Preparation of chiral [2]paracyclo(5,8)quinolinophane - based cinchonoid analogue organocatalysts for stereoselective syntheses

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UNIVERSITY OF ZAGREB
FACULTY OF CHEMICAL ENGINEERING AND TECHNOLOGY
GRADUATE UNIVERSITY STUDY PROGRAMME

Silvija Petković

MASTER THESIS

Zagreb, July 2015.

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MASTER THESIS

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Zagreb, July 2015.

SVEUČILIŠTE U ZAGREBU
FAKULTET KEMIJSKOG INŽENJERSTVA I TEHNOLOGIJE
DIPLOMSKI SVEUČILIŠNI STUDIJ

Silvija Petković

Priprava kiralnih derivata cinhonidina temeljenih na [2]paraciklo(5,8)kinolinofanu kao organokatalizatora u stereoselektivnim sintezama

DIPLOMSKI RAD

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Zagreb, srpanj 2015.

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SUMMARY

The aim of this thesis was to synthesize chiral cinchonoid analogues, [2](5,8)quinolinophane and quinoline organocatalysts that could be used in stereoselective syntheses. The presence of the quinoline system makes the molecule of quinolinophane a great "building block" for the synthesis of chiral cinchona analogues as potential organocatalysts. In other words, it would be sufficient to introduce into the molecule a tertiary amino group and a chiral carbon bounded to a hydroxyl group to obtain a molecule that has all the elements of chirality as the natural cinchonoids. The only difference lies in the fact that a central chirality associated with quinuclidine ring of cinchonoids is replaced by the planar chirality associated with the system "quinolinophane". In addition, the quinolinophane constitutes a chiral "building block" of extreme versatility. In fact, through simple transformations, it is possible to obtain different structural combinations in which the determined elements for the asymmetric induction (the tertiary amino group, the hydroxylated chiral carbon and the planar chirality system) can be differently assembled.

With that in mind, the scope was to determine contribution of planar and central chirality of (*R*)-[2]paracyclo[2](5,8)quinolinophane derivatives exhibiting both type of chirality to the asymmetric induction (Figure 1**).** For sake of comparison envisaged was to prepare also some chiral (*S*)- and (*R*)-trifluoromethylsulfoxyamide derived from 4-bromoquinoline.

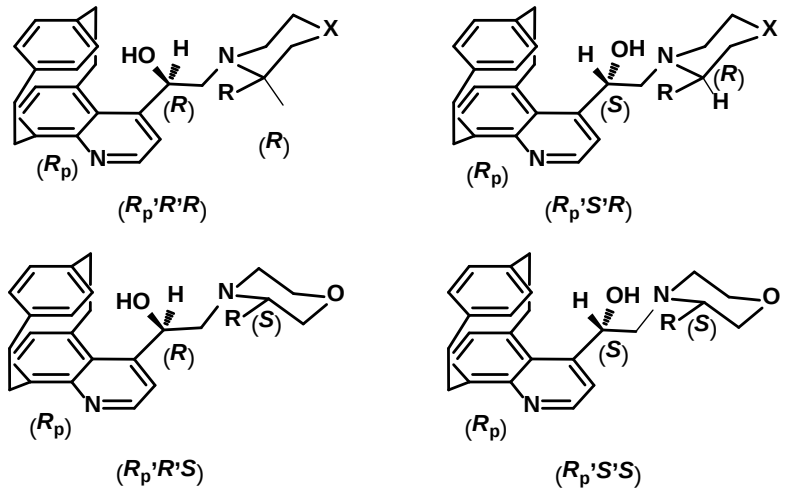


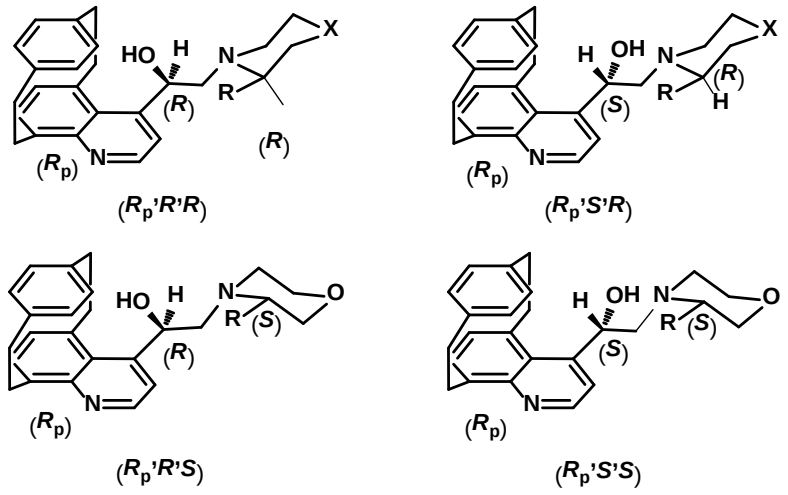
Figure 1. (*R*)-[2]paracyclo[2](5,8)quinolinophane derivatives exhibiting both type of chirality

Key word: organocatalysis, cinchona analogues, asymmetric induction, chirality

SAŽETAK RADA

Cilj ovog rada bio je sintetizirati kiralne analoge cinhonoidina, [2]paraciklo(5,8)kinolinofane i kinolinske organokatalizatore koji bi se mogli koristiti u stereoselektivnim sintezama. Zbog prisutnosti kinolinskog sustava molekula kinolinofana je izvrstan *building block* za sintezu kiralnih *cinchona* analoga kao potencijalnih organokatalizatora. Drugim riječima, dovoljno je uvesti u molekulu tercijarnu amino skupinu i kiralni ugljik vezan na hidroksilnu skupinu, čime se dobije molekula koja ima sve elemente kiralnosti kao prirodni cinchonoidi. Jedina razlika je u tome što je centralna kiralnost povezana s kinuklidinskim prstenom cinchonoida zamjenjena planarnom kiralnošću kinolinofanskog sustava. Nadalje, kinolinofan predstavlja kiralni *building block* izuzetne raznovrsnosti. U stvari, jednostavnim transformacijama moguće je dobiti različite strukturne kombinacije u kojoj su utvrđeni elementi za asimetričnu indukciju (tercijarna amino skupina, hidroksilirani kiralni ugljik, planarni kiralni sustav).

Imajući to na umu, opseg je utvrditi doprinos planarne i središnje kiralnosti (*R*)-[2]paraciklo[2](5,8)kinolinofanskih derivata koji pokazuju oba tipa kiralnosti u asimetričnoj indukciji (Slika 1). Radi usporedbe pripremljeni su i kiralni (*S*)- i (*R*)-trifluorometilsulfoksiamidi izvedeni iz 4-bromkinolina.



Slika 1. (*R*)-[2]paraciklo[2](5,8)kinolinofanski derivati s planarnom i centralnom kiralnošću

Ključne riječi: organokataliza, *cinchona* analozi, asimetrična indukcija, kiralnost

CONTENTS

1. INTRODUCTION

Chirality is one of the most important features of many organic compounds and is of fundamental importance, particularly in biological chemistry. Two enantiomers can exhibit completely different biological activities with sometimes opposed and even dangerous effects. Therefore, it's not surprising that since Van't Hoff's discovery of chirality, the research in this area has been largely directed to the synthesis of chiral organic molecules in optically pure form. However, the imitation of nature, which usually produces chiral molecules of absolute optical purity, is an arduous task and the road to acceptable results in the synthesis of chiral molecules is long and extremely circuitous. There are several methods to obtain optically pure molecules, each with its advantages and disadvantages (Figure 2).[1]

