Alma Mater Studiorum – Università di Bologna

DOTTORATO DI RICERCA IN

CHIMICA

Ciclo XXVIII

**Settore Concorsuale di afferenza: 03/C1**

**Settore Scientifico disciplinare: CHIM/06**

TITOLO TESI

# DEVELOPMENT OF INNOVATIVE ORGANOCATALYTIC METHODOLOGIES AND SYNTHESIS OF NEW QCA CANDIDATES THROUGH REACTIONS WITH CARBOCATIONS

**Presentata da:** **Luca Mengozzi**

| **Coordinatore Dottorato** | **Relatore** |
| --- | --- |
| **Prof. Aldo Roda** | **Prof. Pier Giorgio Cozzi** |

**Esame finale anno 2016**

**Index**

# 1 Introduction to carbocations

During my three years of Ph.D. under the supervision of Prof. Pier Giorgio Cozzi, I have investigated different topics, from the development of organocatalytic reactions to metal complexes for material science applications, all related to the generation of carbenium ions, either isolated or produced as reaction intermediates.
In the first part of the thesis I will discuss and present the new organocatalytic methodologies that I developed, either as the main contributor either in collaboration with the other members of the research group. This research is inserted in the general investigation that the research group has carried on the organocatalytic $S_N1$ alkylation reaction with carbenium ions since 2008. Chapter 2.5 is instead dedicated to the new adventure we recently have undertaken in the field of photocatalytic promoted synthetic reactions.
In this first part I have included a chapter regarding the project I have developed during my stay in Prof. Miquel A. Pericàs group, as its main topic is organocatalysis even if carbenium ions are not involved.
The second part of the thesis is instead devoted to the research I have carried out in the context of the European project MolarNet. The goal of the project is to develop a molecular devices able to perform simple logic operations and hopefully to insert these devices into an operating logic system. The objective of Prof. Cozzi's unit was the synthesis of suitable molecules and our strategy, whose motivations will be discussed in detail in chapter 3, relies on the introduction of ferrocene moieties on different scaffolds through $S_N1$ reactions with stabilized carbenium ions. The chemistry on carbenium ions derived from ferrocene containing molecules was thus applied to frontier applications in molecular electronics.
As carbenium ions are the leitmotif of my research I will present a brief introduction about their history and reactivity.

## 1.1 Carbocation history[1]

The term carbocation[2] is used to define a generic carbon atom bearing a positive charge, but its use is quite recent.
The term carbonium ion[3] was the most widely historical name for such species and has been used until the 1980's. However other definitions for carbon species bearing a positive charge were proposed since their discovery in the beginning of the XX$^{th}$ century arousing unclear and controversial identification of these species.
It was only in the 1970's that Olah[4] proposed a new and unambiguous nomenclature that was accepted by scientific community in the following years and stated by IUPAC in 1983.[5]
According to Olah a carbocation is the more general name for a specie bearing a positive charge on a carbon. Carbenium ions can be distinguished between carbenium ions and carbonium ions, otherwise called non-classical carbenium ions. Thus the term carbonium ion is nowadays correctly used to refer to a precise type of carbenium ions while in the literature before the 1980's was used with the current meaning of carbocation.
A carbenium ion, or classical carbocation, is carbon with six valence electrons located in three sp$^2$ orbitals, occupied in the bonds with three substituents, and an empty p orbital. Due to its hybridization, the carbenium ion geometry is planar with the empty p orbital perpendicular to the plane where the three substituents lay. It must be reminded that the presence of sterical constraints can deviate this geometry from the perfect planarity.
From another point of view a carbenium ion can be seen as the protonated form of a carbene in its singlet state. This consideration suggests that stabilized carbenium ions can form the corresponding carbenes under basic conditions thus leading to totally different reaction pathways such as dimerization that is favored by the absence of hindered substituents.

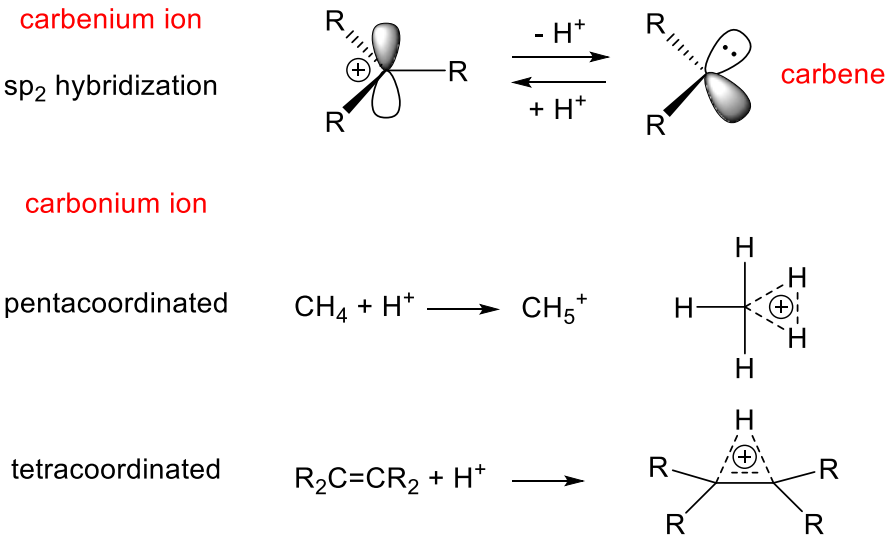



*Figure 1: carbenium ions and carbonium ions.*

A carbonium ion is instead a hypervalent carbon atom bearing a positive charge, in according to the well-known used terms ammonium and oxonium that refer nitrogen or oxygen species bearing an additional substituent. As a carbon atom do not possess any lone pair to expand its coordination sphere this can occur by the formation of two electrons three centers species in which the carbon valence results expanded. This concept is perfectly clarified through two simple examples. The first one is the addition of $H^+$ to methane that originates a $CH_5^+$ specie that can be observed only in mass spectrometry. Its structure is represented in figure 1 and the electron couple initially located on one C-H bond, engages a bonding interaction with the proton forming a three membered ring hold together by two electrons in which a positive charge is present all over the three nuclei. This hypervalent carbocation is defined by Olah as the parent carbonium ion with 5 atom valence.
The other possible carbonium ion bears a carbon with 4 atom valence that results from the addition of $H^+$ to a double bond that originates another three centers two electron system in which the proton is bound to both carbons and the positive charge is spread on the three nuclei.
The first example of a non-classical carbocation (or carbonium ion) dates back to 1922[6] when Meerwein proposed a carbocationic intermediate to explain the racemization of isobornylchloride. After the formation of the carbocation by action of the Lewis acid, a [1,3]-hydride shift responsible for the racemization occurs. During this process the positive charge is not localized on a specific carbon but is distributed over two carbons and the moving hydrogen being an example of non-classical carbocation.

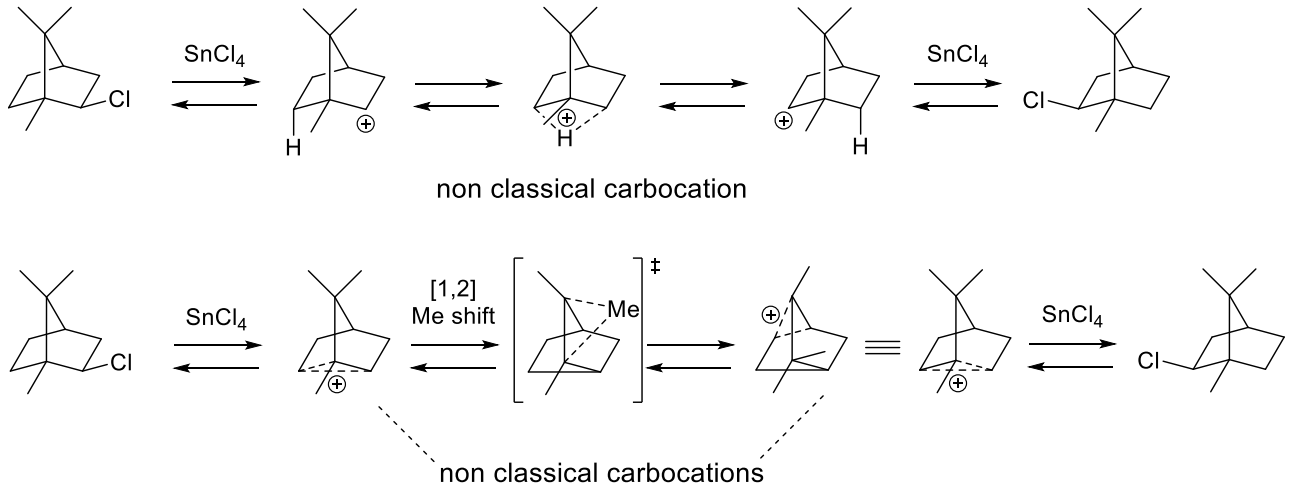



*Figure 2: mechanistic pathways for the isobornylchloride racemization*

Another possible explanation for the racemization in which a methylene shift is invoked has been proposed in 1933.[7] Also in this case two carbonium ions intermediates having three centers two electron systems are involved in the mechanism. The effective distribution of the positive charge over the two carbons was unanbiguosly determined by Olah[4] by NMR studies proving the existence of these non-classical carbenium ions.
The tropylium ion was the first carbocation being synthetized and isolated in 1891 from the reaction between bromine and cycloheptatriene.[8] However Merling reported the synthesis of a new specie

having brute structure $C_7H_6Br$, but he did not recognize, or propose, the carbocationic nature of the compound that was clarified only in 1954, when it was identified as tropilium bromide.[9]

The idea of the existence of a carbocationic specie was first advanced in 1899 by Norris[10] and Kerhmann[11] that observed the formation of colored solutions when trityl chloride or trityl alcohol solutions were treated with strong acidic solutions, usually Lewis acids such as $SnCl_4$, $ZnCl_2$ or $AlCl_3$ or concentrated sulfuric acid were employed. These reports immediately attracted great interest from the scientific community and the contributions from Von Baeyer,[12] Walden, Hofmann[13] and Gomberg[14] reinforced the first hypothesis of the existence of a carbocationic specie whose salt like nature was then unambiguously determined by conductibility measurements.

Carbocationic species were started to be considered also as possible reaction intermediates that could account for reactivity that could not be explained only with the classical valence theory. The discovery of the carbocation, that followed only of a year that of the first stable radical, marked the end of the rigidity of the valence bond theory opening the doors to the modern mechanistic theories of organic chemistry. As for every deeply innovative (or revolutionary) idea, it was skeptically welcomed by the older members of the scientific community that refused the collapsing of the $XIX^{th}$ century theories.

Indeed even if some pioneers such as Stieglitz,[15] who in 1899 tried unsuccessfully to demonstrate the existence of carbocationic intermediates in the addition of HCl to imines due to the transient nature of the iminium specie that could not be observed with the techniques of the time, supported the idea of that carbenium ions were involved in several reaction mechanisms, it took several decades for these hypothesis to be demonstrated and fully accepted.

It was Meerwein's explantion of the racemization of isobornylchloride in 1922[6] the first unambiguous evidence that a carbocationic specie was a reaction intermediate.

Whitmore[16] generalized these first examples into the heterolytic bond dissociation theory marking a turning point in theoretical chemistry that opened the way to other theories, substitution and elimination reaction overall, and contributed to rationalize a multitude of chemical transformations that had been regarded as obscure and bizarre exceptions so far. With its own words: "the time has arrived when a multitude of explanations of organic rearrangements can be discarded and the fact must be realized that these interesting reactions are not merely freaks to be expected from certain complex compounds but are dependent on properties inherent in even the simplest molecules. As soon as this important fact is recognized it will be possible to focus attention on the fundamental changes taking place in all rearranged molecule instead of considering each type of rearrangement as an isolated exception".

Indeed in the following years carbenium ions were recognized as crucial intermediates in many classical reactions such as Friedel Crafts alkylations and polymerizations, hydrobromination, dibromination, hydrochlorination of alkenes, Baeyer Villiger oxidation.

With the advance of the experimental techniques and the advent of efficient NMR analysis a multitude of carbenium ions were generated and characterized in particular in the 1960's and 70's thanks to the contributions of several research groups among whom Doering and Olah's gave fundamental contributions.

The synthetic methodologies and the reaction conditions to generate the carbenium ion are multiple and strongly depend on their stability that can span from species only stable at low temperatures for

short times to others stable in presence of air and moisture for years. Despite these differences four general strategies can be identified to generate a carbocation:

1) heterolytic cleavage of a carbon heteroatom bond usually promoted by the action of a Lewis or Brønsted acid,
2) electrophilic addition to an unsaturated double bond,
3) oxidative generation from a C-H bond either using a chemical oxidant (e.g. DDQ, CAN) either by electrochemical oxidation under classical conditions or through the cation pool methodology that consist in generating by irreversible oxidation the carbocation that is accumulated in the absence of a nucleophile and subsequently reacted,
4) addition of cations to neutral species, as in the case of the addition of $H^+$ to methane to give $CH_5^+$ or more generally in the formation of clusters between neutral substrates and $H^+$, $Na^+$ $K^+$. This latter class of carbenium ions are usually very unstable and have been detected almost exclusively by mass spectroscopy analysis. No applications in organic synthesis are known so far.

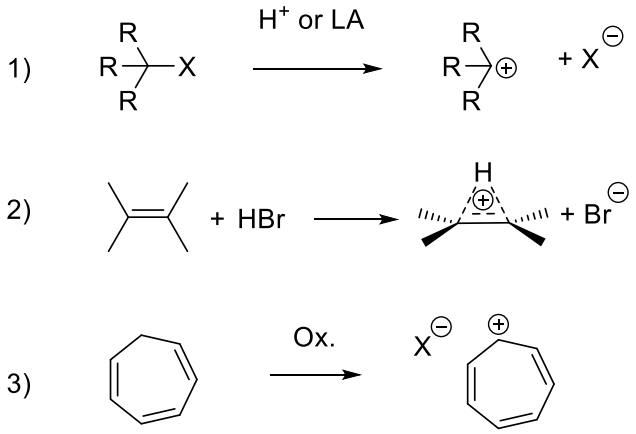
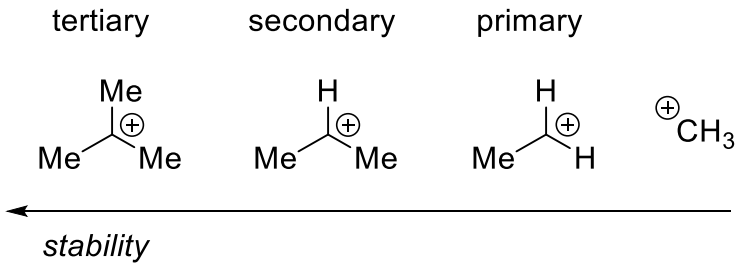



*Fig 3: representative examples of the general strategies for the generation of carbenium ions*

## 1.2 Stability of carbenium ions and the Mayr scale

A carbocation lifetime can span from micro seconds under ultravacuum conditions to years inside simply capped vials at room temperature, even without protective atmosphere. The stability of these species depends on the nature of the neighboring groups and in their ability to stabilize the positive charge: the more it is distributed by inductive or delocalization effects the more the carbenium ion is stabilized.
In general the presence of electrodonating groups stabilizes the charge, while electronwithdrawing ones exercise a destabilizing effect. The mechanism of stabilization dramatically determines its impact on the carbocation stability: the conjugation with π-systems determines a much more important stabilization than the presence of groups that donate charge by inductive effects.
The groups that stabilize the positive charge can be divided as follows:

1) The presence of ***α-alkyl groups*** stabilize the carbocation by ipercojugation effects, that is the partial overlapping of the sigma orbitals of the neighboring C-H with the empty p orbital of the carbocation, resulting in a mild redistribution of the positive charge. On the basis of this effect the stability scale for alkylic carbocations is the following:




Indeed, tertiary alkylic carbenium ions were observed in superacidic media at low temperatures and were characterized by NMR and spectrometric measurements. Their relative stability is also demonstrated by their presence as intermediates in organic reactions such as the tertbutylcarbamate deprotection under acidic conditions.
With similar strategies even secondary alkylic carbenium ions have been generated while primary alkylic carbenium ions have never been characterized so far.

2) The ***conjugation with a π system*** adjacent to the carbocation allows the delocalization of the positive charge over the allylic or aromatic system resulting in a greater stabilization compared to the presence of even three alkyl groups. Indeed the trytilium ion is perfectly stable at room temperature and on air. Less stabilized carbenium ions such as allylic, diallylic and benzhydrylic carbenium ions were generated from their corresponding alcohols since the 1960's in concentrated $H_2SO_4$, were characterized by NMR and spectroscopy and are relatively long lived species even at room temperature. A peculiar feature of these carbenium ions is that they can be generated also in diluted acidic solutions but they react with the starting alcohol to give the corresponding ether. This latter is usually irreversibly

formed under Brønsted acid conditions while in presence of specific Lewis Acids such as In(III) salts this mechanism can become reversible.
An exceptional example of this class of carbenium ions is the tropylium carbenium ion that is not only stabilized by π-conjugation but also thanks to the aromaticity conquered after the carbocation formation.

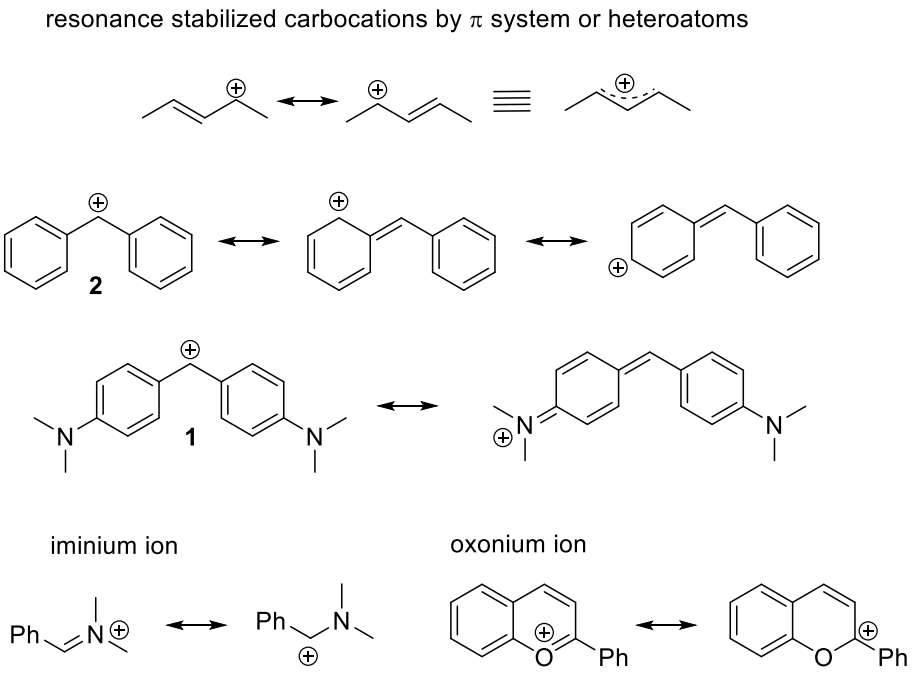



*Figure 4: stabilization of carbocation by conjugation or by the presence of an heteroatom.*

3) The presence of a ***neighboring or conjugated heteroatom*** that can donate a lone pair forming a resonance structure that greatly contributes to the stability of the carbocation. The most important heteroatoms for this purpose are nitrogen, oxygen and sulfur. Instead halogen's lone pairs are too attracted by their nuclei to be efficiently shared in resonance structures with the carbenium ion. Moreover the electronwithdrawing effect that they exercise destabilizes the carbenium ion.
In case of oxygen or nitrogen bounded to the carbenium ions, these species are often referred as oxonium or iminium ions (figure 4). In case of oxygen the importance of the two limit resonance structures is quite balanced, and the bond character results intermediate between a single and a double bond, while in case of nitrogen the iminium form is by far predominant over the carbocationic structure. Nevertheless the electrophilic site for a nucleophilic addition is the carbon atom.
Nitrogen or oxygen strongly contribute to the stabilization of carbenium ions also when they are conjugated through π-systems, for example in case of 4,4'-bisdimethylamminobenzydrilium ion **1** and xantenium ion. The importance of the stability of the conjugated nitrogen atoms can be well understood comparing 4,4'-bisdimethylamminobenzydrilium **1**, a stable and persistent carbocation even in neutral

water, with the corresponding benzydrilium ion **2**. This latter, that lacks the ammino groups, cannot be generated in presence of moisture and is a very short lived specie.

4) The ***coordination with a transition metal center*** stabilizes the carbocation by donation of electron density form the occupied d orbitals of the metal center. The most famous examples are the allylic cations coordinated by palladium or iridium complexes and the ferrocenyl carbocation (figure 5). For the latter the positive charge is not only stabilized by the conjugation with the cyclopentadienyl ring, but also by the overlapping with the d orbitals of the iron center that determines a bending of the alkyl chain towards the iron that effectively shields one prostereogenic face of the carbenium ion. In particular in case the carbenium ion is generated by the heterolytic cleavage of the bond with a leaving group, the face opposite to that occupied by the leaving group results shielded by the iron so that the $S_N1$ reaction occurs with retention of configuration. This property has been widely exploited to perform enantiospecific $S_N1$ reactions starting from enantioenriched substrates to obtain chiral phosphine ligands[17] such as JosiPHOS and I too have taken advantage of this property in my research on QCA candidates (chapter 3.2).

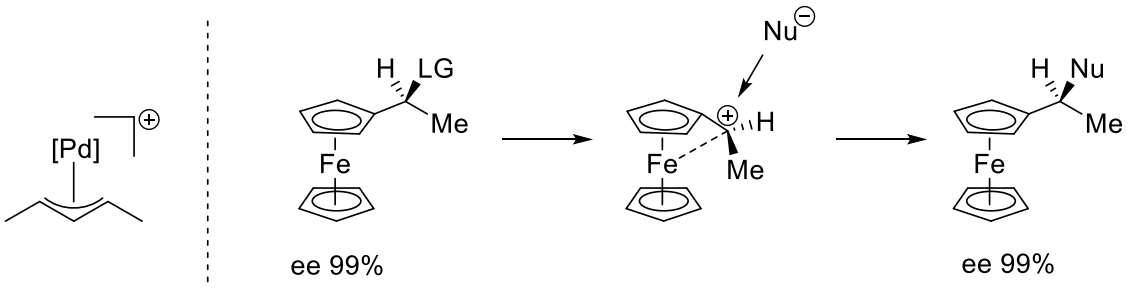



*Figure 5: carbenium ions stabilized by formation of complexes with transition metals.*

Several scientists have developed quantitative methods to translate these general considerations into a real stability scale of carbenium ions. The measurements of physical and thermodynamic properties were the first being investigated: Lossing determined the stabilization energy and the ion size of carbenium ions in the gas phase[18] and Arnett[19] studied their stability through calorimetric measurements. However, a real turning point in the evaluation of carbenium ions stability for its application in organic reactions, as it is intimately connected with their reactivity and formation, has been made by H. Mayr. Instead of focusing on thermodynamic measurements he concentrated on the kinetics of the reaction of carbocationic species with various nucleophiles eventually establishing a protocol to translate these results in parameters able to quantify the reactivity of electrophilic and nucleophilic species and roughly predict if a reaction between an electrophile and a nucleophile would occur. He has introduced then a scale of reactivity, able to classify carbenium ion species, in function of their reactivity. Carbenium ions are one of the protagonists of Mayr scale being the first electrophilic species that were investigated.
To build the scale,[20] Mayr and coworkers measured the kinetics of various nucleophiles, used in large excess to obtain first order kinetic equations, with 4,4'-dimethoxybenzydrilium ion whose electrophilicity parameter *E* was arbitrarily assigned to zero. Based on the reaction rates two

parameters were assigned to each nucleophile: the nucleophilicity parameter *N* and nucleophile-specific sensitivity parameter $s_N$. For an approximative evaluation of the predicted reactivity only the parameter *N* can be considered, while $s_N$ considers the specific interactions and the intrinsic behavior typical of the single nucleophile when it reacts with an electrophile.
These standard nucleophiles were then reacted with other electrophiles allowing the measurements of their electrophilicity parameters and the core of the scale was built.
The measured parameters are related to the reaction rate *k* by the Mayr equation:

$$\log k_{20\,°C} = s_N (N + E) \qquad (1)$$

*E* = electrophilicity parameter
*N* = nucleophilicity parameter (solvent dependent)
$s_N$ = nucleophile-specific sensitivity parameter (solvent dependent)

It must be underlined that the scale is logarithmic so that one point in difference between two species on the scale corresponds to three orders of magnitude of variation on the reaction rate. Moreover the *N* and $s_N$ parameters are solvent dependent so changing the reaction solvent may result in significant variations. These parameters only consider the polar effect of a nucleophile or an electrophile so that steric hindrance or different effects that may be encountered in different combinations of reagents are not taken into account. Based on these considerations, Mayr and his collaborators stated that the real rate constants *k* for the reactions are expected with a deviation by a factor of 10 to 100 from the predicted ones, so that this reactivity scale should not be considered strictly but as a general indication of reactivity.
Detailed information and the complete database of nucleophiles and electrophiles can be found on the Mayr group website.[21]
In the last twenty years the scale has been greatly enriched so that it now contains several hundreds of chemical species spanning over a range of 25 orders of magnitude both on the electrophilic and nucleophilic sides.
A simple and straightforward rule of thumb was derived by Mayr to predict if a polar reaction will occur at room temperature:

if $E + N > -5$ a polar reaction is expected to occur.

When $E + N > 5$, no activation barrier is present and the reaction rate is limited only by the diffusion of the reagents inside the reaction media. The extreme reactivity of these reactant couples do not allow any control over the reaction pathway and selective transformations are difficult to achieve. In particular in case of enantioselective or more generally stereoselective transformations, it would be impossible to favor one specific stereoisomer over the others. Indeed the majority of the polar reactions occurs in the range $-5 < E + N < 5$. On the other hand with $E + N < -5$ the predicted reaction rate is so slow that the transformation is expected to occur in months or years!
A great variety of carbenium ions are present on the Mayr scale ranging from persistent ones stable also in water to others extremely sensitive and difficult to generate, and thus extremely reactive.

The more reactive a carbenium ion is, the more difficult it is to generate it as it will easily react with water or weak nucleophiles hampering the reaction with the desired nucleophilic partner. On the other side too stabilized carbenium ions are easily generated but they can react only with strong nucleophiles. The most employed carbenium ions in polar reactions are located between these two extremes, between 0 and -10 on the Mayr scale, affording a good compromise between reactivity and stability.

The most unstable carbocation located on the Mayr scale is a secondary benzylic carbocation with $E = 6.04$. Primary benzylic or allylic carbenium bearing alkylic substituents that are not stabilized by the cohordination with a metal center such as Pd, are too reactive to allow the measurements of kinetic rates, so they are out of Mayr scale as well as all the alkylic carbenium ions.

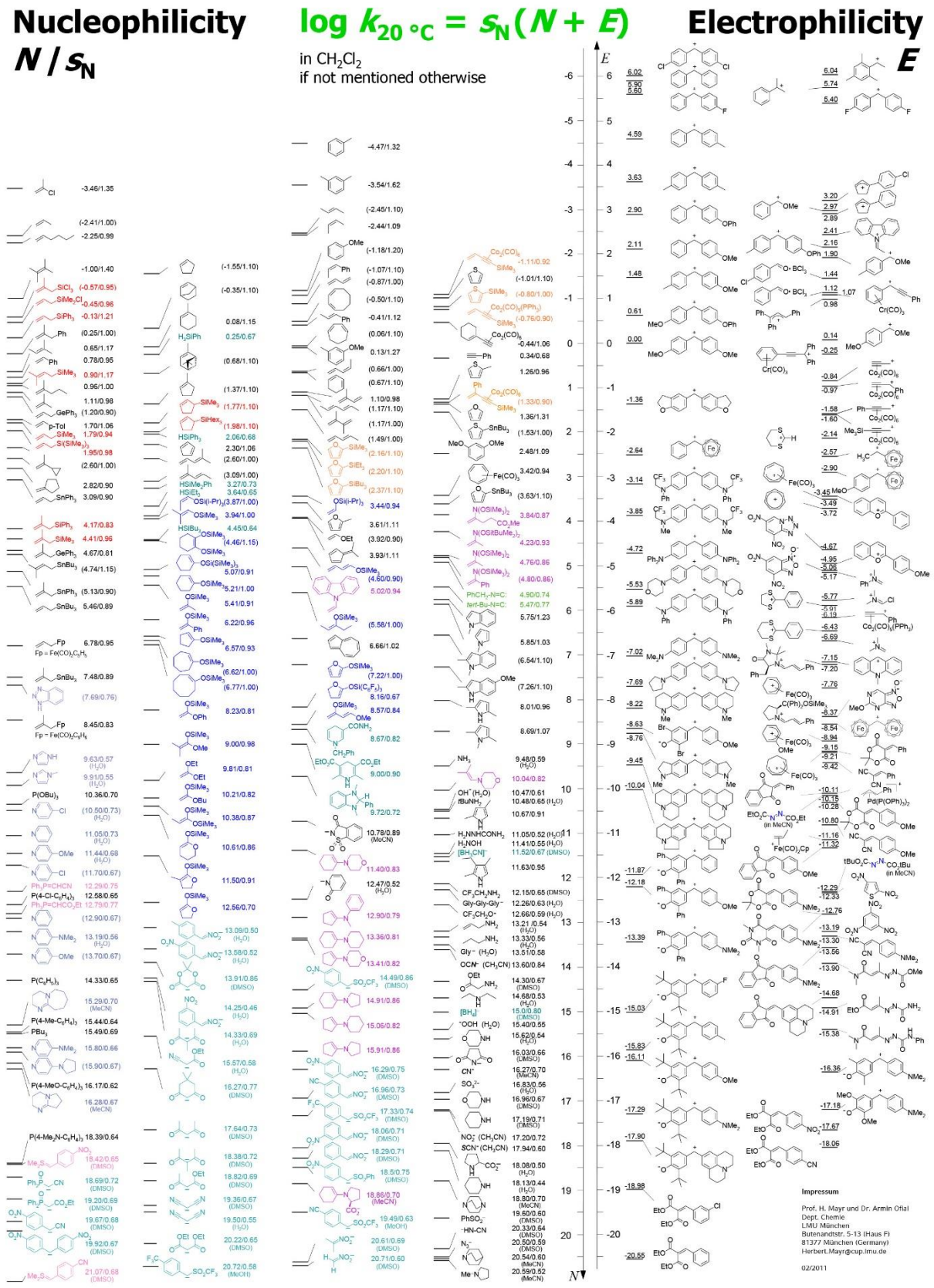



*Figure 6: Mayr scale (available from the Mayr website).*

## 1.3 Reactivity of carbenium ions

Carbenium ions are electrophilic species that lack electrons so they will ultimately try to gain electrons either by reaction with nucleophiles or by elimination processes to form neutral species. However these reactions require a certain time to occur, so that very unstable carbenium ions rapidly undergo intramolecular rearrangements to afford more substituted and stable carbocationic species that will be the effective reaction partner for a nucleophile. Carbenium ions can also react with bases to afford carbenes.
This general reactive trend gives rise to many possible reactions that can be however divided into four classes depending on the mechanism, reactant partner and final product.

1) ***Reactions with a nucleophile to afford a neutral product***, known as $S_N1$ reactions. These nucleophilic substitutions proceed through a planar carbocationic intermediate and are distinguished from the $S_N2$ type reactions that proceed through a concerted five membered transition state in which a carbocationic specie is not involved. $S_N1$ reactions can be classified depending on the nature of the nucleophile:
   - classical $S_N1$ reactions involving non aromatic nucleophiles, either negative charged such as azides or enolates, or neutral such as amines, enamines or alcohols that will lose a proton subsequently to the nucleophilic addition affording the neutral product;
   - Friedel-Crafts reactions in which an aromatic nucleophile attacks the carbocation and subsequently loses a proton to regain the aromaticity;
   - hydride transfer reactions in case a reducing agent donates an hydride anion leading to the formation a C-H bond.

2) ***Elimination reactions*** in which the carbocation loses a positive fragment from the α-position relatively to the positive charge to give an olefin. Usually a proton is lost and by consequence this process in favored by bases and protic solvents that solvates the anions reducing their nucleophilicity and the possibility of a substitution reaction. On the other hand the use of polar solvents with exposed negative dipoles stabilize the carbocation and enhance the reactivity of the nucleophile favoring the substitution reaction. Of course carbenium ions lacking a proton (or a leaving group) on the α-position, for example benzydrylic carbenium ions, cannot undergo an elimination reaction.

3) ***Rearrangements to afford a more stabilized carbocation***. These reactions are quite common for unstable carbenium ions, especially primary or secondary carbenium ions that rearrange by alkyl, or hydride transfer to afford more stable carbenium ions, while in case of $S_N1$ reactions or eliminations a neutral product is obtained.
   The rearrangement of the isobornyl cation (figure 2) and the impossibility to obtain carbocation **3** (figure 6) clearly exemplify these reactions. Even if the carbocation is generated in presence of nucleophilic species it is not possible to trap it because the

rearrangement, that is an intramolecular process, is faster than the nucleophilic addition, especially for very unstable species.

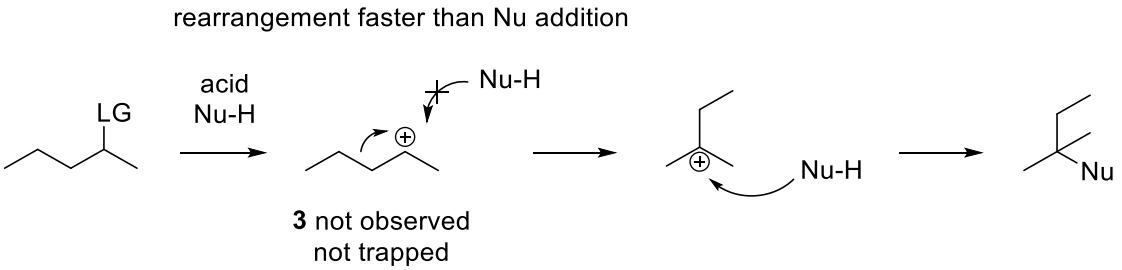



*Figure 6: rearrangement of an unstable carbocation vs nucleophilic addition.*

The rearrangements of carbenium ions can be used as an efficient synthetic strategy: the generation of a relatively unstable carbocation can trigger a cascade forming several carbon-carbon bonds eventually forming a more stable carbocation that is trapped by a nucleophile affording the final product as in the case of terpenes biomimetic cyclizations.[22]

4) The ***deprotonation*** of a primary or secondary carbenium ion by action of a base affords the corresponding carbene. Of course tertiary carbenium ions cannot undergo this reaction. The so formed carbenes are very reactive species that can undergo a series of side reactions such as dimerization to form the corresponding olefins, unless the process is disfavored by steric hindrance.

## 1.4 $S_N1$ reactions

During my PhD I have focused my attention on $S_N1$ reactions on stabilized carbenium ions, thus I will introduce this subject more in detail. $S_N1$ reactions proceed through a planar carbocationic intermediate and this distinguish them from $S_N2$ reactions in which a concerted nucleophilic attack and heterolytic bond cleavage with the leaving group occurs. $S_N2$ reactions occurs with inversion of configuration and in case of enantioenriched substrates the stereochemical information is maintained, while in case of $S_N1$ reactions the carbocationic planar transition state erases this information.[23]

Only a few stable carbenium ions are commercially available and a limited number of those that can be prepared are bench stable, so that the more common strategy is the generation of such intermediates directly *in situ*.

Historically alcohols and halogens have been used to generate carbenium ions, but harsh conditions as concentrated acids, typically $H_2SO_4$, trifluoroacetic or triflic acid, or stoichiometric amounts of strong Lewis acids, $AlCl_3$ and $SnCl_4$ for example, were used for their generation considerably limiting the nucleophiles that could be employed.

In order to use milder conditions, an extensive research was conducted in the second half of last century to identify better leaving groups such as mesylates tosylates, acetates, quaternary ammonium salts (generated *in situ*) that allowed the formation of the carbocation under milder conditions, such as the use of catalytic amounts of acids establishing $S_N1$ reactions as a powerful tool in organic synthesis. However the introduction of these groups requires extra steps and increases the amount of chemical waste.

The growing conscience of the ecological impact of chemistry and the need to develop shorter and more economical methodologies avoiding extra steps, prompted the reinvestigation of the direct $S_N1$ reaction of alcohols under new and milder conditions that could allow its extensive application in organic synthesis.[24]

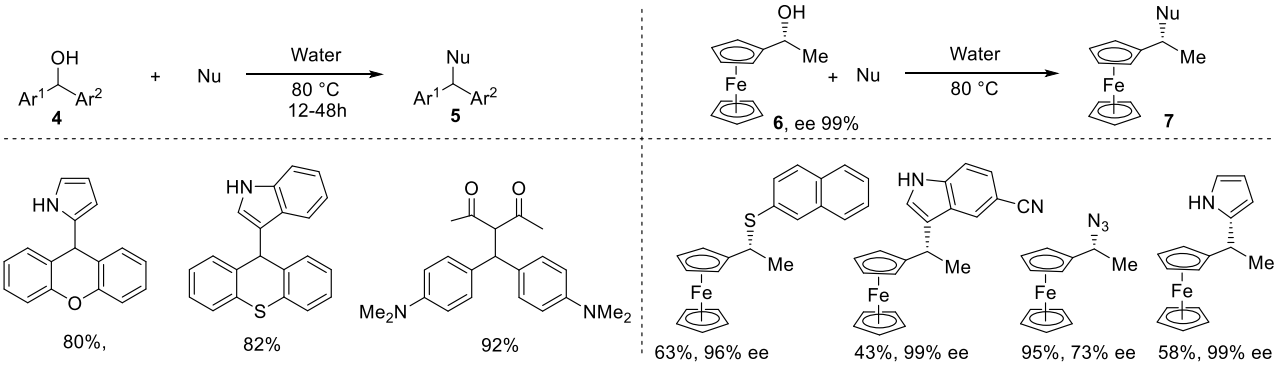
Kobayashi played a fundamental role in this direction demonstrating that water could be used as efficient reaction media for Lewis acid mediated reactions,[25] and he reported the $S_N1$ reaction of alcohols on water mediated by the use of acidic surfactants.[26]

These additives formed micelles inside which the organic reactants were confined by homophobic interactions with the water phase maximizing the productive interactions which lead to superior reaction rates than in homophasic conditions using organic solvents.

A further advance is represented by the direct $S_N1$ reaction of alcohols on water with various nucleophiles without any surfactants or acid that was reported in 2008 by Prof. P.G. Cozzi and Luca Zoli (scheme 1).[27]

It is believed that the hydrogen bonding network of hot water at the water-oil (composed by the organic reagents) interface promotes the carbocation formation from the alcohols. Stabilized carbenium ions that react reversibly with water must be used, and these species are located between -1.5 and -7 on the Mayr scale. Moreover the presence of water minimizes unproductive side reactions of the isolated carbocation such as the formation of the ether. Ferrocenyl ethanol is a suitable substrate in this reaction and the use of enantioenriched alcohol allowed the realization of enantiospecific $S_N1$ reactions on water.

The alcohols that generate less stable carbenium ions, such as 4,4'-dimethoxybenzydrilium ion ($E$ = 0) are not suitable substrates for $S_N1$ reactions on water because their increased electrophilicity makes the reaction with water too fast and irreversible. The use of trifluoroethanol, that combines a strong dipole and hydrogen bonding properties with a significant decreased nucleophlicity compared to water, enabled the direct $S_N1$ reactions with the before mentioned alcohol and the use of nitro alkanes as nuclephiles.[28]




*Scheme 1: "on water" $S_N1$ reactions with stabilized carbenium ions.*

## 1.4.1 Enantioselective $S_N1$ reactions

The planar nature of the carbocation has long been considered a disadvantage because it causes the loss of the stereochemical information stored in that stereocenter during the nucleophilic substitution reaction. However this offers the possibility to realize enantioselective $S_N1$ reactions, also starting from racemic prochiral substrates that generate the carbenium ions, in case chiral nucleophiles, counteranions or chiral auxiliaries are employed.

This concept was first developed generating carbenium ions having an enantiopure chiral center on the α-position. These type of substrates were efficiently employed to perform diastereospecific intramolecular reactions as in the polyene cyclization cascade reported by Corey.[29]

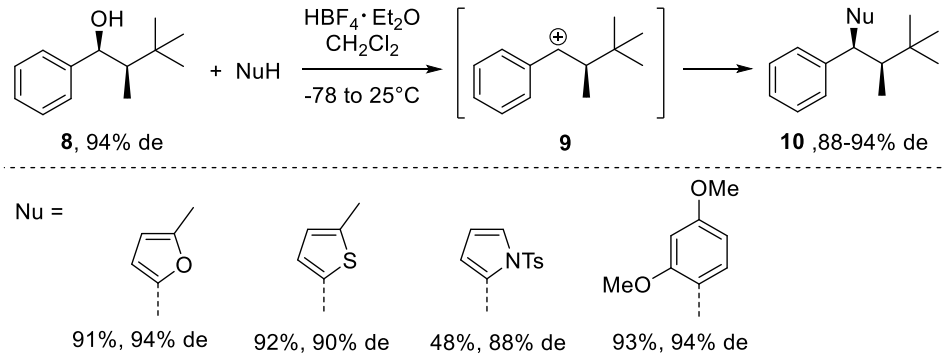
The diastereoselective intermolecular $S_N1$ reaction using alcohols **8** having an α-stereocenter as chiral auxiliary was first reported by Bach in 2006 (scheme 2). Upon treatment with a $HBF_4$ the carbocation **9** was generated and efficiently engaged in highly *syn* selective Friedel Crafts reactions with electron rich aromatics.[30]

The complementary methodology that affords the *anti* products, even if in moderate to good diastereoselectivities, was described by Chung a couple of years later.[31]

These diastereospecific $S_N1$ reactions were successfully applied to the synthesis of natural products such as podophyllotoxyn[32] and drug candidates.[33]

To perform catalytic enantioselective reactions on carbenium ions[34] two general approaches are possible. The first one is the generation of the carbocation by action of a chiral acid whose anion forms an intimate chiral ion pair with the carbocation. In such intermediates it is possible to efficiently shield one of the two enantiotopic faces of the carbocation achieving an enantioselective

reaction. The second approach consists in the catalytic generation of a chiral nucleophile that is alkylated by the carbocation on one enantiotopic face.

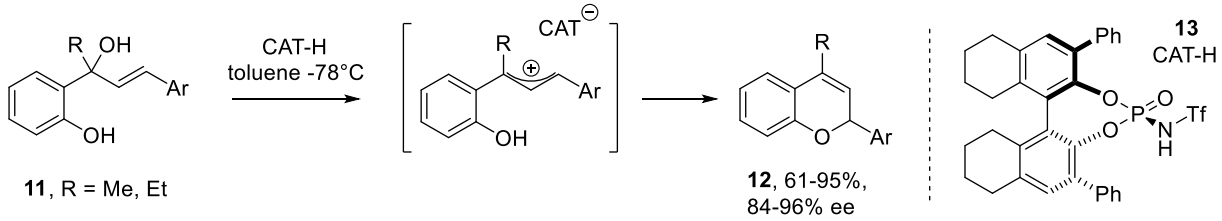



*Scheme .2: F. C. reaction on carbenium ions bearing a stereocenter on the α-position.*

## Chiral counterions

The use of a chiral Lewis acid to promote enantioselective polyene cyclizations was known since 1999[35] and several advances were made on the subject.[22,36]

With the advent of organocatalysis the realization of ion pairs between carbenium ions and phosphoric acids or phosphoramides was efficiently exploited in several Friedel Crafts,[37] polyene cyclizations[38] or $S_N1$ reactions[39] (scheme 3). In case of intermolecular processes to achieve optimal enantioselectivities it is important that the nuclephile bears a hydrogen bond donor site that allows it to interact with the active site of the phosphoric acid or phosphoramide to be guided on one enantiotopic face.




*Scheme 3: selected example of $S_N1$ reaction promoted by chiral Brønsted acid.*

## Chiral nucleophile

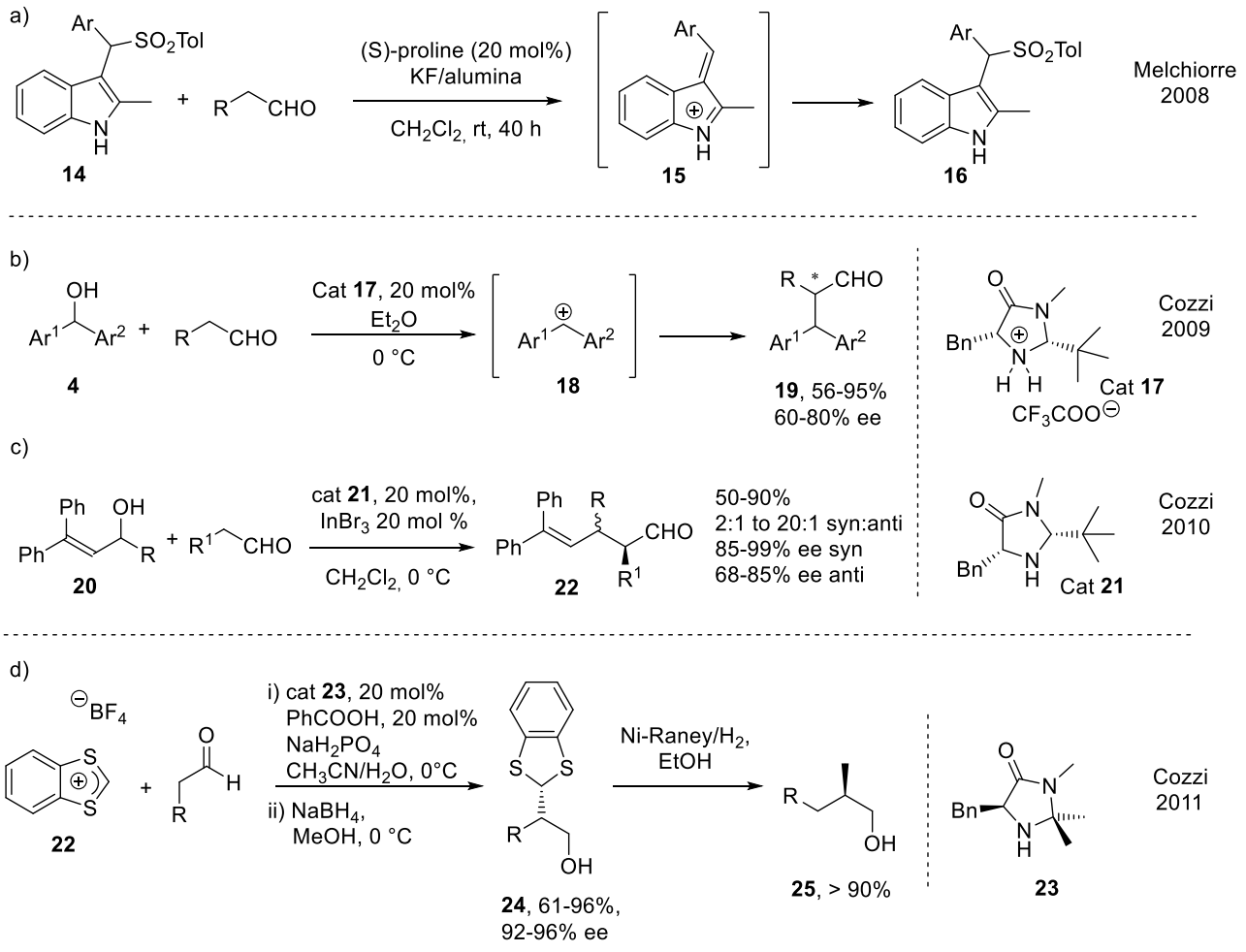
The use of chiral nucleophiles in catalytic enantioselective $S_N1$ reactions was first reported in 2008 by Melchiorre *via* enamine catalysis (scheme 4a).[40] The indolyl carbenium ions were generared *in situ* from aryl sulfonates precursors **14** and were attacked by the catalytically generated enamines from the aldehyde and the proline catalyst. The alkylated aldehydes **16** were obtained in moderate

to good diastereoselectivities and good to optimal enantioselectivities thanks to the directed approach of the electrophile by hydrogen bonding with the proline carboxylate.

A year after this seminal report that launched chiral amines as privileged catalysts for the enantioselective alkylations of aldehydes with carbenium ions, Cozzi and coworkers reported the first enantioselective $S_N1$ reaction on alcohols via enamine catalysis (scheme 4b).[41]

In this case Macmillan catalyst as the TFA salt **17** was used to promote the reaction. The acid plays a fundamental role in promoting both the condensation between the amine and the aldehyde and the carbenium ion formation. Contrary to the report of Melchiorre in which hydrogen bonding controls the stereoselective outcome, in this case the stereochemical information is transferred thanks to the sterical hindrance exercised by the benzyl substituent on the oxazolidinone ring that shields one face of the enamine intermediate. In both cases it is remarkable that the secondary amine catalysts do not react, at least irreversibly, with the carbenium ions allowing efficient transformations.

The alcohols used in this first report were the stabilized benzhydrylic alcohols **4** previously employed in the on water reaction that are located between -1.5 and -8 of Mayr scale.




*Scheme 4: selected examples of $S_N1$ reactions via enamine catalysis.*

It also is possible to use stabilized allylic **20** (scheme 4c),[42] propargylic and even activated benzylic alcohols[43] in enantiosective alkylations of aldehydes, but the use of a Lewis acid cocatalyst[44] is necessary to form these more reactive (and less stabilized) carbenium ions located close to 0 or +1 on the Mayr scale. Moreover the Lewis acid is fundamental to allow a reversible equilibrium between the free alcohol and the ether derived by its homo-condensation process that would otherwise be irreversible subtracting a great amount of reactant from the productive pathway. The choice of the Lewis acid is crucial because amines and water are present in the reaction mixture as they are necessary for enamine catalysis. Kobayashi[45] studied in detail the compatibility of LA with water and amines and published a table classifying them. The key factors for a LA to be water compatible are two: first its inner sphere substituents should not be hydrolyzed by water to give the hydroxide, second the water coordinated in the outer sphere must be fast exchanged with the substrate to guarantee its activation and to avoid that the LA is deactivated by the water solvent.

In the following years other secondary amine catalysts were efficiently used to perform α-alkylation of aldehydes or ketones.[46]

PG Cozzi[47] and others[48] reported also the possibility to use radical oxidative protocols for the generation of carbenium ions in enamine compatible protocols. The choice of the oxidant is crucial to allow the oxidation of the substrate avoiding the oxidation of the enamine that could lead to the intermediates on which SOMO activation mode is based (see chapter 2.1). Moreover it is important that the water traces present in the reaction mixture do not react rapidly with the carbocation affording the alcohol that would readily be oxidized to the ketone.

Isolated carbenium ions are suitable substrates for $S_N1$ type reactions with enamines.[49] Among the suitable carbenium ions, benzodithiolylium tetrafluoroborate is worth of mention because it allows a formal enantioselective and catalytic α-alkylation of aldehydes (scheme 4d).[50] Indeed the reaction of this carbocation with aldehydes under enamine catalysis affords the corresponding product in optimal yields and enantiomeric excesses after reduction to the corresponding alcohols to avoid racemization. The chameleonic properties of the benzodithiol moiety, able to stabilize both a positive or a negative charge, allows a wide range of manipulations of these derivatives that can be converted into the α-methylated products, homologated, converted into the corresponding ketones, carboxylic acids or gem difluorinated compounds.[51] This methodology was successfully applied to the synthesis of bisabolanes,[52] odorants[53] and arundic acid. The alkylation of aldehydes with benzodithiolylium can be performed also using supported Macmillan catalysts on flow conditions[54] and by the use of primary amines also α-branched aldehydes can be employed with moderate to good enantioselectivities.[55]

All the employed carbenium ions employed for enantioselective $S_N1$ reactions via enamine catalysis are located between +1 and -8 on the Mayr scale. A single report in which a benzhydrilium carbenium ion with higher electrophilicity (E = 5.90) could be generated and reacted with a catalytically generated enamine has been reported. The use of a bifunctional thiourea-primary amine catalyst was mandatory to generated the carbenium ion from the bromine precursor in proximity of the enamine and achieve a successful transformation avoiding the side reactions that a so reactive intermediate could undergo.[56]

However the corresponding reaction using benzhydrilium alcohols was not reported so far testifying the difficulties in employing these very electrophilic intermediates. On the other hand species with $E < 10$ react too slowly with enamines. It must be noted that even if the enamines generated with

secondary amine catalysts are quite nucleophilic species ( 5 < N < 10), they are always present in low concentrations inside the reaction mixture as they are catalytic intermediates, so that their real nucleophilic power is lower.

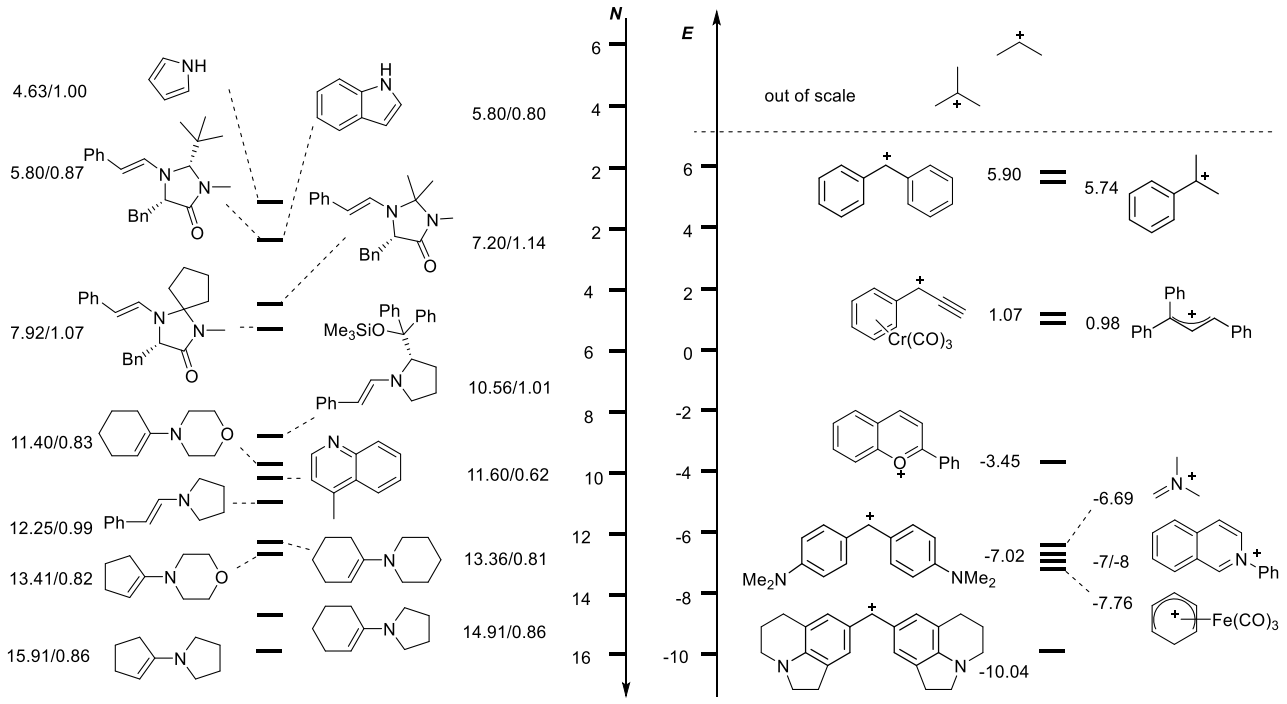



*Figure 6: enamines and carbenium ions on the Mayr Scale.*

## 1.5 References


[1] C. D. Nenitzescu, *Historical outlook*, chapter 1 in Carbonium ions vol 1: general aspects and methods of investigation, Edited by G. A. Olah and P. Von. R. Schleyer, John Wiley, 1968, New York, and references therein.

[2] J. G. Traynham *J. Chem. Ed.* **1986**, *63*, 930.

[3] M. G. Schwartz *J. Chem. Ed.* **1987**, *64*, 92.

[4] G. A. Olah *J. Am. Chem. Soc.* **1972**, *94*, 808.

[5] V. Gold *Pure Appl. Chem.* **1983**, *56*, 1281 (see especially pp 1296-1297).

[6] a) H. Meerwein, K. van Emster, *Chem. Ber.* 1922, 55, 2500, b) H. Meerwein, R. Wortman, *Justus Liebigs Ann. Chem.* **1924**, *435*, 190; c) H. Meerwein, F. Monfort, *Justus Liebigs Ann. Chem.* **1924**, *435*, 207; c) Henry S. Rzepa and Charlotte S. M. Allan *J. Chem. Ed.* **2010**, *87*, 221.

[7] (a) J. Houben, E. Pfankuch, *Ann.* **1931**, *489*, 193; (b) J. Houben, E. Pfankuch, *Ann.* **1933**, *501*, 219.

[8] G. Merling, Chem. Ber. **1891**, *24*, 3108.

[9] W. Von E. Doering, L. H. Knox, *J. Am. Chem. Soc.*, **1954**, *76*, 3203.

[10] J. F. Norris *Am. Chem. J.*, **1901**, *25*, 117. J. F. Norris *Chem. Zentr.*, **1901**, *I*, 699.

[11] F. Kehrmann, F. Wentzel *Chem. Ber.*, **1901**, *34*, 3815. F. Kehrmann, F. Wentzel *Chem. Ber.*, **1902**, *35*, 622.

[12] A. Baeyer, V. Villiger *Chem. Ber.*, **1902**, *35*, 1189. A. Baeyer, V. Villiger *Chem. Ber.*, **1902**, *35*, 3013.

[13] K. A. Hofmann, H. Kirmreuther *Chem. Ber.*, **1909**, *42*, 4856.

[14] M. Gomberg *Chem. Ber.*, **1902**, *35*, 2397. M. Gomberg, L. H. Cone *Ann. Chem.*, **1910**, *376*, 183.

[15] J. Stieglitz *Am. Chem. J.* **1899**, *21*, 101.

[16] F. C. Whitmore *J. Am. Chem. Soc.*, **1932**, *54*, 3274.

[17] J. F. Buergler, K. Niedermann, A. Togni, Chem. Eur. J. 2012, 18, 632-640; and ref. therein; M. Lotz, R. Schuecker, K. Mereiter, P. Knochel, Organometallics, 2010, 29, 6503-6508; and ref. therein; G. Arrayas, R. Adrio, J. C. Carretero. *Angew. Chem.* **2006**, *103*, 2921-2944; *Angew. Chem. Int. Ed.* **2006**, *45*, 7674-7715.

[18] F. P. Lossing, J. L. Holmes**,** *J. Am. Chem. Soc.*, **1984**, *106*, 6917.

[19] E. M. Arnett, R. A. Flowers II, *Chem. Soc. Rev.*, **1993**, *22*, 9.

[20] H. Mayr, A. R. Ofial**,** *Pure Appl. Chem.* **2005**, *77*, 1807; H. Mayr, A. R. Ofial *J. Phys. Org. Chem.* **2008**, *21*, 584; H. Mayr, B. Kempf, A. R. Ofial *Acc. Chem. Res.*, **2003**, *36*, 66.

[21] Mayr website: http://www.cup.uni-muenchen.de/oc/mayr/DBintro.html, on 27/12/2015.

[22] For reviews see: (a) R. A. Yoder, J. N. Johnston, *Chem. Rev.* **2005**, *105*, 4730; (b) D. J. Tantillo, *Nat. Prod. Rep.* **2011**, *28*, 1035; for recent examples see: (c) S. V. Pronin, R. A. Shenvi, *Nat. Chem.* **2012**, *4*, 915; (d) T. Isaka, M. Hasegawa, H. Toshima, *Biosci. Biotechnol. Biochem*. **2011**, *11*, 2213; (e) K. Surendra, E. J. Corey, *J. Am. Chem. Soc*. **2008**, *130*, 8865.

[23] An example in which a $S_N1$ reaction might occur with inversion of configuration has recently been described. However the authors could not exclude also a $S_N2$ pathway even if they favor the $S_N1$ pathway. Pronin, S. V.; Reiher, C. A.; Shenvi, R. A. *Nature*, **2013**, *501*, 195-199.

[24] For reviews see: a) E. Emer, R. Sinisi, M. Guiteras Capdevila, D. Petruzziello, F. De Vincentiis, P. G. Cozzi, *Eur. J. Org. Chem.* **2011**, 647; a) Y. X. Zhu, L. Sun, P. Lu, Y. G. Wang, *ACS Catalysis* **2014**, *4*, 1911; b) A. Baeza, C. Najera, *Synthesis* **2014**, *46*, 25.

[25] a) W. M. C. Sameera, M. Hatanaka, T. Kitanosono, S. Kobayashi, K. Morokuma, *J. Am. Chem. Soc.* **2015**, *137*, 11085 and ref. therein; b) S. Kobayashi, K. Manabe, *Acc. Chem. Res.* **2002**, *35*, 209.

[26] S. Shirakawa, S. Kobayashi, *Org. Lett.* **2007**, *9*, 311.

[27] P. G. Cozzi, L. Zoli, *Angew. Chem.* **2008**, *120*, 4230-4234; *Angew. Chem. Int. Ed.* **2008**, *47*, 4162-4166.

[28] D. Petruzziello, A. Gualandi, S. Grilli, P: G: Cozzi, *Eur. J. Org. Chem.* **2012**, 6697-6701.

[29] E. J. Corey, G. Luo, L. S. Lin *Angew. Chem. Int. Ed.* **1998**, *37*, 1126.

[30] F. Mühlthau, D. Stadler, A. Goeppert, G. A. Olah, G. K. Surya Prakash, T. Bach*, *J. Am. Chem. Soc.* **2006**, *128*, 9668.

[31] J. Y. L. Chung, D. Mancheno, P. G. Dormer, N. Variankaval, R. G. Ball, N. N. Tsou, *org. let.* **2008,** *10***,** 3037**.**

[32] D. Stadler, T. Bach, *Angew. Chem., Int. Ed.* **2008**, *47*, 7557.

[33] J. Y. L. Chung, D. Steinhuebel, S. W. Krska, F. W. Hartner, C. Cai, J. Rosen, D. E. Mancheno, T. Pei, L. DiMichele, R. G. Ball, C.-y. Chen, L. Tan, A. D. Alorati, S. E. Brewer, J. P. Scott, *Org. Process Res. Dev*. **2012**, *16*, 1832.

[34] A. Gualandi, P. G. Cozzi, *SYNLETT* **2013**, *24*, 281.

[35] K. Ishihara, S. Nakamura, H. Yamamoto, *J. Am. Chem. Soc.* **1999**, *121*, 4906.

[36] K. Kumazawa, K. Ishihara, H. Yamamoto, org. let. **2004,** *6***,** 2551.

[37] a) S.-G. Wang, L. Han, M. Zeng, F.-L. Sun, W. Zhang, S.-L. You, *Org. Biomol. Chem.* **2012**, *10*, 3202; b) D. Wilcke, E. Herdtweck, T. Bach, SYNLETT **2011**, 22, 1235.

[38] A. Sakakura, A. Ukai, K. Ishihara, *Nature* **2007,** *445*, 900.

[39] a) M . Rueping, U. Uria, M.-Y. Lin, I. Atodiresei, *J. Am. Chem. Soc.* **2011**, *133*, 3732; b) Q.-X. Guo, Y.-G. Peng, J.-W. Zhang, L. Song, Z. Feng, L.-Z. Gong, *Org. Lett.* **2009**, *11*, 4620.

[40] R. R. Shaikh, A. Mazzanti, M. Petrini, G. Bartoli, P. Melchiorre, *Angew. Chem., Int. Ed.* **2008**, *47*, 8707.

[41] P. G. Cozzi, F. Benfatti, L. Zoli, *Angew. Chem. Int. Ed*. **2009**, *48*, 1313.

[42] a) M. G. Capdevila, F. Benfatti, L. Zoli, M. Stenta, P. G. Cozzi, *Chem. Eur. J.* **2010**, *16*, 11237; b) M. Chiarucci, M. di Lillo, A. Romaniello, P. G.
Cozzi, G. Cera, M. Bandini, *Chem. Science* **2012**, *3*, 2859.

[43] M. G. Capdevila, E. Emer, F. Benfatti, A. Gualandi, C. M. Wilson, P. G. Cozzi, *Asian J. Org. Chem.* **2012**, *1*, 38.

[44] A. Gualandi, L. Mengozzi, C. M. Wilson, P. G. Cozzi, *Chem. Asian J.* **2014**, *9*, 984.

[45] a) S. Kobayashi, C. Ogawa, *Chem. Eur. J.* **2006**, *12*, 5954; b) S. Kobayashi, M. Sugiura, H. Kitagawa, W. W.-L. Lam, Chem. Rev. **2002**, *102*, 2227; c) S. Kobayashi, *Eur. J. Org. Chem.* **1999**, 15.

[46] a) J. Xiao, Org. Lett. **2012**, *14*, 1716; b) L. Zhang, L. Cui, X. Li, J. Li, S. Luo, J.-P. Cheng, *Chem. Eur. J.* **2010**, *16*, 2045; c) L. Zhang, L. Cui, X. Li, J. Li, S. Luo, J.-P. Cheng, *Eur. J. Org. Chem.* **2010**, 4876; d) M. Trifonidou, C. G. Kokotos, *Eur. J. Org. Chem.* **2012**, 1563.

[47] F. Benfatti, M. G. Capdevila, L. Zoli, E. Benedetto, P. G. Cozzi, *Chem. Commun.* **2009**, 5919-5921.

[48] a) C. Xu, L. Zhang, S. Luo, *Org. Lett.* **2015**, *17*, 4392; b) M. Rueping, H. Sunden, L. Hubener, E. Sugiono, *Chem Commun*. **2012**, *48*, 2201; c) B. Zhang, S. K. Xiang, L. H. Zhang, Y. X. Cui, N. Jiao, *Org. Lett.* **2011**, *13*, 5212.

[49] a) F. Benfatti, E. Benedetto, Pier Giorgio Cozzi *Chem. Asian J.* **2010**, *5*, 2047 – 2052; b) N. Armenise, S. Dughera, A. Gualandi, L. Mengozzi, M. Barbero, P. G. Cozzi, *Asian J. Org. Chem.* **2015**, *4*, 337-345; For the synthesis of indolyl carbocartions see c) M. Barbero, R. Buscaino, S. Cadamuro, S. Dughera, A. Gualandi, D. Marabello, P. G. Cozzi, *J. Org. Chem.* **2015**, *80*, 4791-4796.

[50] a) A. Gualandi, E. Emer, M G. Capdevila, P. G. Cozzi, *Angew. Chem.* **2011**, *123*, 7988-7992; *Angew. Chem. Int. Ed.***2 011**, *50*, 7842-7846; b) A. Gualandi, L. Mengozzi, J. Giacoboni, S. Saulnier, M. Ciardi, P. G. Cozzi, *Chirality* **2014**, *26*, 607-613; c) A. Gualandi, L. Mengozzi, P.G. Cozzi, *Chem. Today* **2014**, *32*, 14-17.

[51] S. Saulnier, M. Ciardi, V. Lopez-Carrillo, A. Gualandi, P. G. Cozzi, *Chem. Eur. J.* **2015**, *21*, 13689-13695.

[52] A. Gualandi, A. Canestrari, E. Emer, P. G. Cozzi, *Adv. Synth. Catal.* **2014**, *356*, 528-536.

[53] A. Gualandi, M. G. Emma, J. Giacoboni, L. Mengozzi, P. G. Cozzi, *Synlett* **2013**, *24*, 449–452.

[54] R. Porta, M. Benaglia, A. Puglisi, A. Mandoli, A. Gualandi, P. G. Cozzi, *ChemSusChem* **2014**, *7*, 3534-3540.

[55] A. Gualandi, D. Petruzziello, E. Emer, P. G. Cozzi, *Chem. Commun*. **2012**, *48*, 3614–3616.

[56] A. R. Brown, W.-H. Kuo, E. N. Jacobsen, *J. Am. Chem. Soc.* **2010**, *132*, 9286.

# 2 New organocatalytic methodologies for the alkylation of stabilized carbenium ions and carbon electrophiles

## 2.1 Introduction to organocatalysis

In the last fifteen years organocatalysis[1] emerged as a powerful strategy, to be added to the already established enzymatic and metal catalysis, to perform asymmetric transformations promoted by substoichiometric amounts of small organic molecules. However the first two non-enzymatic asymmetric catalytic reactions, the hydrocyanation of aldehydes promoted by cinchona alkaloids[2] and the thiamine catalyzed benzoyn condensation[3] were known respectively since the 1950's and 1960's and are, to our eyes, truly organocatalytic transformations. Also the first proline catalyzed process via enamine catalysis, the Hajos Parrish reaction[4] was disclosed in 1971, even if its mechanism remained unclear at the time. Indeed the general concepts that lie behind such early discoveries were not rationalized or fully appreciated at the time so that they remained isolated examples and the potentiality of this chemistry was still not disclosed. The two seminal papers reported in 2000 in which simple chiral secondary amines catalyzed highly asymmetric transformations represented the turning point. List, Lerner and Barbas III[5] used proline as catalyst for a cross aldol reaction, while MacMillan and coworkers[6] reported an asymmetric Diels Alder reaction promoted by a chiral secondary amine catalyst derived from phenylalanine. Moreover MacMillan used the term organocatalysis to describe his transformation underlining that such highly efficient and asymmetric process was promoted by a secondary amine catalysts, small and cheap, and occurred under non anhydrous conditions and on air.

Either the power of the name, the advances in theoretical chemistry or the different historical context of the new millennium in which the concepts of green chemistry were being established versus the 1970's when the Hayos Parrish reaction was disclosed and left in a drawer, immediately attracted a huge interest of the scientific community over this new topic and the gold rush in organocatalysis began.

Initially organocatalysis was identified with amine catalysis, but in a few years other efficient catalysts were designed or rediscovered for other organocatalytic strategies. Among these emerged chiral thioureas, BINOL derived phosphoric acids, N-heterocylclic carbenes (NHCs) and the cinchona alkaloids. A few general strategies in organocatalysis were recognized and classified as activation modes[1a] by MacMillan: the power of this view is that once an activation mode has been identified it can be applied to many transformations with its concepts remaining unaltered.

Here are briefly presented the organocatalytic activation modes enabled by each class of organocatalysts as I have applied some of them during my research.

### 2.1.1 Covalent amine catalysis

**Enamine catalysis or HOMO activation mode**[1a,5]

Species involved: enolizable aldehyde, chiral secondary amine catalyst (usually employed as its salt **1** with an acid) and electrophile.

The principle of this activation mode is the raising of the energy of the aldehyde HOMO via formation of the corresponding enamine **7** after condensation with the secondary amine catalyst **1** and deprotonation of the iminium **6** initially obtained. The deprotonation is favored by the lowering

of the LUMO in the iminium intermediate **6** and is usually performed by the conjugated base $X^-$ of the acid's cocatalyst. The more nucleophilic enamine is able to engage a successful polar reaction with the electrophile while the aldehyde cannot avoiding a background reaction. Eventually hydrolysis of iminium **9** closes the catalytic cycle affording product **10** and catalyst **1**. The presence of a stereogenic center on the amine catalyst scaffold allows the discrimination of the prochiral faces of **7**, so that the electrophile's approach is favored on one enantiotopic face (figure 1).

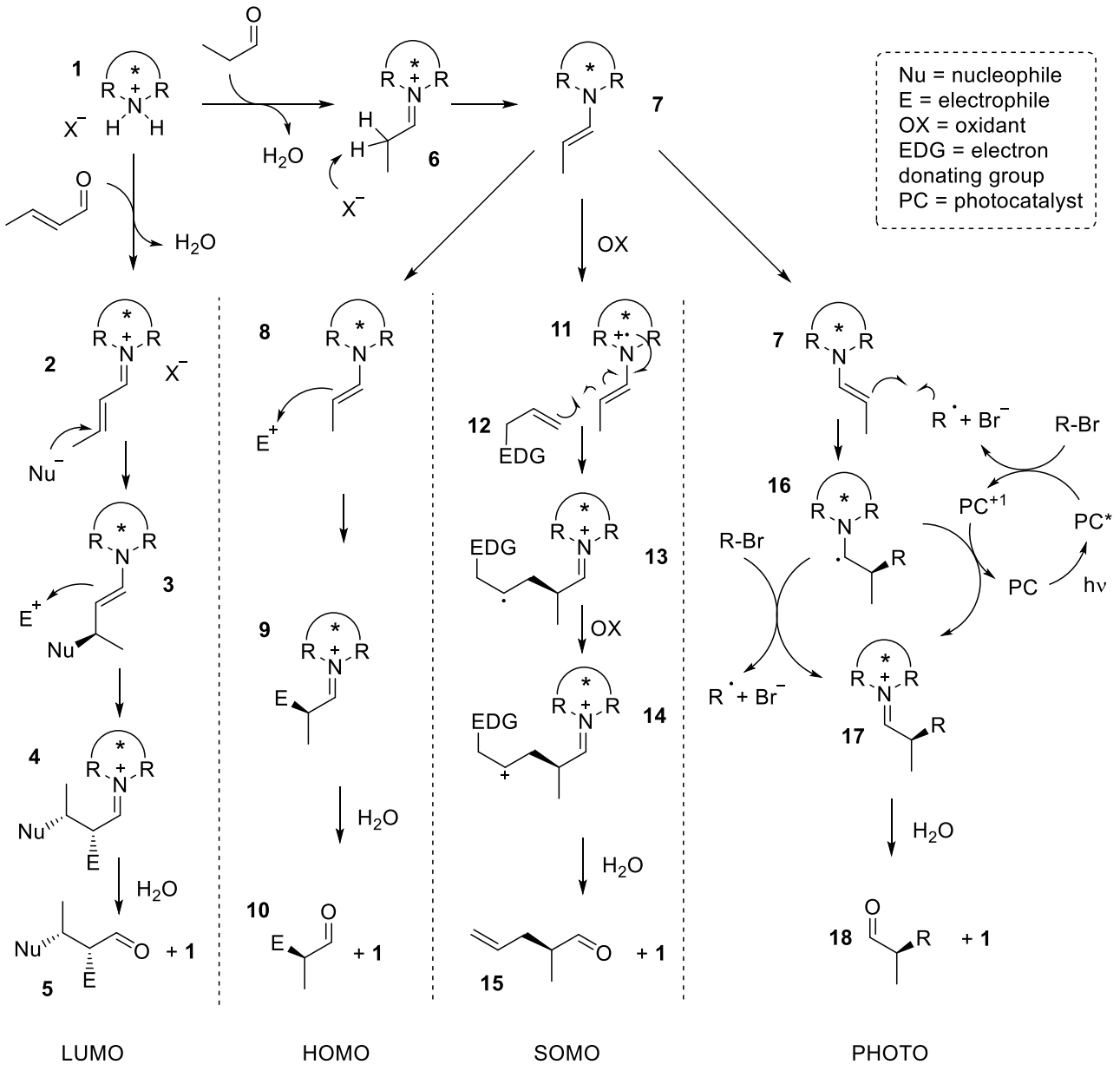



*Figure 1: activation modes with amine catalysis*

**Iminium catalysis or LUMO activation**[6,7]

Species involved: α,β-unsaturated aldehyde, chiral secondary amine catalyst (usually employed as its salt **1** with an acid) and nucleophile.

The condensation of the secondary amine catalyst with the α,β-unsaturated aldehyde leads to the formation of conjugated iminium ion **2** whose LUMO orbital is significantly decreased in energy so

that relatively weak nucleophiles, unable to react with the Michael acceptor in the aldehyde form, can efficiently perform the 1,4-conjugate addition to give the enamine **3**. This intermediate exploits its nucleophilicity further reacting with an electrophilic reaction partner, as in case of a Diels Alder reaction, or being protonated by water. In both case the iminium ion **4** is obtained, that upon hydrolysis releases the aldehyde product **5** and the catalyst **1** (figure 1).

**SOMO catalysis**[8]

Single occupied molecular orbital (SOMO) catalysis takes advantage from the possibility of enamines to undergo single electron oxidation in presence of strong oxidants such as cerium ammomìnium nitrate (CAN).[9] The open shell radical cation **11**, that has three electrons on a three atom p orbital system, is highly reactive and can undergo a single electron recombination process with suitable carbon nucleophile (SOMOphiles, e.g. **12**). An example of somophiles are allyl silanes,[8a] that initially react with the radical **11**. The resulting intermediate of type **13** undergoes a second oxidation affording carbocation **14**, that after elimination and hydrolysis affords product **15** and catalyst **1**. Alternatively, the carbocation **13** can be trapped by an external nucleophile (figure 1).[10]

This is the first activation mode of organocatalysis that requires very strict experimental conditions: involving radical intermediates the process is highly sensible to oxygen; moreover the amount of water, necessary to allow the catalyst turnover, must be carefully regulated in order for the reaction to happen.

Thanks to this new concept a wide range of transformations could be achieved, e.g. the asymmetric α-allylation, α-arylation, α-vinylation, α-enolation of aldehydes.

**Photocatalysis merged with enamine catalysis**[11]

Also in this case catalytically generated enamines are coupled with radicals, but despite the SOMO activation mode where strong oxidants are required, the radical is generated thanks to irradiation with visible light.

In a merely illustrative model (for a more detailed discussion see chapter 2.6), the photocatalyst (PC)[12] adsorbs visible light reaching its excited state (PC*) that via single electron transfer is responsible for the formation of an electron poor radical from an alkyl bromide precursor. This radical is then intercepted by the electron rich enamine **7** affording intermediate **16** that is oxidized to iminium **17** by the action of the oxidized state of the photocatalyst (or by another molecule of alkyl bromide) closing the photocatalytic cycle (or leading to a radical chain process) (figure 1).

The before mentioned example highlights the necessity to build two consistent catalytic cycles, organo and photo, that is the principle of this activation mode. Alternative strategies such as electron donor acceptor (EDA) complexes[13] have been successfully applied expanding the scope of this rapidly growing field (see chapter 2.6 for a more detailed discussion).

The mechanism of photocatalysis is reversed compared to SOMO catalysis in which an electron poor radical is generated by single electron oxidation of the enamine and is coupled with an electron rich specie (SOMOphile), while in photocatalysis an electron poor radical reacts with the electron rich enamine.

## 2.1.2 Non covalent catalysis

### Hydrogen bonding catalysis

The formation of a hydrogen bond network between the catalyst and the substrate is an efficient activation mode that has been exploited in many asymmetric transformations.[14] Usually the catalyst contains a hydrogen bond donor, a thiourea for example, that binds the substrate determining its LUMO activation. The more reactive chiral complex **19** is then attacked by the nucleophile. To have an efficient catalytic process it is necessary that the product is released by the catalyst avoiding its poisoning. Usually a secondary site is present on the catalyst to activate or direct the nucleophile in order to have optimal enantioselectivities (figure 2a).[15]

### Counterion catalysis

The formation of an ionic couple between the substrate and a chiral catalyst achieving the activation of the substrate and the formation of an intimate ion pair able to direct the asymmetric transformation is the concept of this activation mode.[16]

Two main strategies are possible: 1) the use of a chiral acid, binol derived phosphoric acids or phosphoramides for example, that protonates the substrate forming the ionic couple **20** and activating the substrate for the nucleophilic addition; 2) the use of a chiral hydrogen bond donor, such as a thiourea, able to promote the dissociation of a polar bond, usually abstracting an halogen, and promoting the formation of a carbenium ion.

In both cases to achieve high stereocontrol, the nucleophile should interact with a secondary functionality of the catalyst (figure 2b).[17]

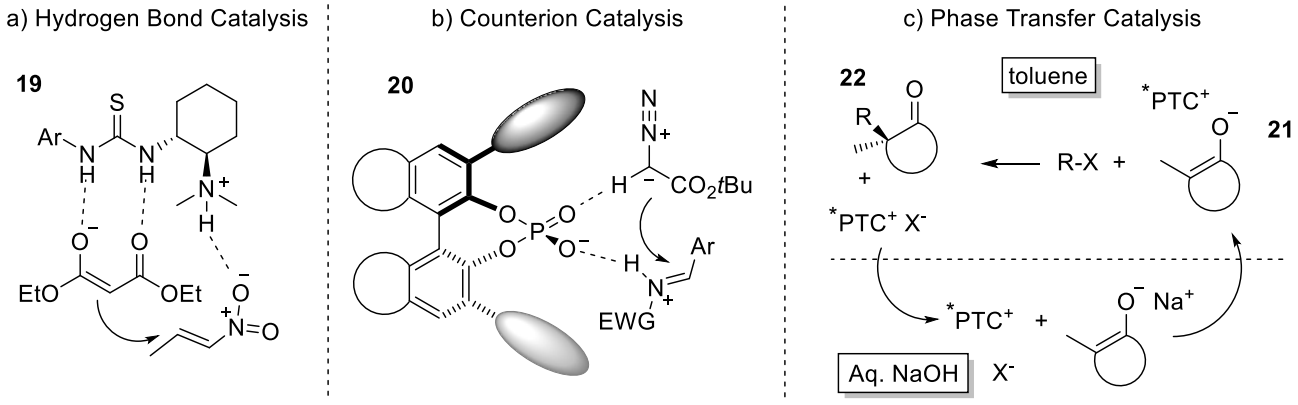



*Figure 2: non-covalent activation modes in organocatalysis.*

### Phase transfer catalysis (PTC)

PTC requires the use of a biphasic system in which each of the reaction partners is confined in a different phase to avoid their background reaction.[18] The phase transfer catalyst is able to act as a

shuttle between the two phases forming a chiral complex with one reagent and then migrating into the other phase where the reaction occurs.
A common example is the use of a biphasic system composed by basic water and a non miscible organic phase (figure 2c). As chiral phase transfer catalyst (PCT) is employed an organic cationic molecule having a small inorganic counteranion such as chlorine or bromine. This salt is more affine to the water phase where it interacts with the first reaction partner, the sodium enolate forming a close complex **21** that becomes more affine to the organic phase where it rapidly migrates. Here **21** meets the electrophilic reaction partner affording with which it reacts in a stereoselective manner thanks to the close ion pair with the chiral PTC. The resulting product **22** should be less affine with the catalyst so that the product-catalyst complex is broken affording the cationic catalyst that migrates back to the water phase. The same concept can be exploited using a chiral anionic catalyst that binds a carbocationic reagent, for example.

### 2.1.3 Lewis base catalysis

This activation mode relies in the basicity of NHCs[19] or isothioureas[20] that allow them to react with electrophylic compounds, such as aldehydes, anhydrides or activated esters (figure 3).

#### Aldehydes

When a NHC reacts with an aldehyde, the Breslow intermediate[21] **23**, basically an aldehyde unpolung reactive[22], is formed. This nucleophilic compound can react with different electrophiles such as an aldehyde in case of the benzoin condensation or a Michael acceptor in the Stetter reaction.
In case of an α,β-unsaturated aldehyde, the vinylogous unpolung **27** is obtained under basic conditions and it is called homenolate chemistry. Homoenolate **27** can alternatively be protonated, typically in buffer like conditions, affording the classical enolate **29** that reacts with the electrophile.[23]

#### Anhydrides or activated esters

In case of anhydrides or activated esters the NHC or the isothiourea reacts with the carbonyl group causing the elimination of the leaving group and the formation of the acyl cation: the acidity of the α-proton of these intermediates in considerably increased allowing its deprotonation by relative weak bases. The so generated enolates **32** are efficiently engaged in 4+2 or 2+2 cyclizations.[19,20]
The reaction scope has been widened by the β-activation of esters to give the corresponding homoenolates **34**[24] and by the efficient LUMO activation of α,β-unsaturated esters.[25]
The key step of this chemistry is the release of the catalyst after the reaction that is usually achieved by intramolecular attack by an oxygen or nitrogen nucleophile generated after the first nucleophilic addition step.
The enantioselectivity is achieved thanks to the presence of a chiral substituent on the NHC or isothiourea scaffold that allows the efficient shielding of one enantiotopic face of the Breslow, enolate or homoenolate intermediates.
Recently the use of NHCs as a non-covalent asymmetric catalyst was reported.[26]

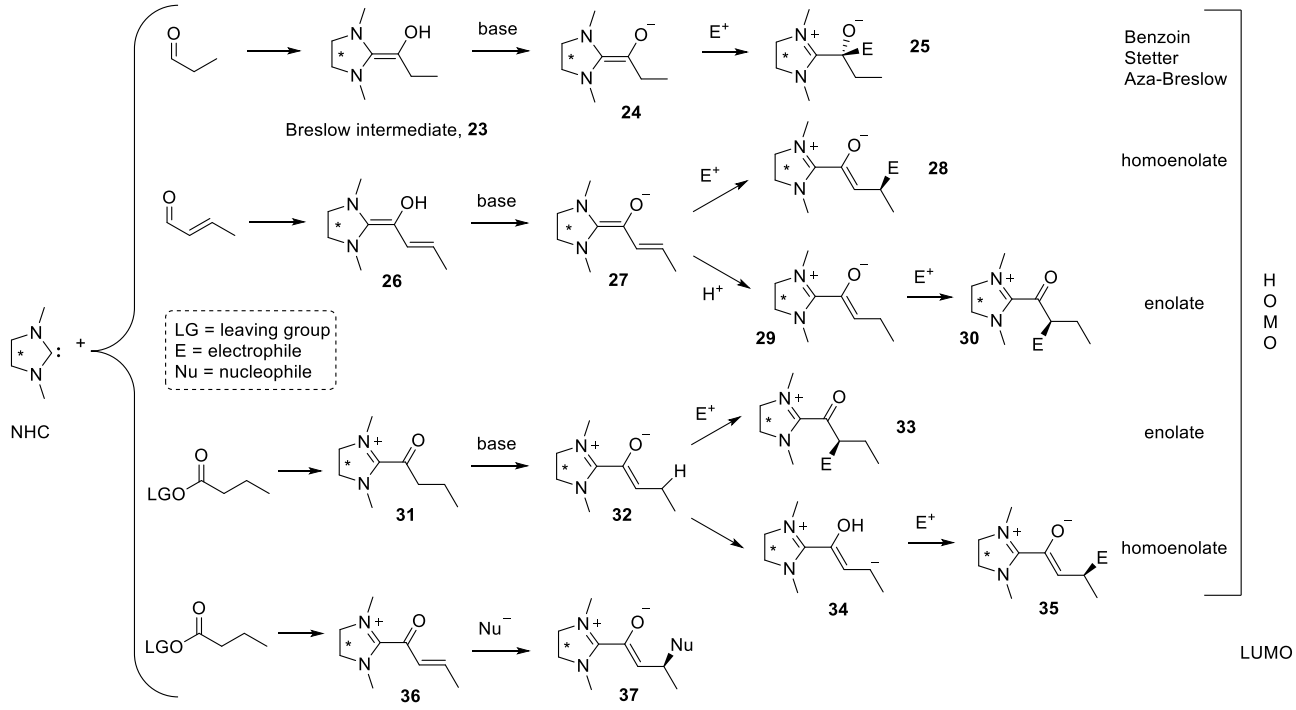



*Figure 3: covalent activation modes with NHCs.*

## References


[1] a) D. W. C. MacMillan, *Nature*, **2008**, *455*, 304; b) P. Melchiorre, M. Marigo, A. Carlone, G. Bartoli, *Angew. Chem.* **2008**, *120*, 6232; *Angew. Chem. Int. Ed.* **2008**, *47*, 6138; c) S. Mukherjee, J. W. Yang, S. Hoffmann, B. List, *Chem. Rev.* **200**7, *107*, 5471.

[2] a) G. Bredig, P. S. Fiske, *Biochem. Z.*, **1912**, *46*, 7; b) G. Bredig, M. Minaeff, *ibid.*, **1932**, *249*, 241; c) V. Prelog, M. Wilhelm, *Helv. Chim. Acta*, **1954**, *37*, 1634.

[3] a) J. C**.** Sheehan, D. H. Hunneman, *J. Am. Chem. Soc.* **1966**, **88**, 3666; b) J. C. Sheehan, T. Hara, *J. Org. Chem.*, **1974**, *39*, 1196.

[4] a) Z. G. Hajos, D. R. Parrish, Asymmetric synthesis of optically active polycyclic organic compounds. German patent DE 2102623, **1971**; b) Z. G. Hajos, D. R. Parrish, *J. Org. Chem.* **1974**, *39*, 1615.

[5] B. List, R. A. Lerner, C. F. Barbas III, *J. Am. Chem. Soc*. **2000**, *122*, 2395.

[6] K. A. Ahrendt, C. J. Borths, D. W. C. MacMillan, *J. Am. Chem. Soc*. **2000**, *122*, 4243.

[7] G. Lelais, D. W. C. MacMillan, *Aldrichim. Acta* **2006**, *39*, 79.

[8] a) T. D. Beeson, A. Mastracchio, J.-B. Hong, K. Ashton, D. W. C. MacMillan, *Science* **2007**, *316*, 582; b) P. V. Pham, K. Ashton, D. W. C. MacMillan, *Chem. Sci*., **2011**, *2*, 1470 and ref. therein.

[9] K. Narasaka, T. Okauchi, K. Tanaka and M. Murakami, *Chem. Lett*. **1992**, *21*, 2099.

[10] T. H. Graham, C. M. Jones, N. T. Jui, D. W. C. MacMillan, *J. Am. Chem. Soc*. **2008**, *130*, 16494.

[11] C. K. Prier, D. A. Rankic, D. W. C. MacMillan, *Chem. Rev*. **2013**, *113*, 5322.

[12] a) D. A. Nicewicz and D. W. C. MacMillan, *Science* **2008**, *322*, 77; b) M. Neumann, S. Füldner, B. König, K. Zeitler, *Angew. Chem., Int. Ed.* **2011**, *50*, 951; c) For the use of Rose Bengal, see: K. Fidaly, C. Ceballos,
A. Falguie`res, M. S.-I. Veitia, A. Guy and C. Ferroud, *Green Chem*. **2012**, *14*, 1293; d) P. Riente, A. M. Adams, J. Albero, E. Palomares and M. A. Pericás, *Angew. Chem. Int. Ed.* **2014**, *53*, 9613.

[13] E. Arceo, I. D. Jurberg, A. Álvarez-Fernández and P. Melchiorre, *Nat. Chem*. **2013**, *5*, 750.

[14] A. G. Doyle, E. N. Jacobsen, *Chem. Rev.* **2007,** *107*, 5713.

[15] T. Okino, Y. Hoashi, Y. Takemoto, *J. Am. Chem. Soc.* **2003**, *125*, 12672.

[16] a) S. E. Reisman, A. G. Doyle, E. N. Jacobsen, *J. Am. Chem. Soc*. **2008**, *130*, 7198; b) D. Parmar, E. Sugiono, S. Raja, M. Rueping, *Chem. Rev*. **2014**, *114*, 9047; b) R. J. Phipps, G. L. Hamilton, F. D. Toste, *Nat. Chem*. **2012**, *4*, 603.

[17] D. Uraguchi, K. Sorimachi, M. Terada, *J. Am. Chem. Soc.* **2005**, *127*, 9360.

[18] S. Shirakawa, K. Maruoka, *Angew. Chem. Int. Ed.* **2013**, *52*, 4312.

[19] D. M. Flanigan, F. Romanov-Michailidis, N. A. White, T. Rovis, *Chem. Rev*. **2015**, *115*, 9307.

[20] L. C. Morrill, A. D. Smith, *Chem. Soc. Rev.* **2014**, *43*, 6214.

[21] R. Breslow, *J. Am. Chem. Soc.* **1958**, *80*, 3719.

[22] B.-T. Gröbel and D. Seebach, *Synthesis* **1977**, 357.

[23] J. W. Bode, *Nat. Chem.* **2013**, *5*, 813.

[24] Z. Fu, J. Xu, T. Zhu, W. W. Y. Leong, Y. R. Chi, *Nat. Chem.* **2013**, *5*, 835.

[25] a) S. J. Ryan, L. Candish, D. W. Lupton, *J. Am. Chem. Soc.* **2009**, *131*, 14176; b) J. Cheng, Z. Huang, Y. R. Chi, *Angew. Chem. Int. Ed.* **2013**, *52*, 8592.

[26] J. Chen, S. Meng, L. Wang, H. Tang, Y. Huang, *Chem. Sci.* **2015**,*6*, 4184.

## 2.2 Enantioselective alkylation of aldehydes with quinolinium ions and its application to the synthesis of 13-alkyl protoberberine alkaloids[1]

When I joined as a master student Prof. Pier Giorgio Cozzi research group, I started to investigate the alkylation of aldehydes with isoquinolinium ions. This research represented a widening of the general investigation that the group had carried on in the previous years about the asymmetric alkylations of aldehydes with carbenium ions. Moreover if the project was successful a direct methodology to obtain 2-substituted tetrahydroisoquinolines, a recurring motif in many natural products, would be realized.
During my Master I developed the synthetic methodology, that will be presented, and during the Ph.D. I completed the project realizing the total synthesis of 13-methyl tetrahydroprotoberberine.

**Index**

## 2.2.1 Introduction

Tetrahydroisoquinoline derivatives are structural motifs occurring in the largest groups of natural products: isoquinoline alkaloids (Figure 1).[2] The tetrahydroisoquinoline skeleton is a basic building block of various types of alkaloids including benzylisoquinolines (among them papaverine, hygenamine, laudanosine and micovarium), protopines, benzo[c]phenanthridines, protoberberines, naphtylisoquinolines, bisbenzylisoquinolines (berbamine, dauricine, fangchinoline, pavines and isopavines), phtalide isoquinoline (bicuculline), emetine group, aporphinoid alkaloids, morphine, colchicines, and many others. These natural products are found in a great variety of plants and vegetables and they often exhibit a range of pharmacologically and biological activities such as antitumor, antibiotic, antivirus, anti-inflammatory, anticoagulation, and bronchodilation.[3] Therefore, the frequent occurrence of chiral 1-substituted-1,2,3,4-tetrahydroisoquinoline ring systems in a large number of alkaloids possessing a broad spectrum of biological and pharmaceutical properties has led to significant increasing interest in their synthesis.[4]

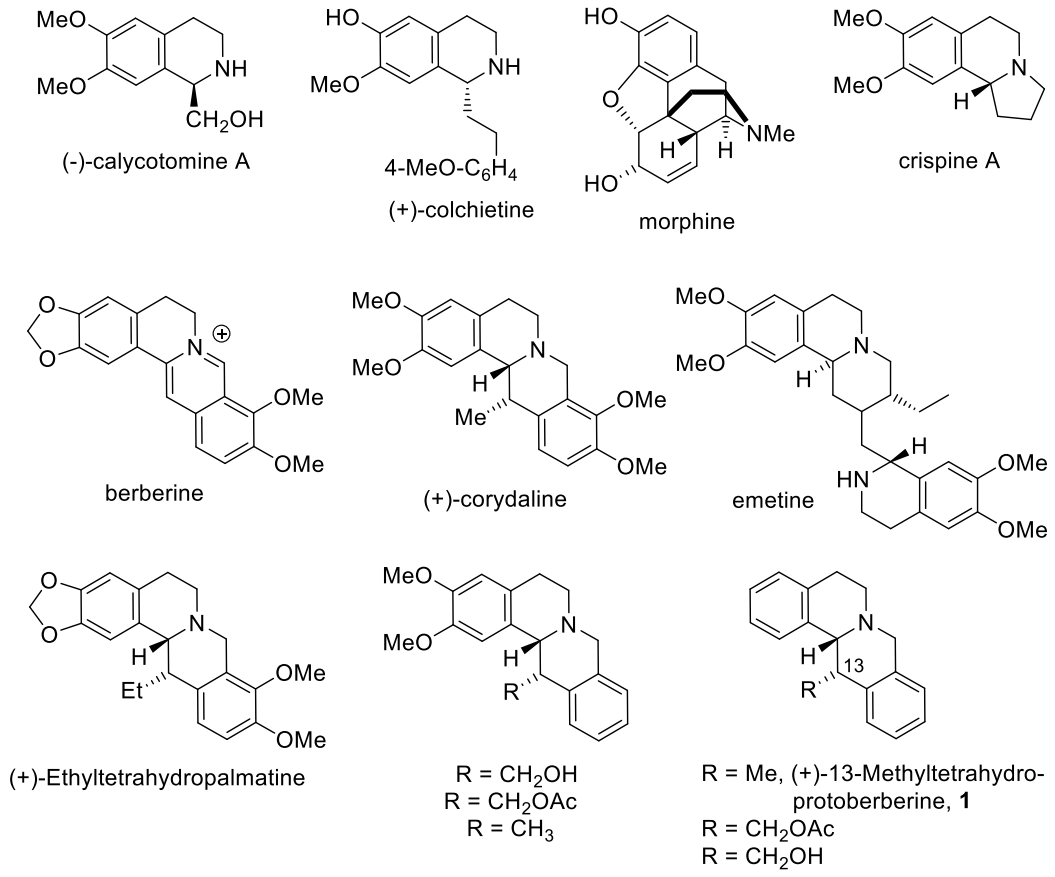



*Figure 1: Relevant biologically active 1-substituted tetrahydroisoquinolines and 13-alkyl-tetrahydroprotoberberine alkaloids.*

To date, most of the traditional synthetic approaches are based on procedures employing chiral building blocks, chiral auxiliaries, or chiral reagents.[5] In order to address issues related to economic and ecologically valuable processes, in recent years considerable effort has been directed towards the development of catalytic stereoselective transformations to obtain enantioenriched 1-substituted-tetrahydroisoquinoline frameworks with a high level of selectivity as the biological activity of such alkaloids is often displayed by a specific stereoisomer.[6] Many methodologies focus on the introduction of a substituent at the C1 position,[7] as this stereocenter is present in most of the natural products in this compound class.[8]
There are three main catalytic strategies to address the asymmetric construction of 1-substituted tetrahydroisoquinolines:

1) Catalytic ***asymmetric hydrogenation***[9] and ***asymmetric transfer hydrogenation***[10] of 1-substituted-3,4-dihydroisoquinolines (DHIQ). These methodologies are able to conjugate operational efficiency with atom economy, however only a few catalytic systems for asymmetric reduction of 1-aryl-substituted-3,4- DHIQs has only been described and this process is still considered a challenge in the field of asymmetric hydrogenation.[11] A redox based deracemization process has also been reported recently.[12]
2) ***Nucleophilic addition to quinolinium or dihydroquinolinium ions***. This chemistry was first explored by Reissert[13] a century ago in non-asymmetric fashion using chloroformate or benzoyl chloride to activate either isoquinolines or quinolines which react *via* the corresponding acyl iminium ions with cyanide anions. The enantioselective catalytic version of the Reissert reaction was introduced by Shibasaki only in 2000,[14] indicating the difficulties encountered during the reaction development.
3) ***Asymmetric construction of the isoquinoline ring***. The most important methodologies for the construction of the isoquinoline ring are the Pictet Spengler,[15] Bishler Napieralsky[16] and Pomerantz-Fritsch reactions.[17] However only in case of the Pictet Spenlger reaction a few asymmetric catalytic variants have been developed for the tetrahydroisoquinoline scaffold and they will be discussed in chapter 2.3.

The use of enzymatic reactions is also a valuable alternative in the desymmetrization of racemic substrates as demonstrated by the work of Kroutil,[18] but the limited substrate scope hampers the wide applicability of the method.

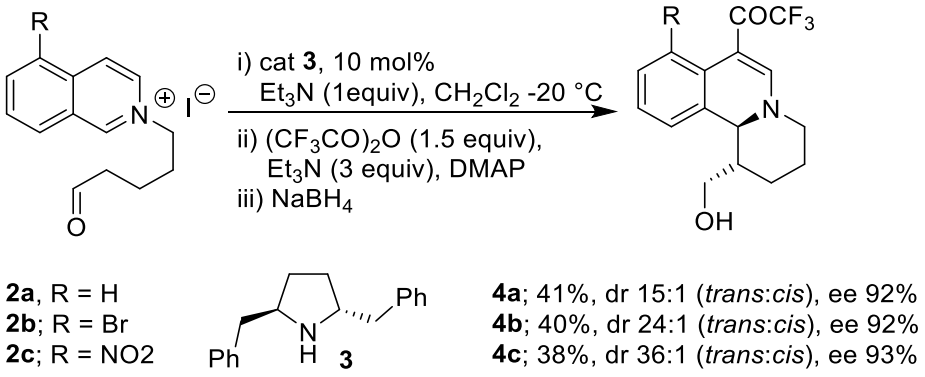
**Metal catalyzed asymmetric nucleophilic additions to quinolinium or dihydroquinolinium ions**

As already mentioned before the first example of such methodology was reported in 2000 by Shibasaki that described the addition of cyanide anions to quinolinium or isoquinolinium ions catalysed by a bifunctional Lewis base and Lewis acid catalyst bearing two phosphine oxides on the aluminium binol backbone.

After this pioneering report, a number of enantioselective metal catalysed methodologies for the addition of nucleophiles to isoquinolinium ions were reported including the allylation,[19] alkynylation,[20] and enolate addition reactions.[21] The allylation methodology was applied to the synthesis of several natural alkaloids such as crispine, homolaudanosine and emetine by Li even if the enantiomeric excesses were below 80%. Despite the number of reports, only the alkynylation reported by Ma[20a] and the enolate addition described by Sodeoka[21a] present a broad substrate scope and high enatioselectivities leaving a great space for significant advances.

**Organocatalytic addition of nucleophiles to isoquinolinium or dihydroquinolinium ions**

Organocatalitic activation modes have been efficiently used to design alternative and efficient additions to isoquinolinium and dihydroquinolinium ions with the advantage that no toxic metals are needed in these methodologies and more user friendly reaction conditions are possible.
The pioneering use of enamine catalysis to perform the α-alkylation of aldehydes with quinolinium ions was reported by Jørgensen[22] in 2005. Thanks to the use of chiral C2-symmetric secondary amine **3**, the diastereo- and enantioselective annulation reaction of 2-(5-oxopentyl)isoquinolinium **2** was achieved. The substrates for the intramolecular annulations reaction are stable isoquinolinium salts that are obtained after isoquinoline alkylation with the corresponding iodide. As in the catalytic cycle iodidridic acid (HI) is formed as by-product, it is necessary to use a base ($Et_3N$) in order to recycle the catalyst. The aldehyde/enamine products proved to be rather unstable, and could be isolated only after a double derivatization process, trifluoroacetylation and reduction, in moderate yields, high diastereoselectivity (up to 98:2) and excellent enantioselectivity (85–96% ee) for neutral or electron-poor substrates. Scheme 1)




*Scheme 1. Alkylation of isoquinolinium salt promoted by the organocatalyst* ***4.***

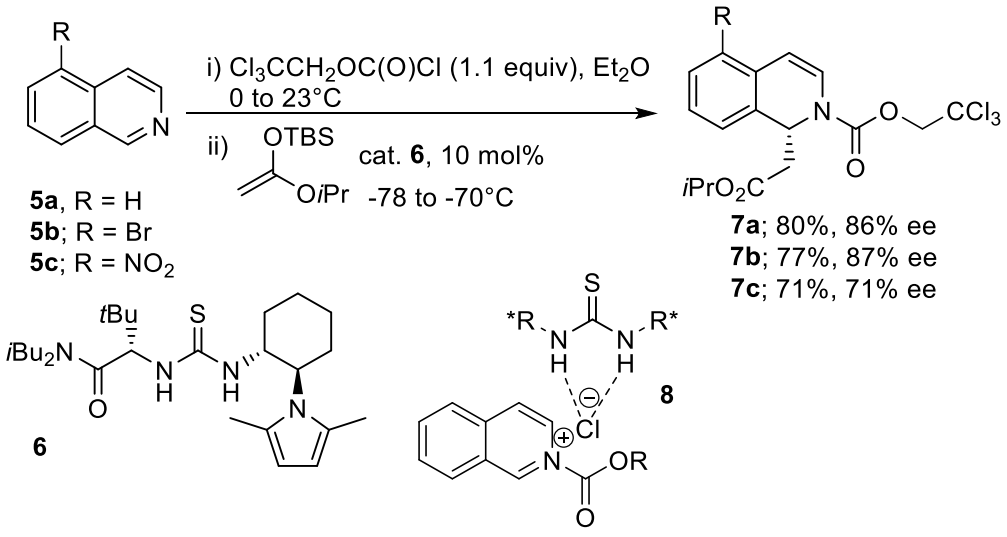
Quite remarkably it was reported that the corresponding intermolecular reaction, activating isoquinoline with ethyl chloroformate in presence of 3-methylbutyraldehyde and various organocatalysts, gave low yield/stereoselectivity. No further details are furnished, but probably the ethyl chloroformate is deactivating the organocatalyst by formation of the corresponding carbamate.

This work established the possibility to use quinolinium ions as suitable reaction partners in organocatalytic reactions and a few years later Jørgensen[23] reported a three-component organocatalytic asymmetric reaction of imines, α-bromoesters or α-bromoketones with α,β-unsaturated aldehydes to give optically active pyrrolo-isoquinolines with excellent enantioselectivity for a large number of substituents.

Other multicomponent reaction that allow the synthesis of the tetrahydroisoquinoline skeleton have been reported by Zhu and Sun[24] and Gongand Luo.[25]

A different organocatalytic approach was explored by Jacobsen (Scheme 2)[26] that took advantage from the activation of *N*-acylisoquinolinium chlorides with chiral isothioureas. These catalysts are able to bind the chlorine anion activating the electrophile towards the nucleophilic addition of silyl enolates. The tight ionic couple **8** between the catalyst-chlorine complex and the isoquinolinium ion that is further reinforced by interactions with the carbamate moiety, efficiently controls the nucleophile's approach allowing to obtain linear C1 substituted products **7** in high enantiomeric excesses (tipically > 90 % ee). The methodology is limited to the use of non substituted silyl enolates, that need to be pre-synthetized from the corresponding acetates.

The enantioselectivity was strongly influenced by the solvent and the activating agent, with chloroformates performing better than acetyl chloride, in according with its control by non-covalent interactions. The facile reduction of the intermediate to give dihydroisoquinoline derivatives was reported, in conjunction with the cleavage of the carbamate giving 1-substituted tetrahydroisoquinolines with no loss of enantiomeric excess.



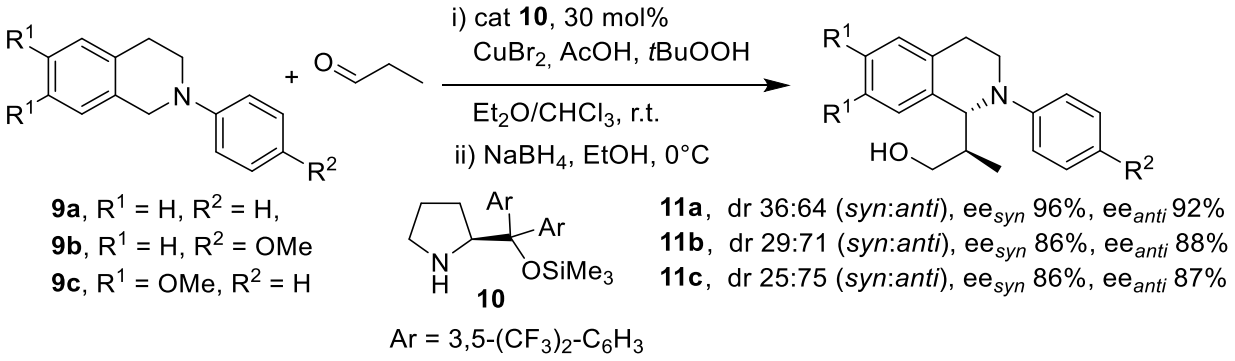

*Scheme 2. Acyl Mannich reaction of substituted isoquinolines*

Chiral silane diols[27] and halogen binding catalysts having helical chirality[28] were also able to promote this reaction but the results were poor in term of enantioselectivities.

Azaenolethers are also suitable nucleophiles in presence of hydrogen bonding thiourea catalysts, [30,31] In this case both reaction partners are generated in situ by nucleophilic attack of isoquinoline on *O*-acylated azalactones that affords the isoquinolinium ion and the nucleophilic partner through a highly atom economically Steglich[32] rearrangement.
A formal, highly diastereoselective, chiral catalyst-controlled aza-Diels Alder reaction between 9-Tosyl-3,4-dihydro-β-carboline imines or 3,4-dihydroquinolines and enones was also described by Jacobsen.[33]

**Stereoselective dehydrogenative cross couplings**

The cross-dehydrogenative coupling (CDC) reaction has been extensively investigated in the last decade[34] and various methods have been described for the generation *via* oxidative process of an iminium activated specie from a tetrahydroisoquinoline derivative. However in these published procedures, the nucleophilic attack was not stereoselective, even when proline or proline derivatives were used as organocatalysts.[35,36,37] The first successful example of addition of chiral nucleophiles (enamines) through cross dehydrogenative coupling was reported by Chi in 2012.[38] As it was well discussed by Klussmann,[39] the oxidation of *N*-aryltetrahydroisoquinolines **20** forms an electrophilic iminium derivative whose electrophilicity parameter was estimated around -7/-8 of the Mayr scale. Indeed also Chi used a pyrrolidine derived catalyst, in particular the Hayashi Jørgensen catalyst, as in the two previous mentioned reports from Jørgensen. This is because this enamines are much more nucleophilic ($N \approx 10$, see chapter 1, figure 4, p 18) compared to the enamines generated with MacMillan imidazolinones. ($5 < N < 8$).
Chi used a combination of *tert*-butyl hydroperoxide in the presence of $CuBr_2$ to perform the oxidation, and the reaction was catalysed by the Jørgensen diarylprolinol catalyst **10**. (Scheme 3).




*Scheme 3. Dehydrogenative stereoselective coupling catalyzed by Jørgensen catalyst III.*

The products were obtained in 31-71% yield but with low diastereoselectivity, although the enantioselectivity was good. The aldehyde compounds, as the adducts obtained by Jørgensen,[22]

suffered of low stability, and they were reduced to their corresponding alcohols to avoid racemization and decomposition. Although the authors reported the use of 4-MeO-$C_6H_4$ (PMP) as aryl group (**9b**), they did not report an effective procedure for its cleavage clearly limiting the application of the products in effective synthetic strategies.

The procedure was extended to the addition of ketones by the work of Wang and co-workers.[40] *L*-phenylalanine was employed as chiral catalyst in the presence of anhydrous *i*PrOH as additive, and 2,3-dichloro-5,6-dicyanoquinone (DDQ) as oxidant and the products were obtained in good yields and from good to excellent diastereo- and enantioselectivities. The use of ketones was limited to cyclohexanone derivatives, while the *N*-aryl group was varied considerably.

Wang also explored the possibility of using cooperative organocatalysis in a different reaction describing an aerobic oxidative aza-Baylis-Hillman reaction of *N*-aryltetrahydroisoquinolines.[41] The oxidation was carried out with a combination of $Cu(OTf)_2$ and 1 atm of molecular $O_2$ as oxidant system, and quinine was used as catalyst. For this reaction the scope was quite large concerning the *N*-substitution of tetrahydroisoquinolines. The desired products were obtained in 47-82% yield and 69-99% enantiomeric excess for the reaction with various olefins.

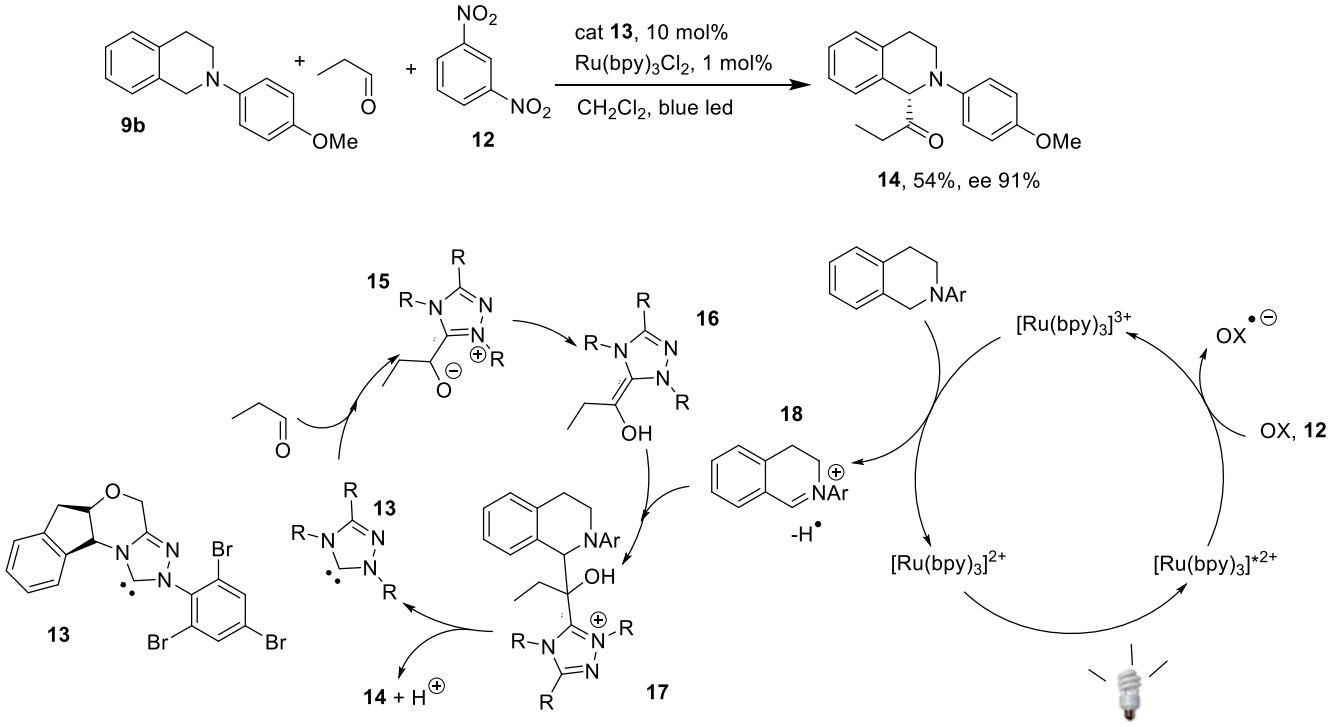
Toste applied the chiral counteranion catalysis in an example of enantioselective CDC, describing the synthesis of a C−N bond-forming reaction to produce 1,2,3,4-tetrahydroisoquinoline-derived cyclic aminals.[42]

For many of the transformation discussed in this section a single-electron transfer (SET) induced by the oxidant is assumed.[43] Quenching experiment with 2,6-di-*tert*-butyl-4-methylphenol (BHT) were reducing the yield of the coupling showing the probable presence of radical cation.

The generation of the required N-aryl quinolinium ion can be achieved also thanks to photoredox catalysis, in a synergistic organo and photo dual catalytic cycle. Two key transformations were recently described in which the stereoselective addition of chiral nucleophiles to tetrahydroisoquinoline is achieved through photocatalysis. The first report is the combination of photoredox catalysis with *N*-heterocyclic carbene catalysis developed by Rovis.[44] The nucleophilicity of carbene enolates measured by Mayr is sufficient for the reaction with iminium intermediates, and the possibility of the reaction is quite predictable. However, the difficulties in the oxidative coupling is determined by the possibility to oxidize the Breslow intermediate to unproductive pathways.[45] As illustrated in Scheme 4, the irradiation of $[Ru(bpy)_3]^{2+}$ with blue light populates the $[Ru(bpy)_3]^{*2+}$ excited state, giving rise to a powerful oxidant or reductant. If the oxidant $[Ru(bpy)_3]^{3+}$ (1.29 V vs SCE) is generated by reduction of an oxidative quencher, this specie is capable of a single-electron oxidation of a *N*-aryl tetrahydroisoquinoline, giving after hydrogen atom abstraction, a radical intermediate that is further oxidized to the activated iminium **18**. This electrophile is then intercepted by the nucleophilic Breslow intermediate **16** obtained by reaction of the aldehyde with the carbene catalyst.

The reaction is possible using $[Ru(bpy)_3]Cl_2$ as the photocatalyst in the presence of *m*-dinitrobenzene (*m*-DNB) **12** and chiral NHC **13** under irradiation with blue light. A careful optimization of the catalyst was necessary, giving optimal yields and high enantioselectivity (92% ee) for a series of various functionalized α-amino ketones **14**. This methodology allows the introduction of a wide range of linear

chains on the 1 position of the quinoline ring, a task not possible with the previously described organocatalytic methodologies.



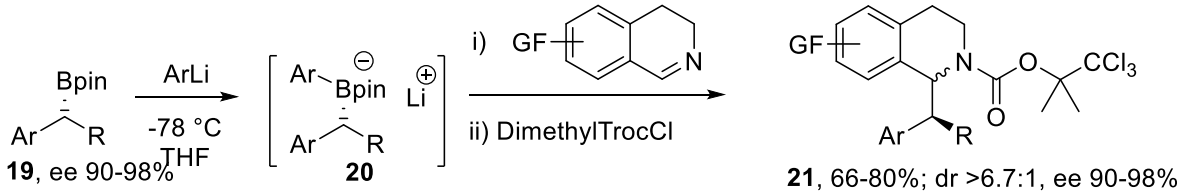

*Scheme 4. Asymmetric acylation of tetrahydroisoquinoline mediated by photoredox catalysis in the presence of a chiral carbene.*

Irradiation of photoactive catalysts and asymmetric anion-binding catalysis can also be merged in a quite interesting and innovative process. Jacobsen and Stephenson have described in 2014 the stereoselective addition of not stereogenic silyl ketene acetal to isoquinoline by the use of chiral anion-binding catalysts in combination with photocatalysis. In this transformation the photocatalyzed oxidation is generating a reactive specie that is trapped by an H-bond donor chiral thiourea. The stoichiometric oxidant that is used in this reaction is $CCl_4$.[46]

Instead of many papers published on this subject, the authors were able to describe a new protocol for *N*-dearylation of the products to provide derivatives that could be used in alkaloid synthesis. The *ortho* methoxy derivative was deprotected in good yield by the use of a specific reagent, $[Fe(bpy)_3](PF_6)_2]$. Application of other standard oxidative protocol (CAN, $PhI(TFA)_2$, or DDQ) led to low yields or extensive decomposition *via* over-oxidation.

As it emerges from this introduction, a direct alkylation of aldehydes with isoquinolinium salts had not yet been disclosed in 2012. The CDC couplings developed by Chi and Rovis suffer from the harsh conditions for the deprotection of the aryl group on the nitrogen, necessary to allow further

functionalization and to access natural products. The procedures developed by Jacobsen with silyl enol ethers and Ma's alkynylation do not use branched nucleophiles reducing the complexity of the scaffolds that can be obtained. While we were completing our work an efficient diasterocontrolled addition of chiral boronate complexes **20** to dihydroisoquinolinium salts was reported by Aggarwal (scheme 5). This procedure allows to obtain the enantioenriched heterocyclic structures **21** with very high diastereocontrol over two contiguous stereogenic centers (dr > 6.7:1; ee 90-98%). However, it is necessary to preform the highly enantioenriched boronate complexes and the application of the methodology to the synthesis of alkaloids was not reported.[47]




*Scheme 5 Aggarwal diastereoselective addition of boronates to dihydroquinolinium salts.*

Tetrahydoprotoberberine alkaloids (figure 1) are a series natural products that can be found in a large variety of plants. These compounds have been used in Chinese and folk medicine.[48] They can be seen as hydrogenated derivatives of Berberine **1a**, that has shown anti-bacterial activity,[49] and anti-inflammatory activity.[50]

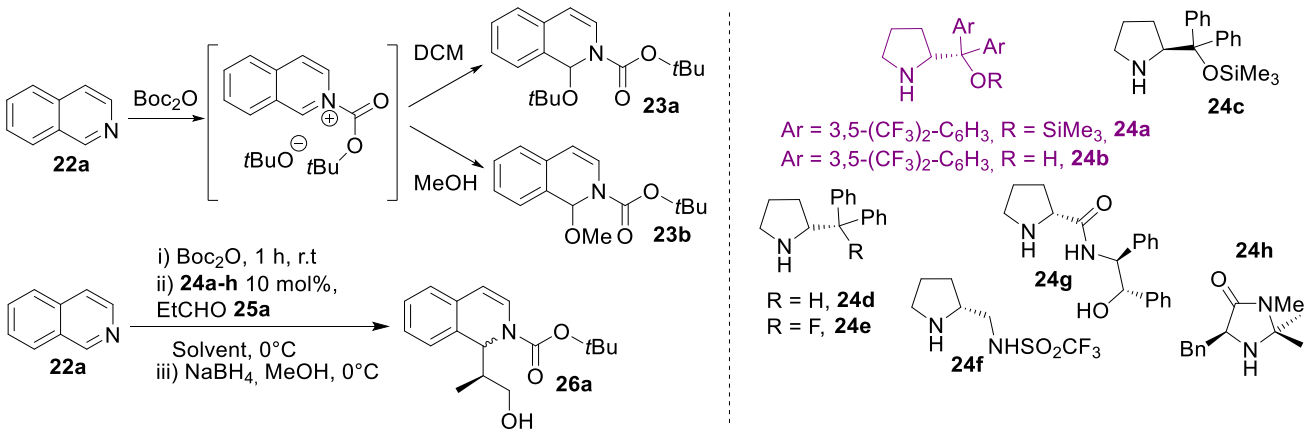
Among these isoquinoline alkaloids, 13-alkyltetrahydroprotoberberine alkaloids[51] are characterized by the presence of an additional methyl or alkyl substituent at the C13 position.

They show significant cytotoxicities and therapeutic effects, alleviating pain and promoting blood circulation. Although a small number of stereoselective synthetic approaches have been described for this class of protoberberine alkaloids,[52] to the best of our knowledge, stereoselective methodologies to access 13-alkyl tetrahydroprotoberberine alkaloids have not been reported.

## 2.2.2 Results and discussion

### Discovery and optimization of the reaction protocol

We envisioned that the intermolecular alkylation aldehydes with acyl-isoquinolinium ions via enamine catalysis could give us a methodology to access the before mentioned class of alkaloids in an enantio and diastereocontrolled manner.
In order to obtain easily derivatizable products we choose acylating agents to form the isoquinolinium ions in presence of the aldehyde and the amine catalyst. The main issue to address was to avoid the catalyst de-activation due to the reaction with the acylating agent.
We selected adduct **23a**,[53] that is obtained by reaction of isoquinoline **22a** with $Boc_2O$ and can be formed either is situ or isolated as a solid and stored without particular precautions in capped vials in fridge. Product **23b** can be obtained by conducing the reaction in methanol.
Even if adduct **23a** was known as a transfer acylating agent, we envisioned that the N,O-acetal form could be in dynamic equilibrium with the acyl iminium form, thus giving the desired electrophilic reaction partner. A similar mechanism was hypothesized also by Sodeoka to explain the necessity to preactivate 3,4-dihydroquinolines with $Boc_2O$ in her reaction protocol.[21a]
Therefore, we decided to investigate the organocatalytic addition of aldehydes using **23a** or **23b**, avoiding the direct reaction of $Boc_2O$ with the secondary chiral amine. Isoquinoline **22a** and $Boc_2O$ were mixed in equimolar amounts in dichloromethane (DCM) at room temperature for an hour to obtain adduct **23a**. The reaction temperature was lowered to 0°C and propionaldehyde **25a** (4 eq) was added along with various organocatalysts (**24a-h**) in 10 mol%. To our delight TLC and GC-MS showed the formation of the desired product when various pyrrolidine-based organocatalysts were employed. The highest enantiomeric excesses and diastereomeric ratio values were obtained with Hayashi-Jørgensen catalyst **24a** (Table 1).
The unsuccessful employment of the MacMillan catalyst **24h** to promote the reaction can be explained by the reduced nucleophilicity (3 orders of magnitude) of the enamine obtained from this catalyst and the one obtained with the Hayashi-Jørgensen catalysts (see chapter 1 table X).
Although the electrophilicities of acyl isoquinolinium salts have yet to be determined,[54] their electrophilicity is only moderate and in the range of the phenyl dihydroisoquinolinium salts whose electrophilicity parameter has been determined between −8 and −9 by Klussmann in agreement with the electrophilicity parameters determined by Mayr et al. for the comparable iminium ions.[55]
Conducting the reaction at room temperature lead to reduced stereoselectivity (Table 1, entry 2).




| Entry[a] | Cat. | Solvent[b] | Conv.[c] | dr[d] *syn/anti* | ee% (*syn*)[d] | ee% (*anti*)[d] |
|---|---|---|---|---|---|---|
| 1 | **24a** | DCM | 93 | 38/62 | 95 | 80 |
| 2[e] | **24a** | DCM | 97 | 44/56 | 87 | 76 |
| 3[f] | **24b** | DCM | 0 | - | - | - |
| 4 | **24c** | DCM | 92 | 39/61 | -90 | -78 |
| 5 | **24d** | DCM | 68 | 39/61 | 68 | 68 |
| 6 | **24e** | DCM | 73 | 42/58 | 60 | 75 |
| 7 | **24f** | DCM | 14 | 49/51 | 4 | -18 |
| 8 | **24g** | DCM | 65 | 41/59 | 0 | 4 |
| 9[f] | **24h** | DCM | 0 | - | - | - |
| 10 | **24a** | Hex | 53 | 82/18 | 91 | 55 |
| 11 | **24a** | Toluene | 26 | 88/12 | 91 | 12 |
| 12 | **24a** | THF | 44 | 78/22 | 85 | 75 |
| 13 | **24a** | MeCN | 82 | 43/57 | 82 | 94 |
| 14 | **24a** | $Et_2O$ | 59 | 81/19 | 94 | 80 |
| 15 | **24a** | TBE | 56 | 87/13 | 94 | 67 |
| 16 | **24a** | AcOEt | 31 | 67/33 | 82 | 72 |
| 17 | **24a** | TBE/DCM 2/8 | 88 | 43/57 | 90 | 99 |
| 18 | **24a** | TBE/DCM 8/2 | 69 (57)[g] | 88/12 | 97 | 93 |
| 19 | **24a** | Hex/DCM 2/8 | 84 | 42/58 | 86 | 97 |
| 20 | **24a** | Hex/DCM 8/2 | 67 | 84/16 | 96 | 79 |
| 21[h] | **24a** | TBE/DCM 8/2 | 89 (79)[g] | 80/20 | 95 | 86 |
| 22[i] | **24a** | TBE/DCM 8/2 | 91 (80)[g] | 87/13 | 97 | 85 |

[a] All reactions were conducted on 0.1 mmol of **22a**, 0.1 mmol $Boc_2O$, 0.4 mmol of **25a** and 0.01 mmol **24a-h**, in 1 mL of solvent at 0°C. After 15 hours the mixture was reduced with $NaBH_4$ in MeOH at -40 °C. [b] DCM = $CH_2Cl_2$; Hex = *n*-hexane; TBE =

*t*BuOMe. [c] Conversion determined by $^1$HNMR of the crude mixture after reduction. [d] Enantiomeric excesses and diastereomeric ratios were determined by HPLC analysis after reduction without further purification. [e] The reaction was performed at 25°C. [f] No product was obtained. [g] Isolated yield after chromatographic purification. The aldehyde product is rather unstable and decomposes during chromatographic purification. [h] Isolated **23b** was used as starting material. [i] Isolated **23a** was used as starting material.

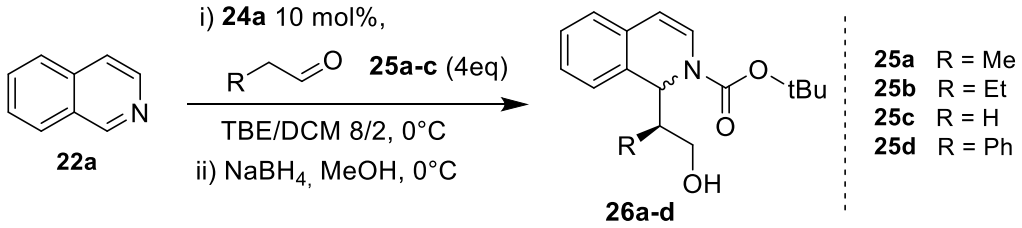
*Table 1. Conditions screening for the organocatalytic alkylation of isoquinoline **22a**.*

The screening of reaction solvents (Table 1, entries 10-16) showed that the best diastereomeric ratios were obtained with *tert*-butyl methyl ether (TBE), toluene and *n*-hexane while the best enantiomeric excess was afforded with DCM (Table 1, entry 1). It is worth noting that it is possible to obtain the opposite diastereomeric selectivity by changing the reaction solvent. MeCN and DCM gave the product with the opposite dr to that obtained in *n*-hexane and ethereal solvents. Moreover, we observed that conducting the reaction in DCM lead to a better conversion than in the other solvents mentioned. For these reasons we conducted the reaction in mixtures of TBE/DCM and *n*-hexane/DCM at various ratios (Table 1, entries 17-20). The 8:2 TBE/DCM mixture afforded the best result (Table 1, entry 18) in terms of diastereoisomeric ratio. Starting from preformed adducts **23a** and **23b** gave a significant increase in the reaction yield (Table 1, entries 21, 22), and did not significantly decrease the stereoselective outcome in the case of **23a**.

The aldehyde products proved to be quite unstable, in particular during chromatographic purification, so after the indicated reaction time, the crude mixture was directly diluted with methanol and $NaBH_4$ was added to reduce the aldehyde to the corresponding alcohols that could be purified without any appreciable decomposition on silica.

To explore the scope of the reaction, other aldehydes were tested under the optimized conditions (table 2). Butanal gave the corresponding product in moderate yield and diastereomeric ratios and excellent enantiomeric excesses. In case of phenylacetaldheyde the product was obtained in 49% yield, but in reduced stereoselectivity compared with propanal and butanal. While the use of acetaldehyde allowed to obtain the desired product in low yield and 60% ee, that corresponds roughly to the diastereomeric ratios obtained with the other aliphatic aldehydes which is consistent to the fact that the stereogenic center formed is far from the chiral part of the enamine.

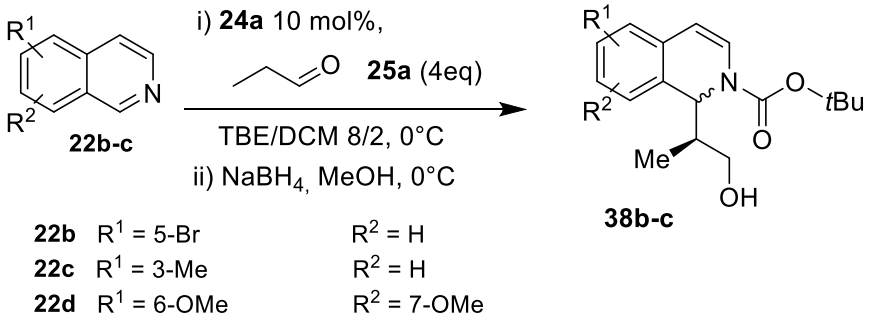
The limit of secondary amines, that relies its stereochemical induction on sterical effects, in controlling efficiently the stereocenters formed on the electrophilic partner of the reaction was confirmed also in our protocol. A few examples of how it is possible to control remote stereocenters through enamine catalysis have been published and they mainly rely on secondary non covalent interactions with the electrophile to achieve this goal.[56]




| Entry[a] | Product | Yield[b] | dr[c] | ee%(*syn*)[c] | ee%(*anti*)[c] |
|---|---|---|---|---|---|
| 1 | **26a** | 57 | 88/12 | 97 | 93 |
| 2[d] | **26a** | 80 | 87/13 | 97 | 85 |
| 3 | **26b** | 44(35/9)[e] | 79/21 | 97 | 93 |
| 4 | **26c** | 26 | - | 60[f] | - |
| 5 | **26d** | 49 | 68/32 | 86 | - |

[a] All reactions were conducted on 0.2 mmol of **22a**, 0.2 mmol $Boc_2O$, 0.8 mmol of **25a-c** and 0.02 mmol **24a**, in 1 mL of a mixture of TME/DCM 8/2 at 0°C. After 15 hours the mixture was reduced with $NaBH_4$ in MeOH at 0°C. [b] After chromatographic purification. [c] Enantiomeric excesses and diastereomeric ratios were determined by HPLC-analysis after reduction and chromatographic purification. Dr were reported as *syn*/*anti*. [d] Isolated **23b** was used as starting material. [e] The compound **26b** was isolated as pure diastereoisomers after chromatographic purification. In all other cases, the adducts were obtained as inseparable mixture of *syn* and *anti* stereoisomers. The dr for **26b** was determined by $^1$HNMR of the crude mixture after reduction. [f] Enantiomeric excess of the product.

*Table 2: stereoselective alkylation of aldehydes with isoquinoline activated with $Boc_2O$.*




| Entry[a] | Product | Yield[b] | dr[c] | ee%(*syn*)[c] | ee%(*anti*)[c] |
|---|---|---|---|---|---|
| 1 | **38b** | 0 | - | - | - |
| 2 | **38c** | 0 | - | - | - |
| 3 | **38d** | 0 | - | - | - |

[a] All reactions were conducted on 0.2 mmol of **22a**, 0.2 mmol $Boc_2O$, 0.8 mmol of **25a-c** and 0.02 mmol **24a**, in 1 mL of a mixture of TME/DCM 8/2 at 0°C. After 15 hours the mixture was reduced with $NaBH_4$ in MeOH at 0°C.

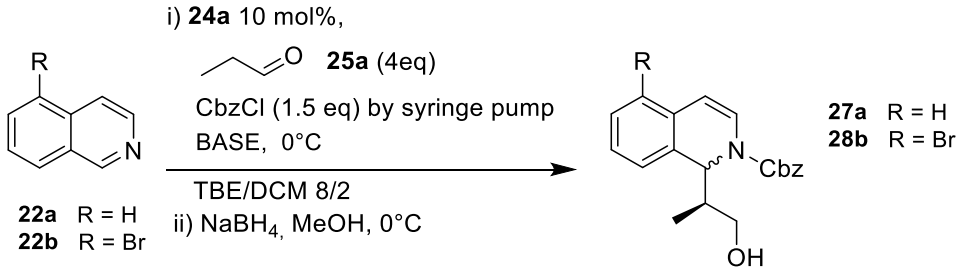
*Table 3: attempted activation of substituted isoquinolines activated with $Boc_2O$.*

Unfortunately when substituted isoquinolines **22b**, **22c**, **22d** were reacted with $Boc_2O$ at room temperature, the adducts corresponding to **23a** could not be obtained. I also attempted to run the reaction according to the *in situ* activation protocol with $Boc_2O$ but also in this case no product could be obtained (table 3). In case of 5-Br isoquinoline, the failure was attributed to its reduced nucleophilicity that disfavors the reaction with the acylating agent, while in case of 3-methyl isoquinoline the steric hindrance that the substituent exercises on the nitrogen is probably responsible for non-activation of this substrate.

The failure of $Boc_2O$ to activate substituted quinolines, in particular those bearing electron withdrawing or electrondonating groups (EWG), prompted us to investigate the use of more electrophilic acylating agents such as chloroformates, among which we selected CbzCl because it guarantees an easy deprotection under hydrogenation conditions to access the tetrahydroisoquinoline scaffold. So the activation of isoquinolines was attempted using this reagent, employing the same protocol established with $Boc_2O$ with the addition of sodium bicarbonate (3 eq) to neutralize the hydrochloridric acid generated as byproduct. Unfortunately the simultaneous addition of all the reagents lead to the formation of only traces of the desired product, as revealed by GC-MS analysis of the crude reaction mixture. Moreover we observed that the Hayashi-Jørgensen organocatalyst had been completely acylated during the reaction, resulting in its de-activation. In order to minimize the acylation of the catalyst during the reaction, we reasoned that the slow addition of the activating agent should be beneficial. Indeed when CbzCl (1.5 eq) was added in five portions every hour a significant increase in the conversion was observed and when a solution of this acylating agent was added by syringe pump over a long time (15 hours) we could isolate the desired product even if in low yield (table 4 entry 1). What encouraged us to pursue in the optimization of the reaction conditions was that using this reaction protocol also 5-Br isoquinoline could be activated and the product **28b** was isolated in yields comparable to **27a** (table 4 entry 2).

Under these conditions several inorganic bases were screened, but only a weak inorganic base such as $NaHCO_3$ proved to be efficient in trapping the HCl by product that could otherwise form the corresponding salt with isoquinoline preventing its reaction with CbzCl. The use of round bottomed tubes to perform the reaction in order to have an efficient stirring of the heterogeneous system (solid base – organic solution) was very important in order to obtain reproducible results. No conversion was observed in the absence of the base. Increasing the amount of acylating agent to 2.25 eq, and of catalyst and aldehyde, respectively to 20 mol% and 5 equivalents, in order to have a higher concentration of the reactive enamine inside the reaction mixture, allowed to increase the yield to 42%. The excess of CbzCl is probably necessary because the reaction is run under non anhydrous conditions so part of the acylating agent may decompose during the reaction course.

The products were always isolated after reduction with $NaBH_4$ to the corresponding alcohols because the aldehyde intermediates were not stable during chromatography purification, as in case Boc2O was used.



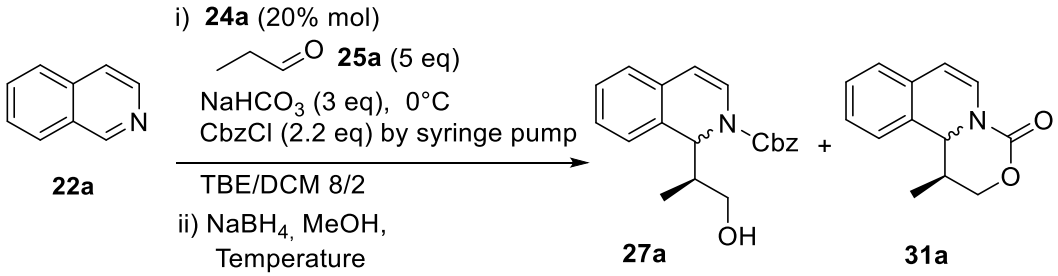

| Entry[a] | Product | Yield[b] | dr[c] | ee%(*syn*)[c] | ee%(*anti*)[c] | Base |
|---|---|---|---|---|---|---|
| 1 | **27a** | 15 | 75/25 | 98 | 88 | $NaHCO_3$ |
| 2 | **28b** | 21 | 83/27 | 86 | 88 | $NaHCO_3$ |
| 3[d] | **28b** | - | 68/32 | 94 | 83 | $NaHCO_3$ |
| 4 | **27a** | 0 | - | - | - | *t*-$Bu_4NOH{\cdot}30H_2O$ |
| 5 | **27a** | 0 | - | - | - | $K_2HCO_3$ |
| 6 | **27a** | 0 | - | - | - | $Cs_2HCO_3$ |
| 7 | **27a** | traces | - | - | - | $NaHCO_3$ aq.sat. |
| 8[e] | **27a** | 42 | - | - | - | $NaHCO_3$ |
| 9[e] | **27a** | 33 | - | - | - | $NaHCO_3$[f] |

[a] All reactions were conducted on 0.2 mmol of **22a-b**, 0.3 mmol CbzCl, 0.8 mmol of **25a**, 0.6 mmol of base and 0.02 mmol **24a**, in 0.5 mL of a mixture of TME/DCM 8/2. After 15 hours the mixture was reduced with $NaBH_4$ in MeOH at -40°C. [b] After chromatographic purification. [c] Enantiomeric excesses and diastereomeric ratios were determined by HPLC-analysis after reduction and chromatographic purification. Dr were reported as *syn*/*anti*. [d] reaction conducted in presence of 0.02 mmol *p*-$NO_2PhCOOH$. [e] Reaction conducted using 0.45 mmol CbzCl, 1.0 mmol of **25a** and 0.04 mmol **24a**; **31a** was detected in 17% yield after chromatographic purification. [f] Reaction conducted using 1.0 mmol of $NaHCO_3$.

*Table 5. Screening test for the alkylation of propionaldehyde with isoquinolines activated with CbzCl*

However after we performed the reduction in situ we observed the formation of a second product that was identified as the lactone **31a**, clearly formed after the reduction to alcohol. Reasoning that the presence of the excess of base together with the increased reactivity of the Cbz would favor this undesired process, I washed the crude reaction mixture with a saturated solution of $NH_4Cl$ prior to perform the reduction. Moreover instead of quenching the excess of $NaBH_4$ with water, generating basic aqueous conditions, 1M HCl was used. These precautions allowed to reduce the amount of the lactone byproduct but not to avoid its formation that could be achieved only lowering the reduction temperature to -40°C. Under these conditions we obtained a moderate but satisfactory, if compared with the other organocatalytic methodologies, yield of 53% for the model substrate **27a** with excellent ee and moderate dr (table 6).

When I performed the addition of the acylating agent more rapidly a poor result was obtained, confirming that 15 hours was the optimal time.




| Entry[a] | Yield[b] **27a** | Yield[b] **31a** | Temperature (°C) | CbzCl addition time (h) |
|---|---|---|---|---|
| 1 | 42 | 17 | 0 | 15 |
| 2[c] | 44 | 8 | -20 | 15 |
| 3[c] | traces | - | -20 | 2 |
| 4[c] | 42 | traces | -30 | 28 |
| 5[c] | 53 | 0 | -40 | 15 |

[a] All reactions were conducted on 0.2 mmol of **22a**, 0.45 mmol CbzCl, 1.0 mmol of **25a**, 0.6 mmol of $NaHCO_3$ and 0.04 mmol **24a**, in 0.5 mL of a mixture of TME/DCM 8/2. After the CbzCl addition was completed the mixture was reduced with $NaBH_4$ in MeOH at the indicated temperature. [b] After chromatographic purification. [c] the crude reaction mixture was washed with a saturated solution of $NH_4Cl$ prior to perform the reduction that was quenched using 1M HCl.

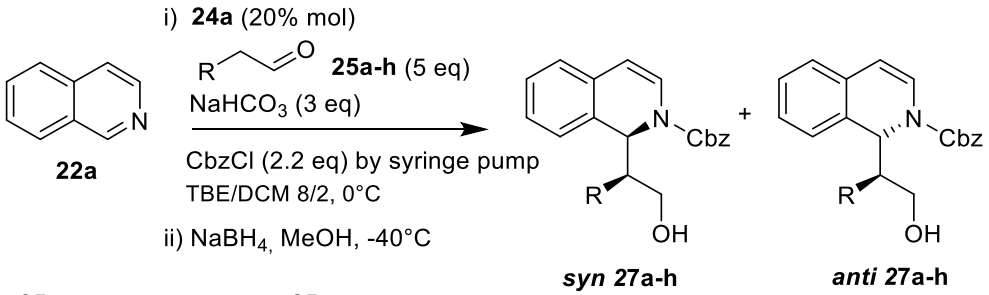
*Table 6: Temperature effect in the reduction step and rate effect in the addition of CbzCl*

**Reaction scope**

The reaction conditions optimized with CbzCl as activating agent proved to be efficient for the activation of electron rich and electron poor isoquinolines and a significantly increased substrate scope was achieved.

The reaction of **22a** was successful with a large range of linear aliphatic aldehydes (**25b,d**) and with phenyl acetaldehyde **25h** (Table 7, entries 2, 4 and 7), but the presence of other bulky groups on the alkyl chain reduced the product yields (Table 7, entries 5-7). Acetaldehyde gave product **27c** in low yield and moderate ee (Table 7, entry 3). We tested isoquinolines with electron withdrawing or electron donating substituents on the 3,4,5,6,7-positions, with propionaldehyde **25a**. All substrates afforded the corresponding products except 5-(*N*)-pyrrolydinylisoquinoline **22h**, probably due to the presence of the amine functional group on this particular substrate. 6-Methyl isoquinoline **22g**, electron rich isoquinolines (**22d**, **22f**), 5-allyl isoquinoline **22e** and 4-benzyl-isoquinoline **22i** afforded the corresponding products in satisfactory yields (Table 8, entries 3-9), comparable to other published procedures.[14a,b] On the other hand 5-Br isoquinoline (**22b**) gave **28b** with a slightly decreased yield (Table 8, entry 1), as would be expected based on its low nucleophilicity. 3-Methyl isoquinoline **22c** gave **28c** in poor yield probably due to the steric hindrance at the 3-position (Table 8, entry 2). It is

worth noting that the sterical hindrance presented by this substituent had a positive influence on the dr ratio.




**25a** R = Me **25e** R = -$(CH_2)_3Cl$
**25b** R = Et **25f** R = -$CH_2$-Ph
**25c** R = H **25g** R = *cis*-$CH_2CH{=}CHCH_2CH_3$
**25d** R = -$(CH_2)_5CH_3$ **25h** R = Ph

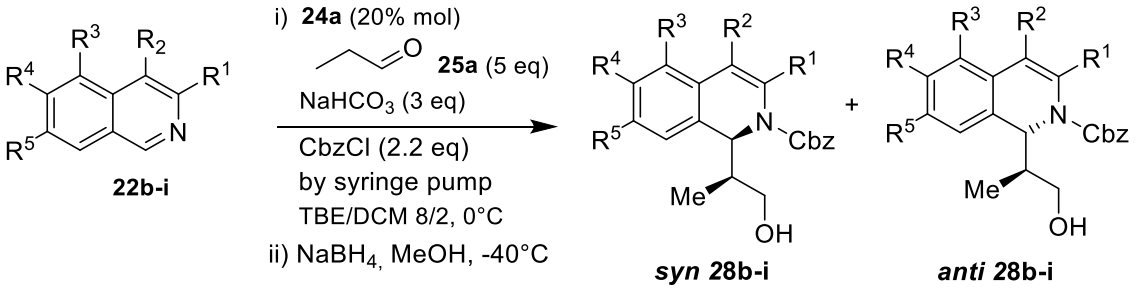
| Entry[a] | 27 | Yield[b] | dr[c] | ee%(*syn*)[c] | ee%(*anti*)[c] |
|---|---|---|---|---|---|
| 1 | **27a** | 53 | 74/26 | 96 | 87 |
| 2 | **27b** | 51 (39/12)[e] | 77/23 | 98 | 98 |
| 3 | **27c** | 10 | 50[d] | - | - |
| 4 | **27d** | 65 | 79/21 | 99 | 96 |
| 5 | **27e** | 13 | 73/27 | 97 | 80 |
| 6 | **27f** | 9 (7/2)[e] | 81/19 | 91 | 93 |
| 7[f] | **27g** | 23 | 32/68 | 81 | 94 |
| 8 | **27h** | 62 | 33/67 | 82 | 90 |

[a] All reactions were conducted on 0.2 mmol of **22a**, 0.44 mmol CbzCl (slow addition by syringe pump) 1.0 mmol of **25a-h**, 0.6 mmol of $NaHCO_3$ and 0.04 mmol **24a**, in 0.5 mL of a mixture of TBE/DCM 8/2. After 15 hours the mixture was reduced with $NaBH_4$ in MeOH at -40°C. [b] After chromatographic purification. [c] Enantiomeric excesses and diastereomeric ratios were determined by HPLC analysis after reduction and chromatographic purification. Dr are reported as *syn*/*anti*. [d] Enantiomeric excess of the product. [e] The compounds **27b** and **27f** were isolated as pure diastereoisomers after chromatographic purification. In all other cases, the adducts were obtained as inseparable mixture of *syn* and *anti* stereoisomers. The dr for **27b** and **27f** was determined by $^1$HNMR of the crude product after reduction. [f] The reaction was performed in DCM.

*Table 7. Organocatalytic alkylation of the isoquinoline 22a with different aldehydes.*

In contrast, substituents at the 6-position caused a drop in both enantioselectivity and diastereoselectivity (Table 8, entries 6 and 7), while **28d** was obtained with good diasteromeric ratio for the opposite diastereoisomer although with poor enantiomeric excess (Table 8, entry 3). Conducting the reaction in DCM, the alkylation of **22d** and **22g** gave **28d** and **28g** in good enantiomeric excesses and moderate dr favoring the anti diastereoisomer (Table 8, entries 4 and 8). We assume that the hindrance

caused by the substituents in position 6 and 7 of the isoquinolines and their interaction with the aryl or $SiMe_3$ groups of the catalyst alters the diasteroselectivity of the reaction.




