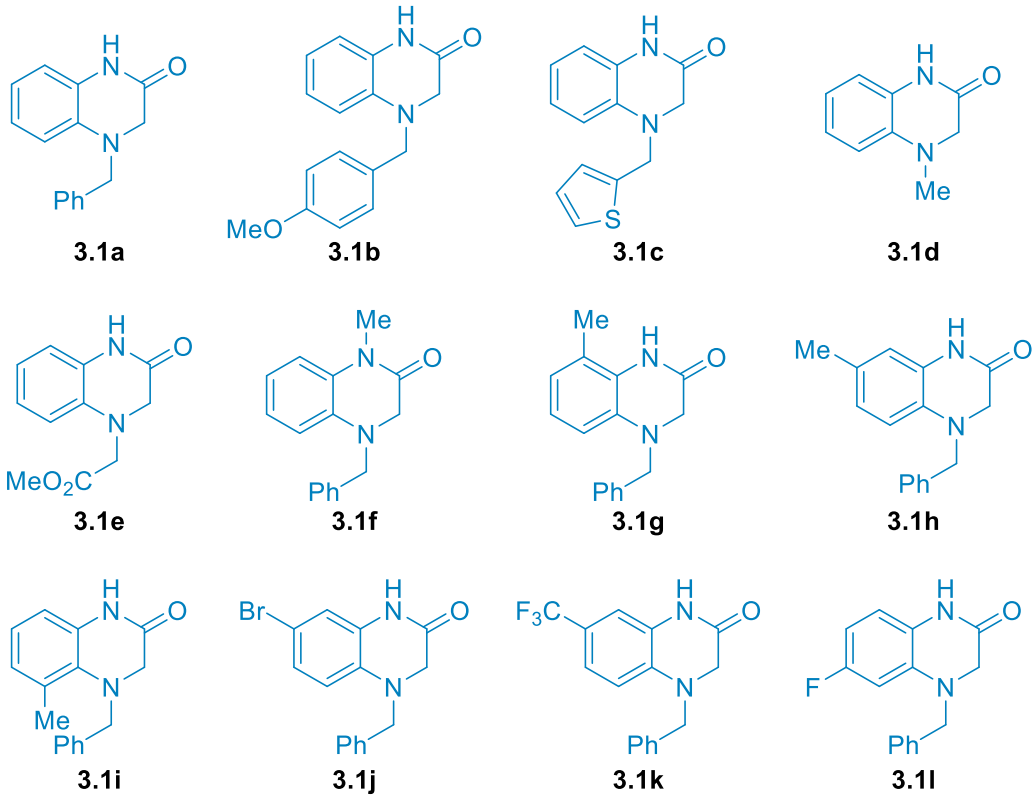


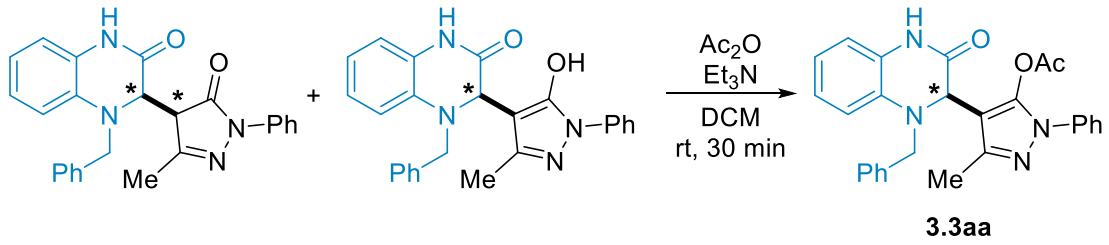
Figure 3.3: Summary of all 3,4-dihydroquinoxalin-2-ones **3.1a**-**3.1l** synthesized.

3.3.2 Optimization of the Reaction Conditions

Once all the required 3,4-dihydroquinoxalin-2-ones **3.1** have been prepared, we started the optimization process for the alkylation reaction between 4-benzyl-3,4-dihydroquinoxalin-2-one **3.1a** and edaravone **3.2a**. After several preliminary assays, the necessity of an alkyl chain at N-4 in the skeleton of 3,4-dihydroquinoxalin-2-one was imperative, as the N-4 unprotected analogue did not show the desired reactivity.

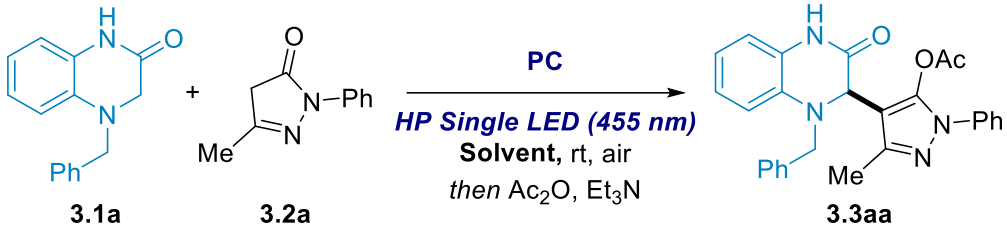
Moreover, these preliminary tests shown how difficult it is to isolate and characterize the alkylation product between **3.1a** and **3.2a**. In fact, this product has two stereogenic centers, one of them with no configurational stability due to ceto-enol tautomerism (Scheme 3.4). Based on previous experience of our research group,[154,156,160] we decided to add an extra step after the photochemical reaction to trap the pyrazol-3-one enolate via an *O*-acetylation. This treatment gave product **3.3aa**, which was much easier to isolate and to characterize.

After addressing these issues, the optimization process began with the evalutation of the best solvent to perform the reaction. Then, an array of photocatalysts will be screened to select the one that maximizes the yield of **3.3aa**. Lastly, some final adjustments will be done (Scheme 3.5). Given the structural similarity between 3,4-dihydro-1,4-benzoxazin-



Scheme 3.4: Tautomeric forms in the reaction product between **3.1a** and **3.2a**. *O*-acetylated product **3.3aa**.

2-ones **1.1** and 3,4-dihydroquinoxalin-2-ones **3.1**, we decided to start the optimization process using a slight excess of amine with regard to edaravone (**3.2a**). According to our results in *Chapter 1*, once the iminium ion of **1.1** is generated it could suffer the attack of other nucleophiles (water, O_2...) to form undesired products. We thought that the iminium cation of 3,4-dihydroquinoxalin-2-ones **3.1** would share the same fate as their oxygenated analogues **1.1**. Accordingly, the optimization will be initially conducted using 0.13 mmol of **3.1a** and 0.1 mmol of **3.2a**.

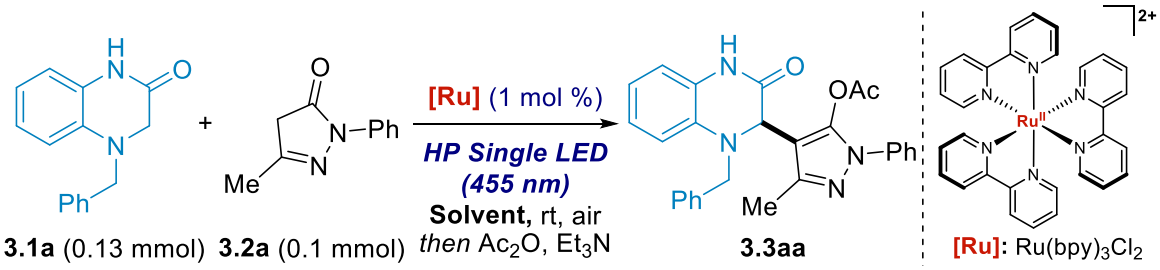


Scheme 3.5: Overview of the model reaction to carry out the optimization of the reaction conditions.

Evaluation of the Solvent

Preliminary assays shown that $Ru(bpy)_3Cl_2$ (**A**) was able to generate the expected product **3.3aa** in MeCN. Consequently, we decided to try first different solvents using $Ru(bpy)_3Cl_2$ (**A**) as photocatalyst (Scheme 3.6). Contrary to other studies from our laboratory, we could perform the *O*-acetylation in the same reaction medium (one-pot), without the need of exchanging the solvent to DCM.

Pleasingly, when the reaction was launched using MeCN as solvent, product **3.3aa** was generated in 39% yield after 24 hours of irradiation (Table 3.1, Entry 1). Switching the solvent to EtOAc or acetone did not improve the yield in which compound **3.3aa** was formed (Table 3.1, Entries 2 and 3). DMF was tried as solvent, as it shown a good performance in the asymmetric oxidative Mannich reaction of *Chapter 2* but, unfortunately, in



Scheme 3.6: Effect of the solvent in the reaction between **3.1a** and **3.2a** using $Ru(bpy)_3Cl_2$ (**A**) as photocatalyst.

this case the yield was as low as 29% after 23 hours of reaction (Table 3.1, Entry 4). Besides, neither THF nor MeOH were found to be suitable for this transformation, since they generated **3.3aa** in 25% and 13% yield respectively (Table 3.1, Entries 5 and 6). However, within the family of chlorinated solvents we were pleased to find a better performance in terms of yield. Specifically, DCM and $CHCl_3$ provided product **3.3aa** in 72% and 75% yield after two chemical steps (Table 3.1, Entries 7 and 8).

Table 3.1: Evaluation of the solvent in the reaction between **3.1a** and **3.2a** using $Ru(bpy)_3Cl_2$ (**A**) as photocatalyst. Yield of **3.3aa** after two steps.

Entry[a]	Solvent	t (h)	Yield 3.3aa (%)[b]
1	MeCN	24	39
2	EtOAc	24	9
3	Acetone	8	54
4	DMF	23	29
5	THF	23	25
6	MeOH	23	13
7	DCM	23	72
8	$CHCl_3$	23	75

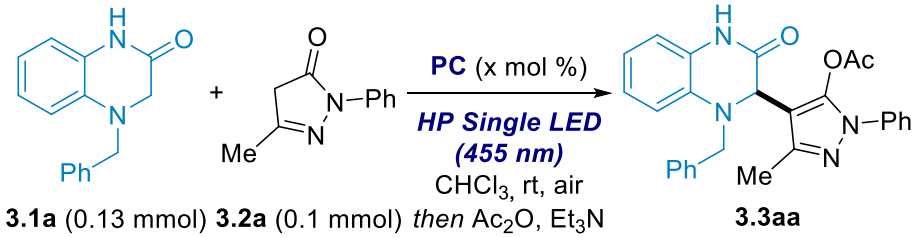
[a]Reaction conditions: **3.1a** (0.13 mmol), **3.2a** (0.1 mmol), **A** (1 mol %), Solvent (1 mL), under air atmosphere and under HP Single LED (455 nm) irradiation for the indicated time. Then, Ac_2O (0.2 mmol), Et_3N (0.1 mmol), rt for 0.5 h.

[b]Yield determined after purification by column chromatography.

In light of these findings, we selected $CHCl_3$ as the optimal solvent to carry out the reaction. Consequently, the optimization process was continued using this solvent.

Evalutation of the Photoredox Catalyst

Once determined the optimal solvent, the next step in the path was to evaluate a selection of photoredox catalysts (Scheme 3.7). In principle, the photoredox catalyst is the responsible to generate the iminum cation of 3,4-dihydroquinoxalin-2-one **3.1a** in combination with molecular oxygen from air.



Scheme 3.7: Effect of the photoredox catalyst in the reaction between **3.1a** and **3.2a** using $CHCl_3$ as solvent.

Some of the most employed photocatalysts were subjected to our preliminary conditions to test their competence in generating product **3.3aa** compared to that of $Ru(bpy)_3Cl_2$ (**A**) . Notably, when $Ir(ppy)_3$ (**K**) was employed, the corresponding product **3.3aa** was only generated in 47% yield (Table 3.2, Entry 2).

In the view of developing a more sustainable chemical process, avoiding the use of metal-based catalysts, we moved to organophotocatalysts as candidates for promoting the photochemical reaction. In this sense, after showing high ability in the oxidation of 3,4-dihydroquinoxalin-2-one **2.1a** (*Chapter 2*), Eosin-Y-Na_2 (**E**) was tested in this photochemical alkylation with edaravone (**3.2a**). Unfortunately, in this case, the expected product **3.3aa** was generated only in 34% yield (Table 3.2, Entry 3). Other purely-organic photocatalysts were tried, for example 4CzIPN (**M**), which was implemented as photocatalyst few years ago along with other structural analogues.[33] Sadly, in our case was just able to produce **3.3aa** in 46% yield (Table 3.2, Entry 4). Nevertheless, when [2,4,6-Ph_3-pyrillium][BF_4] (**G**) was used, product **3.3aa** was generated in 89% yield after 24 of irradiation, offering an interesting alternative to $Ru(bpy)_3Cl_2$ (**A**) (Table 3.2, Entry 5). Motivated with this last result, we also decided to test the ability of [Mes-Acr-Me][BF_4] (**H**), obtaining in this case a slightly lower yield (Table 3.2, Entry 6).

Finally, given the good performance of 9,10-phenanthrenequinone (**J**) in the photocatalytic Friedel-Crafts reaction between 3,4-dihydro-1,4-benzoxazin-2-ones and indoles (*Chapter 1*), we decided to try it in this transformation. Thankfully, we obtained product **3.3aa** in 89% yield after only 7 hours of irradiation (Table 3.2, Entry 7).

On the other hand, we decided to repeat the reaction but without photocatalyst, as we noted in Chapter 2 that the oxidation of these kind of amines may proceed without

it. As expected, product **3.3aa** was generated in 69% yield after 24 hours of irradiation (Table 3.2, Entry 8). This result is line with our previous observations and other reports,[78] in which there has to be a complementary non-photocatalytic pathway that oxidizes 4-benzyl-3,4-dihydroquinoxalin-2-one **3.1a**. However, this pathway was found to be less efficient, since the yield in which **3.3aa** is formed is lower, and it also requires longer irradiation times.

Table 3.2: Evaluation of the photoredox catalyst in the reaction between **3.1a** and **3.2a** using $CHCl_3$ as solvent. Yield of **3.3aa** in each case after two steps.

Entry[a]	**PC (x mol %)**	**t (h)**	**Yield 3.3aa (%)**[b]
1	$Ru(bpy)_3Cl_2$ (**A**) (1)	23	75
2	*fac*-$Ir(ppy)_3$ (**K**) (1)	23	47
3	Eosin-Y-Na_2 (**E**) (5)	23	34
4	4CzIPN (**M**) (2)	23	46
5	[2,4,6-Ph_3-pyrillium][BF_4] (**G**) (5	24	89
6	[Mes-Acr-Me][BF_4] (**H**) (5)	24	71
7	9,10-Phenanthrenequinone (**J**) (5)	7	89
8	-	24	69

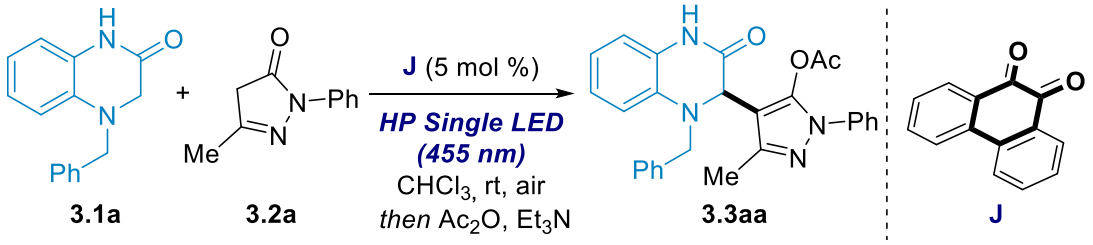
[a]Reaction conditions: **3.1a** (0.13 mmol), **3.2a** (0.1 mmol), **PC** (x mol %), $CHCl_3$ (1 mL), under air atmosphere and under HP Single LED (455 nm) irradiation for the indicated time. Then, Ac_2O (0.2 mmol), Et_3N (0.1 mmol), rt for 0.5 h.

[b]Yield determined after purification by column chromatography.

At this point, we were in a position to select 9,10-phenanthrenequinone (**J**) as photoredox catalyst. However, we assume that our reaction could work in a photocatalyst-free manner, which is also interesting in terms of a more practical methodology. For comparative purposes, some of the examples of the scope will be done with and without photocatalyst.

Evaluation of the Molar Ratio

Having selected $CHCl_3$ as optimal solvent and 9,10-phenanthrenequinone (**J**) as the best photocatalyst, we only need to adjust the molar ratio for our reaction. As has been noted earlier, we wanted to use a slight excess of **3.1a** over **3.2a** in anticipation of potential side mechanisms that would consume **3.1a** unproductively. However, we also wanted to check if this phenomenon operates in our present case of study (Scheme 3.8).



Scheme 3.8: Evaluation of the molar ratio in the reaction between **3.1a** and **3.2a** using $CHCl_3$ as solvent and **J** as photoredox catalyst.

Conversely, when 0.1 mmol of **3.1a** and 0.1 mmol of **3.2a** reacted, the expected product was obtained in 86% yield, namely without a notable erosion in the yield (Table 3.3, Entry 2). Even when an equimolar amount of **3.1a** and **3.2a** was used, product **3.3aa** was isolated in 87% yield (Table 3.3, Entry 3). These results shown how this reaction seems to be unaffected to secondary pathways that destroy amine **3.1a**, so in principle an equimolar quantity of **3.1a** and **3.2a** could be employed as optimal conditions.

Table 3.3: Evaluation of the molar ratio in the reaction between **3.1a** and **3.2a** using $CHCl_3$ as solvent and **J** as photoredox catalyst. Yield of **3.3aa** in each case after two steps.

Entry[a]	3.1a (mmol)	3.2a (mmol)	t (h)	Yield 3.3aa (%)[b]
1	0.13	0.1	7	89
2	0.1	0.13	6	86
3	0.1	0.1	6	87

[a]Reaction conditions: **3.1a** (x mmol), **3.2a** (x mmol), **J** (5 mol %), $CHCl_3$ (1 mL), under air atmosphere and under HP Single LED (455 nm) irradiation for the indicated time. Then, Ac_2O (0.2 mmol), Et_3N (0.1 mmol), rt for 0.5 h.

[b]Yield determined after purification by column chromatography.

To sum up, we found that the best conditions to carry out the reaction between 4-benzyl-3,4-dihydroquinoxalin-2-one (**3.1a**) and edaravone (**3.2a**) include the use of 9,10-phenanthrenequinone (**J**) as photoredox catalyst and $CHCl_3$ as solvent in a 1:1 **3.1a**:**3.2a** molar ratio. Moreover, we have identified that the reaction could proceed without photocatalyst, although requiring longer light exposure times.

3.3.3 Scope of the Reaction

Having established the optimal reaction conditions to perform the photocatalytic alkylation reaction, in this *Section* a broad study of how different substitution patterns affect the performance of both the 3,4-dihydroquinoxalin-2-one **3.1** and the pyrazol-3-one **3.2**

counterparts will be done. But initially, the use of several electrophiles to trap the enol will be studied.

Evaluation of the Trapping Agent

Although the treatment of the crude reaction mixture with Ac_2O after the photocatalytic step delivered acetylated product **3.3aa** cleanly, we wanted to test if we could efficiently introduce other protecting groups for two reasons: 1) obtain the corresponding product in higher yield and 2) expand the substitution versatility over the oxygen atom (Figure 3.4).

Once the photochemical reaction finished, the electrophilic reagent was added to the reaction mixture. Specifically, when it was treated with benzoyl chloride, the corresponding benzoylated product **3.4aa** was generated in 47% yield (Figure 3.4). Alternatively, the reaction was stopped with tosyl chloride, and in this case the corresponding product was obtained in 86% yield (Figure 3.4). After testing three trapping agents, we decided to choose Ac_2O as the most convenient reagent because it provides the expected product in the highest yield and the product is more easily analyzed by ressonance techniques.

Additionally, we decided to incorporate a more valuable motif to our alkylation product. Concretely, we were pleased to incorporate the indomethacin[161,162] scaffold, by using indomethacin acid chloride, obtaining product **3.6aa** in 55% yield (Figure 3.4). Although it was not a high-yield reaction, we build in a straightforward way a molecule that contains three nitrogen-containing pharmacophores: 3,4-dihydroquinoxalin-2-one, pyrazol, and indomethacin.

Scope of the Reaction with Pyrazol-3-ones

On one hand, the substitution on the pyrazol-3-one (**3.2**) counterpart was explored (Figure 3.5). Fortunately, all the pyrazol-3-ones needed were available in our laboratory.

Initially we wanted to evaluate how robust was our catalytic protocol if a phenyl moiety was placed in the C-5 position of pyrazol-3-one. Sadly, using the optimal conditions we observed a large decrease in the yield until 42% (**3.3ab**). With the aim of getting a higher yield for the same product, we moved back to use 0.13 mmol of **3.1a** and, gratefully, product **3.3ad** was this time generated in 80% yield. Seizing this situation, we also conducted the same reaction without photocatalyst **J**, and in this case the yield drastically dropped until 8%.

Although using of 0.13 mmol of **3.1a** was clearly beneficial for the reaction outcome, we decided to give another chance to 1:1 molar ratio using this time 2,5-dimethylpyrazol-3-one (**3.2c**) as nucleophile. In the same vain, product **3.3ac** was isolated in only 44% yield. However, when 0.13 mmol of **3.1a** were used, the yield discretely increased until

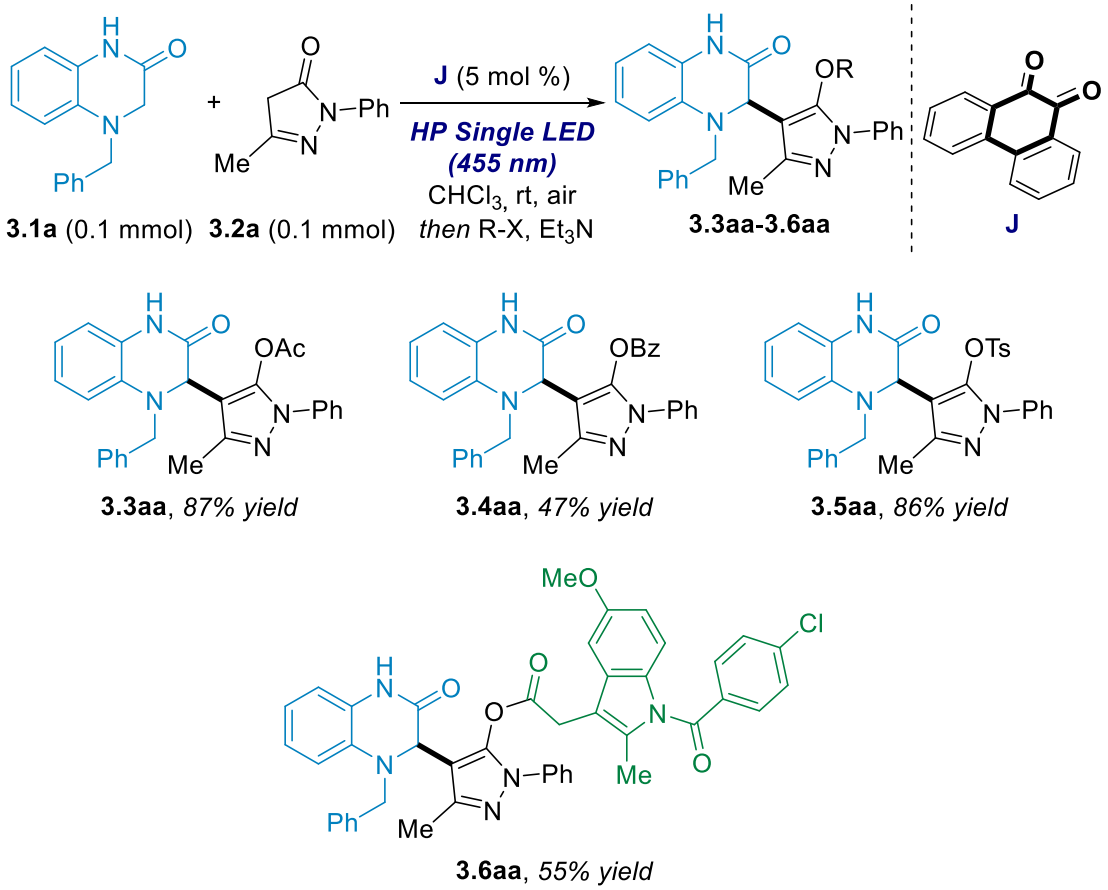


Figure 3.4: Evaluation of other trapping agents in the reaction between **3.1a** and **3.2a** using $CHCl_3$ as solvent and **J** as photoredox catalyst. Yields of products **3.3aa**-**3.6aa**.[a]

[a]Reaction conditions: **3.1a** (0.1 mmol), **3.2** (0.1 mmol), **J** (5 mol %), $CHCl_3$ (1 mL), under air atmosphere and under HP Single LED (455 nm) irradiation. Then, R−X (0.2 mmol), Et_3N (0.1 mmol), rt for 0.5 h. Yield determined after purification by column chromatography.

52%. Again, just 15% yield was observed when the reaction was done without photocatalyst.

After verifying, that by using 0.13 mmol of **3.1a** the yields in which the corresponding products were generated were substantially higher, at this point we decided to continue the whole study of the scope of the reaction using this slightly higher amount of **3.1a**.

With these conditions, the substitution at C-5 position (R^4) in pyrazol-3-ones was examined. Pleasingly, when either an ethyl or a *n*-propyl group was present in the pyrazol-3-one moiety, the corresponding products **3.3ad** and **3.3ea** were generated in 95 and 91% yield. Accordingly, when a cyclopropyl substituent was placed in C-5, product **3.3af** was generated quantitatively. Finally, the presence of a $-CF_3$ group in the same position allowed us to obtain the expected product (**3.3af**) in 89% yield .

Interestingly, pyrazol-3-one with no substitution at N-2 (R^5) was found to be a suitable

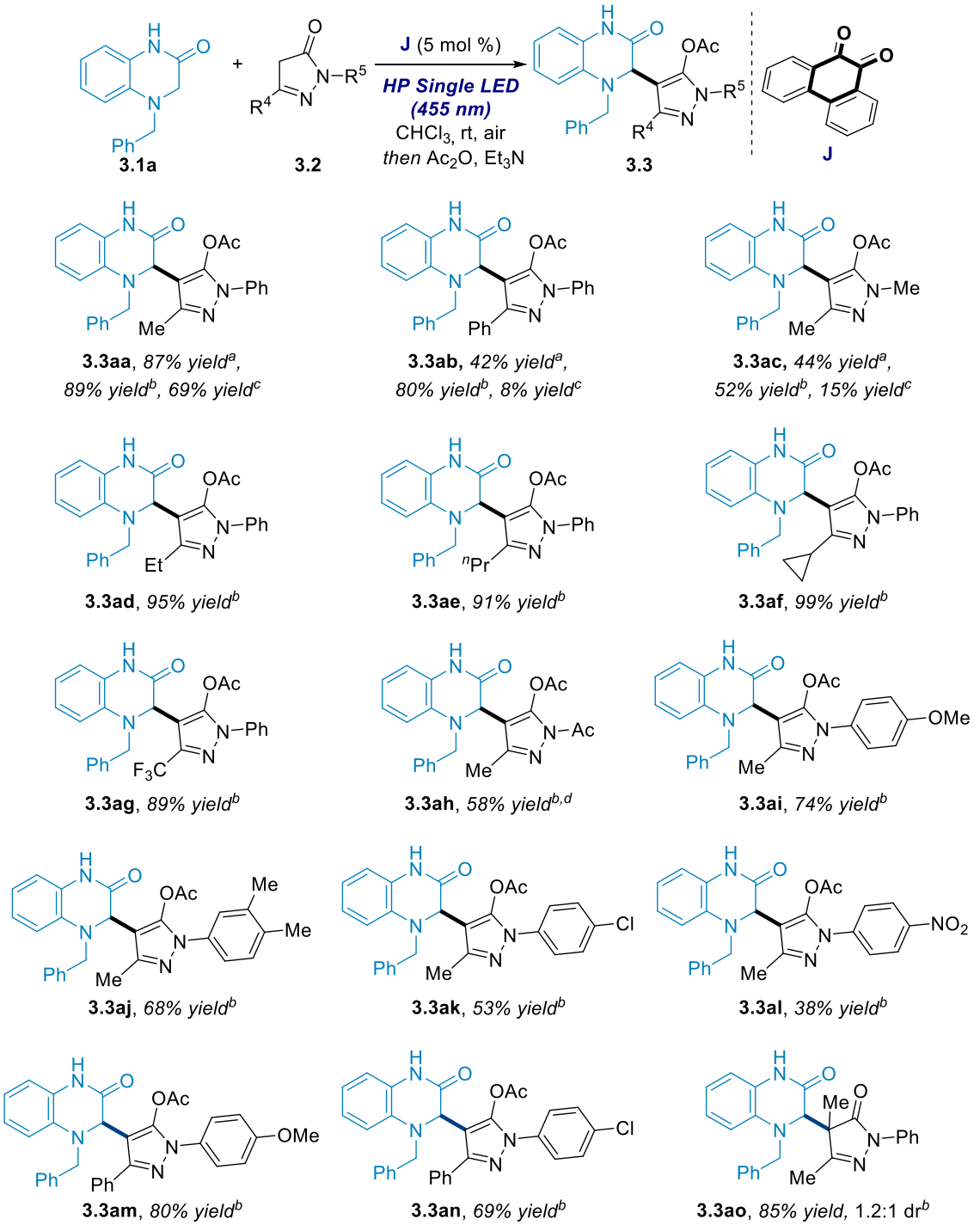


Figure 3.5: Scope of the reaction using 3,4-dihydroquinoxalin-2-one **3.1a** and different pyrazol-3-ones **3.2**[abcd]

[a]Reaction conditions: **3.1a** (0.1 mmol), **3.2** (0.1 mmol), **J** (5 mol %), $CHCl_3$ (1 mL), under air atmosphere and under HP Single LED (455 nm) irradiation. Then, Ac_2O (0.2 mmol), Et_3N (0.1 mmol), rt for 0.5 h. Yield determined after purification by column chromatography.

[b]0.13 mmol of **3.1a** were used.

[c]Without photocatalyst **J**.

[d]Compound **3.3ah** was obtained as a mixture of the two *N*-acetylation regioisomers in 1.1:1 ratio. Combined yield.

substrate for our reaction. However, the acetylation process was not regioselective, as both *N*-acetyl regioisomers of product **3.3ah** were obtained in a 1.1:1 ratio with a combined yield of 58%.

Having verified that a wide range of substituents can be placed at C-5, the substitution at the aromatic ring of C-2 was subjected to study. Electro-withdrawing groups such as *p*-OMe or *m*,*p*-diMe) had little influence in generating the expected products **3.3ai** and **3.3aj**, as they were isolated in 74% and 68% yield respectively. Moreover, pyrazol-3-ones bearing electro-withdrawing groups were also subjected to our photocatalytic reaction. Precisely, a *p*-Cl aromatic ring at C-2 resulted in a drop in the yield for product **3.3al** (53% yield), whereas in presence of the strong electro-withdrawing $-NO_2$ group, the decrease in which product **3.3al** was obtained was more pronounced (38% yield).

The effect of either electro-donating and electro-withdrawing groups over the N-2 aromatic ring was also examined with 5-phenyl-substituted pyrazol-3-ones (**3.2m** and **3.2n**). In this case, the effect of these groups was much lower, since products **3.3am** and **3.3an** bearing a *p*-OMe and a *p*-Cl substituents were isolated in 80% and 69% yield respectively.

Finally, we wondered if we could extend the scope of pyrazol-3-ones to the use of 4-substituted analogues to forge a quaternary all-carbon center. Delightfully, when 2-phenyl-4,5-dimethylpyrazol-3-one (**3.2o**) was employed as nucleophile, the corresponding product **3.3ao** was afforded in 85% yield, albeit with a poor 1.2:1 dr.

Scope of the Reaction with 3,4-Dihydroquinoxalin-2-ones

On the other hand, and after realizing that our reaction protocol tolerates a wide substitution pattern in pyrazol-3-ones **3.2**, the scope of this transformation was completed by studying the effect of several functional groups on the skeleton of 3,4-dihydroquinoxalin-2-one **3.1** (Scheme 3.9).

First of all, the effect of the benzylic substituent at N-4 was examined. The more electron-rich 3,4-dihydroquinoxalin-2-one **3.1b** delivered the expected product **3.3ba** in a significantly lower yield of 54%. This may arise from its greater reactivity, which would lead to a higher propensity to suffer side reactions. In the same vain, the thiophene-substituted 3,4-dihydroquinoxalin-2-one **3.3c** delivered the corresponding product in a low 37% yield.

The presence of other substituents rather than $-CH_2Ar$ at N-4 such as methyl or $-CH_2CO_2Me$ had minor influence in the reaction performance, as products **3.3da** and **3.3ea** were isolated in 74% and 65% respectively. In the case of the 3,4-dihydroquinoxalin-2-one bearing the $-CH_2CO_2Me$ group (**3.1e**), it has to be highlighted that only the formation of the endocyclic iminium cation was observed, instead of the one that arises from

the glycine-like part of the scaffold.

Besides, *N*,*N*-1,4-disubstituted-3,4-dihydroquinoxalin-2-one **3.1f** was able to generate its expected product in only 55% yield.

The effect over the reaction performance of the substitution at the parent aromatic ring of 3,4-dihydroquinoxalin-2-ones **3.1** was also interrogated. In this sense, 3,4-dihydroquinoxalin-2-ones bearing a methyl substituent in either C-8, C-7 and C-5 were tested as pre-electrophiles. To our delight, products **3.3ga**, **3.3ha** and **3.3ia** were isolated in 62%, 63% and 42% yield respectively. The lower reactivity that derivative **3.2i** displayed may arise from the high steric demand near to the aminic nitrogen, which could have encountered issues to interact with the photocatalyst.

Finally, the substitution at the same aromatic ring with electro-withdrawing groups was evaluated. The presence of either a bromine or a trifluoromethyl group at C-7, which reduces the electron density over the aminic nitrogen, was positive for the reaction outcome, as the corresponding products **3.3ja** and **3.3ka** were obtained in 81% and 78% yield respectively. On the contrary, the occupation of the C-6 position with a fluorine atom dropped the yield in which the expected product **3.la** was generated to 45%.

Scope of the Reaction with 5-Aminopyrazoles

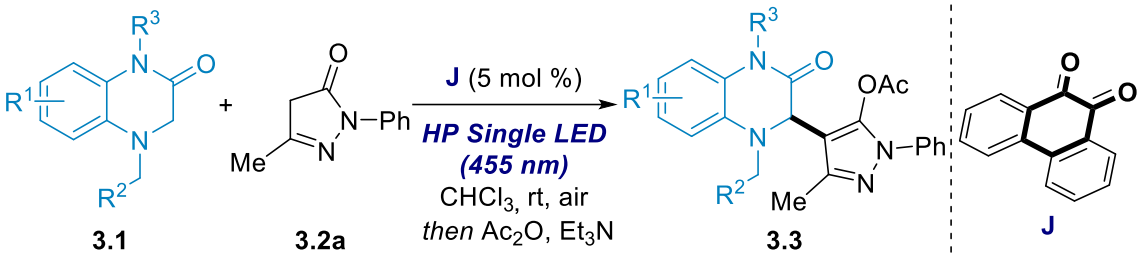
With the aim to further extend the generality of our protocol, we were interested in the use of 5-aminopyrazoles (**3.7**) as pyrazol-3-one analogues (Scheme 3.10). Pleasingly, three differently substituted 5-aminopyrazoles at C-3 could efficiently react with 3,4-dihydroquinoxalin-2-one **3.1a**. Specifically, 3-methyl-1-phenyl-5-aminopyrazole (**3.7a**) was able to generate the expected product **3.8aa** in 60% yield. Besides, 5-aminopyrazoles **3.7b** and **3.7c** bearing either a phenyl or a *p*-MePh substituent at C-3 afforded alkylated 3,4-dihydroquinoxalin-2-ones **3.8ab** and **3.8ac** in 74% and 95% yield respectively.

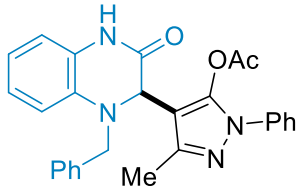
Interestingly, products **3.8** did not suffer from imine-enamine tautomerism in contrast to the ceto-enol tautomerism of products **3.3**, and therefore the acetylation reaction was not necessary.

3.3.4 Large-Scale Reaction under Sunlight Irradiation

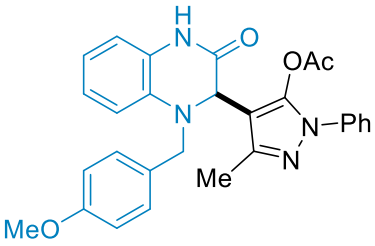
To demonstrate the utility of our protocol, we decided to scale-up the reaction to 1 mmol using sunlight as energy source (Scheme 3.11). Pleasingly, the photochemical reaction between 1.1 mmol of **3.1a** and 1 mmol of **3.2a**, and the subsequent *O*-acetylation, yielded expected product **3.3aa** in 60% after 7.5 hours of sunlight irradiation. The temperature was estimated to be in the range of 25-30 °C.

Here it is important to note that although the power of sunlight is greater than that

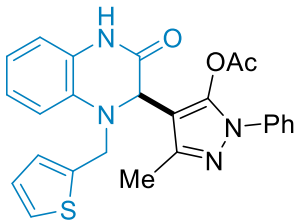




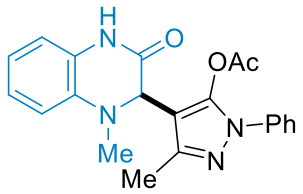
3.3aa, *89% yield*



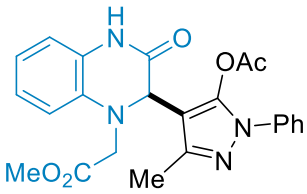
3.3ba, *54% yield*



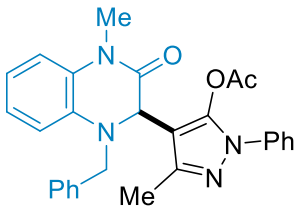
3.3ca, *37% yield*



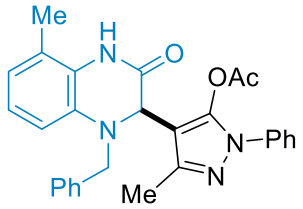
3.3da, *74% yield*



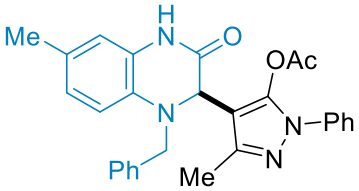
3.3ea, *65% yield*



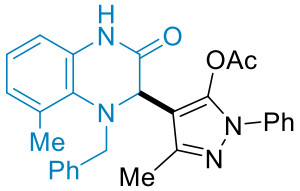
3.3fa, *55% yield*



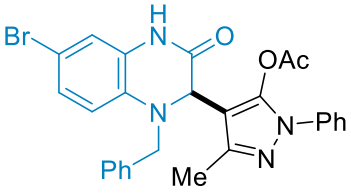
3.3ga, *62% yield*



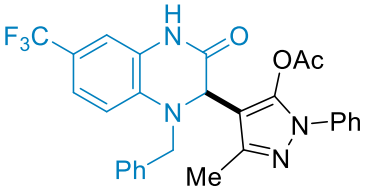
3.3ha, *63% yield*



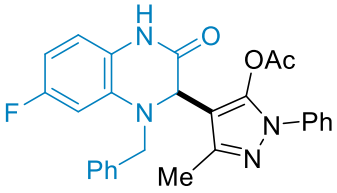
3.3ia, *42% yield*



3.3ja, *81% yield*



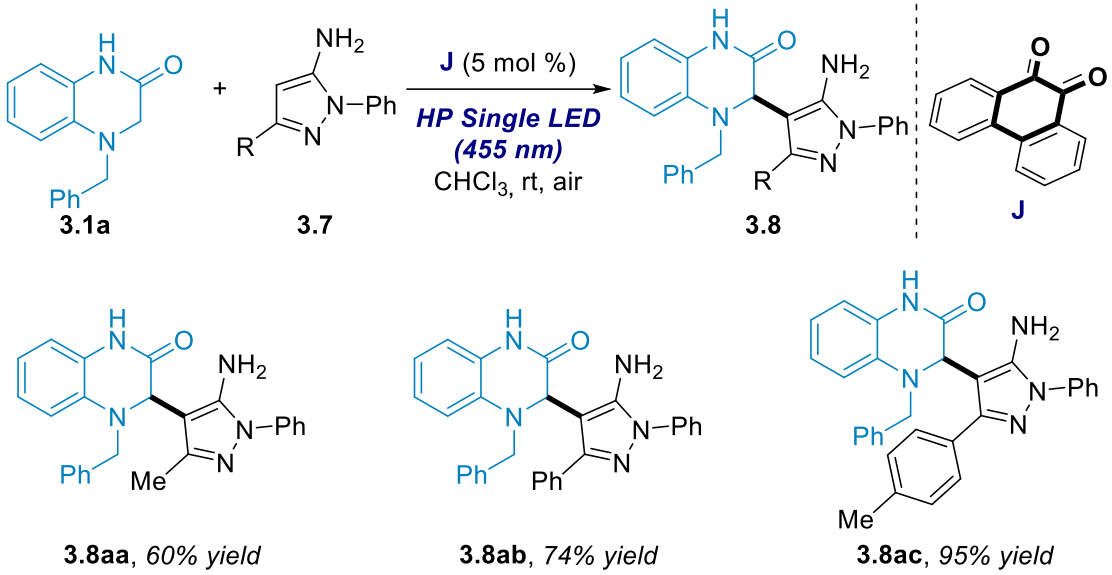
3.3ka, *78% yield*



3.3la, *45% yield*

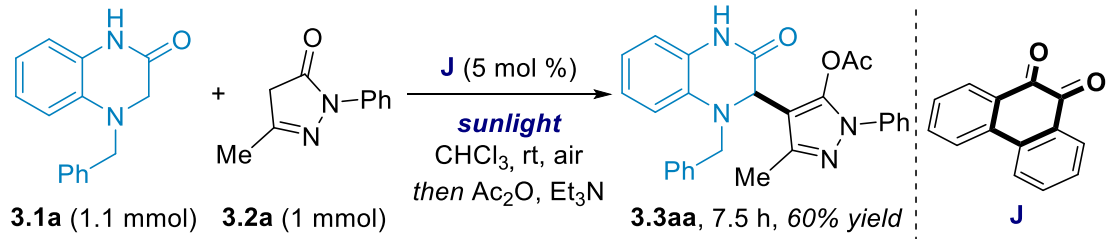
Scheme 3.9: Scope of the reaction using different 3,4-dihydroquinoxalin-2-ones **3.1** and edaravone (**3.2a**)[a]

[a]Reaction conditions: **3.1** (0.13 mmol), **3.2a** (0.1 mmol), **J** (5 mol %), $CHCl_3$ (1 mL), under air atmosphere and under HP Single LED (455 nm) irradiation. Then, Ac_2O (0.2 mmol), Et_3N (0.1 mmol), rt for 0.5 h. Yield determined after purification by column chromatography.



Scheme 3.10: Scope of the reaction using 3,4-dihydroquinoxalin-2-ones **3.1a** and different 5-aminopyrazoles (**3.7**)[a]

[a]Reaction conditions: **3.1a** (0.13 mmol), **3.7** (0.1 mmol), **J** (5 mol %), $CHCl_3$ (1 mL), under air atmosphere and under HP Single LED (455 nm) irradiation. Yield determined after purification by column chromatography.



Scheme 3.11: Reaction between **3.1a** and **3.2a** using sunlight as energy source[a]

[a]Reaction conditions: **3.1a** (1.1 mmol), **3.2a** (1 mmol), **J** (5 mol %), $CHCl_3$ (10 mL), under air atmosphere and under sunlight irradiation. Then, Ac_2O (2 mmol), Et_3N (1 mmol), rt for 0.5 h. Yield determined after purification by column chromatography.

of HP Single LED (455 nm), the variable and substantially higher temperature may lead to undesired thermal decomposition pathways, thus decreasing the final yield of product **3.3aa**. After all, we think that it is noteworthy to show how the reaction can efficiently take place using such a *green* source of energy.

3.3.5 Mechanistic Investigations

Mechanistic Experiments

After addressing all the synthetic aspects, we were interested in finding out about the reaction mechanism. In this sense, all the necessity of all the parameters of our photocatalytic protocol were interrogated (Table 3.4). We already knew that the reaction could proceed in the absence of 9,10-phenanthrenequinone (**J**), albeit requiring longer irradiation times and forming product **3.3aa** in lower yield (Table 3.4, Entry 2). Next, the necessity of light irradiation was confirmed, as product **3.3aa** was isolated in only a 5% yield after 44 hours of reaction in the dark (Table 3.4, Entry 3).

Interestingly, when 1.5 equivalents of TEMPO were also added to the reaction mixture, the expected product was obtained in 34% yield after 23 hours (Table 3.4, Entry 4). This could be in sharp contrast to our assumptions, because a radical-mediated mechanism was thought to happen. However, according to several reports,[163–165] we thought that in our case TEMPO could serve as oxidation catalyst in the presence of molecular oxygen to generate the iminium cation of **3.1a**.

Finally, for convenience, we performed the reaction between **3.1a** and **3.7a** under an argon atmosphere. After 24 hours less than a 5% of product **3.8aa** was observed, revealing the role of molecular oxygen as terminal oxidant (Table 3.4, Entry 5).

Table 3.4: Control reactions in the photochemical reaction between **3.1a** and **3.2a**.

Entry[a]	Deviation	t (h)	Yield 3.3aa (%)
1	*none*	7	89
2	without **J**	20	69
3	darkness	44	5
4	with TEMPO (1.5 equiv.)	23	34
5[b]	Ar atmosphere	24	<5

[a]Reaction conditions: **3.1a** (0.13 mmol), **3.2a** (0.1 mmol), **J** (5 mol %), $CHCl_3$ (1 mL), under air atmosphere and HP Single LED (455 nm) irradiation. Note deviations for each case. Then, Ac_2O (0.2 mmol), Et_3N (0.1 mmol), rt for 0.5 h. Yield determined after purification by column chromatography.

[b]5-Aminopyrazole **3.7a** was used as nucleophile instead of pyrazol-3-one **3.2a**.

As it has been noted in *Chapter 1* (page 60), 9,10-phenanthrenequinone (**J**) is not a fluorescent compound so it was not possible to perform luminiscence quenching experiments to find out accurately the interaction between the substrates and the excited state form of the photocatalyst.

Proposed Mechanism

In light of all this information, we wanted to propose a tentative mechanism by which the photocatalytic reaction between 3,4-dihydroquinoxalin-2-one **3.1a** and edaravone (**3.2a**) proceeds (Figure 3.6).

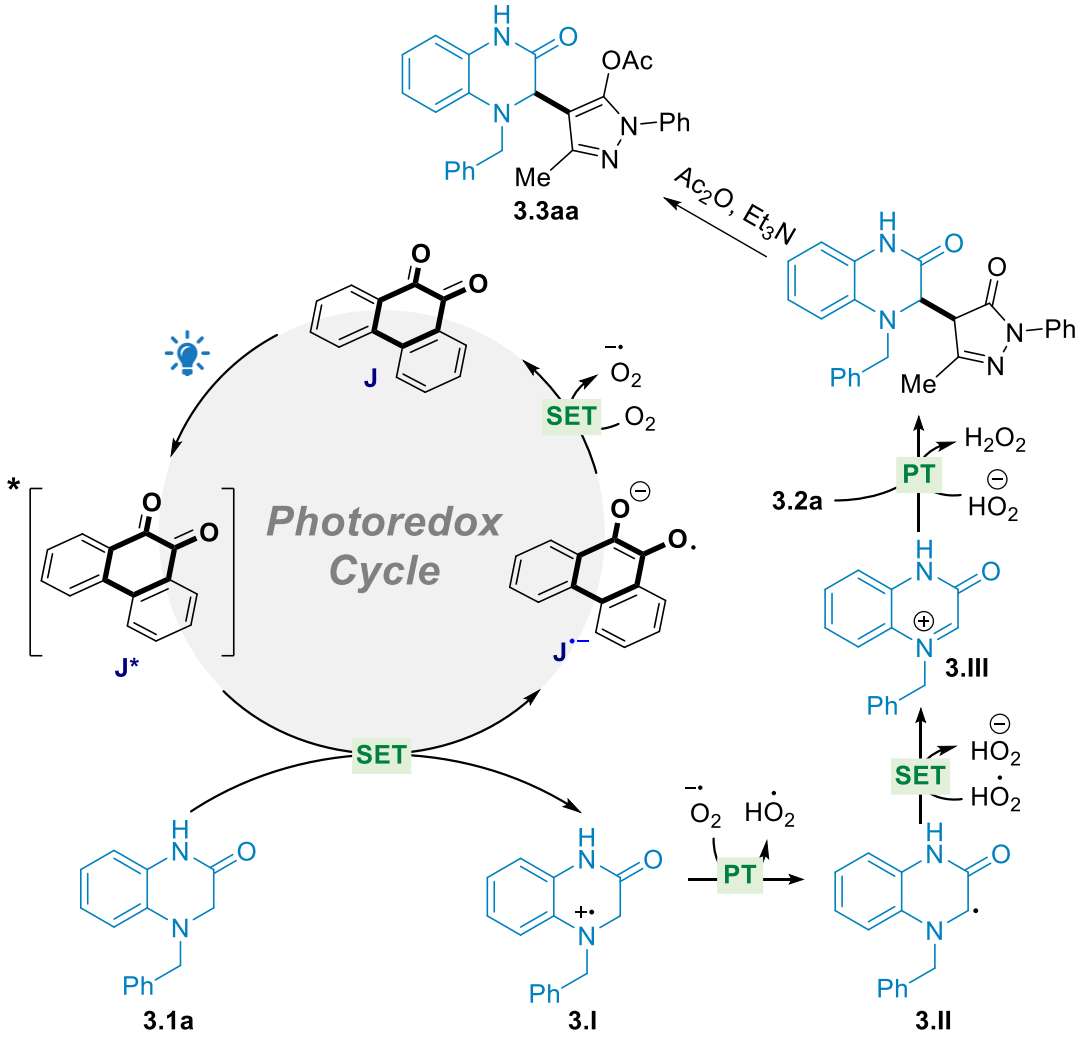


Figure 3.6: Mechanism for the photocatalytic reaction between **4.1a** and **4.2a**.

Visible-light excites 9,10-phenanthrenequinone (**J**) to its excited state, in which it is oxidant enough to trigger a SET with 3,4-dihydroquinoxalin-2-one **3.1a**, and therefore generate the radical cation **3.I** as well as the reduced form of **J** ($\mathbf{J}^{-\bullet}$). Through another SET

with molecular oxygen from air, the neutral form **J** of the photocatalyst can be recovered, accompanied by the generation of superoxide radical anion $O_2^{-\bullet}$.

Moreover, radical cation **3.I** suffers a proton transfer event with superoxide anion to form the corresponding α-amino radical **3.II** and the radical hydroperoxide. Next, simply through a SET with hydroperoxide radical, α-amino radical **3.II** is converted in the desired iminium cation **3.III**.[†] The nucleophilic attack of edaravone (**3.2a**) via its C-4 position allows the formation of the desired alkylation product as mixture of diastereomers and tautomers. Finally, the *O*-acetylation of its enol with Ac_2O delivers the expected product **3.3aa**. Additionally, we determined the presence of H_2O_2 by means of the iodide-starch test.

[†]The conversion of **3.I** to **3.III** could also be possible directly via a HAT with superoxide radical anion.

3.4 Experimental Section

3.4.1 General Methods

Experimental methods regarding **Melting Points**, **Chromatographic Methods**, **Nuclear Magnetic Resonance (NMR)** and **High Resolution Mass Spectrometry (HRMS)** can be found in Section 1.4.1 of *Chapter 1* (page 62).

Reaction Flasks, Reagents and Substrates

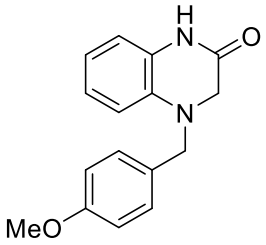
- Photocatalytic reactions were carried out in 10 mL culture tubes under air unless otherwise indicated.
- Commercial reagents were used as purchased.
- All photocatalysts, 5-aminopyrazoles **3.7** and some pyrazol-3-ones **3.2** were commercially available.
- The other pyrazol-3-ones were available in the laboratory.
- 4-Substituted-3,4-Dihydroquinoxalin-2-ones **3.1a**-**3.1c** and **3.1f**-**3.1l** were prepared from its N-4 unprotected precursors using the *N*-benzylation procedure described in page 67 of *Chapter 1*. 4-methyl-3,4-dihydroquinoxalin-2-one **3.1d** was prepared following a reported procedure.[158] 3,4-dihydroquinoxalin-2-one **3.1e** was synthesized following a reported procedure.[159]

3.4.2 Synthetic Procedures and Characterization

Synthesis of 3,4-dihydroquinoxalin-2-ones 3.1a-3.1c and 3.1f-3.1l

The procedure followed for the synthesis of 3,4-dihydroquinoxalin-2-one **3.1a** is described in *Section 2.4.2* of *Chapter 2* (page 113). 3,4-Dihydroquinoxalin-2-ones **3.1b**-**3.1c** and **3.1f**-**3.1l** were prepared using the same methodology.

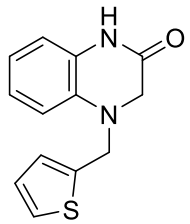
4-(4-Methoxybenzyl)-3,4-dihydroquinoxalin-2(1*H*)-one (3.1b)



^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.48 (s, 1H), 7.23 (d, J = 8.7 Hz, 2H), 6.88 (d, J = 8.7 Hz, 2H), 6.81 (d, J = 1.4 Hz, 1H), 6.79 – 6.73 (m, 3H), 4.34 (s, 2H), 3.80 (s, 3H), 3.76 (s, 2H). **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 159.16 (C), 135.02 (C), 129.71 (C), 129.14 (CH), 127.76 (C), 126.28 (C), 124.22 (CH), 119.39 (CH), 115.57 (CH), 114.23 (CH), 112.66 (CH) 55.29 (CH_3), 53.25 (CH_2), 51.83

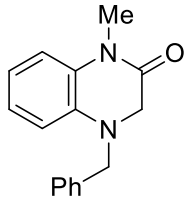
(CH_2); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{16}H_{17}N_2O_2^+$ 268.1285, found 268.1288.

4-(Thiophen-2-ylmethyl)-3,4-dihydroquinoxalin-2(1*H*)-one (3.1c)



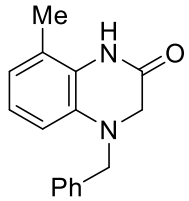
^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.97 (s, 1H), 7.24 (dd, *J* = 5.0, 1.3 Hz, 1H), 7.06 – 6.94 (m, 3H), 6.88 (d, *J* = 7.9 Hz, 1H), 6.84 – 6.75 (m, 2H), 4.60 (s, 2H), 3.82 (s, 2H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 167.2 (C), 138.6 (C), 134.5 (C), 126.8 (CH), 126.8 (CH), 126.3 (C), 125.5 (CH), 124.2 (CH), 119.5 (CH), 115.8 (CH), 112.3 (CH), 51.7 (CH_2), 48.4 (CH_2); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{13}H_{13}N_2OS^+$ 245.0743, found 245.0739.

4-Benzyl-1-methyl-3,4-dihydroquinoxalin-2(1*H*)-one (3.1f)



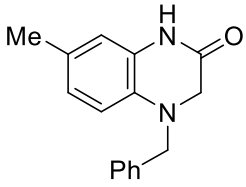
^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.43 – 7.20 (m, 5H), 7.04 – 6.95 (m, 2H), 6.93 – 6.84 (m, 1H), 6.79 (dd, *J* = 8.3, 1.2 Hz, 1H), 4.37 (s, 2H), 3.77 (s, 2H), 3.39 (s, 3H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 166.2 (C), 137.2 (C), 136.3 (C), 128.8 (CH), 127.8 (CH), 127.6 (CH), 123.8 (CH), 119.3 (CH), 114.7 (CH), 112.4 (CH), 53.8 (CH_2), 52.6 (CH_2), 28.9 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{16}H_{17}N_2O^+$ 253.1335, found 253.1338.

4-Benzyl-8-methyl-3,4-dihydroquinoxalin-2(1*H*)-one (3.1g)



^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.75 (bs, 1H), 7.40 – 7.26 (m, 5H), 6.86 (t, *J* = 7.8 Hz, 1H), 6.75 – 6.48 (m, 2H), 4.41 (s, 2H), 3.78 (s, 2H), 2.25 (s, 3H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 166.6 (C), 136.3 (C), 135.3 (C), 128.8 (CH), 127.7 (CH), 127.6 (CH), 124.5 (C), 123.5 (CH), 123.0 (C), 121.3 (CH), 110.8 (CH), 54.0 (CH_2), 52.1 (CH_2), 16.8 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{16}H_{17}N_2O^+$ 253.1335, found 253.1339.

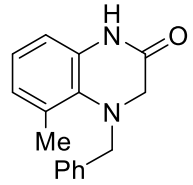
4-Benzyl-7-methyl-3,4-dihydroquinoxalin-2(1*H*)-one (3.1h)



^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.26 (bs, 1H), 7.54 – 7.13 (m, 5H), 6.75 (ddd, *J* = 8.2, 1.9, 0.7 Hz, 1H), 6.66 (d, *J* = 5.1 Hz, 1H), 6.64 (s, 1H), 4.37 (s, 2H), 3.77 (s, 2H), 2.24 (s, 3H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 167.9 (C), 155.9 (C), 136.5 (C), 133.1 (C), 128.8 (CH), 127.7 (CH), 126.9 (CH), 126.1 (C), 124.6 (CH),

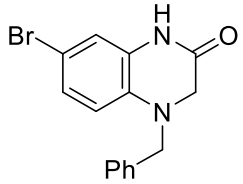
116.6 (CH), 112.3 (CH), 53.7 (CH_2), 52.3 (CH_2), 20.3 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{16}H_{17}N_2O^+$ 253.1335, found 253.1334.

4-Benzyl-5-methyl-3,4-dihydroquinoxalin-2(1*H*)-one (3.1i)



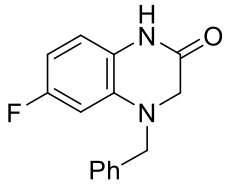
^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.28 (s, 1H), 7.43 – 7.26 (m, 5H), 7.03 (t, J = 7.6 Hz, 1H), 6.95 (ddd, J = 7.6, 1.5, 0.7 Hz, 1H), 6.67 (dd, J = 7.7, 1.0 Hz, 1H), 3.98 (s, 2H), 3.55 (s, 2H), 2.45 (s, 3H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 168.8 (C), 136.9 (C), 134.3 (C), 133.6 (C), 132.9 (C), 128.8 (CH), 128.5 (CH), 127.7 (CH), 125.9 (CH), 125.2 (CH), 113.9 (CH), 57.6 (CH_2), 51.4 (CH_2), 17.4 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{16}H_{17}N_2O^+$ 253.1335, found 253.1337.

4-Benzyl-7-bromo-3,4-dihydroquinoxalin-2-one (3.1j)



^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.59 (bs, 1H), 7.70 – 7.18 (m, 5H), 7.02 (dd, J = 8.6, 2.2 Hz, 1H), 6.90 (d, J = 2.2 Hz, 1H), 6.59 (d, J = 8.6 Hz, 1H), 4.39 (s, 2H), 3.83 (s, 2H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 166.8 (C), 135.7 (C), 134.3 (C), 128.9 (CH), 127.9 (C), 127.8 (CH), 127.5 (CH), 126.7 (CH), 118.1 (CH), 113.6 (CH), 110.6 (C), 53.7 (CH_2), 52.1 (CH_2); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{15}H_{14}BrN_2O^+$ 317.0284, found 317.0288.

4-Benzyl-6-fluoro-3,4-dihydroquinoxalin-2(1*H*)-one (3.1l)

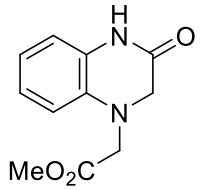


^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.04 (bs, 1H), 7.69 – 7.11 (m, 5H), 6.70 (dd, J = 8.4, 5.4 Hz, 1H), 6.53 – 6.34 (m, 2H), 4.39 (s, 2H), 3.83 (s, 2H); **^{19}F{^{1}H}-NMR (282 MHz, $CDCl_3$)** δ -117.71; **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 166.4 (C), 160.0 (C, d, J_{C-F} = 240.1 Hz), 136.5 (C, d, J_{C-F} = 10.3 Hz), 135.5 (C), 129.0 (CH), 127.8 (CH), 127.5 (CH), 122.0 (C, d, J_{C-F} = 2.4 Hz), 116.0 (CH, d, J_{C-F} = 10.1 Hz), 104.7 (CH, d, J_{C-F} = 23.4 Hz), 99.9 (CH, d, J_{C-F} = 28.2 Hz), 53.6 (CH_2), 51.7 (CH_2); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{15}H_{14}FN_2O^+$ 257.1085, found 257.1081.

Synthesis of 3,4-dihydroquinoxalin-2-one 3.1e

The procedure followed for the synthesis of 3,4-dihydroquinoxalin-2-one **3.1e** was reported in the bibliography.[159]

Methyl 2-(3-oxo-3,4-dihydroquinoxalin-1(2*H*)-yl)acetate (3.1e)

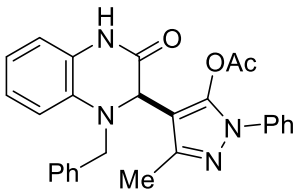


^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.90 (s, 1H), 6.99 – 6.92 (m, 1H), 6.82 – 6.76 (m, 2H), 6.56 – 6.46 (m, 1H), 4.07 (s, 2H), 4.01 (s, 2H), 3.77 (s, 3H); **^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$)** δ 170.1 (C), 166.7 (C), 134.1 (C), 126.1 (C), 124.2 (CH), 119.6 (CH), 115.7 (CH), 111.4 (CH), 53.4 (CH_2), 52.1 (CH_3), 51.1 (CH_2).

General Procedure 1 (GP-1) for the Photocatalytic Alkylation Reaction between 3,4-dihydroquinoxalin-2-ones 3.1 and pyrazol-3-ones 3.2

In a 10 mL culture tube, the corresponding 3,4-dihydroquinoxalin-2-one (**3.1**, 0.13 mmol, 1.3 equiv.), the corresponding pyrazol-3-one (**3.2**, 0.1 mmol, 1 equiv.) and 9,10-phenanthrenequinone (**J**, 1.0 mg, 0.005 mmol, 5 mol %) were placed. Then, $CHCl_3$ (1 mL) was added and the reaction mixture was placed 2 cm over HP Blue LED (455 nm) (see page 433 for further details about the photochemical setup). The conversion of the starting materials was traced regularly by TLC. When pyrazol-3-one **3.2** was consumed, the reaction mixture was taken off the HP Single LED and Et_3N (14 μL, 0.1 mmol, 1 equiv.) and Ac_2O (19 μL, 0.2 mmol, 2 equiv.) were added and the resulting mixture was stirred at room temperature for 30 minutes. Thereafter, the reaction mixture was purified by column chromatography using hexane:EtOAc mixtures (from 90:10 to 70:30) to obtain the expected pure compound **3.3**.

4-(1-Benzyl-3-oxo-1,2,3,4-tetrahydroquinoxalin-2-yl)-3-methyl-1-phenyl-1*H*-pyrazol -5-yl acetate (3.3aa)

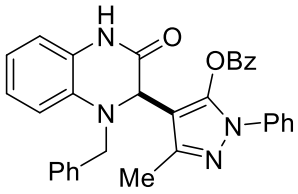


Using 4-benzyl-3,4-dihydroquinoxalin-2-one (**3.1a**, 31.0 mg, 0.13 mmol, 1.3 equiv.) and 5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one (**3.2a**, 17.4 mg, 0.1 mmol, 1 equiv.), according to GP-1, compound **3.3aa** (40.3 mg, 0.089 mmol, 89% yield, brown solid) was purified by column chromatography using hexane:EtOAc mixtures (from 9:1 to 7:3).

Mp = 224-230 °C; **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 9.31 (s, 1H), 7.48 – 7.27 (m, 10H), 7.01 – 6.87 (m, 1H), 6.81 (d, J = 7.4 Hz, 1H), 6.71 (t, J = 7.2 Hz, 1H), 6.64 (d, J = 8.1 Hz, 1H), 5.07 (s, 1H), 4.67 (d, J = 15.6 Hz, 1H), 4.11 (d, J = 15.6 Hz, 1H), 2.14 (s, 3H), 1.48 (s, 3H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 167.4 (C), 165.4 (C), 148.4 (C), 142.5 (C), 137.6 (C), 136.2 (C), 133.9 (C), 129.2 (CH), 128.8 (CH), 127.6 (CH), 124.9 (C), 124.5 (CH), 123.0 (CH), 118.1 (CH), 115.6 (CH), 111.6 (CH), 106.9 (C), 55.7 (CH), 50.5 (CH_2), 19.4 (CH_3), 12.9 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for

$C_{27}H_{25}N_4O_3^+$ 453.1921, found 453.1912.

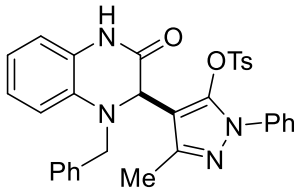
4-(1-benzyl-3-oxo-1,2,3,4-tetrahydroquinoxalin-2-yl)-3-methyl-1-phenyl-1*H*-pyrazol -5-yl benzoate (3.4aa)



Using 4-benzyl-3,4-dihydroquinoxalin-2-one (**3.1a**, 23.8 mg, 0.1 mmol, 1 equiv.) and 5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one (**3.2a**, 17.4 mg, 0.1 mmol, 1 equiv.), according to GP-1, compound **3.4aa** (24.2 mg, 0.047 mmol, 47% yield, dark oil) was purified by column chromatography using hexane:EtOAc mixtures (from 9:1 to 7:3).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.46 (s, 1H), 7.74 – 7.63 (m, 2H), 7.63 – 7.48 (m, 2H), 7.48 – 7.40 (m, 2H), 7.34 – 7.23 (m, 8H), 7.24 – 7.12 (m, 1H), 6.54 – 6.43 (m, 3H), 6.32 – 6.17 (m, 1H), 5.12 (s, 1H), 4.68 (d, J = 15.7 Hz, 1H), 4.20 (d, J = 15.7 Hz, 1H), 2.18 (s, 3H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 165.9 (C), 162.8 (C), 148.5 (C), 142.7 (C), 137.7 (C), 136.4 (C), 134.0 (CH), 133.6 (C), 133.3 (CH), 130.4 (CH), 130.1 (CH), 129.1 (CH), 128.7 (CH), 128.2 (CH), 127.5 (CH), 126.8 (C), 124.4 (C), 124.2 (CH), 122.8 (CH), 118.1 (CH), 115.4 (CH), 111.7 (CH), 106.8 (C), 55.9 (CH), 50.7 (CH_2), 13.2 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* [M + H]$^+$ calcd for $C_{32}H_{27}N_4O_3^+$ 515.2078, found 515.2079.

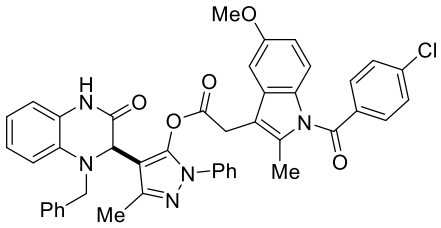
4-(1-benzyl-3-oxo-1,2,3,4-tetrahydroquinoxalin-2-yl)-3-methyl-1-phenyl-1*H*-pyrazol -5-yl 4-methyl benzenesulfonate (3.5aa)



Using 4-benzyl-3,4-dihydroquinoxalin-2-one (**3.1a**, 23.8 mg, 0.1 mmol, 1 equiv.) and 5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one (**3.2a**, 17.4 mg, 0.1 mmol, 1 equiv.), according to GP-1, compound **3.5aa** (48.6 mg, 0.086 mmol, 86% yield, dark oil) was purified by column chromatography using hexane:EtOAc mixtures (from 9:1 to 7:3).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.35 (s, 1H), 7.37 (d, J = 8.4 Hz, 2H), 7.33 – 7.26 (m, 2H), 7.25 – 7.19 (m, 6H), 7.15 – 7.06 (m, 2H), 6.96 (d, J = 8.1 Hz, 2H), 6.90 (td, J = 8.0, 1.7 Hz, 1H), 6.84 (dd, J = 7.7, 1.5 Hz, 1H), 6.74 (td, J = 7.5, 1.1 Hz, 1H), 6.68 (d, J = 8.1 Hz, 1H), 5.45 (s, 1H), 4.65 (d, J = 16.9 Hz, 1H), 4.37 (d, J = 16.9 Hz, 1H), 2.32 (s, 3H), 2.13 (s, 3H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 166.2 (C), 148.4 (C), 146.0 (C), 141.7 (C), 137.2 (C), 137.1 (C), 134.8 (C), 130.4 (C), 129.5 (CH), 128.59 (CH), 128.56 (CH), 128.5 (CH), 127.0 (CH), 126.7 (CH), 125.3 (C), 124.2 (CH), 123.1 (CH), 118.8 (CH), 115.5 (CH), 113.0 (CH), 107.2 (C), 56.2 (CH), 51.6 (CH_2), 21.6 (CH_3), 14.0 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* [M + H]$^+$ calcd for $C_{32}H_{29}N_4O_4S^+$ 565,1904, found 565,1900.

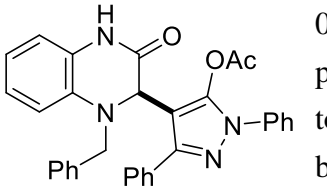
4-(1-Benzyl-3-oxo-1,2,3,4-tetrahydroquinoxalin-2-yl)-3-methyl-1-phenyl-1*H*-pyrazol -5-yl 2-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl) acetate (3.6aa)



Using 4-benzyl-3,4-dihydroquinoxalin-2-one (**3.1a**, 23.8 mg, 0.1 mmol, 1 equiv.) and 5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one (**3.2a**, 17.4 mg, 0.1 mmol, 1 equiv.), according to GP-1, compound **3.6aa** (41.3 mg, 0.055 mmol, 55% yield, brown oil) was purified by column chromatography using hexane:EtOAc mixtures (from 9:1 to 7:3).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.22 (s, 1H), 7.52 (d, J = 8.6 Hz, 2H), 7.44 (d, J = 8.7 Hz, 2H), 7.39 – 7.24 (m, 5H), 7.09 – 6.94 (m, 5H), 6.91 (dd, J = 7.6, 1.3 Hz, 1H), 6.88 – 6.77 (m, 3H), 6.74 (d, J = 8.3 Hz, 1H), 6.72 – 6.64 (m, 2H), 5.08 (s, 1H), 4.68 (d, J = 15.6 Hz, 1H), 4.14 (d, J = 15.6 Hz, 1H), 3.75 (s, 3H), 3.03 (d, J = 14.9 Hz, 1H), 2.93 (d, J = 14.9 Hz, 1H), 2.11 (s, 3H), 1.97 (s, 3H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 168.1 (C), 167.0 (C), 165.2 (C), 156.1 (C), 148.3 (C), 142.1 (C), 139.4 (C), 136.9 (C), 136.1 (C), 136.0 (C), 134.2 (C), 133.6 (C), 131.0 (CH), 130.7 (C), 130.1 (C), 129.1 (CH), 128.9 (CH), 128.5 (CH), 127.6 (CH), 127.6 (CH), 127.4 (CH), 125.0 (C), 124.7 (CH), 123.1 (CH), 118.2 (CH), 115.6 (CH), 114.9 (CH), 111.9 (CH), 111.6 (CH), 110.1 (C), 106.7 (C), 101.1 (CH), 55.9 (CH), 55.6 (CH_3), 50.7 (CH_2), 29.0 (CH_2), 13.1 (CH_3), 12.9 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{44}H_{36}ClN_5O_5^+$ 750.2478, found 750.2476.

4-(1-Benzyl-3-oxo-1,2,3,4-tetrahydroquinoxalin-2-yl)-1,3-diphenyl-1*H*-pyrazol-5-yl acetate (3.3ab)

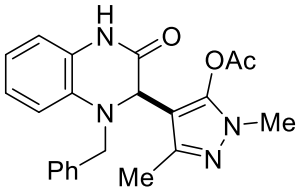


Using 4-benzyl-3,4-dihydroquinoxalin-2-one (**3.1a**, 31.0 mg, 0.13 mmol, 1.3 equiv.) and 5-phenyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one (**3.2b**, 23.6 mg, 0.1 mmol, 1 equiv.), according to GP-1, compound **3.3ab** (41.2 mg, 0.080 mmol, 80% yield, brown solid) was purified by column chromatography using hexane:EtOAc mixtures (from 9:1 to 7:3).

Mp = 202-208 °C. **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 8.73 (s, 1H), 7.90 (dd, J = 7.4, 2.2 Hz, 2H), 7.58 – 7.47 (m, 2H), 7.46 – 7.36 (m, 5H), 7.35 – 7.28 (m, 1H), 7.12 – 7.03 (m, 3H), 6.98 (dd, J = 6.6, 3.1 Hz, 2H), 6.93 – 6.84 (m, 1H), 6.79 (dt, J = 7.7, 1.4 Hz, 1H), 6.68 (td, J = 7.5, 1.2 Hz, 1H), 6.55 (d, J = 8.3 Hz, 1H), 5.40 (s, 1H), 4.49 (d, J = 15.8 Hz, 1H), 3.88 (d, J = 15.8 Hz, 1H), 1.38 (s, 3H). **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 167.5 (C), 165.2 (C), 151.9 (C), 142.8 (C), 137.7 (C), 135.9 (C), 133.6 (C), 132.3 (C), 129.2 (CH), 129.0 (CH), 128.6 (CH), 128.49 (CH), 128.47 (CH), 127.9 (CH), 127.3 (CH),

127.2 (CH), 124.54 (CH), 124.51 (C), 123.2 (CH), 117.6 (CH), 115.2 (CH), 111.5 (CH), 107.5 (C), 55.2 (CH), 50.4 (CH_2), 19.2 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{32}H_{27}N_4O_3^+$ 515.2078, found 515.2083.

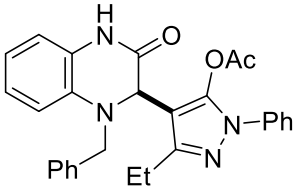
4-(1-Benzyl-3-oxo-1,2,3,4-tetrahydroquinoxalin-2-yl)-1,3-dimethyl-1*H*-pyrazol-5-yl acetate (3.3ac)



Using 4-benzyl-3,4-dihydroquinoxalin-2-one (**3.1a**, 31.0 mg, 0.13 mmol, 1.3 equiv.) and 5-methyl-2-methyl-2,4-dihydro-3*H*-pyrazol-3-one (**3.2c**, 11.2 mg, 0.1 mmol, 1 equiv.), according to GP-1, compound **3.3ac** (20.3 mg, 0.052 mmol, 52% yield, white solid) was purified by column chromatography using hexane:EtOAc mixtures (from 9:1 to 7:3).

Mp = decomposes at 205 °C. **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 9.51 (s, 1H), 7.41 – 7.19 (m, 5H), 6.92 (ddd, *J* = 8.0, 7.3, 1.6 Hz, 1H), 6.82 (dd, *J* = 7.7, 1.6 Hz, 1H), 6.71 (td, *J* = 7.5, 1.2 Hz, 1H), 6.62 (d, *J* = 8.1 Hz, 1H), 4.98 (s, 1H), 4.60 (d, *J* = 15.6 Hz, 1H), 4.02 (d, *J* = 15.6 Hz, 1H), 3.47 (s, 3H), 2.03 (s, 3H), 1.65 (s, 3H). **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 167.7 (C), 165.8 (C), 146.6 (C), 142.8 (C), 136.2 (C), 133.9 (C), 128.8 (CH), 127.52 (CH), 127.49 (CH), 124.9 (C), 124.4 (CH), 118.0 (CH), 115.6 (CH), 111.5 (CH), 104.8 (C), 55.6 (CH), 50.3 (CH_2), 34.6 (CH_3), 19.2 (CH_3), 12.7 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{22}H_{23}N_4O_3^+$ 391.1765, found 391.1769.

4-(1-Benzyl-3-oxo-1,2,3,4-tetrahydroquinoxalin-2-yl)-3-ethyl-1-phenyl-1*H*-pyrazol-5-yl acetate (3.3ad)

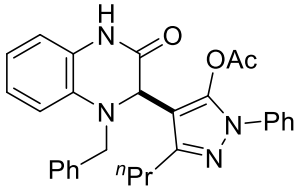


Using 4-benzyl-3,4-dihydroquinoxalin-2-one (**3.1a**, 31.0 mg, 0.13 mmol, 1.3 equiv.) and 5-ethyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one (**3.2d**, 18.8 mg, 0.1 mmol, 1 equiv.), according to GP-1, compound **3.3ad** (44.3 mg, 0.095 mmol, 95% yield, brown solid) was purified by column chromatography using hexane:EtOAc mixtures (from 9:1 to 7:3).

Mp = 214-220 °C. **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 9.74 (s, 1H), 7.48 – 7.26 (m, 10H), 6.95 – 6.85 (m, 1H), 6.82 (dd, *J* = 7.7, 1.6 Hz, 1H), 6.69 (td, *J* = 7.5, 1.2 Hz, 1H), 6.60 (d, *J* = 8.3 Hz, 1H), 5.14 (s, 1H), 4.64 (d, *J* = 16.0 Hz, 1H), 4.13 (d, *J* = 16.0 Hz, 1H), 2.54 (qd, *J* = 7.6, 1.5 Hz, 2H), 1.42 (s, 3H), 1.29 (t, *J* = 7.5 Hz, 3H). **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 167.5 (C), 165.5 (C), 153.4 (C), 142.3 (C), 137.8 (C), 136.3 (C), 133.7 (C), 129.1 (CH), 128.8 (CH), 127.49 (CH), 127.47 (CH), 127.3 (CH), 124.7 (C), 124.4 (CH), 123.0 (CH), 117.9 (CH), 115.6 (CH), 111.4 (CH), 106.6 (C), 55.8 (CH), 50.4

(CH_2), 20.4 (CH_2), 19.3 (CH_3), 13.2 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{28}H_{27}N_4O_3^+$ 467.2078, found 467.2073.

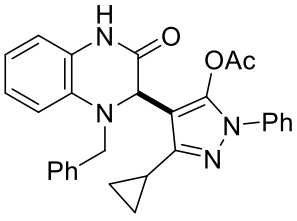
4-(1-Benzyl-3-oxo-1,2,3,4-tetrahydroquinoxalin-2-yl)-1-phenyl-3-propyl-1*H*-pyrazol -5-yl acetate (3.3ae)



Using 4-benzyl-3,4-dihydroquinoxalin-2-one (**3.1a**, 31.0 mg, 0.13 mmol, 1.3 equiv.) and 5-propyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one (**3.2e**, 20.2 mg, 0.1 mmol, 1 equiv.), according to GP-1, compound **3.3ae** (43.6 mg, 0.091 mmol, 91% yield, brown solid) was purified by column chromatography using hexane:EtOAc mixtures (from 9:1 to 7:3).

Mp = 167-171 °C. **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 8.77 (s, 1H), 7.46 – 7.27 (m, 10H), 6.90 (ddd, *J* = 8.1, 7.2, 1.7 Hz, 1H), 6.78 (dd, *J* = 7.7, 1.6 Hz, 1H), 6.69 (td, *J* = 7.5, 1.2 Hz, 1H), 6.60 (d, *J* = 8.1 Hz, 1H), 5.13 (s, 1H), 4.63 (d, *J* = 16.1 Hz, 1H), 4.13 (d, *J* = 16.1 Hz, 1H), 2.57 – 2.32 (m, 2H), 1.83 – 1.64 (m, 2H), 1.44 (s, 3H), 0.92 (t, *J* = 7.3 Hz, 3H). **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 167.5 (C), 165.0 (C), 152.3 (C), 142.3 (C), 137.8 (C), 136.4 (C), 133.8 (C), 129.1 (CH), 128.8 (CH), 127.52 (CH), 127.48 (CH), 127.3 (CH), 124.7 (C), 124.5 (CH), 123.1 (CH), 117.9 (CH), 115.3 (CH), 111.6 (CH), 106.7 (C), 55.9 (CH), 50.5 (CH_2), 29.3 (CH_2), 22.3 (CH_2), 19.3 (CH_3), 14.1 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{29}H_{29}N_4O_3^+$ 481.2234, found 481.2238.

4-(1-Benzyl-3-oxo-1,2,3,4-tetrahydroquinoxalin-2-yl)-3-cyclopropyl-1-phenyl-1*H*-pyrazol-5-yl acetate (3.3af)

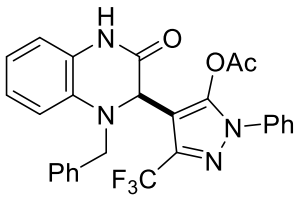


Using 4-benzyl-3,4-dihydroquinoxalin-2-one (**3.1a**, 31.0 mg, 0.13 mmol, 1.3 equiv.) and 5-cyclopropyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one (**3.2f**, 20.0 mg, 0.1 mmol, 1 equiv.), according to GP-1, compound **3.3af** (47.4 mg, 0.099 mmol, 99% yield, dark oil) was purified by column chromatography using hexane:EtOAc mixtures (from 9:1 to 7:3).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.71 (s, 1H), 7.45 – 7.27 (m, 10H), 6.93 – 6.86 (m, 1H), 6.83 (dd, *J* = 7.7, 1.5 Hz, 1H), 6.69 (td, *J* = 7.5, 1.2 Hz, 1H), 6.61 (d, *J* = 8.1 Hz, 1H), 5.33 (s, 1H), 4.66 (d, *J* = 16.0 Hz, 1H), 4.20 (d, *J* = 16.0 Hz, 1H), 1.71 (ddd, *J* = 13.5, 8.3, 5.1 Hz, 1H), 1.49 (s, 3H), 1.11 – 1.04 (m, 1H), 0.86 (ddd, *J* = 10.8, 4.2, 2.0 Hz, 1H), 0.82 – 0.73 (m, 2H). **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 167.4 (C), 165.7 (C), 152.9 (C), 142.3 (C), 137.8 (C), 136.5 (C), 133.8 (C), 129.1 (CH), 128.7 (CH), 127.44 (CH), 127.38 (CH), 127.3 (CH), 124.9 (C), 124.4 (CH), 123.0 (CH), 117.9 (CH), 115.6 (CH), 111.6 (CH), 107.6 (C), 55.8 (CH), 50.5 (CH_2), 19.4 (CH_3), 7.7 (CH), 7.3 (CH_2),

6.5 (CH_2); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{29}H_{27}N_4O_3^+$ 479.2078, found 479.2081.

4-(1-Benzyl-3-oxo-1,2,3,4-tetrahydroquinoxalin-2-yl)-1-phenyl-3-(trifluoromethyl)-1*H*-pyrazol-5-yl acetate (3.3ag)

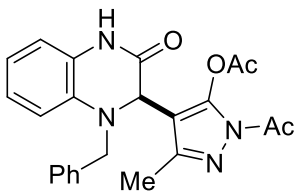


Using 4-benzyl-3,4-dihydroquinoxalin-2-one (**3.1a**, 31.0 mg, 0.13 mmol, 1.3 equiv.) and 2-phenyl-5-(trifluoromethyl)-2,4-dihydro-3*H*-pyrazol-3-one (**3.2g**, 22.8 mg, 0.1 mmol, 1 equiv.), according to GP-1, compound **3.3ag** (45.1 mg, 0.089 mmol, 89% yield, purple oil) was purified by column chromatography using hexane:EtOAc mixtures (from 9:1 to 7:3).

^{1}H-NMR (300 MHz, DMSO-d_6) δ 10.89 (s, 1H), 7.59 – 7.40 (m, 5H), 7.39 – 7.15 (m, 5H), 6.89 (dd, J = 7.6, 1.4 Hz, 1H), 6.82 (dd, J = 7.8, 1.4 Hz, 1H), 6.73 – 6.57 (m, 2H), 5.31 (s, 1H), 4.61 (d, J = 16.6 Hz, 1H), 4.16 (d, J = 16.6 Hz, 1H), 1.55 (s, 3H); **^{19}F{^{1}H}-NMR (282 MHz, DMSO-d_6)** δ -59.95; **^{13}C{^{1}H}-NMR (75 MHz, DMSO-d_6)** δ 166.8 (C), 162.3 (C), 143.1 (C), 139.0 (C, q, J_{C-F} = 36.8 Hz), 136.9 (C), 136.2 (C), 132.7 (C), 129.8 (CH), 129.1 (C, q, J_{C-F} = 1.0 Hz), 128.5 (CH), 127.1 (CH), 126.8 (CH), 125.2 (CH), 123.5 (C), 123.0 (CH), 120.9 (C, q, J_{C-F} = 270.2 Hz), 117.7 (CH), 115.2 (CH), 111.5 (CH), 108.8 (CH), 55.4 (CH), 50.7 (CH_2), 18.8 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{27}H_{22}F_3N_4O_3^+$ 507.1639, found 507.1642.

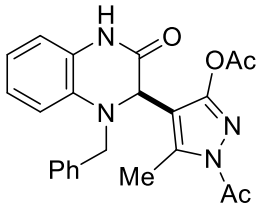
1-Acetyl-4-(1-benzyl-3-oxo-1,2,3,4-tetrahydroquinoxalin-2-yl)-3-methyl-1*H*-pyrazol-5-yl acetate (3.3ah') and 1-acetyl-4-(1-benzyl-3-oxo-1,2,3,4-tetrahydroquinoxalin-2-yl)-5-methyl-1*H*-pyrazol-3-yl acetate (3.3ah")

Using 4-benzyl-3,4-dihydroquinoxalin-2-one (**3.1a**, 31.0 mg, 0.13 mmol, 1.3 equiv.) and 5-methyl-2,4-dihydro-3*H*-pyrazol-3-one (**3.2h**, 9.8 mg, 0.1 mmol, 1 equiv.), according to GP-1, regioisomeric compounds **3ah'** (13.0 mg, 0.031 mmol, 31% yield, brown solid) and **3ah"** (11.3 mg, 0.027 mmol, 27% yield, brown solid) were purified by column chromatography using hexane:EtOAc mixtures (from 9:1 to 7:3).



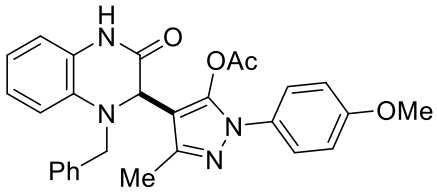
Mp = 224-240 °C;**^{1}H-NMR (400 MHz, $CDCl_3$)** δ 8.71 (s, 1H), 7.40 – 7.28 (m, 3H), 7.27 – 7.22 (m, 2H), 6.96 (ddd, J = 8.8, 6.5, 2.5 Hz, 1H), 6.82 – 6.72 (m, 2H), 6.69 (d, J = 8.1 Hz, 1H), 4.93 (s, 1H), 4.66 (d, J = 15.0 Hz, 1H), 4.00 (d, J = 15.0 Hz, 1H), 2.55 (s, 3H), 2.01 (s, 3H), 1.68 (s, 3H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 169.7 (C), 168.0 (C), 164.6 (C), 151.0 (C), 145.1 (C), 135.7 (C), 134.1 (C), 128.9 (CH), 127.9 (CH), 127.8 (CH), 124.9 (C), 124.6

(CH), 118.5 (CH), 115.4 (CH), 111.6 (CH), 110.4 (C), 55.0 (CH), 50.7 (CH_2), 23.1 (CH_3), 19.6 (CH_3), 13.1 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{23}H_{23}N_4O_4^+$ calcd for 419.1714, found 419.1709.



Mp = 220-230 °C; **^{1}H-NMR (400 MHz, $CDCl_3$)** δ 8.90 (s, 1H), 7.45 – 7.27 (m, 3H), 7.24 – 7.15 (m, 2H), 7.00 – 6.91 (m, 1H), 6.78 (d, *J* = 7.2 Hz, 1H), 6.75 – 6.70 (m, 1H), 6.67 (d, *J* = 8.1 Hz, 1H), 5.08 (s, 1H), 4.67 (d, *J* = 15.8 Hz, 1H), 3.96 (d, *J* = 15.7 Hz, 1H), 2.59 (s, 3H), 2.37 (s, 3H), 1.56 (s, 3H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 171.2 (C), 168.6 (C), 164.5 (C), 154.5 (C), 144.3 (C), 135.7 (C), 133.5 (C), 128.9 (CH), 127.7 (CH), 127.5 (CH), 124.7 (CH), 124.3 (C), 118.1 (CH), 115.6 (CH), 111.9 (C), 111.6 (CH), 54.6 (CH), 50.2 (CH_2), 23.4 (CH_3), 19.6 (CH_3), 12.8 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{23}H_{23}N_4O_4^+$ calcd for 419.1714, found 419.1720

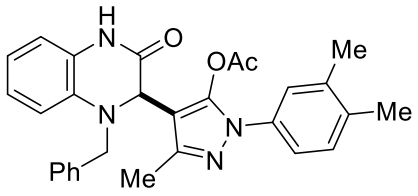
4-(1-Benzyl-3-oxo-1,2,3,4-tetrahydroquinoxalin-2-yl)-1-(4-methoxyphenyl)-3-methyl-1*H*-pyrazol-5-yl acetate (3.3ai)



Using 4-benzyl-3,4-dihydroquinoxalin-2-one (**3.1a**, 31.0 mg, 0.13 mmol, 1.3 equiv.) and 2-(4-methoxyphenyl)-5-methyl-2,4-dihydro-3*H*-pyrazol-3-one (**3.2i**, 20.4 mg, 0.1 mmol, 1 equiv.), according to GP-1, compound **3.3ai** (35.7 mg, 0.074 mmol, 74% yield, dark oil) was purified by column chromatography using hexane:EtOAc mixtures (from 9:1 to 7:3).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.21 (s, 1H), 7.36 – 7.27 (m, 7H), 6.95 – 6.84 (m, 3H), 6.80 (dd, *J* = 7.7, 1.6 Hz, 1H), 6.70 (td, *J* = 7.5, 1.2 Hz, 1H), 6.63 (d, *J* = 8.1 Hz, 1H), 5.05 (s, 1H), 4.65 (d, *J* = 15.6 Hz, 1H), 4.10 (d, *J* = 15.6 Hz, 1H), 3.80 (s, 3H), 2.12 (s, 3H), 1.46 (s, 3H). **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 167.5 (C), 165.4 (C), 159.0 (C), 147.9 (C), 142.4 (C), 136.2 (C), 134.0 (C), 130.7 (C), 128.8 (CH), 127.6 (CH), 127.5 (CH), 124.9 (CH), 124.9 (CH), 124.4 (CH), 118.0 (CH), 115.5 (CH), 114.2 (CH), 111.6 (CH), 106.3 (C), 55.8 (CH), 55.4 (CH_3), 50.5 (CH_2), 19.3 (CH_3), 12.9 (CH_3). **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{28}H_{27}N_4O_4^+$ 483.2027, found 483.2025.

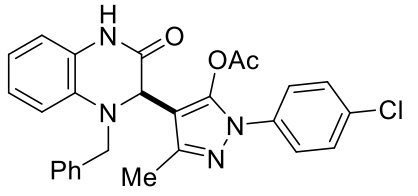
4-(1-Benzyl-3-oxo-1,2,3,4-tetrahydroquinoxalin-2-yl)-1-(3,4-dimethylphenyl)-3-methyl-1*H*-pyrazol-5-yl acetate (3.3aj)



Using 4-benzyl-3,4-dihydroquinoxalin-2-one (**3.1a**, 31.0 mg, 0.13 mmol, 1.3 equiv.) and 2-(3,4-dimethylphenyl)-5-methyl-2,4-dihydro-3*H*-pyrazol-3-one (**3.2j**, 20.2 mg, 0.1 mmol, 1 equiv.), according to GP-1, compound **3.3aj** (32.3 mg, 0.068 mmol, 68% yield, brown solid) was purified by column chromatography using hexane:EtOAc mixtures (from 9:1 to 7:3).

Mp = 156-161 °C; **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 9.60 (s, 1H), 7.38 – 7.20 (m, 6H), 7.09 (d, *J* = 1.3 Hz, 2H), 6.91 (ddd, *J* = 8.0, 7.3, 1.6 Hz, 1H), 6.82 (dd, *J* = 7.7, 1.6 Hz, 1H), 6.70 (td, *J* = 7.5, 1.2 Hz, 1H), 6.63 (d, *J* = 8.6 Hz, 1H), 5.06 (s, 1H), 4.65 (d, *J* = 15.6 Hz, 1H), 4.11 (d, *J* = 15.6 Hz, 1H), 2.24 (s, 6H), 2.14 (s, 3H), 1.47 (s, 3H). **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 167.4 (C), 165.6 (C), 148.0 (C), 142.3 (C), 137.7 (C), 136.3 (C), 136.1 (C), 135.4 (C), 133.9 (C), 130.0 (CH), 128.8 (CH), 127.6 (CH), 127.5 (CH), 124.9 (C), 124.4 (CH), 124.3 (CH), 120.0 (CH), 118.0 (CH), 115.6 (CH), 111.5 (CH), 106.6 (C), 55.8 (CH), 50.5 (CH_2), 19.7 (CH_3), 19.4 (CH_3), 19.3 (CH_3), 12.9 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{29}H_{29}N_4O_3^+$ 481.2234, found 481.2231.

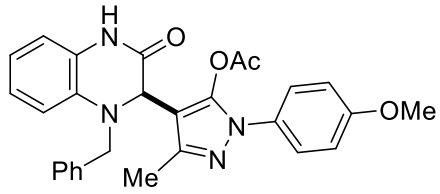
4-(1-Benzyl-3-oxo-1,2,3,4-tetrahydroquinoxalin-2-yl)-1-(4-chlorophenyl)-3-methyl-1*H*-pyrazol-5-yl acetate (3.3ak)



Using 4-benzyl-3,4-dihydroquinoxalin-2-one (**3.1a**, 31.0 mg, 0.13 mmol, 1.3 equiv.) and 2-(4-chlorophenyl)-5-methyl-2,4-dihydro-3*H*-pyrazol-3-one (**3.2k**, 20.9 mg, 0.1 mmol, 1 equiv.), according to GP-1, compound **3.3ak** (25.8 mg, 0.053 mmol, 53% yield, brown solid) was purified by column chromatography using hexane:EtOAc mixtures (from 9:1 to 7:3).

Mp = 148-155 °C; **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 9.37 (s, 1H), 7.39 – 7.27 (m, 9H), 6.92 (ddd, *J* = 8.1, 7.3, 1.6 Hz, 1H), 6.81 (dd, *J* = 7.7, 1.6 Hz, 1H), 6.71 (td, *J* = 7.5, 1.2 Hz, 1H), 6.64 (d, *J* = 8.1 Hz, 1H), 5.05 (s, 1H), 4.66 (d, *J* = 15.6 Hz, 1H), 4.08 (d, *J* = 15.6 Hz, 1H), 2.12 (s, 3H), 1.50 (s, 3H). **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 167.3 (C), 165.4 (C), 148.8 (C), 142.4 (C), 136.2 (C), 136.1 (C), 133.9 (C), 133.2 (C), 129.3 (CH), 128.8 (CH), 127.62 (CH), 127.57 (CH), 124.8 (C), 124.5 (CH), 124.1 (CH), 118.2 (CH), 115.6 (CH), 111.6 (CH), 107.2 (C), 55.6 (CH), 50.5 (CH_2), 19.4 (CH_3), 12.9 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{27}H_{24}ClN_4O_3^+$ 487.1531, found 487.1534.

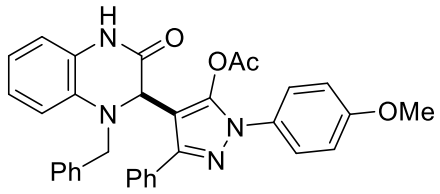
4-(1-Benzyl-3-oxo-1,2,3,4-tetrahydroquinoxalin-2-yl)-3-methyl-1-(4-nitrophenyl)-1*H*-pyrazol-5-yl acetate (3.3al)



Using 4-benzyl-3,4-dihydroquinoxalin-2-one (**3.1a**, 31.0 mg, 0.13 mmol, 1.3 equiv.) and 5-methyl-2-(4-nitrophenyl)-2,4-dihydro-3*H*-pyrazol-3-one (**3.2l**, 21.9 mg, 0.1 mmol, 1 equiv.), according to GP-1, compound **3.3al** (18.9 mg, 0.038 mmol, 38% yield, dark red solid) was purified by column chromatography using hexane:EtOAc mixtures (from 9:1 to 7:3).

Mp = 158-162 °C; **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 9.26 (s, 1H), 8.26 (d, J = 9.1 Hz, 2H), 7.66 (d, J = 9.1 Hz, 2H), 7.39 – 7.24 (m, 5H), 6.95 (ddd, J = 8.1, 7.3, 1.7 Hz, 1H), 6.82 (dd, J = 7.7, 1.7 Hz, 1H), 6.74 (td, J = 7.5, 1.2 Hz, 1H), 6.68 (d, J = 8.1 Hz, 1H), 5.06 (s, 1H), 4.68 (d, J = 15.5 Hz, 1H), 4.07 (d, J = 15.5 Hz, 1H), 2.13 (s, 3H), 1.57 (s, 3H). **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 167.1 (C), 165.0 (C), 150.3 (C), 145.9 (C), 142.8 (C), 142.7 (C), 135.8 (C), 133.8 (C), 128.9 (CH), 127.8 (CH), 127.6 (CH), 124.9 (CH), 124.7 (CH), 121.9 (CH), 118.4 (CH), 115.7 (CH), 111.6 (CH), 108.7 (C), 55.5 (CH), 50.6 (CH_2), 19.5 (CH_3), 13.0 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{27}H_{24}N_5O_5^+$ 498.1772, found 498.1768.

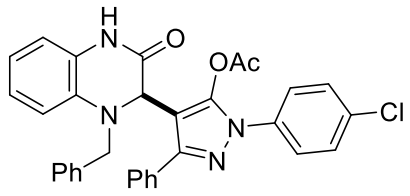
4-(1-Benzyl-3-oxo-1,2,3,4-tetrahydroquinoxalin-2-yl)-1-(4-methoxyphenyl)-3-phenyl-1*H*-pyrazol-5-yl acetate (3.3am)



Using 4-benzyl-3,4-dihydroquinoxalin-2-one (**3.1a**, 31.0 mg, 0.13 mmol, 1.3 equiv.) and 2-(4-methoxyphenyl)-5-phenyl-2,4-dihydro-3*H*-pyrazol-3-one (**3.2m**, 26.6 mg, 0.1 mmol, 1 equiv.), according to GP-1, compound **3.3am** (43.6 mg, 0.080 mmol, 80% yield, brown solid) was purified by column chromatography using hexane:EtOAc mixtures (from 9:1 to 7:3).

Mp = decomposes at 100 °C;**^{1}H-NMR (300 MHz, $CDCl_3$)** δ 9.51 (s, 1H), 7.91 (dd, J = 7.7, 1.8 Hz, 2H), 7.45 – 7.37 (m, 5H), 7.15 – 7.04 (m, 3H), 7.02 – 6.95 (m, 2H), 6.93 – 6.79 (m, 4H), 6.67 (td, J = 7.5, 1.2 Hz, 1H), 6.55 (d, J = 8.1 Hz, 1H), 5.40 (s, 1H), 4.50 (d, J = 15.8 Hz, 1H), 3.89 (d, J = 15.8 Hz, 1H), 3.81 (s, 3H), 1.36 (s, 3H). **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 167.6 (C), 165.6 (C), 159.2 (C), 151.5 (C), 142.8 (C), 136.0 (C), 133.5 (C), 132.4 (C), 130.7 (C), 129.0 (CH), 128.51 (CH), 128.46 (CH), 128.4 (CH), 127.3 (CH), 127.2 (CH), 125.0 (CH), 124.6 (C), 124.5 (CH), 117.6 (CH), 115.4 (CH), 114.3 (CH), 111.4 (CH), 107.1 (C), 55.5 (CH_3), 55.1 (CH), 50.3 (CH_2), 19.1 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{33}H_{29}N_4O_4^+$ 545.2183, found 545.2179.

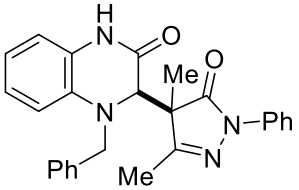
4-(1-Benzyl-3-oxo-1,2,3,4-tetrahydroquinoxalin-2-yl)-1-(4-chlorophenyl)-3-phenyl-1*H*-pyrazol-5-yl acetate (3.3an)



Using 4-benzyl-3,4-dihydroquinoxalin-2-one (**3.1a**, 31.0 mg, 0.13 mmol, 1.3 equiv.) and 2-(4-chlorophenyl)-5-phenyl-2,4-dihydro-3*H*-pyrazol-3-one (**3.2n**, 27.1 mg, 0.1 mmol, 1 equiv.), according to GP-1, compound **3.3an** (37.0 mg, 0.069 mmol, 69% yield, brown solid) was purified by column chromatography using hexane:EtOAc mixtures (from 9:1 to 7:3).

Mp = 115-122 °C; **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 9.66 (s, 1H), 7.93 – 7.88 (m, 2H), 7.52 – 7.27 (m, 8H), 7.09 (dd, *J* = 4.9, 2.2 Hz, 2H), 6.97 (dd, *J* = 7.4, 2.3 Hz, 2H), 6.93 – 6.82 (m, 2H), 6.69 (td, *J* = 7.5, 1.1 Hz, 1H), 6.56 (d, *J* = 7.6 Hz, 1H), 5.40 (s, 1H), 4.50 (d, *J* = 15.8 Hz, 1H), 3.86 (d, *J* = 15.8 Hz, 1H), 1.39 (s, 3H). **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 167.4 (C), 165.5 (C), 152.2 (C), 142.9 (C), 136.2 (C), 135.9 (C), 133.6 (C), 133.4 (C), 132.1 (C), 129.4 (CH), 128.9 (CH), 128.6 (CH), 128.5 (CH), 127.3 (CH), 127.2 (CH), 126.8 (CH), 124.6 (CH), 124.5 (C), 124.3 (CH), 117.7 (CH), 115.6 (CH), 111.4 (CH), 107.9 (C), 55.0 (CH), 50.3 (CH_2), 19.2 (CH_3). **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{32}H_{26}ClN_4O_3^+$ 549.1688, found 549.1688.

4-Benzyl-3-(3,4-dimethyl-5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazol-4-yl)-3,4-dihydroquinoxalin-2-one (3.3ao)

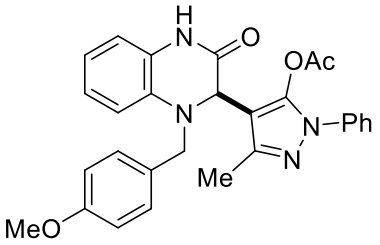


Using 4-benzyl-3,4-dihydroquinoxalin-2-one (**3.1a**, 31.0 mg, 0.13 mmol, 1.3 equiv.) and 4,5-dimethyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one (**3.2o**, 18.8 mg, 0.1 mmol, 1 equiv.), according to GP-1, compound **3.3ao** (36.1 mg, 0.085 mmol, 85% yield, 1.2:1 dr, brown oil) was purified by column chromatography using hexane:EtOAc mixtures (from 9:1 to 7:3). The major and the minor diastereomers are labelled with one and two asterisks respectively.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.52 (s, 1H**), 9.41 (s, 1H*), 8.01 – 7.80 (m, 3H*+1H**), 7.57 – 7.34 (m, 2H*+3H***), 7.31 – 6.99 (m, 5H*+6H**), 6.87 (td, *J* = 7.7, 1.6 Hz, 1H*), 6.83 – 6.75 (m, 1H*+4H**), 6.70 (dd, *J* = 7.7, 1.6 Hz, 1H*), 6.60 (d, *J* = 8.0 Hz, 1H*), 4.76 (d, *J* = 15.3 Hz, 1H**), 4.56 (d, *J* = 15.5 Hz, 1H*), 4.49 (s, 1H*), 4.37 (d, *J* = 15.5 Hz, 1H*), 4.34 – 4.24 (m, 2H**), 1.90 (s, 3H**), 1.79 (s, 3H*), 1.44 (s, 3H*), 1.42 (s, 3H**); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 174.35 (C), 173.20 (C), 164.40 (C), 164.16 (C), 161.33 (C), 161.22 (C), 137.91 (C), 137.46 (C), 136.78 (C), 136.40 (C), 132.60 (C), 132.19 (C), 128.92 (CH), 128.75 (CH), 128.51 (C+CH), 128.47 (CH), 127.88 (CH), 127.77 (C), 127.52 (CH), 127.44 (CH), 127.20 (CH), 125.22 (CH), 124.89 (CH),

124.57 (CH), 124.16 (CH), 121.81 (CH), 121.05 (CH), 119.00 (CH), 118.87 (CH), 118.46 (CH), 117.94 (CH), 115.78 (CH), 115.59 (CH), 66.61 (CH), 66.35 (CH), 59.07 (C), 58.66 (CH_2), 58.58 (C), 57.14 (CH_2), 17.72 (CH_3), 17.22 (CH_3), 14.32 (CH_3), 14.25 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{26}H_{25}N_4O_2^+$ 425.1972, found 425.1977.

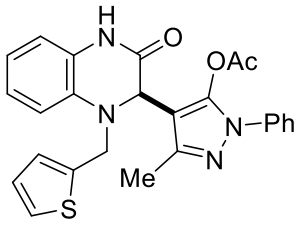
4-(1-(4-Methoxybenzyl)-3-oxo-1,2,3,4-tetrahydroquinoxalin-2-yl)-3-methyl-1-phenyl-1*H*-pyrazol-5-yl acetate (3.3ba)



Using 4-(4-methoxybenzyl)-3,4-dihydroquinoxalin-2-one (3.1b, 34.9 mg, 0.13 mmol, 1.3 equiv.) and 5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one (**3.2a**, 17.4 mg, 0.1 mmol, 1 equiv.), according to GP-1, compound 3.3ba (26.1 mg, 0.054 mmol, 54% yield, brown solid) was purified by column chromatography using hexane:EtOAc mixtures (from 9:1 to 7:3).

Mp = 148-154 °C; **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 9.45 (s, 1H), 7.44 – 7.27 (m, 5H), 7.20 (d, *J* = 8.7 Hz, 2H), 6.93 (dd, *J* = 7.7, 1.3 Hz, 1H), 6.91 – 6.84 (m, 2H), 6.80 (dd, *J* = 7.7, 1.5 Hz, 1H), 6.71 (dd, *J* = 7.5, 1.2 Hz, 1H), 6.66 (d, *J* = 8.4 Hz, 1H), 5.03 (s, 1H), 4.61 (d, *J* = 15.1 Hz, 1H), 4.02 (d, *J* = 15.1 Hz, 1H), 3.80 (s, 3H), 2.14 (s, 3H), 1.47 (s, 3H). **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 167.4 (C), 165.5 (C), 159.1 (C), 148.4 (C), 142.4 (C), 137.7 (C), 134.1 (C), 129.1 (CH), 128.9 (CH), 127.9 (C), 127.5 (CH), 124.9 (C), 124.4 (CH), 123.0 (CH), 118.0 (CH), 115.5 (CH), 114.2 (CH), 111.5 (CH), 106.9 (C), 55.34 (CH), 55.29 (CH_3), 49.9 (CH_2), 19.4 (CH_3), 13.0 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{28}H_{27}N_4O_4^+$ 483.2027, found 483.2029.

3-Methyl-4-(3-oxo-1-(thiophen-2-ylmethyl)-1,2,3,4-tetrahydroquinoxalin-2-yl)-1-phen-yl-1*H*-pyrazol-5-yl acetate (3.3ca)

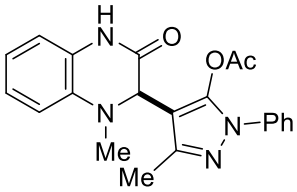


Using 4-(thiophen-2-ylmethyl)-3,4-dihydroquinoxalin-2-one (**3.1c**, 31.8 mg, 0.13 mmol, 1.3 equiv.) and 5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one (**3.2a**, 17.4 mg, 0.1 mmol, 1 equiv.), according to GP-1, compound **3.3ca** (17.0 mg, 0.037 mmol, 37% yield, light brown solid) was purified by column chromatography using hexane:EtOAc mixtures (from 9:1 to 7:3).

Mp = 180-189 °C; **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 9.31 (s, 1H), 7.44 – 7.23 (m, 6H), 7.00 – 6.88 (m, 3H), 6.84 – 6.66 (m, 3H), 5.15 (s, 1H), 4.79 (d, *J* = 15.8 Hz, 1H), 4.33 (d, *J* = 15.8 Hz, 1H), 2.22 (s, 3H), 1.53 (s, 3H). **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 167.4 (C), 165.3 (C), 148.5 (C), 142.4 (C), 139.6 (C), 137.6 (C), 133.3 (C), 129.1 (CH), 127.6 (CH), 126.9 (CH), 126.4 (CH), 125.4 (CH), 125.0 (C), 124.4 (CH), 123.0 (CH),

118.5 (CH), 115.7 (CH), 111.6 (CH), 106.6 (C), 55.4 (CH), 45.8 (CH_2), 19.5 (CH_3), 13.0 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{25}H_{23}N_4O_3S^+$ 459.1485, found 459.1488.

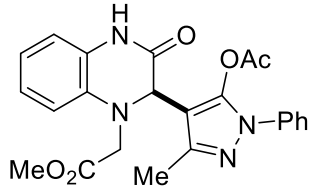
3-Methyl-4-(1-methyl-3-oxo-1,2,3,4-tetrahydroquinoxalin-2-yl)-1-phenyl-1*H*-pyrazol-5-yl acetate (3.3da)



Using 4-methyl-3,4-dihydroquinoxalin-2-one (**3.1d**, 21.1 mg, 0.13 mmol, 1.3 equiv.) and 5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one (**3.2a**, 17.4 mg, 0.1 mmol, 1 equiv.), according to GP-1, compound **3.3da** (27.9 mg, 0.074 mmol, 74% yield, brown oil) was purified by column chromatography using hexane:EtOAc mixtures (from 9:1 to 7:3).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.26 (s, 1H), 7.45 – 7.22 (m, 5H), 6.98 (ddd, *J* = 8.0, 7.3, 1.7 Hz, 1H), 6.78 (dd, *J* = 7.7, 1.6 Hz, 1H), 6.71 (td, *J* = 7.5, 1.2 Hz, 1H), 6.58 (d, *J* = 8.0 Hz, 1H), 5.01 (s, 1H), 2.81 (s, 3H), 2.36 (s, 3H), 1.59 (s, 3H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 167.24 (C), 165.49 (C), 148.18 (C), 142.40 (C), 137.64 (C), 134.51 (C), 129.12 (CH), 127.54 (CH), 124.90 (C), 124.52 (CH), 122.95 (CH), 117.97 (CH), 115.13 (CH), 111.15 (CH), 106.31 (C), 58.41 (CH), 35.23 (CH_3), 19.47 (CH_3), 13.18 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{21}H_{21}N_4O_3^+$ 377.1608, found 377.1609.

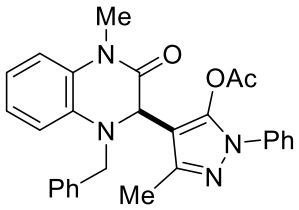
Methyl 2-(2-(5-acetoxy-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-3-oxo-3,4-dihydroquinoxalin-1(2*H*)-yl)acetate (3.3ea)



Using methyl 2-(3-oxo-3,4-dihydroquinoxalin-1(2H)-yl)acetate (**3.1e**, 28.6 mg, 0.13 mmol, 1.3 equiv.) and 5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one (**3.2a**, 17.4 mg, 0.1 mmol, 1 equiv.), according to GP-1, compound **3.3ea** (28.2 mg, 0.065 mmol, 65% yield, brown oil) was purified by column chromatography using hexane:EtOAc mixtures (from 9:1 to 7:3).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.26 (s, 1H), 7.60 – 7.45 (m, 2H), 7.45 – 7.37 (m, 2H), 7.37 – 7.26 (m, 1H), 6.94 (ddd, *J* = 8.1, 5.9, 3.1 Hz, 1H), 6.85 – 6.67 (m, 2H), 6.48 (d, *J* = 8.0 Hz, 1H), 5.34 (s, 1H), 4.02 (d, *J* = 18.1 Hz, 1H), 3.89 (d, *J* = 18.2 Hz, 1H), 3.69 (s, 3H), 2.30 (s, 3H), 1.92 (s, 3H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 170.69 (C), 167.52 (C), 166.02 (C), 148.43 (C), 143.71 (C), 137.67 (C), 133.72 (C), 129.16 (CH), 127.51 (CH), 125.29 (C), 124.25 (CH), 122.82 (CH), 119.49 (CH), 115.71 (CH), 111.56 (CH), 105.01 (C), 56.34 (CH), 51.90 (CH_3), 47.95 (CH_2), 19.86 (CH_3), 13.25 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{23}H_{23}N_4O_5^+$ 435.1663, found 435.1666.

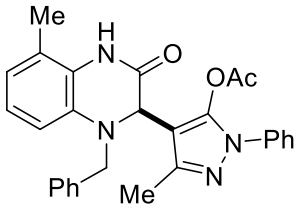
4-(1-Benzyl-4-methyl-3-oxo-1,2,3,4-tetrahydroquinoxalin-2-yl)-3-methyl-1-phenyl-1*H*-pyrazol-5-yl acetate (3.3fa)



Using 4-benzyl-1-methyl-3,4-dihydroquinoxalin-2-one (**3.1f**, 32.8 mg, 0.13 mmol, 1.3 equiv.) and 5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one (**3.2a**, 17.4 mg, 0.1 mmol, 1 equiv.), according to GP-1, compound **3.3fa** (25.7 mg, 0.055 mmol, 55% yield, brown solid) was purified by column chromatography using hexane:EtOAc mixtures (from 9:1 to 7:3).

Mp = 160-171 °C; **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 7.46 – 7.26 (m, 10H), 7.03 – 6.90 (m, 2H), 6.82 (td, *J* = 7.7, 1.4 Hz, 1H), 6.68 (dd, *J* = 8.1, 1.3 Hz, 1H), 5.10 (s, 1H), 4.65 (d, *J* = 15.3 Hz, 1H), 4.10 (d, *J* = 15.3 Hz, 1H), 3.45 (s, 3H), 2.08 (s, 3H), 1.50 (s, 3H). **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 167.3 (C), 164.4 (C), 148.5 (C), 142.3 (C), 137.7 (C), 136.1 (C), 135.4 (C), 129.1 (CH), 128.8 (CH), 128.4 (C), 127.7 (CH), 127.6 (CH), 127.5 (CH), 124.1 (CH), 123.1 (CH), 118.2 (CH), 114.5 (CH), 111.8 (CH), 106.8 (C), 56.1 (CH), 51.0 (CH_2), 29.1 (CH_3), 19.54 (CH_3), 13.0 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{28}H_{27}N_4O_3^+$ 467.2078, found 467.2074.

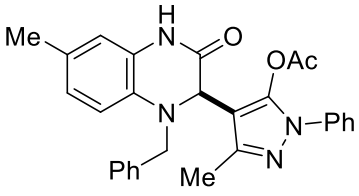
4-(1-Benzyl-5-methyl-3-oxo-1,2,3,4-tetrahydroquinoxalin-2-yl)-3-methyl-1-phenyl-1*H*-pyrazol-5-yl acetate (3.3ga)



Using 4-benzyl-8-methyl-3,4-dihydroquinoxalin-2-one (**3.1g**, 32.8 mg, 0.13 mmol, 1.3 equiv.) and 5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one (**3.2a**, 17.4 mg, 0.1 mmol, 1 equiv.), according to GP-1, compound **3.3ga** (28.9 mg, 0.062 mmol, 62% yield, brown solid) was purified by column chromatography using hexane:EtOAc mixtures (from 9:1 to 7:3).

Mp = 185-190 °C; **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 8.24 (s, 1H), 7.44 – 7.28 (m, 10H), 6.84 (t, *J* = 7.9 Hz, 1H), 6.57 (dd, *J* = 12.7, 7.8 Hz, 2H), 5.04 (s, 1H), 4.66 (d, *J* = 15.6 Hz, 1H), 4.11 (d, *J* = 15.5 Hz, 1H), 2.27 (s, 3H), 2.11 (s, 3H), 1.49 (s, 3H). **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 167.2 (C), 165.0 (C), 148.4 (C), 142.4 (C), 137.7 (C), 136.3 (C), 134.0 (C), 129.1 (CH), 128.8 (CH), 127.6 (CH), 127.5 (CH), 123.8 (CH), 123.1 (C), 123.0 (CH), 122.8 (C), 120.2 (CH), 110.1 (CH), 106.7 (C), 55.7 (CH), 51.0 (CH_2), 19.4 (CH_3), 16.7 (CH_3), 13.0 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{28}H_{27}N_4O_3^+$ 467.2078, found 467.2075.

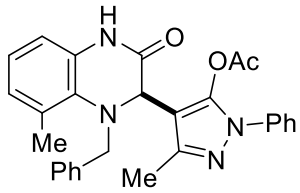
4-(1-Benzyl-6-methyl-3-oxo-1,2,3,4-tetrahydroquinoxalin-2-yl)-3-methyl-1-phenyl-1*H*-pyrazol-5-yl acetate (3.3ha)



Using 4-benzyl-7-methyl-3,4-dihydroquinoxalin-2-one (**3.1h**, 32.8 mg, 0.13 mmol, 1.3 equiv.) and 5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one (**3.2a**, 17.4 mg, 0.1 mmol, 1 equiv.), according to GP-1, compound 3.3ha (29.4 mg, 0.063 mmol, 63% yield, brown solid) was purified by column chromatography using hexane:EtOAc mixtures (from 9:1 to 7:3).

Mp = 182-187 °C; **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 8.76 (s, 1H), 7.45 – 7.27 (m, 10H), 6.72 (dd, *J* = 8.2, 1.2 Hz, 1H), 6.61 (d, *J* = 1.5 Hz, 1H), 6.54 (d, *J* = 8.2 Hz, 1H), 5.03 (s, 1H), 4.62 (d, *J* = 15.5 Hz, 1H), 4.08 (d, *J* = 15.6 Hz, 1H), 2.23 (s, 3H), 2.12 (s, 3H), 1.52 (s, 3H). **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 167.3 (C), 165.6 (C), 148.5 (C), 142.4 (C), 137.7 (C), 136.4 (C), 131.8 (C), 129.1 (CH), 128.8 (CH), 127.7 (C), 127.59 (CH), 127.55 (CH), 127.5 (CH), 124.9 (C), 124.8 (CH), 123.0 (CH), 116.1 (CH), 111.8 (CH), 106.6 (C), 55.9 (CH), 50.7 (CH_2), 20.2 (CH_3), 19.4 (CH_3), 13.0 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{28}H_{27}N_4O_3^+$ 467.2078, found 467.2069.

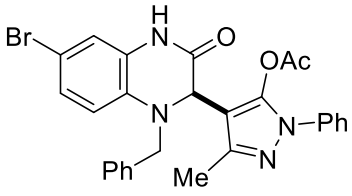
4-(1-Benzyl-8-methyl-3-oxo-1,2,3,4-tetrahydroquinoxalin-2-yl)-3-methyl-1-phenyl-1*H*-pyrazol-5-yl acetate (3.3ia)



Using 4-benzyl-5-methyl-3,4-dihydroquinoxalin-2-one (**3.1i**, 32.8 mg, 0.13 mmol, 1.3 equiv.) and 5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one (**3.2a**, 17.4 mg, 0.1 mmol, 1 equiv.), according to GP-1, compound **3.3ha** (19.6 mg, 0.042 mmol, 42% yield, brown solid) was purified by column chromatography using hexane:EtOAc mixtures (from 9:1 to 7:3).

Mp = 170-179 °C; **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 9.30 (s, 1H), 7.44 – 7.28 (m, 10H), 7.01 (t, *J* = 7.6 Hz, 1H), 6.92 (d, *J* = 6.7 Hz, 1H), 6.74 (dd, *J* = 8.1, 1.6 Hz, 1H), 4.69 (s, 1H), 4.15 – 3.98 (m, 2H), 2.42 (s, 3H), 2.02 (s, 3H), 1.87 (s, 3H). **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 168.3 (C), 166.5 (C), 148.6 (C), 141.7 (C), 137.7 (C), 136.6 (C), 134.5 (C), 132.71 (C), 132.65 (C), 129.7 (CH), 129.0 (CH), 128.6 (CH), 128.0 (CH), 127.3 (CH), 126.4 (CH), 125.2 (CH), 122.9 (CH), 113.8 (CH), 104.7 (C), 58.7 (CH_2), 55.5 (CH), 20.0 (CH_3), 17.6 (CH_3), 13.0 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{28}H_{27}N_4O_3^+$ 467.2078, found 467.2076.

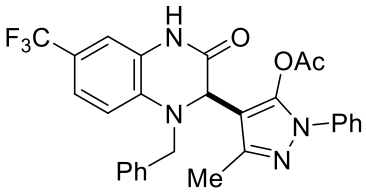
4-(1-Benzyl-6-bromo-3-oxo-1,2,3,4-tetrahydroquinoxalin-2-yl)-3-methyl-1-phenyl-1*H*-pyrazol-5-yl acetate (3.3ja)



Using 4-benzyl-7-bromo-3,4-dihydroquinoxalin-2-one (**3.1j**, 41.2 mg, 0.13 mmol, 1.3 equiv.) and 5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one (**3.2a**, 17.4 mg, 0.1 mmol, 1 equiv.), according to GP-1, compound **3.3ja** (43.0 mg, 0.081 mmol, 81% yield, light brown solid) was purified by column chromatography using hexane:EtOAc mixtures (from 9:1 to 7:3).

Mp = decomposes at 215 °C; **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 8.67 (s, 1H), 7.44 – 7.23 (m, 10H), 7.01 (dd, *J* = 8.7, 2.2 Hz, 1H), 6.92 (d, *J* = 2.2 Hz, 1H), 6.50 (d, *J* = 8.7 Hz, 1H), 5.04 (s, 1H), 4.59 (d, *J* = 15.6 Hz, 1H), 4.11 (d, *J* = 15.6 Hz, 1H), 2.13 (s, 3H), 1.59 (s, 3H). **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 167.3 (C), 165.1 (C), 148.3 (C), 142.4 (C), 137.6 (C), 135.6 (C), 133.1 (C), 129.2 (CH), 128.9 (CH), 127.8 (CH), 127.7 (CH), 127.5 (CH), 126.8 (CH), 126.2 (C), 123.1 (CH), 117.9 (CH), 113.1 (CH), 109.5 (C), 106.3 (C), 55.8 (CH), 50.9 (CH_2), 19.5 (CH_3), 13.0 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{27}H_{24}BrN_4O_3^+$ 531.1026, found 531.1030.

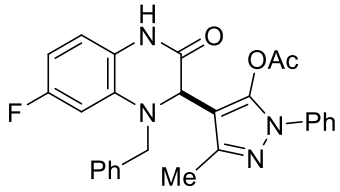
4-(1-Benzyl-3-oxo-6-(trifluoromethyl)-1,2,3,4-tetrahydroquinoxalin-2-yl)-3-methyl-1-phenyl-1*H*-pyrazol-5-yl acetate (3.3ka)



Using 4-benzyl-7-trifluoromethyl-3,4-dihydroquinoxalin-2-one (**3.1k**, 39.8 mg, 0.13 mmol, 1.3 equiv.) and 5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one (**3.2a**, 17.4 mg, 0.1 mmol, 1 equiv.), according to GP-1, compound **3.3ka** (40.6 mg, 0.078 mmol, 78% yield, light brown solid) was purified by column chromatography using hexane:EtOAc mixtures (from 9:1 to 7:3).

Mp = 168-174 °C; **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 9.96 (s, 1H), 7.45 – 7.27 (m, 10H), 7.18 (dd, *J* = 8.5, 1.3 Hz, 1H), 7.06 (d, *J* = 2.0 Hz, 1H), 6.67 (d, *J* = 8.5 Hz, 1H), 5.12 (s, 1H), 4.68 (d, *J* = 15.8 Hz, 1H), 4.19 (d, *J* = 15.7 Hz, 1H), 2.18 (s, 3H), 1.49 (s, 3H). **^{19}F{^{1}H}-NMR (282 MHz, $CDCl_3$)** δ -61.81. **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 167.2 (C), 165.2 (C), 148.3 (C), 142.4 (C), 137.5 (C), 136.5 (C), 135.2 (C), 129.2 (CH), 129.0 (CH), 127.9 (CH), 127.8 (CH), 127.4 (CH), 124.7 (C), 124.3 (q, *J* = 270.8 Hz, CF3), 123.0 (CH), 121.62 (q, J_{C-F} = 4.1 Hz, CH), 119.80 (q, J_{C-F} = 33.2 Hz, C), 112.46 (q, J_{C-F} = 3.7 Hz, CH), 110.8 (CH), 106.5 (C), 55.7 (CH), 50.8 (CH_2), 19.3 (CH_3), 12.9 (CH_3). **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{28}H_{24}F_3N_4O_3^+$ 521.1795, found 521.1795.

4-(1-Benzyl-7-fluoro-3-oxo-1,2,3,4-tetrahydroquinoxalin-2-yl)-3-methyl-1-phenyl-1*H*-pyrazol-5-yl acetate (3.3la)



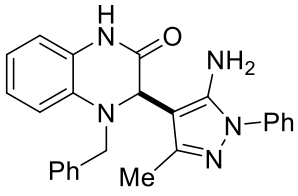
Using 4-benzyl-6-fluoro-3,4-dihydroquinoxalin-2-one (**3.1l**, 33.3 mg, 0.13 mmol, 1.3 equiv.) and 5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one (**3.2a**, 17.4 mg, 0.1 mmol, 1 equiv.), according to GP-1, compound **3.3la** (21.2 mg, 0.045 mmol, 45% yield, light brown solid) was purified by column chromatography using hexane:EtOAc mixtures (from 9:1 to 7:3).

Mp = 155-163 °C; **^{1}H-NMR (300 MHz, DMSO-d$_6$)** δ 10.77 (s, 1H), 7.52 – 7.18 (m, 10H), 6.82 (dd, J = 8.9, 5.9 Hz, 1H), 6.54 – 6.38 (m, 2H), 5.03 (s, 1H), 4.58 (d, J = 15.9 Hz, 1H), 4.15 (d, J = 15.9 Hz, 1H), 2.05 (s, 3H), 1.71 (s, 3H); **^{19}F{^{1}H}-NMR (282 MHz, DMSO-d$_6$)** δ -119.71. **^{13}C{^{1}H}-NMR (75 MHz, DMSO-d$_6$)** δ 167.2 (C), 163.4 (C), 158.90 (d, J_{C-F} = 236.3 Hz, C), 147.6 (C), 141.9 (C), 137.4 (C), 136.7 (C), 134.9 (d, J_{C-F} = 11.0 Hz, C), 129.5 (CH), 128.6 (CH), 127.32 (CH), 127.29 (CH), 122.30 (d, J_{C-F} = 2.5 Hz, C), 121.9 (CH), 115.37 (d, J_{C-F} = 9.8 Hz, CH), 107.1 (C), 103.18 (d, J_{C-F} = 23.3 Hz, CH), 99.15 (d, J_{C-F} = 28.7 Hz, CH), 55.5 (CH), 50.8 (CH_2), 19.3 (CH_3), 12.7 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* [M + H]$^+$ calcd for $C_{27}H_{24}FN_4O_3^+$ 471.1827, found 471.1822.

General Procedure for the Photocatalytic Alkylation Reaction between 3,4-dihydro-1,4-benzoxazin-2-ones 3.1 and 5-aminopyrazoles 3.7

In a 10 mL culture tube, 4-benzyl-3,4-dihydroquinoxalin-2-one (**3.1a**, 0.13 mmol, 1.3 equiv.), the corresponding 5-aminopyrazole (**3.7**, 0.1 mmol, 1 equiv.) and 9,10-phenanthrenequinone (**J**, 1.0 mg, 0.005 mmol, 5 mol %) were placed. Then, $CHCl_3$ (1 mL) was added and the reaction mixture was placed 2 cm over HP Blue LED (455 nm) (455 nm) (see page 433 for further details about the photochemical setup). The conversion of the starting materials was traced regularly by TLC. When 5-aminopyrazole **3.7** was consumed, the reaction mixture was taken off the HP Single LED and Et_3N (14 μL, 0.1 mmol, 1 equiv.) and Ac_2O (19 μL, 0.2 mmol, 2 equiv.) were added and the resulting mixture was stirred at room temperature for 30 minutes. Thereafter, the reaction mixture was purified by column chromatography using hexane:EtOAc mixtures (from 90:10 to 70:30) to obtain the expected pure compound **3.8**.

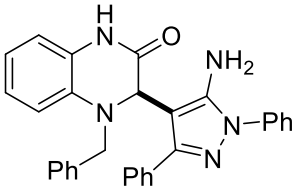
3-(5-Amino-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-4-benzyl-3,4-dihydroquinoxalin-2-one (3.8aa)



Using 4-benzyl-3,4-dihydroquinoxalin-2-one (**3.1a**, 31.0 mg, 0.13 mmol, 1.3 equiv.) and 3-methyl-1-phenyl-1*H*-pyrazol-5-amine (**3.7a**, 17.3 mg, 0.1 mmol, 1 equiv.), according to GP-2, compound **3.8aa** (24.6 mg, 0.060 mmol, 60% yield, yellow oil) was purified by column chromatography using hexane:EtOAc mixtures (from 9:1 to 7:3).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.15 (s, 1H), 7.46 – 7.26 (m, 10H), 6.98 – 6.89 (m, 1H), 6.84 – 6.68 (m, 3H), 5.02 (s, 1H), 4.71 (d, J = 15.7 Hz, 1H), 4.22 (d, J = 15.7 Hz, 1H), 3.75 (s, 2H), 1.96 (s, 3H). **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 166.8 (C), 147.9 (C), 143.8 (C), 138.2 (C), 136.5 (C), 134.5 (C), 129.4 (CH), 128.8 (CH), 127.5 (CH), 127.43 (CH), 127.37 (CH), 124.7 (CH), 124.6 (C), 124.1 (CH), 118.5 (CH), 115.7 (CH), 111.9 (CH), 99.0 (C), 57.0 (CH), 50.9 (CH_2), 13.3 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{25}H_{24}N_5O^+$ 410.1975, found 410.1971.

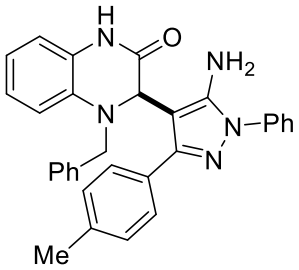
3-(5-Amino-1,3-diphenyl-1*H*-pyrazol-4-yl)-4-benzyl-3,4-dihydroquinoxalin-2-one (3.8ab)



Using 4-benzyl-3,4-dihydroquinoxalin-2-one (**3.1a**, 31.0 mg, 0.13 mmol, 1.3 equiv.) and 1,3-diphenyl-1*H*-pyrazol-5-amine (**3.7b**, 23.5 mg, 0.1 mmol, 1 equiv.), according to GP-2, compound **3.8ab** (34.9 mg, 0.074 mmol, 74% yield, light brown solid) was purified by column chromatography using hexane:EtOAc mixtures (from 9:1 to 7:3).

Mp = 190-192 °C; **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 8.88 (s, 1H), 7.65 (ddd, J = 5.4, 3.0, 1.4 Hz, 2H), 7.58 – 7.47 (m, 2H), 7.47 – 7.39 (m, 2H), 7.38 – 7.31 (m, 1H), 7.31 – 7.27 (m, 3H), 7.18 – 7.11 (m, 3H), 7.06 (dd, J = 6.6, 3.1 Hz, 2H), 6.86 (ddd, J = 8.1, 7.2, 1.7 Hz, 1H), 6.78 (dd, J = 7.7, 1.7 Hz, 1H), 6.70 (td, J = 7.5, 1.2 Hz, 1H), 6.56 (d, J = 7.9 Hz, 1H), 5.31 (s, 1H), 4.45 (d, J = 16.0 Hz, 1H), 4.08 (d, J = 16.1 Hz, 1H), 3.72 (s, 2H). **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 166.6 (C), 152.5 (C), 143.9 (C), 138.1 (C), 136.6 (C), 134.4 (C), 133.0 (C), 129.4 (CH), 129.0 (CH), 128.5 (CH), 128.2 (CH), 128.0 (CH), 127.7 (CH), 127.2 (CH), 127.1 (CH), 124.7 (CH), 124.5 (CH), 124.3 (C), 118.5 (CH), 115.5 (CH), 112.0 (CH), 99.1 (C), 56.8 (CH), 50.9 (CH_2); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{30}H_{26}N_5O^+$ 472.2132, found 472.2135.

3-(5-Amino-1-phenyl-3-(p-tolyl)-1*H*-pyrazol-4-yl)-4-benzyl-3,4-dihydroquinoxalin-2-one (3.8ac)



Using 4-benzyl-3,4-dihydroquinoxalin-2-one (-2(1H)-one, 31.0 mg, 0.13 mmol, 1.3 equiv.)and 1-phenyl-3-(p-tolyl)-1*H*-pyrazol-5-amine (**3.7c**, 24.9 mg, 0.1 mmol, 1 equiv.), according to GP-2, compound **3.8ac** (55.2 mg, 0.095 mmol, 95% yield, brown solid) was purified by column chromatography using hexane:EtOAc mixtures (from 9:1 to 7:3).

Mp = 189-196 °C; **^{1}H-NMR (300 MHz, MeOD)** δ 7.58 – 7.44 (m, 4H), 7.44 – 7.33 (m, 3H), 7.20 – 7.09 (m, 3H), 7.09 – 6.98 (m, 4H), 6.90 – 6.75 (m, 2H), 6.70 – 6.62 (m, 1H), 6.59 (d, J = 8.2 Hz, 1H), 5.23 (s, 1H), 4.47 (d, J = 16.2 Hz, 1H), 4.10 (d, J = 16.2 Hz, 1H), 2.31 (s, 3H); **^{13}C{^{1}H}-NMR (75 MHz, MeOD)** δ 168.3 (C), 153.9 (C), 146.9 (C), 139.4 (C), 139.2 (C), 138.5 (C), 135.7 (C), 131.2 (C), 130.5 (CH), 130.0 (CH), 129.8 (CH), 129.4 (CH), 129.1 (CH), 128.2 (CH), 127.9 (CH), 126.2 (C), 125.9 (CH), 125.3 (CH), 119.3 (CH), 116.6 (CH), 113.2 (CH), 100.3 (C), 57.8 (CH), 52.0 (CH_2), 21.3 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{31}H_{28}N_5O^+$ 486.2288, found 486.2291.

Chapter 4

Copper-Catalyzed Alkynylation of 3,4-Dihydroquinoxalin-2-ones

4.1 Introduction and state of the art

The generation of chemical diversity from a common intermediate represents one of the most important cornerstones in organic chemistry. In fact, the development of methodologies that introduce versatile functional groups has contributed to the enhancement of the chemical space.[166]

In this sense, the carbon-carbon triple bond, namely an alkyne, offers many synthetic possibilities, since it can be converted in several functional groups.[167,168] To mention some, alkynes can easily undergo hydrogenation (partial or complete), halogenation, hydroboration, hydrosilylation, hydrometalation or cycloadditions, among many of them (Figure 4.1). It is important to note that many of them require transition-metal catalysis.[169,170] Additionally, the simplest alkyne, acetylene, is considered a key feedstock in the chemical industry.[171]

Consequently, the development of methodologies to insert a triple bond in a molecule has attracted the attention of the organic chemistry community, being the most straightforward way the generation of nucleophilic metal alkynylides from terminal alkynes. This strategy relies on the relative high acidity of $-C{\equiv}C-H$ bond, due to its higher *s*-character compared to that of alkenes or alkanes. Thus, the activation of terminal alkynes via deprotonation can be accessed using stoichiometric strong bases ($NaNH_2$, *n*-BuLi...) or weak bases in combination with a transition metal (Figure 4.2).

Metal ions such as Ag(I), Au(I), Cu(I) among others have a strong affinity to triple bonds. Hence, the formation of a π complex between the metal and the alkyne leads to

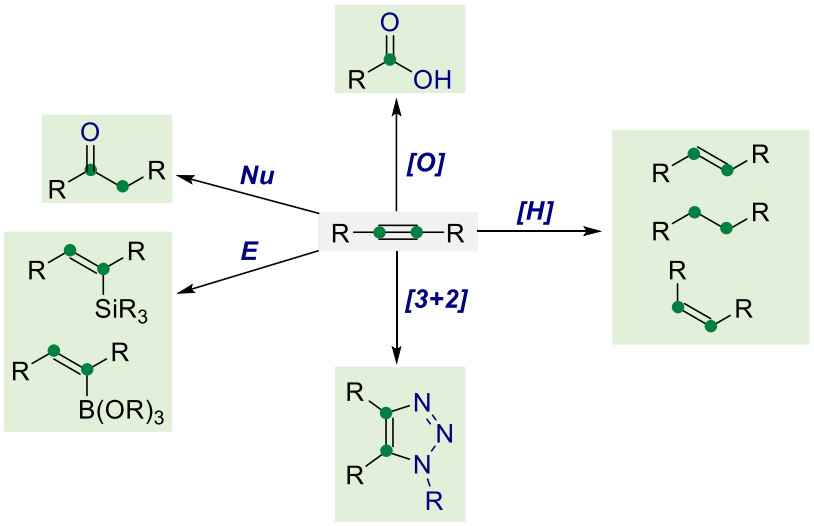


Figure 4.1: Activation of terminal alkynes.

an enhancement of the acidity in −C≡C−H bond, and therefore the presence of a weak base is capable enough to deprotonate and to generate the corresponding metal alkynylide, which has nucleophilic character (Figure 4.2).