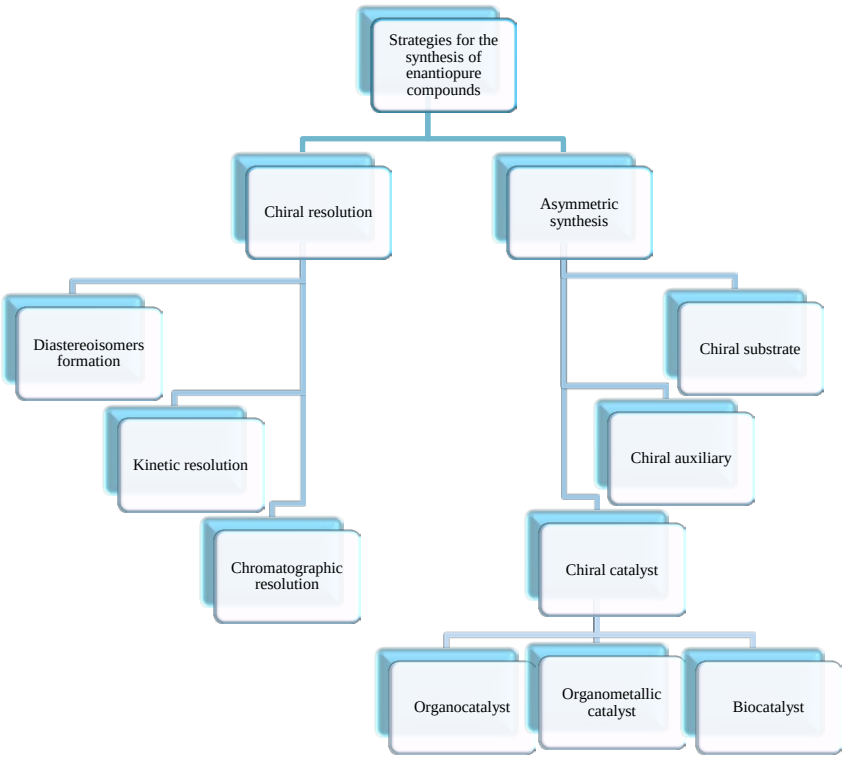


Figure 2. Methods for optically pure obtained molecules

Chiral resolution consists of the resolution of racemic mixtures through the formation of diastereomeric compounds and salts obtained by reacting the racemate with reagents, typically bases or chiral acids. In such way, diastereomeric compounds are formed and can be isolated by fractional crystallization or chromatographic methods, by which it is possible to obtain the enantiomers in optically pure form. Obviously, the major disadvantage of this method is the low yield of one enantiomer that can only reach a maximum of 50%. The use of chiral auxiliaries, optically pure molecules of natural or synthetic origin, which are covalently bonded to a substrate with prochiral elements and are able to induce in it with a certain degree

of enantioselectivity, allows reaching results sometimes appreciable in the synthesis of chiral molecules. One method that still may be advantageous consists of preparing chiral compounds of a certain complexity using as "building block" simple molecules of absolute optical purity, generally natural products such as amino acids, tartaric acid etc. Obviously such a method is limited by the availability of different chiral building block. Among the various enantioselective processes, those catalyzed by chiral complexes of transition metals have dominated for decades in the field of asymmetric synthesis. This has stimulated the development of a myriad of chiral ligands, both of natural origin (amino acids, terpenoids) and synthetic, that combined with different transition metals have provided a myriad of chiral catalysts suitable for any class of reaction – from nucleophilic substitutions to electrophilic aromatic substitutions, from electrophilic additions to nucleophilic addition, from Diels-Alder reactions to metathesis reactions. However, this type of catalysis, although it in many cases provides an excellent results of enantioselectivity, carries the drawback of excessive costs, due to both extremely complex synthetic ligands and the presence of a rather expensive metals, such as palladium, platinum, ruthenium and recently, gold. But, above all, the toxicity of the latter, even if they are present in traces, make these processes little appreciable, especially in pharmaceutical chemistry.[2] Moreover, the majority of organometallic catalysts are sensitive to moisture and/or oxygen what leads to difficulties in their use and storage, and also generates environmental pollution and bioaccumulation.[3] To overcome these inconveniences, since long, researchers resorted to the enzymatic catalysis by developing the techniques that allowed isolating and using enzymes, either free or supported on organic materials, for easy recover and reuse. They do not involve environmental problems because they can be easily degraded, but they require very controlled and restricted experimental conditions of usage. In addition, each enzyme is capable of catalyzing only well defined reactions.[1]

This has prompted many researchers to a new frontier of asymmetric synthesis which bases its development in the imitation of nature, in particular enzymes, employing low molecular weight chiral organic molecules as catalysts which are able to perform a wide range of enantioselective reactions – this strategy goes by the name *organocatalysis*.[4]

2. THEORETICAL PART

2.1. THE ORGANOCATALYSIS

There are several ways by which an organocatalyst carries on its activities[4]:

- covalent binding to the substrate by generating a reactive intermediate capable of evolving to product (Figure 3);
- stabilization of the transition state in a chiral pocket through weak interactions such as hydrogen bonds;
- operating as a phase transfer catalyst, a chiral "shuttle" able to carry only one enantiomer in the reaction environment from different phase.

In the second type of catalysis, the substrate that has a prochiral centre is temporarily tied to the catalyst and is fixed in a chiral pocket in such a way to favour a particular trajectory of the reaction with respect to the other possibility.[4]

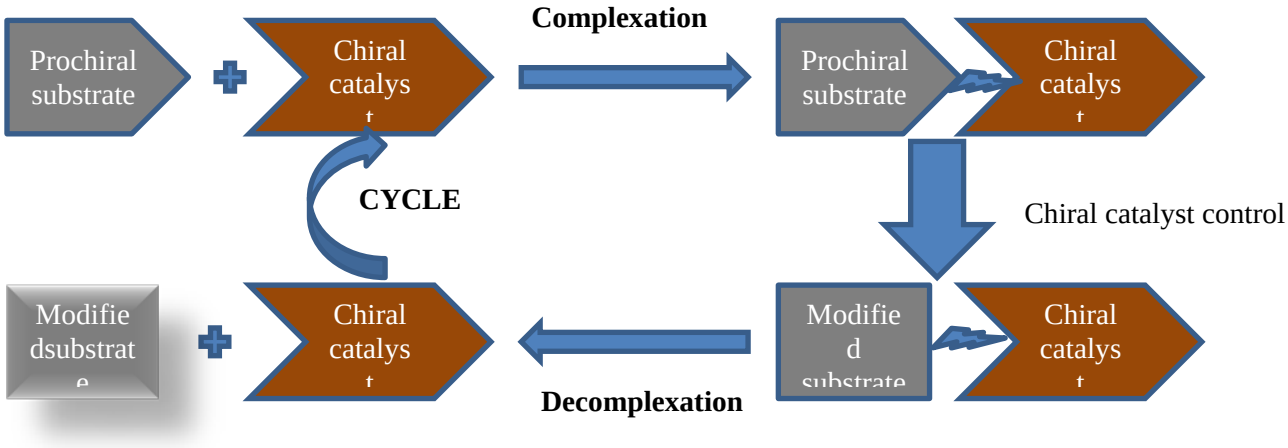


Figure 3. The mechanism of a chiral catalyst bonded to a prochiral substrate

2.2. THE MECHANISM OF "DUAL ACTIVATION"

Firstly, the construction of enantiomerically pure molecules contemplates two fundamental aspects: the formation of carbon-carbon bonds (or carbon-heteroatom), and the generation of stereogenic centres on the correctly oriented formed bonds. In most cases the assembly of complex molecules is performed by using the reagents with discriminating electronic properties, either electrophilic or nucleophilic. Therefore, "dual activation" term stays for the simultaneous activation of both nucleophilic and electrophilic species by two catalytic functionalities present in the same molecule of the chiral organocatalyst. The consequence is an increase in the reaction efficiency and chemoselectivity (Figure 4). In this way, the two reaction partners are in such a close proximity in order to compel the transition state where is assumed a well-defined geometry. The decrease of the degrees of freedom in

the transition state causes a reduction of activation entropy of the process, especially in the least favourable transition state.[5]

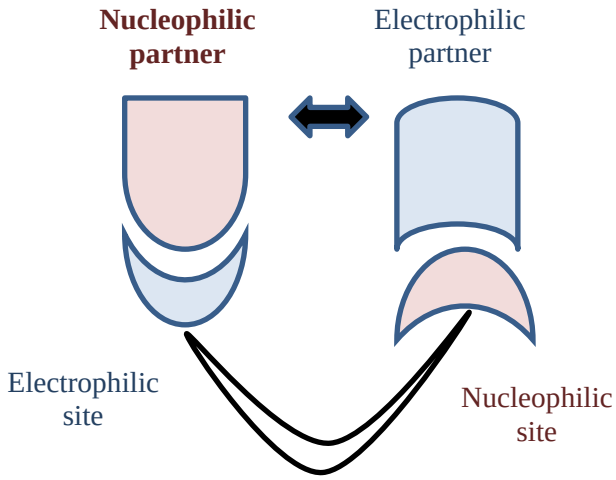


Figure 4. The concept of "dual activation"

