Tutor

Dr. Albert Moyano Baldoire
Departament de Química Inorgànica i Orgànica

Grau de Química

Treball Final de Grau

Asymmetric synthesis by combining photoredox with organocatalysis
Síntesi asimètrica per combinació d'organocatàlisi i catàlisi fotoredox

Diego Fernando Meneses Sánchez

January 2022

Universitat de Barcelona

B:KC Barcelona Knowledge Campus
Campus d'Excel·lència Internacional

Aquesta obra esta subjecta a la llicència de:
Reconeixement–NoComercial-SenseObraDerivada

http://creativecommons.org/licenses/by-nc-nd/3.0/es/

The most exciting phrase to hear in science,

the one that heralds new discoveries,

is not 'Eureka!' but 'That's funny...'

Isaac Asimov

Gràcies als meus companys i companyes per haver fet tant amè estar-se la gran part del dia al laboratori més fred de la facultat. Al Pol Torres per la seva enorme disposició en ajudar; i a la Lucija, la Nour i el David per fer un bon ambient de treball, amb música de tot tipus!

Estic especialment agraït al doctor Albert Moyano per la seva manera d'ensenyar i dirigir aquest treball. També al doctor Xavier Companyó per ensenyar-me valors importants a l'hora de treballar en un laboratori de recerca.

Gràcies sobretot a la meva família per ser un suport indispensable durant els moments més difícils del treball i la carrera.

REPORT

CONTENTS

1. SUMMARY

With the rise of metal-mediated reactions, numerous enantioselective oxidation, reduction, and Lewis acid-catalyzed processes have been reported over the last 50 years. Curiously, few articles using organic molecules as asymmetric catalysts appear in the literature until 2000, with the impressive work of MacMillan and List (2021 Chemistry Nobel Prize). The increasing interest of the research community towards visible light-driven processes, have made photoredox catalysis merge with asymmetric organocatalysis to become one of the most important frontiers of academic research in organic synthesis.

The combination of two catalysts working in tandem fashion for a single reaction is called dual catalysis. This technique opens new paths of non-toxic, sustainable reactions that enable the synthesis of a wide range of organic molecules and the formation of C-C and C-Het bonds; such as the reaction of α-alkylation of aldehydes with ethyl diazoacetates, which uses a porphyrin derivative (TPP-S_4-H_2) as a photocatalyst and a proline derivative as an organocatalyst.

In this context, the enantioselectivity of two new L-prolineamide derivatives is tested with different aldehydes in the mentioned reaction. The results obtained with one of them (the *N*-neopentyl prolineamide **4**) are outstanding in terms of enantioselectivity, and the stereochemical outcome of the reaction (unambiguously ascertained by chemical correlation with a known compound) can be rationalized by a simple mechanistic model in terms of both steric hindrance and hydrogen bond-directing effects.

Keywords: Organocatalysis, photoredox catalysis, dual catalysis, α-alkylation, porphyrin, prolineamide, enantioselectivity.

2. RESUM

Amb l'auge de les reaccions promogudes per metalls, en els darrers 50 anys s'han desenvolupat nombrosos processos enantioselectius d'oxidació, reducció i catalitzats per àcids de Lewis. Curiosament, a la literatura apareixen pocs articles que utilitzin molècules orgàniques com a catalitzadors asimètrics fins a l'any 2000, amb els impressionants treballs de MacMillan i List (Premi Nobel de Química al 2021). L'interès creixent de la comunitat investigadora pels processos impulsats per la llum visible, ha fet que la catàlisi fotoredox es fusioni amb l'organocatàlisi asimètrica per convertir-se en una de les fronteres més importants de la recerca acadèmica en síntesi orgànica.

La combinació de dos catalitzadors que treballen conjuntament per a una mateixa reacció s'anomena catàlisi dual. Aquesta tècnica obre noves vies de reaccions no tòxiques i sostenibles que permeten la síntesi duna àmplia gamma de molècules orgàniques i la formació d'enllaços C-C i C-Het; com la reacció d'α-alquilació d'aldehids amb diazoacetat d'etil, que utilitza un derivat de porfirina (TPP-S_4-H_2) com a fotocatalitzador i un derivat de prolina com a organocatalitzador.

En aquest context, es comprova l'enantioselectivitat de dos nous derivats de la L-prolinamida amb diferents aldehids, en la reacció esmentada. Els resultats obtinguts amb un d'ells (la *N*-neopentilprolinamida **4**) són remarcables pel que fa a l'enantioselectivitat, i el biaix estereoquímic de la reacció (que s'ha determinat inequívocament per correlació química amb un compost de configuració coneguda) es pot racionalitzar mitjançant un model mecanístic senzill basat en l'impediment estèric i en els efectes directors de l'enllaç d'hidrogen.

Paraules clau: Organocatàlisi, catàlisi fotoredox, catàlisi dual, α-alquilació, porfirina, prolinamida, enantioselectivitat.

3. INTRODUCTION

3.1. MOLECULAR CHIRALITY AND ASYMMETRIC CATALYSIS

It is well known that Louis Pasteur (1822–1895) was observing with a microscope an optically inactive salt of tartaric acid (TA) when he noticed that the apparently homogeneous set of crystals was in fact a 1:1 mixture of enantiomorphic (hemihedral) crystals (Figure 1). He manually separated them and found that when submitted to linearly polarized light, each hemihedral class rotated the plane of polarization by equal absolute magnitudes, but opposite in direction. Most importantly, the same thing happened with the corresponding aqueous solutions. Proceeding by deduction, he established the foundations of *molecular chirality* by stating that molecules with identical physical and chemical properties can present dissimilar 3D structure[1].

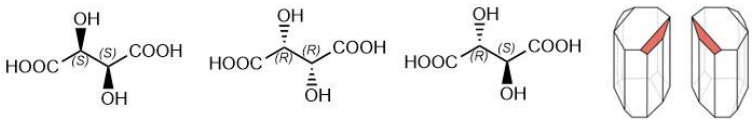


Figure 1. From left to right: The two TA enantiomers, the meso-compound and the hemihedral crystals. (Brighterorange, via Wikimedia Commons, Creative Commons Attribution).

Thanks to this and to more contributions throughout history, enantiomers were eventually described as pairs of compounds with the same molecular connectivity that cannot be superimposed. This type of stereoisomers shares the exact physical and chemical properties and can only be differentiated by their interaction with polarized light (Table 1).

Albeit the task of separating a mixture of enantiomers may seem almost impossible, classical methods achieved quantitative resolutions of racemic mixtures (1:1) by converting them into diastereomeric salts, which have different properties and can be separated (by fractional crystallization)[2].

Stereoisomer	*Conf.*	*M.P. (°C)*	*$[\alpha]_D$ (degree)*	*Density (g/ml)*	*Solubility at 20 °C (g/100 ml H_2O)*
(+)-Tartaric acid	(2*R*,3*R*)	168 - 170	+ 12	1.7598	139.0
Racemate of tartaric acid	(2*R*,3*R*) & (2*S*,3*S*)	206	0	1.7880	20.6
meso-Tartaric acid	*(2R,3S) or (2S,3R)*	*146 - 148*	*0*	*1.6660*	*125.0*

Table 1. Differences between enantiomers and racemic mixture of tartaric acid. The (-)-(2S,3S)-tartaric acid only differs in the sign of the rotation from the shown (+)-(2R,3R) enantiomer.

The reader may be wondering why all the struggle to master this molecular chirality concept. The incentive is as momentous as the understanding of the dissymmetry of the universe or nature's tendency to discriminate one enantiomer from the other, leading to the phenomenon of *biological homochirality* (the fact that in living beings most molecules are chiral and appear always as single enantiomers with the same type of chirality). An important consequence of the intrinsic chirality of life are the different effects of opposite enantiomers of chiral drugs, pesticides, and fragrance molecules on biological receptors[3] (Figure 2); which has inspired chemists to develop the concept of *asymmetric synthesis* as a complementary method to racemic resolution for the preparation of chiral substances in enantiomerically homogeneous form.

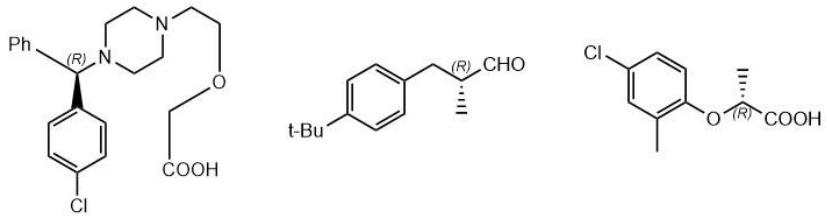
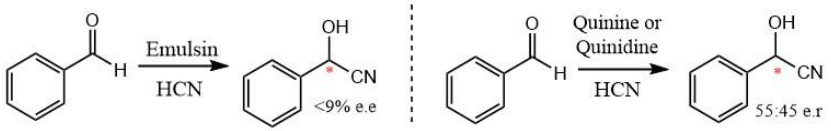


Figure 2. From left to right: a drug (cetirizine), a fragrant (lilial) and a pesticide (mecoprop). Only the enantiomer shown in the figure presents the desired biological activity.

This last-mentioned notion can be described, in many instances, as the selective formation of a new chiral center (or more) from non-chiral starting compounds[4]. Initially, it could be achieved either by the use of chiral auxiliaries or with stoichiometric amounts of chiral reactants; but the expensiveness of the enantio-pure reagents or the additional steps involved in the auxiliary process made it evolve towards *asymmetric catalysis*, which uses substoichiometric amounts of a chiral substance (that can be a purely organic compound or a metallic complex) to catalyze the kinetically controlled preferential formation of one of the two enantiomers of a chiral compound.

3.2. ASYMMETRIC ORGANOCATALYSIS

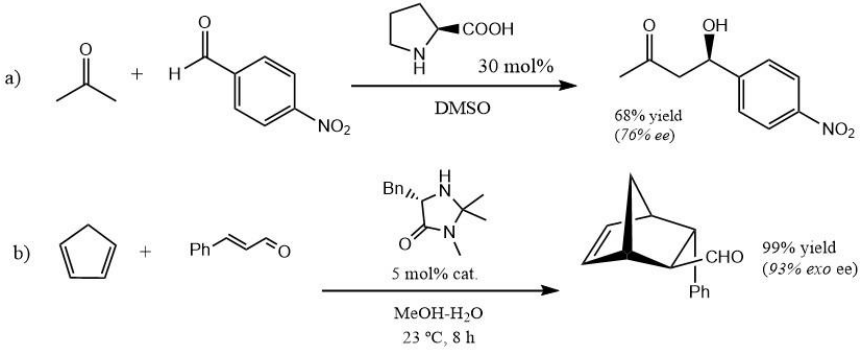
The use of organic molecules for asymmetric catalysis was unsuccessfully performed with purified enzymes until 1908, when Rosenthaler[5] used emulsin to obtain a 9% ee of a cyanohydrin from benzaldehyde and HCN. Later on, and with the same reaction, Bredig and Fiske[6] obtained the poor similar ee; but using quinine or quinidine as catalysts and raising the foundations of organocatalyzed enantioselective reactions (Scheme 1).



