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An approach to an intramolecular organocatalysed asymmetric Friedel-Crafts reaction

Tesi di laurea sperimentale

CANDIDATO

Caterina Bacchelli

RELATORE

Chiar.mo Prof. Paolo Righi

CORRELATORE

Dr. Giorgio Bencivenni

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To my incredible classmates

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Abbreviations and synonims

9-amino(9-deoxy)epi-chinidine : (*S*)-(6-methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methanamine

9-epi-NH_2-Thiourea-QD : 1-(3,5-bis(trifluoromethyl)phenyl)-3-((1*R*)-(6-methoxyquinolin-4-yl)((2*R*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)thiourea

DCM : dichloromethane

THF : tetrahydrofuran

TBME : methyl tert-butyl ether

DMSO-d_6 : dimethylsulfoxide

TMS : tetramethylsilane

HPLC : high pressure liquid chromatography

TLC : thin layer chromatograpy

NMR : nuclear magnetic resolution

GC-MS : gas chromatography mass spectrometry

R.T. : room temperature

1. Introduction

1.1 Chirality and Asymmetric Synthesis

Chirality represents the property, for any object, of having a nonsuperimposable mirror image , the essential condition for a molecule to be chiral is the absence of any plane of symmetry.

Another important concept, is **prochirality**: one molecule is defined as prochiral if the molecule itself can be transformed from achiral to chiral after only one chemical step, such as in the transformation of 2-butanone to 2-butanol after the addition of hydrogen.

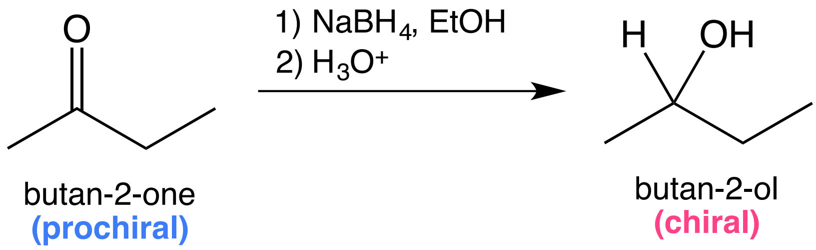

Fig. 1 Example of prochirality

A molecule like aldehyde cyanohydrin is chiral[1], it cannot have a plane of symmetry, because this molecule has a tetrahedral carbon that is bonded to four different groups, this carbon atom is known as stereogenic centre or chiral centre; within the structure of a chiral molecule there must be at least one stereogenic element, chirality is a property owned by the whole molecule, while a stereogenic element could be the cause of chirality itself.

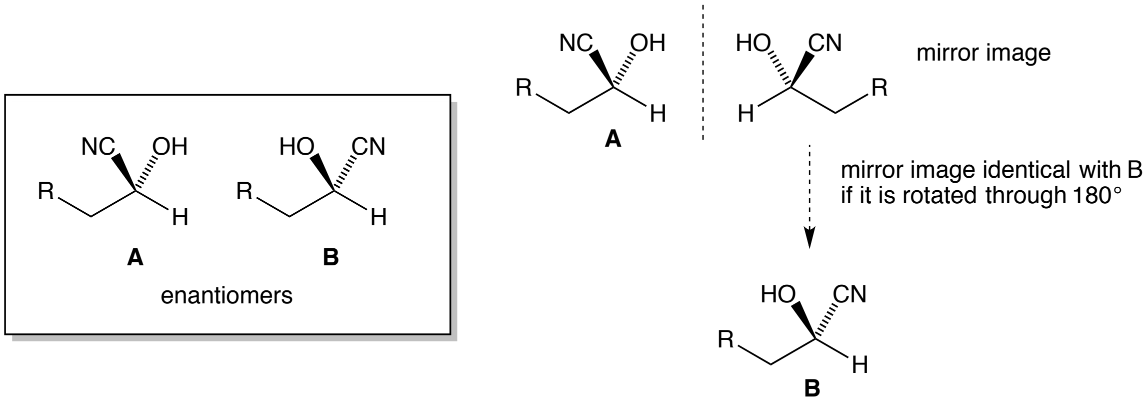

Fig. 2 Couple of enantiomers of aldehyde cyanohydrin

Two structures that have: the same connectivity of their atoms but two different spatial structures, are a particular type of isomers that are called stereoisomers. If two stereosiomers are mirror images of each other but are not identical, we call them **enantiomers**; enantiomers have: opposite configurations in every chiral centre (absolute stereochemistry), same chemical and physical properties but different specific rotation and biological properties.

Stereoisomers that are not mirror images of each other are **diastereoisomers**,; diastereoisomers present opposite configurations only in some chiral centres (relative stereochemistry), and different chemical and physical properties.

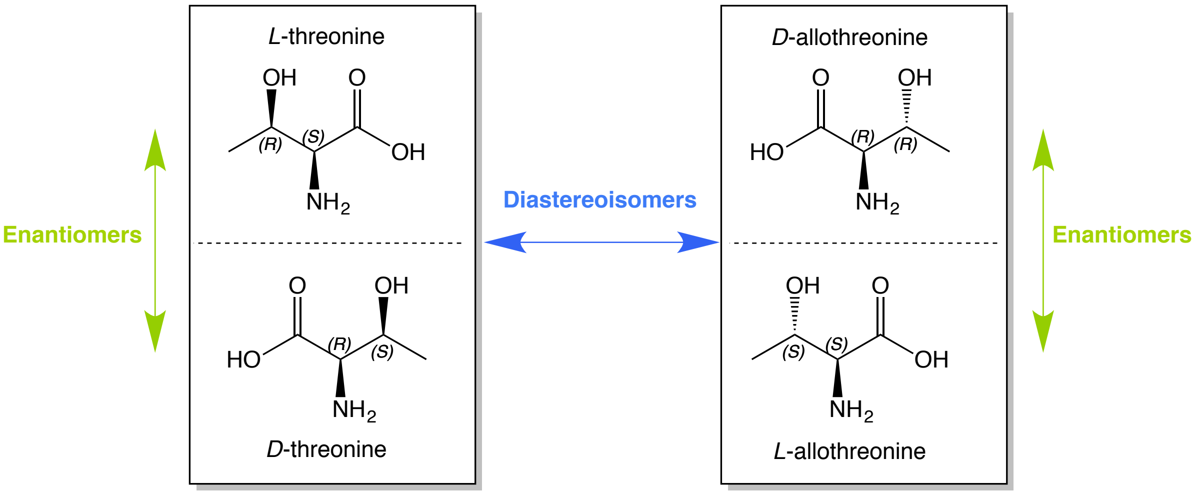

Fig. 3 Diastereoisomers and enantiomers of threonine

The importance of chirality has grown during the last decades, in particular: the preparation and study of this kind of products, their properties and applications, has begun to be reported in scientific literature. The majority of biomolecules has an inherent chirality, thus they present at least one stereogenic element that promotes the distinction of two optical isomers; the main interactions between molecules of biological interest are guided by a highly stereospecific recognition, for example, a chiral molecule with a certain biological activity must fit the shape of the target receptor, in that way it could carry out its action. This is the case of L-aminoacids and D-monosaccharides, that are found in the majority of biological organisms[2].

Obviously, since the biological properties owned by the two enantiomers of a given molecule are different, especially in the pharmaceutical field, we need to obtain just one enantiomer of an active ingredient, because the other enantiomer could be inactive, or worse, it could affect the pharmacological activity or it could be toxic for the organism.

The goal of this branch of chemistry is the synthesis of chiral molecules with certain functions and properties, in particular it would be very important the development of synthetic strategies to obtain enantiopure compounds since, as mentioned above, are needed in pharmaceuticals.

The main methods to get a single enantiomer of one molecule are: the resolution of a racemic mixture, synthesis from the chiral pool and the asymmetrical synthesis, which is divided into asymmetrical synthesis with chiral auxiliaries and reagents, and asymmetric catalysis.

In the first case, when we obtain a chiral product from achiral reagents, we will be in the presence of a racemic mixture that can be resolved into its components through the use of a enantiopure reagent; this molecule reacts with the substrate to give to diastereoisomers with different properties, in this way we can separate easily the diastereoisomers and, after other steps of reaction to restore the starting materials, we will have a new mixture enantioenriched in one of the two enantiomers.

The pharmaceutical industry currently realizes its chiral products mainly through racemic resolution or employing natural molecules from the chiral pool, molecules with defined chirality and commercially available, after some derivatizations we can obtain our products of interests.

The asymmetric synthesis promotes the direct preparation of enantioenriched, or enantiopure, compounds employing chiral auxiliaries that promote the synthesis of a single enantiomer. Chiral auxiliaries (chiral reagents or chiral catalysts) can induce the chirality in prochiral starting materials creating an asymmetric contour and then controlling the molecule 3-D structure during its formation.

In that way, when we talk about asymmetrical catalysis, we refer to the use of chiral catalysts. In general selectivity towards one enantiomer is indicated through the enantiomeric excess (ee%), calculated as:

$$ee\% = \frac{R-S}{R+S} * 100$$

where R and S are the two enantiomers. In this kind of synthesis, a large number of transition metals chiral catalysts and enzymes have been used.

Nowadays, the asymmetric catalysis has taken on a very important role within the asymmetric synthesis, in particular many efforts have been done with the aim of develop new methods for the enantioselective catalysis, which is a very efficient and cheap approach to get chiral molecules, three pioneers in this field William S. Knowles, K. Barry Sharpless and Ryoji Noyori shared the Nobel Prize in 2001[3].

In this type of catalysis, enantiopure catalysts can guide the reactants during the transition state, facilitating the attack of only one side of the substrate, and finally promoting the formation of the desired enantiomeric form of the product.

1.2 Asymmetric Organocatalysis

In the last decade, the **asymmetric organocatalysis** has begun to go ahead, this particular type of catalysis exploit small organic molecules to catalyze a wide range of reactions, in which are often involved carbonyl compounds.

Compared to other methods, transition metal catalysis and enzymatic catalysis, organocatalysis shows some practical advantages, in particular: the catalysts can be synthesized easily, they're stable in air so they don't need inert atmosphere and anhydrous solvents, they're non-toxic and they don't contain heavy metals; the majority of organocatalysts are natural molecules, like amino acids or alkaloids, they can be used unmodified or they can be derivatized.

Nowadays, organocatalysis has still some limitations that make this kind of catalysis not very competitive at industrial level, for example the low turnover number (TON) and consequently the need of a larger amount of catalyst (from 2 to 20% mol), compared to metal catalysis and enzymatic catalysis.

Anyway, some organic and organometallic molecules can mediate efficiently a variety of mechanistically distinct reactions.

When we consider two very related reactions, their similarities in the reaction profiles can be understood and exploited, thus if one catalyst performs well in one reaction, we can expected that this kind of catalyst could mediate a similar reaction. However, also less closely related reactions may be promoted by catalysts of the same class[4].

For example, chiral thiourea derivatives and Cinchona alkaloids are two examples of privileged catalysts, in particular the latter ones have an incredible ability to mediate an astonishingly wide variety of enantioselective transformations, as for chiral thioureas, they can for example catalyze the asymmetric hydrocyanation of imines (Strecker reaction) as well as asymmetric Mannich reactions[5], two reactions with quite different reactivity and stereo induction profiles.

During last years, site-selective reactions with organic catalysts have been developed and improved, in fact these reactions are very useful from a practical point of view since they allow the use of non-protected substrates in synthesis.

Organocatalytic reactions could be divided into two main classes, the first one includes catalysts that form a covalent bond with the substrate, while the second one induces enantioselectivity without covalent interactions with the substrate; in the first case we can talk about "covalent catalysis", in the second one we can talk about "non-covalent catalysis", one example are the catalysts that involve hydrogen bonding or ion pairing.

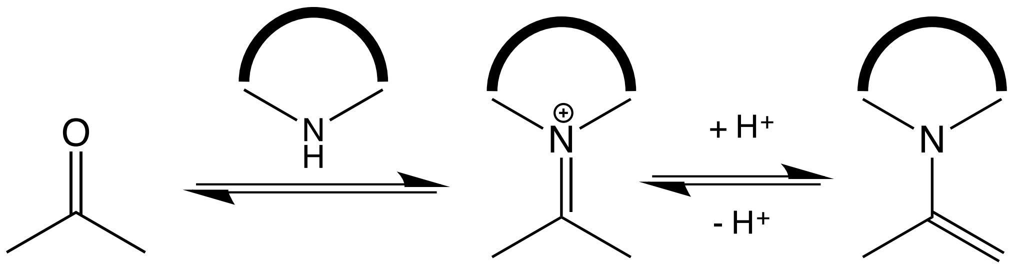

Fig. 4 Covalent Catalysis

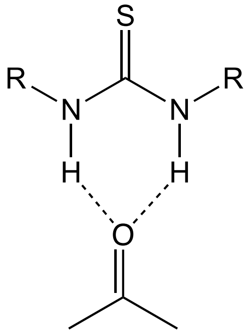

Fig. 5 Non-covalent catalysis

Organocatalysts are also very useful because they can be used in reactions, such as couplings (Suzuki, Sonogashira, Ullmann..), that till now have been performed only through transition metal catalysts; this kind of catalysts, with a higher molecular weight and a very complex structure, often improve not only the selectivity of the catalyst itself , but also the reaction kinetic.

Some of the most important organic molecules, used in organocatalysts till nowadays, would be mentioned below.

- Cinchona Alkaloids

Cinchona alkaloids[6] are organic molecules isolated from the bark of several species of cinchona trees. The four main alkaloids are quinine, cinchonine and their corresponding pseudoenantiomers quinidine and cinchonidine.

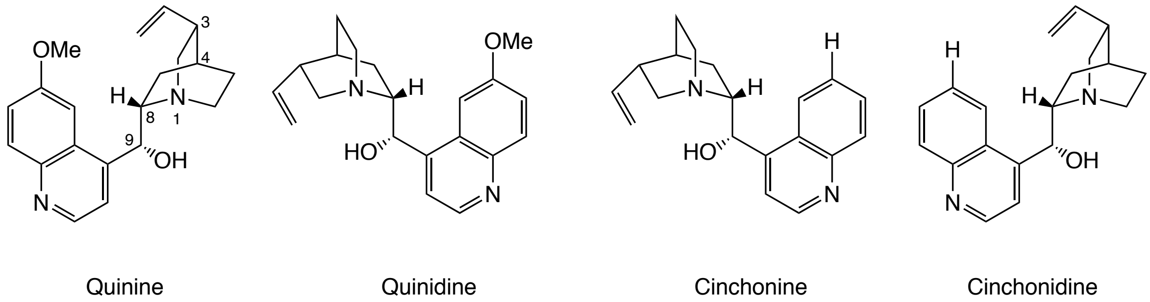

Fig. 6 Cinchona alkaloids

The four cinchona alkaloids contain five stereogenic centers (N1, C3, C4, C8 and C9)[5]. The absolute configurations at N1, C3 and C4 are identical in all the alkaloids, while the other two chiral centers (C8 and C9) have opposite absolute configurations. Quinine and Quinidine, like Cinchonidine and Cinchonine, are two diastereoisomers and they are defined as pseudoenantiomers because during a chemical reaction, their centres C8 and C9 are the responsible for the asymmetric induction, as if they are a couple of enantiomers. As a result, when we use a quinine derivative as a chiral organocatalyst (or ligand), we obtain one enantiomer of our product, while the employment of the corresponding pseudoenantiomer usually gives the other enantiomer of the same product with comparable selectivity.

The importance of cinchona alkaloids in organic chemistry started in 1853, when Pasteur's studies on racemate resolutions showed their potential as resolving agents; after that, cinchona alkaloids has been used in a large number of different reactions, for example two German chemists, Breding and Fiske, made the first asymmetric reaction using a cinchona base in 1912, than Wynberg and coworkers carried out many studies on the use of these alkaloids in asymmetric catalysis as a chiral Lewis base/nucleophilic catalysts, proving their versatility in many enantioselective transformations. Nowadays, cinchona alkaloids are one of the most "privileged organic chirality inducers", they're largely used since they're readily available in the two pseudoenantiomeric forms, relatively cheap, and they're very effective in wide range of different reactions.

The main features of this kind of molecules are:

- the presence of an hydroxyl function capable of coordinating electrophiles through H bond
- the presence of the highly basic and bulky quinuclidinic nitrogen, which could deprotonate the substrate of interest.

The quinuclidine base functionality also makes this alkaloids effective ligands for many metal-catalyzed reactions.

To increase the performances of these catalysts, we can derivatize the 9-OH group into other groups with selective retention or inversion of the configuration, in this way we can increase the power of the acidic site or the H-bond donor; the same thing could be applied to the 6^{I}-OMe group, in quinine and quinidine, using thiourea which is an effectiv H-bond donor.