**22b** $R^1$= $R^2$= $R^4$= $R^5$= H; $R^3$= Br
**22c** $R^2$= $R^3$= $R^4$= $R^5$= H; $R^1$= Me
**22d** $R^1$= $R^2$= $R^3$= H; $R^4$= $R^5$= OMe
**22e** $R^1$= $R^2$= $R^4$= $R^5$= H; $R^3$= allyl
**22f** $R^1$= $R^2$= $R^3$= $R^5$= H; $R^4$= OMe
**22g** $R^1$= $R^2$= $R^3$= $R^5$= H; $R^4$= Me
**22h** $R^1$= $R^2$= $R^4$= $R^5$= H; $R^3$= Pyrrolidinyl
**22i** $R^1$= $R^3$= $R^4$= $R^5$= H; $R^2$= Bn

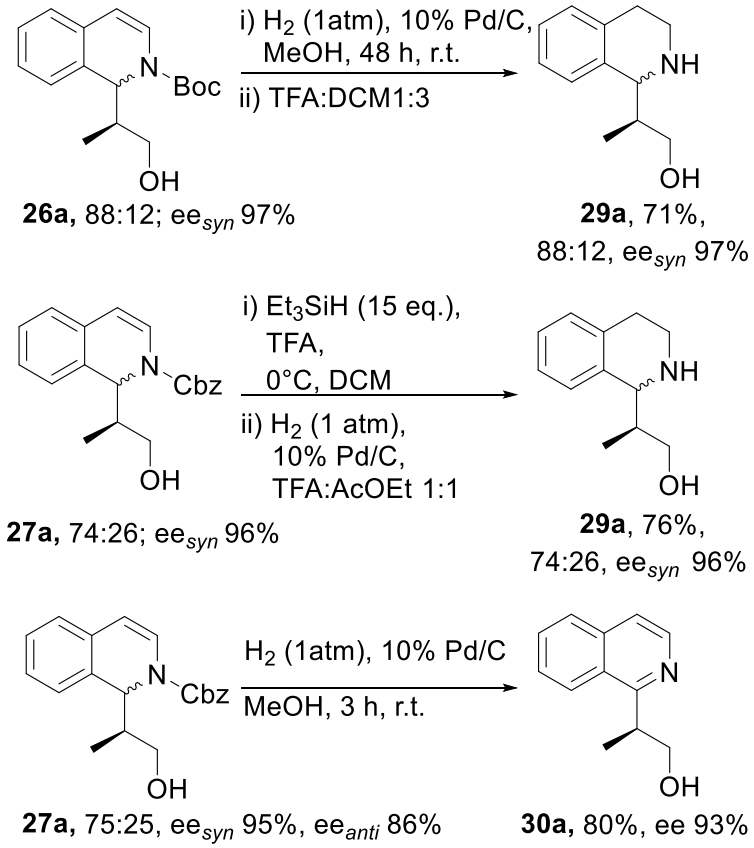
| Entry[a] | **28** | Yield[b] | dr[c] | ee%(*syn*)[c] | ee%(*anti*)[c] |
|---|---|---|---|---|---|
| 1 | **28b** | 40 | 73/27 | 95 | 88 |
| 2 | **28c** | 23 | 87/13 | 99 | 94 |
| 3 | **28d** | 54 | 19/81 | 54 | 48 |
| 4[d] | **28d** | 53 | 29/71 | -77[e] | 91 |
| 5 | **28e** | 56 | 76/44 | 96 | 86 |
| 6 | **28f** | 56 | 54/46 | 78 | 25 |
| 7 | **28g** | 68 | 58/42 | 83 | 7 |
| 8[d] | **28g** | 75 | 47/53 | 88 | 92 |
| 9 | **28i** | 60 | 81/19 | 97 | 74 |

[a] All reactions were conducted on 0.2 mmol of **22b-i**, 0.44 mmol CbzCl (slow addition by syringe pump), 1.0 mmol of **25a**, 0.6 mmol of $NaHCO_3$ and 0.04 mmol **24a**, in 0.5 mL of a mixture of TBE/DCM 8/2. After 15 hours the mixture was reduced with $NaBH_4$ in MeOH at -40°C. [b] After chromatographic purification. [c] Enantiomeric excesses and diastereomeric ratios were determined by HPLC analysis after reduction and chromatographic purification. Dr are reported as *syn/anti*. [d] The reaction was performed in DCM. [e] Opposite enantioselectivity was observed for *syn* **28d**.

*Table 8. Organocatalytic alkylation of different isoquinolines with **25a**.*

**Derivatization to enantioenriched tetrahydroisquinolines and isquinolines**

The advantage of the present methodology over the previously published organocatalytic methods is the easy deprotection[16] of adducts **26**, **27** and **28** (Scheme 6). Deprotection without reduction of the enamide double bond resulted in decomposition and formation of uncharacterized material. The deprotection of Boc adduct **26a** after reduction gave the tetrahydroisoquinoline derivative **29a** in good yield and high ee. Attempts were made to deprotect the Cbz adduct **27a** by simple reduction with hydrogen in the presence of Pd/C but surprisingly, instead of the desired 1,2,3,4-tetrahydroisoquinoline **29a**, the 1-substituted chiral isoquinoline **30a** was produced. It is thought that this product was generated by the aromatisation of the dihydropyridine ring. Full conversion was achieved after three hours with 10% wt Pd/C and the product was isolated in 80% yield with elevated enantiomeric excess (ee 93%, the weighted average of the enantiomeric ratio for the two diastereoisomers).



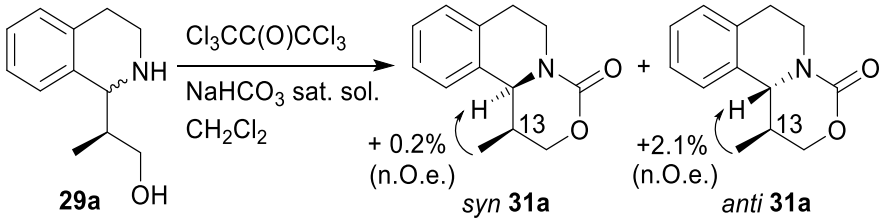

*Scheme 6. Reductive removal of the protective groups in compounds **26a** and **27a**.*

Due to re-aromatisation the stereogenic center at the C1 position of the tetrahydroisoquinoline is lost and the result obtained indicates that the remaining stereocenter has the same absolute configuration for both diastereoisomers. This result presents an interesting new route for the synthesis of chiral

isoquinoline derivatives. In order to cleave the Cbz adducts, we first reduced the C3-C4 double bond using triethylsilane in the presence of trifluoroacetic acid[14c] and then removed the Cbz group by hydrogenation (Scheme 6) in a 1:1 mixture of trifluoroacetic acid/ethyl acetate.

**Determination of the relative and absolute configuration and stereochemical model**

To determine the relative configuration of the obtained products **26**, **27** and **28**, the oxazolidinone **31a** was prepared starting from **29a**. The major and the minor diastereoisomers were separated by preparative TLC and the relative configuration of the stereogenic centers 1 and 2' was determined by NOESY1D NMR analysis. The major diastereoisomer obtained was *syn* while the minor was *anti.*

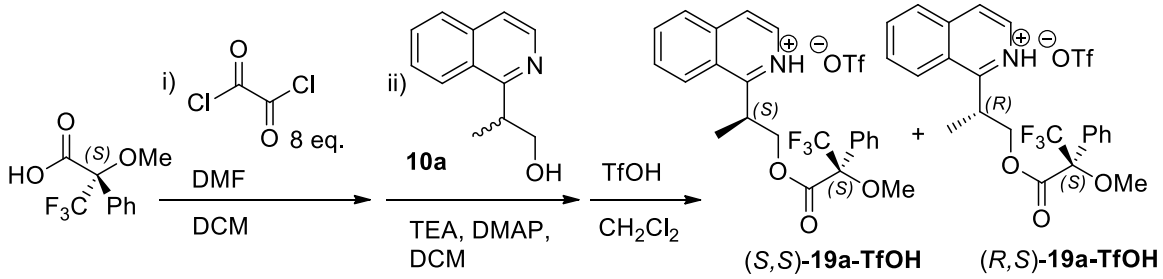



*Scheme 7. Determination of the relative configuration of compounds **29a**.*

The absolute configuration of the products was determined by derivatization of rearomatized product **30a** using Modified Mosher's method.[S6]

This methods allows to determine the absolute configurations of chiral centers, with a branched methyl, having a primary alcohol on the C2 position by NMR measurements on the corresponding Mosher esters.

Specifically, from the literature, in (*S*)-MPTA ester of a C2 branched primary alcohol the distance between the double doublet signals for the diastereomeric protons on C1 is larger if the absolute configuration of the C2 chiral center is *S*, while it is closer for the *R* stereoisomer. The reverse is also true for the (*R*)-MPTA ester.




*Scheme 8. Determination of the absolute configuration of compound **30a**.*

The Mosher esters **39** were synthetized according to standard protocols starting from the racemic and active (93% ee) **30a** (scheme 8). For the salts of **39** with trific acid the desired splitting of the $^{1}$H NMR signals was observed allowing to attribute the (*S*) absolute configuration of the stereocenter in the C2 position. In conclusion the absolute configuration of the *syn*-**27a** was assigned (2'*S*,1*S*) while for the *anti*-**27a** was (2'*S*,1*R*). The same absolute configuration were suggested for **26a-c**, **27a-h** and **28b-i**.
To resume, the relative configuration of the major diastereoisomer was assigned as *syn*, while the absolute configuration at C13 (fixed for both diastereoisomers) was assigned as *S*. The relative and absolute configurations of the obtained products are in agreement with a mechanistic model in which the isoquinolinium is attacked by the enamine from the less hindered face (figure 2).[27]

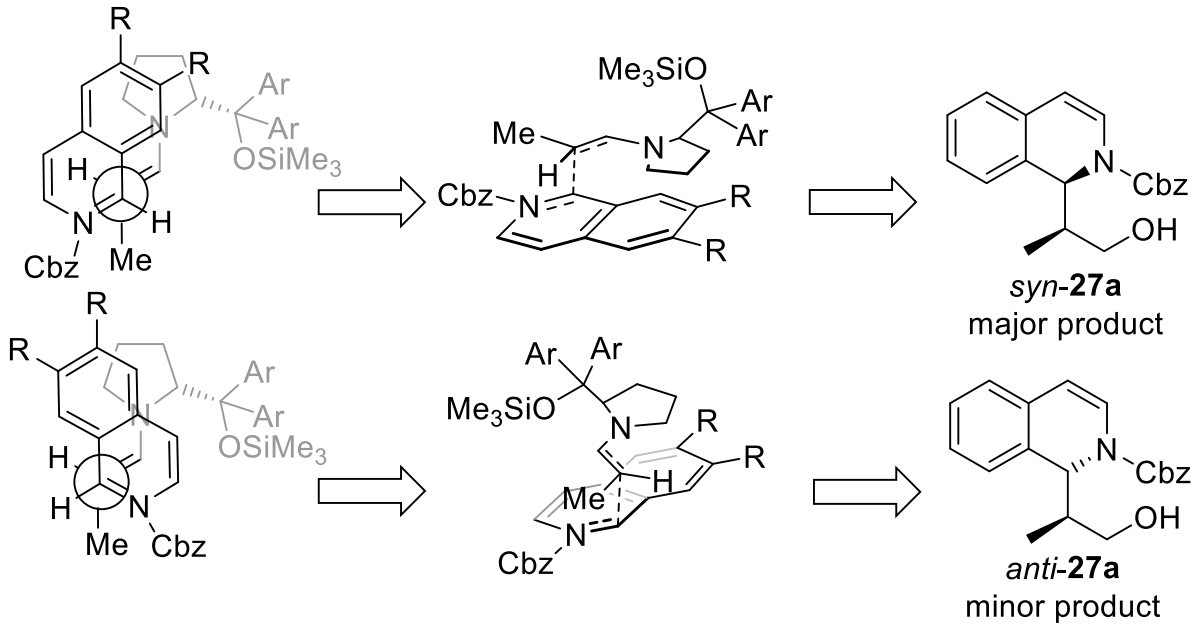



*Figure 2. Stereochemical proposal for the nucleophilic addition of Jørgensen enamine to isoquinolinium ions.*

This model does not account for the reversal of the diastereoselectivity observed using different reaction solvents. It was reported by Gschwind[57] that the solvent properties cannot affect the conformational preferences of diaryl prolinol ether enamine conformers. She has reported that in different solvents the favored *sc-exo* conformer, stabilized by CH/π interactions, is exclusively observed. This rules out the possibility that in our case the diastereoselectivity is determined by a different enamine rotamer, favored by the reaction solvent. However, it has been reported that diastereoselectivity in reactions can be altered by solvents and solvent mixtures due to solute-solvent clusters.[58] Tentatively, we suggest that our reaction solvents are altering the energy of the possible transition states, specifically modifying the approach of the isoquinolinium to diaryl prolinol enamine,

favoring the *syn* or *anti* diastereoisomer. Further investigation on this matter requires high level DFT calculations, that will be addressed in future studies.

**Attempted synthesis of corydaline**

To validate this methodology we decided to apply it to the synthesis of 13-alkyl-tetrahydroprotoberberine alkaloids. Among these we initially selected corydaline (figure 1) as our target and the retrosynthetic approach depicted in figure 3 was planned. The relative configuration of intermediate **50** is *anti* so the alkylation of the aldehyde must be performed in DCM to obtain the desired diastereosisomer as the major product.

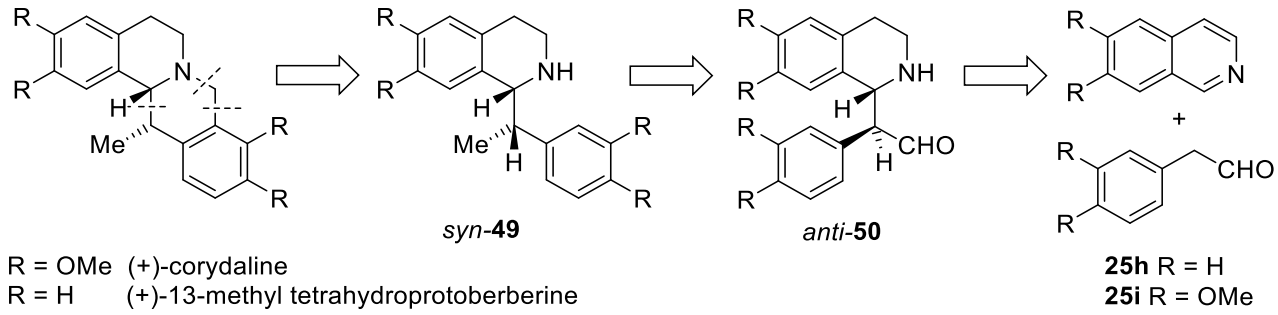
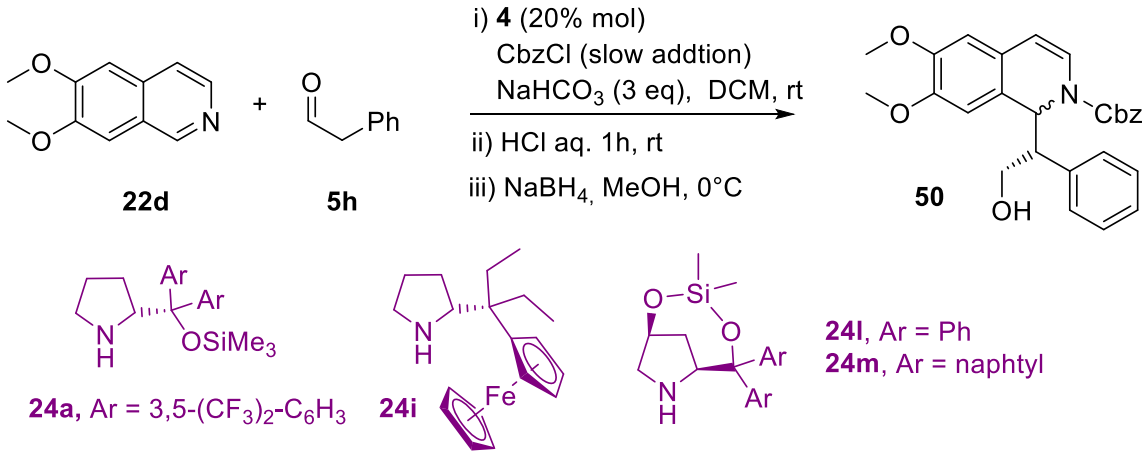



*Figure 3: retrosynthetic analysis to access 13-methyl tetrahydroprotoberberine alkaloids.*

The two initial reactions partners, isoquinoline **22d** and aldehyde **25i** are not commercially available but can be prepared easily in one step. Unfortunately the initial attempts to perform the reaction between **22d** and **25i** under the established protocol did not lead to the formation of the product.

So I studied more in detail the alkylation of commercially available phenylacetaldehyde with dimethoxy isoquinoline **22d** (table 9). The racemic product **51** was obtained performing the alkylation reaction with the isolated enamine **41** obtained by condensation of phenylacetaldehyde and pyrrolidine. Unfortunately when the standard catalytic conditions using CbzCl as activating agent and catalyst **4a** were tried only a low conversion to was observed and more importantly the product **50** was obtained as a perfect racemate. A drop in the enantioselectivity had been already observed in the reaction between **22d** and propionaldehyde **25a** (table 8), and from this result the increase of the bulkiness of the aldehyde substituents plays a totally detrimental effect for this reaction couple. In order to try and obtain a better result both in term of yields and enantioselectivity, I tried different prolinol organcatalysts (table 9). However using ferrocene substituted pirrolidine **24i**[59] as catalyst lead to the same poor result. The use of bridged catalysts **24l** and **24m**, generously furnished by our colleague Professor Lombardo,[60] afforded better results, moderate conversion and up to 75% ee, but still unsatisfactory.




| Entry[a] | 24 | Conversion [b] | dr (*anti/syn*)[c] | ee%(*anti*)[c] | ee%(*syn*)[c] |
|---|---|---|---|---|---|
| 1 | **24a°** | ≈ 20 | 75/25 | 0 | 0 |
| 2 | **24i** | ≈ 20 | 60/40 | 0 | 0 |
| 3 | **24l** | ≈ 40 | 76/24 | 75 | 18 |
| 4 | **24m** | ≈ 20 | 63/37 | 60 | 6 |

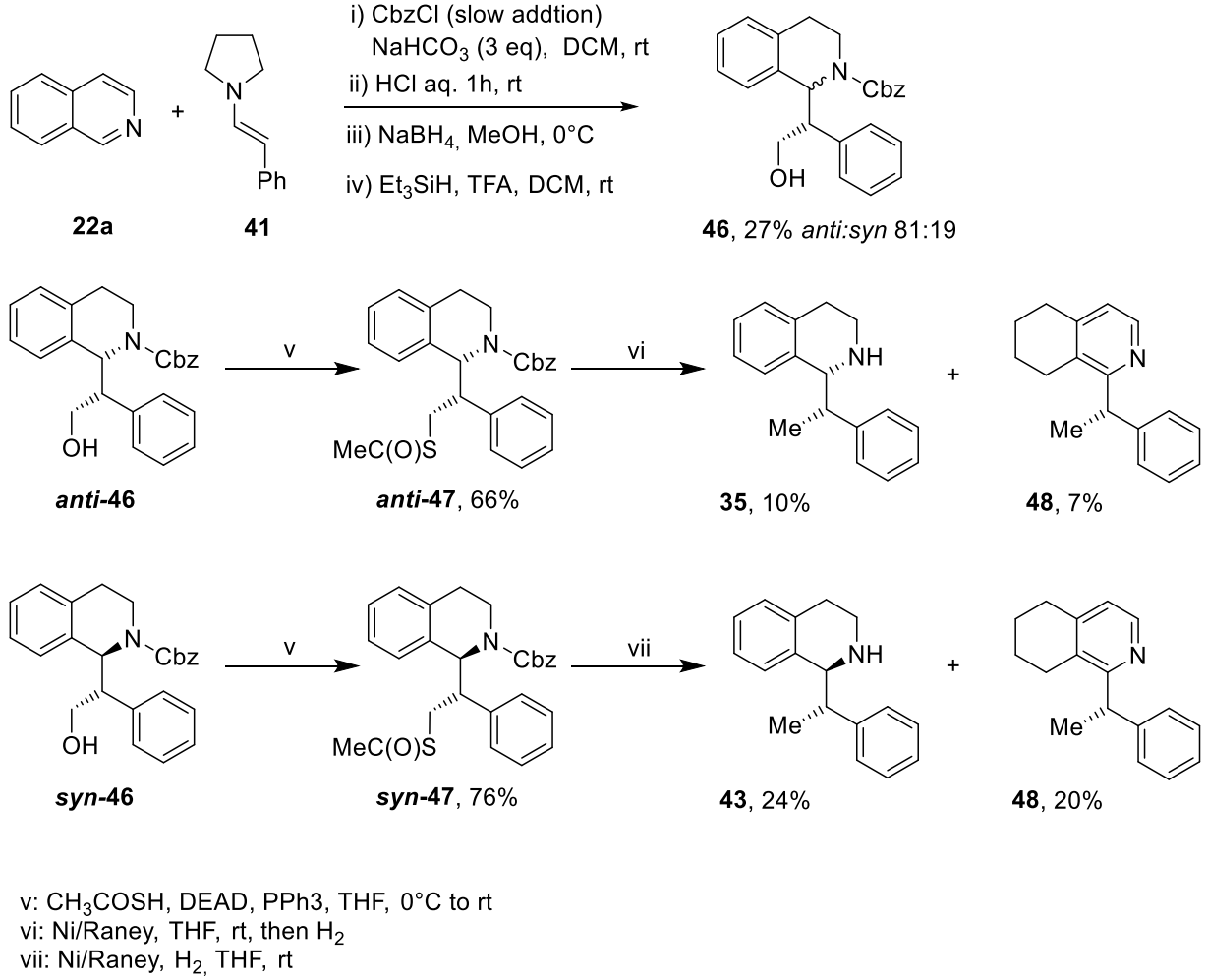
[a] All reactions were conducted on 0.1 mmol of **22d**, 0.22 mmol CbzCl (slow addition by syringe pump), 0.5 mmol of **25h**, 0.3 mmol of $NaHCO_3$ and 0.02 mmol **24a,i-m**, in 0.25 mL of DCM. After 15 hours the mixture was reduced with $NaBH_4$ in MeOH at -40°C. [b] Estimated by $^1H$ NMR on the crude reaction mixture after redcution. [c] Enantiomeric excesses and diastereomeric ratios were determined by HPLC analysis on the crude reaction mixture after reduction.

*Table 9: different conditions for the synthesis of intermediate **50**.*

**Attempted synthesis of (+)-13-methyl tetrahydroprotoberberine 1g with Cbz as activating group**

These negative results prompted us to look for a new alkaloid that has the isoquinoline ring non substituted and 13-methyl tetrahydroprotoberberine[61] was chosen as suitable candidate as it could be obtained from commercially available quinoline and phenylacetaldehyde. Also in this case the *anti* diastereoisomer was needed and the alkylation reaction was performed in DCM under the standard conditions using CbzCl as activating agent. The desired product **27h** was obtained in good yield and ees and moderate dr favouring the *anti* diastereoisomer (Table 7, entry 8).
Having verified the possibility to have the desired enantioenriched starting material we evaluated the feasibility of the postulated synthetic route on racemic **27h** that was obtained using isolated enamine **41** (scheme 9). The first task to accomplish was the separation of the desired anti diastereoisomer from the syn, that could be achieved by simple column chromatography on intermediate **46** obtained after the reduction of the enamide double bond using the conditions previously established. I then proceeded on parallel synthesis on both ***syn*-46** and ***anti*-46**.

The next task was the reduction of the alcohol moiety to methyl group. I initially attempted to deoxynate **46** by mesylation of the alcohol and reduction with $LiAlH_4$. However when **46** was treated with MsCl in pyridine, the mesylated product could not be obtained due to the exclusive formation of cyclic carbamate derived from the attack of the alcohol moiety on the Cbz group promoted by the base. The chosen alternative was to replace the alcohol with a thioester that could be removed by treatment with Nichel/Raney®. The Mitsunobu reaction using thioacetic acid[62] proceeded smoothly on the condition that freshly open acid was used, otherwise the yield of **27** decreased together with the formation of significant amounts of $Ph_3P=S$.




*Scheme 9: Attempted synthesis of (+)-13-methyl tetrahydroprotoberberine **1g** with Cbz as activating group.*

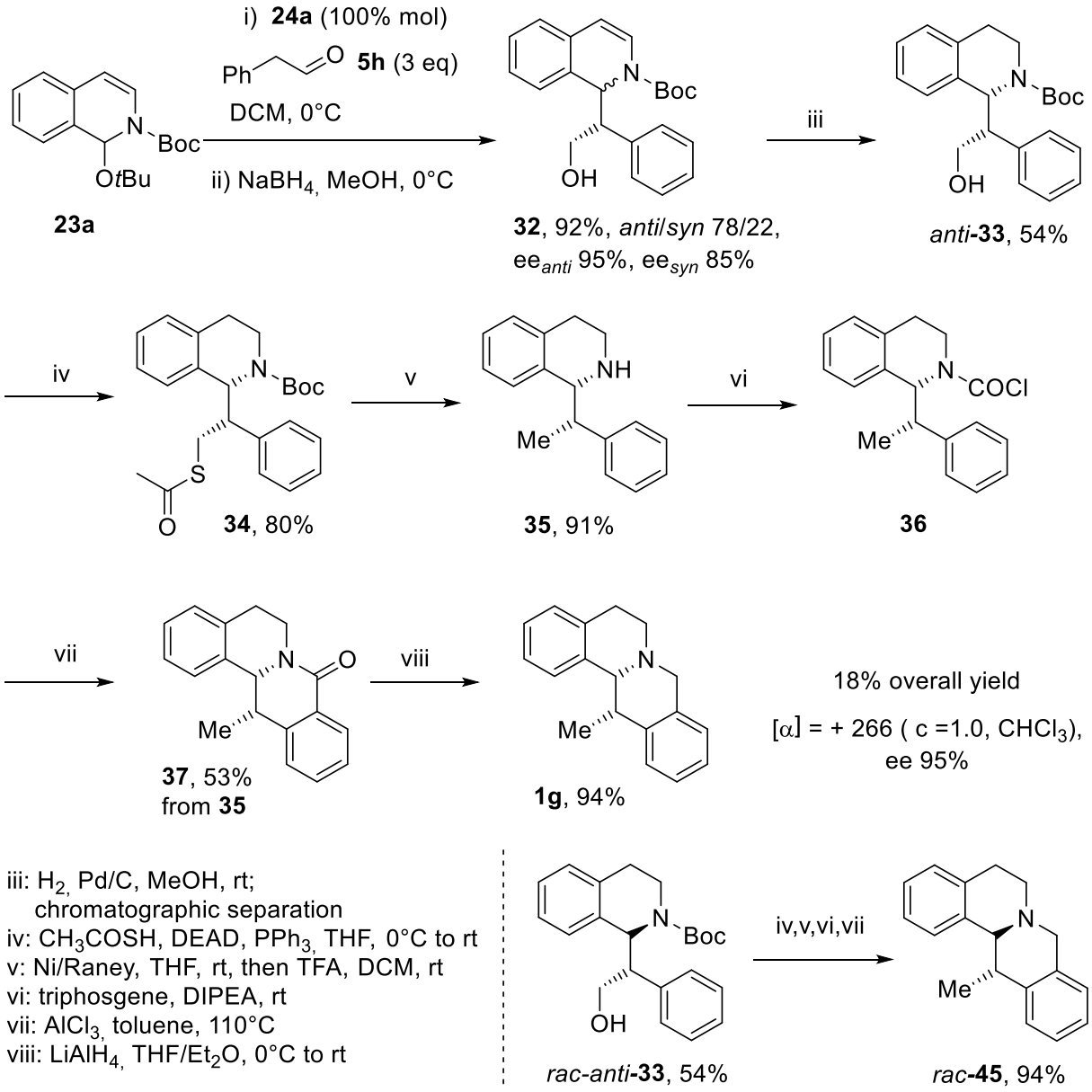
We attempted to perform the ring closure taking advantage of the presence of the carbamate moiety: intermediate **27** was dissolved in Eaton acid[63] and heated for 7 h at 120°C. Unfortunately the desired Friedel Craft reaction of the benzene on the carbamate did not occur, instead a partial loss of the

thioether was observed. The reduction of the thioether and the removal of the Cbz were then necessary in order to proceed in the synthesis. Unfortunately, the desired removal of the thioester moiety using Nickel/Raney® followed by reductive cleavage of the Cbz protecting group simply by switching to hydrogen atmosphere lead to desired product **35** in low yield and to a mixture of by-products, the major of which was pyridine **48**. We suppose that during the first reaction step with Ni/Raney alone also the Cbz was removed causing the re-aromatisation to the isoquinoline ring. When the reaction mixture was placed under hydrogen atmosphere during the second step the benzene ring was reduced leading to pyridine **48.** In an attempt to avoid the re-aromatisation the reaction was conducted directly under hydrogen atmosphere, but a similar mixture of by-products was obtained.
Due to the low yields and the substantial amount of byproducts obtained in the concomitant de-sulfuration and de-protection of Cbz, we turned on the Boc as activating agent.

**Synthesis of (+)-13-methyl tetrahydroprotoberberine 1g with Boc as activating group**

As Boc adduct **23a** gave better isolated yields with aldehyde **25a** (Table 1, entry 21) in the model reaction, **23a** was used as the starting material for the synthesis of 13-methyl tetrahydroprotoberberine. Unfortunately, catalytic conditions gave us only moderate results, in particular in terms of enantiomeric excesses when **23a** was reacted with **25h** (49% yield, *anti/syn* 68:32, ee anti 86%). In order to improve both enantiomeric and diastereoisomeric excesses in the reaction we therefore decided to increase the amount of the chiral promoter **24a** to 1 equivalent. Although the reaction was no longer "organocatalytic" the use of stoichiometric quantities of **24a** gave the adduct **32** in good dr (78:22) for the *anti* diastereoisomer and excellent ees (95%). Importantly, **24a** can be easily recovered in 80% yield after the reaction work-up, as the stable isolated enamine of **24a**,[64] which could then be directly employed in another stoichiometric reaction to obtain **32** in same yield, dr and ee (see experimental part for full details). The adduct **32** was hydrogenated with Pd/C and the *syn* and *anti* diastereoisomers were easily separated by column chromatography at this stage. The major *anti* diastereoisomer was subjected to a Mitsunobu reaction with MeCOSH, followed by treatment with Raney nickel to give product X. As a mere test I tried to perform the Friedel Craft cyclization using Eaton acid that of course lead to the loss of the Boc group. The deprotection of the Boc group was then performed using standard conditions (TFA in DCM) on the crude reaction mixture after the reaction with the Raney nickel affording **35** in an overall yield of 91% (scheme 10).
The cyclization was initially attempted by formation of the iminium with formaldehyde in presence of acetic acid under reflux conditions. However the desired product was not obtained even if ESI-MS analysis revealed the presence of the iminium intermediate highlighting the necessity to use a much more electrophilic partner to have a successful Friedel Craft with a simple phenyl group. After a careful research we found that by using triphosgene[65] the stable and isolable carbamoyl chloride **36** could be obtained and this intermediate could be subjected to straightforward Friedel-Crafts reaction in presence of strong Lewis acids. Carbamoyl **36** is stable to hydrolysis and was isolated after aqueous work up with a $NaHCO_3$ solution. The crude was directly treated either with $AlCl_3$ either with $SnCl_4$ and in both

cases a complete conversion was obtained even if a slightly more clean crude was obtained with $AlCl_3$ that was chosen for the cyclization on active **36** to afford amide **37** in good overall yield from **35**.




*Scheme 10. Synthesis of the 13-methyl tetrahydroprotoberberine **1g** through the key intermediate **32**.*

The *syn* stereochemistry of **37** was confirmed by n.O.e. experiments (see experimental part for details). The successive reduction of **37** with $LiAlH_4$ afforded the desired (+)-13-methyl tetrahydroprotoberberine **1g**[66] in 94% yield (18% overall yield starting from **23a**). The enantiomeric excess was determined to be 95% by HPLC, confirming that no racemization occurred during the

reaction sequence. The $[\alpha]_D$ registered for **1g** confirmed our stereochemical assignment and therefore confirms the proposed model for the stereoselective addition of aldehydes to isoquinoline.[67]
The total synthesis of the active molecule was carried on only on *anti*-**32** to obtain (+)-13-methyl tetrahydroprotoberberine. When the alkylation reaction was carried with the pirrolidine enamine, racemic **32** was obtained with a diastereomeric ratio slightly favoring the anti diastereoisomer (60:40). In order to unambiguously determine the structure of both diastereoisomers, the syhthetic route was carried on for both diastereoisomers and (+/-)-anti-13-methyl tetrahydroprotoberberine and the corresponding *syn* non natural product were obtained in racemic form (see experimental part).
Both of the obtained alkaloids were subjected to biological tests on two resistant tumor cell lines, HT 29 and IGROV, thanks to the collaboration with prof. Calonghi research group. The results were encouraging showing an IC 50 in the range of 50 μM for both diastereoisomers.

| Product | ee% | IC 50 | |
|---|---|---|---|
| | | HT 29 | IGROV |
| **1g** | 95 | 49 μm | 32 μm |
| **45** | 0 | 44 μm | 35 μm |
| HT 29, human colorectal adenocarcinoma<br>IGROV, human ovarian adenocarcinoma | | | |

*Table 9: preliminary tests of alkaloids **1g** and **45** on resistant tumor cell lines.*

We decided to investigate which parts of the molecule were important in determining the biological activity and we started by varying the groups on the C13 position by manipulation of the aldehyde moiety obtained after the alkylation of phenylacetaldehyde with quinoline.
This project was successfully developed by Edoardo Jun Mattioli who prepared five different molecules that were furnished to our partners for the biological tests. The detailed results are illustrated in Edoardo Bachelor Thesis.[68]

### 2.2.3 Conclusions

In conclusion, we have developed the intermolecular alkylation of aldehydes with in situ generated isoquinolinium ions promoted by prolinol amine catalysts that gives access isoquinoline building blocks in high enantiomeric excesses through a facile reaction. Two different activating agents, $Boc_2O$ and CbzCl can be used form the reactive isoquinolinium ions avoiding the deactivation of the amine catalyst. To this purpose, we set up an effective protocol to perform slow addition of the CbzCl to the reaction mixture achieving the activation of the isoquinoline without the acylation of the amine catalyst. This strategy can represent a solution for the activation of other heterocycles in organocatalytic reactions. The product were obtained in moderate to good yields for, moderate dr and good to excellent enantioselectivities. The presence of chlorine or insaturations on the aldehyde lead to poor in term of yields.It is noteworthy that the diastereomeric ratio is can be reversed by simply changing the reaction solvent.
The methodology was applied to the first enantioselective synthesis of a 13-alkyl-tetrahydroprotoberberine alkaloid. Preliminary biological tests have shown interesting cytotoxic activity on resistant tumor cell lines and we are currently carrying on a collaboration to test different tetrahydroprotoberberine derivatives in order to achieve an increased cytotoxicyty.

### 2.2.4 Contributions

I developed the synthetic methodology during my master Thesis under the supervision of Prof. Pier Giorgio Cozzi and Dr. Andrea Gualandi. I continued the project during my Ph.D. realizing the synthesis of (+)-13-methyl tetrahydroprotoberberine. The biological test were performed by Prof. Calonghi and her coworkers.

## 2.2.5 Experimental part

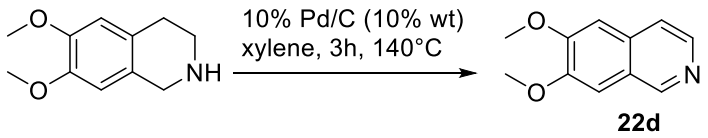
**Table of contents**

**General methods.** $^{1}H$ NMR spectra were recorded on Varian Gemini 200, Varian Mercury 400 and Inova 600 spectrometers. Chemical shifts are reported in ppm from TMS with the solvent resonance as the internal standard (deuterochloroform: $\delta$ = 7.27 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = duplet, t = triplet, q = quartet, dd = double duplet, dt = double triplet, bs = broad signal, pd = pseudo duplet, pt = pseudo triplet, m = multiplet), coupling constants (Hz). $^{13}C$ NMR spectra were recorded on Varian Gemini 200, Varian MR400 spectrometers. Chemical shifts are reported in ppm from TMS with the solvent as the internal standard (deuterochloroform: $\delta$= 77.0 ppm). If rotamers are present, the splitted signals are labeled as A (major rotamer) and B (minor rotamer). GC-MS spectra were taken by EI ionization at 70 eV on a Hewlett-Packard 5971 with GC injection. LC-electrospray ionization mass spectra (ESI-MS) were obtained with Agilent Technologies MSD1100 single-quadrupole mass spectrometer. They are reported as: *m/z* (rel. intense). Chromatographic purification was done with 240-400 mesh silica gel. Purification on preparative thin layer chromatography was done on Merck TLC silica gel 60 $F_{254}$ and on Merck TLC aluminum oxide 60 $F_{254}$ neutral. Determination of diastereomeric ratio and of enantiomeric excess was performed on Agilent Technologies 1200 instrument equipped with a variable wave-length UV detector (reference 420 nm), using Daicel Chiralpak® columns (0.46 cm I.D. x 25 cm), Phenomenex® Lux columns and HPLC grade isopropanol and *n*-hexane as eluting solvents. Optical rotations were determined in a 1 mL cell with a path length of 1 dm ($Na_D$ line).

**Materials.** If not otherwise stated, all reactions were carried out in sealed vials in open air without nitrogen atmosphere. Anhydrous solvents were supplied by Aldrich in Sureseal® bottles and were used as received avoiding further purification.

Reagents were purchased from Aldrich and used without further purification unless otherwise stated. The aldehydes **25a** and **25c** were supplied by Aldrich and used after distillation.
The isoquinolines **22e**,[69] **22f**,[70] **22g**,[70] **22i**,[71] and aldehyde **25e**[72] were prepared according to literature procedure.

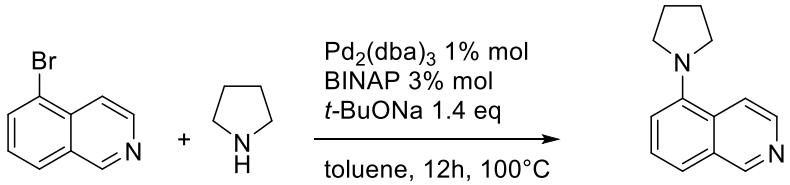
**Synthesis of 6,7-dimethoxy-isoquinoline (22d).**




**22d**

In a 25 mL balloon under nitrogen atmosphere, 10% palladium on carbon (10% wt, 393 mg) and xylene (4 mL) were added. The mixture was refluxed for 1 h (T = 140°C), then it was allowed to cool and 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (2.7 mmol, 532 mg) was added. The mixture was refluxed for other 3 hours until complete conversion of the starting material. Then the mixture was allowed to cool to room temperature, diluted with $CH_2Cl_2$ (5 mL) and filtered thought Celite®. After solvent removal under reduced pressure, the crude mixture was purified by flash chromatography on silica gel ($CH_2Cl_2$/MeOH, 95/5) to give 6,7-dimethoxy-isoquinoline **(22d)** in 77% yield as orange sticky solid.
(**22d**): $^1$H NMR (200 MHz, $CDCl_3$, 25°C): $\delta$ = 4.04 (s, 6H), 7.07 (s, 1H), 7.20 (s, 1H), 7.51 (d, $J$ = 5.5 Hz, 1H), 8.39 (d, $J$ = 5.5 Hz, 1H), 9.05 (s, 1H).

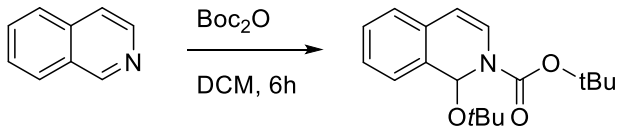
**Synthesis of 5-(*N*)-pyrrolidin-isoquinoline (22h).**




**22b** 1.2 eq **22h**

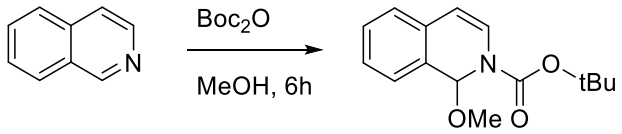
In a Schlenck tube were added toluene (0.5 mL), BINAP (0.003 mmol, 1.9 mg) and $Pd_2(dba)_3$ (0.001 mmol, 1.0 mg) under nitrogen atmosphere. The violet solution was stirred at room temperature for 1 hour during which it turned red. Then *t*-BuONa (0.14 mmol, 13.4 mg), pyrrolidine (0.12 mmol, 10 μL) and 5-bromo isoquinoline **22b** (0.1 mmol, 20.8 mg) were added and the temperature was raised to 100°C. The mixture was stirred at this temperature for 12 h, then it was allowed to cool to room temperature and it was filtered through Celite® washing with $CH_2Cl_2$ (4 x 20 ml). The organic layer was concentrated under reduced pressure and 5-(*N*)-pyrrolydin-isoquinoline (**22h**) was isolated after flash chromatography on silica gel (cyclohexane/ethyl acetate 9/1) in 70 % yield as white sticky solid.
**(22h):** $^1$H NMR (200 MHz, $CDCl_3$, 25°C): $\delta$ = 1.99–2.09 (m, 4H), 3.46 (t, $J$ = 5.6 Hz, 4H), 7.00-7.06 (m, 1H), 7.44-7.49 (m, 2H), 7.96 (d, $J$ = 5.9 Hz, 1H), 8.43 (d, $J$ = 5.9 Hz, 1H), 9.18 (s, 1H).

**Synthesis of adducts 23a and 23b.**




**22a** **23a**

To a solution of **22a** (2.0 mmol, 240 µL) in $CH_2Cl_2$ (5 mL), $Boc_2O$ (2.0 mmol, 440 µL) was added. The mixture was stirred under at room temperature for 6 h and the solvent was evaporated to give pure **23a** that was stored at -20°C without purification.




**22a** **23b**

To a solution of **22a** (2.0 mmol, 240 µL) in MeOH (5 mL), $Boc_2O$ (2.0 mmol, 440 µL) was added. The mixture was stirred under at room temperature for 6 h and the solvent was evaporated to give pure **23b** that was stored at -20°C without purification.

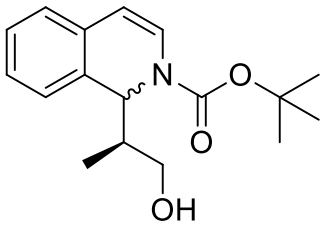
Spectral properties of **23a** and **23b** were according with the literature.[73]

**General procedure for the *in situ* activation of isoquinoline with $Boc_2O$:** To a 5 mL vial equipped with a stirring magnetic bar, 1 mL of *t*-BuOMe/$CH_2Cl_2$ (8/2), isoquinoline **22a** (0.2 mmol, 24 µL) and $Boc_2O$ (0.2mmol, 44 µL) were added. The mixture was stirred at room temperature for 1 h. Then the temperature was lowered to 0°C and aldehyde **25a** (0.8 mmol, 54 µL), Jørgensen catalyst **24a** (0.02 mmol, 12 mg) were added. After 15 hours, a few drops of MeOH and $NaBH_4$ (2 mmol, 76 mg) were added. When complete conversion was obtained (monitored by TLC), water (2 mL) was added. The organic layer was separated and the aqueous layer was extracted with $Et_2O$ (2 x 10 mL). The collected organic layers were washed with brine (10 mL), dried over $MgSO_4$ and concentrated under reduced pressure to afford **26a**.

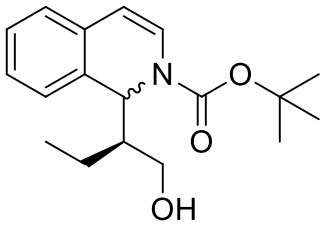
The racemic products were synthesized with the same procedure except for using pyrrolidine (0.1 mmol, 8.3 µL) instead of **24a** and dichloromethane as reaction solvent.

**General procedure using 23a or 23b as starting materials: 23a** (0.2 mmol, 60.6 mg) was dissolved in 1 mL of *t*-BuOMe/$CH_2Cl_2$ (8/2). Then the temperature was lowered to 0°C and aldehyde **25a** (0.8 mmol, 54 μL), Jørgensen catalyst **24a** (0.02 mmol, 12 mg) were added. After 15 hours, a few drops of MeOH and $NaBH_4$ (2 mmol, 76 mg) were added. When complete conversion was obtained (monitored by TLC), water (2 mL) was added. The organic layer was separated and the aqueous layer was extracted with $Et_2O$ (2 x 10 mL). The collected organic layers were washed with brine (10 mL), dried over $MgSO_4$ and concentrated under reduced pressure to afford **26a**.
The same procedure was followed using **23b** instead of **23a**.

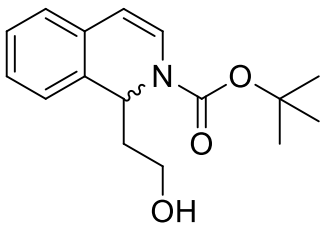
**Note:** the enantiomeric excesses and diastereomeric ratios of the compounds remain unaltered after column flash chromatography or after preparative thin layer chromatography on neutral alumina.




**(26a):** yellowish oil; 57% yield; the title compound was isolated by preparative thin layer chromatography on neutral alumina (cyclohexane/acetone 85/15) as mixture of diastereoisomers in 88/12 ratio (*syn*-**26a**:*anti*-**26a**). *Syn* diastereoisomer ee = 97%; *anti* diastereoisomer ee = 93%. The dr and ee were determined by HPLC analysis Phenomenex® Lux Amylose-2 column: hexane/*i*-PrOH from 93:7 to 90:10 in 20 min., then 90:10, flow rate 0.70 mL/min, 40°C, λ = 295 nm: *syn* diastereoisomer $\tau_{major}$ = 17.75 min., $\tau_{minor}$ = 19.29 min.; *anti* diastereoisomer $\tau_{major}$ = 26.41 min., $\tau_{minor}$ = 16.94 min. $^1$H NMR (400 MHz, $CDCl_3$, 25°C) (two rotamers A:B, 7:1 ratio): $\delta_{syn}$= 0.68 (d, $J$ = 6.6 Hz, $3H_A$), 0.96 (d, $J$ = 6.6 Hz, $3H_B$), 1.53 (s, $9H_A$), 1.56 (s, $9H_B$), 1.92-2.01 (m, 1H), 3.30 (pt, $J$ = 11.2 Hz, 1H), 3.34-3.45 (m, 1H), 4.17-4.24 (m, 1H), 5.61 (d, $J$ = 3.2 Hz, 1H), 5.75 (d, $J$ = 7.4 Hz, 1H), 6.81 (d, $J$ = 7.4 Hz, 1H), 7.00-7.07 (m, 1H), 7.10-7.16 (m, 1H), 7.17-7.24 (m, 2H); $\delta_{anti}$= 0.86 (d, $J$ = 6.6 Hz, 3H), 1.53 (s, 9H), 1.92-2.01 (m, 1H), 3.30 (pt, $J$ = 11.2 Hz, 1H), 3.34-3.45 (m, 1H), 3.60 (d, $J$ = 11.2 Hz, 1H), 5.09 (d, $J$ = 10.4 Hz, 1H), 5.91 (d, $J$ = 7.6 Hz, 1H), 6.73 (dd, $J_1$ = 7.6 Hz, $J_2$ = 0.9 Hz, 1H), 7.00-7.07 (m, 1H), 7.08 (d, $J$ = 1.2 Hz, 1H), 7.10 (d, $J$ = 1.4 Hz, 1H), 7.17-7.24 (m, 1H); $^{13}$CNMR (100 MHz, $CDCl_3$, 25°C): $\delta_{syn}$= 10.5, 28.2 (3C), 46.6, 54.0, 63.8, 82.3, 109.2, 124.2, 126.4, 126.5, 127.2, 127.4, 131.0, 132.1, 154.0; $\delta_{anti}$= 14.1, 28.1 (3C), 36.7, 55.9, 63.6, 82.4, 109.7, 124.6, 126.3, 126.5, 127.4, 127.6, 130.42, 130.9, 153.4; ESI-MS: *m/z* = 290.4 $[M+H]^+$, 312.3 $[M+Na]^+$; HMRS calcd for $C_{17}H_{23}NO_3$ : 289.16779; found 289.16769.



**(26b):** reddish oil; 44% yield (35% *syn*, 9% *anti*); the title compounds were isolated by preparative thin layer chromatography on neutral alumina (cyclohexane/acetone 80/20). *Syn* diastereoisomer ee = 97%; *anti* diastereoisomer ee = 93%. The dr was determined by integration of the NC(1)H signals of the two diastereoisomers in the $^1$HNMR of the crude mixture after reduction. The ee were determined by HPLC analysis Phenomenex® Lux Amylose-2 column: hexane/*i*-PrOH 95:5, flow rate 0.70 mL/min, 40°C, λ = 295 nm: *syn* diastereoisomer $\tau_{major}$ = 17.18 min., $\tau_{minor}$ = 19.12 min.; *anti* diastereoisomer $\tau_{major}$ = 21.86 min., $\tau_{minor}$ = 12.70 min. $^1$H NMR (400 MHz, $CDCl_3$, 25°C) (two rotamers A:B, 8:1): $\delta_{syn}$= 0.72 (t, *J* = 7.8 Hz, 3H), 1.05-1.14 (m, 1H), 1.34-1.42 (m, 1H), 1.53 (s, $9H_A$), 1.56 (s, $9H_B$), 1.67-1.77 (m, 1H), 3.26-3.33 (m, $1H_A$), 3.37-3.42 (m, $2H_B$), 3.60-3.68 (m, $1H_A$), 4.12-4.18 (dd, $J_1$ = 10.2 Hz, $J_2$ = 4.6 Hz, 1H), 5.63 (d, *J* = 3.1 Hz, 1H), 5.77 (d, *J* = 7.5 Hz, 1H), 6.78 (d, *J* =7.5 Hz, 1H), 7.02-7.06 (m, 1H), 7.13-7.17 (m, 1H), 7.18-7.23 (m, 2H); $\delta_{anti}$= 0.77 (t, *J* = 7.1 Hz, 3H), 1.04-1.16 (m, 1H), 1.41-1.57 (m, 2H), 1.53 (s, $9H_A$), 1.56 (s, $9H_B$), 3.22-3.32 (bs, 1H), 3.48 (pd, *J* = 12.3 Hz, 1H), 3.58 (pd, *J* = 12.3 Hz, 1H), 5.12 (d, *J* = 10.1 Hz, 1H), 5.92 (d, *J* = 7.8 Hz, 1H), 6.72 (d, *J* = 7.8 Hz,1H), 7.05-7.10 (m, 2H), 7.11-7.26 (m, 2H); $^{13}$CNMR (100 MHz, $CDCl_3$, 25°C): $\delta_{syn}$ (two rotamers A:B, 8:1) = 12.5, 17.9, 28.2 ($3C_A$), 28.4 ($3C_B$), 53.2, 54.0, 61.0, 82.2, 109.5, 124.3, 126.4, 126.6, 127.3, 127.4, 131.2, 132.3, 154.0; $\delta_{anti}$= 11.8, 19.2, 28.2 (3C), 43.0, 55.5, 58.8, 82.4, 110.0, 124.6 (2C), 126.3, 127.6, 128.1, 130.5, 130.9, 153.5; ESI-MS: *m/z* = 304.3 $[M+H]^+$, 326.2 $[M+Na]^+$; HMRS calcd for $C_{18}H_{25}NO_3$: 303.18344; found 303.18359.

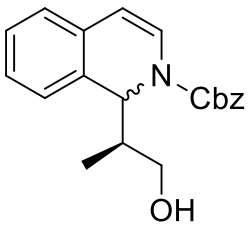


**(26c):** colourless oil; 26% yield; 60% ee; the title compound was isolated by preparative thin layer chromatography on neutral alumina (cyclohexane/acetone 85/15). The ee was determined by HPLC analysis Phenomenex® Lux Amylose-2 column: hexane/*i*-PrOH 95:5, flow rate 1.00 mL/min, 40°C, λ = 295 nm: $\tau_{major}$ = 12.02 min., $\tau_{minor}$ = 19.74 min. $^1$H NMR (400 MHz, $CDCl_3$, 25°C) (two rotamers A:B, 9:1 ratio): $\delta$ = 1.54 (s, $9H_A$), 1.58 (s, $9H_B$), 1.60-1.71 (m, 1H), 1.85-1.95 (m, 1H), 3.45 (pt, *J* = 11.3 Hz, 1H), 3.50-3.61 (bs, 1H), 3.61-3.69 (bs, 1H), 5.49 (dd, $J_1$ = 11.3 Hz, $J_2$ = 2.3 Hz, 1H), 5.86 (d, *J* = 7.5 Hz, $1H_A$), 5.93 (d, *J* = 7.5 Hz, $1H_B$), 6.72 (d, *J* = 7.8 Hz, $1H_A$), 6.92 (d, *J* = 7.8 Hz, $1H_B$), 7.04-7.09 (m, 1H), 7.11-7.15 (m, 1H), 7.17-7.22 (m, 2H); $^{13}$CNMR (100 MHz, $CDCl_3$, 25°C): $\delta$ = 28.2 (3C), 37.9, 51.3, 58.0, 82.3, 109.0, 124.1, 124.7, 125.9, 127.3, 127.5, 129.9, 133.4, 153.4; ESI-MS: *m/z* = 276.4 $[M+H]^+$, 298.3 $[M+Na]^+$, 573.5 $[2M+Na]^+$; HMRS

calcd for $C_{16}H_{21}NO_3$ : 275.15214; found : 275.15228.

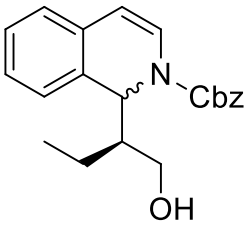
**General procedure for the stereoselective alkylation of aldehydes with isoquinoline activated with CbzCl:** To a solution of isoquinoline **22a** (0.2 mmol) in 0.5 mL *t*-BuOMe/$CH_2Cl_2$ (8/2) inside a round-bottomed flask equipped with a stirring magnetic bar and cooled at 0°C, $NaHCO_3$ (0.6 mmol, 51 mg), Jørgensen catalyst **24a** (0.04 mmol, 24 mg) and aldehyde **25a-h** (1.0 mmol) were added. To the mixture a solution of CbzCl (0.45 mmol, 78 μL CbzCl in 1 mL *t*BuOMe/$CH_2Cl_2$ 8/2) was added dropwise by a syringe pump during 15 h. After that 2 mL of an aqueous saturated solution of $NH_4Cl$ were added and the organic layer was extracted with $Et_2O$ (3 x 5 mL). The collected organic layers were dried over $MgSO_4$. The residue was diluted in MeOH and the resulting solution was cooled at -40°C. Then $NaBH_4$ (2 mmol, 76 mg) was added. When complete conversion was obtained (monitored by TLC), HCl 1N was added (at -40°C) until pH = 1. The organic layer was separated and the aqueous layer was extracted with $Et_2O$ (2 x 10 mL). The collected organic layers were washed with brine (5 mL), dried over $MgSO_4$ and concentrated under reduced pressure to give **27a-h**.
The racemic products were synthesized with the same procedure except for using pyrrolidine (0.1 mmol, 8.3 μL) instead of **24a**, $CH_2Cl_2$ as reaction solvent and for conducing the reaction at room temperature.

**Note:** the enantiomeric excesses and the diasteromeric ratios of the compounds remain unaltered after flash chromatography or after preparative thin layer chromatography on neutral alumina.



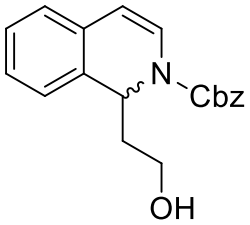

**(27a):** yellowish oil; 53% yield; the title compound was isolated by preparative thin layer chromatography on neutral alumina (cyclohexane/acetone 85/15) as mixture of diastereoisomers in 74/26 ratio (*syn*-**27a**:*anti*-**27a**). *Syn* diastereoisomer ee = 96%; *anti* diastereoisomer ee = 87%. The dr and ee were determined by HPLC analysis Daicel Chiralpak® AD column: hexane/*i*-PrOH from 90:10 to 70:30 in 20 min., flow rate 0.70 mL/min, 40°C, λ = 295 nm: *syn* diastereoisomer $\tau_{major}$ = 23.87 min., $\tau_{minor}$ = 14.64 min.; *anti* diastereoisomer $\tau_{major}$ = 13.79 min., $\tau_{minor}$ = 20.95 min. $^1$H NMR (400 MHz, $CDCl_3$, 25°C): $\delta_{syn}$ (two rotamers A:B, 7:1 ratio) = 0.70 (d, $J$ = 6.8 Hz, $3H_A$), 0.90 (d, $J$ = 6.8 Hz, $3H_B$), 1.89-2.04 (bs, 1H), 3.35-3.48 (bs, 2H), 3.90-4.00 (bs, 1H), 5.22-5.32 (m, 2H), 5.64 (d, $J$ = 3.0 Hz, 1H), 5.81 (d, $J$ = 7.8 Hz, $1H_A$), 5.99 (d, $J$ = 7.8 Hz, $1H_B$), 6.87 (d, $J$ =7.8 Hz, 1H), 7.03-7.07 (m,

1H), 7.13-7.17 (m, 1H), 7.20-7.24 (m, 2H), 7.38-7.42 (m, 5H); $\delta_{anti}$ = 0.87 (d, $J$ = 6.83 Hz, 3H), 1.89-2.04 (bs, 1H), 3.31 (pt, $J_1$ = 11.7 Hz, $J_2$ = 11.2 Hz, 2H), 3.59 (d, $J$ = 11.7 Hz, 1H), 5.16 (d, $J$ = 10.1 Hz, 1H), 5.22-5.32 (m, 2H), 5.95 (d, $J$ =7.6 Hz, 1H), 6.80 (d, $J$ = 7.6 Hz, 1H), 7.08-7.12 (m, 2H), 7.20-7.24 (m, 2H), 7.38-7.42 (m, 5H); $^{13}$CNMR (100 MHz, $CDCl_3$, 25°C): $\delta_{syn}$ = 10.5, 46.4, 54.9, 63.8, 68.5, 110.3, 124.5, 125.5, 126.5, 127.4, 127.5, 128.1 (2C), 128.4, 128.6 (2C), 130.6, 132.0, 135.6, 154.9; $\delta_{anti}$ = 14.0, 36.0, 56.6, 63.6, 68.5, 110.7, 123.8, 124.7, 126.6, 127.7, 127.8, 128.2 (2C), 128.6 (2C), 128.7, 130.2, 130.8, 135.5, 154.3; ESI-MS: $m/z$ = 324.4 $[M+H]^+$, 347.3 $[M+Na]^+$, 669.5 $[2M+Na]^+$; HMRS calcd for $C_{20}H_{21}NO_3$ : 323.15214; found 323.15228.

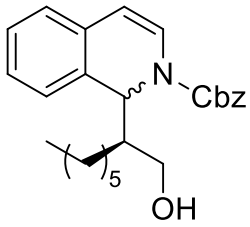



**(27b):** reddish oil; 51% yield (39% *syn*, 12% *anti*); the title compounds were isolated by preparative thin layer chromatography (cyclohexane/acetone 97/3) on neutral alumina. *Syn* diastereoisomer ee = 98%; *anti* diastereoisomer ee = 98%. The dr was determined by integration of the NC(1)H signals of the two diastereoisomers in the $^1$HNMR of the crude mixture after reduction. The ee were determined by HPLC analysis Daicel Chiralpak® AD column: hexane/*i*-PrOH from 90:10 to 70:30 in 20 min. then 70:30, flow rate 0.70 mL/min, 40°C, λ = 295 nm: *syn* diastereoisomer $\tau_{major}$ = 25.46 min., $\tau_{minor}$ = 16.41 min.; *anti* diastereoisomer $\tau_{major}$ = 14.20 min., $\tau_{minor}$ = 20.20 min. $^1$H NMR (400 MHz, $CDCl_3$, 25°C) (two rotamers A:B, 12:1 ratio): $\delta_{syn}$ = 0.73 (t, $J$ = 7.8 Hz, $3H_A$), 0.84 (t, $J$ = 7.8 Hz, $3H_B$), 1.04-1.19 (m, 1H), 1.32-1.42 (m, 1H), 1.75-1.80 (m, 1H), 3.31 (dd, $J_1 = J_2$ = 10.5 Hz, 1H), 3.56-3.66 (bs, 2H), 3.71-3.80 (bs, 1H), 5.24 (d, $J$ = 12.3 Hz, 1H), 5.28 (d, $J$ = 12.3 Hz, 1H), 5.66 (d, $J$ = 3.1 Hz, 1H), 5.76 (d, $J$ = 7.9 Hz, $1H_B$), 5.82 (d, $J$ = 7.9 Hz, $1H_A$), 6.85 (d, $J$ =7.9 Hz, 1H), 7.03-7.07 (m, 1H), 7.15-7.18 (m, 1H), 7.19-7.24 (m, 2H), 7.35-7.42 (m, 5H); $\delta_{anti}$ = 0.73 (t, $J$ = 7.1 Hz, $3H_B$), 0.78 (t, $J$ = 7.1 Hz, $3H_A$), 1.07-1.19 (m, 1H), 1.42-1.54 (m, 1H), 1.56-1.64 (m, 1H), 3.03-3.11 (bs, 1H), 3.45-3.52 (bs, 1H), 3.55-3.63 (bs, 1H), 5.18 (d, $J$ = 9.9 Hz, 1H), 5.24 (d, $J$ = 12.2 Hz, 1H), 5.30 (d, $J$ = 12.2 Hz, $1H_A$), 5.35 (d, $J$ = 12.2 Hz, $1H_B$), 5.97 (d, $J$ = 7.5 Hz, $1H_A$), 6.02 (d, $J$ = 7.5 Hz, $1H_B$), 6.78 (dd, $J_1$ = 7.3 Hz, $J_2$ = 0.9 Hz, $1H_A$), 6.96 (d, $J$ = 7.3 Hz, $1H_B$), 7.05-7.10 (m, 2H), 7.13-7.23 (m, 2H), 7.26-7.42 (m, 5H); $^{13}$CNMR (100 MHz, $CDCl_3$, 25°C): $\delta_{syn}$ = 12.4, 18.0, 52.8, 54.8, 60.9, 68.5, 110.6, 124.5, 125.4, 126.6, 127.4, 127.5, 128.2 (2C), 128.4, 128.7 (2C), 130.8, 132.1, 135.6, 154.9; $\delta_{anti}$ = 11.8, 19.2, 43.1, 56.1, 58.7, 68.6, 111.1, 123.7, 124.8, 126.5, 127.7, 128.1, 128.3 (2C), 128.5 (2C), 128.6, 130.2, 130.9, 134.6, 154.9; ESI-MS: $m/z$ = 338.3 $[M+H]^+$, 360.2 $[M+Na]^+$; 360.50 $[2M+Na]^+$; HMRS calcd

for $C_{21}H_{23}NO_3$ : 337.16779; found 337.16743.

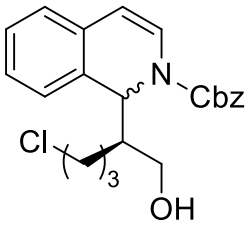



**(27c):** colourless oil; 9% yield; 50% ee; the title compound was isolated by preparative thin layer chromatography on neutral alumina (cyclohexane/acetone 85/15). The ee was determined by HPLC analysis Daicel Chiralpak® AD column: hexane/*i*-PrOH from 90:10 to 70:30 in 20 min. then 70:30, flow rate 0.70 mL/min, 40°C, λ = 295 nm: $\tau_{major}$ = 23.87 min., $\tau_{minor}$ = 13.79 min. $^1$H NMR (400 MHz, $CDCl_3$, 25°C) (two rotamers A:B, 9:1 ratio): 1.66-1.75 (m, 1H), 1.88-1.97 (m, 1H), 3.33-3.40 (bs, 1H), 3.41-3.50 (dd, $J_1 = J_2$ = 11.7 Hz, 1H), 3.51-3.60 (bs, 1H), 5.23 (d, $J$ = 12.4 Hz, $1H_B$), 5.25 (d, $J$ = 12.4 Hz, $1H_A$), 5.30 (d, $J$ = 12.4 Hz, $1H_A$), 5.34 (d, $J$ = 12.4 Hz, $1H_B$), 5.53 (dd, $J_1$ = 10.9 Hz, $J_2$ = 3.3 Hz, 1H), 5.90 (d, $J$ = 7.8 Hz, $1H_A$), 5.98 (d, $J$ = 7.8 Hz, $1H_B$), 6.78 (dd, $J_1$ = 7.8 Hz, $J_2$ = 1.0 Hz, $1H_A$), 6.95 (dd, $J_1$ = 7.8 Hz, $J_2$ = 1.0 Hz, $1H_B$), 7.06-7.10 (m, 1H), 7.12-7.15 (m, 1H), 7.20-7.24 (m, 2H), 7.35-7.42 (m, 5H); ESI-MS: *m/z* = 310.4$[M+H]^+$, 332.3 $[M+Na]^+$; HMRS calcd for $C_{19}H_{19}NO_3$ : 309.13649; found 309.13673.



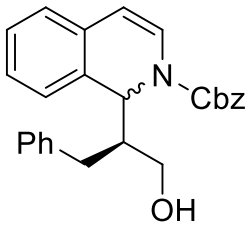

**(27d):** yellowish oil; 65% yield; the title compound was isolated by preparative thin layer chromatography on neutral alumina (cyclohexane/acetone 97/3) as mixture of diastereoisomers in 79/21 ratio (*syn*-**27d**:*anti*-**27d**). The dr ratio was determined by integration of the $\delta_{major}$= 6.86 and $\delta_{minor}$= 6.79 $^1$H NMR signals relative to the proton on the C3 carbon of the isoquinoline ring. *Syn* diastereoisomer ee = 99%; *Anti* diastereoisomer ee = 96%. The ee were determined by HPLC analysis Daicel Chiralpak® AD column: hexane/*i*-PrOH from 95:5 to 70:30 in 40 min., flow rate 0.70 mL/min, 40°C, λ = 295 nm: *syn* diastereoisomer $\tau_{major}$ = 23.20 min., $\tau_{minor}$ = 18.94 min.; *anti* diastereoisomer $\tau_{major}$ = 16.97 min., $\tau_{minor}$ = 17.56 min. $^1$H NMR (400 MHz, $CDCl_3$, 25°C) (two rotamers A:B, 10:1 ratio): $\delta_{syn}$ = 0.81 (t, $J$ = 7.3 Hz, $3H_A$), 0.82 (t, $J$ = 7.3 Hz, $3H_B$), 1.03-1.13 (m, 2H), 1.13-1.24 (m, 2H), 1.24-1.42 (m, 6H), 1.78-1.88 (m, 1H), 3.27-3.36 (m, 1H), 3.54-3.62 (bs, 1H), 3.79-3.87 (bs, 1H), 5.23 (d, $J$ = 12.2 Hz, 1H), 5.29 (d, $J$ = 12.2 Hz, 1H), 5.66 (d, $J$ = 3.9 Hz, 1H), 5.83 (d, $J$ = 7.8 Hz, $1H_A$), 5.99 (d, $J$ = 7.8 Hz, $1H_B$), 6.86 (d, $J$ =7.8 Hz, 1H), 7.03-7.07 (m, 1H), 7.14-7.17 (m, 1H), 7.18-7.25 (m, 2H), 7.32-7.46 (m, 5H); $\delta_{anti}$ = 0.90 (t, $J$ = 6.9 Hz, 3H), 1.03-1.13 (m, 2H), 1.13-1.24 (m, 2H), 1.24-1.42 (m, 6H), 1.78-1.88 (m, 1H), 3.11-3.17 (bs, 1H), 3.27-3.36 (m, 1H), 3.46-3.54 (bs, 1H), 5.24 (d, $J$ = 12.2 Hz, 1H), 5.30 (d, $J$ = 12.2 Hz, 1H), 5.41 (d, $J$ = 7.2 Hz, 1H), 5.75 (d, $J$ = 7.8 Hz, $1H_B$), 5.97 (d, $J$ = 7.8 Hz,

1H$_A$), 6.79 (dd, $J_1$ = 7.4 Hz, $J_2$ = 1.1 Hz, 1H), 7.01-7.13 (m, 2H), 7.18-7.25 (m, 2H), 7.32-7.46 (m, 5H); $^{13}$CNMR (100 MHz, $CDCl_3$, 25°C): $\delta_{syn}$ (two rotamers, A:B 5:1 ratio) = 14.0, 22.5, 24.9 (1C$_A$), 25.3 (1C$_B$), 27.5, 29.2, 31.4 (1C$_A$), 33.4 (1C$_B$), 50.7, 54.9 (1C$_A$), 56.4 (1C$_B$), 60.8 (1C$_B$), 61.3 (1C$_A$), 68.4, 110.5, 124.5, 125.4, 126.6, 127.4, 127.5, 128.1 (2C), 128.4, 128.6 (2C), 130.7, 132.1, 135.7, 154.8; $\delta_{anti}$ = 14.1, 22.6, 25.7, 27.2, 29.3, 32.1, 41.5, 56.2, 59.5, 68.5, 111.0, 123.7, 124.7, 126.5, 127.4, 127.7, 128.0, 128.2 (2C), 128.5 (2C), 130.7, 132.1, 135.6, 154.2; ESI-MS: *m/z* = 394.2 $[M+H]^+$; HMRS calcd for $C_{25}H_{31}NO_3$ : 393.23039; found 393.23068.

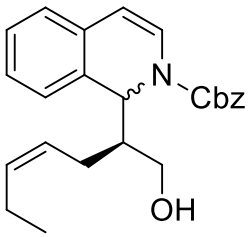



**(27e):** colourless oil; 13% yield; the title compound was isolated by preparative thin layer chromatography on neutral alumina (cyclohexane/acetone 90/10) as mixture of diastereoisomers in 79/21 ratio (*syn*-**27e**:*anti*-**27e**) containing some impurities. Further purification by preparative thin layer chromatography on silica (cyclohexane/ethyl acetate 80/20) lead to pure compound as mixture of diastereoisomers in 53/47 ratio (*syn*-**27e**:*anti*-**27e**). *Syn* diastereoisomer ee = 97%; *anti* diastereoisomer ee = 80%. The dr and ee were determined by HPLC analysis Daicel Chiralpak® AD column: hexane/*i*-PrOH from 95:5 to 70:30 in 40 min., flow rate 0.70 mL/min, 40°C, λ = 295 nm: *syn* diastereoisomer $\tau_{major}$ = 32.23 min., $\tau_{minor}$ = 26.01 min.; *anti* diastereoisomer $\tau_{major}$ = 24.71 min., $\tau_{minor}$ = 28.00 min. $^1$H NMR (400 MHz, $CDCl_3$, 25°C) (two rotamers A:B, 10:1 ratio): $\delta_{syn}$ = 1.18-1.32 (m, 1H), 1.33-1.51 (m, 1H), 1.54-1.76 (m, 2H), 1.76-1.86 (m, 1H), 3.24-3.38 (m, 3H), 3.48-3.58 (m, 1H), 3,74 (dd, $J_1$ = 9.1 Hz, $J_2$ = 4.8 Hz, 1H), 5.16-5.41 (m, 2H), 5.66 (d, $J$ = 3.5 Hz, 1H), 5.85 (d, $J$ = 7.5 Hz, 1H$_A$), 6.04 (d, $J$ = 7.5 Hz, 1H$_B$), 6.87 (dd, $J_1$ = 7.5 Hz, $J_2$ = 0.8 Hz, 1H$_A$), 7.02 (d, $J$ = 7.5 Hz, 1H$_B$), 7.05-7.18 (m, 2H), 7.18-7.29 (m, 2H), 7.32-7.48 (m, 5H); $\delta_{anti}$ = 1.18-1.32 (m, 1H), 1.33-1.51 (m, 1H), 1.54-1.76 (m, 2H), 1.76-1.86 (m, 1H), 3.11 (t, $J$ = 7.3 Hz, 1H), 3.35 (t, $J$ = 7.0 Hz, 2H), 3.48-3.58 (m, 2H), 5.19 (d, $J$ = 10.2 Hz, 1H), 5.16-5.41 (m, 2H), 5.97 (d, $J$ = 7.9 Hz, 1H$_A$), 6.00 (d, $J$ = 7.9 Hz, 1H$_B$), 6.79 (dd, $J_1$ = 7.9 Hz, $J_2$ = 1.3 Hz, 1H$_A$), 6.97 (d, $J$ = 7.9 Hz, 1H$_B$), 7.05-7.18 (m, 2H), 7.18-7.29 (m, 2H), 7.32-7.48 (m, 5H); $^{13}$CNMR (100 MHz, $CDCl_3$, 25°C): $\delta_{syn}$ (two rotamers, A:B 7:1 ratio) = 22.7 (1C$_A$), 24.2 (1C$_B$), 30.8, 44.8, 50.1, 54.7, 61.3, 66.9 (1C$_B$), 68.5 (1C$_A$), 110.5, 124.7, 125.4, 126.6, 127.7, 127.9, 128.2 (2C), 128.4, 128.7 (2C), 130.7, 131.7, 135.5, 154.9; $\delta_{anti}$ = 24.1, 30.5, 41.7, 44.8, 55.9, 59.5, 68.6, 111.0, 123.7, 124.9, 126.8, 127.6, 127.9, 128.0 (2C), 128.5, 128.7 (2C), 130.2, 130.3, 135.6, 153.2; ESI-MS: *m/z* = 386.3 $[M(^{35}Cl)+H]^+$, 388.3 $[M(^{37}Cl)+H]^+$, 408.2 $[M(^{35}Cl)+Na]^+$, 410.1 $[M(^{37}Cl)+Na]^+$;

HMRS calcd for $C_{22}H_{24}ClNO_3$ : 385.14447; found 385.14415.

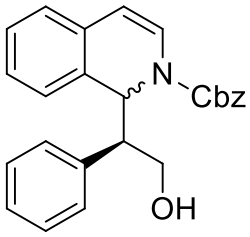



**(27f):** yellowish oil; 9% yield (7% *syn*, 2% *anti*); the title compound was isolated by column chromatography on silica (cyclohexane/ethyl acetate, gradient elution from 90/10 to 80/20) as separated diastereoisomers in 81/19 ratio (*syn*-**27f**:*anti*-**27f**). *Syn* diastereoisomer ee = 91%; *anti* diastereoisomer ee = 93%. The dr was determined by integration of the NCHC(4)H signals of the two diastereoisomers in the $^1$HNMR of the crude mixture after reduction. The ee were determined by HPLC analysis Daicel Chiralpak® AD column: hexane/*i*-PrOH from 90:10 to 70:30 in 20 min. then 70:30, flow rate 0.70 mL/min, 40°C, λ = 295 nm: *syn* diastereoisomer $\tau_{major}$ = 19.50 min., $\tau_{minor}$ = 17.22 min.; *anti* diastereoisomer $\tau_{major}$ = 25.36 min., $\tau_{minor}$ = 23.21 min. $^1$H NMR (400 MHz, $CDCl_3$, 25°C): $\delta_{syn}$ (two rotamers A:B, 7:1 ratio) = 2.13-2.20 (m, 1H), 2.27 (dd, $J_1 = J_2$ = 13.2 Hz, 1H), 2.53-2.61 (m, 1H$_B$), 2.72 (dd, $J_1$ = 13.2 Hz, $J_2$ = 1.4 Hz, 1H$_A$), 3.20-3.41 (m, 2H), 3.59-3.76 (bs, 1H), 5.22-5.37 (m, 2H), 5.57 (d, $J$ = 5.8 Hz, 1H$_B$), 5.78 (d, $J$ = 3.0 Hz, 1H$_A$), 5.89 (d, $J$ = 7.7 Hz, 1H$_A$), 6.01 (d, $J$ = 7.7 Hz, 1H$_B$), 6.86-6.94 (m, 3H), 6.97-7.33 (m, 7H), 7.35-7.46 (m, 5H); $\delta_{anti}$ (two rotamers A:B, 9:1 ratio)= 1.91-2.04 (m, 1H), 2.36 (dd, $J_1 = J_2$ = 12.9 Hz, 1H$_B$), 2.44 (dd, $J_1$ = 12.9 Hz, $J_2$ = 2.8 Hz, 1H$_A$), 2.53 (dd, $J_1$ = 12.9 Hz, $J_2$ = 2.8 Hz, 1H$_B$), 2.73 (dd, $J_1 = J_2$ = 12.9 Hz, 1H$_B$), 3.12-3.44 (m, 3H), 5.18 (d, $J$ = 21.0 Hz, 1H$_B$), 5.25 (d, $J$ = 12.1 Hz, 1H$_A$), 5.31 (d, $J$ = 12.1 Hz, 1H$_A$), 5.32 (d, $J$ = 10.9 Hz, 1H$_A$), 5.36-5.44 (m, 2H$_B$), 6.03 (d, $J$ = 7.4 Hz, 1H$_A$), 6.07 (d, $J$ = 7.4 Hz, 1H$_B$), 6.79 (d, $J$ = 7.4 Hz, 1H$_A$), 6.93 (d, $J$ = 7.4 Hz, 1H$_B$), 6.95-6.99 (m, 2H), 7.08-7.33 (m, 7H), 7.35-7.46 (m, 5H); $^{13}$CNMR (50 MHz, $CDCl_3$, 25°C): $\delta_{syn}$ (two rotamers, A:B 8:1 ratio) = 31.8, 52.6, 54.9, 60.7, 68.6, 107.6 (1C$_B$), 110.6 (1C$_A$), 124.7, 125.3, 125.9, 126.6, 127.7, 127.8, 128.2 (2C), 128.3 (2C), 128.5, 128.6 (2C), 128.7 (2C), 130.7, 131.8, 135.6, 140.2, 154.9; $\delta_{anti}$ = 32.7, 44.2, 55.9, 58.3, 68.6, 111.0, 123.7, 125.0, 125.7, 126.7, 128.0, 128.1 (2C), 128.2 (2C), 128.5, 128.7 (2C), 129.0, 129.1 (2C), 130.2, 130.5, 135.5, 140.4, 154.3; ESI-MS: *m/z* = 400.2 $[M+H]^+$, 422.3 $[M+Na]^+$, 821.6 $[2M+Na]^+$; HMRS calcd for $C_{26}H_{25}NO_3$: 399.18344; found 399.18361.




**(27g):** yellowish oil; 23% yield; the title compound was isolated by column chromatography on silica (cyclohexane/ethyl acetate, gradient elution from 95/5 to 90/10) as mixture of diastereoisomers in 68/32 ratio (*anti*-**27g**:*syn*-**27g**). *Anti*

diastereoisomer ee = 94%; *syn* diastereoisomer ee = 81%. The dr and ee were determined by HPLC analysis Daicel Chiralpak® AD column: hexane/*i*-PrOH from 90:10 to 70:30 in 30 min. then 70:30, flow rate 0.70 mL/min, 40°C, λ = 295 nm: *anti* diastereoisomer $\tau_{major}$ = 20.39 min., $\tau_{minor}$ = 18.82 min.; *syn* diastereoisomer $\tau_{major}$ = 12.66 min., $\tau_{minor}$ = 16.12 min. $^1$H NMR (400 MHz, $CDCl_3$, 25°C): $\delta_{anti}$ (two rotamers, A:B 9:1 ratio) = 0.86 (t, *J* = 7.6 Hz, 3H), 1.71-1.97 (m, 4H), 2.24-2.38 (m, 1H), 3.11-3.19 (m, 1H), 3.47-3.60 (m, 2H), 5.05-5.17 (m, 1H), 5.19-5.39 (m, 4H), 5.97 (d, *J* = 7.9 Hz, $1H_A$), 6.02 (d, *J* = 7.9 Hz, $1H_B$), 6.78 (d, *J* = 7.9 Hz, 1H), 7.08-7.15 (m, 2H), 7.18-7.26 (m, 2H), 7.33-7.45 (m, 5H); $\delta_{syn}$ = 0.85 (t, *J* = 7.6 Hz, 3H), 1.71-1.97 (m, 3H), 1.98-2.12 (m, 2H), 3.28-3.37 (m, 1H), 3.47-3.60 (m, 1H), 3.77-3.82 (bs, 1H), 5.05-5.17 (m, 1H), 5.19-5.39 (m, 3H), 5.66 (d, *J* = 2.7 Hz, 1H), 5.84 (d, *J* = 7.9 Hz, 1H), 6.87 (d, *J* = 7.9 Hz, 1H), 7.08-7.15 (m, 2H), 7.18-7.26 (m, 2H), 7.33-7.45 (m, 5H); $^{13}$CNMR (100 MHz, $CDCl_3$, 25°C): $\delta_{anti}$ = 14.1, 20.3, 24.3, 42.5, 55.8, 59.5, 68.6, 111.0, 123.7, 124.8, 126.6, 126.7, 127.8, 127.9, 128.2 (2C), 128.5, 128.7 (2C), 130.2, 130.6, 133.5, 135.6, 154.2; $\delta_{syn}$ = 14.0, 20.3, 23.1, 51.2, 54.6, 61.3, 68.4, 110.5, 121.9, 124.6, 125.2, 126.8, 127.5, 127.6, 128.1 (2C), 128.4, 128.7 (2C), 130.7, 131.8, 133.1, 135.7, 154.8; ESI-MS: *m/z* = 378.4 $[M+H]^+$, 400.2 $[M+Na]^+$, 777.5 $[2M+Na]^+$; HMRS calcd for $C_{24}H_{27}NO_3$ : 377.19909; found 282.1114.



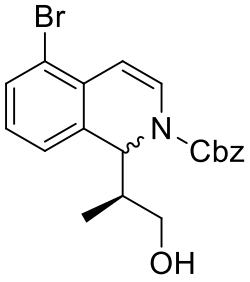

**(27h):** the compound was prepared according to the general procedure using DCM as reaction solvent. Yellowish oil; 62% yield; the title compound was isolated after column chromatography on silica (cyclohexane/ethyl acetate 9/1) as mixture of diastereoisomers in 67/32 ratio (*anti*-**27h**:*syn*-**27h**) determined by integration of the COOC$\underline{H_2}$Ph signals of the Cbz groups. *Anti* diastereoisomer ee = 90%; *syn* diastereoisomer ee = 82%. The ees were determined by HPLC analysis Daicel Chiralpak® AD column: hexane/*i*-PrOH from 90:10 to 80:20 in 20 min., flow rate 1.0 mL/min, 25°C, λ = 295 nm: *anti* diastereoisomer $\tau_{major}$ = 10.79 min., $\tau_{minor}$ = 11.87 min.; *syn* diastereoisomer $\tau_{major}$ = 13.32 min., $\tau_{minor}$ = 14.70 min. $^1$H NMR (400 MHz, $CDCl_3$, 25°C) (*anti:syn* 1:1 mixture): $\delta_{anti}$ (two rotamers A:B, 4:1 ratio) = 2.93-3.06 (m, 1H+$1H_A$), 3.16-3.27 (m, $1H_B$), 3.67-3.83 (m, 1H), 3.84-3.93 (m, 1H), 5.27 (d, *J* = 12.5 Hz, 1H), 5.32 (d, *J* = 12.5 Hz, 1H), 5.49 (d, *J* = 10.5 Hz, $1H_B$), 5.61 (d, *J* = 10.5 Hz, $1H_A$), 5.85 (d, *J* = 7.9 Hz, $1H_B$), 5.94 (d, *J* = 7.9 Hz, $1H_A$), 6.29 (d, *J* = 7.8 Hz, $1H_A$), 6.46 (d, *J* = 7.8 Hz, $1H_B$), 6.74-6.82 (m, 2H), 6.98-7.48 (m, 12H); $\delta_{syn}$ (two rotamers A:B, 3:1 ratio) = 3.06-3.14 (m, $1H_A$), 3.16-3.27 (m, $1H_B$), 3.67-3.81 (m, 2H), 3.84-3.93 (m, 1H), 5.13 (d, *J* = 12.5 Hz, 1H), 5.20 (d, *J* = 12.5

Hz, 1H), 5.45 (d, $J$ = 7.0 Hz, $1H_A$), 5.53 (d, $J$ = 7.0 Hz, $1H_B$), 5.81 (d, $J$ = 5.3 Hz, $1H_A$), 5.94 (d, $J$ = 7.9 Hz, $1H_B$), 6.56 (d, $J$ = 7.0 Hz, 1H), 6.84-6.92 (m, 3H), 6.98-7.48 (m, 11H); $^{13}$CNMR (100 MHz, $CDCl_3$, 25°C) (two rotamers A:B, 6:1 ratio) $\delta_{anti}$ = 50.0 ($1C_A$), 51.2 ($1C_B$), 56.8 ($1C_A$), 58.2 ($1C_B$), 63.0 ($1C_A$), 63.1 ($1C_B$), 68.3 ($1C_B$), 68.5 ($1C_A$), 110.2 ($1C_B$), 110.9 ($1C_A$), 123.3, 124.4, 126.2, 126.9, 127.4, 127.5, 128.0 (2C), 128.2, 128.5, 128.6 (2C), 128.7 (2C), 129.4, 129.8, 130.5, 135.8 ($1C_A$), 138.1 ($1C_B$), 139.3 ($1C_A$), 141.0 ($1C_B$), 154.0; $\delta_{syn}$ = 52.5 ($1C_B$), 54.6 ($1C_A$), 56.0 ($1C_A$), 59.9 ($1C_B$), 61.7 ($1C_A$), 62.2 ($1C_B$), 67.9 ($1C_B$), 68.2 ($1C_A$), 109.7, 124.6, 125.0, 126.6, 127.0, 127.1, 127.7 (2C), 127.8, 128.0 (2C), 128.3, 128.6, 129.0, 129.1 (2C), 130.7, 131.1, 135.6, 137.5 ($1C_A$), 138.2 ($1C_B$), 154.1; ESI-MS: *m/z* = 386.3 $[M+H]^+$, 408.2 $[M+Na]^+$.

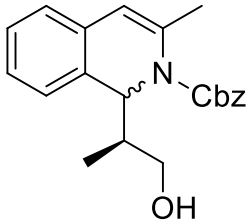
**General procedure for the stereoselective alkylation of isoquinolines activated with CbzCl with propionaldheyde:** To a solution of isoquinoline **22b-i** (0.2 mmol) in 0.5 mL *t*-BuOMe/$CH_2Cl_2$ (8/2) inside a round-bottomed flask equipped with a stirring magnetic bar and cooled at 0°C, $NaHCO_3$ (0.6 mmol, 51 mg), Jørgensen catalyst **24a** (0.04 mmol, 24 mg) and aldehyde **25a** (1.0 mmol) were added. To the mixture a solution of CbzCl (0.45 mmol, 78 μL CbzCl in 1 mL *t*BuOMe/$CH_2Cl_2$ 8/2) was added drop wise by a syringe pump during 15 h. After that 2 mL of an aqueous saturated solution of $NH_4Cl$ were added and the organic layer was extracted with $Et_2O$ (3 x 5 mL). The collected organic layers were dried over $MgSO_4$. The residue was diluted in MeOH and the resulting solution was cooled at -40°C. Then $NaBH_4$ (2 mmol, 76 mg) was added. When complete conversion was obtained (monitored by TLC), HCl 1N was added (at -40°C) until pH = 1. The organic layer was separated and the aqueous layer was extracted with $Et_2O$ (2 x 10 mL). The collected organic layers were washed with brine (5 mL), dried over $MgSO_4$ and concentrated under reduced pressure to give **28b-i**.

The racemic products were synthesized with the same procedure except for using pyrrolidine (0.1 mmol, 8.3 μL) instead of **24a**, $CH_2Cl_2$ as reaction solvent and for conducing the reaction at room temperature.

**Note:** the enantiomeric excesses and the diasteromeric ratios of the compounds remain unaltered after flash chromatography or after preparative thin layer chromatography on neutral alumina.

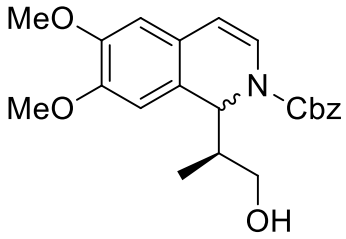



**(28b):** colourless oil; 40% yield; the title compound was isolated by preparative thin layer chromatography on neutral alumina (cyclohexane/acetone 85/15) as mixture of diastereoisomers in 73/27 ratio (*syn*-**28b**:*anti*-**28b**). *Syn* diastereoisomer ee = 95%; *anti* diastereoisomer ee = 88%. The dr and ee were determined by HPLC analysis Daicel Chiralpak® AD column: hexane/*i*-PrOH from 90:10 to 70:30 in 20 min., flow rate 0.70 mL/min, 40°C, λ = 295 nm: *syn* diastereoisomer $\tau_{major}$ = 16.16 min., $\tau_{minor}$ = 13.42 min.; *anti* diastereoisomer $\tau_{major}$ = 12.71 min., $\tau_{minor}$ = 14.51 min. $^1$H NMR (400 MHz, $CDCl_3$, 25°C) (two rotamers A:B, 7:1 ratio): $\delta_{syn}$ = 0.72 (d, *J* = 7.0 Hz, $3H_A$), 0.86 (d, *J* = 7.0 Hz, $3H_B$), 1.92-2.02 (bs, 1H), 3.31 (dd, $J_1$ = 12.1 Hz, $J_2$ = 10.0 Hz, 1H), 3.37-3.45 (m, 1H), 3.67-3.90 (bs, 1H), 5.27 (s, $2H_A$), 5.28 (s, $2H_B$), 5.60 (d, *J* = 3.1 Hz, 1H), 6.20 (d, *J* = 8.0 Hz, $1H_A$), 6.35 (d, *J* = 8.0 Hz, $1H_B$), 6.96 (d, *J* = 8.0 Hz, 1H), 7.02-7.10 (m, 2H), 7.34-7.41 (m, 5H), 7.44 (dd, $J_1$ = 7.3 Hz, $J_2$ = 1.7 Hz, 1H); $\delta_{anti}$ = 0.60 (d, *J* = 7.0 Hz, $3H_B$), 0.85 (d, *J* = 7.0 Hz, $3H_A$), 1.92-2.02 (bs, 1H), 3.37-3.45 (m, 1H), 3.58 (dd, $J_1$ = 12.1 Hz, $J_2$ = 2.4 Hz, 1H), 3.67-3.90 (bs, 1H), 5.14 (d, *J* = 10.1 Hz, 1H), 5.18-5.33 (m, 2H), 6.24 (d, *J* = 8.0 Hz, $1H_B$), 6.31 (d, *J* = 8.0 Hz, $1H_A$), 6.89 (d, *J* = 8.0 Hz, 1H), 7.02-7.10 (m, 2H), 7.34-7.41 (m, 5H), 7.47 (dd, $J_1$ = 6.7 Hz, $J_2$ = 2.3 Hz, 1H); $^{13}$CNMR (100 MHz, $CDCl_3$, 25°C): $\delta_{syn}$ = 10.7, 43.8 ($1C_B$), 46.1 ($1C_A$), 55.0, 63.5, 68.7, 108.9, 120.1, 125.8, 127.2, 128.2 (2C), 128.3, 128.6, 128.7 (2C), 130.2, 131.6, 134.0, 135.4, 154.7; $\delta_{anti}$ = 14.0, 36.5, 56.8, 63.4, 68.7, 109.3, 120.5, 125.5, 127.0, 127.5, 128.2 (2C), 128.5, 128.6 (2C), 129.8, 131.9, 132.5, 135.3, 153.4; ESI-MS: *m/z* = 402.4 [M($^{79}$Br)+H]$^+$, 404.3 [M($^{81}$Br)+H]$^+$, 425.3 [M($^{79}$Br)+Na]$^+$, 427.2 [M($^{81}$Br)+Na]$^+$; HMRS calcd for $C_{20}H_{20}BrNO_3$ : 401.06266; found 401.06251.



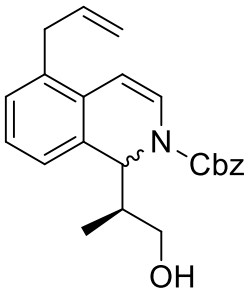

**(28c):** colourless oil; 23% yield; the title compound was isolated by preparative thin layer chromatography on neutral alumina (cyclohexane/acetone 85/15) as mixture of diastereoisomers in 87/13 ratio (*syn*-**28c**:*anti*-**28c**). *Syn* diastereoisomer ee = 99%; *anti* diastereoisomer ee = 94%. The dr and ee were determined by HPLC analysis Daicel Chiralpak® AD column: hexane/*i*-PrOH from 95:5 to 85:15 in 40 min. then 85:15, flow rate 0.70 mL/min, 40°C, λ = 295 nm: *syn* diastereoisomer $\tau_{major}$ = 41.21 min., $\tau_{minor}$ = 30.31 min.; *anti* diastereoisomer $\tau_{major}$ = 21.58 min., $\tau_{minor}$ = 31.20 min. $^1$H NMR (400 MHz, $CDCl_3$, 25°C): $\delta_{syn}$= 0.71-0.80 (bs, 3H), 1.96-2.05 (m, 1H), 2.14-2.24 (bs, 3H), 3.37-3.51 (bs, 3H), 5.17 (d, *J* = 12.5 Hz, 1H), 5.26 (d, *J* = 12.5 Hz, 1H), 5.50-5.58 (bs, 1H), 5.94-5.99 (bs, 1H), 7.02-7.10 (m, 1H), 7.13-7.18 (m, 1H), 7.18-7.25 (m, 1H), 7.29-7.34 (m, 1H), 7.34-

7.40 (m, 4H), 7.40-7.43 (m, 1H); $\delta_{anti}$= 0.90 (d, $J$ = 6.9 Hz, 3H), 1.68-1.76 (bs, 1H), 2.14-2.24 (bs, 3H), 3.37-3.51 (bs, 1H), 3.76-3.81 (bs, 2H), 5.12 (d, $J$ = 10.9 Hz, 1H), 5.14-5.28 (m, 2H), 5.99-6.02 (bs, 1H), 7.02-7.10 (m, 1H), 7.13-7.18 (m, 1H), 7.18-7.25 (m, 1H), 7.29-7.34 (m, 1H), 7.34-7.40 (m, 4H), 7.40-7.43 (m, 1H); $^{13}$CNMR (100 MHz, $CDCl_3$, 25°C): $\delta_{syn}$ (two rotamers, A:B 5:1 ratio) = 11.8 ($1C_A$), 13.8 ($1C_B$), 21.7, 29.7 ($1C_A$), 33.8 ($1C_B$), 57.4, 64.0, 65.4 ($1C_B$), 68.4 ($1C_A$), 115.2, 124.2, 126.0, 126.8, 127.0, 127.4, 128.4 (2C), 128.5, 128.6 (2C), 131.4, 133.2, 135.6, 140.9; $\delta_{anti}$ = 14.1, 21.7, 35.8, 59.0, 63.8, 68.6, 115.0, 124.2, 126.1, 127.2, 127.5, 127.6, 128.5, 128.6 (2C), 128.7 (2C), 130.8, 132.1, 135.4, 140.9; ESI-MS: $m/z$ = 338.3 $[M+H]^+$, 360.4 $[M+Na]^+$, 697.5 $[2M+Na]^+$; HMRS calcd for $C_{21}H_{23}NO_3$ : 337.16779; found 337.16789.

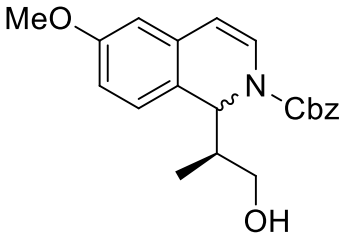



**(28d):** (Reaction carried out in $CH_2Cl_2$ as reaction solvent); yellowish oil; 53% yield; the title compound was isolated by preparative thin layer chromatography on neutral alumina (cyclohexane/acetone 80/20) as mixture of diastereoisomers in 71/29 ratio (*anti*-**28d**:*syn*-**28d**). *Anti* diastereoisomer ee = 91%; *syn* diastereoisomer ee = 77%. The dr and ee were determined by HPLC analysis Daicel Chiralpak® AD column: hexane/*i*-PrOH 80:20, flow rate 0.70 mL/min, 40°C, λ = 295 nm: *anti* diastereoisomer $\tau_{major}$ = 19.62 min., $\tau_{minor}$ = *25*.51 min.; *syn* diastereoisomer $\tau_{minor}$ = 21.04 min., $\tau_{major}$ = *2*4.99 min. $^1$H NMR (400 MHz, $CDCl_3$, 25°C): $\delta_{anti}$ (two rotamers A:B, 13:1 ratio) = 0.74 (d, $J$ = 7.2 Hz, $3H_B$),0.89 (0.74 rotamer) (d, $J$ = 7.2 Hz, $3H_A$), 1.86-2.00 (m, 1H), 3.02-3.18 (bs, 1H), 3.38 (dd, $J_1$ = 12.0 Hz, $J_2$ = 2.6 Hz, 1H), 3.57 (dd, $J_1$ = 12.0 Hz, $J_2$ = 2.6 Hz, 1H), 3.87 (s, 6H), 5.11 (d, $J$ = 9.8 Hz, 1H), 5.23 (d, $J$ = 12.2 Hz, 1H), 5.29 (d, $J$ = 12.2 Hz, 1H), 5.87 5.90 (d, $J$ = 7.9 Hz, $1H_A$), 5.90 (d, $J$ = 7.9 Hz, $1H_B$), 6.63 (s, 1H), 6.65 (s, 1H), 6.70 (dd, $J_1$ = 7.6 Hz, $J_2$ = 1.0 Hz, 1H), 7.28-7.42 (m, 5H); $\delta_{syn}$ = 0.69 (d, $J$ = 7.2 Hz, 3H), 2.00-2.04 (m, 1H), 3.00-3.02 (bs, 1H), 3.27-3.33 (bs, 1H), 3.48 (dd, $J_1$ = 10.9 Hz, $J_2$ = 4.7 Hz, 1H), 3.88 (s, 6H), 5.20 (d, $J$ = 11.9 Hz, 1H), 5.33 (d, $J$ = 11.9 Hz, 1H), 5.60 (d, $J$ = 3.0 Hz, 1H), 5.73 (d, $J$ = 7.9 Hz, 1H), 6.58 (s, 1H), 6.68 (s, 1H), 6.78 (d, $J$ = 7.3 Hz, 1H), 7.16-7.22 (m, 1H), 7.28-7.42 (m, 3H), 7.43-7.48 (m, 1H); $^{13}$CNMR (100 MHz, $CDCl_3$, 25°C): $\delta_{anti}$ = 14.1, 37.3, 55.9, 56.1, 56.3, 63.7, 68.4, 108.1, 110.6, 111.5, 122.2, 123.4, 126.9, 128.1 (2C), 128.4, 128.6 (2C), 135.6, 147.8, 148.4, 154.3; $\delta_{syn}$ = 10.3, 46.2, 54.6, 56.1, 56.3, 65.3, 68.4, 107.8, 109.8, 110.2, 123.2, 123.9, 127.6, 128.5 (2C), 128.6 (3C), 135.7, 147.8, 148.4, 154.3; ESI-MS: $m/z$ = 384.4 $[M+H]^+$, 406.4 $[M+Na]^+$, 789.5 $[2M+Na]^+$; HMRS calcd for $C_{22}H_{25}NO_5$ :

383.17327; found 383.17338.

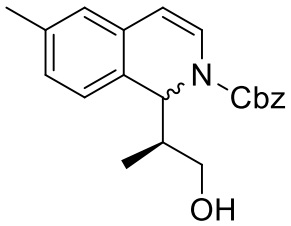



**(28e):** colourless oil; 56% yield; the title compound was isolated by preparative thin layer chromatography on neutral alumina (cyclohexane/acetone 80/20) as mixture of diastereoisomers in 81/19 ratio (*syn*-**28e**:*anti*-**28e**). *Syn* diastereoisomer ee = 54%; *anti* diastereoisomer ee = 48%. The dr and ee were determined by HPLC analysis Daicel Chiralpak® AD column: hexane/*i*-PrOH from 90:10 to 70:30 in 20 min., flow rate 0.70 mL/min, 40°C, λ = 295 nm: *syn* diastereoisomer $\tau_{major}$ = 16.18 min., $\tau_{minor}$ = 12.19 min.; *anti* diastereoisomer $\tau_{major}$ = 11.53 min., $\tau_{minor}$ = 14.23 min. $^1$H NMR (400 MHz, $CDCl_3$, 25°C): $\delta_{syn}$ (two rotamers A:B, 10:1 ratio) = 0.70 (d, *J* = 7.3 Hz, $3H_A$), 0.94 (d, *J* = 7.3 Hz, $3H_B$), 1.97-2.04 (m, 1H), 3.27-3.35 (m, 1H), 3.35-3.47 (m, 3H), 3.83-3.92 (bs, 1H), 4.96 (d, *J* = 17.0 Hz, 1H), 5.06 (d, *J* = 9.8 Hz, 1H), 5.21-5.32 (m, 2H), 5.61 (d, *J* = 2.6 Hz, 1H), 5.89-6.01 (m, 1H), 5.97 (d, *J* = 7.8 Hz, $1H_A$), 6.15 (d, *J* = 7.8 Hz, $1H_B$), 6.88 (d, *J* = 7.8 Hz, 1H), 6.96-7.11 (m, 2H), 7.12-7.19 (m, 1H), 7.33-7.44 (m, 5H); $\delta_{anti}$= 0.86 (d, *J* = 7.3 Hz, 3H), 1.97-2.04 (m, 1H), 3.01-3.08 (bs, 1H), 3.27-3.35 (m, 1H), 3.35-3.47 (m, 2H), 3.55-3.61 (bs, 1H), 5.00 (d, *J* = 17.0 Hz, 1H), 5.12 (d, *J* = 9.8 Hz, 1H), 5.21-5.32 (m, 2H), 5.29 (d, *J* = 10.6 Hz, 1H), 5.89-6.01 (m, 1H), 6.10 (d, *J* = 7.8 Hz, 1H), 6.80 (d, *J* = 7.8 Hz, 1H), 6.96-7.11 (m, 2H), 7.12-7.19 (m, 1H), 7.33-7.44 (m, 5H); $^{13}$CNMR (100 MHz, $CDCl_3$, 25°C): $\delta_{syn}$ = 10.7, 29.6, 36.8, 46.3, 55.1, 68.5, 107.1, 115.9, 125.0, 125.5, 127.4, 128.2 (2C), 128.5, 128.6 (2C), 128.7, 128.9, 132.5, 133.7, 135.6, 136.7, 154.8; $\delta_{anti}$ = 14.1, 22.7, 36.9, 46.4, 56.9, 63.8, 107.6, 115.9, 123.8, 126.3, 126.5, 128.3 (2C), 128.5, 128.6 (2C), 128.8, 128.9, 132.5, 133.7, 135.6, 136.6, 154.8; ESI-MS: *m/z* = 364.2 $[M+H]^+$, 386.3 $[M+Na]^+$, 749.6 $[2M+Na]^+$; HMRS calcd for $C_{23}H_{25}NO_3$ : 363.18344; found 363.18362.



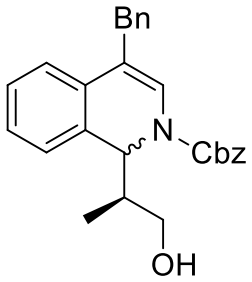

**(28f):** yellowish oil; 56% yield; the title compound was isolated by preparative thin layer chromatography on neutral alumina (cyclohexane/acetone 85/15) as mixture of diastereoisomers in 54/46 ratio (*syn*-**28f**:*anti*-**28f**). *Syn* diastereoisomer ee = 78%; *anti* diastereoisomer ee = 25%. The dr and ee were determined by HPLC analysis Daicel Chiralpak® AD column: hexane/*i*-PrOH from 90:10 to 70:30 in 20 min. then 70:30, flow rate 0.70 mL/min, 40°C, λ = 295 nm: *syn* diastereoisomer $\tau_{major}$ = 31.40 min., $\tau_{minor}$ = 17.33 min.; *anti* diastereoisomer $\tau_{major}$ = 16.58 min., $\tau_{minor}$ = 25.73 min. $^1$H NMR (400 MHz, $CDCl_3$, 25°C) (two

rotamers A:B, 10:1 ratio): $\delta_{syn}$ = 0.72 (d, $J$ = 7.0 Hz, 3H$_A$), 0.90 (d, $J$ = 7.0 Hz, 3H$_B$), 1.87-2.00 (m, 1H), 3.31 (pt, $J_1$ = 12.5 Hz, $J_2$ = 10.0 Hz, 1H), 3.35-3.44 (bs, 1H), 3.80 (s, 3H), 3.88-3.95 (bs, 1H), 5.21-5.32 (m, 2H), 5.59 (d, $J$ = 3.0 Hz, 1H), 5.77 (d, $J$ = 8.2 Hz, 1H$_A$), 5.94 (d, $J$ = 8.2 Hz, 1H$_B$), 6.64 (d, $J$ = 3.5 Hz, 1H), 6.76 (dd, $J_1$ = 15.1 Hz, $J_2$ = 2.3 Hz, 1H), 6.89 (d, $J$ = 7.5 Hz, 1H), 7.06 (d, $J$ = 8.2 Hz, 1H), 7.33-7.45 (m, 5H); $\delta_{anti}$ = 0.72 (d, $J$ = 7.0 Hz, 3H$_B$), 0.86 (d, $J$ = 7.0 Hz, 3H$_A$), 1.87-2.00 (m, 1H), 3.04-3.12 (bs, 1H), 3.35-3.44 (bs, 1H), 3.57 (dd, $J_1$ = 12.0 Hz, $J_2$ = 3.6 Hz, 1H), 3.80 (s, 3H), 5.13 (d, $J$ = 10.0 Hz, 1H), 5.21-5.32 (m, 2H), 5.89 (d, $J$ = 7.8 Hz, 1H), 6.60 (d, $J$ = 3.5 Hz, 1H), 6.75-6.77 (bs, 1H), 6.81 (d, $J$ = 7.5 Hz, 1H), 7.02 (d, $J$ = 7.8 Hz, 1H), 7.33-7.45 (m, 5H); $^{13}$CNMR (100 MHz, $CDCl_3$, 25°C): $\delta_{syn}$ = 10.6, 46.4, 54.5, 55.3, 63.8, 68.5, 109.7, 110.2, 112.8, 124.2, 125.9, 127.4, 128.1, 128.2, 128.6 (2C), 128.7, 131.7, 135.6, 154.8, 159.1; $\delta_{anti}$ = 13.9, 37.4, 55.3, 56.2, 63.2, 65.2, 110.0, 110.6, 112.0, 123.2, 124.3, 126.9, 127.5, 128.42, 128.45, 128.5 (2C), 131.3, 135.6, 154.1, 158.9; ESI-MS: *m/z* = 354.4 $[M+H]^+$, 376.3 $[M+Na]^+$, 729.5 $[2M+Na]^+$; HMRS calcd for $C_{21}H_{23}NO_2$ : 353.16271; found 353.16277.



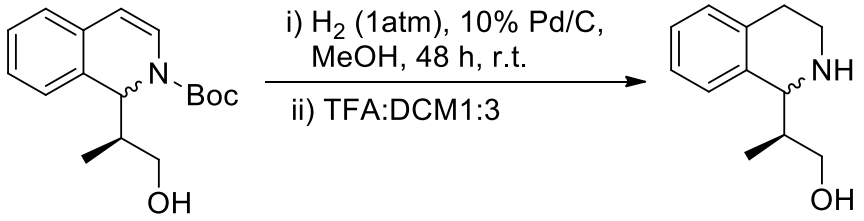

**(28g):** (Reaction carried out in $CH_2Cl_2$ as reaction solvent); colourless oil; 68% yield; the title compound was isolated by preparative thin layer chromatography on neutral alumina (cyclohexane/acetone 85/15) as mixture of diastereoisomers in 53/47 ratio (*anti*-**28g**:*syn*-**28g**). *Syn* diastereoisomer ee = 88%; *anti* diastereoisomer ee = 92%. The dr and ee were determined by HPLC analysis Daicel Chiralpak® AD column: hexane/*i*-PrOH from 90:10 to 70:30 in 20 min. then 70:30, flow rate 0.70 mL/min, 40°C, λ = 295 nm: *syn* diastereoisomer $\tau_{major}$ = 27.05 min., $\tau_{minor}$ = 14.04 min.; *anti* diastereoisomer $\tau_{major}$ = 13.30 min., $\tau_{minor}$ = 21.83 min. $^1$H NMR (400 MHz, $CDCl_3$, 25°C) (two rotamers A:B, 10:1 ratio): $\delta_{anti}$ = 0.70 (d, $J$ = 7.0 Hz, 3H$_A$), 0.90 (d, $J$ = 7.0 Hz, 3H$_B$),1.87-2.01 (m, 1H), 2.32 (s, 3H), 3.32 (dd, $J_1$ = $J_2$ = 10.2 Hz, 1H), 3.36-3.45 (bs, 1H), 3.90-3.99 (bs, 1H), 5.23-5.32 (m, 2H), 5.60 (d, $J$ = 3.0 Hz, 1H), 5.77 (d, $J$ = 7.7 Hz, 1H$_A$), 5.94 (d, $J$ = 7.7 Hz, 1H$_B$), 6.87 (d, $J$ = 7.7 Hz, 1H), 6.88 (s, 1H), 6.98-7.05 (m, 2H), 7.34-7.41 (m, 5H); $\delta_{syn}$ = 0.74 (d, $J$ = 6.9 Hz, 3H$_B$), 0.87 (d, $J$ = 6.9 Hz, 3H$_A$), 1.87-2.01 (m, 1H), 2.33 (s, 3H), 3.06-3.15 (bs, 1H), 3.36-3.45 (bs, 1H), 3.59 (dd, $J_1$ = 12.2 Hz, $J_2$ = 2.5 Hz, 1H), 5.14 (d, $J$ = 10.0 Hz, 1H), 5.23-5.32 (m, 2H), 5.90 (d, $J$ = 7.7 Hz, 1H$_A$), 5.93 (d, $J$ = 7.7 Hz, 1H$_B$), 6.78 (dd, $J_1$ = 7.6 Hz, $J_2$ = 1.0 Hz, 1H), 6.92 (s, 1H), 6.98-7.05 (m, 2H), 7.34-7.41 (m, 5H); $^{13}$CNMR (100 MHz, $CDCl_3$, 25°C): $\delta_{anti}$ (two rotamers, A:B 8:1 ratio) = 10.6, 21.0, 46.3, 54.7,

63.8 ($1C_A$), 65.3 ($1C_B$), 68.4, 110.4, 125.1, 125.4, 126.3, 127.6, 127.9, 128.1, 128.2, 128.6 (2C), 129.1, 130.5, 135.7, 137.0, 154.9; $\delta_{syn}$ (two rotamers A:B, 5:1 ratio)= 14.0 ($1C_A$), 14.1 ($1C_B$), 21.1, 37.2, 56.4, 60.2 ($1C_B$), 63.6 ($1C_A$), 63.9, 110.8, 123.8, 125.5, 127.0, 127.3, 127.5, 128.0 (2C), 128.3, 128.4 128.5, 130.0, 135.6, 137.3, 154.2; ESI-MS: *m/z* = 338.3 $[M+H]^+$, 360.4 $[M+Na]^+$, 697.5 $[2M+Na]^+$; HMRS calcd for $C_{21}H_{23}NO_3$ : 337.16779; found 337.16761.




**(28i):** yellowish oil; 60% yield; the title compound was isolated by preparative thin layer chromatography on neutral alumina (cyclohexane/acetone 85/15) as mixture of diastereoisomers in 81/19 ratio (*syn*-**28i**:*anti*-**28i**). *Syn* diastereoisomer ee = 97%; *anti* diastereoisomer ee = 74%. The dr and ee were determined by HPLC analysis Daicel Chiralpak® AD column: hexane/*i*-PrOH from 90:10 to 70:30 in 20 min. then 70:30, flow rate 0.70 mL/min, 40°C, λ = 295 nm: *syn* diastereoisomer $\tau_{major}$ = 27.42 min., $\tau_{minor}$ = 15.48 min.; *anti* diastereoisomer $\tau_{major}$ = 13.65 min., $\tau_{minor}$ = 24.98 min. $^1$H NMR (400 MHz, $CDCl_3$, 25°C) (two rotamers A:B, 8:1 ratio): $\delta_{syn}$ = 0.69 (d, *J* = 7.1 Hz, $3H_A$), 0.92 (d, *J* = 7.1 Hz, $3H_B$), 1.88-2.03 (m, 1H), 3.33 (pt, $J_1$ = 11.9 Hz, $J_2$ = 10.2 Hz, 1H), 3.37-3.47 (m, 1H), 3.72 (d, *J* = 16.0 Hz, 1H), 3.80 (d, *J* = 16.0 Hz, 1H), 3.93-4.01 (bs, 1H), 5.22 (d, *J* = 12.3 Hz, $1H_B$), 5.23 (d, *J* = 12.3 Hz, $1H_A$), 5.28 (d, *J* = 12.3 Hz, $1H_A$), 5.32 (d, *J* = 12.3 Hz, $1H_B$), 5.62 (d, *J* = 3.2 Hz, 1H), 6.70 (s, $1H_A$), 6.92 (s, $1H_B$), 7.15-7.27 (m, 6H), 7.27-7.33 (m, 3H), 7.33-7.47 (m, 5H); $\delta_{anti}$ = 0.73 (d, *J* = 6.9 Hz, $3H_B$), 0.88 (d, *J* = 6.9 Hz, $3H_A$), 1.88-2.03 (m, 1H), 3.12-3.21 (bs, 1H), 3.37-3.47 (m, 1H), 3.59-3.66 (m, 1H), 3.72 (d, *J* = 16.0 Hz, 1H), 3.89 (d, *J* = 16.0 Hz, 1H), 5.15 (d, *J* = 10.4 Hz, 1H), 5.24 (d, *J* = 12.3 Hz, 1H), 5.30 (d, *J* = 12.3 Hz, 1H), 6.66 (s, $1H_A$), 6.88 (s, $1H_B$), 7.01-7.14 (m, 2H), 7.15-7.27 (m, 4H), 7.27-7.33 (m, 3H), 7.33-7.47 (m, 5H); $^{13}$CNMR (100 MHz, $CDCl_3$, 25°C): $\delta_{syn}$ = 10.7, 36.2, 45.9, 54.9, 63.8, 68.3, 119.0, 122.2, 124.1, 126.3, 126.6, 127.3, 127.5, 127.9 (2C), 128.2, 128.4 (2C), 128.6 (2C), 128.7 (2C), 131.3, 133.0, 135.7, 139.0, 154.9; $\delta_{anti}$ = 14.1, 35.9, 37.2, 56.8, 63.6, 68.4, 119.8, 122.2, 122.5, 126.3, 126.7, 126.9, 127.6, 128.0 (2C), 128.3, 128.5 (2C), 128.60 (2C), 128.7 (2C), 129.1, 131.7, 135.6, 139.2, 154.2; ESI-MS: *m/z* = 414.2 $[M+H]^+$, 436.1 $[M+Na]^+$, 849.2 $[2M+Na]^+$; HMRS calcd for $C_{27}H_{27}NO_3$ : 413.19909; found 413.19979.

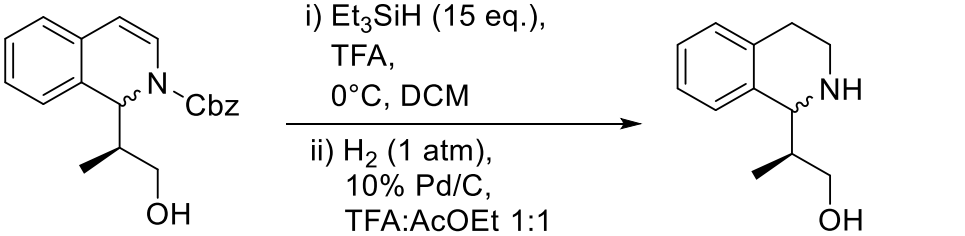
**Synthesis of compound 29a**




**6a,** *syn*/*anti* 88/12; $ee_{syn}$ 97%

**9a**, 71%, *syn*/*anti* 88/12, $ee_{syn}$ 97%

**Procedure starting from 26a:** To a 25 mL balloon equipped with a magnetic stirring bar, 3 mL MeOH and 10% Pd/C (20% wt, 60 mg), were added and the mixture was stirred under hydrogen atmosphere (1 atm) for 30 min. Then **26a** (0.2 mmol, 58.7 mg) was added and the mixture was stirred under hydrogen atmosphere for 48 hours. After that the mixture was diluted with $CH_2Cl_2$ (5 mL), filtered trough Celite® and concentrated under reduced pressure. The crude product was dissolved in $CH_2Cl_2$ (7.5 mL) and trifluoroacetic acid (33 mmol, 2.5 mL) was added and the mixture was stirred for 4 h. The solution was concentrated under reduced pressure, water (5 mL) was added and the solution was basified with $NaHCO_3$ and subsequently extracted with $Et_2O$ (3 x 5 mL). The organic layers were collected and washed with HCl 1N (3 x 5 mL). The aqueous layers were collected and basified at 0°C with KOH and subsequently extracted with $Et_2O$ (3 x 5 mL). The collected organic layers were washed with brine (5 mL), dried over $MgSO_4$ and concentrated under reduced pressure to give pure **29a** in 71% yield.




**27a,** *syn*/*anti* 74/26, $ee_{syn}$ 96%

**29a**, 76%, *syn*/*anti* 74/26, $ee_{syn}$ 96%

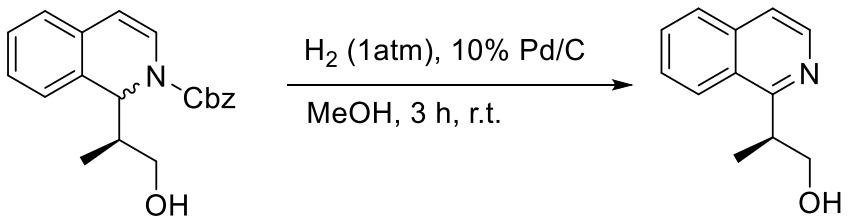
**Procedure starting from 27a:** To a solution of **27a** (0.24 mmol, 77.5 mg) in $CH_2Cl_2$ (2 mL) at 0°C, triethylsilane (3.7 mmol, 586 µL) and trifluoroacetic acid (46 mmol, 3.5 mL) were added and the mixture was stirred at 0°C. After 3 hours the solution was concentrated under reduced pressure.

The residue was diluted in AcOEt (1 mL) and trifluoroacetic acid (1 mL). 10% Pd/C (10% wt, 45 mg) was added and the mixture was kept under hydrogen atmosphere (1 atm) for 2 hours. Then the mixture

was diluted with $CH_2Cl_2$ (10 mL) and filtered through Celite®. The solution was concentrated under reduced pressure, water (5 mL) was added and the solution was basified with $NaHCO_3$ and subsequently extracted with $Et_2O$ (3 x 5 mL). The organic layers were collected and washed with HCl 1N (3 x 5 mL). The aqueous layers were collected and basified at 0°C with KOH and subsequently extracted with $Et_2O$ (3 x 5 mL). The collected organic layers were washed with brine (5 mL), dried over $MgSO_4$ and concentrated under reduced pressure to give pure **29a** in 76% yield.

**(29a):** yellowish oil; $^1$H NMR (400 MHz, $CDCl_3$, 25°C): $\delta_{syn}$ = 0.91 (d, $J$ = 7.2 Hz, 3H), 2.34-2.44 (m, 1H), 2.29-2.74 (bs, 2H), 2.66-2.75 (m, 1H), 2.81-2.95 (m, 1H), 2.96-3.05 (m, 1H), 3.24-3.34 (m, 1H), 3.76 (dd, $J_1$ = 10.9 Hz, $J_2$ = 3.4 Hz, 1H), 4.00 (dd, $J_1$ = 10.9 Hz, $J_2$ = 5.0 Hz, 1H), 4.30 (d, $J$ = 2.65 Hz, 1H), 7.07-7.21 (m, 4H); $\delta_{anti}$ = 1.22 (d, $J$ = 7.2 Hz, 3H), 2.17-2.27 (m, 1H), 2.29-2.74 (bs, 2H), 2.66-2.75 (m, 1H), 2.81-2.95 (m, 1H), 2.96-3.05 (m, 1H), 3.24-3.34 (m, 1H), 3.45 (ddd, $J_1$ = 10.8 Hz, $J_2$ = 4.6 Hz, $J_3$ = 0.9 Hz, 1H), 3.66 (dd, $J_1$ = 10.8 Hz, $J_2$ = 2.4 Hz, 1H), 4.17 (d, $J$ = 4.60 Hz, 1H), 7.07-7.21 (m, 4H); $^{13}$CNMR (100 MHz, $CDCl_3$, 25°C): $\delta_{syn}$ (two rotamers, A:B 10:1 ratio) = 10.7, 29.7 ($1C_A$), 30.2 ($1C_B$), 37.9, 42.3, 59.6, 67.9, 125.3, 126.1, 126.2, 129.5, 135.7, 137.3; $\delta_{anti}$ = 15.1, 29.6, 37.8, 41.6, 61.6, 66.1, 125.8, 126.3, 126.4, 129.3, 135.7, 137.3; ESI-MS: $m/z$ = 192.2 $[M+H]^+$; HMRS calcd for $C_{12}H_{17}NO$ : 191.13101; found 191.13152.

**Synthesis of 1-alkyl isoquinoline 30a**




**27a,** *syn*/*anti* 75/25, $ee_{syn}$ 95%, $ee_{anti}$ 86%

**30a,** 80%, ee 93%

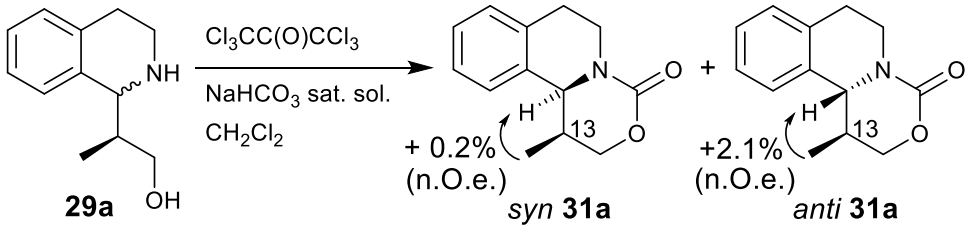
A mixture of 10% Pd/C (10% wt, 15 mg) was stirred under hydrogen atmosphere for 30 min. Then **27a** (0.12 mmol, 39.2 mg) was added and the mixture was stirred under hydrogen atmosphere (1atm) for further 3 hours. The mixture was diluted with $CH_2Cl_2$ (10 mL) and filtered through Celite®. The solvent was concentrated under reduced pressure to give crude **30a**. The title compound was isolated by

column chromatography on silica (cyclohexane/acetone 75/25) as colorless oil (80% yield; 93% ee). The ee was determined by HPLC analysis Daicel Chiralpak® IC column: hexane/*i*-PrOH 90:10, flow rate 0.70 mL/min, 40°C, λ = 214 nm: $\tau_{major}$ = 17.48 min., $\tau_{minor}$ = 18.40 min.

**(30a):** $[\alpha]_D^{20}$=-52.4 (*c*=1.7, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$, 25°C): $\delta$ = 1.48 (d, *J* = 7.0 Hz, 3H), 3.82-3.90 (m, 1H), 4.04 (dd, $J_1$ = 10.9 Hz, $J_2$ = 5.1 Hz, 1H), 4.21 (dd, $J_1$ = 10.9 Hz, $J_2$ = 3.1 Hz, 1H), 4.75-4.97 (bs, 1H), 7.52 (d, *J* = 5.6 Hz, 1H), 7.60 (ddd, $J_1$ = 8.2 Hz, $J_2$ = 6.9 Hz, $J_3$ = 1.1 Hz, 1H), 7.67 (ddd, $J_1$ = 8.2 Hz, $J_2$ = 6.9 Hz, $J_3$ = 1.1 Hz, 1H), 7.82 (d, *J* = 8.2 Hz, 1H), 8.16 (d, *J* = 8.2 Hz, 1H), 8.38 (d, *J* = 5.6 Hz, 1H); $^{13}$CNMR (100 MHz, $CDCl_3$, 25°C): δ= 17.8, 37.2, 66.3, 119.5, 124.7, 126.4, 127.2, 127.5, 130.0, 136.4, 140.9, 165.3; ESI-MS: *m/z* = 188.1 $[M+H]^+$; HMRS calcd for $C_{12}H_{13}NO$ : 187.09971; found 187.09964.

**Determination of the relative configuration of 29a**

To determine the relative configuration of the obtained products **26**, **27** and **28**, the oxazolidinone **31a** was prepared starting from **29a**. The major and the minor diastereoisomers were separated by preparative TLC and the relative configuration of the stereogenic centers 1 and 2' was determined by NOESY1D NMR analysis.




**Preparation of the oxazolidinone:** In a 5 mL vial equipped with stirring bar, **29a** (dr *syn*:*anti* 2.57:1.0) (0.06 mmol, 12.0 mg) was dissolved in 1 mL of $CH_2Cl_2$. The solution was cooled to 0°C and 1 mL of a saturated solution of $NaHCO_3$ was added under vigorous agitation. Then triphosgene (0.24 mmol, 56 mg) was added in two portions after a two hours gap. After six hours the reaction was allowed to warm to room temperature overnight. $Et_2O$ (10 mL) and water (1 mL) were added and the organic layer was separated. The aqueous layer was extracted with $Et_2O$ (2 x 5 mL). The combined organic layers were washed with brine (5 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude

product was purified with preparative thin layer chromatography on silica (cyclohexane/AcOEt 6/4) to afford product **31a** in 64% yield.

**(31a)** $^{1}$H NMR (400 MHz, $CDCl_3$, 25°C): $\delta_{syn}$ = 0.78 (d, $J$ = 6.8 Hz, 3H), 2.48-2.57 (m, 1H), 2.65-2.74 (m, 1H), 2.89-3.00 (m, 2H), 4.21 (dd, $J_1$ = 10.7 Hz, $J_2$ = 1.9 Hz, 1H), 4.52 (dd, $J_1$ = 10.7 Hz, $J_2$ = 2.4 Hz, 1H), 4.68-4.73 (m, 1H), 4.99 (d, $J$ = 3.8 Hz, 1H), 7.10-7.29 (m, 4H); $\delta_{anti}$ = 1.32 (d, $J$ = 6.9 Hz, 3H), 2.46-2.56 (m, 1H), 2.79 (dt, $J_1$ = 15.9 Hz, $J_2$ = 4.9 Hz, 1H), 3.04-3.13 (m, 1H), 3.18-3.26 (m, 1H), 3.98 (dd, $J_1$ = 10.8 Hz, $J_2$ = 8.3 Hz, 1H), 4.14 (dd, $J_1$ = 10.8 Hz, $J_2$ = 3.8 Hz, 1H), 4.22 (dt, $J_1$ = 12.7 Hz, $J_2$ = 5.3 Hz, 1H), 4.32 (d, $J$ = 6.7 Hz, 1H), 7.18-7.28 (m, 4H); $^{13}$C NMR (100 MHz, $CDCl_3$, 25°C): $\delta_{syn}$ = 16.2, 28.5, 31.9, 43.8, 60.3, 69.3, 126.5, 126.7, 127.5, 129.0, 135.9, 136.5, 153.7; $\delta_{anti}$ = 10.2, 29.0, 32.1, 41.3, 58.4, 70.9, 124.1, 125.3, 126.8, 129.3, 133.9, 135.6, 152.8; ESI-MS: $m/z$ = 218.1 $[M+H]^+$, 435.2 $[2M+H]^+$, 457.1 $[2M+Na]^+$; HMRS calcd for $C_{13}H_{15}NO_2$ : 217.11028; found 217.11014.

Selective excitation of the C1 methyl signal of the major diastereoisomer, shows a positive n.O.e. on the proton $H^{11}$ that could be estimated 0.2 considered 100 the intensity of the irradiated signal. The same analysis was conducted on the minor diastereoisomer and a positive n.O.e. was observed for the proton $H^{11}$ with an intensity of 2.1 considered 100 the intensity of the irradiated signal. On the basis of this evidence the relative configuration *syn* was assigned to the major diastereoisomer and the relative configuration *anti* was assigned to the minor diastereoisomer.

**Figure S1.** Major diasteroisomer *syn* **31a** (Obtained 600 MHz in $CDCl_3$ using a DPFGSE-NOE sequence with a 50 Hz 'rsnob' pulse and a mixing time of 2 s)

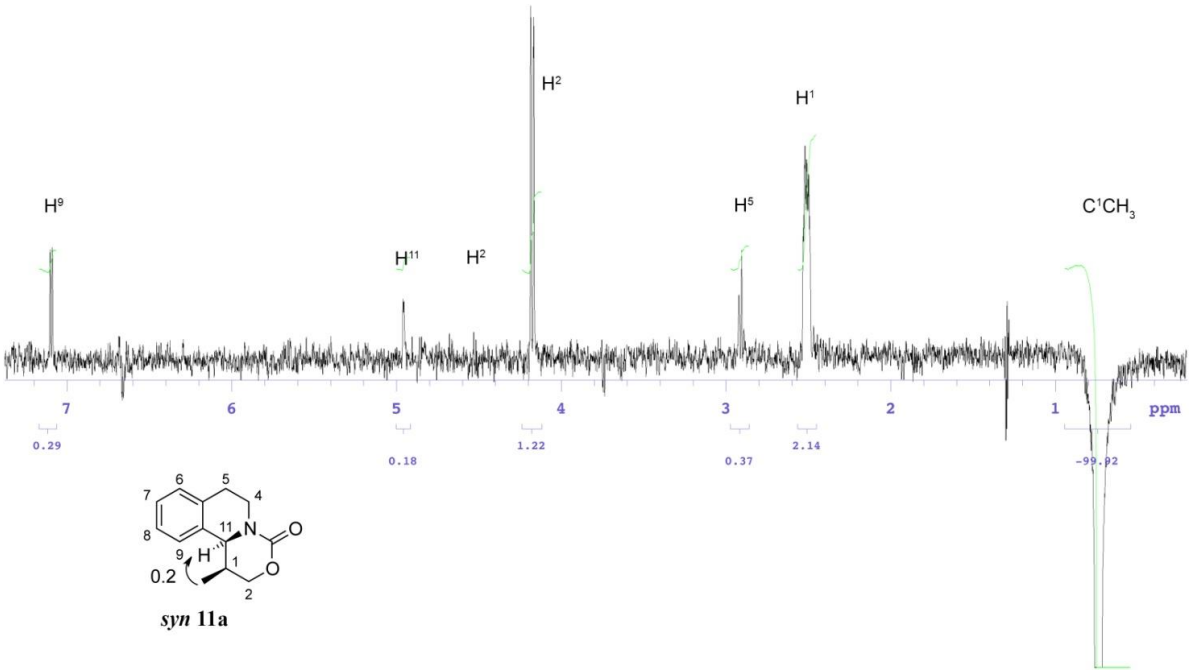
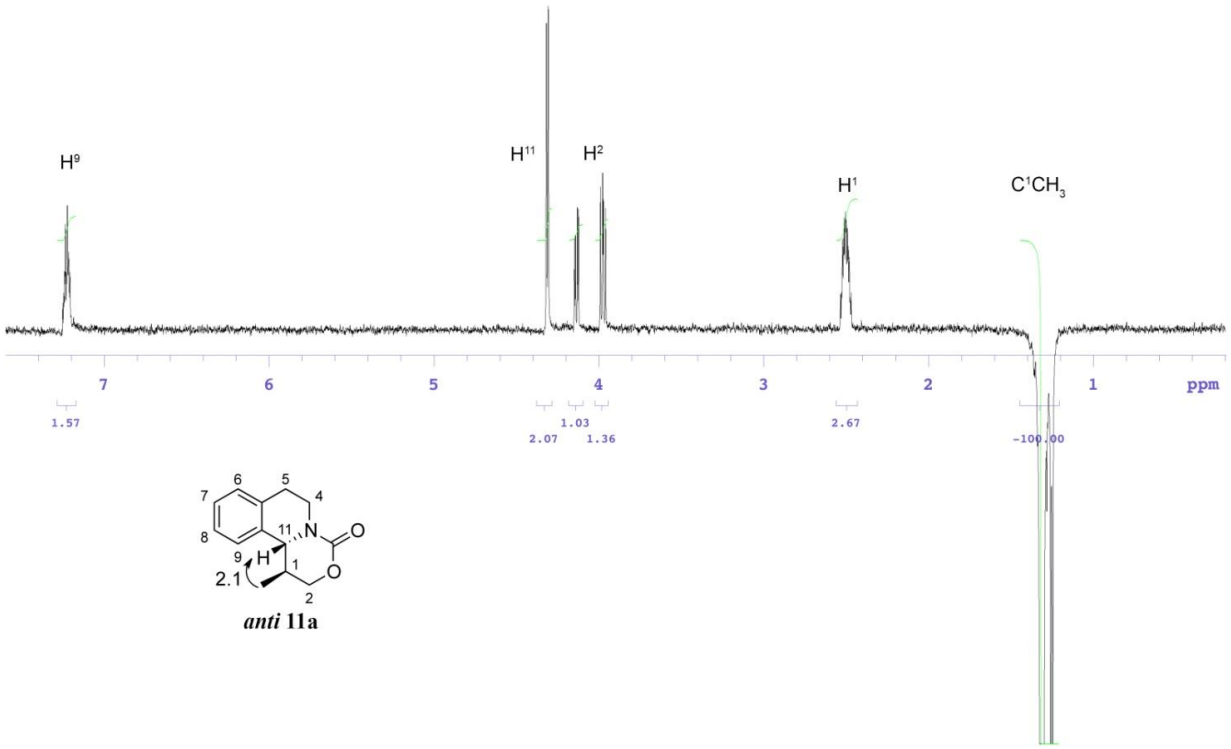
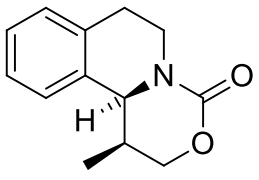
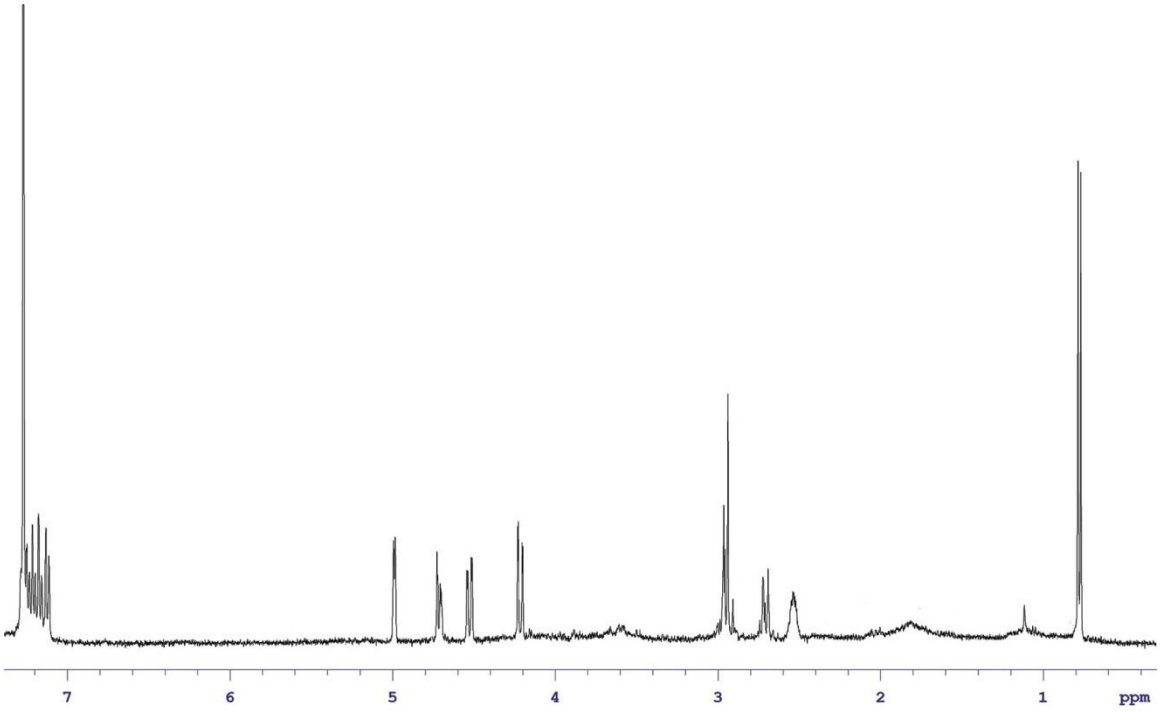


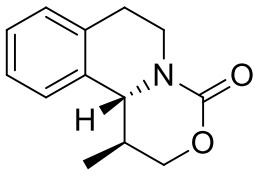

**Figure S2.** Minor diasteroisomer *anti* **31a** (Obtained 600 MHz in $CDCl_3$ using a DPFGSE-NOE sequence with a 50 Hz 'rsnob' pulse and a mixing time of 2 s)



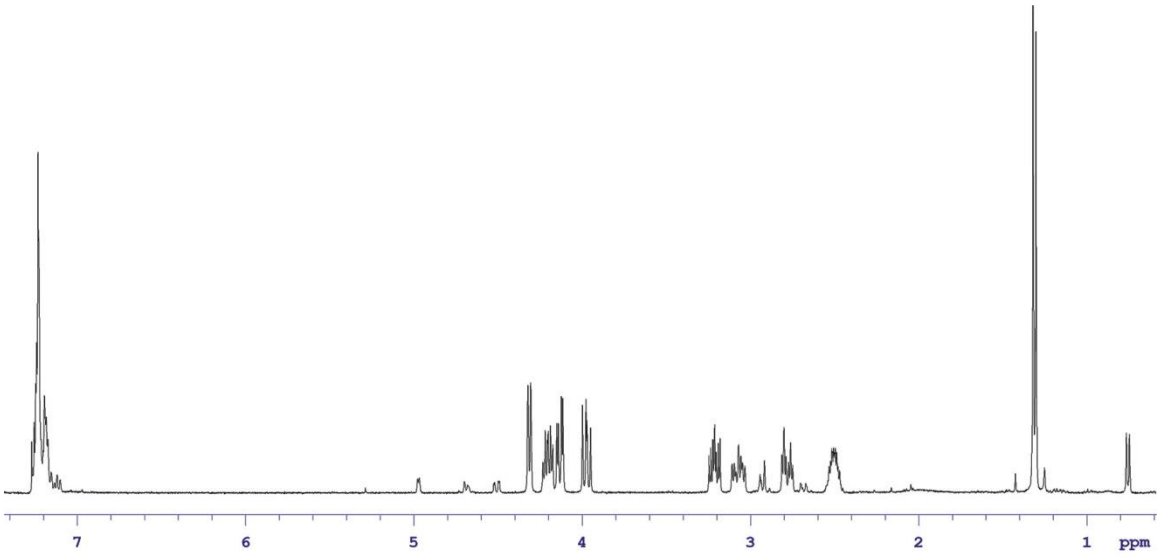


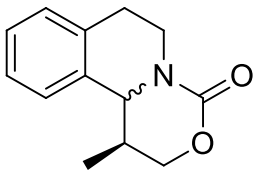

*syn*-**31a**



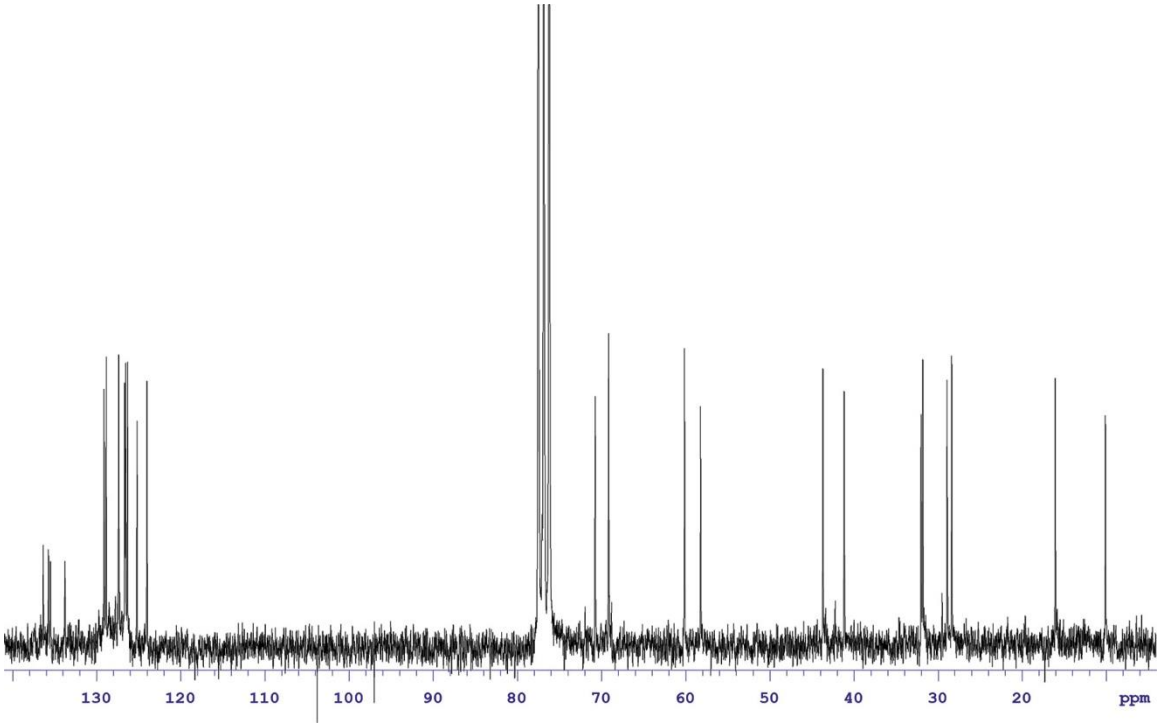




*anti*-**31a**



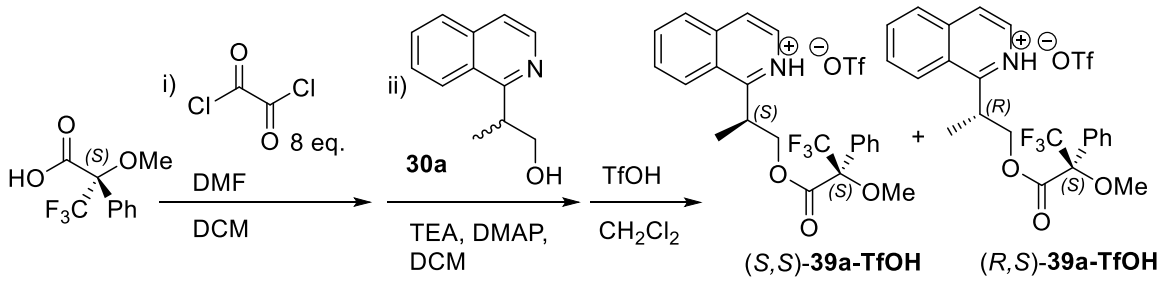


**31a,** *syn-anti* 1.2:1




**Determination of the absolute configuration of 30a**

To determinate the absolute configuration of the products **26, 27** and **28** the α-methoxy-α-trifluoromethylphenylacetyl (MPTA) esters of **30a** was prepared. As during the rearomatisation the stereogenic center on the C1 position of the tetrahydroisoquinoline is lost, the obtained result indicates that the remaining stereocenter has the same absolute configuration for both the obtained diastereoisomers. Furthermore, considering that **29a** was obtained with the same relative configuration of the major diastereoisomer starting either from **26a** or from **27a**, the configuration of the stereocenters of the compounds obtained using either $Boc_2O$ or CbzCl is the same.




(**39a-TfOH**). In a Schlenk tube under nitrogen atmosphere equipped with a stirring bar, (*S*)-MPTA (0.2 mmol, 46.8 mg) and DMF (0.005 mmol, 0.3 μL) were dissolved in 400 μL of dichloromethane. Then oxalyl chloride (1.6 mmol, 137 μL) was added and the solution was stirred for 4 hours. Subsequently the solvent and the excess of oxalyl chloride were evaporated under reduced pressure. To the residue a solution of racemic alcohol **30a** (0.1 mmol, 18.7 mg), triethylamine (0.4 mmol, 56 μL) and 4-dimethylaminopyridine (0.02 mmol, 2.5 mg) in dichloromethane (500 μL) were added under nitrogen atmosphere. The mixture was stirred overnight, then a solution of satured $NaHCO_3$ (2 mL) and $Et_2O$ (10 mL) were added and the organic layer was separated. The aqueous layer was extracted with $Et_2O$ (2 x 10 mL). The combined organic layers were washed with brine (5 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified with preparative thin layer chromatography on silica (cyclohexane/AcOEt 8/2) to afford product **39a** as 1:1 mixture of the two diastereoisomers.

Mosher ester **39a** was dissolved in DCM (2 mL) and trifluoromethansulfonic acid (0.1 mmol, 9 μL) was added under stirring. After two hours the solvent and the excess of trifluoromethansulfonic acid were evaporated under reduced pressure to afford triflate salt **39a·TfOH** in quantitative yield.

The same procedure was used to obtain Mosher ester **39a·TfOH** as single diastereoisomer (quantitative yield) using active alcohol **30a** (ee 93%) as starting material. The $^1$HNMR samples were prepared dissolving **39a·TfOH** in solution of deuterated chloroform and deuterated acetonitrile in a 2.5/1.0 ratio.

The absolute configuration of chiral centers of primary alcohols with a branched methyl at C2 could be determinate by Modified Mosher's method.[74]

$^1$HNMR spectra of the mixture of (*S,S*)-**39a·TfOH** and (*R,S*)-**39a·TfOH** showed a clear separation between one of C1 methylene protons relative to the two diasteroisomer.

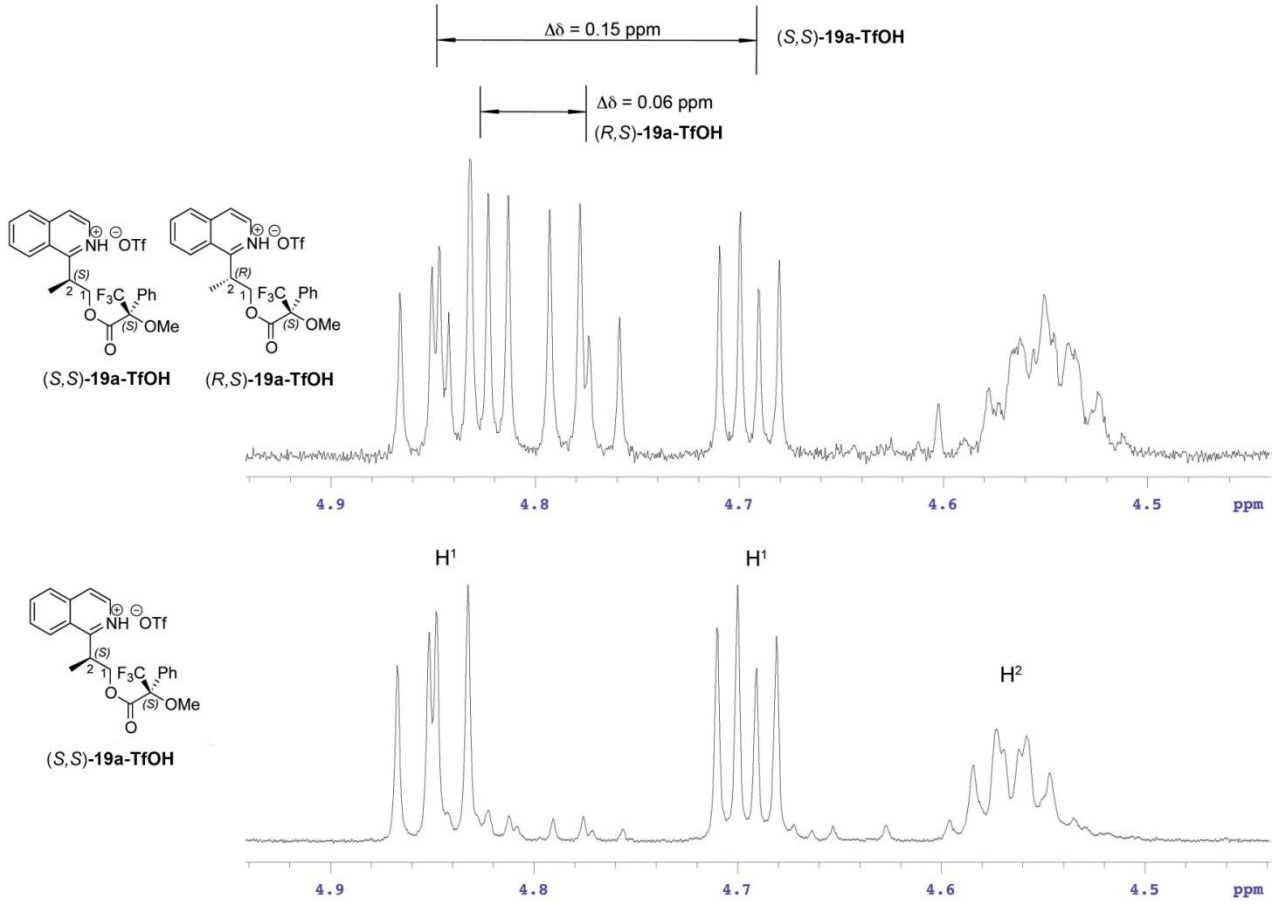
From the literature, in (*S*)-MPTA ester of a C2 branched primary alcohol the distance between the double doublet signals for the diastereomeric protons on C1 is larger if the absolute configuration of the

C2 chiral center is *S*, while it is closer for the *R* stereoisomer. The reverse is also true for the (*R*)-MPTA ester. Considering this, it is possible to attribute the correct diastereoisomer to $^1$H NMR signals: the double doublet signals for the diastereomeric protons of (*R,S*)-**39a·TfOH** were closer (0.06 ppm), while the same signal relative to (*S,S*)-**39a·TfOH** were more separated (0.15 ppm).

The same analysis was conducted to **39a·TfOH** prepared from enantioriched **27a** (see above) obtained from the organocatalytic alkylation of isoquinoline. Based on the $^1$H NMR signals it is possible to attribute (*S*) absolute configuration of the stereocenter in the C2 position. In conclusion the absolute configuration of the *syn*-**27a** was assigned (2'*S*,1*S*) while for the *anti*-**27a** was (2'*S*,1*R*). The same absolute configuration were suggested for **26a-c**, **27a-h** and **28b-i**.

**Note**: free **29a** did not present an adequate splitting of the two diasteroisomeric protons for the assignment of the absolute configuration.

**Figure S3.** $^1$H NMR (600 MHz, $CDCl_3/CD_3CN$ 2.5/1, 25°C) spectra of (*S,S*)+(*R,S*)-**39a·TfOH** above and (*S,S*)-**39a·TfOH** below.



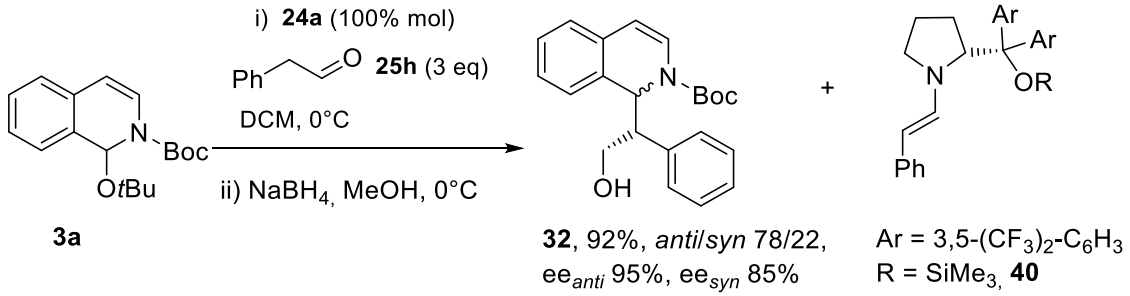

**Synthesis of (+)-13-methyl tetrahydroprotoberberine 1g using Boc as activating group.**

The alkylation reaction of adduct **23a** with phenylacetaldehyde **23h** afforded **32** as mixture of diastereoisomers. After reduction of the enamide double bond, *syn*-**33** and *anti*-**33** were separated. Starting from *anti*-**13**, 13-methyl tetrahydroprotoberberine **1g** was obtained, while *syn*-**33** lead to product **45** (diastereoisomer of **1g**).