Scheme 1. Rosenthaler (expressed in enantiomeric excess) and Bredig and Fiske's (express in the proportions of enantiomers) approaches to the cyanohydrin synthesis.

In the second half of the last century, the use of some chiral metallic complexes as asymmetric catalysts showed remarkably high ee's. These pioneering investigations performed by Noyori[7], Knowles[8] and Sharpless[9] were awarded with the chemistry Nobel prize in 2001 and constituted huge steps towards the optimization of metal-mediated asymmetric synthesis. Nonetheless, the toxicity, the expensiveness and the sensitivity to air and moisture of transition metal complexes were the drawbacks that gave rise to the alternative of simple chiral organic catalysts.

Some isolated examples with significant enantioselectivity of the latter reactions can be found in the literature[10]; but it was not until 2000 that MacMillan[11] and List[12] showed that efficient asymmetric catalysis could be accomplished using small, stable, and inexpensive chiral organic molecules like proline or imidazolidinones (Scheme 2); work that finally resulted in the award of the Nobel prize in chemistry to both researchers in 2021.



Scheme 2. a) List's proline-catalyzed direct asymmetric aldol reaction. b) MacMillan's Diels-Alder reaction

To understand the magnitude of this achievement, is it necessary to go besides the purely numerical results and remark the following features: the easy availability of both enantiopure isomeric forms, the low molecular weight, the low prices, the renewability, the absence of sensitivity to air and moisture and the very low toxicity due to the lack of metals.

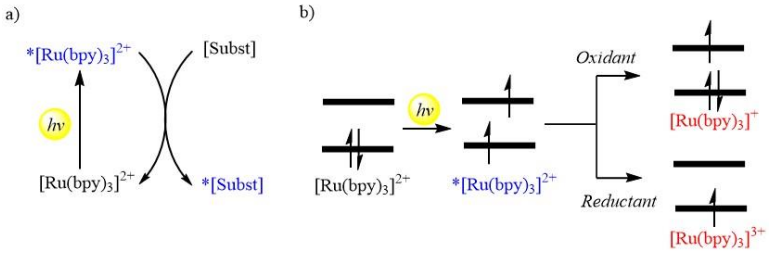
Unlike the mechanistically complicated metallic cycles, this kind of reactivity can moreover be easily understood by means of simple mechanistic explanations and is compatible with radical catalysis and especially, with photocatalysis.

3.3. VISIBLE LIGHT PHOTOCATALYSIS AND ORGANOPHOTOCATALYSIS

Photochemistry was particularly recognized as a synthetic tool in 1900 by the chemist Giacomo Ciamician, who discovered many important photochemical reactions and envisioned its use in organic chemistry and as a green energy source. Nevertheless, until recently it has been an unexplored field in the context of asymmetric catalysis because of drawbacks such as the lack of enantioselectivity, the absence of appropriate artificial radiation sources and the many open-shell radicals that can interfere in the reaction.[13]

Many organic molecules don't absorb in the visible light region and the use of high energy UV light sources is inevitable. To avoid the use of the latter, photocatalysis emerges as one of the options that utilize visible light and has found many applications. It is a process in which the photonic energy given to the photocatalyst excites it and engages it in reaction paths that are impossible with thermal conditions, such as the following ones (Scheme 3):

- Photosensitization: Uses a compound called photosensitizer, which can absorb light in the visible region and easily reach its triplet excited state. This enables the indirect excitation of the organic substrate through energy transfer that occurs between the excited photosensitizer and the ground state substrate[13].
- Photoredox catalysis: This technique excites a photocatalyst to its triplet energy state and engages it into SET processes which are more studied, predictable, and similar to radical chemistry. The most common visible-light photocatalysts were initially polypyridyl complexes of ruthenium and iridium[14], which have a large redox window, present a long-lived photoredox state and can undergo either oxidative or reductive quenching.



Scheme 3. Photocatalysis examples with the Ruthenium complex: a) Photosensitization process b) Photoredox process (Simplified Molecular Orbital Depiction)

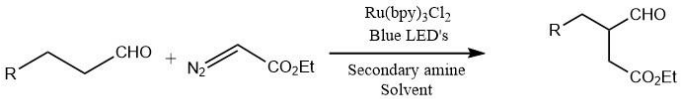
3.3.1. Asymmetric photoredox catalysis: Dual strategy

The inconvenience of using chiral photocatalysts is that in most instances chiral products are obtained as racemic mixtures. This is due to the high reactivity and the low activation barriers of the radical intermediates that take part in the photocatalytic process, so that the chirality of the catalyst is not efficiently transferred to the products. Despite this handicap, asymmetric photocatalytic reactions have been successfully accomplished using a dual catalytic system. In this methodology, an achiral photocatalyst is combined with an asymmetric organocatalyst such as: a chiral secondary amine, a chiral Bronsted acid, a chiral thio-urea, or *N*-heterocyclic carbenes[15].

Regarding C-C and C-heteroatom bond formation, MacMillan and co-workers demonstrated how aldehydes can react with bromomalonate compounds to obtain alkylated derivatives with good yields and estereoselectivy[16]. The reaction was done under visible light, with the presence of a metal-based photocatalyst and with chiral imidazolidinones.

3.4. ASYMMETRIC α-ALKYLATION OF ALDEHYDES WITH α-DIAZOESTERS

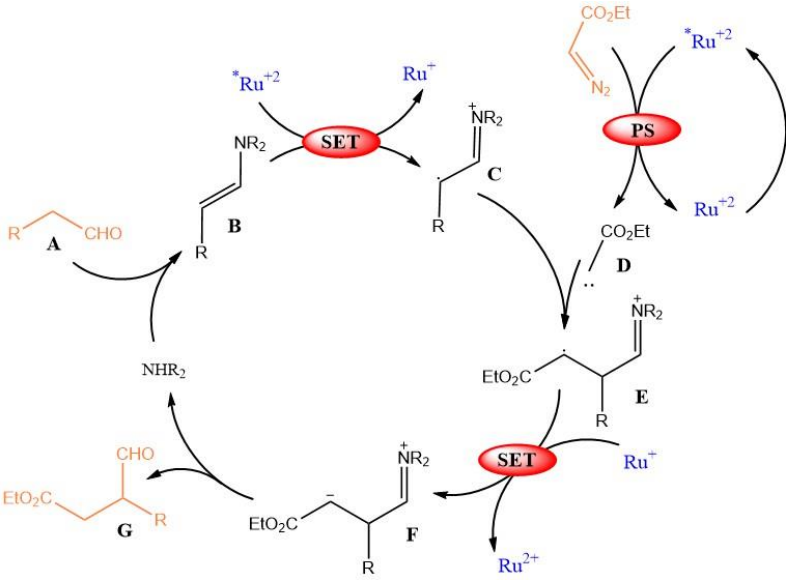
With similar conditions as in the MacMillan reaction, Gryko and co-workers studied the chemistry of diazocompounds, a relatively unexploited functional group in organic chemistry. Interestingly enough, they found that the use of $Ru(bpy)_3Cl_2$ as a photocatalyst, in conjunction with a cyclic secondary amine co-catalyst, allowed the α-alkylation of α-unbranched aldehydes with ethyl diazoacetate **1**, a stable, readily available reagent (Scheme 4).[17]



1

*Scheme 4. Photocatalytic alkylation of α-unbranched aldehydes with EDA **1** under visible light*

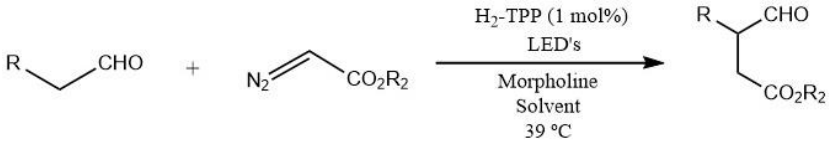
Their report is remarkable for the mechanistic studies that reveal that the photocatalyst is involved in both photosensitization and photoredox catalysis processes (Scheme 5). The cycle begins with the formation of the enamine **B** from the aldehyde **A** and a secondary amine (plus a molecule of water, not shown). The ruthenium(II) complex is excited to its triplet state and engages in a SET to form an β-iminium radical-cation **C**, being itself reduced to Ru(I). On the other hand, the same excited ruthenium ($*Ru^{2+}$) decomposes the EDA (with loss of dinitrogen) to a triplet carbene **D**, which reacts with the iminium radical **C** to give the γ-amino radical-cation **E**. Then, another SET takes place (with the Ru(I) of the first SET that goes back to the Ru(II) ground state, closing the photoredox catalytic cycle), to obtain the zwitterionic compound **F**. The latter is protonated and hydrolyzed (by the initially formed molecule of water) to obtain the alkylated compound **G** and to recover the amine, which restarts the organocatalytic cycle.



Scheme 5. Proposed cycle for photocatalytic reaction of aldehydes and EDA.

3.4.1. Porphyrins as photocatalysts

Subsequent studies by Zawada, Kadish, Gryko and co-workers[18] showed that excited-state porphyrins can also engage in both energy and electron transfer processes, producing a carbene in the triplet state and an enamine radical that can functionalize aldehydes (47–90% yields) in the α position, just exactly as the ruthenium complex shown before in Scheme 5 (Scheme 6). It is worth noting however that they used only achiral amines (such as piperidine or morpholine) as organocatalysts, so that the alkylated aldehydes were of course obtained in racemic form.



Scheme 6. Porphyrin-mediated photocatalytic alkylation of aldehydes with Gryko's conditions

Porphyrins belong to a class of organic compounds called porphyrinoids that share the general structure of four pyrrole rings connected by four methylene bridges. These tetrapyrrolic constructions, often called pigments of life, are well-known for their role in essential biological processes such as oxygen transport or photosynthesis (the archetypal visible-light photoredox catalysis reaction).

The 18 π electron aromatic system of the porphyrin ring provides it with planarity, stability, and special electronic features that made these molecules firstly used as photosensitizers for singlet oxygen generation[19]. Nonetheless, their properties can be tuned by placing a variety of substituents at the periphery of the macrocycle, which makes it an ideal replacement for the metallic photocatalysts described until now (Figure 3).