The substitution of 9-OH into the amino group with inversion of the absolute configuration at C9, leads to derivatives like 9-*epi*-(9-deoxy)aminoquinine, that enable enantioselective aminocatalysis, which includes reactions of the enamine cycle and charge accelerated reactions via the formation of iminium intermediates. In general, these active sites in cinchona alkaloids and their derivatives act together to activate the starting material simultaneously.

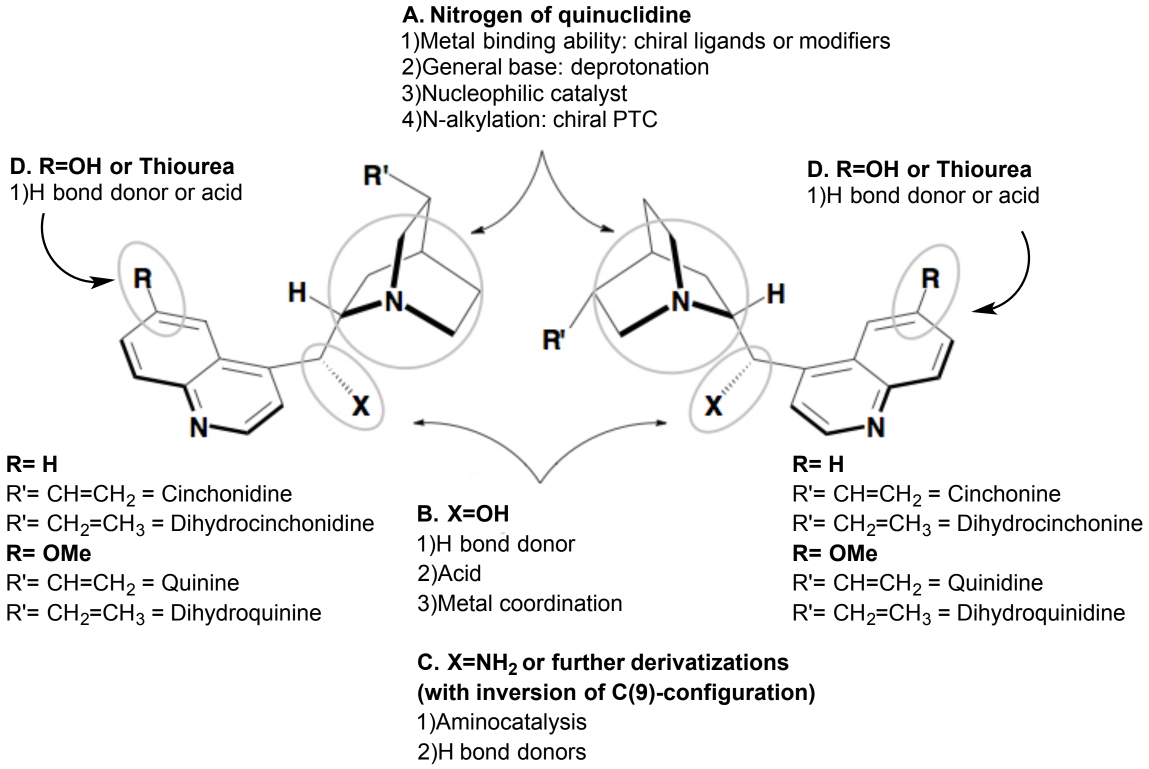

Fig. 7 Active sites potentialities of Cinchona alkaloids and derivatives[6]

- Thiourea derivatives

Jacobsen and Taylor, after several studies on Schiff bases and their capacity of catalyze asymmetric Strecker reaction of various imine substrates, developed a series of catalysts based upon urea and thiourea derivatives which are useful in enantioselective reactions[7].

The thiourea catalyst activates the substrate for the nucleophilic attack via double H-bond between the acidic NH protons and the electrophile; the H-bonds of thioureas are non-covalent but they're strong and highly directed to the electrophile. The ability to donate via H-bond could be increased by the introduction of electron withdrawing substituents near the NH groups to increase thier acidity.

Chiral thioureas, like **1**, can catalyze a wide range of enantioselective reactions and nowadays are one of the most used chiral H-bond donors.

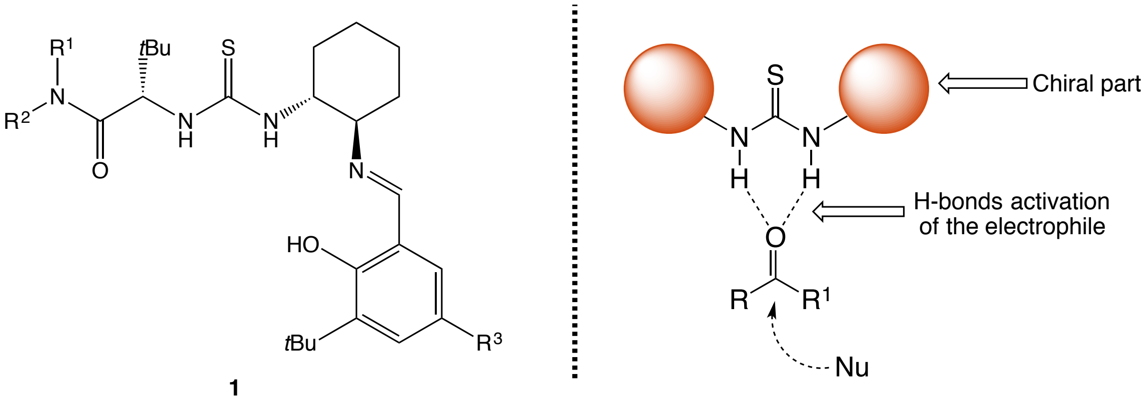

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Fig. 8 Activation mechanism promoted by thiourea derivatives

The thioureas developed by Jacobsen et al. are monofunctional catalysts, given this, during last years, researchers have started to develop new bifunctional organocatalysts based upon the thioureas structure, new catalysts contain both the H-bond donors and the new Brønsted/Lewis base functionalities; in this way, besides the activation of the electrophile, we also have the activation of the nucleophile[8].

An effective example is reported by Takemoto and co-workers, that used a bifunctional amine thiourea to catalyze the Michael addition between a malonate and a nitroolefin; the Michael acceptor is activated by the H-bond donors, while the nucleophilic enol is activated by the tertiary amine.

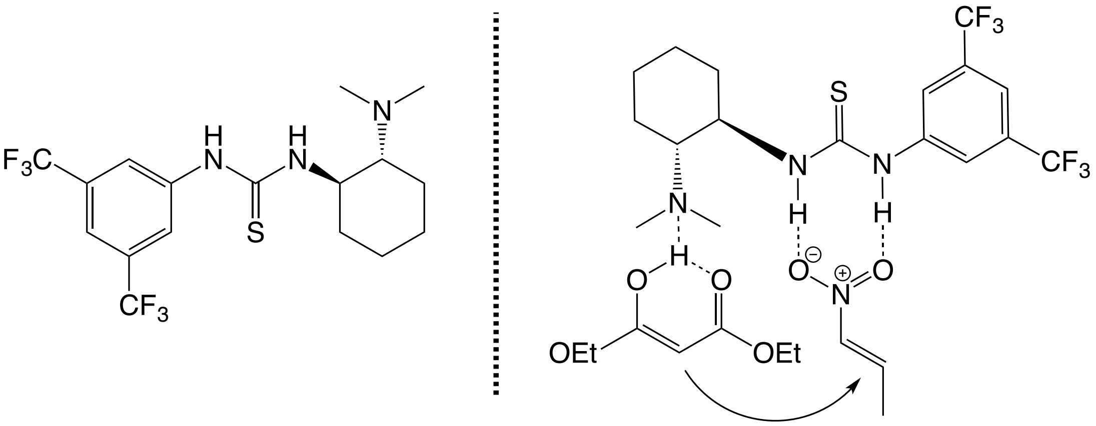
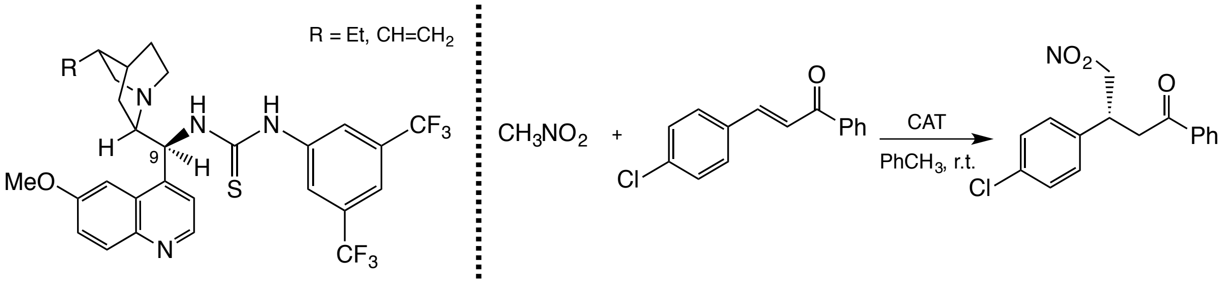


Fig. 9 Michael addiction catalyzed by amino thiourea

Cinchona alkaloids could be used to create new bifunctional catalysts with the introduction of thiourea moieties, as we can see in the pioneering work of Soòs and co-workers, that produced cinchona alkaloid derived thioureas for the Michael addition of nitromethane to calchones.



Scheme 1 Michael addition catalyzed by cinchona alkaloid derived thioureas

- Phosphoric Acid and derivatives

Another important class of chiral Brønsted acid catalysts is the chiral phosphoric acids derived from axially chiral biaryls; in particular, this kind of catalysts has been developed by modifying the substituents of BINOL molecule, in this way it was possible to obtain 1,1^{I}-bi-2-naphthol (BINOL)-derived mono phosphoric acids which are very useful chiral Brønsted acid catalysts for highly enantioselective transformations, as demonstrated by the two research groups of Akiyama and Terada[9].

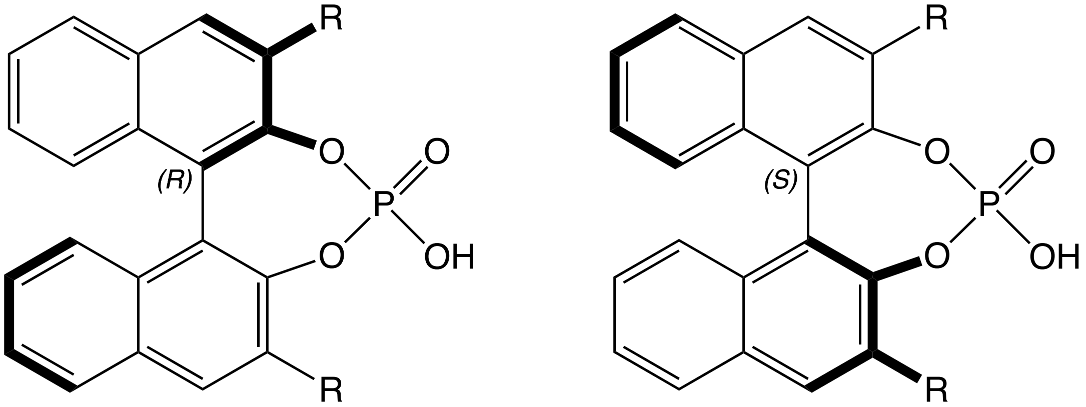


Fig. 10 enantiomers of BINOL-derived monophosphoric acids

The main and desirable features of phosphoric acids for this type of catalysis are:

- The presence of an acidic site, which is capable to form H-bond interactions with the electrophilic part of the substrate but without the loss of the proton.
- The presence of the phosphoryl oxygen, which represents the Brønsted basic site of the catalyst
- The presence of a ring system, that can restrict the flexibility of the chiral backbone
- The introduction of substituents into the ring system, especially in positions 3 and 3^{I}, that provide the chiral environment for the reactions

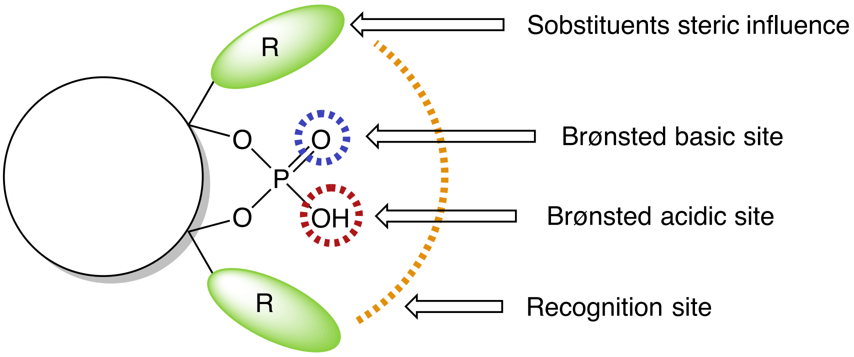


Fig. 11 Bifunctional catalytic site

All these aspects contribute to create a catalyst that contains both acidic and basic functions, as for bifunctional catalysts, and the steric influence, promoted by the ring substituents, in that way we obtain a catalyst with an efficient recognition site for many substrates.

As mentioned above, BINOL derivatives are largely employed as starting materials for the synthesis of these catalysts, they have C2-symmetry and both the two enantiomers are available and they could be easily modified according to steric and electronic requirements.

Recently, BINOL phosphates have become stronger Brønsted chiral acids thanks to the introduction of electron-withdrawing groups, for example Yamamoto and Nakashima developed N-triflylphosphoramide (NTPAs) after the introduction of a triflylamide group.

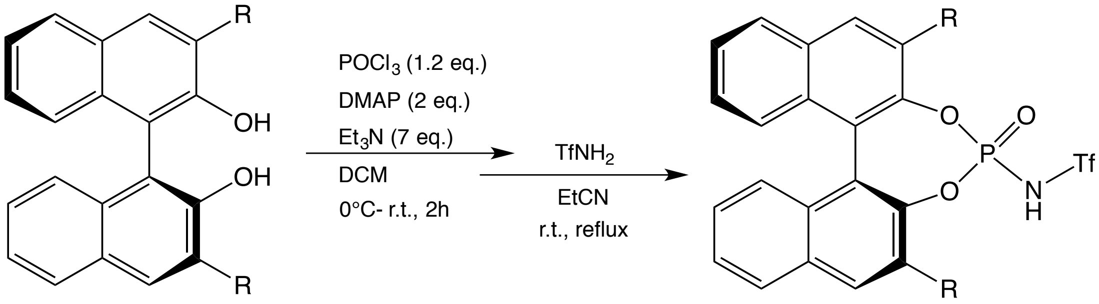


Fig. 12 Synthesis of NTPAs

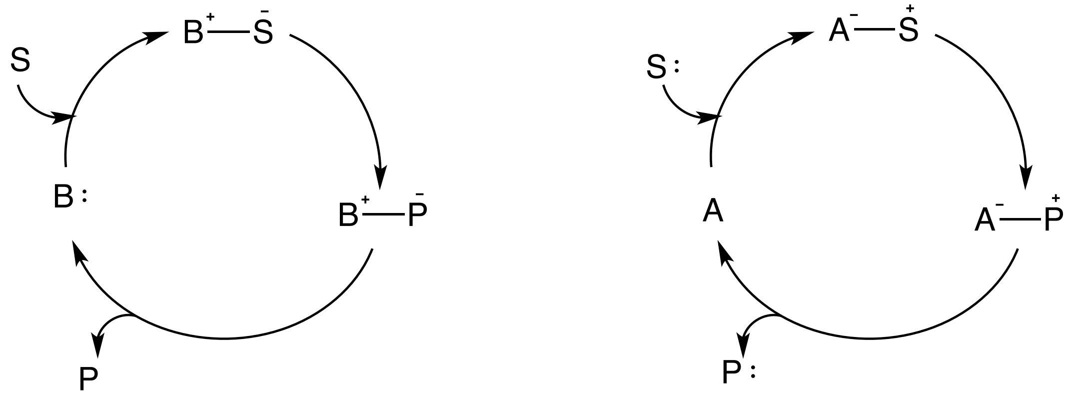
Phosphoric acids and derivatives are used in many enantioselective reactions: asymmetric Diels-Alder of α,β-unsaturated ketones[10], Mannich and Strecker reaction and activation of imines that forms the basis for aza-Friedel-Crafts of many substrates. The presence of the two aryl substituents in the catalyst scaffold is very important, in each of these reactions, for high enantioselectivity, and even small differences of the substituents properties (sterics and electronics) could cause pronounced variations[7].

1.3 Base and Acid Catalysis

The majority of organocatalysts can be broadly classified as : Lewis acids or bases and Brønsted acids or bases, everyone has its own catalytic cycle, as shown in Scheme 2[11].