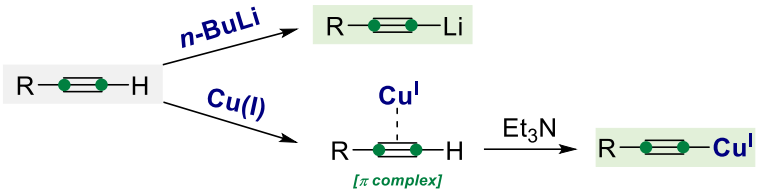
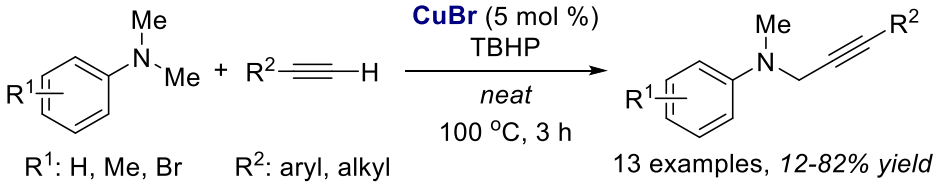


Figure 4.2: Synthetic versatility of the alkyne moiety.

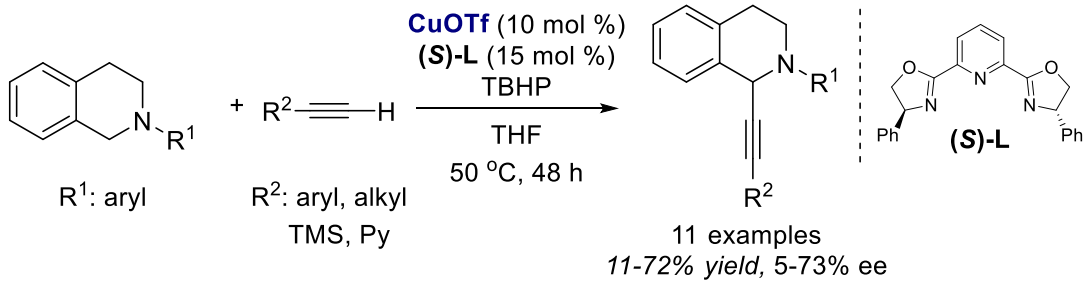
Due to the facility in which terminal alkynes can be activated, the use of them as nucleophilies have found a vast number of applications in organic chemistry, especially in enantioselective synthesis.[172] In fact, our research group has an ongoing portfolio about enantioselective alkynylation to electrophilic double bonds.[173–176]

On the other hand, transition metals may also mediate the activation of terminal alkynes as well as other chemical processes. For the purposes of this *thesis* it is of special interest the metal-catalyzed generation of iminum cations from tertiary amines, and the subsequent addition of the metal-activated terminal alkynes. This challenging strategy was firstly unlocked in 2004 by Li and collaborators, who developed an alkynylation of *N*,*N*-dimethylanilines with terminal alkynes using CuBr as catalyst and TBHP as terminal oxidant.[177] As mentioned earlier, in this case the copper catalyst is the responsible of generating the iminium cation of *N*,*N*-dimethylanilines in combination with TBHP and also of generating the corresponding copper(I)-alkynylide (Scheme 4.1).



Scheme 4.1: Copper-catalyzed oxidative alkynylation of *N*,*N*-dimethylanilines (Li).

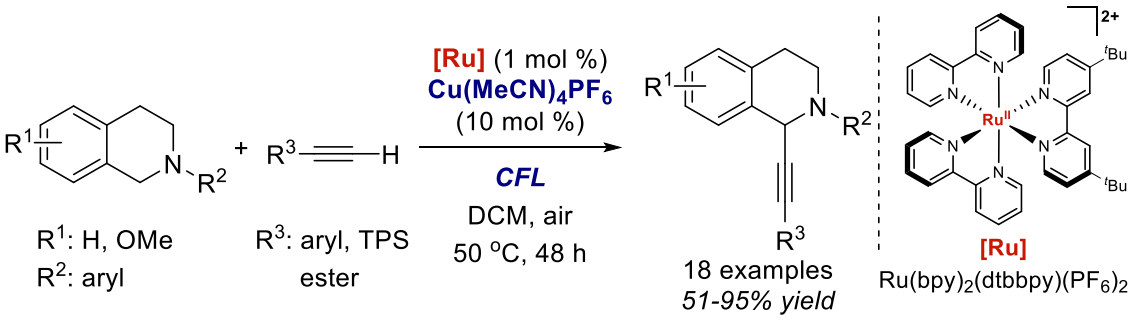
In the same year, the research group of Li also reported the oxidative alkynylation of *N*-aryl tetrahydroisoquinolines with terminal alkynes using a chiral pyBOX-Cu(I) complex, and therefore generating the expected propargyl amines in an enantioselective manner (Scheme 4.2).[178] In the same vain, the Cu(I) complex generates the corresponding iminium cation of *N*-aryl tetrahydroisoquinoline using TBHP employed as final oxidant, and activates the terminal alkyne as well.



Scheme 4.2: Copper-catalyzed asymmetric oxidative alkynylation of *N*-aryl tetrahydroisoquinolines (Li).

Nevertheless, as it has been discussed in this *thesis*, photoredox catalysis also serves to oxidyze tertiary amines to iminium cations, which can react with the corresponding transition-metal-activated terminal alkyne. It was the laboratory of Rueping who in 2012 reported the oxidative alkynylation of *N*-aryl tetrahydroisoquinolines using a dual catalytic system consisting of $Cu(MeCN)_4PF_6$ and $Ru(bpy)_2(dtbbpy)(PF_6)$ as photoredox catalyst (Scheme 4.3).[179] In this case, the oxidation of *N*-aryl tetrahydroisoquinolines was achieved using molecular oxygen from air as terminal oxidant.

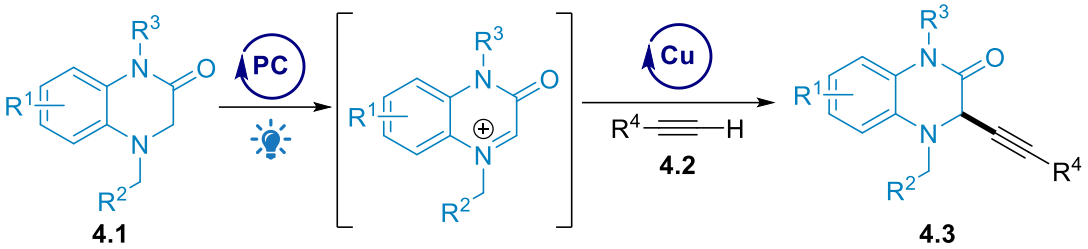
In light of this precedents, we thought that it would be of interest the development of an alkynylation protocol for the C-3 functionalization of 3,4-dihydroquinoxalin-2-ones with terminal alkynes using a combination of visible-light photoredox catalysis and transition-metal catalysis. This approach will be addressed by generating the iminium cation of 4-alkyl-3,4-dihydroquinoxalin-2-ones through aerobic photocatalysis, and the subsequent trapping of this electrophile by the activated metal alkynylide.



Scheme 4.3: Copper-catalyzed aerobic oxidative alkynylation of *N*-aryl tetrahydroisoquinolines (Rueping).

4.2 Objectives

The main objective for this *Chapter* is to develop a methodology to functionalize 3,4-dihydroquinoxalin-2-ones (**4.1**) with terminal alkynes (**4.2**) employing visible-light photoredox catalysis and transition-metal catalysis. To achieve this objective, several partial objectives are postulated:



1. Optimization of the reaction conditions between 4-benzyl-3,4-dihydroquinoxalin-2-one **4.1a** and phenylacetylene (**4.2a**) to obtain the corresponding alkynylated product **4.3aa** with the highest yield.

2. Study of the scope of the reaction between different 3,4-dihydroquinoxalin-2-ones (**4.1**) and different terminal alkynes (**4.2**).

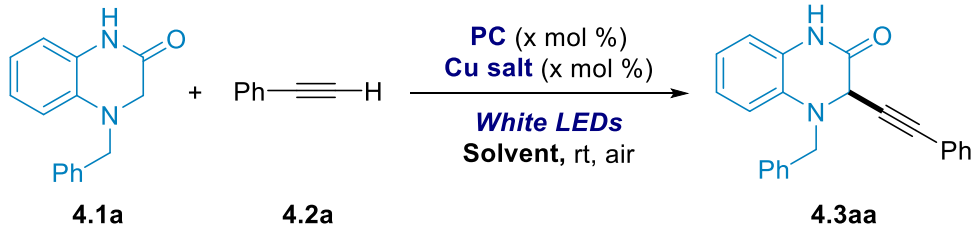
3. Development of an enantioselective version.

4. Synthetic transformations of the reaction products **4.3**.

4.3 Results and Discussion

4.3.1 Optimization of the Reaction Conditions

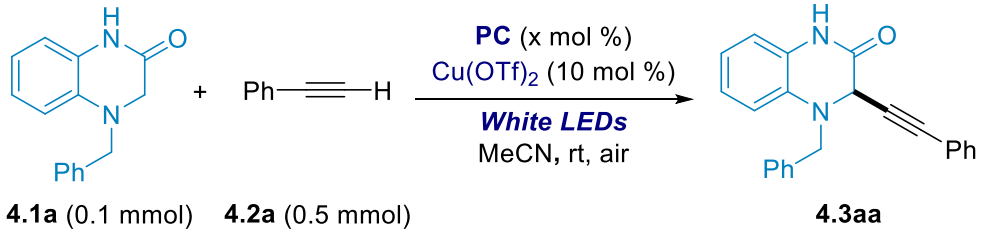
4-Benzyl-3,4-dihydroquinoxalin-2-one (**4.1a**) and phenylacetylene (**4.2a**), which eventually may form alkynylated product **4.3aa**, were selected as model substrates to initiate the optimization procedure (Scheme 4.4). The first variable of consideration will be the photoredox catalyst. After that, a screening to determine the best copper specie will be conducted. Thereafter, the reaction will be performed in different solvents to choose the best one in terms of performance.



Scheme 4.4: Overview of the model reaction to carry out the optimization of the reaction conditions.

Evaluation of the Photoredox Catalyst

The first step in the optimization process is the selection of the best photocatalyst to perform the oxidative alkynylation reaction. According to our envisions, the photoredox catalyst is the responsible of generating the corresponding iminium cation of 3,4-dihydroquinoxalin-2-ones **4.1**, with the final assistance of O_2. Based on previous experiences of our research group, we decided to set $Cu(OTf)_2$ as preliminary copper source and MeCN as solvent (Scheme 4.5).



Scheme 4.5: Evaluation of the photoredox catalyst in the reaction between **4.1a** and **4.2a** using $Cu(OTf)_2$ and MeCN.

The reaction was initially launched using 1 mol % of $Ru(bpy)_3Cl_2$ (**A**) and 10 mol % of $Cu(OTf)_2$. To our delight, we could isolate the desired product **4.3aa** in 47% yield

after 20 hours of irradiation (Table 4.1, Entry 1). Encouraged by this preliminary result, we also tested $Ir(ppy)_3$ (**K**) as photocatalyst, and a moderate increase of the yield until 59% was observed (Table 4.1, Entry 2). Besides, the reaction was found to be possible using organophotocatalysts such as Rose Bengal (**D**) or [Mes-Acr-Me][BF_4] (**H**), which were able to deliver product **4.3aa** in 55% and 51% yield respectively (Table 4.1, Entries 3 and 4). Finally, our promising photocatalyst 9,10-phenanthrenequinone (**J**) was also competent to generate the corresponding product in 63% yield (Table 4.1, Entry 5).

However, at this point we were surprised by the narrow difference between the yields in which product **4.3aa** was isolated. Our suspicion was confirmed when the reaction was performed without any photocatalyst, obtaining compound **4.3aa** in 54% after the same time of irradiation (Table 4.1, Entry 6). Besides, the requirement of light irradiation was interrogated at this point, obtaining product **4.3aa** in 47% yield after 15 hours of stirring in the dark (Table 4.1, Entry 7). Finally, the necessity of $Cu(OTf)_2$ was demonstrated, as no product **4.3aa** was generated after 15 hours of irradiation in the absence of the copper salt (Table 4.1, Entry 8).

Table 4.1: Evaluation of the photoredox catalyst in the reaction between **4.1a** and **4.2a** using $Cu(OTf)_2$ and MeCN. Yield of **4.3aa**.

Entry[a]	PC (x mol %)	t (h)	Yield 4.3aa (%)[b]
1	$Ru(bpy)_3Cl_2$ (**A**) (1)	20	47
2	*fac*-$Ir(ppy)_3$ (**K**) (1)	15	59
3	Rose Bengal (**D**) (5)	15	55
4	[Mes-Acr-Me][BF_4] (**H**) (5)	15	51
5	9,10-Phenanthrenequinone (**J**) (5)	15	63
6	-	15	54
7[c]	-	15	47
8[d]	-	15	-

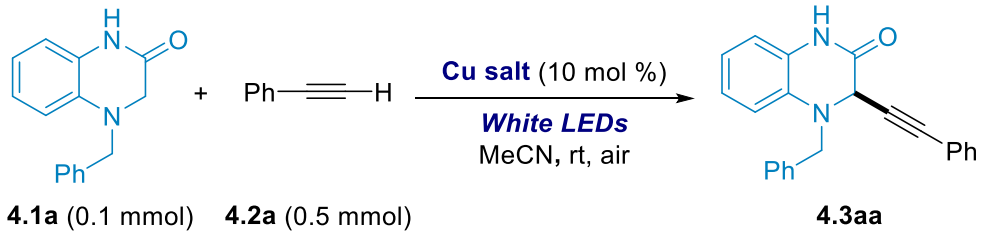
[a]Reaction conditions: **4.1a** (0.1 mmol), **4.2a** (0.5 mmol), **PC** (x mol %), $Cu(OTf)_2$ (10 mol %), MeCN (1 mL), under air atmosphere and under white LEDs irradiation for the indicated time.
[b]Yield determined after purification by column chromatography.
[c]The reaction was performed in the dark.
[d]The reaction was performed without $Cu(OTf)_2$.

Apparently, our reaction did not require the presence of a photoredox catalyst to generated the corresponding iminium cation of **4.1a**. According to reported works,[79,80,177,178,180] copper can mediate the oxidation between of **4.1a** and stoichiometric oxidants such as DDQ or TBHP, but in our case, the final oxidant is O_2 from air. Somehow, although the

reaction can take place without visible light, the performance under irradiation is slightly better, and therefore the optimization process will continue without photocatalyst but irradiating the reaction mixture.

Evaluation of the Copper Catalyst

After determining that the reaction between 3,4-dihydroquinoxalin-2-one **4.1a** and phenylacetylene (**4.2a**) could be done without photocatalyst, the precise selection of the copper salt is very meaningful. In consequence, a screening of both Cu(I) and Cu(II) salts will be performed (Scheme 4.6).



Scheme 4.6: Evaluation of the copper catalyst in the reaction between **4.1a** and **4.2a** using MeCN.

The formal exchange of a triflate counteranion in $Cu(OTf)_2$ for a chloride or a bromide resulted in a decrease of the yield from 54% to 27% and 32% (Table 4.2, Entries 2 and 3). Unfortunately, copper(II) acetate did not work properly in the formation of product **4.3aa**, as it was isolated in only 21% yield after two days (Table 4.2, Entry 4). Monovalent copper salts were also tested in their ability of promoting the reaction and, although CuCl was responsible of generating **4.3aa** in 44% yield, when CuI was engaged, the desired product was not even detected in the reaction mixture (Table 4.2, Entries 5 and 6).

After these experimental evidences we decided to select $Cu(OTf)_2$ as the proper copper source for both activating phenylacetylene (**4.2a**) and oxidizing 3,4-dihydroquinoxalin-2-one **4.1a** (Table 4.2, Entry 1).

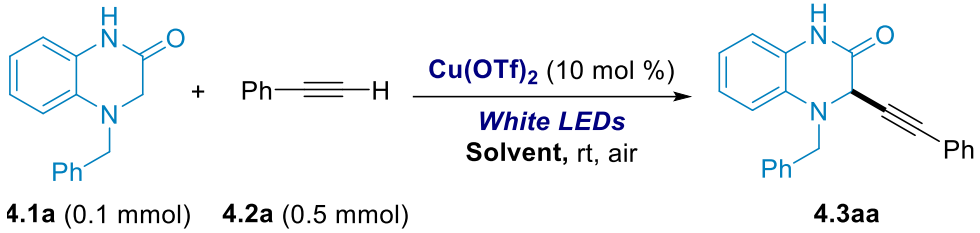
Evaluation of the Solvent

The use of methanol as solvent produced the decomposition of 3,4-dihydroquinoxalin-2-one **4.1a** with almost no formation of the desired product (Table 4.2, Entry 2). Moreover, when toluene was employed, the corresponding product **4.3aa** was isolated in 50% yield but it required 5 days, probably due to the low solubility of $Cu(OTf)_2$ in that solvent (Table 4.2, Entry 3). Neither chloroform nor tetrahydrofuran were suitable matrix for the oxidative alkynylation reaction, as product **4.3aa** was generated in 29% and 30% yield respectively (Table 4.2, Entries 4 and 5). Finally, as representatives of polar aprotic

Table 4.2: Evaluation of the copper catalyst in the reaction between **4.1a** and **4.2a** using MeCN. Yield of **4.3aa** in each case.

Entry[a]	Copper salt	t (h)	Yield 4.3aa (%)[b]
1	$Cu(OTf)_2$	15	54
2	$CuCl_2$	1.5	27
3	$CuBr_2$	24	32
4	$Cu(OAc)_2{\cdot}H_2O$	48	21
5	CuCl	1.5	44
6	CuI	48	-

[a]Reaction conditions: **4.1a** (0.1 mmol), **4.2a** (0.5 mmol), copper salt (10 mol %), MeCN (1 mL), under air atmosphere and under white LEDs irradiation for the indicated time.
[b]Yield determined after purification by column chromatography.



Scheme 4.7: Evaluation of the solvent in the reaction between **4.1a** and **4.2a** using MeCN.

solvents, DMF and DMSO were tested. Unfortunately, in both cases the desired product **4.3aa** was delivered in lower yield (Table 4.2, Entries 6 and 7).

Consequently, MeCN was selected as the best solvent to perform the oxidative alkynylation of 3,4-dihydroquinoxalin-2-one **4.1a** with phenylacetylene (**4.2a**) using $Cu(OTf)_2$ (Table 4.2, Entry 1).

Effect of Additives

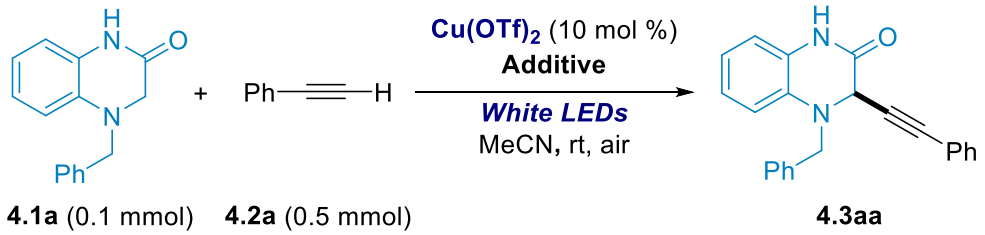
Although after these optimization steps we were pleased to find very simple reaction conditions, we were still unsatisfied with the yield in which alkynylated 3,4-dihydroquinoxalin-2-one **4.3aa** is formed. With the aim of improving the efficiency of our methodology, we focused in the effect that some additives would have over the reaction performance (Scheme 4.8).

We started the study of the effect of additives by using several Brønsted acids such as benzoic acid, acetic acid, trifluoroacetic acid, *p*-toluenesulfonic acid and diphenylphosphoric acid. Among them, only acetic acid was able to increase the yield in which product

Table 4.3: Evaluation of the solvent in the reaction between **4.1a** and **4.2a** using $Cu(OTf)_2$. Yield of **4.3aa** in each case.

Entry[a]	Copper salt (10 mol %)	t (h)	Yield 4.3aa (%)[b]
1	MeCN	15	54
2	MeOH	19	3
3	Toluene	120	50
4	$CHCl_3$	21	29
5	THF	16	30
6	DMF	26	23
7	DMSO	20	33

[a]Reaction conditions: **4.1a** (0.1 mmol), **4.2a** (0.5 mmol), $Cu(OTf)_2$ (10 mol %), solvent (1 mL), under air atmosphere and under white LEDs irradiation for the indicated time.
[b]Yield determined after purification by column chromatography.



Scheme 4.8: Evaluation of additives in the reaction between **4.1a** and **4.2a** using $Cu(OTf)_2$ and MeCN.

4.3aa was formed from 54% to 66% (Table 4.4, Entry 2). Moreover, DIPEA was tested as basic additive, but the desired product was not even detected in the reaction mixture after 35 hours (Table 4.4, Entry 6).

In addition, two heterogeneous acid additives were also evaluated in their competence to promote the formation of product **4.3aa**. Specifically, 3Å MS was employed, the desired product was isolated in only 38% yield (Table 4.4, Entry 7), whereas when SiO_2 was added, we were pleased to obtain product **4.3aa** in a substantially higher 68% yield (Table 4.4, Entry 8).

Hence, we realized that the addition of one equivalent of SiO_2 is beneficial for the oxidative alkynylation reaction. Consequently, the optimization process will continue using that heterogeneous acid additive.

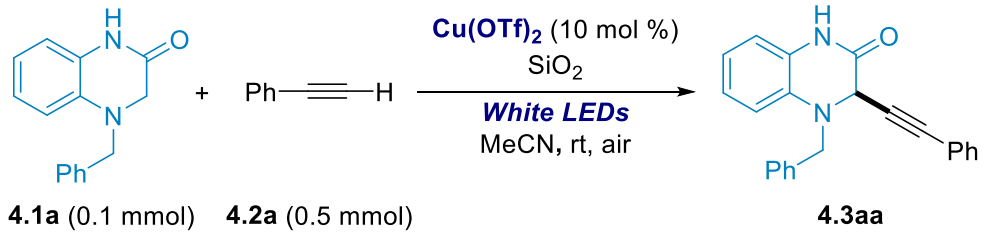
Table 4.4: Evaluation of additives in the reaction between **4.1a** and **4.2a** using $Cu(OTf)_2$ and MeCN. Yield of **4.3aa**.

Entry[a]	Additive (1 equiv.)	t (h)	Yield 4.3aa (%)[b]
1	$PhCO_2H$	48	47
2	AcOH	26	66
3	TFA	3	20
4	PTSA	27	24
5	$(PhO)_2PO_2H$	35	44
6	DIPEA	72	-
7	3Å MS	29	38
8	SiO_2	27	68

[a]Reaction conditions: **4.1a** (0.1 mmol), **4.2a** (0.5 mmol), $Cu(OTf)_2$ (10 mol %), additive (1 equiv.), MeCN (1 mL), under air atmosphere and under white LEDs irradiation for the indicated time.
[b]Yield determined after purification by column chromatography.

Final Adjustments

To finish, some assays were conducted to polish the optimal reaction conditions. Namely the effect of the light source, the catalytic loading of $Cu(OTf)_2$ as well as the molar ratio between **4.1a** and **4.2a** will be investigated (Scheme 4.9).



Scheme 4.9: Final adjustments in the reaction between **4.1a** and **4.2a** using $Cu(OTf)_2$, SiO_2 and MeCN.

When the reaction mixture was irradiated with more powerful light sources (CFL or blue LEDs), the conversion of 3,4-dihydroquinoxalin-2-one **4.1a** sped up from 27 to 6 hours, providing the desired product in 60% in both cases (Table 4.5, Entries 2 and 3) . Since our protocol suffers from the yield of product **4.3aa**, we prioritized the conditions where the highest yield is achieved, so we selected white LEDs as the optimal light source (Table 4.5, Entry 1).

Although we knew that our transformation did not require light irradiation, we de-

cided to repeat it in the dark with the optimal conditions. As expected, product **4.3aa** was isolated in 53% yield after 25 hours (Table 4.5, Entry 4). Again, the irradiation of the reaction mixture with white LEDs seems to be beneficial, and therefore we will conclude that the reaction should be done under visible light. Moreover, the alkynylation reaction was also conducted under a protective argon atmosphere, revealing the key role of molecular oxygen as terminal oxidant, as no product **4.3aa** was observed in the reaction mixture after 24 hours of irradiation (Table 4.5, Entry 5).

Finally, we performed some assays to determine the best molar ratio between **4.1a** and **4.2a**, and the best catalytic loading of $Cu(OTf)_2$ as well. Most of the alkynylation methodologies often require a large excess of terminal alkyne over the electrophile. In our case, we started the optimization process by using five equivalents of phenylacetylene (**4.2a**), according to the experience of the research group. In fact, when this excess was diminished from 5 to 2.5 equivalents, the yield of **4.3aa** decreased from 68% to 53% (Table 4.5, Entry 6). Moreover, when the catalytic loading of 10 mol % of $Cu(OTf)_2$ was reduced to 5 mol %, the desired alkynylated product was isolated in just a 22% yield (Table 4.5, Entry 7).

Table 4.5: Final adjustments in the reaction between **4.1a** and **4.2a** using $Cu(OTf)_2$, SiO_2 and MeCN. Yield of **4.3aa**.

Entry[a]	Light Source	t (h)	Yield 4.3aa (%)[b]
1	White LEDs	27	68
2	CFL	6	60
3	Blue LEDs	6	60
4	dark	25	51
5[c]	White LEDs	24	-
6[d]	White LEDs	25	53
7[e]	White LEDs	25	22

[a] Reaction conditions: **4.1a** (0.1 mmol), **4.2a** (0.5 mmol), $Cu(OTf)_2$ (10 mol %), SiO_2 (1 equiv.), MeCN (1 mL), under air atmosphere and under light source irradiation for the indicated time.
[b] Yield determined after purification by column chromatography.
[c] The reaction was run under an argon atmosphere.
[d] 0.25 mmol of **4.2a** were used.
[e] 5 mol % of $Cu(OTf)_2$ were used.

In light of these findings, we conclude the optimization process by stating that our protocol needs 0.1 mmol of 3,4-dihydroquinoxalin-2-one **4.1a**, 0.5 mmol of phenylacetylene (**4.2a**), 10 mol % of $Cu(OTf)_2$, 1 equivalent of SiO_2, 1 mL of MeCN and the irradiation

with white LEDs under an air atmosphere (Table 4.5, Entry 1).

4.3.2 Scope of the Reaction

Once we determined the optimal reaction conditions for the alkynylation of 4-benzyl-3,4-dihydroquinoxalin-2-one (**4.1a**) and phenylacetylene (**4.2a**) we focused on establishing the generality of this transformation. Thus, the reaction was performed using differently substituted 3,4-dihydroquinoxalin-2-ones (**4.1**) and terminal alkynes (**4.2**).

Scope of the Reaction with 3,4-Dihydroquinoxalin-2-ones

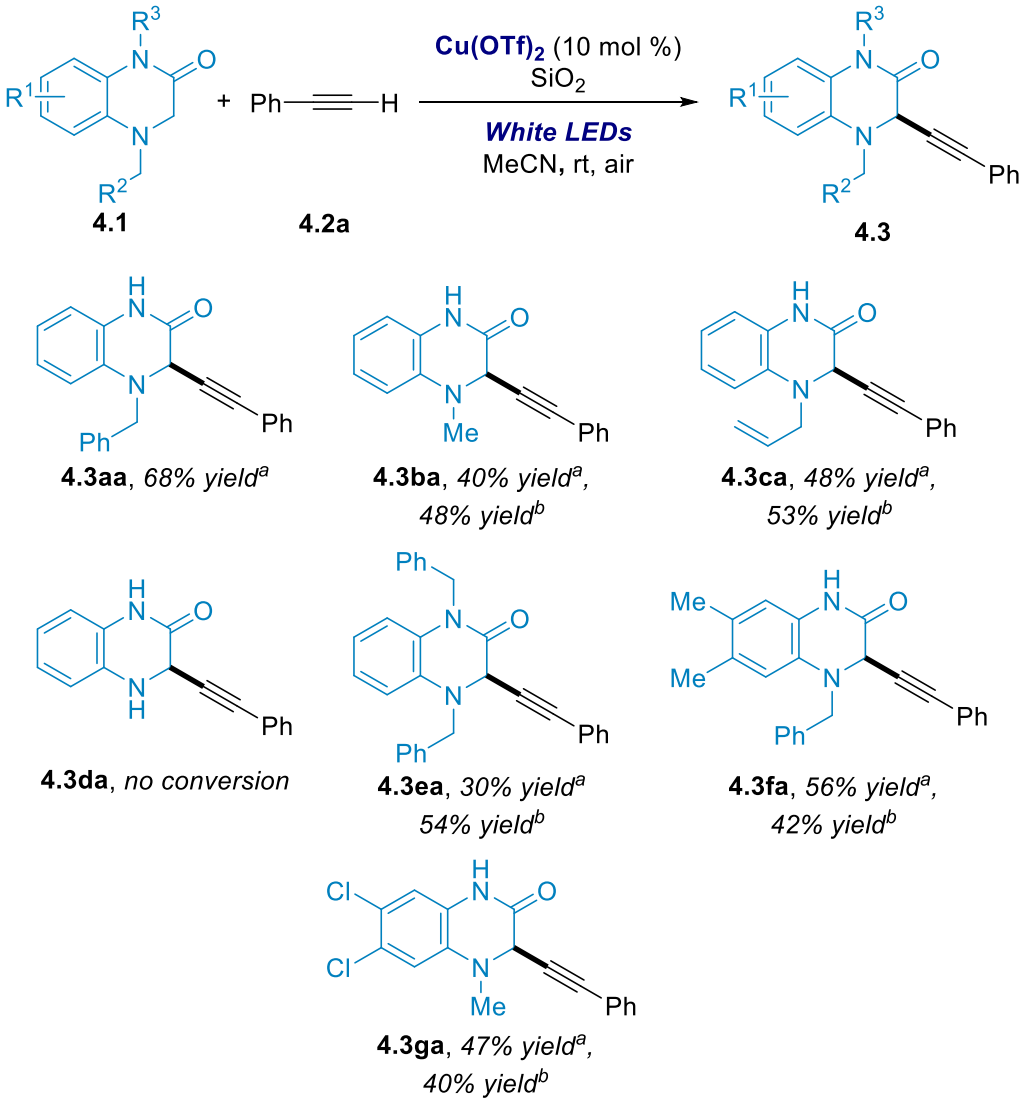
Initially, we decided to explore how robust our methodology was regarding the substitution at the 3,4-dihydroquinoxalin-2-one (**4.1**) moiety (Scheme 4.10). First of all, the effect of different alkyl groups at N-4 was investigated. Nevertheless, when we subjected to our optimal conditions, 3,4-dihydroquinoxalin-2-one **4.1b**, which bears a methyl group at N-4, the corresponding product **4.3ba** was generated in only 40% yield. With the aim of improving that result, we decided to do the reaction without light irradiations but increasing the temperature to 50 °C. With these thermal conditions, we could slightly improve the yield of product **4.3ba** to 48%. In the same vain, the use 3,4-dihydroquinoxalin-2-one **4.1c** resulted in the corresponding product with 48% yield, whereas when the reaction mixture was heated to 50 °C, the same product was generated in 53% yield. Unfortunately, N-4 unprotected 3,4-dihydroquinoxalin-2-one **4.1d** did not lead to the formation of the desired product.

Moreover, the use of 1,4-dibenzyl-3,4-dihydroquinoxalin-2-one (**4.1e**) provided the expected product **4.3ea** in a lower yield of 30% under photochemical conditions. Delightfully, under thermal conditions we could increase the yield to 54%.

Different 3,4-dihydroquinoxalin-2-one bearing alternative substitution at the aromatic ring were also tested. Namely, 6,7-dimethyl-3,4-dihydroquinoxalin-2-one (**4.1f**) with methyl groups afforded the corresponding alkynylated product **4.3fa** in 56% yield under photochemical conditions and in 42% yield under thermal conditions. Similarly, 3,4-dihydroquinoxalin-2-one with chlorine atoms at the same positions and a methyl group at N-4 was able to generate the corresponding product **4.3ga** in 47% and 40% yield under photochemical or thermal conditions, respectively.

Scope of the Reaction with Terminal Alkynes

Once the limits of our protocol have been established with regard of the substitution in 3,4-dihydroquinoxalin-2-ones (**4.1**), we decided to study which terminal alkynes could fit in (Scheme 4.11).



Scheme 4.10: Scope of the reaction using different 3,4-dihydroquinoxalin-2-ones **4.1** and phenylacetylene (**4.2a**)[ab]

[a]Reaction conditions: **4.1** (0.1 mmol), **4.2a** (0.5 mmol), $Cu(OTf)_2$ (10 mol %), SiO_2 (1 equiv.), MeCN (1 mL), under air atmosphere and under white LEDs irradiation. Yield determined after purification by column chromatography.

[b]The reaction was conducted at 50 °C instead of under irradiation of white LEDs.

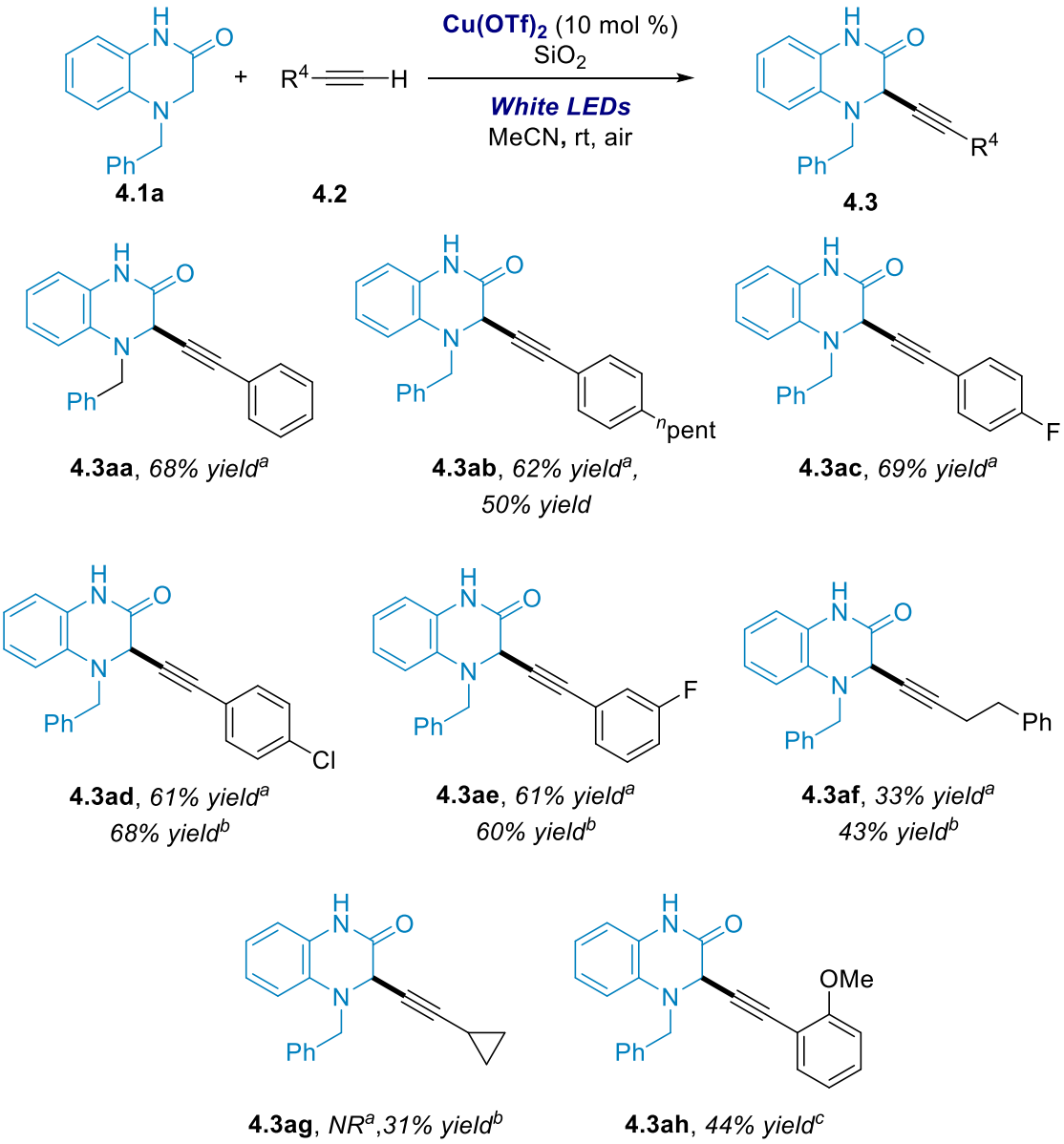
Different aromatic terminal alkynes were subjected to the oxidative alkynylation reaction. Specifically, a *n*-pentyl chain at the *para* position was efficiently tolerated, as the corresponding product **4.3ab** was obtained in 62% yield. In the same way than before, for comparative purposes, this reaction was also done under thermal conditions (50 °C), obtaining the same product but in a lower yield of 50%. Pleasingly, aromatic acetylene bearing a fluorine atom at the *para* position produced the expected alkynylated 3,4-dihydroquinoxalin-2-one **4.3ac** in 69% under visible-light irradiation. In the case of *p*-Cl phenylacetylene (**4.2d**), the expected product **4.3ad** was obtained in 61% yield under photochemical conditions and in 68% yield under thermal conditions, whereas *m*-F phenylacetylene **4.2e** delivered the expected product **4.3ae** in 61% regardless of the methodology.

Moving to aliphatic terminal alkynes, we were pleased to get the alkynylated 3,4-dihydroquinoxalin-2-one **4.3af** with 4-phenyl-1-butyne (**4.2f**) in 33% and 43% yield under photochemical and thermal conditions, respectively. In the case of cyclopropyl-derived acetylene, we only could obtain the expected product under thermal conditions, although in a low 31% yield.

Interestingly, when 1-ethynyl-2-methoxybenzene (**4.2h**) was used as pre-nucleophile, the isolated product was not the corresponding alkynylated 3,4-dihydroquinoxalin-2-one. It seems that the triple bond in the alkynylation product is regioselectively hydrated, leading to the corresponding ketone. However, excluding water from the reaction media, we could perform the reaction with the same alkyne **4.2h** and isolate the expected product **4.3ah** in 44% yield.

In light that the use of 1-ethynyl-2-methoxybenzene (**4.2h**) resulted in a product where the C≡C bond got hydrated, we decided to explore if that was a particular case or otherwise it is a common phenomenon for electron-rich aryl acetylenes. In fact, by using MeCN as received we were pleased to obtain selectively the corresponding 3,4-dihydroquinoxalin-2-ones bearing an acetophenone moiety **4.4** when several electron-rich aromatic alkynes were employed (Scheme 4.12). Indeed, the copper-catalyzed hydration of internal alkynes is known.[181]

Specifically, 1-ethynyl-2-methoxybenzene **4.2h** generated the corresponding product **4.4ah** in 65% yield when the presence of water was not avoided in the reaction mixture. Similarly, 1-ethynyl-4-methoxybenzene (**4.2i**) delivered the corresponding hydrated product **4.4ai** in 33% yield under photochemical conditions and in 56% yield under thermal conditions. This behaviour can be also extended to terminal alkynes bearing five-membered heteroaromatic groups, as they are electron rich too. Indeed, the use of 2-ethynylthiophene (**4.2j**) resulted in the expected product **4.4aj** in 53% and 41% yield under photochemical and thermal conditions, respectively.

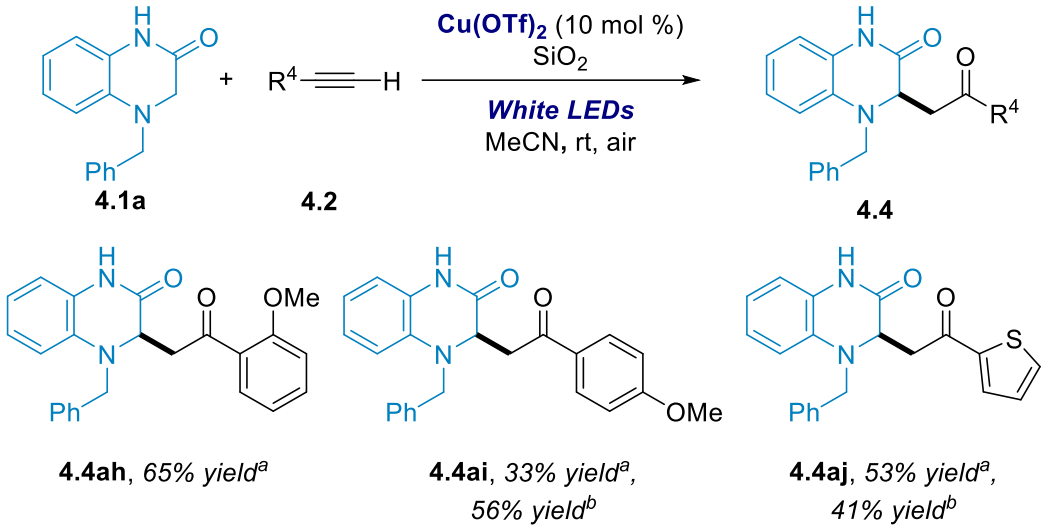


Scheme 4.11: Scope of the reaction using 4-benzyl-3,4-dihydroquinoxalin-2-one (**4.1a**) and different terminal alkynes (**4.2**).[abc]

[a]Reaction conditions: **4.1a** (0.1 mmol), **4.2** (0.5 mmol), $Cu(OTf)_2$ (10 mol %), SiO_2 (1 equiv.), MeCN (1 mL), under air atmosphere and under white LEDs irradiation. Yield determined after purification by column chromatography.

[b]The reaction was conducted at 50 °C instead of under irradiation of white LEDs.

[c]The reaction was performed using dry MeCN and O_2 atmosphere.



Scheme 4.12: Scope of the reaction using 4-benzyl-3,4-dihydroquinoxalin-2-one (**4.1a**) and different electron-rich terminal alkynes (**4.2**).[abc]

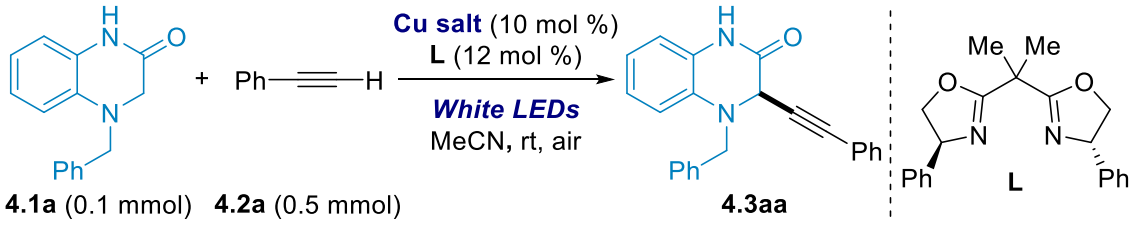
[a]Reaction conditions: **4.1a** (0.1 mmol), **4.2** (0.5 mmol), $Cu(OTf)_2$ (10 mol %), SiO_2 (1 equiv.), MeCN (1 mL), under air atmosphere and under white LEDs irradiation. Yield determined after purification by column chromatography.

[b]The reaction was conducted at 50 °C instead of under irradiation of white LEDs.

[c]The reaction was performed using dry MeCN and O_2 atmosphere.

4.3.3 Development of the Enantioselective Version

Given the importance of stereo-defined molecules in several fields, at this point we embarked on the task of developing an asymmetric version of the oxidative alkynylation of 3,4-dihydroquinoxalin-2-ones. With this objective, our attention was focused on the construction of a chiral copper complex that eventually could induce enantioselectivity to the reaction, through an asymmetric transfer of the copper alkynylide to the iminium cation. Based on the experience of our research group, we decided to try C_2-symmetric chiral bisoxazolines (BOX) ligands to form the corresponding chiral copper complex (Scheme 4.13).



Scheme 4.13: Evaluation of the copper salt in the enantioselective reaction between **4.1a** and **4.2a**.

Specifically, we started the optimization by testing different copper sources, while

using a BOX ligand (**L**), MeCN as solvent and under the irradiation of white LEDs. Initially, just by adding 12 mol % of BOX ligand to our previous optimized conditions, the corresponding product **4.3aa** was isolated in yield as low as 10% after 3 days of reaction, although with a promising 50% ee (Table 4.6, Entry 1). Apparently, the main consequence of surrounding the copper catalyst with BOX ligand was the evident worse ability of the complex to generate the iminium cation of **4.1a**. In the same line, many other copper salts were tested as chiral complex precursors, but in any of the cases the yield was high enough for our requirements. Even in the best case, where CuCl was employed, product **4.3aa** was isolated in 18% yield and 68% ee (Table 4.6, Entry 3). For us was no worth to continue the optimization of this asymmetric reaction.

Table 4.6: Evaluation of the copper catalyst in the enantioselective reaction between **4.1a** and **4.2a**. Yield and enantiomeric excess of **4.3aa**.

Entry[a]	Copper salt	t (days)	Yield 4.3aa (%)[b]	ee (%)[c]
1	$Cu(OTf)_2$	3	10	50
2	$CuCl_2$	4	7	28
3	CuCl	4	18	68
4	$(CuOTf)_2 \cdot PhMe$	4	7	47
5	$Cu(MeCN)_4BF_4$	4	11	52
6	$CuBr_2 \cdot SMe_2$	4	9	62
7[d]	$Cu(OTf)_2$	4	12	39

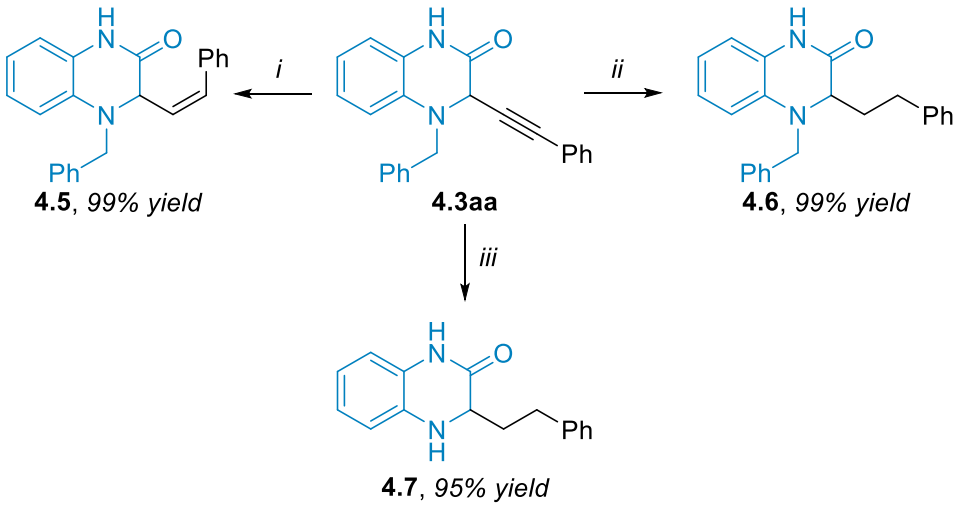
[a]Reaction conditions: **4.1a** (0.1 mmol), **4.2a** (0.5 mmol), copper salt (10 mol %), L (12 mol %), MeCN (1 mL), under air atmosphere and under white LEDs irradiation for the indicated time.
[b]Yield determined after purification by column chromatography.
[c]Enantiomeric excess determined by chiral HPLC analysis.
[d]The reaction was conducted at 50 °C instead of under irradiation of white LEDs.

4.3.4 Synthetic Transformations

After establishing the scope of the reaction and trying the enantioselective version of the oxidative alkynylation of 3,4-dihydroquinoxalin-2-ones, we thought that it would be of interest the synthetic modification of products **4.3**. As stated earlier, the $-C{\equiv}C-$ bond is a versatile functional group because it offers several transformations, especially hydrogenations. Consequently, we decided to conduct three different transformations over product **4.3aa** using three particular hydrogenation conditions (Scheme 4.14).

Pleasingly, alkynylated product **4.3aa** was partially hydrogenated with H_2 in the pres-

ence of Lindlar's catalyst to afford diastereoselectively *cis*-alkene **4.5** in quantitative yield. Moreover, full alkyne hydrogenation of **4.3aa** with no C−N hydrogenolysis was achieved with Pd over $CaCO_3$, delivering compound **4.6** in 99% yield. Finally, with the more active Pd/C catalyst, both complete −C≡C− bond saturation and benzylic C−N hydrogenolysis were accomplished, as product **4.7** was isolated in 95% yield.



Scheme 4.14: Synthetic transformations over product **4.3aa**[a].

[a]Reaction conditions: *i*) **4.3aa** (0.061 mmol), Lindlar catalyst (4 mg), H_2 (1 atm), benzene (1 mL); *ii*) **4.3aa** (0.066 mmol), Pd 5% over $CaCO_3$ (7.4 mg), H_2 (1 atm), EtOH (5 mL); *iii*) **4.3aa** (0.066 mmol), Pd/C 10% (8.6 mg), H_2 (1 atm), EtOH (5 mL).

4.3.5 Control Experiments and Proposed Mechanism

Finally, to conclude this project we postulated a mechanism by which our oxidative alkynylation should proceed. But before, several control experiments were conducted. As we stated in the optimization section, our protocol needs a copper catalyst (Table 4.1, Entry 8) and an aerobic atmosphere (Table 4.5, Entry 5), but the role of visible light in this transformation is not clear. Additionally, we performed the reaction under the optimal conditions but also adding 1.5 equivalents of TEMPO. Under these conditions, no product **4.3aa** formation was observed, but we could detect by means of HRMS the formation of an adduct between 3,4-dihydroquinoxalin-2-one **4.1a** and that radical scavenger. According to that, as expected, radical intermediates are formed throughout the reaction. With all this information, a mechanism for the reaction is proposed (Figure 4.3).

As discussed in the introduction of this *Chapter*, in this kind of transformations the copper catalysts has two roles: 1) act as a redox mediator between substrate **4.1a** and molecular oxygen and 2) activate phenylacetylene (**4.2a**) via formation of copper alkynylide. According to this, in the redox copper catalysis manifold, Cu(II) specie can oxidize

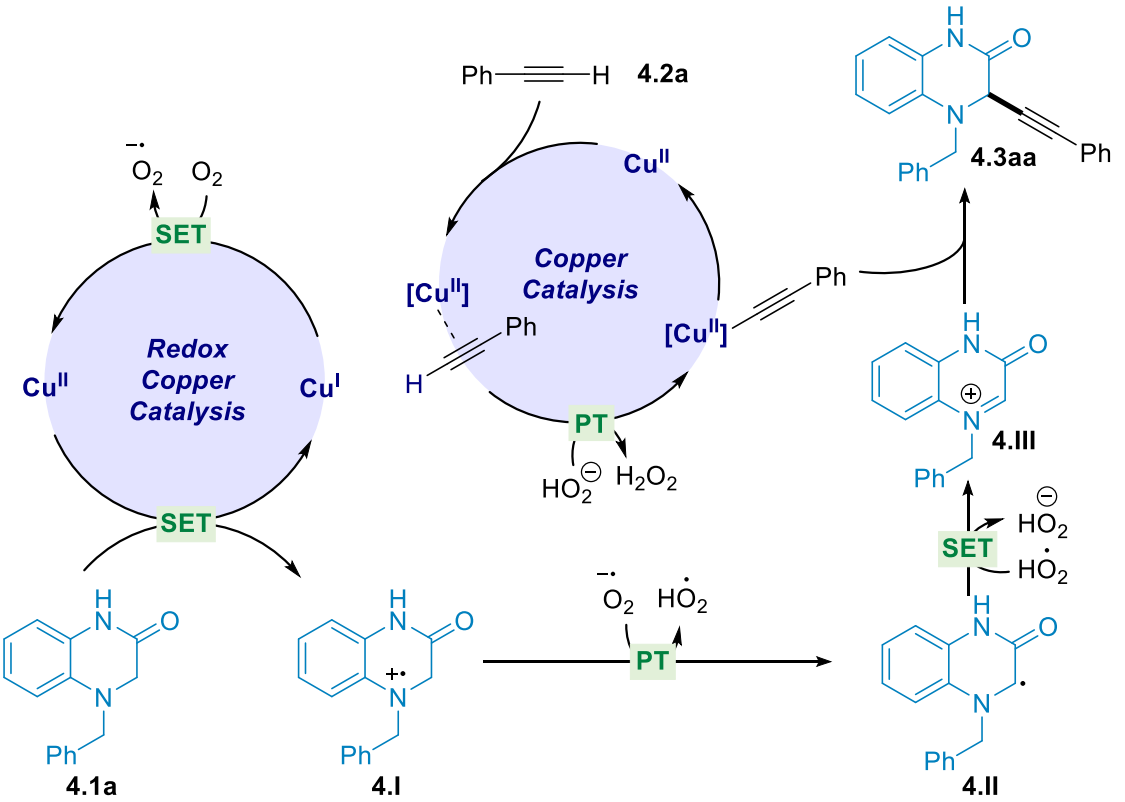


Figure 4.3: Mechanism for the copper-catalyzed oxidative alkynylation between **4.1a** and **4.2a**.

3,4-dihydroquinoxalin-2-one **4.1a** to its corresponding radical cation **4.I** through a SET, with the concomitant formation of Cu(I). Cu(II) active form is regenerated via another SET between Cu(I) and O_2.

The fate of the radical cation **4.I** is the same as that discussed in previous chapters. After a proton transfer, radical cation **4.I** is converted into the α-amino radical **4.II**, which was probably trapped by TEMPO in the control experiment. Thereafter, α-amino radical **4.II** was oxidized to the corresponding electrophilic iminium cation **4.III**. This highly-electrophilic specie can react unproductively with water or molecular oxygen to form the corresponding hemiaminal or peroxide, respectively. We think that SiO_2 may participate in the regeneration of iminum cation **4.III** from these oxygenated by-products.

On the other hand, in the redox-neutral copper catalysis manifold, phenylacetylene (**4.2a**) forms a π complex with Cu(II), thus enhancing the acidity of the terminal hydrogen $-C{\equiv}C-\mathbf{H}$ and therefore facilitating its deprotonation to yield the nucleophilic copper alkynylide. Finally, the transfer of the alkynylide to the iminium cation **4.III** generates the desired alkynylation product **4.3aa**.

4.4 Experimental Section

4.4.1 General Methods

Experimental methods regarding **Melting Points**, **Chromatographic Methods**, **Nuclear Magnetic Resonance (NMR)** and **High Resolution Mass Spectrometry (HRMS)** can be found in Section 1.4.1 of *Chapter 1* (page 62).

Reaction Flasks, Reagents and Substrates

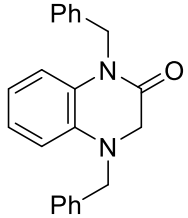
- Photocatalytic reactions were carried out in 5 mL vials under air unless otherwise indicated.
- Commercial reagents were used as purchased.
- All photocatalysts, copper salts and terminal alkynes **4.2** were commercially available.
- 4-Substituted-3,4-Dihydroquinoxalin-2-ones **4.1a**, **4.1e** and **4.1f** were prepared form its N-4 unprotected precursors using the *N*-benzylation procedure described in page 67 of *Chapter 1*. 4-methyl-3,4-dihydroquinoxalin-2-ones **4.1b** and **4.1g** were prepared following a reported procedure.[158]

4.4.2 Synthetic Procedures and Characterization

Synthesis of 3,4-dihydroquinoxalin-2-ones 4.1a, 4.1e and 4.1f

The procedure followed for the synthesis of 3,4-dihydroquinoxalin-2-one **4.1a** is described in *Section 1.4.2* of *Chapter 1* (page 67). 3,4-Dihydroquinoxalin-2-ones **4.1f** was prepared using the same methodology.

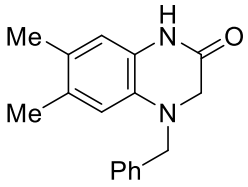
1,4-Dibenzyl-3,4-dihydroquinoxalin-2(1*H*)-one (4.1e)



^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.50 – 7.15 (m, 10H), 6.99 – 6.90 (m, 1H), 6.88 (dd, J = 8.1, 1.4 Hz, 1H), 6.80 (dd, J = 8.1, 1.3 Hz, 1H), 6.77 – 6.70 (m, 1H), 5.21 (s, 2H), 4.42 (s, 2H), 3.90 (s, 2H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 166.1 (C), 137.4 (C), 136.5 (C), 136.3 (C), 129.3 (C), 128.8 (CH), 128.8 (CH), 127.8 (CH), 127.6 (CH), 127.2 (CH), 126.4 (CH), 123.9 (CH), 119.4 (CH), 115.7 (CH), 112.6 (CH), 54.0 (CH_2), 52.8 (CH_2),

45.8 (CH_2); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{22}H_{21}N_2O^+$ 329.1648, found 329.1642.

4-Benzyl-6,7-dimethyl-3,4-dihydroquinoxalin-2(1*H*)-one (4.1f)

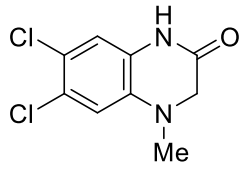


^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.46 (s, 1H), 7.76 – 7.14 (m, 5H), 6.58 (s, 1H), 6.57 (s, 1H), 4.37 (s, 2H), 3.72 (s, 2H), 2.70 – 1.83 (m, 6H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 167.2 (C), 136.6 (C), 132.1 (C), 128.8 (CH), 127.8 (C), 127.8 (C), 127.5 (CH), 127.2 (CH), 123.9 (C), 116.9 (CH), 113.8 (CH), 53.7 (CH2), 52.2 (CH2), 19.7 (CH3), 18.7 (CH3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{17}H_{19}N_2O^+$ 267.1492, found 267.1495.

Synthesis of 3,4-dihydroquinoxalin-2-ones 4.1b and 4.1g

The procedure followed for the synthesis of 3,4-dihydroquinoxalin-2-one **4.1b** was reported in the bibliography by Qiao.[158] 3,4-Dihydroquinoxalin-2-ones **4.1g** was prepared using the same methodology.

6,7-Dichloro-4-methyl-3,4-dihydroquinoxalin-2(1*H*)-one 4.1g

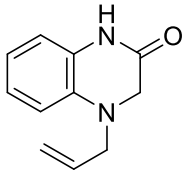


^{1}H-NMR (300 MHz, DMSO-d_6) δ 10.61 (s, 1H), 6.90 (s, 1H), 6.83 (s, 1H), 3.73 (s, 2H), 2.78 (s, 3H); **^{13}C{^{1}H}-NMR (75 MHz, DMSO-d_6)** δ 165.5 (C), 136.3 (C), 127.4 (C), 124.4 (C), 118.9 (C), 115.2 (CH), 112.3 (CH), 53.3 (CH2), 36.9 (CH3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_9H_9Cl_2N_2O^+$ 231.0086, found 231.0083.

Synthesis of 3,4-dihydroquinoxalin-2-one 4.1c

The procedure for the synthesis of 3,4-dihydroquinoxalin-2-one **4.1c** is the same that the one for the preparation of **4.1a** in *Section 1.4.2* of *Chapter 1* (page 67) but using allyl chloride instead of benzyl chloride.

4-Allyl-3,4-dihydroquinoxalin-2(1*H*)-one (4.1c)



^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.66 (s, 1H), 6.97 (ddd, J = 7.9, 5.9, 3.1 Hz, 1H), 6.83 – 6.66 (m, 3H), 5.88 (ddt, J = 17.5, 10.0, 5.8 Hz, 1H), 5.37 – 5.30 (m, 1H), 5.30 – 5.24 (m, 1H), 3.86 (dt, J = 5.8, 1.4 Hz, 2H), 3.83 (s, 2H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)**

δ 167.2 (C), 134.9 (C), 131.6 (CH), 126.1 (C), 124.2 (CH), 118.9 (CH2), 118.9 (CH), 115.6 (CH), 112.1 (CH), 52.2 (CH2), 51.9 (CH2); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{11}H_{13}N_2O^+$ 189.1022, found 189.1023.

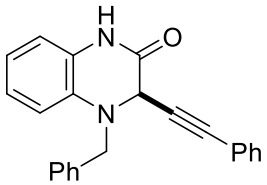
General Procedure 1 (GP-1) for the Oxidative Alkynylation Reaction between 3,4-dihydroquinoxalin-2-ones 4.1 and terminal alkynes 4.2 under photochemical conditions

In a 5 mL vial $Cu(OTf)_2$ (3.6 mg, 10 mol %, 0.01 mmol), SiO_2 (6 mg, 1 equiv., 0.1 mmol) and MeCN (1 mL) were placed. Then, the proper terminal alkyne was added (**4.2**, 0.5 mmol, 5 equiv.) and the resulting solution was stirred for 10 minutes. After this time, the proper 3,4-dihydroquinoxalin-2-ones (**4.1**, 0.1 mmol, 1 equiv.) was added and the resulting mixture was stirred under the irradiation of white LEDs (5 W) (see page 432 for further details about the photochemical setup) until the starting material disappeared (as showed by TLC). Then, the solvent was removed under reduced pressure and the residue was purified by column chromatography to afford product **4.3**.

General Procedure 2 (GP-2) for the Oxidative Alkynylation Reaction between 3,4-dihydroquinoxalin-2-ones 4.1 and terminal alkynes 4.2 under thermal conditions

In a 5 mL vial $Cu(OTf)_2$ (3.6 mg, 10 mol %, 0.01 mmol), SiO_2 (6 mg, 1 equiv., 0.1 mmol) and MeCN (1 mL) were placed. Then, the proper terminal alkyne was added (**4.2**, 0.5 mmol, 5 equiv.) and the resulting solution was stirred for 10 minutes. After this time, the proper 3,4-dihydroquinoxalin-2-ones (**4.1**, 0.1 mmol, 1 equiv.) was added and the resulting mixture was heated to 50 °C until the starting material disappeared (as showed by TLC). Then, the solvent was removed under reduced pressure and the residue was purified by column chromatography to afford product **4.3**.

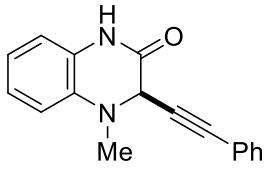
4-Benzyl-3-(phenylethynyl)-3,4-dihydroquinoxalin-2(1*H*)-one (4.3aa)



Using 4-benzyl-3,4-dihydroquinoxalin-2-one (**4.1a**, 23.8 mg, 0.1 mmol, 1 equiv.) and phenylacetylene (**4.2a**, 55 μL, 0.5 mmol, 5 equiv.), according to GP-1, compound **4.3aa** (23.4 mg, 0.068 mmol, 68% yield, yellow solid) was obtained and purified by column chromatography using hexane:DCM mixtures (from 5:5 to 2:8). **Mp** = 174-180 °C; **IR (neat)**: 1694, 1655, 1504, 1377, 977, 747, 690 cm^{1}; **^{1}H-NMR (300 MHz, DMSO-d$_6$)** δ 10.81 (bs, 1H), 7.62 – 7.12 (m, 10H), 6.98 – 6.87 (m, 2H), 6.87 – 6.78 (m, 2H), 4.75 (s, 1H), 4.68 (d, J = 14.6 Hz, 1H), 4.30 (d, J = 14.5 Hz, 1H); **^{13}C{^{1}H}-NMR (75 MHz, DMSO-d$_6$)** δ 162.7 (C), 136.8 (C), 133.6

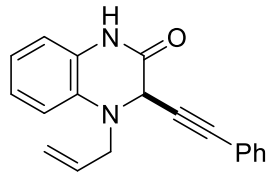
(C), 131.6 (CH), 129.1 (CH), 128.7 (CH), 128.7 (CH), 128.0 (CH), 127.5 (CH), 127.4 (C), 123.2 (CH), 121.1 (C), 120.0 (CH), 115.4 (CH), 114.2 (CH), 85.5 (C), 82.8 (C), 53.8 (CH), 51.6 (CH_2); **HRMS (ESI/Q-TOF)** *m/z* [M + H]$^+$ calcd for $C_{23}H_{19}N_2O^+$ 339.1489, found 339.1492.

4-Methyl-3-(phenylethynyl)-3,4-dihydroquinoxalin-2(1*H*)-one (4.3ba)



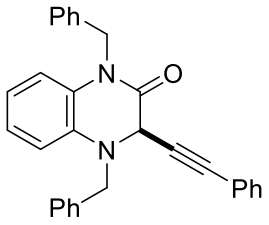
Using 4-methyl-3,4-dihydroquinoxalin-2(1*H*)-one (**4.1b**, 16.2 mg, 0.1 mmol, 1 equiv.) and phenylacetylene (**4.2a**, 55 μL, 0.5 mmol, 5 equiv.), according to GP-1, compound **4.3ba** (10.5 mg, 0.040 mmol, 40% yield, yellow solid) was obtained and purified by column chromatography using hexane:DCM mixtures (from 5:5 to 2:8). Following GP-2, compound **4.3ba** (12.6 mg, 0.048 mmol, 48% yield, yellow solid) was also obtained. **Mp** = 172-176 °C; **IR (neat)**: 1687, 1508, 1388, 744, 684 cm^{-1}; **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 8.80 (bs, 1H), 7.24 – 7.10 (m, 5H), 7.04 – 6.94 (m, 1H), 6.79 (dd, *J* = 4.9, 0.8 Hz, 2H), 6.71 (d, *J* = 8.0 Hz, 1H), 4.74 (s, 1H), 2.90 (s, 3H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 163.9 (C), 134.5 (C), 132.0 (CH), 128.6 (CH), 128.1 (CH), 126.2 (C), 124.4 (CH), 121.9 (C), 120.1 (CH), 115.5 (CH), 113.4 (CH), 86.8 (C), 80.9 (C), 56.9 (CH), 36.0 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* [M + H]$^+$ calcd for $C_{17}H_{15}N_2O^+$ 263.1184, found 263.1180.

4-Allyl-3-(phenylethynyl)-3,4-dihydroquinoxalin-2(1*H*)-one (4.3ca)



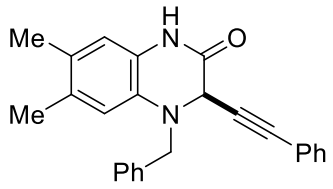
Using 4-allyl-3,4-dihydroquinoxalin-2(1*H*)-one (**4.1c**, 18.8 mg, 0.1 mmol, 1 equiv.) and phenylacetylene (**4.2a**, 55 μL, 0.5 mmol, 5 equiv.), according to GP-1, compound **4.3ca** (13.9 mg, 0.048 mmol, 48% yield, brown oil) was obtained and purified by column chromatography using hexane:DCM mixtures (from 5:5 to 2:8). Following GP-2, compound **4.3ca** (15.3 mg, 0.053 mmol, 53% yield, brown oil) was also obtained. **IR (neat)**: 1685, 1500, 1217, 923, 751, 686 cm^{-1}; **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 8.76 (bs, 1H), 7.33 – 7.16 (m, 5H), 7.12 – 6.98 (m, 1H), 6.93 – 6.82 (m, 3H), 5.96 (dddd, *J* = 17.5, 10.1, 7.5, 4.9 Hz, 1H), 5.47 (ddd, *J* = 17.2, 2.9, 1.5 Hz, 1H), 5.35 (ddd, *J* = 10.2, 2.6, 1.3 Hz, 1H), 4.92 (s, 1H), 4.14 (ddd, *J* = 14.4, 3.4, 1.5 Hz, 1H), 3.75 (dd, *J* = 14.4, 7.5 Hz, 1H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 164.1 (C), 133.9 (C), 132.8 (CH), 131.9 (CH), 128.6 (CH), 128.1 (CH), 126.4 (C), 124.2 (CH), 121.9 (C), 120.2 (CH), 119.7 (CH_2), 115.7 (CH), 113.9 (CH), 86.5 (C), 81.4 (C), 53.6 (CH), 50.9 (CH_2); **HRMS (ESI/Q-TOF)** *m/z* [M + H]$^+$ calcd for $C_{19}H_{17}N_2O^+$ 289.1341, found 289.1336.

1,4-Dibenzyl-3-(phenylethynyl)-3,4-dihydroquinoxalin-2(1*H*)-one (4.3ea)



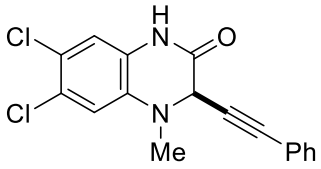
Using 1,4-dibenzyl-3,4-dihydroquinoxalin-2(1*H*)-one (**4.1e**, 32.8 mg, 0.1 mmol, 1 equiv.) and phenylacetylene (**4.2a**, 55 μL, 0.5 mmol, 5 equiv.), according to GP-1, compound **4.3ea** (12.8 mg, 0.030 mmol, 30% yield, yellow solid) was obtained and purified by column chromatography using hexane:DCM mixtures (from 5:5 to 2:8). Following GP-2, compound **4.3ea** (23.1 mg, 0.055 mmol, 55% yield, brown solid) was also obtained. **Mp** = 110-115 °C; **IR (neat)**: 1679, 1502, 1396, 1027, 690 cm^{1}; **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 7.49 – 7.21 (m, 15H), 7.07 – 6.97 (m, 1H), 6.96 – 6.87 (m, 2H), 6.87 – 6.78 (m, 1H), 5.63 (d, *J* = 16.3 Hz, 1H), 4.85 (d, *J* = 16.4 Hz, 1H), 4.81 (s, 1H), 4.73 (d, *J* = 13.6 Hz, 1H), 4.20 (d, *J* = 13.6 Hz, 1H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 163.3 (C), 136.4 (C), 135.9 (C), 135.8 (C), 132.0 (CH), 129.5 (C), 128.9 (CH), 128.8 (CH), 128.7 (CH), 128.6 (CH), 128.21 (CH), 128.0 (CH), 127.1 (CH), 126.0 (CH), 124.0 (CH), 122.0 (C), 120.6 (CH), 115.6 (CH), 114.3 (CH), 86.8 (C), 81.5 (C), 53.8 (CH), 52.3 (CH_2), 45.9 (CH_2); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{30}H_{25}N_2O^+$ 429.1967, found 429.1665.

4-Benzyl-6,7-dimethyl-3-(phenylethynyl)-3,4-dihydroquinoxalin-2(1*H*)-one (4.3fa)



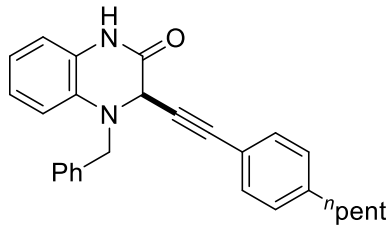
Using 4-benzyl-6,7-dimethyl-3,4-dihydroquinoxalin-2(1*H*)-one (**4.1f**, 26.6 mg, 0.1 mmol, 1 equiv.) and phenylacetylene (**4.2a**, 55 μL, 0.5 mmol, 5 equiv.), according to GP-1, compound **4.3fa** (20.5 mg, 0.056 mmol, 56% yield, yellow oil) was obtained and purified by column chromatography using hexane:DCM mixtures (from 5:5 to 2:8). Following GP-2, compound **4.3fa** (15.4 mg, 0.042 mmol, 42% yield, yellow oil) was also obtained. **IR (neat)**: 1683, 1519, 1396, 1221, 865, 751 cm^{1}; **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 8.64 (bs, 1H), 7.45 – 7.26 (m, 8H), 7.25 – 7.18 (m, 2H), 6.68 (s, 1H), 6.65 (s, 1H), 4.70 (d, *J* = 13.5 Hz, 1H), 4.64 (s, 1H), 4.13 (d, *J* = 13.4 Hz, 1H), 2.20 (s, 3H), 2.17 (s, 3H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 164.2 (C), 135.9 (C), 132.1 (C), 132.0 (CH), 132.0 (C), 128.8 (CH), 128.7 (CH), 128.5 (CH), 128.4 (C), 128.1 (CH), 127.9 (CH), 124.2 (C), 122.1 (C), 117.0 (CH), 115.4 (CH), 86.5 (C), 81.4 (C), 53.2 (CH), 51.7 (CH_2), 19.8 (CH_3), 18.8 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{25}H_{23}N_2O^+$ 367.1810, found 367.1813.

6,7-dichloro-4-methyl-3-(phenylethynyl)-3,4-dihydroquinoxalin-2(1*H*)-one (4.3ga)



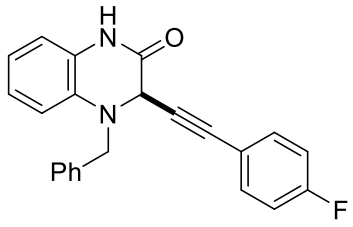
Using 6,7-dichloro-4-methyl-3,4-dihydroquinoxalin-2(1*H*)-one (**4.1f**, 23.1 mg, 0.1 mmol, 1 equiv.) and phenylacetylene (**4.2a**, 55 μL, 0.5 mmol, 5 equiv.), according to GP-1, compound **4.3ga** (15.6 mg, 0.047 mmol, 47% yield, yellow solid) was obtained and purified by column chromatography using hexane:DCM mixtures (from 5:5 to 2:8). Following GP-2, compound **4.3ga** (13.3 mg, 0.040 mmol, 40% yield, yellow solid) was also obtained. **Mp** = decomposes over 200 °C; **IR (neat)**: 1685, 1500, 870, 757 cm^{1}; textbf^{1}H-NMR (400 MHz, Acetone-d$_6$) δ 9.89 (bs, 1H), 7.39 – 7.29 (m, 5H), 7.16 (s, 1H), 7.02 (s, 1H), 4.94 (s, 1H), 3.06 (s, 3H); **^{13}C{^{1}H}-NMR (100 MHz, Acetone-d$_6$)** δ 163.0 (C), 135.9 (C), 132.6 (CH), 129.9 (CH), 129.4 (CH), 128.6 (C), 126.6 (C), 122.7 (C), 122.6 (C), 116.9 (CH), 115.7 (CH), 87.1 (C), 82.2 (C), 56.8 (CH), 36.4 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* [M + H]$^+$ calcd for $C_{17}H_{12}Cl_2N_2O^+$ 330.0327, found 330.0331.

4-Benzyl-3-((4-pentylphenyl)ethynyl)-3,4-dihydroquinoxalin-2(1*H*)-one (4.3ab)



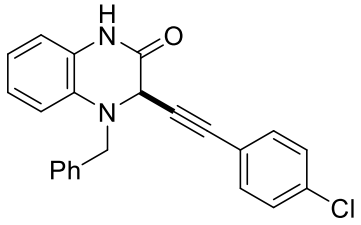
Using 4-benzyl-3,4-dihydroquinoxalin-2-one (**4.1a**, 23.8 mg, 0.1 mmol, 1 equiv.) and 1-ethynyl-4-pentylbenzene (**4.2b**, 97 μL, 0.5 mmol, 5 equiv.), according to GP-1, compound **4.3ab** (25.4 mg, 0.062 mmol, 62% yield, yellow oil) was obtained and purified by column chromatography using hexane:DCM mixtures (from 5:5 to 2:8). Following GP-2, compound **4.3ab** (20.5 mg, 0.050 mmol, 50% yield, yellow oil) was also obtained. **IR (neat)**: 2926, 2855, 1687, 1504, 740, 697 cm^{1}; **^{1}H-NMR (300 MHz, CDCl$_3$)** δ 9.17 (bs, 1H), 7.46 – 7.28 (m, 5H), 7.22 (d, *J* = 8.2 Hz, 2H), 7.10 – 6.97 (m, 3H), 6.93 – 6.85 (m, 3H), 4.71 (d, *J* = 13.8 Hz, 1H), 4.68 (s, 1H), 4.19 (d, *J* = 13.6 Hz, 1H), 2.61 – 2.50 (m, 2H), 1.62 – 1.48 (m, 2H), 1.35 – 1.21 (m, 4H), 0.87 (t, *J* = 6.9 Hz, 3H); **^{13}C{^{1}H}-NMR (75 MHz, CDCl$_3$)** δ 164.6 (C), 143.9 (C), 135.8 (C), 134.3 (C), 131.9 (CH), 128.9 (CH), 128.6 (CH), 128.3 (CH), 127.9 (CH), 126.6 (C), 124.2 (CH), 120.4 (CH), 119.0 (C), 115.8 (CH), 114.0 (CH), 86.9 (C), 80.4 (C), 53.3 (CH), 51.8 (CH_2), 35.8 (CH_2), 31.3 (CH_2), 30.9 (CH_2), 22.5 (CH_2), 14.0 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* [M + H]$^+$ calcd for $C_{28}H_{29}N_2O^+$ 409.2280, found 409.2277.

4-Benzyl-3-((4-fluorophenyl)ethynyl)-3,4-dihydroquinoxalin-2(1*H*)-one (4.3ac)



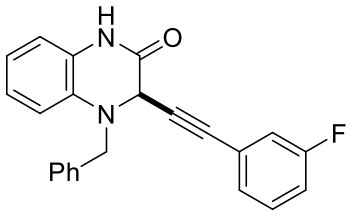
Using 4-benzyl-3,4-dihydroquinoxalin-2-one (**4.1a**, 23.8 mg, 0.1 mmol, 1 equiv.) and 1-fluoro-4-ethynylbenzene (**4.2c**, 57 μL, 0.5 mmol, 5 equiv.), according to GP-1, compound **4.3ac** (24.6 mg, 0.069 mmol, 69% yield, yellow oil) was obtained and purified by column chromatography using hexane:DCM mixtures (from 5:5 to 2:8). **IR (neat)**: 1669, 1247, 727, 689 cm^{1}; **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 9.38 (bs, 1H), 7.48 – 7.22 (m, 8H), 7.09 – 7.00 (m, 1H), 7.00 – 6.88 (m, 4H), 4.74 (d, J = 13.8 Hz, 1H), 4.70 (s, 1H), 4.20 (d, J = 13.6 Hz, 1H); **^{19}F{^{1}H}-NMR (282 MHz, $CDCl_3$)** δ -110.08; **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 164.5 (C), 162.7 (d, J_{C-F} = 250.3 Hz, C), 135.7 (C), 134.1 (C), 133.9 (d, J_{C-F} = 8.4 Hz, CH), 128.9 (CH), 128.6 (CH), 128.0 (CH), 126.5 (CH), 124.3 (CH), 120.5 (CH), 117.9 (d, J_{C-F} = 3.6 Hz, C), 115.9 (CH), 115.5 (d, J_{C-F} = 22.1 Hz, CH), 114.0 (CH), 85.6 (C), 80.9 (d, J_{C-F} = 1.5 Hz, C), 53.2 (CH), 51.9 (CH_2); **HRMS (ESI/Q-TOF)** *m/z* [M + H]$^+$ calcd for $C_{23}H_{18}FN_2O^+$ 357.1398, found 357.1393.

3-((4-Chlorophenyl)ethynyl)-4-benzyl-3,4-dihydroquinoxalin-2(1*H*)-one (4.3ad)



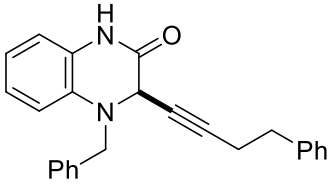
Using 4-benzyl-3,4-dihydroquinoxalin-2-one (**4.1a**, 23.8 mg, 0.1 mmol, 1 equiv.) and 1-chloro-4-ethynylbenzene (**4.2d**, 68.3 mg, 0.5 mmol, 5 equiv.), according to GP-1, compound **4.3ad** (22.8 mg, 0.061 mmol, 61% yield, yellow solid) was obtained and purified by column chromatography using hexane:DCM mixtures (from 5:5 to 2:8). Following GP-2, compound **4.3ad** (25.2 mg, 0.068 mmol, 68% yield, yellow solid) was also obtained. **Mp** = 160-163 °C; **IR (neat)**: 1682, 1489, 1504, 822, 742, 699 cm^{1}; **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 9.07 (bs, 1H), 7.45 – 7.31 (m, 5H), 7.21 (s, 4H), 7.03 (dd, J = 8.1, 4.8 Hz, 1H), 6.97 – 6.85 (m, 3H), 4.72 (d, J = 13.8 Hz, 1H), 4.69 (s, 1H), 4.18 (d, J = 13.7 Hz, 1H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 164.2 (C), 135.6 (C), 134.8 (C), 134.1 (C), 133.2 (CH), 128.9 (CH), 128.6 (CH), 128.5 (CH), 128.0 (CH), 126.5 (C), 124.4 (C), 120.5 (C), 120.3 (C), 115.9 (CH), 114.0 (CH), 85.6 (C), 82.2 (C), 53.2 (CH), 51.9 (CH_2); **HRMS (ESI/Q-TOF)** *m/z* [M + H]$^+$ calcd for $C_{23}H_{18}ClN_2O^+$ 373.1096, found 373.1102.

4-Benzyl-3-((3-fluorophenyl)ethynyl)-3,4-dihydroquinoxalin-2(1*H*)-one (4.3ae)



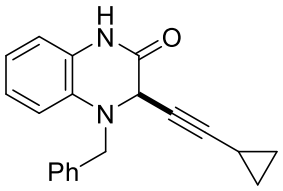
Using 4-benzyl-3,4-dihydroquinoxalin-2-one (**4.1a**, 23.8 mg, 0.1 mmol, 1 equiv.) and 1-fluoro-3-ethynylbenzene (**4.2e**, 58 μL, 0.5 mmol, 5 equiv.), according to GP-1, compound **4.3ae** (21.8 mg, 0.061 mmol, 61% yield, yellow oil) was obtained and purified by column chromatography using hexane:DCM mixtures (from 5:5 to 2:8). Following GP-2, compound **4.3ad** (21.5 mg, 0.060 mmol, 60% yield, yellow oil) was also obtained. **IR (neat)**: 1672, 1247, 727, 695 cm^{1}; **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 9.42 (bs, 1H), 7.54 – 7.22 (m, 5H), 7.20 – 6.84 (m, 8H), 4.73 (d, J = 13.6 Hz, 1H), 4.70 (s, 1H), 4.18 (d, J = 13.6 Hz, 1H); **^{19}F{^{1}H}-NMR (282 MHz, $CDCl_3$)** δ -109.54; **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 164.4 (C), 162.1 (C, d, J_{C-F} = 246.7 Hz), 135.6 (C), 134.1 (C), 129.8 (CH, d, J = 8.6 Hz), 128.9 (CH), 128.6 (CH), 128.0 (CH), 127.9 (CH, d, J_{C-F} =3.2 Hz), 126.5 (C), 124.4 (CH), 123.6 (C, d, J_{C-F} = 9.4 Hz), 120.6 (CH), 118.8 (CH, d, J_{C-F} = 23.0 Hz), 116.1 (CH, d, J_{C-F} = 21.2 Hz), 116.0 (CH), 114.0 (CH), 85.4 (C, d, J_{C-F} = 3.3 Hz), 82.2 (C), 53.1 (CH), 51.9 (CH_2); **HRMS (ESI/Q-TOF)** *m/z* [M + H]$^{+}$ calcd for $C_{23}H_{18}FN_2O^{+}$ 357.1398, found 357.1396.

4-Benzyl-3-(4-phenylbut-1-yn-1-yl)-3,4-dihydroquinoxalin-2(1*H*)-one (4.3af)



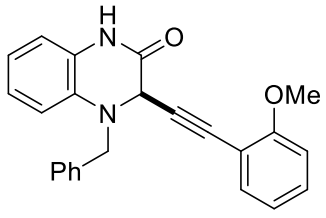
Using 4-benzyl-3,4-dihydroquinoxalin-2-one (**4.1a**, 23.8 mg, 0.1 mmol, 1 equiv.) and 4-phenyl-1-butyne (**4.2f**, 70 μL, 0.5 mmol, 5 equiv.), according to GP-1, compound **4.3af** (12.1 mg, 0.033 mmol, 33% yield, yellow oil) was obtained and purified by column chromatography using hexane:DCM mixtures (from 5:5 to 2:8). Following GP-2, compound **4.3ad** (15.6 mg, 0.043 mmol, 43% yield, yellow oil) was also obtained. **IR (neat)**: 1685, 1504, 740, 695 cm^{1}; **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 8.59 (bs, 1H), 7.29 – 7.19 (m, 5H), 7.18 – 7.08 (m, 3H), 7.03 – 6.91 (m, 3H), 6.85 – 6.75 (m, 2H), 6.73 (d, J = 8.1 Hz, 1H), 4.47 (d, J = 13.7 Hz, 1H), 4.32 (t, J = 2.1 Hz, 1H), 3.88 (d, J = 13.7 Hz, 1H), 2.62 (dd, J = 10.8, 4.2 Hz, 2H), 2.33 (ddd, J = 4.6, 3.4, 1.8 Hz, 2H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 164.7 (C), 140.3 (C), 135.8 (C), 134.3 (C), 128.7 (CH), 128.5 (CH), 128.5 (CH), 128.3 (CH), 127.8 (CH), 126.5 (C), 126.2 (CH), 124.2 (CH), 120.2 (CH), 115.6 (CH), 114.0 (CH), 86.7 (C), 72.8 (C), 52.8 (C), 51.5 (CH_2), 34.6 (CH_2), 20.7 (CH_2); **HRMS (ESI/Q-TOF)** *m/z* [M + H]$^{+}$ calcd for $C_{25}H_{23}N_2O^{+}$ 367.1805, found 367.1809.

4-Benzyl-3-(cyclopropylethynyl)-3,4-dihydroquinoxalin-2(1*H*)-one (4.3ag)



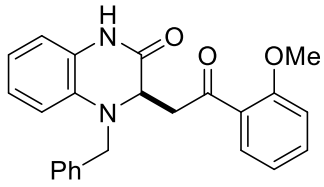
Using 4-benzyl-3,4-dihydroquinoxalin-2-one (**4.1a**, 23.8 mg, 0.1 mmol, 1 equiv.) and cyclopropylacetylene (**4.2g**, 42 μL, 0.5 mmol, 5 equiv.), according to GP-2, compound **4.3ag** (9.4 mg, 0.031 mmol, 31% yield, colorless oil) was obtained and purified by column chromatography using hexane:DCM mixtures (from 5:5 to 2:8). **IR (neat)**: 1690, 1504, 744, 701 cm^{1}; **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 8.58 (bs, 1H), 7.41 – 7.28 (m, 5H), 7.01 (ddd, *J* = 7.9, 6.8, 2.2 Hz, 1H), 6.92 – 6.77 (m, 3H), 4.63 (d, *J* = 13.8 Hz, 1H), 4.41 (d, *J* = 1.8 Hz, 1H), 4.09 (d, *J* = 13.8 Hz, 1H), 1.19 – 1.07 (m, 1H), 0.74 – 0.64 (m, 2H), 0.60 – 0.51 (m, 2H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 164.6 (C), 135.9 (C), 134.3 (C), 128.8 (CH), 128.5 (CH), 127.8 (CH), 126.5 (C), 124.1 (CH), 120.2 (CH), 115.6 (CH), 114.0 (CH), 90.8 (C), 66.9 (C), 53.0 (CH), 51.7 (CH_2), 8.5 (CH_2), -0.6 (CH); **HRMS (ESI/Q-TOF)** *m/z* [M + H]$^+$ calcd for $C_{20}H_{19}N_2O^+$ 303.1497, found 303.1499.

4-benzyl-3-((2-methoxyphenyl)ethynyl)-3,4-dihydroquinoxalin-2(1*H*)-one (4.3ah)



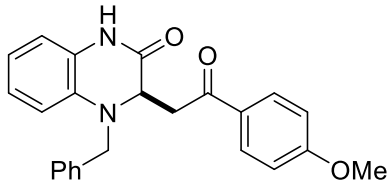
Using 4-benzyl-3,4-dihydroquinoxalin-2-one (**4.1a**, 23.8 mg, 0.1 mmol, 1 equiv.) and 2-ethynylanisole (**4.2h**, 65 μL, 0.5 mmol, 5 equiv.), according to GP-1 but using dry MeCN, compound **4.3ah** (16.2 mg, 0.044 mmol, 44% yield, brown oil) was obtained and purified by column chromatography using hexane:DCM mixtures (from 5:5 to 2:8). **IR (neat)**: 1685, 1493, 1259, 1026, 728, 700 cm^{1}; **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 8.72 (bs, 1H), 7.46 (dd, *J* = 7.9, 1.5 Hz, 2H), 7.40 – 7.30 (m, 3H), 7.25 – 7.18 (m, 2H), 7.08 – 6.97 (m, 1H), 6.94 – 6.76 (m, 5H), 4.71 (d, *J* = 14.0 Hz, 1H), 4.69 (s, 1H), 4.23 (d, *J* = 13.5 Hz, 1H), 3.75 (s, 3H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 164.4 (C), 160.5 (C), 135.8 (C), 134.5 (C), 133.6 (CH), 130.0 (CH), 128.8 (CH), 128.8 (CH), 127.9 (CH), 126.7 (C), 124.1 (CH), 120.3 (CH), 120.2 (CH), 115.7 (CH), 114.2 (CH), 111.4 (C), 110.8 (CH), 85.1 (C), 83.2 (C), 55.7 (CH_3), 53.4 (CH), 51.7 (CH_2); **HRMS (ESI/Q-TOF)** *m/z* [M + H]$^+$ calcd for $C_{24}H_{20}N_2O_2^+$ 368.1525, found 368.1529.

4-Benzyl-3-(2-(4-methoxyphenyl)-2-oxoethyl)-3,4-dihydroquinoxalin-2(1*H*)-one (4.4ah)



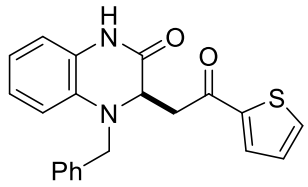
Using 4-benzyl-3,4-dihydroquinoxalin-2-one (**4.1a**, 23.8 mg, 0.1 mmol, 1 equiv.) and 4-ethynylanisole (**4.2h**, 70 μL, 0.5 mmol, 5 equiv.), according to GP-1, compound **4.4ah** (12.8 mg, 0.033 mmol, 33% yield, yellow oil) was obtained and purified by column chromatography using hexane:DCM mixtures (from 5:5 to 2:8). Following GP-2, compound **4.4ah** (21.6 mg, 0.056 mmol, 56% yield, yellow oil) was also obtained. **IR (neat)**: 1683, 1593, 1506, 740, 695 cm^{1}; **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 9.12 (bs, 1H), 7.80 (d, J = 9.0 Hz, 2H), 7.28 – 7.21 (m, 5H), 6.86 (d, J = 8.9 Hz, 1H), 6.80 – 6.75 (m, 2H), 6.64 (d, J = 7.9 Hz, 2H), 4.69 (dd, J = 7.5, 4.4 Hz, 1H), 4.55 (d, J = 15.6 Hz, 1H), 4.42 (d, J = 15.6 Hz, 1H), 3.82 (s, 3H), 3.28 (dd, J = 15.7, 7.5 Hz, 1H), 3.11 (dd, J = 15.7, 4.4 Hz, 1H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 195.5 (C), 168.2 (C), 163.7 (C), 137.1 (C), 133.1 (C), 130.6 (CH), 129.6 (C), 128.6 (CH), 127.3 (CH), 127.3 (CH), 126.2 (C), 124.2 (CH), 119.4 (CH), 115.6 (CH), 114.6 (CH), 113.8 (CH), 59.3 (CH), 55.4 (CH_3), 53.6 (CH_2), 38.6 (CH_2); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{24}H_{23}N_2O_3^+$ 387.1703, found 387.1697.

4-Benzyl-3-(2-(2-methoxyphenyl)-2-oxoethyl)-3,4-dihydroquinoxalin-2(1*H*)-one (4.4ahi)



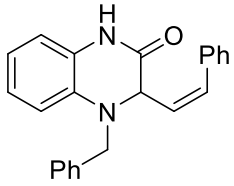
Using 4-benzyl-3,4-dihydroquinoxalin-2-one (**4.1a**, 23.8 mg, 0.1 mmol, 1 equiv.) and 2-ethynylanisole (**4.2i**, 65 μL, 0.5 mmol, 5 equiv.), according to GP-1, compound **4.4ai** (25.1 mg, 0.065 mmol, 65% yield, yellow oil) was obtained and purified by column chromatography using hexane:DCM mixtures (from 5:5 to 2:8). **IR (neat)**: 1679, 1595, 1506, 1290, 1245, 746 cm^{1}; **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 8.50 (bs, 1H), 7.65 (dd, J = 7.7, 1.8 Hz, 1H), 7.43 (ddd, J = 8.4, 7.3, 1.9 Hz, 1H), 7.29 – 7.16 (m, 5H), 7.00 – 6.94 (m, 1H), 6.92 – 6.83 (m, 2H), 6.76 (dd, J = 5.0, 0.9 Hz, 2H), 6.62 (d, J = 7.8 Hz, 1H), 4.70 (dd, J = 7.8, 4.3 Hz, 1H), 4.56 (d, J = 15.8 Hz, 1H), 4.41 (d, J = 15.8 Hz, 1H), 3.73 (s, 3H), 3.41 (dd, J = 15.9, 7.9 Hz, 1H), 3.20 (dd, J = 15.9, 4.4 Hz, 1H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 198.9 (C), 168.0 (C), 158.6 (C), 137.4 (C), 133.9 (CH), 133.4 (C), 130.7 (CH), 128.6 (CH), 127.5 (C), 127.2 (CH), 127.2 (CH), 126.3 (C), 124.1 (CH), 120.7 (CH), 119.1 (CH), 115.3 (CH), 114.6 (CH), 111.5 (CH), 59.4 (CH), 55.3 (CH_3), 53.6 (CH_2), 43.7 (CH_2); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{24}H_{23}N_2O_3^+$ 387.1703, found 387.1708.

4-Benzyl-3-(2-oxo-2-(thiophen-2-yl)ethyl)-3,4-dihydroquinoxalin-2(1*H*)-one (4.4aj)



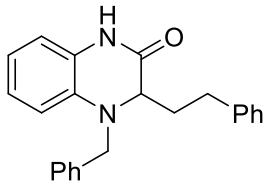
Using 4-benzyl-3,4-dihydroquinoxalin-2-one (**4.1a**, 23.8 mg, 0.1 mmol, 1 equiv.) and 2-ethynylthiophene (**4.2j**, 54 μL, 0.5 mmol, 5 equiv.), according to GP-1, compound **4.4aj** (19.2 mg, 0.053 mmol, 53% yield, yellow solid) was obtained and purified by column chromatography using hexane:DCM mixtures (from 5:5 to 2:8). Following GP-2, compound **4.4ai** (14.9 mg, 0.041 mmol, 41% yield, yellow solid) was also obtained. **Mp** = 202-208 °C; **IR (neat)**: 1681, 1599, 1234, 1305, 623 cm^{1}; **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 8.36 (bs, 1H), 7.88 (dd, *J* = 2.9, 1.3 Hz, 1H), 7.45 (dd, *J* = 5.1, 1.3 Hz, 1H), 7.28 (d, *J* = 2.9 Hz, 1H), 7.26 – 7.18 (m, 5H), 6.92 (ddd, *J* = 8.0, 6.7, 2.3 Hz, 1H), 6.88 – 6.73 (m, 2H), 6.66 (d, *J* = 7.9 Hz, 1H), 4.65 (dd, *J* = 7.5, 4.3 Hz, 1H), 4.55 (d, *J* = 15.6 Hz, 1H), 4.41 (d, *J* = 15.6 Hz, 1H), 3.22 (dd, *J* = 15.5, 7.6 Hz, 1H), 3.07 (dd, *J* = 15.5, 4.3 Hz, 1H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 191.2 (C), 167.6 (C), 141.7 (C), 137.0 (C), 133.1 (C), 132.7 (CH), 128.7 (CH), 127.4 (CH), 127.4 (CH), 126.9 (CH), 126.6 (CH), 126.1 (C), 124.3 (CH), 119.5 (CH), 115.4 (CH), 114.7 (CH), 59.1 (CH), 53.6 (CH_2), 40.3 (CH_2); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{21}H_{17}N_2OS^+$ 345.1062, found 345.1068.

(*Z*)-4-Benzyl-3-styryl-3,4-dihydroquinoxalin-2(1*H*)-one (4.5)



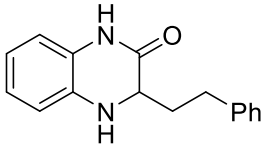
In a 25 mL round bottomed flask was added compound **4.3aa** (20.6 mg, 0.061 mmol) and it was dissolved in benzene (1 mL). Then, Lindlar catalyst (4 mg, 5 wt. % over $CaCO_3$, poisoned with lead) was added and the resulting mixture was stirred at rt for 24 hours in the presence of an hydrogen-filled balloon. When the starting material disappeared (as showed by TLC) the reaction mixture was filtered through a pad of silica to afford compound **4.5** (20.5 mg, 0.060 mmol, 99% yield, yellow oil). **IR (neat)**: 1677, 1504, 1375, 740, 697 cm^{1}; **^{1}H-NMR (400 MHz, $CDCl_3$)** δ 8.98 (bs, 1H), 7.61 – 7.53 (m, 2H), 7.41 – 7.28 (m, 4H), 7.13 – 6.92 (m, 5H), 6.89 – 6.76 (m, 3H), 6.73 (d, *J* = 8.0 Hz, 1H), 5.57 (dd, *J* = 11.4, 10.4 Hz, 1H), 4.83 (d, *J* = 10.5 Hz, 1H), 4.48 (d, *J* = 14.3 Hz, 1H), 3.80 (d, *J* = 14.3 Hz, 1H); **^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$)** δ 167.7 (C), 136.0 (C), 135.6 (CH), 134.0 (C), 128.9 (CH), 128.3 (CH), 127.9 (CH), 127.8 (CH), 127.2 (CH), 126.1 (C), 124.2 (CH), 122.6 (CH), 119.3 (CH), 115.5 (CH), 113.3 (CH), 58.2 (CH), 51.3 (CH_2); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{23}H_{21}N_2O^+$ 341.1648, found 341.1647.

4-Benzyl-3-phenethyl-3,4-dihydroquinoxalin-2(1*H*)-one (4.6)



In a 25 mL round bottomed flask was added compound **4.3aa** (19.4 mg, 0.057 mmol) and it was dissolved in EtOH (5 mL). Then, Pd 5% over $CaCO_3$ (7.4 mg, 0.003 mmol) was added and the resulting mixture was stirred at rt for 5 hours in the presence of an hydrogen-filled balloon. When the starting material disappeared (as showed by TLC) the reaction mixture was filtered through a pad of silica to afford compound **4.6** (19.4 mg, 0.057 mmol, 99% yield, yellow oil). **IR (neat)**: 1672, 1495, 742, 697 cm^{-1}; **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 8.64 (bs, 1H), 7.35 – 7.20 (m, 7H), 7.20 – 7.08 (m, 3H), 6.98 – 6.88 (m, 1H), 6.81 – 6.76 (m, 2H), 6.72 (d, J = 7.9 Hz, 1H), 4.63 (d, J = 15.0 Hz, 1H), 4.21 (d, J = 15.0 Hz, 1H), 3.97 – 3.84 (m, 1H), 2.78 – 2.56 (m, 2H), 2.02 – 1.81 (m, 2H). **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 168.2 (C), 141.0 (C), 136.7 (C), 134.1 (C), 128.7 (CH), 128.4 (CH), 128.3 (CH), 127.7 (CH), 127.6 (CH), 126.3 (C), 126.0 (CH), 124.2 (CH), 119.3 (CH), 115.3 (CH), 114.0 (CH), 61.3 (CH), 53.1 (CH_2), 31.7 (CH_2), 30.7 (CH_2); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{23}H_{23}N_2O^+$ 343.1805, found 343.1804.

3-Phenethyl-3,4-dihydroquinoxalin-2(1*H*)-one (4.7)



In a 25 mL round bottomed flask was added compound **4.3aa** (22.4 mg, 0.066 mmol) and it was dissolved in EtOH (5 mL). Then, Pd 10% over C (8.6 mg, 0.008 mmol) was added and the resulting mixture was stirred at rt for 2.5 hours in the presence of an hydrogen-filled balloon. When the starting material disappeared (as showed by TLC) the reaction mixture was filtered through a pad of silica to afford compound **4.7** (15.8 mg, 0.063 mmol, 95% yield, brown solid). **Mp** = 195-200 °C; **IR (neat)**: 3058, 3027, 1664, 1603, 1504, 1370, 1303, 740, 695 cm^{-1}. **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 8.65 (bs, 1H), 7.34 – 7.27 (m, 2H), 7.25 – 7.17 (m, 3H), 6.88 (ddd, J = 7.8, 6.2, 2.7 Hz, 1H), 6.82 – 6.67 (m, 2H), 6.56 (d, J = 7.6 Hz, 1H), 3.96 (ddd, J = 7.6, 4.6, 2.1 Hz, 1H), 3.80 (bs, 1H), 2.81 (td, J = 9.2, 4.6 Hz, 2H), 2.32 – 2.14 (m, 1H), 2.05 (ddd, J = 15.9, 14.4, 7.4 Hz, 1H). **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 168.7 (C), 140.9 (C), 132.8 (C), 128.6 (CH), 128.4 (CH), 126.2 (CH), 125.2 (C), 123.9 (CH), 119.4 (CH), 115.3 (CH), 114.2 (CH), 56.1 (CH), 33.3 (CH_2), 31.9 (CH_2); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{16}H_{17}N_2O^+$ 253.1335, found 253.1334.

Part III

Electrophilic Functionalization of 3,4-dihydro-1,4-benzoxazin-2-ones and 3,4-dihydroquinoxalin-2-ones

Chapter 5

Photocatalytic Giese Addition of 3,4-Dihydroquinoxalin-2-ones to Electron-Poor Alkenes

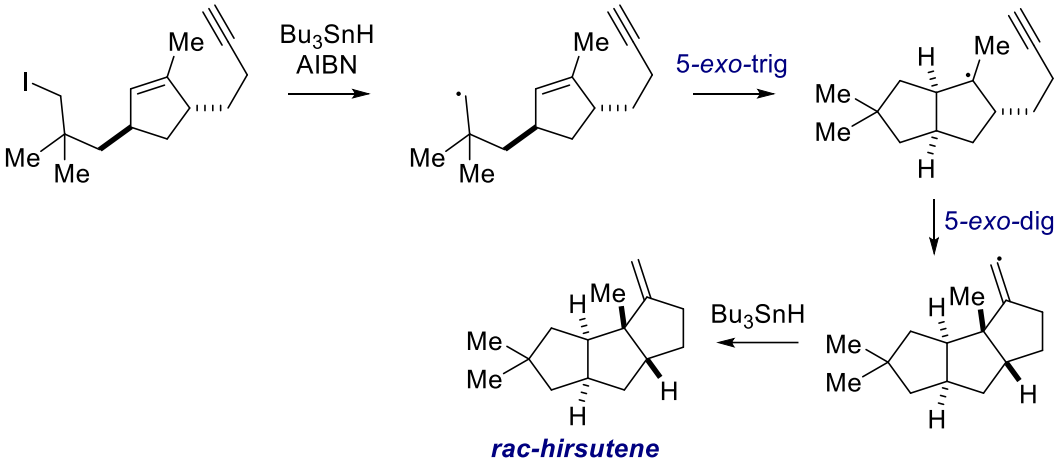
5.1 Introduction and state of the art

5.1.1 The Chemistry of Radicals in Organic Synthesis

Since the isolation and identification of triphenylmethyl radical by Moses Gomberg in 1900, the field of radical chemistry has rapidly evolved to the present day.[182] Radicals are open-shell species with unpaired electrons, which lends them a high reactivity and a general short life. Due to this high reactivity, traditionally it was thought that radical reactions were not suitable for controlled organic synthesis, as they proceed with scarce selectivity. But after years of extensive research, this statement has been found to be untrue.[41,183]

However, radicals have found a fair number of applications in modern synthesis of complex molecular scaffolds, especially due to their ability to undergo cascade processes.[184] One of the most representative examples is the diastereoselective synthesis of hirsutene accomplished by Curran in 1985. In that work, the key intermediate with a primary alkyl iodide is treated with tributyltin hydride and with a substoichiometric amount of AIBN as radical initiator (Scheme 5.1).[185] After the initiation step, $Bu_3Sn\cdot$ can easily abstract the iodine atom, generating the primary alkyl radical. This radical triggers a 5-*exo*-trig cyclization to generate the *cis*-fused bicyclic system, which bears a tertiary carbon-centered radical. This tertiary radical can also participate in another cyclization process through a 5-*exo*-dig to finally yield the tricyclic scaffold. A hydrogen atom abstraction from Bu_3SnH generates the desired *rac*-hirsutene. This process where each reaction occurs

only in virtue of the chemical functionality formed in the previous step is known as cascade reaction, an it is a powerful strategy implemented with radicals to build complex molecular architectures.



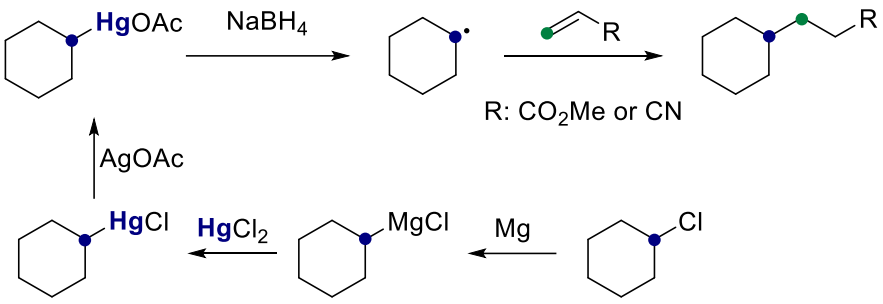
Scheme 5.1: Diastereoselective synthesis of hirsutene based on a radical cascade process (Curran).

5.1.2 The Giese Reaction and Photocatalysis in Radical Generation

Traditionally, the generation of organic radicals has relied on the use of initiators and stoichiometric amounts of silicon,[186] germanium or tin[187] compounds among many others.[188]

Among all relevant reactions, and for the purposes of this *thesis*, it is important to highlight the addition of carbon-centered radicals to electrophilic double bonds. This transformation was initially reported by Bernd Giese in 1977,[189–192] and therefore it is widely known as **Giese reaction** or **Giese radical addition** (Scheme 5.2). Initially, Giese accessed carbon radicals treating alkylmercuric salts with $NaBH_4$, although shortly after he reached them using Bu_3SnH.[193] In the presence of an electron-poor alkene, the radical reacts with the electrophilic double bond to obtain the 1,4-addition product, or Giese product.

The classical mercury- or tin-mediated Giese reaction has driven meaningful research into the scientific underpinnings of radical-mediated reactions and remain synthetically useful. However, the use of large amounts of tin or other metal hydrides generates large amounts of neurotoxic residues. In fact, for some applications, there are strict rules on the concentration of certain metals, and therefore all these classical approaches remain impractical for industrial-scale synthesis. In this context, visible-light photocatalysis constitutes a powerful and straightforward tool to access radicals employing usually non-toxic catalysts and low-energy visible light.[194,195]



Scheme 5.2: Original work from Giese on the radical addition of carbon radicals to electron-poor alkenes.

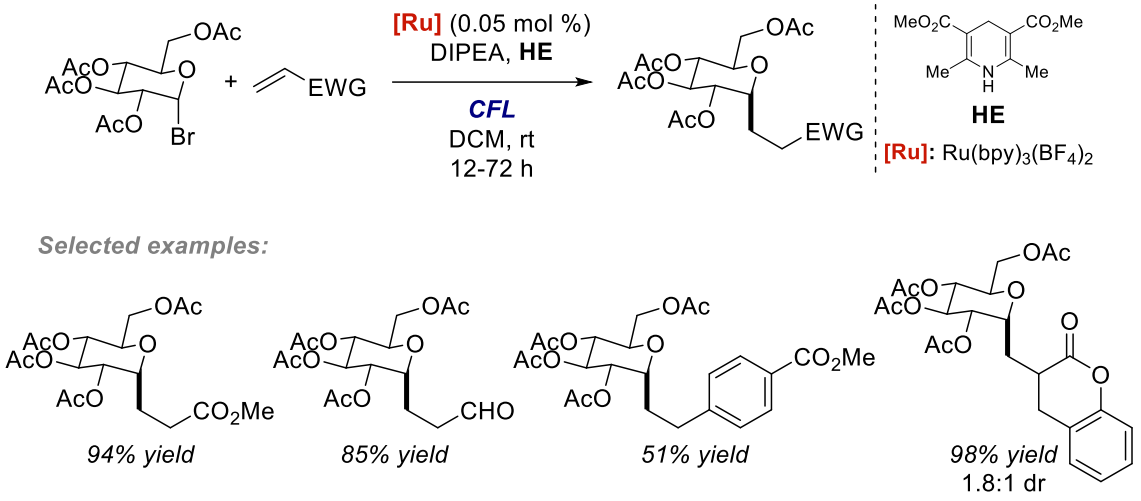
In this sense, several classical radical reactions have recently encountered their equivalents by means of visible-light photocatalysis, such as the Barton or the Hofmann–Löffler –Freytag reaction.[196] In the same vain, Giese reaction is not an exception, and it has been revitalized as a convenient way to forge C−C bonds using visible-light photocatalysis[197,198]

Selected Giese Reactions using Visible-Light Photocatalysis

Actually, the protocol developed by the research group of Knowles in 2016 is a perfect example of merged Hofmann–Löffler–Freytag reaction and Giese addition by means of visible-light photocatalysis.[38] It can be found in Figure 17 in the *Introduction* (page 22). Additionally, the work of Reiser and collaborators that is depicted in Figure 24 (page 27) is one of the pioneering reports on the visible-light-mediated Giese reaction.[49]

One interesting example of visible-light-mediated Giese reaction comes from the laboratory of Gagné in 2010 (Scheme 5.3).[199] In that work, the authors employed glycosyl bromides as carbon radical precursors. Specifically, these alkyl bromides suffer a single electron reduction by the action of the reduced form of $Ru(bpy)_3(BF_4)_2$, which was accessed via a SET with DIPEA. The newly formed carbon-centered radical reacts with several electrophilic alkenes to yield the corresponding C-glycosides, which are particular interesting compounds in drug discovery.[200,201]

The next example constitutes a tangible evidence of the benefits of visible-light photocatalysis compared to traditional methods in radical generation. In this report, Li and collaborators pursued the total synthesis of four alkaloids: *Indotertine A* and *Drimentines A*, *F* and *G*. In their efforts, they identified a key step for the synthesis of Drimentine A, which consists in the generation of a carbon-centered radical from a complex tertiary alkyl bromide and its subsequent Giese reaction with an α,β-unsaturated ketone derived from (+)-*sclareolide*. Following a classical approach, they initially attempted the reaction using AIBN as radical initiator and Bu_3SnH as hydrogen atom source, but under these

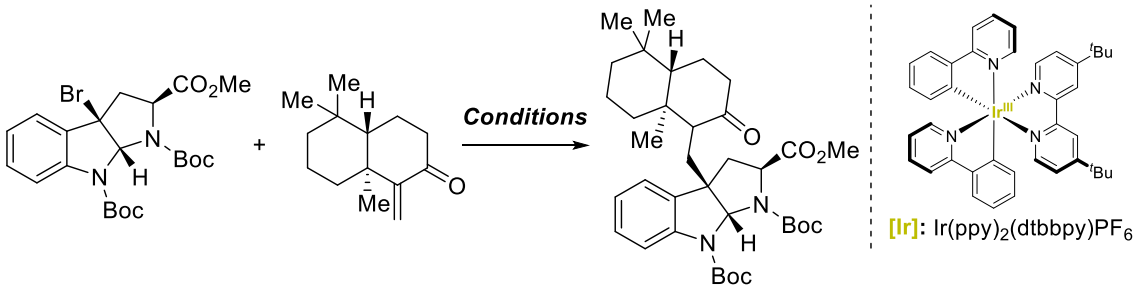


Scheme 5.3: *C*-Glycosylation of glycosyl bromides with electron-poor alkenes using photoredox catalysis (Gagné).

conditions the desired product was not formed (Scheme 5.4, Entry 1). However, the slow addition of Bu_3SnH in benzene at 80 °C did provide the expected product in 58% yield (Scheme 5.4, Entry 2). Finally, they tackled the transformation using visible-light photoredox catalysis. Pleasingly, in the presence of $Ir(ppy)_2(dtbbpy)PF_6$ and Et_3N under the irradiation of blue LEDs they could produce the desired product in 91% while conducting the reaction at room temperature (Scheme 5.4, Entry 3). These results show how important the generation of small amounts of radical is for the successful outcome of several reactions. In this context, photoredox catalysis offers a suitable platform to generate radicals in low concentration.

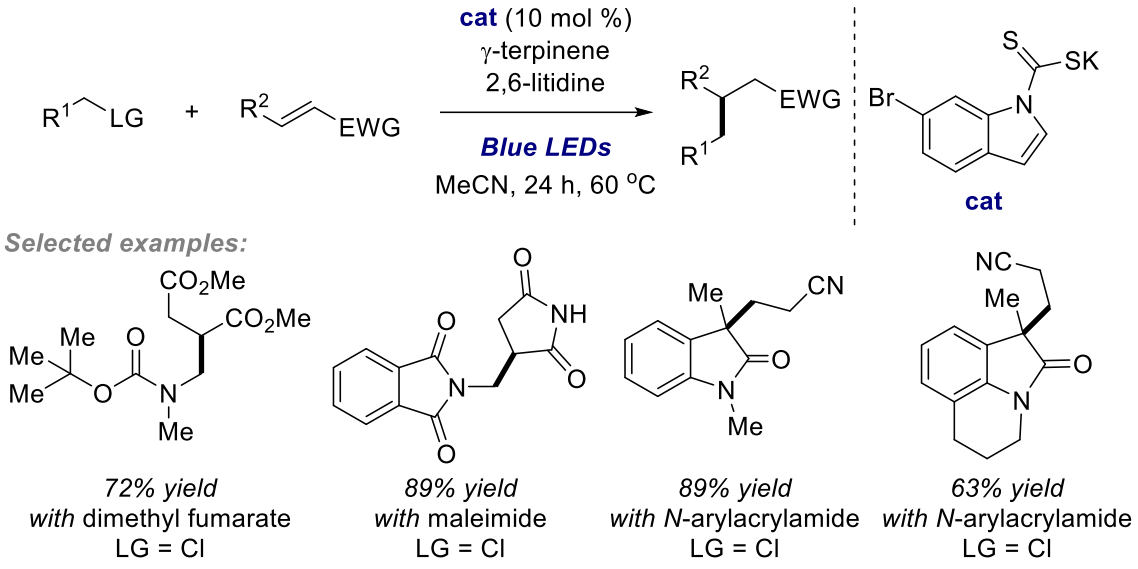
Moreover, it is important to highlight the sophisticated approach towards carbon centered radicals developed by the research group of Melchiorre in 2019 (Scheme 5.5).[202] In this work, the authors envisioned the ability of C−S bonds to suffer an homolytic cleavage upon light irradiation, thus generating the carbon radical. For this purpose they developed an array of dithiocarbonyl salts which could undergo an alkylation reaction with the proper alkyl halide through an S_N2 mechanism. If the dithiocarbonyl salt bears a chromophoric motif such as carbazole or indole, the product of the S_N2 reaction strongly absorbs light in the visible region, thus permitting the C−S homolysis using visible light. After the optimization process, they selected a bromoindole-derived nucleophilic catalyst (**cat** in Scheme 5.5), in combination with 2,6-lutidine as base and γ-terpinene as hydrogen atom source to ensure the turnover of the photocatalyst. The formed carbon-centered radical was engaged in Giese-type reactions with several electron-poor alkenes.

For the purposes of this *thesis*, a special consideration has to be done with alkyl amines as carbon radical precursors. As stated in Figure 20 of the *Introduction* (page 24),



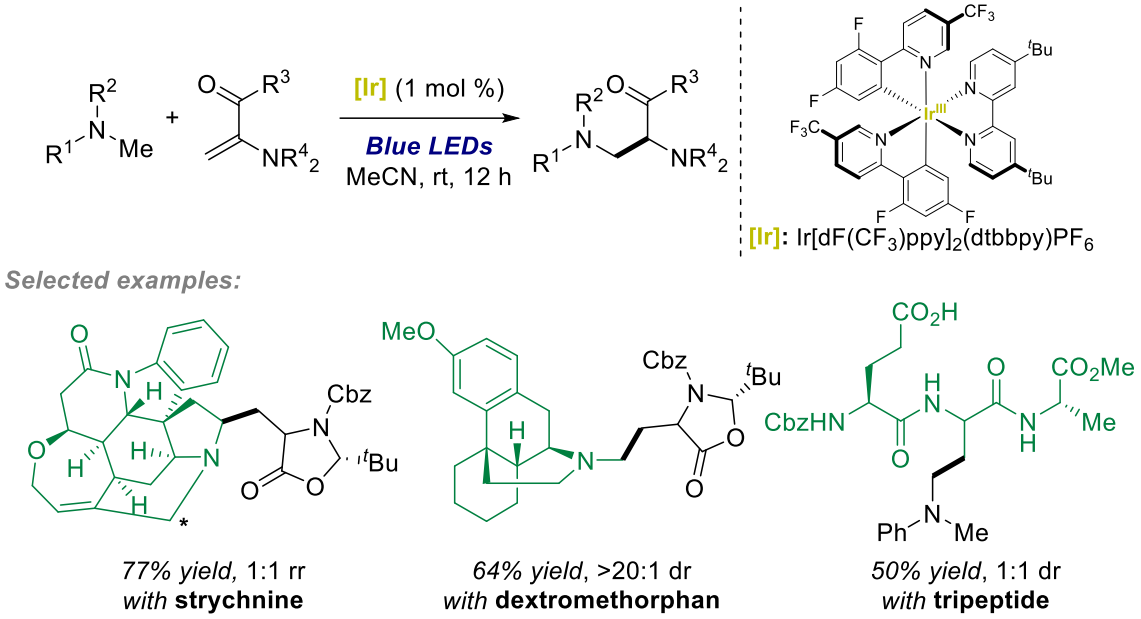
Entry	Conditions	T (°C)	Yield (%)
1	AIBN, Bu_3SnH, toluene	80	0
2	Bu_3SnH (slow addition), benzene	80	58
3	[Ir] (2.5 mol %), ***Blue LEDs***, Et_3N, DMF	rt	91

Scheme 5.4: Comparative reaction conditions in a conjugate radical addition as key step in the total synthesis of *Drimentine G* (Li).



Scheme 5.5: Generation of carbon radicals using a nucleophilic photocatalyst under visible light (Melchiorre).

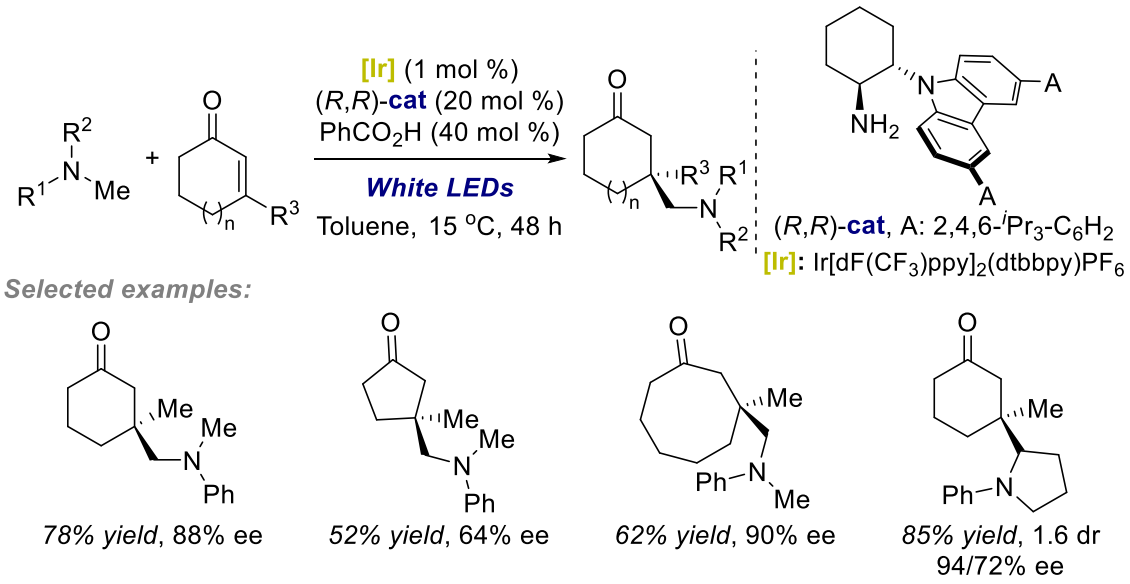
α-amino radicals are formed as intermediates in the photoredox oxidation of amines to iminium ions. In fact, by simply adjusting the reaction conditions, these α-amino radicals can be used as nucleophiles in Giese-type reactions. Indeed, in 2018, the research group of Jui took advantage of several tertiary amines to generate α-amino radicals under visible-light photoredox catalysis (Scheme 5.6).[203] Interestingly, their methodology could accommodate very challenging substrates, such as natural occurring tertiary amines like strychnine or dextromethorphan, and several polipeptides bearing a dehydroalanine unit as radical acceptor.



Scheme 5.6: Generation of α-carbon radicals from tertiary amines (Jui).

The last example to give prominence is the asymmetric addition of α-amino radicals derived from *N*,*N*-dialkylanilines to cyclic enones, which was developed by Melchiorre and collaborators in 2016 (Scheme 5.7).[204] To this end, they employed a dual catalytic system, comprising a chiral primary amine derived from 1,2-diaminocyclohexane as organocatalyst and Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)PF$_6$ as photoredox catalyst. A first SET between the photocatalyst and the *N*,*N*-dialkylaniline delivers the corresponding α-amino radical, which experiments a Giese-type reaction to the chiral iminium cation that is formed through a condensation between the organocatalyst and the enone.

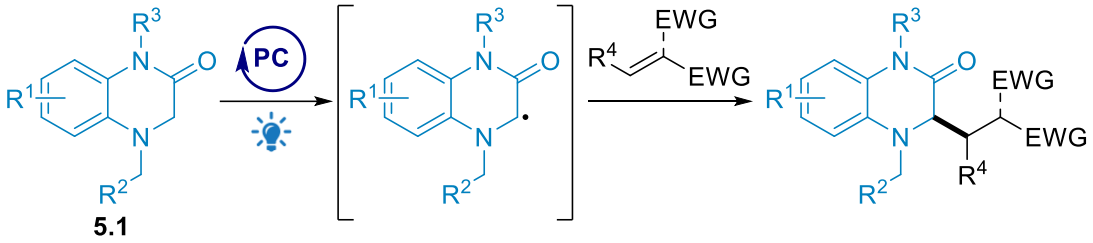
According to all these antecedents, we thought that it would be of interest the development of a methodology to generate the α-amino radical in the endocyclic methylene group of 3,4-dihydroquinoxalin-2-ones **5.1** using photoredox catalysis, and thereafter engaging them in Giese-type processes.



Scheme 5.7: Enantioselective addition of α-amino radicals to enones (Melchiorre).

5.2 Objectives

The main objective for this *Chapter* is to develop a methodology to functionalize 3,4-dihydroquinoxalin-2-ones (**5.1**) with electron-poor alkenes employing visible-light photoredox catalysis to generate the α-amino radical of **5.1**. To achieve this objective, several partial objectives are postulated:



1. Optimization of the reaction conditions between 4-benzyl-3,4-dihydroquinoxalin-2-one (**5.1a**) and dimethyl 2-benzylidenemalonate (**5.2a**) to obtain the corresponding Giese product **5.3aa** with the highest yield.

2. Study of the scope of the reaction between different 3,4-dihydroquinoxalin-2-ones (**5.1**) and different electron-poor alkenes.

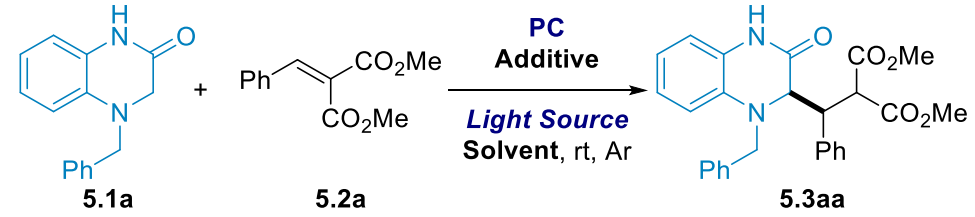
3. Synthetic transformations of the Giese products.

4. Mechanistic investigations to unveil the reaction mechanism.

5.3 Results and Discussion

5.3.1 Optimization of the Reaction Conditions

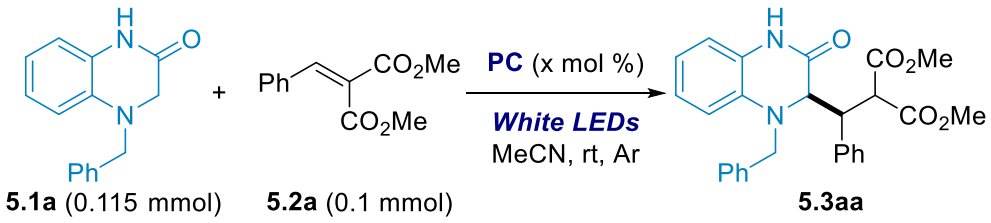
To start the optimization process we selected 4-benzyl-3,4-dihydroquinoxalin-2-one (**5.1a**) as α-amino radical precursor, and dimethyl 2-benzylidenemalonate (**5.2a**) as electrophilic alkene to trigger the Giese reaction that yields product **5.3aa**. Among all the parameters that will be enhanced to ensure a high yield of product **5.3aa**, it will be of special consideration the photoredox catalyst and the necessity of an acid additive to promote the reaction (Scheme 5.8).



Scheme 5.8: Overview of the model reaction to carry out the optimization of the reaction conditions.

Evaluation of the Photoredox Catalyst

We started the optimization of the Giese reaction by screening different photocatalysts (Scheme 5.9). As has been discussed in other Chapters, the photoredox catalyst is the responsible of oxidizing the tertiary amine moiety in **5.1a** and therefore promoting the formation of reactive species, namely the α-amino radical in this precise case.



Scheme 5.9: Evaluation of the photoredox catalyst in the reaction between **5.1a** and **5.2a** using MeCN as solvent.

We started the photoredox catalyst evaluation using 0.115 mmol of **5.1a** and 0.1 mmol of **5.2a**. According to previous experiences, it is convenient to use at least a slight excess of amine **5.1a** to supress the influence of potential decomposition pathways in the yield of the desired product **5.3aa**. Besides, we selected MeCN as the starting point solvent.

Our designed plan of this transformation requires the formation of the α-amino radical of **5.1a** to act as a nucleophile. According to general mechanisms and to our experience in nucleophilic functionalizations (Part II), the tertiary amine suffers two single-electron oxidations: one from the excited state of the photocatalyst and the second one from a O_2-derived reactive specie. Hence, if it is desired to stop the oxidation process in the stage where the α-amino radical is formed, strict conditions to avoid the presence of molecular oxygen in the reaction medium must be taken. Consequently, these photochemical reactions must be conducted in an inert atmosphere, argon in our case, and the solvents employed must be properly dried and degassed.

Table 5.1: Evaluation of the photoredox catalyst in the reaction between **5.1a** and **5.2a** using MeCN. Yield of **5.3aa**.

Entry[a]	**PC (x mol %)**	**Yield 5.3aa (%)**[b]
1	$Ru(bpy)_3Cl_2$ (**A**) (1)	–
2[c]	$Ru(bpy)_3Cl_2$ (**A**) (1)	78
3[c]	*fac*-$Ir(ppy)_3$ (**K**) (1)	26
4[c]	Rose Bengal (**D**) (5)	–
5[c]	Eosin-Y-Na_2 (**E**) (5)	–
6[c]	9,10-Phenanthrenequinone (**J**) (5)	–
7[c]	[Mes-Acr-Me][BF_4] (**H**) (5)	–

[a]Reaction conditions: **5.1a** (0.115 mmol), **5.2a** (0.1 mmol), **PC** (x mol %), MeCN (1 mL), under argon atmosphere and under white LEDs irradiation. Reaction time: 48 hours. In all cases a 1:1 dr was observed by ^{1}H-NMR.

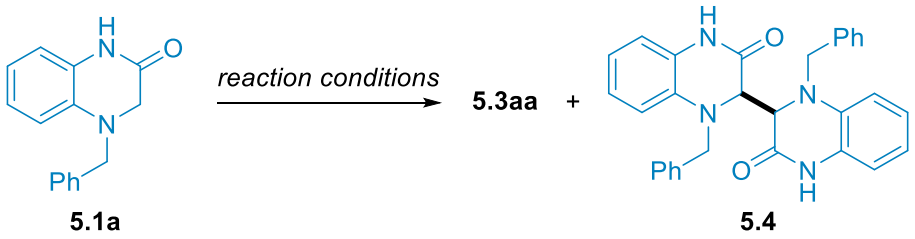
[b]Yield determined after purification by column chromatography.

[c]$(PhO)_2PO_2H$ (10 mol %) was also added.

Our first attempt was to try the reaction using $Ru(bpy)_3Cl_2$ (**A**) as photoredox catalyst. However, after 48 hours of light irradiation we could not even detect the expected product **5.3aa** (Table 5.1, Entry 2). Indeed, the amine **5.1a** remained without noticeable decomposition. At this point we thought of adding a Brønsted acid cocatalyst with the aim of 1) increasing the electrophilicity of the alkene **5.2a** by coordination and 2) to mediate in the acid-base processes in the generation of the α-amino radical of **5.1a**. However, we were aware that an acid cocatalyst may establish an acid-base equilibrium where tertiary amine gets partially protonated, thus avoiding it to participate in photoredox-enabled redox processes. But since this hypothetical protonation would be partial, there will be always neutral amine to suffer oxidation processes.

In this vain, we repeated the reaction but also adding a 10 mol % of $(PhO)_2PO_2H$.

To our delight, we isolated the expected product **5.3aa** in a promising 78% yield with 1:1 dr (Table 5.1, Entry 2)[†]. Moving to other photocatalysts, the use of *fac*-Ir(ppy)$_3$ (**K**) delivered product **5.3aa** with lower yield (26%) (Table 5.1, Entry 3). However, unfortunately, any of the organophotoredox catalysts that were available in our laboratory were capable of generating the desired product **5.3aa**. Instead, in many cases amine **5.1a** evolved to the formation of its dimer **5.4**, allegedly through a radical-radical homocoupling (Scheme 5.10).

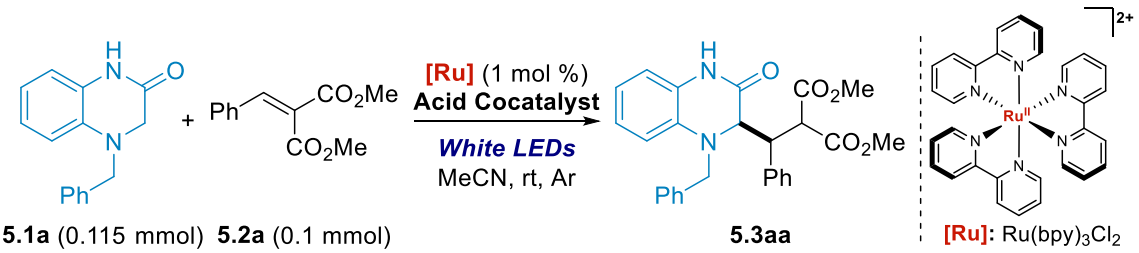


Scheme 5.10: Formation of the dimeric compound **5.4** under photoredox conditions.

In light of these results, we decided to continue the optimization process using Ru(bpy)$_3$Cl$_2$ (**A**) as photoredox catalysis and a 10 mol % of diphenyl phosphoric acid (DPP, (PhO)$_2$PO$_2$H) as Brønsted acid cocatalyst.

Evaluation of the Brønsted Acid Cocatalyst

According to the previous observations in this optimization process, it is of imperious necessity the presence of DPP as cocatalyst to promote the reaction between **5.1a** and **5.2a**. We anticipated the potential role of this catalyst, but we also wanted to test other Brønsted acids with the goal of obtaining **5.3aa** in a better yield (Scheme 5.11).



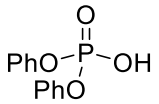
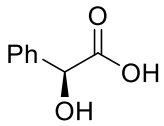
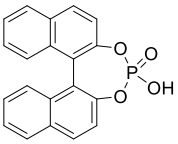
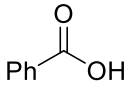
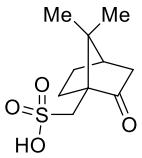
Scheme 5.11: Evaluation of the Brønsted acid cocatalyst in the reaction between **5.1a** and **5.2a** using Ru(bpy)$_3$Cl$_2$ (**A**) and MeCN.

The survey of Brønsted acid catalysts revealed that (*S*)-mandelic acid could also promote the photochemical Giese reaction between **5.1a** and **5.2a**, but in a lower yield of 54%

[†]From this point to the end of the optimization process, Giese product **5.3aa** is always obtained in 1:1 dr and, for clarity, it will be omitted in the following Tables and Schemes.

(Table 5.2, Entry 2). Besides, we thought if this chiral acid could have induced enantioselectivity to the reaction, but wretchedly product **5.3aa** was obtained with 0% ee for both diastereomers. Racemic phosphoric acid derived from BINOL was also tested under our reaction conditions, obtaining a very promising 72% yield of **5.3aa** (Table 5.2, Entry 3). Moreover, simpler benzoic acid almost failed in favouring the reaction, as product **5.3aa** was isolated in only 17% yield (Table 5.2, Entry 4). Finally, (*S*)-camphorsulfonic acid was also able to facilitate the reaction in 62% yield but, again, any chirality was transferred to product **5.3aa** (Table 5.2, Entry 5).

Table 5.2: Evaluation of the Brønsted acid cocatalyst in the reaction between **5.1a** and **5.2a** using $Ru(bpy)_3Cl_2$ (**A**) and MeCN. Yield of **5.3aa**.

Entry[a]	**Acid Cocatalyst**	**Yield 5.3aa (%)**[b]
1		78
2[c]		54
3		72
4		17
5[c]		62

[a]Reaction conditions: **5.1a** (0.115 mmol), **5.2a** (0.1 mmol), $Ru(bpy)_3Cl_2$ (1 mol %), acid cocatalyst (10 mol %), MeCN (1 mL), under argon atmosphere and under white LEDs irradiation. Reaction time: 48 hours. In all cases a 1:1 dr was observed by ^{1}H-NMR.

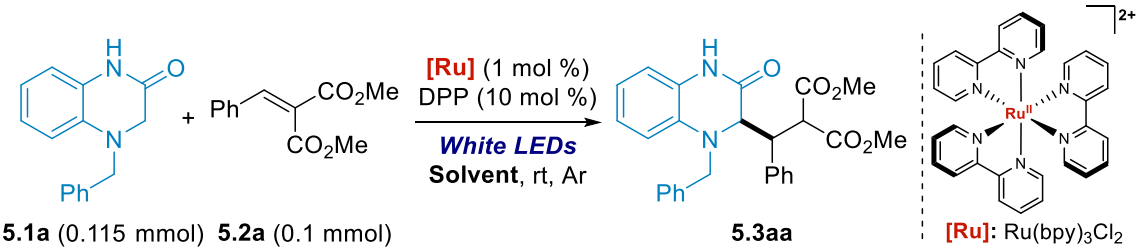
[b]Yield determined after purification by column chromatography.

[c]Both diastereomers of **5.3aa** were isolated as racemic mixtures.

After stating that the presence of a Brønsted acid cocatalyst was mandatory for the profitable outcome of the reaction, we decided to continue the optimization process selecting DPP as the most convenient one (Table 5.2, Entry 1).

Evaluation of the Solvent

Although the yield in which **5.3aa** was obtained was sufficiently high, we decided to explore the effect of some solvents over the reaction performance. Initially, we selected MeCN as the default solvent for reaction optimization based on our own previous experience and because it can be easily dried and degassed. Nonetheless, a selection of different solvents was tested under our potential optimal conditions (Scheme 5.12).



Scheme 5.12: Evaluation of the solvent in the reaction between **5.1a** and **5.2a** using $Ru(bpy)_3Cl_2$ (**A**) and DPP.

With MeCN serving as starting point (Table 5.3, Entry 1), we conducted photochemical Giese reaction between 3,4-dihydroquinoxalin-2-one **5.1a** and electron-poor alkene **5.2a** in other solvents. Initially, we tested toluene as solvent but, unfortunately, product **5.3aa** was not even detected in the reaction mixture after 48 hours (Table 5.3, Entry 2). This result may arise from the low solubility of both $Ru(bpy)_3Cl_2$ (**A**) and DPP in toluene, which is in consistence with previous results. In contrast, when dichloromethane was employed we were able to isolate product **5.3aa**, although in only 26% yield (Table 5.3, Entry 3). Besides, *N*,*N*-dimethylformamide, a solvent which gave us a good performance in *Chapter* 2, was not suitable for this Giese reaction, as product **5.3aa** could only be isolated in 27% yield (Table 5.3, Entry 4). Finally, THF was tested as solvent for the reaction but no product was detected after 48 hours of irradiation (Table 5.3, Entry 5).

Therefore, in light of these results, we decided to select MeCN as the best solvent to perform the photochemical Giese reaction between **5.1a** and **5.2a** (Table 5.3, Entry 1).

Evaluation of the Light Source and Final Adjustments

The last part of the optimization process was to study the different outcome of the reaction with regard to the light source. From the beginning, the photochemical Giese reaction between **5.1a** and **5.2a** has been being irradiated with white LEDs. However, since we have available additional light sources, it is of interest to study the comparative behaviour of all of them over the reaction (Scheme 5.13).

