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**LIGHT AND ELECTRICITY: POWERFUL TOOLS FOR
NEW SUSTAINABLE STEREOSELECTIVE SYNTHESIS**

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***"Tieniti la terra uomo, io voglio
la luna."***

- Caparezza-

A mamma e papà

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**1 CHAPTER 1. ELECTROCHEMISTRY, PHOTOCATALYSIS AND
ELECTROPHOTOCATALYSIS: INNOVATIVE SOLUTIONS FOR NEW
SUSTAINABLE SYNTHESIS**

Rising environmental challenges such as climate change, resource depletion, and pollution, have highlighted an urgent need for sustainable practices across all productive sectors. In response, green chemistry, defined by the twelve principles established by Paul Anastas and John Warner,¹ seeks to minimize the environmental impact of chemical processes and products.

Organic chemistry, in particular, plays a crucial role in advancing sustainable solutions, as it drives the development of essential compounds in fields like agrochemicals, pharmaceuticals, and materials science. Therefore, new synthetic methodologies to achieve these molecules need to be developed with the aim to avoid, or minimize, wastes in chemical processes and the use of toxic and/or hazardous substances.² A crucial point relies in finding efficient techniques which reduce the energy required for chemical transformations and allow for the individuation of unexplored mechanistic pathways. Although these targets may appear challenging to achieve, several effective methods have already been developed to address these issues. These approaches can be categorized into four distinct groups, each offering innovative solutions to facilitate progress in this area.

- **New efficient catalytic processes:** these tools include the individuation of efficient metal-free catalysts and their implementation in supported and phase/transfer catalysis.
- **Use of non-usual media or environmentally benign reagents:** In these new pathways, organic solvents have been replaced with greener alternatives, such as water or deep eutectic solvents (DES). Also, super critical fluid and biphasic media can be used.
- **New selective and efficient synthetic methods:** New processes which adopt flow chemistry under homogeneous and heterogeneous conditions along with the development of microreactors and new purification/separation technologies.
- **New techniques based on alternative energy sources:** among all the methods available, it is important to highlight several innovative techniques such as photochemistry (which harnesses light to drive chemical reactions), electrochemistry, electrophotocatalysis (which combines both light and electricity to enhance catalytic processes), mechanochemistry (which employs mechanical force to induce chemical changes) and microwave irradiation (which uses microwave energy to accelerate reactions).

Starting from this last point, aimed from the increasing need to identify new reactions exploiting green energy sources, three different synthetic routes have been developed and analysed during this thesis work. In particular, *chapter 1* will introduce the techniques employed: electrochemistry,

photocatalysis and electrophotocatalysis. Chapter 2 will present an investigation into the *stereoselective photocyclization of aryl enones under homogeneous and heterogeneous conditions*. Chapter 3 will focus on the *Electrochemical stereoselective dehydrogenative homo-coupling of β -naphthylamines derivatives* while, in Chapter 4, the results related to *Fe(III)-catalyzed electrophotochemical decarboxylative late-stage C–H fluoroalkylation* will be discussed. This last topic was investigated during the visiting period at Göttingen University, under the supervision of prof. Lutz Ackemann.

1.1 ELECTROORGANIC SYNTHESIS

The increasing need to introduce green energy sources in our society has led the scientific community to reconsider the chemical synthesis and to address the development of new sustainable techniques.³

Among the latest approaches, electrochemistry has been re-evaluated in synthetic organic chemistry methodologies after being neglected for several years, even though electrolysis has always been widely used for a bulk scale chemical production such as ammonia, aluminium and caustic soda.⁴ One of the first example of electrochemical C–C bond formation is represented by the Kolbe electrolysis (1847)⁵ which, along with Monsanto adiponitrile process (1980-1990)⁶ and the Simons fluorination reaction (1960-1980) ⁷, highlighted the innate ability of electrolysis to accomplish challenging chemical transformations, also in large scale (**Figure 1**).

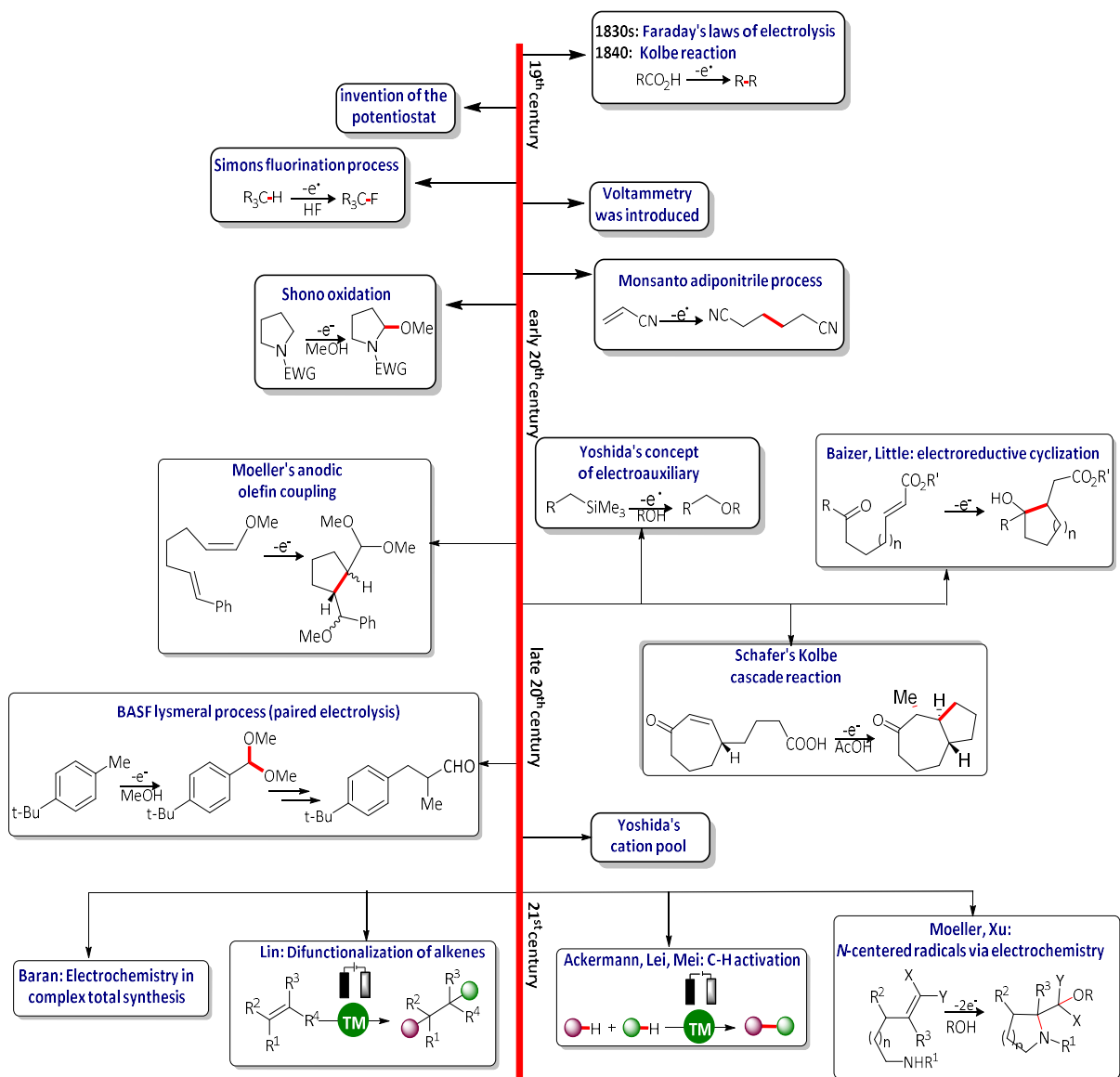


Figure 1: selected examples of representative approaches in electroorganic chemistry.⁸

Electrosynthetic transformations have quickly demonstrated their ability to eliminate the need for harsh oxidizing and reducing agents typically employed in traditional synthetic methods. This approach has proven to be both mild and atom-efficient, allowing for the conversion of substrates into challenging intermediates that are often only accessible through electrochemical pathways. By utilizing electricity as a driving force, these transformations minimize waste and enhance reaction selectivity, making

them an attractive alternative for modern organic synthesis. In addition, electrochemistry could offer new reaction pathways that are complementary to traditional synthetic chemistry procedures and can be particularly interesting for late-stage functionalisation due to its mild and selective nature. Despite the easy application, precise control and safety, electrochemistry has *represented a technique employed as a “last resort” rather than a routinely surveyed method*. According to Baran and his group,⁹ the weak applicability, especially for laboratory organic transformations, lied on the relatively complex instruments required along with a strong engineering background of the operator. Moreover, the non-standardized setup introduced numerous variabilities which severely affect the reproducibility of the process. Unfortunately, such unpredictability didn't fit with the increasing requirements of synthetic organic and pharmaceutical chemistry, therefore the employment of classic synthetic methods have always been preferred compared to the methods based on the electrochemical approach. The technological development of the last 15 years has driven the investigation of newly easy and standardized devices to meet the needs of scientific community (**Figure 2**).⁹

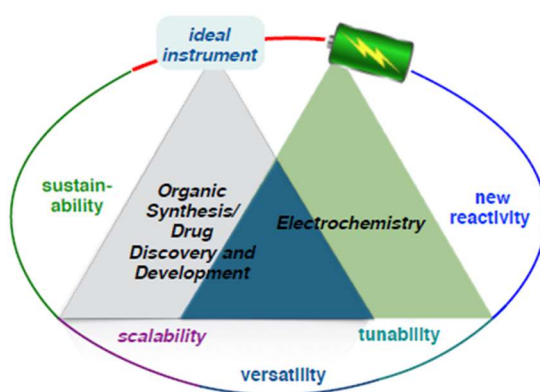


Figure 2: Implementation of an ideal instrument which meet the needs of modern synthetic organic chemistry

Baran and coworkers. specified seven parameters which define an “Ideal instrument” in synthetic organic electrochemistry: The most significant are here reported.

- Standardization. Reproducibility is the key of the experimental chemistry. Electrochemical processes are influenced by different factors such as: electrode, electrolyte, current, potential, and resistance. The use of standardized electrochemical devices, including reaction vessels, electrodes, and potentiostats, can ensure consistent and reproducible results.

- Modularity. The development of new electrochemical reactions requires the systematic investigation of many reaction parameters. This could be even challenging if multiple reactions are conducted at the same time. An ideal instrument should permit the modular setup of reactions in different sizes. Specifically, it should possess a broad potential/current range and be equipped with cells or electrodes of different sizes. Moreover, it should be compatible with different electrodes and cell types.
- Analytical Capability. Cyclic voltammetries play a pivotal role in the investigation of redox properties. An ideal device, in contrast, should combine preparative and analytical capabilities to allow the easy individuation of the potential of electrochemical reactions.
- Versatility. Different devices are required to set-up an electrochemical reaction, such as potentiostat, electrodes, a reaction vessel and a stirrer plate. According to Baran and his group.⁹, an ideal electrochemical instrument should be an all-inclusive apparatus with condensed preparative, analytical, and stirring capabilities all in the size of a stirring plate.
- User-friendly interface. In electrochemical transformations, electricity can be considered as a reagent. In the ideal instrument, an easy interface would facilitate the selection and individuation of electrochemical parameters.

1.1.1 PRINCIPLES OF ELECTROCHEMICAL REACTIONS

Electroorganic synthesis relies on the fundamental principles of redox reactions using electric current as the essential reagent. The simplest and standardized electrochemical set-up (**Figure 3**) consists of a reaction vessel with two electrodes (anode and cathode) which are directly connected to a power supply and plunged in the reaction solution. The anode is conventionally defined as the oxidation electrode while the cathode is the reductive. It is usually named as “working” the electrode where the reaction of interest occurs and “counter” the other one, essential to balance the redox reaction.

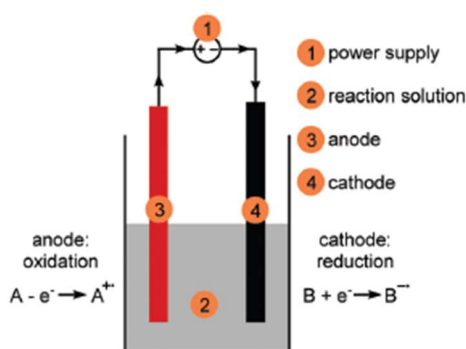


Figure 3: The simplest set-up for electrosynthesis; red: anode, black: cathode, grey: reaction solution.

The power supply moves electrons from the anode to the cathode creating an electrochemical potential, which must be greater than the substrate's redox potential to pull off the chemical reaction. Thanks to the voltage created by the power supply and the reaction media, reactants can be oxidized or reduced by Single Electron Transfer (SET) process at the electrodes surface generating charged species. The ions produced flow through the reaction medium following an opposite direction respect the electron flow (black arrow), thus completing the electrical circuit. The most important parameters for an electrochemical reaction are the current (I) and the potential (U), which are correlated by the resistance (R) in the Ohm's equation (**Equation 1**).

$$U = R * I$$

U : potential in volt [V]; R : resistance in Ohm [Ω]; I : current in Ampere [A].

Equation 1: Ohm's law

The current (I) describes the “charge velocity” of the electrons flow while the potential (U) the energy necessary for their movement. The Resistance (R) depends on different parameters such as the electrodes and the reaction solution itself which affect the ions movement inside the reaction medium: high resistance values indicate low charge transfer, resulting in significant difficulties in completing the electron cycle. Another important factor is the Charge (Q) which is related to the total number of electrons released into the reaction medium, and it can be considered the analogous to stoichiometry in traditional chemical reactions, as it quantifies the electron flow necessary for the completion of electrochemical processes.

Electrochemical transformations can be carried out under either **galvanostatic** or **potentiostatic** conditions. In the galvanostatic mode, a constant current is applied, using a simple and cost-effective setup that consists of an electrochemical cell equipped with only a working electrode and a counter electrode. One of the advantages of galvanostatic reaction include the possibility to calculate the total charge with the reported **equation 2**.

$$Q = I t = n N F$$

Q : charge in Coulomb [C]; n : number of electrons per substrate; N : moles [mol]; F : Faraday constant [96485 s A mol⁻¹].

Equation 2: Application of Faraday’s law for charge calculation

Exploiting the same formula, for a specific current, it is possible to evaluate the time (t) for the required charge Q to go through the reaction.

$$t = \frac{n N F}{I}$$

Equation 3: Application of Faraday’s law for time calculations

Another important parameter which allows to compare reactions with different electron equivalents is the Faradaic efficiency (n), or current efficiency. This value defines how many electrons transferred in the reaction mixture are converted in the product (**Equation 4**).

$$n = \frac{Q (theo)}{Q(exp)} \%$$

$Q(theo)$: theoretical charge in Coulomb [C], $Q(exp)$: experimental charge in Coulomb [C]

Equation 4: calculation of Faradaic efficiency

Q_{Theo} refers to the charge theoretically required to obtain the amount of product achieved while Q_{exp} describes the total charge transferred inside the mixture, taking into account the F/mol and the number of mol used. When the experimental charge (Q_{exp}) is comparable to the theoretic Q_{Theo} (n close to 100%), means that all the charge transferred in the reaction media is used for the desired electrochemical process. However if Q_{exp} is higher respect Q_{Theo} (n less than 100%) indicates the presence of side reactions or losses. Considering these assumptions, it is possible to calculate the Faradaic efficiency according to the **equation 5**.

$$Q_{theo} = Z_p * N_p * F = z * N * Y * F$$

$$Q_{exp} = I * t = z * N * Y * F * equiv.$$

$$n = \frac{z * N * F * Y}{z * N * F * equiv.} = \frac{Y}{equiv.}$$

n : Faradaic efficiency in percent [%], Q_{theo} : theoretical charge in Coulomb [C], Q_{exp} : experimental charge in Coulomb [C], *equiv.*: electron equivalents, Z_p : Number of electrons per product [-], N_p : Number of mols of the product [mol], Y : yield in percent [%].

Equation 5: Calculation of Faradaic efficiency considering the Yield and the electrons equivalents

While electrolysis performed under a galvanostatic approach enables rapid reactions and is highly relevant for scaling up organic synthesis, it lacks control over the potential. To keep the current constant, the potential varies according to the resistance value. Sometimes high voltage value can be reached, thus bringing to the formations of undesired by-products. However, if the substrates are more sophisticated and lack of selectivity, a three-electrode setup with constant potential can be used.

This **potentiostatic electrolysis** offers selectivity towards the desired functionalities by controlling the applied potential but prolongs electrolysis times in an elaborated setup. Analogously to galvanostatic reactions, under potentiostatic conditions the current is not actively controlled and will vary to maintain a constant potential. Therefore, the charge (Q) and the Faradaic efficiency (n) cannot be calculated. Moreover, the potential recorded is an adduct of the inherent setup resistance and the chemical reaction. In order to decouple these two processes and to guarantee a good selectivity, a reference electrode, which is not involved in the reaction but measures the potential at the working electrode, must be used. The operating potential selected needs to be comparable to the oxidation or reductive potential of reactants, which can be determined from tables of standard potentials

reported in literature (**Figure 4**). As alternative, when the potential of a given substrate is not known, it can be measured by Cyclic Voltammetry (CV) analysis. The standard potentials are referenced to standard conditions, which correspond to a temperature of 25 °C, a concentration of 1 mol L⁻¹ and 1 atm as pressure, using a standard hydrogen electrode (SHE).

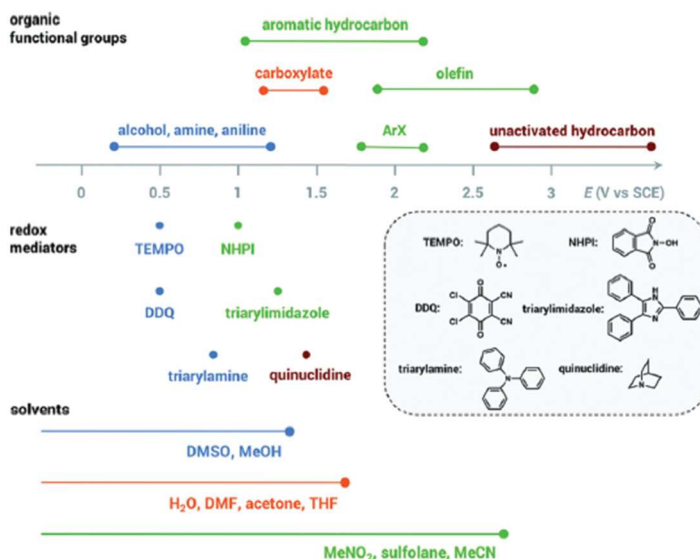


Figure 4: Standard oxidation potential of some organic functional groups and solvent adapted from ref.¹⁰

In most cases, reactions are not carried out under standard conditions and the concentration influences the redox potential. If the reaction is reversible (the reactant can be oxidised and reduced back) the Nernst's Equation can be applied. It assumes that, at a certain potential, both species of the redox couple are in equilibrium (**equation 6**).



$$E = E^\circ + \frac{RT}{nF} \ln \frac{C_{\text{Ox}}}{C_{\text{Red}}}$$

R : gas constant, T : temperature, C_{Ox} : concentration of oxidised species Ox, C_{Red} : concentration of reduced species Red, n : number of electrons per substrate; F : Faraday constant [96485 s A mol⁻¹].

Equation 6: Nernst's Equation

At 25°C the **equation 6** can be rewritten according to **equation 7**:

$$E = E^{\circ} + \frac{0.059V}{n} \ln \frac{C_{ox}}{C_{red}}$$

Equation 7: Nerst's Equation at 25°C

As previously mentioned, if the potential cannot be identified by standard oxidation table or using the Nerst' equation, **Cyclic Voltammetry (CV)** can be performed. Comprehensive guidelines in the field, especially for synthetic chemistry, are well-documented in literature.¹¹ Specifically, cyclic voltammetry set-up consist of three electrode systems: working (glassy carbon rode), counter (platinum plate) and reference electrodes. During the analysis, the current is acquired while the potential at the working is scanned in a cyclic manner (**Figure 5-a**) at a selected "speed" named scan rate (mV/s). A cyclic voltammogram is obtained (**Figure 5-b**).

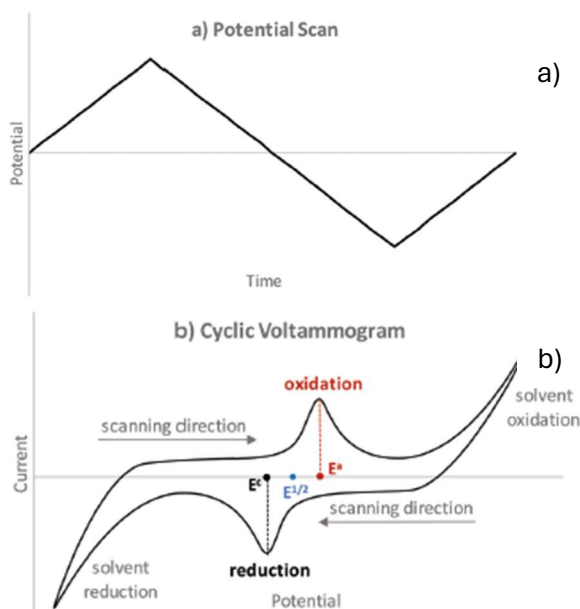


Figure 5: (a) Scanning of potential, (b) cyclic voltammetry analysis

If the potential is increased without any reaction occurring, no current peak will be observed. However, when a specific voltage is applied that allows the species to be oxidized or reduced, a current will flow until the species is depleted at the electrode surface, resulting in the appearance of a peak. The potential at which the maximum current is observed are depicted as E^a and E^c for the anodic and the cathodic potential respectively. Cyclic Voltammetry gives information about the redox system and helps to understand at which potential the desired reaction occurs. Moreover,

reveals to be particularly useful for mechanistic studies of electrochemical reactions and photocatalytic processes. Cyclic voltammetry gives also information regarding the electrochemical reversibility. Basing on the cyclic voltammogram shape, the electrochemical reversibility is classified in: reversible, quasi reversible and irreversible.

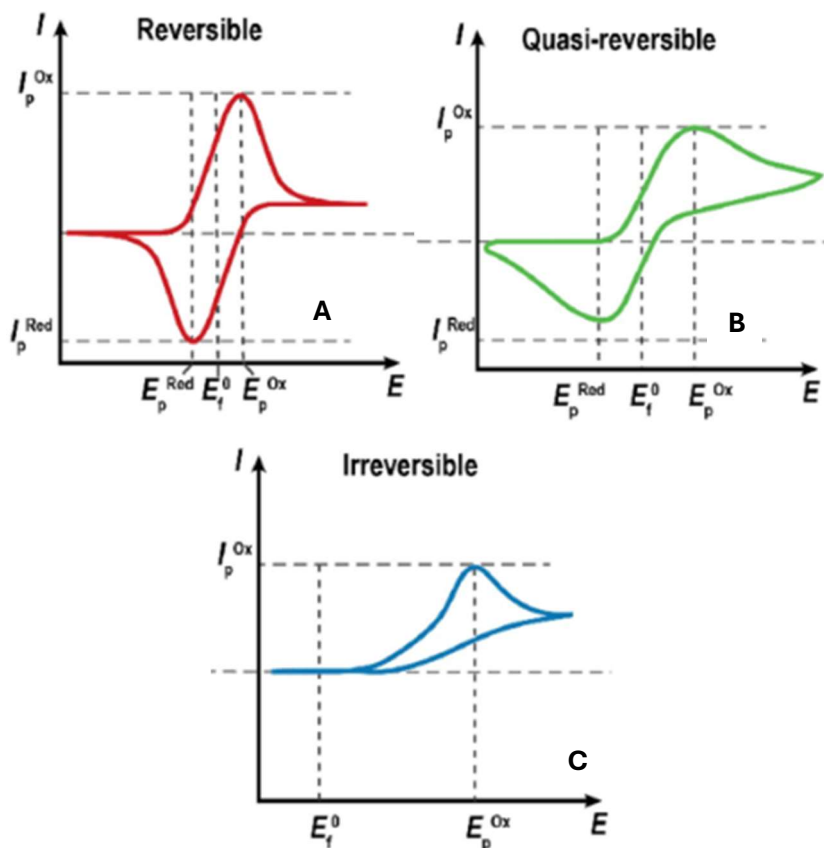


Figure 6: Cyclic Voltammogram. A) Reversible waveform, B) Quasi-reversible waveform, C) Irreversible waveform¹²

In a reversible reaction, the cyclic voltammetry shows two symmetric current peaks with equal magnitude and the difference between anodic and cathodic potentials (ΔE_p) is less than 59 mV at 25°C (**Figure 6-A**). This behaviour shows that the forward and reverse electrochemical processes (oxidation and reduction) occur with equal efficiency. However, in a quasi-reversible reaction, the current peaks are asymmetric, with the anodic peak usually more intense and larger than the cathodic (**Figure 6-B**). Moreover, the electrochemical process is not easily reversed due to kinetic limitations, such as a slow electron transfer rate or the formation of reaction intermediates that are not easily reduced. Lastly, an irreversible behaviour is

showed by a single anodic or cathodic peak. In this case, the oxidized or reduced intermediate undergoes to further reactions with prevent the regeneration of the original form (**Figure 6-C**). Naturally, potentials values are influenced by the type of reference electrode used (Ag/AgCl, calomel electrode, SHE) and the scan rate employed (express in mV/s).

1.1.2 ELECTROCHEMICAL REACTION TYPES

In literature different types of electrochemical reactions are reported (**Figure 6**): Direct electrochemical reaction with solvent degradation as counter reaction (**Figure 7-1a,1b**), Direct electrochemical reaction with non-solvent degradation as counter reaction (**Figure 7-2a,2b**), mediated or catalysed electrochemical reaction (**Figure 7-3**) and Redox combined electrochemical reaction (**Figure 7-4**).

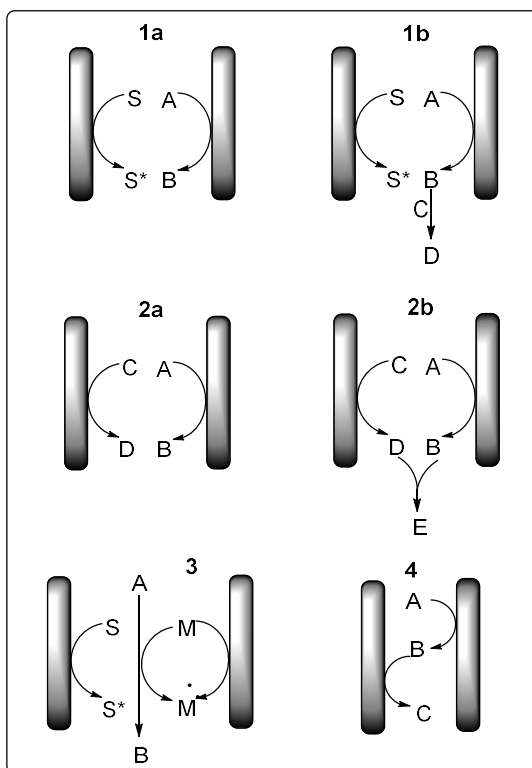
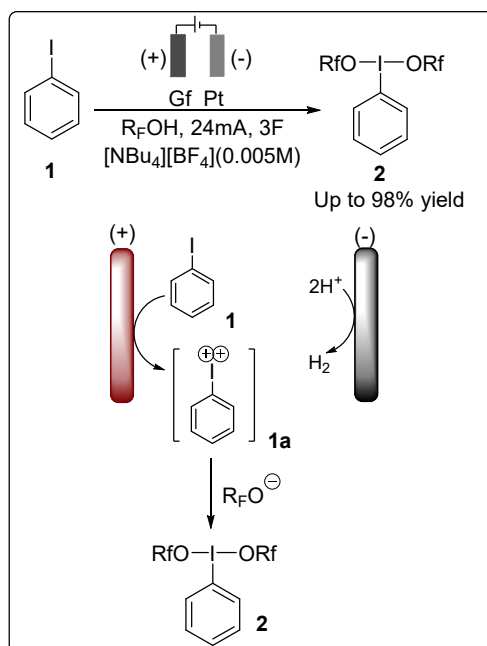


Figure 7: Different types of electrochemical reactions. S: solvent; S*: solvent degradation product; A and C: reagents; B, D and E: products; M: mediator or catalyst; M*: activated mediator or catalyst.

- 1) Direct electrochemical reaction with solvent degradation as counter reaction.

This represents the simplest case: the substrate is oxidized or reduced on the working electrode and the solvent decomposition occurs at the counter electrode. It is important to notice that the substrate usually reacts further to form the final product, as most electrochemical reactions lead to the formation of highly reactive intermediates. One example of this approach was reported by Wirth and co-workers who investigated the formation of hypervalent iodine compounds by the oxidation of iodobenzene in fluorinated media (RfOH) (**Scheme 1**).¹³

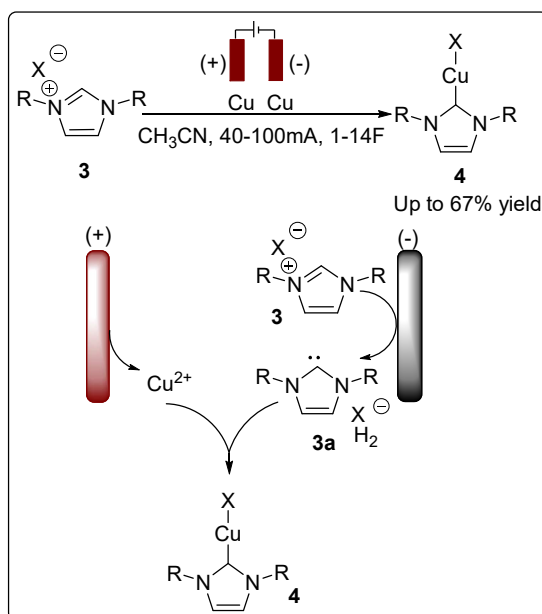


Scheme 1: Electrochemical reaction with solvent degradation as counter reaction.

- 2) Direct electrochemical reaction with non-solvent degradation as counter reaction.

This approach provides several advantages when (a) the counter reaction is rate limiting or incompatible with the reaction of interest, (b) the counter reaction results in a useful material or (c) the products generated at both electrodes can later react to form a new desired product. Willans group demonstrated the electrochemical formation of NHC-complexes where an imidazolium salt is reduced to the NHC on the cathode and the anode metal is oxidised to release metal cations into solution. The two products then react together to form the NHC complex. (**Scheme 2**).¹⁴ The electrochemical transformation was carried out using Copper electrodes as anode and cathode, in

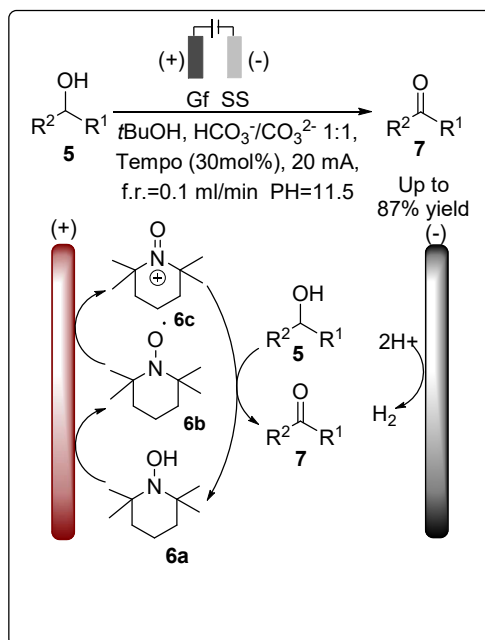
acetonitrile under galvanostatic conditions (40-100 mA). Reaction conditions depends on the counter anion (X^-) and the substituents R.



Scheme 2: Electrochemical reaction with no solvent degradation as counter reaction.

3) Mediated or catalysed electrochemical reaction.

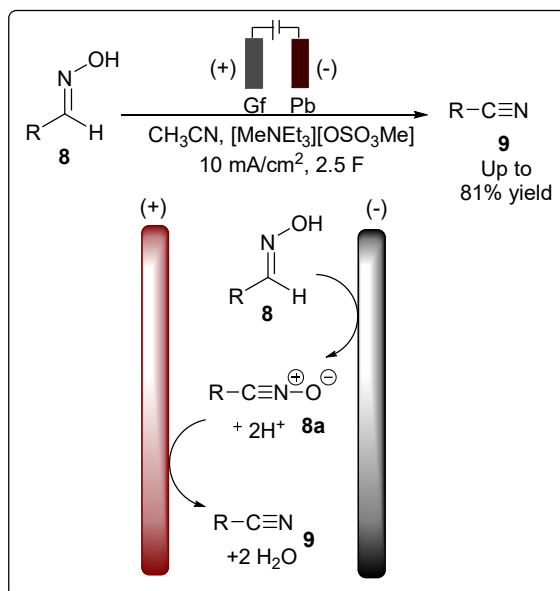
In this scenario there is a redox active species, which can be a mediator or a catalyst, that has a lower oxidation or reductive potential compared to the substrate. The direct interaction of the mediator and the electrode surface produces a highly reactive intermediate that chemically oxidizes or reduces the substrate of interest. This represents a winning strategy for the species in which the substrate potential is outside the solvent window. As example, on the basis of the seminal work of Brown and co-workers,¹⁵ TEMPO, has emerged as one of the most commonly used compounds for mediating the oxidation of alcohols. In *t*BuOH/buffer solution (PH=11.5) at 20 mA, TEMPO (**6a**) interacts with the anode generating the oxoammonium cationic specie (**6c**). This latter oxidizes the desired alcohol to the corresponding ketone (**7**), promoting the regeneration of hydroxylamine **6a** (**Scheme 3**).



Scheme 3: TEMPO acts as redox mediator in alcohol oxidation

4) Redox combined electrochemical reaction.

This method is also known as “domino-oxidation-reduction sequence” and consists in a combined process in which the substrate initially interacts with one electrode, generating an intermediate that can subsequently react with the other electrode. This type of electrochemical reaction is often combined with the use of continuous flow setup. This approach was employed by Waldvogel and co-workers in the redox combined synthesis of nitriles from oximes *via* nitrile-N-oxide formation (**Scheme 4**).¹⁶ According to this protocol, using Graphite anode and lead cathode, at constant current of 10 mA/cm², strong reaction conditions can be avoided.



Scheme 4: Domino-oxidation-reduction sequence of nitriles

1.1.3 STEREOSELECTIVE ELECTROORGANIC SYNTHESIS

Stereoselective electroorganic synthesis refers to electrochemical approaches that leads to the formation of enantioenriched products through stereoselective pathways. Starting from an achiral compound, various strategies can be adopted, including the use of chiral catalysts and/or mediators, as well as the introduction of chiral auxiliaries onto the substrate molecular framework. These methods enable precise control over stereochemistry, enhancing the selectivity and efficiency of enantioselective transformations. A comprehensive summary of the most significant efforts in this field was provided by Rueping in 2019,¹⁷ where the authors classify the elements responsible of transferring stereochemical information into three main classes: chiral electrode surfaces, chiral reaction media, and chiral auxiliaries (**Figure 7**) .

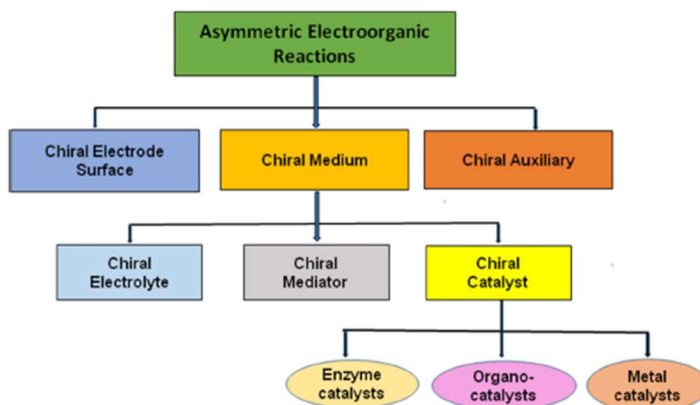
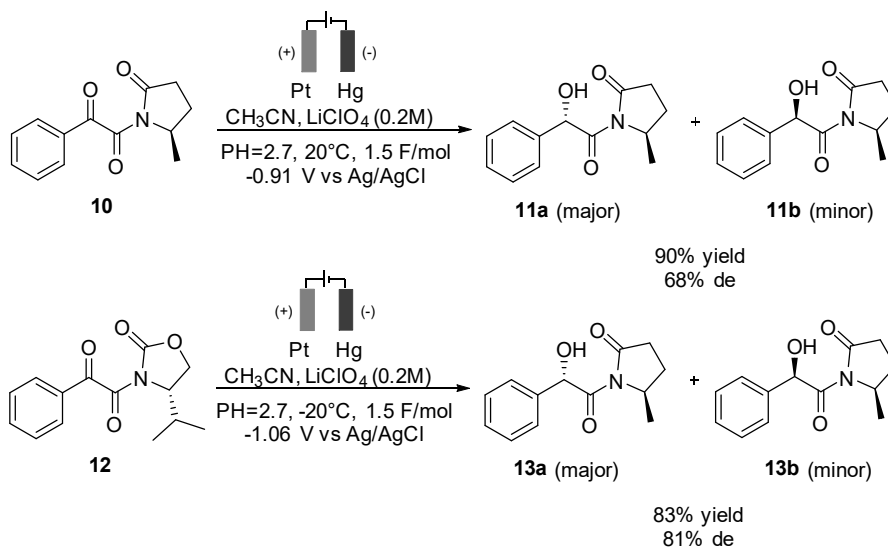


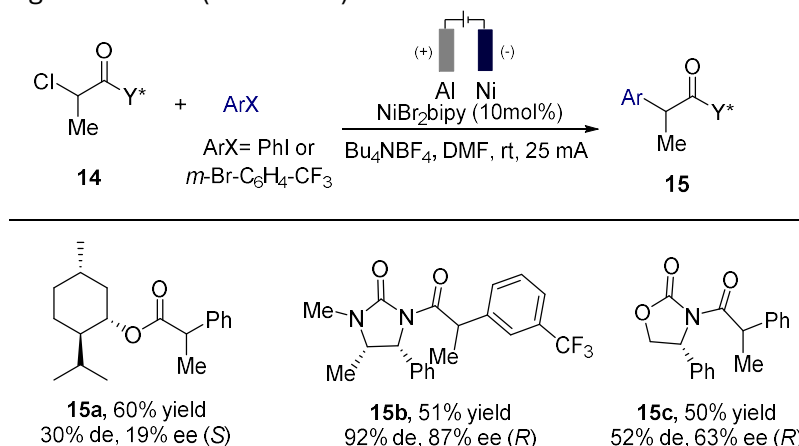
Figure 7: Classification of chiral inductors

Among all these methods, the use of chiral auxiliary is the less explored. Only a few examples are reported in literature, with one of the earliest by Zielinski and Schäfer in 1994. They investigated the diastereoselective cathodic reduction of phenylglyoxylic acids, using Evan's oxazolidinones and chiral lactams as chiral auxiliaries.¹⁸ Mandelic acid derivatives **11** and **13**, have been obtained upon reduction at a mercury pool cathode (**Scheme 5**). The electrolysis afforded an excellent chemical yield (90% yield for **15a-b**, 83% yield for **13a-b**) along with a moderate diastereomeric excesses (68% de for **11a-b**, 81% de for **13a-b**). Moreover, the recovery of chiral auxiliaries upon hydrolysis of the major diastereomers of **11a** and **13a**, allowed access to optically pure mandelic acid esters.



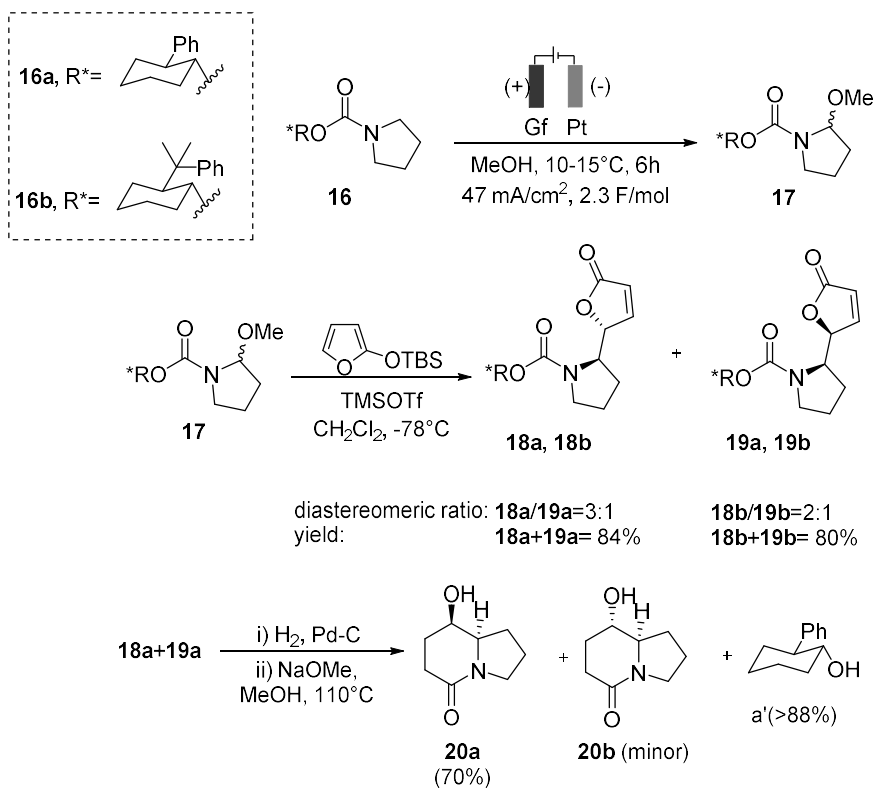
Scheme 5: Cathodic reduction of phenylglyoxalic acids substituted with chiral auxiliaries.

In 1997, Durandetti and his team introduced a Ni-catalyzed approach for the electroreductive coupling of aryl halides with α -chloropropionic acid derivatives **14**. This process induced asymmetry through the use of chiral auxiliaries attached to the propionic acid derivatives. The cross-coupling products **15** were obtained with satisfactory yields and favorable diastereomeric ratios. Furthermore, the enantiomeric excess of the products **15a-c** was determined after they were converted into the corresponding esters or imides, and no racemization was observed during the reaction (Scheme 6).¹⁹



Scheme 6: Ni-catalyzed asymmetric electroreductive cross coupling of aryl halides with α -chloropropanoic acid derivatives bearing chiral auxiliaries.

In 2000, Pilli and co-workers reported a vinylogous Mannich addition of silyloxyfuran to chiral *N*-acyliminium ions, which were generated in situ from compound **17**. This compound was synthesized through the anodic oxidation of **16**, which contained a cyclohexyl-based chiral auxiliary. The researchers found that the Mannich addition occurred exclusively on the Si-face of the *N*-acyliminium ions, leading to the *threo*-isomer as the predominant product, with good yields and moderate diastereomeric ratios. After catalytic hydrogenation and methanolysis, *threo*-**18a** and **19a** were further transformed into the corresponding lactams **20a** and **20b**, facilitating the efficient recovery of chiral auxiliaries (Scheme 7).²⁰



Scheme 7: Electrochemical Mannich addition of silyloxyfuran to in situ-generated *N*-acyliminium ions

Recently, the use of a chiral catalyst, is gaining significant attention since no functionalization of the starting material is required and due to the minimal amount of catalyst required and its recoverability at the end of the transformation.²¹ Therefore, the high tunability properties of metals along with the powerful of organocatalysis and enzymatic activity are often the first choice to furnish the asymmetric information.

1.1.4 LIGHT PROPERTIES: ABSORPTION AND EMISSION

“Light must be absorbed by a chemical substance in order for a photochemical reaction to take place” *Grotthuss-Draper law*
(1812, 1842)

The wave-particle theory is a fundamental principle of quantum physics that describes how particles of light (photons) and other subatomic particles, such as electrons, possess both wave-like and particle-like properties. The wave properties of light are associated with electromagnetic radiation, a form of energy that propagates through space at extremely high speeds. Unlike mechanical waves, electromagnetic radiation does not require a medium for transmission and can therefore propagate even in a vacuum. In classical physics, the characteristics of electromagnetic radiation are described using the sinusoidal wave model. In this model, electromagnetic radiation is represented as an electric field (E) and a magnetic field (M) that oscillate sinusoidally in phase, perpendicular to each other and to the direction of propagation. Their variation occurs at the same frequency and is always in phase (**Figure 9**).

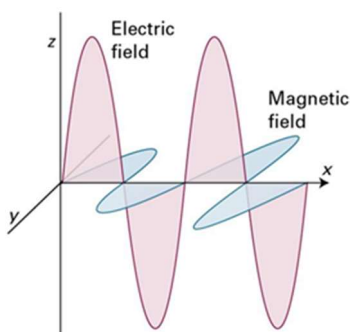


Figure 9: Graphic representation of electromagnetic radiation

The magnetic field cannot exist without the electric field, and vice versa. Since the magnetic field varies sinusoidally, according to Faraday's law, it induces a perpendicular electric field that also varies sinusoidally. However, since this electric field varies sinusoidally, it induces, according to Maxwell's law, a perpendicular magnetic field that again varies sinusoidally. These two effects thus occur endlessly, with the two fields continuously generating each other. The resultant sinusoidal variation of the field intensity propagates as a wave and is called an electromagnetic wave. The key parameters of this model include:

1. **Amplitude (A):** The amplitude of the sinusoidal wave is represented by the length of the electric vector (or the electromagnetic vector) at the maximum of the wave.
2. **Period of the radiation (p):** This is the time required to complete one full oscillation (or to travel a distance equal to the wavelength) and is measured in seconds.
3. **Propagation velocity (v):** The propagation velocity refers to the speed at which an electromagnetic wave moves through space. In a vacuum, this velocity is constant and corresponds to the speed of light, which is 299,792,458 meters per second (m/s), commonly denoted as c. In the presence of a medium, such as air or glass, the propagation velocity is lower and depends on the refractive index of the medium.
4. **Frequency (v):** The frequency represents the number of oscillations of the wave per second and is the inverse of the period of the radiation ($v = 1/p$). It is measured in s^{-1} , called Hertz (Hz). The frequency of an electromagnetic wave is determined by the source that generates it and remains unchanged during propagation, even when the wave passes through different media. This means that while the propagation velocity and wavelength may change when the wave enters a new medium, the frequency remains constant.
5. **Wavelength (λ):** The wavelength is the linear distance between two equivalent points (either two maxima or two minima) of the wave. The wavelength is inversely proportional to the frequency of the wave, meaning that as the frequency increases, the wavelength decreases, and vice versa. The wavelength determines the properties of the electromagnetic radiation and influences how the wave interacts with materials and objects. It is measured in meters (m), micrometers (μm), nanometers (nm), or angstroms (Å) ($1 \mu m = 10^{-6} m$, $1 nm = 10^{-9} m$, $1 \text{ Å} = 10^{-10} m$). Since frequency and wavelength are inversely proportional, they are related by the **equation 8**:

$$\lambda = c/v$$

c: speed of light, v: frequency

Equation 8: Wavelength determination

6. **Power (P):** This refers to the energy of the beam reaching a certain area per second.
7. **Intensity (I):** This refers to the power per unit of solid angle.

This descriptive model is capable of explaining phenomena such as diffraction and reflection, but it cannot account for phenomena like absorption and emission of energy, which are discrete and not continuous. For this reason, in quantum physics, the wave model is replaced by the particle model, where electromagnetic radiation is represented as a flow of discrete particles or "wave packets" called photons or quanta. The wave-like properties are attributed to the probability of finding a photon with a given energy in a specific region of space. The energy of photons is quantized and is related to frequency by the **Equation 9**:

$$E = h\nu$$

Equation 9: Planck's equation.

which, based on the relationship between frequency and wavelength, can also be rewritten as:

$$E = \frac{hc}{\lambda}$$

where h is the Planck's constant, equal to 6.63×10^{-34} Joule*seconds, ν is the frequency, c is the speed of light, and λ is the wavelength. The energy of a photon can also be expressed in electron-volts, where $1 \text{ eV} = 1.6 \times 10^{-19} \text{ J}$

Equation 10: Redefinition of Planck's equation

Energy and frequency are directly proportional; a beam of light can be more or less intense depending on whether it carries many or few photons per unit of time, but the energy associated with each photon (the quantum of energy) is always the same for a given frequency of radiation. There are different types of electromagnetic radiation, all generated by accelerated charges, and they differ in their wavelength (and consequently in their frequency and energy). The collection of all these radiations forms the electromagnetic radiation spectrum, which is schematically represented in **Figure 10**

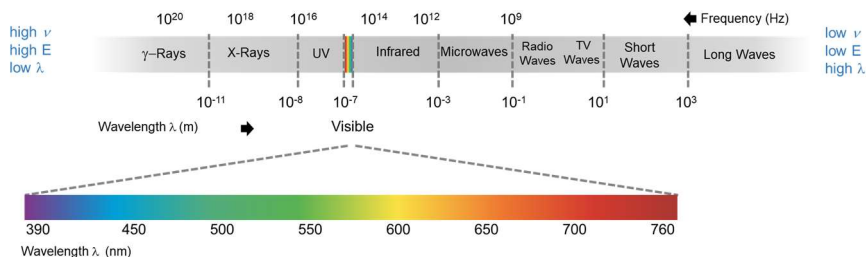


Figure 10: Classification of electromagnetic radiation

Light Absorption and Emission

When a substance is irradiated by light, certain frequencies can be selectively removed through absorption, which is a process in which electromagnetic energy is transferred to the atoms, ions, or molecules of the substance. This absorption can promote the transition from the ground state to an excited state, according to the relation:



According to quantum theory, atoms and molecules possess only a limited number of discrete energy levels, and for the phenomenon of absorption to occur, the energy of the exciting photon (i.e., the electromagnetic radiation striking the material) must be exactly equal to the energy difference between these two states.

Since the energy of a molecule is quantized, there are only discrete energy levels corresponding to different states of the molecule. Each electronic level is associated with a series of vibrational levels, and each vibrational level is further divided into rotational levels. The energy required to transition from one energy level to another depends on the amount of energy provided. Electronic levels are the energy levels associated with the electrons of the molecule. The transition between these levels requires a significant amount of energy. Each electronic level contains several vibrational levels, which correspond to the energy associated with the vibrational motion of the atoms in the molecule. In turn, the vibrational levels are divided into rotational levels, which are related to the energy associated with the rotation of the molecule in space.

Jablonski diagram shows all the possible transitions that may occur between the different energy levels (**Figure 11**).

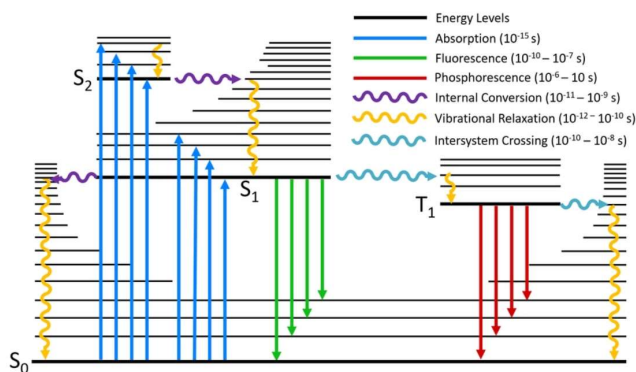


Figure 11=Jablonski Diagram

The different electronic energy levels are depicted with tick black line and correspond to the ground state (S_0) and the excited singlet state (S_1/S_2) and triplet state (T_1). When a photon with a specific energy interacts with a chemical specie, promotes the vertical electronic transition from the ground state (S_0) to the Singlet State (S_1), if the two spins are parallel, or to the triplet state (T_1), when the two spins are unparallel. After light absorption, the molecule returns to its ground state emitting energy through radiative (straight arrow for absorption and emission) and non-radiative transitions (wavy arrows). Radiative transitions include phosphorescence and fluorescence, and in both cases a photon is ejected from the molecule with a net loss of energy. Phosphorescence occurs when an excited triplet state is involved, while the second occurs in presence of an excited singlet state. The non-radiative processes include the internal conversion that verifies when the lower-energy vibrational state of a higher excited state is coupled with a vibrational state of a lower-energy electronic state. While the intersystem crossing consists of a change in the multiplicity of spin (from the singlet state to the triplet state) and can be followed by radiative processes.

The excited state of some substrates may be promoted by the absorption of visible light irradiations at specific wavelength. (**Figure 12**) This excitation can lead to the bond cleavage or the formation of new bonds, depending on the specific molecular structure and the nature of the reaction. Bond cleavage is promoted when light provides enough energy to break certain chemical bonds. This is often observed in photochemical reactions where specific bonds in a molecule absorb light and undergo homolytic or heterolytic cleavage, leading to the formation of radicals or ions. However, in some cases, the energy from light can facilitate the formation of new chemical bonds. This usually happen in reactions like photopolymerization or photoredox reactions.

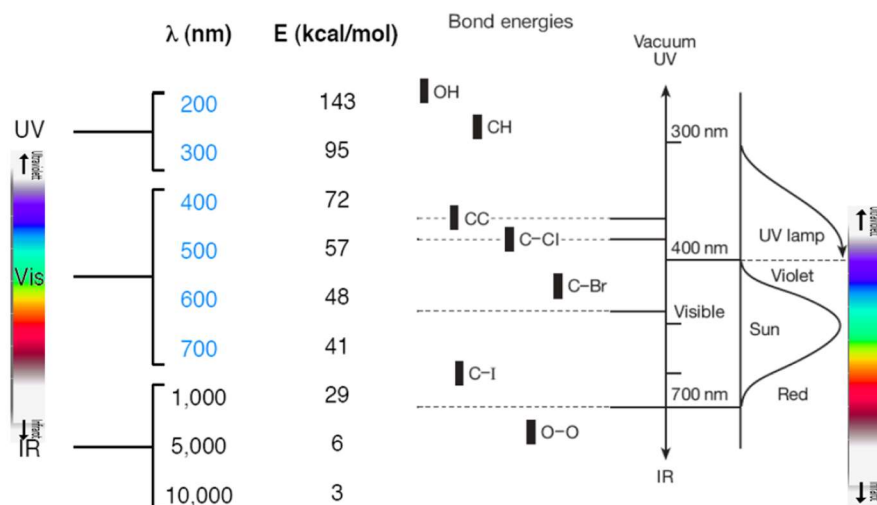


Figure 12: Absorption of visible light irradiation by specific chemical bonds

The overall efficiency of any process is governed by several deactivation processes (as shown in the **Figure 15**) each of them can be described quantitative in terms of a rate constant.

