Alma Mater Studiorum - Università di Bologna

SCUOLA DI SCIENZE

Dipartimento di Chimica Industriale "Toso Montanari"

Corso di Laurea Magistrale in

Chimica Industriale

Classe LM-71 - Scienze e Tecnologie della Chimica Industriale

Synthesis of a chiral, water soluble porphyrin containing a pyrrolidine unit and initial study of its catalytic activity

Tesi di laurea sperimentale

CANDIDATO

Federico Curati

RELATORE

Prof. Luca Bernardi

CORRELATORE

Prof. Albert Moyano Baldoire

Aitor Arlegui Chamizo

Anno Accademico 2017-2018

Abstract

Asymmetric organocatalysis have taken hold in the last decades due to affordability and lack of toxicity of their catalysts. Unfortunately, organocatalytic enantioselective reactions in an environmentally friendly and safe solvent as water are still scarce.

During the training internship our aim has been to find an effective water soluble organocatalyst able to drive in an enantioselective fashion a reaction, to maximize the diasteromeric and the enantiomeric excess. Pursuing this objective we synthesized a *meso* 3-sulfonatophenyl porphyrin with a chiral aminoaldehyde substituent, with the sulfonate-groups allowing its solubilization in water and the chiral group which should improve the enantioselectivity.

The chiral aldehyde has been prepared starting from *L*-proline, a widely used organocatalyst, and finally tried in an aldol reaction, giving excellent yield, moderate diastereoselectivity and very low enantiomeric excess.

The reaction products can be easily removed washing in organic solvent and the catalyst can be recovered by aggregation in acidic medium.

Contents

Introduction

Asymmetric organocatalysis

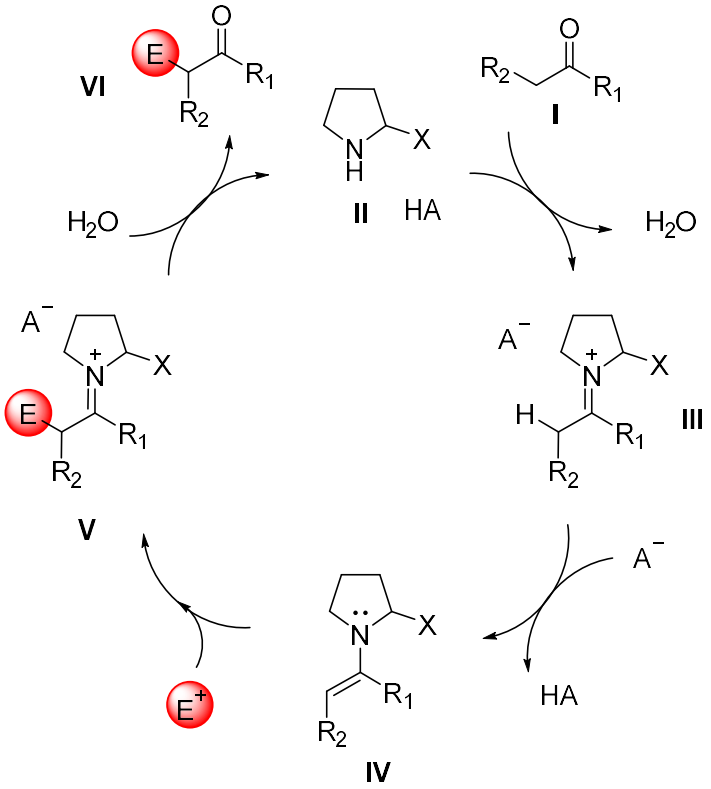
Asymmetric organocatalysis has been a highly pursued field of research since the beginning of the century and it allows to perform asymmetric organic synthesis using metal-free low molecular-weight molecules as catalysts. This approach, almost ignored for decades, makes it possible to overcome some typical drawbacks of organometallic catalysis as the high cost and effort for the preparation of the catalysts, the use of noxious metals, the lack of orthogonality with a wide range of functional groups, and in some cases the need to operate under rigorously anhydrous or anaerobic conditions (1).

These important features allowed an exponential growth of this approach as a powerful alternative tool for organic synthesis in the last years and led to a discovery of several activation modes of a wide range of different catalysts (2)

For our purposes we highlight only one of these activation modes, the enamine-activation.

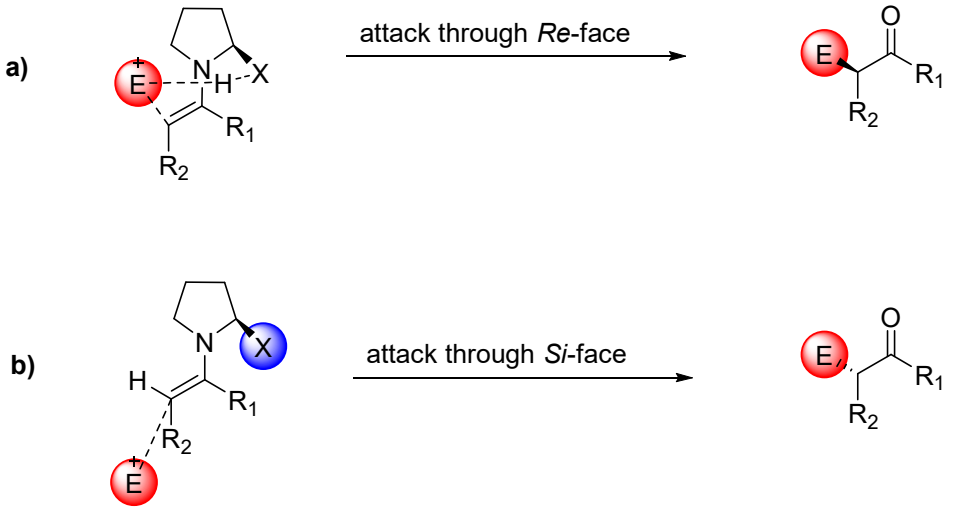
This mechanism permits the enantioselective α-functionalization of enolizable aldehydes and ketones with several electrophiles (3). It consists in the formation of an iminium ion from a carbonyl compound and an amine, followed by tautomerization to the enamine. The latter is a nucleophilic species and can react with an electrophile forming again an iminium ion, which upon hydrolysis gives back the catalyst and an α-functionalised carbonyl (**Scheme 1**).

Scheme 1 General Mechanism for the α-functionalization of carbonyl compounds through enammine catalysis



The catalytic cycle starts with a condensation between the carbonyl compound **I** and the aminocatalyst **II**, promoted by an acid, to form the iminium ion **III**. This ion enhances the acidity of α-proton and the conjugated base of the acid cocatalyst (A^-) can abstract it to produce nucleophilic enamine **IV**. Then, this enamine attacks the electrophile (E^+) to generate a second iminium ion (**V**), which after a hydrolysis step releases the final product **VII** and regenerates the aminocatalyst **II**.

Scheme 2 Stereochemistry models for α-functionalisation of carbonyl compounds through enamine catalysis. a) Houk-List model; b) steric model.

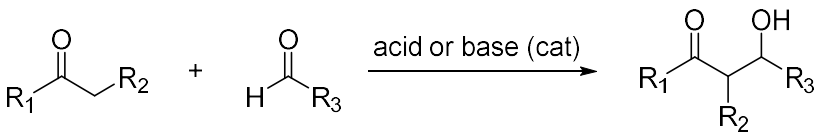


As you can see in the image above (**Scheme 2**) is the nature of the catalyst which can predict the stereochemistry of the new-formed stereocentre (4) (3). The presence in the catalyst of a director group in C2 able to perform hydrogen bond (i.e. protonated amine, amide or carboxylic acid) can drive the enamine attack from the *Re*-face. In the other way, the lack of acidic protons in C2 causes a predominance of steric factors. The enamine attack takes place from the *Si*-face because the other one is blocked by the bulky substituent.

Aldol reactions

The aldol reaction is one of the most effective way to create a new C-C bond in organic chemistry. Starting from a carbonyl acceptor and an enolate donor (formed by an aldehyde or a ketone) the mechanism involves the addition of the second-one to the first leading to the final product (**Fig.1**).

Fig.1 General aldol reaction



The ability to control the absolute configuration of the newly formed stereogenic centers has been investigated thoroughly in the last years and has been improved through the use of chiral starting materials, chiral auxiliaries or asymmetric (organo)catalysts. Both chiral starting materials and chiral auxiliaries show some drawbacks including additional steps to introduce and

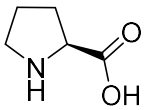
remove the pre-existing chiral portion [5]. On the contrary the presence of an asymmetric catalyst can drive the reaction in an enantioselective fashion without further intervention.

Proline, a catalyst that can be improved

At the beginning of 2000, List, Lerner and Barbas III developed an enantioselective intermolecular aldol reaction using proline as organocatalyst, beginning a very profitable field of research and making known to the world this useful little molecule in driving the enantioselectivity.

L-proline (**Fig.2**) is the only one of the 21 proteinogenic amino acids with a secondary amine in its structure, giving a great advantage over the rest of amino acids in the formation of enamine. The List and co-workers' previous knowledge about the direct aldolization with an enamine-based mechanism catalysed by class I aldolases enzymes [6], is probably why they decided to try this catalyst in an aldol reaction [7].

Fig.2 *L*-Proline's structure



The use of this organocatalyst showed important positive features as nontoxicity, inexpensiveness and ready availability in the two enantiomeric forms. The reactions performed also do not require inert conditions and run a room temperature. Unfortunately, several limitations were observed with *L*-proline like its low solubility in organic solvents and formation of inactive sub-products between proline and aldehydes. Many of these problems occur due to the possible decarboxylation of the carboxylic group [8], so changing this group for another one could prevent these side reactions. At the same time, these derivatives could introduce new groups to modify the catalytic nature of proline.

Aldol reactions in water

Water is an environmentally friendly and safe solvent (Green Chemistry), which removes the typical problem of pollution inherent to organic solvents, and it is obviously inexpensive. Furthermore, in aldol reactions it has been observed that a little amount of water can improve the stereoselectivity. At the same time, however, water as reaction solvent could inhibit catalyst

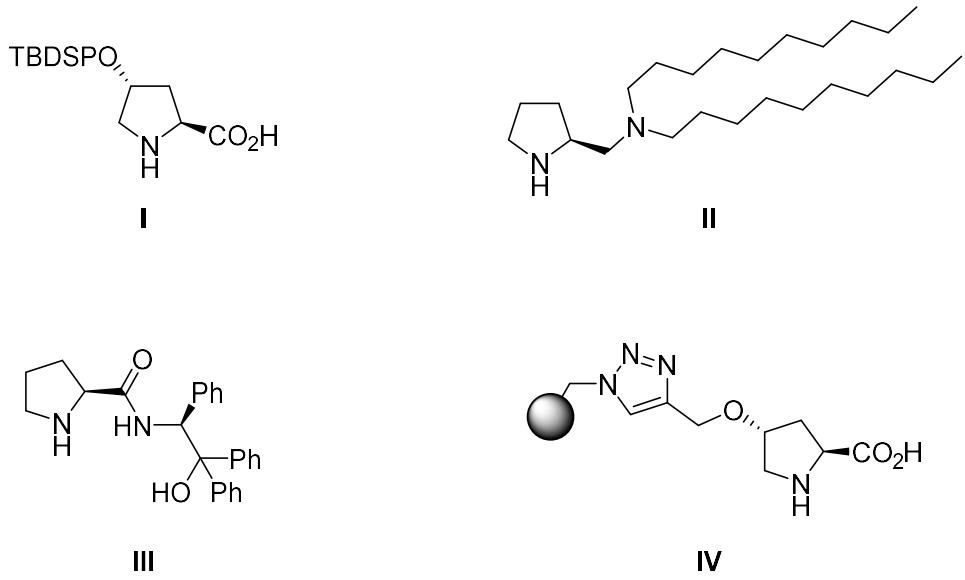
activity and lower the enantioselectivity, introducing competitive ionic interactions which can penalise the transition state (9).