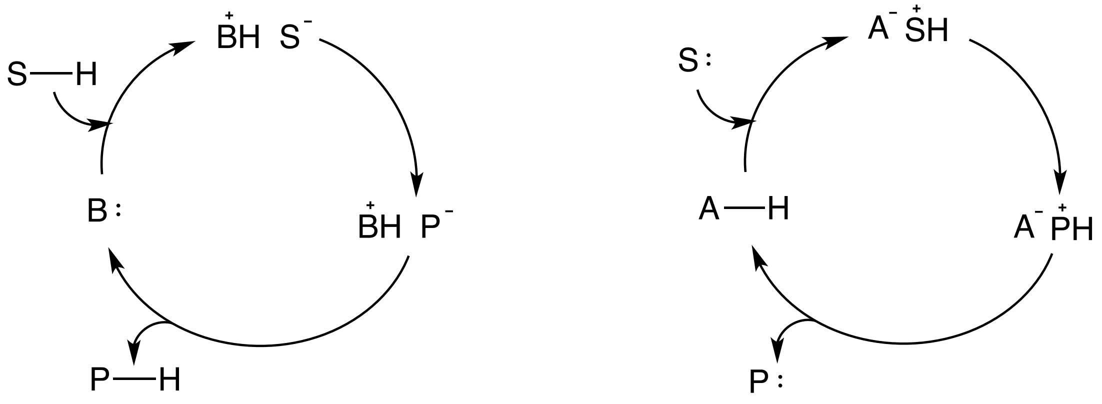
Lewis base catalysis starts the cycle via nucleophilic addition of the catalyst to the substrate, while Lewis acid catalysis starts the cycle via nucleophilic addition of the substrate, anyway in each case the obtained complex undergoes a reaction and it allows the recovery of the starting catalyst and the final product.

Brønsted base and acid catalysis starts via partial deprotonation or protonation of the substrate, respectively.



Lewis Base Catalysis

Lewis Acid Catalysis



Brønsted Base Catalysis

Brønsted Acid Catalysis

Scheme 2 Organocatalytic cycles

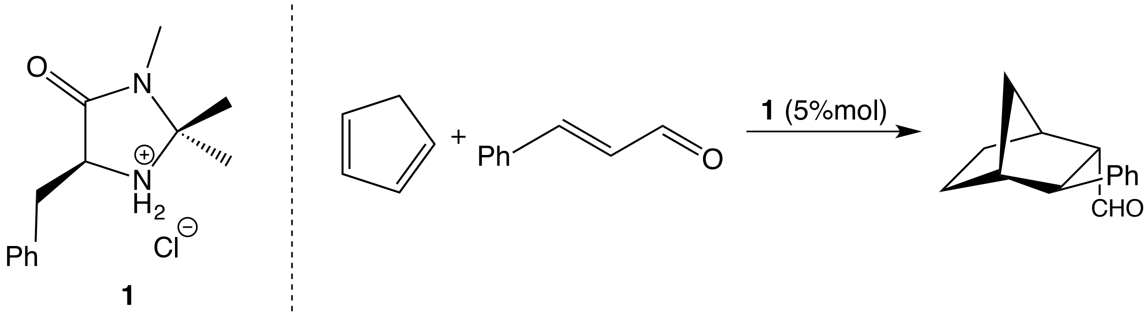
- Lewis base catalysis

The majority of organocatalysts tend to react as heteroatom-centered Lewis bases that can activate both nucleophilic and electrophilic substrates; typical intermediates are: iminium ions and enamines.

Iminium Ion Catalysis

Reactions via **iminium catalysis** proceed through the formation of the active specie, the iminium ion, after a reversible reaction between the catalyst, which contains the amine group, and the carbonyl substrate; the iminium ion is very reactive and this aspect allows it to be employed in many reactions as Knoevenagel condensations, cycloadditions, nucleophilic additions and breaking of σ-bonds next to α-carbon, Friedel-Crafts alkylations (with pyrroles, indoles and benzenes) and some Michael additions (malonates and nitroalkanes to enones).

Macmillan's enantioselective Diels-Alder between α,β-unsaturated aldehydes and ketones with dienes, using chiral amino acid derived imidazolidinones as catalysts, is one of the first examples of iminium catalysis in the field of organocatalysis.

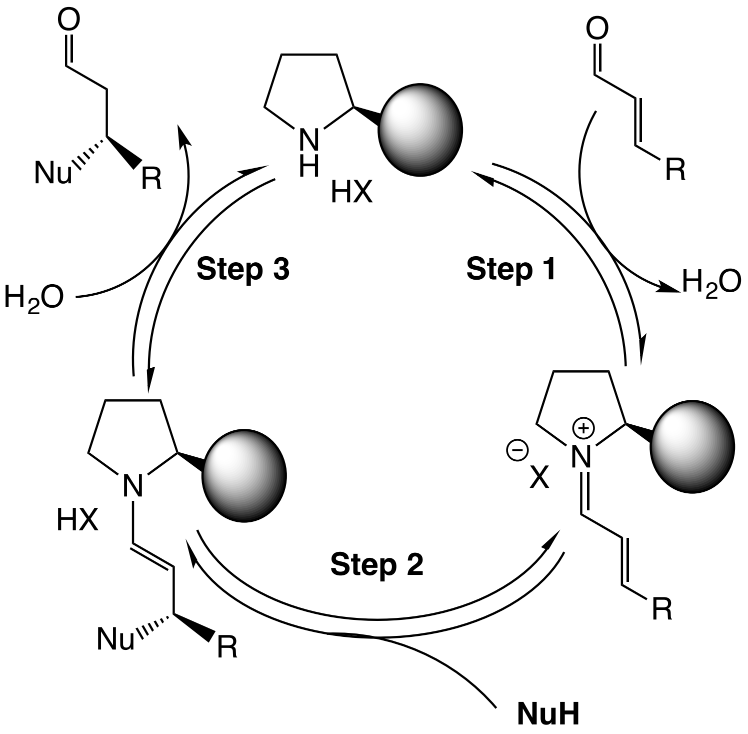


Scheme 3 Example of iminium catalysis with Macmillan's catalyst

α,β-Unsaturated carbonyl compounds can undergo various nucleophilic additions reactions and cycloadditions, this kind of reactions can be accelerated using Lewis Acid compounds that complex the carbonyl group, in this way the reactivity of the system grows because the energy of the LUMO is lowered[12].

The iminium catalysis simulate the Lewis acids activation of carbonyl compounds, the LUMO energy decreases and the reaction is favoured.
The main steps of the iminium catalytic cycle are:
- Formation of the iminium ion
- Key bond forming reaction
- Hydrolysis of the iminium ion

Together with the amine, that can be a secondary or a primary one, in these reactions is added a small amount of a co-acid, this secondary proton source helps in the formation of the iminium ion and the hydrolysis.



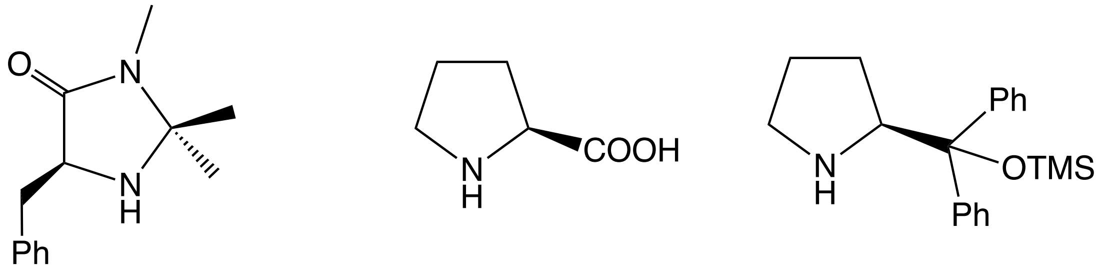
Scheme 4 Catalytic cycle via iminium ion

The first step in iminium ion catalysis is the formation of the iminium ion itself, after the condensation of the catalyst to the substrate. In the second step, the iminium ion can undergo the key bond forming reaction, in the case of a conjugate addition we obtain an enamine, after that we have the last one step, where the intermediate is hydrolysed and we obtain our final product and the regenerated amine, which is ready for another cycle.

Aldehydes and ketones condense with both primary and secondary amines, in the first case we can obtain imines that are basic and in acidic solution exist as iminium ions, in the second case, after the condensation, we obtain an iminium ion that can be isolated as salt of strong acids, because it cannot be deprotonated to give the correspondent imine[13].

The formation of the iminium salt activates the carbonyl substrate toward the nucleophilic attack, thus the iminium salt is more electrophilic than the corresponding starting material.

For iminium catalysis, the most used are secondary amines, like molecules from the imidazolidinone family, cyclic amines, pyrrolidines, proline and its derivatives.



imidazolidinone

proline and derivatives

Fig. 13 Secondary amines

After many studies about the formation of enamine and iminium ion intermediates, it was found that primary amine catalysis is better when we need to functionalize sterically hindered carbonyls, in fact the equilibrium constants for iminium ion formation show that secondary amines are more influenced by the structure of the substrate than primary amines[14].

Moreover, secondary enamines hydrolyze faster than the tertiary ones, this is due also to steric factors, tertiary enamines are very hindered at the nitrogen atom thus the entire system cannot reach the planar conformation necessary to maximize the interactions between the double bond and the ion pair on the nitrogen.

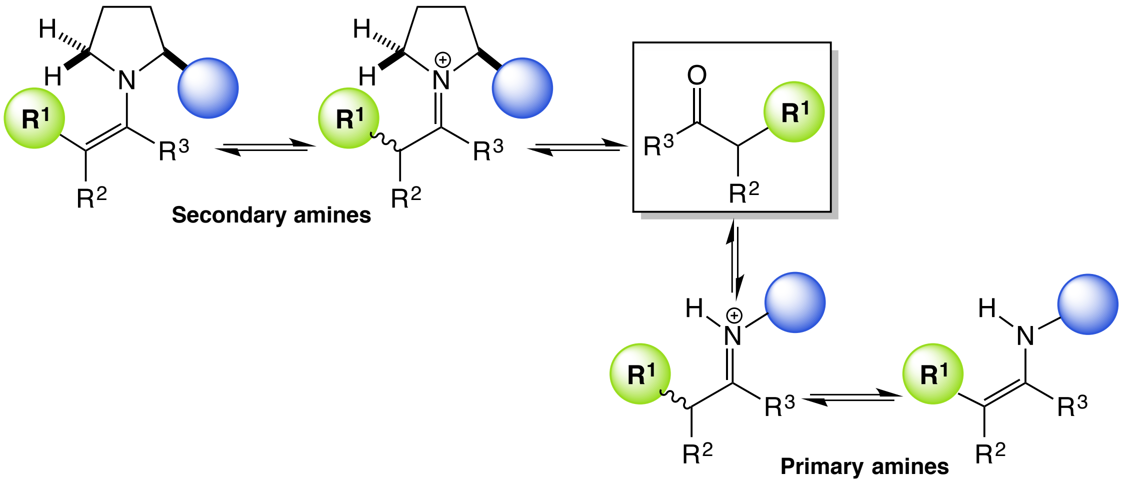
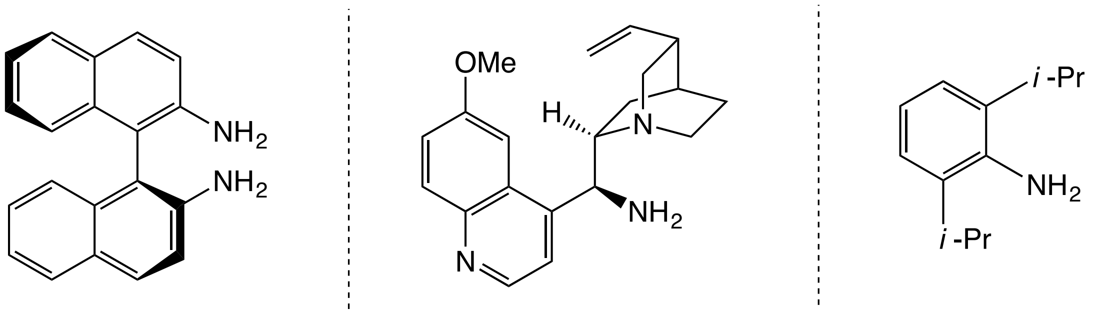


Fig. 14 Secondary and primary amines with hindered substrates

Primary amine are largely used nowadays, very useful molecules of this type are aromatic amines, like aniline derivatives, diamines like BINAM and 9-amino(9-deoxy)-epi-cinchona alkaloids; the recent introduction of a primary amine moiety inside the scaffold of cinchona alkaloids, make them effective covalent-based activators of hindered carbonyl compounds.



BINAM

Cinchona-based diamine

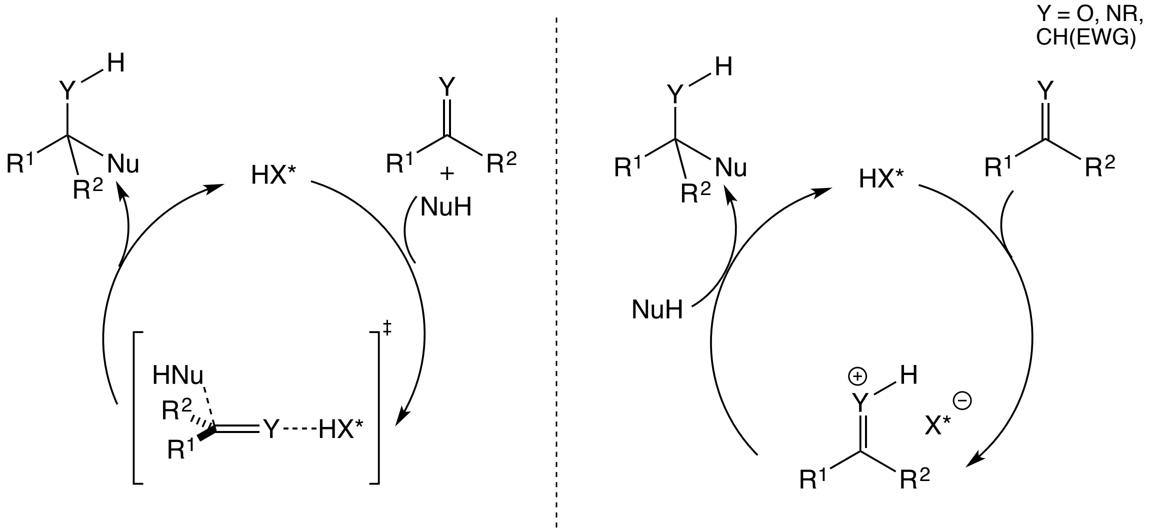
Aniline derivative

Fig. 15 Primary amines

- Brønsted base catalysis

The use of this kind of catalysis, as a valid method to obtain enantiopure compounds, is relatively recent[12]. Brønsted acid catalysis can be divided into two class:

- General acid catalysis (2), here the substrate is activated via H-bond
- Specific acid catalysis (3), here the substrate is activated via protonation



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Scheme 5 Asymmetric Brønsted acid catalysis

The first class includes catalysts as thioureas and TADDOL derivatives, while the second one includes phosphoric acids, *N*-triflyl phosphoramides and dicarboxylic acids.

Jacobsen and co-workers[11] developed a series of enantioselective reactions, like Mannich and Strecker, employing ureas and thioureas, while the research group of McDougal and Schaus developed the enantioselective asymmetric Morita–Baylis–Hillman reaction using a chiral BINOL-derived Brønsted acid.

During the last years, many bifunctional catalysts have been developed, one of the two functionalities present in these catalysts is often a Brønsted acid, which is coupled, for exemple, with a Lewis base.