A useful parameter in quantitative photochemistry which relates the rate constant ratios is the quantum yield (Φ). This is a measure of the efficiency of photon usage (**Equation 11**).

$$\Phi = \frac{\text{number of moles molecules of product formed}}{\text{number of einstein photons of radiation absorbed}} \\ = \frac{\text{rate of formation of product}}{\text{intensity of absorbed radiation}}$$

Equation 11: Quantum Yield

Another important parameter is the duration of the excited state τ . The time a molecule A remains in its excited state A^* before relaxation decay is determined by the overall kinetic constants k (**Equation 12**): k_p for photochemical processes, k_r for radiative decays and k_{nr} for non-radiative deactivations.

$$(\tau(A^*)) = \frac{1}{k_p + k_r + k_{nr}}$$

Equation 12: Duration of excited state

The excited-state lifetime can be on the order of picoseconds to microseconds, but it depends on various factors, including the specific molecule, the type of excited state, and the environment in which the molecule is situated. A longer-lived excited state enhances the probability of photochemical reactions, such as bond formation or bond cleavage, by providing sufficient time for these processes to occur. Furthermore, molecules with extended excited-state lifetimes are particularly advantageous for energy transfer processes, as they facilitate efficient energy transfer between donor and acceptor systems.

1.2 PHOTOCHEMICAL APPROACHES IN ORGANIC SYNTHESIS

The increasing need for more efficient and sustainable method led to rethink known concept for the evolution of an innovative chemistry. In this context, photochemistry emerged as a green tool which exploit light as energy source to drive new synthetic transformations. The use of light in chemical reaction dates back to the beginning of 20th century when Giacomo Ciamician, often regarded as the father of photochemistry, studied the effects of sunlight on matter (**Figure 8**).²²

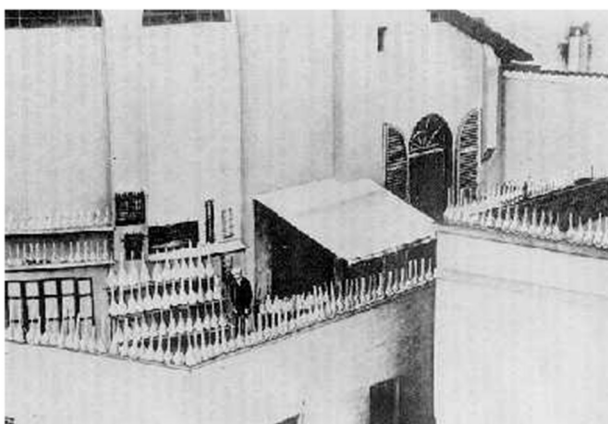


Figure 8: On the balcony of the University of Bologna, Professor Giacomo Ciamician (1912) ambled among the several glass bottles he employed for his photochemistry studies.

Nowadays, the interaction between the “optical radiations” of the electromagnetic field (ultraviolet radiation (UVR), visible light (VL), infrared (IR)) and the organic molecules are deeply investigated by the modern photochemistry as powerful ways to break and build non traditional C-C, C-H, C-N, C-O, and C-X bonds.

1.2.1 PHOTOREDOX CATALYSIS

“Photocatalysis” refers to those reactions which require light as energy source and a catalytic amount of light-adsorbing specie, named photocatalyst, like metal complexes and organic dyes. Such systems take advantage of the enhanced redox reactivity of the photocatalyst in its excited state to facilitate a reaction that would not proceed otherwise. In this sense, light provides the added energy needed to make the reaction thermodynamically viable.²³ Five different mechanistic pathways can be described, based on the species and transformations involved: photoredox catalysis (**Figure 13-A**), hydrogen atom transfer (**Figure 13-B**), proton-coupled electron transfer (**Figure 13-C**), Energy transfer (**Figure 13-D**) and electron-donor acceptor complex formation (**Figure 13-E**).

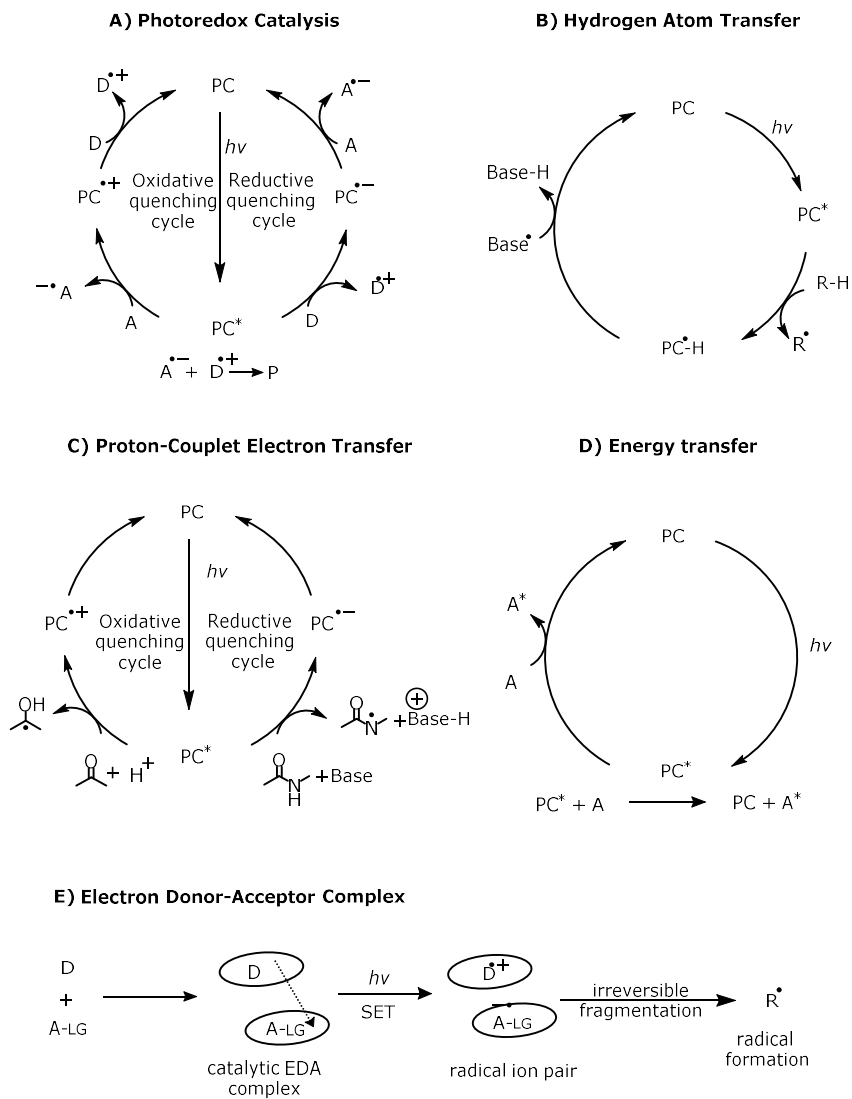


Figure 13: Mechanistic photochemical pathways

Among all these possibilities we focused our attention in the photoredox catalysis (**Figure 14**) .

A) Photoredox Catalysis

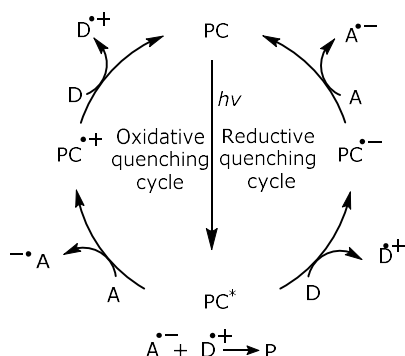


Figure 14: Catalytic cycles for photocatalyst regeneration

In a typical photoredox cycle, the photocatalyst absorbs a photon at a specific wavelength, generating the excited state photocatalyst (PC^*) which is chemically more reactive than the corresponding ground state. Depending on the reaction partner, this specie may undergo to a reductive or an oxidative quenching cycle, both ending with the regeneration of the catalyst. In the first scenario, in presence of a donor, the reduced state photocatalyst ($PC^{\bullet-}$) is generated. This highly reducing agent interacts with the reactant A by single electron transfer (SET) and it is reoxidized back to its ground state. In the oxidative quenching cycle, the PC^* oxidize the reactant A by SET, producing the $PC^{\bullet+}$. The ground state PC is re-obtained by interaction with the donor D. Formally, reactants A and D's radical anion and cation respectively recombine to form product P.^{24,25}

Photocatalyst and photosensitizer can be metal based complex salts with polyaromatic ligands like ruthenium-tris (bipyridine) or iridium-tris (phenylpyridine) or organic dyes like Eosin Y, Rhodamine G, or 1,2,3,5-Tetrakis(carbazol-9-yl)-4,6-dicyanobenzene (4 CzIPN). In order to select the appropriate photocatalyst for a specific chemical transformation, it is essential to evaluate its stability in the excited state. Generally, it should remain in this state long enough to react via single-electron transfer (SET) with another molecule. Moreover, UV spectra allow for the identification of the absorption wavelengths for each catalyst, facilitating the selection of the most suitable light source. Additionally, since electron transfer occurs when the catalyst is in its excited state, it is crucial to evaluate the redox potentials associated with the system.

Metal based photocatalysts

Metal-based photocatalysts, such as iridium (Ir) and ruthenium (Ru) complexes, are widely utilized in photochemical transformations due to their long-lived excited states, typically lasting around 1000 nanoseconds.²⁶ This extended lifetime enhances their efficiency in facilitating various photochemical reactions, making them valuable tools in synthetic chemistry. For metal complexes, the absorption and emission processes are complex because the transitions can involve orbitals of the metal, the ligands, or a combination of both (**Figure 15**). The possible transitions that can take place are:

- ❖ **LC (ligand-centred)**: the transition is only within the electron shell of the ligand.
- ❖ **MC (metal-centred)**: the transition occurs on the electronic sphere of the metal.

The interaction between the two electronic spheres of the metal and the binder also allows transitions from each other.

- ❖ **MLCT (charge transfer from metal to ligand)**: the electron transition occurs from the ground state of the metal to the excited state of the ligand. This can be seen as a formal oxidation of the metal centre and a reduction of the ligand.
- ❖ **LMCT (charge transfer from ligand to metal)**: the electronic transition occurs from the ground state of the ligand to the excited state of the metal. The ligand will be formally oxidized and the center of the metal will be reduced.

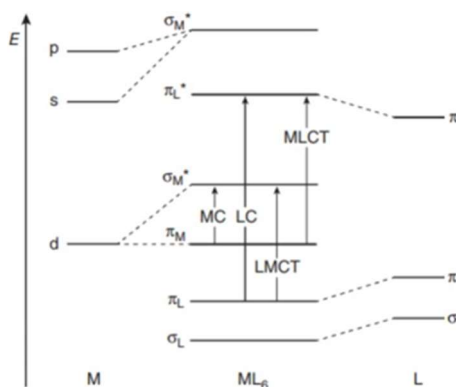


Figure 15: Energy absorption of metal complexes.

In metal-based complexes, the MLCT is the most common process.²⁷ In **figure 16** are depicted the most used complexes in photochemical transformations.

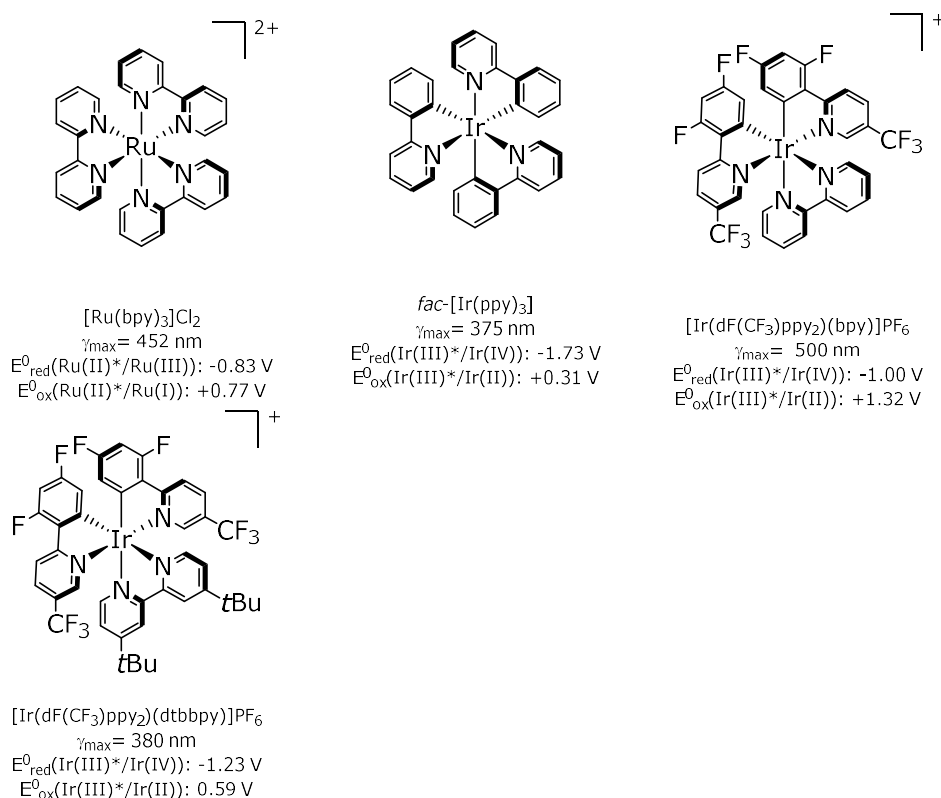


Figure 16: Most commonly used metal-based photocatalyst

Organic dyes photocatalyst

The excitation process of organic dyes is simpler compared to that of the metal complexes, since the metal and the ligand shield have not to be considered. The use of organic dye as photocatalyst has been widely explored, since they can be obtained at low cost and present good availability. In **figure 17** are reported some examples of organocatalyst like Acridium dye, Rhodamine G, or 1,2,3,5- 4 CzIPN and Eosin Y, typically employed in photochemical transformations due to their low sensitivity to oxygen.

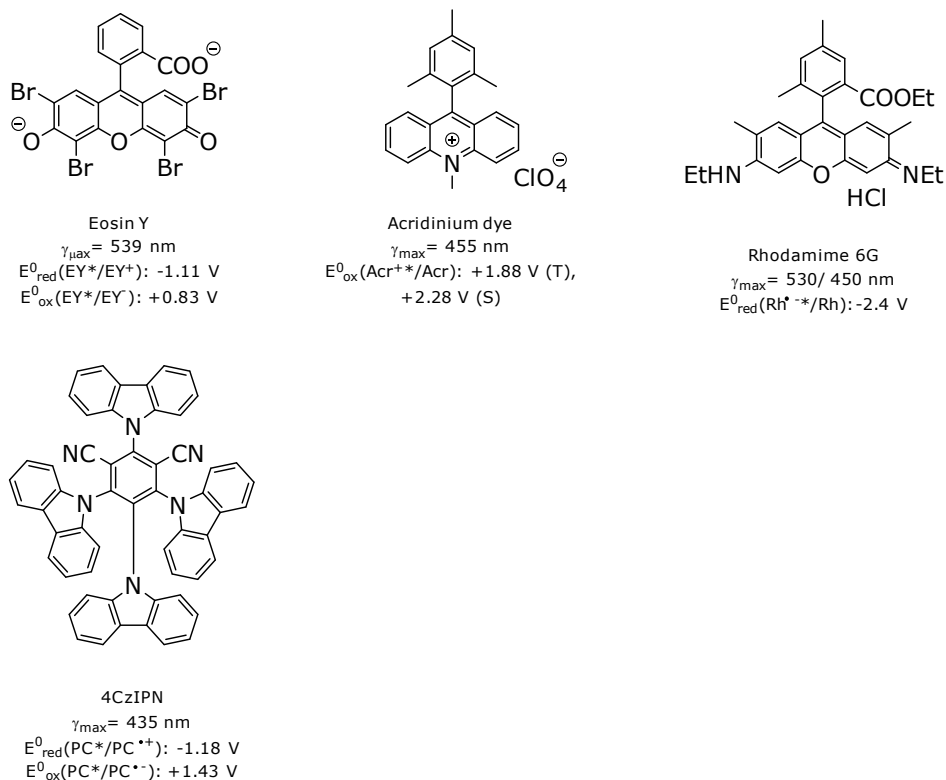


Figure 17: Commonly employed organocatalysts

Among all the organic dyes, Eosin Y (EY) is one of the most popular because it displays a suitable range of potential values (**Figure 18**).²⁸

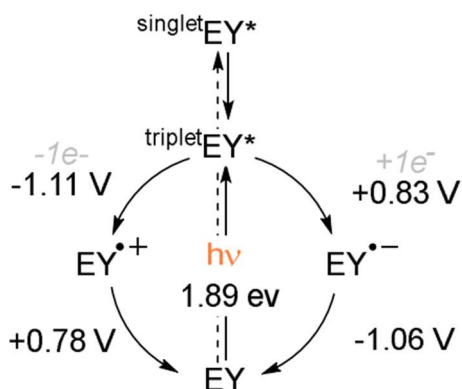
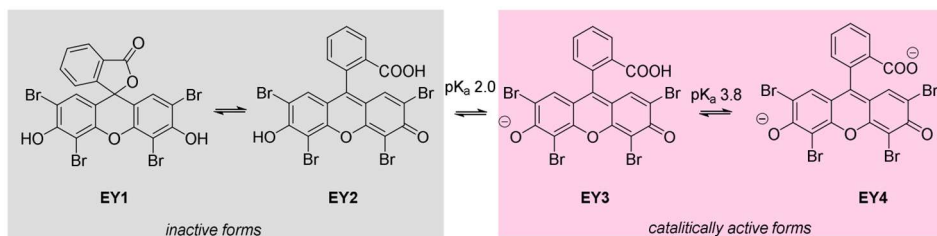


Figure 18: Light absorption and emission of Eosin Y

The maximum of absorption sits at 539 nm and for this reason, green lights are usually employed for Eosin Y activation. Upon excitation by light, Eosin Y is excited to a singlet state which undergoes, through a rapid intersystem crossing, to the lowest energy triplet state.^{28,29} In solution, Eosin Y exists in four different forms that are pH-dependent, due to the presence of two relatively acidic protons (pKa 2.0, 3.8 in water, **Scheme 8**).

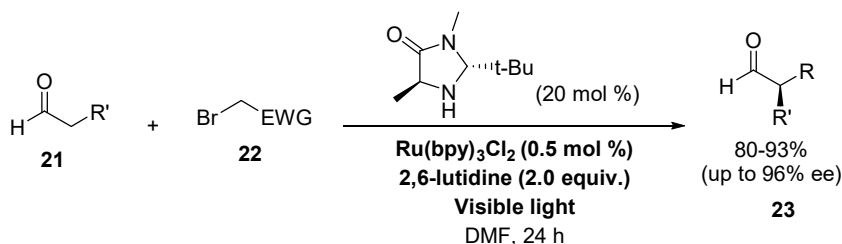


Scheme 8: Eosin Y forms pH dependent

As shown in **Scheme 8**, at pH < 2, the phenolic spirocyclic form **EY1** that appears like a yellow solid, is in equilibrium with the neutral form **EY2**, whereas at $2 < \text{pH} < 3.8$, the monoanionic form **EY3** is in equilibrium with the dianionic form **EY4**, which becomes predominant at pH > 3.8. Only **EY3** and **EY4**, which present a deep red colour, are catalytically active.²⁵ Over the last years, photoredox catalysis found application in different synthetic approaches. The use of a photocatalyst in **homogeneous** solutions with the other reaction components has been widely explored, as well as under **flow** conditions, to improve the process efficiency.³⁰ Also, the possibility to immobilize the photocatalyst onto a solid support and to use it in a **heterogeneous** environment was implemented in batch and flow. Few examples related to these synthetic applications mentioned are shown below.

1.2.2 PHOTOREDOX CATALYSIS UNDER HOMOGENEOUS CONDITIONS

One of the pioneer work in this field, was reported by MacMillan's group in 2008. The authors developed a green and sustainable approach for the enantioselective α -alkylation of aldehyde with α -bromocarbonyl compounds using $\text{Ru}(\text{bpy})_3\text{Cl}_2$ (0.5mol%) as photocatalyst in the presence of 2,6-lutidine and 20 mol % of imidazolidinone organocatalyst, under visible light irradiation (**Scheme 9**).³¹



Scheme 9: Photoredox enantioselective α -alkylation of aldehydes.

In this work, photocatalysis was merged with organocatalysis to achieve α -substituted aldehydes in up to 93% yield and 96% of e.e. Specifically, a chiral imidazolidinone organocatalyst was chosen to form an electron-rich enamine with an aldehyde, which then interacts stereospecifically with an electron-deficient alkyl radical generated from haloalkanes. This radical can be produced through the $\text{Ru}(\text{bpy})_3^+$ catalytic cycle, where, upon irradiation at a specific wavelength, the photoexcited state facilitates oxidation and regenerates the organocatalyst. Subsequently, the scope of the reaction was enlarged to trifluoromethylations,³² cyanoalkylations,³³ benzylations,³⁴ and related transformations.³⁵

1.2.3 PHOREDOXCATALYSIS IN FLOW

The goal of continuous flow chemistry is to overcome the problems and the challenges of the in batch reactions: less efficient process control, moderate conversion and selectivity, high energy consumption and long reaction time. Thanks to the small reactor volumes along with the efficient mixing of the substrates with reagents, flow chemistry allows to increase the productivity and the space time yield respect the in batch process. The use of flow chemistry in photochemical transformation guarantee a full irradiation of the small reactor used (films and capillars). Microfluidic systems provide more uniform irradiation of the reactive mixture compared to batch reactors. According to the Lambert-beer law (**equation 13**), light transmittance drops exponentially with distance from the light source

$$A = \varepsilon \cdot l \cdot c$$

A: absorbance, ε : molar attenuation coefficient of the molecule, l : distance from the light source, c : concentration

Equation 13: Lambert-Beer law

In **Figure 19**, indeed, it possible to observe how in a normal batch reactor, light intensity significantly decreases from the vial walls to 1 cm in the middle

of the reaction mixture (Transmission = 0.1 %), causing delayed reactions and nonhomogeneous irradiation. When photochemical reactions are carried out in microchannels with an internal diameter of 2.54 or 5.08 cm, the transmission is 80-90 %. Under these conditions, a greater and more uniform photon flow is possible, leading to shorter reaction times and reducing the formation of by-products caused by over-irradiation, a common issue in batch reactors.³⁰

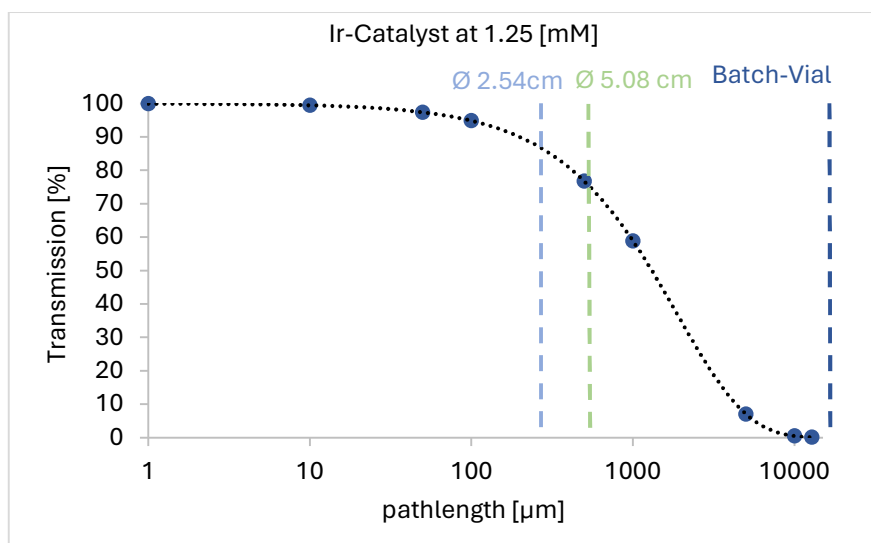
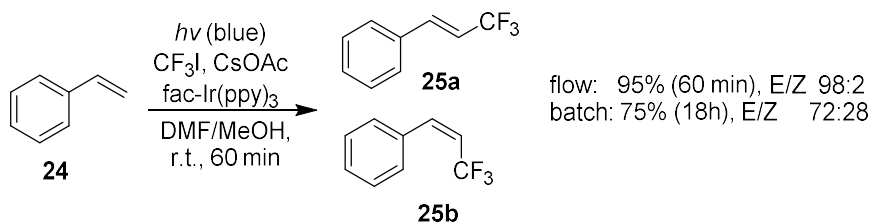


Figure 19: % transmittance plotted against the path length for an Iridium catalyst. The dashed vertical lines represent the inner diameter of 0.01 in, 0.02 in. tubing and 1 cm of batch vial.

Also, the modern LED technology allows the construction of adaptable light sources for flow photoreactors with less energy consumption and safety issues compared with standard mercury or xenon lamps.³⁶

Considering all of these advantages, in 2016 Noel's group developed an in continuous flow approach for the incorporation of fluorine building block into organic molecules. The inexpensive gaseous CF_3I was used as precursor for the photocatalyzed trifluoromethylation of styrene (**Scheme 10**).



Scheme 10: Photocatalyzed trifluoromethylation of styrene

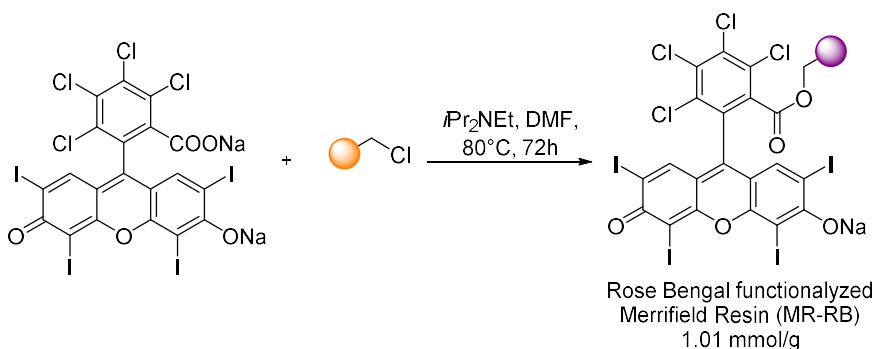
After a deep investigation under batch conditions, the desired trifluoromethylated olephines were achieved in 18h in up to 75% yield and 72:28 of diastereoisomeric ratio. Interestingly, the use of the flow photoreactor setup not only improves the productivity of the process (95% yield in 60 min), but affects the E/Z ratio as well, tending towards a higher amount of the E isomer.³⁷ This selectivity could be attributed to the shorter residence time in the flow photoreactor and, consequently, to a shorten irradiation. Under these reaction conditions, the photocatalyzed isomerization of the E isomer to the Z isomer by energy transfer from the exited photocatalyst to the vinyl double bond is suppressed.^{38, 39}

1.2.4 PHOTOREDOX CATALYSIS UNDER HETEROGENEOUS CONDITIONS

Recently, the use of supported catalyst and the possibility to carry out photochemical transformation under heterogeneous conditions has been investigated. The immobilization of a photocatalyst onto a solid support, like resin or inorganic matrix, allows to easily remove the catalytic species upon a completed reaction, facilitating the work-up and, possibly, to reuse it in further transformations.^{40,41} First examples in this field were reported by Blechert and his group in 2014, where the heterogeneous perfluoroalkylation of different heterocycles on carbon nitride was carefully investigated.⁴² Soon After, Savateev and Antonietti showed the activity of graphitic carbon nitrides photocatalyst (CNP) in photochemical oxidative transformations such as the selective conversion of alcohols in carbonyl compounds or oxidation of secondary amines.⁴³ Since 2003, our group demonstrated particular interest in supported catalysis onto polymeric matrix.⁴⁴ Therefore, considering the displayed advantages and the experience in this field, in 2023, we envisioned to investigate immobilized Rose Bengal onto a Marrifield resin (**Scheme 11**) in photocatalyzed metal-free C-3 thiocyanation of indoles and imidazo[1,2-*a*]pyridines

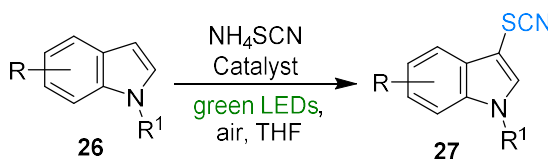
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Scheme 11: Synthesis of supported Rose Bengal

Firstly, the photocatalyst activity was tested under batch conditions and green light irradiation (530 nm) giving the desired product in up to 98% yield (**Scheme 12**).



Scheme 12: thiocyanation of indoles under batch conditions

The possibility to recover and reuse the supported catalyst was confirmed until the fifth run, although with a slight decrease in the yield (89 %). Also, the reaction demonstrates good tolerance to various functional groups although electron-poor azaheterocycles reacts in lower yields compared to their electron-rich counterpart. Even if modest yields were obtained, a continuous flow process was developed, and the products have been afforded in higher productivities compared to the in-batch reactions (batch: 16h, 96%, flow: 100 min, 56%).⁴⁵

1.3 ELECTROPHOTOCATALYSIS: INTRODUCTION

In this paragraph, I aim to provide a concise overview of electrophotocatalysis, a topic I began exploring only in the final months of my PhD during my research visit with Ackerman's group. Although I did not develop new electrophotocatalytic conditions, I applied established methods to achieve the functionalization of specific substrates.

Electrophotocatalysis is an innovative approach that synergistically combines photocatalysis and electrochemistry, **using light** and **electrical** fields to perform chemical reactions. This synergistic combination allows the strengths of each technique to compensate for the other's limitations, enabling new reaction pathways that would be impossible with either method alone.⁴⁶ One of the limitations of photoredox catalysis relies on the limited number of reactions which can give access. The energy available to a photocatalyst from excitation by a single visible-light photon is typically insufficient for challenging chemical transformations such as the conversion of CO₂ and H₂O into glucose and water,⁴⁷ or the direct SET activation of many moieties of interest to organic chemists. For example, SET oxidations of hydrocarbon C-H bonds,⁴⁸ electron-neutral/poor aromatic π -systems⁴⁹. However, a key challenge in synthetic organic electrochemistry (SOE) is the conductivity of organic solvents, usually low compared to water-based systems. Also, a significant "ohmic drop" between the two electrodes, requires elevated cell potentials to achieve effective reaction conversions. These high potentials can inevitably promote non-selective and harmful redox reactions with the targeted organic substrate.⁵⁰

"Light and electricity combination approaches" may be divided into two main categories:

- electrochemically mediated photoredox catalysis (e-PRC), where the electrochemical and photochemical components have interdependent roles;
- interfacial photoelectrochemistry (iPEC), where reactions occur at photoelectrode surfaces.⁵⁰

The e-PRC is the most used method employed in synthetic organic transformations. Oxidative and Reductive electrophotocatalysis can be distinguished.

In the **Oxidative electrophotocatalysis**, the light irradiation promotes the photocatalyst excitation. In its photoexcited state, the catalyst acts as oxidizing agent towards the substrate; as a consequence, the radical anion of the photocatalyst is generated. Upon oxidation at the anode surface of

this radical anion, the photocatalyst in its ground state can be restored. Hydrogen evolution at the cathode is needed for redox balancing (**Figure 20**).

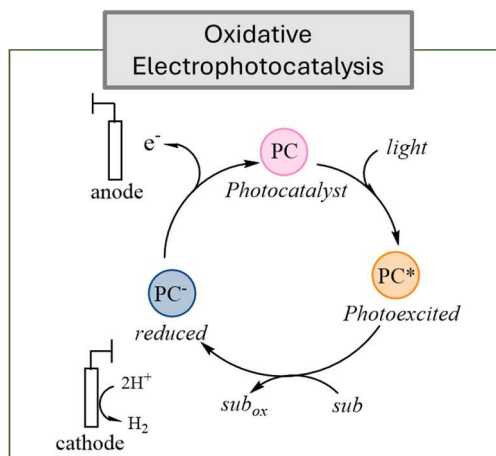
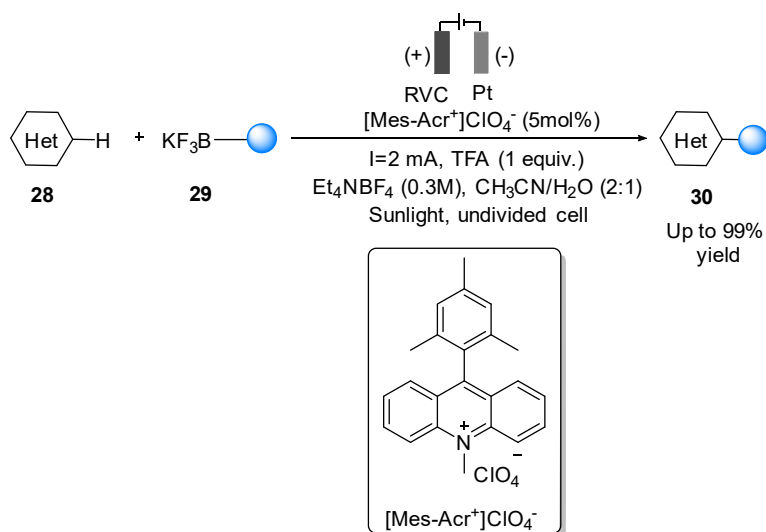


Figure 20: Oxidative electrophotocatalytic cycle

As example, Minisci alkylation of heteroarenes using photoredox catalysis typically requires a stoichiometric quantity of an oxidizing agent, such as a peroxydisulfate salt ($S_2O_8^{2-}$) or hypervalent iodine.⁵¹ However, substituting these oxidants with reagent-free electrochemistry, as shown by Xu and co-workers, enabled the generation of various functionalized heteroarenes using primary, secondary, and tertiary alkyltrifluoroborates (or 1,4-dihydropyridine) while achieving excellent regio- and chemoselectivity (**Scheme 13**).⁵²



Scheme 13: Electrophotocatalytic (hetero)arenes functionalization using alkyltrifluoroborates

In the **reductive electrophotocatalysis** cycle, light irradiation promotes the light excitation of the photocatalyst, which is further reduced at the cathode surface producing the $PC^{\cdot-}$. This latter undergoes by a single electron transfer reduction with the substrate, regenerating the photocatalyst in its ground state. Using Zinc electrode or a sacrificial compound is possible to balance the redox transformation (**Figure 21**).

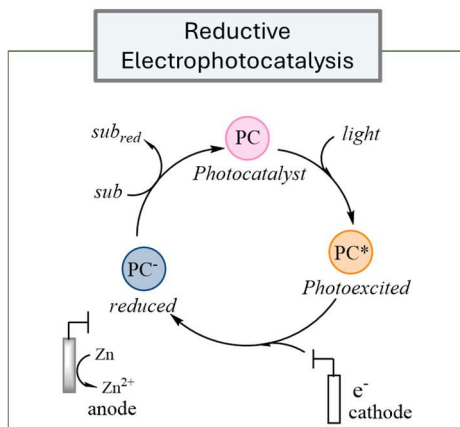
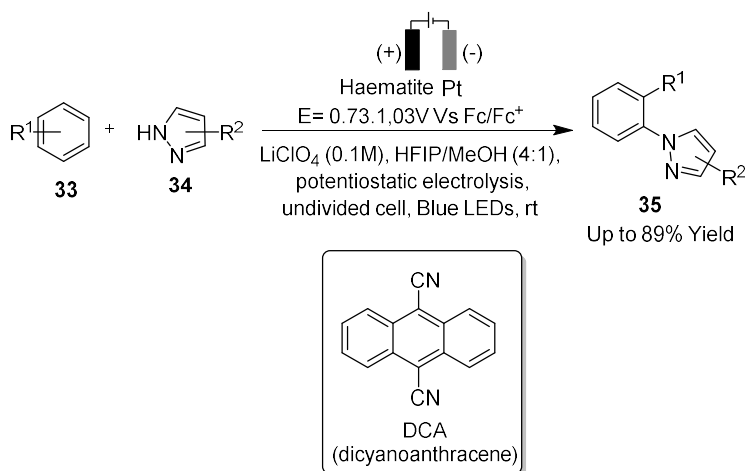


Figure 21: Reductive electrophotocatalytic cycle

the reductive electrophotocatalytic approach for the borylation of aryl chlorides under metal-free conditions was reported by Lambert and Lin⁵² can be considered an example of this approach, in which the chemoselective activation of unreactive substrates was obtained even if they present highly negative reduction potentials (**Scheme 14**).

Figure 22: General photoelectrocatalytic mechanism

By applying a potential to photoanodes (which enhances charge separation) under irradiation, electron transfer from the valence band to the conduction band occurs, generating a hole that is subsequently used to oxidize the substrate. The regeneration of the catalyst was then realized via the migration of photoexcited electrons to the counter electrode to form hydrogen. Hu et al. demonstrated that the abundant and durable haematite photoanode can be effectively used in highly ortho-selective, non-directed C–H amination reactions of arenes with various azoles in 0.1 M solution of Lithium perchlorate in hexafluoroisopropanol/MeOH (4:1) (**Scheme 15**), under blue light irradiation.⁵³



Scheme 15: Photoelectrocatalytic direct amination of arenes with azoles

2 CHAPTER 2: ELECTROCHEMICAL DEHYDROGENATIVE HOMO-COUPLING OF B-NAPHTHYLAMINES DERIVATIVES.

2.1 BIARYL SCAFFOLDS IN ORGANIC CHEMISTRY: BACKGROUND

Biaryl systems are pluripotent scaffolds in numerous bioactive natural product⁵⁴, in material science as chiroptical switch and fluorescent sensor⁵⁵ and find application as chiral ligands in organocatalysis (such as BINAM and BINOL)⁵⁶ (**Figure 23**).

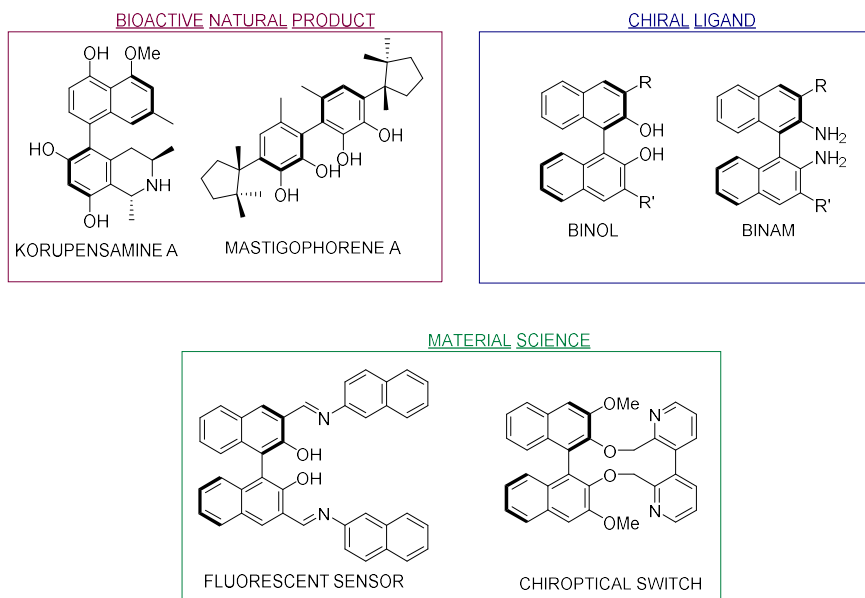
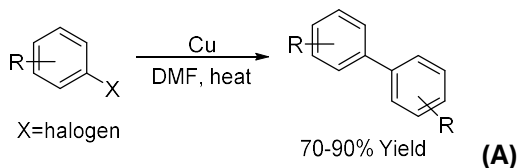
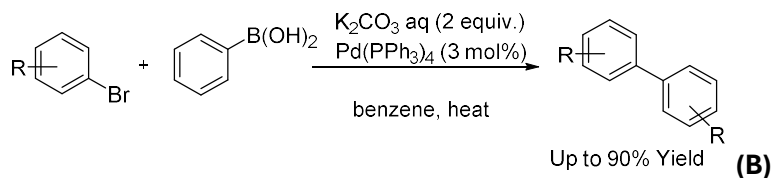


Figure 23: Different applications of Biaryl scaffolds

Biaryl scaffolds are usually prepared via transition-metal-catalyzed coupling transformations such as Ullmann reaction^{57,58} (**Scheme 16-A**), using Cu(0) in DMF, or the Suzuki coupling⁵⁹, with palladium catalyst using benzene as reaction solvent (**Scheme 16-B**). According to these strategies, the substrates must contain a specific leaving group (typically a halogen atom) that is introduced onto the substrate. Furthermore, these transformations often require harsh reaction conditions and rely on complex and expensive catalysts. This approach not only generates significant toxic waste but also results in low atom economy.



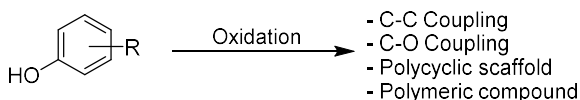


Scheme 16: Traditional approaches for biaryl scaffolds synthesis. A: Ullmann reaction, B: Suzuki-Miyaura coupling.

In 2011, Kirste et al.⁶⁰ showed the possibility to access to biphenols compounds through an electrochemical approach. Starting from this pioneer work (reported in the next paragraph), electrochemistry emerged as innovative route to directly oxidize aryl substrate using electrons as chemical reagents, without further modifications.^{61,62}

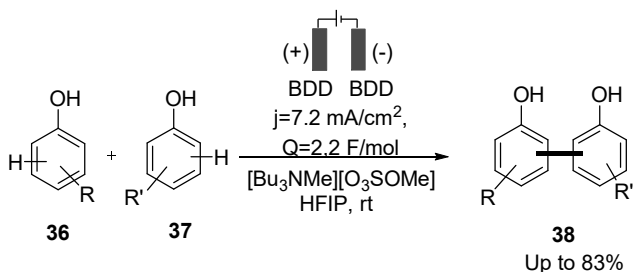
2.1.1 ELECTROCOUPLING of PHENOLS AND NAPHTOLS

The direct oxidation of phenols by conventional methods or by direct anodic electrochemical oxidation often produces a complex mixture of products where the desired biphenol represents only the minor component (**Scheme 17**).



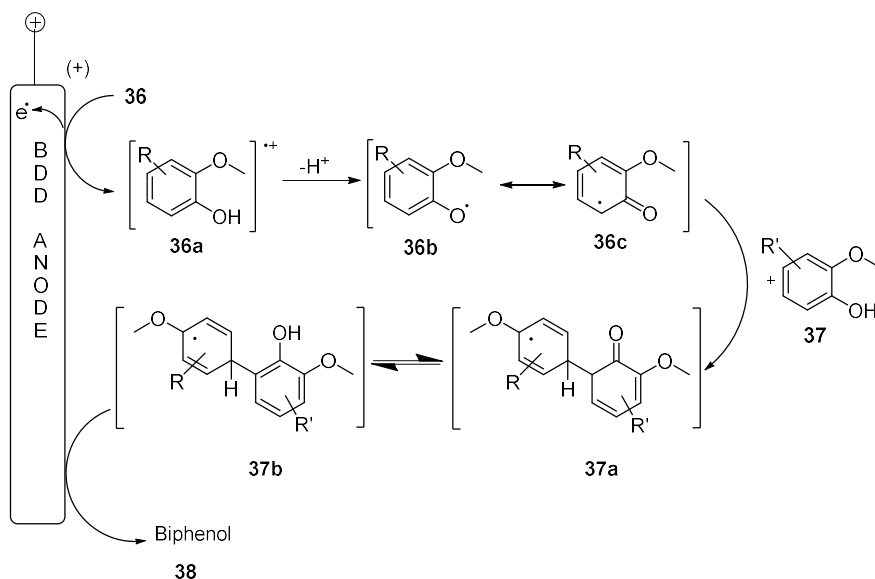
Scheme 17: Mixture of product achievable by phenols oxidation

As aforementioned, in 2011, Kirste et al.⁶⁰ have explored the direct anodic homo and cross-coupling of guaiacol derivatives. Their works demonstrated that the combination of Boron Doped Diamond (BDD) electrodes with 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) proved highly effective for these transformations (**Scheme 18**). BDD electrodes guarantee high selectivity since allow the formation of hydroxyl radical at low potential without the generation of O₂,⁶³ while HFIP exerts a stabilizing effect that might be attributed to the trapping of intermediate oxyl species in a hydrogen-bonding network.⁶⁴ Using BDD anode and cathode and electrolyzing the HFIP solution of the two substituted phenols (2:1 ratio) at 7.2 mA/cm², it was possible to achieve the desired adducts in up to 83% yield.



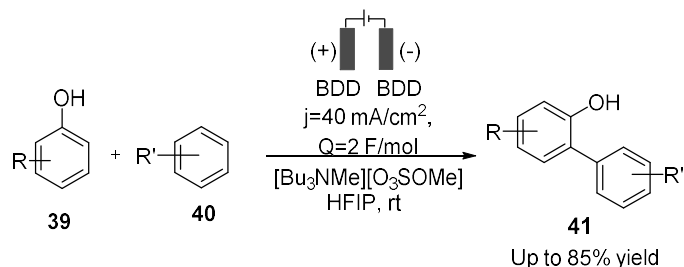
Scheme 18: Direct anodic cross-coupling of guaiacol

The HFIP shielding capability can also prevent the product from further oxidation and polymerization reactions. The authors proposed a mechanism for the reported transformation (**Scheme 19**), which starts from the direct oxidation of guaiacol **36** to the BDD anode surface.



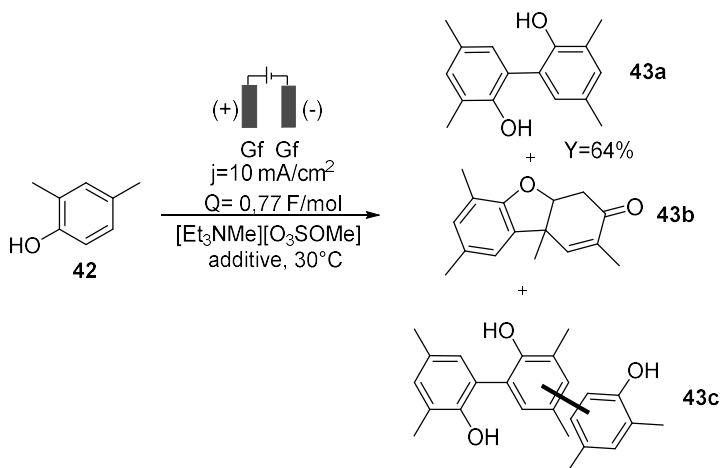
Scheme 19: Mechanism of guaiacol cross-coupling

The hydroxyl radical produced (**36a**) spontaneously deprotonate due to its enhanced acidity, generating the phenoxyl radical **36b/36c**. This intermediate is then trapped by another molecule of starting material **37** giving **37a** in tautomeric equilibrium with **37b** that undergoes to a single electron transfer (SET) affording the desired biphenol **38**. The increasing in the current density at 40 mA/cm² (respect 7.2 mA/cm² reported in **Scheme 18**) allowed to perform the electrochemical coupling between phenols and different substituted aromatic substrates, without free OH and NH-moiety. The transformation gave the desired products in up to 85% yield (**Scheme 20**)⁶⁵



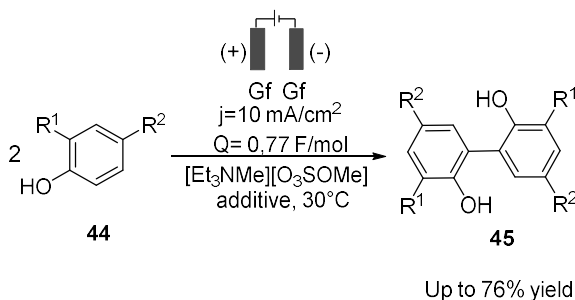
Scheme 20: Direct anodic cross-coupling of different substituted phenols and arenes

With the aim to replace BDD with a less expensive electrode, the authors studied the activity of graphite, known to be an alternative material suitable for this kind of reaction.⁶⁶ Unfortunately, the use of graphite electrodes in combination with HFIP favoured the formation of byproducts **43b**, **43c** reported in **Scheme 21**. Gratefully, a better selectivity towards compound **43a** was observed when HFIP was replaced with TFA, where the desired product was obtained in 64% yield (Ratio 43a/43b/43c:16/0/1).⁶⁷



Scheme 21: Direct anodic homo-coupling of 2,4-dimethyl phenol

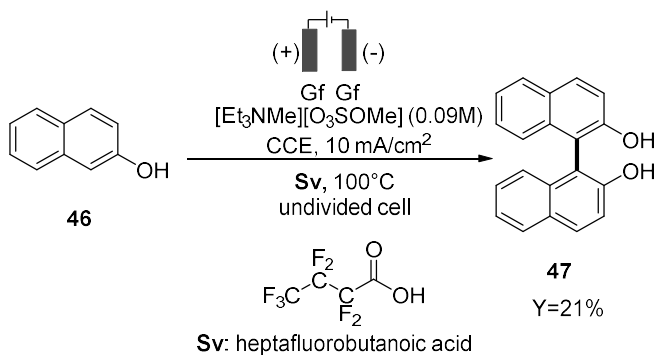
Different substituted phenols were also tested affording the substituted biphenols in up to 76% yield (**Table 1**).



Entry	R ¹ , R ²	Isolated Yield
1	R ¹ =R ² =Me	30
2	R ¹ =Br R ² =Me	76
3	R ¹ =F R ² =M	21
4	R ¹ =Cl R ² =Me	47

Table 1: Direct anodic homo-coupling of 2,4-disubstituted phenols

Interestingly, the use of heptafluorobutyric acid at 100°C allows to perform the electrochemical homo-coupling of naphthol in 21% of yield (**Scheme 22**).⁶⁷

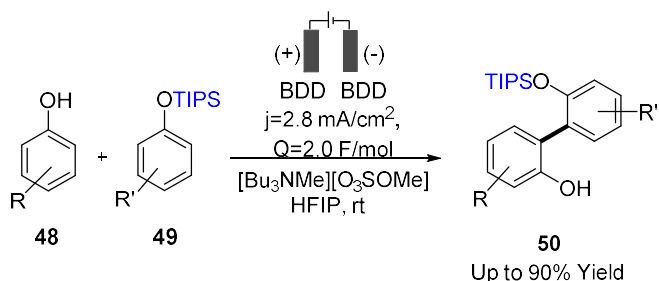


Scheme 22: Direct anodic homo-coupling of β-Naphthol

Despite the effectiveness of this method, it is important to note that achieving chemo- and regioselective synthesis of 2,2'-biphenols starting from non-symmetric substrates remains challenging. This difficulty arises from the similar reactivity of the two hydroxyl groups of the two naphthyl rings, which complicates selective modification.

This issue can be circumvented by blocking one of the two group with an easily removable protecting group stable to the electrolysis conditions. In addition, the protecting group should have minimal influence on the

electronic properties of the corresponding phenols. Initial electroorganic screening performed by Waldvogel in 2016, indicated that trimethylsilyl (TMS) ethers are not stable under electrolysis conditions and only unprotected nonsymmetric biphenols were obtained. However, bulkier silicon based protecting groups such as triisopropylsilyl (TIPS) and dimethyl-tertbutylsilyl (TBDMS) exhibit sufficient stability under reaction conditions and gave access to the desired cross-coupling products. TIPS shown the best activity in terms of yields and was selected for substrate scope (**Scheme 23**).⁶⁸ The electrochemical coupling was carried out in presence of 1/3 ratio between the unprotected and TIPS functionalized phenols, in a 0.09M solution of tributylmethylammonium methyl sulphate in HFIP, using BDD anode and cathode under galvanostatic conditions ($j=2.8 \text{ mA/cm}^2$).



Scheme 23: Direct anodic cross-coupling of substituted and protected phenols

A comparison of the chemical efficiency of protocols for the direct electrochemical cross-coupling of unprotected phenols⁶⁰ and phenol-arene⁶⁵ (**Scheme 18, 20 and 21**) reveals that the presence of a protective group is crucial for achieving good yields under electrochemical conditions. Waldvogel et al attributed this phenomenon to a double effect: 1) the solvation effect of HFIP in presence of TIPS increased due to the lipophilicity of the protecting group, 2) the presence of a bulky group, such as TIPS, leads to a strong twist in the structure of the biphenol (**Figure 24**).

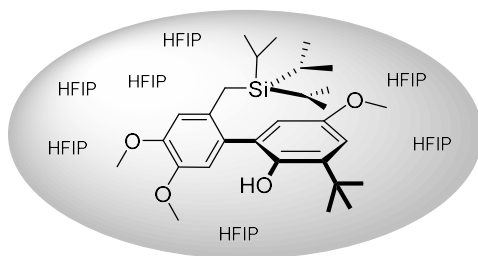
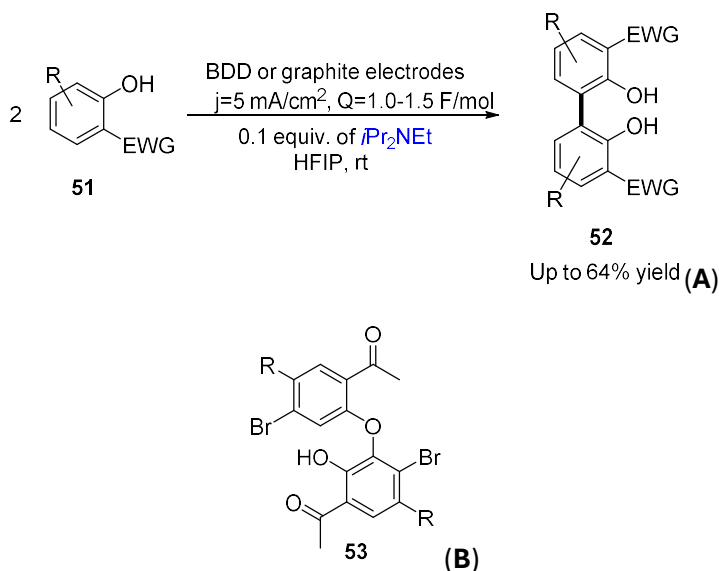


Figure 24: Solvation of twisted biphenol by HFIP

The intramolecular hydrogen bonding between the OH and the silyl ether limits the torsion to 53° such that the two system are not in conjugation. Therefore, the aryl moiety acts as an EWG, protecting the final product from over oxidation.

The authors also investigated the direct anodic homo and cross- coupling of phenols substituted with electron withdrawing groups. Also in this case, the conjugation in the π systems is disfavoured making the product less prone to overoxidation. One of the principal changes respect the previous mentioned work (**Scheme 23**), relies on the use of catalytic amount of *i*Pr₂NEt as electrolyte (**Scheme 24-A**), which can also lower the oxidation potential of the starting material. Dissolving this latter in fluorinated media inside an undivided cell equipped with BDD or graphite electrodes and electrolyzing the reaction solution at 5 mA/cm², afforded the desired homo-coupling adducts in up to 64% yield. If pyridine is used instead of *i*Pr₂NEt, the formation of C-O bond occurs (**Scheme 24-B**).