A catalyst very soluble in water and effective in aldolic systems is proline, but when it has been tried it has shown low enantioselectivities and its improvement to achieve good yields and stereoselectivities has been a highly sought-after goal for years.

For these reasons several proline derivates have been developed to increase their effectiveness in aldol reactions (**Fig.3**).

In 2006 Hayashi and co-workers (10) achieved a highly effective asymmetric aldol reaction in water using a TBDPS-protected-4-hydroxyproline (**I**). They found out that only a very little amount of catalyst (<1%) was enough to get a great enantiomeric excess (>99%) employing electron-deficient and neutral aldehydes. Nevertheless, the enantioselectivity decreased remarkably when acetone or hydroxyacetone were used as substrates.

Fig.3 Alternative derivatives of *L*-proline



Barbas et al. (6) tried to catalyse direct aldol reactions in water using a diamine derived from proline (**II**) and TFA as co-catalyst. They showed this reaction with cyclic ketones worked well (>99% ee) but not with acyclic ketones, giving low results as in Hayashi's work.

Finally, Singh and co-workers (11) found out a prolinamide with two geminals phenyl groups (**III**) which can catalyse an aldol reaction between aldehydes and acetone with good yields and enantiomeric excess.

Taking a cue from enzymatic behaviour, some polymers have been applied as scaffolds to support proline in aldol reaction in water. Thanks to their long aliphatic chain they develop

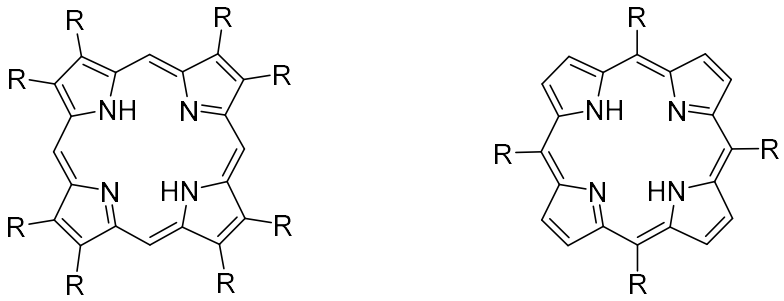
hydrophobic conditions to improve the enantioselectivity. Pericas et al. (12) tried a 3-hydroxyproline (**IV**) supported on polystyrene (PS), getting good yields and enantioselectivities.

Porphyrins

Porphyrins are one of the most studied macrocyclic rings, composed by a tetrapyrrolic circular structure, and their interest arises from the very important roles played in biological organisms and from their reactivity. Thanks to these features, it is possible to synthesize porphyrins with several substituent groups for a wide variety of applications (13).

The macrocyclic ring can react in two different position (**Fig.4**): β-pyrrolic position (the pyrroles are functionalized before the porphyrin synthesis) and *meso*-position (where substituents are attached during the porphyrin synthesis) (14).

Fig.4 Structure of porphyrin



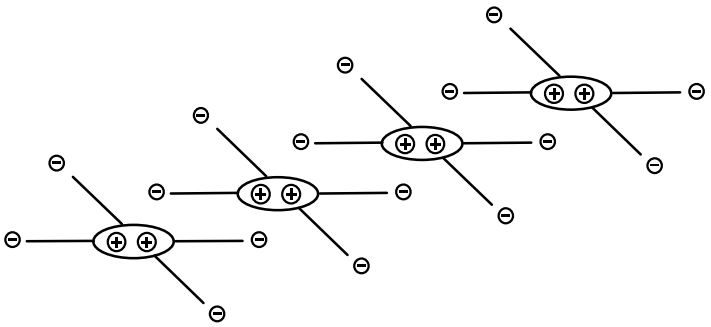
Self-assembly of Porphyrins

Although phenyl groups substituted porphyrins are soluble only in organic solvent, a simple sulfonation in *para*-position with sulfuric acid gives them water solubility. The reaction occurs *via* electrophilic aromatic substitution (S_EAr), with the sulfonate-group which replaces one hydrogen atom in the phenyl ring.

A little acidification of the water solution can create intramolecular association between the positively charged porphyrin ring and the negatively charged sulfonate-groups, leading to homoassociation of the molecules. Other features which can influence the aggregates formation are the large size of the area of the ring, its planarity, concentration, ionic strength, electronic and stereochemical effects and counter ions of inorganic metal-salts (15).

These aggregations may be of two types: J-aggregates (edge-to-edge interactions of the chromophores) and H-aggregates (face-to-face interactions of the chromophores). As shown in the figure below, thanks to its zwitterionic form two sulfonate groups from a neighbour porphyrin interact with the positive charges of the internal macrocycle of another one creating a long mono-dimensional J-aggregate (16) (17) (**Fig.5**).

Fig.5 J-Aggregates



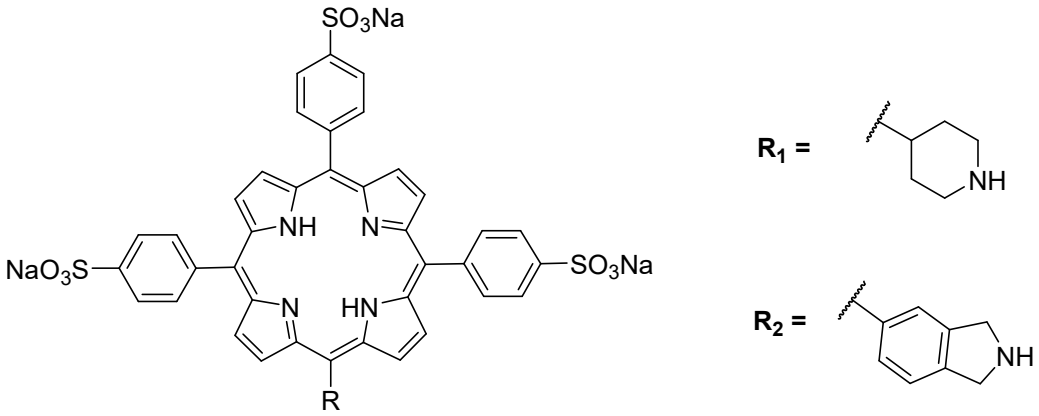
Regarding *meso*-substituted porphyrins with *p*-sulfonate-groups there is a pH range where the ring is completely protonated and the sulfonate-groups are completely deprotonated. Working in these pH values allows the aggregates formation (18).

The aggregation of some porphyrins gives a supramolecular chirality, called SMSB process (spontaneous mirror symmetry breaking process), which can be observed by circular dichroism. In one case (trisulfonated *meso*-tetraphenylporphyrin) this chirality can be controlled simply by the direction of macroscopic vortical stirring, slowly concentrating an acidic porphyrin solution (19) (20).

Aim of the thesis

In 2014 Moyano's research group decided to try to exploit the specific characteristics of porphyrins in organocatalysis. They decided to use a trisulfonated *meso*-tetraphenylporphyrin monosubstituted with a cyclic secondary amine, to perform aldol reaction in water *via* enamine mechanism.

Fig.6 Structure of the two monosubstitued porphyrins



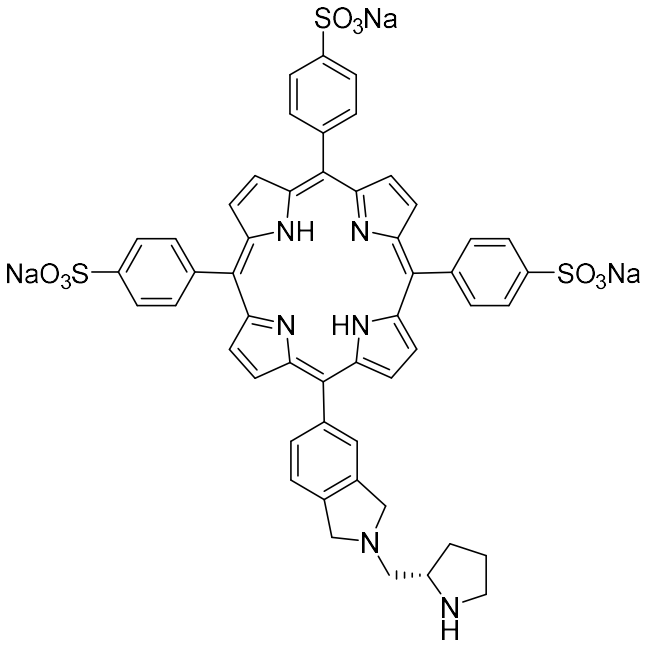
Two porphyrins were synthesized (**Fig.6**) and tried in reaction between cyclohexanone and *p*-nitrobenzaldehyde in neutral water, giving good yields and diastereoselectivities but their products were totally racemic, as porphyrins were in their achiral monomer form at this pH.
They tried to perform the reactions in aqueous solution at pH 3.6, hoping the chiral supramolecular J-aggregates could improve the enantioselectivities of the asymmetric reactions, but no reaction occurred. Based upon these negative results, the group wondered if it was possible to induce stereoselectivities in these reactions by inserting a chiral amine unit in the porphyrin hybrid catalysts.
This work aimed at synthesizing a chiral porphyrin **1** (**Fig.7**) as a water-soluble catalyst that could drive in an enantioselective fashion a reaction, and at maximizing the diastereomeric and the enantiomeric excess of the product.

To this purpose, the objectives pursued during this project were multiple. The first aim was the synthesis and the characterization of the trisodium salt of the chiral meso-substitued porphyrin **1**.
The second one was the subsequent test of the catalyst in some asymmetric reactions, to verify if it is able to drive the reaction with a reasonable enantiomeric and diastereomeric excess.

In order to achieve these objectives we came across other implicit sub-goals like:

- To design a synthetic route to prepare the aldehydes needed in the synthesis of the porphyrin;
- To improve the reaction conditions all through the synthesis.