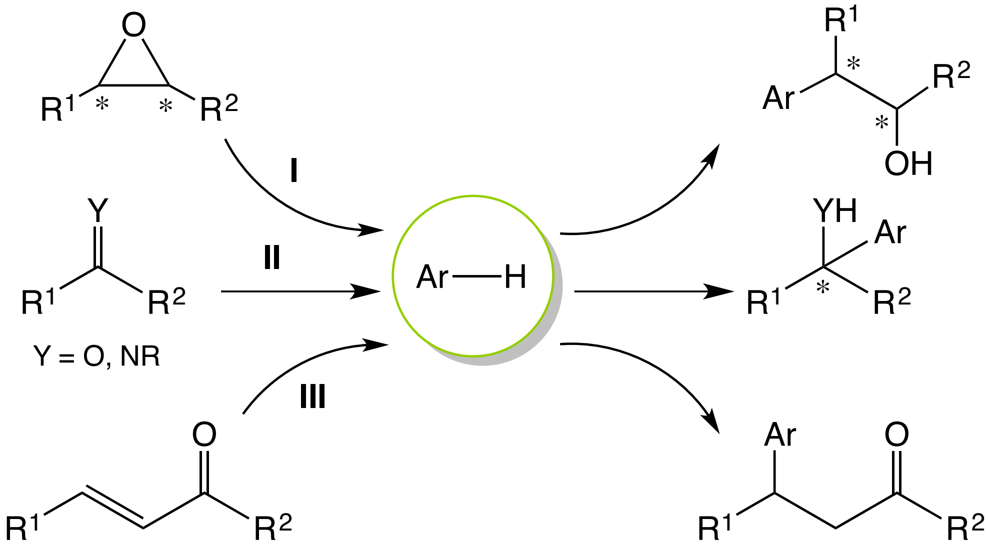
1.4 Friedel-Crafts Alkylation Reaction

The F-C reaction usually involves treating benzene with an alkyl chloride and a Lewis acid, such as $AlCl_3$. The Lewis acid removes the chlorine atom from the substrate and generates the electrophilic carbocation for the alkylation, after that, the nucleophilic double bond of the arene attacks the carbocation giving a new carbocationic intermediate; finally, we obtain our product by deprotonation.

The Friedel-Crafts (F-C) alkylation is one of the most important reactions that enable to synthesize enantiopure aromatic derivatives, after the insertion of unsaturated compounds to the arene; first examples of asymmetric and catalytic F-C, date back to the 80s, they were performed using metal-based catalysts, nowadays the use of organocatalysts is increased considerably[15].

Using an acid chloride, instead of the alkyl chloride, we promote the F-C acylation, through the formation of an acylium ion, to obtain an aromatic ketone.

Herein are reported some approaches for asymmetric F-C alkylation like: ring-opening of epoxides (I), enantioselective 1,2-additions of aromatic systems to carbonyl groups (II) and 1,4-conjugate additions to α,β-unsaturated carbonyl compounds (III) [16].



Scheme 6 Asymmetric Friedel-Crafts alkylation approaches

1.4.1 Stereocontrolled ring opening of epoxides

The reaction between epoxides and arenes, catalyzed by Lewis acids or bases, could be a very interesting way to synthesyze optically active aromatic compounds, even if sometimes there could be absence of regioselectivity.
We can find examples of F-C alkylations using Indium(III) salts, such as $InBr_3$ or $InCl_3$, which promote alkylation of aromatic compounds with high stereoselectivity.
The research group of Umani-Ronchi, Bandini and Melchiorre developed the alkylation of functionalyzed indoles with enantiomerically pure aryl epoxides and $InBr_3$ (Fig. 22a), the reaction proceeds exclusively through a regio- and stereoselective SN2-type pathway at the benzylic position of the epoxide[16].
Another reaction presented by the same research group, is the first example of catalytic kinetic resolution of racemic epoxides through a carbon–carbon bond-forming (Fig.22b). The reaction between 2-methylindole with styrene oxide using [Cr(salen)Cl] as catalyst, gave the unconverted styrene oxide and the indolyl derivative with ee% of 55% and 56% respectively.

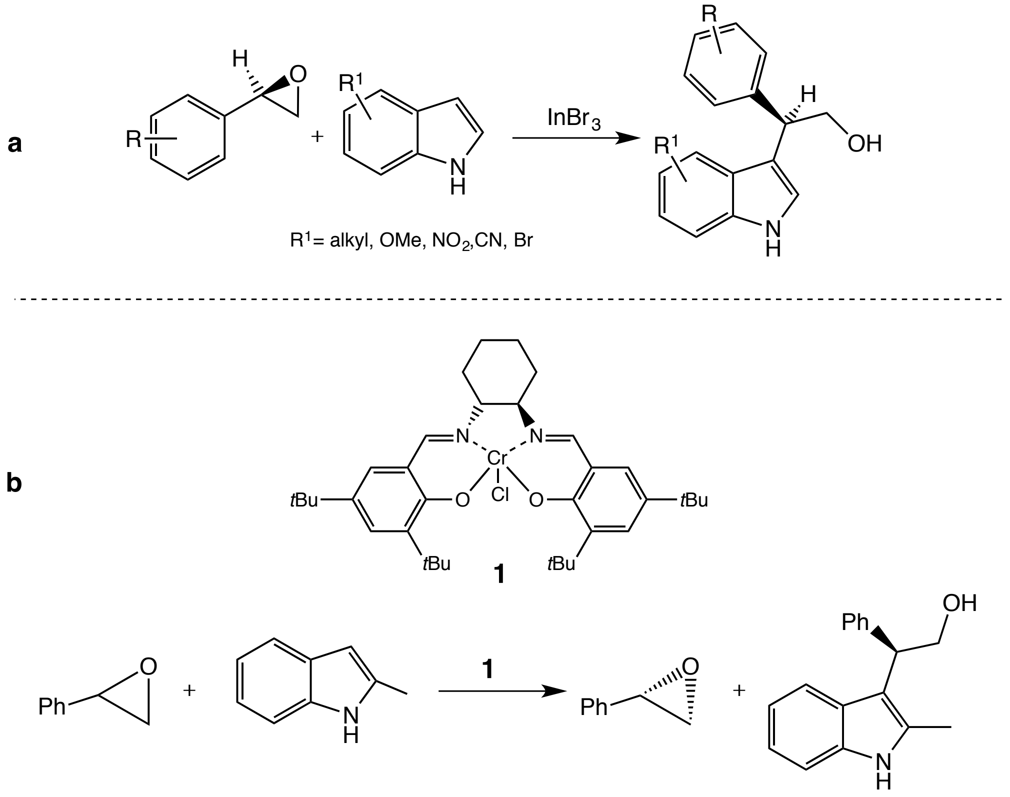


Fig. 16 Exemples of stereocontrolled ring-opening of epoxide

1.4.2 Asymmetric addition to carbonyl compounds

A wide number of functionalized compounds are obtained after the addition of arenes to carbonyl compounds like aldehydes, ketones, and imines.

One of the first examples in this area was the reaction between 1-naphthol and pyruvic acid esters, using a zirconocene chiral complex. Many progress have been made by Johannsen and Mikami and co-workers, they produced *N*-tosyl-α-amino acids and organofluoro compounds respectively with tol-binap/$CuPF_6$ and a chiral substituted binol–titanium complex as catalysts.

Jørgensen and co-workers demonstrate the versatility of F-C alkylation obtaining aromatic mandelic acid esters and heteroaromatic hydroxytrifluoromethyl acid esters, the high stereoselectivity is given by a tBu-box–copper(II) triflate complex and chelating substrates; under these conditions many substrates, such as aromatic amines, anisoles, and heteroaromatic compounds, can undergo highly enantioselective F-C alkylations, demonstrating the wide applicability of the catalytic system.

1.4.3 Asymmetric addition to α,β-unsaturated carbonyl compounds

α,β-unsaturated carbonyl compounds are valid substrates for F-C reaction, even if stereoselective examples are still few.

We can find highly enantioselective 1,4-additions in the presence of a chiral box-copper(II) complex and a pseudo-C3-symmetric trisoxazoline complexed with $Cu(ClO_4)_2 \cdot 6\,H_2O$, reported by Jørgensen and Zhou and Tang respectively; thus, one of the best strategies to obtain high stereoselectivity, is the employment of chelating substrates together with chiral cationic Lewis acids.

Michael-type additions of arenes to nonchelating α,β-unsaturated carbonyl compounds were reported by the research groups of MacMillan and Umani-Ronchi, Bandini and Melchiorre; the first group showed examples of 1,4-additions of pyrroles, indoles and aniline derivatives to α,β-unsaturated aldehydes, using organocatalysts (chiral tailored benzyl imidazolidinone·HX salts) instead of metal-based catalysts, as reported in the previous examples.

Unfortunately this procedure doesn't work well with ketones, thus the second research group tried a new procedure for the enantioselective 1,4-addition of indoles to α,β-unsaturated aryl ketones, using the chiral [Al(salen)Cl] complex in the presence 2,6-lutidine as catalyst, the aluminium complex and the amine promote enantio-discrimination during the alkylation step.

1.4.4 Organocatalysts for asymmetric Friedel-Crafts reactions

The majority of the F-C alkylation examples reported above, are conducted through the use of metal-based catalysts.

Nowadays, we can find several exemples of enantioselective F-C alkylation involving many different organocatalysts like: imidazolidinones, cinchona alkaloids, thioureas, phosphoric acids and N-triflyl phosphoramides; the last three are classified as chiral Brønsted acids, they're very useful because they combine their strong acidity with a good chiral environment, they facilitate the activation of substrates as carbonyl compounds, imines and α,β-unsaturated compounds, through the decreasing in energy of the LUMO that promotes the nucleophilic attack to the double bond[17].

Herein, I'll report just some reactions conducted through the use of some of the main organocatalysts that I've mentioned in the previous chapter.

- Cinchona Alkaloids

These catalysts have been employed in order to realize:

- Enantioselective hydroxyalkylation of indoles with ethyl trifluoropyruvate, reaction developed by Török, Parkash et al., they find out that the catalyst is responsible of both the chiral environment and the activation of the carbonyl compound through the formation of an intermediate between the two substrates and the catalyst itself.
- Enantioselective hydroxyalkylation of indoles with α-keto esters (e.g. aryl, alkynyl or alkyl α-keto esters) or glyoxalate derivatives, developed by Deng et al. using 6-OH bifunctional cinchona alkaloids (QD-PHN or Q-PHN).

- First mediated F-C alkylation of phenols with ethyl trifluoropyruvate, reported by Liu, Chen et al., phenols are not very good nucleophiles so they're less reactive for F-C alkylations, and in addition their OH-group could interact with the catalyst, promoting a decrease in selectivity; using cinchona alkaloids derivatives they obtained a wide range of para-substituted phenols.
- Reaction of 8-amino-2-naphthol derivatives for the synthesis of non-biaryl atropisomers, reported by Jørgensen et al., employing dihydrocupreidines; they also demonstrate that cinchona alkaloids themselves are a suitable substrate for this kind of amination, thus new derivatives with better enantioselective features can be obtained.
- Enantioselective alkylation between indole and α,β-unsaturated ketones using primary amine catalysts, developed by the two research groups of Chen and Melchiorre, the first one showed the validity of cinchonine derivatives in these transformations, while the second one performed the reactions with the help of an acid and chiral co-catalyst.

- Thiourea derivatives

We have several examples of asymmetric F-C reaction carried out with this family of organocatalysts:

- Enantioselective Pictet-Spengler reaction for the production of tetrahydro-β-carbolines, by Jacobsen et al., using a thiourea catalysts together with an acylating agent, the second one promotes the formation of a more reactive intermediate that is further activated by the catalyst.
- Asymmetric synthesis of 3-indolyl methanamines, developed by Deng et al., employing the two enantiomers of chiral thiourea functionalized with a cinchona alkaloid; this reaction can be performed with different imine derivatives, including alkyl imines, obtaining both the enantiomers of the product.
- F-C reaction between 2-naphthol and nitroolefins, by Chen et al., using thiourea derived from cinchonine; some variations have been applied

to this reaction, such as the use of substituted naphthols, other nitroalkenes and other types of electrophiles.

- Sequence F-C alkylation/cyclization for the synthesis of naphthopyrans using α,α-dicyanoolefins as starting material, reported by Yang, Zhao et al., the use of dicyanoolefins substituted with electron-withdrawing groups gives better yields and in addition, they also described the synthesis of naphthopyran derivatives through the use of β,γ-unsaturated α-keto esters bearing electron-withdrawing substituents.

- Phosphoric acid derivatives

These catalysts have started to be employed in asymmetric F-C reactions only in the last decade:

- First asymmetric F-C alkylation of 2-methoxyfuran with N-Boc aldimines, developed by Terada et al., various aldimines have been tested with differences in the sostitution of the phenyl ring and also naphthyl and furyl substrates have been tried.
- Asymmetric Pictet-Spengler reaction between aldehydes and geminally disubstituted tryptamines, by List et al., using chiral phosphoric acids; this reaction has been subsequently investigated by Hiemstra et al., they reported the same reaction employing sulfenyl-substituted tryptamines, in this way the iminium ion is stabilized by the presence of the sulfenyl group, the intramolecular cyclization is favored and the geminal disubstitution of the tryptamine becomes unnecessary.
- Addition of indoles to N-sulfonylaldimines, by You et al., some variations have been applied to this reaction, such as the use of different indole ring bearing electron-withdrawing or electron-donating groups.
- Synthesis of an α-amino acid from indoles, reported by Hiemstra et al.,employing N-sulfenyl protected imines.
- Synthesis of asymmetric indolylmethanamines using electronrich alkenes, by Terada et al., they tried enamines with linear, branched alkyl group and aromatic substituents, in addition they noticed that the

reaction proceeds through the imine intermediate generated by the tautomerization of the N-protected enamine.

- Synthesis of indolylethylamine which bears a quaternary asymmetric center, reported by Zhou et al., α-aryl enamines employed as substrates for the reaction can have an electron-withdrawing or electron-donor substituent in meta or in para of the ring, both the nitrogens of the enamine and the indole don't have to be protected because in these conditions the reaction does not work.
- Alkylation of indoles with β,γ-unsaturated α-keto esters, by Rueping et al., using an acidic N-triflylphosphoramide as catalyst; other tests have been done with different catalysts containing a binaphthol core. This same reaction has been proposed by Zhou, He et al. and Acocella et al. employing indoles and α,β-unsaturated aromatic ketones.
- Intramolecular F-C alkylation of indoles with α,β-unsaturated ketones, developed by You et al.; subsequently, they proposed a tandem double F-C alkylation, where the phosphoric acid catalyst is used to activate the aldehyde and promote the intermolecular F-C of the indole, the final product is obtained through the intramolecular F-C of the carbocation intermediate created in the previous step.

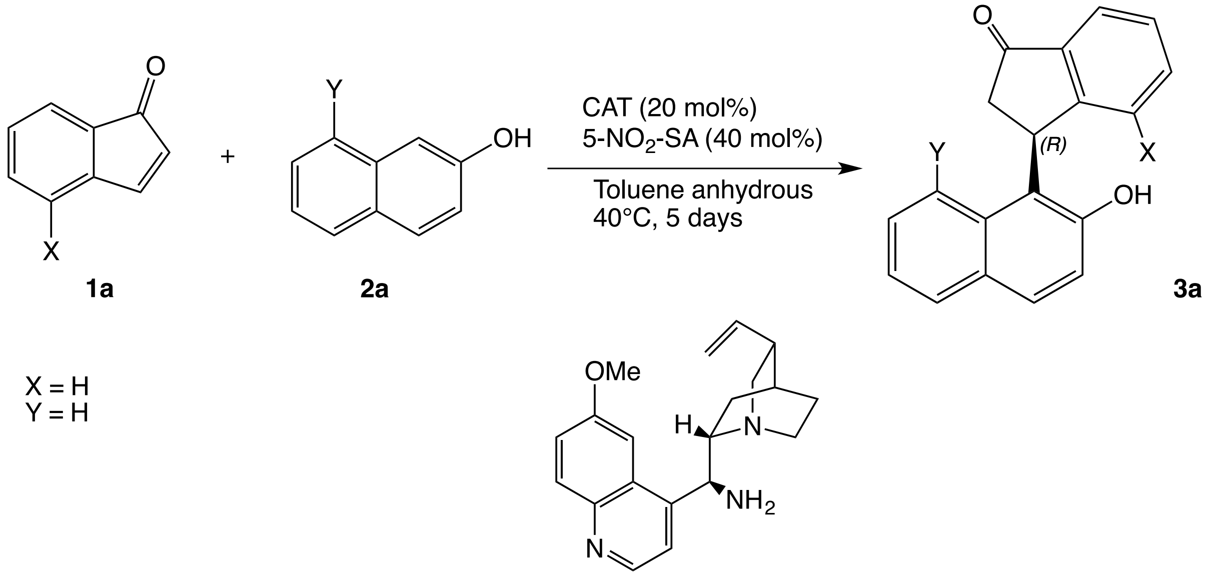
2. Projects and results

2.1. Aim of the project

In this thesis project, which has been performed at the department of Industrial Chemistry "Toso Montanari", we tried to develop an intramolecular and asymmetric Friedel-Crafts alkylation of chalcones, exploiting mostly organocatalysts, in order to simultaneously obtain a new chiral center and a chiral axis, in the moment in which the new C-C bond is formed.