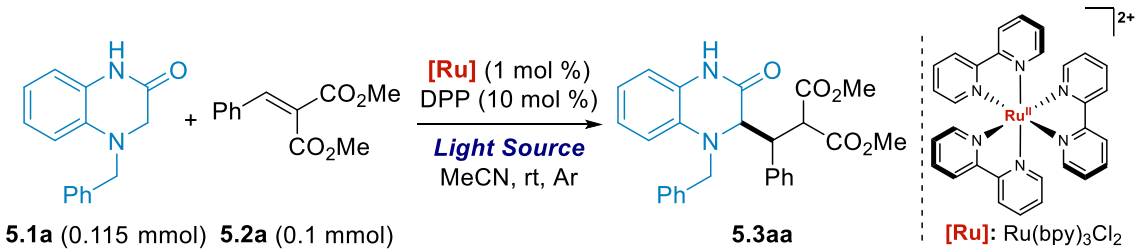
Although the reaction proceeded well using white LEDs as energy source (Table 5.4, Entry 1), the reaction was also conducted using a CFL but, in this case, the yield in

Table 5.3: Evaluation of the solvent in the reaction between **5.1a** and **5.2a** using $Ru(bpy)_3Cl_2$ (**A**) and DPP. Yield of **5.3aa**.

Entry[a]	Solvent	Yield 5.3aa (%)[b]
1	MeCN	78
2	Toluene	–
3	DCM	26
4	DMF	27
5	THF	–

[a]Reaction conditions: **5.1a** (0.115 mmol), **5.2a** (0.1 mmol), $Ru(bpy)_3Cl_2$ (1 mol %), DPP (10 mol %), solvent (1 mL), under argon atmosphere and under white LEDs irradiation. Reaction time: 48 hours. In all cases a 1:1 dr was observed by ^{1}H-NMR.

[b]Yield determined after purification by column chromatography.



Scheme 5.13: Evaluation of the light source in the reaction between **5.1a** and **5.2a** using $Ru(bpy)_3Cl_2$ (**A**), DPP and MeCN.

which product **5.3aa** was obtained significantly diminished to 49% (Table 5.4, Entry 2). Switching to the more powerful blue LEDs, we could note that the yield increased to 82% after only 16 hours of irradiation (Table 5.4, Entry 3).

Finally, to further increase the yield in which **5.3aa** is obtained, we decided to use a largeer excess of **5.1a** over **5.2a**. Specifically, when the reaction was performed using 0.13 mmol of **5.1a** and blue LEDs as energy source, product **5.3aa** was isolated in 92% yield after just 6 hours (Table 5.4, Entry 4). Moreover, as final verification, the reaction was repeated without DPP and, predictably, product **5.3aa** was not generated (Table 5.4, Entry 5).

To conclude the optimization process we decided to perform some control experiments. When the reaction was performed in the dark, no product was observed after 48 hours of stirring (Table 5.4, Entry 6). Besides, the necessity of an inert atmosphere was demonstrated, as product **5.3aa** was not even detected after 48 hours when the reaction was performed under a regular air atmosphere (Table 5.4, Entry 7).

Table 5.4: Evaluation of the light source in the reaction between **5.1a** and **5.2a** using $Ru(bpy)_3Cl_2$ (**A**), DPP and MeCN. Yield of **5.3aa**.

Entry[a]	Light Source	t (h)	Yield 5.3aa (%)[b]
1	White LEDs	48	78
2	CFL	48	49
3	Blue LEDs	16	82
4[c]	Blue LEDs	6	92
5[d]	Blue LEDs	48	–
6[e]	Blue LEDs	48	–
7[f]	Blue LEDs	48	–

[a]Reaction conditions: **5.1a** (0.115 mmol), **5.2a** (0.1 mmol), $Ru(bpy)_3Cl_2$ (1 mol %), DPP (10 mol %), MeCN (1 mL), under argon atmosphere and under light source irradiation for the indicated time. In all cases a 1:1 dr was observed by ^{1}H-NMR.

[b]Yield determined after purification by column chromatography.

[c]The reaction was performed using 0.13 mmol of **5.1a**.

[d]The reaction was performed without DPP.

[e]The reaction was performed in the dark.

[f]The reaction was performed under air atmosphere.

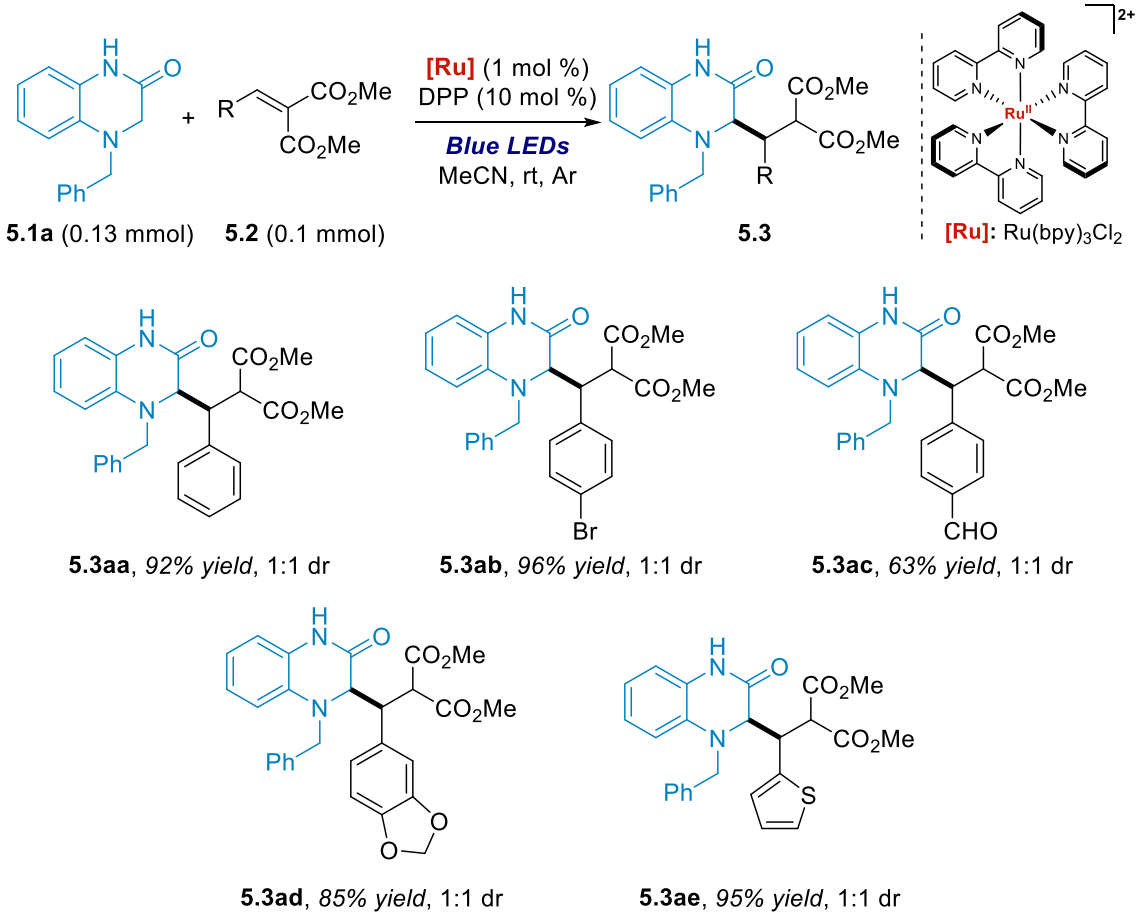
To sum up, we concluded the optimization of the reaction by stating that the best conditions to carry out the Giese reaction between 3,4-dihydroquinoxalin-2-one **5.1a** and 2-benzylidenemalonate (**5.2a**) involves the use of 0.13 mmol of **5.1a**, 0.1 mmol of **5.2a**, 1 mol % of $Ru(bpy)_3Cl_2$ (**A**), 10 mol % of DPP, 1 mL of dry and degassed MeCN, an argon atmosphere and blue LEDs as light source (Table 5.4, Entry 5).

5.3.2 Scope of the Reaction

Once the optimization process was complete and successful, we decided to make efforts in determining the generality of our transformation. To accomplish this objective, a vast array of different electron-poor alkenes will be tested in the Giese-type reaction. Moreover, we will study if differently substituted 3,4-dihydroquinoxalin-2-one can be accommodated to our dual catalytic methodology.

Scope of the Reaction with 2-Arylidenemalonates

We first started the scope of the reaction using differently substituted 2-arylidenemalonates (**5.2**). Pleasingly, a bromine atom can be placed at the *para* position of the aromatic ring, obtaining the corresponding product **5.3ab** in 96%. The electron-withdrawing group



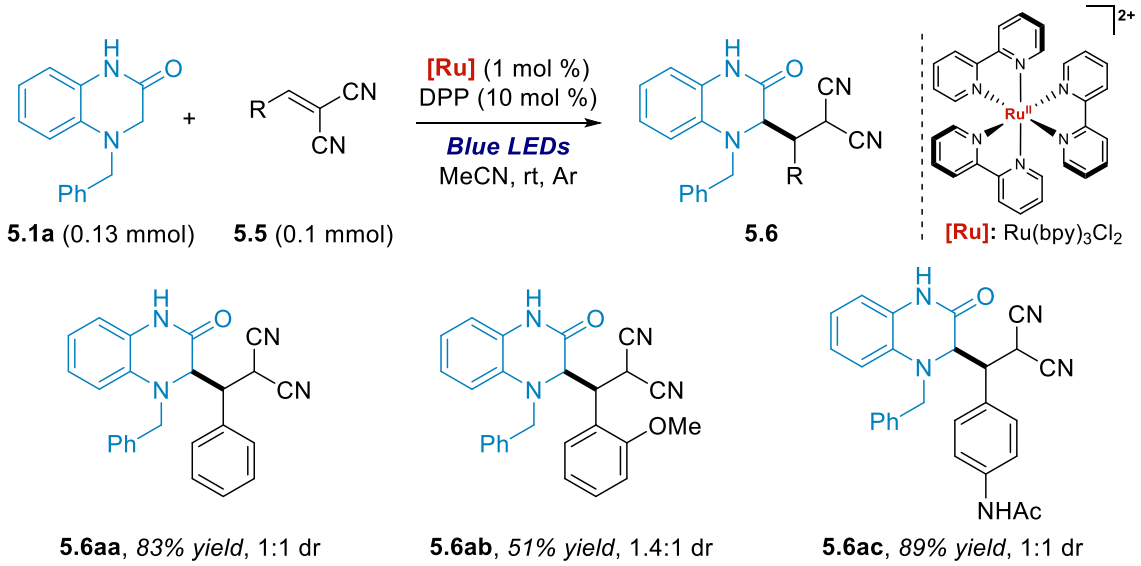
Scheme 5.14: Scope of the reaction using 4-benzyl-3,4-dihydroquinoxalin-2-one (**5.1a**) and different 2-arylidenemalonates (**5.2**).[a]

[a]Reaction conditions: **5.1a** (0.13 mmol), **5.2** (0.1 mmol), $Ru(bpy)_3Cl_2$ (1 mol %), DPP (10 mol %), MeCN (1 mL), under argon atmosphere and under blue LEDs irradiation. Diastereomeric ratio was determined by ^{1}H-NMR of the crude reaction mixture. Yield determined after purification by column chromatography.

but more sensitive aldehyde functional group could also be present in the electron-poor alkene, as the corresponding product **5.3ac** was isolated in 63% yield. A strong electron-donating group, such as the one derived from piperonal, was also well-tolerated, obtaining product **5.3ad** in 85% yield. Finally, we tested if five-member electron-rich aromatic heterocycles can also be proper substituents of electrophilic alkenes. For this purpose, 2-arylidenemalonate derived from 2-thiophene carbaldehyde (**5.2e**) was engaged to the Giese reaction, which delivered the expected product **5.3ae** in 95% yield.

Scope of the Reaction with 2-Arylidenemalononitriles

Having realized that the Giese reaction proceeded well with several 2-arylidenemalonates (**5.2**), we wanted to know if our photocatalytic protocol could be extended to other electron-



Scheme 5.15: Scope of the reaction using 4-benzyl-3,4-dihydroquinoxalin-2-one (**5.1a**) and different 2-arylidenemalononitriles (**5.5**).[a]

[a]Reaction conditions: **5.1a** (0.13 mmol), **5.5** (0.1 mmol), $Ru(bpy)_3Cl_2$ (1 mol %), DPP (10 mol %), MeCN (1 mL), under argon atmosphere and under blue LEDs irradiation. Diastereomeric ratio was determined by ^{1}H-NMR of the crude reaction mixture. Yield determined after purification by column chromatography.

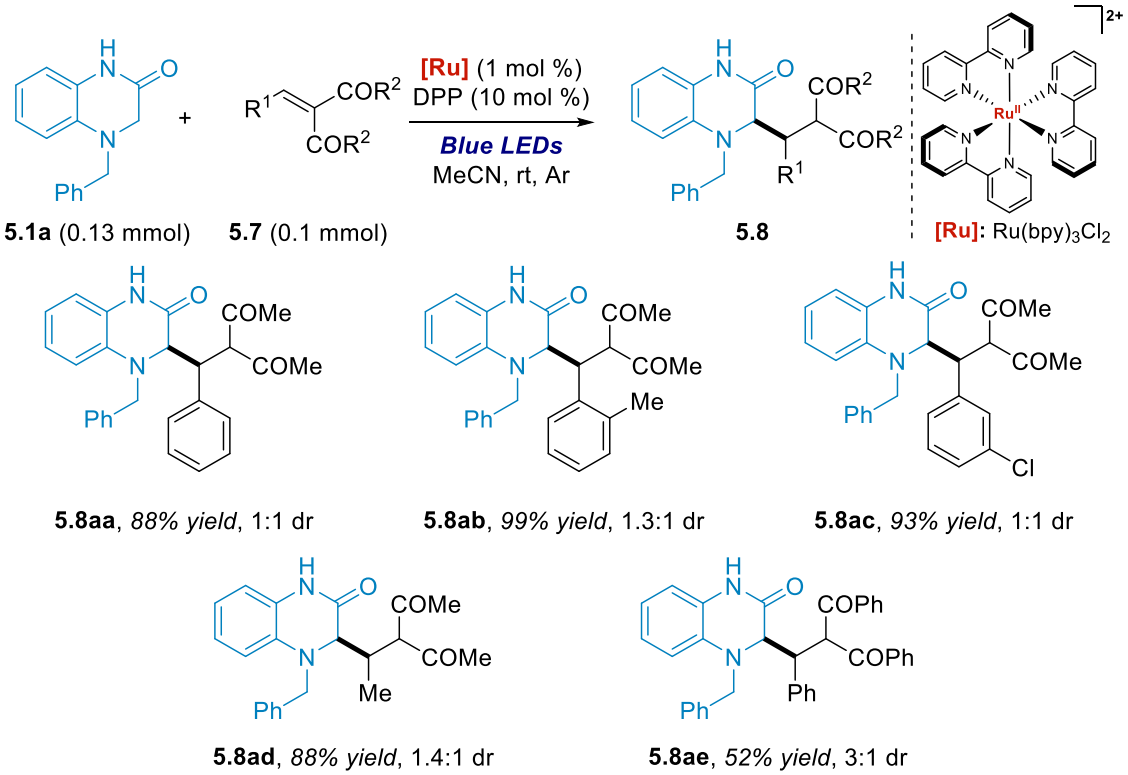
poor alkenes. Given the structural resemblance, we selected 2-arylidenemalononitriles (**5.5**) as potential electrophiles for the Giese reaction (Scheme 5.15).

To our delight, we could obtain product **5.6aa** from 3,4-dihydroquinoxalin-2-one **5.1a** and 2-benzylidenemalononitrile (**5.5a**) in 83% yield. Other 2-arylidenemalononitriles (**5.5**) were able to produce the expected product. Specifically, the *o*-OMe derivative **5.5b** furnished the corresponding product **5.6ab** in 51% yield, whereas 2-benzylidenemalononitrile bearing a −NHAc group at its para position (**5.5c**) was efficiently tolerarted, as the expected product **5.6ac** was generated in 89% yield.

Scope of the Reaction with 2-Arylidene-1,3-diketones

To conclude with the scope using distinct Knoevenagel-derived substrates, we decided to perform the reaction with 2-arylidene-1,3-diketones (**5.7**) as electrophiles (Scheme 5.16). Since the reaction was able to proceed with Knoevenagel adducts **5.2** and **5.5**, the performance towards a nucleophilic attack of 2-arylidene-1,3-diketones (**5.7**) is expected to be also high.

In fact, when substrate **5.7a** bearing a phenyl ring and two methyl ketones was subjected to the Giese reaction, the expected product **5.8aa** was isolated in 88% yield. Interestingly, moving to a more challenging analogue with high steric congestion near the



Scheme 5.16: Scope of the reaction using 4-benzyl-3,4-dihydroquinoxalin-2-one (**5.1a**) and different 2-arylidene-1,3-diketones (**5.7**).[a]

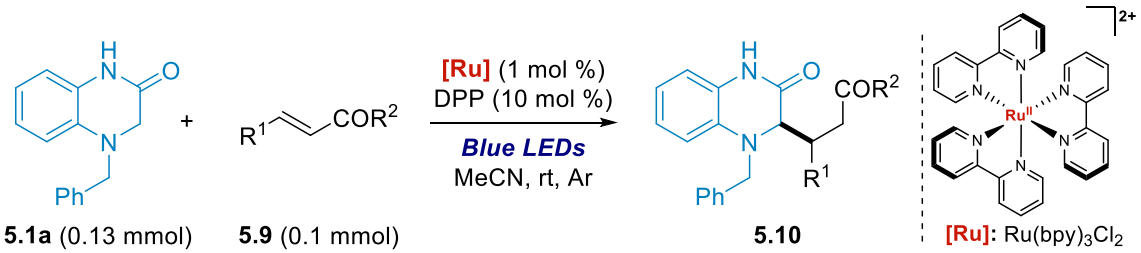
[a]Reaction conditions: **5.1a** (0.13 mmol), **5.7** (0.1 mmol), $Ru(bpy)_3Cl_2$ (1 mol %), DPP (10 mol %), MeCN (1 mL), under argon atmosphere and under blue LEDs irradiation. Diastereomeric ratio was determined by ^{1}H-NMR of the crude reaction mixture. Yield determined after purification by column chromatography.

reactive center with an *o*-Me substituent (**5.7b**) provoked the generation of product **5.8ab** in quantitative yield. In the same vain, a *m*-Cl substituted 2-arylidene-1,3-diketone **5.7c** delivered the expected product **5.8ac** in similarly high yield of 93%.

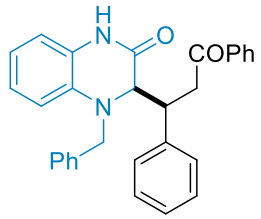
After stating how these kind of electrophiles were well accommodated to our protocol, the reaction was performed using a Knoevenagel adduct derived from 2,4-pentanedione which bears a methyl substituent at its β position (**5.7d**). Pleasingly, the expected product **5.8ad** was efficiently generated in 88% yield. Finally, a full phenyl derivative in all the substitution positions **5.7e** was selected as substrate, affording the expected product **5.8ae** in a lower 52% yield, probably due to the challenging approximation of both substrates given the high steric hindrance.

Scope of the Reaction with α,β-unsaturated Ketones

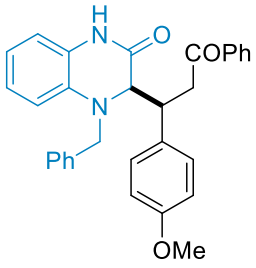
After subjecting strong electrophiles derived from dimethyl malonate (**5.2**), malononitrile (**5.5**) and 1,3-diketones (**5.7**) to our reaction conditions, we decided to explore the



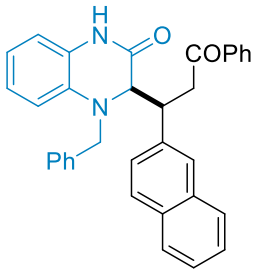
5.1a (0.13 mmol) **5.9** (0.1 mmol) **5.10**



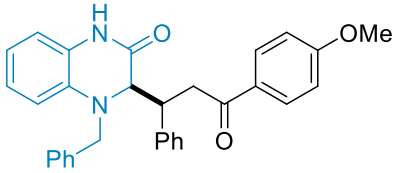
5.10aa, *76% yield*, 1.5:1 dr



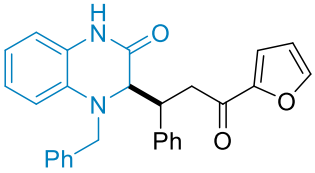
5.10ab, *91% yield*, 1.1:1 dr



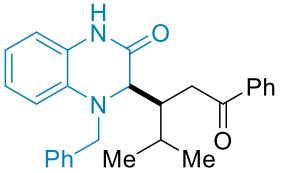
5.10ac, *83% yield*, 1.1:1 dr



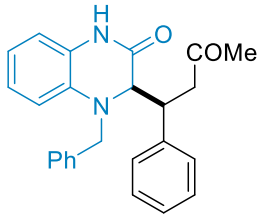
5.10ad, *81% yield*, 1.2:1 dr



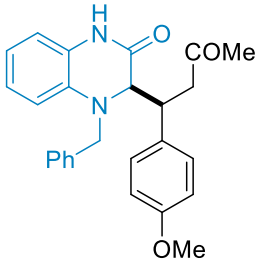
5.10ae, *91% yield*, 1:1 dr



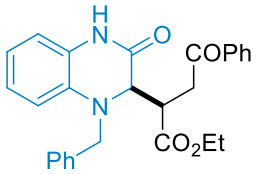
5.10af, *77% yield*, 1.5:1 dr



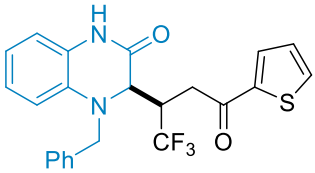
5.10ag, *86% yield*, 1.1:1 dr



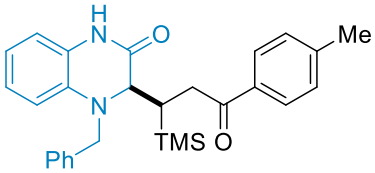
5.10ah, *91% yield*, 1:1 dr



5.10ai, *52% yield*, 3:1 dr



5.10aj, *70% yield*, 1:1 dr



5.10ak, *60% yield*, 2:1 dr

Scheme 5.17: Scope of the reaction using 4-benzyl-3,4-dihydroquinoxalin-2-one (**5.1a**) and different α,β-unsaturated ketones (**5.9**).[a]

[a]Reaction conditions: **5.1a** (0.13 mmol), **5.9** (0.1 mmol), $Ru(bpy)_3Cl_2$ (1 mol %), DPP (10 mol %), MeCN (1 mL), under argon atmosphere and under blue LEDs irradiation. Diastereomeric ratio was determined by ^{1}H-NMR of the crude reaction mixture. Yield determined after purification by column chromatography.

feasibility of this methodology with less electrophilic alkenes. For this purpose, we identified simple α,β-unsaturated ketones **5.9** as potential electrophilic counterparts.

Gratefully, the reaction between 3,4-dihydroquinoxalin-2-one **5.1a** with chalcone (**5.9a**) produced the expected product **5.10aa** in 76% yield. After confirming that this kind of ketones can be suitable substrates for our Giese reaction, several derivatives were also studied. Concretely, different β-aryl substitution with either a *p*-OMe group or a 2-naphthyl moiety was also well tolerated, as the expected product **5.10ab** and **5.10ac** were isolated in 91% and 83% yield respectively. *Chalcone* analogues with different aromatic groups near the ketone were also tried. Specifically, chalcone **5.9d** with a *p*-OMe group was able to generate the expected product **5.10ad** in 81% yield. In the same line, substrate **5.9e** that bears a 2-furyl moiety efficiently delivered product **5.10ae** in 91% yield.

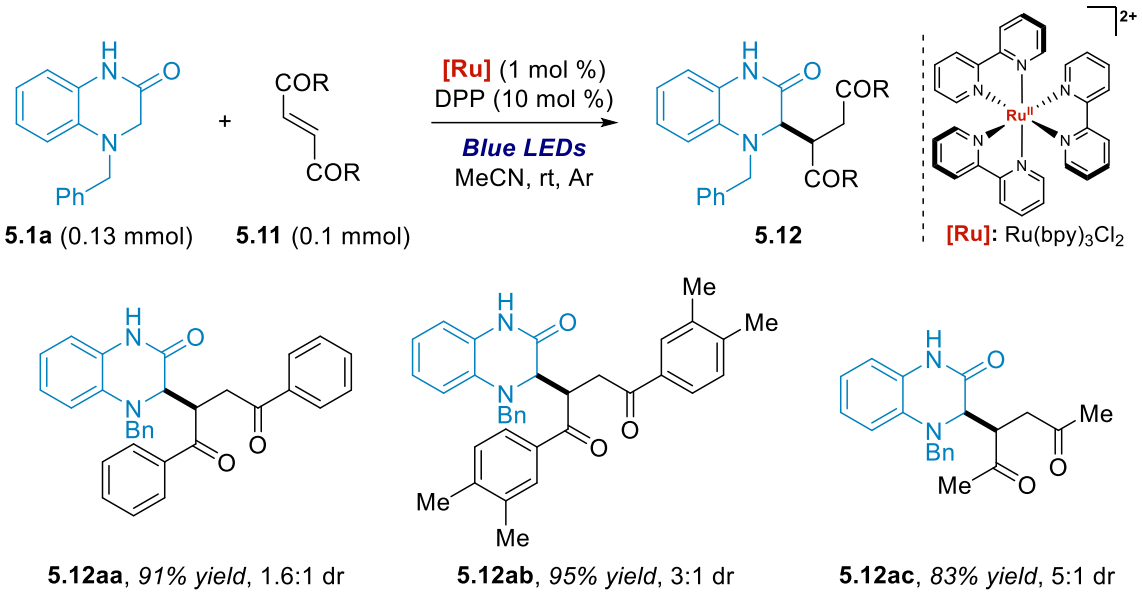
Simple enones bearing a β aliphatic group were also suitable substrates for our photocatalytic methodology. In fact, the corresponding β-^{i}Pr analogue **5.9f** allowed us to obtain the expected product **5.10af** in 77% yield. Moreover, we moved to (*E*)-4-phenylbut-3-en-2-one derivatives **5.9g** and **5.9h**, obtaining the corresponding products **5.10ag** and **5.10ah** in 86% and 91%, respectively.

In light of these successful results, we decided to try more challenging enone architectures as electrophiles in the Giese reaction. In fact, a phenyl enone with a β-CO_2Et substituent (**5.9i**) was able to participate in the reaction, providing the expected product **5.10ai** in a moderate 52% yield but with a surprising high dr of 3:1. Besides, the more sophisticated enone **5.9j** bearing a β-CF_3 group and a 2-thiophene heterocycle near the ketone was able to generate product **5.10aj** in 70% yield. Finally, the presence of a TMS group at the β position was also efficiently permitted, as product **5.10ak** was obtained in a moderate 60% yield and with a 2:1 dr.

Scope of the Reaction with Endiones

Since simple α,β-unsaturated ketones **5.9** worked well as electrophiles, we were confident enough to check the performance of several (*E*)-1,4-disubstituted-2-butene-1,4-diones, also known as endiones (**5.11**), in the Giese reaction (Scheme 5.18).

When diphenyl endione **5.11a** was subjected to the optimal reaction conditions, the expected product **5.12aa** was conveniently obtained in an excellent 91% yield. Besides, its tetramethyl derivative **5.11b** produced the expected Giese product **5.12ab** in an even higher 95% yield and with an interesting 3:1 dr. Finally, the simpler aliphatic analogue **5.11c** still behaved well as electrophile, affoding product **5.12ac** in 83% yield and with an unexpected good diastereoselectivity of 5:1.



Scheme 5.18: Scope of the reaction using 4-benzyl-3,4-dihydroquinoxalin-2-one (**5.1a**) and different endiones (**5.11**).[a]

[a]Reaction conditions: **5.1a** (0.13 mmol), **5.11** (0.1 mmol), $Ru(bpy)_3Cl_2$ (1 mol %), DPP (10 mol %), MeCN (1 mL), under argon atmosphere and under blue LEDs irradiation. Diastereomeric ratio was determined by ^{1}H-NMR of the crude reaction mixture. Yield determined after purification by column chromatography.

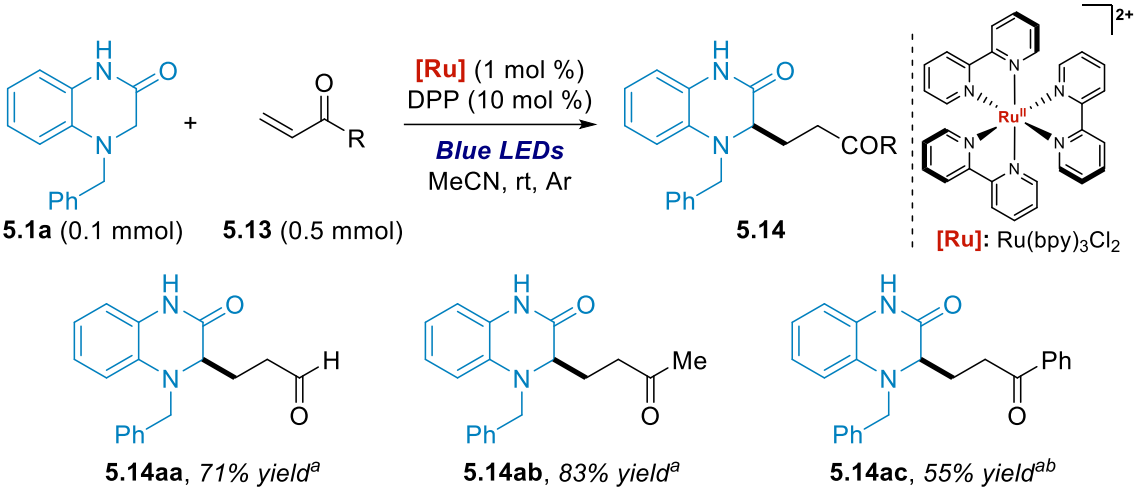
Scope of the Reaction with Vinyl Ketones

Very simple β-unsubstituted vinyl ketones **5.13** were also subjected to our photocatalytic protocol (Scheme 5.19). However, due to the low molecular weight of acrolein (**5.13a**) and methyl vinyl ketone (**5.13b**), we decided to modify the reaction conditions to facilitate the operation with these electrophiles. In fact when alkenes **5.13a** or **5.13b** were used we conducted the reaction with 0.1 mmol of **5.1a** and 0.5 mmol of **5.13a/5.13b**.

Using these slightly different conditions, we were also pleased to obtain product **4.14aa** derived from acrolein in 71% yield. In fact, the use of this very simple chemical feedstock to produce value-added derivatives is quite remarkable. In the same vain, methyl vinyl ketone derivative **5.14ab** was obtained in 83% yield. Finally, phenyl vinyl ketone **5.13c** was also capable of producing the expected product **5.14ac** although in a lower yield of 55%.

Scope of the Reaction with Miscellaneous Electron-Poor Alkenes

To conclude the regular scope of the reaction with different electron-poor alkenes, we encompassed in this section all the electrophilic substrates that can not be categorized in other parts or because they are singular enough that deserve a particular differentiation



Scheme 5.19: Scope of the reaction using 4-benzyl-3,4-dihydroquinoxalin-2-one (**5.1a**) and different β-unsubstituted alkenes (**5.13**).[ab]

[a]Reaction conditions: **5.1a** (0.1 mmol), **5.13** (0.5 mmol), $Ru(bpy)_3Cl_2$ (1 mol %), DPP (10 mol %), MeCN (1 mL), under argon atmosphere and under blue LEDs irradiation. Yield determined after purification by column chromatography.

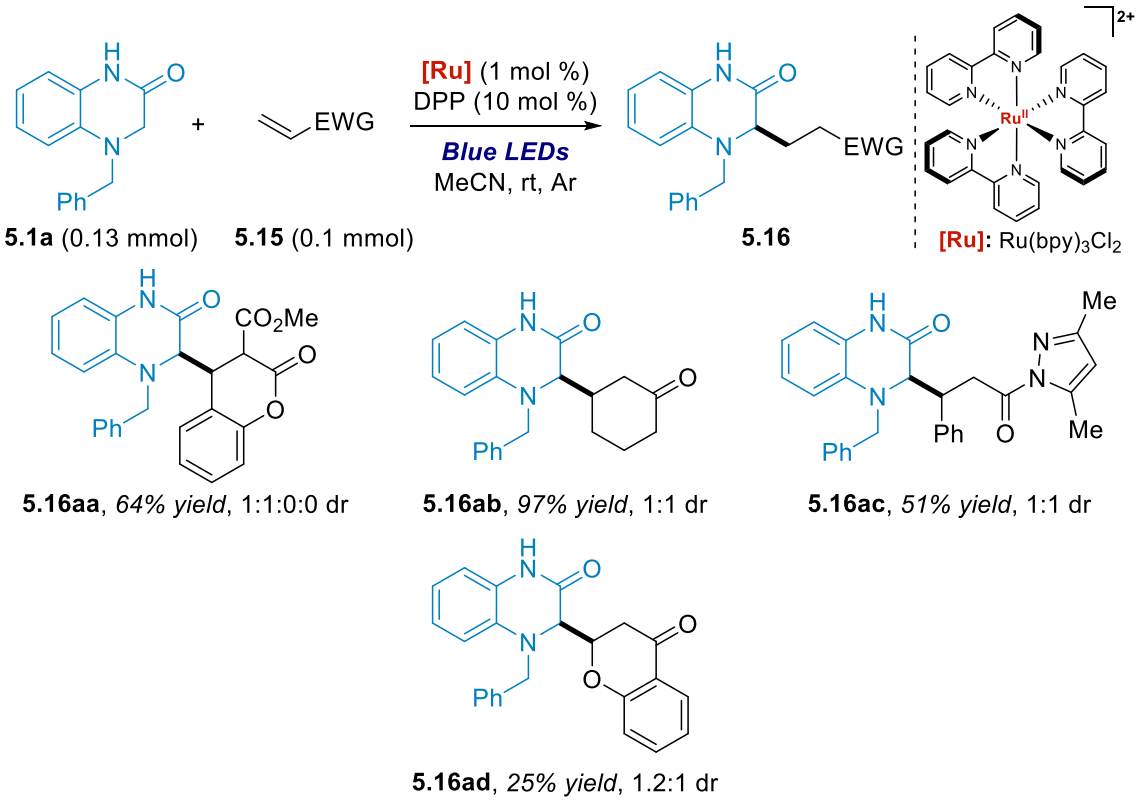
[b]0.13 mmol of **5.1a** and 0.1 mmol of **5.13c** were used.

(Scheme 5.20).

The first of these miscellaneous electrophilic alkenes is the coumarin derivative **5.15a**, which was able to participate in the Giese reaction furnishing product **5.16aa** in 64% yield. Additionally, cyclohexenone (**5.15b**) was also a suitable nucleophile acceptor, being capable of generating the corresponding β-cyclohexane derivative **5.16ab** in an excellent 97% yield. Interestingly, the α,β-unsaturated amide derived from pyrazole **5.15c** was found to be a suitable substrate for the Giese reaction, as expected product **5.16ac** was obtained in 51% yield. Finally, chromone (**5.16d**) was also engaged, but product **5.16ad** was isolated in only 25% yield.

Scope of the Reaction with α,β-unsaturated Ketones derived from Relevant Substrates

To further expand the relevance of our Giese reaction protocol, we prepared two substrates derived from vinyl aryl ketone that also bear either a natural-occurring molecule or a biologically-relevant scaffold (Scheme 5.21). Specifically, we synthesized an electron-poor alkene derived form oleic acid (**5.17a**), a fatty acid that can be found in several animals and plants, and another one derived from indomethacin (**5.17b**), a non-steroidal anti-inflammatory drug.[161,162] With this strategy we intend to build novel molecular entities with two different complex and interesting scaffolds, and also to test if our photocatalytic protocol tolarates the presence of several functional groups within the same



Scheme 5.20: Scope of the reaction using 4-benzyl-3,4-dihydroquinoxalin-2-one (**5.1a**) and different alkenes (**5.15**).[a]

[a]Reaction conditions: **5.1a** (0.13 mmol), **5.15** (0.1 mmol), $Ru(bpy)_3Cl_2$ (1 mol %), DPP (10 mol %), MeCN (1 mL), under argon atmosphere and under blue LEDs irradiation. Yield determined after purification by column chromatography.

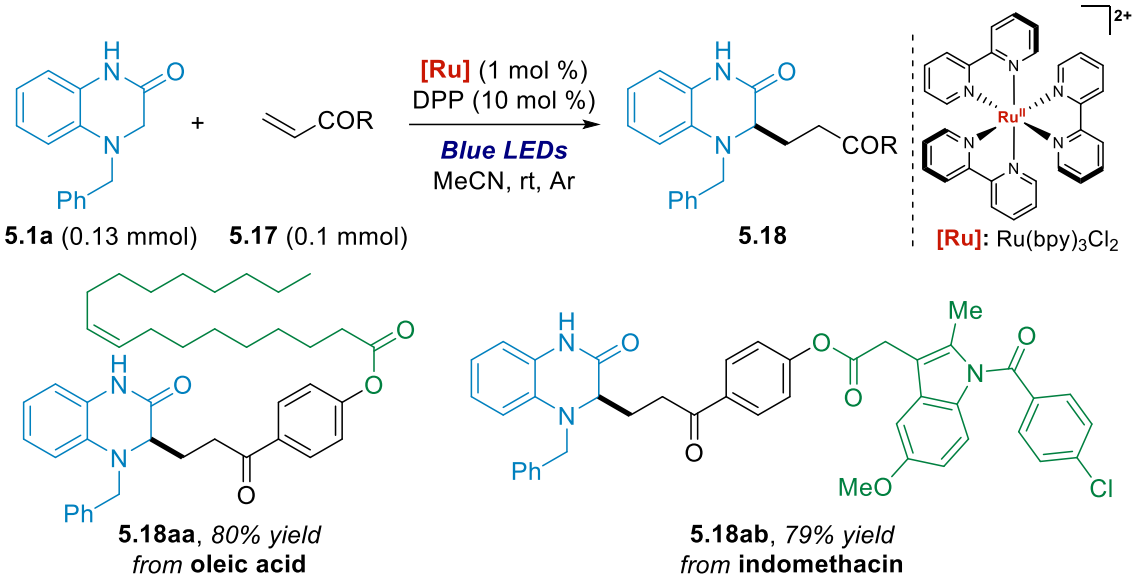
structure.

Delightfully, the corresponding products were incorporated to the 3,4-dihydroquinoxalin-2-one core in 80% yield for compound **5.18aa** and in 79% yield for compound **5.18ab**.

Scope of the Reaction with 3,4-Dihydroquinoxalin-2-ones

Having established the generality of the photochemical Giese reaction between 3,4-dihydroquinoxalin-2-one **5.1a** and a wide assortment of electron-poor alkenes, we moved to explore the effect of different substituents at the 3,4-dihydroquinoxalin-2-one (**5.1**) counterpart.

Initially, we considered that it would be of interest the use of acrolein (**5.13a**) as electrophile to build the scope with several differently-substituted 3,4-dihydroquinoxalin-2-ones (**5.1a**). For this purpose both the 1,4-dibenzyl derivative **5.1b** as well as the 6-F analogue were subjected to the reaction conditions using acrolein as electrophilic alkene.



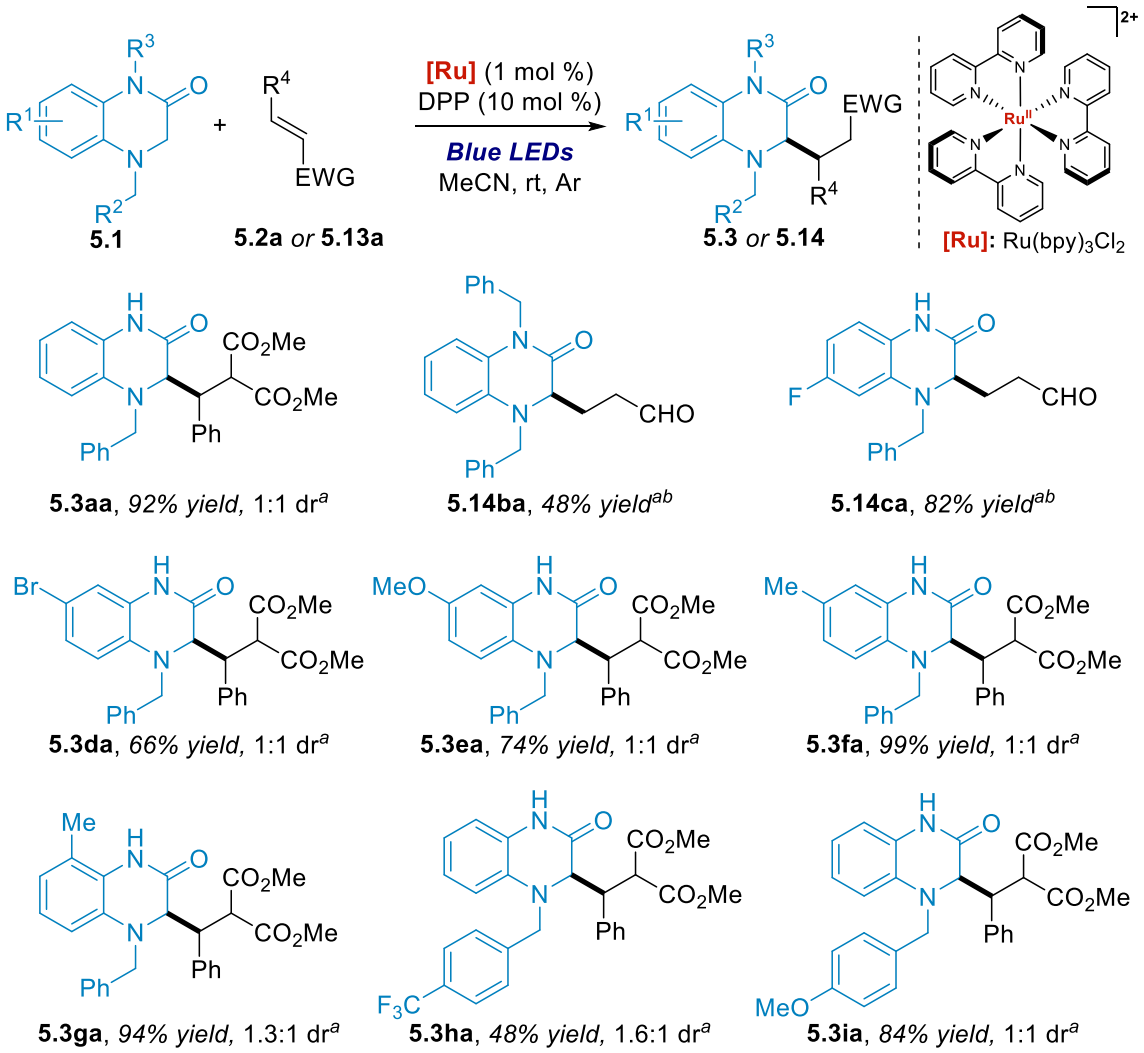
Scheme 5.21: Scope of the reaction using 4-benzyl-3,4-dihydroquinoxalin-2-one (**5.1a**) and different α,β-unsaturated ketones derived from relevant substrates (**5.17**).[a]

[a]Reaction conditions: **5.1a** (0.13 mmol), **5.17** (0.1 mmol), $Ru(bpy)_3Cl_2$ (1 mol %), DPP (10 mol %), MeCN (1 mL), under argon atmosphere and under blue LEDs irradiation. Diastereomeric ratio was determined by ^{1}H-NMR of the crude reaction mixture. Yield determined after purification by column chromatography.

Consequently, the corresponding products **5.14ba** and **5.14ca** were isolated in 48% and 82% yield, respectively.

Moreover, for comparative purposes, we also decided to study the scope of the reaction of 3,4-dihydroquinoxalin-2-ones **5.1** with dimethyl 2-benzylidenemalonate (**5.2a**). In this sense, several derivatives bearing either electron-withdrawing or electron-donating groups at C-7 were subjected to the Giese reaction with electron-poor alkene **5.2a**. In the precise case of 7-Br substrate, the corresponding product **5.3da** was generated in 66% yield, whereas with electron-donating 7-OMe and 7-Me analogues, the expected products **5.3ea** and **5.3fa** were delivered in 74% and 99% yield respectively. Besides, 8-methyl-3,4-dihydroquinoxalin-2-one (**5.1g**) generated the corresponding product **5.3ga** in an excellent 94% yield.

Finally, the effect of electronically-different benzylic substituents at the N-4 position was interrogated. As expected, the less electron-rich substrate **5.1h** that bears a *p*-CF_3 group provided product **5.3ha** in 48% yield, whereas the more electron-rich **5.1i**, due to the presence of a *p*-OMe group, delivered product **5.3ia** in 84% yield.



Scheme 5.22: Scope of the reaction using different 3,4-Dihydroquinoxalin-2-ones (**5.1**) and dimethyl 2-benzylidenemalonate (**5.2a**) or acrolein (**5.13a**).[ab]

[a]Reaction conditions: **5.1** (0.13 mmol), **5.2a** (0.1 mmol), $Ru(bpy)_3Cl_2$ (1 mol %), DPP (10 mol %), MeCN (1 mL), under argon atmosphere and under blue LEDs irradiation. Diastereomeric ratio was determined by ^{1}H-NMR of the crude reaction mixture. Yield determined after purification by column chromatography.

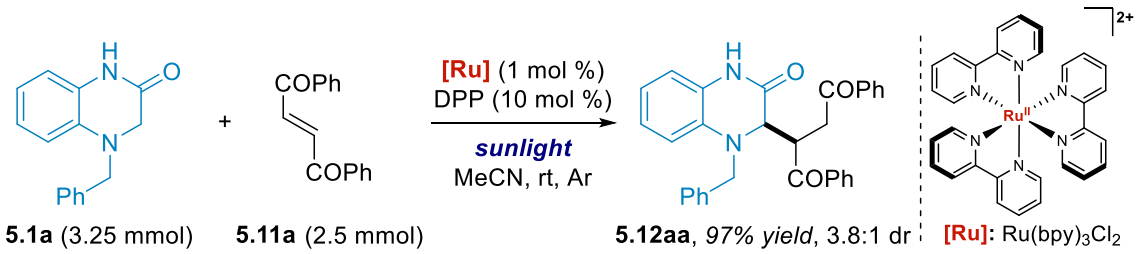
[b]0.1 mmol of **5.1** and 0.5 mmol of **5.13a** were used.

5.3.3 Gram-Scale Reaction and Synthetic Transformations

Gram-Scale Reaction

Having determined the boundaries of the photocatalytic Giese-type reaction, we decided to scale-up the process to 2.5 mmol-scale (Scheme 5.23). For enhancing the practicability of our methodology, we decided to change the irradiation source from blue LEDs to the more convenient and renewable sunlight irradiation.

In light of future synthetic derivatizations, we decided to use endione **5.11a** as electrophile rather than 2-arylidenemalonate **5.2a**. To our delight, the expected product **5.12aa** was isolated in 97% yield and 3.8:1 dr after only 3 hours of solar irradiation. It has to be noted that the same reaction at 0.1 mmol scale provided product **5.12aa** in 91% yield and 1.6:1 dr but required up to 9 hours of blue LEDs light. For that reason, it is important to highlight the excellent efficiency of this reaction, which was carried out on a scale twenty-five times larger and using sunlight.

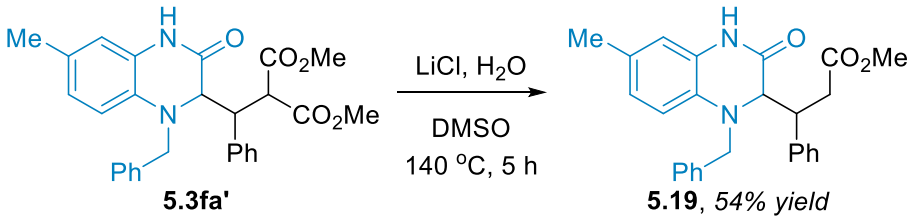


Scheme 5.23: Gram-scale reaction using 3,4-dihydroquinoxalin-2-one **5.1a**, endione **5.11a** and sunlight as energy source[a].

[a]Reaction conditions: **5.1a** (3.25 mmol), **5.11a** (2.5 mmol), $Ru(bpy)_3Cl_2$ (1 mol %), DPP (10 mol %), MeCN (25 mL), under argon atmosphere and under sunlight irradiation.

Synthetic Transformations

To show the versatility of our methodology, we wanted to attempt several synthetic modifications over the Giese products. Initially, the 1,3-diester moiety of product **5.3fa** (only one diastereomer, **5.3fa'**) was subjected to a Krapcho decarboxylation with LiCl, generating the monoester derivative **5.19** in 54% yield after 5 hours at 140 °C (Scheme 5.24). The obtention of product **5.19** is quite a few remarkable, since cinnamate esters could not be engaged in this photochemical Giese reaction.

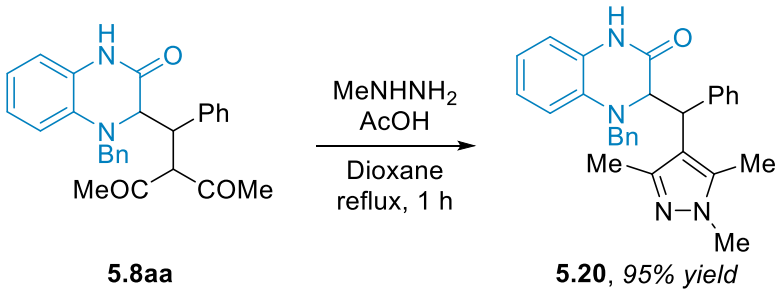


Scheme 5.24: Krapcho decarboxylation of compound **5.3fa**.[a]

[a]Reaction conditions: **5.3fa** (0.055 mmol), LiCl (5 equiv.) H_2O (6 equiv.) and DMSO (1 mL).

Besides, taking advantage of the 1,3-relationship between carbonyl groups, compound **5.8aa** was efficiently converted to the corresponding *N*-methylpyrazole **5.20** in 95% yield

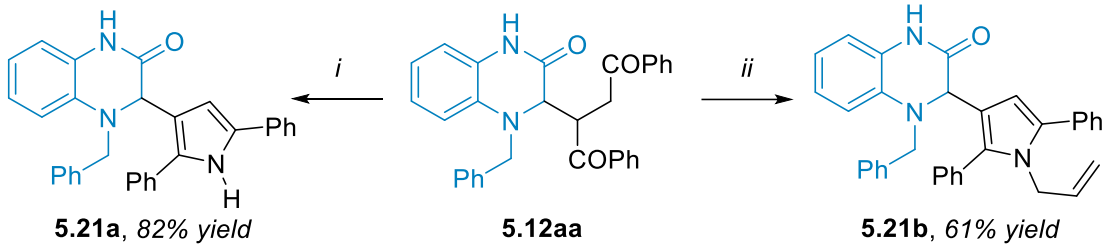
upon treatment with methylhydrazine in AcOH through a Knorr synthesis (Scheme 5.25).



Scheme 5.25: Synthesis of pyrazole **5.20** from 1,3-diketone **5.8aa**.[a]

[a]Reaction conditions: **5.8aa** (0.073 mmol), $MeNHNH_2$ (2 equiv.), AcOH (2 equiv.) and dioxane (2 mL).

Finally, with the large amount of compound **5.12aa** that was produced in the gram-scale reaction (Scheme 5.23), we endeavored the synthesis of two pyrrole derivatives using a Paal-Knorr synthesis, as there is a 1,4-relationship between the two carbonyl functionalities (Scheme 5.26). Specifically, we conducted the reaction in the presence of ammonium acetate, obtaining the corresponding *N*-H pyrrole **5.21a** in 82% yield. Thereafter, its *N*-allyl analogue **5.21a** was generated by the reaction between **5.12aa** with allylamine in 61% yield



Scheme 5.26: Synthesis of pyrroles **5.21a** and **5.21b** from 1,4-diketone **5.12aa**.[a]

[a]Reaction conditions: *i*) **5.12aa** (0.25 mmol), NH_4OAc (20 equiv.), EtOH (4 mL) and $CHCl_3$ (6 mL) at 50 °C for 24 hours; *ii*) **5.12aa** (0.25 mmol), allylamine (7 equiv.), AcOH (16 equiv.), EtOH (4 mL) and $CHCl_3$ (6 mL) at 50 °C for 24 hours.

5.3.4 Mechanistic Investigations and Proposed Mechanism

Mechanistic Investigations

After performing the gram-scale reaction and different derivatizations of the products, the synthetic part of this project was considered completed. At this point we decided to explore the reaction mechanism behind our transformation. According to our hypothesis,

the reaction starts with the oxidation of 3,4-dihydroquinoxalin-2-one **5.1a** by $Ru(bpy)_3Cl_2$ (**A**) in its excited state. To prove this conjecture, we initially verified the quantum yield of our Giese reaction, after determining the photon flux of our photochemical setup by means of ferrioxalate actinometry as described by Hatchard and Parker[205] and the modifications implemented by Yoon[206] and Melchiorre.[207] As expected, $\Phi = 0.15$, which made us consider that our reaction proceeds through a closed photoredox cycle.

Thereafter, we resorted to Stern-Volmer luminescence *quenching* experiments to prove the interaction between 3,4-dihydroquinoxalin-2-one **5.1a** and the excited state of photocatalyst $Ru(bpy)_3Cl_2$ (**A**). As stated in the *Introduction* and in *Chapter* 2, if the luminescence of a given photocatalyst decreases when a particular substrate is present, it can be assumed that the substrate (the *quencher*) and the photocatalyst have a positive interaction, either by energy or electron transfer. Assuming that our mechanism should be based in electron-transfer events due to the nature of the substrates, we prepared five solutions in degassed MeCN containing 0.02 mM of $Ru(bpy)_3Cl_2$ (**A**) and varying amounts of 3,4-dihydroquinoxalin-2-one **5.1a** (from 0 to 19.2 mM). Afterwards, their luminiscence spectra were recorded, knowing that the emission band of the $Ru(bpy)_3Cl_2$ (**A**) is centered at 600 nm (Figure 5.1).

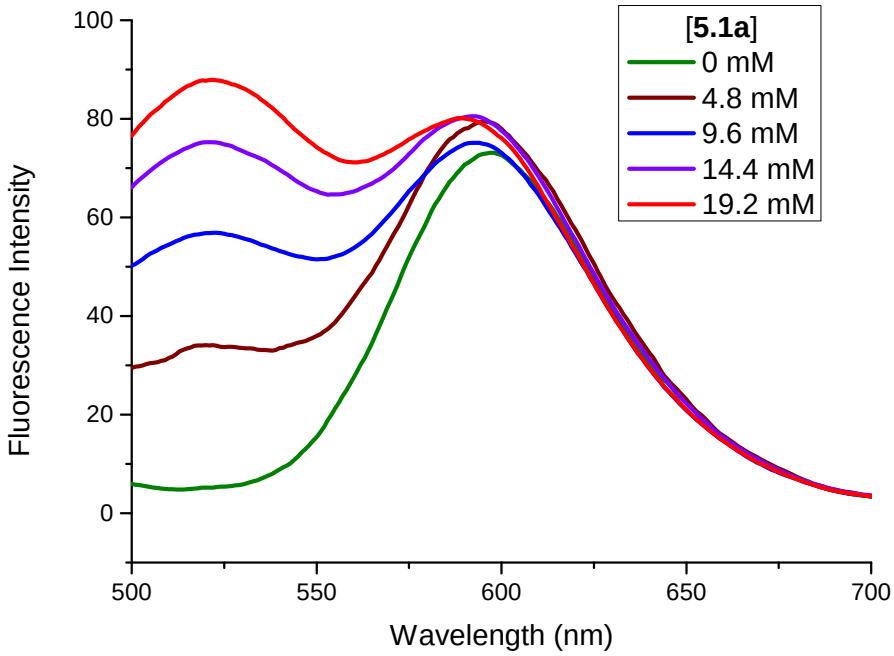


Figure 5.1: Emission spectra of different solutions containing 0.02 mM of $Ru(bpy)_3Cl_2$ (**A**) and varying amounts of 3,4-dihydroquinoxalin-2-one **5.1a**.

To our surprise, the luminiscence of $Ru(bpy)_3Cl_2$ (**A**) in each sample remained unaltered, which means that, in principle, there are not any interaction between substrate **5.1a** and $Ru(bpy)_3Cl_2$ (**A**). Moreover, one can observe an emission band nearly at 520

nm, which may arise from 3,4-dihydroquinoxalin-2-one **5.1a** itself, as the greater is the amount of **5.1a** in the solution, the greater is the emission intensity.

Having encountered that our main mechanism standpoint did not actually apply in this case, we decided to find out if the electron transfer from substrate **5.1a** to the excited state of the photocatalyst is thermodynamically possible. To address this, we determined the redox potential of 3,4-dihydroquinoxalin-2-one **5.1a** by means of cyclic voltammetry (Table 5.5). After performing this assay, we could say that the redox potential was $E_{red}(\mathbf{5.1a}^{+\bullet}/\mathbf{5.1a}) = +0.80$ V (vs SCE). On the other hand, the redox potentials of $Ru(bpy)_3Cl_2$ (**A**) are well known, being $E_{red}([\mathbf{Ru^{II*}}]/[\mathbf{Ru^{I}}]) = +0.77$ V (vs SCE). Hence, these findings reveal that the oxidation of **5.1a** by the excited state of $Ru(bpy)_3Cl_2$ (**A**) is not thermodynamically spontaneous.

Table 5.5: Redox potentials of $Ru(bpy)_3Cl_2$ (**A**) from the excited state, **5.1a**, **5.1a**+DPP and **5.2a**.

Specie	$E_{red}(\mathbf{A}^{+n}/\mathbf{A}^{n})$ (V vs SCE)	$E_{red}(\mathbf{A}^{n}/\mathbf{A}^{-n})$ (V vs SCE)
***[Ru]**	+0.77	−0.81
5.1a	+0.80	–
5.1a+DPP	+0.77	–
5.2a	–	−1.57

Therefore, we focused in alternative reaction mechanisms, as for example the direct reduction of **5.2a** by the excited $Ru(bpy)_3Cl_2$ (**A**). In this case the scenario is even worse, because the reduction of **5.2a** was determined to be $E_{red}(\mathbf{5.2a}/\mathbf{5.2a}^{-\bullet}) = -1.57$ V (vs SCE), and the pair for the oxidation of $Ru(bpy)_3Cl_2$ (**A**) is $E_{red}([\mathbf{Ru^{III}}]/[\mathbf{Ru^{II*}}]) = -0.81$ V (vs SCE). Accordingly, dimethyl 2-benzylidenemalonate (**5.2a**) did not exhibit luminescence quenching of $Ru(bpy)_3Cl_2$ (**A**) in Stern-Volmer experiments.

In this scenario where neither 3,4-dihydroquinoxalin-2-one **5.1a** nor dimethyl 2-benzylidenemalonate (**5.2a**) were able to interact with the excited state of the $Ru(bpy)_3Cl_2$ (**A**), we centered our attention on the role of diphenyl phosphoric acid (DPP) in this reaction. Since this Giese reaction did not take placed in the absence of DPP, it has to play a major role in the mechanism. Thus, the redox potential of 3,4-dihydroquinoxalin-2-one **5.1a** was determined again but in the presence of DPP. Surprisingly the reduction potential for the pair $\mathbf{5.2a}/\mathbf{5.2a}^{-\bullet}$ decreased from +0.80 V (vs SCE) without DPP to +0.77 V (vs SCE) in the presence of DPP. Although it was not a drastic drop, it made **5.1a** more prone to oxidation and, in fact, it fit in the window of action of $Ru(bpy)_3Cl_2$ (**A**).

At this point, Stern-Volmer luminescence quenching experiments were repeated but also adding DPP (Figure 5.2). Two facts can be drawn from these experiences. Firstly,

the addition of DPP makes substrate **5.1a** quench the excited state of $Ru(bpy)_3Cl_2$ (**A**)[†], and secondly that the luminescence emission of 3,4-dihydroquinoxalin **5.1a** at 525 nm increases a lot but it exhibits a self-quenching behaviour, since when DPP is present (Figure 5.2), the greater the concentration of **5.1a**, the smaller the emission intensity, in contrast with the behaviour of **5.1a** alone (Figure 5.1).

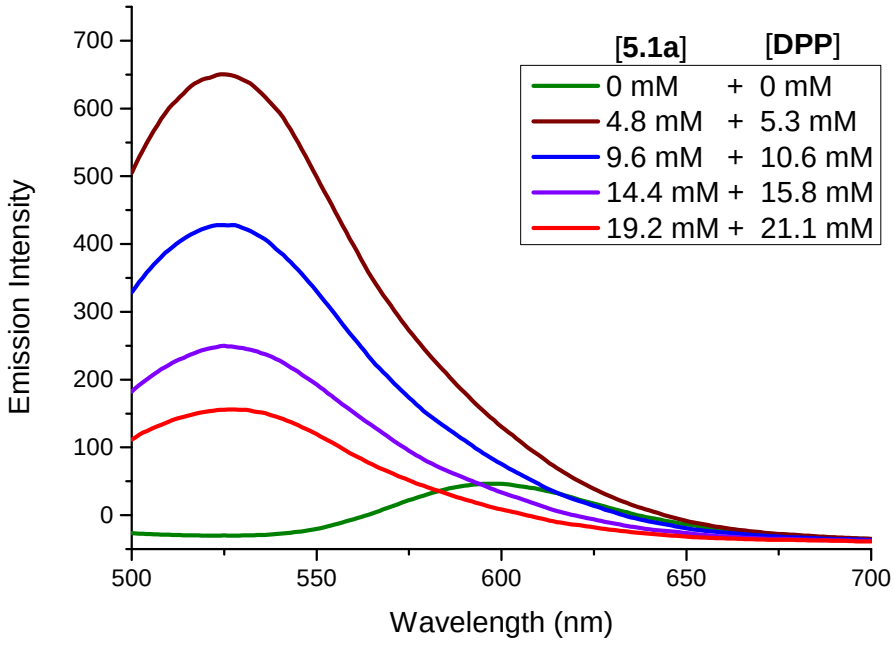


Figure 5.2: Emission spectra of different solutions containing 0.02 mM of $Ru(bpy)_3Cl_2$ (**A**) and varying amounts of 3,4-dihydroquinoxalin-2-one **5.1a** and DPP.

To ensure the quenching of the excited state of $Ru(bpy)_3Cl_2$ (**A**) by 3,4-dihydroquinoxalin-2-one **5.1a** in the presence of DPP, we decided to record the emission spectrum of a solution containing 0.02 mM of $Ru(bpy)_3Cl_2$ (**A**) and a premixed blend of **5.1a** and DPP (Figure 5.3). In this case, we could assure that the emission of $Ru(bpy)_3Cl_2$ (**A**) is strongly quenched in the presence of a combination of **5.1a** and DPP. Apparently, 3,4-dihydroquinoxalin-2-one **5.1a** and DPP may eventually form an adduct, which is the actual specie that quenches the excited state of $Ru(bpy)_3Cl_2$ (**A**).

To further detect this adduct, we analyzed the mixture of **5.1a** and DPP by absorption spectroscopy (Figure 5.4), revealing a remarkable absorption spectrum with superior intensity, which was attributed to the formation of a **5.1a**·DPP adduct.

After stating that an adduct between **5.1a** and DPP was generated, to elucidate its stoichiometry we planned to prepare several solutions with the same amount of **5.1a** and

[†]In Figure 5.2, although the emission band at 525 nm disguises the emission band of $Ru(bpy)_3Cl_2$ (green line), it can be noted that for the most concentrated solution of **5.1a** (red line), the emission intensity around 600 nm is lower than the emission intensity of purely $Ru(bpy)_3Cl_2$ (green line).

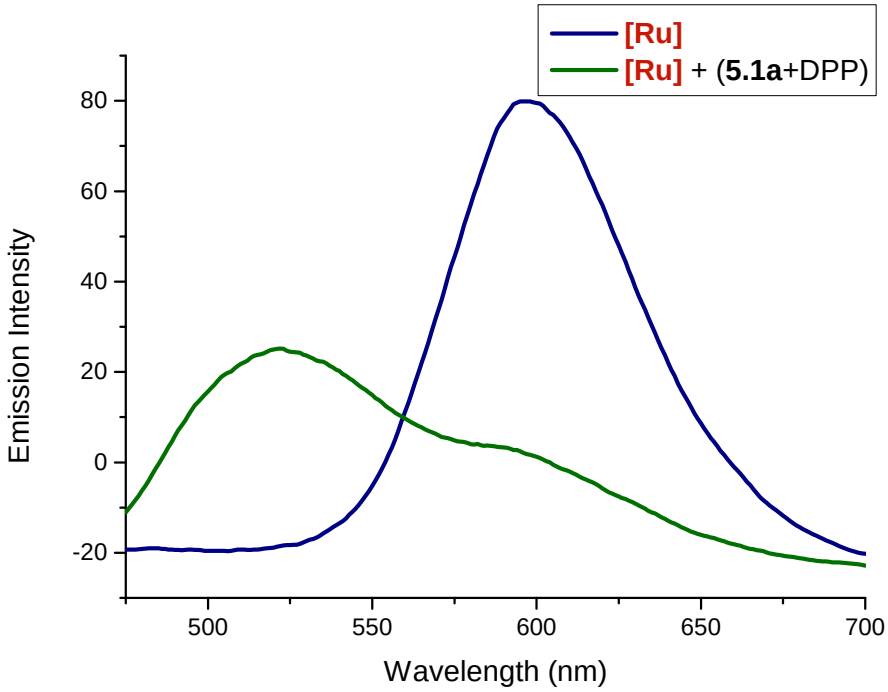


Figure 5.3: Emission spectra of a solution containing 0.02 mM of $Ru(bpy)_3Cl_2$ (**A**) and a premixed blend of **5.1a** and DPP.

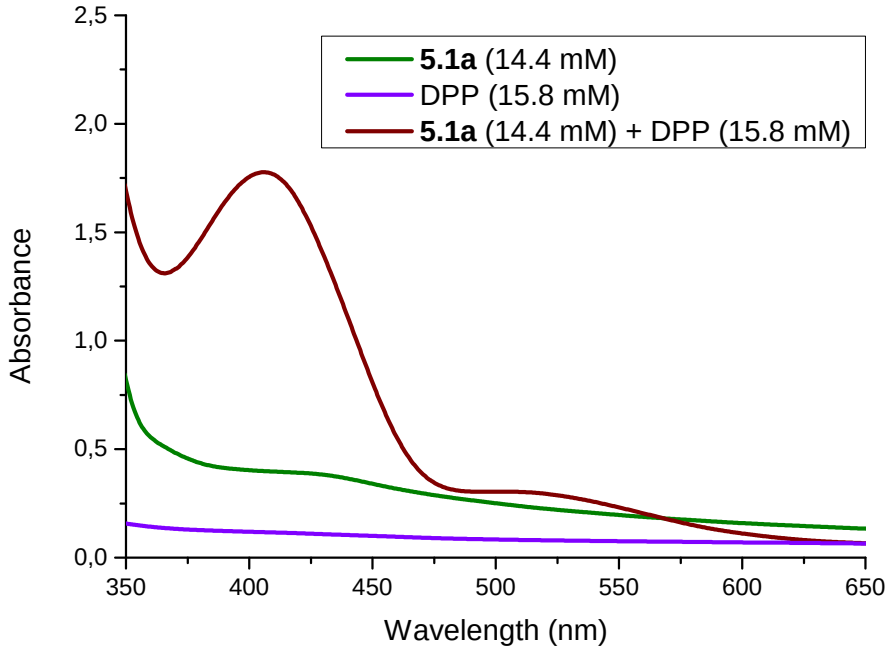


Figure 5.4: Absorption spectra of **5.1a**, DPP and a mixture of **5.1a** and DPP.

increasing quantities of DPP. Therefore, their emission spectra were recorded (Figure 5.5). Qualitatively, it can be inferred that the emission intensity of 3,4-dihydroquinoxalin-2-one **5.1a** band at 525 nm increases as the concentration of DPP does. However, when the 1:1 molar ratio was reached, the emission only slightly increased, showing that a 1:1 stoichiometry between **5.1a** and DPP is likely for the adduct.

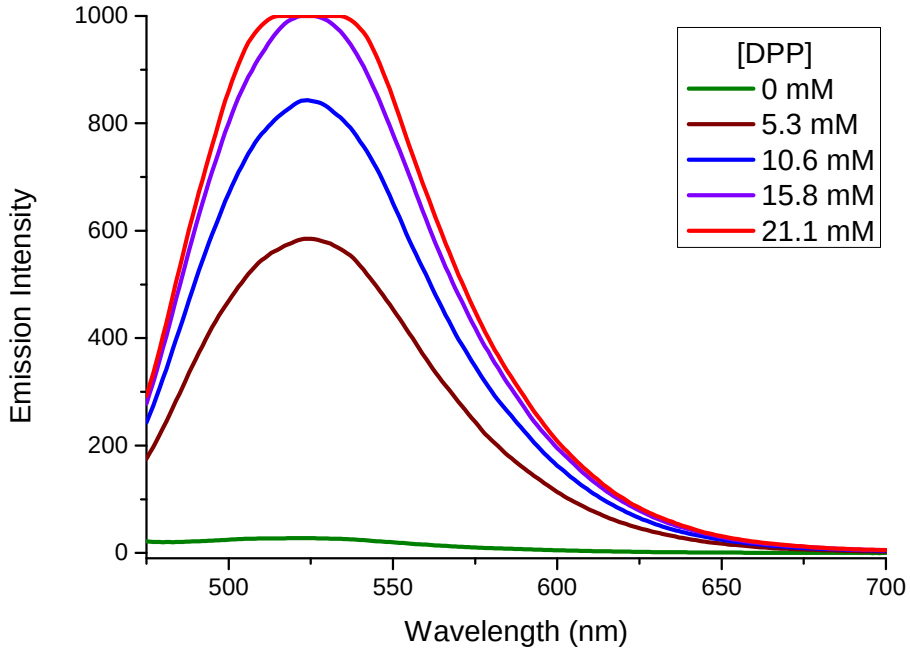


Figure 5.5: Emission spectra of different solutions containing 14.4 mM of **5.1a** and varying amounts of DPP.

Finally, in our interest of endowing a molecular structure of the adduct between **5.1a** and DPP, we performed an analysis of the mixture by means of ^{1}H-NMR (Figure 5.6). Based on signal shifting, we could tentatively suggest the formation of a **5.1a**·DPP adduct via two hydrogen bonds. In fact, the amidic proton at N-1 of **5.1a** is probably deshielded due to the coordination with the oxygen atom in DPP (from 8.94 ppm to 11.21 ppm). Moreover, the appearance of a thin singlet at 9.5 ppm is consistent with the formation of a hydrogen bond between the acidic proton of DPP and the carbonyl group in **5.1a**.

Proposed Mechanism

With all this information in hand, we were able to postulate a mechanism by which our redox-neutral photocatalytic Giese reaction between 3,4-dihydroquinoxalin-2-one **5.1a** and dimethyl 2-benzylidenemalonate (**5.2a**) may proceed (Figure 5.7). Initially, 3,4-dihydroquinoxalin-2-one **5.1a** and DPP form the above discussed adduct **5.1a**:DPP. This adduct is the specie which suffers the SET from the excited state of $Ru(bpy)_3Cl_2$ (**A**),

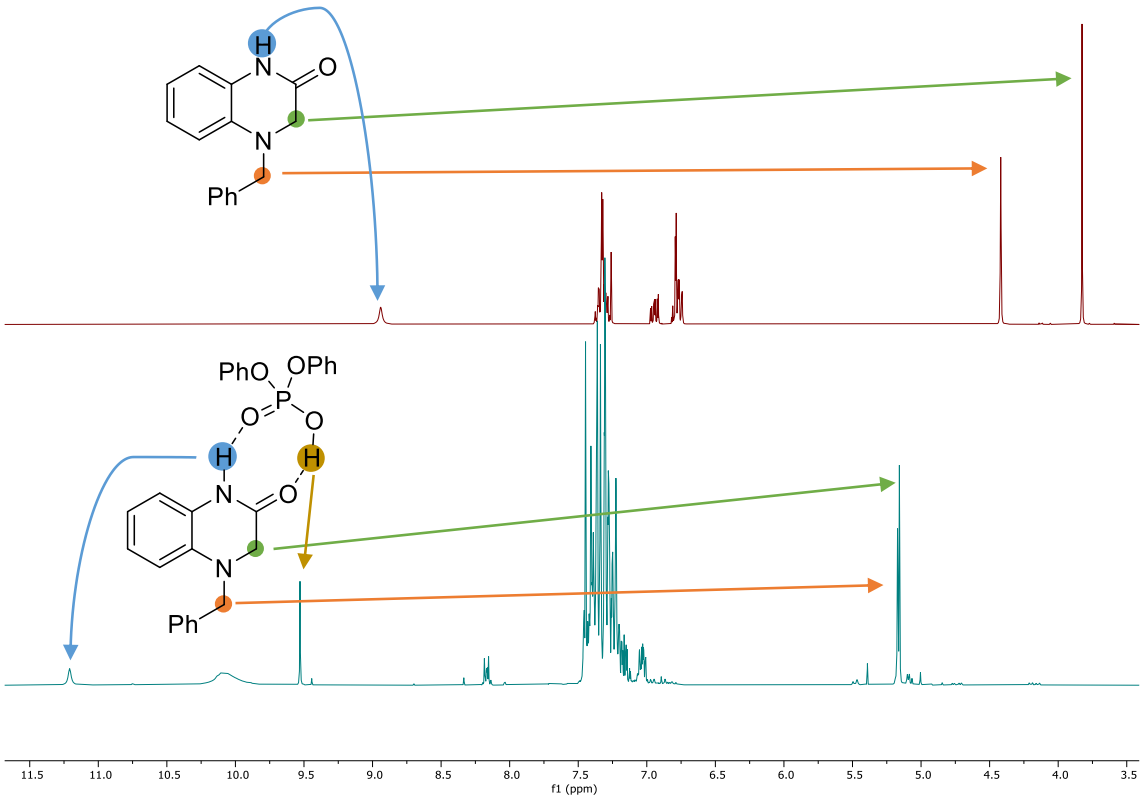


Figure 5.6: ^{1}H-NMR of pure **5.1a** (*up*) and ^{1}H-NMR spectrum of a mixture of **5.1a** and DPP (*down*).

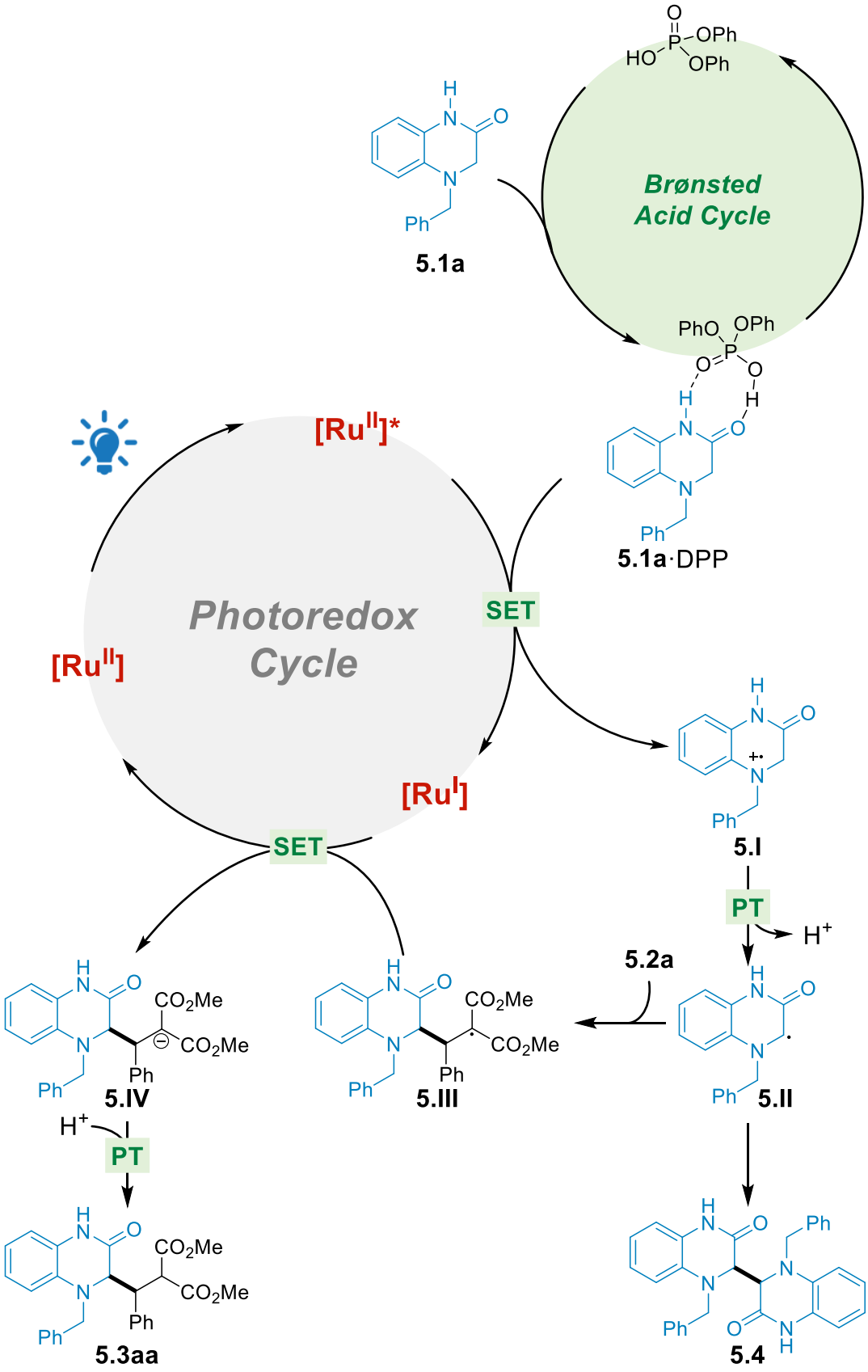


Figure 5.7: General mechanism for the photocatalytic Giese reaction between 3,4-dihydroquinoxalin-2-one **5.1a** and dimethyl 2-benzylidenemalonate (**5.2a**).

producing the corresponding radical cation **5.I** and the Ru(I) form of the photocatalyst. Thereafter, radical cation **5.I** experiments the loss of a proton to yield the nucleophilic α-amino radical **5.II**.

Continuedly, radical **5.II** reacts with 2-benzylidenemalonate (**5.2a**) to furnish carbon-centered highly-stabilized radical **5.III**. Nevertheless, α-amino radical **5.II** may participate in a non productive reaction pathway thorough a radical homocoupling to produce dimer **5.4**. In fact, the isolation of this dimer **5.4** is an experimental evidence of α-amino radical **5.II** formation.

Finally, radical **5.III** is engaged in another SET with the Ru(I) form of the photocatalyst, thus regenerating it and generating enolate **5.IV**, which after protonation is turned into the desired product **5.3aa**.

5.4 Experimental Section

5.4.1 General Methods

Experimental methods regarding **Melting Points**, **Chromatographic Methods**, **Nuclear Magnetic Resonance (NMR)** and **High Resolution Mass Spectrometry (HRMS)** can be found in Section 1.4.1 of *Chapter 1* (page 62).

Reaction Flasks, Reagents and Substrates

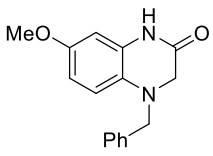
- Photocatalytic reactions were carried out in 10 mL Schlenk flasks under argon unless otherwise indicated.
- Commercial reagents were used as purchased.
- MeCN was degassed by three freeze-pump-thaw cycles and stored over 3Å MS for 48 h at least. Prior to use, MeCN was bubbled with Ar for 10 min.
- All photocatalysts and Brønsted acids were commercially available.
- 4-Substituted-3,4-dihydroquinoxalin-2-ones **5.1a**-**5.1i** were prepared form its N-4 unprotected precursors using the *N*-benzylation procedure described in page 67 of *Chapter 1*.
- All electron-poor alkenes were commercially available or were already prepared in the laboratory, except **5.17a** and **5.17b**.

5.4.2 Synthetic Procedures and Characterization

Synthesis of 3,4-dihydroquinoxalin-2-ones 5.1a-5.1i

The procedure followed for the synthesis of 3,4-dihydroquinoxalin-2-one **3.1a** is described in *Section 2.4.2* of *Chapter 2* (page 113). 3,4-Dihydroquinoxalin-2-ones **5.1b**-**3.1i** were prepared using the same methodology.

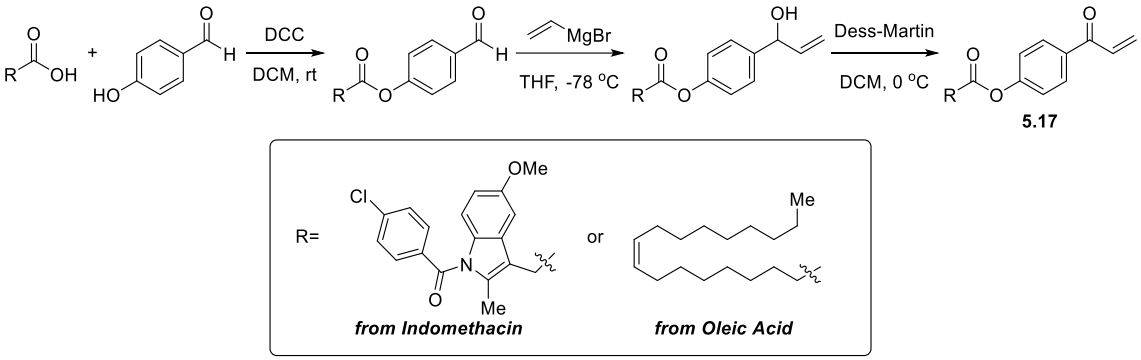
4-Benzyl-7-methoxy-3,4-dihydroquinoxalin-2(1*H*)-one (5.1e)



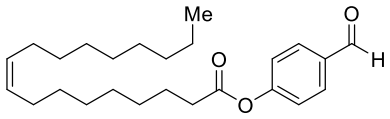
^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.77 (bs, 1H), 7.51 – 7.11 (m, 5H), 6.69 (d, J = 8.4 Hz, 1H), 6.35 (d, J = 2.5 Hz, 1H), 6.29 (dd, J = 8.4, 2.5 Hz, 1H), 4.39 (s, 2H), 3.80 (s, 2H), 3.71 (s, 3H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 166.4 (C), 156.9 (C), 136.4 (C), 136.1 (C), 128.9 (CH), 127.6 (2xCH), 119.9 (C), 115.9 (CH),

102.5 (CH), 99.8 (CH), 55.5 (CH_3), 53.6 (CH_2), 52.1 (CH_2); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{16}H_{17}N_2O_2^+$ 269.1285, found 269.1288.

Synthesis of Electron-Poor Alkenes 5.17a and 5.17b



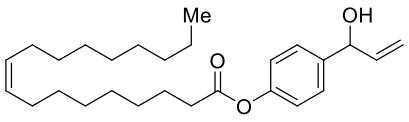
4-Formylphenyl oleate



To a stirred solution of commercially available oleic acid (287 mg, 1 mmol, 1 equiv.) in DCM (5 mL) were added *p*-hydroxybenzaldehyde (146 mg, 1.2 mmol, 1.2 equiv.) and DCC (310 mg, 1.5 mmol, 1.5 equiv.) and the resulting mixture was stirred at room temperature for 16 h. Then, the crude reaction mixture was filtered over a pad of Celite eluting with EtOAc. This yellow solution was concentrated by rotary evaporation and the residue was purified by column chromatography using hexane:EtOAc mixtures as eluent to afford the desired compound (124 mg, 0.32 mmol, 32% yield) as a colourless oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.99 (s, 1H), 7.92 (d, J = 8.7 Hz, 2H), 7.27 (d, J = 8.5 Hz, 2H), 5.42 – 5.28 (m, 2H), 2.59 (t, J = 7.5 Hz, 2H), 2.08 – 1.95 (m, 4H), 1.76 (p, J = 7.4 Hz, 2H), 1.48 – 1.19 (m, 20H), 0.88 (t, J = 6.9 Hz, 3H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 190.9 (CH), 171.6 (C), 155.5 (C), 133.9 (C), 131.2 (CH), 130.1 (CH), 129.7 (CH), 122.4 (CH), 34.4 (CH_2), 31.9 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 29.1 (CH_2), 29.1 (CH_2), 29.0 (CH_2), 27.2 (CH_2), 27.1 (CH_2), 24.8 (CH_2), 22.7 (CH_2), 14.1 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{25}H_{39}O_3^+$ 387.2894, found 387.2890.

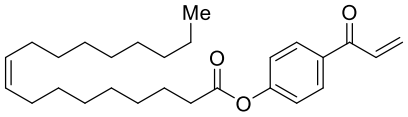
4-(1-Hydroxyallyl)phenyl oleate



4-Formylphenyl oleate (124 mg, 0.32 mmol, 1 equiv.) was placed in a round bottomed flask and that was purged with N_2. Then, freshly distilled THF (3 mL) was added and the resulting solution

was cooled down to -78 °C (using dry ice-acetone bath). Vinylmagnesium bromide (0.32 mL, 0.32 mmol, 1 eq., 1 M in THF) was added dropwise and the resulting mixture was stirred at -78 °C for 3 h. After this period of time, the reaction was quenched with saturated aqueous NH_4Cl and extracted with DCM (x3). The combined organic phases were dried over $MgSO_4$. After concentration by rotary evaporation, the resulting mixture was purified by column chromatography using hexane:EtOAc mixtures as eluent to obtain the desired compound (83.5 mg, 0.20 mmol, 63% yield) as a colourless oil. **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 7.38 (d, *J* = 8.6 Hz, 2H), 7.06 (d, *J* = 8.6 Hz, 2H), 6.12 – 5.94 (m, 1H), 5.41 – 5.29 (m, 3H), 5.26 – 5.13 (m, 2H), 2.55 (t, *J* = 7.5 Hz, 2H), 2.09 – 1.93 (m, 4H), 1.75 (p, *J* = 7.4 Hz, 2H), 1.47 – 1.23 (m, 20H), 0.94 – 0.83 (m, 3H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 172.3 (C), 150.2 (C), 140.0 (C), 130.0 (CH), 129.7 (CH), 127.4 (CH), 121.6 (CH), 115.4 (CH_2), 74.8 (CH), 34.4 (CH_2), 31.9 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 29.1 (CH_2), 29.1 (CH_2), 27.2 (CH_2), 27.1 (CH_2), 24.9 (CH_2), 22.7 (CH_2), 14.1 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{27}H_{43}O_3^+$ 415.3207, found 415.3209.

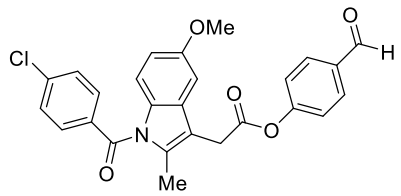
4-Acryloylphenyl oleate (5.17a)



A stirred solution of 4-(1-hydroxyallyl)phenyl oleate (83.5 mg, 0.20 mmol) in DCM (3 mL) was cooled down to 0 °C and Dess-Martin periodinane (102 mg, 0.24 mmol, 1.2 equiv.) was added. The resulting suspension was stirred at 0 °C (using a ice water bath) for 2.5 h (as indicated by TLC) and then, the reaction mixture was filtered through a pad of silica eluting with EtOAc. The crude mixture was concentrated under reduced pressure and the residue was purified by column chromatography using hexane:EtOAc mixtures as eluent to afford the desired compound (67.9 mg, 0.17 mmol, 82% yield) as a colourless oil. This compound needs to be stored at -20 °C to avoid its vinylic polymerization.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.7 Hz, 2H), 7.34 – 7.05 (m, 3H), 6.44 (dd, *J* = 17.1, 1.7 Hz, 1H), 5.93 (dd, *J* = 10.6, 1.7 Hz, 1H), 5.35 (ddd, *J* = 5.7, 3.5, 2.3 Hz, 2H), 2.58 (t, *J* = 7.5 Hz, 2H), 2.01 (q, *J* = 6.7, 5.1 Hz, 4H), 1.76 (p, *J* = 7.4 Hz, 2H), 1.48 – 1.22 (m, 20H), 0.95 – 0.81 (m, 3H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 189.7 (C), 171.7 (C), 154.4 (C), 134.7 (C), 132.1 (CH), 130.3 (CH_2), 130.3 (CH), 130.0 (CH), 129.7 (CH), 121.8 (CH), 34.4 (CH_2), 31.9 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 29.1 (CH_2), 29.0 (CH_2), 29.0 (CH_2), 27.2 (CH_2), 27.1 (CH_2), 24.8 (CH_2), 22.7 (CH_2), 14.1 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{27}H_{41}O_3^+$ 413.3050, found 416.3041.

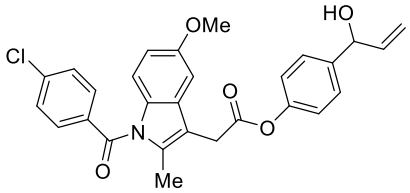
4-Formylphenyl 2-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl)acetate



To a stirred solution of commercially available indomethacin (358 mg, 1 mmol, 1 equiv.) in DCM (5 mL) were added *p*-hydroxybenzaldehyde (146 mg, 1.2 mmol, 1.2 equiv.) and DCC (310 mg, 1.5 mmol, 1.5 equiv.) and the resulting mixture was stirred at room temperature for 16 h. Then, the crude reaction mixture was filtered over a pad of Celite eluting with EtOAc. This yellow solution was concentrated by rotary evaporation and the residue was purified by column chromatography using hexane:DCM mixtures as eluent to afford the desired compound (461 mg, 0.99 mmol, 99% yield) as a yellow foam.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.98 (s, 1H), 7.90 (d, J = 8.7 Hz, 2H), 7.68 (d, J = 8.7 Hz, 2H), 7.48 (d, J = 8.7 Hz, 2H), 7.25 (d, J = 8.5 Hz, 2H), 7.04 (d, J = 2.5 Hz, 1H), 6.88 (d, J = 9.0 Hz, 1H), 6.70 (dd, J = 9.0, 2.5 Hz, 1H), 3.94 (s, 2H), 3.84 (s, 3H), 2.47 (s, 3H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 190.8 (CH), 168.6 (C), 168.3 (C), 156.1 (C), 155.3 (C), 139.5 (C), 136.4 (C), 134.1 (C), 133.7 (C), 131.2 (CH), 131.2 (CH), 130.8 (C), 130.3 (C), 129.2 (CH), 122.2 (CH), 115.1 (CH), 111.8 (CH), 111.4 (C), 101.2 (CH), 55.7 (CH_3), 30.6 (CH_2), 13.4 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{26}H_{21}ClNO_5^+$ 462.1103, found 462.1110.

4-(1-Hydroxyallyl)phenyl-2-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl)acetate

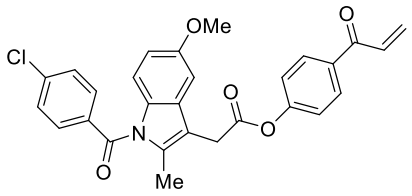


4-Formylphenyl 2-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetate (461 mg, 0.99 mmol, 1 equiv.) was placed in a round bottomed flask and that was purged with N_2. Then, freshly distilled THF (5 mL) was added and the resulting solution was cooled down to -78 °C (using dry ice-acetone bath). Vinylmagnesium bromide (1 mL, 1 mmol, 1 eq., 1 M in THF) was added dropwise and the resulting mixture was stirred at -78 °C for 3 h. After this period of time, the reaction was quenched with saturated aqueous NH_4Cl and extracted with DCM (x3). The combined organic phases were dried over $MgSO_4$. After concentration by rotary evaporation, the resulting mixture was purified by column chromatography using hexane:EtOAc mixtures as eluent to obtain the desired compound (382 mg, 0.78 mmol, 78% yield) as a yellow foam.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.68 (d, J = 8.7 Hz, 2H), 7.47 (d, J = 8.7 Hz, 2H), 7.36 (d, J = 8.5 Hz, 2H), 7.10 – 6.99 (m, 3H), 6.90 (d, J = 9.0 Hz, 1H), 6.69 (dd, J = 9.0, 2.5 Hz, 1H), 6.11 – 5.92 (m, 1H), 5.40 – 5.28 (m, 1H), 5.25 – 5.14 (m, 2H), 3.90 (s, 2H), 3.83 (s, 3H), 2.45 (s, 3H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 169.3 (C), 168.3 (C), 156.1

(C), 150.1 (C), 140.3 (C), 140.0 (CH), 139.4 (C), 136.2 (C), 133.8 (C), 131.2 (CH), 130.8 (C), 130.5 (C), 129.1 (CH), 127.4 (CH), 121.4 (CH), 115.4 (CH_2), 115.0 (CH), 112.0 (C), 111.8 (CH), 101.2 (CH), 74.7 (CH), 55.7 (CH_3), 30.5 (CH_2), 13.4 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{28}H_{25}ClNO_5^+$ 490.1416, found 490.1420.

4-Acryloylphenyl 2-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl)acetate (5.17b)



A stirred solution of 4-(1-hydroxyallyl)phenyl-2-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl)acetate (257 mg, 0.52 mmol) in DCM (5 mL) was cooled down to 0 °C (using ice-water bath) and Dess-Martin periodinane (267 mg, 0.63 mmol, 1.2 equiv.) was added. The resulting suspension was stirred at 0 °C for 1.5 h (as indicated by TLC) and then, the reaction mixture was filtered through a pad of silica eluting with EtOAc. The crude mixture was concentrated under reduced pressure and the residue was purified by column chromatography using hexane:EtOAc mixtures as eluent to afford the desired compound (197 mg, 0.40 mmol, 78% yield) as a yellow foam. This compound needs to be stored at -20 °C to avoid its vinylic polymerization.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.97 (d, *J* = 8.8 Hz, 2H), 7.68 (d, *J* = 8.6 Hz, 2H), 7.48 (d, *J* = 8.6 Hz, 2H), 7.19 (d, *J* = 8.8 Hz, 2H), 7.12 (dd, *J* = 17.1, 10.6 Hz, 1H), 7.05 (d, *J* = 2.5 Hz, 1H), 6.89 (d, *J* = 9.0 Hz, 1H), 6.70 (dd, *J* = 9.0, 2.5 Hz, 1H), 6.43 (dd, *J* = 17.1, 1.6 Hz, 1H), 5.93 (dd, *J* = 10.6, 1.6 Hz, 1H), 3.93 (s, 2H), 3.84 (s, 3H), 2.47 (s, 3H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 189.7 (C), 168.7 (C), 168.3 (C), 156.1 (C), 154.3 (C), 139.4 (C), 136.4 (C), 134.9 (C), 133.7 (C), 132.1 (CH), 131.2 (CH), 130.8 (C), 130.5 (CH_2), 130.4 (C), 130.3 (CH), 129.2 (CH), 121.7 (CH), 115.0 (CH), 111.8 (CH), 111.6 (C), 101.2 (CH), 55.7 (CH_3), 30.6 (CH_2), 13.4 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{28}H_{23}ClNO_5^+$ 488.1259, found 488.1254.

General Procedure 1 (GP-1) for the Photocatalytic Giese Reaction between 3,4-dihydroquinoxalin-2-ones 5.1 and Electron-Poor Alkenes

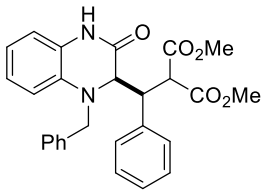
To an ovendried Schlenck tube containing a teflon-coated stir bar were added the photocatalyst $Ru(bpy)_3Cl_2$ (0.7 mg, 1 mol %), diphenyl phosphoric acid (2.5 mg, 10 mol %), the proper electron-poor alkene (0.1 mmol, 1 equiv.) [if it is liquid, it was added after the MeCN] and the proper 3,4-dihydroquinoxalin-2-one (**5.1**, 0.13 mmol, 1.3 equiv.). The reaction vessel was evacuated and backfilled with argon three times. After this, freshly degassed and dried MeCN (1 mL) was added via syringe and the reaction mixture was stirred while being irradiated at a distance of 3 cm of blue LEDs (see page 432 for fur-

ther details about the photochemical setup) under a positive pressure of argon. When electron-poor alkene disappears (as determined by TLC) the reaction mixture was filtered through a pad of silica eluting with EtOAc and ^{1}H-NMR spectrum was recorded to determine the diastereomeric ratio. Then, the crude mixture was purified by flash column chromatography to afford the corresponding Giese product.

General Procedure 2 (GP-2) for the Photocatalytic Giese Reaction between 3,4-dihydroquinoxalin-2-ones 5.1 and light Electron-Poor Alkenes

To an ovendried Schlenck tube containing a teflon-coated stir bar were added photocatalyst $Ru(bpy)_3Cl_2$ (0.7 mg, 1 mol %), diphenyl phosphoric acid (2.5 mg, 10 mol %), the proper electron-poor alkene (0.5 mmol, 5 equiv.) [if it is liquid, it was added after the MeCN] and the proper 3,4-dihydroquinoxalin-2-one (**5.1**, 0.1 mmol, 1 equiv.). The reaction vessel was evacuated and backfilled with argon three times. After this, freshly degassed and dried MeCN (1 mL) was added via syringe and the reaction mixture was stirred while being irradiated at a distance of 3 cm of blue LEDs (see page 432 for further details about the photochemical setup) under a positive pressure of argon. When electron-poor alkene disappears (as determined by TLC) the reaction mixture was filtered through a pad of silica eluting with EtOAc and ^{1}H-NMR spectrum was recorded to determine the diastereomeric ratio. Then, the crude mixture was purified by flash column chromatography to afford the corresponding Giese product.

Dimethyl 2-((1-benzyl-3-oxo-1,2,3,4-tetrahydroquinoxalin-2-yl)(phenyl)methyl) malonate (5.3aa)



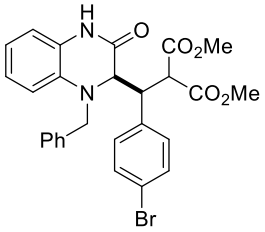
Using 4-benzyl-3,4-dihydroquinoxalin-2(1*H*)-one (**5.1a**, 31.0 mg, 0.13 mmol) and dimethyl 2-benzylidenemalonate (**5.2a**, 22.0 mg, 0.1 mmol), in accordance with GP-1, product **5.3aa** was obtained (42.2 mg, 0.92 mmol, 92% yield, colorless oil) as a mixture of diastereoisomers (dr 1:1) that can be separated by column chromatography using hexane-diethyl ether (from 5:5 to 2:8) mixtures.

Characterization data for **5.3aa'**: **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 8.01 (bs, 1H), 7.35 – 7.27 (m, 4H), 7.26 – 7.18 (m, 1H), 7.08 – 7.00 (m, 2H), 6.97 – 6.88 (m, 3H), 6.64 (ddd, *J* = 8.1, 7.5, 1.4 Hz, 1H), 6.39 (d, *J* = 7.9 Hz, 1H), 6.34 (td, *J* = 7.6, 1.1 Hz, 1H), 6.12 (d, *J* = 7.6 Hz, 1H), 4.88 (d, *J* = 16.1 Hz, 1H), 4.76 (d, *J* = 16.1 Hz, 1H), 4.52 (d, *J* = 12.0 Hz, 1H), 4.48 (d, *J* = 3.2 Hz, 1H), 3.96 (dd, *J* = 12.1, 3.1 Hz, 1H), 3.77 (s, 3H), 3.37 (s, 3H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 168.9 (C), 167.9 (C), 166.1 (C), 137.0 (C), 134.9 (C), 133.4 (C), 129.5 (CH), 128.6 (CH), 127.6 (CH), 127.5 (CH), 127.3 (CH), 127.0 (CH), 124.5 (C), 123.7 (CH), 117.8 (CH), 114.4 (CH), 112.4 (CH), 64.8 (CH), 53.9 (CH),

53.0 (CH_3), 52.4 (CH_3), 51.7 (CH_2), 47.1 (CH); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{27}H_{27}N_2O_5^+$ 459.1914, found 459.1910.

Characterization data for **5.3aa"**: **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 8.72 (bs, 1H), 7.31 – 7.23 (m, 3H), 7.23 – 7.07 (m, 5H), 6.98 – 6.89 (m, 3H), 6.81 (d, *J* = 4.1 Hz, 2H), 6.57 (d, *J* = 7.9 Hz, 1H), 4.19 (d, *J* = 9.6 Hz, 1H), 4.14 (d, *J* = 10.3 Hz, 1H), 4.03 (d, *J* = 15.4 Hz, 1H), 3.75 (t, *J* = 10.0 Hz, 1H), 3.68 (s, 3H), 3.35 (d, *J* = 15.4 Hz, 1H), 3.30 (s, 3H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 168.2 (C), 167.6 (C), 167.2 (C), 137.5 (C), 136.9 (C), 133.1 (C), 129.5 (CH), 128.5 (CH), 128.4 (CH), 127.8 (CH), 127.4 (CH), 127.4 (CH), 127.1 (C), 124.0 (CH), 119.9 (CH), 115.9 (CH), 115.5 (CH), 65.7 (CH), 55.0 (CH_2), 54.4 (CH), 52.8 (CH_3), 52.2 (CH_3), 45.4 (CH); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{27}H_{27}N_2O_5^+$ 459.1914, found 459.1909.

Dimethyl 2-((1-benzyl-3-oxo-1,2,3,4-tetrahydroquinoxalin-2-yl)(4-bromophenyl) methyl) malonate (5.3ab)



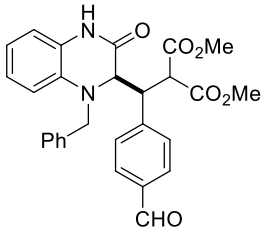
Using 4-benzyl-3,4-dihydroquinoxalin-2(1*H*)-one (**5.1a**, 31.0 mg, 0.13 mmol) and dimethyl 2-(4-bromobenzylidene)malonate (**5.2b**, 29.9 mg, 0.1 mmol), in accordance with GP-1, product **5.3ab** was obtained (51.7 mg, 0.096 mmol, 96% yield, colorless oil) as a mixture of diastereoisomers (dr 1:1) that can be separated by column chromatography using hexane-diethyl ether (from 5:5 to 2:8) mixtures.

Characterization data for **5.3ab'**: **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 8.30 (bs, 1H), 7.34 – 7.22 (m, 5H), 7.04 (d, *J* = 8.4 Hz, 2H), 6.89 (d, *J* = 8.5 Hz, 2H), 6.69 (td, *J* = 7.9, 1.4 Hz, 1H), 6.54 – 6.36 (m, 2H), 6.18 (dd, *J* = 7.7, 1.3 Hz, 1H), 4.85 (d, *J* = 16.0 Hz, 1H), 4.73 (d, *J* = 16.0 Hz, 1H), 4.47 (d, *J* = 6.2 Hz, 1H), 4.44 (d, *J* = 2.5 Hz, 1H), 3.92 (dd, *J* = 12.0, 3.2 Hz, 1H), 3.77 (s, 3H), 3.41 (s, 3H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 168.7 (C), 167.7 (C), 166.1 (C), 136.8 (C), 134.0 (C), 133.3 (C), 131.1 (CH), 130.5 (CH), 128.7 (CH), 127.4 (CH), 127.0 (CH), 124.5 (C), 124.0 (CH), 121.8 (C), 118.1 (CH), 114.7 (CH), 112.6 (CH), 64.6 (CH), 53.6 (CH), 53.1 (CH_3), 52.5 (CH_3), 51.8 (CH_2), 46.6 (CH); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{27}H_{26}BrN_2O_5^+$ 537.1020, found 537.1026.

Characterization data for **5.3ab"**: **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 8.89 (bs, 1H), 7.35 (t, *J* = 5.5 Hz, 2H), 7.27 – 7.15 (m, 3H), 7.10 – 6.90 (m, 5H), 6.83 (td, *J* = 7.5, 1.2 Hz, 1H), 6.77 (dd, *J* = 7.7, 1.6 Hz, 1H), 6.63 (d, *J* = 7.7 Hz, 1H), 4.24 – 4.06 (m, 3H), 3.77 – 3.67 (m, 1H), 3.65 (s, 3H), 3.51 (d, *J* = 15.3 Hz, 1H), 3.37 (s, 3H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 167.9 (C), 167.5 (C), 167.0 (C), 136.7 (C), 136.5 (C), 133.1 (C), 131.3 (CH), 131.2 (CH), 128.6 (CH), 127.5 (CH), 127.2 (C), 124.1 (CH), 121.8 (C), 120.3 (CH), 116.6 (CH), 115.7 (CH), 65.1 (CH), 56.0 (CH_2), 53.9 (CH), 52.9 (CH_3), 52.4 (CH_3), 45.3

(CH); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{27}H_{26}BrN_2O_5^+$ 537.1020, found 537.1021.

Dimethyl-2-((1-benzyl-3-oxo-1,2,3,4-tetrahydroquinoxalin-2-yl)(4-formylphenyl) methyl) malonate (5.3ac)

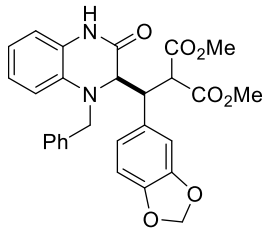


Using 4-benzyl-3,4-dihydroquinoxalin-2(1*H*)-one (**5.1a**, 31.0 mg, 0.1 mmol) and dimethyl 2-(4-formylbenzylidene)malonate (**5.2c**, 24.8 mg, 0.1 mmol, 1 equiv.), in accordance with GP-1, product **5.3ac** was obtained (30.6 mg, 0.063 mmol, 63% yield, colorless oil) as a mixture of diastereoisomers (dr 1:1) that can be separated by column chromatography using hexane-diethyl ether (from 5:5 to 2:8) mixtures.

Characterization data for **5.3ac'**: **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 9.78 (s, 1H), 7.70 (bs, 1H), 7.45 (d, *J* = 8.2 Hz, 2H), 7.33 – 7.26 (m, 5H), 7.21 (d, *J* = 8.3 Hz, 2H), 6.66 (td, *J* = 8.1, 1.4 Hz, 1H), 6.44 (d, *J* = 8.1 Hz, 1H), 6.32 (td, *J* = 7.6, 1.1 Hz, 1H), 6.04 (dd, *J* = 7.7, 1.3 Hz, 1H), 4.89 (d, *J* = 15.9 Hz, 1H), 4.76 (d, *J* = 16.0 Hz, 1H), 4.54 (d, *J* = 12.0 Hz, 1H), 4.50 (d, *J* = 3.2 Hz, 1H), 4.06 (dd, *J* = 12.0, 3.2 Hz, 1H), 3.78 (s, 3H), 3.39 (s, 3H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 191.7 (CH), 168.5 (C), 167.6 (C), 165.6 (C), 142.6 (C), 136.7 (C), 135.4 (C), 133.2 (C), 130.3 (CH), 128.7 (CH), 128.7 (CH), 127.4 (CH), 127.0 (CH), 124.4 (C), 124.1 (CH), 118.4 (CH), 114.5 (CH), 112.7 (CH), 64.7 (CH), 53.5 (CH), 53.1 (CH_3), 52.6 (CH_3), 51.9 (CH_2), 47.4 (CH); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{28}H_{27}N_2O_6^+$ 487.1864, found 487.1868.

Characterization data for **5.3ac"**: **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 9.99 (s, 1H), 8.10 (bs, 1H), 7.74 (d, *J* = 8.3 Hz, 2H), 7.29 (d, *J* = 8.2 Hz, 2H), 7.26 – 7.15 (m, 3H), 7.01 – 6.89 (m, 3H), 6.81 (td, *J* = 7.6, 1.2 Hz, 1H), 6.69 (dd, *J* = 7.8, 1.4 Hz, 1H), 6.65 (d, *J* = 7.8 Hz, 1H), 4.27 (d, *J* = 8.8 Hz, 1H), 4.21 – 4.10 (m, 2H), 3.85 (dd, *J* = 10.4, 8.9 Hz, 1H), 3.68 (s, 3H), 3.53 (d, *J* = 15.2 Hz, 1H), 3.34 (s, 3H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 191.8 (CH), 167.8 (C), 167.4 (C), 166.3 (C), 144.7 (C), 136.5 (C), 135.7 (C), 133.0 (C), 130.2 (CH), 129.4 (CH), 128.6 (CH), 127.7 (CH), 127.6 (CH), 127.3 (C), 124.2 (CH), 120.7 (CH), 117.1 (CH), 115.5 (CH), 65.1 (CH), 56.5 (CH_2), 53.8 (CH), 53.0 (CH_3), 52.5 (CH_3), 46.1 (CH); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{28}H_{27}N_2O_6^+$ 487.1864, found 487.1857.

Dimethyl-2-(benzo[d][1,3]dioxol-5-yl(1-benzyl-3-oxo-1,2,3,4-tetrahydroquinoxalin-2-yl)methyl)malonate (5.3ad)

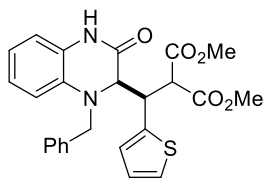


Using 4-benzyl-3,4-dihydroquinoxalin-2(1*H*)-one (**5.1a**, 31.0 mg, 0.1 mmol) and dimethyl 2-(benzo[d][1,3]dioxol-5-ylmethylene)malonate (**5.2d**, 26.4 mg, 0.1 mmol, 1 equiv.), in accordance with GP-1, product **5.3ad** was obtained (42.7 mg, 0.085 mmol, 85% yield, colorless oil) as a mixture of diastereoisomers (dr 1:1) that can be separated by column chromatography using hexane-diethyl ether (from 5:5 to 2:8) mixtures.

Characterization data for **5.3ad'**: **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 8.43 (bs, 1H), 7.43 – 7.26 (m, 4H), 7.26 – 7.12 (m, 1H), 6.68 (td, *J* = 7.7, 1.5 Hz, 1H), 6.59 – 6.47 (m, 2H), 6.47 – 6.36 (m, 3H), 6.28 (dd, *J* = 7.8, 1.4 Hz, 1H), 5.76 (d, *J* = 1.5 Hz, 1H), 5.68 (d, *J* = 1.5 Hz, 1H), 4.84 (d, *J* = 15.9 Hz, 0H), 4.71 (d, *J* = 16.1 Hz, 0H), 4.45 (d, *J* = 1.2 Hz, 0H), 4.42 (d, *J* = 9.7 Hz, 0H), 3.88 (dd, *J* = 12.0, 3.4 Hz, 0H), 3.76 (s, 3H), 3.45 (s, 3H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 168.8 (C), 167.9 (C), 166.5 (C), 146.9 (C), 146.8 (C), 136.9 (C), 133.6 (C), 128.6 (CH), 128.3 (C), 127.3 (CH), 127.0 (CH), 124.7 (C), 123.8 (CH), 117.8 (CH), 114.5 (CH), 112.5 (CH), 107.4 (CH), 100.7 (CH_2), 64.8 (CH), 53.9 (CH), 53.0 (CH_3), 52.5 (CH_3), 51.7 (CH_2), 46.7 (CH); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{28}H_{27}N_2O_7^+$ 503.1813, found 503.1818.

Characterization data for **5.3ad''**: **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 8.74 (bs, 1H), 7.25 – 7.12 (m, 3H), 7.06 – 6.97 (m, 2H), 6.97 – 6.88 (m, 1H), 6.87 – 6.75 (m, 2H), 6.70 (d, *J* = 8.0 Hz, 1H), 6.67 – 6.60 (m, 2H), 6.56 (dd, *J* = 8.0, 1.7 Hz, 1H), 5.97 (d, *J* = 1.5 Hz, 1H), 5.94 (d, *J* = 1.5 Hz, 1H), 4.26 – 4.12 (m, 2H), 4.05 (d, *J* = 10.3 Hz, 1H), 3.72 – 3.61 (m, 4H), 3.54 (d, *J* = 15.3 Hz, 1H), 3.40 (s, 3H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 168.2 (C), 167.6 (C), 167.3 (C), 147.5 (C), 147.1 (C), 137.0 (C), 133.2 (C), 131.0 (C), 128.6 (CH), 127.5 (CH), 127.5 (CH), 127.1 (C), 124.1 (CH), 123.0 (CH), 119.9 (CH), 116.1 (CH), 115.6 (CH), 109.8 (CH), 108.2 (CH), 101.1 (CH_2), 65.5 (CH), 55.4 (CH_2), 54.4 (CH), 52.9 (CH_3), 52.4 (CH_3), 45.3 (CH); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{28}H_{27}N_2O_7^+$ 503.1813, found 503.1815.

Dimethyl 2-((1-benzyl-3-oxo-1,2,3,4-tetrahydroquinoxalin-2-yl)(thiophen-2-yl) methyl) malonate (5.3ae)



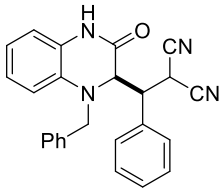
Using 4-benzyl-3,4-dihydroquinoxalin-2(1*H*)-one (**5.1a**, 31.0 mg, 0.13 mmol) and dimethyl 2-(thiophen-2-ylmethylene)malonate (**5.2e**, 22.6 mg, 0.1 mmol), in accordance with GP-1, product **5.3ae** was obtained (44.3 mg, 0.095 mmol, 95% yield, colorless oil) as a mixture of diastereoisomers (dr 1:1) that can be separated by column chromatog-

raphy using hexane-diethyl ether (from 5:5 to 2:8) mixtures.

Characterization data for **5.3ae'**: **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 8.29 (bs, 1H), 7.39 – 7.18 (m, 5H), 6.91 (dd, *J* = 5.1, 1.0 Hz, 1H), 6.79 (dd, *J* = 3.6, 0.7 Hz, 1H), 6.76 – 6.67 (m, 1H), 6.65 (dd, *J* = 5.1, 3.6 Hz, 1H), 6.49 – 6.42 (m, 2H), 6.33 (dd, *J* = 8.0, 1.5 Hz, 1H), 4.88 (d, *J* = 16.1 Hz, 1H), 4.71 (d, *J* = 16.1 Hz, 1H), 4.56 (d, *J* = 3.6 Hz, 1H), 4.46 (d, *J* = 11.7 Hz, 1H), 4.21 (dd, *J* = 11.7, 3.6 Hz, 1H), 3.76 (s, 3H), 3.46 (s, 3H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 168.5 (C), 167.6 (C), 165.9 (C), 137.0 (C), 136.7 (C), 133.1 (C), 128.6 (CH), 127.3 (CH), 127.1 (CH), 127.1 (CH), 126.4 (CH), 125.2 (CH), 124.6 (C), 123.8 (CH), 117.9 (CH), 114.6 (CH), 112.9 (CH), 64.8 (CH), 55.1 (CH), 53.0 (CH_3), 52.6 (CH_3), 51.8 (CH_2), 42.3 (CH); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{25}H_{25}N_2O_5S^+$ 465.1479, found 465.1456.

Characterization data for **5.3ae''**: **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 8.94 (bs, 1H), 7.31 – 7.15 (m, 4H), 7.05 – 6.98 (m, 2H), 6.98 – 6.90 (m, 2H), 6.87 (dd, *J* = 3.5, 1.0 Hz, 1H), 6.84 – 6.80 (m, 2H), 6.64 (d, *J* = 8.0 Hz, 1H), 4.39 (d, *J* = 9.4 Hz, 1H), 4.19 (d, *J* = 15.6 Hz, 1H), 4.05 (d, *J* = 8.6 Hz, 1H), 3.94 (t, *J* = 9.0 Hz, 1H), 3.65 (d, *J* = 15.5 Hz, 1H), 3.59 (s, 3H), 3.56 (d, *J* = 4.4 Hz, 3H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 167.9 (C), 167.6 (C), 166.6 (C), 139.2 (C), 137.1 (C), 132.45(C), 128.8 (CH), 128.5 (CH), 128.2 (CH), 127.3 (CH), 126.8 (CH), 126.7 (C), 125.9 (CH), 124.1 (CH), 119.8 (CH), 116.2 (CH), 115.6 (CH), 65.9 (CH), 54.8 (CH_2), 54.5 (CH), 52.7 (CH_3), 52.5 (CH_3), 40.7 (CH); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{25}H_{25}N_2O_5S^+$ 465.1479, found 465.1459.

2-((1-Benzyl-3-oxo-1,2,3,4-tetrahydroquinoxalin-2-yl)(phenyl)methyl)malononitrile (5.6aa)



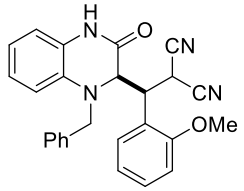
Using 4-benzyl-3,4-dihydroquinoxalin-2(1*H*)-one (**5.1a**, 31.0 mg, 0.13 mmol) and 2-benzylidenemalononitrile (**5.5a**, 15.4 mg, 0.1 mmol), in accordance with GP-1, product **5.6aa** was obtained (32.6 mg, 0.083 mmol, 83% yield, colorless oil) as a mixture of diastereoisomers (dr 1:1) that can be separated by column chromatography using hexane-diethyl ether (from 5:5 to 2:8) mixtures.

Characterization data for **5.6aa'**: **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 7.86 (bs, 1H), 7.39 – 7.27 (m, 5H), 7.22 – 7.09 (m, 5H), 6.95 – 6.88 (m, 1H), 6.84 (d, *J* = 6.9 Hz, 1H), 6.71 (td, *J* = 7.5, 1.5 Hz, 1H), 6.39 (dd, *J* = 7.8, 1.3 Hz, 1H), 4.72 (d, *J* = 14.8 Hz, 1H), 4.65 (d, *J* = 8.9 Hz, 1H), 4.48 (d, *J* = 6.8 Hz, 1H), 4.44 (d, *J* = 14.9 Hz, 1H), 3.37 (dd, *J* = 8.9, 6.6 Hz, 1H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 164.2 (C), 135.6 (C), 132.1 (C), 131.8 (C), 129.5 (CH), 129.1 (CH), 128.7 (CH), 128.6 (CH), 128.4 (CH), 128.2 (CH), 126.5 (C), 124.6 (CH), 121.4 (CH), 117.4 (CH), 115.4 (CH), 112.1 (C), 111.4 (C), 63.0 (CH), 56.5 (CH_2), 47.3 (CH), 26.4 (CH); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for

$C_{25}H_{21}N_4O^+$ 393.1710, found 393.1717.

Characterization data for **5.6aa''**: **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 8.88 (bs, 1H), 7.50 – 7.36 (m, 3H), 7.30 – 7.20 (m, 5H), 7.03 – 6.96 (m, 3H), 6.90 (td, *J* = 7.5, 1.3 Hz, 1H), 6.83 (d, *J* = 7.8 Hz, 1H), 6.62 (d, *J* = 7.9 Hz, 1H), 4.43 (d, *J* = 10.0 Hz, 1H), 4.31 (d, *J* = 5.8 Hz, 1H), 4.08 (d, *J* = 15.2 Hz, 1H), 3.59 (d, *J* = 15.2 Hz, 1H), 3.31 (dd, *J* = 10.0, 5.8 Hz, 1H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 165.4 (C), 136.0 (C), 133.9 (C), 132.3 (C), 129.7 (CH), 129.3 (CH), 128.8 (CH), 128.7 (CH), 127.9 (CH), 127.5 (CH), 126.5 (C), 124.9 (CH), 121.1 (CH), 116.9 (CH), 115.9 (CH), 111.6 (C), 111.5 (C), 63.6 (CH), 55.9 (CH_2), 45.6 (CH), 26.3 (CH); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{25}H_{21}N_4O^+$ 393.1710, found 393.1705.

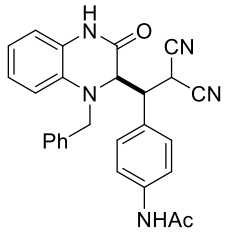
2-((1-Benzyl-3-oxo-1,2,3,4-tetrahydroquinoxalin-2-yl)(2-methoxyphenyl)methyl) malononitrile (5.6ab)



Using 4-benzyl-3,4-dihydroquinoxalin-2(1*H*)-one (**5.1a**, 31.0 mg, 0.13 mmol) and 2-(2-methoxybenzylidene)malononitrile (**5.5b**, 18.4 mg, 0.1 mmol), in accordance with GP-1, product **5.6ab** was obtained (21.5 mg, 0.051 mmol, 51% yield, yellowish oil) as a mixture of diastereoisomers (dr 1.5:1) that cannot be separated by column chromatography using hexane-diethyl ether (from 5:5 to 2:8) mixtures. Representative signals for the major and for the minor diastereoisomer have been labelled with one and two asterisks respectively.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.28 (bs, 1H**), 8.44 (bs, 1H*), 7.51 – 7.42 (m, 1H**), 7.40 – 7.28 (m, 6H), 7.24 – 6.76 (m, 14H), 6.70 (d, *J* = 7.9 Hz, 1H*), 6.67 – 6.50 (m, 3H), 6.37 (dd, *J* = 7.7, 1.1 Hz, 1H*), 4.73 (d, *J* = 14.8 Hz, 1H*), 4.68 – 4.59 (m, 1H*+1H**), 4.56 – 4.48 (m, 1H*+1H**), 4.43 (d, *J* = 14.7 Hz, 1H*), 4.12 – 3.99 (m, 1H**), 4.05 (d, *J* = 15.1 Hz, 1H*), 3.74 (s, 3H*), 3.70 (s, 3H**), 3.61 – 3.52 (m, 1H**), 3.45 (d, *J* = 15.1 Hz, 1H**); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 165.8 (C), 165.3 (C), 157.6 (C), 157.4 (C), 136.2 (C), 135.7 (C), 132.5 (C), 132.4 (C), 131.0 (CH), 130.5 (CH), 129.0 (CH), 128.6 (CH), 128.2 (CH), 128.1 (CH), 127.0 (CH), 127.5 (CH), 126.4 (C), 126.1 (C), 124.6 (CH), 124.0 (CH), 122.5 (C), 121.4 (CH), 120.7 (CH), 120.5 (CH), 120.4 (CH), 116.1 (CH), 115.7 (CH), 115.0 (CH), 112.8 (C), 112.6 (C), 111.9 (C), 111.7 (C), 111.3 (CH), 110.4 (CH), 62.5 (2 CH), 62.0 (CH), 61.9 (CH), 55.1 (2 CH3), 54.7 (2 CH2), 25.9 (CH), 24.9 (CH); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{26}H_{23}N_4O_2^+$ 423.1816, found 423.1904.

N-(4-(1-(1-Benzyl-3-oxo-1,2,3,4-tetrahydroquinoxalin-2-yl)-2,2-dicyanoethyl)phenyl) acetamide (5.6ac)

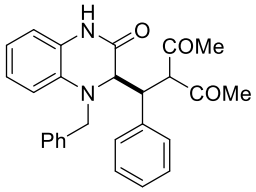


Using 4-benzyl-3,4-dihydroquinoxalin-2(1*H*)-one (**5.1a**, 31.0 mg, 0.13 mmol) and *N*-(4-(2,2-dicyanovinyl)phenyl)acetamide (**5.5c**, 21.1 mg, 0.1 mmol), in accordance with GP-1, product **5.6ac** was obtained (40.1 mg, 0.089 mmol, 89% yield, colorless oil) as a mixture of diasteromers that can be separated by column chromatography using hexane-diethyl ether (from 5:5 to 2:8) mixtures.

Characterization data for **5.6ac'**: **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 9.04 (bs, 1H), 7.56 (d, *J* = 8.6 Hz, 2H), 7.38 (bs, 1H), 7.30 – 7.15 (m, 4H), 7.09 – 6.94 (m, 3H), 6.94 – 6.81 (m, 2H), 6.74 – 6.56 (m, 1H), 4.40 (d, *J* = 9.9 Hz, 1H), 4.30 (d, *J* = 5.8 Hz, 1H), 4.14 (d, *J* = 15.4 Hz, 1H), 3.65 (d, *J* = 15.1 Hz, 1H), 3.29 (dd, *J* = 10.1, 5.8 Hz, 1H), 2.22 (s, 3H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 168.4 (C), 165.5 (C), 139.2 (C), 136.0 (C), 132.2 (C), 129.4 (CH), 129.2 (C), 128.7 (CH), 127.9 (CH), 127.6 (CH), 126.5 (C), 124.9 (CH), 121.1 (CH), 120.0 (CH), 117.0 (CH), 116.0 (CH), 111.6 (C), 111.5 (C), 63.5 (CH), 56.1 (CH_2), 45.1 (CH), 26.3 (CH_3), 24.7 (CH); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{27}H_{24}N_5O_2^+$ 450.1925, found 450.1930.

Characterization data for **5.6ac''**: **^{1}H-NMR (300 MHz, acetone-d_6)** δ 9.48 (bs, 1H), 9.01 (bs, 1H), 7.48 – 7.31 (m, 4H), 7.31 – 7.16 (m, 3H), 7.11 (d, *J* = 8.6 Hz, 2H), 6.76 – 6.61 (m, 2H), 6.56 – 6.37 (m, 2H), 5.06 (d, *J* = 10.5 Hz, 1H), 4.93 (d, *J* = 15.5 Hz, 1H), 4.59 (d, *J* = 15.5 Hz, 1H), 4.49 (d, *J* = 5.3 Hz, 1H), 3.82 (dd, *J* = 10.5, 5.3 Hz, 1H), 1.96 (s, 3H); **^{13}C{^{1}H}-NMR (75 MHz, acetone-d_6)** δ 168.8 (C), 164.7 (C), 140.8 (C), 138.0 (C), 133.4 (C), 130.4 (CH), 129.6 (CH), 128.7 (CH), 128.4 (CH), 128.4 (C), 127.4 (C), 124.1 (CH), 120.0 (CH), 119.2 (CH), 115.7 (CH), 115.6 (CH), 114.1 (C), 113.6 (C), 64.3 (CH), 54.3 (CH_2), 46.9 (CH), 27.6 (CH_3), 24.2 (CH); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{27}H_{24}N_5O_2^+$ 450.1925, found 450.1927.

3-((1-Benzyl-3-oxo-1,2,3,4-tetrahydroquinoxalin-2-yl)(phenyl)methyl)pentane-2,4-dione (5.8aa)

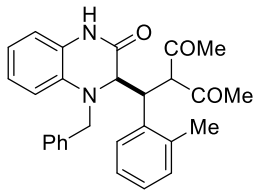


Using 4-benzyl-3,4-dihydroquinoxalin-2(1*H*)-one (**5.1a**, 31.0 mg, 0.13 mmol) and 3-benzylidenepentane-2,4-dione (**5.7a**, 18.8 mg, 0.1 mmol), in accordance with GP-1, product **5.8aa** was obtained (37.7 mg, 0.088 mmol, 88% yield, pale yellow oil) as a mixture of diastereoisomers (dr 1:1) that cannot be separated by column chromatography using hexane-diethyl ether (from 5:5 to 2:8) mixtures.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.91 (bs, 1H), 8.62 (bs, 1H), 7.44 – 7.27 (m, 7H),

7.24 – 6.81 (m, 16H), 6.73 – 6.57 (m, 2H), 6.47 – 6.29 (m, 2H), 6.16 (dd, *J* = 7.7, 1.4 Hz, 1H), 4.97 (d, *J* = 12.1 Hz, 1H), 4.88 (d, *J* = 16.0 Hz, 1H), 4.67 (d, *J* = 16.0 Hz, 1H), 4.60 (d, *J* = 9.7 Hz, 1H), 4.18 (t, *J* = 4.7 Hz, 1H), 4.17 – 3.82 (m, 4H), 3.11 (d, *J* = 15.3 Hz, 1H), 2.41 (s, 3H), 2.25 (s, 3H), 1.87 (s, 3H), 1.61 (s, 3H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 203.0 (C), 201.9 (C), 201.7 (C), 201.6 (C), 167.3 (C), 166.0 (C), 138.3 (C), 136.8 (C), 136.7 (C), 135.1 (C), 133.3 (C), 133.1 (C), 129.5 (CH), 129.0 (CH), 128.6 (CH), 128.5 (CH), 128.0 (CH), 127.9 (CH), 127.7 (CH), 127.4 (CH), 127.4 (CH), 127.3 (CH), 127.0 (CH), 127.0 (C), 124.4 (C), 124.1 (CH), 123.8 (CH), 119.9 (CH), 117.8 (CH), 115.7 (CH), 115.5 (CH), 114.5 (CH), 112.3 (CH), 72.9 (CH), 71.2 (CH), 66.5 (CH), 64.6 (CH), 54.4 (CH_2), 51.9 (CH_2), 46.7 (CH), 44.1 (CH), 31.4 (CH_3), 30.4 (CH_3), 28.6 (CH_3), 27.6 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{27}H_{27}N_2O_3^+$ 427.2016, found 427.2011.

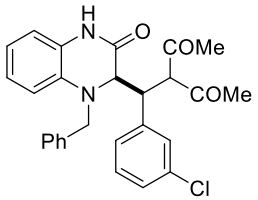
3-((1-Benzyl-3-oxo-1,2,3,4-tetrahydroquinoxalin-2-yl)(*o*-tolyl)methyl)pentane-2,4-dione (5.8ab)



Using 4-benzyl-3,4-dihydroquinoxalin-2(1*H*)-one (**5.1a**, 31.0 mg, 0.13 mmol) and 3-(2-methylbenzylidene)pentane-2,4-dione (**5.7b**, 20.2 mg, 0.1 mmol), in accordance with GP-1, product **5.8ab** was obtained (43.8 mg, 0.099 mmol, 99% yield, colorless oil) as a mixture of diastereoisomers (dr 1.3:1) that cannot be separated by column chromatography using hexane-diethyl ether (from 5:5 to 2:8) mixtures. Representative signals for the major and for the minor diastereoisomer have been labelled with one and two asterisks respectively.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.94 (bs, 1H**), 8.58 (bs, 1H*), 7.34 – 7.10 (m, 14H), 7.02 – 6.78 (m, 6H), 6.74 – 6.65 (m, 2H*), 6.62 – 6.52 (m, 1H*+1H**), 6.37 (td, *J* = 7.6, 1.1 Hz, 1H*), 6.18 (dd, *J* = 7.7, 1.3 Hz, 1H*), 4.97 (d, *J* = 11.8 Hz, 1H*), 4.88 (d, *J* = 16.1 Hz, 1H*), 4.67 (d, *J* = 10.4 Hz, 1H**), 4.54 (d, *J* = 16.1 Hz, 1H*), 4.39 – 4.17 (m, 1H*+1H**), 4.10 – 3.93 (m, 1H*+2H**), 3.23 (d, *J* = 15.5 Hz, 1H**), 2.37 (s, 1H*), 2.28 (s, 3H*), 2.24 (s, 3H**), 2.04 (s, 3H**), 1.84 (s, 3H*), 1.63 (s, 3H**); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 202.8 (C), 201.6 (C), 201.4 (C), 201.1 (C), 166.8 (C), 166.3 (C), 137.8 (C), 137.1 (C), 136.9 (C), 136.8 (C), 136.7 (C), 133.8 (C), 133.3 (C), 132.6 (C), 131.3 (CH), 130.1 (CH), 128.6 (CH), 128.4 (CH), 128.3 (CH), 127.5 (CH), 127.5 (CH), 127.4 (CH), 127.3 (CH), 127.3 (CH), 127.2 (CH), 127.1 (CH), 126.5 (CH), 125.6 (CH), 124.8 (C), 124.1 (CH), 123.7 (CH), 119.6 (CH), 118.2 (CH), 115.8 (CH), 115.1 (CH), 114.5 (CH), 111.9 (CH), 72.8 (CH), 71.7 (CH), 67.4 (CH), 64.5 (CH), 54.2 (CH_2), 52.1 (CH_2), 41.7 (CH), 39.1 (CH), 31.4 (CH_3), 30.4 (CH_3), 29.3 (CH_3), 28.6 (CH_3), 19.8 (CH_3), 19.6 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{28}H_{29}N_2O_3^+$ 441.2173, found 441.2179.

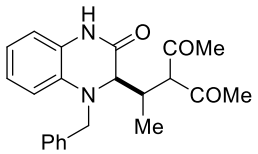
3-((1-Benzyl-3-oxo-1,2,3,4-tetrahydroquinoxalin-2-yl)(3-chlorophenyl)methyl) pentane-2,4-dione (5.8ac)



Using 4-benzyl-3,4-dihydroquinoxalin-2(1*H*)-one (**5.1a**, 31.0 mg, 0.13 mmol) and 3-(3-chlorobenzylidene)pentane-2,4-dione (**5.7c**, 22.2 mg, 0.1 mmol), in accordance with GP-1, product **5.8ac** was obtained (42.8 mg, 0.093 mmol, 93% yield, colorless oil) as a mixture of diastereoisomers (dr 1:1) that cannot be separated by column chromatography using hexane-diethyl ether (from 5:5 to 2:8) mixtures.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.78 (bs, 1H), 8.59 (bs, 1H), 7.40 – 7.27 (m, 6H), 7.25 – 7.15 (m, 4H), 7.10 – 6.83 (m, 11H), 6.74 – 6.62 (m, 2H), 6.48 – 6.30 (m, 2H), 6.22 (dd, *J* = 7.7, 1.4 Hz, 1H), 4.98 – 4.82 (m, 2H), 4.64 (d, *J* = 15.9 Hz, 1H), 4.55 (d, *J* = 9.9 Hz, 1H), 4.17 (d, *J* = 3.7 Hz, 1H), 4.14 – 4.00 (m, 2H), 3.96 – 3.79 (m, 2H), 3.18 (d, *J* = 15.0 Hz, 1H), 2.41 (s, 3H), 2.23 (s, 3H), 1.92 (s, 3H), 1.66 (s, 3H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 202.5 (C), 201.4 (C), 201.2 (C), 201.0 (C), 166.7 (C), 165.8 (C), 140.5 (C), 137.4 (C), 136.6 (C), 136.3 (C), 134.8 (C), 133.8 (C), 133.3 (C), 133.1 (C), 130.2 (CH), 129.1 (CH), 128.7 (CH), 128.6 (CH), 128.2 (CH), 127.9 (CH), 127.6 (CH), 127.4 (CH), 127.2 (C), 127.1 (CH), 124.3 (CH), 124.3 (C), 124.2 (CH), 120.4 (CH), 118.2 (CH), 116.1 (CH), 115.8 (CH), 114.6 (CH), 112.4 (CH), 72.4 (CH), 70.7 (CH), 65.7 (CH), 64.3 (CH), 55.1 (CH_2), 51.9 (CH_2), 46.4 (CH), 44.0 (CH), 31.4 (CH_3), 30.3 (CH_3), 28.9 (CH_3), 28.0 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{27}H_{26}ClN_2O_3^+$ 461.1626, found 461.1616.

3-(1-(1-Benzyl-3-oxo-1,2,3,4-tetrahydroquinoxalin-2-yl)ethyl)pentane-2,4-dione (5.8ad)

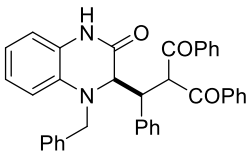


Using 4-benzyl-3,4-dihydroquinoxalin-2(1*H*)-one (**5.1a**, 31.0 mg, 0.13 mmol) and 3-ethylidenepentane-2,4-dione (**5.7d**, 12.6 mg, 0.1 mmol), in accordance with GP-1, product **5.8ad** was obtained (31.2 mg, 0.088 mmol, 88% yield, brown oil) as a mixture of diastereoisomers (dr 1.4:1) that cannot be separated by column chromatography using hexane-diethyl ether (from 5:5 to 2:8) mixtures. Representative signals for the major and for the minor diastereoisomer have been labelled with one and two asterisks respectively.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.82 (bs, 1H*), 8.72 (bs, 1H**), 7.38 – 7.14 (m, 4H*+7H**), 7.02 – 6.91 (m, 1H*), 6.91 – 6.73 (m, 1H*+2H**), 6.70 – 6.64 (m, 2H*), 6.61 (d, *J* = 8.0 Hz, 1H*), 4.76 (d, *J* = 15.4 Hz, 1H**), 4.69 (d, *J* = 16.3 Hz, 1H*), 4.51 (d, *J* = 16.3 Hz, 1H*), 4.31 (d, *J* = 15.4 Hz, 1H**), 4.19 (d, *J* = 11.1 Hz, 1H*), 4.07 (d, *J* = 3.8 Hz, 1H*), 3.93 – 3.78 (m, 2H**), 2.85 (ddd, *J* = 10.9, 7.0, 3.9 Hz, 1H*), 2.72 (q, *J*

= 7.7 Hz, 1H**), 2.28 (s, 3H*), 2.14 (s, 3H*), 2.11 (s, 3H**), 1.96 (s, 3H**), 0.96 (d, *J* = 7.1 Hz, 3H**), 0.78 (d, *J* = 7.0 Hz, 3H*); **$^{13}C\{^1H\}$-NMR (75 MHz, $CDCl_3$)** δ 203.9 (C), 203.5 (C), 203.5 (C), 202.9 (C), 166.8 (C), 165.6 (C), 137.2 (C), 136.8 (C), 134.0 (C), 133.1 (C), 128.7 (CH), 128.7 (CH), 127.6 (CH), 127.6 (CH), 127.4 (CH), 126.9 (CH), 126.8 (C), 124.9 (C), 124.5 (CH), 124.5 (CH), 120.0 (CH), 118.2 (CH), 116.1 (CH), 115.5 (CH), 115.1 (CH), 112.7 (CH), 72.6 (CH), 69.7 (CH), 65.4 (CH), 63.8 (CH), 56.5 (CH_2), 52.6 (CH_2), 36.9 (CH), 35.0 (CH), 31.4 (CH_3), 30.3 (CH_3), 29.6 (CH_3), 29.3 (CH_3), 14.1 (CH_3), 12.2 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{22}H_{25}N_2O_3^+$ 365.1860, found 365.1873.