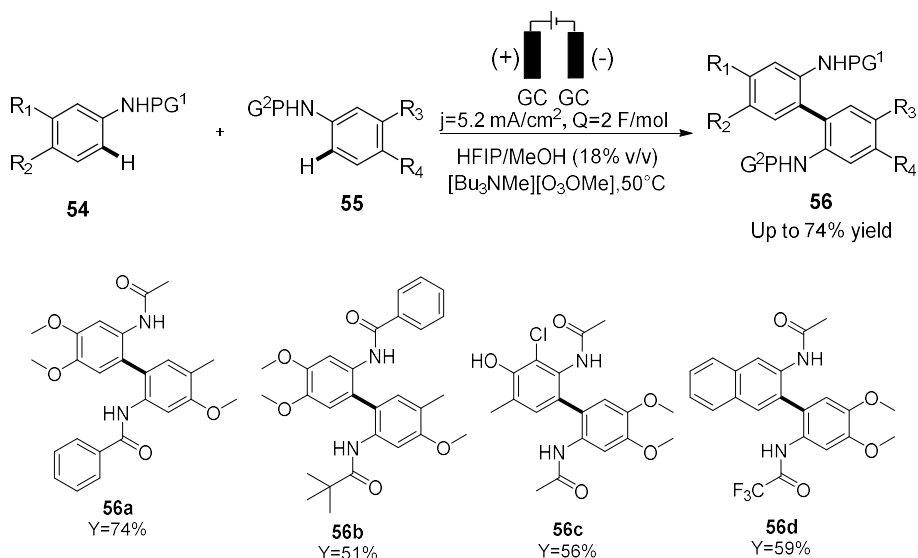


Scheme 24: A: Direct anodic homo-coupling of phenols bearing electron withdrawing groups. B: C-O coupling

Aside from aldehydes, which tend to produce overoxidation by-products,⁶⁹ the method exhibits excellent tolerance toward a range of electron-withdrawing groups, including halogens. These groups are well-suited for the reaction conditions, allowing for efficient coupling without significant side reactions, thereby enhancing the overall yield and selectivity of the process. Moreover, the presence of an halogen atom such as bromine on the biphenol backbone give easily access to further functionalization, particularly challenging with conventional synthetic methods.⁶⁹

2.1.2 ELECTROCOUPLING of ANILINES

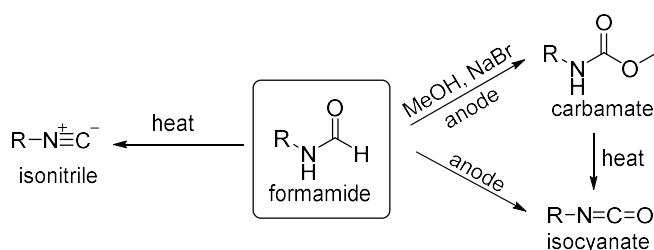
Similar to phenols, anilines biaryl systems play crucial role in pharmaceutical field and, when optically pure, can be enrolled as chiral ligands in organocatalysis (like BINAM). Despite their importance, the synthesis of biaryl diamines from anilines is still a challenging task. Unlike phenols, the electrochemical oxidation of anilines is much less studied due to their very low oxidation potential, which often leads to overoxidation and subsequent polymerization, a process commonly referred to as the "black aniline phenomenon." In 2017, Waldvogel group's investigate the direct anodic homo and cross-coupling of anilines, but complex mixture of by-products were always detected.⁷⁰ Different easily removal protecting groups have been tested to avoid the over oxidation. Amides and carbamates have proven to be effective groups for *N*-protection, demonstrating excellent stability throughout the electrolysis process. Cyclic Voltammetry analysis of *N*-functionalized anylines shows a notable increasing in the oxidation potential respect the unprotected ones, which make them less prone to be overoxidized. As example, the cyclic voltammetry measurement of 3,4-dimethoxyaniline and *N*-acetyl derivative present 0.82V and 1.59V of oxidation potential respectively. This phenomenon could be attributed to the strong hydrogen bonding interaction with HFIP. The addition of methanol, reduces the solvation of amides, causing a noticeable shift in oxidation potentials to lower values. Different aromatic amides have been tested in the electrochemical cross coupling reaction performed using GC electrodes under galvanostatic conditions at 5.2 mA/cm² and in all cases (compound **56a-d**, **scheme 25**) no deprotections were detected.



Scheme 25: Direct anodic cross-coupling of different substituted aryl amides.

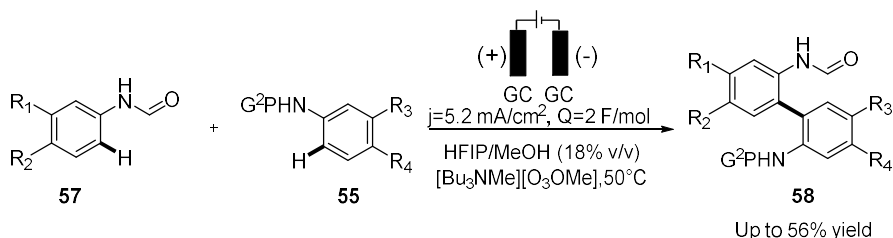
Also, cyclic voltammetry of the components allowed to address the reaction stoichiometry. Usually, the component with the lower oxidation potential is preferentially oxidized at the anode. To statistically favour the cross-coupling over the homocoupling product, the aniline with the higher oxidation potential, was reacted in slight excess (**Scheme 25**).⁷¹

Since formamides are an essential class of compounds in medicinal and organic chemistry and serve as key intermediates in synthesizing isocyanates, nitriles, and carbamates, an extensive study was conducted on various formyl derivatives. (**Scheme 26**).



Scheme 26: Synthesis of isonitriles, carbamates and isocyanates starting from formamides

In 2020 Shoulz et al. investigated the reactivity of the *N*-formyl anilines in the direct anodic cross-coupling reaction with *N*-protected anilines.⁷² It was found that this highly atom-economic protecting groups exhibits sufficient stability during the electrochemical coupling and many of the desired non-symmetrical biaryls could be exclusively obtained in up to 56% isolated yield (**Table 2-entry 1-3**).

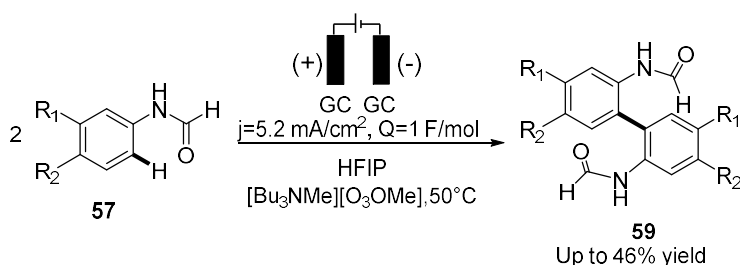


Entry	R ¹ , R ² , R ³ , R ⁴	PG ²	Isolated Yield%
1	R ¹ =R ² =R ³ =OMe R ⁴ =Me	benzyl	56
2	R ¹ (R ²)= -OCH ₂ O-	acetyl	52

$R^3=R^4=OMe$			
$R^1(R^2)= -OCH_2O-$			
3	$R^3=Me$	acetyl	51
$R^4=OMe$			

Table 2: Direct anodic cross-coupling of formyl amides with *N*-protected anilines.

In order to address the regioselectivity of the reaction, aromatic anilines properly substituted in 3,4 positions were subjected to cross coupling reaction performed under constant current (5.2 mA/cm^2) in presence of glassy carbon electrodes. Unfortunately, oligomerization and homo-coupling remained the significant side reactions decreasing the yield of the cross-coupling. Overall, the cross-coupling of one formamide with another amide often provided slightly better yield compared to the homo-coupling of two formyl-protected amides (**Table 3**).⁷²



Entry	R^1, R^2	Isolated Yield%
1	$R^1=I$ $R^2=OMe$	30
2	$R^1=Me$ $R^2=Me$	47
3	$R^1=OMe$ $R^2=OMe$	16

Table 3: Direct anodic homo-coupling two formyl amides

In another study, the investigation of homo-coupling of *N*-(3,4-dimethylphenyl)formamide was carried out under the reaction condition reported in **table 3**, on understanding how varying the current density influenced the reaction outcomes. This analysis elucidated the relationship between current density and the efficiency of product formation, providing valuable insights into optimizing reaction conditions for improved yields (**Figure 25**).⁷³

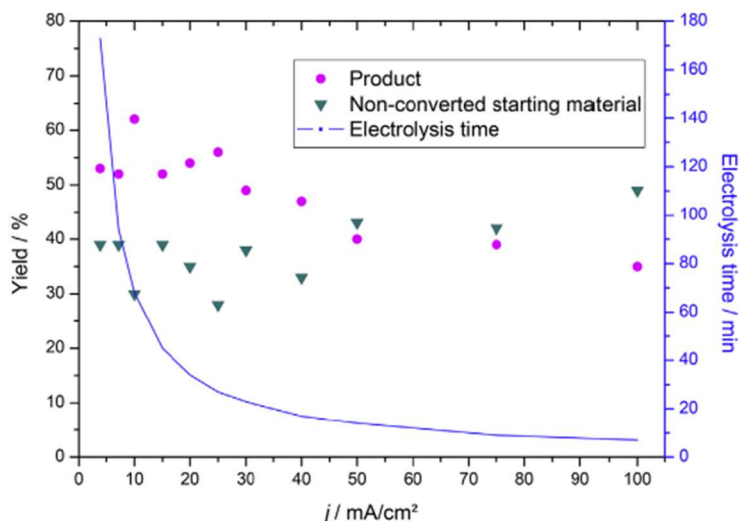


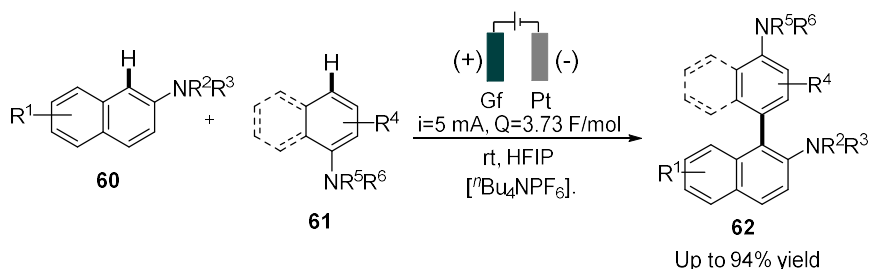
Figure 25: Influence of the current density in the electrochemical homo-coupling. Anode/cathode: glassy carbon, $Q=1.0$ F, $j=3.9$ -100 mA/cm², 0.75 mmol A, $T=50$ °C, solvent: 5 mL HFIP + 0.09 M [Bu₃NMe][OSO₃Me]. *GC-yield, determined by using 3,3',5,5'-tetramethyl-2,2'-biphenol as internal standard.

As shown in **figure 25**, the reaction is highly susceptible to the current density parameter. High current values are associated to an increased rate of heterogeneous electron transfer at the electrodes, which may also promote side reactions. As shown in **Figure 25**, the maximum yield is obtained at 10 mA/cm². At higher current densities, the starting material conversion decreased; however it can be recycled after reaction, minimizing losses due to polymerization. Unexpectedly, 29% of yield was verified also at 100 mA, carrying out the reaction for 7 min instead of 1.5 h.⁷³

2.1.3 ELECTROCHEMICAL CROSS COUPLING of β -NAPHTHYLAMINES

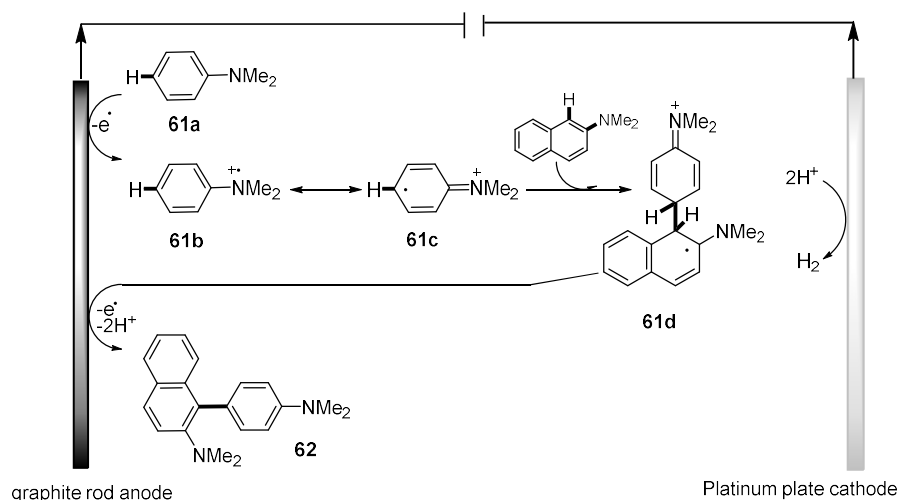
As previously mentioned, the extremely low oxidation potential of anilines, combined with challenges in achieving *ortho/para* regioselectivity, has limited research into the development of their electrochemical coupling. However, in 2020, He and co-workers reported a dehydrogenative cross-coupling of anilines and naphthyl amines for the synthesis of a wide range of unsymmetrical and functionalized binaphthylamines in good to excellent yields under mild oxidant-free conditions with excellent selectivity, broad substrate scope, and wide functional group tolerance.⁷⁴ Various naphthalen-2-amine derivatives underwent efficient electrochemical cross-coupling with a wide range of common tertiary anilines to assemble

unsymmetrical binaphthyl amines, in the presence of graphite anode and platinum cathode, in HFIP at 5 mA as shown in **scheme 27**.



Scheme 27: Direct Anodic cross-coupling of 2-Naphtylamines and anilines

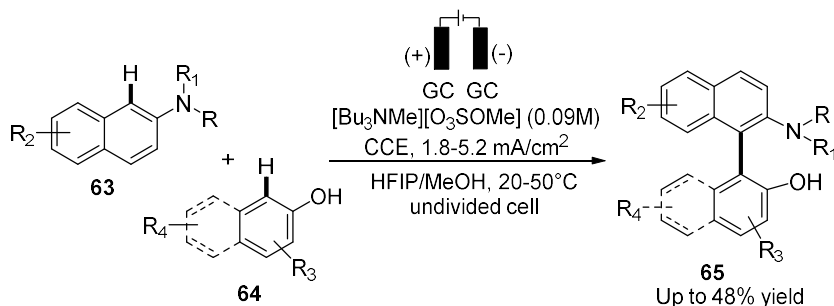
The mechanism was also investigated by cyclic voltammetry analysis. Based on the oxidation potential observed under the reaction conditions, the oxidation of anilines and naphthylamines at the anode surface is the initial step. This process generates a radical cation **61b** intermediate, which delocalizes the radical to the most accessible para position (**61c**). Interaction between this radical and an additional aniline molecule then produces a radical adduct **61d**, which undergoes re-oxidation to yield the desired product **62**. (**Scheme 28**).



Scheme 28: Mechanism of the direct anodic cross-coupling of 2-Naphtylamines and anilines

After investigating the reactivity of naphthalene-2-amine derivatives, in 2018, Waldvogel explored the electrochemical cross-coupling of β -Naphthylamines derivatives with various substituted phenols and

naphthols, focusing particularly on the synthesis of the chiral ligand NOBIN. (**Scheme 29**).



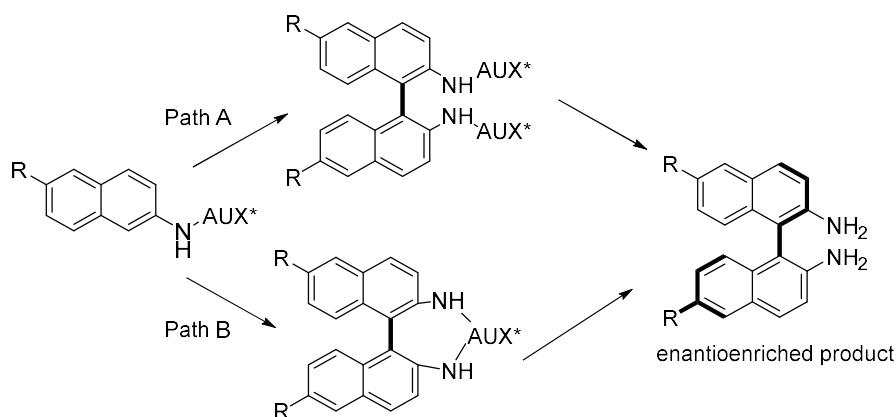
Scheme 29: Electrochemical cross-coupling of β -Naphthylamines derivatives with various substituted phenols and naphthols.

Using Glassy carbon electrodes, in a constant current electrolysis (1.8-5.2 mA/cm²) in HFIP/MeOH, the biaryl systems were achieved in moderate to good yields, with a maximum of 48%. As observed for phenols, regioselectivity issues can be mitigated by introducing bulky, electron-donating groups at the 4 and 6 positions. The formation of byproducts derived by a C-O cross coupling were observed only with phenols that lack substituents at the 6 position. Among the tested substrates, the highest yield of 45% was achieved using a combination of *N,N*-dimethyl-2-naphthylamine and 6-methoxy-2-naphthol. The methoxy substituent at the 6 position, an electron-donating group, enhances nucleophilicity and promotes cross-coupling. Furthermore, the use of the optically pure naphthylamine derivatives directly leads to the corresponding diastereomers in a 1:1 ratio.⁷⁰

2.2 ENANTIOSELECTIVE SYNTHESIS OF BYARIL SCAFFOLDS: RESULTS AND DISCUSSIONS

Given the significant importance of naphthylamine biaryl scaffolds and the relatively limited exploration of their electrochemical coupling compared to phenol derivatives, we envisioned the possibility to develop a stereoselective synthesis of these molecules through electrochemical methods. Since only a few methods involving specific chiral electrodes or chiral catalysts have been explored, and among them, the use of chiral auxiliaries has been less studied,¹⁷ we decided to focus on this approach. While this latter requires an additional synthetic step, it offers a cost-effective alternative to the other two methods. Moreover, in some cases, the chiral auxiliary can be removed and recovered at the end of the process,

making it an attractive option for sustainable and efficient synthesis. Based on this, we investigated the oxidative electrochemical homo-coupling of β -naphthylamine derivatives functionalized with a chiral auxiliary directly bounded onto the heteroatom. In order to address the regioselectivity of the homo-coupling different chiral auxiliaries have been explored. In **Scheme 30** are depicted two synthetic strategies which have been investigated to get enantioenriched compounds.



Scheme 30: Hypothesized strategies for the enantioselective synthesis of β -Naphthylamines by aryl scaffold

Pathway A, consists in an intermolecular coupling between two identical substrates, where the reaction occurs between two separate molecules. In contrast, Pathway B employs a bidentate chiral auxiliary, which interacts with two nitrogen atoms of the aromatic systems, enabling an intramolecular coupling. In both cases, the resulting diastereoisomers can be separated, and the removal of the chiral auxiliary yields the enantiopure forms of the product.

This chapter will outline the electrochemical coupling of chiral β -naphthylamine derivatives, promoted according to both of these approaches.⁷⁵

2.2.1 ELECTROCHEMICAL SET-UP

The commercially available Electrasyn 2.0 platform has been employed for the electrochemical experiments. This advanced system includes a potentiostat (**Figure 26-A**), which provides the flexibility to perform both galvanostatic (constant current) and potentiostatic (constant potential) electrolysis. Additionally, the platform is compatible with a reference electrode, allowing for precise control and monitoring of the

electrochemical conditions. This versatility enables accurate and reproducible results, making it ideal for investigating various electrochemical reactions, including those requiring precise control over current or potential during the coupling processes. Electrasyn 2.0 apparatus includes specific caps (**Figure 26-B**) that can be magnetically connected to the potentiostat support. When the reaction is carried out at different temperature respect 25°C, a mobile support can be used, allowing the electrochemical cell to be immersed in an oil or refrigerated bath. The Electrasyn caps show specific metallic sites where the electrodes can be connected. Moreover, when inert atmosphere needs to be used, the gases can be flow by the screw top (**Figure 26-C**). For our purposes, undivided baker type cell of 5ml (visible in **Figure 26**) has been adopted.



Figure 26: A Electrasyn 2.0 apparatus, B Cap, C Electrodes

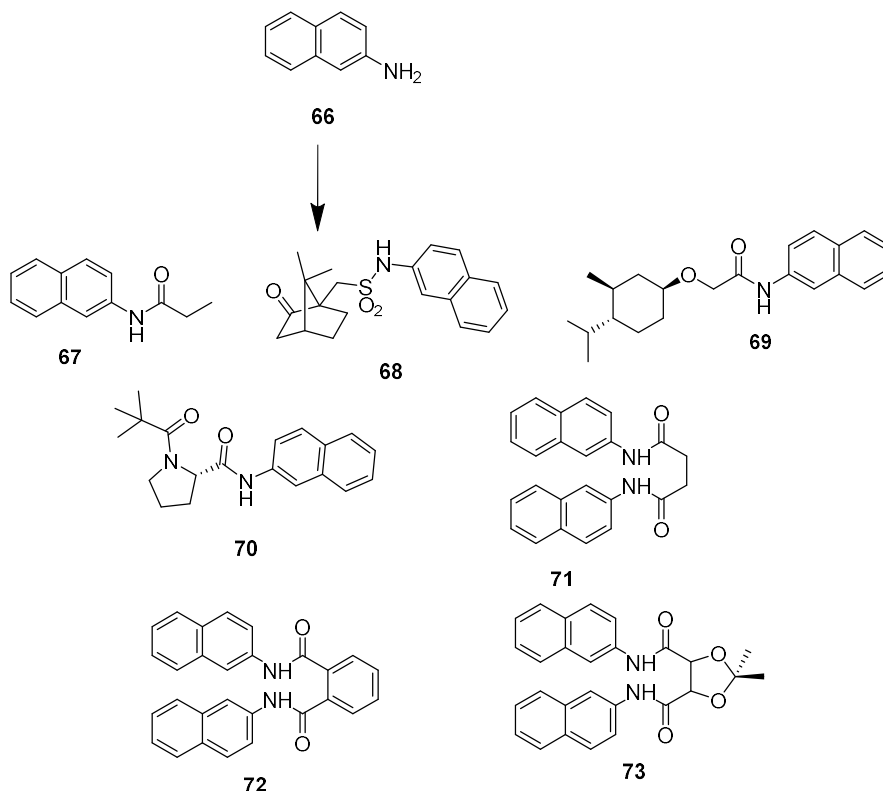
In **Figure 27** is shown the set-up used for the electrochemical coupling of the secondary chiral aromatic amines, which are particularly sensitive to oxygen. In this case, all the reagents were dissolved in the fluorinated media in 5mL baker type cell, then the electrochemical set-up was assembled with selected electrodes and degassed with Argon for two minutes to ensure the removal of any dissolved oxygen. Under Argon atmosphere, provide by a gas bag, the solution was electrolyzed at constant current.



Figure 27: Electrochemical set-up for secondary chiral amines homo-coupling

2.2.2 INTERMOLECULAR and INTRAMOLECULAR ELECTROCHEMICAL HOMO-COUPLING of β -NAPHTHYLAMIDES

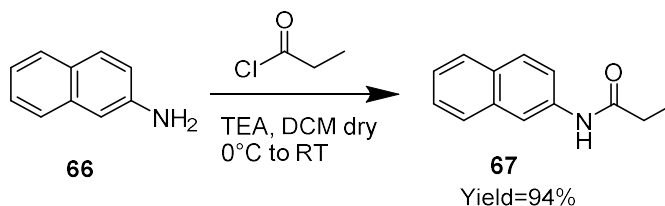
This paragraph presents a preliminary investigation into the electrochemical homo-coupling of β -naphthylamides derivatives, functionalized with suitable chiral auxiliaries. To perform this transformation, we operated using the commercially available Electrasyn 2.0. as an easily handle apparatus which could guarantee an optimal reproducibility and control of the reaction parameters. At this purpose, different β -naphthylamines were synthesized, and they are shown in **Scheme 31**.



Scheme 31: β -Naphthylamides synthesized and tested in the intermolecular (**67**, **68**, **69**, **70**) and intramolecular coupling (**71**, **72**, **73**).

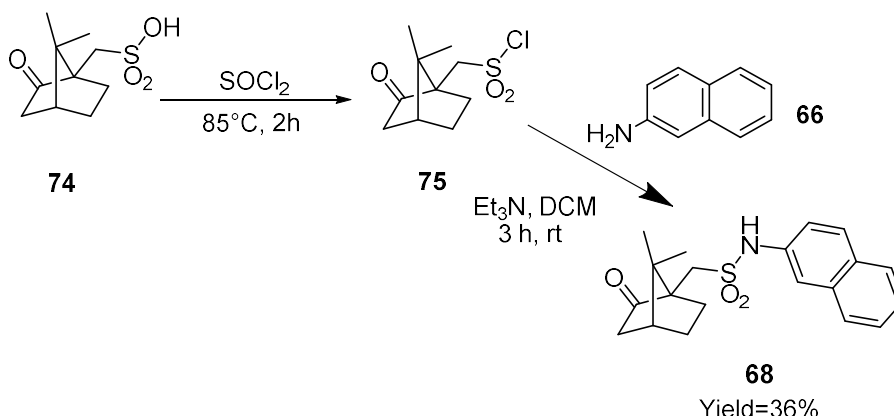
As first attempt, we tried to apply Waldvogel conditions for the electrochemical homo-coupling of the easily available *N*-(naphthalen-2-yl) propionamide .

N-(naphthalen-2-yl) propionamide **67** was synthesized dissolving 2.1 mmol of β -naphthylamine **66** and NEt_3 in dichloromethane at room temperature (**Scheme 32**) followed by a dropwise addition of propionyl chloride.⁷⁶ The desired product was obtained in 94% yield, affording a white solid which was isolated without the need for further purification.



Scheme 32: Synthesis of *N*-(naphthalen-2-yl)propionamide.

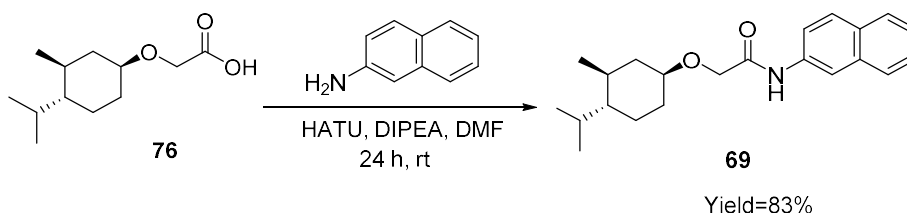
β -naphthyl sulfonamide **68** was obtained according a two steps procedure.⁷⁷ (1*R*)-(-)-10 Camphorsulphonic Acid **74** was refluxed with of thionyl chloride for two hours achieving the corresponding chloride **75** which was then reacted with β -Naphthylamine in the presence of triethylamine. The chloride **75** was solubilized in DCM and poured dropwise in β -Naphthylamine mixture, obtaining the desired sulphonamide **68** (**Scheme 33**).



Scheme 33 : Synthesis of Camphorsulphonic acid derivative

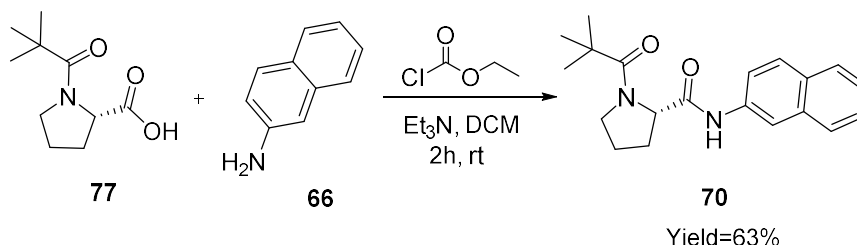
Product **68** was isolated with an overall yield of 36%, due to challenges in crystallization, and a further purification step through column chromatography was necessary in order to isolate the product in its pure form.

Substrate **69** was synthesized according the procedure reported in **Scheme 34**.⁷⁸ (-)-menthyloxyacetic acid **76** were reacted in stoichiometric amount with β -naphthylamine in presence of HATU (HexafluorophosphateAzabenzotriazoleTetramethylUronium), an excess of *i*-Pr₂NEt as a base, and using DMF as solvent. After 24h at room temperature, product **69** was achieved in 83% yield, which was isolated without the need for further purification.



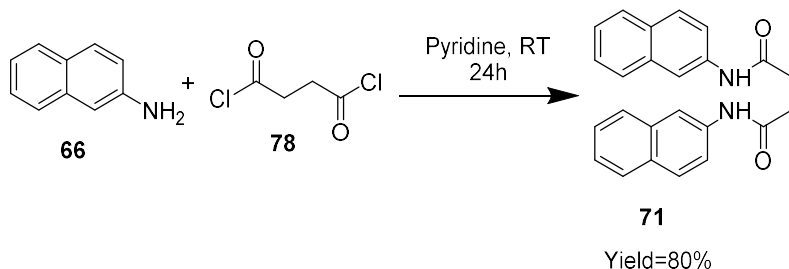
Scheme 34: Synthesis of the menthyloxyacetic derivative.

N-Boc-*L*-Proline was also tested as chiral auxiliary . Compound **70** was obtained by reaction of proline **77** with β -naphthylamine **66**, in the presence of ethyl chloroformate and triethylamine in dichloromethane, for 2 hours at room temperature (**Scheme 35**).⁷⁹ In this case, a chromatographic purification was required in order to obtain desired compound **70** in 63% yield.



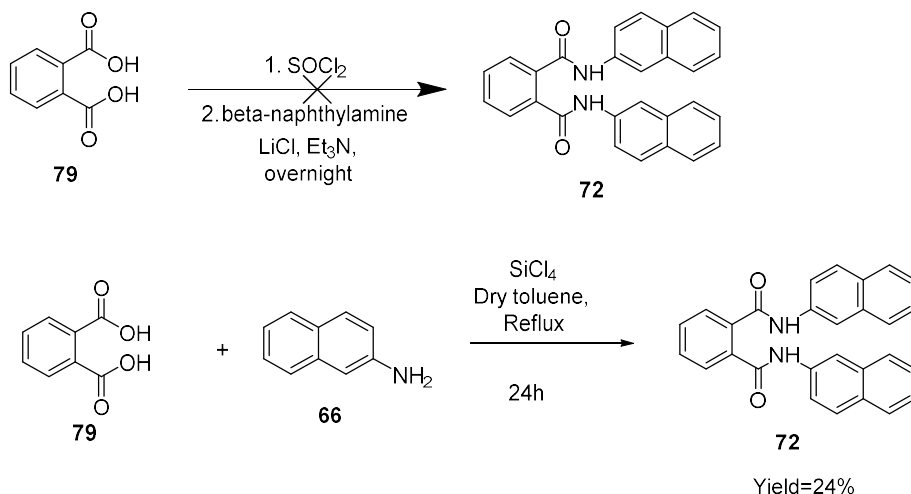
Scheme 35: Synthesis of *N*-Boc-*L*-Proline derivative

The strategy for the synthesis of the bis-amide **71** is instead reported in **Scheme 36**.⁸⁰ 2 equiv. of β -Naphthylamine were dissolved in pyridine, followed by a dropwise addition of freshly distilled succinyl dichloride **78**. After 24h, the desired product **71** was isolated in 80% yield.



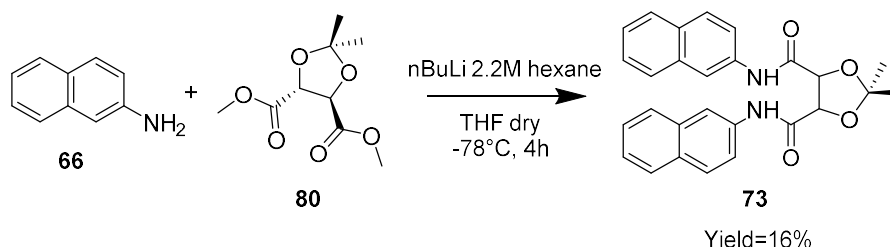
Scheme 36: Synthesis of *N*¹,*N*⁴-di(naphthalen-2-yl)succinamide

Compound **72** was synthesized starting from phthalic acid **79** using two different strategies. The first approach involved converting phthalic acid into phthaloyl dichloride, which was then reacted with 2 equiv. of β -naphthylamine in the presence of 2 equiv. of triethylamine.⁸¹ However, this method consistently resulted in the formation of mono-functionalized phthalic acid as the primary product (**Scheme 37**). The second strategy employed the use of SiCl_4 , as a coupling agent, which was reacted with compound **79** and 2 equiv. of β -Naphthylamine in dry toluene under reflux conditions.⁸² In that case, the desired product **72** was obtained, although in a modest 24%, likely due to the sensitivity of SiCl_4 to moisture, which may have led to partial decomposition or side reactions.



Scheme 37: Two synthetic approaches for N^1, N^2 -di(naphthalen-2-yl)phthalamide

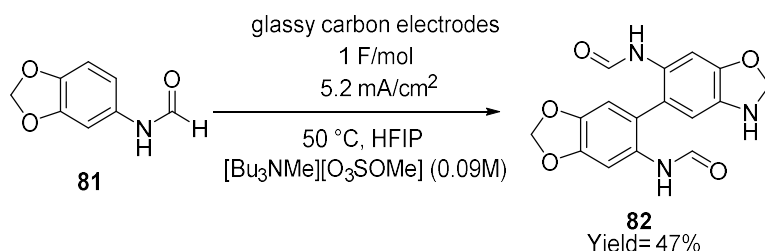
We also tried to synthesize a chiral bidentate structure **73** using dimethyl (*4R,5R*)-2,2-dimethyl-1,3-dioxolane-4,5-dicarboxylate **80** as chiral auxiliary; 2 equiv. of β -Naphthylamine were reacted with **80** in the presence of butyl lithium in dry THF, at -78°C (**Scheme 38**).⁸³ The desired amide was isolated in a low yield of 16%. This reduced yield can be attributed to the small-scale nature of the reaction, where significant product loss occurred during the crystallization step, a common issue when working with limited material quantities.



Scheme 38: Synthesis of tartaric bidentate amide

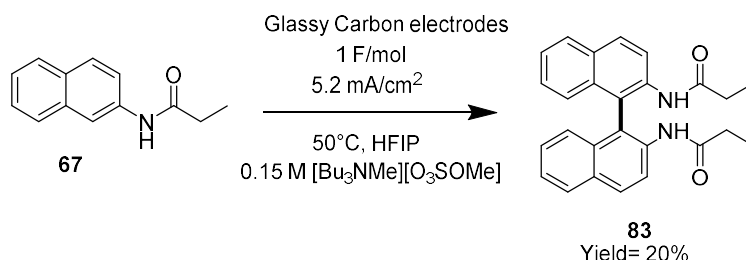
After successfully synthesizing the required starting materials, we proceeded to replicate the intermolecular homo-coupling of 3,4-dimethoxyindene formamide as described by Waldvogel using Electrasyn system.⁷² Using glassy carbon electrodes and a 0.09 M solution of $[\text{Bu}_3\text{NMe}][\text{O}_3\text{SOMe}]$ in HFIP as the electrolyte, the reaction medium was subjected to electrolysis at a current density of 5.2 mA/cm^2 . The desired product was obtained in a yield comparable to the literature (45%),

demonstrating the reproducibility of the reported procedure under the specified conditions (**Scheme 39**).



Scheme 39: Electrochemical anodic homo-coupling of 2,4-dimethoxyindene formamide.

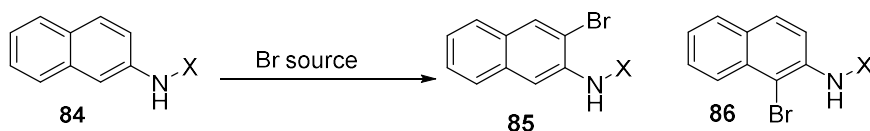
Using the same reaction conditions, we evaluated the reactivity of *N*-(naphthalen-2-yl)propionamide to investigate the regioselectivity of the process. Consistent with Waldvogel's observations, we selected an amide with a higher oxidation potential than the corresponding unprotected amine. This choice was aimed at minimizing the formation of undesired byproducts and improving the overall selectivity of the reaction (**Scheme 40**). By applying the same electrochemical reaction conditions to substrate **67**, a mixture of coupling products involving also the reactive positions 3 and 6 was obtained. After a challenging purification process, the desired compound was successfully isolated, albeit in a modest yield of 20%.



Scheme 40: Electrochemical dehydrogenative homo-coupling of *N*-(naphthalen-2-yl) propionamide

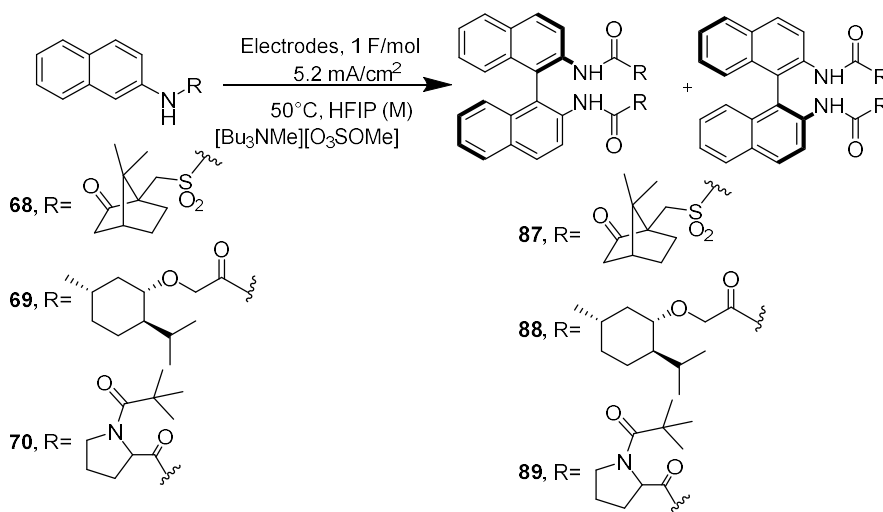
Based on this result, we hypothesized that functionalizing position 3 with a halogen, such as bromine, could improve the regioselectivity of the reaction. This approach would also be strategically advantageous from a synthetic perspective, as bromine can be easily substituted with either an aromatic or aliphatic group, providing a versatile intermediate for the synthesis of various biaryl systems. Unfortunately, despite several attempts at bromination starting from unsubstituted β -naphthylamides or amines, all

reactions led to the formation of the undesired compound **86**, as depicted in **scheme 41**.



Scheme 41: Bromination attempts in 3 position of β -Naphthylamines derivatives

Although this result did not provide access to the desired product **5**, it allowed us to identify position 1 of β -naphthylamine derivative as the most reactive site on the binaphthyl ring, which can be easily targeted for directing the coupling reaction. Despite the low yields obtained from the direct anodic homo-coupling of N-(naphthalen-2-yl)propionamide, we decided to explore the use of several chiral auxiliaries under slightly modified Waldvogel conditions. The goal was to identify a chiral moiety that, even if resulting in low yields, could promote the formation of the C1-C1' coupling product while simultaneously controlling the stereochemistry of the reaction. According to that, three different commercially available chiral auxiliaries were tested in the electrochemical intermolecular coupling, as outlined in **Scheme 42**.



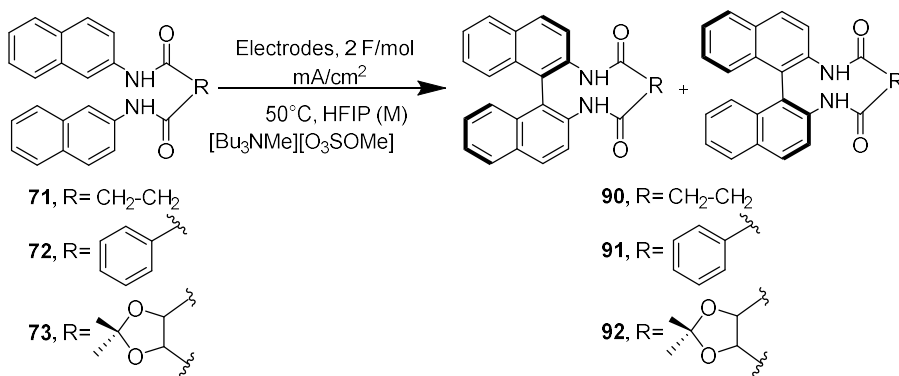
Scheme 42: Electrochemical intermolecular homo-coupling of chiral aryl amides

The electrochemical coupling of compound **68** under Waldvogel conditions afforded C3-C3' coupling products as a mixture of diastereoisomers in 1:1 ratio, as detected by H-NMR. A similar outcome was observed for compound **69**, which generates mixture of degradation by-products and traces of the desired adduct. Changing the reaction media concentration,

no improvements were observed. Attempts to improve the reaction by altering the concentration of the reaction medium did not lead to any significant improvements. Furthermore, the *N*-Boc-Proline derivative **70** only yielded the desired product in trace amounts when both glassy carbon and platinum electrodes were used. Unreacted starting material was recovered in all cases after a chromatographic purification.

The steric hinderance of the chiral moieties tested likely directed the coupling reaction to positions other than the desired C1-C1', resulting in a preference for the formation of other coupling products and favouring the generation of undesired coupling compounds. With the aim to improve the regioselectivity of this transformation, we envisioned the possibility to introduce an easily removal chiral bidentate moiety. Initially we tested the activity of the achiral compounds **71** (**Scheme 43**) which was expected to display similar redox properties of compound **67**. Unfortunately, this substrate exhibited very poor solubility in HFIP. The electrochemical coupling under heterogeneous conditions led to a complete degradation of the starting material. As a result, we decided to investigate compound **72**, characterized by the presence of a phthalic acid group as a bidentate moiety, to enhance solubility in fluorinated media. Despite modifying the current density and substrate concentration, we the reaction consistently led to the formation of intermolecular coupling products.

Ultimately, we expanded the study to include a chiral bidentate moiety, such as tartaric acid (Compound **73**). We evaluated the activity of glassy carbon and platinum electrodes and we reduced the substrate concentrations. However, the reaction only yielded unreacted starting material and intermolecular coupling products. This outcome is likely due to the high rigidity and steric constraints of the starting material, which prevent the two C1-C1 positions of interest from effectively reacting together. This hypothesis was further supported by computational studies conducted within our group, also with a chelating metal like Zinc.

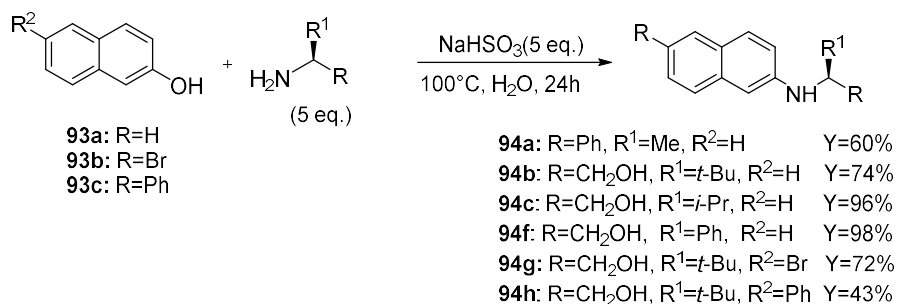


Scheme 43 : Intramolecular coupling of N,N-dinaphthylamides

2.2.3 INTERMOLECULAR and INTRAMOLECULAR ELECTROCHEMICAL HOMO-COUPLING of β -NAPHTHYLAMINES DERIVATIVES

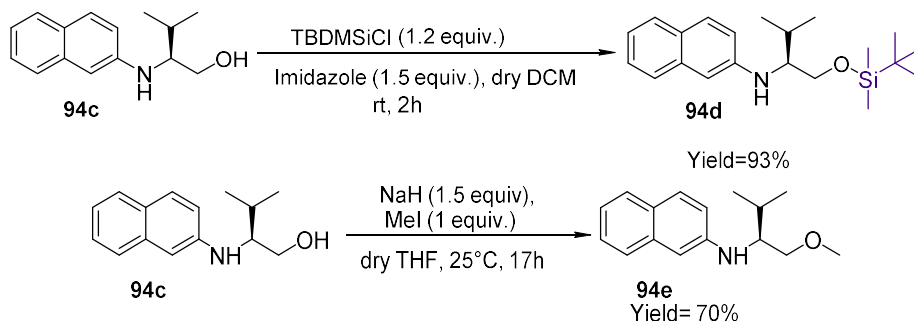
The preliminary studies discussed in the previous paragraph, prompted us to re-evaluate the literature and explore the potential of secondary and tertiary aromatic chiral amines for our purposes. As mentioned in the introduction section, Waldvogel pioneered an innovative electrochemical approach for the synthesis of the chiral ligand NOBIN, starting from the enantiopure (S)-N-(1-phenylethyl)naphthalen-2-amine and various substituted phenols and naphthols (see **Scheme 29**). Given the optimal reactivity of this chiral amine in cross-coupling reactions,⁷⁰ we envisioned the possibility to investigate the electrochemical homo-coupling transformation of (S)-N-(1-phenylethyl)naphthalen-2-amine) **94a** electrochemical homo-coupling transformation as starting precursor for the synthesis of BINAM.

The enantiopure secondary β -naphthylamines, used as starting materials in the electrochemical coupling reactions, were synthesized following the Bucherer procedure (**Scheme 44**).⁸⁴ β -Naphthols **93a-b** were reacted with an excess of a chiral amine or a chiral aminoalcohol in water, using an excess of sodium bisulfite. The desired enantiopure substrates were achieved in up to 98% yield after an easy chromatographic purification.



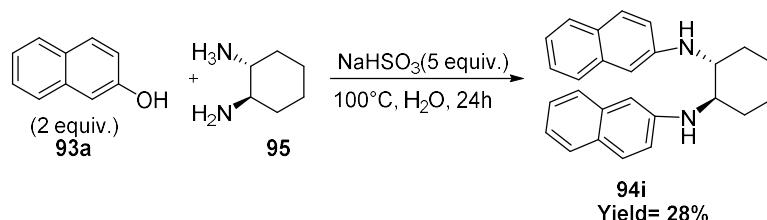
Scheme 44: Synthesis of enantiopure β -Naphthylamines by Bucherer reaction

Compound **94d** and **94e** were instead obtained starting from compound **94c**. In particular, compound **94d** was obtained from compound **94c** by reaction with *tert*-Butyldimethyl silyl chloride in 93% Yield. Whereas, **94e** was achieved after a treatment of **94c** with NaH and MeI in dry THF,⁸⁵ leading to the formation of the desired product in 70% yield (**Scheme 45**).



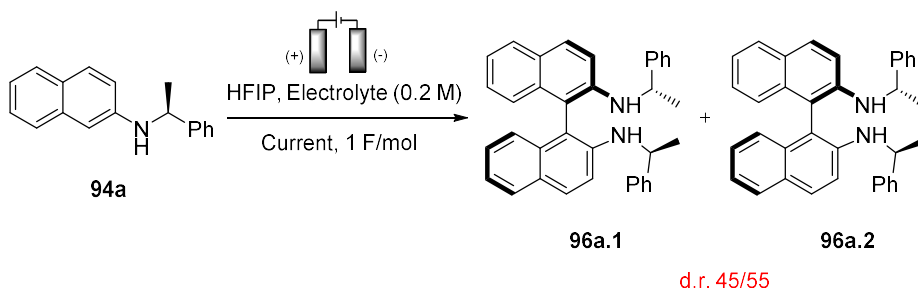
Scheme 45: Synthesis of compound **94d** and **94e**

The use of bidentate chiral β -naphthyl diamine was also investigated. For this purpose, compound **94i** was synthesized according to Bucherer reaction, starting from β -naphthol **93a** that was reacted with enantiopure (*R,R*)-*trans*-diaminocyclohexane **95** in the presence of an excess of sodium sulphite. Desired product **94i** was obtained in 28% after chromatographic purification.



Scheme 46: (*1R,2R*)-*N*¹,*N*²-di(naphthalen-2-yl)cyclohexane-1,2-diamine

After having synthesized these substrates, we performed preliminary tests using β -naphthylamine **94a** as a test compound. The homo-coupling reaction was performed according to Waldvogel conditions,⁷⁰ which are well-established for promoting C–C bond formation through sustainable electrochemical processes. Desired product **96** was obtained as a mixture of two diastereoisomers with a 55:45 ratio and with a global yield of 15% (**Table 4, entry 1**), providing a good starting point for a better tuning of the reaction conditions.



Entry	Current (mA)	Electrodes	Switched Polarity (S)	Electrolyte	Isolated Yield (%)
1	5.5	GC GC	No	[Bu ₃ NMe][O ₃ SO Me]	15%
2	10	GC GC	No	[Bu ₄ N][BF ₄]	12%
3	5.5	GC GC	No	[Bu ₄ N][BF ₄]	20%
4	5.5	GC GC	8s	[Bu ₄ N][BF ₄]	traces
5	5.5	GC GC	No	[Bu ₄ N][ClO ₄]	25%
6	2	GC GC	No	[Bu ₄ N][ClO ₄]	10%
7	5.5	GC GC	No	Zn(OAc)	traces
8	5.5	Gf Gf	No	[Bu ₃ NMe][O ₃ SO Me]	traces

Table 4: Preliminary optimization of electrochemical homo-coupling of (S)-N-(1-phenylethyl)naphthalen-2-amine)

As shown in the **table 4**, changing the electrolyte from [Bu₃NMe][O₃SOMe] to [Bu₄N][BF₄] slightly improved the reaction yield (**entry 3** vs **entry 1**), leading to the formation of a 45:55 **96a.1:96a.2** mixture with 20% of global yield. The replacement of [Bu₄N][BF₄] with [Bu₄N][ClO₄] allowed to further increase reaction yield up to 25% yield (**entry 5**). Increasing or decreasing the current intensity (**entry 2** vs **entry 6**) or changing the electrode material (**entry 8**) further reduced the efficiency. In all cases, the reaction resulted in a black crude mixture containing numerous by-products, making the purification and separation of the two diastereoisomers highly challenging.

Compounds **96a.1** and **96a.2** correspond to the first and second isomers eluted during chromatographic purification, respectively. The crude colour indicated the presence of N-oxide by-products, likely formed in the presence of oxygen under oxidative conditions. Additionally, oxygen can generate superoxide and peroxide radicals, which may trap radical intermediates and promote the formation of undesired side products. A second optimization of the reaction conditions was then performed (**Table 5**), degassing the reaction mixture with Argon before the electrolysis and maintaining the Argon atmosphere for all the reaction time.

Entry ^[a]	Electrodes	Electrolyte Concentration (M)	Charge (F/Mol)	Substrate Concentration (M)	Isolated Yield (%)
1*	GC GC	0.2 M	1	0.15	25% ^[b,c]
2	GC GC	0.3 M	1	0.15	25% ^[c]
3	Pt foil Pt foil	0.3 M	1	0.15	37%
4	Pt foil Pt foil	0.3 M	1.3	0.15	45%
5	Pt foil Pt foil	0.3 M	1.3	0.10	47%
6	Pt foil Pt foil	0.3 M	1.7	0.15	34%
7	Pt foil Pt foil	0.3 M	0.5	0.15	Not Purified

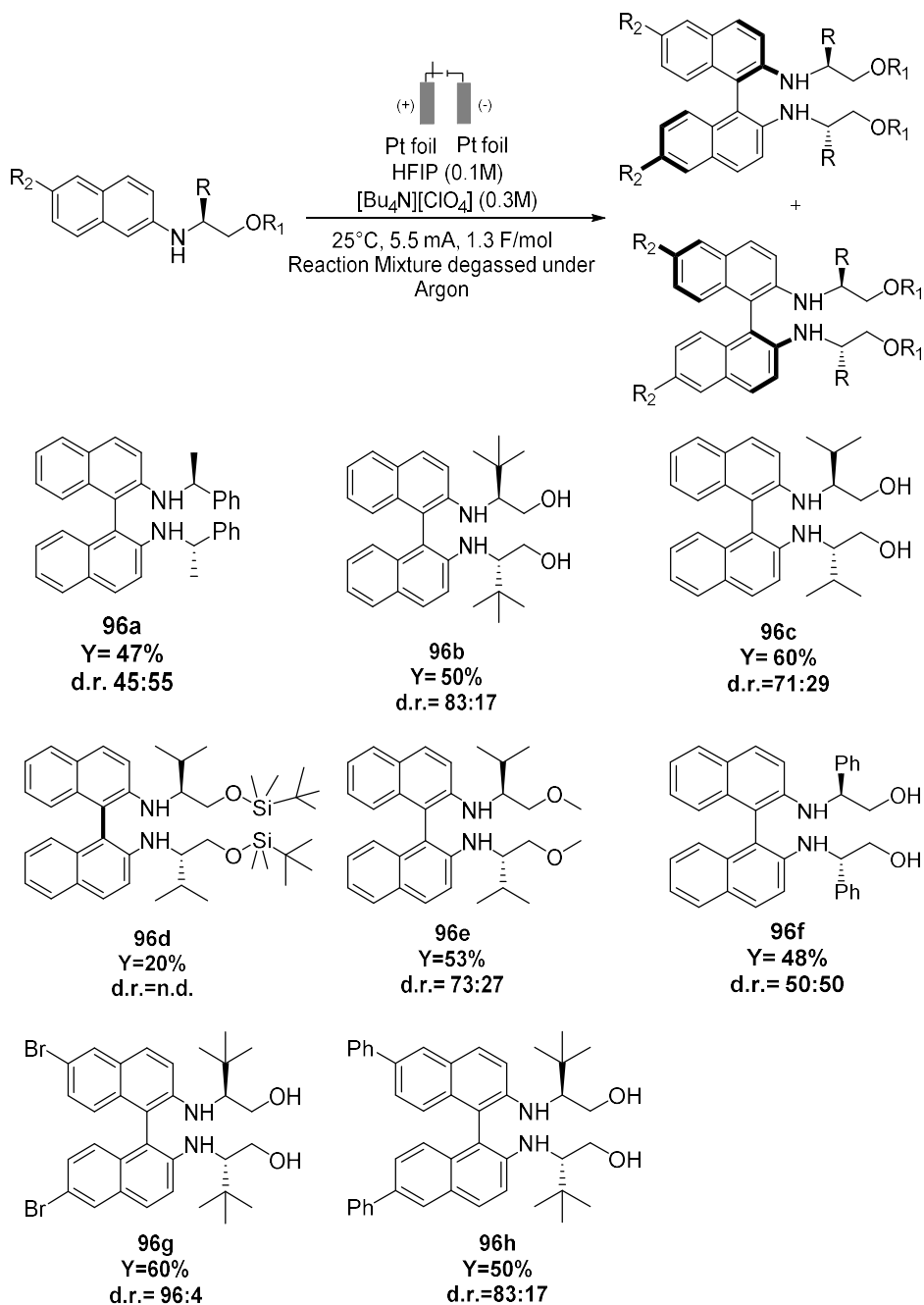
a) Electrolysis conditions: 25 °C, constant current (5.5 mA), undivided cell, solvent: HFIP. Reaction mixture degassed with Argon before the electrolysis. Reaction carried out under Argon atmosphere. [b] No degassing and no Argon atmosphere [c] Formation of significant amounts of by-products [d] Crude not purified since a large amount of unreacted starting material was detected by TLC,

*Like entry 5 of **Table 4**

Table 5: Second reaction condition optimization of the (S)-N-(1-phenylethyl)naphthalen-2-amine) homo-coupling, without oxygen in the reaction media

In all cases, **96a.1** and **96a.2** diastereoisomers were separated through a not trivial purification on column chromatography. Often, particularly in presence of a notable amount of unreacted starting material, two purification steps were required. In order to maintain the cell potential in the range of 1.5-2.5V, the conductivity of the reaction mixture was increased by adding more electrolyte and the electrochemical coupling was carried out in presence of Glassy Carbon electrodes and Platinum foil electrodes respectively (**entries 2** and **3**). The latter option proved to be optimal since **96a** products were isolated in 37% overall yield with minimal side products. Thus, using Platinum foil electrodes, F/mol parameter was taken into account. Notably, when 1.3 F/mol was applied to the reaction mixture, **96a** was obtained in up to 47% yield (**entry 5**), whereas the use of 1.7 F/mol was detrimental, since the product was isolated in 34% yield only (**entry 6**).