Compound **1g** was synthesized in both active and racemic form, while **45** was synthesized in racemic form.

The relative configuration of the enamides **37** and **44** was determined by n.O.e analysis.

**Synthesis of active 32.**



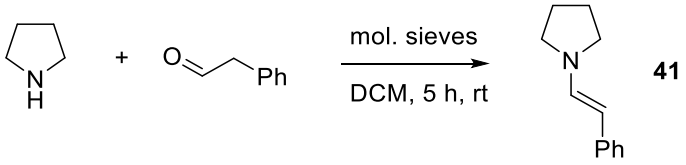

**(32):** To a 5 mL vial equipped with a magnetic stirring bar, $CH_2Cl_2$ (1 mL), phenylacetaldehyde **25h** (0.6 mmol, 68 μL) and **24a** (0.2 mmol, 120 mg) were added. After 5 h the reaction mixture was cooled at 0°C and **23a** (0.2 mmol, 60.6 mg) was added. 500 μL MeOH and $NaBH_4$ (1.2 mmol, 48 mg) were added after 16 hours. When reduction reaction was complete (monitored by TLC), the reaction was quenched with aqueous HCl 1M until pH = 1. The mixture was diluted with diethyl ether (3 mL), the organic layer was separated and the aqueous layer was extracted with $Et_2O$ (2 x 3 mL). The collected organic layers were washed with brine, dried on $MgSO_4$ and concentrated under reduced pressure. The crude mixture was purified by column chromatography on silica gel (cyclohexane/ethyl acetate 90/10) to afford **32** (64.7 mg, 92% yield, colourless oil) and enamine **40** as yellowish oil (112 mg, 0.16 mmol, 80% recovered catalyst).

**(32):** diastereomeric ratio 77/23 (*anti*-**32**:*syn*-**32**); *anti* diastereoisomer ee = 95%; *syn* diastereoisomer ee = 66%. The d.r. and e.e. were determined by HPLC analysis Daicel Chiralcel AD column: hexane/*i*-PrOH 95:5 for 20 min, then gradient elution from 95:5 to 85:5 in 10 min, flow rate 0.70 mL/min, 40°C, λ = 295 nm: *anti* diastereoisomer $\tau_{major}$ = 29.93 min., $\tau_{minor}$ = 15.60 min.; *syn* diastereoisomer $\tau_{major}$ = 19.74 min., $\tau_{minor}$ = 24.17 min. $^1$H NMR (400 MHz, $CDCl_3$, 25°C): $\delta_{anti}$ (two rotamers A:B, 9:1 ratio) = 1.57 (s, 9H$_A$), 1.60 (s, 9H$_B$), 2.50-2.76 (bs, 1H), 2.98-3.04 (m, 1H), 3.76 (dd, $J_1$ = 12.2 Hz, $J_2$ = 2.9 Hz, 1H), 3.93 (dd, $J_1$ = 12.2 Hz, $J_2$ = 4.9 Hz, 1H), 5.44 (d, $J$ = 9.8 Hz, 1H$_B$), 5.59 (d, $J$ = 9.8 Hz, 1H$_A$), 5.94 (d, $J$ = 7.7 Hz, 1H$_A$), 5.99 and 5.88 (d, $J$ = 7.7 Hz, 1H$_B$), 6.27 (d, $J$ = 7.7 Hz, 1H$_A$), 6.40 (d, $J$ = 7.7 Hz, 1H$_B$), 6.77 (d, $J$ = 7.7 Hz, 1H), 6.88-6.94 (m, 1H), 6.97-7.34 (m, 7H); $\delta_{syn}$= 1.44 (s, 9H), 2.50-2.76 (bs, 1H), 3.05-3.15 (m, 1H), 3.73-3.76 (m, 1H), 3.88-3.96 (m, 1H), 5.44 (d, $J$ = 7.7 Hz,1H), 5.78 (d, $J$ = 5.6 Hz,1H), 6.52 (d, $J$ = 7.7 Hz,1H), 6.74-6.77 (m,1H), 6.88-6.94 (m, 1H), 6.97-7.34 (m, 7H); $^{13}$C NMR (100 MHz, $CDCl_3$, 25°C): $\delta_{anti}$ (two rotamers A:B, 9:1 ratio) = 27.7 (3C$_B$), 28.2 (3C$_A$), 46.3 (1C$_B$), 49.8 (1C$_A$), 56.0 (1C$_A$), 56.5 (1C$_B$), 61.0 (1C$_B$), 63.0 (1C$_A$), 79.9 (1C$_B$), 82.5 (1C$_A$), 109.6 (1C$_B$), 109.9 (1C$_A$), 124.1 (1C$_A$), 124.2 (1C$_A$), 125.2 (1C$_B$), 125.7 (1C$_B$), 125.9 (1C$_A$), 126.2 (1C$_B$), 126.3 (1C$_B$), 126.5 (1C$_B$), 126.7 (1C$_A$), 127.3 (1C$_A$), 127.4 (1C$_B$), 127.5 (1C$_A$), 127.7 (1C$_A$), 127.9 (2C$_A$), 128.0

($2C_B$), 128.41 ($1C_B$), 128.43 ($1C_B$), 129.5 ($1C_A$), 130.0 ($1C_A$), 130.6 ($1C_A$), 134.6 ($1C_B$), 134.7 ($1C_B$), 139.6 ($1C_A$), 142.3 ($1C_B$), 153.0 ($1C_B$), 153.3 ($1C_A$); $\delta_{syn}$ = 28.1 (3C), 54.4, 55.2, 61.8, 81.9, 108.6, 124.4, 125.8, 126.6, 126.8, 126.9, 127.6, 128.3, 128.5, 129.1 (2C), 131.0, 131.2, 137.8, 157.1; ESI-MS: *m/z* = 374.0 $[M+Na]^+$, 390.2 $[M+K]^+$.

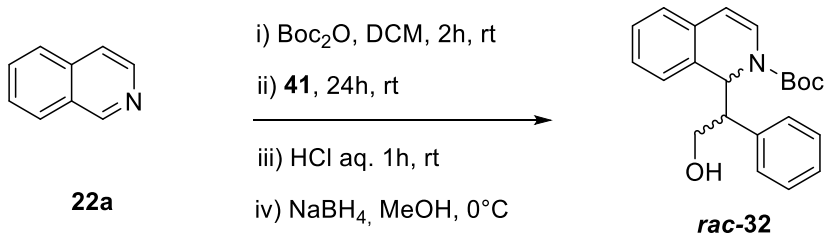
**(40)**: $^1$H NMR (400 MHz, $CDCl_3$, 25°C): $\delta$ = -0.14 (s, 9H), 0.33-0.47 (m, 1H), 1.50-1.62 (m, 1H), 1.76-1.86 (m, 1H), 2.11-2.23 (m, 1H), 2.52 (td, $J_1$ = 9.1 Hz, $J_2$ = 2.8 Hz, 1H), 2.94 (q, $J$ = 10.5 Hz, 1H), 4.63 (dd, $J_1$ = 9.1 Hz, $J_2$ = 1.5 Hz, 1H), 5.12 (d, $J$ = 13.9 Hz, 1H), 6.97-7.25 (m, 4H), 7.74-8.03 (m, 8H).

**Preparation of enamine 41.**




In a two necked round bottomed flask, molecular sieves 4 Å (1g) were heated under vacuum for 10 minutes. Then the flask was cooled at room temperature and filled with nitrogen. DCM (5 mL), phenylacetaldehyde (10 mmol, 1.11 mL), pyrrolidine (10 mmol, 830 µL) and *p*-toluenesulfonic acid monohydrate (0.1 mmol, 19 mg) were added. After 1 hour the yellow and sluggish solution became clear. After 5 hours the solution was filtered through Celite pad under nitrogen atmosphere and concentrated to give enamine **41** as a yellow oil in quantitative yield. It was used without further purification in the next steps and it can be stored under nitrogen atmosphere for several weeks without any appreciable hydrolysis. Spectroscopic data was according to the literature.[75]

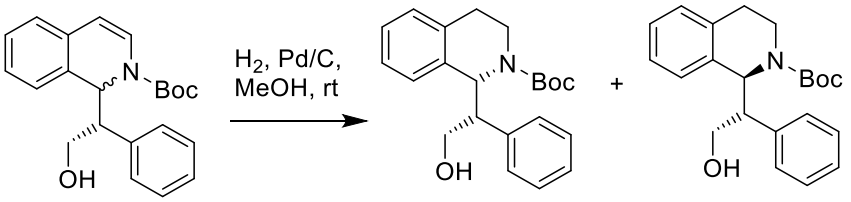
**Synthesis of racemic 32**




To a solution of isoquinoline **22a** (8.67 mmol 1.02 mL) in DCM (5 mL), $Boc_2O$ (8.67 mmol, 2.0 mL) was added. The resulting solution was stirred for 2 hours at room temperature, then enamine **41** (8.67

mmol, 1.5 g) was added. After 24 hours the reaction was quenched with HCl 1M (10 mL) and the mixture was vigorously stirred for 1 hour. The organic phase was separated and the aqueous layer was extracted with DCM (2 x 8 mL). The collected organic layers were dried over $Na_2SO_4$. The residue was diluted with MeOH (3 mL) and cooled to 0°C, then $NaBH_4$ (13 mmol, 494 mg) was added. After 2 hours complete conversion was observed by TLC analysis and the reaction was quenched by careful addition of HCl 1M until pH = 1. The organic layer was separated and the aqueous layer was extracted with DCM (2 x 10 mL). The collected organic layers were dried over $Na_2SO_4$ and concentrated under vacuum. The crude product was purified by column chromatography on silica gel (cyclohexane/ethyl acetate 90/10) to afford racemic **32** (974 mg, 2.77 mmol, 32% yield, diastereomeric ratio *anti-syn* 75:25) as colourless oil.

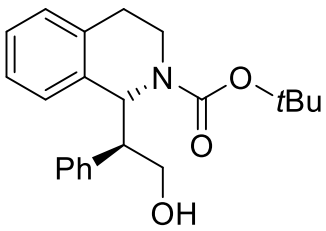
**Preparation of compounds 33**




**32**, 92%, *anti*/*syn* 78/22, $ee_{anti}$ 95%, $ee_{syn}$ 85% ***anti*-33**, 54% ***syn*-33**, 23%

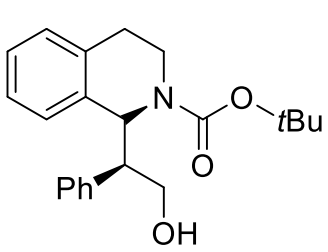
In a 25 mL two necked round bottomed flask, **32** (0.57 mmol, 200 mg), MeOH (5 mL) and 10% Pd/C (50%, 100 mg) were sequentially added and kept under $H_2$ (1 atm). The reaction mixture was stirred for 16 hours, then it was filtered through Celite pad and was washed with DCM (15 mL). The solvent was removed under reduced pressure to afford a mixture of ***syn*-33** ($R_f$ = 0.4, 8:2 cyclohexane:ethyl acetate) and ***anti*-33** ($R_f$ = 0.2). The two diasteroisomers were separated by column chromatography (cyclohexane/ethyl acetate 85/15).

The same procedure was followed to obtain racemic ***anti*-33** and ***syn*-33**.



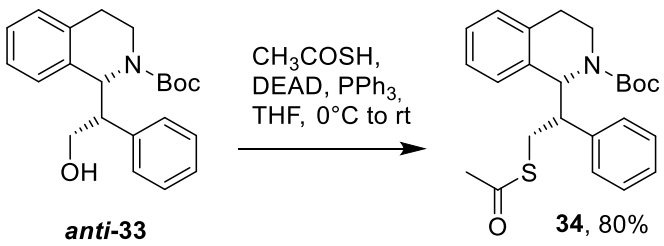

**(*anti*-33)**: sticky white solid, 109 mg, 54% yield; $[\alpha]_D^{20}$ = -37.3 (c=1.4, $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$, 25°C) (two rotamers A:B, 8:1 ratio): $\delta_{anti}$ = 1.53 (s, 9H), 2.50-2.61 (m, $2H_B$), 2.79-2.90 (m, $2H_A$), 2.90-2.97 (m, 1H), 3.21-3.30 (m, $1H_B$), 3.40-3.49 (m, $1H_B$), 3.61-3.69 (m, $2H_A$), 3.82 (dd, $J_1$ = 11.9 Hz, $J_2$ = 3.0 Hz, 1H), 3.86-3.98 (bs, 1H), 4.07 (dd, $J_1$ = 11.9 Hz,

$J_2$ = 4.5 Hz, 1H), 5.29 (d, $J$ = 6.2 Hz, 1$H_B$), 5.43 (d, $J$ = 10.2 Hz, 1$H_A$), 6.31 (d, $J$ = 7.9 Hz, 1$H_A$), 6.37 (d, $J$ = 5.7 Hz, 1$H_B$), 6.76-6.82 (m, 1$H_A$), 6.84-6.92 (m, 1$H_B$), 7.02-7.13 (m, 2H), 7.15-7.23 (bs, 4H), 7.25-7.30 (bs 1H); $^{13}$C NMR (100 MHz, $CDCl_3$, 25°C) (two rotamers A:B, 8:1 ratio): $\delta_{anti}$ = 27.9, 28.4 (3C), 39.6 (1$C_B$), 41.3 (1$C_A$), 53.5 (1$C_A$), 54.2 (1$C_B$), 56.8 (1$C_A$), 58.0 (1$C_B$), 63.8, 80.6, 125.3, 126.8 (2C), 127.6, 128.1 (2C), 128.3, 129.5 (2C), 134.4 (1$C_A$), 134.9 (1$C_B$), 135.4 (1$C_B$), 136.0 (1$C_A$), 139.8 (1$C_B$), 140.6 (1$C_A$), 155.2 (1$C_B$), 156.7 (1$C_A$); ESI-MS: *m/z* = 376.2 $[M+Na]^+$, 392.2 $[M+K]^+$, 729.4 $[2M+Na]^+$.




**(*syn*-33)** colourless oil, 47 mg, 23% yield; $[\alpha]_D^{20}$ = +4.7 (c=0.8, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$, 25°C): $\delta$ (two rotamers A:B, 9:1 ratio) = 1.50 (s, 9H), 1.85 (dt, $J_1$ = 16.1 Hz, $J_2$ = 5.6 Hz, 1H), 2.40-2.50 (m, 1$H_A$), 2.51-2.58 (m, 1$H_B$), 2.64-2.72 (m, 1$H_A$), 2.73-2.84 (m, 1$H_B$), 3.34-3.40 (m, 1H), 3.59 (dt, $J_1$ = 13.1 Hz, $J_2$ = 5.7 Hz, 1H), 3.81 (dd, $J_1$ = 11.9 Hz, $J_2$ = 4.9 Hz, 1$H_A$), 3.86-4.05 (m, 2$H_B$), 4.10 (t, $J$ = 11.4 Hz, 1$H_A$), 4.43-4.63 (bs, 1H), 5.41 (d, $J$ = 4.2 Hz, 1$H_B$), 5.65 (d, $J$ = 3.4 Hz, 1$H_A$), 6.84 (d, $J$ = 6.8 Hz, 2H), 6.94 (d, $J$ = 7.8 Hz, 1H), 7.09-7.19 (m, 4H), 7.20-7.36 (m, 1H), 7.42 (d, $J$ = 7.8 Hz, 1H); $^{13}$C NMR (50 MHz, $CDCl_3$, 25°C) (two rotamers A:B, 4:1 ratio): $\delta_{syn}$ = 27.8, 28.3 (3$C_A$), 28.5 (3$C_B$), 40.9, 45.8, 54.5, 62.4, 79.5 (1$C_B$), 80.5 (1$C_A$), 126.2, 126.5, 126.9, 127.3, 128.0 (2C), 128.3, 128.9 (2C), 135.3, 136.1, 138.5, 154.8 (1$C_B$), 157.3 (1$C_A$); ESI-MS: *m/z* = 376.2 $[M+Na]^+$, 392.2 $[M+K]^+$, 729.4 $[2M+Na]^+$.

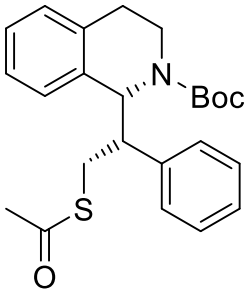
**General procedure for the Mitsunobu reaction.**




***anti*-33** **34**, 80%

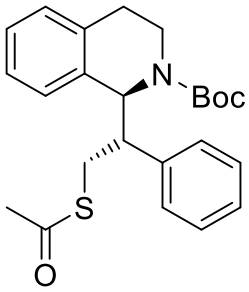
**(34).** In a 10 mL round bottomed flask under nitrogen atmosphere, triphenyl phosphine (1.21 mmol, 317 mg) was dissolved in 1 mL THF at 0°C. Then diethyl diazodicarboxylate (DEAD) (40% solution in toluene, 1.24 mmol, 568 μL) was slowly added and the solution stirred for 30 min. while its color turned from yellow to orange. A solution of thioacetic acid (1.24 mmol, 90 μL) and ***anti*-33** (0.31 mmol, 109 mg) in 1 mL THF, was rapidly added to the reaction mixture, whose color changed rapidly to dark brown and then to yellow. After 30 min the reaction mixture was allowed to warm to room temperature and stirred for 15 hours. The solvent was evacuated under vacuum, the solid residue dissolved in DCM (3 mL) and revacuated under vacuum for three times to eliminate any trace of thioacetic acid. The crude mixture was purified by column chromatography (cyclohexane/diethyl ether from 95/5 to 90/10) to afford the desired product.

The same procedure was followed to obtain racemic **34.**



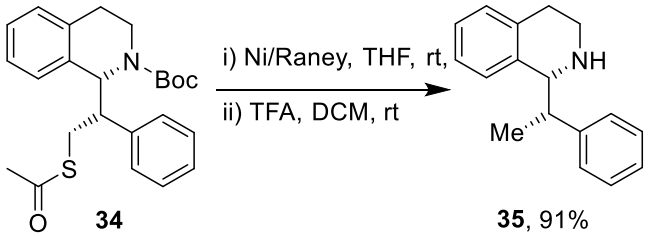

**(34):** pinkish oil, 80% yield (102.5 mg), $[\alpha]_D^{20}$ = + 42.2 (c=1.1, $CHCl_3$). $^1H$ NMR (400 MHz, $CDCl_3$, 25°C): $\delta$ (two rotamers A:B, 1.4:1 ratio) = 1.53 (s, $9H_A$), 1.57 (s, $9H_B$), 2.24 (s, $3H_B$), 2.25 (s, $3H_A$), 2.44-2.56 (m, $2H_B$), 2.68-2.85 (m, $2H_A$), 3.00-3.09 (m, $2H_B$), 3.12-3.24 (m, $2H_A$), 3.49-3.88 (m, 3H), 5.22 (d, $J$ = 9.7 Hz, $1H_B$), 5.35 (d, $J$ = 9.7 Hz, $1H_A$), 6.19 (d, $J$ = 7.9 Hz, $1H_B$),6.30 (d, $J$ = 7.9 Hz, $1H_A$), 6.78-6.96 (m, 2H), 6.98-7.05 (bs, 1H), 7.06-7.18 (m, 2H), 7.21-7.28 (m, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$, 25°C): $\delta$ (two rotamers A:B, 1.4:1 ratio) = 27.5 ($1C_B$), 27.8 ($1C_A$), 28.4 ($3C_A$), 28.5 ($3C_B$), 30.4 ($1C_B$), 30.5 ($1C_A$), 32.2 ($1C_B$), 32.3 ($1C_A$), 39.7 ($1C_B$), 40.8 ($1C_A$), 51.5 ($1C_B$), 52.0 ($1C_A$), 59.6 ($1C_A$), 60.3 ($1C_B$), 79.9 ($1C_A$), 80.3 ($1C_B$), 125.1 ($1C_B$), 125.2 ($1C_A$), 126.9 ($1C_A$), 127.0 ($1C_B$), 127.1 ($1C_A$), 127.3 ($1C_B$), 127.7 ($1C_B$), 127.8 ($1C_A$), 127.9 ($1C_A$), 128.2 ($2C_A$ + $1C_B$), 128.3 ($2C_B$), 128.4 ($1C_B$), 128.9 ($1C_A$), 129.0 ($1C_B$), 129.1 ($1C_A$), 134.7 ($1C_A$), 135.0 ($1C_B$),

135.1 ($1C_B$), 135.7 ($1C_A$), 140.5 ($1C_B$), 140.9 ($1C_A$), 154.9 ($1C_B$), 155.9 ($1C_A$), 195.4 ($1C_B$), 196.0 ($1C_A$); ESI-MS: *m/z* = 434.2 $[M+Na]^+$, 845.2 $[2M+Na]^+$.




**(rac-42):** Obtained carrying out the Mitsunobu reaction on **rac-*syn*-33** following the procedure described for **34.** Pinkish oil, 87% yield; $^1H$ NMR (400 MHz, $CDCl_3$, 25°C): $\delta$ (two rotamers A:B, 1.1:1 ratio) = 1.37 (s, $9H_A$), 1.42 rotamer) (s, $9H_B$), 2.25 (s, 3H), 2.51-2.58 (m, 1H), 2.59-2.88 (m, 2H), 3.28-3.42 (m, 2H), 3.43-3.60 (m, $2H_A$), 3.78-3.89 (m, $2H_B$), 5.33 (bs, $1H_A$), 5.50 (bs, $1H_B$), 6.98-7.13 (m, 3H), 7.17-7.30 (m, 6H); $^{13}C$ NMR (50 MHz, $CDCl_3$, 25°C): $\delta$ (two rotamers, 1.1:1 ratio) = 27.6 ($1C_B$), 27.9 ($1C_A$), 28.3 (3C), 30.5, 32.4, 38.6 ($1C_A$), 40. ($1C_B$), 51.4 ($1C_A$), 51.9 ($1C_B$), 58.0 ($1C_A$), 59.3 ($1C_B$), 79.5 ($1C_B$), 80.3 ($1C_A$), 125.9, 127.0, 127.7, 127.9, 128.2, 128.6 (3C), 129.0, 134.9 ($1C_B$), 135.2 ($1C_A$), 136.1 ($1C_B$), 135.7 ($1C_A$), 139.2 ($1C_A$), 139.5 ($1C_B$), 154.9 ($1C_A$), 155.4 ($1C_B$), 195.9. ESI-MS: *m/z* = 434.2 $[M+Na]^+$, 845.2 $[2M+Na]^+$.

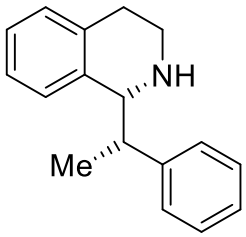
**Preparation of compound 35**



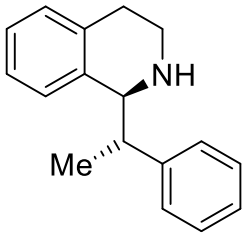

In a round bottomed flask, to a solution of **34** (0.25 mmol, 102.5 mg) in THF (4 mL), Ni/Raney (1.5 g, slurry in water) was added. The reaction mixture was stirred for 16 hours at room temperature until TLC analysis revealed complete conversion. The solution was separated and Nickel/Raney washed 4 times with DCM (5 mL). The collected organic phases were filtered through a Celite pad and concentrated under vacuum. The resulting oil was dissolved in DCM (750 μL) and trifluoroacetic acid (2.5 mL) was added. The solution was stirred at room temperature for 4 hours until complete conversion (monitored with TLC). The solvent was evaporated under reduce pressure and the residue was dissolved in DCM (10 mL) and washed with $NaHCO_3$ sat. sln. until basic pH. The organic layer was separated and the aqueous layer was extracted with DCM (3 x 10 mL). The collected organic layers were dried over $Na_2SO_4$ and concentrated under vacuum to give pure 14 (49.8 mg, 91% yield).

This compound is air sensitive, but it can be stored as its hydrochloride salt at -20°C for several weeks without any appreciable decomposition.

The same procedure was followed to obtain racemic **35.**

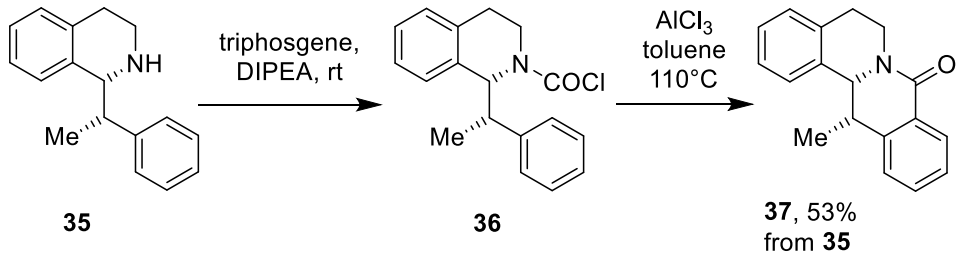



**(35):** Colourless oil, 49.8 mg, 91% yield, $[\alpha]_D^{20}$ = +31.4 (=1.1, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$, 25°C): $\delta$ = 1.18 (d, $J$ = 7.2 Hz, 3H), 1.72-1.80 (bs, 1H), 2.61-2.68 (m, 1H), 2.81 (dt, $J_1$ = 10.9 Hz, $J_2$ = 2.7 Hz, 1H), 2.90-3.00 (m, 1H), 3.13-3.20 (m, 1H), 3.50-3.58 (m, 1H), 4.25 (d, $J$ = 3.4 Hz, 1H), 7.08-7.29 (m, 5H), 7.33-7.39 (m, 4H); $^{13}$C NMR (100 MHz, $CDCl_3$, 25°C): $\delta$ = 12.7, 30.6, 42.7, 43.7, 61.8, 125.9, 126.1 (2C), 126.6, 128.4 (2C), 128.7 (2C), 129.4, 136.7, 138.0, 144.7; ESI-MS: *m/z* = 238.3 $[M+H]^+$.




**(rac-43):** Obtained from **42** following the procedure described for **35.** Colorless oil, 82% yield; $^1$H NMR (400 MHz, $CDCl_3$, 25°C): $\delta$ = 1.45 (d, $J$ = 6.7 Hz, 3H), 2.57-2.66 (m, 1H), 2.71-2.81 (m, 1H), 2.82-2.90 (m, 1H), 3.17-3.31 (m, 2H), 3.40 (dq, $J_1$ = $J_2$ = 6.7 Hz, 1H), 4.24 (d, $J$ = 6.7 Hz, 1H), 7.06-7.09 (m, 1H), 7.16-7.26 (m, 6H), 7.27-7.33 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$, 25°C): $\delta$ = 19.3, 29.2, 39.9, 44.0, 61.0, 125.1, 126.2, 126.4, 127.9 (2C), 127.9, 128.3 (2C), 129.1, 135.5, 137.0, 143.2; ESI-MS: *m/z* = 238.3 $[M+H]^+$.

**Preparation of compound 37.**




**35** **36** **37**, 53% from **35**

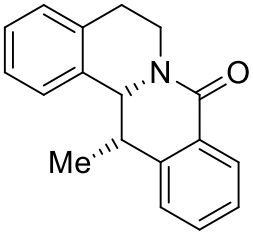
To a solution of **35** (0.20 mmol, 49.8 mg) in DCM (1 mL) under nitrogen atmosphere, triphosgene (0.11 mmol, 33 mg) and DIPEA (0.44 mmol, 76 μL) were subsequently added at room temperature. The reaction mixture was stirred for 16 hours until complete conversion was observed by TLC analysis. The solution was diluted with MeOH (500 μL) and $NaHCO_3$ sat. sln. (3 mL) was added after 10 min..

The organic phase was separated, and the aqueous layer was extracted with DCM (2 x 5 mL). The collected organic layers were washed with brine, dried over $Na_2SO_4$ and concentrated under vacuum.

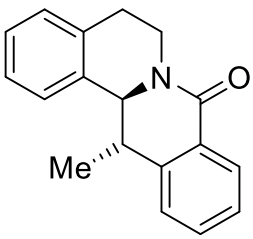
The obtained crude product (**36**) was dissolved in toluene (1 mL) in a sealed tube under nitrogen atmosphere and aluminium trichloride (0.36 mmol, 48 mg) was added. The reaction mixture was refluxed for 6 hours (until complete conversion was observed by TLC), was cooled at 0°C and quenched with ice. DCM (3 mL) was added, the organic phase was separated and the aqueous layer was extracted with DCM (4 x 3 mL). The collected organic layers were washed with brine, dried over $Na_2SO_4$ and concentrated under vacuum.

The crude mixture was purified by column chromatography (cyclohexane/ethyl acetate from 90/10 to 70/30) to give pure **37** (53% yield, 28 mg).

The same procedure was followed to obtain racemic **37.**

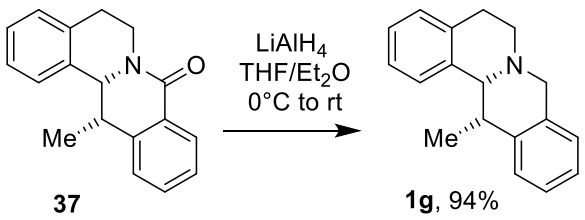



**(37):** Yellow sticky solid; $[\alpha]_D^{20}$ = +491 (c=1.9, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$, 25°C): $\delta$ = 0.83 (d, $J$ = 7.0 Hz, 3H), 2.78-2.89 (m, 1H), 2.90-3.03 (m, 2H), 3.21-3.29 (m, 1H), 4.98-5.03 (m, 1H), 5.13 (d, $J$ = 3.4 Hz, 1H), 7.20-7.33 (m, 5H), 7.38 (dt, $J_1$ = 7.8 Hz, $J_2$ = 1.3 Hz, 1H), 7.48 (dt, $J_1$ = 7.3 Hz, $J_2$ = 1.6 Hz, 1H), 8.16 (dd, $J_1$ = 7.8 Hz, $J_2$ = 1.3 Hz, 1H); $^{13}$C NMR (50 MHz, $CDCl_3$, 25°C): $\delta_{anti}$ = 14.7, 29.2, 38.1, 40.8, 58.6, 125.9, 126.3, 126.6, 126.8, 127.1, 127.9, 128.6, 128.8, 131.9, 134.5, 136.2, 144.1, 164.3; ESI-MS: *m/z* = 264.2 $[M+H]^+$, 286.2 $[M+Na]^+$, 549.2 $[2M+Na]^+$.




**(rac-44):** Obtained from **43** following the procedure described for **37.** Yellow sticky solid, 66% yield; $^1$H NMR (400 MHz, $CDCl_3$, 25°C): $\delta$ = 1.44 (d, $J$ = 7.2 Hz, 3H), 2.81-2.91 (m, 1H), 3.10-3.20 (m, 2H), 3.39 (p, $J$ = 6.9 Hz, 1H), 4.63 (d, $J$ = 6.4 Hz, 1H), 4.88-4.98 (m, 1H), 7.14-7.23 (m, 4H), 7.34 (t, $J$ = 7.5 Hz, 2H), 7.47 (dt, $J_1$ = 7.5 Hz, $J_2$ = 1.6 Hz, 1H), 8.09 (dd, $J_1$ = 8.4 Hz, $J_2$ = 1.7 Hz, 1H); $^3$C NMR (50 MHz, $CDCl_3$, 25°C): $\delta$ = 19.2, 29.3, 36.3, 41.9, 62.2, 125.7, 125.8, 126.3, 127.0, 127.3, 128.3, 128.5, 129.1, 132.1, 135.3, 136.8, 142.3, 164.4; ESI-MS: *m/z* = 264.2 $[M+H]^+$, 286.2 $[M+Na]^+$, 549.2 $[2M+Na]^+$.

**Preparation of compound 1g**

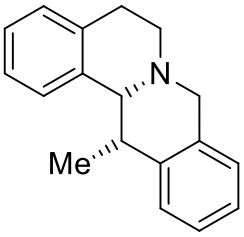



**37** **1g**, 94%

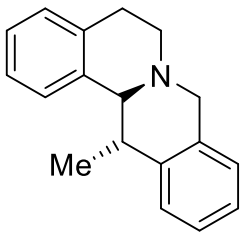
In a 10 mL round bottomed flask under nitrogen atmosphere, diethyl ether (600 μL) and $LiAlH_4$ (1 M in THF, 0.11 mmol, 110 μL) were added at 0°C. A solution of **37** (0.07 mmol, 18.8 mg) in THF (750 μL), was added dropwise, and the reaction mixture was allowed to warm to room temperature. After two hours complete conversion was observed by TLC analysis. The reaction mixture was cooled to 0°C and quenched following Fieser Method. The mixture was filtered through a Celite pad and was washed with DCM (15 mL). The collected organic layers were washed with brine, dried over $Na_2SO_4$ and concentrated under vacuum. The crude mixture was purified by column chromatography on silica gel (cyclohexane/ethyl acetate from 100/0 to 90/10) to give pure **1g** (94% yield, 16.4 mg). Such compound is air sensitive, but it can be stored as its hydrochloride salt at -20°C without any appreciable decomposition.

The same procedure was followed to obtain racemic **1g.**

The spectroscopic data for **1g** and **45** are according with literature,[76] confirming the relative configuration assigned for such compounds.




**(1g):** Colourless oil, $[\alpha]_D^{20}$ = +266 (c=1.0, $CHCl_3$); 95% e.e. determined by HPLC analysis Daicel Chiralcel OD-H column: hexane, flow rate 0.70 mL/min, 40°C, λ = 210 nm: $\tau_{major}$ = 21.51 min., $\tau_{minor}$ = 15.75 min.; $^1$H NMR (400 MHz, $CDCl_3$, 25°C): $\delta$ = 1.00 (d, $J$ = 6.8 Hz, 3H), 2.59-2.74 (m, 2H), 3.14-3.25 (m, 2H), 3.34-3.42 (m, 1H), 3.72 (d, $J$ = 14.7 Hz, 1H), 3.87 (bs, 1H), 4.07 (d, $J$ = 14.7 Hz, 1H), 7.07-7.29 (m, 8H); $^{13}$C NMR (50 MHz, $CDCl_3$, 25°C): $\delta$ = 18.3, 29.7, 38.8, 51.1, 58.9, 63.5, 125.7 (2C), 125.8, 126.0, 126.1, 126.2, 128.6, 128.9, 134.1, 136.0, 136.7, 141.5; ESI-MS: *m/z* = 250.2 $[M+H]^+$; HMRS calcd for $C_{18}H_{19}N$: 249.15175; found 249.15166.

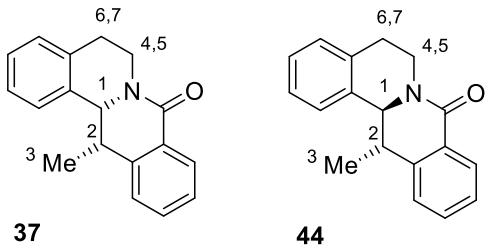


**(rac-45).** Obtained from **44** following the procedure described for **1g.** The title compound was isolated by column chromatography on silica gel (cyclohexane/ethyl acetate 70/30). Colourless oil, 84% yield; $^{1}$H NMR (400 MHz, $CDCl_3$, 25°C): $\delta$ = 1.53 (d, $J$ = 6.9 Hz, 3H), 2.82-2.91 (m, 1H), 2.96-3.08 (m, 2H), 3.09-3.20 (m, 2H), 3.79 (d, $J$ = 7.4 Hz, 1H), 3.85 (d, $J$ = 15.8 Hz, 1H), 4.23 (d, $J$ = 15.8 Hz, 1H), 7.08 (d, $J$ = 7.3 Hz, 1H), 7.13-7.31 (m, 7H); $^{13}$C NMR (100 MHz, $CDCl_3$, 25°C): $\delta$ = 22.2, 28.2, 35.0, 46.8, 56.5, 64.8, 125.2, 125.8, 126.5, 126.7, 126.8, 127.0, 127.7, 129.2, 132.8, 133.7, 138.0, 139.3; ESI-MS: $m/z$ = 250.2 $[M+H]^+$.

**Organocatalytic alkylation performed with recovered Jørgensen enamine 40**

In a 5 mL vial, chiral enamine **40** (0.1 mmol, 70 mg) and phenylacetaldehyde **25h** (0.2 mmol, 22 μL) were dissolved in DCM (500 μL) at 0°C. After 10 minutes, **23a** (0.1 mmol, 30 mg) was added and the solution was stirred for 16 hours at 0°C. Then MeOH (250 μL) and $NaBH_4$ (0.6 mmol, 23 mg) were added and the reaction was stirred until TLC analysis showed complete conversion. The reaction was quenched with aqueous HCl 1M until pH = 1. The mixture was diluted with diethyl ether (3 mL), the organic layer was separated and the aqueous layer was extracted with $Et_2O$ (2 x 3 mL). The collected organic layers were washed with brine, dried on $MgSO_4$ and concentrated under reduced pressure. The title compound was purified by column chromatography on silica gel (90:10 cyclohexane/ethyl acetate) to afford product **32** (Rf = 0.4, 8:2 cyclohexane/ethyl acetate, 0.099 mmol, 34.7 mg, 99% yield) and enamine **40** ($R_f$ = 0.7 eluting mixture 8:2 cyclohexane/ethyl acetate, 53 mg, 0.076 mmol, 76% recovered catalyst).

**Determination of the relative configurations of amides 17 and 24**




**37** **44**

The $^{1}$HNMR signals of **37** and **44** were assigned by g-COSY experiments of such compounds (Figure S4 and S6).

The relative configuration was established by comparison of the 1DNOESY NMR experiments carried on these two compounds.

Selective excitation of the $Me^{3}$ signal of **37**, showed a positive n.O.e on the proton $H^{1}$ that could be estimated 0.26 considering 100 the intensity of the irradiated signal (Figure S5).

Instead, when the same experiment was conducted on **44**, the positive n.O.e observed was respectively 1.14 (Figure S7).

On the basis of such results the relative configuration of **37** (referred to the protons $H^{1}$ and $H^{2}$) was assigned *syn*, while the relative configuration of **44** was assigned *anti*.

**Figure S4:** g-COSY spectra of **17.**

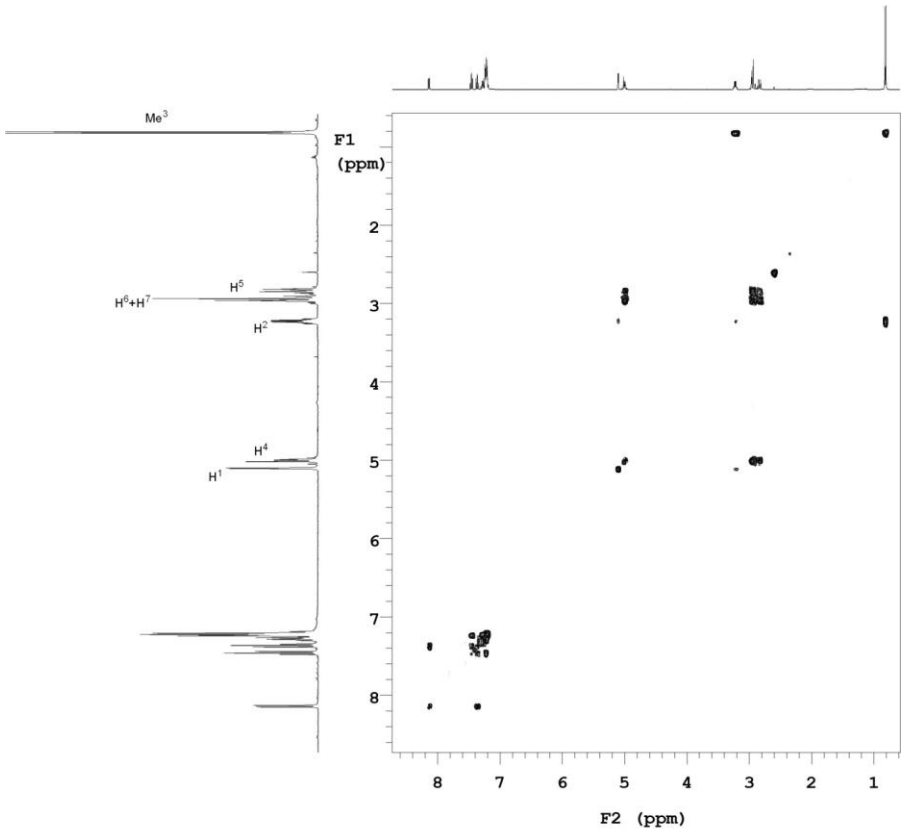


**Figure S5.** selective n.O.e excitation of $Me^3$ of **37.**

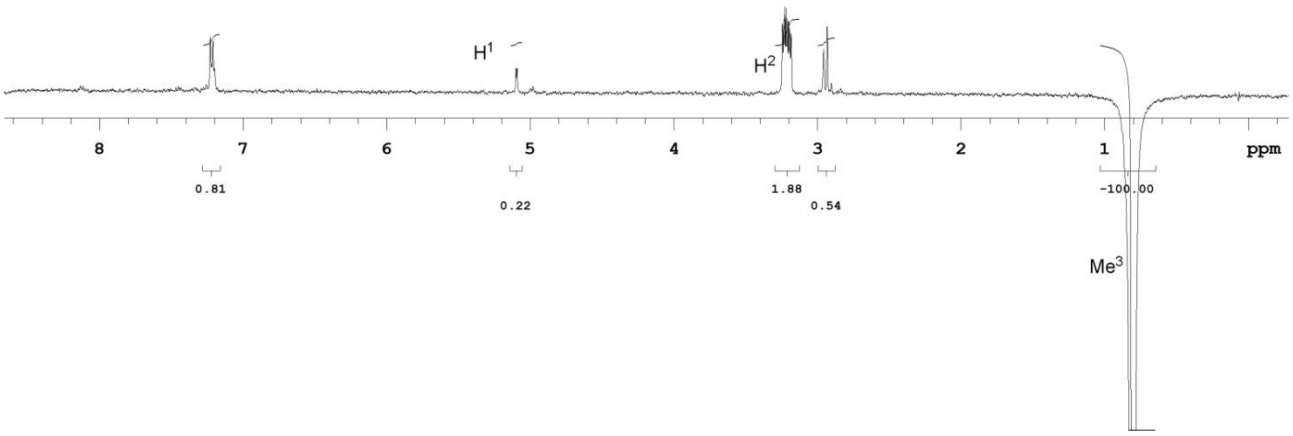



**Figure S6:** g-COSY spectra of **44.**

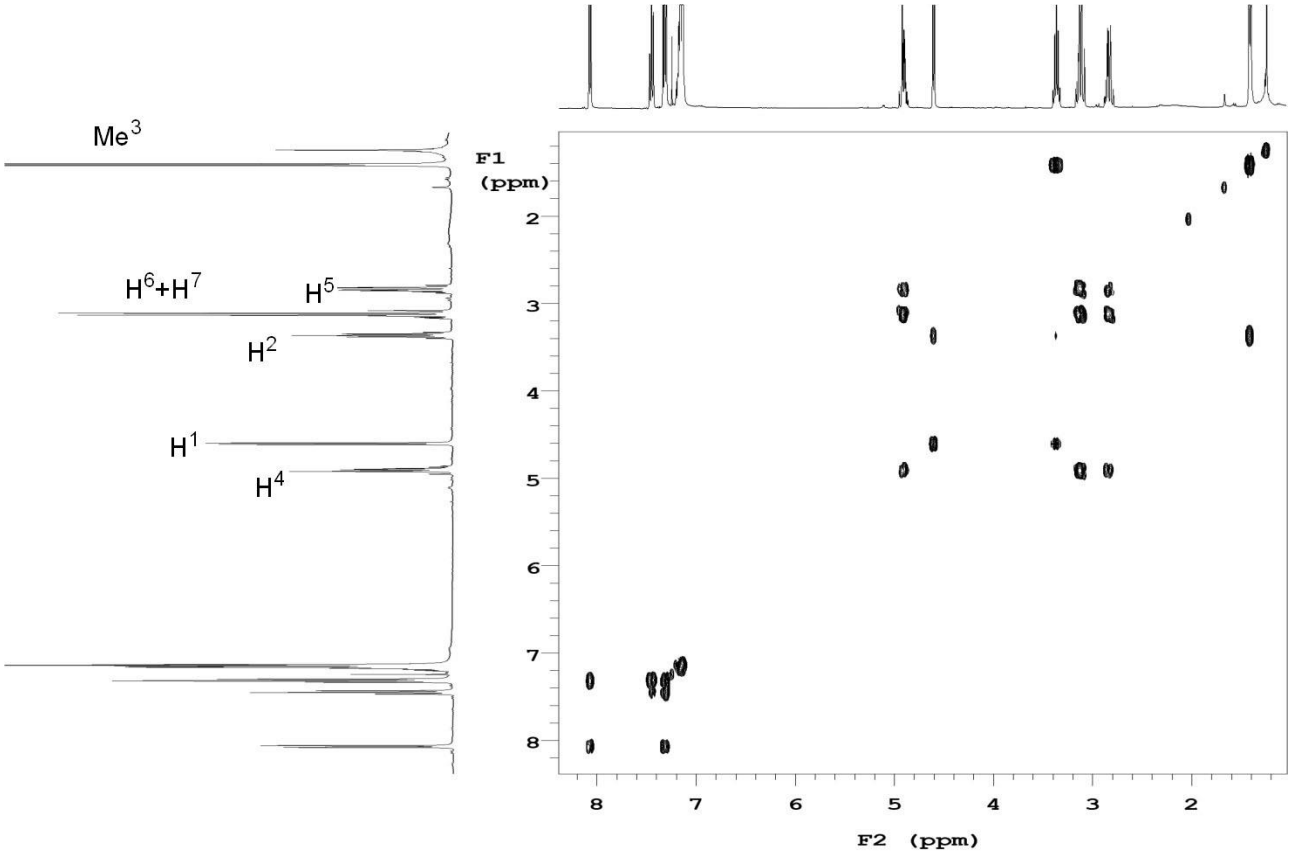
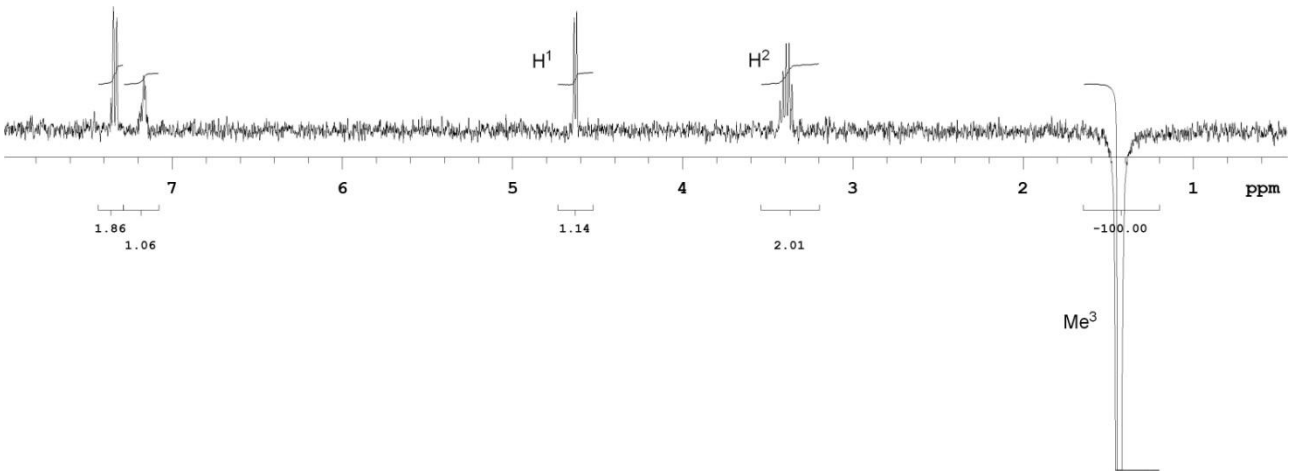


**Figure S7.** selective n.O.e excitation of $Me^3$ of **24.**

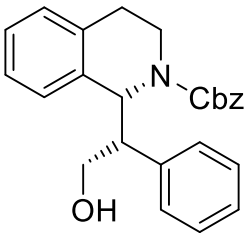



**Attempted synthesis of (+)-13-methyl tetrahydroprotoberberine 1g with Cbz as activating group**

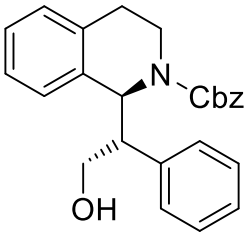
**Synthesis of racemic 46**

To a stirred solution of isoquinoline (8.00 mmol, 939 µL) and enamine **41** (8.0 mmol, 1.38 g) in DCM (5 mL), a solution of CbzCl (8.00 mmol, 1.15 mL) in DCM (4 mL) was added by syringe pump over the course of 15 hours. After the addition was complete the solution was stirred for 2 more hours, then the HCl 1M (10 mL) was added and the mixture was vigorously stirred for 1 hour. The organic layer was separated and the aqueous layer was extracted with DCM (2 x 8 mL). The collected organic layers were dried over $Na_2SO_4$ and diluted with MeOH (3 mL). The solution was cooled to 0°C and $NaBH_4$ (13 mmol, 494 mg) was added. After 2 hours complete conversion was observed by TLC analysis and the reaction was quenched by cautious addition of HCl 1M until pH = 1. The mixture was diluted with DCM (3 mL), the organic layer was separated and the aqueous layer was extracted with DCM (2 x 10 mL). The collected organic layers were washed with brine, dried on $MgSO_4$ and concentrated under reduced pressure. The crude product was transferred in a two necked round bottomed flask under nitrogen atmosphere and dissolved in DCM (7 mL), then TFA (15 mL) and triethlysilane (40 mmol, 6.3 mL) were added. The mixture was stirred for 18 hours at room temperature, then solvent was removed under reduce pressure. The residue was dissolved in diethyl ether (20 mL) and washed with $NaHCO_3$ sat. sln. until basic pH. The organic layer was separated and the aqueous layer was extracted with diethyl ether (2 x 10 mL). The collected organic layers were washed with brine, dried on $MgSO_4$ and

concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (cyclohexane/ethyl acetate 85/15) to give ***anti*-46** (774 mg of 3.5:1 mixture ***anti*-46**: *N*-Cbz pyrrolidine, 672 mg ***anti*-46**, 1.74 mmol, 22% yield) and ***syn*-46** (235 mg of 1.2:1 mixture ***syn*-46**: *N*-Cbz pyrrolidine, 164 mg ***syn*-46,** 0.42 mmol, 5% yield).

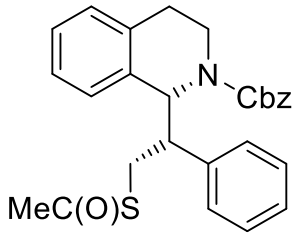



**(*anti*-46)**: Colourless sticky solid. $^{1}$H NMR (400 MHz, $CDCl_3$, 25°C) (two rotamers A:B, 3:1 ratio): $\delta$ = 2.41-2.53 (m, 2H$_B$), 2.76-2.85 (m, 2H$_A$), 3.00-3.06 (m, 1H), 3.20-3.32 (m, 1H), 3.48-3.57 (m, 2H$_B$), 3.68-3.76 (m, 2H$_A$), 3.86 (dd, $J_1$ = 11.9 Hz, $J_2$ = 3.7 Hz, 1H$_A$), 3.96-3.92 (m, 2H$_B$), 4.06 (dd, $J_1$ = 11.9 Hz, $J_2$ = 4.9 Hz, 1H$_A$), 5.23 (d, $J$ = 12.2 Hz, 1H), 5.27 (d, $J$ = 12.2 Hz, 1H), 5.39 (d, $J$ = 10.2 Hz, 1H$_B$), 5.47 (d, $J$ = 10.2 Hz, 1H$_A$), 6.36 (d, $J$ = 7.7 Hz, 1H$_A$), 6.42 (d, $J$ = 6.5 Hz, 1H$_B$), 6.79-6.86 (m, 1H), 6.88-6.98 (m, 1H), 7.03-7.47 (m, 11H); $^{13}$CNMR (100 MHz, $CDCl_3$, 25°C) $\delta_{anti}$ = 27.6, 41.1, 53.3, 57.4. 63.7, 67.6, 125.5, 126.9, 127.0, 127.7, 127.9 (2C), 128.1 (2C), 128.2, 128.3, 128.6 (2C), 129.5 (2C), 134.2, 135.3, 136.4, 140.1, 157.1; ESI-MS: *m/z* = 388.3 $[M+H]^+$, 797.6 $[2M+Na]^+$.

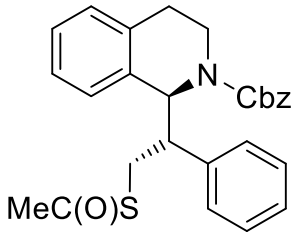



**(*syn*-46)**: Colourless oil. $^{1}$H NMR (400 MHz, $CDCl_3$, 25°C) (two rotamers A:B, 4:1 ratio): $\delta$ = 1.58-1.81 (bs, 1H), 1.82-1.91 (m, 1H), 2.43-2.57 (m, 1H), 2.69-2.79 (m 1H), 3.27-3.34 (m, 1H$_B$), 3.35-3.45 (m, 1H$_A$), 3.70 (dt, $J_1$ = 13.0 Hz, $J_2$ = 5.2 Hz, 1H), 3.81 (dd, $J_1$ = 11.8 Hz, $J_2$ = 5.2 Hz, 1H$_A$), 3.84 (dd, $J_1$ = 11.8 Hz, $J_2$ = 5.2 Hz, 1H$_B$), 3.98-3.91 (m, 1H$_B$), 4.10 (dd, $J_1$ = $J_2$ = 11.8 Hz, 1H$_A$), 5.01 (d, $J$ = 12.2 Hz, 1H$_B$), 5.09 (d, $J$ = 12.2 Hz, 1H$_B$), 5.20 (d, $J$ = 12.2 Hz, 1H$_A$), 5.24 (d, $J$ = 12.2 Hz, 1H$_A$), 5.51 (d, $J$ = 6.8 Hz, 1H$_B$), 5.70 (d, $J$ = 3.0 Hz, 1H$_A$), 6.82 (d, $J$ = 7.5 Hz, 1H), 6.95 (d, $J$ = 7.5 Hz, 1H$_A$), 7.00 (d, $J$ = 7.5 Hz, 1H$_B$), 7.08-7.21 (m, 4H), 7.24-7.44 (m, 8H); $^{13}$CNMR (100 MHz, $CDCl_3$, 25°C) $\delta$ = 27.6, 40.7, 54.4, 55.0, 62.3, 67.6, 126.2, 126.6, 126.9, 127.1, 127.6 (2C), 127.9 (2C), 128.0, 128.3, 128.4 (2C), 128.7 (2C), 134.8, 135.6, 136.4, 138.1, 157.8; ESI-MS: *m/z* = 388.3 $[M+H]^+$, 797.6 $[2M+Na]^+$.

The Mitsunobu reaction was performed on ***anti*-46** and ***syn*-46** according to the procedure described for **33** to obtain respectively ***anti*-47** and ***syn*-47.** The products were isolated by column chromatography on silica gel (cyclohexane/diethyl ether from 99/1 to 8/2).




**(*anti*-47)**. Colourless oil, 66% yield. $^{1}$H NMR (400 MHz, $CDCl_3$, 25°C) (two rotamers A:B 2:1 ratio): $\delta$ = 2.21 (s, 3H$_B$), 2.26 (s, 3H$_A$), 2.49-2.58 (m, 1H$_B$), 2.62-2.71 (m, 1H$_A$), 2.74-2.88 (m, 1H), 2.97-3.06 (m, 1H$_B$), 3.08-3.22 (m, 1H+1H$_A$), 3.50 (dd, $J_1$ = 13.5 Hz, $J_2$ = 5.5 Hz, 1H$_B$), 3.59-3.66 (m, 1H$_A$), 3.69-3.80 (m, 1H), 3.83-3.92 (m, 1H), 5.14-5.31 (m, 2H+1H$_B$), 5.38 (d, $J$ = 8.7 Hz, 1H$_A$), 6.26 (d, $J$ = 8.0 Hz, 1H$_A$), 6.28 (d, $J$ = 8.7 Hz, 1H$_B$), 6.79-6.90 (m, 2H), 6.92-6.97 (m, 1H), 7.04-7.14 (m, 2H), 7.16-7.26 (m, 3H), 7.29-7.47 (m, 5H); $^{13}$CNMR (100 MHz, $CDCl_3$, 25°C) (two rotamers A:B 2:1 ratio): $\delta$ = 27.3 (1C$_B$), 27.5 (1C$_A$), 30.4 (1C$_B$), 30.5 (1C$_A$), 32.1 (1C$_B$), 32.3 (1C$_A$), 40.2 (1C$_B$), 40.7 (1C$_A$), 51.4 (1C$_B$), 51.7 (1C$_A$), 60.1 (1C$_B$), 60.4 (1C$_A$), 67.2 (1C$_A$), 67.5 (1C$_B$), 125.5 (1C$_B$), 125.2 (1C$_A$), 126.9 (1C$_A$), 127.0 (1C$_B$), 127.1 (1C$_A$), 127.2 (1C$_B$), 127.5 (1C$_B$), 127.6 (2C$_A$+1C$_B$), 127.8 (1C$_A$), 127.9 (2C), 128.0 (1C$_B$), 128.1 (2C), 128.2 (1C$_A$), 128.3 (1C$_B$), 128.4 (2C), 128.5 (1C$_A$), 129.0 (1C$_B$), 134.5 (1C$_A$), 134.6 (1C$_B$), 134.7 (1C$_B$), 135.1 (1C$_A$), 136.4 (1C$_B$), 136.7 (1C$_A$), 140.2 (1C$_B$), 140.4 (1C$_A$), 155.5 (1C$_B$), 156.4 (1C$_A$), 195.3 (1C$_B$), 195.7 (1C$_A$); ESI-MS: *m/z* = 446.3 $[M+H]^+$, 468.4 $[M+Na]^+$.

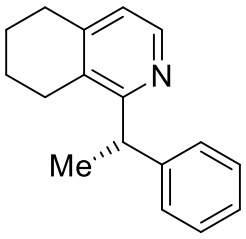



**(*syn*-47)**. Colourless oil, 76% yield. $^{1}$H NMR (400 MHz, $CDCl_3$, 25°C) (two rotamers A:B 1.2:1 ratio): $\delta$ = 2.23 (s, 3H$_B$), 2.28 (s, 3H$_A$), 2.44-2.54 (m, 1H$_A$), 2.58-2.89 (m, 2H+1H$_B$), 3.20-3.30 (m, 1H$_B$), 3.31-3.45 (m, 2H), 3.55 (dd, $J_1$ = 12.5 Hz, $J_2$ = 5.7 Hz, 1H$_A$), 3.63-3.72 (m, 1H$_A$), 3.82-3.91 (m, 1H$_B$), 4.98 (d, $J$ = 13.0 Hz, 1H$_B$), 5.08 (d, $J$ = 13.0 Hz, 1H), 5.14 (d, $J$ = 13.0 Hz, 1H$_A$), 5.41 (d, $J$ = 3.6 Hz, 1H$_B$), 5.58 (d, $J$ = 4.7 Hz, 1H$_A$), 6.96 (d, $J$ = 6.7 Hz, 1H), 7.00-7.13 (m, 2H), 7.14-7.42 (m, 11H); $^{13}$CNMR (100 MHz, $CDCl_3$, 25°C) (two rotamers A:B 1.2:1 ratio): $\delta$ = 27.5 (1C$_B$), 27.9 (1C$_A$), 30.4 (1C$_B$), 30.5 (1C$_A$), 32.1 (1C$_B$), 32.2 (1C$_A$), 39.5 (1C$_B$), 40.1 (1C$_A$), 51.3 (1C$_B$), 52.0 (1C$_A$), 58.8 (1C$_A$), 59.0 (1C$_B$), 67.1 (1C$_A$), 67.5 (1C$_B$), 125.9 (1C$_B$), 126.1 (1C$_A$), 127.0 (1C$_A$), 127.08 (1C$_B$), 127.09 (1C$_B$), 127.2 (1C$_A$), 127.6 (1C), 127.7 (1C$_B$), 127.8 (1C), 128.0 (1C), 128.1 (1C$_A$), 128.2 (1C), 128.38 (1C), 128.41 (1C$_B$), 128.45 (1C+1C$_A$), 128.48 (1C$_A$), 128.49 (1C$_B$), 128.50 (1C$_A$), 128.6 (1C), 129.0 (1C$_B$), 134.6 (1C$_A$), 134.9 (1C$_B$), 135.3 (1C$_B$), 135.6 (1C$_A$), 136.3 (1C$_B$), 136.8 (1C$_A$), 139.0 (1C$_B$), 139.2 (1C$_A$), 155.6 (1C$_B$), 156.3 (1C$_A$), 195.4 (1C$_B$), 195.7 (1C$_A$); ESI-MS: *m/z* = 446.3 $[M+H]^+$, 468.4 $[M+Na]^+$.

**Reaction with Ni-Raney of compounds *anti*-47 and *syn*-47.**

In a two necked round bottomed flask, to a solution of ***anti*-47** (0.34 mmol, 150 mg) in THF (5 mL) and Ni/Raney (2.0 g, slurry in water) was added. The mixture was stirred for 24 hours at room temperature until complete conversion was observed by TLC analysis. The reaction mixture was kept under $H_2$ atmosphere (1 atm) and stirred for further 16 h. The solution was separated and Nickel/Raney washed 4 times with DCM (5 mL). The collected organic phases were filtered through a Celite pad and concentrated under vacuum. The reaction was subjected to column chromatography on silica gel (cyclohexane/ethyl acetate from 9/1 to 5/5) to give **35** (8.1 mg, 0.034 mmol, 10% yield) and **48** (5.5 mg, 0.023 mmol, 7 % yield).

In a two necked round bottomed flask, to a solution of ***anti*-46** (0.31 mmol, 136 mg) in THF (5 mL) and Ni/Raney (2.0 g, slurry in water) was added. The reaction mixture was kept under $H_2$ atmosphere (1 atm) and stirred for 24 h at room temperature until complete conversion was observed by TLC analysis. The solution was separated and Nickel/Raney washed 4 times with DCM (5 mL). The collected organic phases were filtered through a Celite pad and concentrated under vacuum. The reaction crude was a complex mixture of products and after column chromatography on silica gel (cyclohexane/ethyl acetate from 9/1 to 5/5) **43** (18 mg, 0.076 mmol, 24% yield) and **48** (15 mg, 0.063 mmol, 20 % yield) were isolated.




**48:** Yellowish oil. $^1$H NMR (400 MHz, $CDCl_3$, 25°C): $\delta$ = 1.53-1.86 (m, 4H), 1.70 (d, $J$ = 7.0 Hz, 3H), 2.41-2.51 (m, 1H), 2.80-2.69 (m, 3H), 4.36 (q, $J$ = 7.0 Hz, 1H), 6.90 (d, $J$ = 5.1 Hz, 1H), 7.14-7.19 (m, 1H), 7.21-7.28 (m, 4H), 8.36 (d, $J$ = 5.1 Hz, 1H); ESI-MS: $m/z$ = 238.3 $[M+H]^+$.

## 2.2.6 Recent advances in the addition of nucleophiles to quinolinium or dihydroquinolinium ions.

After the publication of our paper, further advances in the field were achieved. Dypolar cycloadditions have been efficiently used in the asymmetric construction of isoquinoline [1,2]-fused-polycyclic compounds. In 2014 Wang reported the alkylation of aldehydes with C,N-cyclic azomethine promoted by Jorgensen catalyst with high diastereo and enantio control.[77] Studer reported the alkylation of carboxylixc acids activated as anhydrides with isothiorea as catalysts that subsequently are released to form the product.[78] Glorious disclosed a divergent protocol to access 3+2 or 4+2 adducts by changing the reaction conditions starting from XX and alfa beta unsaturated aldehydes.[79] Also allenoates have been efficiently used in such transformation catalyzed by a chiral phosphine.[80]

Several CDC were also reported.[81] Of particular interest are two CDC process that have been developed using Boc or Cbz protected THIQ. The difficulty of the process is due to the less stabilized radical intermediate that is generated in absence of the aryl group. The first report is non asymmetric arylation[82] while Liu reported a vinylation and arylation reactions that proceed in good to excellent yields and enantioselectivities affording easily derivatizable products.[83] Other non asymmetric CDC processes have been coupled with photocatalysis to generate the radical intermediate avoiding the use of strong oxidants.[84]

Other synthesis of isoquinoline alkaloids have been reported, including an interesting paper on protoberberine alkaloids that were obtained by Palladium-Catalyzed Enolate Arylation. However none of these procedres are enantioselective.[85]

## 2.2.7 References


[1] The methodology and the total syntehsis were published: L. Mengozzi, A. Gualandi, P. G. Cozzi, *Chem. Sci*., **2014**, *5*, 3915; the biological data are unpublished results.

[2] J.H. Clark *Acc Chem Res* **2002**, *35*, 791.

[3] K. Prasat , M. Chulabhorn , R. Somsak *Curr Top Med Chem* **2014**, *14*: 239.

[4] M. Hesse M, *Alkaloids: Nature's Curse or Blessing?* **2002**, Wiley-VCH, Weinheim.

[5] M.D. Rozwadowska, *Heterocycles* **1994**, *39*, 903.

[6] Z. Czarnocki , A. Siwicka , J. Szawkato , *Curr Org Chem* **2005**, *2*, 301.

[7] M. Ahamed , M.H. Todd *Eur J Org Chem* **2010**, 5935.

[8] K.W. Bentley, *Nat. Prod. Rep.* **2006**, *23*, 444 and previous reviews in this series.

[9] a) Z. S. Ye , R. N. Guo , X. F. Cai, M. W. Chen, L. Shi, Y. G. Zhou, *Angew Chem Int Ed* **2013**, *52*: 3685; b) Y. Kita, K. Yamaji, K. Higashida, K. Sathaiah, A. Iimuro, K. Mashima, *Chem. Eur. J.* **2015**, *21*, 1915.

[10] Z. Wu , M. Perez, M. Scalone, T. Ayad, V. Ratovelomanana-Vidal, *Angew Chem Int Ed* **2013**, *52*, 4925; M. Perez, Z. Wu, M. Scalone, T. Ayad, V. Ratovelomanana-Vidal, *Eur. J. Org. Chem.* **2015**, 6503.

[11] Y. M. Wilson, M. Dürrenberger, E. S. Nogueira, T. R. Ward, *J. Am. Chem. Soc.* **2014**, *136*, 8928; b) for a review see: D. Zhao, F. Glorius, *Angew. Chem. Int. Ed.* 2013, **52**, 9616.

[12] Y. Ji, L. Shi, M.-W. Chen, G.-S. Feng, Y.-G. Zhou *J. Am. Chem. Soc.* **2015**, *137*, 10496.

[13] A. Reissert, *Ber.Dtsch. Chem. Ges.* **1905**, *38*, 1603.

[14] a) M. Takamura, K. Funabashi, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2000**, *122*, 6327; b) M. Takamura, K. Funabashi, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2001**, *123*, 6801-6808.

[15] a) A. Pictet, T. Spengler, *Ber. Dtsch. Chem. Ges*., **1911**, *44*, 2030; b) A. Yokoyame, T. Ohwade, K. Shudo, *J. Org. Chem*., **1999**, *64*, 611; c) E. J. Corey, D.Y. Gin, *Tetrahedron Lett*., **1996**, *37*, 7163.

[16] A. Bishler, B. Napieralski, *Ber. Dtsch. Chem. Ges*., **1893**, *26*, 1903; b) T.-C. Wang, P.E. Georghiou, *Org. Lett.*, **2002**, *4*, 2675; c) A.R. Hajipour, M. Hantehzdeh, *J. Org. Chem*., **1999**, *64*, 8475; d) M. Kitamura, Y. Hsiao, M. Ohta, M. Tsukamoto, T. Ohta, H. Tokaya, R. Noyori, *J. Org. Chem*., **1994**, *59*, 297.

[17] a) C. Pomerantz, *Monatsh. Chem*, **1893**, *14*, 116; b) C. Fritsch, *Ber. Dtsch. Chem. Ges*., **1893**, *26*, 419; c) R. Cucznierz, J. Dickhaut, H. Leinert, W. von der Saal, *Synth. Commun.*, **1999**, *29*, 1617.

[18] J. H. Schrittwieser, V. Resch, J. H. Sattler, W.-D. Lienhart, K. Durchschein, A. Winkler, K. Gruber, P. Macheroux, W. Kroutil, *Angew. Chem. Int. Ed.* **2011**, *50*, 1068 –1071.

[19] M. Miyazaki, N. Ando, K. Sugai, Y. Seito, H. Fukuoka, T. Kanemitsu, K. Nagata, Y. Odanaka, K. T. Nakamura, T. Itoh, *J. Org. Chem.* **2011**, *76*, 534-542.

[20] a) W. L. Lin, T. Cao, W. Fan, Y. L. Han, J. Q. Kuang, H. W. Luo, B. K. Y. Miao, X. J. Tang, Q. Yu, W. M. Yuan, J. S. Zhang, C. Zhu, S. M. Ma, *Angew Chem Int Ed* **2014**, *53*, 277 and references therein; b) T. Hashimoto, M. Omote, K. Maruoka, *Angew. Chem. Int. Ed.* **2011**, *50*, 8952-8955; c) V. Bisai, A. Suneja, V. K. Singh, *Angew. Chem. Int. Ed.* **2014**, *53*, 10737 –10741.

[21] a) N. Sasamoto, C. Dubs, Y. Hamashima, M. Sodeoka, *J. Am. Chem. Soc.* **2006**, *128*, 14010; b) C. Dubs, Y. Hamashima, N. Sasamoto, T. M. Seidel, S. Suzuki, D. Hashizume and M. Sodeoka, *J. Org. Chem.* **2008**, *73*, 5859-5871; c) G. Zhang, Y. Zhang, R. Wang, *Angew. Chem. Int. Ed.* **2011**, *50*, 10429 –10432.

[22] K. Frisch, A. Lauda, S. Saaby, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2005**, *44*, 6058-6063.

[23] A. Fraile, D. M. Scarpino Schietroma, A. Albrecht, R. L. Davis, K. A. Jørgensen, *Chem.-Eur. J.* **2012**, *18*, 2773-2776.

[24] Z. Chen, B. Wang, Z. Wang, G. Zhu, J. Sun Angew. Chem. Int. Ed. **2013**, *52*, 2027.

[25] J. Huang, S. Luo, L. Gong, *Acta Chim Sin* **2013**, *71*, 879.

[26] M. S. Taylor, N. Tokunaga, E. N. Jacobsen, *Angew. Chem. Int. Ed.* **2005**, *44*, 6700-6704.

[27] A. G. Schafer, W. J. Wieting, T. J. Fisher, A. E. Mattson, *Angew. Chem. Int. Ed.* **2013**, *52*, 11321.

[28] M. Zurro, S. Asmus, J. Bamberger, S. Beckendorf, O. Garcìa Mancheño, *Chem. Eur. J.* **2016**, *DOI:10.1002/chem.201504094.*

[30] D. C. Kanta, N. Mittal, D. Seidel *J Am Chem Soc* **2011**, *133*, 16802.

[31] D. C. Kanta, D. Seidel *J Am Chem Soc* **2011**, *133*, 14538.

[32] G. Hoefle, W. Steglich, H. Vorbrueggen, *Angew Chem Int Ed Engl* **1978**, *17*, 569.

[33] M. P. Lalonde, M. A. McGowan, N. S. Rajapaksa, E. N. Jacobsen, J Am Chem Soc **2013**, *135*, 1891.

[34] S. A. Girard, T. Knauber, C. J. Li, *Angew Chem Int Ed* **2014**, *53*, 74.

[35] M. Cherevatskaya, M. Neumann, S. Füldner, C. Harlander, S. Kümmel, S. Dankesreiter, A. Pfitzner, K. Zeitler, B. König, *Angew Chem Int Ed* **2012**, *51*, 4062.

[36] J. Dhineshkumar, M. Lamani, K. Alagiri, K. R. Prabhu, *Org Lett* **2013**, *15*, 1092.

[37] Q. Xue, J. Xie, H. Jin, Y. Cheng, C. Zhu, *Org Biomol Chem* **2013**, *11*, 1606.

[38] J. Zhang, B. Tiwari, C. Xing, X. Chen, Y. R. Chi, *Angew. Chem. Int. Ed.* **2012**, *51*, 3649-3652.

[39] a) E. Boess, D. Sureshkumar, A. Sud, C. Wirtz, C. Farès, M. Klussmann, *J. Am. Chem. Soc.* **2011**, *133*, 8106-8109; b) E. Boess, C. Schimtz, M. Klussmann, *J. Am. Chem. Soc.* **2012**, *134*, 5317-5325.

[40] G. Zhang, Y. Ma, S. Wang, W. Konga, R. Wang, *Chem Sci* **2013**, *4*, 2645.

[41] G. Zhang, Y. Ma, S. Wang, W. Kong, Y. Zhang , R. Wang, *J. Am. Chem. Soc.* **2012**, *134*, 12334.

[42] A. J. Neel, J. P. Hehn, P. F. Tripet, F. D. Toste, *J. Am. Chem. Soc.* **2013**, *135*, 14044.

[43] Z. Shi, C. Zhang, C. Tang, N. Jiao, *Chem. Soc. Rev.* **2012**, *41*, 3381.

[44] D. A. Di Rocco, T. Rovis, *J. Am. Chem. Soc.* **2012**, *134*, 8094.

[45] For the chemistry related of carbene intermediate oxidation, see for example: M. Junming, S. Liang, R. Y. Chi,
*Angew. Chem. Int. Ed.* **2013**, *52*, 8588.

[46] D. B. Freeman, L. Furst, A. G. Condie, C. R. J. Stephenson, *Org. Lett.* **2012**, *14*, 94.

[47] M. Mohiti, C. Rampalakos, K. Feeney, D. Leonori, V. K. Aggarwal, *Chem. Sci.* **2014**, *5*, 602-607. Recently, a practical metal-free addition of nucleophiles to carbamates and to chiral isoquinolinescarbamates was reported, see: Z. Xie, L. Liu, W. Chen, H. Zheng, Q. Xu, H. Yuan, H.

Lou, *Angew. Chem. Int. Ed.* **2014**, *53*, 3904-3908. However, the addition of aldehydes and ketones to chiral carbamates was not described in this paper.

[48] V. Preininger, In: *The Alkaloids* (Brossi A., cd) Academic, **1996**, New York, Vol. 29, pp 1-98.

[49] K. Iwasal, M. Kamigauchil, M. Uek and M Taniguch, *Eur. J. Med. Chem.* 1996, **31**, 469-478.

[50] H. Otuka, H. Fujimura, T. Sawada, M. Goto, *Yakugaku Zaashi* **1981**, *101*, 883-890.

[51] a) H. Y. Ji, K. H. Liu, H. Lee, S. R. Im, H. J. Shim, M. Son, H. S. Lee, *Molecules* **2011**, ***16***, 6591-6602; b) C. Saà, E. Guitih, L. Castedo, R. Suau, J. M. Saà, *J. Org. Chem.* **1986**, *51*, 2781-2784; c) K. Isawa, M. Cushman, *J. Org. Chem.* **1982**, *47*, 545-552; d) K. Isawa, M. Sugiura, N. Takao, *J. Org. Chem.* **1982**, *47*, 4275-4280.

[52] a) For a review, see: M. Chrzanowska, M. D. Rozwadowska, *Chem. Rev.* **2004**, *104*, 3341-3370; b) H. Liu, G. Li, J. Wang, J. Liu, PCT application, WO2010/075469A1, **2010**.

[53] H. Ouchi, Y. Saito, Y. Yamamoto, H. Takahata, *Org. Lett.* **2002**, *4*, 585-587.

[54] 23 Acyl-soquinolinium salts can be isolated only by the use of not coordinating counter ions, see: K. Akida, M. Nakatani, M. Wada and Y. Yamamoto, *J. Org. Chem*, **1985**, *50*, 63–68; the nucleophilicity parameters of acyl isoquinolinium ylides were recently reported by Mayr, see: T. A. Nigst, H. Mayr, *Eur. J. Org. Chem*., **2013**, 2155–2163.

[55] S. Lakhdar, T. Tokuyasu, H. Mayr, *Angew. Chem., Int. Ed*. **2008**, *47*, 8723-8726.

[56] a) L. Caruana, F. Kniep, T. K. Johansen, P. H. Poulsen, K. A. Jørgensen, *J. Am. Chem. Soc.* **2014**, *136*, 15929−15932; b) P. Garía-García, A. Ladépêche, R. Halder, B. List, *Angew. Chem. Int. Ed.* **2008**, *47*, 4719 –4721; c) A. Claraz, G. Sahoo, D. Berta, Á. Madarász, I. Pápai, P. M. Pihko, *Angew. Chem. Int. Ed.* **2016**, *55*, 669.

[57] M. B. Schmid, K. Zeitler, R. M. Gschwind. *Chem. Sci.*, **2011**, *2*, 1793-1803.

[58] G. Cainelli, P. Galletti and D.. Giacomini, *Chem. Soc. Rev.* **2009**, *38*, 990-1001.

[59] D. Petruzziello, M. Stenta, A. Mazzanti, P. G. Cozzi, *Chem. Eur. J.* **2013**, *19*, 7696.

[60] M. Lombardo, L. Cerisoli, E. Manoni, E. Montroni, A. Quintavalla, C. Trombini, *Eur. J. Org. Chem.* **2014**, 5946-5953.

[61] K. Tagahara, J. Koyama, T. Okatani, Y. Suzuta, *Bull. Chem. Soc. Jpn.*, 1986, *34*, 5166–5169, and ref. therein.

[62] M. D. Radwadowska, *Tetrahedron* **1997**, *53*, 10615-10622.

[63] P. E. Eaton, , G. R. Carlson, J. T. Lee, *J. Org. Chem.* **1973**, *38*, 4071.

[64] The enamine is formed by the reaction between phenylacetaldehyde, present in excess in the reaction mixture, and the chiral catalyst **4a**. Stable enamines of Hayashi-Jørgensen catalysts were isolated and characterized by Seebach, see: U. Grošelj, D. Seebach, D. M. Badine, W. B. Schweizer, A. K. Beck, *Hel. Chim.Acta* **2009**, *92*, 1225-1259.

[65] J. F. Stambach, L. Lung, *Tetrahedron* **1985**, *41*, 169-172.

[66] M. A. Aimova, N. M. Mollow, S. C. Ivanova, A. I. Dimitrova, V. I. Ognyanov, *Tetrahedron* **1977**, *33*, 331-336.

[67] a) W. Leithe, *Chem. Ber*. **1934**, *67*, 1261-1263; b) P. W. Jeffs, *Experientia*, **1965**, *21*, 690-692.

[68] E. J. Mattioli, Bachelor thesis, Supervisor P. G. Cozzi, Co-supervisors A. Gualandi, L. Mengozzi, **2014**, Università di Bologna.

[69] U.S. Pat. Appl. Publ., 20030083352, 01 May 2003.

[70] J. B. Hendrickson, C. Rodriguez, *J. Org. Chem.* 1983, **48**, 3344.

[71] D. E. Minter, M. A. Re , *J. Org. Chem.* 1988, **53**, 2653.

[72] A. C. Cutter, I. R. Miller, J. F. Kelly, R. K. Bellinghan, M. E. Light, R. C. D. Brown, *Org. Lett.*, 2011, **13**, 3988.

[73] Y. Saito, H. Ouchi, H. Takahata, *Tetrahedron*, 2006, **62**, 11529.

[74] a) E. Finamore, L. Minale, R. Riccio, G. Rinaldo, F. Zollo, *J. Org. Chem.* 1991, **56**, 1146-1153; b) F. Dericcardis, L. Minale, R. Riccio, B. Giovannitti, M. Iorizzi, C. Debitus, *Gazz. Chim. Ital.* 1993, **123**, 79-86.

[75] G. Bélanger, M. Doré, F. Ménard, V. Darsigny, *J. Org. Chem.* 2006, **71**, 7481–7484.

[76] a) I.-S. Cho, S. S.S. Chang, C. Ho, C.-P. Lee, H. L. Ammon, P. S. Mariano, *Heterocycles* 1991, **32**, 2161-2192. b) M. Sugiura, N. Takao, K. Iwasa, Y. Sasaki, *Chem. Pharm. Bull.* 1976, **26**, 1168-1176.

[77] W. Li, Q. Jia, Z. Du, K. Zhang, J. Wang *Chem. Eur. J.* **2014**, *20*, 4559 – 4562.

[78] L. Hesping, A. Biswas, C. G. Daniliuc, C. Mück-Lichtenfeld, A. Studer, *Chem. Sci*., **2015**, *6*, 1252.

[79] C. Guo, M. Fleige, D. Janssen-Müller, C. G. Daniliuc, F. Glorius, *Nat. Chem.* **2015**, *7*, 842-847.

[80] D. Wang, Y. Lei, Y. Wei, M. Shi, *Chem. Eur. J.* **2014**, *20*, 15325 – 15329.

[81] Y. Ma, G. Zhang, J. Zhang, D. Yang, R. Wang *Org. Lett.*, **2014**, *16*, 5358–5361; b) X. Liu, J. Zhang, S. Ma, Y. Ma, R. Wang, *Chem. Commun.*, **2014**, *50*, 15714

[82] W. Chen, H. Zheng , X. Pan, Z. Xie, X. Zan, B. Sun, L. Liu, H. Lou, *Tetrahedron Lett.* **2014**, *55*, 2879–2882.

[83] X. Liu, S. Sun, Z. Meng, H. Lou, L. Liu, *Org. Lett.* **2015**, *17*, 2396–2399.

[84] a) F. Rusch, L.-N. Unkel, D. Alpers, F. Hoffmann, M Brasholz, *Chem. Eur. J.* **2015**, *21*, 8336 – 8340; b) D. Shi, C. He, B. Qi, C. Chen, J. Niu, C. Duan, *Chem. Sci*., **2015**, *6*, 1035; b) Y. Chen, G. Feng, *Org. Biomol. Chem*., **2015**, *13*, 4260; c) X. Liu, X. Ye, F. Bureš, H. Liu, Z. Jiang, *Angew. Chem., Int. Ed*. **2015**, *54*, 11443–11447, d) D. Prakash Shelar, T.-T. Li, Y. Chen, W.-F. Fu, *ChemPlusChem* **2015**, *80*, 1541-1546.

[85] a) A. F. C. Rossini, A. C. A. Muraca, G. A. Casagrande, C. Raminelli, *J. Org. Chem*. **2015**, *80*, 10033−10040; b) J. Zhang,, J. Chen, X. Zhang, X. Lei, *J. Org. Chem*. **2014**, *79*, 10682−10688; c) A. E. Gatland, B. S. Pilgrim, P. A. Procopiou, T. J. Donohoe, *Angew. Chem. Int. Ed.* **2014**, *53*, 14555 – 14558.

## 2.3 Pictet-Spengler cyclization of allenamides for the enantioselective synthesis of 1-vinyl THIQ promoted by phosphoric acids[1]

**Index**

## 2.3.1 Introduction

1-Substituted tetrahydroisquinolines are a recurring motif in many alkaloids.[2] Among these a consistent number bears a linear substituent on the C1 position. The control of such a stereocenter is particularly difficult via enamine catalysis: indeed only poor results were obtained using acetaldehyde.[3] The addition of silyl enol ethers developed by Jacobsen,[4] the alkynylation developed by Ma[5] and the aza-benzoin reaction reported by Rovis[6] are the only catalytic methodologies that allow to access such scaffolds in high enantioselectivities by addition of nucleophiles to quinolinium or dihydroquinolinium ions. Asymmetric hydrogenation can also be used to access such intermediates in high ee.[7]

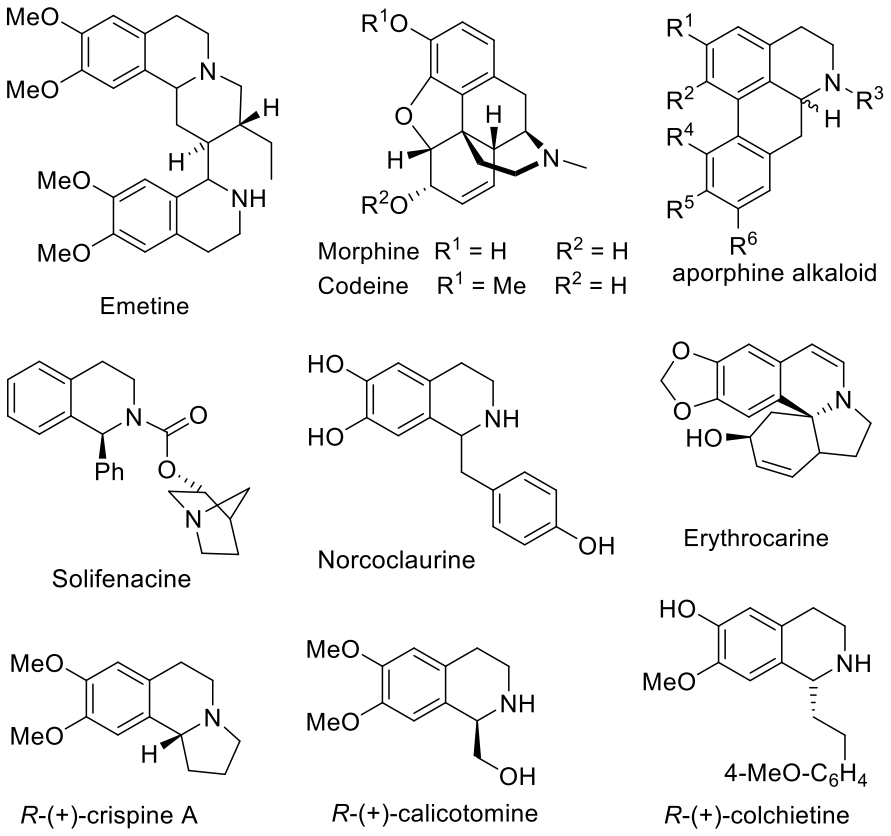



*Figure 1. Relevant examples of isoquinoline C1 substituted THIQ alkaloids.*

An alternative metal free approach is the bio-mimetic Pictet−Spengler condensation[8] in presence of a chiral catalyst. This process is highly attractive because of its high atom economy and because by the choice of the suitable substrate it is possible to modulate the C1 substituent.

The Pictet–Spengler reaction was discovered in 1911 and it is now widely used for the synthesis of a large variety of heterocyclic compounds named alkaloids.[9]

The first enantioselective catalytic Pictet–Spengler reaction was described by Jacobsen.[10] Following this initial report other asymmetric catalytic Pictet–Spengler reactions were reported using chiral

thioureas,[11] phosphoric acids[12] as catalysts, but in all cases the nucleophiles were limited to triptamine and its derivatives.[13] This observation is not surprising as a quick inspection in the Mayr scale can give a clear idea of the higher nucleophilicity of indole systems compared to benzene rings that allows them to react with iminium ions. Moreover the use of N(1)-free indoles enables the establishment of hydrogen bond recognition with the Brønsted acid catalyst or the thiourea. Thanks to the its peculiar electronic properties, the indolyl core is able to engage secondary interactions with aromatic substituents of the chiral organocatalyst offering an additional tool to control the reactivity.

The first example of a Friedel Craft reaction to access THIQ catalysed by chiral phosphoric acid TRIP was reported by Lete and coworkers.[14] They used electron rich benzene derivatives as internal nucleophiles on the N-acyl iminium ions generated in situ by the action of the chiral phosphoric acid that promoted the elimination of a water molecule. The resulting ion pair with the chiral catalyst allowed to obtain the product in 74% ee, but the reaction yields were quite low because of the low nucleophilicity of the benzene rings.

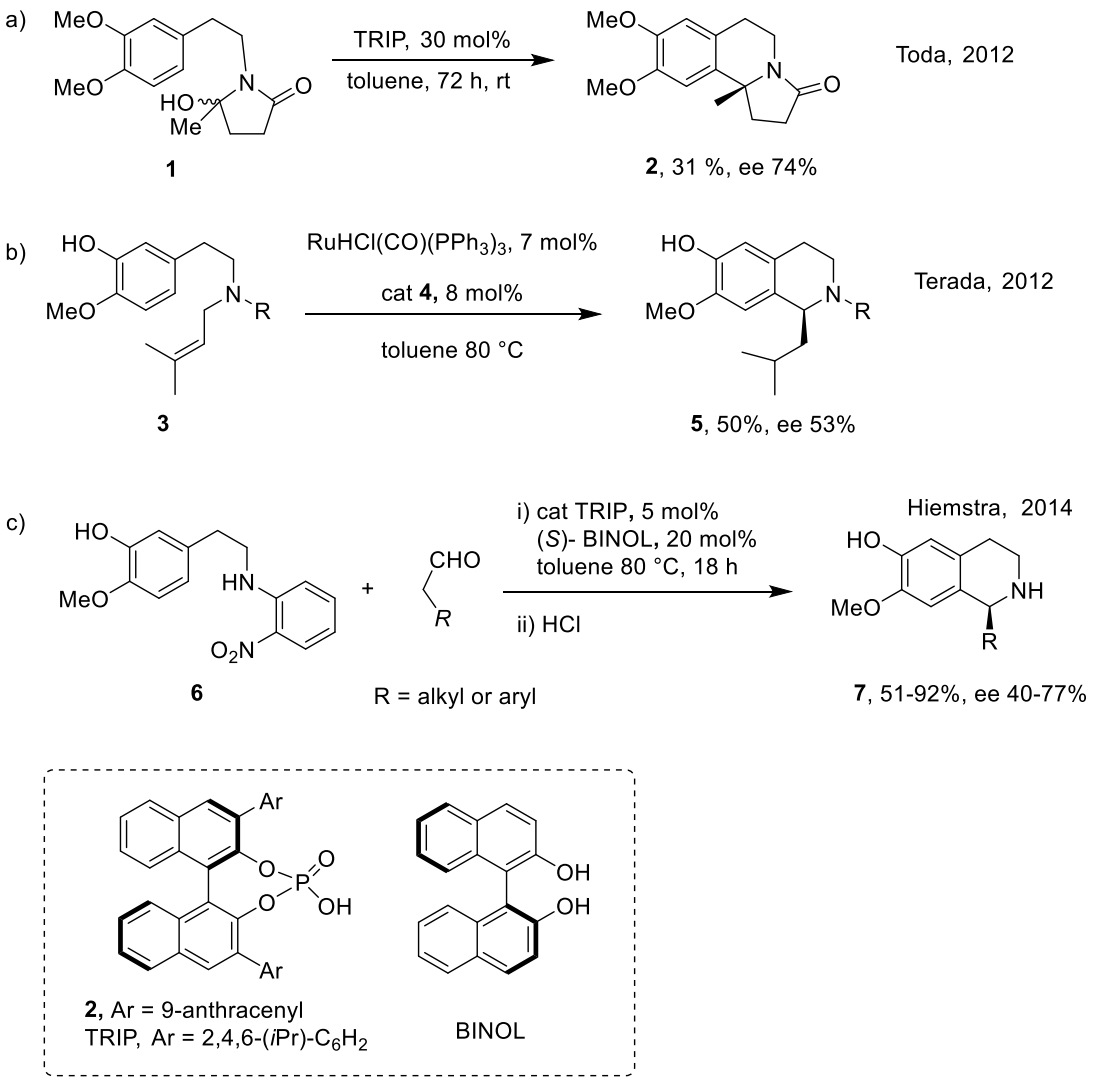
An alternative process has been reported by Toda and Terada,[15]. They described a ruthenium-catalyzed alkene isomerization combined with an enantioselective organocatalyzed Pictet−Spengler type cyclization reaction promoted by chiral phosphoric acid (Scheme 1). The products were obtained in moderate yield and ee.

A fully organocatalytic enantioselective Pictet-Spengler cyclization was also described by Hiemstra,[16] *N*-(*o*-nitrophenylsulfenyl)-phenylethylamines were condensed with aldehydes and the cyclization was promoted by [(*R*)-TRIP]-BINOL-phosphoric acid **43**. By using this new methodology, 10 natural products among which (*R*)-crispine A **62**, (*R*)-calycotomine **63** and (*R*)-colchietine **64** (Scheme 2) were obtained in good ee.

However, extra steps were required for the preparation of suitable starting materials and for the preparation of the final alkaloids (Scheme 1). In both cases, the use of a free OH group is necessary in order to enhance both enantioselectivity and nucleophilic reactivity of the thematic moiety.

In our general research interest on the development of new organocatalytic asymmetric methodologies to access tetrahydroisoquinoline scaffolds, we selected α-vinyl-substituted tetrahydroisoquinolines as a versatile and valuable building block bearing an moiety from which a wide class of alkaloids having a C1 linear substituent would be accessible. Moreover this would be a complementary methodology to the alkylation of aldehydes with isoquinolinium ions (chapter 2.2) that allows access to α-branched C1 substituted 1,2-dihydroisoquinolines.

The development of a highly enantioselective and effective Pictet-Spengler or Bischler-Napieralski approaches is problematic and unsuitable due the difficulties to use acrylaldehyde as an electrophile.[17] Indeed, it has been demonstrated that only substituted vinyl moieties can be introduced through the Pictet-Spengler condensation.




*Scheme 1. Previous catalytic asymmetric intramolecular cylcizations to obtain THIQs.*

The generation of an equivalent of acrylaldehyde, and its synthetically flexible route to α-vinyl-substituted tetrahydroisoquinoline building blocks, was described by Hiemstra and Rutjes in a [Sn(II)] or TFA-catalyzed cyclisation of allylic *N,O*-acetals (Figure 2).[18]
Allenamide appears as a suitable alternative synthetic route for the generation of this important intermediate. In particular, allenamides are highly susceptible towards metal and Brønsted acid promoted electrophilic activation[19] and this was clearly demonstrated by Navarro–Vazquez and Dominquez in the TFA-catalyzed synthesis of α-vinyl-substituted tetrahydroisoquinolines (Figure 2).[20] Moreover, allenamides were also used to access vinyl-isoquinoline by electrophilic activation with [gold(I)] complexes.[21]

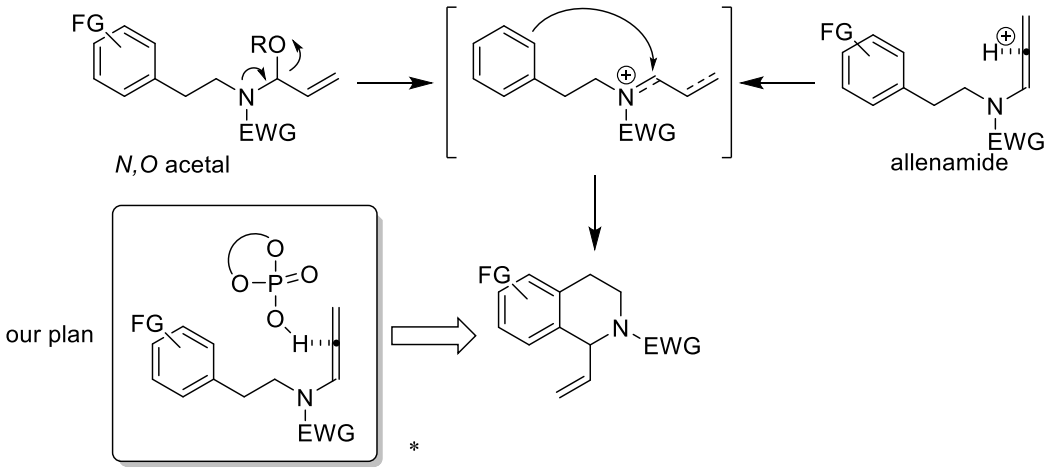
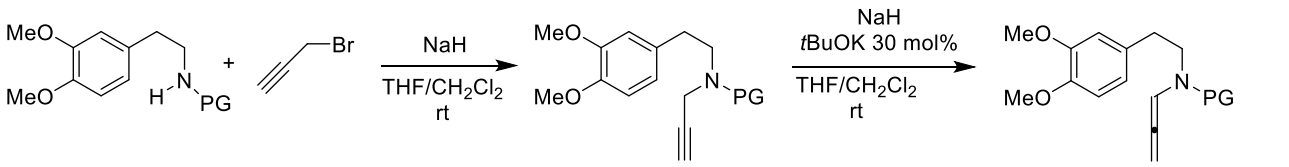



*Figure 2. Different approaches to obtain the key synthetic intermediate for the synthesis of 1-vinyl tetrahydroisoquinolines.*

## 2.3.2 Results and discussion

Based on these literature precedents and recent findings by some of us, we envisioned the use of chiral Brønsted acids with allenamides,[22] as a potent and effective way to prepare useful enantioenriched 1-vinyl tetrahydroisoquinoline precursors. We started our endeavor with the synthesis of the allenamides **18-22** carrying different electronwithdrawing groups (EWGs) at the nitrogen atom. The preparation of the amides **8-12** was straightforward and it is described in the experimental part. In order to improve the yield in the reaction with propargyl bromide, we carried out the propargylation of amides **8-12** in THF/$CH_2Cl_2$ due to the low solubility of the amides. During this step traces of corresponding allenamides **18-22** were isolated from the reaction mixture. The isolated propargylic amides 13-17 were then treated with *t*BuOK in THF following the described procedure[20] to give the desired allenamides **18-22** that, however, were only obtained in low yields. After considerable efforts we found a more suitable and reproducible last-step procedure employing NaH as base (1 equiv.) in the presence of a catalytic amount of *t*BuOK (30 mol%). The corresponding allenamides were obtained in low to excellent yields.
Therefore, allenamides **18-22** were efficiently cyclized to the desired racemic tetrahydroquinolines employing the reaction conditions described by Navarro–Vazquez and Dominquez (TFA 20 mol%, $CH_2Cl_2$, rt). The vinyl-substituted heterocyclic compounds **28-32** were isolated in moderate to good yields, through the Friedel-Crafts reaction of the intermediated iminium ion substituted with EWG groups. We have not investigated inactivated aromatic rings because it had already been reported that only electron-rich aromatic ring are capable to perform nucleophilic attach of the iminium ion. In fact, substrates lacking of methoxy groups on the aromatic ring failed to give the desired product also after prolonged reaction time and harsh conditions (50% TFA, DMF, 70 °C).[20] The formation of the six-membered ring was already shown to be favoured as homologous compounds failed to cyclize under the standard reaction condition. It is worth to mention that adventitious water can result in hydrolysis of the secondary amide, as the iminium ion is quite unstable. Therefore, anhydrous conditions proved to be essential for the reaction.




**8**, PG = Ts (Ts = 4-$MeC_6H_4SO_2$)
**9**, PG = PhCO
**10**, PG = 3,5 -$(CF_3)_2C_6H_3$
**11**, PG = Boc
**12**, PG = CHO

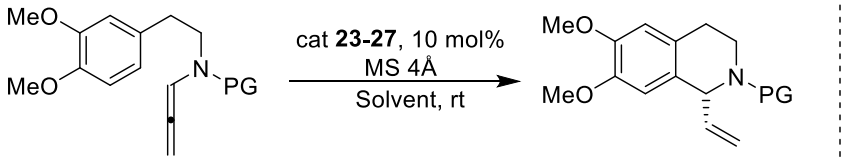
**13**, PG = Ts, 89 %
**14**, PG = PhCO, 18 %
**15**, PG = 3,5 -$(CF_3)_2C_6H_3$, 63 %
**16**, PG = Boc, 86 %
**17**, PG = CHO, 38 %

**18**, PG = Ts, 91 %
**19**, PG = PhCO, 10 %
**20**, PG = 3,5 -$(CF_3)_2C_6H_3$, 27 %
**21**, PG = Boc, 68 %
**22**, PG = CHO, 36 %

*Scheme 2. Preparation of the key allenamides compounds through a propargylation/rearrangement reaction sequence.*

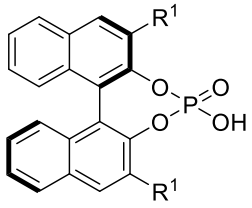
With the desired starting material in hand, we have investigated in details the stereoselective reaction by varying Brønsted acid, solvent, temperature, and using the differently substituted

allenamides **18**-**22** (Table 1). The Brønsted phosphoric acids screened were commercially available (**23**,**26**) or were prepared using standard protocols published in literature.[23]
A selection of results is depicted in Table 1, clearly outlining the importance of the EWGs in stabilizing the allenamide.




**18**, PG = Ts
**19**, PG = PhCO
**20**, PG = 3,5 -$(CF_3)_2C_6H_3$
**21**, PG = Boc
**22**, PG = CHO

**28**, PG = Ts
**29**, PG = PhCO
**30**, PG = 3,5 -$(CF_3)_2C_6H_3$
**31**, PG = Boc
**32**, PG = CHO




**23**, $R^1$ = 2,4,6-(*i*Pr)$_3$-$C_6H_2$
**24**, $R^1$ = 2,6-(*i*Pr)$_2$-4-adamantyl-$C_6H_2$
**25**, $R^1$ = 2,6-(*i*Pr)$_2$-4-Si(*i*Pr)$_3$-$C_6H_2$
**26**, $R^1$ = $SiPh_3$
**27**, $R^1$ = 2,4,6-Cyclohexyl-$C_6H_2$

| Entry[a] | allenamide | Solvent | cat | Yield (%)[b] | Ee (%)[c] |
|---|---|---|---|---|---|
| 1 | **18** | DCM | **23** | 63 | 24 |
| 2 | **19** | DCM | **23** | 65 | 20 |
| 3 | **20** | DCM | **23** | 30 | 34 |
| 4 | **21** | DCM | **23** | 63 | 0 |
| 5 | **22** | DCM | **23** | 40 | 47 |
| 6 | **22** | Toluene | **23** | 18 | 72[d] |
| 7 | **22** | $C_6H_5CF_3$ | **23** | 48 | 75[d] |
| 8 | **22** | Fluorobenzene | **23** | 36 | 70[d] |
| 9 | **22** | $C_6H_5CF_3$ | **24** | 27 | 79[d] |
| 10 | **22** | $C_6H_5CF_3$ | **25** | 33 | 78[d] |
| 11 | **22** | $C_6H_5CF_3$ | **26** | 40 | 81[d] |
| 12 | **22** | $C_6H_5CF_3$ | **27** | 26 | 72[d] |

[a] All the reactions were carried out in dried conditions under nitrogen atmosphere by using 0.1 mmol of allenamides, and 10 mol % of the catalyst, in 1 mL of solvent for 24 hours. [b] Isolated yields after chromatographic purification. [c] Determined by chiral HPLC analysis performed on the crude reaction mixture. [d] Determined by chiral HPLC analysis performed on the crude reaction mixture after reduction with $LiAlH_4$ of the formyl protecting group to the corresponding methyl group (See experimental part for details).

*Table 1. Friedel-Crafts reaction of protected allenamides in the presence of different Brønsted acids and conditions.*

In particular, although tosyl or other robust protecting groups (i.e. BOC, benzoyl, 3,5-$(CF_3)_2$-$C_6H_3CO$) proved competent under optimal conditions (cat TFA or cat Brønsted acids), low enantiomeric excesses were generally recorded (entries 1-4).
To address the lack of stereoselectivity we hypothesized that the presence of a hydrogen-donor site in the substrate could positively impact onto the stereochemical outcome of the protocol through the

instauration of supplementary binding sites and the chiral phosphates. As a results, we designed and realized the *N*-formyl allenamide **22**. The desired amide can easily be obtained by treating the corresponding amine with ethylformate under refluxing conditions for several hours (See SI for details).

With our delight, the prediction was verified and the enantiomeric excess for the product **32** improved considerably (Table 1, entry 5). The fine-tuning of the solvent and the catalyst (entry 6-12) allowed reaching an unprecedented ee of 81% for the synthesis of vinyl tetrahydroquinolines promoted by Brønsted acid catalysis.

As we have already mentioned in the article, the presence of activated molecular sieves is quite crucial to obtain satisfying yields. When very hindered chiral Brønsted acids are used, the reaction becomes quite slow, and even if all the precautions are taken, the presence of adventitious water can hydrolyze the iminium intermediate. The enantiomeric excesses were evaluated by chiral HPLC analysis for all the derivatives. However, in case of product **32** it was necessary to transform the formyl protecting group into the corresponding methyl by reduction ($LiAlH_4$) in order to properly separate the enantiomers. The absolute configuration of the obtained with product (*R,R*)-Brønsted phosphoric acid was established to be *R* by comparison of optical rotation with the value reported in literature.[24]

On the basis of this finding the model illustrated in Figure 3 is suggested for the transition state of the reaction. In particular, given the importance of the formyl group, we assume that the recognition and the high enantiomeric excess obtained for the reaction is determined by the hydrogen bonding of the catalyst with the hydrogen of the formyl group.[25]

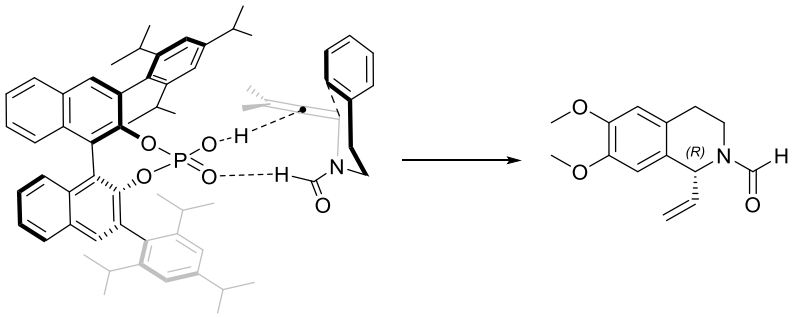



*Figure 3. Proposed transition state for the reaction.*

In order to evaluate the scope of this procedure, we have prepared the allenamides **33-36** (Figure 4), and we have submitted them to the optimized reactions conditions. Unfortunately, in all case we were unable to isolate any traces for the desired products. In the case of the allenamides **33**, **35**, and **36** the major hindrance of the substrates is probably retarding considerably the cyclization. In such conditions the hydrolysis of the iminium by adventitious water is competitive and we observed the presence of the corresponding. In case of allenamide **34** we can suggest that the reduced nucleophilicity of the aromatic ring can be responsible for the failure of the reaction.

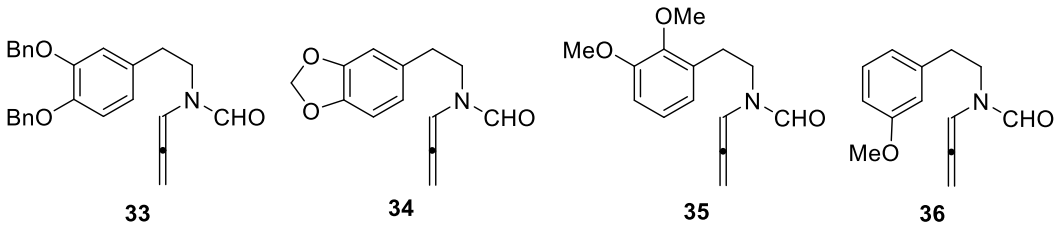



*Figure 4. Inert allenamides in the present protocol.*

### 2.3.3 Conclusions

In conclusion, by a careful design of the 2-phenylethylamine precursors, it is was possible to catalyze its cyclization to 1-vinyl tetrahydroisoquinoline in presence of chiral phosphoric acids, obtaining the highest enantiomeric excess reported for this type of transformation. The formyl protecting group turned out to be crucial for the catalysis by improving substrate/catalyst recognition via hydrogen bond interaction. The use of formyl group in other Brønsted acid catalyzed reactions is suggested. The obtained vinyl isoquinoline adduct is an useful and versatile building block to access isoquinoline alkaloids.[26]

### 2.3.4 Contributions

Dr. Andrea Gualandi was involved in the discovery of the reaction protocol. I contributed in the optimization of the reaction conditions. Dr. Andrea Gualandi and Elisabetta Manoni developed the project that was coordinated by Prof. Pier Giorgio Cozzi and Prof. Marco Bandini.

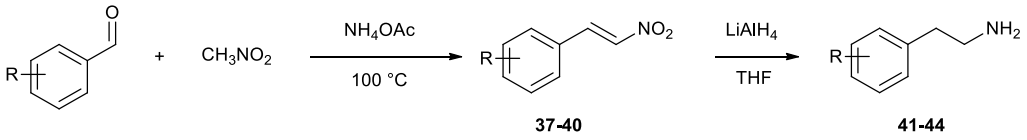
## 2.3.5 Experimental part.



**General methods.** $^{1}$H NMR spectra were recorded on Varian Gemini 200 and Varian MR400 spectrometers. Chemical shifts are reported in ppm from TMS with the solvent resonance as the internal standard (deuterochloroform: $\delta$ = 7.27 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = duplet, t = triplet, q = quartet, dd = double duplet, dt = double triplet, bs = broad signal, pd = pseudo duplet, pt = pseudo triplet, m = multiplet), coupling constants (Hz). $^{13}$C NMR spectra were recorded on Varian Gemini 200, Varian MR400 spectrometers. Chemical shifts are reported in ppm from TMS with the solvent as the internal standard (deuterochloroform: $\delta$ = 77.0 ppm). If rotamers are present, the splitted signals are labeled as A (major rotamer) and B (minor rotamer). GC-MS spectra were taken by EI ionization at 70 eV on a Hewlett-Packard 5971 with GC injection. LC-electrospray ionization mass spectra (ESI-MS) were obtained with Agilent Technologies MSD1100 single-quadrupole mass spectrometer. They are reported as: *m/z* (rel. intense). Chromatographic purification was done with 240-400 mesh silica gel. Purification on preparative thin layer chromatography was done on Merck TLC silica gel 60 $F_{254}$. Determination of enantiomeric excess was performed on Agilent Technologies 1200 instrument equipped with a variable wave-length UV detector (reference 420 nm), using Daicel Chiralpak® columns (0.46 cm I.D. x 25 cm) and HPLC grade isopropanol and *n*-hexane as eluting solvents. Optical rotations were determined in a 1 mL cell with a path length of 1 dm ($Na_D$ line). Melting points (m.p.) were determined on Bibby Stuart Scientific Melting Point Apparatus SMP3 and were not corrected.

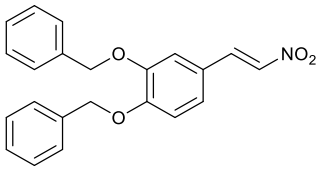
**Materials.** If not otherwise stated, all reactions were carried out in sealed vials in open air without nitrogen atmosphere. Anhydrous solvents were supplied by Aldrich in Sureseal® bottles and were used as received avoiding further purification.
Reagents were purchased from Aldrich and used without further purification unless otherwise stated.
The phosphoric acids **23-27** were preparing according to literature procedure.[27]

**General procedures for the synthesis of 2-aryl-ethylamines 41-44.**[28]

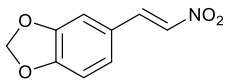



**Synthesis of nitrostyrene derivatives 37-40**

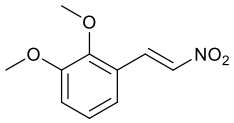
To a solution of aldehyde (15 mmol, 1 equiv.) in $CH_3NO_2$ (30 mL) was added $NH_4OAc$ (3.73 mmol, 287 mg, 0.25 equiv.) in one portion. The resultant mixture was stirred at 100 °C, until complete conversion was obtained (4h, monitored by TLC), cooled at room temperature and water was added. Nitromethane was removed under reduced pressure and the residue was extracted with AcOEt (3 x 10 mL).The combined organic layers were dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by column chromatography on silica gel (cyclohexane/ethyl acetate from 10:0 to 8:2) or by re-crystallization from ethanol (80-98% yield).



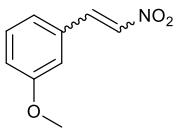
**(37)**: yellow solid, 4.39 g, 81% yield; m.p. 109-111°C; $^1$H NMR (400 MHz, $CDCl_3$): δ 5.20 (2H, s), 5.24 (2H, s), 6.97 (1H, d, *J* = 8.3 Hz), 7.08 (1H, d, *J* = 2.0 Hz), 7.12 (1H, dd, *J* = 8.3 Hz, *J* = 1.9 Hz), 7.33 (11H, m), 7.90 (1H, d, *J* = 13.6 Hz); $^{13}$CNMR (101 MHz, $CDCl_3$): δ 70.9, 71.4, 114.1, 114.3, 123.1, 124.8, 127.1 (2C), 127.2 (2C), 128.1 (2C), 128.7 (4C), 135.6, 136.2, 136.45, 139.1, 149.1, 152.7; Spectroscopic data are according to those reported in literature.[28]



**(38)**: yellow solid, 2.46 g, 85% yield; m.p. 148-150°C; $^1$H NMR (400 MHz, $CDCl_3$): δ 6.07 (2H, s), 6.88 (1H, d, *J* = 7.7 Hz), 7.01 (1H, d, *J* = 1.6 Hz), 7.09 (1H, dd, *J* = 8.2 Hz, *J* = 1.6 Hz), 7.48 ( 1H, d, *J* = 13.5 Hz), 7.94 (1H, d, *J* = 13.5 Hz); $^{13}$C NMR (101 MHz, $CDCl_3$): δ 102.1, 107.0, 109.0, 124.2, 126.6, 135.3, 139.1, 148.7, 151.4; Spectroscopic data are according to those reported in literature.[29]



**(39)**: yellow solid, 2.76 g, 88% yield; m.p. 80-83°C; Spectroscopic data are according to those reported in literature.[29]



**(40)**: yellow sticky solid, 1.88 g, 70% yield; $^1$H NMR (400 MHz, $CDCl_3$): δ 3.86 (3H, s), 7.04-7.07 (2H, m), 7.15 (1H, d, *J* = 7.9 Hz), 7.36-7.40 (1H, m), 7.58 (1H, d, *J* = 13.7 Hz), 7.98 (1H, d, *J* = 13.8 Hz); $^{13}$C NMR (101 MHz, $CDCl_3$): δ 55.4, 114.0, 117.9, 121.7, 130.4, 131.3, 137.3, 139.0, 160.1; Spectroscopic data are according to those reported in literature. [29]

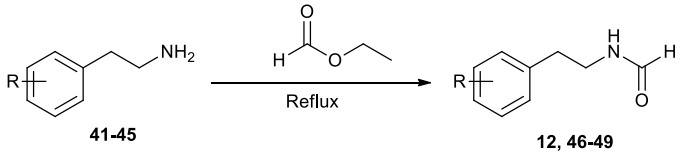
**Reduction of nitrostyrenes derivatives 37-40.**

To a stirred suspension of $LiAlH_4$ (30 mmol, 1.14 g, 3 equiv.) in THF (30 mL) at 0 °C, a solution of nitrostyrene derivative **37-40** (10 mmol, 1 equiv.) in THF (10 mL) was added dropwise. The mixture was allowed to reach room temperature and refluxed for 24 h. The mixture was cooled at 0

°C, diluted with $Et_2O$ (5 mL) and water (1.14 mL) was slowly added. After 15 minutes, 15% (*w/w)* aqueous NaOH solution (1.14 mL) was added followed after further 15 minutes by addition of water (3.42 mL). The resultant mixture was stirred at room temperature for 30 minutes, then $MgSO_4$ was added and it was filtered through a Celite pad and it was washed with $Et_2O$ (20 mL). The solvent was removed under reduced pressure to afford desired amine **41-44** that was used as such in the next reaction steps.

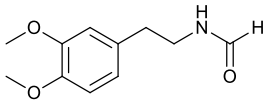
**General Procedure for the synthesis of allenamide derivatives 18-22 and 33-36.**

**Synthesis of formamide derivatives.**

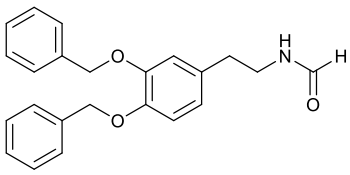



41-45 12, 46-49

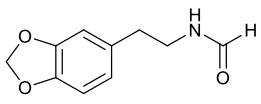
Amine **41-44** or 3,4-dimethoxyphenethylamine **45** (10 mmol, 1 equiv.) was dissolved in ethyl formate (20 mL) and the solution was refluxed for 24 h until complete conversion (monitored by $^1$HNMR). The solvent was removed under reduced pressure and the crude residue was purified by column chromatography on silica gel (cyclohexane/ethyl acetate from 8:2 to 1:1) to afford formamides **12**, **46-49**.



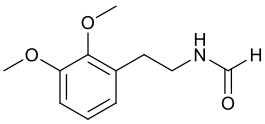
**(12)**: yellow oil, 1.43 g, 86% yield; Spectroscopic data are according to those reported in literature.[30]



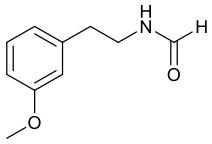
**(46)**: yellow oil, 1.91 g, 53% yield (two steps, from **37**); $^1$H NMR (400 MHz, $CDCl_3$, 25 °C) (two rotamers A:B, ratio 5.8:1): δ 2.70 ($2H_B$, t, *J* = 6.8 Hz), 2.72 ($2H_A$, t, *J* = 6.8 Hz), 3.39 ($2H_B$, q, *J* = 6.8 Hz), 3.48 ($2H_A$, q, *J* = 6.5 Hz), 5.16 ($4H_A$+$2H_B$, s), 5.18 ($2H_B$, s), 5.32 ($1H_A$, bs), 5.50 ($1H_B$, bs), 6.68-6.75 ($2H_A$+$2H_B$, m), 6.89 ($1H_A$+$1H_B$, d, *J* = 8.2 Hz), 7.30-7.46 ($10H_A$+$10H_B$, m), 7.89 ($1H_B$, d, *J* = 12Hz), 8.03 ($1H_A$, s); $^{13}$C NMR (101 MHz, $CDCl_3$): δ 34.9, 39.2, 71.3, 71.4, 115.4, 115.8, 121.6, 127.4 (2C), 127.4 (2C), 127.9, 127.9, 128.5 (4C), 132.0, 137.2, 137.3, 147.7, 148.8, 161.3;



**(47)**: yellow oil, 888 mg, 46% yield (two steps, from **38**); $^1$H NMR (400 MHz, $CDCl_3$) (two rotamers A:B, ratio 4.9:1): δ 2.70-2.77 ($2H_A$+$2H_B$, m), 3.38-3.45 ($2H_B$, m), 3.47-3.54 ($2H_A$, m), 5.92-5.94 ($2H_A$+$2H_B$, m), 6.60-6.76 ($3H_A$+$3H_B$, m), 7.90 ($1H_B$, t, *J* = 11.7 Hz), 8.11 ($1H_A$, d, *J* = 7.3 Hz); $^{13}$C NMR (101 MHz, $CDCl_3$): δ 35.0 ($1C_A$), 37.1 ($1C_B$), 39.4 ($1C_A$), 43.3 ($1C_B$), 100.7 ($1C_A$), 100.8 ($1C_B$), 108.1 ($1C_A$), 108.2 ($1C_B$) 108.9 ($1C_A$), 109.0 ($1C_B$), 121.5 ($1C_A$), 121.7 ($1C_B$), 131.5 ($1C_B$), 132.4 ($1C_A$), 146.0 ($1C_A$), 146.2 ($1C_B$), 147.6 ($1C_A$), 147.7 ($1C_B$), 161.6 ($1C_A$), 164.8 ($1C_B$);

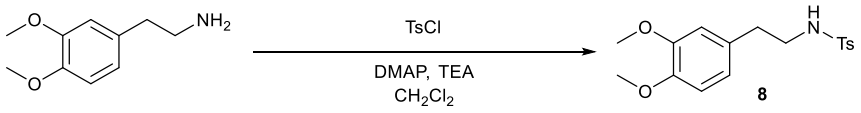


**(48)**: yellow oil, 1.11 g 53% yield (two steps, from **39**); $^{1}$H NMR (400 MHz, $CDCl_3$) (two rotamers A:B, ratio 1.1:1) : δ 2.84 ($2H_B$, t, *J* = 6.7 Hz), 2.87 ($2H_A$, t, *J* = 6.7 Hz), 3.48 ($2H_A$, pq, *J* = 6.2 Hz), 3.54 ($2H_B$, pq, *J* = 6.0 Hz), 3.85 ($3H_A$, s), 3.86 ($3H_B$, s), 3.88 ($3H_A$ + $3H_B$, s), 6.77-6.80 ($1H_A$+$1H_B$, m), 6.82-6.85 ($1H_A$+$1H_B$, m), 7.00-7.05 ($1H_A$+$1H_B$, m), 8.11 ($1H_A$+$1H_B$, s); $^{13}$C NMR (101 MHz, $CDCl_3$): δ29.57 ($1C_A$), 29.63 ($1C_B$), 39.0 ($1C_A$), 40.5 ($1C_B$), 55.6 ($2C_A$), 60.5 ($2C_B$), 110.8 ($1C_B$), 110.9 ($1C_A$), 122.16 ($1C_A$), 122.17 ($1C_B$), 124.1 ($1C_B$), 124.2 ($1C_A$), 132.5 ($1C_A$), 132.8 ($1C_B$), 146.99 ($1C_B$), 147.01 ($1C_A$), 152.57 ($1C_A$), 152.58 ($1C_B$), 161.6 ($1C_A$), 170.5 ($1C_B$);

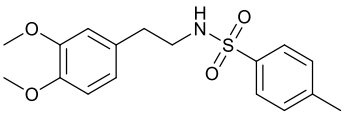


**(49)**: yellow oil, 1.22 g 68% yield (two steps, from **40**); Spectroscopic data are according to those reported in literature.[31]

**Preparation of compound 8.**

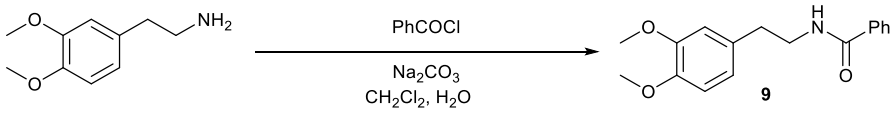



To a solution of 3,4-dimethoxyphenethylamine **45** (3 mmol, 543 mg, 1 equiv.) in DCM (10 mL), $Et_3N$ (4.5 mmol, 0.624 mL, 1.5 equiv.) and DMAP (0.075 mmol, 9.15 mg, 0.025 equiv.) were added. To the resulting solution at 0 °C, tosyl chloride (3.6 mmol, 688 mg, 1.2 equiv.) was slowly added in small portions. The mixture was allowed to reach room temperature and stirred for 24 h. Subsequently, water (10 mL) was added, the organic phase was separated and the aqueous layer was extracted with DCM (3 x 5 mL). The combined organic layers were washed with HCl 1M (10 mL), $NaHCO_3$ sat. sln. (10 mL) and brine (10 mL). The organic layers was dried with $Na_2SO_4$, filtered and concentrated under reduced pressure to give pure **8**, that was used as such, without further purification in the next steps.

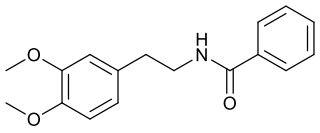


**(8)**: yellow solid, 894 mg, 89% yield; m.p. 133-135°C; $^{1}$H NMR (400 MHz, $CDCl_3$): δ 2.43 (3H, s), 2.71 (2H, t, *J* = 6.7 Hz), 3.19 (2H, q, *J* = 6.4 Hz), 3.82 (3H, s), 3.86 (3H, s), 4.37 (1H, bs), 6.57 (1H, s), 6.63 (1H, d, *J* = 8.5 Hz), 6.77 (1H, d, *J* = 8.5 Hz), 7.29 (2H, d, *J* = 7.6 Hz), 7.68 (2H, d, *J* = 7.8 Hz); $^{13}$C NMR (101 MHz, $CDCl_3$): δ 21.5, 35.3, 44.30, 55.7, 55.9, 111.3, 111.7, 120.7, 127.0 (2C), 129.6 (2C), 130.1, 136.8, 144.3, 147.8, 149.0; EI-MS: *m/z* = 335 (60), 184 (14), 151 (100), 91 (84).

**Preparation of compound 9.**

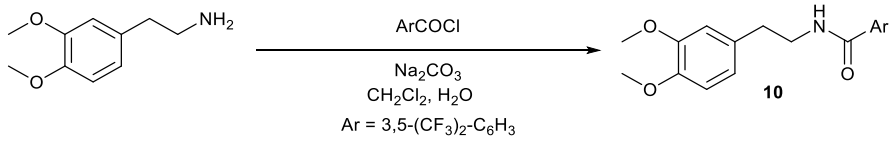



To a solution of 3,4-dimethoxyphenethylamine **45** (3 mmol, 543 mg, 1 equiv.) and $Na_2CO_3$ (6 mmol, 636 mg, 2 equiv.), in $H_2O$/DCM (1/1, 20 mL), PhCOCl (4.5 mmol, 0.521 mL, 1.5 equiv.) was added dropwise. The mixture was stirred for 72 h, then water (10 mL) and DCM (10 mL) were added. The organic phase was separated and the aqueous layer was extracted with $Et_2O$ (3 x 10 mL). The combined organic layers were washed with HCl 1M (15 mL), $NaHCO_3$ sat. sln. (15 mL) and brine (15 mL). The organic layers was dried with $Na_2SO_4$, filtered and concentrated under reduced pressure. The crude product was washed with *n*-hexane and then it was used such as, without further purification in the next steps.

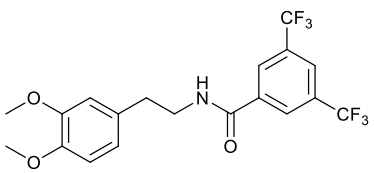


**(9)**: white solid, 710 mg, 83% yield; m.p. 63-65°C; $^1$H NMR (400 MHz, $CDCl_3$): δ 2.71-2.78 (2H, m), 3.38 (2H, m), 3.84 (3H, s), 3.85 (3H, s), 6.71-6.81 (3H, m), 7.34 (5H, s);$^{13}$C NMR (101 MHz, $CDCl_3$): δ 35.2 ($1C_A$+$1C_B$), 41.3 ($1C_A$+$1C_B$), 55.8 ($1C_A$+$1C_B$), 55.9 ($1C_A$+$1C_B$), 111.4 ($1C_A$+$1C_B$), 111.9 ($1C_A$+$1C_B$), 120.6 ($1C_A$+$1C_B$), 126.8 ($2C_A$+$2C_B$), 128.4 ($1C_B$), 128.5 ($2C_A$+$2C_B$), 130.1 ($1C_A$), 131.3 ($1C_B$), 131.4 ($1C_A$), 133.5 ($1C_A$), 134.5 ($1C_B$), 147.7 ($1C_A$+$1C_B$), 149.0 ($1C_A$+$1C_B$), 167.6 ($1C_A$+$1C_B$); EI-MS: *m/z* = 285 (8), 164 (100), 105 (53), 77 (48).

**Preparation of compound 10.**



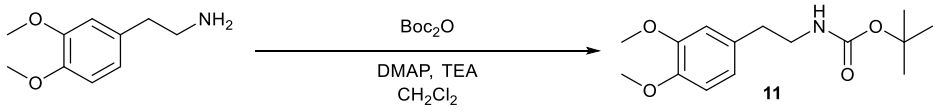

To a solution of 3,4-dimethoxyphenethylamine **45** (3 mmol, 543 mg, 1 equiv.) and $Na_2CO_3$ (6 mmol, 636 mg, 2 equiv.), in $H_2O$/DCM (1/1, 20 mL), 3,5-$(CF_3)_2$-$C_6H_3$-COCl (3.6 mmol, 0.637 mL, 1.2 equiv.) was added dropwise. The mixture was stirred for 72 h and then water (10 mL) and DCM (10 mL) were added.The organic phase was separated and the aqueous layer was extracted with $Et_2O$ (3 x 10 mL). The combined organic layers were washed with HCl 1M (15 mL), $NaHCO_3$ sat. sln. (15 mL) and brine (15 mL). The organic layers was dried with $Na_2SO_4$, filtered and concentrated under reduced pressure. The crude product was washed with *n*-hexane and then it was used such as, without further purification in the next steps.



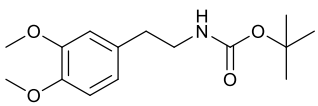
**(10)**: white solid, 1.23 g, 97% yield; m.p. 99-101°C; $^1$H NMR (400 MHz, $CDCl_3$): δ 2.93 (2H, t, *J* = 6.9 Hz), 3.75 (2H, q, *J* = 6.5 Hz), 3.88 (3H, s), 3.89 (3H, s), 6.18 (1H, bs), 6.77-6.80 (2H, m), 6.85 (1H, d, *J* = 7.8 Hz), 8.00 (1H, s), 8.14 (2H, s); $^{13}$C NMR (101 MHz,

$CDCl_3$): δ 35.1, 41.6, 55.8, 55.9, 111.4, 111.8, 120.7, 122.7 (2C, q, $J_{C-F}$ = 273.3 Hz), 124.9 (2C, t, $J_{C-F}$ = 4.1 Hz), 127.1 (2C, q, $J_{C-F}$ = 3.4 Hz), 130.8, 132.4, 136.7, 148.0, 149.3, 164.5; EI-MS: *m/z* = 421 (25), 241 (46), 213 (36), 164 (100).

**Preparation of compound 11.**[32]

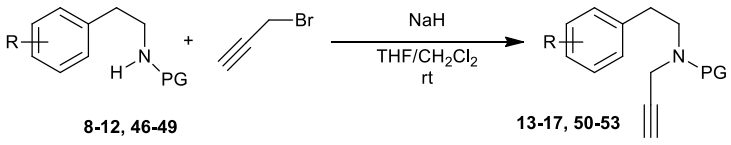



To a solution of 3,4-dimethoxyphenethylamine **45** (3 mmol, 543 mg, 1 equiv.) in DCM (10 mL), $Et_3N$ (4.5 mmol, 0.624 mL, 1.5 equiv.), DMAP (0.075 mmol, 9.15 mg, 0.025 equiv.) were added. To the resulting solution at 0 °C, $Boc_2O$ (3.6 mmol, 785 mg, 1.2 equiv.) was slowly added in small portions. The mixture was allowed to reach room temperature and stirred for 24 h. Subsequently, water (10 mL) was added, the organic phase was separated and the aqueous layer was extracted with $Et_2O$ (3 x 5 mL). The combined organic layers were washed with HCl 1M (10 mL), $NaHCO_3$ sat. sln. (10 mL) and brine (10 mL). The organic layers was dried with $Na_2SO_4$, filtered and concentrated under reduced pressure. The crude product was washed with *n*-hexane and then it was used such as, without further purification in the next steps.

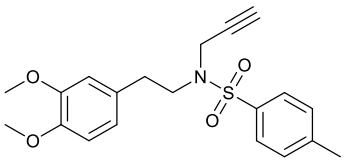


**(11)**: sticky yellow solid, 767 mg, 91% yield; $^1$H NMR (400 MHz, $CDCl_3$): δ 1.45 (9H, s), 2.75 (2H, t, *J* = 7.0 Hz), 3.33-3.38 (2H, m), 3.87 (3H, s), 3.88 (3H, s), 4.54 (1H, bs), 6.72-6.75 (2H, m), 6.82 (1H, d, *J* = 8.0 Hz); $^{13}$C NMR (101 MHz, $CDCl_3$): δ 28.4 (3C), 35.7, 41.9, 55.8, 55.9, 79.2, 111.3, 111.9, 120.6, 131.5, 147.5, 148.9, 155.8; EI-MS: *m/z* =281 (129, 225 (14), 209 (13), 165 (58), 151 (100), 57 (63). Spectroscopic proprieties are according to those reported in literature.[32]

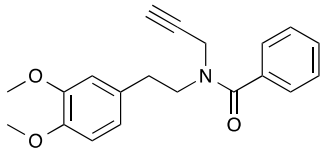
**General Procedure for the propargylation of amides.**



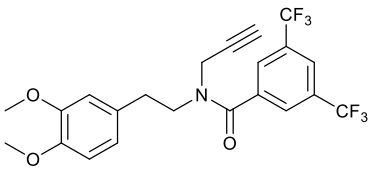

To a solution of **8-12**, **50-53** (5 mmol, 1 equiv.) in anhydrous THF (15 mL) and $CH_2Cl_2$ (5 mL) at 0 °C, NaH (6.5 mmol, 156 mg, 1.3 equiv.) was slowly added. After 20 minutes, propargyl bromide (6 mmol, 0.539 mL, 1.2 equiv.) was added at 0°C. The reaction mixture was allow to reach room temperature and it was stirred for 24 h. Water (10 mL) was slowly added at 0 °C and organic volatiles were removed under reduced pressure. The residue was extracted with AcOEt (3 x 5mL). The combined organic layers were dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by column chromatography on silica gel silica gel (cyclohexane/EtOAc 7/3) to give the desired products **13-17, 50-53**.



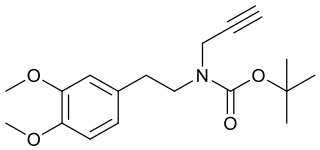
**(13)**: yellow solid, 1.66 g, 89% yield; m.p. 10-103°C; $^{1}$H NMR (400 MHz, $CDCl_3$): δ 2.06 (1H, t, *J* = 2.4 Hz), 2.42 (3H, s), 2.86 (2H, pt, *J* = 7.6 Hz), 3.42 (2H, pt, *J* = 7.6 Hz), 3.87 (3H, s), 3.88 (3H, s), 4.08 (2H, d, *J* = 2.5 Hz), 6.74 (1H, s), 6.75 (1H, d, *J* = 6.9 Hz), 6.80 (1H, d, *J* = 8.7 Hz), 7.28 (2H, d, *J* = 6.6 Hz), 7.71 (2H, d, *J* = 8.2 Hz); $^{13}$C NMR (101 MHz, $CDCl_3$): δ 21.5, 34.3, 36.8, 48.0, 55.86, 55.87, 73.7, 76.7, 111.3, 112.0, 120.7, 127.6 (2C), 129.4 (2C), 130.7, 135.9, 143.5, 147.7, 148.9; EI-MS: *m/z* = 373 (42), 222 (100), 155 (95), 151 (86), 91 (75).



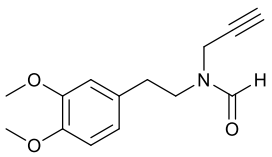
**(14)**: yellow oil, 291 mg, 18% yield; Although numerous attempts by changing solvent and temperature, it has never been possible to obtain a well resolved spectrum of the product. $^{1}$H NMR (400 MHz, $CDCl_3$, 25 °C) : δ 2.30 (2H, t, *J* = 2.5 Hz), 2.76 (1H, bs), 2.98 (1H, bs), 3.62 (1H, bs), 3.73 (1H, bs), 3.84 (6H, bs), 4.42 (2H, bs), 6.41 (1H, bs), 6.75 (2H, bs), 7.20 (1H, bs), 7.39 (4H, bs); $^{13}$C NMR (101 MHz, $CDCl_3$): δ 33.0 ($1C_B$), 34.2 ($1C_A$), 40.0 ($1C_A$+$1C_B$), 47.3 ($1C_A$), 50.2 ($1C_B$), 55.8 ($2C_A$), 55.9 ($2C_A$), 72.4 ($1C_A$), 73.0 ($1C_B$), 78.8 ($1C_A$+$1C_B$), 113.3 ($1C_A$+$1C_B$), 111.8 ($1C_B$), 112.0 ($1C_A$), 120.7 ($2C_A$+$2C_B$), 126.7 ($2C_A$+$2C_B$), 128.4 ($1C_A$+$1C_B$), 129.9 ($1C_B$), 130.2 ($1C_A$), 131.3 ($1C_A$), 131.4 ($1C_A$), 135.7 ($1C_A$+$1C_B$), 147.7 ($2C_B$), 148.9 ($1C_A$), 171.1 ($1C_A$+$1C_B$); EI-MS: *m/z* = 323 (4), 164 (100), 105 (89), 77 (64).



**(15)**: yellow oil, 291 mg, 18% yield; Although numerous attempts by changing solvent and temperature, it has never been possible to obtain a well resolved spectrum of the product. $^{1}$H NMR (400 MHz, $CDCl_3$, 25 °C) (two rotamers A:B, ratio 1:1):δ 2.73 ($1H_A$+$1H_B$, t, *J* = 2.5 Hz), 2.80 ($2H_A$, bs), 2.99 ($2H_B$, bs),3.60 ($2H_A$, bs),3.75 ($2H_A$+$2H_B$, bs),3.84 ($6H_A$+$6H_B$, bs), 4.47 ($2H_B$, bs), 6.44 ($1H_A$, bs),6.50 ($1H_B$, bs),6.74 ($2H_A$, bs),6.80 ($2H_B$, bs), 7.51 ($1H_A$+$1H_B$, bs), 7.87 ($2H_A$, bs), 7.96 ($2H_B$, bs); $^{13}$C NMR (101 MHz, $CDCl_3$): δ 33.0 ($1C_B$), 33.6 ($1C_A$), 34.2 ($1C_A$), 39.9 ($1C_B$), 47.7 ($2C_B$), 50.3 ($2C_A$), 73.2 ($1C_A$), 73.8 ($1C_B$), 77.9 ($1C_A$+$1C_B$), 112.2 ($1C_A$+$1C_B$), 111.9 ($1C_A$+$1C_B$), 120.7 ($1C_A$+$1C_B$), 122.9 ($2C_A$+$2C_B$, q, $J_{C\text{-}F}$ = 271.5 Hz), 123.3 ($1C_A$), 123.7 ($1C_B$), 124.1 ($1C_A$+$1C_B$), 127.0 ($1C_A$+$1C_B$, bs), 129.3 ($1C_B$), 130.8 ($1C_A$), 131.2 ($2C_A$+$2C_B$), 137.7 ($1C_A$+$1C_B$), 147.9 ($1C_A$), 148.0 ($1C_B$), 149.1 ($1C_A$+$1C_B$), 168.0 ($1C_B$), 168.5 ($1C_A$); EI-MS: *m/z* = 459 (9), 241 (88), 213 (67), 164 (100).

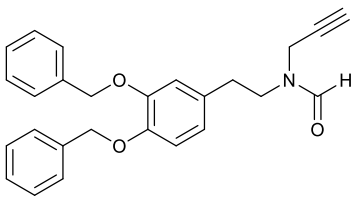


**(16)**: sticky white solid, 1.37 g, 86% yield; $^{1}$H NMR (400 MHz, $CDCl_3$): δ 1.46 (9H, s), 2.22 (1H, s), 2.83 (2H, bs), 3.52 (2H, pt, *J* = 7.4 Hz), 3.86 (3H, s), 3.88 (3H, s), 4.03 (2H, bs), 6.74-6.82 (3H, m); $^{13}$C NMR (101 MHz, $CDCl_3$): δ 28.3, 29.7, 30.9, 48.5, 55.8, 55.9, 71.5, 79.9, 80.1, 111.3, 111.0, 120.7, 131.7, 147.5, 148.9, 154.8; EI-MS: *m/z* = 319 (31), 246 (25), 151 (100), 57 (87).

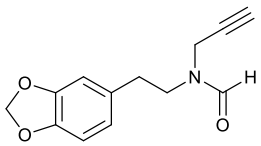


**(17)**: yellow oil, 469 mg, 38% yield; $^{1}$H NMR (400 MHz, $CDCl_3$) (two rotamers A:B, ratio 2:1): δ 2.28 ($1H_B$, t, *J* = 2.3 Hz), 2.34 ($1H_A$, t, *J* = 2.5 Hz), 2.85 ($2H_A$, pt, *J* = 6.8 Hz), 2.86 ($2H_B$, pt, *J* = 6.4 Hz), 3.60 ($2H_A$, pt, *J* = 6.8 Hz), 3.63 ($2H_B$, pt, *J* = 6.8 Hz), 3.86 ($3H_A$, s), 3.87 ($3H_A$+$3H_B$, s), 3.88

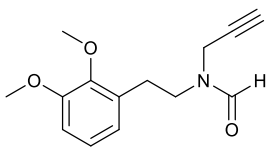
($3H_B$, s), 4.18 ($2H_A$+$2H_B$, d, *J* = 2.4 Hz), 6.67-6.83 ($3H_A$+$3H_B$, m), 7.80 ($1H_A$, bs), 8.10 ($1H_B$, bs); $^{13}$C NMR (101 MHz, $CDCl_3$): δ 31.4 ($1C_A$), 32.8 ($1C_B$), 34.4 ($1C_A$), 37.5 ($1C_B$), 43.9 ($1C_B$), 48.7 ($1C_A$), 55.8 ($2C_A$+ $2C_B$), 72.5 ($1C_A$), 73.6 ($1C_B$), 77.7 ($1C_B$), 78.0 ($1C_A$), 111.3 ($1C_B$), 111.4 ($1C_A$), 111.8 ($1C_B$), 111.9 ($1C_A$), 120.6 ($1C_B$), 120.8 ($1C_A$), 130.1 ($1C_A$), 130.9 ($1C_B$), 147.6 ($1C_B$), 147.8 ($1C_A$), 148.9 ($1C_B$), 149.0 ($1C_A$), 162.1 ($1C_A$), 162.1 ($1C_B$); ESI-MS: *m/z* = 248.2 $[M+H]^+$, 270.0 $[M+Na]^+$, 495.2 $[2M+H]^+$; ESI-MS: *m/z* = 248.0 $[M+H]^+$, 270.0 $[M+Na]^+$, 495.2 $[2M+H]^+$.



**(50)**: brown oil, 1.26 g, 63% yield;$^1$H NMR (400 MHz, $CDCl_3$) (two rotamers A:B, ratio 1.7:1): δ 2.23 ($1H_A$, t, *J* = 2.2 Hz), 2.29 ($1H_B$, t, *J* = 2.0 Hz), 2.78 ($2H_A$, t, *J* = 6.8 Hz), 2.80 ($2H_B$, t, *J* = 7.02 Hz), 3.49 ($2H_B$, t, *J* = 6.9 Hz), 3.52 ($2H_A$, t, *J* = 6.8 Hz), 3.68 ($2H_B$, d, *J* = 1.6 Hz), 4.13 ($2H_A$, d, *J* = 2.2 Hz), 5.14 ($2H_A$+$2H_B$, s), 5.16 ($2H_A$, s), 5.18 ($2H_B$, s), 6.67 ($1H_A$, d, *J* =8.3 Hz), 6.73 ($1H_A$, s), 6.74 ($1H_B$, s), 6.80 ($1H_B$, s), 6.88 ($1H_A$+$1H_B$, d, *J* = 8.0 Hz), 7.30-7.45 ($10H_A$+$10H_B$, m), 7.71 ($1H_A$, s), 8.00 ($1H_B$, s); $^{13}$C NMR (101 MHz, $CDCl_3$)(two rotamers A:B, ratio 6:1): δ 31.4 ($1C_A$), 32.9 ($1C_B$), 34.3 ($1C_A$), 37.6 ($1C_B$), 44.1 ($1C_B$), 48.5 (1CA), 71.4 (1CB), 71.4 (1CA), 71.5 ($1C_A$), 73.5 ($1C_B$), 77.8 ($1C_B$), 78.0 ($1C_A$), 115.4 ($1C_A$), 115.5 ($1C_B$), 115.8 ($1C_B$), 116.0 ($1C_A$), 121.6 ($1C_B$), 121.8 ($1C_A$), 127.3 ($4C_A$), 127.4 ($4C_B$), 127.76 ($2C_B$), 127.80 ($1C_A$), 127.82 ($1C_A$), 128.44 ($2C_B$), 128.46 ($2C_A$), 128.48 ($2C_B$), 128.5 ($2C_A$), 131.0 ($1C_A$), 132.0 ($1C_B$), 137.2 ($1C_A$+$1C_B$), 137.2 ($1C_A$ +$1C_B$), 147.6 ($1C_B$), 147.9 ($1C_A$), 148.9 ($1C_B$), 149.0 ($1C_A$), 162.1 ($1C_A$), 162.1 ($1C_B$); ESI-MS: *m/z* = 400.2 $[M+H]^+$, 422.2 $[M+Na]^+$, 799.4 $[2M+H]^+$.

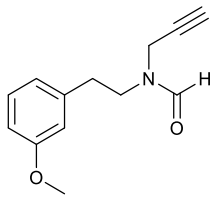


**(51)**: yellow oil, 658 mg, 57% yield; $^1$H NMR (400 MHz, $CDCl_3$) (two rotamers A:B, ratio 1.9:1): δ 2.28 ($1H_A$, t, *J* = 2.6 Hz), 2.34 ($1H_B$, t, *J* = 2.5 Hz), 2.83 ($2H_A$+$2H_B$, t, *J* = 6.7 Hz), 3.58 ($2H_A$, t, *J* =7.5 Hz), 3.62 ($2H_B$, pt, *J* = 7.4 Hz), 3.90 ($2H_B$, d, *J* = 2.1 Hz), 4.19 ($2H_A$, d, *J* = 2.2 Hz), 5.94 ($2H_B$, s), 5.95 ($2H_A$, s), 6.60-6.76 ($3H_A$+$3H_B$, m), 7.82 ($1H_A$, s), 8.11 ($1H_B$, s); $^{13}$C NMR (101 MHz, $CDCl_3$): δ 31.2 ($1C_A$), 32.9 ($1C_B$), 34.4 ($1C_A$), 37.4 ($1C_B$), 44.1 ($1C_B$), 48.5 ($1C_A$),72.6 ($1C_A$), 73.7 ($1C_B$), 77.9 ($1C_B$), 78.0 ($1C_A$), 100.8 ($1C_B$), 100.9 ($1C_A$), 108.2 ($1C_B$), 108.3 ($1C_A$), 108.9 ($1C_A$), 109.0 ($1C_B$), 121.5 ($1C_B$), 121.7 ($1C_A$), 131.3 ($1C_A$), 132.2 ($1C_B$), 146.0 ($1C_B$), 146.3 ($1C_A$), 147.6 ($1C_B$), 147.8 ($1C_A$), 162.0 ($1C_A$), 162.1 ($1C_B$); ESI-MS: *m/z* = 232.2 $[M+H]^+$, 254.0 $[M+Na]^+$, 463.2 $[2M+H]^+$.



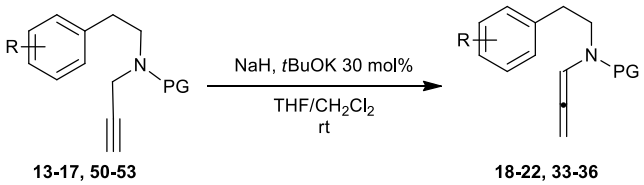
**(52)**: yellow oil, 630 mg, 51% yield;$^1$H NMR (400 MHz, $CDCl_3$) (two rotamers A:B, ratio 2.2:1): δ 2.26 ($1H_A$, t, *J* = 2.6 Hz), 2.31 ($1H_B$, t, *J* = 2.5 Hz), 2.91 ($2H_A$, t, *J* = 6.9Hz), 2.92 ($2H_B$, t, *J* = 7.0 Hz), 3.61 ($2H_A$, t, *J* = 7.0 Hz), 3.67 ($2H_B$, t, *J* = 7.3 Hz), 3.85 ($6H_B$, s), 3.87 ($6H_A$, s), 3.92 ($2H_B$, d, *J* = 2.5 Hz), 4.22 ($2H_A$, d, *J* = 2.5 Hz), 6.72 ($1H_A$, dd, $J_1$ = 7.7 Hz, $J_2$ = 1.4 Hz), 6.81-6.84 ($1H_A$ + $2H_B$, m), 6.99 ($1H_A$ + $1H_B$, pt, *J* = 8.0 Hz), 7.82 ($1H_A$, s), 8.10 ($1H_B$, s); $^{13}$C NMR (101 MHz, $CDCl_3$): δ27.6 ($1C_B$), 29.4 ($1C_A$), 31.1 ($1C_A$), 37.3 ($1C_B$), 43.0 ($1C_B$), 47.3 ($1C_A$), 55.50 ($1C_B$), 55.51 ($1C_A$), 60.4 ($1C_A$), 60.6 ($1C_B$), 72.4 ($1C_A$), 73.5 ($1C_B$), 78.0 ($1C_B$), 78.1 ($1C_A$), 110.9 ($1C_B$), 111.3 ($1C_A$), 122.11 ($1C_A$), 122.13 ($1C_B$), 123.9 ($1C_B$), 124.0 ($1C_A$), 131.2 ($1C_A$), 132.1 ($1C_B$), 147.15 ($1C_A$),

147.23 ($1C_B$), 152.55 ($1C_B$), 152.62 ($1C_A$), 162.0 ($1C_A$), 162.1 ($1C_B$); ESI-MS: *m/z* = 248.2 $[M+H]^+$, 270.0 $[M+Na]^+$, 494.2 $[2M+H]^+$.