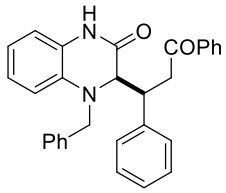
2-((1-Benzyl-3-oxo-1,2,3,4-tetrahydroquinoxalin-2-yl)(phenyl)methyl)-1,3-diphenyl propane-1,3-dione (5.8ae)



Using 4-benzyl-3,4-dihydroquinoxalin-2(1*H*)-one (**5.1a**, 31.0 mg, 0.13 mmol) and 2-benzylidene-1,3-diphenylpropane-1,3-dione (**5.7e**, 31.2 mg, 0.1 mmol), in accordance with GP-1, product **5.8ae** was obtained (28.8 mg, 0.052 mmol, 52% yield, colorless oil) as a mixture of diastereoisomers (dr 3:1) that cannot be separated by column chromatography using hexane-diethyl ether (from 5:5 to 2:8) mixtures. Representative signals for the major and for the minor diastereoisomer have been labelled with one and two asterisks respectively.

^1H-NMR (300 MHz, $CDCl_3$) δ 8.90 (bs, 1H*), 8.87 (bs, 1H**), 8.29 – 8.20 (m, 2H*), 8.02 – 7.95 (m, 2H**), 7.75 (dd, *J* = 8.3, 1.1 Hz, 2H*), 7.65 – 7.58 (m, 2H**), 7.58 – 7.50 (m, 1H*), 7.50 – 7.41 (m, 2H*), 7.40 – 6.69 (m, 13H*+18H**), 6.65 (td, *J* = 8.2, 1.4 Hz, 1H*), 6.60 (d, *J* = 7.8 Hz, 1H**), 6.38 (d, *J* = 8.0 Hz, 1H*), 6.32 (td, *J* = 7.5, 1.1 Hz, 1H*), 6.14 (dd, *J* = 7.7, 1.4 Hz, 1H*), 6.08 (d, *J* = 9.8 Hz, 1H**), 4.93 (d, *J* = 16.2 Hz, 1H*), 4.77 (d, *J* = 16.2 Hz, 1H*), 4.62 (dd, *J* = 11.6, 3.0 Hz, 1H*), 4.41 – 4.34 (m, 1H*+1H**), 4.29 (d, *J* = 9.8 Hz, 1H**), 4.01 (d, *J* = 15.4 Hz, 1H**), 3.28 (d, *J* = 15.4 Hz, 1H**); **$^{13}C\{^1H\}$-NMR (75 MHz, $CDCl_3$)** δ 195.1 (C*), 194.3 (C**), 193.5 (C**), 193.4 (C*), 167.5 (C**), 167.4 (C*), 138.0 (C), 137.5 (C), 137.1 (C), 137.0 (C), 137.0 (C), 137.0 (C), 135.3 (C), 133.6 (CH), 133.5 (C), 133.3 (C), 133.1 (CH), 133.0 (CH), 132.8 (CH), 130.2 (C), 129.7 (CH), 129.2 (CH), 128.8 (CH), 128.8 (CH), 128.7 (CH), 128.7 (CH), 128.6 (CH), 128.4 (CH), 128.4 (CH), 128.3 (CH), 128.2 (CH), 127.6 (CH), 127.4 (CH), 127.3 (CH), 127.3 (CH), 127.2 (C), 127.2 (CH), 127.0 (CH), 124.4 (C), 124.0 (CH), 123.9 (CH), 119.8 (CH), 117.6 (CH), 115.7 (CH), 115.5 (CH), 114.4 (CH), 112.1 (CH), 66.5 (CH**), 65.1 (CH*), 61.5 (CH**), 59.4 (CH*), 54.6 (CH_2**), 51.5 (CH_2*), 49.2 (CH*), 46.1 (CH**); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{37}H_{31}N_2O_3^+$ 551.2329, found 551.2318.

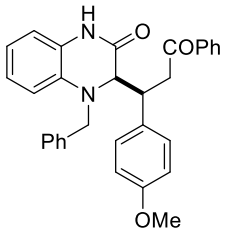
4-Benzyl-3-(3-oxo-1,3-diphenylpropyl)-3,4-dihydroquinoxalin-2(1*H*)-one (5.10aa)



Using 4-benzyl-3,4-dihydroquinoxalin-2(1*H*)-one (**5.1a**, 31.0 mg, 0.13 mmol) and *trans*-chalcone (**5.9a**, 20.8 mg, 0.1 mmol), in accordance with GP-1, product **5.10aa** was obtained (34.0 mg, 0.076 mmol, 76% yield, colorless oil) as a mixture of diastereoisomers (dr 1.5:1) that cannot be separated by column chromatography using hexane-diethyl ether (from 5:5 to 2:8) mixtures. Representative signals for the major and for the minor diastereoisomer have been labelled with one and two asterisks respectively.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.14 (bs, 1H*), 8.63 (bs, 1H**), 7.99 – 7.94 (m, 2H**), 7.87 – 7.80 (m, 2H*), 7.60 – 7.51 (m, 1H**), 7.50 – 7.40 (m, 2H*+1H**), 7.37 – 7.27 (m, 8H), 7.25 – 7.08 (m, 9H), 7.03 – 6.92 (m, 6H), 6.89 – 6.79 (m, 2H*), 6.78 – 6.69 (m, 1H**), 6.60 (d, J = 7.9 Hz, 1H*), 6.53 (d, J = 7.9 Hz, 1H**), 6.41 (td, J = 7.6, 1.2 Hz, 1H**), 6.21 (dd, J = 7.7, 1.4 Hz, 1H**), 4.87 (d, J = 15.7 Hz, 1H**), 4.73 (d, J = 15.8 Hz, 1H**), 4.34 (d, J = 3.3 Hz, 1H**), 4.09 – 3.93 (m, 2H*+2H**), 3.71 (ddd, J = 10.4, 8.7, 4.9 Hz, 1H*), 3.65 – 3.45 (m, 2H*), 3.40 – 3.25 (m, 1H*+1H**); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 198.5 (C), 197.3 (C), 166.9 (C), 166.8 (C), 141.4 (C), 138.8 (C), 137.0 (C), 137.0 (C), 136.9 (C), 136.9 (C), 133.8 (C), 133.5 (C), 133.1 (CH), 132.9 (CH), 129.0 (CH), 128.7 (CH), 128.6 (CH), 128.6 (CH), 128.5 (CH), 128.4 (CH), 128.1 (CH), 127.9 (CH), 127.6 (CH), 127.6 (CH), 127.3 (CH), 127.3 (CH), 127.3 (CH), 127.0 (CH), 126.7 (C), 125.2 (C), 124.2 (CH), 123.8 (CH), 119.4 (CH), 118.1 (CH), 115.7 (CH), 115.1 (CH), 114.6 (CH), 112.8 (CH), 66.4 (CH), 66.2 (CH), 54.2 (CH_2), 52.7 (CH_2), 42.7 (CH), 41.1 (CH_2), 41.0 (CH_2), 40.4 (CH); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{30}H_{27}N_2O_2^+$ 447.2067, found 447.2061.

4-Benzyl-3-(1-(4-methoxyphenyl)-3-oxo-3-phenylpropyl)-3,4-dihydroquinoxalin-2(1*H*)-one (5.10ab)

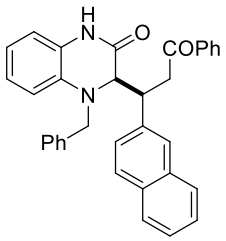


Using 4-benzyl-3,4-dihydroquinoxalin-2(1*H*)-one (**5.1a**, 31.0 mg, 0.13 mmol) and (*E*)-3-(4-methoxyphenyl)-1-phenylprop-2-en-1-one (**5.9b**, 23.8 mg, 0.1 mmol), in accordance with GP-1, product **5.10ab** was obtained (43.6 mg, 0.091 mmol, 91% yield, yellowish oil) as a mixture of diastereoisomers (dr 1.1:1) that cannot be separated by column chromatography using hexane-diethyl ether (from 5:5 to 2:8) mixtures.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.26 (bs, 1H), 8.76 (bs, 1H), 8.02 – 7.89 (m, 2H), 7.89 – 7.79 (m, 2H), 7.64 – 6.69 (m, 26H), 6.61 (d, J = 7.6 Hz, 1H), 6.54 (td, J = 4.3, 1.4 Hz, 3H), 6.44 (td, J = 7.6, 1.2 Hz, 1H), 6.26 (dd, J = 7.7, 1.4 Hz, 1H), 4.84 (d, J =

15.7 Hz, 1H), 4.70 (d, *J* = 15.7 Hz, 1H), 4.28 (d, *J* = 3.6 Hz, 1H), 4.09 (d, *J* = 15.3 Hz, 1H), 4.01 (dd, *J* = 10.5, 0.9 Hz, 1H), 3.93 (dd, *J* = 7.9, 4.3 Hz, 2H), 3.82 (s, 3H), 3.77 – 3.61 (m, 1H), 3.62 (s, 3H), 3.57 – 3.21 (m, 4H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 198.6 (C), 197.5 (C), 167.1 (C), 167.0 (C), 158.8 (C), 158.5 (C), 137.1 (C), 137.0 (C), 136.9 (C), 133.9 (C), 133.6 (C), 133.2 (C), 133.1 (CH), 132.9 (CH), 130.7 (C), 129.9 (CH), 129.5 (CH), 128.6 (CH), 128.5 (CH), 128.5 (CH), 128.4 (CH), 128.1 (CH), 127.9 (CH), 127.6 (CH), 127.3 (CH), 127.3 (CH), 126.7 (C), 125.3 (C), 124.1 (CH), 123.8 (CH), 119.3 (CH), 118.2 (CH), 115.8 (CH), 114.9 (CH), 114.7 (CH), 114.0 (CH), 113.2 (CH), 112.9 (CH), 66.5 (CH), 66.3 (CH), 55.3 (CH_3), 55.1 (CH_3), 54.2 (CH_2), 52.9 (CH_2), 41.9 (CH), 41.2 (CH_2), 41.1 (CH_2), 39.7 (CH); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{31}H_{29}N_2O_3^+$ 477.2173, found 477.2175.

4-Benzyl-3-(1-(naphthalen-2-yl)-3-oxo-3-phenylpropyl)-3,4-dihydroquinoxalin-2 (1*H*)-one (5.10ac)

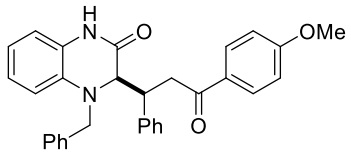


Using 4-benzyl-3,4-dihydroquinoxalin-2(1*H*)-one (**5.1a**, 31 mg, 0.13 mmol) and (*E*)-3-(naphthalen-2-yl)-1-phenylprop-2-en-1-one (**5.9c**, 25.8 mg, 0.1 mmol), in accordance with GP-1, product **5.10ac** was obtained (41.1 mg, 0.083 mmol, 83% yield, yellow oil) as a mixture of diastereoisomers (dr 1.1:1) that cannot be separated by column chromatography using hexane-diethyl ether (from 5:5 to 2:8) mixtures. Representative signals for the major and for the minor diastereoisomer have been labelled with one and two asterisks respectively.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.30 (bs, 1H*), 8.74 (bs, 1H**), 8.49 (s, 1H**), 8.40 (s, 1H*), 8.01 (dd, *J* = 8.7, 1.7 Hz, 1H**), 7.95 (d, *J* = 7.8 Hz, 1H*), 7.91 – 7.83 (m, 3H), 7.78 (d, *J* = 8.0 Hz, 1H*), 7.73 (d, *J* = 8.7 Hz, 1H*), 7.68 – 7.45 (m, 4H), 7.38 – 7.28 (m, 7H), 7.28 – 7.12 (m, 8H), 7.07 – 6.67 (m, 10H), 6.61 (d, *J* = 7.9 Hz, 1H*), 6.56 (d, *J* = 7.9 Hz, 1H**), 6.40 (td, *J* = 7.6, 1.1 Hz, 1H**), 6.23 (dd, *J* = 7.7, 1.4 Hz, 1H**), 4.88 (d, *J* = 15.7 Hz, 1H**), 4.74 (d, *J* = 15.8 Hz, 1H**), 4.39 (d, *J* = 3.5 Hz, 1H**), 4.21 – 3.99 (m, 3H*+1H**), 3.92 – 3.56 (m, 2H*+1H**), 3.46 (dd, *J* = 15.9, 3.6 Hz, 1H**), 3.30 (d, *J* = 15.2 Hz, 1H*); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 198.5 (C**), 197.3 (C*), 167.1 (C*), 166.9 (C**), 141.5 (C), 138.9 (C), 137.1 (C), 137.0 (C), 135.7 (C), 135.5 (C), 134.3 (C), 134.3 (C), 133.9 (C), 133.6 (C), 132.5 (C), 132.5 (C), 130.0 (CH), 129.7 (CH), 129.7 (CH), 129.6 (CH), 129.1 (CH), 128.9 (CH), 128.8 (CH), 128.7 (CH), 128.7 (CH), 128.5 (CH), 128.4 (CH), 128.3 (CH), 128.3, (CH) 127.8 (CH), 127.7 (CH), 127.7 (CH), 127.7 (CH), 127.6 (CH), 127.4 (CH), 127.4 (CH), 127.1 (CH), 126.8 (CH), 126.7 (CH), 125.4 (C), 124.2 (CH), 123.9 (CH), 123.9 (CH), 123.7 (CH), 119.5 (CH), 118.3 (CH), 115.8

(CH), 115.1 (CH), 114.8 (CH), 112.9 (CH), 66.5 (CH*), 66.4 (CH**), 54.2 (CH_2*), 52.9 (CH_2**), 42.9 (CH*), 41.2 (CH_2**), 41.1 (CH_2*), 40.6 (CH**); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{34}H_{29}N_2O_2^+$ 497.2224, found 497.2231.

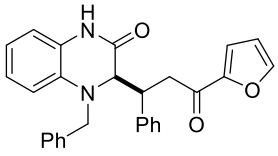
4-Benzyl-3-(3-(4-methoxyphenyl)-3-oxo-1-phenylpropyl)-3,4-dihydroquinoxalin-2(1*H*)-one (5.10ad)



Using 4-benzyl-3,4-dihydroquinoxalin-2(1*H*)-one (**5.1a**, 31.0 mg, 0.13 mmol) and (*E*)-1-(4-methoxyphenyl)-3-phenylprop-2-en-1-one (**5.9d**, 23.8 mg, 0.1 mmol), in accordance with GP-1, product **5.10ad** was obtained (38.8 mg, 0.081 mmol, 81% yield, yellowish oil) as a mixture of diastereoisomers (dr 1.1:1) that cannot be separated by column chromatography using hexane-diethyl ether (from 5:5 to 2:8) mixtures. Representative signals for the major and for the minor diastereoisomer have been labelled with one and two asterisks respectively.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.38 (bs, 1H*), 8.76 (bs, 1H**), 8.05 – 7.87 (m, 2H**), 7.86 – 7.70 (m, 2H*), 7.42 – 7.26 (m, 6H), 7.25 – 7.06 (m, 9H), 7.06 – 6.63 (m, 13H), 6.60 (d, *J* = 8.2 Hz, 1H*), 6.51 (d, *J* = 7.9 Hz, 1H**), 6.47 – 6.30 (m, 1H**), 6.20 (dd, *J* = 7.7, 1.3 Hz, 1H**), 4.86 (d, *J* = 15.8 Hz, 1H**), 4.73 (d, *J* = 15.8 Hz, 1H**), 4.34 (d, *J* = 3.3 Hz, 1H**), 4.12 – 3.87 (m, 4H), 3.85 (s, 3H**), 3.74 (s, 3H*), 3.71 – 3.11 (m, 5H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 197.0 (C), 195.7 (C), 167.0 (C), 166.9 (C), 163.5 (C), 163.3 (C), 141.6 (C), 138.9 (C), 137.1 (C), 137.0 (C), 133.8 (C), 133.5 (C), 130.4 (CH), 130.1 (CH), 130.1 (C), 129.9 (C), 129.0 (CH), 128.6 (CH), 128.6 (CH), 128.4 (CH), 127.6 (CH), 127.6 (CH), 127.3 (CH), 127.21 (CH), 127.0 (CH), 126.8 (C), 125.2 (C), 124.1 (CH), 123.7 (CH), 119.4 (CH), 118.0 (CH), 115.8 (CH), 115.0 (CH), 114.6 (CH), 113.7 (CH), 113.5 (CH), 112.6 (CH), 66.6 (CH), 66.3 (CH), 55.4 (CH_3), 55.3 (CH_3), 54.1 (CH_2), 52.6 (CH_2), 42.9 (CH), 40.6 (CH_2), 40.5 (CH), 40.5 (CH_2); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{31}H_{29}N_2O_3^+$ 477.2173, found 477.2181.

4-Benzyl-3-(3-(furan-2-yl)-3-oxo-1-phenylpropyl)-3,4-dihydroquinoxalin-2(1*H*)-one (5.10ae)

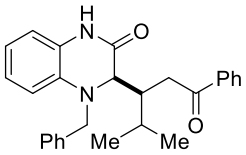


Using 4-benzyl-3,4-dihydroquinoxalin-2(1*H*)-one (**5.1a**, 31.0 mg, 0.13 mmol) and (*E*)-1-(furan-2-yl)-3-phenylprop-2-en-1-one (**5.9e**, 19.8 mg, 0.1 mmol), in accordance with GP-1, product **5.10ae** was obtained (39.6 mg, 0.091 mmol, 91% yield, colorless oil) as a mixture of diastereoisomers (dr 1:1) that can be separated by column chromatography using hexane-diethyl ether (from 5:5 to 2:8) mixtures.

Characterization data for **5.10ae'**: **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 8.08 (bs, 1H), 7.55 (dd, *J* = 1.7, 0.7 Hz, 1H), 7.28 (d, *J* = 4.3 Hz, 4H), 7.29 – 7.17 (m, 2H), 7.13 – 7.04 (m, 2H), 7.04 – 6.94 (m, 3H), 6.79 – 6.68 (m, 1H), 6.53 (d, *J* = 8.2 Hz, 1H), 6.50 (dd, *J* = 3.6, 1.7 Hz, 1H), 6.42 (td, *J* = 7.6, 1.2 Hz, 1H), 6.19 (dd, *J* = 7.7, 1.4 Hz, 1H), 4.84 (d, *J* = 15.7 Hz, 1H), 4.65 (d, *J* = 15.7 Hz, 1H), 4.28 (d, *J* = 3.8 Hz, 1H), 3.94 (ddd, *J* = 9.1, 5.5, 3.9 Hz, 1H), 3.76 (dd, *J* = 17.4, 8.7 Hz, 1H), 3.20 (dd, *J* = 17.3, 5.6 Hz, 1H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 187.4 (C), 166.3 (C), 152.6 (C), 146.5 (CH), 138.5 (C), 136.9 (C), 133.7 (C), 129.0 (CH), 128.6 (CH), 127.7 (CH), 127.4 (CH), 127.3 (CH), 127.1 (CH), 125.2 (C), 123.81 (CH), 118.2 (CH), 117.6 (CH), 114.5 (CH), 112.9 (CH), 112.2 (CH), 66.2 (CH), 52.7 (CH_2), 42.4 (CH), 40.9 (CH_2); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{28}H_{25}N_2O_3^+$ 437.1860, found 437.1853.

Characterization data for **5.10ae''**: **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 8.75 (bs, 1H), 7.45 (dd, *J* = 1.7, 0.7 Hz, 1H), 7.34 – 7.25 (m, 3H), 7.24 – 7.09 (m, 5H), 7.06 (dd, *J* = 3.6, 0.7 Hz, 1H), 7.01 – 6.90 (m, 3H), 6.90 – 6.75 (m, 2H), 6.58 (d, *J* = 7.9 Hz, 1H), 6.40 (dd, *J* = 3.6, 1.7 Hz, 1H), 4.08 – 3.96 (m, 2H), 3.65 (dt, *J* = 10.4, 7.0 Hz, 1H), 3.43 – 3.35 (m, 2H), 3.29 (d, *J* = 15.2 Hz, 1H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 186.5 (C), 166.5 (C), 152.6 (C), 146.2 (CH), 141.0 (C), 136.9 (C), 133.5 (C), 128.7 (CH), 128.6 (CH), 128.5 (CH), 127.6 (CH), 127.4 (CH), 127.3 (CH), 126.7 (C), 124.1 (CH), 119.4 (CH), 117.0 (CH), 115.7 (CH), 115.1 (CH), 112.1 (CH), 66.5 (CH), 54.2 (CH_2), 40.7 (CH_2), 40.2 (CH); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{28}H_{25}N_2O_3^+$ 437.1860, found 437.1851.

4-Benzyl-3-(4-methyl-1-oxo-1-phenylpentan-3-yl)-3,4-dihydroquinoxalin-2(1*H*)-one (5.10af)

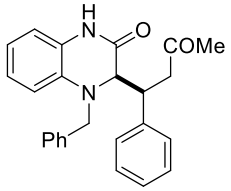


Using 4-benzyl-3,4-dihydroquinoxalin-2(1*H*)-one (**5.1a**, 31.0 mg, 0.13 mmol) and (*E*)-4-methyl-1-phenylpent-2-en-1-one (**5.9f**, 17.4 mg, 0.1 mmol), in accordance with GP-1, product **5.10af** was obtained (31.9 mg, 0.077 mmol, 77% yield, colorless oil) as a mixture of diastereoisomers (dr 1.4:1) that cannot be separated by column chromatography using hexane-diethyl ether (from 5:5 to 2:8) mixtures. Representative signals for the major and for the minor diastereoisomer have been labelled with one and two asterisks respectively.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.81 (bs, 1H), 8.70 (bs, 1H), 8.02 – 7.89 (m, 2H**), 7.83 – 7.69 (m, 2H*), 7.62 – 7.12 (m, 16H), 6.95 – 6.52 (m, 8H), 4.71 (d, *J* = 15.1 Hz, 1H*), 4.53 (d, *J* = 15.7 Hz, 1H**), 4.42 (d, *J* = 15.7 Hz, 1H**), 4.33 (d, *J* = 15.1 Hz, 1H*), 4.00 (d, *J* = 6.8 Hz, 1H**), 3.95 – 3.87 (m, 1H*), 3.44 (dd, *J* = 17.3, 9.0 Hz, 1H**), 3.15 (dd, *J* = 18.2, 6.6 Hz, 1H*), 2.82 – 2.66 (m, 1H*+1H**), 2.66 – 2.49 (m,

1H*+1H**), 2.18 – 1.93 (m, 1H*+1H**), 1.03 – 0.74 (m, 6H*+6H**); **$^{13}C\{^{1}H\}$-NMR (75 MHz, $CDCl_3$)** δ 199.3 (C**), 198.6 (C*), 167.7 (C*), 167.1 (C**), 137.4 (C), 137.4 (C), 137.1 (C), 137.1 (C), 133.9 (C), 133.5 (C), 132.8 (CH), 132.6 (CH), 128.6 (CH), 128.5 (CH), 128.5 (CH), 128.3 (CH), 128.1 (CH), 127.9 (CH), 127.8 (CH), 127.5 (CH), 127.5 (CH), 127.4 (C), 127.3 (CH), 126.8 (C), 124.0 (CH), 120.0 (CH), 119.5 (CH), 116.3 (CH), 115.7 (CH), 115.3 (CH), 115.3 (CH), 64.5 (CH*), 63.3 (CH**), 55.8 (CH_2**), 55.6 (CH_2*), 42.6 (CH**), 39.8 (CH*), 35.6 (CH_2*), 35.5 (CH_2**), 27.8 (CH*), 26.8 (CH**), 22.6 (CH_3**), 21.2 (CH_3*), 17.9 (CH_3*), 17.2 (CH_3**); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{27}H_{29}N_2O_2^+$ 413.2224, found 413.2229.

4-Benzyl-3-(3-oxo-1-phenylbutyl)-3,4-dihydroquinoxalin-2(1*H*)-one (5.10ag)

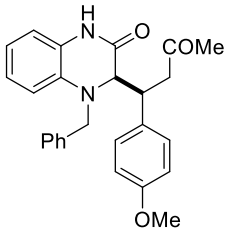


Using 4-benzyl-3,4-dihydroquinoxalin-2(1*H*)-one (**5.1a**, 31.0 mg, 0.13 mmol) and (*E*)-4-phenylbut-3-en-2-one (**5.9g**, 14.6 mg, 0.1 mmol), in accordance with GP-1, product **5.10ag** was obtained (33.1 mg, 0.086 mmol, 86% yield, colorless oil) as a mixture of diastereoisomers (dr 1.1:1) that can be separated by column chromatography using hexane-diethyl ether (from 5:5 to 2:8) mixtures.

Characterization data for **5.10ag'**: **^{1}H-NMR (400 MHz, $CDCl_3$)** δ 8.08 (bs, 1H), 7.34 – 7.17 (m, 5H), 7.08 – 6.91 (m, 5H), 6.78 – 6.65 (m, 1H), 6.50 (d, *J* = 8.0 Hz, 1H), 6.41 (td, *J* = 7.6, 1.2 Hz, 1H), 6.19 (dd, *J* = 7.7, 1.4 Hz, 1H), 4.82 (d, *J* = 15.7 Hz, 1H), 4.61 (d, *J* = 15.7 Hz, 1H), 4.21 (d, *J* = 3.8 Hz, 1H), 3.76 (ddd, *J* = 9.1, 5.6, 3.8 Hz, 1H), 3.36 (dd, *J* = 18.0, 8.7 Hz, 1H), 2.82 (dd, *J* = 18.0, 5.7 Hz, 1H), 2.12 (s, 3H); **$^{13}C\{^{1}H\}$-NMR (100 MHz, $CDCl_3$)** δ 207.2 (C), 166.3 (C), 138.6 (C), 137.0 (C), 133.8 (C), 128.9 (CH), 128.7 (CH), 127.7 (CH), 127.4 (CH), 127.3 (CH), 127.1 (CH), 125.1 (C), 123.8 (CH), 118.1 (CH), 114.5 (CH), 112.7 (CH), 66.0 (CH), 52.6 (CH_2), 45.9 (CH_2), 42.4 (CH), 30.6 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{25}H_{25}N_2O_2^+$ 385.1911, found 385.1987.

Characterization data for **5.10ag''**: **^{1}H-NMR (400 MHz, $CDCl_3$)** δ 8.66 (bs, 1H), 7.38 – 7.27 (m, 3H), 7.24 – 7.13 (m, 3H), 7.13 – 7.05 (m, 2H), 6.97 (ddd, *J* = 8.0, 7.2, 1.8 Hz, 1H), 6.95 – 6.91 (m, 2H), 6.88 (dd, *J* = 7.7, 1.8 Hz, 1H), 6.86 – 6.82 (m, 1H), 6.57 (d, *J* = 7.9 Hz, 1H), 4.00 (d, *J* = 15.2 Hz, 1H), 3.91 (d, *J* = 10.5 Hz, 1H), 3.49 (ddd, *J* = 10.5, 7.8, 5.9 Hz, 1H), 3.25 (d, *J* = 15.2 Hz, 1H), 3.08 (dd, *J* = 17.6, 5.8 Hz, 1H), 2.84 (dd, *J* = 17.6, 7.9 Hz, 1H), 1.97 (s, 3H); **$^{13}C\{^{1}H\}$-NMR (100 MHz, $CDCl_3$)** δ 206.0 (C), 166.6 (C), 141.3 (C), 136.9 (C), 133.5 (C), 128.7 (CH), 128.5 (CH), 128.5 (CH), 127.5 (CH), 127.4 (CH), 127.3 (CH), 126.7 (C), 124.2 (CH), 119.5 (CH), 115.6 (CH), 115.1 (CH), 66.6 (CH), 54.2 (CH_2), 46.0 (CH_2), 40.3 (CH), 30.5 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{25}H_{25}N_2O_2^+$ 385.1911, found 385.1984.

4-Benzyl-3-(1-(4-methoxyphenyl)-3-oxobutyl)-3,4-dihydroquinoxalin-2(1*H*)-one (5.10ah)

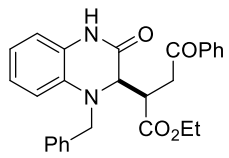


Using 4-benzyl-3,4-dihydroquinoxalin-2(1*H*)-one (**5.1a**, 31.0 mg, 0.13 mmol) and (*E*)-4-(4-methoxyphenyl)but-3-en-2-one (**5.9h**, 17.6 mg, 0.1 mmol), in accordance with GP-1, product **5.10ah** was obtained (37.6 mg, 0.091 mmol, 91% yield, yellowish oil) as a mixture of diastereoisomers (dr 1:1) that can be separated by column chromatography using hexane-diethyl ether (from 5:5 to 2:8) mixtures.

Characterization data for **5.10ah'**: **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 8.14 (bs, 1H), 7.37 – 7.18 (m, 5H), 6.99 – 6.85 (m, 2H), 6.73 (ddd, *J* = 8.1, 7.4, 1.4 Hz, 1H), 6.61 – 6.47 (m, 3H), 6.43 (td, *J* = 7.6, 1.2 Hz, 1H), 6.23 (dt, *J* = 7.7, 1.4 Hz, 1H), 4.79 (d, *J* = 15.7 Hz, 1H), 4.58 (d, *J* = 15.7 Hz, 1H), 4.15 (d, *J* = 3.8 Hz, 1H), 3.72 – 3.65 (m, 1H), 3.64 (s, 3H), 3.30 (dd, *J* = 17.9, 8.5 Hz, 1H), 2.79 (dd, *J* = 17.9, 6.0 Hz, 1H), 2.11 (s, 3H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 207.31 (C), 166.5 (C), 158.5 (C), 137.0 (C), 133.9 (C), 130.4 (C), 129.9 (CH), 128.7 (CH), 127.4 (CH), 127.3 (CH), 125.1 (C), 123.8 (CH), 118.1 (CH), 114.6 (CH), 113.2 (CH), 112.7 (CH), 66.1 (CH), 55.2 (CH_3), 52.7 (CH_2), 46.0 (CH_2), 41.6 (CH), 30.6 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{26}H_{27}N_2O_3^+$ 415.2016, found 415.2020.

Characterization data for **5.10ah''**: **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 8.64 (bs, 1H), 7.25 – 7.13 (m, 3H), 7.04 – 6.92 (m, 5H), 6.91 – 6.78 (m, 4H), 6.58 (d, *J* = 7.9 Hz, 1H), 4.05 (d, *J* = 15.3 Hz, 1H), 3.84 (m, 4H), 3.42 (ddd, *J* = 10.5, 8.1, 5.7 Hz, 1H), 3.31 (d, *J* = 15.3 Hz, 1H), 3.03 (dd, *J* = 17.5, 5.7 Hz, 1H), 2.81 (dd, *J* = 17.5, 8.2 Hz, 1H), 1.96 (s, 3H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 206.2 (C), 166.8 (C), 158. (C), 136.9 (C), 133.5 (C), 133.0 (C), 129.4 (CH), 128.5 (CH), 127.5 (CH), 127.3 (CH), 126.6 (C), 124.2 (CH), 119.4 (CH), 115.6 (CH), 114.9 (CH), 114.1 (CH), 66.6 (CH), 55.3 (CH_3), 54.2 (CH_2), 46.1 (CH_2), 39.5 (CH), 30.6 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{26}H_{27}N_2O_3^+$ 415.2016, found 415.2024.

Ethyl 2-(1-benzyl-3-oxo-1,2,3,4-tetrahydroquinoxalin-2-yl)-4-oxo-4-phenylbutanoate (5.10ai)

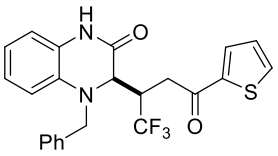


Using 4-benzyl-3,4-dihydroquinoxalin-2(1*H*)-one (**5.1a**, 31.0 mg, 0.13 mmol) and ethyl (*E*)-4-oxo-4-phenylbut-2-enoate (**5.9i**, 20.4 mg, 0.1 mmol), in accordance with GP-1, product **5.10ai** was obtained (23.1 mg, 0.052 mmol, 52% yield, pale yellow oil) as a mixture of diastereoisomers (dr 1.1:1) that cannot be separated by column chromatography using hexane-diethyl ether (from 5:5 to 2:8) mixtures. Repre-

sentative signals for the major and for the minor diastereoisomer have been labelled with one and two asterisks respectively.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.06 (bs, 1H*), 8.95 (bs, 1H**), 7.92 – 7.86 (m, 2H**), 7.86 – 7.76 (m, 2H*), 7.59 – 7.12 (m, 17H), 7.01 – 6.61 (m, 7H), 4.82 (d, J = 15.4 Hz, 1H**), 4.71 (d, J = 15.5 Hz, 1H*), 4.58 – 4.29 (m, 1H*+2H**), 4.23 – 4.05 (m, 2H*), 3.93 – 3.77 (m, 1H*), 3.65 – 3.25 (m, 2H*+5H**), 3.17 – 3.02 (m, 1H*), 1.24 (t, J = 7.1 Hz, 3H*), 1.03 (t, J = 7.2 Hz, 3H**); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 197.6 (C), 197.4 (C), 172.7 (C), 172.2 (C), 165.6 (C), 165.5 (C), 136.5 (C), 136.5 (C), 136.3 (C), 133.3 (C), 133.3 (CH), 133.2 (CH), 128.8 (CH), 128.7 (CH), 128.5 (CH), 128.4 (CH), 128.1 (CH), 128.0 (CH), 127.6 (CH), 127.6 (CH), 127.5 (CH), 125.9 (C), 125.8 (C), 124.4 (CH), 124.2 (CH), 119.6 (CH), 119.3 (CH), 115.5 (CH), 115.3 (CH), 114.9 (CH), 114.0 (CH), 63.5 (CH), 63.1 (CH), 61.3 (CH_2), 61.2 (CH_2), 53.9 (CH_2), 53.2 (CH_2), 42.0 (CH), 42.0 (CH), 38.2 (CH_2), 36.6 (CH_2), 14.0 (CH_3), 13.6 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* [M + H]$^+$ calcd for $C_{27}H_{27}N_2O_4^+$ 443.1965, found 443.1972.

4-Benzyl-3-(1,1,1-trifluoro-4-oxo-4-(thiophen-2-yl)butan-2-yl)-3,4-dihydroquinoxalin-2(1*H*)-one (5.10aj)

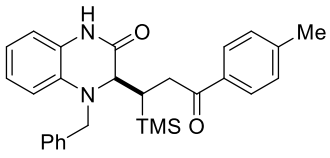


Using 4-benzyl-3,4-dihydroquinoxalin-2(1*H*)-one (**5.1a**, 31 mg, 0.13 mmol) and (*E*)-4,4,4-trifluoro-1-(thiophen-2-yl)but-2-en-1-one (**5.9j**, 20.6 mg, 0.1 mmol), in accordance with GP-1, product **5.10aj** was obtained (31.0 mg, 0.070 mmol, 70% yield, colorless oil) as a mixture of diastereoisomers (dr 1.1:1) that cannot be separated by column chromatography using hexane-diethyl ether (from 5:5 to 2:8) mixtures.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.96 (bs, 1H), 8.84 (bs, 1H), 7.63 (dd, J = 4.9, 1.1 Hz, 1H), 7.57 (m, 2H), 7.52 (dd, J = 5.0, 1.1 Hz, 1H), 7.36 – 7.17 (m, 9H), 7.08 (dd, J = 4.9, 3.8 Hz, 1H), 7.00 (dd, J = 4.9, 3.8 Hz, 1H), 6.95 – 6.71 (m, 6H), 6.69 (d, J = 7.9 Hz, 1H), 6.62 (td, J = 7.4, 1.2 Hz, 1H), 6.57 (dd, J = 7.7, 1.7 Hz, 1H), 4.85 – 4.75 (m, 2H), 4.51 (d, J = 15.9 Hz, 1H), 4.46 (d, J = 3.3 Hz, 1H), 4.35 (d, J = 15.3 Hz, 1H), 4.26 (d, J = 8.0 Hz, 1H), 3.67 (dd, J = 17.6, 9.3 Hz, 1H), 3.62 – 3.41 (m, 2H), 3.36 (dd, J = 18.1, 6.3 Hz, 1H), 3.08 (m, 2H); **^{19}F{^{1}H}-NMR (282 MHz, $CDCl_3$)** δ -66.93, -67.47; **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 188.5 (C), 187.7 (C), 165.0 (C), 164.2 (C), 143.0 (C), 142.7 (C), 136.7 (C), 136.5 (C), 134.3 (CH), 134.1 (CH), 132.9 (C), 132.6 (CH), 132.5 (C), 132.2 (CH), 128.7 (CH), 128.1 (CH), 128.0 (CH), 127.7 (CH), 127.6 (CH), 127.3 (CH), 126.3 (C), 125.6 (C), 124.5 (CH), 124.3 (CH), 120.2 (CH), 119.4 (CH), 116.0 (CH), 115.8 (CH), 115.5 (CH), 114.6 (CH), 60.9 (CH), 60.6 (CH), 54.6 (CH_2, q, J = 1.6 Hz), 54.0 (CH_2, q, J = 0.6 Hz), 41.6 (CH, q, J = 26.0 Hz), 37.5 (CH, q, J = 25.6 Hz), 35.2 (CH_2, q, J = 2.4 Hz), 34.8 (CH_2, q, J = 2.2 Hz); **HRMS (ESI/Q-TOF)** *m/z* [M + H]$^+$ calcd for

$C_{23}H_{20}F_3N_2O_2S^+$ 445.1192, found 445.1199.

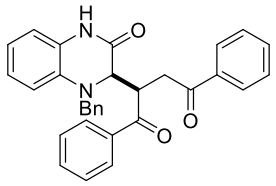
4-Benzyl-3-(3-oxo-3-(*p*-tolyl)-1-(trimethylsilyl)propyl)-3,4-dihydroquinoxalin-2(1*H*)-one (5.10ak)



Using 4-benzyl-3,4-dihydroquinoxalin-2(1*H*)-one (**5.1a**, 31 mg, 0.13 mmol) and (*E*)-1-(*p*-tolyl)-3-(trimethylsilyl)prop-2-en-1-one (**5.9k**, 21.8 mg, 0.1 mmol), in accordance with GP-1, product **5.10ak** was obtained (27.3 mg, 0.060 mmol, 60% yield, colorless oil) as a mixture of diastereoisomers (dr 2:1) that cannot be separated by column chromatography using hexane-diethyl ether (from 5:5 to 2:8) mixtures. Representative signals for the major and for the minor diastereoisomer have been labelled with one and two asterisks respectively.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.40 (bs, 1H*), 9.09 (bs, 1H**), 7.86 (d, J = 8.2 Hz, 2H**), 7.57 – 7.42 (m, 2H*), 7.35 – 7.27 (m, 7H), 7.25 – 7.11 (m, 5H), 7.07 (d, J = 7.9 Hz, 2H*), 6.87 (ddd, J = 8.0, 6.9, 2.1 Hz, 1H**), 6.80 – 6.70 (m, 2H**), 6.64 – 6.49 (m, 2H*+1H**), 6.50 – 6.37 (m, 2H*), 4.59 (d, J = 15.0 Hz, 1H*), 4.53 (d, J = 15.7 Hz, 1H**), 4.38 (d, J = 15.1 Hz, 1H**), 4.30 (d, J = 14.9 Hz, 1H*), 4.21 (d, J = 8.4 Hz, 1H**), 4.18 (d, J = 5.0 Hz, 1H*), 3.39 (dd, J = 18.3, 7.3 Hz, 1H**), 3.18 (dd, J = 18.5, 7.5 Hz, 1H*), 2.94 (dd, J = 18.3, 4.2 Hz, 1H**), 2.58 (dd, J = 18.5, 3.8 Hz, 1H*), 2.43 (s, 3H**), 2.34 (m, 4H*), 1.81 (td, J = 7.4, 4.2 Hz, 1H**), 0.04 (s, 9H*+9H**); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 199.4 (C**), 198.6 (C*), 168.0 (C**), 167.7 (C*), 143.7 (C**), 143.2 (C*), 137.5 (C**), 136.6 (C*), 134.8 (C**), 134.1 (C*), 133.9 (C*), 133.0 (C**), 129.2 (CH), 128.7 (CH), 128.6 (CH), 128.4 (CH), 128.1 (CH), 127.9 (CH), 127.5 (CH), 127.4 (C), 127.2 (CH), 125.7 (C), 124.1 (CH*), 123.9 (CH**), 119.7 (CH**), 118.3 (CH*), 116.5 (CH**), 115.3 (CH**), 114.8 (CH*), 114.1 (CH*), 63.4 (CH**), 61.8 (CH*), 55.7 (CH_2**), 52.3 (CH_2*), 37.1 (CH_2**), 34.5 (CH_2*), 25.4 (CH**), 23.1 (CH*), 21.6 (CH_3**), 21.5 (CH_3*), -1.3 (CH_3**), -2.0 (CH_3*). **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{28}H_{33}N_2O_2Si^+$ 457.2306, found 457.2311.

2-(1-Benzyl-3-oxo-1,2,3,4-tetrahydroquinoxalin-2-yl)-1,4-diphenylbutane-1,4-dione (5.12aa)

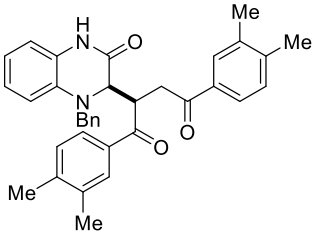


Using 4-benzyl-3,4-dihydroquinoxalin-2(1*H*)-one (**5.1a**, 31.0 mg, 0.13 mmol) and (*E*)-1,4-diphenylbut-2-ene-1,4-dione (**5.11a**, 23.6 mg, 0.1 mmol), in accordance with GP-1, product **5.12aa** was obtained (43.0 mg, 0.091 mmol, 91% yield, colorless oil) as a mixture of diastereoisomers (dr 3:1) that cannot be separated by column chromatography using hexane-diethyl ether (from 5:5 to 2:8) mixtures. Repre-

sentative signals for the major and for the minor diastereoisomer have been labelled with one and two asterisks respectively.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.45 (s, 1H**), 9.40 (s, 1H*), 7.99 – 7.74 (m, 8H), 7.62 – 7.44 (m, 4H), 7.42 – 7.06 (m, 18H), 6.91 – 6.66 (m, 6H), 6.45 (d, J = 7.6 Hz, 1H**), 6.27 – 6.17 (m, 1H*), 4.74 – 4.61 (m, 2H**), 4.54 – 4.28 (m, 3H*+2H**), 4.11 (d, J = 15.3 Hz, 1H*), 3.82 (dd, J = 18.4, 9.6 Hz, 1H*), 3.81 (dd, J = 18.2, 9.6 Hz, 1H**), 3.42 (dd, J = 18.4, 3.5 Hz, 1H*), 3.34 (dd, J = 18.3, 4.1 Hz, 1H**); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 201.7 (C*), 200.4 (C**), 197.7 (C**), 197.7 (C*), 166.5 (C**), 165.6 (C*), 136.8 (C), 136.7 (C), 136.5 (C), 136.4 (C), 136.2 (C), 136.0 (C), 133.2 (CH), 133.0 (CH), 132.9 (CH), 132.8 (C), 128.7 (CH), 128.7 (CH), 128.6 (CH), 128.5 (CH), 128.4 (CH), 128.4 (CH), 128.4 (CH), 128.1 (CH), 127.6 (CH), 127.6 (CH), 127.5 (CH), 126.7 (C), 126.1 (C), 124.3 (CH), 124.2 (CH), 120.2 (CH), 119.6 (CH), 116.3 (CH), 115.8 (CH), 115.5 (CH), 114.3 (CH), 64.1 (CH*), 63.8 (CH**), 55.3 (CH_2*), 54.1 (CH_2**), 44.5 (CH**), 41.4 (CH*), 39.2 (CH_2*), 38.5 (CH_2**); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{31}H_{27}N_2O_3^+$ 475.2016, found 475.2012.

2-(1-Benzyl-3-oxo-1,2,3,4-tetrahydroquinoxalin-2-yl)-1,4-bis(3,4-dimethylphenyl) butane-1,4-dione (5.12ab)

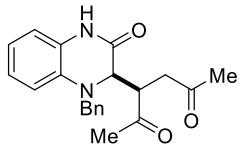


Using 4-benzyl-3,4-dihydroquinoxalin-2(1*H*)-one (**5.1a**, 31 mg, 0.13 mmol) and (*E*)-1,4-bis(3,4-dimethylphenyl)but-2-ene-1,4-dione (**5.11b**, 29.2 mg, 0.1 mmol), in accordance with GP-1, product **5.12ab** was obtained (50.6 mg, 0.095 mmol, 95% yield, yellowish oil) as a mixture of diastereoisomers (dr 3:1) that cannot be separated by column chromatography using hexane-diethyl ether (from 5:5 to 2:8) mixtures. Representative signals for the major and for the minor diastereoisomer have been labelled with one and two asterisks respectively.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.25 (bs, 1H*), 9.24 (bs, 1H**), 7.72 (dd, J = 7.9, 1.6 Hz, 1H**), 7.67 – 7.44 (m, 7H), 7.36 – 7.03 (m, 14H), 6.92 – 6.67 (m, 6H), 6.51 – 6.41 (m, 1H**), 6.24 (dd, J = 6.0, 2.6 Hz, 1H*), 4.69 (d, J = 15.6 Hz, 1H**), 4.63 (dt, J = 9.1, 4.3 Hz, 1H**), 4.53 – 4.40 (m, 1H*+1H**), 4.38 – 4.28 (m, 2H*+1H**), 4.08 (d, J = 15.4 Hz, 1H*), 3.84 – 3.67 (m, 1H*+1H**), 3.40 (dd, J = 18.4, 3.6 Hz, 1H*), 3.30 (dd, J = 18.2, 4.3 Hz, 1H**), 2.31 (s, 3H*), 2.28 (s, 3H**), 2.24 (s, 3H*+9H**), 2.21 (s, 3H*), 2.19 (s, 3H*); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 201.7 (C*), 200.3 (C**), 197.6 (C**), 197.5 (C*), 166.6 (C**), 165.7 (C*), 142.7 (C), 142.6 (C), 142.5 (C), 136.7 (C), 136.7 (C), 136.7 (C), 136.6 (C), 136.5 (C), 134.8 (C), 134.6 (C), 134.2 (C), 134.0 (C), 133.3 (C), 132.9 (C), 130.2 (CH), 129.7 (CH), 129.3 (CH), 129.3(CH), 129.2 (CH), 128.6 (CH), 128.5 (CH), 127.5 (CH), 127.5 (CH), 127.4 (CH), 127.4 (CH), 126.6 (C), 126.3

(CH), 126.2 (CH), 125.8 (CH), 125.8 (CH), 124.1 (CH), 124.0 (CH), 119.8 (CH), 119.3 (CH), 116.2 (CH), 115.8 (CH), 115.4 (CH), 114.2 (CH), 64.4 (CH*), 64.1 (CH**), 55.0 (CH_2*), 54.1 (CH_2**), 44.7 (CH**), 40.9 (CH*), 39.5 (CH_2*), 38.2 (CH_2**), 20.0 (CH_3), 19.9 (CH_3), 19.8 (CH_3), 19.7 (CH_3), 19.6 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{35}H_{35}N_2O_3^+$ 531.2642, found 531.2635.

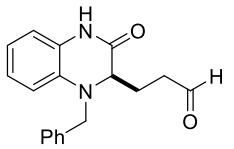
3-(1-Benzyl-3-oxo-1,2,3,4-tetrahydroquinoxalin-2-yl)hexane-2,5-dione (5.12ac)



Using 4-benzyl-3,4-dihydroquinoxalin-2(1*H*)-one (**5.1a**, 31 mg, 0.13 mmol) and (*E*)-hex-3-ene-2,5-dione (**5.11c**, 11.2 mg, 0.1 mmol), in accordance with GP-1, product **5.12ac** was obtained (28.9 mg, 0.083 mmol, 83% yield, colorless oil) as a mixture of diastereoisomers (dr 5:1) that cannot be separated by column chromatography using hexane-diethyl ether (from 5:5 to 2:8) mixtures. Representative signals for the major and for the minor diastereoisomer have been labelled with one and two asterisks respectively.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.20 (bs, 1H*+1H**), 7.29 – 7.05 (m, 10H), 6.96 – 6.62 (m, 8H), 4.68 (d, *J* = 15.3 Hz, 1H**), 4.56 (d, *J* = 15.0 Hz, 1H*), 4.23 (d, *J* = 15.3 Hz, 1H**), 4.17 (d, *J* = 8.0 Hz, 1H*), 4.12 (d, *J* = 15.0 Hz, 1H*), 4.06 (d, *J* = 4.7 Hz, 1H**), 3.35 (ddd, *J* = 9.2, 8.1, 4.1 Hz, 1H*+1H**), 3.00 (dd, *J* = 18.6, 10.1 Hz, 1H**), 2.91 (dd, *J* = 18.4, 9.4 Hz, 1H*), 2.53 (dd, *J* = 18.4, 4.2 Hz, 1H**), 2.44 (dd, *J* = 18.4, 4.1 Hz, 1H*), 2.10 (s, 3H*), 1.99 (s, 3H**), 1.94 (s, 3H**), 1.86 (s, 3H*); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 208.9 (C**), 208.3 (C*), 206.7 (C*), 206.5 (C**), 166.4 (C**), 165.4 (C*), 136.2 (C**), 136.0 (C*), 133.1 (C**), 133.0 (C*), 128.8 (CH**), 128.8 (CH*), 127.9 (CH*), 127.9 (CH*), 127.8 (CH**), 127.6 (CH**), 126.4 (C*), 126.3 (C**), 124.6 (CH*), 124.4 (CH**), 120.2 (CH*), 120.1 (CH**), 115.9 (CH*), 115.9 (CH**), 115.5 (CH*), 114.5 (CH**), 62.7 (CH**), 62.3 (CH*), 54.6 (CH_2*), 54.2 (CH_2**), 49.4 (CH**), 47.6 (CH*), 43.2 (CH_2**), 41.4 (CH_2*), 30.8 (CH_3**), 30.7 (CH_3*), 29.8 (CH_3*), 29.7 (CH_3**); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{21}H_{23}N_2O_3^+$ 351.1703, found 351.1711.

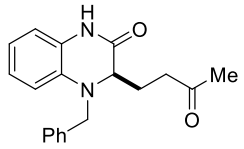
3-(1-Benzyl-3-oxo-1,2,3,4-tetrahydroquinoxalin-2-yl)propanal (5.14aa)



Using 4-benzyl-3,4-dihydroquinoxalin-2(1*H*)-one (**5.1a**, 23.8 mg, 0.1 mmol) and acrolein (**5.13a**, 33 µL, 0.5 mmol, 5 equiv.), in accordance with GP-2, product **5.14aa** was obtained (21.0 mg, 0.071 mmol, 71% yield, colorless oil) after column chromatography using hexane-diethyl ether (from 5:5 to 2:8) mixtures.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.67 (t, J = 1.0 Hz, 1H), 9.03 (bs, 1H), 7.41 – 7.13 (m, 5H), 6.99 – 6.89 (m, 1H), 6.86 – 6.65 (m, 3H), 4.64 (d, J = 15.0 Hz, 1H), 4.28 (d, J = 15.0 Hz, 1H), 3.97 – 3.75 (m, 1H), 2.64 – 2.44 (m, 2H), 2.18 – 1.94 (m, 1H), 1.94 – 1.79 (m, 1H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 200.8 (CH), 167.9 (C), 136.6 (C), 133.6 (C), 128.8 (CH), 127.7 (CH), 126.1 (C), 124.3 (CH), 119.6 (CH), 115.5 (CH), 114.4 (CH), 60.8 (CH), 53.2 (CH_2), 39.7 (CH_2), 21.0 (CH_2); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{18}H_{19}N_2O_2^+$ 295.1441, found 295.1444.

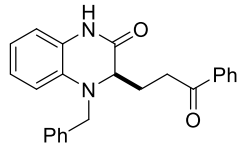
4-Benzyl-3-(3-oxobutyl)-3,4-dihydroquinoxalin-2(1*H*)-one 8 (5.14ab)



Using 4-benzyl-3,4-dihydroquinoxalin-2(1*H*)-one (**5.1a**, 23.8 mg, 0.1 mmol) and methyl vinyl ketone (**5.13b**, 42 µL, 0.5 mmol), in accordance with GP-2, product **5.14ab** was obtained (25.5 mg, 0.083 mmol, 83% yield, colorless oil) after column chromatography using hexane-diethyl ether (from 5:5 to 2:8) mixtures.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.15 (bs, 1H), 7.37 – 7.23 (m, 5H), 6.92 (ddd, J = 8.0, 6.5, 2.5 Hz, 1H), 6.82 – 6.73 (m, 2H), 6.69 (d, J = 7.9 Hz, 1H), 4.64 (d, J = 15.1 Hz, 1H), 4.30 (d, J = 15.1 Hz, 1H), 3.86 (dd, J = 9.4, 4.7 Hz, 1H), 2.53 (dd, J = 10.6, 4.6 Hz, 2H), 2.05 (s, 3H), 2.02 – 1.90 (m, 1H), 1.90 – 1.78 (m, 1H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 207.6 (C), 168.3 (C), 136.8 (C), 133.9 (C), 128.8 (CH), 127.7 (CH), 127.6 (CH), 126.0 (C), 124.3 (CH), 119.2 (CH), 115.5 (CH), 113.9 (CH), 61.0 (CH), 52.5 (CH_2), 39.0 (CH_2), 30.1 (CH_3), 22.1 (CH_2); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{19}H_{21}N_2O_2^+$ 309.1598, found 309.1603.

4-Benzyl-3-(3-oxo-3-phenylpropyl)-3,4-dihydroquinoxalin-2(1*H*)-one (5.14ac)

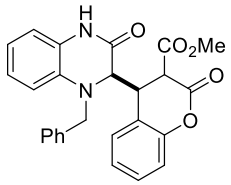


Using 4-benzyl-3,4-dihydroquinoxalin-2(1*H*)-one (**5.1a**, 31 mg, 0.13 mmol) and phenyl vinyl ketone (**5.13c**, 13.1 mg, 0.1 mmol, 1 equiv.), in accordance with GP-1, product **5.14ac** was obtained (20.3 mg, 0.055 mmol, 55% yield, colorless oil) after column chromatography using hexane-diethyl ether (from 5:5 to 2:8) mixtures.

^{1}H-NMR (300 MHz, DMSO-d_6) δ 10.47 (bs, 1H), 7.92 – 7.82 (m, 2H), 7.68 – 7.56 (m, 1H), 7.50 (ddd, J = 8.3, 6.6, 1.4 Hz, 2H), 7.40 – 7.18 (m, 5H), 6.90 – 6.75 (m, 2H), 6.68 (dd, J = 7.7, 6.5 Hz, 2H), 4.70 (d, J = 15.5 Hz, 1H), 4.37 (d, J = 15.5 Hz, 1H), 3.87 (dd, J = 8.9, 5.4 Hz, 1H), 3.16 – 3.00 (m, 2H), 2.06 – 1.85 (m, 1H), 1.85 – 1.66 (m, 1H); **^{13}C{^{1}H}-NMR (75 MHz, DMSO-d_6)** δ 199.3 (C), 167.4 (C), 138.4 (C), 137.0 (C), 133.8 (C), 133.6 (CH), 129.2 (CH), 129.0 (CH), 128.2 (CH), 127.9 (CH), 127.6 (CH), 127.5 (CH), 123.5 (CH), 119.0 (CH), 115.4 (CH), 113.9 (CH), 61.6 (CH), 52.2 (CH_2), 34.5

(CH_2), 23.0 (CH_2); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{24}H_{23}N_2O_2^+$ 371.1754, found 371.1761.

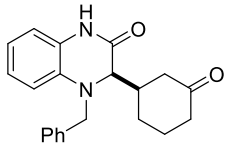
Methyl-4-(1-benzyl-3-oxo-1,2,3,4-tetrahydroquinoxalin-2-yl)-2-oxochromane-3-carboxylate (5.16aa)



Using 4-benzyl-3,4-dihydroquinoxalin-2(1*H*)-one (**5.1a**, 31 mg, 0.13 mmol) and methyl 2-oxo-2H-chromene-3-carboxylate (**5.15a**, 20.4 mg, 0.1 mmol), in accordance with GP-1, product **5.16aa** was obtained (28.3 mg, 0.064 mmol, 64% yield, colorless oil) as a mixture of diastereoisomers (dr 1.3:1) that cannot be separated by column chromatography using hexane-diethyl ether (from 5:5 to 2:8) mixtures. Representative signals for the major and for the minor diastereoisomer have been labelled with one and two asterisks respectively.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.27 (bs, 1H**), 8.81 (bs, 1H*), 7.27 – 6.64 (m, 25H), 6.47 (dd, *J* = 7.7, 1.3 Hz, 1H*), 4.73 (d, *J* = 15.0 Hz, 1H**), 4.38 (d, *J* = 15.1 Hz, 1H*), 4.12 (d, *J* = 15.0 Hz, 1H**), 4.06 – 3.98 (m, 4H), 3.87 – 3.69 (m, 3H), 3.59 (s, 3H*), 3.57 (s, 3H**); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 167.2 (C**), 167.0 (C*), 166.0 (C*), 164.9 (C**), 163.2 (C*), 162.9 (C**), 151.2 (C*), 151.2 (C**), 136.0 (C), 135.9 (C), 132.5 (C), 132.4 (C), 129.9 (CH), 129.7 (CH), 129.3 (CH), 128.9 (CH), 128.7 (CH), 128.0 (CH), 127.9 (CH), 127.9 (CH), 127.8 (CH), 127.1 (C), 126.4 (C), 124.8 (CH), 124.7 (CH), 124.4 (CH), 124.4 (CH), 124.4 (CH), 121.4 (CH), 120.9 (CH), 119.3 (C), 118.7 (C), 118.2 (CH), 117.0 (CH), 116.7 (CH), 116.4 (CH), 116.0 (CH), 115.5 (CH), 65.0 (CH**), 64.7 (CH*), 58.4 (CH_2*), 56.2 (CH_2**), 53.3 (CH_3**), 53.3 (CH_3*), 49.5 (CH*), 48.8 (CH**), 42.7 (CH*), 42.2 (CH**); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{26}H_{23}N_2O_5^+$ 443.1601, found 443.1597.

4-Benzyl-3-(3-oxocyclohexyl)-3,4-dihydroquinoxalin-2(1*H*)-one (5.16ab)

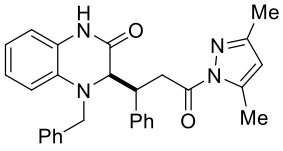


Using 4-benzyl-3,4-dihydroquinoxalin-2(1*H*)-one (**5.1a**, 23.8 mg, 0.1 mmol) and cyclohexenone (**5.15b**, 48 µL, 0.5 mmol), in accordance with GP-2, product **5.16ab** was obtained (32.3 mg, 0.097 mmol, 97% yield, colorless oil) as a mixture of diastereoisomers (dr 1:1) that cannot be separated by column chromatography using hexane-diethyl ether (from 5:5 to 2:8) mixtures.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.56 (bs, 1H), 9.54 (bs, 1H), 7.39 – 7.17 (m, 5H+5H), 7.04 – 6.90 (m, 1H+1H), 6.86 – 6.73 (m, 3H+3H), 4.78 (d, *J* = 15.2 Hz, 1H), 4.75 (d, *J* = 15.3 Hz, 1H), 4.36 (d, *J* = 15.2 Hz, 1H), 4.35 (d, *J* = 15.2 Hz, 1H), 3.84 (d, *J* = 5.7 Hz, 1H), 3.79 (d, *J* = 6.1 Hz, 1H), 2.56 – 1.41 (m, 9H+9H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)**

δ 210.3 (C), 210.2 (C), 166.5 (C), 166.3 (C), 136.7 (C), 133.8 (C), 128.8 (CH), 127.7 (C), 127.6 (CH), 127.5 (CH), 126.6 (C), 126.5 (C), 124.3 (CH), 119.7 (CH), 119.6 (CH), 115.7 (CH), 115.6 (CH), 114.8 (CH), 114.8 (CH), 66.1 (CH), 65.9 (CH), 55.6 (CH_2), 55.4 (CH_2), 45.4 (CH_2), 44.1 (CH_2), 41.4 (CH), 41.1 (CH), 41.1 (CH_2), 41.0 (CH_2), 28.5 (CH_2), 27.2 (CH_2), 25.0 (CH_2), 24.9 (CH_2); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{21}H_{23}N_2O_2^+$ 335.1754, found 335.1758.

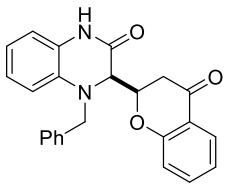
4-Benzyl-3-(3-(3,5-dimethyl-1*H*-pyrazol-1-yl)-3-oxo-1-phenylpropyl)-3,4-dihydroquinoxalin-2(1*H*)-one (5.16ac)



Using 4-benzyl-3,4-dihydroquinoxalin-2(1*H*)-one (**5.1a**, 31.0 mg, 0.13 mmol) and (*E*)-1-(3,5-dimethyl-1H-pyrazol-1-yl)-3-phenylprop-2-en-1-one (**5.15c**, 22.6 mg, 0.1 mmol), in accordance with GP-1, product **5.16ac** was obtained (24.2 mg, 0.052 mmol, 52% yield, colorless oil) as a mixture of diastereoisomers (dr 1.1:1) that cannot be separated by column chromatography using hexane-diethyl ether (from 5:5 to 2:8) mixtures. Representative signals for the major and for the minor diastereoisomer have been labelled with one and two asterisks respectively.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.06 (bs, 1H*), 8.54 (bs, 1H**), 7.44 – 7.08 (m, 16H), 7.06 – 6.68 (m, 8H), 6.56 (m, 1H*+1H**), 6.47 (td, *J* = 7.6, 1.2 Hz, 1H*), 6.28 (dd, *J* = 7.7, 1.4 Hz, 1H**), 5.92 (d, *J* = 0.7 Hz, 1H**), 5.80 (d, *J* = 0.7 Hz, 1H*), 4.83 (d, *J* = 15.5 Hz, 1H**), 4.64 (d, *J* = 15.6 Hz, 1H**), 4.34 (d, *J* = 4.5 Hz, 1H*), 4.11 – 3.53 (m, 4H*+4H**), 3.30 (d, *J* = 15.2 Hz, 1H*), 2.45 (d, *J* = 0.8 Hz, 3H**), 2.31 (d, *J* = 0.8 Hz, 3H*), 2.23 (s, 3H**), 2.18 (s, 3H*); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 172.3 (C**), 171.5 (C*), 166.7 (C*), 166.4 (C**), 151.9 (C), 151.7 (C), 143.9 (C), 143.7 (C), 140.7 (C), 138.6 (C), 137.0 (C), 136.9 (C), 133.6 (C), 133.5 (C), 129.0 (CH), 128.8 (CH), 128.7 (CH), 128.5 (CH), 128.5 (CH), 127.7 (CH), 127.6 (CH), 127.5 (CH), 127.4 (CH), 127.4 (CH), 127.3 (CH), 127.1 (CH), 126.7 (C), 125.7 (C), 124.0 (CH), 123.7 (CH), 119.3 (CH), 118.5 (CH), 115.7 (CH), 115.0 (CH), 114.8 (CH), 113.4 (CH), 111.0 (CH), 110.9 (CH), 66.3 (CH**), 66.1 (CH*), 54.2 (CH_2*), 53.3 (CH_2**), 43.0 (CH**), 41.1 (CH*), 38.0 (CH_2**), 37.7 (CH_2*), 14.4 (CH_3**), 14.3 (CH_3*), 13.8 (CH_3**), 13.8 (CH_3*); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{29}H_{29}N_4O_2^+$ 465.2285, found 465.2281.

4-Benzyl-3-(4-oxochroman-2-yl)-3,4-dihydroquinoxalin-2(1*H*)-one (5.16ad)

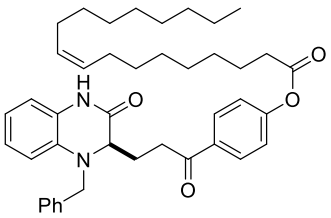


Using 4-benzyl-3,4-dihydroquinoxalin-2(1*H*)-one (**5.1a**, 31.0 mg, 0.13 mmol) and 4*H*-chromen-4-one (**5.15d**, 14.6 mg, 0.1 mmol), in accordance with GP-1, product **5.16ad** was obtained (9.6 mg, 0.025 mmol, 25% yield, yellowish oil) as a mixture of di-

astereoisomers (dr 1.2:1) that cannot be separated by column chromatography using hexane-diethyl ether (from 5:5 to 2:8) mixtures. Representative signals for the major and for the minor diastereoisomer have been labelled with one and two asterisks respectively.

^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.56 (bs, 1H*+1H**), 7.88 – 7.78 (m, 2H), 7.49 – 7.38 (m, 2H), 7.36 – 7.27 (m, 9H), 7.04 – 6.89 (m, 6H), 6.83 – 6.74 (m, 6H), 6.71 (d, *J* = 8.0 Hz, 1H*), 4.89 (d, *J* = 14.9 Hz, 1H**), 4.85 – 4.74 (m, 2H*), 4.66 – 4.57 (m, 1H*+1H**), 4.53 (d, *J* = 15.2 Hz, 1H*), 4.36 (d, *J* = 3.0 Hz, 1H**), 4.23 (d, *J* = 7.3 Hz, 1H**), 2.99 – 2.83 (m, 1H*+1H**), 2.71 (dd, *J* = 16.9, 3.1 Hz, 1H**), 2.56 (dd, *J* = 16.9, 2.7 Hz, 1H*); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 191.2 (C*), 190.7 (C**), 164.4 (C*), 164.3 (C**), 160.7 (C*), 160.6 (C**), 136.6 (C), 136.4 (C), 136.1 (C), 136.0 (CH), 134.3 (C), 133.4 (C), 128.9 (CH), 128.8 (CH), 127.9 (CH), 127.8 (CH), 127.8 (CH), 127.7 (CH), 127.0 (CH), 126.6 (CH), 126.1 (C), 125.6 (C), 124.6 (CH), 124.5 (CH), 121.8 (CH), 121.8 (CH), 120.9 (C), 120.7 (C), 119.9 (CH), 119.4 (CH), 117.9 (CH), 117.8 (CH), 115.6 (CH), 115.4 (CH), 114.9 (CH), 113.5 (CH), 78.7 (CH**), 77.2 (CH*), 65.0 (CH**), 64.4 (CH*), 55.5 (CH_2**), 54.0 (CH_2*), 39.9 (CH_2**), 39.6 (CH_2*); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{24}H_{21}N_2O_3^+$ 385.1547, found 385.1549.

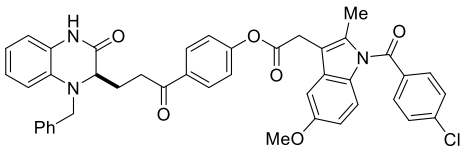
4-(3-(1-Benzyl-3-oxo-1,2,3,4-tetrahydroquinoxalin-2-yl)propanoyl)phenyl oleate (5.18aa)



Using 4-benzyl-3,4-dihydroquinoxalin-2(1*H*)-one (**5.1a**, 31 mg, 0.13 mmol) and 4-acryloylphenyl oleate (**5.17a**, 41.2 mg, 0.1 mmol, 1 equiv.), in accordance with GP-1, product **5.18aa** was obtained (51.9 mg, 0.080 mmol, 80% yield, colorless oil) after column chromatography using hexane-diethyl ether (from 5:5 to 2:8) mixtures.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.30 (s, 1H), 7.91 (d, *J* = 8.7 Hz, 2H), 7.38 – 7.21 (m, 5H), 7.13 (d, *J* = 8.7 Hz, 2H), 6.91 (ddd, *J* = 7.9, 6.6, 2.4 Hz, 1H), 6.84 – 6.66 (m, 3H), 5.35 (m, 2H), 4.67 (d, *J* = 15.1 Hz, 1H), 4.36 (d, *J* = 15.1 Hz, 1H), 3.96 (dd, *J* = 9.5, 4.7 Hz, 1H), 3.22 – 2.90 (m, 2H), 2.57 (t, *J* = 7.5 Hz, 2H), 2.16 (dtd, *J* = 12.3, 7.5, 4.8 Hz, 1H), 2.09 – 1.89 (m, 5H), 1.84 – 1.67 (m, 2H), 1.54 – 1.21 (m, 20H), 1.07 – 0.79 (m, 3H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 197.6 (C), 171.6 (C), 168.4 (C), 154.4 (C), 136.8 (C), 134.1 (C), 133.9 (C), 130.0 (CH), 129.7 (CH), 129.6 (CH), 128.7 (CH), 127.6 (CH), 127.5 (CH), 126.1 (C), 124.2 (CH), 121.7 (CH), 119.3 (CH), 115.5 (CH), 114.0 (CH), 61.0 (CH), 52.7 (CH_2), 34.3 (CH_2), 34.1 (CH_2), 31.9 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 29.1 (CH_2), 29.0 (CH_2), 29.0 (CH_2), 27.2 (CH_2), 27.1 (CH_2), 24.8 (CH_2), 22.6 (CH_2), 22.6 (CH_2), 14.1 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{42}H_{55}N_2O_4^+$ 651.4156, found 651.4161.

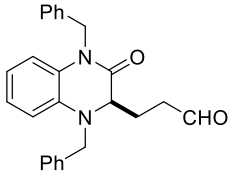
4-(3-(1-Benzyl-3-oxo-1,2,3,4-tetrahydroquinoxalin-2-yl)propanoyl)phenyl 2-(1-(4-chloro- benzoyl)-5-methoxy-2-methyl-1H-indol-3-yl)acetate (5.18ab)



Using 4-benzyl-3,4-dihydroquinoxalin-2(1*H*)-one (**5.1a**, 31 mg, 0.13 mmol) and 4-acryloylphenyl 2-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl)acetate (**5.17b**, 48.8 mg, 0.1 mmol, 1 equiv.), in accordance with GP-1, product **5.18ab** was obtained (57.3 mg, 0.079 mmol, 79% yield, colorless oil) after column chromatography using hexane-diethyl ether (from 5:5 to 2:8) mixtures.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.15 (bs, 1H), 7.88 (d, J = 8.8 Hz, 2H), 7.68 (d, J = 8.5 Hz, 2H), 7.47 (d, J = 8.5 Hz, 2H), 7.39 – 7.19 (m, 5H), 7.11 (d, J = 8.7 Hz, 2H), 7.05 (d, J = 2.5 Hz, 1H), 6.89 (d, J = 9.3 Hz, 2H), 6.80 – 6.61 (m, 4H), 4.66 (d, J = 15.1 Hz, 1H), 4.34 (d, J = 15.1 Hz, 1H), 4.02 – 3.90 (m, 3H), 3.83 (s, 3H), 3.23 – 2.87 (m, 2H), 2.46 (s, 3H), 2.25 – 2.06 (m, 1H), 2.06 – 1.87 (m, 1H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 197.6 (C), 168.7 (C), 168.3 (C), 156.1 (C), 154.3 (C), 139.4 (C), 136.7 (C), 136.3 (C), 134.3 (C), 133.8 (C), 133.7 (C), 131.2 (CH), 130.8 (C), 130.4 (C), 129.6 (CH), 129.1 (CH), 128.7 (CH), 127.6 (CH), 127.6 (C), 127.5 (CH), 126.0 (C), 124.2 (CH), 121.5 (CH), 119.3 (CH), 115.4 (CH), 115.0 (CH), 114.0 (CH), 111.7 (CH), 111.6 (C), 101.2 (CH), 61.0 (CH), 55.7 (CH_3), 52.7 (CH_2), 34.1 (CH_2), 30.5 (CH_2), 22.5 (CH_2), 13.4 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{43}H_{37}ClN_3O_6^+$ 726.2365, found 726.2358.

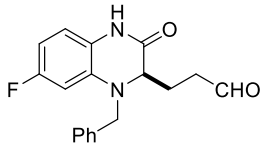
3-(1,4-Dibenzyl-3-oxo-1,2,3,4-tetrahydroquinoxalin-2-yl)propanal (5.14ba)



Using 1,4-dibenzyl-3,4-dihydroquinoxalin-2(1*H*)-one (**5.1b**, 32.8 mg, 0.1 mmol) and acrolein (**5.13a**, 33 µL, 0.5 mmol, 5 equiv.), in accordance with GP-2, product **5.14ba** was obtained (18.5 mg, 0.048 mmol, 48% yield, colorless oil) after column chromatography using hexane-diethyl ether (from 5:5 to 2:8) mixtures.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.81 – 9.64 (m, 1H), 7.43 – 7.14 (m, 10H), 7.00 – 6.70 (m, 4H), 5.43 (d, J = 16.2 Hz, 1H), 4.91 (d, J = 16.3 Hz, 1H), 4.65 (d, J = 14.8 Hz, 1H), 4.28 (d, J = 14.8 Hz, 1H), 3.97 (dd, J = 9.3, 5.7 Hz, 1H), 2.66 – 2.40 (m, 2H), 2.09 – 1.93 (m, 1H), 1.92 – 1.77 (m, 1H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 200.8 (CH), 166.7 (C), 136.7 (C), 136.6 (C), 135.0 (C), 129.3 (C), 128.8 (CH), 128.8 (CH), 127.8 (CH), 127.7 (CH), 127.2 (CH), 126.2 (CH), 124.1 (CH), 119.9 (CH), 115.5 (CH), 115.1 (CH), 61.3 (CH), 53.6 (CH_2), 45.8 (CH_2), 39.9 (CH_2), 20.3 (CH_2); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{25}H_{25}N_2O_2^+$ 385.1911, found 385.1919.

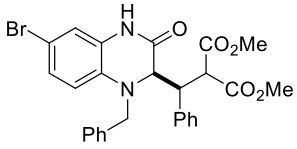
3-(1-Benzyl-7-fluoro-3-oxo-1,2,3,4-tetrahydroquinoxalin-2-yl)propanal (5.14ca)



Using 4-benzyl-6-fluoro-3,4-dihydroquinoxalin-2(1*H*)-one (**5.1c**, 25.6 mg, 0.1 mmol) and acrolein (**5.13a**, 33 μL, 0.5 mmol, 5 equiv.), in accordance with GP-2, product **5.14ca** was obtained (25.6 mg, 0.082 mmol, 82% yield, colorless oil) after column chromatography using hexane-diethyl ether (from 5:5 to 2:8) mixtures.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.70 (s, 1H), 8.93 (bs, 1H), 7.43 – 7.20 (m, 5H), 6.78 – 6.64 (m, 1H), 6.62 – 6.37 (m, 2H), 4.59 (d, *J* = 15.2 Hz, 1H), 4.30 (d, *J* = 15.1 Hz, 1H), 3.89 (dd, *J* = 9.3, 4.8 Hz, 1H), 2.74 – 2.50 (m, 2H), 2.02 (dtd, *J* = 14.1, 7.6, 4.9 Hz, 1H), 1.85 (dddd, *J* = 13.9, 9.3, 7.4, 6.2 Hz, 1H); **^{19}F{^{1}H}-NMR (282 MHz, $CDCl_3$)** δ -117.37; **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 200.6 (CH), 167.2 (C), 160.0 (C, d, JC-F = 240.7 Hz), 135.9 (C), 135.1 (C, d, JC-F = 10.5 Hz), 128.9 (CH), 127.9 (CH), 127.6 (CH), 121.9 (C, d, JC-F = 2.3 Hz), 115.9 (CH, d, JC-F = 9.8 Hz), 105.2 (CH, d, JC-F = 23.4 Hz), 101.5 (CH, d, JC-F = 27.4 Hz), 60.5 (CH), 52.7 (CH_2), 39.6 (CH_2), 21.0 (CH_2); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{18}H_{18}FN_2O_2^+$ 313.1347, found 313.1350.

Dimethyl 2-((1-benzyl-6-bromo-3-oxo-1,2,3,4-tetrahydroquinoxalin-2-yl)(phenyl) methyl) malonate (5.3da)



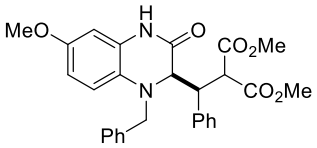
Using 4-benzyl-7-bromo-3,4-dihydroquinoxalin-2(1*H*)-one (**5.1d**, 41.2 mg, 0.13 mmol) and dimethyl 2-benzylidenemalonate (**5.2a**, 22 mg, 0.1 mmol, 1 equiv.), in accordance with GP-1, product **5.3da** was obtained (35.8 mg, 0.066 mmol, 66% yield, yellowish oil) as a mixture of diastereoisomers (dr 1:1) that can be separated by column chromatography using hexane-diethyl ether (from 5:5 to 2:8) mixtures.

Characterization data for **5.3da'**: **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 8.24 (bs, 1H), 7.35 – 7.17 (m, 5H), 7.12 – 6.86 (m, 5H), 6.71 (dd, *J* = 8.6, 2.2 Hz, 1H), 6.24 (d, *J* = 2.2 Hz, 1H), 6.21 (d, *J* = 8.7 Hz, 1H), 4.79 (d, *J* = 16.2 Hz, 1H), 4.78 (d, *J* = 16.3 Hz, 1H), 4.51 (d, *J* = 3.3 Hz, 1H), 4.48 (d, *J* = 12.1 Hz, 1H), 3.95 (dd, *J* = 12.0, 3.3 Hz, 1H), 3.79 (s, 3H), 3.38 (s, 3H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 168.9 (C), 167.8 (C), 166.3 (C), 136.4 (C), 134.5 (C), 132.6 (C), 128.7 (CH), 127.8 (CH), 127.7 (CH), 127.7 (CH), 127.5 (CH), 126.9 (CH), 126.2 (CH), 125.8 (C), 117.1 (CH), 113.7 (CH), 109.3 (C), 64.8 (CH), 53.7 (CH), 53.0 (CH_3), 52.5 (CH_3), 51.9 (CH_2), 47.1 (CH); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{27}H_{26}BrN_2O_5^+$ 537.1020, found 537.1026.

Characterization data for **5.3da''**: **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 8.66 (bs, 1H), 7.32 – 7.24 (m, 4H), 7.23 – 7.08 (m, 4H), 7.02 (dd, *J* = 8.5, 2.2 Hz, 1H), 6.97 – 6.86 (m, 3H),

6.40 (d, *J* = 8.6 Hz, 1H), 4.21 (d, *J* = 9.6 Hz, 1H), 4.11 (d, *J* = 10.3 Hz, 1H), 3.93 (d, *J* = 15.4 Hz, 1H), 3.73 (d, *J* = 10.0 Hz, 1H), 3.68 (s, 3H), 3.38 (d, *J* = 15.5 Hz, 1H), 3.31 (s, 3H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 168.2 (C), 167.4 (C), 167.1 (C), 137.2 (C), 136.4 (C), 132.2 (C), 129.4 (CH), 128.6 (CH), 128.5 (CH), 128.3 (C), 128.0 (CH), 127.6 (CH), 127.3 (CH), 126.6 (CH), 118.2 (CH), 117.1 (CH), 111.7 (C), 65.7 (CH), 55.2 (CH_2), 54.3 (CH), 52.9 (CH_3), 52.3 (CH_3), 45.5 (CH); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{27}H_{26}BrN_2O_5^+$ 537.1020, found 537.1029.

Dimethyl 2-((1-benzyl-6-methoxy-3-oxo-1,2,3,4-tetrahydroquinoxalin-2-yl)(phenyl) methyl) malonate (5.3ea)

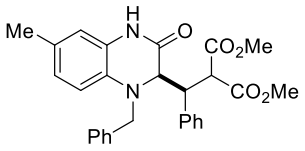


Using 4-benzyl-7-methoxy-3,4-dihydroquinoxalin-2(1*H*)-one (**5.1e**, 34.8 mg, 0.13 mmol) and dimethyl 2-benzylidenemalonate (**5.2a**, 22 mg, 0.1 mmol, 1 equiv.), in accordance with GP-1, product **5.3ea** was obtained (36 mg, 0.074 mmol, 74% yield, yellowish oil) as a mixture of diastereoisomers (dr 1.2:1) that can be separated by column chromatography using hexane-diethyl ether (from 5:5 to 2:8) mixtures.

Characterization data for **5.3ea'**: **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 7.98 (bs, 1H), 7.37 – 7.17 (m, 5H), 7.12 – 6.99 (m, 2H), 6.99 – 6.84 (m, 3H), 6.08 – 5.94 (m, 2H), 5.88 (dd, *J* = 8.4, 2.5 Hz, 1H), 4.83 (d, *J* = 16.1 Hz, 1H), 4.76 (d, *J* = 16.2 Hz, 1H), 4.53 (d, *J* = 12.1 Hz, 1H), 4.46 (d, *J* = 3.2 Hz, 1H), 3.95 (dd, *J* = 12.1, 3.1 Hz, 1H), 3.77 (s, 3H), 3.57 (s, 3H), 3.37 (s, 3H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 169.0 (C), 167.9 (C), 165.5 (C), 156.6 (C), 136.9 (C), 134.8 (C), 134.5 (C), 128.7 (CH), 127.6 (CH), 127.5 (CH), 127.3 (CH), 127.3 (CH), 127.0 (CH), 118.6 (C), 114.6 (CH), 101.7 (CH), 99.7 (CH), 64.7 (CH), 55.4 (CH_3), 53.8 (CH), 53.0 (CH_3), 52.4 (CH_3), 51.6 (CH_2), 47.1 (CH); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{28}H_{29}N_2O_6^+$ 489.2020, found 489.2014.

Characterization data for **5.3ea''**: **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 8.39 (bs, 1H), 7.36 – 7.23 (m, 4H), 7.21 – 7.12 (m, 4H), 7.01 – 6.88 (m, 2H), 6.72 (d, *J* = 8.5 Hz, 1H), 6.36 (dd, *J* = 8.5, 2.6 Hz, 1H), 6.13 (d, *J* = 2.5 Hz, 1H), 4.17 (d, *J* = 9.7 Hz, 1H), 4.12 (d, *J* = 10.3 Hz, 1H), 3.96 (d, *J* = 15.3 Hz, 1H), 3.76 (d, *J* = 10.0 Hz, 1H), 3.71 (s, 3H), 3.68 (s, 3H), 3.31 (d, *J* = 16.3 Hz, 1H), 3.30 (s, 3H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 168.1 (C), 167.6 (C), 166.4 (C), 156.7 (C), 137.6 (C), 136.8 (C), 134.3 (C), 129.5 (CH), 128.5 (CH), 128.4 (CH), 127.9 (CH), 127.4 (CH), 120.9 (C), 115.8 (CH), 104.0 (CH), 102.7 (CH), 65.9 (CH), 55.5 (CH_3), 54.8 (CH_2), 54.4 (CH), 52.8 (CH_3), 52.2 (CH_3), 45.4 (CH); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{28}H_{29}N_2O_6^+$ 489.2020, found 489.2031.

Dimethyl 2-((1-benzyl-6-methyl-3-oxo-1,2,3,4-tetrahydroquinoxalin-2-yl)(phenyl) methyl) malonate (5.3fa)

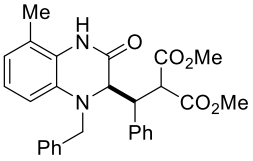


Using 4-benzyl-7-methyl-3,4-dihydroquinoxalin-2(1*H*)-one (**5.1f**, 32.8 mg, 0.13 mmol) and dimethyl 2-benzylidenemalonate (**5.2a**, 22 mg, 0.1 mmol, 1 equiv.), in accordance with GP-1, product **5.3fa** was obtained (47.1 mg, 0.099 mmol, 99% yield, colorless oil) as a mixture of diastereoisomers (dr 1.2:1) that can be separated by column chromatography using hexane-diethyl ether (from 5:5 to 2:8) mixtures.

Characterization data for **5.3fa'**: **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 8.32 (bs, 1H), 7.36 – 7.17 (m, 5H), 7.11 – 6.99 (m, 3H), 6.99 – 6.88 (m, 2H), 6.46 (dd, *J* = 8.2, 1.0 Hz, 1H), 6.30 (d, *J* = 8.2 Hz, 1H), 5.97 (d, *J* = 1.4 Hz, 1H), 4.82 (d, *J* = 16.0 Hz, 1H), 4.70 (d, *J* = 16.0 Hz, 1H), 4.49 (d, *J* = 11.9 Hz, 1H), 4.44 (d, *J* = 3.6 Hz, 1H), 3.93 (dd, *J* = 11.9, 3.6 Hz, 1H), 3.76 (s, 3H), 3.37 (s, 3H), 2.02 (s, 3H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 168.9 (C), 168.0 (C), 166.5 (C), 137.2 (C), 135.1 (C), 131.0 (C), 129.4 (CH), 128.6 (CH), 127.5 (C), 127.5 (CH), 127.3 (CH), 127.2 (CH), 127.1 (CH), 124.8 (C), 124.1 (CH), 115.3 (CH), 112.9 (CH), 64.9 (CH), 54.0 (CH), 52.9 (CH_3), 52.3 (CH_3), 52.2 (CH_2), 47.1 (CH), 20.1 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{28}H_{29}N_2O_5^+$ 473.2071, found 473.2062.

Characterization data for **5.3fa''**: **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 8.89 (bs, 1H), 7.32 – 7.24 (m, 3H), 7.21 – 7.07 (m, 5H), 6.99 – 6.85 (m, 2H), 6.74 (ddd, *J* = 7.9, 1.8, 0.6 Hz, 1H), 6.66 (d, *J* = 1.2 Hz, 1H), 6.47 (d, *J* = 8.1 Hz, 1H), 4.15 (d, *J* = 9.8 Hz, 1H), 4.14 (d, *J* = 10.3 Hz, 1H), 3.96 (d, *J* = 15.3 Hz, 1H), 3.74 (t, *J* = 10.0 Hz, 1H), 3.67 (s, 3H), 3.34 (d, *J* = 15.4 Hz, 1H), 3.29 (s, 3H), 2.27 (s, 3H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 168.2 (C), 167.7 (C), 167.6 (C), 137.7 (C), 137.1 (C), 130.7 (C), 129.7 (C), 129.5 (CH), 129.5 (CH), 128.4 (CH), 128.3 (CH), 127.7 (CH), 127.5 (CH), 127.3 (CH), 127.2 (C), 124.5 (CH), 116.2 (CH), 65.9 (CH), 55.3 (CH_2), 54.4 (CH), 52.8 (CH_3), 52.2 (CH_3), 45.2 (CH), 20.6 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{28}H_{29}N_2O_5^+$ 473.2071, found 473.2065.

Dimethyl-2-((1-benzyl-5-methyl-3-oxo-1,2,3,4-tetrahydroquinoxalin-2-yl)(phenyl) methyl) malonate (5.3ga)



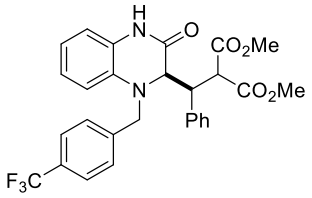
Using 4-benzyl-8-methyl-3,4-dihydroquinoxalin-2(1*H*)-one (**5.1g**, 32.8 mg, 0.13 mmol) and dimethyl 2-benzylidenemalonate (**5.2a**, 22 mg, 0.1 mmol, 1 equiv.), in accordance with GP-1, product **5.3ga** was obtained (44.4 mg, 0.094 mmol, 94% yield, colorless oil) as a mixture of diastereoisomers (dr 1.3:1) that can be sepa-

rated by column chromatography using hexane-diethyl ether (from 5:5 to 2:8) mixtures.

Characterization data for **5.3ga'**: **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 7.77 (bs, 1H), 7.36 – 7.26 (m, 4H), 7.24 – 7.14 (m, 1H), 7.07 – 6.97 (m, 2H), 6.97 – 6.80 (m, 3H), 6.56 (t, *J* = 7.8 Hz, 1H), 6.31 (d, *J* = 8.1 Hz, 1H), 6.20 (d, *J* = 7.5 Hz, 1H), 4.87 (d, *J* = 16.0 Hz, 1H), 4.74 (d, *J* = 16.1 Hz, 1H), 4.50 (d, *J* = 12.1 Hz, 1H), 4.41 (d, *J* = 3.0 Hz, 1H), 3.94 (dd, *J* = 12.1, 3.0 Hz, 1H), 3.76 (s, 3H), 3.37 (s, 3H), 1.83 (s, 3H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 168.9 (C), 167.8 (C), 166.2 (C), 137.2 (C), 134.9 (C), 133.4 (C), 129.3 (CH), 128.6 (CH), 127.5 (CH), 127.2 (CH), 127.1 (CH), 127.0 (CH), 123.1 (CH), 122.8 (C), 122.1 (C), 119.9 (CH), 110.7 (CH), 64.7 (CH), 53.8 (CH), 53.0 (CH_3), 52.4 (CH_3), 51.9 (CH_2), 47.0 (CH), 16.1 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{28}H_{29}N_2O_5^+$ 473.2071, found 473.2069.

Characterization data for **5.3ga"**: **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 8.00 (bs, 1H), 7.28 – 7.22 (m, 3H), 7.22 – 7.11 (m, 3H), 7.12 – 7.01 (m, 2H), 7.01 – 6.89 (m, 2H), 6.84 (t, *J* = 7.7 Hz, 1H), 6.67 (d, *J* = 7.2 Hz, 1H), 6.47 (d, *J* = 8.0 Hz, 1H), 4.17 (d, *J* = 9.4 Hz, 1H), 4.11 (d, *J* = 10.4 Hz, 1H), 4.04 (d, *J* = 15.3 Hz, 1H), 3.83 – 3.61 (m, 4H), 3.39 (d, *J* = 15.4 Hz, 1H), 3.28 (s, 3H), 2.25 (s, 3H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 168.0 (C), 167.6 (C), 166.9 (C), 137.4 (C), 137.0 (C), 133.1 (C), 129.4 (CH), 128.4 (CH), 128.2 (CH), 127.7 (CH), 127.4 (CH), 127.3 (CH), 125.4 (C), 123.4 (C), 123.3 (CH), 121.7 (CH), 114.14 (CH), 65.5 (CH), 55.3 (CH_2), 54.3 (CH), 52.7 (CH_3), 52.2 (CH_3), 45.1 (CH), 16.7 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{28}H_{29}N_2O_5^+$ 473.2071, found 473.2088.

Dimethyl-2-((1-(4-trifluoromethylbenzyl)-3-oxo-1,2,3,4-tetrahydroquinoxalin-2-yl) (phenyl)methyl) malonate (5.3ha)



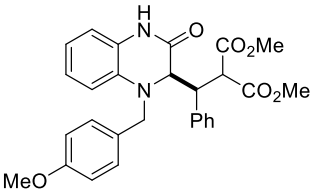
Using 4-(4-trifluoromethylbenzyl)-3,4-dihydroquinoxalin-2-(1*H*)-one (**5.1h**, 39.8 mg, 0.1 mmol) and dimethyl 2-benzylidenemalonate (**5.2a**, 22 mg, 0.1 mmol, 1 equiv.), in accordance with GP-1, product **5.3ha** was obtained (25.4 mg, 0.048 mmol, 48% yield, yellowish oil) as a mixture of diastereoisomers (dr 1.6:1) that can be separated by column chromatography using hexane-diethyl ether (from 5:5 to 2:8) mixtures.

Characterization data for **5.3ha'**: **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 7.84 (bs, 1H), 7.54 (d, *J* = 8.2 Hz, 2H), 7.41 (d, *J* = 8.1 Hz, 2H), 7.13 – 6.97 (m, 2H), 6.97 – 6.87 (m, 3H), 6.65 (td, *J* = 8.0, 1.4 Hz, 1H), 6.36 (td, *J* = 7.6, 1.1 Hz, 1H), 6.31 (d, *J* = 8.1 Hz, 1H), 6.12 (dd, *J* = 7.7, 1.4 Hz, 1H), 4.93 (d, *J* = 16.5 Hz, 1H), 4.83 (d, *J* = 16.6 Hz, 1H), 4.52 (d, *J* = 12.0 Hz, 1H), 4.48 (d, *J* = 3.0 Hz, 1H), 3.95 (dd, *J* = 12.1, 3.1 Hz, 1H), 3.78 (s, 3H), 3.37 (s, 3H); **^{19}F{^{1}H}-NMR (282 MHz, $CDCl_3$)** δ -62.48 (s); **^{13}C{^{1}H}-NMR (75**

MHz, $CDCl_3$) δ 169.1 (C), 167.9 (C), 166.0 (C), 141.3 (C), 134.6 (C), 132.9 (C), 129.6 (C, q, JC-F = 32.1 Hz), 129.5 (CH), 127.7 (CH), 127.5 (CH), 127.2 (CH), 125.6 (CH, q, JC-F = 3.9 Hz), 124.6 (C), 124.1 (C, q, JC-F = 271.5 Hz), 123.8 (CH), 118.3 (CH), 114.5 (CH), 112.2 (CH), 65.0 (CH), 53.8 (CH), 53.0 (CH_3), 52.4 (CH_3), 51.2 (CH_2), 47.2 (CH); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{28}H_{26}F_3N_2O_5^+$ 527.1788, found 527.1785.

Characterization data for **5.3ha''**: **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 8.52 (bs, 1H), 7.43 (d, *J* = 8.1 Hz, 2H), 7.36 – 7.27 (m, 3H), 7.18 – 7.10 (m, 2H), 7.03 (d, *J* = 8.1 Hz, 2H), 6.98 – 6.90 (m, 1H), 6.87 – 6.82 (m, 2H), 6.51 (d, *J* = 7.8 Hz, 1H), 4.22 – 4.08 (m, 2H), 4.00 (d, *J* = 15.9 Hz, 1H), 3.82 – 3.70 (m, 1H), 3.68 (s, 3H), 3.42 (d, *J* = 16.0 Hz, 1H), 3.31 (s, 3H); **^{19}F{^{1}H}-NMR (282 MHz, $CDCl_3$)** δ -62.52 (s); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 168.2 (C), 167.5 (C), 167.1 (C), 141.2 (C, q, JC-F = 1.7 Hz), 137.5 (C), 132.5 (C), 129.8 (C), 129.4 (CH, q, JC-F = 1.7 Hz), 128.5 (CH), 128.0 (CH), 127.6 (CH), 127.2 (C), 125.5 (CH, q, JC-F = 3.9 Hz), 124.1 (CH), 124.0 (C, q, JC-F = 272.0 Hz), 120.4 (CH), 115.9 (CH), 115.7 (CH), 66.3 (CH), 54.5 (CH_2), 54.4 (CH), 52.8 (CH_3), 52.3 (CH_3), 45.3 (CH); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{28}H_{26}F_3N_2O_5^+$ 527.1788, found 527.1791.

Dimethyl-2-((1-(4-methoxybenzyl)-3-oxo-1,2,3,4-tetrahydroquinoxalin-2-yl)(phenyl) methyl) malonate (5.3ia)



Using 4-(4-methoxybenzyl)-3,4-dihydroquinoxalin-2(1*H*)-one (**5.1i**, 34.8 mg, 0.1 mmol) and dimethyl 2-benzylidenemalonate (**5.2a**, 22 mg, 0.1 mmol, 1 equiv.), in accordance with GP-1, product **5.3ia** was obtained (41.1 mg, 0.084 mmol, 84% yield, yellowish oil) as a mixture of diastereoisomers (dr 1:1) that can be separated by column chromatography using hexane-diethyl ether (from 5:5 to 2:8) mixtures.

Characterization data for **5.3ia'**: **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 8.21 (bs, 1H), 7.14 (d, *J* = 8.7 Hz, 2H), 7.02 – 6.91 (m, 2H), 6.90 – 6.80 (m, 3H), 6.74 (d, *J* = 8.7 Hz, 2H), 6.62 – 6.55 (m, 1H), 6.34 (d, *J* = 8.0 Hz, 1H), 6.27 (td, *J* = 7.6, 1.1 Hz, 1H), 6.07 (dd, *J* = 7.7, 1.4 Hz, 1H), 4.74 (d, *J* = 15.7 Hz, 1H), 4.59 (d, *J* = 15.8 Hz, 1H), 4.43 (d, *J* = 12.0 Hz, 1H), 4.39 (d, *J* = 3.3 Hz, 1H), 3.87 (dd, *J* = 12.0, 3.3 Hz, 1H), 3.74 – 3.69 (m, 4H), 3.68 (s, 3H), 3.29 (s, 3H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 168.9 (C), 167.9 (C), 166.3 (C), 158.8 (C), 134.9 (C), 133.4 (C), 129.4 (CH), 128.9 (C), 128.3 (CH), 127.6 (CH), 127.5 (CH), 124.7 (C), 123.7 (CH), 117.8 (CH), 114.5 (CH), 114.0 (CH), 112.6 (CH), 64.5 (CH), 55.2 (CH_3), 53.9 (CH), 53.0 (CH_3), 52.4 (CH_3), 51.3 (CH_2), 47.1 (CH); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{28}H_{29}N_2O_6^+$ 489.2020, found 489.2017.

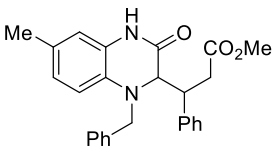
Characterization data for **5.3ia''**: **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 8.71 (bs, 1H), 7.28

– 7.24 (m, 3H), 7.14 – 7.08 (m, 2H), 6.99 – 6.90 (m, 1H), 6.89 – 6.79 (m, 4H), 6.72 (d, J = 8.8 Hz, 2H), 6.59 (d, J = 7.9 Hz, 1H), 4.17 (d, J = 9.6 Hz, 1H), 4.13 (d, J = 10.4 Hz, 1H), 4.00 (d, J = 14.9 Hz, 1H), 3.86 – 3.71 (m, 5H), 3.67 (s, 3H), 3.29 (s, 3H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 168.2 (C), 167.6 (C), 167.3 (C), 158.9 (C), 137.5 (C), 133.3 (C), 129.5 (CH), 128.8 (C), 128.8 (CH), 128.3 (CH), 127.8 (CH), 127.2 (C), 124.0 (CH), 119.9 (CH), 116.1 (CH), 115.5 (CH), 113.9 (CH), 65.1 (CH), 55.2 (CH_3), 54.6 (CH_2), 54.4 (CH), 52.8 (CH_3), 52.2 (CH_3), 45.4 (CH); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{28}H_{29}N_2O_6^+$ 489.2020, found 489.2022.

Specific Procedure 1 (SP-1) for the Gram-Scale Photocatalytic Giese Reaction between 3,4-dihydroquinoxalin-2-one 5.1a and Endione 5.11a under Sunlight Irradiation

An ovendried 100 mL Schlenck tube was charged with $Ru(bpy)_3Cl_2$ (18.7 mg, 0.025 mmol, 1 mol %), diphenyl phosphoric acid (62.5 mg, 0.25 mmol, 10 mol %), 4-benzyl-3,4-dihydroquinoxalin-2(1*H*)-one (**5.1a**, 774 mg, 3.25 mmol, 1.3 equiv.) and (*E*)-1,2-dibenzoylethylene (**5.11a**, 591 mg, 2.5 mmol, 1 equiv.). The reaction vessel was evacuated and backfilled with argon three times. After this, freshly degassed and dried MeCN (25 mL) was added via syringe and the reaction mixture was placed at the upper part of the building in sunny hours under vigorous stirring (see page 434 for further details about the photochemical setup). After consumption of (*E*)-1,2-dibenzoylethylene (3 hours) the reaction mixture was filtered through a pad of silica eluting with EtOAc and ^{1}H-NMR spectrum was recorded to determine the diastereomeric ratio. Then, the crude mixture was purified by flash column chromatography using hexane-diethyl ether (from 5:5 to 2:8) mixtures. to afford 2-(1-benzyl-3-oxo-1,2,3,4-tetrahydroquinoxalin-2-yl)-1,4-diphenylbutane-1,4-dione (**5.12aa**, 1.15 g, 2.425 mmol, 97% yield) as an inseparable mixture of diastereoisomers (3.8:1 dr), whose spectroscopic data match with the ones for the product obtained using GP-1.

Methyl 3-(1-benzyl-6-methyl-3-oxo-1,2,3,4-tetrahydroquinoxalin-2-yl)-3-phenylpropanoate (5.19)

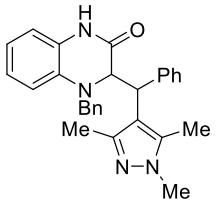


To a solution of **5.3fa'** (25.9 mg, 0.055 mmol, 1 equiv.) in DMSO (1 mL), water (6 μL, 0.35 mmol, 6.3 equiv.) and LiCl were added (11.9 mg, 0.28 mmol, 5.1 equiv.) and the resulting reaction mixture was stirred at 140 °C for 5 hours. After this period of time, the reaction mixture was diluted with water and the aqueous phase was extracted with EtOAc (x3). The combined organic phases were dried over $MgSO_4$, filtered and evaporated under reduced pressure. Finally, the residue was purified by column chromatography using hexane:DCM mixtures to afford decarboxylated product **5.19** (12.4 mg, 0.030 mmol, 54%

yield, yellowish oil).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.21 (bs, 1H), 7.64 – 7.18 (m, 5H), 7.05 (m, 5H), 6.64 – 6.59 (m, 1H), 6.54 (d, J = 8.2 Hz, 1H), 6.15 (d, J = 1.3 Hz, 1H), 4.68 (d, J = 15.4 Hz, 1H), 4.34 (d, J = 15.4 Hz, 1H), 4.13 (d, J = 5.2 Hz, 1H), 3.62 – 3.54 (m, 1H), 3.55 (s, 3H), 3.05 (dd, J = 16.4, 7.3 Hz, 1H), 2.72 (dd, J = 16.4, 8.0 Hz, 1H), 2.13 (s, 3H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 172.4 (C), 166.4 (C), 138.6 (C), 137.0 (C), 131.2 (C), 128.9 (C), 128.6 (CH), 128.6 (CH), 127.9 (CH), 127.6 (CH), 127.5 (CH), 127.0 (CH), 126.1 (C), 124.4 (CH), 115.7 (CH), 114.7 (CH), 66.4 (CH), 54.5 (CH_2), 51.6 (CH_3), 43.7 (CH), 36.6 (CH), 20.3 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{26}H_{27}N_2O_3^+$ 415.2016, found 415.2018.

4-Benzyl-3-(phenyl(1,3,5-trimethyl-1*H*-pyrazol-4-yl)methyl)-3,4-dihydroquinoxalin-2(1*H*)-one (5.20)



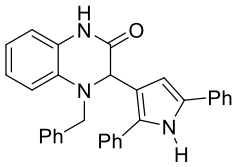
A solution of **5.8aa** (31.2 mg, 0.073 mmol, 1 eq., 1:1 dr), methylhydrazine (77 μL, 1.46 mmol, 2 equiv.) and acetic acid (84 μL, 1.46 mmol, 2 equiv.) in dioxane (2 mL) was stirred at reflux temperature for 1 hour. Then, the solvent was removed under reduced pressure and the residue was partitioned between EtOAc and water. After the separation of the layers, the organic phase was washed with saturated aqueous $NaHCO_3$ and with brine. The organic phase was dried over $MgSO_4$ and concentrated under vacuum. Finally, the residue was purified by column chromatography using hexane:EtOAc mixtures to obtain pyrazole **5.20** (30.2 mg, 0.069 mmol, 95% yield, colorless oil) as a 1:1 mixture of separable diasteromers.

Characterization data for **5.20'**: **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 8.43 (bs, 1H), 7.40 – 7.14 (m, 7H), 7.14 – 7.06 (m, 3H), 6.96 (td, J = 7.7, 1.5 Hz, 1H), 6.84 (td, J = 7.6, 1.2 Hz, 1H), 6.74 (dd, J = 7.7, 1.5 Hz, 1H), 6.64 (d, J = 7.7 Hz, 1H), 4.69 (dd, J = 10.1, 0.8 Hz, 1H), 4.31 (d, J = 15.3 Hz, 1H), 4.01 (d, J = 10.1 Hz, 1H), 3.91 (d, J = 15.3 Hz, 1H), 3.68 (s, 3H), 1.97 (s, 3H), 1.85 (s, 3H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 165.7 (C), 145.3 (C), 139.3 (C), 136.9 (C), 136.6 (C), 133.5 (C), 128.6 (CH), 128.5 (CH), 127.9 (CH), 127.5 (CH), 127.4 (CH), 127.1 (C), 126.5 (CH), 124.1 (CH), 119.7 (CH), 115.8 (C), 115.6 (CH), 115.2 (CH), 63.5 (CH), 54.5 (CH_2), 41.9 (CH_3), 36.0 (CH), 13.0 (CH_3), 10.3 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{28}H_{28}N_4O^+$ 437.2336, found 437.2329.

Characterization data for **5.20''**: **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 8.13 (bs, 1H), 7.35 – 7.18 (m, 6H), 7.16 – 7.05 (m, 2H), 7.05 – 6.91 (m, 3H), 6.86 (td, J = 7.6, 1.2 Hz, 1H), 6.77 (dd, J = 7.7, 1.4 Hz, 1H), 6.68 (d, J = 7.7 Hz, 1H), 4.67 (dd, J = 10.4, 1.0 Hz, 1H), 4.21 (d, J = 15.1 Hz, 1H), 3.98 (d, J = 10.4 Hz, 1H), 3.61 (d, J = 15.0 Hz, 1H), 3.56 (s,

3H), 2.13 (s, 3H), 2.10 (s, 3H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 164.8 (C), 145.6 (C), 141.7 (C), 136.8 (C), 136.7 (C), 133.3 (C), 128.6 (CH), 128.5 (CH), 128.5 (CH), 127.7 (CH), 127.4 (CH), 127.1 (C), 126.9 (CH), 124.0 (CH), 119.6 (CH), 115.3 (CH), 115.2 (CH), 114.36 (C), 63.5 (CH), 54.5 (CH_2), 42.3 (CH_3), 35.8 (CH), 13.3 (CH_3), 11.2 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* [M + H]$^+$ calcd for $C_{28}H_{28}N_4O^+$ 437.2336, found 437.2331.

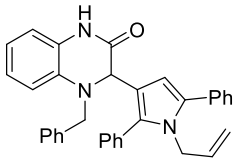
4-Benzyl-3-(2,5-diphenyl-1*H*-pyrrol-3-yl)-3,4-dihydroquinoxalin-2(1*H*)-one (5.21a)



A solution of **5.12aa** (118.6 mg, 0.25 mmol, 1 equiv.) and ammonium acetate (385 mg, 5 mmol, 20 equiv.) in a mixture of EtOH (4 mL) and $CHCl_3$ (6 mL) was stirred at 50 °C until completion. Then, the solvent mixture was removed under reduced pressure and the residue was purified by column chromatography using hexane:EtOAc mixtures to afford N-H pyrrole **5.21a** (92.8 mg, 0.204 mmol, 82% yield, colorless oil).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.45 (bs, 1H), 8.69 (bs, 1H), 7.78 – 7.56 (m, 2H), 7.51 – 7.23 (m, 7H), 7.17 (t, *J* = 7.1 Hz, 1H), 7.13 – 6.75 (m, 7H), 6.68 (d, *J* = 8.0 Hz, 1H), 6.06 (d, *J* = 2.6 Hz, 1H), 5.09 (s, 1H), 4.41 (d, *J* = 14.8 Hz, 1H), 3.80 (d, *J* = 14.8 Hz, 1H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 176.1 (C), 168.9 (C), 136.4 (C), 134.9 (C), 132.7 (C), 132.4 (C), 131.9 (C), 128.9 (CH), 128.8 (CH), 128.3 (CH), 128.1 (CH), 127.7 (CH), 127.5 (CH), 127.0 (CH), 126.5 (CH), 125.8 (C), 124.4 (CH), 123.8 (CH), 118.7 (CH), 117.6 (C), 115.4 (CH), 112.7 (CH), 105.2 (CH), 56.8 (CH), 51.0 (CH_2); **HRMS (ESI/Q-TOF)** *m/z* [M + H]$^+$ calcd for $C_{28}H_{27}N_2O_6^+$ 456.2070, found 456.2077.

3-(1-Allyl-2,5-diphenyl-1*H*-pyrrol-3-yl)-4-benzyl-3,4-dihydroquinoxalin-2(1*H*)-one (5.21b)



Allylamine (131 μL, 1.75 mmol, 7 equiv.) and acetic acid (0.23 mL, 4 mmol, 16 equiv.) were added to a solution of **5.12aa** (118.6 mg, 0.25 mmol, 1 equiv.) in a mixture of EtOH (4 mL) and $CHCl_3$ (6 mL). The reaction mixture was stirred at 50 °C until completion. Then, the solvent was removed under reduced pressure and the residue was purified by column chromatography using hexane-EtOAc mixtures. to obtain the corresponding allyl pyrrole **5.21b** (76.8 mg, 155 mmol, 61% yield, colorless oil).

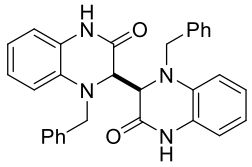
^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.25 (bs, 1H), 7.62 – 7.22 (m, 10H), 7.22 – 7.11 (m, 3H), 7.10 – 7.02 (m, 2H), 6.92 – 6.80 (m, 2H), 6.73 (td, *J* = 7.6, 1.1 Hz, 1H), 6.57 (d, *J* = 7.9 Hz, 1H), 5.88 (s, 1H), 5.56 (ddt, *J* = 17.0, 10.3, 4.5 Hz, 1H), 4.94 (dd, *J* = 10.4, 1.3 Hz, 1H), 4.85 (s, 1H), 4.57 (dd, *J* = 17.1, 1.2 Hz, 1H), 4.47 – 4.39 (m, 2H), 4.36 (d,

J = 15.6 Hz, 1H), 3.95 (d, *J* = 15.6 Hz, 1H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 168.4 (C), 137.3 (C), 135.2 (C), 134.8 (CH), 134.6 (C), 133.2 (C), 131.3 (C), 129.1 (CH), 128.3 (CH), 128.2 (CH), 128.1 (CH), 127.9 (CH), 127.2 (CH), 127.1 (CH), 126.8 (CH), 125.9 (C), 124.0 (CH), 118.3 (CH), 117.7 (C), 116.1 (CH_2), 115.18 (CH), 112.8 (CH), 107.1 (CH), 58.5 (CH), 51.5 (CH_2), 47.2 (CH_2); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{34}H_{29}N_3O^+$ 496.2383, found 496.2375.

Isolation and characterization of 3,4-dihydroquinoxalin-2-one dimer (5.4)

In low-yielding reactions, a large amount of 3,4-dihydroquinoxalin-2-one dimer (**5.4**) was obtained. It was isolated as a single diasteromer by removing the mother liquor and washing the solid with DCM. Dimer **5.4** was characterized by ^{1}H-NMR, ^{13}C-NMR and HRMS.

1,1'-Dibenzyl-1,1',4,4'-tetrahydro-[2,2'-biquinoxaline]-3,3'(2*H*,2'*H*)-dione (5.4)



^{1}H-NMR (300 MHz, DMSO-d_6) δ 10.68 (bs, 1H), 7.25 – 7.11 (m, 3H), 7.07 – 6.96 (m, 2H), 6.88 (dd, J = 7.3, 1.9 Hz, 1H), 6.79 – 6.63 (m, 2H), 6.41 (dd, J = 7.5, 1.7 Hz, 1H), 4.65 (d, J = 15.7 Hz, 1H), 4.02 (d, J = 15.8 Hz, 1H), 3.94 (s, 1H); **^{13}C{^{1}H}-NMR (75 MHz, DMSO-d_6)** δ 164.4 (C), 137.5 (C), 132.4 (C), 128.4 (CH), 127.2 (CH), 127.1 (CH), 127.0 (C), 123.0 (CH), 118.7 (CH), 115.0 (CH), 114.1 (CH), 63.2 (CH), 53.2 (CH_2); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for C30H27N4O2 475.2129, found 475.2133.

Chapter 6

Light-Accelerated Amination of 3,4-Dihydroquinoxalin-2-ones with Dialkyl Azodicarboxylates

6.1 Introduction and state of the art

Diazenes, namely molecules that contain the azo (−N=N−) functional group, are a particular class of compounds with deep implications in organic chemistry for both fundamental and applied research.[208–210] Typically, the groups directly attached to the azo group are aromatics. One of the most studied diazenes are, in fact, azobenzene (Figure 6.1) and its derivatives, which exhibit an efficient *E*,*Z*-isomerization promoted by light that has applications in, for example, pharmacology.[211–214] Moreover, the azo group is quite prominent in the dye industry, given that it may behave as chromophore, thus conferring the molecule a strong absorption in the visible region. In *Chapter* 4, tartrazine was shown as pyrazolone-containing dye, but it also contains the −N=N− group so it is also considered an azo dye (Figure 3.2). Other azo dyes are Pigment Yellow 10 or Basic Red 18 (Figure 6.1).

Another particular azo derivatives are dialkyl azodicarboxylates. In these compounds, the −N=N− motif is directly linked to ester groups. The placement of these two electron-withdrawing groups confers electrophilic character to the two nitrogen atoms, which has already been exploited in organic synthesis.[215,216] A relevant transformation that relies in the use of dialkyl azodicarboxylates as reagents is the widely-employed Mitsunobu reaction, which efficiently converts alcohols in many other functional groups thorough an S_N2 mechanism.[217] In this transformation, a dialkyl azodicarboxylate reacts as electrophile

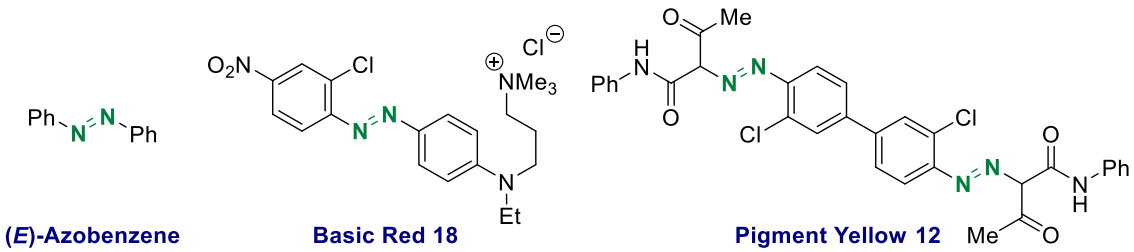


Figure 6.1: Relevant molecules containing the azo functional group.

with a tertiary phosphine to form a zwitterionic specie (Huisgen zwitterion). When the corresponding alcohol reacts with this zwitterion, the result is the formation of a phosphaoxonium cation, which can be considered an activated alcohol to undergo substitution reactions. The final S_N2 reaction of it with a nucleophile yields the desired product with an inversion of the configuration at the carbon center.

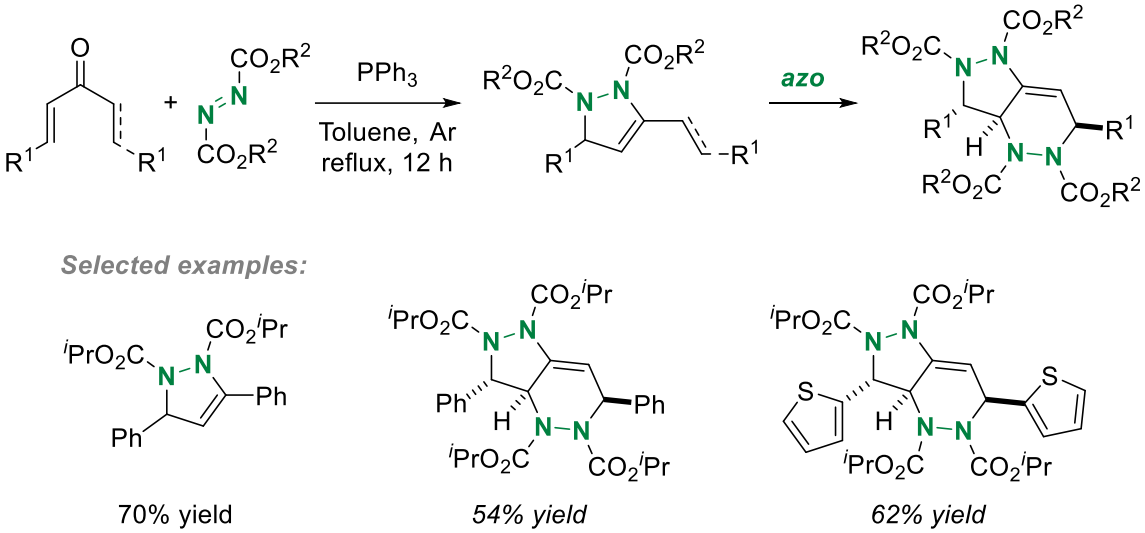
Dialkyl azodicarboxylates can also play an oxidant role in several organic transformations. Specifically, they have been applied to the oxidation of tertiary amines to the corresponding iminium cations, which subsequently suffer a nucleophilic attack.[180,218–223]

Selected Examples

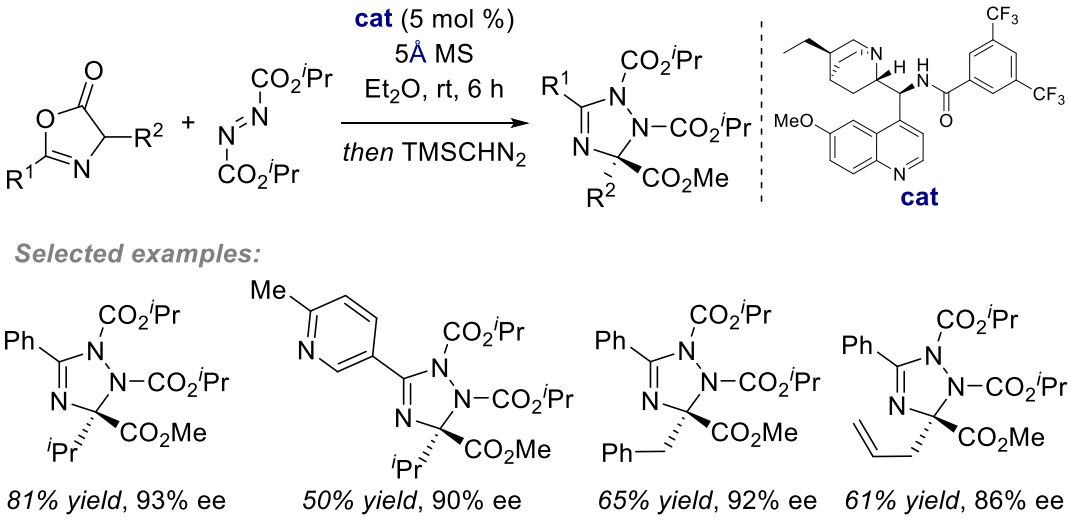
Nonetheless, dialkyl azodicarboxylates have also been employed as substrates for a broad range of reactions. Its strong electrophilic character offers a straightforward strategy towards the incorporation of two consecutive nitrogen atoms to several molecular architectures. Besides they can grant access to nitrogen-containing heterocycles, as in the case of the report from the laboratory of Nair in 2013.[224] In that work they identified that the reaction between chalcones and different dialkyl azodicarboxylates could access highly substituted pyrazole derivatives (Scheme 6.1). Moreover, if dibenzalacetones are subjected to this reaction, the resultant pyrazole-derived product bears a perfect platform for a subsequent [4+2]-cycloaddition with another equivalent of diazo compound, leading to the formation of complex pyrazolopyridazines.

Later on, in 2013, the research group of Huang, envisioned that the asymmetric reaction of isoxazol-5-ones with diisopropyl azodicarboxylate (DIAD), and the subsequent treatment of the intermediate with $TMSCHN_2$ would access to complex 1,2,3-triazines in an enantioselective manner (Scheme 6.2).[225] In this case, they employed a chiral amide derived from dihydroquinine as organocatalyst.

On the other hand, dialkyl azodicarboxylates have found a particular role as electrophilic amination reactants for the formation of new C−N bonds. In fact, they are specially useful for the α-amination of tertiary amines as demonstrated by the laboratory of Nishibayashi in 2012.[226] In that report, the authors resorted to the use of an iridium pho-

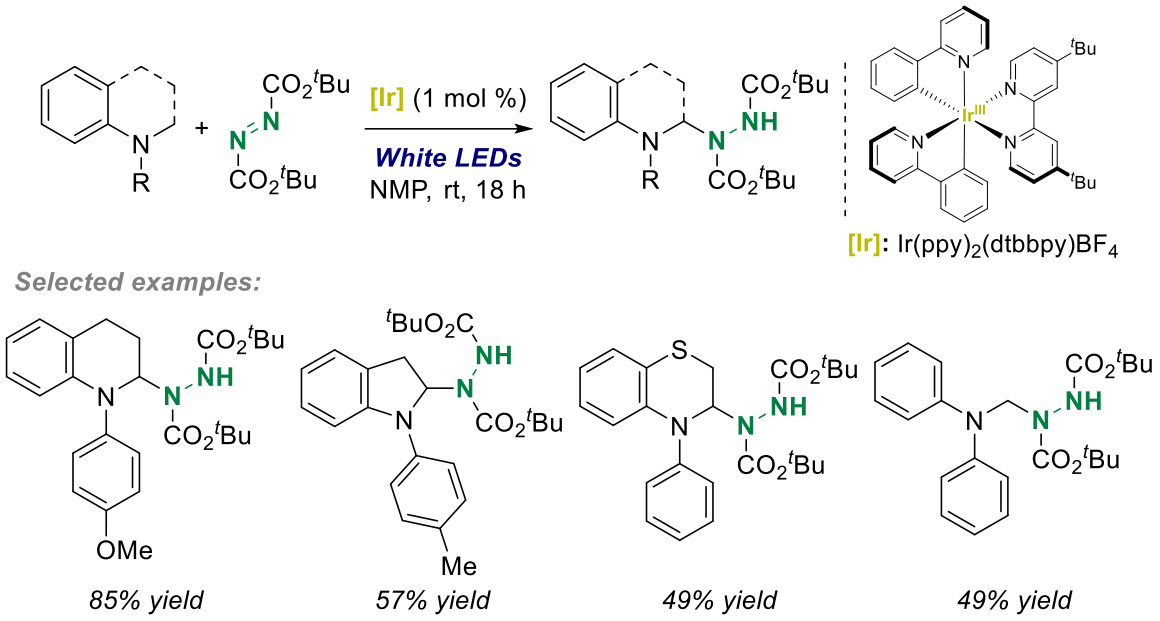


Scheme 6.1: Synthesis of pyrazoles or pyrazolopyridazines from enones and dialkyl azodicarboxylates (Nair).



Scheme 6.2: Enantioselective synthesis of 1,2,4-triazolines from isoxazon-5-one derivatives and DIAD (Huang).

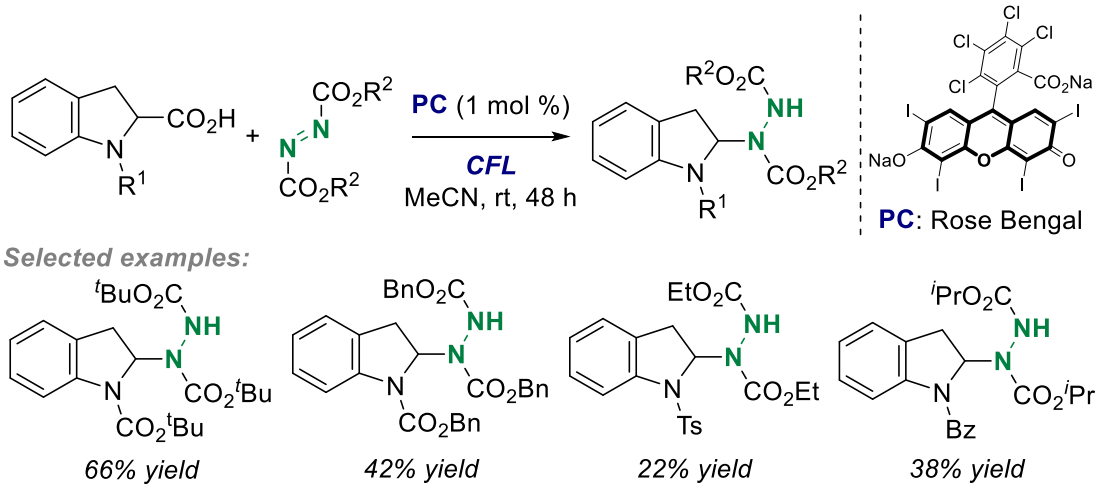
tocatalyst to generate the corresponding nucleophilic α-amino radical of tertiary anilines. That radical reacted with di-*tert*-butylazodicarboxylate to form an assortment of aminals in moderate to good yields (Scheme 6.3). However, it is important to note that, although the performance of the reaction is better under visible-light photoredox catalysis, it can also proceed in the dark.



Scheme 6.3: α-Amination of tertiary anilines with di-*tert*-butylazodicarboxylate under photoredox catalysis (Nishibayashi).

In 2016, the group of He and Guan moved the same transformation as above to organophotoredox catalysis.[227] However, for that purpose they had to use more sophisticated α-amino carboxylic acids as α-amino radical precursors after decarboxylation (Scheme 6.4). Using Rose Bengal as photocatalyst they attained the reaction with different dialkyl azodicarboxylates, although the corresponding products were generated in low to moderate yields.

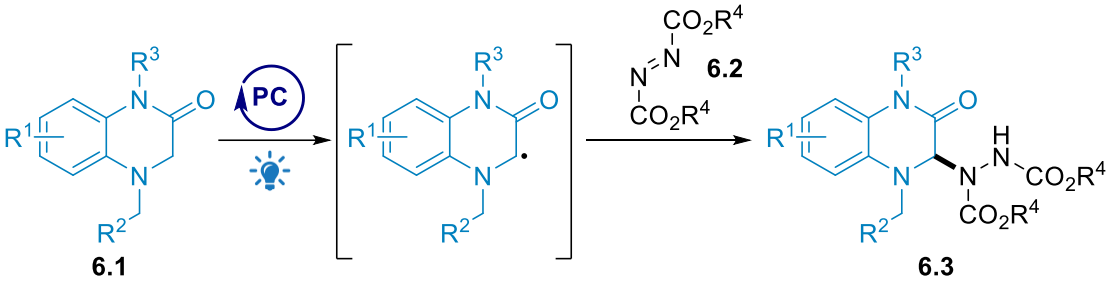
In light of these antecedents, and after realizing in *Chapter* 5 that the 1,4-addition of the α-amino radical of 3,4-dihydroquinoxalin-2-one to electron-poor alkenes was efficient, we interrogated if dialkyl azodicarboxylates could also serve as 1,4-substrates in the radical amination of 3,4-dihydroquinoxalin-2-ones using under visible-light photoredox catalysis.



Scheme 6.4: α-Amination of cyclic tertiary amines with dialkyl azodicarboxylates under organophotoredox catalysis (He and Guan).

6.2 Objectives

The main objective for this *Chapter* is to develop a methodology to functionalize 3,4-dihydroquinoxalin-2-ones (**6.1**) with dialkyl azodicarboxylates (**6.2**) employing visible-light photoredox catalysis to generate the α-amino radical of **6.1**. To achieve this objective, several partial objectives are postulated:



1. Optimization of the reaction conditions between 4-benzyl-3,4-dihydroquinoxalin-2-one **6.1a** and diisopropyl azodicarboxylate (**6.2a**) to obtain the corresponding amination product **6.3aa** with the highest yield.

2. Study of the scope of the reaction between different 3,4-dihydroquinoxalin-2-ones (**6.1**) and different dialkyl azodicarboxylates (**6.2**).

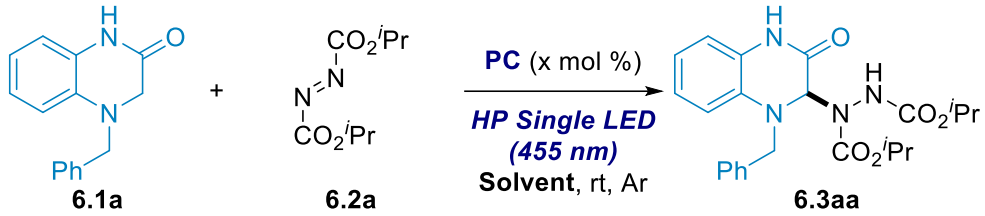
3. Synthetic transformations of the amination products **6.3**.

4. Mechanistic investigations to find out the reaction mechanism.

6.3 Results and Discussion

6.3.1 Optimization of the Reaction Conditions

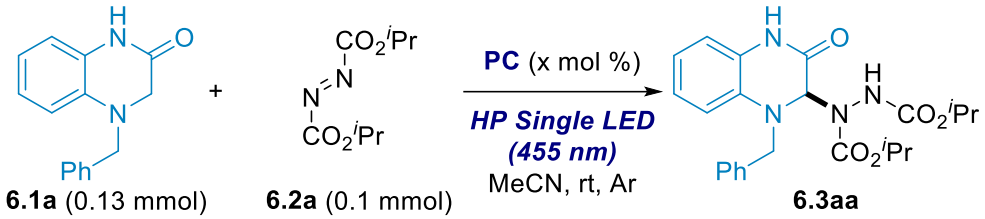
The optimization process will be conducted using 4-benzyl-3,4-dihydroquinoxalin-2-one (**6.1a**) as α-amino radical precursor and diisopropyl azodicarboxylate (**6.2a**) as electrophile to furnish aminated 3,4-dihydroquinoxalin-2-one **6.3aa**. Initially, a screening of potential photoredox catalysts will be conducted, followed by the evaluation of the best solvent to perform the reaction (Scheme 6.5).



Scheme 6.5: Overview of the model reaction to carry out the optimization of the reaction conditions.

Evaluation of the Photoredox Catalyst

Based in our previous results on 1,4-addition of 3,4-dihydroquinoxalin-2-one radical to electrophilic double bonds in *Chapter* 5, we decided to start the optimization process using dry and degassed MeCN as matrix for the amination reaction in the initial evaluation of photoredox catalysts (Scheme 6.6). Additionally, as we were aware of the potential side-reactions that 3,4-dihydroquinoxalin-2-one **6.1a** can experiment, we decided to use 0.13 mmol of **6.1a** and 0.1 mmol of **6.2a**.



Scheme 6.6: Evaluation of the photoredox catalyst in the reaction between **6.1a** and **6.2a** using MeCN as solvent.

The amination reaction between **6.1a** and **6.2a** was initially attempted using the optimal conditions that we employed for the Giese reaction in *Chapter* 5. Thus, $Ru(bpy)_3Cl_2$

Table 6.1: Evaluation of the photoredox catalyst in the reaction between **6.1a** and **6.2a** using MeCN. Yield of **6.3aa**.

Entry[a]	PC (x mol %)	t (h)	Yield 6.3aa (%)[b]
1[c]	$Ru(bpy)_3Cl_2$ (**A**) (1)	2.5	76
2	$Ru(bpy)_3Cl_2$ (**A**) (1)	3	99
3	*fac*-$Ir(ppy)_3$ (**K**) (1)	23	55
4	Rose Bengal (**D**) (5)	23	50
5	Eosin-Y-Na_2 (**E**) (5)	23	65
6	9,10-Phenanthrenequinone (**J**) (5)	20	30
7	[Mes-Acr-Me][BF_4] (**H**) (5)	18	73
8[d]	$Ru(bpy)_3Cl_2$ (**A**) (1)	1.5	98
9[d]	–	2	99
10[de]	–	24	91

[a]Reaction conditions: **6.1a** (0.13 mmol), **6.2a** (0.1 mmol), **PC** (x mol %), MeCN (1 mL), under argon atmosphere and under HP Single LED (455 nm) LEDs irradiation for the indicated time.
[b]Yield determined after purification by column chromatography.
[c]10 mol % of $(PhO)_2PO_2H$ was used.
[d]The reaction was performed with 0.1 mmol of **6.1a** and 0.13 mmol of **6.2a**.
[e]The reaction was performed in the dark.

(**A**) as photocatalyst and $(PhO)_2PO_2H$ as acid catalyst were used. To our delight, the expected aminated product **6.3aa** was isolated in 76% yield after 2.5 hours of irradiation by HP Single LED (455 nm) (Table 6.1, Entry 1). However, in a posterior assay where $(PhO)_2PO_2H$ was not added, product **6.3aa** was obtained in quantitative yield after 3 hours (Table 6.1, Entry 2). This result was really shocking for us, as we demonstrated in *Chapter* 5 that the use of $(PhO)_2PO_2H$ was essential in order to engage 3,4-dihydroquinoxalin-2-one **6.1a** in a SET event. Hence, this amination reaction must proceed through a different mechanism than the Giese reaction.

Moreover, the ability of *fac*-$Ir(ppy)_3$ (**K**) was also checked, offering just a 55% yield of **6.3aa** after 23 hours (Table 6.1, Entry 3). Organophotoredox catalyst were interrogated in their competence to promote the reaction. Specifically, when the reaction was carried out in the presence of either Rose Bengal (**D**) or Eosin-Y-Na_2 (**E**), the yield of product **6.3aa** was 50% and 65% respectively (Table 6.1, Entries 4 and 5). Besides, our surprisingly very active 9,10-phenanthrenequinone (**J**) was also tested in this reaction. However, the expected aminated 3,4-dihydroquinoxalin-2-one **6.3aa** was obtained in only 30% yield

(Table 6.1, Entry 6). Finally, [Mes-Acr-Me][BF_4] (**H**) was investigated as organophotoredox catalyst, being able to generate product **6.3aa** in 73% yield after 18 hours (Table 6.1, Entry 7).

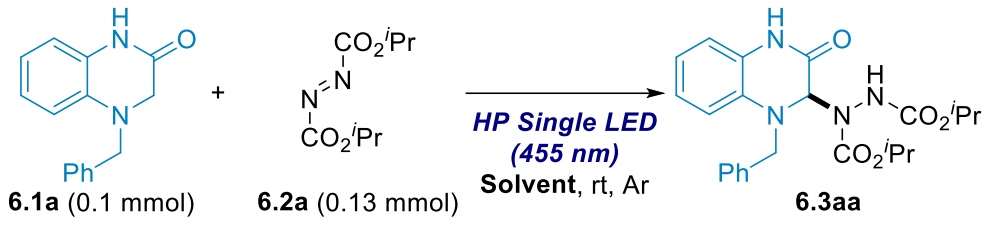
At this point we decided to switch the molar ratio between **6.1a** and **6.2a**, due to the fact that 3,4-dihydroquinoxalin-2-one **6.1a** has to be prepared, whereas diisopropyl azodicarboxylate (**6.2a**) is commercially available. Pleasingly, using 0.1 mmol of **6.1a** and 0.13 mmol of **6.2a**, in the presence of $Ru(bpy)_3Cl_2$ (**A**), the corresponding amination product **6.3aa** was isolated in 98% yield after just 1.5 hours of reaction (Table 6.1, Entry 8).

The necessity of $Ru(bpy)_3Cl_2$ (**A**) was investigated. In fact, when the reaction was performed in the absence of that photocatalyst, the expected aminated product **6.3aa** was equally isolated in 99% yield after 2 hours (Table 6.1, Entry 9). Moreover, since a photoredox catalytic cycle has been excluded for this reaction, the role of the light was determined by repeating the reaction without in the dark. Surprisingly, the product was still generated in 91% yield, although the rate of the reaction was much lower, as it required 24 hours (Table 6.1, Entry 10).

Even though visible light is not required for the amination reaction of 3,4-dihydroquinoxalin-2-one **6.1a** with diisopropyl azodicarboxylate (**6.2a**), since it proceeds faster when irradiated, we decided to continue the optimization process using visible-light, but without photocatalyst.

Evaluation of the Solvent

After stating that the amination reaction 3,4-dihydroquinoxalin-2-one **6.1a** with diisopropyl azodicarboxylate (**6.2a**) can proceed without photocatalyst, the next step in the optimization process is to evaluate other solvents (Scheme 6.7). Despite being able to obtain product **6.3aa** in 99% yield using MeCN, this evaluation will be done for comparative purposes or to try to reduce reaction time.



Scheme 6.7: Evaluation of the solvent in the reaction between **6.1a** and **6.2a**.

Although the performance of the amination reaction between **6.1a** and **6.2a** in MeCN was exquisite, when it was attempted using either DCM or THF as solvent, the reaction

Table 6.2: Evaluation of the solvent in the reaction between **6.1a** and **6.2a**. Yield of **6.3aa**.

Entry[a]	Solvent	t (h)	Yield 6.3aa (%)[b]
1	MeCN	2	99
2	DCM	24	<5
3	THF	24	<5
4	DMF	2	86

[a]Reaction conditions: **6.1a** (0.1 mmol), **6.2a** (0.13 mmol), solvent (1 mL), under argon atmosphere and under HP Single LED (455 nm) irradiation for the indicated time.
[b]Yield determined after purification by column chromatography.

product **6.3aa** was formed in less than a 5% in both cases (Table 6.2, Entry 2 and 3). Apparently, the reaction is quite a bit sensitive to the solvent, and the polar aprotic ones seem to work better. In fact, when DMF was used, the expected aminated product was isolated in 86% yield (Table 6.2, Entry 4).