With the best conditions in hands, we extend the scope of this transformation to previous synthesized compounds **94b-94h**. (**Scheme 47**)



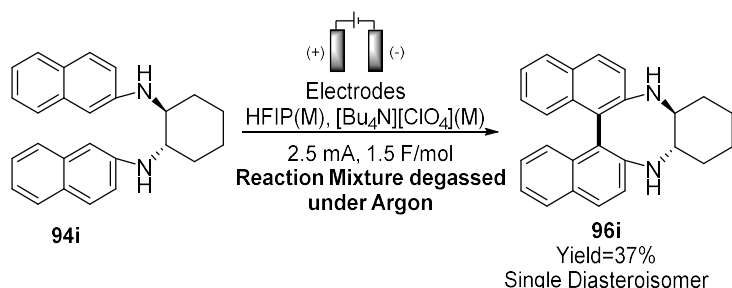
Scheme 47: Direct anodic Homo-coupling between β -naphthylamines **96b-96h** featuring a chiral amino alcohols unit as chiral auxiliaries

The reactivity of the *t*-leucinol derivative **94b** was firstly investigated, and gratefully, the electrocoupling occurred with good yield (50%) and 83/17

diastereoselectivity. Moreover, the two diastereoisomers **96b.1** and **96b.2** were easily separated by column chromatography and no unreacted starting material was observed. The reaction of the *N*-valinol naphthyl amine **94c** led to a higher yield of **96c** mixture (60% isolated yield) although with lower diastereoselectivity (**96c.1**:**96c.2** 71/29), probably due to the decreasing steric hindrance of the R group. To understand the possible role of hydrogen bonding interactions in the improved selectivity and diastereocontrol of the reaction in presence of the aminoalcohol auxiliaries, we decided to protect the hydroxy group of valinol as silyl ether (compound **94d**). Unfortunately, the electrochemical coupling led to a very complex reaction mixture with an abundant amount of starting material unreacted. Only one of the two diastereoisomer (**96d**) was eluted together with the starting material and the yield was calculated by H-NMR. Therefore, we selected the methyl ether, as a more stable and less hindered protecting group (compound **94e**). The electrochemical coupling afforded two diastereoisomers **96e.1** and **96e.2** with comparable yield and diastereoselectivity of **96c**, even if more byproducts were observed. The electrochemical coupling of **94f** using 1.7 F/mol led to products **96f.1** and **96f.2** in 45% yield and in 50/50 ratio. With the aim to investigate the reactivity of functionalised BINAM scaffolds in the coupling reaction, we synthesized compound **94g** and **94h** using *t*-leucinol as chiral auxiliary. The diastereoisomers **96g.1** and **96g.2** were achieved with good yields and excellent diastereoselectivity, in up to 96/4 ratio, whereas the presence of Ph in 6 position didn't affect the diastereoselectivity (**96h**).

Based on these results, we performed a preliminary investigation of an intramolecular electrochemical coupling. (*1R,2R*)-*trans*-1,2-Diaminocyclohexane was employed as a bidentate chiral unit for the synthesis of the β -Naphthylamine derivative **94i** in enantiopure form

A brief reaction condition optimization was carried out by adjusting the electrode material and substrate concentration. As expected, substrate concentration was a key point to be addressed to prevent or reduce intermolecular coupling reactions. As observed in the case of intermolecular electrochemical coupling, the presence of oxygen significantly affected the reaction yields by promoting the formation of by-products. This undesirable effect was mitigated in all attempts (**Table 6, entries 1–4**) by performing the reactions under an argon atmosphere.

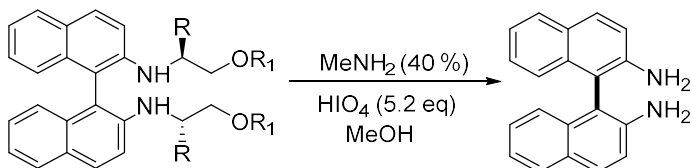


Entry ^[A]	Electrodes	Substrate Concentration (M)	Electrolyte Concentration (M)	Charge (F/mol)	Isolated Yield (%)
1	Ptfoil Ptfoil	0.03 M	0.3	1	n.d.
2	GC GC	0.03 M	0.3	1	n.d.
3	GC GC	0.03 M	0.15	1	10%
4	GC GC	0.017 M	0.01	1.5	37%

Table 6: Reaction condition optimization for the intramolecular coupling

As showed in **Table 6**, no desired product was obtained when platinum electrodes were used (**entry 1**). When the reaction was performed at higher electrolyte concentrations (0.3 M, **entry 2**), intermolecular coupling product was observed. However, when the concentration was reduced to 0.15 M, desired product **96i** was obtained in 10% yield (**entry 3**). This result was further improved by decreasing the substrate concentration to 0.017 M (**entry 4**), leading to the formation of compound **96i** as a single diastereoisomer in 37% yield.

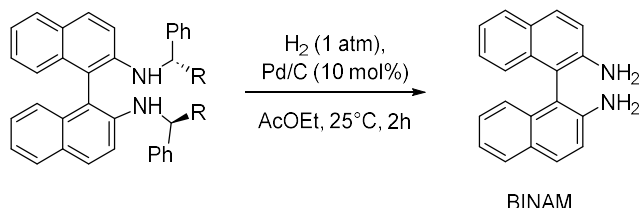
The final goal of this project was focused onto the removal of the chiral auxiliary from the separated diastereoisomers to obtain the enantiopure forms of BINAM. At first, compound **96b**, **96c** and **96e** were treated with a solution of methylamine (40% in water) and periodic acid in methanol⁸⁶, but all the procedure tested revealed unsuccessful.



Scheme 48: Chiral auxiliary removal of compound **14b**, **14c** and **14e**

Therefore, we selected compounds **96a** and **96f** which display a more reactive benzylic position. Upon hydrogenation (1 atm) on Pd/C (10 mol %)

for 2h, chiral auxiliaries were successfully removed, leading to the formation of BINAM compound in up to 48% yield (**Table 7**).



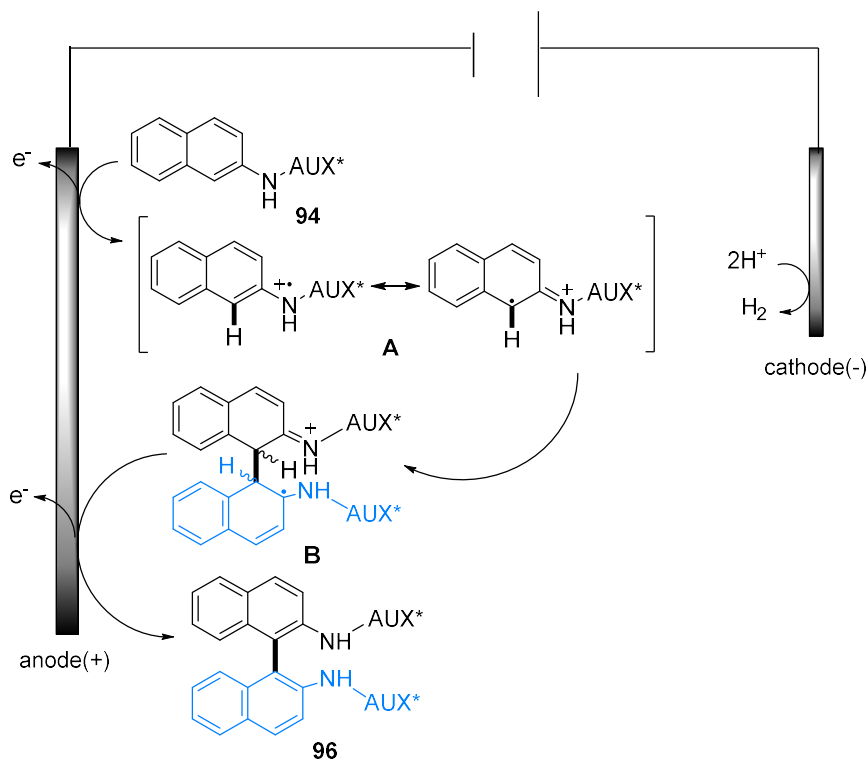
Entry	Starting Material	R	BINAM configuration	BINAM yield	[α] _D
1	96a.1	CH ₃	(R)	47	(+)
2	96a.2	CH ₃	(S)	40	(-)
3	96f.1	CH ₂ OH	(S)	48	(-)
4	96f.2	CH ₂ OH	(R)	48	(+)

Table 7: Hydrogenation of compound **14a** and **14f** to achieve BINAM enantiopure forms

Hydrogenation of compounds **14a.1** and **14f.2** led to the selective formation of the (*R*) enantiomer, while **14a.2** and **14f.1** yielded the (*S*) enantiomer. The optical purity and absolute configuration of the isolated compounds were determined using HPLC on a chiral stationary phase and by measuring their optical rotation.

2.2.4 HYPOTHESIZED MECHANISM

Following previous publications in the field,⁷⁰⁻⁷¹ a tentative mechanism has been proposed (**Scheme 49**). After a single electron oxidation of the amine, the radical cation **A** is produced. This latter can delocalize the unpaired electron on the most reactive position **1**. The interaction between this spiced and another molecule of naphthylamine, afford the intermediate **B** that by a further anodic oxidation is converted in the desired binaphthyl diamine. Redox balancing is obtained by hydrogen evolution at the cathode surface.



Scheme 49: Hypothesized mechanism

2.3 CONCLUSIONS

In conclusion, the stereoselective electrochemical dehydrogenative homo-coupling of β -Naphthylamines derivatives was successfully achieved.⁷⁵ Notably, the intermolecular coupling of chiral β -Naphthylamides bearing camphorsulfolnic (**68**), menthyloxyacetic (**69**) and *N*-Boc Proline (**70**) groups as chiral auxiliary, led to a C3-C3'-coupling adducts along with degradation by-products. Attempts to introduce a halogen at the 3-position of the β -Naphthylamine backbone, aimed at improving regioselectivity towards the 1-position, consistently resulted in halogenation at the more reactive C1 position.

Furthermore, the intramolecular homo-coupling of bidendate diamides, bearing succinyl (**71**), Phthalic (**72**) and tartrate (**73**) residue, which could ideally address the reaction towards the desired position, predominantly yielded intermolecular coupling derivatives and unreacted starting materials. Conversely, the electrochemical homo-coupling of chiral β -Naphthylamines derivatives **94a-h** proved to be the most effective strategy.

Under argon atmosphere and in presence of platinum electrodes and when operating at 5.5 mA, the desired C3-C3' coupled diastereoisomers were obtained in up to 47% yield and 45:55 of diastereomeric ratio.

The same approach was also extended to functionalized β -Naphthylamines bearing chiral aminoalchols. The best results in terms of diastereoselectivity were achieved when a *tert*-leucinol moiety was installed on the nitrogen atom, achieving the desired substrate in 83:17 of d.r. The introduction of a halogen atom at the 6-position further enhanced the diastereoselectivity, achieving a 96:4 diastereomeric ratio.

As the final objective, the chiral auxiliary was removed from the diastereoisomers **96a** and **96f** following separation by column chromatography, resulting in the efficient isolation of the desired enantiopure forms of BINAM.

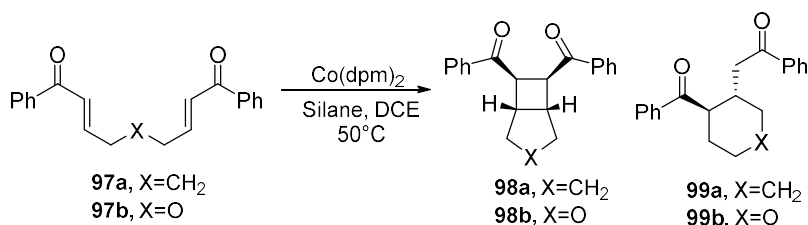
3 CHAPTER 3: STEREOSELECTIVE CYCLIZATION OF ARYL ENONES UNDER HOMOGENEOUS AND HETEROGENEOUS CONDITIONS

3.1 STEREOSELECTIVE CYCLIZATION OF ARYL ENONES: BACKGROUND

The photocyclization of aryl enones for the synthesis of highly functionalized cycloalkanes exemplifies such light-driven transformations, whereby the existence of a transition metal complex or an organic dye promotes the biscyclization of aryl enones under visible light exposure.

3.1.1 PRELIMINARY STUDIES ON THE METAL-CATALYZED CYCLIZATION OF ARYL ENONES

The first investigation on the aryl enone cyclization dates back to 2001, when Krische et al. proposed the first Cobalt catalyzed [2+2] cycloaddition of alkenes.⁸⁷ In particular, during the study of Michael cycloreduction, the authors found out that the nature and the equivalent of the silane employed, affect the reaction outcome (Table 1).



Substrate	Co(dpm) ₂ (equiv.)	Silane (equiv.)	Yield [2+2]	Yield Michael
97a	0.05	PhSiH ₃ 1.2	38%	41%
97a	0.05	PhSiH ₃ 2.4	-	73%
97a	0.10	PhMeSiH ₂ 4.0	72%	11%
97b	0.05	PhSiH ₃ 1.2	16%	31%
97b	0.05	PhSiH ₃ 2.4	-	63%
97b	0.10	PhMeSiH ₂ 4.0	69%	9%

Table 8: Cobalt catalyzed [2+2] cycloaddition of alkenes

As reported in the table, when 2.4 equiv. of PhSiH₃ were used, the Michael cycloreduction product **99** was the predominantly formed, while in presence of 4.0 equiv. of PhMeSiH₂ and 10 mol% of Cobalt catalyst only the product **98** derived from [2+2] cycloaddition was observed. In both cases, the isolated compounds were obtained as single diastereoisomer. Specifically, the photocycloaddition led to the *cis* bicycle according to the coordination model proposed in **Figure 28**.

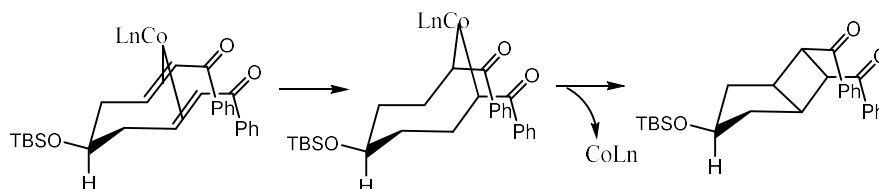
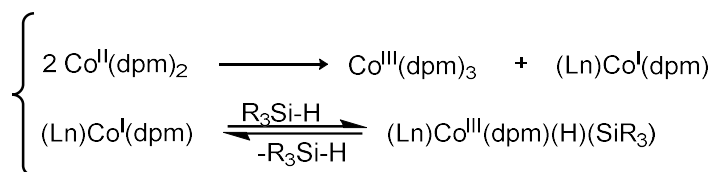


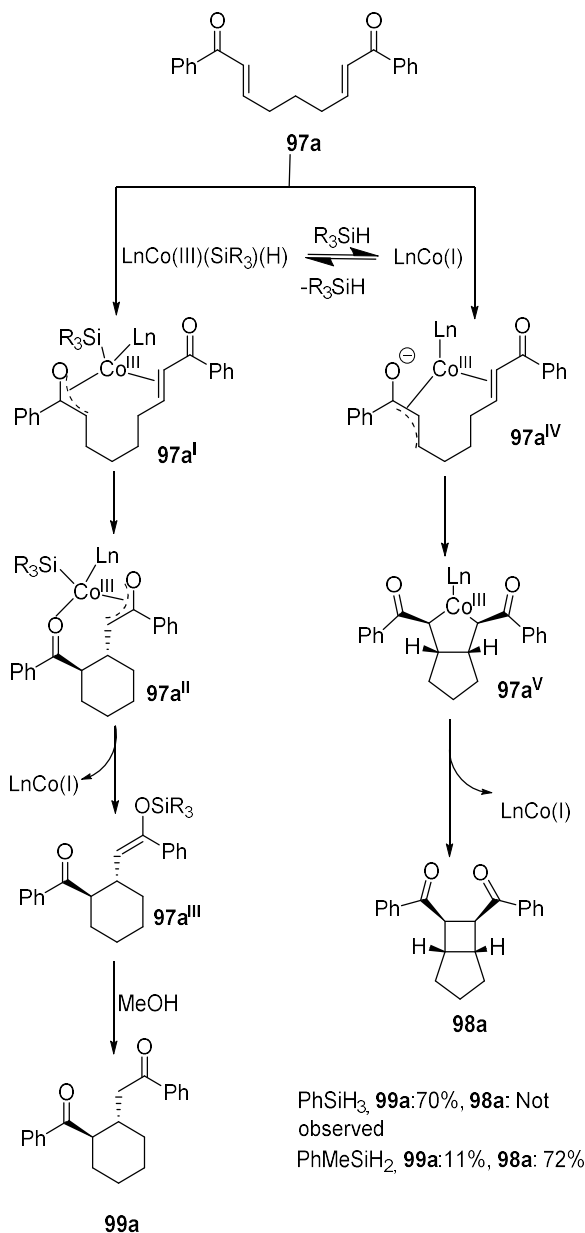
Figure 28: Structural model of cobalt-bisenone intermediates

Based on these results, it was found that the stereochemical outcome of the cycloaddition is independent of the initial alkene geometry. A deep investigation on the mechanism was then carried out in order to explain the different reaction behaviour observed according to the type of silane used.⁸⁸ The key step in these mechanistic pathways is the interaction between the catalyst and the silane. It is well-known that Tetrahedral d⁷-metal complexes such as Co(dpm)₂ (confirmed by X-ray analysis) undergoes single electron oxidative addition.⁸⁹ Additionally, the disproportionation of Co (II) is well documented.⁹⁰ Given these findings and the results of HR-MS analysis, the authors hypothesized that the first event of the mechanism was the disproportionation followed by a two-electron oxidative addition of silane to Co(I) (**Scheme 50**).



Scheme 50: Disproportionation of Cobalt (II) and oxidative addition of silane

According to that, a catalytic mechanism based on a Co(I)-Co(III) cycle was proposed. In particular an hydrometallative and a radical anion pathways were presented for the cycloreduction and the cycloaddition respectively (**Scheme 51**).

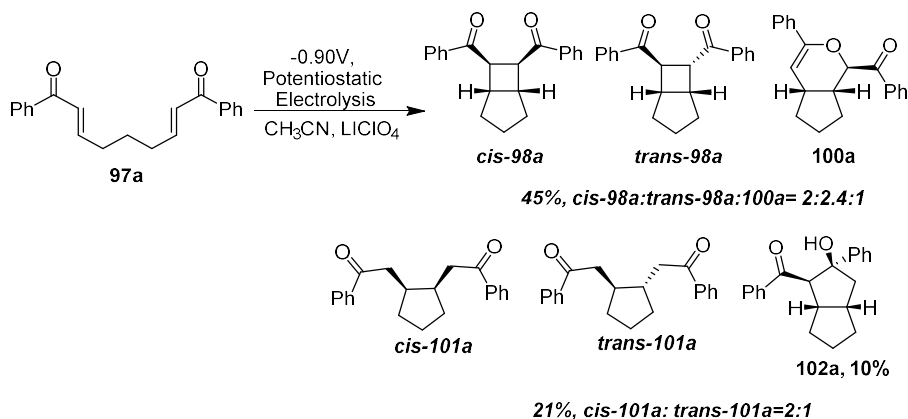


Scheme 51: Hypothesized mechanism of Michael cycloaddition and [2+2] cycloaddition

In the first pathway, the cobalt complex with phenyl silane promotes the hydrometallation of the aryl enone forming the enolate **97a^I**, which then undergoes carbonyl addition to provide cobalt-alkoxide **97a^{II}**. Oxygen-silicon reductive elimination liberates the aldol product in the form of the silyl enol ether **97a^{III}** and regenerates LnCo(I) to complete the catalytic

cycle. In the second mechanism, in the presence of methylphenylsilane, the oxidative addition of the secondary silicon center to the Co (I) is slower probably due to the steric hinderance of the incipient adduct and the [2+ 2] cycloaddition via formation of a Co(III)-oxy- π -allyl intermediate is promoted. This Co(III)-enolate **97a^{IV}** is subject to rapid π -facial interconversion. Equilibration of this intermediate should favour the isomer **97a^V** in which the benzoyl substituents reside on the convex face of the metallobicyclo ring system (as shown in **Figure 28**). Reductive elimination then provides the bicycle product with a *cis*-stereochemical relationship between the benzoyl moieties (**Scheme 51**-compound **98a**). Additional experiment demonstrates that the *cis*-stereochemistry of cycloadducts does not represent the thermodynamically preferred configuration since its exposure to either Brønsted or Lewis acid catalysts at 30 °C results in a conversion into the corresponding *trans*-isomer.⁸⁸

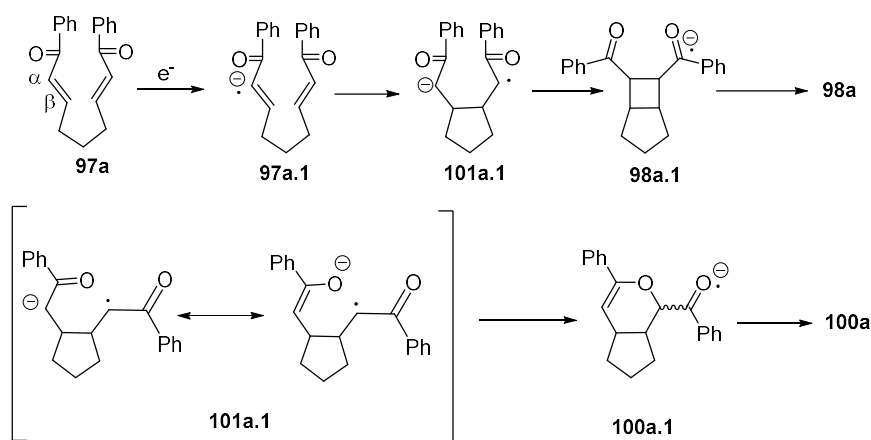
According to the mechanism proposed for the [2+2] cycloaddition, an anion radical intermediate is formed. With the aim to investigate this anionic pathway, the cycloaddition was carried out under electrochemical condition (**Scheme 52**) at voltage -0.9 V, the cathodic potential detected in the Cyclic voltammetry experiment of the aryl-enone.⁹¹



Scheme 52: Cathodic reduction of **97a**

As shown in **Scheme 52**, the potentiostatic reduction proceeded with an overall yield of 76% leading to the formation of different products. The ***Cis*-98a** and the ***trans*-98a** bicyclic product along with an unexpected hetero Diels-Alder type adduct **100a** were achieved in up to 45% yield. The formation of *cis* and *trans* cyclopentane **101a** isomers and the aldol type product **102a** were obtained in 21% and 10% yield respectively. According to the authors, the formation of the *cis* and *trans* bicyclic isomer suggests a stepwise

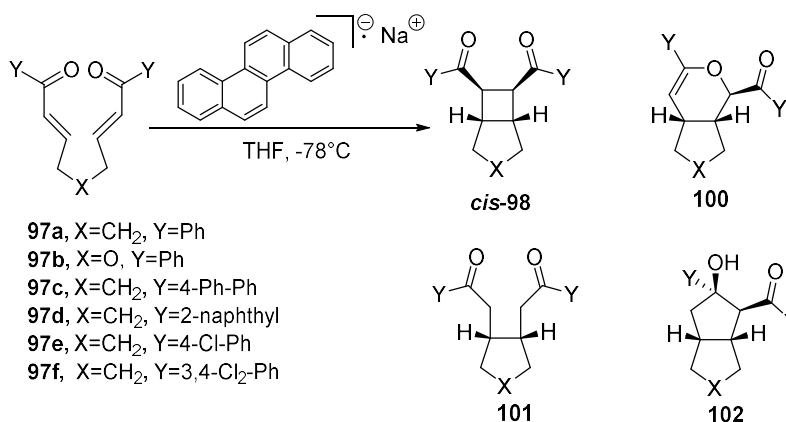
cycloaddition process involving distonic anion radical **101a.1** intermediate formed via β - β coupling of the monoanion radical **97a.1** (Scheme 22).



Scheme 53: Stepwise mechanism for anion radical cyclobutanation

The distonic anion radical of **101a** (**101a.1**) contains both enolate anion and enolyl radical moieties and is subject to α - α coupling to yield the anion radical of **98a** (**98a.1**). This coupling is energetically feasible by the presence of the benzoyl moiety owing to delocalization of the anion radical onto both the carbonyl and phenyl moieties. Instead, the “formal Diels-Alder” adduct **100a**, derives from the coupling between the enolate oxygen and the α -carbon of the enolyl radical **101a** (**101a.1**). The authors also proposed that the reaction undergoes by a chain propagation which is achieved by an exergonic electron transfer from the radical anion **98a** (**98a.1**) to **97a**.

Based on these results, in 2004, the anion radical cycloaddition induced by an homogeneous electron transfer from chemical agent was investigated.⁹² Specifically, the exposure of bis(enone) **97** to chrysenes anion radical at -78 °C in THF results in the formation of the *cis*-**98** [2 + 2] cycloaddition product and the [4+2] cycloaddition Diels-Alder adduct **100** as single stereoisomers, following the same mechanism reported for the electrochemical transformation which undergoes through the distonic radical formation. The simple reductive cyclization product **101** and the reductive cyclization-aldolization product **102** are also obtained (Table 9).



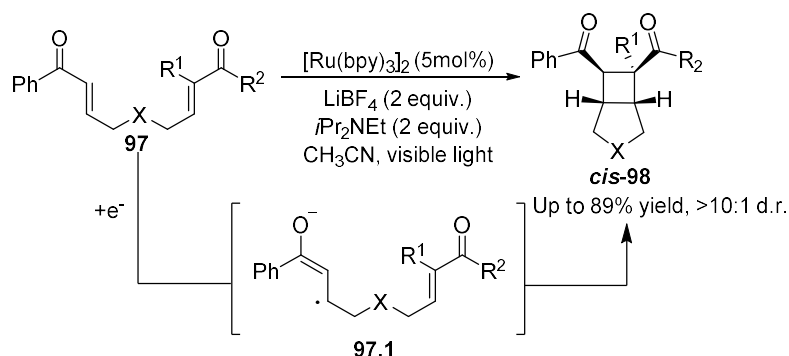
Substrate	<i>cis</i> - 98 (yield%)	100 (yield%)	101 (yield%)	102 (yield%)
97a	31.5	9.2	2.9	20.1
97b	35.0	5.0	-	35.8
97c	60.4	-	4.0	14.0
97d	61.7	-	10.0	18.0
97e	50.8	9.8	16.4	16.4
97f	41.4	4.0	6.2	8.0

Table 9: Bisenone reduction using chrysenesene anion

As shown in **Table 9** aryl enone substituents affect the selectivity of the reaction. In particular, it can be noted that the yields of *cis*-**98** are modest in the case of substrates **97a** and **97b** because of the competing formation of **100**, **101** and **102**. When the benzoyl substituents of **97a** are replaced by acetyl or carboethoxy groups (not shown), neither cyclobutane nor Diels-Alder products are formed, since the second bond-forming step (α - α coupling) would then require placement of the anion radical moiety in the LUMO of an acetyl or ester group, which is much higher in energy than the LUMO of a benzoyl group. According to this assumption, the introduction of a substituent which stabilize the radical anion in a lower energy LUMO, could enhance the rate of the second C-C bond formation and address the reaction towards the bicycle products. This hypothesis was investigated introducing moieties which provide a more extensive delocalization of the radical anion (**97c**, **97d**). As assumed, the generation of the bicycle product is observed in 62% yield.⁹²

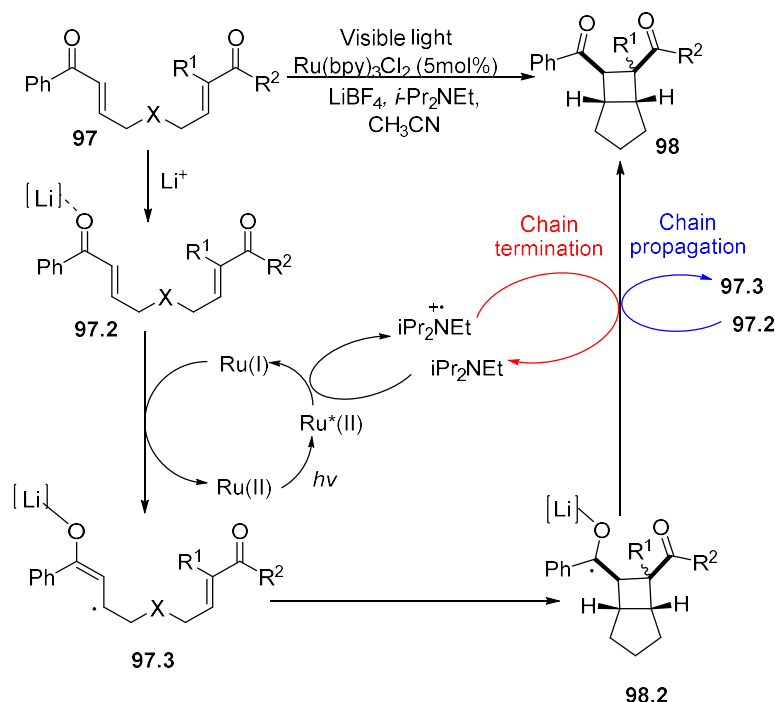
3.1.2 RUTHENIUM-CATALYSED PHOTOCYCLIZATION OF ARYL ENONES

In the previously mentioned work, Krische reported that catalyzed [2+2] cyclizations of bis(enones)⁸⁷ starts by a single electron reduction of the enone operated by the Cobalt-based photocatalyst. This was also confirmed by further investigation, in which the same radical anion intermediate was obtained upon cathodic⁹¹ and homogeneous⁹² reduction. Inspired by these papers, in 2009 Yoon et al. investigated the single electron reduction of the aryl enone under photochemical conditions in presence of $\text{Ru}(\text{bpy})_3^{2+}$ as photocatalyst (**Scheme 54**).⁹³



Scheme 54: [2+2] aryl enone cycloaddition under photochemical conditions

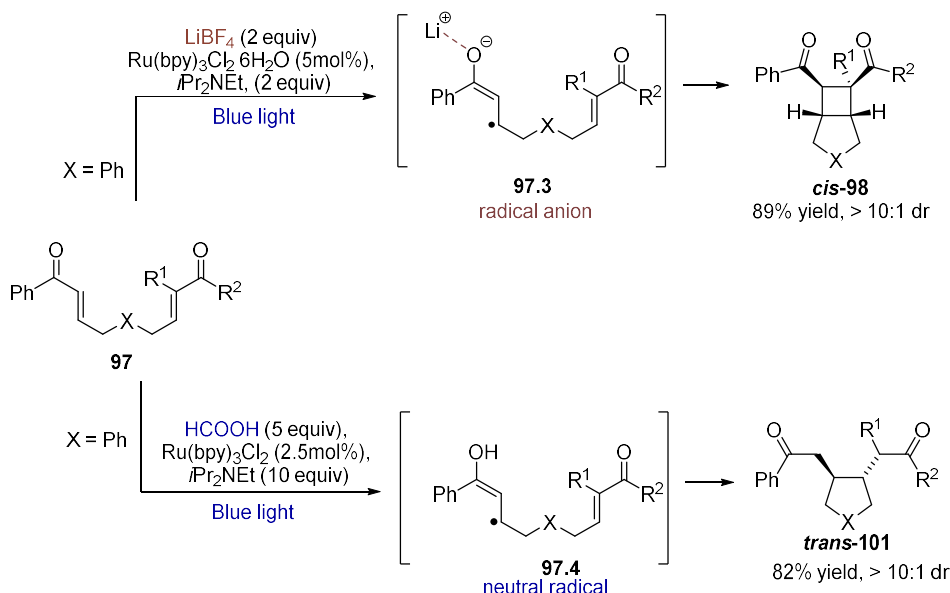
The photochemical transformation led to the *meso* bicyclic diastereoisomer **98** in excellent yield and diastereoselectivity. Different experiments showed that lithium cation was also essential for successful cycloaddition; replacement of the LiBF_4 additive with either $\text{Bu}_4\text{N}^+\cdot\text{BF}_4^-$ or NaBF_4 resulted in a homogeneous reaction mixture but led to no observable consumption of enone **97**. This suggests that the lithium cation functions as a Lewis acid in this reaction and likely activates the enone toward one-electron reduction.⁹⁴ A series of structurally varied enones were tested under optimized conditions: excellent results were obtained in presence of symmetrical aryl enones bearing electron donating and electron withdrawing groups, while no cyclization was observed with aliphatic enones or enotates. A reaction mechanism was proposed (**Scheme 55**).



Scheme 55: Proposed mechanism for photocatalytic reductive coupling in presence of $\text{Ru}(\text{bpy})_3]^{2+}$ as photocatalyst

The reported pathway starts from reductive quenching of photoexcited $\text{Ru}^*(\text{bpy})_3]^{2+}$ by $i\text{-Pr}_2\text{NEt}$. This step produces $\text{Ru}(\text{bpy})_3]^+$, which reacts with Lewis's acid-activated enone **97.2** in a one-electron reduction process to generate the key radical anion **97.3**. The enone radical anion then undergoes [2 + 2] cycloaddition to afford the cyclobutyl ketyl radical **98.2**, which loses an electron to generate the neutral product **98**. This final product could either be achieved by a chain-terminating reduction of photogenerated amine radical cation $i\text{-Pr}_2\text{NEt}^+$, or by a chain-propagating reduction of another equivalent of Li-activated enone **97.2**.

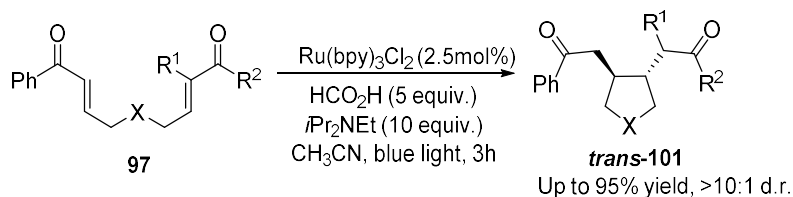
Starting from this pioneer work, in 2011, the author found out that the reaction proceeds through different pathways depending on whether a Lewis acid or a Brønsted acid additive is present (**Scheme 56**).⁹⁵



Scheme 56: Different reaction pathways in presence of Lewis and Brønsted acids.

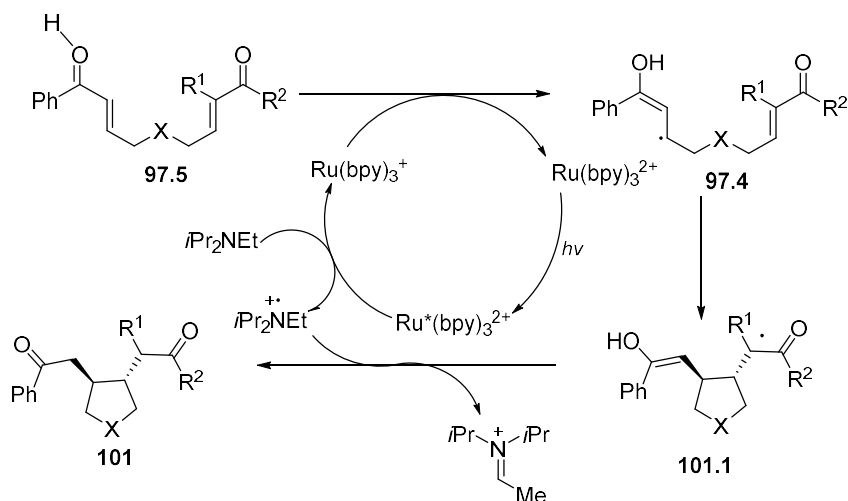
- The presence of Lewis acids (non protic conditions) lead to a *cis*-bicycle product through a [2+2] cycloaddition with a radical anion as intermediate, stabilized by Li^+ .
- The presence of Brønsted acid (protic conditions) lead to a *trans* cyclopentane through a reductive cyclization with a neutral radical intermediate, promoted by the hydrogen transfer.

Thus, the effect of Brønsted acid additives on the photocatalytic one-electron reduction was studied and reaction condition optimization was implemented for the stereoselective synthesis of the *trans* cyclopentanes derivatives **101** (Scheme 57).



Scheme 57: Metal-catalyzed reductive cyclization of aryl enones

A library of different enones were tested under the optimized conditions and, contrary from the [2+2] cycloaddition, aliphatic bisenones underwent reductive cyclization in high yields, although these substrates required extended reaction times. (Scheme 58).

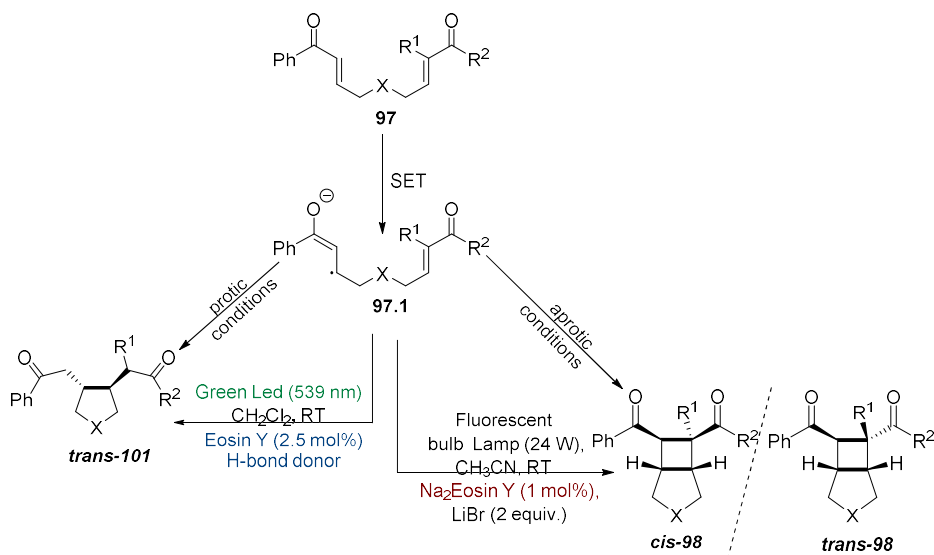


Scheme 58: Hypothesized mechanism of reductive cyclization of aryl enones with Brønsted acid.

According to this pathway, visible light irradiation of $\text{Ru}(\text{bpy})_3^{2+}$ generates a photoexcited state ($\text{Ru}^*(\text{bpy})_3^{2+}$) that can be reductively quenched by *i*- Pr_2NEt to afford an amine radical cation ($i\text{-Pr}_2\text{NEt}^{\bullet+}$) and a $\text{Ru}(\text{bpy})_3^+$ complex. This latter can transfer an electron to the protonated oxocarbenium ion **97.5** producing the key neutral radical intermediate **97.4**, which undergoes 5-exo-trig cyclization to yield α -ketoradical **101.1**. Hydrogen atom transfer from the photogenerated amine radical cation, would then afford the reductive cyclization product **101**.

3.1.3 METAL-FREE PHOTOCYCLIZATION

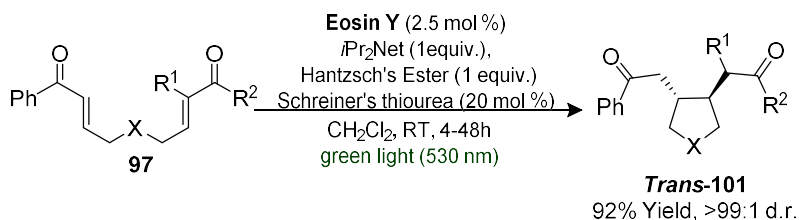
In 2013, the aforementioned cyclizations reported by Yoon in 2008 and 2011, have been investigated by Zeitler group. In particular, metal free approaches were developed which replace the Ru (II) and Ir (III) catalysts with the organic dyes Eosin Y and $\text{Na}_2\text{Eosin Y}$ (**Scheme 59**).

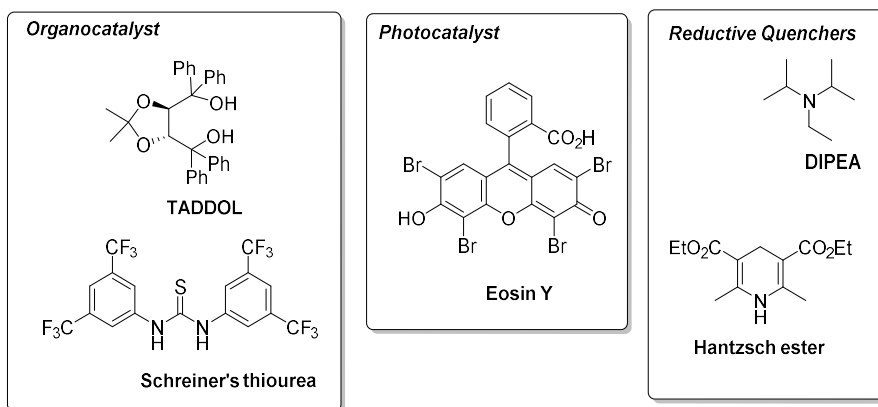


Scheme 59: Metal-free cyclization under protic and aprotic conditions.

Differently from Yoon transformation, under aprotic conditions, the **trans-98** bicyclic product was achieved in excellent yield and diastereoselectivity using $\text{Na}_2\text{Eosin Y}$ as photocatalyst. According to the author, LiBr along with milder reaction condition respect to those employed by Yoon (26 W of irradiation with Fluorescent Bulb Lamp instead of 275 W of irradiation with GE Sunlamp), results in the formation of the *Trans* thermodynamic product as major product.⁹⁶ As shown by Yoon, when the photochemical cyclization is carried out under protic conditions, the **trans-101** cyclopentane ring is selectively obtained. Zeitler group developed a photoredox multicycatalytic strategy for this transformation (**Scheme 60**), combining the activity of a photocatalyst, like Eosin Y with an organocatalyst as Schreiner's thiourea. Also, different reductive quenchers have been tested and the use of Hantzsch ester with *i*- Pr_2NEt gave the best result in terms of time and yield.

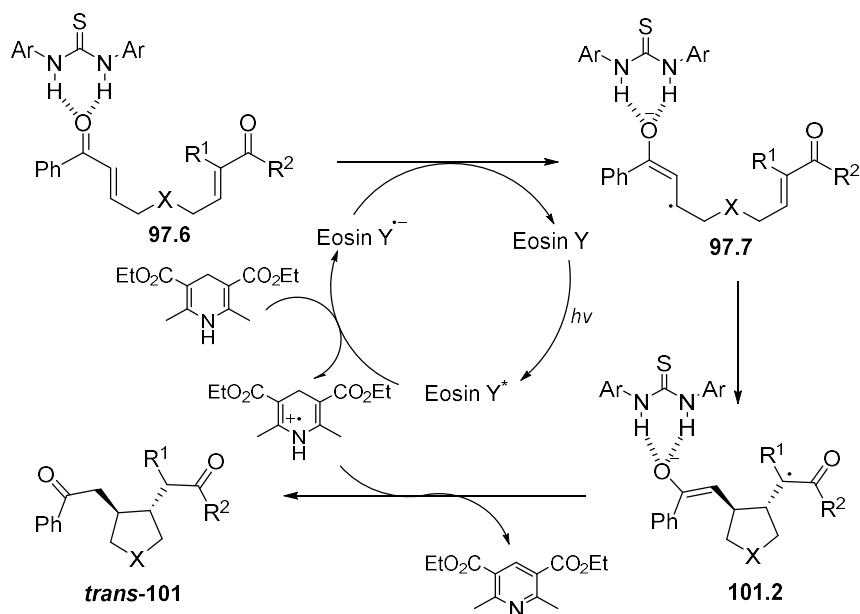
96





Scheme 60: Photoredox multicycatalytic strategy for the synthesis of trans cyclopentane rings.

Symmetric and Non-symmetric Electron-rich, electron-poor and heteroaryl enones proved to be suitable substrates for this transformation. Also, a variety of α,β -unsaturated carbonyl compounds showed good to excellent acceptor properties as a function of their electrophilic character.^{93,95,96} Unfortunately, the use of chiral hydrogen bond donor, such as chiral thioureas and TADDOL, to induce enantioselectivity was unsuccessful. The mechanism proposed is shown in **Scheme 61**.



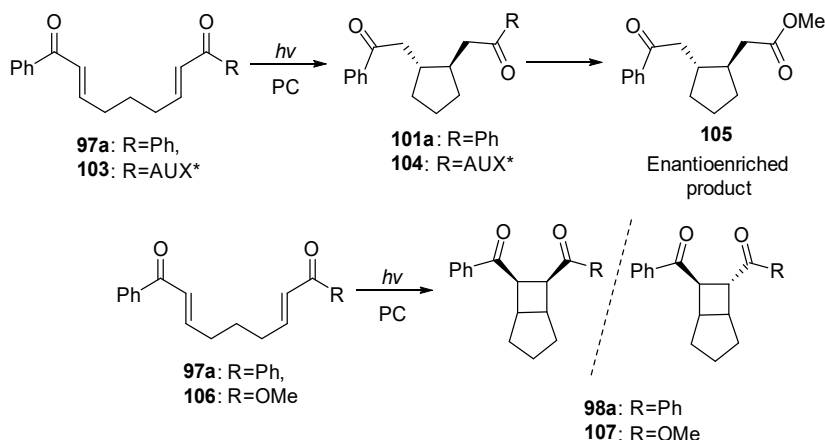
Scheme 61: Proposed mechanism of cooperative reductive cyclization in presence of Eosin Y as photocatalyst

After irradiation with visible green light at 530 nm, the excited state of Eosin Y undergoes a SET reductive quenching with *i*-Pr₂NEt or Hantzsch's ester (HEH) to generate the corresponding Eosin Y radical anion and the amino radical cation. The radical anion of Eosin Y in its photoexcited state is a strong reducing agent and can promote a SET with the hydrogen bond activated unsaturated arylketone **97.6**, thus restoring the photocatalyst. The resulting 1,4-distonic radical anion **97.7** undergoes to a 5-*exo-trig* cyclization generating a stabilized α -carbonyl-radical **101.2**, that can be trapped by direct hydrogen transfer from the radical cation of the reductive quencher to release the cyclopentane product ***trans*-101**. It is possible to assume that the hydrogen bond donor has a double role: to activate the enone towards SET by hydrogen bonding, and to promote the transfer of protons to selectively obtain the monocyclic product.⁹⁶

3.2 STEREOSELECTIVE PHOTOCYCLIZATION OF ARYL ENONES: RESULTS AND DISCUSSION

As shown in the previous section, visible light can be efficiently employed as an efficient and green method for the cyclization of aryl enones, leading to the stereoselective formation of cyclopentanes and bicyclo[3.2.0]heptanes. On the basis of this literature background, we aimed to extend this approach to the synthesis of enantiomerically enriched functionalized cyclopentane rings, while retaining the same mechanism to achieve high stereoselectivity.

The use of chiral catalysts is the most attractive option,⁹⁷ but the setup of a successful chiral photocatalytic system is a very challenging task. We thought that the use of a chiral auxiliary on the bisenone to be cyclized could offer a straightforward and convenient option to exert a stereocontrol on the light-driven cyclization. The removal of the auxiliary, that can be conveniently recovered, would afford enantiomerically enriched cyclopentanes and bicycloheptanes rings (**Scheme 62**).



Scheme 62: Photochemical approach for the enantioselective synthesis of *trans* cyclopentane rings and bicycloheptanes

3.2.1 PHOTOCHEMICAL SET-UP

All the presented works have been performed using the two home-made photoreactors, depicted in the **Figure 29** below.

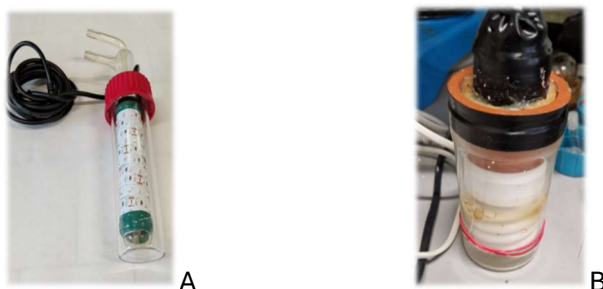


Figure 29: A. Photoreactor#1, B. Photoreactor#2

Photoreactor#1 (**Figure 29-A**) is a homemade system characterized by LEDs strip (530 nm, 424 mW/cm²) wrapped around a central sublimator glass-piece. The central sublimator glass-piece is first wrapped to the desired length with heavy duty aluminium foil to generate a socket for the LED-strip that possesses high heat conductive properties. Around this first layer is then coiled and glued (doublesided adhesive tape) the LED-strip which is further secured in place at the top and bottom with electric isolating tape. The cable is guided through the silicon rubber seal by puncturing it. In all the experimental setup, the reaction vessel is directly attached to the external photoreactor surface. The irradiation from photoreactor#1 raised the

reaction mixture to 40 °C; this temperature was consistently maintained over all the irradiation period.

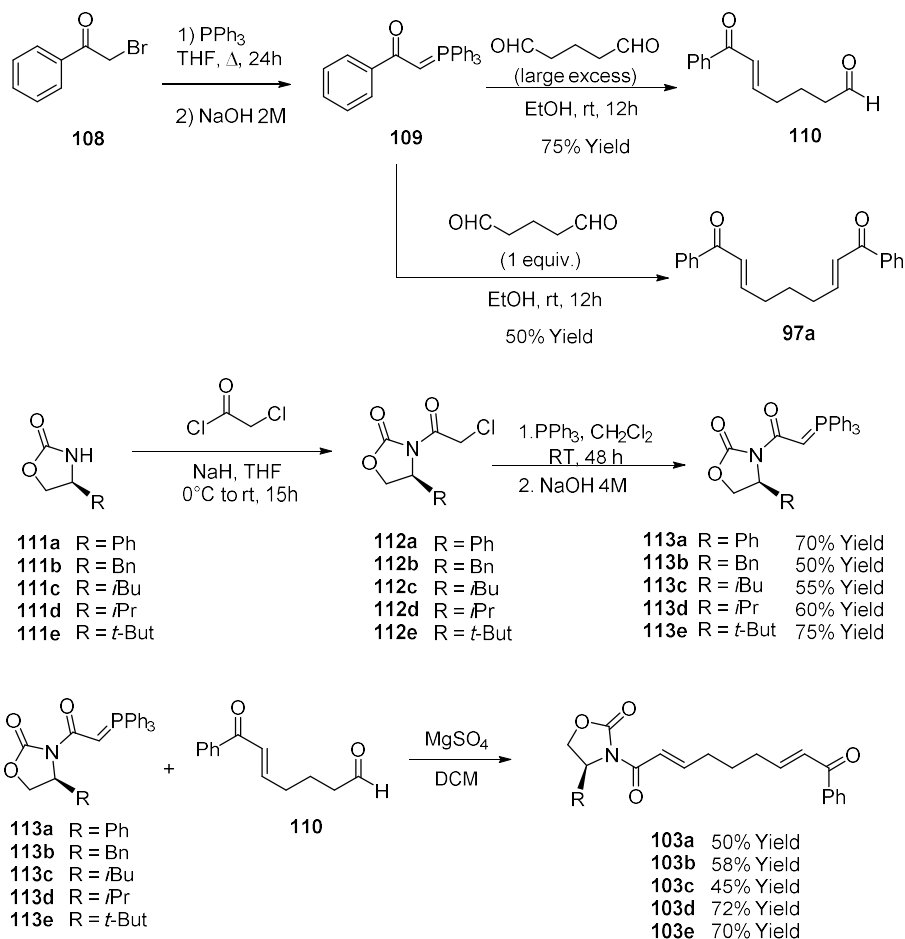
Photoreactor#2 consists of a commercially available fluorescent bulb lamp (CFL) of 24 Watt (**Figure 29-B**). Similar to previous configurations, the reaction vessel was directly attached to the external surface of the photoreactor. To prevent overheating, two external cooling system can be adopted. In one case, the entire setup is immersed in a thermostated water bath, typically maintained at 40 °C, to regulate the temperature. Alternatively, an external fan can be used to keep the solution at a stable temperature of 26 °C.

It is worth noting that even if these photoreactors are home-made, due to the simplicity of the design and the availability of common materials, these setups can be easily reproduced in various laboratories, ensuring a high level of standardization and accessibility for similar experiments.

3.2.2 ENANTIOSELECTIVE SYNTHESIS OF *TRANS*-1,2-CYCLOPENTANE RINGS

In 2021, we started our investigation on the photocyclization of aryl enones. In particular, we focused our attention on Zeitler's approach where the activity of Eosin Y as photocatalyst was combined with Schreiner's thiourea as organocatalyst and two reductive quenchers like Hantzsch's ester and *i*-Pr₂NEt (**Scheme 60**). Starting from this point, we envisioned the possibility to develop an enantioselective route to obtain enantioenriched *trans*-1,2-cyclopentane rings. The development of a stereoselective version of such transformation was then investigated in the presence of the metal-free catalyst Eosin Y and using a chiral auxiliary directly bounded on the bisenone to be cyclized. The removal of the auxiliary, that can be conveniently recovered, would afford enantiomerically enriched cyclopentanes.

We initiated our study by synthesizing phenyl bis-enones **103a-103e** incorporating various chiral oxazolidinones (**Scheme 63**). This approach aimed to evaluate the chemical compatibility of the chiral auxiliaries under photoredox conditions and to assess their effectiveness in controlling the stereochemical outcome of the cyclization.