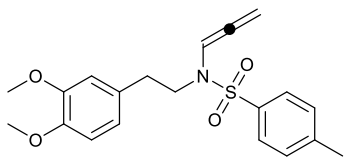


**(53)**: yellow oil, 521 mg, 48% yield;$^1$H NMR (400 MHz, $CDCl_3$) (two rotamers A:B, ratio 1.8:1): δ 2.28 ($1H_A$, t, *J* = 2.5 Hz), 2.34 ($1H_B$, t, *J* = 2.5 Hz), 2.87-2.91 ($2H_A$+$2H_B$, m), 3.63 ($2H_A$, t, *J* = 7.1Hz), 3.68 ($2H_B$, t, *J* =7.5 Hz), 3.80 ($3H_A$, s), 3.81 ($3H_B$, s), 3.88 ($2H_B$, d, *J* = 2.6 Hz), 4.20 ($2H_A$, d, *J* = 2.6 Hz), 6.72-6.85 ($3H_A$+$3H_B$, m), 7.21-7.26 ($1H_A$+$1H_B$), 7.84 ($1H_A$, s), 8.11 ($1H_B$, s); $^{13}$C NMR (101 MHz, $CDCl_3$): δ 31.3 ($1C_A$), 33.3 ($1C_B$), 34.7 ($1C_A$), 37.4 ($1C_B$), 43.8 ($1C_B$), 48.3 ($1C_A$), 55.01 ($1C_B$), 55.02 ($1C_A$), 72.6 ($1C_A$), 73.8 ($1C_B$), 77.9 ($1C_B$), 78.1 ($1C_A$), 111.88 ($1C_B$), 111.91 ($1C_A$), 114.3 ($1C_B$), 114.6 ($1C_A$), 120.96 ($1C_A$), 120.98 ($1C_B$), 129.5 ($1C_B$), 129.7 ($1C_A$), 139.3 ($1C_A$), 140.1 ($1C_B$), 159.7 ($1C_B$), 159.8 ($1C_A$), 162.0 ($1C_B$), 162.3 ($1C_A$); ESI-MS: *m/z* = 218.2 $[M+H]^+$, 240.2 $[M+Na]^+$, 435.2 $[2M+H]^+$.

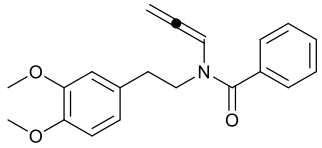
**General Procedure for the isomerization to allenamide compounds 18-22, 33-36.**




To a solution of propargylic amide (**13-17, 50-53**) (1.5 mmol, 1 equiv.) in THF (8 mL) at 0°C, *t*BuOK (0.3 mmol, 33.6 mg, 0.2 equiv.) and NaH (1.5 mmol, 36 mg, 1 equiv.) were added. The reaction was stirred for 24 h at room temperature, and then it was quenched with water (5 mL) at 0 °C. THF was removed under reduced pressure and the aqueous layer was extracted with ethyl acetate (3 x 5 mL). The combined organic layers were dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by column chromatography on silica gel silica gel (cyclohexane/EtOAc 7/3) to give the desired products **18-22, 33-36**.

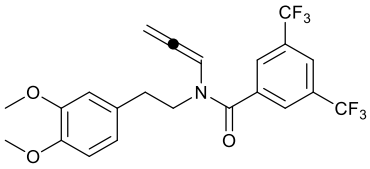


**(18)**: yellow oil, 509 mg, 91% yield;$^1$H NMR (400 MHz, $CDCl_3$): δ 2.42 (3H, s), 2.82 (2H, pt, *J* = 8.0 Hz), 3.32 (2H, pt, *J* = 8.0 Hz), 3.85 (3H, s), 3.87 (3H, s), 5.39 (2H, d, *J* = 6.4 Hz), 6.70 (2H, bs), 6.77-6.79 (1H, m), 6.88 ( 1H, t, *J* = 6.2 Hz), 7.30 (2H, d, *J* = 7.8 Hz), 7.68 (2H, d, *J* =7.80 Hz);$^{13}$C NMR (101 MHz, $CDCl_3$): δ 21.4, 34.0, 48.1, 55.6, 55.7, 87.6, 100.0, 111.1, 112.0, 120.6, 126.9 (2C), 129.6 (2C), 130.8, 135.3, 143.6, 147.5, 148.7, 201.4; ESI-MS: *m/z* = 374.0 $[M+H]^+$, 396.0 $[M+Na]^+$, 769.0 $[2M+H]^+$.

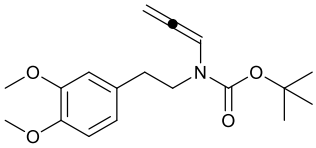


**(19)**: brown oil, 49 mg, 64% yield; although numerous attempts by changing solvent and temperature, it has never been possible to obtain a well resolved spectrum of the product. $^1$H NMR (400 MHz, $CDCl_3$, 25 °C) (two rotamers A:B, ratio 2:1): δ2.78 ($2H_B$, bs), 2.94 ($2H_A$, bs), 3.64 ($2H_B$, bs),3.77 ($2H_A$, bs), 3.89 ($6H_A$+$6H_B$, bs), 5.40 ($2H_A$, bs), 5.53 ($2H_B$, bs), 6.68 ($3H_b$, bs), 6.83

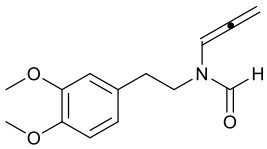
(3$H_A$, bs), 7.18 (1$H_A$+1$H_B$, m), 7.46 (5$H_A$+5$H_B$, bs); $^{13}$C NMR (50 MHz, $CDCl_3$): δ 35.4 (1$C_A$+1$C_B$), 41.3 (1$C_A$+1$C_B$), 55.9 (1$C_A$+1$C_B$), 56.0 (1$C_A$+1$C_B$), 111.4 (1$C_B$), 111.5 (1$C_B$), 111.6 (1$C_A$), 112.1 (1$C_A$), 120.8 (1$C_A$), 120.9 (1$C_A$), 121.0 (2$C_B$), 126.9 (2$C_A$+2$C_B$), 128.5 (1$C_A$+1$C_B$), 128.7 (2$C_A$+2$C_B$), 131.5 (1$C_A$+1$C_B$), 134.7 (1$C_A$+1$C_B$), 147.9 (1$C_A$), 149.0 (1$C_B$), 149.1 (1$C_B$), 149.2 (1$C_A$), 151.1 (1$C_B$), (1$C_A$+1$C_B$), 167.5 (1$C_A$+1$C_B$), 198.1 (1$C_A$+1$C_B$); ESI-MS: *m/z* = 324.2 $[M+H]^+$.



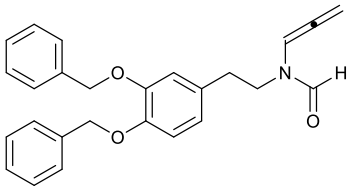

**(20)**: yellow oil, 185 mg, 27% yield; although numerous attempts by changing solvent and temperature, it has never been possible to obtain a well resolved spectrum of the product. $^1$H NMR (400 MHz, $CDCl_3$, 25 °C) (two rotamers A:B, ratio 3:1):δ 2.77 (2$H_B$, bs), 2.93 (2$H_B$, t, *J* = 7.2 Hz), 2.80 (2$H_A$, bs),3.59 (2$H_B$, bs),3.75 (2$H_A$, bs), 3.84 (6$H_A$+6$H_B$, bs), 5.40 (2$H_A$, d, *J* = 5.9 Hz),5.57 (2$H_B$, bs), 6.36-6.45 (1$H_A$+1$H_B$, bs),6.71-6.80 (2$H_A$+2$H_B$, bs), 7.40 (2$H_A$, bs),7.62 (2$H_B$, bs), 7.86 (2$H_A$, bs),7.94 (2$H_B$, bs); $^{13}$C NMR (101 MHz, $CDCl_3$): δ 33.1, 46.4, 55.9 (2C), 87.5, 101.4, 112.3, 113.2, 121.0 (2C), 122.3 (2C, q, $J_{C-F}$ = 272.4 Hz), 123.9 (1C, m), 128.3 (2C, bs), 131.9 (2C), 137.4, 149.1, 151.1, 168.3, 198.1; ESI-MS: *m/z* = 460.2 $[M+H]^+$, 492.0 $[M+Na]^+$.




**(21)**: yellow oil, 325 mg, 80% yield; Although numerous attempts by changing solvent and temperature, it has never been possible to obtain a well resolved spectrum of the product. $^1$H NMR (200 MHz, $CDCl_3$, 25 °C) (two rotamers A:B, ratio 1:1): δ1.38 (9$H_A$, bs), 1.47(9$H_B$, bs), 2.73 (2$H_A$+2$H_B$, bs),3.52 (2$H_A$+2$H_B$, bs),3.83 (3$H_A$+3$H_B$, bs),3.84 (3$H_A$+3$H_B$, bs), 5.37 (2$H_A$+2$H_B$, bs), 6.65-6.78 (3$H_A$+3$H_B$, m), 6.98 (1$H_A$, m),7.16 (1$H_A$, m); ESI-MS: *m/z* = 319.1 $[M+H]^+$, 342.0 $[M+Na]^+$, 639.2 $[2M+H]^+$;

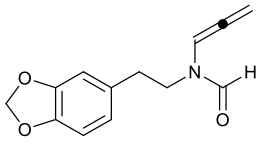



**(22)**: brown oil, 133 mg, 36% yield;$^1$H NMR (400 MHz, $CDCl_3$) (two rotamers A:B, ratio 1.2:1): δ 2.77-2.83 (2$H_A$ + 2$H_B$, m), 3.56 (2$H_A$, t, *J* = 6.6 Hz), 3.63-3.67 (2$H_B$, m), 3.86 (6$H_B$,s), 3.87 (3$H_A$, s), 3.88 (3$H_A$, s), 5.48 (2$H_B$, d, *J* = 6.3 Hz), 5.51 (2$H_A$, d, *J* = 6.6 Hz), 6.58 (1$H_A$, t, *J* = 6.3 Hz), 6.64-6.82 (3$H_A$ + 3$H_B$, m), 7.30 (1$H_B$, t, *J* = 6.4 Hz), 7.76 (1$H_B$, s), 8.20 (1$H_A$, s);$^{13}$C NMR (101 MHz, $CDCl_3$): δ 32.8 (1$C_B$), 34.0 (1$C_A$), 43.5 (1$C_B$), 48.2 (1$C_A$), 55.8 (2$C_B$), 55.9 (2$C_A$), 87.3 (1$C_A$), 87.9 (1$C_B$), 97.4 (1$C_A$), 100.4 (1$C_B$), 111.2 (1$C_B$), 111.4 (1$C_A$), 112.0 (1$C_B$), 112.0 (1$C_A$), 120.7 (1$C_B$), 120.9 (1$C_A$), 130.4 (1$C_A$), 131.0 (1$C_B$), 147.6 (1$C_A$), 147.9 (1$C_B$), 148.8 (1$C_B$), 149.0 (1$C_A$), 160.3 (1$C_B$), 160.5 (1$C_A$), 200.4 (1$C_A$), 202.2 (1$C_B$); ESI-MS: *m/z* = 248.0 $[M+H]^+$, 270.0 $[M+Na]^+$, 495.2 $[2M+H]^+$.

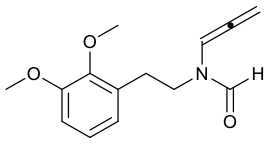



**(33)**: yellow oil, 479 mg, 80% yield; $^1$H NMR (400 MHz, $CDCl_3$) (two rotamers A:B, ratio 1.7:1): δ 2.71-2.75 (2$H_A$+2$H_B$, m), 3.46-3.52 (2$H_A$, m), 3.59 (2$H_B$, t, *J* = 7.7 Hz), 5.14 (4$H_A$, s), 5.15 (2$H_B$, s), 5.17 (2$H_B$, s), 5.38 (2$H_B$, d, *J* = 6.2 Hz), 5.45 (2$H_A$, d, *J* = 6.4 Hz), 6.45 (1$H_A$, t, *J* = 6.3 Hz), 6.64 (1$H_A$, d, *J* = 8.3 Hz), 6.69 (1$H_B$, s), 6.72 (1$H_B$, d, *J* = 8.3 Hz), 6.79 (1$H_A$, s), 6.87 (1$H_A$+1$H_B$, d, *J* = 8.0 Hz), 7.25 (1$H_A$, t, *J* = 6.6 Hz), 7.30-

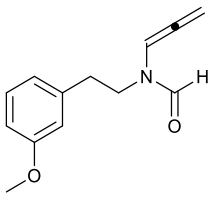
7.47 (10$H_A$+10$H_B$, m), 7.67 (1$H_A$, s), 8.10 (1$H_B$, s); $^{13}$C NMR (101 MHz, $CDCl_3$): δ 32.7 (1$C_B$), 33.4 (1$C_A$), 43.4 (1$C_B$), 48.1 (1$C_A$), 71.2 (1$C_A$), 71.35 (1$C_B$), 71.40 (1$C_B$), 71.5 (1$C_A$), 87.2 (1$C_A$), 87.9 (1$C_B$), 95.4 (1$C_A$), 100.4 (1$C_B$), 115.27 (1$C_B$), 115.31 (1$C_A$), 115.9 (1$C_A$), 116.1 (1$C_B$), 121.7 (1$C_B$), 121.9 (1$C_A$), 127.27 (2$C_B$), 127.31 (2$C_B$+2$C_A$), 127.3 (2$C_A$), 127.7 (1$C_A$+1$C_B$), 127.7 (1$C_A$), 127.9 (1$C_B$), 128.44 (2$C_B$), 128.46 (2$C_A$+2$C_B$), 128.49 (2$C_A$), 131.2 (1$C_B$), 131.9 (1$C_A$), 137.3 (1$C_A$+1$C_B$), 137.4 (1$C_A$+1$C_B$), 147.6 (1$C_B$), 148.0 (1$C_A$), 148.8 (1$C_A$), 149.0 (1$C_B$), 160.3 (1$C_A$), 160.5 (1$C_B$), 200.3 (1$C_A$), 202.2 (1$C_B$); ESI-MS: *m/z* = 400.0 $[M+H]^+$, 422.0 $[M+Na]^+$, 799.0 $[2M+H]^+$.



**(34)**: yellow oil, 208 mg, 60% yield; $^1$H NMR (400 MHz, $CDCl_3$) (two rotamers A:B, ratio 1.1:1): δ 2.74-2.80 (2$H_A$+2$H_B$, m), 3.54 (2$H_A$, t, *J* = 6.8 Hz), 3.62 (2$H_B$, pt, *J* = 7.8 Hz), 5.48 (2$H_B$, d, *J* = 6.2 Hz), 5.50 (2$H_A$, d, *J* = 6.2 Hz), 5.93 (2$H_B$, s), 5.95 (2$H_A$, s), 6.56-6.76 (3$H_A$+4$H_B$, m), 7.30 (1$H_A$, t, *J* = 6.3 Hz), 7.79 (1$H_A$, s), 8.10 (1$H_B$, s);$^{13}$C NMR (101 MHz, $CDCl_3$): δ 32.9 (1$C_B$), 34.1 (1$C_A$), 43.5 (1$C_B$), 48.2 (1$C_A$), 87.3 (1$C_A$), 88.0 (1$C_B$), 95.4 (1$C_A$), 100.4 (1$C_B$), 100.8 (1$C_B$), 100.9 (1$C_A$), 108.2 (1$C_B$), 108.4 (1$C_A$), 109.0 (1$C_A$), 109.2 (1$C_B$), 121.7 (1$C_B$), 121.9 (1$C_A$), 131.5 (1$C_A$), 132.1 (1$C_B$), 146.1 (1$C_A$), 146.4 (1$C_B$), 147.5 (1$C_B$), 147.8 (1$C_A$), 160.3 (1$C_B$), 160.5 (1$C_A$), 200.24 (1$C_B$), 202.18 (1$C_A$); ESI-MS: *m/z* = 270.0 $[M+Na]^+$.



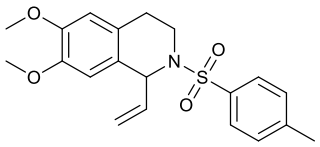
**(35)**: yellow oil, 256 mg, 69% yield; $^1$H NMR (400 MHz, $CDCl_3$) (two rotamers A:B, ratio 1.3:1): δ 2.86-2.90 (2$H_A$+2$H_B$, m), 3.59 (2$H_A$, t, *J* = 7.2 Hz), 3.67 (2$H_B$, t, *J* = 7.7 Hz, 3.84-3.87 (6$H_A$+6$H_B$, m), 5.43 (2$H_B$, d, *J* = 6.2 Hz), 5.50 (2$H_A$, d, *J* = 6.5 Hz), 6.56 (1$H_B$, t, *J* = 6.6 Hz), 6.68 (1$H_A$, d, *J* = 7.5 Hz), 6.82 (1$H_A$+2$H_B$, pt, *J* = 7.9 Hz), 6.98 (1$H_A$+1$H_B$, pt, *J* = 7.5 Hz), 7.26-7.29 (1$H_A$, m), 7.83 (1$H_A$, s ), 8.20 (1$H_B$, s); $^{13}$C NMR (101 MHz, $CDCl_3$): δ 27.8 (1$C_B$), 29.6 (1$C_A$), 42.5 (1$C_B$), 46.9 (1$C_A$), 55.6 (1$C_A$ + 1$C_B$), 60.6 (1$C_A$), 60.7 (1$C_B$), 87.2 (1$C_A$), 87.9 (1$C_B$), 95.5 (1$C_A$), 100.4 (1$C_B$), 110.9 (1$C_B$), 111.3 (1$C_A$), 122.4 (1$C_B$), 122.4 (1$C_A$), 123.8 (1$C_B$), 124.1 (1$C_A$), 131.5 (1$C_A$), 132.3 (1$C_B$), 147.2 (1$C_A$), 147.5 (1$C_B$), 152.7 (1$C_B$), 152.8 (1$C_A$), 160.4 (1$C_B$), 160.6 (1$C_A$), 200.1 (1$C_B$), 200.2 (1$C_A$); ESI-MS: *m/z* = 248.0 $[M+H]^+$, 270.0 $[M+Na]^+$, 495.2 $[2M+H]^+$.



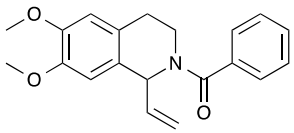
**(36)**: brown oil, 208 mg, 64% yield; $^1$H NMR (400 MHz, $CDCl_3$) (two rotamers A:B, ratio 1.1:1): δ 2.80-2.86 (2$H_A$+2$H_B$, m), 3.58 (2$H_A$, t, *J* = 7.2 Hz), 3.67 (2$H_B$, pt, *J* = 7.8 Hz), 3.80 (3$H_A$, s), 3.81 (3$H_B$, s), 5.48 (2$H_B$, d, *J* = 6.5 Hz), 5.51 (2$H_A$, d, *J* =6.6 Hz), 6.58 (1$H_B$, t, *J* = 6.1 Hz) 6.68-6.83 (3$H_A$+3$H_B$, m), 7.20-7.25 (1$H_A$+1$H_B$, m), 7.30 (1$H_A$, t, *J* = 6.5 Hz), 7.80 (1$H_A$, s), 8.20 (1$H_B$, s); $^{13}$C NMR (101 MHz, $CDCl_3$): δ 33.3 (1$C_B$), 34.5 (1$C_A$), 43.2 (1$C_B$), 47.9 (1$C_A$), 55.1 (1$C_B$), 55.1 (1$C_A$), 87.3 (1$C_A$), 87.9 (1$C_B$), 95.4 (1$C_A$), 100.4 (1$C_B$), 111.8 (1$C_B$), 111.9 (1$C_A$), 114.5 (1$C_A$), 114.7 (1$C_B$), 121.10 (1$C_B$), 121.13 (1$C_A$), 129.4 (1$C_B$), 129.7 (1$C_A$), 139.5 (1$C_B$), 140.0 (1$C_A$), 159.6 (1$C_B$), 159.8 (1$C_A$), 160.3 (1$C_B$), 160.5 (1$C_A$), 200.3 (1$C_B$), 202.2 (1$C_A$); ESI-MS: *m/z* = 218.0 $[M+H]^+$, 240 $[M+Na]^+$.

**General Procedure for the organocatalytic enantioselective cyclization of compounds 18-22, 33-36.**

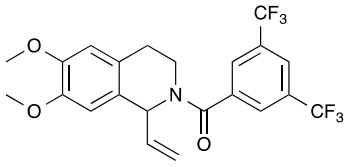
To a solution of allenammide (0.1 mmol, 1 equiv.) in trifluorotoluene (1 mL), Brønsted acid (0.01 mmol, 0.1 equiv.) and MS 4Å (0.05 g) were added and the reaction was stirred for 24h. The solvent was removed under reduced pressure and the crude was purified by flash chromatography on silica gel (cyclohexane/ethyl acetate 3/7) to obtain the desired products.



**(28)**: sticky white solid, 23.5 mg, 63% yield, 21% *ee*; the *ee* was determined by HPLC analysis, Daicel Chiralpak® ia column: hexane/*i*-PrOH from 70:30, flow rate 1.0 mL/min, 40°C, λ = 280 nm: $\tau_{major}$ = 8.18 min., $\tau_{minor}$ = 6.98 min; $^{1}$H NMR (400 MHz, $CDCl_3$): δ 2.38 (3H, s), 2.48-2.54 (1H, m), 2.65-2.74 (1H, m), 3.27-3.34 (1H, m), 3.82 (3H, s), 3.84 (3H, s), 3.85-3.89 (1H, m), 5.05 (1H, d, *J* = 17.14 Hz), 5.18 (1H, d, *J* = 10.20 Hz), 5.46 (1H, d, *J* = 5.98 Hz), 5.91 (1H, ddd, *J* = 5.72 Hz, *J* = 10.12 Hz, *J* = 16.98 Hz), 6.47 (1H, s), 6.53 (1H, s), 7.20 (2H, d, *J* = 8.08 Hz), 7.67 (2H, d, *J* = 8.33 Hz); $^{13}$C NMR (101 MHz, $CDCl_3$): δ 21.5, 27.2, 39.1, 55.8, 55.9, 57.7, 110.4, 111.3, 117.7, 125.4, 125.6, 127.1 (2C), 129.4 (2C), 137.3, 137.9, 143.9, 147.4, 148.0; EI-MS: *m/z* = 373 (12), 346 (84), 308 (75), 217 (82), 198 (87), 91 (100); ESI-MS: *m/z* = 374.0 $[M+H]^+$, 396.0 $[M+Na]^+$, 769.0 $[2M+Na]^+$; HMRS calcd for $C_{18}H_{19}N$: 373.13478; found 373.13486.

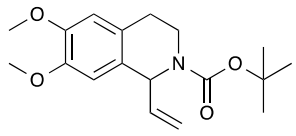


**(29)**: sticky white solid, 21.0 mg, 65% yield, 14% *ee*; the *ee* was determined by HPLC analysis, Daicel Chiralpak® IA column: hexane/*i*-PrOH from 60:40 , flow rate 0.50 mL/min, 40°C, λ = 280 nm: $\tau_{major}$ = 11.62 min., $\tau_{minor}$ = 16.86 min; although numerous attempts by changing solvent and temperature, it has never been possible to obtain a well resolved spectrum of the product. $^{1}$H NMR (400 MHz, $CDCl_3$, 25 °C) (two rotamers A:B, ratio 2:1): δ 2.61 ($1H_A$, bs), 2.89 ($1H_A$, bs), 3.22 ($1H_B$, bs), 3.40 ($1H_B$, bs), 3.75 ($2H_A$+$2H_B$, bs), 3.85 ($6H_A$+$6H_B$, bs), 4.72-5.11 ($2H_A$+$2H_B$, m), 5.26 ($1H_A$+$1H_B$, bs), 6.07 ($1H_A$+$1H_B$, bs), 6.17 ($1H_A$, bs), 6.36 ($1H_B$, bs), 6.61 ($2H_A$, bs), 6.67 ($2H_B$, bs),7.38 ($5H_A$+$5H_B$, bs); $^{13}$C NMR (101 MHz, $CDCl_3$): δ 28.9 ($1C_B$), 29.7 ($1C_A$), 41.2 ($1C_A$+$1C_B$), 54.2 ($1C_A$+$1C_B$), 55.8 ($1C_A$+$1C_B$), 56.0 ($1C_A$+$1C_B$), 111.4 ($1C_A$+$1C_B$), 117.4 ($1C_A$+$1C_B$), 120.6 ($1C_A$+$1C_B$), 126.0 ($1C_A$+$1C_B$), 126.7 ($2C_A$+$2C_B$), 128.5 ($2C_A$+$2C_B$), 129.2 ($2C_A$+$2C_B$), 131.4 ($1C_A$+$1C_B$), 136.3 ($1C_A$), 137.1 ($1C_B$), 147.6 ($1C_A$+$1C_B$), 148.1 ($1C_A$+$1C_B$), 170.4 ($1C_A$+$1C_B$); ESI-MS: *m/z* = 323 (25), 308 (20), 280 (6), 264 (11), 218 (34), 105 (100), 77 (85); ESI-MS: *m/z* = 324.2 $[M+H]^+$, 346.0 $[M+Na]^+$, 669.2 $[2M+Na]^+$;

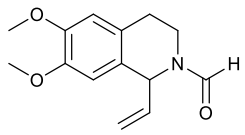


**(30)**: sticky yellow solid, 28.9 mg, 63% yield, 0% *ee*; the *ee* was determined by HPLC analysis, Daicel Chiralpak® IA colum hexane/*i*-PrOH from 90:10, flow rate 0.5 mL/min, 40°C, λ = 285 nm: $\tau_{major}$ = 14.66 min., $\tau_{minor}$ = 16.76 min; although numerous attempts by changing solvent and temperature, it has never been possible to obtain a well resolved spectrum of the product. $^{1}$H NMR (400 MHz, $CDCl_3$, 25 °C) (two rotamers A:B, ratio 2:1): δ2.60 ($1H_A$+$1H_B$, bs), 2.89 ($1H_A$+$1H_B$, bs), 3.00 ($2H_A$, bs), 3.28 ($1H_B$, bs),3.53 ($1H_A$, bs),3.85 ($6H_A$+$6H_B$, bs), 4.72-5.16 ($2H_A$+$2H_B$, m),5.34 ($1H_A$+$1H_B$, d, *J* = 9.4 Hz),6.09 ($1H_A$, bs),6.37 ($1H_B$, bs),6.67 ($2H_A$+$2H_B$, bs),7.45 ($1H_A$+$1H_B$, bs),7.89 ($2H_A$+$2H_B$, bs); The presence of rotamers avoids the detection of some signals, that result too broad to be identified from the noise.$^{13}$C NMR (101 MHz, $CDCl_3$): δ 34.2

($1C_A$), 35.1 ($1C_B$), 41.6 ($1C_A$), 41.7 ($1C_B$), 55.9 ($2C_A$), 56.0 ($1C_B$), 77.2 ($1C_A$+$1C_B$), 110.9 ($1C_A$+$1C_B$), 111.4 ($1C_A$+$1C_B$), 117.2 ($1C_A$), 118.3 ($1C_B$), 119.8 ($2C_B$, q, $J_{C\text{-}F}$ = 274.2 Hz), 122.8 ($2C_A$, q, $J_{C\text{-}F}$ = 272.4 Hz), 123.6 ($2C_A$+$2C_B$), 124.9 ($1C_B$), 125.1 ($1C_A$), 125.4 ($1C_B$), 125.6 ($1C_A$), 127.2 ($1C_A$+$1C_B$, bs), 136.5 ($1C_A$), 136.8 ($1C_B$), 138.1 ($1C_A$+$1C_B$), 147.9 ($1C_A$+$1C_B$), 148.4 ($1C_A$+$1C_B$); EI-MS: *m/z* = 459 (22), 430 (76), 241 (100), 213 (84); ESI-MS: *m/z* = 460.0 $[M+H]^+$, 482.0 $[M+Na]^+$, 941.0 $[2M+Na]^+$;



**(31)**: yellowish oil, 10.0 mg, 30% yield, 32% *ee*; the *ee* was determined by HPLC analysis, Daicel Chiralpak® ia column: hexane/*i*-PrOH from 90:10, flow rate 0.70 mL/min, 40°C, λ = 280 nm: $\tau_{major}$ = 11.80 min., $\tau_{minor}$ = 18.4 min; $^1$H NMR (400 MHz, $CDCl_3$, 25 °C): δ 1.47 (9H, s), 2.60 (1H, dt,*J* = 3.4 Hz, *J* = 15.5 Hz), 2.71-2.77 (1H, m), 2.80-2.88 (1H, m), 3.13 (1H, bs), 3.83 (3H, s), 3.84 (3H, s), 3.85 (1H, d*J* = 4.0 Hz), 5.05 (1H, d,*J* = 17.0 Hz), 5.14 (1H, dt,*J* = 1.4 Hz, *J* = 10.2 Hz), 5.89-5.97 (1H, m), 6.58 (s, 1H), 6.59 (s, 1H); $^{13}$C NMR (101 MHz, $CDCl_3$) (due to rotamers it was not possible to obtain a spectra performing a $^{13}$C NMR experiment; the signals have been determined from gHSQC and gHMBC experiments): δ 28.9 ($1C_A$+$1C_B$), 29.6 ($3C_A$), 32.5 ($3C_B$), 42.3 ($1C_A$+$1C_B$), 56.0 ($1C_A$+$1C_B$), 56.5 ($1C_A$+$1C_B$), 57.3 ($1C_A$+$1C_B$), 80.4 ($1C_A$), 85.6 ($1C_B$), 111.4 ($1C_A$), 111.3 ($1C_A$), 111.6 ($1C_B$), 112.4 ($1C_B$), 116.8 ($1C_A$+$1C_B$), 127.3 ($1C_A$), 128.7 ($1C_B$), 129.2 ($1C_A$+$1C_B$), 148.3 ($1C_A$+$1C_B$), 148.8 ($1C_A$+$1C_B$), 149.5 ($1C_A$+$1C_B$), 181.6 ($1C_A$+$1C_B$); ESI-MS: *m/z* = 342.2 $[M+Na]^+$, 661.2 $[2M+Na]^+$;



**(32)**: sticky white solid, 9.9 mg, 40% yield, 81% *ee*; to perform the HPLC analysis of product **32**, it was necessary to reduce the amide moiety to methyl group ($LiAlH_4$ (1.5 equiv.) was added to **32**. After 2h, a few drops of water were added, followed by $MgSO_4$. The mixture was filtered and directly subjected to HPLC analysis); Daicel Chiralpak® OD-H column: hexane/*i*-PrOH from 90:10, flow rate 0.70 mL/min, 40°C, λ = 285 nm: $\tau_{major}$ = 7.87 min., $\tau_{minor}$ = 14.93 min; $^1$H NMR (400 MHz, $CDCl_3$) (two rotamers A:B, ratio 1:1): δ 2.62-2.72 ($2H_B$, m), 2.78-2.91 ($2H_A$, m), 3.13 ($1H_B$, ddd, *J* = 4.7 Hz, *J* = 11.0 Hz, *J* = 15.6 Hz), 3.45 ($1H_A$, ddd, *J* = 4.2 Hz, *J* = 13.0 Hz, *J* = 13.0 Hz), 3.65 ($1H_A$, dd, *J* = 5.8 Hz, *J* = 13.2 Hz), 3.80 ($3H_A$, s), 3.81 ($3H_A$ + $3H_B$, bs), 3.82 ($3H_B$, s), 4.29 ($1H_B$, m), 5.02 ($1H_B$, d, *J* = 5.7 Hz), 5.09 ($1H_A$, d, *J* = 17 Hz), 5.11 ($1H_B$, d, *J* = 17.0 Hz), 5.19 ($1H_A$, d, *J* = 10.1 Hz), 5.20 ($1H_B$, d, *J* = 10.1 Hz), 5.78 ($1H_A$, d, *J* = 5.6 Hz), 5.86-5.99 ($1H_A$ +$1H_B$, m), 6.55 ($1H_A$, s), 6.56 ($1H_A$ +$1H_B$, bs), 6.59 ($1H_B$, s), 8.15 ($1H_A$, s), 8.25 ($1H_B$, s);$^{13}$C NMR (101 MHz, $CDCl_3$): δ 27.6 ($1C_B$), 29.2 ($1C_A$), 35.1 ($1C_B$), 40.2 ($1C_A$), 52.7 ($1C_A$), 55.8 ($1C_A$), 55.8 ($1C_A$), 55.9 ($1C_A$), 56.0 ($1C_B$), 58.7 ($1C_B$), 110.1 ($1C_B$), 110.6 ($1C_A$),111.3 ($1C_A$), 111.5 ($1C_B$), 117.0 ($1C_B$), 117.3 ($1C_A$), 125.2 ($1C_A$ + $1C_B$), 125.4 ($1C_A$), 126.5 ($1C_B$), 136.4 ($1C_A$), 138.0 ($1C_B$), 147.6 ($1C_B$), 147.7 ($1C_A$), 148.0 ($1C_A$), 148.3 ($1C_B$), 161.1 ($1C_A$), 161.6 ($1C_B$); ESI-MS: *m/z* = 248.2 $[M+H]^+$, 270.0 $[M+Na]^+$, 495.2 $[2M+H]^+$; HMRS calcd for $C_{18}H_{19}N$: 247.12084; found 247.12075.

## 2.3.6 References


[1] This work has been published: E. Manoni, A. Gualandi, L. Mengozzi, M. Bandini, P. G. Cozzi, *RSC Adv.*, **2015**, *5*, 10546-10550.

[2] 1a) D. Jack and R. Williams, *Chem. Rev.* **2002**, *102*, 1669; b) K. W. Bentley, *Nat. Prod. Rep.* **2006**, *23*, 444; c) Q. Y. Zhang, G. Z. Tu, Y. Y. Zhao, T. M. Cheng, *Tetrahedron* **2002**, *58***,** 6795; d) A. J. Aladesanmi, C. J. Kelly, J. D. Leary, *J. Nat. Prod.* **1983**, *46*, 127; e) A. Zhang, J. L. Neumeyer, R. J. Baldessarini, *Chem. Rev.* **2007**, *107*, 274; f) K. Ye, Y. Ke, N. Keshava, J. Shanks, J. A. Kapp, R. R. Tekmal, J. Petros, H. C. Joshi, *Proc. Natl. Acad. Sci. USA* **1998**, *95*, 1601.

[3] see chapter 2.2 or L. Mengozzi, A. Gualandi, P. G. Cozzi, *Chem. Sci*., **2014**, *5*, 3915.

[4] M. S. Taylor, N. Tokunaga, E. N. Jacobsen, *Angew. Chem. Int. Ed.* **2005**, *44*, 6700-6704.

[5] a) W. Lin, T. Cao, W. Fan, Y. Han, J. Kuang, H. Luo, B. Miao, X. Tang, Q. Yu, W. Yuan, J. Zhang, C. Zhu, S. Ma, *Angew. Chem. Int. Ed.* **2014**, *53*, 277; b) D. Ma, J. Dai, Y. Qiu, C. Fu, S. Ma, *Org. Chem. Front*. **2014**, *1*, 782.

[6] D. A. Di Rocco, T. Rovis, *J. Am. Chem. Soc.* **2012**, *134*, 8094.

[7] Y. M. Wilson, M. Dürrenberger, E. S. Nogueir, T. R. Ward, *J. Am. Chem. Soc.* **2014**, *136*, 8928 and refer. therein.

[8] E. D. Cox and J. M. Cook, *Chem. Rev.* **1995**, *95*, 1797.

[9] J. Stöckigt, A. P. Antonchick, F. Wu, H. Waldmann, *Angew. Chem. Int. Ed.* **2011**, *50*, 8538.

[10] M. S. Taylor, E. N. Jacobsen, *J. Am. Chem. Soc.* **2004**, *126*, 10558.

[11] a) R. S. Klausen, E. N. Jacobsen, *Org. Lett.* **2009**, *11*, 887; b) Y. Lee, R. S. Klausen, E. N. Jacobsen, *Org. Lett.* **2011**, *13*, 5564.

[12] a) B. Herlé, M. J. Wanner, J. H. van Maarseveen, H. Hiemstra, *J. Org. Chem.* **2011**, *76*, 8907; b) I. Kerschgens, E. Claveau, M. J. Wanner, S. Ingemann, J. H. van Maarseveen, H. Hiemstra, *Chem. Commun.* **2012**, *48*, 12243; c) N. Sewgobind, M. J. Wanner, S. Ingemann, R. de Gelder, J. H. van Maarseveen, H. Hiemstra, *J. Org. Chem.* **2008**, *73*, 6405; d) J. Seayad, A. M. Seayad, B. List, *J. Am. Chem. Soc.* **2006**, *128*, 1086.

[13] D. Huang, F. Xu, X. Lin and Y. Wang, *Chem.-Eur. J.* **2012**, *18*, 3148.

[14] A. Gòmez-SanJuan, N. Sotomayor, E. Lete, *Tetrahedron Lett*. **2012**, *53*, 2157.

[15] Y. Toda, M. Terada, *Synlett* **2013**, 752.

[16]E. Mons, M. J. Wanner, S. Ingemann, J. H. van Maarseveen, H. Hiemstra, *J. Org. Chem.* **2014**, *79*, 7380.

[17] a) H. Wang, A. Ganesan, *Org. Lett.* **1999**, *1*, 1647. b) A. van Loevezijn, J. D. Allen, A. H. G.-J. Schinkel, Koomen, *Bioorg. Med. Chem. Lett.* **2001**, *11*, 29; c) A. Ruiz-Olalla, M. A. Würdemann, M. J. Wanner, S. Ingemann, J. H. van Maarseveen, H. Hiemstra, *J. Org. Chem.*, **2015**, *80*, 5125–5132.

[18] S. S. Kinderman, M. M. T. Wekking, J. H. van Maarseveen, H. E. Schoemaker, H. Hiemstra, F. P. J. T. Rutjes, *J. Org. Chem.* **2005**, *70*, 5519.

[19] T. Lu, Zhenjie L, Z.-X. Ma, Y. Zhang, R. P. Hsung, *Chem. Rev.* **2013**, *113*, 4862.

[20] A. Navarro-Vázquez, D. Rodríguez, M. F. Martínez-Esperón, A. García, C. Saá, D. Domínguez, *Tetrahedron Lett.* **2007**, *48*, 2741.

[21] I. Singh, M. R. J. Elsegood, M. C. Kimber, *Synlett* **2012**, 565.

[22] a) M. Jia, G. Cera, D. Perrotta, M. Bandini, *Chem. Eur. J.* **2014**, *20*, 9875; b) C. Romano, M. Jia, M. Monari, E. Manoni and M. Bandini, *Angew. Chem. Int. Ed.* **2014**, *53*, 13854 –13857.

[23] For selected reviews of chiral phosphoric acid catalysis, see: a) M. Terada, *Chem. Commun.* **2008**, 4097; b) M. Terada *Bull. Chem. Soc. Jpn.* **2010**, *83*, 101; c) M. Terada, *Synthesis* **2010**, 1929; d) M. Terada, *Curr.Org. Chem.* **2011**, *15*, 2227; e) T. Akiyama, *Chem. Rev.* **2007**, *107*, 5744.

[24] Y. Toda, M. Terada, *Synlett* **2013**, 752.

[25] K. Kanomata, Y. Toda, Y. Shibata, M. Yamanaka, S. Tsuzuki, I. D. Gridneva, M. Terada, *Chem. Sci.* **2014**, *5*, 3515.

[26] M. Fañanás-Mastral, J. F. Teichert, J. A. Fernández-Salas, D. Heijnen, B. L. Feringa, *Org. Biom. Chem.* **2013**, *11*, 4521.

[27] F. Romanov-Michailidis, L. Guénée, A. Alexakis, *Angew. Chem. Int. Ed.*, **2013**, *52*, 9266-9270; F. Romanov-Michailidis, L. Guénée and A. Alexakis, *Org. Lett.*, **2013**, *15*, 5890-5893; V. Rauniyar, A. D. Lackner, G. L. Hamilton and F. D. Toste, *Science*, **2011**, *334*, 1681-1684; Y.-M. Wang, J. Wu, C. Hoong, V. Rauniyar and F. D. Toste, *J. Am. Chem. Soc.*, **2012**, *134*, 12928-12931; V. Rauniyar, Z. J. Wang, H. E. Burks and F. D. Toste, *J. Am. Chem. Soc.*, **2011**, *133*, 8486-8489; T. Akiyama, H. Morita and K. Fuchibe, *J. Am. Chem. Soc.*, **2006**, *128*, 13070-13071.

[28] J. Párraga, N. Cabedo, S. Andujar, L. Piqueras, L. Moreno, A. Galán, E. Angelina, R. D. Enriz, M. D. Ivorra, M. J. Sanz, D. Cortes, *Eur. J. Med. Chem.*, **2013**, *68*, 150-166.

[29] S. H. Yang, C.-H. Song, H. T. M. Van, E. Park, D. B. Khadka, E.-Y. Gong, K. Lee and W.-J. Cho, *J. Med. Chem.*, **2013**, *56*, 3414-3418.

[30] C. Zhang, Z. Xu, T. Shen, G. Wu, L. Zhang, N. Jiao *Org. Lett.* **2012**, *14*, 2362–2365.

[31] T. M. Böhme, C. E. Augelli-Szafran, H. Hallak, T. Pugsley, K. Serpa, R. D. Schwarz, *J. Med. Chem.*, **2002**, *45*, 3094-3102.

[32] D. S. Ermolat'ev, J. B. Bariwal, H. P. L. Steenackers, S. C. J. De Keersmaecker, E. V. Vander Eycken, *Angew. Chem. Int. Ed.*, **2010**, *49*, 9465-9468**.**

## 2.4 Asymmetric alkylation of aldehydes with quinolines activated with CbzCl promoted by prolinol catalysts[1]

**Index**

## 2.4.1 Introduction

Quinoline is a common motif retrieved in several families of natural alkaloids.[2] Among these cinchona alkaloids are the most known due to the well known anti-malarian activity of quinine and its synthetic derivatives. Tetrahydroquinoline alkaloids are another very important class of natural compounds that have been identified in many plants and vegetables and that often exhibit interesting biological activities.[3]

Thus there have been several studies to indentify the chemical components of their extracts. Most of these compounds are characterized by bearing substituents on the hydrogenated pyridine ring in particular on the 2 position. Martinellic acid, [4] a nonpeptide bradykinin antagonist, and the galipea alkaloids[5] are examples of biologically active THQ. This latter family of alkaloids has been found in the Genus Galipea Aublet plants, approximately 20 species that grow in the northern part of South America, and their structure has been identified.[6] The therapeutic effects of the extracts of these plants in treating paralytic affections, dyspepsia, dysentery and chronic diarrhea have been well known,[7] while the activity of augustereine against Mycobacterium tuberculosis has recently been reported.[8]

The THQ core is present also in synthetic molecules that have shown important activities: for example Torcetrapib is a recent hypocholesterolemia drug candidate[9] and THQ 3 is an acetyl-coA carboxylase 2 inhibitor.[10]

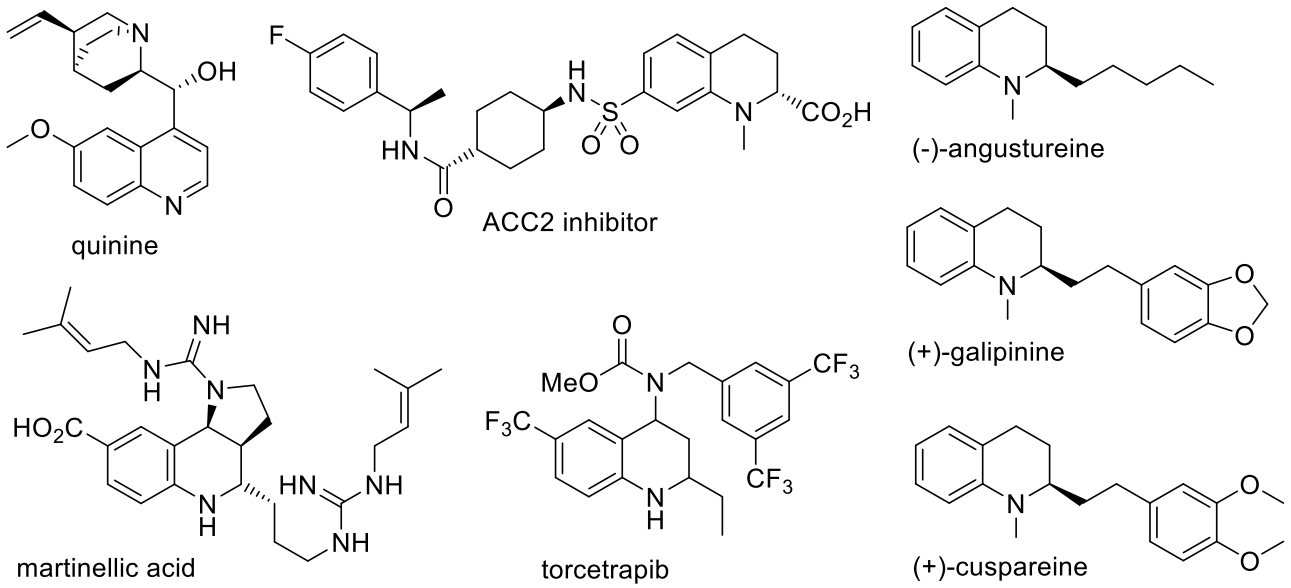
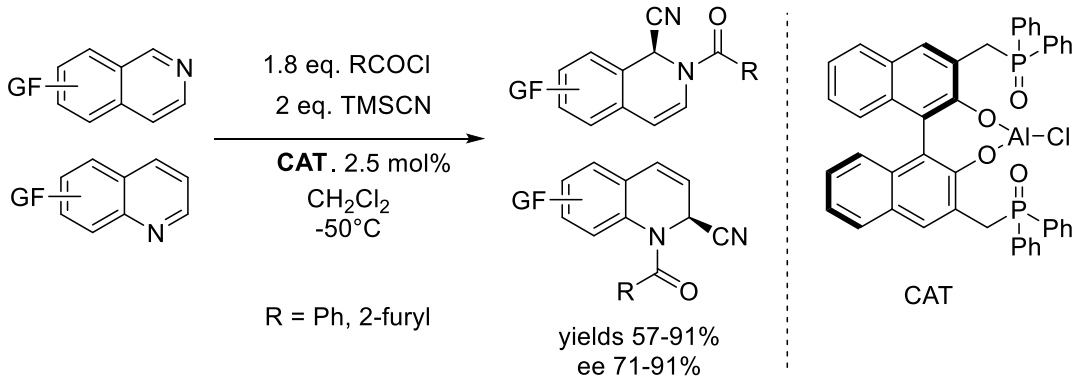



*Figure 1: representative examples of THQ alkaloids.*

The asymmetric synthesis of the 2-substituted-1,2,3,4-THQ motif, common to the before mentioned alkaloids, can be addressed by strategies similar to those described for the tetrahydroisoquinoline alkaloids even if substantial differences must be taken into account due to the different position of nitrogen.

Metal catalyzed asymmetric hydrogenation[11] and organocatalyzed asymmetric transfer hydrogenation[12] of 2-substituted quinolines have been disclosed only in the last 15 years but they are very efficient methods both in terms of yields and selectivity. More recently, 2,3 or 3,4 substituted scaffolds have been efficiently dearomatized with reduction protocols.[13] This strategy has been efficiently applied to the synthesis of the galipea alkaloids.[14]

The position of the nitrogen atom on the 1 position makes quinoline reactivity towards nucleophiles more similar to pyridine than to isoquinoline. Two electrophilic sites are present in the quinoline ring, the 2 and 4 positions and the first one is usually preferred for nucleophilic addition even if it is hard to obtain total regioselectivity. The reaction of quinoline with an acylating agent to form the corresponding acyl quinolinium ion is usually necessary to promote the reaction with a nucleophile, and this process was first explored by Reissert.[15] The first asymmetric catalytic variant of this reaction was reported in 2000 by Shibasaki[16] and it also represented the first example catalytic enatioselective addition of a nucleophile on quinolinium and isoquinolinium salts (scheme 1). After this seminal report, quite a number of catalytic asymmetric methodologies on isoquinolinium ions were reported (see chapter 2.2), while only a few reports were disclosed for quinolinium ions.

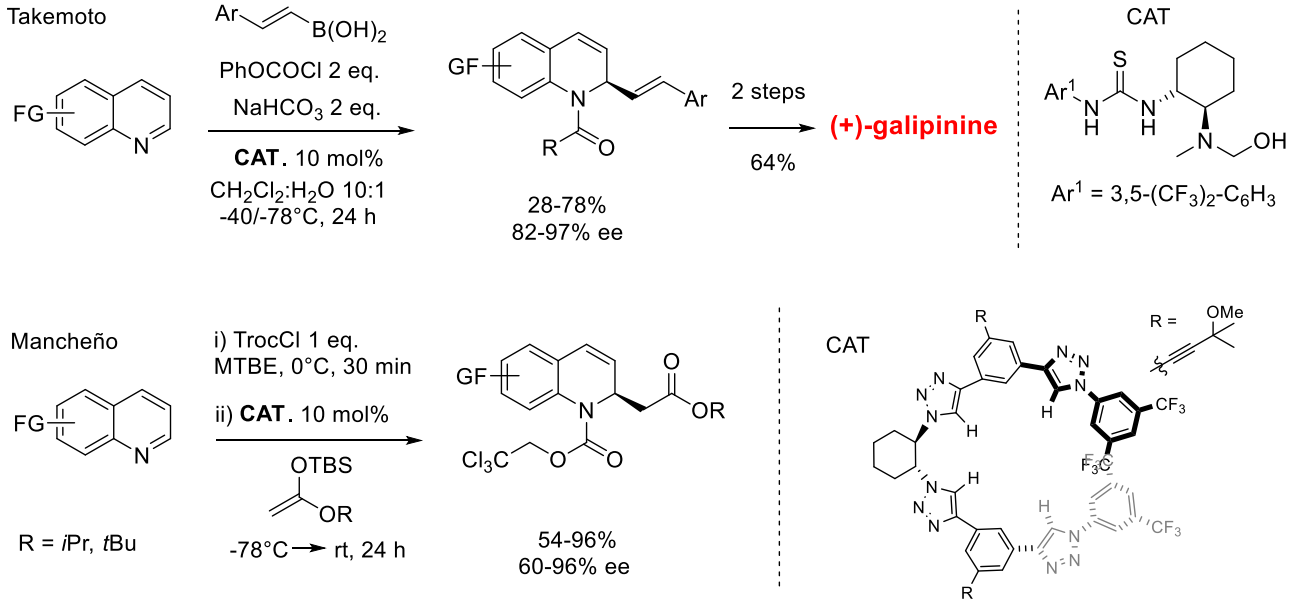



*Scheme 1: Shibasaki asymmetric version of the Reissert reaction.*

At the end of 2014 only two organocatalitic methodologies had been reported in the asymmetric alkylation of quinolinium ions: Takemoto[17] vinylation with styrene boronic acids in 2007 and the addition of silyl enol ethers by Mancheño[18] (scheme 2).

Takemoto used phenyl chloroformate to activate quinoline and realized the alkylation of the resulting quinolinium ions with styrene boronic acids under the control of a bifunctional catalyst. The thiourea moiety is able to bind the chlorine anion forming a chiral ion pair with the quinolinium ion that results more reactive towards the nuclephilic addition. The amino-alcohol functionality binds the boronic acid forming a more reactive boronate that is directed on the electrophile in a highly regioselective and enantioselective manner thanks to the presence of both the directing functionalities on the same optimized catalyst structure. This methodology has been applied to the total synthesis of galipinine.

Mancheño reported the alkylation of quinolinium ions with silyl enol ethers in presence of a helicoidal chiral catalyst that is able to bind the chlorine anion via hydrogen bonding interactions and TrocCl as acylating agent. Probably the chlorine atoms of this particular activating agent engage non covalent interaction with the catalyst allowing to achieve optimal enantioselectivities. In Mancheño protocol the quinolinium ion is pre-formed by addition of the acylating agent on a solution of quinoline at 0°C.




*Scheme 2: Takemoto and Mancheño alkylations of quinolinium ions*

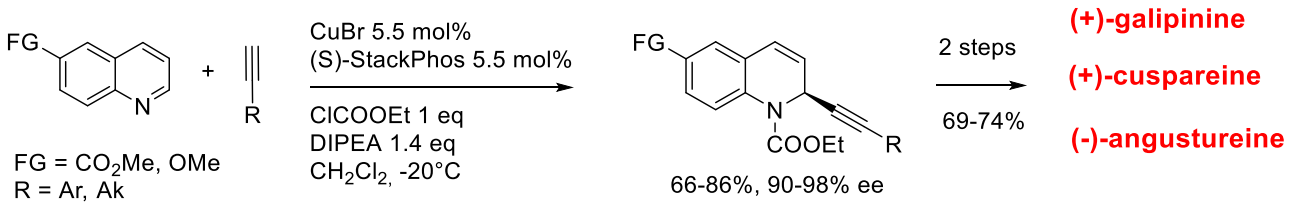
As the nucleophilicity of the silyl enol ether is comparable with that of the enamines obtained with the Hayashi-Jørgensen catalyst, I reasoned that this activation protocol might be suitable to realize the unprecedented alkylation of aldehydes with quinolinium ions via enamine catalysis.

On the basis of our experience in the alkylation of aldehydes with isoquinolinium ions, we started to investigate this new process: quinoline was activated by addition of CbzCl at 0°C in anhydrous tertbutylmethylether. After 30 minutes, propionaldehyde, secondary amine Jørgensen catalyst **2ac** and $NaHCO_3$ as a base were added to the mixture.

To our delight the desired product was obtained in good conversion, enantioselectivity and moderate diastereoselectivity. A control experiment performed on air and in non anhydrous conditions afforded no product. This result highlighted the sensibility to air and moisture of the quinolinium ion. However this intermediate tolerates the catalytic amount of the water generated during the enamine catalytic cycle (and traces adventitiously present) that efficiently ensure the turnover of the catalyst.

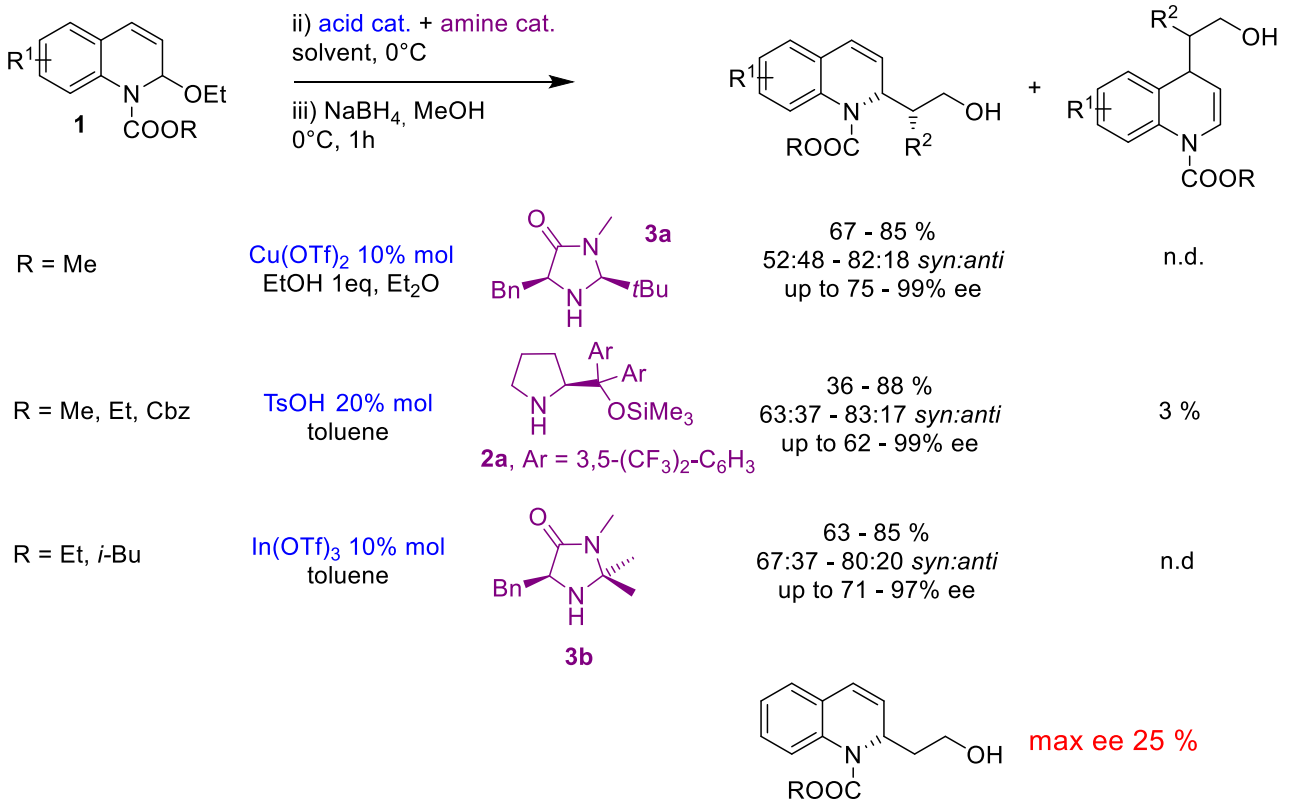
While I was developing this methodology, important advances were published. A highly efficient protocol for the 2 alkynilation of quinolinium ions was reported by Aponick.[19] This protocol is particularly important because it gives access to 2 alkyl substituted quinolines, a structural motif that was not accessible with Takemoto methodology. Indeed the direct total synthesis of galipinine, cuspareine and angustureine was accomplished. It is correct mentioning that also the products

obtained by Mancheño's protocol could be used to obtain the before mentioned alkaloids after manipulation of the ester moiety. However attempts in this direction were not reported by the authors.




*Scheme 3: alkynilation of quinolinium ions as a direct approach to galipea alkaloids.*

Moreover three reports by Lu, Pineschi and Rueping were published in rapid succession on the asymmetric alkylation of quinoline N-O acetals **1** with aldehydes by means of synergistic enamine-acid catalysis.[20] In all cases adduct **1**, that needs to be pre-formed by addition of the opportune acylating agent to quinolines in presence of ethanol, was used as starting material while the *in situ* activation of quinolines was not successful with their protocols. To generate the quinolinium ion from N-O acetals **1** it is necessary to add either a Lewis acid (Lu, Rueping) or a Bronsted acid (Pineschi).




*Scheme 4: previous reports of asymmetric alkylation of quinolinium ions with aldehydes.*

It is worth mentioning that when a Lewis acid was used, MacMillan catalysts **3** afforded better results, while in order to obtain optimal results with Jørgensen catalyst **2a** a Brønsted acid was employed. This because the Lewis acid can desilylate the Jørgensen catalyst reducing its catalytic activity and selectivity.

In all cases good yields, optimal enantioselectivities and moderate diastereoselectivities were obtained with a variety of 2 substituted aldehydes. While in case of acetaldehyde, 25 % ee was the best result reported, a value lower if compared to the average dr obtained with the other aldehydes.

Our methodology substantially differs from the already reported ones because there is no need to pre-synthetize quinoline N,O-acetals and by consequence to use an acid cocatalyst.

## 2.4.2 Results and discussion

The alkylation of aldehydes with quinolines activated in situ with benzyl chloroformate was optimized by screening different solvents and temperatures. Four equivalents of propionaldehyde **5a** and 10 mol% of (R)-Jørgensen catalyst (***ent*–2a**) were used. GC-MS analysis allowed to evaluate the conversions on the crude reaction mixture after 16 h. Then the crude was directly reduced by dilution with methanol and addition of $NaBH_4$ to afford the corresponding alcohol **6aa**. Diastereomeric ratios and enantiomeric excesses were determined by HPLC on chiral stationary phase on the crude alcohols. The use of toluene at 0°C with one equivalent of $NaHCO_3$ afforded the best result (table 1, entry 8): **6aa** was obtained in 81% yield with moderate dr and 94% ee for the syn and 92% ee for the anti diastereoisomers. A limited amount of product **7aa**, between 6% and 18% compared to **6aa**, resulting from the enamine attack on the 4 position of the quinoline scaffold, was always observed.

Increasing the amount of base lead to slightly reduced conversion, while in its absence the reaction proceeded to a much lower extent (table 1, entries 9 and 10). Performing the reaction at lower temperatures did not allow to increase significantly the diastereoselectivity or regioselectivity of the reaction, instead a decrease in the conversion was observed (table 1, entries 11-12). One equivalent of acylating agent allowed the efficient activation of quinoline avoiding the catalyst deactivation. Other acylating agents were tested instead of benzyl chloroformate: ethyl chloroformate afforded similar results in terms of stereoselectivity but reduced yields were obtained (table 1, entry 13), while using TrocCl no product was obtained (table 1, entry 14).

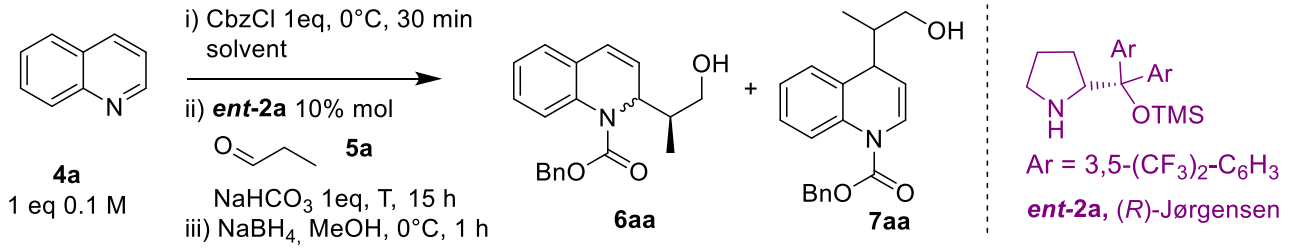
The aldehyde product, derived from propionaldehyde **2a** and quinoline **4a**, can be isolated after quenching the reaction with MeOH to consume adventitious unreacted CbzCl, evaporation of the solvent and direct purification on silica gel column in slightly reduced yields (ca. 70 %) compared to the alcohol **7a**. However it was not possible to obtain the analytically pure product because it is eluted together with the secondary amine catalyst **2a**. Moreover the syn diastereoisomer could not be separated neither from the minor anti, neither from the product resulting from the attack on the 4 position of quinoline. For such reasons and for the higher stability of the alcohol products **7**, I decided to isolate the products after reduction.

With the optimized conditions on hand I explored the scope of the methodology both on the aldehyde and on the quinoline reaction partners.

All the tested aldehydes in the reaction with quinoline **4a**, afforded the products in good yields (table 2, entries 1-6). Enantioselectivities were optimal for linear aliphatic aldehydes and hydrocinnamaldehyde, while when on the 2 position of the aldehyde was present a bulky group, such as phenyl (**5c**) or isopropyl (**5e**), the ee decreased around 80%.

The substitution pattern of the quinolines **4a-f** strongly influenced the reaction outcome: substituents on the 5 and 6 positions were well tolerated affording the corresponding products in good ee and moderate diastereoselectivities (table 2, entries 7-11). Yields were good for neutral or electrondonating groups, while in case of the bromine substituent a decrease in the reaction yield was observed. Strong electronwithdrawing groups such as nitro (**4g**) were not compatible with the reaction system.

The precence of a methyl group on the 8 position totally inhibits the reactivity, according to previous reports,[18] probably hampering the acylation of 8-Me-quinoline (**4h**) to form the corresponding quinolinium ion.

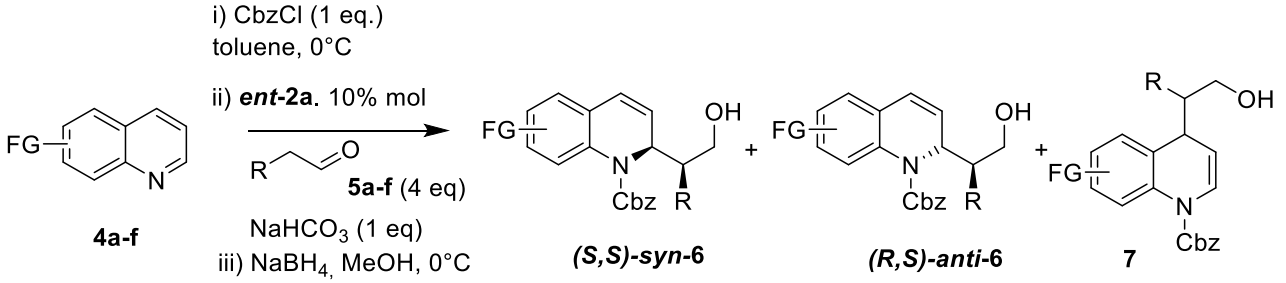



| entry | Solvent | T | syn-**6aa**/ anti-**6aa**/**7aa**[a] | Conv.[b] | ee syn-**6aa**[a] | ee anti-**6aa**[a] | deviations from standard conditions |
|---|---|---|---|---|---|---|---|
| 1 | TBE | 0°C | 64:23:13 | 78 | 86 | 82 | |
| 2 | DCM | 0°C | 70:19:11 | 88 | 94 | 61 | |
| 3 | $CH_3CN$ | 0°C | 71:23:6 | 93 | 81 | 6 | |
| 4 | $CHCl_3$ | 0°C | 71:17:12 | 47 | 95 | 63 | |
| 5 | THF | 0°C | 62:29:9 | 87 | 22 | -50 | |
| 6 | n-esane | 0°C | 62:20:18 | 32 | 93 | 99 | |
| 7 | DMF | 0°C | 58:36:6 | 13 | 20 | -48 | |
| 8 | toluene | 0°C | 63:21:16 | 90 (81)[c] | 94 | 92 | |
| 9 | toluene | 0°C | - | 87 | - | - | 2 eq $NaHCO_3$ |
| 10 | toluene | 0°C | - | 68 | - | - | 0 eq $NaHCO_3$ |
| 11 | toluene | -20°C | 65:19:16 | 53 | 94 | 91 | |
| 12 | toluene | -50°C | 73:21:6 | 18 | 93 | 90 | |
| 13 | toluene | 0°C | 65:21:11 | 46 (37)[c] | 94 | 92 | $ClCO_2Et$ instead of CbzCl (product **10**) |
| 14 | toluene | 0°C | - | <5 | - | - | TrocCl instead of CbzCl |

All reactions were carried on 0.1 mmol of quinoline **4a**, CbzCl, $NaHCO_3$, 0.4 mmol aldehyde **5a** and 0.01 mmol of **2a** for 16h at the indicated temperature; [(a)] regioisomeric, diastereomeric ratios and enantiomeric excesses were calculated by HPLC analysis on chiral stationary phase on the crude product after reduction; [(b)] conversions were determined by GC-MS analysis before reduction; [(c)] yield of isolated products after chromatographic purification.

*Table 1: optimization of the reaction conditions for the alkylation of propionaldehyde **2a** with quinolinium ion.*

The use of 4-hydroxy quinoline **4i** lead instead of the selective benzylation of the hydroxyl group preventing its activation towards nucleophilic addition. Thus I tried 4-OMe-quinoline **4l** that proved to be unreactive too. Initially I hypothesized it might be due to its insolubility in toluene, but changing the solvent a 1:1 mixture of DCM:toluene 1:1 to guarantee its solubility did not afford any product either. It is possible that the increased steric hindrance might hamper the approach of the nucleophile.




| entry | R | FG | **6** | *syn*:*anti*:**7**[a] | Yield[b] (*syn*:*anti*:**7**) | ee *syn*-**6aa**[c] | ee *anti*-**6aa**[c] |
|---|---|---|---|---|---|---|---|
| 1 | Me | H | **6aa** | 63:21:16 | 81 (53:16:12) | 94 | 93 |
| 2 | $C_6H_{13}$ | H | **6ab** | 70:16:14 | 82 (58:13:11) | 93 | 95 |
| 3 | Ph | H | **6ac** | 58:26:16 | 54 (*syn*-**6ac**) | 82 | 34 |
| 4 | $CH_2Ph$ | H | **6ad** | 54:23:23 | 72 (43:13:16) | 99 | 96 |
| 5 | $(CH_3)_2CH$ | H | **6ae** | 63:37:0 | 60 (39:21:0) | 81 | 77 |
| 6 | H | H | **6af** | 100[d]:0 | 76 | 4 | - |
| 7 | Me | 6-Br | **6ba** | 61:28:11 | 49 (31:18:0) | 94 | 92 |
| 8 | Me | 6-OMe | **6ca** | 74:15:11 | 69 (57:12:0) | 96 | 90 |
| 9 | Me | 5-Br | **6da** | 46:39:15 | 48 (28:15:5) | 91 | 89 |
| 10 | Me | 6-allyl | **6ea** | 64:20:16 | 76 (54:15:7) | 90 | 91 |
| 11 | Me | 6-Ph | **6fa** | 50:32:18 | 54 (34:13:7) | 92 | 82 |

All reactions were carried on 0.2 mmol of quinoline, CbzCl, $NaHCO_3$, 0.4 mmol aldehyde and 0.01 mmol CAT for 16h at 0°C; [(a)] determined by $^1H$ NMR on the crude reaction mixture; **7** is present as a mixture of diastereoisomers [(b)] yield of isolated products after chromatographic purification; [(c)] enantiomeric excesses were calculated by HPLC analysis on chiral stationary phase after after chromatographic purification; [(d)] no diastereoismers are present for **6af.**

*Table 2: substrate scope for the alkylation of aldehydes with quinolinium ions.*

Finally I tested 2 Me quinoline **4m** to verify if the hindrance on the 2 position would selectively lead to the formation of the 4 alkylated product, but no reactivity was observed.
In all cases, except for isovaleraldehyde **5e**, small amounts of the 4 addition products **7** were observed (5-16% yield). The products could be efficiently purified by flash column chromatography or on preparative TLC on silica after reduction to the corresponding alcohols. In all cases, except for **6fa**, the syn major diastereoisomer could be separated from a mixture of anti diastereoismer and the 4 addition product. In case of **6ac** and **6ad** the minor product could not be separated from the high boiling point alcohols derived from the excess of aldehyde.
The products **6** are very stable compounds that can be conserved at -20 °C in sealed vials under air for one year without any degradation. Instead products **7** are more unstable: isolated **7ab** decomposed in a few weeks.

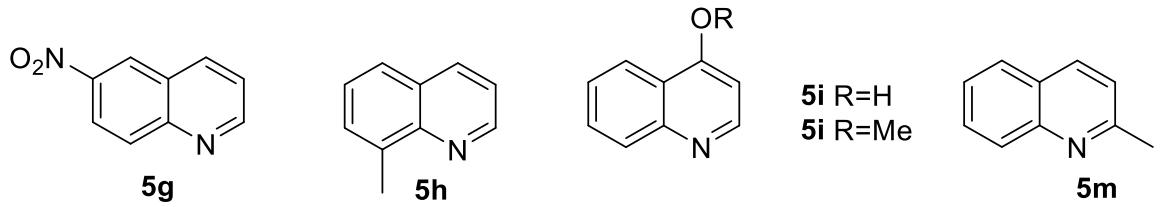
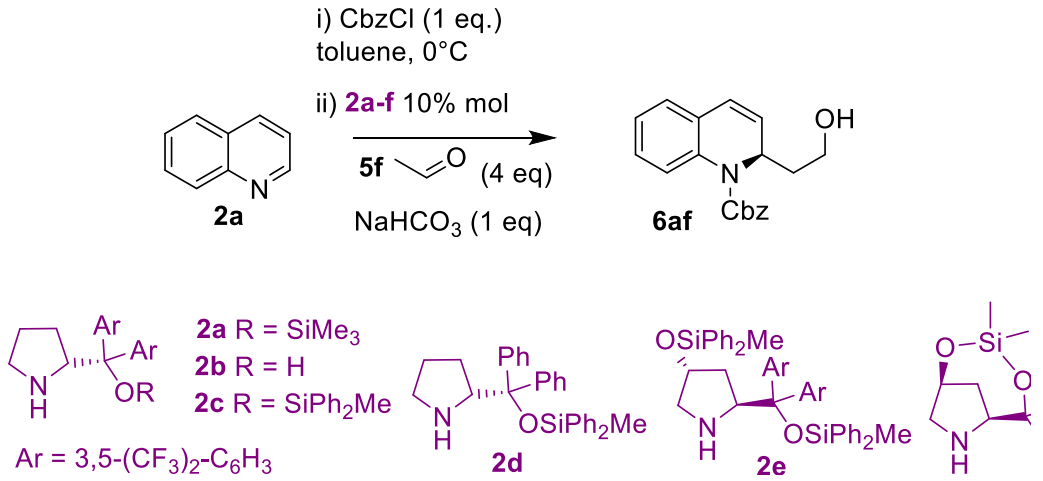



*Figure 2: unreactive quinolines under the developed protocol.*

The reaction between acetaldehyde **5f** and quinoline **4a** affords the corresponding product **6af** in good yield, but without enantioselective induction from the catalyst (*S*)-*ent*-**2a**. We decided to investigate more in detail this transformation testing different catalysts and conditions because the product **6af** is a valuable starting material for the synthesis of the galipea alkaloids.
I first investigated the use of catalyst (*S*)-**2b**[21] in different solvents: a significant increase of ee up to -39% was obtained in $CH_3CN$, but the conversion was low. The use of a bulkier silyl substituent on prolinol catalyst **2c** lead to a further increase to an unprecedented -46% ee maintaining a good yield. Performing the reaction with **2d**, that bears the phenyl groups instead of the trifluoromethylated aryls, lead to a slight decrease in the ee. The use of bridged catalyst **2f**,[22] generously furnished by our colleagues Prof. Marco Lombardo and Claudio Trombini, did not afford a positive result.
In order to achieve a better result it is necessary impose a higher control on the electrophile's approach to the enamine. We hypothesized that the presence of a bulkier group on the less hindered face of the catalyst[23] would reduce the possible approaches for the electrophile to approach the enamine and lead to an increase in the enantioselectivity. For this purpose I synthetized novel catalyst **2e** derived from trans hydroxy proline. The trans substituent had a strong, but detrimental, effect on the reaction outcome and the product was obtained with +10% ee. The use of (*S*)-**2e** having the trans bulky substituent on the 4 position of the pyrrolidine ring leads to an inversion of enantioselectivity compared to the all the other (*S*)-catalysts employed. We have rationalized this by hypothesizing that the steric hindrance due to the trans substituent reverses the otherwise favored approach of the quinolinium ion towards the enamine.
Recently Pihko reported the use of a 5-trans aryl substituted prolinol catalyst to efficiently control the formation of remote stereocenter in the Mukayama Michael reaction of alkylated silyl ketenes thioacetals with acrolein via LUMO catalysis.[24] A careful optimization of the catalyst evidenced

that the presence of para methoxy substituent is fundamental in order to obtain high enantiomeric excesses. DFT calculations suggested that a non covalent interaction between this functional group and the silyl ketene thioacetal is responsible for the efficient discrimination of the diastereoisomeric transition states that does not only depend on steric effects.




| Catalyst **2a-f** | solvent | conv.[a] | Yield[b] | ee[c] |
|---|---|---|---|---|
| *ent*-**2a** | toluene | 89 | 76 | +4 (*R*) |
| **2b** | DMF | 19 | - | -37 (*S*) |
| **2b** | $CH_3CN$ | 23 | - | -39 (*S*) |
| **2b** | toluene | 0 | - | - |
| **2c** | toluene | 74 | 62 | -46 (*S*) |
| **2d** | toluene | 32 | - | -40 (*S*) |
| **2e** | toluene | 48 | - | +10 (*R*) |
| **2f** | toluene | 56 | - | -22 (*R*) |

All reactions were carried on 0.1 mmol of quinoline, CbzCl, $NaHCO_3$, 0.5 mmol acetaldehyde and 0.01 mmol of catalysts for 16h at 0°C; [(a)] conversions were determined by GC-MS analysis before reduction; [(b)] yield of isolated product after chromatographic purification; [(c)] enantiomeric excesses were calculated by HPLC analysis on chiral stationary phase on the crude reaction mixture after reduction.

*Table 3: optimization of the conditions for the alkylation of acetaldehyde with quinolinium ion.*

Based on our investigation and on these recent findings, a possible approach to address the enatioselective reaction with acetaldehyde could be the use of a hydrogen bonding directing group on the prolinol catalyst to guide the electrophile in synergy with the enamine formation. In order to

design such a catalyst computational calculations on the possible transitions state would be of valuable aid.

**Determination of the relative configuration**

The relative configuration of the obtained products was assigned by comparing the $^1$H NMR traces of products *syn*-**6aa** and *anti*-**6aa** with the corresponding ones already reported in the literature whose relative configuration had already been determined.[20b]
From the literature the characteristic NMR signals of *syn*-**6aa** and *anti*-**6aa** are: 6.15 (dd, 1H$_{syn}$, $J$ = 9.5, 5.9 Hz), 5.98 (dd, 1H$_{anti}$, $J$ = 9.6, 5.8 Hz) and 1.03 (d, 3H$_{syn}$, $J$ = 6.8 Hz), 0.56 (bs, 3H$_{anti}$).
The characteristic signals of *major*-**6aa** are: 6.16 (dd, $J_1$ = 9.5 Hz, $J_2$ = 6.0 Hz, 1H) and 1.04 (d, $J$ = 6.4 Hz, 3H), thus we assigned the *syn* relative configuration to the major product.
The characteristic signals of *minor*-**6aa** are: 5.99 (dd, $J_1$ = 9.3 Hz, $J_2$ = 6.1 Hz, 1H) and 0.50-0.63 (bs, 3H), thus we assigned the *anti* relative configuration to the minor product.
The assigned relative configuration is further confirmed by comparing the elution orders of the peaks of **6aa** that we obtained (AD column, hexane:iPrOH eluting solvents):
$\tau_{syn\ minor}$ = 17.78 min., $\tau_{syn\ major}$ = 20.96 min., $\tau_{anti\ major}$ = 22.68 min., $\tau_{anti\ minor}$ = 26.74 min.;
with those obtained by Pineschi (AD-H column, hexane:iPrOH eluting solvents):
$\tau_{syn\ major}$ = 23.5 min., $\tau_{syn\ minor}$ = 30.2 min., $\tau_{anti\ major}$ = 34.1 min., $\tau_{anti\ minor}$ = 43.4 min.
The same relative configuration was assigned by analogy to all products **6**.

**Determination of the absolute configuration**

The absolute configuration of product *syn*-**6ac** was determined by comparing the specific rotation power with the previously reported one in the literature.[20b] Pineschi et al. reported for (*R,R*)-*syn*-**6ac** $[\alpha]_D^{20}$ = +374.4 (c 0.73, $CHCl_3$, 96% ee), while we measured for *syn*-**6ac** $[\alpha]_D^{20}$ = -135.3 (c 1.2, $CHCl_3$, 82% ee), thus we can assign the absolute configuration (*S,S*)-*syn*-**6ac** to our product.
The same absolute configuration was assigned by analogy to all products *syn*-**6**, while by consequence the (*R,S*) absolute configuration was assigned to *anti*-**6** products.
The assignation is further confirmed by comparing the $[\alpha]_D^{20}$ of product **10**. Rueping reported for (*R,R*)- *syn*-**10** $[\alpha]_D^{20}$ = +290.4 (c = 6.8, CHCl3, 94% ee), while we measured $[\alpha]_D^{20}$ = -239 (c = 0.68, $CHCl_3$, 94% ee) for (*S,S*)- *syn*-**10**.

**Stereochemical models**

On the basis of the results obtained and in according to the determined relative and absolute configuration, the following stereochemical model is proposed (figure 3). The enamine is alkylated on the less hindered face affording the *S* configurated stereocenter on the alkyl chain for both diastereoisomers.
Based on this model the *major syn* diastereoisomer is favored because of the more intense repulsive interaction between the aldehyde chain and the more flexible Cbz, while a more favorable approach is realized over the flat quinoline ring.

Indeed when acetaldehyde is employed this discriminating interaction is lost and a racemic product is obtained (figure 4a). It must be noted that the absolute stereochemical indicator for the stereocenter of **6af** is opposite to all the other products due to priority rules.

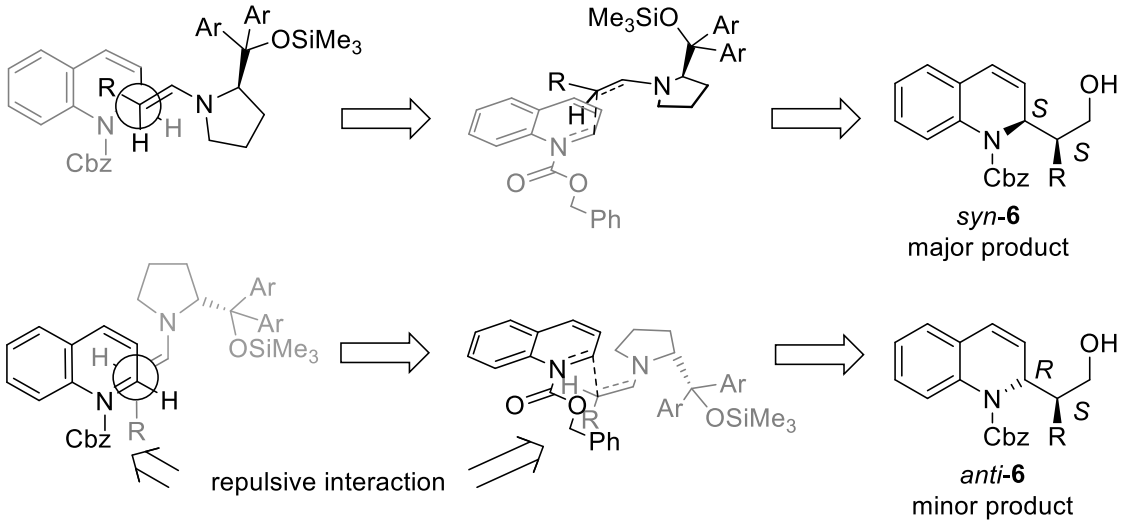



*Figure 3: stereochemical model for the alkylation of 2 substituted aldehydes with quinolinium ion.*

For the sake of clarity also the models in figure 4b and figure 4c are built using the (*R*)-catalysts, while in the real experiment the (*S*)-catalysts were employed. This accounts for the reversal of the sign of the ee for figure 4b and figure 4c if compared with table 3.

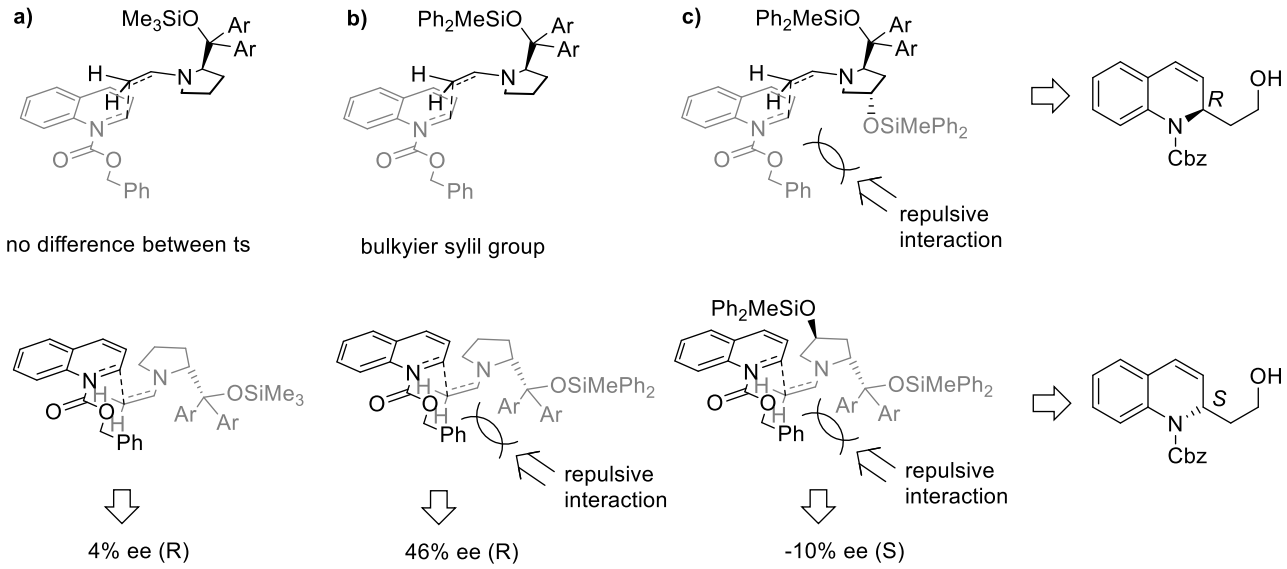



*Figure 4: models to rationalize the effect of the catalyst substitution pattern in the alkylation of acetaldehyde.*

The bulkyier sylil group in figure 4b may engage an interaction with Cbz marking a difference between the diastereoisomeric transitions states that is reflected in a significant increase to 46% ee. Instead, the presence of the trans group on the 4 position destabilizes the so far favored transition state causing a reversal of enantioinduction (figure 4c).

**Derivatization**

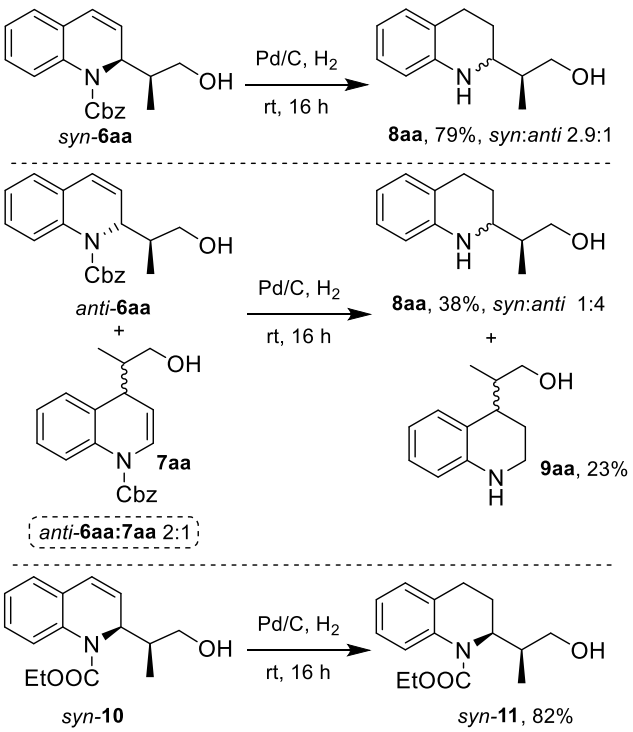
Having verified the scope and limitations of the methodology, I have investigated the possible derivatizations on the model substrate **6aa**.

I first tried the standard hydrogenation conditions to remove the Cbz group and reduce the 3,4-double bond in a one step procedure, but the unexpected epimerization of the substrate on the stereocenter on the THQ ring occurred (scheme 5).

When *syn*-**6aa** was dissolved in methanol and reacted under hydrogen atmosphere in presence of 10% wt Pd/C, the tetrahydroquinoline product *syn*-**8aa** was obtained in good yield, but as a 2.9:1 mixture of *syn:anti* diastereoisomers. The relative configuration of the tetrahydroquinolines diastereoismers, was clarified by subjecting *anti*-**6aa** to the same hydrogenation conditions. In this case a less significant epimerization was observed and the product *anti*-**8aa** was obtained with a reversed diastereomeric ratio *syn:anti* of 1:4.

It was evident that during the depretection of the CbzCl group a partial epimerization for both *syn*-**6aa** and *anti*-**6aa** happened, even if in case of *syn*-**6aa** it occurred to a larger extent.

As the final diastereoisomeric ratio is different starting from *syn*-**6aa** or *anti*-**6aa**, it is reasonable to assume that the deprotection-hydrogenation reaction occurs faster than the epimerization process that cannot reach its thermodynamic equilibrium.



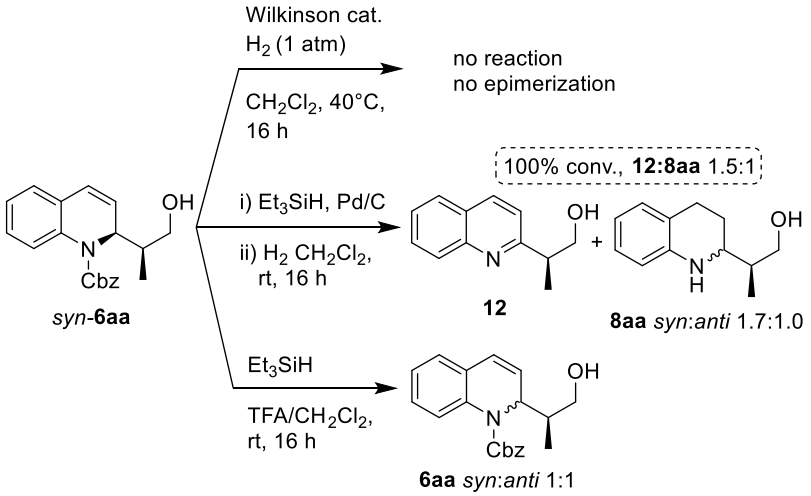

*Scheme 5: deprotection of **6aa** to THQ **8aa** and hydrogenation of **10**.*

In order to have a better insight on this behaviour, I subjected to the same hydrogenation conditions products *syn*-**10** and *anti*-**10** having the ethyl carbamate: in this case no epimerization was observed and the corresponding products *syn*-**11** and *anti*-**11** were obtained as single diastereoisomers in according to Rueping report (scheme 5). [20c]

This evidence suggests that the epimerization process might be closely connected with the Cbz cleavage, while it is unprobable that it might happen before the Cbz is lost. To rule out this latter possibility, I leaved *syn*-**6aa** for one night in presence of Pd/C in MeOH under nitrogen atmosphere. After work up, the starting material was recovered and no epimerization was observed ruling out a possible $\eta^3$ coordination of the Pd to the allylic anyline that could cause the epimerization by opening the system to $\eta^3$ cation and subsequent nuclephilic closure. The more reasonable explanation is that after (or concomitant to) the Cbz cleavage the free amine undergoes oxidation losing the chiral information on the C2. Subsequent hydrogenation of the planar imine leads to a mixture of diastereoisomers.

On the basis of such hypothesis I tried the hydrogenation under mild acidic conditions to see if the protonation of the amine would avoid the coordination to the metal catalyst and reduce the epimerization. The hydrogenation was conducted in a 1:1 mixture of AcOEt and acetic acid, however no significant decrease in the epimerization was observed while unidentified byproducts were detected.

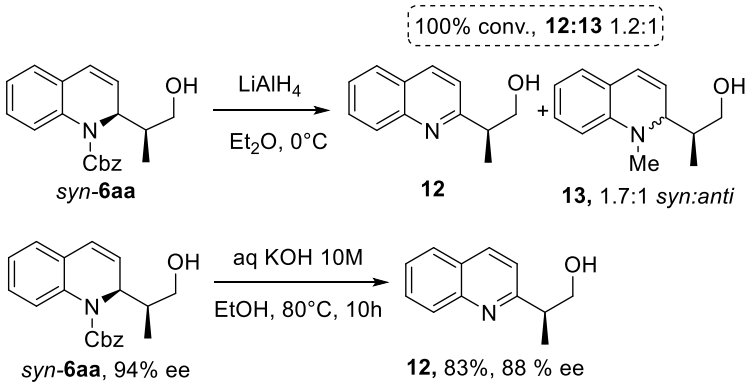
I tried other procedures to obtain product **8aa** avoiding the epimerization but they were not successful (scheme 6). The hydrogenation using Wilkinson catalyst leaved completely untouched the starting material: no conversion, as well as no epimerization occurred. In the conditions reported by Mancheño[18] for the hydrogenation of the N-Troc dihydroquinolines, a 1.5:1 mixture of re-aromatized quinoline **12** and of the desired product **8aa** was obtained.




*Scheme 6: unsuccessful conditions to hydrogenate syn-**6aa** avoiding epimerization.*

I also tried to first reduce selectively the double bond by treating *syn*-**6aa** with $Et_3SiH$ in TFA/DCM at room temperature, but no conversion was observed, while the recovered starting material was a 1:1 *syn:anti* mixture.

The treatment of *syn*-**6aa** with $LiAlH_4$ at 0°C to reduce the Cbz group to methyl, a structural motif recurring in most of the tetrahydroquinoline alkaloids, afforded a complex mixture of products. The major one was the re-aromatized product **12**, while desired product **13** was present as 2.1:1 mixture of diastereoisomers. (**12:***major*-**13:***minor*-**13**, 3.7:2.1:1).
The re-aromatization might be due to the action of $LiAlH_4$ as a base on the 2 allylic proton followed by the loss of the Cbz group or by hydrolysis of the benzyl carbamate by adventitious water followed by decarboxylation.




*Scheme 7: rearomatization of syn-**6aa** to quinoline **12**.*

The re-aromatized product **12** could be selectively obtained from *syn*-**6aa** in high yield albeit with a slight loss of enantiopurity by basic hydrolysis as reported by Rueping[20c] for the N-ethylcarbamate-2-alkyl-3,4-dihydroquinolines.

## 2.4.3 Conclusions

In conclusion, we have reported the first enantioselective alkylation of aldehydes with quinolines, activated with benzylchloroformate, promoted by prolinol catalysts without the aid of an acidic cocatalyst. The reaction is successfull with all the tested aldehydes, and with 5 or 6 substituted quinolines affording the 2 alkylation products in moderate to good yields, good regioselectivity vs the 4 alkylation process, moderate diastereoselectivities and good or optimal enantioselectivities. The synthesis of a modified Jørgensen catalyst allowed to obtain 46 % ee for the alkylation of acetaldehyde with quinoline, that is the best result so far achieved.
The obtained products can be efficiently rearomatized to the corresponding 2 alkyl quinolines having a stereocenter on the position adjacent to the aromatic ring. A detailed investigation on the depretection and hydrogenation of the Cbz products to give the 2-alkyl tetrahydroquinolines revealed an unexpected epimerization process on the stereocenter present on the tetrahydroquinoline ring.
Further investigations to apply this methodology to the synthesis of natural products will be object of future studies.

## 2.4.4 Contributions

I discovered and developed the methodology under the supervision of Prof. Pier Giorgio Cozzi and with precious advices from Dr. Andrea Gualandi.

## 2.4.5 Experimental part

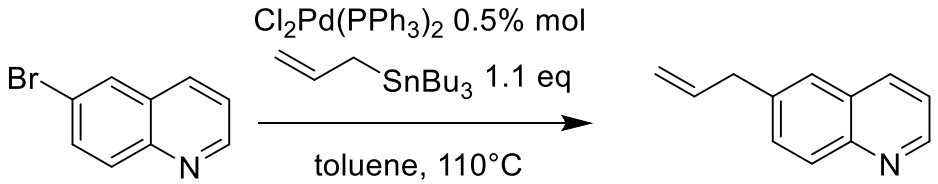
**Table of contents:**

**General methods.** $^{1}$H NMR spectra were recorded on Varian Gemini 200, Varian Mercury 400 and Inova 600 spectrometers. Chemical shifts are reported in ppm from TMS with the solvent resonance as the internal standard (deuterochloroform: $\delta$ = 7.27 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = duplet, t = triplet, q = quartet, dd = double duplet, dt = double triplet, pd = penta dublet, bs = broad signal, bd = broad duplet, m = multiplet), coupling constants (Hz). $^{13}$C NMR spectra were recorded on Varian Gemini 200, Varian MR400 spectrometers. Chemical shifts are reported in ppm from TMS with the solvent as the internal standard (deuterochloroform: $\delta$= 77.0 ppm). If rotamers are present, the splitted signals are labeled as A (major rotamer) and B (minor rotamer). GC-MS spectra were taken by EI ionization at 70 eV on a Hewlett-Packard 5971 with GC injection. LC-electrospray ionization mass spectra (ESI-MS) were obtained with Agilent Technologies MSD1100 single-quadrupole mass spectrometer. They are reported as: *m/z* (rel. intense). Chromatographic purification was done with 240-400 mesh silica gel. Purification on preparative thin layer chromatography was done on Merck TLC silica gel 60 $F_{254}$. Determination of diastereomeric ratio was determined by $^{1}$HNMR on the crude reaction mixture and determination of enantiomeric excess was performed on Agilent Technologies 1200 instrument equipped with a variable wave-length UV detector (reference 420 nm), using Daicel Chiralpak® columns (0.46 cm I.D. x 25 cm), Phenomenex® Lux columns and HPLC grade isopropanol and *n*-hexane as eluting solvents. Optical rotations were determined in a 1 mL cell with a path length of 1 dm ($Na_D$ line).

**Materials.** If not otherwise stated, all reactions were carried out in flame dried glassware under nitrogen atmosphere. Anhydrous solvents were supplied by Aldrich in Sureseal® bottles and were used as received avoiding further purification.

Reagents were purchased from Aldrich and used without further purification unless otherwise stated. Quinoline **4a**, propionaldehyde **5a** and isovaleraldehyde **5e** were supplied by Aldrich and used after distillation.

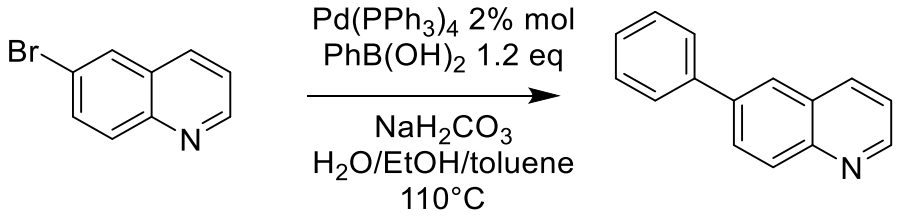
**Synthesis of 6-allyl-quinoline (4e)**




In a flame dried Schlenk tube under nitrogen atmosphere, 6-bromo quinoline (90 µL, 0.66 mmol), allyltributylstannane (227 µL, 0.73 mmol), and $Cl_2Pd(PPh_3)_2$ (23 mg, 0.033 mmol) were dissolved in degassed toluene (2 mL). The mixture was heated to reflux for 8 h, until TLC analysis revealed complete conversion. The mixture was filtered over a Celite® pad that was washed with a 1:1 mixture of DCM and ethyl acetate (15 mL). The organic phase was concentrated under reduced pressure and the residue was purified by column chromatography on silica (cyclohexane:ethylacetate from 8:2 to 5:5) to give **4e** together with alkylstannane. This product was dissolved in $Et_2O$ (10 mL) and washed with 1M aq. HCl (3 x 6 mL). The acidic water phases were collected and basified with NaOH at 0°C. Then extraction with DCM (3 x 10 mL) of the basic water phase afforded pure **4e** as a colourless oil (52.3 mg, 0.3 mmol, 45% yield).

(**4e**): $^1$H NMR (400 MHz, $CDCl_3$, 25°C): $\delta$ = 3.56 (d, $J$ = 7.2 Hz, 2H), 5.08-5.17 (m, 2H), 5.97-6.09 (m, 1H), 7.34 (dd, $J_1$ = 7.8 Hz, $J_2$ = 3.9 Hz, 1H), 7.52-7.59 (m, 2H), 7.98-8.08 (m, 2H), 8.85 (dd, $J_1$ = 4.2 Hz, $J_2$ = 1.6 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$, 25°C): $\delta$ = 40.0, 116.4, 121.0, 126.3, 128.3, 129.3, 130.9, 135.5, 136.7, 138.4, 147.2, 149.7.

**Synthesis of 6-phenyl-quinoline (4f)**



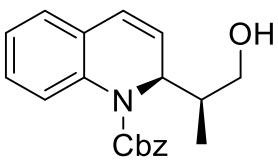

In a Schlenk tube under nitrogen atmosphere, 6-bromo quinoline (135 µL, 1.0 mmol) was dissolved in toluene (2 mL). A solution of $Na_2CO_3$ (424 mg, 4 mmol) in $H_20$ (2 mL) was added and the mixture was degassed by nitrogen bubbling. Phenyl boronic acid (147 mg, 1.2 mmol) dissolved in EtOH (1 mL) was added and the mixture was further degassed by nitrogen bubbling. Then $Pd(PPh_3)_4$ (23 mg, 0.02 mmol) was added, the Shlenk tube was sealed and refluxed under magnetic stirring for 9 h. The volatiles were evaporated under reduced pressure, the residue diluted with ethyl acetate (5 mL) and filtered over a Celite® pad that was washed with a 1:1 mixture of DCM and

ethyl acetate (20 mL). The organic phase was concentrated under reduced pressure and the residue was purified by column chromatography on silica (cyclohexane:ethylacetate from 8:2 to 5:5) to give pure **4f** as a white sticky solid (130 mg, 0.63 mmol, 63% yield).
(**4f**): $^{1}$H NMR (200 MHz, $CDCl_3$, 25°C): $\delta$ = 7.34-7.59 (m, 4H), 7.66-7.78 (m, 2H), 7.93-8.06 (m, 2H), 8.13-8.28 (m, 2H), 8.89-8.98 (m, 1H); $^{13}$C NMR (50 MHz, $CDCl_3$, 25°C): $\delta$ = 121.4, 125.4, 127.4 (2C), 127.7, 128.4, 128.9 (2C), 129.2, 129.9, 136.2, 139.3, 140.2, 147.6, 150.2.

**General procedure for the alkylation of aldehydes with quinolines activated with CbzCl:** In a flame dried two necked round bottom flask equipped with a magnetic stirring bar under nitrogen atmosphere, quinoline **4a-4f** (0.2 mmol) was dissolved in anhydrous toluene (2 mL) at 0°C. Then CbzCl (0.2 mmol, 31 μL) was added and the solution turned rapidly to a white suspension. After 30 min., $NaHCO_3$ (0.2 mmol, 17 mg), Jørgensen catalyst (*R*)-ent-**2a** (0.02 mmol, 12 mg) and aldehyde **5a-f** (0.8 mmol) were added and the mixture was stirred for 16 h at 0°C. Then methanol (0.5 mL) and $NaBH_4$ (1.6 mmol, 61 mg) were added and after complete conversion as judged by TLC analysis (1-2 h), the reaction was quenched by addition of aq. HCl 1M until pH = 2 at 0°C. Then AcOEt (10 mL) was added and the organic layer was separated. The aqueous layer was extracted with AcOEt (2 x 8 mL). The collected organic layers were washed with brine (10 mL), dried over $Na_2SO_4$ and concentrated under reduced pressure to give the crude products.

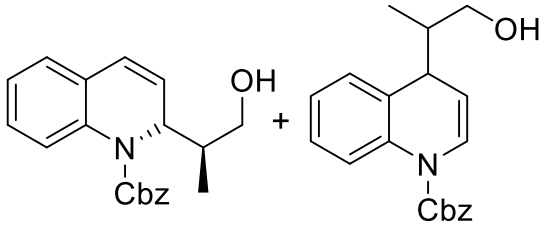
**The racemic products** were synthesized with the same procedure except for using pyrrolidine (0.1 mmol, 8.3 μL, 50% mol) instead of *ent*-**2a** for products **6aa**, **6ba**, **6ca**, **6da**, while for the other products an equimolar mixture of (*R)* and (*S)*-**2a** (total amount 0.02 mmol, 20% mol) was used.

**Product 6aa** (2.5:1 ratio *syn-anti* determined by $^{1}$H NMR on the crude reaction mixture) and **7aa**, were obtained following the general procedure using quinoline **4a** and aldehyde **5a**. The crude reaction mixture was purified by column chromatography on silica (cyclohexane:ethylacetate from 85:15 to 80:20) to afford *syn*-**6aa** and an inseparable mixture of *anti*-**6aa** : **7aa**. Spectroscopic data were according to the literature.[20b]




**(*syn*-6aa):** colourless oil; 34 mg, 53% yield; ee = 94%; determined by HPLC analysis Daicel Chiralpak® AD column: hexane/*i*-PrOH from 95:5 to 90:10 in 10 min., then 90:10, flow rate 0.70 mL/min, 40°C, λ = 280 nm:

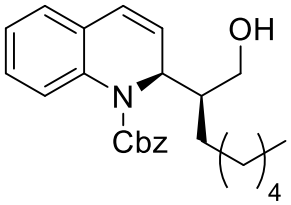
$\tau_{major}$ = 20.96 min., $\tau_{minor}$ = 17.78 min.; Spectroscopic data were according to the literature.[1] $^1$H NMR (400 MHz, $CDCl_3$, 25°C): $\delta$ = 1.04 (d, $J$ = 6.4 Hz, 3H), 1.58-1.70 (m, 1H), 2.98-3.26 (bs, 1H), 3.33 (pt, $J$ = 10.2 Hz, 1H), 3.69 (bd, $J$ = 10.6 Hz, 1H), 4.85 (dd, $J_1$ = 10.6 Hz, $J_2$ = 6.0 Hz, 1H), 5.21 (bd, $J$ = 12.6 Hz, 1H), 5.36 (bd, $J$ = 11.6 Hz, 1H), 6.16 (dd, $J_1$ = 9.5 Hz, $J_2$ = 6.0 Hz, 1H), 6.53 (d, $J$ = 9.5 Hz, 1H), 7.04-7.12 (m, 2H), 7.13-7.20 (m, 1H), 7.27-7.43 (m, 6H); $^{13}$CNMR (50 MHz, $CDCl_3$, 25°C): $\delta$ = 13.0, 38.2, 54.0, 63.8, 68.3, 124.5, 124.7, 125.0, 126.2, 127.4, 127.5, 128.1 (2C), 128.3, 128.6 (2C), 129.0, 133.5, 135.6, 155.6; ESI-MS: *m/z* = 324.2 $[M+H]^+$, 347.0 $[M+Na]^+$, 669.2 $[2M+Na]^+$; HMRS calcd for $C_{20}H_{21}NO_3$ : 323.15214. $[\alpha]_D^{20}$ = -237 (c 0.73, $CHCl_3$).



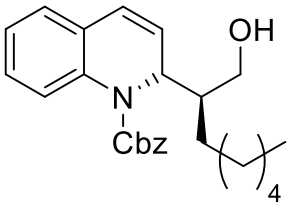

**(*anti*-6aa:7aa,** 1.3:1 ratio. **7aa** is present as a mixture of diastereoisomers A:B in 2:1 ratio): yellowish oil; 18 mg, 28% yield; $ee_{anti\text{-}XX}$ = 93%; determined by HPLC analysis Daicel Chiralpak® AD column: hexane/*i*-PrOH from 95:5 to 90:10 in 10 min., then 90:10, flow rate 0.70 mL/min, 40°C, λ = 280 nm: $\tau_{major}$ = 22.68 min., $\tau_{minor}$ = 26.74 min.; Spectroscopic data were according to the literature.[1] $^1$H NMR (400 MHz, $CDCl_3$, 25°C): $\delta_{anti\text{-}\mathbf{6aa}}$ = 0.50-0.63 (bs, 3H), 1.36-1.41 (bs, 1H), 1.80-1.88 (m, 1H), 3.44-3.63 (m, 2H), 5.15-5.20 (m, 2H), 5.39 (dd, $J_1$ = 7.6 Hz, $J_2$ = 6.1 Hz, 1H), 5.99 (dd, $J_1$ = 9.3 Hz, $J_2$ = 6.1 Hz, 1H), 6.58 (d, $J$ = 9.3 Hz, 1H), 7.03-7.20 (m, 3H), 7.20-7.27 (m, 1H), 7.30-7.46 (m, 5H); $\delta_{\mathbf{7aa}}$ = 0.79 (d, $J$ = 6.5 Hz, $3H_A$), 0.82 (d, $J$ = 7.1 Hz, $3H_B$), 1.36-1.41 (bs, $1H_{A+B}$), 1.89-1.99 (m, $1H_{A+B}$), 3.44-3.63 (m, $3H_{A+B}$), 5.29 (dd, $J_1$ = 7.7 Hz, $J_2$ = 6.1 Hz, $1H_A$), 5.32 (s, $2H_{A+B}$), 5.33-5.37 (m, $1H_B$), 7.03-7.20 (m, $3H_{A+B}$), 7.20-7.27 (m, $1H_{A+B}$), 7.30-7.46 (m, $5H_{A+B}$), 7.98 (d, $J$ = 7.3 Hz, $1H_B$), 7.99 (d, $J$ = 7.3 Hz, $1H_A$); $^{13}$CNMR (100 MHz, $CDCl_3$, 25°C): $\delta_{anti\text{-}\mathbf{6aa}}$ = 13.0, 39.8, 53.6, 64.9, 67.9, 124.5, 125.6, 126.1, 126.4, 127.96, 128.03, 128.23, 128.28, 128.6 (2C), 129.3, 130.7, 135.4, 135.9, 152.4; $\delta_{\mathbf{7aa}}$ = 11.8 ($1C_A$), 14.0 ($1C_B$), 39.4 ($1C_A$), 41.1 ($1C_B$), 42.3 ($1C_B$), 43.3 ($1C_A$), 63.8 ($1C_B$), 65.4 ($1C_A$), 67.9 ($1C_A$), 68.3 ($1C_B$), 110.7 ($1C_A$), 112.9 ($1C_B$), 121.5 ($1C_A$), 121.6 ($1C_B$), 124.6 ($1C_B$), 124.7 ($1C_B$), 124.9 ($1C_A$), 126.3 ($1C_A$), 127.0 ($1C_B$), 127.4 ($1C_A$), 127.6 ($1C_B$), 128.00 ($2C_{A+B}$), 128.26 ($1C_{A+B}$), 128.4 ($1C_A$), 128.6 ($2C_{A+B}$), 128.7 ($1C_B$), 129.2 ($1C_A$), 135.7 ($1C_B$), 135.8 ($1C_A$), 136.9 ($1C_A$), 137.1 ($1C_B$), 152.4 ($1C_{A+B}$); ESI-MS: *m/z* = 324.2 $[M+H]^+$, 347.0 $[M+Na]^+$, 669.2 $[2M+Na]^+$; HMRS calcd for $C_{20}H_{21}NO_3$ : 323.15214.

**Product 6ab** (4.3:1 ratio *syn-anti* determined by $^1$H NMR on the crude reaction mixture) and **7ab**

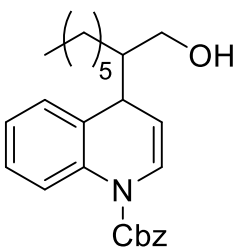
were obtained following the general procedure using quinoline **4a** and aldehyde **5b**. The crude reaction mixture was purified by column chromatography on silica (cyclohexane:ethylacetate from 95:5 to 90:10) to afford ***syn*-6ab** and a mixture of ***anti*-6ab** : **7ab** : 1-octanol. Further purification on preparative TLC on silica (cyclohexane:diethylether 60:40) allowed to separate ***anti*-6ab** and **7ab** that were obtained as pure compounds.




**(*syn*-6ab):** yellowish oil; 46 mg, 58% yield; ee = 93%; determined by HPLC analysis Daicel Chiralpak® AD column: hexane/*i*-PrOH from 95:5 to 90:10 in 10 min., then 90:10, flow rate 0.70 mL/min, 40°C, λ = 280 nm: $\tau_{major}$ = 20.05 min., $\tau_{minor}$ = 14.79 min.; $^1$H NMR (400 MHz, $CDCl_3$, 25°C): $\delta$ = 0.86 (t, $J$ = 7.2 Hz, 3H), 1.06-1.45 (m, 10H), 1.53-1.66 (m, 2H), 3.47 (d, $J$ = 12.3 Hz, 1H), 3.61 (d, $J$ = 12.3 Hz, 1H), 4.88 (dd, $J_1$ = 10.6 Hz, $J_2$ = 6.1 Hz, 1H), 5.21 (bd, $J$ = 12.9 Hz, 1H), 5.37 (d, $J$ = 11.4 Hz, 1H), 6.20 (dd, $J_1$ = 10.2 Hz, $J_2$ = 6.1 Hz, 1H), 6.53 (d, $J$ = 10.2 Hz, 1H), 7.05-7.13 (m, 2H), 7.14-7.20 (m, 1H), 7.28-7.40 (m, 6H); $^{13}$CNMR (100 MHz, $CDCl_3$, 25°C): $\delta$ = 14.1, 22.6, 26.1, 27.2, 29.6, 31.8, 43.3, 53.2, 59.6, 68.4, 124.6, 124.7, 124.9, 126.3, 127.3, 127.5, 128.1 (2C), 128.4, 128.6 (2C), 129.3, 133.5, 135.6, 157.8; ESI-MS: *m/z* = 394.2 $[M+H]^+$, 416.2 $[M+Na]^+$; HMRS calcd for $C_{25}H_{31}NO_3$ : 393,23039. $[\alpha]_D^{20}$ = -233 (c 1.43, $CHCl_3$).



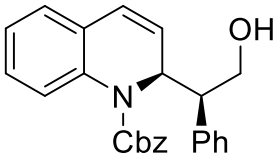

**(*anti*-6ab):** colourless oil; 13% yield; ee = 95%; determined by HPLC analysis Daicel Chiralpak® AD column: hexane/*i*-PrOH from 95:5 to 90:10 in 10 min., flow rate 0.70 mL/min, 40°C, λ = 280 nm: $\tau_{major}$ = 16.82 min., $\tau_{minor}$ = 23.13 min.; $^1$H NMR (400 MHz, $CDCl_3$, 25°C): $\delta$ = 0.81 (t, $J$ = 7.1 Hz, 3H), 0.98-1.13 (m, 6H), 1.14-1.24 (m, 4H), 1.68-1.78 (m, 2H), 3.39-3.47 (m, 1H), 3.60 (dd, $J_1$ = 12.0 Hz, $J_2$ = 4.6 Hz, 1H), 5.13-5.21 (m, 1H), 5.22-5.28 (m, 1H), 5.29-5.39 (m, 1H), 6.01 (dd, $J_1$ = 9.5 Hz, $J_2$ = 5.5 Hz, 1H), 6.57 (d, $J$ = 9.5 Hz, 1H), 7.03-7.08 (m, 2H), 7.09-7.19 (m, 2H), 7.29-7.46 (m, 5H); $^{13}$CNMR (100 MHz, $CDCl_3$, 25°C): $\delta$= 14.0, 22.5, 25.2, 27.5, 29.2, 31.6, 45.6, 53.6, 61.6, 68.2, 124.7, 124.8, 125.8, 126.1, 127.4, 127.8, 128.0 (2C), 128.2, 128.6 (2C), 128.9, 135.2, 135.8, 156.1; ESI-MS: *m/z* = 394.2 $[M+H]^+$, 416.2 $[M+Na]^+$; HMRS calcd for $C_{25}H_{31}NO_3$ : 393,23039. $[\alpha]_D^{20}$ = +197 (c 0,46 $CHCl_3$).



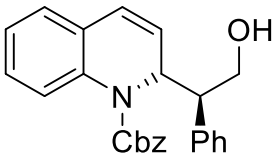

**(7ab):** yellowish oil; 11% yield; $^1$H NMR (400 MHz, $CDCl_3$, 25°C): $\delta$ = 0.88 (t, $J$ = 6.7 Hz, 3H), 1.20-1.43 (m, 10H), 1.69-1.78 (m, 2H), 3.50-3.68 (m, 3H),

5.31 (s, 2H), 5.36 (dd, $J_1$ = 7.6 Hz, $J_2$ = 5.8 Hz, 1H), 7.04-7.18 (m, 3H), 7.19-7.26 (m, 1H), 7.32-7.46 (m, 5H), 7.99 (d, $J$ = 7.6 Hz, 1H); ESI-MS: *m/z* = 394.2 $[M+H]^+$, 416.2 $[M+Na]^+$, HMRS calcd for $C_{25}H_{31}NO_3$ : 393,23039.

**Product 6ac** (1.8:1 ratio *syn-anti* determined by $^1$H NMR on the crude reaction mixture) and **7ac**, were obtained following the general procedure using quinoline **4a** and aldehyde **5c**. The crude reaction mixture was purified by column chromatography on silica (cyclohexane:ethylacetate from 90:10 to 85:15) to afford ***syn*-6ac** and a mixture of ***anti*-6ac** : **7ac** : 2-phenyl propanol and other unindentified species from which it was not possible to obtain ***anti*-6ac** in pure form.



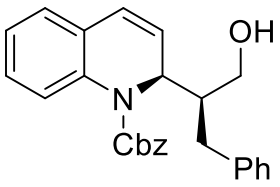

**(*syn*-6ac):** yellowish oil; 42 mg, 54% yield; ee = 82%; determined by HPLC analysis Daicel Chiralpak® AD column: hexane/*i*-PrOH 85:15, flow rate 0.70 mL/min, 40°C, λ = 300 nm: $\tau_{major}$ = 18.95 min., $\tau_{minor}$ = 15.88 min.; Spectroscopic data were according to the literature. [20b] $^1$H NMR (400 MHz, $CDCl_3$, 25°C): $\delta$ = 2.63-2.77 (bs, 1H), 3.12-3.34 (bs, 1H), 3.57-3.72 (m, 1H), 3.91-4.02 (m, 1H), 5.24 (bd, $J$ = 12.8 Hz, 1H), 5.34-5.46 (m, 2H), 5.65 (dd, $J_1$ = 8.8 Hz, $J_2$ = 5.9 Hz, 1H), 6.42 (d, $J$ = 8.8 Hz, 1H), 7.09-7.16 (m, 2H), 7.17-7.47 (m, 12H); $^{13}$CNMR (50 MHz, $CDCl_3$, 25°C): $\delta$ = 49.9, 53.4, 63.5, 68.4, 124.7, 124.9 (2C), 126.4, 127.1, 127.5, 128.1 (2C), 128.4, 128.5 (3C), 128.6 (2C), 129.0 (2C), 129.2, 133.3, 135.7, 139.2, 155.6; ESI-MS: *m/z* = 386.2 $[M+H]^+$, 408.0 $[M+Na]^+$, 771.2 $[2M+Na]^+$; HMRS calcd for $C_{25}H_{23}NO_3$ : 385,16779. $[\alpha]_D^{20}$ = -135 (c 1.2, $CHCl_3$).



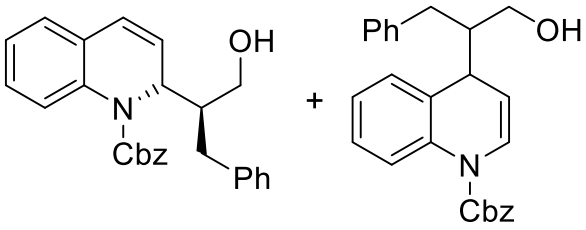

**(*anti*-6ac):** ee = 34%; determined by HPLC analysis Daicel Chiralpak® AD column: hexane/*i*-PrOH 85:15, flow rate 0.70 mL/min, 40°C, λ = 300 nm:$\tau_{major}$ = 23.48 min., $\tau_{minor}$ = 21.10 min.; $^1$H NMR (400 MHz, $CDCl_3$, 25°C): characteristic signals: $\delta$= 4.90-6.90 (bd, $J$ = 12.4 Hz, 1H), 5.20 (dd, $J_1$ = 7.4 Hz, $J_2$ = 6.2 Hz, 1H), 6.12 (dd, $J_1$ = 9.7 Hz, $J_2$ = 6.2 Hz, 1H), 6.45-6.51 (bs, 1H).

**Product 6ad** (2.4:1 ratio *syn-anti* determined by $^1$H NMR on the crude reaction mixture) and **7ad**, were obtained following the general procedure using quinoline **4a** and aldehyde **5d**. The crude reaction mixture was purified by column chromatography on silica (cyclohexane:ethylacetate from 90:10 to 80:20) to afford ***syn*-6ad** and a mixture of ***anti*-6ad** : **7ad** : 3-phenyl propanol (29 mg,

1:0.9:1.5 ratio).



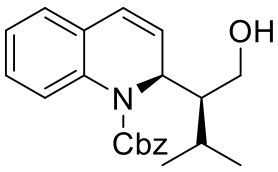

**(*syn*-6ad):** yellowish oil; 34 mg, 43% yield; ee = 99%; determined by HPLC analysis Daicel Chiralpak® AD column: hexane/*i*-PrOH 85:15, flow rate 0.70 mL/min, 40°C, λ = 280 nm: $\tau_{major}$ = 22.63 min., $\tau_{minor}$ = 15.04 min.; $^1$H NMR (400 MHz, $CDCl_3$, 25°C): $\delta$ = 1.65-1.75 (m, 1H), 1.93-2.12 (bs, 1H), 2.74-2.89 (m, 2H), 3.20 (dd, $J_1$ = 12.6 Hz, $J_2$ = 1.8 Hz, 1H), 3.50 (dd, $J_1$ = 12.2 Hz, $J_2$ = 1.8 Hz, 1H), 5.03 (dd, $J_1$ = 11.0 Hz, $J_2$ = 5.8 Hz, 1H), 5.23 (bd, $J$ = 12.9 Hz, 1H), 5.39 (bd, $J$ = 12.9 Hz, 1H), 6.30 (dd, $J_1$ = 9.7 Hz, $J_2$ = 5.8 Hz, 1H), 6.63 (d, $J$ = 9.7 Hz, 1H), 7.08-7.20 (m, 6H), 7.20-7.25 (m, 3H), 7.29-7.40 (m, 5H); $^{13}$CNMR (50 MHz, $CDCl_3$, 25°C): $\delta$ = 32.4, 45.9, 53.0, 58.6, 68.5, 124.5, 124.8, 125.3, 125.9, 126.4, 127.4, 127.5, 128.1 (2C), 128.2, (2C), 128.4, 128.6 (2C), 128.7, 129.3 (2C), 133.6, 135.6, 140.1, 155.6; ESI-MS: *m/z* = 400.2 $[M+H]^+$, 422.2 $[M+Na]^+$, 799.2 $[2M+Na]^+$; HMRS calcd for $C_{26}H_{25}NO_3$ : 399,18344. $[\alpha]_D^{20}$ = -266 (c 1.6, $CHCl_3$).



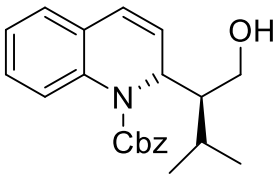

**(*anti*-6ad:7ad:3-phenyl propanol,** 1:0.9:1.5 ratio, **7ad** is present as a single diastereoisomer**):** yellowish oil, 29 mg, 29% yield, $ee_{anti}$ = 96%; determined by HPLC analysis Daicel Chiralpak® AD column: hexane/*i*-PrOH 85:15, flow rate 0.70 mL/min, 40°C, λ = 280 nm: $\tau_{major}$ = 20.96 min., $\tau_{minor}$ = 26.13 min.; $^1$H NMR (400 MHz, $CDCl_3$, 25°C): $\delta_{anti\text{-}\mathbf{6ad}}$ = 1.91-1.97 (m, 1H)*, 2.49-2.61 (m, 1H), 2.62-2.71 (m, 1H)*, 3.36-3.56 (m, 3H), 5.17 (bd, $J$ = 12.5 Hz, 1H), 5.31-5.37 (m, 1H), 5.40 (t, $J$ = 7.0 Hz, 1H), 6.09 (dd, $J_1$ = 9.8 Hz, $J_2$ = 6.2 Hz, 1H), 6.60 (d, $J$ = 9.8 Hz, 1H), 6.89-7.42 (m, 14H)*; * = signal partially overlapped with 3-phenyl propanol signals; $\delta_{\mathbf{7ad}}$ = 1.99-2.09 (m, 2H), 2.49-2.61 (m, 1H), 3.36-3.56 (m, 3H), 3.59 (t, $J$ = 5.6 Hz, 1H), 5.29 (s, 2H), 5.31-5.37 (m, 1H), 6.89-7.42 (m, 14H)*, 7.98 (d, $J$ = 7.9 Hz, 1H).

**Product 6ae** (1.7:1 ratio *syn-anti* determined by $^1$H NMR on the crude reaction mixture) was obtained following the general procedure using quinoline **4a** and aldehyde **5e**. The crude reaction mixture was purified by column chromatography on silica to (cyclohexane:ethylacetate from 90:10 to 80:20) afford pure ***syn*-6ae** while for ***anti*-6ae** further purification by preparative TLC on silica (cyclohexane:ethylacetate 80:20) was necessary to afford the pure diastereoisomer. **7ae** was not

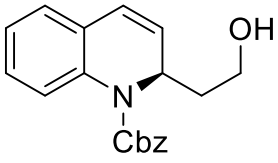
present in the crude reaction mixture.




**(*syn*-6ae):** yellowish oil; 27 mg, 39% yield; ee = 77%; determined by HPLC analysis Daicel Chiralpak® AD column: hexane/*i*-PrOH from 95:5 to 90:10 in 10 min., then 90:10, flow rate 0.70 mL/min, 40°C, λ = 300 nm: $\tau_{major}$ = 16.00 min., $\tau_{minor}$ = 15.24 min.; $^1$H NMR (400 MHz, $CDCl_3$, 25°C): $\delta$ = 0.96 (d, $J$ = 6.9 Hz, 3H), 1.11 (d, $J$ = 6.9 Hz, 3H), 1.71 (dd, $J_1$ = 10.3 Hz, $J_2$ = 2.4 Hz, 1H), 1.90-2.00 (m, 1H), 3.16-3.43 (bs, 1H), 3.58-3.72 (m, 2H), 5.12-5.27 (m, 2H), 5.36 (bd, $J$ = 12.3 Hz, 1H), 6.20 (dd, $J_1$ = 9.6 Hz, $J_2$ = 5.9 Hz, 1H), 6.54 (d, $J$ = 9.6 Hz, 1H), 7.05-7.14 (m, 2H), 7.14-7.23 (m, 1H), 7.26-7.44 (m, 6H); $^{13}$CNMR (50 MHz, $CDCl_3$, 25°C): $\delta$ = 18.7, 21.9, 26.8, 47.6, 52.2, 59.3, 68.3, 124.9 (3C), 126.2, 127.3, 127.7, 128.0 (2C), 128.3, 128.6 (2C), 129.4, 133.7, 135.7, 155.6; ESI-MS: *m/z* = 352.2 $[M+H]^+$, 374.0 $[M+Na]^+$; HMRS calcd for $C_{22}H_{25}NO_3$ : 351,18344. $[\alpha]_D^{20}$ = -154 (c 0.88, $CHCl_3$).



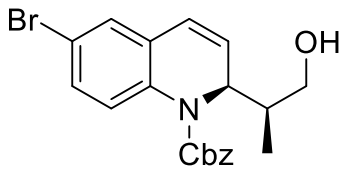

**(*anti*-6ae):** colourless oil; 15 mg, 21% yield, ee = 81%; determined by HPLC analysis Daicel Chiralpak® AD column: hexane/*i*-PrOH from 95:5 to 90:10 in 10 min., then 90:10, flow rate 0.70 mL/min, 40°C, λ = 300 nm: $\tau_{major}$ = 21.80 min., $\tau_{minor}$ = 24.16 min.; $^1$H NMR (400 MHz, $CDCl_3$, 25°C): $\delta$ = 0.80 (d, $J$ = 6.0 Hz, 3H), 0.88 (d, $J$ = 7.2 Hz, 3H), 1.44-1.52 (m, 1H), 1.53-1.75 (bs, 1H), 1.77-1.87 (m, 1H), 3.59-3.68 (m, 2H), 5.20 (d, $J$ = 12.9 Hz, 1H), 5.22-5.28 (m, 1H), 5.31 (d, $J$ = 12.9 Hz, 1H), 6.13 (dd, $J_1$ = 9.6 Hz, $J_2$ = 6.4 Hz, 1H), 6.56 (d, $J$ = 9.6 Hz, 1H), 7.09 (d, $J$ = 4.2 Hz, 2H), 7.15-7.23 (m, 1H), 7.29-7.40 (m, 5H), 7.42-7.56 (m, 1H); $^{13}$CNMR (50 MHz, $CDCl_3$, 25°C): $\delta$ = 18.4, 22.3, 25.5, 50.3, 53.2, 59.7, 68.0, 124.7, 125.4, 125.5, 126.2, 127.4, 127.6, 128.1 (2C), 128.2, 128.5 (2C), 129.4, 134.8, 136.0, 155.2; ESI-MS: *m/z* = 352.2 $[M+H]^+$, 374.0 $[M+Na]^+$; HMRS calcd for $C_{22}H_{25}NO_3$ : 351,18344. $[\alpha]_D^{20}$ = +61 (c 1.0, $CHCl_3$).



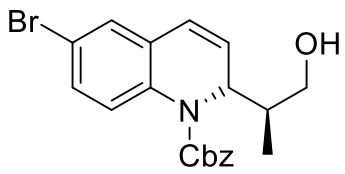

**Product 6af** was obtained following the general procedure using quinoline **4a**, aldehyde **5f** and catalyst **2e** instead of *ent*-**2a**. Product **7af** was not present. The crude reaction mixture was purified by column chromatography on silica (cyclohexane:ethylacetate from 75:25 to 70:30) to afford a colourless oil (19 mg, 62% yield; ee = -46%; determined by HPLC analysis Daicel Chiralpak® AD column: hexane/*i*-PrOH 85:15, flow rate 0.70 mL/min, 40°C, λ = 280 nm: $\tau_{major}$ = 11.78 min., $\tau_{minor}$ = 14.40

min.; $^{1}$H NMR (400 MHz, $CDCl_3$, 25°C): $\delta$ = 1.45-1.57 (m, 1H), 1.66-1.77 (m, 1H), 3.52-3.65 (m, 2H), 5.15-5.27 (m, 2H), 5.31-5.41 (m, 1H), 6.06 (dd, $J_1$ = 9.6 Hz, $J_2$ = 5.7 Hz, 1H), 6.50 (d, $J$ = 9.6 Hz, 1H), 7.05-7.11 (m, 2H), 7.13-7.21 (m, 1H), 7.31-7.46 (m, 6H); (the signal relative to O*H* was not detected); $^{13}$CNMR (50 MHz, $CDCl_3$, 25°C): $\delta$ = 34.7, 49.9, 58.0, 68.3, 124.6, 124.7, 124.8, 126.3 (2C), 127.1, 127.4, 128.1, 128.3, 128.6 (2C), 129.8, 133.3, 135.7, 155.5; ESI-MS: *m/z* = 310.2 $[M+H]^+$, 332.0 $[M+Na]^+$, 641.0 $[2M+Na]^+$; HMRS calcd for $C_{19}H_{19}NO_3$: 309,13649. $[\alpha]_D^{20}$ = +76 (c 1.6, $CHCl_3$).

**Product 6ba** (1.9:1 ratio *syn-anti* determined on the crude reaction mixture) and **7ba**, were obtained following the general procedure using quinoline **4b** and aldehyde **5a**. The crude reaction mixture was purified by preparative TLC on silica (cyclohexane:ethylacetate 75:25) to afford ***syn*-6ba** and ***anti*-6ba**.



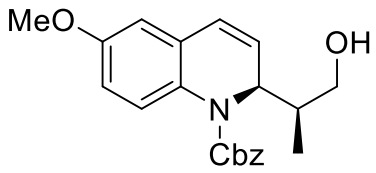

**(*syn*-6ba):** reddish oil; 25 mg, 31% yield; ee = 94%; determined by HPLC analysis Daicel Chiralpak® AD column: hexane/*i*-PrOH from 95:5 to 85:15 in 5 min, then 85:15 for 17 min, then from 85:15 to 75:25 in 8 min, flow rate 0.70 mL/min, 40°C, λ = 280 nm: $\tau_{major}$ = 21.86 min., $\tau_{minor}$ = 18.42 min.; $^{1}$H NMR (400 MHz, $CDCl_3$, 25°C): $\delta$ = 1.02 (bd, $J$ = 5.8 Hz, 3H), 1.52-1.69 (bs, 2H), 3.33 (bd, $J$ = 12.5 Hz, 1H), 3.64 (bd, $J$ = 12.0 Hz, 1H), 4.86 (dd, $J_1$ = 10.7 Hz, $J_2$ = 6.4 Hz, 1H), 5.20 (bd, $J$ = 12.1 Hz, 1H), 5.27-5.40 (m, 1H), 6.16-6.24 (m, 1H), 6.47 (d, $J$ = 9.2 Hz, 1H), 7.12-7.22 (m, 1H), 7.23-7.26 (bs, 2H), 7.30-7.43 (m, 5H); $^{13}$CNMR (100 MHz, $CDCl_3$, 25°C): $\delta$ = 13.0, 40.7, 54.0, 63.7, 68.5, 117.6, 124.0, 126.1 (2C), 128.2 (2C), 128.5, 128.6, 128.7 (2C), 128.9, 129.3, 130.1, 135.4, (the signal relative to C=O of the carbamate was not detected). ESI-MS: *m/z* = 402.0 $[M(^{79}Br)+H]^+$, 404.0 $[M(^{81}Br)+H]^+$; HMRS calcd for $C_{20}H_{20}BrNO_3$ : 401,06266. $[\alpha]_D^{20}$ = -116 (c 1.2, $CHCl_3$).



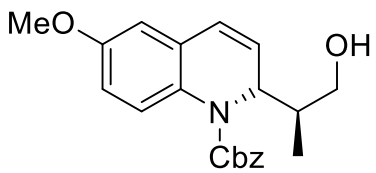

**(*anti*-6ba):** reddish oil; 14 mg, 18% yield; ee = 92%; determined by HPLC analysis Daicel Chiralpak® AD column: hexane/*i*-PrOH from 95:5 to 85:15 in 5 min, then 85:15 for 17 min, then from 85:15 to 75:25 in 8 min, flow rate 0.70 mL/min, 40°C, λ = 280 nm: $\tau_{major}$ = 21.25 min., $\tau_{minor}$ = 34.74 min.; $^{1}$H NMR (400 MHz, $CDCl_3$, 25°C): $\delta$ = = 0.46-0.63 (bs, 3H), 1.22-1.45 (bs, 1H), 1.77-1.89 (bs, 1H), 3.37-3.50 (m, 2H), 5.14-5.28 (m, 2H), 5.39-5.40 (m, 1H), 6.03

(dd, $J_1$ = 9.4 Hz, $J_2$ = 6.0 Hz, 1H), 6.51 (d, $J$ = 9.4 Hz, 1H), 7.19 (s, 1H), 7.21-7.28 (m, 2H), 7.32-7.43 (m, 5H); $^{13}$CNMR (100 MHz, $CDCl_3$, 25°C): $\delta$ = 11.0, 41.4, 53.8, 63.8, 68.6, 117.6, 124.8, 126.5, 128.3 (2C), 128.6, 128.8 (2C), 128.8, 129.6, 130.3 (2C), 134.6, 135.6, 156.0; ESI-MS: *m/z* = 402.0 [M($^{79}$Br)+H]$^+$, 404.0 [M($^{81}$Br)+H]$^+$; HMRS calcd for $C_{20}H_{20}BrNO_3$ : 401,06266. $[\alpha]_D^{20}$ = +171 (c 0.69, $CHCl_3$).

**Product 6ca** (4.9:1 ratio *syn-anti* determined by $^1$H NMR on the crude reaction mixture) and **7ca**, were obtained following the general procedure using quinoline **4c** and aldehyde **5a**. The crude reaction mixture was purified by column chromatography on silica (cyclohexane:ethylacetate from 80:20 to 70:30) to afford pure ***syn*-6ca** and an impure mixture of ***anti*-6ca** and **7ca**. Further purification by preparative TLC on silica (cyclohexane:ethylacetate 6:4) allowed to obtain pure ***anti*-6ca**.



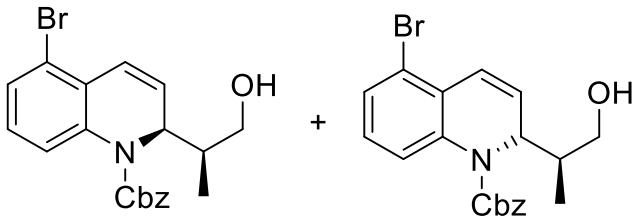

**(*syn*-6ca):** yellowish oil; 40 mg, 57% yield; ee = 96%; determined by HPLC analysis Daicel Chiralpak® IC column: hexane/*i*-PrOH 85:15, flow rate 0.70 mL/min, 40°C, λ = 300 nm: $\tau_{major}$ = 22.83 min., $\tau_{minor}$ = 18.70 min.; $^1$H NMR (400 MHz, $CDCl_3$, 25°C): $\delta$ = 0.96-1.12 (bs, 3H), 1.20-1.37 (bs, 1H), 1.56-1.68 (bs, 1H), 3.32 (bd, $J$ = 11.7 Hz, 1H), 3.68 (bd, $J$ = 10.1 Hz, 1H), 3.80 (3,81 rotamer) (s, 3H), 4.83 (dd, $J_1$ = 10.1 Hz, $J_2$ = 5.9 Hz, 1H), 5.13-5.23 (m, 1H), 5.30-5.42 (bs, 1H), 6.13-6.23 (bs, 1H), 6.49 (d, $J$ = 9.4 Hz, 1H), 6.64 (d, $J$ = 3.1 Hz, 1H), 6.67-6.76 (bs, 1H), 7.14-7.25 (bs, 1H), 7.30-7.42 (bs, 5H); $^{13}$CNMR (50 MHz, $CDCl_3$, 25°C): $\delta$ = 13.1, 38.0, 54.1, 55.5, 63.9, 68.2, 110.9, 113.1, 125.1, 125.6 (2C), 128.1, 128.3 (2C), 128.5, 128.6 (2C), 129.8, 135.8, 155.6, 156.6; ESI-MS: *m/z* = 354.0 [M+H]$^+$, 376.0 [M+Na]$^+$, 729.2 [2M+Na]$^+$; HMRS calcd for $C_{21}H_{23}NO_4$ : 353,16271. $[\alpha]_D^{20}$ = -220 (c 0.81, $CHCl_3$).




**(*anti*-6ca):** yellowish oil; 8 mg, 12% yield; ee = 90%; determined by HPLC analysis Daicel Chiralpak® IC column: hexane/*i*-PrOH 85:15, flow rate 0.70 mL/min, 40°C, λ = 300 nm: $\tau_{major}$ = 22.83 min., $\tau_{minor}$ = 18.70 min.; $^1$H NMR (400 MHz, $CDCl_3$, 25°C): $\delta$ = 0.41-0.62 (bs, 3H), 1.60-1.77 (bs, 1H), 1.78-1.91 (bs, 1H), 3.46 (d, $J$ = 5.9 Hz, 2H), 3.80 (3,81 rotamer) (s, 3H), 5.09-5.27 (m, 2H), 5.30-5.42 (m, 1H), 6.00 (dd, $J_1$ = 9.5 Hz, $J_2$ = 5.9 Hz, 1H), 6.53 (d, $J$ = 9.5 Hz, 1H), 6.60 (d, $J$ = 3.0 Hz, 1H), 6.65-6.74 (bs, 1H), 7.12-7.24 (bs, 1H), 7.29-7.44 (bs, 5H); $^{13}$CNMR

(100 MHz, $CDCl_3$, 25°C): $\delta$ = 10.6, 41.3, 53.6, 55.4, 63.9, 68.1, 110.8, 113.1, 125.6, 125.7, 128.0, 128.3, 128.4, 128.5 (2C), 128.6 (2C), 129.5, 135.9, 156.4 (2C); ESI-MS: *m/z* = 354.0 $[M+H]^+$, 376.0 $[M+Na]^+$, 729.2 $[2M+Na]^+$; HMRS calcd for $C_{21}H_{23}NO_4$ : 353,16271. $[\alpha]_D^{20}$ = +17 (c 0.42, $CHCl_3$).

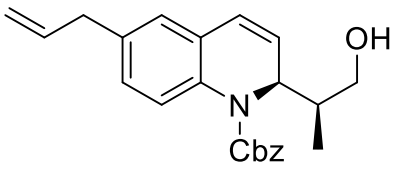
**Product 6da** (1.7:1 ratio *syn-anti* determined on the crude reaction mixture) and **7da**, were obtained following the general procedure using quinoline **4d** and aldehyde **5a**. The crude reaction mixture was purified by preparative TLC on silica (cyclohexane:diethylether 60:40) to afford a 1.2:1.0:0.4 mixture of ***syn*-6da**:***anti*-6da:7da** (35 mg, 0.088 mmol, 44 %) as a yellowish oil.



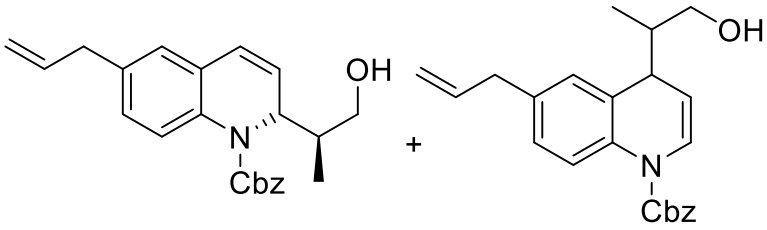

**(6da):** enantiomeric excesses were determined by HPLC analysis Daicel Chiralpak® AD column: hexane/*i*-PrOH from 90:10 to 80:20 in 10 min, then 80:20, flow rate 0.70 mL/min, 40°C, λ = 280 nm: $ee_{syn}$ = 91%; $\tau_{major}$ = 14.28 min., $\tau_{minor}$ = 13.02 min.; $ee_{anti}$ = 89%; $\tau_{major}$ = 13.69 min., $\tau_{minor}$ = 18.56 min.; $^1$H NMR (400 MHz, $CDCl_3$, 25°C): $\delta_{syn\text{-}\mathbf{6da}}$ = 1.04 (d, $J$ = 6.6 Hz, 3H), 1.59-1.66 (m, 1H), 3.30-3.37 (m, 1H), 3.61-3.68 (m, 1H), 4.01-4.10 (bs, 1H), 4.86 (dd, $J_1$ = 10.5 Hz, $J_2$ = 6.3 Hz, 1H), 5.16-5.24 (m, 1H), 5.30-5.38 (m, 1H), 6.27 (dd, $J_1$ = 10.0 Hz, $J_2$ = 6.3 Hz, 1H), 6.89 (d, $J$ = 10.0 Hz, 1H), 6.98-7.04 (m, 1H), 7.27-7.41 (m, 7H); $\delta_{anti\text{-}\mathbf{6da}}$ = 0.56-0.64 (bs, 3H), 1.78-1.86 (m, 1H), 3.44-3.50 (m, 2H), 3.57-3.61 (bs, 1H), 5.16-5.24 (m, 2H), 5.30-5.38 (m, 1H), 6.13 (dd, $J_1$ = 10.0 Hz, $J_2$ = 6.1 Hz, 1H), 6.96 (d, $J$ = 10.0 Hz, 1H), 6.98-7.04 (m, 1H), 7.27-7.41 (m, 7H); $^{13}$CNMR (100 MHz, $CDCl_3$, 25°C): $\delta_{syn\text{-}\mathbf{6da}}$ = 13.0, 38.0, 53.7, 63.7, 68.6, 124.0 (3C), 127.0, 127.9, 128.2 (2C), 128.5, 128.7 (2C), 128.8, 130.7, 130.9, 135.4, 155.4; $\delta_{anti\text{-}\mathbf{6da}}$ = 40.8, 53.5, 63.8, 68.5, 121.3, 124.2, 124.6, 127.0, 127.9, 128.1, 128.4, 128.5, 128.7 (2C), 128.8, 130.7, 130.9, 135.4, (the signals relative to $\underline{C}H_3$, due to broadening caused by rotamers, and the one relative to C=O of the carbamate were not detected); ESI-MS: *m/z* = 402.0 $[M(^{79}Br)+H]^+$, 404.0 $[M(^{81}Br)+H]^+$; HMRS calcd for $C_{20}H_{20}BrNO_3$ : 401,06266.

**Product 6ea** (3.2:1 ratio *syn-anti* determined by $^1$H NMR on the crude reaction mixture) and **7ea**, were obtained following the general procedure using quinoline **4e** and aldehyde **5a**. The crude reaction mixture was purified by preparative TLC on silica (cyclohexane:ethylacetate 80:20) to

afford ***syn*-6ea** and a mixture of ***anti*-6ea** and **7ea**.



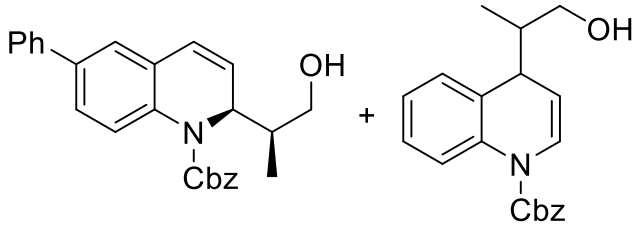

**(*syn*-6ea):** colourless oil; 39 mg, 54% yield; ee = 90%; determined by HPLC analysis Daicel Chiralpak® AD column: hexane/*i*-PrOH 90:10 for 10 min, then from 90:10 to 70:30 in 10 min, flow rate 0.70 mL/min, 40°C, λ = 280 nm: $\tau_{major}$ = 18.28 min., $\tau_{minor}$ = 12.51 min.; $^1$H NMR (400 MHz, $CDCl_3$, 25°C): $\delta$ = 1.04 (d, $J$ = 6.4 Hz, 3H), 1.56-1.71 (m, 2H), 3.28-3.38 (m, 3H), 3.67 (d, $J$ = 11.8 Hz, 1H), 4.84 (dd, $J_1$ = 9.8 Hz, $J_2$ = 5.4 Hz, 1H), 5.06-5.14 (m, 2H), 5.20 (bd, $J$ = 13.6 Hz, 1H), 5.37 (bd, $J$ = 13.6 Hz, 1H), 5.90-6.02 (m, 1H), 6.10-6.19 (m, 1H), 6.51 (d, $J$ = 9.8 Hz, 1H), 6.94 (s, 1H), 7.00 (d, $J$ = 7.6 Hz, 1H), 7.22-7.32 (m, 1H), 7.32-7.43 (m, 5H); $^{13}$CNMR (50 MHz, $CDCl_3$, 25°C): $\delta$ = 13.1, 38.1, 39.6, 54.0, 63.8, 68.3, 116.0, 124.4, 125.1, 126.2, 127.0, 127.4, 127.6, 128.1, 128.3, 128.6 (2C), 129.2, 131.7, 135.7, 136.5, 137.1, 155.8; ESI-MS: *m/z* = 364.2 $[M+H]^+$, 386.0 $[M+Na]^+$, 749.2 $[2M+Na]^+$; HMRS calcd for $C_{23}H_{25}NO_3$ : 363,18344. $[\alpha]_D^{20}$ = -129 (c 1.2, $CHCl_3$).



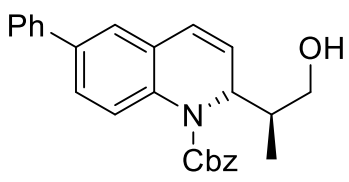

**(*anti*-6ea:7ea,** 1:0.35 ratio. **7ea** is present as mixture of diastereoisomers A:B in 2:1 ratio): colourless oil; 16 mg, 22% yield; $ee_{anti}$ = 91%; determined by HPLC analysis Daicel Chiralpak® AD column: hexane/*i*-PrOH 90:10 for 10 min, then from 90:10 to 70:30 in 10 min, flow rate 0.70 mL/min, 40°C, λ = 280 nm: $\tau_{major}$ = 16.27 min., $\tau_{minor}$ = 28.78 min.; $^1$H NMR (400 MHz, $CDCl_3$, 25°C): $\delta_{anti\text{-}\mathbf{6ea}}$ = 0.47-0.67 (bs, 3H), 1.53-1.67 (bs, 1H), 1.78-1.97 (m, 1H), 3.31-3.38 (m, 3H), 3.42-3.48 (m, 1H), 5.04-5.12 (m, 3H), 5.13-5.23 (m, 1H), 5.32-5.42 (m, 1H), 5.90-6.02 (m, 2H), 6.54 (d, $J$ = 9.5 Hz, 1H), 6.88 (d, $J$ = 1.7 Hz, 1H), 6.98 (d, $J$ = 7.7 Hz, 1H), 7.30-7.45 (m, 6H); $\delta_{\mathbf{7ea}}$ = 0.78 (d, $J$ = 6.7 Hz, $3H_B$), 0.84 (d, $J$ = 9.5 Hz, $3H_A$), 1.53-1.67 (bs, $1H_{A+B}$), 1.78-1.97 (m, $1H_{A+B}$), 3.46-3.62 (m, $5H_{A+B}$), 5.23-5.29 (m, $1H_{A+B}$), 5.31 (s, $2H_{A+B}$), 5.90-6.02 (m, $1H_{A+B}$), 6.92 (d, $J$ = 1.7 Hz, $1H_A$), 6.94 (d, $J$ = 1.7 Hz, $1H_B$), 7.03-7.11 (m, $2H_{A+B}$), 7.30-7.45 (m, $5H_{A+B}$), 7.90 (d, $J$ = 8.1 Hz, $1H_A$), 7.92 (d, $J$ = 7.2 Hz, $1H_B$); $^{13}$CNMR (50 MHz, $CDCl_3$, 25°C): $\delta_{anti\text{-}\mathbf{6ea}}$ = 10.8, 39.5, 41.2, 53.6, 63.7, 68.2, 116.0, 124.5, 125.8, 126.2, 127.6, 128.0 (2C), 128.3, 128.6 (3C), 133.5, 135.8, 136.3, 137.2, 137.3, 156.7; $\delta_{\mathbf{7ea}}$ = 11.8 ($1C_B$), 13.3 ($1C_A$), 39.5 ($1C_{A+B}$), 40.1 ($1C_{A+B}$), 42.5 ($1C_A$), 43.5 ($1C_B$), 65.0 ($1C_A$), 65.5 ($1C_B$), 67.9 ($1C_{A+B}$), 110.5 ($1C_B$), 112.5 ($1C_A$), 115.8 ($1C_{A+B}$), 121.5 ($1C_B$), 121.6 ($1C_A$), 126.6 ($1C_B$), 126.7 ($1C_A$), 127.1 ($1C_{A+B}$),

127.6 ($1C_{A+B}$), 128.0 ($2C_{A+B}$), 128.3 ($1C_{A+B}$), 128.6 ($2C_{A+B}$), 129.1 ($1C_A$), 129.4 ($1C_B$), 135.1 ($1C_B$), 135.2 ($1C_A$), 135.9 ($1C_{A+B}$), 136.5 ($1C_{A+B}$), 136.6 ($1C_{A+B}$), 152.4 ($1C_{A+B}$); ESI-MS: *m/z* = 364.2 $[M+H]^+$, 386.0 $[M+Na]^+$, 749.2 $[2M+Na]^+$; HMRS calcd for $C_{23}H_{25}NO_3$ : 363,18344.

**Product 6fa** (2.2:1 ratio *syn-anti* determined by $^1H$ NMR on the crude reaction mixture) and **7fa**, were obtained following the general procedure using quinoline **4f** and aldehyde **5a**. The crude reaction mixture was purified by preparative TLC on silica (cyclohexane:DCM:ethylacetate 6:2:2) to afford a mixture of ***syn*-6fa**:**7fa** and pure ***anti*-6fa**.