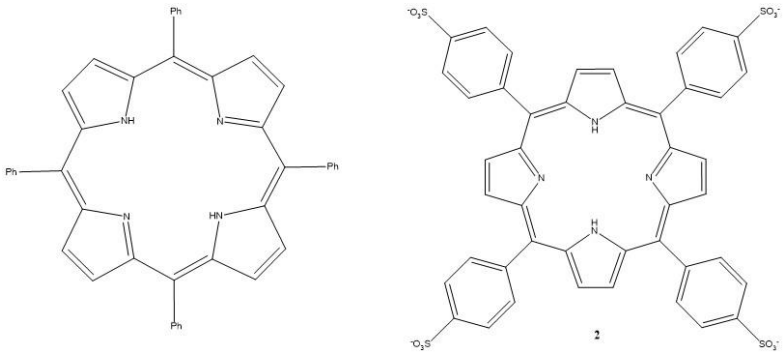
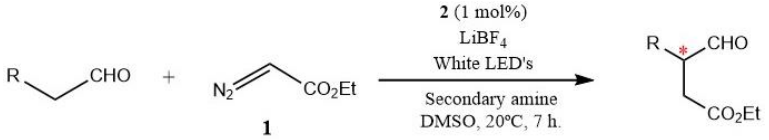


Figure 3. Tetraphenylporphyrin (TPP-H_2) and the tetrasulfonated derivative used in this project: TPP-S_4-H_2 ***2****.*

3.4.1. Asymmetric α-alkylation of aldehydes Using TPP-S_4-H_2

This process became of interest to the research group because when using a variety of neutral amino-functionalized porphyrins as photocatalysts for his PhD project, and with the aim of developing an organocatalytic asymmetric version of the aldehyde alkylation reaction, Pol Torres realized the difficulty of separating the porphyrin from the product and envisioned the possibility of using water soluble porphyrins as photocatalysts. From that work derives the choice of TPP-S_4-H_2 **2** as a photocatalyst for this project. Pol Torres also optimized the conditions of the reaction (Scheme 7) by previously degassing the solvent DMSO and eliminating aqueous buffers in the reaction mixture, which led to the formation of aldolic condensation by-products. Then different chiral organocatalysts were tested to study their enantioselectivity with the new conditions[20] (Figure 4).



*Scheme 7. Alkylation of aldehydes using Ethyl diazoacetate **1** with TPP-S_4-H_2 **2** as a photocatalyst*

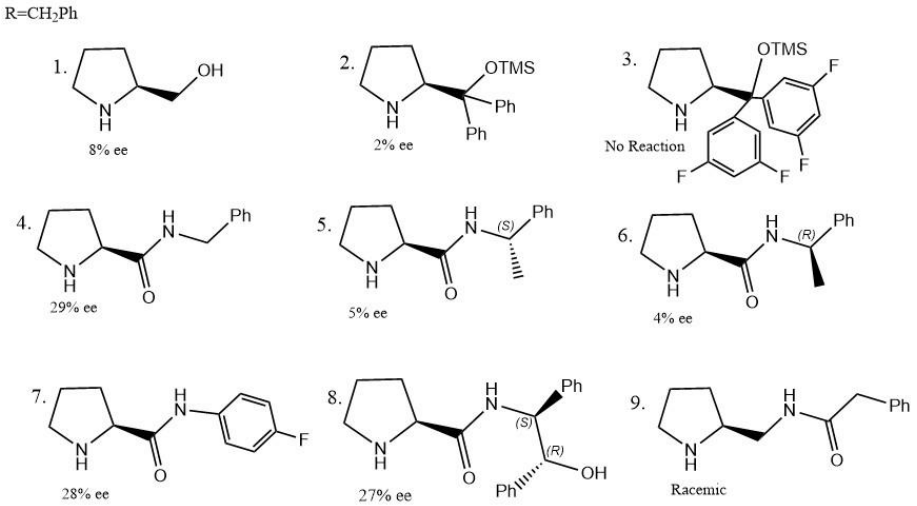


Figure 4. Organocatalysts tested by Pol Torres, together with the enantiomeric excess obtained in the alkylation of 3-phenylpropanal.

4. OBJECTIVES

The main aim of this project is to improve the procedure established by the research group to obtain new alkylated aldehydes using porphyrins or $Ru(bpy)_3Cl_2$ as photocatalysts and new chiral secondary amines that allow to attain higher enantioselectivities than those previously observed. To achieve that, it is necessary to synthesize and characterize these new chiral proline derivatives, **3** and **4**. (Figure 5):

Figure 5. Proline organocatalysts that are to be synthesized in this project

Both will be tested with 3-phenylpropionaldehyde **5** in the benchmark photoredox-catalyzed alkylation with ethyl diazoacetate **1**, before using new aldehydes. The one with best results is to be fully characterized using ^{1}H-NMR, ^{13}C-NMR and ESI-HRMS.

Once having found which one is the better enantioselective organocatalyst for the alkylation of **5**, these are the aldehydes initially planned to be tested with the dual catalytic system (Figure 6):

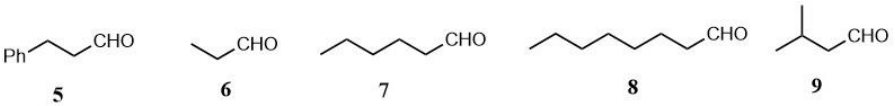
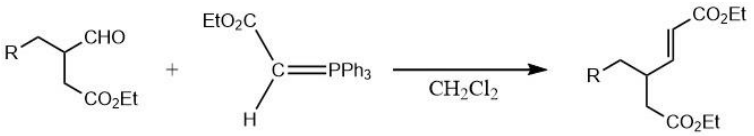


Figure 6. Aldehydes that are to be tested in this project

Once the alkylation of the new aldehydes (**6**-**9**) is completed, the crude product mixture would be analyzed by ^{1}H-NMR spectroscopy and, if the desired alkylation product is detected, the Wittig derivative would be prepared without previous purification (Scheme 8) to allow the determination of its enantiomeric purity by chiral HPLC.

The HPLC uses UV/Vis light to detect the separated products. Thus, it is necessary to add a chromophore group to intensify the peaks of the spectra via the formation of an unsaturated ester.



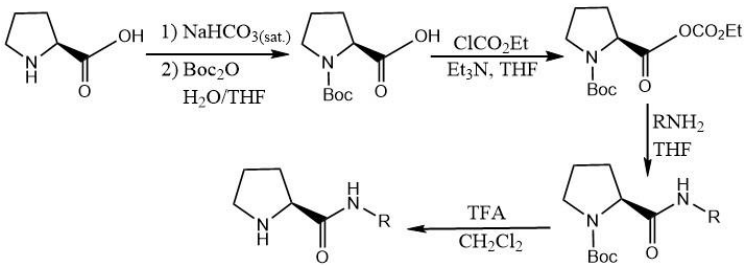
Scheme 8. Preparation of the Wittig derivatives

Finally, if good enantioselectivities can be achieved, we planned to determine the absolute configuration of the major enantiomer of the product of the benchmark reaction by transforming it into a compound of previously known absolute stereochemistry and comparing the specific rotation values (chemical correlation).

5. RESULTS AND DISCUSSION

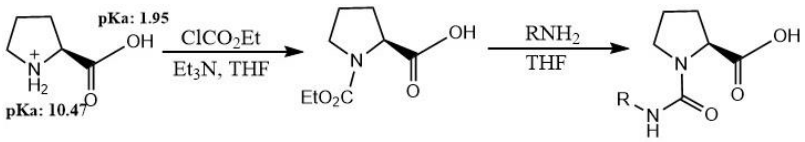
5.1. SYNTHESIS OF THE ORGANOCATALYSTS 3 AND 4

The synthesis of the prolineamide organocatalysts starts with the protection of the proline nitrogen that is responsible for the formation of the enamine in the catalytic reaction.[21] Then, the desired primary amines (R-NH_2) engage in an addition-elimination reaction with the previously acylated carboxylic acid (the intermediate anhydride is not isolated).[22,23] Finally, the deprotection of the endocyclic nitrogen[24] leaves the desired proline derivative, which is an amide in both cases (Scheme 9).



Scheme 9. General preparation of the organocatalysts

If the proline nitrogen is not protected, the amino group would get acylated quicker to form a carbamide and eventually a urea derivative (Scheme 10). This is because nitrogen is more nucleophilic than oxygen, which is related to the more basic character of the former. Oxygen is more electronegative and supports better negative charges, thus, its conjugated base is more stable and considered weaker. Going further, this is related to the higher proton charge of oxygen, which pulls the electrons to its nucleus.

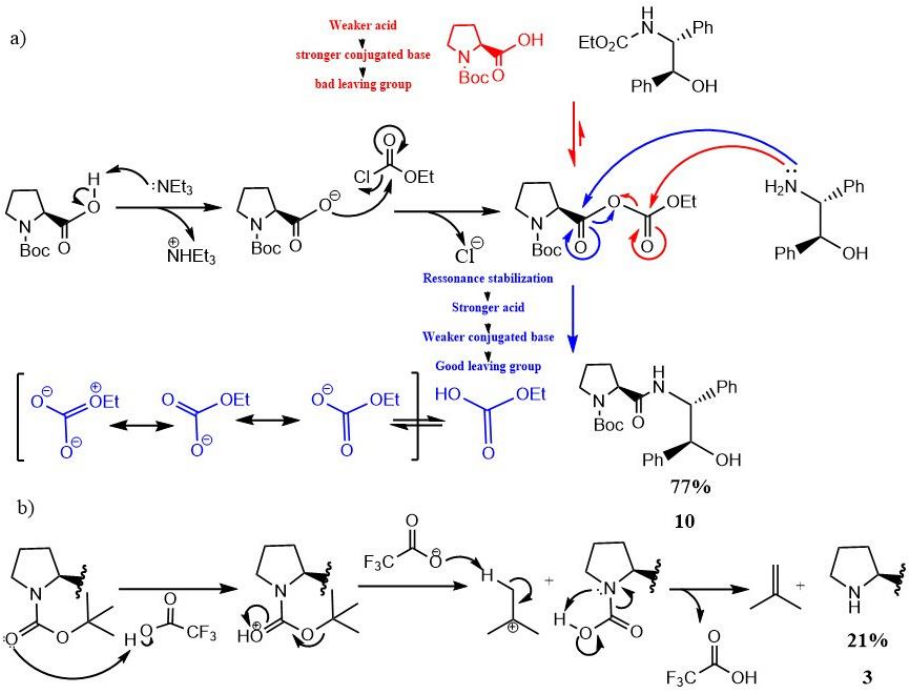


Scheme 10. Reaction that would take place if the protection of the amino group is not done

Is it necessary to say that the two first organocatalysts were obtained directly from *N*-Boc-L-proline, previously synthesized by Pol Torres by the procedure shown in the first step of Scheme 9.[21] It is also noticeable that the percentages under the photoredox products are conversion estimated from the relative areas of the aldehyde peaks in the ^{1}H-NMR spectra if the contrary is not stated.