2.2. Starting point

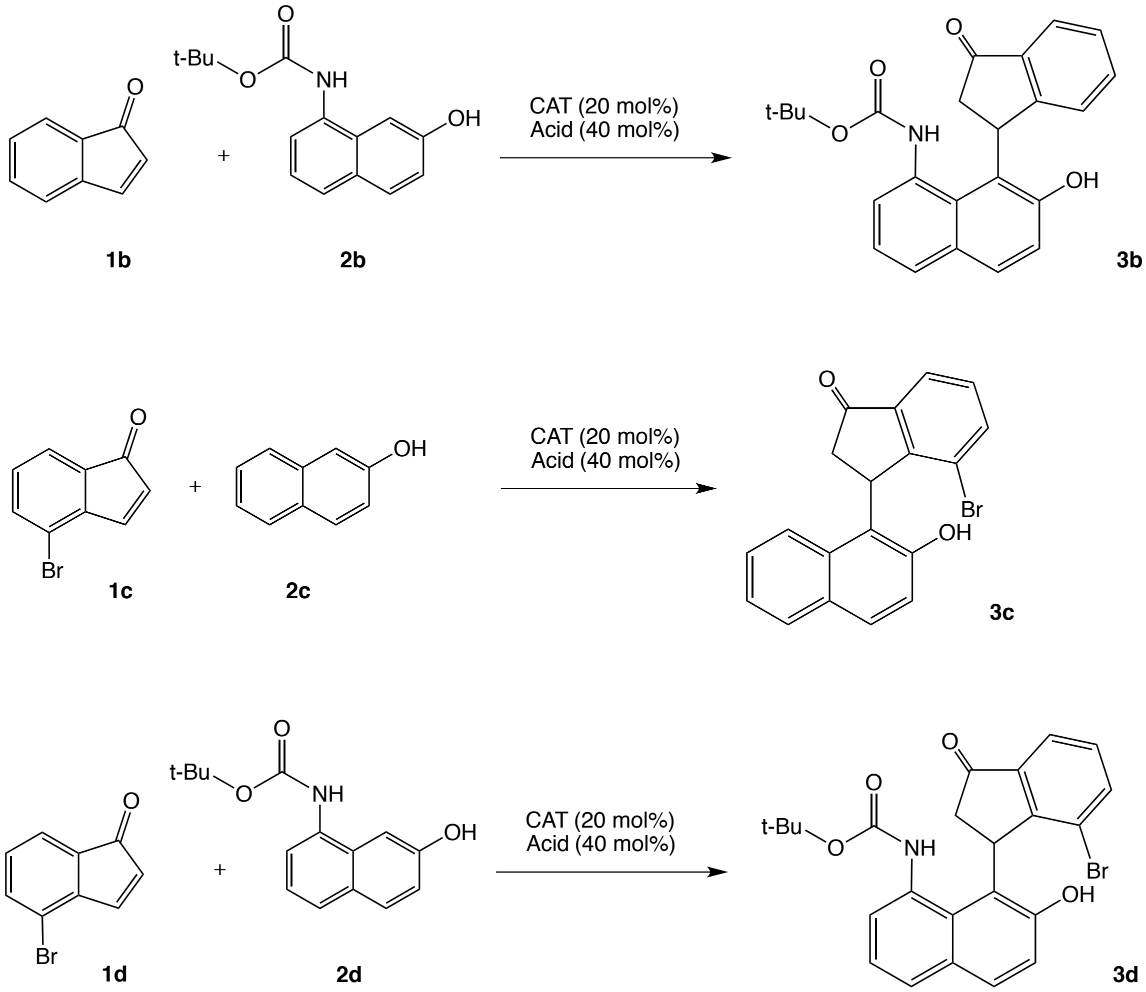
In a previous study carried out by the same research group[18] in which I have done this project, an enantioselective intermolecular F-C alkylation between indenones and α- and β-naphtholes via iminium ion has been reported, the catalysts used were primary amines and, in particular, the best results have been gained using 9-amino(9-deoxy)epi-quinidine.



CAT = 9-amino(9-deoxy)epi-quinidine

Scheme 7 Reaction between indenones and α- and β- naphtholes via iminium ion

During following studies it has been evaluated how the presence of possible substituents, like -OH group and -Br, which were strategically positioned inside the structure of the two starting products, 2-naphthols and indenones, could support the control of the absolute configuration of both the chiral centre and the chiral axis, which are formed after the reaction[2].



Scheme 8 Study upon the substituents inside the reaction between 2-naphthols and indenones

To develop this project of thesis, we started from the informations previously gathered inside this research group and, after that, we modified the approach to this kind of reaction.

In fact, in our case, we have used a chalcone as starting material for the reaction and, upon this molecule we have tried to carry out an intramolecular and asymmetric F-C alkylation, arriving to the same product of interest.

In this way we wanted to provide both a continuation of the previous studies we have done and a new contribution to the examples of F-C alkylation, since an intramolecular and organocatalysed F-C reaction upon this kind of substrates is still not known. Many examples of F-C reaction have been reported using different substrates and catalytic systems like:

- indoles and β-substituted α,β-unsaturated phosphonates and α,β-unsaturated 2-acyl imidazoles, catalyzed by Bis(oxazolinyl)pyridine-Scandium(III) triflate complexes [19]
- pyrroles and indoles with α′-hydroxy enones under Cu(II)-simple bis(oxazoline) catalysis [20]

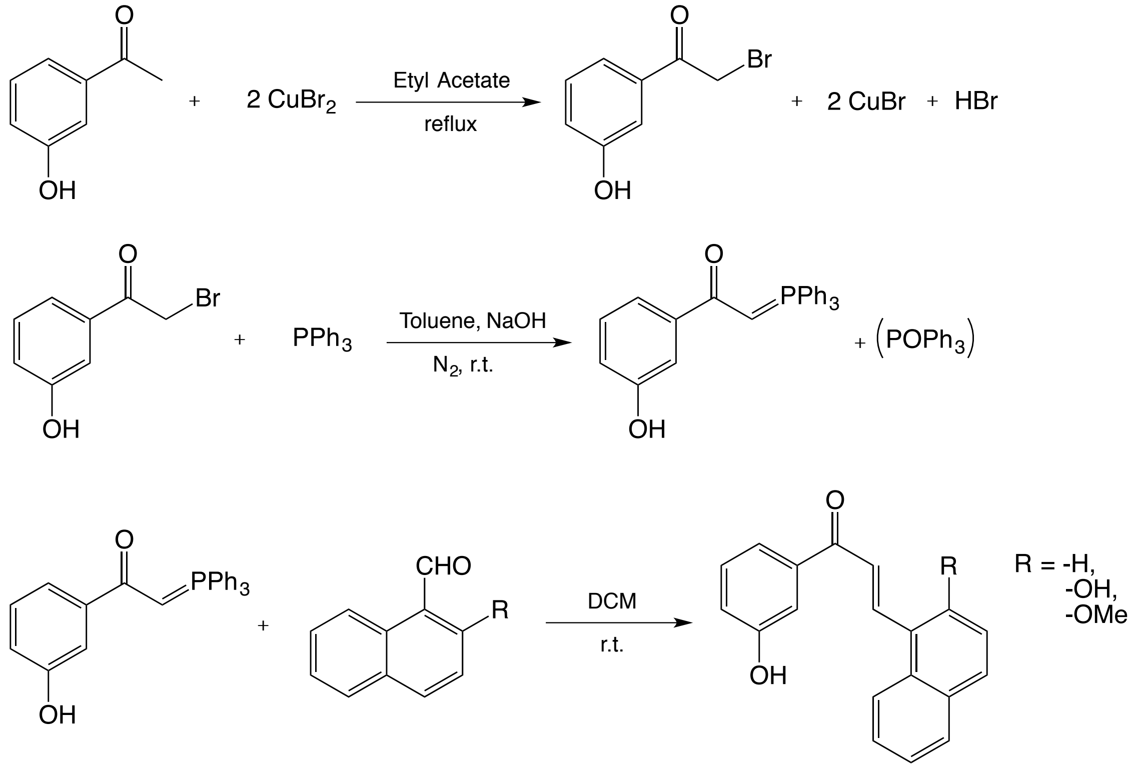
2.3. Synthesis of substrates

For the synthesis of chalcones, our substrates for the F-C reaction, we have followed two different pathways. We focused on the use of 3'-hydroxyacetophenone, since our previous researches showed that the presence of the -OH group, inside the structure of the starting product for the intermolecular alkylation, was necessary (see chapter 2.4).

At first we focused on the synthesis of chalcones via Wittig reaction; this choice was made because of hte presence of the -OH group, since we feared that the synthesis via aldol condensation, the main used reaction for the synthesis of our wanted substrates[21], could have many problems and it could be less effective.

This first pathway we have chosen has 3 reaction steps:

- Bromination of the starting material 3'-hydroxyacetophenone, synthesis of 2-bromo-3'-hydroxyacetophenone
- Synthesis of the phosphorane
- Wittig reaction between the phosphorane and various substituted naphthaldehydes



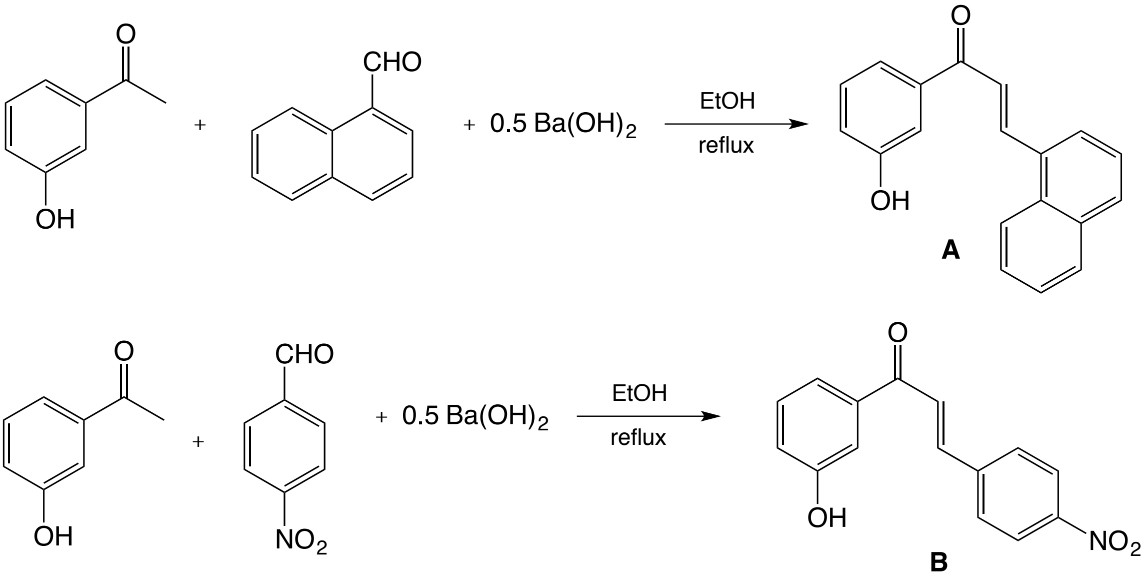
Scheme 9 Synthesis of chalcones via Wittig reaction

The first step of reaction was performed employing a procedure found in literature[22], which involved the use of ground $CuBr_2$ as brominating agent and ethyl acetate as solvent, the reaction mixture had to be maintained under reflux for at about 6 hours; we were able to optimize the reaction through a few additions of $CuBr_2$, as it deactivated it was filtered and replaced, in that way we obtained high conversion and we were able to characterize the product 2-bromo-3'-hydroxyacetophenone.

The second step of reaction, for the synthesis of the phosphonium ylide, was also performed employing a reported procedure[23], in this case we added a solution of 2-bromo-3'-hydroxyacetophenone in toluene to a solution of PPh_3 in toluene, we left the reaction mixture stirring overnight under nitrogen. The phosphonium salt was filtered and it was suspended in a flask together with a mixture of H_2O/MeOH (1:1), after 1 hour of stirring, we added 2M NaOH and we left the reaction mixture stirring for other 30 minutes. In the end we obtained the phosphonium ylide after extraction with DCM.

The final Wittig reaction has been performed employing the phosphonium ylide obtained in the previous steps and two different aldehydes, 1-naphthaldehyde and 2-methoxy-1-naphthaldehyde, in DCM. The final chalcones were obtained in very low yield and then in inadequate quantity to perform the following tests for the F-C reaction; there probably have been problems during the synthesis of the phosphonium ylide or in the Wittig reaction itself.

Given the impracticability of the first synthetic pathway, we moved to the synthesis of chalcones via aldol condensation, in particular we followed a procedure described in an american patent[24], the only one example reported in literature about an aldol condensation between 3'-hydroxyacetophenone and aromatic aldehydes; this reaction which consisted of a single step compared to the Wittig reaction, required that 3'-hydroxyacetophenone was placed under reflux for 3 hours together with the aromatic aldehyde, in our case 1-naphthaldehyde or *p*-nitrobenzaldehyde, $Ba(OH)_2$ and ethanol as solvent.

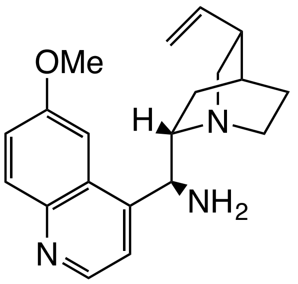


Scheme 10 Synthesis of chalcones via Aldol Condensation

The reaction mixture was cooled and put in 1M HCl, the precipitate was filtered and dried in vacuo. The aldol condensation allowed us to obtain the desired chalcones in high yields and high purity.

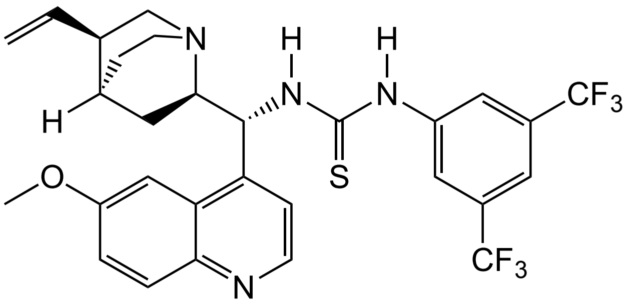
2.4. Study upon the intramolecular Friedel-Crafts alkylation

After the synthesis of chalcones, we began the tests for the reaction of interest, for these tests we used both organocatalysts and Lewis Acids.



9-amino(9-deoxy)epi-chinidine

C1



9-epi-NH_2-Thiourea-QD

C2

$NiCl_2$ $InCl_3$ $Mg(ClO_4)_2$

C3 **C4** **C5**

Fig. 17 Catalysts for the intramolecular F-C alkylation

The presence of the -OH group, in the meta position of the aromatic ring present in acetophenone, turns out to be very useful now, thanks to the electron releasing effect, it allows an increase in nucleophilicity in the ortho and para position, in this way the aromatic ring can be activated and the nucleophilic attack towards the β carbon of the double bond, the chalcone electrophilic carbon, should be favoured.

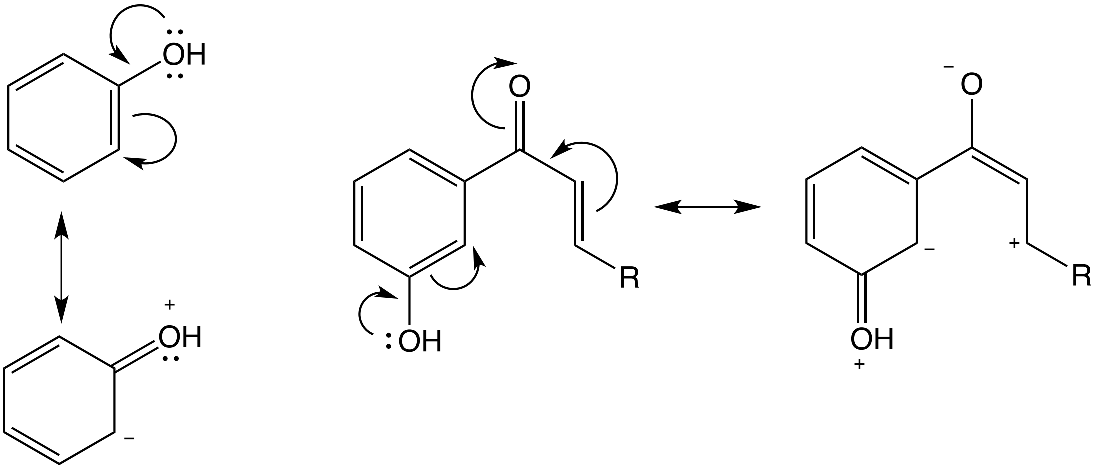
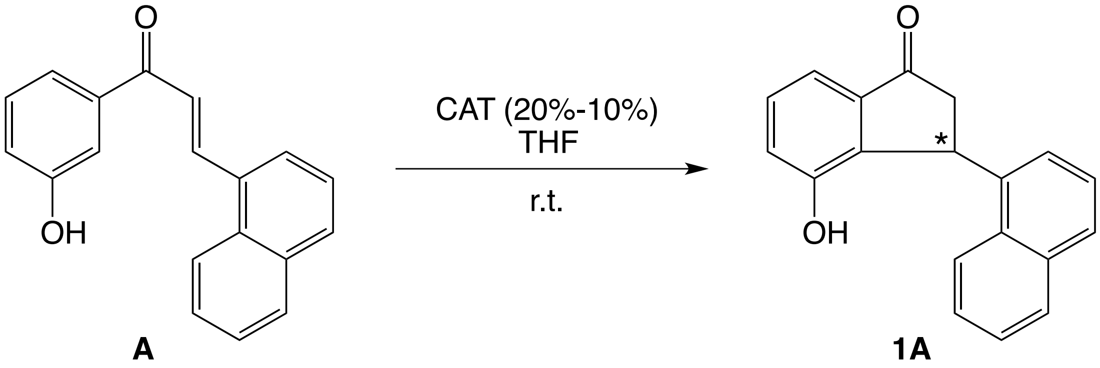


Fig. 18 Effect of the -OH group and activation of the meta position

Catalytic system C1 should provide the activation of the chalcone via iminium ion, while catalyst C2 provide the activation of the β-position of the chalcone via H bond and the aromatic moiety via base catalysis. The choice of these two systems was made with the intention to check if their utilization is possible also for the intramolecular reaction. The first system exploits an organic acid as co-catalyst, this one operate as counterion to increase the effectiveness of the catalysts itself and to form a catalytic salt; in this case we should obtain the condensation of the chalcone carbonyl group with subsequent formation of the iminium ion, the chiral nature of the catalyst, together with its steric hindrance, should drive the attack of the nucleophilic carbon in the 2' position of the aromatic ring to the electrophilic carbon of the double bond, towards the less hindered and face of the molecule, determining in that way the configuration of the new chiral centre. The second catalytic system is bifunctional, in fact it should activate the β-position of the chalcone through H bond between the chalcone carbonyl group and the two hydrogens of the thiourea moiety, while the aromatic moiety of our chalcone should be activated through base catalysis, which promotes the deprotonation of the nucleophile.