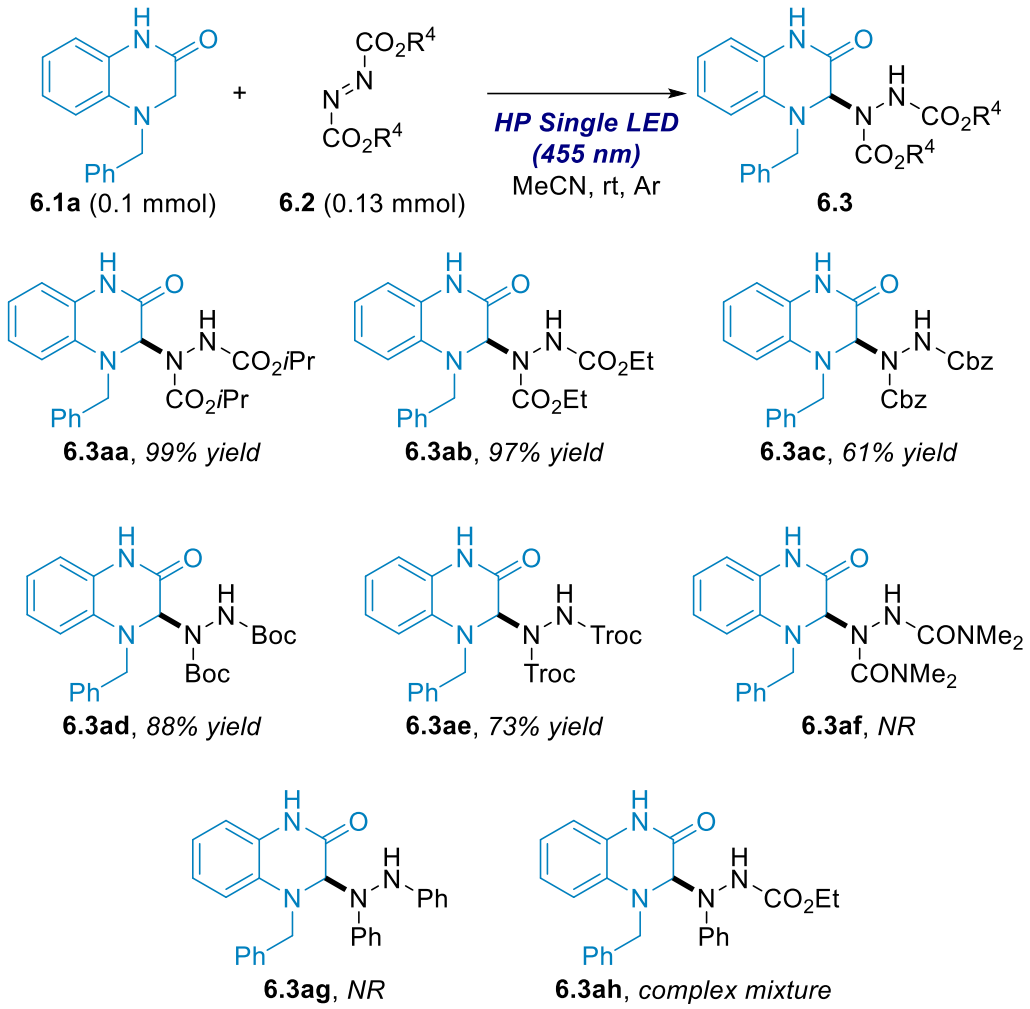
To conclude the optimization process, we selected MeCN as the best solvent to carry out the amination of 3,4-dihydroquinoxalin-2-one **6.1a** with diisopropyl azodicarboxylate (**6.2a**) (Table 6.2, Entry 1). Furthermore, no need of photocatalyst was observed, although the irradiation of the reaction mixture with visiblelight was beneficial for the rate of the reaction.

6.3.2 Scope of the Reaction

Having established the conditions for the amination of 3,4-dihydroquinoxalin-2-one **6.1a** with diisopropyl azodicarboxylate (**6.2a**), according to the *Objectives* of this *Chapter*, the next step is to explore the boundaries of this transformation. For this purpose, a set of electrophilic azo compounds (**6.2**) will be tested as aminating reagents for 3,4-dihydroquinoxalin-2-one **6.1a**. Thereafter, the generality of the reaction regarding the substitution at the 3,4-dihydroquinoxalin-2-one **6.1** counterpart will be explored.

Scope of the Reaction with Dialkyl Azodicarboxylates

Initially, the very similar diethyl azodicarboxylate (**6.2b**) was subjected to reaction with 3,4-dihydroquinoxalin-2-one **6.1a**, obtaining the desired aminated product **6.3ab** in an excellent 97% yield. On the other hand, dibenzyl (**6.2c**, Cbz) or di-*tert*-butyl(**6.3d**, Boc) azodicarboxylates were assayed as aminating reactants, being able to generate their corresponding products **6.3ad** and **6.3ae** in 61% and 88% yield, respectively. Afterwards, a more sophisticated trichloroethyl-derived (Troc) azodicarboxylate **6.2e** was employed



Scheme 6.8: Scope of the reaction using 4-benzyl-3,4-dihydroquinoxalin-2-one (**6.1a**) and different dialkyl azodicarboxylates (**6.2**).[a]

[a]Reaction conditions: **6.1a** (0.1 mmol), **6.2** (0.13 mmol), MeCN (1 mL), under argon atmosphere and under HP Single LED (455 nm) irradiation. Yield determined after purification by column chromatography.

as electrophile, providing the desired product **6.3ae** in 73% yield. Unfortunately, the reaction with amide-derived azo compound **6.2f** did not deliver the expected product.

Finally, the amination reaction was also tried with azobenzene (**6.2g**) but, since their nitrogen atoms do not exhibit electrophilic behaviour, the corresponding product **6.3ag** was not even detected. Additionally, the amination of 3,4-dihydroquinoxalin-2-one **6.1a** was attempted with an azo compound bearing just one ester group (**6.2h**). Apparently, it was not electrophilic enough to favour the reaction.

Scope of the Reaction with 3,4-Dihydroquinoxalin-2-ones

Once determined the scope of the reaction by using different dialkyl azodicarboxylates (**6.2**), we were in a position to explore the limits of this amination methodology regarding the substitution at the 3,4-dihydroquinoxalin-2-one (**6.1**) counterpart (Scheme 6.9). For this purpose, we chose diisopropyl azodicarboxylate (**6.2a**) as electrophilic amination reactant.

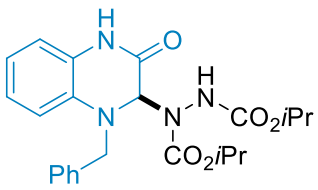
Initially, the effect of different substitution patterns at N-4 (R^2) was investigated. Pleasingly, when a 3,4-dihydroquinoxalin-2-one bearing an allyl group at that position was used, the corresponding product **6.3ba** was generated in 69% yield. In the same line, the CH_2CO_2Me functionality was well-tolarated, provided that the expected product **6.3ca** was isolated in 63% yield. These two results were quite significant because the amination reaction could efficiently take place without being interfered with these light-sensitive moieties.

The substitution at the aminic nitrogen was further explored using two benzylic groups with different electronic properties. Surprisingly, the less electron-rich 3,4-dihydroquinoxalin-2-one **6.1d**, which bears the strong electron-withdrawing $-CF_3$ group, was able to generate the expected amination product **6.3da** in 87% yield, whereas product **6.3ea** with a −PMB substituent was isolated in 72% yield.

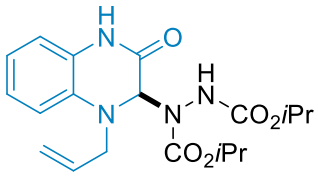
1,4-disubstituted 3,4-dihydroquinoxalin-2-ones **6.1** were also tested in this amination reaction. This substitution was found to be beneficial for the reaction outcome, since the expected products **6.3fa** and **6.3ga**, which bear either a 1-benzyl or 1-methyl group, were delivered in 93% and 91% yield respectively.

Finally, the substitution at the parent aromatic ring was also subjected to investigations. Hence, the use of the 8-methyl derivative **6.1h** generated the expected product **6.3ha** in 79% yield. Moreover, the effect over the reaction of the C-5 position of 3,4-dihydroquinoxalin-2-one unit was studied. Specifically, the presence of the strong electron-donating group −OMe produced the corresponding product **6.3ia** in just 56% yield. According to previous results, this may arise from a huge tendency of substrate **6.1i** to undergo undesired secondary processes. Nonetheless, the presence at the same position of either a methyl group or a bromine atom did not affect that much to the yield, as the corresponding products **6.3ja** and **6.3ka** were generated in 73% and 92%, respectively. In the same line, the use of a 3,4-dihydroquinoxalin-2-one derivative with a fluorine atom at C-6 (**6.1l**) allowed us to obtain the desired product **6.3la** in 75% yield, even scaling up the process to 0.5 mmol. However, 3,4-dihydroquinoxalin-2-one **6.1m**, which bears two methyl substituents at C-6 and C-7 was not found to be a suitable substrate for our amination protocol, as the expected product **6.3ma** was isolated in just 15% yield.

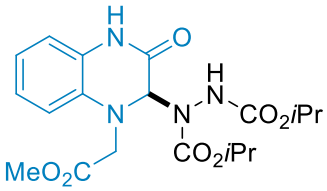
6.1 (0.1 mmol) **6.2a** (0.13 mmol) **6.3**



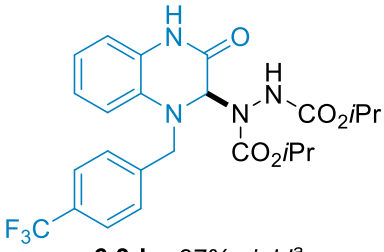
6.3aa, *99% yield*[a]



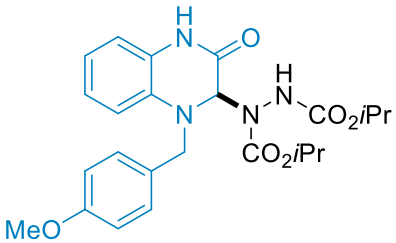
6.3ba, *69% yield*[a]



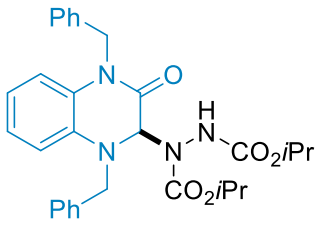
6.3ca, *63% yield*[a]



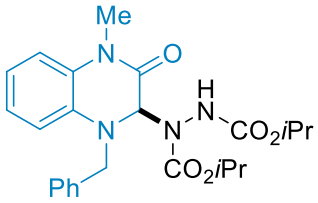
6.3da, *87% yield*[a]



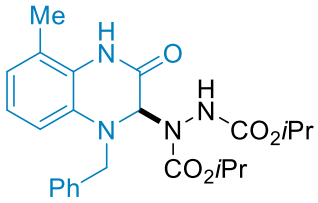
6.3ea, *72% yield*[a]



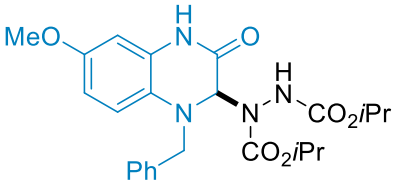
6.3fa, *93% yield*[a]



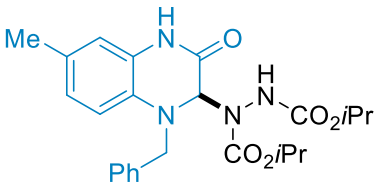
6.3ga, *91% yield*[a]



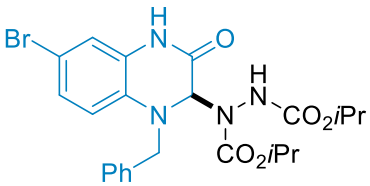
6.3ha, *79% yield*[a]



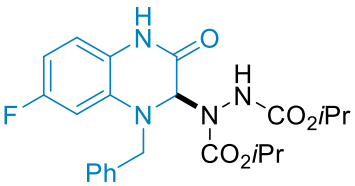
6.3ia, *56% yield*[a]



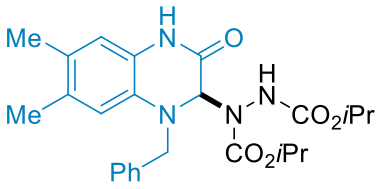
6.3ja, *73% yield*[a]



6.3ka, *82% yield*[a]



6.3la, *75% yield*[b]



6.3ma, *15% yield*[a]

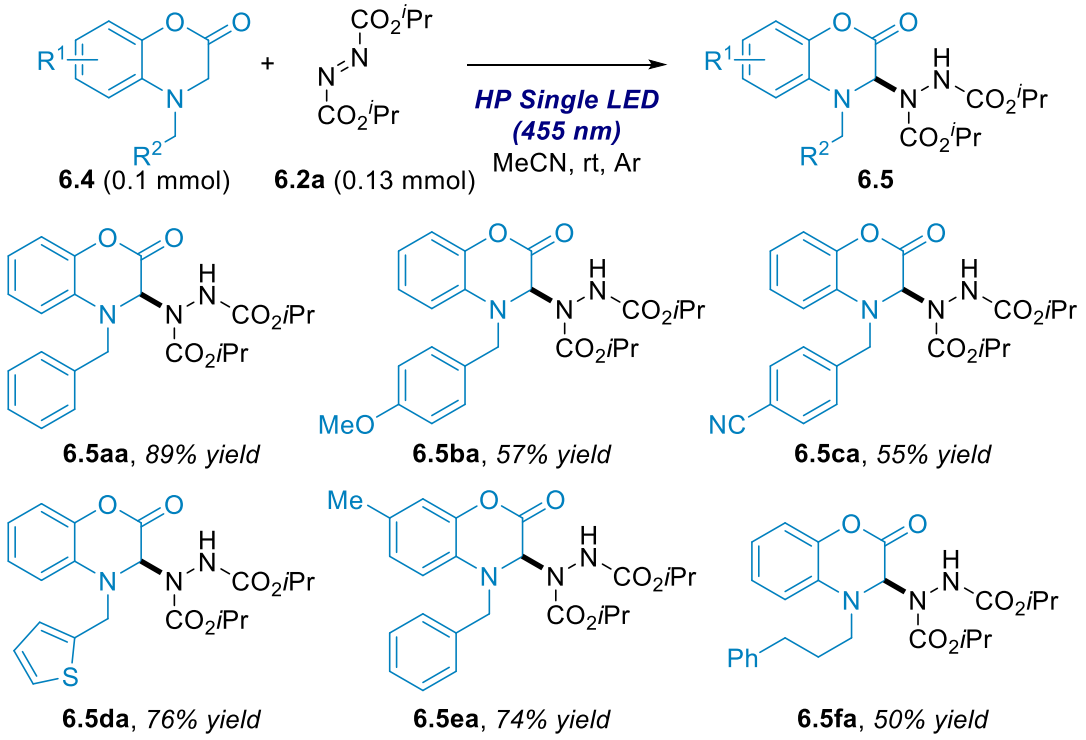
Scheme 6.9: Scope of the reaction using different 3,4-dihydroquinoxalin-2-ones (**6.1**) and diisopropyl azodicarboxylate (**6.2a**).[ab]

[a]Reaction conditions: **6.1** (0.1 mmol), **6.2a** (0.13 mmol), MeCN (1 mL), under argon atmosphere and under HP Single LED (455 nm) irradiation. Yield determined after purification by column chromatography.

[b]The reaction was performed at 0.5 mmol scale.

Scope of the Reaction with 3,4-Dihydro-1,4-benzoxazin-2-ones

With the aim of further expanding the boundaries of our amination protocol, we decided to engage 3,4-dihydro-1,4-benzoxazin-2-ones (**6.4**) to the optimal conditions also using diisopropyl azodicarboxylate (**6.2a**). To our delight, when 3,4-dihydro-1,4-benzoxazin-2-one **6.4a** was used, the desired product **6.5aa** was generated in a promising 89% yield. In light of this finding, we further applied these conditions to other 3,4-dihydro-1,4-benzoxazin-2-ones (**6.4**) (Scheme 6.10).



Scheme 6.10: Scope of the reaction using different 3,4-dihydro-1,4-benzoxazin-2-ones (**6.4**) and diisopropyl azodicarboxylate (**6.2a**).[ab]

[a]Reaction conditions: **6.4** (0.1 mmol), **6.2a** (0.13 mmol), MeCN (1 mL), under argon atmosphere and under HP Single LED (455 nm) irradiation. Yield determined after purification by column chromatography.
[b]The reaction was performed at 0.5 mmol scale.

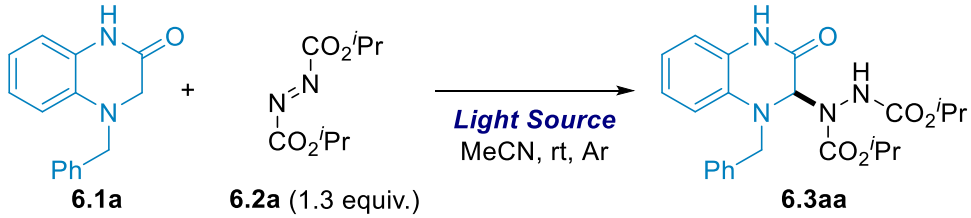
The behaviour of different benzylic or heterobenzylic substituents at the aminic nitrogen of 3,4-dihydro-1,4-benzoxazin-2-ones (**6.4**) was investigated. In this sense, the use of either electron-donating or electron-withdrawing groups at that position exerted a negative performance over the reaction. In fact, in the case of the PMB-substituted derivative **6.4b**, the expected aminated 3,4-dihydro-1,4-benzoxazin-2-one **6.5ba** was isolated in 57% yield, and with similar results was obtained the *p*-CN benzyl product **6.5ca** (55% yield). Nevertheless, the presence of a 2-thiophene substituent increased the yield in which the corresponding product **6.5da** is generated until 76%.

Finally, the C-7-substituted 3,4-dihydro-1,4-benzoxazin-2-one with a methyl group (**6.4e**) delivered the expected product with diisopropyl azodicarboxylate (**6.2a**) in 74% yield, whereas the one bearing a longer aliphatic carbon chain (**6.4f**) produced the desired aminated product in 50% yield.

6.3.3 Gram-Scale Reaction and Synthetic Transformations

Gram-Scale Reaction

After determining the scope of the reaction between different 3,4-dihydroquinoxalin-2-ones (**6.1**) or 3,4-dihydro-1,4-benzoxazin-2-ones (**6.4**) and dialkyl azodicarboxylates (**6.2**), we decided to perform the amination reaction at a larger scale, in order to prove the practicability of our protocol. With the purpose of developing further derivatizations of the reaction products, we required large amounts of aminated 3,4-dihydroquinoxalin-2-one **6.3aa**. Hence, several large-scale batch reactions were carried out, using either sunlight or blue LEDs as light sources (Scheme 6.11).



6.1a **6.2a** (1.3 equiv.) **6.3aa**

Entry[a]	Light Source	1a (mmol)	t (h)	3aa (%)
1	Sunlight	3.8	6	88
2	Blue LEDs	5.0	14	90
3	Blue LEDs	6.6	14	83

Scheme 6.11: Large-scale reaction using 3,4-dihydroquinoxalin-2-one **6.1a**, diisopropyl azodicarboxylate (**6.2a**) and and a given energy source.

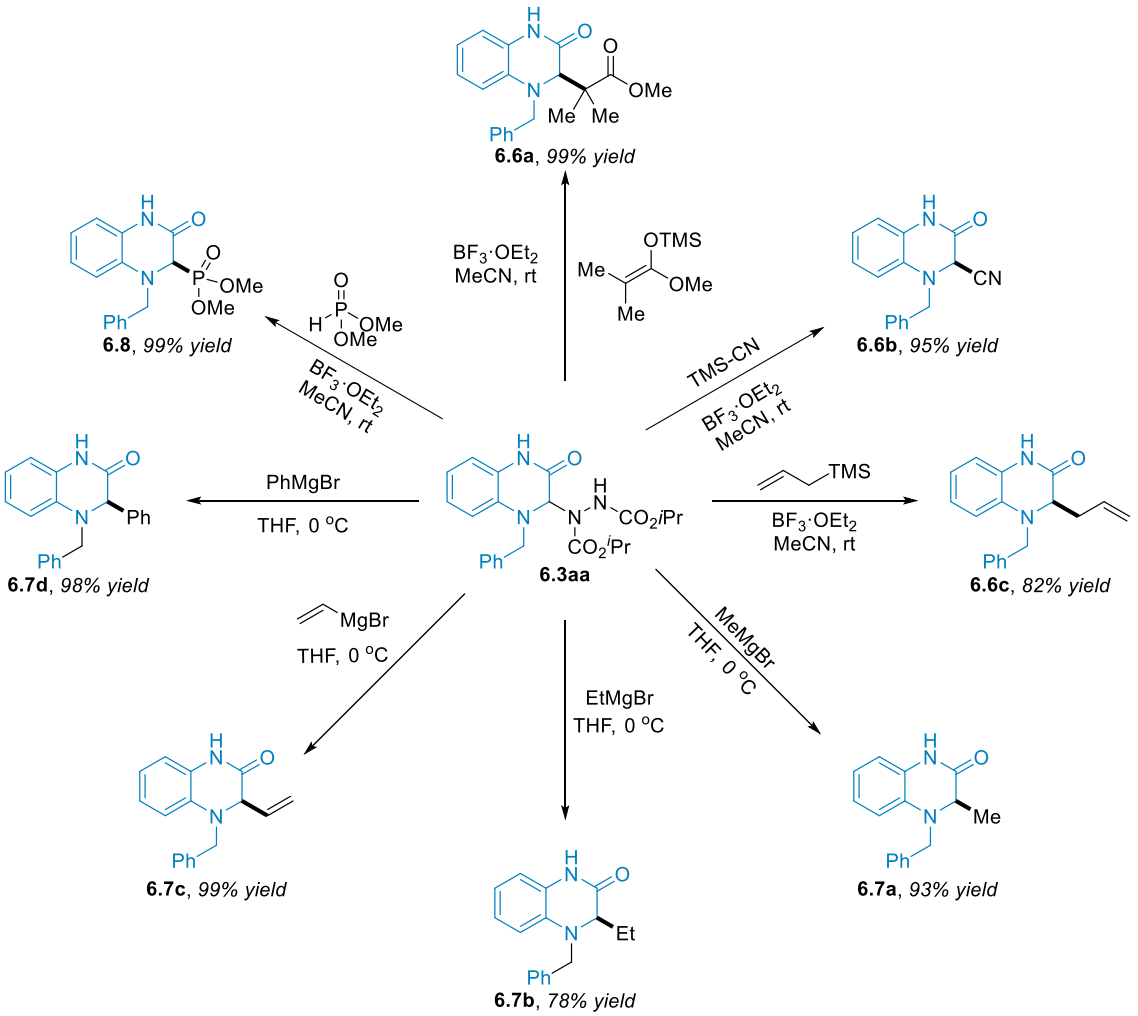
[a]Reaction conditions: **6.1a**, **6.2a** (1.3 equiv.), MeCN (0.2 M), under argon atmosphere and under irradiation.

Delightfully, when the reaction between **6.1a** and **6.2a** at a 3.8-mmol scale was conducted under sunlight irradiation, we obtained 1.47 g (88% yield) of **6.3aa** (Scheme 6.11, Entry 1). On the contrary, from a more lab-convenient point of view, we decided to carry out the same reaction under blue LEDs light. In this case, we were able to generate 1.98 g (90% yield) of **6.3aa** in the first run in a 5-mmol scale (Scheme 6.11, Entry 2), and 2.41 g (83% yield) in the second run in a 6.6-mmol scale (Scheme 6.11, Entry 3). These results

were quite consistent with our previous observations, since the use of sunlight was found to be beneficial in terms of reaction time.

Synthetic Transformations

During the realization of this project, we noted the high synthetic versatility of this kind of hydrazine moiety like the one that products **6.3** and **6.5** have. In fact, the engagement of this functionality in several derivatizations was already known.[221,226,228–230] In our case, we identified the hydrazine moiety in product **6.3aa** as a valuable leaving group for the synthesis of a wide array of differently C-3-substituted 3,4-dihydroquinoxalin-2-one (Scheme 6.12).



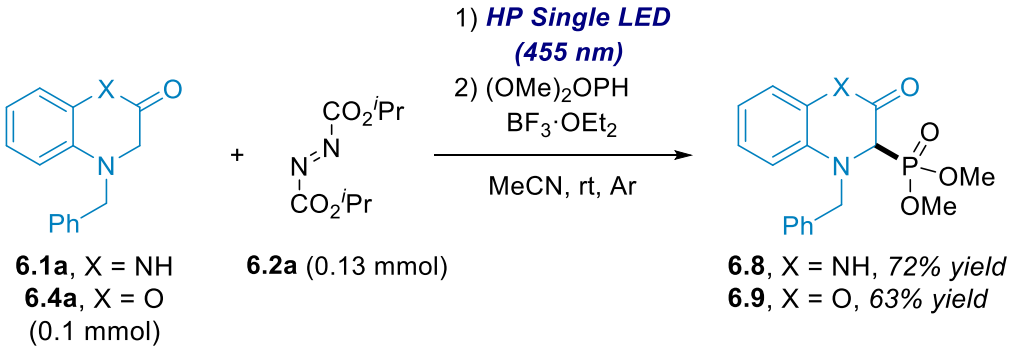
Scheme 6.12: Synthetic modifications of product **6.3aa**. See *Experimental Section* (page 302) for further experimental details.

Initially, we wanted to exchange the $^{i}PrO_2C-NH-N-CO_2^{i}Pr$ group for several silicon nucleophiles. Immediately, we realized that it was imperative the presence of a strong

Lewis acid like $BF_3{\cdot}OEt_2$ for the success of the substitution reaction. Thus, when **6.3aa** was treated with the trimethylsilyl ether of methyl isobutyrate in the presence of a stoichiometric amount of $BF_3{\cdot}OEt_2$, the expected alkylation product **6.6a** was delivered in quantitative yield. After obtaining this product with exquisite performance, we subjected other silicon nucleophiles to the substitution reaction. Specifically, when **6.3aa** reacted with trimethylsilyl cyanide in the presence of $BF_3{\cdot}OEt_2$, the corresponding Strecker product was isolated in 95% yield. Thereafter, the treatment of **6.3aa** with allyl-TMS provided the desired allylated 3,4-dihydroquinoxalin-2-one **6.6c** in 82% yield.

After realizing the superior performance of silicon nucleophiles in this transformation, we envisioned that harder nucleophiles such as Grignard reagents could also offer the same reactivity. Pleasingly, the simple MeMgBr reacted with **6.3aa** to deliver product **6.7a** in 93% yield. In this case, the use of $BF_3{\cdot}OEt_2$ was not necessary, presumably due to the higher reactivity of these organometallic nucleophiles. In the same vain, an ethyl substituent could be introduced in the skeleton of 3,4-dihydroquinoxalin-2-one by simply treating **6.3aa** with EtMgBr, obtaining the desired product **6.7b** in 78% yield. Besides, 3,4-dihydroquinoxalin-2-ones bearing either a vinyl (**6.7c**) or a phenyl (**6.7d**) group at the C-3 position could also be synthesized in 99% and 98% yield respectively using the corresponding Grignard reagent.

Finally, we were able to subject aminal **6.3aa** to the substitution reaction with diphenyl phosphite. In this particular case, $BF_3{\cdot}OEt_2$ was mandatory for the reaction, obtaining the corresponding product **6.8** in quantitative yield. Having noticed the ability of compound **6.3aa** to be engaged in this phosphonylation reaction, we decided to try the same transformation but in a *one-pot* fashion (Scheme 6.13).



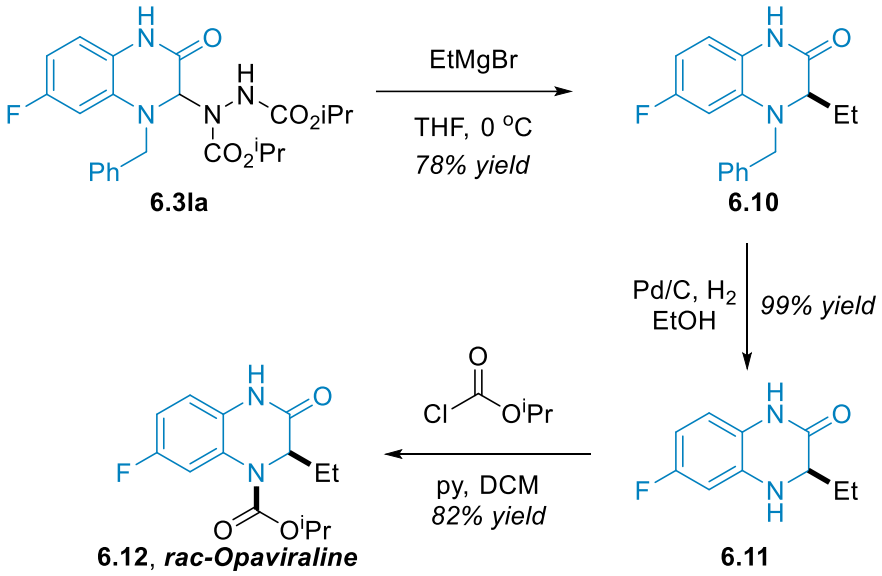
Scheme 6.13: *One-pot* synthesis of phosphonates **6.8** and **6.9** from **6.1a** and **6.4a**. See *Experimental Section* (page 302) for further details.

Bearing this in mind, 3,4-dihydroquinoxalin-2-one **6.1a** was subjected to the optimized amination reaction with **6.2a** and afterwards, when it was determined to be completed, $HPO(OMe)_2$ and $BF_3{\cdot}OEt_2$ were added. To our delight, we could isolate phos-

phonate **6.8** in 72% overall yield. The same strategy was also applied to 3,4-dihydro-1,4-benzoxazin-2-one **6.4a**, being able to obtain phosphonate **6.9** in a 63% yield after two consecutive steps.

Synthesis of *rac*-Opaviraline

Giving the easiness in which compound **6.3aa** experimented substitution reactions, we identified this strategy as a very straightforward way to generate molecular complexity at the C-3 position of the 3,4-dihydroquinoxalin-2-one skeleton. Hence, we decided to apply it to the synthesis of *rac*-Opaviraline, a compound that exhibits antiviral activity against HIV-1[65,231] (Scheme 6.14).



Scheme 6.14: Synthesis of *rac*-Opaviraline (**6.12**) from aminal **6.3la**. See *Experimental Section* (page 302) for further experimental details.

For this purpose, we prepared the fluorinated derivative **6.3la**, and thereafter it was subjected to the substitution reaction with EtMgBr, obtaining the corresponding alkylated product **6.10** in 78% yield. Thereafter, tertiary amine **6.10** involved in a catalytic hydrogenolysis with Pd over carbon and H_2, generating the expected secondary amine **6.11** in quantitative yield. Finally, a protection of the aminic nitrogen of **6.11** as isopropyl carbamate using isopropyl chloroformate delivered the desired *rac*-Opaviraline (**6.12**) in 82% yield. The combined yield for the three-step sequence was 63%.

6.3.4 Mechanistic Investigations and Proposed Mechanism

Mechanistic Investigations

At this point of the project, we were interested in determining the mechanism behind the amination reaction of 3,4-dihydroquinoxalin-2-ones (**6.1**) or 3,4-dihydro-1,4-benzoxazin-2-ones (**6.4**) with dialkyl azodicarboxylates (**6.2**). Our initial design hypothesis was based in the generation of the α-amino radical of **6.1a** and its subsequent nucleophilic attack to the electrophilic aminating reactant **6.2a**. At this stage, we were reluctant enough to consider the actual formation of the α-amino radical of **6.1a**, since we had extensively studied how this radical has to be generated in *Chapter* 5. The considerable simple conditions in which this amination took place led us consider other reaction mechanisms.

Initially, we performed the reaction between 0.1 mmol of **6.1a** and 0.13 mmol of **6.2a** under the optimal conditions, but also adding 1.5 equivalents of TEMPO. As expected, product **6.3aa** could be obtained in 72% yield, revealing that a radical-mediated process is unlikely. The reaction between **6.1a** and **6.2a** was performed now under an O_2 atmosphere. Again, aminated product **6.3aa** was formed in 81% yield. After these two simple experiment we could assert that radical species are not generated through the course of the reaction. Hence, α-amino radical does not seem to be the reactive specie in this process.

Thereafter, we speculated if the reaction between **6.1a** and **6.2a** may arise from an electron donor-acceptor (EDA) complex. In fact, these aggregates have shown how they can trigger various light-induced transformations.[232,233] To detect the formation of this complexes, we recorded the absorption spectrum of **6.1a**, **6.2a** and a 1:1 mixture of **6.1a** and **6.2a** (Figure 6.2). Unfortunately, we could not prove the formation of this aggregate, given that the absorption band of **6.2a** was not shifted in the presence of **6.1a**. The same experiment was also performed for 3,4-dihydro-1,4-benzoxazin-2-one **6.4a**, but with similar outcome (Figure 6.3).

Proposed Mechanism

With no evidences of both radical formation and EDA complex involvement in the process, we focused our attention on classical polar mechanisms for amination of tertiary amines with dialkyl azodicarboxylates[221,226,228–230] (Figure 6.4).

Since the use of visible light made the reaction more efficient from the point of view of yield and reaction time, we speculate that diisopropyl azodicarboxylate (**6.2a**) could suffer a light-enabled $E \rightarrow Z$ isomerization process. Hence, the more reactive **(*Z*)-6.2a** reacts with 3,4-dihydroquinoxalin-2-one **6.1a** to form the zwitterionic intermediate **6.I**. This intermediate **6.I** abstracts an α proton to form the iminium cation **6.II** and the nitrogen

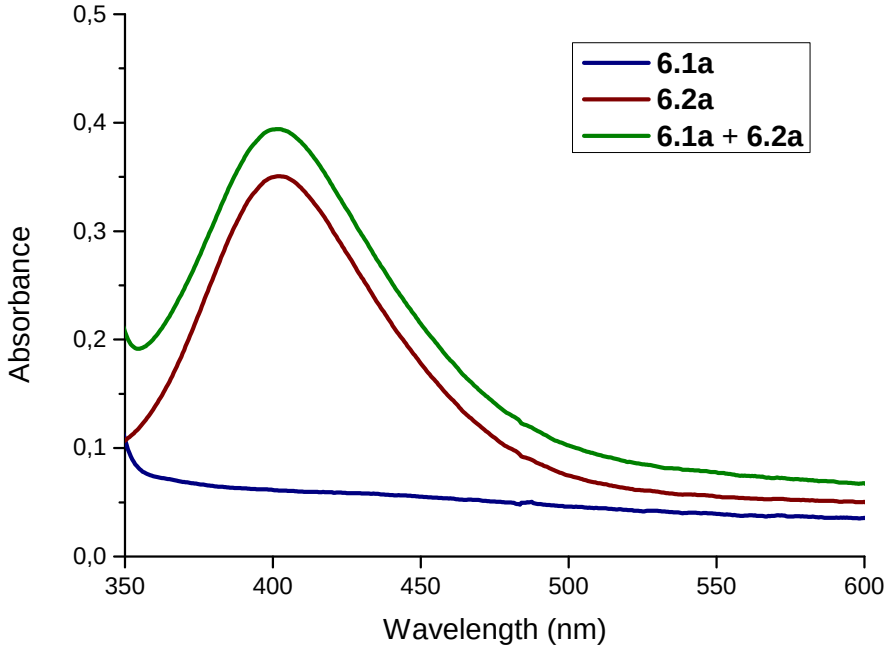


Figure 6.2: Absorption spectra of **6.1a**, **6.2a** and a mixture between **6.1a** and **6.2a**.

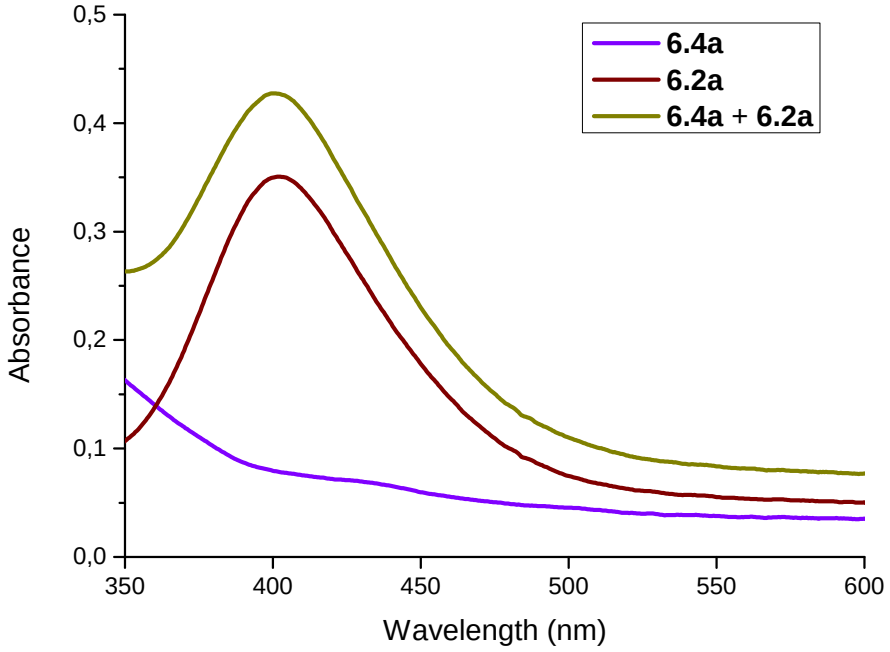


Figure 6.3: Absorption spectra of **6.4a**, **6.2a** and a mixture between **6.4a** and **6.2a**.

anion **6.III**. Finally, a nucleophilic attack of **6.III** to **6.II** generates the expected product **6.3aa**.

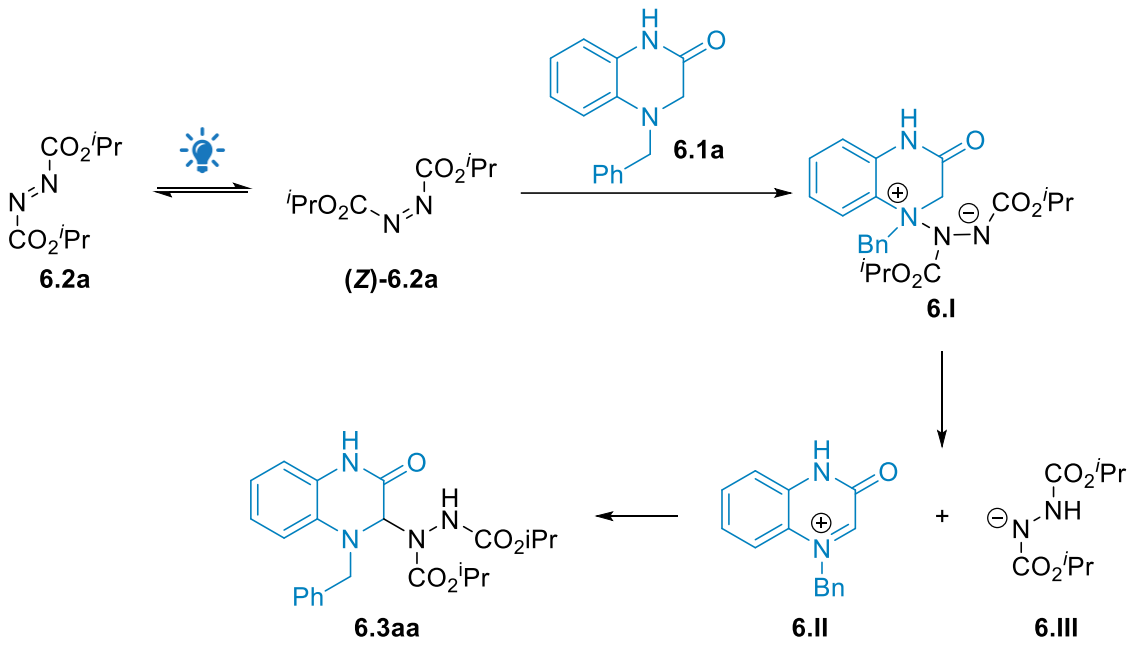


Figure 6.4: General mechanism for the light-accelerated amination reaction between 3,4-dihydroquinoxalin-2-one **6.1a** and diisopropyl azodicarboxylate (**6.2a**).

6.4 Experimental Section

6.4.1 General Methods

Experimental methods regarding **Melting Points**, **Chromatographic Methods** and **High Resolution Mass Spectrometry (HRMS)** can be found in Section 1.4.1 of *Chapter 1* (page 62).

Reaction Flasks, Reagents and Substrates

- Photochemical reactions were carried out in 10 mL Schlenk flasks under argon unless otherwise indicated.
- Commercial reagents were used as purchased.
- MeCN was degassed by three freeze-pump-thaw cycles and stored over 3Å MS for 48 h at least. Prior to use, MeCN was bubbled with Ar for 10 min.
- All photocatalysts and dialkyl azodicarboxylates (**6.2**) were commercially available.
- 4-Substituted-3,4-dihydroquinoxalin-2-ones **6.1a**-**6.1m** were prepared form its N-4 unprotected precursors using the *N*-benzylation procedure described in page 67 of *Chapter 1*.

Nuclear Magnetic Resonance (NMR)

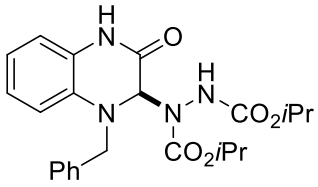
- NMR spectra were run in a Bruker Avance 300 DPX at 300 MHz for ^{1}H, 282 MHz for ^{19}F and 75 MHz for ^{13}C using residual nondeuterated solvent as internal standard ($CHCl_3$: δ 7.26 and δ 77.00 ppm respectively, MeOH: δ 3.34 ppm and δ 49.87 ppm respectively, acetone-d_6: δ 2.05 ppm and δ 29.84 ppm respectively).
- All the aminated 3,4-dihydroquinoxalin-2-ones **6.3** and 3,4-dihydro-1,4-benzoxazin-2-ones **6.5** exhibit high rotation energy barriers in, at least, two bonds. These energy barriers cannot be overcome at 298 K and therefore several rotameric isomers were detected by NMR. As a result, NMR experiments must be done at high temperature, trying to overcome the rotation energy barrier. All the compounds **6.3** and **6.5** have been characterized using VT-NMR at 353 K in DMSO-d_6 at 500 MHz for ^{1}H and at 125 MHz for ^{13}C. In most of the cases the rotamers have been resolved but, in other cases, a significant rotation barrier is still present even at 353 K.
- Chemical shifts (δ) are given in ppm and coupling constants (J) in Hz.
- The carbon multiplicity was established by DEPT experiments.

6.4.2 Synthetic Procedures and Characterization

General Procedure 1 (GP-1) for the Light-Accelerated Amination Reaction between 3,4-dihydroquinoxalin-2-ones 6.1 and Dialkyl Azodicarboxylates (6.2)

To an ovendried Schlenck tube containing a teflon-coated stir bar were added the proper 3,4-dihydroquinoxalin-2-one **6.1** or 3,4-dihydro-1,4-benzoxazin-2-one **6.4** (0.1 mmol, 1 equiv.) and the proper dialkyl azodicarboxylate **6.2** (0.13 mmol, 1.3 equiv.) *[if it is liquid, it was added after the MeCN]*. The reaction vessel was evacuated and backfilled with argon three times. After this, freshly degassed and dried MeCN (1 mL) was added via syringe and the reaction mixture was stirred while being irradiated with HP Single LED (455 nm) (see page 433 for further details about the photochemical setup) under a positive pressure of argon. The course of the reaction was monitored by TLC. The desired aminated product **6.3** or **6.5** was isolated from the reaction mixture by flash column chromatography using hexane:Et_2O mixtures.

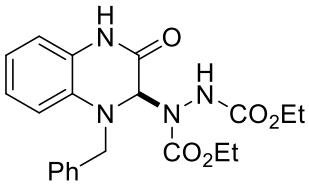
Diisopropyl 1-(1-benzyl-3-oxo-1,2,3,4-tetrahydroquinoxalin-2-yl)hydrazine-1,2-dicarboxylate (6.3aa)



Using 4-benzyl-3,4-dihydroquinoxalin-2-one (**6.1a**, 23.8 mg, 0.1 mmol) and diisopropyl azodicarboxylate (**6.2a**, 25.6 μL, 0.13 mmol, 1.3 equiv.), in accordance with GP-1, product **6.3aa** was obtained (43.6 mg, 0.099 mmol, 99% yield, colorless oil) after column chromatography using hexane:Et_2O (from 5:5 to 2:8) mixtures.

^{1}H-NMR (500 MHz, 353K, DMSO-d$_6$) δ 10.62 (bs, 1H), 8.82 (bs, 1H), 7.37 – 7.19 (m, 5H), 6.84 (dd, J =7.8, 1.5 Hz, 1H), 6.81 – 6.74 (m, 1H), 6.72 – 6.61 (m, 2H), 5.89 (s, 1H), 4.94 – 4.77 (m, 2H), 4.63 – 4.53 (m, 1H), 4.52 – 4.39 (m, 1H), 1.20 (d, J =6.1 Hz, 3H), 1.16 (d, J =6.3 Hz, 3H), 1.08 (d, J =6.3 Hz, 3H), 0.94 – 0.81 (m, 3H); **^{13}C{^{1}H}-NMR (126 MHz, 353K, DMSO-d$_6$)** δ 159.8 (C), 155.7 (C), 155.0 (C), 137.1 (C), 131.8 (C), 128.1 (CH), 126.8 (CH), 126.6 (CH), 125.3 (C), 122.1 (CH), 117.6 (CH), 114.4 (CH), 111.9 (CH), 71.1 (CH), 69.4 (CH), 67.7 (CH), 49.8 (CH_2), 21.3 (CH_3), 21.3 (CH_3), 21.2 (CH_3), 21.1 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{23}H_{29}N_4O_5^+$ 441.2132, found 441.2130.

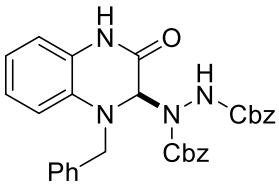
Diethyl 1-(1-benzyl-3-oxo-1,2,3,4-tetrahydroquinoxalin-2-yl)hydrazine-1,2-dicarboxylate (6.3ab)



Using 4-benzyl-3,4-dihydroquinoxalin-2-one (**6.1a**, 23.8 mg, 0.1 mmol) and diethyl azodicarboxylate (**6.2b**, 20.4 μL, 0.13 mmol, 1.3 equiv.), in accordance with GP-1, product **6.3ab** was obtained (40.0 mg, 0.097 mmol, 97% yield, colorless oil) after column chromatography using hexane:Et_2O (from 5:5 to 2:8) mixtures.

^{1}H-NMR (500 MHz, 353K, DMSO-d_6) δ 10.64 (bs, 1H), 8.94 (bs, 1H), 7.38 – 7.19 (m, 5H), 6.85 (dd, *J* =7.7, 1.5 Hz, 1H), 6.81 – 6.75 (m, 1H), 6.73 – 6.62 (m, 2H), 5.90 (s, 1H), 4.83 (d, *J* =16.2 Hz, 1H), 4.45 (d, *J* =16.2 Hz, 1H), 4.22 – 3.93 (m, 2H), 3.81 (bs, 2H), 1.16 (t, *J* =6.6 Hz, 3H), 0.96 (bs, 3H); **^{13}C{^{1}H}-NMR (126 MHz, 353K, DMSO-d_6)** δ 159.8 (C), 156.1 (C), 155.3 (C), 137.0 (C), 131.8 (C), 128.1 (CH), 126.9 (CH), 126.7 (CH), 125.3 (C), 122.2 (CH), 117.8 (CH), 114.4 (CH), 111.9 (CH), 71.2 (CH), 61.6 (CH_2), 60.0 (CH_2), 49.8 (CH_2), 14.0 (CH_3), 13.8 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{21}H_{25}N_4O_5^+$ 413.1819, found 413.1817.

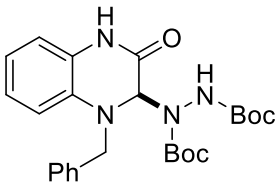
Dibenzyl 1-(1-benzyl-3-oxo-1,2,3,4-tetrahydroquinoxalin-2-yl)hydrazine-1,2-dicarboxylate (6.3ac)



Using 4-benzyl-3,4-dihydroquinoxalin-2-one (**6.1a**, 23.8 mg, 0.1 mmol) and dibenzyl azodicarboxylate (**6.2a**, 38.8 mg, 0.13 mmol, 1.3 equiv.), in accordance with GP-1, product **6.3ac** was obtained (32.7 mg, 0.061 mmol, 61% yield, yellowish oil) after column chromatography using hexane:Et_2O (from 3:7 to 2:8) mixtures.

^{1}H-NMR (500 MHz, 353K, DMSO-d_6) δ 10.70 (bs, 1H), 9.31 (bs, 1H), 7.41 – 7.17 (m, 15H), 7.11 – 7.04 (m, 1H), 6.87 (dd, *J* =7.9, 1.4 Hz, 1H), 6.80 (t, *J* =7.6 Hz, 1H), 6.71 – 6.67 (m, 1H), 5.98 (bs, 1H), 5.15 (s, 2H), 4.84 (m, 3H), 4.44 (s, 1H); **^{13}C{^{1}H}-NMR (126 MHz, 353K, DMSO-d_6)** δ 159.6 (C), 156.0 (C), 155.4 (C), 136.9 (C), 136.3 (C), 135.8 (C), 135.7 (C), 128.1 (CH), 127.9 (CH), 127.8 (CH), 127.5 (CH), 127.4 (CH), 127.2 (C), 127.0 (CH), 126.8 (CH), 126.7 (CH), 125.2 (CH), 122.3 (CH), 117.9 (CH), 114.5 (CH), 111.9 (CH), 71.4 (CH), 67.0 (CH_2), 65.6 (CH_2), 49.8 (CH_2); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{31}H_{29}N_4O_5^+$ 537.2132, found 537.2135.

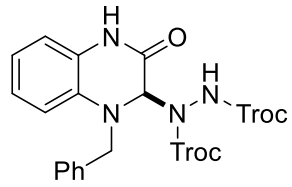
Di-*tert*-butyl 1-(1-benzyl-3-oxo-1,2,3,4-tetrahydroquinoxalin-2-yl)hydrazine-1,2-dicarboxylate (6.3ad)



Using 4-benzyl-3,4-dihydroquinoxalin-2-one (**6.1a**, 23.8 mg, 0.1 mmol) and di-tert-butyl azodicarboxylate (**6.2d**, 29.9 μL, 0.13 mmol, 1.3 equiv.), in accordance with GP-1, product **6.3ad** was obtained (41.2 mg, 0.088 mmol, 88% yield, colorless oil) after column chromatography using hexane:Et_2O (from 4:6 to 3:7) mixtures.

^{1}H-NMR (500 MHz, 353K, DMSO-d$_6$) δ 10.57 (bs, 1H), 8.27 (bs, 1H), 7.39 – 7.17 (m, 5H), 6.84 (dd, *J* =7.7, 1.1 Hz, 1H), 6.81 – 6.67 (m, 2H), 6.66 – 6.60 (m, 1H), 5.87 (bs, 1H), 4.84 (d, *J* =16.2 Hz, 1H), 4.48 (d, *J* =15.4 Hz, 1H), 1.40 (s, 9H), 1.21 (s, 9H); **^{13}C{^{1}H}-NMR (126 MHz, 353K, DMSO-d$_6$)** δ 159.9 (C), 155.2 (C), 154.4 (C), 137.3 (C), 132.0 (C), 128.1 (CH), 126.8 (CH), 126.6 (CH), 125.3 (C), 122.2(CH), 117.5 (CH), 114.3 (CH), 111.8 (CH), 80.3 (C), 78.5 (C), 70.6 (CH), 49.6 (CH_2), 27.5 (CH_3), 27.4 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{25}H_{33}N_4O_5^+$ 469.2445, found 469.2444.

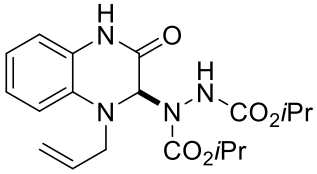
Bis(2,2,2-trichloroethyl) 1-(1-benzyl-3-oxo-1,2,3,4-tetrahydroquinoxalin-2-yl)hydrazine-1,2-dicarboxylate (6.3ae)



Using 4-benzyl-3,4-dihydroquinoxalin-2-one (**6.1a**, 23.8 mg, 0.1 mmol) and bis(2,2,2-trichloroethyl) azodicarboxylate (**6.2e**, 49.5 mg, 0.13 mmol, 1.3 equiv.), in accordance with GP-1, product **6.3ae** was obtained (45.2 mg, 0.073 mmol, 73% yield, colorless oil) after column chromatography using hexane:Et_2O (from 5:5 to 2:8) mixtures.

^{1}H-NMR (500 MHz, 353K, DMSO-d$_6$) δ 10.78 (bs, 1H), 9.66 (bs, 1H), 7.45 – 7.16 (m, 5H), 7.01 – 6.56 (m, 4H), 6.06 (s, 1H), 5.03 – 4.81 (m, 3H), 4.64 – 4.41 (m, 3H); **^{13}C{^{1}H}-NMR (126 MHz, 353K, DMSO-d$_6$)** δ 163.1 (C), 154.3 (C), 153.9 (C), 136.7 (C), 131.1 (C), 128.1 (CH), 127.1 (CH), 126.7 (CH), 125.0 (C), 122.3 (CH), 118.1 (CH), 114.7 (CH), 112.1 (CH), 95.4 (C), 94.8 (C), 74.7 (CH), 73.7 (CH_2), 73.7 (CH_2), 49.9 (CH_2); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{21}H_{19}Cl_6N_4O_5^+$ 616.9481, found 616.9483.

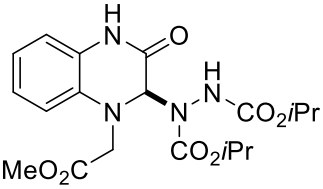
Diisopropyl 1-(1-allyl-3-oxo-1,2,3,4-tetrahydroquinoxalin-2-yl)hydrazine-1,2-dicarboxylate (6.3ba)



Using 4-allyl-3,4-dihydroquinoxalin-2-one (**6.1b**, 18.8 mg, 0.1 mmol) and diisopropyl azodicarboxylate (**6.2a**, 25.6 μL, 0.13 mmol, 1.3 equiv.), in accordance with GP-1, product **6.3ba** was obtained (27.1 mg, 0.069 mmol, 69% yield, yellow oil) after column chromatography using hexane:Et_2O (from 5:5 to 2:8) mixtures.

^{1}H-NMR (500 MHz, 353K, DMSO-d$_6$) δ 10.56 (bs, 1H), 8.72 (bs, 1H), 6.87 – 6.78 (m, 2H), 6.69 (d, *J* =7.8 Hz, 1H), 6.68 – 6.57 (m, 1H), 6.01 – 5.81 (m, 2H), 5.23 (dd, *J* =17.2, 1.7 Hz, 1H), 5.20 – 5.13 (m, 1H), 4.90 – 4.73 (m, 1H), 4.63 – 4.48 (m, 1H), 4.21 (dd, *J* =16.5, 5.3 Hz, 1H), 3.89 (dd, *J* =16.5, 5.5 Hz, 1H), 1.22 (d, *J* =6.1 Hz, 3H), 1.19 (d, *J* =4.6 Hz, 3H), 1.06 (d, *J* =6.3 Hz, 3H), 0.89 – 0.86 (m, 3H); **^{13}C{^{1}H}-NMR (126 MHz, 353K, DMSO-d$_6$)** δ 159.7 (C), 155.7 (C), 154.9 (C), 133.5 (CH), 131.7 (C), 125.2 (C), 122.1 (CH), 117.4 (CH), 116.5 (CH_2), 114.3 (CH), 111.6 (CH), 70.8 (CH), 69.3 (CH), 68.1 (CH), 48.8 (CH_2), 21.5 (CH_3), 21.3 (CH_3), 21.2 (CH_3), 21.1 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{19}H_{27}N_4O_5^+$ 391.1976, found 391.1977.

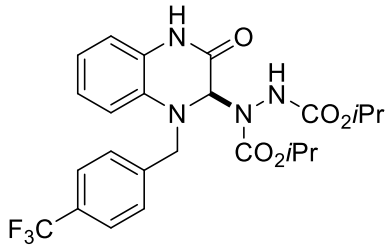
Diisopropyl 1-(1-(2-methoxy-2-oxoethyl)-3-oxo-1,2,3,4-tetrahydroquinoxalin-2-yl) hydrazine-1,2-dicarboxylate (6.3ca)



Using methyl 2-(3-oxo-3,4-dihydroquinoxalin-2-yl)acetate (**6.1c**, 20.0 mg, 0.1 mmol) and diisopropyl azodicarboxylate (**6.2a**, 25.6 μL, 0.13 mmol, 1.3 equiv.), in accordance with GP-1, product **6.3ca** was obtained (26.3 mg, 0.063 mmol, 63% yield, yellow solid) after column chromatography using hexane:Et_2O (from 5:5 to 2:8) mixtures.

Mp = 178 – 183 °C;**^{1}H-NMR (500 MHz, 353K, DMSO-d$_6$)** δ 10.65 (bs, 1H), 8.56 (bs, 1H), 6.86 – 6.81 (m, 2H), 6.72 – 6.67 (m, 1H), 6.59 (d, *J* =7.0 Hz, 1H), 5.93 (bs, 1H), 4.88 – 4.76 (m, 1H), 4.55 (s, 1H), 4.40 (d, *J* =18.0 Hz, 1H), 4.17 (d, *J* =18.0 Hz, 1H), 3.69 (s, 3H), 1.23 – 1.16 (m, 9H), 1.06 (d, *J* =6.3 Hz, 3H); **^{13}C{^{1}H}-NMR (126 MHz, 353K, DMSO-d$_6$)** δ 169.7 (C), 159.5 (C), 155.7 (C), 155.0 (C), 131.3 (C), 125.0 (C), 122.3 (CH), 118.2 (CH), 114.5 (CH), 111.0 (CH), 69.6 (CH), 67.9 (CH), 67.5 (CH), 51.4 (CH_3), 48.0 (CH_2), 21.3 (CH_3), 21.2 (CH_3), 21.1 (CH_3), 21.0 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{19}H_{27}N_4O_7^+$ 423.1874, found 423.1881.

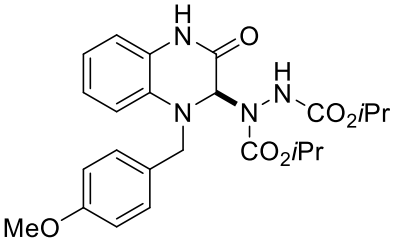
Diisopropyl 1-(3-oxo-1-(4-(trifluoromethyl)benzyl)-1,2,3,4-tetrahydroquinoxalin-2-yl)hydrazine-1,2-dicarboxylate (6.3da)



Using 4-(4-(trifluoromethyl)benzyl)-3,4-dihydroquinoxalin-2-one (**6.1d**, 30.6 mg, 0.1 mmol) and diisopropyl azodicarboxylate (**6.2a**, 25.6 μL, 0.13 mmol, 1.3 equiv.), in accordance with GP-1, product **6.3da** was obtained (44.3 mg, 0.087 mmol, 87% yield, colorless oil) after column chromatography using hexane:Et_2O (from 5:5 to 2:8) mixtures.

^{1}H-NMR (500 MHz, 353K, DMSO-d$_6$) δ 10.67 (bs, 1H), 8.87 (bs, 1H), 7.66 (d, J =8.1 Hz, 2H), 7.52 (d, J =8.0 Hz, 2H), 6.86 (dd, J =7.7, 1.5 Hz, 1H), 6.77 (td, J =7.7, 1.5 Hz, 1H), 6.66 (td, J =7.5, 1.2 Hz, 1H), 6.63 (d, J =8.3 Hz, 1H), 5.91 (bs, 1H), 4.94 (d, J =16.7 Hz, 1H), 4.82 (hept, J =6.3 Hz, 1H), 4.66 – 4.43 (m, 2H), 1.19 (d, J =6.2 Hz, 3H), 1.16 (d, J =6.2 Hz, 3H), 1.08 (d, J =6.3 Hz, 3H), 0.88 (bs, 3H); **^{19}F{^{1}H}-NMR (471 MHz, 353K, DMSO-d$_6$)** δ -61.04; **^{13}C{^{1}H}-NMR (126 MHz, 353K, DMSO-d$_6$)** δ 159.8 (2C), 155.1 (C), 142.2 (C), 131.5 (C), 127.6 (C, q, J_{C-F} = 31.9 Hz), 127.6 (CH), 125.4 (C), 124.9 (CH, q, J_{C-F} = 3.6 Hz), 123.9 (C, q, J_{C-F} = 272.0 Hz), 122.2 (CH), 118.0 (CH), 114.5 (CH), 111.9 (CH), 71.3 (CH), 69.5 (CH), 67.8 (CH), 49.6 (CH_2), 21.3 (CH_3), 21.3 (CH_3), 21.1 (CH_3), 21.1 (CH_3); **HRMS (ESI/Q-TOF)** m/z [M + H]$^+$ calcd for $C_{24}H_{28}F_3N_4O_5^+$ 509.2006, found 509.2008.

Diisopropyl-1-(1-(4-methoxybenzyl)-3-oxo-1,2,3,4-tetrahydroquinoxalin-2-yl) hydrazine-1,2-dicarboxylate (6.3ea)

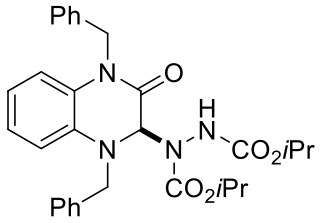


Using 4-(4-methoxybenzyl)-3,4-dihydroquinoxalin-2-one (**6.1e**, 26.8 mg, 0.1 mmol) and diisopropyl azodicarboxylate (**6.2a**, 25.6 μL, 0.13 mmol, 1.3 equiv.), in accordance with GP-1, product **6.3ea** was obtained (33.7 mg, 0.072 mmol, 72% yield, colorless oil) after column chromatography using hexane:Et_2O (from 5:5 to 2:8) mixtures.

^{1}H-NMR (500 MHz, 353K, DMSO-d$_6$) δ 10.59 (bs, 1H), 8.79 (bs, 1H), 7.20 (d, J =8.7 Hz, 2H), 6.88 (d, J =8.7 Hz, 2H), 6.83 (dd, J =7.7, 1.6 Hz, 1H), 6.78 (td, J =7.7, 1.4 Hz, 1H), 6.70 (d, J =7.2 Hz, 1H), 6.64 (td, J =7.5, 1.3 Hz, 1H), 5.86 (bs, 1H), 4.82 (hept, J =6.3 Hz, 1H), 4.77 (s, 1H), 4.56 (s, 1H), 4.38 (d, J =15.8 Hz, 1H), 3.74 (s, 3H), 1.20 (d, J =6.1 Hz, 3H), 1.17 (d, J =6.2 Hz, 3H), 1.11 – 1.03 (m, 3H), 0.88 (s, 3H); **^{13}C{^{1}H}-NMR (126 MHz, 353K, DMSO-d$_6$)** δ 159.9 (C), 158.3 (C), 155.0 (C), 154.1 (C), 131.9 (C), 128.9 (C), 128.2 (CH), 125.3 (C), 122.1 (CH), 117.5 (CH), 114.3 (CH), 113.8 (CH), 111.9 (CH), 70.8 (CH), 69.3 (CH), 67.6 (CH), 54.8 (CH_3),

49.2 (CH_2), 21.3 (CH_3), 21.3 (CH_3), 21.2 (CH_3), 21.1 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{24}H_{31}N_4O_6^+$ 471.2238, found 471.2249.

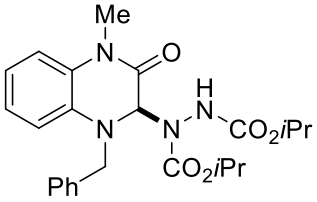
Diisopropyl 1-(1,4-dibenzyl-3-oxo-1,2,3,4-tetrahydroquinoxalin-2-yl)hydrazine-1,2-dicarboxylate (6.3fa)



Using 1,4-dibenzyl-3,4-dihydroquinoxalin-2-one (**6.1f**, 32.8 mg, 0.1 mmol) and diisopropyl azodicarboxylate (**6.2a**, 25.6 μL, 0.13 mmol, 1.3 equiv.), in accordance with GP-1, product **6.3fa** was obtained (49.3 mg, 0.093 mmol, 93% yield, colorless oil) after column chromatography using hexane:Et_2O (from 5:5 to 2:8) mixtures.

^{1}H-NMR (500 MHz, 353K, DMSO-d$_6$) δ 8.85 (bs, 1H), 7.58 – 7.14 (m, 10H), 6.96 (dd, *J* =8.1, 1.3 Hz, 1H), 6.88 – 6.79 (m, 1H), 6.75 (d, *J* =8.2 Hz, 1H), 6.69 – 6.60 (m, 1H), 6.15 (s, 1H), 5.39 (d, *J* =16.2 Hz, 1H), 5.15 (d, *J* =16.3 Hz, 1H), 4.90 (d, *J* =16.0 Hz, 1H), 4.85 (hept, *J* =6.2 Hz, 1H), 4.59-4.52 (m, 2H), 1.22 (d, *J* =6.3 Hz, 3H), 1.19 (d, *J* =6.2 Hz, 3H), 1.08 (d, *J* =6.3 Hz, 3H), 0.89 (bs, 3H); **^{13}C{^{1}H}-NMR (126 MHz, 353K, DMSO-d$_6$)** δ 160.1 (C), 155.0 (C), 154.0 (C), 136.9 (C), 136.4 (C), 133.3 (C), 128.1 (CH), 128.0 (CH), 126.9 (CH), 126.7 (CH), 126.5 (C), 126.5 (CH), 126.3 (CH), 122.7 (CH), 118.0 (CH), 114.6 (CH), 112.8 (CH), 71.3 (CH), 69.5 (CH), 67.8 (CH), 50.2 (CH_2), 44.5 (CH_2), 21.3 (CH_3), 21.3 (CH_3), 21.2 (CH_3), 21.1 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{30}H_{35}N_4O_5^+$ 531.2602, found 531.2600.

Diisopropyl 1-(1-benzyl-4-methyl-3-oxo-1,2,3,4-tetrahydroquinoxalin-2-yl)hydrazine-1,2-dicarboxylate (6.3ga)

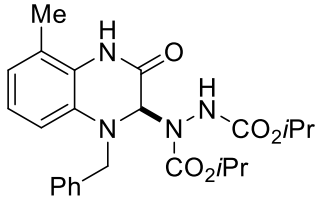


Using 4-benzyl-1-methyl-3,4-dihydroquinoxalin-2-one (**6.1g**, 25.2 mg, 0.1 mmol) and diisopropyl azodicarboxylate (**6.2a**, 25.6 μL, 0.13 mmol, 1.3 equiv.), in accordance with GP-1, product **6.3ga** was obtained (41.3 mg, 0.091 mmol, 91% yield, colorless oil) after column chromatography using hexane:Et_2O (from 5:5 to 2:8) mixtures.

^{1}H-NMR (500 MHz, 353K, DMSO-d$_6$) δ 8.74 (bs, 1H), 7.37 – 7.18 (m, 5H), 7.03 (dd, *J* =7.9, 1.5 Hz, 1H), 6.86 (dt, *J* =7.6, 4.4 Hz, 1H), 6.78 (td, *J* =7.6, 1.4 Hz, 1H), 6.76 – 6.70 (m, 1H), 5.99 (s, 1H), 4.93 – 4.76 (m, 2H), 4.63 – 4.51 (m, 1H), 4.46 (d, *J* =16.0 Hz, 1H), 3.37 (s, 3H), 1.19 (d, *J* =6.1 Hz, 3H), 1.16 (d, *J* =6.2 Hz, 3H), 1.06 (s, 3H), 0.88 (s, 3H); **^{13}C{^{1}H}-NMR (126 MHz, 353K, DMSO-d$_6$)** δ 159.7 (C), 159.1 (C), 154.8 (C), 136.8 (C), 133.1 (C), 128.1 (CH), 127.6 (C), 127.0 (CH), 126.7 (CH), 122.5 (CH), 118.0 (CH), 113.7 (CH), 112.1 (CH), 70.7 (CH), 69.4 (CH), 67.7 (CH), 50.0 (CH_2), 28.5 (CH_3),

21.4 (CH_3), 21.3 (CH_3), 21.3 (CH_3), 21.1 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{24}H_{31}N_4O_5^+$ 455.2289, found 455.2292.

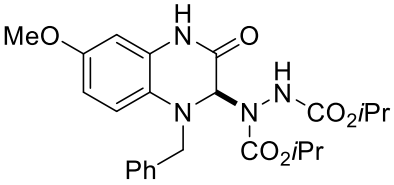
Diisopropyl 1-(1-benzyl-5-methyl-3-oxo-1,2,3,4-tetrahydroquinoxalin-2-yl)hydrazine-1,2-dicarboxylate (6.3ha)



Using 4-benzyl-8-methyl-3,4-dihydroquinoxalin-2-one (**6.1h**, 25.2 mg, 0.1 mmol) and diisopropyl azodicarboxylate (**6.2a**, 25.6 μL, 0.13 mmol, 1.3 equiv.), in accordance with GP-1, product **6.3ha** was obtained (35.9 mg, 0.079 mmol, 79% yield, colorless oil) after column chromatography using hexane:Et_2O (from 5:5 to 2:8) mixtures.

^{1}H-NMR (500 MHz, 353K, DMSO-d$_6$) δ 9.84 (bs, 1H), 8.77 (bs, 1H), 7.37 – 7.15 (m, 5H), 6.69 (t, *J* =7.8 Hz, 1H), 6.56 (d, *J* =7.7 Hz, 1H), 6.54 (d, *J* =7.5 Hz, 1H), 5.89 (bs, 1H), 4.91 – 4.77 (m, 2H), 4.54 (s, 1H), 4.46 (d, *J* =16.1 Hz, 1H), 2.23 (s, 3H), 1.19 (d, *J* =4.6 Hz, 3H), 1.16 (d, *J* =6.2 Hz, 3H), 1.07 (d, *J* =6.6 Hz, 3H), 0.90 (s, 3H); **^{13}C{^{1}H}-NMR (126 MHz, 353K, DMSO-d$_6$)** δ 160.3 (C), 155.7 (C), 154.9 (C), 137.2 (C), 132.1 (C), 128.1 (CH), 126.9 (CH), 126.6 (CH), 123.5 (C), 122.6 (C), 121.8 (CH), 120.1 (CH), 110.3 (CH), 71.1 (CH), 69.3 (CH), 67.6 (CH), 50.3 (CH_2), 21.5 (CH_3), 21.3 (CH_3), 21.2 (CH_3), 21.1 (CH_3), 16.6 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{24}H_{31}N_4O_5^+$ 455.2289, found 455.2291.

Diisopropyl 1-(1-benzyl-6-methoxy-3-oxo-1,2,3,4-tetrahydroquinoxalin-2-yl)hydrazine-1,2-dicarboxylate (6.3ia)

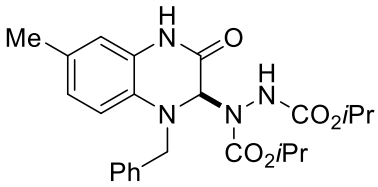


Using 4-benzyl-7-methoxy-3,4-dihydroquinoxalin-2-one (**6.1i**, 26.8 mg, 0.1 mmol) and diisopropyl azodicarboxylate (**6.2a**, 25.6 μL, 0.13 mmol, 1.3 equiv.), in accordance with GP-1, product **6.3ia** was obtained (26.2 mg, 0.056 mmol, 56% yield, greenish solid) after column chromatography using hexane:Et_2O (from 5:5 to 2:8) mixtures.

Mp = 172 °C – 174 °C; **^{1}H-NMR (500 MHz, 353K, DMSO-d$_6$)** δ 10.47 (bs, 1H), 8.83 (bs, 1H), 7.36 – 7.20 (m, 5H), 6.73 (d, *J* =9.0 Hz, 1H), 6.24 (d, *J* =6.6 Hz, 2H), 5.87 (bs, 1H), 4.87 – 4.72 (m, 2H), 4.62 – 4.54 (m, 1H), 4.45 (d, *J* =16.0 Hz, 1H), 3.59 (s, 3H), 1.20 (d, *J* =6.3 Hz, 3H), 1.17 (d, *J* =6.3 Hz, 3H), 1.09 (d, *J* =5.0 Hz, 3H), 0.92 – 0.80 (m, 3H); **^{13}C{^{1}H}-NMR (126 MHz, 353K, DMSO-d$_6$)** δ 155.7 (C), 155.2 (C), 155.0 (C), 137.0 (C), 133.0 (C), 128.1 (CH), 126.9 (CH), 126.7 (CH), 119.3 (C), 114.6 (CH), 102.4 (CH), 99.5 (CH), 71.2 (CH), 69.4 (CH), 67.8 (CH), 54.8 (CH_3), 50.0 (CH_2),

21.5 (CH_3), 21.3 (CH_3), 21.2 (CH_3), 21.0 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{24}H_{31}N_4O_6^+$ 471.2238, found 471.2242.

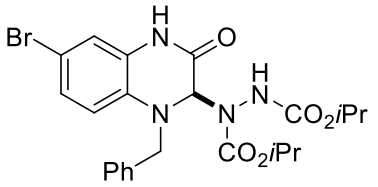
Diisopropyl 1-(1-benzyl-6-methyl-3-oxo-1,2,3,4-tetrahydroquinoxalin-2-yl)hydrazine-1,2-dicarboxylate (6.3ja)



Using 4-benzyl-7-methyl-3,4-dihydroquinoxalin-2-one (**6.1j**, 25.2 mg, 0.1 mmol) and diisopropyl azodicarboxylate (**6.2a**, 25.6 μL, 0.13 mmol, 1.3 equiv.), in accordance with GP-1, product **6.3ja** was obtained (33.1 mg, 0.073 mmol, 73% yield, yellow solid) after column chromatography using hexane:Et_2O (from 5:5 to 2:8) mixtures.

Mp = 180 °C decompose; **^{1}H-NMR (500 MHz, 353K, DMSO-d$_6$)** δ 10.54 (bs, 1H), 8.79 (bs, 1H), 7.42 – 7.18 (m, 5H), 6.65 (s, 1H), 6.57 (t, *J* =7.0 Hz, 2H), 5.86 (bs, 1H), 4.87 – 4.74 (m, 2H), 4.56 (s, 1H), 4.43 (d, *J* =16.2 Hz, 1H), 2.14 (s, 3H), 1.19 (d, *J* =6.2 Hz, 3H), 1.16 (d, *J* =6.3 Hz, 3H), 1.11 – 1.07 (m, 3H), 0.91 – 0.81 (m, 3H); **^{13}C{^{1}H}-NMR (126 MHz, 353K, DMSO-d$_6$)** δ 160.0 (C), 155.7 (C), 155.0 (C), 137.3 (C), 129.5 (C), 128.0 (CH), 126.8 (CH), 126.6 (CH), 126.4 (C), 125.2 (C), 122.5 (CH), 114.9 (CH), 111.9 (CH), 71.2 (CH), 69.3 (CH), 67.6 (CH), 49.8 (CH_2), 21.34 (CH_3), 21.29 (CH_3), 21.2 (CH_3), 21.0 (CH_3), 19.6 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{24}H_{31}N_4O_5^+$ 455.2289, found 455.2281.

Diisopropyl 1-(1-benzyl-6-bromo-3-oxo-1,2,3,4-tetrahydroquinoxalin-2-yl)hydrazine-1,2-dicarboxylate (6.3ka)

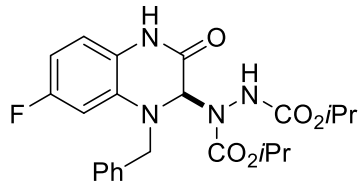


Using 4-benzyl-7-bromo-3,4-dihydroquinoxalin-2-one (**6.1k**, 31.7 mg, 0.1 mmol) and diisopropyl azodicarboxylate (**6.2a**, 25.6 μL, 0.13 mmol, 1.3 equiv.), in accordance with GP-1, product **6.3ka** was obtained (43.1 mg, 0.083 mmol, 83% yield, colorless oil) after column chromatography using hexane:Et_2O (from 5:5 to 2:8) mixtures.

^{1}H-NMR (500 MHz, 353K, DMSO-d$_6$) δ 10.76 (bs, 1H), 8.91 (bs, 1H), 7.38 – 7.22 (m, 5H), 6.99 (d, *J* =2.3 Hz, 1H), 6.91 (dd, *J* =8.7, 2.4 Hz, 1H), 6.62 (d, *J* =8.7 Hz, 1H), 5.88 (bs, 1H), 4.93 – 4.74 (m, 2H), 4.65 – 4.52 (m, 1H), 4.46 (d, *J* =16.2 Hz, 1H), 1.20 (d, *J* =6.3 Hz, 3H), 1.17 (d, *J* =6.2 Hz, 3H), 1.10 (d, *J* =6.3 Hz, 3H), 0.93 (s, 3H); **^{13}C{^{1}H}-NMR (126 MHz, 353K, DMSO-d$_6$)** δ 159.9 (C), 159.8 (C), 155.0 (C), 136.6 (C), 131.3 (C), 128.1 (CH), 127.1 (C), 126.9 (CH), 126.8 (CH), 124.3 (CH), 116.5 (CH), 113.8 (CH), 108.8 (C), 70.7 (CH), 69.5 (CH), 67.8 (CH), 50.0 (CH_2), 21.3

(CH_3), 21.3 (CH_3), 21.2 (CH_3), 21.0 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{23}H_{28}BrN_4O_5^+$ 519.1238, found 519.1249.

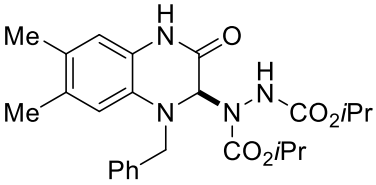
Diisopropyl 1-(1-benzyl-7-fluoro-3-oxo-1,2,3,4-tetrahydroquinoxalin-2-yl)hydrazine-1,2-dicarboxylate (6.3la)



Using 4-benzyl-6-fluoro-3,4-dihydroquinoxalin-2-one (**6.1l**, 128.14 mg, 0.5 mmol) and diisopropyl azodicarboxylate (**6.2a**, 128 μL, 0.65 mmol, 1.3 equiv.), in accordance with GP-1, product **6.3la** was obtained (171.3 mg, 0.374 mmol, 75% yield, colorless oil) after column chromatography using hexane:Et_2O (from 5:5 to 2:8) mixtures.

^{1}H-NMR (500 MHz, 353K, DMSO-d$_6$) δ 10.67 (bs, 1H), 8.91 (bs, 1H), 7.38 – 7.21 (m, 5H), 6.81 (dd, *J* =8.5, 5.7 Hz, 1H), 6.49 (d, *J* =11.3 Hz, 1H), 6.44 (td, *J* =8.5, 2.6 Hz, 1H), 5.87 (bs, 1H), 4.88 – 4.76 (m, 2H), 4.68 – 4.53 (m, 1H), 4.46 (d, *J* =16.2 Hz, 1H), 1.20 (d, *J* =6.3 Hz, 3H), 1.17 (d, *J* =6.3 Hz, 3H), 1.09 (d, *J* =5.6 Hz, 3H), 0.99 – 0.78 (m, 3H); **^{19}F{^{1}H}-NMR (282 MHz, 353K, DMSO-d$_6$)** δ -120.11 (s); **^{13}C{^{1}H}-NMR (126 MHz, 353K, DMSO-d$_6$)** δ 159.4 (C), 159.4 (C), 158.2 (d, *J* =235.3 Hz, C), 155.1 (C), 136.6 (C), 133.5 (C), 128.2 (CH), 126.9 (CH), 126.8 (CH), 121.9 (C), 114.8 (d, J_{C-F} = 10.1 Hz, CH), 103.4 (d, J_{C-F} = 23.0 Hz, CH), 99.5 (d, J_{C-F} = 30.1 Hz, CH), 70.5 (CH), 69.5 (CH), 67.8 (CH), 50.0 (CH_2), 21.30 (CH_3), 21.27 (CH_3), 21.1 (CH_3), 21.0 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{23}H_{28}FN_4O_5^+$ 459.2038, found 459.2040.

Diisopropyl 1-(1-benzyl-6,7-dimethyl-3-oxo-1,2,3,4-tetrahydroquinoxalin-2-yl) hydrazine-1,2-dicarboxylate (6.3ma)

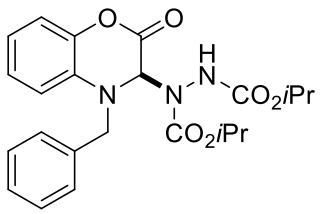


Using 4-benzyl-6,7-dimethyl-3,4-dihydroquinoxalin-2-one (**6.1m**, 26.6 mg, 0.1 mmol) and diisopropyl azodicarboxylate (**6.2a**, 25.6 μL, 0.13 mmol, 1.3 equiv.), in accordance with GP-1, product **6.3ma** was obtained (7.0 mg, 0.015 mmol, 15% yield, colorless oil) after column chromatography using hexane:Et_2O (from 5:5 to 2:8) mixtures.

^{1}H-NMR (500 MHz, 353K, DMSO-d$_6$) δ 10.44 (bs, 1H), 8.78 (bs, 1H), 7.36 – 7.21 (m, 5H), 6.60 (s, 1H), 6.49 (s, 1H), 5.81 (bs, 1H), 4.86 – 4.75 (m, 2H), 4.55 (bs, 1H), 4.41 (d, *J* =16.2 Hz, 1H), 2.05 (s, 3H), 2.03 (s, 3H), 1.19 (d, *J* =6.2 Hz, 3H), 1.16 (d, *J* =6.2 Hz, 3H), 1.07 (d, *J* =6.2 Hz, 3H), 0.96 – 0.80 (m, 3H); **^{13}C{^{1}H}-NMR (126 MHz, 353K, DMSO-d$_6$)** δ 155.7 (C), 154.9 (C), 154.2 (C), 137.4 (C), 129.7 (C), 129.2 (C), 128.0 (CH), 126.9 (CH), 126.6 (CH), 115.6 (C), 113.3 (C), 109.6 (CH), 108.6 (CH), 71.1 (CH),

69.3 (CH), 67.6 (CH), 49.6 (CH_2), 21.5 (CH_3), 21.3 (CH_3), 21.3 (CH_3), 21.2 (CH_3), 18.6 (CH_3), 17.8 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{25}H_{33}N_4O_5^+$ 469.2445, found 469.2437.

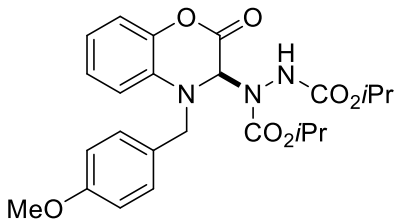
Diisopropyl 1-(4-benzyl-2-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-3-yl)hydrazine-1,2-dicarboxylate (6.5aa)



Using 4-benzyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-one (**6.4a**, 23.9 mg, 0.1 mmol) and diisopropyl azodicarboxylate (**6.2a**, 25.6 μL, 0.13 mmol, 1.3 equiv.), in accordance with GP-1, product **6.5aa** was obtained (32.3 mg, 0.074 mmol, 74% yield, brown oil) after column chromatography using hexane-EtOAc 8:2 mixture.

^{1}H-NMR (500 MHz, 353K, DMSO-d$_6$) δ 9.04 (bs, 1H), 7.41 – 7.31 (m, 4H), 7.30 – 7.22 (m, 1H), 7.05 – 6.92 (m, 2H), 6.84 (d, *J* =7.8 Hz, 1H), 6.79 (td, *J* =7.8, 1.4 Hz, 1H), 6.09 (bs, 1H), 4.89 – 4.75 (m, 2H), 4.65 – 4.53 (m, 1H), 4.46 (d, *J* =15.6 Hz, 1H), 1.24 – 1.13 (m, 6H), 1.07 (d, *J* =5.8 Hz, 3H), 1.00 – 0.90 (m, 3H); **^{13}C{^{1}H}-NMR (126 MHz, 353K, DMSO-d$_6$)** δ 159.1 (C), 154.9 (C), 153.7 (C), 140.0 (C), 136.0 (C), 131.3 (C), 128.2 (CH), 127.2 (CH), 126.9 (CH), 124.3 (CH), 118.7 (CH), 115.2 (CH), 113.2 (CH), 70.0 (CH), 68.9 (CH), 68.1 (CH), 49.7 (CH_2), 21.23 (CH_3), 21.16 (CH_3), 21.09 (CH_3), 21.05 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{23}H_{28}N_3O_6^+$ 442.1973, found 442.1983.

Diisopropyl 1-(4-(4-methoxybenzyl)-2-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-3-yl) hydrazine-1,2-dicarboxylate (6.5ba)

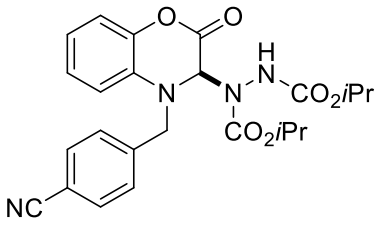


Using 4-(4-methoxybenzyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-one (**6.4b**, 26.9 mg, 0.1 mmol) and diisopropyl azodicarboxylate (**6.2a**, 25.6 μL, 0.13 mmol, 1.3 equiv.), in accordance with GP-1, product **6.5ba** was obtained (27.1 mg, 0.057 mmol, 57% yield, reddish oil) after column chromatography using hexane-EtOAc 8:2 mixture.

^{1}H-NMR (500 MHz, 353K, DMSO-d$_6$) δ 9.01 (s, 1H), 7.31 – 7.18 (m, 2H), 7.02 – 6.94 (m, 2H), 6.93 – 6.87 (m, 2H), 6.87 (dd, *J* =5.7, 3.0 Hz, 1H), 6.79 (td, *J* =7.7, 1.4 Hz, 1H), 6.05 (s, 1H), 4.81 (hept, *J* =6.3 Hz, 1H), 4.74 (d, *J* =15.3 Hz, 1H), 4.61 – 4.53 (m, 1H), 4.38 (d, *J* =15.1 Hz, 1H), 3.75 (s, 3H), 1.21 – 1.14 (m, 6H), 1.07 (d, *J* =5.8 Hz, 3H), 1.00 – 0.92 (m, 3H); **^{13}C{^{1}H}-NMR (126 MHz, 353K, DMSO-d$_6$)** δ 159.0 (C), 158.5 (C), 154.9 (C), 140.0 (C), 131.4 (C), 128.6 (CH), 127.7 (C), 124.3 (CH), 118.6

(CH), 115.6 (C), 115.1 (CH), 113.8 (CH), 113.2 (CH), 70.0 (CH), 68.5 (CH), 68.1 (CH), 54.8 (CH_3), 49.1 (CH_2), 21.23 (CH_3), 21.17 (CH_3), 21.11 (CH_3), 21.05 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{24}H_{30}N_3O_7^+$ 472.2078, found 472.2072.

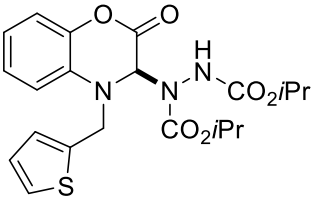
Diisopropyl 1-(4-(4-cyanobenzyl)-2-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-3-yl) hydrazine-1,2-dicarboxylate (6.5ca)



Using 4-((2-oxo-2,3-dihydro-4*H*-benzo[*b*][1,4]oxazin-4-yl)methyl)benzonitrile (**6.4c**, 26.4 mg, 0.1 mmol) and diisopropyl azodicarboxylate (**6.2a**, 25.6 μL, 0.13 mmol, 1.3 equiv.), in accordance with GP-1, product **6.5ca** was obtained (25.5 mg, 0.055 mmol, 55% yield, reddish oil) after column chromatography using hexane-EtOAc 8:2 mixture.

^{1}H-NMR (500 MHz, 353K, DMSO-d$_6$) δ 9.09 (s, 1H), 7.75 (d, *J* =8.4 Hz, 2H), 7.57 (d, *J* =8.4 Hz, 2H), 7.01 (dd, *J* =7.9, 1.4 Hz, 1H), 6.98 – 6.92 (m, 1H), 6.80 (td, *J* =7.7, 1.3 Hz, 1H), 6.72 (d, *J* =7.9 Hz, 1H), 6.16 (s, 1H), 4.90 (d, *J* =16.6 Hz, 1H), 4.85 – 4.74 (m, 1H), 4.61 – 4.52 (m, 2H), 1.19 (d, *J* =3.2 Hz, 3H), 1.17 (d, *J* =6.4 Hz, 3H), 1.07 (d, *J* =6.3 Hz, 3H), 0.97 – 0.92 (m, 3H); **^{13}C{^{1}H}-NMR (126 MHz, 353K, DMSO-d$_6$)** δ 158.9 (C), 155.7 (C), 154.9 (C), 142.3 (C), 140.0 (C), 132.0 (CH), 130.8 (C), 128.1 (CH), 124.4 (CH), 119.0 (CH), 118.2 (CN), 115.3 (CH), 113.2 (CH), 109.9 (C), 70.1 (CH), 69.4 (CH), 68.2 (CH), 49.7 (CH_2), 21.22 (CH_3), 21.16 (CH_3), 21.1 (CH_3), 21.0 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{24}H_{27}N_4O_6^+$ 467.1925, found 467.1928.

Diisopropyl 1-(2-oxo-4-(thiophen-2-ylmethyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-3-yl)hydrazine-1,2-dicarboxylate (6.5da)

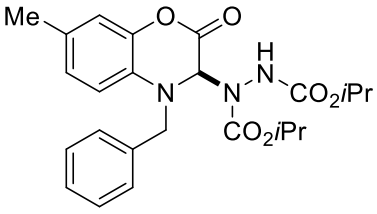


Using 4-(thiophen-2-ylmethyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-one (**6.4d**, 24.5 mg, 0.1 mmol) and diisopropyl azodicarboxylate (**6.2a**, 25.6 μL, 0.13 mmol, 1.3 equiv.), in accordance with GP-1, product **6.5da** was obtained (33.8 mg, 0.076 mmol, 76% yield, colorless oil) after column chromatography using hexane-EtOAc 8:2 mixture.

^{1}H-NMR (500 MHz, 353K, DMSO-d$_6$) δ 9.04 (bs, 1H), 7.42 (dd, *J* =5.1, 1.3 Hz, 1H), 7.11 (dd, *J* =3.5, 1.2 Hz, 1H), 7.06 – 6.95 (m, 4H), 6.83 (ddd, *J* =8.2, 7.2, 1.7 Hz, 1H), 6.11 (s, 1H), 5.03 (d, *J* =16.0 Hz, 1H), 4.83 (hept, *J* =6.2 Hz, 1H), 4.64 (d, *J* =16.0 Hz, 1H), 4.61 – 4.55 (m, 1H), 1.20 (d, *J* =6.3 Hz, 3H), 1.18 (d, *J* =6.2 Hz, 3H), 1.07 (d, *J* =6.3 Hz, 3H), 0.97 (bs, 3H); **^{13}C{^{1}H}-NMR (126 MHz, 353K, DMSO-d$_6$)** δ 159.1 (C), 155.0 (C), 153.8 (C), 140.0 (C), 139.1 (C), 130.8 (C), 126.6 (CH), 126.3 (CH),

125.3 (CH), 124.4 (CH), 119.0 (CH), 115.3 (CH), 113.2 (CH), 70.1 (CH), 68.2 (2CH), 44.8 (CH_2), 21.2 (CH_3), 21.2 (CH_3), 21.1 (CH_3), 21.0 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{21}H_{26}N_3O_6S^+$ 448.1537, found 448.1539.

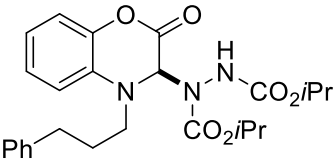
Diisopropyl 1-(4-benzyl-7-methyl-2-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-3-yl) hydrazine-1,2-dicarboxylate (6.5ea)



Using 4-benzyl-7-methyl-3,4-dihydro-2*H*-benzo[*b*][1,4] oxazin-2-one (**6.4e**, 25.3 mg, 0.1 mmol) and diisopropyl azodicarboxylate (**6.2a**, 25.6 μL, 0.13 mmol, 1.3 equiv.), in accordance with GP-1, product **6.5ea** was obtained (34.0 mg, 0.074 mmol, 74% yield, reddish oil) after column chromatography using hexane-EtOAc 8:2 mixture.

^{1}H-NMR (500 MHz, 353K, DMSO-d$_6$) δ 9.01 (bs, 1H), 7.39 – 7.30 (m, 4H), 7.29 – 7.23 (m, 1H), 6.82 (d, *J* =1.4 Hz, 1H), 6.80 – 6.76 (m, 1H), 6.70 (d, *J* =7.9 Hz, 1H), 6.05 (bs, 1H), 4.88 – 4.72 (m, 2H), 4.62 – 4.53 (m, 1H), 4.43 (d, *J* =15.7 Hz, 1H), 2.20 (s, 3H), 1.26 – 1.14 (m, 6H), 1.07 (d, *J* =6.0 Hz, 3H), 1.02 – 0.89 (m, 3H); **^{13}C{^{1}H}-NMR (126 MHz, 353K, DMSO-d$_6$)** δ 159.29 (C), 159.25 (C), 154.9 (C), 139.9 (C), 136.2 (C), 128.8 (C), 128.1 (CH), 128.0 (C), 127.2 (CH), 126.9 (CH), 124.7 (CH), 115.6 (CH), 113.2 (CH), 70.0 (CH), 69.0 (CH), 68.1 (CH), 49.8 (CH_2), 21.21 (CH_3), 21.16 (CH_3), 21.1 (CH_3), 21.0 (CH_3), 19.4 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{24}H_{30}N_3O_6^+$ 456.2129, found 456.2131.

Diisopropyl 1-(2-oxo-4-(3-phenylpropyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-3-yl) hydrazine-1,2-dicarboxylate (6.5fa)



Using 4-(3-phenylpropyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-one (**6.4f**, 24.5 mg, 0.1 mmol) and diisopropyl azodicarboxylate (**6.2a**, 25.6 μL, 0.13 mmol, 1.3 equiv.), in accordance with GP-1, product **6.5fa** was obtained (23.5 mg, 0.050 mmol, 50% yield, colorless oil) after column chromatography using hexane-EtOAc 8:2 mixture.

^{1}H-NMR (500 MHz, 353K, DMSO-d$_6$) δ 8.95 (bs, 1H), 7.31 – 7.25 (m, 2H), 7.24 – 7.16 (m, 3H), 7.02 (td, *J* =7.7, 1.5 Hz, 1H), 6.96 (dd, *J* =7.8, 1.4 Hz, 1H), 6.84 – 6.75 (m, 2H), 6.07 (bs, 1H), 4.82 (h, *J* =6.3 Hz, 1H), 4.54 (s, 1H), 3.59 (ddd, *J* =14.1, 8.3, 5.6 Hz, 1H), 3.25 (dt, *J* =14.5, 7.4 Hz, 1H), 2.65 (t, *J* =7.5 Hz, 2H), 2.04 (ddd, *J* =14.4, 8.1, 6.5 Hz, 1H), 1.99 – 1.86 (m, 1H), 1.20 - 1.15 (m, 6H), 1.04 (d, *J* =6.2 Hz, 3H), 0.94 (s, 3H); **^{13}C{^{1}H}-NMR (126 MHz, 353K, DMSO-d$_6$)** δ 158.9 (C), 154.8 (C), 153.7 (C), 140.9 (C), 139.9 (C), 131.2 (C), 127.8 (CH), 127.7 (CH), 125.4 (CH), 124.4 (CH), 118.2

(CH), 115.2 (CH), 112.6 (CH), 69.9 (CH), 68.8 (CH), 68.0 (CH), 45.6 (CH_2), 32.0 (CH_2), 27.0 (CH_2), 21.2 (CH_3), 21.2 (CH_3), 21.1 (CH_3), 21.0 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{25}H_{32}N_3O_6^+$ 470.2286, found 470.2289.

Specific Procedure 1 (SP-1) for the Gram-Scale Light-Accelerated Amination Reaction between 3,4-dihydroquinoxalin-2-one 6.1a and Diisopropyl Azodicarboxylate (6.2a) under Sunlight Irradiation

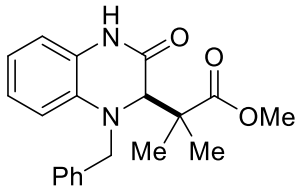
To an ovendried 250 mL-Schlenck tube containing a teflon-coated stir bar were added 4-benzyl-3,4-dihydroquinoxalin-2-one (**6.1a**, 0.92 g, 3.8 mmol, 1 equiv.). The reaction vessel was evacuated and backfilled with argon three times. After this, freshly degassed and dried MeCN (20 mL) and diisopropyl azodicarboxylate (**6.2a**, 0.97 mL, 4.94 mmol, 1.3 equiv.) were added via syringe and the reaction mixture was placed at the upper part of the building in sunny hours under vigorous stirring and under a positive pressure of argon (see page 434 for further details about the photochemical setup). The course of the reaction was monitored by TLC. The desired aminated product (**6.3aa**, 1.47 g, 3.34 mmol, 88% yield) was isolated from the reaction mixture by flash column chromatography using hexane:Et_2O mixtures.

Specific Procedure 2 (SP-2) for the Gram-Scale Light-Accelerated Amination Reaction between 3,4-dihydroquinoxalin-2-one 6.1a and Diisopropyl Azodicarboxylate (6.2a) under blue LEDs Irradiation

To an ovendried 250 mL-Schlenck tube containing a teflon-coated stir bar were added 4-benzyl-3,4-dihydroquinoxalin-2-one (**6.1a**, 1.2 g or 1.57 g, 5.0 mmol or 6.6 mmol, 1 equiv.). The reaction vessel was evacuated and backfilled with argon three times. After this, freshly degassed and dried MeCN (20 mL) and diisopropyl azodicarboxylate (**6.2a**, 1.28 mL or 1.68 mL, 6.5 mmol or 8.6 mmol, 1.3 equiv.) were added via syringe and the reaction mixture was irradiated with a strip of blue LEDs (450 nm) under vigorous stirring under a positive pressure of argon. The course of the reaction was monitored by TLC. The desired aminated product (**6.3aa**, 1.98 g or 2.41 g, 4.5 mmol or 5.47 mmol, 90% yield or 83% yield) was isolated from the reaction mixture by flash column chromatography using hexane:Et_2O mixtures.

Specific Procedures for the Derivatization of Compound 6.3aa

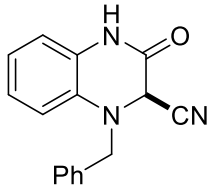
Methyl 2-(1-benzyl-3-oxo-1,2,3,4-tetrahydroquinoxalin-2-yl)-2-methylpropanoate (6.6a)



In a 25 mL round bottomed flask was weighted aminated dihydroquinoxalinone **6.3aa** (44.0 mg, 0.1 mmol). After the addition of a teflon-coated stir bar, the flask was purged with N_2. MeCN (2 mL) and methyl trimethylsilyl dimethylketene acetal (60.9 μL, 0.3 mmol, 3 equiv.) were sequentially added. Then, $BF_3{\cdot}OEt_2$ (13.6 μL, 0.11 mmol, 1.1 equiv.) was added dropwise and the reaction mixture was stirred for 1 h at room temperature. The reaction mixture was directly purified by column chromatography to afford compound **6.6a** (33.7 mg, 0.099 mmol, 99% yield) as a colourless oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.35 (bs, 1H), 7.34 – 7.08 (m, 5H), 6.90 (ddd, J =8.1, 5.9, 2.8 Hz, 1H), 6.84 – 6.79 (m, 1H), 6.77 – 6.70 (m, 2H), 4.86 (d, J =15.8 Hz, 1H), 4.45 – 4.30 (m, 2H), 3.61 (s, 3H), 1.22 (s, 3H), 1.19 (s, 3H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 175.9 (C), 165.0 (C), 137.2 (C), 133.9 (C), 128.7 (CH), 127.5 (CH), 127.3 (C), 127.2 (CH), 124.2 (CH), 119.8 (CH), 116.6 (CH), 115.1 (CH), 68.9 (CH), 57.7 (CH_2), 52.2 (CH_3), 49.4 (C), 22.7 (CH_3), 22.0 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{20}H_{23}N_2O_3^+$ 339.1703, found 339.1700.

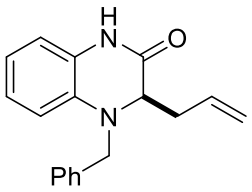
1-Benzyl-3-oxo-1,2,3,4-tetrahydroquinoxaline-2-carbonitrile (6.6b)



In a 25 mL round bottomed flask was weighted aminated dihydroquinoxalinone **6.3aa** (44.0 mg, 0.1 mmol). After the addition of a teflon-coated stir bar, the flask was purged with N_2. MeCN (2 mL) and TMS-CN (37.5 μL, 0.3 mmol, 3 equiv.) were sequentially added. Then, $BF_3{\cdot}OEt_2$ (13.6 μL, 0.11 mmol, 1.1 equiv.) was added dropwise and the reaction mixture was stirred for 1 h at room temperature. The reaction mixture was directly purified by column chromatography to afford compound **6.6b** (25.1 mg, 0.095 mmol, 95% yield) as a colourless oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.64 (bs, 1H), 7.57 – 7.32 (m, 5H), 7.19 – 7.08 (m, 1H), 7.04 – 6.91 (m, 3H), 4.82 (d, J =13.4 Hz, 1H), 4.59 (s, 1H), 4.09 (d, J =13.4 Hz, 1H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 159.9 (C), 133.8 (C), 132.4 (C), 129.3 (CH), 128.8 (CH), 125.8 (C), 125.2 (CH), 122.1 (CH), 116.6 (CH), 114.4 (CH), 112.8 (CH), 52.1 (CH_2), 51.9 (CH); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{16}H_{14}N_3O^+$ 264.1131, found 264.1135.

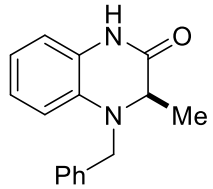
3-Allyl-4-benzyl-3,4-dihydroquinoxalin-2-one (6.6c)



In a 25 mL round bottomed flask was weighted aminated dihydroquinoxalinone **6.3aa** (44.0 mg, 0.1 mmol). After the addition of a teflon-coated stir bar, the flask was purged with N_2. MeCN (2 mL) and allyl-TMS (47.8 μL, 0.3 mmol, 3 equiv.) were sequentially added. Then, $BF_3{\cdot}OEt_2$ (13.6 μL, 0.11 mmol, 1.1 equiv.) was added dropwise and the reaction mixture was stirred for 1 h at room temperature. The reaction mixture was directly purified by column chromatography to afford compound **6.6c** (22.7 mg, 0.082 mmol, 82% yield) as a colourless oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.35 (bs, 1H), 7.47 – 7.13 (m, 5H), 6.93 (ddd, *J* =8.0, 6.9, 2.0 Hz, 1H), 6.87 – 6.74 (m, 2H), 6.70 (d, *J* =7.9 Hz, 1H), 5.77 (dddd, *J* =17.0, 10.0, 7.6, 6.9 Hz, 1H), 5.19 – 4.98 (m, 2H), 4.69 (d, *J* =15.1 Hz, 1H), 4.32 (d, *J* =15.1 Hz, 1H), 4.00 (td, *J* =6.6, 0.6 Hz, 1H), 2.67 – 2.27 (m, 2H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 168.1 (C), 136.7 (C), 133.9 (C), 133.3 (CH), 128.7 (CH), 127.6 (CH), 127.6 (CH), 126.2 (C), 124.1 (CH), 119.1 (CH), 118.4 (CH_2), 115.5 (CH), 113.6 (CH), 62.0 (CH), 53.1 (CH_2), 34.2 (CH_2); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{18}H_{19}N_2O^+$ 279.1492, found 279.1498.

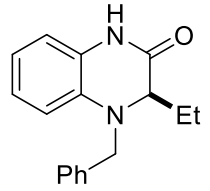
4-Benzyl-3-methyl-3,4-dihydroquinoxalin-2-one (6.7a)



In a 25 mL round bottomed flask was weighted aminated dihydroquinoxalinone **6.3aa** (44.0 mg, 0.1 mmol). After the addition of a teflon-coated stir bar, the flask was purged with N_2. Freshly distilled THF (2 mL) was added, and the solution was cooled down to 0 °C. MeMgBr (3 M in Et_2O, 0.11 mL, 3.3 equiv.) was slowly added and the reaction mixture was stirred for 1 h at 0 °C. Then, the reaction was quenched with aq. sat. NH_4Cl (5 mL) and the mixture was extracted with DCM (x3). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and evaporated under vacuum to obtain a residue which was directly purified by column chromatography using hexane:EtOAc mixtures to finally afford compound **6.7a** (23.4 mg, 0.093 mmol, 93% yield) as a colourless oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.41 (bs, 1H), 7.34 – 7.16 (m, 5H), 6.85 (ddd, *J* =8.0, 7.1, 1.9 Hz, 1H), 6.80 – 6.71 (m, 1H), 6.69 (dd, *J* =7.7, 1.2 Hz, 1H), 6.62 (dd, *J* =8.0, 1.2 Hz, 1H), 4.52 (d, *J* =14.9 Hz, 1H), 4.12 (d, *J* =14.9 Hz, 1H), 3.90 (q, *J* =6.8 Hz, 1H), 1.14 (d, *J* =6.8 Hz, 3H); **^{13}C{^{1}H}-NMR (126 MHz, $CDCl_3$)** δ 170.1 (C), 136.6 (C), 133.6 (C), 128.8 (CH), 127.7 (CH), 127.6 (CH), 126.3 (C), 124.1 (CH), 119.2 (CH), 115.5 (CH), 113.7 (CH), 57.2 (CH), 51.9 (CH_2), 13.0 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{16}H_{17}N_2O^+$ 253.1335, found 253.1341.

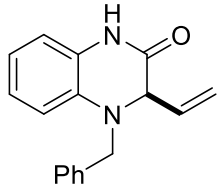
4-Benzyl-3-ethyl-3,4-dihydroquinoxalin-2-one (6.7b)



In a 25 mL round bottomed flask was weighted aminated dihydroquinoxalinone **6.3aa** (44.0 mg, 0.1 mmol). After the addition of a teflon-coated stir bar, the flask was purged with N_2. Freshly distilled THF (2 mL) was added, and the solution was cooled down to 0 °C. EtMgBr (3 M in Et_2O, 0.11 mL, 3.3 equiv.) was slowly added and the reaction mixture was stirred for 1 h at 0 °C. Then, the reaction was quenched with aq. sat. NH_4Cl (5 mL) and the mixture was extracted with DCM (x3). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and evaporated under vacuum to obtain a residue which was directly purified by column chromatography using hexane:EtOAc mixtures to finally afford compound **6.7b** (20.7 mg, 0.078 mmol, 78% yield) as a colourless oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.24 (bs, 1H), 7.38 – 7.18 (m, 5H), 6.90 (ddd, *J* =8.0, 7.0, 2.0 Hz, 1H), 6.80 (dd, *J* =7.7, 1.9 Hz, 1H), 6.80 – 6.69 (m, 1H), 6.69 (d, *J* =8.0 Hz, 1H), 4.67 (d, *J* =15.1 Hz, 1H), 4.28 (d, *J* =15.0 Hz, 1H), 3.83 (ddd, *J* =7.6, 5.8, 0.7 Hz, 1H), 1.88 – 1.51 (m, 2H), 0.93 (t, *J* =7.5 Hz, 3H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 168.7 (C), 136.9 (C), 134.2 (C), 128.7 (CH), 127.6 (CH), 127.5 (CH), 126.3 (C), 124.0 (CH), 119.0 (CH), 115.4 (CH), 113.5 (CH), 63.1 (CH), 53.1 (CH_2), 22.6 (CH_2), 10.2 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{17}H_{19}N_2O^+$ 267.1492, found 267.1495.

4-Benzyl-3-vinyl-3,4-dihydroquinoxalin-2-one (6.7c)

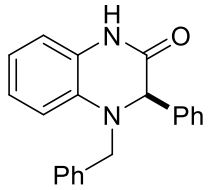


In a 25 mL round bottomed flask was weighted aminated dihydroquinoxalinone **6.3aa** (44.0 mg, 0.1 mmol). After the addition of a teflon-coated stir bar, the flask was purged with N_2. Freshly distilled THF (2 mL) was added, and the solution was cooled down to 0 °C. Vinylmagnesium bromide (3 M in Et_2O, 0.11 mL, 3.3 equiv.) was slowly added and the reaction mixture was stirred for 1 h at 0 °C. Then, the reaction was quenched with aq. sat. NH_4Cl (5 mL) and the mixture was extracted with DCM (x3). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and evaporated under vacuum to obtain a residue which was directly purified by column chromatography using hexane:EtOAc mixtures to finally afford compound **6.7c** (26.1 mg, 0.099 mmol, 99% yield) as a colourless oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.32 (bs, 1H), 7.37 – 7.18 (m, 5H), 6.95 (ddd, *J* =8.0, 7.0, 1.9 Hz, 1H), 6.83 (dd, *J* =7.7, 1.9 Hz, 1H), 6.81 – 6.72 (m, 2H), 5.77 (ddd, *J* =17.3, 10.2, 7.2 Hz, 1H), 5.30 (dt, *J* =17.2, 1.1 Hz, 1H), 5.27 (dt, *J* =10.2, 1.1 Hz, 1H, 4.68 (d, *J* =14.7 Hz, 1H), 4.34 (dt, *J* =7.1, 1.2 Hz, 1H), 4.16 (d, *J* =14.7 Hz, 1H); **^{13}C{^{1}H}-NMR**

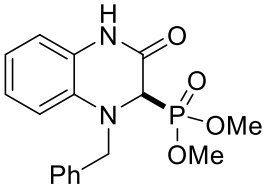
(75 MHz, $CDCl_3$) δ 167.3 (C), 136.4 (C), 134.2 (C), 130.5 (CH), 128.8 (CH), 127.9 (CH), 127.6 (CH), 125.8 (C), 124.2 (CH), 120.2 (CH_2), 119.2 (CH), 115.7 (CH), 113.0 (CH), 64.1 (CH), 51.7 (CH_2); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{17}H_{17}N_2O^+$ 265.1335, found 265.1330.

4-Benzyl-3-phenyl-3,4-dihydroquinoxalin-2-one (6.7d)



In a 25 mL round bottomed flask was weighted aminated dihydroquinoxalinone **6.3aa** (44.0 mg, 0.1 mmol). After the addition of a teflon-coated stir bar, the flask was purged with N_2. Freshly distilled THF (2 mL) was added, and the solution was cooled down to 0 °C. Phenylmagnesium bromide (3 M in Et_2O, 0.11 mL, 3.3 equiv.) was slowly added and the reaction mixture was stirred for 1 h at 0 °C. Then, the reaction was quenched with aq. sat. NH_4Cl (5 mL) and the mixture was extracted with DCM (x3). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and evaporated under vacuum to obtain a residue which was directly purified by column chromatography using DCM:EtOAc mixtures to finally afford compound **6.7d** (30.8 mg, 0.098 mmol, 98% yield) as a white solid. **Mp** = 167 °C – 169 °C; **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 9.62 (bs, 1H), 7.42 – 7.15 (m, 10H), 6.96 (ddd, *J* =7.9, 7.3, 1.7 Hz, 1H), 6.81 (td, *J* =7.3, 1.4 Hz, 1H), 6.80 – 6.68 (m, 2H), 4.99 (s, 1H), 4.68 (d, *J* =15.2 Hz, 1H), 4.10 (d, *J* =15.2 Hz, 1H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 167.2 (C), 137.0 (C), 136.4 (C), 134.2 (C), 128.77 (CH), 128.76 (CH), 128.4 (CH), 127.7 (CH), 127.6 (CH), 127.1 (CH), 125.4 (C), 124.4 (CH), 118.7 (CH), 115.7 (CH), 112.2 (CH), 65.0 (CH), 51.6 (CH_2); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{21}H_{19}N_2O^+$ 315.1492, found 315.1490.

Dimethyl (1-benzyl-3-oxo-1,2,3,4-tetrahydroquinoxalin-2-yl)phosphonate (6.8)



In a 25 mL round bottomed flask was weighted aminated dihydroquinoxalinone **6.3aa** (44.0 mg, 0.1 mmol). After the addition of a teflon-coated stir bar, the flask was purged with N_2. MeCN (2 mL) and dimethyl phosphite (27.5 μL, 0.3 mmol, 3 equiv.) were sequentially added. Then, $BF_3{\cdot}OEt_2$ (13.6 μL, 0.11 mmol, 1.1 equiv.) was added dropwise and the reaction mixture was stirred for 1 h at room temperature. The reaction mixture was directly purified by column chromatography to afford compound **6.8** (34.3 mg, 0.099 mmol, 99% yield) as a colourless oil.

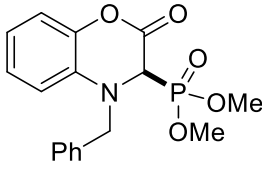
^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.44 (bs, 1H), 7.44 – 7.20 (m, 5H), 6.97 (ddd, *J* =8.1, 6.9, 1.9 Hz, 1H), 6.91 – 6.75 (m, 3H), 4.78 (dd, *J* =14.3, 2.0 Hz, 1H), 4.50 (dd, *J* =14.3,

4.0 Hz, 1H), 4.32 (d, J =14.5 Hz, 1H), 3.68 (d, J =11.0 Hz, 3H), 3.35 (d, J =10.9 Hz, 3H); **^{31}P{^{1}H}-NMR (121 MHz, $CDCl_3$)** δ 20.89; **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 164.1 (C, d, J_{C-P} = 5.7 Hz), 135.8 (C, d, J_{C-P} = 1.7 Hz), 134.1 (C), 128.8 (CH), 128.4 (CH), 127.9 (CH), 126.8 (C), 124.4 (CH), 119.9 (CH), 115.7 (CH), 113.6 (CH, d, J_{C-P} = 2.0 Hz), 59.6 (CH, d, J_{C-P} = 129.4 Hz), 53.0 (CH3, d, J =6.8 Hz), 53.0 (CH_2, d, J_{C-P} = 0.8 Hz), 52.9 (CH_3, d , J_{C-P} = 6.4 Hz.); **HRMS (ESI/Q-TOF)** *m/z* [M + H]$^+$ calcd for $C_{17}H_{20}N_2O_4P^+$ 347.1155, found 347.1156.

Specific Procedure for the One-Pot amination-phosphonylation

To an ovendried Schlenck tube containing a teflon-coated stir bar were added 4-benzyl-3,4-dihydroquinoxalin-2-one (**6.1a**, 23.8 mg, 0.1 mmol, 1 equiv.) or 4-benzyl-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-2-one (**6.4a**, 23.9 mg, 0.1 mmol, 1 equiv.). The reaction vessel was evacuated and backfilled with argon three times. After this, freshly degassed and dried MeCN (1 mL) and diisopropyl azodicarboxylate (**6.2a**, 25.6 μL, 0.13 mmol, 1.3 equiv.) were added via syringe and the reaction mixture was stirred while being irradiated with HP Single LED (455 nm) under a positive pressure of argon. The course of the reaction was monitored by TLC. When complete consumption of **6.1a** or **6.4a** was observed, the reaction vessel was removed from the light and dimethyl phosphite (27.5 μL, 0.3 mmol, 3 equiv.) and $BF_3{\cdot}OEt_2$ (13.6 μL, 0.11 mmol, 1.1 equiv.) were sequentially added and the reaction was stirred at room temperature until completion (TLC). The reaction mixture was directly purified by column chromatography to afford compound **6.8** (24.9 mg, 0.072 mmol, 72% yield) or compound **6.9** (21.9 mg, 0.063 mmol, 63% yield).

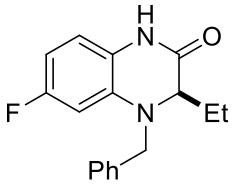
Dimethyl (4-benzyl-2-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-3-yl)phosphonate (6.9)



^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.59 – 7.28 (m, 5H), 7.15 – 7.05 (m, 2H), 7.03 – 6.85 (m, 2H), 4.75 (dd, J =14.0, 1.9 Hz, 1H), 4.49 (dd, J =14.0, 4.2 Hz, 1H), 4.42 (d, J =15.7 Hz, 1H), 3.69 (d, J =11.1 Hz, 3H), 3.29 (d, J =11.0 Hz, 3H); **^{31}P{^{1}H}-NMR (121 MHz, $CDCl_3$)** δ 18.20; **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 161.90 (C, d, J_{C-P} = 5.6 Hz), 142.19 (C), 135.01 (C, d, J_{C-P} = 1.6 Hz), 133.09 (C), 128.95 (CH), 128.52 (CH), 128.19 (CH), 125.55 (CH), 120.56 (CH), 116.48 (CH), 114.14 (CH, d, J_{C-P} = 1.7 Hz), 57.37 (CH, d, J_{C-P} = 131.3 Hz), 53.29 (CH_3, d, J_{C-P} = 7.2 Hz), 53.04 (CH_3, d, J_{C-P} = 6.7 Hz), 52.48 (CH_2); **HRMS (ESI/Q-TOF)** *m/z* [M + H]$^+$ calcd for $C_{17}H_{19}NO_5P^+$ 348.0995, found 348.0988.

Specific Procedure for the Synthesis of *rac*-Opaviraline (6.12)

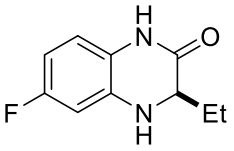
4-Benzyl-3-ethyl-6-fluoro-3,4-dihydroquinoxalin-2-one (6.10)



In a 25 mL round bottomed flask was weighted aminated dihydroquinoxalinone **6.3la** (91.7 mg, 0.2 mmol). After the addition of a teflon-coated stir bar, the flask was purged with N_2. Freshly distilled THF (4 mL) was added, and the solution was cooled down to 0 °C. EtMgBr (3 M in Et_2O, 0.22 mL, 3.3 equiv.) was slowly added and the reaction mixture was stirred for 1 h at 0 °C. Then, the reaction was quenched with aq. sat. NH_4Cl (5 mL) and the mixture was extracted with DCM (x3). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and evaporated under vacuum to obtain a residue which was directly purified by column chromatography using DCM:EtOAc mixtures to finally afford compound **6.10** (44.2 mg, 0.155 mmol, 78% yield) as a colourless oil.

^{1}H-NMR (500 MHz, $CDCl_3$) δ 9.27 (bs, 1H), 7.42 – 7.17 (m, 5H), 6.70 (dd, J =8.4, 5.5 Hz, 1H), 6.48 – 6.34 (m, 2H), 4.61 (d, J =15.3 Hz, 1H), 4.29 (d, J =15.1 Hz, 1H), 3.85 (dd, J =7.5, 5.5 Hz, 1H), 1.79 – 1.70 (m, 1H), 1.71 – 1.61 (m, 1H), 0.93 (t, J =7.6 Hz, 3H); **^{19}F{^{1}H}-NMR (471 MHz, 353K, $CDCl_3$)** δ -117.95 (s); **^{13}C{^{1}H}-NMR (126 MHz, $CDCl_3$)** δ 168.0 (C), 160.0 (d, J_{C-F} = 239.9 Hz, C), 136.2 (C), 135.7 (d, J_{C-F} = 11.0 Hz, C), 128.9 (CH), 127.8 (CH), 127.5 (CH), 122.1 (d, J_{C-F} = 2.8 Hz, C), 115.7 (d, J_{C-F} = 10.1 Hz, CH), 104.6 (d, J_{C-F} = 23.0 Hz, CH), 100.8 (d, J_{C-F} = 27.6 Hz, CH), 62.8 (CH), 52.9 (CH_2), 22.9 (CH_2), 10.0 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{17}H_{18}FN_2O^+$ 285.1398, found 285.1403.

3-Ethyl-6-fluoro-3,4-dihydroquinoxalin-2-one (6.11)

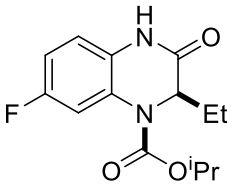


In a 25 mL round bottomed flask was weighted compound 15 (44.2 mg, 0.155 mmol) and was dissolved in EtOH (6 mL). After that, Pd/C 10% (20.2 mg, 0.019 mmol) was added and the resulting suspension was stirred at room temperature under H_2 (1 atm). After complete conversion (TLC), the reaction mixture was filtered through a pad of silica. Finally, the solvent was removed under reduced pressure to afford debenzylated compound **6.11** (30.1 mg, 0.155 mmol, 99% yield) as a colourless oil.

^{1}H-NMR (500 MHz, $CDCl_3$) δ 9.44 (bs, 1H), 6.69 (dd, J =8.2, 5.3 Hz, 1H), 6.48 – 6.35 (m, 2H), 3.88 (dd, J =7.6, 4.8 Hz, 1H), 3.66 (bs, 1H), 1.96 – 1.65 (m, 2H), 1.03 (t, J =7.5 Hz, 3H); **^{19}F{^{1}H}-NMR (471 MHz, $CDCl_3$)** δ -118.95 (s); **^{13}C{^{1}H}-NMR (126 MHz, $CDCl_3$)** δ168.8 (d, J_{C-F} = 4.6 Hz, C), 159.6 (d, J_{C-F} = 240.8 Hz, C), 134.2 (d,

J_{C-F} = 10.1 Hz, C), 121.3 (d, J_{C-F} = 1.8 Hz, C), 116.0 (d, J_{C-F} = 10.1 Hz, CH), 105.2 (d, J_{C-F} = 23.9 Hz, CH), 101.2 (d, J_{C-F} = 26.7 Hz, CH), 57.1 (CH), 25.4 (CH_2), 9.5 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{10}H_{12}FN_2O^+$ 195.0928, found 195.0930.

***rac*-Opaviraline (6.12)**



In a 25 mL round bottomed flask was weighted debenzylated compound **6.11** (30.1 mg, 0.155 mmol) and was purged with N_2. Then, freshly distilled DCM (1 mL), pyridine (20.2 μL, 0.25 mmol) and isopropyl chloroformate (0.155 mL, 2 M in toluene, 0.23 mmol) were sequentially added and the resulting mixture was stirred at room temperature for 45 minutes. After that, the reaction mixture was diluted with DCM (20 mL), washed with water (10 mL) and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by column chromatography using DCM:EtOAc to afford *rac*-Opaviraline (**6.12**, 35.5 mg, 0.127 mmol, 82% yield) as a white solid.

Mp = 152 °C – 154 °C; **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 10.00 (bs, 1H), 7.50 (bs, 1H), 7.04 – 6.54 (m, 2H), 5.07 (p, J =6.2 Hz, 1H), 4.97 (dd, J =9.8, 5.0 Hz, 1H), 1.72 (ddd, J =13.8, 7.4, 5.2 Hz, 1H), 1.54 – 1.42 (m, 1H), 1.34 (d, J =6.2 Hz, 3H), 1.30 (d, J =6.2 Hz, 3H), 0.95 (t, J =7.4 Hz, 3H); **^{19}F{^{1}H}-NMR (282 MHz, $CDCl_3$)** δ -117.90; **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 170.4 (C), 158.6 (d, J_{C-F} = 241.6 Hz, C), 153.1 (C), 125.8 (d, J_{C-F} = 11.1 Hz, C), 125.7 (d, J_{C-F} = 2.2 Hz, C), 116.6 (d, J_{C-F} = 9.4 Hz, CH), 112.04 (d, J_{C-F} = 24.0 Hz, CH), 111.95 (d, J_{C-F} = 27.8 Hz, CH), 70.9 (CH), 58.0 (CH), 23.5 (CH_2), 21.94 (CH_3), 21.90 (CH_3) , 9.8 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{14}H_{18}FN_2O_3^+$ 281.1296, found 281.1288.

Chapter 7

Radical Addition of 3,4-Dihydroquinoxalin-2-ones to Trifluoromethyl Ketones under Visible-Light Photoredox Catalysis

7.1 Introduction and state of the art

7.1.1 Historical Notes

The position of fluorine in the periodic table confers this light element several particular properties compared to the rest of the halogens. In fact, the isolation of F_2 is not possible using classical chemical methods, being imperative to resort to electrochemical protocols. This important landmark in chemistry was made possible by the French chemist Henri Moissan in 1886.[234,235] For his contribution, Moissan was awarded the Nobel Prize in Chemistry in 1906 *for his investigation and isolation of the element fluorine*. Since this important landmark, fluorine has found many relevant industrial applications such as the enrichment of uranium. Natural occurring uranium oxide readily forms UF_6 upon treatment with HF and F_2. Afterwards, $U^{238}F_6$ anf $U^{235}F_6$ can be partially separated to produce nuclear fuel, which has to be 3-5% in U^{235}.

7.1.2 Fluorine in Medicinal Chemistry

The presence of fluorine atoms in potential biologically-active molecules was inconceivable in the forties, since it was thought that incorporating this atom would instantaneously make a compound toxic or incompatible for life. This primigeneous assumptions

were based in the high reactivity and toxicity of F_2. However, the synthesis of Fludrocortisone[236,237] (Figure 7.1, *left*) in 1953 revealed how the incorporation of fluorine could enhance the bioactivity of a given drug.[238–240]

Since this initial achievement, many drugs and other biologically-relevant compounds have appeared in the marked to this day.[241–243] For example, Efavirenz, (Figure 7.1, *center*) which exhibits antiviral activity, contains a trifluoromethyl group attached to an aliphatic carbon. Additionally, Silidosin, which has proven its efficiency against benign prostatic hyperplastia, bears a CH_2CF_3 moiety (Figure 7.1, *right*).

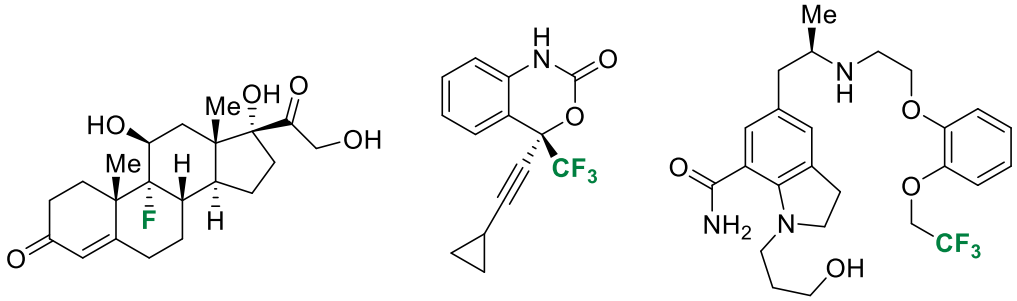


Figure 7.1: Relevant drugs containing either a fluorine atom or a CF_3 group.

In fact, it has been demonstrated that the incorporation of fluorine atoms radically change many pharmacological properties of drugs. For example, the presence of fluorine increases the lipophilicity of a drug, thus making it more able to pass through the bilayer lipid membrane. Additionally, fluorine is often used to block a metabolic soft spot, which can hamper the formation of reactive metabolites. Indeed, the metabolic stability of fluorine-containing drugs is much higher than its non-fluorinated analogues due to the fact that it is difficult to enzymatically break C−F bonds.

7.1.3 Synthetic Incorporation of Fluorine

Fluorination and Trifluoromethylation Reagents

There are several strategies to incorporate fluorine atoms or groups in molecules.[244] At laboratory-scale processes, the use of highly-toxic reagents, such as F_2 or HF, is often avoided. Several easy-to-handle shelf-stable fluorinating reagents have been developed to this day, offering different reactivity modes.[245] These reagents are often separated into two main classes: nucleophilic and electrophilic reagents. Nucleophilic fluorination can be accessed using fluoride (F^-) in any of its salts as nucleophile.[246] However, there are

some reagents that can address more difficult nucleophilic fluorinations, as for example, diethylaminosulfur trifluoride (DAST)[247] or its more sophisticated analogue Deoxo-Fluor™[248] (Figure 7.2). These two nucleophilic reagents are usually employed for fluorodeoxygenation reactions. On the other hand, electrophilic fluorination can be achieved, for example, using the so called N−F reagents.[249,250] Among them, it is important to highlight Selectfluor™ and *N*-fluorobenzenesulfonimide (NFSI) (Figure 7.2). These reagents are synthetic equivalents of F^+, thus promoting electrophilic fluorinations.

Moreover, the incorporation of trifluoromethyl groups is also a central topic in organic chemistry, likely because of its ability to serve as a bioisostere.[251] In the same vain, trifluoromethylation can be either nucleophilic or electrophilic (Figure 7.2). While in the case of nucleophilic trifluoromethylation the Ruppert-Prakash reagent[252] is almost ubiquitous, for electrophilic trifluoromethylation several reagents have been developed. Specifically, some of the most exmployed ones are Togni's reagent[253] and Umemoto's reagent.[254]

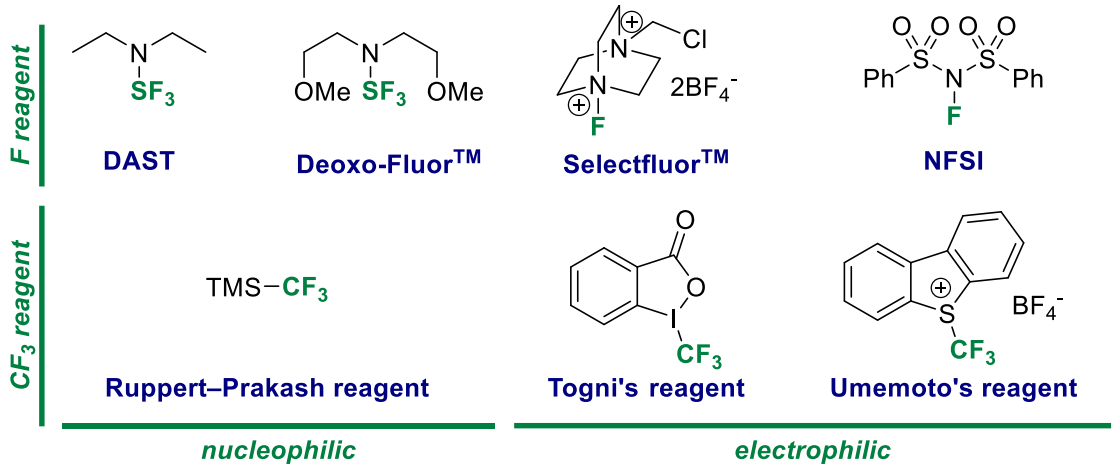


Figure 7.2: Selection of fluorinating and trifluoromethylating reagents.

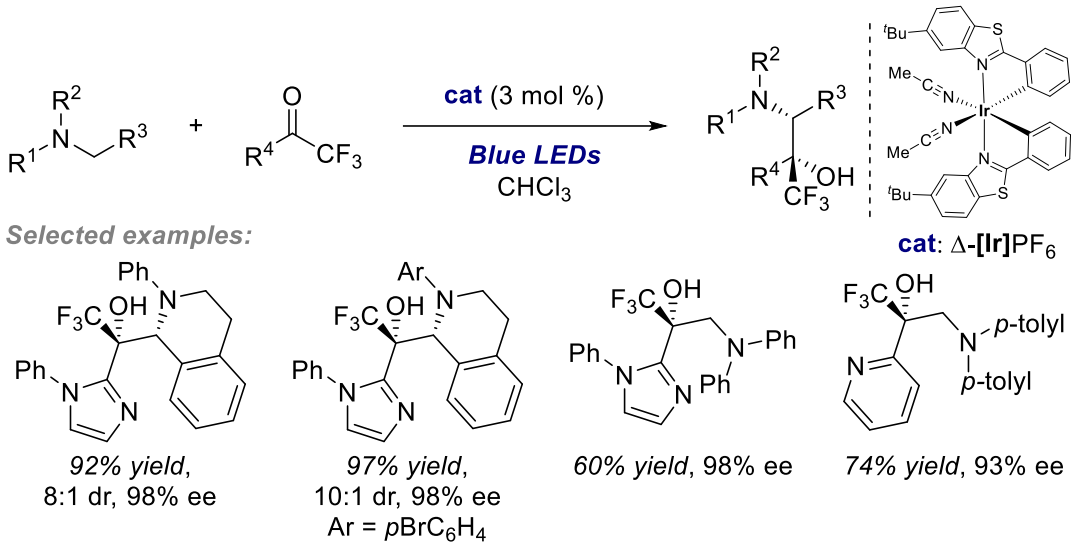
Fluorine-Containing Substrates

Another strategy to introduce fluorine atoms is to employ substrates with their own reactivities that also bear the desired fluorine-containing moiety. Of course, these kind of substrates must be prepared through a previous fluorination step.

In this sense, trifluoromethyl ketones could fit in this category because they bear the desired fluorine group (CF_3 in this case) but they also have a reactive carbonyl group that could be engaged in several nucleophilic functionalization reactions.[255] Indeed, trifluoromethyl ketones have been used as fluorine-containing reactants in the synthesis of relevant pharmacophores such as Efavirenz (Figure 7.1, *center*).[256,257]

Trifluoromethyl ketones have been extensively used in organic synthesis as electrophiles.

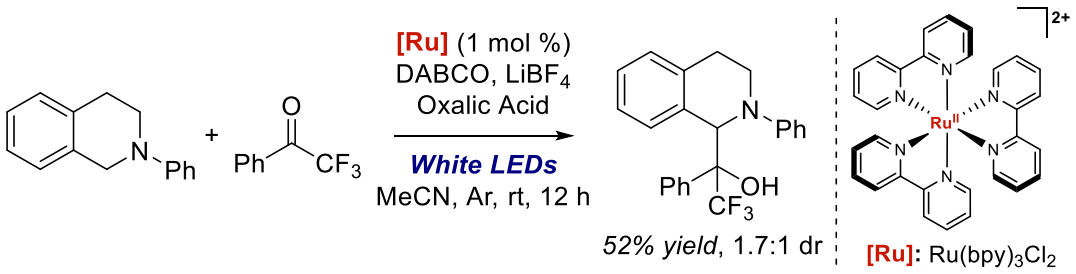
However, for the scope of this *thesis*, only reactions of these ketones under photochemical conditions will be considered. In this sense, in 2015 the research group of Meggers reported an enantioselective reaction between *N*-aryl tetrahydroisoquinolines or *N*,*N*-diaryl methylamines and trifluoromethyl ketones using visible-light photoredox catalysis (Scheme 7.1).[258] They employed a chiral-at-iridium complex, which served as photocatalyst to generate the radical species and also as asymmetric catalyst to induce enantioselectivity. It is important to note that the trifluoromethyl ketones must bear a coordinating moiety, such as imidazole or pyridine, to interact with the catalyst properly.



Scheme 7.1: Enantioselective radical-radical coupling between tertiary amines and trifluoromethyl ketones (Meggers).

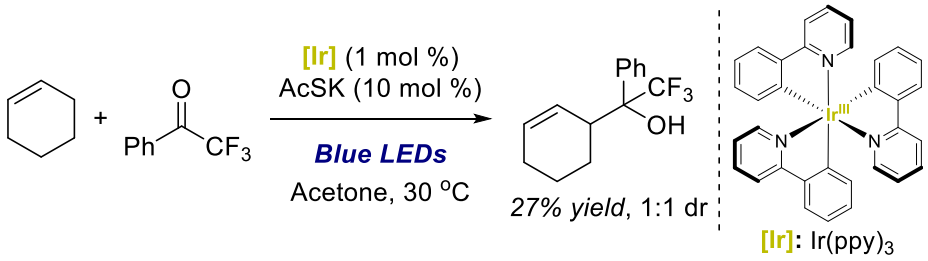
In 2018, the laboratory of Wang reported a general method to functionalize *N*-aryl tetrahydroisoquinolines with a wide array of electrophiles such as aldehydes, ketones or imines using a particular combination of catalyst to unlock proton-coupled electron transfer reactivity (PCET).[259] Specifically, protonated DABCO enables the concerted transfer of a proton and an electron to the carbonylic compound to produce the corresponding ketyl-type radical. An ulterior radical-radical coupling generates the desired product. Among all the examples, it can be found just one example of reaction between *N*-phenyl tetrahydroisoquinoline and trifluoroacetophenone, obtaining the expected product in a moderate 52% yield and with 1.7:1 dr (Scheme 7.2).

One year later, Liu and collaborators described a methodology to prepare tertiary alcohols by engaging carbon-centered radicals, which are generated under photoredox catalysis, with ketones.[260] They were able to generate carbon radicals from unactivated C-H bonds using *fac*-Ir(ppy)$_3$ as photocatalyst and potassium thioacetate as hydrogen atom transfer (HAT) catalyst. However, they only reported one example with trifluoroacetophe-



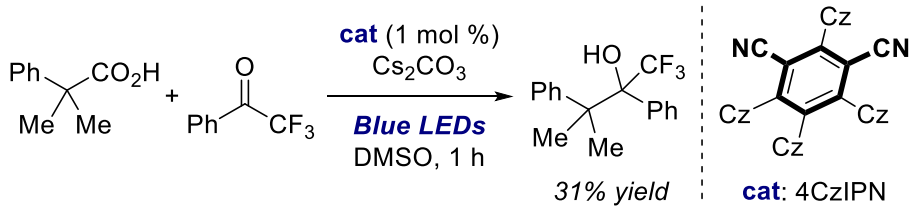
Scheme 7.2: Reaction between *N*-phenyl tetrahydroisoquinoline and trifluoroacetophenone by means of proton-coupled electron transfer (Wang).

none, which delivered the corresponding trifluoromethyl carbinol in just 27% yield upon reaction with cyclohexene (Scheme 7.3).



Scheme 7.3: Reaction between cyclohexene and trifluoroacetophenone under photoredox catalysis and HAT catalysis (Liu).

Finally, in 2021, Nagao and Ohmiya employed carboxylic acids as carbon radical precursors under visible-light photoredox catalysis.[261] Within the photocatalytic process, the corresponding ketone is reduced to its ketyl radical, which is engaged in a radical-radical cross coupling to furnish the desired tertiary alcohol. Although this process was initially conceived for α-keto esters, the authors were pleased to test trifluoroacetophenone as ketyl radical precursor. Under their conditions, the corresponding trifluoromethyl carbinol with two consecutive quaternary carbons is obtained in 27% yield (Scheme 7.4).