5.1.1. Preparation of the aminoalcohol (3).

This aminoalcohol is one diastereomer from the compound 8 in Figure 4 and is likely to present similar enantiomeric excess. The already protected *L*-proline engages in a reaction with an ethyl chloroformate using a tertiary amine. The triethylamine acts a base to deprotonate the acid, that forms the mixed anhydride and the ammonium salt in an addition-elimination reaction. The same type of reaction occurs when the aminoalcohol is added and attacks the carbonyl that releases the best leaving group (Scheme 11a).[22] Finally, the deprotection of the Boc-prolinamide is completed after adding TFA (Scheme 11b).[24] Regrettably enough, this step afforded a surprisingly low yield (21%) of the desired amide **3**, difficult to recover from the chromatographic column due to its high polarity.



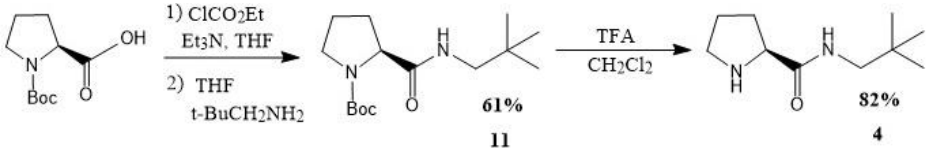
*Scheme 11. a) Formation of the amide **10** b) Deprotection of the proline to obtain the organocatalyst **3***

As mentioned before, the organocatalyst **3** is tested in the photoredox reaction with the 3-phenylpropionaldehyde **5** to give the alkylated product. The ^{1}H-NMR of the reaction crude showed a 53% conversion for this step. However, the formation of the Wittig derivative was unsuccessful, so that it was not possible to calculate the enantioselectivity. Due to the low yield of the deprotection reaction of **10**, no more amide **3** was available and further work with this catalyst was discontinued.

5.1.2. Preparation and characterization of *(S)-N*-neopentylpyrrolidine-2-carboxamide (4)

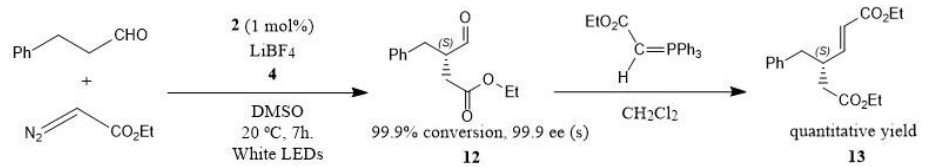
Since the introduction of steric hindrance next to the amide nitrogen seemed to diminish the catalytic activity (compare compounds 4, 5 and 6 in Figure 4 above), we decided to move one carbon away the bulky group. As a simple model to validate this hypothesis, we decided to prepare and test the L-*N*-neopentylprolinamide **4**. The synthesis is the same as the one mentioned before for **3**, but with the neopentylamine attacking the acylated group (Scheme 12). As it can be seen, the intermediate protected amide **11** was obtained in 61% from *N*-Boc-L-prolineamide. The deprotection took place in this instance satisfactorily, affording **4** in 82% yield.

It is worth noting that **4** had been previously prepared in the context of a medicinal chemistry project,[23] but had not been correctly characterized, and never used as an organocatalyst.



*Scheme 12. Synthesis of (S)-N-neopentylpyrrolidine-2-carboxamide **4***

This organocatalyst was tested in the alkylation of **5** with both TPP-S_4-H_2 **2** and $Ru(bpy)_3Cl_2$ photocatalysts to compare with the results obtained by Pol Torres (Scheme 13). The products **12** were derivatized and the ee's obtained were so remarkable that the one with **2** was replicated, obtaining the same results (Table 2). The chromatogram obtained by Pol Torres(Figure 7a). corroborated that the enantiopure compound (Figure 7b) is one of the peaks of a racemic mixture



*Scheme 13. Results from the photoredox between **1** and **5** using the organocatalyst **4***

Photocatalyst	Photocatalysis (%)	Enantiomeric excess (%)
2	99.9%**	99.9*
$Ru(bpy)_3Cl_2$	99.9%***	99.9

Table 2. Comparison of the two photocatalyst in the photoreaction

**A replicate was done with the exact result*

*** Expressed in yield obtained with the known quantity of the standard TMB (Using ^{1}H-NMR)*

**** Expressed in conversion from the integration of the signals from the obtained and the spare aldehydes*

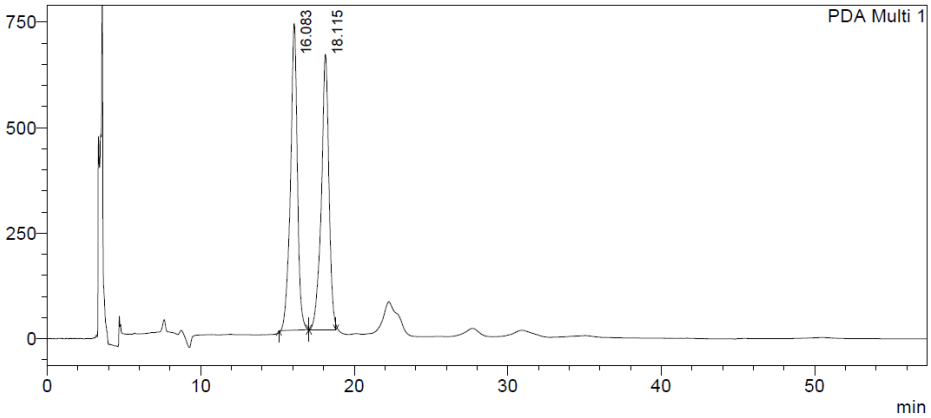


Figure 7a. Results from Pol Torres using piperidine as a non-chiral secondary amine to obtain a racemic mixture

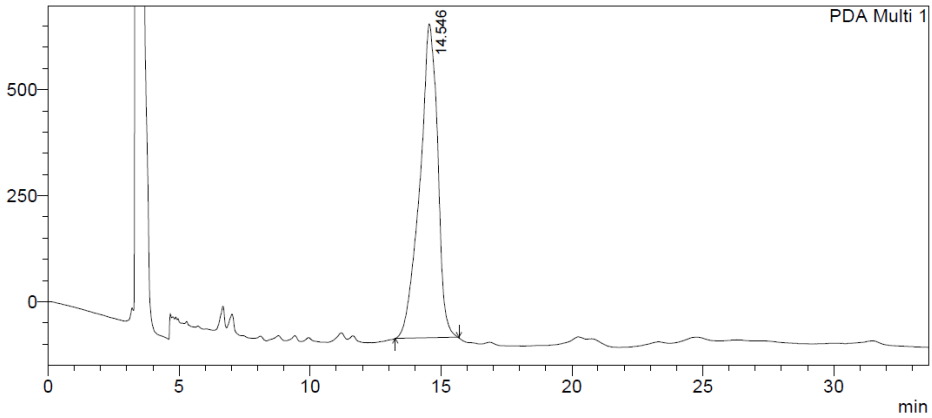
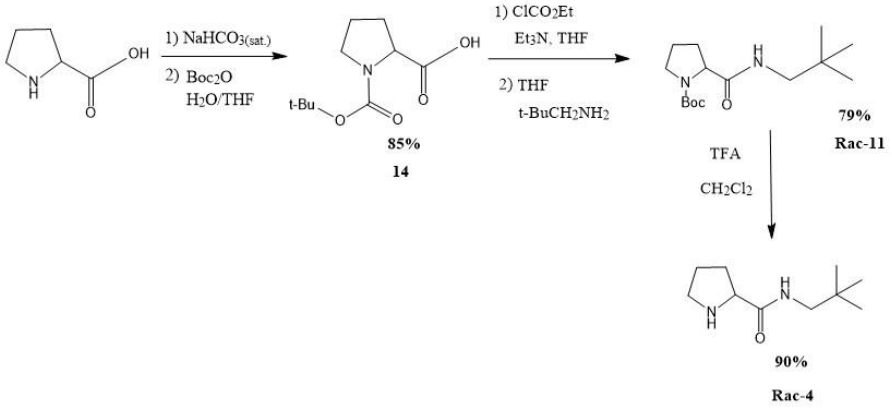


*Figure 7b. Results from Scheme 13 using photocatalyst **2.** The chromatogram using the Ruthenium complex is the same.*

5.1.3. Preparation of (±)-N-neopentylpyrrolidine-2-carboxamide (*rac*-4)

To obtain the racemic mixture of the new aldehydes, the racemic organocatalyst *rac*-**4** was obtained from commercial racemic proline by the same procedure employed with the enantiopure compound and took place with similar yields (Scheme 14).[21,23,24]



Scheme 14. Mechanism of the N-protection and the synthesis of the racemic organocatalyst

This racemic organocatalyst *rac*-**4** was only tested with isovaleraldehyde **9** and derivatized with good results. The HPLC sample was prepared but, unfortunately, it was not possible to perform the analysis by lack of time.

5.2. PHOTOREDOX REACTION: α-ALKYLATION OF THE ALDEHYDES

Once the organocatalyst **4** was fully characterized, all four proposed aldehydes (**6**-**9**) were tested with it. The option for making the racemic mixture of the first three was piperidine, whereas isovaleraldehyde **9** was later tested with the racemic prolineamide *rac*-**4**. No alkylation products were observed with both racemic and non-racemic organocatalysts with propionaldehyde **6**, whose crude reaction products were discarded for derivatization.

The non-racemic hexanal, **7** octanal **8** and isovaleraldehyde **9** alkylated products were considered acceptable to derivatize and injected in the HPLC. Due to the inefficient reaction with piperidine, the nearly racemic (5% ee) product mixture arising from hexanal **6** was prepared using (*S*)-*N*-((*S*)-1-phenylethyl)pyrrolidine-2-carboxamide (**15,** see compound 5 in Figure 4) as the organocatalyst. All the products are presented in Figure 8.