In effort to imitate nature, the first studied organocatalysts were certain amino acids, either because of their structural simplicity, or for their abundance in nature in optically pure form. Among these, L-proline and its derivatives were the most used organocatalysts in the reactions of aldol condensation and in the Mannich type reactions of aldehydes and ketones. The following diagram (Figure 5) illustrates the mechanism of a proline derivative action in a typical aldol condensation. According to the universally accepted mechanism, nitrogen pyrrolidine (nucleophile) attacks the carbonyl carbon (electrophile) of ketone generating a nucleophilic enamine that can attack an electrophilic centre, as is the carbonyl of aldehyde.[6]

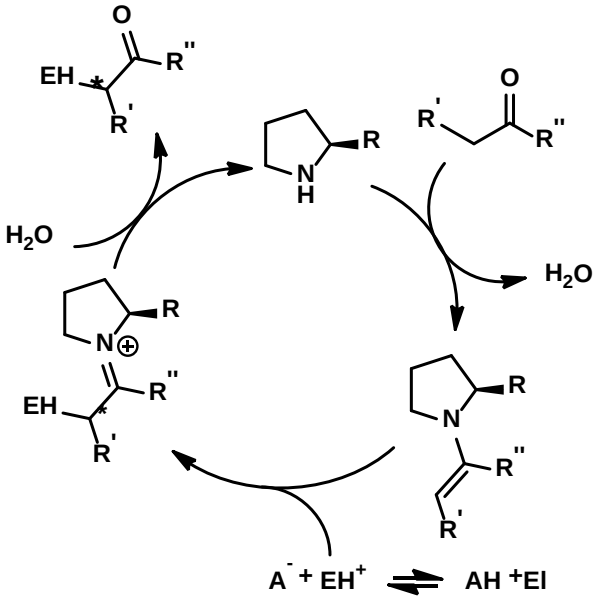


Figure 5. Catalytic mechanism of proline

Therefore, in the transition state, proline binds simultaneously to both, the nucleophile (with covalent bond to the nitrogen) and electrophile (through a hydrogen bond with the carboxyl group).[6]

However, List, Houk and co-workers in 2003 have shown that these catalysts effect, indeed, a double concerted activation.[7] Furthermore, in addition to the activation of the ketone via enamminic intermediate by the pyrrolidine nitrogen mentioned above, the carboxyl functionality of the proline is able to generate a hydrogen bond with the carbonylic/aldehydic oxygen, making, in this way, bigger electrophilic character of the carbonylic carbon (Figure 6).[8]

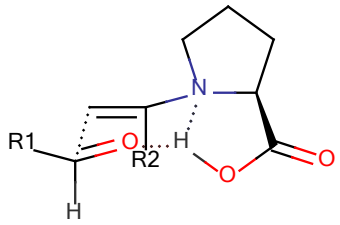


Figure 6. State transition of an aldol condensation catalysed by proline

2.3. CINCHONA ALKALOIDS AS ORGANOCATALYSTS

Since the seventeenth century, some natural alkaloids extracted from the bark of a tree-like plant of the family *Rubiaceae*, called Cinchona, are used as antimalarials, antineoplastics, analgesics, germicides, fungicides, and insecticides, antibacterial and as flavourings in bitter drinks.[9] Although it's known about existence of thirty different natural alkaloids, those which exhibit a marked biological activity are only four: quinine, quinidine, cinchonine and cinchonidine (Figure 7). The quinine was isolated for the first time in 1820 by Pelletier and Caventou, and its structure was determined by Rabe in 1907 and confirmed in 1967 from X-ray crystallography studies. It has been completely synthesized for the first time by Stork in 2001.[10]

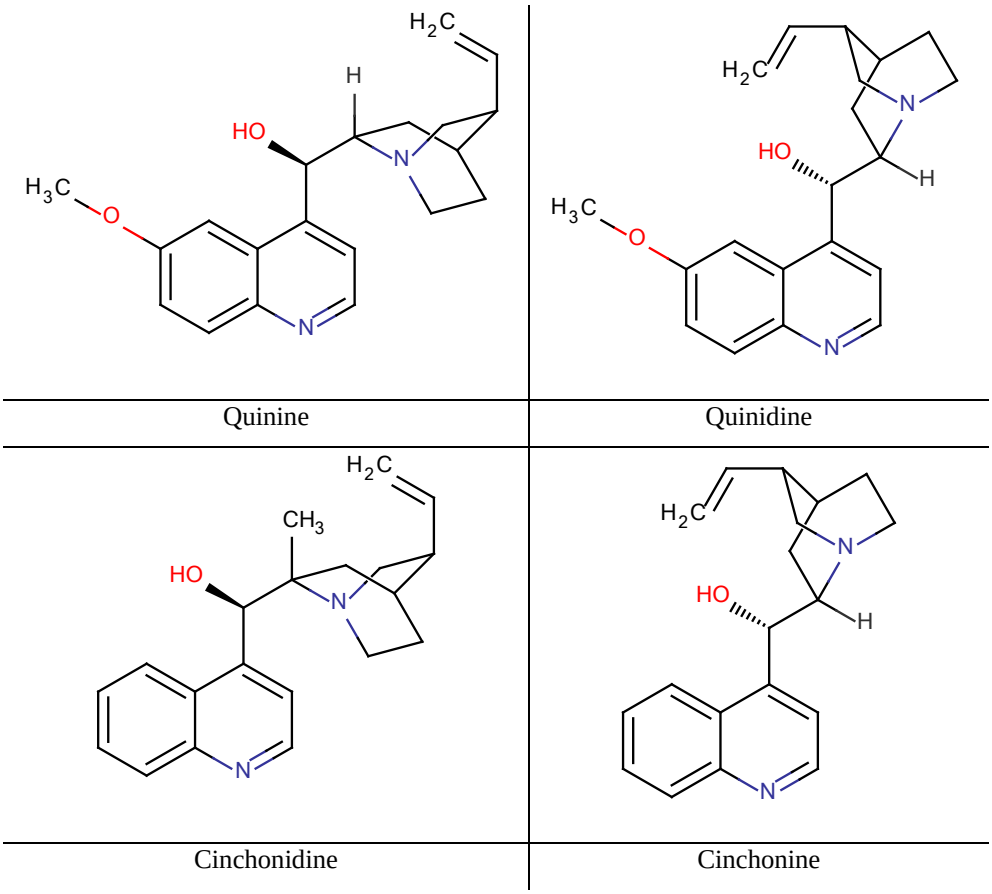


Figure 7. The four best-known alkaloids extracted from the cinchona

The chiral properties of these molecules have been known since 1853, but only since in the '80-ies were considered as possible chiral auxiliaries, and above all, as catalysts in asymmetric synthesis. In the last decade, these compounds have met with considerable success as organocatalysts of a multitude of stereoselective reactions. The advantages attributable to them are different. In fact, they are stable, can be easily found in nature and modified according to the catalytic applications for which they are intended. All these molecules contain a quinuclidine ring with the tertiary nitrogen as the basic centre, a secondary alcohol group which acts as a quinolinic acid, and all three parts are bound to a chiral carbon of well-defined configuration (C-9), as it's shown on Figure 8. There are four more stereocentres C-3, C-4, N-1, and C-8. The four alkaloids are different because of the presence of a methoxy group on the homocyclic ring of quinoline and the configuration of carbon linked to hydroxyl group, while the absolute configuration of the centres C-3, C-4 and N-1 remains unchanged.[9] The absolute configuration of the quinine is (1*S*,3*R*,4*S*,8*S*,9*R*) while that of quinidine is (1*S*,3*R*,4*S*,8*R*,9*S*). Although being diastereoisomers, they behave as enantiomers; in fact, the enantioselective reactions catalyzed by them provide mixtures of scalemic products with the same value of enantiomeric excess (*ee*). This could mean that the

configuration at the C-3 does not have any implications on the enantioselectivity of a reaction catalyzed by these compounds.[11]

