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ESCOLA DE CIÊNCIAS E TECNOLOGIA

DEPARTAMENTO DE QUÍMICA

Development of an Organocatalytic Method for the Enantioselective Synthesis of Rivastigmine

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Mestrado em Química

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Acknowledgments

Any achievement in life requires ward work, sacrifice, dedication and appreciation. The work presented in this dissertation is no different, representing a new and exciting journey full of ups and downs. At the end of the day, all the disappointments and frustrations were insignificant in the face of all the knowledge that I gained, not just on a professional but also on a personal level. None of this would be possible without the fantastic supportive people that surrounded me during this challenging time of my life. No amount of words are enough to describe my appreciation for them, but I can surely try.

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Abstract

Development of an Organocatalytic Method for the Enantioselective Synthesis of Rivastigmine

The focus of this thesis was the study of a recently developed class of picolinamide cinchona alkaloid derivatives for the synthesis of Rivastigmine, a biologically active compound used for the treatment of Alzheimer's disease.

Six 9-picolinamide-cinchona alkaloid derivatives were successfully synthesized through simple and effective methods. These catalysts were then applied in the enantioselective reduction of *O*-protected ketimines (intermediates of Rivastigmine). The hydrosilylation of the *N*-phenyl ketimines afforded good results with excellent yields and high enantioselectivities, while much lower values, in terms of both enantioselectivity and yield, were obtained in the reduction of *N*-benzyl ketimines.

Preliminary studies on the immobilization of these organocatalysts to different solid supports were conducted, with the purpose of applying them in continuous flow systems, which to date has never been reported.

Keywords: Ketimine reduction, Chiral amines, Cinchona alkaloid derivatives, Rivastigmine.

Resumo

Desenvolvimento de um Método Organocatalítico para a Síntese Enantiosseletiva de Rivastigmina

No âmbito deste trabalho, foi estudada a síntese de um composto biologicamente ativo usado para o tratamento da doença de Alzheimer, Rivastigmina, usando uma classe de picolinamidas derivadas de alcaloides de cinchona recentemente desenvolvida.

Seis 9-picolinamida derivados de alcaloides de cinchona foram preparados com êxito através de metodologias simples e eficazes. Os organocatalisadores foram posteriormente aplicados na redução enantiosseletiva de cetiminas *O*-protegidas (intermediários de Rivastigmina). Foram obtidos bons resultados na hidrossililação de *N*-fenilo cetiminas, com rendimentos excelentes e elevadas enantiosseletividades, enquanto a redução de *N*-benzilo cetiminas proporcionou valores muito mais baixos, tanto em termos de rendimento como de enantiosseletividade.

Com o objetivo de serem aplicados em sistemas de fluxo contínuo, realizaram-se estudos preliminares sobre a imobilização destes organocatalisadores em diferentes suportes sólidos, a qual, ate à data, ainda não foi descrita na literatura.

Palavras-chave: Redução de cetiminas, Aminas quirais, Derivados de alcaloides de cinchona, Rivastigmina.

Abbreviations

ACh	Acetylcholine
AChE	Acetylcholinesterase
AcOEt	Ethyl acetate
AD	Alzheimer's disease
AIBN	Azobisisobutyronitrile
Ar	Aromatic group
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binahthalene
BINOL	1,1'-Bi-2-naphtol
Bn	Benzyl
BnBr	Benzyl bromide
BOC	*tert*-Butylcarbonyl
br	Broad
BuChE	Butylcholinesterase
***i*BuOH**	2-Butanol
cat	Catalyst
CD	Cinchonidine
CDI	Carbonyl-*di*-imidazole
CN	Cinchonine
CuAAc	Copper(I)-catalyzed alkyne-azide cycloaddition
C_q	Quaternary carbon
d	Doublet
dd	Double doublet
DCE	1,2-Dichloroethene
DFT	Density functional theory
DIPEA	*N,N'*-Diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DMF	*N,N'*-Dimethyl formamide
DMSO	Dimethyl sulfoxide
dr	Diastereomeric ratio
DVB	Divinylbenzene
E^+	Electrophile