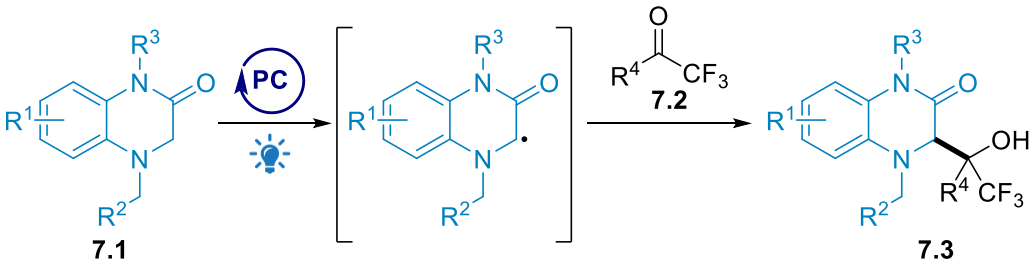
Scheme 7.4: Synthesis of a trifluoromethyl carbinol from a carboxylic acid and trifluoroacetophenone under photoredox catalysis (Ohmiya and Nagao).

According to this antecedents, we envisioned that it would be of interest the develop-

ment of a general methodology based on photoredox catalysis for the functionalization of 3,4-dihydroquinoxalin-2-ones with trifluoromethyl ketones. Moreover, considering that in Chapters 5 and 6 we established protocols for 1,4-additions, the exploration of direct 1,2-additions was also desirable.

7.2 Objectives

The main objective for this *Chapter* is to develop a methodology to functionalize 3,4-dihydroquinoxalin-2-ones (**7.1**) with trifluoromethyl ketones (**7.2**) employing visible-light photoredox catalysis to generate the α-amino radical of **7.1**. To achieve this objective, several partial objectives are postulated:



1. Optimization of the reaction conditions between 4-benzyl-3,4-dihydroquinoxalin -2-one (**7.1a**) and trifluoroacetophenone (**7.2a**) to obtain the corresponding trifluoromethyl carbinol **7.3aa** with the highest yield.

2. Study of the scope of the reaction between different 3,4-dihydroquinoxalin-2-ones (**7.1**) and different trifluoromethyl ketones (**7.2**).

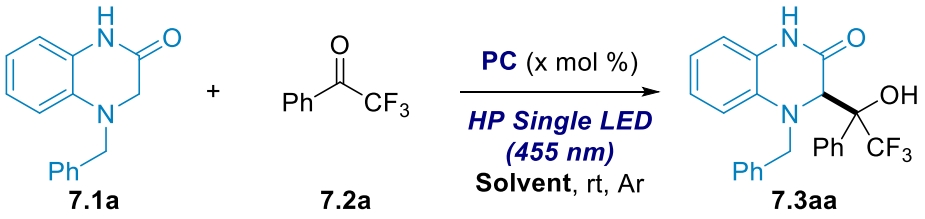
3. Synthetic transformations of the 1,2-addition products **7.3**.

4. Mechanistic investigations to unveil the reaction mechanism.

7.3 Results and Discussion

7.3.1 Optimization of the Reaction Conditions

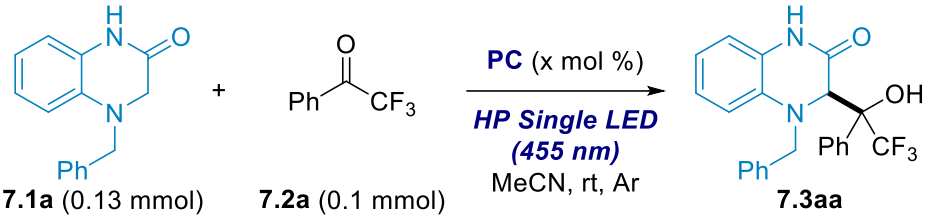
To optimize the reaction conditions we selected 4-benzyl-3,4-dihydroquinoxalin-2-one (**7.1a**) and trifluoroacetophenone (**7.2a**) as model substrates. The first parameter to consider was the photoredox catalyst, given its importance in generating the α-amino radical of **7.1a**. Thereafter, the role of the solvent will be investigated to obtain product **7.3aa** with the highest yield. Lastly, some molar ratio adjustements will be conducted to maximize the performance and practicability of the reaction (Scheme 7.5).



Scheme 7.5: Overview of the model reaction to carry out the optimization of the reaction conditions.

Evaluation of the Photoredox Catalyst

Based on our previous results, we decided to start the optimization process using dried and freshly degassed MeCN. It is important to recall that the α-amino radical is generated under O_2-free conditions, otherwise it would be overoxidized to iminium cation. Moreover, we initially employed 0.13 mmol of 3,4-dihydroquinoxalin-2-one **7.1a** and 0.1 mmol of trifluoroacetophenone (**7.2a**) due to the existence of potential unproductive pathways of **7.1a**.



Scheme 7.6: Evaluation of the photoredox catalyst in the reaction between **7.1a** and **7.2a** using MeCN.

We started the evaluation of the photocatalyst using our previous optimal conditions for the generation of the α-amino radical of **7.1a**, namely $Ru(bpy)_3Cl_2$ (**A**) as photocat-

Table 7.1: Evaluation of the photoredox catalyst in the reaction between **7.1a** and **7.2a** using MeCN. Yield of **7.3aa** in each case.

Entry[a]	PC (x mol %)	t (h)	Yield 7.3aa (%)[b]
1[c]	$Ru(bpy)_3Cl_2$ (**A**) (1)	24	26
2	$Ru(bpy)_3Cl_2$ (**A**) (1)	2.5	73
3	Eosin-Y-Na_2 (**E**) (5)	24	–
4	4CzIPN (**M**) (2)	24	–

[a]Reaction conditions: **7.1a** (0.13 mmol), **7.2a** (0.1 mmol), **PC** (x mol %), MeCN (1 mL), under argon atmosphere and under HP Single LED (455 nm) irradiation for the indicated time. In all cases a 1:1 dr was observed by ^{1}H-NMR.

[b]Yield determined after purification by column chromatography.

[c]10 mol % of $(PhO)_2PO_2H$ was used.

alyst and $(PhO)_2PO_2H$ as additive. Using these reaction conditions we were pleased to obtain the desired product **7.3aa** in a promising 26% yield and 1:1 dr[†] after 24 hours of irradiation (Table 7.1, Entry 1). However, we interrogated at this point the necessity of this acid cocatalyst by conducting the same reaction without adding it. Surprisingly, the reaction proceeded much faster and with better performance, since product **7.3aa** was isolated in 73% after only 2.5 hours of irradiation (Table 7.1, Entry 2). Again, this result was shocking for us, as we proved in *Chapter* 5 that an acid additive was mandatory for the photocatalytic generation of the α-amino radical of **7.1a** using $Ru(bpy)_3Cl_2$ (**A**). With this preliminary observation we could assert that this 1,2-addition reaction must proceed through an alternative mechanism.

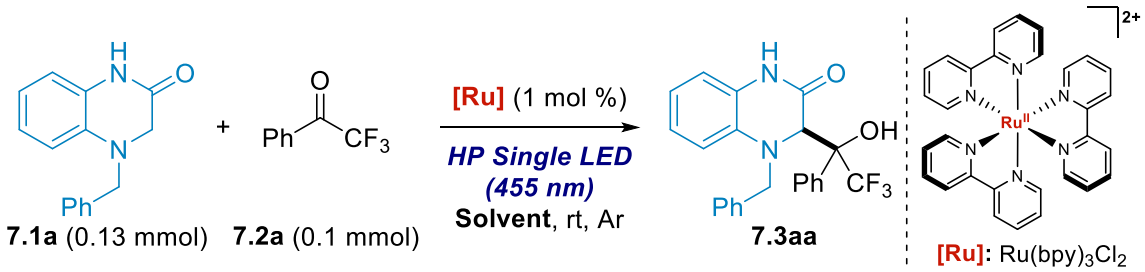
Unfortunately, any other photocatalyst like Eosin-Y-Na_2 (**E**) and 4CzIPN (**M**) could not favour the formation of product **7.3aa** (Table 7.1, Entries 3 and 4). Hence, we decided to select $Ru(bpy)_3Cl_2$ (**A**) as the best photocatalyst for this 1,2-addition reaction (Table 7.1, Entry 2).

Evalutation of the Solvent

After determining that the best photocatalyst was $Ru(bpy)_3Cl_2$ (**A**) we decided to continue the optimization process looking to the solvent. Given the high yield in which product **7.3aa** is generated, we conducted the solvent screening rapidly and just for comparative purposes (Scheme 7.7).

The first solvent to be evaluated was DMF, since it gave us a positive performance

[†]From this point to the end of the optimization process, carbinol **7.3aa** is always obtained in 1:1 dr and, for clarity, it will be omitted in the following Tables and Schemes.



Scheme 7.7: Evaluation of the solvent in the reaction between **7.1a** and **7.2a** using $Ru(bpy)_3Cl_2$ (**A**).

in previous experiences. In this case, the corresponding trifluoromethyl carbinol **7.3aa** could be isolated in a good 63% yield after 5 hours of irradiation (Table 7.2, Entry 2). Nonetheless, when the same reaction was performed using either DCM or THF, the expected product **7.3aa** could only be detected in the reaction mixture (Table 7.2, Entries 3 and 4).

Table 7.2: Evaluation of the solvent in the reaction between **7.1a** and **7.2a** using $Ru(bpy)_3Cl_2$ (**A**). Yield of **7.3aa** in each case.

Entry[a]	Solvent	t (h)	Yield 7.3aa (%)[b]
1	MeCN	2.5	73
2	DMF	5	63
3	DCM	24	<5
4	THF	24	<5

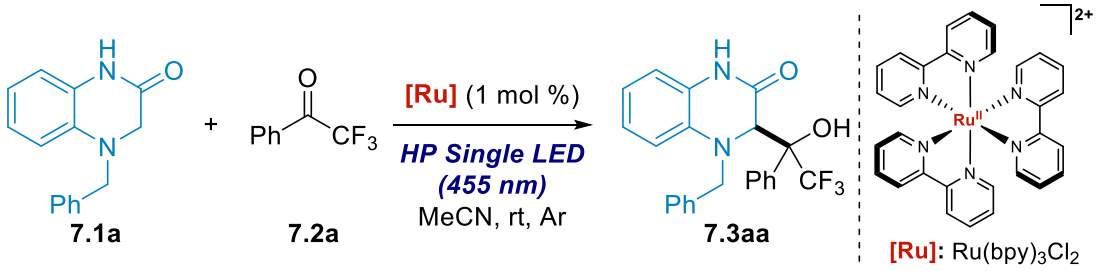
[a]Reaction conditions: **7.1a** (0.13 mmol), **7.2a** (0.1 mmol), $Ru(bpy)_3Cl_2$ (1 mol %), solvent (1 mL), under argon atmosphere and under HP Single LED (455 nm) irradiation for the indicated time. In all cases a 1:1 dr was observed by ^{1}H-NMR.

[b]Yield determined after purification by column chromatography.

In light of these results, we decided to continue the optimization process using dried and degassed MeCN as solvent for the reaction between 3,4-dihydroquinoxalin-2-one **7.1a** and trifluoroacetophenone **7.2a** (Table 7.2, Entry 1).

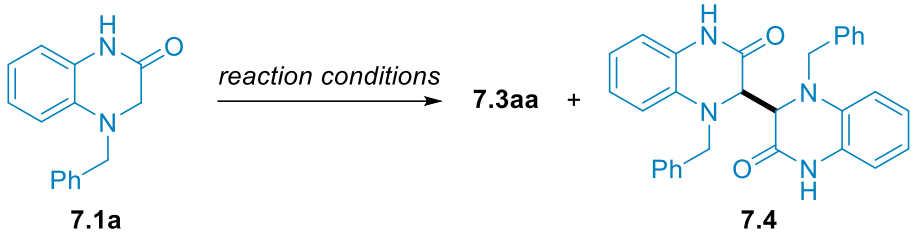
Evaluation of the Molar Ratio

After realizing that $Ru(bpy)_3Cl_2$ (**A**) and MeCN were the best photocatalyst and the best solvent respectively, we decided to modulate the molar ratio between 3,4-dihydroquinoxalin-2-one **7.1a** and trifluoroacetophenone (**7.2a**) with the aim of improving the yield of product **7.3aa** (Scheme 7.8).



Scheme 7.8: Evaluation of the molar ratio in the reaction between **7.1a** and **7.2a** using $Ru(bpy)_3Cl_2$ (**A**) and MeCN.

Initially, we switched the molar ratio in order to use 0.1 mmol of **7.1a** and 0.13 mmol of **7.2a**. Using this conditions we accessed product **7.3aa** in a lower 58% yield, revealing the existence of secondary reactions that partially consume 3,4-dihydroquinoxalin-2-one **7.1a** (Table 7.3, Entry 2). Since trifluoroacetophenone (**7.2a**) and most of the trifluoromethyl ketones are commercially available, we further tried to identify certain conditions that allowed us to employ **7.1a** as limiting reagent. In this sense, the reaction with a larger excess of **7.2a** was attempted to speed up the rate of the formation of **7.3aa** with the intention of overcoming the dimerization of **7.1a** (**7.4**, Scheme 7.9), which was actually the main secondary process that **7.1a** suffered. Hence, when the reaction was launched with 0.1 mmol of **7.1a** and 0.2 mmol of **7.2a**, the desired product **7.3aa** was obtained in 56% yield (Table 7.3, Entry 3). In the same line, the use of 0.3 mmol of **7.2a** provided the expected product **7.3aa** in a higher 66% yield, but it was still lower than that with the initial conditions (Table 7.3, Entry 4).



Scheme 7.9: Formation of dimer **7.4** from **7.1a** under reaction conditions.

According to these results, with the use of a larger excess of trifluoroacetophenone (**7.2a**) we could not overcome the formation of the dimer **7.4**. Thus, apparently, for the convenience of the reaction it is mandatory to use a larger amount of **7.1a** over **7.2a**. In this regard, we doubled the scale of the reaction to have access to more quantities of product **7.3aa** and facilitate the characterization process. In this case, the reaction proceeded comparatively equally to the one at 0.1 mmol scale, as product **7.3aa** was isolated in 72% yield.

Table 7.3: Evaluation of the molar ratio in the reaction between **7.1a** and **7.2a** using $Ru(bpy)_3Cl_2$ (**A**) and MeCN. Yield of **7.3aa** in each case.

Entry[a]	7.1a (mmol)	7.2a (mmol)	t (h)	Yield 7.3aa (%)[b]
1	0.13	0.1	2.5	73
2	0.1	0.13	2.5	58
3	0.1	0.2	2.5	56
4	0.1	0.3	2.5	66
5[c]	0.26	0.2	2.5	72

[a]Reaction conditions: **7.1a**, **7.2a**, $Ru(bpy)_3Cl_2$ (1 mol %), MeCN (1 mL), under argon atmosphere and under HP Single LED (455 nm) irradiation for the indicated time. In all cases a 1:1 dr was observed by ^{1}H-NMR.

[b]Yield determined after purification by column chromatography.

[c]2 mL of MeCN were used.

To conclude the optimization process, we where in a position to define that the best conditions for the reaction between 3,4-dihydroquinoxalin-2-one **7.1a** and trifluoroacetophenone (**7.2a**) involve the use of 0.26 mmol of **7.1a**, 0.2 mmol of **7.2a**, 1 mol % of $Ru(bpy)_3Cl_2$ (**A**) and 2 mL of dried and degassed MeCN under the irradiation of HP Single LED (455 nm) (Table 7.3, Entry 5).

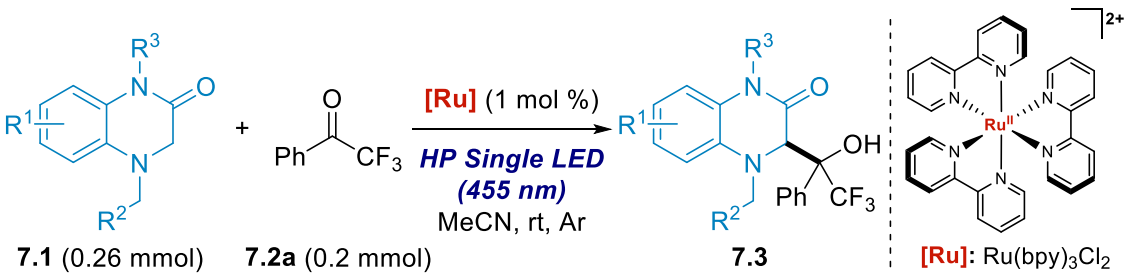
7.3.2 Scope of the Reaction

Having established the conditions for the 1,2-addition of 3,4-dihydroquinoxalin-2-one **7.1a** to trifluoroacetophenone (**7.2a**), according to the *Objectives* of this *Chapter*, the next step is to study the scope of this transformation. In this sense, differently substituted 3,4-dihydroquinoxalin-2-ones **7.1** will be engaged in this photochemical rection. Thereafter, the generality of the reaction with regard of the trifluoromethyl ketone **7.2** counterpart will be explored.

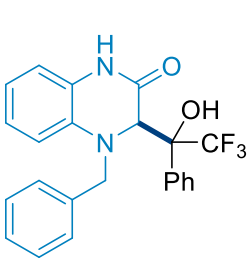
Scope of the Reaction with 3,4-Dihydroquinoxalin-2-ones

Initially, we decided to explore the scope of this reaction using a collection of 3,4-dihydroquinoxalin-2-ones **7.1** bearing different substituents at either the parent aromatic ring (R^1), the aminic nitrogen (R^2) or the amidic nitrogen (R^3) (Scheme 7.10).

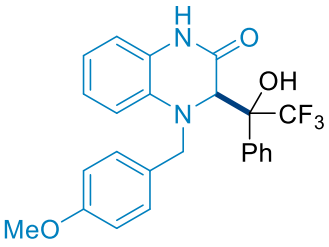
Initially, the *para* substitution of the benzylic group with either a $-$OMe or a $-CF_3$ was investigated. As expected, the more electron-rich 3,4-dihydroquinoxalin-2-one **7.1b** was efficiently engaged in the 1,2-addition reaction, obtaining the corresponding prod-



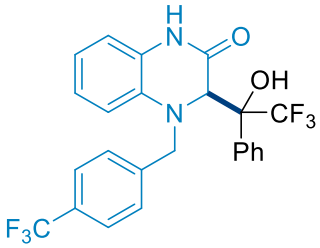
7.1 (0.26 mmol) **7.2a** (0.2 mmol) **7.3**



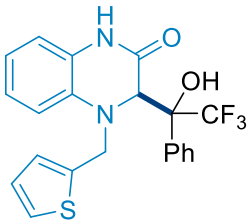
7.3aa, *73% yield*, 1:1 dr



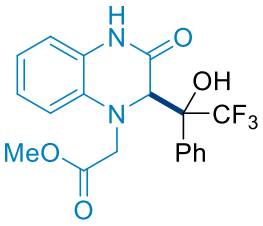
7.3ba, *90% yield*, 1.1:1 dr



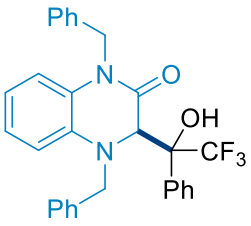
7.3ca, *76% yield*, 1.1:1 dr



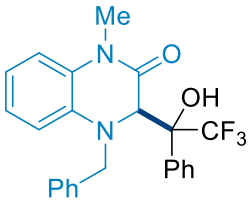
7.3da, *61% yield*, 1.4:1 dr



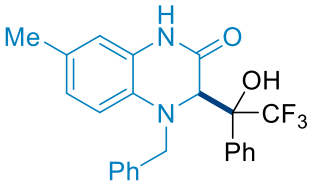
7.3ea, *55% yield*, 1:1 dr



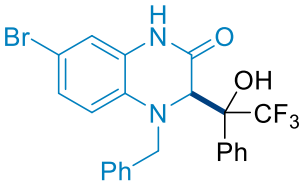
7.3fa, *60% yield*, 1.1:1 dr



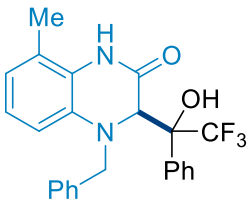
7.3ga, *60% yield*, 1.1:1 dr



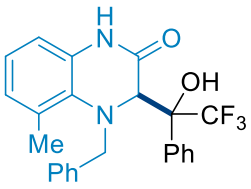
7.3ha, *59% yield*, 1:1 dr



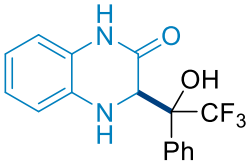
7.3ia, *68% yield*, 1:1 dr



7.3ja, *NR*



7.3ka, *NR*



7.3la, *41% yield*, 1:1 dr

Scheme 7.10: Scope of the reaction using different 3,4-dihydroquinoxalin-2-ones (**7.1**) and trifluoroacetophenone (**7.2a**).[a]

[a]Reaction conditions: **7.1** (0.26 mmol), **7.2a** (0.2 mmol), $Ru(bpy)_3Cl_2$ (1 mol %), MeCN (2 mL), under argon atmosphere and under HP Single LED (455 nm) irradiation. Diastereomeric ratio was determined by ^{1}H-NMR of the crude reaction mixture. Yield determined after purification by column chromatography.

uct **7.3ba** in 90% yield. Additionally, the its electron-poor analogue **7.1c** was also able to participate in the reaction neatly, as the expected trifluoromethyl carbinol **7.3ca** was isolated in 76% yield. Moreover, the substitution at the same position was also studied with a substrate bearing a 2-thiophene heterobenzylic substituent (**7.1d**), which generated the expected product **7.3da** in 61% yield. Lastly, 3,4-dihydroquinoxalin-2-one **7.1e** with a $-CH_2CO_2Me$ substituent was also engaged in the reaction, but in this case the corresponding product was delivered in only 55% yield.

Two N-1-substituted 3,4-dihydroquinoxalin-2-one were also subjected to the optimal reaction conditions. Specifically, with the 1,4-dibenyl derivative (**7.1f**), the desired carbinol **7.3fa** was isolated in 60% yield, whereas if a methyl group was placed at N-1, the expected 3-substituted 3,4-dihydroquinoxalin-2-one **7.3ga** was obtained in 60% yield.

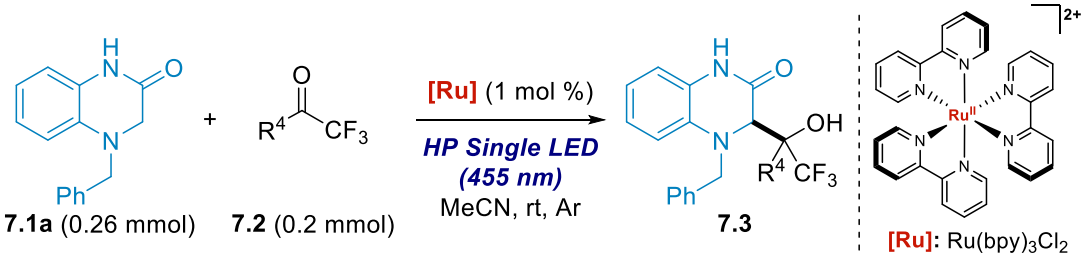
Additionally, the substitution at the parent aromatic ring of 3,4-dihydroquinoxalin-2-one was also interrogated. Unfortunately, we found that the scope regarding the substitution at this position was quite narrow, because we only could access products **7.3ha** with a 7-methyl, and **7.3ia** with a 7-bromine in 59% and 68% yield respectively. Other substrates such as 3,4-dihydroquinoxalin-2-ones **7.1j** and **7.3k**, which bear a methyl substituent at either C-8 or C-5, were not tolerated.

Nevertheless, we were pleased to engage N-4-unsubstituted 3,4-dihydroquinoxalin-2-one **7.1l** with trifluoroacetophenone (**7.2a**) under our photochemical conditions, obtaining the corresponding product **7.3la** in 41% yield. This result is quite a few remarkable, since we were not able to react 3,4-dihydroquinoxalin-2-one **7.1l** until now.

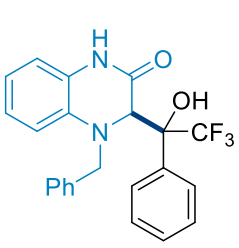
Scope of the Reaction with Trifluoromethyl Ketones

Having established the scope of the reaction with different 3,4-dihydroquinoxalin-2-ones **7.1**, we focused our interest in performing the same study but now with differently substituted trifluoromethyl ketones **7.2** (Scheme 7.11).

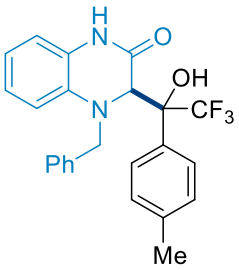
The effect of various substituents in the skeleton of trifluoromethyl ketone was evaluated depending on the position of that substituent at the aromatic ring as well as its electronic character. Initially, different trifluoroacetophenones bearing a *para* substituent were subjected to study. The presence of a slight electron-donating group such as methyl or ethyl, resulted in a significant drop in the yield, due to the fact that products **7.3ab** and **7.3ac** were isolated in 50% and 29% yield respectively. In the same vain, the presence of $-OMe$ as strong electron-donating group in ketone **7.2d** produced the expected trifluoromethyl carbinol **7.3ad** in 50% yield. To finish with *para* subtituents, two trifluoroacetophenones bearing either a chlorine (**7.1e**) or a bromine (**7.1f**) atom were tested as electrophiles. In this case, the expected products **7.3ae** and **7.3af** were generated in 54% and 64% yield, respectively.



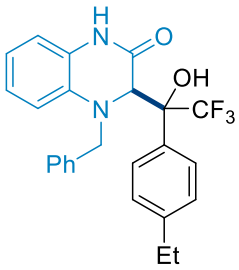
7.1a (0.26 mmol) **7.2** (0.2 mmol) **7.3**



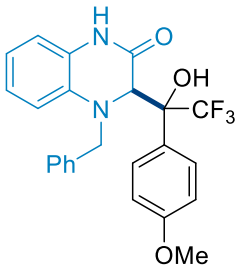
7.3aa
73% yield, 1:1 dr



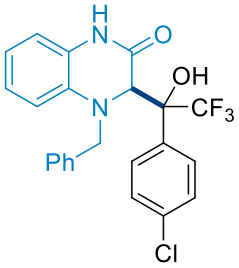
7.3ab
50% yield, 1.5:1 dr



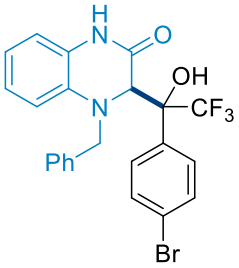
7.3ac
29% yield, 1.1:1 dr



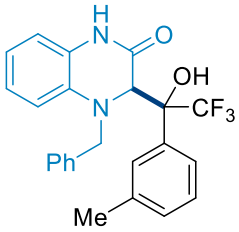
7.3ad
50% yield, 1.2:1 dr



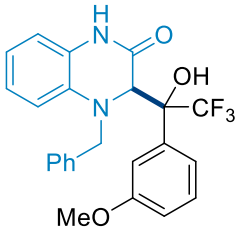
7.3ae
54% yield, 1:1 dr



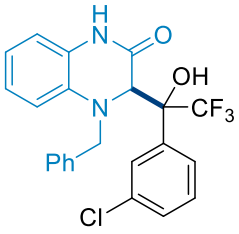
7.3af
64% yield, 1.4:1 dr



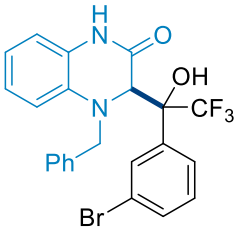
7.3ag
55% yield, 1.3:1 dr



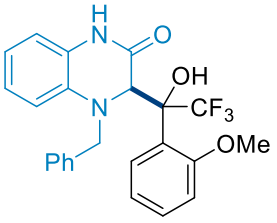
7.3ah
50% yield, 1.1:1 dr



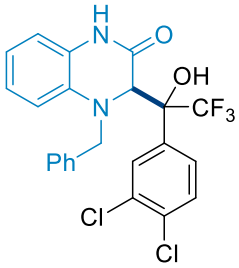
7.3ai
61% yield, 1.2:1 dr



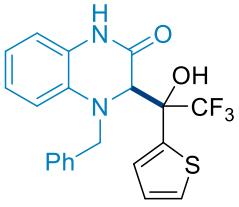
7.3aj
64% yield, 1.2:1 dr



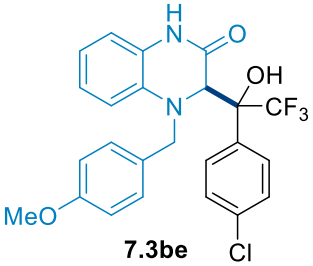
7.3ak
37% yield, 1.4:1 dr



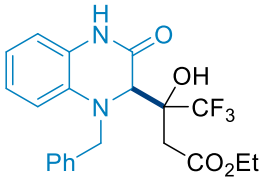
7.3al
43% yield, 1.3:1 dr



7.3am
52% yield, 1.4:1 dr



7.3be
62% yield, 1.5:1 dr[b]



7.3an
20% yield, 1.2:1 dr

Scheme 7.11: Scope of the reaction using 3,4-dihydroquinoxalin-2-one **7.1a** and different trifluoromethyl ketones **7.2**.[ab]

[a]Reaction conditions: **7.1a** (0.26 mmol), **7.2** (0.2 mmol), $Ru(bpy)_3Cl_2$ (1 mol %), MeCN (2 mL), under argon atmosphere and under HP Single LED (455 nm) irradiation. Diastereomeric ratio was determined by ^{1}H-NMR of the crude reaction mixture. Yield determined after purification by column chromatography.

[b]In this reaction **7.1c** was used instead of **7.1a**.

Afterwards, *meta* substitution at the same aromatic ring was also investigated. Trifluoroacetophenones with electron-donating groups like −OMe and −Me were equally tolerated, obtaining the corresponding products **7.3ag** and **7.3ah** in 55% and 50% yield respectively. In addition, the presence of electro-withdrawing atoms such as Cl and Br at the *meta* position had little effect over the yield, since products **7.3ai** and **7.3aj** were isolated in 61% and 64% yield respectively.

Moreover, the use of the *ortho*-substituted trifluoroacetophenone **7.2k**, which bears a −OMe group, resulted in the corresponding product **7.3ak** in a moderate 37% yield, probably due to steric congestion around the electrophilic center and also due to the electron-donating ability of that substituent as well.

At this point, a *meta*,*para*-disubstituted trifluoroacetophenone with two chlorine atoms was subjected to the photocatalytic 1,2-addition reaction. The expected trifluoromethyl carbinol **7.3al** was obtained in 43% yield. Besides, trifluoromethyl ketone bearing an heteroaromatic ring like 2-thiophene was also tested, obtaining the desired product **7.3am** in 52% yield.

Interestingly, we could increase the yield of the product when *p*-Cl trufluoroacetophenone **7.2e** is used by just changing from 3,4-dihydroquinoxalin-2-one **7.1a** to the more electron-rich **7.1b**. In this case, the expected product **7.3be** was isolated in 62% yield.

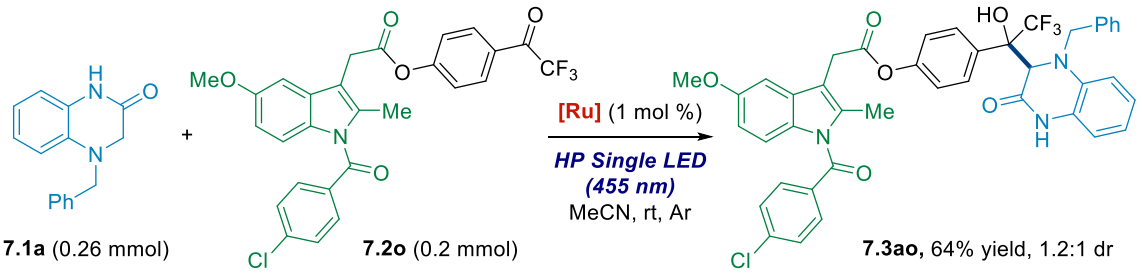
Finally, with the aim of further expanding the generality of this transformation, we wanted to make use of ethyl 4,4,4-trifluoroacetoacetate (**7.2n**) as representative of aliphatic trifluoromethyl ketones. Unfortunately, we only could isolate the corresponding product **7.3an** in 20% yield, thus stating one of the limitations of our methodology.

Reaction with Indomethacin-derived Trifluoroacetophenone

To apply our approach to the synthesis of relevant scaffolds, we installed the trifluoroacetophenone skeleton to commercially available indomethacin by means of a DCC-mediated esterification reaction. Thereafter, this indomethacin-derived trifluoroacetophenone **7.2o** was subjected to the photocatalytic 1,2-addition with 3,4-dihydroquinoxalin-2-one **7.1a** in the presence of $Ru(bpy)_3Cl_2$ (**A**), obtaining the sophisticated trifluoromethyl carbinol **7.3ao** in 64% yield (Scheme 7.12).

Reaction with Ethyl Trifluoropyruvate

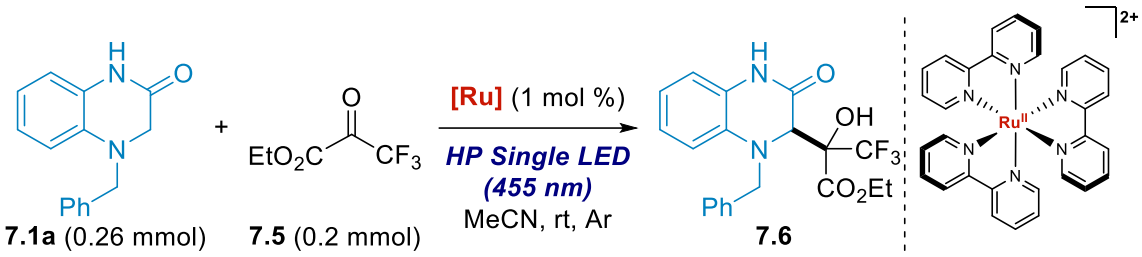
To conclude the study of the scope of the reaction, we questioned if ethyl trifluoropyruvate (**7.5**) could serve as a proper electrophile in this photocatalytic 1,2-addition (Scheme 7.13). When 0.26 mmol of 3,4-dihydroquinoxalin-2-one **7.1a** and 0.2 mmol of ethyl trifluoropyruvate (**7.5**) were reacted under our optimal conditions, only 18% of the desired product **7.6** was obtained. With the intention of increasing this yield, we repeated



Scheme 7.12: Reaction of 3,4-dihydroquinoxalin-2-one **7.1a** with indomethacin-derived trifluoroacetophenone **7.2o**.[a]

[a]Reaction conditions: **7.1a** (0.26 mmol), **7.2o** (0.2 mmol), $Ru(bpy)_3Cl_2$ (1 mol %), MeCN (2 mL), under argon atmosphere and under HP Single LED (455 nm) irradiation. Diastereomeric ratio was determined by ^{1}H-NMR of the crude reaction mixture. Yield determined after purification by column chromatography.

the reaction but exchanging the molar quantities of reactants, namely using 0.2 mmol of **7.1a** and 0.26 mmol of **7.5**. However, we could only increase that yield to 25%.



Scheme 7.13: Reaction of 3,4-dihydroquinoxalin-2-one **7.1a** with ethyl trifluoropyruvate (**7.5**).[ab]

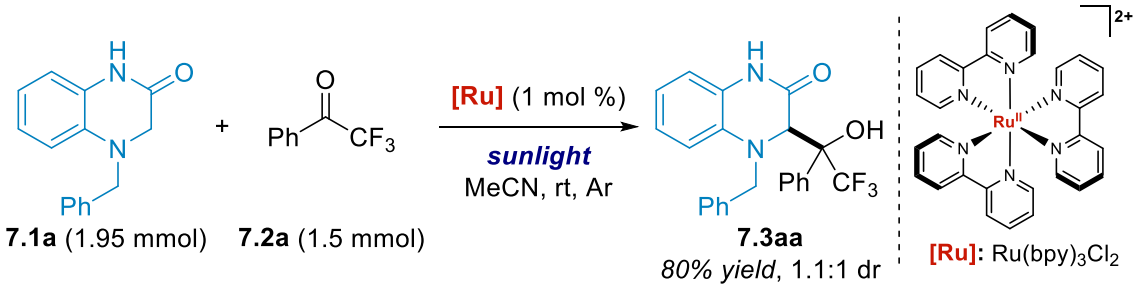
[a]Reaction conditions: **7.1a** (0.26 mmol), **7.5** (0.2 mmol), $Ru(bpy)_3Cl_2$ (1 mol %), MeCN (2 mL), under argon atmosphere and under HP Single LED (455 nm) irradiation. Diastereomeric ratio was determined by ^{1}H-NMR of the crude reaction mixture. Yield determined after purification by column chromatography.
[b]0.2 mmol of **7.1a** and 0.26 mmol of **7.5** were used.

7.3.3 Large-Scale Reaction and Synthetic Transformations

Large-Scale Reaction

Having determined the generality of the photocatalytic 1,2-addition reaction, we decided to scale-up the process to 1.5 mmol-scale (Scheme 7.14). For enhancing the practicability of our methodology, we decided to change the irradiation source from HP Single LED (455 nm) to the more convenient and renewable sunlight irradiation.

To our delight, we could isolate 495 mg of the corresponding trifluoromethyl carbinol **7.3aa** (80% yield) after 2.5 hours of solar irradiation.



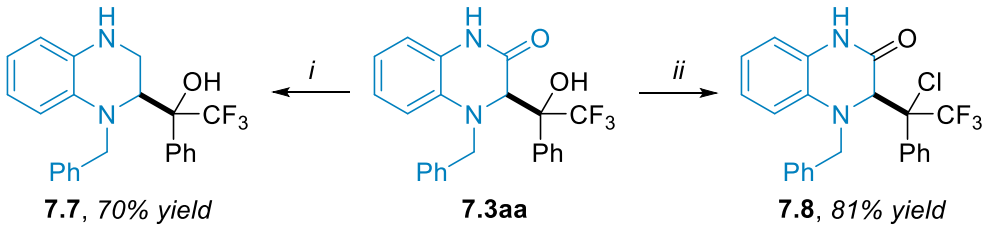
Scheme 7.14: Large-scale reaction using 3,4-dihydroquinoxalin-2-one **7.1a**, trifluoroacetophenone (**7.2a**) and sunlight as energy source.[a]

[a]Reaction conditions: **7.1a** (1.95 mmol), **7.2a** (1.5 mmol), $Ru(bpy)_3Cl_2$ (1 mol %), MeCN (10 mL), under argon atmosphere and under sunlight irradiation.

Synthetic Transformations

With this large amount of product **7.3aa** we decided to try several synthetic modifications to extend the applicability of our reaction. Specifically, we tried to get rid of the amidic carbonil through a reduction with $LiAlH_4$. Fortunately, the corresponding 1,2,3,4-tetrahydroquinoxaline **7.7** was obtained in 70% yield (Scheme 7.15, *left*).

Besides, we speculated about taking advantage of the tertiary alcohol moiety in **7.3aa** for promoting an elimination reaction and generate a very interesting exocyclic double bond. Initially, this elimination was attempted using acid catalysis at high temperature, but these conditions led to **7.3aa** decomposition. Thereafter, we wanted to apply milder elimination conditions. Speficically, we treated carbinol **7.3aa** with $SOCl_2$ in the presence of pyridine at room temperature.[262] Unfortunately, we obtained a product in which the hydroxyl group is substituted by a chlorine atom (**7.8**) in 81% yield (Scheme 7.15, *right*).



Scheme 7.15: Synthetic transformations over trifluoromethyl carbinol **7.3aa**.[a]

[a]Reaction conditions: *i*) **7.3aa** (0.19 mmol), $LiAlH_4$ (4 equiv.), THF (5 mL) at reflux for 2 hours; *ii*) **7.3aa** (0.07 mmol), $SOCl_2$ (2 equiv.), pyridine (2 equiv.), DCM (2 mL) at room temperature for 2 hours.

7.3.4 Mechanistic Investigations and Proposed Mechanism

Mechanistic Investigations

At this point we needed to explore the mechanism behind our transformation. Initially we performed several simple control experiments to determine the need of either the photocatalyst or the light, among other experiences (Table 7.4). As expected, when the reaction was conducted in the dark, product **7.3aa** was not detected in the reaction mixture and both substrates **7.1a** and **7.2a** remained unreacted as shown by ^{1}H-NMR (Table 7.4, Entry 2). Moreover, the necessity of the ruthenium photocatalyst was proven, since trifluoromethyl carbinol **7.3aa** could not be detected when the reaction was run without $Ru(bpy)_3Cl_2$ (**A**) (Table 7.4, Entry 3). In addition, the reaction was completely inhibited in the presence of 1.5 equivalents of TEMPO (Table 7.4, Entry 4). Finally, **7.1a** was fully oxidized supposedly to the corresponding C-3 hydroperoxide, without noticing the formation of product **7.3aa** (Table 7.4, Entry 5).

Table 7.4: Control experiments for the photocatalytic reaction between **7.1a** and **7.2a**.

Entry[a]	Deviation	**7.3aa** (%)
1	*none*	73
2	darkness	–
3	without **[Ru]**	–
4	with TEMPO (1.5 equiv.)	no conversion
5	air atmosphere	–

[a]Reaction conditions: **7.1a** (0.13 mmol), **7.2a** (0.1 mmol), $Ru(bpy)_3Cl_2$ (1 mol %), MeCN (1 mL), under argon atmosphere and under HP Single LED (455 nm) irradiation. Note deviations for each case. Reaction time: 2.5 h.

Thereafter, we determined the quantum yield of the process after determining the photon flux of our photochemical setup by means of ferrioxalate actinometry.[205–207] Thereafter, we could obtain the quantum yield for the photocatalytic 1,2-addition reaction between **7.1a** and **7.2a**, and it was as low as $\Phi = 0.21 \pm 0.02$. Thus, a radical chain mechanism is excluded whereas a closed photocatalytic cycle is more likely. This assumption was further confirmed by the classical *on-off* experiment, in which product **7.3aa** was only formed when HP Single LED (455 nm) was turned on (Figure 7.3).

Considering that our photocatalytic reaction should proceed through electron-transfer events, we conducted several experiences in this line. Based on our previous works, we could exclude the direct formation of the α-amino radical of **7.1a** from the excited

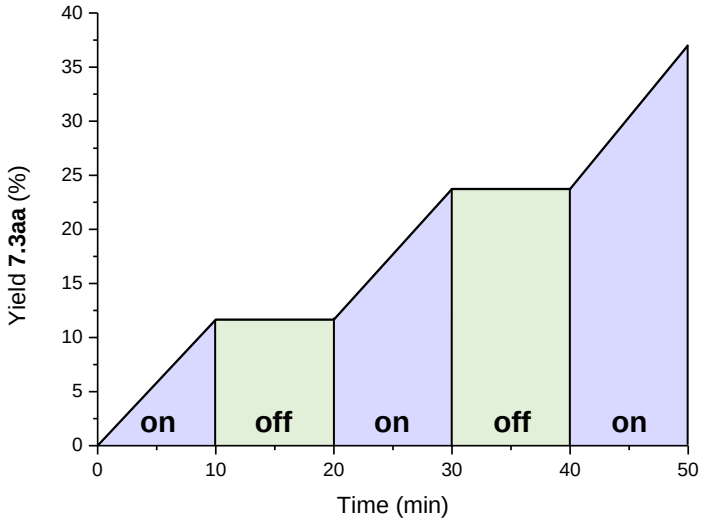


Figure 7.3: *On-off* experiment for the reaction between **7.1a** and **7.2a**.

state of the photocatalyst (see *Chapter* 5). Initially, we examined the redox potentials of all the species involved in the process. The redox potentials of $Ru(bpy)_3Cl_2$ (**A**) are well known, presenting E_{red}([**Ru^{II*}**]/[**Ru^{I}**]) = +0.77 V (vs SCE) as oxidant and E_{red}([**Ru^{III}**]/[**Ru^{II*}**]) = −0.81 V (vs SCE) as reductant (Table 7.5). On the other hand, in *Chapter* 5 (page 235) we reported the reduction potential of 3,4-dihydroquinoxalin-2-one **7.1a**, E_{red}(**7.1a$^{+\bullet}$**/**7.1a**) = +0.80 V (vs SCE) (Table 7.5). Besides, the reduction potential of trifluoroacetophenone (**7.2a**) was reported in the bibliography,[263] and it was E_{red}(**7.2a**/**7.2a^{+-}**) = −1.4 V (vs SCE) (Table 7.5).

Table 7.5: Redox potentials of $Ru(bpy)_3Cl_2$ (**A**) from the excited state, **7.1a** and **7.2a**.

Specie	$E_{red}(\mathbf{A}^{+n}/\mathbf{A}^{n})$ (V vs SCE)	$E_{red}(\mathbf{A}^{n}/\mathbf{A}^{-n})$ (V vs SCE)
***[Ru]**	+0.77	−0.81
7.1a	+0.80	–
7.2a	–	−1.40

In the same vain that in *Chapter* 5, in light of these redox potentials we could exclude the direct interaction of $Ru(bpy)_3Cl_2$ (**A**) via a SET with both 3,4-dihydroquinoxalin-2-one **7.1a** and trifluoroacetophenone (**7.2a**). As expected, when we performed the canonical Stern-Volmer luminescence quenching experiments we did not observe that the emission of $Ru(bpy)_3Cl_2$ (**A**) decreases in the presence of either 3,4-dihydroquinoxalin-2-one **7.1a**[†] or trifluoroacetophenone (**7.2a**) (Figure 7.4).

[†]For the luminescence quenching experiment involving 3,4-dihydroquinoxalin-2-one **7.1a** and $Ru(bpy)_3Cl_2$ (**A**), the reader is encouraged to check *Chapter* 5, page 234.

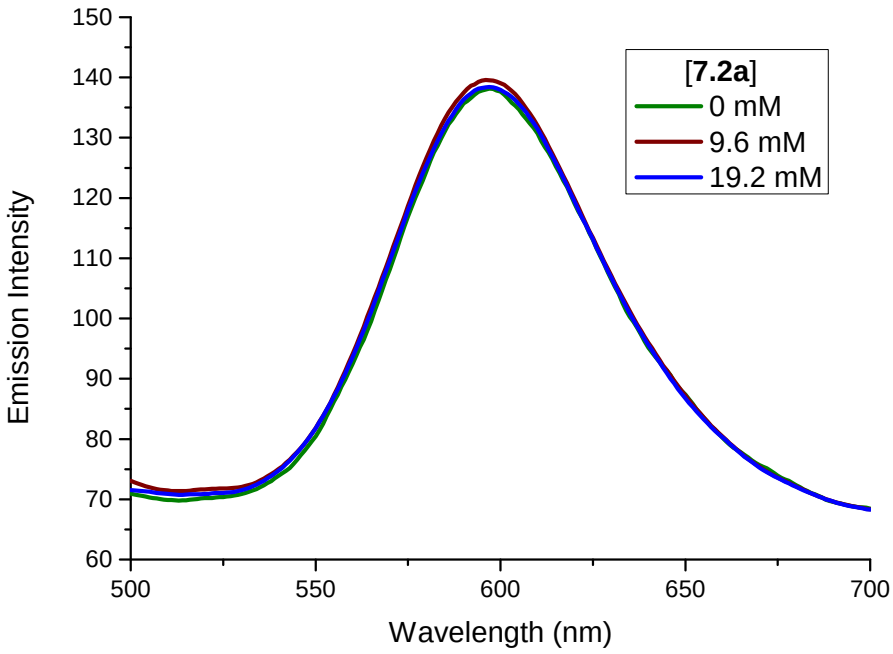


Figure 7.4: Emission spectra of different solutions containing 0.02 mM of $Ru(bpy)_3Cl_2$ (**A**) and varying amounts of trifluoroacetophenone (**7.2a**).

The impossibility to prove a mechanism based on the redox behaviour of **7.1a** and **7.2a** separately led us to inspect if the observed reactivity arose from an interaction between **7.1a** and **7.2a**. For this purpose, we repeated the Stern-Volmer experiment in a different way. Firstly, we prepared solutions containing the same amount of $Ru(bpy)_3Cl_2$ (**A**) (0.2 mM) and 3,4-dihydroquinoxalin-2-one **7.1a** (9.6 mM) and varying quantities of trifluoroacetophenone (**7.2a**). However, in this case, we did not observe any change in $Ru(bpy)_3Cl_2$ (**A**) emission (Figure Figure 7.5). In contrast, when the concentration of trifluoroacetophenone (**7.2a**) is maintained (9.6 mM) and the amount of 3,4-dihydroquinoxalin-2-one **7.1a** increases, we did observe a significant decrease in the emission of $Ru(bpy)_3Cl_2$ (**A**) (Figure Figure 7.6). This finding supports that there has to be a kind of interaction between **7.1a** and **7.2a** that allows the engagement of **7.1a** with the excited state of $Ru(bpy)_3Cl_2$ (**A**) through, allegedly, a SET event.

To detect the eventual formation of a kind of aggregate between **7.1a** and **7.2a**, we decided to perform a ^{1}H-NMR titration of a solution of **7.1a** with trifluoroacetophenone (**7.2a**) in MeCN-d_6. The amount of trifluoroacetophenone (**7.2a**) varied from 0 to 100 mol % (Figure 7.7). Unfortunately, we did not observe any significant NMR signal shift that could be attributed to an interaction of **7.1a** and **7.2a**, specially in the ^{1}H-NMR region of the amidic nitrogen of **7.1a**, where a kind of PCET could eventually happened.[37]

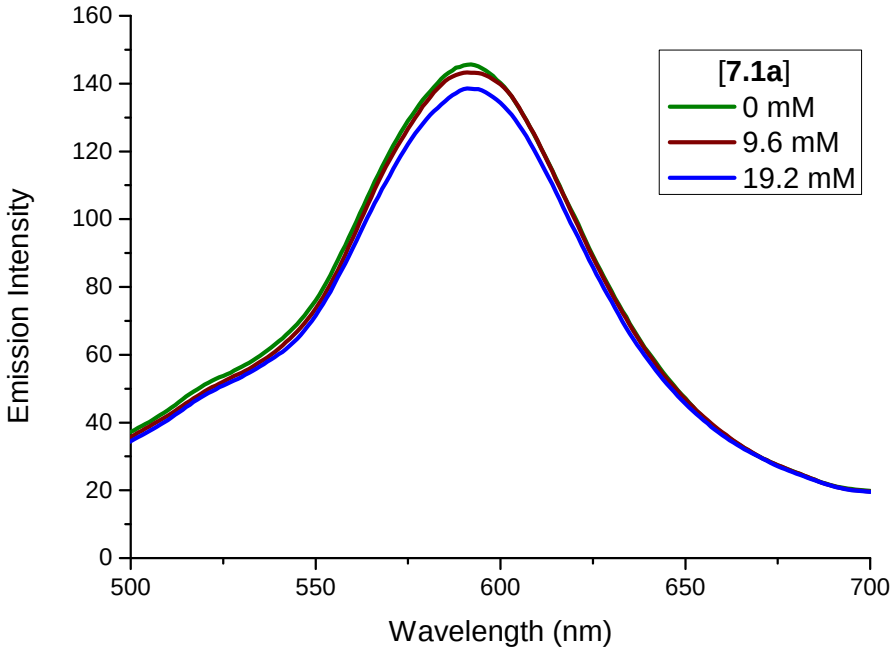


Figure 7.5: Emission spectra of different solutions containing 0.02 mM of $Ru(bpy)_3Cl_2$ (**A**), 9.6 mM of **7.1a** and varying amounts of **7.2a**.

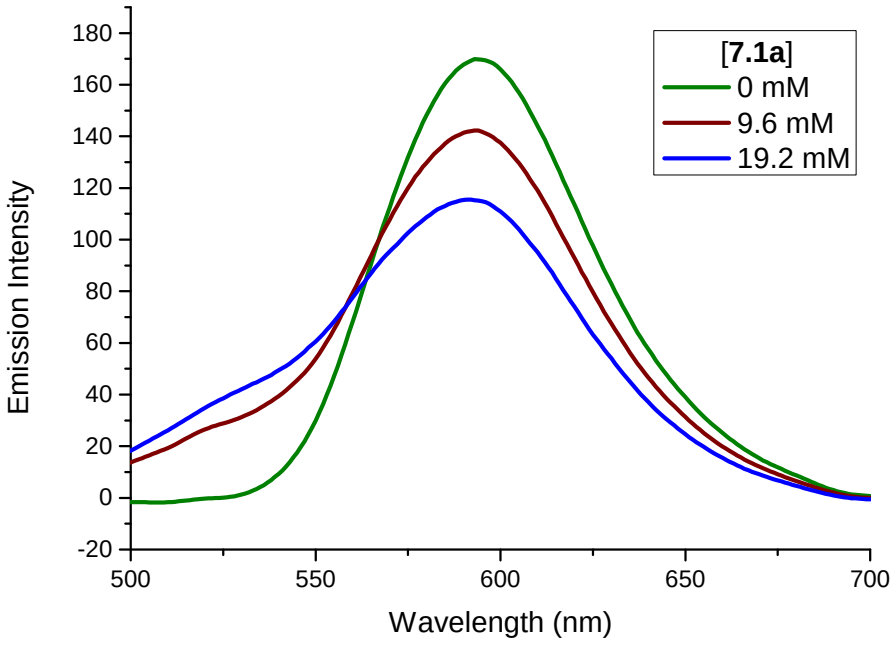


Figure 7.6: Emission spectra of different solutions containing 0.02 mM of $Ru(bpy)_3Cl_2$ (**A**), 9.6 mM of **7.2a** and varying amounts of **7.1a**.

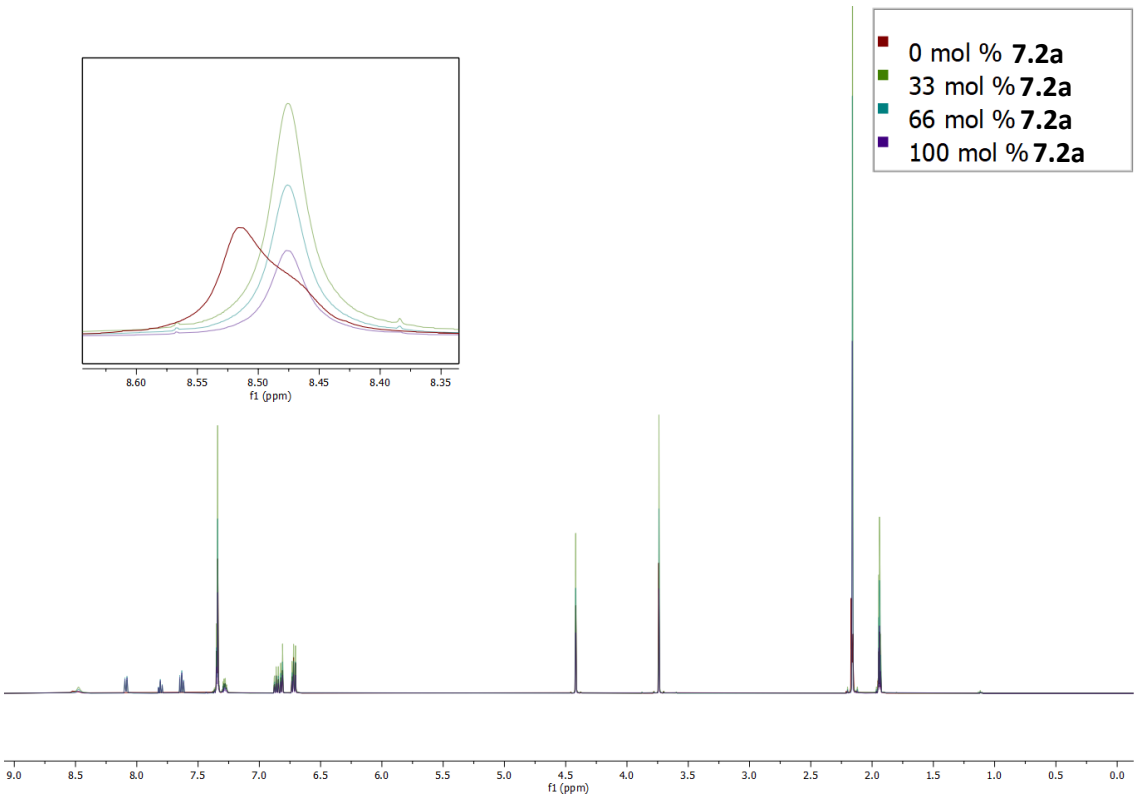


Figure 7.7: ^{1}H-NMR titration of a **7.1a** solution in MeCN-d_3 with **7.2a**. The NMR region of the amidic proton of **7.1a** is highlighted.

Proposed Mechanism

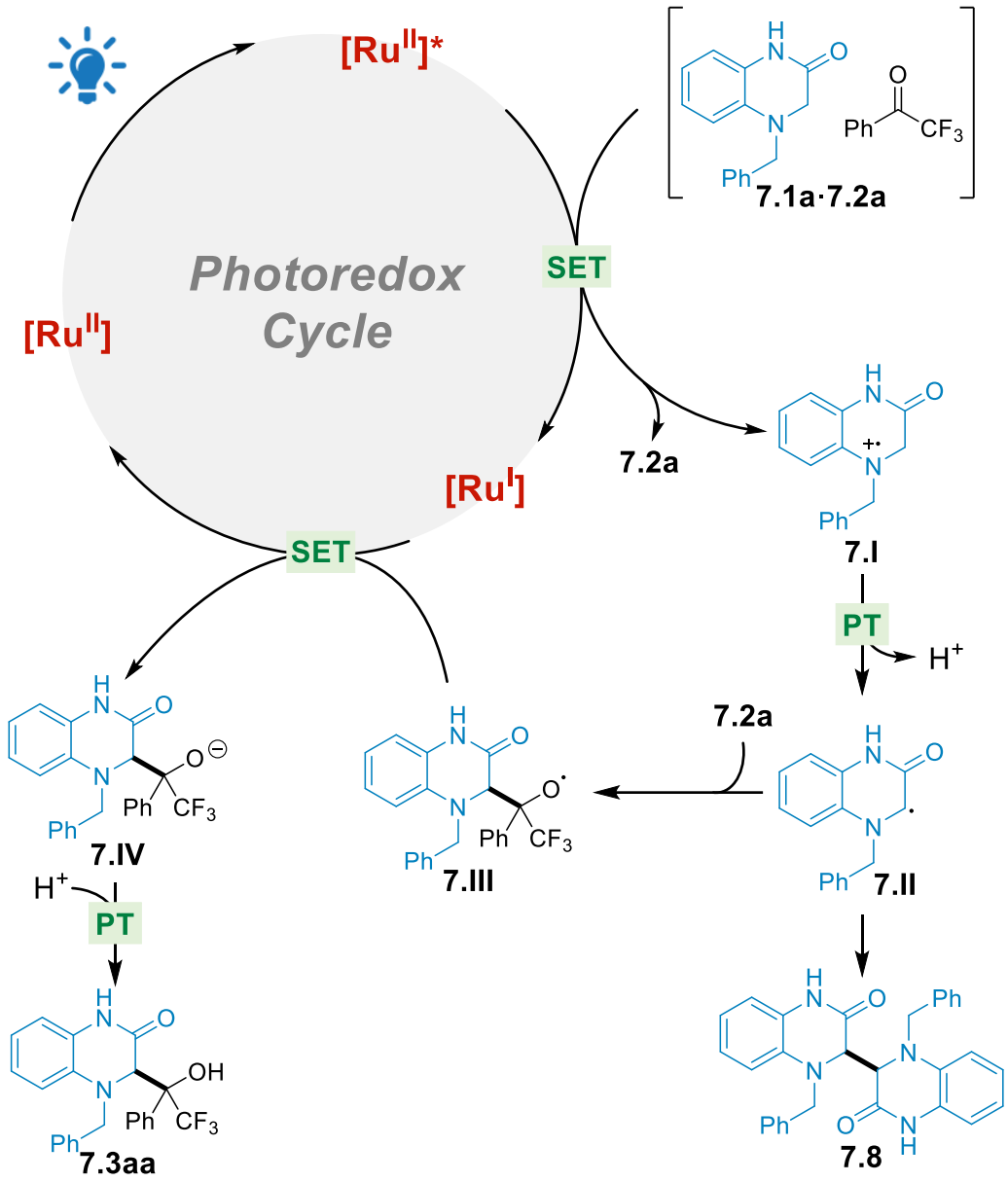


Figure 7.8: General mechanism for the photocatalytic 1,2-addition reaction between 3,4-dihydroquinoxalin-2-one **7.1a** and trifluoroacetophenone (**7.2a**).

Although we could not determine the molecular entity of the aggregate between **7.1a** and **7.2a** that enables the participation of the first one in electron-transfer events, with all this information we were in disposition to propose a tentative mechanism through which this transformation should proceed (Figure 7.8).

Initially, the excited state of $Ru(bpy)_3Cl_2$ (**A**) triggers a SET with the aggregate of **7.1a** and **7.2a**, facilitating the formation of radical cation **7.I** and the Ru(I) form of the photocatalyst. Then, the loss of a proton in radical cation **7.I** delivers the desired α-

amino radical **7.II**, which can suffer an homocoupling reaction to furnish its dimer **7.4**[†]. However, this α-amino radical **7.II** can also attack the electrophilic carbon of trifluoroacetophenone (**7.2a**) via a radical addition, thus allowing the formation of *O*-centered radical **7.III**. This alcoxy radical is readly reduced by the Ru(I) form of the photocatalyst, generating the corresponding alcoxyde anion **7.IV**. Finally, a proton transfer event furnishes the desired trifluoromethyl carbinol **7.3aa**.

[†]See *Chapter* 5 (page 280) for the complete characterization of dimer **7.4**.

7.4 Experimental Section

7.4.1 General Methods

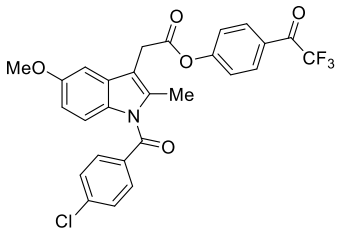
Experimental methods regarding **Melting Points**, **Chromatographic Methods**, **Nuclear Magnetic Resonance (NMR)** and **High Resolution Mass Spectrometry (HRMS)** can be found in Section 1.4.1 of *Chapter 1* (page 62).

Reaction Flasks, Reagents and Substrates

- Photochemical reactions were carried out in 10 mL Schlenk flasks under argon unless otherwise indicated.
- Commercial reagents were used as purchased.
- MeCN was degassed by three freeze-pump-thaw cycles and stored over 3Å MS for 48 h at least. Prior to use, MeCN was bubbled with Ar for 10 min.
- All photocatalysts and trifluoromethyl ketones **7.2** were commercially available.
- 4-Substituted-3,4-dihydroquinoxalin-2-ones **7.1a**-**7.1d** and **7.1f**-**7.1k** were prepared form its N-4 unprotected precursors using the *N*-benzylation procedure described in page 67 of *Chapter 1*. 3,4-dihydroquinoxalin-2-one **7.1e** was synthesized following a reported procedure.[159] 3,4-dihydroquinoxalin-2-one **7.1l** was synthesized following a reported procedure described in *Chapter* 1, page 67.

Synthetic Procedures and Characterization

Specific Procedure 1 (SP-1) for the synthesis of indomethacin-derived trifluoroacetophenone 7.2o



To a stirred solution of commercially available indomethacin (196.8 mg, 0.55 mmol, 1.1 equiv.) in DCM (5 mL) were added *p*-hydroxytrifluoroacetophenone (95.1 mg, 0.5 mmol, 1 equiv.) and DCC (155 mg, 0.75 mmol, 1.5 equiv.) and the resulting mixture was stirred at room temperature for 16 h. Then, the crude reaction mixture was filtered through a pad of Celite eluting with Et_2O. This yellow solution was concentrated under reduced pressure and the residue was purified by column chromatography using hexane:EtOAc as eluent to afford the desired product **7.2o** (257 mg, 0.485 mmol, 97% yield) as a white solid.

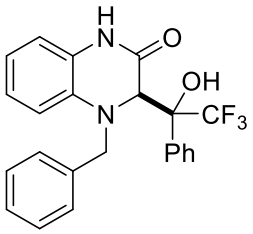
^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.29 – 7.93 (m, 2H), 7.68 (d, J = 8.6 Hz, 2H), 7.48 (d, J = 8.7 Hz, 2H), 7.28 (d, J = 9.0 Hz, 2H), 7.04 (d, J = 2.5 Hz, 1H), 6.88 (d, J =

9.0 Hz, 1H), 6.71 (dd, J = 9.0, 2.5 Hz, 1H), 3.95 (s, 2H), 3.84 (s, 3H), 2.47 (s, 3H); **^{19}F{^{1}H}-NMR (282 MHz, $CDCl_3$)** δ -71.87; **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 179.2 (q, J_{C-F}= 35.4 Hz, C), 168.3 (C), 168.2 (C), 156.1 (C), 139.4 (C), 136.4 (C), 133.6 (C), 131.9 (q, J_{C-F}= 2.0 Hz, CH), 131.2 (CH), 130.8 (C), 130.3 (C), 129.2 (C+CH), 127.4 (C), 122.3 (CH), 116.5 (q, J_{C-F} = 290.8 Hz, C), 115.0 (CH), 111.7 (CH), 111.2 (C), 101.2 (CH), 55.7 (CH_3), 30.5 (CH_2), 13.4 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{27}H_{20}ClF_3NO_5^+$ 530.0977, found 530.0984.

General Procedure 1 (GP-1) for the Photocatalytic Reaction between 3,4-dihydroquinoxalin-2-ones 7.1 and trifluoromethyl ketones 7.2

In an ovendried Schlenk tube, the corresponding 3,4-dihydroquinoxalin-2-one (**7.1**, 0.26 mmol, 0.13 equiv.) and $Ru(bpy)_3Cl_2$ (**A**, 1.5 mg, 1 mol %) were placed, and the flask was evacuated and backfilled with Ar (x3). Then, anhydrous and degassed MeCN (2 mL), as well as the corresponding trifluoromethyl ketone (**7.2**, 0.2 mmol, 0.1 equiv.), was added via syringe. The reaction mixture was stirred under the irradiation of a HP Single LED (455 nm) (see page 433 for further details about the photochemical setup) while being cooled with a fan to keep the temperature at approximately 25 °C. Once the reaction was finished (TLC), the mixture was purified by column chromatography using hexane:EtOAc or hexane:Et_2O mixtures to afford compound **7.3**.

4-Benzyl-3-(2,2,2-trifluoro-1-hydroxy-1-phenylethyl)-3,4-dihydroquinoxalin-2-one (7.3aa)



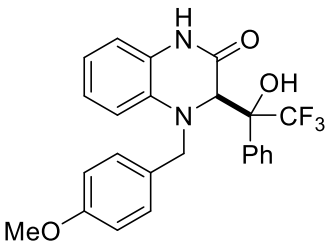
Using 4-benzyl-3,4-dihydroquinoxalin-2-one (**7.1a**, 62 mg, 0.26 mmol, 1.3 equiv.) and 2,2,2-trifluoroacetophenone (**7.2a**, 28.1 μL, 0.2 mmol, 1 equiv.), according to GP-1, compound **7.3aa** was obtained as a mixture of diastereomers (1:1 dr) that were separated by column chromatography using hexane:EtOAc mixtures (from 9:1 to 7:3): **7.3aa'** (29.7 mg, 0.07 mmol, 36% yield, brown oil) and **7.3aa''** (30.1 mg, 0.07 mmol, 36% yield, brown oil).

Characterization of **7.3aa'**: **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 9.64 (s, 1H), 7.64 (dd, J = 6.6, 2.9 Hz, 2H), 7.46–7.36 (m, 3H), 7.22 (tdd, J = 4.5, 3.6, 1.5 Hz, 3H), 7.01 (ddd, J = 8.6, 7.3, 1.4 Hz, 1H), 6.97–6.90 (m, 3H), 6.82 (td, J = 7.5, 1.4 Hz, 1H), 6.63 (dd, J = 7.8, 1.3 Hz, 1H), 4.82 (s, 1H), 4.59 (d, J = 15.8 Hz, 1H), 4.38 (s, 1H), 3.48 (d, J = 15.8 Hz, 1H); **^{19}F{^{1}H}-NMR (282 MHz, $CDCl_3$)** δ -73.17; **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 165.7 (C), 136.3 (C), 134.7 (C), 133.1 (C), 128.9 (CH), 128.8 (CH), 128.3 (CH), 127.8 (CH), 127.4 (CH), 126.6 (C), 126.5 (q, J_{C-F} = 1.8 Hz, CH), 125.19 (q, J_{C-F} = 287.2 Hz, CF_3), 124.7 (CH), 120.8 (CH), 116.9 (CH), 116.0 (CH), 79.4 (q, J_{C-F}

= 28.2 Hz, C), 67.2 (CH), 57.4 (CH_2); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{23}H_{20}F_3N_2O_2^+$ 413.1471, found 413.1465.

Characterization of **7.3aa''**: **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 8.95 (s, 1H), 7.47 (d, J = 7.6 Hz, 2H), 7.24–7.14 (m, 4H), 7.13–7.02 (m, 4H), 6.92 (ddd, J = 8.2, 7.4, 1.4 Hz, 1H), 6.79 (d, J = 7.7 Hz, 1H), 6.63 (td, J = 7.7, 1.2 Hz, 1H), 6.38 (dd, J = 7.8, 1.3 Hz, 1H), 4.81 (d, J = 16.0 Hz, 1H), 4.73 (s, 1H), 4.66 (s, 1H), 4.21 (d, J = 16.0 Hz, 1H). **^{19}F{^{1}H}-NMR (282 MHz, $CDCl_3$)** δ -74.24. **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 164.8 (C), 136.6 (C), 134.2 (C), 133.6 (C), 128.82 (CH), 128.79 (CH), 127.8 (CH), 127.7 (CH), 127.3 (CH), 126.9 (q, J_{C-F} = 1.8 Hz, CH), 125.7 (C), 124.72 (CH), 124.68 (q, J_{C-F} = 265.9 Hz, CF_3), 120.0 (CH), 116.4 (CH), 115.5 (CH), 78.6 (q, J_{C-F} = 27.1 Hz, C), 66.4 (CH), 56.5 (CH_2); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{23}H_{20}F_3N_2O_2^+$ 413.1471, found 413.1462.

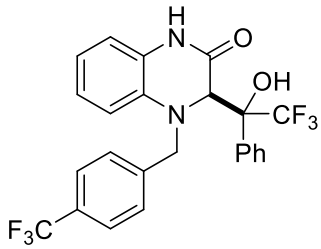
4-(4-Methoxybenzyl)-3-(2,2,2-trifluoro-1-hydroxy-1-phenylethyl)-3,4-dihydroquinoxalin-2-one (7.3ba)



Using 4-(4-methoxybenzyl)-3,4-dihydroquinoxalin-2-one (**7.1b**, 69.8 mg, 0.26 mmol, 1.3 equiv.) and 2,2,2-trifluoroacetophenone (**7.2a**, 28.1 μL, 0.2 mmol, 1 equiv.), according to GP-1, compound **7.3ba** was obtained as a mixture of diastereomers (1.1:1 dr) that cannot be separated by column chromatography using hexane:EtOAc mixtures (from 9:1 to 8:2): **7.3ba' + 7.3ba''** (74.5 mg, 0.16 mmol, 90% yield, brown oil).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.42 (s, 1H), 9.03 (s, 1H), 7.61 (dd, J = 6.6, 2.9 Hz, 2H), 7.48 (d, J = 7.6 Hz, 2H), 7.41–7.32 (m, 3H), 7.22–7.14 (m, 1H), 7.13-7.04 (m, 2H), 7.04–6.90 (m, 5H), 6.88–6.71 (m, 9H), 6.68–6.57 (m, 1H), 6.33 (dd, J = 7.8, 1.4 Hz, 1H), 4.90–4.69 (m, 3H), 4.65 (s, 1H), 4.51 (d, J = 15.3 Hz, 1H), 4.34 (s, 1H), 4.14 (d, J = 15.6 Hz, 1H), 3.75–3.67 (m, 6H), 3.42 (d, J = 15.3 Hz, 1H). **^{19}F{^{1}H}-NMR (282 MHz, $CDCl_3$)** δ -73.26, -74.23. **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 165.8 (C), 165.0 (C), 159.3 (C), 159.2 (C), 134.8 (C), 134.3 (C), 133.78 (C), 133.3 (C), 128.9 (CH), 128.8 (CH), 128.7 (CH), 128.6 (C), 128.3 (CH), 128.2 (C), 127.7 (CH), 127.0 (q, J_{C-F} = 1.7 Hz, CH), 126.8 (C), 126.6 (q, J_{C-F} = 1.7 Hz, CH), 125.9 (C), 124.8 (CH), 124.7 (CH), 120.9 (CH), 120.0 (CH), 117.3 (CH), 116.8 (CH), 115.9 (CH), 115.6 (CH), 114.22 (CH), 114.19 (CH), 79.3 (q, J_{C-F} = 28.2 Hz, C), 78.5 (q, J_{C-F} = 27.1 Hz, C), 66.6 (CH), 66.0 (CH), 57.2 (CH_2), 56.4 (CH_2), 55.4 (CH_3), 55.2 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{24}H_{22}F_3N_2O_3^+$ 443.1577, found 443.1583.

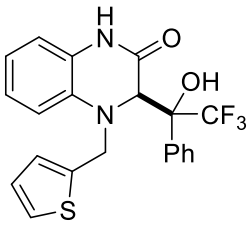
3-(2,2,2-Trifluoro-1-hydroxy-1-phenylethyl)-4-(4-(trifluoromethyl)benzyl)-3,4-dihydroquinoxalin-2-one (7.3ca)



Using 4-(4-(trifluoromethyl)benzyl)-3,4-dihydroquinoxalin-2-one (**7.1c**, 79.6 mg, 0.26 mmol, 1.3 equiv.) and 2,2,2-trifluoroacetophenone (**7.2a**, 28.1 μL, 0.2 mmol, 1 equiv.), according to GP-1, compound **7.3ca** was obtained as a mixture of diastereomers (1.1:1 dr) that cannot be separated by column chromatography using hexane:EtOAc mixtures (from 9:1 to 7:3): **7.3ca' + 7.3ca"** (73.0 mg, 0.152 mmol, 76% yield, brown oil).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.61 (s, 1H), 9.19 (s, 1H), 7.63 (dd, J = 6.6, 2.8 Hz, 2H), 7.52–7.37 (m, 9H), 7.24–7.06 (m, 5H), 7.08–6.95 (m, 3H), 6.91 (td, J = 8.2, 1.4 Hz, 1H), 6.87–6.78 (m, 2H), 6.76–6.69 (m, 2H), 6.65 (td, J = 7.7, 1.1 Hz, 1H), 6.38 (dd, J = 7.8, 1.3 Hz, 1H), 4.82 (d, J = 16.4 Hz, 1H), 4.72–4.55 (m, 4H), 4.36 (s, 1H), 4.24 (d, J = 16.5 Hz, 1H), 3.53 (d, J = 16.4 Hz, 1H). **^{19}F{^{1}H}-NMR (282 MHz, $CDCl_3$)** δ -62.58, -62.61, -73.09, -74.16. **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 165.5 (C), 164.7 (C), 140.8 (q, J_{C-F} = 1.1 Hz, C), 140.6 (q, J_{C-F} = 1.1 Hz, C), 134.6 (C), 134.0 (C), 132.9 (C), 132.5 (C), 130.00 (q, J_{C-F} = 32.5 Hz, C), 129.98 (q, J_{C-F} = 32.4 Hz, C), 129.1 (CH), 129.0 (CH), 128.4 (CH), 127.8 (CH), 127.44 (CH), 127.41 (CH), 126.8 (q, J_{C-F} = 1.6 Hz, CH), 126.5 (q, J_{C-F} = 1.7 Hz, CH), 126.4 (C), 125.8 (q, J_{C-F} = 2.6 Hz, CH), 125.7 (q, J_{C-F} = 2.6 Hz, CH), 125.0 (CH), 124.8 (CH), 120.9 (CH), 120.3 (CH), 116.2 (CH), 116.1 (CH), 116.0 (CH), 115.7 (CH), 79.7 (q, J_{C-F} = 27.6 Hz, C), 78.8 (q, J_{C-F} = 27.6 Hz, C), 67.9 (CH), 66.9 (CH), 56.3 (CH_2), 55.7 (CH_2); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{24}H_{19}F_6N_2O_2^+$ 481.1345, found 481.1341.

4-(Thiophen-2-ylmethyl)-3-(2,2,2-trifluoro-1-hydroxy-1-phenylethyl)-3,4-dihydroquinoxalin-2-one (7.3da)

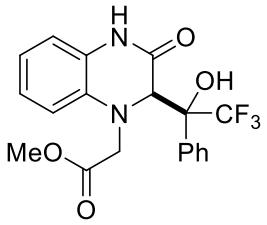


Using 4-(thiophen-2-ylmethyl)-3,4-dihydroquinoxalin-2-one (**7.1d**, 63.5 mg, 0.26 mmol, 1.3 equiv.) and 2,2,2-trifluoroacetophenone (**7.2a**, 28.1 μL, 0.2 mmol, 1 equiv.), according to GP-1, compound **7.3da** was obtained as a mixture of diastereomers (1.4:1 dr) that cannot be separated by column chromatography using hexane:EtOAc mixtures (from 9:1 to 8:2): **7.3da' + 7.3da"** (51.0 mg, 0.12 mmol, 61% yield, brown oil).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.73 (s, 1H), 8.31 (s, 1H), 7.69 – 7.60 (m, 2H), 7.48 (d, J = 7.6 Hz, 2H), 7.44 – 7.36 (m, 3H), 7.20 – 6.80 (m, 13H), 6.73 – 6.62 (m, 3H), 6.30 (dd, J = 7.8, 1.2 Hz, 1H), 5.02 – 4.92 (m, 2H), 4.88 (s, 1H), 4.69 – 4.59 (m, 2H),

4.40 (d, J = 16.2 Hz, 1H), 4.35 – 4.29 (m, 1H), 3.49 (d, J = 16.1 Hz, 1H); **^{19}F{^{1}H}-NMR (282 MHz, $CDCl_3$)** δ -73.61, -74.77; **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 165.4 (C), 164.8 (C), 139.3 (C), 138.8 (C), 134.7 (C), 134.0 (C), 132.8 (C), 132.3 (C), 129.0 (CH), 128.8 (CH), 128.3 (CH), 127.6 (CH), 127.0 (C), 127.0 (C), 127.0 (CH), 126.8 (CH), 126.7 (CH), 126.6 (CH), 126.6 (CH), 126.6 (CH), 125.7 (CH), 125.6 (CH), 124.8 (CH), 124.8 (CH), 121.5 (CH), 120.8 (CH), 117.8 (CH), 117.5 (CH), 115.9 (CH), 115.5 (CH), 79.1 (q, J_{C-F} = 26.2 Hz, C), 78.1 (q, J_{C-F} = 25.9 Hz, C), 66.6 (CH), 65.7 (CH), 53.1 (CH_2), 52.6 (CH_2); **HRMS (ESI/Q-TOF)** m/z $[M + H]^+$ calcd for $C_{21}H_{18}F_3N_2O_2S^+$ 419.1036, found 419.1037.

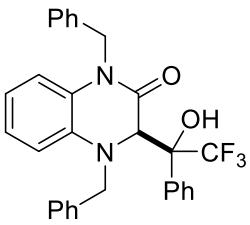
Methyl 2-(3-oxo-2-(2,2,2-trifluoro-1-hydroxy-1-phenylethyl)-3,4-dihydroquinoxalin-1-yl) acetate (7.3ea)



Using methyl 2-(3-oxo-3,4-dihydroquinoxalin-1-yl)acetate (**7.1e**, 57.3 mg, 0.26 mmol, 1.3 equiv.) and 2,2,2-trifluoroacetophenone (**7.2a**, 28.1 μL, 0.2 mmol, 1 equiv.), according to GP-1, compound **7.3ea** was obtained as a mixture of diastereomers (1:1 dr) that cannot be separated by column chromatography using hexane:Et_2O mixtures (from 5:5 to 2:8): **7.3ea' + 7.3ea''** (43.2 mg, 0.11 mmol, 55% yield, brown oil).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.55 (s, 1H), 9.16 (s, 1H), 7.63 (dd, J = 6.8, 2.9 Hz, 2H), 7.56–7.47 (m, 2H), 7.38–7.30 (m, 3H), 7.19–7.04 (m, 3H), 7.02–6.80 (m, 4H), 6.80–6.73 (m, 1H), 6.73–6.64 (m, 2H), 6.39 (dd, J = 7.8, 1.4 Hz, 1H), 5.56 (s, 1H), 5.27 (s, 1H), 4.53 (s, 1H), 4.38 (d, J = 18.5 Hz, 1H), 4.23 (s, 1H), 4.07 (d, J = 18.5 Hz, 1H), 3.93 (d, J = 18.5 Hz, 1H), 3.64 (s, 3H), 3.63 (s, 3H), 3.09 (d, J = 18.5 Hz, 1H). **^{19}F{^{1}H}-NMR (282 MHz, $CDCl_3$)** δ -73.38, -74.14. **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 171.2 (C), 170.9 (C), 165.2 (C), 164.5 (C), 134.4 (C), 133.8 (C), 132.7 (C), 132.3 (C), 128.9 (CH), 128.8 (CH), 128.1 (CH), 127.6 (CH), 127.1 (C), 127.0 (q, J_{C-F} = 1.8 Hz, CH), 126.6 (C), 126.60 (q, J_{C-F} = 1.8 Hz, CH), 125.1 (q, J_{C-F} = 281.9 Hz, CF_3), 124.9 (q, J_{C-F} = 286.9 Hz, CF_3), 124.6 (CH), 124.5 (CH), 121.9 (CH), 121.3 (CH), 117.3 (CH), 116.1 (CH), 115.9 (CH), 79.0 (q, J_{C-F} = 27.6 Hz, C), 77.9 (q, J_{C-F} = 26.5 Hz, C), 69.0 (CH), 67.9 (CH), 56.9 (CH_2), 56.3 (CH_2), 52.4 (CH_3), 52.3 (CH_3); **HRMS (ESI/Q-TOF)** m/z $[M + H]^+$ calcd for $C_{19}H_{18}F_3N_2O_4^+$ 395.1213, found 395.1217.

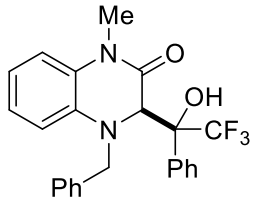
1,4-Dibenzyl-3-(2,2,2-trifluoro-1-hydroxy-1-phenylethyl)-3,4-dihydroquinoxalin-2-one (7.3fa)



Using 1,4-dibenzyl-3,4-dihydroquinoxalin-2-one (**7.1f**, 85.4 mg, 0.26 mmol, 1.3 equiv.) and 2,2,2-trifluoroacetophenone (**7.2a**, 28.1 μL, 0.2 mmol, 1 equiv.), according to GP-1, compound **7.3fa** was obtained as a mixture of diastereomers (1.1:1 dr) that cannot be separated by column chromatography using hexane:EtOAc mixtures (from 9:1 to 7:3): **7.3fa' + 7.3fa"** (60.8 mg, 0.12 mmol, 60% yield, brown oil).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.64 – 7.58 (m, 2H), 7.49 (d, J = 7.9 Hz, 2H), 7.42 – 7.34 (m, 3H), 7.32 – 7.17 (m, 13H), 7.17 – 7.03 (m, 5H), 7.02 – 6.86 (m, 5H), 6.85 – 6.74 (m, 4H), 6.59 (t, J = 6.9 Hz, 1H), 6.47 (d, J = 8.1 Hz, 1H), 5.24 (d, J = 16.0 Hz, 1H), 5.11 – 4.76 (m, 6H), 4.71 – 4.58 (m, 2H), 4.56 (s, 1H), 4.32 (d, J = 15.9 Hz, 1H), 3.60 (d, J = 15.6 Hz, 1H); **^{19}F{^{1}H}-NMR (282 MHz, $CDCl_3$)** δ -73.67, -74.55. **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 164.4 (C), 163.9 (C), 136.7 (C), 136.3 (C), 135.9 (C), 135.5 (C), 134.9 (C), 134.7 (C), 134.4 (C), 134.3 (C), 129.6 (C), 128.86 (CH), 128.79 (CH), 128.75 (CH), 128.70 (CH), 128.64 (CH), 128.59 (CH), 128.1 (CH), 127.9 (CH), 127.8 (CH), 127.7 (CH), 127.6 (CH), 127.4 (CH), 127.3 (CH), 127.2 (CH), 126.9 (CH), 126.5 (q, J_{C-F} = 1.8 Hz, CH), 126.2 (CH), 124.8 (q, J_{C-F} = 286.4 Hz, CF_3), 124.5 (CH), 124.4 (CH), 121.1 (CH), 120.1 (CH), 117.9 (CH), 117.2 (CH), 115.9 (CH), 115.7 (CH), 78.33 (q, J_{C-F} = 27.1 Hz, C), 78.33 (q, J_{C-F} = 27.1 Hz, C), 67.4 (CH), 66.8 (CH), 57.9 (CH_2), 56.9 (CH_2), 46.2 (CH_2), 45.7 (CH_2); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{30}H_{26}F_3N_2O_2^+$ 503.1941, found 503.1937.

4-Benzyl-1-methyl-3-(2,2,2-trifluoro-1-hydroxy-1-phenylethyl)-3,4-dihydroquinoxalin -2-one (7.3ga)

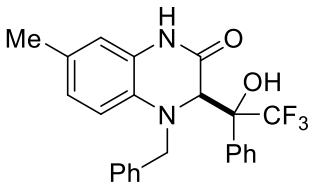


Using 4-benzyl-1-methyl-3,4-dihydroquinoxalin-2-one (**7.1g**, 65.6 mg, 0.26 mmol, 1.3 equiv.) and 2,2,2-trifluoroacetophenone (**7.2a**, 28.1 μL, 0.2 mmol, 1 equiv.), according to GP-1, compound **7.3ga** was obtained as a mixture of diastereomers (1.1:1 dr) that cannot be separated by column chromatography using hexane:EtOAc mixtures (from 9:1 to 7:3): **7.3ga' + 7.3ga"** (50.4 mg, 0.12 mmol, 60% yield, colorless oil). Representative NMR signals for either the major and the minor diastereoisomer are labelled with one or two asterisks, respectively.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.56–7.49 (m, 2H*), 7.40–7.30 (m, 6H), 7.26–7.17 (m, 5H), 7.12–6.99 (m, 5H), 6.98–6.85 (m, 6H), 6.77 (ddd, J = 12.9, 8.1, 1.4 Hz, 2H), 6.65 (ddd, J = 8.1, 7.3, 1.5 Hz, 1H**), 6.42 (dd, J = 8.1, 1.4 Hz, 1H**), 5.07 (s, 1H*),

4.96 (s, 1H**), 4.87 (d, J = 16.0 Hz, 1H**), 4.72 (s, 1H**), 4.48 (d, J = 15.4 Hz, 1H*), 4.37 - 4.32 (m, 2H), 3.52 (d, J = 15.4 Hz, 1H*), 3.26 (s, 3H*), 3.13 (s, 3H**). **^{19}F{^{1}H}-NMR (282 MHz, $CDCl_3$)** δ -73.88*, -74.11**. **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 164.3 (C*), 163.9 (C**), 136.5 (C), 136.0 (C), 134.9 (C), 134.3 (C), 134.2 (C), 133.9 (C), 130.4 (C), 128.73 (CH), 128.71 (CH), 128.7 (CH), 128.6 (CH), 128.0 (CH), 127.9 (CH), 127.72 (CH), 127.70 (CH), 127.65 (CH), 127.3 (CH), 126.8 (q, J_{C-F} = 1.7 Hz, CH), 126.5 (q, J_{C-F} = 2.2 Hz, CH), 125.1 (q, J_{C-F} = 286.9 Hz, CF_3), 124.9 (q, J_{C-F} = 293.0 Hz, CF_3), 124.3 (CH), 124.2 (CH), 121.3 (CH), 119.7 (CH), 117.8 (CH), 116.2 (CH), 114.7 (CH*), 114.4 (CH**), 78.4 (q, J_{C-F} = 28.2 Hz, C), 77.9 (q, J_{C-F} = 27.1 Hz, C), 67.0 (CH), 66.8 (CH), 58.1 (CH_2), 56.23 (q, J_{C-F} = 1.6 Hz, CH_2), 29.0 (CH_3), 28.9 (CH_3); **HRMS (ESI/Q-TOF)** m/z $[M + H]^+$ calcd for $C_{24}H_{22}F_3N_2O_2^+$ 427.1628, found 427.1629.

4-Benzyl-7-methyl-3-(2,2,2-trifluoro-1-hydroxy-1-phenylethyl)-3,4-dihydroquinoxalin -2-one (7.3ha)



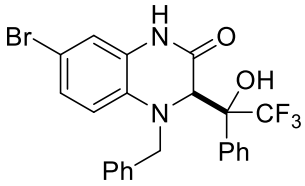
Using 4-benzyl-7-methyl-3,4-dihydroquinoxalin-2-one (**7.1h**, 65.6 mg, 0.26 mmol, 1.3 equiv.) and 2,2,2-trifluoroacetophenone (**7.2a**, 28.1 μL, 0.2 mmol, 1 equiv.), according to GP-1, compound **7.3ha** was obtained as a mixture of diastereomers (1:1 dr) that were separated by column chromatography using hexane:EtOAc mixtures (from 9:1 to 7:3): **7.3ha'** (25.7 mg, 0.06 mmol, 30% yield, colorless oil) and **7.3ha''** (24.7 mg, 0.06 mmol, 29% yield, colorless oil).

Characterization of **7.3ha'**: **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 9.25 (s, 1H), 7.61 (dd, J = 6.8, 3.0 Hz, 2H), 7.41 – 7.34 (m, 3H), 7.24 – 7.18 (m, 3H), 7.00 – 6.91 (m, 2H), 6.87 – 6.79 (m, 2H), 6.42 (d, J = 1.6 Hz, 1H), 4.81 (s, 1H), 4.53 (d, J = 15.6 Hz, 1H), 4.33 (d, J = 0.9 Hz, 1H), 3.48 (d, J = 15.6 Hz, 1H), 2.24 (s, 3H); **^{19}F{^{1}H}-NMR (282 MHz, $CDCl_3$)** δ -73.34; **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 165.6 (C), 136.4 (C), 134.8 (C), 130.9 (C), 130.5 (C), 128.8 (CH), 128.7 (CH), 128.2 (CH), 127.8 (CH), 127.5 (CH), 126.7 (C), 126.5 (q, J_{C-F} = 1.7 Hz, CH), 125.4 (CH), 117.4 (CH), 116.5 (CH), 79.2 (q, J_{C-F} = 27.8 Hz, C), 67.1 (CH), 57.9 (CH_2), 20.6 (CH_3); **HRMS (ESI/Q-TOF)** m/z $[M + H]^+$ calcd for $C_{24}H_{22}F_3N_2O_2^+$ 427.1628, found 427.1633.

Characterization of **7.3ha''**: **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 8.83 (s, 1H), 7.40 (d, J = 7.6 Hz, 2H), 7.20 – 7.07 (m, 4H), 7.07 – 7.02 (m, 2H), 7.02 – 6.93 (m, 2H), 6.67 – 6.56 (m, 2H), 6.12 (s, 1H), 4.72 – 4.60 (m, 2H), 4.53 (s, 1H), 4.08 (d, J = 15.9 Hz, 1H), 2.06 (s, 3H); **^{19}F{^{1}H}-NMR (282 MHz, $CDCl_3$)** δ -74.21; **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 165.0 (C), 136.8 (C), 135.5 (C), 134.4 (C), 131.1 (C), 128.7 (CH), 128.7 (CH), 127.7 (CH), 127.7 (CH), 127.4 (CH), 126.9 (q, J_{C-F} = 2.3 Hz, CH), 125.8 (C), 125.3 (CH),

116.7 (CH), 116.1 (CH), 78.6 (q, J_{C-F} = 27 Hz, C), 66.5 (CH), 57.0 (CH_2), 20.4 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{24}H_{22}F_3N_2O_2^+$ 427.1628, found 427.1619.

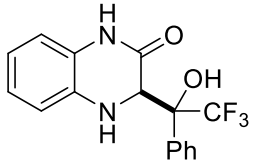
4-Benzyl-7-bromo-3-(2,2,2-trifluoro-1-hydroxy-1-phenylethyl)-3,4-dihydroquinoxalin -2-one (7.3ia)



Using 4-benzyl-7-bromo-3,4-dihydroquinoxalin-2-one (**7.1i**, 82.5 mg, 0.26 mmol, 1.3 equiv.) and 2,2,2-trifluoroacetophenone (**7.2a**, 28.1 μL, 0.2 mmol, 1 equiv.), according to GP-1, compound **7.3ia** was obtained as a mixture of diastereomers (1:1 dr) that cannot be separated by column chromatography using hexane:EtOAc mixtures (from 9:1 to 7:3): **7.3ia' + 7.3ai"** (66.8 mg, 0.136 mmol, 68% yield, colorless oil). Representative NMR signals for either the major and the minor diastereoisomer are labelled with one or two asterisks, respectively.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.73 (s, 1H**), 9.23 (s, 1H*), 7.57 – 7.45 (m, 2H**), 7.37 (d, J = 7.5 Hz, 2H*), 7.33 – 7.24 (m, 1H*+2H**), 7.16 – 7.05 (m, 8H), 7.00 (dd, J = 8.6, 2.1 Hz, 1H**), 6.97 – 6.83 (m, 6H), 6.72 – 6.61 (m, 2H**), 6.50 (d, J = 8.6 Hz, 1H*), 6.38 (d, J = 2.2 Hz, 1H*), 4.63 – 4.53 (m, 2H*), 4.48 (d, J = 15.8 Hz, 1H**) 4.32-4.35 (m, 1H*+1H**), 4.25 (s, 1H**), 4.03 (d, J = 15.9 Hz, 1H*), 3.53 (d, J = 15.8 Hz, 1H**); **^{19}F{^{1}H}-NMR (282 MHz, $CDCl_3$)** δ -73.17**, -74.01*; **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 165.1 (C), 164.4 (C), 136.1 (C), 135.9 (C), 134.4 (C), 134.0 (C), 132.7 (C), 132.3 (C), 129.2 (CH), 129.0 (CH), 128.9 (CH), 128.4 (CH), 128.0 (CH), 128.0 (CH), 127.9 (CH), 127.8 (C), 127.3 (CH), 127.2 (CH), 127.1 (C), 126.7 (q, J_{C-F} = 1.8 Hz, CH), 126.3 (q, J_{C-F} = 1.7 Hz, CH), 118.6 (CH), 118.2 (CH), 117.7 (CH), 117.5 (CH), 112.3 (C), 111.5 (C), 79.8 (q, J_{C-F} = 27.9 Hz, C), 78.9 (q, J_{C-F} = 27.4 Hz, C), 67.2 (CH), 66.5 (CH), 57.0 (CH_2), 56.6 (CH_2); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{23}H_{19}BrF_3N_2O_2^+$ 491.0577, found 491.0582.

3-(2,2,2-Trifluoro-1-hydroxy-1-phenylethyl)-3,4-dihydroquinoxalin-2-one (7.3la)

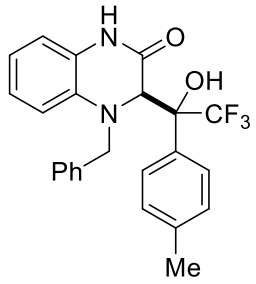


Using 3,4-dihydroquinoxalin-2-one (**7.1l**, 38.5 mg, 0.26 mmol, 1.3 equiv.) and 2,2,2-trifluoroacetophenone (**7.2a**, 28.1 μL, 0.2 mmol, 1 equiv.), according to GP-1, compound **7.3la** was obtained as a mixture of diastereomers (1:1 dr) that cannot be separated by column chromatography using hexane:EtOAc mixtures (from 9:1 to 7:3): **7.3la' + 7.3la"** (26.4 mg, 0.082 mmol, 41% yield, colorless oil).

^{1}H-NMR (300 MHz, DMSO-d_6) δ 10.43 (s, 1H), 10.31 (s, 1H), 7.60 – 7.50 (m, 2H), 7.49 – 7.41 (m, 2H), 7.35 – 7.26 (m, 3H), 7.25 – 7.16 (m, 3H), 6.82 (s, 1H), 6.74 – 6.66 (m, 1H), 6.66 – 6.60 (m, 3H), 6.56 (d, J = 7.1 Hz, 1H), 6.51 (dd, J = 7.8, 1.4

Hz, 1H), 6.49 – 6.35 (m, 3H), 6.16 (d, J = 2.6 Hz, 1H), 5.87 (d, J = 3.3 Hz, 1H), 4.56 (d, J = 3.3 Hz, 1H), 4.46 (d, J = 2.5 Hz, 1H); **^{19}F{^{1}H}-NMR (282 MHz, DMSO-d$_6$)** δ -72.18, -72.44; **^{13}C{^{1}H}-NMR (75 MHz, DMSO-d$_6$)** δ 162.7 (C), 162.1 (C), 136.1 (C), 135.7 (C), 133.0 (C), 132.6 (C), 128.3 (CH), 128.0 (CH), 127.8 (CH), 127.4 (CH), 126.7 (CH), 126.4 (CH), 125.4 (C), 124.8 (C), 122.8 (CH), 122.4 (CH), 117.1 (CH), 117.0 (CH), 114.3 (CH), 114.0 (CH), 112.9 (CH), 112.9 (CH), 79.4 (q, J_{C-F} = 26.0 Hz, C), 79.3 (q, J_{C-F} = 25.7 Hz, C), 60.9 (CH), 60.3 (CH); **HRMS (ESI/Q-TOF)** *m/z* [M + H]$^+$ calcd for $C_{16}H_{14}F_3N_2O_2^+$ 323.1002, found 323.1004.

4-Benzyl-3-(2,2,2-trifluoro-1-hydroxy-1-(*p*-tolyl)ethyl)-3,4-dihydroquinoxalin-2-one (7.3ab)



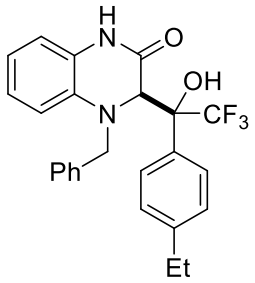
Using 4-benzyl-3,4-dihydroquinoxalin-2-one (**7.1a**, 62 mg, 0.26 mmol, 1.3 equiv.) and 2,2,2-trifluoro-1-(*p*-tolyl)ethan-1-one (**7.2b**, 31 μL, 0.2 mmol, 1 equiv.), according to GP-1, compound **7.3ab** was obtained as a mixture of diastereomers (1.5:1 dr) that were separated by column chromatography using hexane:EtOAc mixtures (from 95:5 to 75:25): **7.3ab'** (28.0 mg, 0.06 mmol, 30% yield, brown oil) and **7.3ab"** (18.7 mg, 0.04 mmol, 20% yield, brown oil).

Characterization of **7.3ab'**: **^{1}H-NMR (300 MHz, CDCl$_3$)** δ 9.21 (s, 1H), 7.50 (d, J = 8.3 Hz, 2H), 7.24–7.15 (m, 5H), 7.06–6.86 (m, 4H), 6.81 (td, J = 7.6, 1.4 Hz, 1H), 6.62 (dd, J = 7.8, 1.3 Hz, 1H), 4.65 (s, 1H), 4.59 (d, J = 15.8 Hz, 1H), 4.35 (s, 1H), 3.50 (d, J = 15.8 Hz, 1H), 2.38 (s, 3H). **^{19}F{^{1}H}-NMR (282 MHz, CDCl$_3$)** δ -73.34. **^{13}C{^{1}H}-NMR (75 MHz, CDCl$_3$)** δ 165.5 (C), 138.8 (C), 136.4 (C), 133.2 (C), 131.7 (C), 129.0 (CH), 128.7 (CH), 127.8 (CH), 127.4 (CH), 126.5 (C), 126.4 (q, J_{C-F} = 1.8 Hz, CH), 125.2 (q, J_{C-F} = 286.9 Hz, CF_3), 124.7 (CH), 120.7 (CH), 116.7 (CH), 115.8 (CH), 79.4 (q, J_{C-F} = 27.9 Hz, C), 67.3 (CH), 57.3 (CH_2), 21.1 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* [M + H]$^+$ calcd for $C_{24}H_{22}F_3N_2O_2^+$ 427.1628, found 427.1621.

Characterization of **7.3ab"**: **^{1}H-NMR (300 MHz, CDCl$_3$)** δ 8.85 (s, 1H), 7.34 (d, J = 8.2 Hz, 2H), 7.24–7.16 (m, 3H), 7.06 (dd, J = 7.2, 2.2 Hz, 2H), 6.97–6.85 (m, 3H), 6.78 (d, J = 7.8 Hz, 1H), 6.65 (td, J = 7.6, 1.2 Hz, 1H), 6.39 (dd, J = 7.7, 1.3 Hz, 1H), 4.79 (d, J = 16.0 Hz, 1H), 4.63 (s, 1H), 4.59 (s, 1H), 4.19 (d, J = 16.0 Hz, 1H), 2.22 (s, 3H). **^{19}F{^{1}H}-NMR (282 MHz, CDCl$_3$)** δ -74.38. **^{13}C{^{1}H}-NMR (75 MHz, CDCl$_3$)** δ 164.8 (C), 138.6 (C), 136.7 (C), 133.6 (C), 131.2 (C), 128.8 (CH), 128.4 (CH), 127.7 (CH), 127.3 (CH), 126.8 (q, J_{C-F} = 1.8 Hz, CH), 125.8 (C), 124.6 (CH), 119.8 (CH), 116.4 (CH), 115.5 (CH), 78.6 (q, J_{C-F} = 27.1, 26.5 Hz, C), 66.4 (CH), 56.5 (CH_2), 20.9

(CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{24}H_{22}F_3N_2O_2^+$ 427.1628, found 427.1624.

4-Benzyl-3-(1-(4-ethylphenyl)-2,2,2-trifluoro-1-hydroxyethyl)-3,4-dihydroquinoxalin -2-one (7.3ac)

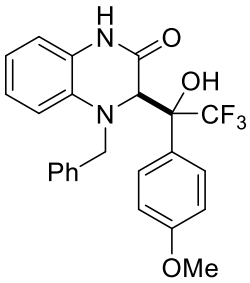


Using 4-benzyl-3,4-dihydroquinoxalin-2-one (**7.1a**, 62 mg, 0.26 mmol, 1.3 equiv.) and 1-(4-ethylphenyl)-2,2,2-trifluoroethan-1-one (**7.2c**, 33 μL, 0.2 mmol, 1 equiv.), according to GP-1, compound **7.3ac** was obtained as a mixture of diastereomers (1.1:1 dr) that were separated by column chromatography using hexane:EtOAc mixtures (from 95:5 to 75:25): **7.3ac'** (13.6 mg, 0.03 mmol, 15% yield, yellow oil) and **7.3ac''** (12.1 mg, 0.03 mmol, 14% yield, yellow oil).

Characterization of **7.3ac'**: **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 8.80 (s, 1H), 7.51 (d, *J* = 8.2 Hz, 2H), 7.24–7.17 (m, 5H), 6.99 (ddd, *J* = 8.6, 7.3, 1.4 Hz, 1H), 6.95–6.86 (m, 3H), 6.80 (td, *J* = 7.5, 1.4 Hz, 1H), 6.62 (dd, *J* = 7.8, 1.4 Hz, 1H), 4.69 (s, 1H), 4.56 (d, *J* = 15.7 Hz, 1H), 4.33 (s, 1H), 3.45 (d, *J* = 15.8 Hz, 1H), 2.68 (q, J_{C-F} = 7.6 Hz, 2H), 1.25 (t, *J* = 7.6 Hz, 3H). **^{19}F{^{1}H}-NMR (282 MHz, $CDCl_3$)** δ -73.29. **^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$)** δ 165.4 (C), 145.1 (C), 136.4 (C), 133.2 (C), 132.0 (C), 128.8 (CH), 127.81 (CH), 127.77(CH), 127.4 (CH), 126.5 (CH), 124.7 (CH), 120.6 (CH), 116.9 (CH), 115.7 (CH), 79.4 (q, J_{C-F} = 26.3 Hz, C), 67.3 (CH), 57.3 (CH_2), 28.5 (CH_2), 15.4 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{25}H_{24}F_3N_2O_2^+$ 441.1784, found 441.1791.

Characterization of **7.3ac''**: **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 8.32 (s, 1H), 7.35 (d, *J* = 8.1 Hz, 2H), 7.24-7.21 (m, 3H), 7.06 (dd, *J* = 7.4, 2.1 Hz, 2H), 6.93-6.86 (m, 3H), 6.76 (d, *J* = 8.1 Hz, 1H), 6.61 (td, *J* = 7.6, 1.3 Hz, 1H), 6.34 (dd, *J* = 7.8, 1.9 Hz, 1H), 4.80 (d, *J* = 16.0 Hz, 1H), 4.62 (s, 1H), 4.58 (s, 1H), 4.21 (d, *J* = 15.9 Hz, 1H), 2.51 (q, J_{C-F} = 7.6 Hz, 2H), 1.13 (t, *J* = 7.6 Hz, 3H). **^{19}F{^{1}H}-NMR (282 MHz, $CDCl_3$)** δ -74.38. **^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$)** δ 164.7 (C), 144.9 (C), 136.7 (C), 133.6 (C), 131.2 (C), 128.8 (CH), 127.7 (CH), 127.3 (CH), 127.2 (CH), 126.9 (q, J_{C-F} = 2.5 Hz, CH), 125.8 (C), 124.6 (CH), 119.8 (CH), 116.4 (CH), 115.4 (CH), 78.5 (q, J_{C-F} = 27.1 Hz, C), 66.5 (CH), 56.5 (CH_2), 28.3 (CH_2), 15.4 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{25}H_{24}F_3N_2O_2^+$ 441.1784, found 441.1793.

4-Benzyl-3-(2,2,2-trifluoro-1-hydroxy-1-(4-methoxyphenyl)ethyl)-3,4-dihydroquinoxalin-2-one (7.3ad)

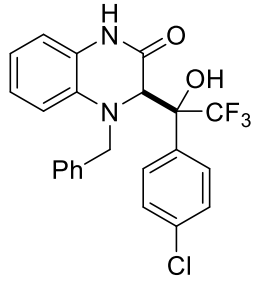


Using 4-benzyl-3,4-dihydroquinoxalin-2-one (**7.1a**, 62 mg, 0.26 mmol, 1.3 equiv.) and 2,2,2-trifluoro-1-(4-methoxyphe- nyl)ethan-1-one (**7.2d**, 31 μL, 0.2 mmol, 1 equiv.), according to GP-1, compound **7.3ad** was obtained as a mixture of diastereomers (1.2:1 dr) that were separated by column chromatography using hexane:EtOAc mixtures (from 95:5 to 75:25): **7.3ad'** (22.7 mg, 0.05 mmol, 27% yield, yellow oil) and **7.3ad"** (20.2 mg, 0.05 mmol, 23% yield, yellow oil).

Characterization of **7.3ad'**: **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 8.92 (s, 1H), 7.52 (d, J = 8.8 Hz, 2H), 7.23-7.18 (m, 3H), 7.04–6.89 (m, 6H), 6.81 (td, J = 7.5, 1.4 Hz, 1H), 6.63 (dd, J = 7.8, 1.4 Hz, 1H), 4.68 (s, 1H), 4.59 (d, J = 15.8 Hz, 1H), 4.32 (s, 1H), 3.81 (s, 3H), 3.52 (d, J = 15.8 Hz, 1H). **^{19}F{^{1}H}-NMR (282 MHz, $CDCl_3$)** δ -73.56. **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 165.4 (C), 160.0 (C), 136.4 (C), 133.1 (C), 128.8 (CH), 127.9 (CH), 127.8 (CH), 127.4 (CH), 126.7 (C), 126.5 (C), 125.2 (q, J_{C-F} = 287.5 Hz, CF_3), 124.7 (CH), 120.7 (CH), 116.9 (CH), 115.8 (CH), 113.6 (CH), 79.19 (q, J_{C-F} = 27.6 Hz, C), 67.3 (CH), 57.4 (CH_2), 55.2 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* [M + H]$^+$ calcd for $C_{24}H_{22}F_3N_2O_3^+$ 443.1577, found 443.1574.

Characterization of **7.3ad"**: **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 8.50 (s, 1H), 7.37 (d, J = 8.8 Hz, 2H), 7.24–7.19 (m, 3H), 7.07 (dd, J = 7.3, 2.2 Hz, 2H), 6.92 (ddd, J = 8.1, 7.3, 1.4 Hz, 1H), 6.80 (d, J = 8.6 Hz, 1H), 6.70–6.57 (m, 3H), 6.38 (dd, J = 7.8, 1.4 Hz, 1H), 4.83 (d, J = 16.0 Hz, 1H), 4.66 (s, 1H), 4.62 (s, 1H), 4.24 (d, J = 16.0 Hz, 1H), 3.70 (s, 3H). **^{19}F{^{1}H}-NMR (282 MHz, $CDCl_3$)** δ -74.63. **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 164.9 (C), 159.8 (C), 136.7 (C), 133.6 (C), 130.9 (q, J_{C-F} = 283.6 Hz, CF_3), 128.8 (CH), 128.3 (q, J_{C-F} = 2.2 Hz, CH), 127.8 (CH), 127.3 (CH), 125.9 (C), 125.7 (C), 124.7 (CH), 119.9 (CH), 116.4 (CH), 115.4 (CH), 113.0 (CH), 78.2 (q, J_{C-F} = 27.6 Hz, C), 66.5 (CH), 56.5 (CH_2), 55.2 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* [M + H]$^+$ calcd for $C_{24}H_{22}F_3N_2O_3^+$ 443.1577, found 443.1582.

4-Benzyl-3-(1-(4-chlorophenyl)-2,2,2-trifluoro-1-hydroxyethyl)-3,4-dihydroquinoxalin-2-one (7.3ae)



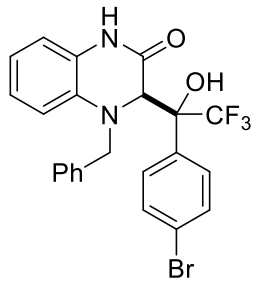
Using 4-benzyl-3,4-dihydroquinoxalin-2-one (**7.1a**, 62 mg, 0.26 mmol, 1.3 equiv.) and 2,2,2-trifluoro-1-(4-chlorophenyl)-ethan-1-one (**7.2e**, 30 μL, 0.2 mmol, 1 equiv.), according to GP-1, compound **7.3ae** was obtained as a mixture of diastereomers (1:1 dr) that were separated by column chromatography using hexane:EtOAc mixtures (from 95:5 to 75:25): **7.3ae'**

(24.1 mg, 0.05 mmol, 27% yield, yellow oil) and **7.3ae''** (24.4 mg, 0.05 mmol, 27% yield, yellow oil).

Characterization of **7.3ae'**: **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 8.90 (s, 1H), 7.53 (d, J = 8.7 Hz, 2H), 7.34 (d, J = 8.9 Hz, 2H)., 7.24-7.21 (M, 3H), 7.04–6.91 (m, 4H), 6.84 (ddd, J = 7.8, 7.1, 1.6 Hz, 1H), 6.57 (dd, J = 7.8, 1.4 Hz, 1H), 4.65 (s, 1H), 4.60 (d, J = 15.5 Hz, 1H), 4.32 (s, 1H), 3.60 (d, J = 15.6 Hz, 1H). **^{19}F{^{1}H}-NMR (282 MHz, $CDCl_3$)** δ -73.70. **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 165.0 (C), 136.0 (C), 135.1 (C), 133.2 (C), 132.8 (C), 128.9 (CH), 128.4 (CH), 128.0 (CH), 127.5 (CH), 126.8 (C), 124.9 (CH), 124.6 (q, J_{C-F} = 283.3 Hz, CF_3), 121.4 (CH), 117.6 (CH), 115.9 (CH), 79.0 (q, J_{C-F} = 28.2 Hz, C), 66.9 (CH), 58.1 (CH_2); **HRMS (ESI/Q-TOF)** m/z [M + H]$^+$ calcd for $C_{23}H_{19}ClF_3N_2O_2^+$ 447.1082, found 447.1088.

Characterization of **7.3ae''**: **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 8.41 (s, 1H), 7.39 (d, J = 8.7 Hz, 2H), 7.25 7.20 (m, 3H), 7.10-7.07 (m, 2H), 7.02 (d, J = 8.9 Hz, 2H), 6.94 (ddd, J = 8.1, 7.4, 1.4 Hz, 1H), 6.83 (d, J = 7.7 Hz, 1H), 6.68 (td, J = 7.7, 1.3 Hz, 1H), 6.35 (dd, J = 7.8, 1.4 Hz, 1H), 4.96–4.81 (m, 1H), 4.63 (s, 1H), 4.31 (d, J = 15.8 Hz, 1H). **^{19}F{^{1}H}-NMR (282 MHz, $CDCl_3$)** δ -74.60. **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 164.7 (C), 136.4 (C), 135.0 (C), 133.3 (C), 132.6 (C), 128.9 (CH), 128.6 (q, J_{C-F} = 2.2 Hz, CH), 127.9 (CH), 127.7 (CH), 127.4 (CH), 125.5 (C), 125.0 (CH), 124.7 (q, J_{C-F} = 286.4 Hz, CF_3), 120.3 (CH), 116.9 (CH), 115.5 (CH), 77.8 (q, J_{C-F} = 27.6 Hz, C), 66.3 (CH), 56.9 (CH_2); **HRMS (ESI/Q-TOF)** m/z [M + H]$^+$ calcd for $C_{23}H_{19}ClF_3N_2O_2^+$ 447.1082, found 447.1085.

4-Benzyl-3-(1-(4-bromophenyl)-2,2,2-trifluoro-1-hydroxyethyl)-3,4-dihydroquinoxalin-2-one (7.3af)



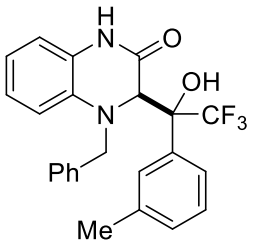
Using 4-benzyl-3,4-dihydroquinoxalin-2-one (**7.1a**, 62 mg, 0.26 mmol, 1.3 equiv.) and 1-(4-bromophenyl)-2,2,2-trifluoroethan-1-one (**7.2f**, 30 μL, 0.2 mmol, 1 equiv.), according to GP-1, compound **7.3af** was obtained as a mixture of diastereomers (1.4:1 dr) that were separated by column chromatography using hexane:EtOAc mixtures (from 95:5 to 75:25): **7.3af'** (36.3 mg, 0.08 mmol, 37% yield, yellow oil) and **7.3af''** (26.4 mg, 0.05 mmol, 27% yield, yellow oil).

Characterization of **7.3af'**: **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 9.10 (s, 1H), 7.63–7.38 (m, 4H), 7.24-7.21 (m, 3H), 7.07–6.92 (m, 4H), 6.87 (td, J = 7.5, 1.6 Hz, 1H), 6.58 (dd, J = 7.8, 1.4 Hz, 1H), 4.66 (s, 1H), 4.63 (d, J = 15.4 Hz, 1H), 4.34 (s, 1H), 3.63 (d, J = 15.5 Hz, 1H). **^{19}F{^{1}H}-NMR (282 MHz, $CDCl_3$)** δ -73.68. **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 165.0 (C), 136.0 (C), 133.7 (C), 132.8 (C), 131.3 (CH), 128.9 (CH), 128.3

(q, J_{C-F} = 1.8 Hz, CH), 128.0 (CH), 127.5 (CH), 126.9 (C), 124.9 (q, J_{C-F} = 286.9 Hz, CF_3), 124.86 (CH), 123.4 (C), 121.5 (CH), 117.6 (CH), 115.9 (CH), 79.1 (q, J_{C-F} = 28.2 Hz, C), 66.8 (CH), 58.1 (CH_2); **HRMS (ESI/Q-TOF)** *m/z* [M + H]$^+$ calcd for $C_{23}H_{19}BrF_3N_2O_2^+$ 491.0577, found 491.0570.

Characterization of **7.3af"**: **^{1}H-NMR (500 MHz, $CDCl_3$)** δ 7.55 (s, 1H), 7.32 (d, *J* = 8.7 Hz, 2H), 7.27 – 7.21 (m, 3H), 7.17 (d, *J* = 8.7 Hz, 2H), 7.08 (d, *J* = 8.1 Hz, 2H), 6.94 (t, *J* = 7.8 Hz, 1H), 6.84 (d, *J* = 8.0 Hz, 1H), 6.69 (t, *J* = 7.6 Hz, 1H), 6.32 (d, *J* = 7.8 Hz, 1H), 4.90 (d, *J* = 16.0 Hz, 1H), 4.85 (s, 1H), 4.63 (s, 1H), 4.34 (d, *J* = 15.9 Hz, 1H). **^{19}F{^{1}H}-NMR (282 MHz, $CDCl_3$)** δ -74.60. **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 164.6 (C), 136.4 (C), 133.3 (C), 133.1 (C), 130.7 (CH), 128.9 (CH), 127.9 (CH), 127.4 (CH), 125.5 (C), 125.0 (CH), 123.4 (C), 120.4 (CH), 117.0 (CH), 115.5 (CH), 77.8 (q, J_{C-F} = 27.1 Hz), 66.3 (CH), 57.0 (CH_2); **HRMS (ESI/Q-TOF)** *m/z* [M + H]$^+$ calcd for $C_{23}H_{19}BrF_3N_2O_2^+$ 491.0577, found 491.0572.

4-Benzyl-3-(2,2,2-trifluoro-1-hydroxy-1-(m-tolyl)ethyl)-3,4-dihydroquinoxalin-2-one (7.3ag)

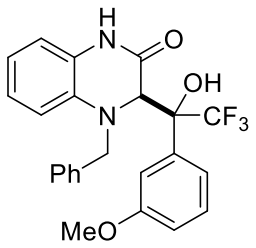


Using 4-benzyl-3,4-dihydroquinoxalin-2-one (**7.1a**, 62 mg, 0.26 mmol, 1.3 equiv.) and 2,2,2-trifluoro-1-(m-tolyl)ethan-1-one (**7.2g**, 31 μL, 0.2 mmol, 1 equiv.), according to GP-1, compound **7.3ag** was obtained as a mixture of diastereomers (1.4:1 dr) that were separated by column chromatography using hexane:EtOAc mixtures (from 95:5 to 75:25): **7.3ag'** (24.8 mg, 0.06 mmol, 31% yield, yellow oil) and **7.3ag"** (19.6 mg, 0.05 mmol, 24% yield, yellow oil).

Characterization of **7.3ag'**: **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 8.89 (s, 1H), 7.40 (d, *J* = 10.2 Hz, 2H), 7.32–7.25 (m, 1H), 7.26–7.15 (m, 4H), 7.00 (td, *J* = 7.8, 7.4, 1.5 Hz, 1H), 6.96–6.87 (m, 3H), 6.81 (td, *J* = 7.6, 1.3 Hz, 1H), 6.62 (dd, *J* = 7.8, 1.1 Hz, 1H), 4.73 (s, 1H), 4.56 (d, *J* = 15.7 Hz, 1H), 4.34 (s, 1H), 3.45 (d, *J* = 15.8 Hz, 1H), 2.36 (s, 3H). **^{19}F{^{1}H}-NMR (282 MHz, $CDCl_3$)** δ -73.13. **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 165.5 (C), 138.0 (C), 136.3 (C), 134.7 (C), 133.2 (C), 129.7 (CH), 128.8 (CH), 128.1 (CH), 127.8 (CH), 127.4 (CH), 127.2 (q, J_{C-F} = 1.8 Hz, CH), 126.5 (C), 124.7 (CH), 123.6 (q, J_{C-F} = 2.8 Hz, CH), 120.7 (CH), 116.8 (CH), 115.8 (CH), 79.4 (q, J_{C-F} = 27.9 Hz, C), 67.3 (CH), 57.3 (CH_2), 21.6 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* [M + H]$^+$ calcd for $C_{24}H_{22}F_3N_2O_2^+$ 427.1628, found 427.1633. Characterization of **7.3ag"**: **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 8.32 (s, 1H), 7.41–7.17 (m, 5H), 7.14–7.04 (m, 2H), 7.03–6.89 (m, 3H), 6.83 (d, *J* = 7.8 Hz, 1H), 6.64 (td, *J* = 7.6, 1.3 Hz, 1H), 6.37 (dd, *J* = 7.8, 1.4 Hz, 1H), 4.85 (d, *J* = 16.0 Hz, 1H), 4.72 (s, 1H), 4.65 (s, 1H), 4.25 (d, *J* = 16.0 Hz, 1H), 2.08

(s, 3H). **^{19}F{^{1}H}-NMR (282 MHz, $CDCl_3$)** δ -74.36. **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 164.8 (C), 137.5 (C), 136.6 (C), 134.0 (C), 133.7 (C), 129.5 (CH), 128.8 (CH), 127.8 (CH), 127.6 (CH), 127.3 (CH), 126.1 (q, J_{C-F} = 281.4 Hz, CF_3), 125.6 (C), 124.7 (CH), 123.9 (q, J_{C-F} = 1.8 Hz, CH), 119.9 (CH), 116.3 (CH), 115.3 (CH), 78.5 (q, J_{C-F} = 27.6 Hz, C), 66.5 (CH), 56.4 (q, J_{C-F} = 1.7 Hz, CH_2), 21.3 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{24}H_{22}F_3N_2O_2^+$ 427.1628, found 427.1621.

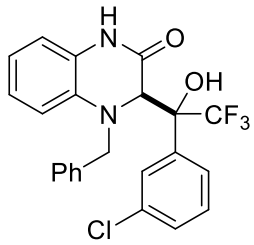
4-Benzyl-3-(2,2,2-trifluoro-1-hydroxy-1-(3-methoxyphenyl)ethyl)-3,4-dihydroquinoxalin-2-one (7.3ah)



Using 4-benzyl-3,4-dihydroquinoxalin-2-one (**7.1a**, 62 mg, 0.26 mmol, 1.3 equiv.) and 2,2,2-trifluoro-1-(3-methoxyphenyl)ethan-1-one (**7.2h**, 32 μL, 0.2 mmol, 1 equiv.), according to GP-1, compound **7.3ah** was obtained as a mixture of diastereomers (1.1:1 dr) that were separated by column chromatography using hexane:EtOAc mixtures (from 95:5 to 75:25): **7.3ah'** (23.1mg, 0.05 mmol, 26% yield, yellow oil) and **7.3ah"** (20.6 mg, 0.05 mmol, 24% yield, yellow oil).

Characterization of **7.3ah'**: **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 9.26 (s, 1H), 7.31 (t, J = 8.2 Hz, 1H), 7.23–7.17 (m, 5H), 7.10–6.87 (m, 5H), 6.81 (td, J = 7.5, 1.4 Hz, 1H), 6.64 (dd, J = 7.8, 1.4 Hz, 1H), 4.83 (s, 1H), 4.59 (d, J = 15.7 Hz, 1H), 4.35 (s, 1H), 3.78 (s, 3H), 3.49 (d, J = 15.7 Hz, 1H). **^{19}F{^{1}H}-NMR (282 MHz, $CDCl_3$)** δ -73.15. **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 165.6 (C), 159.6 (C), 136.3 (C), 133.1 (C), 129.3 (CH), 128.8 (CH), 127.9 (CH), 127.4 (CH), 126.5 (C), 125.1 (q, J_{C-F} = 287.5 Hz, CF_3), 124.8 (CH), 120.8 (CH), 118.9 (q, J_{C-F} = 2.2 Hz, CH), 116.9 (CH), 115.9 (CH), 114.6 (CH), 112.2 (q, J_{C-F} = 2.0 Hz, CH), 79.3 (q, J_{C-F} = 27.6 Hz, C), 67.2 (CH), 57.4 (CH_2), 55.2 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{24}H_{22}F_3N_2O_3^+$ 443.1577, found 443.1579.
Characterization of **7.3ah"**: **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 8.97 (s, 1H), 7.25–7.15 (m, 3H), 7.09-7.00 (m, 5H), 6.92 (ddd, J = 8.7, 7.3, 1.5 Hz, 1H), 6.80 (dd, J = 8.1, 1.3 Hz, 1H), 6.74 (ddd, J = 7.7, 2.5, 1.4 Hz, 1H), 6.65 (td, J = 7.6, 1.3 Hz, 1H), 6.44 (dd, J = 7.8, 1.4 Hz, 1H), 4.81 (d, J = 16.0 Hz, 1H), 4.74 (s, 1H), 4.66 (s, 1H), 4.19 (d, J = 16.0 Hz, 1H), 3.60 (s, 3H). **^{19}F{^{1}H}-NMR (282 MHz, $CDCl_3$)** δ -74.18. **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 164.7 (C), 159.1 (C), 136.6 (C), 135.9 (C), 133.7 (C), 128.8 (CH), 128.8 (CH), 127.8 (CH), 127.3 (CH), 125.8 (C), 124.7 (CH), 119.9 (CH), 119.3 (q, J_{C-F} = 1.7 Hz, CH), 116.2 (CH), 115.5 (CH), 114.8 (CH), 112.5 (q, J_{C-F} = 1.7 Hz, CH), 78.7 (q, J_{C-F} = 27.6 Hz, C), 66.4 (CH), 56.4 (CH_2), 55.0 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{24}H_{22}F_3N_2O_3^+$ 443.1577, found 443.1583.

4-Benzyl-3-(1-(3-chlorophenyl)-2,2,2-trifluoro-1-hydroxyethyl)-3,4-dihydroquinoxalin -2-one (7.3ai)

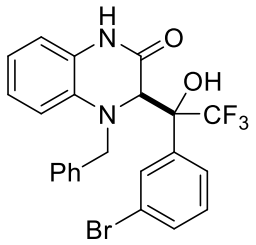


Using 4-benzyl-3,4-dihydroquinoxalin-2-one (**7.1a**, 62 mg, 0.26 mmol, 1.3 equiv.) and 1-(3-chlorophenyl)-2,2,2-trifluoroethan-1-one (**7.2i**, 29 μL, 0.2 mmol, 1 equiv.), according to GP-1, compound **7.3ai** was obtained as a mixture of diastereomers (1.2:1 dr) that were separated by column chromatography using hexane:EtOAc mixtures (from 95:5 to 75:25): **7.3ai'** (30.0 mg, 0.07 mmol, 33% yield, yellow oil) and **7.3ai''** (24.6 mg, 0.05 mmol, 28% yield, yellow oil).

Characterization of **7.3ai'**: **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 8.38 (s, 1H), 7.48 (t, J = 2.0 Hz, 1H), 7.37 (d, J = 7.9 Hz, 1H), 7.26–7.20 (m, 3H), 7.17–7.05 (m, 3H), 7.01 (d, J = 8.0 Hz, 1H), 6.98–6.91 (m, 1H), 6.86 (d, J = 7.3 Hz, 1H), 6.66 (td, J = 7.7, 1.4 Hz, 1H), 6.37 (dd, J = 7.8, 1.3 Hz, 1H), 4.94 (s, 1H), 4.90 (d, J = 16.0 Hz, 1H), 4.64 (s, 1H), 4.31 (d, J = 16.0 Hz, 1H); **^{19}F{^{1}H}-NMR (282 MHz, $CDCl_3$)** δ -74.58; **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 164.6 (C), 136.4 (C), 136.1 (C), 135.5 (C), 134.0 (C), 133.3 (C), 129.0 (CH), 128.9 (CH), 128.8 (CH), 127.9 (CH), 127.7 (q, J_{C-F} = 2.2 Hz, CH), 127.4 (CH), 125.4 (C), 125.3 (q, J_{C-F} = 1.6 Hz, CH), 125.1 (CH), 124.6 (q, J_{C-F} = 285.8 Hz, CF_3), 120.5 (CH), 117.0 (CH), 115.5 (CH), 77.8 (q, J_{C-F} = 27.6 Hz, C), 66.2 (CH), 57.0 (q, J_{C-F} = 1.7 Hz, CH_2); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{23}H_{19}ClF_3N_2O_2^+$ 447.1082, found 447.1085.

Characterization of **7.3ai''**: **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 8.97 (s, 1H), 7.60 (t, J = 1.7 Hz, 1H), 7.49 (d, J = 7.6 Hz, 1H), 7.37 (dt, J = 8.0, 1.5 Hz, 1H), 7.32 (d, J = 7.9 Hz, 1H), 7.26–7.19 (m, 3H), 7.03 (ddd, J = 8.5, 7.3, 1.4 Hz, 1H), 6.99–6.91 (m, 3H), 6.88–6.80 (m, 1H), 6.63 (dd, J = 7.8, 1.3 Hz, 1H), 4.78 (s, 1H), 4.61 (d, J = 15.5 Hz, 1H), 4.33 (s, 1H), 3.56 (d, J = 15.5 Hz, 1H); **^{19}F{^{1}H}-NMR (282 MHz, $CDCl_3$)** δ -73.52; **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 165.1 (C), 136.7 (C), 135.9 (C), 134.5 (C), 132.8 (C), 129.4 (CH), 129.1 (CH), 128.9 (CH), 128.0 (CH), 127.5 (CH), 127.1 (q, J_{C-F} = 2.2 Hz, CH), 127.02 (q, J_{C-F} = 295.8 Hz, CF_3), 126.7 (C), 124.9 (CH), 124.7 (q, J_{C-F} = 2.2 Hz, CH), 121.4 (CH), 117.6 (CH), 115.9 (CH), 78.9 (q, J_{C-F} = 28.2 Hz, C), 66.9 (CH), 58.1 (CH_2); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{23}H_{19}ClF_3N_2O_2^+$ 447.1082, found 447.1090.

4-Benzyl-3-(1-(3-bromophenyl)-2,2,2-trifluoro-1-hydroxyethyl)-3,4-dihydroquinoxalin-2-one (7.3aj)

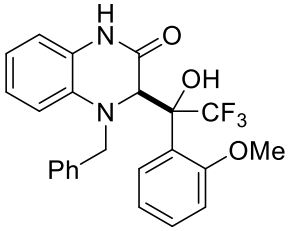


Using 4-benzyl-3,4-dihydroquinoxalin-2-one (**7.1a**, 62 mg, 0.26 mmol, 1.3 equiv.) and 1-(3-bromophenyl)-2,2,2-trifluoroethan-1-one (**7.2j**, 30 μL, 0.2 mmol, 1 equiv.), according to GP-1, compound **7.3aj** was obtained as a mixture of diastereomers (1.2:1 dr) that were separated by column chromatography using hexane:EtOAc mixtures (from 95:5 to 75:25): **7.3aj'** (33.9 mg, 0.07 mmol, 35% yield, yellow oil) and **7.3aj"** (28.8 mg, 0.06 mmol, 29% yield, yellow oil).

Characterization of **7.3aj'**: **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 8.96 (s, 1H), 7.76 (t, J = 1.9 Hz, 1H), 7.53 (tdd, J = 7.9, 1.9, 1.0 Hz, 2H), 7.30–7.17 (m, 4H), 7.03 (ddd, J = 8.5, 7.2, 1.4 Hz, 1H), 6.99–6.92 (m, 3H), 6.85 (td, J = 7.5, 1.5 Hz, 1H), 6.62 (dd, J = 7.8, 1.4 Hz, 1H), 4.80 (s, 1H), 4.61 (d, J = 15.5 Hz, 1H), 4.32 (d, J = 1.0 Hz, 1H), 3.55 (d, J = 15.6 Hz, 1H); **^{19}F{^{1}H}-NMR (282 MHz, $CDCl_3$)** δ -73.48; **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 165.1 (C), 136.9 (C), 135.9 (C), 132.8 (C), 132.1 (CH), 130.0 (q, J_{C-F} = 2.2 Hz, CH), 129.7 (CH), 128.9 (CH), 128.0 (CH), 127.6 (CH), 126.8 (C), 125.2 (q, J_{C-F} = 2.2 Hz, CH), 125.0 (CH), 122.6 (C), 121.4 (CH), 117.6 (CH), 115.9 (CH), 78.8 (q, J_{C-F} = 28.2 Hz, C), 66.9 (CH), 58.2 (CH_2); **HRMS (ESI/Q-TOF)** *m/z* [M + H]$^+$ calcd for $C_{23}H_{19}BrF_3N_2O_2^+$ 491.0577, found 491.0580.

Characterization of **7.3aj"**: **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 8.81 (s, 1H), 7.64 (d, J = 1.9 Hz, 1H), 7.43 (d, J = 7.9 Hz, 1H), 7.30 (dd, J = 1.9, 1.0 Hz, 1H), 7.25–7.20 (m, 4H), 7.08 (dd, J = 7.2, 2.3 Hz, 1H), 6.98–6.92 (m, 2H), 6.87 (dd, J = 7.9, 1.3 Hz, 1H), 6.67 (td, J = 7.5, 1.4 Hz, 1H), 6.38 (dd, J = 7.8, 1.4 Hz, 1H), 4.97 (s, 1H), 4.90 (d, J = 15.8 Hz, 1H), 4.64 (s, 1H), 4.30 (d, J = 15.9 Hz, 1H); **^{19}F{^{1}H}-NMR (282 MHz, $CDCl_3$)** δ -74.53; **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 164. (C), 136.39 (C), 136.36 (C), 133.3 (C), 131.9 (CH), 130.5 (q, J_{C-F} = 2.2 Hz, CH), 129.0 (CH), 128.9 (CH), 127.9 (CH), 127.4 (CH), 125.7 (q, J_{C-F} = 1.8 Hz, CH), 125.5 (C), 125.2 (CH), 124.6 (q, J_{C-F} = 286.4 Hz, CF_3), 122.1 (C), 120.5 (CH), 116.9 (CH), 115.6 (CH), 77.7 (q, J_{C-F} = 27.6 Hz, C), 66.1 (CH), 57.0 (CH_2); **HRMS (ESI/Q-TOF)** *m/z* [M + H]$^+$ calcd for $C_{23}H_{19}BrF_3N_2O_2^+$ 491.0577, found 491.05781.

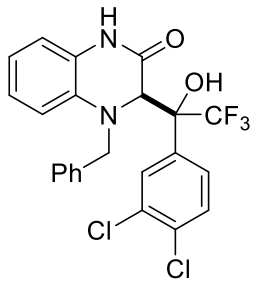
4-Benzyl-3-(2,2,2-trifluoro-1-hydroxy-1-(2-methoxyphenyl)ethyl)-3,4-dihydroquinoxalin-2-one (7.3ak)



Using 4-benzyl-3,4-dihydroquinoxalin-2-one (**7.1a**, 62 mg, 0.26 mmol, 1.3 equiv.) and 2,2,2-trifluoro-1-(2-methoxyphenyl)ethan-1-one (**7.2k**, 32 μL, 0.2 mmol, 1 equiv.), according to GP-1, compound **7.3ak** was obtained as a mixture of diastereomers (1.4:1 dr) that cannot be separated by column chromatography using hexane:EtOAc mixtures (from 95:5 to 75:25): **7.3ak' + 7.3ak"** (32.7 mg, 0.07 mmol, 37% yield, yellow oil). Representative NMR signals for either the major and the minor diastereoisomer are labelled with one or two asterisks, respectively.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.36 (s, 1H*), 9.17 (s, 1H**), 7.49-7.46 (m, 2H), 7.37 (ddd, J = 8.8, 7.4, 1.6 Hz, 1H), 7.33–7.10 (m, 10H), 7.05–6.79 (m, 10H), 6.76–6.68 (m, 2H), 6.63 (dd, J = 7.7, 1.5 Hz, 1H*), 6.61–6.51 (m, 2H), 6.02 (s, 1H**), 4.96 (d, J = 15.8 Hz, 1H**), 4.75 (s, 1H*), 4.46 (d, J = 16.0 Hz, 1H*), 4.40 (d, J = 15.5 Hz, 1H**), 3.84 (d, J = 15.5 Hz, 1H*), 3.72 (s, 3H*), 3.63 (s, 3H**); **^{19}F{^{1}H}-NMR (282 MHz, $CDCl_3$)** δ -72.60 *, -74.25**; **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 163.8 (C**), 163.2 (C*), 158.0 (C*), 157.7 (C*), 137.0 (C**), 136.8 (C*), 135.8 (C*), 134.9 (C**), 134.1 (C**), 133.9 (C*), 130.3 (CH), 130.2 (CH), 128.7 (CH), 128.6 (CH), 128.54 (CH), 128.51 (CH), 128.46 (CH), 127.53 (CH), 127.48 (CH), 127.4 (CH), 123.9 (CH), 123.5 (CH), 122.9 (C), 121.5 (CH), 121.0 (CH), 120.7 (C), 119.40 (CH), 119.38 (CH), 115.3 (CH), 115.2 (CH), 112.4 (CH), 112.2 (CH), 83.7 (q, J_{C-F} = 27.1 Hz, C*), 83.3 (q, J_{C-F} = 26.5 Hz, C**), 66.51 (CH*), 66.48 (CH**), 55.96 (CH_2), 55.94 (CH_3**), 55.86 (CH_3*); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{24}H_{22}F_3N_2O_3^+$ 443.1577, found 443.1589.

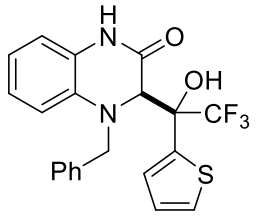
4-Benzyl-3-(1-(3,4-dichlorophenyl)-2,2,2-trifluoro-1-hydroxyethyl)-3,4-dihydroquinoxalin-2-one (7.3al)



Using 4-benzyl-3,4-dihydroquinoxalin-2-one (**7.1a**, 62 mg, 0.26 mmol, 1.3 equiv.) and 1-(3,4-dichlorophenyl)-2,2,2-trifluoroethan-1-one (**7.2l**, 32 μL, 0.2 mmol, 1 equiv.), according to GP-1, compound **7.3al** (41.2 mg, 0.09 mmol, 43% yield, yellow oil) was obtained as a mixture of diastereomers (1.3:1 dr) that were separated by column chromatography using hexane:EtOAc mixtures (from 95:5 to 75:25): **7.3al'** (23.4 mg, 0.05 mmol, 25% yield, yellow oil) and **7.3al"** (17.8 mg, 0.04 mmol, 18% yield, yellow oil).