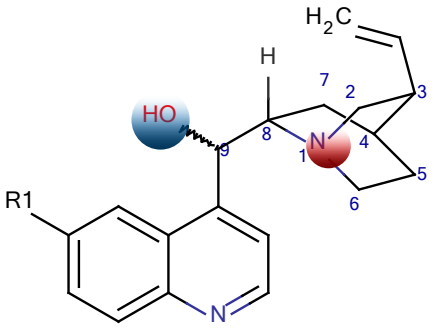


Figure 8. Structural characteristics of cinchonoids (with acidic OH and basic N portion)

In order to elucidate the mechanism of enantioselective catalysis by these cinchonoids it is appropriate to make some considerations about their structure, both on configurational and conformational level[9]:

- The relative positions of the two rings generate a pocket chiral similar to the active site of an enzyme;
- The rotation around the bonds that bind the two carbon ring bearing the hydroxyl group creates a dynamic environment where are possible different conformations, each with a different capacity of asymmetric induction. Dijkastra and collaborators, by means of NMR analysis, have found that the quinidine can assume four different conformations (Figure 9) and that the stability of a conformation depends on the nature of the substituents linked to the C-9. Thus, for example, by replacing the hydroxyl functionality with an ester it is observed that the most stable conformation is the anti-closed, while if substituted with a methoxy group the most stable is the anti-open conformation. The substituent at C-9 plays a vital role in determining the population of the different conformations in solution;
- The conformation adopted by the molecule is affected by the substituent groups R1 and R2 of the quinoline and quinuclidine rings, for which, modulating their size, is observed a substantial variation of the rigidity of the molecule that is reflected in enantioselectivity of the organocatalyzed reaction;
- In the water, the tertiary nitrogen of the quinuclidine ring has a pKa three times higher than that of the quinoline nitrogen, and for this reason it can serve either as binding site in the processes catalyzed by transition metals, either as reactive centre capable of activating reaction partners;

- The ring of the quinoline constitutes a second site with binding potential that can be used to anchor the molecule on a solid support for heterogeneous catalysis and, being a site electron donor, it can act as a ligand for molecules in complexes with electron deficient transition metal;
- The configuration of the chiral centre of the product obtained by prochiral reaction partner is determined by the absolute configuration at carbon C-9, and both epimers at C-9 exhibit very similar stereoselectivity.[9]

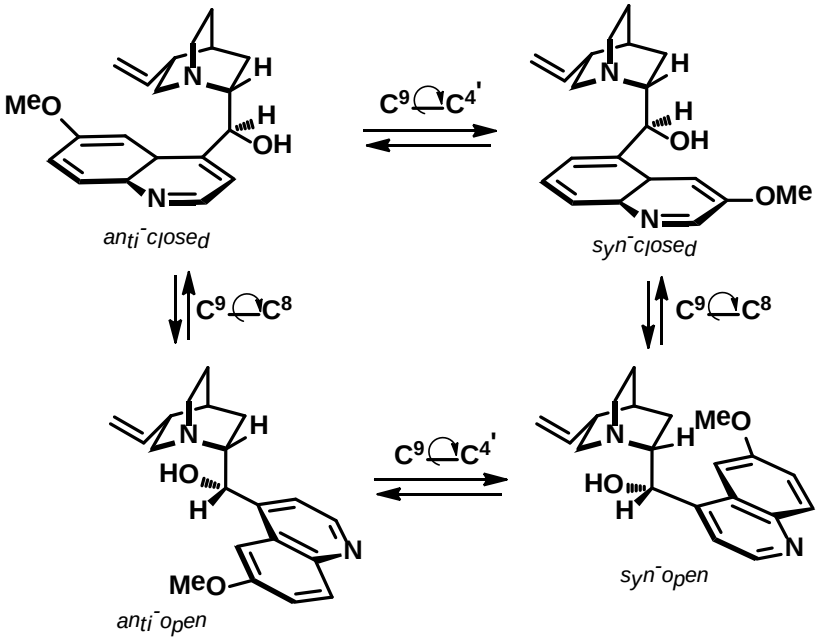


Figure 9. Four different conformations of the quinidine

As it was observed in the case of L-proline, also Cinchona alkaloids implement "dual activation" catalysis in which the hydroxyl group at C-9 acts as an Brønsted acid able to coordinate by hydrogen bond a basic centre of one of the reaction partners by activating the electrophilic site. Meanwhile, the nitrogen atom of the quinuclidine ring is able to perform a general basic catalysis by activating the nucleophilic species. These two synergetic effects are able to pre-arrange and orient the reagents towards the diastereoisomeric transition state of less energy. A very important observation on the catalysis mechanism was performed by Cucinotta and collaborators, who have observed that by replacing the hydroxyl group at C-9 with a group OCH_3 or using solvents capable of forming hydrogen bonds with the catalyst (methanol, ethanol, tetrahydrofuran, acetonitrile...), there is a drastic loss in enantioselectivity, which confirms the role of hydrogen bond to the asymmetric induction.[12]

2.4. THE QUINOLINOPHANE AS IMPORTANT BUILDING BLOCK FOR THE SYNTHESIS OF ORGANOCATALYSTS

The research group where this thesis has been carried out has a decade of experience in the application of derivatives of [2.2]paracyclophane as chiral ligands with transition metals used as catalysts in enantioselective reactions. In 2005 in this laboratory has been developed a strategy of synthesis of 2,4-dimethyl[2]paracyclo[2](5.8)quinolinophane, optically pure in large scale. Both enantiomers of this compound have been used as building block for the synthesis of new chiral bidentate ligands of the type *NO*, *NP*, *NN* (Figure 10).[13]

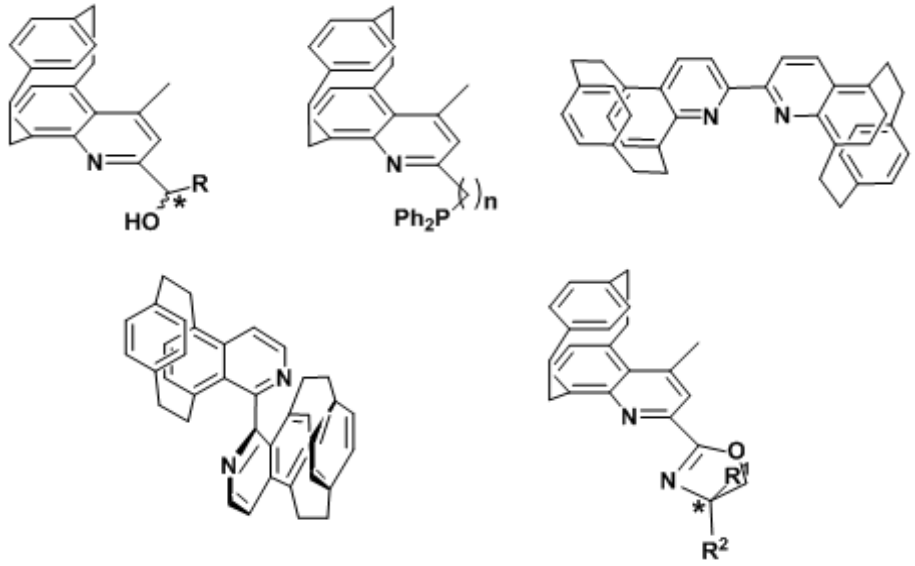


Figure 10. Some bidentate ligands derived from quinolinophane prepared in laboratory mentioned above

NO type of ligands has been successfully used in the enantioselective addition of diethyl zinc to aldehydes to give 1-phenilpropanoles with *ee* up to 99%. In this specific case, it is proper to mention important effects of *matching* and *mismatching* between the planar chirality of the quinolinophane system and the central chirality due to the presence of the stereogenic carbon in the side chain linked to the hydroxyl group on the asymmetric induction (Figure 10). Ligands with configuration (R_p,*R*) provide significantly lower *ee* than those provided by the ligand with only planar chirality (R = H), while the corresponding epimeric carbon (R_p,*S*) provide 1-arylpropanoles up to 99% *ee*.[11]

3. EXPERIMENTAL PART

3.1. GENERAL PROCEDURE

Most of the reagents and solvents were purchased from Aldrich chemicals and used without purification. Unless indicated, all anhydrous solvents were distilled under nitrogen condition. All reactions were performed under nitrogen/argon atmosphere.

Diethyl ether and tetrahydrofuran were dried by 3 hours reflux over NaOH, distilled the first time in the presence of CuCl and the second time after 3 hours reflux over sodium wires in the presence of benzophenone. 1,2-Dichloroethane and dichloromethane were distilled after 3 hours of refluxing over P_2O_5.