The employment of Lewis acids exploits the coordination of the carbonyl oxygen through the empty valence orbitals owned by the metal, which can accept lone pair of the oxygen, we chose to use also some of these compounds because some examples of F-C reactions, which employ these systems, are present in literature[21].

2.4.1. Reaction A: synthesis of 4-hydroxy-3-(naphthalen-1-yl)-2,3-dihydro-1*H*-inden-1-one



Scheme 11 Reaction A: intramolecular F-C

We made some tests of intramolecular F-C reaction upon chalcone A using THF as solvent and trying different catalytic systems:

- 9-amino(9-deoxy)epi-quinidine + 2-hydroxy-5-nitrobenzoic acid
- 9-epi-NH_2-Thiourea-QD
- $NiCl_2$
- $InCl_3$
- $Mg(ClO_4)_2$

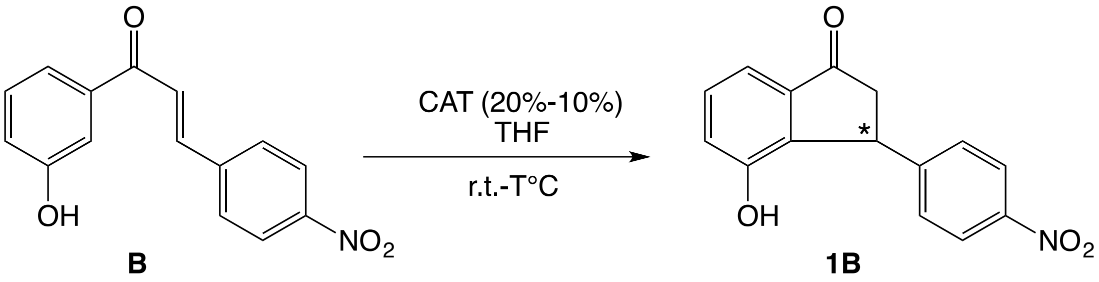
Reaction	Catalyst	Solvent	T(C°)	Time(h)	Conversion(%)
R41	C1	Toluene	rt	24	/
R41b	C1	THF	40	72	/
R42	C1	THF	rt	72	/
R43	C3	THF	rt	72	/
R44	C4	THF	rt	72	/
R45	C5	THF	rt	72	/
R46	C2	THF	rt	72	/

Table 1 Reaction A: catalysts tests

Reaction R41 has been done first in toluene, which was the solvent used in the previous researches, however our chalcone did not dissolve very well and after 24 hours we never noticed any differences. We decided to reproduce the same reaction changing solvents and temperature, while all the other tests were done at room temperature.

In anyone of the tests we obtained good results, the ^{1}H NMR analysis shows, in fact, that the signals related to the α and β carbons of the double bond conjugated to the carbonyl are still present, in their place no new singal, we could trace back to the formation of our product of interest, was found.

2.4.2 Reaction B: synthesis of 4-hydroxy-3-(4-nitrophenyl)-2,3-dihydro-1*H*-inden-1-one



Scheme 12 Reactioin B: intramolecular F-C

Since chalcone A revealed to be unreactive for the intramolecular FC alkylation we decided to focus on the use of chalcone B in which the presence of a nitro groups should increase the reactivity of the double bond. This fact led us to focus our efforts in assessing the possibility of making only the intramolecular reaction, leaving aside the synthesis of the chiral axis. Thus we tested the reactivity of chalcone B, using THF as solvent and trying some of the catalytic systems we used for reaction A:

- 9-amino(9-deoxy)epi-quinidine + 2-hydroxy-5-nitrobenzoic acid
- 9-epi-NH$_2$-Thiourea-QD
- Mg(ClO$_4$)$_2$

Reaction	Catalyst	Solvent	T(C°)	Time(h)	Conversion(%)
R51	C5	THF	rt	24	/
R51b	C5	THF	50	72	/
R52	C2	THF	rt	24	/
R52b	C2	THF	50	72	/
R53	C1	THF	rt	24	/
R53b	C1	THF	50	72	/

Table 2 Reaction B: catalysts tests

Each reaction, after 24 hours, was brought from r.t. to 50°C because we did not see any difference in the reaction mixture composition, which was controlled by TLC. Also in this case we had bad results and the ^{1}H NMR analysis confirmed the absence of the reaction product.

2.5 Study upon the intramolecular Friedel-Crafts reaction of epoxy derivatives

Given the poor results obtained with the tests reported above upon the direct intramolecular F-C reaction, we decided to adopt a different strategy.

We decided to change the electrophilic partner of our reaction. Instead of using a Michael acceptor we envisaged to use an expoxide (Fig. 19), which could be easily obtained from our chalcone by a simple oxidation reaction. In this way, we hoped to exploit the high reactivity that epoxides show towards the classical ring opening reactions. Moreover, the use of the epoxide as the starting material brings about an additional degree of complexity to the system. In fact, the starting epoxide is chiral and performing the asymmetric intramolecular F-C reaction on the racemic mixture may result in a kinetic resolution of the epoxide that, in the best case, would lead us to a single enantiomer of our product (Fig.19).

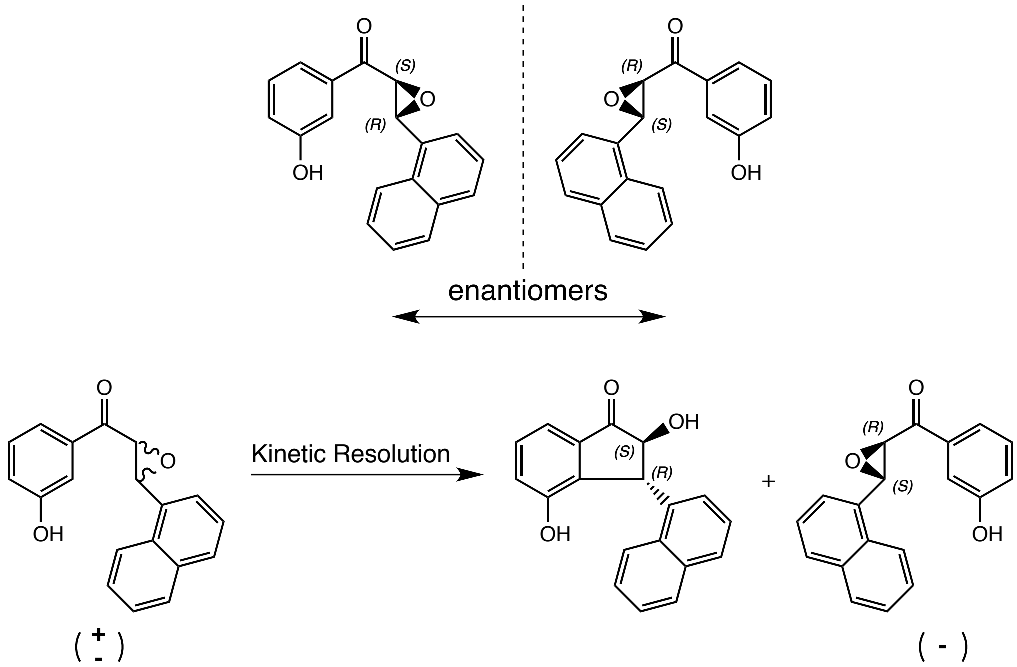
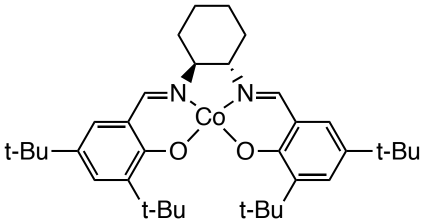


Fig. 19 Epoxide enantiomers and example of kinetic resolution

For the kinetic resolution we used different catalytic systems: organocatalysts and Lewis acids.

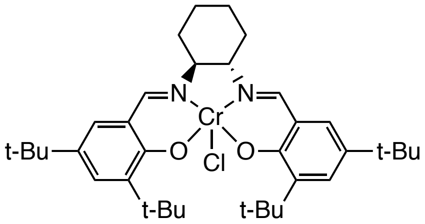
Among all the organocatalysts, we primarily tested phosphoric acids and their derivatives; these catalysts are Brønsted acids which are widely used to activate substrates in many reactions, such as Mannich, Friedel-Crafts and Diels-Alder[25], furthermore the presence of their substituents in 3,3' position increases the enantioselectivity of these systems.

Of the category of Lewis acids, we used mainly $InCl_3$ and some metal complexes which are generally called salen. Salen are a category of organic compounds that are often used as ligands for metals, we usually obtain them from the reaction between pro-ligands and metal precursors, for example the research group of Jacobsen et al. developed a type of salen which contains Mn and it is called Jacobsen's catalyst; this kind of catalysts is usually used for kinetic resolutions of racemic epoxides to obtain enantioenriched mixtures[26]. Inside the structure of these catalysts it is necessary the presence of bulky groups to promote tha catalytic activity, and elements of chirality can be included into the structure via the diamine backbone, via the phenyl ring, or both[27].



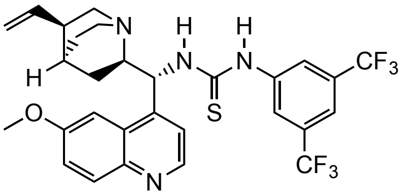
(*S,S*)-(+)-*N,N'*-Bis(3,5-di-*tert*-butylsalicylidene)
-1,2-cyclohexanediaminocobalt(II)

C6



(*S,S*)-(+)-*N,N'*-Bis(3,5-di-*tert*-butylsalicylidene)
-1,2-cyclohexanediaminocromium(III) chloride

C7

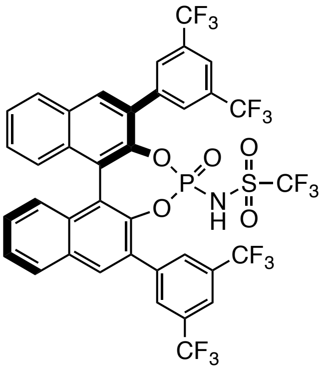


9-epi-NH_2-Thiourea-QD

C8

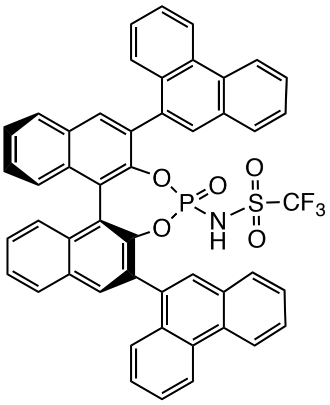
$InCl_3$

C9



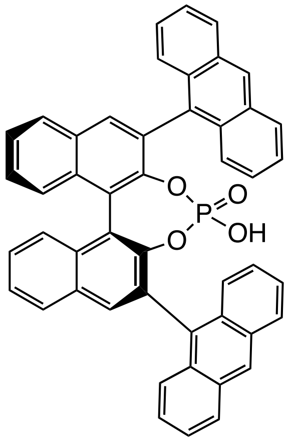
N-((11b*R*)-2,6-bis(3,5-bis(trifluoromethyl)phenyl)
-4-oxidodinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepin-4-yl)
-1,1,1-trifluoromethanesulfonamide

C10



1,1,1-trifluoro-*N*-((11b*S*)-4-oxido-2,6-di(phenanthren-9-yl)
dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepin-4-yl)
methanesulfonamide

C11

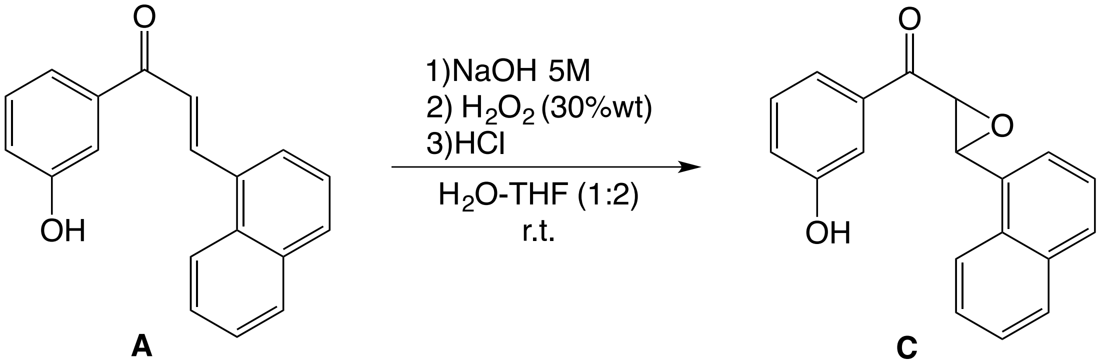


(11b*S*)-2,6-di(anthracen-9-yl)-4-hydroxydinaphtho
[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepine 4-oxide

Fig. 20 Catalysts for the kinetic resolution

2.5.1 Synthesis of epoxides

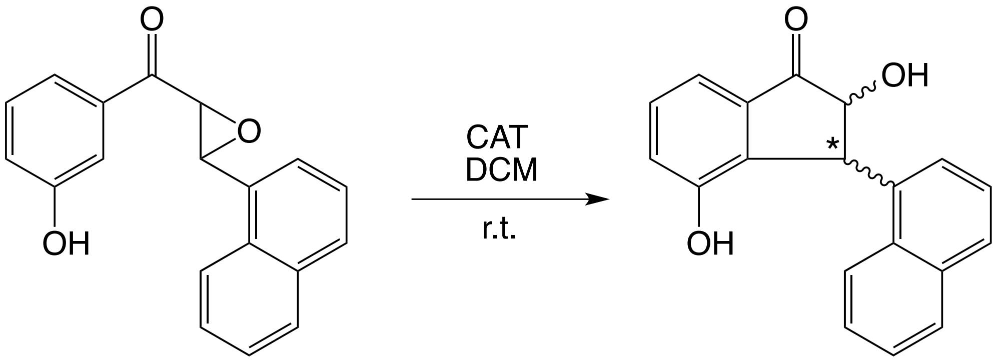
The epoxide of chalcone A was synthesized employing a procedure found in literature[21]. The chalcone of interest was dissolved in a mixture of H_2O-THF (1:2) and then a solution of 5M NaOH was added dropwise keeping the reaction mixture stirring, after 10 minutes we added a solution of H_2O_2 maintaining the stirring. After 10 hours we made the work-up and the reaction mixture was added to a flask with H_2O, the resulting epoxide should be in form of a precipitate but no differences were observed; since that the presence of the -OH group of the chalcone can give some problems when the reaction suffers pH changes, we tried to acidify the reaction mixture using HCl till neutrality.



Scheme 13 Synthesis of the epoxides

The product precipitated and it was filtered.