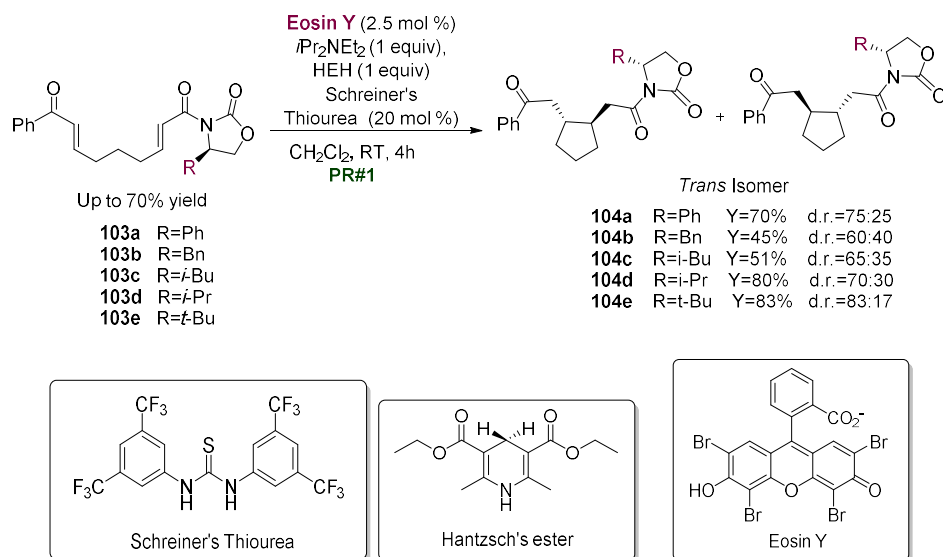
Scheme 63: Overall synthesis of aryl-enones bearing chiral auxiliary

Bromo Acetophenone **108** reacted with PPh_3 under anhydrous condition to form the Ylide **109** which, upon a Wittig reaction with a large excess of glutaraldehyde, afforded the common monoaldehyde **110** in 75% yield. When the reaction was performed with stoichiometric amount of glutaraldehyde, symmetrical bisenone **97a** was formed in 60% isolated yield.

At the same time, commercially available chiral oxazolidinones **111a-111e** bearing respectively phenyl, benzyl, isobutyl, isopropyl and tert-butyl groups, were acylated with chloro acetyl chloride in presence of NaH as base at 0°C , giving the desired products (**112a-112e**) in up to 99% yield. As reported for Bromo acetophenone, chloroacylated compounds **112a-112e** treated with PPh_3 furnished compounds **113a-113e** in up to 75%. The phosphorous ylides obtained were reacted according to a Wittig reaction

with aldehyde **110** affording the enantiopure bisenones **103a-103e** in 50-70% yield.

Based on the experimental conditions reported by Zeitler the cyclization of derivatives **103a-e** was then studied in the presence of light (green LED at 530 nm) and Eosin Y using Photoreactor#1. In a 10 ml Schlenk tube equimolar amounts of the bisenone, *i*Pr₂NEt and Hantzsch ester, in the presence of 1,3-bis(3,5-bis(trifluoromethyl)phenyl)thiourea (0.2 equiv.) and 2.5% of Eosin Y in CH₂Cl₂ were irradiated for 4 h using green LEDs. The diastereoisomeric ratio of the two *trans* diastereoisomers was evaluated by H-NMR of the crude.



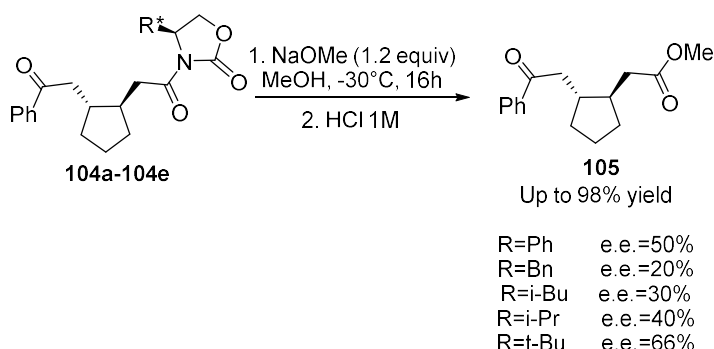
Scheme 64: Photocyclization of aryl-enones bearing chiral auxiliaries

As shown in the **Scheme 64**, the cyclization of compound **103a**, featuring the (*S*)-4-phenyloxazolidinone ring, produced *trans* cyclopentane **104a** in 70% yield and 75:25 diastereoisomeric ratio. The use of other chiral oxazolidinones in compounds **103b-d** did not lead to any improved diastereoselectivity. However, the reaction of bisenone **103e**, featuring the (*S*)-4-*t*-butyloxazolidinone, led to the formation of cyclopentane **104e** in 80% yield, as single *trans* isomer and 83/17 diastereoselectivity. With these data in hands, we proposed that the steric hindrance of the substituent on the oxazolidinone ring is responsible for the observed selectivity, since tert-butyl oxazolidinone which presents the most steric hindered substituent gives the best results in terms of yields and diastereoselectivity. Moreover, we need to underlie that many different orientations in the space are possible for the chiral auxiliary moiety, therefore we tested some chelating

metal to “lock” the auxiliary in a well-defined conformation. Unfortunately, no improvements have been observed.

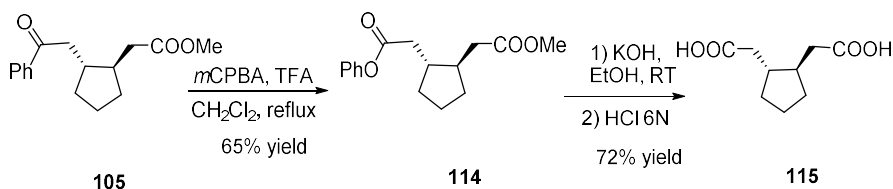
Chiral auxiliary removal and determination of absolute configuration

The removal of the chiral auxiliary was realized by reaction with sodium methoxide in methanol at -78°C ⁹⁸ to give in excellent yield the enantiomerically enriched cyclopentane **105** (**Scheme 65**). The enantiomeric excess was evaluated by HPLC analysis on chiral stationary phase and confirmed the diastereoisomeric ratio evaluated by NMR. The best results was observed with the chiral *tert*-butyl oxazolidinone, which afforded the methyl ester derivative in 66% of enantiomeric excess.



Scheme 65: Chiral auxiliary removal with basic conditions

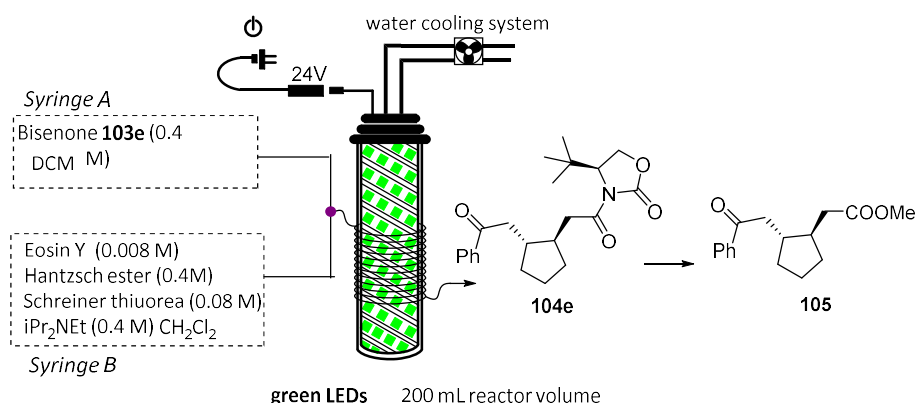
The absolute configuration of the major enantiomer of cyclopentane **105** was established by chemical correlation (**Scheme 66**). Bayer-Villiger oxidation⁹⁹ of **105** led to the diester derivative **114**, that was hydrolyzed to 2,2'-(cyclopentane-1,2-diyl)diacetic acid **115**, whose absolute configuration was established to be (1*R*,2*R*) by comparison of the sample optical rotatory power with the data reported in literature.¹⁰⁰



Scheme 66: Bayer-Villiger oxidation of compound **105** and basic hydrolysis of compound **114**

Photoreductive cyclization of aryl enones under flow conditions.

The advantages and the beneficial effects of performing a light-driven transformation in flow, and the possibility to overcome the well known limitations of the in batch reactions are well documented.¹⁰¹ Therefore, we decided to perform the cyclization of bisenone **103e** in a homemade coil photoredox reactor, using photoreactor#1.



Scheme 67: Photocyclization of aryl enones under flow conditions

In the displayed experiment (**scheme 67**), syringe A was filled with a 0.4 M solution of bisenone **103e** in CH₂Cl₂ (total volume 500 μ l). Syringe B was filled with a mixture obtained dissolving 0,004 mmol of Eosin Y, 0.2 mmol of Hantzsch ester, 0.04 mmol of Schreiner thiourea and 0.2 mmol of *i*PrNEt₂ in CH₂Cl₂ (total volume 500 μ l). Syringes A and B were connected to a syringe pump and the reagents were fed into PFA reactor through a T-junction at the desired flow rate (6.66 μ L/min for 30 min residence time and 5 μ L/min for 40 min residence time) at room temperature. One reactor volume was discarded before starting sample collection in order to achieve steady-state conditions. Reaction outcome was collected in the dark into a vial and the crude was purified by column chromatography.

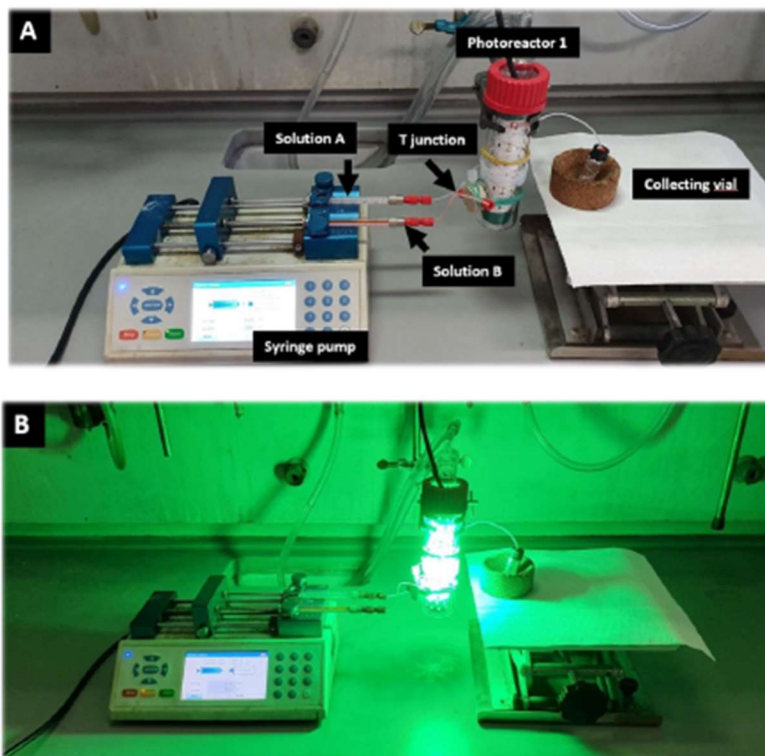
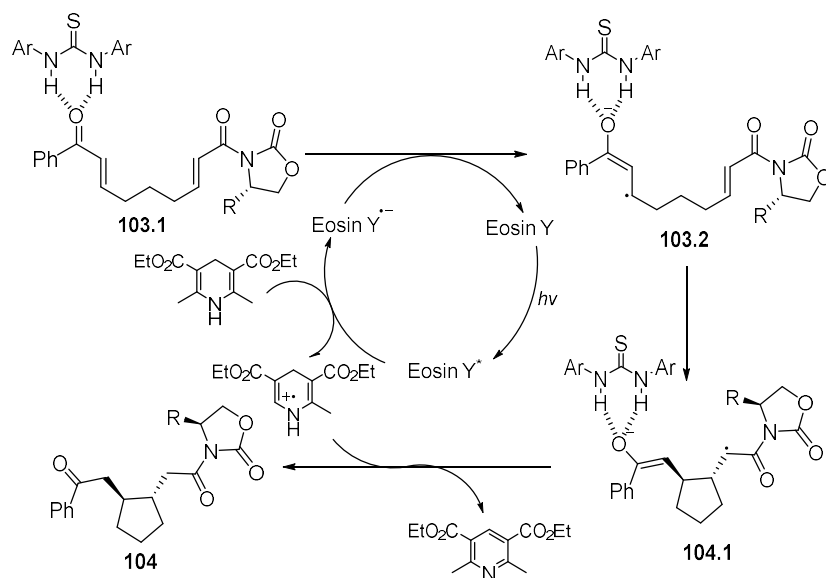


Figure 30: Reaction setup using homemade coil photoreactor. A) Device with green LEDs off, B) Device with green LEDs on.

We were pleased to find out that under continuous flow conditions product **104e** was obtained with the same diastereoselectivity as the batch reaction, as demonstrated by conversion of **104e** to ester **105** and determination of e.e. by HPLC analysis. With 30 minutes residence time, 65% conversion was observed and **104e** was produced in 45% isolated yield; however, operating with a residence time of 40 minutes, a 90% conversion and 87% isolated yields were observed.

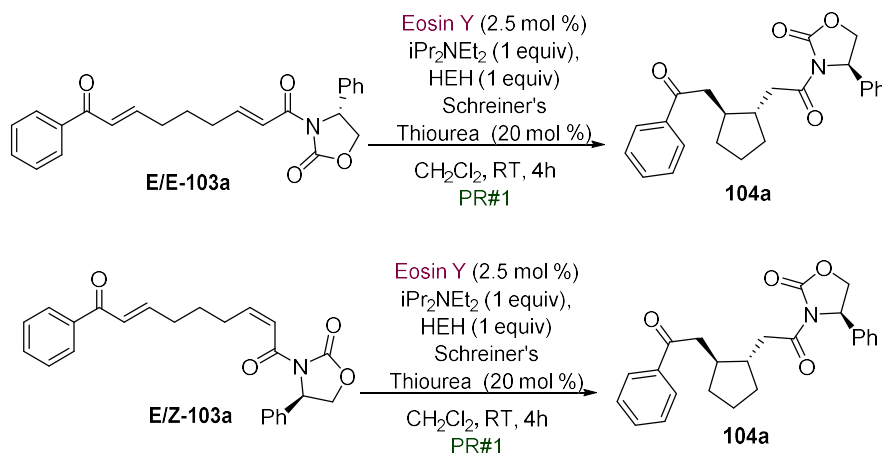
Proposed mechanism

Since no modifications in the reaction conditions were adopted respect with Zeitler's protocol,⁹⁶ we assumed the same mechanistic pathways of the photoreductive cyclization of symmetric and non-symmetric achiral aryl enones. However, the presence of the chiral oxazolidinone directly connected on the bisenone could address the 5-exotrig cyclization (**scheme 68**-intermediate **104.1**) towards the predominant formation of one of the two diastereoisomers.



Scheme 68: Photoreductive cyclization with aryleneone bearing the chiral oxazolidinone

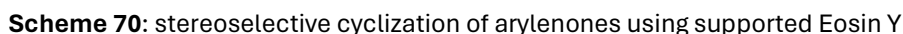
Additional experiments were carried out in our group to understand the influence of double bond stereochemistry of the aryleneone on the photocyclization. Bisenone **103a** E,E and E,Z bearing the Phenyl oxazolidinone were isolated and tested under Zeitler's conditions (**Scheme 69**).



Scheme 69: Photocyclization under Zeitler's conditions of Bisenone **103a** E,E and E,Z bearing the Phenyl oxazolidinone

This is most probably due to the orientations of the chiral auxiliaries in the two isomers. In the E/E substrate **103a** the oxazolidinone is in an external conformation, hence lowering the stereo control on the reactive site, while the E/Z isomer allows the chiral auxiliary to be closer to the reactive site, favouring stereoselection. This preliminary result set the basis for new investigations on substrate conformation on the stereoselectivity of the process.

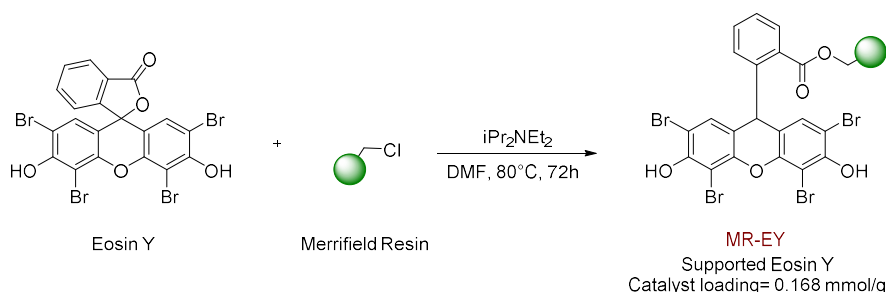
Although photocatalytic transformations afford the products with good chemical and stereochemical efficiency, the separation of the product from the photocatalyst usually requires long chromatographic purifications. Furthermore, none of the previous cited works related to photocyclization of bisenones describe a recycling procedure. Therefore, taking into account the results achieved for the synthesis of *trans*-1,2-cyclopentane under homogeneous conditions,¹⁰² we decided to investigate this transformation in presence of photocatalyst Eosin Y supported on polymeric matrix (**Scheme 70**).^{103,104,105}



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Synthesis of the supported photocatalyst

We selected Merrifield Resin as polymeric matrix where support Eosin Y. This resin is a terpolymer of styrene and 4-vinylbenzylchloride with divinylbenzene as a crosslinker which have found many applications in solid phase peptide synthesis. The immobilization of Eosin Y onto Merrifield resin was performed according to a literature procedure,¹⁰⁵ where 1.0 equiv of Eosin Y in its inactive form undergoes deprotonation by 2 equiv of *i*Pr₂NEt and reacts in a nucleophilic pathway with Merrifield-Resin High-Load 100–200 mesh at 80 °C for 72h (**Scheme 71**)

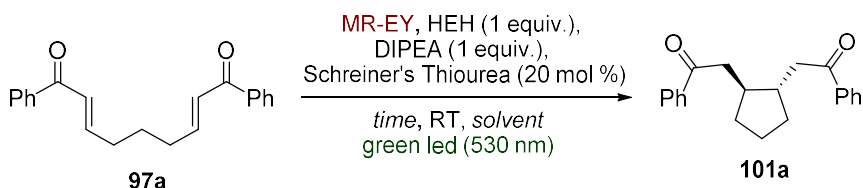


Scheme 71: Synthesis of Supported Eosin Y

Following this procedure, 20 g of supported catalyst were synthesized. The chemical composition of the new material was investigated and it was found that the loading of the material was 0.168 mmol/g, as determined by weight difference and confirmed by elemental analysis (see Experimental Part).

Reaction condition optimization

With the supported catalyst in hands, we selected the photocyclization of the symmetric bisenone **97a** as model reaction for a preliminary investigation of MR-EY activated by green light. Photoreactor#1 was used for this study. 1 equiv. of compound **97a** was dissolved in 0.8 mL of the desired solvent (0.2 M) and reacted in the presence of 1 equiv of *i*Pr₂NEt, 1 equiv of Hantzsch ester and 20 mol% of Schreiner thiourea under vigorous stirring, according to Zeitler's conditions.⁹⁶



Entry	MR-EY (mol %)	Solvent	Time (h)	Isolated yield (%)
1	-	CH ₂ Cl ₂	5	-
2	3	CH ₂ Cl ₂	5	53
3	5	CH ₂ Cl ₂	5	37
4	5	CH ₃ CN	18	54
5 ^a	5	CH ₃ CN	18	-

^aReaction performed using MR-EY catalyst derived from entry 2

Table 10: Screening of the reaction condition

According to the results reported in **table 10**, it was found that the substrate remains unchanged when irradiated in the absence of the catalyst (**entry 1**), whereas compound **101a** was isolated by chromatographic purification in 53 % yield as a *trans*-isomer after 5 h reaction time using dichloromethane as a solvent in the presence of 3 mol% of MR-EY (**entry 2**). Increasing the amount of MR-EY catalyst from 3 mol% to 5 mol% was not beneficial, and yield dropped to 37 % (**entry 3**). One possible explanation of this behaviour is related to the fact that the heterogeneous catalyst remains undissolved. Also, despite the increment in the catalyst loading, the vial surface exposed to light remains unchanged. Consequently, the intensity of light which irradiate the solution and activating the catalyst is reduced compared to the condition with a 3% catalyst loading, resulting in incomplete irradiation of the entire catalyst mass. Switching to Acetonitrile the desired product was obtained in comparable yields (**entry 4**), even if long reaction times were required. In addition to the isolated product, it is noteworthy that in all instances, the unreacted compound **97a** was recovered after chromatographic purification and, as reported, the formation of the *cis*-1,2-cycloalkane was never observed.⁹⁶ Unfortunately, despite these encouraging preliminary results, the supported catalyst was recovered as a light yellow solid (**Figure 31-B**), which was completely inactive in the subsequent recycling test (**entry 5**).

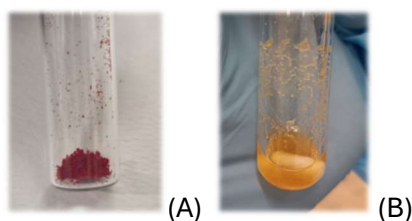
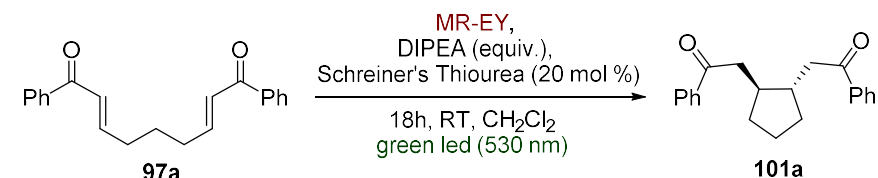


Figure 31: Supported Eosin Y before (A) and after the reaction (B)

We hypothesized that the colour change of the catalyst (from red to yellow-**Figure 31 A-B**) could be ascribed to catalyst deactivation process or

leaching. Therefore, we continued our investigation in the reaction condition with the aim to verify the effect of Hantzsch's ester or *i*Pr₂NEt on the supported catalyst.

At first, compound **97a** was subjected to light-driven reductive cyclization promoted by MR-EY catalyst in the presence of *i*Pr₂NEt but in the absence of Hantzsch ester (**Table 11**).



Entry	<i>i</i> Pr ₂ NEt (equiv)	MR-EY (mol %)	Yield (%) ^a
1	1	5	traces
2	2	3	50
3	2	5	32 ^b
4 ^c	2	5	-

^a Calculated by ¹H NMR using 1,3,5-trimethoxybenzene as internal standard.

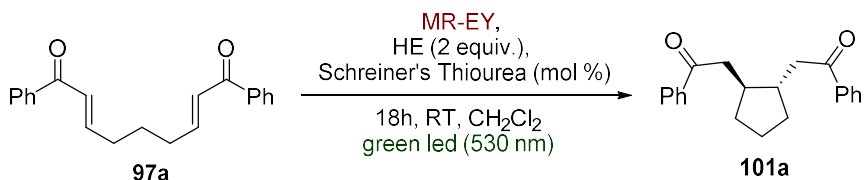
^b Confirmed by chromatographic purification

^c Reaction performed using MR-EY catalyst derived from entry 2.

Table 11: Cyclization of **97a** promoted by supported Eosin Y in the absence of Hantzsch ester

From this screening, it was found that the use of 2 equiv of *i*Pr₂NEt was necessary to promote the reaction up to 50 % yield (entry 2). However, with this protocol, it was observed a deep pink coloration of the reaction solution, suggesting a leaching of the catalyst into the solution, possibly due to the hydrolysis of the ester bond connecting Eosin Y to the MR-resin performed by *i*Pr₂NEt.

In another set of experiments, the cyclization of bisenone **97a** was studied under base free reaction conditions (**Table 12**), only using Hantzsch's ester as reductive quencher.



Entry	Schreiner thiourea (mol%)	MR-EY (mol %)	Time (h)	Yield (%)
1	20	5	5	24
2	30	5	18	60
3	20	3	18	50
4 ^a	20	5	18	36
5 ^b	20	5	18	21
6	20	5	18	44
7 ^c	20	5	18	-

^a Reaction performed without stirring ^b Reaction performed in the presence of 1,3,5-trimethoxybenzene as internal standard. MR-EY removed after 3h. ^c

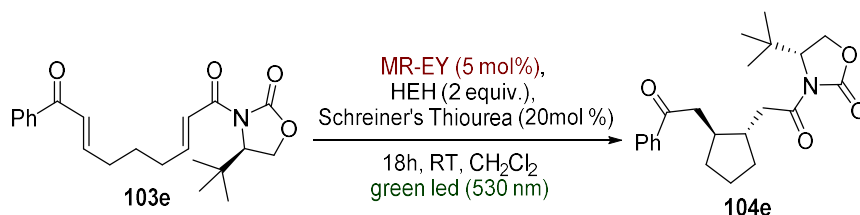
Reaction performed using MR-EY catalyst recovered from entry 4.

Table 12: Cyclization of **97a** promoted by supported Eosin Y in the absence of *i*Pr₂NEt

Gratefully, compound **97a** was successfully converted into the corresponding *trans*-2- cycloalkane derivate **101a** in 60 % when operating in the presence of 30 mol% of Schreiner thiourea and 5 mol% of MR-EY catalyst (**entry 2**). Shorter reaction times (**entry 1**), lower catalyst loading (**entry 3**) or lack of stirring (**entry 4**) showed a decrement in terms of yields. Noteworthy, under these reaction conditions, the crude mixture did not show a pink colour, suggesting that no leaching phenomena had occurred during the time. To confirm our hypothesis, compound **97a** was reacted for 3 h only (**entry 5**), then the irradiation was switch-off, the MR-EY resin was removed by millipore filtration and the formation of the product **101a** in 21 % yield was determined by ¹H NMR analysis (using 1,3,5-trimethoxybenzene as internal standard). The solution obtained after filtration free by the MR-EY catalyst, underwent a subsequent 15-hour irradiation. After this time, ¹H NMR confirmed that the reaction did not progress further, since the yield obtained remain 21% compared to 44 % obtained in entry 6, conclusively demonstrating that there was no free Eosin Y in solution acting as homogeneous catalyst. However, the use of a recovered MR-EY sample was not successful (**entry 7**).

Catalyst recycling

In order to demonstrate the feasibility of the reaction even in presence of chiral bisenone, we selected the chiral derivate **103e**, featuring the (S)-4-*t*-butyloxazolidinone ring as chiral auxiliary. The photocyclization was carried out under the optimized conditions reported in the entry 2 of **table 13**, affording the desired product **104e** in 52% yield and 8:2 diastomeric ratio (**Table 13, entry 1**).



Entry	Run	<i>drratio</i>	Yield of 4 (%)
1	1	80/20	52
2 ^a	2	80/20	43
3 ^b	3	80/20	25

^a Reaction performed using “regenerated” MR-EY catalyst recovered from entry 1 ^b Reaction performed using “regenerated” MR-EY catalyst recovered from entry 2

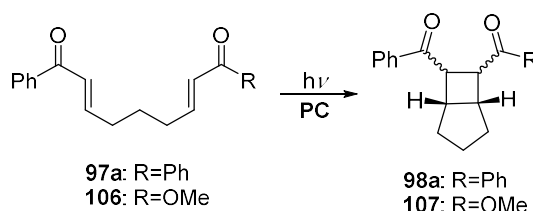
Table 13: Cyclization of **103e** promoted by MR-EY recycled catalyst

Also in this case, the immobilized Eosin Y was recovered as yellow solid. After having proved the eosin Y activity even with different substrate, we decided to investigate the reactivation of the photocatalyst. Several attempts have been made and the best results were obtained when the supported Eosin Y catalyst was suspended in acetonitrile, and irradiated by green light for 1 h, blowing in air at 1 atm. After this time, the colour of the supported catalyst changed from yellow to deep pink, thus confirming that the photo-active form of Eosin Y had been restored.²⁵ The so activated MR-EY was used in a subsequent cyclization of chiral compound **103e** (**entry 2**, **Table 13**). After 18 h, MR-EY was filtered onto a sintered glass funnel, copiously washed with dichloromethane and dried under vacuum until constant weight. The crude was purified by column chromatography to afford the *trans* pure compound **104e** in 43 % yield and the same 80/20 diastereoselectivity (**entry 2**). The recovered MR-EY was subjected to reactivation protocol and used in a further photocyclization, that afforded the desired product, although in lower yield, but with unchanged stereoselectivity (**entry 3**, **Table 13**).

In conclusion, the incorporation of a chiral auxiliary on the aryl enone backbone proved to be an effective strategy for achieving enantioselective synthesis of *trans*-1,2-cyclopentanones. Furthermore, the use of supported Eosin Y demonstrated a significant advantage by enabling catalyst recovery and reuse in subsequent transformations.

3.2.4 DIASTEROSELECTIVE [2+2] CYCLOADDITION

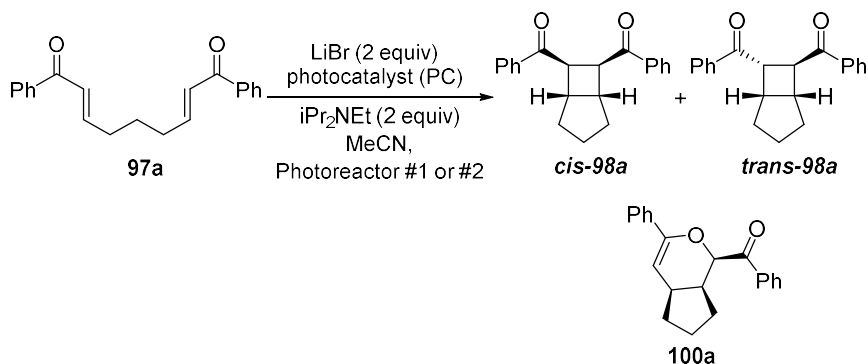
As shown by Yoon⁹⁵ and Zeitler⁹⁶, by tuning the reaction conditions, it is possible to observe a divergent preference for the synthesis of either monocyclic or bicyclic alkanes. Under protic reaction media and in the presence of Brønsted acid species, the formation of 1,2-substituted cycloalkanes is favoured, whereas, in the presence of a Lewis acid (such as LiBr), a [2+2] cycloaddition process could occur, resulting in the generation of the corresponding bicyclic species. Having demonstrated that the *trans*-1,2-cyclopentanes can be achieved with high levels of enantioselectivity by using chiral auxiliaries directly bounded on the substrates, we set out to explore the [2+2] photocycloaddition of the same substrates promoted by Eosin Y (**scheme 71**).



Scheme 71: [2+2] Photocyclization of non-symmetric aryl enones

Our investigation began with the evaluation of different light sources (Photoreactor#1 and Photoreactor#2) for the general photocycloaddition of the symmetric unsaturated aryl diketone **97a** in order to evaluate if the formation of the *cis* bicycle product **98a** could be observed also under using a organodye as photocatalyst. The photocycloaddition was initially carried out according to a slightly modified Zeitler protocol, involving the use of 2 equiv of LiBr as Lewis acid, 2 equiv of *i*Pr₂NEt as reductive quencher, catalytic amount of Eosin Y (or its sodium salt) as photocatalyst with acetonitrile acting as solvent of choice (**Table 14**).

During the preliminary study, in our experimental setup devices, *cis*-**98a** functionalized bicyclo[3.2.0]heptane was predominantly obtained over its *trans*-**98a** counterpart. Moreover, the formation of byproduct **100a**, previously reported by Krishe and Bauld⁹¹, was also observed.



Entry	PC	PC loading (mol%)	Light source	Time (h)	<i>Cis-98a:trans-98a:100a</i> ratio	Overall Yield (%)
1	Eosin Y	0.5	PR #1	14	84:15:1	30
2	Eosin Y	0.5	PR #1	2	93:7:0	54
3	Eosin Y	0.5	PR #2	2	81:19:0	50
4	$\text{Na}_2\text{Eosin Y}$	0.5	PR #1	2	80:19:1	43
5	$\text{Na}_2\text{Eosin Y}$	0.5	PR #2	2	69:21:10	84
6	Eosin Y	1	PR #2	2	73:7:20	87
7	$\text{Na}_2\text{Eosin Y}$	1	PR #1	14	56:29:15	Quant.
8 ^a	Eosin Y	0.5	PR #1	2	76:16:8	45
9 ^b	Eosin Y	0.5	PR #1	2	-	0
10 ^c	Eosin Y	1	PR #2	14	12:74:14	64
11 ^c	$\text{Na}_2\text{Eosin Y}$	1	PR #2	14	14:64:22	97

^a The same reaction performed using non-dry solvent resulted in <10 % yield.

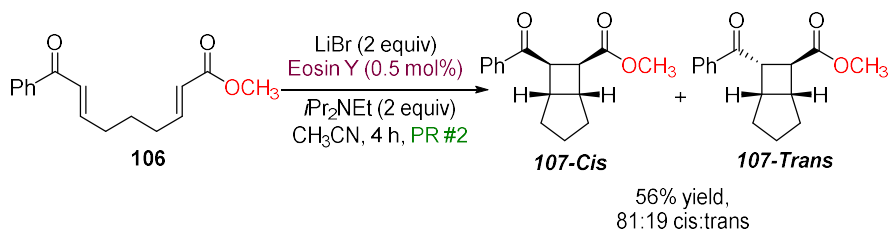
^b The tube adheres to the outer wall of the photoreactor. ^c Reaction performed using photoreactor #1 assembled with green LEDs working at 6.06 mW/cm². ^d Distance between light source and the test tube is fixed at 2 cm. ^e Reaction performed at 26 °C

Table 14: Photocatalytic [2+2] cycloaddition of compound **97a** promoted by organodyes: screening of the reaction conditions

The irradiation of compound **97a** for 14 hours using photoreactor #1, with 0.5 mol % of Eosin Y, leads to the formation of product **98a** in 30% yield, with

a ***cis*-98a:*trans*-98a:100a** ratio of 84:15:1 (**entry 1**). Reducing the reaction time to 2 hours improved both the yield and diastereoselectivity, resulting in a 51% yield of product **98a** with a 93:7 *cis* ratio, while the formation of byproduct **100a** was significantly reduced (**entry 2**). Similar results were observed when the reaction was carried out using [photoreactor#2](#) under the same reaction conditions (**entry 3**). Increasing the Eosin Y loading to 1 mol% enhanced the yield of product **98a** up to 87%, however, also the formation of byproduct **100a** increased (**entry 3** vs. **entry 6**). Complete conversion of the starting material was achieved by doubling the Na₂Eosin Y loading and extending the reaction time to 14 hours, resulting in a quantitative yield of the ***cis*-98a:*trans*-98a:100a** mixture (**entry 4** vs. **entry 7**). However, reducing the intensity of the LEDs (**entry 8**) or increasing the distance between the light source and the reaction mixture (**entry 9**) led to a notable decrease in catalytic efficiency. Across all experimental conditions, the ***cis*-98a** isomer was consistently the major product, over the ***trans*-98a** isomer. Despite these efforts, the ***trans*-98a** isomer, as reported by Zeitler's group, was never observed. Considering that the reaction media in our setup reached 40°C, in contrast to the 26°C reported in the literature, we speculated that temperature might influence the stereoselectivity of the process. To investigate this, we conducted additional experiments by introducing a cooling fan system to lower the temperature to 26°C. Under these conditions, the [2+2] photocycloaddition of compound **97a** predominantly produced the ***trans*-98a** isomer, achieving a ***cis*-98a:*trans*-98a:100a** ratio of 14:64:22 with an overall yield of 97% (entries 10 and 11). However, the formation of byproduct **100a** was still observed, even at lower temperatures.

To further explore the applicability of the diastereoselective reductive [2+2] photocyclization mediated by Eosin Y and promoted by light, we investigated the reaction with the unsymmetrical aryl-enone **106**. Using traditional homogeneous reaction conditions (2 equiv. of LiBr, 2 equiv. of *i*Pr₂NEt, and 0.5 mol% of Eosin Y as the photocatalyst) unsaturated keto-ester **106** was irradiated with light at 40°C for 4 hours in [photoreactor#2](#). This led to the successful formation of the corresponding bicycloalkane product **107**, which was isolated in 56% yield with a *cis* ratio of up to 81:19¹⁰⁶ after chromatographic purification (**Scheme 72**).

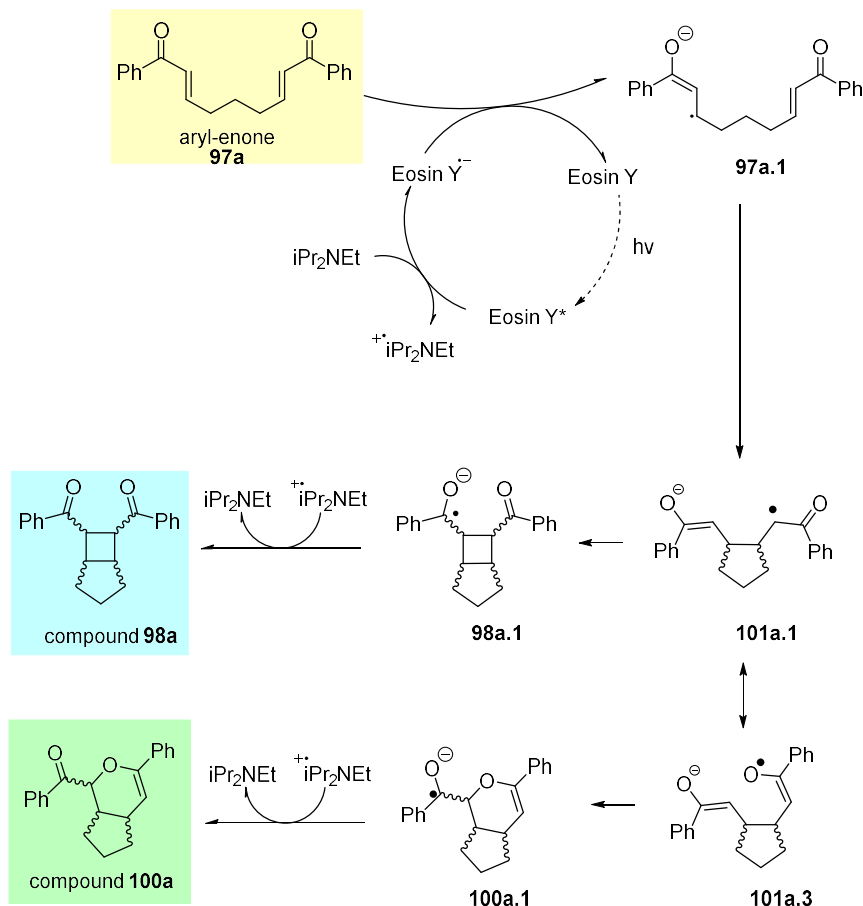


Scheme 72: [2+2] photocycloaddition of unsymmetric aryl enones

3.2.5 MECHANISTIC INVESTIGATION: DFT CALCULATION, KINETIC STUDIES AND CONTROLL EXPERIMENTS

Mechanistic proposal

The reaction mechanism of this transformation was further explored through computational analysis. Based on a previous study,⁸⁷ it is widely accepted that the excited state of Eosin Y¹⁰⁷ generated by light irradiation is reductively quenched by *i*Pr₂NEt, leading to the formation of the Eosin Y radical anion species which acts as a potent reductant reagent (**Scheme 73**). Upon a single electron transfer to the unsaturated aryl-enone activated by coordination with LiBr, the photoredox catalyst returns to its ground state, whereas the resulting radical anion **97a.1** undergoes a 5-*exo-trig* cyclization affording the 1,4-distonic radical anion **101a.1** constructing the first five-membered ring. This species, proceeds through intramolecular radical cycloaddition, evolving in the bicyclic radical anion **98a.1** by a formal [2+2] photocycloaddition process. The new radical anion formed is then oxidized to the corresponding bicyclo[3.2.0]heptane product **98a** by the presence of the *i*Pr₂NEt^{•+}, with consequent regeneration of the base.



Scheme 73: Proposed mechanism

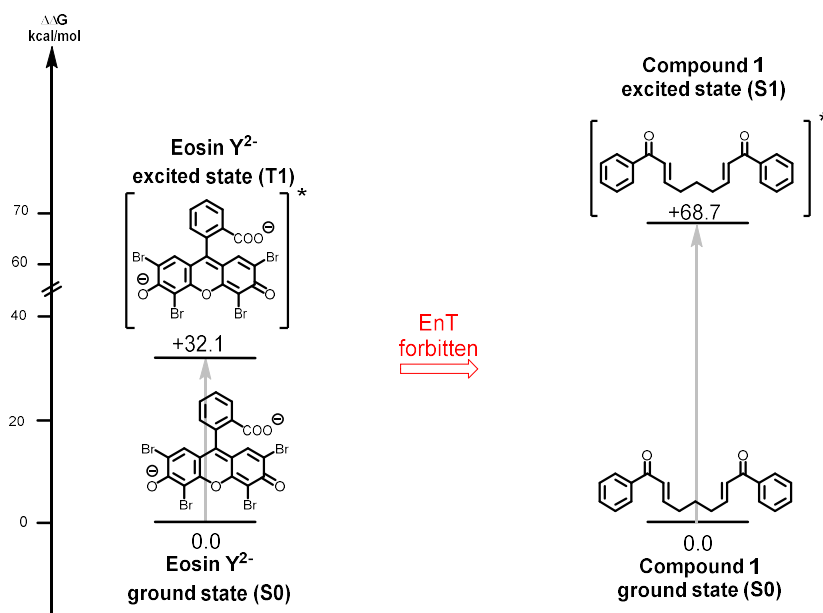
However, as reported by Krishe⁹¹, in some cases, the radical anion **101a.1**, rather than undergoing a radical-carbon/neutral-carbon coupling to produce the anion radical **98a.1**, might be engaged in a second possible pathway in which intermediate **101a.3**, (a resonance form of species **101a.1**) might be engaged in a radical-oxygen/neutral-carbon coupling, leading to the formation of byproduct **100a**.¹⁰⁸

DFT Calculations

To explore these hypotheses, we performed a comprehensive study of the proposed mechanism (**Scheme 73**) using the Density Functional Theory (DFT) approach. Geometries of species involved in the [2+2] photocycloaddition were obtained by Monte Carlo conformational analysis performed with Molecular Mechanics calculations using the MMFFs force field¹⁰⁹ of the Macromodel package in the Schrodinger suite. Then, the so obtained structures were fully optimized by the DFT approach

using the unrestricted M062X functional¹¹⁰ with the 6-31G(d,p) basis set of the Gaussian package,¹¹¹ including solvation effects of acetonitrile using the PCM model.¹¹² M062X functional was selected since is known to give a better description for long-range dispersive interactions compared to B3LYP functional.^{113,114}

Then, we investigated whether the photoexcitation of aryl-enone **97a** could occur through either a single electron transfer (SET) mechanism or an energy transfer (ET) process, both facilitated by Eosin Y. In a SET pathway, the catalytically relevant triplet state of Eosin Y (T1) is achieved through intersystem crossing (ISC) from the excited singlet to the excited triplet state ($S1 \rightarrow T1$), since the direct excitation from the ground state to the triplet state ($S0 \rightarrow T1$) is prohibited due to spin restrictions (**Figure 18**). Computational analysis revealed that the energy required for the initial excitation of Eosin Y from the ground state to the singlet excited state ($S0 \rightarrow S1$) is 32.1 kcal/mol, significantly lower than the energy required for the energy transfer process responsible of bisenone **97a** excitation, which was estimated in 68.7 kcal/mol (**Scheme 74**).



Scheme 74: Energy required for excitation from ground state (S₀) to the excited state (T₁/S₁) of Eosin Y and symmetric bisenone

Moreover, DFT calculation confirmed that the coordination between aryl-enone **97a** and LiBr is fundamental in order to decrease the energy gap of the initial reductive process promoted by Eosin Y radical anion (This result

was also confirmed by previous mechanistic studies carried out in our laboratories, in absence of LiBr) Given the 2:1 stoichiometry of LiBr:bisenone, two distinct pathways have been considered. In one scenario, each carbonyl group of compound **97a** could independently coordinate with LiBr. Alternatively, a single molecule of lithium bromide could simultaneously interact with both carbonyl groups. Facilitated by the presence of the activated form of Eosin Y, these two structures underwent reduction to yield the corresponding radical anions **97a.3**, where LiBr bridges both C=O bonds, or radical **97a.3'**, characterized by a bis coordination. The energy difference of +9.2 kcal/mol favours the more stable structure **97a.3** (Figure 32). Consequently, structure **97a.3'** adopts a conformation where the two carbonyl groups are oriented in *anti* configuration, while the more rigid bridged structure **97a.3** exhibits a *cis* conformation.

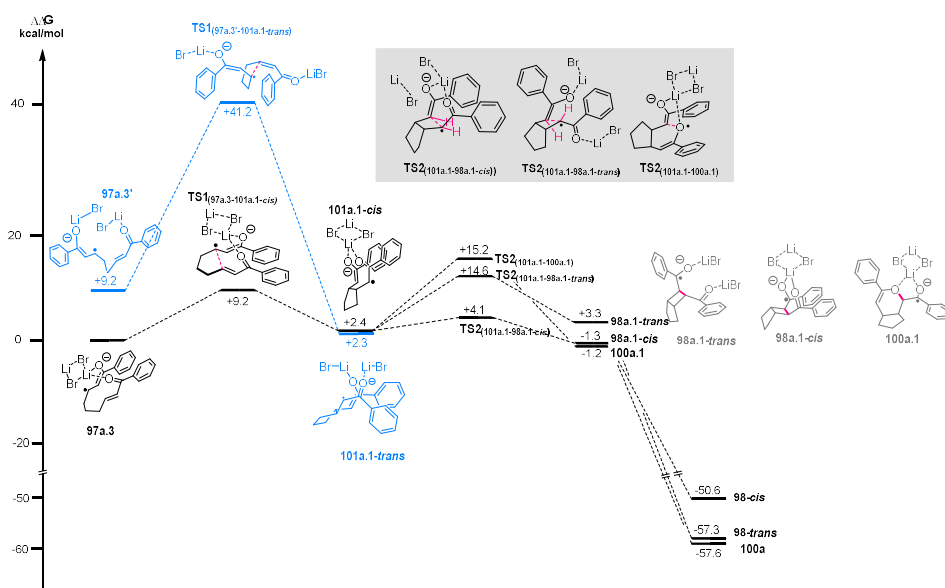


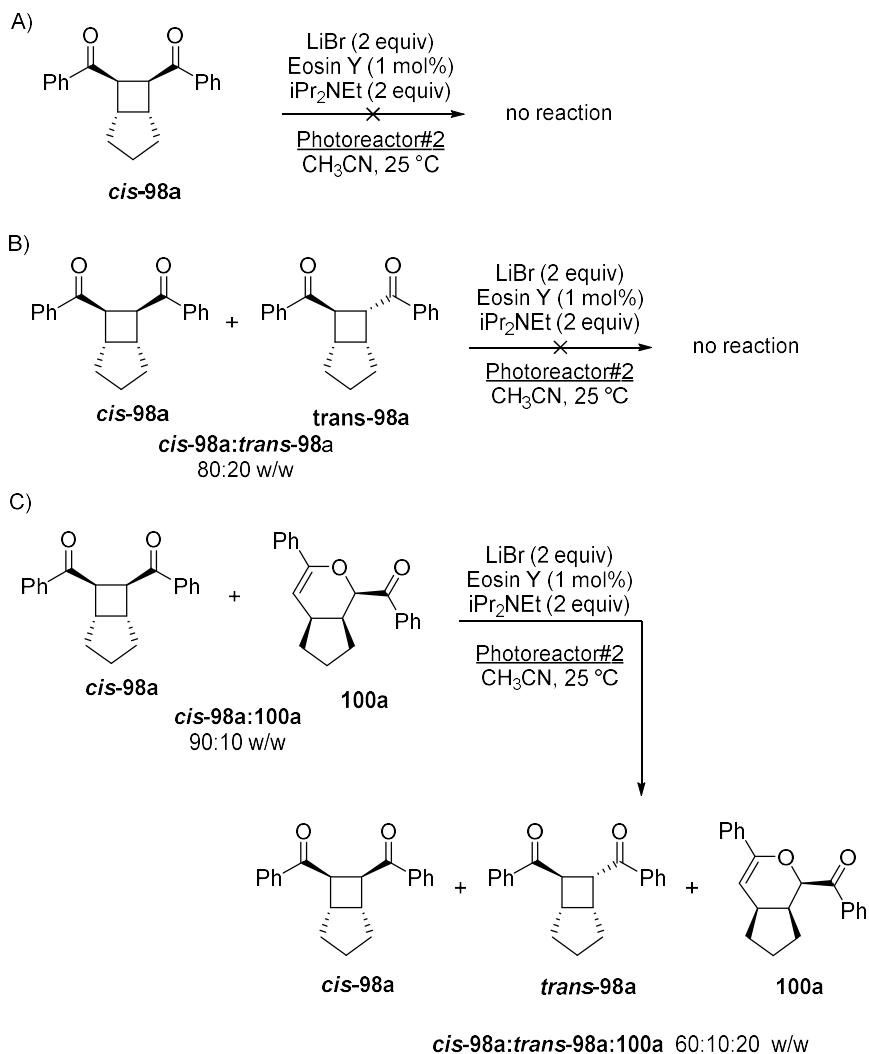
Figure 32: Gibbs free energy profiles (in kcal mol⁻¹) for the anion radical [2+2] photocyclizations starting from radical anion **97a.3** and **97a.3'** computed at the MO62X/6-31G(d,p) / PCM (CH₃CN) level

Radicals **97a.3** and **97a.3'** will then undergoes an intramolecular cyclization process, leading to the formation of *cis*-**101a.1** and *trans*-**101a.1** cyclic 1,4-distonic radical anions respectively. Transition state **TS1(97a.3'-101a.1 trans)** derived from the cycloaddition of **97a.3'**, is responsible of the formation of cyclopentane *trans*-**101a.1** (Figure 32, blue pathway) and it exhibits notably higher energy compared to **TS1(97a.3-101a.1 cis)** (+32 kcal/mol). Due to this large difference in energy, the evolution of this

pathway has not been further investigated. This observation agrees with the fact that the final cyclic product in which the substituents of the cyclopentane ring are in the *trans* configuration was never observed. Starting from radical **cis-101a.1**, a second cyclization process can then be hypothesized involving three distinct pathways leading to the formation of both **cis-98a** and **trans-98a** compounds, alongside the generation of byproduct **100a**. All transition states **TS2(101a.1-98a.1 cis)**, **TS2(101a.1-98a.1 trans)** and **TS2(101a.1-100a.1)**, which are respectively involved in the synthetic pathways of compounds **cis-98a**, **trans-98a** and **100a**, were computationally located. It was found that **TS2(101a.1-98a.1 cis)**, leading to the formation of compound **cis-98a.1**, is favoured over its counterpart by 10.5 kcal mol⁻¹. Additionally, **TS2(101a.1-100a.1)**, responsible for the formation of the undesired byproduct **100a**, exhibits the highest energy demand among all the transition states, thereby confirming that the production of this species is not the preferred pathway. Following the cyclization process, radical anions **98a.1-cis**, **98a.1-trans**, and **100a.1** were generated. Compound **cis-98a.1** (derived from **TS2(101a.1-98a.1 cis)**) demonstrated marginally higher stability compared to its **trans-98a.1** counterpart. However, subsequent to the oxidative step facilitated by *i*Pr₂NEt⁺⁺, neutral and stable compounds **cis-98a**, **trans-98a**, and **100a** were produced. Notably, the stability of **trans-98a** was estimated in 6.7 kcal/mol more stable than **cis-98a**, suggesting that the **trans-98a** isomer is the thermodynamically favoured product of the reaction.

Control Experiments

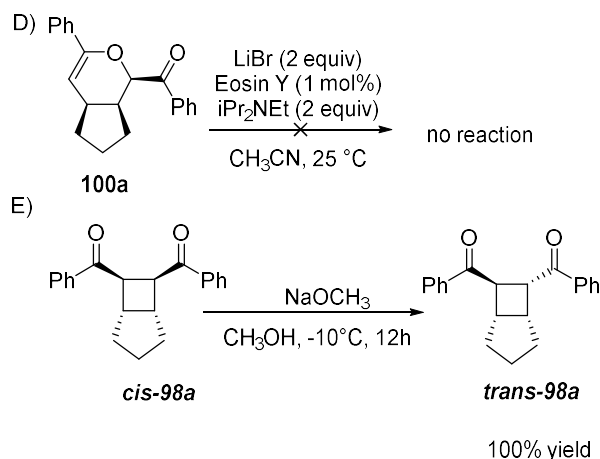
To validate the findings from computational analysis, additional experiments were carried out to investigate the potential interconversion of compound **cis-98a** into the **trans-98a** and **100a** products under the given reaction conditions. In these experiments, pure compound **cis-98a** was dissolved in CH₃CN and treated with Na₂Eosin Y (1 mol%), LiBr (2 equiv.), and *i*Pr₂NEt (2 equiv.) in photoreactor #2, but in the absence of light. After 24 hours, no changes in the composition of the mixture were observed, confirming that there was no chemical interconversion of **cis-98a** into other products under these conditions (**Scheme 75, A**). Next, the reaction mixture was exposed to light irradiation at room temperature for an additional 24 hours. After this period, compound **cis-98a** was recovered without any alteration, further supporting the absence of interconversion. A similar experiment was performed¹¹⁵ using a mixture of **cis-98a** and **trans-98a** in an 80:20 ratio. This was carried out in photoreactor#2 with CH₃CN and a 1:5 DMF:CH₃CN mixture. Again, no changes in the composition of the reaction mixture were detected after 24 hours (**Scheme 75, B**).



Scheme 75: mechanistic studies.

We then subjected a mixture of *cis*-98a and 100a in a 9:1 w/w ratio to the same treatment. In the absence of light, the ratio of the mixture remained unchanged. However, after 18 hours of light exposure, the quantity of byproduct 100a remained constant, while the concentration of *cis*-98a decreased, leading to the formation of the *trans*-98a isomer in 20% w/w (**Scheme 75, C**). This result clearly demonstrates that a photoactivated form of byproduct 100a can catalyse the conversion of *cis*-98a to *trans*-98a. Therefore, it is crucial to minimize the presence of byproduct 100a in order to maintain high cis diastereoselectivity during the cyclization process.

In a follow-up experiment, compound **100a** was isolated and stirred in the dark for 24 hours. After this period, only the starting material was detected, with no evidence of transformation. A similar outcome was observed when compound **100a** was irradiated with Photoreactor #1 at 26°C for 24 hours, where again only the starting material was recovered (**Scheme 76, D**)



Scheme 76: Additional mechanistic studies

Finally, it was also shown that the transformation of the *cis-98a* isomer into its respective *trans-98a* form can be accomplished with high yield through treatment with NaOMe in methanol at -10°C (**scheme 76- E**).

Kinetic Studies

After confirming that the *cis-98a* product could be converted into its *trans-98a* counterpart over time in the presence of compound **100a**, we performed a kinetic study to gain deeper insight into the process. In this study, the concentrations of the reagents and products were monitored at regular intervals throughout the reaction. Compound **97a** was reacted with iPr_2NEt (2 equiv.), $\text{Na}_2\text{Eosin Y}$ (1 mol%), and LiBr (2 equiv.) in dry acetonitrile. The reaction was then irradiated using photoreactor#2 for 930 minutes. Trimethoxybenzene was used as the internal standard, and the concentration of the components was evaluated by LC-MS analysis. The results of this kinetic study are summarized in **Figure 33**.