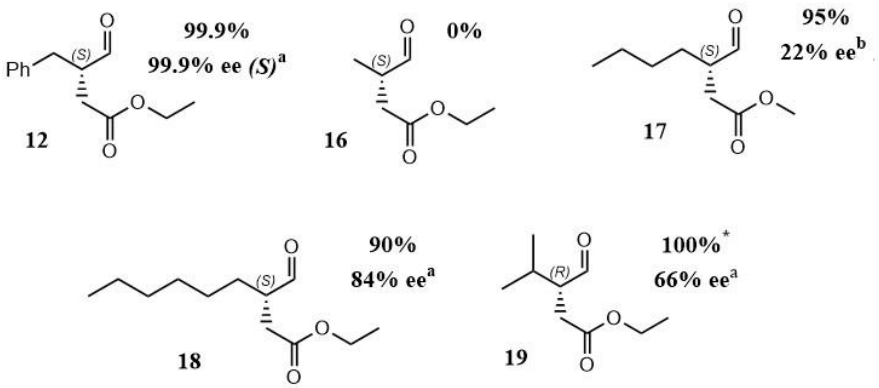


*Figure 8. Results from the non-racemic photocatalytic reaction (using **2** as a photocatalyst) and the enantiomeric excesses of the Wittig derivatives. *Expressed in conversion. [a]. Racemic obtained with piperidine. [b]. Racemic obtained with **15**. [c]. Racemic obtained with rac-**4**.*

The reaction with aldehyde **5** was scaled from 0.25 mmol to 1 mmol with lower conversion rates and the formation of aldolic condensation by-products. It was also difficult to purify the crude with flash chromatography, obtaining low yields as if the silica gel decomposed the product.

As mentioned before, the conversions of the alkylated aldehydes are calculated from the integration of the aldehyde peaks from the ^{1}H-NMR at low field. The standard 1,3,5-trimethylbenzene (TMB) was used to express the results in yields and not conversion, since it gives a clear singlet in the aromatic region, which can be related to the amount of mols added to the mixture of the reaction (Figure 9)

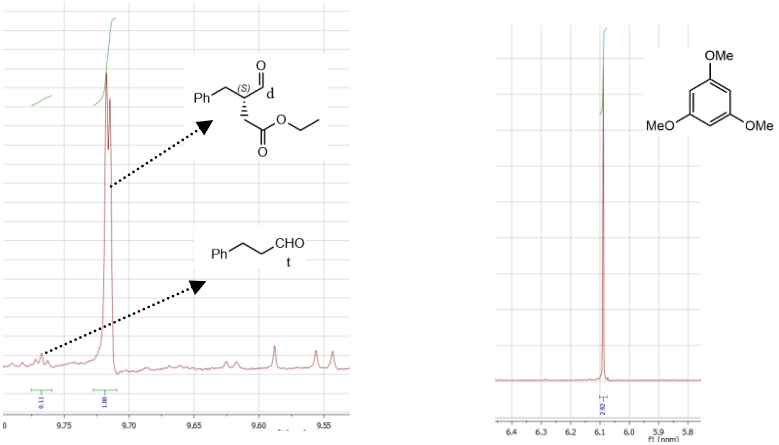
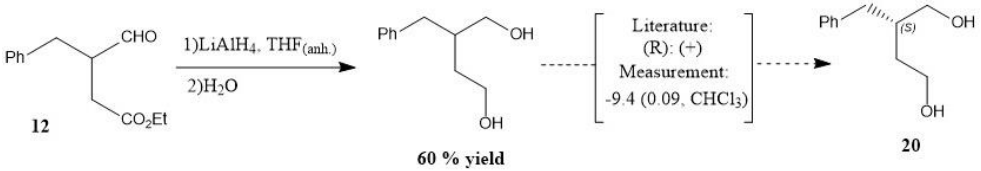


Figure 9. Parts of the ^{1}H-NMR spectra of the compound. The desired aldehyde shows a doublet that integrates to 1, whereas the other presents a triplet.

5.3 ABSOLUTE CONFIGURATION OF COMPOUND 12 AND MECHANISTIC EXPLANATION

The absolute configuration of an enantiomerically pure compound can be ascertained by a limited number of techniques (X-ray diffraction analysis of a monocrystal containing heavy atoms, comparison of chiroptical or vibrational circular dichroism data with theoretical calculations, exciton chirality method, etc.). However, the most practical method is that of chemical correlation, which implies the chemical transformation (if necessary) of our compound into a different one for which a) the absolute configuration has previously been established by one of the techniques mentioned before, and b) the specific rotation is known. Then, by simple comparison of the magnitude and the sign of the specific rotations, the stereochemical identity of our enantiomerically enriched sample can be ascertained.

In our case, a bibliographic search showed that the chiral diol **20**, that should be easily obtained by reduction of the aldehyde and ester groups in **12**, had been previously obtained in enantiomerically enriched form, and that the dextrorotatory enantiomer had an (*R*) absolute configuration.[25] We were delighted to find that when a THF solution of nonracemic **12**, obtained in the conditions of Table 3 (entry 1) was treated with an excess of lithium aluminum hydride, the desired diol **20** was obtained in 60% yield after chromatographic purification (Scheme 15). When we measured its specific rotation, we found a value of -9.4 (0.09, $CHCl_3$). This establishes unambiguously an absolute *(S)* configuration for this compound, and for the aldehyde ester **12**.



Scheme 15. Reduction of the carbonyls with $LiAlH_4$ to obtain the diol.

This absolute configuration matches with the mechanistic model involving a non-covalent hydrogen bond between the NH and the carbonyl oxygen, which directs the attack of the carbene to the C2—*Re* face of the (*E*)-configured enamine. Probably, the steric hindrance exerted by the bulky neopentyl group ensures that the reaction takes place almost exclusively in the *s-trans* conformer of the enamine (Figure 10).

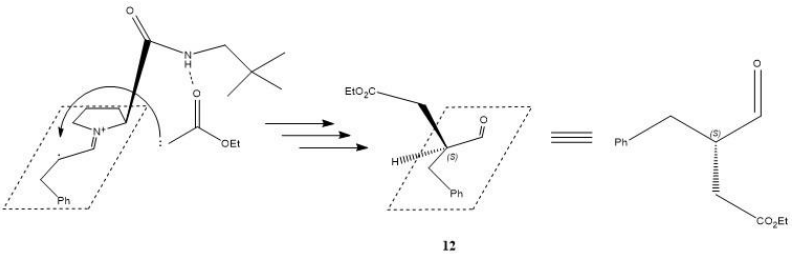


Figure 10. Mechanism explanation to the configuration obtained

6. EXPERIMENTAL SECTION

6.1. MATERIALS AND METHODS

All the reagents and starting materials were obtained from commercial suppliers and were used without further purification. All the solvents used were purified according to standards laboratory procedures.

NMR spectra were acquired using a Varian Mercury 400 instrument at room temperature. ^{1}H NMR spectra were referenced to TMS (δ = 0 ppm) or to residual non-deuterated solvent peaks as internal standards. ^{13}C NMR spectra were referenced to residual solvent peaks. Multiplicities are noted as: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet or unresolved and combinations of these multiplicities (e. g. dd, dt, td etc.). Coupling constants J are given in Hz.

HPLC analysis were performed on a Shimadzu instrument containing LC-20-AD solvent delivery unit, DGU-20As degasser unit and SPD-M20A UV/Vis Photodiode Array Detector, with chiral stationary phase (PHENOMENEX LC Column 250 x 4.6 mm Lux® 5 µm i-Cellulose-5).

HRMS analysis were recorded using a Bruker MicroTOF electrospray ionization spectrometer (ESI).

Thin layer chromatography (TLC) was performed on SiliaPlate TLC Aluminum Backed TLC (Silicycle Inc.). Visualization of the developed chromatogram was performed by fluorescence quenching, $KMnO_4$ stain or Phosphomolybdic acid stain.

6.2. SYNTHESIS OF THE ORGANOCATALYSTS

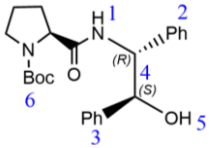
6.2.1 General procedure for *N*-Boc Deprotection[24]

In a round-bottomed flask equipped with a magnetic stirring that contains 1 eq of the *N*-Boc-prolineamide, the solvent CH_2Cl_2 is added, and the mixture is stirred and cooled down to 0 ºC using an ice bath. After closing it with a serum and a bubbler, 24 eq of TFA are added dropwise and the mixture is left stirring for 1 h at 0 ºC. Then, the solution is diluted with more CH_2Cl_2 and concentrated under reduced pressure to eliminate the TFA, which is a highly volatile acid. Having obtained the yellowish oil, the minimum amount of MeOH is added to dilute it and be able to extract it with NaOH 1M and CH_2Cl_2. After having dried the organic phase with $MgSO_4$ and filtered into a new round-bottomed flask, the solution is again concentrated under reduced pressure and evaporated under vacuum to obtain the prolineamide, after chromatographic purification on silica gel.

6.2.2 Synthesis of *(S)-N-((1R,2S)*-2-hydroxy-1,2-diphenylethyl)pyrrolidine-2-carboxamide. (3)

6.2.2.1 Synthesis of tert-butyl (S)-2-(((1R,2S)-2-hydroxy-1,2 diphenylethyl)carbamoyl)pyrrolidine-1-carboxylate[22].(10)

In a carefully dried 10 mL round-bottomed flask equipped with a stirring magnet, 100 mg (0.47 mmol) of *N*-Boc-L-proline were mixed with 79 µL of Et_3N (0.57 mmol) and 0.9 mL of THF. The solution was cooled down to -15 ºC using an ice-salt bath and MeOH. Then, a solution of 0.65 mL of THF with 45 µL of ECF was added dropwise to the mixture. After that, another solution of 0.25 mL of THF containing the 200 mg of the amino alcohol (0.94 mmol) were added to the mixture. The reaction was left stirring overnight and then extractions with DCM and 30% citric acid, $NaCl_{(sat)}$ and $NaHCO_{3(sat)}$ were performed. The resulting organic phase was dried with $MgSO_4$, filtered, concentrated under reduced pressure, and finally evaporated under vacuum.

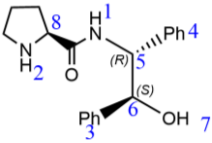


Yellowish oil, 148 mg, 77% yield.

^{1}H NMR ($CDCl_3$, 400 MHz), δ 7.91 (s, 1H, NH_1), 7.3-7.2 (m, 6H, *mp*-$Ph_{2,3}$), 7.1-6.9 (m, 4H, *o*-$Ph_{3,4}$), 5.24 (dd, 1H, CH_4O), 5.10 (t,

1H, CHN), 4.5-0.8 (m, 17H, OH, CH-CH_2-CH_2-CH_2, Boc) ppm

6.2.2.2 *(S)-N*-((1R,2S)-2-hydroxy-1,2-diphenylethyl)pyrrolidine-2-carboxamide.[24] (3)



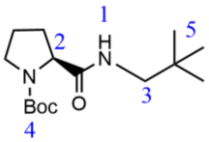
Brownish oil, 29 mg, 21% yield.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.45 (brd, 1H, NH_1), 7.3-7.2 (m, 6H, *mp*-$Ph_{3,4}$), 7.1-7.0 (m, 4H, *o*-$Ph_{3,4}$), 5.25 (m, 1H, CH_6OH), 5.05 (m, 1H, CH_5N), 3.8 (m, 1H, CH_8N), 3.4-3.2 (m, 2H, OH, NH), 3.0-2.8 (m, 2H, CH_2N), 2.2-1.6 (m, 4H, CH_2-CH_2) ppm.