Fig.7 Chiral porphyrin 1



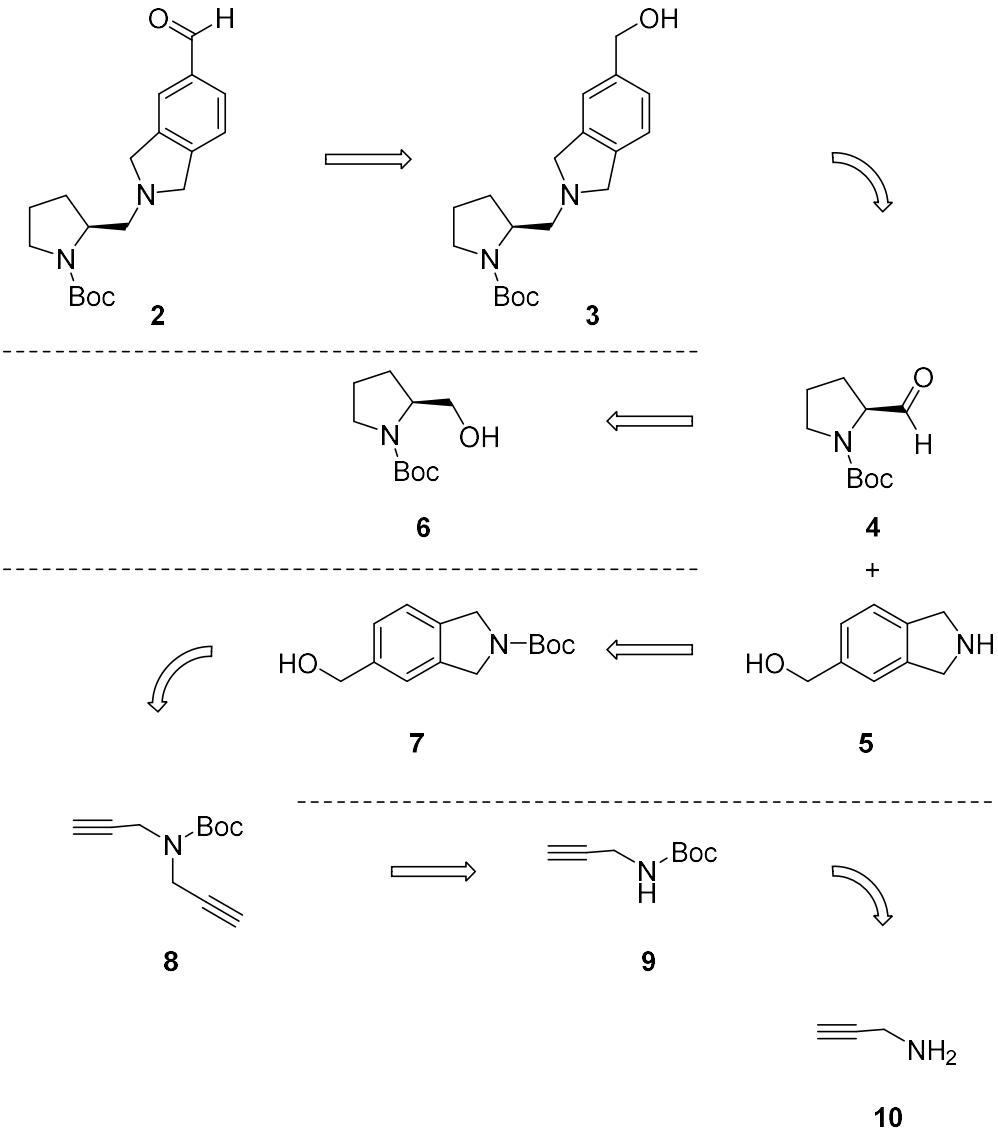
Results and discussion

Synthesis of tert-butyl (s)-2-((5-formylisoindolin-2-yl)methyl)pyrrolidine-1-carboxylate 2

According to initial hypotheses the chiral aldehyde **2** could be suitable reagent for carrying out the synthesis of the porphyrin, if it were not for the difficult commercial availability. For this reason, Victor Cuesta, the last trainee student before my arrival, has envisaged a synthetic route (**Fig.8**) to get the compound **2** starting from ordinary compounds (an N-Boc prolinol **6** and propargylamine **10**) (4).

Furthermore, several studies about the synthesis of chiral porphyrin **1** have showed previously that the most time-consuming task is the preparation of the chiral appendage, with the formation of the porphyrin being carried out in a single step. However, because of the very low yield of the porphyrin formation by condensation and oxidation to obtain the final product **1**, the first goal we have set ourselves has been to optimize where possible all the reactions above, in order to achieve a large amount as possible of the aldehyde **2**. In the synthesis of **2** the key step is a reductive amination via imine between (L)-N-Boc-prolinal **4** and aminoalcohol **5** with $ZnCl_2$ as Lewis acid and $NaBH_3CN$ as reducing agent (21). However, we have also found problems during the cyclisation reaction to obtain **7** and the subsequent deprotection of the *tert*-butyloxycarbonyl (-Boc) group (**5**).

Fig.8 Retrosynthetic analysis of chiral aldehyde

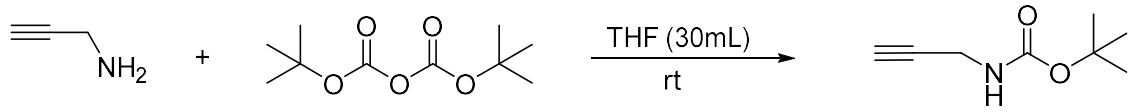


To get to the reductive amination we have followed two parallel synthetic tracks. One to obtain the aminoalcohol **5** and the other to get the prolinal **4**.

Synthesis of 5

The synthesis started with a protection reaction of the amino group in propargylamine **10** with a *tert*-butyloxycarbonyl (Boc) moiety (**Fig.9**), followed by an alkylation with an alkyne group carried out with propargyl bromide (**Tab.1**).

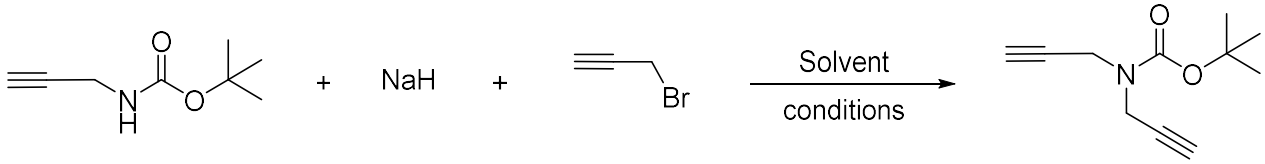
Fig.9 Protection reaction of propargylamine 9



10 **9**

Although the protection was not fully reproducible, the yield of different batches in the synthesis of **9** was always good (around 80%).

Tab.1 Optimization of the akylation reaction



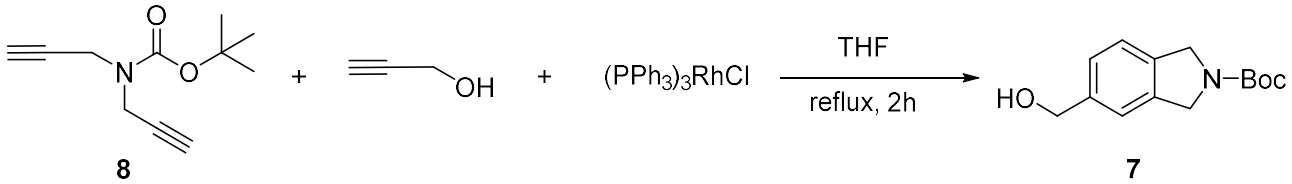
9 **8**

Reaction	T	Solvent	Conditions	Yield
1	reflux	THF (90mL)	1) NaH, 0.5h, rt 2) Propargyl bromide, reflux 1h	60%
2	reflux	THF (65mL)	1) NaH, 0,5h, rt 2) NaI (10mol%), propargyl bromide, reflux 1h and then rt overnight	83.5%

Two conditions were tested for the alkylation reaction. While the first step involved deprotonation with NaH, we got the best result adding NaI in catalytic amount to the second step of the reaction. Probably, the improvement achieved is due the iodine replacing the bromine in propargyl bromide as a better leaving group.

Once we obtained **8** we have focussed on an alkyne cyclotrimerization reaction with Wilkinson's catalyst to afford **7** (22). The only difference identified between the four reactions reported in **Tab.2** is the different batch of the Wilkinson catalyst. In entries 1,2 and 4 we have used an old one while in 3 a new one. Indeed, the yield increased a lot in the latter reaction.

Tab.2 Optimization cyclization reaction

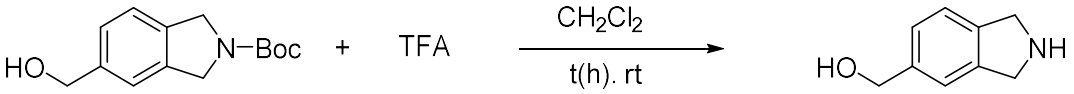


8 7

Reaction	Yield
1	25.5%
2	56%
3	85%
4	50%

The first really Gordian knot we have come across has been the deprotection reaction to get the aminoalcohol **5** (**Tab.3**). This kind of reaction is as easy to get as troublesome, and no one has optimized it for this specific compound before us. We have tried two different procedures with different work up strategies.

Tab.3 Deprotection reaction



7 5

Reaction	Time	Conditions	Yield
1	1h	After quenching with MeOH	50%
2	3h	After evaporation, redissolving in THF and stirring with 5M NaOH (aq) 10mL	45%
3	3h	After evaporation, redissolving in THF and stirring with 5M NaOH (aq) 5mL	12%

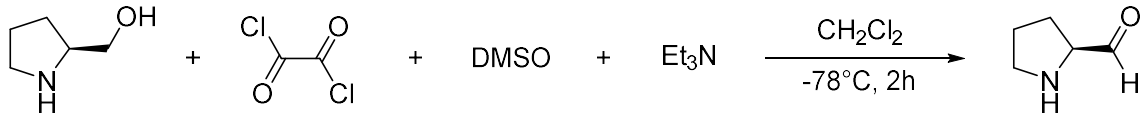
The first is a simple one-step reaction with TFA as deprotecting reagent, followed by quench with MeOH. The second instead is a two-step protocol that always starts with TFA but then involves a second reaction with 5M NaOH. Considering TFA is a very strong deprotecting reagent we suppose the low yields obtained are for the weak effectiveness of the work-up, leading to product loss. Especially in the second reaction, we hypothesised the amine could dissolve in the water phase; however, more extractions did not improve product recovery. To

solve this problem, we have tried to decrease the amount of water used in the NaOH solution, but the very low yield we got told us this was not the solution.

Synthesis of 4

The synthesis is very efficient and involves only one simple reaction. We have started from (*L*)-N-Boc-prolinol **6** commercially available to get to the relative aldehyde **4** *via* Swern oxidation (**Tab.4**). Because of the widespread use of compound **6** in organic chemistry, this reaction has been completely optimized in the past, and we did not need to focus on it (Yield obtained around 60-80%, depending on the amount of solvent used).

Tab.4 Swern oxidation of (L)-N-Boc-prolinol 6



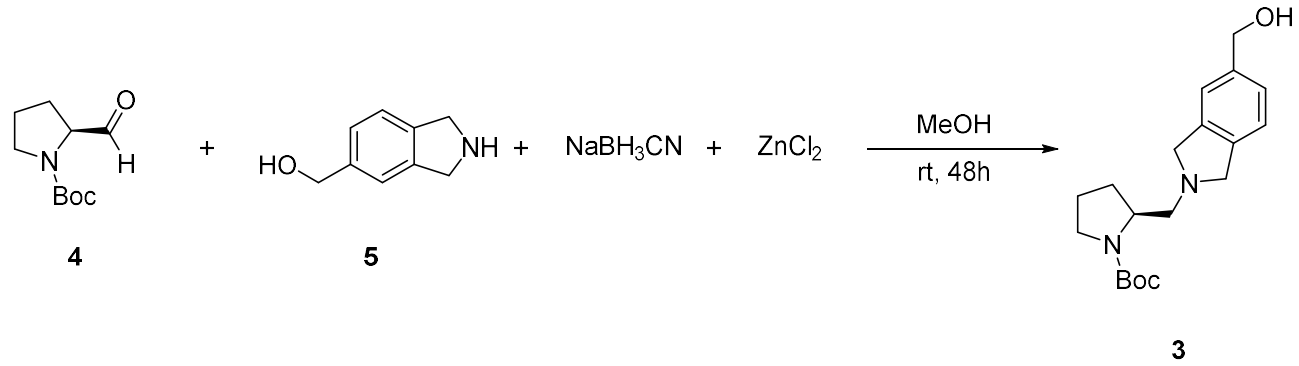
6 **4**

Reaction	CH_2Cl_2 V(mL)	Yield
1	6 mL	62%
2	8 mL	81%

Synthesis of 2

As mentioned above, the reductive amination between compounds **4** and **5** to get **3** is the synthetic key step of the total synthesis (**Tab.5**).