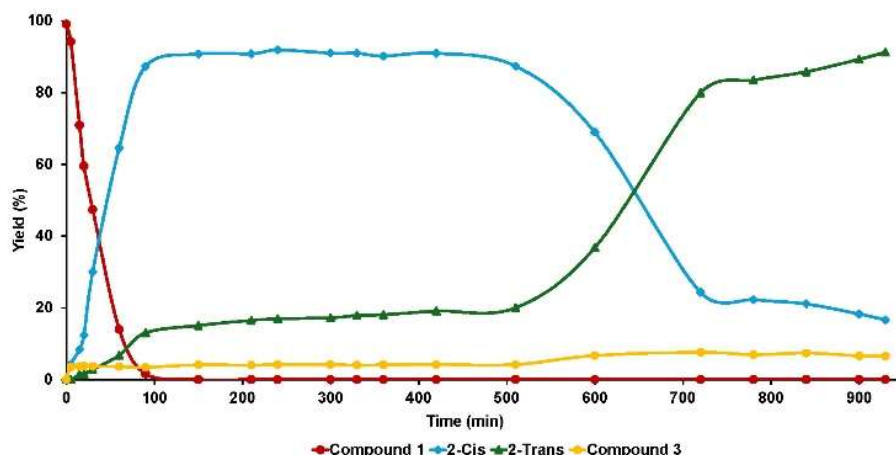


Figure 33: Kinetic study

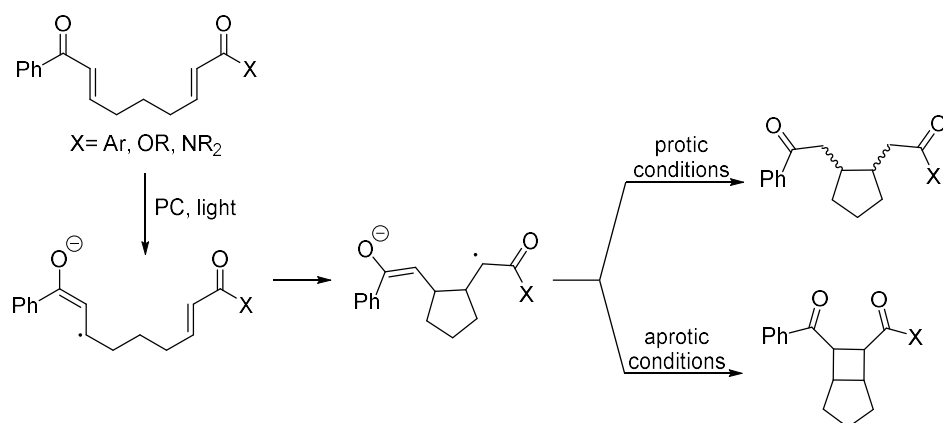
As shown in the kinetic study, the starting aryl-enone **97a** (represented by the red line) is rapidly converted into both the *cis*-**98a** and *trans*-**98a** products (blue and green lines, respectively), with *cis*-**98a** being the major isomer. This behaviour aligns well with the DFT calculations, which predict that the *cis*-**98a** isomer, formed via the transition state **TS2(101a.1-98a.1-cis)**, is more thermodynamically stable than its *trans*-**98a** counterpart. During the first 510 minutes (approximately 9 hours), the concentrations of *cis*-**98a** and compound **100a** (yellow line) remain constant, while the amount of the *trans*-**98a** isomer increases slightly over time. After 510 minutes, the *cis*-**98a** isomer begins to undergo interconversion into the *trans*-**98a** isomer. By the end of the reaction (930 minutes), the *trans*-**98a** isomer becomes the predominant product. A similar kinetic study was conducted using [photoreactor#1](#). In agreement with the data reported in entry 7 of **Table 14**, no interconversion of the *cis*-**98a** isomer into the *trans*-**98a** isomer was observed, with the *cis*-**98a** isomer being isolated as the major product. Together, the results from the kinetic studies and the control experiments (**Scheme 75, C**) strongly suggest that the formation of the *trans*-**98a** isomer is due to the interconversion of *cis*-**98a** mediated by the presence of compound **100a**, rather than being directly generated from the [2+2] photocycloaddition reaction.

Finally, our investigation in the [2+2] photocycloaddition of symmetric and non symmetric bisenone successfully yielded the target *cis* and *trans* bicyclo[3.2.0]heptanes. Furthermore, additional studies conducted in our laboratories provided valuable insights, supporting and validating the experimental findings

3.3 CONCLUSIONS

In conclusion, a photocatalytic approach for the synthesis of highly functionalized *trans*-1,2-cyclopentanes was successfully disclosed.¹⁰²

The photocyclization of bisenone bearing *tert*-butyl oxazolidinone as chiral auxiliary (compound **103e**), afforded the best result in terms of yield (83%) and enantioselectivity (66% e.e.) calculated on the methyl ester derivative **105**. The selected transformation was also accomplished under flow conditions, displaying an increased productivity compared to the in batch protocol (87% yield in 40 min). The activity of immobilized Eosin Y, was successfully demonstrated in the photocyclization of symmetric and non-symmetric substrates, achieving *trans*-1,2-cyclopentane products in up to 60%.¹¹⁶ The catalyst reactivation under air with green light irradiation, allowed to reuse it in up to three cycles. However, new and more efficient methods to regenerate the catalyst need to be explored.



Scheme 77: Photochemical approach for the stereoselective synthesis of *trans* cyclopentane and bicyclo[3.2.0]heptane

In addition, an intense study in the symmetric bisenone [2+2] photocycloaddition revealed that the stereoselectivity of the transformation was strongly dependent on the temperature: at 40°C, with 2 hours of irradiation using Eosin Y as catalyst, the *cis*-**98a** isomer was obtained in 77% yield and 84:16 of diastereoselectivity. Whereas, at 26°C after 14h of irradiation the *trans*-**98a** bicycle product was achieved in 79% yield and 19:81 of d.r. The mechanistic understanding derived from DFT calculations along with the results obtained from kinetic studies and control experiments, confirmed the experimental observations and defined the *cis* isomer as the kinetic and the *trans* as the thermodynamic product.¹¹⁷

4 CHAPTER 4: LATE-STAGE C-H IRON(III) CATALYZED ELECTROPHOTOCHEMICAL PERFLUOROALKYLATION

4.1 FLUORINATED GROUPS IN MEDICINAL CHEMISTRY

The modern pharmaceutical market features a broad range of drugs that include organic fluorine compounds. It is estimated that approximately 20% of all drugs prescribed or administered in clinical settings contain a fluorine atom. Additionally, 30% of the top 30 bestselling drugs by sales also incorporate fluorine.¹¹⁸ Fluorine-containing compounds have garnered significant attention due to their distinctive physicochemical properties, which include: metabolic stability, bioavailability and membrane permeability.¹¹⁹ As example, 5-fluorouracil and fludarabine are characterized by monofluoromethyl moiety, while Colecoxib and fulvestrant by trifluoromethyl and pentafluoromethyl respectively (**Figure 34**).

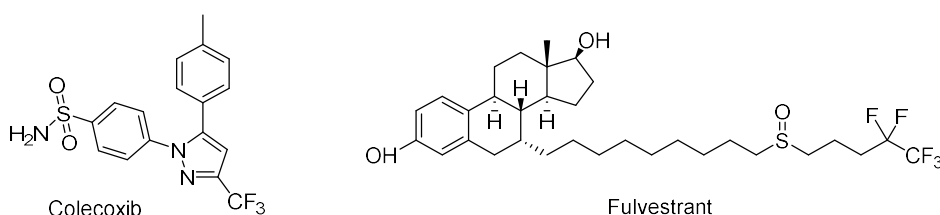


Figure 34: Active Pharmaceutical Ingredients containing fluorinated groups

Moreover, fluorine containing substrates are widely used components of agrochemicals and advanced materials.¹¹⁹ Therefore, the development of new and efficient methods to introduce fluorine containing groups into organic molecules represents an important and competitive topic for the scientific community. Unfortunately, the formation of carbon-fluorine bonds is a particularly challenging chemical transformation, primarily due to the high electronegativity of fluorine and the substantial hydration energy of the fluoride anion.¹²⁰ The most commonly used intermediates in fluorination processes are fluorinated radicals. Three main approaches can be employed to generate these radicals :

- Single electron transfer (SET) reduction of electrophilic fluoromethylating reagents (Figure 35), such as RfHal¹²¹, N-hydroxybenzimidoyl chloride esters¹²², Umemoto's or Togni's reagents¹²³ with photoredox or metal catalysts.

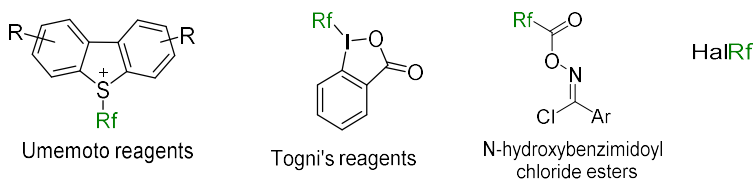


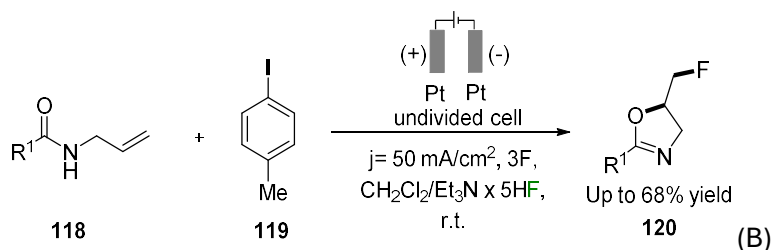
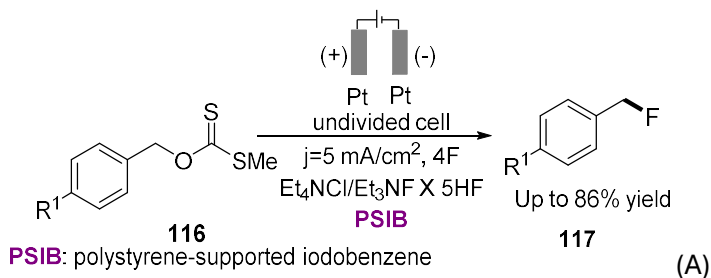
Figure 35: Electrophilic fluoromethylating reagents

- SET oxidation of metal derivatives such as AgRf and CuRf (Eox= 2.0V).¹²⁴
- SET oxidation of Sodium sulphinate salts (RfSO₂Na, Eox= 1.3V) or carboxylic acids like trifluoroacetic acids (TFA, Eox=2.4V) in presence of chemical oxidants, such as peroxides, or by photo- and electrochemichemistry;¹²⁵

Despite the potentialities displayed by the first two methods, they suffer of some limitations. First, the synthesis of the electrophilic fluoromethylating compounds require toxic and unstable starting materials. Moreover, the use of stoichiometric amounts of expensive metal derivatives (like AgCF₃) is detrimental. In this context, the direct oxidation of the stable sodium sulphinates along with the commercially available carboxylic acids, represents a valid alternative. Additionally, with the advent of emerging green methods such as photochemistry and electrochemistry, it is now possible to avoid the use of superstoichiometric amounts of chemical oxidants. Starting from this point, the following paragraph will focused on the applications of photochemistry, electrochemistry and electrophotocatalysis in the fluoroalkilation of organic compounds.

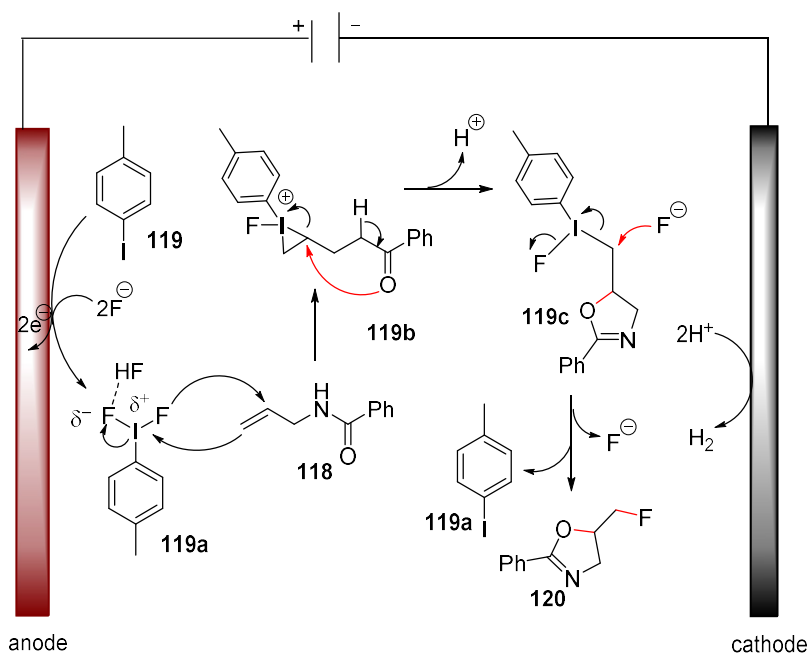
4.1.1 MONOFLUOROMETHYLATION

The introduction of monofluorinated groups into small molecules, using new and green synthetic methodologies, has been less explored compared to the difluoromethylation and the trifluoromethylation. One of the first contribution in this field, was reported by Fushigami in 2010. The author developed an indirect anodic fluorination of xanthates using polystyrene supported iodobenzene (PSIB) as mediator and Et₃Nx5HF as fluorine source.¹²⁶ Exploiting this approach, in 2018, Waldvogel and co. investigated the synthesis of fluoromethyl-2-oxazolines, since constitute useful substrates in pharmaceutical and organic chemistry. Using electrochemistry, they present the first example of 5-fluoromethyl-2-oxazolines by fluorocyclization of simply accessible *N*-allylcarboxamides with a hypervalent iodoarene mediator (**Scheme 78**).



Scheme 78: A. Anodic fluorination of xanthates using polystyrene supported iodobenzene B. Electrochemical fluorocyclization of N-Allylcarboxamide

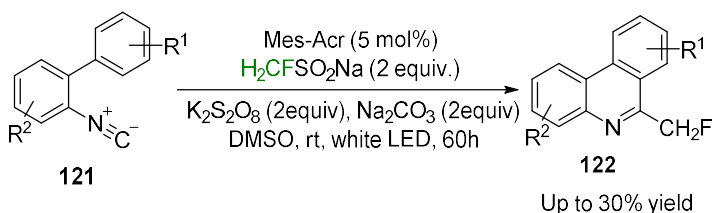
Under the present optimized conditions, a wide substrates scope was carried out revealing that desired product can be achieved in higher yield when an electron withdrawing group is present (up to 95% yield) compared to when electron-donating groups are used.¹²⁷ The mechanism of this transformation is reported in **Scheme 79**.



Scheme 79: Proposed mechanism for electrochemical fluorocyclization of N-Allylcarboxamide

The anodic oxidation of the iodoarene **119** result in the formation of the intermediate **119a**, then the hypervalent iodine atom undergoes nucleophilic attack by the double bond of compound **118**, leading to the formation of iodonium species **119b**. Intramolecular ring opening of the three-membered heterocycle by the carbonyl led to the 5-(λ3-iodanyl)methyl oxazoline **119c**, which is converted into product **120** after an SN2-type substitution with fluoride acting as the nucleophile.¹²⁷

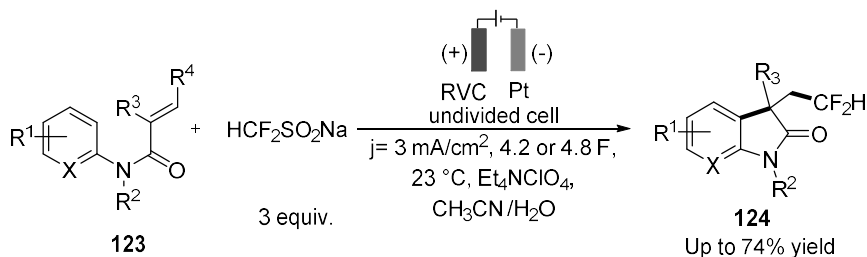
More recently, Liu disclosed a visible-light metal-free protocol for the synthesis of 6-tri-/di-/monofluoromethylated phenanthridine derivatives with sodium sulfinate RfSO_2Na (**Scheme 80**).¹²⁸ Reaction conditions involves the use of Mesitylmethylacridinium catalyst (5 mol%) in presence of fluoromethyl, sulfinate sodium salt and potassium persulfate as chemical oxidant under white irradiation.¹²⁸ Although the yields are lower compared to previous works (**Scheme 78**), this example represents one of the first instances in which photoredox catalysts have been successfully applied to the synthesis of monofluorinated organic compounds, marking a significant advancement in the field.



Scheme 80: Synthesis of monofluorinated phenanthridine derivatives using $\text{CH}_2\text{FSO}_2\text{Na}$.

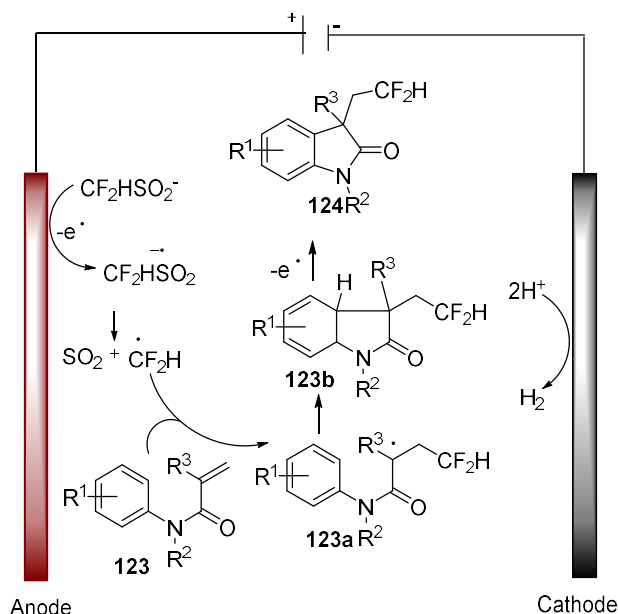
4.1.2 DIFLUOROMETHYLATION

The difluoromethyl group serves as a key structural motif, acting both as a lipophilic hydrogen-bond donor and as an isostere for OH or SH groups.^{129,130} As previously reported for the monomethylation, also sodium difluoromethylsulfinate ($\text{HCF}_2\text{SO}_2\text{Na}$) has emerged as an economic and easily handle CF_2H radical precursor.¹²⁵ Ackermann and coworkers developed a difluoromethylation-cyclization sequence of *N*-substituted acrylamides **123** giving access to different substituted oxindoles **124** (**Scheme 81**).¹³¹



Scheme 81: Electrochemical difluoromethylation-cyclization of *N*-substituted acrylamides

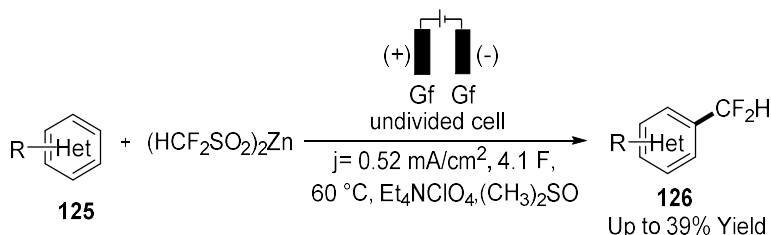
Cyclic voltammetry analysis revealed that the anodic oxidation of $\text{CF}_2\text{HSO}_2\text{Na}$ occur with an irreversible behaviour at 1.1V, which is lower compared to the oxidation potential of substrate **123** (1.8V). This suggests that the oxidation of the *N*-acrylamide is unlikely to occur at modest cell potentials. Based on this experimental data, a mechanism was proposed (**Scheme 82**).



Scheme 82: Proposed mechanism for difluoromethylation-cyclization of *N*-substituted acrylamides.

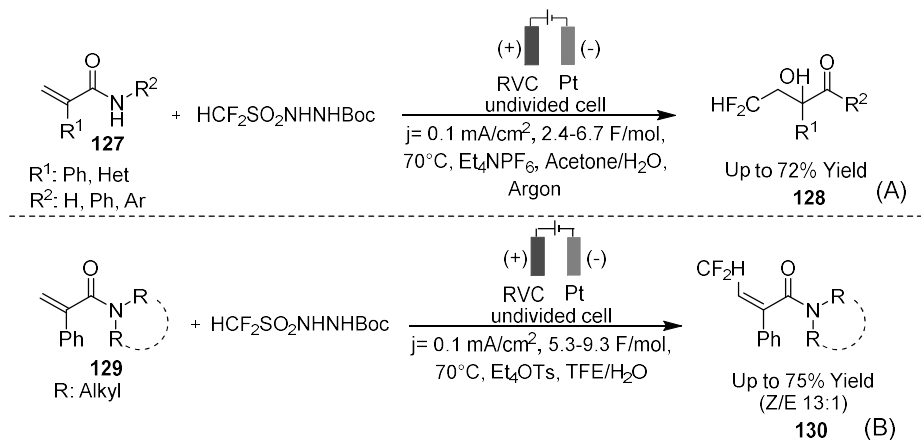
The anodic oxidation of the sulfinate produces a sulfynyl radical that decomposes to the CF_2H radical. Attack of the CF_2H radical to the alkene, results in intermediate **123a**, which is further intramolecularly cyclized to the intermediate **123b**. Finally, further aromatization affords the corresponding product **124** under anodic oxidation conditions. Hydrogen

cations are concurrently reduced on the cathode, releasing molecular hydrogen.¹³¹ Blackmond and Baran can be considered the pioneers of the electrochemical difluoromethylation. In 2014, they reported the difluoromethyl addition of six different *N*-heterocycle (mostly pyrrole and Pyrazole) in up to 39% yield using $(\text{HCF}_2\text{SO}_2)_2\text{Zn}$ as CF_2H as radical source (**Scheme 83**).¹³⁰



Scheme 83: Electrochemical difluoromethylation of (hetero)arenes using $(\text{HCF}_2\text{SO}_2)_2\text{Zn}$

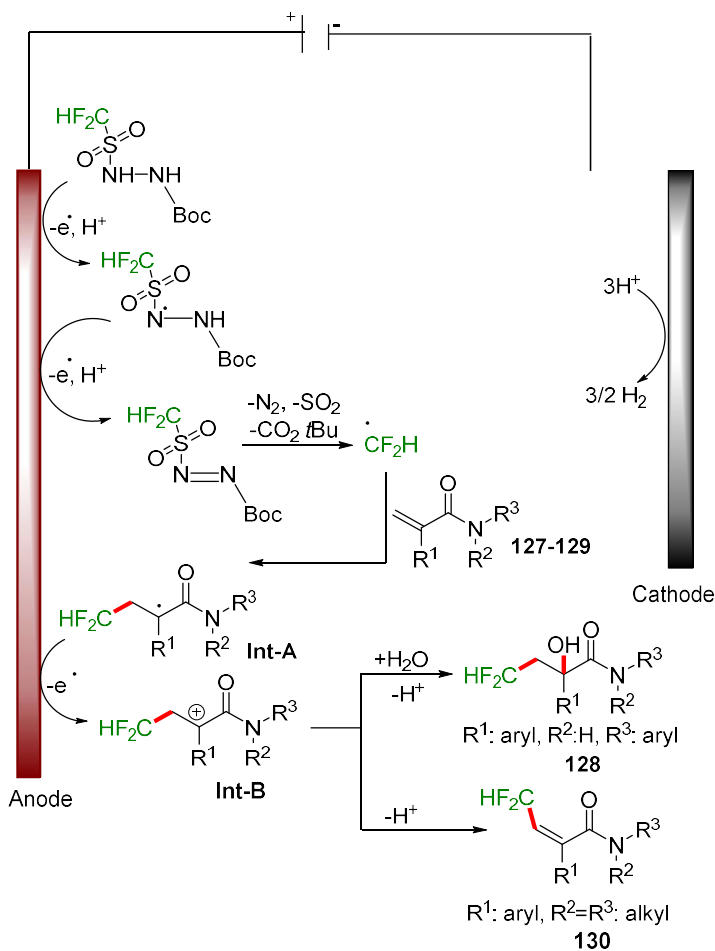
A few years later, Xu and co-workers reported the difluoromethylation of alkynes for the synthesis of fluorinated dibenzazepines in which the CF_2H radical was generated through ferrocene-mediated oxidation of $\text{HCF}_2\text{SO}_2\text{NHNHBoc}$.¹³² As improved version of this methodology, in 2019, the 1,2-hydroxydifluoromethylation (**Scheme 84-A**) and C-H difluoromethylation (**Scheme 84-B**) of acrylamides **127** and **129** were performed without using Ferrocene as redox mediator.¹³⁰



Scheme 84: Electrochemical hydroxydifluoromethylation and C-H difluoromethylation of acrylamides

In this case, CF_2H radical was directly generated by the anodic oxidation and subsequent fragmentation of $\text{HCF}_2\text{SO}_2\text{NHNHBoc}$ (**Scheme 85**). Addition of CF_2H radical to acrylamide followed by one electron oxidation furnishes the

carbocation intermediate Int-A. In presence of secondary aromatic amides (**Scheme 84-A**, compound **127**), the carbocation reacts with H₂O to afford the difunctionalized product **128**. However, tertiary aliphatic amides (**Scheme 84-B**, compound **129**) undergoes proton elimination to give the C-H functionalization product **130**.



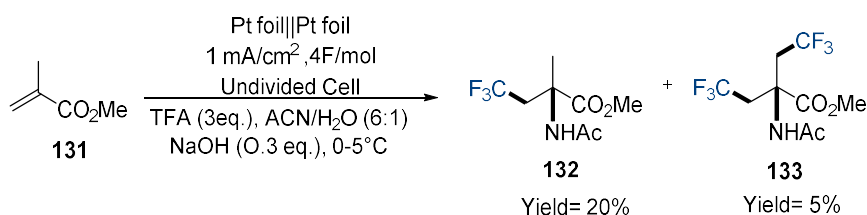
Scheme 85: Hypothesized mechanism for hydroxydifluoromethylation and C-H difluoromethylation of acrylamides

4.1.3 TRIFLUOROMETHYLATION

Trifluoromethylated compounds are attracting considerable interest for their increasing prevalence in biologically active molecules and their essential use in materials for optoelectronic devices. In particular, trifluoromethylated amines are essential in medicinal chemistry, prompting

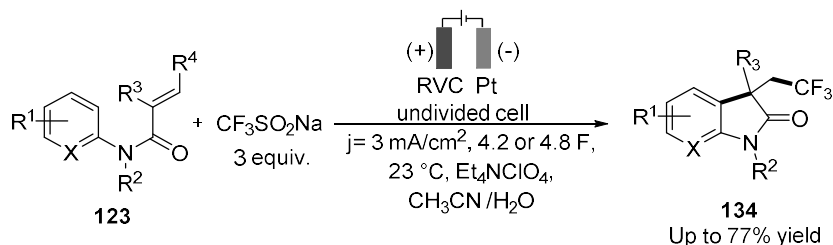
the development of various innovative strategies for their synthesis.¹³³ In this contest, the efficient use of affordable and atom-economical trifluoroacetates as sources of trifluoromethyl radicals, typically reliant on costly or toxic reagents,¹³⁴ would represent a major breakthrough. One of the major challenges limiting the use of trifluoroacetic acids and trifluoroacetates as sources of the CF₃ group in the trifluoromethylation of complex substrates is the high oxidation potential of these precursors (+2.4 V vs SCE in MeCN).¹³⁵ This has led to the development of methodologies that require harsh reaction conditions, such as the use of strong oxidants (e.g., XeF₂)¹³⁶ and highly oxidizing electrochemical conditions,¹³⁵ which have limited applicability.

One of the first application of trifluoroacetic acid as CF₃ source dates back to 1989, when Kenji Uneyama and Hiromi Nanbu investigated the trifluoromethylation of methylacrilamide under electrochemical conditions.¹³⁷ Although the methodology requires the use of low temperatures, high current densities, and an excess of trifluoroacetic acid (3 equiv), it results in the formation of the desired product in relatively low yields and selectivities (**Scheme 86**). Despite these limitations, this approach represents an initial attempt in the field, offering a foundational step for further optimization and refinement of the process



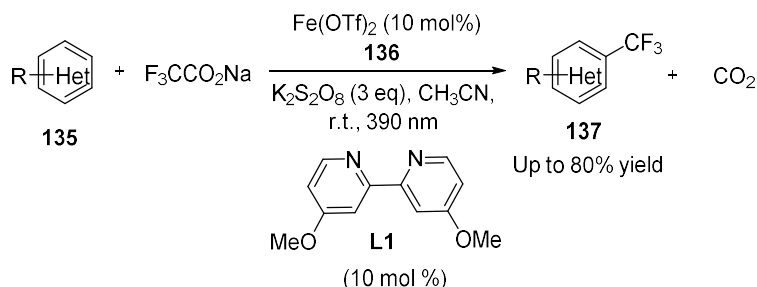
Scheme 86: Electrochemical trifluoromethylation of methylacrilamide using trifluoroacetic acid.

As an alternative to TFA, Langlois's reagent (CF₃SO₂Na) has emerged as a stable and easy-to-handle CF₃ precursor with a lower oxidation potential of 1.4 V vs. Ag/AgCl, making it a promising choice for applications requiring milder conditions.¹²⁵ Several CF₃ introductions reported in literature involve the anodic oxidation CF₃SO₂Na. The previous mentioned strategy for the difluoromethylation of *N*-substituted acrylamides with CF₂HSO₂Na (**Scheme 81**) was also carried out using Langlois's reagent. The trifluoromethylated oxindoles were obtained in up to 77% yields (**Scheme 87**).¹³¹ The reaction undergoes following the same mechanism reported in **Scheme 82**, but lower reaction times were required compared to the difluoromethylation.



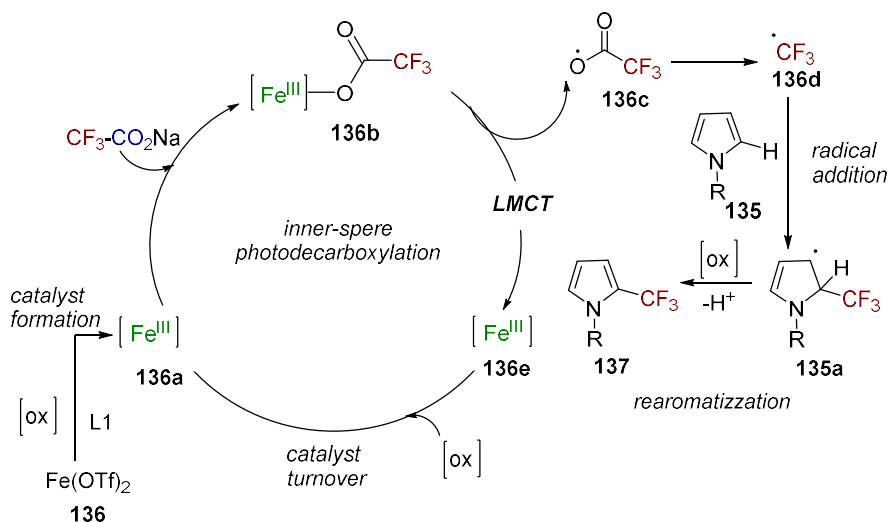
Scheme 87: Electrochemical difluoromethylation-cyclization of *N*-substituted acrylamides

While $\text{CF}_3\text{SO}_2\text{Na}$ has proven highly effective in various applications, the generation of CF_3 radicals from trifluoroacetic acid or its salts continues to be a focal point of intense interest within the scientific community. In this context, photoredox catalysis has emerged as a powerful tool for promoting the decarboxylation of weakly reactive carboxylic acids and then facilitating the generation of CF_3 radicals.¹³⁸ The photocatalyst forms a carboxylate complex with the carboxylic acids: upon visible-light absorption, the excited-state photocatalyst promotes the decarboxylation of the carboxylate conjugate generating a C-centered radical.¹³⁹ This excitation process undergoes by a Ligand to Metal charge transfer (LMCT), which involve the transfer of electron density to the metal centre (**Figure 15**). Typically only electrophilic metals in higher valent oxidation states are engaged in LMCT photochemistry such as: Cu(II) ^{140,141}, Co(III) ^{142,143}, Fe(III) ^{144,145}, complexed metal ions. Exploiting this reactivity, in 2024, Julià-Hernandez described an iron(III) photocatalyzed decarboxylative approach for the trifluoromethylation of $\text{C(sp}^2\text{)-H}$ bond (**Scheme 88**).¹⁴⁶ Reaction condition optimization was carried out using an (hetero)arene as model compound¹⁴⁶. In presence of Fe(OTf)_2 (10mol%) as catalyst, sodium trifluoroacetate as radical source and potassium persulfate as chemical oxidant, under 390nm of irradiation, various electron-rich trifluoromethylated (hetero)aromatics were obtained in up to 80% yield.



Scheme 88: Iron (II) photocatalyzed trifluoromethylation of (hetero)arenes.

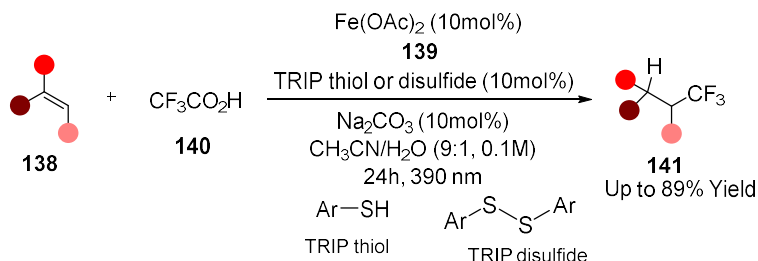
Thanks to this approach, it was possible to promote the direct decarboxylation of sodium trifluoroacetate (+2.4 V vs SCE) in presence of substrates with less positive potentials. A mechanism was also hypothesized (**Scheme 89**), according to the control experiments performed



Scheme 89: Mechanistic hypothesis

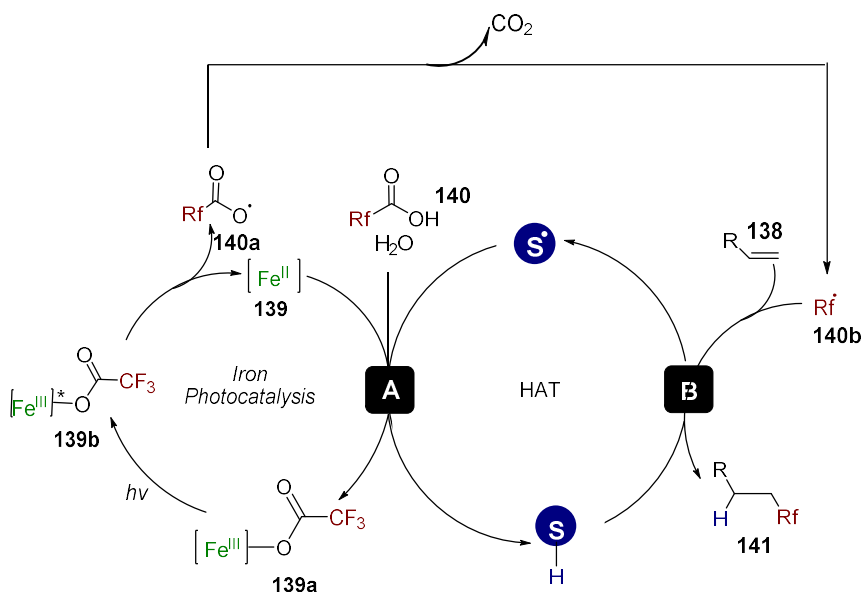
The catalytically active Fe(III) species (**136a**) are formed in situ via coordination of **L1** to $\text{Fe}(\text{OTf})_2$ and subsequent oxidation with $\text{K}_2\text{S}_2\text{O}_8$. Coordination of trifluoroacetate afford the carboxylate **136b** and its subsequent irradiation promote the inner-sphere photodecarboxylation via Fe-O homolytic cleavage in **136c**, resulting in the formation of $\cdot\text{CF}_3$. The radical addition to the substrate generates a radical intermediate which, after rearomatization, gives the product. Catalyst turnover is achieved by Fe(II) (**136e**) to Fe(III) (**135a**) oxidation with $\text{K}_2\text{S}_2\text{O}_8$.¹⁴⁶

Using an analogous approach, recently, West and co-workers reported the hydrotrifluoroalkylation of unactivated alkenes starting from commercially available carboxylic acids and pent-4-en-1-yl benzoate as the model substrate (**Scheme 90**).¹⁴⁷



Scheme 90: Photocatalytic trifluoromethylation of alkenes using Trifluoroacetic acid

The hydrotrifluoromethylation of different unactivated alkenes **138** was disclosed in up to 89% yield when operating in presence of $\text{Fe}(\text{OAc})_2$ (10mol%) as catalyst with TRIP thiol or disulfide (10mol%) under 390nm irradiation. Differently from the previous case, the reaction mechanism displays two combined catalytic cycles: the iron photocatalysis cycle and the hydrogen atom transfer cycle (HAT) (**Scheme 91**).



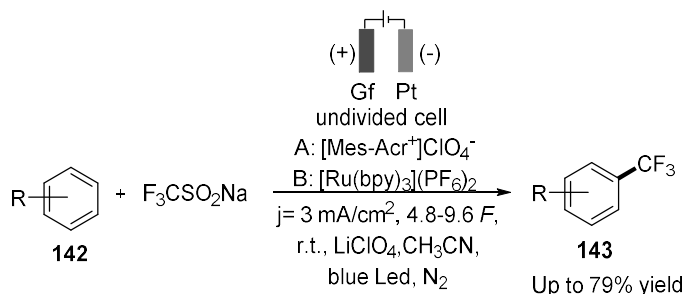
Scheme 91: The two combined catalytic cycle for the trifluoromethylation of alkenes

In the *iron photocatalysis* cycle, under 390 nm irradiation, the homolytic cleavage of the O-Fe bond of the photoexcited fluoroalkyl carboxylate **139b** takes place, leading to the formation of a carboxyl radical **140a** and a lower-valent iron species **139** (**Scheme 91**). Radical **140a** can then undergo decarboxylation to access fluoroalkyl radical species **140b**, which engage in

radical addition onto the alkene **138**, providing a transient carbon-centred radical intermediate. In the HAT cycle, the thiol function **SH** as the Hydrogen atom transfer reagent to furnish the hydrofluoroalkylation product **141** and an oxidizing thiyl radical. Finally, the thiyl radical **S[•]** reoxidizes the lower-valent iron intermediate while receiving a proton from another equivalent of acid substrate or H₂O, closing both catalytic cycles. The removal of water led to a decreased reaction yield, demonstrating that is detrimental for thiol regeneration.

4.1.4 ELECTROPHOTOCHEMICAL TRIFLUOROMETHYLATION

The first electrophotochemical C-H trifluoromethylation using Langlois reagent was developed by Ackermann in 2020.¹⁴⁸ The study started from the investigation of CF₃ addition to the easily available mesitylene Reaction condition optimization revealed [Mes-Acr]⁺ClO₄⁻ or the use of [Ru(bpy)₃](PF₆)₂ as photocatalyst allow to synthesized desired trifluoromethylated arenes with high yield and regioselectivity (**Scheme 92**).



Scheme 92: Electrophotochemical trifluoromethylation of (hetero)arenes using Langlois's reagent.

Cyclic voltammetry experiments were performed to confirm the electrophotocatalytic process which is reported in **Scheme 93**. Sodium sulfinate shows an irreversible oxidation behaviour at 1.02V vs SCE (**Figure 36-a-red line 2**). In the presence of the photocatalyst (PC) this behavior remained unaltered (**Figure 36-a-blue line PC+2**). However, upon blue light irradiation, a consumption of sodium trifluoromethanesulfonate was observed (**Figure 36-b-red line PC+2**)..

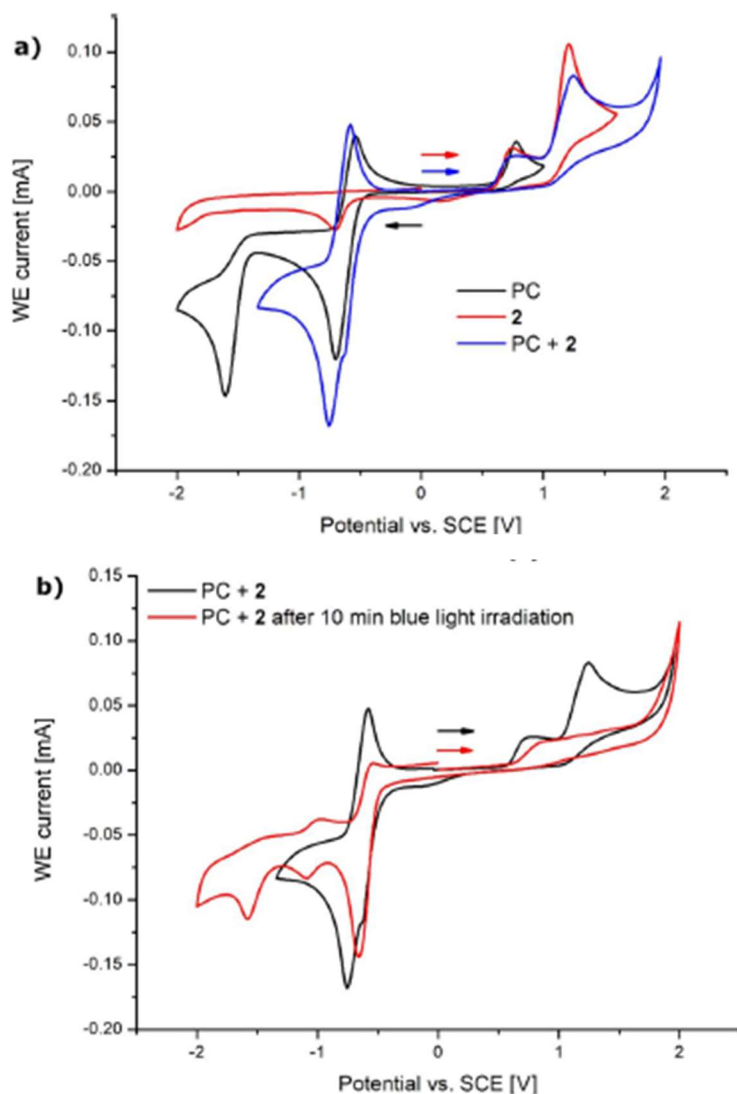
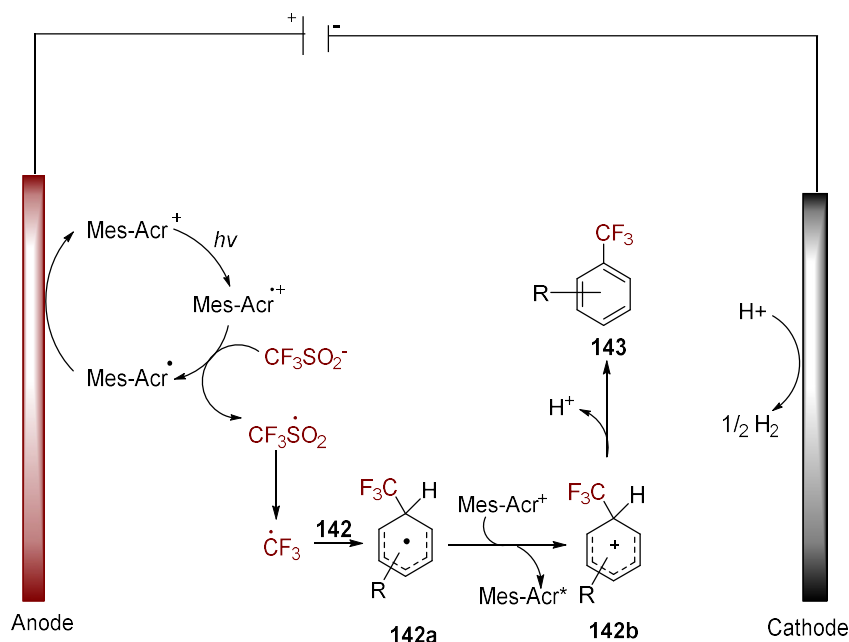


Figure 36: Cyclic voltammetry analysis. **2**= $\text{CF}_3\text{SO}_2\text{Na}$. (a) and (b): substrates (5mmol/L), LiClO_4 (100 mmol/L), MeCN, 100 mV/s. (a) PC (black), **2** (red), PC+**2** (blue). (b) PC+**2** (black), PC+**2** after being irradiated for 10 minutes with blue light (red).

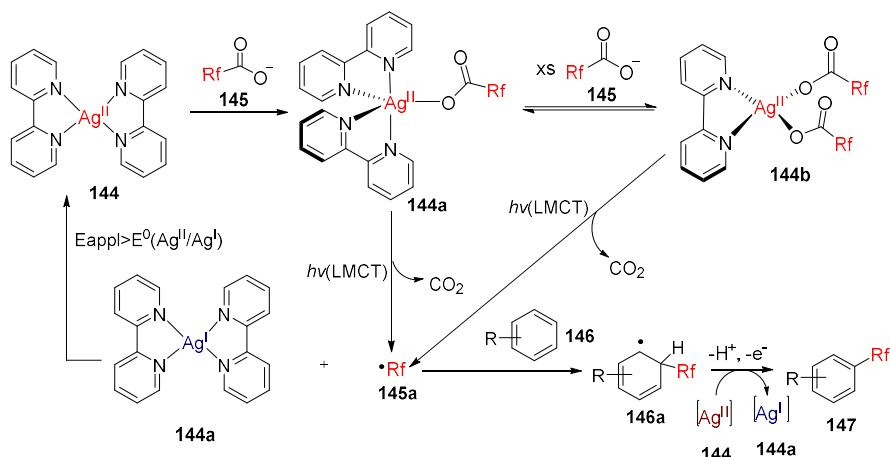
These findings suggest the formation of the CF_3 radical, which occurs by oxidation with the excited state of the PC. The mechanism proposed by the authors (**Scheme 93**) starts with the irradiation of the organic dye Mes-Acr⁺ which generates its oxidized excited state Mes-Acr⁺*. A SET process between Mes-Acr⁺* and the sulfinate anion results in the generation of the acridinyl radical and the CF_3SO_2 radical. Anodic electrooxidation of the

acridinyl radical subsequently reforms the ground state catalyst Mes-Acr⁺. Simultaneously, attack of the trifluoromethyl radical on the substrate **142** produces the **142a** radical, which undergoes SET oxidation to the cationic complex **142b**. In the meantime, **142a** could also be directly oxidized at the anode. Finally, proton abstraction delivers the desired product **143**, whereas protons are reduced to generate H₂ at the cathode.



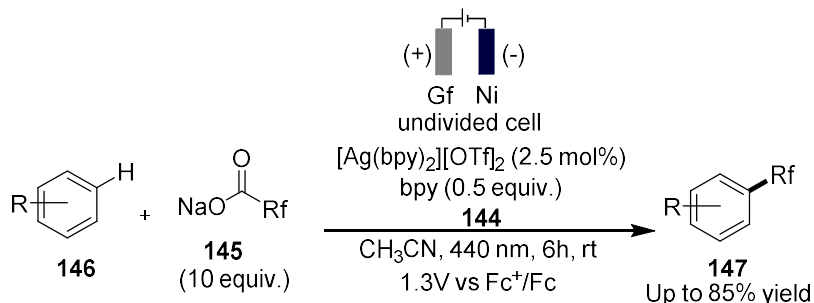
Scheme 93: Hypothesized mechanism of the electrophotocatalytic trifluoromethylation of arenes

With the aim to generate CF_3 radical starting from TFA, new electrophotocatalytic methods have been developed. In particular, in the last year, Nocera and co-workers reported synthesis, isolation, and structural characterization of $[\text{Ag}(\text{bpy})_2][\text{OTf}]_2$ and $[\text{Ag}(\text{bpy})_n(\text{O}_2\text{CCF}_3)_m][\text{OTf}]_{2-m}$ complexes ($\text{bpy}=2,2'$ -bipyridine; $\text{OTf}=\text{CF}_3\text{SO}_3^-$) in which Ag(II) does not present an electrophilic behaviour.¹⁴⁹ Notably, Although Ag(I) is a strong oxidant ($E^{\text{ox}}=0.799$ Vs NHE), Ag(II) shows a d9 electronic configuration which yields a greater oxidative power ($E^{\text{ox}} = 1.980$ V versus NHE)¹⁵⁰ by virtue of the hole in its 4d subshell.¹⁵¹ Therefore Ag(II) may promote the LMCT and photolysis of the photoexcited Ag(II)–TFA complexes under irradiation at 400nm. This results in rapid decarboxylation of the intermediate to generate trifluoromethyl radicals (**Scheme 94**). This latter interacts with the substrate, producing the radical cation intermediate **146a** which undergoes by a second single electron transfer oxidation with Ag(II) producing the desired product and the reduced Ag (I)



Scheme 94: Electrophotocatalytic pathway of arenes trifluoromethylation using Ag(II) complex and trifluoroacetic acid.

The use of $[\text{Ag}(\text{bpy})_2][\text{OTf}]_2$ together with a large excess of sodium trifluoroacetate and in presence of graphite anode and Nickel cathode at 1.3V, allowed to perform the electrophotocatalytic trifluoromethylation of electron poor arenes in up to 85% yield (**Scheme 95**).



Scheme 95: Electrophotocatalytic trifluoromethylation of arenes using Ag(II) complex and trifluoroacetic acid.

4.1.5 PERFLUOROALKYLATION

Unlike radical promoted C-H aromatic difluoromethylation and C-H aromatic trifluoromethylation functionalization, only a few examples of radical C-H perfluoroalkylation of aromatic compounds have been reported in literature. One of the most recent and synthetically interesting approaches was reported by West et al.,¹⁴⁸ where different long-chain fluorinated carboxylic acids have been tested as radical precursors along

with trifluoroacetic acids for the hydrotrifluoroalkylation of unactivated alkenes (**Figure 37**).

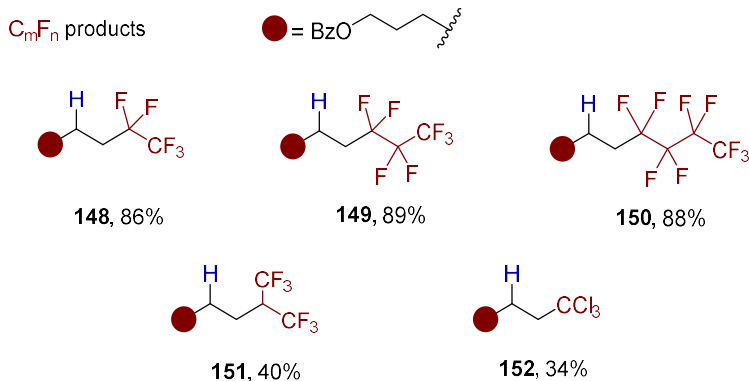
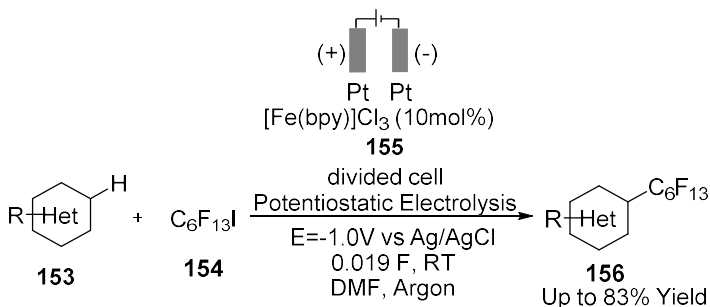


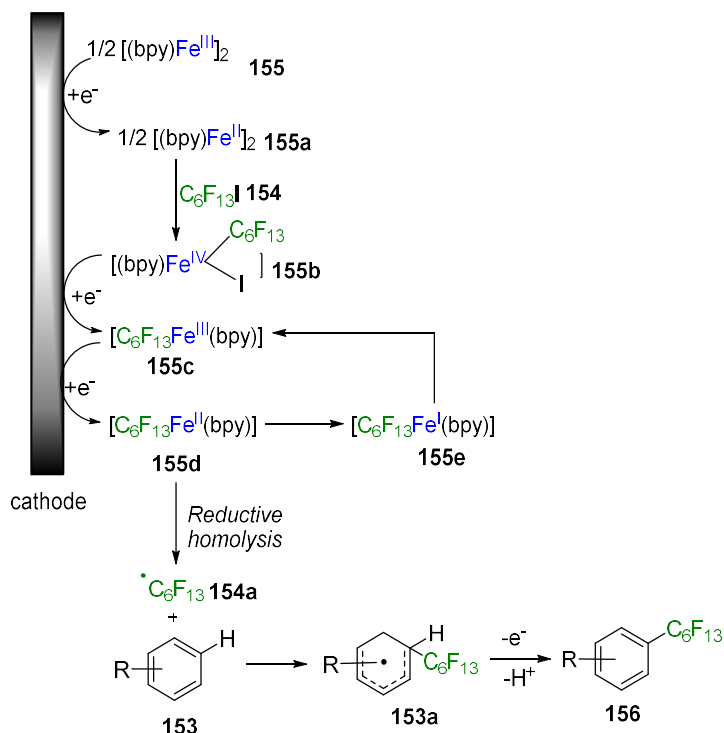
Figure 37: Examples of perfluoroalkylated substrates

In another example, the introduction of perfluoroalkyl group on aromatic and heteroaromatic substrates was investigated in the presence of IC_6F_{13} as fluorinated precursor and using $[(\text{bpy})\text{FeCl}_3]$ or $[(\text{bpy})\text{FeCl}_2]$ as photocatalyst (**Scheme 96**).¹⁵²



Scheme 96: Electrochemical perfluoroalkylation of (hetero)arenes

Five perfluoroalkylated arenes were prepared in yields up to 83%. The mechanism of this reaction is depicted in scheme **97** and involves the oxidative addition of $C_6F_{13}I$ to $[(bpy)Fe(II)]$ giving perfluoroalkylated iron complexes (**154b-154e**). Subsequently, the $Fe(III)$ specie **155c** is reduced, followed by reductive homolysis generating a perfluoroalkyl radical **154a**, that attacks the arene **153**. Upon oxidation and deprotonation, the desired product **156** is obtained.

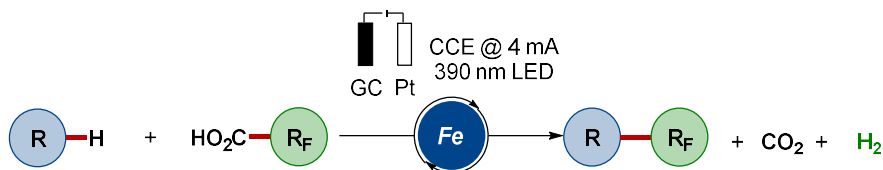


Scheme 97: Reaction mechanism of electrochemical perfluoroalkylation.