A concentration (1.5 M in hexane) of *tert*-butyllithium was determined by the method of double titration. The procedure is following: in a flask that contained approximately 50 mL of water and ice was added 5 mL of the solution of tert-butyllithium in hexane, and the resulting mixture was titrated with a solution of 0.1 N sulphuric acid using phenolphthalein as the indicator. The volume of sulphuric acid (V_1) necessary for determining the total basicity of *n*-butyllithium was calculated as follows:

$$\text{Total basicity} = \frac{V_1 \times 0.1}{5}$$

In the solution of 1,2-dibromoethane in 10 mL of anhydrous ethyl ether, 5 mL of the solution of *tert*-butyllithium in hexane was added under nitrogen at 0°C. The ice bath was removed and the reaction occurred at room temperature for 20 min. The solution was poured in 50 mL of ice water and titrated with 0.1 N sulphuric acid in the presence of phenolphthalein as indicator. The volume of sulphuric acid needed to neutralize non-organometallic basic impurities (mainly LiH, LiOH, and Li2CO3) was registered and the concentration of *tert*-butyllithium was calculated according to the formula:

$$\text{Concentracion} = \frac{(V_1 - V_2) \times 0.1}{5}$$

Column chromatography was performed using silica gel 60 (230-400 mesh, Merck) with the indicated eluents. Progress of reactions was checked by thin-layer chromatography (TLC), which was performed using Kieselgel 60F-254 plates (Merck) with the indicated solvents. For the compounds detection was used UV light with length of 254 nm.

For the identification of synthesised compounds NMR spectra were recorded on a Brucker spectrometer (^{1}H 400 MHz, ^{13}C 100 MHz, ^{19}F 376 MHz) in $CDCl_3$, or in the case of poorly soluble products DMSO-d6 was used. Chemical shifts are expressed in *parts per million* (ppm, δ) relative to an internal standard. ^{1}H NMR data are reported in the order of

chemical shifts, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet and/or multiple resonances), number of protons and coupling constant in hertz (Hz).

The GC-MS analysis was performed on a capillary column 25 m HPSMS from the mass spectrum was recorded at 70 eV.

The melting points of solid compounds were determined by instrument Büchi 535, and were corrected being determined after thermometer calibration with known melting point standards.

The optical rotation was measured with JASCO Dip 360 apparatus in a chloroform solution.

3.2. PREPARATION OF THE COMPOUNDS

(*R*)-3-Acetyl-2-amino[2.2]paracyclophane (1)

To a solution of boron trichloride (8.96 mL, 8.96 mmol, 1M solution in dichloromethane) was added a solution of 4-amino[2.2]paracyclophane (1.00 g, 4.48 mmol) in 1,2-dichloromethane (7 mL) at 0°C. To the mixture was added aluminium chloride (0.66 mg, 4.93 mmol) and acetonitrile (0.47 mL, 8.96 mmol) and the mixture was stirred under reflux temperature for 20 h. After the reaction was completed, the reaction mixture was cooled to 0°C, and then 2N HCl was added. The mixture was stirred at 80°C for 30 min. The reaction mixture was extracted with dichloromethane. The organic layer was washed with 1 N NaOH and brine, dried over anhydrous Na_2SO_4, and concentrated in *vacuo* to give a yellow solid **1** (663.0 mg; 56%), mp=136-138°C

(*R*)-[2]Paracyclo[2](5,8)quinolinophane-4-one (2)

Sodium (59.3 mg, 2.58 mmol) was added to a solution of compound **1** (645.3 mg, 2.43 mmol) in an excess of ethyl formate (8 mL), and the reaction mixture was stirred at reflux temperature under a nitrogen atmosphere. After 6 h, methanol (3 mL) was added to the reaction mixture to destroy the remaining sodium and the mixture was poured into water (15 mL) and ice (8 g). The organic layer was extracted with ethyl acetate, dried over anhydrous Na_2SO_4, and the solvent evaporated to dryness. The residue was purified by flash chromatography column using a mixture of dichloromethane:acetone=6:1 as eluents. The solvent was evaporated to dryness to give a brown solid **2** (73.7 mg; 11%), mp=164-166°C

(*R*)-4-Bromo-[2]paracyclo[2](5,8)quinolinophane (3)

To a stirred solution of compound **2** (73.7 mg, 0.27 mmol) in *N*,*N*-dimethylformamide (0.5 mL) phosphorus tribromide (0.03 mL, 0.27 mmol) was added portion-wise at ambient temperature. The reaction mixture was stirred for 1 h and quenched with water. The resulting mixture was extracted; organic layer was dried over Na_2SO_4, filtered and concentrated to give a brown solid. Chromatography of the crude on silica gel (eluents, petroleum ether:diethyl ether=8:2) afforded pure brown compound **3** (73.0 mg; 80%), mp=214-216°C

4-(2,2-Dimethoxyethyl)morpholine (4)

Colourless oil **4** (5.66 g; 6%) was prepared by stirring a mixture of morpholine (17.49 mL, 0.2 mol) and bromoacetaldehyde diethyl acetal (11.82 mL, 0.1 mol) in methanol (30 mL) for 18 h

at 50-60°C. Methanol was distilled, the residue was taken up with diethyl ether and extracted with diluted cold 5N NaOH. Diethyl ether was evaporated at reduced pressure.

2-Chloro-*N*-[(1*S*)-2-hydroxy-1-phenylethyl]acetamide (5)

A saturated solution of K_2CO_3 (3.11 g, 22.47 mmol) was added to (2*S*)-2-amino-2-phenylethan-1-ol (1.03 g, 7.49 mmol) in tetrahydrofuran (28 mL) at –10°C. Chloroacetyl chloride (1.19 mL, 8.24 mmol) was added from a syringe with vigorous stirring, and the mixture was stirred at –10 °C for 1 h. After evaporation of tetrahydrofuran the mixture was extracted with ethyl acetate. The organic layer was separated, dried over Na_2SO_4, filtered, and concentrated to give colourless oil **5** (1.61 g; 99%)

2-Chloro-*N*-[(1*R*)-2-hydroxy-1-phenylethyl]acetamide (6)

A saturated solution of K_2CO_3 (4.78 g, 34.56 mmol) was added to (2R)-2-amino-2-phenylethan-1-ol (1.58 g, 11.52 mmol) in tetrahydrofuran (43 mL) at –10°C. Chloroacetyl chloride (1.83 mL, 12.67 mmol) was added from a syringe with vigorous stirring, and the mixture was stirred at –10 °C for 1 h. After evaporation of tetrahydrofuran the mixture was extracted with ethyl acetate. The organic layer was separated, dried over Na_2SO_4, filtered, and concentrated to give colourless oil **6** (2.20 g; 89%)

(5*S*)-5-Phenylmorpholin-3-one (7)

A solution of potassium *tert*-butoxide (3.32 g, 29.60 mmol) in *iso*-propanol (75 mL) was added drop-wise to a solution of compound **5** (1.61 g, 7.40 mmol) in dichloromethane (75 mL) at 0°C. The solution was stirred at room temperature for 1 h then neutralized by slow addition of 2M HCl. The solvent was removed under reduced pressure to give a white solid and the solid was taken up in ethyl acetate. The organic layer was separated, dried over Na_2SO_4, filtered, and concentrated to give colourless oil **7** (655.0 mg; 50%)

(5*R*)-5-Phenylmorpholin-3-one (8)

A solution of potassium *tert*-butoxide (4.62 g, 41.20 mmol) in *iso*-propanol (103 mL) was added drop-wise to a solution of compound **6** (2.20 g, 10.30 mmol) in dichloromethane (103 mL) at 0°C. The solution was stirred at room temperature for 1 h then neutralized by slow addition of 2M HCl. The solvent was removed under reduced pressure to give a white solid and the solid was taken up in ethyl acetate. The organic layer was separated, dried over Na_2SO_4, filtered, and concentrated to give colourless oil **8** (1.59 g; 87%)

(3*S*)-3-Phenylmorpholine (9)