6.2.3 Synthesis of *(S)-N*-neopentylpyrrolidine-2-carboxamide (4)

6.2.3.1 Synthesis of *tert*-butyl (*S*)-2-(neopentylcarbamoyl)pyrrolidine-1-carboxylate (11)[23].

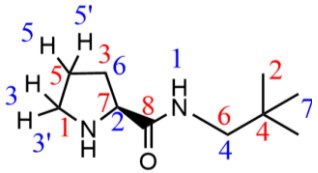
In a carefully dried 250 mL round-bottomed flask equipped with a stirring magnet, 1.0 g (4.64 mmol) of were mixed with 4.5 mL of Et_3N (4 mmol) and 15 mL of dry THF. The solution was cooled down to 0 ºC using an ice bath. Then, 0.37 mL of ECF (4.0 mmol) were added dropwise to the mixture, which was stirred for 30 min. After that, 1.15 ml of neopentylamine (10 mmol) were added dropwise to the mixture. The reaction was left stirring at 0 ºC for 1 h and then at room temperature overnight. The product was washed with AcOEt in a filter plate, concentrated under reduced pressure, and evaporated under vacuum.



Yellowish oil, 0.807 g, 61% yield.

^{1}H NMR ($CDCl_3$, 400 MHz), Selected peaks: δ 7.5 (s, 1H, NH_1), 4.30 (s,1H, CH_2N), 2.52 (s, $1H_3$), 1.48 (s, $9H_4$), 0.83 (s, $9H_5$) ppm.

6.2.3.2 Synthesis of *(S)-N*-neopentylpyrrolidine-2-carboxamide (4)[24].



Partially solidified oil, 326 mg, 82% yield.

^{1}H NMR (APPENDIX 2) ($CDCl_3$, 400 MHz): δ 7.73 (s, 1H, NH_1), 3.81 (dd, 1H, CH_2N), 3.1-3.0 (m, 2H, $CH_{3,3'}N$), 2.97 (d, 2H, NCH_4), 2.2-2.0 (m, 2H, $CH_{5,5'}$; 1H, NH), 1.95 (m, 1$H_{5'}$), 1.74 (m, 2H, CH_6), 0.90 (s, 9H,$(CH_3)_3$) ppm.

^{13}C NMR (APPENDIX 3) ($CDCl_3$, 100.6 MHz): δ 138.28 (s, 1C_1), 60.59 (s, 1C_2), 50.10 (s, 1C_3), 47.22 (s, 1C_4), 31.91 (s, 1C_5), 30.89 (s, 1C_6), 27.18 (s, 3C_7), 26.14 (s, 1C_8)

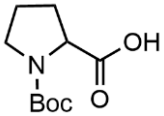
[α]$_D$: -0.55 (c 0.98,$CHCl_3$).

HRMS (+ESI) m/z calc. for $C_{10}H_{21}N_2O$ $[M+H]^+$ 185.1648, found 185.1649.

6.2.4 Synthesis of (±)-(*tert*-butoxycarbonyl)proline (14)[21].

(The procedures involved in *rac*-**11** and rac-**4** are mentioned previously)

In a 100 ml round-bottomed dried flask equipped with a stirring magnet, 2.0 g of (±)-proline were diluted in 25 ml of $NaHCO_{3(sat)}$ and the solution was cooled down to 0 ºC using an ice bath. Then, a solution 10 ml of THF with 4,17 g of Boc_2O were added dropwise to the flask and were left stirring overnight. The mixture was concentrated under reduced pressure and cooled down to 0 ºC before adding 30 ml of HCl 3M (until pH=2). The product was extracted with AcOEt, dried with $MgSO_4$, filtered, and evaporated under vacuum to obtain a white solid.



Crystalline white solid, 3.18 g, 85% yield.

^{1}H NMR ($CDCl_3$, 400 MHz) 5.0-0.8 (m, 17H, OH, CH-CH_2-CH_2-CH_2, Boc) ppm

6.3. α-ALKYLATION OF THE ALDEHYDES[19]

6.3.1. General procedure

The photocatalyst (1 mol%) and $LiBF_4$ (0.2 eq) are placed in a 3 mL dried vial equipped with a stirring magnet. Then, the aminocatalyst (0.10 mmol, 0.4 eq), the aldehyde (0.25 mmol) and degassed DMSO (1.9 mL) are added to the mixture. The vial is closed with a septum and put under reduced pressure. Meanwhile, a solution with the EDA (0.25 mmol) and 1 mL of DMSO is prepared. Once the bubbling in the vial has decreased considerably, the latter solution is added, and the mixture is placed in the photoreactor (Figure 11; white light LEDs for TPP and blue light LEDs for the Ru complex) with a fan to avoid overheating for 7 h. Once the reaction was completed, the vial was extracted from the photoreactor and diluted with AcOEt. The organic phase was washed and extracted with distilled H_2O, dried with $MgSO_4$, filtered, concentrated under reduced pressure, and evaporated under vacuum to obtain a yellowish oil.

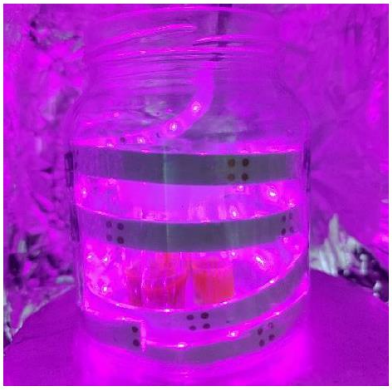
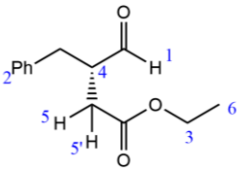


Figure 11. Experimental setting for the photocatalytic reactions

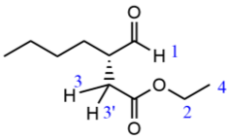
6.3.2. Synthesis of ethyl (*S*)-3-benzyl-4-oxobutanoate (12)



Yellowish oil, 79 mg, 100% yield

^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.80 (d, 1H$_1$, CHO), 7.30 (m, 5H$_2$, Ph), 4.10 (q, 2H$_3$, OCH_2), 3.08 (m, 1H$_4$, CH), 2.13-1.85 (m, 2H$_{5,5'}$, CH_2CO_2), 1.5-1.3 (m, 2H, CH_2Ph) 1.23 (t, 3H$_6$, CH_3) ppm. **ee (%): 99.9 *(S)***

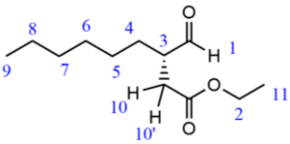
6.3.3. Synthesis of ethyl (*S*)-3-formylheptanoate (17)



Yellowish oil, 53 mg, 95% conversion.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.72 (d, 1H$_1$, CHO), 4.13 (q, 2H$_3$, OCH_2), 3.2 (m, 1H, CH), 2.63-2.43 (m, 2H$_{3,3'}$, CH_2CO_2), 1.26 (t, 3H$_4$, CH_3), 1.2-0.8 (m, 9H, $(CH_2)_3$-CH_3)ppm. **ee (%): 22 *(S)***

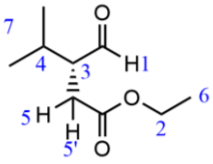
6.3.4. Synthesis of ethyl (*S*)-3-formylnonanoate (18)



Yellowish oil, 33 mg, 90% conversion.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.72 (d, 1H$_1$, CHO), 4.13 (q, 2H$_2$, OCH_2), 3.1 (m, 1H, CH), 2.7-2.5 (m, 2H$_{10,10'}$, CH_2CO_2), 1.26 (t, 3H$_{11}$, CH_3), 1.2-0.8 (m, 13H, $(CH_2)_5$-CH_3). **ee (%): 84 (*S*)**

6.3.5. Synthesis of ethyl (S)-3-formyl-4-methylpentanoate (19)



Yellowish oil, 31 mg, full conversion

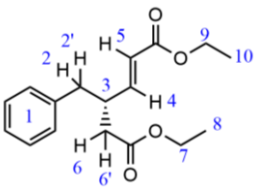
^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.72 (d, 1H$_1$, CHO), 4.13 (q, 2H$_2$, OCH_2), 3.2 (m, 1H$_3$, CH), 2.63-2.43 (m, 2H$_{5,5'}$, CH_2CO_2), 1.26 (t, 3H$_6$, CH_3), 1.2-0.8 (m, 6H, $(CH_3)_2$) ppm. **ee (%): 66 (*S*)**

6.4. Preparation of the Wittig 6erivatives

6.4.1. General procedure

In a previously dried 50 mL round-bottomed flask equipped with a stirring magnet, the aldehyde from the photoredox (0.25 mmol scale) is diluted with 3 mL of DCM. Then, an excess of the Wittig reactant (1.0 mmol) is added, and the mixture is heated to reflux and stirred for 2 h. After that, the mixture is washed with 1 M aqueous HCl and extracted with DCM, then washed with $NaHCO_3$ and extracted again with DCM. The organic phase is dried with $MgSO_4$, filtered, concentrated under reduced pressure, and evaporated under vacuum to obtain a brownish oil. The crude product is purified by flash chromatography using silica gel (Hexane/AcOEt 5:1)

6.4.2. Synthesis of diethyl (*S,E*)-4-benzylhex-2-enedioate (13)

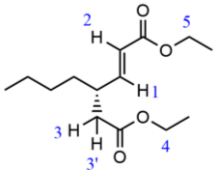


Brownish oil, quantitative yield.

^{1}H NMR (APPENDIX 4) ($CDCl_3$, 400 MHz): δ 7.30 – 7.14 (m, $5H_1$), 6.91– 6.83 (dd, $1H_4$), 5.74 (d, $1H_5$), 4.17 (q, $2H_7$), 4.08 (q, $2H_9$), 3.05 (m, $1H_3$), 2.99 (dd, $1H_2$), 2.43 (dd, $1H_{2'}$), 2.34 (dd, $1H_6$), 2.37 – 2.28 (m, $1H_{6'}$), 1.30 – 1.21 (m, $6H_{8,10}$).

HPLC (Phenomenex i-cellulose 5 column; (hexane/IPA) (99:1); flow rate 1 mL/min; 220 nm) t_R = 18.0 min (*R*), 21.0 min (*S*). **$[\alpha]_D$:** -0.17 (c 0.3, $CHCl_3$).