4.2 ELECTROPHOTOCHEMICAL IRON(III)-CATALYSIS FOR LATE-STAGE C–H FLUOROALKYLATIONS: RESULTS AND DISCUSSIONS

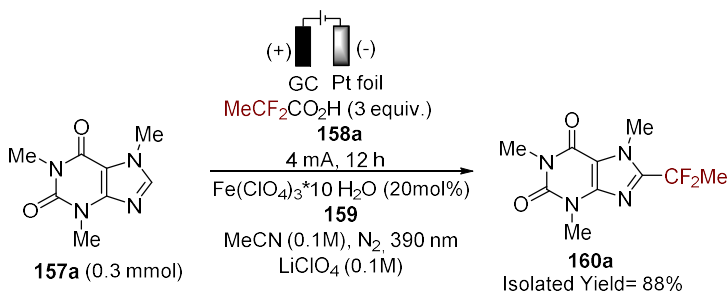
During my visiting period at the University of Göttingen, under the supervision of Prof. Lutz Ackermann, I had the opportunity to contribute to a project that was already underway within the research group. While I will not discuss into details of the contributions made by other co-authors, but I will present the studies that are essential for explaining the results of my work.

Before my arrival, the group, driven by an interest in developing new and efficient methods for introducing fluorinated groups into organic molecules, had undertaken a thorough investigation in this area. In particular, considering the recent literature, they envisioned a versatile strategy to generate fluorinated radicals (both electrophilic and nucleophilic) through decarboxylative Iron (III) electrophotocatalysis starting from commercially available carboxylic acids as starting materials (**Scheme 98**). With this approach in hands, a late stage fluoroalkylation could be performed.



Scheme 98: Iron(III) electrophotocatalytic perfluoroalkylation of biological active compound

Initially, caffeine was selected as model substrate for the iron catalyzed 1,2-difluoroethylation reaction, using 2,2-difluoroproionic acid **158a** as the fluorinated reagent. In presence of Iron(III) perchlorate as pre-catalyst, glassy carbon anode (GC), Pt cathode (Pt) at 4.0 mA galvanostatic electrolysis with 390 nm irradiation, the desired compound **160a** was afforded in 88% yield (**Scheme 99**).



Scheme 99: Optimized conditions for the 1,2-difluoroethylation of caffeine

Using these reaction conditions, the versatility of the method was demonstrated across various substrates. Xantines derivatives **160b-160e** (**Figure 38**) were successfully functionalized; additionally, the method proved effective for medicinally relevant heterocyclic scaffolds **161-162** and nucleobase analogues **163-164**. Moreover, caffeine was reacted with other fluorinate carboxylic acids (such as $\text{CF}_2\text{CF}_2\text{HCOOH}$, $\text{CF}_2\text{CH}_2\text{CH}_2\text{COOH}$ and $\text{CF}_2\text{C}_6\text{H}_5\text{COOH}$) affording corresponding caffeine perfluoroalkylated compounds **165-169** in up to 68% yield (**Figure 38**).

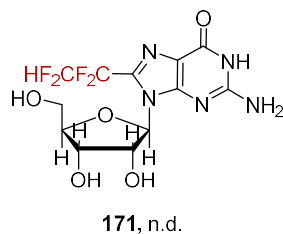
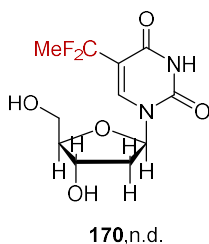
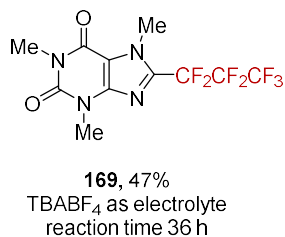
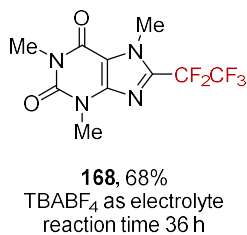
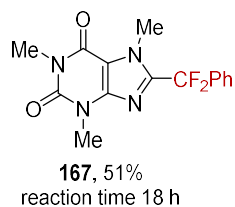
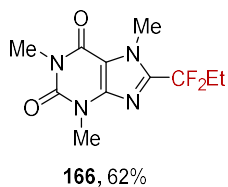
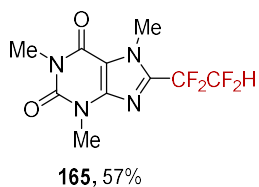
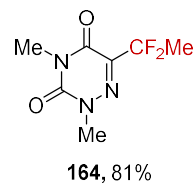
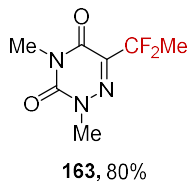
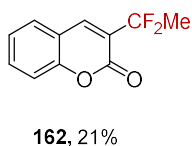
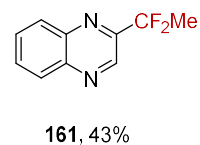
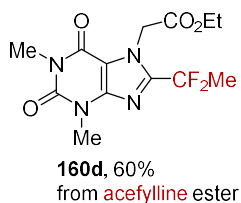
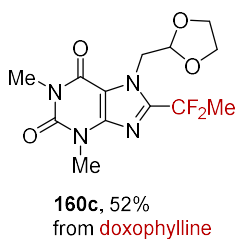
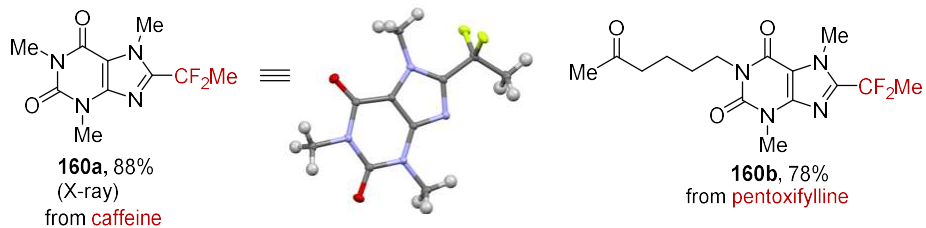
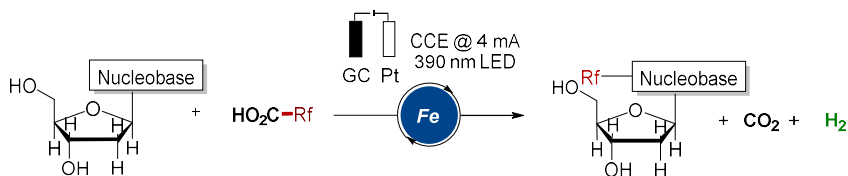


Figure 38: Late-stage Functionalization

Although the method displayed good applicability, it could not be applied to free nucleoside analogues, such as deoxyuridine and guanosine derivatives **170-171** (**Figure 38**). Since these compounds are of significant interest due to their antiretroviral activity, as exemplified by trifluorouridine, we focus our attention on the perfluoroalkylation of these challenging substrates (**Scheme 100**) and then expanded to other nucleosides and nucleobase analogues. The selection of substrates and reaction conditions was guided by their radical philicity, calculated through DFT analyses.¹⁵³



Scheme 100: Perfluoroalkylation of Nucleoside

4.2.1 ELECTROPHOTOCHEMICAL SET-UP

The electrophotocatalytic set-up adopted in order to perform such transformation is reported in **Figure 39**. The reaction media (usually 3 ml) and the stirring bar are placed in a 10 ml Schlenk type undivided electrochemical cell (**Figure 39-A**) fitted with a cap that holds two metallic electrode holders. These latter can be moved inside the cell in order to regulate the electrodes immersion in the solution. Moreover, the two holders are placed at specific and standardized distance to avoid undesirable contacts between anode and cathode. The electrochemical cell is connected at Metrohm MULTI AUTOLAB M204 potentiostat (**Figure 39-B**) and placed between two 75 W violet 390 nm LED Kessil lamps, over a stirring plate. In order to avoid overheating, two fans are used as cooling system (**Figure 39-C**).

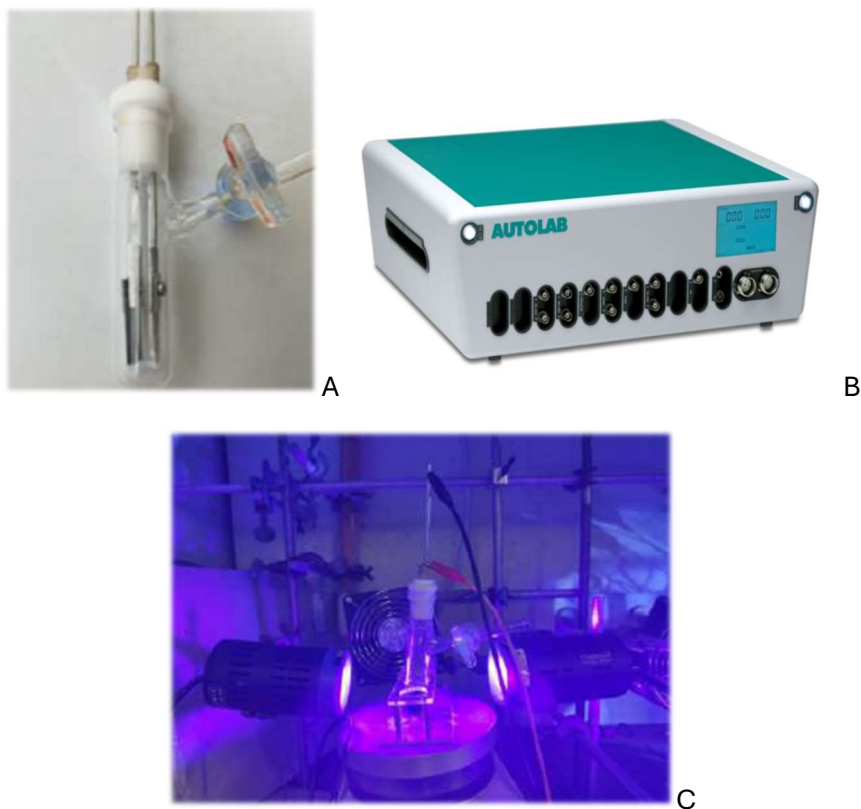


Figure 39: Electrophotochemical set-up

4.2.2 PYRIMIDINE ANALOGUES PERFLUOROALKYLATION

To predict the reactivity of fluorinated groups,^{154,155} computational studies were conducted to assess the philicity character of various fluorinated radicals in comparison to the well-studied CF_3 and CF_2H radicals.¹⁵³ As shown in **Figure 40** perfluoroalkyl chain radicals exhibit an electrophilic nature; however, they are also more nucleophilic than the CF_3 radical and occupy an intermediate position between CF_3 and CF_2Me on the philicity scale. Radicals such as CF_2Me , CF_2Et , and CF_2Ph display a pronounced nucleophilic character, even more distinct than that of CF_2H . The observed results obtained by DFT calculation confirmed the experimentally reactivity of substrates towards various fluoroalkyl radicals.

It was envisioned that xanthines derivatives present an ambident character, which are prone to the addition of both nucleophilic and electrophilic radicals.

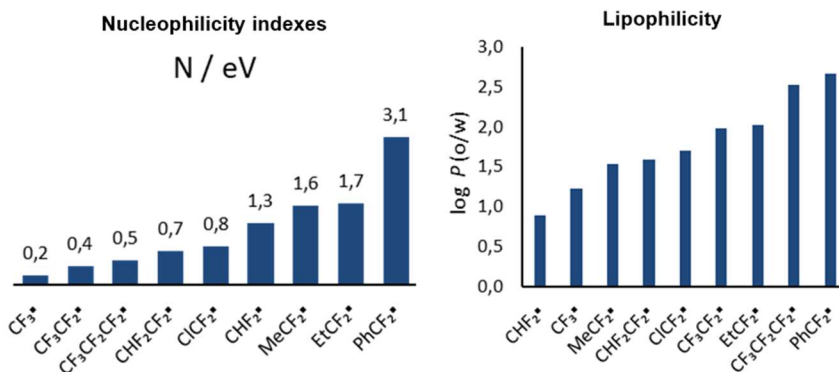
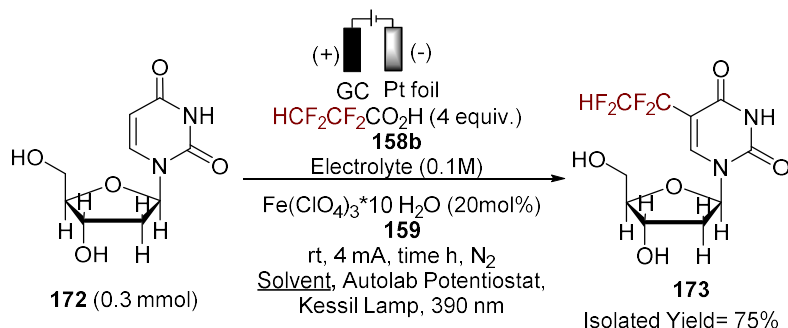


Figure 40: Calculation of fluorinated radicals nucleophilicity and lipophilicity

Using the same approach, the radical lipophilicity, characterized by log *p* values^{156,157} was also evaluated. CF₂Me radical is characterized by log *P* (n-octanol/water) = 1.5, which makes it more lipophilic than CF₂H and CF₃. Instead CF₂Ph group possesses the highest lipophilicity. Noteworthy, the developed functionalization can thus give a variety of options to alter lipophilicity of the target molecule in the drug design.

Initially, deoxyuridine **172** was selected as a model substrate to explore the fluoroalkylation of nucleosides. This choice was driven by its relevance as a simple nucleoside analogue, which allowed for a clearer understanding of the reactivity and challenges associated with introducing fluoroalkyl groups into nucleoside structures. Evaluating its electronic properties, we hypothesized that deoxyuridine could easily react with electrophilic radicals (such as CF₂CF₂H, CF₂CF₃) due to the more pronounced activation of position 5 by the enamide moiety. Therefore, 3*H*-tetrafluoropropionic acid (CF₂CF₂HCO₂H) was selected as radical source to investigate the electrophotocatalytic perfluoroalkylation of substrate **172** in the presence of 20 mol% of iron perchlorate decahydrate catalyst (20 mol%) and the electrolyte under Nitrogen atmosphere. The electrochemical cell was then connected to the Autolab potentiostat and placed between the two Kessil Lamp. The electrolysis was carried out at 4 mA for 12h. (**Table 15**).



Entry	Time (h)	Solvent	Electrolyte	*Nmr Yield (%)
1	12h	CH ₃ CN	LiClO ₄	traces
2	12h	DMSO	LiClO ₄	13%
3	12h	DMSO/H ₂ O 9:1	LiClO ₄	46%
4	12h	DMSO/H ₂ O 1:1	LiClO ₄	70%
5	18h	DMSO/H ₂ O 1:1	LiClO ₄	50%
6	12h	DMSO/H₂O 2:1	LiClO₄	85%**
7	9h	DMSO/H ₂ O 2:1	LiClO ₄	78%
8	12h	DMSO/H ₂ O 1:4	LiClO ₄	25%
9	12h	DMSO/H ₂ O 2:1	TBABF ₄	53%
10	12h	DMA/H ₂ O 2:1	LiClO ₄	-
11	12h	HFIP	LiClO ₄	-
12	12h	H ₂ O	LiClO ₄	-

*using trifluorotoluene as Internal Standard

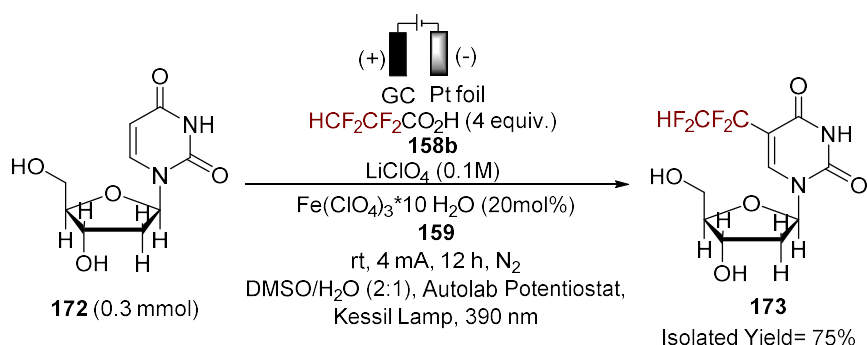
**75% Isolated Yield

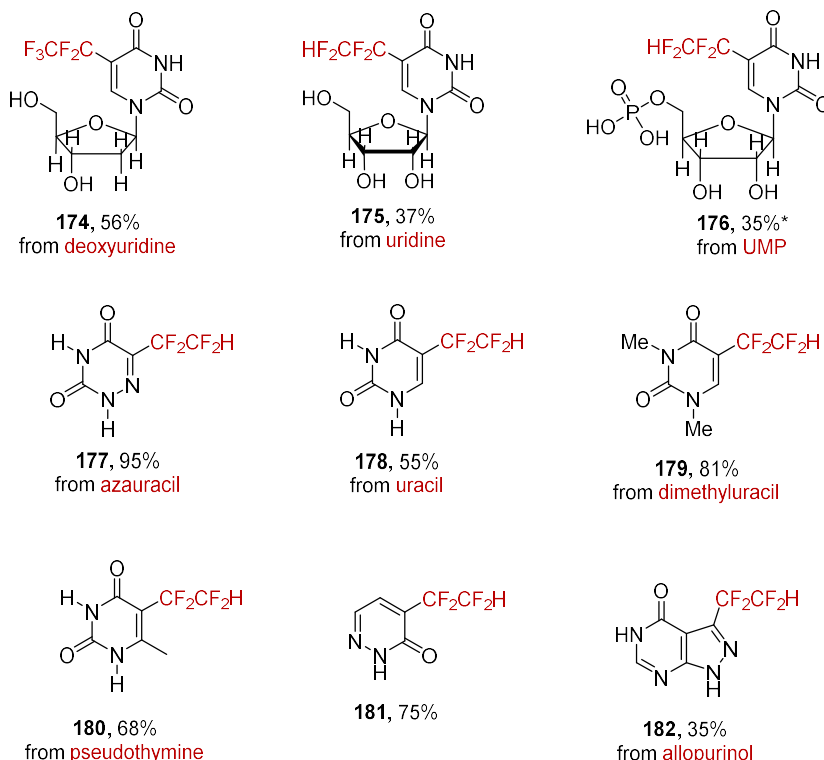
Table 15: Screening of reaction conditions

A preliminary screening of the reaction conditions was conducted to investigate the effects of time, solvent, and electrolyte on the transformation. Reaction conditions adopted for the fluoroalkylation of caffeine revealed unsuccessful due to the insolubility of deoxyuridine in the solvent media (**entry 1**), whereas DMSO ensured the total solubility of the starting material leading to 13% of NMR yield (**entry 2**). The mixture DMSO/H₂O 9:1 afforded the product in 46% (**entry 3**), probably due to the facilitated cathodic H₂ evolution. This was also confirmed by **entry 4**, where DMSO/H₂O 1:1 achieved the product in 70% yield. The reaction time increasing to 18 hours led to a reduction in the NMR yield (**entry 5**), probably due to degradation and by-product phenomena. This behaviour was also demonstrated by kinetic studies, which established 12h as the best reaction time. Modulating the DMSO:H₂O ratio to 2:1, the desired fluorinated deoxyuridine **173** was achieved in 75% of isolated yield (**entry 6**-NMR, 85%

yield) TBABF₄ was also tested under optimized reaction conditions reported in **entry 6**, but a lower efficiency was detected (**entry 9**). Besides, other solvents activity such as DMA, HFIP and H₂O revealed unsuccessful.

Inspired by the result obtained with deoxyuridine **173**, we then focused our attention on the challenging late-stage modification of other free nucleosides to provide direct access to the API Trifluridine analogues. In the displayed experiment, the starting material (0.3 mmol), the Iron perchlorate decahydrate catalyst (20 mol%) and the electrolyte (0.1M) were dissolved in DMSO/H₂O 2:1 under Nitrogen atmosphere. Ones homogeneous solution was obtained, 3*H*-tetrafluoropropionic acid was added. The electrochemical cell was then connected to the Autolab potentiostat and placed between the two Kessil Lamp. The electrolysis was carried out at 4 mA for 12h.



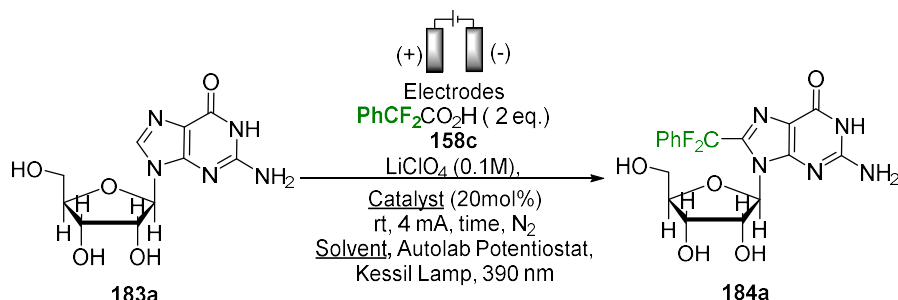


Scheme 101: Late stage functionalization in DMSO/H₂O 2:1

To our delight, fluoroalkylation of deoxyuridine **172** also afforded the pentafluoroalkylation products **174** as fluorinated analogs of antiviral drug Edoxyuridine¹⁵⁸. Moreover, the functionalization of uridine with three free-OH groups afforded compound **175** in 35% yield, due to the detected hydrolysis of glycosidic bond. Unexpectedly, the direct fluoroalkylation of the unprotected nucleotide uridine-5'-monophosphate (UMP) **176** was achieved in comparable yield with uridine, thus demonstrating that the phosphate group didn't affect the reaction efficiency. The use of DMSO/H₂O 2:1 enabled the late-stage functionalizations of the unsubstituted 6-azauracil to give tetrafluoroethyl derivative **177**. The ferraphotoelectrocatalysis was also applicable to the parent uracil nucleobase **178**, as well as its N,N'-dimethyl derivative **179**. Efficient fluoroalkylation of nucleobase analog pseudothymine was also achieved **180**. Moreover, we tested the robustness of the photoelectrocatalysis for the direct functionalization of the medically relevant heterocycles pyridazinone **181** and the purine analogue allopurinol **182**. This latter was functionalized in chemo- and site-selective way in the C3 position without affecting the otherwise reactive C6 position.

4.2.3 PURINE ANALOGUES PERFLUOROALKYLATION

Although the previous method displayed good versatility with a variety of substrates, it proved unsuccessful when applied to guanosine and its analogues. Despite optimizing the reaction conditions, the fluoroalkylation did not proceed efficiently, possibly due to the unique electronic properties and steric hindrance of the guanosine structure. After having evaluated the electronic properties of this molecules, we hypothesized that the only the 7-position is sufficiently electrophilic to undergo radical perfluoroalkylation. This assumption was based on the electron density distribution and the likely reactivity of the guanosine ring system. Moreover, guanosine contains three free hydroxyl groups and both NH and NH₂ groups, which could potentially coordinate to the iron catalyst. This coordination may decrease the catalyst activity, as the binding of these functional groups to the metal center could hinder the formation of the active catalytic species and interfere with the desired fluoroalkylation process. Moreover, the presence of such hydrophilic groups could complicate the extraction from water and the subsequent purification of the product. Based on these considerations, and taking into account the previously calculated philicity scale, we selected PhCF₂COOH as the fluorinated group for the functionalization of guanosine. A deep screening of the reaction condition was then performed. Selected examples are reported in **Table 16**.



Entry	Time (h)	Catalyst (mol %)	Solvent	Electrodes	PhCF ₂ CO ₂ H (equiv.)	*Nmr Yield (%)
1	12	Fe(ClO ₄) ₃ ·10H ₂ O	DMSO/H ₂ O 2:1	GC Pt	4	16
2	12	Fe(ClO ₄) ₃ ·10H ₂ O	DMSO/H ₂ O 4:1	GC Pt	3	31%
3	12	Fe(ClO ₄) ₃ ·10H ₂ O	DMSO/H ₂ O 4:1	GC Pt	2	43%
4	12	Fe(ClO ₄) ₃ ·10H ₂ O	DMSO/H ₂ O 4:1	Gf Pt	2	51%

5	12	Fe(ClO ₄) ₃ *10H ₂ O	DMSO/H ₂ O 4:1	RVC Pt	2	63(65)%
6	9h	Fe(ClO ₄) ₃ *10H ₂ O	DMSO/H ₂ O 2:1	RVC Pt	2	50%**
7	12h	Fe(OAc) ₂	DMSO/H ₂ O 4:1	RVC Pt	2	20%
8	12h	Fe(Cl) ₃ *6H ₂ O	DMSO/H ₂ O 4:1	RVC Pt	2	20%

* Using trifluorotoluene as Internal Standard

** 75% Isolated Yield

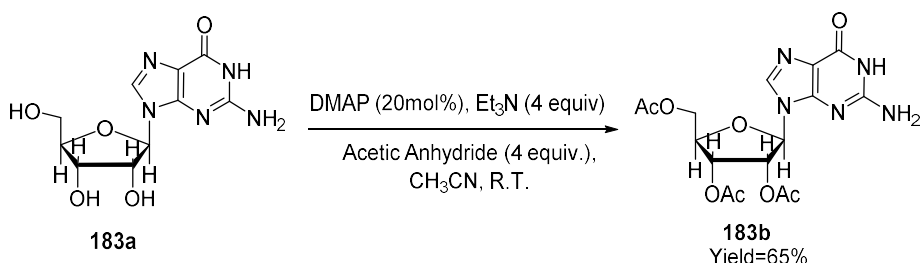
Table 16: Screening of reaction conditions

As reported for deoxyuridine **172**, a careful tuning of the reaction conditions was required to achieve a satisfactory level of efficiency in the fluoroalkylation of guanosine **183a**. This adjustment involved optimizing factors such as reaction time, solvent choice, temperature, and catalyst concentration to enhance the reactivity of guanosine and ensure the desired functionalization occurred efficiently. Upon employing 4 equivalents of α,α -difluorobenzeneacetic acid as the fluorinating reagent, under the optimized reaction conditions reported for deoxyuridine, the desired product was obtained in a notably low yield of 16% (**entry 1**). The crude mixture revealed also the formation of PhCF₂-CF₂Ph by-product, which arises from the tendency of the PhCF₂ radical to self-dimerize. To address this issue, the equivalents of PhCF₂CO₂H were reduced to 2 and employing a DMSO/H₂O (4:1) solvent mixture led to a significant improvement in yield, reaching up to 43% yield (**entries 2 and 3**). The use of graphite electrodes afforded the product in 51% yield (**entry 4**) whereas the combination RVC/Pt gave the best result, leading to the formation of compound **184a** in 65% yield (**entry 5**). We further optimized the reaction by reducing the reaction time to 9 hours, achieving **184a** in a 50% NMR yield (**entry 6**). Finally, the use of different iron catalysts resulted in a decrease in yield to 20% (**entries 7-8**), accompanied by the deposition of iron on the cathode electrode. These results suggest that the catalyst was not effectively regenerated at the anode, leading to a reduction of iron to its metallic (0) state, which likely hindered the catalytic cycle and decreased the overall yield.

Having established a suitable protocol for the perfluoroalkylation of purine **183a**, the scope of this methodology was then extended to other purines such as **183b** and **183c**.

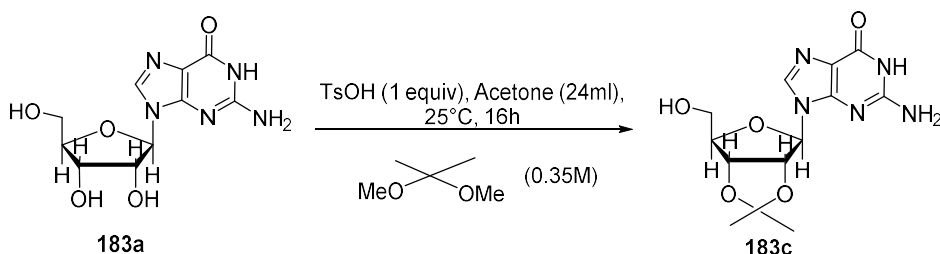
Acetate guanosine **183b** was synthesized by reacting guanosine **183a** in acetonitrile with DMAP, triethylamine and acetic anhydride for 14 h at RT.

After this time, the desired product **183b** was obtained as white solid in 65% yield after chromatographic purification ¹⁵⁹



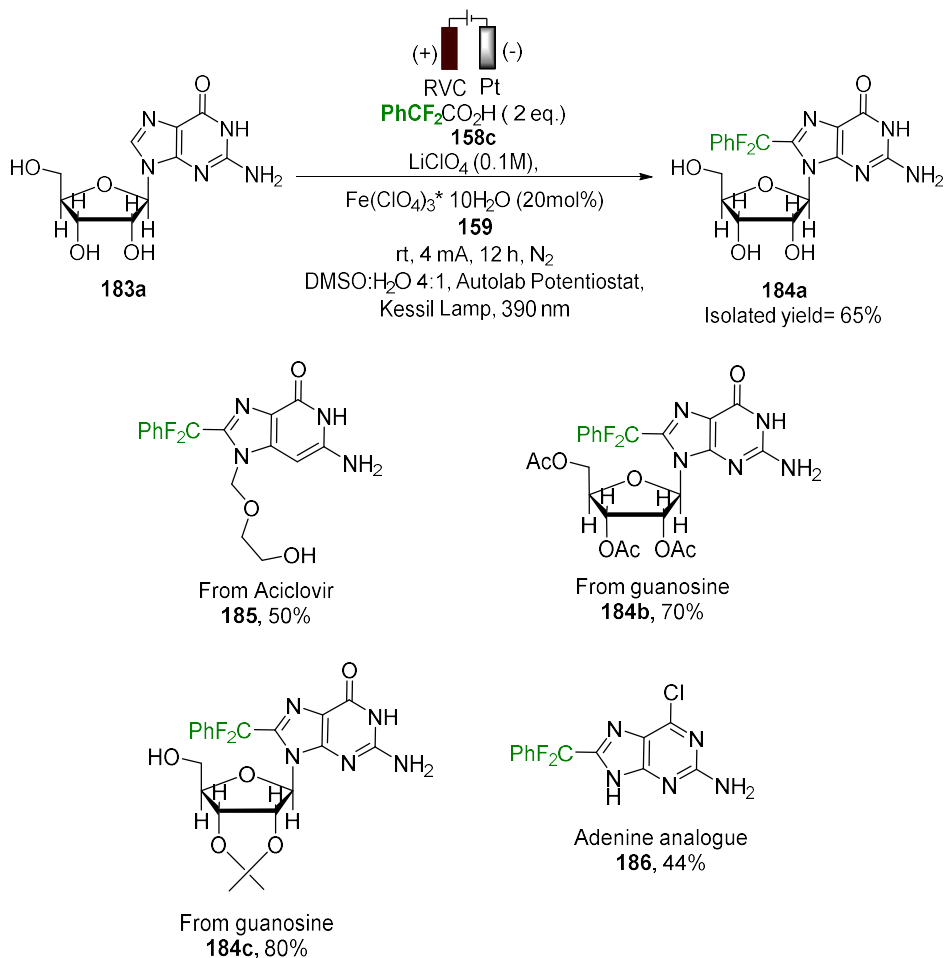
Scheme 102: Protection of guanosine OH groups with Acetic Anhydride

The dimethoxytetrahydrofuranyl derivative **183c** was instead obtained by dissolving guanosine **183a** in acetone followed by the addition of p-Toluenesulfonic acid and a large excess of 2,2- dimethoxypropane. The reaction mixture was stirred overnight at 25 °C, and after a workup with NaHCO₃, product **183c** was obtained as white solid in 34% yield. ¹⁶⁰



Scheme 103: Protection of guanosine OH group with 2,2-dimethoxypropane

These substrates, and others such as compound **185** and **186** were then subject to standard reaction condition for perfluoroalkylation functionalization: the starting material, the Iron perchlorate decahydrate catalyst (20 mol%) and the electrolyte were dissolved in DMSO/H₂O 2:1 under Nitrogen atmosphere. Once an homogeneous solution was obtained, the α,α -Difluorobenzeneacetic acid were added. The electrochemical cell was assembled with RVC anode and Pt cathode and connected to the Autolab potentiostat between the two Kessil Lamp. The electrolysis was carried out at 4 mA for 12h.



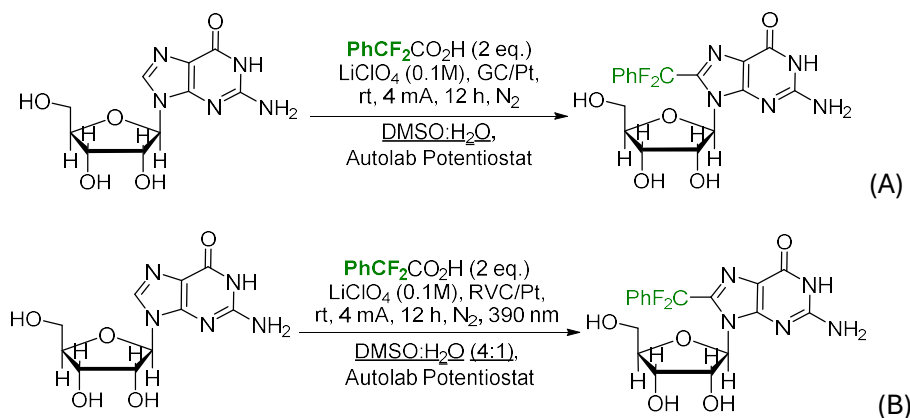
Scheme 104: Brief late-stage functionalization with guanosine analogues

As shown in Scheme **104**, the fluorination of the antiretroviral compound Aciclovir (compound **185**) was accomplished in moderate yield, while the protection of the free OH groups led to conspicuous improvement, affording the compound **184b** and **184c** in 70% and 80% yield respectively. Moreover, the efficiency of the electrophotocatalytic method was also demonstrated with adenine analogue **186** in 44% yield.

Mechanistic studies

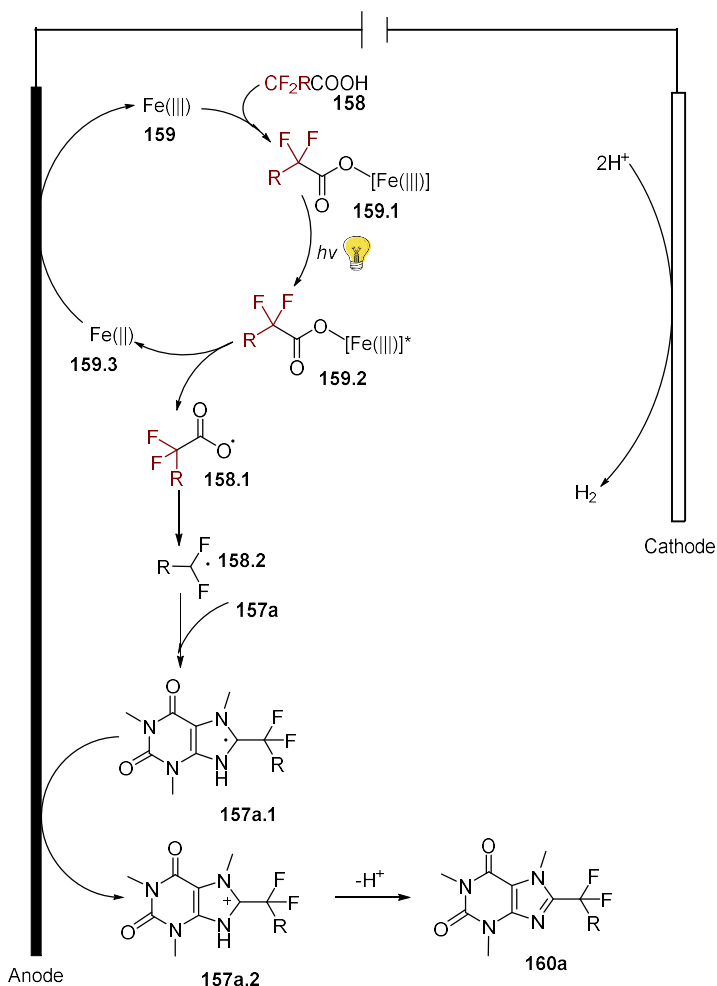
To assess the utility of the developed method, we conducted two control experiments. In **Scheme 105-A**, we report our findings on the electrochemical oxidation of 2,2-difluorobenzene carboxylic acid. The reaction was carried out under galvanostatic conditions, without light or photocatalyst; however, only unreacted starting material was recovered.

Additionally, we tested the activity of RVC as a photoanode,¹⁶¹ performing the transformation under light irradiation during constant current electrolysis without a photocatalyst (**Scheme 105-B**). In this case, the desired product was obtained in trace amounts.



Scheme 105: Control experiments

Additional ON/OFF experiments performed by Ackermann's group, kinetic studies and the measurement of H_2 evolution by GC, allowed to elucidate the mechanism for this transformation, which is schematized in **Scheme 106**.



Scheme 106: proposed mechanism

Initially, the Iron(III) precatalyst forms a carboxylate complex **159.1** with the carboxylic acid, which upon photochemical excitation undergoes ligand-to-metal charge transfer (LMCT). The photoexcited complex decarboxylates releasing the fluoroalkyl radicals **158.2** along with iron (II) species which is then anodically reoxidize to iron (III). The generated fluoroalkyl radical adds to the substrate, followed by oxidation and deprotonation, to furnish the desired product **160a**. On the other hand, the released protons are reduced at the cathode to generate molecular hydrogen.

4.3 CONCLUSION

The Iron (III)-electrophotocatalytic strategy for direct late-stage fluoroalkylation with different fluorinated carboxylic acids was accomplished. The addition of CF_2Me was firstly investigated by Ackermann's group using caffeine as model substrate in presence of Glassy Carbon anode and Platinum cathode, and blue light irradiation. The scope was then expanded to other xantines derivatives, nucleobase analogues and medicinally important heterocyclic scaffolds in up to 78% isolated yield). The perfluoroalkylation of deoxyuridine was achieved in 75% of isolated yield in presence of the electrophilic $\text{CF}_2\text{CF}_2\text{H}$ radical, using $\text{DMSO}/\text{H}_2\text{O}$ 2:1 as solvent. The functionalization of uridine and nucleobase analogues was achieved in up to 95% yield. The possibility to directly functionalize the UMP (uridine monophosphate) was successfully demonstrated in 35% of yield. Moreover, the functionalization of guanosine with the nucleophilic PhCF_2 radical was afforded in 65% of yield in $\text{DMSO}/\text{H}_2\text{O}$ 4:1 using RVC and Platinum electrodes. Other guanosine analogues have been tested, demonstrating that the protection of the OH groups improve the reaction efficiency (up to 80% yield).

These results obtained highlight the significant versatility and the potential of perfluorofunctionalization by electrophoto approach in the functionalization of a wide range of biologically relevant molecules, including xanthine derivatives, nucleobase analogues, and important medicinal scaffolds. The ability to efficiently introduce fluorinated groups into these structures open up new possibilities for the development of bioactive compounds, particularly in the fields of drug discovery and medicinal chemistry. By enabling selective late-stage functionalization, the strategy offers a powerful tool for the modification of complex molecules, which is critical for optimizing their pharmacological properties, such as potency, selectivity, and stability. Furthermore, the success of this approach in overcoming challenges associated with nucleosides and their analogues, including guanosine and uridine derivatives, underscores its broad applicability and potential to enhance the synthesis of novel therapeutic agents with enhanced bioactivity.

5 CHAPTER 5: EXPERIMENTAL PART

5.1 GENERAL METHODS

All chemicals were obtained from standard commercial suppliers and were used without any further purification.

Dry solvents were commercially available and they were stored under nitrogen over molecular sieves (bottles with crown cap)

Reactions were monitored by analytical thin-layer chromatography (TLC) using silica gel glass plates (0.25 mm thickness) and visualized using UV light. Flash chromatography was carried out on silica gel (230-400 mesh).

Proton NMR spectra were recorded on spectrometers operating at 300 MHz (Bruker Avance 300). Proton chemical shifts are δ (TMS) employed as the internal standard (CDCl_3 , $\delta = 7.26$ ppm). ^1H -NMR yireported in ppm (δ) with the solvent reference relative to tetramethylsilane~~nd~~ were calculated using 1,3,5-trimethoxybenzene as internal standard. ^{13}C NMR spectra were recorded on 300 MHz spectrometers (Bruker Avance 300) operating at 75 MHz, with complete proton decoupling. Carbon chemical shifts are reported in ppm (δ) relative to TMS with the respective solvent resonance as the internal standard (CDCl_3 , $\delta = 77.0$ ppm). Carbon spectra of compound **182** was measured with Bruker Avance III HD 400, ^{31}P NMR spectra were recorded on a 300 MHz spectrometer (Bruker Avance 300) operating at 121.2 MHz, with complete proton decoupling. ^{19}F NMR spectra were recorded on 300 MHz spectrometers (Bruker Avance 300) operating at 282.1 MHz; fluorine chemical shifts are reported in ppm (δ) relative to CFCl_3 with the respective solvent resonance as the internal standard (CFCl_3 ; $\delta = 77.0$ ppm). For ^{19}F NMR yields of electrophotocatalytic experiments, PhCF_3 was used as an internal standard. Coupling constants (J) are reported in Hertz. The following abbreviations are used to indicate the multiplicity in NMR spectra: s - singlet; d - doublet; t - triplet; q - quartet; pq - pseudo quartet; dd - double doublet; tt - triplet of triplets, sext - sextuplet; sept - septuplet; bs - broad signal; m - multiplet.

Enantiomeric excess determinations of compounds **104a-e**, **105** were performed under the conditions reported below with Agilent 1100 series. BINAM enantiomers were discriminated by Agilent Technologies 1260 Infinity HPLC analysis. The corresponding chiral stationary phases are indicated in the experimental part.

Mass spectra of compounds **94a-1** and **96a-1** were carried out using Mass spectra were registered on Synapt G2-Si(Waters) equipped with an ESI ion source. Mass characterization of **104a-e** were registered were on an APEX II & Xmass software (Bruker Daltonics) instrument or on a thermo Finnigan

LCQ Advantage instrument, equipped with an ESI ion source. High resolution mass spectra (HRMS) of Supported Eosin Y and compounds **98a** and **107**) were acquired using a Bruker solarix. XR Fourier transform ion cyclotron resonance mass spectrometer (Bruker Daltonik GmbH, Bremen, Germany) equipped with a 7 T refrigerated actively-shielded superconducting magnet. The samples were ionized in positive ion mode using a MALDI or ESI ionization sources. HRMS of compounds **173-186** were measured with APEX IV 7T FTICR.

$[\alpha]_D^{25}$: Optical rotations of compounds **94a-e** and **96a-e** were obtained on a JASCO P-1030 polarimeter (Series: A014060839) at 589 nm using a 1 mL cell, with a length of 1 dm, at 14°C. Optical rotation of **104a-e** were measured on a Perkin-Elmer 241 polarimeter at 589 nm using a 5 mL cell, with a length of 1 dm.

Melting points of **173-186** were measured using Stuart melting point apparatus SMP3, Barloworld Scientific

IKA Electrasyn 2.0 apparatus was used for the electrochemical coupling of compounds **94a-i**.

LEDs employed for the home Photoreactor#1: Commercially available SMD LED 2835 60 led/m 24V, with an IP95 “plug and play system” without extra wiring connection. (See paragraph 5.3.1-Description of photoredox set-up for further information)

Syringe pumps and fluidic devices description: Chemyx Fusion 100-X syringe pumps were used. Fluidic device was realized with a coil tube of PFA inner diameter: 0.020 inches/0.0508 cm, outer diameter 1/16”, length: 67.1 and a total reactor volume of: 136 μ L) purchased from IDEX.

Iron perchlorate hydrate “ $\text{Fe}(\text{ClO}_4)_3 \cdot x\text{H}_2\text{O}$ ” was purchased from Sigma-Aldrich; iron content corresponding to the formula $x = 10.08 \pm 0.10$ was determined by complexometric titration using EDTA and salicylic acid as an indicator. ICP-MS analysis showed less than 50 ppm content of other metals (Cu, Ni, Co).

Electrophotochemical apparatus includes: Metrohm Autolab PGSTAT204 potentiostat and Platinum electrodes (10 mm $\times$ 15 mm $\times$ 0.25 mm, 99.9%; obtained from ChemPur® Karlsruhe, Germany) and glassy carbon (GC) electrodes (25 mm $\times$ 10 mm $\times$ 1.5 mm), SIGRACELL®GFA 6 EA, obtained from SGL Carbon (Wiesbaden, Germany). The electrochemical cell was irradiated by two 75 W violet 390 nm LED Kessil lamps

5.2 ELECTROCHEMICAL DEHYDROGENATIVE HOMO-COUPLING OF β -NAPHTHYLAMINES DERIVATIVES

5.2.1 DESCRIPTION OF ELECTROCHEMICAL SET-UP

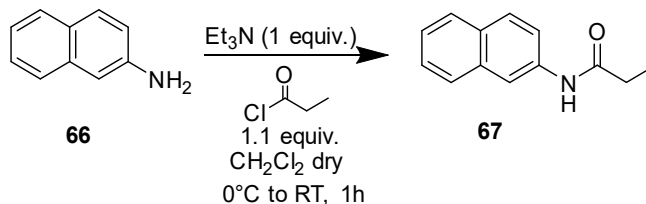


Figure 41: Electrochemical set-up for the dehydrogenative homo-coupling of compounds **94a-e**

The commercially available Electasyn 2.0 was used for the electrochemical intermolecular and intramolecular coupling of compounds **94a-i** (**Figure 41**). Firstly, all the reagents were dissolved in a fluorinated medium within a 5 ml beaker-type cell. Then, the electrochemical system was assembled with Platinum foil anode and cathode and degassed with Argon for two minutes to eliminate any dissolved oxygen. With an Argon atmosphere supplied by a gas bag, the solution was electrolyzed at a constant current of 5.5 mA.

5.2.2 SYNTHESIS OF β -NAPHTHYLAMIDES

Synthesis of compound **67** ⁷⁶

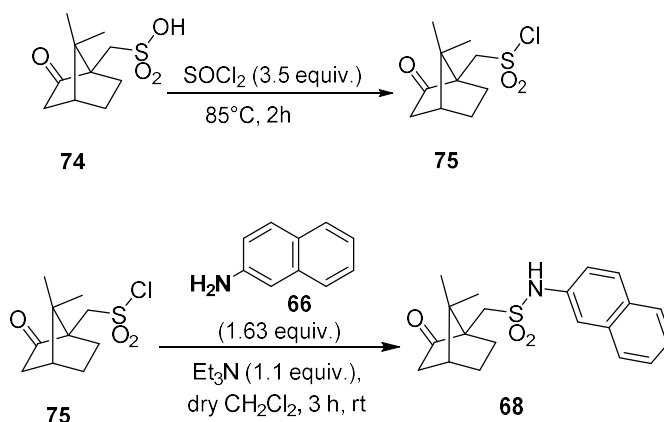


In a 10 mL round bottom flask, conditioned under nitrogen, was added **1** (1 equiv., 2.1 mmol, 300 mg) and triethylamine (1 equiv., 2.1 mmol, 290 μ L) in dry CH_2Cl_2 (0.5 M, 4 mL). The flask was positioned in an iced bath. Then, the propionyl chloride (1.1 equiv., 2.31 mmol, 200 μ L) was added slowly to the solution. The reaction mixture was allowed to warm to room temperature (25°C). After 1 hour of stirring the reaction was quenched with HCl 1M. The aqueous phase was extracted with dichloromethane (3 times) and the combined organic layers were dried over sodium sulphate, filtrated and concentrated under vacuum. The obtained residue was purified by flash column chromatography on silica gel (eluent: hexane/ethyl acetate 7:3). The desired product **67** was obtained as a white solid in 96% yield. .

^1H NMR (300 MHz, Chloroform-*d*) δ 8.24 (s, 1H), 7.80 (m, 4H), 7.45 (m, 2H), 2.48 (q, $J=7.42$ Hz, 2H), 1.31 (t, $J=7.42$ Hz, 3H).

All analytical data are in agreement with literature.⁷⁶

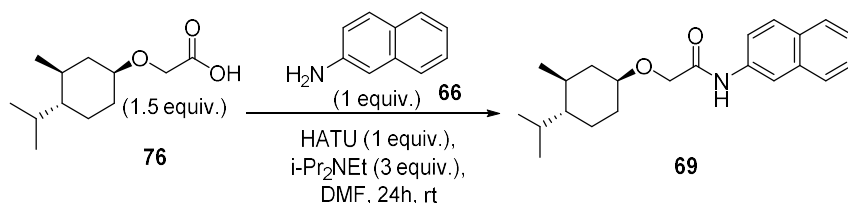
Synthesis compound **68**⁷⁷



In a round bottom flask, purged with N₂, were added (1R)-(-)-10 Camphorsulphonic acid **74** (1 equiv., 0.85 mmol, 197 mg) and SOCl₂ (3.5 equiv., 2.97 mmol, 350 µl). The solution was stirred for 10 minutes at room temperature and then for 2 hours at reflux. Then the temperature was cooled again at room temperature and the thionyl chloride was evaporated. In another flask was prepared a solution with β-naphthylamine (1.63 equiv., 1.39 mmol, 200 mg), triethylamine (1.1 equiv., 0.93 mmol, 128 µL) and dry DCM (5 mL), that was immersed in an ice bath. Then the chloride, diluted with 1 mL of dry DCM, was slowly added to the amine solution. The mixture was stirred for 2 hours and 30 minutes at room temperature. At the end, 9 mL of AcOEt and subsequently 3 mL of water were added in the flask. The organic phase was washed with HCl 1M and NaCl s.s. The organic phase was dried over sodium sulphate, filtrated and concentrated under vacuum. The obtained residue was purified by recrystallization from EtOH absolute and also by flash column chromatography on silica gel (eluent: hexane/ethyl acetate 8:2). The desired product **68** was obtained as pale beige solid in 36% yield.

¹H NMR (300 MHz, CDCl₃) δ 7.85 (s, 1H), 7.78 (m, 3H), 7.44 (m, 3H), 3.42 (d, *J*=15.2 Hz, 1H), 2.94 (d, *J*=15.2 Hz, 1H), 2.48 (m, 1H), 2.14 (m, 5H), 1.49 (m, 1H), 0.96 (s, 3H), 0.85 (s, 3H). **¹³C NMR** (75 MHz, CDCl₃) δ 217.51, 135.23, 133.83, 131.25, 129.43, 127.68, 127.65, 126.70, 125.56, 121.69, 118.81, 59.76, 49.13, 49.08, 43.13, 42.85, 27.65, 27.09, 19.88, 19.35. **MS (APCI)** *m/z* (%): calculated for C₂₀H₂₃NO₃S (M+H)⁺: 357.14; found: 358.5

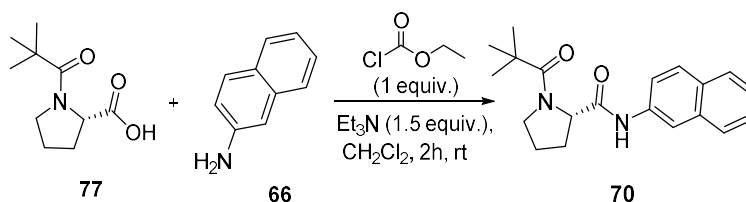
Synthesis of compound **69**⁷⁸



In a round bottom flask, purged with N_2 , were added in the following order: (-)-menthyloxyacetic acid **76** (1.5 equiv., 2.19 mmol, 470 mg), β -naphthylamine (1 equiv., 1.46 mmol, 211 mg), $i\text{Pr}_2\text{NEt}$ (3 equiv., 4.38 mmol, 760 μl) and dry DMF (14 ml, 0.1M). The solution was stirred for 5 minutes. Then, HATU (1 equiv., 1.46 mmol, 555 mg) was added and the reaction mixture was stirred for 24 hours at room temperature. The organic phase was washed with HCl 1M and NaCl s.s. An additional basic work up was done due to the presence of the acid unreacted. The organic phase was dried over sodium sulphate, filtrated and concentrated under vacuum. The clean product **69** was obtained as beige solid in 83% yield.

$^1\text{H NMR}$ (300 MHz, CDCl_3) δ 8.55 (s, 1H), 8.27 (s, 1H), 7.54 (m, 3H), 7.45 (m, 3H), 4.28 (d, $J=16.2$ Hz, 1H), 4.08 (d, $J=16.2$ Hz, 1H), 3.30 (m, 1H), 2.23 (m, 1H), 2.14 (m, 1H), 1.73 (m, 3H), 1.41 (m, 1H), 0.96 (m, 12H). **MS (APCI)** m/z (%): calculated for $\text{C}_{22}\text{H}_{29}\text{NO}_2$ ($\text{M}+\text{H}$) $^+$: 339.22; found: 340.1.

Synthesis of compound **70**⁷⁹

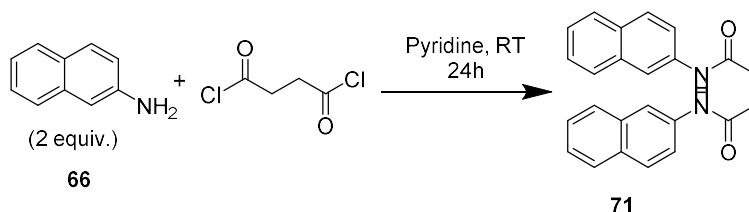


In a round bottom flask, to a solution of *N*-Boc-*L*-Proline **77** (1 equiv., 0.69 mmol, 149 mg) ethyl chloroformate (1 equiv., 0.69 mmol, 64 μl) and CH_2Cl_2 (1.6 ml), was added dropwise the triethylamine (1.5 equiv., 1.04 mmol, 143 μl) at -10°C . After 10 minutes, the solution was filtered. The solid was washed with CH_2Cl_2 . This solution was added dropwise at -5°C to another solution of **66** (1 equiv., 0.69 mmol, 100 mg) and CH_2Cl_2 (1.3 ml). The mixture was stirred for 2 hours at room temperature. Then, 2 ml of water were added in the flask. The aqueous phase was extracted with CH_2Cl_2 and the combined organic layers were dried over sodium sulphate, filtrated and concentrated

under vacuum. The desired product **70** was obtained as a white solid in 64% yield.

¹H NMR (300 MHz, CDCl₃) δ 8.26 (s, 1H), 7.79 (m, 3H), 7.44 (m, 3H), 4.53 (s, 1H), 3.48 (s, 2H), 2.61 (s, 1H), 2.01-1.99 (m, 3H), 1.53 (s, 9H). **MS (APCI)** m/z (%): calculated for C₂₀H₂₄N₂O₂ (M+H)⁺: 324.18; found: 325.8

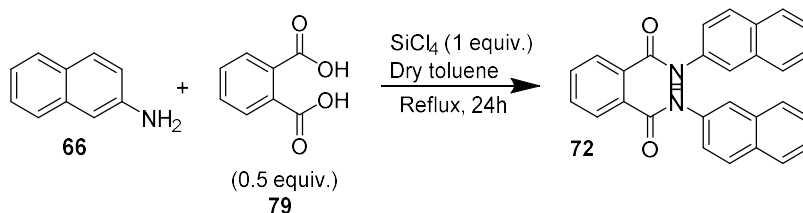
Synthesis of compound **71** ⁸⁰



In a 10 mL round bottom flask, purged with N₂, were added **66** (2 equiv., 1.4 mmol, 200 mg), the pyridine (5 mL) and lastly, dropwise at 0°C, the succinyl chloride (1 equiv., 0.7 mmol, 76 µL). The colour of the reaction mixture changed from violet to pink. The reaction was stirred for 24 hours at room temperature. After this time, a big amount of starting was still present, so another 20 µL of succinyl chloride were added to the mixture. After an additional 8 hours, the reaction was quenched with distilled water. The solid was recovered by filtration on Buchner. The desired product **71** was obtained as a pale beige solid in 80% yield.