Tab.5 Reductive amination



4 **5** **3**

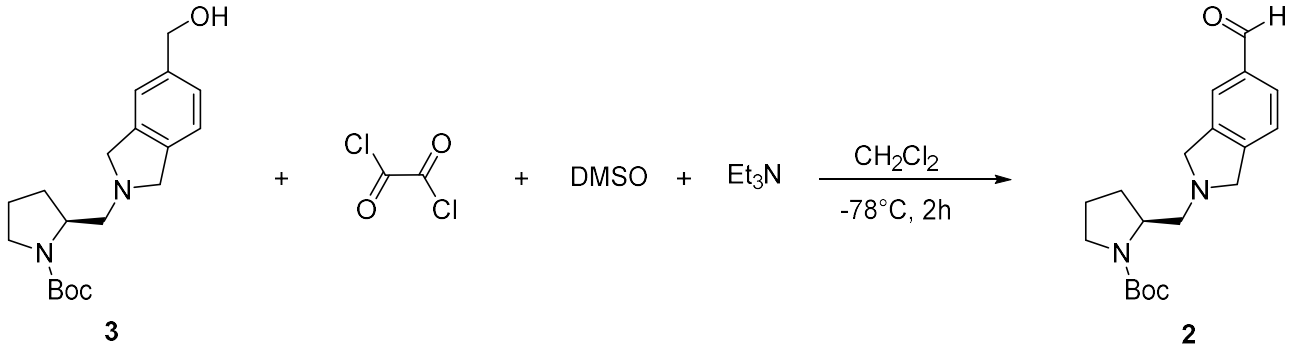
Reaction	Yield
1	12.7%
2	63.5%

In the literature, there are different procedures to obtain a reductive amination from an aldehyde and an amine, but not with our specific molecules. The goal has been to find the correct reducing agent which could react with the iminium cation intermediate generated by the condensation between **4** and **5**. Before me, the master student Victor Cuesta has made more tests to find it. Ultimately, he found that $NaBH_3CN$ and $ZnCl_2$ are a very good combination.

The reaction reported in entry 1 had a very low yield probably caused by a contamination with silicon of compound **5** occurred during the previous deprotection reaction. Indeed, the uncontaminated sample used in the reaction reported in entry 2 showed a good result.

Once the diamino alcohol was synthetized, another Swern reaction was applied (**Tab.6**), under the same conditions mentioned above.

Tab.6 Second Swern oxidation reaction



Reaction	Conditions	Yield
13	After quenching with 10% of aqueous solution of ammonium chloride	40%
21	Stirring at r.t. overnight before quenching	55%

In this case, the reaction was slower and needed more time. As shown in entry 2 of the table we got the best result when we have left the mixture stirring at room temperature overnight.

Final steps and obtainment of the porphyrin 1

After getting the compound **2** we have started to synthetize the porphyrin **11** making a condensation between benzaldehyde, substrate **2** and pyrrole (**Fig.10**) with a catalytic amount of $BF_3 \cdot Et_2O$, to obtain a porphyrogen. Then, this one has been oxidized in presence of *p*-chloranil (**Fig.11**), and after two purifications by column chromatography we have obtained the target product **11** with a 6% yield.

Fig.10 First step, synthesis of porphyrinogen 11

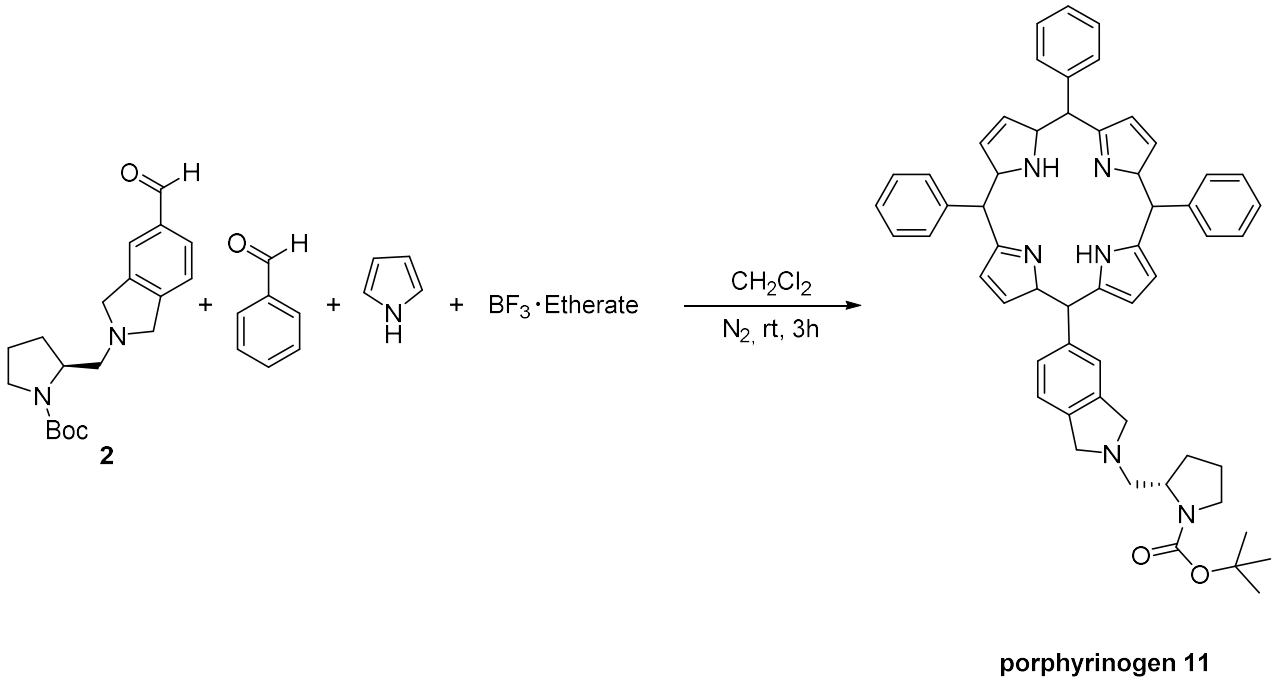
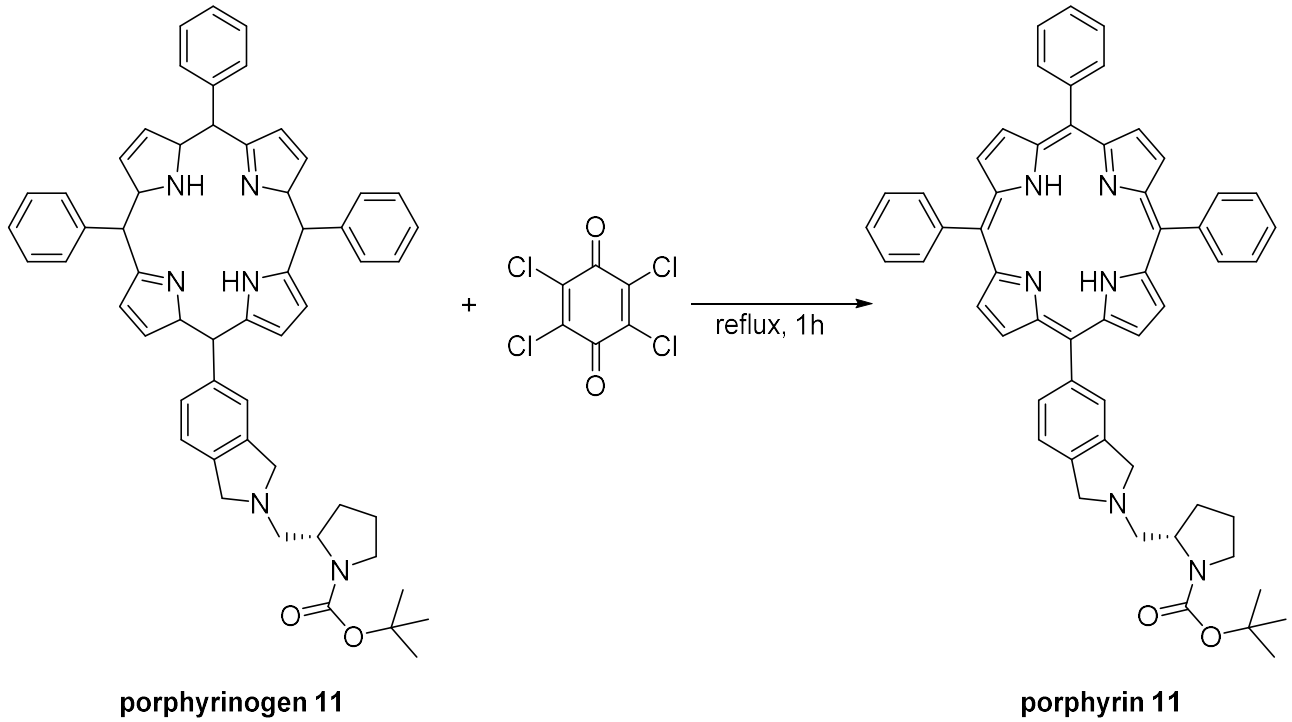


Fig.11 Second step of the synthesis of porphyrin 11

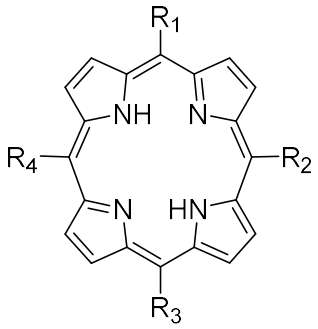


The biggest problem of these last two reactions is the very low final yield caused by the presence of sub-products. Indeed, besides the desired porphyrin, several by-products were recovered from

the reaction mixture as tetraphenylporphyrin, caused from the reaction only between pyrrole and benzaldehyde, or di- and trisubstituted porphyrins and polypirrole.

In fact, the synthesis of a monosubstituted porphyrin becomes complicated and needs specific conditions, when two different groups have to be bound, due to different reactivity of each aldehyde and to the statistical formation of product mixtures. For instance, assuming both aldehydes have the same reactivity and the equivalents are 3 for A (in our case benzaldehyde) and 1 for B (in our case compound **2**), the probability that A reacts is 0,75 and for B is 0,25. Through the binomial theorem of Newton we can calculate the maximum probability to obtain our desired product (**Fig.12**).