To a solution of compound **7** (655.0 mg, 3.70 mmol) in tetrahydrofuran (15 mL) cooled in an ice bath was added lithium aluminium hydride (280.5 mg, 7.40 mmol) in tetrahydrofuran (2 mL) slowly over 5 min. On complete addition mixture was warmed to reflux temperature and stirred for 7 h. The reaction mixture was cooled in the ice bath and ethyl acetate (1 mL) was slowly added, and the resulting mixture was stirred for 30 min at room temperature. In mixture were added small amount of water until no vigorous reaction occurred, and methanol (1 mL), followed by a small amount of 5M NaOH to make mixture basic. The mixture was filtered through celite, washing through with methanol, and filtered in *vacuo* to give solidified on standing yellow oil **9** (366.5 mg; 61%)

(3*S*)-3-Phenylmorpholine (10)

To a solution of compound **8** (1.59 g, 8.99 mmol) in tetrahydrofuran (36 mL) cooled in an ice bath was added lithium aluminium hydride (682.3 mg, 17.98 mmol) in tetrahydrofuran (6 mL) slowly over 5 min. On complete addition mixture was warmed to reflux temperature and stirred for 7 hour. The reaction mixture was cooled in the ice bath and ethyl acetate (3 mL) was slowly added, and the resulting mixture was stirred for 30 min at room temperature. In mixture were added small amount of water until no vigorous reaction occurred, and methanol (3 mL), followed by a small amount of 5M NaOH to make mixture basic. The mixture was filtered through celite, washing through with methanol, and filtered in *vacuo* to give solidified on standing yellow oil **10** (1.12 g; 76%)

4-Bromoquinoline (11)

To a suspension of the requisite 4-hydroxyquinoline (3.68 g, 25.32 mmol) in *N*,*N*-dimethylformamide (42 mL) phosphorus tribromide (2.4 mL, 25.32 mmol) was added portion-wise at ambient temperature. The resulting mixture was stirred for 1 h and quenched with water. The mixture was extracted, organic layer was dried over Na_2SO_4, filtered and concentrated to give the yellow oil **11** (4.90 g; 93%)

(*R*,*S*$_s$)- and **(*S*,*S*$_s$)-2-Methyl-*N*-[2,2,2-trifluoro-1-(quinolin-4-yl)ethyl]propane-2-sulfinamide (12** and **13)**

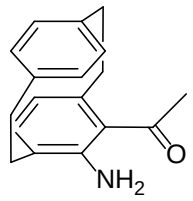
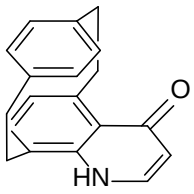
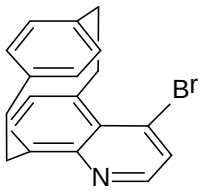
tert-Butyllithium (1.63 M in hexane, 3.00 mL, 4.89 mmol) was added drop-wise in 5 min to a solution of a 4-bromoquinoline (1.00 g, 4.81 mmol) in diethyl ether (22 mL) at -100°C. After

90 min of stirring at the same temperature a solution of (*S*)-trifluoromethylsulfoxyimide (1.00 g, 4.97 mmol) in diethyl ether (3 mL) was added, and the reaction mixture was stirred for another 90 mins. The cold bath was removed and the temperature was allowed to rise to 25°C before brine (25 mL) was added. The organic phase was separated and extracted with diethyl ether (3 × 25 mL), the collected organic phases were dried over Na_2SO_4 and the solvent was evaporated at reduced pressure. The crude product consisted of a mixture of two diastereomeric products in 8:2 molar ratio as determined by ^{19}F NMR analysis. Chromatography on silica gel (eluent mixture, diethyl ether:ethyl acetate=7:3) allowed to obtain a white solid (136.5 mg; 8.5%), mp>250°C as the first eluted product. The second eluted product was obtained as a yellow oily product (0.258 g; 2.1%).

(*R*,*R*$_S$)- and **(*S*,*R*$_S$)-2-Methyl-*N*-[2,2,2-trifluoro-1-(quinolin-4-yl)ethyl]propane-2-sulfinamide (14** and **15)**

tert-Butyllithium (1.63 M in hexane, 3.00 mL, 4.89 mmol) was added drop-wise in 5 min to a solution of a 4-bromoquinoline (1.00 g, 4.81 mmol) in diethyl ether (22 mL) at -100°C. After 90 min of stirring at the same temperature a solution of (*R*)-trifluoromethylsulfoxyimide (1.00 g, 4.97 mmol) in diethyl ether (3 mL) was added, and the reaction mixture was stirred for further 90 min. The cold bath was removed and the temperature was allowed to rise to 25°C before brine (25 mL) was added. The organic phase was separated and extracted with diethyl ether (3 × 25 mL), the collected organic phases were dried over Na_2SO_4 and the solvent was evaporated at reduced pressure. The crude product consisted of a mixture of two diastereomeric products in 8:2 molar ratio as determined by ^{19}F NMR analysis. Chromatography on silica gel (eluent mixture, diethyl ether:ethyl acetate mixture=7:3) allowed to obtain a white solid (1.03 g; 65%), mp>250°C, $[\alpha]_D^{24}$ = + 85 ($c = 0.5$, CH_3OH) as the first eluted product. The second eluted product was obtained as a yellow oily product (258.0 mg; 16%), $[\alpha]_D^{24}$ = - 201 ($c = 0.5$, CH_3OH).

3.3. STRUCTURES OF SYNTHESIZED COMPOUNDS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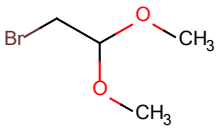
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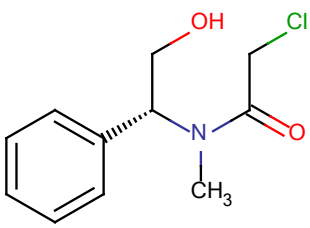	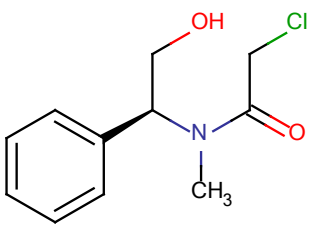
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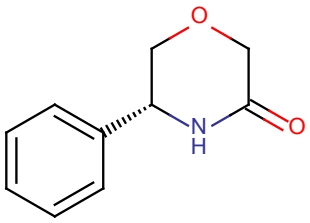	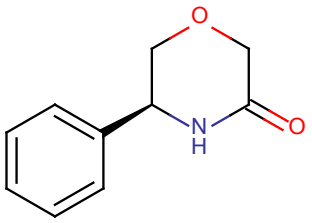
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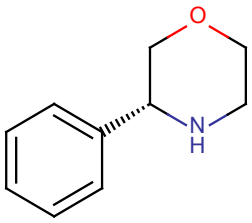
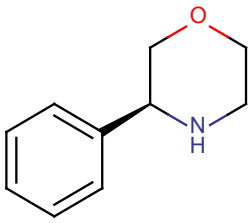
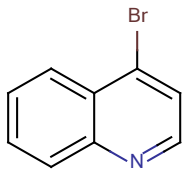
	
9	**10**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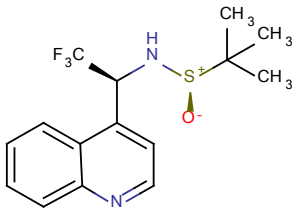
N

11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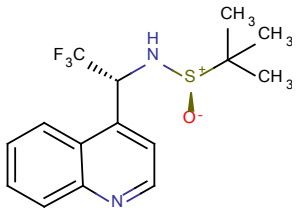
CH3
CH3
N

12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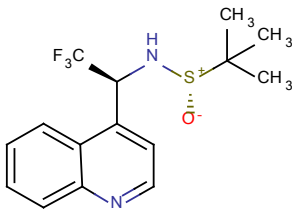
CH3
N

13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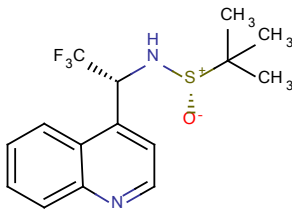
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N
S+
O-
CH3
CH3
CH3
N