6.4.3. Synthesis of diethyl (*S,E*)-4-butylhex-2-enedioate (21)

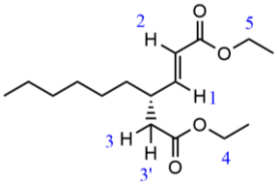


Brownish oil, quantitative yield

^{1}H NMR (CDCl3, 400 MHz): δ 6.85 (dd, $1H_1$), 5.85 (d, $1H_2$), 4.08 (q, $2H_4$), 4.06 (q, $2H_5$), 3.2 (m, 1H, CH), 2.40 (dd, $1H_3$;dd, $1H_{3'}$), 1.5-0.8 (m, 9H, $(CH_2)_3$-CH_3) ppm.

HPLC (Phenomenex i-cellulose 5 column; (hexane/IPA) (99:1); flow rate 1 mL/min; 218 nm) t_R = 20.0 min (*R*), 22.0 min (*S*).

6.4.4. Synthesis of diethyl (*S,E*)-4-hexylhex-2-enedioate (22)

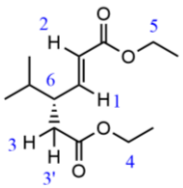


Brownish oil, quantitative yield

^{1}H NMR (CDCl3, 400 MHz): δ 6.83 (dd, $1H_1$), 5.79 (d, $1H_2$), 4.08 (q, $2H_4$), 4.06 (q, $2H_5$), 3.0 (m, 1H, CH), 2.59 (m, $1H_6$), 2.40 (dd, $1H_3$;dd, $1H_{3'}$), 1.3-0.8 (m, 13H, $(CH_2)_5$-CH_3), 1.3-1.2 (m, 6H, $(CH_3)_2$) ppm.

HPLC (Phenomenex i-cellulose 3 column; (hexane/IPA) (99:1); flow rate 1 mL/min; 218 nm) t_R = 21.9 min (*R*), 23.3 min (*S*).

6.4.5. Synthesis of diethyl (*S,E*)-4-isopropylhex-2-enedioate (23)



Brownish oil, quantitative yield

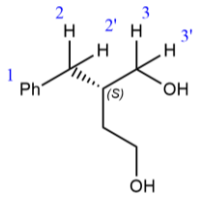
^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.80 (s, $1H_1$), 7.30 (m, $5H_2$), 4.10 (q, $2H_3$), 3.08 (m, $1H_4$), 2.13-1.85 (dd, H_5;dd, $H_{5'}$), 1.23 (dd, $1H_6$), 1.2-0.8 (m, 12H, $(CH_3)_4$) ppm.

HPLC (Phenomenex i-cellulose 3 column; (hexane/IPA) (99:1); flow rate 1 mL/min; 218 nm) t_R)= 21.0 min (*S*), 22.0 min (*R*)

6.5. PREPARATION OF THE DIOL 20

6.5.1. Synthesis of (S)-2-benzylbutane-1,4-diol (20).

In a 50 mL round-bottomed dried flask equipped with a stirring magnet, the enantiopure aldehyde **12** (0.34 mmol) was diluted with 3 mL of anhydrous THF. The $LiAlH_4$ (1.36 mmol) was added, and the mixture was put under Argon atmosphere and stirred at rt for 1 day. After that, 75 µL of H_2O, NaOH 15% (w/w) and H_2O were consecutively added before the 3 mL of Et_2O. The organic phase was extracted several times with AcOEt, was dried with $MgSO_4$, filtered, and evaporated under vacuum to obtain a yellowish oil. The crude product was purified by flash chromatography using silica gel (Hexane/AcOEt.)



Yellowish oil, 37 mg, 60% yield.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.20 (m, $5H_1$), 3.78 (dd, $1H_2$), 3.54 (dd $1H_{2'}$), 3.0-2.8 (brs, 2H, OH) 2.56 (dd, $1H_3$), 2.44 (dd $1H_{3'}$) 2.0-1.8 (m, 4H, CH_2-CH_2) ppm.[25] **$[\alpha]_D$**: -9.4 (c 0.09, $CHCl_3$). [Lit. (for (*R*)-**14**): $[\alpha]_D^{24}$ +6.6 (c 1.5, EtOAc)][25]

7. CONCLUSIONS

The conclusions that can be drawn from this project are:

- The synthesis of both organocatalysts **3** and **4** has been successfully accomplished.
- Although **3** afforded the alkylation product **12** with good conversion, the enantiomeric excess of this product could not be evaluated due to the failure of the derivatization reaction.
- The characterization of organocatalyst **4** has been properly done using ^{1}H-NMR, ^{13}C-NMR, HRMS and polarimetry.
- The water-soluble sulfonated porphyrin TPP-S_4-H_2 **2** is confirmed to be an adequate photocatalytic substitute for the Ruthenium metallic complex in the visible-light mediated α-alkylation of aldehydes with ethyl diazoacetate **1**.
- The asymmetric photocatalytic activity of the dual system (**2** or $Ru(bpy)_3Cl_2$ and the proline derivatives **3** and **4**) has been tested. The α-alkylated products were detected through ^{1}H-NMR spectroscopy of the crude reaction mixture and were formed with remarkably high conversions (90-100%).
- Most importantly, the simple *N*-neopentyl L-prolinamide **4** affords very high enantioselectivities (up to 99.9% ee) in the reaction.
- The absolute configuration of the product **12**, arising from the alkylation of 3-phenylpropanal **5**, has been established by chemical correlation with the *(–)-(S)*-diol **20.**
- The mechanism initially proposed by Gryko for the racemic process, modified by us by assuming the intermediate formation of a chiral enamine, matches with the absolute configuration found with the diol derivative. The steric hindrances in the enamine and the non-covalent hydrogen bonds are thought to be crucial in the stereoselectivity of the final product.

8. REFERENCES AND NOTES

1. Vantomme, G; Crassous, J. Pasteur and chirality: A story of how serendipity favors the prepared minds. *Chirality,* **2021**, *33*, 597-601.
2. Kagan, H. B.; Gopalaiah, K. Early history of asymmetric synthesis: who are the scientists who set up the basic principles and the first experiments? *New J. Chem.,* **2011**, *35*, 1933-1937.
3. Mannschreck, A.; Kiesswetter, R.; von Angerer, E. Unequal Activities of Enantiomers via Biological Receptors: Examples of Chiral Drug, Pesticide, and Fragrance Molecules. *J. Chem. Ed., **2007**, 84,* 2012-2017.
4. Morrison, J. D.; Mosher, H. S. *Asymmetric Organic Reactions*, Prentice Hall: Englewood Cliffs, New Jersey, 1971. ISBN 13-049551-4.
5. Rosenthaler, L. Durch enzyme bewirkte asymmetrische synthesen. *Biochem. Z.,* **1908**, *14*, 238-253.
6. Bredig, G.; Fiske, P. S. Asymmetric synthesis caused by catalyst. *Biochem. Z*, **1913**, *46*, 7-23.
7. Noyori, R. Asymmetric Catalysis: Science and Opportunities (Nobel Lecture). *Angew. Chem. Int. Ed. Engl. ,* **2002**, *41*, 2008-2022.
8. Knowles, W. S. Asymmetric Hydrogenations (Nobel Lecture). *Angew. Chem. Int. Ed. Engl*., **2002**, 41, 1998-2007.
9. Katsuki, T.; Sharpless, K. B. The first practical method for asymmetric epoxidation. *J. Am. Chem. Soc*., **1980**, *102*, 5974-5976.
10. (a) Pracejus, H. *Justus.* Asymmetrische Synthesen mit Ketenen. *Liebig's Ann. Chem.,* **1960**, *634*, 9-22. (b) Hajos, Z. G.; Parrish, D.R. Asymmetric Synthesis of Bicyclic Intermediates of Natural Product. *J. Org. Chem.*, **1974**, *39*, 1615-1621.
11. (a) Ahrendt, K. A.; Borths, C.; MacMillan, D.W.C. New Strategies for Organic Catalysis: The First Highly Enantioselective Organocatalytic Diels-Alder Reaction *J. Am. Chem. Soc*., **2000**, *122*, 4243-4244 (b) Jen, W. S.; Wiener, J.J.M.; MacMillan, D.W.C. New Strategies for Organic Catalysis: The First Enantioselective Organocatalytic 1,3-Dipolar Cycloaddition. *J. Am. Chem. Soc*. **2000**, *122*, *40*, 9874–9875
12. List, B.; Lerner, R. A.; Barbas III, C. F. Proline-Catalyzed Direct Asymmetric Aldol Reactions. *J. Am. Chem. Soc.,* **2000**, *122*, 2395-2396.
13. Rigotti ,T.; Alemán, J. Visible Light Photocatalysis–from Racemic to Asymmetric Activation Strategies. *Chem. Commun.*, **2020**, *56*, 11169-11190.
14. Kalyanasundaram, K. Photophysics, photochemistry and solar energy conversion. *Coord. Chem. Rev.,* **1982**, *46*, 159-244.
15. Skubi, K. L.; Blum, T. R.; Yoon, T. P. Dual Catalysis Strategies in Photochemical Synthesis. *Chem. Rev*. **2016**, *116*, 10035–10074.
16. Nicewicz, D. A.; MacMillan, D. W. C. Merging Photoredox Catalysis with Organocatalysis: The Direct Asymmetric Alkylation of Aldehydes. *Science*, **2008**, *322*, 77–80.

17. Rybicka-Jasińska, K.; Ciszewski, Ł. W.; Gryko, D. Photocatalytic Reaction of Diazo Compounds with Aldehydes. *Adv. Synth. Catal.,* **2016**, *358*, 1671–1678.
18. Rybicka-Jasińska, K.; Shan, W.; Zawada, K.; Kadish, K. M.; Gryko, D. Porphyrins as Photoredox Catalysts: Experimental and Theoretical Studies. *J. Am. Chem. Soc.,* **2016**, *138*, 15451−15458.
19. Clennan, E. L.; Pace, A. Advances in singlet oxygen chemistry. *Tetrahedron,* **2005**, *61*, 6665-6691.
20. Torres, P. personal communication (unpublished results from ongoing Ph.D. Thesis, University of Barcelona)
21. Elina M. *et al.*, 2(*S*)-(Cycloalk-1-enecarbonyl)-1-(4-phenyl-butanoyl)pyrrolidines and 2(*S*)-(aroyl)-1-(4-phenylbutanoyl)pyrrolidines as prolyl oligopeptidase inhibitors. *Bioorg. Med. Chem.* **2007,** *15*, 2024-2031.
22. Tang Z.; Jiang, F.; Yu, L.-T.; Cui, X.; Gong, L.-Z.; Mi, A.-Q.; Jiang, Y.-Z.; Wu, Y.-D. Novel Small Organic Molecules for a Highly Enantioselective Direct Aldol Reaction. *J. Am. Chem. Soc.* **2003,** *125*, 5262-5263.
23. Mimoto T. *et al*., Structure–Activity Relationship of Orally Potent Tripepide-Based HIV Protease Inhibitors Containing Hydroxymethylcarbonyl Isostere. *Chem. Pharm. Bull*. **2000**, *48*, 1310-1326.
24. Huy, P.; Neudörfl, J.-M.; Schmalz, H.-G. A practical synthesis of *trans*-3-substituted proline derivatives through 1,4-addition. *Org. Lett.,* **2011,** *13*, 216-219.
25. Carella, A.; Ramos Ferronatto, G.; Marotta, E.; Mazzanti, A.; Righi, P.; Paolucci, C. Betti's base for crystallization-induced deracemization of substituted aldehydes: synthesis of enantiopure amorolfine and fenpropimorph. *Org. Biomol. Chem.,* **2017**, *15*, 2968–2978.