Fig.12 Probability to get monosubstituted porphyrin



$$\mathbf{AAAA \rightarrow \binom{4}{0}(0{,}75^4) = 0{,}316}$$

$$\mathbf{AAAB \rightarrow \binom{4}{1}(0{,}75^3 \cdot 0{,}25) = 0{,}422}$$

$$\mathbf{AABB \rightarrow \binom{4}{2}(0{,}75^2 \cdot 0{,}25^2) = 0{,}211}$$

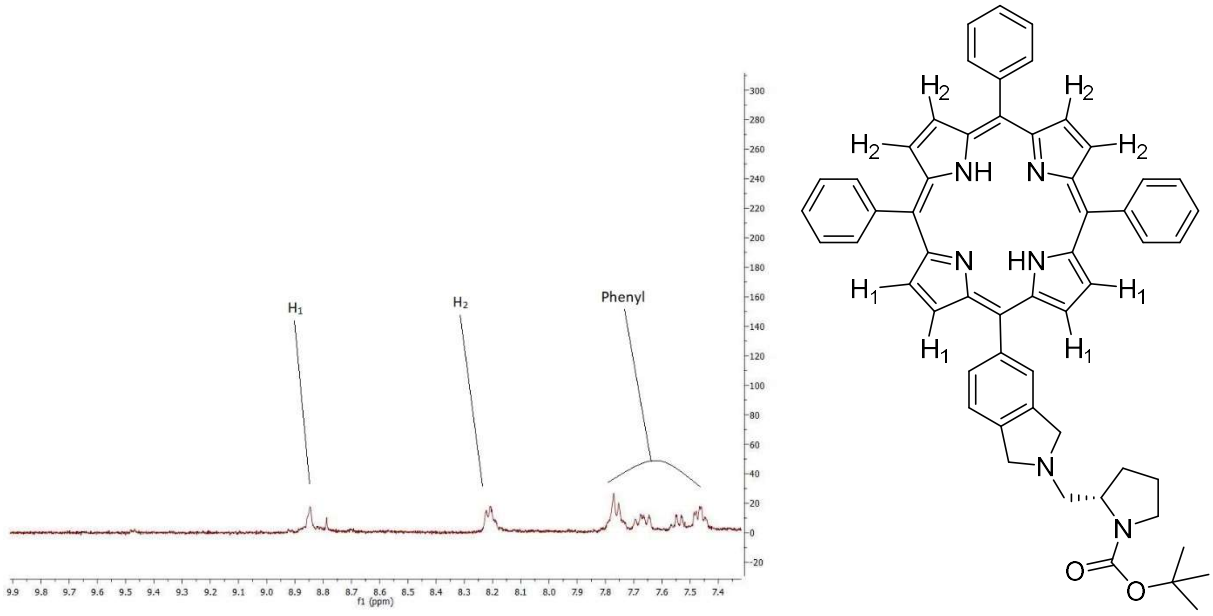
$$\mathbf{ABBB \rightarrow \binom{4}{3}(0{,}75 \cdot 0{,}25^3) = 0{,}047}$$

$$\mathbf{BBBB \rightarrow \binom{4}{4}(0{,}25^4) = 0.004}$$

As you can see the hypothetical probability to get the monosubstituted porphyrin (AAAB) is 42%, but obviously you have all the other products. This is one of the reasons we got a low final yield.

We have characterized the porphyrin **11** by ^{1}H-NMR, considering that the pyrrolic protons of monosubstitued porphyrins in *meso* position have a specific pattern. As you can see in the aromatic zone of the spectra (**Fig.13**) there are two different shielded protons, where H_2 is the more shielded due of anisotropic effect of phenyls group while H_1 not as much as H_2.

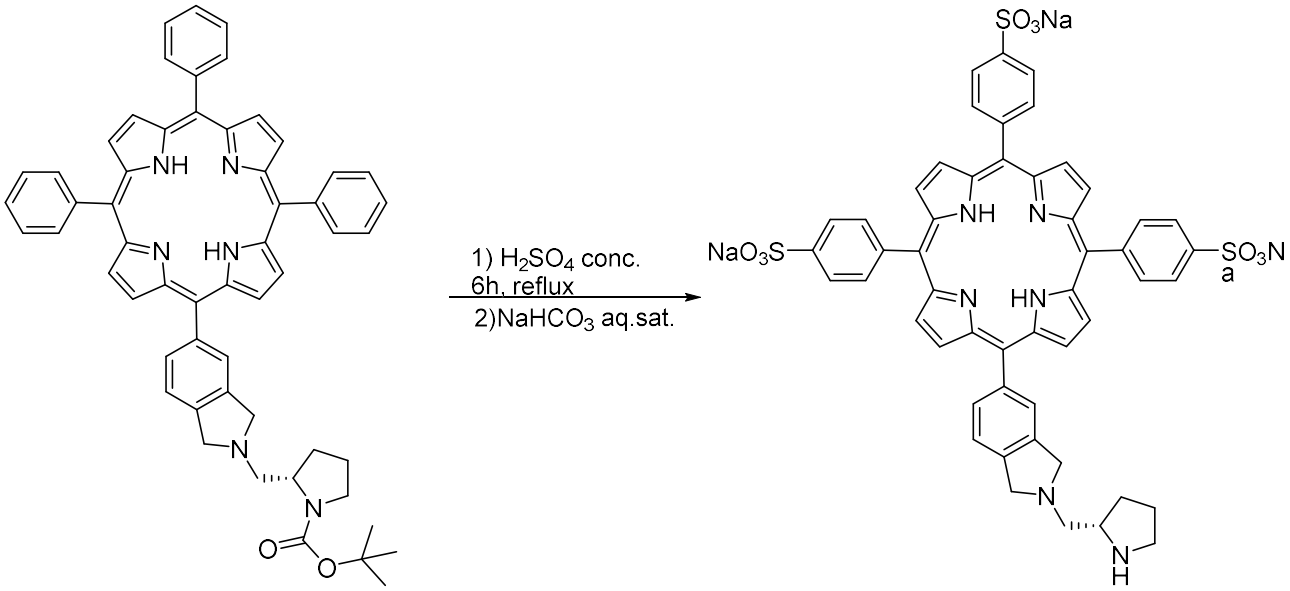
Fig.13 H-NMR of aromatic zone of protected porphyrin 11



Furthermore MS (ESI) analysis gave a mass of 839.3 ($C_{56}H_{50}N_6O_2$), which is very close to the calculated value (839.4).

Finally, the last step has been the sulfonation of the porphyrin **11** and Boc deprotection with concentrated H_2SO_4 (**Fig.14**). After the reaction has finished, the mixture has been centrifugated to separate the supernatant and then the precipitate has been neutralized with aqueous sodium carbonate. The salt formed with carbonate has been removed by a reverse phase chromatography eluting with H_2O to eliminate any inorganic salt and subsequently with H_2O/MeOH to afford the desired porphyrin **1** (trisodium salt). The product has been lyophilized.

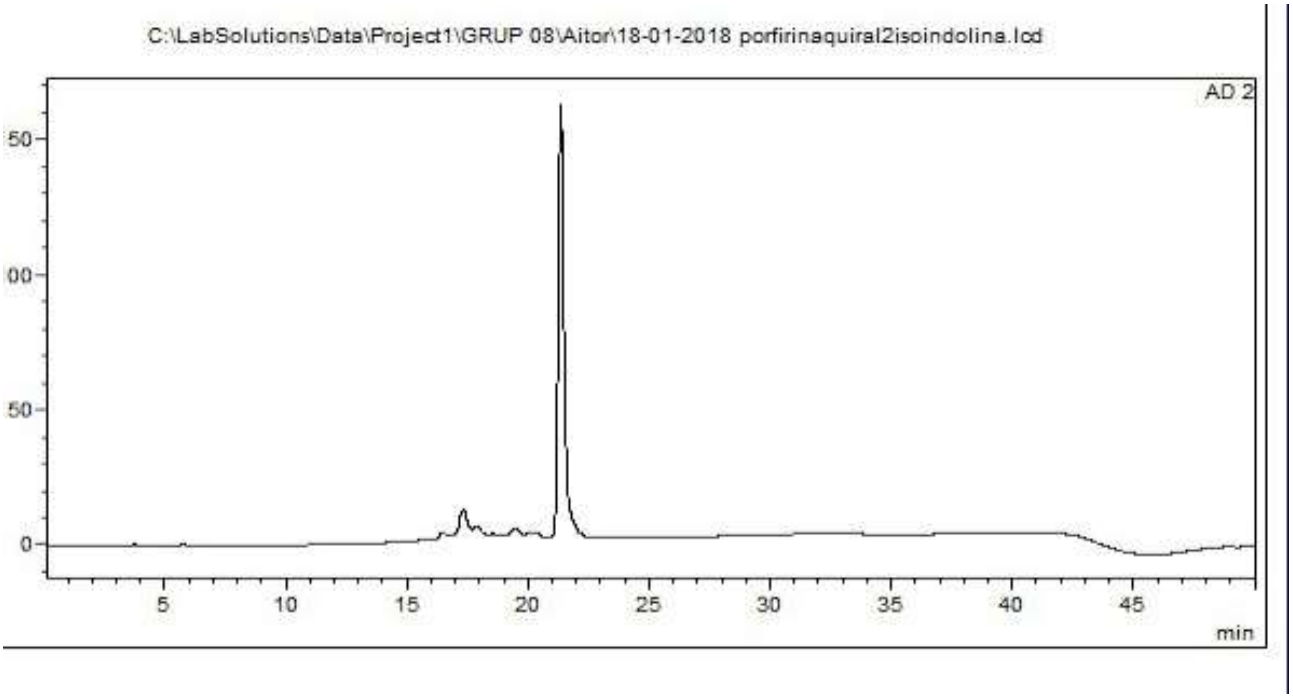
Fig.14 Sulfonation of porphyrin 11 to porphyrin 1



porphyrin 11 **porphyrin 1**

HPLC analysis in reverse phase has been used to verify the purity of the final product (**Fig.15**).