ee	Enantiomeric excess
equiv	Equivalent
FDA	Food and Drug Administration
Hex	Hexane
HPLC	High-performance liquid chromatography
Hz	Hertz
J	Nuclear Magnetic Resonance Coupling Constant
m	Multiplet
Me	Methyl
MeI	Iodomethane
MeOH	Methanol
MHz	Megahertz
MM	Molecular Modeling
m.p.	Melting point
MW	Microwave
MS	Molecular sieves
MsCl	Methanesulfonyl chloride
NEt_3	Triethylamine
NMR	Nuclear Magnetic Resonance
NHC	*N*-Heterocyclic carbene
Nu	Nucleophile
PD	Parkinson's disease
PEG	Polyethylene glycol
Ph	Phenyl
PMP	*p*-Methoxyphenyl
PPh_3	Triphenylphosphine
ppm	Parts per million
***i*PrOH**	2-Propanol
q	Quartet
QD	Quinidine
QN	Quinine
rt	Room temperature
s	Singlet

SEM	Scanning Electron Microscopy
S_N2	Bimolecular nucleophilic substitution
SOMO	Singly Occupied Molecular Orbital
t	Triplet
TADDOL	α,α,α',α'-Tetraaryl-1,3-dioxolan-4,5-dimethanol
Temp	Temperature
TFAA	Trifluoroacetic anhydride
TGA	Thermogravimetric analysis
THF	Tetrahydrofuran
THP	Tetrahydropyridine
TLC	Thin Layer Chromatography
TMS	Tetramethylsilane
TOF	Turnover Frequency
TON	Turnover Number
t_R	Retention time
***p*-TSA**	*p*-Toluenesulfonic acid
UV	Ultraviolet

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Highlights

"*Nothing in life is to be feared, it is only to be understood. Now is the time to understand more, so that we may fear less*"
Marie Curie

In the last few decades, neurodegenerative diseases have become a worldwide worrying issue, due to the significant ageing of the world population. Currently, Alzheimer's disease (AD) is the most common neurodegenerative disease, there being about 35 million people worldwide suffering from this disease, a number that is expected to increase 3 to 4 times before 2050.[1] Indeed, AD has become a public health issue on a global scale and there is no cure for it. However, there are some therapeutic strategies available to treat the symptoms associated with AD.[2]

Many of the current drugs used to treat these diseases, such as Rivastigmine and Amgen's hydroxyethylamine-based secretase inhibitor, possess a chiral amine unit in their structure.[3] Thus there is an increasing interest in the development of more efficient methods to obtain these chiral amine units. Inducing chirality during chemical synthesis by catalytic methods represents one of the most important fields in modern organic chemistry. Among the various approaches to achieve this objective, the use of chiral organocatalysts represents a particularly appealing strategy, because the enantiomeric control is often achieved by the simple combination of purely organic catalysts with the substrate/reagent, without the possibility of any metal residues in the final product. Indeed, in the last two decades, organocatalysis has emerged as an attractive and efficient alternative to the so called conventional catalytic methods – transition metal-based catalysis and biocatalysis.[4]

The main industrial process for the preparation of chiral amines is via catalytic asymmetric hydrogenation of imines. Currently, this preparation is mainly done employing transition metal-based catalysts, which makes the process very expensive and wasteful, as well as increases the possible toxicity of the final product.[5] The hydrosilylation of ketimines with an active efficient organocatalyst and trichlorosilane is a very attractive alternative. Thrichlorosilane mediated reductions are especially attractive from the pharmaceutical point of view, due to the low cost of the reagent.[6]

The main objective of this project is the development of a new and more efficient organocatalytic synthetic pathway for the preparation of drugs used in AD treatment, more specifically Rivastigmine. We employed a recently developed and highly active class of organocatalysts – cinchona-derived picolinamides[7] – in the hydrosilylation of ketimine intermediates of Rivastigmine (derived mainly from 3'-hydroxyacetophenone). Besides the homogenous version of this synthetic system, we did some preliminary work in its heterogeneous counterpart, with the immobilization of these catalysts to the solid phase. This was done in order to apply enabling technologies, such as flow chemistry[8], in the hydrosilylation reactions.