2.5.2 Reaction C: synthesis of 2-hydroxy-3-(naphthalen-1-yl)-2,3-dihydro-1*H*-inden-1-one



C **1C**

Scheme 14 Reaction C: kinetic resolution

All the test were done using the epoxide C because the epoxide D was obtained in low yield and we had not enogh of it for our tests. The reactions were performed in DCM as solvent and different catalytic systems:

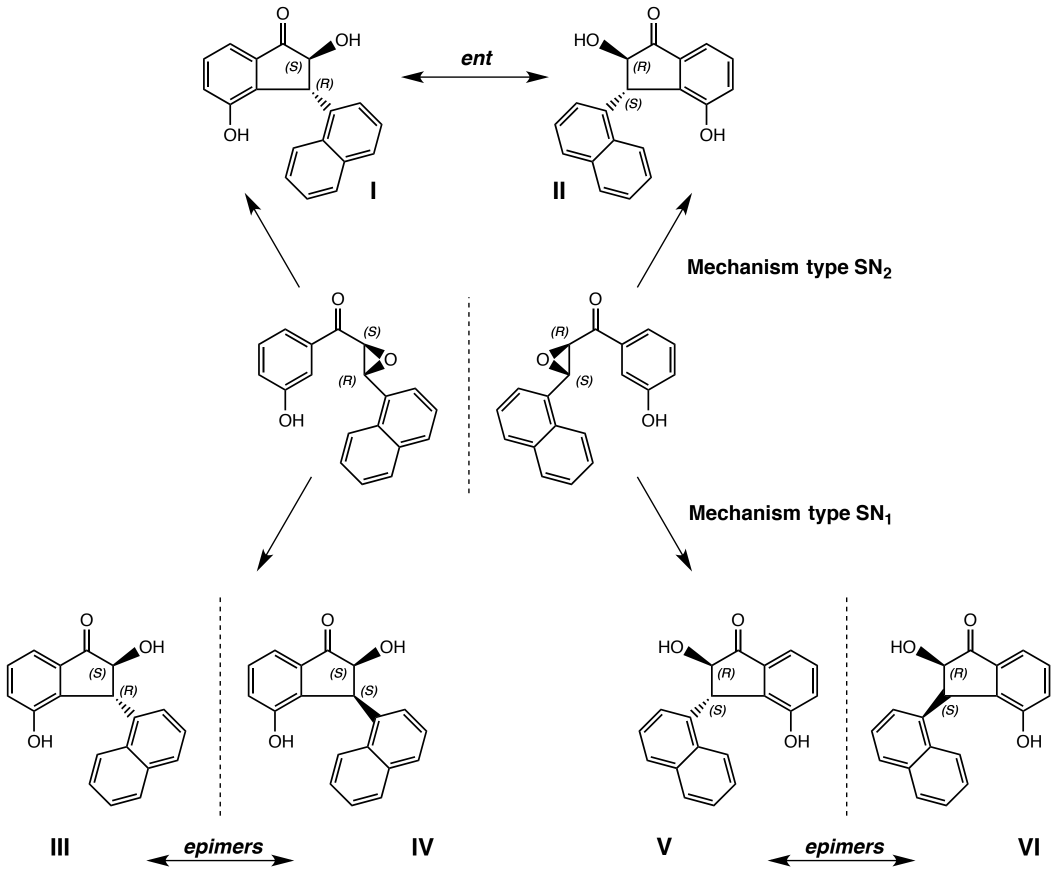
- (*S,S*)-(+)-*N,N'*-Bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminocromium(III) chloride
- (*S,S*)-(+)-*N,N'*-Bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminocobalt(II)
- (*S,S*)-(+)-*N,N'*-Bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminocromium(III) chloride + 4-metoxy-aniline
- $InCl_3$
- 9-epi-NH_2-Thiourea-QD
- *N*-(2,6-bis(3,5-bis(trifluoromethyl)phenyl)-4-oxidodinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepin-4-yl)-1,1,1-trifluoromethanesulfonamide
- (2*s*,11b*S*)-2,6-di(anthracen-9-yl)-4-hydroxydinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepine 4-oxide
- 1,1,1-trifluoro-*N*-((11b*S*)-4-oxido-2,6-di(phenanthren-9-yl) dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepin-4-yl) methanesulfonamide

Reaction	Catalyst	Solvent	T(C°)	Time(h)	Conversion(%)
R56	**C7**	DCM+TBME	rt	72	/
R57	**C6**	DCM+TBME	rt	72	/
R58	**C9**	DCM	rt	72	/
R59	**C7+4-OMe-aniline**	DCM	rt	72	/
R60	**C10**	DCM	rt	96	100
R61	**C8**	DCM	rt	96	/
R62	**C12**	DCM	rt	24	/
R63	**C11**	DCM	rt	24	100

Table 3 Reaction C: catalysts tests

No one of the catalytic system used has led to the opening of the epoxide. From the ^{1}H NMR analysis in fact we should have observed: a reduction of the signals corresponding to the hydrogens bonded to the two carbon of the epoxide ring, together with the formation of new signal corresponding to the product of opening of the epoxide, which was promoted by our intramolecular F-C reaction. We actually do not see any variations between the ^{1}H NMR spectrum of the starting epoxide and the ^{1}H NMR spectra of the reaction mixtures.

The only two tests which have shown some variations in their initial spectra were tests R60 and R63. The crudes of these reactions were purified by column chromatography, however we were not able to obtain a perfectly pure product due to the presence of some impurities. Anyway, from the ^{1}H NMR analysis, we were able to see that the signals related to the hydrogens of the epoxide ring (4.28 and 4.70 ppm) were all gone. This means that the epoxide ring has been opened but not in a selective way, as we expected from our kinetic resolution, it could be that both the two enentiomers of the starting epoxide reacted.



Scheme 15 Example of possible reaction pathways

The ring opening could be occurred in two different ways (Scheme 9). If the ring opening has followed a reaction mechanism type SN_2, we would get two enantiomers of our product, each of them derived from its starting epoxide. If the ring opening has followed a reaction mechanism type SN_1, we would get two couples of epimers derived from the two starting epoxides, due to the loss of selectivity promoted by a carbocation intermediate, moreover the two couples III/V and IV/VI are enantiomers respectively.

The presence of other signals in the spectrum, that could be related to our desired product, combined with a GC-MC analysis allowed us to confirm our hypothesis. In the GC-MC analysis the presence of a peak with a the same m/z of our product of interest (M = 290), together with other signals that could be related to the loss of the two -OH groups and of the naphthalene were a confirmation of the presence of our product.

2.6 Conclusions

The tests done so far have shown that employing these catalytic systems and these reaction conditions, we were not be able to obtain any results in the intramolecular and asymmetric Friedel-Crafts alkylation of chalcones to produce the indenones obtained in our previous researches through the intermolecular F-C.

Also the tests based upon the kinetic resolution have not given very good results, except for two test.

These tests show that we have reached our goal to obtain our intramolecular F-C reaction, but the kinetic resolution has not occurred as we expected. We will probably have to study better the reaction conditions and the reaction pathway to develop a better intramolecular F-C reaction.

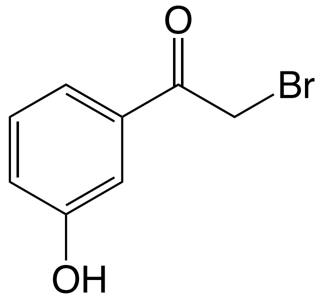
3. Experimental section

All the ^{1}H NMR spectra have been done using the spectrometers Gemini 300 MHz and Mercury 400 MHz, the samples have been prepared using deuterochloroform or DMSO-d_6 containing TMS as internal standard. Chemical shifts δ are reported in ppm with respect to TMS, while the coupling constants J are reported in Hz. To indicate the multiplicity of protons we have used the following abbreviations: s, singlet; d, doublet; t, triplet; dd, double doublet; ddd, double doublet of doublets; bs, broad signal; m, multiplet. The conversions have been determined through the ^{1}H NMR spectra of the crudes. The reaction progress has been monitored with TLC, purifications of all the crudes have been done through column chromatography employing silica gel as fixed phase.

The purification of 2-bromo-3'-hydroxyacetophenone was made through the use of the reversed-phase chromatography HPLC, column Synergi 4U Polar-RP 80A, the azeotropic mixture Acetonitrile/Water 70:30.

The mass spectra have been aquired through the spectrometer Focus-DSQ Thermo Scientific, capillary column in dimethylsilicon with 5% of phenylsilicon Thermo Scientific (0.25 mm Ø x 15 m).

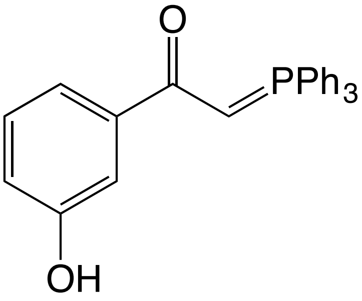
3.1 Synthesis of 2-bromo-3'-hydroxyacetophenone[22]



To a 150 mL round bottom flask equipped with a magnetic stirrer and reflux condenser, was charged 11,34 g (50 mmol) of $CuBr_2$, previously ground in a mortar, with 25 mL of Ethyl Acetate, this mixture was brought to reflux on a magnetic stirrer-hot plate. 4,08 g of 3'-hydroxyacetophenone (30 mmol) were dissolved in 25 mL of Ethyl Acetate and then added to the flask. The reaction mixture was initially green, the stirring was maintained vigorous to ensure the complete exposure of the $CuBr_2$, we can see that the reaction is finished when the $CuBr_2$ turn white, at the beginning of the reaction it was black, and we can't see anymore the evolution of HBr from the top of the condenser. After 2 hours the reaction mixture was cooled and filtered upon a layer of celite and graphite to remove the CuBr, the filtrate was washed with Ethyl Acetate to remove the product which has been collected in a round bottom flask. After the ^{1}H NMR analysis we saw that inside the reaction mixture there was still some starting material left, thus we equipped again the flask containing the reaction mixture with a magnetic stirrer and the reflux condenser. We made a proportion between the mmol of product obtained and the mmol of starting material left, in that way we have calculated the amount of $CuBr_2$ (18,36 mmol, 4,10 g) to add to the reaction mixture. The reaction mixture was left under reflux for 2 hours, after that we have followed the same procedure for the filtration. We obtained a very viscous amber oil. To further purification of the crude, we used reversed-phase chromatography HPLC, the azeotropic mixture was Acetonitrile/Water 70:30, flux 20 mL/min, column Synergi 4U Polar-RP 80A, retention time of the peak 4.80 min.

^{1}H NMR: (300 MHz, $CDCl_3$) δ (ppm) 4.47 (s, 2H), 6.08 (s,1H), 7.15 (ddd, *J* = 1.04 Hz, 2.60 Hz, 8.14 Hz, 1H), 7.35 (t, *J* = 7.89 Hz, 1H), 7.48-7.56 (m, 2H).

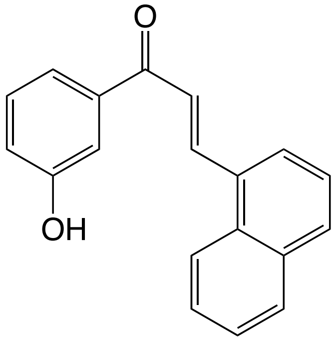
3.2 Synthesis of 3'-hydroxyphenylcarbonylmethylenetriphenylphosphorane[23]



To a 150 mL round bottom flask equipped with a magnetic stirrer, was charged 10,50 g PPh_3 (40 mmol) dissolved in 25 mL of Toluene, after that, a solution of 8,72 g of 2-bromo-3'-hydroxyacetophenone (40 mmol) in 25 mL of Toluene and 5 mL of DCM was added dropwise to the reaction mixture, keeping everything under nitrogen. The mixture was stirred overnight and the resulting crude was filtered and washed with Toluene. The gluey solid obtained was put in a flask together with a mixture of H_2O/MeOH 1:1 (150 mL + 150 mL) and stirred for 1 hour. A solution of NaOH 1,5M was added to the mixture until we reached pH 8, and then stirred vigorously for another hour. In the end we added DMC and extract the organic phase, which contained the phosphorane, we dried it in vacuo, we recrystallized the phosphorane from Ethyl Acetate and then we dried it again.

^1H NMR: (400 MHz, $CDCl_3$) δ (ppm) 4.41 (d, 24.89 Hz, 1H), 6.83 (ddd, *J* = 0.89 Hz, 2.51 Hz, 8.03 Hz, 1H), 7.09 (t, *J* = 7.84 Hz, 1H), 7.11-7.19 (bs, 2H).

3.3 Synthesis of (*E*)-1-(3-hydroxyphenyl)-3-(naphthalen-1-yl)prop-2-en-1-one (Wittg Reaction)



To a 50 mL round bottom flask equipped with a magnetic stirrer, was charged 679 μL of 1-naphtaldehyde (5 mmol) in 5 mL of DCM, and a solution with 1,98 g of 3'-hydroxyphenylcarbonylmethylenetriphenylphosphorane in 10 mL of DCM.

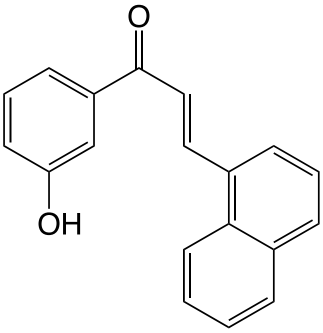
The reaction mixture has been left at r.t. for a week, after that the reaction mixture has been separated using DCM and water, the organic phase was collected and dried in vacuo. Column chromatography was made to purify our crude, mixture hexane/ethyl acetate 7:3, we obtained the purified product.

^1H NMR: (300 MHz, $CDCl_3$) δ (ppm) 7.12 (ddd, *J* = 0.98 Hz, 2.68 Hz, 8.12 Hz, 1H), 7.41 (t, *J* = 7.97 Hz, 1H), 7.49-7.67 (m, 6H), 7.86-7.99 (m, 3H), 8.26 (d, *J* = 8.79 Hz, 1H), 8.68 (d, *J* = 15.48 Hz, 1H).

3.4 General procedure for the synthesis of 3'-hydroxychalcone (Aldol Condensation)[24]

To a round bottom flask equipped with a magnetic stirrer and reflux condenser, was charged 1 eq. of 3'-hydroxyacetophenone, 1 eq. of aromatic aldheyde, 0,5 eq. of $Ba(OH)_2$ and absolute Ethanol. The reaction mixture is maintained under reflux for 3 hours, we can observe a drastic change of colour and the reaction mixture became very thick. Upon cooling, we added 1M HCl and we observed the precipitation of a solid, which has been filtered and washed with H_2O and Hexane. The solid was dried in vacuo overnight.

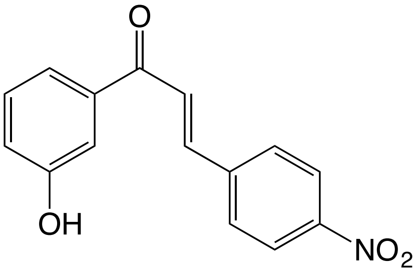
3.4.1 Synthesis of (*E*)-1-(3-hydroxyphenyl)-3-(naphthalen-1-yl)prop-2-en-1-one



Following the general procedure for the synthesis of 3'-hydroxychalcone, we added 2,72 g of 3'-hydroxyacetophenone (20 mmol), 2,72 mL of 1-naphtaldheyde (20 mmol), 3,47 g of $Ba(OH)_2$ • $8H_2O$ (11 mmol) and 20 mL of absolute Ethanol, to a 200 mL round bottom flask equipped with a magnetic stirrer and reflux condenser. After 3 hours the reaction mixture became orange and very thick, upon cooling we added 100 mL of 1M HCl and a yellow solid was formed. Column chromatography was made to purify our crude, mixture hexane/ethyl acetate 7:3, we obtained the purified product.

^{1}H NMR: (300 MHz, $CDCl_3$) δ (ppm) 7.12 (ddd, *J* = 0.98 Hz, 2.68 Hz, 8.12 Hz, 1H), 7.41 (t, *J* = 7.97 Hz, 1H), 7.49-7.67 (m, 6H), 7.86-7.99 (m, 3H), 8.26 (d, *J* = 8.79 Hz, 1H), 8.68 (d, *J* = 15.48 Hz, 1H).