**(*syn*-6fa:7fa,** 4.8:1 ratio. **7fa** is present as mixture of diastereoisomers A:B in 5:1 ratio): colourless oil; 33 mg, 41% yield; $ee_{syn}$ = 92%; determined by HPLC analysis Daicel Chiralpak® AD column: hexane/*i*-PrOH from 85:15 for 15 min, then from 85:15 to 80:20 in 5 min., flow rate 0.70 mL/min, 40°C, λ = 280 nm: $\tau_{major}$ = 20.73 min., $\tau_{minor}$ = 13.34 min.; $^1H$ NMR (400 MHz, $CDCl_3$, 25°C): $\delta_{syn\text{-}\mathbf{6fa}}$ = 1.07 (d, *J* = 6.8 Hz, 3H), 1.65-1.76 (m, 1H), 2.96-3.22 (bs, 1H), 3.37 (bd, *J* = 12.0 Hz, 1H), 3.71 (bd, *J* = 11.4 Hz, 1H), 4.90 (dd, $J_1$ = 9.7 Hz, $J_2$ = 5.6 Hz, 1H), 5.23 (bd, *J* = 12.1 Hz, 1H), 5.35-5.46 (m, 1H), 6.21 (dd, $J_1$ = 9.7 Hz, $J_2$ = 5.6 Hz, 1H), 6.61 (d, *J* = 9.7 Hz, 1H), 7.30-7.50 (m, 10H), 7.55-7.62 (m, 3H); $\delta_{\mathbf{7fa}}$ = 0.82 (d, *J* = 6.8 Hz, $3H_A$), 0.87 (d, *J* = 7.3 Hz, $3H_B$), 1.87-1.96 (m, $1H_{A+B}$), 2.96-3.22 (bs, $1H_{A+B}$), 3.51-3.64 (m, $3H_{A+B}$), 5.34 (s, $2H_{A+B}$), 5.35-5.42 (m, $1H_{A+B}$), 7.12 (d, *J* = 7.7 Hz, $1H_A$), 7.15 (d, *J* = 7.7 Hz, $1H_B$), 7.30-7.50 (m, $10H_{A+B}$), 7.55-7.62 (m, $2H_{A+B}$), 8.00 (d, *J* = 8.8 Hz, $1H_A$), 8.09 (d, *J* = 7.7 Hz, $1H_B$); $^{13}$CNMR (50 MHz, $CDCl_3$, 25°C): $\delta_{syn\text{-}\mathbf{6fa}}$ = 13.1, 38.3, 54.3, 63.8, 68.4, 124.7, 124.8, 125.1, 126.0, 126.8 (2C), 127.3, 127.7, 128.2 (2C), 128.4, 128.7 (2C), 128.8 (2C), 129.3, 133.0, 135.6, 137.6, 140.3, 155.6; $\delta_{\mathbf{7fa}}$ (only the major diastereoisomer was observed) = 13.1, 40.0, 42.4, 64.5, 68.1, 112.6, 121.9, 124.7, 124.8, 125.2, 126.8 (2C), 127.0, 127.2, 128.2, 128.4, 128.7 (2C), 128.8 (2C), 129.7, 130.0, 135.8, 136.4, 140.4, 152.4; ESI-MS: *m/z* = 400.0 $[M+H]^+$, 422.0 $[M+Na]^+$, 821.2 $[2M+Na]^+$; HMRS calcd for $C_{26}H_{25}NO_3$ : 399,18344.

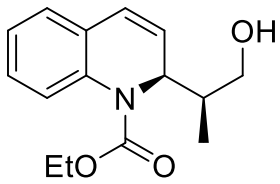



**(*anti*-6fa):** yellowish oil; 13% yield; ee = 82%; determined by HPLC analysis Daicel Chiralpak® AD column: hexane/*i*-PrOH from 85:15 for 15 min, then from 85:15 to 80:20 in 5 min., flow rate 0.70 mL/min,

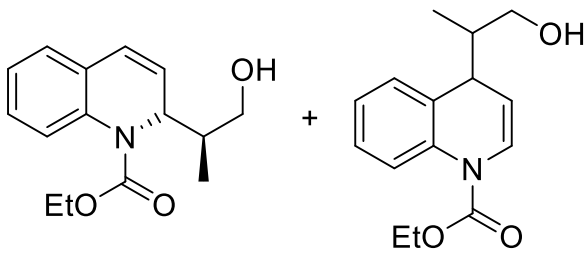
40°C, λ = 280 nm: $\tau_{major}$ = 17.70 min., $\tau_{minor}$ = 28.80 min.; $^1$H NMR (400 MHz, $CDCl_3$, 25°C): $\delta$ = 0.51-0.70 (bs, 3H), 1.82-1.93 (m, 1H), 3.48 (d, $J$ = 6.7 Hz, 2H), 3.73-3.93 (bs, 1H), 5.15-5.30 (m, 2H), 5.39 (bd, $J$ = 11.7 Hz, 1H), 6.04 (dd, $J_1$ = 9.8 Hz, $J_2$ = 6.0 Hz, 1H), 6.64 (d, $J$ = 9.8 Hz, 1H), 7.28-7.50 (m, 10H), 7.51-7.61 (m, 3H); $^{13}$CNMR (50 MHz, $CDCl_3$, 25°C): $\delta$ = 11.2, 41.4, 53.9, 63.9, 68.5, 124.8, 124.9, 125.9, 126.7, 126.9 (2C), 127.4, 128.0, 128.2 (2C), 128.5, 128.8 (2C), 128.9 (2C), 129.1, 134.9, 135.8, 137.5, 140.3, 156.4; ESI-MS: *m/z* = 400.0 $[M+H]^+$, 422.0 $[M+Na]^+$, 821.2 $[2M+Na]^+$; HMRS calcd for $C_{26}H_{25}NO_3$ : 399,18344. $[\alpha]_D^{20}$ = 145 (c 0.51, $CHCl_3$).

**Stereoselective alkylation of propionaldehyde with quinoline activated with ethyl chloroformate**

**Product 10** (3.1:1 *syn-anti* ratio determined on the crude reaction mixture) and **14**, were obtained following the general procedure using quinoline **4a**, aldehyde **5a** and ethyl chloroformate (19 μL, 0.2 mmol) instead of CbzCl. The crude reaction mixture was purified by column chromatography on silica (cyclohexane:ethylacetate 80:20) to afford a mixture of ***syn*-10**, ***anti*-10** and **14**. Further purification by preparative TLC on silica (cyclohexane:ethylacetate 7:3) allowed to obtain pure ***syn*-10** (Rf =0.4) and a mixture of ***anti*-10** : **14** (Rf =0.3).



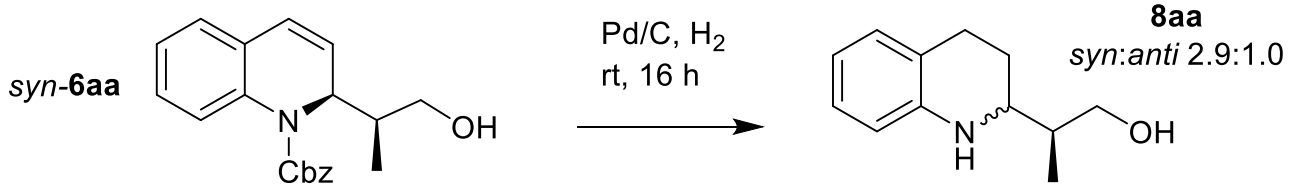

**(*syn*-10):** yellowish oil; 25% yield; ee = 94%; determined by HPLC analysis Daicel Chiralpak® AD column: hexane/*i*-PrOH from 95:5 to 85:15 in 10 min, then 85:15, flow rate 0.70 mL/min, 40°C, λ = 280 nm: $\tau_{major}$ = 22.61 min., $\tau_{minor}$ = 14.80 min.; Spectroscopic properties were according to the literature.[20c] $^1$H NMR (400 MHz, $CDCl_3$, 25°C): $\delta$ = 1.05 (d, $J$ = 6.8 Hz, 3H), 1.33 (t, $J$ = 7.5 Hz, 3H), 1.55-1.69 (m, 2H), 3.33 (bd, $J$ = 11.9 Hz, 1H), 3.72 (dd, $J_1$ = 11.9 Hz, $J_2$ = 2.4 Hz, 1H), 4.18-4.30 (m, 1H), 4.31-4.44 (m, 1H), 4.82 (dd, $J_1$ = 10.7 Hz, $J_2$ = 6.0 Hz, 1H), 6.17 (dd, $J_1$ = 9.9 Hz, $J_2$ = 6.0 Hz, 1H), 6.54 (d, $J$ = 9.9 Hz, 1H), 7.04-7.14 (m, 2H), 7.16-7.23 (m, 1H), 7.31-7.43 (bs, 1H); $^{13}$CNMR (50 MHz, $CDCl_3$, 25°C): $\delta$ = 13.1, 14.4, 38.1, 53.8, 62.7, 63.8, 124.3, 124.4, 124.8, 126.1, 127.2, 127.3, 129.0, 133.8, 155.7; ESI-MS: *m/z* = 261.0 $[M+H]^+$, 284.0 $[M+Na]^+$, 545.2 $[2M+Na]^+$; HMRS calcd for $C_{15}H_{19}NO_3$ : 261.13649. $[\alpha]_D^{20}$ = -239 (c 0.68, $CHCl_3$).



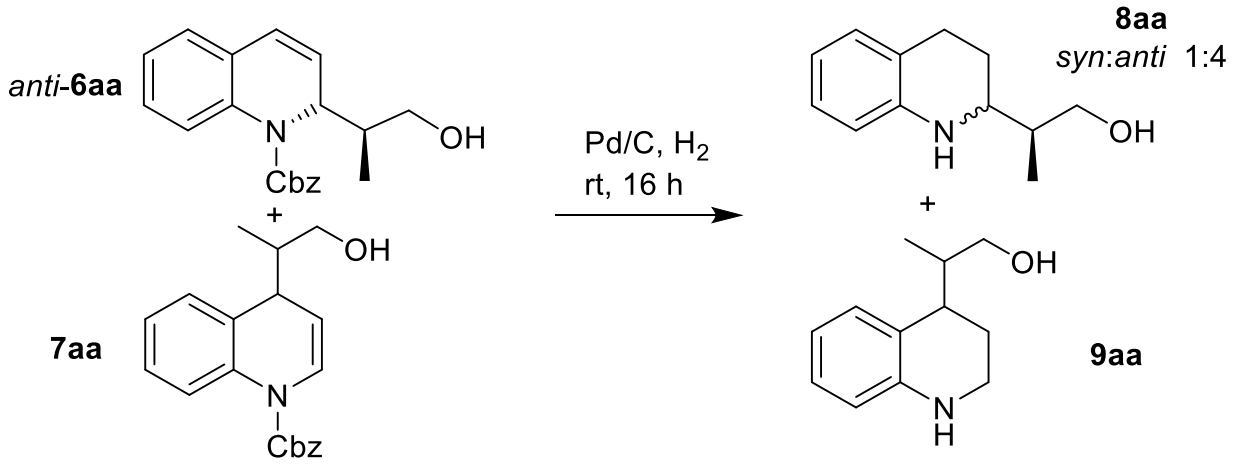

**(*anti*-10:14,** 1:0.3 ratio. **14** is present as mixture of

diastereoisomers A:B in 2:1 ratio**):** yellowish oil; 11% yield; ee = 92%; determined by HPLC analysis Daicel Chiralpak® AD column: hexane/*i*-PrOH from 95:5 to 85:15 in 10 min, then 85:15, flow rate 0.70 mL/min, 40°C, λ = 280 nm: $\tau_{major}$ = 20.61 min., $\tau_{minor}$ = 25.79 min.; $^1$H NMR (400 MHz, $CDCl_3$, 25°C): $\delta_{anti\text{-}\mathbf{10}}$ = 0.48-0.62 (bs, 3H), 1.33 (t, $J$ = 7.3 Hz, 3H), 1.79-1.88 (m, 1H), 3.47 (bd, $J$ = 7.3 Hz, 2H), 4.16-4.28 (m, 1H), 4.29-4.41 (m, 1H), 5.16-5.24 (bs, 1H), 5.98 (dd, $J_1$ = 9.9 Hz, $J_2$ = 5.7 Hz, 1H), 6.58 (d, $J$ = 9.9 Hz, 1H), 7.02-7.08 (m, 2H), 7.09-7.25 (m, 1H), 7.31-7.44 (bs, 1H), (the signal relative to O*H* was not detected); $\delta_{\mathbf{14}}$ = 0.81 (d, $J$ = 6.7 Hz, $3H_A$), 0.84 (d, $J$ = 7.3 Hz, $3H_B$), 1.38 (t, $J$ = 7.3 Hz, $3H_{AB}$), 1.89-1.97 (m, $1H_{AB}$), 3.49-3.54 (m, $1H_{AB}$), 3.55-3.63 (m, $2H_{AB}$), 4.29-4.41 (m, $2H_{AB}$), 5.28 (dd, $J_1$ = 7.8 Hz, $J_2$ = 6.0 Hz, $1H_A$), 5.38 (dd, $J_1$ = 7.8 Hz, $J_2$ = 6.0 Hz, $1H_B$), 7.02-7.08 (m, $1H_{AB}$), 7.03-7.25 (m, $3H_{AB}$), 7.93-8.00 (m, $1H_{AB}$), (the signal relative to O*H* was not detected); $^{13}$CNMR (100 MHz, $CDCl_3$, 25°C): $\delta_{anti\text{-}\mathbf{10}}$ = 10.5, 14.3, 41.2, 53.3, 62.7, 63.8, 124.4, 124.5, 125.7, 126.2, 127.4, 127.6, 128.7, 133.7, (we could not detect the signal relative to *C*OOEt); $\delta_{\mathbf{14}}$ (only the major diastereoisomer was observed) = 11.9, 14.5, 39.5, 43.3, 62.4, 65.5, 110.3, 121.5, 124.8, 126.3, 126.4, 127.5, 128.5, 135.7 (we could not detect the signal relative to *C*OOEt); ESI-MS: *m/z* = 261.0 $[M+H]^+$, 284.0 $[M+Na]^+$, 545.2 $[2M+Na]^+$; HMRS calcd for $C_{15}H_{19}NO_3$ : 261.13649.

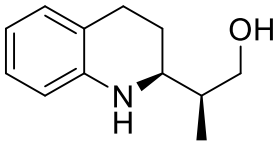
**Derivatization of product 6aa**



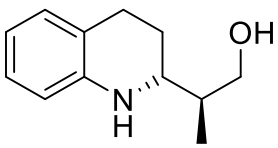

**(8aa):** In a two necked round bottomed flask, ***syn*-6aa** (31 mg, 0.096 mmol) was dissolved in methanol (1.5 mL). Then 10% wt Pd/C (10% wt, 3.1 mg), was added, the flask was evacuated and refilled with hydrogen by connection with a hydrogen filled balloon. The mixture was stirred at room temperature for 16 h, until complete conversion was observed by TLC, then it was diluted with $CH_2Cl_2$ (3 mL) and filtered through a Celite® pad that was washed with DCM (15 mL). Evaporation of the solvent afforded the crude product that was purified by column chromatography on silica (cyclohexane:ethyl acetate from 9:1 to 8:2) to give a mixture of ***syn*-8aa:*anti*-8aa** in 2.9:1 ratio as a colourless oil (14.5 mg, 0.076 mmol, 79 %).



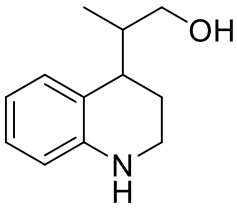

**(*anti*-8aa and 9aa):** The mixture of ***anti*-6aa** and **7aa** (2:1) (60 mg, 0.12 mmol + 0.06 mmol) was deprotected following the same procedure described for ***syn*-6aa**. The crude reaction mixture was purified by column chromatography on silica (cyclohexane:ethyl acetate from 9:1 to 8:2) to give a mixture of ***syn*-8aa:*anti*-8aa** in 1:7.6 ratio (13.3 mg, 0.069 mmol, 58%, Rf = 0.3, cyclohexane:ethyl acetate 8:2) and **9aa** (A:B 2:1) (8.0 mg, 0.042 mmol, 70%, Rf = 0.2, cyclohexane:ethyl acetate 8:2) as colourless oils.



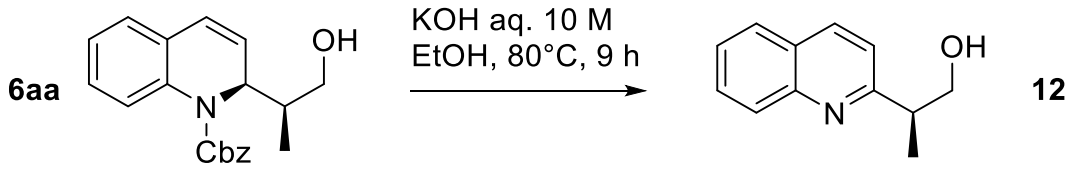

**(*syn*-8aa):** $^{1}$H NMR (400 MHz, $CDCl_3$, 25°C): $\delta$ = 1.04 (d, $J$ = 7.2 Hz, 3H), 1.56-1.76 (bs, 1H), 1.79-1.92 (m, 2H), 1.95-2.06 (m, 1H), 2.74-2.90 (m, 3H), 3.36 (ddd, $J_1$ = 9.6 Hz, $J_2$ = 6.8 Hz, $J_3$ = 2.8 Hz, 1H), 3.67 (dd, $J_1$ = 11.3 Hz, $J_2$ = 6.2 Hz, 1H), 3.88 (dd, $J_1$ = 10.2 Hz, $J_2$ = 4.5 Hz, 1H), 6.63-6.70 (m, 1H), 6.71-6.78 (m, 1H), 6.98-7.05 (m, 2H); $^{13}$CNMR (100 MHz, $CDCl_3$, 25°C): $\delta$ = 13.6, 25.4, 26.3, 39.3, 55.5, 66.6, 115.1, 117.8, 122.0, 126.7, 129.2, 144.0; ESI-MS: *m/z* = 192.2 $[M+H]^+$; HMRS calcd for $C_{12}H_{17}NO$: 191,13101.




**(*anti*-8aa):** $^{1}$H NMR (400 MHz, $CDCl_3$, 25°C): $\delta$ = 0.99 (d, $J$ = 6.9 Hz, 3H), 1.77-1.89 (m, 1H), 1.91-2.07 (m, 3H), 2.75-2.93 (m, 3H), 3.42 (dt, $J_1$ = 10.4 Hz, $J_2$ = 3.0 Hz, 1H), 3.66 (dd, $J_1$ = 10.8 Hz, $J_2$ = 4.8 Hz, 1H), 3.80 (dd, $J_1$ = 10.8 Hz, $J_2$ = 7.4 Hz, 1H), 6.56 (dd, $J_1$ = 8.6 Hz, $J_2$ = 1.3 Hz, 1H), 6.68 (td, $J_1$ = 7.2 Hz, $J_2$ = 1.1 Hz, 1H), 6.95-7.02 (m, 2H); $^{13}$CNMR (100 MHz, $CDCl_3$, 25°C): $\delta$ = 12.7, 23.6, 26.9, 39.2, 55.9, 66.2, 115.4, 118.3, 122.4, 126.7, 129.3, 144.2; ESI-MS: *m/z* = 192.2 $[M+H]^+$; HMRS calcd for $C_{12}H_{17}NO$: 191,13101.



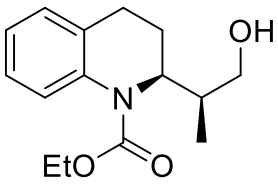
**(9aa, two diastereoisomers A:B in 2:1 ratio):** $^{1}$H NMR (400 MHz, $CDCl_3$, 25°C): $\delta$ = 0.93 (d, $J$ = 7.0 Hz, $3H_A$), 1.04 (d, $J$ = 7.0 Hz, $3H_B$), 1.46-1.75 (bs, $1H_{AB}$), 1.76-1.87 (m, $1H_{AB}$), 1.88-1.99 (m, $2H_{AB}$), 2.02-2.14 (m, $1H_{AB}$), 2.80 (q, $J$ = 5.5 Hz, $1H_B$), 2.87 (q, $J$ = 5.5 Hz, $1H_A$), 3.26-3.39 (m, $2H_{AB}$), 3.52-3.60 (m, $1H_{AB}$), 3.64-3.72 (m, $1H_{AB}$), 6.48 (d, $J$ = 7.9 Hz, $1H_{AB}$), 6.62 (t, $J$ = 7.5 Hz, $1H_{AB}$), 6.95-7.06 (m, $2H_{AB}$); $^{13}$CNMR (100 MHz, $CDCl_3$, 25°C): $\delta_A$ = 13.4, 23.0, 37.4, 38.4, 39.3, 66.5, 114.2, 116.6, 123.5, 127.00, 128.8, 144.8; $\delta_B$ = 16.0, 23.9, 38.3, 39.5, 65.6, 114.1, 116.5, 123.3, 126.99, 129.4, 144.6; ESI-MS: $m/z$ = 192.2 $[M+H]^+$; HMRS calcd for $C_{12}H_{17}NO$: 191,13101.




**(12):** In Shlenk tube, racemic ***syn*-6aa** (15 mg, 0.046 mmol) was dissolved in ethanol (500 µL). Then 10 M aq. KOH (0.46 mmol, 46 µL) was added and the solution was stirred under reflux for 9 h, until complete conversion was observed by TLC. Then it was diluted with $H_2O$ (3 mL) and ethanol was evaporated under reduced pressure. The remaining aqueous phase was acidified to pH = 1 with 1 M HCl and it was washed with $Et_2O$ (3 x 5 mL). Then the aqueous phase was basified with NaOH and extracted with AcOEt (3 x 5 mL). The combined organic layers were dried over $Na_2SO_4$ and concentrated under reduced pressure to afford pure **12** (7.5 mg, 0.040 mmol, 87%).

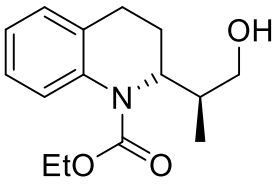
The same procedure was used to convert active ***syn*-6aa** (4.0 mg, 0.012 mmol, 94% ee) into active **12** (1.8 mg, 0.010 mmol, 83%, 88% ee). Enantiomeric excess was determined by HPLC analysis Daicel Chiralpak® IC column: hexane/*i*-PrOH 90:10, 0.70 mL/min, 40°C, λ = 230 nm: $\tau_{major}$ = 14.39 min., $\tau_{minor}$ = 15.30 min.; $^{1}$H NMR (400 MHz, $CDCl_3$, 25°C): $\delta$ = 1.44 (d, $J$ = 7.0 Hz, 3H), 3.26 (pd, $J_1$ = 7.0 Hz, $J_2$ = 3.5 Hz, 1H), 3.98 (dd, $J_1$ = 11.1 Hz, $J_2$ = 6.6 Hz, 1H), 4.11 (dd, $J_1$ = 11.1 Hz, $J_2$ = 3.5 Hz, 1H), 7.34 (d, $J$ = 8.8 Hz, 1H), 7.52 (ddd, $J_1$ = 8.2 Hz, $J_2$ = 7.0 Hz, $J_3$ = 1.2 Hz, 1H), 7.71 (ddd, $J_1$ = 8.2 Hz, $J_2$ = 6.8 Hz, $J_3$ = 1.4 Hz, 1H), 7.80 (d, $J$ = 8.2 Hz, 1H), 8.02 (d, $J$ = 8.2 Hz, 1H), 8.13 (d, $J$ = 8.8 Hz, 1H), (the signal relative to O*H* was not detected); $^{13}$CNMR (100 MHz, $CDCl_3$, 25°C): $\delta$ = 17.4, 42.3, 66.7, 120.7, 126.1, 126.9, 127.5, 128.8, 129.7, 136.9, 147.0, 165.6; ESI-MS: $m/z$ = 188.2 $[M+H]^+$, 210.2 $[M+Na]^+$, 397.2 $[2M+Na]^+$; HMRS calcd for $C_{12}H_{13}NO$ : 187.24200.

**Derivatization of product 10**



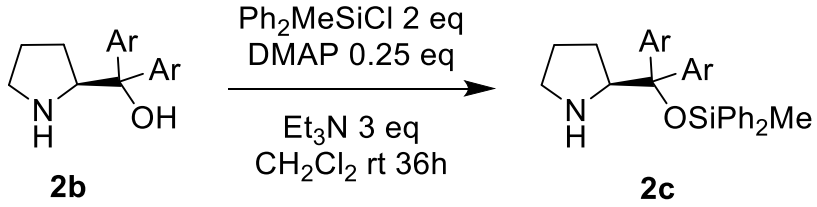

**(*Syn*-11): *Syn*-10** (7.0 mg, 0.027 mmol) was hydrogenated following the same procedure described for ***syn*-6aa**. The crude reaction mixture was purified by preparative TLC on silica (cyclohexane:ethyl acetate 7:3) to give ***syn*-11** as a colourless oil (5.8 mg, 0.022 mmol, 82%). Spectroscopic properties were according to the literature. [20c]

$^1$H NMR (400 MHz, $CDCl_3$, 25°C): $\delta$ = 10.4 (d, $J$ = 6.7 Hz, 3H), 1.30 (t, $J$ = 6.7 Hz, 3H), 1.46-1.56 (bs, 1H), 1.72-1.83 (m, 1H), 2.19-2.31 (m, 1H), 2.64-2.73 (m, 2H), 2.88-3.26 (bs, 1H), 3.37 (bd, $J$ = 10.7 Hz, 1H), 3.74 (bd, $J$ = 10.7 Hz, 1H), 4.10-4.24 (m, 1H), 4.25-4.37 (m, 1H), 4.39-4.49 (m, 1H), 7.03-7.20 (m, 3H), 7.33 (d, $J$ = 8.6 Hz, 1H); $^{13}$CNMR (100 MHz, $CDCl_3$, 25°C): $\delta$ = 13.7, 14.4, 24.7, 27.1, 37.5, 54.1, 62.4, 64.5, 124.6, 125.4, 126.1, 128.0, 132.0, 136.4, 156.4; ESI-MS: *m/z* = 264.2 $[M+H]^+$, 386.0 $[M+Na]^+$, 549.2 $[2M+Na]^+$; HMRS calcd for $C_{15}H_{21}NO_3$ : 263,15214. $[\alpha]_D^{20}$ = -87 (c 0.21, $CHCl_3$).




**(*anti*-11):** The mixture of ***anti*-10** and **14** (2:1) (4 mg, 0.010 mmol + 0.005 mmol) was hydrogenated following the same procedure described for ***syn*-6aa**. The crude reaction mixture was purified preparative TLC on silica (cyclohexane:ethyl acetate 7:3) to give ***anti*-11** (1.6 mg, 0.61 mmol, 61% related to 0.01 mmol of ***anti*-10**) as a colourless oil. $^1$H NMR (400 MHz, $CDCl_3$, 25°C): $\delta$ = 0.60 (d, $J$ = 7.1 Hz, 3H), 1.26 (t, $J$ = 7.11 Hz, 3H), 1.66-1.77 (m, 1H), 1.78-1.87 (m, 1H), 2.22-2.34 (m, 1H), 2.50-2.72 (m, 2H), 3.43-3.55 (m, 2H), 3.55-3.68 (m, 1H), 3.99-4.16 (m, 1H), 4.22-4.34 (m, 1H), 4.67-4.78 (m, 1H), 7.05-7.15 (m, 2H), 7.18 (t, $J$ = 7.2 Hz, 1H), 7.27-7.33 (m, 1H); $^{13}$CNMR (100 MHz, $CDCl_3$, 25°C): $\delta$ = 11.2, 14.4, 26.2, 29.1, 40.1, 53.4, 62.2, 65.1, 124.9, 126.2 (2C), 126.6, 127.1, 138.4, 156.8; ESI-MS: *m/z* = 264.2 $[M+H]^+$, 386.0 $[M+Na]^+$, 549.2 $[2M+Na]^+$; HMRS calcd for $C_{15}H_{21}NO_3$ : 263,15214.

**Catalyst 2c**



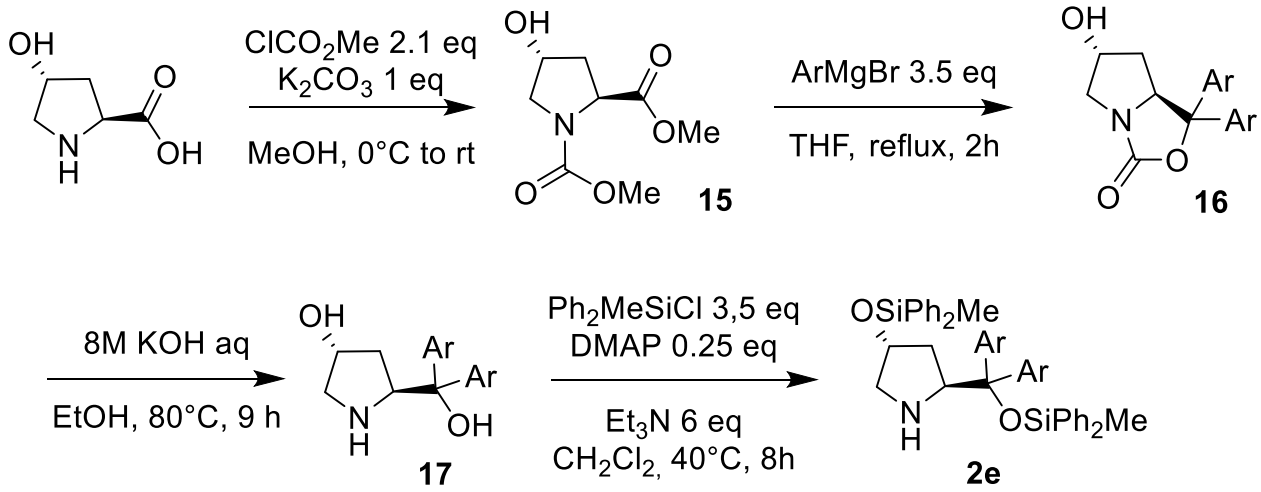

Ar = 3,5-$(CF_3)_2$-$C_6H_3$

In a flame dried two necked flask equipped with a magnetic stirring bar under nitrogen atmosphere, **2b** (52 mg, 0.1 mmol) was dissolved in $CH_2Cl_2$ (1 mL). Triethylamine (42 µL, 0.3 mmol), $Ph_2MeSiCl$ (41 µL, 0.2 mmol), DMAP (3 mg, 0.025 mmol) were added in this order and the mixture was stirred for 36 h at rt. Then it was diluted with $CH_2Cl_2$ (5 mL) and quenched by addition of water (5 mL). The organic layer was separated and the aqueous one was extracted with $CH_2Cl_2$ (3 x 5 mL) and AcOEt (5 mL). The combined organic layers were dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to afford an amber oil that was purified by column chromatography to afford **2c** (53 mg, 0.073 mmol, 73 %) as a colourless oil.

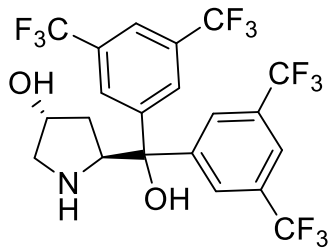
$^1$H NMR (400 MHz, $CDCl_3$, 25°C): $\delta$ = 0.31 (s, 3H), 0.78-0.91 (m, 1H), 1.35-1.59 (m, 2H), 1.66-1.81 (m, 1H), 1.81-1.95 (bs, 1H), 2.35-2.44 (m, 1H), 2.75-2.85 (m, 1H), 4.17 (t, $J$ = 7.1 Hz, 1H), 7.20-7.41 (m, 10H), 7.59 (s, 2H), 7.71 (s, 1H), 7.81 (s, 1H), 8.05 (s, 2H); $^{13}$CNMR (100 MHz, $CDCl_3$, 25°C): $\delta$ = -0.9, 25.2, 27.8, 47.1, 63.9, 83.2, 121.5-121.7 (m, 1C), 121.8-122.0 (m, 1C), 123.0 (q, $J$ = 287.4 Hz, 2C), 123.3 (q, $J$ = 287.4 Hz, 2C), 127.90 (2C), 127.92 (2C), 128.5-128.6 (m, 2C), 128.8-129.0 (m, 2C), 129.9, 130.0, 130.7 (q, $J$ = 33.2 Hz, 2C), 131.4 (q, $J$ = 33.2 Hz, 2C), 133.9 (2C), 134.0 (2C), 136.0, 136.3, 145.8, 147.0; $^{19}$FNMR (377 MHz, $CDCl_3$, 25°C): $\delta$ = -61.56, -61.58; HMRS calcd for $C_{34}H_{27}F_{12}NOSi$: 721,16703.

**Catalyst 2d** was prepared according to literature procedure.[25]

**Catalyst 2e**

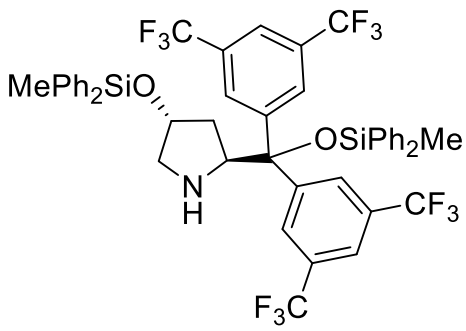



**Lactone 16** was prepared according to the literature.[26]




**(17):** Lactone **16** (1.3 g, 2.3 mmol) was dissolved in EtOH (6.5 mL), then 8 M aq. KOH (1.5 mL) was added and the mixture was refluxed under stirring for 10 h, until complete conversion was observed by TLC. Then EtOH was evaporated under reduced pressure, the mixture was diluted with water (10 mL), and extracted with AcOEt (2 x 15 mL) and DCM (2 x 15 mL). The combined organic layers were dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to afford pure **17** (1.2 g, quantitative yield) as a chubby yellow solid.

$^1$H NMR (400 MHz, $CDCl_3$, 25°C): $\delta$ = 1.45 (dd, $J_1$ = 13.6 Hz, $J_2$ = 6.2 Hz, 1H), 1.73 (ddd, $J_1$ = 13.6 Hz, $J_2$ = 10.2 Hz, $J_3$ = 4.4 Hz, 1H), 2.08-2.64 (bs, 2H), 3.06 (d, $J$ = 11.7 Hz, 1H), 3.15 (dd, $J_1$ = 11.8 Hz, $J_2$ = 3.5 Hz, 1H), 4.42 (s, 1H), 4.47-5.01 (bs, 1H), 4.72 (dd, $J_1$ = 10.2 Hz, $J_2$ = 6.8 Hz, 1H), 7.74 (s, 1H), 7.77 (s, 1H), 7.92 (s, 2H), 8.04 (s, 2H); $^{13}$CNMR (100 MHz, $CDCl_3$, 25°C): $\delta$ = 36.3, 55.4, 63.1, 72.3, 76.4, 121.3-121.5 (m, 1C), 121.6-121.8 (m, 1C), 123.1 (q, $J$ = 273.1 Hz, 4C), 125.5 (d, $J$ = 2.8 Hz, 2C), 126.1 (d, $J$ = 2.8 Hz, 2C), 131.9 (q, $J$ = 33.2 Hz, 2C), 132.1 (q, $J$ = 33.2 Hz, 2C), 145.9, 148.9; $^{19}$FNMR (377 MHz, $CDCl_3$, 25°C): $\delta$ = -61.55, -61.63; HMRS calcd for $C_{21}H_{15}F_{12}NO_2$: 541,09112.




**(2e):** In a flame dried two necked flask equipped with a magnetic stirring bar and a reflux condenser under nitrogen atmosphere, **17** (400 mg, 0.74 mmol) was dissolved in $CH_2Cl_2$ (8 mL). Triethylamine (618 µL, 4.4 mmol), $Ph_2MeSiCl$ (542 µL, 2.6 mmol), DMAP (23 mg, 0.18 mmol) were added in this order and the mixture was stirred for 8 h at 40°C. Then it was diluted with $CH_2Cl_2$ (15 mL) and quenched by addition of water (10 mL). The organic layer was separated and the aqueous one was extracted with $CH_2Cl_2$ (3 x 15 mL) and AcOEt (2 x 15 mL). The combined organic layers were dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to afford an amber oil that was purified by column chromatography to afford **2e** (394 mg, 0.42 mmol, 57 %) as a colourless oil.

$^1$H NMR (400 MHz, $CDCl_3$, 25°C): $\delta$ = 0.31 (s, 3H), 0.59 (s, 3H), 1.38-1.48 (m, 1H), 1.86 (dd, $J_1$ = 13.4 Hz, $J_2$ = 7.0 Hz, 1H), 1.95-2.13 (bs, 1H), 2.05 (bd, $J$ = 10.2 Hz, 1H), 2.76 (d, $J$ = 12.0 Hz, 1H), 3.93 (s, 1H), 4.48 (t, $J$ = 8.2 Hz, 1H), 7.27-7.46 (m, 16H), 7.48-7.54 (m, 4H), 7.57 (s, 2H), 7.74 (s, 1H), 7.80 (s, 1H), 8.07 (s, 2H); $^{13}$CNMR (100 MHz, $CDCl_3$, 25°C): $\delta$ = -2.8, -1.0, 37.8, 55.5, 62.6, 73.3, 83.0, 121.4-121.7 (m, 1C), 121.9-122.1 (m, 1C), 123.1 (q, $J$ = 272.5 Hz, 2C), 123.3 (q, $J$ = 272.5 Hz, 2C), 127.94 (2C), 127.96 (2C), 127.98 (2C), 128.00 (2C), 128-6-128.9 (m, 4C), 129.96, 130.01, 130.04, 130.1, 130.8 (q, $J$ = 33.2 Hz, 2C), 131.4 (q, $J$ = 33.2 Hz, 2C), 133.9 (2C), 134.0 (2C), 134.20 (2C), 134.22 (2C), 135.81, 135.82, 135.90, 136.2, 145.7, 146.9; $^{19}$FNMR (377 MHz, $CDCl_3$, 25°C): $\delta$ = -61.56, -61.58; HMRS calcd for $C_{47}H_{39}F_{12}NO_2Si_2$: 933,23277.

**Catalyst 2f** was generously furnished by our colleagues Prof. Trombini and Prof. Lombardo that publisched the procedure for its preparation.[22]

## 2.4.6 References


[1] This work will be submitted soon.

[2] For reviews on the chemistry of quinoline, quinazoline, and acridone alkaloids, see J. P. Michael, *Nat. Prod. Rep.* **2008**, *25*, 166–187 and previous reports in this series.

[3] (a) A. Kumar, S. Srivastava, G. Gupta, V. Chaturvedi, S. Sinha, R. Srivastava, *ACS Comb. Sci.* **2011**, *13*, 65–71; b) E. H. Demont, N. S. Garton, R. L. M. Gosmini, T. G. C. Hayhow, J. Seal, D. M. Wilson, M. D. Woodrow, *Tetrahydroquinolines derivatives and their pharmaceutical use, Europe Patent PCT Int. Appl. WO2011054841A1,* **2011**; c) Z. X. Jia, Y. C. Luo, P. F. Xu, *Org. Lett*. **2011**, *13*, 832 –835; d) G. Satyanarayana, D. Pflasterer, G. Helmchen, *Eur. J. Org. Chem*. **2011**, 6877–6886 and references cited therein; e) P. M. Dewick, *Medicinal Natural Products—A Biosynthetic Approach, 2nd ed*., Wiley, Chichester, **2001**, pp. 291 –398; f) G. Diaz Muñoza, G. B. Dudley, *Org. Prep. Proc. Int.* **2015**, *47*, 179-206.

[4] a) K. M. Witherup, R. W. Ransom, A. C. Graham, A. M. Bernard, M. J. Salvatore, W. C. Lumma, P. S. Anderson, S. M. Pitzenberger, S. L. Varga, *J. Am. Chem. Soc.* **1995**, *117*, 6682 – 6685; b) S. G. Davies, A. M. Fletcher, J. A. Lee, T. J. A. Lorkin, P. M. Roberts, J. E. Thomson, Org. Lett. **2013**, *15*, 2050–2053 and references cited therein. For reviews on synthetic studies towards martinella alkaloids see: c) M. Nyerges, Heterocycles **2004**, *63*, 1685–1712; d) C. J. Lovely, V. Badarinarayana, Curr. Org. Chem. **2008**, *12*, 1431–1453.

[5] I. Jacquemond-Collet, S. Hannedouche, N. Fabre, I. Fouraste, C. Moulis, *Phytochemistry* **1999**, *51*, 1167–1169; b) I. Jacquemond-Collet, F. Benoit-Vical, M. A. Valentin, E. Stanislas, M. Mallie, I. Fouraste, *Planta Med.* **2002**, *68*, 68– 69.

[6] a) I. Jacquemond-Collet, J.-M. Bessière, S. Hannedouche, C. Bertrand, I. Fourasté, C. Moulis *Phytochem. Anal. 2001* **12**, 312–319; b) S. Chacko, R. Rapanicker, *J. Heteroc. Chem.* **2015**, *52*, 1902-1906.

[7] E. F. Steinmetz, Materia Medica Vegetabilis, I, **1954**, 110.

[8] Y. Garg, S. Gahalawat, S. K. Pandey, *RSC Adv*. **2015**, *5*, 38846–38850, and references cited therein.

[9] Brousseau, E. J. Schaefer, M. L. Wolfe, L. T. Bloedon, A. G. Digenio, R. W. Clark, J. P. Mancuso, D. J. Rader, *N. Engl. J. Med.* **2004**, *350*, 1505–1515; c) M. Pal, *Tetrahedron* **2009**, *65*, 433–447; d) M. DePasquale, G. Cadelina, D. Knight, W. Loging, S. Winter, E. Blasi, D. Perry, J. Keiser, *Drug Dev. Res*. **2009**, *70*, 35– 48; e) D. B. Damon, R. W. Dugger, G. Magnus-Aryitey, R. B. Ruggeri, R. T. Wester, M. Tu, Y. Abramov, *Org. Proccess. Res. Dev*. **2006**, *10*, 464–471.

[10] a) D. W. Barnes, G. R. Bebernitz, K. Clairmont, S. L. Cohen, R. E. Damon, R. F. Day, S. K. Dodd, C. Gaul, H. B. Gulgeze Efthymiou, M. Jain, R. G. Karki, L. C. Kirman, K. Lin, J. Y. C. Mao, T. J. Patel, B. K. Raymer, L. Su, *Bicyclic acetyl-coa carboxylase inhibitors and uses thereof, U.S. Patent 8697739 B2,* April 15, 2014; b) L. Tong, H. J. Harwood Jr., *J. Cell. Biochem.* **2006**, *99*, 1476–1488.

[11] a) W.-B. Wang, S.-M. Lu, P.-Y. Yang, X.-W. Han, Y.-G. Zhou *J. Am. Chem. Soc.* **2003**, *125*, 10536-10537; b) Y.-L. Du, Y. Hu, Y.-F. Zhu, X.-F. Tu, Z.-Y. Han, L.-Z. Gong *J. Org. Chem*. **2015**, *80*, 4754−4759; c) T. Wang, L.-G. Zhuo, Z. Li, F. Chen, Z. Ding, Y. He, Q.-H. Fan, J. Xiang, Z.-X. Yu, A. S. C. Chan, *J. Am. Chem. Soc.* **2011**, *133*, 9878–9891.

[12] a) M. Rueping, A. P. Antonchick, T. Theissmann *Angew. Chem. Int. Ed*. **2006**, *45*, 3683 –3686; b) C. Zheng S.-L. You *Chem. Soc. Rev*., **2012**, *41*, 2498–2518.

[13] a) X.-F. Cai, R.-N. Guo, G.-S. Feng, B. Wu, Y.-G. Zhou *Org. Lett.* **2014**, *16*, 2680−2683 and refs therein; b) Z. Zhang, H. Du *Org. Lett*. **2015**, *17*, 6266−6269.

[14] a) P.-Y. Yang, Y.-G. Zhou *Tetrahedron: Asymmetry* **2004**, *15*, 1145–1149; b) M. Rueping, A. P. Antonchick, T. Theissmann, *Angew. Chem.* **2006**, *118*, 3675-3678; *Angew. Chem. Int. Ed.* **2006**, *45*, 3683 –3686.

[15] A. Reissert, *Ber.Dtsch. Chem. Ges.* **1905**, *38*, 1603.

[16] a) Kanai, M.; Kato, N.; Ichikawa, E.; Shibasaki, M. *Synlett* **2005**, 1491-1508; b) Takamura, M.; Funabashi, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2000**, *122*, 6327-6328.

[17] Y. Yamaoka, H. Miyabe, Y. Takemoto, *J. Am. Chem. Soc.* **2007**, *129*, 6686-6687.

[18] M. Zurro, S. Asmus, S. Beckendorf, C. Mück-Lichtenfeld, O. García Mancheño, *J. Am. Chem. Soc*. **2014**, *136*, 13999−14002.

[19] M. Pappoppula, A. Apomnick, *Angew. Chem.* **2015**, *127*, 16053-16056 ; *Angew. Chem. Int. Ed.* **2015**, *54*, 15827-15830.

[20] a) S. Sun, Y. Mao, H. Lou, L. Liu, *Chem. Commun.* **2015**, *51*, 10691-10694; b) F. Berti, F. Malossi, F. Marchetti, M. Pineschi, *Chem. Commun.* **2015**, *51*, 13694-13697; c) C. M. R. Volla, E. Fava, I. Atodiresei, M. Rueping, *Chem. Commun.* **2015**, *51*, 15788-15791.

[21] a) Catalyst **2b** was used by Hayashi in the cross and self aldol reaction of acetalydeyde : Y. Hayashi, T. Itoh, S. Aratake, H. Ishikawa, Angew. Chem. **2008**, *120*, 2112–2114; Angew.Chem. Int.Ed. **2008**, *47*, 2082–2084; Y. Hayashi, S. Samanta, T. Itoh, H. Ishikawa, *Org. Lett.* **2008**, *10*, 5581–5583; b) b) P. Garía-García, A. Ladépêche, R. Halder, B. List, *Angew. Chem. Int. Ed.* **2008**, *47*, 4719 –4721.

[22] M. Lombardo, L. Cerisoli, E. Manoni, E. Montroni, A. Quintavalla, C. Trombini, *Eur. J. Org. Chem.* **2014**, 5946-5953.

[23] L. Caruana, F. Kniep, T. K. Johansen, P. H. Poulsen, K. A. Jørgensen, *J. Am. Chem. Soc.* **2014**, *136*, 15929−15932.

[24] A. Claraz, G. Sahoo, D. Berta, Á. Madarász, I. Pápai, P. M. Pihko, *Angew. Chem. Int. Ed.* **2016**, *55*, 669.

[25] U. Grošelj, D. Seebach, D. M. Badine, W. B. Schweizer, A. K. Beck, I. Krossing, P. Klose, Y. Hayashi, T. Uchimaru *Helv. Chim. Acta* **2009**, *92*, 1225-1259.

[26] J. I. Martìnez, E. Reyes, U. Uria, L. Carrillo, J. L. Vicario *ChemCatChem* **2013**, *5*, 2240-2247.

## 2.5 Asymmetric alkylation of carboxylic acids with carbenium ions promoted by stoichiometric amounts of isothioureas [1]

**Index**

## 2.5.1 Introduction

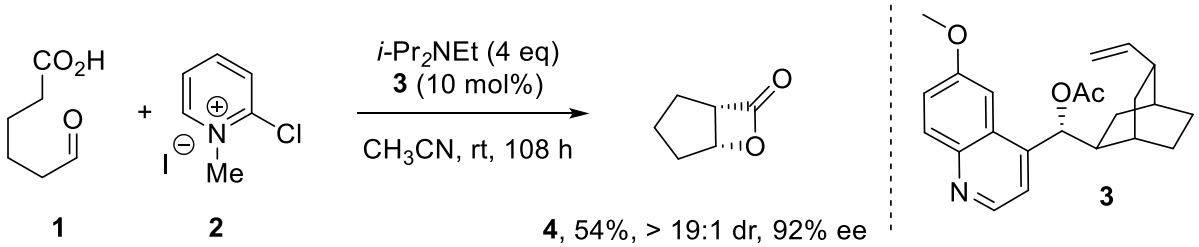
The functionalization of aldehydes via enolate, enamine or unpolung strategies is one of the most studied areas of organic chemistry and a wide number of asymmetric methodologies have been developed. However, aldehydes can easily undergo oxidation, condensation or other degradative pathways, so that their purification or preparation prior to use is often necessary. The most common aldehyde precursors are the corresponding carboxylic acids, that are usually perfectly stable compounds insensitive to air and moisture. Unfortunately the presence of the acid moiety has limited the development of direct strategies to address their functionalization, especially in an asymmetric fashion.

Recently two different strategies to achieve the asymmetric α-alkylation of carboxylic acids, or of direct derivatives, have been developed through the formation of the corresponding enolates by the action of a suitable catalyst:

1) Lewis Bases activation of carboxylic acid derivatives with tertiary amines, isothioureas or NHC.
2) Formation of metal enolates directly from the carboxylic acids.

### 1a) Tertiary amines

The use of tertiary amines has been the first successful strategy[2] to form C1 enolates[3] from carboxylic acids in situ activated by Mukaiyama reagent **2**, an α-chloro iminium salt.[4] The resulting activated ester reacted with the tertiary amine of the cinchona catalyst **3** to afford an azolium enolate that was deprotonated by DIPEA to form the C1 chiral enolate that attacked intramolecularly the aldehyde (scheme 1). Following this report other reactions that took advantage from this activation mode were reported always as intramolecular processes.[5]



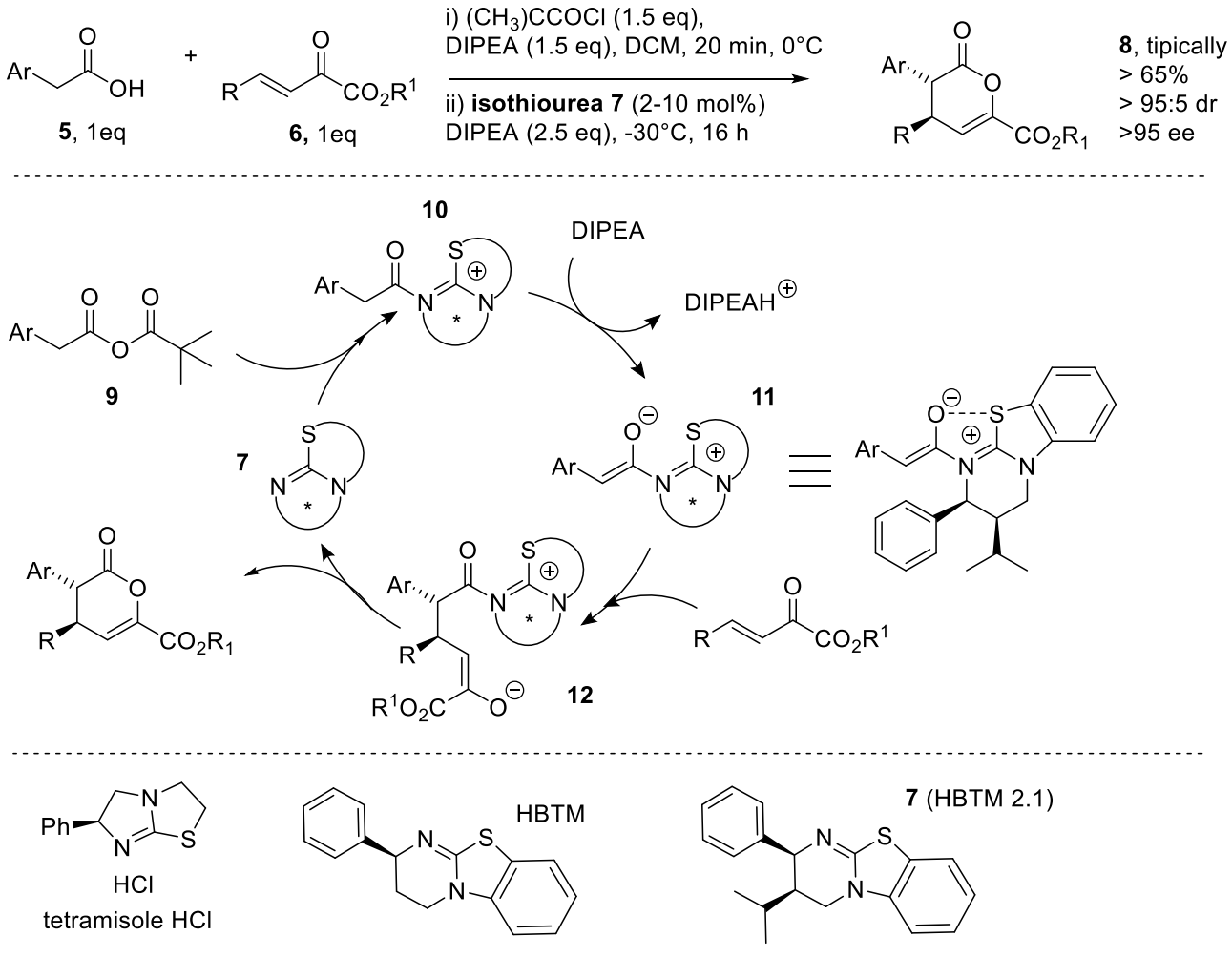

*Scheme 1: tertiary amine as catalyst for C1 enolate from activated carboxylic acids*

### 1b) Isothioureas[6]

Isothioureas are strong Lewis bases whose nucleophilicities have been determined by Mayr around 15 of his scale, values comparable or even superior to DMAP.[7] A carboxylic acid can be activated by the formation of the corresponding anhydride by reaction with an acylating agent in presence of a base. Strong Lewis bases such as isothioureas efficiently engage an acylic nucleophilic

substitution reaction with these compounds affording the corresponding acyl cations. The presence of the positive charge on the isothiourea moiety in acyl intermediate **10** exercises a strong electron withdrawing action on the carbonyl group enhancing of several orders of magnitude the acidity of the α-protons so that even moderate bases such as DIPEA, or relatively stronger as $CsCO_3$ or DBU, efficiently deprotonate **10** to afford enolate **11**. This concept was first exploited by Romo using tetramisole (see scheme 2) as chiral promoter in stoichiometric amount to promote the formation of the C1 enolate from a carboxylic acid and its subsequent ring closure on an aldehyde moiety.[8] Homobenzotetramisole (HBTM), that had been introduced as an asymmetric transfer acylating agent,[9] was the first isothiourea successfully employed in catalytic amounts to activate a carboxylic acid.[10]

Smith reported the first non intermolecular process in a formal 4+2 Hetero-Diels Alder (HDA) reaction using a Michael acceptor as the electrophilic partner (scheme 2).[11] Phenyl acetic acids **5** were activated in situ by reaction with pivaloyl chloride.




*Scheme 2: example of isothiourea catalyzed HDA with mixed anhydrides*

The excellent enantioselectivities are due to the rigid and predictable geometry of enolate **11** due to the presence of the partial positive charge on the sulfur atom that interacts with the negative charged

oxygen of the enolate. Thanks to such geometry, the presence of a stereocenter bearing a bulky phenyl group adjacent to the isothiourea moiety allows to efficiently shield one prochiral face of the enolate. The catalytically generated acyl enolate **11** attacks the electrophile **6** generating a new enolate (**12**). The nucleophilic heteroatom subsequently attacks the acyl cation affording the lactone and guarantees the turnover of the catalyst.

This strategy has been applied to other Michael acceptors and also to activated imines for the formation of β-lactames.[12]

The formation of the acyl enolate does not require anhydrous conditions, that are however necessary to avoid the hydrolysis of the mixed anhydride used as the starting material. The use of homoanhydrides of variously substituted phenylacetic acids allowed to perform the reaction under non anhydrous conditions.[13]

It must be noted that only carboxylic acids having an aromatic substituent on the α-position, such as phenyl acetic acids, that stabilize the negative charge can be engaged in isothiourea catalyzed intermolecular processes, while in case of intramolecular processes also alkylic carboxylic acids can be employed.

The key point of this chemistry is the generation of an internal nucleophile after the enolate addition that attacks the acyl cation in an intramoloecular process releasing the catalyst. The use of an additional (that operates in an intermolecular mechanism) nucleophile (e.g. an alcohol or a primary amine), is not possible because it would compete with the isothiourea to react with the starting anhydride to give the unreactive esters or amides. Instead when the nuclephile is generated as the reaction proceeds in an intramolecular ring closure process, no free nucleophile is present in the reaction mixture and optimal yields are obtained.

Only in one report the turnover of the catalyst is guaranteed by an intermolecular nucleophilic addition: precisely by the phenate that is generated from the substrate activation by attack of the isothiourea.[14] In this case para nitro phenyl esters, that are obtained in a two step process from the carboxylic acids, are used. However, the addition of HOBT is necessary in order to increase the yield of the process. The authors suggest that HOBT initially releases the catalyst and the resulting adduct is attacked by the terminal nucleophile.

### 1c) NHC

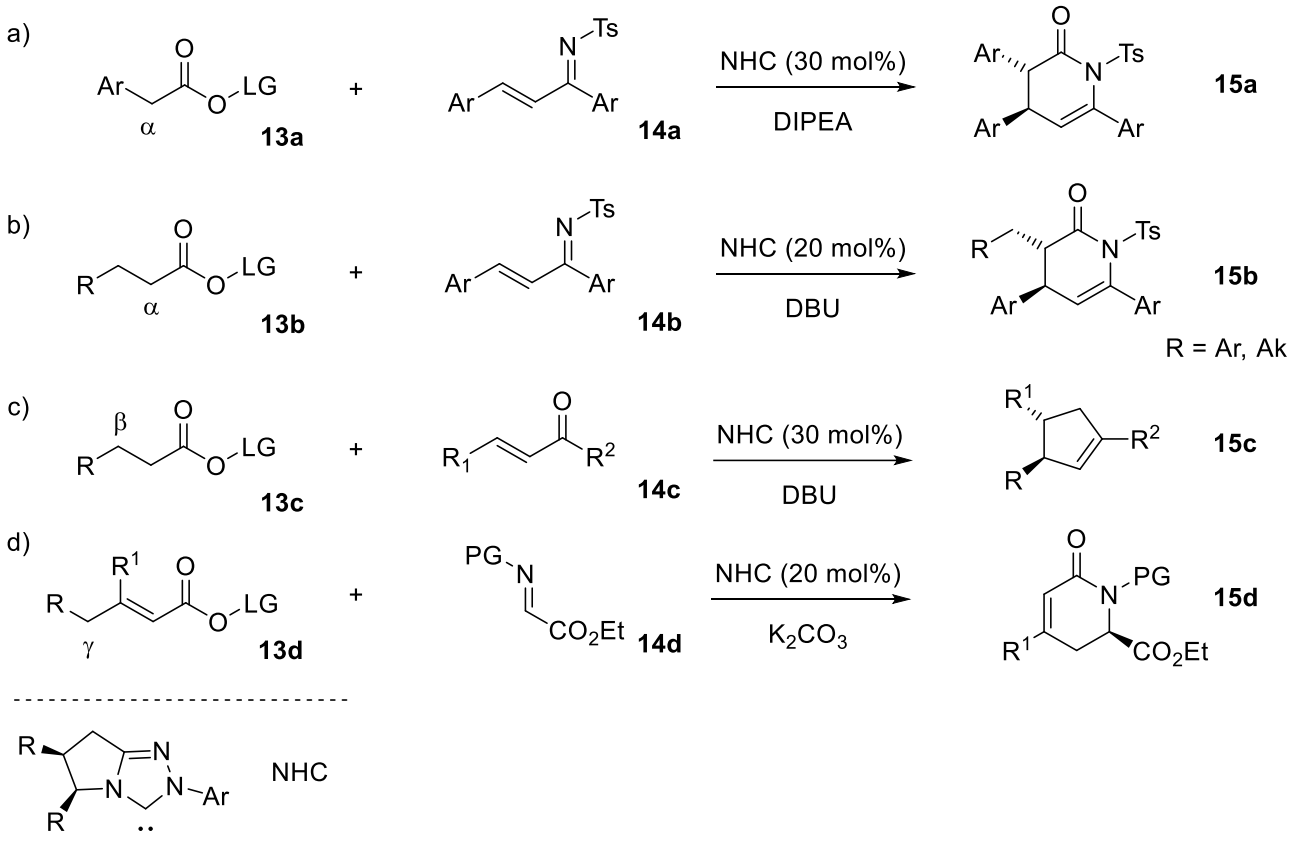
NHC are extremely powerful Lewis bases and can be used instead of isothioureas to form acyl enolates from para nitro benzoates (PNB) or anhydrides.[15] A few differences should be noted: 1) the active carbenes are not isolable species and their protonated salts are used as precursors, so at least catalytic amount of stronger base is needed to generate the NHC, 2) the NHC moiety is a stronger electronwithdrawing group that enables the activation also of aliphatic carboxylic acids derivatives to form the corresponding enolates.

In scheme 3a and 3b are shown the general conditions that allow the formation of C1 enolates (α activation) from phenyl acetic acids **13a**[16] and alkyl acetic acids **13b**[17] that are subsequently engaged in cycloaddition reactions with different Michael acceptors.

Moreover Chi developed also a protocol to activate the β-position of para nitro benzoates to form the corresponding homoenolates (scheme 3c).[18] It is noteworthy that the same substrates can be activated on the α or β positions by careful tuning of the reaction conditions.[19]

α,β-Unsaturated activated esters **13d** can be efficiently used to form vinilogous γ enolates (scheme 3d).[20]

As for isothioureas, the catalyst release is guaranteed by an intramolecular nucleophilic attack to afford a cyclic product. No examples of intermolecular attacks by nucleophiles have been reported using para nitro phenyl esters or anhydrides, while several examples have been described with aldehydes.[21]

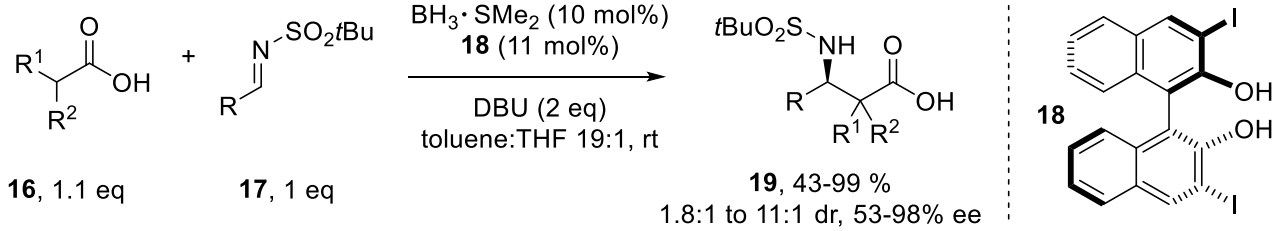



*Scheme 3: general reactivity modes of activated esters or anhydrides enolates via NHC catalysis.*

**2) Metal enolates**

The formation of metal enolates from carboxylic acids and their reaction with nucleophiles has been reported in 2009 using an achiral boron complex.[22] In the following years Zacharian described a methodology to achieve the asymmetric alkylation of carboxylic enolates using a stoichiometric amount of chiral lithium amides.[23]

The only catalytic asymmetric methodology to generate C1 enolates from carboxylic acids derivatives has been described in 2015 by Shimuzu and Kanai using binol boron complexes as catalysts.[24] The reaction conditions are more sensitive compared to isothioureas but the advantage is the direct employment of the carboxylic acids that do not need any preactivation (scheme 4).

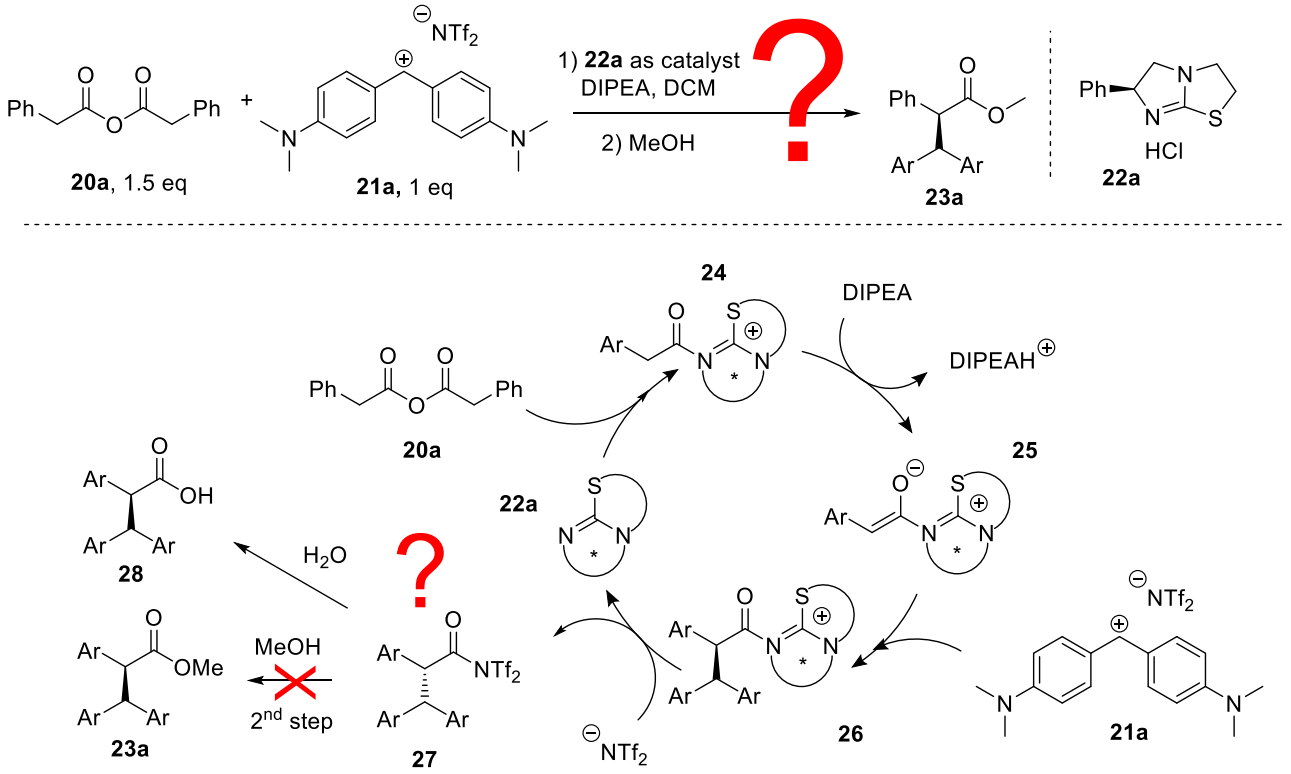



*Scheme 4: asymmetric Mannich reaction of catalytically generated carboxylic acids boron enolates.*

## 2.5.2 Results and discussion

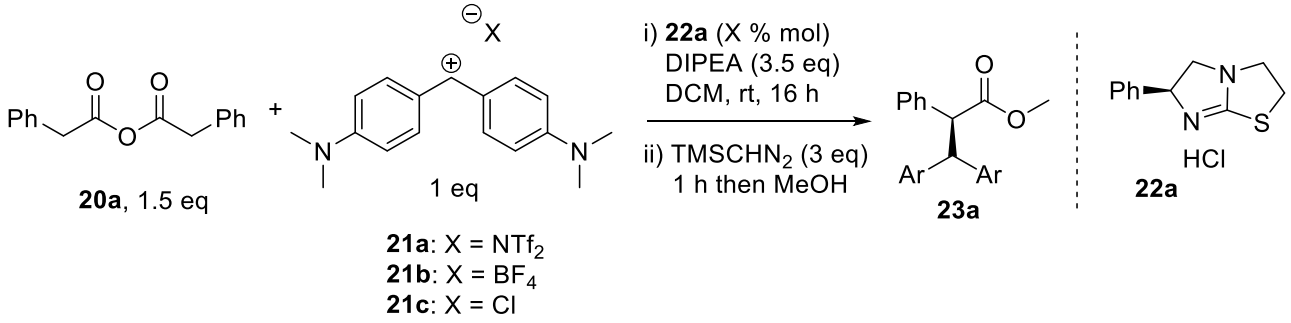
The reported procedures to functionalize carboxylic acids via their corresponding enolates regards intermolecular cyclizations mainly with Michael acceptors or activated imines, a few examples of intramolecular cyclizations with aldehydes or ketones and only one example of addition to imines but using a metal catalyst. PG Cozzi group had carried an intensive study over the alkylation of aldehydes with carbenium ions[25] and the development of a corresponding methodology with carboxylic acids would be a great advance as it would allow to access useful intermediates from cheap and more stable materials.

We choose isothioureas as chiral promoters and we started investigating the alkylation of phenylacetic homoanhydride **20a** with bisdimethylamino benzydrilium bistriflamide **21a** in presence of DIPEA as a base. The first issue to address in the reaction design was the presence of a scavenger to release the catalyst **22a** after the alkylation reaction that must be compatible with the anhydride. For such reason we used bistriflamide as counterion instead of cheaper tetrafluoroborate, hoping that the bistriflamide would attack acyl cation **26** affording adduct **27**. When the reaction would be complete, $S_NAc$ of this postulated intermediate by water, alcohol or primary amine would afford the desired α-alkylated acid, ester or amide.




*Scheme 5: reaction plan for the alkylation of phenyl acetic acid with carbenium ions.*

The first test was conducted by adding the base and the carbocation to a solution of the anhydride and tetramisole HCl **22a** (20 mol%) in anhydrous DCM under inert atmosphere. After one night MeOH was added to the mixture that had a deep violet color (the carbocation alone has a metal blue color). Unfortunately no product could be observed by GC-MS or NMR (table 1, entry 1).




| Entry | **21** | **22a** (mol%) | Yield[a] | ee[b] | Deviations from standard |
|---|---|---|---|---|---|
| 1 | **21a** | 20 | 0 | - | ii) MeOH |
| 2 | **21a** | 150 | 49 | 82 | |
| 3 | **21a** | 150 | 0 | | ii) $BnNH_2$ |
| 4 | **21a** | 150 | 27 | 82 | ii) NaHCO3 aq sat 1h, then TMS-$CH_2N_2$ (6eq) |
| 5 | **21a** | 20 | 47 | 19 | |
| 6 | **21a** | 20 | < 5[c] | 0 | $NaHCO_3$ instead of DIPEA |
| 7 | **21a** | 20 | < 10[c] | 0 | MeCN/$H_20$ 1/1 instead of DCM |
| 8 | **21a** | 20 | 37 | 0 | 0°C instead of rt |
| 9 | **21b** | 20 | 35 | 0 | |
| 10 | **21c** | 20 | 31 | 0 | |
| 11 | **21a** | 20 | < 5[c] | - | **21a** (0.05 mL in DCM) was added via syringe pump over 15 h |

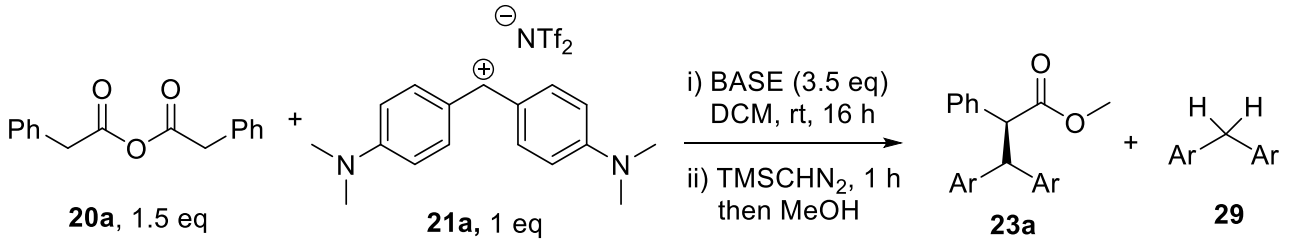
All reactions were carried on 0.05 mmol of carbocation **21a**, 0.075 mmol **20a**, 3.5 eq DIPEA in 1 mL DCM unless otherwise stated; standard work up: TMS-$CHN_2$ followed by addition of MeOH for 1h.; for the detailed experimental procedure see methods A and B in the experimental section; [(a)] yield of isolated products after chromatographic purification; [(b)] enantiomeric excesses were determined by HPLC analysis on chiral stationary phase after after chromatographic purification; [(c)] yield estimated on the crude mixture by $^1H$ NMR.

*Table 1: initial tests for the alkylation of homoanhydride 20a with carbenium ion **21a**.*

This initial failure could be due to the fact that bistriflamide may not guarantee the catalyst turnover, so I repeated the reaction using a stoichiometric amount of tetramisole HCl **22a**. Again when MeOH was added after one night no product was detected and it occurred to us that adventitious water could lead to hydrolysis of intermediates **26** or **27** affording the acid **28**. To verify this hypothesis I directly added to the crude mixture trimethylsylildiazomethane. In this case (table 1, entry 2), I detected the presence of the product that was isolated after column chromatography in 49% yield and 82% ee.

I tried, with the stoichiometric conditions, to convert the postulated intermediates **26** or **27**, in the corresponding amide by adding benzylamine to the crude, but the amide product was not obtained. I also tried aqueous basic conditions as a work up to see if an increased yield of product was obtained: an aqueous saturated solution of $NaHCO_3$ was added to the crude and the mixture was stirred vigorously for one hour, then the organic layer was separated, washed with $NH_4Cl$ aq. sat. sol., dried, concentrated, re-dissolved in anhydrous DCM and treated with trimethylsylildiazomethane. However only 27% yield product was obtained (table 1, entry 4).

Encouraged form the positive result obtained with stoichiometric promoter, I repeated the reaction using 20 mol% tetramisole to see what effect could have on the reaction yield. Surprisingly the product was isolated in similar yield to the stoichiometric conditions but only in 19% ee. This unexpected result indicated that a competing background reaction was operating. This hypothesis was demonstrated by conducing the reaction with different bases without tetramisole: using DIPEA and $Cs_2CO_3$ a significant amount of product was detected by GC-MS, while in case of a weak base, $NaHCO_3$, only traces of product were detected (scheme 6).




| BASE | yield |
|---|---|
| DIPEA | ca. 30% |
| $CsCO_3$ | ca. 30% |
| $NaHCO_3$ | trace |

*Scheme 6: control experiment in the absence of tetramisole. Yield estimated by GC-MS analysis.*

No reports of background reactions were ever reported by Smith in his isothiourea catalyzed processes, which is reasonable considering that DIPEA alone is not able to form the enolate from the non activated carboxylate. The only possibility was that the carbocation, or a derivative, is able to activate either the acid or the anhydride to form a racemic enolate responsible for the racemic reaction. In presence of a base the carbenium ion can form the corresponding carbene that could, in

principle, act in a similar manner as an NHC. However I was not able to gain any evidence of such a behavior and more in general on the mechanism of the background reaction.
Initially we thought that the turnover of the catalyst did not occur because it remained blocked as the acyl cation after the alkylation, so that the supposed slow background reaction contributed significantly. Thus I conducted the reaction in a mixture of MeCN and $H_2O$ to facilitate the turnover of the catalyst, but only traces of product were detected probably because the anhydride is hydrolyzed (table 1 entry 7).
An experiment with 1.5 eq of anhydride **20a**, 3.5 eq DIPEA and 20 mol% **22a** in which the carbenium ion was added in five portions (20 mol% each) every hour was conducted. If the isothiourea promoted reaction was faster than the background one, a high ee should be obtained on the reaction aliquot taken after one hour, before the addition of the second portion of the carbocation. In the following analysis of the enantiomeric excess performed every hour, a progressive decrease of ee should be observed if the catalyst resulted deactivated. Surprisingly, all samples collected at the different reaction times were racemates! The logic conclusion was that the background reaction was faster than the tetramisole promoted one using an excess of anhydride compared to the carbenium ion. Instead when 1.5 eq of anhydride were used with 20 mol% of tetramisole **22a**, product **23a** was obtained in 19% ee, suggesting that in these conditions the two reactions proceeded at similar reaction rate (table 1, entry 5).
I tried the catalytic conditions lowering the temperature to 0°C, but this caused a total loss of enantioinduction suggesting that the background reaction is less affected than the isothiourea promoted one by the lowering of the temperature (table 1, entry 8).
Finally I explored whether the counterion had an influence on the stereochemical outcome in the catalytic conditions: unfortunately either using tetrafluoroborate carbocation **22b** or chloride carbocation **22c** lead to a racemic product (table 1, entries 9 and 10).
The remote possibility of a racemization of product **23a** after its formation by action of the base was ruled out by mixing product **23a** (82% ee) with DIPEA in DCM for one night: recovered **23a** had 80% ee.
A good stability of the product over silica gel was confirmed by passing through column 11 mg of pure product, that was recovered in 81 % yield (8.9 mg). This loss of product cannot be accounted for the obtained yields in the order of 50%, which are due to the formation of side-products deriving from the carbenium ion. Indeed TLC analysis of the reactions highlighted the formation of several sideproducts that rapidly became blue on the silica, indicating that they were derived from the carbocation. Probably the base is able to abstract the methylene proton forming the corresponding carbene that forms the sideproducts. Among these sideproducts, GC-MS analysis revealed the formation in variable amounts (20-50% estimated from GC-MS) of **29** derived from the reduction of the carbocation. The hypothesized mechanism is a hydride transfer from the base to the carbocation.
However **29** was detected also in case inorganic bases were employed so that its formation via carbene intermediate cannot be excluded. The stability of the carbocation under basic conditions strongly depends on the counterion. Mixing the carbocation bistriflamide **21a** with DIPEA in DCM lead to an immediate change of color from blue to violet, probably because the base coordinates to the carbocation and a charge redistribution occurs. After 24 hours the solution was still violet and GC-MS revealed the formation of a significant amount of reduced product **29**. Interestingly when

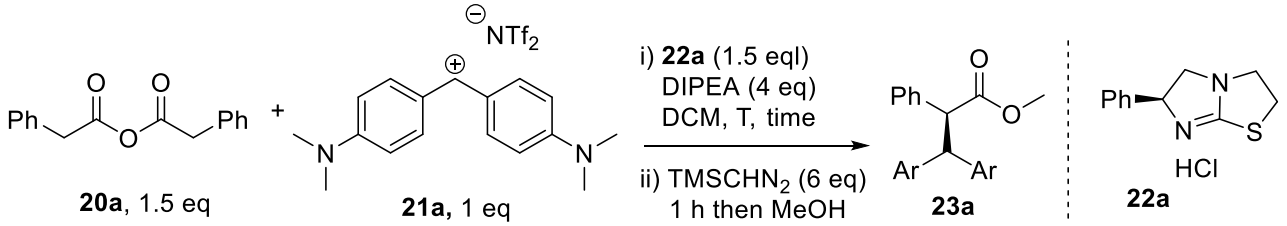
the same experiment was conducted with the tetrafluoroborate carbenium ion **21b**, the blue solution turned yellow in five minutes and the following morning it was completely colorless. These experiments demonstrates that the base is responsible for the carbocation reduction and that the bistriflamide counter ion strongly stabilizes the carbenium ion slowing down this unwanted side-reaction and allowing its reaction with the C1 enolate.

The bistriflamide carbenium ion **21a** is very hygroscopic and should be stored in a desiccator to keep it as a solid salt and avoid that it becomes a chubby gum. The use of this gum in the reaction is detrimental and leads to significantly decreased yields. The tetrafluoroborate carbenium ion **21b** can be stored in sealed vials under air for years without any appreciable changes.

I attempted to perform the slow addition of the carbocation over the mixture of the reagents to see if the amount of byproducts were reduced, instead no product at all was obtained (table 1, entry 11).

As we were unable to suppress the racemic reaction, we decided to explore the transformation using a stoichiometric amount of chiral tetramisole, that is commercially available and cheap (table 2). A moderate increase of the enantioselectivity was obtained performing the reaction under non anhydrous conditions, but the yield decreased from 49 % to 30 %. Probably the anhydride is partially hydrolyzed during the reaction course.

Also in these conditions performing the reaction at low temperature lead to a significant decrease in the reaction yield and enantioselectivity. On the other hand heating the reaction mixture to 35°C lead to an increase in the reaction yield and the ee was slightly diminished.

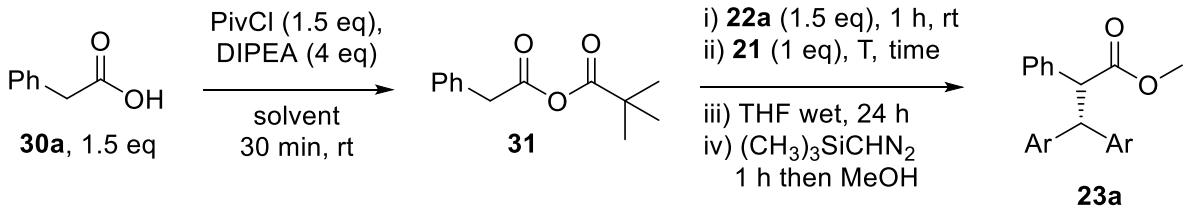


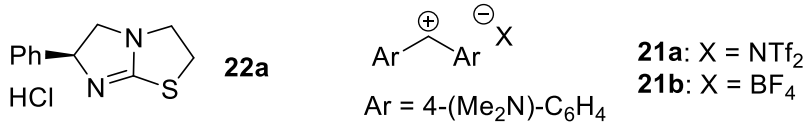

| Entry | $N_2$ | T (°C) | Reaction time | Yield[a] | ee[a] |
|---|---|---|---|---|---|
| 1 | Yes | rt | 16 h | 49 | 82 |
| 2 | No | rt | 16 h | 30 | 87 |
| 3 | No | -78 | 16 h | 26% | 13 |
| 4 | No | rt | 10 min | trace | |
| 5 | No | 35°C | 16 h | 74 | 84 |

All reactions were carried on 0.05 mmol of carbocation **21a**, 0.075 mmol **20a**, 4 eq DIPEA in 1 mL DCM; for the detailed experimental procedure see method B in the experimental section; [(a)] yield of isolated products after chromatographic purification; [(b)] enantiomeric excesses were determined by HPLC analysis on chiral stationary phase after chromatographic purification.

*Table 2: further investigation on the alkylation of homoanhydride **20a** using stoichiometric amounts of tetramisole **22a**.*

We decided to change the starting anhydride with the hope to obtain better results. Phenylacetic acid **30a** was reacted with pivaloyl chloride, previously distilled and stored under inert atmosphere, in presence of DIPEA to form the corresponding mixed anhydride **31a**. After 30 minutes, a stoichiometric amount of tetramisole HCl **22a** was added and the mixture was allowed to stir for further one hour at room temperature to form the enolate **25**. Then the carbocation was added and the mixture was stirred overnight.




| Entry | T | solvent | **21** | Time (h) | yield[a] | ee[b] |
|---|---|---|---|---|---|---|
| 1 | rt | DCM | **21a** | 20 | 51 | 89 |
| 2 | 80 | toluene | **21a** | 20 | ≈ 50[c] | 89 |
| 3 | 0 | DCM | **21a** | 20 | 53 | 92 |
| 4 | -10 | DCM | **21a** | 20 | 13 | nd |
| 5 | -50 | DCM | **21a** | 20 | ≈ 40[c] | 91 |
| 6 | 0 | DCM | **21b** | 20 | 0 | 0 |
| 7 | 0 | MeCN | **21a** | 5 | < 5[c] | nd |
| 8 | 0 | THF | **21a** | 5 | 20 | 89 |
| 9 | 0 | DMF | **21a** | 5 | 0 | - |
| 10 | 0 | toluene | **21a** | 5 | 0 | - |
| 11 | 0 | hexane | **21a** | 5 | 0 | - |
| 12 | 0 | $Et_2O$ | **21a** | 5 | 0 | - |

All reactions were carried on 0.05 mmol of carbocation **21a**, 0.075 mmol **30a**, 0.075 mmol **21a**, 4 eq DIPEA in 1 mL DCM; for the detailed experimental procedure see method C in the experimental section; [(a)] yield of isolated products after chromatographic purification; [(b)] enantiomeric excesses were determined by HPLC analysis on chiral stationary phase after chromatographic purification; [(c)] yield estimated by $^1$H NMR on the crude mixture.

*Table 3: screening of solvents and temperatures using mixed anhydride **31a**.*

To be sure that an adequate amount of water was present inside the reaction mixture to hydrolyze intermediate **26**, wet THF (1 mL/0.05 mmol carbenium ion) was added to the crude the following morning and the solution that was stirred for further 24 h. Then the usual methylation allowed to obtain the ester product **23**. Wet THF is obtained by adding one drop of water for each mL of non anhydrous solvent. In these conditions the product was obtained in 51% yield and 89% ee, the best enantioselectivity so far achieved (table 3, entry 1) with a good yield compared to the previous results.

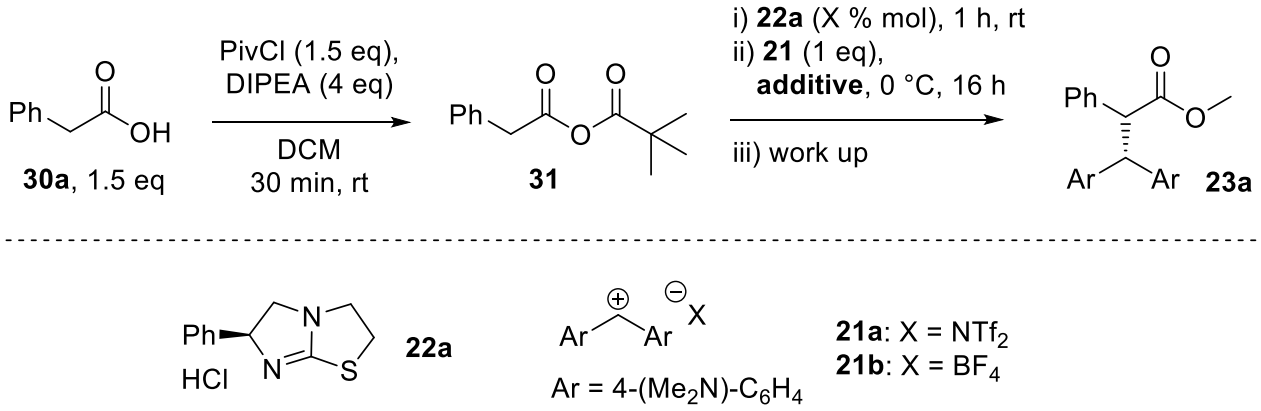
The use of wet MeCN instead of wet THF to ensure the hydrolysis step lead to a diminished yield of product, while using water solutions was even worse. Probably a small amount of water needs to be dissolved in a homogeneous organic solution to efficiently hydrolyze intermediate **26** and THF accomplishes this task in the best way.

I tried to perform the reaction at higher temperatures changing the solvent to toluene in order to see if an increase in the yield or enantioselectivity could be achieved. However the result was substantially the same. With this new protocol the acyl enolate is pre-formed so that no anhydride is left for a possible racemic reaction when the carbenium ion is added. This consideration lead me to perform the reaction with a different procedure in order to increase the enantioselectivity: the enolate was formed at room temperature, then the reaction mixture was cooled in order to perform the nucleophilic addition at a lower temperature and increase the enantioselectivity of the process. Among the different temperatures tested, 0°C afforded the best result both in terms of yield (53%) and enantioselectivity, that was eventually 92% (table 3). Lowering the temperature to -50°C lead to the same enantioselective outcome but the yield was inferior.

Having found promising conditions with the bistriflamide counter ion, I tested if cheaper tetrafluoroborate carbenium ion **22b** could be employed in this reaction protocol, but the product was not obtained while a great amount of reduced byproduct **29** was detected. Probably under these new conditions the tetrafluoroborate carbenium ion is much more unstable and decomposes rapidly without reacting with the enolate.

The reaction was performed in different solvents than DCM but only in THF a moderate amount of product was obtained. The carbenium ion is poorly soluble in apolar solvents so this may explain their failure (table 3).

We tried also on the protocol involving mixed anhydride **31a** to avoid the use of toxic trimethylsilyldiazomethane by trapping the acyl cation **26** with methanol after the alkylation step, but unfortunately it was unsuccessful (table 4). We hypothesized that conducing the reaction in presence of molecular sieves should prevent the hydrolysis of the acyl cation **26** thus favoring its trapping by methanol, but again no product was obtained. We also tried to perform the hydrolysis step by adding sodium methoxyde after the alkylation reaction, but also in this case the product was not obtained. According to several reports in the literature[14,21b,c] we added HOBT during the reaction work up because it could mediate the removal of the tetramisole from the acyl cation **26**. Unfortunately a slight decrease in the product yield was observed (table 4, entry 4).




| entry | **22a (**% mol) | **21** | additive | Work up | yield[a] |
|---|---|---|---|---|---|
| 1 | 20 | **21a** | - | MeOH | 0 |
| 2 | 20 | **21a** | 4Å mol. sieves | MeOH | trace |
| 3 | 150 | **21b** | 4Å mol. sieves | THF wet, 24 h, $TMSCH_2N_2$ | 0 |
| 4 | 150 | **21a** | - | HOBT + THF wet, 24 h, $TMSCH_2N_2$ | 41 |

All reactions were carried on 0.05 mmol of carbocation **21a**, 0.075 mmol **30a**, 0.075 mmol **21a**, 4 eq DIPEA in 1 mL DCM; for the detailed experimental procedure see method C in the experimental section; [(a)] yield of isolated products after chromatographic purification.

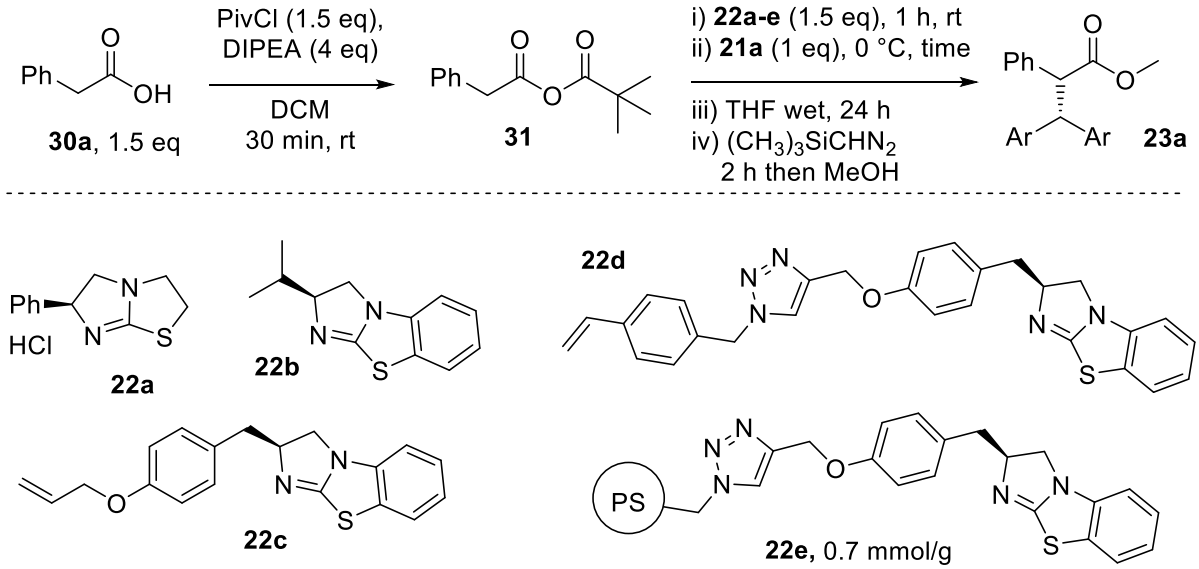
*Table 4: additives and different work up procedures.*

The previously described conditions (table 3 entry 3) represented the best result achieved so we tested different isothioureas we had prepared (see experimental part). Benzotetramisole **22b** gave only trace amount of product, while **22c**, derived from tyrosine, gave a better result than tetramisole (table 5). The use of **22c** in catalytic amount lead to the expected drop of enantioselectivity. The good results obtained with isothiourea **22c** were very important because we had designed it with an allyl group that could be used to attach it to a solid support in order to recover it at the end of the reaction. The use of a supported isothiourea would partly compensate the use of a stoichiometric amount of chiral promoter, that could be easily recovered by filtration and hopefully reused in another cycle.

Moreover at the time, autumn 2014, no reports of isothioureas linked to a solid support had been published. A year later Miguel Pericás and Javier Izquierdo reported the efficient use of polystirene supported isothioureas as catalysts for HDA reactions.[26]

Thus we started a collaboration with Prof. Maurizio Benaglia in Milan, with whom the group had already collaborated to develop organocatalyzed supported reactions with carbenium ions.[27] Riccardo Porta, PhD student with Prof. Benaglia, took care of the immobilization of monomer **22b** on a solid support. Unfortunately his attempts to copolymerize **22a** with styrene monomers were not successful, so he changed the supporting strategy. He prepared the analogous catalyst having a propargyl instead of the allyl group and through a standard click reaction with a polystirene resin

functionalized with the azide, he obtained resin **22e**. He also prepared the corresponding monomer **22d**. Riccardo performed the reaction using the supported catalyst **22e** and the homoanhydride **20** at 0°C in batch conditions, but he obtained the product only in 18% yield, even if with an impressive 96% ee.




| Entry | Time (h) | Cat | yield[a] | ee[b] | Deviations from standard |
|---|---|---|---|---|---|
| 1 | 20 | **22a** | 53 | 92 | |
| 2 | 5 | **22b** | < 10[c] | - | |
| 3 | 3 | **22c** | 58 | 93 | |
| 4 | 20 | **22c** | ≈ 40[c] | 35 | 20 % mol **22c** |
| 5 | 20 | **22d** | 35 | 96 | |
| 6 | 20 | **22e** | 52 | 42 | |
| 7 | 20 | **22e** | 38 | 0 | **22e** recycled from entry 6 |

All reactions were carried on 0.05 mmol of carbocation **21a**, 0.075 mmol **30a**, 0.075 mmol **21a**, 4 eq DIPEA in 1 mL DCM; for the detailed experimental procedure see method C in the experimental section; [(a)] yield of isolated products after chromatographic purification; [(b)] enantiomeric excesses were determined by HPLC analysis on chiral stationary phase after chromatographic purification; [(c)] yield estimated by $^1$H NMR on the crude mixture.

*Table 5: screening of different isothioureas.*

I too performed the reaction with the supported catalyst **22e** that Riccardo had shipped to Bologna, but I used mixed anhydride **30** as starting material. In this case I obtained a moderate yield of 52%, comparable to those obtained with the non supported catalysts, but the ee dropped to 42%. (table 5

entry 6). I performed the reaction again with the recycled catalyst but the product obtained from this second cycle was a perfect racemate (table 5 entry 7). IR analysis of the isothiourea catalyst before and after the reaction revealed a slight difference in the intensity of some peaks in the fingerprint region, but no additional peaks that could reveal a modification in the catalyst structure were observed. In the future I am planning to test supported catalyst **22e** in a HDA reaction reported with non supported isothioureas to see if our supported catalyst is effective in well studied protocols and in this case to verify if the catalyst used in the alkylation with carbenium ions has been deactivated during the reaction.

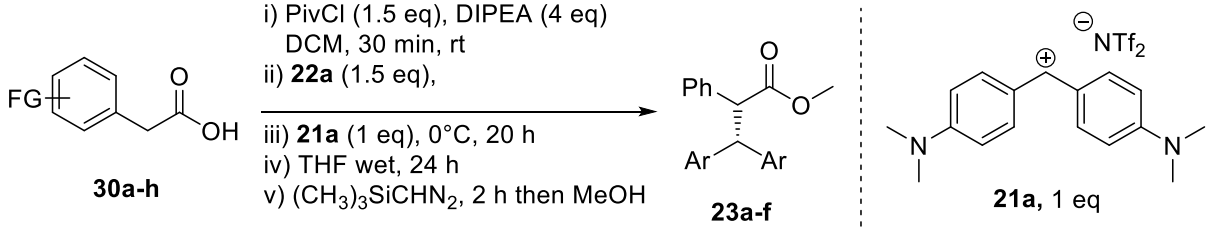
In contrast, monomer **22d** promoted the reaction affording the product in excellent ee and moderate yield, excluding that the triazole group might be responsible for the lack of enantioselectivity. In conclusion either a catalyst deactivation or an excessive hindrance on the catalytic site due to the polymer could be responsible for the negative results using the resin **22e**. Further investigations to verify my results and those obtained by Riccardo are necessary in order to clarify the discrepancies in the enantioselectivities observed.

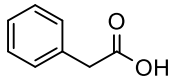
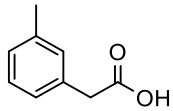
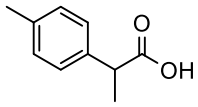
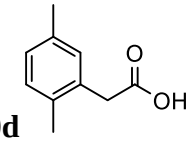
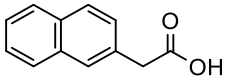
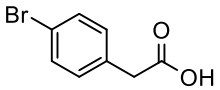
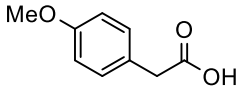
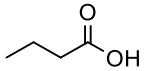
Due to the problems encountered using the supported catalyst, we decided to explore the scope of this transformation using tetramisole HCl **22a** (table 6). Differently substituted phenyl acetic acids **30a-h** were tested under the optimized conditions, but only **30b** and **30f**, respectively bearing p-Br and o-methyl substituents, afforded the corresponding products that were detected by HPLC-MS. However the NMR analysis of the crudes revealed complex mixtures of products and the yield of **23b** and **23f** was evaluated around 20%. Branched acids **30c** and orto substituted **30d** are probably too hindered to react with the carbenium ion. The presence of an electron donating OMe group on the aromatic ring (**30g**) probably destabilizes the acyl enolates and also for these substrates the reaction was unsuccessful, as in case of naphtyl acetic acid **30e**. As expected from the literature precedents, butyric acid could not be alkylated because isothiourea activation and DIPEA fail to generate the corresponding acyl enolate.

To sum up, the scope concerning the aryl acetic acids appears to be limited to neutral or electron withdrawing groups on the para or meta positions.

The alkylation of phenyl acetic acid was investigated also with different carbenium ions (table 7). More electrophilic tropilium ion **32** (E=-3.49 vs E = -7.02 of bisdimethylamminobenzhydrilium ion **22b**) is a suitable substrate on condition that it is used as the bistriflamide salt, that can be easily prepared from the tetrafluoroborate one by ion exchange.[28] Product **33** was obtained in low yield and moderate enantioselectivity after chromatographic purification. It should be noted that also in the alkylation of aldehydes, tropilium ions products were obtained with lower enantioselectivities compared to other carbenium ions.

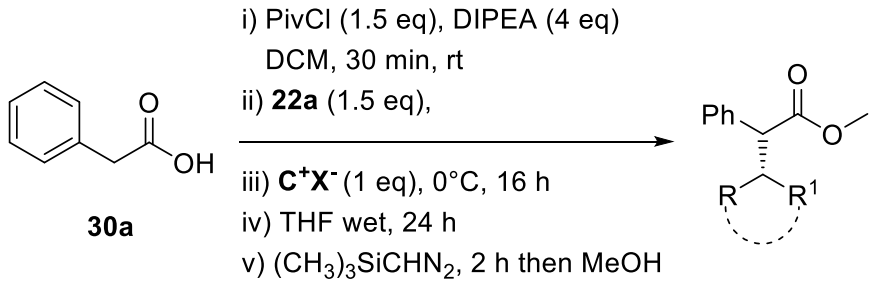
Unfortunately benzodithiolylium, either as tetrafluoroborate or bistriflamide salt, and indolyl substituted carbenium ion **35** did not afford the corresponding products.

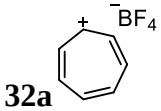
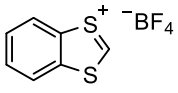
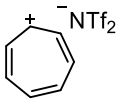
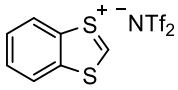
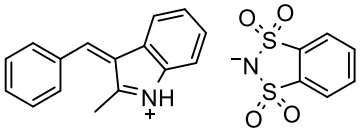


| entry | Acid | P | Yield[a] | ee[b] |
|---|---|---|---|---|
| 1 |  **30a** | **23a** | 50 | 92 |
| 2 |  **30b** | **23b** | ≈20[c] | - |
| 3 |  **30c** | | 0 | - |
| 4 |  **30d** | | 0 | - |
| 5 |  **30e** | | 0 | - |
| 6 |  **30f** | **4f** | ≈20[c] | - |
| 7 |  **30g** | | 0 | - |
| 8 |  **30h** | | 0 | - |

All reactions were carried on 0.05 mmol of carbocation **21a**, 0.075 mmol **30a-h**, 0.075 mmol **21a**, 4 eq DIPEA in 1 mL DCM; for the detailed experimental procedure see method C in the experimental section; [(a)] yield of isolated products after chromatographic purification; [(b)] enantiomeric excesses were determined by HPLC analysis on chiral stationary phase after chromatographic purification, [(c)] yield estimated by $^{1}$H NMR on the crude reaction mixture.

*Table 6: preliminary substrate scope respect to the acid partner*




| entry | $C^+X^-$ | P | Y[a] | Ee[b] | entry | $C^+X^-$ | P | Y[a] | Ee[b] |
|---|---|---|---|---|---|---|---|---|---|
| 1 |  **32a** | | 0 | - | 4 |  **34a** | | 0 | - |
| 2 |  **32b** | **33** | 27 | 69 | 5 |  **34b** | | 0 | - |
| 3 | |  **35** | | | | | | 0 | - |

All reactions were carried on 0.05 mmol of carbocation, 0.075 mmol **30a**, 0.075 mmol **21a**, 4 eq DIPEA in 1 mL DCM; for the detailed experimental procedure see method C in the experimental section; [(a)] yield of isolated products after chromatographic purification; [(b)] enantiomeric excesses were determined by HPLC analysis on chiral stationary phase after chromatographic purification.

*Table 7: preliminary substrate scope respect to the carbocation partner*

The difficulties in exploring the reaction scope were due also to the problems in preparing the racemates, that were of valuable help as references in identifying the presence of the products from the complex mixtures obtained from the enantioselective reactions. Initially we tried to prepare the racemates by the direct reaction of the lithium enolates of the phenyl acetic esters with the carbenium ions. Unfortunately it was successful only in case bisdimethylamminobenzhydrilium tetrafluoroborate **21b** was employed. For example, when tropilium tetrafluoroborate was treated with the lithium enolate of O-methyl-2-phenyl acetate, only decomposition products deriving from the carbocation were detected. Probably the enolate acts as a base generating the carbene from the carbocation.

Racemic **33** was obtained by alkylation of phenylacetaldehyde with **32b** catalyzed by pyrrolidine. The crude product was directly oxidized, by treatment with $NaClO_2$ in presence of catalytic TEMPO and NaClO in a MeCN/buffer phosphate (pH = 6.7) mixture, to the carboxylic acid that after acidic work up and extraction was directly methylated to obtain racemic **33**.

This long but solid procedure was applied to variously substituted phenylacetic aldehydes (p-$NO_2$, p-Me, p-Br) that were successfully alkylated with dimethylamminobenzhydrilium tetrafluoroborate

**21b**. Unfortunately the oxidation of the alkylated aldehydes to the acids lead to a massive oxidation of the dimethyl aniline moieties and the desired products were not obtained. Probably the same problem would be encountered with benzodithiolilium that is also sensible to oxidative conditions.
The alternative for the evaluation of the enantiomeric excesses of products **23b** and **23f** is their reduction to the corresponding alcohols and the comparing of the HPLC traces with the racemic products obtained by the akylation of the aldehydes with the carbenium ion **21b**.

### 2.5.3 Conclusions

We have developed the first enantioselective α-alkylation of carboxylic acids with carbenium ions via the formation of the corresponding C1 enolates under mild basic conditions promoted by stoichiometric amounts of chiral isothioureas. Unfortunately, the methodology appears limited to the alkylation of phenyl acetic acid with dimethylamminobenzhydrilium bistriflamide and tropilium bistriflamide, even if some preliminary results have been obtained with para or meta substituted phenylacetic acids. The use of the bistriflamide counterion is crucial for the success of the reaction as it appears to stabilize the carbenium ion that under basic conditions can be reduced and can form the carbene that rapidly decomposes. In order to try and recycle the chiral promoter in an easy and chromatography free methodology, we designed a new supported isothiourea. However the first tests using this supported isothiourea gave inferior results compared to the homogeneous conditions.

### 2.5.4 Contributions

I was involved in the discovery and development of the project. Alba Catot, bachelor Erasmus student from Barcelona University, worked on the optimization of the process and to the synthesis of the isothiourea catalysts under my supervision. Professor Maurizio Benaglia and Riccardo Porta (Milano University) synthetized and performed the first tests with supported catalyst **22e**. Professor Pier Giorgio Cozzi supervised and directed the project. I thank Dr. Andrea Gualandi for precious advices and discussion.

## 2.5.5 Experimental part

### Materials and methods

$^1$H NMR spectra were recorded on Varian Gemini 200 and Varian Mercury 400 spectrometers. Chemical shifts are reported in ppm from TMS with the solvent resonance as the internal standard (deuterochloroform: δ= 7.27 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = duplet, t = triplet, q = quartet, dd = double duplet, dt = double triplet, bs = broad signal, m = multiplet), coupling constants (Hz).

GC-MS spectra were taken by EI ionization at 70 eV on a Hewlett-Packard 5971 with GC injection. They are reported as: m/z (rel. intense).

Chromatographic purification was done with 240-400 mesh silica gels. Purification on preparative thin layer chromatography was done on Merck TLC silica gel 60 F254 and on Merck TLC aluminium oxide 60 F254 neutral.

Determination of enantiomeric excess was performed by HPLC analysis Daicel Chiralcel AMY column: hexane/*i*-PrOH from 93:7 to 90:10 in 20 min. then 90:10, flow rate 0.70 mL/min, 40°C, λ = 295 nm: major diastereoisomer τmajor = 17.75 min., τminor = 19.29 min.; minor diastereoisomer τmajor = 26.41 min., τminor = 16.94 min.

Benzoyl chloride and chlorotrimethylsilane were supplied by Aldrich and used after distillation. Carboxylic acids used for the esterification were supplied by Aldrich avoiding purification.

### Materials and methods

$^1$H NMR spectra were recorded on Varian Gemini 200 and Varian Mercury 400 spectrometers. Chemical shifts are reported in ppm from TMS with the solvent resonance as the internal standard (deuterochloroform: δ= 7.27 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = duplet, t = triplet, q = quartet, dd = double duplet, dt = double triplet, bs = broad signal, m = multiplet), coupling constants (Hz).

GC-MS spectra were taken by EI ionization at 70 eV on a Hewlett-Packard 5971 with GC injection. They are reported as: m/z (rel. intense).

Chromatographic purification was done with 240-400 mesh silica gels. Purification on preparative thin layer chromatography was done on Merck TLC silica gel 60 F254 and on Merck TLC aluminium oxide 60 F254 neutral.

Determination of enantiomeric excess was performed by HPLC analysis Daicel Chiralcel AMY column: hexane/*i*-PrOH from 93:7 to 90:10 in 20 min. then 90:10, flow rate 0.70 mL/min, 40°C, λ = 295 nm: major diastereoisomer τmajor = 17.75 min., τminor = 19.29 min.; minor diastereoisomer τmajor = 26.41 min., τminor = 16.94 min.

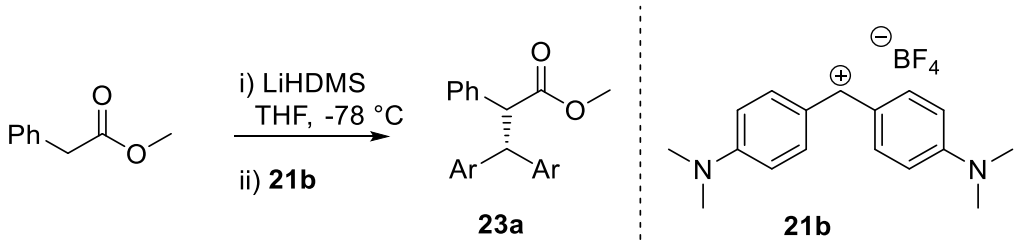
Benzoyl chloride and chlorotrimethylsilane were supplied by Aldrich and used after distillation. Carboxylic acids used for the esterification were supplied by Aldrich avoiding purification.

**Preparation of homoanhydride 20a**

According to the literature. [29] Into a flame dried flask was added the acid (1 equiv.). It was dissolved with toluene (750 μL per 0.5 mmol of acid) and then DCC (0.5 equiv.) was added and reacted overnight. The mixture was filtered with a Büchner and washed with cyclohexane, the filtrate was concentrated to obtain the anhydride. Spectroscopical data were according to the literature.

**Carbocations 32b and 34b were prepared according to the literature.[28]**

**Synthesis of racemic 23a**




LiHMDS (0.36 mmol) was added in a balloon with THF (3 mL per 0.30 mmol of ester) and was added dropwise a mixture of the ester (0.30 mmol) dissolved with THF (5 mL). After 30 min the carbocation (0.30 mmol) was added. After 1 h the reaction was controlled by TLC, when complete conversion was observed was quenched with water and concentrated to evaporate the solvent. Then the aqueous phase was extracted with EtOAc, dried with $Na_2SO_4$, filtered and concentrated. The crude of the product was purified by column chromatography on silica gel (eluent 95:5 Cyclohexane/EtOAc) to afford the product.

**Enantioselective alkylation of carboxylic acids acitivated with mixed anhydrides**

**General procedure A: Alkylation of homoanhydride 20a with catalytic tetramisole HCl 22a**

To a solution of anhydride **20a** (19 mg, 0.075 mmol) in $CH_2Cl_2$ (0.5 mL), DIPEA (29 μL, 0.175 mmol), tetramisole·HCl **22a** (2.4 mg, 0.01 mmol), and bis(4-dimethylaminophenyl)methylium trifliuoromethylsulfonimide **21a** (25 mg, 0.05 mmol) were added at room temperature. The reaction mixture was reacted overnight at rt. Then diazomethane (150 μL) was added, and 2 h later it was quenched with MeOH (500 μL). The mixture was concentrated to afford the crude product that was directly purified by column chromatography.

**General procedure B: Alkylation of homoanhydride 20a with stoichiometric tetramisole HCl 22a**

To a solution of anhydride **20a** (19 mg, 0.075 mmol) in $CH_2Cl_2$ (0.5 mL), DIPEA (38 μL, 0.225 mmol), tetramisole·HCl **22a** (2.4 mg, 0.01 mmol), and bis(4-dimethylaminophenyl)methylium trifliuoromethylsulfonimide **21a** (25 mg, 0.05 mmol) were added at room temperature. The reaction mixture was reacted overnight at rt. Then diazomethane (150 μL) was added, and 2 h later it was quenched with MeOH (500 μL). The mixture was concentrated to afford the crude product that was directly purified by column chromatography.

**General procedure C: Alkylation of carboxylic acids activated with PivCl with catalytic tetramisole HCl 22a**

To a solution of phenylacetic acid **30a** (10.2 mg, 0.075 mmol) in $CH_2Cl_2$ (0.5 mL), DIPEA (13 μL, 0.075 mmol) followed by pivaloyl chloride (10 μL, 0.08 mmol) were added at room temperature. The reaction mixture was allowed to stir at room temperature for 30 min. Tetramisole·HCl (2.4 mg, 0.01 mmol), DIPEA (17 μL, 0.1 mmol) and bis(4-dimethylaminophenyl)methylium trifliuoromethylsulfonimide **21a** were then added at room temperature. The reaction mixture was reacted overnight at rt. Then it was treated with wet THF and stirred for 24 h. Diazomethane (150 μL) was added, and 2 h later it was quenched with MeOH (500 μL). The mixture was concentrated to afford the crude product that was directly purified by column chromatography.

**7.4.1. General procedure D: Alkylation of carboxylic acids activated with PivCl with stoichiometric tetramisole HCl 22a**

To a solution of phenylacetic acid (10.2 mg, 0.075 mmol) in $CH_2Cl_2$ (0.5 mL), DIPEA (13 μL, 0.075 mmol) followed by pivaloyl chloride (10 μL, 0.08 mmol) were added at room temperature. The reaction mixture was allowed to stir at room temperature for 30 min. Tetramisole·HCl (18.05

mg, 0.075 mmol) and DIPEA (13 μL, 0.075 mmol) were then added at room temperature. The reaction mixture was stirred for another 30 min and then DIPEA (13 μL, 0.075 mmol) was added. It was stirred for 30 min and finally the carbocation (0.05 mmol) was added at 0ºC. The mixture reacted overnight.
Then it was treated with wet THF and reacted overnight. Diazomethane (150 μL) was added, and 2 h later it was quenched with MeOH (500 μL). The mixture was concentrated to afford the crude product that was directly purified by column chromatography.

### 7.4.2. General procedure E: Alkylation of carboxylic acids activated with PivCl with stoichiometric isothioureas 22b-e

To a solution of phenylacetic acid (10.2 mg, 0.075 mmol) in $CH_2Cl_2$ (0.5 mL) DIPEA (13 μL, 0.075 mmol) followed by pivaloyl chloride (10 μL, 0.08 mmol) were added at room temperature. The reaction mixture was allowed to stir at room temperature for 30 min. The requisite isothiourea (1.5 equiv.) was then added at room temperature. The reaction mixture was stirred for another 30 min and then DIPEA (13 μL, 0.075 mmol) was added. It was stirred for 30 min and finally bis(4-dimethylaminophenyl)methylium trifliuoromethylsulfonimide (24.65 mg, 0.05 mmol) was added at 0ºC. The mixture was reacted overnight.
Then it was treated with wet THF and it was reacted overnight. Diazomethane (150 μL) was added, and 2 h later it was quenched with MeOH (500 μL).
The mixture was concentrated to afford the crude product that was directly purified by column chromatography.

(**23a**). Following general procedure E, using isothiourea **22c** (24.15 mg, 0.075 mmol) afforded the desired product (11.6 mg, 58% yield**,** 93% ee). The crude was purified by column chromatography on silica gel using 90:10 Cyclohexane/EtOAc as eluent. HPLC analysis Daicel Chiralcel AD column: hexane/*i*-PrOH 80:20, flow rate 0.7 mL/min, 40 ºC, $\lambda = 266$ nm $\tau_{major} = 17.72$ min., $\tau_{minor} = 10.58$ min.
$^1$H NMR (400 MHz, $CDCl_3$, 25°C): $\delta$ = 2.80 (s, 6H), 2.90 (s, 6H), 3.49 (s, 3H), 4.38 (d, $J$ = 12.0 Hz, 1H), 4.56 (d, $J$ = 12.0 Hz, 1H), 6.47 (d, $J$ = 8.7 Hz, 2H), 6.68 (d, $J$ = 8.7 Hz, 2H), 6.90 (d, $J$ = 8.7 Hz, 2H), 7.11-7.16 (m, 1H), 7.17-7.22 (m, 2H), 7.25 (d, $J$ = 8.7 Hz, 2H), 7.30-7.35 (m, 2H).

(**33**). Following general procedure D, using isothiourea **22a** (18 mg, 0.075 mmol) afforded the desired product (11.6 mg, 58% yield**,** 93% ee). The crude was purified by preparative TLC on silica gel using 90:10 Cyclohexane/EtOAc as eluent. HPLC analysis Daicel Chiralcel AD column: hexane/*i*-PrOH 98:2, flow rate 0.7 mL/min, 40 ºC, $\lambda = 210$ nm $\tau_{major} = 7.45$ min., $\tau_{minor} = 7.78$ min.
$^1$H NMR (400 MHz, $CDCl_3$, 25°C): $\delta$ = 2.68 (dt, $J_1$ = 11.2 Hz, $J_1$ = 6.5 Hz, 1H), 3.68 (s, 3H), 3.84 (d, $J$ = 11.2 Hz, 1H), 5.01 (dd, $J_1$ = 9.1 Hz, $J_1$ = 6.3 Hz, 1H), 5.38 (dd, $J_1$ = 9.1 Hz, $J_1$ = 6.3 Hz, 1H), 6.11 (dd, $J_1$ = 9.1 Hz, $J_1$ = 5.6 Hz, 1H), 6.27 (dd, $J_1$ = 9.1 Hz, $J_1$ = 6.3 Hz, 1H), 6.59-6.74 (m, 2H), 7.27-7.35 (m, 5H).

## 2.5.6 References


[1] Unpublished data

**[2]** G. S. Cortez, R. L. Tennyson and D. Romo, *J. Am. Chem. Soc*., **2001**, *123*, 7945.

**[3]** M. J. Gaunt and C. C. C. Johansson, *Chem. Rev*., **2007**, *107*, 5596 and references therein.

**[4]** T. Mukaiyama, M. Usui and K. Saigo, *Chem. Lett*., **1976**, *5*, 49.

**[5]** a) H. Nguyen, S. H. Oh, H. Henry-Riyad, D. Sepulveda, D. Romo, *Org. Synth*., **2011**, *88*, 121; b) 16 D. Sikriwal and D. K. Dikshit, *Tetrahedron*, **2011**, *67*, 210; c) K. A. Morris, K. M. Arendt, S. H. Oh and D. Romo, *Org. Lett*., **2010**, *12*, 3764; d) G. Liu, M. E. Shirley and D. Romo, *J. Org. Chem*., **2012**, *77*, 2496 and refs. therein.

[6] L. C. Morrill, A. D. Smith, *Chem. Soc. Rev.* **2014**, *43*, 6214.

[7] B. Maji, C. Joannesse, T. A. Nigst, A. D. Smith, H. Mayr, *J. Org. Chem*. **2011**, *76*, 5104–5112.

**[8]** C. A. Leverett, V. C. Purohit and D. Romo, *Angew. Chem., Int. Ed.*, **2010**, *49*, 9479.

**[9]** X. Yang, G. Lu and V. Birman, *Org. Lett*., **2010**, *12*, 892.

**[10]** C. A. Leverett, V. C. Purohit, A. G. Johnson, R. L. Davis, D. J. Tantillo and D. Romo, *J. Am. Chem. Soc*., **2012**, *134*, 13348.

**[11]** D. Belmessieri, L. C. Morrill, C. Simal, A. M. Z. Slawin and A. D. Smith, *J. Am. Chem. Soc*., **2011**, *133*, 2714.

**[12]** D. Belmessieri, D. B. Cordes, A. M. Z. Slawin and A. D. Smith, *Org. Lett*., **2013**, *15*, 3472; b) L. C. Morrill, T. Lebl, A. M. Z. Slawin and A. D. Smith, *Chem. Sci*., **2012**, *3*, 2088; c) C. Simal, T. Lebl, A. M. Z. Slawin and A. D. Smith, *Angew. Chem., Int. Ed.*, **2012**, *51*, 3653; d) S. R. Smith, J. Douglas, H. Prevet, P. Shapland, A. M. Z. Slawin and A. D. Smith, *J. Org. Chem*., **2014**, *79*, 1626; e) L. C. Morrill, S. M. Smith, A. M. Z. Slawin and A. D. Smith, *J. Org. Chem*., **2014**, *79*, 1640.

[13] L. C. Morrill, J. Douglas, T. Lebl, A. M. Z. Slawin, D. J. Fox**,** A. D. Smith, *Chem. Sci*., **2013**, *4***,** 4146.

**[14]** T. H. West, D. S. B. Daniels, A. M. Z. Slawin and A. D. Smith *J. Am. Chem. Soc*., **2014**, *136*, 4476–4479.

[15] Pankaj Chauhan and Dieter Enders, *Angew. Chem. Int . Ed*. **2014**, *53*, 1485 – 1487.

**[16]** a) L. Hao, Y. Du, H. Lv, X. Chen, H. Jiang, Y. Shao, Y. R. Chi, *Org. Lett*. **2012**, *14*, 2154; b) L. Hao, C. W. Chuen, R. Ganguly and Y. R. Chi, *Synlett*, **2013**, 1197.

[17] **a)** L. Hao, S. Chen, J. Xu, B. Tiwari, Z. Fu, T. Li, J. Lim and Y. R. Chi, *Org. Lett*., **2013**, *15*, 4956; b) S. Chen, L. Hao, Y. Zhang, B. Tiwari and Y. R. Chi, *Org. Lett*., **2013**, *15*, 5822.

[18] **a)** Z. Fu, J. Xu, T. Zhu, W. W, Y. Leong, Y. R. Chi, *Nature Chem.* **2013**, *5*, 835; b) Z. Fu, K. Jiang, T. Zhu, J. Torres, Y. R. Chi, *Angew. Chem. Int. Ed*. **2014**, *53*, 6506-6510; b) Z. Jin, K. Jiang, Z. Fu, J. Torres, P. Zheng, S. Yang, B-A Song, Y. R. Chi, *Chem. Eur.J.* **2015,** *21*, 9360 –9363.

[19] Compare ref 17 and 18a.

[20] Y. Xiao, J. Wang, W. Xia, S. Shu, S. Jiao, Y Zhou, H. Liu, *Org. Lett*. **2015**, *17*, 3850−3853.

[21] For asymmetric reactions on aldehydes or enals see: M. H. Wang, D. T. Cohen, C. B. Schwamb, R. K. Mishra, K. A. Scheidt, *J. Am. Chem. Soc.*, **2015**, *137*, 5891–5894; b) P. Wheeler, H. U. Vora, T. Rovis, *Chem. Sci*., **2013**, *4*, 1674; c) H. U. Vora and Tomislav Rovis, *J. Am. Chem. Soc.*, **2007**, *129*, 13796-13797; d) S. S. Sohn and J. W. Bode, *Angew. Chem. Int. Ed.* **2006**, *45*, 6021 –6024; for esterifications: e) G. A. Grasa, R. M. Kissling, S. P. Nolan *Org Lett* **2002**, *4*, 3583.

[22] D. Lee, S. G. Newman, and M. S. Taylor, *Org Lett* **2009**, *11*, 5486.

[23] a) C. E. Stivala and A. Zakarian, *J. Am. Chem. Soc.* **2011**, *133*, 11936–11939; b) P. Lu, J. J. Jackson, J. A. Eickhoff, and A. Zakarian, *J. Am. Chem. Soc*. **2015**, *137*, 656−659.

[24] Y. Morita, T. Yamamoto, H. Nagai, Y. Shimizu, M. Kanai, *J. Am. Chem. Soc.*, **2015**, *137*, 7075–7078.

[25] A. Gualandi, P. G. Cozzi, *SYNLETT* **2013**, *24*, 281 and refs therein.

[26] J. Izquierdo, and M. A. Pericàs, *ACS Catal.*, **2016**, *6*, 348–356.

[27] R. Porta, M. Benaglia, A. Puglisi, A. Mandoli, A. Gualandi, P.G. Cozzi *ChemSusChem*, **2014**, *7*, 3534-3540.

[28] M. Drusan, E. Rakovsky, J. Marek, R. Sebesta, *Adv. Synth. Cat*. **2015**, *357*, 1493-1498.

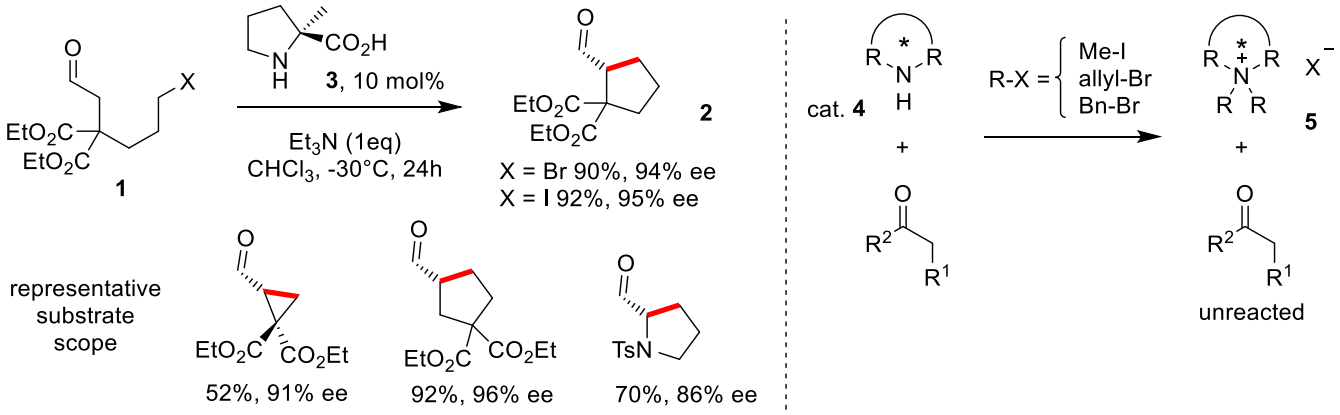
[29] L. C. Morrill, L. A. Ledingham, J.-P. Couturier, J. Bickel, A. D. Harper, C. Fallan and A. D. Smith, *Org. Biomol. Chem*., **2014**, *12*, 624.

# 2.6 Organocatalytic Enantioselective Alkylation of Aldehydes with $[Fe(bpy)_3]Br_2$ Catalyst and Visible Light

Table of contents

## 2.6.1 Introduction

The asymmetric direct alkylation of aldehydes with alkyl iodides or bromides has represented one of the main challenges for organocatalysis since the early 2000's. The first example has been the intramolecular process between 6-iodo-alkyl-aldehydes promoted by 2-methyl-proline. The reaction proceeds in optimal yields and enantioselectivities for specific substrates **1**.[1] However the corresponding intermolecular process is not possible because the alkyl, allyl, benzyl iodides or bromides react with the secondary amine catalyst forming the inactive ammonium salt **5**. The impossibility to realize this direct and useful alkylation reaction has earned it the name of "The Holy Grail of Organocatalysis".




*Scheme 1: direct organocatalytic asymmetric alkylation of aldehydes with alkyl iodides or bromides: limited scope and catalyst deactivation.*

The alkylation of catalytically generated enamines with less electrophilic bromo malonates or α-bromo acetophenones has been realized but only as the second intramolecular step of domino processes. These processes starts with the activation of α,β-unsaturated aldehydes via the formation of the corresponding iminium ions that are attacked by the enolate of the bromo malonate or of the bromo acetophenone. After the nucleophilic attack an enamine is generated that undergoes an alkylation reaction with the alkyl bromide forming a carbocycle.[2] A highly efficient cycloprapanation reaction has been realized with bromomalonates, while in case of bromoacetophenones the process, that affords five or six membered carbocycles, suffers from severe limitations. Another intermolecular domino process in which the alkylation of alkyl iodides has been realized in the second intramolecular step has been described by Enders in 2008.[3]

In 2014 List reported the first example of α-benzylation of aldehydes with simple benzyl bromides. The reaction requires a particular combination of base and catalyst and is limited to α-branched aryl substituted aldehydes.[4]

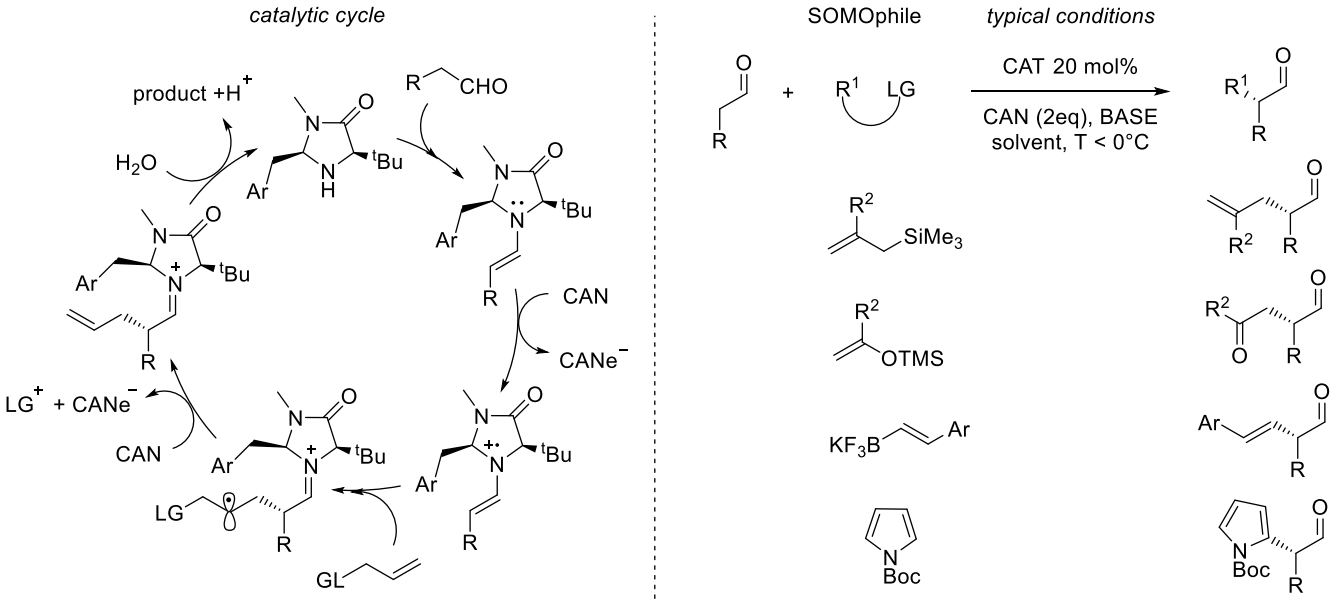
The α-alkylation of aldehydes with carbenium ions has represented a valuable alternative to the direct alkylation process with alkyl halogen compounds (see chapter 1). A very useful process is the formal α-

methylation of aldehydes with benzodithiolylium tetrafluoroborate developed by Cozzi and coworkers.[5] The procedure has been successfully applied to the synthesis of bisabolanes, flavours and fluorinated analogues of relevant compounds.[6] Unfortunately other very useful carbenium ions, such as benzylic or non substituted allylic carbocations, are too electrophilic to be generated in conditions compatible with enamine catalysis.

The development of single electron transfer (SET) processes with enamine catalysis has opened the route to unprecedented transformations that resulted impossible with the two electron polar chemistry furnishing a possible answer to the Holy Grail quest.

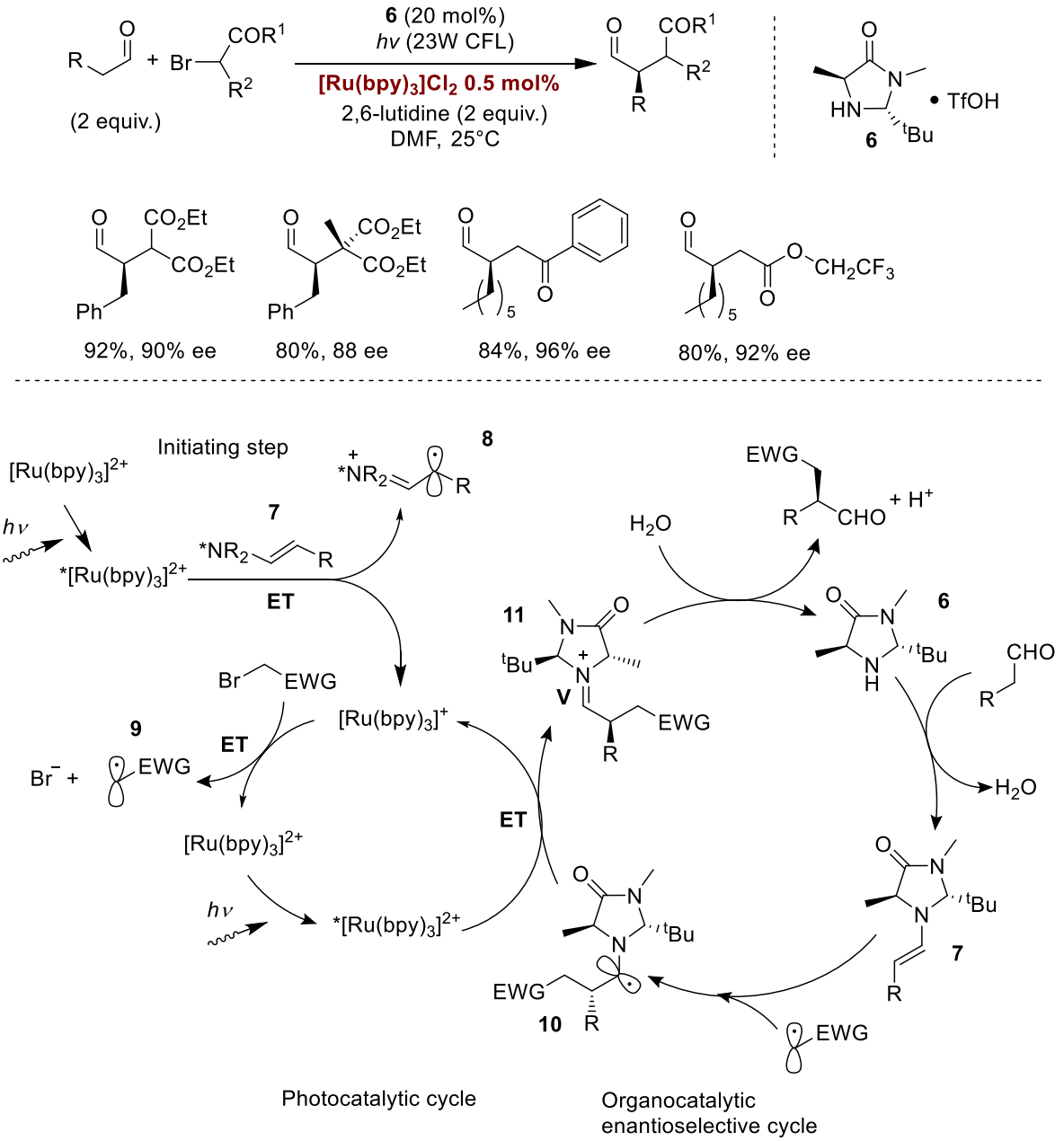
SOMO catalysis has been reported for the first time in 2007 by MacMillan and coworkers who managed to realize a single electron oxidation of the catalytically generated enamine with strong oxidants such as CAN. The resulting chiral radical cation engaged an enantioselective radical reaction with electron rich SOMOphiles, electron rich olfins such as allyl sylanes. The resulting radical was further oxidized to a stabilized carbenium ion that was quenched either by elimination or by attack of an external nucleophile. Finally the obtained iminium was hydrolyzed to afford the alkylated aldehyde and the secondary amine catalyst (scheme 2).

Through this strategy the enantioselective α-allylation, α-enolation, α-vinylation, α-arylation, α-chlorination, α-epoxydation, α-nitroalkylation of aldehydes were realized.[7]




*Scheme 2: catalytic cycle of SOMO catalysis and representative examples of its synthetic applications.*

SOMO reactions are very sensitive to air and a precise amount of water must be present in the reaction mixture to allow the turnover of the catalyst without hampering the radical process. Moreover a stoichiometric amount of strong oxidant is needed.




*Scheme 3: MacMillan photoalkylation of aldehydes: representative scope and dual catalytic cycle.*

The merging of enamine activation mode and photocatalysis in a double red-ox self-consistent catalytic cycle allowed the realization SET alkylation reactions of aldehydes without the need of stoichiometric oxidants. Moreover as visible light furnishes the energy to promote the transformation, this usually occurs under mild reaction conditions.

Again, MacMillan and Nicewitz first applied this concept reporting in 2008 the enantioselective alkylation of aldehydes with bromo malonates or α-bromo acetophenones promoted by MacMillan

catalyst **6** and $Ru(bpy)_2^{2+}$ (scheme 3).[8] The use of less hindered MacMillan catalyst **6** is fundamental in order to have high yields and optimal enantioselectivities. DFT calculations have shown that the tertbutyl group controls the geometry of the enamine imposing the trans conformation while the trans methyl group efficiently shields one prostereogenic face of the enamine **7**.

The reaction needs an initiating step in which the excited state of $Ru(bpy)_2^{2+}$ ($^*Ru(bpy)_2^{2+}$) is reduced to $Ru(bpy)_2^{+}$ that is able to reduce the alkyl bromide leading to the formation of radical **9** and bromide anion. A sacrificial amount of enamine **7** acts as reducing agent forming radical **8**, that is the reactive intermediate in SOMO catalysis while in this conditions remains inactive and this amount of **6** is lost. Electron poor radical **8** reacts with the electron rich enamine forming radical **10** that reduces ($^*Ru(bpy)_2^{2+}$ reinitiating the photocatalytic cycle and giving iminium **11** that upon hydrolysis affords the product and the amine catalyst **6** (scheme 3).

A radical chain competing process in which radical **10** reduces the bromo malonate giving **8** is also possible. Measurements of the quantum yield of reactions promoted by Ru and Ir revealed values lower than 1, indicating that probably both mechanisms are operating.[9]

$Ru(bpy)_2^{2+}$ is one of the most employed and used photocatalysts due to a strong absorption band in the visible region of light and the long lifetimes of its excited states, in the order of ns. Such features are common to the most employed photocatalysts including iridium complexes, whose typical excited states lifetimes are in the order of μs.[10]

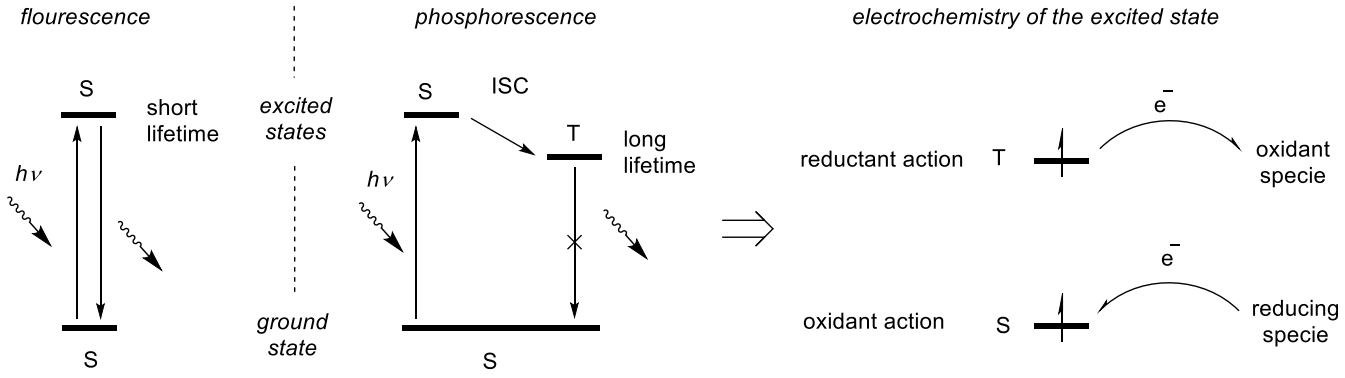



*Figure 1: fluorescence and phophorescence phenomena and the influence of the electronic structure of the excited state on its reactivity.*

The reason of such lifetimes lies in the properties of these materials: the photon absorbed by the singlet ground state promotes the transition of one electron to the singlet excited state. Thanks to the strong spin orbit interactions due to the heavy metal center, an inter system crossing (ISC) process readily occurs and the singlet state decays into an excited triplet state. The radiative decay, i.e. the emission of a photon, from the triplet state to the singlet ground state is forbidden by symmetry accounting for the long life time of this excited state. This phenomena is called phosphorescence and differs from the fluorescence typical of the species that undergo a rapid (typical fs) decay from the singlet excited state to the singlet ground state because the ISC cannot occur (figure 1 left side).

The presence of two single electron occupied orbitals in the excited state (M*) opens the door to a totally different chemistry compared to the ground state, in particular due to SET red-ox processes (figure 1 right side). The high energetic electron present on the excited state gives this specie reducing properties: in case a suitable oxidant substrate is present the red-ox process can occur affording the ground state oxidized $M^{+1}$ complex and the reduced substrate. The $M^{+1}$ specie is not stable and is reduced to the $M^0$ complex if a suitable reducing agent is present.
On the other hand, the electronic hole on the ground state of M* makes the excited complex a good oxidant able to take an electron from a specie with a lower reduction potential. In this case the ground state $M^{-1}$ is obtained, whose tendency is being oxidized to the $M^0$ ground state by an oxidant.
The potentials of the excited states can be calculated with a good approximation by the following equations:[11]

Oxidative quenching: $E_{red}\,[PC^{+1} / {}^*PC] = E_{red}\,[PC^{+1} / PC] - E_{0,0}$ (eq. 1)

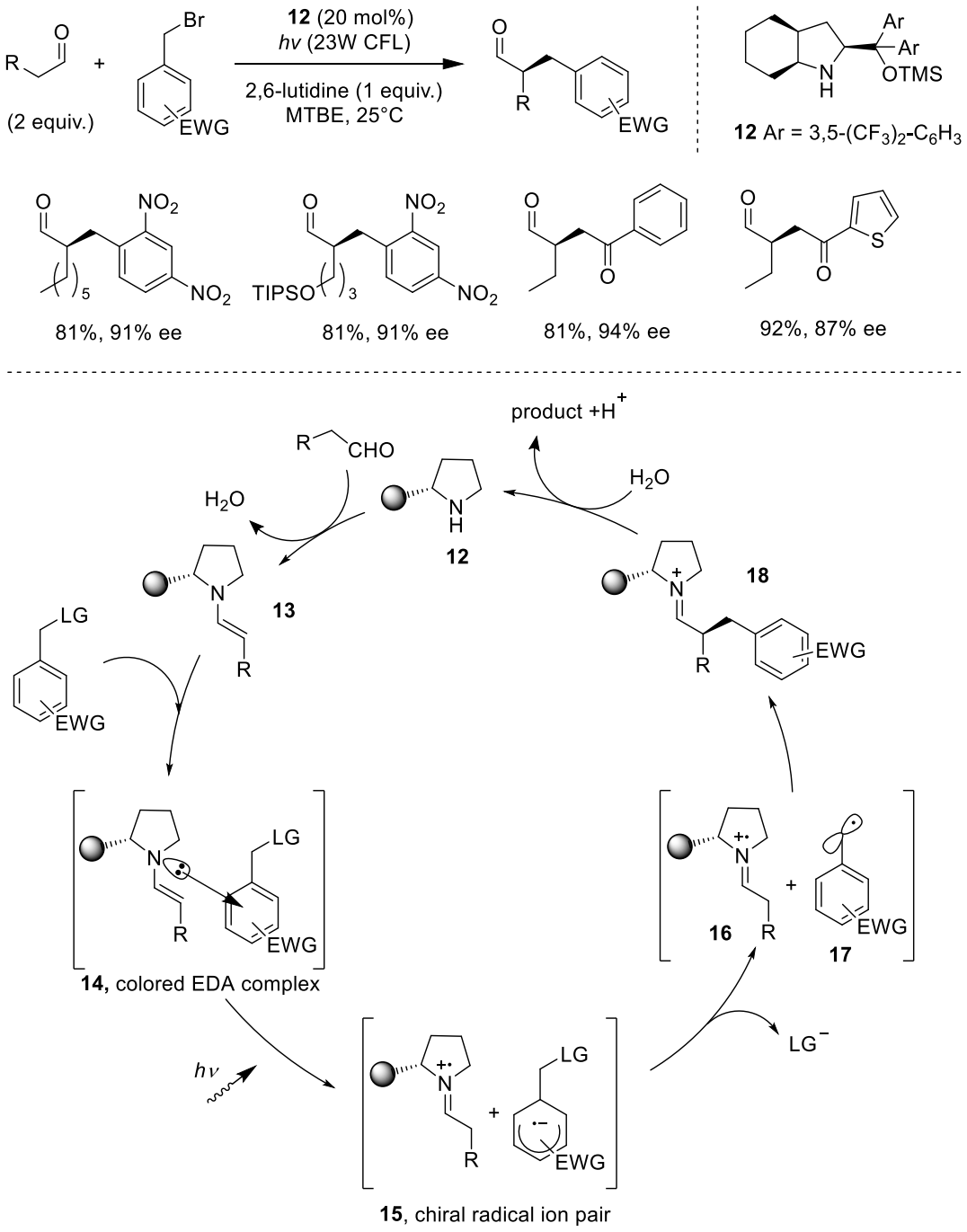
Ex.: ${}^*Ru(bpy)_3^{2+} + e^- \longrightarrow Ru(bpy)_3^{+}$

Reductive quenching: $E_{red}\,[{}^*PC / PC^{-1}] = E_{red}\,[PC / PC^{-1}] + E_{0,0}$ (eq. 2)

Ex.: ${}^*Ru(bpy)_3^{2+} \longrightarrow Ru(bpy)_3^{3+} + e^-$

$E_{0,0} = h(c/\lambda_{emission})$ ; for $\lambda_{emission}\,[Ru(bpy)_3^{2+}] = 482$ nm; $E_{0,0} = 482 \cdot 0.00366 = 2.13$ eV

They depend on the maximum intensity wavelength of the emission peak ($\lambda_{emission}$) and on the reduction potentials of the corresponding red-ox process between the two ground states.
The before described cycles are the two red-ox photocatalytic cycles that can be driven by visible light irradiation. The "choice" between the reduction-starting cycle and the oxidizing one depends on the properties of the photocatalyst and on the species present in solution.
Another important approach that has been successfully exploited in organophotocatalysis is the formation of electron donor acceptor (EDA) complexes between electron rich enamines, in situ generated from secondary amine catalyst **12** and aldehydes, and electron deficient benzyl bromides.[12] Visible light irradiation promotes an electron on the excited state of the EDA complex that corresponds to a charge transfer from the enamine to the benzyl bromide. The excited state can either relax to the ground state or the alkyl bromide radical anion partner can eliminate the bromide generating benzyl radical **17** that recombines with the enamine radical cation leading to the formation of the α-benzylated aldehyde. This process was the first organocatalytic asymmetric benzylation of aldehydes.

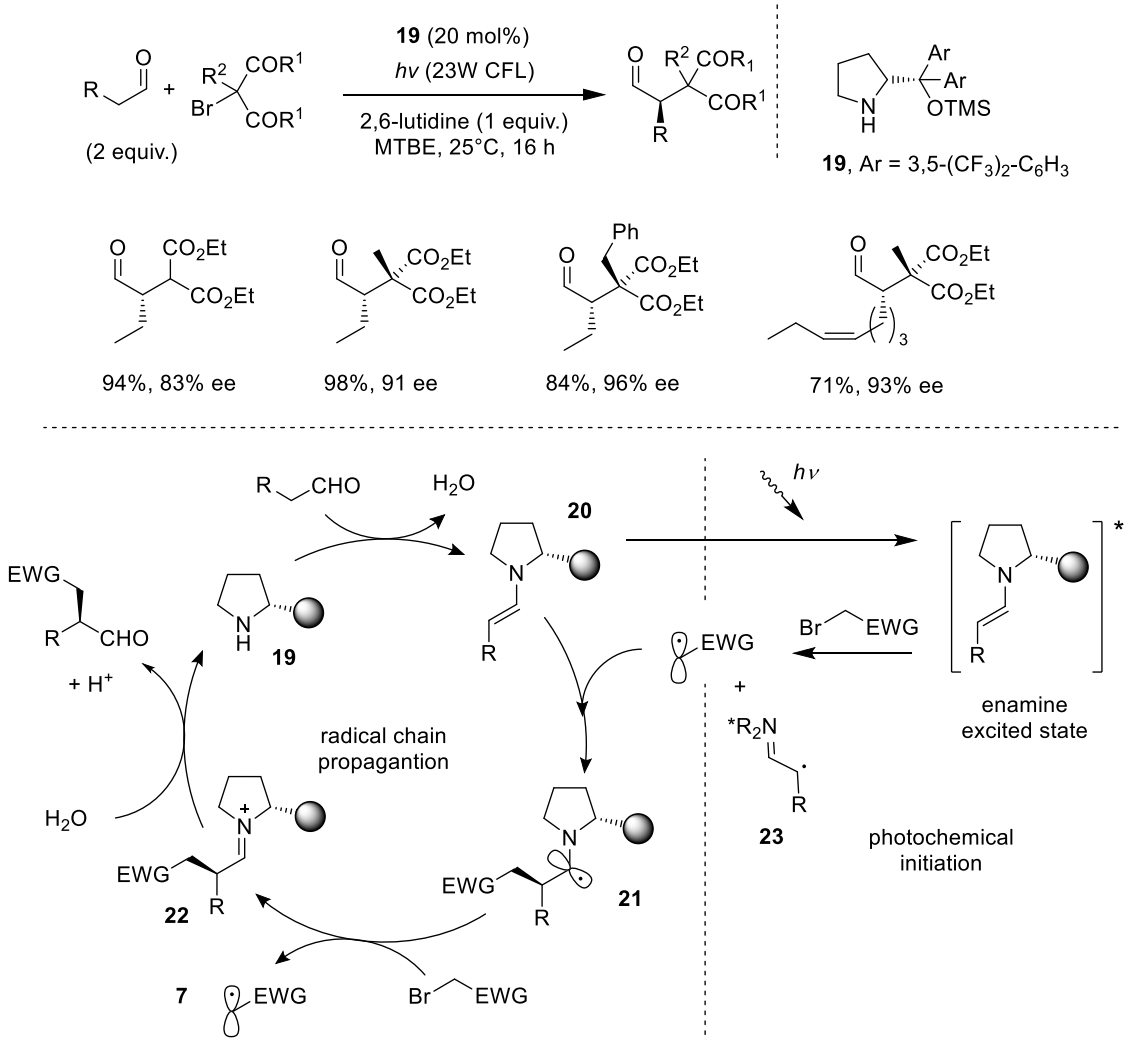



*Scheme 4: EDA complexes to perform the asymmetric photoinduced benzylation of aldehydes realized by Melchiorre.*

The application of visible light photocatalysis has grown incredibly after these early reports and several reviews have been published on this topic.[13]

Ruthenium and iridium complexes having bis-chelating aromatic ligands are by far the most employed photosensitizers due to their suitable and established photophysical properties briefly highlighted before. The drawback of these metal complexes are the high cost of the metal, especially for iridium, due to their limited abundance on earth and their toxicity, in particular for ruthenium. Thus efficient alternative photosensitizers based on earth abundant metal complexes, organic molecules or recyclable materials are of great importance. Simple and cheap, at least compared to Ir or Ru, organic dyes such as eosin Y,[14] mesyl acridinium[15] and more abundant copper[16] or chromium[17] complexes have been reported as photosensitizers.