This dissertation is divided in four main parts. First, we present the theoretical background of organocatalysis, were we give a comprehensive, but brief global overview of the literature published to date. This is followed by the presentation and discussion of the complete laboratorial results obtained during the execution of this project, divided by preparation of organocatalysts, preparation of ketimine precursors and, lastly, the application of the catalysts in the hydrosilylation of the prepared imines. Thirdly, we show the conclusions obtained during this project, as well as some future perspectives for its continuation. And lastly, but definitely not least, the experimental procedures used for the synthesis of organocatalysts, of ketimine intermediates and catalytic reactions are gathered, as well as the characterization of the obtained products. All the bibliographical references used for the preparation of this dissertation are shown at the end.

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1. Introduction

"*Science is like a love affair with nature; an elusive, tantalizing mistress. It has all the turbulence, twists and turns of romantic love, but that's part of the game*"
Vilayanur Ramachandran

1.1 Organocatalysis

1.1.1 Overview

The enantioselective production of compounds is a central theme in current research. One of the main objectives of organic chemists resides in the study and development of methodologies to provide valuable products from readily available starting materials.[1-4] In organic chemistry, valuable products are usually associated with enantiomerically enriched products due to the unique properties presented by each enantiomer of a racemic mixture.[5] In the past two decades the number of methods available for high yielding and enantioselective transformations of organic compounds has increased exponentially.[6] Currently the preparation of enantiopure compounds can be done mainly by three different methods – resolution of racemic mixtures, *chiral pool* synthesis or asymmetric catalysis. Traditionally, on the industrial scale, with some exceptions, this enantiopure compounds are obtained by resolution.[7] However, this method presents some relatively serious gaps – the time constraints on discovery chemists and the potential waste of organic material, due to the limitation of the amount of enantiomer obtain that is naturally set at 50%. In some cases, the latter limitation can be reduced when the conversion of the opposite enantiomer into the desired one is possible, either by a dynamic kinetic resolution or by an alternative synthetic scheme, however increasing even more the time constraints.[8]

Asymmetric synthesis, the ability of controlling the three dimensional structure of the molecular architecture, has assumed a featured role in the preparation of enantiopure compounds, and was responsible for revolutionizing chemistry in the second half of the XXth century.[9] Asymmetric synthesis – which can be divided in a stoichiometric or catalytic approach – unlike the previous method, does not resolve racemic mixtures, but is in turn responsible for the creation of stereogenic centers, common feature of many natural and synthetic pharmaceutical agents.[10] Asymmetric catalysis is a prominent area of investigation, since “a small amount of an enantiomerically pure catalyst, enzymatic or not, is used to produce large amounts of an optically active compound from a chiral or achiral precursor”,[11] providing economic advantages as well as “atom economy”. Due to these advantages, the interest in this area has increased tremendously over the last five decades, and the development of efficient asymmetric catalytic systems for valuable organic transformations has been a main concern for organic chemists.[12] Perhaps one of the best illustrations of the importance of asymmetric catalysis was the Nobel Prize in Chemistry

awarded in 2001 to three of the greatest chemists for their contributions to this area, namely to William R. Knowles[13] and Ryoji Navori[14] "for their work on chirally catalyzed hydrogenation reactions" and to K. Barry Sharpless[15] "for his work on chirally catalyzed oxidation reaction".