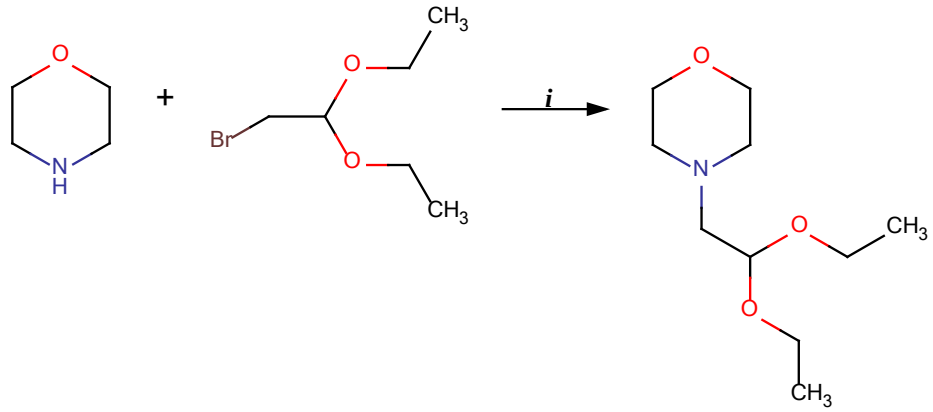
15

4. RESULTS AND DISCUSSION

4.1. SYNTHESIS OF THE COMPOUNDS

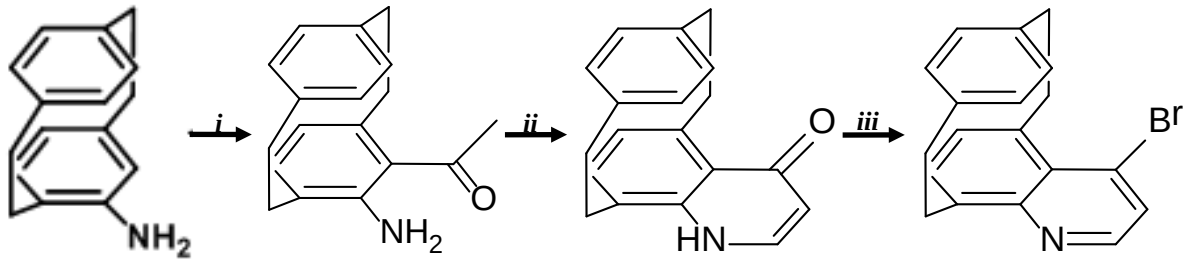
During this thesis work, an attention was focused on obtaining possible stereoisomerism out of coupling reactions of product **3** with products **9** and **10**, and furthermore, to achieve stereoisomeres in products **12** – **15.** For this purpose two different starting materials have been used – 4-amino[2.2]paracyclophane and 4-hydroxyquinoline.

Product **4** should have served as a model molecule for coupling reaction that could have been used in studying the effects of morpholine ring while coupled with paracyclophane system.



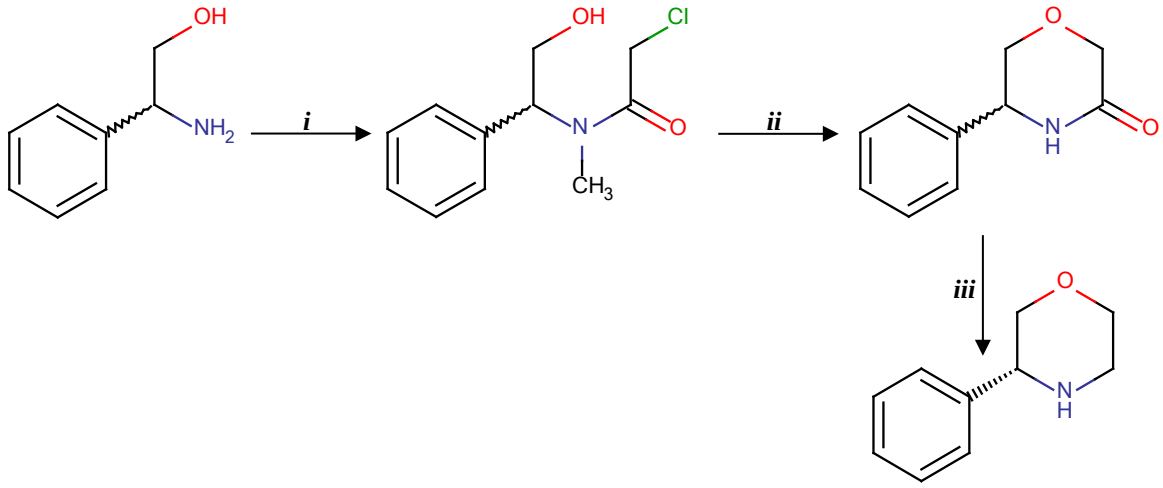
Scheme 1. *i*) methanole

The acetylation of 4-amino[2.2]paracyclophane with boron trichloride, catalyzed by $AlCl_3$ in dichloromethane at 0°C, provided the product **1**, with a yield of 56%. Later on, product **1** was subjected to the cyclization with ethyl formate in the presence of sodium at reflux temperature, and after purification, product **2** was obtained with a yield of 11%. Final step included bromination of product **2** with phosphorus tribromide at room temperature, where was obtained product **3** in a yield of 80%.



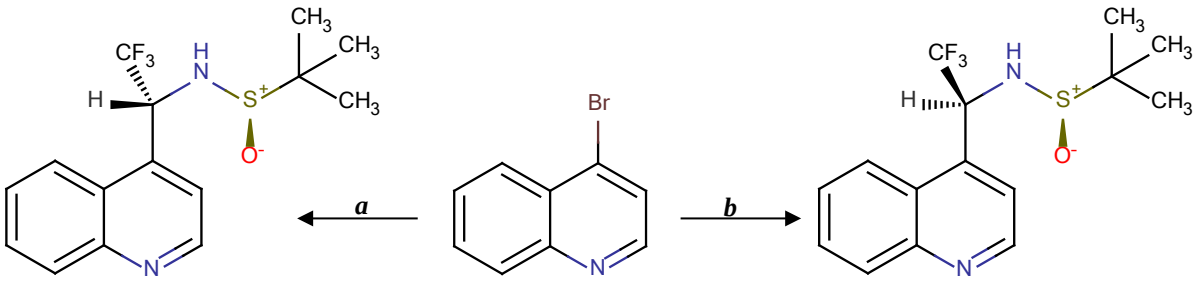
Scheme 2. *i*) 1 M solution of boron trichloride in dichloromethane, aluminium chloride, acetonitrile, dichloromethane; *ii*) ethyl formate, sodium; *iii*) phosphorus tribromide, *N*,*N*-dimethylformamide

Products **9** and **10** were obtained through a three-step reaction. First step included chloroacetylation of (*S*)- and (*R*)-2-amino-2-phenylethan-1-ol at -10°C, in a presence of K_2CO_3 as a base, which gave enantiomers **5** and **6**, in 99% and 89% of yield. Next step involved deprotonation of hydroxyl group with a strong alkoxide base, potassium *tert*-butoxide, and the ring closure with *iso*-propanol used as a solvent, which granted 50% yield of product **7** and 87% yield of product **8**. Last step covered reduction of carbonyl group with incremental addition of lithium aluminium hydride at 0°C, which finally gave products **9** and **10**, with a 61% and 76% yield, respectively.



Scheme 3. *i*) chloroacetyl chloride, K_2CO_3, tetrahydrofuran; *ii*) *iso*-propanol, potassium *tert*-butoxide, dichloromethane; *iii*) lithium aluminium hydride, tetrahydrofuran

As mentioned above, 4-hydroxyquinoline was used for preparing product **11** in a 93% yield, with phosphorus tribromide as bromination reagent. Obtained 4-bromoquinoline entered the metallation under -100°C in a solvent of low polarity, diethyl ether, with *tert*-butyl lithium which served as a deprotonating reagent. At the same temperature were added (*S*)- and (*R*)-trifluoromethyl-sulfoxyimide, which provided diastereomeric mixture of (*S*)- products **12** and **13**, and (*R*)- products **14** and **15**.



Scheme 4. *a)* (*S*)-trifluoromethylsulfoxyimide, *tert*-butyllithium, diethyl ether; *b*) (*R*)-trifluoromethylsulfoxyimide, *tert*-butyllithium, diethyl ether

4.2. ANALYSIS OF ^{1}H, ^{13}C AND ^{19}F NMR SPECTRA

The structures of the synthesized compounds **1-2**, **5-10**, **12-15** were determined on the basis of the chemical shift, the size of the signal and the multiplicity of spin-spin coupling between the nuclei of H-H. ^{1}H NMR spectra weren't recorded for compounds **4** and **11**, as these compounds have already been synthesized and characterized before, and the data is known. The chemical shifts and coupling constants in the ^{1}H and ^{13}C NMR spectra of the compounds **1-2** are shown in Table 1, ^{1}H NMR spectra for the compounds **5-10** in Table 2, and ^{1}H, ^{13}C and ^{19}F for the compounds **12-15** in Table 3.