3.4.2 Synthesis of (*E*)-1-(3-hydroxyphenyl)-3-(4-nitrophenyl)prop-2-en-1-one

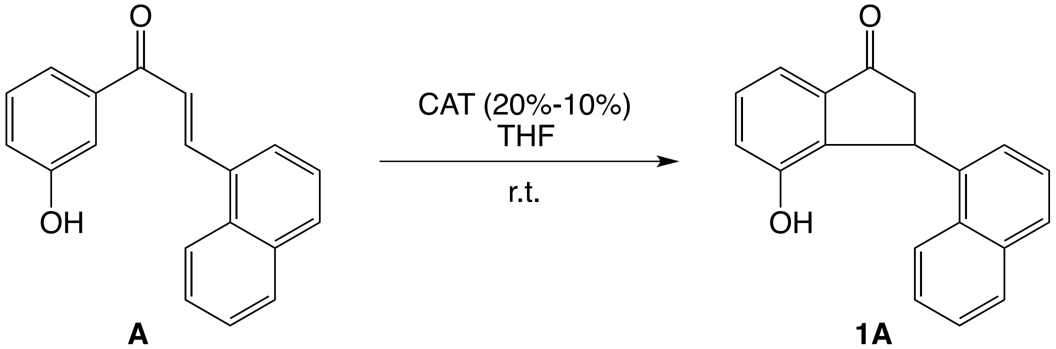


Following the general procedure for the synthesis of 3'-hydroxychalcone, we added 2,04 g of 3'-hydroxyacetophenone (15 mmol), 2,27 g of p-nitrobenzaldheyde (15 mmol), 2,60 g of $Ba(OH)_2$ • $8H_2O$ (8,25 mmol) and 25 mL od absolute Ethanol, to a 200 mL round bottom flask equipped with a magnetic stirrer and reflux condenser. After 3 hours the reaction mixture became orange and very thick, upon cooling we added 100 mL of 1M HCl and a yellow-brown solid was formed.

^{1}H NMR: (300 MHz, DMSO-d_6) δ (ppm) 7.10 (ddd, *J* = 0.95 Hz, 2.58 Hz, 8.23 Hz, 1H), 7.40 (t, *J* = 8.17 Hz, 1H), 7.49 (t, *J* = 2.09 Hz, 1H), 7.65-7.70 (m, 1H), 7.79 (d, *J* = 15.70 Hz, 1H), 8.05 (d, *J* = 16.08 Hz, 1H), 8.16 (d, *J* = 8.91 Hz, 2H), 8.29 (d, *J* = 8.90 Hz, 2H).

3.5 General procedure for the intramolecular F-C reaction and synthesis of 4-hydroxy-3-(naphthalen-1-yl)-2,3-dihydro-1*H*-inden-1-one

All the tests have been developed using the conditions reported in the scheme above and in the catalysts chart (Table 4).



A **1A**

In a 1,5 mL vial, equipped with a screw cap and a magnetic stirrer, was charged 54,9 mg of (*E*)-1-(3-hydroxyphenyl)-3-(naphthalen-1-yl)prop-2-en-1-one (0,2 mmol), 0,02 mmol of catalyst (10%) and 0,8 mL of THF. The reaction mixtures were left at r.t. for 72 hours, the crude was obtained after separation using DCM. The wanted product was not obtained.

The exception for this procedure are reaction R41, R41b and R42.

R41: In a 1,5 mL vial, equipped with a screw cap and a magnetic stirrer, was prepared the catalytic salt using 13 mg of 9-amino(9-deoxy)epi-chinidine (0,04 mmol, 20%) and 14,6 mg 2-hydroxy-5-nitrobenzoic acid (0,08 mmol) in 0,9 mL of Toluene. After 10 minutes 54,9 mg of (*E*)-1-(3-hydroxyphenyl)-3-(naphthalen-1-yl)prop-2-en-1-one (0,2 mmol) were added. After 24 hours the reaction mixture was controlled by TLC, no product was formed, so the reaction was brought to 40 °C for 72 hours (R41b). The crude was obtained after separation using DCM. The wanted product was not obtained.

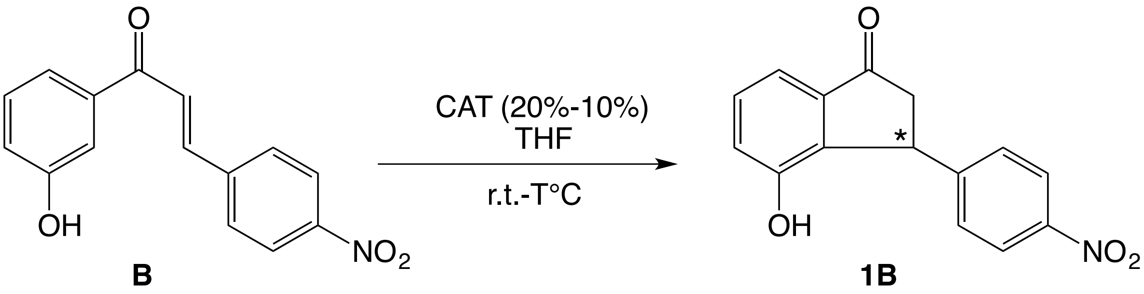
R42: In a 1,5 mL vial, equipped with a screw cap and a magnetic stirrer, was prepared the catalytic salt using 13 mg of 9-amino(9-deoxy)epi-chinidine (0,04 mmol, 20%) and 14,6 mg 2-hydroxy-5-nitrobenzoic acid (0,08 mmol) in 0,9 mL of THF. After 10 minutes 54,9 mg of (*E*)-1-(3-hydroxyphenyl)-3-(naphthalen-1-yl)prop-2-en-1-one (0,2 mmol) were added. The reaction mixture was left at r.t. for 72 hours,the crude was obtained after separation using DCM. The wanted product was not obtained.

Reaction	Cat	mmol	%	mg
R41	9-amino(9-deoxy)epi-chinidine	0,04	20	13,00
R41b	9-amino(9-deoxy)epi-chinidine	0,04	20	13,00
R42	9-amino(9-deoxy)epi-chinidine	0,04	20	13,00
R43	$NiCl_2$	0,02	10	4,8
R44	$InCl_3$	0,02	10	4,4
R45	$Mg(ClO_4)_2$	0,02	10	4,5
R46	9-epi-NH_2-Thiourea-QD	0,02	10	11,9

Table 4 Catalysts Reaction A

3.6 General procedure for the intramolecular F-C reaction and synthesis of 4-hydroxy-3-(4-nitrophenyl)-2,3-dihydro-1*H*-inden-1-one

All the tests have been developed using the conditions reported in the scheme above and in the catalysts chart (Table 5).

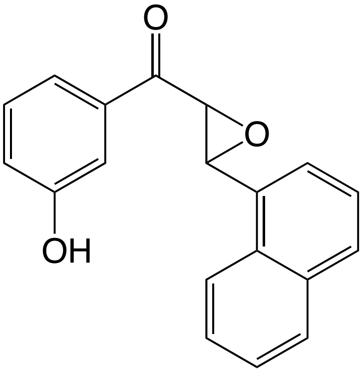


In a 1,5 mL vial, equipped with a screw cap and a magnetic stirrer, was charged 53,9 mg of (*E*)-1-(3-hydroxyphenyl)-3-(4-nitrophenyl)prop-2-en-1-one (0,2 mmol), 0,02 mmol of catalyst (10%) and 0,8 mL of THF. The reaction mixtures were left at r.t. for 24 hours, since no difference was found between the starting materials and the reaction mixture after that time, all the reaction were brought to 50°C and left in those conditions for 72 hours. The crude was obtained after separation using DCM. The wanted product was not obtained.

Reaction	Cat	mmol	%	mg
R51	$Mg(ClO_4)_2$	0,02	10	4,5
R52	9-epi-NH_2-Thiourea-QD	0,02	10	11,9
R53	9-amino(9-deoxy)epi-chinidine	0,04	20	13,00

Table 5 Catalysts Reaction B

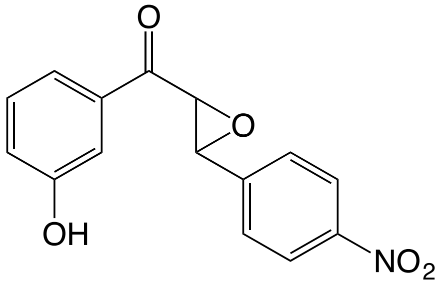
3.7 Synthesis of (3-hydroxyphenyl)(3-(naphthalen-1-yl)oxiran-2-yl)methanone[21]



To a round bottom flask equipped with a magnetic stirrer, was charged 2,5 g of (*E*)-1-(3-hydroxyphenyl)-3-(naphthalen-1-yl)prop-2-en-1-one (9,11 mmol) and 30 mL of H_2O-THF mixture (1:2), after that, 5 mL of NaOH 5M were added dropwise keeping the reaction mixture stirred for 10 minutes. Then, 7,5 mL of H_2O_2 (30% wt) were added dropwise and the mixture was stirred at r.t. overnight. The resulting mixture was poured into H_2O but we didn't see any precipitate, thus we added HCl 1M to neutralize the base. When we reached neutrality, we observed the formation of a precipitate which has been filtered and dried in vacuo. Column chromatography was made to purify our crude, mixture hexane/ethyl acetate 8:2, we obtained the purified product.

^1H NMR: (300 MHz, $CDCl_3$) δ (ppm) 4.28 (d, *J* = 2.05 Hz, 1H), 4.70 (d, 1.84 Hz, 1H), 7.13 (ddd, *J* = 0.94 Hz, 2.48 Hz, 8.06 Hz, 1H), 7.33 (t, *J* = 7.80 Hz, 1H), 7.44-7.60 (bs, 6H), 7.80-8.00 (bs, 3H).

3.8 Synthesis of (3-hydroxyphenyl)(3-(4-nitrophenyl)oxiran-2-yl)methanone

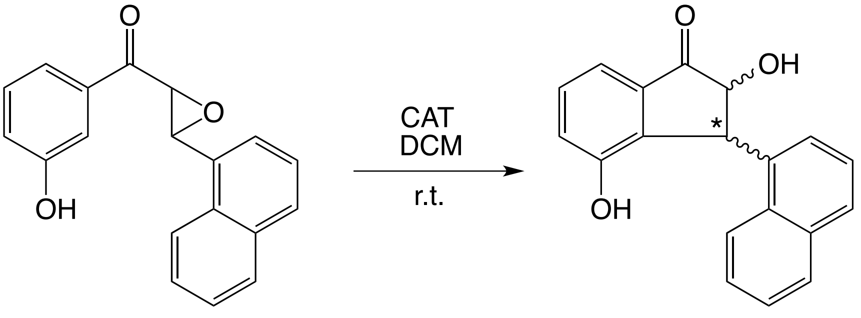


To a round bottom flask equipped with a magnetic stirrer, was charged 2,5 g of (*E*)-1-(3-hydroxyphenyl)-3-(4-nitrophenyl)prop-2-en-1-one (9,28 mmol) and 30 mL of H_2O-THF mixture (1:2), after that, 5 mL of NaOH 5M were added dropwise keeping the reaction mixture stirred for 10 minutes. Then, 7,5 mL of H_2O_2 were added dropwise and the mixture was stirred at r.t. overnight. The resulting mixture was poured into H_2O and acidified with HCl 1M to neutralize the base. When we reached neutrality, we observed the formation of a small amount of precipitate which has been filtered, the reaction mixture was extracted with DCM but we can not recover other product.

^{1}H NMR: (300 MHz, DMSO-d_6) δ (ppm) 4.35 (d, *J* = 1.86 Hz, 1H), 4.82 (d, *J* = 1.99 Hz, 1H), 7.09 (ddd, *J* = 0.95 Hz, 2.74 Hz, 8.07 Hz, 1H), 7.36 (t, *J* = 8.30 Hz, 2H), 7.48 (d, *J* = 8.36 Hz, 1H), 7.72 (d, *J* = 8.80 Hz, 2H), 8.28 (d, *J* = 8.87 Hz, 2H).

3.9. General procedure for the kinetic resolution and synthesis of 4-hydroxy-3-(naphthalen-1-yl)-2,3-dihydro-1*H*-inden-1-one

All the tests have been developed using the conditions reported in the scheme above and in the catalysts chart (Table 6).



C **1C**

Since there are many differences between the tests, the procedures for the synthesis of this compound will be devided according to the type of catalyst.

Reaction	Cat	mmol	%	mg
R56	(*S,S*)-(+)-*N,N'*-Bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminocromium(III) chloride	0,01	3,4	6,3
R57	(*S,S*)-(+)-*N,N'*-Bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminocobalt(II)	0,01	3,4	6,0
R58	$InCl_3$	0,03	10	6,6
R59	(*S,S*)-(+)-*N,N'*-Bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminocromium(III) chloride	0,0075	10	4,7
R60	*N*-(2,6-bis(3,5-bis(trifluoromethyl)phenyl)-4-oxidodinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepin-4-yl)-1,1,1-trifluoromethanesulfonamide	0,01	5	9,0
R61	9-epi-NH_2-Thiourea-QD	0,02	10	11,9
R62	(2*s*,11b*S*)-2,6-di(anthracen-9-yl)-4-hydroxydinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepine 4-oxide	0,01	5	7,0
R63	1,1,1-trifluoro-*N*-((11b*S*)-4-oxido-2,6-di(phenanthren-9-yl) dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepin-4-yl) methanesulfonamide	0,01	5	8,3

Table 6 Catalysts Reaction C

3.9.1 Salen complexes (R56, R57)

In a 1,5 mL vial, equipped with a screw cap and a magnetic stirrer, was charged 87,1 mg of (*E*)-1-(3-hydroxyphenyl)-3-(naphthalen-1-yl)prop-2-en-1-one (0,3 mmol), 0,01 mmol of catalyst (3,4%) and 0,8 mL of TBME and 0,2 mL of DCM.

The reaction mixtures were left at r.t. for 72 hours, the crude was obtained after separation using DCM. The wanted product was not obtained.

3.9.2 Salen complex with 4-methoxyaniline (R59)

In a 1,5 mL vial, equipped with a screw cap and a magnetic stirrer, was charged 21,8 mg of (*E*)-1-(3-hydroxyphenyl)-3-(naphthalen-1-yl)prop-2-en-1-one (0,075 mmol), 0,0075 mmol of catalyst (10%), 3,6 mg of 4-methoxyaniline and 0,8 mL of DCM.

The reaction mixtures were left at r.t. for 72 hours, the reaction mixture was controlled by TLC but the wanted product was not obtained.

3.9.3 Lewis Acid $InCl_3$ (R58)

In a 1,5 mL vial, equipped with a screw cap and a magnetic stirrer, was charged 87,1 mg of (*E*)-1-(3-hydroxyphenyl)-3-(naphthalen-1-yl)prop-2-en-1-one (0,3 mmol), 0,03 mmol of catalyst (10%) and 1 mL of DCM.

The reaction mixtures were left at r.t. for 72 hours, the crude was obtained after separation using DCM. The wanted product was not obtained.

3.9.4. Phosforic Acid derivatives (R60,R62,R63)

In a 1,5 mL vial, equipped with a screw cap and a magnetic stirrer, was charged 58,1 mg of (*E*)-1-(3-hydroxyphenyl)-3-(naphthalen-1-yl)prop-2-en-1-one (0,2 mmol), 0,01 mmol of catalyst (5%) and 0,8 mL of DCM.

The reaction mixtures were left at r.t. for 96 hours (R60) and 24 hours (R62, R63), the crude was obtained after separation using DCM. The product was obtained, coloumn chromatography hexane/acetone (75:25)

3.9.5. Quinidine Thiourea (R61)

In a 1,5 mL vial, equipped with a screw cap and a magnetic stirrer, was charged 58,1 mg of (*E*)-1-(3-hydroxyphenyl)-3-(naphthalen-1-yl)prop-2-en-1-one (0,2 mmol), 0,02 mmol of catalyst (10%) and 0,8 mL of DCM.

The reaction mixture was left at r.t. for 96 hours, the crude was obtained after separation using DCM. The wanted product was not obtained.

R60 ^{1}H NMR: (300 MHz, $CDCl_3$) δ (ppm) 4.84 (d, *J* = 4.31 Hz, 2H), 4.96 (s, 1H), 5.44 (s, 1H), 6.71 (ddd, *J* = 1.12 Hz, 2.57 Hz, 7.94 Hz, 1H), 6.80 (m, 2H), 6.90 (t, *J* = 7.88, 1H), 7.11 (ddd, *J* = 1.15 Hz, 2.71 Hz, 8.01 Hz, 1H), 7.31 (dd, *J* = 1.23 Hz, 7.06 Hz, 1H), 7.34-7.52 (bs, 6H), 7.82-7.90 (bs, 3H). GC-MC: m/z (%) 209 (70) [M^+], 121 (100).

R63 ^{1}H NMR: (300 MHz, $CDCl_3$) δ (ppm) 6.66-6.71 (bs, 1H), 6.73-6.91 (bs, 2H), 7.30 (dd, *J* = 1.19 Hz, 7.01 Hz, 1H), 7.37-7.50 (bs, 3H), 7.53-7.73 (bs, 3H), 7.80-7.90 (bs, 2H).

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