Characterization of **7.3al'**: **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 8.84 (s, 1H), 7.68 (t, J = 1.2 Hz, 1H), 7.42 (t, J = 1.1 Hz, 2H), 7.25-7.23 (m, 3H), 7.09–6.95 (m, 4H), 6.88 (ddd, J = 7.8, 7.0, 1.8 Hz, 1H), 6.60 (dd, J = 7.8, 1.4 Hz, 1H), 4.69 (s, 1H), 4.64 (d, J = 15.4 Hz, 1H), 4.33 (s, 1H), 3.71 (d, J = 15.4 Hz, 1H); **^{19}F{^{1}H}-NMR (282 MHz, $CDCl_3$)** δ -73.87; **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 164.7 (C), 135.7 (C), 134.8 (C), 133.3 (C), 132.6 (C), 132.6 (C), 130.0 (CH), 129.0 (q, J_{C-F} = 1.9 Hz, CH), 128.9 (CH), 128.2 (CH), 127.6 (CH), 127.0 (C), 125.94 (q, J_{C-F} = 1.8 Hz, CH), 125.91 (q, J_{C-F} = 274.5 Hz, CF_3), 125.0 (CH), 121.9 (CH), 118.1 (CH), 115.9 (CH), 78.5 (q, J_{C-F} = 28.2 Hz, C), 66.7 (CH), 58.7 (CH_2); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{23}H_{18}Cl_2F_3N_2O_2^+$ 481.0692, found 481.0699. Characterization of **7.3al''**: **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 8.00 (s, 1H), 7.57 (d, J = 2.2 Hz, 1H), 7.31 (dd, J = 8.6, 2.3 Hz, 1H), 7.26–7.21 (m, 3H), 7.14–7.06 (m, 3H), 6.97 (ddd, J = 8.6, 7.2, 1.4 Hz, 1H), 6.91–6.86 (m, 1H), 6.70 (td, J = 7.6, 1.4 Hz, 1H), 6.36 (dd, J = 7.8, 1.4 Hz, 1H), 5.02 (s, 1H), 4.93 (d, J = 15.9 Hz, 1H), 4.63 (s, 1H), 4.37 (d, J = 15.8 Hz, 1H); **^{19}F{^{1}H}-NMR (282 MHz, $CDCl_3$)** δ -74.83; **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 164.4 (C), 136.3 (C), 134.2 (C), 133.2 (C), 133.2 (C), 132.1 (C), 129.7 (q, J_{C-F} = 2.2 Hz, CH), 129.4 (CH), 128.9 (CH), 128.0 (CH), 127.4 (CH), 126.6 (q, J_{C-F} = 2.2 Hz, CH), 125.31 (CH), 125.28 (C), 120.7 (CH), 117.3 (CH), 115.4 (CH), 77.2 (q, J_{C-F} = 32.1 Hz, C), 66.1 (CH), 57.3 (q, J_{C-F} = 1.7 Hz, CH_2); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{23}H_{18}Cl_2F_3N_2O_2^+$ 481.0692, found 481.0697.

4-Benzyl-3-(2,2,2-trifluoro-1-hydroxy-1-(thiophen-2-yl)ethyl)-3,4-dihydroquinoxalin-2-one (7.3am)



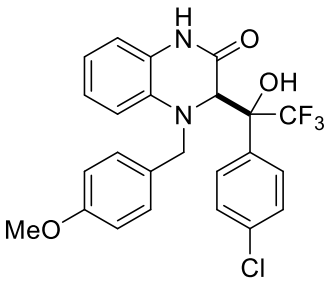
Using 4-benzyl-3,4-dihydroquinoxalin-2-one (**7.1a**, 62 mg, 0.26 mmol, 1.3 equiv.) and 2,2,2-trifluoro-1-(thiophen-2-yl)ethan-1-one (**7.2m**, 26 μL, 0.2 mmol, 1 equiv.), according to GP-1, compound **7.3am** was obtained as a mixture of diastereomers (1.4:1 dr) that were separated by column chromatography using hexane:EtOAc mixtures (from 95:5 to 75:25): **7.3am'** (25.1mg, 0.06 mmol, 30% yield, yellow oil) and **7.3am''** (18.4 mg, 0.04 mmol, 22% yield, yellow oil).

Characterization of **7.3am'**: **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 8.74 (s, 1H), 7.38 (dd, J = 5.1, 1.2 Hz, 1H), 7.24–7.17 (m, 4H), 7.06 (dd, J = 5.1, 3.7 Hz, 1H), 7.03–6.92 (m, 4H), 6.84 (ddd, J = 7.8, 6.8, 1.9 Hz, 1H), 6.67 (dd, J = 7.7, 1.3 Hz, 1H), 5.37 (s, 1H), 4.64 (d, J = 15.7 Hz, 1H), 4.34 (s, 1H), 3.47 (d, J = 15.7 Hz, 1H); **^{19}F{^{1}H}-NMR (282 MHz, $CDCl_3$)** δ -75.61; **^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$)** δ 166.0 (C), 138.8 (C), 136.2 (C), 133.0 (C), 128.80 (CH), 127.96 (CH), 127.5 (CH), 126.7 (CH), 126.53 (q, J_{C-F} = 2.2 Hz, CH), 126.4 (C), 124.9 (CH), 124.5 (q, J_{C-F} = 286.9 Hz, CF_3), 121.2 (CH), 117.9 (CH),

115.8 (CH), 78.5 (q, J_{C-F} = 29.3 Hz, C), 67.4 (CH), 58.2 (CH_2); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{21}H_{18}F_3N_2O_2S^+$ 419.1036, found 419.1039.

Characterization of **7.3am"**: **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 8.17 (s, 1H), 7.29–7.18 (m, 4H), 7.16–7.05 (m, 3H), 7.02–6.87 (m, 1H), 6.82 (dt, *J* = 3.6, 1.1 Hz, 1H), 6.73–6.61 (m, 2H), 6.39 (dd, *J* = 7.8, 1.3 Hz, 1H), 5.41 (s, 1H), 4.98 (d, *J* = 16.1 Hz, 1H), 4.66 (s, 1H), 4.39 (d, *J* = 16.0 Hz, 1H); **^{19}F{^{1}H}-NMR (282 MHz, $CDCl_3$)** δ -76.67; **^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$)** δ 165.1 (C), 138.0 (C), 137.9 (C), 136.6 (C), 133.5 (C), 129.1 (CH), 128.9 (CH), 127.9 (CH), 127.3 (CH), 127.1 (CH), 126.7 (CH), 125.0 (CH), 120.1 (CH), 116.9 (CH), 115.4 (CH), 78.5 (q, J_{C-F} = 29.6 Hz, C), 66.2 (CH), 56.7 (CH_2); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{21}H_{18}F_3N_2O_2S^+$ 419.1036, found 419.1037.

3-(1-(4-Chlorophenyl)-2,2,2-trifluoro-1-hydroxyethyl)-4-(4-methoxybenzyl)-3,4-dihydroquinoxalin-2-one (7.3be)



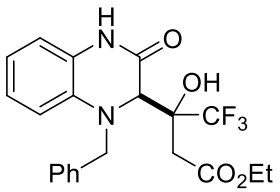
Using 4-(4-methoxybenzyl)-3,4-dihydroquinoxalin-2-one (**7.1b**, 69.8 mg, 0.26 mmol, 1.3 equiv.) and 1-(4-chlorophenyl)-2,2,2-trifluoroethan-1-one (**7.2e**, 30 μL, 0.2 mmol, 1 equiv.), according to GP-1, compound **7.3be** was obtained as a mixture of diastereomers (1.5:1 dr) that were separated by column chromatography using hexane:EtOAc mixtures (from 95:5 to 75:25): **7.3be'** (35.3 mg, 0.07 mmol, 37% yield, yellow oil) and **7.3be"** (23.7 mg, 0.05 mmol, 25% yield, yellow oil).

Characterization of **7.3be'**: **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 8.90 (s, 1H), 7.50 (d, *J* = 8.7 Hz, 2H), 7.32 (d, *J* = 8.9 Hz, 1H), 7.07–6.95 (m, 2H), 6.92–6.84 (m, 3H), 6.75 (d, *J* = 8.7 Hz, 1H), 6.56 (dd, *J* = 7.7, 1.3 Hz, 1H), 4.71 (s, 1H), 4.54 (d, *J* = 15.2 Hz, 1H), 4.31 (s, 1H), 3.73 (s, 3H), 3.58 (d, *J* = 15.2 Hz, 1H); **^{19}F{^{1}H}-NMR (282 MHz, $CDCl_3$)** δ -73.81; **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 165.1 (C), 159.3 (C), 135.0 (C), 133.2 (C), 132.9 (C), 129.0 (CH), 128.3 (CH), 127.8 (C), 127.1 (C), 124.9 (q, J_{C-F} = 272.0 Hz, CF_3), 124.8 (CH), 121.5 (CH), 118.0 (CH), 115.8 (CH), 114.2 (CH), 78.8 (q, J_{C-F} = 28.2 Hz, C), 66.3 (CH), 58.0 (CH_2), 55.2 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{24}H_{21}ClF_3N_2O_3^+$ 477.1187, found 477.1192.

Characterization of **7.3be"**: **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 8.24 (s, 1H), 7.38 (d, *J* = 8.6 Hz, 2H), 7.02 (d, *J* = 6.5 Hz, 2H), 6.99 (d, *J* = 6.0 Hz, 2H), 6.97–6.81 (m, 2H), 6.77 (d, *J* = 8.7 Hz, 2H), 6.69 (td, *J* = 7.6, 1.3 Hz, 1H), 6.32 (dd, *J* = 7.8, 1.4 Hz, 1H), 4.88 (s, 1H), 4.80 (d, *J* = 15.5 Hz, 1H), 4.60 (s, 1H), 4.23 (d, *J* = 15.6 Hz, 1H), 3.74 (s, 3H); **^{19}F{^{1}H}-NMR (282 MHz, $CDCl_3$)** δ -72.34; **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 164.7 (C), 159.3 (C), 135.0 (C), 133.5 (C), 132.6 (C), 128.8 (CH), 128.6 (q, J_{C-F} = 2.2 Hz,

CH), 128.3 (C), 127.7 (CH), 125.7 (C), 124.9 (CH), 120.4 (CH), 117.3 (CH), 115.4 (CH), 114.2 (CH), 77.72 (q, J_{C-F} = 27.6 Hz, C), 65.9 (CH), 56.8 (CH_2), 55.2 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* [M + H]$^+$ calcd for $C_{24}H_{21}ClF_3N_2O_3^+$ 477.1187, found 477.1189.

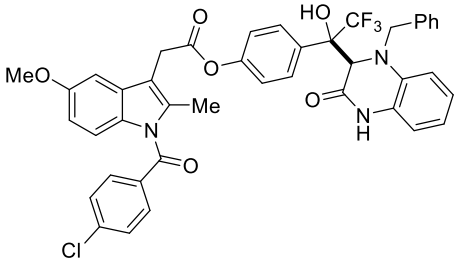
Ethyl 3-(1-benzyl-3-oxo-1,2,3,4-tetrahydroquinoxalin-2-yl)-4,4,4-trifluoro-3-hydroxybutanoate (7.3an)



Using 4-benzyl-3,4-dihydroquinoxalin-2-one (**7.1a**, 62 mg, 0.26 mmol, 1.3 equiv.) and ethyl 4,4,4-trifluoro-3-oxobutanoate (**7.2n**, 29 uL, 0.2 mmol, 1 equiv.), according to GP-1, compound **7.3an** was obtained as a mixture of diastereomers (1.2:1 dr) that cannot be separated by column chromatography using hexane:EtOAc mixtures (from 95:5 to 75:22): **7.3an' + 7.3an"** (16.9 mg, 0.04 mmol, 20% yield, yellow oil).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.27 (s, 1H), 8.25 (s, 1H), 7.32 – 7.19 (m, 6H), 7.17-7.12 (m, 4H), 7.00-6.95 (m, 2H), 6.93 – 6.86 (m, 2H), 6.85-6.79 (m, 2H), 6.74-6.69 (m, 2H), 5.80 (s, 1H), 5.46 (s, 1H), 4.91-4.84 (m, 2H), 4.58-4.43 (m, 3H), 4.34 (s, 1H), 4.26 – 4.02 (m, 4H), 3.07 (d, *J* = 16.5 Hz, 1H), 2.88 (d, *J* = 16.4 Hz, 1H), 2.76 (d, *J* = 16.3 Hz, 1H), 2.66 (d, *J* = 16.4 Hz, 1H), 1.29-1.21 (m, 6H); **^{19}F{^{1}H}-NMR (282 MHz, $CDCl_3$)** δ -77.50, -77.68; **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 171.7 (C), 171.5 (C), 163.8 (C), 163.2 (C), 136.7 (C), 136.5 (C), 133.8 (C), 133.0 (C), 128.7 (CH), 128.7 (CH), 127.8 (CH), 127.7 (CH), 127.7 (CH), 127.5 (CH), 127.1 (C), 127.0 (C), 124.4 (CH), 124.4 (CH), 120.6 (CH), 120.2 (CH), 117.2 (CH), 116.6 (CH), 115.3 (CH), 115.1 (CH), 65.1 (CH), 64.8 (CH), 61.7 (CH_2), 61.7 (CH_2), 57.9 (CH_2), 56.9 (CH_2), 35.2 (q, J_{C-F} = 1.7 Hz, CH_2), 33.9 (CH_2), 13.91 (CH_3), 13.85 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* [M + H]$^+$ calcd for $C_{21}H_{22}F_3N_2O_4^+$ 423.1526, found 423.1527.

4-(1-(1-Benzyl-3-oxo-1,2,3,4-tetrahydroquinoxalin-2-yl)-2,2,2-trifluoro-1-hydroxyethyl)phenyl 2-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl)acetate (7.3ao)



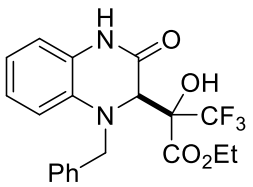
Using 4-benzyl-3,4-dihydroquinoxalin-2-one (**7.1a**, 62 mg, 0.26 mmol, 1.3 equiv.) and 4-(2,2,2-trifluoroacet-yl)phenyl 2-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl)acetate (**7.2o**, 106 mg, 0.2 mmol, 1 equiv.), according to GP-1, compound **7.3ao** was obtained as a mixture of diastereomers (1.2:1 dr) that were separated by column

chromatography using DCM:EtOAc mixtures (from 99:1 to 95:5): **7.3ao'** (54.1 mg, 0.07 mmol, 35% yield, yellow oil) and **7.3ao"** (44.2 mg, 0.06 mmol, 29% yield, yellow oil).

Characterization of **7.3ao'**: **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 8.50 (s, 1H), 7.68 (d, J = 8.7 Hz, 2H), 7.59 (d, J = 8.8 Hz, 2H), 7.48 (d, J = 8.7 Hz, 2H), 7.23 – 7.16 (m, 3H), 7.09 (d, J = 8.9 Hz, 2H), 7.06 (d, J = 2.5 Hz, 1H), 7.03 – 6.95 (m, 1H), 6.94 – 6.86 (m, 4H), 6.80 (td, J = 7.5, 1.5 Hz, 1H), 6.71 (dd, J = 9.0, 2.5 Hz, 1H), 6.61 (dd, J = 7.8, 1.3 Hz, 1H), 4.82 (s, 1H), 4.56 (d, J = 15.6 Hz, 1H), 4.29 (s, 1H), 3.92 (s, 2H), 3.84 (s, 3H), 3.48 (d, J = 15.6 Hz, 1H), 2.47 (s, 3H); **^{19}F{^{1}H}-NMR (282 MHz, $CDCl_3$)** δ -73.95; **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 169.0 (C), 168.3 (C), 165.0 (C), 156.1 (C), 151.1 (C), 139.4 (C), 136.3 (C), 136.0 (C), 133.8 (C), 133.0 (C), 132.4 (C), 131.2 (CH), 130.9 (C), 130.5 (C), 129.2 (CH), 128.8 (CH), 127.9 (CH), 127.9 (q, J_{C-F} = 1.5 Hz, CH), 127.5 (CH), 126.6 (C), 124.8 (CH), 121.2 (CH), 121.2 (CH), 117.4 (CH), 115.8 (CH), 115.0 (CH), 111.8 (C), 111.7 (CH), 101.3 (CH), 78.9 (q, J_{C-F} = 28.2 Hz, C), 67.0 (CH), 57.9 (CH_2), 55.8 (CH_3), 30.6 (CH_2), 13.4 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* [M + H]$^+$ calcd for $C_{42}H_{34}ClF_3N_3O_6^+$ 768.2083, found 768.2099.

Characterization of **7.3ao"**: **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 8.21 (s, 1H), 7.66 (d, J = 8.7 Hz, 2H), 7.53 – 7.36 (m, 4H), 7.25 – 7.14 (m, 3H), 7.10 – 7.03 (m, 2H), 7.00 (d, J = 2.5 Hz, 1H), 6.94 – 6.83 (m, 2H), 6.82 – 6.74 (m, 3H), 6.69 (dd, J = 9.0, 2.5 Hz, 1H), 6.60 (td, J = 7.6, 1.3 Hz, 1H), 6.35 (dd, J = 7.8, 1.3 Hz, 1H), 4.89 – 4.77 (m, 2H), 4.61 (s, 1H), 4.25 (d, J = 15.9 Hz, 1H), 3.85 (s, 2H), 3.83 (s, 3H), 2.42 (s, 3H); **^{19}F{^{1}H}-NMR (282 MHz, $CDCl_3$)** δ -74.88; **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 168.8 (C), 168.3 (C), 164.6 (C), 156.1 (C), 151.0 (C), 139.4 (C), 136.5 (C), 136.2 (C), 133.8 (C), 133.3 (C), 131.8 (C), 131.2 (CH), 130.8 (C), 130.4 (C), 129.2 (CH), 128.8 (CH), 128.3 (d, J_{C-F} = 1.4 Hz, CH), 127.8 (CH), 127.3 (CH), 125.6 (C), 124.8 (CH), 120.5 (CH), 120.2 (CH), 116.5 (CH), 115.6 (CH), 115.0 (CH), 111.8 (C), 111.6 (CH), 101.3 (CH), 78.1 (d, J_{C-F} = 27.4 Hz, C), 66.5 (CH), 56.6 (CH_2), 55.7 (CH_3), 30.5 (CH_2), 13.4 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* [M + H]$^+$ calcd for $C_{42}H_{34}ClF_3N_3O_6^+$ 768.2083, found 768.2102.

Ethyl 2-(1-benzyl-3-oxo-1,2,3,4-tetrahydroquinoxalin-2-yl)-3,3,3-trifluoro-2-hydroxypropanoate (7.6)



Using 4-benzyl-3,4-dihydroquinoxalin-2-one (**7.1a**, 23.8 mg, 0.1 mmol, 1 equiv.) and ethyl 3,3,3-trifluoropyruvate (**7.5**, 17 μL, 0.13 mmol, 1.3 equiv.), according to SP-1, compound **7.6** was obtained as a mixture of diastereomers (1.2:1 dr) that were separated by column chromatography using hexane:EtOAc mixtures (from 95:5 to 75:25): **7.6'** (5.5 mg, 0.014 mmol, 14% yield, yellow oil) and **7.6"** (4.7 mg, 0.011 mmol, 11% yield, yellow oil).

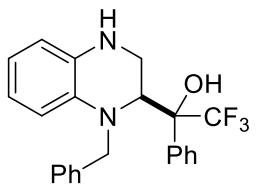
Characterization of **7.6'**: **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 8.49 (s, 1H), 7.26–7.22 (m, 3H), 7.07 (dd, *J* = 7.2, 2.4 Hz, 2H), 7.01–6.83 (m, 3H), 6.72 (dd, *J* = 7.9, 1.6 Hz, 1H), 4.63 (d, *J* = 15.1 Hz, 1H), 4.57 (s, 1H), 4.53–4.36 (m, 1H), 4.29–4.16 (m, 1H), 4.19 (d, *J* = 15.0 Hz, 1H), 3.78 (s, 1H), 1.35 (t, *J* = 7.2 Hz, 3H); **^{19}F{^{1}H}-NMR (282 MHz, $CDCl_3$)** δ -73.97; **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 167.95 (q, J_{C-F} = 1.1 Hz, C), 161.8 (C), 136.1 (C), 133.2 (C), 129.2 (C), 128.7 (CH), 128.0 (CH), 127.8 (CH), 125.6 (q, J_{C-F} = 266.5 Hz, CF_3), 124.0 (CH), 121.9 (CH), 119.1 (CH), 115.6 (CH), 81.3 (q, J_{C-F} = 29.3 Hz, C), 64.3 (CH_2), 63.6 (CH), 59.3 (CH_2), 13.9 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{20}H_{20}F_3N_2O_4^+$ 409.1370, found 409.1373.

Characterization of **7.6''**: **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 8.62 (s, 1H), 7.25–7.21 (m, 2H), 7.15 (dd, *J* = 7.9, 1.7 Hz, 2H), 6.99-6.84 (m, 3H), 6.79 (td, *J* = 7.5, 1.4 Hz, 1H), 6.70 (dd, *J* = 7.8, 1.5 Hz, 1H), 4.94 (d, *J* = 15.9 Hz, 1H), 4.77 (s, 1H), 4.50–4.18 (m, 4H), 1.34 (t, *J* = 7.2 Hz, 3H); **^{19}F{^{1}H}-NMR (282 MHz, $CDCl_3$)** δ -73.71; **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 167.7 (C), 163.8 (C), 136.7 (C), 133.2 (C), 128.7 (CH), 127.6 (CH), 127.3 (CH), 127.1 (C), 124.3 (CH), 120.1 (CH), 116.3 (CH), 115.0 (CH), 79.8 (q, J_{C-F} = 28.7 Hz, C), 65.4 (CH), 64.6 (CH_2), 56.0 (q, J_{C-F} = 1.7 Hz, CH_2), 13.7 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{20}H_{20}F_3N_2O_4^+$ 409.1370, found 409.1378.

Specific Procedure 1 (SP-1) for the Large-Scale Photocatalytic Reaction between 3,4-dihydroquinoxalin-2-one 7.1a and Trifluoroacetophenone (7.2a) under Sunlight Irradiation

In an ovendried Schlenk tube, 4-benzyl-3,4-dihydroquinoxalin-2-one (**7.1a**, 465 mg, 1.95 mmol, 1.3 equiv.) and $Ru(bpy)_3Cl_2$ (**A**, 7.5 mg, 1 mol %) were placed and the flask was evacuated and backfilled with Ar (x3). Then, anhydrous and degassed MeCN (10 mL), as well as 2,2,2-trifluoroacetophenone (**7.2a**, 316 μL, 1.5 mmol 1 equiv.) was added via syringe. The reaction mixture placed at the upper part of the building in sunny hours and was stirred for 2.5 h (see page 434 for further details about the photochemical setup). Once the reaction was finished (TLC), the mixture was purified by column chromatography using hexane:EtOAc mixtures to afford compound **7.3aa** (495 mg, 1.2 mmol, 80% yield) as a mixture of diastereomers (**3aa'** and **3aa''**, 1.1:1 dr).

Specific Procedure 2 (SP-2) for the reduction of compound 7.3aa



In a 50 mL round bottomed flask equipped with a condenser, compound **7.3aa** (78.4 mg, 0.19 mmol, 1 eq.) was placed. The flask was purged with N_2 and then dry THF (5 mL) was added. The solution was cooled down to 0 °C and $LiAlH_4$ (125 μL, 0.76 mmol, 4 equiv., 4M in THF) was added dropwise. The

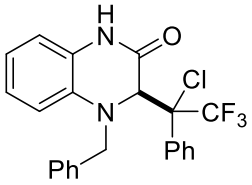
reaction mixture was progressively warmed up and heated (in an oil bath) at reflux temperature for 2 h. After this period, the reaction mixture was cooled down again to 0 °C and the excess of $LiAlH_4$ was quenched with sat. aq. NH_4Cl (5 mL) and the organics were extracted with DCM (x3). The combined organic layers were washed with brine (x1) and dried over anhydrous $MgSO_4$. After evaporating the solvent, the residue was purified by column chromatography using hexane:EtOAc mixtures, obtaining quinoxaline derivative **7.7'** (27.8 mg, 0.068 mmol, 36% yield, yellow oil) and **7.7"** (25.7 mg, 0.062 mmol, 34% yield, yellow oil).

1-(1-Benzyl-1,2,3,4-tetrahydroquinoxalin-2-yl)-2,2,2-trifluoro-1-phenylethan-1-ol (7.7)

Characterization of **7.7'**: **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 7.62 (dd, J = 6.4, 2.8 Hz, 2H), 7.52–7.33 (m, 4H), 7.22–7.08 (m, 3H), 6.90 (dd, J = 7.4, 2.2 Hz, 2H), 6.79–6.67 (m, 2H), 6.60 (td, J = 7.5, 1.2 Hz, 1H), 6.49 (dd, J = 8.3, 1.0 Hz, 1H), 4.11 (d, J = 17.1 Hz, 1H), 4.07–3.97 (m, 2H), 3.32–3.21 (m, 1H), 3.01 (d, J = 17.1 Hz, 1H); **^{19}F{^{1}H}-NMR (282 MHz, $CDCl_3$)** δ -71.82; **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 137.8 (C), 137.5 (C), 135.3 (C), 130.4 (C), 128.4 (CH), 128.3 (CH), 128.2 (CH), 126.90 (CH), 126.88 (CH), 126.3 (CH), 126.2 (q, J_{C-F} = 289.7 Hz, CF_3), 122.2 (CH), 116.7 (CH), 116.0 (CH), 112.9 (CH), 82.5 (q, J_{C-F} = 25.4 Hz, C), 60.1 (CH), 54.0 (CH_2), 42.6 (q, J_{C-F} = 2.2 Hz, CH_2); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{23}H_{22}F_3N_2O^+$ 399.1679, found 399.1677.

Characterization of **7.7"**: **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 7.64 (d, J = 7.2 Hz, 2H), 7.53–7.37 (m, 4H), 7.34–7.20 (m, 5H), 6.88–6.78 (m, 2H), 6.74–6.56 (m, 2H), 5.12 (d, J = 17.1 Hz, 1H), 4.57 (d, J = 17.1 Hz, 1H), 4.19 (dd, J = 3.5, 1.7 Hz, 1H), 3.02 (dd, J = 11.2, 1.7 Hz, 1H), 2.91 (dd, J = 11.2, 3.4 Hz, 1H); **^{19}F{^{1}H}-NMR (282 MHz, $CDCl_3$)** δ -72.58; **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 138.4 (C), 137.6 (C), 134.5 (C), 129.8 (C), 128.7 (CH), 128.62 (CH), 128.56 (CH), 127.3 (CH), 127.2 (CH), 126.2 (q, J_{C-F} = 1.4 Hz, CH), 122.4 (CH), 117.2 (CH), 116.3 (CH), 113.8 (CH), 81.5 (q, J_{C-F} = 27.1 Hz, C), 59.2 (CH), 54.6 (q, J_{C-F} = 3.3 Hz, CH_2), 41.0 (CH_2); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{23}H_{22}F_3N_2O^+$ 399.1679, found 399.1675.

Specific Procedure 3 (SP-3) for the chlorination of compound 7.3aa



In a 10 mL round bottomed flask equipped, compound **7.3aa** (26.9 mg, 0.07 mmol, 1 eq.) was placed. The flask was purged with N_2 and then DCM (2 mL) was added. $SOCl_2$ (10 μL, 0.13 mmol, 2 equiv.) and pyridine (11 μL, 0.13 mmol, 2 equiv.) were successively added and the reaction mixture was stirred at room temperature under N_2 for 2 h. The reaction mixture was directly purified by column chromatog-

raphy using hexane:Et_2O mixture to afford compound **7.8'** (11.3 mg, 0.025 mmol, 40% yield, yellow oil) and **7.8"** (11.5 mg, 0.025 mmol, 40% yield, yellow oil).

4-Benzyl-3-(1-chloro-2,2,2-trifluoro-1-phenylethyl)-3,4-dihydroquinoxalin-2-one (7.8)

Characterization of **7.8'**: **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 9.11 (s, 1H), 7.67 (d, J = 6.5 Hz, 2H), 7.46–7.35 (m, 3H), 7.22 – 7.12 (m, 3H), 6.98–6.84 (m, 3H), 6.77 (td, J = 7.6, 1.2 Hz, 1H), 6.71–6.62 (m, 2H), 4.86 (s, 1H), 4.32 (d, J = 15.8 Hz, 1H), 3.42 (d, J = 15.9 Hz, 1H); **^{19}F{^{1}H}-NMR (282 MHz, $CDCl_3$)** δ -67.14; **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 161.0 (C), 136.3 (C), 133.4 (C), 133.3 (C), 129.5 (CH), 128.7 (CH), 128.4 (CH), 127.9 (q, J_{C-F} = 2.2 Hz, CH), 127.7 (CH), 127.3 (C), 127.2 (CH), 124.1 (CH), 124.0 (q, J_{C-F} = 284.7 Hz, CF_3), 120.1 (CH), 116.1 (CH), 115.4 (CH), 77.1 (q, J_{C-F} = 27.7 Hz, C), 67.9 (CH), 56.4 (CH_2); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{23}H_{19}ClF_3N_2O^+$ 431.1133, found 431.1136.

Characterization of **7.8"**: **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 8.30 (s, 1H), 7.57 (d, J = 8.3 Hz, 2H), 7.45–7.20 (m, 6H), 7.14 (dd, J = 7.6, 1.7 Hz, 2H), 6.97 (ddd, J = 8.3, 7.0, 1.4 Hz, 1H), 6.92 (dd, J = 8.0, 1.6 Hz, 1H), 6.82–6.71 (m, 1H), 6.46 (dd, J = 7.7, 1.2 Hz, 1H), 5.01 (d, J = 15.7 Hz, 1H), 5.00 (s, 1H), 4.48 (d, J = 15.7 Hz, 1H); **^{19}F{^{1}H}-NMR (282 MHz, $CDCl_3$)** δ -69.14; **^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$)** δ 161.1 (C), 136.5 (C), 133.3 (C), 132.5 (C), 129.2 (CH), 128.9 (CH), 128.1 (CH), 127.9 (CH), 127.7 (q, J_{C-F} = 2.0 Hz, CH), 127.5 (CH), 127.2 (C), 124.2 (CH), 120.3 (CH), 116.4 (CH), 115.0 (CH), 68.2 (CH), 56.9 (CH_2); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{23}H_{19}ClF_3N_2O^+$ 431.1133, found 431.1132.

Chapter 8

Organophotoredox 1,6-Addition of 3,4-Dihydroquinoxalin-2-ones to *p*-Quinone Methides using Visible Light

8.1 Introduction and state of the art

The propagation of electronic features of a given functional group along an unsaturation or a long conjugated system has vast implications in organic chemistry. This meaningful precept is widely known as the principle of vinylogy and it was introduced by Fuson in 1935.[264] According to this American chemist, the β position of a given α,β-unsaturated carbonylic compound remains electrophilic due to the fact that the electrophilicity of the carbonyl group is transmitted alongside the double bond. Although the β electrophilicity in that kind of organic molecules is widely assumed, the principle of vinylogy allows the design of novel structured with unusual reactivities.

One of the most important representative structures of this principle are *p*-quinone methides. This kind of compound can be viewed as $\alpha,\beta,\gamma,\delta$-diunsaturated ketone, which is formally accessed by the change of a carbonyl group in *p*-quinone for a trigonal carbon group (Figure 8.1). The presence of the remaining carbonyl group enables the *p*-quinone methide to exhibit electrophilicity at its δ position, thus permitting 1,6-type nucleophilic additions. However, to prevent easier 1,2- or 1,4-additions, *p*-quinone methides are usually decorated with bulky groups at both α positions (Figure 8.1). It is interesting to note that the nucleophilic addition at the δ position allows the system to generate an aromatic phenolic structure, providing a superior stability to the reaction products (Figure 8.1).

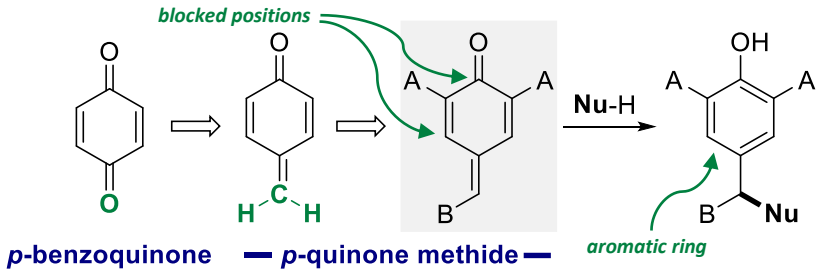


Figure 8.1: *p*-Quinone and *p*-Quinone methide.

In fact, the *p*-quinone methide scaffold can be found in several products with biological activity.[265–268] Indeed, in most of the cases, this biological activity arises from the electrophilicity of the corresponding δ carbon. Among them, it is important to highlight the curious case of macrolide Elansolid A,[269,270] with antibiotic activity and whose total synthesis was just accomplished.[271] (Figure 8.2). Elansolid A presents an opened structure with a *p*-quinone methide moiety directly attached to a *trans*-fused tetrahydroindane scaffold, which is known as Elansolid A3. Elansolid A3 also bears a conjugated carboxylic acid which is situated 17 carbon atoms away from the electrophilic carbon of *p*-quinone methide, but it is quite proximal in space. Actually, in solution, this carboxylic acid reacts with the *p*-quinone methide intramolecularly to form the 19-membered macrolactone Elansolid A1.[272]

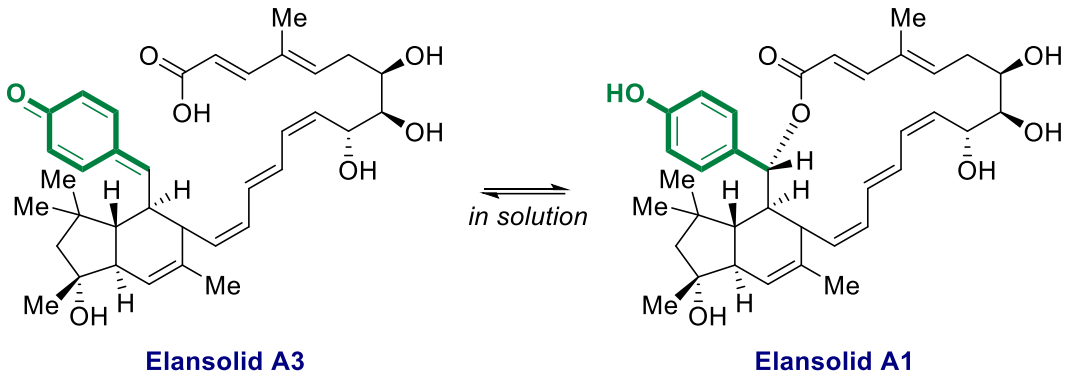


Figure 8.2: Equilibrium between Elansolid A3 and Elansolid A1.

Typically, to provide more stability to the whole system, the substituent directly linked to the exocyclic carbon in *p*-quinone methides (B in Figure 8.1) is an aromatic ring.[273–275] Therefore, the resulting structures that appear after a 1,6-addition reaction to this kind of *p*-quinone methides bear an interesting 1,1-diarylalkane scaffold, which is widely present in numerous active pharmacological ingredients. For example, lasofoxidene[276] exhibits an estrogen agonist activity, fenoldopam[277,278] is a DA-1 receptor agonist and cetirizine[279,280] is a broadly used second-generation antihistamine (Figure 8.3).

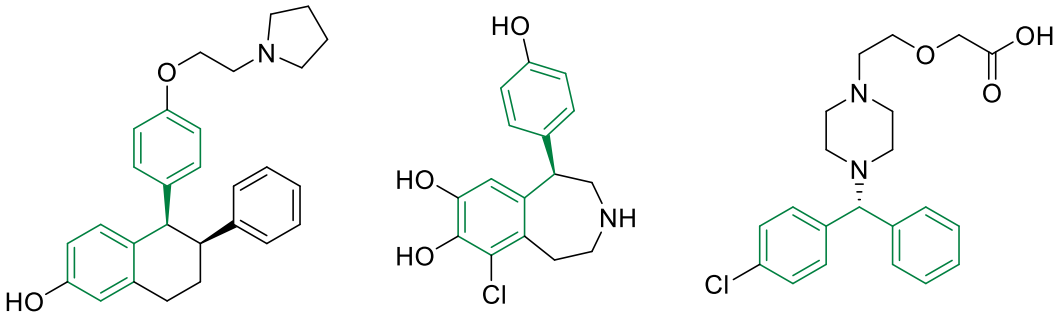


Figure 8.3: Biologically active 1,1-diarylalkanes.

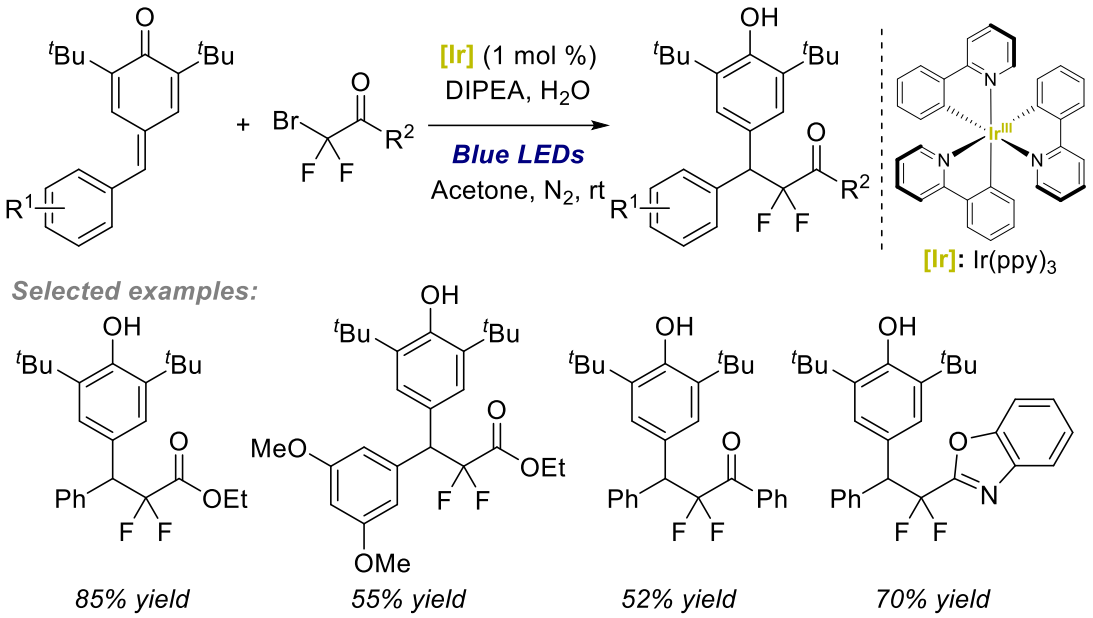
Selected Examples

Giving this remarkable importance, *p*-quinone methides have extensively been used as 1,6-electrophiles in a wide variety of transformations.[273–275] Nonetheless, for the purpose of this *thesis*, it is necessary to highlight some synthetic protocols enabled by visible-light photocatalysis.

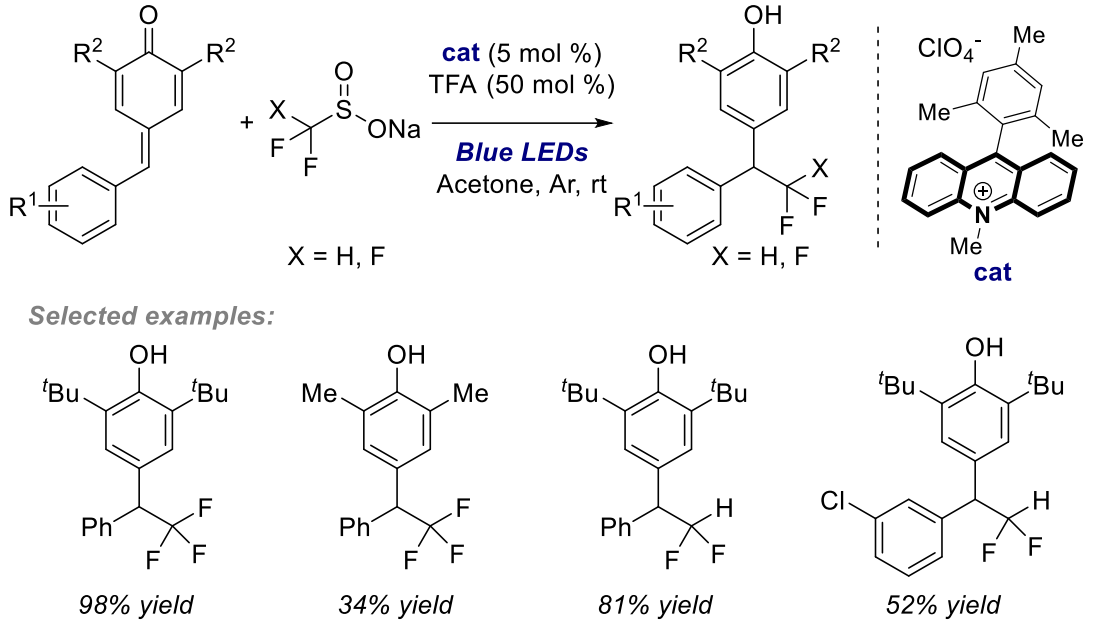
The first example came from the laboratory of Xu in 2018. In this work, they employed $Ir(ppy)_3$ as photoredox catalyst and DIPEA as sacrificial electron donor to react α-bromodifluoro carbonylic compounds with *p*-quinone methides (Scheme 8.1).[281] Using these net-reductive reaction conditions, they could trigger this kind of 1,6-photocatalytic Reformatsky reaction and obtain a library of fluorinated 1,1-diarylalkanes bearing different substituents. In this case, two *tert*-butyl groups were conveniently placed to block the 1,2- and 1,4-addition reactions. As will be noted later, this kind of *p*-quinone methide derivative is the most important substrate to favour 1,6-addition reactions.

In the same year, the research group of Ao and Liu reported a di- and trifluoromethylation of *p*-quinone methides under photoredox catalysis (Scheme 8.2).[282] Specifically, fluorinated sodium methyl sulfinates were engaged in a reductive quenching cycle with the well-known acridinium organophotocatalyst of Fukuzumi.[283] Once the fluorinated methyl radical is generated, it reacts with electrophilic *p*-quinone methide in a 1,6-fashion to yield other kind of highly interesting fluorinated 1,1-diarylalkane derivatives. Notably, two methyl groups could also provide enough hindrance to prevent either 1,2- or 1,4-addition reaction in *p*-quinone methides, although with less efficiency.

Also in 2018, the same research group resorted to almost the same reaction conditions to develop a protocol to alkylate *p*-quinone methides using 4-alkyl Hantzsch esters as radical precursors (Scheme 8.3).[284] In fact, this kind of dihydropyridines have found a relevant role in photoredox catalysis as radical precursors or hydrogen donors.[285] Using these conditions, the authors were able to obtain a assortment of 1,1-diarylalkanes with



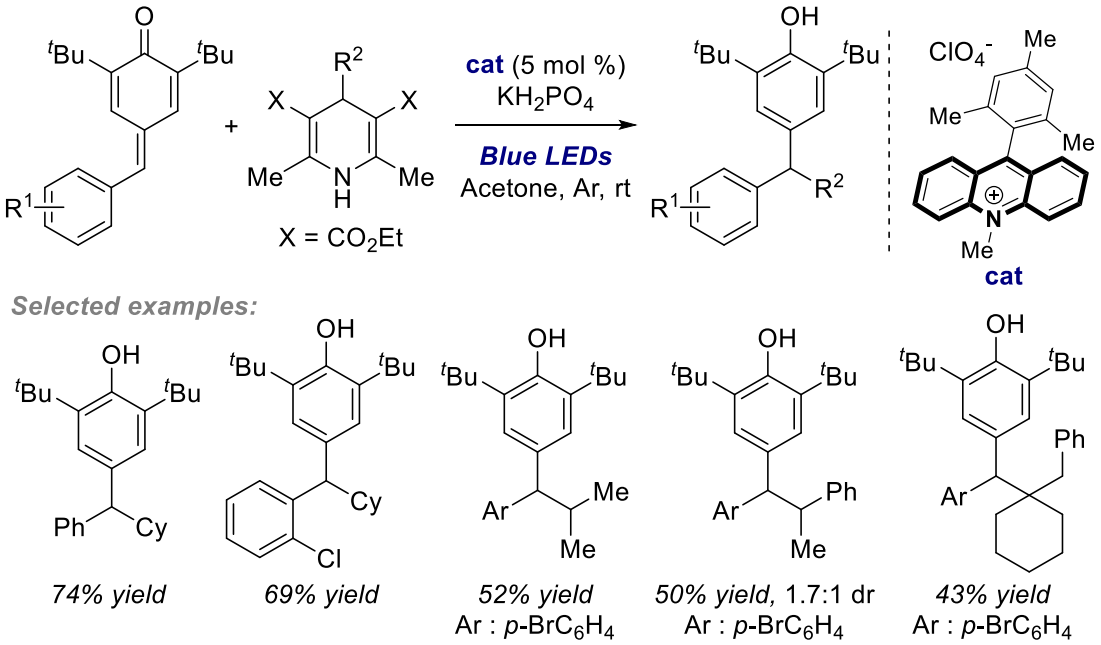
Scheme 8.1: Radical difluoroalkylation of *p*-quinone methides enabled by photoredox catalysis (Xu).



Scheme 8.2: Di- and trifluoromethylation of *p*-quinone methides under organophotoredox catalysis (Ao and Liu).

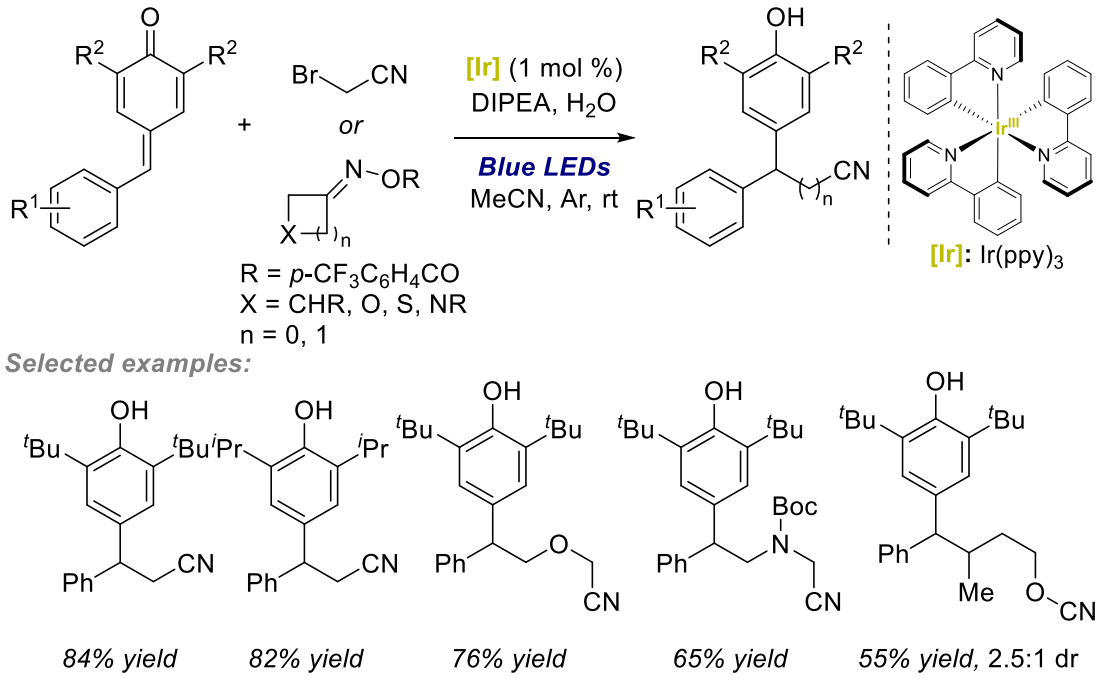
different substitution patterns, specially regarding the alkyl radical counterpart.

In 2019, Liu and collaborators reported the use of either bromoacetonitrile or several cyclic oximes as cyanated carbon radical precursors for the 1,6-addition reaction to *p*-quinone methides (Scheme 8.4).[286] The generation of these radicals was granted by photoredox catalysis, employing $Ir(ppy)_3$ and DIPEA as stoichiometric reductant. Using this strategy, the authors could access a library of 1,1-diarylalkanes bearing a versatile



Scheme 8.3: Radical alkylation of *p*-quinone methides enabled by organophotoredox catalysis (Ao and Liu).

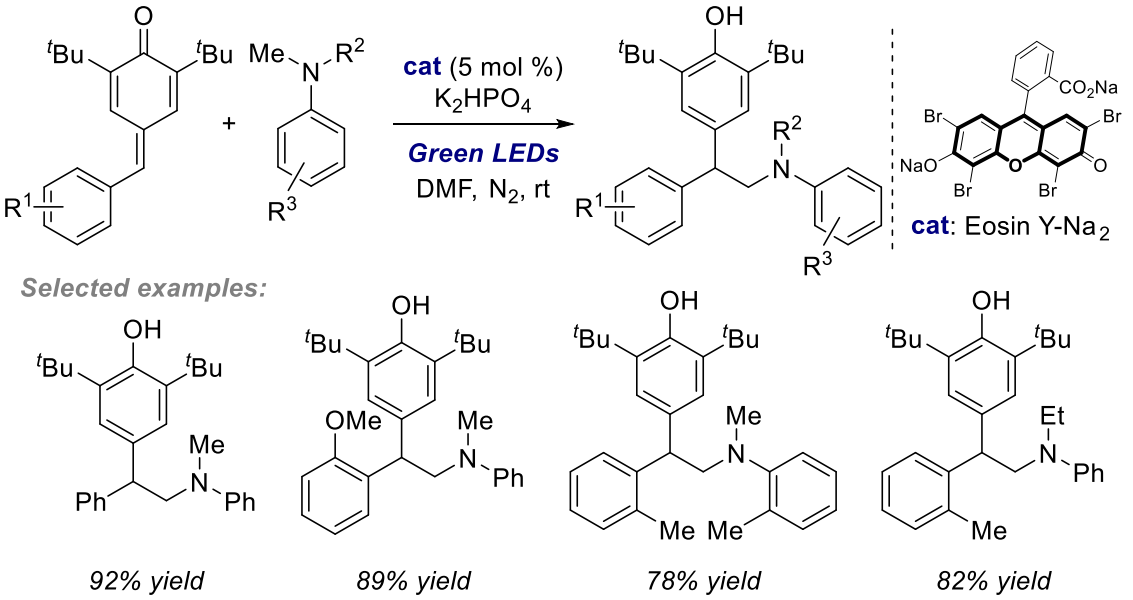
nitrile group. Additionally, they applied this approach to the formal synthesis of GPR40 agonists.[287]



Scheme 8.4: Radical alkylation of *p*-quinone methides with bromoacetonitrile or cyclic oximes (Li).

The first example on the use of tertiary amines as α-carbon radical precursors came

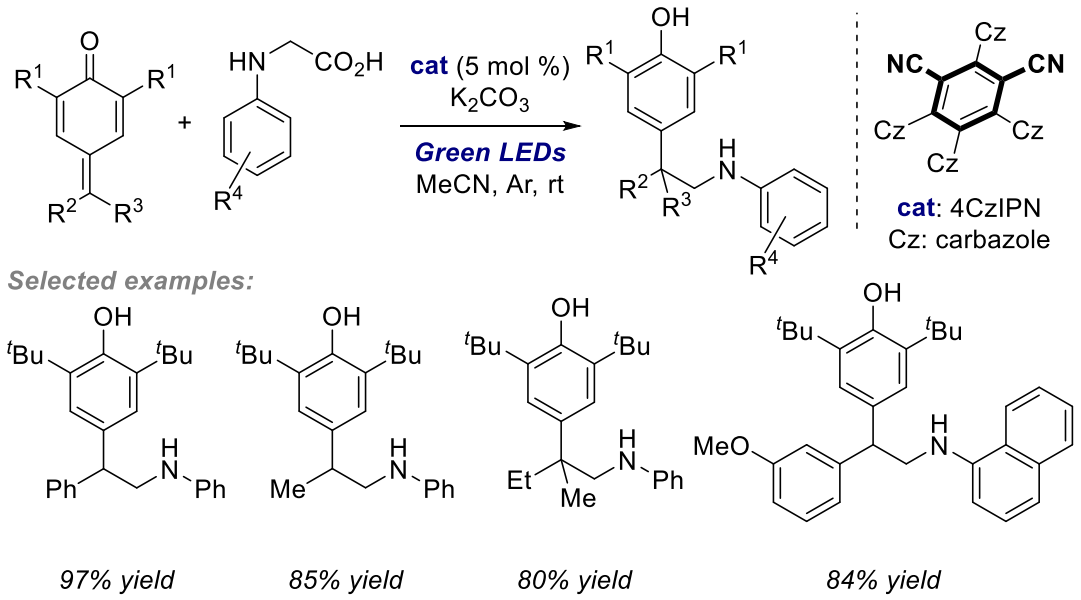
from the research group of Weng in 2020. Specifically, the authors employed Eosin Y-Na_2 as photoredox catalyst to generate the α-amino radical of different *N*,*N*-dialkylanilines (Scheme 8.5).[288] Thereafter, this radical reacted in a 1,6 manner with the corresponding *p*-quinone methide to yield valuable 2,2-diarylethanamines. In fact, this method provides an alternative synthetic route to the anti-Markovnikov hydroamination of 1,1-diarylethenes with secondary amines.[289,290]



Scheme 8.5: Photoredox-catalyzed reaction between *p*-quinone methides and *N*,*N*-dialkylanilines (Weng).

Finally, in 2021, Wang, Hang and Jing developed a methodology to engage secondary amines in the radical 1,6-addition to *p*-quinone methides using photoredox catalysis (Scheme 8.6).[291] Specifically, they took advantage of *N*-aryl glycine derivatives as α-amino radical precursors after photoredox oxidation and subsequent decarboxylation. Using 4CzIPN as photocatalyst, they could obtain interesting secondary 2,2-diarylethanamines in generally high yields, being even able to employ disubstituted *p*-quinone methides at the electrophilic carbon.

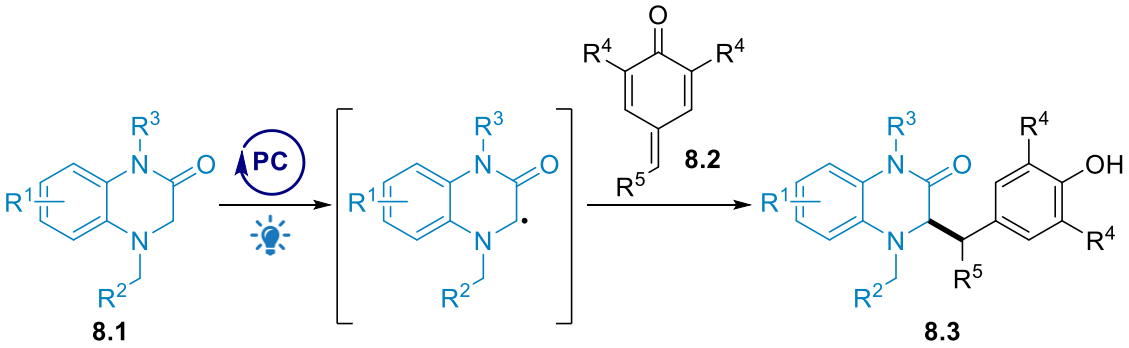
In light of these bibliographic precedents, the use of amines as carbon radical precursors under photoredox catalysis is quite underexplored. Moreover, once we have described two protocols for 1,4-like additions and one for 1,2-addition of 3,4-dihydroquinoxalin-2-ones, we thought that it would be of interest the development of a methodology to C-3-functionalize these heterocycles through a 1,6-addition reaction with *p*-quinone methides.



Scheme 8.6: Radical reaction between *p*-quinone methides and *N*-aryl glycines (Wang, Hang and Jing).

8.2 Objectives

The main objective for this *Chapter* is the development of a methodology to functionalize 3,4-dihydroquinoxalin-2-ones (**8.1**) with *p*-quinone methides (**8.2**) employing visible-light photoredox catalysis to generate the α-amino radical of **8.1**. To achieve this objective, several partial objectives are postulated:



1. Optimization of the reaction conditions between 4-benzyl-3,4-dihydroquinoxalin-2-one (**8.1a**) and *p*-quinone methide derived from benzaldehyde **8.2a** to obtain the corresponding diarylethanamine **8.3aa** with the highest yield.

2. Study of the scope of the reaction between different 3,4-dihydroquinoxalin-2-ones (**8.1**) and different *p*-quinone methide derivatives (**8.2**).

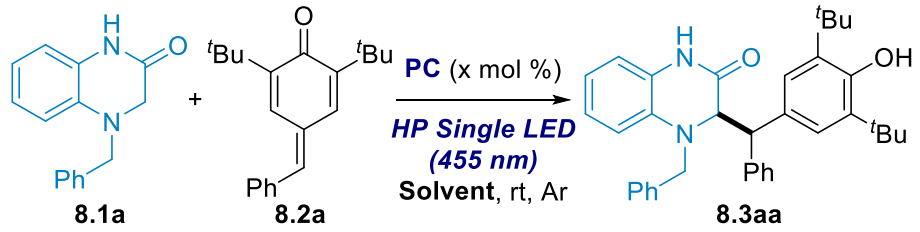
3. Synthetic transformations of the 1,6-addition products **8.3**.

4. Mechanistic investigations to find out the reaction mechanism.

8.3 Results and Discussion

8.3.1 Optimization of the Reaction Conditions

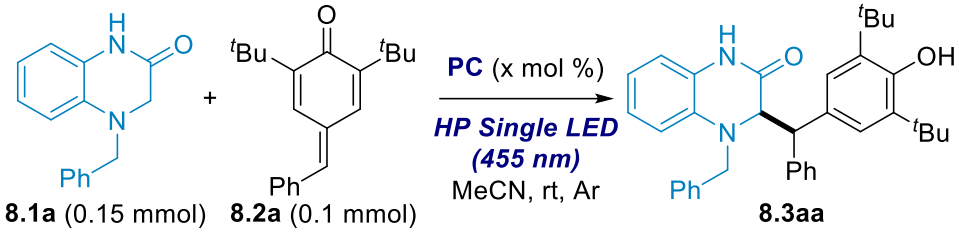
To optimize the reaction conditions we chose 4-benzyl-3,4-dihydroquinoxalin-2-one (**8.1a**) and *p*-quinone methide **8.2a** as model substrates. The initial and most important variable to optimize was the photoredox catalyst, due to the fact that it is the main responsible of generating the α-amino radical of **8.1a**. Thereafter, the role of the solvent will be investigated to obtain product **8.3aa** with the highest yield. Lastly, some molar ratio adjustements will be conducted to maximize the performance and practicability of the reaction (Scheme 8.7).



Scheme 8.7: Overview of the model reaction to carry out the optimization of the reaction conditions.

Evaluation of the Photoredox Catalyst

Our previous observations in this field prompted us to start the optimization of the reaction between **8.1a** and **8.2a** focusing on the photoredox catalyst. Specifically, we decided to screen several photoredox catalyst while using dried and degassed MeCN as solvent, 0.15 mmol of **8.1a**, 0.1 mmol of **8.2a** and HP Single LED (455 nm) as light source (Scheme 8.8).



Scheme 8.8: Evaluation of the photoredox catalyst in the reaction between **8.1a** and **8.2a** using MeCN.

Our first attempt involved the use of 1 mol % of $Ru(bpy)_3Cl_2$ (**A**) as photoredox catalyst. After 24 hours of reaction, we were pleased to observe a quantitative conversion of

8.2a towards the two potential diastereomers of **8.3aa**, as judged by TLC. However, we could only isolate by column chromatography **8.3aa** in 37% yield with surprising 3.2:1 dr. This result led us consider the instability of product **8.3aa** during the isolation process. In fact, we confirmed this hypotheses when a DCM solution of product **8.3aa** and a small amount of silica gel resulted in complete decomposition of **8.3aa** after 16 hours of stirring. In the absence of a reliable purification protocol, we decided to perform the optimization process using ^{1}H-NMR to determine both the yield and the diastereomeric ratio.

For convenience, we decided to employ *p*-methoxyacetophenone as internal standard for yield and dr determination. We repeated the reaction with $Ru(bpy)_3Cl_2$ (**A**), obtaining this time a more reasonable 72% yield of **8.3aa** by ^{1}H-NMR (Table 8.1, Entry 1). Using the same method to determine the yield of product **8.3aa**, we observed how the use of Eosin-Y-Na_2 (**E**) as photocatalyst resulted in a lower 27% yield after 24 hours (Table 8.1, Entry 2). Surprisingly, when the versatile 4CzIPN photocatalyst was used, we could not even detect the desired product **8.3aa** in the reaction mixture (Table 8.1, Entry 3). The performance of [2,4,6-Ph_3-pyrillium][BF_4] (**G**) was not better, since product **8.3aa** could only be detected in a moderate 43% yield (Table 8.1, Entry 4). To our delight, when [Mes-Acr-Me][BF_4] (**H**) (also known as Fukuzumi's catalyst) was employed, we could detect by ^{1}H-NMR the expected product **8.3aa** in 94% yield after 19 hours of irradiation (Table 8.1, Entry 5). Lastly, 9,10-phenanthrenequinone (**J**) was not a suitable photocatalyst to promote the reaction between **8.1a** and **8.2a** (Table 8.1, Entry 6).

Table 8.1: Evaluation of the photoredox catalyst in the reaction between **8.1a** and **8.2a** using MeCN. Yield of **8.3aa**.

Entry[a]	**PC (x mol %)**	**t (h)**	**dr**[b]	**Yield 8.3aa (%)**[c]
1	$Ru(bpy)_3Cl_2$ (**A**) (1)	24	1.2:1	72
2	Eosin-Y-Na_2 (**E**) (5)	24	1.1:1	27
3	4CzIPN (**M**) (2)	24	–	–
4	[2,4,6-Ph_3-pyrillium][BF_4] (**G**) (5)	19	1.1:1	43
5	[Mes-Acr-Me][BF_4] (**H**) (5)	19	1.3:1	94
6	9,10-Phenanthrenequinone (**J**) (10)	14	–	–

[a]Reaction conditions: **8.1a** (0.15 mmol), **8.2a** (0.1 mmol), **PC** (x mol %), MeCN (1 mL), under argon atmosphere and under HP Single LED (455 nm) irradiation for the indicated time.

[b]Determined by ^{1}H-NMR.

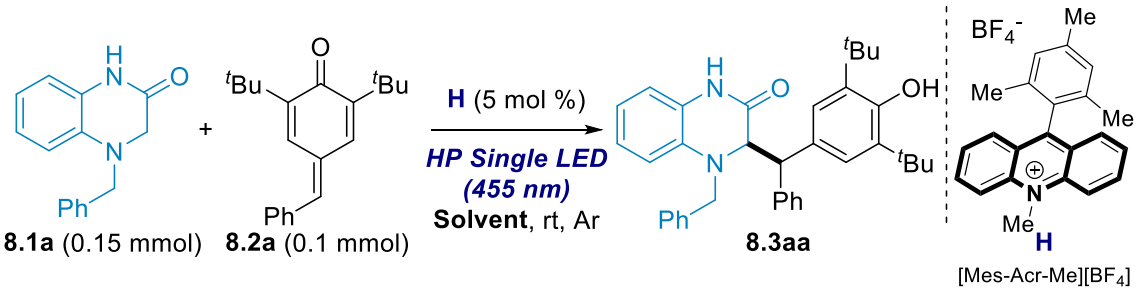
[c]Yield determined by ^{1}H-NMR using *p*-acetophenone as internal standard.

According to these results, we selected [Mes-Acr-Me][BF_4] (**H**) as the best photocat-

alyst to perform the reaction between 3,4-dihydroquinoxalin-2-one **8.1a** and *p*-quinone methide **8.2a** (Table 8.1, Entry 5).

Evaluation of the Solvent

After choosing [Mes-Acr-Me][BF_4] (**H**) as the best photocatalyst, we wanted to explore the effect of the solvent over the reaction outcome (Scheme 8.9). When the reaction between 3,4-dihydroquinoxalin-2-one **8.1a** and *p*-quinone methide **8.2a** was conducted in MeCN, we obtained product **8.3aa** in 94% yield (Table 8.2, Entry 1). With the aim of diminishing the reaction time, we tested other solvents to carry out this transformation.



Scheme 8.9: Evaluation of the solvent in the reaction between **8.1a** and **8.2a** using [Mes-Acr-Me][BF_4] (**H**).

The first solvent to test was DMF, since it is also a polar aprotic solvent like MeCN. However, it required 24 hours of reaction time to deliver just a 41% yield of product

Table 8.2: Evaluation of the solvent in the reaction between **8.1a** and **8.2a** using [Mes-Acr-Me][BF_4] (**H**). Yield of **8.3aa**.

Entry[a]	Solvent	t (h)	dr[b]	Yield 8.3aa (%)[c]
1	MeCN	19	1.3:1	94
2	DMF	24	1.9:1	41
3	DCM	9	1.2:1	99
4	Toluene	26	–	–
5	1,2-DCE	6	93	1.3:1
6	$CHCl_3$	8	1:1	87

[a]Reaction conditions: **8.1a** (0.15 mmol), **8.2a** (0.1 mmol), **H** (5 mol %), solvent (1 mL), under argon atmosphere and under HP Single LED (455 nm) irradiation for the indicated time.
[b]Determined by ^{1}H-NMR.
[c]Yield determined by ^{1}H-NMR using *p*-acetophenone as internal standard.

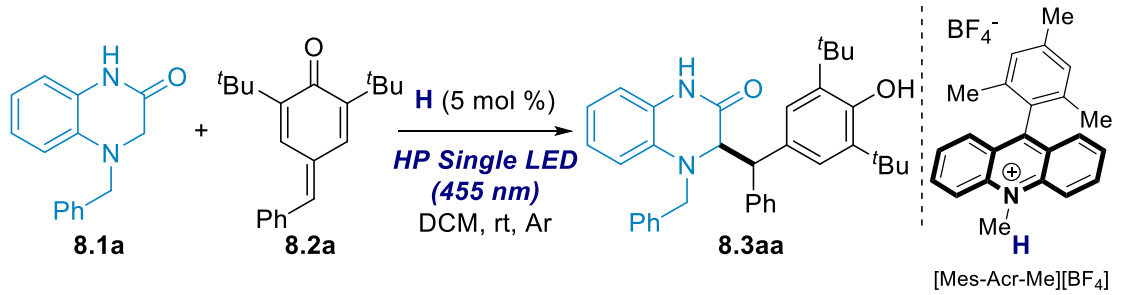
8.3aa (Table 8.2, Entry 2). Delightfully, when the reaction was performed in DCM, we were able to detect product **8.3aa** in quantitative yield after only 9 hours of irradiation (Table 8.2, Entry 3). However, the reaction did not proceed at all in toluene, probably due to the low solubility of both the photocatalyst and 3,4-dihydroquinoxalin-2-one **8.1a** in this solvent (Table 8.2, Entry 4).

Having realized that the use of DCM was beneficial for the outcome of the reaction, we decided to test other chlorinated solvents such as 1,2-DCE and $CHCl_3$. In fact, when 1,2-DCE was used, we could shorten the reaction time to 6 hours, although the desired product **8.3aa** was generated in a slightly lower 93% yield (Table 8.2, Entry 5). Besides, a comparable satisfactory performance was observed when $CHCl_3$ was used, as product **8.3aa** could be formed in 87% yield after 8 hours (Table 8.2, Entry 6).

After noticing that chlorinated solvents exhibited a superior performance in the photocatalytic reaction between 3,4-dihydroquinoxalin-2-one **8.1a** and *p*-quinone methide **8.2a**, we decided to select DCM as the most convenient solvent to run the reaction, given the high yield in which product **8.3aa** was formed (Table 8.2, Entry 3).

Evaluation of the Molar Ratio

Once the best photocatalyst and the best solvent were revealed, the final step in the optimization process was to adjust the molar ratio of both reactants to ensure a satisfactory formation of product **8.3aa** while minimizing the use of overstoichiometric amounts of substrates (Scheme 8.10).



Scheme 8.10: Evaluation of the molar ratio in the reaction between **8.1a** and **8.2a** using [Mes-Acr-Me][BF_4] (**H**) and DCM.

After all the experience on 3,4-dihydroquinoxalin-2-one **8.1a** reactivity, we started the optimization process using 1.5 equivalents of **8.1a** over **8.2a**. Nonetheless, at this point, we questioned if this excess could be diminished to 1.2 equivalents without losing performance. Sadly, when the reaction was carried out using 0.12 mmol of **8.1a** and 0.1 mmol of **8.2a**, the desired product was generated in only 71% yield (Table 8.3, Entry 2). On the other hand, we hypothesized if the reaction could be speeded up enough to prevent

Table 8.3: Evaluation of the molar ratio in the reaction between **8.1a** and **8.2a** using [Mes-Acr-Me][BF_4] (**H**) and DCM. Yield of **8.3aa**.

Entry[a]	8.1a (mmol)	8.2a (mmol)	t (h)	dr[b]	Yield 8.3aa (%)[c]
1	0.15	0.1	9	1.2:1	99 (99)[d]
2	0.12	0.1	9	1:2:1	71
3	0.1	0.12	9	1.4:1	60

[a]Reaction conditions: **8.1a**, **8.2a**, **H** (5 mol %), MeCN (1 mL), under argon atmosphere and under HP Single LED (455 nm) irradiation for the indicated time.
[b]Determined by ^{1}H-NMR.
[c]Yield determined by ^{1}H-NMR using *p*-acetophenone as internal standard.
[d]Yield determined after purification by column chromatography using Et_3N-deactivated silica gel.

8.1a decomposition by using now an excess of **8.2a**. However, when 0.1 mmol of **8.1a** and 0.12 mmol of **8.2a** were used, product **8.3aa** was observed by ^{1}H-NMR in only 60% yield (Table 8.3, Entry 3).

Therefore, although it was not quite efficient, we decided to state that the best conditions to perform the reaction between 3,4-dihydroquinoxalin-2-one **8.1a** and *p*-quinone methide **8.2a** involve the use of 0.15 mmol of **8.1a**, 0.1 mmol of **8.2a**, [Mes-Acr-Me][BF_4] (**H**) as photoredox catalyst and dried and degassed DCM as solvent (Table 8.3, Entry 1).

However, we needed to assay different purification conditions that avoid partial decomposition of product **8.3aa**. In this sense, we decided to resort to the same purification conditions that we used in Chapter 2 for the purification of product **2.3aa** after the asymmetric oxidative Mannich reaction (page 96). Pleasingly, the use of Et_3N-deactivated silica gel as stationary phase resulted in complete prevention of product **8.3aa** decomposition, as it was isolated in 99% yield (Table 8.3, Entry 1).

8.3.2 Scope of the Reaction

After establishing the conditions to carry out the photocatalytic 1,6-addition reaction of 3,4-dihydroquinoxalin-2-one **8.1a** to *p*-quinone methide **8.2a**, we wanted to explore the generality of this transformation. For this purpose, we subjected differently substituted 3,4-dihydroquinoxalin-2-ones **8.1** and *p*-quinone methides **8.2** under our optimal reaction conditions. However, it is important to note that, for a matter of time, the study of the scope is not completed yet, and just a few examples will be shown.

Scope of the Reaction with 3,4-dihydroquinoxalin-2-ones

First of all, we decided to explore the scope of this reaction using several 3,4-dihydroquinoxalin-2-ones **8.1** bearing different substituents patterns at either the parent aromatic ring (R^1), the aminic nitrogen (R^2) or the amidic nitrogen (R^3) (Scheme 8.11).

Initially, the effect of different substituents at the aminic nitrogen (R^2) of 3,4-dihydroquinoxalin-2-one **8.1** was studied. The presence of a more elctron-rich benzylic substituent such as the PMB group resulted in the corresponding product **8.3ba** in an excellent 99% yield, comparable with that of compound **8.3aa**. Even though, the use of a 3,4-dihydroquinoxalin-2-one derivative that bears a $-CH_2CO_2Me$ group at N-4 (**8.1c**) allowed us to obtain the corresponding product **8.3ca** in 81% yield, and no product at exocyclic CH_2 was observed.

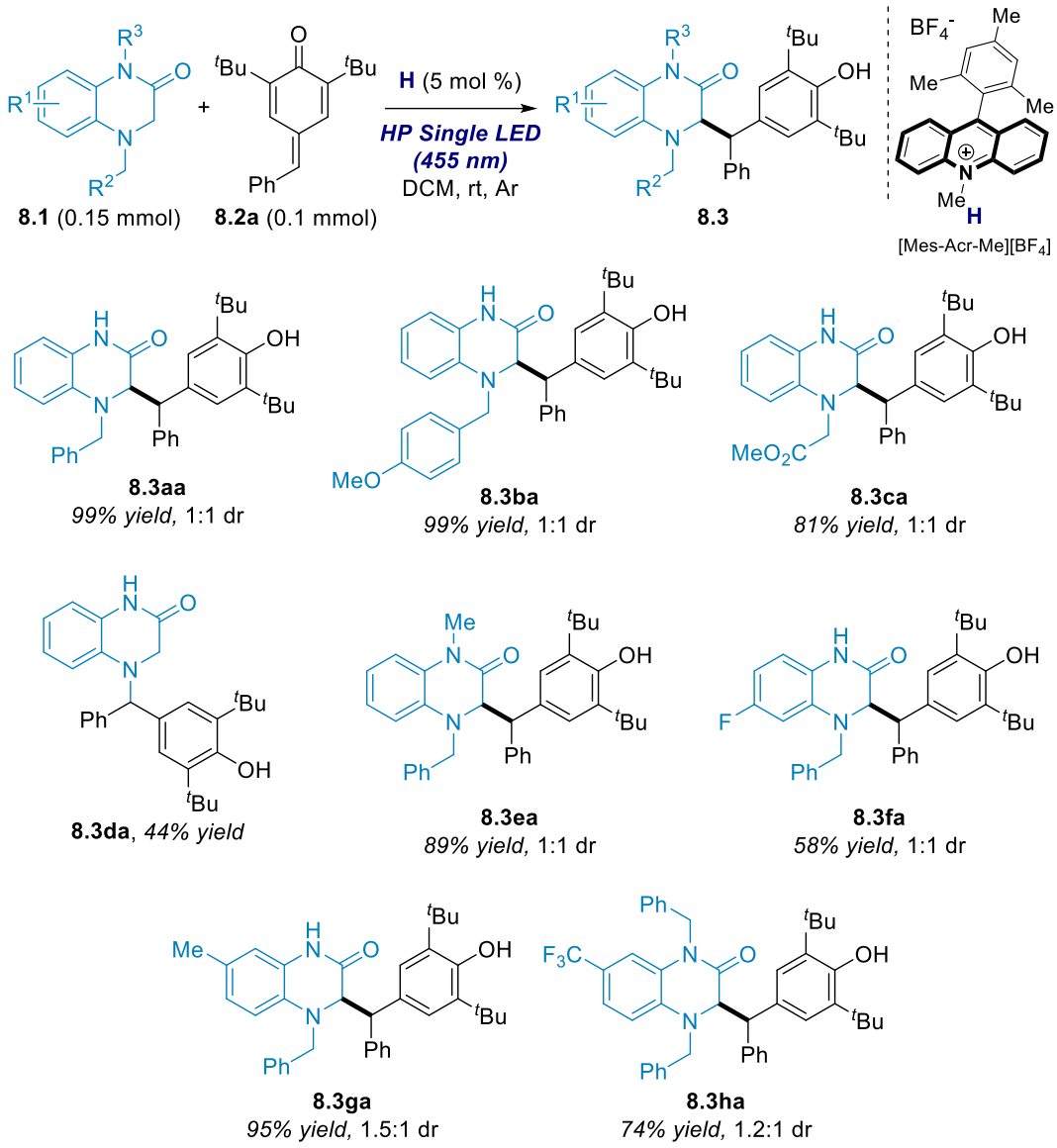
Interestingly, when we intended to carry out the reaction with N-4 unprotected derivative **8.1d**, the 1,6-addition reaction to *p*-quinone methide **8.2a** took place through N-4, obtaining the corresponding *N*-alkylated product **8.3da** in 44% yield after 15 hours. Actually, we confirmed that this reaction arose from a photochemical manifold, since if it is performed in the dark, product **8.3da** was isolated in only 11% yield after 3 days.

On the other hand, our reaction protocol efficiently tolerated the presence of a methyl substituent at the amidic nitrogen (R^3), providing the expected product **8.3ea** in 89% yield.

Finally, the study of the scope of this 1,6-addition reaction was completed by testing the performance of 3,4-dihydroquinoxalin-2-ones **8.1** bearing different substitution patterns at their parent aromatic ring (R^1). Precisely, when a fluorine atom was placed at the C-6 position, the corresponding product **8.3fa** was isolated in a moderate 58% yield. Besides, 3,4-dihydroquinoxalin-2-one **8.1g**, which bears a methyl moiety at C-7, was efficiently engaged in our photocatalytic protocol to generate the expected product **8.3ga** in an excellent 95% yield. Surprisingly, the presence of a $-CF_3$ at C-7 (**8.1h**), which withdraws electron density of the reactive aminic nitrogen, was not an impediment for our photocatalytic methodology to generate product **8.3ha** in 74% yield.

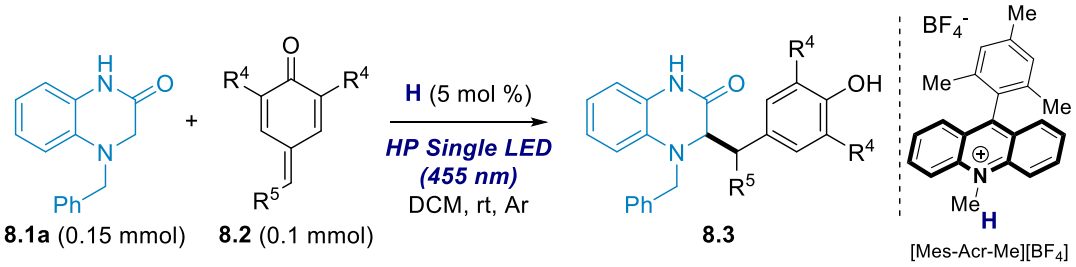
Scope of the Reaction with *p*-Quinone Methides

In the same vain, we wanted to explore the effect of different substituents at the *p*-quinone methide scaffold over the reaction performance. Initially, we envisioned that it would be of interest to carry out this photochemical reaction with all the regioisomeric $-$OMe-substituted *p*-quinone methides at the aromatic ring (R^5). Pleasingly when *ortho* derivative **8.2b** was used, we could isolate the corresponding product **8.3ab** in 97% yield. Apparently, the steric congestion around the electrophilic carbon of *p*-quinone methide **8.2b** was efficiently overcame. In the same line, the *meta* analogue **8.2c** allowed us to obtain product **8.3ac** in 97% yield. Finally, the *para*-substituted derivative also permitted

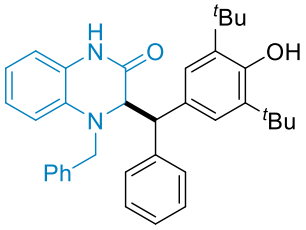


Scheme 8.11: Scope of the reaction using different 3,4-dihydroquinoxalin-2-ones (**8.1**) and *p*-quinone methide **8.2a**.[a]

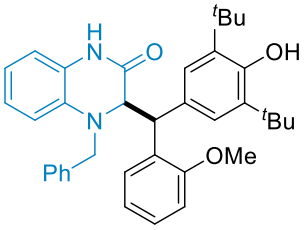
[a]Reaction conditions: **8.1** (0.15 mmol), **8.2a** (0.1 mmol), **H** (5 mol %), DCM (1 mL), under argon atmosphere and under HP Single LED (455 nm) irradiation for 6-16 hours. Diastereomeric ratio was determined by ^{1}H-NMR of the crude reaction mixture. Yield determined after purification by column chromatography using Et_3N-deactivated silica gel.



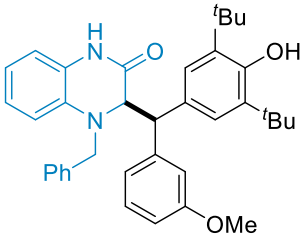
8.1a (0.15 mmol) **8.2** (0.1 mmol) **8.3**



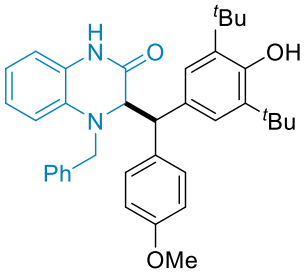
8.3aa
99% yield, 1:1 dr



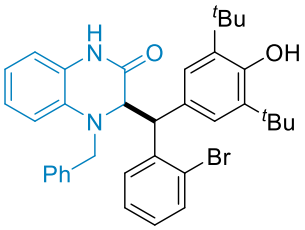
8.3ab
97% yield, 1.5:1 dr



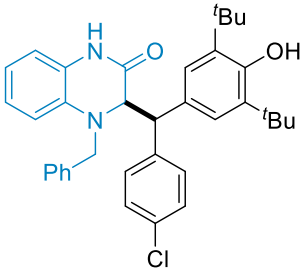
8.3ac
97% yield, 1.4:1 dr



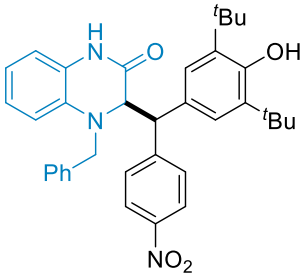
8.3ad
86% yield, 1:1 dr



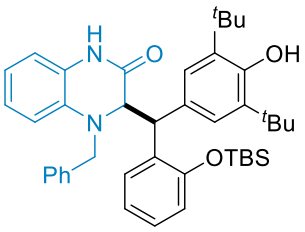
8.3ae
89% yield, 1.4:1 dr



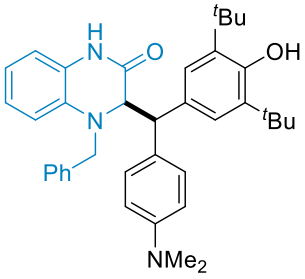
8.3af
96% yield, 1:1 dr



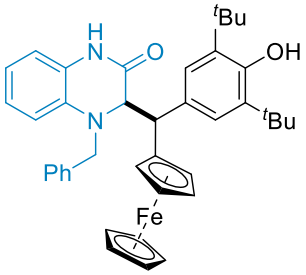
8.3ag
99% yield, 1:1 dr



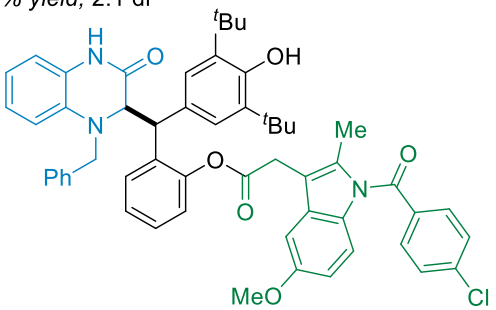
8.3ah
97% yield, 2:1 dr



8.3ai, *NR*



8.3aj, *NR*



8.3ak,
79% yield, 1:1 dr

Scheme 8.12: Scope of the reaction using 3,4-dihydroquinoxalin-2-one **8.1a** and different *p*-quinone methides (**8.2**).[a]

[a]Reaction conditions: **8.1a** (0.15 mmol), **8.2** (0.1 mmol), **H** (5 mol %), DCM (1 mL), under argon atmosphere and under HP Single LED (455 nm) irradiation for 6-16 hours. Diastereomeric ratio was determined by ^{1}H-NMR of the crude reaction mixture. Yield determined after purification by column chromatography using Et_3N-deactivated silica gel.

the obtention of the desired product, but this time in 86% yield. It is interesting to note that in these three products (**8.3ab**, **8.3ac** and **8.3ad**) the larger the steric demand near the reactive center, the better the diastereomeric ratio (form 1.5:1 for **8.3ab** to 1:1 for **8.3ad**).

Next, different *p*-quinone methides bearing halogen atoms at diverse position of the aromatic ring were also tested under our conditions. Again, the *ortho*-bromine derivative **8.2e** efficiently generated product **8.3ae** in 89% yield and with an appreciably higher 1.4:1 dr. Additionally, when the reaction was conducted using a *p*-quinone methide bearing a chlorine atom at the *para* position (**8.2f**), the expected product **8.3af** was isolated in an excellent 96% yield with 1:1 dr.

At this point, we decided to move forward and employ more challenging *p*-quinone methides **8.2**. In this sense, we carried out the photochemical 1,6-addition reaction using *p*-quinone methide **8.2g**, which bears a $p-NO_2$ group. It is important to notice that, usually, the nitro group could interfere in the photochemical mechanism, thus not causing the desired outcome. Nonetheless, in our case, the reaction proceeded smoothly towards the corresponding product **8.3ag** in quantitative yield. Now, we wanted to know how far our methodology can go regarding the steric hindrance near the electrophilic carbon center. For this purpose, we prepared a *p*-quinone methide derivative with the bulky −OTBS group as *ortho* substituent (**8.2h**). Pleasingly, the corresponding product **8.3ah** was adroitly generated in excellent 97% yield and with the highest diastereomeric ratio (2:1 dr).

Moreover, we envisioned that the use of a *p*-quinone methide derivative with a $p-NMe_2$ substituent (**8.2i**) would be interesting in terms of introducing another redox-active tertiary amine. Indeed, it would allow us to design an orthogonal photochemical approach in which the two tertiary amines would be engaged in different photochemical transformations just by adjusting the reaction conditions. However, when *p*-quinone methide **8.2i** was subjected to our reaction conditions, we could not even detect the desired product **8.3ai**. Additional experiments to tackle this transformation are in progress in our laboratory.

Besides, the use of ferrocene-derived substrate **8.2j** did not result in the formation of the expected product **8.3aj**, probably due to the fact that ferrocene is also redox active and it can interfere in the photoredox catalytic cycle.

Finally, to further extend the interest of this transformation, and having realized that the reaction tolerated the presence of large substituents at the *ortho* position of *p*-quinone methides **8.2**, we prepared substrate **8.2k**, which incorporates the indomethacin skeleton. Delightfully, product **8.3ak** could be isolated in 79% yield, although with a 1:1 diastereomeric ratio.

8.3.3 Mechanistic Investigations and Proposed Mechanism

Mechanistic Investigations

At this point we needed to explore the mechanism behind our transformation. Initially we performed several simple control experiments to reveal the necessity of all the reaction parameters (Table 8.4).

Table 8.4: Control experiments for the photocatalytic reaction between **8.1a** and **8.2a**.

Entry[a]	Deviation	**8.3aa** (%)
1	*none*	99
2	darkness	–
3	without **H**	–
4	with TEMPO (1.5 equiv.)	no conversion
5	air atmosphere	–

[a]Reaction conditions: **8.1a** (0.15 mmol), **8.2a** (0.1 mmol), **H** (5 mol %), DCM (1 mL), under argon atmosphere and under HP Single LED (455 nm) irradiation. Note deviations for each case. Reaction time: 9 h.

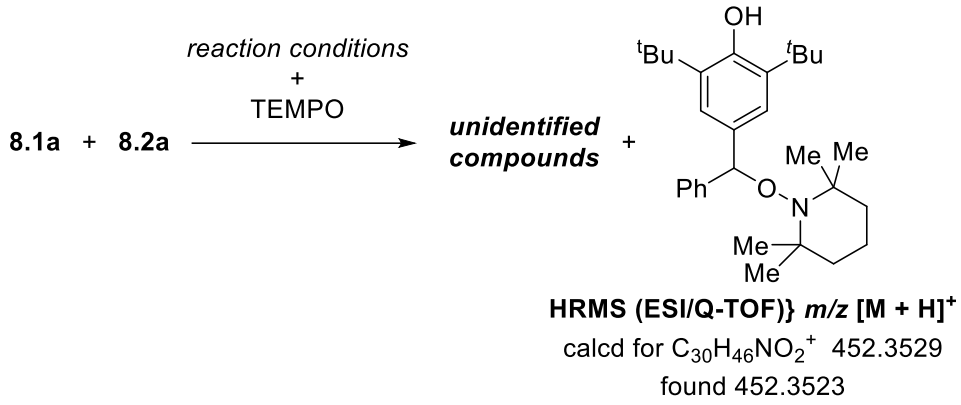
Initially, when the reaction was performed in the dark, the expected product **8.3aa** was not even detected after 9 hours of stirring, showing that the reaction proceeds once the photocatalyst is excited by visible light (Table 8.4, Entry 2). Accordingly, the reaction did not proceed when photocatalyst [Mes-Acr-Me][BF_4] (**H**) was excluded from the reaction media (Table 8.4, Entry 3).

As expected, when the reaction was conducted in the presence of 1.5 equivalents of radical scavenger TEMPO, we could not detect product **8.3aa** in the reaction mixture (Table 8.4, Entry 4). Interestingly, analysis of this mixture by means of HRMS revealed the presence of an adduct between **8.2a** and TEMPO, presumably formed via radical-radical homocoupling (Scheme 8.13). Thus, this experiment demonstrated that dibenzylic radical derived from **8.2a** is generated throughout the reaction.

Finally, the imperious necessity of an inert atmosphere was demonstrated by conducting the reaction between **8.1a** and **8.2a** under a regular air atmosphere. As expected, no product **8.3aa** was observed after 9 hours of irradiation (Table 8.4, Entry 5).

All these results suggest the implication of a photoredox catalytic cycle in the reaction mechanism. Hence, at this point, we decided to examine carefully the redox potentials of all the species involved in the reaction (Table 8.5).

According to the bibliography, [Mes-Acr-Me][BF_4] (**H**) has a quantum yield for its



Scheme 8.13: Detection of **8.2a**·TEMPO adduct by means of HRMS.

Table 8.5: Redox potentials of [Mes-Acr-Me][BF_4] (**H**) from the excited state, **8.1a** and **8.2a**.

Specie	$E_{red}(\mathbf{A}^{+n}/\mathbf{A}^{n})$ (V vs SCE)	$E_{red}(\mathbf{A}^{n}/\mathbf{A}^{-n})$ (V vs SCE)
***H**	+1.45	–
8.1a	+0.80	–
8.2a	–	−1.18

intersystem crossing $S_1 \rightarrow T_1$ of 0.38.[292] Therefore, the photoinduced electron transfer probably happens from its S_1 state, although the actual electron-transfer active specie is still under debate.[25] In the less-favourable scenario, [Mes-Acr-Me][BF_4] (**H**) has a reduction potential of +1.45 V (vs SCE) in its excited state.[25] Curiously, since [Mes-Acr-Me][BF_4] (**H**) does not exhibit reductive abilities, it can only participate in reductive quenching cycles. Regarding both substrates, the reduction potential of 3,4-dihydroquinoxalin-2-one **8.1a** was already determined in Chapter 5, and it was +0.80 V (vs SCE). On the other hand, the reduction potential of *p*-quinone methide **8.2a** was determined by Tang and Cai, and it was found to be −1.18 V (vs SCE).[293]

Hence, according to these data, the most probable pathway is the oxidation of 3,4-dihydroquinoxalin-2-one **8.1a** to the corresponding radical cation by the excited state of [Mes-Acr-Me][BF_4] (**H**). To prove this thermodynamic assumption, we decided to perform steady-state luminescence quenching experiments. The study of the luminescence quenching of [Mes-Acr-Me][BF_4] (**H**) by **8.2a** was already reported in the bibliography by Ao and Liu.[282] These researchers unequivocally found that *p*-quinone methide **8.2a** was not able to quench the excited state of [Mes-Acr-Me][BF_4] (**H**). Therefore, we only tested the ability of 3,4-dihydroquinoxalin-2-one **8.1a** to quench the excited state photocatalyst. For this purpose, we prepared different DCM solutions containing 0.02 mM of

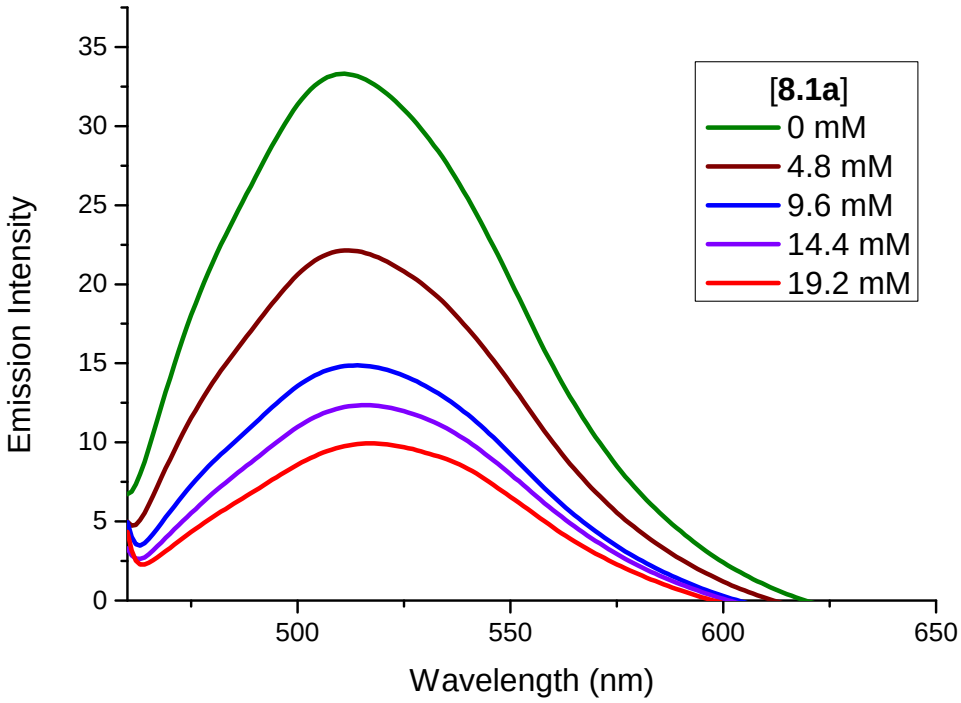


Figure 8.4: Emission spectra of different DCM solutions containing 0.02 mM of [Mes-Acr-Me][BF_4] (**H**) and varying amounts of 3,4-dihydroquinoxalin-2-one **8.1a**.

[Mes-Acr-Me][BF_4] (**H**) and varying amounts of 3,4-dihydroquinoxalin-2-one **8.1a** (from 0 to 19.2 mM). Thereafter, the emission spectrum for each solution was recorded using $\lambda_{exc} = 450$. All spectra are superimposed in Figure 8.4.

As expected, the greater the concentration of **8.1a**, the smaller the emission intensity, which is consistent with our assumption. Besides, according to the Stern-Volmer relationship shown in Equation (11) (page 12), the quotient I^0/I, where I^0 is the emission intensity of the solution without **8.1a** and I is the emission intensity of each solution, has to be directly proportional to the concentration of the quencher (**8.1a** in this case). Therefore, the plot of I^0/I against the concentration of **8.1a**, should be linear, and it is possible to extract the Stern-Volmer constant (K_{SV}) for the photocatalytic process (Figure 8.5). In this case, K_{SV} has a value of 127 M^{-1}.

Nonetheless, the detection of **8.2a**·TEMPO adduct did not seem consistent with the redox ability of [Mes-Acr-Me][BF_4] (**H**). The formation of **8.2a**·TEMPO requires the formation of the corresponding distopic dibenzylic radical anion, which should arise from the direct single-electron reduction of *p*-quinone methide **8.2a**. However, the reduction potential of **8.2a** was reported to be as low as -1.18 V (vs SCE), whereas the reduction potential of $\mathbf{H}^{\bullet}$ in the ground state is only -0.49 V (vs SCE). This implies that the direct reduction of **8.2a** under these photochemical conditions is unlikely. Thus, we did not have a rational explanation of **8.2a**·TEMPO adduct formation.

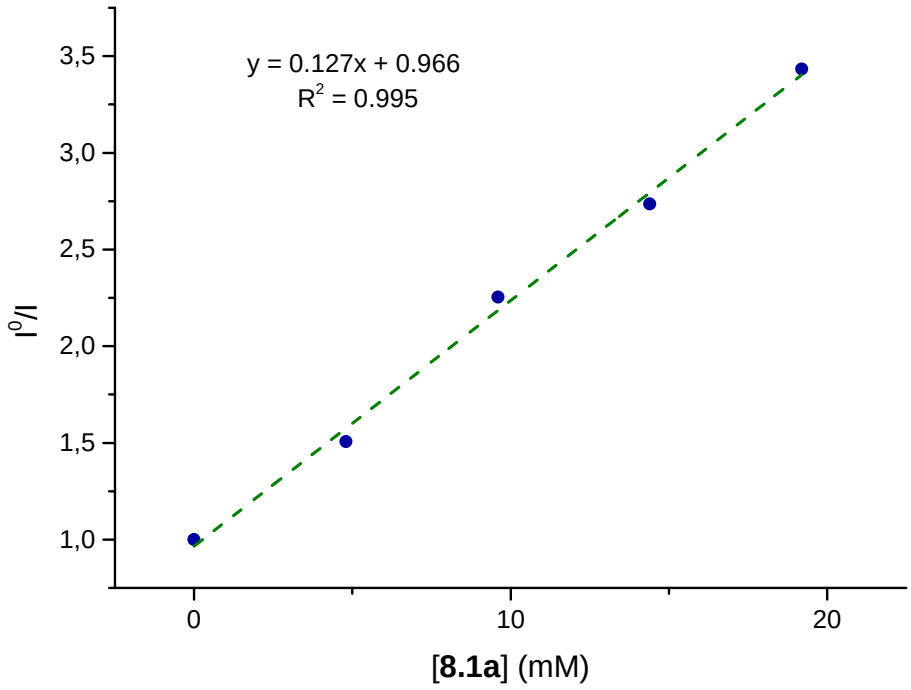


Figure 8.5: Stern-Volmer plot of I^0/I vs [**8.2a**]. Determination of K_{SV} through linear regression.

Proposed Mechanism

After gathering all these information, we were in a position to propose a mechanism by which our photocatalytic transformation between **8.1a** and **8.2a** may proceed (Figure 8.6). The first electron-transfer event comes from the excited state of [Mes-Acr-Me][BF_4] (**H**) and 3,4-dihydroquinoxalin-2-one **8.1a**, which results in the formation of radical cation **8.I** and the reduced form of the photocatalyst $\mathbf{H}^{\bullet}$. As always, radical cation **8.I** experiments the loss of a proton at the α position to generate the nucleophilic α-amino radical **8.II**. This carbon centered radical **8.II** is nucleophilic enough to react with the electrophilic exocyclic carbon of *p*-quinone methide **8.2a** in a 1,6-fashion. The product of this radical addition may be *O*-centered radical **8.III**, which undergoes a SET event with the reduced form of the photocatalyst $\mathbf{H}^{\bullet}$, to yield alcoxide **8.IV** and the photocatalyst base form. Finally, a proton transfer over **8.IV** affords the desired product **8.3aa**.

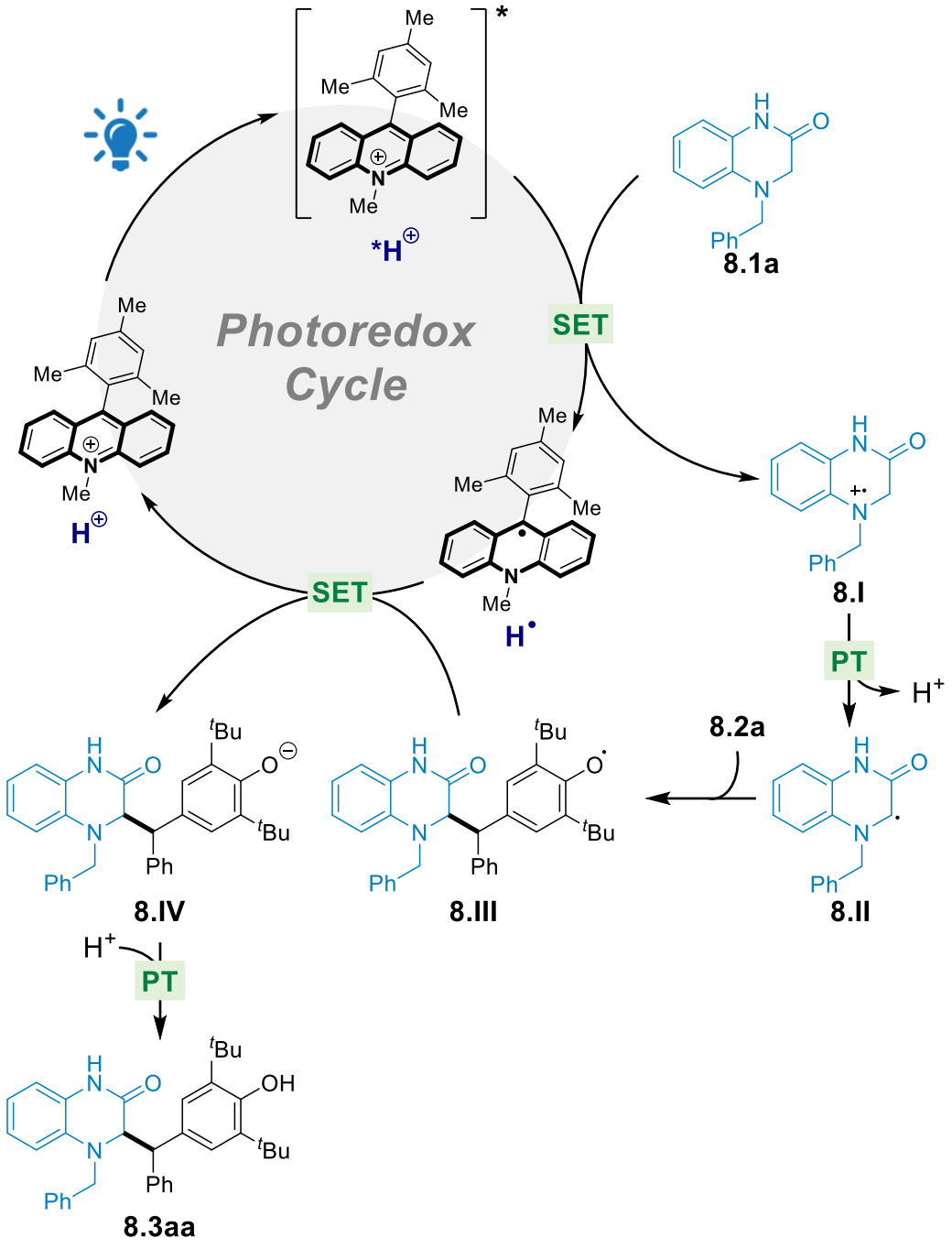


Figure 8.6: General mechanism for the photocatalytic reaction between 3,4-dihydroquinoxalin -2-one **8.1a** and *p*-quinone methide **8.2a**.

8.4 Experimental Section

8.4.1 General Methods

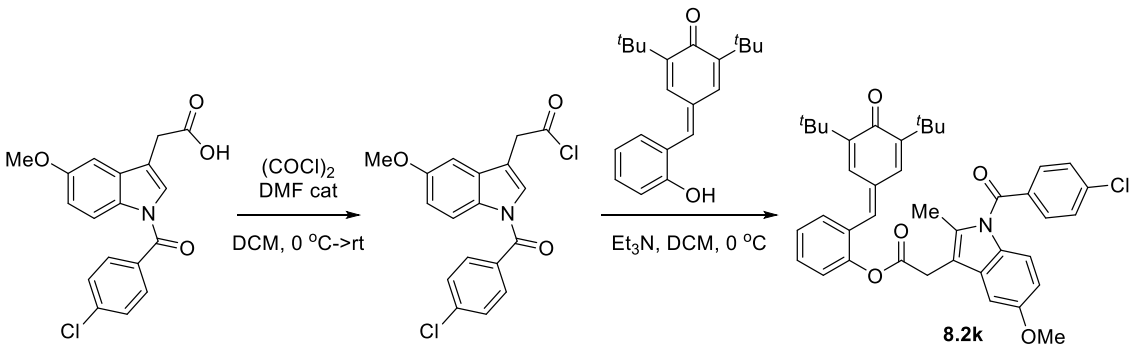
Experimental methods regarding **Melting Points**, **Chromatographic Methods**, **Nuclear Magnetic Resonance (NMR)** and **High Resolution Mass Spectrometry (HRMS)** can be found in Section 1.4.1 of *Chapter 1* (page 62).

Reaction Flasks, Reagents and Substrates

- Photochemical reactions were carried out in 10 mL culture tubes under argon unless otherwise indicated.
- Commercial reagents were used as purchased.
- DCM was degassed by Ar bubbling and stored over 3Å MS for 48 h at least. Prior to use, DCM was bubbled with Ar for 10 min.
- All photocatalysts were commercially available.
- 4-Substituted-3,4-dihydroquinoxalin-2-ones **8.1a**-**8.1b** and **8.1f**-**7.1h** were prepared form its N-4 unprotected precursors using the *N*-benzylation procedure described in page 67 of *Chapter 1*. 3,4-dihydroquinoxalin-2-one **8.1c** was synthesized following a reported procedure.[159] 3,4-dihydroquinoxalin-2-one **8.1e** was synthesized following a reported procedure described in *Chapter* 1, (page 67).
- *p*-Quinone methides **8.2a**-**8.2j** were available in our laboratory.

Synthetic Procedures and Characterization

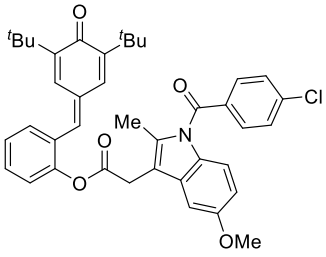
Specific Procedure 1 (SP-1) for the synthesis of indomethacin-derived *p*-quinone methide 8.2k



In a 50 mL round bottomed flask was placed commercially available indomethacin (394 mg, 1.1 mmol, 1 equiv.). It was dissolved in DCM (10 mL) and the resulting solution was cooled down to 0 °C. Then, a catalytic amount of DMF (2 drops) was added. Thereafter, oxalyl chloride (121 μL, 1.43 mmol, 1.1 equiv.) was added dropwise at that temperature and then the resulting solution was stirred for 3 hours at room temperature. After this time, the reaction mixture was evaporated to dryness under reduced pressure. Indomethacin acid chloride (398 mg, 1.1 mmol, 99% yield) was obtained as a brown solid, which was directly used in the next step without further purification.

In a 50 mL round bottomed flask was placed 2,6-di-*tert*-butyl-4-(2-hydroxybenzylidene)cyclohexa-2,5-dien-1-one (310 mg, 1 mmol, 1 equiv.) and was dissolved in DCM (10 mL). Then, Et_3N (0.17 mL, 1.2 mmol, 1.2 equiv.) was added. The resulting reaction mixture was cooled down to 0 °C, and a solution of indomethacin acid chloride (398 mg, 1.1 mmol, 1.1 equiv.) in DCM (5 mL) was added dropwise. The reaction was further stirred for 2 hours at 0 °C. After this time, the solution was partitioned with H_2O and separated. The aqueous phase was further extracted with DCM (x2) and the combined organic layers were dried over $MgSO_4$, filtered and evaporated under reduced pressure. The oily residue was purified by column chromatography using hexane:DCM 1:1 as eluent to afford the *p*-quinone methide **8.2k** (453 mg, 0.70 mmol, 70% yield) as a bright yellow solid.

2-((3,5-Di-*tert*-butyl-4-oxocyclohexa-2,5-dien-1-ylidene)methyl)phenyl 2-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl)acetate (8.2k)



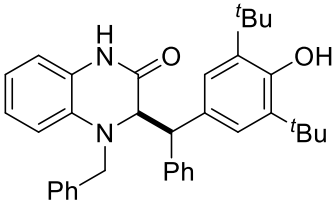
^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.64 (d, J = 8.7 Hz, 2H), 7.51 – 7.27 (m, 6H), 7.22 – 7.13 (m, 1H), 7.03 (d, J = 2.4 Hz, 1H), 6.96 – 6.90 (m, 1H), 6.86 (s, 1H), 6.77 – 6.64 (m, 2H), 3.92 (s, 2H), 3.77 (s, 3H), 2.43 (s, 3H), 1.27 (s, 9H), 1.26 (s, 9H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 186.5 (C), 168.8 (C), 168.2 (C), 156.1 (C), 149.5 (C), 149.3 (C), 148.1 (C), 139.5 (C), 136.2 (C), 135.8 (CH), 134.2 (CH), 133.6 (C), 133.2 (C), 132.0 (CH), 131.2 (CH), 130.8 (C), 130.3 (C), 130.3 (CH), 129.1 (CH), 128.7 (C), 127.8 (CH), 126.1 (CH), 122.7 (CH), 115.1 (CH), 111.9 (CH), 111.6 (C), 101.1 (CH), 55.6 (CH_3), 35.4 (CH_2), 34.9 (C), 30.5 (C), 29.5 (CH_3), 29.4 (CH_3), 13.4 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{40}H_{41}ClNO_5^+$ 650.2668, found 650.2671.

General Procedure 1 (GP-1) for the Photocatalytic Reaction between 3,4-dihydroquinoxalin-2-ones 8.1 and *p*-quinone methides 8.2

In an ovendried 10 mL culture tube, the corresponding 3,4-dihydroquinoxalin-2-one (**8.1**, 0.15 mmol, 0.15 equiv.), the corresponding *p*-quinone methide (**8.2**, 0.1 mmol, 1

equiv.) and [Mes-Acr-Me][BF_4] (**H**, 2 mg, 5 mol %) were placed. Then, anhydrous and degassed DCM (1 mL) was added, and the solution was bubbled with Ar for 10 minutes at 0 ° to prevent evaporation. The reaction mixture was stirred under the irradiation of a HP Single LED (455 nm) (see page 433 for further details about the photochemical setup) while being cooled with a fan to keep the temperature at approximately 25 °C. Once the reaction was finished (TLC), the mixture was analyzed by ^{1}H-NMR to determine the diastereomeric ratio. Thereafter, it was purified by column chromatography using hexane:EtOAc mixtures to afford the corresponding compound **8.3**.

4-Benzyl-3-((3,5-di-*tert*-butyl-4-hydroxyphenyl)(phenyl)methyl)-3,4-dihydroquinoxalin-2(1*H*)-one (8.3aa)

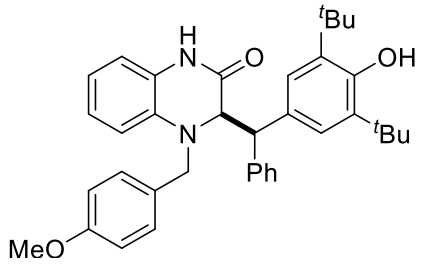


Using 4-benzyl-3,4-dihydroquinoxalin-2-one (**8.1a**, 38.4 mg, 0.15 mmol, 1.5 equiv.) and 4-benzylidene-2,6-di-*tert*-butylcyclohexa-2,5-dien-1-one (**8.2a**, 29.4 mg, 0.1 mmol, 1 equiv.), according to GP-1, compound **8.3aa** (52.5 mg, 0.099 mmol, 99% yield) was obtained as a mixture of diastereomers (1:1 dr) that were separated by column chromatography using hexane:EtOAc mixtures (from 9:1 to 8:2).

Characterization of **8.3aa'**: **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 8.33 (s, 1H), 7.31 – 7.27 (m, 5H), 7.25 – 7.16 (m, 3H), 7.05 (dd, *J* = 7.5, 2.0 Hz, 2H), 7.00 (s, 2H), 6.93 (td, *J* = 7.7, 1.5 Hz, 1H), 6.76 (td, *J* = 7.6, 1.3 Hz, 1H), 6.61 (td, *J* = 7.8, 1.4 Hz, 2H), 5.00 (s, 1H), 4.59 (dd, *J* = 8.1, 0.8 Hz, 1H), 4.23 (d, *J* = 15.4 Hz, 1H), 4.08 (d, *J* = 8.1 Hz, 1H), 3.76 (d, *J* = 15.5 Hz, 1H), 1.33 (s, 18H).**^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 165.5 (C), 152.52 (C), 142.37 (C), 136.96 (C), 135.13 (C), 133.63 (C), 129.82 (C), 128.85 (C), 128.79 (CH), 128.52 (CH), 128.48 (CH), 127.52 (CH), 127.32 (CH), 126.72 (CH), 125.66 (CH), 123.89 (CH), 119.16 (CH), 115.21 (CH), 114.52 (CH), 66.77 (CH), 53.97 (CH_2), 52.87 (CH), 34.26 (C), 30.27 (CH_3). **HRMS (ESI/Q-TOF)** *m/z* [M + H]$^+$ calcd for $C_{36}H_{41}N_2O_2^+$ 533.3163, found 533.3179.

Characterization of **8.3aa"**: **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 8.40 (s, 1H), 7.40 – 7.32 (m, 2H), 7.29 – 7.11 (m, 6H), 7.03 – 6.93 (m, 5H), 6.83 (td, *J* = 7.6, 1.2 Hz, 1H), 6.70 (dd, *J* = 7.7, 1.4 Hz, 1H), 6.53 (dd, *J* = 8.1, 1.2 Hz, 1H), 5.19 (s, 1H), 4.51 (dd, *J* = 10.5, 1.1 Hz, 1H), 4.06 – 3.93 (m, 2H), 3.48 (d, *J* = 15.3 Hz, 1H), 1.43 (s, 18H).**^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 165.69 (C), 153.11 (C), 140.01 (C), 137.13 (C), 136.14 (C), 133.51 (C), 131.63 (C), 128.75 (CH), 128.57 (CH), 128.21 (CH), 127.44 (CH), 127.38 (CH), 126.91 (C), 126.89 (CH), 125.47 (CH), 123.87 (CH), 119.21 (CH), 115.60 (CH), 114.89 (CH), 66.27 (CH), 54.00 (CH_2), 52.06 (CH), 34.44 (C), 30.36 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* [M + H]$^+$ calcd for $C_{36}H_{41}N_2O_2^+$ 533.3163, found 533.3168.

3-((3,5-Di-*tert*-butyl-4-hydroxyphenyl)(phenyl)methyl)-4-(4-methoxybenzyl)-3,4-dihydroquinoxalin-2(1*H*)-one (8.3ba)

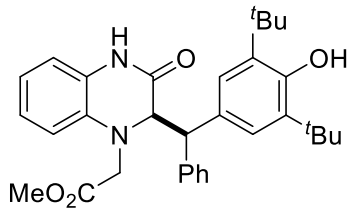


Using 4-(4-methoxybenzyl)-3,4-dihydroquinoxalin-2(1*H*)-one (**8.1b**, 40.2 mg, 0.15 mmol, 1.5 equiv.) and 4-benzylidene-2,6-di-*tert*-butylcyclohexa-2,5-dien-1-one (**8.2a**, 29.4 mg, 0.1 mmol, 1 equiv.), according to GP-1, compound **8.3ba** (55.7 mg, 0.099 mmol, 99% yield) was obtained as a mixture of diastereomers (1:1 dr) that were separated by column chromatography using hexane:EtOAc mixtures (from 9:1 to 8:2).

Characterization of **8.3ba'**: **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 8.08 (sa, 1H), 7.29 – 7.21 (m, 5H), 6.99 – 6.94 (m, 4H), 6.92 (dd, *J* = 8.0, 1.4 Hz, 1H), 6.81 – 6.71 (m, 3H), 6.61 (ddd, *J* = 7.7, 6.3, 1.3 Hz, 2H), 4.99 (s, 1H), 4.57 (d, *J* = 8.0 Hz, 1H), 4.19 (d, *J* = 15.0 Hz, 1H), 4.06 (d, *J* = 8.0 Hz, 1H), 3.75 (s, 3H), 3.69 (d, *J* = 15.0 Hz, 1H), 1.33 (s, 18H). **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 165.53 (C), 158.82 (C), 152.47 (C), 142.41 (C), 135.07 (C), 133.77 (C), 129.84 (C), 128.83 (CH), 128.75 (C), 128.42 (CH), 126.93 (C), 126.64 (CH), 125.65 (CH), 123.81 (CH), 119.08 (CH), 115.05 (CH), 114.56 (CH), 113.90 (CH), 66.19 (CH), 55.21 (CH), 53.35 (CH_2), 52.80(CH_3), 34.23 (C), 30.26 (CH_3). **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{37}H_{43}N_2O_3^+$ 563,3268, found 563.3252.

Characterization of **8.3ba''**: **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 8.39 (s, 1H), 7.34 (d, *J* = 7.0 Hz, 1H), 7.28 – 7.20 (m, 3H), 7.20 – 7.07 (m, 1H), 7.04 – 6.95 (m, 3H), 6.90 (d, *J* = 8.7 Hz, 2H), 6.83 (td, *J* = 7.6, 1.2 Hz, 1H), 6.76 (d, *J* = 8.7 Hz, 2H), 6.68 (dd, *J* = 7.7, 1.5 Hz, 1H),6.56 (d, *J* = 7.6 Hz, 1H), 5.18 (s, 1H), 4.48 (dd, *J* = 10.5, 1.0 Hz, 1H), 4.01 – 3.85 (m, 2H), 3.76 (s, 3H), 3.38 (d, *J* = 14.8 Hz, 1H), 1.43 (s, 18H). **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 165.62 (C), 158.86 (C), 153.04 (C), 140.01 (C), 136.03 (C), 133.66 (C), 131.62 (C), 128.90 (C), 128.75 (CH), 128.73 (CH), 128.16 (CH), 126.90 (C), 126.83 (CH), 125.43 (CH), 123.79 (CH), 119.09 (CH), 115.49 (CH), 114.87 (CH), 113.94 (CH), 65.52 (CH), 55.20 (CH), 53.34 (CH_2), 51.95 (CH_3), 34.40 (C), 30.32 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{37}H_{43}N_2O_3^+$ 563.3268, found 563.3271.

Methyl 2-(2-((3,5-di-*tert*-butyl-4-hydroxyphenyl)(phenyl)methyl)-3-oxo-3,4-dihydroquinoxalin-1(2*H*)-yl)acetate (8.3ca)

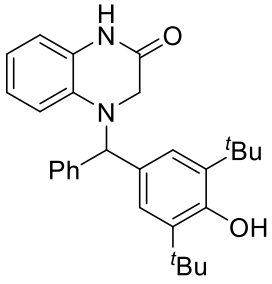


Using methyl 2-(3-oxo-3,4-dihydroquinoxalin-1(2*H*)-yl) acetate (**8.1c**, 33.0 mg, 0.15 mmol, 1.5 equiv.) and 4-benzylidene-2,6-di-*tert*-butylcyclohexa-2,5-dien-1-one (**8.2a**, 29.4 mg, 0.1 mmol, 1 equiv.), according to GP-1, compound **8.3ca** (41.7 mg, 0.081 mmol, 81% yield) was

obtained as a mixture of diastereomers (1:1 dr) that cannot be separated by column chromatography using hexane:EtOAc mixtures (from 9:1 to 8:2).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.97 (s, 1H), 8.86 (s, 1H), 7.39 (d, J = 7.1 Hz, 2H), 7.31 – 7.13 (m, 8H), 7.10 (s, 2H), 7.00 (s, 2H), 6.99 – 6.91 (m, 2H), 6.85-6.75 (m, 2H), 6.67 (dd, J = 7.7, 1.4 Hz, 1H), 6.59-6-55 (m, 2H), 6.48 (dd, J = 8.1, 1.1 Hz, 1H), 5.14 (s, 1H), 5.04 (s, 1H), 4.55-4.51 (m, 2H), 4.10 (d, J = 8.1 Hz, 1H), 3.96 (d, J = 9.7 Hz, 1H), 3.84 (d, J = 18.0 Hz, 1H), 3.69 (d, J = 17.8 Hz, 1H), 3.59 (s, 6H), 3.42 (d, J = 18.0 Hz, 1H), 3.17 (d, J = 17.9 Hz, 1H), 1.38 (s, 18H), 1.36 (s, 18H). **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 170.46 (C), 170.24 (C), 165.48 (C), 165.31 (C), 152.86 (C), 152.52 (C), 141.72 (C), 139.85 (C), 136.02 (C), 135.18 (C), 132.60 (C), 132.42 (C), 130.98 (C), 129.74 (C), 128.73 (CH), 128.68 (CH), 128.35 (CH), 128.19 (CH), 127.19 (C), 127.12 (C), 126.80 (CH), 126.71 (CH), 125.57 (CH), 125.26 (CH), 123.79 (CH), 119.92 (CH), 115.92 (CH), 115.73 (CH), 114.58 (CH), 114.49 (CH), 68.27 (CH), 67.82 (CH), 53.82 (CH_2), 53.73 (CH), 52.98 (CH_2), 52.91 (CH), 52.05 (2xCH3), 34.32 (C), 34.24 (C), 30.26 (CH_3), 3.25 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{32}H_{39}N_2O_4^+$ 515.2904, found 515.2909.

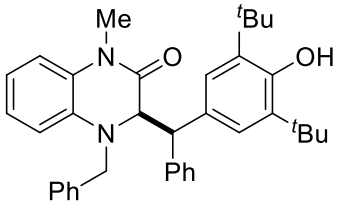
4-((3,5-Di-*tert*-butyl-4-hydroxyphenyl)(phenyl)methyl)-3,4-dihydroquinoxalin-2(1*H*)-one (8.3da)



Using 3,4-dihydroquinoxalin-2(1*H*)-one (**8.1d**, 22.2 mg, 0.15 mmol, 1.5 equiv.) and 4-benzylidene-2,6-di-*tert*-butylcyclohexa-2,5-dien-1-one (**8.2a**, 29.4 mg, 0.1 mmol, 1 equiv.), according to GP-1, compound **8.3da** (19.5 mg, 0.044 mmol, 44% yield) was obtained after column chromatography using hexane:EtOAc mixtures (from 9:1 to 8:2).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.73 (s, 1H), 7.38–7.27 (m, 5H), 6.97 (d, J = 0.6 Hz, 2H), 6.89 (ddd, J = 8.2, 6.3, 2.6 Hz, 1H), 6.81–6.70 (m, 3H), 5.93 (s, 1H), 5.22 (s, 1H), 3.77 (d, J = 2.5 Hz, 2H), 1.36 (s, 18H). **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 167.45 (C), 153.25 (C), 139.92 (C), 135.92 (C), 135.47 (C), 129.11 (C), 128.52 (CH), 128.32 (CH), 127.31 (CH), 126.45 (C), 125.92 (CH), 123.98 (CH), 118.81 (CH), 115.50 (CH), 114.03 (CH), 66.05 (CH), 48.68 (CH_2), 34.32 (C), 30.25 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{29}H_{35}N_2O_2^+$ 443.2693, found 443.2697.

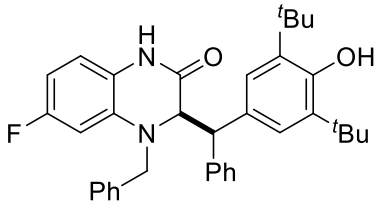
4-Benzyl-3-((3,5-di-*tert*-butyl-4-hydroxyphenyl)(phenyl)methyl)-1-methyl-3,4-dihydroquinoxalin-2(1*H*)-one (8.3ea)



Using 4-benzyl-1-methyl-3,4-dihydroquinoxalin-2(1*H*)-one (**8.1e**, 37.8 mg, 0.15 mmol, 1.5 equiv.) and 4-benzylidene-2,6-di-*tert*-butylcyclohexa-2,5-dien-1-one (**8.2a**, 29.4 mg, 0.1 mmol, 1 equiv.), according to GP-1, compound **8.3ea** (48.7 mg, 0.089 mmol, 89% yield) was obtained as a mixture of diastereomers (1:1 dr) that cannot be separated by column chromatography using hexane:EtOAc mixtures (from 9:1 to 8:2).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.41 – 7.37 (m, 2H), 7.33 – 7.27 (m, 5H), 7.25 – 7.17 (m, 9H), 7.10 (dd, *J* = 7.3, 2.3 Hz, 2H), 7.03 – 6.98 (m, 6H), 6.96-6.91 (m, 2H), 6.87 – 6.80 (m, 3H), 6.74 (dd, *J* = 7.9, 1.5 Hz, 1H), 6.67 (dd, *J* = 8.0, 1.4 Hz, 1H), 6.56 (d, *J* = 7.7 Hz, 1H), 5.18 (s, 1H), 4.99 (s, 1H), 4.67 (d, *J* = 6.0 Hz, 1H), 4.61 (d, *J* = 9.9 Hz, 1H), 4.38 (d, *J* = 15.1 Hz, 1H), 4.06 (d, *J* = 6.0 Hz, 1H), 4.00 (d, *J* = 6.4 Hz, 1H), 3.97 – 3.85 (m, 2H), 3.58 (d, *J* = 15.2 Hz, 1H), 3.29 (s, 3H), 3.19 (s, 3H), 1.43 (s, 18H), 1.33 (s, 18H). **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 164.87 (C), 164.72 (C), 152.98 (C), 152.28 (C), 142.94 (C), 140.20 (C), 137.00 (C), 136.64 (C), 136.03 (C), 134.97 (C), 134.95 (C), 134.75 (C), 131.85 (C), 130.58 (C), 130.51 (C), 130.23 (C), 128.71 (CH), 128.60 (CH), 128.49 (CH), 128.46 (CH), 128.41 (CH), 128.10 (CH), 127.66 (CH), 127.44 (CH), 127.29 (CH), 127.27 (CH), 126.75 (CH), 126.44 (CH), 125.58 (CH), 125.44 (CH), 123.39 (CH), 123.29 (CH), 119.24 (CH), 119.18 (CH), 114.72 (CH), 114.64 (CH), 114.16 (CH), 114.00 (CH), 66.87 (CH), 66.52 (CH), 53.91 (CH_2), 53.50 (CH_2), 53.13 (CH), 51.89 (CH), 34.37 (C), 34.13 (C), 30.31 (CH_3), 30.21 (CH_3), 29.38 (CH_3), 29.06 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{37}H_{43}N_2O_2^+$ 547.3319, found 547.3327.

4-Benzyl-3-((3,5-di-*tert*-butyl-4-hydroxyphenyl)(phenyl)methyl)-6-fluoro-3,4-dihydroquinoxalin-2(1*H*)-one (8.3fa)



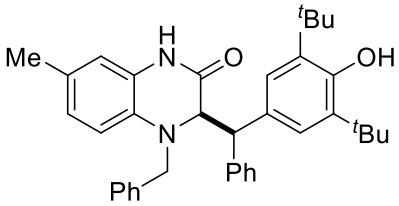
Using 4-benzyl-6-fluoro-3,4-dihydroquinoxalin-2(1*H*)-one (**8.1f**, 38.4 mg, 0.15 mmol, 1.5 equiv.) and 4-benzylidene-2,6-di-*tert*-butylcyclohexa-2,5-dien-1-one (**8.2a**, 29.4 mg, 0.1 mmol, 1 equiv.), according to GP-1, compound **8.3fa** (31.9 mg, 0.058 mmol, 58% yield) was obtained as a mixture of diastereomers (1:1 dr) that were separated by column chromatography using hexane:EtOAc mixtures (from 9:1 to 8:2).

Characterization of **8.3fa'**: **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 8.44 (d, *J* = 18.7 Hz, 1H), 7.32 – 7.18 (m, 8H), 7.06 (dd, *J* = 7.4, 2.1 Hz, 2H), 7.00 (s, 2H), 6.48 (dd, *J* = 8.5, 5.6 Hz, 1H), 6.41 (td, *J* = 8.3, 2.5 Hz, 1H), 6.30 (dd, *J* = 10.7, 2.5 Hz, 1H), 5.01 (s, 1H),

4.60 (d, *J* = 7.8 Hz, 1H), 4.16 (d, *J* = 15.6 Hz, 1H), 4.09 (d, *J* = 7.8 Hz, 1H), 3.78 (d, *J* = 15.5 Hz, 1H), 1.33 (s, 18H). **^{19}F{^{1}H}-NMR (282 MHz, $CDCl_3$)** δ -118.71.**^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 165.25 (C), 152.58 (C), 141.97 (C), 136.21 (C), 135.18 (C), 129.49 (C), 128.64 (CH), 127.55 (CH), 127.43 (CH), 126.84 (CH), 125.64 (CH), 122.83 (d, J_{C-F} = 2.3 Hz, C), 115.47 (d, J_{C-F} = 10.0 Hz, CH), 101.56 (d, *J* = 27.2 Hz, CH), 101.56 (d, *J* = 27.2 Hz, CH), 66.46 (CH), 53.80 (CH_2), 53.05 (CH), 34.22 (C), 30.23 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* [M + H]$^+$ calcd for $C_{36}H_{40}FN_2O_2^+$ 551.3068, found 551.3072.

Characterization of **8.3fa''**: **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 8.32 (s, 1H), 7.36 – 7.31 (m, 2H), 7.29 – 7.13 (m, 6H), 6.98 (d, *J* = 7.9 Hz, 4H), 6.60 (dd, *J* = 8.5, 5.5 Hz, 1H), 6.50 (td, *J* = 8.4, 2.6 Hz, 1H), 6.22 (dd, *J* = 10.6, 2.6 Hz, 1H), 5.20 (s, 1H), 4.50 (dd, *J* = 10.4, 1.0 Hz, 1H), 3.95 (d, *J* = 10.4 Hz, 1H), 3.89 (d, *J* = 15.3 Hz, 1H), 3.47 (d, *J* = 15.3 Hz, 1H), 1.42 (s, 18H). **^{19}F{^{1}H}-NMR (282 MHz, $CDCl_3$)** δ -118.61.**^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 165.04 (C), 153.20 (C), 139.73 (C), 136.36 (C), 136.23 (C), 131.19 (C), 128.67 (CH), 128.25 (CH), 127.60 (CH), 127.34 (CH), 126.96 (CH), 125.39 (CH), 122.85 (d, J_{C-F} = 1.8 Hz, C), 115.92 (d, J_{C-F} = 9.7 Hz, CH), 105.17 (d, J_{C-F} = 23.6 Hz, CH), 102.14 (d, J_{C-F} = 27.8 Hz, CH), 65.99 (CH), 54.01 (CH_2), 52.31 (CH), 34.40 (C), 30.27 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* [M + H]$^+$ calcd for $C_{36}H_{40}FN_2O_2^+$ 551.3068, found 551.3071.

4-Benzyl-3-((3,5-di-*tert*-butyl-4-hydroxyphenyl)(phenyl)methyl)-7-methyl-3,4-dihydroquinoxalin-2(1*H*)-one (8.3ga)



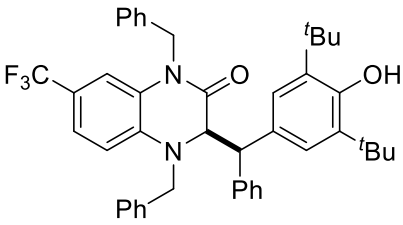
Using 4-benzyl-7-methyl-3,4-dihydroquinoxalin-2(1*H*)-one (**8.1g**, 37.4 mg, 0.15 mmol, 1.5 equiv.) and 4-benzylidene-2,6-di-*tert*-butylcyclohexa-2,5-dien-1-one (**8.2a**, 29.4 mg, 0.1 mmol, 1 equiv.), according to GP-1, compound **8.3ga** (51.9 mg, 0.095 mmol, 95% yield) was obtained as a mixture of diastereomers (1.5:1 dr) that were separated by column chromatography using hexane:EtOAc mixtures (from 9:1 to 8:2).

Characterization of **8.3ga'**: **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 8.38 (s, 1H), 7.29 (m, 4H), 7.25 – 7.16 (m, 4H), 7.04 (dd, *J* = 7.4, 2.1 Hz, 2H), 7.00 (s, 2H), 6.73 (ddd, *J* = 8.1, 1.9, 0.8 Hz, 1H), 6.50 (d, *J* = 5.9 Hz, 1H), 6.48 (d, *J* = 0.7 Hz, 1H), 4.99 (s, 1H), 4.56 (dd, *J* = 8.1, 0.9 Hz, 1H), 4.19 (d, *J* = 15.4 Hz, 1H), 4.09 (d, *J* = 8.1 Hz, 1H), 3.77 (d, *J* = 15.4 Hz, 1H), 2.25 (s, 3H), 1.34 (s, 18H). **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 165.95 (C), 152.47 (C),142,6 (C), 137.19 (C), 135.05 (C), 131.25 (C), 130.36 (C), 129.90 (C), 128.85 (CH), 128.45 (CH), 127.55 (CH), 126.99 (CH), 126.86 (C), 126.63 (CH),

125.69 (CH), 124.42 (CH), 115.95 (CH), 114.75 (CH), 66.92 (CH), 54.21 (CH_2), 52.65 (CH), 34.25 (C), 30.25 (CH_3), 20.57 (CH_3). **HRMS (ESI/Q-TOF)** *m/z* [M + H]$^+$ calcd for $C_{37}H_{43}N_2O_2^+$ 547.3319, found 547.3336.

Characterization of **8.3ga"**: **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 8.47 (s, 1H), 7.39 – 7.33 (m, 2H), 7.33 – 7.27 (m, 1H), 7.25 – 7.07 (m, 5H), 7.02 (s, 2H), 6.97 (dd, *J* = 7.4, 2.1 Hz, 2H), 6.78 (ddd, *J* = 8.1, 2.0, 0.8 Hz, 1H), 6.52 (s, 1H), 6.43 (d, *J* = 8.1 Hz, 1H), 5.18 (s, 1H), 4.47 (dd, *J* = 10.5, 1.1 Hz, 1H), 3.99-3.93 (m, 2H), 3.47 (d, *J* = 15.3 Hz, 1H), 2.30 (s, 3H), 1.43 (s, 18H).**^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 165.96 (C), 153.04 (C), 140.12 (C), 137.37 (C), 136.06 (C), 131.70 (C), 131.12 (C), 128.85 (C), 128.75 (CH), 128.48 (CH), 128.14 (CH), 127.42 (CH), 127.25 (CH), 126.91 (C), 126.81 (CH), 125.46 (CH), 124.34 (CH), 116.22 (CH), 115.05 (CH), 66.50 (CH), 54.20 (CH_2), 51.85 (CH), 34.42 (C), 30.34 (CH_3), 20.60 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* [M + H]$^+$ calcd for $C_{37}H_{43}N_2O_2^+$ 547.3319, found 547.3328.

1,4-Dibenzyl-3-((3,5-di-*tert*-butyl-4-hydroxyphenyl)(phenyl)methyl)-7-(trifluoromethyl)-3,4-dihydroquinoxalin-2(1*H*)-one (8.3ha)



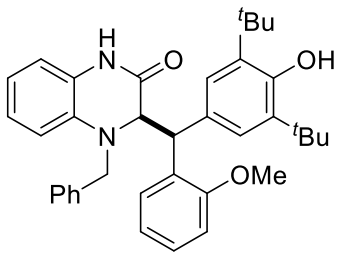
Using 1,4-dibenzyl-7-(trifluoromethyl)-3,4-dihydroquinoxalin-2(1*H*)-one (**8.1h**, 59.5 mg, 0.15 mmol, 1.5 equiv.) and 4-benzylidene-2,6-di-*tert*-butylcyclohexa-2,5-dien-1-one (**8.2a**, 29.4 mg, 0.1 mmol, 1 equiv.), according to GP-1, compound **8.3ha** (50.8 mg, 0.074 mmol, 74% yield) was obtained as a mixture of diastereomers (1.2:1 dr) that were separated by column chromatography using 95:5 hexane:EtOAc mixture.

Characterization of **8.3ha'**: **^{1}H-NMR (500 MHz, $CDCl_3$)** δ 7.37 – 7.13 (m, 12H), 7.10 – 6.93 (m, 7H), 6.62 (d, *J* = 8.4 Hz, 1H), 5.15 (d, *J* = 15.9 Hz, 1H), 5.10 (s, 1H), 4.92 (d, *J* = 15.9 Hz, 1H), 4.88 (d, *J* = 8.5 Hz, 1H), 4.17 (d, *J* = 15.6 Hz, 1H), 4.10 (d, *J* = 8.5 Hz, 1H), 3.79 (d, *J* = 15.6 Hz, 1H), 1.39 (s, 18H); **^{19}F{^{1}H}-NMR (471 MHz, $CDCl_3$)** δ -61.26; **^{13}C{^{1}H}-NMR (126 MHz, $CDCl_3$)** δ 164.1 (C), 152.7 (C), 142.3 (C), 137.6 (C), 136.3 (C), 136.1 (C), 135.4 (C), 129.7 (C), 129.4 (C), 128.7 (CH), 128.7 (CH), 128.6 (CH), 127.6 (CH), 127.3 (CH), 127.3 (CH), 127.0 (CH), 126.7 (2CH), 125.6 (CH), 124.5 (C, q, J_{C-F} = 273.8 Hz), 120.9 (CH, q, J_{C-F} = 3.6 Hz), 120.6 (C, q, J_{C-F} = 32.9 Hz), 113.7 (CH), 112.4 (CH, q, J_{C-F} = 3.9 Hz), 67.2 (CH), 54.1 (CH_2), 53.1 (CH), 46.3 (CH_2), 34.3 (C), 30.3 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* [M + H]$^+$ calcd for $C_{44}H_{46}F_3N_2O_2^+$ 691.3506, found 691.3509.