Until recently, and due to all the developments and obtained results in this area, the catalysts employed for enantioselective synthesis of organic compounds fell into two general categories – transition metal complexes and enzymes. However, during the last decade, this dogma changed when several reports confirmed that relatively simple molecules, such as proline, could be highly effective and remarkably enantioselective catalysts of a variety of fundamentally important transformations. And so, between the extremes of transition metal catalysis and enzymatic transformations, a third approach to the catalytic production of enantiomerically pure organic compounds has emerged – Asymmetric Organocatalysis.[1,5,9]

Organocatalysis, a relatively new and popular field of asymmetric catalysis, had its *boom* in the scientific community in the year 2000 mostly due to the work of two independent research groups and their respective publications. Both publications converged on the use of small molecular weight chiral molecules, without any metals in their structure, for the asymmetric synthesis of organic compounds. David MacMillan and his team[16] used imidazolidinones as organocatalyst in the asymmetric version of the Diels-Alder cycloadditions, while Benjamin List and his team[17] worked on enantioselective aldol reactions using L-proline as organocatalyst, in which both obtained very good results. MacMillan himself, in that same year, defined "Organocatalysis" as "the use of small molecular weight molecules to catalyze organic transformations".[16]

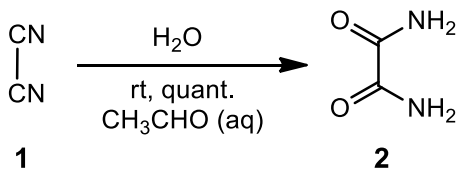
Organocatalysis provides a means of accelerating chemical reactions with a substoichiometric amount of organic molecules, which do not contain a metal element.[9] Organocatalysts can be defined as purely "organic" molecules, i.e. composed (mainly) of carbon, hydrogen, nitrogen, sulfur and phosphorus.[5] Organocatalysts have several advantages that led to a complementary mode of catalysis, with the potential for savings in terms of costs, time and energy, reductions in chemical waste, and simplified experimental procedures. This benefits arise essentially from three factors. First, organic catalysts are generally insensitive to oxygen and moisture (i.e. not hygroscopic) in the atmosphere, so there is no need for special reaction conditions or storage, such as inert atmosphere, as well as for ultra-dry reagents and solvents. Second, a wide variety of organic molecules – such as amino acids, carbohydrates and hydroxy acids – are naturally available from biological sources as single enantiomers. Simple organocatalysts are therefore usually cheap to prepare and readily accessible in a wide range of quantities, making them suitable to work

in small-scale reactions as well as industrial-scale reactions. Third, because these catalysts do not possess any metal in their structure, these molecules are typically non-toxic and environmentally friendly, increasing the safety of the catalysis for both the operator and the environment, on an industrial and academic level.[1819]

Despite its rich historical past, the use of small organic molecules as chiral catalysts has only recently been recognized as a valuable addition and/or alternative to existing, well-established, often metal-based methodologies in asymmetric synthesis. Organocatalysis has seen a tremendous rise in popularity, having captured the attention and curiosity of several research groups from all around the world.[9,21] Enantioselective organocatalytic processes have reached maturity in recent years with an impressive and steadily increasing number of publications on the application of this type of reaction, which paints a comprehensive picture of their real possibilities in organic chemistry.[20] In a little more than a decade after its *boom,* organocatalysis has expanded to practically every area of organic chemistry, from polymer synthesis,[22,23] to total synthesis,[24,25] being used in both homogenous and heterogeneous catalysis with catalysts being immobilized in several different types of supports. It has been used in numerous chemical transformations, such as addition, substitution, elimination and rearrangement reactions[7]. There doesn't seem to be any limitations to the application of organocatalysis, except perhaps those imposed by the "person" working with it.