However only dyes[18] and semiconductors[19] have been applied to the asymmetric organophotocatalytic alkylation of aldehydes with bromo malonates efficiently replacing $Ru(bpy)_2^{2+}$.




*Scheme 5: enamine excited state as photosensitizer for the alkylation of aldehydes.*

In 2015 Melchiorre reported a photo driven variant of this reaction without the presence of any additional photocatalyst (scheme 5).[20] The catalytic enamine **20**, generated from the aldehyde and the Jørgensen catalyst **19**, acts as photosensitizer: its excited state is able to reduce the bromo malonate starting a radical chain process in which the remaining amount of the secondary amine plays the conventional role of organocatalyst. Clearly the fraction of enamine oxidized (**23**) to start the radical chain is subtracted from the amount available for the organocatalytic cycle. Only the Jørgensen derived enamine displays suitable photophysical properties to generate the radical **7** from the alkyl bromides affording the products in good yields. In order to have optimal enantiomeric excesses α-alky-α-bromo malonates must be employed, while in case of non substituted bromo malonates, the excesses are around 80%. Unfortunately the enamine of MacMillan catalyst **6**, that guarantees optimal enantioselectivities for the process, is not a good photosensitizer and only low yields (around 30%) are obtained.

Due to the large availability, abundance, and low toxicity, the use of iron(II) complexes would be attractive for photocatalytic stereoselective reactions. The development of photosensitizers based on iron complexes would also be interesting for application in solar cell devices to convert sunlight into available energy. Also in this fields rare, expensive and toxic ruthenium polypyridine complexes are now widely used.

Iron is just above ruthenium in the periodic table and forms Fe(II)–polypyridine complexes structurally quite similar to those of Ru(II). However the photophysical properties of these complexes are deeply different. The prototypical $[Fe(bpy)_3]^{2+}$ complex displays a metal-to-ligand charge-transfer (MLCT) band in the visible region.[21] The lowest energy excited state is a metal-centered (MC) state, which is formed within a hundred femtoseconds from the MLCT excited states and it is not luminescent, due to fast non-radiative decay to the ground state (ca. 650 ps lifetime).[22] This crucial difference with $[Ru(bpy)_3]^{2+}$ complexes that have excited state lifetimes in the microsecond range, makes Fe(II)–polypyridines not good candidates for dynamic electron-transfer processes. The origin of this unfavorable behaviour is well understood, and is due by the deactivation of $^1$MLCT and $^3$MLCT photoactive excited states by intersystem crossing into low-lying, metal-centred ligand-field states.

Nevertheless, in a pioneering report Ferrere demonstrated that iron(II) polypyridyl complexes act as photosensitizers of $TiO_2$[23] demonstrating ultrafast electron injection. After the publication of our paper, another report of iron based photosensitizers have been described. In this case NHC ligands were employed in order to improve the photophysical properties of the complex.[24]

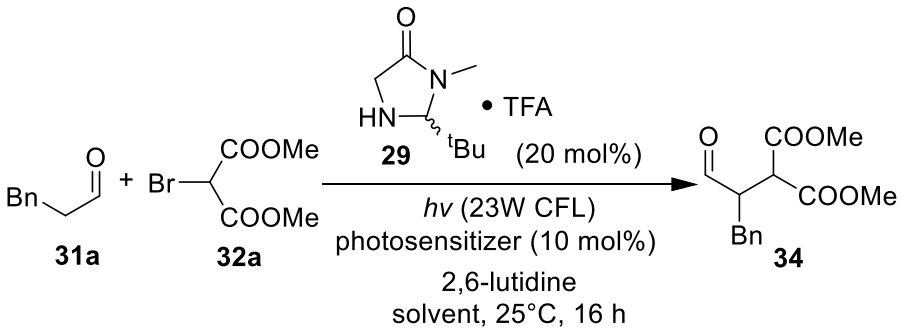
## 2.6.2 Results and discussion

Based on Ferrere precedent and strongly behaving in our intuition, we started to investigate the use of iron(II) polypyridyl complexes as photosensitizers in asymmetric organocatalytic transformations and we choose the α-alkylation of aldehydes with bromo malonates, first reported by MacMillan using $Ru(bpy)_2^{2+}$ as model reaction.

Methyl bromo malonate **31a** and hydrocynnamaldhyde **32a** were chosen as model substrates and several iron salts (10 mol%) were screened starting from the conditions previously reported with $[Ru(bpy)_3]Cl_2$. For the initial screening we used racemic catalyst **29** (20 mol%) due to its easy preparation. After the initial attempts in which we optimized the experimental set-up to efficiently degass the reaction mixture, my colleague Andrea obtained positive results using either iron(II) phenantroline or bypyridine complexes. Using these complexes the product **34** was obtained in high yields. The exclusion of air from the reaction mixture is crucial as its presence inhibits the photocatalytic activity of the iron(II) complex and reduced yields or no reaction are observed. The screening of various solvents, including MeCN and DMSO, revealed that the initially chosen DMF gave the best results.

We then investigated the enantioselective transformation using the chiral catalysts represented in table 2. MacMillan catalysts as salts with a Brønsted acid cocatalyst proved superior to Jørgensen catalyst and amine **H**. In the absence of the acid cocatalyst, low yields were obtained (table 2, entry 1). Among MacMillan catalysts, **A** was the only one that allowed to reach optimal levels of enantioselectivities. The use of a strong acid such as TfOH was necessary to have a good yield near to 80%. The significant reduction of the reaction yield observed changing from racemic catalyst **29** to substituted active catalysts is due to the increased hindrance of the derived enamines that slightly hampers the reaction with the generated radical but efficiently transfers the enantiomeric information.

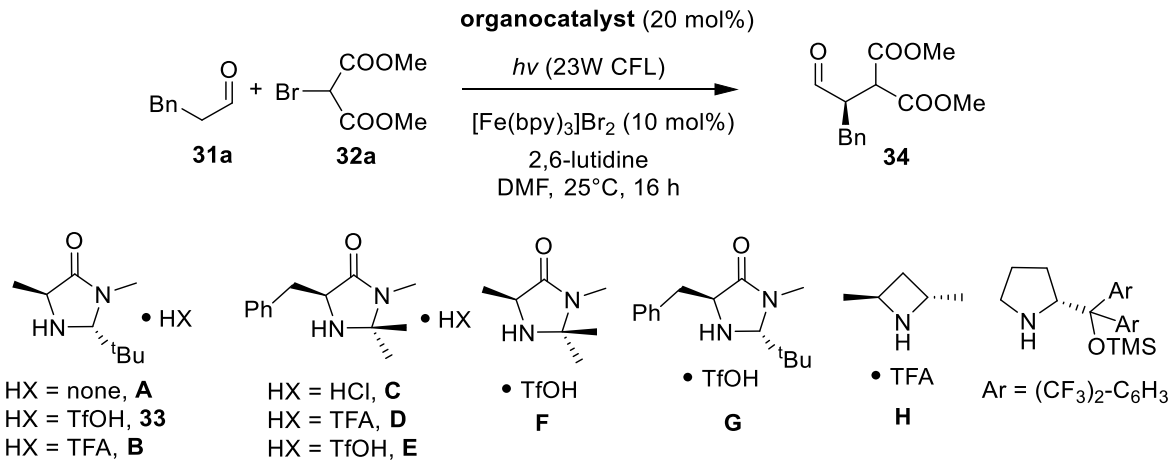
In order to increase the yield of the process, we evaluated the effect that the amount of photosensitizer and the concentration of the reaction mixture may have (table 3). We found that increasing the concentration of the limiting reagent bromomalonate from 0.1 M to 0.5 M gave a slightly increased yield, that could be further enhanced to 89% by decreasing the amount of iron(II) salt to 2.5 mol%. Further reduction to 1 mol% lead to a decrease in the reaction yield.




| Entry[a] | Photosensitizer | solvent | Yield **4** (%)[b] |
|---|---|---|---|
| 1 | $FeBr_2$ | DMF | 0 |
| 2 | $[Fe(bpy)_3]Br_2$ | DMF | 99 |
| 3 | $[(PPh_3)_2Fe(NO_2)_2]$ | DMF | 5 |
| 4 | $[Fe(phen)_3]Cl_2$ | DMF | 89 |
| 5 | $[Fe(phen)_3](PF_6)_2$ | DMF | 92 |
| 6 | $[Fe(bpy)_3]Br_2$ | DMF | 99 |
| 7 | $[Fe(bpy)_3]Br_2$ | DCE | 11[c] |
| 8 | $[Fe(bpy)_3]Br_2$ | $CH_3CN$ | 42[c] |
| 9 | $[Fe(bpy)_3]Br_2$ | DMF/$H_2O$ (9/1) | 88 |

[a] The reactions were performed at r.t. with 0.1 mmol of bromomalonate (**32a**), 2 equiv of aldehyde (**31a**) and 2 equiv of 2,6-lutidine, in the presence of 20 mol% of organocatalyst **29** and 10 mol% of photosensitizer in the indicated solvent (0.1 M), and stopped after 16 h. [c] Determined by GC-MS analysis. [c] Reaction stopped after 4 h.

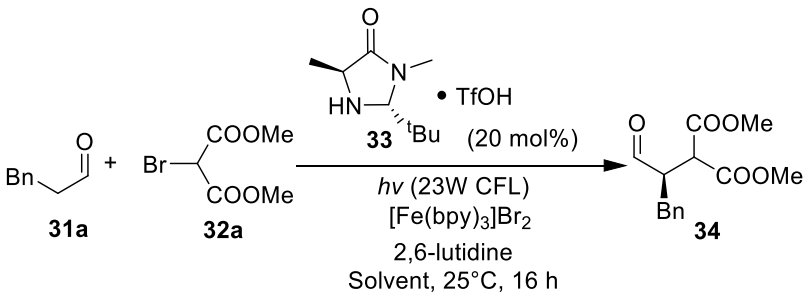
*Table 1. Effect of photosensitizer nature and of solvent..*




| Entry[a] | Organocatalyst | Yield **34** (%)[b] | ee **34** (%)[c] |
|---|---|---|---|
| 1 | **A** | 29 | 93 |
| 2 | **3** | 79 | 93 |
| 3 | **B** | 52 | 73 |
| 4 | **A**+LutTFA[d] | 77 | 81 |
| 5 | **A**+LutTfOH[e] | 65 | 93 |
| 6 | **C** | 32 | 89 |
| 7 | **D** | 63 | 62 |
| 8 | **E** | 73 | 83 |
| 9 | **F** | 76 | 58 |
| 10 | **G** | 54 | 36 |
| 11 | **H** | 28 | n.d. |
| 12 | **I** | 20 | -70 |

[a] The reactions were performed at r.t. with 0.1 mmol of bromomalonate (**32a**), 2 equiv of aldehyde (**31a**) and 2 equiv of 2,6-lutidine, in the presence of 20 mol% of organocatalyst and 10 mol% of $[Fe(bpy)_3]Br_2$ in DMF (0.1 M), and stopped after 16 h. [b]Determined by GC-MS analysis. [c] Determined by HPLC analysis on chiral stationary phase. [d] Lutidinium trifluoroacetate. [e]Lutidiniumtriflate.

*Table 2. Effect of organocatalyst on the enantioselective reaction.*



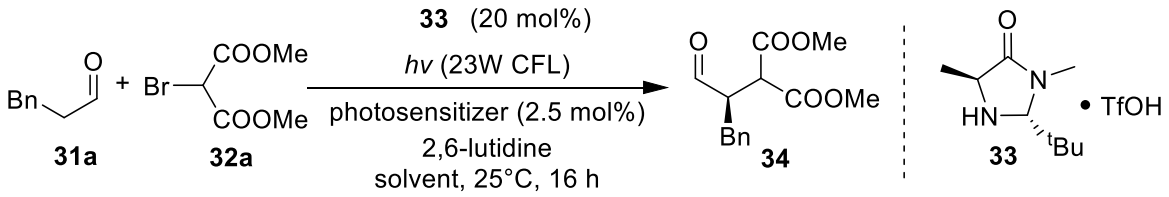

| Entry[a] | Photosensitizer (mol%) | Concentration of **2a** (M) | Yield **4** (%)[b] | Ee **4** (%)[c] |
|---|---|---|---|---|
| 1 | 10 | 0.1 | 79 | 93 |
| 2 | 10 | 0.5 | 81 | 92 |
| 3 | 5 | 0.5 | 74 | 93 |
| 4 | 5 | 0.2 | 61 | 93 |
| 5 | 2.5 | 0.5 | 89 | 93 |
| 6 | 1 | 0.5 | 70 | 92 |

[a] The reactions were performed at r.t with 0.1 mmol of bromomalonate (**32a**), 2 equiv of aldehyde (**31a**) and 2 equiv of 2,6-lutidine, in the presence of 20 mol% of organocatalyst and of the reported percentage of $[Fe(bpy)_3]Br_2$ in DMF. The reaction was stopped after 16 h. [b] Determined by GC-MS analysis. [c] Determined by HPLC analysis on chiral stationary phase.

*Table 4. Effect of concentration and iron catalyst loading.*

The solvent and the iron salt that had afforded the best results in the initial screening with racemic catalyst **29** were tested again under the optimized conditions, confirming the established reaction protocol. It is worth noting that the enantiomeric excess remains unalterated in all these different conditions highlighting that it depends only on the MacMillan catalyst salt.

No decomposition of the photosensitizer was observed at the end of the reaction, as monitored by the absorption band in the visible region (Figure 2, page 16).



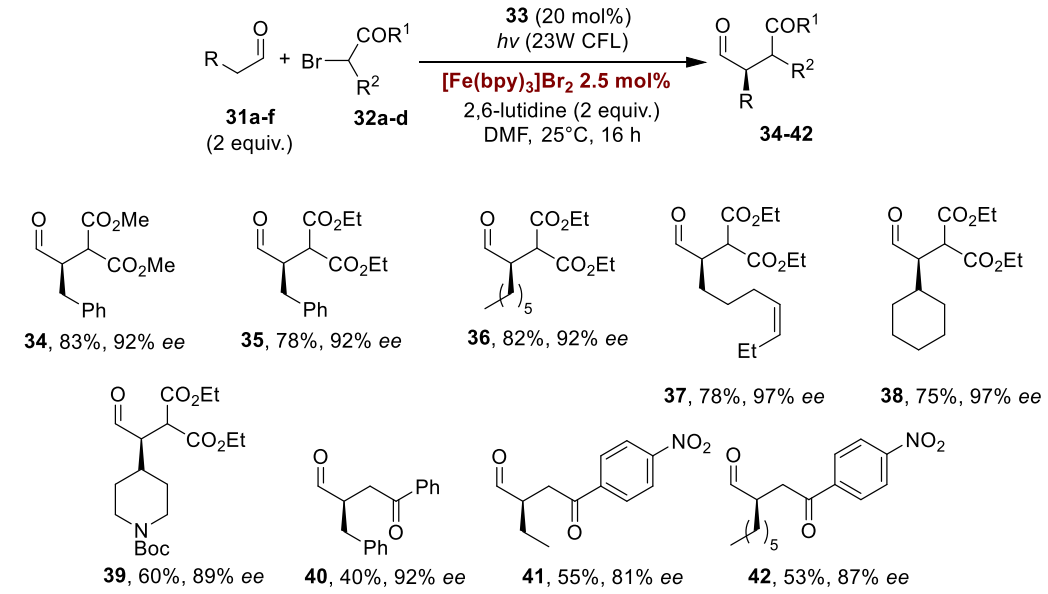

| Entry[a] | Photosensitizer | Solvent | Yield (%)[b] | ee (%)[c] |
|---|---|---|---|---|
| 1 | $[Fe(bpy)_3](PF_6)_2$ | DMF | 63 | 92 |
| 2 | **$[Fe(bpy)_3]Br_2$** | **DMF** | **89 (83)** [d] | **93** |
| 3 | $[Fe(bpy)_3]Br_2$ | $CH_3CN$ | 19 | n.d. |
| 4 | $[Fe(bpy)_3]Br_2$ | DMSO | 27 | 93 |

[a] The reactions were performed at r.t with 0.1 mmol of bromomalonate (**32a**), 2 equiv of aldehyde (**31a**) and 2 equiv of 2,6-lutidine, in the presence of 20 mol% of **3** and 2.5 mol% ofiron catalyst in the reported solvent (0.5 M). The reaction was stopped after 16 h. [b] Determined by GC-MS analysis. [c] Determined by HPLC analysis on chiral stationary phase. [d] Isolated yield after chromatographic purification.

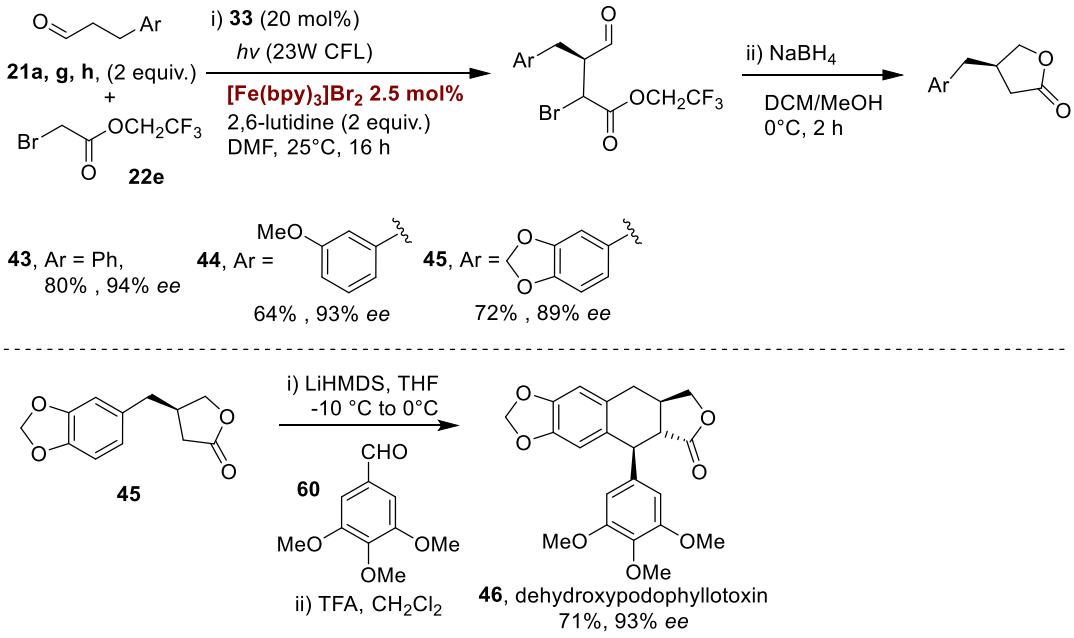
*Table 4. Further iron salts and solvents screened under the so far optimized conditions*

With the optimized conditions on hand we explored the scope of the transformation with various aldehydes and bromo derivatives (scheme 6). As in the case of the literature precedents in which ruthenium, dyes or semiconductors had been employed, bromomalonates and bromoacetophenones were suitable precursors to efficiently generate electrophilic radicals. The scope regarding the aldehydes is broad as both alkylic and aromatic substituents are tolerated, as well as various functional groups such as amines and alkenes. In particular no side reactions were observed with aldehydes bearing alkene functional groups.

α-Bromo esters are not enough activated substrates to generate the corresponding radicals under photocatalytic conditions. However the introduction of a strong electronwithdrawing group on the alcoholic side chain, such as trifluoroethanol, of the ester affords suitable substrate **22e** to be engaged in the stereoselective alkylation of aldehydes. Indeed the addition of bromo ester **22e** to hydrocinnamic aldehydes **21a,g,h** (see experimental part for preparation) afforded the corresponding aldehydes products in good to complete conversions. These products are not perfectly stable during chromatographic separation, so we reduced them in situ to afford lactons **43-45**, key intermediates for the synthesis of biologically active compounds.[25]




*Scheme 6. Scope of the stereoselective alkylation promoted by $[Fe(bpy)_3]Br_2$.*




*Scheme 7. Preparation of enantioenriched lactones via alkylation of aldehydes and synthesis of dehydroxypodophyllotoxin.*

The lacton **45** was transformed into the natural product **46** by a straightforward transformation: formation of the enolate and its diastereoselective addition to aldehyde **60** afforded the secondary alcohol intermediate that was successfully cyclized by a Friedel Crafts reaction as illustrated in scheme 7.[26]

As the excited state of $[Fe(bpy)_3]Br_2$ is extremely short lived and moreover it does not emit, we could not perform Stern Volmer experiment to measure the quenching of the excited state by the action of one reactant, in particular bromo malonate, to prove that the alkyl radical was formed by SET with the photosensitizer excited state.

Nevertheless, we investigated ground- and excited state interactions between the photosensitizer $[Fe(bpy)_3]Br_2$ and each component of the reaction mixture (figure 2). As it evident from the overlapped spectra in figure 2, the absorption band in the visible region of the $[Fe(bpy)_3]Br_2$ complex (figure 2, red line) is not affected by the reagents and, as previously stated, does not change at the end of the irradiation (figure 2, blue line). In figure 3 are depicted the visible adsorption bands of the single reactants.

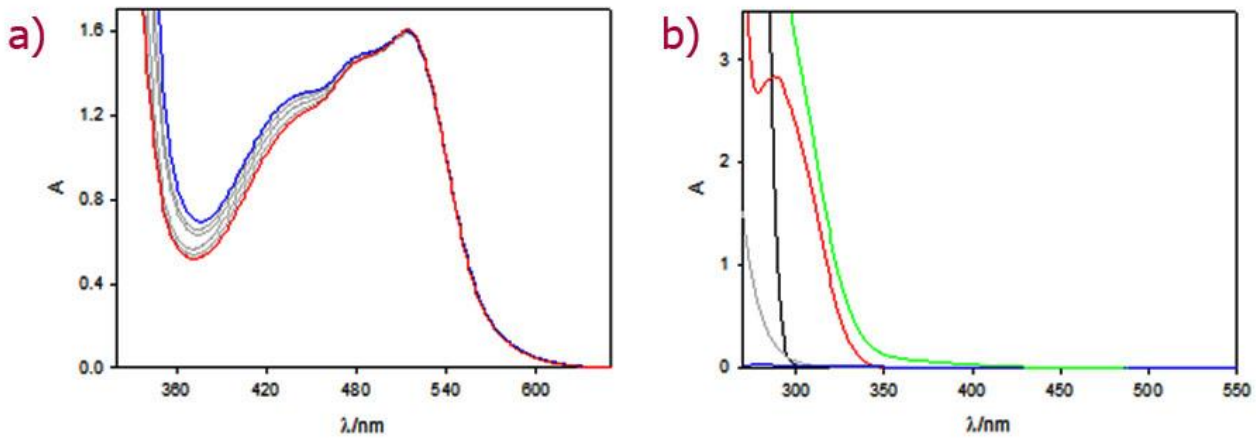



*Figure 2.*

a) *Absorption spectra of the reaction mixture at different times. Reaction mixture composed of: $[Fe(bpy)_3]Br_2$1.2 × $10^{-3}$ M, 2,6-lutidine 1 M, dimethyl bromomalonate* ***22a*** *0.5 M, 3-phenylpropanal* ***21a*** *1 M and MacMillan catalyst* ***33*** *0.1 M in DMF solution irradiated for 0 min (red solid line), 30 min, 80 min, 130 min, 240 min (grey solid lines) and 360 min (blue solid line).*

b) *Absorption spectra of 2,6-lutidine 1 M (black solid line), dimethyl bromomalonate2a 0.5 M (grey solid line), 3-phenylpropanal 31a 1 M (red solid line), MacMillan catalyst 33 0.1 M (blue solid line) and complete reaction mixture without [Fe(bpy)3]Br2 (green solid line) in DMF. The amount of the species in solution is the same used during the photoreaction.*

Due to the very short lifetime of the lowest energy excited state of the iron(II) complex, we used femtosecond laser absorption spectroscopy to monitor the possibility of excited state interactions that

could reveal its action as photosensitizer. Upon irradiation at 510 nm of a 5.7 x $10^{-4}$ M solution of $[Fe(bpy)_3]Br_2$ in DMF, the characteristic bleaching of the MLCT absorption band was observed at very short time delay (t = 1.2 ps, Figure 3a). This transient then decays monotonically to the baseline. Plot of the absorbance change (ΔA) at 535 nm as a function of time resulted in a mono exponential decay with a lifetime of 570 ps (Figure 3b, black line), very similar to the literature reported values for the ligand field excited state (MC). Upon addition of bromomalonate (in the range 0.5-6.8M) or enamine **59** obtained from (5*S*)-2,2,3-trimethyl-5-phenylmethyl-4-imidazolidinone (0.06 M), no appreciable changes in the transient absorption feature were measured (Figure 3b).

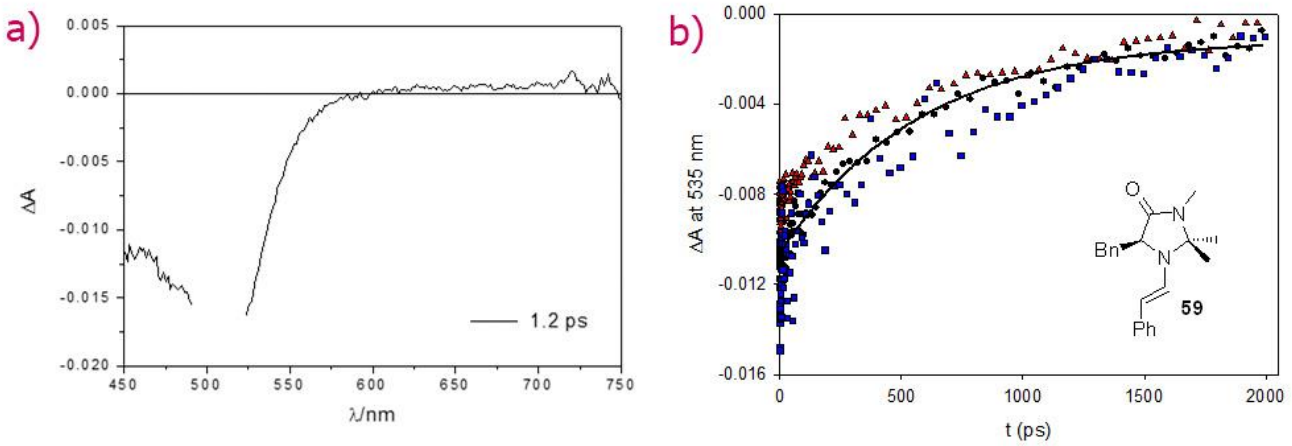


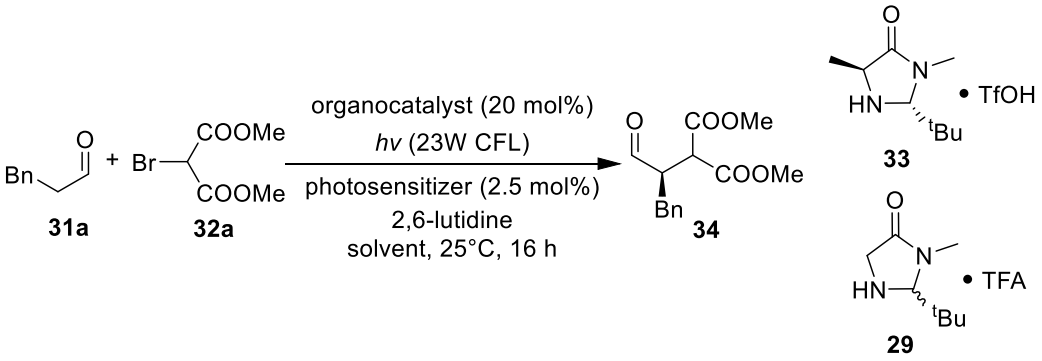

*Figure 3.*

a) *Transient absorption spectrum at 1.2 ps time-delay obtained by ultrafast spectroscopy (excitation at 510 nm) of [Fe(bpy)3]Br2(concentration 5.7 x 10-4 M in DMF).*

b) *Exponential decay (upon laser excitation at 510 nm) of absorption changes at 535 nm of: [Fe(bpy)3]Br2(5.7 x 10-4 M, black circle), [Fe(bpy)3]Br2+(5.7 x 10-4 M) with dimethyl bromomalonate (22a) 0.5 M (red triangle) and [Fe(bpy)3]Br2 (5.7 x 10-4 M) with enamine 59 0.06 M (blue square) in DMF stirred solution. The amount of dimethyl bromomalonate (22a)in solution is the same used to perform the photoreaction. The black solid line is the fitting curve of [Fe(bpy)3]Br2exponential decay: the lifetime obtained from the fitting in 570 ps.*

As CLF lamp contains UV emission (see figure S14 in the experimental section), we have investigated if this portion of radiation was responsible of the reaction, by using selected wavelength. Melchiorre reported that the enamine of the aldehyde absorbs the near UV component of CFL lamp that is responsible for the action of the enamine as photosensitizer. However enamine derived from MacMillan imidazolinone **33** acts inefficiently as photosensitizers in affording around 30% product yield,[20] while with our protocol the yields are up to 80%. Indeed, performing the reaction without $[Fe(bpy)_3]Br_2$ under CFL irradiation we too observed a low yield of product (table 5, entry 9) in case

**33** was employed, while using less hindered racemic **29** a very high yield was achieved (table 5, entry 1).




| Entry [a] | Photosensitizer (mol%) | Cat. | Light | Time (h) | Yield **4** (%)[b] | ee **4** (%)[c] |
|---|---|---|---|---|---|---|
| 1 | - | **19** | YES (23W CFL) | 16 | 95[d] | - |
| 2 | - | **19** | YES (λ>420, 250W) | 6 | 0 | - |
| 3 | $[Fe(bpy)_3]Br_2$ (0.004 mol%) | **19** | YES (λ >420, 250W) | 10 | 82 | |
| 4 | $[Fe(bpy)_3]Br_2$ (0.25 mol%) | **19** | YES (λ >420, 250W) | 6 | 87 | - |
| 5 | $[Fe(bpy)_3]Br_2$ (0.25 mol%) | **3** | YES (λ >420, 250W) | 6 | 49 | 93 |
| 6 | $[Fe(bpy)_3]Br_2$ (2.5 mol%) | **3** | YES (23W CFL) | 16 | 89 | 93 |
| 7 | $[Fe(bpy)_3]Br_2$ (2.5 mol%) | **3** | NO | 16 | 0 | - |
| 8 | - | **3** | YES (λ >420, 23W CFL) | 16 | 0 | - |
| 9 | - | **3** | YES (23W CFL) | 16 | 32[d] | 93 |

[a] The reactions were performed at r.t with 0.2 mmol of bromomalonate (**22a**), 2 equiv of aldehyde (**21a**) and 2 equiv of 2,6-lutidine, in the presence of 20 mol% of organocatalyst and of the reported catalytic amount of iron complexes in DMF (0.5 M). The reaction was stopped after the reported time. [b] Determined by GC-MS analysis. [c] Determined by HPLC analysis on chiral stationary phase.[d] As reported by Melchiorre photoexcited state of enamines are able to transfer electron to bromomalonates starting a radical-chain reaction[20] under not filtered CFL light. Better yields were obtained with the catalyst **29** are due to the less sterical hindrance. The result obtained with the catalyst **33** was also reported by Melchiorre.

*Table 5. Light effect.*

Instead when the reaction mixture was irradiated with only visible light, applying a filter that selected λ > 420 nm, the reaction did not proceed in the absence of the photosensitizer $[Fe(bpy)_3]Br_2$ using either **29** or **33** (table 5, entries 2 and 8), in agreement with the fact that the reaction mixture does not absorb light at this wavelengths (Figure 2b). Using the same filter the reaction occurs in the presence of

$[Fe(bpy)_3]Br_2$ (Table 5, entries 3-5). On the other hand, in the presence of the iron sensitizer and in the absence of light, the reaction does not proceed. (see table 5, entries 7, and EPR experiments).
In order to prove the formation of radicals species under the combined action of light and $[Fe(bpy)_3]Br_2$ we undertook the study of the formation of radicals with EPR, in the presence of a radical trap.[27] The spin trap experiments were performed in the presence of PBN. We initially fully characterized the spin adducts by irradiating the reaction mixture with light containing also near UV (λ >310 nm). Actually, irradiation at λ >310 nm of a deoxygenated DMF solution containing bromomalonate **22a** (0.5 M), $[Fe(bpy)_3]Br_2$ (10 mol%) and PBN (*N-tert*-butyl-α-phenylnitrone) (0.1 M), resulted in a very good EPR signal consisting of a characteristic doublet of triplets (Figure 5a).

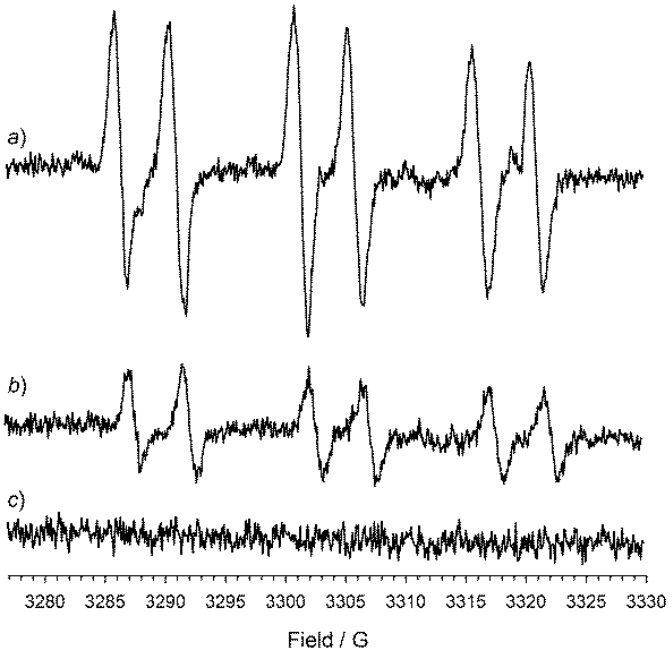
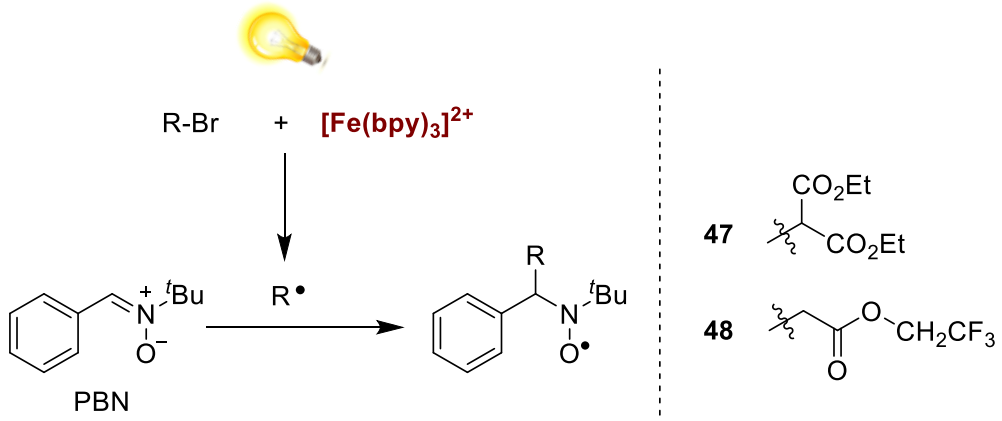



*Figure 5. EPR spectra of spin adduct **47** generated in DMF in the presence of dimethyl bromomalonate **22a** (0.5 M) and PBN (0.1 M) as the spin trap at room temperature. Reaction conditions: a) $[Fe(bpy)_3]Br_2$(10 mol%), irradiation with UV-visible light (λ>320 nm); b) $[Fe(bpy)_3]Br_2$(10 mol%), irradiation with visible light (λ>420 nm); c) $[Fe(bpy)_3]Br_2$(10 mol%) no irradiation.*

The spectrum was attributed to spin adduct **47** (Scheme 8), resulting from addition of malonate alkyl radical to PBN, as suggested by the values of the EPR parameters (aN = 14.95 G, aH = 4.75 G, g = 2.0057) which are typical for PBN adducts with alkyl radicals having carbonyl groups in α-position.[28]
We then repeated the same experiment by employing visible light (λ > 420 nm), thus miming the synthetic reaction conditions. Also in this case the signal due to the radical adduct **47** was clearly detected although the intensity of the signals was ca. three times weaker with respect to that recorded in the presence of UV-visible light (figure 5b). Blank experiment performed with visible light in the

absence of $[Fe(bpy)_3]Br_2$ still gave rise to a weak EPR signal of the adduct **47** (about one half compared to the previous spectrum), suggesting that visible light is able to promote the formation of alkyl radicals also in the absence of $[Fe(bpy)_3]Br_2$. However, the weak intensity of this signal confirms that the formation of alkyl radical is a less efficient process in the absence of photosensitizer. No signals were instead observed in the absence of light or after irradiation of a solution containing only the photosensitizer and the spin trap (figure 5c). A similar trend was also observed in the presence of bromoester **22e** (figure 6). The PBN-adduct was characterized by the following EPR parameters: aN = 14.85 G, aH = 5.55 G, g = 2.0057. In this case, however, the intensities of EPR spectra were lower if compared to those observed in the spectra recorded with bromomalonate **22a** under the same experimental conditions. This indicates that the formation of the less stable alkyl radical from **22e** is more difficult.[29]




*Scheme 8. Radical trapping with PBN for EPR analysis.*

The EPR experiments showed the excited state of $[Fe(bpy)_3]^{2+}$ is able to generate the required radicals from the alkyl bromides, even if the process is not very efficient so that the efficiency of quenching is so low that cannot be detected. The evidence of a radical mechanism is further confirmed by the complete shut down of the alkylation reaction in the presence of variable amount (20 mol% and 100 mol%) of TEMPO.

The high efficiency of the alkylation reaction vs the inefficient generation of the radicals suggests that a radical chain process, in which the photochemical event is only the starting step, may be operating.[20,30]

An experiment with light turned alternatively on and off showed (Figure 7) that the reaction proceeds also during the dark periods, even if to a lower reaction rate. Moreover irradiation of the reaction mixture for an initial induction period, followed by continuing the reaction in the total absence of light revealed that the reaction proceeds to almost 50% yield in 7 h, while the control experiment continuously irradiated reached 90 % yield in the same time. These experiments prove that a very efficient radical chain process in which the photocatalytic event serves as initiator and to keep the level of radicals constant renewing the radical chain processes and avoiding that the reaction rate slowly decreases to zero.

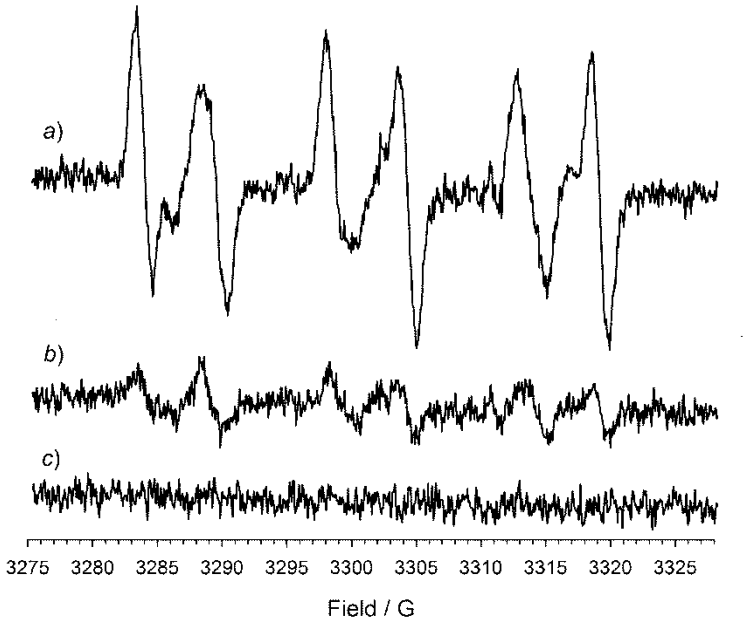



*Figure 6. EPR spectra of spin adduct* ***48*** *generated in DMF in the presence of bromo ester* ***22e*** *(0.5 M) and PBN (0.1 M) as the spin trap at room temperature (microwave power, 5 mW; modulation frequency, 100 kHz; modulation amplitude, 0.4 G). Reaction conditions: a) $[Fe(bpy)_3]Br_2$ (10 mol %), irradiation with UV-visible light (λ>320 nm); b) $[Fe(bpy)_3]Br_2$ (10 mol%), irradiation with visible light (λ>420 nm); c) $[Fe(bpy)_3]Br_2$ (10 mol%) no irradiation.*

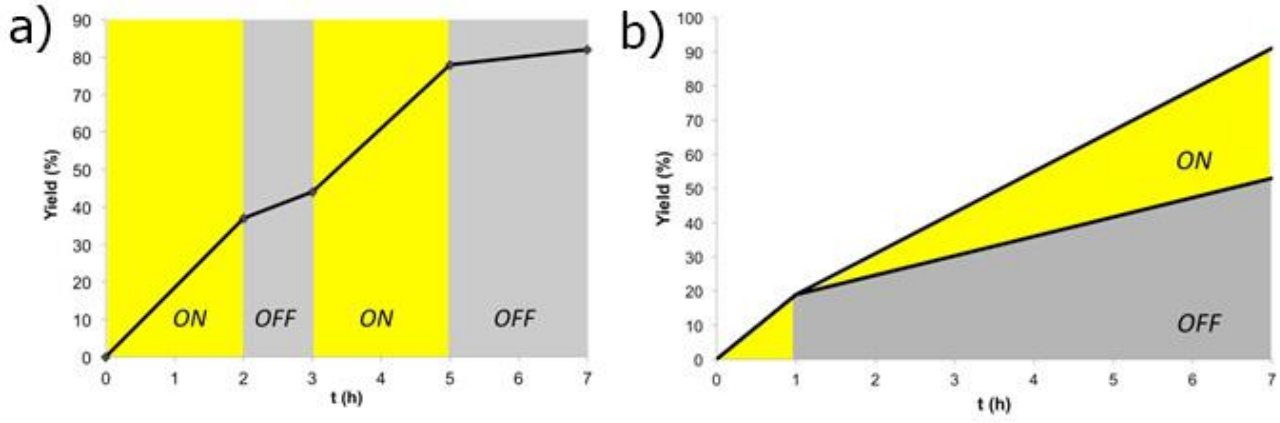



*Figure 7. Light/dark effect.*

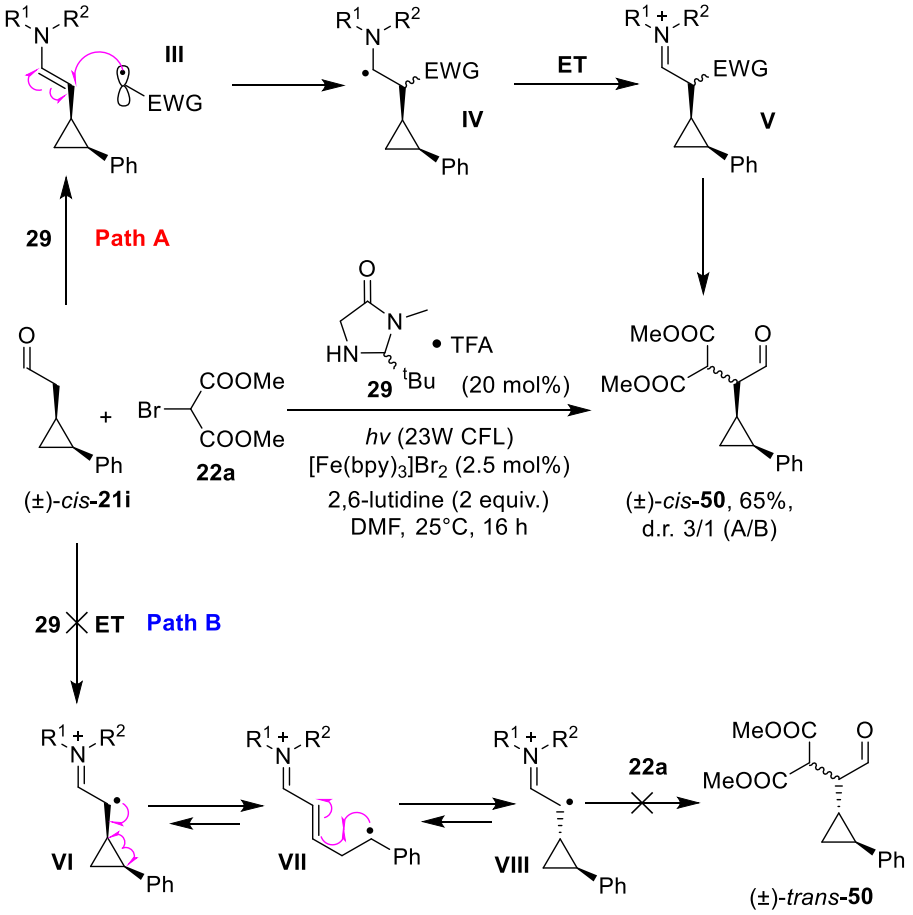
- ***a)*** *Successive intervals of irradiation and dark periods. The reaction was performed at r.t with 0.2 mmol of bromomalonate (**2a**), 2 equiv of aldehyde (**1a**) and 2 equiv of 2,6-lutidine, in the presence of 20 mol% of **3** and 2.5 mol% of [Fe(bpy)$_3$]Br$_2$ in DMF (0.5 M). Yield was determined by GC-MS analysis from an aliquot of the reaction mixture.*
- ***b)*** *Two separate but identical reaction were simultaneously performed. The first one was irradiated for 1h and it was kept in the dark for 6 hours. The second one was irradiate for 6 hours. The reactions were performed at r.t with 0.2 mmol of bromomalonate (**2a**), 2 equiv of aldehyde (**1a**) and 2 equiv of 2,6-lutidine, in the presence of 20 mol% of **3** and 2.5 mol% of [Fe(bpy)$_3$]Br$_2$ in DMF (0.5 M). Yield was determined by GC-MS analysis from an aliquot of the reaction mixture.*

We rationalized two possible radical mechanism that could be operating: in the first one the *Fe(II) reduced the bromomalonate forming the radical **III** and Fe(III); the second hypothesis was that Fe(II) was able to coordinate both of the reaction partners (enamine and alkyl bromide) and upon light driven excitation it was acting as a mediator for an internal SET transfer from the enamine to the bromide forming a radical cation / radical anion ion pair similar to the one that operates in Melchiorre EDA complex.[12] In order to get a better insight on the reaction mechanism we performed the reaction with radical clock-containing aldehydes **22i**.

Photoalkylation of *cis*-cyclopropane-substituted aldehyde **(±)-*cis*-21i** with dimethyl bromomalonate (**22a**) was performed to demonstrate that reaction proceeded through a traditional enamine catalysis pathway, with the EWG stabilized carbon-centred radical (**III**) species adding to the generated enamine (**II**) as the propagation step (Path A).

If the reaction proceeded through a radical-cation pathway (Path B), the cyclopropylcarbinyl radical (**VI**) formed after electron transfer process should undergo fast ring-opening (**VII**) and ring closing prior to C-C bond formation leading to the thermodynamically more stable intermediate (**VIII**) and consequentially to the product **(±)-*trans*-50**.

When **(±)-*cis*-21i** was subjected to the photocatalytic alkylation protocol with bromide **22a** the **(±)-*cis*-50** product was exclusively formed, excluding the reaction pathway B and confirming the reaction pathway A.




*Scheme 9. Radical clock experiment to establish the reaction mechanism.*

Therefore, we propose that the reaction is proceeding through a radical chain propagation pathway. The addition of the radical **III** to enamine **II** is the enantio-discriminating step. The $[Fe(bpy)_3]Br_2$ photosensitizer acts as a reductant for initiating the chain mechanism, as proposed in Figure 8. The ability of the amidoalkyl radical **IV** to behave as strong reducing agent[31] would induce the reduction of bromomalonate, regenerating the radical **III**. In this mechanistic picture, the reaction proceeds through a radical chain propagation, in which the $[Fe(bpy)_3]Br_2$ serves as initiator.[32]

An atom transfer mechanism, in which the α-aminoalkyl radical is abstracting a bromine atom, has been also suggested as key step for ruthenium catalyzed reaction. In this alternative mechanism, the α-amidoalkyl radical after abstraction of the bromine is forming an α-bromo amine adduct, that is decomposed to the iminium ion pair. The [Fe(bpy)3]Br2 is not decomposed or oxidized during the

reaction. As possible steps for the reduction of Fe(III) to Fe(II) we propose that the α-aminoalkyl radical produced after the addition of the malonate, or the oxidation of sacrificial enamine are the compelling reductants.

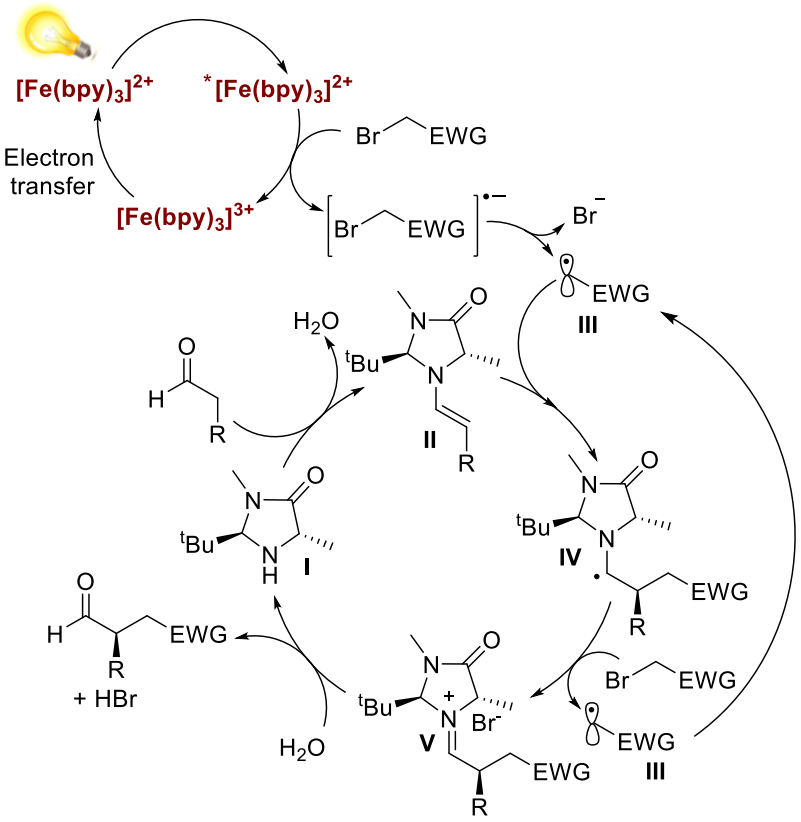



*Figure 8. Proposed reaction pathway.*

### 2.6.3 Conclusions

We discovered another class of valuable photosensitizers based on first-row transition metals in the arena of light-activated catalysis for synthetic transformations. To our knowledge, this work represents the first report of the use of iron(II) polypyridine complexes being applied in stereoselective photocatalysis. Not only this work opens new perspectives in the area of asymmetric transformations, but raises new questions about the use of cobalt and manganese complexes as alternative photosensitizers based on earth-abundant metals. Further synthetic applications in photocatalysis of iron complexes, and other first row metals will be reported in due course.

### 2.6.4 Contributions

Dr. Andrea Gualandi was involved in the discovery and development of the photochemichal reaction. I contributed to the synthetic part of the project once it had been optimized by Andrea. Marianna Marchini, Mirco Natali and Prof. Paola Ceroni designed and performed the photophysical measurements. Prof. Marco Lucarini designed and performed the EPR experiments. Prof. Pier Giorgio Cozzi conceived and directed the project.
Prof. Sandro Gambarotta is acknowledged for sharing unpublished result and for a fruitful discussion.

## 2.6.5 Experimental section

Table of contents:

**General methods.** $^{1}H$ NMR spectra were recorded on Varian Gemini 200, Varian Mercury 400 spectrometers. Chemical shifts are reported in ppm from TMS with the solvent resonance as the internal standard (deuterochloroform: $\delta$ = 7.27 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = duplet, t = triplet, q = quartet, dd = double duplet, dt = double triplet, bs = broad signal, pd = pseudo duplet, pt = pseudo triplet, m = multiplet), coupling constants (Hz). $^{13}C$ NMR spectra were recorded on Varian Gemini 200, Varian MR400 spectrometers. Chemical shifts are reported in ppm from TMS with the solvent as the internal standard (deuterochloroform: $\delta$= 77.0 ppm).GC-MS spectra were taken by EI ionization at 70 eV on a Hewlett-Packard 5971 with GC injection. LC-electrospray ionization mass spectra (ESI-MS) were obtained with Agilent Technologies MSD1100 single-quadrupole mass spectrometer. They are reported as: *m/z* (rel. intense). Chromatographic purification was done with 240-400 mesh silica gel. Purification on preparative thin layer chromatography was done on Merck TLC silica gel 60 $F_{254}$ and on Merck TLC aluminum oxide 60 $F_{254}$ neutral. Determination of diastereomeric ratio and of enantiomeric excess was performed on Agilent Technologies 1200 instrument equipped with a variable wave-length UV detector (reference 420 nm), using Daicel Chiralpak® columns (0.46 cm I.D. x 25 cm) and HPLC grade isopropanol and *n*-hexane as eluting solvents. Optical rotations were determined in a 1 mL cell with a path length of 1 dm ($Na_D$ line).

**Materials**. Anhydrous solvents were supplied by Aldrich in Sureseal® bottles and were used as received avoiding further purification. Reagents were purchased from Aldrich and used without further purification unless otherwise stated. The aldehydes and 2,6-lutidine were supplied by Aldrich and used after distillation.

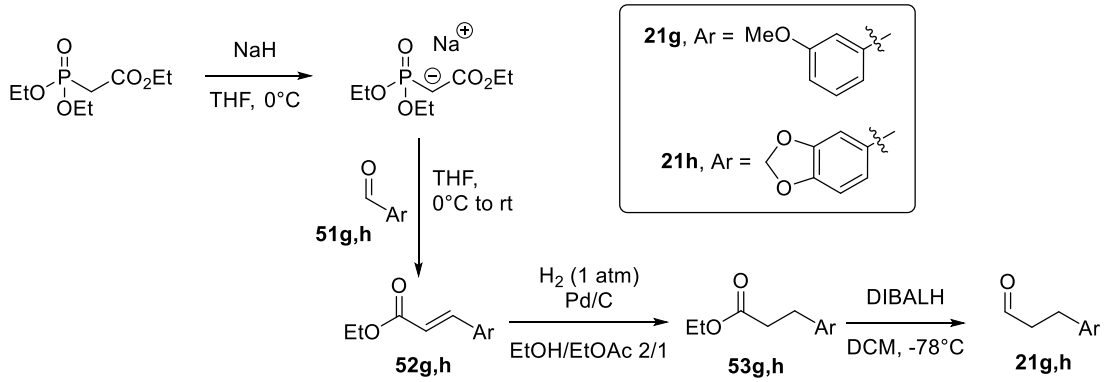
2-Cyclohexylacetaldehyde (**1d**),[33] *tert*-butyl 4-(2-oxoethyl)piperidine-1-carboxylate (**1e**),[34] 2-bromo-1-(4-nitrophenyl)ethan-1-one (**2d**),[35] 2',2',2'-trifluoroethyl 2-bromoacetate (**2e**),[36] (2*R*,5*S*)-2-*t*-butyl-3,5-dimethylimidazolin-4-one hydrochloride[37] and iron complexes[38] were prepared according to literature procedures.

**Synthesis of catalyst 33**

Macmillan catalyst (2*R*,5*S*)-2-*t*-butyl-3,5-dimethylimidazolin-4-one monohydrochloride (321 mg, 1.30 mmol) was dissolved in $NaHCO_3$ aq. sat. solution (4 mL) inside a separator funnel and the aqueous layer was extracted with $CHCl_3$ (5x 5 mL). The collected organic layers were dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. The resulting oil was dissolved in dry $Et_2O$ (5 mL) and cooled to 0°C. TfOH (1.9 mmol, 167 µL) was added dropwise under stirring and a white solid precipitated. After 10 min the solution was filtered on a Gooch septum and the solid was washed with $Et_2O$ (2.5 mL) and pentane (10 mL), recovered and dried under vacuum to furnish **3** (358 mg, 1.12 mmol, 86% yield) as white solid.

The same procedure, using TFA instead of TfOH, was used to obtain the trifluoroacetic salt of catalyst**.**

**Synthesis of aldehydes 31g,h**




**General procedure for homologation reaction.**

**52g:** To a NaH (60% wt dispersion in mineral oil, 332 mg, 8.3 mmol) suspension in THF (5 mL) at 0°C under nitrogen atmosphere, a solution of triethylphosphonoacetate(1.6 mL, 8.3 mmol) in THF (10 mL) was added dropwise over 10 min. After 30 min a solution of 3-methoxy benzaldehyde (**51g**, 1.0 mL, 8.2 mmol) in THF (10 mL) was added dropwise over 10 min. The mixture is allowed to warm to rt overnight. Water (5 mL) was added and the organic solvent was evaporated under reduced pressure. The residue was extracted with AcOEt (3x25 mL). The collected organic phases are dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to afford **52g** (1.60 g, 7.8 mmol, 95% yield) as a yellowish sticky solid. The compound was used in the next step without further purification. Spectroscopic properties were according to those reported in literature.[39]

**52h** was prepared according the protocol for **52g**, using piperonal **51h**[40] (998 mg, 6.65 mmol) as starting material. **52h**(1.23 g, 5.6 mmol, 85% yield) was obtained as a white solid and used in the next step without further purification. Spectroscopic properties were according to those reported in literature.[S41]

**General procedure for the hydrogenation reaction.**

**53g:** To a solution of **52g** (1.6 g, 7.8 mmol) in EtOH/EtOAc (2/1 ratio, 12 mL), 10% wt Pd/C (5.0% wt, 80 mg) was added. The reaction flask evacuated, filled with hydrogen (1 atm) and stirred for 24 h. Then it was diluted with DCM (10 mL) and filtered through a pad composed by silica (bottom) and Celite® (top), and was washed with further 50 mL of DCM. The organic solution was concentrated under reduced pressure to afford pure **52g** (1.52 g, 7.3 mmol, 93% yield) as a white sticky solid. The compound was used in the next step without further purification. Spectroscopic properties were according to those reported in literature.[42]

**53h** was prepared according to the protocol for **53g**, using **52h** (1.23 g, 5.6 mmol) as starting material. **52h**(1.22 g, 5.5 mmol, 98% yield) was obtained as a white solid and used in the next step without further purification. Spectroscopic properties were according to those reported in literature.[43]

**General procedure for the reduction to aldehydes.**

**21g:** To a solution of **53g** (600 mg, 2.88 mmol) in DCM (6 mL) at -78°C under nitrogen atmosphere, a solution of DIBAL-H (1M in DCM, 3.17 mL, 3.17 mmol) in DCM (6 mL) was added dropwise over 15 min. After 2hours complete conversion was observed by TLC and GC-MS analysis. The reaction mixture was diluted with non-anhydrous diethyl ether and warmed to 0°C. Then $H_2O$(127 μL), 15% aq. NaOH (127 μL), $H_2O$ (317 μL) were sequentially added at 10 min intervals, and a white solid precipitated. After 15 min, $MgSO_4$ was added and the mixture was stirred for further 15 min at rt. Then it was filtered through a Celite® pad and washed with AcOEt (20 mL). The solution was concentrated and the crude product was purified by column chromatography ($SiO_2$, cyclohexane/EtOAc 9/1) to afford pure **21g** (382 mg, 2.33 mmol, 81% yield) as a colorless oil. Spectroscopic properties were according to those reported in literature.[S44]

**21h** was prepared according the protocol for **21g**, using **53h** (473 mg, 2.1 mmol) as starting material. Column chromatography ($SiO_2$, cyclohexane/EtOAc 7/3) of the crude mixture gave **21h** (276 mg, 1.56 mmol, 74% yield) as a colorless oil. Spectroscopic properties were according to those reported in literature.[45]

**General procedure for enantioselective photoalkylation of aldehydes**

In a Schlenk tube with rotaflo stopcock under argon atmosphere at r.t., $[Fe(bpy)_3]Br_2$ (3.4 mg, 0.005 mmol) and the Macmillan catalyst **33** (12 mg, 0.04 mmol) were dissolved in 400 μL DMF. Aldehydes **21a-h**(2 eq, 0.4 mmol), bromo derivatives **22a-e** (1 equiv, 0.2 mmol) and 2,6-lutidine (48 μL, 0.4 mmol) were then added.

The reaction mixture was carefully degassed via freeze-pump thaw (three times), and the vessel refilled with argon. The Schlelk tube was stirred and irradiated with a 23 W CFL bulb positioned approximately at 10 cm distance from the reaction vessel. After 16 h of irradiation, aq. HCl 1M (2 mL) was added and the mixture was extracted with AcOEt (4x5 mL). The collected organic layers were dried over $Na_2SO_4$, filtered and concentrated under reduced pressure.

Products **34-42** were purified by column flash chromatography on $SiO_2$.

Lactones **43-45**: The crude mixture was dissolved in DCM/MeOH (1/1 ratio, 4 mL), cooled to 0°C and $NaBH_4$ (30 mg, 0.8 mmol) was added. After 2 hours of stirring, complete conversion was observed by TLC analysis and the mixture was concentrated under reduced pressure. Aq. HCl 1M (5 mL) was added to the residue and the mixture was extracted with EtOAc (3 x 8 mL). The collected organic layers were dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. Title compounds were purified by column chromatography on $SiO_2$ to afford lactones **43-45**.

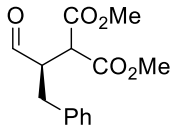
**Racemic compounds** were synthesized according to general procedure using racemic imidazolinone catalyst **29** instead of **33**.

**General procedure for determination of enantiomeric excesses of compounds 36-39.**

Products **36-39** were transformed in their corresponding diastereomeric acetals according to the literature protocol[46] in order to determine their enantiomeric excess.

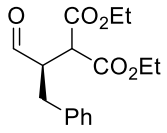
To a solution of **36-39** (0.05 mmol) in DCM (1.0 mL), (2*S*,4*S*)-(+)-pentanediol (>99% ee, 12.5 mg, 0.12mmol) and *p*-toluenesulfonic acid monohydrate (1.9 mg, 0.01 mmol) were added. The solution was stirred at rt until complete conversion was observed by TLC analysis. The mixture was concentrated under reduced pressure. Enantiomeric excesses were calculated from diastereomeric ratios of the resulting acetals, determined either by $^1H$ NMR or GC-MS analysis.

**Characterization data of compounds 34-45**

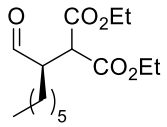



(**34**):The title compound was isolated by flash column chromatography ($SiO_2$,cyclohexane/EtOAc 95/5)as colourless oil (44 mg, 0.17 mmol, 83% yield,

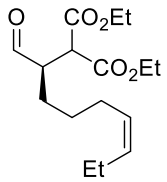
92% ee).Ee was determined by chiral HPLC analysis using Daicel Chiralpak®IC column: hexane/*i*-PrOH 90:10, flow rate 1.00 mL/min, 30°C, λ = 210 nm: $\tau_{major}$= 22.67 min., $\tau_{minor}$ = 18.05 min.;$[\alpha]_D^{20}$=+30.5 (*c*=0.6 in $CH_2Cl_2$).$^1$H NMR and $^{13}$C NMR were according to those reported in literature.[19]



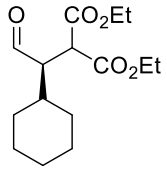

(**35**):The title compound was isolated by flash column chromatography($SiO_2$, cyclohexane/EtOAc 95/5) as colourless oil (46 mg, 0.16 mmol, 78% yield, 92% ee). Ee was determined by chiral HPLC analysis using Daicel Chiralpak®IC column: hexane/*i*-PrOH 90:10, flow rate 1.00 mL/min, 30°C, λ = 210 nm: $\tau_{major}$= 19.48 min., $\tau_{minor}$ = 15.17 min.; $^1$H NMR and $^{13}$C NMR were according to those reported in literature.[19]




(**36**): The title compound was isolated by flash column chromatography($SiO_2$, cyclohexane/EtOAc 95/5) as colourless oil (47 mg, 0.16 mmol, 82% yield, 92% ee). Ee was determined after derivatization of 29 mg of the title compound to its corresponding diastereomeric acetal following general procedure. Ee was determined by integration of the two $^1$H NMR (400 MHz, $CDCl_3$, 25°C) signals at 3.63 ppm (*major*, doublet) and 3.67ppm (*minor*, doublet) corresponding to the two diastereomeric acetals.$^1$H NMR and $^{13}$C NMR were according to those reported in literature. [19]

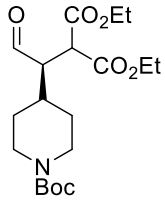



(**37**): The title compound was isolated by flash column chromatography ($SiO_2$, cyclohexane/EtOAc 95/5) as colourless oil (46 mg, 0.16 mmol,78% yield, 97% ee). Ee was determined after derivatization of 30 mg of the title compound to its corresponding diastereomeric acetal following general procedure. Ee wasdetermined by integration of the two $^1$H NMR (400 MHz, $CDCl_3$, 25°C) signals 3.68 (*major*, doublet) and 3.72 ppm (*minor*, doublet) corresponding to the two diastereomeric acetals. The same ee was determined by integration of the signals at 22.98 min (*major*) and 22.85 min (*minor*) corresponding to the two diastereomeric acetals after injection in GC-MS analysis. (Agilent 122-553ui, 5% phenyl 10% dimethylarylenesiloxane column, 1.7 mL/min helium flow rate, 150°C for 2 min, then temperature ramp to 280°C at 2.5°C/min rate). $^1$H NMR and $^{13}$C NMR were according to those reported in literature. [19]

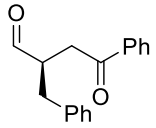



(**38**): The title compound was isolated by flash column chromatography ($SiO_2$,

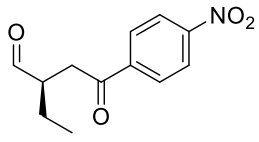
cyclohexane/EtOAc from 100/0 to 90/10) as colourless oil (43 mg, 0.15 mmol, 75% yield, 97% ee). Ee was determined after derivatization of 28 mg of the title compound to its corresponding diastereomeric acetal following general procedure B. Ee was determined by integration of the two $^1$H NMR (400 MHz, $CDCl_3$, 25°C) signals 3.73 (*major*, doublet) and 3.81 ppm (*minor*, doublet) corresponding to the two diastereomeric acetals. The same ee was determined by integration of the signals at 20.47 min (*major*) and 20.39 min (*minor*) corresponding to the two diastereomeric acetals after injection in GC-MS analysis. (GC-MS program: Agilent 122-553ui, 5% phenyl 10% dimethylarylenesiloxane column, 1.7 mL/min helium flow rate, 50°C for 2 min, then temperature ramp to 280°C at 10°C/min rate). $^1$H NMR and $^{13}$C NMR were according to those reported in literature. [19]



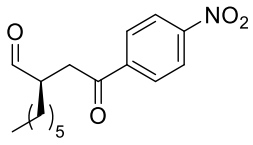

(**39**):The title compound was isolated by flash column chromatography ($SiO_2$, cyclohexane/EtOAc from 9/1 to 7/3) as colourless oil ( 46 mg, 0.12 mmol, 60% yield, 89% ee). Ee was determined after derivatization of 39 mg of the title compound to its corresponding diastereomeric acetal following general procedure B. Ee was determined by integration of the signals at 38.32 min (*major*) and 38.10 min (*minor*) corresponding to the two diastereomeric acetals after injection in GC-MS analysis. (GC-MS analysis: Agilent 122-553ui, 5% phenyl 10% dimethylarylenesiloxane column, 1.7 mL/min helium flow rate, 150°C for 2 min, then temperature ramp to 280°C at 2.5°C/min rate).$^1$H NMR and $^{13}$C NMR were according to those reported in literature. [19]



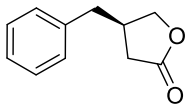

(**40**): The title compound was isolated by flash column chromatography($SiO_2$, cyclohexane/EtOAc 9/1) as a colourless oil (20 mg, 0.08 mmol, 40% yield, 92% ee). Ee was determined by chiral HPLC analysis using Daicel Chiralpak®IC column, hexane/*i*-PrOH 90:10, flow rate 1.00 mL/min, 30°C, λ = 210 nm: $\tau_{major}$= 18.75 min., $\tau_{minor}$ = 15.65 min.; $^1$H NMR and $^{13}$C NMR were according to those reported in literature.[12]



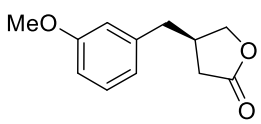

(**41**): The title compound was isolated by flash column chromatography(cyclohexane/EtOAc from 9/1 to 8/2) as colourless oil (26 mg, 0.11 mmol, 55% yield, 81% ee). Ee was determined by chiral HPLC analysis using Daicel Chiralpak®IA column: hexane/*i*-PrOH 80:20, flow rate 1.00 mL/min, 30°C, λ = 260 nm: $\tau_{major}$= 21.93 min., $\tau_{minor}$ = 17.82 min.; $^1$H NMR and $^{13}$C NMR were according to those reported in literature. [12]



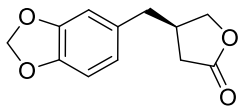
(**42**):The title compound was purified by preparative TLC on silica (cyclohexane/EtOAc 8/2) as colourless oil (31 mg, 0.11 mmol, 53% yield, 87% ee). Ee was determined by chiral HPLC analysis using Daicel Chiralpak®IA column: hexane/*i*-PrOH 90:10, flow rate 1.00 mL/min, 30°C, λ = 260 nm: $\tau_{major}$= 10.91 min., $\tau_{minor}$ = 9.62 min.; $^{1}$H NMR and $^{13}$C NMR were according to those reported in literature.[S46]



(**43**):The title compound was isolated by flash column chromatography($SiO_2$, cyclohexane/EtOAc 9/1)as colourless oil (28 mg, 0.16 mmol, 80% yield, 94% ee).Ee was determined by chiral HPLC analysis using Daicel Chiralpak®AD column: hexane/*i*-PrOH 95:5, flow rate 0.70 mL/min, 40°C, λ = 210 nm: $\tau_{major}$= 17.53 min., $\tau_{minor}$ = 18.79 min.; $[\alpha]_D^{20}$=+15.3 (*c*=0.3 in $CHCl_3$).$^{1}$H NMR and $^{13}$C NMR were according to those reported in literature. [4712]



(**44**):The title compound was purified by preparative TLC on silica (cyclohexane/EtOAc 7/3) as colourless oil (26 mg, 0.13 mmol, 64% yield, 93% ee). Ee was determined by chiral HPLC analysis using Daicel Chiralpak®AD column: hexane/*i*-PrOH from 85:15, flow rate 0.70 mL/min, 30°C, λ = 285 nm: $\tau_{major}$= 13.29 min., $\tau_{minor}$ = 14.40 min.; $^{1}$H NMR and $^{13}$C NMR were according to those reported in literature. [47]



(**45**): The title compound was isolated by flash column chromatography ($SiO_2$, DCM/EtOAc from 100/0 to 95/5)as colourless oil (32 mg, 0.14 mmol, 72% yield, 89% ee). Ee was determined by chiral HPLC analysis using Daicel Chiralpak®IC column: hexane/*i*-PrOH 60:40, flow rate 1.00 mL/min, 30°C, λ = 287 nm: $\tau_{major}$= 25.94 min., $\tau_{minor}$ = 24.80 min.; $^{1}$H NMR and $^{13}$C NMR were according to those reported in literature. [47]

**Synthesis of (-)-isodeoxypodophyllotoxin 46**

To a solution of LiHMDS (1 M in hexanes, 1.2 mL, 1.2 mmol) in THF (1 mL), a solution of lactone **45** (66 mg, 0.3 mmol) and 3,4,5-trimethoxybenzaldehyde (60 mg, 0.3 mmol) in THF (3 mL) was added dropwise at -10 °C. The reaction was stirred at -10°C for 30 minutes and was allowed to raise at 0 °C in 30 min. After complete conversion of the starting lactone (determined by TLC analysis) a

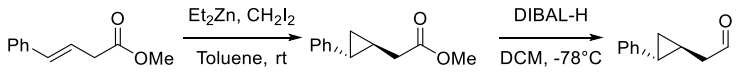
solution of aqueous 15% of HCl pre-cooled at -10 °C was added at -10°C and the reaction mixture was extracted with EtOAc (3x8 mL). The collected organic layers were washed with saturated solution of $NaHCO_3$, dried over $Na_2SO_4$, filtered and concentrated under reduced pressure.

The crude product was dissolved in anhydrous $CH_2Cl_2$ (2.5 mL) and TFA (2.5 mL) was added dropwise. The reaction mixture was stirred overnight and the solvent was evaporated under reduced pressure. The residue was dissolved in EtOAc (25 mL), washed with saturated solution of $NaHCO_3$, and brine. The collected organic layers were dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to give a white solid. The title compound was isolated by flash column chromatography($SiO_2$, cyclohexane/EtOAc 6/4) as white solid (84 mg, 0.21 mmol, 71% yield, 89% ee). After crystallization from boiling EtOH the ee increased to 91%.

Ee was determined by chiral HPLC analysis using Daicel Chiralpak®IA column: hexane/*i*-PrOH 50:50, flow rate 1.00 mL/min, 40°C, λ = 295 nm: $\tau_{major}$= 8.5 min., $\tau_{minor}$ = 7.8 min.; $^1$H NMR and $^{13}$C NMR were according to those reported in literature.[S47] $[\alpha]_D^{20}$ = -79.8 (*c*=1.4 in $CHCl_3$). Lit: $[\alpha]_D^{20}$ = -81.2 (*c*=1.0 in $CHCl_3$).[S48]

**Mechanistic insight**

**Synthesis of aldehyde(±)-*trans*-31i**




**54** **(±)-*trans*-55**, **(±)-*trans*-31i**,

Methyl ester **54** was prepared according to literature procedure.[S49]

**Procedure for the cyclopropanation reaction.**

**(±)-*trans*-55.** In a Schlenk tube under nitrogen atmosphere, **54** (497 μL, 3.00mmol, d = 1.063 g/mL) was dissolved in 2 mL of toluene. Then $Et_2Zn$ (1.1 M in toluene, 10.9 mL, 12 mmol) and $CH_2I_2$ (1.9 mL, 24 mmol) were added. The reaction was stirred for 24 h and during this time a white precipitate was formed. After complete conversion was determined by GC-MS analysis, the mixture was cooled to 0°C and carefully quenched by addition of 1M aq. HCl until acid pH. After addition of EtOAc (15 mL), the organic phase was separated and the aqueous layer extracted with EtOAc (2x15 mL). The collected organic phases were filtered thought a Celite® pad, the solution was concentrated under reduced pressure. The residue was purified by column chromatography ($SiO_2$,

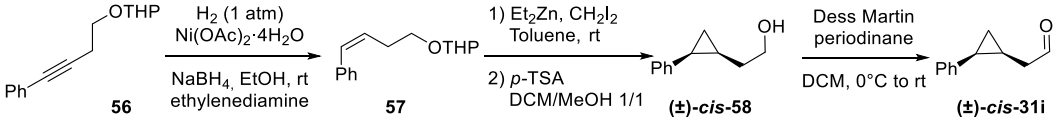
cyclohexane/EtOAc from 100/0 to 95/5) to afford**(±)-*trans*-55** as colourless oil (455 mg, 2.39 mmol, 80% yield).

$^1$H NMR (400 MHz, $CDCl_3$, 25°C) $\delta$= 0.88 (dt, $J_1$ = 8.6 Hz, $J_2$ = 5.3 Hz, 1H), 1.03 (dt, $J_1$ = 8.6 Hz, $J_2$ = 5.3 Hz, 1H), 1.36-1.45 (m, 1H), 1.74-1.82 (m, 1H), 2.37 (dd, $J_1$ = 15.7 Hz, $J_2$ = 7.0 Hz, 1H), 2.48 (dd, $J_1$ = 15.7 Hz, $J_2$ = 7.0 Hz, 1H), 3.72 (s, 3H), 7.10 (pd, $J$ = 7.7 Hz, 2H), 7.17 (pt, $J$ = 7.2 Hz, 1H), 7.68 (pt, $J$ = 7.2 Hz, 2H); $^{13}$CNMR (100 MHz, $CDCl_3$, 25°C): $\delta$= 15.3, 18.4, 22.8, 38.7, 51.6, 125.6, 126.0 (2C), 128.2 (2C), 142.5, 173.1; ESI-MS *m/z*: 191.1 $[M+H]^+$, 213.1 $[M+Na]^+$.

**Procedure for the reduction to aldehyde.**

**(±)-*trans*-1i:**To a solution of **(±)-*trans*-55** (650 µL, 3.64 mmol, d = 1.063 g/mL) in DCM (8 mL) at -78°C under nitrogen atmosphere, a solution of DIBAL-H (1M in DCM, 4.00 mL, 4.00 mmol) in DCM (8 mL) was added dropwise over 20 min. After 2 hours complete conversion was observed by TLC and GC-MS analysis. The reaction mixture was diluted with non-anhydrous diethyl ether and warmed to 0°C. Then $H_2O$ (146 µL), 15% aq. NaOH (146 µL), $H_2O$ (364 µL) were sequentially added at 10 min intervals, and a white solid precipitated. After 15 min, $MgSO_4$ was added and the mixture was stirred for further 15 min at rt. Then it was filtered through a Celite® pad and washed with AcOEt (20 mL). The solution was concentrated and the crude product was purified by column chromatography ($SiO_2$, cyclohexane/EtOAc from 97/3 to 90/10) to afford **(±)-*trans*-31i** (380 mg, 2.38 mmol, 65% yield) as a colourless oil. Spectroscopic properties were according to those reported in literature.[S**Error! Bookmark not defined.**]

**Synthesis of aldehyde (±)-*cis*-31i**




Alkyne **56** was synthesized according to literature procedure.[S50]

**Stereoselective reduction of alkyne 56**

**57:** To a solution of $Ni(OAc)_2{\cdot}4H_2O$ (50 mg, 0.2 mmol) in EtOH (1mL) under nitrogen atmosphere, a solution of $NaBH_4$(67 mg, 1.8 mmol) in EtOH (3mL) was added at rt. The resulting mixture turned immediately black and was stirred for 1 hour, during which a dark precipitate formed. Then a solution of **56** (485 mg, 2.1 mmol) and ethylenediamine (103µL, 1.5 mmol) in EtOH (3 mL) was added and the resulting mixture was stirred for 16hours at rt under nitrogen atmosphere, until complete conversion was observed by GC-MS. The mixture was concentrated and title compound

was purified by column chromatography ($SiO_2$, cyclohexane/EtOAc 8/2) to afford **57** as colorless oil (464 mg, 2.0 mmol, 95% yield).

$^1$H NMR (400 MHz, $CDCl_3$, 25°C) $\delta$= 1.31-1.66 (m, 4H), 1.67-1.78 (m, 1H), 1.79-1.97 (m, 1H), 2.54-2.78 (m, 2H), 3.37-3.62 (m, 2H), 3.72-3.98 (m, 2H), 4.20 (dd, $J_1$ = 4.8 Hz, $J_2$ = 3.3 Hz, 1H), 5.65-5.80 (m, 1H), 6.52 (dt, $J_1$ = 11.8 Hz, $J_2$ = 2.0 Hz, 1H), 7.18-7.26 (m, 1H), 7.29-7.39 (m, 4H); $^{13}$CNMR (50 MHz, $CDCl_3$, 25°C): $\delta$= 19.4, 25.4, 29.1, 30.5, 62.0, 66.8, 98.6, 126.5, 128.0 (2C), 128.6 (2C), 128.7, 130.4, 137.3; ESI-MS *m/z*: 233.1 $[M+H]^+$, 255.1 $[M+Na]^+$.

**Cyclopropanation reaction and removal of THP protecting group**

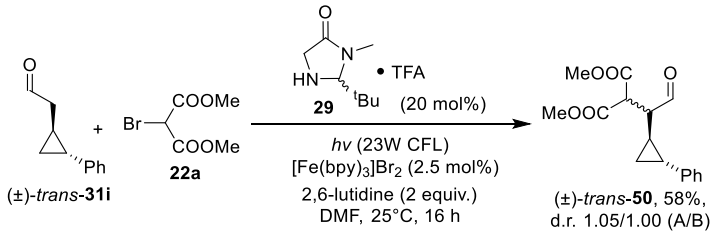
**(±)-*cis*-58:** Compound **57** (464 mg, 2.00mmol) was subjected to the same protocol described for **55** to obtain protected cyclopropane alcohol**.** The crude was dissolved in DCM/MeOH (1/1 ratio, 20 mL) and *p*-toluenesulfonic acid monohydrate (38 mg, 0.2 mmol) was added. The reaction mixture was stirred for 3 hours at rt, and concentrated under reduced pressure. The residue was subjected to flash column chromatography on $SiO_2$to afford **(±)-*cis*-58** (239 mg, 1.48 mmol, 74 % yield) as colourless oil.

$^1$H NMR (400 MHz, $CDCl_3$, 25°C) $\delta$= 0.72 (q, $J$ = 5.6 Hz, 1H), 0.96-1.04 (m, 1H), 1.09-1.23 (m, 2H), 1.33-1.45 (m, 1H), 1.53 (d, $J$ = 4.7 Hz, 1H), 2.11-2.18 (pq, 1H), 3.51-3.57 (m, 2H), 7.13-7.20 (m, 3H), 7.23-7.30 (m, 2H);$^{13}$CNMR (100 MHz, $CDCl_3$, 25°C): $\delta$= 9.1, 15.6, 20.4, 31.6, 62.7, 125.7, 127.9 (2C), 128.9 (2C), 139.1; ESI-MS *m/z*: 163.2 $[M+H]^+$, 185.1 $[M+Na]^+$.

**Oxidation of (±)-*cis*-58 to aldehyde (±)-*cis*-31i.**

**(±)-*cis*-1i:**To a solution of**(±)-*cis*-58** (170 mg, 1.05 mmol) in DCM (5 mL) at 0°C, Dess-Martin periodinane (535 mg, 1.26 mmol) was added. After 30 minutes, the solution was allowed to warm to rt. TLC analysis after 2hours revealed partial conversion, thus further Dess-Martin periodinane (200 mg, 0.47 mmol) was added to achieve complete conversion. The reaction was quenched by addition of $NaHCO_3$ aq. sat. solution (5 mL) and $Na_2S_2O_3$ aq. sat. solution (5 mL). The organic layer was separated and the aqueous one was extracted with DCM (3 x10 mL). The collected organic layers were dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. After purification by flash column chromatography ($SiO_2$, cyclohexane/EtOAc 9/1),**(±)-*cis*-31i** (128 mg, 0.80 mmol, 76% yield) was obtained as colourless oil. Spectroscopic properties were according to those reported in literature.[S]**Error! Bookmark not defined.**

**Photoalkylation of aldehyde (±)-*trans* 31i.**




**(±)-*trans*-50** was prepared according to the general procedure for photoalkylation of aldehydes on 0.5 mmol scale, using **(±)-*trans*-22i** as aldehyde and **29** as Macmillan catalyst. The crude product was purified by column chromatography (cyclohexane/EtOAc from 9/1 to 8/2) to afford pure **(±)-*trans*-50** as a yellowish oil (84 mg, 0.29 mmol, 58% yield) as an inseparable mixture of diastereoisomers (**A:B**, 1.05:1.00 ratio).

$^1$H NMR (400 MHz, $CDCl_3$, 25°C) (two diastereoisomers A:B, 1.05:1.00 ratio):$\delta$ = 0.91-0.97 (m, 1H$_A$), 1.05-1.21 (m, 2H$_A$ +2H$_B$), 1.23-1.30 (m, 1H$_B$), 1.81-1.89 (m, 1H$_B$), 2.09-2.18 (m, 1H$_A$), 2.59 (t, $J$ = 10.1 Hz, 1H$_A$), 2.61 (t, $J$ = 9.8 Hz, 1H$_B$), 3.46 (s, 3H$_B$), 3.70 (s, 3H$_B$), 3.77 (s, 3H$_A$), 3.79 (s, 3H$_A$), 3.89 (d, $J$ = 8.7 Hz, 1H$_A$), 3.90 (d, $J$ = 9.2 Hz, 1H$_B$), 7.02 (d, $J$ = 7.5 Hz, 1H$_A$ +1H$_B$), 7.08 (d, $J$ = 7.4 Hz, 1H$_A$ +1H$_B$), 7.14-7.21 (m, 1H$_A$ +1H$_B$), 7.22-7.30 (m, 2H$_A$ +2H$_B$), 9.85 (s, 1H$_A$), 9.87 (s, 1H$_B$); $^{13}$CNMR (100 MHz, $CDCl_3$, 25°C) (two diastereoisomers A:B, 1.05:1.00 ratio): $\delta$= 14.3 (1C$_A$), 14.5 (1C$_B$), 19.2 (1C$_B$), 19.7 (1C$_A$), 21.6 (1C$_A$), 23.2 (1C$_B$), 51.3 (1C$_B$), 51.4 (1C$_A$), 52.6 (1C$_B$), 52.7 (1C$_A$), 52.8 (1C$_B$), 52.9 (1C$_A$), 54.9 (1C$_A$), 55.0 (1C$_B$), 125.6 (1C$_A$+1C$_B$), 126.0 (2C$_A$+1C$_B$), 126.1 (1C$_B$), 128.3 (2C$_A$), 128.4 (2C$_B$), 140.9 (1C$_A$), 141.2 (1C$_B$), 168.3 (2C$_A$), 168.43 (1C$_B$), 168.44 (1C$_B$), 199.6 (1C$_A$), 199.7 (1C$_B$);ESI-MS *m/z*: 291.2 $[M+H]^+$.

$^1$H NMR signals were assigned by COSY experiment (Figures S3-5). The *trans* stereochemistry of the substituents on cyclopropane ring was established by performing n.O.e. experiments on pure **(±)-*trans*-50** as mixture of diastereoisomers. Selective excitation $^1$H NMR spectra were recorded on Varian Mercury 400 in a mixture of $CDCl_3$ and TFA (10%), using a DPFGSE-NOE sequence with a 50 Hz 'rsnob' pulse and a mixing time of 1.5 seconds.

Selective excitation of H$^4$ signal relative to diastereoisomer **A** (Figure S6) shows a positive n.O.e. on different protons present in the molecule. In particularly it was observed a much more intense positive n.O.e. (0.71 considered 100 the intensity of the irradiated signal) on H$^6$ proton than on H$^3$ and H$^5$ (respectively 0.32 and 0.33 considered 100 the intensity of the irradiated signal).

Similar behaviour was observed in the experiment performed on the diastereoisomer **B** (Figure S7). Also in this case the selective excitation of the proton H$^4$ gives rise to much more intense positive

n.O.e. (1.16 considered 100 the intensity of the irradiated signal) on $H^6$ proton than on $H^3$ and $H^5$ (respectively 0.39 and 0.30 considered 100 the intensity of the irradiated signal).

On the basis of these evidences it is possible to confirm that the two substituents on the cyclopropane ring have *trans* configuration.

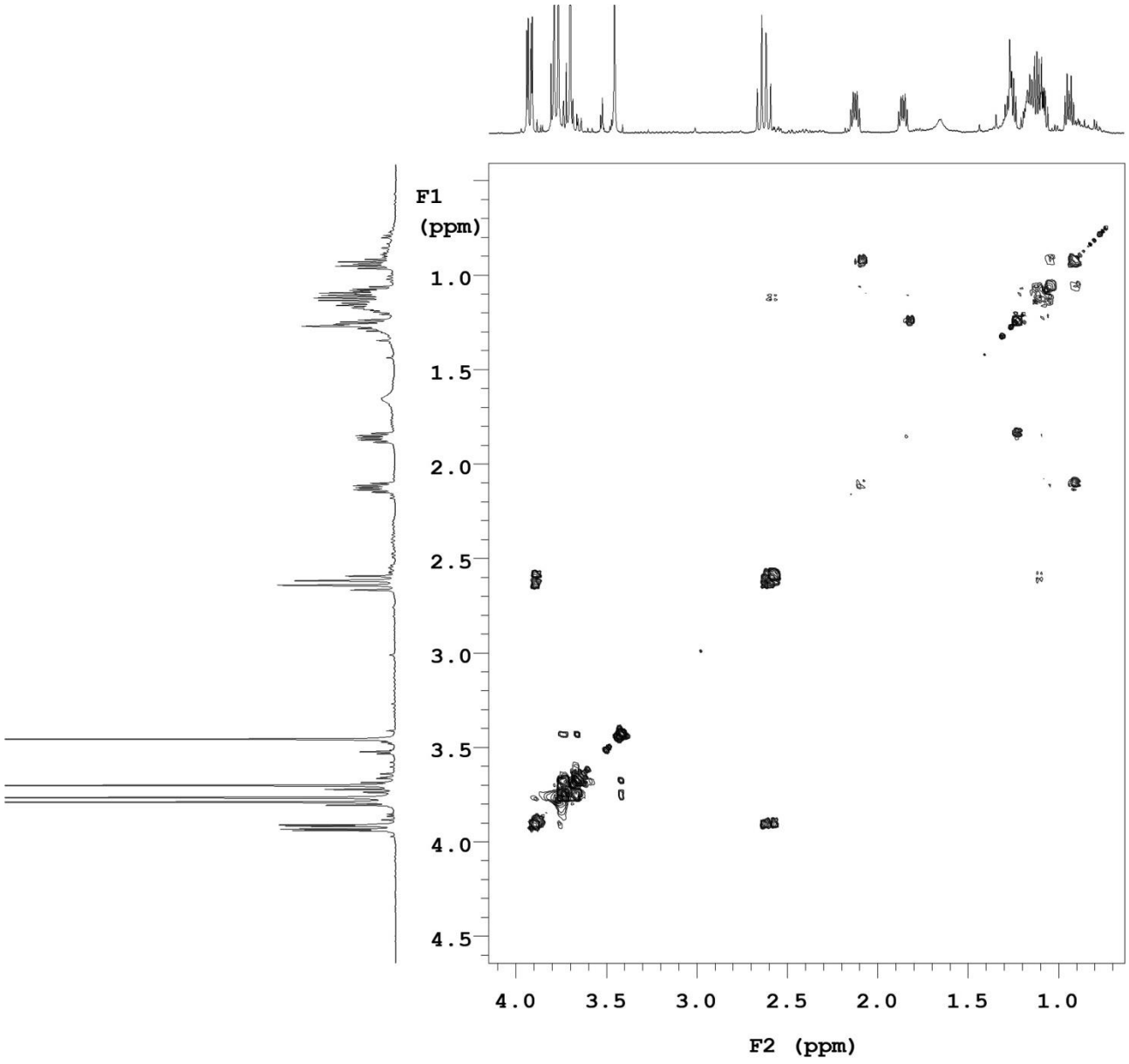



**Figure S3.** COSY spectra of **(±)-*trans*-50 (A+B).**

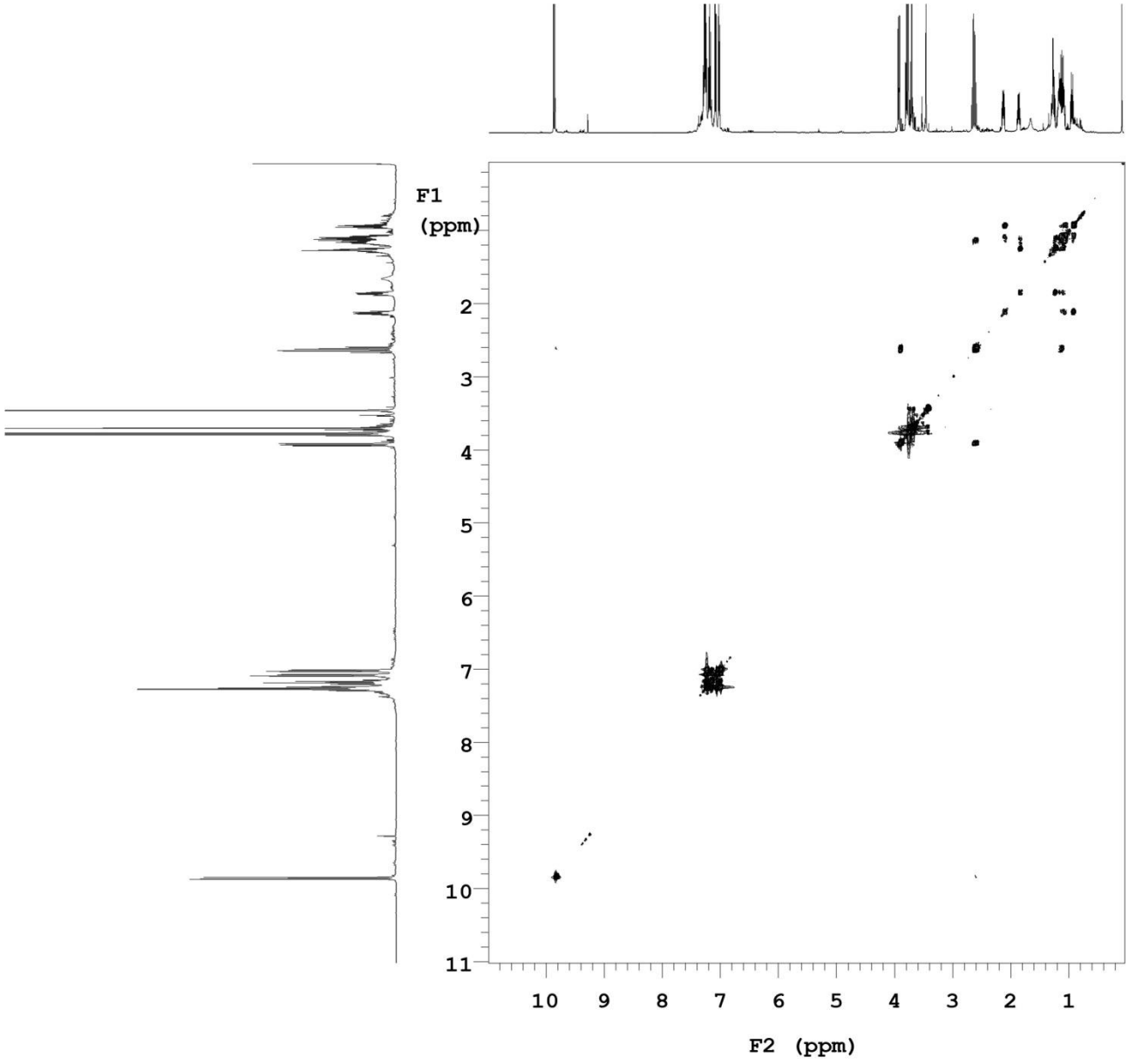



**Figure S4.** Aliphatic region of COSY spectra of **(±)-*trans*-50 (A+B).**

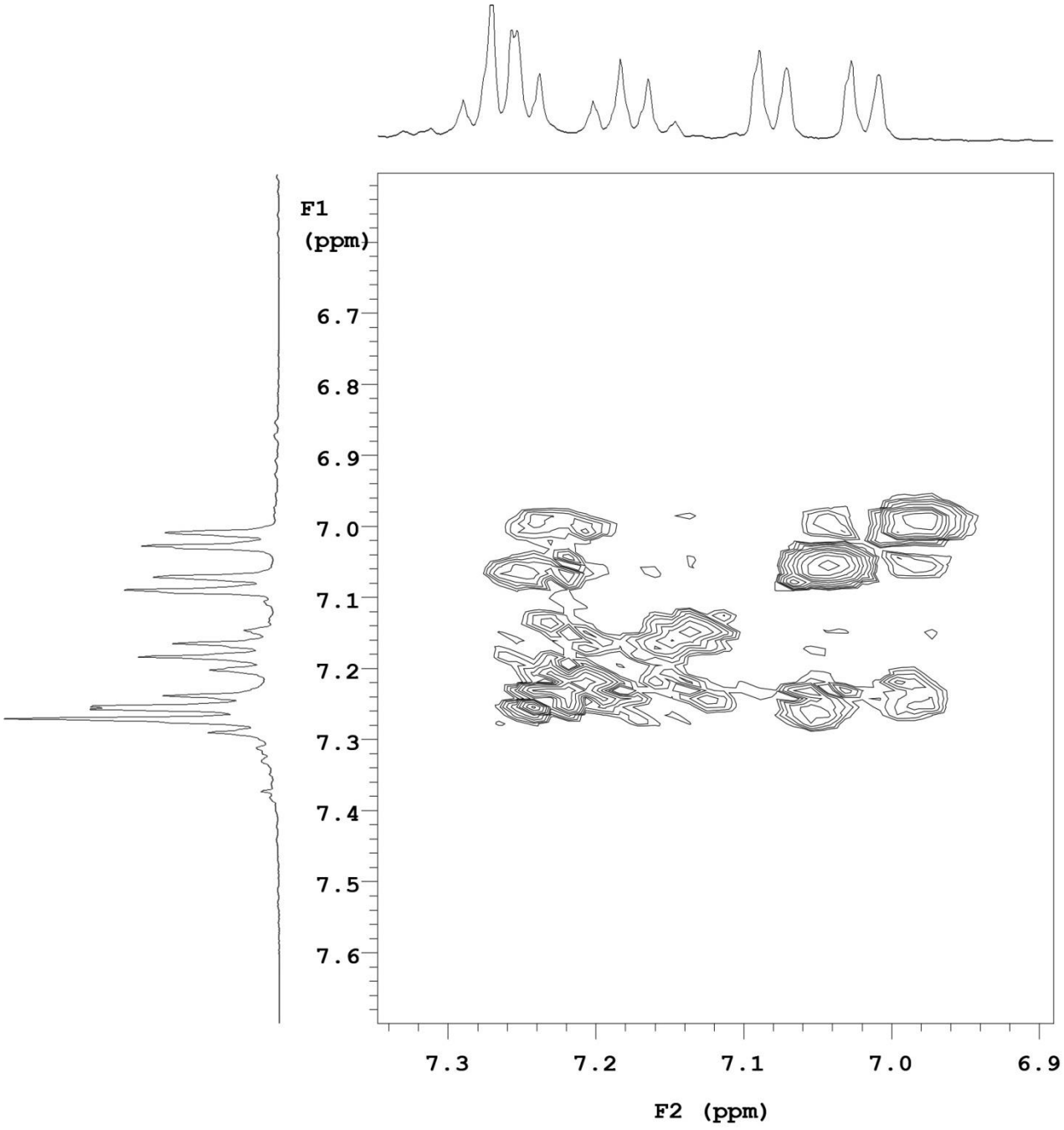



**Figure S5.** Aromatic region of COSY spectra of **(±)-*trans*-50 (A+B).**

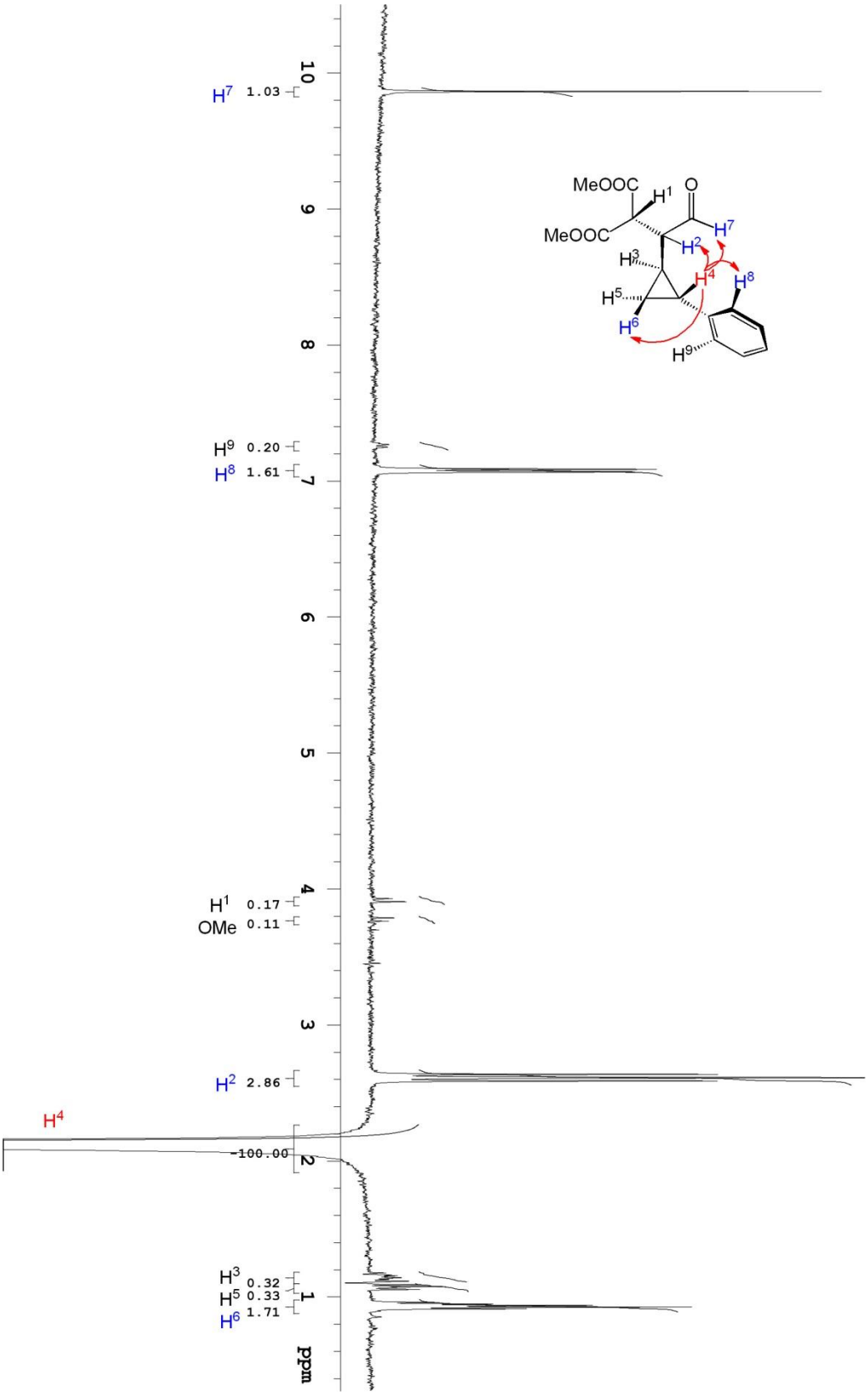



**Figure S6.** Selective excitation experiment of $H^4$on compound **(±)-*trans*-50** diastereoisomer **A.**

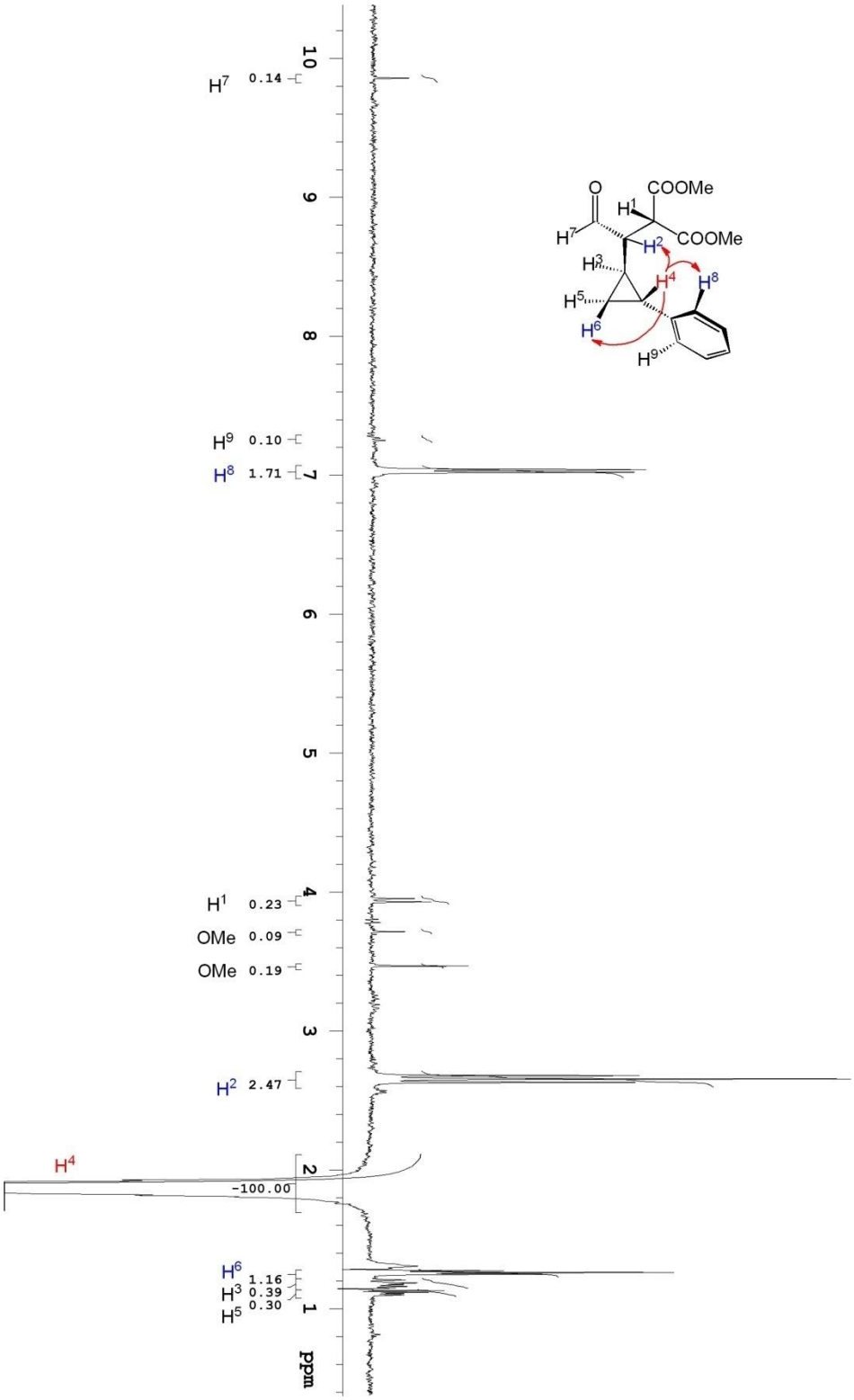
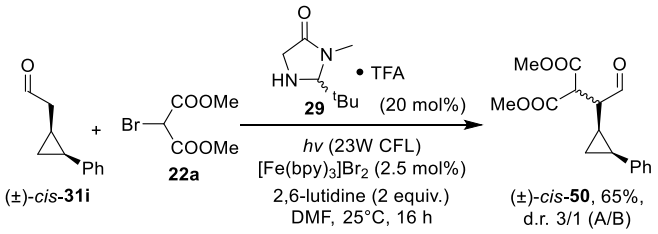



**Figure S7.** Selective excitation experiment of $H^4$on compound **(±)-*trans*-50** diastereoisomer **B**.

**Photoalkylation of aldehyde (±)-*cis*-31i.**




**(±)-*cis*-50** was prepared according to general procedure for photoalkylation of aldehydes on 0.3 mmol scale, using **(±)-*cis*-31i** as aldehyde and **29** as Macmillan catalyst. The crude product was a mixture of two diastereoisomers (A/B, 3/1), that presented different retention times in GC-MS analysis and NMR properties compared to those observed for **(±)-*trans*-50**. The crude product was purified by column chromatography (cyclohexane/EtOAc from 9/1 to 8/2) to afford pure **(±)-*cis*-50** as a yellowish oil (54 mg, 0.19 mmol, 62% yield) as single diastereoisomer **A**.

$^1$H NMR (400 MHz, $CDCl_3$, 25°C): $\delta$ = 0.97-1.04 (m, 1H), 1.10-1.16 (m, 1H), 1.21-1.31 (m, 1H), 2.37-2.44 (m, 1H), 2.57 (dd, $J_1$ = 11.4 Hz, $J_2$ = 8.4 Hz, 1H), 3.72 (3.86 rotamer) (s, 3H), 3.81 (3.87 rotamer) (s, 3H), 3.89 (d, $J$ = 8.4 Hz, 1H), 7.19-7.27 (m, 3H), 7.28-7.36 (m, 2H), 9.28 (s, 1H); $^{13}$CNMR (100 MHz, $CDCl_3$, 25°C): $\delta$ = 8.9, 17.7, 20.4, 49.2, 51.8, 52.7, 52.6, 126.7, 128.4 (2C), 128.6 (2C), 137.5, 168.4, 168.6, 200.5; ESI-MS *m/z*: 291.2 $[M+H]^+$.

Selective excitation $^1$H NMR spectra were recorded on Varian Mercury 400 in a mixture of $CDCl_3$ and TFA (10%), using a DPFGSE-NOE sequence with a 50 Hz 'rsnob' pulse and a mixing time of 1.5 seconds.

Selective excitation of $H^4$ (Figure S8) revealed a positive n.O.e. of comparable intensity of $H^3$ and $H^5$ (2.49 and 1.64 respectively considered 100 the intensity of the irradiated signal), while $H^6$ did not show any n.O.e. effect establishing the *cis* configuration of the cyclopropane ring. This was further confirmed by selective excitation of $H^6$ signal (Figure S9): a positive n.O.e effect was observed on geminal $H^5$ (12.62 considered 100 the intensity of the irradiated signal) while no response was observed either for $H^3$ either for $H^4$ accordingly with the assigned *cis* configuration. Moreover selective excitation of $H^2$ (Figure S8) lead to the observation of a positive n.O.e effect on $H^6$ (2.07 considered 100 the intensity of the irradiated signal), $H^8$ (2.53 considered 100 the intensity of the irradiated signal), $H^7$ (2.87 considered 100 the intensity of the irradiated signal) and one of the malonate methyl groups (2.04 considered 100 the intensity of the irradiated signal). No n.O.e. was observed on $H^3$, $H^4$ and for $H^5$ accordingly with the assigned *cis* configuration.

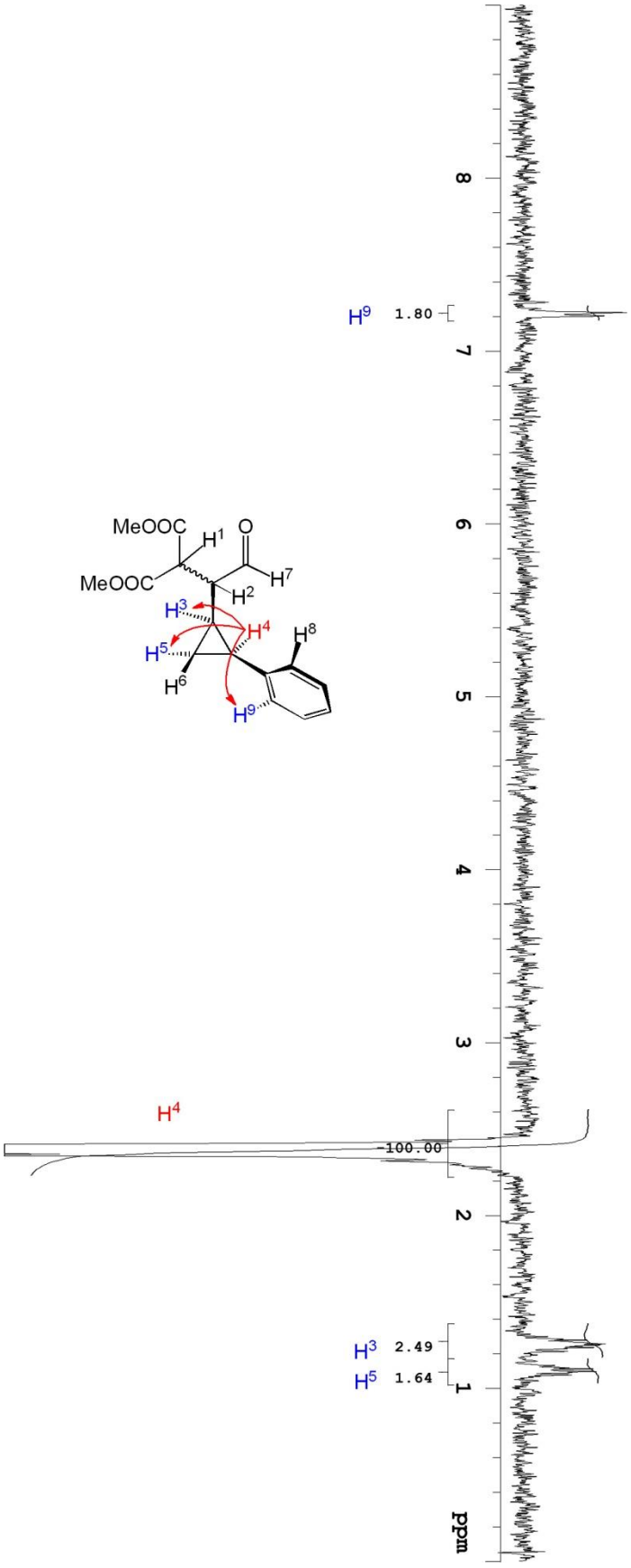



**Figure S8.** Selective excitation experiment of $H^4$ on compound**(±)-*cis*-50** major diastereoisomer.

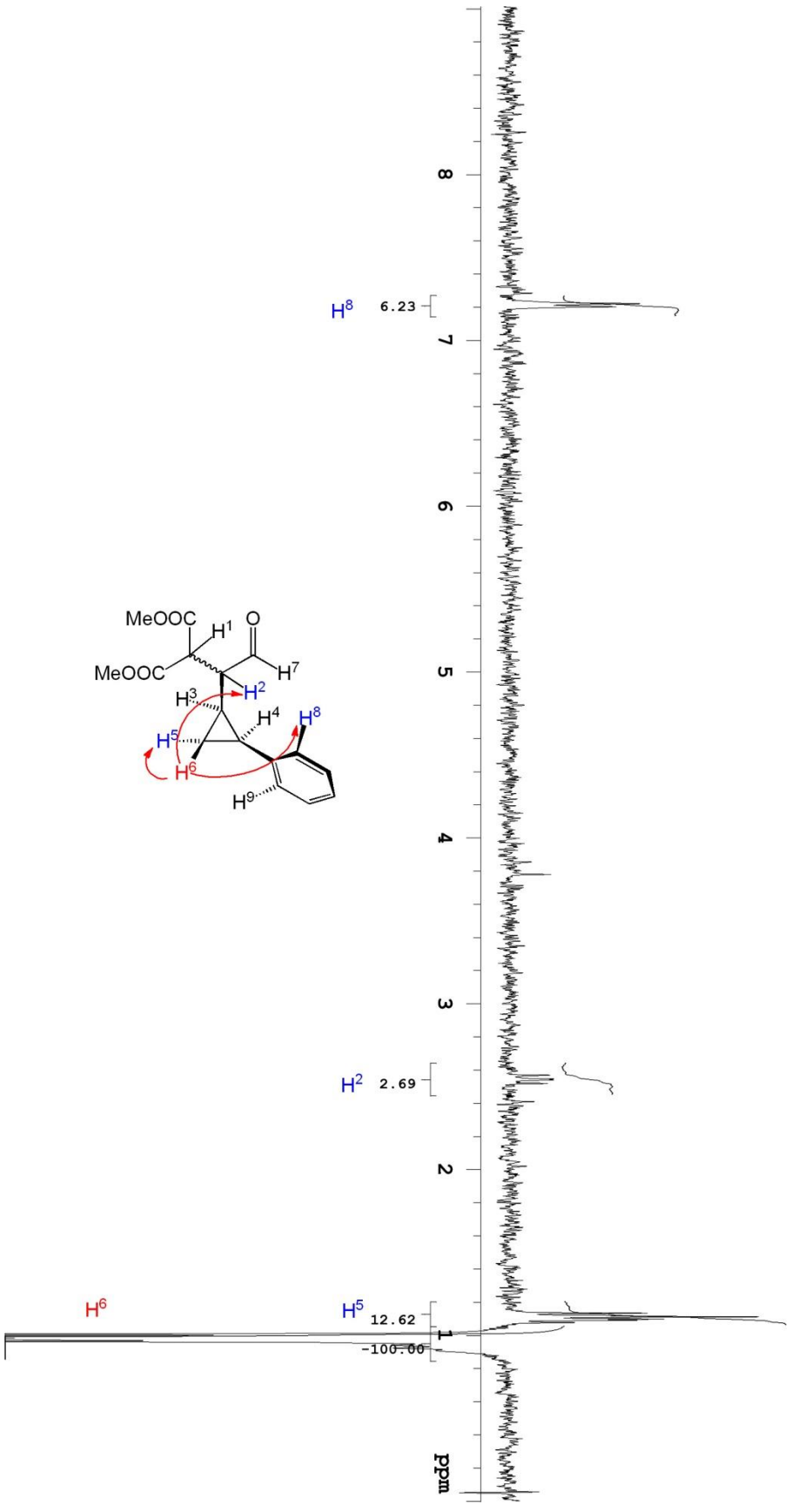

MeOOC
H1
O
MeOOC
H7
H3
H2
H4
H8
H5
H6
H9
H8 6.23
H2 2.69
H6
H5 12.62
-100.00
8
7
6
5
4
3
2
1
ppm

**Figure S9.** Selective excitation experiment of $H^6$ on compound**(±)-*cis*-50** major diastereoisomer.

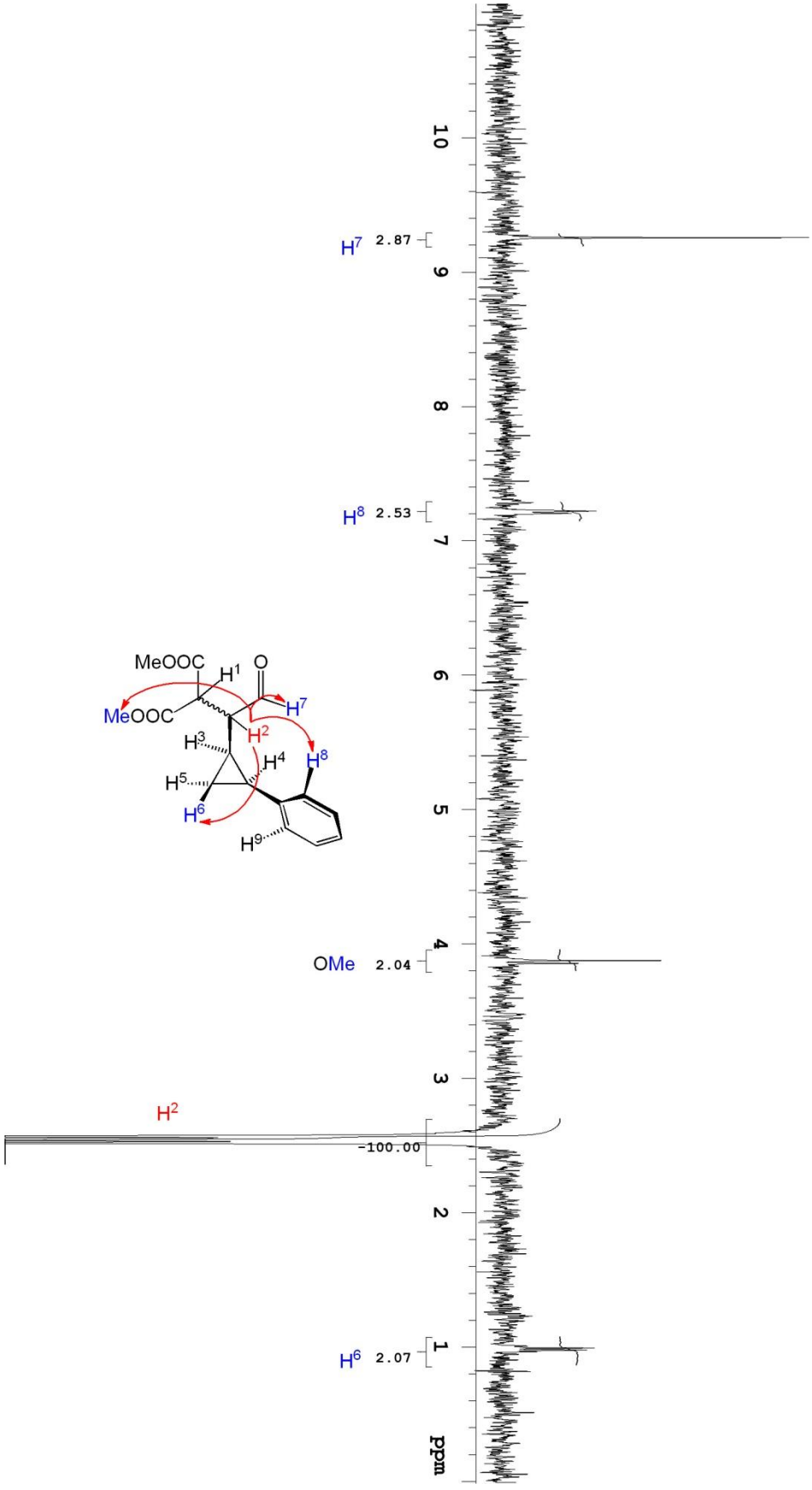


**Figure S10.** Selective excitation experiment of $H^2$ on compound**(±)-*cis*-50** major diastereoisomer.

**Photophysical measurements**

Photochemical experiments were carried out at room temperature in deaerated solutions. All absorption spectra were recorded in a quartz cuvette (optical pathlength 0.1 cm) with a UV/VIS spectrophotometer Perkin Elmer Lambda 650.

The irradiation was performed with an halogen lamp (24V, 250W), cut-off filter at 420 nm, in a reaction mixture containing $[Fe(bpy)_3]Br_2$ (0.0005mmol), dimethylbromomalonate **2a**(0.2 mmol), 2,6-lutidine (0.4 mmol), 3-phenylpropanal **1a**(0.4 mmol) and MacMillan catalyst **20** (0.04 mmol) in 400 μL DMF Uvasol® stirred solution.

The amount of reagents dissolved in DMF for the spectrophotometric measurement comply with quantities used in reaction mixture excluding $[Fe(bpy)_3]Br_2$ that was used in smaller quantities to register the absorption spectrum.

Ultrafast absorption spectroscopy experiments were carried upon 510 nm excitation using a pump-probe detection system based on the Spectra-Physics Hurricane Ti: sapphire laser source and the Ultrafast Systems Helios spectrometer. 510-nm pump pulses were generated by Spectra Physics OPA. Probe pulses were obtained by continuum generation on a sapphire plate (useful spectral range: 450-800 nm). Effective time resolution ca. 300 fs, temporal chirp over the white-light 450-750 nm range ca. 200 fs, temporal window of the optical delay stage 0-2000 ps.

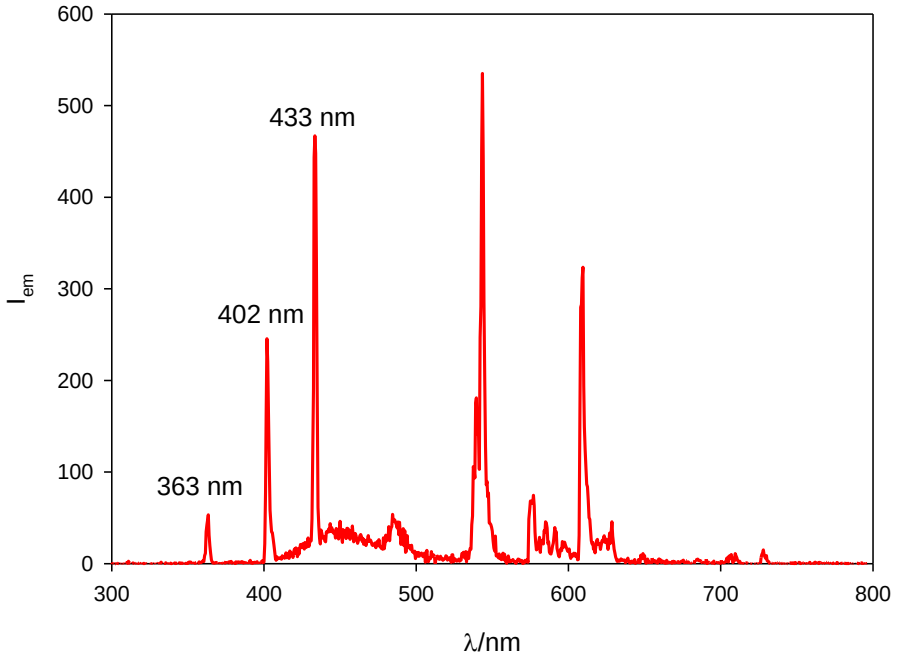



**Figure S14.** Emission profile of the 23W Compact Fluorescent lamp used to irradiate the solutions.

**EPR Studies**

EPR measurements. ESR spectra were obtained by photolysing the reaction mixture with a filtered light from a 500 W high pressure mercury lamp directly inside the cavity of a Bruker ELEXYS spectrometer equipped with a ER033M Field Frequency Lock. The instrument settings were as follows: microwave power 5.0 mW, modulation amplitude 0.05 mT, modulation frequency 100 kHz, scan time 180 s. An iterative least squares fitting procedure based on the systematic application of the Monte Carlo method was performed in order to obtain the experimental spectral parameters of the radical species.[51]

## 2.6.6 References


[1] N. Vignola, B. List, *J. Am. Chem. Soc.* 2004, *126*, 450-451.

[2] a) R. Rios, J. Vesely, H. Sundén, I. Ibrahem, G.-L. Zhao, A. Córdova, *Tetrahedron Lett.* **2007**, *48*, 5835–5839; b) H. Xie, L. Zu, H. Li, J. Wang, W. Wang, *J. Am. Chem. Soc.* **2007**, *129*, 10886-10894.

[3] D. Enders, C. Wang, J. W. Bats, *Angew. Chem. Int. Ed*. **2008**, *47*, 7539 –7542.

[4] B. List, I. Čorić, O. O. Grygorenko, P. S. J. Kaib, I. Komarov, A. Lee, M. Leutzsch, S. Chandra Pan, A. V. Tymtsunik, M. van Gemmeren, *Angew. Chem. Int. Ed*. **2014**, *53*, 282 –285.

[5] A. Gualandi, E. Emer, M G. Capdevila, P. G. Cozzi, *Angew. Chem.* **2011**, *123*, 7988-7992; *Angew. Chem. Int. Ed.***2 011**, *50*, 7842-7846.

[6] a) A. Gualandi, L. Mengozzi, J. Giacoboni, S. Saulnier, M. Ciardi, P. G. Cozzi, *Chirality* **2014**, *26*, 607-613; b) A. Gualandi, L. Mengozzi, P.G. Cozzi, *Chem. Today* **2014**, *32*, 14-17.

[7] a) T. D. Beeson, A. Mastracchio, J.-B. Hong, K. Ashton, D. W. C. MacMillan, *Science* **2007**, *316*, 582; b) P. V. Pham, K. Ashton, D. W. C. MacMillan, *Chem. Sci*., **2011**, *2*, 1470 and ref. therein.

[8] D. A. Nicewicz and D. W. C. MacMillan, *Science* **2008**, *322*, 77.

[9] M. Neumann, S. Füldner, B. König, K. Zeitler, *Angew. Chem.*, *Int. Ed.* **2011**, *50*, 951

[10] For recent reviews, see: (a) L. Flamigni, A. Barieri, C. Sabatini, B. Ventura, F. Barigelletti, *Top. Curr. Chem.* **2007**, *281*, 143; (b) S. Campagna, F. Puntoriero, F. Nastasi, G. Bergamini, V. Balzani, *Top. Curr. Chem.* **2006**, *280*, 117.

[11] a) J. W. Tucker, C. R. J. Stephenson *J. Org. Chem.* **2012**, *77*, 1617−1622; b) for a table of the red-ox potentials of the most employed photosensitizers, see the one compiled by D. Di Rocco: https://www.princeton.edu/chemistry/macmillan/resources/Merck-Photocatalysis-Chart.pdf.

[12] E. Arceo, I. D. Jurberg, A. Álvarez-Fernández and P. Melchiorre, *Nat. Chem*. **2013**, *5*, 750.

[13] C. K. Prier, D. A. Rankic, D. W. C. MacMillan, *Chem. Rev.* **2013**, 113, 5322; (b) J. M. R. Narayanam, C. R. J. Stephenson, *Chem. Soc. Rev.* **2011**, 40, 102; (c) K. L. Skubi, T. P. Yoon, *Nature* **2014**, 515, 45; (d) R. Brimioulle, D. Lenhart, M. M. Maturi, T. Bach, *Angew. Chem. Int. Ed.* **2015**, 54, 3872; (e) E. Meggers, *Chem. Comm.* ***2015***, 51, 3290.

[14] D. Prasad Hari, B. König *Chem. Commun.*, **2014**, *50*, 6688-6699

[15] Jeremy D. Griffin, Mary A. Zeller, and David A. Nicewicz *J. Am. Chem. Soc*. **2015**, *137*, 11340−11348

[16] a) J.-M Kern, J.-P. Sauvage, *J. Chem. Soc. Chem. Commun.* **1987**, 546; b) For reviews on Cu photocatalysis in synthesis, see: S. Paria, O. Reiser, *ChemCatChem* **2014**, 6, 2477.

[17] S. M. Stevenson, M. P. Shores, E. M. Ferreira, *Angew. Chem. Int. Ed.* **2015** DOI: 10.1002/anie.201501220.

[18] M. Neumann, S. Füldner, B. König, K. Zeitler, *Angew. Chem., Int. Ed.* **2011**, *50*, 951.

[19] P. Riente, A. M. Adams, J. Albero, E. Palomares and M. A. Pericás, *Angew. Chem. Int. Ed.* **2014**, *53*, 9613.

[20] M. Silvi, E. Arceo, I. D. Jurberg, C. Cassani, P. Melchiorre, *J. Am. Chem. Soc.* **2015**, 137, 6120.

[21] (a) C. Creutz, M. Chou, T. L. Netzel, M. Okumura, N. Sutin, *J. Am. Chem. Soc.* **1980**, *102*, 1309; (b) E. M. Kober, T. J. Meyer, *Inorg. Chem.* **1983**, *22*, 1614; (c) E. A. Juban, A. L. Smeigh, J. E. Monat, J. K. McCusker, *Coord. Chem. Rev.* **2006**, *250*, 1783; (d) C. Bressler, C. Milne, V.-T. Pham,

A. ElNahhas, R. M. van der Veen, W. Gawelda, S. Johnson, P. Beaud, D. Grolimund, M. Kaiser, C. N. Borca, G. Ingold, R. Abela, M. Chergui, *Science* **2009**, *323*, 489; f) A. Cannizzo, C. J. Milne, C. Consani, W. Gawelda, C. Bressler, F. Van Mourik, M. Chergui, *Coord. Chem. Rev.* **2010**, 254, 2677.
[22] G. Auböck, M. Chergui *Nature Chem.*, **2015**, *7*, 629-633.
[23] a) S. Ferrere, *Chem. Mater*. **2000**, *12*, 1083−1089. (b) S. Ferrere, B. A. Gregg, *J. Am. Chem. Soc*. **1998**, *120*, 843−844.
[24] a) T. C. B. Harlang, Y. Liu, O. Gordivska, L. A. Fredin, C. S. Ponseca Jr, P. Huang, P. Chábera, K. S. Kjaer, H. Mateos, J. Uhlig, R. Lomoth, R. Wallenberg, S. Styring, P. Persson, V. Sundström, K. Wärnmark, *Nature Chem.,* 2015, *7*, XX ; b) Galoppini E. *Nature Chem.,* 2015, *7*, 861-862.
[25] For a photocatalytic approach to lactones, see: E. R. Welin, A. A. Warkentin, J. C. Conrad, D. W. C. MacMillan *Angew. Chem. Int. Ed.*, **2015**; DOI: 10.1002/anie.201503789.
[26] a) Kuhn, M.; Von Wartbung, A. *Helv. Chim. Acta* **1967**, 50, 1546-1565; for precedent enantioselective synthesis of isodeoxypodophyllotoxin see: (b) Itoh, T.; Chika, J.; Takagi, Y.; Nishiyama, S. *J. Org. Chem.* **1993**, 58, 5717-5723; (c) Bode, J. W.; Doyle, M. P.; Protopopova, M. N.; Zhou, Q.-L. *J. Org. Chem.* **1996**, 61, 9146-9155; d) for a photocatalytic approach to lactones, see: Welin, E. R.; Warkentin, A. A.; Conrad, J. C.; MacMillan, D. W. C. *Angew. Chem. Int. Ed.* **2015**, 54, 9668-9672.
[27] (a) Julià, L.; Bosch, M. P.; Rodriguez S.; Guerrero, A. *J. Org. Chem.* **2000**, 65, 5098-5103; (b) Mileo, E.; Benfatti, F.; Cozzi, P.G.; Lucarini, M. *Chem. Commun.* **2009**, 469-470.
(21) Zhang, J.; Campolo, D.; Dumur, F.; Xiao, P.; Fouassier, J. P.; Gigmes, D.; Lalevée, J. *J. Polym. Sci. A Polym. Chem.* **2015**, 53, 42-49.
[28] An iterative least squares fitting procedure based on the systematic application of the Monte Carlo method was performed in order to obtain the experimental spectral parameters of the radical adducts. (a) Franchi, P.; Mezzina, E.; Lucarini, M. *J. Am. Chem. Soc.* **2014**, 136, 1250-1252; (b) Valgimigli, L.; Lucarini, M.; Pedulli, G.F.; Ingold, K.U. *J. Am. Chem. Soc.* **1997**, 119, 8095-8096.
[29] The C-H bond dissociation energies in H-CH2COOEt and H-CH(COOMe)2 are 96 and 90.5 kcal $mol^{-1}$, respectively (Luo, Y.-R. in "*Bond Dissociation Energies in Organic Compounds*", **2003**, CRC Press), p 67 and 68, respectively
[30] For an important study concerning the off-on experiments, and photochemical processes, see: Cismesia, M. A.; Yoon, T. P. *Chem. Sci.* **2015**, *6,* 5426.
[31] Ismaili, H.; Pitre, S. P.; Scaiano, *J. C. Catl. Sci. Technol.* **2013**, 3, 935-937.
[32] For SOMO chemistry performed with Fe polypyridyl complexes in which Fe(III) complexes are used as stoichiometric oxidants of enamines, see: Comito, R. J.; Finelli, F. G.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2013**, 135, 9358-9361.
[33] Righi, G.; Rumboldt, G. *J. Org. Chem.* **1996**, 61, 3557-3560.
[34] Zhao, Y.; Jiang, X.; Yeun, Y-Y *Angew. Chem Int. Ed*. **2013**, 52, 8597-8601.
[35] Cui, M.; Ono, M.; Kimura, H.; Liu, B.; Saji, H. *Bioorg. Med. Chem.* **2011**, 19, 4148–4153.
[36] Morphy, J. R.; Rankovic, Z.; York, M. *Tetrahedron* **2003**, 59, 2137–2145.
[37] Graham, T. H.; Horning, B. D.; MacMillan, D. W. C. *Org. Synth.* **2011**, 88, 42-53.
[38] Bouzaid, J.; Schultz, M.; Lao, Z.; Bartley, J.; Bostrom, T.; McMurtrie, J. *Cryst. Growth Des.* **2012**,12, 3906–3916.

[39]a) Bartels, B.; Schmidt, M.; Pekari, K.; Beckers, T.; Zimmermann, A.; Gekeler, V.; Assignee: Nycomed GmbH, Germany, PCT Int. Appl., 2008020045, 21 Feb 2008; b) Pathania, V.; Sharma, A.; Sinha, A. K. *Helv. Chim. Acta* **2005**, 88, 811-816.

[40] Piperonal was prepared according to literature procedure: Manoni, E.; Gualandi, A.; Mengozzi, L.; Bandini, M.; Cozzi, P. G. *RSC Adv.* **2015**, 5, 10546-10550.

[41] Kona, J. R.; King'ondu, C. K.; Howell, A.R.; Suib, S. L. *ChemCatChem* **2014**, 6, 749–752.

[42] Brown, T. H.; Blakemore, R. C.; Durant, G. J.; Emmett, J. C.; Ganellin, C. R.; Parsons, M. E.; Rawlings, D. A.; Walker, T. F. *Eur. J. Med. Chem.* **1988**, 23, 53-62.

[43] Makhey, J. D.; Li, D.; Zhao, B.; Sim, S.-P.; Li, T.-K.; Liu, A.; Liu, L. F.; LaVoie, E. J. *Bioorg. Med. Chem*. **2003**, 11, 1809–1820.

[44] Browder, C. C.; Marmsater, F. P.; West, F. G. *Cand. J. Chem.* **2004**, 82 , 375-385.

[45] Schobert, R., Siegfried, S.; Gordon, G. J.*J. Chem. Soc*. *Perkin Trans.* **2001**, 1, 2393–2397.

[46] Nicewicz, D. A.; MacMillan, D. W. C. *Science* **2008**, 322, 77–80.

[47] Bode, J. W.; Doyle, M. P.; Protopopova, M. N.; Zhou, Q.-L. *J. Org. Chem.* **1996**, *61*, 9146.

[48] Itoh, T.; Chika, J.; Takagi, Y.; Nishiyama, S. *J. Org. Chem.* **1993**, *58*, 5717.

[49] Izquierdo, J.; Rodríguez, S.; González, F. V. *Org. Lett.* **2011**, 13, 3856-3859.

[50] Fuji, K.; Morimoto, T.; Tsutsumi, K.; Kakiuchi, K. *Chem. Commun*. **2005**, 3295–3297.

[51] a) Franchi, P.; Mezzina, E.; Lucarini, M. *J. Am. Chem. Soc.* **2014**, 136, 1250; b) Valgimigli, L.; Lucarini, M.; Pedulli, G. F.; Ingold, K. U. *J. Am. Chem. Soc.* **2014**, 119, 8095.

# 2.7 On flow approach for the synthesis of (–)-oseltamivir[1]

**Table of contents**

## 2.7.1 Introduction

Biologically active compounds can be extracted from natural sources or synthesized by chemists starting from simple available materials or from more complex intermediates. Usually biologically active compounds are present in the natural sources in small amount, a quantity unsuitable for the preparations of drugs. It is therefore necessary to develop new synthetic methods for the preparation of such compounds.

The ideal synthesis starts from simple available materials and through their reaction in the minimum number of steps furnishes the desired molecule with ideally no by-products. From a realistic point of view this means that efficient multicomponent or multistep reactions, that do not require intermediate purification steps, are highly desirable as well as catalytic processes instead of stoichiometric reagents. Especially in case of stereoselective reactions, the development of efficient catalytic reactions to substitute the traditional chiral auxiliaries represents a great improvement in the atom economy and sustainability of a chemical process.

In the scale up of a process, heat exchange, efficient stirring and the control of the reaction conditions in all the reagent mass, avoiding the formation of hot spots that can favour side reactions, is a crucial task in order to have an efficient and economically fruitful process.

The use of flow reactors[2] allows a better control of all these issues because significantly smaller amounts of reagents are dealt with per time unit. The different concept is not to have all the bulk mass in one place and wait until the reaction is complete, but to flow the reagents through a narrow space, a small pipe usually, where the contact between reactants is favoured, promoting the transformation and collecting the product at the end of the system. A very efficient temperature control can be achieved thanks to the large surface area of the pipe vs the small amount of solution or gas that is circulated. Moreover, integrated systems to perform multistep processes in sequence with engineered and electronic control over the overall process have been developed, guaranteeing a remote control of the system and minimizing the contact of the operator with the chemicals.[3]

The main disadvantage in flow processes is the possible precipitation of species during the course of the reaction that can rapidly obstruct the pipes blocking the flow and causing a dangerous overpressure in the system.[4]

The use of flow chemistry has found a huge success on industrial scale for many chemical processes, in particular those conducted in gas phase, where quite often heterogeneous catalysts are employed. In these processes simple molecules are produced. On the other hand, on a laboratory scale the use of flow chemistry has not been extensively developed historically even if recently it is finding increasing applications in industry and also in academy more groups are concentrating their research efforts in this direction.[5] As a representative example, in figure 1 is reported the recent synthesis of ibuprofen in flow.

Flow reactions performed on a laboratory scale can be divided into two major classes considering the diameter of the channel: 1) diameter in the mm scale order that usually uses HPLC pipes and HPLC like columns inside which a supported catalyst can be packed; 2) microchannels, that have diameter in the order of μm, the so-called microreactors.[6] The advantages of these systems are: 1) the great contact surface between the solution and the reaction channel, which allows for a precise

control of the temperature avoiding the hot spots that can be formed, especially in medium-large scale reactions; this situation could favour the formation of undesired side-products; 2) in case of a catalytic process, the catalyst can be immobilized on the channel surface making easy its re-cycling and increasing considerably its effective TON; 3) in particular for microchannels, a fast and homogeneous mixing time of the reagents, that can result in a decreased reaction time.

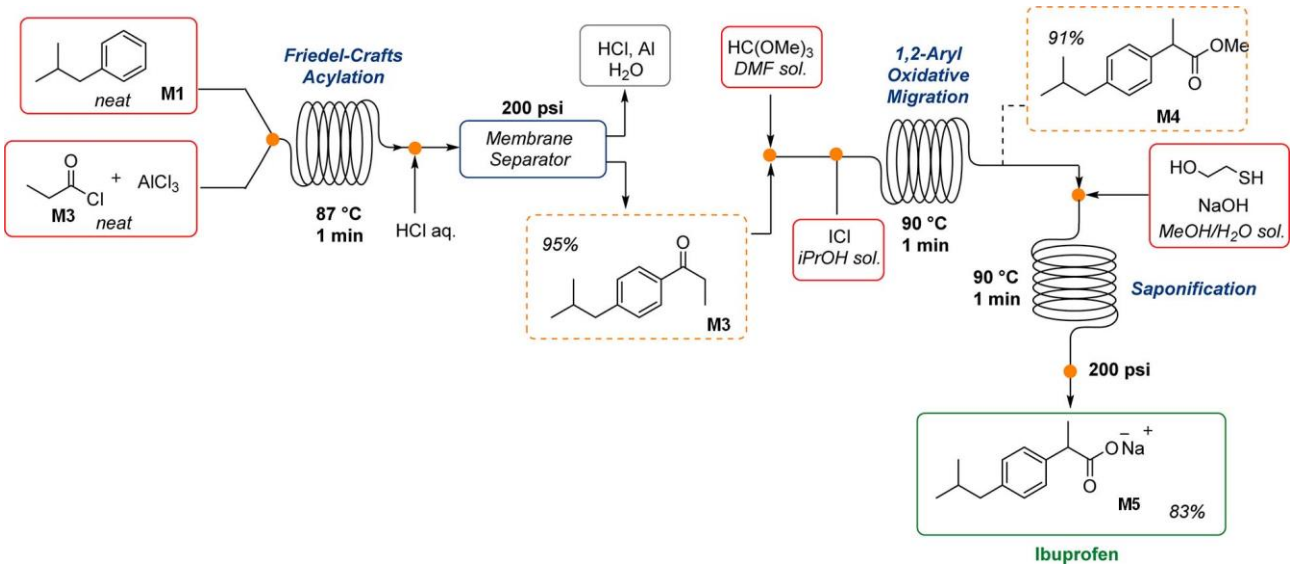



*Figure 1: recent synthesis of ibuprofen in flow (from R. Porta, M. Benaglia, A. Puglisi, Org. Process Res. Dev., 2016, 20, 2–25).*

The obvious disadvantage is the need to engineer the system, and this cost can be balanced by the above mentioned advantages, especially in the case of the continuous production of a valuable intermediate for pharmaceutical or material science applications. Obviuosly once a catalyst has been immobilized, all the reactions (and other new ones) it is known to catalyse can be tested on the same reactor by simply changing the reagents and the experimental parameters (solvent, temperature, flow rate).

In particular, considering the synthesis of active pharmaceutically ingredients (APIs), the introduction of flow reactors to perform catalytic reactions allows for the re-use of the catalyst and avoids the separation of the product from the catalyst itself. This is particularly important in the case of toxic metal catalysts, whose contamination must be removed. In the case of organocatalytic reactions, the organocatalyst loading in batch processes is usually quite high (5-20 mol%), so the catalyst immobilization on a solid support is particularly valuable because it allows its easy recovery and re-cycle and avoids its separation from the product with a concomitant decrease of waste and money.[7] Of course the catalyst must be robust and stable under the reaction conditions to allow its re-use in many processes without a loss of catalytic activity and selectivity, otherwise the immobilization costs would not be balanced.

The development of supported organocatalysts has been realized in the last 10 years and is the main research topic of a few groups. Professor Pericàs research group was a pioneer in the field reporting the efficient immobilization of many organocatalysts such as proline and other amine catalysts,

binol phosphoric acids, thioureas and isothioureas and their application in efficient catalytic processes[8]

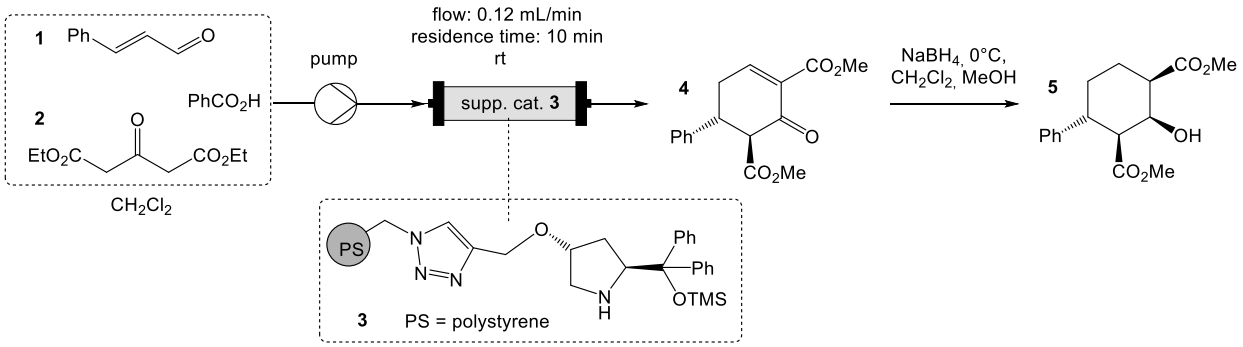
In particular they have studied the use of the Hayashi-Jørgensen catalysts on a polystyrene support. These supported prolinols can perform as well or even better, in terms of conversions and stereoselectivity, than their non-supported analogs in several processes. Such catalysts can be can be re-used several times in batch processes without loss of efficiency or they can be packed inside a HPLC like column to perform the reaction under flow conditions.

Moreover, the immobilization of the Hayashi-Jørgensen catalyst, solves one of its major drawbacks represented by its deactivation due to de-sylilation of the hydroxy group.[9] It has been shown that the immobilized catalyst can be re-sylilated by a simple reaction and re-used without any decrease in its catalytic activity.[10]

Pericàs and co-workers reported the application of immobilized Hayashi-Jørgensen catalysts to the synthesis of enantiopure 6-membered cyclohexanes bearing 3 stereocenters through a domino reaction (Michael

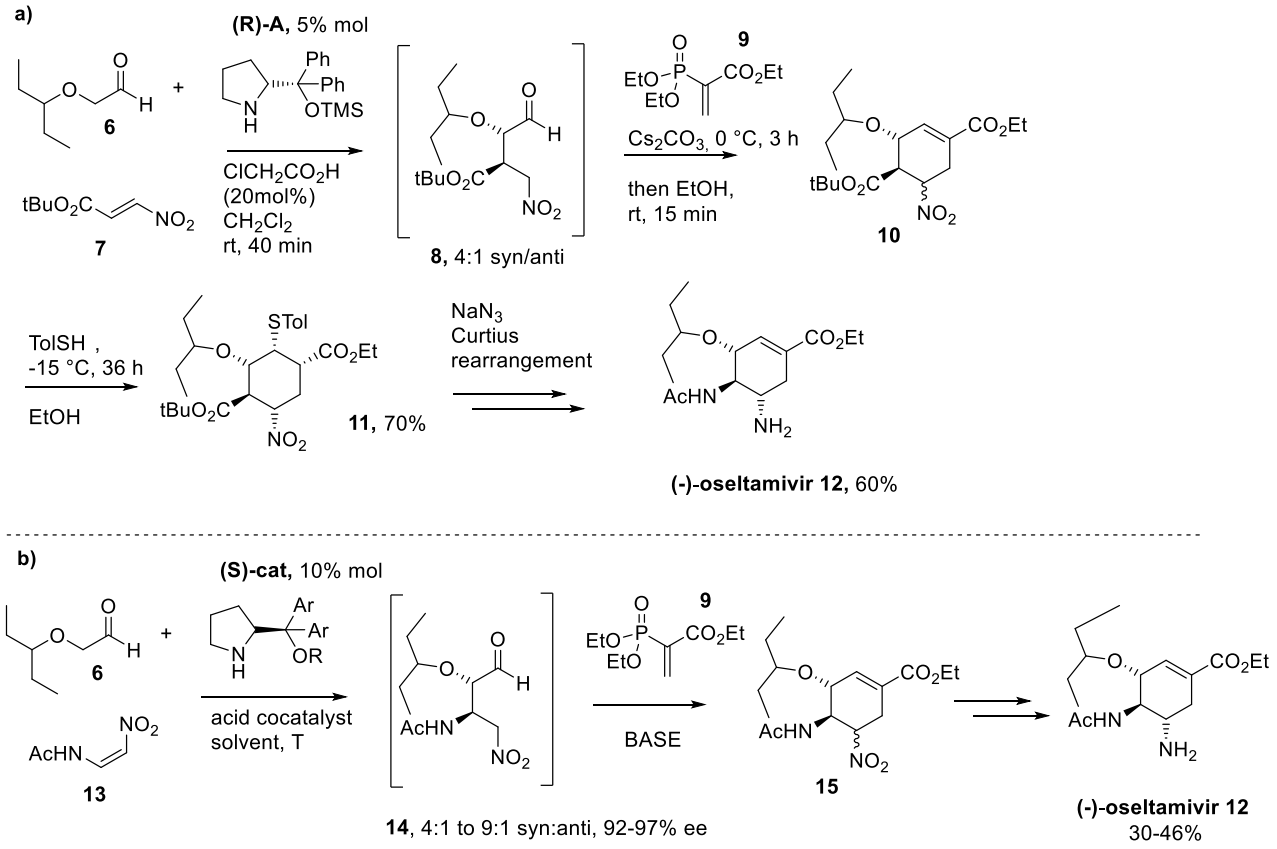
Michael addition followed by cyclisation) in flow conditions (scheme 1).[11]

Highly functionalized cyclohexane rings are the key structures of several antiviral agents such as oseltamivir, lanamivir and zanamivir.[12] Oseltamivir[13] has been discovered in by Gilead Sciences who patented it in 1995. A year later they signed a contract for the co-development of the drug and, two years later a New Drug Application was filed in the United States. The drug was commercially launched in November 1999 as the phosphoric acid salt with the Tamiflu® trademark. Several industrial synthesis were developed starting from cheap chiral building blocks such as Shikimic acid. These synthetic approaches entail very long reaction sequences but cheap reagents and robust reactions are employed. The result is a reliable, but low atom economical and environmentally sustainable, process.