¹H NMR (300 MHz, CDCl₃): δ 10.23 (s, 1H), 8.33 (s, 1H), 7.83 (m, 3H), 7.61 (d, *J*=7.03 Hz, 1H), 7.43 (m, 2H), 2.78 (s, 2H), 2.5 (s, 1H). **MS (APCI)** m/z (%): calculated for C₂₄H₂₀N₂O₂ (M+H)⁺: 368.15; found: 369.7.

Synthesis of compound **72** ⁸¹

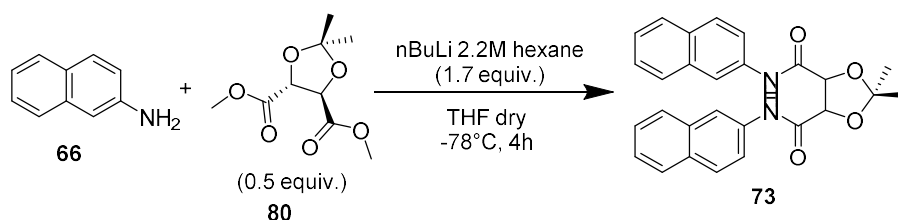


In a -well dried- round bottom flask, equipped with an inlet and a condenser and purged with N₂, were added **79** (0.5 equiv., 0.82 mmol, 136 mg), **66** (1 equiv., 1.65 mmol, 239 mg) and the toluene (3.3 mL). Lastly, the tetra chlorosilane (1 equiv., 1.65 mmol, 190 µL) was added dropwise to the

solution. The reaction mixture was stirred for 24 hours at reflux. Then, the reaction was quenched with NaOH (20%). The aqueous phase was extracted with CH₂Cl₂ (2 times) and the organic phase was washed with NaCl s.s. The combined organic layers were dried over sodium sulphate, filtrated and concentrated under vacuum. The obtained residue was purified by flash column chromatography on silica gel (eluent: hexane/ethyl acetate 6:4). The desired product **72** was obtained as a brown solid in 24% yield.

¹H NMR (300 MHz, DMSO-*d*₆) δ 8.03 (m, 7H), 7.62 (m, 3H). **¹³C NMR** (75 MHz, Chloroform-*d*) δ 167.48, 134.48, 133.30, 132.63, 131.82, 129.02, 128.23, 127.78, 127.60, 126.74, 126.61, 125.80, 125.56, 124.21, 123.81. **MS (APCI)** *m/z* (%): calculated for C₂₈H₂₀N₂O₂ (M+H)⁺: 416.15; found: 417.0.

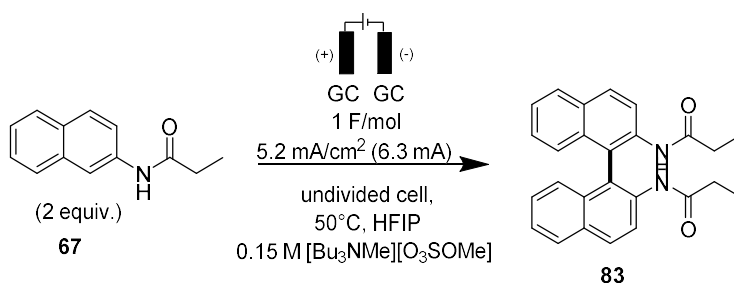
Synthesis of compound **73**⁸³



In a -well dried- round bottom flask, **66** (1 equiv., 4.7 mmol, 670 mg) was dissolved in dry THF (40 ml) and the solution was cooled to -78°C, to which *n*BuLi (2.2 M) (1.7 equiv., 8.04 mmol, 3.7 ml) was added with stirring under nitrogen. Then, (4*R*,5*R*)-2,2-dimethyl-1,3-dioxolane-4,5-dicarboxylate **80** (0.5 equiv., 1.5 mmol, 278 μl) in dry THF (4 ml) was gradually added to the THF solution at -78°C. After 4 hours of stirring at -78°C, the reaction mixture was allowed to warm to room temperature and quenched by saturated aqueous NH₄Cl solution. The product was extracted from the resultant mixture with ethyl acetate (4 times) and purified by recrystallization from 95:5 ether:ethyl acetate to give the desired product **73** in 30% yield.

¹H NMR (300 MHz, CDCl₃) δ 9.01 (s, 2H), 8.32 (d, *J*=1.4 Hz, 2H), 7.88-7.82 (m, 6H), 7.65-7.62 (m, 2H), 7.52-7.46 (m, 4H), 4.93 (s, 2H), 1.67 (s, 6H). **MS (APCI)** *m/z* (%): calculated for C₂₇H₂₄N₂O₄ (M+H)⁺: 440.17; found: 441.3.

5.2.3 GENERAL PROCEDURE FOR THE INTERMOLECULAR HOMO-COUPLING OF COMPOUND **67**

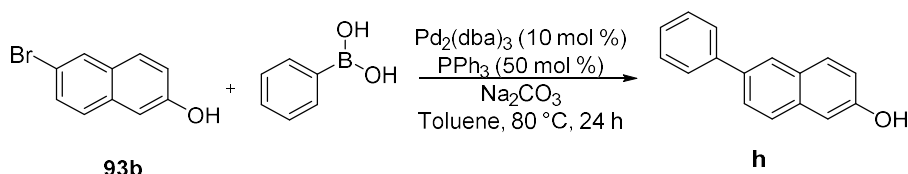


In a 10 ml electrochemical cell were added substrate **67** (2 equiv., 0.83 mmol, 166 mg), the electrolyte (1.2 equiv., 0.49 mmol, 155 mg) in HFIP (0.15M, 5.5 ml). The glassy carbon electrodes were then inserted into the solution and the active surface was measured. After setting all the parameters (6.03 mA, 1 F/mol) in the instrument (Electrasyn 2.0), the reaction mixture was stirred for 3 hours and 42 minutes in an oil bath at 50°C. The aqueous phase was extracted with ethyl acetate and the organic phase was washed with brine (3 times). The combined organic layers were dried over sodium sulphate, filtrated and concentrated under vacuum. The obtained residue was purified by flash column chromatography on silica gel (eluent: hexane/ethyl acetate 8:2). The desired product **83** was obtained as a white solid in 20% yield.

¹H NMR (300 MHz, DMSO-*d*) δ 8.81 (s, 1H), 8.07 (m, 2H), 7.86 (m, 1H), 7.46 (t, , $J=8.1$ Hz , 1H), 7.26 (t, $J=8.1$ Hz, 1H), 6.89 (m, 1H), 1.94 (q, , $J=7.42$ Hz, 2H), 0.68 (t, , $J=7.42$ Hz, 3H). **MS (APCI)** m/z (%): calculated for C₂₆H₂₄N₂O₂ (M+H)⁺: 396.18; found: 396.01.

5.2.4 SYNTHESIS OF ENANTIOPURE β -NAPHTHYLAMINES

Synthesis of compound **h**¹⁶²

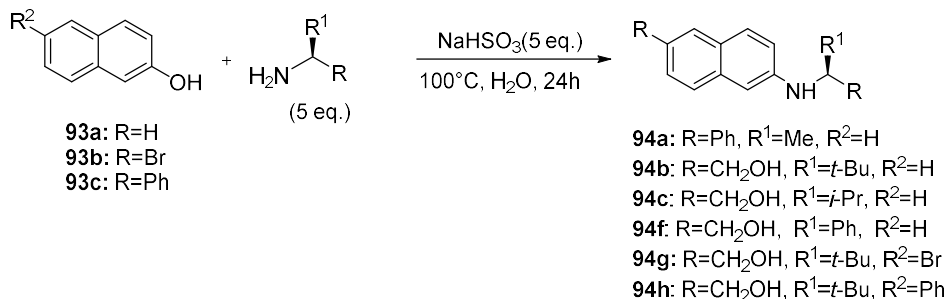


In a two naked 200 mL flask, 6-Bromo (1 g, 4.5 mmol, 1 equiv.), phenyl boronic acid (660 mg, 5.4 mmol, 1.2 equiv.), $\text{Pd}_2(\text{dba})_3$ (260 mg, 0.45 mmol, 0.1 equiv.) and PPh_3 (660 mg, 0.5 mmol, 0.5 equiv.) were dissolved in 50 mL of toluene under nitrogen atmosphere. A solution of Na_2CO_3 (1g, 9 mmol, 2 equiv.) dissolved in 10 mL of water was added and the mixture was left to react at 80 °C for 24 h. At the end of reaction, toluene was removed under reduced pressure. The residue was diluted with dichloromethane and filtered over Celite; the organic phase was washed three times with brine, dried over sodium sulphate and concentrated under vacuum. The product was purified by flash column chromatography on silica gel using a mixture of hexane/ethyl acetate racing from 9:1 to 7:3 as eluent to afford a white solid in 63 % yield.

^1H NMR (300 MHz, CDCl_3) δ 8.02 – 7.97 (m, 1H), 7.87 – 7.78 (m, 1H), 7.78 – 7.67 (m, 4H), 7.50 (dd, J = 8.5, 6.8 Hz, 2H), 7.43 – 7.34 (m, 1H), 7.20 (d, J = 2.5 Hz, 1H), 7.15 (dd, J = 8.7, 2.6 Hz, 1H), 5.00 (s, 1H).

Analytical data are in agreement with those reported in literature¹⁶²

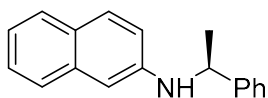
General procedure for the synthesis of β -Naphthylamines derivatives⁸⁴



In a 25ml pressure tube (Pyrex vial), β -naphthol **93** (4.8 mmol, 1 equiv.), the optically pure amine (24 mmol, 5 equiv.) and sodium bisulfite (38 mmol, 5 equiv.) were suspended in water. The mixture was stirred for 24h at 100°C.

The reaction was then brought at room temperature, water was added, and the aqueous layer was extracted three times with ethyl acetate. The combined organic layers were dried over magnesium sulphate and the solvent was removed under vacuum. The residue was then purified by column chromatography and the unreacted starting material was recovered.

Compound 94a



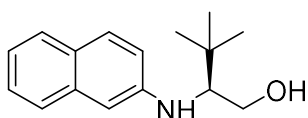
Synthesized according to the general procedure, starting from (S)-1-phenylethan-1-amine. The product was purified by flash column chromatography on silica gel using hexane/ethyl

acetate 8:2 as eluent to afford a yellowish solid (after stored in the fridge) in 60 % yield.

H-NMR (300 MHz, CDCl_3) δ 7.64 (t, J = 9.3 Hz, 2H), 7.51 (d, J = 8.3 Hz, 1H), 7.45 (d, J = 7.1 Hz, 2H), 7.41 – 7.31 (m, 3H), 7.32 – 7.21 (m, 1H), 7.18 (t, J = 7.4 Hz, 1H), 6.92 (dd, J = 8.8, 2.4 Hz, 1H), 6.66 (d, J = 2.3 Hz, 1H), 4.66 (q, J = 6.7 Hz, 1H), 4.24 (s, 1H), 1.61 (d, J = 6.7 Hz, 3H).

Analytical data are in agreement with those reported in literature.⁸⁴

Compound 94b



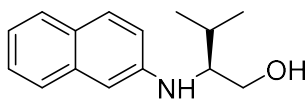
Synthesized according to the general procedure starting from (S)-tert-leucinol. The product was purified by flash column chromatography on silica gel using a mixture

of hexane/ethyl acetate ranging from 9:1 to 7:3 as eluent to afford a reddish solid (after stored in the fridge) in 74 % yield

¹H NMR (300 MHz, CDCl_3) δ 7.74 (d, J = 8.1 Hz, 1H), 7.68 (dd, J = 8.5, 4.3 Hz, 2H), 7.44 (ddd, J = 8.2, 6.8, 1.3 Hz, 1H), 7.27 (ddd, J = 8.0, 6.7, 1.2 Hz, 1H), 7.05 – 6.96 (m, 2H), 3.94 (d, J = 6.6 Hz, 1H), 3.78 (s, 1H), 3.52 (d, J = 6.6 Hz, 2H), 1.02 (s, 9H). **¹³C NMR** (75 MHz, CDCl_3) δ 147.25, 135.25, 129.22, 127.69, 127.66, 126.51, 125.97, 122.17, 118.10, 105.87, 64.29, 62.44, 35.08, 27.13.

HRMS calculated 244.1701; found 244.1699 α_D [1.2 g/ml](CH_3Cl) = -75.03
mp = 91-94°C

Compound 94c

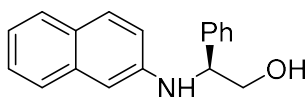


Synthesized according to the general procedure, starting from (S)-valinol. The product was purified by flash column

chromatography on silica gel using a mixture of hexane/ethyl acetate racing from 9:21 to 7:3 to afford a reddish solid (after stored in the fridge) in 96% yield.

¹H NMR (300 MHz, CDCl₃) δ 7.87 – 7.59 (m, 3H), 7.45 (t, *J* = 7.5 Hz, 1H), 7.29 (t, *J* = 7.5 Hz, 1H), 6.96 (d, *J* = 7.5 Hz, 2H), 3.86 (dd, *J* = 11.0, 4.0 Hz, 1H), 3.62 (dd, *J* = 11.0, 6.6 Hz, 1H), 3.48 (q, *J* = 5.9 Hz, 1H), 1.97 (h, *J* = 6.8 Hz, 1H), 1.04 (t, *J* = 6.2 Hz, 6H). **¹³C NMR** (75 MHz, CDCl₃) δ 146.21, 135.25, 129.21, 127.72, 126.52, 125.96, 122.19, 118.30, 105.70, 62.67, 60.90, 30.17, 19.28, 19.18. **HRMS** calculated 230.1545; found 230.1542 α_D [3.5 g/ml] (CHCl₃) = - 49.34

Compound 94f

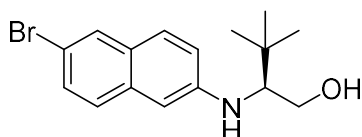


Synthesized according to the general procedure starting from (S)-(+)-2-Phenylglycinol.

The product was purified by flash column chromatography on silica gel using a mixture of hexane/ethyl acetate racing from 8:2 to 7:3 as eluent to afford a yellowish solid in 98 % yield.

¹H NMR (300 MHz, CDCl₃) δ 7.82 (d, *J* = 8.1 Hz, 1H), 7.76 (d, *J* = 8.8 Hz, 1H), 7.65 (d, *J* = 8.2 Hz, 1H), 7.54 – 7.26 (m, 7H), 7.13 – 7.02 (m, 1H), 6.87 – 6.76 (m, 1H), 4.64 (dd, *J* = 7.3, 4.1 Hz, 1H), 3.98 (dd, *J* = 11.2, 4.1 Hz, 1H), 3.78 (dd, *J* = 11.2, 7.2 Hz, 1H). **¹³C NMR** (75 MHz, CDCl₃) δ 145.11, 140.08, 135.24, 129.18, 129.01, 127.90, 126.92, 126.43, 126.24, 122.34, 118.43, 106.58, 67.23, 60.06. **HRMS** calculated 264.1388; found 264.1386. α_D [5.95 g /mL] (CHCl₃) = +14.9

Compound 94g

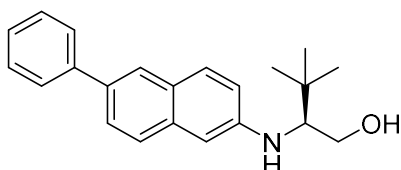


Synthesized according to the general procedure, starting from (S)-tert-leucinol and 6-Bromo-2-naphthol **93b**.

The product was purified by flash column chromatography on silica gel using a mixture of hexane/ethyl acetate racing from 8:2 to 7:3 as eluent to afford a grey solid (after stored in the fridge) in 72 % yield.

¹H NMR (300 MHz, CDCl₃) δ 7.82 (d, *J* = 1.9 Hz, 1H), 7.56 (d, *J* = 8.8 Hz, 1H), 7.51 – 7.39 (m, 2H), 7.00 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.95 (d, *J* = 2.4 Hz, 1H), 3.95 (t, *J* = 7.9 Hz, 1H), 3.82 (d, *J* = 8.5 Hz, 1H), 3.64 – 3.44 (m, 2H), 1.93 (d, *J* = 8.6 Hz, 1H), 1.02 (s, 9H). **¹³C NMR** (75 MHz, CDCl₃) δ 147.41, 133.62, 129.62, 128.32, 127.55, 118.88, 115.28, 105.66, 64.31, 62.50, 35.02, 27.08. **HRMS** calculated 264.1388; found 264.1386. **α_D** [1.7 g /mL] (CHCl₃) = -72.65

Compound 94h

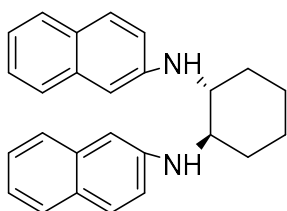


Synthesized according to the general procedure, starting from (*S*)-*tert*-leucinol and compound **h**. The product was purified by flash column

chromatography on silica gel using a mixture of hexane/ethyl acetate racing from 9:1 to 6:4 as eluent to afford a greenish solid (after stored in the fridge) in 43 %.

¹H NMR (300 MHz, CDCl₃) δ 7.90 (s, 1H), 7.70 (d, *J* = 11.7 Hz, 4H), 7.48 (s, 2H), 7.31 (d, *J* = 23.7 Hz, 1H), 7.03 (s, 2H), 3.95 (s, 1H), 3.55 (s, 1H), 1.27 (d, *J* = 12.7 Hz, 2H), 1.03 (s, 9H). **¹³C NMR** (75 MHz, CDCl₃) δ 147.30, 134.92, 134.37, 129.58, 128.80, 128.76, 127.84, 127.06, 126.77, 126.40, 126.11, 125.58, 125.54, 118.42, 105.72, 64.41, 62.50, 35.07, 27.04. **HRMS** calculated 320.2014; found 320.2010

Compound 94i



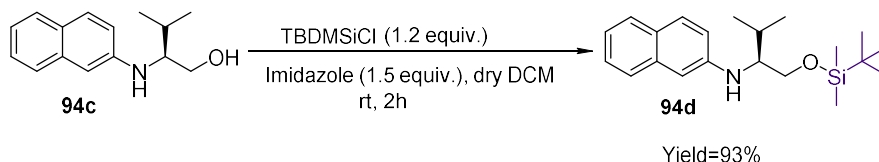
Synthesized according to the general procedure, starting from 1 equiv. of (1*R*,2*R*)-cyclohexane-1,2-diamine and 2 equiv. of β-naphthol **93a**. The product was purified by flash column chromatography on silica gel using

hexane/ethyl acetate 9:1 as eluent to afford a beige solid in 28 % yield.

¹H NMR (300 MHz, CDCl₃) δ 7.79 – 7.65 (m, 3H), 7.47 (ddd, *J* = 8.2, 6.8, 1.3 Hz, 1H), 7.30 (ddd, *J* = 8.1, 6.8, 1.3 Hz, 1H), 6.95 (d, *J* = 2.3 Hz, 1H), 6.89 (dd, *J* = 8.7, 2.3 Hz, 1H), 4.02 (s, 1H), 3.51 – 3.38 (m, 1H), 2.53 (dt, *J* = 13.7, 2.8 Hz, 1H), 1.98 – 1.83 (m, 1H), 1.55 (t, *J* = 10.1 Hz, 1H), 1.44 – 1.25 (m, 1H).

Analytical data are in agreement with those reported in literature.¹⁶³

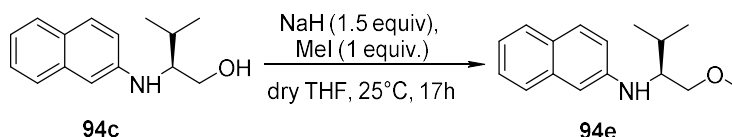
Synthesis of compound **94d**⁸⁵



To a stirred solution of compound **94c** (1 equiv., 2.2 mmol, 500 mg) in dry DCM (3.73 ml) were added TBDMSCl (1.2 equiv., 2.64 mmol, 398 mg) and Imidazole (1.5 equiv., 3.3 mmol, 225 mg) at 0°C. The resulting solution was then warmed to room temperature and it was stirred for 2 hours. The reaction mixture was diluted with water and then aqueous layer was extracted three times with dichloromethane. The combined organic layers were dried over MgSO₄ and the solvent was removed under vacuum. The desired product was obtained in 93% yield without further purification.

¹H NMR (300 MHz, CDCl₃) δ 7.40 – 7.32 (m, 1H), 7.20 (t, *J* = 7.4 Hz, 1H), 6.96 – 6.87 (m, 1H), 3.81 (dd, *J* = 10.2, 3.6 Hz, 1H), 3.70 (dd, *J* = 10.2, 4.8 Hz, 1H), 3.34 (dd, *J* = 10.1, 4.7 Hz, 1H), 2.12 (dq, *J* = 13.3, 6.7 Hz, 1H), 1.06 (dd, *J* = 6.8, 3.7 Hz, 5H), 0.91 (s, 7H), 0.04 (d, *J* = 6.6 Hz, 4H). **¹³C NMR** (75 MHz, CDCl₃) δ 128.95, 127.57, 126.25, 125.80, 121.91, 118.54, 62.03, 29.24, 25.82, 19.54, 18.81.

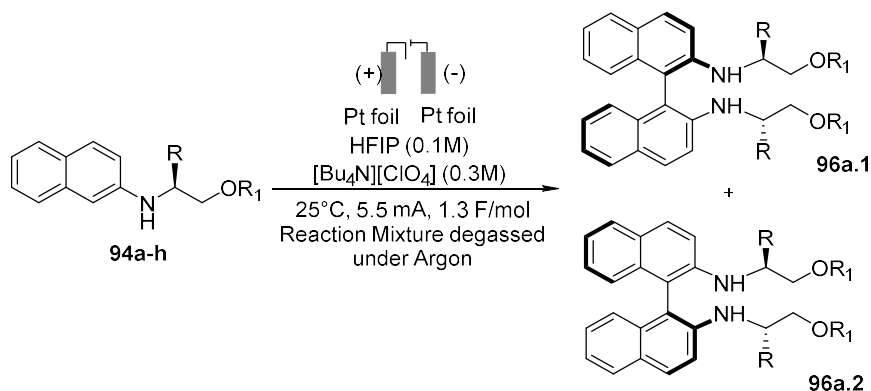
Synthesis of compound **94e**⁸⁵



The amino alcohol **94c** (400mg, 1.74 mmol, 1 equiv.), dissolved in 6 ml of dry THF, was added to a suspension of sodium hydride (63 mg, 2.61 mmol, 1.5 equiv., 60% dispersion in mineral oil) in dry THF (6.3 ml) at 0°C. The mixture was allowed to react at room temperature for 2 h before methyl iodide (371mg, 2.61 mmol, 1.5 equiv.) was added. The mixture was then left to react at room temperature overnight. Distilled water was added, and the ethereal solvent removed under reduced pressure. The residue was extracted three times with dichloromethane and the combined extracts washed with brine, dried over magnesium sulphate and the solvent was removed under reduced pressure. The product was purified by flash column chromatography on silica gel using a hexane/ethyl acetate 8:2 as eluent to afford a yellow solid (after stored in the fridge) in 70% yield.

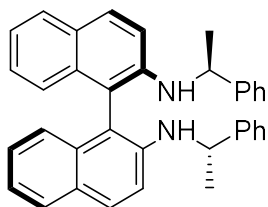
¹H NMR (300 MHz, CDCl₃) δ 7.80 (d, *J* = 8.2 Hz, 1H), 7.75 (d, *J* = 8.4 Hz, 1H), 7.50 (t, *J* = 7.5 Hz, 1H), 7.32 (t, *J* = 7.5 Hz, 1H), 7.01 (dd, *J* = 8.8, 2.3 Hz, 1H), 6.97 (d, *J* = 2.4 Hz, 1H), 3.61 (pd, *J* = 8.9, 4.5 Hz, 1H), 3.47 (s, 3H), 2.20 (h, *J* = 6.8 Hz, 1H), 1.17 (t, *J* = 6.7 Hz, 6H). **¹³C NMR** (75 MHz, CDCl₃) δ 146.03, 135.48, 129.13, 127.78, 127.47, 126.43, 125.94, 121.89, 118.50, 104.86, 72.35, 59.17, 58.27, 29.87, 19.51, 19.04. **HRMS** calculated 244.1701; found 244.1700. **α_D** [0.7 g/mL] (CHCl₃) = -9.34

5.2.5 GENERAL PROTOCOL FOR THE ELECTROCHEMICAL INTERMOLECULAR HOMO-COUPLING OF COMPOUNDS 94a-94h



In a 5 mL IKA ElectraSyn 2.0 vial, equipped with a stir bar, the chiral amine (0.5 mmol, 1equiv.) and Lithium Tetrabutyl ammonium perchlorate (1.5 mmol, 3equiv.) were dissolved in 5 ml of 1,1,1,3,3,3-Hexafluoro-2-propanol. The electrochemical cell was assembled with IKA Platinum foil anode and cathode and the reaction mixture was degassed with Argon for two minutes. Under Argon Atmosphere, the solution was electrolyzed with a constant current of 5.5mA (Cell potential 1.5-2.5V). After 1.3 F/mol were furnished, the reaction mixture was diluted with ethyl acetate and washed two times with brine. The organic phase was then dried over magnesium sulphate and the solvent evaporated under reduced pressure. The crude afforded was purified by column chromatography on flash silica gel to separate the desired diastereoisomers.

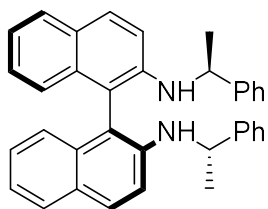
Compound 96a.1



Prepared according to the general procedure starting from **94a**. The product was purified by flash column chromatography on silica gel using a mixture of hexane/ethyl acetate racing from 9.8:0.2 to 9.5:0.5 to afford a white solid (after stored in the fridge) in 18% yield.

¹H NMR (300 MHz, CDCl₃) δ 7.84 – 7.72 (m, 2H), 7.50 – 7.35 (m, 2H), 7.35 – 7.14 (m, 5H), 7.13 – 7.00 (m, 2H), 4.68 (s, 1H), 4.10 (s, 1H), 1.23 (dd, *J* = 6.8, 2.7 Hz, 3H). **¹³C NMR** (75 MHz, CDCl₃) δ 145.69, 144.07, 133.61, 129.50, 128.62, 128.08, 127.68, 126.82, 126.58, 125.81, 123.86, 121.93, 115.05, 53.63, 29.72, 25.14. **HRMS** calculated 493.2644; found 493.2651 **α_D** [0.1 g/mL] (CHCl₃) = -3.27

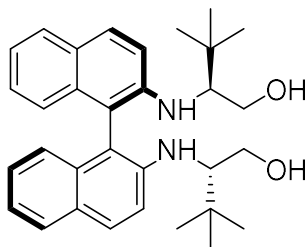
Compound 96a.2



Prepared according to the general procedure starting from **94a**. The product was purified by flash column chromatography on silica gel using a mixture of hexane/ethyl acetate racing from 9.8:0.2 to 9.5:0.5 to afford a yellowish solid (after stored in the fridge) in 29% yield.

¹H NMR (300 MHz, CDCl₃) δ 7.76 (d, *J* = 9.5 Hz, 2H), 7.22 (qt, *J* = 6.8, 2.3 Hz, 7H), 7.08 (dd, *J* = 9.1, 2.7 Hz, 1H), 7.02 – 6.94 (m, 1H), 4.74 (s, 1H), 4.16 (d, *J* = 5.6 Hz, 1H), 1.36 (dd, *J* = 7.2, 2.4 Hz, 3H). **¹³C NMR** (75 MHz, CDCl₃) δ 144.29, 142.55, 132.86, 128.38, 127.41, 126.91, 126.61, 125.72, 125.39, 124.79, 123.27, 120.92, 113.95, 111.03, 52.30, 24.07. **HRMS** calculated 493.2644; found 493.2643 **α_D** [1.6 g/mL] (CHCl₃) = -67.41

Compound 96b.1

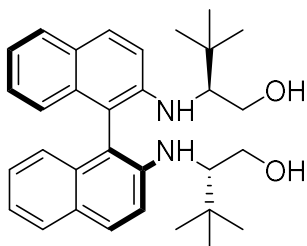


Prepared according to the general procedure starting from **94b**. The product was purified by flash column chromatography on silica gel using hexane/ethyl acetate 8:2 to afford a reddish solid (after stored in the fridge) in 41% yield.

¹H NMR (300 MHz, CDCl₃) δ 7.90 (d, *J* = 9.0 Hz, 1H), 7.86 – 7.76 (m, 1H), 7.37 (dd, *J* = 9.1, 1.6 Hz, 1H), 7.24 (hept, *J* = 4.7 Hz, 2H), 7.12 – 7.02 (m, 1H), 3.65 (dd, *J* = 11.3, 3.6 Hz, 1H), 3.48 (s, 1H), 3.14 (dd, *J* = 11.3, 7.4 Hz, 1H), 0.82 (s,

9H). **¹³C-NMR** (75 MHz, CDCl₃) δ 145.46, 133.47, 129.98, 128.74, 127.72, 127.30, 122.56, 122.20, 114.71, 111.40, 63.37, 62.39, 34.74, 26.95. **HRMS** calculated 485.3168; found 485.3168. **α_D**[2.16 g/mL] (CHCl₃) = -81.23

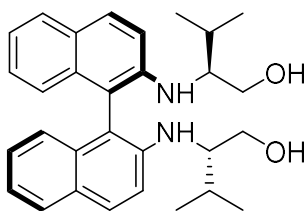
Compound 96b.2



Prepared according to the general procedure starting from **94b**. The product was purified by flash column chromatography on silica gel using hexane/ethyl acetate 8:2 to afford a yellowish solid (after stored in the fridge) in 9% yield.

¹H NMR (300 MHz, CDCl₃) δ 7.90 (d, J = 9.0 Hz, 1H), 7.85 – 7.76 (m, 1H), 7.37 (d, J = 9.1 Hz, 1H), 7.31 – 7.14 (m, 2H), 7.10 (d, J = 7.9 Hz, 1H), 3.79 (dd, J = 11.5, 3.2 Hz, 1H), 3.63 (s, 2H), 3.46 (s, 1H), 3.23 (dd, J = 11.3, 8.5 Hz, 1H), 0.63 (s, 9H). **¹³C NMR** (75 MHz, CDCl₃) δ 144.91, 133.86, 129.81, 129.01, 128.09, 126.80, 124.13, 122.20, 114.54, 112.02, 63.85, 62.76, 34.54, 26.67. **HRMS** calculated 485.3168; found 485.3171 **α_D**[0.1 g/mL] (CHCl₃) = +23.456

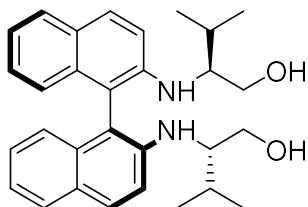
Compound 96c.1



Prepared according to the general procedure starting from **94c**. The product was purified by flash column chromatography on silica gel using hexane/ethyl acetate 7:3 to afford a reddish solid (after stored in the fridge) in 43% yield.

¹H NMR (300 MHz, CDCl₃) δ 7.90 (d, J = 9.0 Hz, 1H), 7.83 (dt, J = 6.2, 3.4 Hz, 1H), 7.33 (d, J = 9.0 Hz, 1H), 7.23 (dt, J = 6.8, 3.4 Hz, 2H), 7.06 (dt, J = 6.1, 3.4 Hz, 1H), 3.57 (dd, J = 17.3, 9.9 Hz, 2H), 3.45 (s, 1H), 3.29 (dd, J = 11.0, 5.9 Hz, 1H), 1.76 – 1.58 (m, 1H), 0.83 (dd, J = 11.6, 6.8 Hz, 6H). **¹³C NMR** (75 MHz, CDCl₃) δ 144.91, 133.58, 129.94, 128.61, 127.87, 127.16, 122.87, 122.29, 114.99, 112.30, 62.77, 60.79, 30.09, 19.26, 18.86. **HRMS** calculated 457.2855; found 457.2856. **α_D**[3.5 g/mL] (CHCl₃) = -92.27

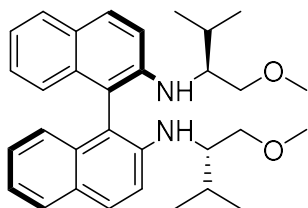
Compound 96c.2



Prepared according to the general procedure starting from **94c**. The product was purified by flash column chromatography on silica gel using hexane/ethyl acetate 7:3 to afford a yellowish solid (after stored in the fridge) in 17% yield.

¹H NMR (300 MHz, CDCl₃) δ 7.91 (d, *J* = 9.0 Hz, 1H), 7.81 (d, *J* = 7.2 Hz, 1H), 7.33 (d, *J* = 9.1 Hz, 1H), 7.29 – 7.14 (m, 4H), 7.03 (d, *J* = 8.3 Hz, 1H), 3.70 (dd, *J* = 11.2, 2.6 Hz, 1H), 3.59 (d, *J* = 11.2 Hz, 2H), 3.43 (s, 1H), 3.35 (dd, *J* = 11.2, 6.6 Hz, 1H), 1.57 (q, *J* = 6.6 Hz, 1H), 0.89 – 0.77 (m, 2H), 0.66 (dd, *J* = 9.5, 6.7 Hz, 7H). **¹³C-NMR** (75 MHz, CDCl₃) δ 144.19, 134.02, 129.91, 128.60, 128.06, 127.16, 126.84, 124.15, 122.84, 122.49, 122.30, 115.09, 113.29, 62.81, 61.59, 60.81, 30.03, 19.23, 19.06, 18.87, 18.72. **HRMS** calculated 457.2855; found 457.2849. α_D [18.75 g/ml] (CHCl₃) = -69.99

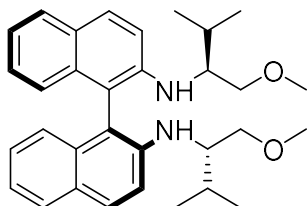
Compound 96e.1



Prepared according to the general procedure starting from **94d**. The product was purified by flash column chromatography on silica gel using a mixture of hexane/ethyl acetate racing from 9.8:0.2 to 9.4:0.6 to afford a yellow solid (after stored in the fridge) in 40% yield.

¹H NMR (300 MHz, CDCl₃) δ 7.87 (d, *J* = 9.0 Hz, 1H), 7.83 – 7.73 (m, 1H), 7.35 – 7.26 (m, 1H), 7.17 (h, *J* = 5.6 Hz, 2H), 7.00 (d, *J* = 6.5 Hz, 1H), 3.85 (s, 1H), 3.41 (d, *J* = 5.4 Hz, 1H), 3.25 (dd, *J* = 9.5, 4.4 Hz, 1H), 3.05 (dd, *J* = 9.5, 5.5 Hz, 1H), 2.94 (s, 2H), 1.79 (h, *J* = 6.6 Hz, 1H), 0.88 (d, *J* = 6.7 Hz, 3H), 0.74 (d, *J* = 6.7 Hz, 3H). **¹³C-NMR** (75 MHz, CDCl₃) δ 144.89, 133.96, 129.47, 127.94, 127.56, 126.42, 123.94, 121.62, 114.73, 112.28, 73.31, 58.62, 29.73, 19.53, 17.97. **HRMS** calculated 485.3168; found 485.3168 α_D [1 g/mL] (CHCl₃) = -53.478

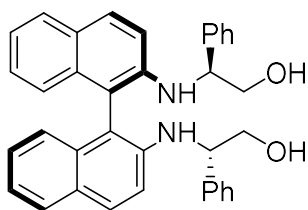
Compound 96e.2



Prepared according to the general procedure starting from **94d**. The product was purified by flash column chromatography on silica gel using a mixture of hexane/ethyl acetate racing from 9.8:0.2 to 9.4:0.6 to afford a beige solid (after stored in the fridge) in 13% yield.

¹H NMR (300 MHz, CDCl₃) δ 7.86 (d, *J* = 9.0 Hz, 1H), 7.77 (dd, *J* = 6.5, 2.6 Hz, 1H), 7.30 – 7.23 (m, 1H), 7.15 (tt, *J* = 6.7, 4.9 Hz, 2H), 7.04 – 6.96 (m, 1H), 3.70 (d, *J* = 9.1 Hz, 1H), 3.59 – 3.43 (m, 1H), 3.37 – 3.22 (m, 5H), 3.13 – 2.93 (m, 1H), 1.89 – 1.65 (m, 1H), 0.68 (d, *J* = 6.8 Hz, 3H), 0.54 (d, *J* = 6.9 Hz, 3H). **¹³C NMR** (75 MHz, CDCl₃) δ 144.21, 134.06, 129.47, 127.91, 127.36, 126.50, 124.07, 123.93, 121.60, 114.00, 111.63, 73.65, 58.92, 57.51, 29.49, 19.17, 17.20. **HRMS** calculated 485.3168; found 485.3167. **α_D** [4 g/ml] (CHCl₃) = -21.85

Compound 96f.1

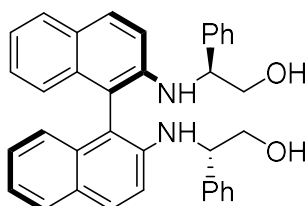


Prepared according to a slightly modified general procedure starting from **94f**. 1.7 F/mol were furnished. The product was purified by flash column chromatography on silica gel using a mixture of hexane/ethyl

acetate racing from 8:2 to 6:4 to afford a brown solid (after stored in the fridge) in 24% yield.

¹H NMR. (300 MHz, CDCl₃) δ 7.79 (dd, *J* = 7.8, 2.7 Hz, 2H), 7.40 – 7.18 (m, 8H), 7.11 (dd, *J* = 9.4, 4.6 Hz, 2H), 4.69 (s, 1H), 4.36 (s, 1H), 3.61 (dd, *J* = 11.3, 4.4 Hz, 1H), 3.38 (dd, *J* = 11.3, 7.3 Hz, 1H). **¹³C NMR** (75 MHz, CDCl₃) δ 144.04, 140.62, 133.48, 130.01, 128.92, 128.58, 128.20, 127.74, 127.06, 126.73, 123.65, 122.55, 115.21, 112.92, 67.10, 60.25. **HRMS** calculated 525.2542; found 525.2538. **α_D** [2.45 g/ml] (CHCl₃) = +67.48

Compound 96f.2

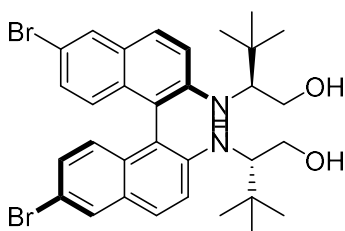


Prepared according to a slight modified general procedure starting from **94f**. 1.7 F/mol were furnished. The product was purified by flash column chromatography on silica gel using a mixture of hexane/ethyl

acetate racing from 8:2 to 6:4 to afford a brown solid (after stored in the fridge) in 24% yield

¹H NMR (300 MHz, CDCl₃) δ 7.80 (d, J = 8.5 Hz, 2H), 7.41 – 7.07 (m, 8H), 7.02 (d, J = 8.2 Hz, 1H), 4.75 (d, J = 8.3 Hz, 1H), 4.48 (s, 1H), 3.82 (d, J = 13.0 Hz, 1H), 3.37 (t, J = 10.2 Hz, 1H), 3.27 (s, 1H). **¹³C NMR** (75 MHz, CDCl₃) δ 143.61, 140.18, 134.02, 129.89, 128.82, 128.65, 128.24, 128.09, 127.50, 126.82, 126.70, 126.50, 126.04, 124.47, 122.52, 115.18, 113.47, 67.30, 60.83, 59.84. **HRMS** calculated 525.2542; found 525.2544. α_D [1.25 g/mL] (CHCl₃) = -35.96

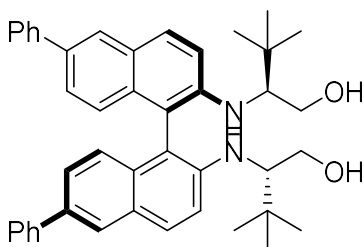
Compound 96g.1



Prepared according to the general procedure starting from **94f**. The product was purified by flash column chromatography on silica gel using hexane/ethyl acetate racing from 95:5 to 7:3 to afford a pinkish solid 58% yield.

¹H NMR (300 MHz, CDCl₃) δ 7.95 (d, J = 2.0 Hz, 1H), 7.80 (d, J = 9.1 Hz, 1H), 7.37 (d, J = 9.1 Hz, 1H), 7.31 – 7.22 (m, 1H), 6.87 (d, J = 8.9 Hz, 1H), 3.68 (dd, J = 18.0, 10.8 Hz, 2H), 3.47 (dt, J = 11.0, 4.3 Hz, 1H), 3.17 (dd, J = 11.1, 7.2 Hz, 1H), 1.28 (s, 1H), 0.82 (s, 9H). **¹³C NMR** (75 MHz, CDCl₃) δ 145.89, 131.94, 130.63, 129.31, 128.73, 124.43, 115.64, 110.74, 63.40, 62.59, 34.67, 26.91. **HRMS** calculated 641.1378; found 641.1367. α_D [1.7 g/mL] (CHCl₃) = -205.25. **mp** = 298-300°C

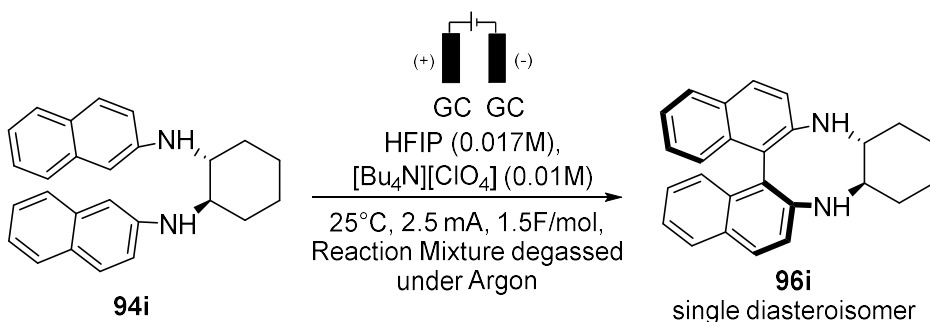
Compound 96h.1



Prepared according to the general procedure starting from **94h**. The product was purified by flash column chromatography on silica gel using hexane/ethyl acetate racing from 95:5 to 7:3 to afford a black oil in 52% yield

¹H NMR (300 MHz, CDCl₃) δ 8.06 (d, J = 2.1 Hz, 1H), 7.98 (d, J = 9.0 Hz, 1H), 7.69 (d, J = 8.1 Hz, 2H), 7.55 (dd, J = 8.8, 2.0 Hz, 1H), 7.50 – 7.40 (m, 3H), 7.35 (d, J = 7.3 Hz, 1H), 7.18 (d, J = 8.7 Hz, 1H), 3.68 (dd, J = 11.3, 3.7 Hz, 1H), 3.49 (t, J = 3.7 Hz, 1H), 3.27 – 3.13 (m, 1H), 0.84 (s, 9H). **¹³C-NMR** (75 MHz, CDCl₃) δ 145.52, 140.98, 134.92, 132.70, 130.45, 128.79, 128.04, 126.99, 126.64, 123.26, 115.35, 111.43, 63.63, 62.41, 34.76, 26.98. **HRMS** calculated 637.3794; found 637.3805. α_D [6.3 g/mL] (CHCl₃) = -27.87

5.2.6 GENERAL PROTOCOL FOR THE ELECTROCHEMICAL INTRAMOLECULAR HOMO-COUPLING OF COMPOUND 94i

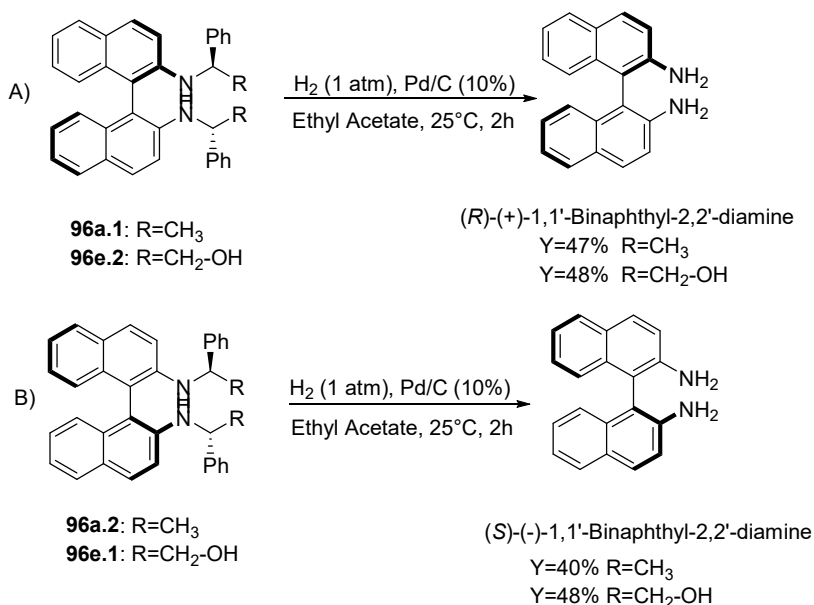


In a 5 mL IKA ElectraSyn vial, equipped with a stir bar, the chiral amine **94i** (0.06 mmol, 1 equiv.) and Lithium Perchlorate (0.037 mmol, 0.6 equiv.) were dissolved in 3.5 ml of 1,1,1,3,3,3-Hexafluoro-2-propanol. The electrochemical cell was assembled with IKA Glassy carbon anode and cathode and the reaction mixture was degassed with Argon for two minutes. Under argon atmosphere, the solution was electrolyzed with a constant current of 2.5 mA (Cell potential 1.5-2.5V). After 1.5 F/mol were furnished, the reaction mixture was diluted with ethyl acetate and washed two times with an equal volume of brine. The organic phase was then dried over magnesium sulphate and the solvent evaporated under reduced pressure. The obtained residue was purified by column chromatography using a

mixture of hexane/ethyl acetate racing from 9.7:0.3 to 9.5:0.5 to afford a brown solid (after stored in the fridge) in 37% yield

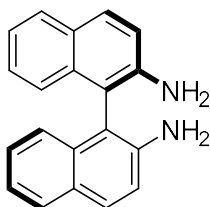
¹H NMR (300 MHz, CDCl₃) δ 7.75 (dd, *J* = 17.3, 8.6 Hz, 2H), 7.62 (d, *J* = 7.5 Hz, 2H), 7.50 (d, *J* = 8.7 Hz, 1H), 7.45 – 7.33 (m, 3H), 7.09 (p, *J* = 6.9 Hz, 2H), 6.96 (d, *J* = 8.7 Hz, 1H), 3.95 (s, 1H), 3.19 (td, *J* = 10.1, 4.3 Hz, 1H), 3.10 – 2.96 (m, 1H), 2.51 (d, *J* = 12.8 Hz, 1H), 2.09 (d, *J* = 12.5 Hz, 1H), 1.86 (d, *J* = 13.2 Hz, 1H), 1.66 (d, *J* = 13.3 Hz, 1H), 1.47 – 1.30 (m, 2H), 1.21 – 1.06 (m, 3H). **¹³C NMR** (75 MHz, CDCl₃) δ 146.38, 136.05, 133.78, 130.90, 128.53, 128.26, 127.85, 127.76, 127.53, 127.42, 126.16, 125.90, 125.77, 125.24, 124.89, 121.87, 121.60, 117.41, 61.51, 50.91, 33.38, 30.41, 29.73, 25.95, 23.57. **HRMS** calculated 365.2018; found 365.2000. **α_D** [1.34 g/ml] (CHCl₃) = -45.52

5.2.7 GENERAL PROCEDURE FOR BYARYL SYSTEMS HYDROGENATION¹⁶⁴



In a two neck round bottom flask was added 10% Pd/C (0.08 mmol, 2 equiv.), followed by the addition of the chiral byaryl amine **96** (0.05 mmol, 1 equiv.) solubilized in ethyl acetate (6 ml). After three cycle vacuum/hydrogen, the reaction was stirred for 2h at room temperature, monitored by TLC. The suspended Pd/C was then removed by filtration through a celite pad, and the filtrate was evaporated under reduced pressure.

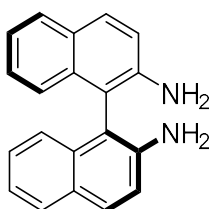
(*R*)-BINAM



Prepared according to the general procedure starting from **96a.1** and **96e.2**. The product was purified by a short flash column chromatography on silica gel using hexane/ethyl acetate 6:4 to afford a white solid in 47% and 48% yield respectively.

Analytical data are in agreement with those obtained for the commercial available *R*-BINAM (CAS N° 18741-85-0). α_D [0.3 g/ml] (CHCl₃) = + 57.04

(*S*)-BINAM



Prepared according to the general procedure starting from **96a.1** and **96e.1**. The product was purified by a short flash column chromatography on silica gel using hexane/ethyl acetate 6:4 to afford a white solid in 40 and 48 % yield respectively.

Analytical data are in agreement with those obtained for the commercial available BINAM (CAS N° 18531-95-8). α_D [0.25 g/ml] (CHCl₃) = -10.72

5.3 PHOTOCYCLIZATION OF ARYL ENONES UNDER HOMOGENEOUS AND HETEROGENEOUS CONDITIONS

5.3.1 DESCRIPTION OF PHOTOREDOX SET-UP

Construction of Photoreactor#1

A making-off video related to the construction of the photoreactor starting from a sublimator apparatus was already reported in literature¹⁶⁵ The central sublimator glass-piece is first wrapped to the de-sired length with heavy duty aluminium foil to generate a socket for the LED-strip that possesses high heat conductive properties. Around this first layer is then coiled and glued (double sided adhesive tape) the LED-strip which is further secured in place at the top and bottom with electric isolating tape. The cable is guided through the silicon rubber seal by puncturing it. The final reactor is then assembled as presented in **Figure 42**.



Figure 42: A) Water-cooled photoreactor scheme. B) Assembled photoreactor (on). C) Assembled photoreactor (off). D) Unassembled photoreactor (without LED strip).

Green LEDs characterization

Commercially available SMD LED 2835 60 led/m 24V, with an IP95 “plug and play system” without extra wiring connection were employed in the realization of photoreactor showed in **figure 41**. The LEDs wavelength emission profile together with their specific light intensity (expressed as mW/cm²) have been determined using a compact CCD spectrometer (model CCS200/M) connected to a multimode optical fiber, purchased by Thorlabs. As clearly depicted in **Figure 43**, green LEDs employed are characterized by an almost monochromatic emission profile showing a maximum of intensity located at ca. 512-514 nm. The light power intensity was thus checked using a Thorlabs PM200 power meter equipped with a S130VC power head with a Si detector. The measured light intensities, though slightly decreasing by moving the maximum of LEDs emission towards longer wavelengths, resulted to be $I = 423.9 \pm 0.6$ mW/cm².

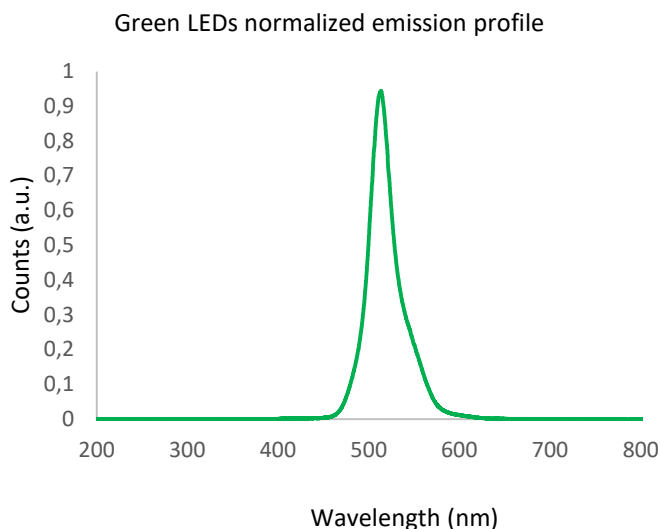


Figure 43: Green LEDs Normalized emission profile.

Photochemical Set-up for continuous flow experiments.

A 200 μ L coil reactor was used for our purposes. This module was constructed using a PFA tubing (1.58 mm outer diameter, 0.508 mm inner diameter, 98.7 cm length, 200 μ L effective volume) coiled around the photoreactor. A New Era NE 300 syringe pumps, equipped with two Hamilton gastight syringes, fed the reactant solutions through a T-junction into the above-mentioned PFA tubing (**Figure 44**).

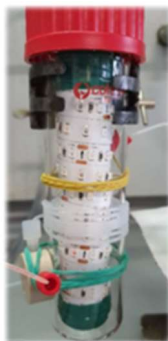
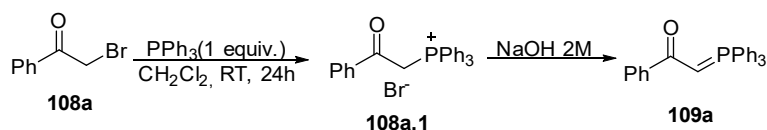


Figure 44: photoreactor #1 with a 200 mL coil reactor.

5.3.2 SYNTHESIS OF STARTING MATERIALS

Synthesis of compound **109a**



Step 1: A solution of α -bromoacetophenone **108a** (1 eq., 5 mmol, 995 mg) in CH_2Cl_2 (3 mL) was added dropwise over 2 min to a solution of triphenylphosphine (1 eq., 5 mmol, 1,31 g) in CH_2Cl_2 (6 mL). The reaction mixture was stirred at room temperature for 24 h, and the resulting mixture was concentrated under reduced pressure. The resulting precipitate was washed with Et_2O . Compound **109a** was obtained in quantitative yield and used without any purification.¹⁶⁶

Step 2: In a 1-necked flask, compound **108a.1** (1.5 mmol, 769 mg) was dissolved in a mixture of CH_2Cl_2 (21 mL), then 15 mL of 2M NaOH aqueous solution were added. The reaction was stirred at room temperature for 3 hours and then ethyl acetate (40 mL) was added. The organic layer was recovered and washed with brine, then dried over Na_2SO_4 and evaporated *in vacuum* to yield the target compound in quantitative yield.

Analytical data are in agreement with those reported in literature.¹⁶⁷