Table 1. Chemical shifts (δ/ppm) and coupling constants (J/Hz) in ^{1}H and ^{13}C NMR spectra of compounds **1** and **2**

(R)-4-amino-5-acetyl[2.2]paracyclophane (1). ^{1}H NMR δ 7.11 (dd, J = 7.9 and 2.0,Hz, 1 H), 6.66 (dd, J = 7.6 and 1.6 Hz, 1 H), 6.49 (dd, J = 7.8 and 1.6 Hz, 1 H), 6.39 (bd, J = 7.5 Hz, 2 H), 6.21 (d, J = 7.5 Hz, 1 H), 3.4 (m, 1 H), 3.1 (Bs, 2 H), 3.0 (m, 5 H), 2.8 (m, 1 H), 2.7 (m, 1 H), 2.46 (s, 3 H). ^{13}C NMR δ 202.1, 148.3, 142.0, 138.6, 138.0 (2 C), 132.6, 131.9, 131.0, 126.9, 124.8 (2 C), 122.9, 36.9, 35.4, 32.8, 32.6, 32.0.
(*R*)-[2]paracyclo[2](5,8)quinolinophan-4(1*H*)-one (2). ^{1}H NMR (DMSO-d_6) δ 10.4 (bs, 1 H), δ 7.67 (d, J = 7.2 Hz, 1 H), 6.80 (d, J = 7.5 Hz, 1 H), 6.66 (d, J = 7.4 Hz, 1 H), 6.60 (dd, J = 7.9 and 1.4 Hz, 1 H), 6.44 (dd, J = 7.9 and 1.6 Hz, 1 H), 6.33 (d, J = 8.1 Hz, 1 H), 6.25 (d, J = 7.3 Hz, 1 H), 6.22 (dd, J = 8.1 and 1.4 Hz, 1 H), 4.81 (m, 1 H), 3.73 (m, 1 H), 3.23-2.87 (m, 6 H). ^{13}C NMR δ 189.9, 142.9, 141.1, 140.5, 139.6, 138.4, 137.7, 134.0, 133.1, 132.4, 130.2, 130.0, 129.8, 127.0, 117.8, 35.5, 34.0, 33.2, 31.3.

Table 2. Chemical shifts (δ/ppm) and coupling constants (J/Hz) in ^{1}H NMR spectra of compounds **5-10.**

(*R*)- and (*S*)-2-chloro-N-(2-hydroxy-1-phenylethyl)acetamide (5, 6). ^{1}H NMR δ 7.3 (m, 5 H), 5.09 (X portion of an ABX system, 1 H), 4.10 (AB system, JAB = 15 Hz, 2 H), 3.92 (d, J = 5 Hz, 2 H), 2.24 (bs, 1 H).
(*R*)- and (*S*)-5-phenylmorpholin-3-one (7, 8). ^{1}H NMR δ 7.3 (m, 5 H), 4.78 (dd, J = 8.8 and 4.0 Hz, 1 H), 4.37-4.24 (AB system, JAB = 16 Hz, 2 H), 4.07 (dd, J = 12 and 3.6 Hz, 1 H), 4.10 (AB system, JAB = 15 Hz, 2 H), 3.58 (dd, J = 12 and 8.0 Hz, 1 H), 6.12 (bs, 1 H).
(*R*)-and (*S*)-3-phenylmorpholine (9, 10). ^{1}H NMR δ 7.3 (m, 5 H), 3.8 (m, 1 H), 3.6 (m, 1 H), 3.42 (t, J = 10 Hz, 1 H), 3.15 (td, J = 11 and 3 Hz, 1 H), 3.02 bd, J = 11 Hz, 1 H) 2.1 (bs, 1 H).

Table 3. Chemical shifts (δ/ppm) and coupling constants (J/Hz) in ^{1}H, ^{13}C and ^{19}F NMR spectra of compounds **12-15**

(X,R_S)- and (Y,S_S)-*N*-[1-(quinolin-4-yl)-2,2,2-trifluoroethyl]-*tert*-butylsulfinamide (12, 14). First eluted product, white rombic crystals, ^{1}H NMR δ 9.03 (d, *J* = 4.6 Hz, 1 H), 8.25 (d, *J* = 8.5 Hz, 1 H), 8.14 (d, *J* = 8.6 Hz, 1 H), 7.83 (t, *J* = 8.1 Hz, 1 H), 7.70 (t, *J* = 8.2 Hz, 1 H), 7.65 (d, *J* = 4.6 Hz, 1 H), 5.80 (m, 1 H), 4.13 (bd, *J* = 4.1 Hz, 1 H), 1.26 (s, 9 H); ^{13}C NMR δ 149.6, 148.5, 137.9, 130.5, 130.0, 127.8, 126.6, 124.3 (q, *J* = 280 Hz), 122.6, 121.3, 56.9, 55.4 (broad), 22.3 (3 C); ^{19}F NMR δ –72.44 (bd, 3 F).
(Y,R_S)- and (X,S_S)-*N*-[1-(quinolin-4-yl)-2,2,2-trifluoroethyl]-*tert*-butylsulfinamide (13, 15). Second eluted product, yellow thick oil ^{1}H NMR δ 9.00 (d, *J* = 4.5 Hz, 1 H), 8.25 (d, *J* = 8.1 Hz, 1 H), 8.19 (d, *J* = 8.5 Hz, 1 H), 7.84 (t, *J* = 7.9 Hz, 1 H), 7.74 (t, *J* = 7.0 Hz, 1 H) 7.61 (d, *J* = 4.5 Hz, 1 H), 5.75 (quint, *J* = 6.7 Hz, 1 H), 3.99 (d, *J* = 6.4 Hz, 1 H), 1.28 (s, 9 H); ^{13}C NMR δ 149.3, 130.4, 130.2, 129.7, 128.2, 126.4, 125.7, 124.4 (q, *J* = 280 Hz), 122.5, 119.6, 57.4, 55.5 (q, *J* = 31 Hz) 22.3 (3 C); ^{19}F NMR δ –72.50 (d, *J* = 7.2 Hz, 3 F).

5. CONCLUSION

- Despite the difficulties encountered during the thesis work, a synthetic strategy for obtaining Cinchona–based derivatives, quinolinophane and quinoline, was developed
- The metallation of product **11** (exchange bromine/lithium) and subsequent reaction with (*S*)- and (*R*)-trifluoromethylsulfoxyimide gave successful results. Diastereomers products **12-15** were acquired in the reaction of product **11** with both (*S*)- and (*R*)-trifluoromethylsulfoxyimide under -100°C. In order to determine the exact configuration of these diastereomers, samples were sent to Prof. Abate, PhD in Brescia, to be analysed by circular dichroism
- The synthesis of the product **3** appears to be more problematic. Synthesis of the precursor, cyclised quinolinophane **4**, was problematic, and all attempts gave poor utilization. If the drastic reaction conditions were applied, it might lead to a polymerization of the products. In this case, the use of organometallic catalysts would, that already showed exemplary results for the synthesis of the compounds **12-15** would possibly achieve better results
- The structures of the prepared compounds were confirmed by spectroscopic methods ^{1}H, ^{13}C NMR and ^{19}F

6. LITERATURE

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7. CURRICULUM VITAE

Silvija Petlović was born on 25/3/1991 in Munich, Germany. She has finished both elementary school and high school in Zagreb. In 2009 she has been enrolled in Faculty of Chemical Engineering and Technology (Zagreb), course of Applied chemistry. In 2012 she participated in European Summer School of Electrochemical Engineering (Zadar). In 2013 she finished undergraduate study programme obtaining a bachelor degree in a field of organic chemistry by giving a presentation "Novel acyclonucleosides by click reactions". In 2013 she continued her studies as a graduate student in the same Faculty, course of Applied organic chemistry. In 2014 she participated in X. Meeting of Young Chemical Engineers (Zagreb) and Ion Chromatography School (Zagreb).