Fig.15 HPLC analysis in reverse phase of porphyrin

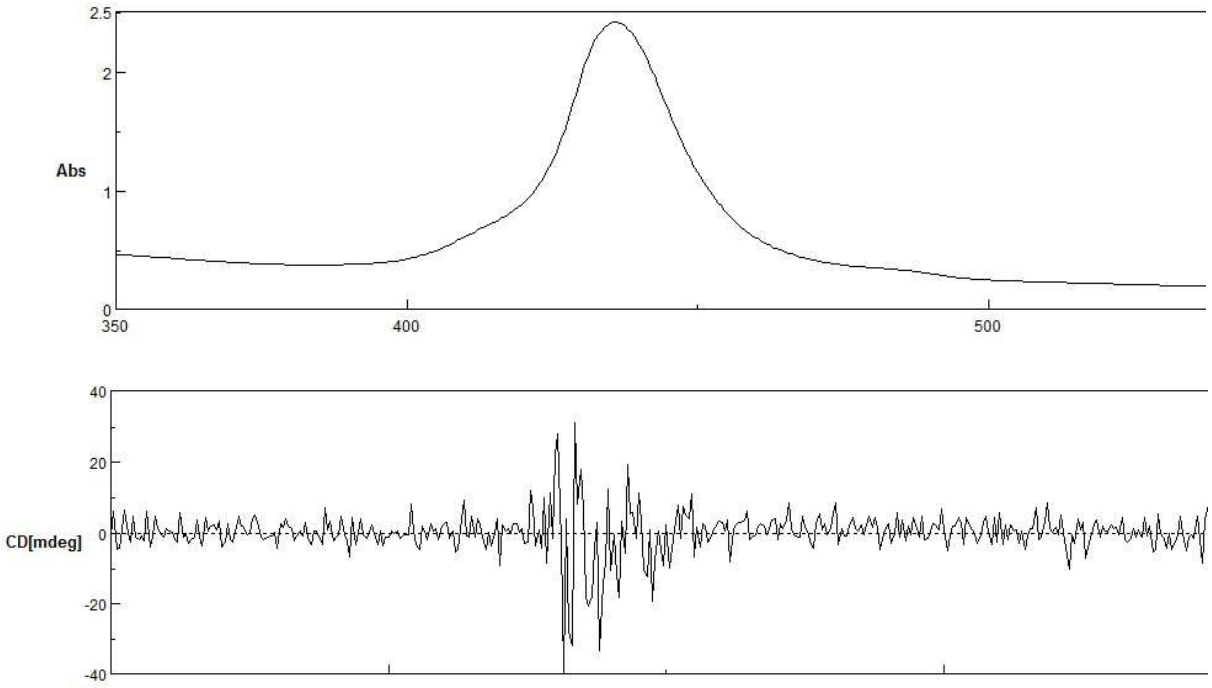


As you can see from the image above finally the catalyst obtained was reasonably pure, the little peaks from 15 to 20 minutes are normal impurities (possibly tetrasulfonated products).

A UV-Vis spectrum has also been carried out to evaluate the absorption band and a circular dichroism analysis has been made to see the chirality of our porphyrin (**Fig.16**). The amount of

catalyst was too poor to see the J-aggregate (which would give full precipitation thus no signal), so in the image you are seeing only the absorption bands of the monomeric species.

Fig.16 UV-Vis spectrum and circular dichroism of porphyrin

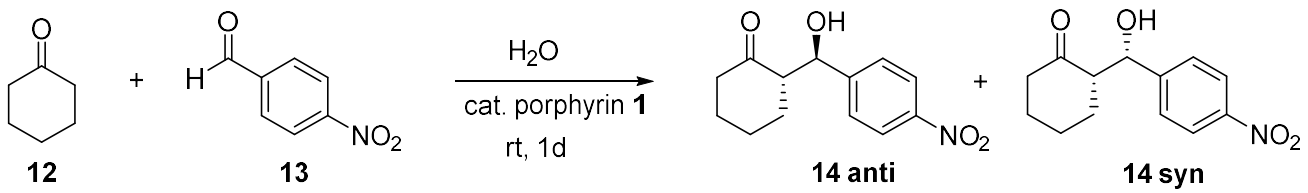


Aldol reaction with porphyrin 1 as organocatalyst

To obtain enough material for catalytic tests, the whole synthetic sequence was repeated three times, delivering ca. 10 mg of product **1**. Due to the very small amount of organocatalyst **1** we obtained, we have tested it only in one asymmetric reaction, to verify at least if it was able to drive the reaction in an enantiomeric fashion.

We have decided to try a very simple aldol reaction, from cyclohexanone **12** and *p*-nitrobenzaldehyde **13** to get aldols **14** (**Fig.17**).

Fig.17 Aldol reaction (porphyrin 1)

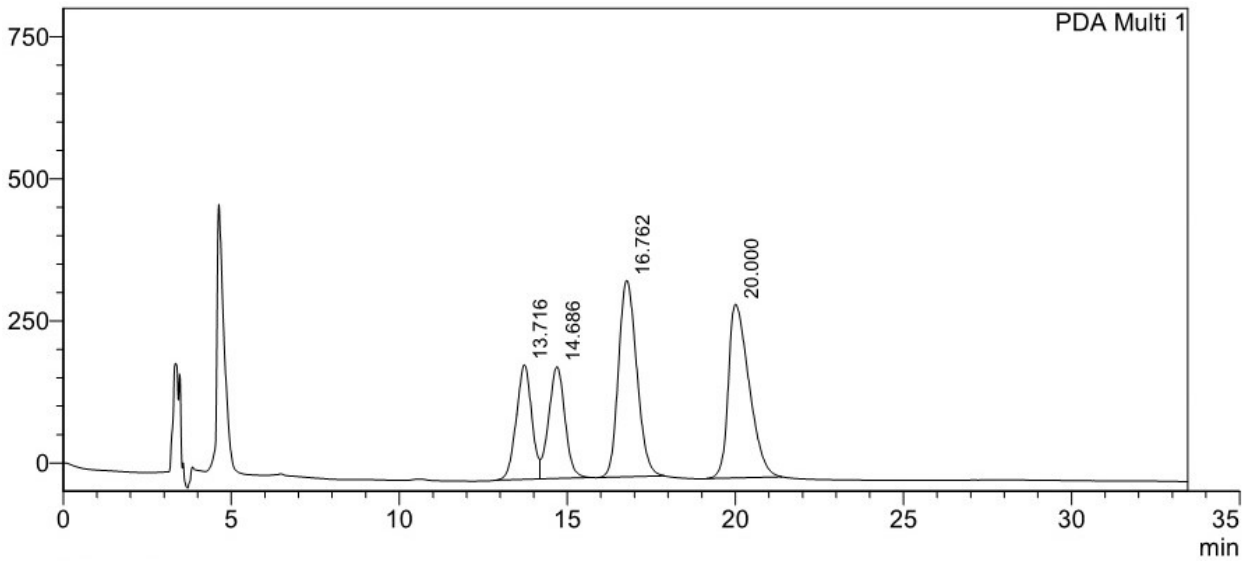


With this organocatalyst, in water, the yield obtained was very good and the simple diasteroselection calculated was.

dr: 66/34 (anti/syn).

Unfortunately, the aldol products were formed in racemic fashion (**Fig.18**).

Fig.18 HPLC in reverse phase of aldol reaction product



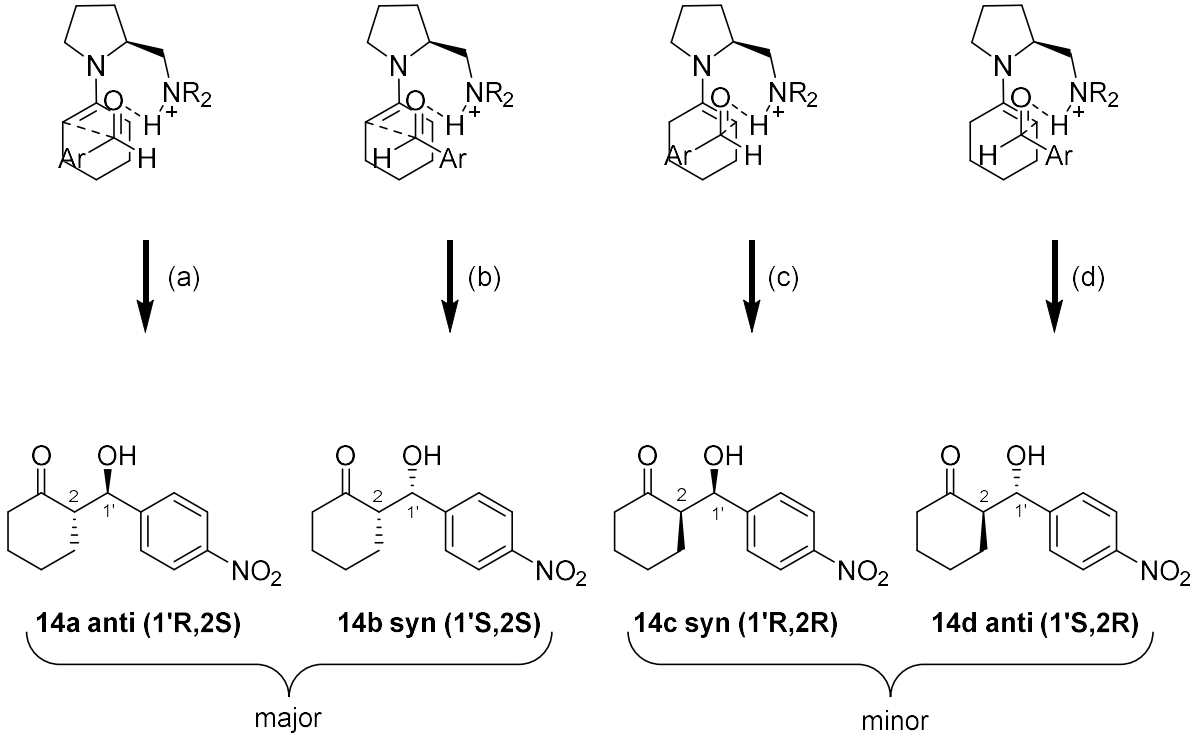
PeakTable

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	13.716	6434056	201396	16.382	19.197
2	14.686	6607528	196716	16.824	18.751
3	16.762	13087719	345509	33.323	32.934
4	20.000	13145752	305476	33.471	29.118
Total		39275055	1049097	100.000	100.000

The asymmetric induction in aldol reactions catalysed by pyrrolidine diamines can be rationalized through the transition states proposed in the Houk-List model (**Fig.19**).

Fig.19 Proposed transition states to get product 14a, 14b and their enantiomers



In this model the director group in C2 of the catalyst is able to create hydrogen bond with the carbonyl of the aldehyde, like in the classic transition state of the proline-catalysed asymmetric aldol reactions, despite changes the electron withdrawing group. In our case the catalyst has a tertiary amine that, after being protonated, can drive the creation of the H-bond, activating the aldehyde for the aldol reaction.

Taking into account of what told above, obviously a catalytic amount of acid could protonate better the amine and then increase the diastereo- and the enantioselectivity, although in this case we could also have aggregation of the porphyrin if the central core is protonated. Unfortunately, we did not have time to test acidic conditions.

Conclusions

We have partially achieved the objectives set at the starting of the training internship. Unfortunately, the problems encountered during the synthesis of compound **1** led to the obtainment of only a very small amount of it, preventing us from focussing more on the asymmetric aldol reaction and to try other types of reactions (e.g. Michael additions).
However, at the end of this work we have reached:

- The optimization of the synthetic route for the synthesis of compound **2**;
- An efficient synthesis and characterization of porphyrin **1** by HPLC and MS-ESI;
- A test in water of porphyrin **1** as catalyst in an asymmetric organocatalytic aldol reaction. The result of the reaction has furnished an excellent yield, moderate diastereoselectivity and no enantioselectivity.

Other goals pursued in the next future to improve the catalyst activity could be:

- Evaluating the effect of co-solvents (THF) or of acidic co-catalysts (for instance, benzoic acid + porphyrin) in the aldol reaction with cyclohexanone;
- Evaluating the effect of the porphyrin moiety, using an aminoalcohol composed of the same chiral amine group of the porphyrin **1** as organocatalyst and trying it in the same aldol reaction;
- Testing other organocatalytic reactions as aldol reactions with different reagents or trying Michael addition.

Experimental section

Material and methods:

All reactions and procedures were performed in previously purified solvents according to standard laboratory procedures.