*Scheme 1. Synthesis of highly functionalized cyclohexanes in flow.*

In 2009 Hayashi reported a straightforward enantioselective organocatalytic approach to oseltamivir (scheme 2a).[14]




*Scheme 1: Organocatalytic approaches to oseltamivir*

The key and enantiodetermining step is the Michael addition of an enamine (generated by condensation of chiral amine catalyst **A** and aldehyde **6**) to nitro alkene **7**. The solvent is then carefully evaporated at 0 °C to minimize the epimerization of the stereocenter on the α-position of the aldehyde, and the mixture is re-dissolved in EtOH. The base and the Michael acceptor **9** are added and the Michael addition of the nitronate to **9** occurs, followed by enolate addition to the aldehyde and elimination to afford the desired cyclohexene **10**. The newly formed stereocenter on position 3 is obtained in a 4:1 ratio of diastereoisomers favouring the undesired one. Hayashi found that the addition of *para*-tolyl thiol to the α,β-unsaturated system causes a retro-Michael reaction and that by a precise control of the temperature the subsequent ring closure affords **11** as the single desired diastereoisomer that can be converted in 6 steps in oseltamivir **12**.

Ma reported a significant improvement of the reaction protocol using nitro alkene **13** that already bears the amine functionalization (scheme 2b).[15] Thanks to this variation, the potentially explosive Curtius rearrangement employed in the Hayashi protocol was avoided. The groups of Lu, Durmis and Šebesta and Hayashi reported several variations and improvements to these reaction conditions.[16]

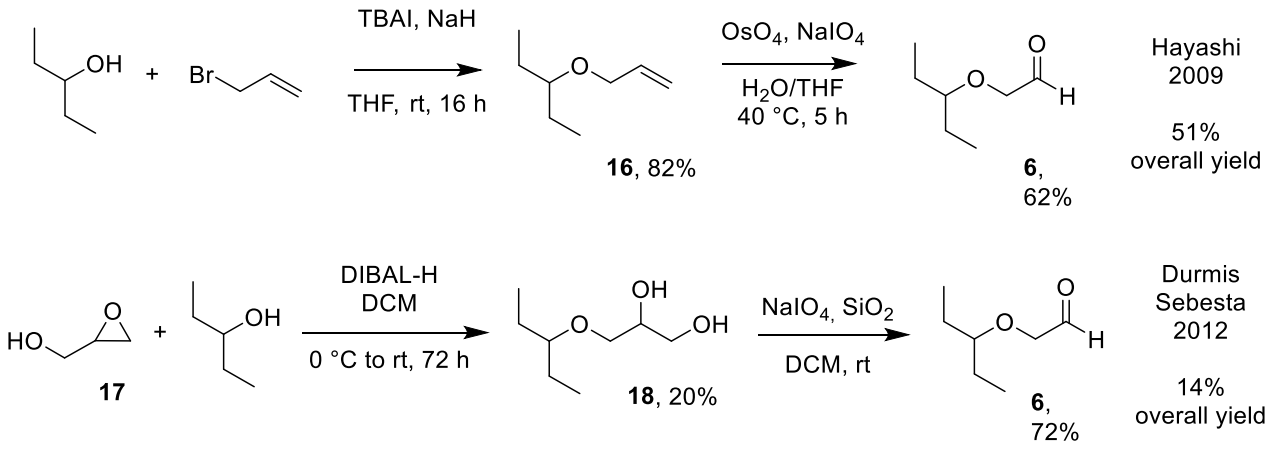
The significant difference compared to the previous linear approaches is that three achiral small highly functionalized organic molecules are used as starting materials in a convergent approach that, in a one pot operation, builds the six membered ring core with full control over the three

stereocenters. The disadvantage is that neither of the starting molecules is commercially available, even if they can be synthesized with chromatography-free procedures.
The objective of my project was to study the key steps of the organocatalytic approach to oseltamivir using flow chemistry and supported catalysts.

## 2.7.2 Results and discussion

### 2.7.2.1 Improved synthesis of aldehyde 6

A close inspection of the synthetic route to aldehyde **6** and nitroalkene **13** revealed that several improvements were necessary in order to establish safe and convenient synthetic procedures.
Two methods had been described in the literature to obtain aldehyde **6**. The first one allows to obtain the aldehyde in good yields by oxidative cleavage of the double bond of **16** with $OsO_4$, a very dangerous reagent, thus we decided to avoid such procedure.[14] The alternative route is the opening of (±)-glycidol **17** by 3-pentanol promoted by DIBALH that acts both as a base forming the alkoxide and as Lewis acid on the epoxide. Unfortunately even if full conversion is observed by GC-MS, yields are very low, around 20%.[16b] Diol **18** is a perfect ligand for aluminium and it is very difficult to break their complex and recover the product. Indeed, when we tried other transition metals to promote the opening of glycidol, I observed complete conversions. The isolated yields of **6** were even lower than those obtained using DIBALH, as illustrated in table 1.

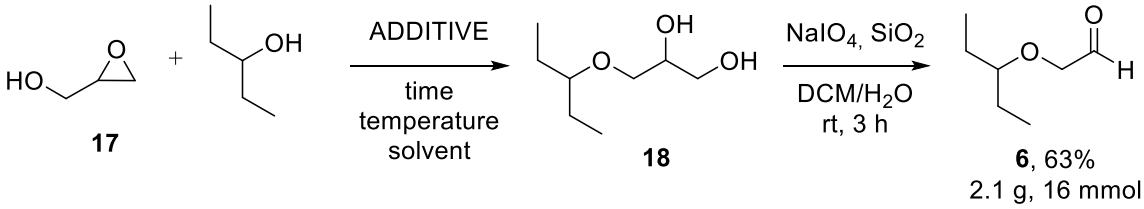



*Scheme 3: previous synthesis of aldehyde **6**.*

The solution was the employment of $LiClO_4$ that does not form stable complexes with the resulting diol. Its weaker Lewis acidity on the other hand imposed harsh reaction conditions: neat alcohol at reflux for three days in presence of a large excess of the lithium salt. The elevated temperature is also necessary to dissolve the perchlorate in the aliphatic alcohol. The original protocol used methanol in which lithium perchlorate is soluble at room temperature.[17]
Using these conditions diol **18** was obtained in good yields (56-72%) after addition of water and extraction with diethyl ether. Concentration and distillation of the excess of 3-pentanol (around 40% of this reagent is recovered with this procedure) affords pure diol **18**. The minimal amount of water necessary to dissolve the $LiClO_4$, that precipitates when the reaction is cooled down, should be used in order to obtain **18** in high yields. The use of an excess of water dissolves too much pentanol bringing also the product **18** into the water phase from where it is hard to recover. When I used

more polar solvents such as ethyl acetate for the extraction I obtained the formation of a homogeneous liquid phase that could not be broken unless the ethyl acetate was removed by rotary evaporation.

It was possible to decrease the excesses of *iso*-pentanol and lithium perchlorate observing only a slight decrease in the reaction yield that can be accounted by the more concentrated conditions that favours the glycidol polymerization. However I never observed this hypothesized side product in the final compound after the work up, so probably it goes into the water phase.




| Glycidol **17** (1 eq.) | pentanol (X eq.) | Additive (X eq) | Conditions | | | Conv.[a] | Yield[b] |
|---|---|---|---|---|---|---|---|
| | | | Solvent | T | time | | |
| 1 mmol | 1.5 | DIBAL-H (1.3) | DCM | 0°C to r.t. | 72 h | 100% | 19% |
| 1 mmol | 3.0 | Ti(O*i*Pr)$_4$ (1.5) | Toluene | 115°C | 18 h | 100% | 5% |
| 1 mmol | 9.3 | Ti(O*i*Pr)$_4$ (1.5) | - | 115°C | 18 h | 100% | 9% |
| 1 mmol | 9.3 | $LiClO_4$ (10) | - | 115°C | 72 h | 100% | 74% |
| 32 mmol | 5.8 | $LiClO_4$ (5.8) | - | 115°C | 72 h | 100% | 61% |
| 64 mmol | 5.8 | $LiClO_4$ (4.35) | - | 115°C | 66 h | 100% | 62% |

The opening of the glycidol reactions were carried out under anhydrous conditions and nitrogen atmosphere with the amounts of reagents and in the experimental conditions indicated. The oxidation of the aldehyde was conducted according to the procedure of Durmis and Sebesta.[16b] (a) conversions determined by GC; (b) yield of pure product obtained simply after work up.

*Table 1: optimization of the reaction conditions for the opening of glycidol.*

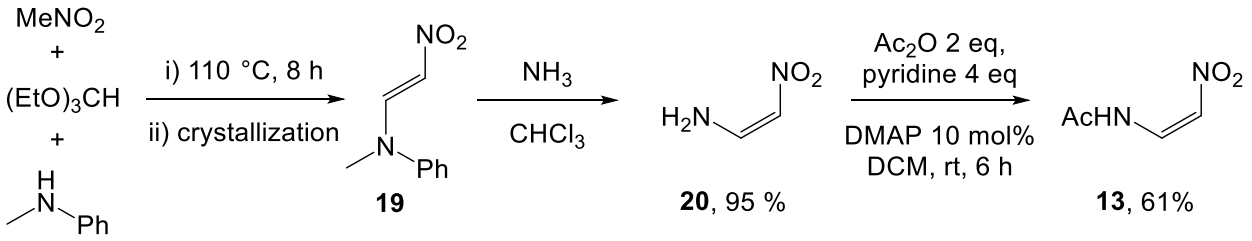
$LiClO_4$ is explosive so safety precautions, such as keeping the reaction behind a protective shield and avoiding to scratch the solid or shake the reaction vessel, must be taken in particular when it is heated in concentrated solutions.

The oxidation of diol **18** to the aldehyde was done according to the procedure of Durmis and Sebesta,[16b] using water solution of periodate that is adsorbed on the silica suspended in a vigorously stirred solution of DCM under inert atmosphere. The use of very diluted conditions is important to guarantee the mobility of the silica avoiding the blocking of the magnetic stirrer. The amount of silica is the exact one to absorb the water solution of the oxidant, already in the maximum concentration possible, avoiding the formation of a liquid-liquid biphasic system. The aldehyde is rather unstable and even if stored under argon atmosphere in the fridge, significant amounts of decomposition products are observed after a week. For this reason, several precautions are important during the reaction and work up: 1) a water bath is useful to control the reaction

temperature in particular if it is run on a medium scale, 2) shielding from light the reaction vessel and the balloon during the solvent evaporation, 3) performingthe work up procedure rapidly. The product obtained was pure enough and we used it without further purification.

### 2.7.2.2 Syntheis of nitroalkene 13 using the tube-in-tube technology

The reported method to access nitroalkene **13** is a three step protocol starting from cheap commercial materials: *N*-methyl aniline, nitromethane and triethylorthoformate are heated at reflux to give **19** that is recrystallized from *n*-hexane and toluene. Replacing cyclohexane with toluene afforded better results in our hands. Then, **19** is dissolved in chloroform and gaseous ammonia is bubbled inside the reaction vessel until its saturation. The reaction is sealed and stored at –20°C for one night during which the substitution of more basic ammonia on the aniline occurs affording product **20**. The driving force of the reaction is the precipitation of **20** that is almost insoluble in chloroform. Indeed, by simple filtration it is possible to obtain ≈ 80% of the product, that is already pure and does not need any purification. Concentration of the liquid phase and recrystallization from chloroform allows to recover the remaining product to obtain a combined yield up to 95%.

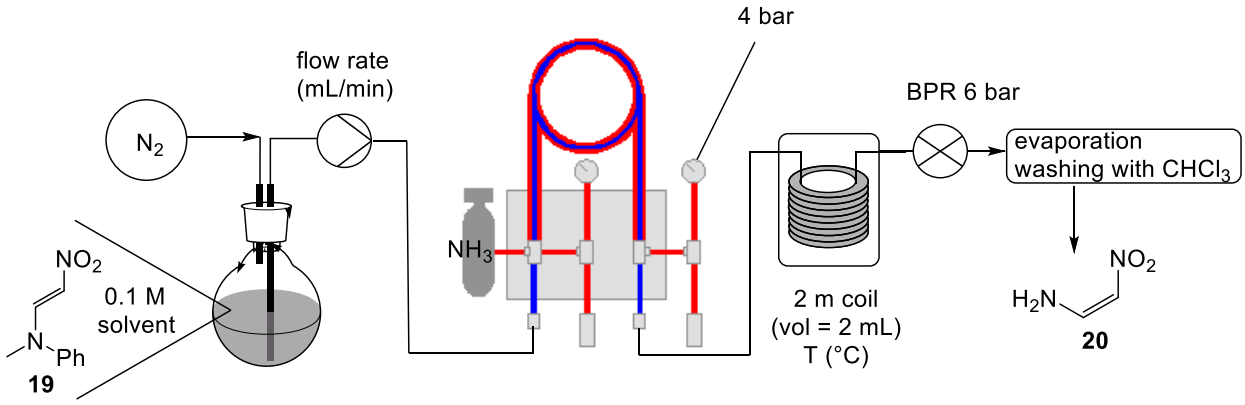



*Scheme 4: reported synthetic pathway to nitroalkene **13**.*

The reported procedure is very efficient but to convert **19** into **20** a large excess of ammonia in a non-confined space is required, which represents a danger for the operator. Moreover the storage of gas saturated solution in a closed vessel is potentially explosive, in particular if the process is run on a large scale. A safer protocol to run this reaction that guarantees a high productivity of intermediate **20** would be a significant advance.

Flow chemistry offers a valuable tool, the tube-in-tube technology, to perform gas-liquid reactions in controlled and safe conditions employing a minimal excess of gaseous reagent. The idea to place two concentric tubes with the inner one characterized by being semipermeable, that is permeable to gases but not to liquids, occurred to Ley that applied this device to many reactions in which a gas reacts with a substrate dissolved in a liquid solution.[18] Among the gases successfully employed with this technology there is ammonia.[19] Several advantages are connected to this system: 1) it is user friendly and adaptable to the research laboratories, 2) the exit manometer allows to regulate the gas pressure inside the system avoiding and preventing the gas flow in the external area, 3) the pressure forces the gas to dissolve into the flowing liquid phase placing the reactants into close contact speeding up the reaction, 4) the flow of liquid brings continuously new solution in contact with the gas thus avoiding the overexposure of the product to the gas reducing problems of selectivity and

side-reactions, 5) the volume of solution and gas inside the system is minimal (around 2-3 $cm^3$ for meter) increasing the security compared to high volume batch reactors, 6) the system is made of plastic tubes so that an eventual explosion would not shoot sharp metal or glass pieces.
The tube in tube is one of the tools to perform flow chemistry in the laboratories of Professor Pericàs and we decided to apply this technique to convert **19** in **20**.
In order to have a successful transformation, the starting material **19** should be dissolved in a solvent able to uptake a sufficient amount of ammonia to guarantee a full conversion. Literature studies outline how alcohols or dimethoxyethane guarantee the best uptake of ammonia, while this gas is minimally dissolved into chloroform or dichloromethane. The experimental set up is represented in the figure that accompanies table 2. The use of a back pressure regulator is fundamental to maintain the gas pressure inside the system so that the gas remains dissolved in the liquid phase available for the reaction and does not form gas bubbles generating an unproductive biphasic system. Moreover, the presence of gas bubbles in the tubes may cause problems to pump that must in any case be powerful to overcome the BPR and maintain a constant flow rate. An HPLC pump is able to fulfill such task only working at flow rate superior than 0.3 mL/min, otherwise a syringe pump should be used.
An initial test using DCM, in which **19** is perfectly soluble, afforded very low conversions confirming the low uptake of ammonia in this solvent (table 2, entry 2). Instead using methanol under the same conditions (0.1 M, 0.2 mL/min, 27 °C, no additional coil) gave 95% conversion of **19** to the product (table 2, entry 3). The conversion could be appreciated also by sight because the starting solution is bright yellow, while when full conversion is achieved it becomes almost colorless. Once the product solution exited the system (so excess ammonia was free to evaporate) and came in contact with air, it immediately became of an opaque yellow. No appreciable decomposition was observed by GC in a limited time frame. Unfortunately **19** is poorly soluble in methanol so 0.1 M was the maximum concentration we could reach. To enhance the productivity of the process we increased the flow rate, but at 0.4 mL/min incomplete conversion was observed. In order to increase the reaction time we added an additional 2 m coil at the end of the tube in tube and under these new conditions we obtained again complete conversion (table 2, entry 4).
The conversion must be checked by GC-MS, because on TLC the reverse reaction takes place favored by the evaporation of ammonia, the presence of the aniline byproduct and the acid residues of silica. Thus, even if complete conversion was achieved, TLC showed a medium conversion.
We then decided to use less toxic ethanol and slightly better results were obtained as we could increase the flow rate up to 0.7 mL/min keeping an almost complete conversion (table 2, entries 5-9). These first experiments were conducted in the high pressure laboratory where the temperature was around 27 °C. When we moved the experimental set up to our laboratory, where the temperature was around 22 °C, we could no longer prepare a 0.1 solution of **19** in ethanol because it re-precipitated almost immediately even after heating or prolonged sonication. Thus, we turned back to methanol that guaranteed similar performances and in which the compound was still soluble enough at 22 °C. However, in order to have a complete conversion it was necessary to heat the coil up to 55 °C using a water bath and decrease the flow rate to 0.5 mL/min. Under these conditions a moderate productivity of 212 mg/h corresponding to 2.41 mmol/h was achieved. The reaction work up consisted in the evaporation of the methanol and in the precipitation of the product, obtained as a pink fluffy solid upon addition of chloroform.



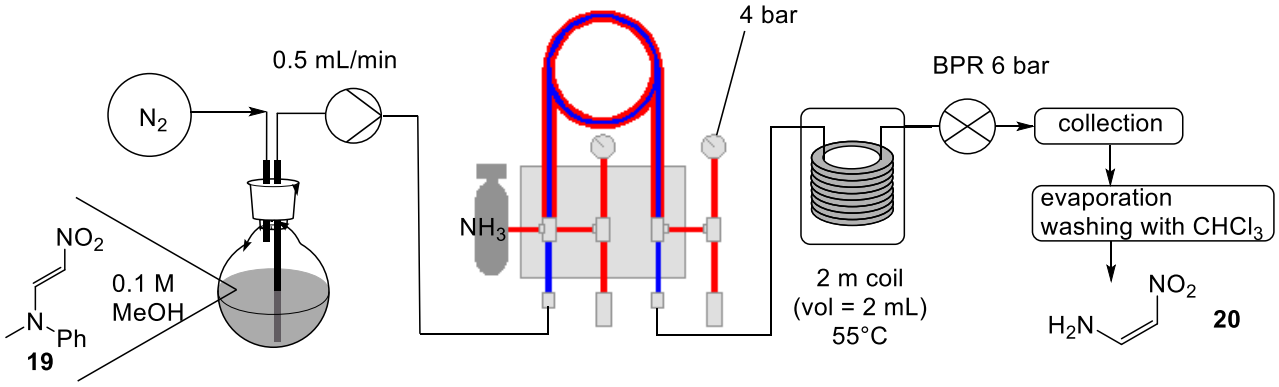

| entry | Solvent | Flow rate | rt | T coil | Conv.[a] | Yield[b] | productivity |
|---|---|---|---|---|---|---|---|
| 1 | DCM | 0.2 | 27 | - | 10 | - | |
| 2 | MeOH | 0.2 | 27 | - | 95 | - | |
| 3 | MeOH | 0.4 | 27 | - | 75 | | |
| 4 | MeOH | 0.4 | 27 | 27 | 100 | | |
| 5 | EtOH | 0.2 | 27 | - | 100 | - | |
| 6 | EtOH | 0.3 | 27 | - | 95 | | |
| 7 | EtOH | 0.4 | 27 | 27 | 100 | | |
| 8 | EtOH | 0.7 | 27 | 27 | >95 | - | |
| 9 | EtOH | 0.8 | 27 | 27 | 90 | - | |
| | SM not totally soluble in EtOH at 22 °C | | | | | | |
| 10 | MeOH | 0.5 | 22 | 22 | 90 | 87 | |
| 11 | MeOH | 0.5 | 22 | 40 | 95 | 89 | |
| 12 | MeOH | 0.5 | 22 | 50 | >95 | 92 | |
| 13 | MeOH | 0.7 | 22 | 60 | 90 | 88 | |
| 14 | MeOH | 0.7 | 22 | 70 | 90 | - | |
| 15 | MeOH | 0.5 | 22 | 50 | >95 | 80 | 212 mg/h[c] |

For the detailed experimental procedure see the experimental part; (a) conversion determined by GC; (b) yield of isolate product after precipitation; (c) 700 mg in 3.3 h.

*Table 2: optimization of the reaction conditions for the tube in tube substitution.*

Using these optimized conditions I prepared a few grams of intermediate **20**. During these experiments I realized that the frequency of the work up procedure was fundamental to obtain the product in high yields and purity. When I optimized the reaction conditions I collected the solution

usually every one or two hours to determine the yield in function of the different experimental parameters.




| entry. | mL[a] | time of w.u.[b] | $CHCl_3$[c] (mL) | precipitation[d] | mg **20** | Yield **20**[e] | Purity **20**[f] | Physical state |
|---|---|---|---|---|---|---|---|---|
| 1 | 213 | 7 h | 10 | Ov.n 0 °C | 1669 | 89% | 85% | sticky red |
| 2 | 190 | 6 h | 10 | Ov.n 0 °C | 1640 | 98% | 85% | sticky red |
| 3 | | further washing of entry 2 | | | 1550 | 92% | 90% | Pink powder |
| 4 | 106 | 3.5 h | 6 | 1 h 0 °C | 768 | 86% | 100% | Pink powder |
| 5 | 52 | 1.7 h | 3 | Ov.n 0 °C | 416 | 86% | 100% | Pink powder |
| 6 | 37 | 1.2 h | 3 | Ov.n 0 °C | 300 | 92% | 100% | Pink powder |
| 7 | 74 | 2.5 h | 7 | Ov.n 0 °C | 605 | 93% | 95% | pink powder |
| 8[g] | 260 | 6.5 h | 15 | 20 min 0 °C | 1850 | 81% | 100% | Yellow solid |

For the detailed experimental procedure see the experimental part; (a) mL of solution collected after the reaction; (b) collection time after which the work up has been performed; (c) mL of chloroform employed for the precipitation of **20**; (d) time during which **20** was allowed to precipitate from the crude suspended in chloroform; (e) yield of isolated product after precipitation; (f) purity determined by NMR; (g) the product solution was collected in a flask under nitrogen at 0 °C.

*Table 3: production of **20** by the tube-in-tube technology.*

When I used this methodology to produce **20** for the first time, I collected the solution after 7 hours and I realized that during this time it had become dark red, from the initial opaque yellow color. In this case washing the crude with the usual amount of chloroform afforded a dark sticky solid (table 3, entries 1 and 2) which purity was around 85%, definitely lower from the almost pure compound obtained during the optimization tests. When I washed this impure product with further chloroform, I obtained a product with 90% purity but of course in decreased yield (table 3, entry 3). Further washing did not increase the purity. Concentration of the chloroform gave a sticky red oil that could contain side-products deriving from the hydrolysis or the polymerization of **20**.

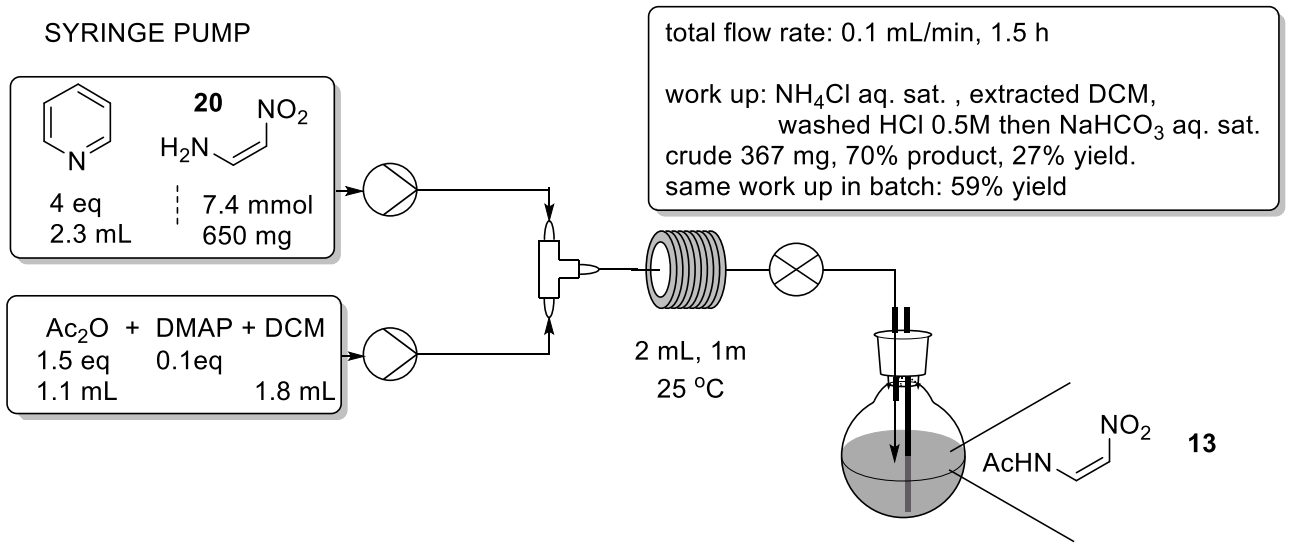
In order to obtain the product in high yields and purity it was necessary to perform the work up every two or three hours and to leave the crude at 0 °C overnight to dissolve the impurities and precipitate the pure **20** (table 3, entries 4-7). This tedious procedure is a limitation to the effective transformation that we developed.

The stability of the product in solution was increased by placing the collecting flask under nitrogen atmosphere at 0 °C. This precaution and performing the precipitation from chloroform in a reduced time of 20 min, allowed to obtain the pure product after 6.5 h of collection albeit in 81% yield (table 3, entry 8).

A more user friendly procedure that allows to obtain a pure product with the tube technology is possible but the yield is around 80%, while with a frequent work up results comparable to the batch process are obtained.

Finally I performed the acetylation step according to the literature.[16b] I found out that this apparently trivial reaction is quite sensitive to the quality of the acetic anhydride: using an old bottle that reasonably contained traces of acetic acid, even if no impurities could be detected by $^1$H NMR of the reagent, led to the formation of a significant amount (20-30%) of the ammonium acetate of **20**. Instead, when a newly opened bottle was used, a clean reaction was obtained. Column chromatography purification was necessary to purify the red sticky crude product and **13** was obtained as a yellow solid. However the elution should be rapid, otherwise the formation of colored bands, revealing a partial decomposition, were observed on the silica gel.

I tried to perform this reaction in flow by mixing through a Y connector two solutions: the first one containing acetic anhydride and DMAP in DCM, the second the starting material **20** in pyridine because it was not soluble either in DCM either in mixtures DCM/pyridine.




*Scheme 4: acetylation of **20** in flow conditions.*

In an initial attempt, I used a syringe pump to maintain a flow of 0.1 mL/min of the mixed solutions through a 1 m coil (2 mL dead volume). The outstream was collected in a balloon containing $NH_4Cl$ aq. sat. solution to form the pyridine salt and quench the reaction. The organic layer was then washed rapidly with HCl 0.5 M and then with water. However the analysis of the crude revealed the

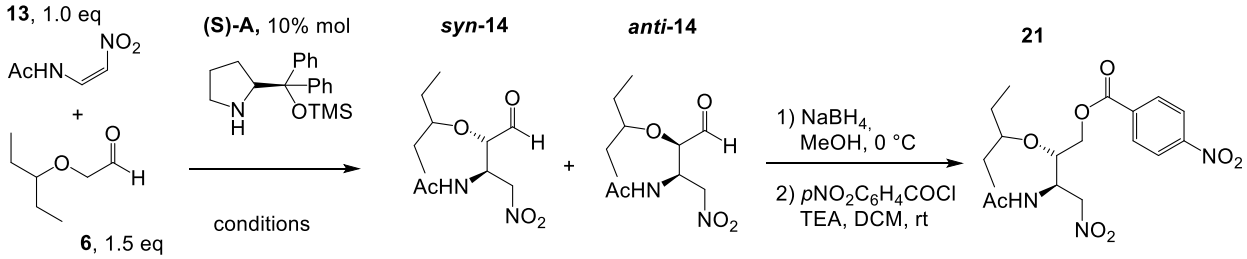
presence of 70% of product that was isolated in 27% yield after chromatographic purification. The reaction performed in batch that was subjected to the same work up gave the product in 57% yield. This is probably due to the decomposition of the amine **20** in pyridine, a hypothesis supported by the fact that this solution turned rapidly deep dark, or by the decomposition due to the prolonged contact of product **13** with the $NH_4Cl$ aq. sat. solution.
Washing the crude solution with aq. HCl may cause partial decomposition of **13** due to hydrolysis of the enamide moiety. Indeed performing the removal of the pyridine by washing the crude solution with $CuSO_4$ aq. solution allows to obtain the product in higher yields. Also the removal of the excess of pyridine under reduced pressure caused a partial degradation of the product **13**.
Because of these problems I decided not to study further the acetylation in flow and focus on the development of the key step of Oseltamivir synthesis using a supported catalyst.

### 2.7.2.3 Supported catalyst to perform the enantiodetermining step of Oseltamivir synthesis

Several conditions have been reported to perform the enantioselective Michael addition of aldehyde **6** to nitro olefin **13**. Hayashi catalysts have always been used as chiral promoters. An elegant study by the Hayashi group revealed that commercially available TMS catalyst **A** can perform the Michael addition on **13**, leading to catalyst deactivation, while the use of bulkier $MePh_2Si$ group avoids this problem.[16c] Different acidic co-catalysts and solvents were employed by different groups. In particular Durmis and Sebesta reported a detailed study on the acidic co-catalyst effect outlining that acids having $pK_a$ between 2 and 4 perform best.[20]
My objective was to adapt this reaction to flow conditions. The supported prolinol catalyst has an average molecular weight of 2000 uma (calculated on the basis of the functionality degree and on the polymer monomer structure; this notion is formally incorrect but it very useful to compare it with the non-supported analogs) and its synthesis requires multiple steps, so usually homogeneous catalysts are used to perform the first investigation in order to find reaction conditions suitable for flow.
The requirements to translate a reaction to flow are: 1) all the reagents and products must be soluble to avoid the occlusion of the reaction channel, 2) the reaction solvent should guarantee a good swelling of the resin to allow the reagents to get into contact with the active catalytic sites, 3) the reaction should be complete in less than 8-10 hours in batch, otherwise the flow rate should be too low to drive the reaction to completion.
The resin is usually a polystyrene polymer and strongly polar solvents such as DMF, DMSO and water are usually not suitable because they repulsively interact with it avoiding the resin swelling.
I started my investigation from the conditions reported in the literature and tried to find out the best fitting to the abovementioned flow requirements.
Ma's conditions (DCM and PhCOOH) afforded total solubility and high conversion in 2 h, but the diastereomeric ratio I obtained was 2:1, instead of the reported 4:1 (table 4 entry 1). Hayashi obtained a 8:1 dr using HCOOH and chlorobenzene, but amine **13** is poorly soluble in this solvent precluding its use in a flow process. Moreover, I obtained only 20% conversion instead of the full conversion reported, while the dr was 8:1 according to Hayashi report (table 4 entry 2). Durmis and

Sebesta biphasic system was perfectly reproducible but the use of water could not be translated on flow (table 4 entry 3). However chloroform alone performed quite well and guaranteed a perfect solubility of all the reagents (table 4 entries 4, 5).

.



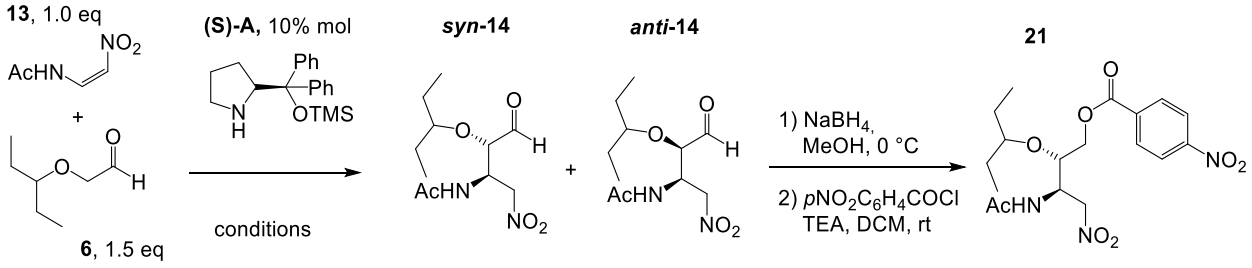

| entry | Solvent | T (°C) | Conc **13** (M) | Acid | mol % | Conversion (time)[a] | d.r.[a] *syn/anti* | ee[b] *syn* |
|---|---|---|---|---|---|---|---|---|
| 1 | $CHCl_3$ | 0 | 0.4 | PhCOOH | 15% | 95% (3 h) | 2:1 | nd |
| 2 | $C_6H_5Cl$ | 22 | 0.25 | HCOOH | 20% | 30% (20 h) | nd | 88 |
| 3 | $CHCl_3/H_20$ 1/1 | 0 | 0.25 | (±)-mand. a.[c] | 20% | 75% (3 h) | 5:1 | 94 |
| 4 | $CHCl_3$ | 0 | 0.25 | (±)-mand. a. | 20% | 78% (3.5 h) | 3:1 | 92 |
| 5 | $CHCl_3$ | 0 | 0.4 | (±)-mand. a. | 20% | 70% (3.5 h) | 3.7:1 | 92 |
| 6 | $CHCl_3$ | -3 | 0.22 | PhCOOH | 30% | 100% (4 h) | 2:1 | 93 |
| 7 | $CHCl_3$ | -3 | 0.22 | (±)-mand. a. | 30% | 80% (4 h) | 4.3:1 | 93 |
| 8 | $CHCl_3$ | -3 | 0.22 | HCOOH | 30% | 50% (4 h)<br>50% (7 h) | 8:1<br>5.5:1 | 90 |
| 9 | $CHCl_3$ | -5 | 0.22 | HCOOH | 50% | 86% (4 h) | 5.4:1 | nd |
| 10 | $CHCl_3$ | -5 | 0.22 | HCOOH | 10% | 32% (4 h) | 5.0:1 | nd |
| 11 | $CHCl_3$ | -5 | 0.22 | $ClCH_2COOH$ | 30% | 15% (3 h) | 3.2:1 | nd |
| 12 | $CHCl_3$ | 0 | 0.22 | $CH_3COOH$ | 30% | >90% (2 h) | 1.5:1 | nd |

All reactions were carried on 0.1 mmol scale; for the detailed experimental procedure see the experimental part. (a) determined by $^1H$ NMR on the crude reaction mixture; (b) determined by HPLC using chiral columns after derivatization to **21** and chromatographic purification; (c) racemic mandelic acid.

*Table 4: investigation of suitable conditions for the flow system using homogeneous catalyst.*

A close investigation of the acidic additives and temperatures in $CHCl_3$ allowed to obtain a 8:1 dr using HCOOH at –3°C, but I obtained only 50% conversion after 3 h (table 4 entries 6-8). The reaction did not proceed any further suggesting that the catalyst might be deactivated. Moreover, during the reaction course I observed a rapid disappearing of the aldehyde signal together with the increase of the signals relative to the pentanol side chain, which is compatible with the

decomposition of the aldehyde or with the formation of its trimolecular acetal during the reaction course.
The use of chloroacetic acid afforded a very poor conversion, while acetic acid gave a complete conversion in two hours albeit with very poor diastereoselectivity, indicating formic acid is the best co-catalyst. Moreover, its increase to 50 mol% allowed to obtain 86% conversion (table 4 entry 9).
The use of other organic solvents led to worse results in terms of yields or selectivity (table 5).
I also tested different solvents on the so far best conditions, but only dichloromethane gave a good conversion, even if the dr was lower compared to chloroform, while in all the other solvents the reaction proceeded to a very limited extent (table 5).

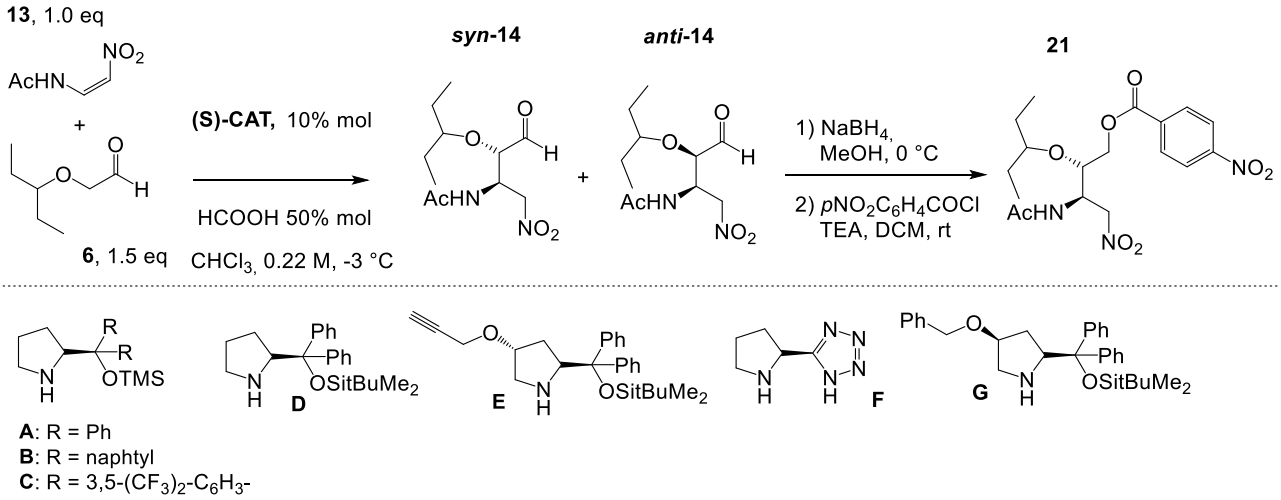



| entry | Solvent | T (°C) | Conc **13** (M) | Acid | mol % | Conversion (time)[a] | d.r.[a] *syn:anti* | ee[b] *syn* |
|---|---|---|---|---|---|---|---|---|
| 1 | $CHCl_3$ | 0 | 0.22 M | HCOOH | 30% | 70% (2h) | 3.6:1 | 89* |
| 2 | AcOEt | 0 | 0.25 M | HCOOH | 30% | 16% (3h) | 2:1 | nd |
| 3 | MeOH | 0 | 0.25 M | HCOOH | 30% | 0% (3h) | nd | nd |
| 4 | $CH_3CN$ | 0 | 0.25 M | HCOOH | 30% | 12% (3h) | 1:1 | nd |
| 5 | DCM | 0 | 0.25 M | HCOOH | 30% | 23% (3h) | 5:1 | 89 |
| 6 | THF | 0 | 0.25 M | HCOOH | 30% | 26% (3h) | 8:1 | 94 |
| 7 | THF/$H_20$ 1/1 | 0 | 0.25 M | HCOOH | 30% | <10 (5h) | 2:1 | nd |

All reactions were carried on 0.1 mmol scale; for the detailed experimental procedure see the experimental part. (a) determined by $^1H$ NMR on the crude reaction mixture; (b) determined by HPLC using chiral columns after derivatization to **21** and chromatographic purification.

*Table 5: effect of the solvent on the reaction outcome.*

Having found good conditions ($CHCl_3$, formic acid, 0 °C) with standard Hayashi catalyst **A**, I tested with the same conditions different prolinol catalysts **B-G** having different silyl and aryl groups to get information on the importance of these moieties on the reaction outcome in order to select the more suitable structure for the supported catalyst.




| entry | **CAT** | Conversion (time)[a] | d.r.[a] *syn:anti* | ee[b] *syn* |
|---|---|---|---|---|
| 1 | **A** | 23% (3 h) | 4:1 | nd |
| 3 | **B** | 17% (3 h) | 2.5:1 | nd |
| 6 | **C** | 0 (3 h) | - | - |
| 2 | **D** | 50% (3 h) | 5:1 | nd |
| 4 | **E** | 18% (3 h) | 1.4:1 | nd |
| 5 | **F** | 0 (3 h) | - | - |
| 7 | **G** | 57% (3 h) | 15:1 | - |
| | | 85% (21 h) | 16:1 | 99 |

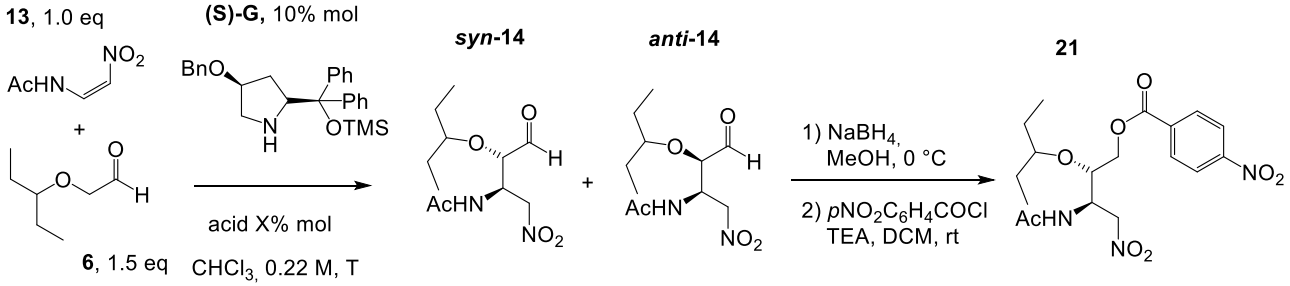
All reactions were carried on 0.1 mmol scale; for the detailed experimental procedure see the experimental part. (a) determined by $^1$H NMR on the crude reaction mixture; (b) determined by HPLC using chiral columns after derivatization to **21** and chromatographic purification.

*Table 6: screening of homogenous catalysts.*

Catalyst **B** having the naphtyl groups afforded a very poor result, that was even worse using Jørgensen catalyst **C** or tetrazole substituted catalyst **F**, which failed to promote the reaction. The presence of bulkier TBS group (cat **D**) on the prolinol gave a good result. The introduction of a substituent on the 4 position of the pyrrolidine ring, that is the usual position where the monomer is linked to the solid support, played a crucial role on the reaction outcome: 4-*trans* substituents are detrimental for the reaction outcome both on conversion and on stereoselectivity, while 4-*cis* substituted catalyst **G** afforded the product in high conversion after 21 h with a very high dr (15:1), a much better result compared to those obtained in the literature. The poor result obtained with *trans* catalyst **E** might be due to the hindrance that the 4-*trans* substituent exercises, which is of

course avoided by the position on the 4-group on the *cis* position. We could not instead propose a solid explanation for the significant increase on the stereoselectivity determined by the use of *cis* benzyl.

This result was particular encouraging because catalyst **G** had been developed by Prof. Pericàs group and Dr. Alessandro Ferrali at CSOL (one of the units of ICIQ).




| entry | T | eq. of **6** added (time)[a] | Acid | Mol % | Conversion[a] | d.r.[b] *syn:anti* | ee *syn*[c] |
|---|---|---|---|---|---|---|---|
| 1 | -5 | | (±)-mand. a.[d] | 30% | >95%(22 h) | 7:1 | 90 |
| 2 | -5 | | $ClCH_2CO_2H$ | 30% | 30% (3 h) | 13:1 | >99 |
| | | +0.75 eq. (6 h) | | | 80% (27 h) | 27:1[e] | |
| | | | | | 90% (40 h) | 16:1 | |
| 3 | -5 | | HCOOH | 50% | 29 (3.5 h) | 19:1 | >99 |
| | | +0.75 eq. (6 h) | | | 95%(20 h) | 18:1 | |
| 4 | 0 | | HCOOH | 50% | 29% (3.5 h) | 67:1[e] | >99 |
| | | +0.75 eq. (6 h) | | | 90%(20 h) | 17:1 | |
| 5 | 12 | | HCOOH | 50% | 65% (3 h) | 27:1 | 96 |
| | | +0.75 eq. (4.5 h) | | | 97%(7 h) | 22:1 | |
| 6 | 22 | | HCOOH | 50% | 89% (3.5h) | 7:1 | 94 |

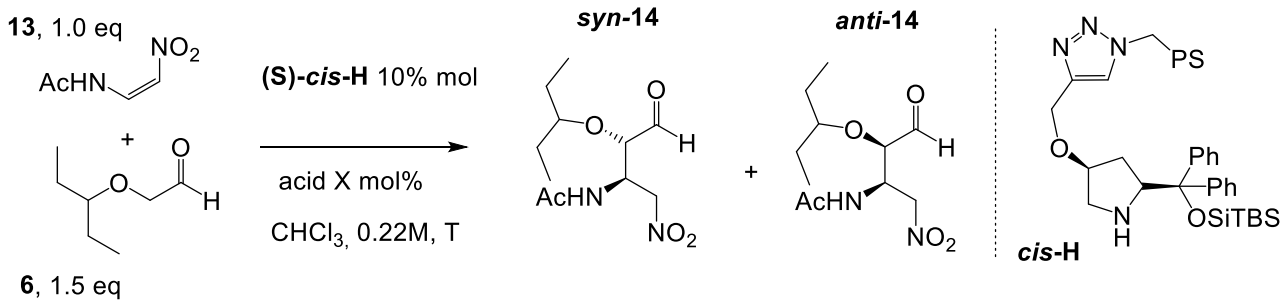
All reactions were carried on 0.1 mmol scale; for the detailed experimental procedure see the experimental part. (a) equivalents of aldehyde **6** added after the indicated time; (b) determined by $^1$H NMR on the crude reaction mixture; (c) determined by HPLC using chiral columns after derivatization to **21** and chromatographic purification; (d) racemic mandelic acid; (e) the signal to noise ratio of minor-anti-**14** was too low to measure a reliable dr.

*Table 7: screening of different conditions with catalyst **G** to increase the reaction rate.*

For this reason I studied in detail the reaction using this catalyst changing the acidic cocatalysts and the temperature to try and decrease the reaction time. Both chloroacetic acid and HCOOH afforded optimal diastereoselectivities and enantioselectivities. However, in all the reactions I observed the

partial decomposition of the aldehyde, that was probably responsible for the drop of the conversion rate after 6-7 hours of reactions. The addition of another portion of aldehyde after 3-6 h allowed to obtain almost full conversion for the reaction that in the best case was achieved in 7 h.
The enantioinduction is always high and I observed minor changes alongside with the variation of the reaction conditions: the ee's were always higher than 90% and tipically around 95%, perfectly reproducible. On the other hand, the diastereomeric ratio not only was strongly influenced by the different conditions, but was not always reproducible as well as the reaction conversion versus time. The purity of the reagents, in particular of the aldehyde **6** can influence this result. It must also be noted that the diastereomeric ratio slowly decreases during time due to the high acidity of the aldehyde α-proton. Maintaining the reaction below 12 °C minimizes this epimerization, that becomes significant when the reaction is warmed to room temperature. The measurement of the dr by $^{1}$H NMR should be done in a limited timeframe from the preparation of the sample, as I observed a significant decrease of the measured dr reacquiring the same sample after 4 h.
I then tested the polystyrene supported catalyst ***cis*-H** under the best conditions (table 7, entry 5). An amount of supported catalyst corresponding to 10% mol of active sites was weighed and added to the reaction mixture that was stirred at the temperature indicated in table 8. I immediately observed a decrease in the reaction rate and in the dr (between 6:1 and 10:1) using the supported catalyst ***cis*-H**. More importantly the conversion stopped around 60% in the first experiment that I performed at room temperature suggesting that the catalyst had been deactivated, a hypothesis confirmed by the unsuccessful attempt to recycle ***cis*-H** in a second reaction after its recovery by filtration (table 8, entry 1).
I managed to obtain a full conversion by lowering the temperature to 12 °C, but also in this case the reuse of the catalyst highlighted its deactivation from the second cycle (table 8, entry 2).
I tried to use chloroacetic acid instead of more reactive formic acid and I obtained a good, but not complete, conversion in the second cycle. However the catalytic activity was totally inhibited in the third cycle showing that formic acid was not responsible for that even if it seemed to accelerate the process (table 8, entry 3).
The recovery of the catalyst was performed by filtration over a Gooch septum of the crude mixture to separate the resin from the other soluble species. The resin was then washed several times with chloroform, dried and reused. The drying of the resin of a secondary amine catalyst is not a correct procedure because if some actives sites are still condensed with the aldehyde, the contact with air in the absence of solvent favors the oxidative degradation of these intermediates causing the catalyst inhibition. Another possible explanation accounting for the catalyst deactivation is the Michael addition to nitroalkene **13**.
I managed to push the reaction to complete conversion in 3 h by adding a large excess of aldehyde **6** portionwise every 30 min. Unfortunately also in this case the recovered catalyst was totally inactive in a second cycle (table 8 entry 4). The use of *para*-nitrobenzoic acid as co-catalyst led to a poor result both in terms of conversion and diastereoselectivity (table 8, entry 5).
It is very difficult to understand what happens to a supported catalyst as standard techniques such as mass spectrometry or $^{1}$H NMR cannot be used due to its polymeric insoluble support, leaving IR as the major source of information. The comparison of the IR spectra of the active resin vs the deactivated one showed the appearance of a new band at 1670 cm$^{-1}$ in the inactive catalyst (figure

2). This band is compatible with stretching of a nitro group caused by the formation of adduct **22**, but we cannot rule out other possibilities such as decomposition or oxidation of enamine **23**.



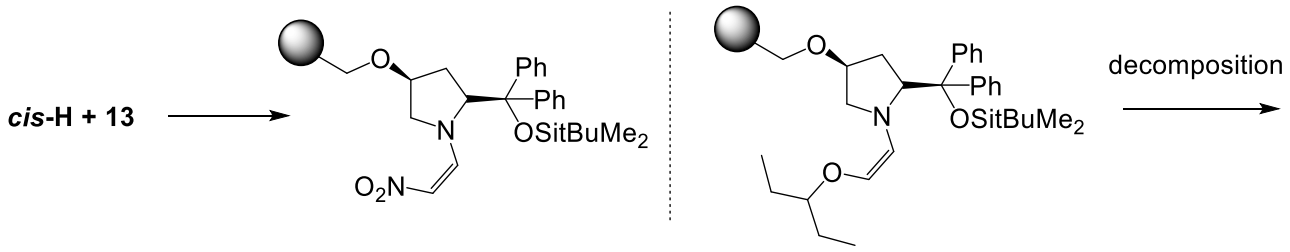

| entry | cycle | T (°C) | acid | mol% | Conv. (time)[a] | dr[a] | ee *syn*[b] |
|---|---|---|---|---|---|---|---|
| 1 | cycle 1 | 26 | HCOOH | 50% | 54% (3h) | 8:1 | |
| | +0.75 eq **6** (4h)[c] | | | | 62% (8h) | 8:1 | |
| | | | | | 58% (24h) | 7:1 | 96 |
| | cycle 2 | 26 | HCOOH | 50% | 0 | - | - |
| 2 | cycle 1 | 12 | HCOOH | 50% | 58% (3h) | 10:1 | |
| | +1 eq **6** (4h)[c] | | | | 96% (20h) | 6.9:1 | 96 |
| | cycle 2 | 12 | HCOOH | 50% | 10% (15h) | N d | |
| | cycle 3 | 12 | HCOOH | 50% | 0% (5h) | N d | |
| | | | | | 0% (24h) | | |
| 3 | cycle 1 | 12 | $ClCH_2COOH$ | 50% | 61% (3h) | 10:1 | |
| | +1 eq **6** (4h)[c] | | | | 90%(20h) | 6.4:1 | 94 |
| | cycle 2 | 12 | $ClCH_2COOH$ | 40% | 41% (15h) | 6:1 | |
| | +0.75 eq **6** (16h)[c] | | | | 60% (23h) | 6/1 | |
| | cycle 3 | 12 | $ClCH_2COOH$ | 40% | 0% (5h) | | |
| | +0.75 eq **6** (6h)[c] | | | | 0% (24h) | | |
| 4[d] | cycle 1 | 0 | $ClCH_2COOH$ | 30% | 100% (3,5h) | 7:1 | |
| | cycle 2 | 12 | $ClCH_2COOH$ | 40% | 0% | | |
| 5 | cycle 1 | 12 | *p*$NO_2C_6H_4OH$ | 30% | 24% (3h) | 5:1 | |
| | +0.75 eq **6** (4h)[c] | | | | 33% (6h) | 5:1 | |

All reactions were carried on 0.1 mmol scale; for the detailed experimental procedure see the experimental part. (a) dr *syn:anti* determined by $^1$H NMR on the crude reaction mixture; (b) determined by HPLC using chiral columns after derivatization to **21** and

chromatographic purification; (c) equivalents of aldehyde **6** added after the indicated time; (d) 4 eq of aldehyde **6** were added portionwise over 3 h.

*Table 8: different conditons tested with supported catalyst **cis-H** in batch.*

If deactivation is due to the formation of **22**, the retro Michael reaction that would give back the active catalyst should be promoted either by strong basic or acid conditions. Therefore, I treated one sample of deactivated resin ***cis*-H** suspended in DCM with DBU and another one with TFA. After 5 h, I filtered the resins and I washed them with DCM (the resin treated with TFA was washed also with DIPEA diluted in DCM), but I did not observe any significant changes in the IR spectra that still displayed the additional bands disfavoring the deactivation by formation of **22**. However, further evidence must be collected to try and understand the deactivation mechanism. In particular, mixing the catalyst with each reaction partner and then testing its activity and measuring its IR spectra might provide some useful evidences.




*Scheme 5: possible deactivation pathways of supported catalyst **cis-H**.*

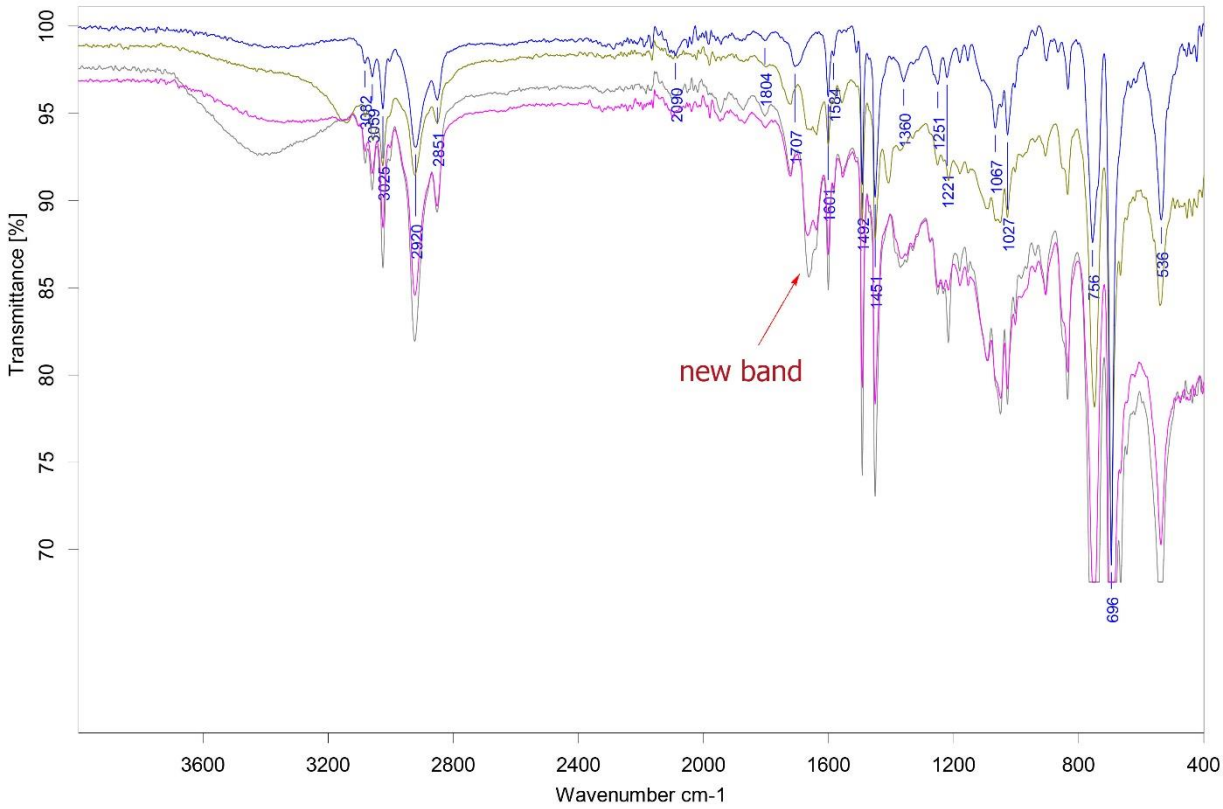
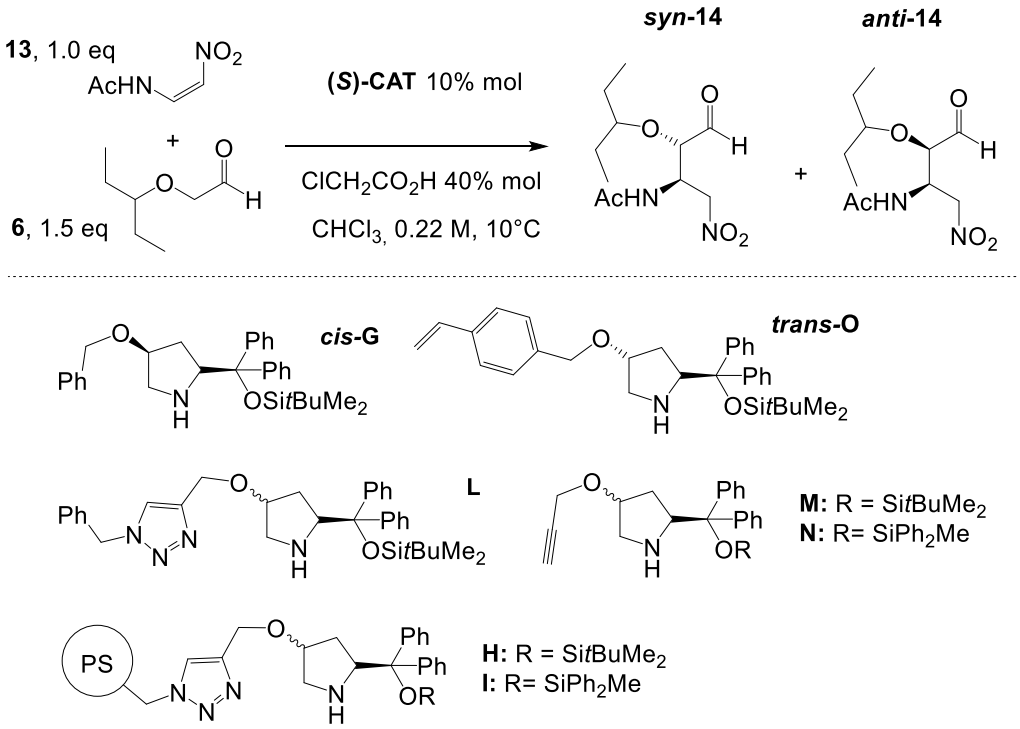



*Figure 2: IR spectra of active catalyst **cis-H** (blue line) and inactive catalysts **cis-H** (gold, grey and pink lines) recovered after the reaction.*

Quite often a decrease in the reaction rate is observed changing from homogeneous to heterogeneous organocatalysts because the hindrance of the polymer support of the latter ones slows down the approach of the reagents to the active site (mass transfer can be the rate determining step).




| entry | ***cis*-cat** | conv. (h)[a] | dr [a] | entry | ***trans*-cat** | conv. (h) [a] | dr [a] |
|---|---|---|---|---|---|---|---|
| 1 | ***cis*-H** | 63% (4.5 h) | 19:1 [b] | 7 | ***trans*-H** | 2% (4.5 h) | 2:1 |
| | | 75% (7h) | 7:1 | | | | |
| 2 | ***cis*-I** | 25% (4h) | 1:0 | | | | |
| 3 | ***cis*-L** | 64% (3h) | 5:1[c] | 8 | ***trans*-L** | 23% (3h) | 1.3:1 |
| | | 85% (7h) | 8:1 | | | | |
| 4 | ***cis*-M** | 51% (3h) | 9:1 [c] | 9 | ***trans*-M** | 17% (3h) | 2.5:1 |
| 5 | ***cis*-N** | 45% (3h) | 8:1 | | | | |
| 6 | ***cis*-G** | 64% (3h) | 7:1 [c] | 10 | ***trans*-O** | 42% (3h) | 1.9:1 |
| | | 76% (7h) | 8:1 | | | | |

All reactions were carried on 0.1 mmol scale; for the detailed experimental procedure see the experimental part. (a) dr *syn:anti* determined by $^1$H NMR on the crude reaction mixture; (b) 4 h after first measurement the dr was 8:1 ; (c) $^1$H NMR recorded 4 h after the probe preparation.

*Table 9: effect of the 4-substituent on the catalyst pyrrolidine ring.*

A structural difference is present between the best performing monomer catalyst **G** and the resin ***cis*-H** consisting in the presence of the triazole ring instead of the phenyl group. The triazole ring is a weak base that can react with the acid cocatalyst slowing down the reaction or engage hydrogen

bonding with the substrates. In order to investigate its influence on the reaction outcome I prepared triazole containing monomers **L** and compared their catalytic activity with those of the other catalysts in a parallel set of experiments where all catalyst in table 9 were tested under identical conditions.

No significant differences in reactivity and selectivity were observed between the *cis* monomers ***cis*-G**, ***cis*-L** and resin ***cis*-H** that have the TBS group in the parallel experiment independently from the presence of phenyl group, tetramisole or the resin support (table 9, entries 1, 3, 6) (in table 8, I observed 90% conversion after 20 h because I ran the reaction overnight so a direct comparison with the result in table 9 is not possible). The use of *cis* propargyl monomers ***cis*-M** and ***cis*-N** gave a slight decrease in the reaction conversion after 3 h (table 9, entries 4, 5). Instead, the presence of the bulky $MePh_2Si$ group in resin ***cis*-I** caused a drop in the reaction conversion (table 9, entry 2).

The use of monomers ***trans*-L**, ***trans*-M**, ***trans*-O** led to a drop in both conversion and diastereoselectivity, while resin ***trans*-H** failed to promote the reaction, confirming the necessity to use a *cis* supported catalyst for this reaction (table 9, entries 7-10).

The tests run using resin ***cis*-H** in batch highlighted a deactivation process after the first cycle, suggesting that the product formation is faster than the catalyst deactivation. Consequently, there is the possibility that performing the reaction on flow might reduce or even solve this problem. Moreover, the catalyst inhibition might be due to the product, that under flow would be continuously removed, minimizing any detrimental interaction with the catalyst.

For these reasons I decided to test the reaction on flow conditions. I introduced 0.5 g of resin inside a HPLC-like glass column and I conditioned it by passing chloroform, the reaction solvent. Then, the reagents solutions in chloroform were circulated by syringe pump through the column and the outstream was analyzed by $^1$H NMR.

As aldehyde **6** is quite unstable, a solution under nitrogen was prepared and the syringe in which it was contained was covered with aluminum foil to minimize its exposure to light. A preliminary test revealed that nitro alkene **13** was stable in solution in presence of chloroacetic acid, so a solution of these two reagents was prepared and pumped through a second syringe (figure 3).

The first experiment was run with 0.2 M solution of **13** with 50% mol chloroacetic acid and a 0.3 M solution of aldehyde **6**. At a flow rate of 0.2 mL/min the conversion was only 19%. Decreasing the flow rate to 0.03 mL/min lead to a moderate increase up to 40% (table 10, entry 1). Based on previous reports that highlighted how the amount of acid cocatalyst required in flow is higher than in batch,[11] I raised the amount of chloroacetic acid to 1 equivalent in the next experiment that was conducted with 0.02 mL/min flow rate. In these conditions the residence time was around one hour, i.e. the time when the aldehyde was first eluted from the column while the product **14** and nitro **13** are more retained inside the resin. However, the conversion was still low (table 10, entry 2). The low conversion observed also with a very low flow rate suggested that the catalyst had already been deactivated during the first experiment.

Moreover, the $^1$H NMR of the collected samples revealed that the amount of aldehyde during the time progressively decreased as it is evident from the aldehyde (**6** + product **14**) / (nitro alkene **13** + product **14**) ratio, that instead of being constant during the reaction time rapidly decreased. Note that the initial ratio **6 / 13** was 1.5. The formation of the enamine between the aldehyde and the catalyst subtracts a significant amount of aldehyde from the solution that could account for this observation as well as a degradation of this reagent.

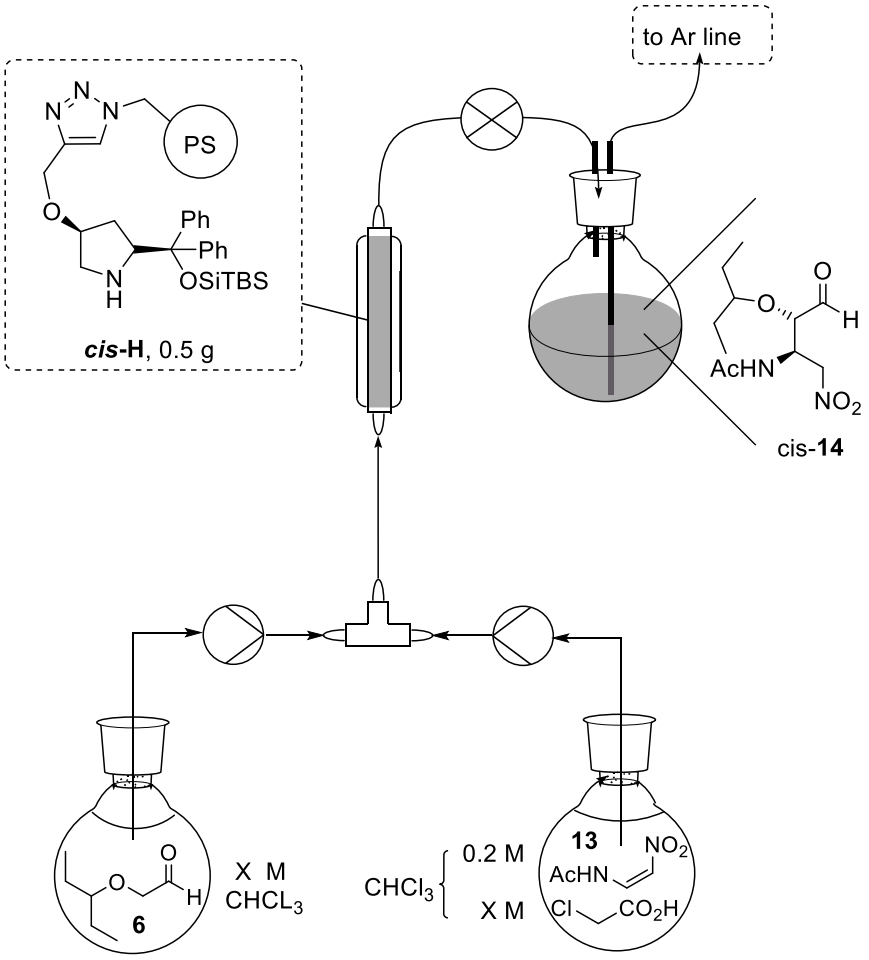



*Figure 3: set up of the flow experiment.*

In order to push the reaction equilibrium towards the formation of the enamine and by consequence towards the product formation, I increased the amount of aldehyde in the third experiment in which I used 0.5 g of new resin to be sure that no previous deactivation had occurred. I raised the flow rate to an acceptable value of 0.08 mL/min and after 75 min the product left the column and 97% conversion was determined by $^{1}H$ NMR. Unfortunately this good result was not kept overtime and just after 2 h the conversion dropped to 57% and it further decreased to 46% in the last sample analyzed after 3 h. These data confirmed that a rapid deactivation of the catalyst occurred but the mechanism is still unknown.

| exp. | Aldehyde **6** (M, n eq) | % acid | time[a] | T[b] (°C) | Flow rate[c] (mL/min) | Conv[d] | d.r. [d] | ee[e] |
|---|---|---|---|---|---|---|---|---|
| 1 | 0.3 M (1.5 eq) | 50% | 22 min | 10 | 0.2 | 19% | 1:0 | - |
| | | | 45 min | 10 | 0.03 | 25% | 4:1 | |
| | | | 68 min | 10 | 0.03 | 30% | 3:1 | |
| 2 | 0.3 M (1.5 eq) | 100% | 20 min | rt | 0.02 | | | |
| | | | 45 min | rt | 0.02 | | | |
| | | | 70 min | rt | 0.02 | [f] | | |
| | | | 2 h | rt | 0.04 | 40% | 7:1 | 99 |
| | | | 2.5 h | rt | 0.04 | 30% | 4:1 | |
| 3 | 0.6 M (3.4 eq) | 100% | 35 min | rt | 0.08 | [f] | | |
| | | | 75 min | rt | 0.08 | 91% | 5:1 | |
| | | | 2 h | rt | 0.08 | 58% | 7:1 | |
| | | | 3 h | rt | 0.08 | 46% | 5:1 | |
| | | | 4.5 h | rt | 0.08 | - | - | |
| | | | total | rt | 0.08 | 67% | 8:1 | |

The experiments were conducted with the experimental set up illustrated in figure 2; for the detailed experimental procedure see the experimental part. (a) elution time at the end of the column; time = 0 when the reagents first entered the packed column; (b) temperature of the packed column; (c) total flow rate of the mixed reagent solutions; (d) dr *syn:anti* determined by $^{1}$H NMR on the crude reaction mixture; (e) determined by HPLC using chiral columns after derivatization to **21** and chromatographic purification; (f ) aldehyde **6** and its autocondensation product were observed by $^{1}$H NMR.

*Table 10: results obtained performing the reaction on flow with resin **cis-H**.*

## 2.7.3 Conclusions

During my stay in Professor Pericàs group I studied the key step for the organocatalytic synthesis of (–)-Oseltamivir using a novel class of Hayashi-Jørgenen catalysts derived from *cis*-4-hydroxy proline. Among them, catalyst **G** proved to be superior to standard Hayashi-Jørgensen catalysts affording intermediate **14** in complete conversion after 7-20 h and in excellent diastereomeric ratio and enantiomeric excess. The reaction can be performed also using polystyrene supported catalyst ***cis*-H**, formally derived from *cis*-4-hydroxy proline. Complete conversion can be achieved in batch in the first cycle, but unfortunately this supported catalyst was readily deactivated and its catalytic activity dropped already in the second cycle in batch and after 2 h in the flow experiment. Preliminary investigations did not allow to understand the mechanism of the deactivation and further analysis is necessary.
I also studied and established a greener and more convenient synthetic route to both the non-commercially starting materials aldehyde **6** and nitro alkene **13**, performing the synthesis of the key precursor of **13** in flow thanks to the tube-in-tube technology.
During this time I have enriched my skills with competences on flow chemistry and on the synthesis of supported organocatalysts thanks to the precious teaching of Professor Pericàs and all the members of his research group.

## 2.7.4 Contributions

I developed the project under the supervision of Professor Pericàs and Dr. Carles Rodriguez-Escrich. I performed the tube-in-tube experiments thanks to the help of Dr. Esther Alza and Dr. Carles Rodriguez Escrich. I want to thank Dr. Laura Osorio and Patricia Llanes for the advices on flow experiments and Dr. Alessandro Ferrali for furnishing catalyst **G** and the recipe for the synthesis of ***cis*-H** and ***cis*-I**.

## 2.7.5 Experimental part

**General Methods.**

Unless otherwise stated, all commercial reagents were used as received and all reactions were carried out directly under open air. Merrifield resin (1% DVB, $f$ = 0.53 mmol Cl $g^{-1}$ resin) was obtained from Novabiochem. All flash chromatography was carried out using 60 mesh silica gel and dry-packed columns. NMR spectra were registered in a Bruker Advance 400 Ultrashield spectrometer in $CDCl_3$ at room temperature, operating at 400.13 MHz ($^1H$) and 100.63 MHz ($^{13}C\{1H\}$). TMS was used as internal standard for 1H NMR and $CDCl_3$ for 13C NMR. Chemical shifts are reported in ppm referred to TMS. IR spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer. Elemental analyses (C; H; N) were performed in a Carlo Erba-ThermoQuest Model 1108 by Servei de Microanalisi, Consell Superior d'Investigacions Científiques, Barcelona, Spain. FAB mass spectra were obtained on a Fisons V6-Quattro instrument, ESI mass spectra were obtained on a Waters LCT Premier instrument and CI and EI spectra were obtained on a Waters GCT spectrometer. Optical rotations were measured on a Jasco P-1030 polarimeter. High performance liquid chromatography (HPLC) was performed on Agilent Technologies chromatographs (Series 1100 and 1200), using Chiralpak columns and guard columns.

**Improved procedure for the opening of glycidol with 3-pentanol.**

In a round bottom flask under nitrogen atmosphere equipped with a magnetic stirring bar and a reflux condenser, glycidol **17** (4.2 mL, 64 mmol) was dissolved in 3-pentanol (40 mL, 370 mmol). Then, $LiClO_4$ (30 g, 272 mmol) was added and the mixture was heated to reflux (115 °C) -so that it became an homogeneous solution- for 66 h behind a protective anti explosion glass. After this time complete conversion was observed by GC analysis. The mixture was allowed to cool to rt and a partial precipitation of $LiClO_4$ occurred. The minimal amount of water to dissolve the $LiClO_4$ was added and the solution was extracted with $Et_2O$ (4 x 30 mL). The organic phases were dried over $Na_2SO_4$, filtered and concentrated by rotary evaporation to give a residue composed by product **18** and 3-pentanol that was removed under reduced pressure (≈ 30 °C, $10^{-1}$ mbar) to afford pure **18** as a yellow liquid (6.40 g, 39.8 mmol, 62 % yield).

The **oxidative cleavage** of diol **18** to obtain aldehyde **6** was done according to the procedure reported by Sebesta.[16b] The aldehyde is unstable and the reaction should be carried on under nitrogen atmosphere and shielded from light. In addition the work up procedure must be conducted rapidly and the product **6**, a pale yellowish liquid, kept under argon at 0 °C to minimize its decomposition over time.

Nitroolefin **19** was prepared according to the procedure described by Ma.[15]

**Synthesis of 20 with the tube-in-tube reactor.**

In table 2 is depicted the experimental set up for the tube in tube experiment.
Standard HPLC pipes and connectors were used.
The solution of **19** (300 mL 0.1 M in MeOH) was connected to the pump via a Teflon pipe through a septum. A nitrogen inlet was connected through a needle to equilibrate the pressure. The outlet of the pump was connected to the inlet of the tube-in-tube (1 m long) that was connected to the ammonia cylinder via stainless steel valves and connectors. The outlet of the tube-in-tube was connected to the 2 m coil (2 mL) merged in a 55 °C water bath. The coil was connected at the other end to the back pressure regulator (BPR) set at 6 bar by connecting it to the argon line. At the exit of the BPR was placed the balloon for the collection at 0 °C and under nitrogen atmosphere.
After setting the BPR to 6 bar, the ammonia cylinder was opened and the gas pressure inside the tube in tube set to 4 bar. Then the pump was started (flow rate 0.5 mL/min). The residence time inside the system was around 8 min.

Work up procedure 1: the collected solution (37 mL after 1.2 h) was concentrated under reduced pressure to give a red residue that was triturated with $CHCl_3$ (3 mL, 1 each 10 mL of collected solution). The precipitation of the product occurred while the solution rested overnight at 0°C. Then it was filtered and the solid washed with 1-2 mL of cold $CHCl_3$. The solid was dried under reduced pressure to afford **20** (300 mg, 3.41 mmol, 92 % yield, 100% purity).

Work up procedure 2: the collected solution (260 mL after 6.5 h) was concentrated under reduced pressure to give a red residue that was triturated with $CHCl_3$ (15 mL). The precipitation of the product occurred while the solution rested for 20 min at 0°C. Then it was filtered and the solid washed with 4 mL of cold $CHCl_3$. The solid was dried under reduced pressure to afford 1.85 g of **20** (1.85 g, 21.0 mmol, 81 % yield, 100% purity).

The yield was calculated on the amount of the volume of the collected solution.
The **acetylation** of **20** to afford **13** was done according to the procedure reported by Sebesta.[16b]

**Typical procedure for the stereoselective synthesis of compound 14 using homogeneous or supported catalysts in batch.**

In a 2 mL vial equipped with a magnetic stirring bar, prolinol catalysts **A-O**, nitroalkene **13** (13 mg, 0.1 mmol), and the chloroacetic acid co-catalyst (2.8 mg, 0.03 mmol) were dissolved in chloroform. The solution was cooled to 4 °C, aldehyde **6** (20 mg, 0.15 mmol) was added and the solution stirred for 3-20 h during which the conversion and the dr were checked by $^1H$ NMR by taking directly aliquots from the reaction mixture and diluting them in $CDCl_3$. After 3-6 h another equivalent of aldehyde **6** (13 mg, 0.1 mmol) was added to the reaction mixture. The dr decreases in a few hours timespan at rt so the NMR samples should be acquired rapidly. After the indicated time the reaction mixture was cooled to 0 °C, diluted with MeOH (500 µL) and the aldehydes reduced to the corresponding alcohols by addition of $NaBH_4$ (15 mg, 0.4 mmol). After complete conversion as

judged by TLC (1-2 h), the reaction was quenched by addition of 1 M aq. HCl and extracted with ethyl acetate (3 x 5 mL). The organic layers were dried over $Na_2SO_4$, filtered and concentrated by rotary evaporation to give the crude product.

**Derivatization to evaluate the enantiomeric excess**. The alcohol product does not absorb in the near UV spectra so it is necessary to derivatize it to the corresponding *p*-nitrobenzoate in order to evaluate the enantiomeric excess.

The crude mixture was dissolved in DCM and *p*-$NO_2$-benzoyl chloride (55 mg, 0.3 mmol) and triethylamine (55 µL, 0.5 mmol) were added. The mixture was stirred for 3 h at rt then it was quenched by addition of water, extracted with ethyl acetate (3 x 5 mL). The organic layers were dried over $Na_2SO_4$, filtered and concentrated by rotary evaporation to give the crude product that was purified by preparative TLC on silica to afford *syn*-**21**.

The spectroscopic data were according to the literature.[16]

The enantiomeric excess of XX was determined by HPLC analysis Daicel Chiralpak® OD-H column: hexane/*i*-PrOH 80:20, flow rate 0.70 mL/min, 25°C, λ = 215, 230 nm: $\tau_{major}$ = 20 min., $\tau_{minor}$ = 25 min. The ee was 90-99% depending on the reaction conditions, see the results and discussion.

**Synthesis of 14 by using supported catalyst *cis*-H in flow.**

The experimental set-up is depicted In figure 2.

Resin *cis*-**H** (0.5 g, functionality 0.5 mmol/g) was packed and conditioned with chloroform inside a glass column able to sustain pressurized conditions. A solution of **13** (130 mg, 1 mmol) and chloroacetic acid (94 mg, 1 mmol) in 5 mL of chloroform and another one of aldehyde **6** in 5 mL chloroform were pumped via syringe pump into HPLC pipes (0.08 mL/min, combined flow rate of both solutions: 0.04 mL/min for the syringe pump). The two solutions were mixed through a Y valve whose exit was connected to the inlet of the column charged with the supported catalyst. The solution coming out of the system was collected into a balloon under nitrogen atmosphere and samples to evaluate the conversion and the dr were directly taken from the outcoming solution. The ee was evaluated with the same procedure described for the reaction in batch and was 99%.

The prolinol catalysts were prepared according to the procedures developed by Professor Pericàs research group.

## 2.7.6 References


[1] Unpublished data.

[2] R. L. Hartman, J. P. McMullen, K. F. Jensen, *Angew. Chem. Int. Ed*. **2011**, *50*, 7502 – 7519.

[3] a) D. Ghislieri, K. Gilmore, P. H. Seeberger, *Angew. Chem. Int. Ed*. **2014**, 53, 678-682; b) R. J. Ingham, C. Battilocchio, D. E. Fitzpatrick, E. Sliwinski, J. M. Hawkins, S. V. Ley, *Angew. Chem. Int. Ed*. **2014**, *53*, 144-148.

[4] For a successful example of the management of solid byproducts on flow see: E. Quevedo, J. Steinbacher, D. T. McQuade *J. Am. Chem. Soc.* **2005,** *127*, 10498.

[5] a) B. Gutmann, D. Cantillo, C. O. Kappe, *Angew. Chem. Int. Ed*. **2015**, *54*, 6688 – 6729; b) R. Porta, M. Benaglia, A. Puglisi, *Org. Process Res. Dev.*, **2016**, *20* , 2–25.

[6] B. P. Mason, K. E. Price, J. L. Steinbacher, A. R. Bogdan, D. T. McQuade *Chem. Rev*. **2007**, *107*, 2300.

[7] For reviews see: a) M. Benaglia, A. Puglisi, F. Cozzi, *Chemical Reviews*, **2003**, *103*, 3401; b) M. Benaglia, *New J. Chem*., **2006**, *30*, 1525–1533; c) C. Rodríguez-Escrich, M. A. Pericàs *Eur. J. Org. Chem*. **2015**, 1173-1188.

[8] a) proline: D. Font, C. Jimeno, M. A. Pericàs, *Org. Lett.* **2006**, *8*, 4653-4655; b) Hayashi prolinol: E. Alza, M. A. Pericàs, *Adv. Synth. Catal*. **2009,** *351*, 3051 – 3056; c) threonine: A. H. Henseler,C. Ayats, M. A. Pericàs, *Adv. Synth. Catal.* **2014**, *356*, 1795 – 1802; d) MacMillan imidazolinone: P. Riente, J. Yadav, M. A. Pericàs, *Org. Lett.* **2012**, *14*, 3668-3671; e) squaramide: P. Kasaplar, C. Rodríguez-Escrich, M. A. Pericàs, *Org. Lett.* **2013**, *15*, 3498-3501; f) thiourea: L. Osorio-Planes, C. Rodríguez-Escrich, M. A. Pericàs *Org. Lett.* **2014**, *16*, 1704−1707; g) quinine alkaloids: J. Izquierdo, C. Ayats, A. H. Henseler, M. A. Pericàs, *Org. Biomol. Chem*., **2015**, 13, 4204; h) binol phosphoric acid: L. Osorio-Planes, C. Rodríguez-Escrich, M. A. Pericàs *Chem. Eur. J.* **2014**, *20*, 2367-2372; i) isothiourea: J. Izquierdo, M. A. Pericàs, *ACS Catal.*, **2016**, *6*, 348–356.

[9] M. H. Haindl, M. B. Schmid, K. Zeitler, R. M. Gschwind *RSC Advances*, **2012**, *2*, 5941.

[10] E. Alza, M. A. Pericas, *Adv. Synth. Cat.* **2009**, *351*, 3051.

[11] E. Alza, S. Sayalero, X. C. Cambeiro, R. Martin-Rapun, P. O. Miranda, M. A. Pericas, *Synlett* **2011**, 464.

[12] J. Tian, J. Zhong, Y. Li, D. Ma, *Angew. Chem. Int. Ed.* **2014,** *53*, 13885–13888.

[13] For a review on the synthesis of oseltamivir and zanamivir see: Javier Magano, *Chem. Rev.* **2009,** *109*, 4398–4438.

[14] H. Ishikawa, T. Suzuki, Y. Hayashi, *Angew. Chem. Int. Ed.* **2009,** *121*, 1330.

[15] S. Zhu, S. Yu, Y. Wang, D. Ma, *Angew. Chem. Int. Ed*. **2010**, *49*, 4656 –4660.

[16] a) J. Weng, Y.-B. Li, R.-B. Wang, G. Lu, *ChemCatChem* **2012**, *4*, 1007 – 1012; b) J. Rehák, M. Huťka, A. Latika, H. Brath, A. Almássy, V. Hajzer, J. Durmis, Š. Toma, R. Šebesta *Synthesis* **2012**, *44*, 2424; c) T. Mukaiyama, H. Ishikawa, H. Koshino, Y. Hayashi, *Chem. Eur. J*. **2013**, *19*, 17789 – 17800.

[17] M. Chini, P. Crotti, L. A. Flippin, C. Gardelli, E Giovani, F. Macchia, M. Pineschit, *J. Org. Chem.* **1993**, *58*, 1221-1227.

[18] M. Brzozowski, M. O'Brien, S. V. Ley, A. Polyzos, *Acc. Chem. Res*. **2015**, *48*, 349−362 and refs. therein.

[19] a) P. B. Cranwell, M. O'Brien, D. L. Browne, P. Koos, A. Polyzos, M Peña-López, S. V. Ley, *Org. Biomol. Chem.*, **2012**, *10*, 5774; b) J. C. Pastre, D. L. Browne, M. O'Brien, S. V. Ley, *Org. Process Res. Dev.* **2013**, 17, 1183−1191.

[20] V. Hajzer, A. Latika, J. Durmis, R. Šebesta, *Helvetica Chimica Acta* **2012**, *95*, 2421.

# 3 Ferrocene carbenium ions to build QCA candidates

**Table of contents**

## 3.1 Introduction to molecular electronics

### 3.1.1 Buttom-up approaches as alternatives to classical electronics

Classical electronic engineer is based on the top-down approach, that is to design the circuits, logic gates and memory units to encode bit over macroscopic pieces of semiconductors, typically silicon. The huge advances in technology, in particular the developments of lithography, have allowed the miniaturization of electronic devices. However it is a widely accepted opinion that this technology has almost reached its limit, dictated both by economical and physical considerations, that set around 100 nm the limit to design a the macroscopic semiconductor.[1]

An alternative and opposite approach has been proposed to build an electronic device by building its components at molecular level and assemble them at the supramolecular level, thus enabling to realize bit storage in the range of 1-10 nm range and an electronic device in the hundreds of nm range.

The base to develop such project was to demonstrate that single molecules, layers or nanoparticles are able to conduce and/or modulate a flow of current between two electrodes. In 1974 Aviram and Ratner predicted that a molecule having a donor-spacer-acceptor structure sandwiched between two electrodes would have rectified properties.[2] In the following years several devices were built demonstrating that the application of a voltage to such a system leads to a flow of current enabled by the low energy zwitterionic state of the donor-spacer-acceptor molecule.[3] Also three terminal molecular devices, i.e. transistors, were realized. Molecular prototypes of OR, AND, NOR logic gates[4] and memory units[5] have also been realized.

Unfortunately the production yields of these devices are low, mainly because the techniques to move the single molecules are very limited, and they usually decompose after a few experiments. The use of self-assembled molecular components would represent a great advance guaranteeing more reproducible and robust structures and would probably enhance the lifetime of such devices.

Alternative approaches to molecular computation have also been explored. For example a quantum approach based on Quantum Interference has been developed to build molecular devices able to perform as logic gates. [6] Biological systems such as DNA strands have also been used to build molecular devices taking advantage from the ordered structures that they are able to make to thanks to intermolecular interactions and self-assembly.[7]

### 3.1.2 QCA: a cold paradigm for molecular computation

In a standard computer the binary information is encoded in the on/off state of a current, which can be reversibly switched on and off by a gate voltage or a voltage pulse.

Quantum Cellular Automata (QCA)[8] is an alternative paradigm proposed by Craig Lent to encode and compute data that does not require a current but relies on static charge interactions inside the

single unit to encode the binary information and on the interactions between neighboring cells to transmit, elaborate and read out the information.
A single cell is composed of four quantum dots each of whom can be in two different states, usually a neutral and a charged state. The quantum dots are connected by tunneling pathways so that when two charges are present inside the cell, their electrostatic repulsion will force them as far as possible on the opposite diagonal positions that define the two low energy states 0 and 1. The presence of these two equally stable states is the called by-stability. Each quantum dot is able to keep the charge localized on itself avoiding the collapsing of the 0 and 1 states in delocalized non defined ones. A higher energy, but still accessible, neutral state must also be present to reset the information upon an external stimulus. For example in case of the example in figure 1, the four charge dots are on a plane and the two neutral dots, having higher energy so that on normal conditions they do not bear the charges, are below them. The application of a perpendicular electric field allows for the clocking (or reset) of the cell by forcing the charges on the neutral state.

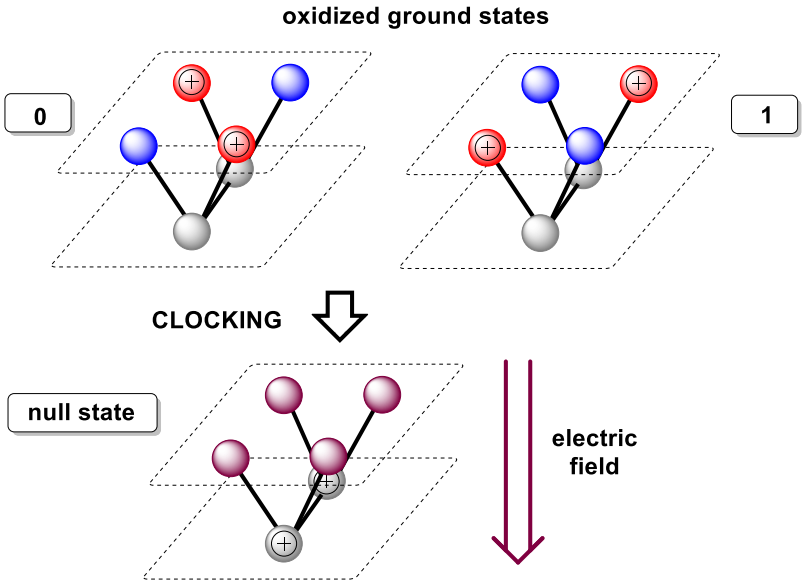



*Figure 1: QCA six dot cell encoding 0 and 1 fundamental states and forced in the null state unpon clocking.*

When the cells are assembled to form wires or more complex architectures, their electric fields interact and an energy gain is realized if the dipoles of neighboring cells are aligned, while a repulsive interaction will occur in the opposite case due to electrostatic repulsion (figure 2a). The interaction of two neighboring cells is called kink energy and if it is comparable or lower than the thermal energy at which the system operates, the cells of an assembled architecture could change their 0 or 1 state randomly and no computation could be possible.
On the other hand if the kink energy is higher than the thermal energy, it is possible to guide the stream of information through a cell wire by imposing to the cell at one end of the wire the 1 state, for example, so that the neighboring ones will be conditioned into the same state in a chain mechanism (figure 2b). For this process to be successful it is necessary that the cells are initially on the null state. Otherwise, when the stimulus is applied the situation in which a central cell would be

surrounded by a left neighbor on the 1 state and by a right neighbor on the 0 state would occur. As the central cell would feel two equal and opposite stimuli, it is reasonable that it could not decide which state go into becoming a "crazy cell" that interrups the communication and makes the system collapse (figure 2c).

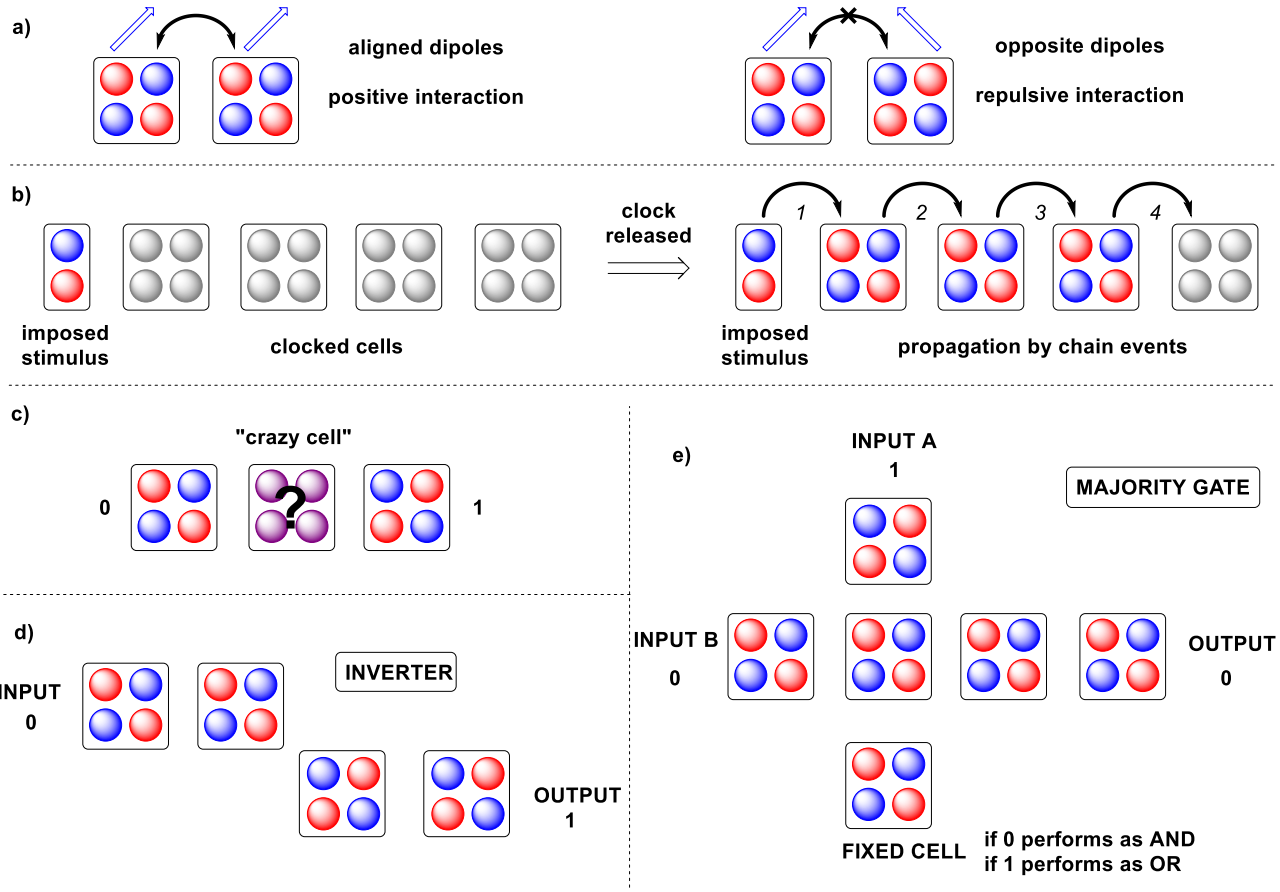



*Figure 2: a) electric field interaction between neighboring cells; b) transmission of signal; c) crazy cell due to opposite neighbors; d) cell arrangement to perform as inverter and e) majority gate.*

The arrangement of the cells into ordered pathways is predicted to perform the logic operations such as the negation (inverter) (figure 2d), AND, OR (performed by the majority gate) (figure 2e).
The first demonstration of QCA operations was done on semiconductors.[9] The lithographically designed dots are large so that the low kink energy allows the system to works only at cryogenic temperatures. Moreover the manufacturing process causes many imperfections in the device so that the fabrication yield is very low.[10]
The first operating QCA was built in 1997 by Lent and coworkers using aluminum metal dots.[11] Aluminum dots connected by $AlO_x$ were deposited on a silicon support to form a 4 dot cell by means of laser beam lithography and shadow evaporation technique. The bi-stability of the cell was demonstrated by moving the charge on the left dots and measuring the induced moving on the right dots. The junction area was around 60 $nm^2$ determining that the system worked at <50 mK temperature. Using these cells a majority gate[12] and the propagation of an input[13] along a QCA wire

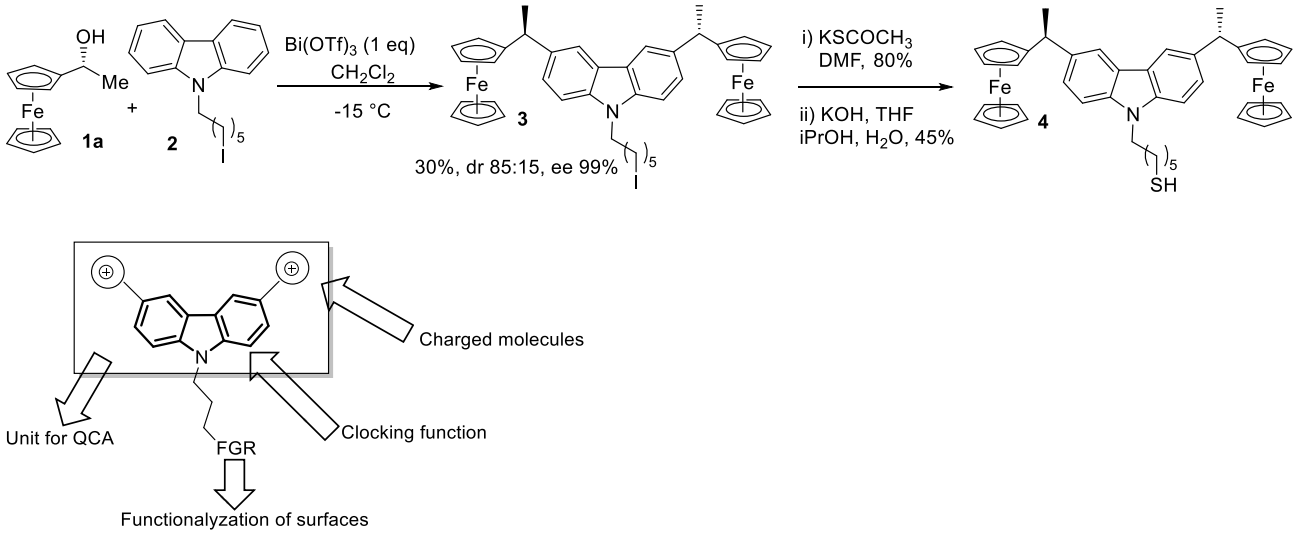
were demonstrated. These cells could not perform the clocking, that was made possible by applying an external voltage to the dot channels that forced the charged on a null state.[14]
The metal based QCA offer higher fabrication yields compared to semiconductors QCA models, but still require cryogenic temperatures.
Molecular QCA instead offer the fundamental advantage to bear the dots very close in space (≈ 1 nm) so that the kink energy is high and they should be able to operate at room temperature.
These molecules should fulfill the following requirements to work as QCA in real devices:

1) They must have four quantum dots that bear two charges to generate a bi-stable cell;
2) The charges must be well confined on the dots to guarantee readable and sharply defined Boolean states;
3) Tunneling (non-classical permeation of the wave-function through the classical barrier that confines the charges) between the dots, in response to stimulus, must be possible to allow the switching between the two bi-stable states;
4) The molecules must be assembled into a controlled array to design the geometry needed to perform the logic operations described in figure 2;
5) After the assembly of the molecules into an array, their geometry must be rigid to guarantee the fixed positions of the dots, that bear the charges, and thus will be subjected to electrostatic repulsion; significant variations in the dots geometry would result in uncontrolled interactions that may cause the system to fail;
6) A neutral state that allows to delete the stored information must be accessible upon application of an external stimulus (clocking), typically a perpendicular electric field.

The generation of a molecule having two charge dots (and one to define the null state), corresponds to half a cell that is composed by the assembly of two these molecules. The design and synthesis of two (or three) dots molecules is easier and indeed the first bi-stable molecules suitable for QCA application were ferrocene ruthenium dinuclear complexes. First computational studies[15] predicted the bi-stability of these molecules that was demonstrated by their synthesis and switching by application of an electric field.[16] The first reports on molecular QCA were all done by researchers, Lent, Fehlner, Snider, Wiest and coworkers, at Notre Dame University of Indiana State. They also reported the first candidates for four dots QCA made by bisferrocene-bisferrocenium molecules.[17] Another suitable candidate, consisting in a $Fe_4$ 2 x 2 grid complex exploiting a pyrazole-bridged binucleating ligand, has been proposed more recently by Meyer.[18]
However, in none of these works the clocking issue was addressed. Lent considered this problem and thanks to simulation studies on a model three dot cell, highlighted the necessity to have a null state in order to have gain in the information transmission. Moreover the null state would guarantee the shift register (avoiding "crazy cells") and the reset of the information stored as already pointed out. The first example of a clockable QCA half cell candidate was reported by Alessandro Bramanti, P. G. Cozzi, Francesco Paolucci and coworkers.[19] Luca Zoli and P.G. Cozzi designed and synthetized a chiral bisferrocene carbazole taking advantage of the $S_N1$ reactions on carbenium ions in situ generated from the corresponding alcohols.[20] The use of highly enantioenriched ferrocene ethanol **1a** allowed to obtain in 30 % yield a mixture consisting of 85:15 (R,R:meso) **4**. The low nucleophilicity of the carbazole is responsible for the modest yields and for partial racemization of the carbenium ion from which arises the formation of the meso compound. It was necessary to use

*N* protected carbazole **4** in order to avoid the *N*-alkylation with the carbenium ion. The molecule was linked to gold surfaces or nanoparticles[21] thanks to the introduction of a thiol moiety on the *N* alkyl chain.

The isolated molecules and the monolayers on gold surfaces were characterized by electrochemistry and scanning tunneling microscopy (STM). Moreover computational simulations were run to mimic their behavior in a working device. All these data consistently indicate that **4** (i) is capable of confining charge on two lateral quantum dots (the ferrocenes) in such a way that paired molecules exhibit antipodal (or diagonal) charge localization; (ii) has charge localized on a middle dot (the carbazole) upon application of a clock field, encoding a neutral state as required for correct QCA operation; and (iii) has shown good stability when immobilized on a solid state.




*Scheme 1: synthesis of 3 dot QCA candidate having carbazole core by Cozzi.*

For the first time a molecular QCA cell prototype met all these requirements. However, for a QCA application it is necessary the development of patterning techniques to have the molecules aligned and positioned in a controlled fashion to design the logic gates. These issues can be addressed by switching the carbazole linker between the ferrocenes, with a chemical functionality that enables self assembly. Moreover, structural modifications to fine-tune the properties in particular to lower the HOMO–LUMO gap for clocking with a smaller field and to increase the ferrocenes oxidation potential split to obtain mono-oxidized species with high yield, avoiding impairment of charge localization at room temperature, must be considered too.

A general consideration must be underlined: the generation of charges on QCA candidates implies the presence counter charges that should not interfere with the bi-stable states. To guarantee this the countercharges should be fixed in a position that does not favor in terms of energy the 0 state vs the 1 state or vice versa. Moreover on an array of molecules that have four charge dots the selective generation of only two charges for each molecule is a serious challenge. The difficulties in realizing such a molecular system have stimulated the design of devices in which dipoles are used instead of the charges to generate the bi-stable cells. Recently, Lent described a three dot QCA candidate

having two ferrocenes as charge dots linked by a carborane unit that both acts as null state and fixed counter ion representing the first solution to the above mentioned problem.[22]

### 3.1.3 The MOLARNET project

Molecular electronics has been since now investigated at the single device scale, while the problem of connecting a large number of devices in complex networks able to solve basic computational tasks has not been really solved yet. The European Fp7 MOLARNET project[23] has brought together the competences of many research groups and ST Microelectronics, an important industrial partner to try and solve the pending problems on the QCA quest in particular to synthetize suitable QCA units, assemble them at the molecular level and demonstrated basic logic operations and read out of data. The first goal is to synthetize and characterize molecules that exploit all the QCA requirements: quantum charge confinement as well as tunneling, clocking properties and electrostatic interaction between neighboring cells to implement digital computation.
To fulfill these goal different competences were gathered together: synthesis from Cozzi and Spada-Masiero groups, electrochemistry from Paolucci Group, surface chemistry from Bolan and Samorì groups, computational support from Cuniberti group, microelectronic engeneer from CNR nano of Lecce and ST Microelectronics and theoretical design from Alessandro Bramanti.
During my Ph.D. I have worked to the synthesis of different QCA candidates in close collaboration with our project partners to exchange data and receive useful feedback for the tuning of the molecular properties by synthetic design.

## 3.2 Guanines ferrocene conjugates[24]

### 3.2.1 Introduction

Guanine is able to form supramolecular structures by interaction with other guanine molecules, a unique peculiarity among the natural occurring nucleobases that usually need the complementary partner to form the supramolecular structures of DNA.
In 1998 the aggregation of four DNA strands in guanine rich regions were characterized and the molecular force that builds this peculiar structures is the interaction of 4 guanines that form a squared unit called G quadruplex (G-4).[25] The study of the behavior of guanines and analogs in solution and on a surface showed that G-4 are formed in presence of mono-charged cations such as $K^+$. Actually the cation is sandwiched between two G quadruplex and quiete often G-4 are intercalated by cations and constitute real pillars whose dimension varies with the concentration (figure 3).
In the absence of cations, guanines form ribbon like supramolecular structures that have been characterized in two different structures: ribbon A and B (figure 3).[26]
The supramolecular structures of guanines are dictated by the formation of a perfect hydrogen bonding donor acceptor match between these molecules. In presence of a cation the electrostatic interaction between electron rich guanines determines a change in the energetically favored self-assembly structure to form the form G-4. The N9 nitrogen is not involved in the hydrogen bonding and in G-4 it is pointing outwards offering a perfect site for the chemical functionalization.
The reaction of purine bases with alkylating agents yields 3-, 7-, or 9-alkyl-substituted derivatives, [27] and the ratio of these derivatives depends on the nature of the alkylating agent and on the reaction conditions. Zhilina reported the reaction of ferrocenylethanol with adenine that occurs in position 9, in a biphasic reaction mixture ($CH_2Cl_2$-$H_2O$) in the presence of HBF4.[28] In the nucleophilic substitution conditions the 9 position results the most reactive position. In a previous study PG Cozzi group was able to react enantioenriched ferrocene alcohols in $S_N1$-type conditions with different nucleophiles with the reaction occurring with retention of stereochemistry.[29] These precedents suggest the possibility to perform $S_N1$-type reaction with chiral and achiral ferrocene alcohols with guanine, presumably on the 9 position affording target molecule **6** (table 1).
If we would be able to self-assemble the ferrocene guanine conjugates to form the G-4 structure represented in figure 3, a good QCA candidate would be synthetized as four equivalent charge dots in symmetric positions would be present on the single cell. The presence of a $sp^3$ bond between the ferrocene and the guanine core should guarantee the charge confinement but should not be an insurmountable barrier for the tunneling of the charge based on the results obtained with the diferrocenecarbazole **4** previously synthetized (see scheme 1). The main challenges will be is if the G-4 core will allow the clocking and the tunneling between the ferrocenes.

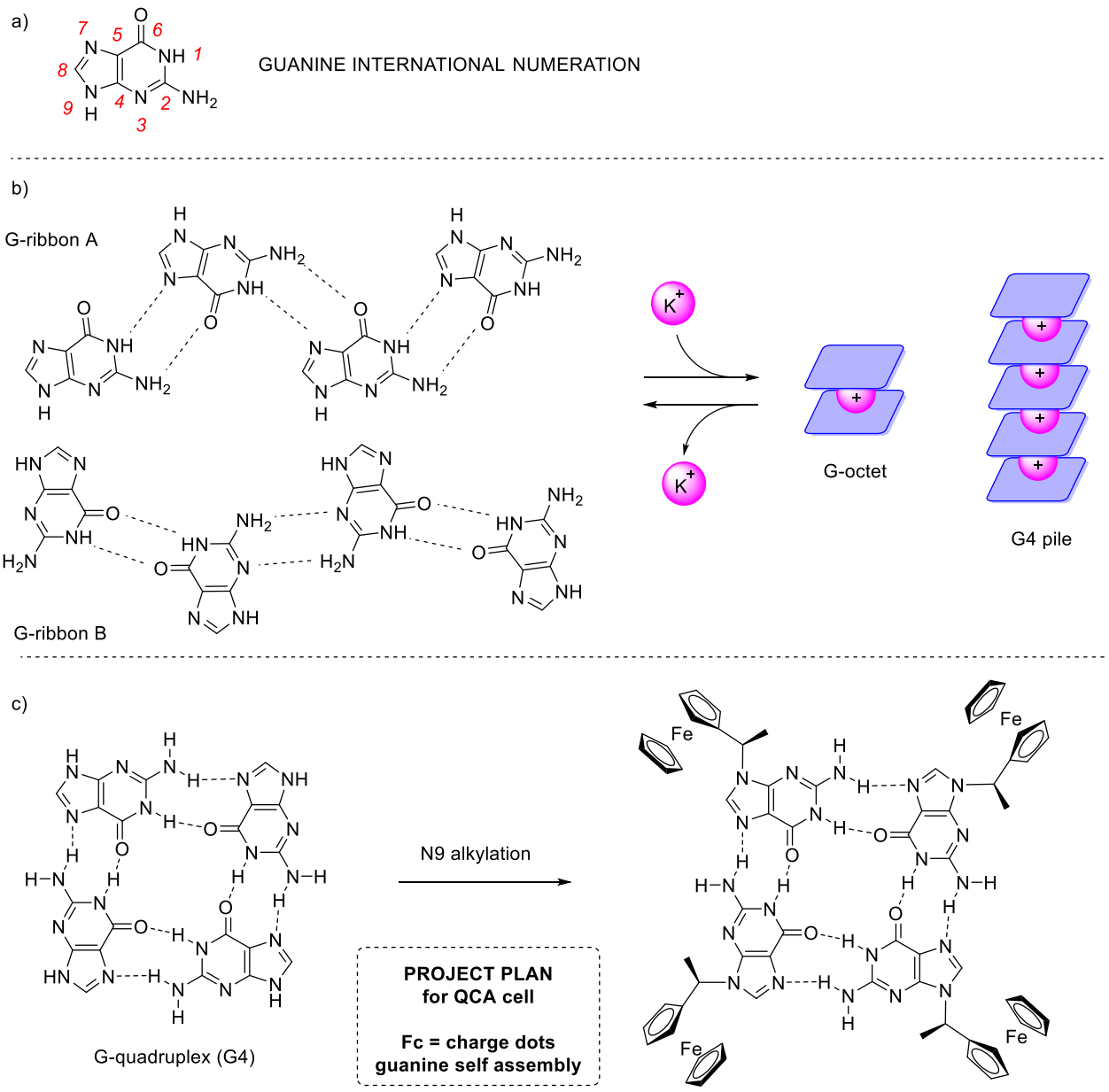
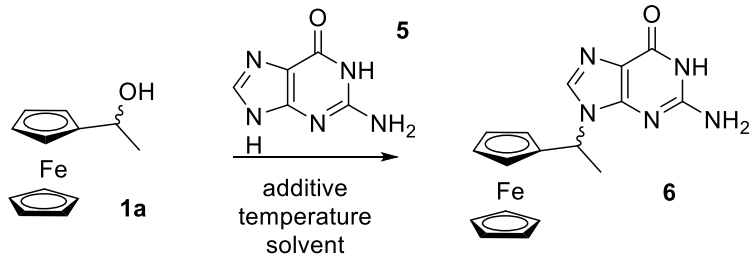



*Figure 3: a) guanine international numeration; b) cation induced shift from G-ribbons to G4 piles; c) project plan for a ferrocene-guanine based QCA.*

## 3.2.2 Synthesis of ferrocene guanine conjugates

The direct $S_N1$ reaction of alcohol **1a** and guanine **5** is an appealing strategy to access a valuable target in only one step and was the first object of my study. The main challenge is the almost complete insolubility of guanine in almost every organic solvent due to the very strong intermolecular interactions in the solid state that disfavor solvation.



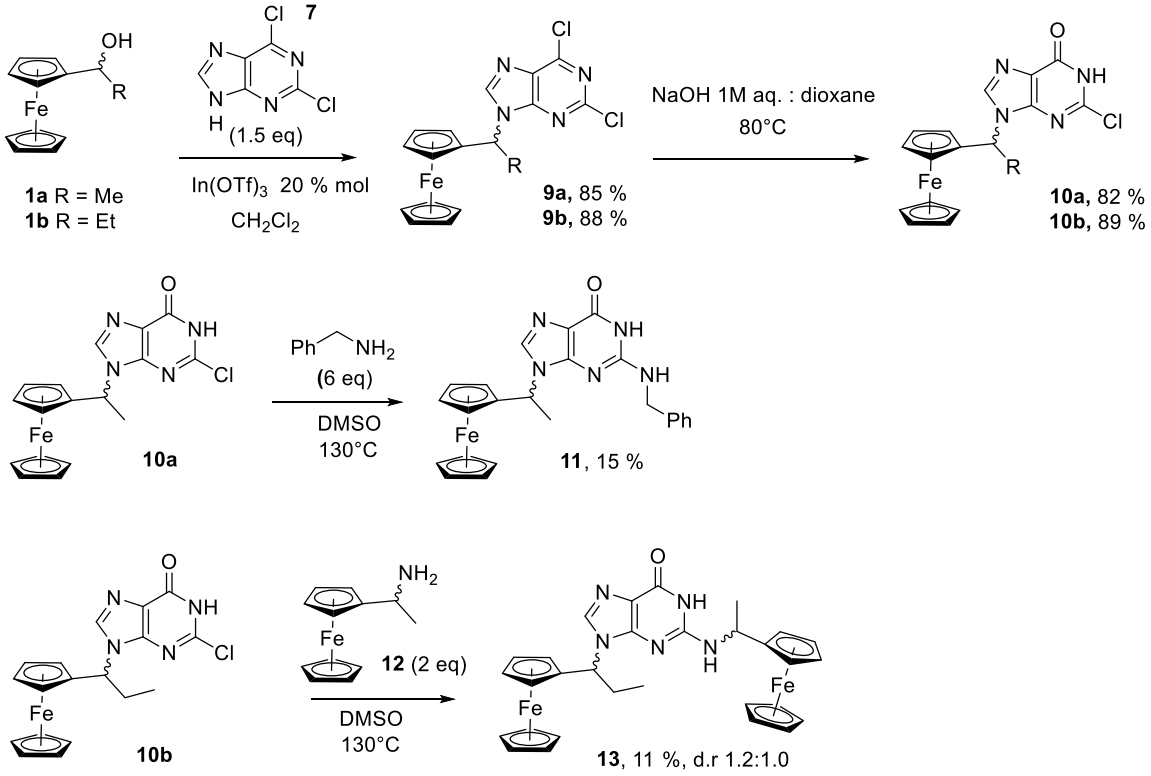

| entry | Solvent | Temperature | Additive | Yield |
|---|---|---|---|---|
| 1 | $H_2O$ | 80°C | | 0 |
| 2 | $H_2O$ | 80°C | $(t\text{Bu})_4\text{NOH}\cdot 30\ H_2O$ | 0 |
| 3 | $H_2O$ | 80°C | $Zn(OAc)_2$ | 0 |
| 4 | DMSO | r.t. | $In(OTf)_3$ | 0 |

Reactions performed on 0.1 mmol **1a**, 0.15 mmol guanine **5**, 0.3 mmol additive in 1 mL solvent at the indicated temperature for 8 h.

*Table 1: unsuccessful attempts to perform the direct $S_N1$ reaction of guanine on 2a.*

$S_N1$ reactions on water are possible with stabilized carbocations (between -7 and -2 on Mayr scale) like **1a**, so I made the first attempts using hot water as solvent media hoping it would be able to break the guanines solid aggregate. Unfortunately guanine resulted insoluble also in neutral hot water and no product was detected even when water compatible Lewis acids or phase transfer additives were employed (table 1). The use of DMSO as reaction solvent was unsuccessful too.
N9 guanine anion can be generated by treatment of guanine with bases and its solubility compared to guanine is considerably increased. I prepared N9 potassium guanine salt by treatment of guanine with an aqueous solution of KOH. Evaporation of the water afforded this salt that is bench stable and I mixed it with bisdimethylamminobenzhydrylium tetrafluoroborate in DMSO at room temperature obtaining the alkylation of the guanine with the carbenium ion on the 9 position. Ferrocenyl carbenium ion must be generated in situ so I treated alcohol **1a** one equivalent $BF_3$-$Et_2O$ at – 78°C in DCM. Then I added the potassium guanine salt and the reaction mixture was allowed to slowly warm to room temperature but unfortunately I did not obtained product **6**. The failure can be addressed either to the low solubility of guanine anion in DCM by the instability of the carbenium ion under basic conditions, a behavior that was also observed in the alkylation of carbenium ions with acyl enolates (chapter 2.5). As the generation of carbenium ion has to be performed at low temperature I could not use DMSO as solvent.

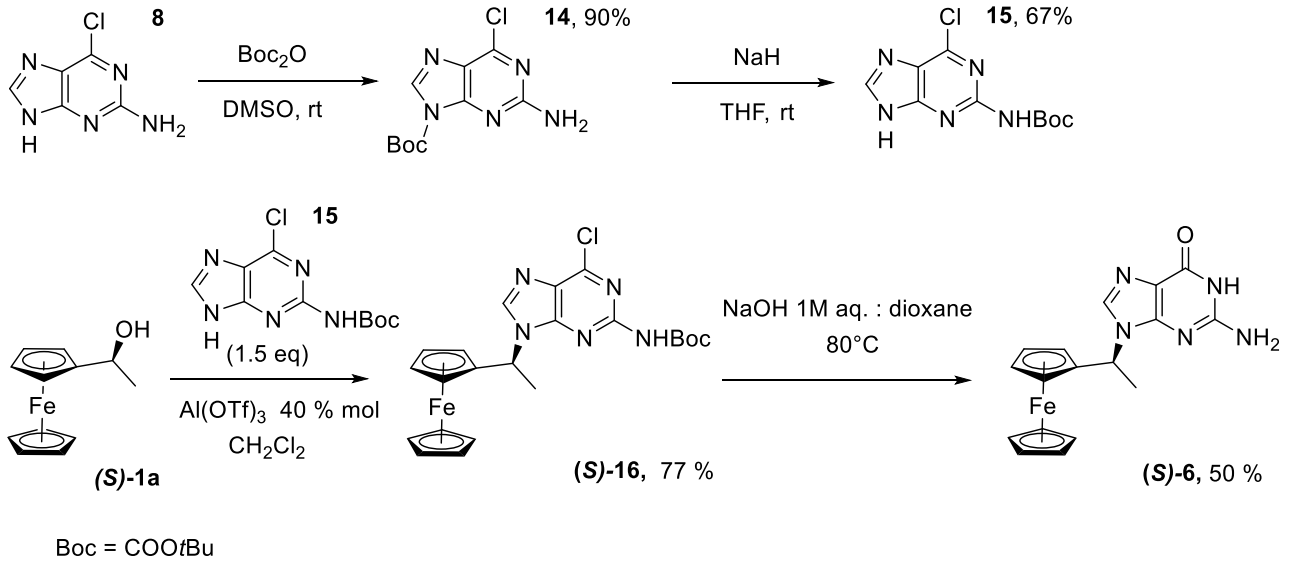
As the direct $S_N1$ reaction was not possible due to the insolubility of guanine or its N9 anion potassium salt, I investigated more lipophilic guanine precursors as efficient nucleophiles to perform the $S_N1$ reaction on alcohol **1a**. Dichloro **6** and monochloro purine **7** are extensively used as precursors of the guanine nucleobase as they are moderately soluble in organic solvents. After the desired functionalization of these scaffolds, they can be converted in a straightforward manner to guanine by nucleophilic aromatic substitution and successive hydrolysis.[30]
The chloro derivatives **7** and **8** were reacted with **1a** in the presence of a catalytic amount of $In(OTf)_3$. While **8** was insoluble in many solvents tested causing the unsuccessful reaction, **7** smoothly reacted with ferrocene **1a** in DCM affording the desired compound **9a** in moderate yield (scheme 2). The hydrolysis of **9a** occurred following the standard procedure in literature[30] and **10a** was obtained in good yield after column chromatography.




*Scheme 2: synthetic pathways to access Fc-guanines from 2,6-dichloropurine.*

The exchange of the chlorine on the 2 position with the amino moiety is the last step to obtain desired **6a**. The $S_NAr$ substitution of the chlorine on the 2 position with 4-methoxy benzyl amine was reported[31] and I attempted to perform this reaction using benzylamine that was added to **10a** dissolved in DMSO. The mixture was refluxed for several hours after which the formation of several species was observed among whose was identified the product. Unfortunately, the product **11** was isolated in low yield after chromatographic purification due to the formation of several unidentified side-products. Probably, the previously formed bond between ferrocene ethanol and the purine is not stable under such harsh conditions. I performed the same reaction using ferrocene

amine **12**, and also in this case product **13** was isolated in low yield after separation from the numerous side-products. **13** was isolated as a 1.2:1 inseparable mixture of diastereoisomers.
Despite the low yields, I obtained two interesting ferrocene guanine conjugates that were shipped to the project partners in order to evaluate if their properties were suitable for the development of a QCA based device. Diferrocene guanine **13** was prepared in order to compare its electrochemical and physical properties with the mono ferrocene adducts. In particular we were interested to see if the two ferrocenes were equivalent or different from the electrochemical point of view.
However the low yields in the last synthetic step required the investigation of an alternative route to access this kind of molecules for larger scale productions.
I focused on unreactive **8** that already bears the amine moiety on the position. To increase its solubility it is necessary to protect the amine group on the 2 position with a lipophilic moiety. From the literature, the treatment of **8** with $Boc_2O$ leads to the selective protection of the 9 position, but by simple metalation of intermediate **15** with NaH, the Boc quantitative shift to obtain **16** is obtained.[32] Boc purine **16** is mildly soluble in DCM and its $S_N1$ reaction on **1a** promoted by $In(OTf)_3$ was possible. Unfortunately, the analysis of the crude mixture revealed the formation of a small amount of product together with a series of side-products such as the ether deriving from the condensation of **1a** and the dialkylated product having a second ferrocene moiety on the 2 amino group that had lost the Boc group. Moreover the loss of the carbamate caused the precipitation of a great amount of purine **8** hampering the reaction conversion and favoring the formation of the alcohol ether due to the absence of the nucleophilic reaction partner.



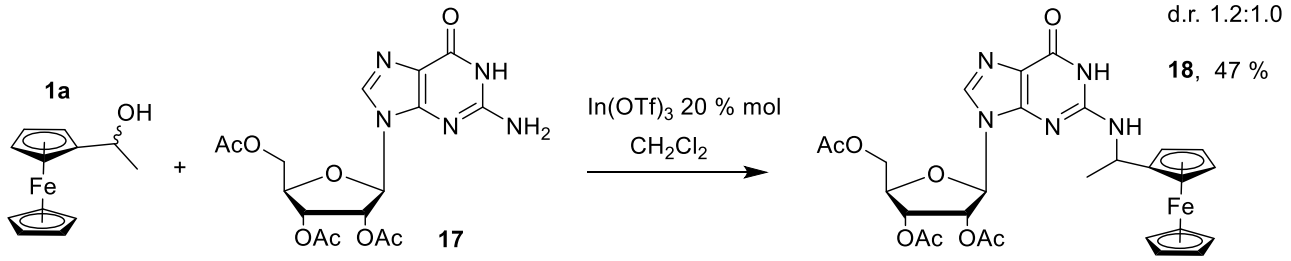

*Scheme 3: synthetic pathway to access target molecule* ***6****.*

The strong Lewis acidity of $In(OTf)_3$ was responsible for the Boc cleavage, so we looked for a different Lewis acid that was compatible with this protecting group. $Al(OTf)_3$ fulfilled these requirements and its use instead of $In(OTf)_3$ promoted the reaction leaving untouched the Boc moiety.[33] The milder Lewis acidity of this catalyst was reflected in a decrease in the reaction rate and its increase to 20 mol % was necessary to obtain a good conversion after one night of reaction.

Under these optimized conditions **16** was obtained in 77% isolated yield. Pleasantly, we found out that treatment of **9** with NaOH 1N in aqueous dioxane not only gave the hydrolysis of chlorine to the desired oxo substituent, but caused also the loss of Boc group affording desired product **6** in one step (scheme 3).

This new synthetic route allowed to obtain **6** in moderate but satisfactory yield trough a two-step procedure from easily obtained starting material **15**. I synthetized active **(S)-6** following the same reaction sequence starting from active **1a** (98% ee) thanks to the retention of configuration characteristic of the $S_N1$ reactions with ferrocenyl carbenium ions (see chapter 1).[34]

I also investigated the reaction with triacetyl guanosine **17** to access a product with a different substitution pattern. Due to the presence of the sugar on the 9 position, the selective alkylation of the amine on the 2 position is predicted. No solubility issues were encountered and the straightforward reaction with **1a** in DCM promoted by $In(OTf)_3$ afforded desired product. The tuning of the reaction temperature from 0°C to rt and the use of 20 mol% of Lewis acid allowed to isolate **18** in 42% yield as a mixture of diastereoisomers due to the presence of the optically active sugar.




*Scheme 4: synthesis of ferrocene guanosine conjugate **18***

This study has shown that guanine precursors **7** and **8** can be employed as nucleophiles in $S_N1$ reactions with ferrocenyl carbenium ions, opening the route to the introduction of other functional groups trough this strategy.

To conclude I have synthetized three different ferrocene guanine conjugates and a ferrocene functionalized guanosine that together with those prepared by Stefano Masiero group constituted a small library of compounds that were studied in detail by the partner projects.

Here I will sum up the significant results of the studies on the molecules that I have prepared and the problems that emerged that led us to investigate scaffolds different from guanines for the QCA candidates.

### 3.2.3 Electrochemical characterization and conclusions

The electrochemical properties of the molecules **11,13,18** were studied by cyclic voltammetry under super dry conditions either in DCM or DMSO by Matteo Iurlo. The results in DCM that presents the wider solvent window are listed in table 2: the reversible Fc oxidation peaks in a similar range of potentials range between 0.4 V and 0.5 V. Interestingly no different oxidation potentials for the two Fc of molecule **13** is observed indicating that the oxidation of the first moiety does not influence the second. This means that there is no communication between the ferrocenes as expected by the presence of the $sp^3$ bond and that good charge confinement is achieved.

| Compound | Fc rev. ox. (V) | guanine irrev. ox. (V) |
|---|---|---|
| **11** | 0.49 | ≈1.3 |
| **13** | 0.43[a] | ≈1.3 |
| **18** | 0.41 | +1.41 |

Oxidation peaks calculated from cyclic voltammetric of compounds (0.8 mM) in 0.05 M TBAHPF/DCM solution; T= 298 K; working electrode Pt disc (d = 125 μm). Potentials are referenced to SCE. Rev. ox. = reversible oxidation; irrev. = irreversible. (a) 2 electron peak.

*Table 2: salient results of the electrochemical analysis of ferrocene guanine conjugates.*

Unfortunately the oxidation peak attributed to the guanine core is detected around 1.3 V, a potential too high to shift the charge from the ferrocene unit to the guanine by means of an external electric field. Moreover the spatial position of the ferrocene relatively to the plane designed by the guanine cannot be easily controlled as it depends on the rotation of a $sp^3$ bond. The lack of a preferred orientation of the ferrocene respect to the guanine leads to a probable presence of some ferrocene units above the guanine plane while others are located under this plane. In this situation, the external field applied to perform the clocking would not be able to force all the cells on the null state causing the failure of this operation. The self-assembled properties at the solid liquid interface were evaluated by Samorì group. This group is specialized in the observation of self-assembled monolayers of molecules under mild (no ultra-vacuum) conditions. The drop casting of a solution of substrate in octanol (typical solvent, others can be employed) over a layer of HOPG (highly oriented pyrolytic graphite) leads to the formation of thin layer of liquid (μm height range) over the solid support. Under these conditions the dissolved molecules interact with the HOPG and can form self-assembled monolayers over this surface. The presence of the solvent allows the mobility of the molecules favoring their dynamic reorganization to form extended self-assembled patterns that can be observed by STM.

Unfortunately, none of our molecules showed any self-assembled properties. However, a second generation of guanine conjugates prepared by Masiero instead showed very nice self-assembled monolayers on HOPG.[35] All these molecule bore a long linear alkyl chain (> C12) that is believed to engage Van der Waals interactions with the graphite being determinant for the formation of the

self-assembled pattern. As the force of the Van der Vaals interaction for a single methylene unit is estimated around 4 kcal/mol, an alkyl chain having 12 methylene units or more generates a significant energy gain when it interacts with HOPG strongly promoting the absorption of the molecule on the graphite. Once this happens, if the molecule forms an ordered H bonding network or other intermolecular interactions, the formation of a self-assembled monolayer is possible and probable for a carefully designed substrate.
The negative results obtained with our guanine ferrocene conjugates together with the predicted difficulties to operate for the guanine based candidates as QCA cell, lead us and our partners to investigate more suitable scaffolds that could address the emerged problems.

### 3.2.4 Contributions

I designed and synthetized the guanine ferrocene conjugates under the supervision of Prof. Cozzi. Dr. Matteo Iurlo (Prof. Paolucci research group) performed the electrochemical characterizations. The unsuccessful surface studies were performed Prof. Samorì research group.

## 3.2.5 Experimental part

**9-(1'-ferrocenyl etyl)-2,6-dichloropurine (9a)**

To a solution of 2,6-dichloropurine **7** (0.3 mmol, 57 mg) in DCM (500 μL), were added 1-ferrocenyl ethanol **1a** (0.2 mmol, 46 mg) and, after 5 minutes, $In(OTf)_3$ (0.04 mmol, 133 μL of a sol. 0.3M in $CH_3CN$). The mixture was stirred for 18 hours at room temperature until complete conversion was observed by TLC. Then the reaction was quenched with water (4 mL). The organic phase was separated and the aqueous one was extracted with DCM (5 mL x 2). The collected organic layers were concentrated under reduced pressure and purified by column chromatography (eluting gradient from 90:10 to 50:50 cyclohexane:ethyl acetate). **9a** was obtained as an orange sticky solid. Yield: 0.17 mmol, 67.3 mg, 85%; $^1$HNMR (400 MHz, $CDCl_3$, 25°C): δ = 7.89 (s, 1H), 5.77 (q, *J* = 7.1 Hz, 1H), 4.38-4.41 (m, 1H), 4.29-4.32 (m, 1H), 4.23-4.26 (m, 1H), 4.22 (s, 5H), 4.15-4.18 (m, 1H), 1.94 (d, *J* = 7.1 Hz, 3H); $^{13}$CNMR (100 MHz, $CDCl_3$, 25°C): δ = 152.3, 152.0, 151.3, 144.0, 130.8, 86.1, 69.4, 69.2 (5C), 68.7, 68.2, 66.1, 51.2, 20.7.

**9-(1'-ferrocenyl etyl)-2-chloro-6-oxopurine (10a)**

In a schlenk tube under nitrogen atmosphere, were added 9-(1'-ferrocenyl etyl)-2,6-dichloropurine **9a** (0.16 mmol, 64.7 mg), dioxane (1.5 mL) and NaOH aq. 1M (0.8 mmol, 800 μL ). The solution was stirred at 80°C for 4 hours until complete conversion was observed by TLC. The dioxane was evaporated under reduced pressure, then $NH_4Cl$ aq. sat. was added until pH was neutral. The aqueous mixture was extracted with DCM (5 mL x 3), the collected organic layers were concentrated under reduced pressure and purified by column chromatography (ethyl acetate until the byproduct was eluted, then 90:10:0.5 DCM:MeOH:triethylamine). **10a** was obtained as an orange sticky solid. Yield: 0.13 mmol, 50.3 mg, 82%; $^1$HNMR (400 MHz, $CDCl_3$, 25°C): δ = 7.61 (s, 1H), 5.62 (q, *J* = 6.9 Hz, 1H), 4.33-4.37 (m, 1H), 4.25-4.29 (m, 1H), 4.21-4.23 (m, 1H), 4.20 (s, 5H), 4.15-4.18 (m, 1H), 1.89 (d, *J* = 6.9 Hz, 3H); $^{13}$CNMR (100 MHz, $CDCl_3$, 25°C): δ = 159.2, 148.2, 143.9, 138.6, 122.6, 86.9, 69.1, 69.0 (5C), 68.4, 68.1, 66.0, 50.7, 21.2.

*9-(1'-ferrocenyl etyl)-2-N-benzyl-guanine (**11**).* In a schlenk tube under nitrogen atmosphere, were added 9-(1'-ferrocenyl etyl)-2-chloro-6-oxopurine 4a (0.15 mmol, 58 mg), DMSO (500 μL) and benzylamine (0.9 mmol, 100 μL ). The solution was stirred at 150°C for 6 hours until complete conversion was observed by TLC. Ethyl acetate (10 mL) was added and an orange precipitate was formed. The solid was filtrated and washed with DCM until a white solid is left: the yellow DCM solution was concentrated to obtain pure **11** as a yellow solid. Yield: 0.022 mmol, 10.3 mg, 15%; $^1$H NMR (600 MHz, DMSO-$d_6$, 25°C): *δ* = 10.42-10.72 (bs, 1H), 7.75 (s, 1H), 7.37-7.46 (m, 4H), 7.29-7.35 (m, 1H), 6.91 (t, *J* = 4.8 Hz, 1H), 5.38 (q, *J* = 7.1 Hz, 1H), 4.51-4.66 m, 2H), 4.33-4.38 (m, 1H), 4.12-4.18 (bs, 6H), 4.09-4.12 (m, 1H), 4.06-4.08 (m, 1H), 1.82 (d, *J* = 7.1 Hz, 3H); $^{13}$CNMR (150 MHz, DMSO-$d_6$, 25°C): *δ* = 157.2, 152.5, 150.5, 139.9, 136.0, 128.8 (2C), 127.8 (2C), 127.4, 117.1, 90.0, 69.0 (5C), 68.3, 67.9, 67.8, 67.7, 49.3, 44.5, 20.4; ESI-MS: *m/z* = 454.1

$[M+H]^+$, 476.0 $[M+Na]^+$, 907.1 $[2M+H]^+$, 1835.4 $[4M+Na]^+$; decomposition at 190°C. Anal. Calcd for $C_{24}H_{23}FeN_5O$: C, 63.59; H, 5.11; N, 15.45. Found: C, 63.69.; H, 5.19; N, 15.41.

**9-(1'-ferrocenyl propyl)-2,6-dichloropurine (9b)**

To a solution of 1-ferrocenyl propanol **1b** (1.38 mmol, 338 mg) in DCM (5 mL), were added 2,6-dichloropurine **7** (2.07 mmol, 391 mg) and, after 5 minutes, $In(OTf)_3$ (0.28 mmol, 1 mL of a sol. 0.3M in CH3CN). The mixture was stirred for 18 hours at rt until complete conversion was observed by TLC. Then the reaction was quenched with water (6 mL). The organic phase was separated and the aqueous one was extracted with DCM (10 mL x 2). The collected organic layers were concentrated under reduced pressure and purified by column chromatography (eluting gradient from 90:10 to 50:50 cyclohexane:ethyl acetate). **9b** was obtained as an orange sticky solid. Yield: 1.21 mmol, 503.5 mg, 88%; $^1$HNMR (400 MHz, $CDCl_3$, 25°C): δ = 8.06 (s, 1H), 5.54 (dd, $J_1$ = 10.8 Hz, J2 = 4.3 Hz, 1H), 4.33-4.35 (m, 1H), 4.24-4.26 (m, 1H), 4.17-4.19 (m, 1H), 4.14 (s, 5H), 4.08-4.10 (m, 1H), 2.41-2.52 (m, 1H), 2.18-2.30 (m, 1H), 0.90 (t, $J$ = 7.3 Hz, 3H); $^{13}$CNMR (100 MHz, $CDCl_3$, 25°C): δ = 153.1, 152.5, 151.3, 144.6, 130.0, 86.7, 68.6 (5C), 68.4, 67.9, 66.9, 66.1, 56.9, 27.9, 10.8.

**9-(1'-ferrocenyl propyl)-2-chloro-6-oxopurine (10b)**

In a schlenk tube under nitrogen atmosphere, were added 9-(1'-ferrocenyl propyl)-2,6-dichloropurine **10b** (1.57 mmol, 650 mg), dioxane (15 mL) and NaOH aq. 1M (7.9 mmol, 7.9 mL). The solution was stirred at 80°C for 7 hours until complete conversion was observed by TLC. The dioxane was evaporated under reduced pressure, then $NH_4Cl$ aq. sat. was added until pH was neutral. The aqueous mixture was extracted with DCM (10 mL x 3) and the collected organic layers were concentrated under reduced pressure and purified by column chromatography ethyl acetate until the byproduct was eluted, then 90:10:2 DCM:MeOH:$NH_3$). **10b** was obtained as an orange sticky solid. Yield: 1.40 mmol, 554.0 mg, 89%; $^1$HNMR (400 MHz, $CDCl_3$, 25°C): δ = 7.80 (s, 1H), 5.36 (dd, $J_1$ = 10.9 Hz, J2 = 4.7 Hz, 1H), 4.27-4.31 (m, 1H), 4.18-4.23 (m, 1H), 4.14-4.17 (m, 1H), 4.07-4.13 (bs, 6H), 2.29-2.41 (m, 1H), 2.10-2.24 (m, 1H), 0.88 (t, $J$ = 7.1 Hz, 3H); $^{13}$CNMR (100 MHz, $CDCl_3$, 25°C): δ = 159.3, 148.9, 144.1, 138.9, 122.3, 87.9, 68.9 (5C), 68.6, 68.1, 67.1, 66.6, 56.6, 29.0, 11.1.

**1'-ferrocenyl ethylamine (12)** (brown solid) was prepared according to the literature. (R. Šebesta, M. Sališová. Chem. Pap. 2001, 55, 297-301). $^1$HNMR (400 MHz, $CDCl_3$, 25°C): δ = 4.13-4.18 (m, 7H), 4.10-4.13 (m, 2H), 3.81 (q, $J$ = 6.4 Hz, 1H), 1.35 (d, $J$ = 6.4 Hz, 3H); $^{13}$CNMR (100 MHz, $CDCl_3$, 25°C): δ = 96.3, 68.2 (5C), 67.4, 67.3, 65.7, 65.6, 45.9, 24.7.

*2-N-(1''-ferrocenyl etyl)-9-(1'-ferrocenyl propyl)-guanine **(13)***. In a schlenk tube under nitrogen atmosphere, were added 9-(1'-ferrocenyl propyl)-2-chloro-6-oxopurine **10b** (0.75 mmol, 299 mg), DMSO (2.3 mL) and 1'-ferrocenyl ethylamine **12** (1.5 mmol, 346 mg). The solution was stirred at 150°C for 11 hours. The crude mixture was directly purified by column chromatography (eluting mixture 90:10:2 DCM:MeOH:$NH_3$) to obtain pure **7** as orange solid in a 1.2:1.0 diastereomeric ratio determined by $^1$H NMR ($\delta_{major}$ = 7.85; $\delta_{minor}$ = 7.83).. Yield: 0.08 mmol, 42.0 mg, 11%; $^1$H

NMR (600 MHz, DMSO-$d_6$, 25°C): $\delta_{major}$ = 10.61 (s, 1H), 7.85 (s, 1H), 6.22 (d, *J* = 8.2 Hz, 1H), 5.14 (dd, $J_1$ = 11.0 Hz, $J_2$ = 4.3 Hz, 1H), 4.88-4.95 (m, 1H), 4.35-4.38 (m, 1H), 4.25-4.27 (m, 1H), 4.19-4.24 (m, 7H), 4.14-4.18 (m, 3H), 4.11-4.14 (m, 1H), 4.07 (s, 5H), 2.25-2.32 (m, 1H), 2.13-2.21 (m, 1H), 1.51 (d, *J* = 6.7 Hz, 3H), 0.76 (q, *J* = 9.0 Hz, 3H); $\delta_{minor}$ = 10.57 (s, 1H), 7.83 (s, 1H), 6.21 (d, *J* = 8.2 Hz, 1H), 5.14 (dd, $J_1$ = 11.0 Hz, $J_2$ = 4.3 Hz, 1H), 4.88-4.95 (m, 1H), 4.35-4.38 (m, 1H), 4.28-4.30 (m, 1H), 4.19-4.24 (m, 8H), 4.14-4.18 (m, 2H), 4.11-4.14 (m, 1H), 4.06 (s, 5H), 2.25-2.32 (m, 1H), 2.13-2.21 (m, 1H), 1.49 (d, *J* = 6.7 Hz, 3H), 0.76 (q, *J* = 9.0 Hz, 3H); $^{13}$CNMR (150 MHz, DMSO-$d_6$, 25°C): $\delta_{major}$ = 156.8, 151.2, 150.6, 136.3, 116.4, 91.5, 89.4, 68.4 (5C), 68.3 (5C), 67.6, 67.5, 67.3, 67.2, 67.0, 66.73, 66.70, 65.6, 55.3, 44.6, 27.5, 21.0, 11.1; $\delta_{minor}$ = 156.8, 151.2, 150.6, 136.4, 116.3, 91.5, 89.6, 68.4 (5C), 68.3 (5C), 67.7, 67.5, 67.3, 67.2 (2C), 66.74, 66.6, 65.6, 55.1, 44.5, 27.5, 20.9, 11.1; ESI-MS: *m/z* = 590.2$[M+H]^+$, 612.3 $[M+Na]^+$; mp: decomposition at 180°C. Anal. Calcd for $C_{30}H_{31}Fe_2N_5O$: C, 61.14; H, 5.30; N, 11.88. Found: C, 61.22; H, 5.39; N, 11.79.

**2-N-Boc-6-chloropurine (12)** was prepared according to the literature (S. Fletcher, V. M. Shahani, A. J. lough, P. T. Gunning, Tetrahedron 2010, 66, 4621-4632). Spectral data were according to those reported.

**9-(1'-ferrocenyl etyl)-2-N-Boc-6-chloropurine (16)**

To a solution of aluminium triflate (0.1 mmol, 47 mg) in DCM (5 mL) at 0°C, were added 2-N-Boc-6-chloropurine **15** (0.5 mmol, 135 mg) and 1-ferrocene ethanol **1a** (0.75 mmol, 175 mg). The solution was stirred for 12 hours at 0°C, then other aluminium triflate (0.1 mmol, 47 mg) and the solution was stirred for other 24 h at room temperature until complete conversion was observed by TLC. Then the reaction was quenched with water (5 mL). The organic phase was separated and the aqueous one was extracted with DCM (10 mL x 2). The collected organic layers were concentrated under reduced pressure. **16** was obtained as an orange sticky solid after chromatographic purification (eluting gradient from 95:5 to 60:40 cyclohexane:ethyl acetate). Yield: 0.35 mmol, 170.5 mg, 71%; $^1$HNMR (400 MHz, $CDCl_3$, 25°C): δ = 7.77 (s, 1H), 7.51 (s, 1H), 5.73 (q, *J* = 7.0 Hz, 1H), 4.33-4.35 (m, 1H), 4.24-4.26 (m, 1H), 4.20-4.22 (bs, 6H), 4.18-4.20 (m, 1H), 1.92 (d, *J* = 7.0 Hz, 3H), 1.57 (s, 9H); $^{13}$CNMR (100 MHz, $CDCl_3$, 25°C): δ = 152.3, 152.1, 150.9, 150.3, 142.6, 127.8, 87.0, 81.5, 69.1 (5C), 69.0, 68.4, 68.1, 66.0, 50.7, 28.2 (3C), 20.7.

*9-(1'-ferrocenyl etyl)-guanine **(6)**.* In a schlenk tube, were added 9-(1'-ferrocenyl etyl)-2-*N*-Boc-6-chloropurine **16** (0.17 mmol, 80 mg), dioxane (1.5 mL) and NaOH aq. 1M (0.8 mmol, 800 μL ). The solution was stirred at 80°C for 8 hours until complete conversion was observed by TLC. The dioxane was evaporated under reduced pressure, then $NH_4Cl$ aq. sat. was added until pH was neutral. The aqueous mixture was extracted with DCM (5 mL x 3) and the collected organic layers were concentrated under reduced pressure. **6** was obtained as an orange solid after chromatographic purification (ethyl acetate until the byproduct was eluted, then 90:10:2 DCM:MeOH:$NH_3$). Yield: 0.084 mmol, 30.6 mg, 50%; $^1$H NMR (400 MHz, DMSO-$d_6$, 25°C): $\delta$ = 10.56 (s, 1H), 7.70 (s, 1H), 6.48 (s, 2H), 5.36 (q, *J* = 7.1 Hz, 1H), 4.37-4.39 (m, 1H), 4.23-4.25 (m, 1H), 4.21-4.23 (m, 1H),

4.18-4.21 (bs, 6H), 1.82 (d, $J$ = 7.1 Hz, 3H); $^{13}$CNMR (100 MHz, DMSO-$d_6$, 25°C): $\delta$ = 157.3, 153.9, 150.9, 136.3, 117.2, 90.5, 69.6 (5C), 69.0, 68.5, 68.2, 67.4, 49.5, 21.7; ESI-MS: $m/z$ = 363.0 $[M]^+$, 364.1 $[M+H]^+$, 727.0 $[2M+H]^+$; mp: decomposition at 230°C. Anal. Calcd for $C_{17}H_{17}FeN_5O_6$: C, 56.22; H, 4.72; N, 19.28. Found: C, 56.30; H, 4.80; N, 19.14.

*9-(1''-ferrocenyl etyl)-2',3',5'-tri-O-acetylguanosine* ***(18).*** To a solution of 1-ferrocenyl ethanol **1a** (0.3 mmol, 69 mg) in DCM (2 mL), were added 2',3',5'-tri-*O*-acetylguanosine **18** (0.2 mmol, 82 mg) and $In(OTf)_3$ (0.04 mmol, 132 μL of a sol. 0.3M in $CH_3CN$). The mixture was stirred for 48 hours at rt. Then the reaction was quenched with water (2 mL). The organic phase was separated and the aqueous one was extracted with DCM (3 mL x 2).The collected organic layers were concentrated under reduced pressure and purified by preparative TLC on silica (95:5 DCM:MeOH as eluting mixture) to give **18** as a yellow solid in a 1.1/1.0 (diastereomeric ratio determined by $^1$H NMR: $\delta_{major}$ = 5.67; $\delta_{minor}$ = 5.62). Yield: 0.93 mmol, 58 mg, 47%; $^1$H NMR (400 MHz, DMSO-$d_6$, 25°C): $\delta_{major}$ = 10.76 (s, 1H), 7.91 (s, 1H), 6.39 (d, $J$ = 8.0 Hz, 1H), 6.11 (d, $J$ = 4.0 Hz, 1H), 6.04 (dd, $J_1 = J_2$ = 6.0 Hz, 1H), 5.67 (dd, $J_1 = J_2$ = 6.0 Hz, 1H), 4.88-5.00 (m, 1H), 4.31-4.46 (m, 3H), 4.25 (s, 5H), 4.18-4.28 (m, 4H), 2.14 (s, 3H), 2.12 (s, 3H), 2.03 (s, 3H), 1.51 (d, $J$ = 6.3 Hz, 3H); $\delta_{minor}$ = 10.76 (s, 1H), 7.92 (s, 1H), 6.40 (d, $J$ = 8.0 Hz, 1H), 6.11 (d, $J$ = 4.0 Hz, 1H), 6.03 (dd, $J_1 = J_2$ = 6.0 Hz, 1H), 5.62 (dd, $J_1 = J_2$ = 6.0 Hz, 1H), 4.88-5.00 (m, 1H), 4.31-4.46 (m, 3H), 4.26 (s, 5H), 4.18-4.28 (m, 4H), 2.13 (s, 3H), 2.10 (s, 3H), 2.01 (s, 3H), 1.52 (d, $J$ = 6.3 Hz, 3H); $^{13}$CNMR (100 MHz, DMSO-$d_6$, 25°C): $\delta_{major}$ = 169.86, 169.23, 169.18, 156.5, 151.69, 150.0, 137.0, 117.3, 91.1, 86.1, 78.4, 71.8, 69.7, 68.31 (5C), 67.5, 67.1, 66.4, 65.5, 62.9, 44.8, 20.9, 20.3, 20.17, 20.12; $\delta_{minor}$ = 169.83, 169.28, 169.20, 156.5, 151.73, 150.1, 136.9 117.4, 91.2, 86.4, 78.5, 71.8, 69.7, 68.28 (5C), 67.5, 67.2, 66.5, 65.6, 62.8, 44.7, 21.1, 20.3, 20.19, 20.15; ESI-MS: $m/z$ = 621.0 $[M]^+$, 622.2 [M+H]+, 1243.1 [2M+H]+; mp: decomposition at 200°C. Anal. Calcd for $C_{28}H_{31}FeN_5O_8$: C, 54.12; H, 5.03; N, 11.27. Found: C, 54.17; H, 5.11; N, 11.24.

## 3.3 Aluminium salophen ferrocene complexes[36]

### 3.3.1 Introduction

Salen and salophen are well established tetradentate ligands that can efficiently bind many metals. These complexes have been widely used as catalysts in organic synthesis[37] and more recently nichel salophens have been employed to form self assembled supramolecular structures. The variations of the chemical structure of the single monomer strongly influence the supramolecular organization and allows to select different structures.[38]

Salophens are flat ligands that bind a metal center that lies on (or is slightly outside of) this plane and were chosen because a more favorable interaction with a surface is predicted compared to twisted cyclohexyldiamine that is usually employed for salens. In case of penta- or exa-coordinated metal centers two additional coordination sites are available on the axis perpendicular to the salophen plane, one above and one below. In case of aluminium(III), it forms a pentacoordinated complex and one additional anionic ligand is located perpendicular to the salophen plane giving rise to a spatial defined model that resembles a tree over the ground and by modifying the tree a wide variety of complexes can be accessed (Figure 5).