Characterization of **8.3ha"**: **^{1}H-NMR (500 MHz, $CDCl_3$)** δ 7.41 (d, *J* = 7.5 Hz, 2H), 7.32 (t, *J* = 7.6 Hz, 2H), 7.26 – 7.13 (m, 9H), 7.07 – 6.88 (m, 6H), 6.53 (d, *J* = 8.2 Hz, 1H), 5.52 (d, *J* = 15.8 Hz, 1H), 5.20 (s, 1H), 4.78 (d, *J* = 10.7 Hz, 1H), 4.59 (d, *J* = 15.8

Hz, 1H), 3.99 (d, *J* = 10.7 Hz, 1H), 3.92 (d, *J* = 15.5 Hz, 1H), 3.53 (d, *J* = 15.5 Hz, 1H), 1.40 (s, 18H); **^{19}F{^{1}H}-NMR (471 MHz, $CDCl_3$)** δ -61.26; **^{13}C{^{1}H}-NMR (126 MHz, $CDCl_3$)** δ 164.1 (C), 153.2 (C), 139.5 (C), 137.5 (C), 136.5 (C), 136.4 (C), 136.2 (C), 131.4 (C), 129.8 (C), 128.9 (CH), 128.8 (CH), 128.7 (CH), 128.3 (CH), 127.7 (CH), 127.4 (CH), 127.3 (CH), 127.1 (CH), 126.8 (CH), 126.1 (C, J_{C-F} = 271.0 Hz), 125.2 (CH), 120.8 (C, q, J_{C-F} = 32.6 Hz), 120.8 (CH, q, J_{C-F} = 3.6 Hz), 114.1 (CH), 112.4 (CH, q, J_{C-F} = 3.7 Hz), 66.5 (CH), 54.2 (CH_2), 52.1 (CH), 46.6 (CH_2), 34.4 (C), 30.3 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{44}H_{46}F_3N_2O_2^+$ 691.3506, found 691.3511.

4-Benzyl-3-((3,5-di-*tert*-butyl-4-hydroxyphenyl)(2-methoxyphenyl)methyl)-3,4-dihydroquinoxalin-2(1*H*)-one (8.3ab)



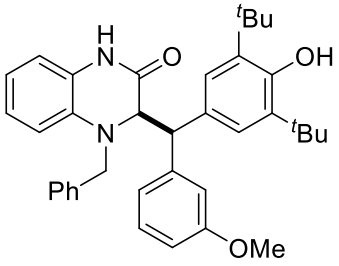
Using 4-benzyl-3,4-dihydroquinoxalin-2-one (**8.1a**, 38.4 mg, 0.15 mmol, 1.5 equiv.) and 2,6-di-*tert*-butyl-4-(2-methoxybenzylidene)cyclohexa-2,5-dien-1-one (**8.2b**, 32.4 mg, 0.1 mmol, 1 equiv.), according to GP-1, compound **8.3ab** (54.6 mg, 0.097 mmol, 97% yield) was obtained as a mixture of diastereomers (1.5:1 dr) that were separated by column chromatography using hexane:EtOAc mixtures (from 9:1 to 8:2).

Characterization of **8.3ab'**: **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 8.22 (s, 1H), 7.42 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.25 – 7.16 (m, 4H), 7.10 (dd, *J* = 7.6, 1.9 Hz, 2H), 7.05 (s, 2H), 6.91 (td, *J* = 7.5, 1.2 Hz, 1H), 6.87 – 6.79 (m, 2H), 6.69 (td, *J* = 7.5, 1.3 Hz, 1H), 6.57 (dd, *J* = 7.7, 1.5 Hz, 1H), 6.49 (d, *J* = 8.3 Hz, 1H), 4.94 (s, 1H), 4.82 (dd, *J* = 7.4, 0.9 Hz, 1H), 4.53 (d, *J* = 7.4 Hz, 1H), 4.29 (d, *J* = 15.5 Hz, 1H), 4.05 (d, *J* = 15.6 Hz, 1H), 3.67 (s, 3H), 1.32 (s, 18H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 166.24 (C), 156.98 (C), 152.24 (C), 137.29 (C), 134.66 (C), 133.81 (C), 130.69 (C), 130.19 (CH), 129.56 (C), 128.42, (CH) 127.72 (CH), 127.36, (CH) 127.12 (CH), 126.83 (C), 126.24, (CH) 123.52 (CH), 120.66 (CH), 118.76 (CH), 114.87 (CH), 114.07 (CH), 110.68 (CH), 65.96 (CH), 55.18 (CH), 53.31 (CH_2), 47.00 (CH_3), 34.17 (C), 30.28 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{37}H_{43}N_2O_3^+$ 563.3268, found 563.3267.

Characterization of **8.3ab''**: **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 8.57 (s, 1H), 7.44 (dd, *J* = 7.6, 1.3 Hz, 1H), 7.24 – 7.18 (m, 2H), 7.16 – 7.11 (m, 1H), 7.10 (s, 2H), 7.06 – 6.98 (m, 2H), 6.96 (dd, *J* = 7.5, 1.6 Hz, 1H), 6.89 (td, *J* = 7.9, 1.4 Hz, 1H), 6.80 (td, *J* = 7.5, 1.2 Hz, 1H), 6.76 – 6.67 (m, 2H), 6.48 (d, *J* = 7.8 Hz, 1H), 5.16 (s, 1H), 4.76 (d, *J* = 10.4 Hz, 1H), 4.42 (d, *J* = 10.5 Hz, 1H), 3.96 (d, *J* = 15.5 Hz, 1H), 3.65 (s, 3H), 3.53 (d, *J* = 15.5 Hz, 1H), 1.43 (s, 18H); **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 166.3 (C), 157.3 (C), 152.9 (C), 137.4 (C), 135.8 (C), 133.5 (C), 131.8 (C), 129.8 (CH), 128.6 (C), 128.4 (CH), 127.8

(CH), 127.4 (CH), 127.2 (CH), 127.0 (C), 126.1 (CH), 123.6 (CH), 120.2 (CH), 118.8 (CH), 115.3 (CH), 114.6 (CH), 110.9 (CH), 65.4 (CH), 55.2 (CH+CH_3), 54.0 (CH_2), 34.4 (C), 30.4 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{37}H_{43}N_2O_3^+$ 563.3268, found 563.3271.

4-Benzyl-3-((3,5-di-*tert*-butyl-4-hydroxyphenyl)(3-methoxyphenyl)methyl)-3,4-dihydroquinoxalin-2(1*H*)-one (8.3ac)

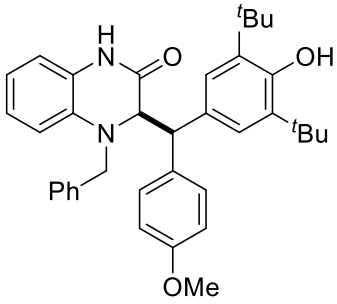


Using 4-benzyl-3,4-dihydroquinoxalin-2-one (**8.1a**, 38.4 mg, 0.15 mmol, 1.5 equiv.) and 2,6-di-*tert*-butyl-4-(3-methoxybenzylidene)cyclohexa-2,5-dien-1-one (**8.2c**, 32.4 mg, 0.1 mmol, 1 equiv.), according to GP-1, compound **8.3ac** (54.6 mg, 0.097 mmol, 97% yield) was obtained as a mixture of diastereomers (1.4:1 dr) that were separated by column chromatography using hexane:EtOAc mixtures (from 9:1 to 8:2).

Characterization of **8.3ac'**: **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 8.41 (s, 1H), 7.25 – 7.13 (m, 4H), 7.07 (dd, *J* = 7.6, 1.9 Hz, 3H), 6.93 (td, *J* = 7.7, 1.4 Hz, 2H), 7.01 (s, 2H), 6.89 – 6.83 (m, 2H), 6.82 – 6.69 (m, 2H), 6.67 – 6.56 (m, 2H), 5.00 (s, 1H), 4.58 (dd, *J* = 8.1, 0.9 Hz, 1H), 4.28 (d, *J* = 15.4 Hz, 1H), 4.05 (d, *J* = 8.1 Hz, 1H), 3.78 (d, *J* = 15.3 Hz, 1H), 3.75 (s, 1H), 1.34 (s, 18H). **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 165.56 (C), 159.56 (C), 152.52 (C), 143.87 (C), 136.93 (C), 135.11 (C), 133.65 (C), 129.64 (C), 129.39 (CH), 128.49 (CH), 127.53 (CH), 127.31 (CH), 126.87 (C), 125.58 (CH), 123.83 (CH), 121.23 (CH), 119.14 (CH), 115.17 (CH), 114.46 (CH), 114.06 (CH), 112.67 (CH), 66.60 (CH), 55.09 (CH), 53.87 (CH_2), 52.89 (CH_3), 34.23 (C), 30.25 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{37}H_{43}N_2O_3^+$ 563.3268, found 563.3264.

Characterization of **8.3ac''**: **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 8.25 (s, 1H), 7.24 – 7.15 (m, 4H), 7.03 – 6.91 (m, 6H), 6.86 (t, *J* = 2.1 Hz, 1H), 6.82 (td, *J* = 7.6, 1.2 Hz, 1H), 6.73 – 6.66 (m, 2H), 6.51 (dd, *J* = 8.1, 1.2 Hz, 1H), 5.18 (s, 1H), 4.49 (dd, *J* = 10.4, 1.0 Hz, 1H), 4.03 – 3.90 (m, 2H), 3.71 (s, 3H), 3.49 (d, *J* = 15.4 Hz, 1H), 1.42 (s, 18H).**^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 165.52 (C), 159.29 (C), 153.13 (C), 141.50 (C), 137.13 (C), 136.10 (C), 133.45 (C), 131.43 (C), 129.12 (CH), 128.57 (CH), 127.39 (CH), 127.36 (CH), 126.90 (C), 125.50 (CH), 123.85 (CH), 120.95 (CH), 119.19 (CH), 115.51 (CH), 115.10 (CH), 114.90 (CH), 112.08 (CH), 66.43 (CH), 55.06 (CH), 54.05 (CH_2), 52.18 (CH_3), 34.43 (C), 30.35 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{37}H_{43}N_2O_3^+$ 563.3268, found 563.3268.

4-Benzyl-3-((3,5-di-*tert*-butyl-4-hydroxyphenyl)(4-methoxyphenyl)methyl)-3,4-dihydroquinoxalin-2(1*H*)-one (8.3ad)

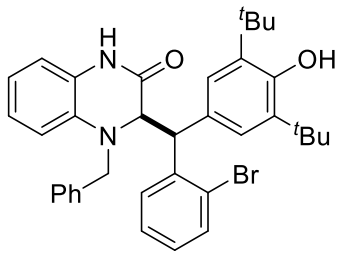


Using 4-benzyl-3,4-dihydroquinoxalin-2-one (**8.1a**, 38.4 mg, 0.15 mmol, 1.5 equiv.) and 2,6-di-*tert*-butyl-4-(4-methoxybenzylidene)cyclohexa-2,5-dien-1-one (**8.2d**, 32.4 mg, 0.1 mmol, 1 equiv.), according to GP-1, compound **8.3ac** (48.4 mg, 0.086 mmol, 86% yield) was obtained as a mixture of diastereomers (1:1 dr) that were separated by column chromatography using hexane:EtOAc mixtures (from 9:1 to 8:2).

Characterization of **8.3ad'**: **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 8.27 (s, 1H), 7.25 – 7.19 (m, 3H), 7.17 (d, *J* = 8.7 Hz, 2H), 7.07 (dd, *J* = 7.6, 1.9 Hz, 2H), 6.99 (s, 2H), 6.92 (td, *J* = 7.7, 1.5 Hz, 1H), 6.83 (d, *J* = 8.7 Hz, 2H), 6.74 (td, *J* = 7.5, 1.3 Hz, 1H), 6.60 (dd, *J* = 7.7, 1.4 Hz, 2H), 4.99 (s, 1H), 4.54 (dd, *J* = 8.1, 0.9 Hz, 1H), 4.27 (d, *J* = 15.4 Hz, 1H), 4.04 (d, *J* = 8.1 Hz, 1H), 3.81-3.76 (m, 4H), 1.34 (s, 18H). **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 165.81 (C), 158.39 (C), 152.42 (C), 137.02 (C), 135.09 (C), 134.40 (C), 133.65 (C), 132.20 (CH), 129.80 (CH),128.50 (CH), 127.49 (CH), 127.28 (C), 126.82 (CH), 125.52 (CH), 123.85 (CH), 119.03 (CH), 115.19 (CH), 114.41 (CH), 114.37 (CH), 113.80 (CH), 66.88 (CH), 55.26 (CH), 54.01 (CH_2), 52.00 (CH_3), 34.23 (C), 30.25 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{37}H_{43}N_2O_3^+$ 563.3268, found 563.3266.

Characterization of **8.3ad"**: **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 8.16 (s, 1H), 7.28 (d, *J* = 2.1 Hz, 1H), 7.26 – 7.17 (m, 3H), 7.01 – 6.92 (m, 6H),6.84 (dd, *J* = 7.6, 1.3 Hz, 1H), 6.79 (d, *J* = 8.8 Hz, 2H), 6.70 (dd, *J* = 7.7, 1.5 Hz, 1H), 6.52 (dd, *J* = 8.1, 1.2 Hz, 1H), 5.17 (s, 1H), 4.45 (dd, *J* = 10.6, 1.0 Hz, 1H), 4.06 – 3.84 (m, 2H), 3.71 (s, 3H), 3.46 (d, *J* = 15.3 Hz, 1H), 1.42 (s, 18H). **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 165.61 (C), 158.34 (C), 153.01 (C), 137.10 (C), 136.08 (C), 133.51 (C), 132.15 (C), 131.98 (C), 129.64 (CH), 128.53 (CH), 127.41 (CH), 127.33 (CH), 126.85 (C), 125.29 (CH), 123.85 (CH), 119.15 (CH), 115.42 (CH), 114.86 (CH), 113.60 (CH), 66.35 (CH) , 55.05 (CH), 53.93 (CH_2), 51.15 (CH_3), 34.40 (C), 30.32 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{37}H_{43}N_2O_3^+$ 563.3268, found 563.3265.

4-Benzyl-3-((2-bromophenyl)(3,5-di-*tert*-butyl-4-hydroxyphenyl)methyl)-3,4-dihydroquinoxalin-2(1*H*)-one (8.3ae)

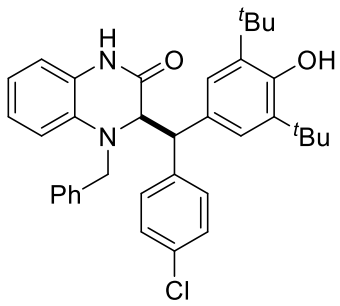


Using 4-benzyl-3,4-dihydroquinoxalin-2-one (**8.1a**, 38.4 mg, 0.15 mmol, 1.5 equiv.) and 4-(2-bromobenzylidene)-2,6-di-*tert*-butylcyclohexa-2,5-dien-1-one (**8.2e**, 37.3 mg, 0.1 mmol, 1 equiv.), according to GP-1, compound **8.3ae**

(54.4 mg, 0.089 mmol, 89% yield) was obtained as a mixture of diastereomers (1.4:1 dr) that cannot be separated by column chromatography using hexane:EtOAc mixtures (from 9:1 to 8:2).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.45 (s, 1H), 8.38 (s, 1H), 7.92 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.75 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.51 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.39 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.31 (td, *J* = 7.6, 1.4 Hz, 3H), 7.25 – 7.16 (m, 4H), 7.12 (dd, *J* = 6.9, 2.6 Hz, 2H), 7.10 – 7.06 (m, 1H), 7.03 – 6.99 (m, 4H), 6.99 – 6.94 (m, 3H), 6.94 – 6.89 (m, 2H), 6.85 (td, *J* = 7.5, 1.2 Hz, 1H), 6.78 (d, *J* = 1.5 Hz, 1H), 6.77 – 6.74 (m, 1H), 6.71 (d, *J* = 7.3 Hz, 2H), 6.54 (d, *J* = 7.9 Hz, 1H), 6.45 (dd, *J* = 8.0, 1.4 Hz, 1H), 5.20 (sa, 1H), 4.97 (sa, 1H), 4.74 (d, *J* = 5.3 Hz, 1H), 4.63 (d, *J* = 10.7 Hz, 1H), 4.58 – 4.44 (m, 3H), 4.07 (d, *J* = 14.9 Hz, 1H), 4.00 (d, *J* = 15.3 Hz, 1H), 3.48 (d, *J* = 15.2 Hz, 1H), 1.42 (s, 18H), 1.28 (s, 18H). **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 166.21 (C), 165.44 (C), 153.14 (C), 152.39 (C), 142.01 (C), 138.89 (C), 137.10 (C), 136.40 (C), 136.01 (C), 134.94 (C), 133.80 (C), 133.38 (C), 132.95 (CH), 132.86 (CH), 130.02 (CH), 129.96 (C), 129.56, (CH) 128.55 (CH), 128.50 (CH), 128.34 (C), 128.19 (CH), 127.86 (CH), 127.82 (CH), 127.67 (CH), 127.41 (CH), 127.37 (CH), 126.97 (C), 126.92 (CH), 126.88 (C), 126.11 (CH), 125.86 (CH), 125.02 (C), 123.78 (CH), 119.54 (CH), 119.43 (CH), 115.62 (CH), 114.96 (CH), 114.90 (CH), 114.31 (CH), 66.32 (CH), 65.52 (CH), 53.98 (CH_2), 53.30 (CH_2), 51.68 (CH), 49.28 (CH), 34.36 (C), 34.11 (C), 30.30 (CH_3), 30.13 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{36}H_{40}BrN_2O_2^+$ 611.2268, found 611.2271.

4-Benzyl-3-((4-chlorophenyl)(3,5-di-*tert*-butyl-4-hydroxyphenyl)methyl)-3,4-dihydroquinoxalin-2(1*H*)-one (8.3af)



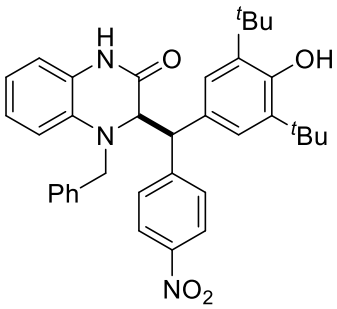
Using 4-benzyl-3,4-dihydroquinoxalin-2-one (**8.1a**, 38.4 mg, 0.15 mmol, 1.5 equiv.) and 2,6-di-*tert*-butyl-4-(4-chlorobenzylidene)cyclohexa-2,5-dien-1-one (**8.2f**, 32.8 mg, 0.1 mmol, 1 equiv.), according to GP-1, compound **8.3af** (54.4 mg, 0.096 mmol, 89% yield) was obtained as a mixture of diastereomers (1:1 dr) that were separated by column chromatography using hexane:EtOAc mixtures (from 9:1 to 8:2).

Characterization of **8.3af'**: **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 8.26 (s, 1H), 7.28 – 7.15 (m, 7H), 7.08 (dd, *J* = 7.4, 2.0 Hz, 2H), 6.99 – 6.89 (m, 3H), 6.76 (td, *J* = 7.6, 1.3 Hz, 1H), 6.66 (d, *J* = 8.0 Hz, 1H), 6.59 (dd, *J* = 7.7, 1.5 Hz, 1H), 5.03 (s, 1H), 4.54 (dd, *J* = 7.6, 0.9 Hz, 1H), 4.35 (d, *J* = 15.2 Hz, 1H), 4.06 (d, *J* = 7.6 Hz, 1H), 3.82 (d, *J* = 15.2 Hz, 1H), 1.33 (s, 18H). **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 165.42 (C), 152.70 (C), 144.42 (C), 136.60 (C), 135.31 (C), 134.14 (C), 133.60 (C), 129.67 (CH), 129.19 (CH), 129.03 (C),

128.64 (CH), 127.69 (CH), 127.52 (CH), 126.89 (CH), 125.67 (CH), 124.04 (CH), 119.50 (CH), 115.22 (CH), 114.65 (CH), 66.10 (CH), 54.19 (CH_2), 52.66 (CH), 34.26 (C), 30.23 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{36}H_{40}ClN_2O_2^+$ 567.2773, found 567.2770.

Characterization of **8.3af''**: **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 8.28 (s, 1H), 7.37 – 7.30 (m, 1H), 7.25 – 7.09 (m, 6H), 7.02 – 6.92 (m, 5H), 6.84 (td, *J* = 7.6, 1.2 Hz, 1H), 6.69 (dd, *J* = 7.7, 1.5 Hz, 1H), 6.53 (d, *J* = 7.9 Hz, 1H), 5.22 (s, 1H), 4.47 (dd, *J* = 10.4, 1.1 Hz, 1H), 4.04 – 3.84 (m, 2H), 3.46 (d, *J* = 15.3 Hz, 1H), 1.42 (s, 18H). **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 165.36 (C), 153.25 (C), 142.04 (C), 136.91 (C), 136.27 (C), 133.88 (C), 133.28 (C) , 130.84 (C), 129.34 (CH), 128.58 (CH), 127.43 (CH), 127.40 (CH), 127.06 (CH), 126.72 (C), 126.56 (CH) , 125.38 (CH), 123.97 (CH), 119.41 (CH), 115.56 (CH), 114.94 (CH), 65.89 (CH), 54.01 (CH_2), 51.69 (CH), 34.42 (C), 30.29 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{36}H_{40}ClN_2O_2^+$ 567.2773, found 567.2775.

4-Benzyl-3-((3,5-di-*tert*-butyl-4-hydroxyphenyl)(4-nitrophenyl)methyl)-3,4-dihydroquinoxalin-2(1*H*)-one (8.3ag)

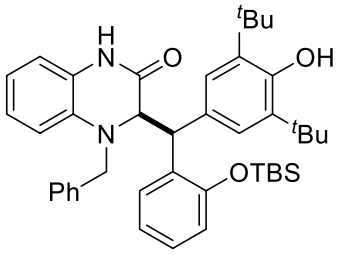


Using 4-benzyl-3,4-dihydroquinoxalin-2-one (**8.1a**, 38.4 mg, 0.15 mmol, 1.5 equiv.) and 2,6-di-*tert*-butyl-4-(4-nitrobenzylidene)cyclohexa-2,5-dien-1-one (**8.2g**, 33.9 mg, 0.1 mmol, 1 equiv.), according to GP-1, compound **8.3ag** (57.6 mg, 0.099 mmol, 99% yield) was obtained as a mixture of diastereomers (1:1 dr) that cannot be separated by column chromatography using hexane:EtOAc mixtures (from 9:1 to 8:2).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.24 (s, 1H), 9.12 (s, 1H), 8.12 (d, *J* = 8.8 Hz, 2H), 8.06 (d, *J* = 8.8 Hz, 2H), 7.52 – 7,44(m, 4H), 7.26 – 7.22 (m, 6H), 7.14 – 7.07 (m, 2H), 7.05 – 6.94 (m, 4H), 6.93 (d, *J* = 6.5 Hz, 4H), 6.85 (td, *J* = 7.6, 1.2 Hz, 1H), 6.72 (m, *J* = 8.0, 1.2 Hz, 3H), 6.58 (dd, *J* = 8.2, 1.2 Hz, 1H), 6.47 (dd, *J* = 7.7, 1.4 Hz, 1H), 5.28 (s, 1H), 5.06 (s, 1H), 4.61 (d, *J* = 6.6 Hz, 1H), 4.54 (dd, *J* = 10.4, 0.9 Hz, 1H), 4.44 (d, *J* = 15.0 Hz, 1H), 4.24 (d, *J* = 6.6 Hz, 1H), 4.07 (dd, *J* = 12.8, 2.4 Hz, 2H), 3.97 (d, *J* = 15.0 Hz, 1H), 3.47 (d, *J* = 15.1 Hz, 1H), 1.43 (s, 18H), 1.31 (s, 18H).**^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 165.82 (C), 165.72 (C), 153.47 (C), 152.85 (C), 150.04 (C), 147.68 (C), 146.58 (C), 146.52 (C), 136.68 (C), 136.54 (C), 136.26 (C), 135.51 (C), 133.39 (C), 133.14(C), 129.94 (C), 129.63 (CH), 129.58 (CH), 128.67 (CH), 128.61 (CH), 128.16 (C), 127.80 (CH), 127.69 (CH), 127.55 (CH), 127.43 (CH), 126.87 (C), 126.60 (C), 125.73 (CH), 125.35 (CH), 124.20 (CH), 124.12 (CH), 123.47 (CH), 123.25 (CH), 119.83 (CH), 119.63 (CH), 115.69 (CH), 115.29 (CH), 115.03 (CH), 114.80

(CH), 65.44 (CH), 65.28 (CH), 54.50 (CH_2), 53.95 (CH_2), 52.98 (CH), 51.76 (CH), 34.43 (C), 34.18 (C), 30.24 (CH_3), 30.11 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{36}H_{40}N_3O_4^+$ 578,3013, found 578.3015.

4-Benzyl-3-((2-((*tert*-butyldimethylsilyl)oxy)phenyl)(3,5-di-*tert*-butyl-4-hydroxyphenyl)methyl)-3,4-dihydroquinoxalin-2(1*H*)-one (8.3ah)

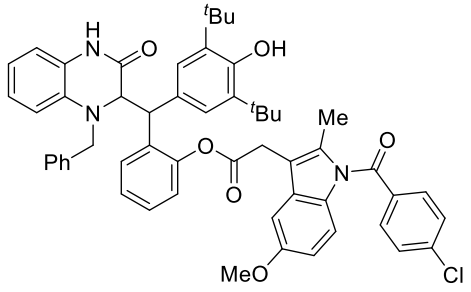


Using 4-benzyl-3,4-dihydroquinoxalin-2-one (**8.1a**, 38.4 mg, 0.15 mmol, 1.5 equiv.) and 2,6-di-*tert*-butyl-4-(2-((*tert*-butyldimethylsilyl)oxy)benzylidene)cyclohexa-2,5-dien-1-one (**8.2h**, 42.5 mg, 0.1 mmol, 1 equiv.), according to GP-1, compound **8.3ah** (64.3 mg, 0.097 mmol, 97% yield) was obtained as a mixture of diastereomers (2:1 dr) that were separated by column chromatography using hexane:EtOAc mixtures (from 9:1 to 8:2).

Characterization of **8.3ah'**: **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 8.15 (s, 1H), 7.68 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.11 (m, 3H), 7.07 – 6.97 (m, 3H), 6.91 (td, *J* = 7.5, 1.3 Hz, 1H), 6.83 – 6.75 (m, 3H), 6.71 (dd, *J* = 8.0, 1.3 Hz, 1H), 6.63 (td, *J* = 7.6, 1.3 Hz, 1H), 6.53 (d, *J* = 8.3 Hz, 1H), 6.49 (dd, *J* = 7.7, 1.5 Hz, 1H), 4.82 (s, 1H), 4.63 (d, *J* = 6.4 Hz, 1H), 4.46 (dd, *J* = 6.4, 0.8 Hz, 1H), 4.34 (d, *J* = 15.2 Hz, 1H), 3.92 (d, *J* = 15.2 Hz, 1H), 1.18 (s, 18H), 0.75 (s, 9H), 0.06 (s, 3H), -0.13 (s, 3H). **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 166.03 (C), 153.08 (C), 152.12 (C), 136.88 (C), 134.70 (C), 133.78 (C), 132.95 (C), 130.05 (C), 129.52 (C), 128.43 (CH), 127.56 (CH), 127.22 (CH), 127.15 (CH), 126.88 (C), 126.02 (CH), 123.85 (CH), 120.94 (CH), 119.26 (CH), 118.32 (CH), 114.95 (CH), 114.22 (CH), 67.32 (CH), 53.34 (CH_2), 44.73 (CH), 34.15 (C), 30.15 (CH_3), 25.95 (CH_3), 18.25 (C), -4.02 (CH_3), -4.17 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{42}H_{55}N_2O_3Si^+$ 663.3976, found 663.3979.

Characterization of **8.3ah''**: **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 7.81 (s, 1H), 7.69 (dd, *J* = 7.4, 2.1 Hz, 1H), 7.25 – 7.16 (m, 3H), 7.08 – 6.92 (m, 7H), 6.80 (td, *J* = 7.5, 1.2 Hz, 1H), 6.77 – 6.63 (m, 2H), 6.53 (d, *J* = 8.2 Hz, 1H), 5.13 (s, 1H), 4.58 (d, *J* = 11.2 Hz, 1H), 4.49 (dd, *J* = 11.2, 1.0 Hz, 1H), 3.92 (d, *J* = 15.4 Hz, 1H), 3.37 (d, *J* = 15.4 Hz, 1H), 1.40 (s, 18H), 0.80 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H). **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 165.18 (C), 153.25 (C), 152.89 (C), 137.30 (C), 135.77 (C), 133.50 (C), 131.21(C), 130.22 (C), 129.33 (CH), 128.49 (CH), 127.40 (CH), 127.27 (CH), 126.74 (C), 125.86 (CH), 123.76 (CH), 120.50 (CH), 118.96 (CH), 118.38 (CH), 115.54 (CH), 114.99 (CH), 66.01 (CH), 54.03 (CH_2), 34.41 (C), 30.32 (CH_3), 25.91 (CH_3), 18.16 (C), -3.63 (CH_3), -4.49 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{42}H_{55}N_2O_3Si^+$ 663.3976, found 663.3977.

2-((1-Benzyl-3-oxo-1,2,3,4-tetrahydroquinoxalin-2-yl)(3,5-di-*tert*-butyl-4-hydroxyphenyl)methyl)phenyl 2-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl) acetate (8.3ak)



Using 4-benzyl-3,4-dihydroquinoxalin-2-one (**8.1a**, 38.4 mg, 0.15 mmol, 1.5 equiv.) and 2-((3,5-di-*tert*-butyl-4- oxocyclohexa- 2,5-dien-1-ylidene) methyl)phenyl 2-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl) acetate (**8.2k**, 64.9 mg, 0.1 mmol, 1 equiv.), according to GP-1, compound **8.3ak** (70.2 mg, 0.079 mmol, 79% yield) was obtained as a mixture of diastereomers (1:1 dr) that were separated by column chromatography using hexane:EtOAc mixtures (from 9:1 to 8:2).

Characterization of **8.3ak'**: **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 8.14 (s, 1H), 7.72 – 7.67 (m, 1H), 7.64 (d, *J* = 8.7 Hz, 1H), 7.45 (d, *J* = 8.7 Hz, 1H), 7.24 – 7.16 (m, 6H), 7.06 – 7.01 (m, 2H), 7.00 – 6.92 (m, 6H), 6.86 (dd, *J* = 9.0, 0.5 Hz, 1H), 6.76 (td, *J* = 7.5, 1.2 Hz, 1H), 6.71 (d, *J* = 8.8 Hz, 1H), 6.69 – 6.61 (m, 2H), 5.00 (bs, 1H), 4.68 (dd, *J* = 7.1, 0.8 Hz, 1H), 4.45 (d, *J* = 7.1 Hz, 1H), 4.36 (d, *J* = 15.4 Hz, 1H), 3.89 (d, *J* = 15.5 Hz, 1H), 3.75 (s, 3H), 3.55 (d, *J* = 16.3 Hz, 1H), 3.39 (d, *J* = 16.2 Hz, 1H), 2.33 (s, 3H), 1.27 (s, 18H). **^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 169.01 (C), 168.23 (C), 165.2 (C),156.10 (C), 152.52 (C), 148.44 (C), 139.29 (C), 136.65 (C), 136.15 (C), 135.17 (C), 134.05 (C), 133.78 (C), 133,66 (C) 131.15 (CH), 130.81 (C), 130.52 (C), 129.84 (CH), 129.11 (CH), 128.50 (CH), 127.51 (CH), 127.49 (CH), 127.34 (CH), 126.75 (C), 126.09 (CH), 125.71 (CH), 124.00 (CH), 122.57 (CH), 119.30 (C), 115.13 (CH),115.02 (CH), 114.97 (CH), 111.93 (C), 111.51 (CH), 101.47 (CH), 66.25 (CH), 55.70 (CH), 53.82 (CH_2),45.34 (CH_3), 34.17 (C), 30.13 (CH_3), 29.67 (CH_2), 13.46 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{55}H_{55}ClN_3O_6^+$ 888.3774, found 888.37784.

Characterization of **8.3ak"**: **^{1}H-NMR (300 MHz, $CDCl_3$)** δ 8.21 (s, 1H), 7.71 – 7.67 (m, 1H), 7.64 (d, *J* = 8.6 Hz, 2H), 7.46 (d, *J* = 8.5 Hz, 2H), 7.24 – 7.16 (m, 4H), 7.12 (td, *J* = 7.8, 1.8 Hz, 1H), 7.06 – 6.95 (m, 6H), 6.91 (d, *J* = 2.5 Hz, 1H), 6.90 – 6.79 (m, 4H), 6.73 – 6.59 (m, 2H), 4.60 (dd, *J* = 10.5, 0.9 Hz, 1H), 4.25 (d, *J* = 10.5 Hz, 1H), 4.10 (d, *J* = 14.9 Hz, 1H), 3.78 (s, 3H), 3.60 – 3.36 (m, 3H), 2.28 (s, 3H), 1.42 (s, 18H).**^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$)** δ 168.56 (C), 168.23 (C), 164.88 (C), 156.03 (C), 153.21 (C), 148.61 (C), 139.26 (C), 136.77 (C), 136.18 (C), 136.09 (C), 133.80 (C), 133.47 (C), 131.66 (C), 131.15 (CH), 130.76 (C), 130.66 (C), 130.48 (C), 129.69 (C), 129.10 (CH), 128.56 (CH), 127.69 (CH), 127.65 (CH), 127.51 (CH), 127.04 (CH), 125.66 (CH), 125.46 (CH), 123.87 (CH), 122.36 (CH), 119.52 (CH), 115.48 (CH), 115.16 (CH), 114.92 (CH), 111.92 (C), 111.47 (CH), 101.48 (CH), 64.68 (CH) , 55.69 (CH), 54.09

(CH_2), 34.37 (C), 30.28 (CH_3), 29.89 (CH_2), 29.36 (CH_3), 13.41 (CH_3); **HRMS (ESI/Q-TOF)** *m/z* $[M + H]^+$ calcd for $C_{55}H_{55}ClN_3O_6^+$ 888.3774, found 888.3783.

Conclusions

En aquesta darrera part de la *tesi* es procedirà a plasmar les conclusions a les quals s'han arribat. Per comoditat, es descriuran individualment les conclusions per a cadascun dels capítols i, finalment, es plantejaran una sèrie de conclusions comunes.

- **Capítol 1**. S'ha desenvolupat una metodologia fotocatalítica per a la funcionalització de 3,4-dihydro-1,4-benzoxazin-2-ones **1.1** amb indoles (**1.2**) i altres sistemes aromàtics rics en electrons. El fotocatalitzador seleccionat ha sigut la 9,10-fenantrenediona (**J**), el qual és extremadament simple, disponible comercialment i de baix pes molecular. Amb aquestes condicions s'ha aconseguit sintetitzar una col·lecció de vint-i-cinc 3,4-dihydro-1,4-benzoxazin-2-ones funcionalitzades en la posició C-3 amb indoles (**1.3**) amb rendiments del 54% fins al 88%. A més a més, s'ha aconseguit dur a terme la reacció utilitzant llum solar com a font d'energia. Finalment, s'ha preparat el *Cephalandole A* a partir del producte de la reacció de Friedel-Crafts, així com un derivat de triptofol.

- **Capítol 2**. En aquest capítol s'ha aconseguit desenvolupar una metodologia one-pot per a la reacció de Mannich asimètrica oxidativa entre 3,4-dihidroquinoxalin-2-ones **2.1** i diferents cetones alifàtiques **2.2**. Per dur a terme aquesta transformació s'ha emprat Eosina groguenca (**E**) com a catalitzador fotoredox, (*S*)-prolina com a organocatalitzador, DMF com a dissolvent i LEDs blaus com a font d'energia. Amb aquestes condicions s'han preparat vint-i-dos derivats amb rendiments moderats (42-94%) i excel·lents excessos enantiomèrics (77-99%). Addicionalment, s'ha pogut escalar la reacció fins als 5 mmol utilitzant llum solar per obtindre el corresponent producte amb un rendiment del 67% i un excés enantiomèric del 99%. En aquest sentit, s'han dut a terme dues transformacions sobre el producte de la reacció de Mannich, concretament una aminació reductiva i la reducció del grup carbonil de cetona. Finalment, per esclarir el mecanisme de la reacció, s'ha dut a terme un assaig de desactivació de la luminescència de l'Eosina groguenca (**E**), i s'ha conclòs que efectivament hi ha una interacció entre la 3,4-dihidroquinoxalin-2-ona **2.1a** i l'estat excitat del fotocatalitzador **E**, que a més segueix una relació de tipus

Stern-Volmer.

- **Capítol 3**. En aquest capítol s'ha estudiat la reacció entre diferents 3,4-dihidroquinoxalin-2-ones **3.1** i pirazol-3-ones (**3.2**) utilitzant catàlisi fotoredox amb llum visible. Els corresponents productes han pogut ser generats utilitzant 9,10-fenantrendiona (**J**) com a fotocatalitzador, cloroform com a dissolvent i un LED d'alta potència (455 nm) com a font lumínica. En aquest cas, s'ha hagut d'afegir una etapa de captació de l'enol amb Ac_2O per poder aïllar i caracteritzar correctament els productes de reacció, però s'ha aprofitat aquest requeriment per a preparar un derivat altament funcionalitzat amb un residu d'indometacina a través del seu clorur d'àcid. Amb aquesta estratègia s'han sintetitzat vint-i-set híbrids quinoxalina-pirazolona (**3.3**) que presenten diferents patrons de substitució amb rendiments des del 37% al 99%. A més a més, s'han pogut utilitzar derivats de 5-aminopirazole (**3.7**) com a nucleòfils i s'han obtingut els corresponents productes (**3.8**) amb rendiments elevats (60-95%). Finalment, la reacció a escala d'1 mmol ha permés generar el producte desitjat amb un rendiment del 60% després de 7.5 hores d'exposició solar.

- **Capítol 4**. S'ha descrit satisfactòriament la reacció entre 3,4-dihidroquinoxalin-2-ones **4.1** i alquins terminals **4.2** utilitzant $Cu(OTf)_2$ com a catalitzador. En aquest cas, el paper d'aquesta sal de coure és dual, ja que per una banda actua d'oxidant de la 3,4-dihidroquinoxalin-2-ona **4.1** en combinació amb l'oxigen de l'aire per formar el corresponent catió imini electrofílic. D'altra banda, també és capaç de generar el corresponent alquinilur de coure mitjançant una desprotonació assistida per la formació d'un complex de tipus π entre l'espècie cúprica i el triple enllaç de l'alquí terminal. Curiosament, en afegir com a additiu SiO_2 el rendiment del procés va millorar. Aquesta estratègia s'ha aplicat a la síntesi de diferents alquins interns amb estructura de 3,4-dihidroquinoxalin-2-ona (**4.3**) amb rendiments moderats. A més a més, s'ha aprofitat la presència del triple enllaç en els productes d'alquinilació per a preparar una sèrie de derivats mitjançant tres procediments d'hidrogenació diferents.

- **Capítol 5**. S'ha desenvolupat de manera favorable la reacció entre les 3,4-dihidroquinoxalin-2-ones **5.1** i un gran assortiment d'alquens pobres en electrons. Aquesta reacció de tipus Giese ha sigut possible utilitzant $Ru(bpy)_3Cl_2$ (**A**) com a catalitzador fotoredox i $(PhO)_2PO_2H$ com a cocatalitzador àcid de Brønsted. Amb aquest sistema catalític dual, i utilitzant LEDs blaus com a font d'energia, s'han pogut preparar més de quaranta productes diferents amb rendiments generalment elevats o excel·lents. A més a més, s'ha pogut escalar la reacció a 5 mmol i s'ha obtingut el corresponent producte amb un 97% de rendiment. Així mateix, s'han dut a terme

una sèrie de transformacions sintètiques, d'entre les quals hi destaca la síntesi de dos derivats de pirrole i una descarboxilació de tipus Krapcho. Finalment, s'ha realitzat un estudi profund del mecanisme d'aquesta reacció fotoquímica utilitzant tècniques com l'espectroscòpia de fluorescència, l'espectroscòpia d'absorció, la voltamperometria cíclica i la ressonància magnètica nuclear. Després d'analitzar totes les dades, s'ha pogut comprovar que l'espècie activa que interacciona amb el fotocatalitzador és un adducte entre la 3,4-dihidroquinoxalin-2-ona **5.1** i el $(PhO)_2PO_2H$. D'aquesta manera s'ha pogut establir un mecanisme de reacció.

- **Capítol 6**. En aquest capítol d'ha estudiat i desenvolupat satisfactòriament la reacció entre diferents 3,4-dihidroquinoxalin-2-ones **6.1** i 3,4-dihidro-1,4-benzoxazin-2-ones **6.4** amb azodicarboxilats de dialquil **6.2**. En aquest cas, la reacció té lloc sense necessitat ni de fotocatalitzador ni de llum visible, encara que els rendiments són majors si s'il·lumina la mescla de reacció amb LEDs blaus. Utilitzant aquestes condicions simples, s'han generat vint-i-tres derivats aminats en la posició C-3 amb rendiments generalment elevats. A més a més, s'ha aprofitat la tendència de l'agrupació de tipus hidrazina dels productes de reacció a actuar com a grup ixent per a funcionalitzar aquesta posició amb diferents nucleòfils com reactius de Grignard, fosfit i nucleòfils de silici. En aquest sentit, s'ha dut a terme la síntesi total de l'Opaviralina en la seua forma racèmica amb un rendiment global del 63% després de tres etapes. Tanmateix, tot i la ressemblança entre els alquens pobres en electrons del capítol anterior, els azodicarboxilats de dialquil **6.2** reaccionen amb a les 3,4-dihidroquinoxalin-2-ones **6.1** i les 3,4-dihidro-1,4-benzoxazin-2-ones **6.4** a través d'un mecanisme diferent.

- **Capítol 7**. S'ha desenvolupat la reacció entre 3,4-dihidroquinoxalin-2-ones **7.1** i trifluorometil cetones **7.2** mitjançant catàlisi fotoredox amb llum visible. En aquest cas també s'ha utilitzat $Ru(bpy)_3Cl_2$ (**A**) com a fotocatalitzador, cosa que ha permés la síntesi de múltiples trifluorometil carbinols que contenen l'estructura de 3,4-dihidroquinoxalin-2-ona. Malauradament, només les trifluorometil cetones aromàtiques han proporcionat rendiments acceptables, encara que s'han pogut obtindre el corresponents productes utilitzant una d'alifàtica i també trifluoropiruvat d'etil. Finalment, una sèrie d'experiments de caire mecanístic han permés concloure que la la formació d'un agregat entre la 3,4-dihidroquinoxalin-2-ona **7.1** i la trifluorometil cetona **7.2** és el que indueix la transferència monoelectrònica amb l'estat excitat del fotocatalitzador.

- **Capítol 8**. En el darrer capítol d'aquesta *tesi* s'ha descrit la reacció d'addició de tipus 1,6 entre 3,4-dihidroquinoxalin-2-ones **8.1** i *p*-quinona metins **8.2**. En aquest

cas s'ha vist que el millor catalitzador és el fotocatalitzador de Fukuzumi (**H**) utilitzant la irradiació d'un LED d'elevada potència (455 nm). Encara que l'estudi de l'abast i les limitacions d'aquesta reacció es troba en una fase preliminar, s'ha pogut comprovar l'elevada eficiència en què transcorre aquesta transformació. De fet, la presència de grups funcionals voluminosos a prop de la posició electrofílica del *p*-quinona metí **8.2** no afecta al transcurs de la reacció. En aquest capítol caldria estendre més encara l'abast i les limitacions d'aquesta transformació, així com preparar una sèrie de derivats dels productes de reacció. Finalment, s'ha estudiat el mecanisme de la reacció mitjançant assajos de desactivació de luminescència i s'ha pogut determinar que la primera transferència electrònica té lloc entre l'estat excitat del fotocatalitzador **H** i la 3,4-dihidroquinoxalin-2-ona **8.1**.

Després d'analitzar en profunditat les conclusions de cada capítol individualment, es pot asseverar que s'ha pogut implementar diverses estratègies basades en la catàlisi fotoredox per a la funcionalització d'estructures de tipus 3,4-dihidroquinoxalin-2-ona i 3,4-dihidro-1,4-benzoxazin-2-ona en la posició C-3 tant amb nucleòfils com amb electròfils. Aquesta reactivitat divergent s'ha pogut aconseguir modulant convenientment les condicions de reacció per generar bé el catió imini en el cas de les funcionalitzacions nucleofíliques (*capítols* 1, 2, 3 i 4) o bé el α-amino radical en el cas de les funcionalitzacions electrofíliques (*capítols* 5, 6, 7 i 8).

References and Notes

(1) *IUPAC. Compendium of Chemical Terminology*, 2nd ed.; McNaught, A. D., Wilkinson., A., Eds.; Blackwell Scientific Publications: Oxford, 1997.

(2) In this quantum-based atomic model, electrons are described as wave functions and are subjected to Heisenberg's uncertainty principle. This means that the position of each electron is given in terms of probabilities.

(3) According to Valence Bond Theory, a covalent bond between two atoms is formed by the overlapping of two atomic orbitals containing an unpaired electron.

(4) The molecular orbital theory describes the electronic structure of a molecule considering that electrons are not assigned to individual bonds. In this theory, a set of molecular orbitals is built for each molecule. The wave function associated to each molecular orbital results from a linear combination of *n* individual atomic orbitals.

(5) Priestley, J., *Experiments and Observations on Different Kinds of Air*; Birmingham: 1790.

(6) Fritzsche, C. J. *J. Prakt. Chemie* **1867**, *101*, 333–343.

(7) Kärkäs, M. D.; Porco, J. A.; Stephenson, C. R. J. *Chem. Rev.* **2016**, *116*, 9683–9747.

(8) Crimmins, M. T.; Mascarella, S. W. *J. Am. Chem. Soc.* **1986**, *108*, 3435–3438.

(9) Winkler, J. D.; Muller, C. L.; Scott, R. D. *J. Am. Chem. Soc.* **1988**, *110*, 4831–4832.

(10) Bach, T.; Brummerhop, H.; Harms, K. *Chem. Eur. J.* **2000**, *6*, 3838–3848.

(11) Nunes, D.; Pimentel, A.; Branquinho, R.; Fortunato, E.; Martins, R. *Catalysts* **2021**, *11*, 504.

(12) McCullagh, C.; Robertson, J. M. C.; Bahnemann, D. W.; Robertson, P. K. J. *Res. Chem. Intermed.* **2007**, *33*, 359–375.

(13) Ciamician, G. *Science* **1912**, *36*, 385–394.

(14) Jo, W.-K.; Tayade, R. J. *Ind. Eng. Chem. Res.* **2014**, *53*, 2073–2084.

(15) Anastas, P. T.; Warner, J., *Green chemistry: Theory and Practice*; Oxford University Press: Oxford, 1998.

(16) United Nations, *THE 17 GOALS Sustainable Development*, Retrieved from https://sdgs.un.org/goals (11th August, 2022).

(17) Arias-Rotondo, D. M.; McCusker, J. K. *Chem. Soc. Rev.* **2016**, *45*, 5803–5820.

(18) Kalyanasundaram, K. *Coord. Chem. Rev.* **1982**, *46*, 159–244.

(19) Graetzel, M. *Acc. Chem. Res.* **1981**, *14*, 376–384.

(20) Takeda, H.; Ishitani, O. *Coord. Chem. Rev.* **2010**, *254*, 346–354.

(21) Hedstrand, D. M.; Kruizinga, W. H.; Kellogg, R. M. *Tetrahedron Lett.* **1978**, *19*, 1255–1258.

(22) Li, Z.; Wang, X.; Xia, S.; Jin, J. *Org. Lett.* **2019**, *21*, 4259–4265.

(23) Zhang, Y.; Wang, Q.; Yan, Z.; Ma, D.; Zheng, Y. *Beilstein J. Org. Chem.* **2021**, *17*, 2520–2542.

(24) Nicholls, T. P.; Bissember, A. C. *Tetrahedron Lett.* **2019**, *60*, 150883.

(25) Romero, N. A.; Nicewicz, D. A. *Chem. Rev.* **2016**, *116*, 10075–10166.

(26) Srivastava, V.; Singh, P. P. *RSC Adv.* **2017**, *7*, 31377–31392.

(27) Hola, E.; Ortyl, J. *Eur. Polym. J.* **2021**, *150*, 110365.

(28) Tlili, A.; Lakhdar, S. *Angew. Chem. Int. Ed.* **2021**, *60*, 19526–19549.

(29) Joshi-Pangu, A.; Lévesque, F.; Roth, H. G.; Oliver, S. F.; Campeau, L.-C.; Nicewicz, D.; DiRocco, D. A. *J. Org. Chem.* **2016**, *81*, 7244–7249.

(30) MacKenzie, I. A.; Wang, L.; Onuska, N. P. R.; Williams, O. F.; Begam, K.; Moran, A. M.; Dunietz, B. D.; Nicewicz, D. A. *Nature* **2020**, *580*, 76–80.

(31) Pitre, S. P.; McTiernan, C. D.; Ismaili, H.; Scaiano, J. C. *J. Am. Chem. Soc.* **2013**, *135*, 13286–13289.

(32) Talvitie, J.; Alanko, I.; Bulatov, E.; Koivula, J.; Pöllänen, T.; Helaja, J. *Org. Lett.* **2021**, *24*, 274–278.

(33) Luo, J.; Zhang, J. *ACS Catal.* **2016**, *6*, 873–877.

(34) Nicewicz, D. A.; MacMillan, D. W. C. *Science* **2008**, *322*, 77–80.

(35) Ischay, M. A.; Anzovino, M. E.; Du, J.; Yoon, T. P. *J. Am. Chem. Soc.* **2008**, *130*, 12886–12887.

(36) Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243–4244.

(37) Gentry, E. C.; Knowles, R. R. *Acc. Chem. Res.* **2016**, *49*, 1546–1556.

(38) Choi, G. J.; Zhu, Q.; Miller, D. C.; Gu, C. J.; Knowles, R. R. *Nature* **2016**, *539*, 268–271.

(39) Becker, M. R.; Wearing, E. R.; Schindler, C. S. *Nat. Chem.* **2020**, *12*, 898–905.

(40) Parker, V. D.; Tilset, M. *J. Am. Chem. Soc.* **1991**, *113*, 8778–8781.

(41) Parsaee, F.; Senarathna, M. C.; Kannangara, P. B.; Alexander, S. N.; Arche, P. D. E.; Welin, E. R. *Nat. Chem. Rev.* **2021**, *5*, 486–499.

(42) Dinnocenzo, J. P.; Banach, T. E. *J. Am. Chem. Soc.* **1989**, *111*, 8646–8653.

(43) Zhong, J.-J.; Meng, Q.-Y.; Wang, G.-X.; Liu, Q.; Chen, B.; Feng, K.; Tung, C.-H.; Wu, L.-Z. *Chem. Eur. J.* **2013**, *19*, 6443–6450.

(44) Zhong, J.-J.; Meng, Q.-Y.; Liu, B.; Li, X.-B.; Gao, X.-W.; Lei, T.; Wu, C.-J.; Li, Z.-J.; Tung, C.-H.; Wu, L.-Z. *Org. Lett.* **2014**, *16*, 1988–1991.

(45) Condie, A. G.; González-Gómez, J. C.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2010**, *132*, 1464–1465.

(46) Rueping, M.; Vila, C. *Org. Lett.* **2013**, *15*, 2092–2095.

(47) Tripolitsiotis, N. P.; Thomaidi, M.; Neochoritis, C. G. *Eur. J. Org. Chem.* **2020**, *2020*, 6525–6554.

(48) Che, C.; Li, Y.-N.; Cheng, X.; Lu, Y.-N.; Wang, C.-J. *Angew. Chem. Int. Ed.* **2021**, *60*, 4698–4704.

(49) Kohls, P.; Jadhav, D.; Pandey, G.; Reiser, O. *Org. Lett.* **2012**, *14*, 672–675.

(50) Murarka, S. *Adv. Synth. Catal.* **2018**, *360*, 1735–1753.

(51) Qin, T.; Cornella, J.; Li, C.; Malins, L. R.; Edwards, J. T.; Kawamura, S.; Maxwell, B. D.; Eastgate, M. D.; Baran, P. S. *Science* **2016**, *352*, 801–805.

(52) Lattanzi, A. *Tetrahedron Chem* **2022**, 100027.

(53) Moffett, R. B. *J. Med. Chem.* **1966**, *9*, 475–478.

(54) Chowdhury, C.; Achari, B.; Mandal, S.; Dutta, P. *Synlett* **2004**, *2004*, 2449–2467.

(55) Pamerla, M.; Reddy, D. R. S.; Rao, B. S.; Bodipati, N.; Murthy, Y. L. N. *Med. Chem. Res.* **2014**, *24*, 611–615.

(56) Bouyssou, T.; Casarosa, P.; Naline, E.; Pestel, S.; Konetzki, I.; Devillier, P.; Schnapp, A. *J. Pharmacol. Exp. Ther.* **2010**, *334*, 53–62.

(57) Liu, C.; Tan, J.-L.; Xiao, S.-Y.; Liao, J.-F.; Zou, G.-R.; Ai, X.-X.; Chen, J.-B.; Xiang, Y.; Yang, Q.; Zuo, H. *Chem. Pharm. Bull.* **2014**, *62*, 915–920.

(58) Blass, B. *ACS Med. Chem. Lett.* **2013**, *4*, 1020–1021.

(59) Sengupta, S. K.; Trites, D. H.; Madhavarao, M. S.; Beltz, W. R. *J. Med. Chem.* **1979**, *22*, 797–802.

(60) Miles, D.; Petrovna, K.; Naser, S.; Yurjevich, S.; Goun, E.; Michailovich, S., *Patent US 6,649,610*, 2003.

(61) Su, S.-S. M., *Patent WO2012151440 A1*, 2012.

(62) Patel, M.; McHugh, R. J.; Cordova, B. C.; Klabe, R. M.; Erickson-Viitanen, S.; Trainor, G. L.; Rodgers, J. D. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1729–1731.

(63) 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.

(64) 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.

(65) Moore, K.; Cass, L.; Dallow, N.; Hardman, T.; Jones, A.; Boyce, M.; Prince, W. *Eur. J. Clin. Pharmacol.* **2001**, *56*, 805–811.

(66) Yang, Y.; Zhao, L.; Xu, B.; Yang, L.; Zhang, J.; Zhang, H.; Zhou, J. *Bioorg. Chem.* **2016**, *68*, 236–244.

(67) Su, D.-S.; Markowitz, M. K.; DiPardo, R. M.; Murphy, K. L.; Harrell, C. M.; O'Malley, S. S.; Ransom, R. W.; Chang, R. S. L.; Ha, S.; Hess, F. J.; Pettibone, D. J.; Mason, G. S.; Boyce, S.; Freidinger, R. M.; Bock, M. G. *J. Am. Chem. Soc.* **2003**, *125*, 7516–7517.

(68) Smil, D. V. et al. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 688–692.

(69) Fabian, L.; Porro, M. T.; Gómez, N.; Salvatori, M.; Turk, G.; Estrin, D.; Moglioni, A. *Eur. J. Med. Chem.* **2020**, *188*, 111987.

(70) Tanimori, S.; Nishimura, T.; Kirihata, M. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 4119–4121.

(71) Wolfer, J.; Bekele, T.; Abraham, C. J.; Dogo-Isonagie, C.; Lectka, T. *Angew. Chem. Int. Ed.* **2006**, *45*, 7398–7400.

(72) Galloway, W. R.; Isidro-Llobet, A.; Spring, D. R. *Nat. Commun.* **2010**, *1*, 80.

(73) Ding, W.; Lu, L.-Q.; Liu, J.; Liu, D.; Song, H.-T.; Xiao, W.-J. *J. Org. Chem.* **2016**, *81*, 7237–7243.

(74) Huo, C.; Dong, J.; Su, Y.; Tang, J.; Chen, F. *Chem. Commun.* **2016**, *52*, 13341–13344.

(75) Dong, J.; Min, W.; Li, H.; Quan, Z.; Yang, C.; Huo, C. *Adv. Synth. Catal.* **2017**, *359*, 3940–3944.

(76) Wang, J.; Li, J.; Wei, Y.; Yang, J.; Huo, C. *Org. Chem. Front.* **2018**, *5*, 3534–3537.

(77) Zhang, G.-Y.; Yu, K.-X.; Zhang, C.; Guan, Z.; He, Y.-H. *Eur. J. Org. Chem.* **2018**, *2018*, 525–531.

(78) Akula, P. S.; Hong, B.-C.; Lee, G.-H. *RSC Adv.* **2018**, *8*, 19580–19584.

(79) Wang, J.; Bao, X.; Wang, J.; Huo, C. *Chem. Commun.* **2020**, *56*, 3895–3898.

(80) Wan, S.; Wang, J.; Huo, C. *Tetrahedron Lett.* **2021**, *78*, 153271.

(81) Xiong, W.; Qin, W.-B.; Zhao, Y.-S.; Fu, K.-Z.; Liu, G.-K. *Org. Chem. Front.* **2022**, *9*, 2141–2148.

(82) Tammisetti, R.; Hong, B.-C.; Chien, S.-Y.; Lee, G.-H. *Org. Lett.* **2022**, *24*, 5155–5160.

(83) Sundberg, R., *The chemistry of indoles*; Elsevier: London, 2012; Vol. 18.

(84) Bronner, S. M.; Im, G.-Y. J.; Garg, N. K. In *Heterocycles in Natural Product Synthesis*; John Wiley & Sons, Ltd; Weinheim, Germany, 2011; Chapter 7, pp 221–265.

(85) Friedel C; Crafts, J. M. *Comptes Rendus Hebd. Seances Acad. Sci.* **1877**, *84*, 1293.

(86) Rueping, M.; Nachtsheim, B. J. *Beilstein J. Org. Chem.* **2010**, *6*, 6.

(87) Kaushik, N. K.; Kaushik, N.; Attri, P.; Kumar, N.; Kim, C. H.; Verma, A. K.; Choi, E. H. *Molecules* **2013**, *18*, 6620–6662.

(88) Zhang, M.-Z.; Chen, Q.; Yang, G.-F. *Eur. J. Med. Chem.* **2015**, *89*, 421–441.

(89) Lancianesi, S.; Palmieri, A.; Petrini, M. *Chem. Rev.* **2014**, *114*, 7108–7149.

(90) Yan, W.; Zhao, S. S.; Ye, Y. H.; Zhang, Y. Y.; Zhang, Y.; Xu, J. Y.; Yin, S. M.; Tan, R. X. *J. Nat. Prod.* **2019**, *82*, 2132–2137.

(91) Manickam, M.; Iqbal, P.; Belloni, M.; Kumar, S.; Preece, J. A. *Isr. J. Chem.* **2012**, *52*, 917–934.

(92) Blay, G.; Fernández, I.; Pedro, J. R.; Vila, C. *Org. Lett.* **2007**, *9*, 2601–2604.

(93) Blay, G.; Fernández, I.; Muñoz, M. C.; Pedro, J. R.; Vila, C. *Chem. Eur. J.* **2010**, *16*, 9117–9122.

(94) Montesinos-Magraner, M.; Vila, C.; Rendón-Patiño, A.; Blay, G.; Fernández, I.; Muñoz, M. C.; Pedro, J. R. *ACS Catal.* **2016**, *6*, 2689–2693.

(95) Vila, C.; Rostoll-Berenguer, J.; Sánchez-García, R.; Blay, G.; Fernández, I.; Muñoz, M. C.; Pedro, J. R. *J. Org. Chem.* **2018**, *83*, 6397–6407.

(96) Wu, C.-J.; Zhong, J.-J.; Meng, Q.-Y.; Lei, T.; Gao, X.-W.; Tung, C.-H.; Wu, L.-Z. *Org. Lett.* **2015**, *17*, 884–887.

(97) Zhong, J.-J.; Meng, Q.-Y.; Liu, B.; Li, X.-B.; Gao, X.-W.; Lei, T.; Wu, C.-J.; Li, Z.-J.; Tung, C.-H.; Wu, L.-Z. *Org. Lett.* **2014**, *16*, 1988–1991.

(98) Meng, Q.-Y.; Zhong, J.-J.; Liu, Q.; Gao, X.-W.; Zhang, H.-H.; Lei, T.; Li, Z.-J.; Feng, K.; Chen, B.; Tung, C.-H.; Wu, L.-Z. *J. Am. Chem. Soc.* **2013**, *135*, 19052–19055.

(99) Li, Q.-Y.; Ma, Z.; Zhang, W.-Q.; Xu, J.-L.; Wei, W.; Lu, H.; Zhao, X.; Wang, X.-J. *Chem. Commun.* **2016**, *52*, 11284–11287.

(100) He, Y.-H.; Xiang, Y.; Yang, D.-C.; Guan, Z. *Green Chem.* **2016**, *18*, 5325–5330.

(101) Zhong, J.-J.; Meng, Q.-Y.; Wang, G.-X.; Liu, Q.; Chen, B.; Feng, K.; Tung, C.-H.; Wu, L.-Z. *Chem. Eur. J.* **2013**, *19*, 6443–6450.

(102) Mandal, T.; Das, S.; De Sarkar, S. *Adv. Synth. Catal.* **2019**, *361*, 3200–3209.

(103) Zhang, Y.; Yang, X.; Zhou, H.; Li, S.; Zhu, Y.; Li, Y. *Org. Chem. Front.* **2018**, *5*, 2120–2125.

(104) Kumar, G.; Pillai, R. S.; Khan, N.-u. H.; Neogi, S. *Appl. Catal., B* **2021**, *292*, 120149.

(105) Ni, C.; Chen, W.; Jiang, C.; Lu, H. *New J. Chem.* **2020**, *44*, 313–316.

(106) Wang, Z.-Q.; Hu, M.; Huang, X.-C.; Gong, L.-B.; Xie, Y.-X.; Li, J.-H. *J. Org. Chem.* **2012**, *77*, 8705–8711.

(107) Freeman, D. B.; Furst, L.; Condie, A. G.; Stephenson, C. R. J. *Org. Lett.* **2012**, *14*, 94–97.

(108) Zhu, S.; Rueping, M. *Chem. Commun.* **2012**, *48*, 11960.

(109) Zidar, N.; Kikelj, D. *Tetrahedron* **2008**, *64*, 5756–5761.

(110) Bonuga, Y. R.; Ravinder-Nathb, A.; Balramc, B.; Ram, B. *Der Pharma Chemica* **2013**, *5*, 296–300.

(111) Jana, S.; Verma, A.; Kadu, R.; Kumar, S. *Chem. Sci.* **2017**, *8*, 6633–6644.

(112) Wu, P.-L.; Hsu, Y.-L.; Jao, C.-W. *J. Nat. Prod.* **2006**, *69*, 1467–1470.

(113) Mason, J. J.; Bergman, J.; Janosik, T. *J. Nat. Prod.* **2008**, *71*, 1447–1450.

(114) Cornford, E. M.; Crane, P. D.; Braun, L. D.; Bocash, W. D.; Nyerges, A. M.; Oldendorf, W. H. *J. Neurochem.* **1981**, *36*, 1758–1765.

(115) Noyori, R. *Angew. Chem. Int. Ed.* **2002**, *41*, 2008.

(116) List, B. *Chem. Rev.* **2007**, *107*, 5413–5415.

(117) Gal, J. *Chirality* **2012**, *24*, 959–976.

(118) Paquette, L. A., *Handbook of Reagents for Organic Synthesis , Chiral Reagents for Asymmetric Synthesis*; John Wiley & Sons Ltd.: Chichester, United Kingdom, 2003.

(119) Diaz-Muñoz, G.; Miranda, I. L.; Sartori, S. K.; Rezende, D. C.; Diaz, M. A. N. *Chirality* **2019**, *31*, 776–812.

(120) Farina, V.; Reeves, J. T.; Senanayake, C. H.; Song, J. J. *Chem. Rev.* **2006**, *106*, 2734–2793.

(121) Sharma, S. K.; Paniraj, A. S. R.; Tambe, Y. B. *J. Agric. Food Chem.* **2021**, *69*, 14761–14780.

(122) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974–5976.

(123) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483–2547.

(124) Knowles, W. S. *Angew. Chem. Int. Ed.* **2002**, *41*, 1998.

(125) Kolodiazhnyi, O. I. In *Asymmetric Synthesis in Organophosphorus Chemistry*; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, 2016, pp 187–252.

(126) Biosca, M.; Diéguez, M.; Zanotti-Gerosa, A. *Adv. Catal.* **2021**, 341–383.

(127) Federsel, H.-J., *Asymmetric Catalysis On Industrial Scale Challenges Approaches And Solutions*; Wiley-VCH Verlag GmbH: Weinheim, Germany, 2010.

(128) Xiang, S.-H.; Tan, B. *Nat. Commun.* **2020**, *11*, 3786.

(129) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615–1621.

(130) List, B.; Lerner, R. A.; Barbas, C. F. *J. Am. Chem. Soc.* **2000**, *122*, 2395–2396.

(131) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471–5569.

(132) Saranya, S.; Harry, N. A.; Krishnan, K. K.; Anilkumar, G. *Asian J. Org. Chem.* **2018**, *7*, 613–633.

(133) Rostoll-Berenguer, J.; Blay, G.; Pedro, J. R.; Vila, C. *Adv. Synth. Catal.* **2020**, *363*, 602–628.

(134) Zhang, G.; Zhang, Y.; Wang, R. *Angew. Chem. Int. Ed.* **2011**, *50*, 10429–10432.

(135) Xie, Z.; Zan, X.; Sun, S.; Pan, X.; Liu, L. *Org. Lett.* **2016**, *18*, 3944–3947.

(136) Tan, Y.; Yuan, W.; Gong, L.; Meggers, E. *Angew. Chem. Int. Ed.* **2015**, *54*, 13045–13048.

(137) Yang, X.; Xie, Z.; Li, Y.; Zhang, Y. *Chem. Sci.* **2020**, *11*, 4741–4746.

(138) Huang, L.; Xu, J.; He, L.; Liang, C.; Ouyang, Y.; Yu, Y.; Li, W.; Zhang, P. *Chin. Chem. Lett.* **2021**, *32*, 3627–3631.

(139) Notz, W.; List, B. *J. Am. Chem. Soc.* **2000**, *122*, 7386–7387.

(140) Lin, J.-F.; Wu, C.-C.; Lien, M.-H. *J. Phys. Chem.* **1995**, *99*, 16903–16908.

(141) Sakthivel, K.; Notz, W.; Bui, T.; Barbas, C. F. *J. Am. Chem. Soc.* **2001**, *123*, 5260–5267.

(142) Yamashita, Y.; Yasukawa, T.; Yoo, W.-J.; Kitanosono, T.; Kobayashi, S. *Chem. Soc. Rev.* **2018**, *47*, 4388–4480.

(143) Verkade, J. M. M.; van Hemert, L. J. C.; Quaedflieg, P. J. L. M.; Rutjes, F. P. J. T. *Chem. Soc. Rev.* **2008**, *37*, 29–41.

(144) Carrër, A.; Brion, J.-D.; Messaoudi, S.; Alami, M. *Org. Lett.* **2013**, *15*, 5606–5609.

(145) Li, D.; Ollevier, T. *Eur. J. Org. Chem.* **2018**, *2019*, 1273–1280.

(146) Varvounis, G. In *Advances in Heterocyclic Chemistry Volume 98*; Elsevier: Oxford, 2009, pp 143–224.

(147) Liu, S.; Bao, X.; Wang, B. *Chem. Commun.* **2018**, *54*, 11515–11529.

(148) Bailly, C.; Hecquet, P.-E.; Kouach, M.; Thuru, X.; Goossens, J.-F. *Bioorg. Med. Chem.* **2020**, *28*, 115463.

(149) Lutz, M. *J. Clin. Pharmacol.* **2019**, *59*, 1433–1442.

(150) Nikolova, I.; Tencheva, J.; Voinikov, J.; Petkova, V.; Benbasat, N.; Danchev, N. *Biotechnol. Biotechnol. Equip.* **2012**, *26*, 3329–3337.

(151) Elhkim, M. O.; Héraud, F.; Bemrah, N.; Gauchard, F.; Lorino, T.; Lambré, C.; Frémy, J. M.; Poul, J.-M. *Regul. Toxicol. Pharm.* **2007**, *47*, 308–316.

(152) Tech. rep. 2009; 7(11):1331; European Food Safety Authority.

(153) Chauhan, P.; Mahajan, S.; Enders, D. *Chem. Commun.* **2015**, *51*, 12890–12907.

(154) Vila, C.; Amr, F. I.; Blay, G.; Muñoz, M. C.; Pedro, J. R. *Chem. Asian J.* **2016**, *11*, 1532–1536.

(155) Vila, C.; Slack, S.; Blay, G.; Muñoz, M. C.; Pedro, J. R. *Adv. Synth. Catal* **2019**, *361*, 1902–1907.

(156) Carceller-Ferrer, L.; Vila, C.; Blay, G.; Fernández, I.; Muñoz, M. C.; Pedro, J. R. *Org. Biomol. Chem.* **2019**, *17*, 9859–9863.

(157) Toonchue, S.; Sumunnee, L.; Phomphrai, K.; Yotphan, S. *Org. Chem. Front.* **2018**, *5*, 1928–1932.

(158) Qiao, J. X. et al. *J. Med. Chem.* **2013**, *56*, 9275–9295.

(159) Weber Eckard; Keana, J. F. W. US Patent, US5514680, 1996.

(160) Amr, F. I.; Vila, C.; Blay, G.; Muñoz, M. C.; Pedro, J. R. *Adv. Synth. Catal.* **2016**, *358*, 1583–1588.

(161) Hart, F. D.; Boardman, P. L. *Br. Med. J.* **1963**, *2*, 965–970.

(162) Nalamachu, S.; Wortmann, R. *Postgrad. Med.* **2014**, *126*, 92–97.

(163) Ciriminna, R.; Pagliaro, M. *Org. Process Res. Dev.* **2009**, *14*, 245–251.

(164) Shibuya, M.; Tomizawa, M.; Suzuki, I.; Iwabuchi, Y. *J. Am. Chem. Soc.* **2006**, *128*, 8412–8413.

(165) Yan, Y.; Tong, X.; Wang, K.; Bai, X. *Catal. Commun.* **2014**, *43*, 112–115.

(166) Reymond, J.-L.; van Deursen, R.; Blum, L. C.; Ruddigkeit, L. *Med. Chem. Comm.* **2010**, *1*, 30.

(167) Hudrlik, P. F.; Hudrlik, A. M. In *The Carbon-Carbon Triple Bond: Vol. 1 (1978)*; John Wiley & Sons, Ltd., pp 199–273.

(168) Trost, B. M.; Li, C.-J., *Modern Alkyne Chemistry, Catalytic and Atom-Economic Transformations*; Wiley-VCH Verlag GmbH: Weinheim, Germany, 2014, p 424.

(169) Fang, G.; Bi, X. *Chem. Soc. Rev.* **2015**, *44*, 8124–8173.

(170) Chinchilla, R.; Nájera, C. *Chem. Rev.* **2013**, *114*, 1783–1826.

(171) Trotuş, I.-T.; Zimmermann, T.; Schüth, F. *Chem. Rev.* **2013**, *114*, 1761–1782.

(172) Blay, G.; Pedro, J. R.; Sanz-Marco, A. *Synthesis* **2018**, *50*, 3281–3306.

(173) Sanz-Marco, A.; García-Ortiz, A.; Blay, G.; Fernández, I.; Pedro, J. R. *Chem. Eur. J.* **2013**, *20*, 668–672.

(174) Sanz-Marco, A.; Blay, G.; Muñoz, M. C.; Pedro, J. R. *Chem. Commun.* **2015**, *51*, 8958–8961.

(175) Sanz-Marco, A.; Blay, G.; Vila, C.; Pedro, J. R. *Org. Lett.* **2016**, *18*, 3538–3541.

(176) Blay, G.; Castilla, A.; Sanz, D.; Sanz-Marco, A.; Vila, C.; Muñoz, M. C.; Pedro, J. R. *Chem. Commun.* **2020**, *56*, 9461–9464.

(177) Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2004**, *126*, 11810–11811.

(178) Li, Z.; Li, C.-J. *Org. Lett.* **2004**, *6*, 4997–4999.

(179) Rueping, M.; Koenigs, R. M.; Poscharny, K.; Fabry, D. C.; Leonori, D.; Vila, C. *Chem. Eur. J.* **2012**, *18*, 5170–5174.

(180) Wang, J.; Sun, Y.; Jiang, M.-H.; Hu, T.-Y.; Zhao, Y.-J.; Li, X.; Wang, G.; Hao, K.; Zhen, L. *J. Org. Chem.* **2018**, *83*, 13121–13131.

(181) Hassam, M.; Li, W.-S. *Tetrahedron* **2015**, *71*, 2719–2723.

(182) Gomberg, M. *J. Am. Chem. Soc.* **1900**, *22*, 757–771.

(183) Studer, A.; Curran, D. P. *Angew. Chem. Int. Ed.* **2015**, *55*, 58–102.

(184) Romero, K. J.; Galliher, M. S.; Pratt, D. A.; Stephenson, C. R. J. *Chem. Soc. Rev.* **2018**, *47*, 7851–7866.

(185) Curran, D. P.; Rakiewicz, D. M. *J. Am. Chem. Soc.* **1985**, *107*, 1448–1449.

(186) RajanBabu, T. V. (; Bulman Page, P. C.; Buckley, B. R. In *Encyclopedia of Reagents for Organic Synthesis*; John Wiley & Sons, Ltd: 2004.

(187) Fry, J. L.; Rahaim Jr., R. J.; Maleczka Jr., R. E. In *Encyclopedia of Reagents for Organic Synthesis*; John Wiley & Sons, Ltd: 2007.

(188) Kuivila, H. G. *Synthesis* **1970**, *1970*, 499–509.

(189) Giese, B.; Meister, J. *Chem. Ber.* **1977**, *110*, 2588–2600.

(190) Giese, B.; Lachhein, S. *Angew. Chem. Int. Ed.* **1981**, *20*, 967–967.

(191) Giese, B.; Dupuis, J. *Angew. Chem. Int. Ed.* **1983**, *22*, 622–623.

(192) Giese, B. *Angew. Chem. Int. Ed.* **1983**, *22*, 753–764.

(193) Giese, B.; González-Gómez, J. A.; Witzel, T. *Angew. Chem. Int. Ed.* **1984**, *23*, 69–70.

(194) Matsui, J. K.; Lang, S. B.; Heitz, D. R.; Molander, G. A. *ACS Catal.* **2017**, *7*, 2563–2575.

(195) Goddard, J.-P.; Ollivier, C.; Fensterbank, L. *Acc. Chem. Res.* **2016**, *49*, 1924–1936.

(196) Guo, W.; Wang, Q.; Zhu, J. *Chem. Soc. Rev.* **2021**, *50*, 7359–7377.

(197) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. *Chem. Rev.* **2013**, *113*, 5322–5363.

(198) Kanegusuku, A. L. G.; Roizen, J. L. *Angew. Chem. Int. Ed.* **2021**, *60*, 21116–21149.

(199) Andrews, R. S.; Becker, J. J.; Gagné, M. R. *Angew. Chem. Int. Ed.* **2010**, *49*, 7274–7276.

(200) Yang, Y.; Yu, B. *Chem. Rev.* **2017**, *117*, 12281–12356.

(201) Liao, H.; Ma, J.; Yao, H.; Liu, X.-W. *Org. Biomol. Chem.* **2018**, *16*, 1791–1806.

(202) Schweitzer-Chaput, B.; Horwitz, M. A.; de Pedro Beato, E.; Melchiorre, P. *Nat. Chem.* **2018**, *11*, 129–135.

(203) Aycock, R. A.; Pratt, C. J.; Jui, N. T. *ACS Catal.* **2018**, *8*, 9115–9119.

(204) Murphy, J. J.; Bastida, D.; Paria, S.; Fagnoni, M.; Melchiorre, P. *Nature* **2016**, *532*, 218–222.

(205) Hatchard, C. G.; Parker, C. A. *Proc. Roy. Soc. (London)* **1956**, *235*, 518–536.

(206) Cismesia, M. A.; Yoon, T. P. *Chem. Sci.* **2015**, *6*, 5426–5434.

(207) Spinnato, D.; Schweitzer-Chaput, B.; Goti, G.; Ošeka, M.; Melchiorre, P. *Angew. Chem. Int. Ed.* **2020**, *59*, 9485–9490.

(208) Jerca, F. A.; Jerca, V. V.; Hoogenboom, R. *Nat. Rev. Chem.* **2021**, *6*, 51–69.

(209) Bandara, H. M. D.; Burdette, S. C. *Chem. Soc. Rev.* **2012**, *41*, 1809–1825.

(210) Beharry, A. A.; Woolley, G. A. *Chem. Soc. Rev.* **2011**, *40*, 4422.

(211) Velema, W. A.; Szymanski, W.; Feringa, B. L. *J. Am. Chem. Soc.* **2014**, *136*, 2178–2191.

(212) Wegener, M.; Hansen, M. J.; Driessen, A. J. M.; Szymanski, W.; Feringa, B. L. *J. Am. Chem. Soc.* **2017**, *139*, 17979–17986.

(213) Szymanski, W.; Ourailidou, M. E.; Velema, W. A.; Dekker, F. J.; Feringa, B. L. *Chem. Eur. J.* **2015**, *21*, 16517–16524.

(214) Hansen, M. J.; Hille, J. I.; Szymanski, W.; Driessen, A. J.; Feringa, B. L. *Chem* **2019**, *5*, 1293–1301.

(215) Singh, P.; Mritunjay *Asian J. Org. Chem.* **2021**, *10*, 964–979.

(216) Usman, M.; Zhang, X.-W.; Wu, D.; Guan, Z.-H.; Liu, W.-B. *Org. Chem. Front.* **2019**, *6*, 1905–1928.

(217) But, T. Y. S.; Toy, P. *Chem. Asian J.* **2007**, *2*, 1340–1355.

(218) Xu, X.; Li, X. *Org. Lett.* **2009**, *11*, 1027–1029.

(219) Singh, K.; Singh, P.; Kaur, A.; Singh, P. *Synlett* **2012**, *23*, 760–764.

(220) Singh, K.; Kessar, S.; Singh, P.; Singh, P.; Kaur, M.; Batra, A. *Synthesis* **2014**, *46*, 2644–2650.

(221) Suga, T.; Iizuka, S.; Akiyama, T. *Org. Chem. Front.* **2016**, *3*, 1259–1264.

(222) Wang, J.; Sun, Y.; Wang, G.; Zhen, L. *Eur. J. Org. Chem.* **2017**, *2017*, 6338–6348.

(223) Sun, M.; Zhao, L.; Ding, M.-W. *J. Org. Chem.* **2019**, *84*, 14313–14319.

(224) Nair, V.; Mathew, S.; Biju, A.; Suresh, E. *Angew. Chem. Int. Ed.* **2007**, *46*, 2070–2073.

(225) Shao, Q.; Chen, J.; Tu, M.; Piotrowski, D. W.; Huang, Y. *Chem. Commun.* **2013**, *49*, 11098.

(226) Miyake, Y.; Nakajima, K.; Nishibayashi, Y. *Chem. Eur. J.* **2012**, *18*, 16473–16477.

(227) Zhang, M.-J.; Schroeder, G. M.; He, Y.-H.; Guan, Z. *RSC Adv.* **2016**, *6*, 96693–96699.

(228) Wang, P.; Luo, Y.; Zhu, S.; Lu, D.; Gong, Y. *Adv. Synth. Catal.* **2019**, *361*, 5565–5575.

(229) Sugihara, T.; Honzawa, S.; Uchida, M. *Heterocycles* **2014**, *88*, 975.

(230) Yang, Z.; Wang, Z.; Bai, S.; Shen, K.; Chen, D.; Liu, X.; Lin, L.; Feng, X. *Chem. Eur. J.* **2010**, *16*, 6632–6637.

(231) Moore, K. H. P.; Cass, L. M.; Dallow, N.; Hardman, T. C.; Jones, A.; Boyce, M.; Prince, W. T. *J. Clin. Pharmacol.* **2001**, *41*, 1098–1105.

(232) Crisenza, G. E. M.; Mazzarella, D.; Melchiorre, P. *J. Am. Chem. Soc.* **2020**, *142*, 5461–5476.

(233) Yuan, Y.-q.; Majumder, S.; Yang, M.-h.; Guo, S.-r. *Tetrahedron Lett.* **2020**, *61*, 151506.

(234) Tressaud, A. *Angew. Chem. Int. Ed.* **2006**, *45*, 6792–6796.

(235) Morachevskii, A. G. *Russ. J. Appl. Chem.* **2002**, *75*, 1720–1722.

(236) Fried, J.; Sabo, E. F. *J. Am. Chem. Soc.* **1953**, *75*, 2273–2274.

(237) Fried, J.; Sabo, E. F. *J. Am. Chem. Soc.* **1954**, *76*, 1455–1456.

(238) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320–330.

(239) Hagmann, W. K. *J. Med. Chem.* **2008**, *51*, 4359–4369.

(240) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881–1886.

(241) Wang, J.; Sánchez-Roselló, M.; Aceña, J. L.; del Pozo, C.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. *Chem. Rev.* **2013**, *114*, 2432–2506.

(242) Inoue, M.; Sumii, Y.; Shibata, N. *ACS Omega* **2020**, *5*, 10633–10640.

(243) Wang, Q.; Song, H.; Wang, Q. *Chin. Chem. Lett.* **2022**, *33*, 626–642.

(244) Neumann, C. N.; Ritter, T. *Angew. Chem. Int. Ed.* **2015**, *54*, 3216–3221.

(245) Kirk, K. L. *Org. Process Res. Dev.* **2008**, *12*, 305–321.

(246) Wu, J. *Tetrahedron Lett.* **2014**, *55*, 4289–4294.

(247) Kaźmierczak Marcin / Bilska-Markowska, M. *Eur. J. Org. Chem.* **2021**, *2021*, 5585–5604.

(248) White, J. M.; Tunoori, A. R.; Turunen, B. J.; Georg, G. I. *J. Org. Chem.* **2004**, *69*, 2573–2576.

(249) Taylor, S. D.; Kotoris, C. C.; Hum, G. *Tetrahedron* **1999**, *55*, 12431–12477.

(250) Rozatian, N.; Hodgson, D. R. W. *Chem. Commun.* **2021**, *57*, 683–712.

(251) Jagodzinska, M.; Huguenot, F.; Candiani, G.; Zanda, M. *ChemMedChem* **2009**, *4*, 49–51.

(252) Liu, X.; Xu, C.; Wang, M.; Liu, Q. *Chem. Rev.* **2014**, *115*, 683–730.

(253) Charpentier, J.; Früh, N.; Togni, A. *Chem. Rev.* **2014**, *115*, 650–682.

(254) Vallejo, S. B.; Lantaño, B.; Postigo, A. *Chem. Eur. J.* **2014**, *20*, 16806–16829.

(255) Kelly, C. B.; Mercadante, M. A.; Leadbeater, N. E. *Chem. Commun.* **2013**, *49*, 11133.

(256) Pierce, M. E. et al. *J. Org. Chem.* **1998**, *63*, 8536–8543.

(257) Nicolaou, K. C.; Krasovskiy, A.; Majumder, U.; Trépanier, V. É.; Chen, D. Y.-K. *J. Am. Chem. Soc.* **2009**, *131*, 3690–3699.

(258) Wang, C.; Qin, J.; Shen, X.; Riedel, R.; Harms, K.; Meggers, E. *Angew. Chem. Int. Ed.* **2015**, *55*, 685–688.

(259) Xia, Q.; Tian, H.; Dong, J.; Qu, Y.; Li, L.; Song, H.; Liu, Y.; Wang, Q. *Chem. Eur. J.* **2018**, *24*, 9269–9273.

(260) Vu, M. D.; Das, M.; Guo, A.; Ang, Z. E.; Dokic, M.; Soo, H. S.; Liu, X.-W. *ACS Catal.* **2019**, *9*, 9009–9014.

(261) Ota, K.; Nagao, K.; Ohmiya, H. *Org. Lett.* **2021**, *23*, 4420–4425.

(262) Hornyák, G.; Fetter, J.; Lempert, K.; Párkányi, L.; Németh, G.; Poszávácz, L.; Simig, G. *J. Fluorine Chem.* **2001**, *108*, 239–244.

(263) Yang, J.-S.; Liu, K.-T.; Su, Y. O. *J. Phys. Org. Chem.* **1990**, *3*, 723–731.

(264) Fuson, R. C. *Chem. Rev.* **1935**, *16*, 1–27.

(265) Takao, K.-I.; Sasaki, T.; Kozaki, T.; Yanagisawa, Y.; Tadano, K.-I.; Kawashima, A.; Shinonaga, H. *Org. Lett.* **2001**, *3*, 4291–4294.

(266) Yuan, Y.; Men, H.; Lee, C. *J. Am. Chem. Soc.* **2004**, *126*, 14720–14721.

(267) Smith, A. B.; Mesaros, E. F.; Meyer, E. A. *J. Am. Chem. Soc.* **2006**, *128*, 5292–5299.

(268) Kupchan, S. M.; Karim, A.; Marcks, C. *J. Am. Chem. Soc.* **1968**, *90*, 5923–5924.

(269) Steinmetz, H.; Gerth, K.; Jansen, R.; Schläger, N.; Dehn, R.; Reinecke, S.; Kirschning, A.; Müller, R. *Angew. Chem. Int. Ed.* **2011**, *50*, 532–536.

(270) Dehn, R.; Katsuyama, Y.; Weber, A.; Gerth, K.; Jansen, R.; Steinmetz, H.; Höfle, G.; Müller, R.; Kirschning, A. *Angew. Chem. Int. Ed.* **2011**, *50*, 3882–3887.

(271) Wang, L.-L.; Yu, Q.; Zhang, W.; Yang, S.; Peng, L.; Zhang, L.; Li, X.-N.; Gagosz, F.; Kirschning, A. *J. Am. Chem. Soc.* **2022**, *144*, 6871–6881.

(272) Jansen, R.; Gerth, K.; Steinmetz, H.; Reinecke, S.; Kessler, W.; Kirschning, A.; Müller, R. *Chem. Eur. J.* **2011**, *17*, 7739–7744.

(273) Wang, J.-Y.; Hao, W.-J.; Tu, S.-J.; Jiang, B. *Org. Chem. Front.* **2020**, *7*, 1743–1778.

(274) Chauhan, P.; Kaya, U.; Enders, D. *Adv. Synth. Catal* **2017**, *359*, 888–912.

(275) Lima, C. G. S.; Pauli, F. P.; Costa, D. C. S.; de Souza, A. S.; Forezi, L. S. M.; Ferreira, V. F.; de Carvalho da Silva, F. *Eur. J. Org. Chem.* **2020**, *2020*, 2650–2692.

(276) Rosati, R. L. et al. *J. Med. Chem.* **1998**, *41*, 2928–2931.

(277) Weinstock, J.; Wilson, J. W.; Ladd, D. L.; Brush, C. K.; Pfeiffer, F. R.; Kuo, G. Y.; Holden, K. G.; Yim, N. C. F.; Hahn, R. A. *J. Med. Chem.* **1980**, *23*, 973–975.

(278) Lokhandwala, M. F. *Drug Dev. Res.* **1987**, *10*, 123–134.

(279) Curran, M. P.; Scott, L. J.; Perry, C. M. *Drugs* **2004**, *64*, 523–561.

(280) Pflum, D. A.; Wilkinson, H. S.; Tanoury, G. J.; Kessler, D. W.; Kraus, H. B.; Senanayake, C. H.; Wald, S. A. *Org. Process Res. Dev.* **2000**, *5*, 110–115.

(281) Zhao, Y.-N.; Luo, Y.-C.; Wang, Z.-Y.; Xu, P.-F. *Chem. Commun.* **2018**, *54*, 3993–3996.

(282) Wu, Q.-Y.; Ao, G.-Z.; Liu, F. *Org. Chem. Front.* **2018**, *5*, 2061–2064.

(283) Fukuzumi, S.; Kotani, H.; Ohkubo, K.; Ogo, S.; Tkachenko, N. V.; Lemmetyinen, H. *J. Am. Chem. Soc.* **2004**, *126*, 1600–1601.

(284) Wu, Q.-Y.; Min, Q.-Q.; Ao, G.-Z.; Liu, F. *Org. Biomol. Chem.* **2018**, *16*, 6391–6394.

(285) Wang, P.-Z.; Chen, J.-R.; Xiao, W.-J. *Org. Biomol. Chem.* **2019**, *17*, 6936–6951.

(286) Zhang, W.; Yang, C.; Zhang, Z.-P.; Li, X.; Cheng, J.-P. *Org. Lett.* **2019**, *21*, 4137–4142.

(287) Song, F.; Lu, S.; Gunnet, J.; Xu, J. Z.; Wines, P.; Proost, J.; Liang, Y.; Baumann, C.; Lenhard, J.; Murray, W. V.; Demarest, K. T.; Kuo, G.-H. *J. Med. Chem.* **2007**, *50*, 2807–2817.

(288) Wu, Q.-L.; Guo, J.; Huang, G.-B.; Chan, A. S. C.; Weng, J.; Lu, G. *Org. Biomol. Chem.* **2020**, *18*, 860–864.

(289) Huang, L.; Arndt, M.; Gooßen, K.; Heydt, H.; Gooßen, L. J. *Chem. Rev.* **2015**, *115*, 2596–2697.

(290) Musacchio, A. J.; Lainhart, B. C.; Zhang, X.; Naguib, S. G.; Sherwood, T. C.; Knowles, R. R. *Science* **2017**, *355*, 727–730.

(291) Luo, C.; Zhou, T.; Wang, W.; Han, P.; Jing, L. *Asian J. Org. Chem.* **2021**, *10*, 2342–2346.

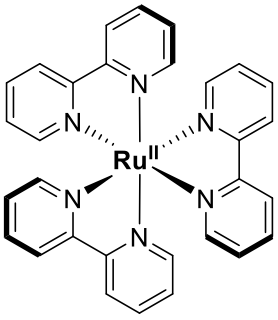
(292) Benniston, A. C.; Harriman, A.; Li, P.; Rostron, J. P.; van Ramesdonk, H. J.; Groeneveld, M. M.; Zhang, H.; Verhoeven, J. W. *J. Am. Chem. Soc.* **2005**, *127*, 16054–16064.

(293) Yang, Q.; Pan, G.; Wei, J.; Wang, W.; Tang, Y.; Cai, Y. *ACS Sustainable Chem. Eng.* **2021**, *9*, 2367–2377.

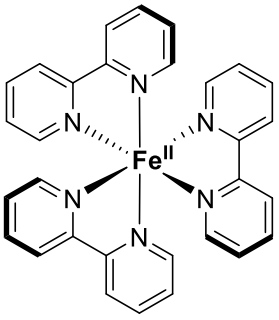
Annex

Photocatalysts

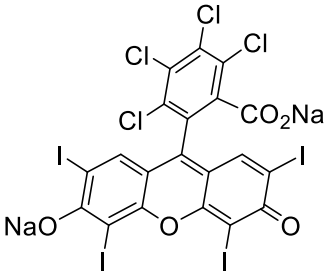
The structure of TiO_2 (**B**) *is omitted.*



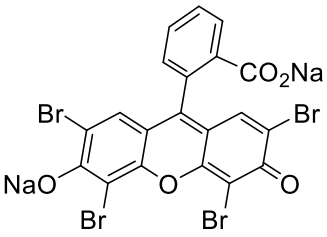
$Ru(bpy)_3Cl_2$ (**A**)



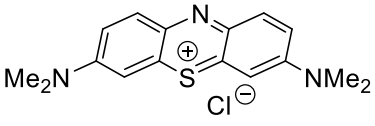
$Fe(bpy)_3SO_4$ (**C**)



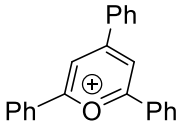
Rose Bengal (**D**)



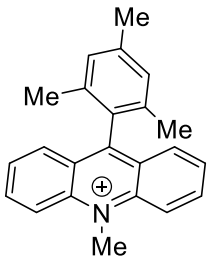
Eosin Y-Na_2 (**E**)



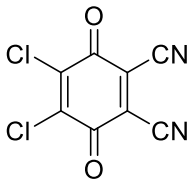
Methylene Blue (**F**)



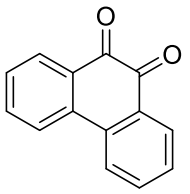
[2,4,6-Ph_3-pyrillium][BF_4] (**G**)



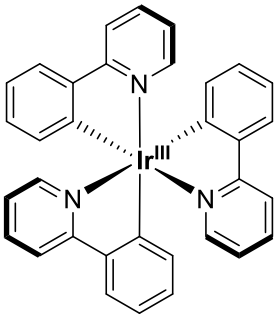
[Mes-Acr-Me][BF_4] (**H**)



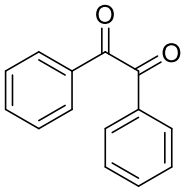
DDQ (**I**)



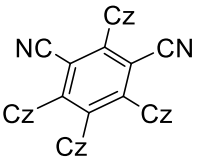
9,10-Phenanthrenequinone (**J**)



fac-Ir(ppy)$_3$ (**K**)



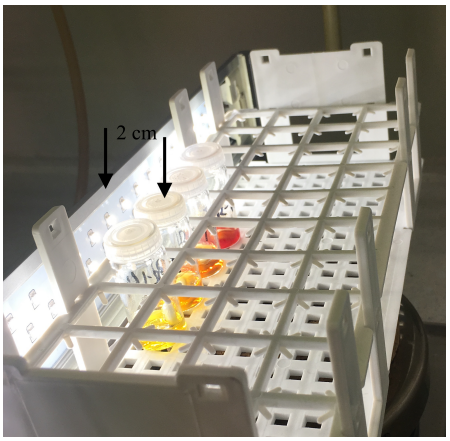
Benzyl (**L**)



4CzIPN (**M**)
Cz: carbazole

Photochemical Setups

- Photochemical Setup 1: **White LEDs** [*Chapters* 1 and 4].
  - Description: 5 W white LED light is placed at 2 cm of the reaction vials.

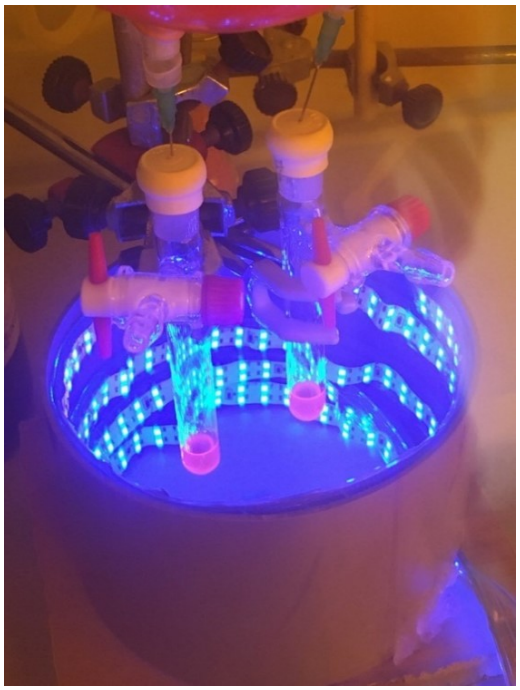


(a)

(b)

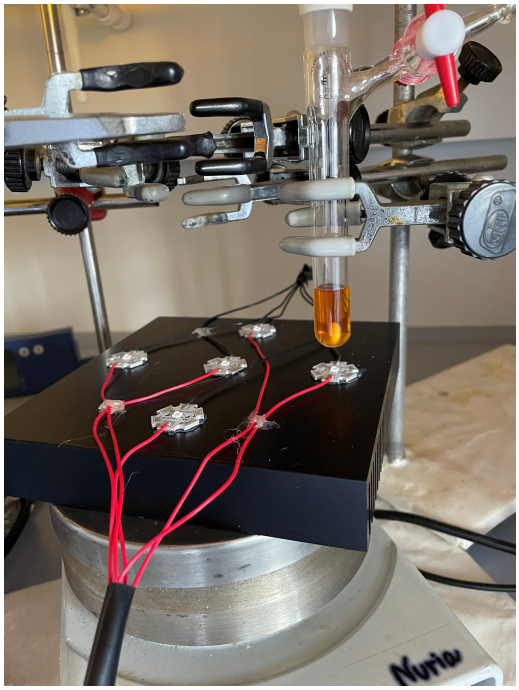
- Photochemical Setup 2: **Blue LEDs** [*Chapters* 2 and 5].
  - Description: a blue LED strip (purchased from Herran Import S.L., LED 3528) is put around a crystallizing dish. The setup is placed in a thermostat-controlled room and the heat is dissipated using a fan.

(a)



(b)

- Photochemical Setup 3: **HP Single LED (455 nm)** [*Chapters* 3, 5, 6, 7 and 8].
  - Description: All the components for the photochemical setup were purchased from Farnell Electronics. Five HP Single LEDs (455 nm) (int. ref. 3583117), assembled with a graphite heat sink pad (int. ref. 3583131), were stuck over an extruded aluminium heat sink (int. ref. 4621931) using thermally conductive epoxy adhesive (int. ref. 2917612). DC power supply was provided by Bench Power Supply (int. ref. 3410526). The setup is placed in a thermostat-controlled room and the heat is dissipated using a fan.



(a)

(b)

- Photochemical Setup 4: **Sunlight Irradiation** .
  - Description: The corresponding flask with all the reactants, catalysts and solvent was placed at the upper part of the F building (Facultat de Química) in sunny hours.

(a)

(b)

Publications

1. **Rostoll-Berenguer, J.**; Blay, G.; Pedro, J.R.; Vila, C. 9,10-Phenanthrenedione as Visible-Light Photoredox Catalyst: A Green Methodology for the Functionalization of 3,4-Dihydro-1,4-Benzoxazin-2-Ones through a Friedel-Crafts Reaction. *Catalysts* **2018**, *8*, 653.

2. **Rostoll-Berenguer, J.**; Blay, G.; Muñoz, M. C.; Pedro, J. R.; Vila, C. A Combination of Visible-Light Organophotoredox Catalysis and Asymmetric Organocatalysis for the Enantioselective Mannich Reaction of Dihydroquinoxalinones with Ketones. *Org. Lett.* **2019**, *21*, 6011– 6015.

3. **Rostoll-Berenguer, J.**; Blay, G.; Pedro, J. R.; Vila, C. Copper-Catalyzed Aerobic Oxidative Alkynylation of 3,4-Dihydroquinoxalin-2-ones. *Synthesis* **2020**, *52*, 544–552.

4. **Rostoll-Berenguer, J.**; Blay, G.; Pedro, J. R.; Vila, C. Recent Advances in Photocatalytic Functionalization of Quinoxalin-2-ones. *Eur. J. Org. Chem.* **2020**, 6148-6172.

5. **Rostoll-Berenguer, J.**; Blay, G.; Pedro, J. R.; Vila, C. Photocatalytic Giese Addition of 1,4-Dihydroquinoxalin-2-ones to Electron-Poor Alkenes Using Visible Light. *Org. Lett.* **2020**, *22*, 8012– 8017.

6. **Rostoll-Berenguer, J.**; Blay, G.; Pedro, J. R.; Vila, C. Asymmetric Oxidative Mannich Reactions. *Adv. Synth. Catal*. **2021**, *363*, 602

7. **Rostoll-Berenguer, J.**; Capella-Argente, M.; Blay, G.; Pedro, J. R.; Vila, C. Visible-light-accelerated amination of quinoxalin-2-ones and benzo[1,4]oxazin-2-ones with dialkyl azodicarboxylates under metal and photocatalyst-free conditions. *Org. Biomol. Chem.* **2021**, *19*, 6250– 6255.

8. **Rostoll-Berenguer, J.**; Martín-López, M.; Blay, G.; Pedro, J. R.; Vila, C. Radical Addition of Dihydroquinoxalin-2-ones to Trifluoromethyl Ketones under Visible-Light Photoredox Catalysis. *J. Org. Chem.* **2022**, *87*, 9343-9356.

9. **Rostoll-Berenguer, J.**; Sierra-Molero, F. J.; Blay, G.; Pedro, J. R.; Vila, C. Photocatalytic Functionalization of Dihydroquinoxalin-2-ones with Pyrazolones. *manuscript submitted*.

10. **Rostoll-Berenguer, J.**; García-García, V.; Blay, G.; Pedro, J. R.; Vila, C. Organophotoredox 1,6-Radical Addition of 3,4-Dihydroquinoxalin-2-ones to *p*-Quinone Methides. *manuscript in preparation*.

Resum en valencià

En aquesta *tesi doctoral* s'han desenvolupat diferents estratègies basades en catàlisi fotoredox per a la funcionalització selectiva de 3,4-dihidroquinoxalin-2-ones i 3,4-dihidro-1,4-benzoxazin-2-ones. Concretament, la presència d'una amina terciària aromàtica en aquests dos sistemes heterocíclics ha permés provocar processos de transferència monoelectrònica en presència d'un catalitzador fotoredox per a generar, en funció de les condicions de reacció, un catió imini electrofílic o un α-amino radical nucleofílic.

Part I

En la **Part I** d'aquesta *tesi doctoral* s'ha detallat de manera general el procés evolutiu que ha sofert el camp de la fotoquímica des dels seus inicis fins a hui en dia. Concretament s'ha parlat de les primeres evidències empíriques de Carl W. Scheele, qui va observar que cristalls de clorur de plata s'enfosquien quan eren exposats a la llum solar. Aquestes experiències van desembocar en la formulació del primer principi general de la fotoquímica el 1817 per Theodor von Grotthuss, que assevera que *només la llum que és absorbida pot ser efectiva en desencadenar un canvi químic*. També, s'inclou una revisió bàsica de com l'adveniment de la teoria quàntica va permetre modernitzar els conceptes de la fotoquímica, fent especial èmfasi en la formulació del segon principi de la fotoquímica o llei de l'equivalència fotoquímica.

Després té lloc una exposició dels diferents processos fotofísics i fotoquímics que tenen lloc una vegada una espècie ha assolit el seu estat excitat. D'entre ells hi destaca la transferència electrònica o la transferència d'energia com a mecanismes de desactivació de tipus fotoquímic. De fet, l'ús de fotocatalitzadors es basa en l'habilitat d'aquestes espècies d'actuar com a acceptors o donadors d'electrons quan es troben en el seu estat excitat, així com també actuar com a donadors d'energia. A més a més, la interacció d'un fotocatalitzador en estat excitat amb una altra espècie pot produir el que s'anomena desactivació bimolecular (conegut en anglés com *quenching*). En aquest sentit, en aquesta tesi doctoral també s'inclou la demostració matemàtica per arribar a l'equació de Stern-Volmer, la qual representa d'una manera senzilla aquests processos de desactivació bimolecular.

La fotoquímica també ha despertat un gran interés en la seua vessant sintètica, ja que des de finals del segle XIX molts químics orgànics sintètics es van servir de la fotoquímica per construir arquitectures moleculars molt complexes, cosa que haguera sigut molt complicat d'altra manera. La síntesi del *silphinene* per Crimmins el 1986 mitjançant una fotocicloaddició [2+2] n'és un bon exemple.

Tanmateix, la branca més interessant des del punt de vista sintètic és la fotocatàlisi, que es basa en l'ús d'una espècie en quantitat subestequiomètrica (que anomenem foto-

catalitzador) i la qual és capaç de provocar processos bé de transferència electrònica o bé de transferència d'energia. Així doncs, es poden diferenciar tres cicles fotocatalítics diferents: el que implica una transferència electrònica, el que implica una transferència d'energia o el que implica la consecució d'una reacció radicalària en cadena.

L'avanç de la fotocatàlisi ha vingut de la mà de la necessitat d'implementar metodologies sintètiques més respectuoses amb el medi ambient. En aquest sentit, l'eclosió de la fotoquímica sintètica ve del desenvolupament a principis del segle XXI de la fotoquímica utilitzant llum visible. Per això, hi ha una extensa col·lecció de fotocalitzadors que són excitats amb llum visible, d'entre els que hi destaquen els complexos polipiridínics de ruteni i d'iridi i, més recentment, molècules purament orgàniques.

Els treballs seminals en l'àrea de la catàlisi fotoredox utilitzant llum visible van vindre l'any 2008 dels laboratoris de MacMillan i de Yoon. El primer va desenvolupar una metodologia per a alquilar la posició en alfa d'aldehids alifàtics amb 2-bromomalonats utilitzant un sistema catalític dual format per $Ru(bpy)_3Cl_3$ com a catalitzador fotoredox i d'una imidazolinona chiral com a organocatalitzador. En irradiar la mescla de reacció amb una pereta comercial es van obtindre els productes desitjats amb rendiments i excessos enantiomèrics elevats. D'altra banda, el mateix any el grup de recerca de Yoon va descriure la cicloaddició [2+2] diastereoselectiva intramolecular d'enones utilitzant el mateix complex metàl·lic de ruteni com a fotocatalitzador. Des de la publicació d'aquests dos treballs, s'hi poden trobar nombroses estratègies per a una infinitat de processos químics, ja que hi ha una gran quantitat de grups de recerca a nivell mundial treballant en fotocatàlisi amb llum visible.

En particular, les amines terciàries que porten un grup metilè a la seva posició alfa es poden incloure en diferents esdeveniments fotoredox que permeten la seva funcionalització selectiva en alfa. L'amina terciària pot patir un SET per generar el catió radical corresponent. Un cop generat aquest catió radical, l'acidesa de l'α-H augmenta significativament. Aquest fenomen fa que el catió radical siga propens a la desprotonació i genera el radical α-amino, que té caràcter nucleòfil. Tanmateix, si es produeix un segon esdeveniment d'oxidació, el radical α-amino es pot convertir en catió imini, que presenta caràcter electròfil. Alternativament, el catió imini es pot generar mitjançant un transferència d'àtom d'hidrogen a partir del catió radical, ja que l'energia de dissociació de l'α-H disminueix en comparació amb la de l'amina neutra.

Els cations imini es poden atacar nucleòfilament per formar un nou enllaç C-C o C-X. Les amines terciàries que s'han utilitzat àmpliament per desenvolupar aquest tipus de transformacions són les *N*-aril tetrahidroisoquinolines, degut al fet que el catió imini es forma mitjançant l'abstracció d'un hidrogen benzílic i el doble enllaç resultant es conjuga amb el sistema aromàtic. A més, les *N*,*N*-dialquilanilines també han demostrat la seva

capacitat per dur a terme la funcionalització en α mitjançant un catió imini mitjançant catàlisi fotoredox.

D'altra banda, Els intermedis radicals α-amino també es poden explotar en química sintètica aprofitant el seu caràcter nucleòfil. De nou, les *N*-aril tetrahidroisoquinolines també han estat sotmeses a una funcionalització electròfila mitjançant catàlisi fotoredox. El treball pioner prové del laboratori de Reiser l'any 2012, que van ser capaços de generar el corresponent radical α-amino de *N*-aril tetrahidroisoquinolines utilitzant $Ru(bpy)_3Cl_2$ sota atmosfera inert, que va reaccionar amb alquens pobres en electrons per obtenir l'esperat. productes amb rendiments moderats.

En aquesta *tesi*, s'han seleccionat 3,4-dihidro-1,4-benzoxazin-2-ones i 3,4-dihidroquinoxalin-2-ones com a substrats per dur a terme transformacions sintètiques mitjançant catàlisi fotoredox a la llum visible. La selecció d'aquestes amines cícliques raonablement similars no va ser per casualitat, sinó per l'escassa existència de protocols de funcionalització donada la importància biològica d'aquests heterocicles. L'esquelet principal de 3,4-dihidro-1,4-benzoxazin-2-ona i 3,4-dihidroquinoxalin-2-ona tenen un nitrogen amínic secundari a la seua posició 4. A més, la instal·lació d'un substituent bencílic a la posició N-4 genera una amina terciària, que és més rica en electrons que la secundària, permetent que aquestes estructures es puguen sofrir transformacions sintètiques basades en esdeveniments de transferència d'electrons. No obstant això, poden sorgir alguns problemes de regioselectivitat ja que hi ha dos grups metilè en α a N-4. Tot i així, la rigidesa del sistema cíclic hauria de permetre que la funcionalització potencial es produeixi a través de la posició C-3.

De fet, les 3,4-dihidro-1,4-benzoxazin-2-ones i les 3,4-dihidroquinoxalin-2-ones són esquelets heterocíclics predominants que es poden trobar en diversos compostos biològicament actius naturals o sintètics. De fet, alguns estudis han posat de manifest la importància d'aquests sistemes heterocíclics per aconseguir activitats farmacològiques interessants. Tradicionalment, la preparació d'estructures complexes de 3,4-dihidro-1,4-benzoxazin-2-ones i 3,4-dihidroquinoxalin-2-ones s'ha basat en la síntesi *de novo* a partir de materials de partida disponibles comercialment. Tanmateix, des d'un punt de vista de síntesi orientat a la diversitat, és interessant desenvolupar metodologies de funcionalització directa per generar immediatament una biblioteca de candidats potencials per al descobriment de fàrmacs.

Part II

La **Part II** se centra en el desenvolupament de metodologies per a la generació de cations de tipus imini a partir de 3,4-dihidroquinoxalin-2-ones i 3,4-dihidro-1,4-benzoxazin-

2-ones utilitzant condicions fotoquímiques oxidants, generalment en presència d'oxigen molecular. Així doncs, aquests potents electròfils són captats per diferents nucleòfils:

Capítol 1

Els indoles s'han utilitzat àmpliament en la síntesi orgànica a causa de l'alta nucleofilicitat de la seva posició C-3 fent ús d'una de les pedres angulars de la química orgànica: la reacció de Friedel-Crafts, que és una de les maneres més senzilles de formar enllaços C-C. A més, hi ha una infinitat de molècules interessants que contenen indole des del punt de vista de la química medicinal, l'agroquímica i la ciència dels materials, entre altres camps. Així doncs, el desenvolupament de metodologies que permeten l'acomodació selectiva d'aquest heterocicle aromàtic és de gran interès. També hi ha moltes metodologies basades en catàlisi fotoredox amb llum visible on els indols serveixen com a nucleòfils. Especialment, s'han implementat àmpliament en α-funcionalització de *N*-aril tetrahidroisoquinolines i *N*-aril glicines. Cal destacar el treball del grup de Stephenson, que l'any 2012 va publicar una metodologia general per funcionalitzar les *N*-aril tetrahidroisoquinolines amb diversos nucleòfils, sent un d'ells l'indol, mitjançant catàlisi fotoredox a llum visible. En aquest cas, els autors van desenvolupar un protocol pas a pas en el qual es va generar el catió imini de *N*-aril tetrahidroisoquinolines en presència de $Ru(bpy)_3Cl_2$ i $BrCCl_3$ com a oxidant estequiomètric. Després, el catió imini va quedar atrapat amb, per exemple, indole, donant el corresponent producte aza-Friedel-Crafts en un 83%.

Per estudiar la reacció aza-Friedel-Crafts catalitzada per fotoredox entre 3,4-dihidro-1,4-benzozazin-2-ones (**1.1**) i indoles (**1.2**), es van seleccionar els compostos **1.1a** i **1.2a** com a substrats model per optimitzar les condicions de reacció. En primer lloc, s'ha realitzat l'avaluació del catalitzador fotoredox, seguida de la valoració de la millor relació molar entre substrats que garantisca que la reacció transcórrega amb el màxim rendiment d'**1.3aa**. A més, s'avaluarà l'efecte de diversos additius àcids sobre el resultat de la reacció. Finalment, s'estudiarà l'elecció del millor dissolvent per realitzar la reacció. Un cop establertes les condicions òptimes per a la reacció, la següent part d'aquest estudi ha sigut determinar com diferents substituents en 3,4-dihidro-1,4-benzoxazin-2-ones **1.1** o indols **1.2** poden afectar el rendiment. Les condicions òptimes impliquen l'ús de 0,15 mmol d'**1.1**, 0,1 mmol d'**1.2**, 5 mol % de 9,10-fenantrendiona (**J**), 2,5 mol % de $Zn(OTf)_2$, 1 mL de MeCN i una atmosfera d'aire. En conseqüència, es presenta una àmplia exploració sobre com els diferents patrons de substitució, tant pel que fa a característiques electròniques com estèriques, afecten el rendiment. En primer lloc, s'explora la substitució en totes les posicions de l'indole **1.2**. A continuació, s'utilitzen diferents 3,4-dihidro-1,4-benzoxazin-2-ones **1.1**. Complementàriament, l'abast d'aquesta metodologia s'estendrà

també a altres arenes riques en electrons.

Capítol 2

Tot i que la majoria dels avenços en catàlisi asimètrica s'han d'imputar als complexos metàl·lics quirals, en els darrers anys la comunitat de la química orgànica ha fet un gran esforç per desenvolupar transformacions asimètriques utilitzant molècules purament orgàniques com a catalitzadors. Aquesta branca de la química orgànica, l'organocatàlisi, ha crescut de manera exponencial des de principis d'aquest segle. No obstant això, un dels primers exemples d'èxit de reacció organocatalitzada asimètrica es va publicar el 1974, on Hajos i Parrish van ser capaços de sintetitzar un cetol bicliclic mitjançant una reacció aldòlica intramolecular. En aquest cas, la (*S*)-prolina va funcionar com a organocatalitzador, però el seu mode d'acció no es va entendre completament fins a l'any 2000.

L'ús de quantitats catalítiques de petites molècules orgàniques per promoure transformacions enantioselectives ofereix diversos avantatges en contrast amb els complexos metàl·lics quirals. Concretament, l'organocatàlisi ofereix una configuració experimental de baix cost i fàcil, alhora que evita la generació de residus que contenen metalls. La culminació de l'organocatàlisi com a ciència es va produir l'any passat, quan Benjamin List i David W. C. MacMillan van rebre el Premi Nobel de química "*pel desenvolupament de l'organocatàlisi asimètrica*".

Fins ara, s'han desenvolupat un gran nombre d'organocatalitzadors amb el seu particular mode d'acció. En aquest capítol, es tracta el desenvolupament d'una reacció de tipus Mannich. Per tant, l'ús de cetones com a nucleòfils en organocatàlisi requereix la formació d'una enamina quiral mitjançant una condensació amb una amina secundària quiral, com la prolina.

L'addició enantioselectiva d'enolats a un doble enllaç electrofílic C-N, la coneguda reacció de Mannich, és una estratègia senzilla i àmpliament utilitzada per a generaramines quirals. No obstant això, un gran nombre d'imines són inestables en condicions de reacció estàndard o, fins i tot, es regeixen per un equilibri que afavoreix la forma no electrofílica d'enamina. Per fer front a aquest problema, la presíntesi dels enllaços C-N electròfils s'evita mitjançant l'oxidació *in situ* d'amines secundàries o terciàries que porten un α-H. Lògicament, si s'oxida una amina terciària, el producte seria un catió imini, mentre que si l'amina és secundària, el resultat seria una imina. En ambdós casos, si hi ha un enolat (o un altre sintó d_2) al medi, així com un catalitzador adequat per induir asimetria, es pot produir una reacció de Mannich enantioselectiva. Aquesta estratègia es va reconèixer ràpidament com una eina poderosa, i es poden trobar diverses metodologies a la bibliografia.

Amb l'objectiu de desenvolupar un protocol per a funcionalitzar 3,4-dihidroquinoxalin-2-ones **2.1** en la posició C-3 amb cetones **2.2** de manera enantioselectiva, es va seleccionar

la reacció entre **2.1a** i **2.2a** per formar **2.3aa** com a model per a realitzar l'optimització del procés. Entre els paràmetres que s'ajusten per obtenir el producte **2.3aa** amb elevat rendiment i alta enantioselectivitat, el primer serà l'amina secundària quiral que serveix d'organocatalitzador. A continuació, s'avalua tant la font de llum com el catalitzador fotoredox. Finalment, es realitza la selecció del millor dissolvent per dur a terme la reacció. Amb les condicions òptimes a la mà (Eosina Groguenca com a fotocatalitzador i (*S*)-Prolina com a organocatalitzador), el següent pas va ser establir la generalitat de la reacció oxidativa de Mannich asimètrica entre les 3,4-dihidroquinoxalin-2-ones (**2.1**) i les cetones (**2.2**). Amb aquesta finalitat, les 3,4-dihidroquinoxalin-2-ones substituïdes de manera diferent (**2.1**) que es van preparar prèviament així com diverses cetones comercials (**2.2**) es van sotmetre a les condicions de reacció òptimes, obtenint els corresponents productes amb rendiments moderats in excessos enantiomèrics excel·lents.

Després d'estudiar l'abast de la reacció oxidativa asimètrica de Mannich, es va decidir augmentar el procés a una escala de 5 mmol, canviant també els LED blaus per la llum solar en el primer pas d'oxidació. Satisfactòriament, l'oxidació de **2.1a** es va produir en 6 hores i, després de la reacció de Mannich amb **2.2a** en presència de (*S*)-prolina, es van obtenir 689 mg de producte **2.3aa** (67% de rendiment) en un 99% ee. En aquest cas, la reacció podria tenir lloc utilitzant només un 0,5% mol de fotocatalitzador **E**.

Capítol 3

La pizazol-3-ona és un heterocicle nitrogenat que deriva del pirazol i, per tant, té dos àtoms de nitrogen consecutius i un grup carbonil en la seva posició C-3. Com molts altres heterocicles d'aquest tipus, la pirazol-3-ona pateix l'existència de diversos equilibris tautomèrics i, en conseqüència, té diferents posicions nucleòfiles. Així mateix, l'esquelet de la pirazol-3-ona es pot trobar en diversos compostos que tenen una infinitat d'aplicacions en molts camps, com ara la indústria agroquímica o com a principis farmacèutics actius (API). És important destacar alguns dels com l'edaravona, un agent neuroprotector, el metamizol, l'antipirètic més potent, que és l'API de Nolotil i la tartrazina, un colorant azoic sintètic utilitzat com a colorant alimentari. En química orgànica, les pirazol-3-ones s'han utilitzat àmpliament com a nucleòfils en una gran varietat de metodologies, especialment en processos enantioselectivos. Tanmateix, segons el que sabem, no hi ha informes sobre l'ús d'aquests heterocicles en processos mediats per la llum visible.

A la vista d'aquests precedents, es va pensar que seria d'interès el desenvolupament d'un protocol per a la funcionalització C-3 de 3,4-dihidroquinoxalin-2-ones amb pirazol-3-ones utilitzant fotocatàlisi amb llum visible. L'enfocament triat consisteix en la generació del catió imini de les 4-alquil-3,4-dihidroquinoxalin-2-ones més riques en electrons mitjançant fotocatàlisi aeròbica, i el posterior atrapament d'aquest electròfil amb les

pirazol-3-ones.

El procés d'optimització de la reacció d'alquilació s'ha dut a terme entre la 4-benzil-3,4-dihidroquinoxalin-2-ona **3.1a** i l'edaravona **3.2a**. Després de diversos assajos preliminars, la necessitat d'una cadena alquílica a N-4 de l'esquelet de 3,4-dihidroquinoxalin-2-ona era imprescindible, ja que l'anàleg sense protecció de N-4 no mostrava la reactivitat desitjada. A més, aquestes proves preliminars van mostrar com de difícil és aïllar i caracteritzar el producte d'alquilació entre **3.1a** i **3.2a**. De fet, aquest producte té dos centres estereogènics, un d'ells sense estabilitat configuracional per tautomerisme de ceto-enol. A partir de l'experiència prèvia del nostre grup de recerca, vam decidir afegir un pas addicional després de la reacció fotoquímica per atrapar l'enolat de la pirazol-3-ona mitjançant una *O*-acetilació. Aquest tractament va donar al producte **3.3aa**, que era molt més fàcil d'aïllar i de caracteritzar. Després d'obtindre les condicions òptimes de reacció (9,10-fenantrendiona com a fotocatalitzador), s'ha estudiat l'abast i les limitacions de la reacció amb diferents 3,4-dihidroquinoxalin-2-ones i altres pirazol-3-ones, obtenint en tots els casos rendiments elevats.

Capítol 4

La generació de diversitat química a partir d'un intermedi comú representa una de les pedres angulars més importants de la química orgànica. De fet, el desenvolupament de metodologies que introdueixen grups funcionals versàtils ha contribuït a la millora de l'espai químic. En aquest sentit, el triple enllaç carboni-carboni, concretament un alquí, ofereix moltes possibilitats sintètiques, ja que es pot convertir en diversos grups funcionals. Per esmentar-ne alguns, els alquins poden experimentar fàcilment hidrogenació (parcial o completa), halogenació, hidroboració, hidrosililació, hidrometalació o cicloaddicions, entre moltes d'elles. És important d'assenyalar que molts d'aquests processos requereixen catàlisi de metalls de transició. A més, l'alquí més simple, l'acetilè, es considera una matèria primera clau en la indústria química.

En conseqüència, el desenvolupament de metodologies per inserir un triple enllaç en una molècula ha cridat l'atenció de la comunitat de química orgànica, sent la forma més senzilla la generació d'alquinilurs metàl·lics nucleòfils a partir d'alquins terminals. Aquesta estratègia es basa en l'acidesa relativament alta de l'enllaç C-H, a causa del seu caràcter *s* més alt en comparació amb el dels alquens o alcans. Així, es pot accedir a l'activació d'alquins terminals mitjançant la desprotonació amb bases fortes estequiomètriques ($NaNH_2$, *n*-BuLi...) o bases febles en combinació amb un metall de transició. Els ions metàl·lics com Ag(I), Au(I), Cu(I) entre d'altres tenen una forta afinitat amb els enllaços triples. Per tant, la formació d'un complex π entre el metall i l'alquí condueix a una millora de l'acidesa en l'enllaç C-H i, per tant, la presència d'una base

feble és prou per desprotonar i generar l'alquinilur metàl·lic corresponent, que té caràcter nucleòfil.

D'altra banda, els metalls de transició també poden mediar l'activació d'alquins terminals així com també altres processos químics. Als efectes d'aquesta *tesi* és d'especial interès la generació de cations iminum a partir d'amines terciàries, i la posterior addició dels alquins terminals activats per metalls. A la llum dels precedents, es va pensar que seria d'interès el desenvolupament d'un protocol d'alquinilació per a la funcionalització C-3 de 3,4-dihidroquinoxalin-2-ones amb alquins terminals mitjançant una combinació de catàlisi metàl·lica i catàlisi fotoredox amb llum visible. Aquest enfocament s'abordarà generant el catió imini de les 4-alquil-3,4-dihidroquinoxalin-2-ones mitjançant fotocatàlisi aeròbica i el posterior atrapament d'aquest electròfil per l'alquinilur metàl·lic activat.

Després del procés d'optimització, es conclou que el nostre protocol necessita 0,1 mmol de 3,4-dihidroquinoxalin-2-ona **4.1a**, 0,5 mmol de fenilacetilè (**4.2a**), 10 mol % de $Cu(OTf)_2$, 1 equivalent de SiO_2, 1 ml de MeCN i la irradiació amb LED blancs sota una atmosfera d'aire. Un cop determinades les condicions de reacció òptimes per a l'alquinilació de 4-benzil-3,4-dihidroquinoxalin-2-ona (**4.1a**) i fenilacetilè (**4.2a**) es va establir la generalitat d'aquesta transformació. Així, la reacció es va dur a terme utilitzant 3,4-dihidroquinoxalin-2-ones (4.1) i alquins terminals (4.2) substituïdes de manera diferent, obtenint els corresponents productes de reacció amb rendiments moderats.

Part III

Tanmateix, la **Part III** detalla les metodologies sintètiques que han sigut desenvolupades per a funcionalitzar 3,4-dihidroquinoxalin-2-ones i 3,4-dihidro-1,4-benzoxazin-2-ones amb electròfils mitjançant, generalment, la formació del corresponent α-amino radical en condicions de catàlisi fotoredox:

Capítol 5

Els radicals orgànics han trobat un bon nombre d'aplicacions en la síntesi moderna d'esquelets moleculars complexos, especialment per la seva capacitat de patir processos en cascada. Un dels exemples més representatius és la síntesi diastereoselectiva d'*hirsutè* realitzada per Curran el 1985. En aquest treball, l'intermedi clau amb un iodur d'alquil primari es tracta amb hidrur de tributilestany i amb una quantitat subestequiomètrica d'AIBN com a iniciador de radicals.

Entre totes les reaccions rellevants, i als efectes d'aquesta *tesi*, és important destacar l'addició de radicals centrats en carboni als dobles enllaços electròfils. Aquesta trans-

formació va ser informada inicialment per Bernd Giese el 1977 i, per tant, és àmpliament coneguda com a reacció de Giese o addició radical de Giese. Inicialment, Giese va accedir als radicals de carboni tractant sals alquilmercúriques amb $NaBH_4$, tot i que poc després els va arribar utilitzant Bu_3SnH. En presència d'un alquè pobre en electrons, el radical reacciona amb el doble enllaç electròfil per obtenir el producte d'addició 1,4 o producte Giese.

La reacció clàssica de Giese promoguda per mercuri o estany ha impulsat una investigació significativa sobre els fonaments de les reaccions radicalàries, ja que aquesta segueix sent útil sintèticament. Tanmateix, l'ús de grans quantitats d'estany o altres hidrurs metàl·lics genera grans quantitats de residus neurotòxics. En aquest context, la fotocatàlisi de llum visible constitueix una eina potent i senzilla per accedir als radicals que utilitzen catalitzadors normalment no tòxics i llum visible de baixa energia. En aquest sentit, recentment diverses reaccions radicalàries clàssiques han trobat els seus equivalents per mitjà de la fotocatàlisi amb llum visible, com ara la reacció de Barton o la reacció de Hofmann–Löffler –Freytag. La reacció de Giese no és una excepció, i s'ha revitalitzat com una manera convenient de forjar enllaços C-C mitjançant fotocatàlisi amb llum visible.

Per iniciar el procés d'optimització s'ha seleccionat la 4-benzil-3,4-dihidroquinoxalin-2-ona (**5.1a**) com a precursor del radical α-amino, i el 2-benzilidemalonat de dimetil (**5.2**a) com alquè electrofílic per desencadenar la reacció de Giese i donat el producte **5.3aa**. Entre tots els paràmetres que es milloraran per assegurar un alt rendiment del producte **5.3aa**, es tindrà en compte el catalitzador fotoredox i la necessitat d'un additiu àcid per afavorir la reacció. Un cop finalitzat el procés d'optimització amb èxit ($Ru(bpy)_3Cl2$ com a catalitzador fotoredox i àcid difenilfosfòric com a cocatalitzador), es va decidir fer esforços per determinar la generalitat de la transformació. Per aconseguir aquest objectiu, es va provar una àmplia gamma de diferents alquens pobres en electrons en la reacció de tipus Giese. A més, es va estudiar si la 3,4-dihidroquinoxalin-2-ona substituïda de manera diferent es pot acomodar a la nostra metodologia catalítica dual. Afortunadament, utilitzant aquesta metodologia es va poder preparar una col·lecció de més de 40 productes de Giese en rendiments elevats.

Capítol 6

Els diazens, és a dir, les molècules que contenen el grup funcional azo, són una classe particular de compostos amb implicacions profundes en la química orgànica tant per a la investigació fonamental com per a la investigació aplicada. Normalment, els grups directament units al grup azo són aromàtics. Un dels diazens més estudiats és, de fet, l'azobenzè i els seus derivats, que presenten una isomerització *E,Z* eficient promoguda

per llum i que a més a més té aplicacions, per exemple, en farmacologia. A més, el grup azo és força destacat a la indústria del colorant, ja que pot comportar-se com a cromòfor, conferint així a la molècula una forta absorció a la regió visible.

Uns altres derivats azoics particulars són els azodicarboxilats de dialquil. En aquests compostos, el motiu azo està directament unit a grups èster. La col·locació d'aquests dos grups retiradors d'electrons confereix un caràcter electròfil als dos àtoms de nitrogen que ha estat explotat en síntesi orgànica. Així doncs, els azodicarboxilats de dialquil han trobat un paper interessant com a reactius d'aminació electrofílica per a la formació de nous enllaços C-N. De fet, són especialment útils per a l'α-aminació d'amines terciàries, tal com va demostrar el laboratori de Nishibayashi el 2012.

A la llum d'aquests antecedents, i després d'adonar-nos al capítol 5 que l'addició 1,4 del radical α-amino de la 3,4-dihidroquinoxalin-2-ona als alquens pobres en electrons era eficaç, es va assajar si els azodicarboxilats de dialquil també podrien servir com a substrats 1,4 en l'aminació radical de 3,4-dihidroquinoxalin-2-ones mitjançant catàlisi fotoredox a la llum visible.

El procés d'optimització es durà a terme utilitzant 4-benzil-3,4-dihidroquinoxalin-2-ona (**6.1a**) com a precursor del radical α-amino i azodicarboxilat de diisopropil (**6.2a**) com a electròfil per proporcionar 3,4-dihidroquinoxalin-2-ones aminades **6.3aa**. Inicialment, es realitzarà un cribratge de possibles catalitzadors fotoredox, seguit de l'avaluació del millor dissolvent per realitzar la reacció. Després del procés d'optimització, es va seleccionar MeCN com el millor dissolvent per dur a terme l'aminació de 3,4-dihidroquinoxalin-2-ona **6.1a** amb azodicarboxilat de diisopropil (**6.2a**). A més, no es va observar cap necessitat de fotocatalitzador, tot i que la irradiació de la mescla de reacció amb llum visible va ser beneficiosa per a la velocitat de la mateixa. Així doncs, es prova un conjunt de compostos azo electròfils (**6.2**) com a reactius d'aminació de la 3,4-dihidroquinoxalin-2-ona **6.1a**. A continuació, s'explora la generalitat de la reacció pel que fa a la substitució a la 3,4-dihidroquinoxalin-2-ona **6.1**. Afortunadament, els corresponents productes d'aminació s'obtenen amb rendiments generalment excel·lents. A més a més,les corresponents 3,4-dihidroquinoxalin-2-ones i 3,4-dihidro-1,4-benzoxazin-2-ones funcionalitzades amb els azodicarboxilats de dialquil poden ser derivatitzades posteriorment amb diferents nucleòfils.

Capítol 7

La presència d'àtoms de fluor en molècules potencialment biològicament actives era inconcebible als anys quaranta, ja que es pensava que la incorporació d'aquest àtom faria instantàniament el compost tòxic o incompatible per a la vida. Aquests supòsits primigenis es basaven en l'alta reactivitat i toxicitat del F_2. Tanmateix, la síntesi de *Fludro-*

cortisona el 1953 va revelar com la incorporació de fluor podria millorar la bioactivitat d'un determinat fàrmac. Des d'aquest assoliment inicial, molts fàrmacs i altres compostos biològicament rellevants han aparegut al marcat fins als nostres dies. Per exemple, l'*Efavirenz*, que presenta activitat antiviral, conté un grup trifluorometil unit a un carboni alifàtic. A més, la *silidosina*, que ha demostrat la seva eficàcia contra la hiperplàstia benigna de pròstata, té una agrupació CH_2CF_3.

Hi ha diverses estratègies per incorporar àtoms o grups de fluor a les molècules. En els processos a escala de laboratori, sovint s'evita l'ús de reactius altament tòxics, com el F_2 o el HF. Fins al dia d'avui s'han desenvolupat diversos reactius fluorats estables i fàcils de manejar, que ofereixen diferents modes de reactivitat. Aquests reactius sovint es divideixen en dues classes principals: reactius nucleòfils i electròfils.

Una altra estratègia per introduir àtoms de fluor és emprar substrats amb les seves pròpies reactivitats que també porten el fragment que conté fluor desitjat. Per descomptat, aquest tipus de substrats s'han de preparar mitjançant un pas previ de fluoració. En aquest sentit, les trifluorometil cetones podrien encaixar en aquesta categoria perquè porten el grup fluor desitjat (CF_3 en aquest cas), però també tenen un grup carbonil reactiu que podria participar en diverses reaccions de funcionalització nucleòfila. De fet, les trifluorometil cetones tenen s'ha utilitzat com a reactius que contenen fluor en la síntesi de farmàcòfors rellevants com *Efavirenz*.

D'acord amb aquests antecedents, es preveu que seria d'interès el desenvolupament d'una metodologia general basada en la catàlisi fotoredox per a la funcionalització de 3,4-dihidroquinoxalin-2-ones amb trifluorometil cetones. A més, tenint en compte que als capítols 5 i 6 vam establir protocols per a les addicions 1,4, també era desitjable l'exploració de les addicions directes.

Per optimitzar les condicions de reacció vam seleccionar 4-benzil-3,4-dihidroquinoxalin-2-ona (**7.1a**) i trifluoroacetofenona (**7.2a**) com a substrats model. El primer paràmetre a tenir en compte va ser el catalitzador fotoredox, donada la seva importància en la generació del radical α-amino de **7.1a**. A continuació, s'investiga el paper del dissolvent per obtenir el producte **7.3aa** amb el rendiment més alt. Finalment, es realitzen alguns ajustos de la relació molar per maximitzar el rendiment i la practicabilitat de la reacció. Per concloure el procés d'optimització, es pot dir que les millors condicions per a la reacció entre la 3,4-dihidroquinoxalin-2-ona **7.1a** i la trifluoroacetofenona (**7.2a**) impliquen l'ús de 0,26 mmol de **7.1a**, 0,2 mmol de **7.2a**, 1% mol de $Ru(bpy)_3Cl_2$ i 2 mL de MeCN assecat i desgasificat sota la irradiació d'HP Single LED (455 nm). El següent pas és estudiar l'abast d'aquesta transformació. En aquest sentit, les 3,4-dihidroquinoxalin-2-ones **7.1** substituïdes de manera diferent van participar en aquesta reacció fotoquímica, obtenint els corresponents productes amb un rendiment elevat. A continuació, s'explora la gener-

alitat de la reacció pel que fa a la substitució en l'esquelet de trifluorometil cetona **7.2**, tot observant que s'obtenen els corresponents productes amb rendiments moderats a elevats quan la trifluorometil cetona és aromàtica, però que quan és alifàtica el rendiment cau fins al 20%.

Capítol 8

La propagació de les característiques electròniques d'un grup funcional al llarg d'una insaturació o d'un sistema llarg conjugat té grans implicacions en química orgànica. Aquest precepte significatiu és àmpliament conegut com a principi de vinilologia i va ser introduït per Fuson l'any 1935. Segons aquest químic nord-americà, la posició β d'un determinat compost carbonílic α,β-insaturat continua sent electròfila a causa del fet que l'electrofilicitat del grup carbonil es transmet al a través del doble enllaç. Tot i que l'electrofilia β en aquest tipus de molècules orgàniques s'assumeix àmpliament, el principi de la vinilologia permet dissenyar noves estructures amb reactivitats inusuals.

Una de les estructures representatives més importants d'aquest principi són els *p*-quinona metins. Aquest tipus de compost es pot veure com a cetona diinsaturada $\alpha,\beta,\gamma,\delta$, a la qual s'accedeix formalment pel canvi d'un grup carbonil en la *p*-quinona per un grup de carboni trigonal. La presència del grup carbonil restant permet que el *p*-quinona metí mostre electrofília a la seva posició δ, permetent així addicions nucleòfiles de tipus 1,6. Tanmateix, per evitar les addicions més fàcils d'1,2 o 1,4, els *p*-quinona metins solen estar decorats amb grups voluminosos a les dues posicions α. És interessant observar que l'addició nucleòfila a la posició δ permet que el sistema genere una estructura fenòlica aromàtica, proporcionant una estabilitat superior als productes de reacció.

Normalment, per proporcionar més estabilitat a tot el sistema, el substituent directament unit al carboni exocíclic en els *p*-quinona metins és un anell aromàtic. Per tant, les estructures resultants que apareixen després d'una addició de tipus 1,6 a aquest tipus d'electròfils té una interessant estructura d'1,1-diarilalcà, que està àmpliament present en nombrosos ingredients farmacològics actius.

A la llum dels precedents, l'ús d'amines com a precursors de radicals centrats al C sota catàlisi fotoredox i la seua reactivitat amb *p*-quinona metins està força poc explorat. A més, una vegada hem descrit dos protocols per a addicions de tipus 1,4 i un per a addicions 1,2 de 3,4-dihidroquinoxalin-2-ones, vam pensar que seria d'interès el desenvolupament d'un metodologia per funcionalitzar en C-3 aquests heterocicles mitjançant una reacció d'addició 1,6 amb *p*-quinona metins. Per optimitzar les condicions de reacció es va triar 4-benzil-3,4-dihidroquinoxalin-2-ona (**8.1a**) i el *p*-quinona metí **8.2a** com a substrats model. La variable inicial i més important a optimitzar és el catalitzador fotoredox, pel fet que és el principal responsable de generar el radical α-amino de **8.1a**.

A continuació, s'investiga el paper del dissolvent per obtenir el producte **8.3aa** amb el rendiment més alt. Finalment, es realitzen alguns ajustos de la relació molar per maximitzar el rendiment i la practicabilitat de la reacció. Després del procés d'optimització es va decidir afirmar que les millors condicions per dur a terme la reacció entre la 3,4-dihidroquinoxalin-2-ona **8.1a** i el*p*-quinona metí **8.2a** impliquen l'ús de 0,15 mmol de **8.1a**, 0,1 mmol de **8.2a** [Mes-Acr-Me][BF_4] (**H**) com a catalitzador fotoredox i DCM assecat i desgasificat com a dissolvent. Amb aquestes condicions es va estudiar l'abast i les limitacions de la transformació utilitzant 3,4-dihidroquinoxalin-2-ones **8.1** i *p*-quinona metins **8.2** amb diferents patrons de substitució. Gustosament, es van poder obtindre els productes esperats amb rendiments generalment excel·lents.

Part Experimental

Després de totes les seccions de *resultats i discussió* de cada *capítol* s'inclou la part *experimental*, on es detallen les tècniques experimentals que s'han utilitzat, així com tots els procediments experimentals i la descripció espectroscòpica i espectromètrica de cada producte de reacció.