Reagents:

All reagents and starting materials were obtained from commercial suppliers and, unless specified otherwise, were used without further purification:

L-(-)-Proline (Acros, 99+%), lithium aluminum hydride (Aldrich, 95%), sodium cyanoborohydride (Aldrich, 95%), p-toluic acid (Aldrich, 98%), p-nitrobenzaldehyde (Aldrich, 98%), acetone (Scharlau, extra pure), ciclohexanone (Aldrich, 99+%), isonipecotic acid (Aldrich,

97%), propargyl amine (Aldrich, 98%), propargyl bromide (Acros, 80%), propargyl alcohol (Janssen, 99%), sodium hydride (TCI, 60% dispersion paraffin liquid), trifluoroacetic acid (Aldrich, 98%), di-tert-butyl dicarbonate (Fluka, 98%), oxalyl chloride (Aldrich, 98%), triethylamine (Aldrich, 99%), benzaldehyde (Acros, 98%), pyrrole (Aldrich, 98%, vacuum distilled before use, 10 mbar, 35 °C), chloranil (Fluka, 98%), boron trifluoride ethyl etherate (Fluka, purum), sulfuric acid (Merck, 98%), hydrochloric acid (Sharlau, 37%), sodium bicarbonate (JEscuder), sodium sulfate (Escuder), acetic acid (Scharlau, 99%) and sodium acetate (Probus, 98%).

General methods:

NMR spectra were recorded at room temperature on a Varian Mercury 400 instrument. ^{1}H NMR spectra were referenced to TMS ($\delta = 0$ ppm) or to residual non-deuterated solvent peaks as internal standards. ^{13}C NMR spectra were referenced to residual solvent peaks. Melting points were measured using a Gallenkamp apparatus. HRMS analysis were recorded using a Bruker MicroTOF electrospray ionization spectrometer (ESI). 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 using Daicel Chiralpak® IB and Daicel Chiralcel® AS-H columns. pH measurements were performed on a CRISON Micro pH 2000 pH-meter (Crison 52-04 glass electrode) at room temperature. The pHmeter was calibrated prior to each measurement with standard buffer solutions at pH=7.00 and

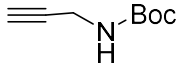
4.00 (Metrohm). UV-Vis spectra were recorded at room temperature on a double beam

spectrophotometer: Cary-Varian 5E, which uses the software Scan Varian. During the measurements, quartz Suprasil cells were used with optical path 10 mm x 10 mm Hellma. Rotofix 32 A from Hettich was used to centrifuge the aggregate samples. Circular dichroism spectra were recorded at room temperature on a JASCO J-810 spectrometer, equipped with a 150 W Xe lamp (air cooled). During the measurements, quartz Suprasil cells were used with different optical paths. Reverse phase HPLC analysis were performed using column C18 250mm x 4mm (Nucleosil 120-5, Scharlab) equipped with an analytic precolumn (Resolve C18,
Waters) on a computer Shimadzu equipped with a UV-Vis detector, and two bombs LC-10 AS pumps and a Shimadzu Class VP programmer. The lyophilised samples were prepared at a vacuum pump cooled with an immersion cooler Crycool CC-100 II, filled with acetone at -80 ºC.

Synthesis of porphyrin 1:

***tert*-butyl prop-2-yn-1-ylcarbamate 9:**

In a 100 mL round-bottomed flask equipped with magnetic stirring and containing propargylamine **10** (2g, 36.3 mmol) in anhydrous THF (30 mL), di(*tert*-butyl) carbonate (8.72g, 39.9 mmol) was added to a stirred solution at room temperature. The mixture was stirred at the same temperature overnight and then the solvent was concentrated in vacuum. The crude was dissolved in EtOAc (50 mL) and the solution was washed with H_2O (3x20 mL) and brine (1x20 mL). The organic fraction was dried over with Na_2SO_4 and concentrated in vacuum to yield the desired product, which was used for the next step without purification.

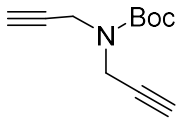


Yellow solid, 85% yield. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.69 (s, 1H), 3.92 (s, 2H), 2.22 (t, 1H), 1.46 (s, 9H).

***tert*-butyl di(prop-2-yn-1-yl)carbamate 8:**

In a 100 mL round-bottomed flask containing **9** (4.75g, 30.6 mmol) in anhydrous THF (75 mL), NaH (60% dispersion in paraffin, 1.03 g, 42.8 mmol) was added under stirring at room temperature. After 30 minutes was added propargyl bromide (7.25g, 49 mmol) and NaI (10 mol%), the mixture was heated at reflux for 2 hours and finally at rt overnight. The reaction was quenched with a saturated solution of NH_4Cl (50 mL) and the mixture was extracted with EtOAc (3x80 mL). The organic fraction was washed with H_2O (3x30 mL) and brine (30 mL)

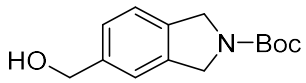
and then dried over with Na_2SO_4 and concentrated in vacuum. The crude product was purified by flash column chromatography (Hexane: EtOAc 10:1) to give the desired product.



Yellow oil, 70% yield. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.17 (s, 4H), 2.24 (t, J = 2.5 Hz, 2H), 1.48 (s, 9H)

***tert*-butyl 5-(hydroxymethyl)isoindoline-2-carboxylate 7:**

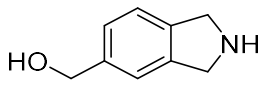
In a 50 round-bottomed flask equipped with magnetic stirring and containing **8** (1g, 5.2 mmol) and propargyl alcohol (0.87g, 15.6 mmol) in anhydrous THF (20 mL), $RhCl(PPh_3)_3$ (0.14g, 0.16 mmol) was added to a stirred solution at room temperature. After the mixture was stirred at reflux for 2 hours, the solvent was concentrated to dryness in vacuum and the crude product was purified by a falsh chromatography column (Hexane: EtOAc 2:1) to give the desired product.



White solid, 85% yield. Mp 105–106º C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38 – 7.12 (m, 3H), 4.70-4.64 (m, 5H), 1.57 (s, 2H), 1.52 (s, 9H).

Isoindoline-5-ylmethanol 5:

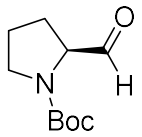
In a 100 mL round-bottomed flask, TFA was slowly added to a stirred solution of compound **7** (1.11 g, 4.5 mmol) in CH_2Cl_2 (7.5 mL) and the resulting mixture was stirred at r.t. for 3 h. Then the solvent and TFA were evaporated under vacuum, the residue was dissolved in THF (10 mL) and treated with 5 M NaOH solution (10 mL). The resulting mixture was stirred at r.t. for 2 h, then the two layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2x50 mL). The combined organic layers were dried over with Na_2SO_4, filtered and the solvent was evaporated under reduced pressure. The resulting product was used for catalysis without purification.



Brown solid, 45% yield. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.32 – 7.16 (m, 3H), 4.81 – 4.72 (m, 2H), 4.69 (d, J = 13.1 Hz, 2H), 4.20 (d, J= 12.5 Hz, 2H), 2.37 (s, 2H).

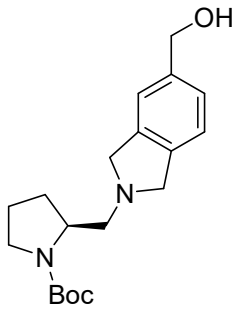
***tert*-butyl (S)-2-formylpyrrolidine-1-carboxylate 4:**

To a solution of oxalyl chloride (0.76 g, 6 mmol) in dry CH_2Cl_2 (2 mL), a solution of anhydrous dimethylsulphoxide (0.62 g, 8 mmol) in dry CH_2Cl_2 (2 mL) was added a -78 °C. The reaction was stirred for 20 minutes at -78 °C, then a solution of **7** (0.8 g, 4 mmol) in dry CH_2Cl_2 (4 mL) was added and the mixture was stirred for other 20 minutes, when triethylamine (1.6 g, 16 mmol) was added. The reaction mixture was stirred for 2 h and then at r.t. overnight. It was added a 10% aqueous solution of ammonium chloride. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3x10 mL). The combined organic layers were washed with hydrogen carbonate (4x20 mL), it was dried over with Na_2SO_4 and the solvent was removed under vacuum.



Yellow oil, 62% yield. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.60 – 9.40 (m, 1H), 4.24 – 3.95 (m, 1H), 3.61 – 3.34 (m, 2H), 2.25 – 1.75 (m, 4H), 1.44 (d, J = 20.1 Hz, 9H). [a]20D= -97.9 (c=0.66; CHCl3)

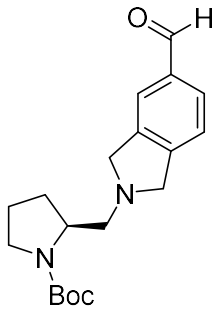
***tert*-butyl (S)-2-((4-(hydroxymethyl)piperidin-1-yl)methyl)pyrrolidine-1-carboxylate 3:**
In a 50 mL round-bottomed flask, compounds **5** (0.31 g, 2.1 mmol) and **4** (0.37 g, 1.9 mmol) were dissolved in dry MeOH (15 mL) at r.t. In another round-bottomed flask cyanoborohydride (0.24 g, 3.8 mmol) and zinc chloride (0.26 g, 1.9 mmol) were dissolved in dry MeOH (15 mL) at r.t. The mixtures were stirred under N_2 atmosphere and after 1.5 h the solution with zinc-modified cyanoborohydride was added to the first mixture *via* canula. The reaction was stirred 48 h under N_2. Then a solution of NaOH 1M (5 mL) was added to reaction mixture and the solvent was removed under vacuum. Afterwards, the crude was redissolved in H_2O (10 mL) and the solution was extracted with EtOAc (5x10 mL). The organic extracts were dried over with Na_2SO_4 and concentrated under reduced pressure.



Yellow oil, 64% yield. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.15 (s, 3H), 4.62 (s, 2H), 4.03 – 3.86 (m, 5H), 3.35 (s, 2H), 2.91 (m, 1H), 2.66 (t, J = 10.2 Hz, 1H), 2.21 (s, 1H), 2.07 – 1.75 (m, 4H), 1.48 (s, 9H).

***tert*-butyl (S)-2-((4-formylpiperidin-1-yl)methyl)pyrrolidine-1-carboxylate 2:**

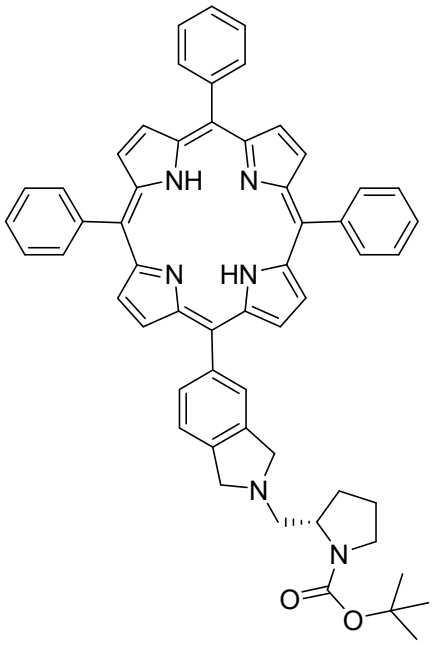
To a solution of oxalyl chloride (0.23 g, 1.8 mmol) in dry CH_2Cl_2 (500 µL), a solution of anhydrous dimethylsulphoxide (0.19 g, 2.4 mmol) in dry CH_2Cl_2 (500 µL) was added a -78 °C. The reaction was stirred for 20 minutes at -78 °C, then a solution of **3** (0.40 g, 1.2 mmol) in dry CH_2Cl_2 (1.5 mL) was added and the mixture was stirred for other 20 minutes, when triethylamine (0.48 g, 4.1 mmol) was added. The reaction mixture was stirred for 2 h and then at r.t. overnight. It was added a 10% aqueous solution of ammonium chloride. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3x5 mL). The combined organic layers were washed with hydrogen carbonate (4x10 mL), it was dried over with Na_2SO_4 and the solvent was removed under vacuum.