9. ACRONYMS

AcOEt: Ethyl Acetate

DCM: Dichloromethane

DMSO: Dimethyl sulfoxide

ECF: Ethyl chloroformate

EDA: Ethyl diazoacetate

ee: Enantiomeric excess

HPLC: High-Performance Liquid Chromatography

IPA: isopropyl alcohol

LED: Light-emitting diode

NMR: Nuclear Magnetic Resonance

SET: Single Electron Transfer

TA: Tartaric Acid

TFA: Trifluoroacetic acid

THF: Tetrahydrofuran

TLC: Thin-Layer Chromatography

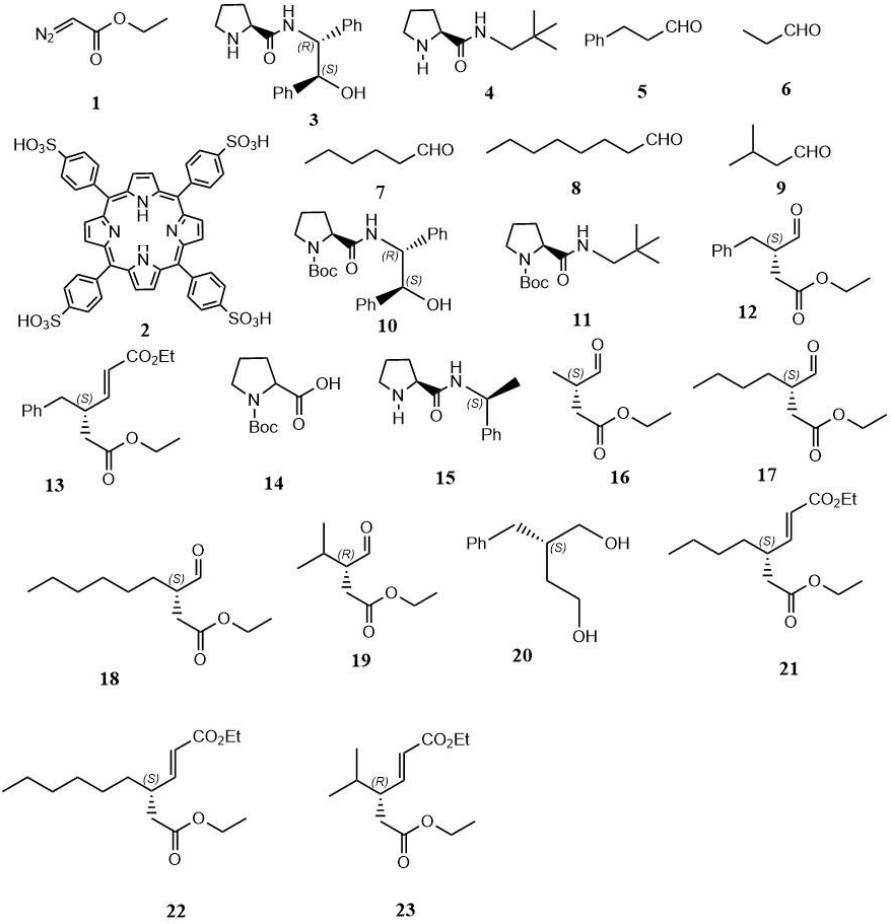
TMB: Trimethoxy benzene

TPP-S_4-H_2: *meso*-tetrakis(4-sulfonatophenyl) porphyrin dihydrate

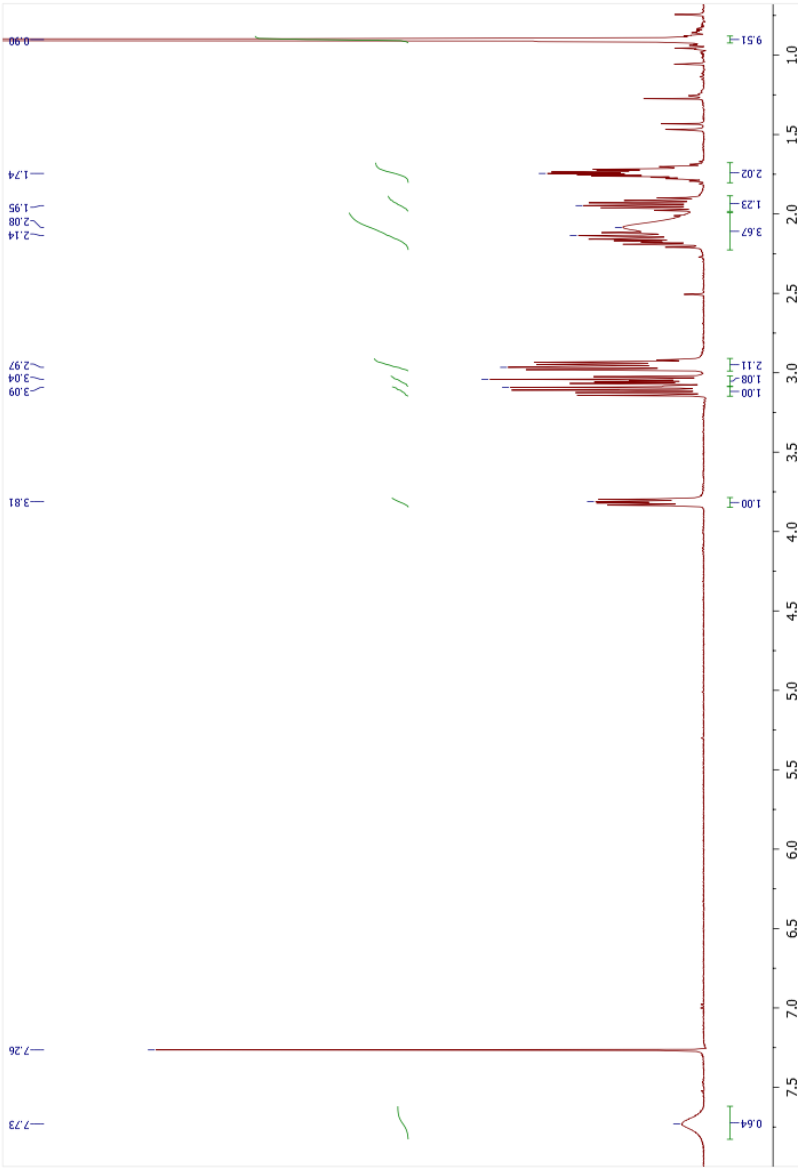
UV-Vis: Ultraviolet–Visible Spectroscopy

APPENDICES

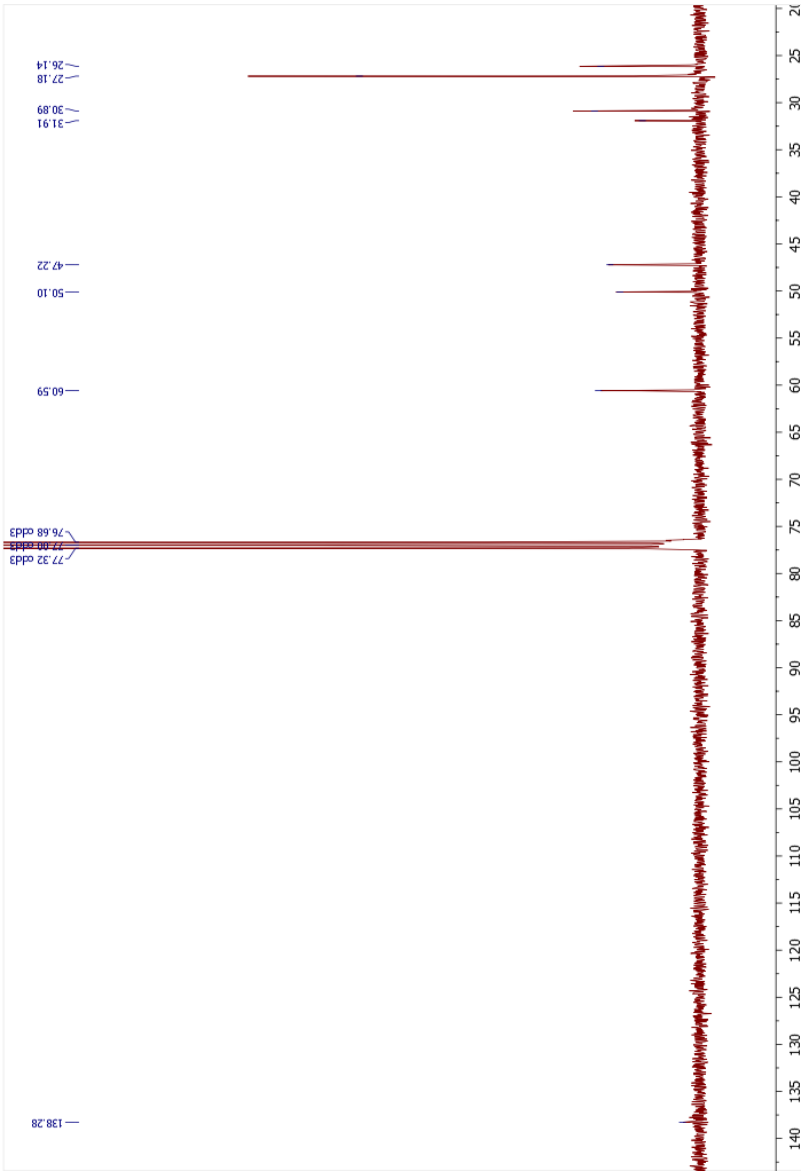
APPENDIX 1: LIST OF COMPOUNDS



APPENDIX 2: ^{1}H-NMR OF COMPOUND 4



APPENDIX 3: ^{13}C-NMR OF COMPOUND 4



APPENDIX 4: ^{1}H-NMR OF COMPOUND 13