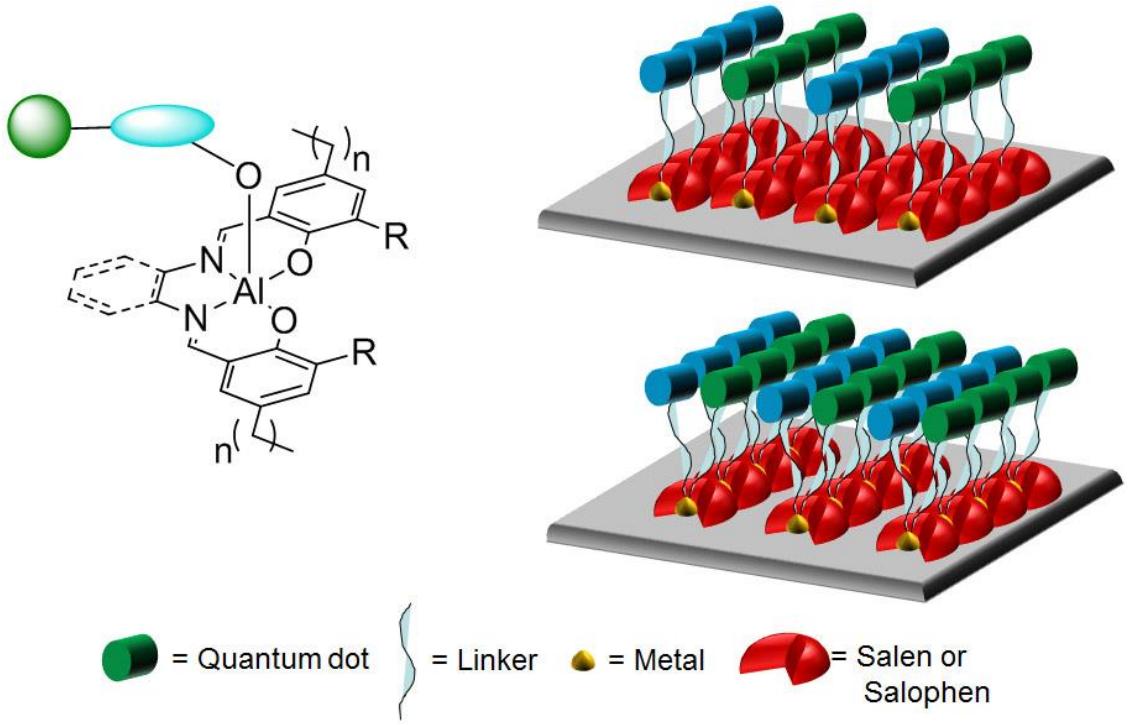
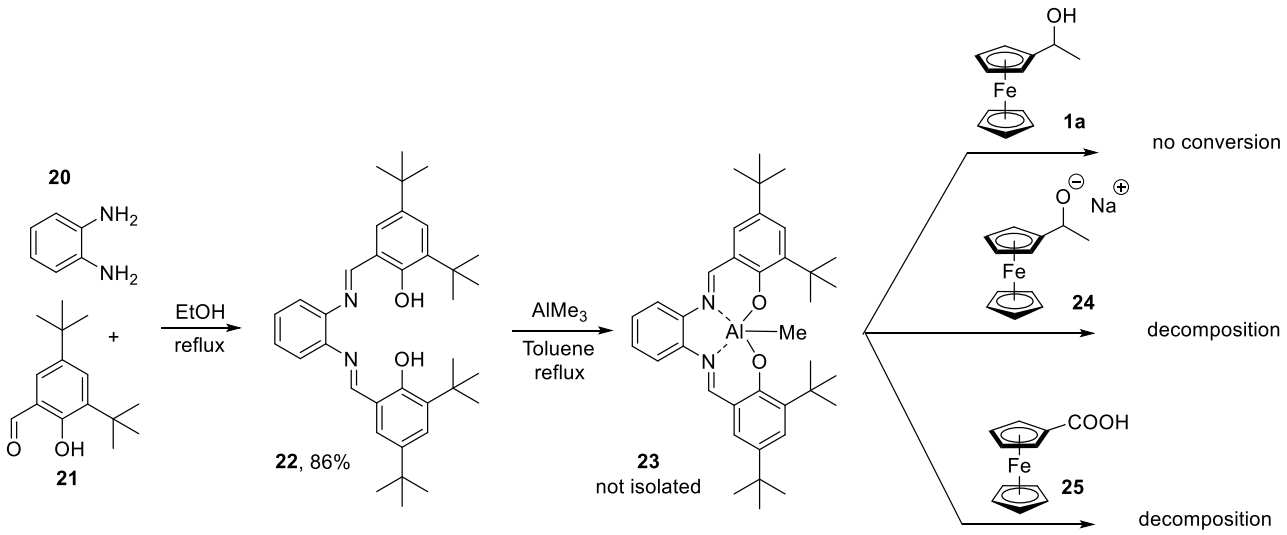



*Figure 5: proposal to employ salophen as scaffolds to form self-assembled monolayers of quantum dots.*

A wide range of salen or salophen aluminium complexes have been described in the literature using different aluminium precursors.[39] In case $AlMe_3$ is used to form the complex with salophen the AlMe salophen is obtained and the exchange between an additional ligand and the methyl is possible in a second step. This strategy allows to obtain a library of complexes by reacting the common AlMe precursor with the additional ligand that can be previously decorated with the desired functionalities, in our case one or more ferrocenes. The use of phenols has been successfully described to perform the exchange reaction with the AlMe-salophen.[39b]

## 3.3.2 Synthesis of the complexes

In order to favor the self assembly of the Al complexes on HOPG, we planned to insert long alkyl chains on the salophen core. We decided to investigate first the ligand exchange reaction using the classical salophen **22** derived from salycil aldehyde **21** that was obtained by standard procedures as showed in scheme 5. A solution of $AlMe_3$ in toluene was added at 0°C to the salophen ligand dissolved in toluene, then the mixture was heated to reflux for 8 h affording the desired AlMe complex **23**. The reaction conversion was checked by $^1H$ NMR analysis and when the reaction was complete the solvent was evaporated to give **23** as an orange solid. If the reaction was complete, the crude product was already enough pure to continue with the reaction sequence. However it can be washed with exane to increase its purity.
$AlMe_3$ is pyrophoric so it must be avoided its contact with air and moisture, as it is immediately hydrolyzed. Moreover one equivalent of the reagent should be used in the reaction to avoid side reactions, with the disadvantage that if traces of oxygen and moisture are present they would react with $AlMe_3$ leading to an incomplete conversion. Once the AlMe complex **23** is formed, it can be handled on air without particular precautions, even if usually I just evaporated the solvent to obtain **23** and in the same reaction vessel I added the precise amount of the ligand with whom I desired to perform the exchange reaction with the methyl group.



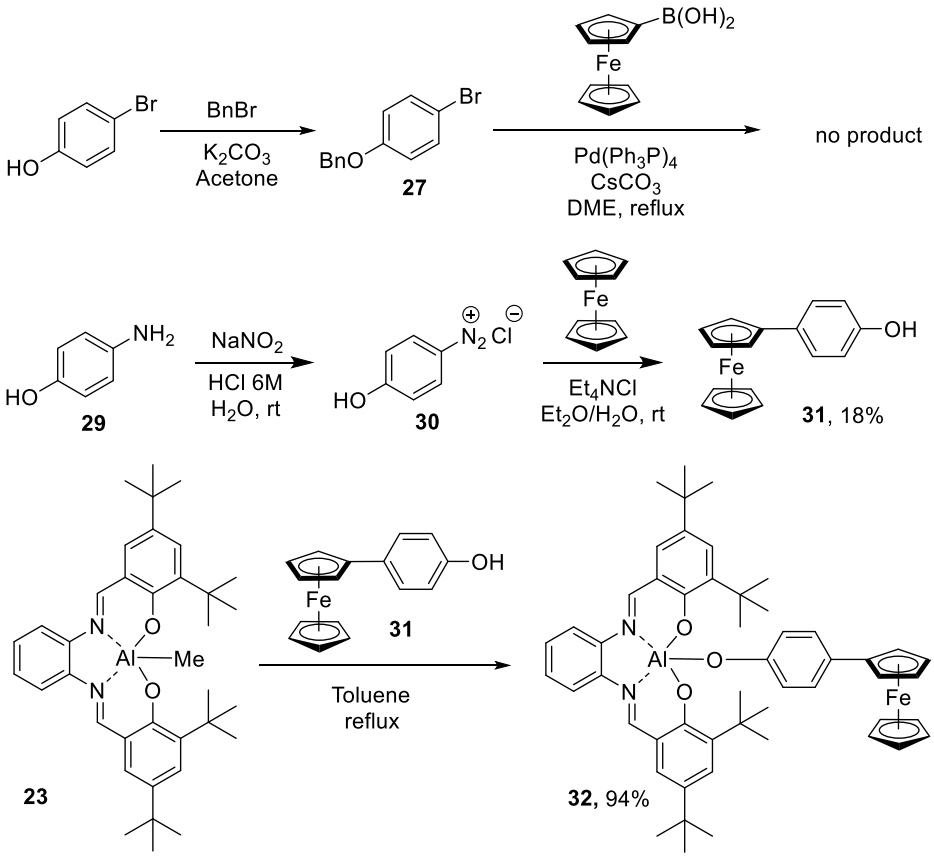

*Scheme 5: unsuccessful attempts to form ferrcocene Al salophen complexes.*

As alcohols form stable salphen aluminium complexes, we initially attempted to perform the ligand exchange directly with ferrocene ethanol **1a** that was refluxed in 1:1 ratio with AlMe salophen **23** in toluene. Surprisingly no reaction occurred and the AlMe complex **23** remained untouched. I tried to use the sodium alkoxide **24** instead of **1a** and also in this case I did not obtain the desired product, instead complex **23** decomposed during the reaction. A possible explanation could be that the alcohol moiety is not enough acid to react with the **23**, so I performed the reaction with

commercially available ferrocene carboxylic acid but also in this case I observed the decomposition of the starting complex **23**.

Para substituted phenols have been reported to efficiently undergo ligand exchange with AlMe salophen complexes,[39b] so we decided to prepare a phenol having a ferrocene moiety on the para position. An initial attempt to perform a cross coupling between ferrocene boronic acid and para bromo phenol was unsuccessfull. So we focused our attention on para ferrocene phenol **31** as target ligand. The starting material is para ammino phenol **29** that is commercially available. The corresponding diazonium salt **30** is obtained by reaction with $NaNO_2$ in aqueous hydrochloridric acid. Then a solution of ferrocene in ether is added via cannula over the diazonium salt to realize the nuclephilic aromatic substitution that gives **31** in 18% isolated yield. Ferrocene is rapidly oxidized to ferrocenium if exposed to acids in presence of oxygen, so it is very important to perform the reaction under inert atmosphere, otherwise the blue colour typical of ferrocenium (III) replaces the orange shade of ferrocene (II) solution. Even if the yield is low the procedure results convenient due to the low cost of all reagents employed and the rapid access to the target molecule.

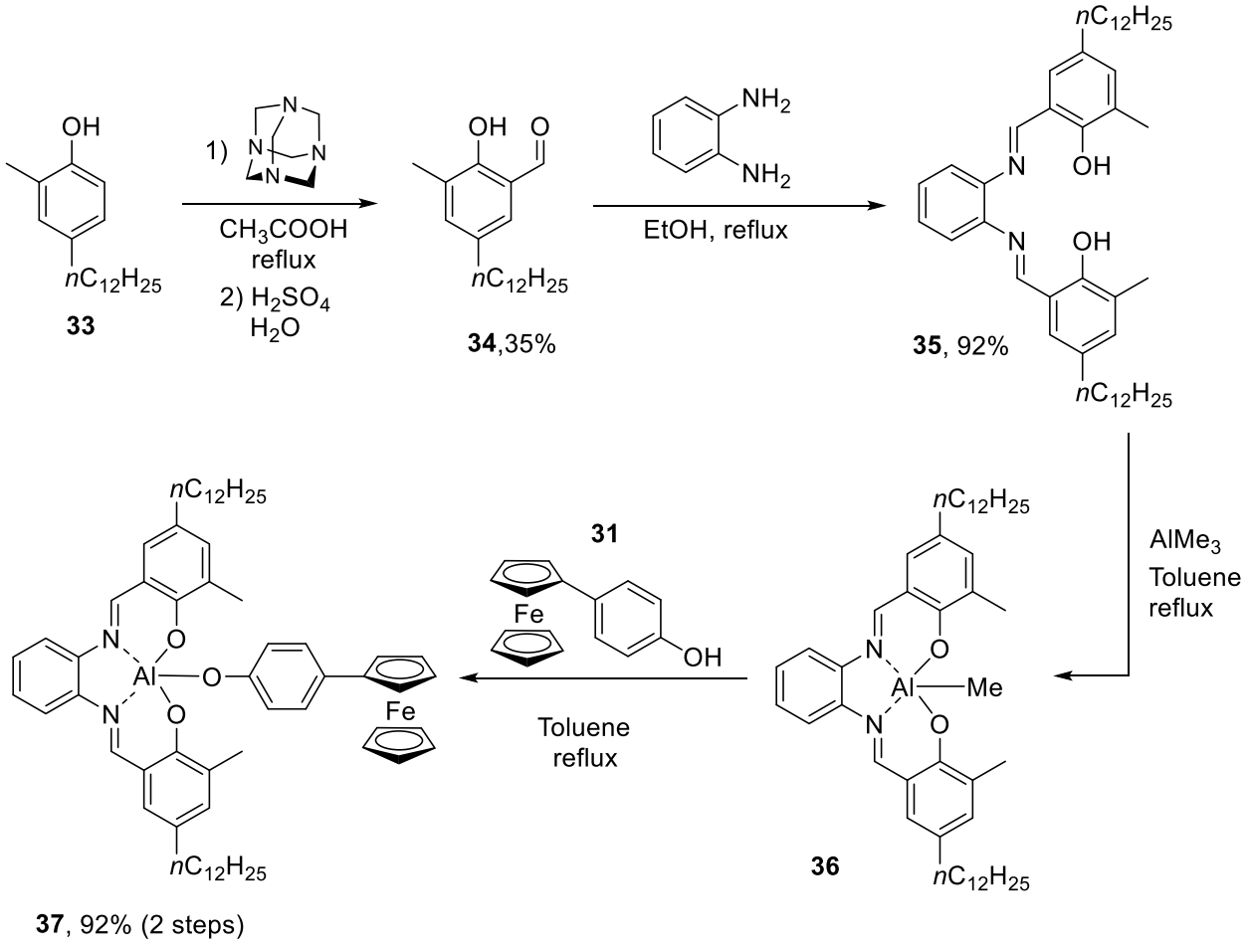
The ligand exchange reaction between **23** and **31**was performed by refluxing the two compounds in 1:1 ratio in toluene for 8h. The analysis of the crude reaction mixture showed total conversion and the product was isolated simply after solvent evaporation in 94% yield.




*Scheme 6: successful synthesis of model substrate Fc-Al-salophen **32**.*

From these preliminary experiments it emerges that the use of a para substituted phenol is mandatory for the successful formation of the desired Fc-Al-salophen complex. Two reasons for the failure of the reactions with ferrocene ethanol and ferrocene carboxylic acids can be adducted: the first one is that the pKa of the hydroxyl moiety plays a crucial role in the complex formation, with the phenol one being suitable while the alcohol or the carboxylic acid are not; the second reason is the possible steric repulsion between the bulky ferrocene and the salophen core in case **1a** or **25** are employed that are instead avoided with **31** that has the ferrocene far away on the phenol para position.

In order to have good suitable molecules to be studied on a surface, we needed to introduce long aliphatic chains on the salophen core and use these ligands to form the Al-salophen complexes. The para position of the phenol salophen portion seemed the most suitable for the introduction of the alkyl chain for several reasons: 1) it is far away from the ligand centre that should not be affected by its presence, 2) considering the probable disposition of the salophens in rows to form of a self assembled monolayer, the alkyl chain in the para position would be in the best position to interact between each other, 3) 2-methyl-4-*n*-dodecyl-phenol **33** is commercially available.



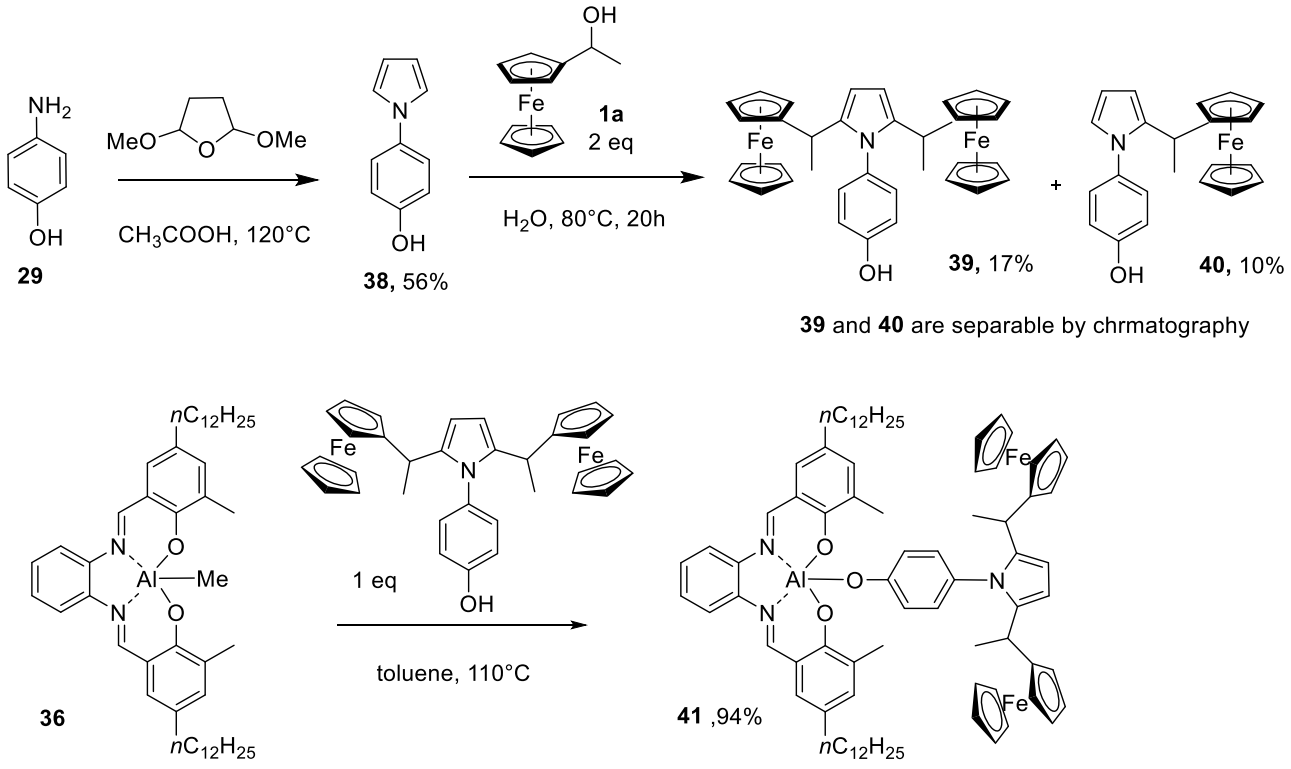

*Scheme 7: synthesis of mono ferrocene complex bearing long alkyl chains.*

The formilation to obtain aldehyde **34** is performed using hexamethylentetramine in refluxing acetic acid.[40] From our experience in the synthesis of salens, this procedure is the most convenient one.

The product is obtained in moderate yield after chromatographic purification and its condensation in 2:1 ratio with 1,2-diammino benzene affords salophen **35** in optimal yield (scheme 7).
The formation of AlMe salophen complex **36** was done following the same procedure used for **23**. However this reaction resulted much more sensible to air and moisture and to the quality of the reagents, in particular the $AlMe_3$. A perfectly clean reaction was obtained only in a few cases affording the product in quantitative yield and high purity. In the other cases variable amounts of unreacted salophen ligand **35** were detected and sometime unidentified species deriving from the decomposition of the salophen were present too. In one case further $AlMe_3$ was added in the attempt to push the conversion to completion, but the almost complete degradation of the salophen **35** was observed. Probably the excess of $AlMe_3$ acted as a nucleophile on Al salophen **36** causing its decomposition.
It should be noted that all reactions were conducted in standard shlenk apparatus without glove box in the 0.05-0.2 mmol scale, so the incomplete conversions and product decomposition are probably due to the presence of traces of water or oxygen that react with $AlMe_3$. In particular water, or the derived aluminium alkoxydes, can cause the rapid hydrolysis of the imine bond that is further activated by the aluminium complexation. These side reactions were not observed for more stable classical salophen **23**. To perform the NMR analysis of these complexes $CDCl_3$ stored over $MgSO_4$ and $NaHCO_3$ under nitrogen atmosphere was used, otherwise the rapid decomposition of the complexes bearing the long alkyl chains was observed.
I carried out several attempts to wash, precipitate or crystallize the impure batches of AlMe complex **36** using anhydrous solvents under inert atmosphere. Unfortunately this complex is very apolar and even in *n*-hexane the selective precipitation of the product (or of the impurities) resulted impossible.
When the reaction of pure AlMe complex **36** with Fc-phenol **31** was performed, complete conversion into the desired product **37** was obtained albeit an excess of the ferrocene phenol ligand was present probably because of an error in the evaluation of the amount of **36** employed.
Even in case impure batches of **36** were employed to perform the exchange with **31**, the desired product was obtained along with the impurities already present in the starting **36** and the excess of phenol ligand **31**. Unfortunately the various attempts to purify **37** by crystallization or precipitation were unsuccessful. In should be noted that either the AlMe complex **36** either the Fc-Al-complex **37** are enough stable at the solid state to be rapidly weighted or handled on air, while when they are dissolved the use of dry solvents is mandatory: In addition any solvent that may carry acidic traces, such as DCM or chloroform, should be avoided or neutralized over an inorganic base such as $NaHCO_3$ prior to use.
With the synthesis of **37**, we demonstrated that it is possible to insert one ferrocene on an aluminium salen complex, but for a QCA application at least two ferrocenes must be present on a single molecule that would correspond to a 2 dot half cell. Taking inspiration from the $S_N1$ chemistry developed in the past by Cozzi research group, we selected pirrole as the suitable scaffold to bear the two ferrocenes moieties. Pirrole should be linked to a phenol for a successful complexation with aluminium salophen **36**. Suitable molecule **38** can be obtained by reaction of para ammino phenol **29** with 2,5-dimethoxy furane under acidic conditions. A simple basic extraction affords **38** in good yield and optimal purity as a grey solid.[41]

The mono Friedel Craft reaction of pyrrole with ferrocene ethanol, had been described either on water[42] or in DCM with a catalytic amount of Lewis Acid. In both cases a large excess of pirrole was employed to favor the monoalkylation and suppress the condensation of two molecules of alcohol to give the ether.

As my objective was the double alkylation of **38**, an excess of alcohol was necessary. A first attempt to perform the reaction in DCM using a catalytic amount of $In(OTf)_3$ (10% mol) was unsuccessful as an extensive decomposition of the starting materials was observed. In particular a significant amount of the ferrocene ethanol ether was detected. In order to disfavor this side reaction and avoid the use of a metal Lewis acid, I performed the reaction on water.



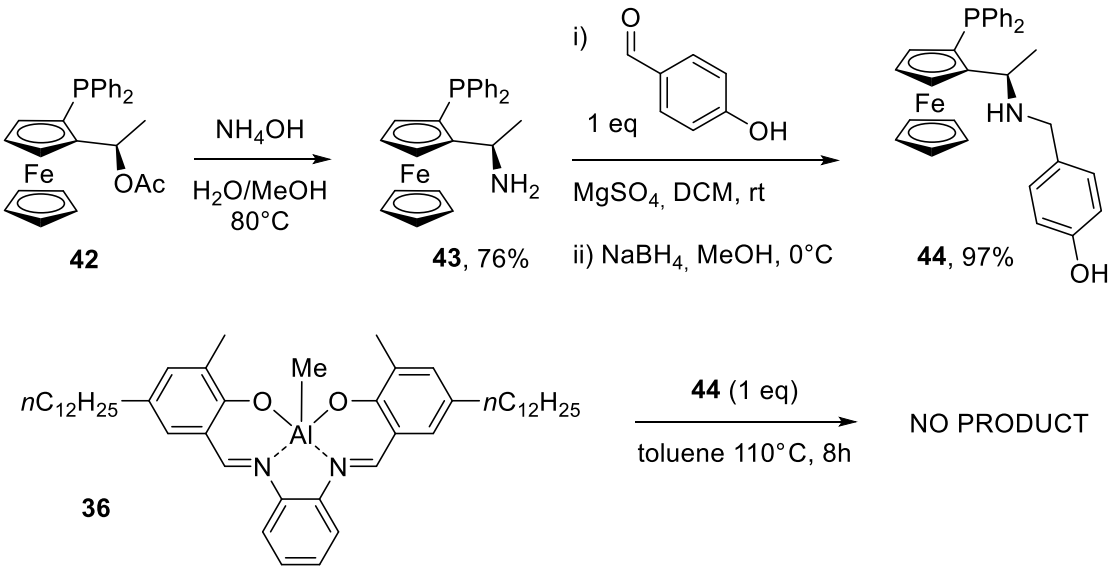

*Scheme 8: synthesis of diferrocene complex **41**.*

Molecule **38** and 2 eq. of ferrocene ethanol **1a** were suspended on water and stirred vigorously at 70°C. TLC analysis revealed the formation of both the monoalkylated product **40** and the desired dialkylated one **39**. After 21 h the ferrocene alcool was completely consumed. The analysis of the reaction crude revealed also the formation of several unidentified sideproducts and the presence of unreacted phenol. Chromatographic purification allowed to isolate impure **39** and pure **40**. Pure **39** was obtained by purification trough preparative HPLC.

Phenol **39** was then refluxed in toluene with Al-Me-complex **36** to give pure **41** in 94% yield after evaporation of the solvent.

We also wanted to install a chiral ferrocene moiety on the aluminium salophen core to study the influence of chirality on the apical ligand on the properties of the final complex. In our laboratory we have 99% ee **42** that bears an additional phosphine substituent on the ferrocene. This molecule is

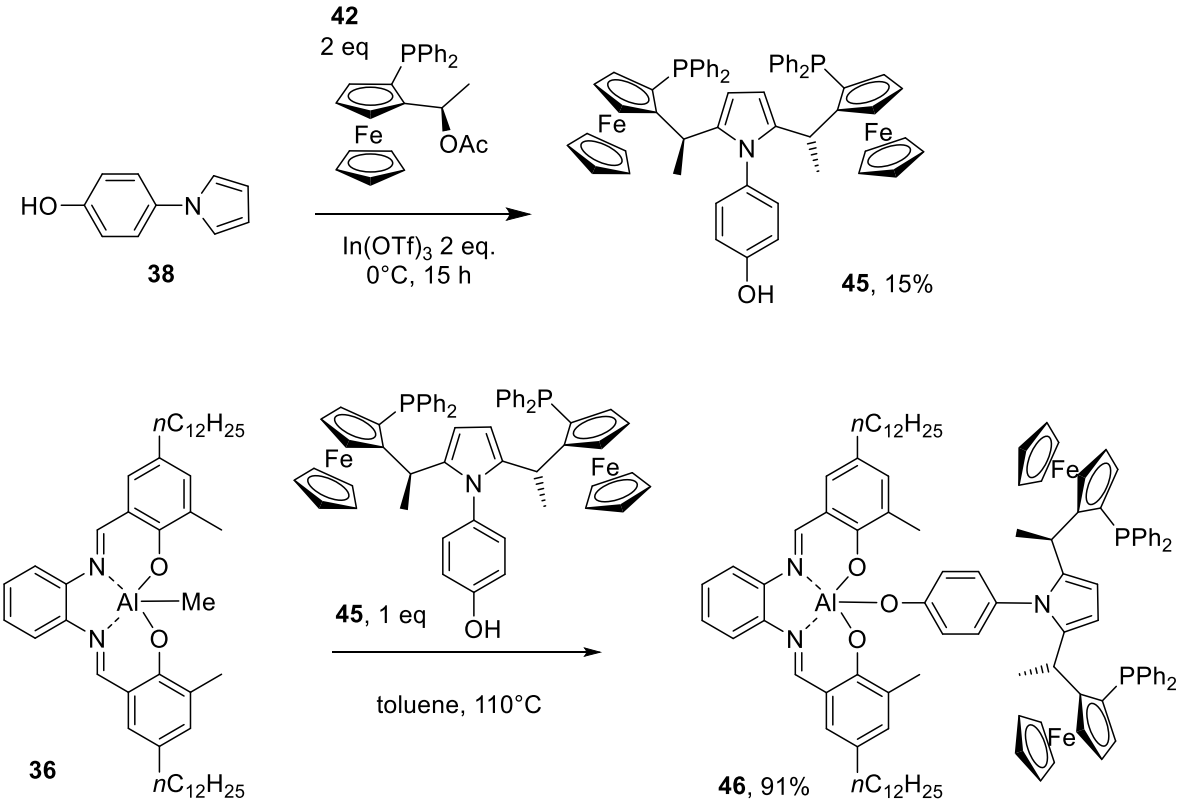
a precursor of well know Josiphos ligands and its introduction on an aluminium salophen complex would allow the possible binding of an additional metal atom, so I investigated several possibilities to synthetize conjugates between **42** and phenols.
In a first attempt I prepared amine **42** that is easily obtained by ammonia substitution of the acetate moiety of **42**. Amine **43** was condensed with paramethoxybenzaldehyde to give the corresponding imine that was directly reduced to give amine **44**.
The ligand exchange reaction of amine **44** with Al-Me-complex **36** was performed using the standard conditions but no product was obtained even if the Al-Me-complex **36** was consumed. We reasoned that the secondary amine could engage a side-reaction leading to the decomposition of **36** and we decided to change the synthetic approach to bind **42** to a phenol.




*Scheme 9: unsuccessful complexation of **44** with **36**.*

We decided to use **42** in the same strategy that allowed the synthesis of **39** to obtain a pirrole-phenol ligand bearing two enantio-enriched ferrocene phosphines. An initial test to evaluate the feasibility of the reaction was performed by reacting 1 eq **42** with 4 eq of **38** on hot water. Unfortunately a low conversion was observed even after several hours at reflux. However the formation of the dialkylation product **45** over the monoalkylated one seemed favored even in presence of an excess of phenol, that was an encouraging indication as we were looking for this product.
When the reaction was performed in DCM in presence of 10% mol of $In(OTf)_3$ at -20°C, the product formation was detected in the initial stage of the reaction but then the conversion stopped and a dark color appeared suggesting the decomposition of the reagents or of the products. I hypothesized that the Lewis acid catalyst could be sequestered either by the starting **42** or by the product **45** that is a tridentate ligand. Indeed, when a stoichiometric amount of $In(OTf)_3$ was employed and the temperature was raised to 0°C, complete conversion of the acetate was observed after several hours. Analysis of the crude revealed a mixture of di and mono alkylated products, unreacted phenol **38** and several unidentified side-products.

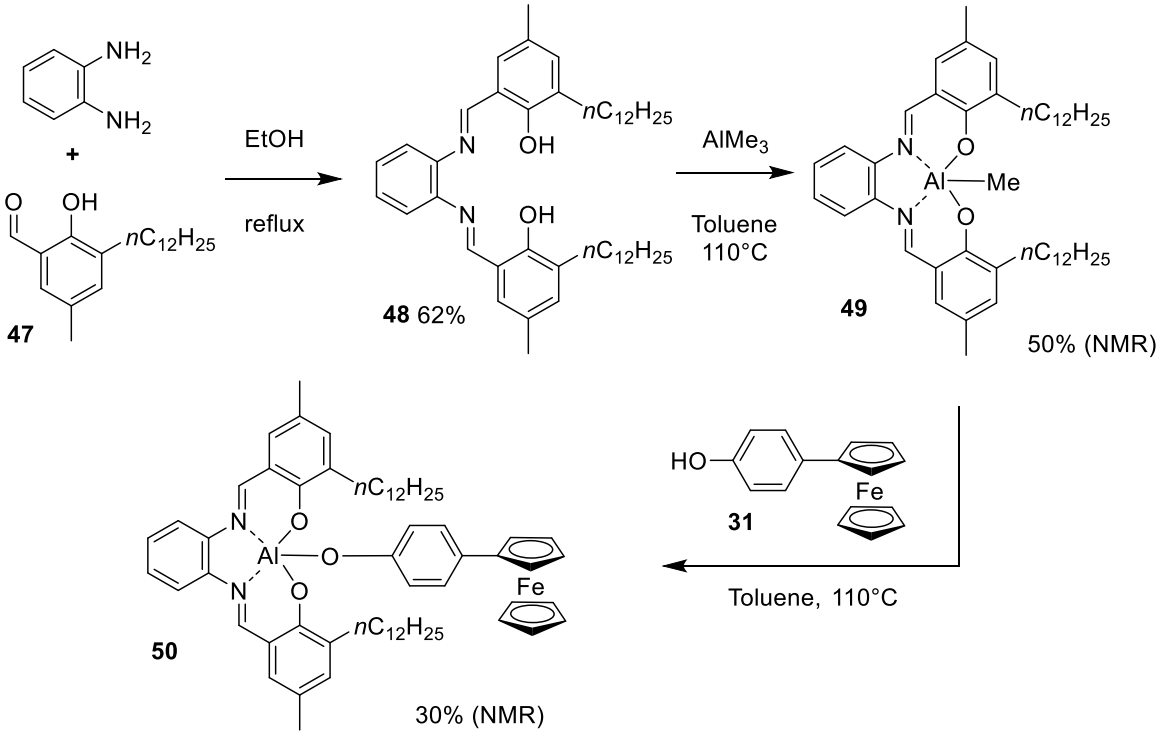
Increasing the equivalents of **42** to 2, and by consequence also those of $In(OTf)_3$, allowed to maximize the formation of the dialkylated product and only small amounts of the mono alkylated compound and unreacted phenol were present after 15 h. Unfortunately the presence of side-products and their very similar polarity with **45** allowed to obtain the pure compound only in 15% yield.
The formation of complex **46** in high yield and high purity was successfully obtained by refluxing pure **36** and ligand **45** in 1:1 ration in toluene for 8 h (scheme 10).




*Scheme 10: synthesis of optically active diferrocene Al-complex **46***

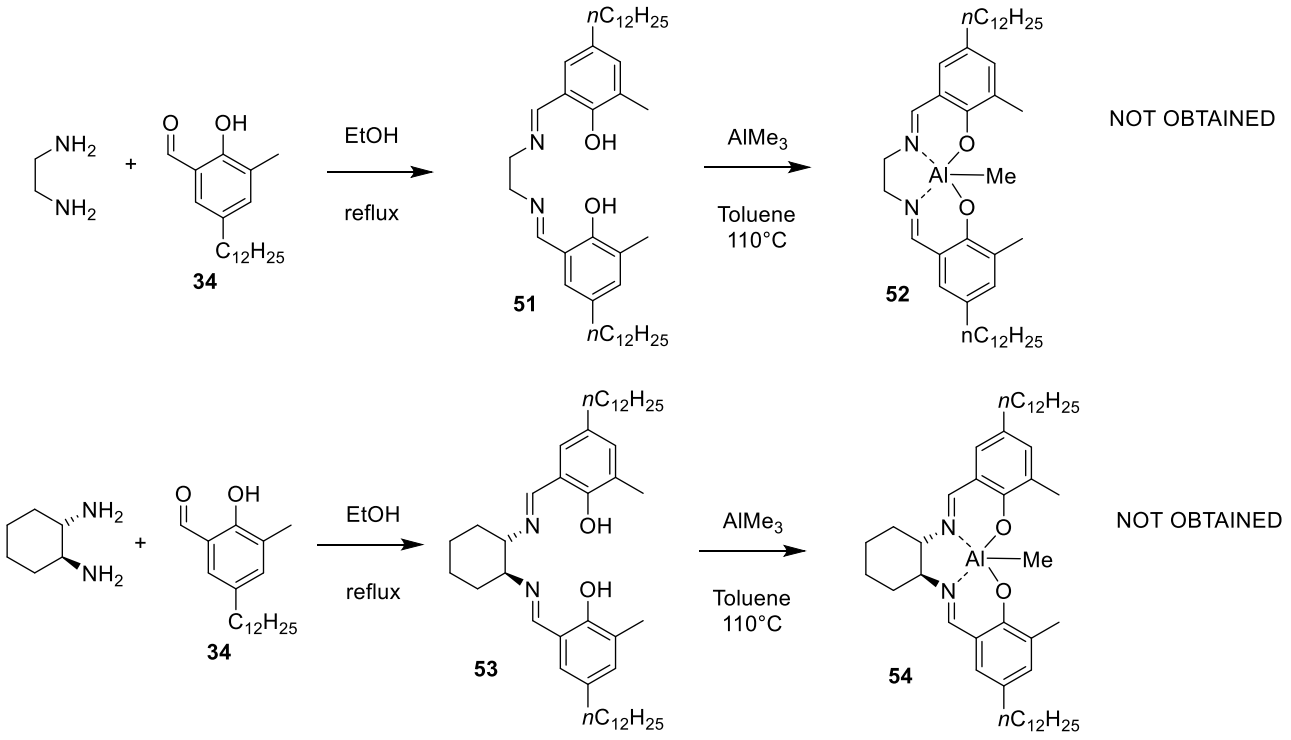
To sum up, we synthetized four ferrocene aluminium salophen complexes, three of whom bearing long alkyl chains suitable for the formation of self-assembled monolayers on HOPG.
Artur Cieselsky, assistant of Professor Samorì, pointed out that different self-assembled patterns can be obtained changing the position of the alkyl chain on the salophen core. As the synthesis of a meta substituted salophen is quite challenging as this is the deactivated position of the phenol, I focused on the orto position.
Aldehyde **47** was prepared following the same procedure used for **34**. Then it was condensed with 1,2-diammino benzene to give salophen **48**. However this salophen was quite unstable and in particular was sensible to hydrolysis, while the previously prepared ones were stable compounds that did not suffer from such a decomposition process. The hydrolysis of **48** rapidly occurs in the NMR sample dissolved in non anhydrous $CDCl_3$ after a few minutes. The use of $CDCl_3$ stored over $MgSO_4$ and $NaHCO_3$ under nitrogen atmosphere was necessary to perform the characterization of

**48**. This instability was reflected in the moderate yield (62%) after precipitation from ethanol. The steric hindrance between the alkyl chains on the orto position probably destabilize the structure of salophen **48**. The synthesis of Al-Me-complex **49** was attempted using the standard procedure, but only 50% yield of the desired complex, determined by $^1$H NMR, along with several decomposition products was achieved despite several attempts. The reaction with phenol **31** was performed directly over the crude and the final desired complex **50** was obtained in 30% yield determined by $^1$H NMR. All the attempts to purify by precipitation or crystallization the Al-Me-complex **49** or the final one **50** were unsuccessful and lead to a more extended decomposition. Non pure complex **50** was sent to Strasbourg to evaluate if it showed any self assembly on HOPG and as these experiments were negative no further efforts were done on this target.




*Scheme 11: synthesis of Fc-Al-complex **50** having the alkyl chains on the orto position.*

We also investigated two salen ligands in our protocol: **51** was obtained by condensation of aldehyde **34** and diethylamine while for **53** cyclohexylamine was employed. Both salen were obtained in good yields and they were reacted with $AlMe_3$ under the standard conditions to afford the corresponding Al-Me complexes **52** and **53**. Unfortunately these complexes were not obtained. Instead the formation of several decomposition products was observed by NMR. I tried slightly different conditions to perform the reaction: in particular $AlMe_3$ was added at -78°C instead of 0°C before refluxing the mixture but the same negative result was obtained (scheme 12).




*Scheme 12: attempted synthesis of long alkyl chain Al salen complexes.*

### 3.3.3 Electrochemical characterization of Fc-Al-salophen complexes

The four Fc-Al-complexes **32, 37, 41** and **46** were characterized by electrochemistry through cyclic voltammetry measurements in super dry conditions by Prof. Paolucci research group and the results are illustrated in table 3.
To understand the properties of these complexes it is better to point out the main features of the salophen ligands and of the Al-Me-complexes.
The salophen ligand bearing long alkyl chains **35** shows two reductions and two oxidations. The cyclic voltammetry response can be rationalized in terms of salophen MOs: HOMO is localized on phenol moieties, while LUMO resides substantially on imine moieties. The two oxidation are ascribed to phenolic oxygens, while the two non-reversible reduction are centred on imine moieties. Concerning the oxidations, the first one is non-reversible and it can be associated to the oxygens with a subsequent deprotonation, in a EC mechanism.[43] The second could be ascribed to oxygen radical oxidation to ketone. From CV de-convolution the ratio of electron is roughly one for each reduction, two for the first and one for the second oxidations.

| Compound | Fc | pyrrole | oxo 1 | oxo 2 | oxo 3 | imine 1 | imine 2 |
|---|---|---|---|---|---|---|---|
| **35** (salophen) | - | - | 1.07 [a] | 1.34 | - | -1.50 [a] | -2.04 [a] |
| **23** (AlMe) | - | - | 1.03 [a] | 1.28 [a] | - | -1.66 [a] | [c] |
| **32** (FcAl) | 0.35 | - | 1.23 [a] | 1.46 [a] | 1.60 [a] | -1.61 [a] | [c] |
| **37** (FcAl) | 0.38 | - | - | - | 1.60 [a,b] | -1.66 [a] | [c] |
| **41** ($Fc_2Al$) | 0.37 | 1.31 [a] | - | - | 1.43 [a,b] | -1.66 [a] | [c] |
| **46** ($Fc_2Al$) | 0.45 | 0.92 | - | - | 1.38 [a,b] | -1.75 [a] | [c] |

Cyclic voltammetry was conducted at T = 298 K. in a three electrode cell: working electrode is Pt disc (Ø=125 μm), counter electrode is Pt spiral and quasi-reference electrode is Ag spiral. Compounds were dissolved in dry dichloromethane (0,1 mM) with tetrabutylammonium hexafluorophosphate (50 mM). Before and throughout the CV experiments, the electrochemical cell is kept free from water and oxygen. (a) Irreversible oxidation peak. (b) Referred to the oxidation of the three oxo groups that occurred at the same potential. (c) The second imine reduction was shifted out of the solvent window after formation of the Al complexes.

*Table 3. Electrochemical properties of metal salophen compounds*

The aluminium methyl complex presents some slight changes in the CV: both oxidations become irreversible probably because they are associated with the breaking of the complex and the reductions are shifted to more negative potentials so that the second one is no more inside the DCM potential window.

All Fc-Al-complexes show the reversible oxidation peaks of Fc. No significant differences are seen in the potentials except for **46** because the electron withdrawing effect of phosphine, directly bound to ferrocene, leads to an increased potential of oxidation. For both diferrocene complexes **46** and **41** a two electron oxidation peak relative to both ferrocenes is observed meaning that there is no electronic communications between them.
The additional oxidation peak observed for **46** and **41** was assigned to the pirrole moiety. Complex **32** having the tertbutyl groups instead of the long alkyl chains, shows three different oxidation peaks, the third one relative to the additional phenol ligand, while for all complexes having the long alkyl chains (**32, 37, 41** and **46**) only one oxidation peak is observed that was assigned to the irreversible oxidation of all three oxo groups. The irreversible oxidations of the oxo-groups causes a strong adsorption of the complexes on the electrode.
The electrochemistry showed the desired oxidation of the ferrocenes around 0.4 V: The complexes are stable at low potentials that allow the reversible oxidation of the ferrocenes, while at potentials major than 1 V the irreversible oxidation of the oxo groups leads to the decomposition of the complexes.

### 3.3.4 Surface studies of Fc-Al-salophen complexes and conclusions

The complexes bearing the long aliphatic chains (**37,41,46**) were sent to Strasbourg where Samori research group observed the formation of self assembled monolayers on HOPG at the solid liquid interface for the three complexes. Also salophen **35** and Al-Me complex **36** show a similar self assembled patter on HOPG. The STM images for **37** and **41** are represented respectively in figures 6 and 7. The bright areas correspond to the high elcectron density portions of the molecules, in particular the circular spots are the ferrocenes and the half moon semicircles the salophen cores. The alkyl chains are the darker lines between the salophen core's rows. Form the molecular model of figure 6 it is possible to appreciate the formation of parallel rows of complex with the ferrocene units pointing upwards and the long alkyl chains that are extended and interdigitated between adjacent rows of complexes. The interaction of the alkyl chains with the surface and between themselves is the driving force that guides the self assembly of these molecules independently from the nature or the presence of the phenolic ligand.
From the STM image of **41** it is possible to appreciate the presence of two ferrocenes for each salophen core. It should be noted that the ferrocenes are ordered despite the rotational freedom on the single bond that connects the phenol ligand to the aluminium metal center.
The STM image of **46** (not shown) does not differ significantly from that of **41** and to the best of our knowledge represents the first example of a surface covered by a self assembled monolayer bearing an ordered pattern of phosphine ligands protruding towards the solution.

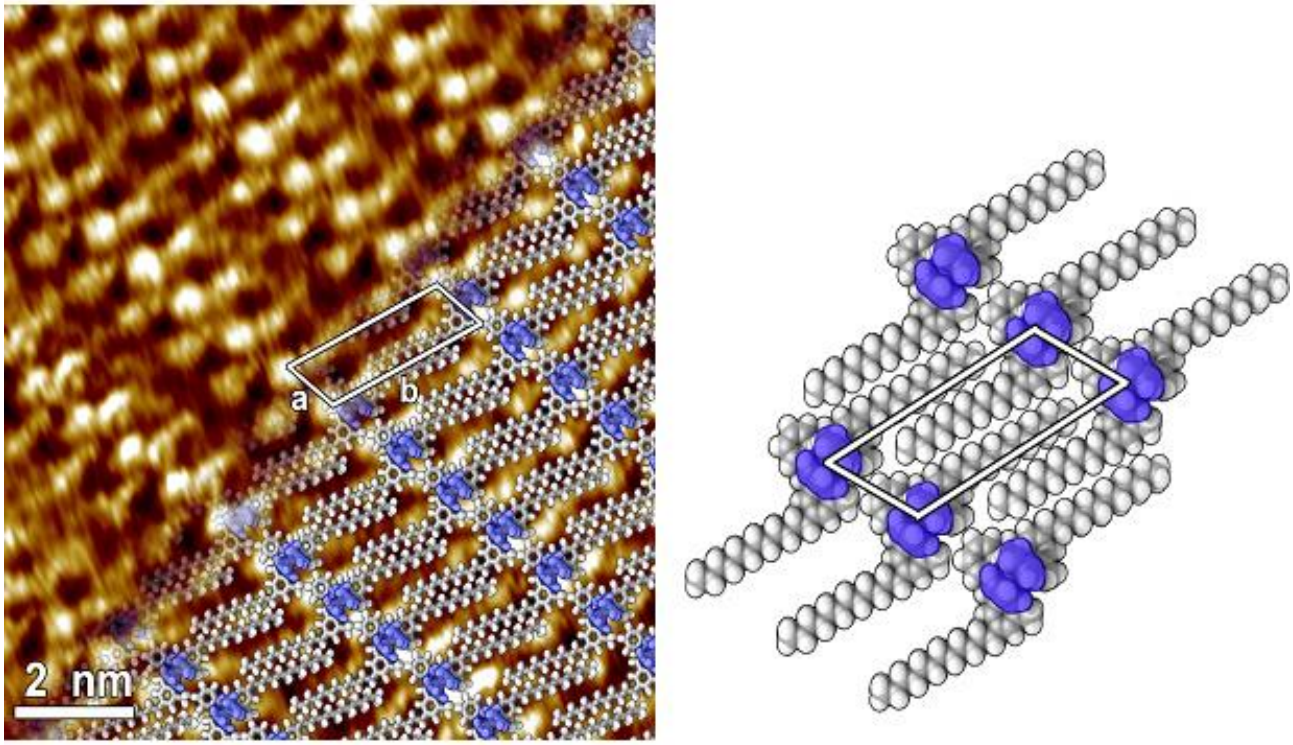



*Figure 6: Height STM image and molecular model of **37**. Tunneling parameters: $I_t$ = 30 pA, $V_t$ = -350 mV.*

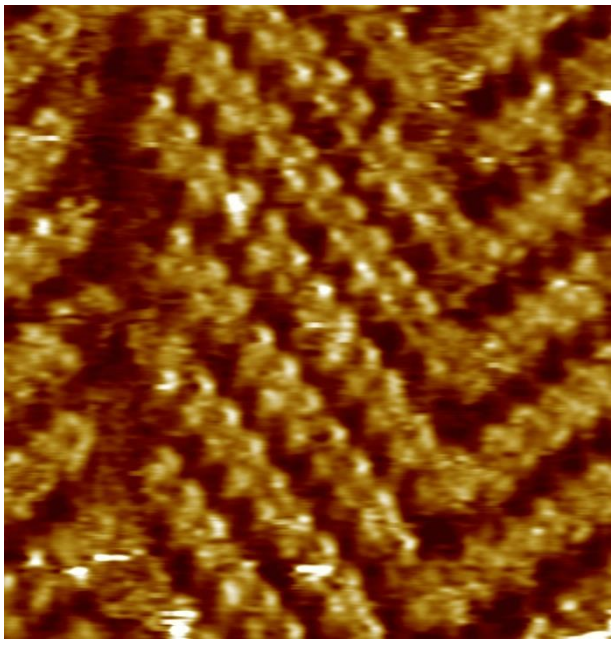


*Figure 7: Height STM image of **41**. Tunneling parameters: $I_t$ = 30 pA, $V_t$ = -350 mV.*

In conclusion we have demonstrated the first self assembly of aluminium complexes on HOPG at the solid liquid interface. The additional phenol ligand points out of the surface towards the liquid

phase. All these complexes are obtained from a common precursor, the Al-Me-complex **36**, by reaction with different phenolic ligands that can be decorated with the desired functionality on the para position without affecting the self assembled pattern that is reproduced in a perfectly predictable manner.
Through this stategy one or two ferrocene moieties were successfully organized on the surface as well as a chiral bisphosphinic potential ligand for an additional metal center.
Concerning the development of QCA candidates, the two ferrocene complexes **41** and **46** organize efficiently on the surface forming potential half cells, but the oxidative decomposition at potentials > 1 V makes these molecules too fragile candidates for an operating device and do not offer the desired requirements to perform the clocking.

### 3.3.5 Contributions

I and Dr. Andrea Gualandi designed and synthetized the ferrocene aluminium complexes. Dr. Matteo Iurlo and Dr. Andrea Fiorani (Prof. Paolucci research group) performed the electrochemical characterizations and Mohamed El Garah and Dr. Artur Cieselsky (Prof. Samorì research group) the surface studies.

## 3.3.6 experimental part

**General methods.** $^{1}H$ NMR spectra were recorded on Varian Gemini 200, Varian Mercury 400 and Inova 600 spectrometers. Chemical shifts are reported in ppm from TMS with the solvent resonance as the internal standard (deuterochloroform: $\delta$ = 7.27 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = duplet, t = triplet, q = quartet, dd = double duplet, dt = double triplet, pd = penta dublet, bs = broad signal, bd = broad duplet, m = multiplet), coupling constants (Hz). $^{13}C$ NMR spectra were recorded on Varian Gemini 200, Varian MR400 spectrometers. Chemical shifts are reported in ppm from TMS with the solvent as the internal standard (deuterochloroform: $\delta$= 77.0 ppm). If rotamers are present, the splitted signals are labeled as A (major rotamer) and B (minor rotamer). GC-MS spectra were taken by EI ionization at 70 eV on a Hewlett-Packard 5971 with GC injection. LC-electrospray ionization mass spectra (ESI-MS) were obtained with Agilent Technologies MSD1100 single-quadrupole mass spectrometer. They are reported as: *m/z* (rel. intense). Chromatographic purification was done with 240-400 mesh silica gel. Purification on preparative thin layer chromatography was done on Merck TLC silica gel 60 $F_{254}$.

**Materials.** If not otherwise stated, all reactions were carried out in flame dried glassware under nitrogen atmosphere. Anhydrous solvents were supplied by Aldrich in Sureseal® bottles and were used as received avoiding further purification.

Reagents were purchased from Aldrich and used without further purification unless otherwise stated.

**Synthesis of phenolic ligands**

4-Ferrocenyl phenol **31**[44] and **38**[41] were prepared according to reported procedures and spectroscopical data were according to those reported.

**(39)**. In a 10 mL vial equipped with a stirring bar 1-ferrocenyl ethanol **38** (70 mg, 0.44 mmol) and **1a** (202 mg, 0.88 mmol) were suspended in 4 mL of water. The vial was capped and the reaction mixture was heated at 80°C under vigorous stirring for 23 h. Then AcOEt was added, the organic layer was separated and the aqueous one extracted with AcOEt (2 x 8 mL). The collected organic layers were dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to give an orange oil that was purified by column chromatography on silica (cyclohexane:AcOEt:Et2O 85:10:5) to afford unpure **39** (116 mg, rf = 0.4) and pure **40** as orange oil (16 mg, 0.044 mmol, 10 % yield, rf = 0.3). Unpure **39** was purified by preparative HPLC (C18 column; flow rate 10 mL/min; $CH_3CN$:$H_2O$ 80:20 for 7 min., then gradient elution to 100:0 in 1 min and from 8 to 25 min 100:0; product **39** eluted between 10-13 min; sideproduct 16-22 min) to afford pure **39** as an orange oil (44 mg, 0.075 mmol, 17 % yield).
**(39)**: $^{1}H$ NMR (400 MHz, $CDCl_3$, 25°C): $\delta$ = 1.40 (d, *J* = 7.5 Hz, 3H), 1.42 (d, *J* = 7.5 Hz, 3H), 3.44 (q, *J* = 7.5 Hz, 2H), 3.84 (d, *J* = 5.5 Hz, 2H), 3.97-4.02 (m, 6H), 4.040 (s, 5H), 4.041 (s, 5H), 5.05

(s, 1H), 5.71 (s, 1H), 5.74 (s, 1H), 6.92 (dd, $J_1$ = 8.8 Hz, $J_2$ = 1.5 Hz, 2H), 7.05 (d, $J$ = 8.3 Hz, 2H); $^{13}$CNMR (100 MHz, $CDCl_3$, 25°C): $\delta$ = 22.0, 22.1, 30.7, 30.8, 66.4, 66.5 (2C), 66.6, 66.9, 67.0, 67.7, 67.8, 68.4 (10C), 94.7 (2C), 103.8, 103.9, 115.6, 130.4, 130.6, 130.7, 131.5, 138.7, 138.8, 155.1; $C_{34}H_{33}Fe_2NO$ Exact Mass: 583.1; M.W.: 583.3.

**(45)**. In a two necked balloon under nitrogen atmosphere equipped with a stirring bar, **38** (16 mg, 0.1 mmol) and **42** (91 mg, 0.2 mmol) were dissolved in 2 mL of DCM and cooled to 0 °C. Then $In(OTf)_3$ (606 µL of a 0.33 M sol. in $CH_3CN$, 0.2 mmol) was added and the solution stirred for 7 h at 0 °C, until almost complete conversion was observed by TLC. Then AcOEt (10 mL) and water (5 mL) were added and the water phase became orange. Aqueous NH4OH was added and the mixture stirred until the orange substances migrated to the organic layer that was separated. The aqueous one was extracted with AcOEt (2 x 8 mL). The collected organic layers were dried over $Na_2SO_4$, filtered and concentrated under reduced pressure to give an orange oil that was purified by column chromatography on silica (cyclohexane:AcOEt:DCM 88:8:4) to afford pure **45** (14 mg, 0.015 mmol, 15 % yield) as an orange oil.

$^1$H NMR (400 MHz, $CDCl_3$, 25°C): $\delta$ = 1.11 (d, $J$ = 7.5 Hz, 6H), 3.37-3.45 (m, 2H), 3.65 (s, 2H), 3.93 (s, 10H), 4.26 (t, $J$ = 1.9 Hz, 2H), 4.47 (s, 2H), 5.32 (s, 2H), 6.12 (d, $J$ = 8.4 Hz, 2H), 6.76 (d, $J$ = 8.4 Hz, 2H), 6.85 (t, $J$ = 7.1 Hz, 4H), 7.05 (t, $J$ = 8.4 Hz, 4H), 7.08-7.14 (m, 2H), 7.29-7.40 (m, 6H), 7.49 (t, $J$ = 7.1 Hz, 4H), the signal relative to O*H* was not observed; $^{13}$CNMR (100 MHz, $CDCl_3$, 25°C): $\delta$ = 23.9 (2C), 29.4 (2C), 68.4 (2C), 69.1 (2C), 69.4 (10C), 70.4 (2C), 70.3 (2C), 100.6, 100.9, 104.3 (2C), 115.3 (2C), 127.0 (2C), 127.6 (2C), 127.7 (2C), 127.8 (2C), 127.9 (2C), 129.0 (2C), 130.3, 130.4 (2C), 131.7 (2C), 131.9 (2C), 135.6 (2C), 135.8 (2C), 137.3 (2C), 137.6 (2C), 139.6 (2C), 155.4; $C_{58}H_{51}Fe_2NOP_2$ Exact Mass: 951,2; M.W.: 951,7.

**Synthesis of salophen ligand**

**Aldehyde 34.**

In a two necked round bottomed flask equipped with a magnetic stirring bar and a reflux condenser, Phenol X and hexamethylentetramine were dissolved in acetic acid (x mL). Then the solution was placed on a mantel preheated to 100?? °C and refluxed for 2 h during which the solution turned red. Then the solution was allowed to cool to 60-70°C and concentrated sulphuric acid (x mL) was added and the mixture heated at 100?? °C for further 3 h. Then it was allowed to cool to rt, XX was added and the organic layer was separated, the aqueous extracted with X (2 x ). The collected organic layers were washed with XXX, dried over Na2SO4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica () to afford pure aldehyde **34** ( ).

Spectroscopical data were according to the literature (klrj 2012 jacs).

**Synthesis of salophen 35.**

**36).** Aldehyde **34** (317 mg, 1.04 mmol), 1,2-diammino benzene (56 mg, 0.52 mmol) and ethanol (5 mL) were added in a Shlenk tube under nitrogen atmosphere. The mixture was heated to reflux under stirring for 6 hours. The reaction conversion was checked by $^1$H NMR and complete conversion was observed. The solution was allowed to cool to room temperature and a yellow solid precipitated. The solid was filtered, washed with cold ethanol and dried under reduced pressure affording pure salophen **35** (259 mg, 0.38 mmol, 73 % yield).

$^1$H NMR (400 MHz, $CDCl_3$, 25°C): $\delta$ = 0.89 (t, $J$ = 7.2 Hz, 6H), 1.21-1.31 (bs, 32H), 1.31-1.36 (bs, 4H), 1.53-1.66 (m, 4H), 2.28 (s, 6H), 2.54 (t, $J$ = 7.9 Hz, 4H), 7.03 (s, 2H), 7.08 (s, 2H), 7.21 (dd, $J_1$ = 5.2 Hz, $J_2$ = 3.4 Hz, 2H), 7.32 (dd, $J_1$ = 5.2 Hz, $J_2$ = 3.4 Hz, 2H), 8.60 (s, 2H), 13.00 (s, 2H); $^{13}$CNMR (100 MHz, $CDCl_3$, 25°C, all signals correspond to the double number of carbon atoms): $\delta$ = 14.1, 15.6, 22.7, 29.2, 29.4, 29.5, 29.60, 29.64, 29.67 (2C), 31.7, 31.9, 34.9, 118.1, 120.2, 126.1, 127.3, 129.3, 132.7, 134.8, 142.7, 157.7, 164.3; $C_{46}H_{68}N_2O_2$ Exact Mass: 680,5; M.W.: 681,1.

**Synthesis of salophen-aluminium-Me complexe 36.**

General note for the analysis of Al-salophen complexes: the NMR samples were prepared under inert atmosphere using $CDCl_3$ previously dried and neutralized over $MgSO_4$ and $NaHCO_3$.

**(36).** In a flame dried Shlenk tube under nitrogen atmosphere, salophen **35** (34 mg, 0.047 mmol) was dissolved in toluene (1.0 mL), previously degassed and by nitrogen bubbling for 10 minutes. The solution was cooled to 0 °C and $AlMe_3$ (24 µL of a 2 M sol. in toluene, 0.047 mmol) was added dropwise via siringe. Then the tube was sealed and the solution refluxed for 8 h. The reaction conversion was checked by $^1$H NMR and complete conversion was observed. The solvent was evaporated under reduced pressure to afford product **36** as a sticky solid in optimal purity and in quantitative yield. The product was either directly used for the following step either stored under inert atmosphere at -20 °C and used in a few days timespan.

$^1$H NMR (400 MHz, $CDCl_3$, 25°C): $\delta$ = -1.16 (s, 3H), 0.88 (t, $J$ = 7.1 Hz, 6H), 1.21-1.29 (bs, 32H), 1.29-1.38 (bs, 4H), 1.55-1.70 (m, 4H), 2.38 (s, 6H), 2.52 (t, $J$ = 7.8 Hz, 4H), 6.98 (d, $J$ = 1.8 Hz, 2H), 7.23 (d, $J$ = 1.8 Hz, 2H), 7.41 (dd, $J_1$ = 6.1 Hz, $J_2$ = 3.5 Hz, 2H), 7.66 (dd, $J_1$ = 6.1 Hz, $J_2$ = 3.5 Hz, 2H), 8.70 (s, 2H);
$^{13}$CNMR (100 MHz, $CDCl_3$, 25°C, all signals correspond to the double number of carbon atoms): $\delta$ = 14.1, 16.1, 22.7, 29.2, 29.4, 29.5, 29.60, 29.63, 29.66 (2C), 31.5, 31.9, 34.8, 116.0, 117.5, 128.1, 129.8, 130.3, 130.8, 138.0, 139.0, 162.2, 164.1, the signal relative to Al*Me* was not observed; $C_{47}H_{69}AlN_2O_2$ Exact Mass: 720,5; M. W.: 721,1.

**Synthesis of phenol-salophen-aluminium complexes.**

**(37).** In a flame dried Shlenk tube under nitrogen atmosphere, Al-Me-salophen **36** (45.4 mg, 0.063 mmol) was dissolved in toluene (1.0 mL). A solution of phenolic ligand **31** (17.5 mg, 0.019 mmol) in toluene (previously prepared under nitrogen atmosphere) was added and the solution was degassed by nitrogen bubbling for a 2-3 minutes. Then the tube was sealed and the solution refluxed

for 8 h. The reaction conversion was checked by $^1$H NMR and complete conversion was observed, even if unreacted phenolic ligand was present, probably due to an error in the weighting. The solvent was evaporated under reduced pressure to afford a sticky orange solid composed by **37** together with unreacted phenol **31** in 1.3:1 ratio (52.4 mg: 43 mg **37** + 9 mg **31**, 0.044 mmol, 70 % yield). The product was stored under inert atmosphere at -20 °C.
$^1$H NMR (400 MHz, $CDCl_3$, 25°C): $\delta$ = 0.89 (t, $J$ = 6.9 Hz, 6H), 1.21-1.31 (bs, 32H), 1.31-1.38 (bs, 4H), 1.54-1.66 (bs, 4H), 2.46 (s, 6H), 2.50-2.59 (bs, 4H), 3.94 (s, 5H), 4.16 (s, 2H), 4.44 (s, 2H), 6.38 (d, $J$ = 7.6 Hz, 2H), 6.70-6.78 (bs, 2H), 6.96-7.08 (m, 4H), 7.30-7.36 (m, 2H), 7.58-7.70 (bs, 2H), 8.75-8.93 (bs, 2H); Remaining ferrocenyl phenol **31**: 4.04 (s, 5H), 4.27 (s, 2H), 4.56 (s, 2H), 7.16-7.21 (m, 2H), 7.36-7.40 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$, 25°C): $\delta$ = 14.1 (2C), 16.1 (2C), 22.7 (2C), 29.2 (2C), 29.4 (2C), 29.5 (2C), 29.63 (2C), 29.64 (2C), 29.68 (4C), 31.4 (2C), 31.9 (2C), 34.9 (2C), 65.6 (2C), 67.9 (2C), 69.3 (5C), 115.3, 117.5 (2C), 119.5 (4C), 126.3 (4C), 127.3 (2C), 129.6 (2C), 130.8 (2C), 131.2 (2C), 138.5, 138.6 (2C), 158.8, 162.0 (2C), 164.1 (2C); Remaining ferrocenyl phenol **31**: 66.0 (2C), 68.4 (2C), 69.4 (5C), 115.7 (2C), 127.1 (2C), 128.3 (2C), 131.1, 154.1; $C_{62}H_{79}AlFeN_2O_2$ Exact Mass: 982,5; M. W.: 983.2.

**(41).** In a flame dried Shlenk tube under nitrogen atmosphere, Al-Me-salophen **36** (13.5 mg, 0.019 mmol) was dissolved in toluene (400 µL). A solution of phenolic ligand **39** (11.1 mg, 0.019 mmol) in 300 µL of toluene (previously prepared under nitrogen atmosphere) was added and the solution was degassed by nitrogen bubbling for a 2-3 minutes. Then the tube was sealed and the solution refluxed for 8 h. The reaction conversion was checked by $^1$H NMR and complete conversion was observed. The solvent was evaporated under reduced pressure to afford product **41** as a sticky solid in optimal purity (23.1 mg, 0.018 mmol, 94 % yield). The product was stored under inert atmosphere at -20 °C.

$^1$H NMR (400 MHz, $CDCl_3$, 25°C): $\delta$ = 0.89 (t, $J$ = 6.9 Hz, 6H), 1.21-1.36 (bs, 36H), 1.31 (d, $J$ = 6.8 Hz, 3H), 1.32 (d, $J$ = 7.3 Hz, 3H), 1.55-1.66 (bs, 4H), 2.46 (s, 6H), 2.59 (t, $J$ = 7.3 Hz, 4H), 3.32-3.41 (m, 2H), 3.77 (s, 1H), 3.78 (s, 1H), 3.90-3.99 (m, 5H), 3.97 (s, 5H), 3.98 (s, 5H), 4.04 (s, 1H), 5.91 (s, 1H), 5.64 (s, 1H), 6.41-6.48 (m, 2H), 6.63-6.71 (m, 2H), 7.04 (s, 2H), 7.31 (s, 2H), 7.37-7.47 (bs, 2H), 7.59-7.60 (bs, 2H), 8.84 (s, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$, 25°C): $\delta$ = 14.1 (2C), 16.1 (2C), 21.9, 22.0, 22.7 (2C), 29.2 (2C), 29.3 (2C), 29.5 (2C), 29.61 (2C), 29.64 (2C), 29.67 (4C), 30.51, 30.52, 31.4 (2C), 31.9 (2C), 34.9 (2C), 66.33, 66.34, 66.46, 66.48, 66.71, 66.73, 67.81, 67.83, 68.28 (10C), 94.90, 94.97, 103.06, 103.09, 115.7, 117.5, 119.6, 119.7, 119.8, 128.0, 128.24, 128.27, 128.29, 129.0, 129.2, 129.4, 129.93, 129.97, 130.0, 130.8 (2C), 131.33, 131.36, 138.4, 138.5, 138.6, 138.7, 160.0, 161.9, 162.0, 162.1, 164.0; $C_{80}H_{98}AlFe_2N_3O_3$ Exact Mass: 1287,6; M. W.: 1288,4.

**(46).** In a flame dried Shlenk tube under nitrogen atmosphere, Al-Me-salophen **36** (11 mg, 0.015 mmol) was dissolved in toluene (400 µL). A solution of phenolic ligand **45** (14 mg, 0.015 mmol) in 300 µL of toluene (previously prepared under nitrogen atmosphere) was added and the solution was degassed by nitrogen bubbling for a 2-3 minutes. Then the tube was sealed and the solution refluxed for 8 h. The reaction conversion was checked by $^1$H NMR and complete conversion was observed.

The solvent was evaporated under reduced pressure to afford product **41** as a sticky solid in optimal purity (23 mg, 0.014 mmol, 91 % yield). The product was stored under inert atmosphere at -20 °C. $^{1}$H NMR (400 MHz, $CDCl_3$, 25°C): $\delta$ = 0.89 (t, $J$ = 6.8 Hz, 6H), 1.00 (d, $J$ = 6.3 Hz, 6H), 1.21-1.51 (bs, 36H), 1.56-1.67 (bs, 4H), 2.45 (s, 3H), 2.50 (s, 3H), 2.56 (t, $J$ = 7.8 Hz, 4H), 3.27-3.35 (m, 2H), 3.58 (s, 2H), 3.91 (s, 10H), 4.20 (s, 2H), 4.28 (s, 2H), 5.20 (s, 2H), 5.67 (d, $J$ = 8.1 Hz, 2H), 6.22 (d, $J$ = 8.1 Hz, 2H), 6.70 (t, $J$ = 7.4 Hz, 4H), 6.93 (t, $J$ = 7.4 Hz, 4H), 6.96-7.03 (m, 2H), 7.04 (s, 2H), 7.08 (s, 2H), 7.14-7.21 (m, 2H), 7.29-7.30 (m, 6H), 7.43-7.52 (m, 4H), 7.76 (dd, $J_1$ = 13.1 Hz, $J_2$ = 7.4 Hz, 2H), 8.89 (s, 1H), 8.95 (s, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$, 25°C): $\delta$ = 14.1 (2C), 16.1, 16.2, 22.7 (2C), 23.9 (2C), 29.2, 29.31, 29.35 (2C), 29.40, 29.47, 29.54, 29.63 (2C), 29.64 (2C), 29.68 (4C), 29.8, 31.4, 31.5, 31.9, 32.0, 34.8, 34.9, 68.2 (2C), 68.9, 69.0, 69.3 (10C), 70.3, 70.4, 73.7, 73.8, 100.9, 101.2, 103.5 (2C), 115.8, 117.5, 117.6, 118.9 (2C), 125.3, 126.7 (2C), 127.4 (2C), 127.5 (2C), 127.8 (2C), 127.9 (2C), 128.2 (2C), 128.8, 129.0 (2C), 129.2, 129.3, 129.9, 130.2, 130.9, 131.0, 131.2, 131.3, 131.8 (2C), 132.0 (2C), 135.6 (2C), 135.8 (2C), 137.2 (2C), 138.4, 138.52, 138.55, 138.6, 138.7, 138.8, 139.8, 139.9, 159.6, 161.8, 162.5, 163.9, 164.2; $C_{104}H_{116}AlFe_2N_3O_3P_2$ Exact Mass: 1287,6; M. W.: 1288,4.

## 3.4 Ferrocene decorated porphyrins[45]

### 3.4.1 Introduction

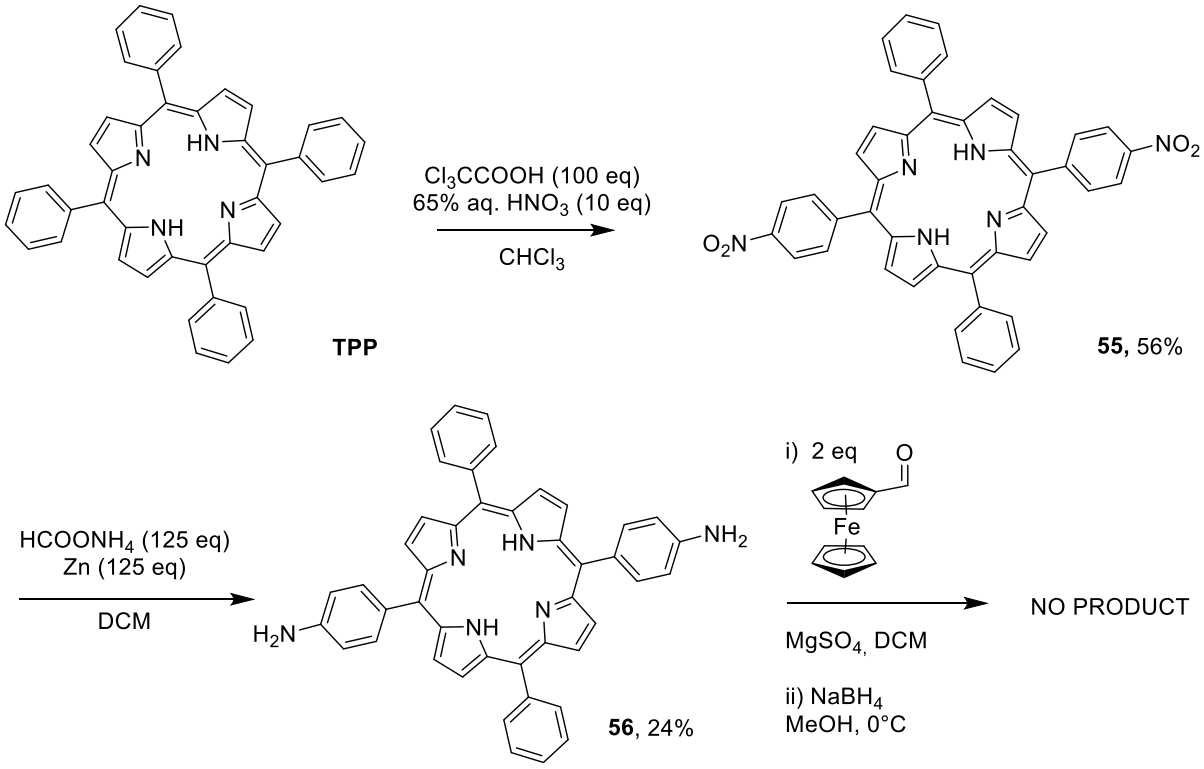
Porphyrins are of interest for their unique opto-electronic properties rendering them key components for numerous applications including solar cells[46] and photo-catalysis.[47] Furthermore, once adsorbed on solid substrate, porphyrins may adopt two possible packing motifs, namely *face-on*[48] and *edge-on.*[49] While in the former the molecules lie flat on the surface, in the former the planes of the porphyrin molecules are oriented vertically to the substrate. Various 1D and 2D porphyrin-based supramolecular structures have been reported, and includes architectures self-assembled *via* hydrogen-bonding,[50] Van der Waals interactions,[51] coordination[52] and covalent bonds.[53] Moreover, owing to the peculiar electronic structure, and functionalization possibilities at both *meso* and β-pyrrolic positions, the porphyrin backbone can be used for molecular scaffolding, i.e. to locate the functional groups in pre-programmed positions.[54] Porphyrins can easy encapsulate a metal center useful both to modulate the electronic properties and to link them to a surface.

Because of their C4 symmetry and properties porphyrins were selected as suitable scaffolds for QCA candidates. The functionalization of the four apical positions was chosen as a privileged strategy because it allowed to install four ferrocene moieties in spatially defined and equivalent positions.

Recently a tetraferrocenyl porphyrin in which the ferrocenes are conjugated to the porphyrin core has been reported.[55] This substrate was successfully immobilized onto a gold surface trough a thiol linker located on one of the ferrocenes. However it did not exhibit self assembly properties and the four ferrocenes were conjugated thanks to the direct bond with the aromatic porphyrin as evidenced by the presence of four separated oxidation peaks in a range of 0.5 V. Such substrate does not appear to be suitable for QCA application as the charge would not be confined on the ferrocenes so that the bi-stale 0 and 1 states would not be defined. For this reason a tetraferrocenyl porphyrin in which the ferrocene moieties are not conjugated with the ferrocene core is predicted to have better properties and was selected as our synthetic target. The ferrocene units should be “close” to the conjugated porphyrin system so that tunneling between the different ferrocenes would be possible allowing for the switching between the 0 and 1 states. One or two $sp^3$ bonds is the quantification of “close” based on calculations and on the previous experience with diferrocenecarbazoles.[19]

### 3.4.2 Synthesis and surface studies of ferrocene decorated porphyrins

Tetraphenyl porphyrin (TPP) was selected as the first candidate due to its low cost. In order to introduce the ferrocenes it is necessary to functionalize the phenyl ring present in the apical position. By treatment of TPP with nitric acid and trichloroacetic in chloroform I achieved the selective double nitration on the para position of the opposite apical phenyl rings. The nitro groups were reduced to the corresponding amine functionalities to afford **56**. Unfortunately the reduction of **55** to **56** was quite sluggish and the product was isolated in 24% yield along with some unidentified impurities (scheme 14). The formation of the imine by condensation of **56** with ferrocene acetaldehyde and its in situ reduction to the bis ferrocene amine porphyrin was unsuccessfully attempted. This strategy, through which we aimed to obtain a double ferrocene porphyrin conjugate, was abandoned due to these problems and we focused on the use of already functionalized tetracarboxylic phenyl porphyrin (TCPP).

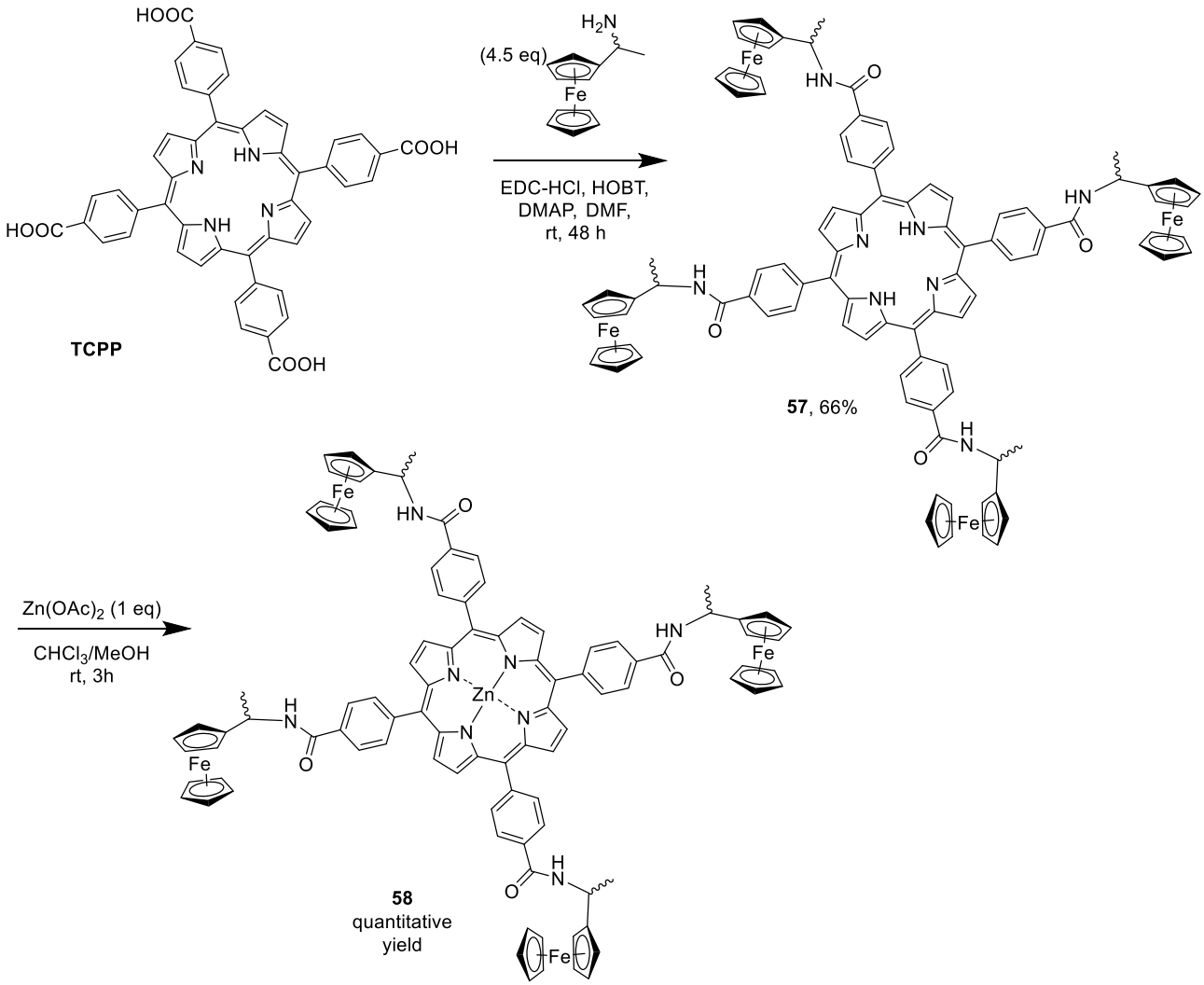



*Schema 14: attempted synthesis of bis ferrocene porphyrins starting from TPP.*

The advantage to use TCPP is that it already bears four functional groups through which the ferrocene moieties can be easily installed. We choose to perform an amide coupling reaction with ferrocene functionalized alkyl amines because of the robustness and efficiency of this reaction.
Ethanol ferrocene amine **12** (6 eq) was coupled with TCPP to study the model reaction that worked well affording the desired product **57** bearing four ferrocenes. Chromatographic purification allowed to isolate the desired product in 66% yield, that was efficiently separated from by-products

and small amounts of side-products deriving from reaction intermediates or still having some free carboxylic moieties.

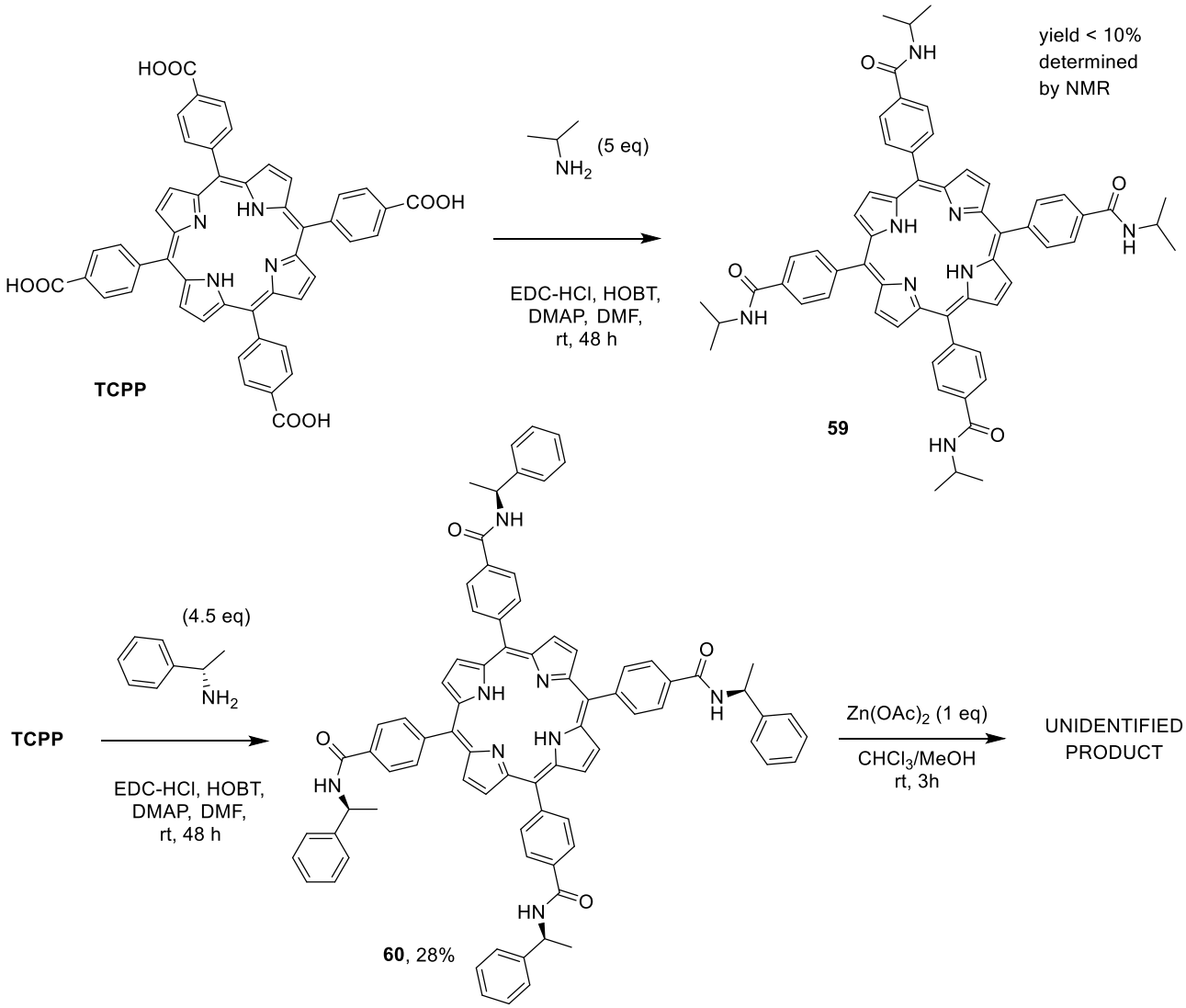
The corresponding Zinc porphyrin can be obtained by simple reaction of **57** with Zinc diacetate followed by aqueous work up to obtain the desired product **58** in quantitative yield (scheme 15).




*Scheme 15: synthesis of tetraferrocenyl porphyrin **57** and of the corresponding Zinc complex **58**.*

This product was sent to the reaction partners: it did not show any self assembly at the solid liquid interface on HOPG as expected due to the lack of long alkyl chains, while Bolan research observed several patterns of self assembly on copper, gold or copper etched with NaCl for the Zinc porphyrin **58**. This porphyrin appeared to form a grid controlled by hydrogen bonding between the amide moieties. This result is particularly important because thanks to the molecular tips of their STM instrumentation, Bolan and his coworkers can position and try to move charges on the single ferrocene moieties attempting the first proof of concepts for the molecular computation.

Moreover the NaCl etching acts as an insulator avoiding the discharge on the solid support that could not be avoided in case a similar experiment was performed by the Samorì group in Strasbourg that uses conductive HOPG as solid support.
In order to assign unambiguously the bright high electron density spots observed by STM with the ferrocenes (the zinc metal center could give similar responses), they investigated also the surface properties of the tetraferrocene porphyrin **57** that did not contain the zinc atom. In addition I tried to synthetize a tetraamide zinc porphyrin without the ferrocenes (scheme 16).



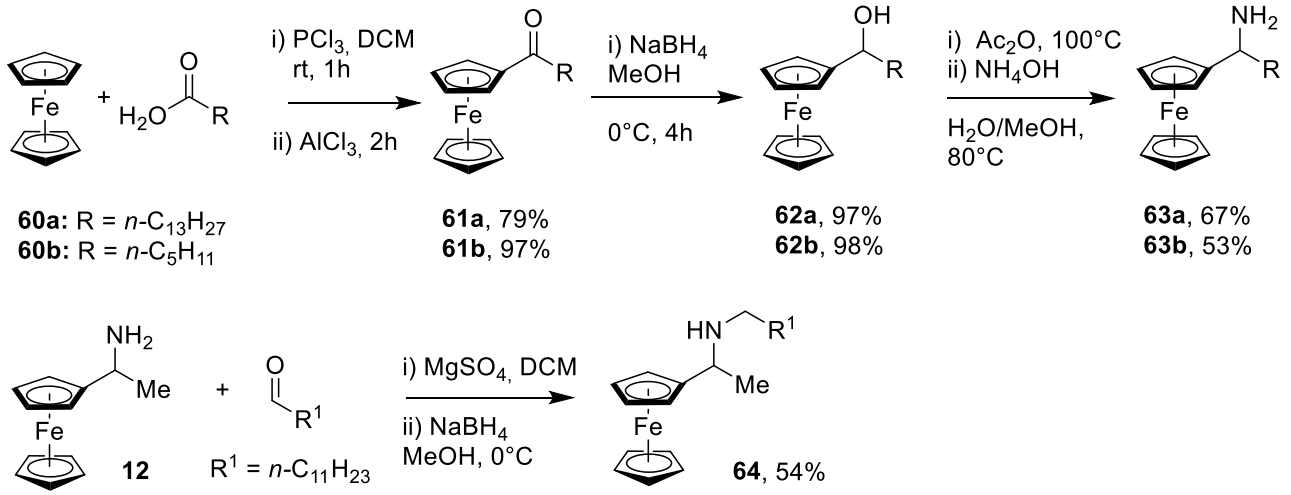

*Scheme 16: attempted synthesis of tetraamide porphyrine without the ferrocene moiety.*

Surprisingly the direct coupling with isopropyl amide afforded product **59** in traces amounts. The use of less volatile 1-phenyl ethyl amine afforded the desired product **60** instead. Unfortunately when I performed the reaction with zinc diacetate I could not observe any conversion by TLC even when an excess of zinc (II) salt was added. The $^{1}$H NMR analysis of the reaction mixture revealed a wide broadening of the peaks. Morever the unidentified product was much less soluble than starting porphyrin **60**. The analysis by mass spectroscopy did not reveal the presence of the product. We

hypothesized that in the absence of the bulky ferrocecene the zync (II) was cohordinated by the more accessible amides leading to the formation of supramolecular aggregates. This competing process hampered the formation of the desired product that had the zinc encaged inside the pophyrin core.

In the meantime we prepared two long alkyl chain ferrocene amines, one primary and one secondary, to obtain suitable molecules to study their surface properties at the solid liquid interface.

Primary amines **63a,b** were obtained from ferrocene and alkylic carboxylic acids **60a,b**. The acids were activated as the corresponding acyl chlorides and subsequent Friedel Craft reaction with ferrocene afforded ketones **61a,b** in good to excellent yields. This substrates were reduced to the corresponding alcohols **61a,b** and the hydroxyl moieties were transformed into the primary amine functionalities after a one pot acetylation and ammonia substitution reaction sequence that occurred in good yields. Chromatographic purification was necessary only for the final compounds **63a,b** (scheme 17).




*Scheme 17: synthesis of long alkyl chain primary and secondary amines.*

Secondary amine was instead obtained by a straightforward procedure involving the condensation between laurylaldehyde and ferrocene amine **12** to give the corresponding imine that was reduced to afford the final product **64** in good yield.

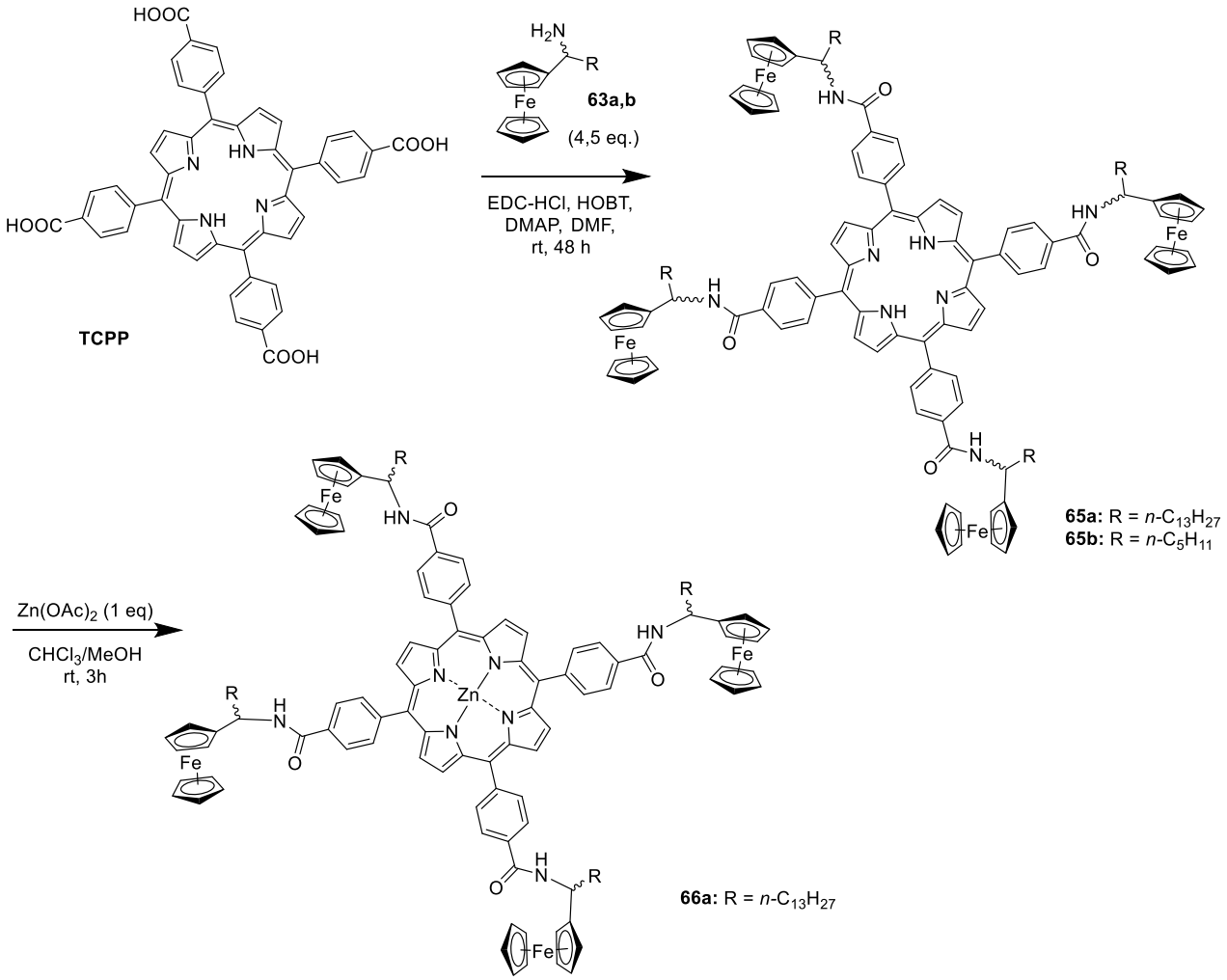
The amide coupling between amines **63a,b** and **64** (4.5 eq) and TCPP was performed and the tetraferrocenyl porphyrins **65a,b** and **67** were obtained in good yields after chromatographic purification (schemes 18 and 19).

In case of **65a** and **67**, I prepared also the corresponding zinc complexes **66** and **68** by the same procedure described before.

The study of the properties of **65a** and **67** on HOPG at the solid liquid interface were done by Mohamed El Garah and Artur Cieselsky (Prof. Samorì research group).

Porphyrin **65a**, that bears a primary amide with a C13 alkyl chain able, forms an ordered grid flattened on the HOPG surface assuming a *face-on* structuration mode. This self assembled structure is dictated by the formation of an hydrogen bond network between the primary amides functionalities. The long alkyl chain may be either flattened over the HOPG inside the holes left

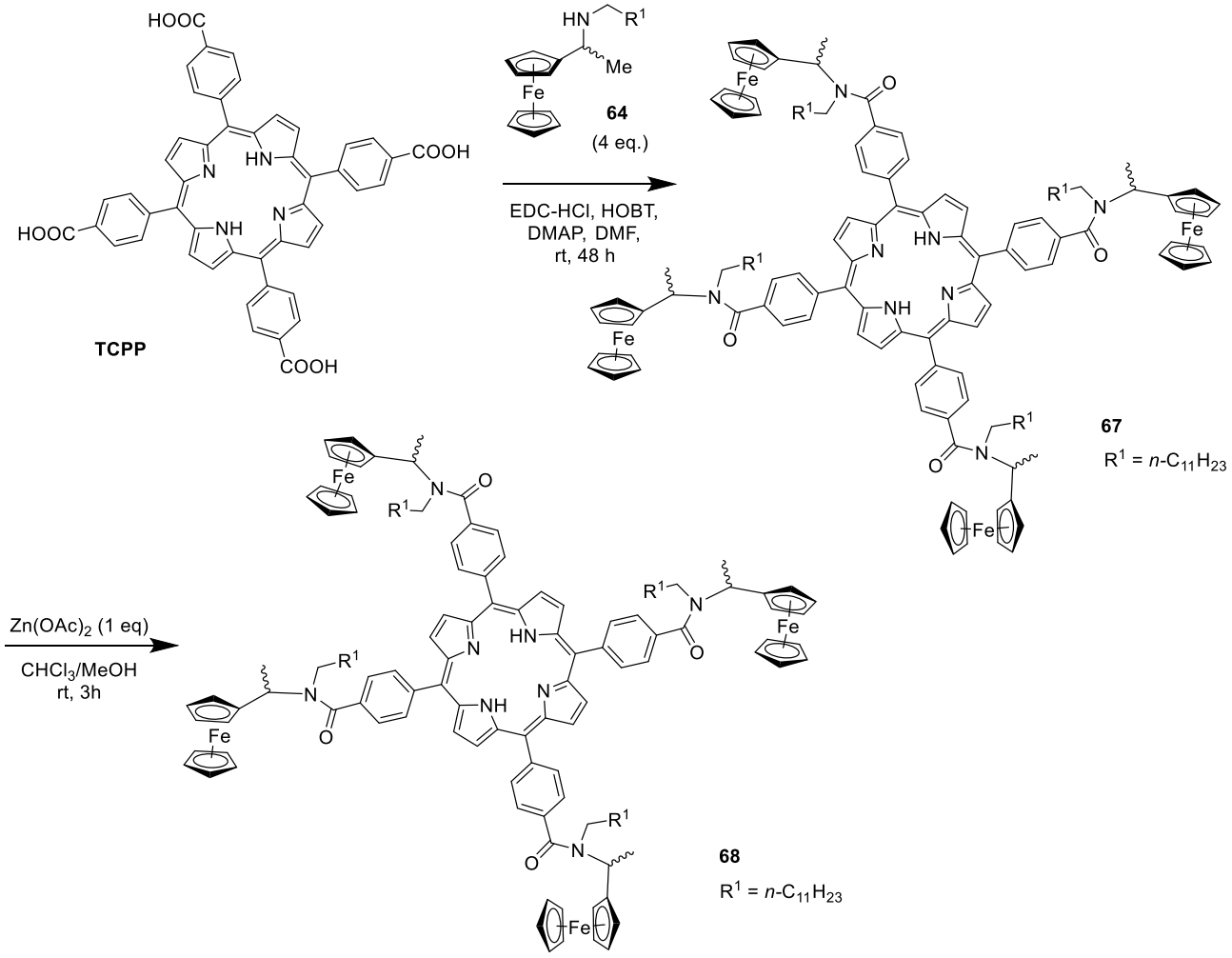
between the neighboring porphyrins in the grid with the ferrocenes pointing out of the surface. Alternatively the opposite situation in which the ferrocenes are physisorbed on HOPG and the alkyl chains are bended over these structures to reach the surface is possible too. DFT calculations to predict the more favorable conformation were performed by Cuniperti research group in Dresden and by Prof. Zerbetto research group (Unibo) and the results indicates that the more stable conformation is the one with the ferrocenes physisorbed on the HOPG substrate, which is in agreement with the electrochemical results (see below chapter 3.4.3).




*Scheme 18: synthesis of primary tetraferrocenyl porphyrins **65a** and **65b** bearing a primary amide and the zinc complex **66a***

On the other hand, secondary amide ferrocene porphyrin **67** shows a totally different self assembled structure. As hydrogen bonds are no more possible, the π-stacking between the porphyrin rings becomes the major force determining the formation of lines of stacked porphyrins perpendicular to the HOPG surface, *edge-off* structuration mode. This disposition allows the physisorbtion of two long alkyl chains for each molecule on the surface controlling the formation of parallel lines of stacked molecules.

It is worth mentioning that when a solution containing both **65a** and **67** was deposited over the surface, STM analysis revealed that the previously observed self assembled structures typical of each of the two molecules, were still formed for the mixed solution of **65a** and **67**. This experiment demonstrated that each of the two moloecules is able to interact selectively with itself.
To investigate more in detail the influence of the long alkyl chains on the formation of the self assembled monolayer and their position on HOPG, we shipped to Strasbourg also the primary amide ferrocene porphyrin **65b** that has a C5 alkyl chain instead of the C13 of **65a**.




*Scheme 19: synthesis of tetraferrocenyl porphyrin **68** bearing a secondary amide and its zinc complex **69**.*

In figure 8 are illustrated the STM images obtained for **65a** and **67** together with the molecular modelling to rationalize the results.
In figure 9 is illustrated the model for the single molecule **67** on the HOPG substrate in *edge-off* conformation.

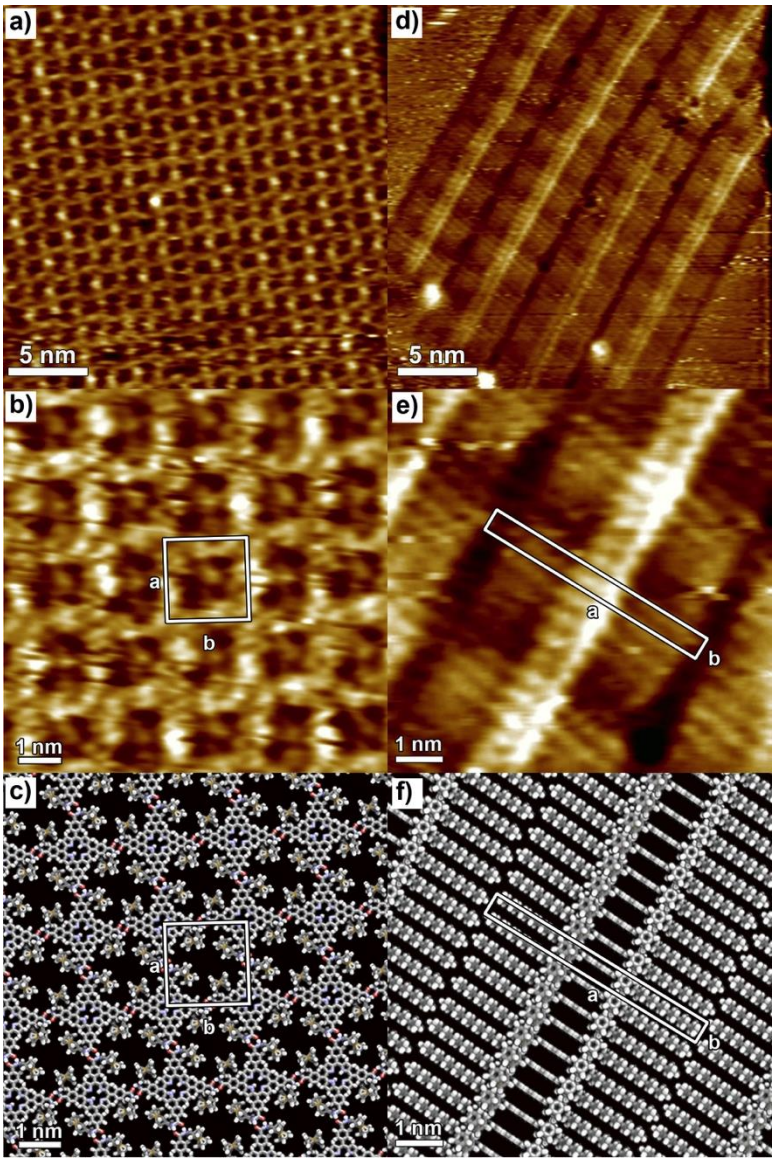



*Figure 8. Height STM images of **65a** (a,b) and **67** (d,e) monolayers at the HOPG/air interface. Scanning parameters (a,b and d,e): Average tunnelling current ($I_t$) = 25-30 pA, tip bias voltage ($V_t$) = 450-500 mV. The self-assembly packing motifs models of **65a** and **67** are shown in (c) and (f), respectively. Dodecyl side chains in (c) are omitted for clarity*

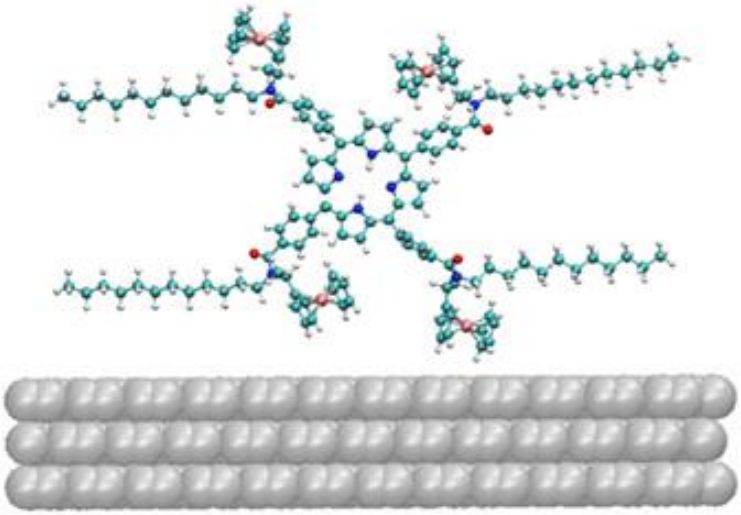


*Figure 9: molecular model of edge off porphyrin **67** based on theoretical calculations.*

### 3.4.3 Electrochemical characterization of 65a and 67 in solution and on HOPG

The electrochemical characterization of the porphyrins was performed by Matteo Iurlo and Andrea Fiorani (Prof. Paolucci research group) both on solution and on the physisorbed monolayers on HOPG substrate of both *face-on* **65a** assemblies and *edge-off* **67**.
Voltammetric studies on HOPG were conducted in a standard three electrodes cell, where HOPG functionalized with **65a** and **67** monolayers served as working electrode. In order to avoid desorption of porphyrins from HOPG surface during the experiments, cyclic voltammetric studies were performed in 0.1 M potassium chloride aqueous solutions as supporting electrolyte. All potentials are referred to Ag/AgCl(sat). Porphyrins **65a** and **67** show five redox couple in dichloromethane (DCM) solutions under ultra-dry conditions (see ESI), involving either the ferrocenyl groups or the porphyrin moiety.[57] However, within the water potential window, the only detectable redox processes were those associated to the one-electron oxidation of each ferrocenyl.
The electrochemistry on solution revealed a predictable behavior with one oxidation peak relative to all four ferrocenes for both **67** ( $E_{1/2}$=0,46 V) and **65a** ($E_{1/2}$=0,53 V). The two oxidations observed at potentials superior to 1 V and the two reductions are instead localized on the TCPP core (table 4).

| | **65a** | | **67** | |
|---|---|---|---|---|
| | Solution | HOPG | Solution | HOPG |
| $I_{Red}$ | -1,18 | | -1,22 | |
| $II_{Red}$ | -1,51 | | -1,52 | |
| $I_{Ox}$ Fc | 0,46 | 0.26 | 0,53 | 1° peak 0,37<br>2° peak 0,56 |
| $II_{Ox}$ | 1,06 | | 1,09 | |
| $III_{Ox}$ | 1,41 | | 1,33 | |
| Electrochemistry in ultradry conditions[56] using DCM and TBAH as supporting electrolyte The working electrode was platinum disk ultramicroelectrodes (Ø =125 µm) sealed in glass. The counter electrode was a platinum spiral, and the quasi-reference electrode was a silver spiral. Potentials were measured with decamethylferrocene standard and were to Ag/AgCl(sat). $I_{Red}$, $II_{Red}$ $II_{Ox}$, $III_{Ox}$ are monoelectronic redox process associated to the porphyrin rings,[57] while $I_{Ox}$ is the redox process of the four ferrocenes. | | | | |

*Table 4: electrochemical characterization of porphyrins **65a** and **67** in solution and as self-assembled monolayers on HOPG.*

We have then performed electrochemical analyses on both types of self-assembled architectures, i.e. columnar structures physisorbed on an HOPG substrate.
Porphyrin **65a** in Figure 10a shows a single oxidation peak at 0.26 V, corresponding to the superimposition of four reversible one-electron ferrocene oxidations. The presence of the single peak is indicative of the electronic equivalence of the four ferrocene units, that is not trivial since adsorption on HOPG could have introduced some electronic anisotropy.[19,24] Interestingly, the first forward scan of each voltammetric curve (obtained at various scan rates, in the range from 10 to

100 mV/s) shows two overlapping waves that would imply some electronic difference between ferrocenes. No separation is instead observed in the reverse peak and in the subsequent forward and reverse scans, even after leaving the electrode to re-equilibrate for some time at open circuit conditions. The behavior is particularly evident in the curve at 20 mV/s, where two separate peaks appear, while at 50-100 mV/s the overlap is greater. By contrast, the curve at 10 mV/s only shows one unresolved peak, already during the first forward scan. The observed, highly reproducible CV behavior is strongly indicative of molecular dynamics in the adsorbed film, triggered by the electrochemical stimulus, and taking place over the timescale investigated in the present experiments. Such a dynamics would imply that the initial (metastable) monolayer structure, containing non-equivalent ferrocenyl units, rearrange, following the injection of positive charges in the ferrocenyl units, in a novel structure where all ferrocenyls are equivalent. Such a structure would be energetically favored since the initial CV behavior cannot be recovered upon removal of the extra charges during the reverse scan.

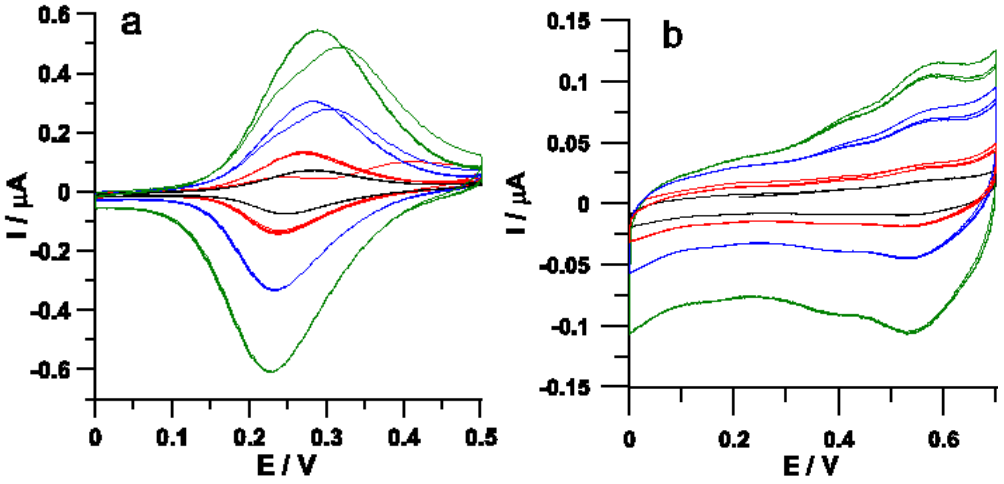



*Figure 10. Cyclic voltammograms of **65a** (a) and **67** (b) adsorbed on HOPG, scan rates: 10 mV/s (black), 20mV/s (red), 50 mV/s (blue) and 100 mV/s (green), T=25°C.*

A very different CV behavior was found for porphyrin **67**, characterized by a stable CV pattern comprising two oxidations, located at 0.37 and 0.56 V respectively and each associated to the removal of two electrons (Figure 10b). This behavior is highly reproducible in the subsequent scans and would suggest the breaking of the electronic symmetry between the four chemically-equivalent ferrocenes. This is in line with the *edge-off* organization of the **P2** within the self-assembled monolayer as described in the previous section, according to which the two ferrocenes that are closer to the HOPG surface experience a different electronic environment with respect to those facing the solution. It is worth noticing that the adsorption of porphyrins on the HOPG surface affects the potentials of ferrocene, both in **65a** and **67** assemblies. Compared to porphyrins in solution (+0.46 V for **65a** and +0.53 V for **67**), and also taking into account the variation of solvent, significantly lower oxidation potentials for the adsorbed porphyrins were found for **65a** and the first set of **67** oxidations, while it was higher in the case of second set of **67**. A possible stabilization of the ferrocenium moieties by the graphitic surface would explain the anticipation of oxidation peaks

while the higher potential of the second oxidation of **67** can be ascribed to electrostatic repulsions between neighboring ferrocenes.

### 3.4.4 Conclusions and overlook on the MOLARNET project

During two years of research on the Molarnet project I have synthetized three different classes of ferrocene conjugates. Guanine precursors and guanosine were efficiently alkylated with ferrocene carbenium ions and the first $S_N1$ reaction of such substrates with carbenium ions was reported together with a detailed electrochemical investigation of their behavior. Even if these molecules proved not to be suitable as QCA candidates, this methodology can represents a starting point for the bioconjugation of ferrocene with nucleobases under mild conditions.
Aluminium salophen scaffolds were studied and the synthesis of new apical phenolic aluminium salpohen complexes bearing long alkyl chains was reported. These complexes form well ordered self assembled monolayers on HOPG and this is the first study on the self assembly of aluminium salophens. The phenolic ligands can bear one or two ferrocenes on the para position without affecting neither the complex formation neither the surface properties. This strategy allows more in general the introduction of the desired functionality in a predictable and ordered manner on a HOPG surface.
The synthesis of ferrocene decorated porphyrins was efficiently achieved introducing four ferrocenes on the apical positions of TCPP by simple and efficient chemistry. The presence or absence of hydrogen bond donors and acceptors allows to control the self assembled patters on HOPG. The presence of self assembled grids of porphyrins controlled by hydrogen bond networks has been achieved also on non conductive solid substrates opening the route for the first proof of concepts to QCA based systems.
The future issues to be addressed will be the degree of conjugation requested between the ferrocene and the porphyrin core to allow the tunneling of the charges to have two bi-stable states maintaining the charge confinement. Another crucial point to be addressed will concern the oxidation potentials of the four ferrocenes: should they be the same or different, and what would be the suitable difference in voltage, in order to selectively oxidaze only two out of four?

### 3.4.5 Contributions

I and Andrea Gualandi designed and synthetized the porphyrins under the supervision of Pier Giorgio Cozzi. Bolan research group performed the surface studies on gold, copper and NaCl etched copper. Mohamed El Garah, Dr. Artur Ciesielski and Prof. Paolo Samorì performed the surface studies on HOPG. Dr. Andrea Fiorani, Dr. Matteo Iurlo, Prof. Massimo Marcaccio and Prof. Francesco Paolucci performed the electrochemical characterization. Alejandro Santana Bonilla Dr. rer. nat. Rafael Gutierrez, Dr. Stefania Rapino, Dr. Matteo Calvaresi, Prof. Francesco Zerbetto and Prof. Gianaurelio Cuniberti performed the DFT calculations.

## 3.4.6 Experimental part

*1.1 General methods.*

$^{1}$H NMR spectra were recorded on Varian Gemini 200, Varian Mercury 400 and Inova 600 spectrometers. Chemical shifts are reported in ppm from TMS with the solvent resonance as the internal standard (deuterochloroform: $\delta$ = 7.27 ppm, $d_6$-DMSO: $\delta$ = 2.50 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = duplet, t = triplet, q = quartet, dd = double duplet, dt = double triplet, bs = broad signal, pd = pseudo duplet, pt = pseudo triplet, m = multiplet), coupling constants (Hz). $^{13}$C NMR spectra were recorded on Varian Gemini 200, Varian MR400 spectrometers and Inova 600 spectrometers. Chemical shifts are reported in ppm from TMS with the solvent as the internal standard (deuterochloroform: $\delta$= 77.0 ppm, $d_6$-DMSO: $\delta$ = 39.51 ppm). If rotamers are present, the splitted signals are labeled as A (major rotamer) and B (minor rotamer). GC-MS spectra were taken by EI ionization at 70 eV on a Hewlett-Packard 5971 with GC injection. LC-electrospray ionization mass spectra (ESI-MS) were obtained with Agilent Technologies MSD1100 single-quadrupole mass spectrometer. They are reported as: *m/z* (rel. intense). Electrospray Ion Trap Mass Spectrometry were obtain ed with Agilent Technologies LC/MSD 1100 ion trap mass spectrometer injecting a solution in chloroform/methanol of the pure compound. Chromatographic purification was done with 240-400 mesh silica gel. Purification on preparative thin layer chromatography was done on Merck TLC silica gel 60 $F_{254}$.

*1.2 Materials*

If not otherwise stated, all reactions were carried under anhydrous conditions using standard Schlenk apparatus. Anhydrous solvents were supplied by Aldrich in Sureseal® bottles and were used as received avoiding further purification.
Reagents were purchased from Aldrich and used without further purification unless otherwise stated.

*1.3 Syhthesis of **65a***

**1-ferrocenyl-tetradecan-1-one 61a**.[58] In a 250 mL balloon under nitrogen atmosphere, myristic acid (548 mg, 2.4 mmol and ferrocene (372 mg, 2.0 mmol) were dissolved in dichloromethane (40 mL). Phosphorous trichloride (200 µL, 2.28 mmol) was added at room temperature. After one hour of stirring aluminium trichloride (399 mg, 3.0 mmol) was added to the reaction mixture that was stirred for 2 hours. Then it was cooled to 0°C and 60 mL of aqueous NaOH 1M were slowly added until pH = 14. The solution turned from violet to orange. After 10 min. of stirring the organic phase was separated and the aqueous one was extracted with diethyl ether (2 x 20 mL). The collected organic phases were filtrated on a

celite pad, dried over sodium sulphate and evaporated under reduced pressure to afford pure 1-ferrocenyl-tetradecan-1-one **61a** as an orange oil (79% yield, 628 mg, 1.58 mmol).

$^1$H NMR (400 MHz, $CDCl_3$, 25°C): $\delta$ = 0.89 (t, $J$ = 7.7 Hz, 3H), 1.20-1.41 (bs, 20H), 1.71 (p, $J$ = 7.4 Hz, 2H), 2.70 (t, $J$ = 7.6 Hz, 2H), 4.20 (s, 5H), 4.50 (t, $J$ = 1.9 Hz, 2H), 4.79 (t, $J$ = 1.9 Hz, 2H); $^{13}$CNMR (100 MHz, $CDCl_3$, 25°C): $\delta$ = 14.1, 22.6, 24.6, 29.3, 29.4 (2C), 29.5, 29.6 (2C), 29.7 (2C), 31.9, 39.7, 69.3 (2C), 69.7 (5C), 72.0 (2C), 79.1, 204.6.

**1-ferrocenyl-1-tetradecanol 62a**. In a 50 mL balloon, 1-ferrocenyl-tetradecan-1-one **61a** (198 mg, 0.5 mmol) was dissolved in methanol (10 mL) and cooled to 0°C. Then $NaBH_4$ (76 mg, 2 mmol) was added. After 4 hours complete conversion was achieved (monitored by TLC) and the reaction was quenched by addition of water and ice. Then methanol was evaporated under reduced pressure and the aqueos phase was extracted with diethyl ether (3 x 10 mL). The collected organic phases were dried over sodium sulphate and evaporated under reduced pressure to afford pure 1-ferrocenyl-1-tetradecanol **62a** as an orange oil (94% yield, 187 mg, 0.47 mmol).
$^1$H NMR (400 MHz, $CDCl_3$, 25°C): $\delta$ = 0.89 (t, $J$ = 7.1 Hz, 3H), 1.16-1.34 (bs, 21H), 1.34-1.47 (bs, 1H), 1.54-1.74 (m, 2H), 1.95 (d, $J$ = 2.5 Hz, 1H), 4.14-4.19 (m, 3H), 4.21 (s, 5H), 4.23-4.76 (bs, 1H), 4.28-4.34 (m, 1H);
$^{13}$CNMR (100 MHz, $CDCl_3$, 25°C): $\delta$ = 14.1, 22.7, 26.0, 29.3, 29.58, 29.60 (2C), 29.64 (3C), 29.70, 31.9, 38.2, 65.1, 67.3, 67.7, 69.9, 68.2 (5C), 69.6, 94.7.

**1-ferrocenyl-1-tetradecyl amine 63a**. In a 50 mL Shlenk tube under nitrogen atmosphere, 1-ferrocenyl-1-tetradecanol **62a** (374 mg, 0.94 mmol), acetic anhydride (1.8 mL, 18.8 mmol), 4-dimethylaminopyridine (11 mg, 0.94 mmol) and pyridine (3.0 mL) were added in the before mentioned order. The mixture was stirred for 24 hours at rt, until complete conversion to 1-ferrocenyl-1-tetradecyl acetate was observed by TLC. Pyridine and excess of acetic anhydride were evaporated under reduced pressure and the residue was dissolved in isopropanol (8 mL). Ammonium hydroxide (30% V/V in water, 2.0 mL, 25 mmol) was added and the mixture was heated at 40°C for 16 hours until complete conversion was observed by TLC. The residue was evaporated under reduced pressure and directly purified by column chromatography (gradient elution from 95:5 to 0:100 cyclohexane:ethyl acetate) to afford pure 1-ferrocenyl-1-tetradecyl amine **63a** (67 % yield, 250 mg, 0.63 mmol) as an orange oil.
$^1$H NMR (400 MHz, $CDCl_3$, 25°C): $\delta$ = 0.89 (t, $J$ = 6.9 Hz, 3H), 1.21-1.35 (bs, 21H), 1.35-1.44 (m, 1H), 1.45-1.66 (m, 2H), 1.70-1.99 (bs, 2H), 3.62 (t, $J$ = 6.5 Hz, 1H), 4.10-4.14 (m, 3H), 4.17 (s, 5H), 4.19-4.22 (bs, 1H); $^{13}$CNMR (100 MHz, $CDCl_3$, 25°C): $\delta$ = 14.0, 22.5, 26.4, 29.2, 29.41, 29.42, 29.44, 29.46 (2C), 29.48 (2C), 31.7, 39.2, 50.4, 64.8, 66.6, 66.9, 69.0, 68.0 (5C), 95.6.

**65a.** In a 10 mL round bottomed flask under nitrogen atmosphere, TCPP (79, 0.1 mmol) was dissolved in DMF (3.5 mL). N-(3-Dimethylaminopropyl)-N′-ethylcarbodiimide (EDC) hydrochloride (114 mg, 0.6 mmol) and HOBT (81mg, 0.6 mmol) were added. The solution was shielded by light and stirred for 1h. Then 1-ferrocenyl-1-tetradecyl amine **63a** (175 mg, 0.44 mmol) and DMAP (54mg, 0.44 mmol) were added. After 48 hours the reaction was diluted with DCM (20 mL) and washed 5 times with water (10 mL). The organic phase was concentrated and purified by

column chromatography (60:40 DCM:cyclohexane, then 90:10 DCM:MeOH) to afford pure **65a** (71 % yield, 166 mg, 0.71 mmol) as a dark purple solid (m.p. not observed up to 320°C).
In $CDCl_3$ the $^1H$ NMR signals resulted broad and not resolved properly. Addition of $d_6$-DMSO allowed to record a higher quality spectra.
$^1H$ NMR (600 MHz, $CDCl_3$:$d_6$-DMSO 4:1, 25°C, TMS as internal reference: 0.00 ppm): $\delta$ = -2.92 (s, 2H), 0.78 (t, $J$ = 7.3 Hz, 12H), 1.13-1.34 (m, 72H), 1.34-1.46 (m , 8H), 1.46-1.58 (m, 8H), 1.80-1.90 (m, 4H), 1.91-1.99 (m, 4H), 4.08-4.18 (bs, 8H), 4.18-4.31 (m, 24H), 4.41-4.52 (bs, 4H), 5.06-5.20 (bs, 4H), 7.86-7.94 (bs, 4H), 8.21 (d, $J$ = 7.3 Hz, 8H), 8.25 (d, $J$ = 7.3 Hz, 8H), 8.79 (s, 8H).
Recording $^{13}C$ NMR $CHCl_3$ or in other deuterated solvents or mixtures did not allow to resolve the signals corresponding to the ferrocene moiety that resulted in a broad band. Only recording the spectra in $d_6$-DMSO allowed to resolve the ferrocene signals, but unfortunately the solubility of **P1** in DMSO is very low (less than 1 mg for 500 μL) so that the porphyrin core signals could not be detected.
$^{13}$CNMR (100 MHz, $CDCl_3$, 25°C): $\delta$ = 14.1 (4C), 22.7 (4C), 26.5 (4C), 29.3 (4C), 29.6 (4C), 29.7 (20C), 29.8 (4C), 31.9 (4C), 36.2 (4C), 48.4 (4C), 68-71 (bs, 40C), 119.3 (8C), 125,4 (8C), 130-132 (bs, 8C), 134.4 (4C), 134.7 (12C), 145.5 (4C), 166.2 (4C).
Electrospray Ion Trap Mass Spectrometry: $[M+H]^+$: 2308.639

*1.4 Synhtesis of **67***

**N-dodecyl-1-ferrocenyl-1-ethyl amine 64**.
In a 25 mL round bottomed flask under nitrogen atmosphere, 1-ferrocenyl-1-ethyl amine **12**[59] (135 mg, 0.59 mmol) was dissolved in dichloromethane (4 mL) at room temperature. Dodecyl aldehyde (131 μL, 0.59 mmol) and $MgSO_4$ (600 mg were subsequently added and the mixture was stirred for 24 hours at room temperature. Then it was filtered over a small celite pad directly into a 25 mL balloon under nitrogen atmosphere. The pad was washed with methanol (5 mL) and the filtrate was cooled to 0°C. $NaBH_4$ (45 mg, 1.18 mmol) was added and the mixture was stirred for 2h. Then the solvent was evaporated under reduced pressure. Water (10 mL) and ethyl acetate (10 mL) were added, the organic phase was separated and the aqueous one was extracted with ethyl acetate (2x10 mL). The collected organic layers were dried over sodium sulphate and evaporated under reduced pressure. The crude was purified by column chromatography (70:29:1 cyclohexane : ethyl acetate : 30% aq. $NH_4OH$ ) to afford pure 1-ferrocenyl-1-tetradecyl amine **64** (54 % yield, 126 mg, 0.32 mmol) as an orange oil.
$^1H$ NMR (400 MHz, $CDCl_3$, 25°C): $\delta$ = 0.78 (t, $J$ = 6.3 Hz, 3H), 1.20-1.37 (bs, 18H), 1.38 (d, , $J$ = 6.2 Hz, 3H), 1.41-1.55 (m, 2H), 1.55-1.72 (bs, 1H), 2.52-2.68 (m, 2H), 3.52 (q, $J$ = 6.2 Hz, 1H), 4.10-4.12 (bs, 2H), 4.14 (s, 5H), 4.18 (s, 1H), (s, 1H); $^{13}$CNMR (100 MHz, $CDCl_3$, 25°C): $\delta$ = 14.1, 21.6, 22.6, 27.4, 29.3, 29.52, 29.54, 29.56, 29.59 (2C), 30.2, 31.9, 47.7, 52.4, 65.8, 67.0, 67.1, 67.2, 68.3 (5C), 93.7.

**67.** In a 10 mL round bottomed flask under nitrogen atmosphere, TCPP (47, 0.06 mmol) was dissolved in DMF (2 mL). N-(3-Dimethylaminopropyl)-N′-ethylcarbodiimide (EDC) hydrochloride (64 mg, 0.33 mmol) and HOBT (45 mg, 0.33 mmol) were added. The solution was shielded by light

and stirred for 1h. Then N-dodecyl-1-ferrocenyl-1-ethyl amine **64** (100 mg, 0.25 mmol) and DMAP (30 mg, 0.25 mmol) were added. After 48 hours the reaction was diluted with DCM (15 mL) and washed 5 times with water (8 mL). The organic phase was concentrated and purified by column chromatography (45:45:10 cyclohexane:EtOAc:DCM) to afford pure **67** (63 % yield, 87 mg, 0.38 mmol) as a dark purple sticky solid.

$^{1}$H NMR (400 MHz, $CDCl_3$, 25°C, two rotamers A/B 1.8/1): $\delta$ = -2.84-(-2.75) (bs, $2H_{A+B}$), 0.64-0.73 (bs, $12H_B$), 0.83-0.94 (bs, $12H_A$), 0.99-1.20 (m, $16H_{A+B}$), 1.21-1.36 (m, $56H_{A+B}$), 1.54-1.66 (m, $8H_{A+B}$), 1.66-1.76 (bs, $12H_{A+B}$), 3.08-3.29 (m, $4H_A$ + $8H_B$), 3.35-3.47 (bs, $4H_A$), 4.05-4.15 (bs, $20H_A$), 4.18-4.46 (m, $16H_A$ + $32H_B$), 4.48-4.58 (bs, $4H_B$), 5.39-5.49 (bs, $4H_A$), 5.91-6.05 (bs, $4H_B$), 7.68-7.77 (bs, $8H_B$), 7.83-7.93 (d, $J$ = 5.1 Hz, $8H_A$), 8.17-8.25 (bs, $8H_B$), 8.28-8.38 (d, $J$ = 5.1 Hz, $8H_A$), 8.77-8.85 (bs, $8H_B$), 8.85-8.95 (bs, $8H_A$).

$^{13}$CNMR (100 MHz, $CDCl_3$, 25°C, two rotamers A/B 1.8/1): $\delta$ = 13.9 ($4C_B$), 14.1 ($4C_A$), 17.8 ($4C_B$), 18.5 ($4C_A$), 22.5 ($4C_B$), 22.7 ($4C_A$), 27.0 ($4C_B$), 27.5 ($4C_A$), 28.8 ($4C_B$), 29.0 ($4C_A$), 29.2 ($4C_B$), 29.3 ($8C_A$), 29.6 ($8C_{A+B}$), 29.7 ($8C_{A+B}$), 30.9 ($4C_B$), 31.7 ($4C_B$), 31.9 ($4C_A$), 42.1 ($4C_A$), 45.1 ($4C_B$), 49.0 ($4C_B$), 54.7 ($4C_A$), 66.6 ($4C_B$), 66.8 ($4C_A$), 67.6 ($4C_{A+B}$), 68.5 ($4C_A$), 68.7 ($4C_{A+B}$), 69.0 ($20C_{A+B}$), 69.3 ($4C_B$), 88.0 ($4C_A$), 88.5 ($4C_B$), 119.4 ($8C_{A+B}$), 124.8 ($8C_B$), 124.9 ($8C_A$), 131.7 ($12C_{A+B}$), 134.3 ($8C_B$), 134.5 ($8C_A$), 137.1 ($4C_{A+B}$), 142.4 ($4C_B$), 142.9 ($4C_A$), 171.1 ($4C_A$), 171.3 ($4C_B$).

Electrospray Ion Trap Mass Spectrometry: $[M+H]^+$: 2308.461

## 3.5 References


[1] G. Maruccio, R. Cingolani, R. Rinaldi *J. Mater. Chem*. **2004**, *14*, 542.

[2] A. Aviram and M. A. Ratner, *Chem. Phys. Lett*., **1974**, *29*, 277–283.

[3] a) R. M. Metzger, B. Chen, U. Holpfner, M. V. Lakshmikantham, D. Vuillaume, T. Kawai, X. Wu, H. Tachibana, T. V. Hughes,
H. Sakurai, J. W. Baldwin, C. Hosch, M. P. Cava, L. Brehmer and G. J. Ashwell, *J. Am. Chem. Soc.*, **1997**, *119*, 10455–10466; b) J. Chen, M. A. Reed, A. M. Rawlett and J. M. Tour, *Science*, **1999**, *286*, 1550–1552.

[4] a) A. Bachtold, P. Hadley, T. Nakanishi and C. Dekker, *Science*, **2001**, *294*, 1317–1320; b) Y. Huang, X. Duan, Y. Cui, L. J. Lauhon, K. Kim and C. M. Lieber, *Science*, **2001**, *294*, 1313–1317.c) for a general dissertation: J. C. Ellenbogen and J. C. Love, Architectures for Molecular Electronic Computers. 1. Logic Structures and an Adder Built from Molecular Electronic Diodes MITRE Research Article (The ‘‘Pink Book’’), available at http://www.mitre.org/tech/nanotech/Arch_for_MolecElec_Comp_1.html.

[5] (a) Y. Chen, G. Jung, D. A. A. Ohlberg, X. Li, D. R. Steward, J. O. Jeppesen, K. A. Nielsen, F. Stoddart J and R. S. Williams, *Nanotechnology*, **2003**, *14*, 462–468; (b) Y. Chen, D. A. A. Ohlberg, X. Li, D. R. Steward, R. S. Williams, J. O. Jeppesen,K. A. Nielsen, F. Stoddart J, D. L. Olynick and E. Anderson, *Appl. Phys. Lett*., **2003**, *82*, 1610–1612.

[6] S. Sangtarash, C. Huang, H. Sadeghi, Gleborohhov, J. Hauser, T. Wandlowski, W. Hong, S. Decurtins, S.-X. Liu, C. J. Lambert *J. Am. Chem. Soc.* **2015**, *137*, 11425–11431.

[7] a) J. E. Poje, T. Kastratovic, A. R. Macdonald, A. C. Guillermo, S. E. Troetti, O. J. Jabado, M. L. Fanning, D. Stefanovic, J. Macdonald, *Angew Chem Int Ed Engl*. **2014**, *53*, 9222-9225; b) D. Y. Tam, Z. Dai, M. S. Chan, L. S. Liu, M. C. Cheung, F. Bolze, C. Tin, P. K. Lo *Angew. Chem. Int. Ed*. **2016**, *55*, 164 –168; c) M. Elstner, J. Axthelm, A. Schiller *Angew. Chem. Int. Ed.* **2014**, *53*, 7339 –7343.

[8] a) C. G. Lent, G. L. Snider, In Field-Coupled Nanocomputing, LNCS 8280 (N.G. Anderson and S. Bhanja Eds.), Springer-Verlag Berlin Heidelberg, 2014, pp 3-20; b) C. S. Lent, P. D. Tougaw, W. Porod, G. H. Bernstein, *Nanotechnology* **1993**, *4*, 49-57.

[9] a) Smith, C., Gardelis, S., Rushforth, A., Crook, R., Cooper, J., Ritchie, D., Linfield, E., Jin, Y., Pepper, M., *Superlattices Microstruct*. **2003**, *34*, 195–203; b) Single, C., Prins, F., Kern, D., *Appl. Phys. Lett*. **2001**, *78*, 1421–1423; c) Mitic, M., Cassidy, M., Petersson, K., Starrett, R., Gauja, E., Brenner, R., Clark, R., Dzurak, A., Yang, C., Jamieson, D., *Appl. Phys. Lett.* **2006**, *89*, 13503; d) Dzurak, A.S., Simmons, M.Y., Hamilton, A.R., Clark, R.G., Brenner, R., Buehler, T.M., Curson, N.J., Gauja, E., McKinnon, R.P., Macks, L.D., *Quantum Inf. Comput*. **2001**, *1*, 82–95.

[10] Davies, J.H., Nixon, J.A., *Phys. Rev. B* **1989**, *39*, 3423.

[11] A. O. Orlov, I. Amlani, G. H. Bernstein, C. S. Lent, G. L. Snider *Science* **1997**, *284*, 928-930.

[12] I. Amlani, A. O. Orlov, G. Tóth, G. H. Bernstein, C. S. Lent, G. L. Snider *Science* **1999**, *284*, 289.

[13] G. Tóth, A. O. Orlov, I. Amlani, C. S. Lent, G. H. Bernstein, G. L. Snider *Phys. Rev. B* **1999**, *49*, 16906-16912.

[14] A. O. Orlov, I. Amlani, R. K. Kummamuru, R. Ramasubramaniam, G. Toth, C. S. Lent, G. H. Bernstein, G. L. Snider *Appl. Phys. Lett.* **2000**, *83*, 295-297.

[15] a) S. B. Braun-Sand and O. J. Wiest, *J. Phys. Chem. A*, **2003**, *107*, 285–291; b) S. B. Braun-Sand and O. J. Wiest, *J. Phys. Chem. B*, **2003**, *107*, 9624–9628.

[16] a) H. Qi, S. Sharma, Z. Li, G. L. Snider, A. O. Orlov, C. S. Lent, T. P. Fehlner, *J. Am. Chem. Soc*., **2003**, *125*, 15250–15259; b) Z. Li, A. M. Beatty and T. P. Fehlner, *Inorg. Chem*., **2003**, *42*, 707–5714; c) M. Manimaran, G. L. Snider, C. S. Lent, V. Sarveswaran, M. Lieberman, Z. Li and T. P. Fehlner, *Ultramicroscopy*, **2003**, *97*, 55–63.

[17] a) J. Jiao, G. J. Long, F. Grandjean, A. M. Beatty and T. P. Fehlner, *J. Am. Chem. Soc*., **2003**, *125*, 7522–7523; b) J. Jiao, G. J. Long, L. Rebbouh, F. Grandjean, A. M. Beatty T. P. Fehlner, *J. Am. Chem. Soc*., **2005**, *127*, 17819–17831.

[18] S. Schneider, S. Demeshko, S. Dechert and F. Meyer, *Angew. Chem. Int. Ed.*, **2010**, *49*, 9274–9277.

[19] V. Arima, M. Iurlo, Z. Zoli, S. Kumar, M. Piacenza, F. Della Sala, F. Matino, G. Maruccio, R. Rinaldi, F. Paolucci, M. Marcaccio, P. G. Cozzi, A. P. Bramanti, *Nanoscale* **2012**, *4*, 813-823.

[20] P. Vicennati, P. G. Cozzi, *Eur. J. Org. Chem*. **2007**, 2248-2253.

[21] S. Karmakar, S. Kumar, P. Marzo, E. Primiceri, R. Di Corato, R. Rinaldi, P. G. Cozzi, A. P. Bramanti, G. Maruccio, *Nanoscale* **2012**, *4*, 2311-2316.

[22] J. A. Christie, R. P. Forrest, S. A. Corcelli, N. A. Wasio, R. C. Quardokus, R. Brown, S. A. Kandel, Y. Lu, C. S. Lent, K. W. Henderson *Angew. Chem.* **2015**, *127*, 15668 –15671.

[23] For more detailed informations see the project website: http://www.molarnet.eu/ (2/3/2016).

[24] This work has been published. Iurlo M.; Mengozzi L.; Rapino S.; Marcaccio M.; Perone R.C.; Masiero S.; Cozzi P.; Paolucci F. *Organometallics*, **2014**, *33*, 4986−4993.

[25] a) D. Sen, W. Gilbert, *Nature*, **1988**, *334*, 364; b) G. Biffi, D. Tannahill, J. McCafferty, S. Balasubramanian, *Nature Chem*. **2013**, *5*, 182.

[26] S. Pieraccini, S. Masiero, O. Pandoli, P. Samorì, G. P. Spada, *Org. Lett*. **2006,** *8*, 3125-3128.

[27] Breugst, M.; Bautista, F. C.; Mayr, H. *Chem. Eur. J.* **2012**, *18*, 127-137, and ref. therein.

[28] a) Zhilina, Z. V.; Gumenyuk, V. V.; Nekrasov, Y. S.; Babin, V. N.;. Snegur, L V.; Starikova, Z. A.; Yanovsky, A. L., *Russ. Chem. Bull.* **1998**, 1781-1784; See also: b) Snegura, L. V.; Nekrasova, Y. S.;. Sergeevab, N. S.; Zhilinaa, Z. V.; Gumenyuka, V. V.; Starikovaa, Z. A.; Simenela, A. A.; Morozovab, N. B.; Sviridganomet. Covab,I. K.; Babina, V. N., *Appl. Organomet. Chem.* **2008**, *22*, 139-147.

[29] a) Vicennati, P.; Cozzi, P. G. *Eur. J. Org. Chem.* **2007**, 2248-2253; (b) Cozzi, P. G. ; Zoli, L. *Green Chem.* **2007**, *9*, 1292-1295; (c) Arima, V.; Iurlo, M.; Zoli, L.; Kumar, S.; Piacenza, M.; Della Sala, F.; Matino, F.; Maruccio, G.; Rinaldi, R.; Paolucci, F.; Marcaccio, M.; Cozzi, P. G.; Bramanti, A. P. *Nanoscale*, **2012**, *4*, 813-823.

[30] Dee Nord, L.; Dalley K. N.; McKernan, P. A.; Robins, R. K. *J. Med Chem.* **1987**, *30*, 1044-1054.

[31] Grant A. Boyle, Christopher D. Edlin, Yongfeng Li, Dennis C. Liotta, Garreth L. Morgans and Chitalu C. Musonda
*Org. Biomol. Chem.*, **2012**, *10*, 1870-1876.

[32] Fletcher, S.; Shahania, V. M.; Loughb, A. J.; Gunning, P. T. *Tetrahedron* **2010**, *66*, 4621-4632.

[33] T. Ohshima, J. Ipposhi,Y. Nakahara, R. Shibuya, K. Mashima, *Adv. Synth. Catal*. **2012**, *354*, 2447-2452.

[34] a) D. Marquarding, H. Klusacek, G. W. Gokel, P. Hoffmann, I. Ugi, *J. Am. Chem. Soc*. **1970**, *92*, 5389–5393; b) G. Gokel, D. Marquarding, I. Ugi, *J. Org. Chem*. **1972**, *37*, 3052–3058; c) A. Togni, C. Breutel, A. Schnyder, F. Spindler, H. Landert, A. Taijani, *J. Am. Chem. Soc*. **1994**, *116*, 4062–4066.

[35] a) Ciesielski, A.; El Garah, M.; Masiero, S.; Samorì, P., *Small*, **2016**, *12*, 83 – 95; b) El Garah, M.; Perone, R. C.; Santana Bonilla, A.; Haar, S.; Campitiello, M.; Gutierrez, R.; Cuniberti, G.; Masiero, S.; Ciesielski, A.; Samorì, P., *Chem. Commun.*, **2015**, *51*, 11677 – 11680; c) Ciesielski, A.; Haar, S.; El Garah, M.; Surin, M.; Masiero, S.; Samorì, P., *L'Actualitè Quimique*, **2015**, *399*, 31 – 36.

[36] Unpublished results.

[37] P. G. Cozzi, *Chem. Soc. Rev.***, 2004,** 33**,** 410-421

[38] G. Salassa, M. J. J. Coenen, S. J. Wezenberg, B. L. M. Hendriksen, S. Speller, J. A. A. W. Elemans, A. W. Kleij, *J. Am. Chem. Soc*. **2012**, *134*, 7186−7192; b) I. P. Oliveri, S. Failla, G. Malandrino, S. Di Bella, *J. Phys. Chem. C*, **2013**, *117*, 15335–15341; c) M. Viciano-Chumillas, J. Hieulle, T. Mallah, F. Silly, *J. Phys. Chem. C* **2012**, *116*, 23404−23407; d) J. A. A. W. Elemans, S. J. Wezenberg, M. J. J. Coenen, E. C. Escudero-Adàn, J. Benet-Buchholz, D. den Boer, S. Speller, A. W. Kleij, S. De Feyter, *Chem. Commun*., **2010**, *46*, 2548–2550.

[39] For examples see: a) J. A. Castro-Osma, M. North, X. Wu, *Chem. Eur. J*. **2016**, *22*, 2100 – 2107; b) K. Y. Hwang, H. Kim, Y. S. Lee, M. H. Lee, Y. Do, *Chem. Eur. J*. **2009**, *15*, 6478 – 6487.

[40] Jay F. Larrow and Eric N. Jacobsen, *J. Org. Chem*. **1994**, *59*, 1939-1942.

[41] A. K. D. Diaw, A. Yassar, D. Gningue-Sall, J.-J. Aarona, *ARKIVOC* **2008**, *xvii*, 122-144.

[42] P. G. Cozzi and L. Zoli, *Green Chem.*, **2007**, *9*, 1292–1295.

[43] Adrian W. Bott, Ph.D. Current Separations 18:1 (1999), 9-16 (http://www.currentseparations.com/issues/18-1/cs18-1b.pdf)

[44] V. O. Nyamori and M. D. Bala *Acta Cryst.* **2008**, *E64*, m1630.

[45] Manuscript submitted. Authors: M. El Garah, A. Ciesielski, A. Gualandi, L. Mengozzi, A. Fiorani, M. Iurlo, M. Marcaccio, A. Santana Bonilla, D. Arezoo, R. Gutierrez, G. Cuniberti, P. G. Cozzi, F. Paolucci, P. Samorì.

[46] Yella, A.; Lee, H.-W.; Tsao, H. N.; Yi, C.; Chandiran, A. K.; Nazeeruddin, M. K.; Diau, E. W.-G.; Yeh, C.-Y.; Zakeeruddin, S. M.; Grätzel, M. *Science* **2011**, *334*, 629-634.

[47] Guo, H.; Jiang, J.; Shi, Y.; Wang, Y.; Liu, J.; Dong, S. *J. Phys. Chem. B* **2004**, *108*, 10185-10191.

[48] Slater, A. G.; Hu, Y.; Yang, L.; Argent, S. P.; Lewis, W.; Blunt, M. O.; Champness, N. R. *Chem. Sci*. **2015**, *6*, 1562-1569.

[49] Zhou, Y. S.; Wang, B.; Zhu, M. Z.; Hou, J. G. *Chem Phys Lett* **2005**, *403*, 140-145.

[50] a) Li, M.; den Boer, D.; Iavicoli, P.; Adisoejoso, J.; Uji-i, H.; Van der Auweraer, M.; Amabilino, D. B.; Elemans, J. A. A. W.; De Feyter, S. *J. Am. Chem. Soc.* **2014**, *136*, 17418-17421; b) Yoshimoto, S.; Yokoo, N.; Fukuda, T.; Kobayashi, N.; Itaya, K. *Chem. Commun.* **2006**, 500-502.

[51] a) den Boer, D.; Li, M.; Habets, T.; Iavicoli, P.; Rowan, A. E.; Nolte, R. J. M.; Speller, S.; Amabilino, D. B.; De Feyter, S.; Elemans, J. A. A. W. *Nat. Chem.* **2013**, *5*, 621-627; b) Otsuki,

J.; Nagamine, E.; Kondo, T.; Iwasaki, K.; Asakawa, M.; Miyake, K. *J. Am. Chem. Soc.* **2005**, *127*, 10400-10405; c) Wang, H.; Wang, C.; Zeng, Q.; Xu, S.; Yin, S.; Xu, B.; Bai, C. *Surf. Interface Anal.* **2001**, *32*, 266-270.

[52] a) El Garah, M.; Ciesielski, A.; Marets, N.; Bulach, V.; Hosseini, M. W.; Samorì, P. *Chem. Commun.* **2014**, *50*, 12250-12253; b) Hanke, F.; Haq, S.; Raval, R.; Persson, M. *ACS Nano* **2011**, *5*, 9093-9103; c) Li, Y.; Lin, N. *Phys. Rev. B* **2011**, *84*, 125418-125424.

[53] Grill, L.; Dyer, M.; Lafferentz, L.; Persson, M.; Peters, M. V.; Hecht, S. *Nat. Nanotechnol.* **2007**, *2*, 687-691.

[54] Surin, M.; Samorì, P.; Jouaiti, A.; Kyritsakas, N.; Hosseini, M. W. *Angew. Chem. Int. Ed.* **2007**, *46*, 245-249.

[55] A. Vecchi, N. R. Erickson, J. R. Sabin, B. Floris, V. Conte,M. Venanzi, P. Galloni, V. N. Nemykin, *Chem. Eur. J.* **2014**, *20*, 269-279.

[56] for the ultradry electrochemical conditions see: Iurlo M.; Mengozzi L.; Rapino S.; Marcaccio M.; Perone R.C.; Masiero S.; Cozzi P.; Paolucci F. *Organometallics*, **2014**, *33*, 4986−4993.

[57] Sooambar C.; Troiani V.; Bruno C.; Marcaccio M.; Paolucci F.; Listorti A.; Belbakra A.; Armaroli N.; Magistrato A.; De Zorzi R.; Geremia S.; Bonifazi D. *Org. Biomol. Chem.* **2009**, *7*, 2402-2413.

[58] Prepared according to: Vukićević, M. D.; Ratković, Z. R.; Teodorović, A. V.; Stojanović, G. S.; Vukićević, R. D. *Tetrahedron* **2002**, *58*, 9001-9006.

[59] Prepared according to experimental part of chapter 3.2 or see Iurlo, M.; Mengozzi, L.; Rapino, S.; Marcaccio, M.; Perone, R. C.; Masiero, S.; Cozzi, P. G.; Paolucci F. *Organometallics* **2014**, *33*, 4986−4993.

## Ringraziamenti

Rapidi e stringati dato che la tesi è venuta fin troppo lunga!

Prima di tutto a mia mamma, mio babbo e alla mia famiglia: i miei nonni Anna e Gigi, mio zio Giuliano, le mie zie Giuliana, Iliana e Diana e i cugini, che mi hanno sempre sostenuto durante questi anni e incoraggiato a seguire i miei sogni e passioni!

Poi ai miei amici Artur, Fede, Aida, Riki, Leta che sono la mia seconda famiglia.

Ai miei amici Andre e Andrea, Betta, Matte, Elia, Edo, Sara, Barto, Lorenz, Tai, Fabio, Raffa, Fra, Piraz, Atomo, Fede, Bastri, Nicola, Elisa, Paltri, Jack, i co…ompagni Fabio, Nico, Pasqua, Diki, Benny, …sicuro mi sono dimenticato qualcuno in questo momento…beh si senta incluso!

Elia, Gaston, Franci, Mike, Giardo, Luca, Abdul, Petr e Mattia (che no Mattia no balli) per le tante perle (e cipolle moderne!) di via Agnesi…che si verificano con cadenza regolare ai 20 (e anche verso i primi ultimamente) del mese!

Ai miei compagni di avventura sotto cappa: Andrea, non potrò mai ringraziarti per i tanti trucchi che mi hai insegnato, Edo…quante risate…ci siamo divertiti tantissimo! Betta, grazie per la pazienza... ! Assu meno male che canti anche tu…sennò mi sentirei solo! Steve, Giampi, Ciro, Moira, Diegus, Veronica, Francesca…per i tempi in cui c'era veramente la gabbia dei matti lì dentro! Matti, Riki, M&M, Noemi per non averli fatto rimpiangere !

Infine, ma non ultimo, grazie PG per la fiducia, gli stimoli, gli insegnamenti e la passione che metti e trasmetti ogni giorno in questo lavoro !

Pero no habemos acabado todavia!

La bomba esta encendida y oh Susana se oye ! Thank you very much guys and Professor Pericàs for welcoming me and making me feel like at home since the first day!

Carles, Laura, Paola, Evgeny, Francesca, Sara, Dina, Carmen Michael and Family, Marta, Pablo FYI, Carles A., Lidia, Esther, Patri, Xavi, Ilario, Giacomo, Caye, Franziska Giacomo, Ilario, y los otros chicos italianos… I miss you !

Yunior, thank you very much for your help with my finger!

Calvin, Noel it was real fun sharing the apartment and my time with you guys (and the cucarachas) !!!