Yellow oil, 55% yield. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10 (s, 1H), 7.7 (s, 2H), 7.35 (d, J = 15 Hz, 1H), 4.15-3.90 (m, 7H), 3.35 (s, 4H), 2.95-2.85 (m, 1H), 2.7 (s, 1H), 1.48 (s, 9H)

***tert*-butyl (S)-2-((5-(10,15,20-triphenylporphyrin-5-yl)isoindolin-2-yl)methyl)pyrrolidine-1-carboxylate 11:**

A 250 mL 3-neck round-bottomed flask was fitted with a reflux condenser (Dimroth), two caps and a magnetic stirrer. The Dimroth condenser was capped with a septum and a globe. CH_2Cl_2 (155 mL) was added and purged with a nitrogen flow for 15 min. At this point compound **2** (0.13 g, 0.39 mmol) was added, followed by benzaldehyde (0.12 g, 1.17 mmol) and by pyrrole (0.11 g, 1.56 mmol). The solution was stirred for 5 min. Finally a catalytic amount of $BF_3{\cdot}Et_2O$ (0.06g, 0.16 mmol) was added. The round-bottomed flask was covered with a black paper and the resulting yellow-coloured suspension was stirred at r.t. for 3 h. The reaction mixture changed its colour from yellow to violet-brown. At this time p-chloranil (0.29g, 1.17 mmol) was added and the solution was refluxed for 1 h, cooled and concentrated und reduced pressure, not to dryness. The crude brown solid was purified by three flash column chromatography through silica using CH_2Cl_2.



Violet solid, 4% yield. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.8-8.8 (m, 4H), 8.2 (m, 4H), 7.8-7.4 (m, 18H), 4.6 (s, 1H), 3.95 (s, 4H), 3.35 (s, 4H), 2.9 (m, 2H), 1.9 (m, 2H), 1.5 (m, 9H), -2.8 (s, 2H)

sodium (S)-4,4',4''-(15-(2-(pyrrolidin-2-ylmethyl)isoindolin-5-yl)porphyrin-5,10,20-triyl)tribenzenesulfonate 1:

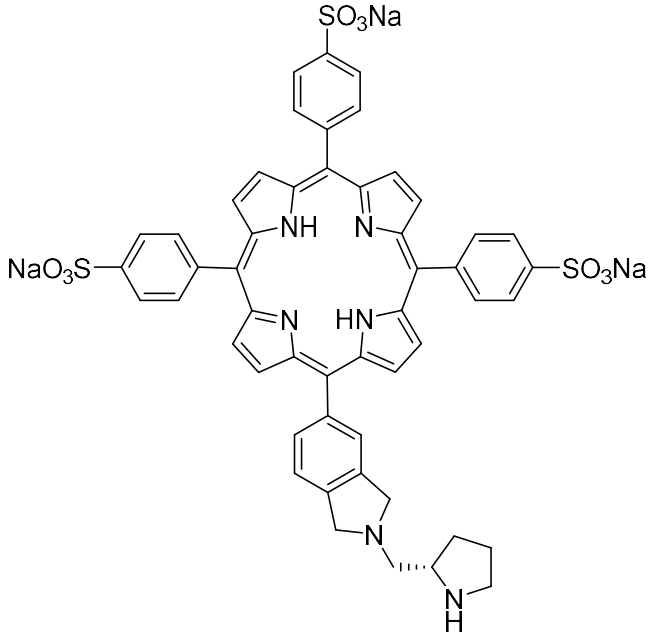
In a 10 mL round-bottomed flask fitted with a condenser (Dimroth) covered with a $CaCl_2$ tube and

with magnetic stirrer, product **11** (13 mg, 0.012 mmol) and H_2SO_4 (96%, 5 ml) were added. The

reaction mixture was heated to 100 ºC for 6 h and stirred at room temperature for 36 h. The resulting green-coloured suspension was placed in centrifugal tubes with 10 mL of H2O in each

one and the tubes were centrifuged to 6000 rpm for 30 min to obtain the J- aggregates of the porphyrin as precipitate. The supernatant was removes and the J-aggregates were placed on a 100 mL round-bottom flask with H_2O. The remaining sulphuric acid was neutralized with $NaHCO_3$, changing the colour of the porphyrin from green to brown-red. After that, H_2O was evaporated under reduced pressure. Finally, the resulting product was purified by chromatography which MCI GEL CHP20P (Dianion ®, Supelco) was used as the stationary phase. The porphyrin is slightly retained in the column, thus allowing the elimination of the inorganic salts by fast elution with H_2O. After that, porphyrin was eluted with H_2O/MeOH 1:1. At this point, the solvents were concentrated under vacuum and then the product was lyophilized

for 2 days to afford 4.2 mg of the desired product.

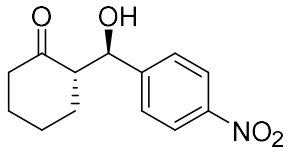


Aqueous asymmetric organocatalytic aldol reaction to obtain 2-(hydroxy(4-nitrophenyl)methyl)cyclohexan-1-one 14:

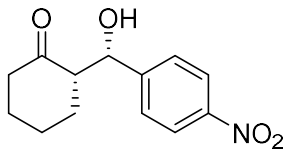
Catalyst **1** (0.0042 g, 0.005 mmol) was dispersed in H_2O (1 mL) in a 10 mL round-bottomed flask

equipped with magnetic stirring. After 10 min cyclohexanone was added (0.025 g, 0.25 mmol) to the reaction mixture, it was stirred for 30 min and then p-nitrobenzaldehyde was added (0.0075 g, 0.05 mmol). The reaction was stirred for 1 d at r.t. The aqueous layer was extracted with CH_2Cl_2

(3x10 mL). The organic layer was dried under Na_2SO_4 and concentrated under reduced pressure to afford the desired products. The diastereomeric ratio was determined by ^1H NMR of a crude sample; enantiomeric excess was determined by chiral HPLC.



Yellow solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.21 (d, J = 8.7 Hz, 2H), 7.51 (d, J = 8.7 Hz, 2H), 4.90 (d, J = 8.4 Hz, 1H), 4.06 (s, 1H), 2.59 (ddd, J = 13.7, 8.2, 5.2 Hz, 1H), 2.50 (d, J = 13.7 Hz, 1H), 2.37 (td, J = 13.2, 6.1 Hz, 1H), 2.12 (ddt, J = 12.1, 5.7, 3.0 Hz, 1H), 1.83 (dd, J = 12.2, 2.4 Hz, 1H), 1.77 – 1.23 (m, 5H) Hz, 1H), 1.83 (dd, J = 12.2, 2.4 Hz, 1H), 1.77 – 1.23 (m, 5H) **HPLC** (Chiralpak© IB, 1 mL·min^{-1}, hexane: IPA 97:3, 270 nm, 24 bar): t_R (major) = 16.8 min (1'R, 2S), t_R (minor) = 20 min (1'S, 2R).



Yellow solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.21 (d, J = 8.6 Hz, 2H), 7.49 (d, J = 8.6 Hz, 2H), 5.49 (m, 1H), 3.16 (d, J = 3.0 Hz, 1H), 2.63 (dd, J = 12.2, 5.4 Hz, 1H), 2.49 (d, J = 13.4 Hz, 1H), 2.40 (td, J = 13.4, 6.0 Hz, 1H), 2.16 – 2.07 (m, 1H), 1.86 (d, J = 13.2 Hz, 1H), 1.79 – 1.46 (m, 4H).
HPLC (Chiralpak© IB, 1 $mL \cdot min^{-1}$, hexane: IPA 97:3, 270 nm, 24 bar): t_R (minor) = 13.7 min (1'R, 2R), t_R (major) = 14.7 min (1'S, 2S).

Bibliography

1. A. Massi, A. Dondoni. *Asymmetric organocatalysis: from Infancy to adolescence.*

2. S. Cabrera, J. Alemán. *Chem. Soc. Rev.* **2013**, 42, 774–793.

3. A. Moyano**.** *in Stereoselective organocatalysis, ed. R. Rios, Wiley,* 1rst edn, **2013**, ch. 2, pp. 11-81.

4. V. Cuesta. *Master Thesis, Universitat de Barcelona.*

5. Timothy D. Machajewski, Chi-Huei Wong. *Angew. Chem. Int.* Ed. **2000**, 39, 1352-1374.

6. Mase, Nakai, Ohara, Yoda, Takabe, and Barbas III. *J. Am. Chem. Soc.* **2006**, 128, 734-735.

7. List, Lerner, Barbas III. *J. Am. Chem. Soc.* **2000**, 122, 2395-2396.

8. G. Valero. *PhD Thesis, Universitat de Barcelona,* **2014.**

9. V. K. Singh, M. Raj. *Chem. Comun.* **2009**, 6687–6703.

10. Y. Hayashi, T. Sumiya, J. Takahashi, H. Gotoh, T. Urushima and M. Shoji. *Angew. Chem. Int. Ed.* **2006**, 45, 958-961.

11. M. Raj, S. K. Ginotra and V. K. Singh. *Org. Lett.* **2006**, 8, 4097–4099.

12. D. Font, C. Jimeno and M. A. Pericàs. *Org. Lett.* **2006**, 8, 4653–4655.

13. J. L. Sessler, D. Seidel. *Angew. Chem. Int. Ed.* **2003**, 42, 5134- 5175.

14. C. Escudero. *PhD thesis, Universitat de Barcelona,* **2007.**

15. N. Vekatramaiah, B. Ramakrishna, R. Venkatesan, F. A. Almeida Paz and J. P. C. Tomé. *New J. Chem.* **2013**, 37, 3745–3754.

16. Z. El-Hachemi, C. Escudero, F. Acosta-Reyes, M. T. Casas, V. Altoe, S. Aloni, G. Oncins, A. Sorrenti, J. Crusats, J. L. Campos and J. M. Ribó. *J. Mater. Chem. C,* **2013**, 1, 3337–3346.

17. A. D'Urso, M. E. Fragalà and R. Purrello. *Chem. Commun.* **2012**, 48, 8165–8176.

18. C. Escudero, Z. El-Hachemi, J. Crusats and J. M. Ribó. *J. Porphyr. Phthalocyanines,* **2006**, 9, 852–863.

19. Z. El-Hachemi, C. Escudero, O. Arteaga, A. Canillas, J. Crusats, G. Mancini, R. Purrello, A. Sorrenti, A. D. Urso and J. M. Ribó. *Chirality.* **2009**, 21, 408–412.

20. Z. El-Hachemi, A. Moyano, C. Blanco and D. Hochberg. *Astrobiology,* **2013**, 13, 132–142.

21. B. R. Allen, E. W. Baxter. *Org. React.* **2002**, 59, 1-714.

22. WO Pat., WO 03064411 A1, **2003**.