1.1.2 Historical Background

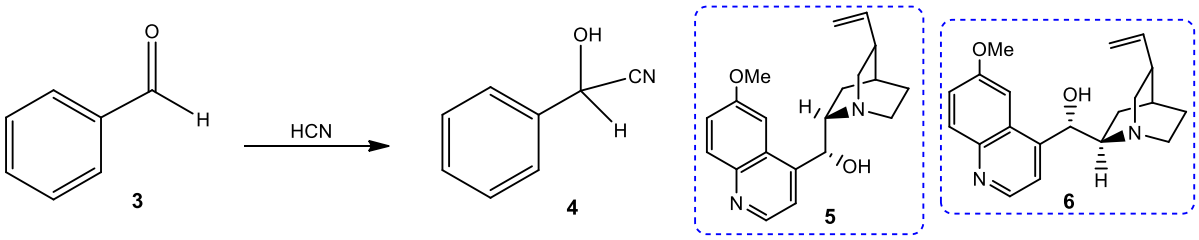
Even though organocatalysis has only recently established itself as an effective field of research, this was not be any means the "genesis" of organic catalysts. The history of organocatalytic reactions has a rich past, with evidence that such catalysis has in the past played a determinant role in the formation of prebiotic key building blocks such as sugars.[26-29] The year 2000 "only" marked the awakening of this very important area of chemistry, since organic molecules have been used as catalysts from the early age of synthetic chemistry. Indeed, the first reference of organic molecules with catalytic properties goes back to the XIXth century when in 1859 Justus von Liebig – accidentally – discovered that dicyan **1** is transformed into oxamide **2** in the presence of an aqueous solution of acetaldehyde (Scheme **1.1**).[9]



Scheme 1.1 von Liebig's oxamide synthesis.[9]

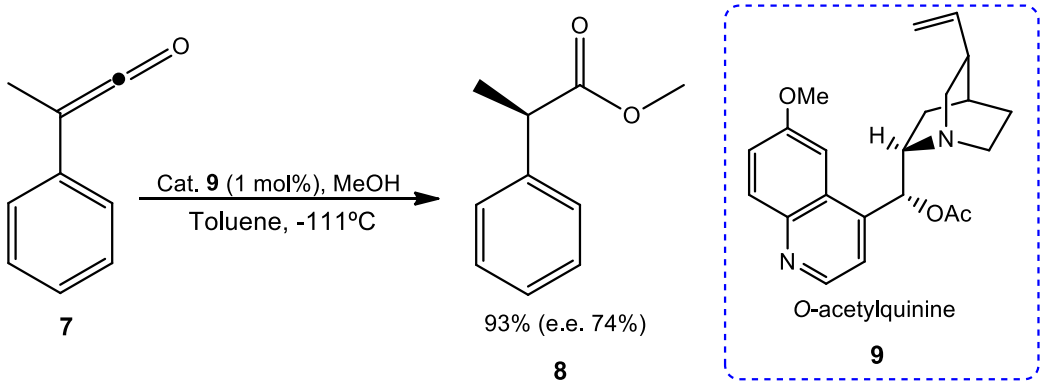
Undoubtedly, the discovery of enzymes and enzyme functions had an important impact on the development of asymmetric catalytic reactions. Despite Liebig's reaction being catalyzed by an organic molecule, this was not the first described asymmetric reaction. The first asymmetric reaction – a decarboxylative kinetic resolution – is attributed to Louis Pasteur that, in 1853, introduced the term "dissymmetry".[30] Pasteur observed that the organism *Penicillium glauca* destroyed more rapidly one the enantiomers from a racemic resolution of ammonium tartrate.[31,32]

In the beginning of the XXth century, asymmetric decarboxylation reactions were re-examined under non-enzymatic conditions by Georg Bredig, a German scientist. Bredig, who had a remarkably wide interdisciplinary interest, was motivated to find the chemical origin of enzyme activity observed in living organisms. He was able to establish the basic kinetic equations of the thermal decarboxylation of optically active camphorcarboxylic acid in *d* and *l* limonemes in the presence of chiral alkaloids, such as nicotine or quinine.[33,34] Based on Rosenthaler's work[35] – who was able to prepare mandelonitrile **4** by the addition of HCN to benzaldehyde **3** in the presence of an isolated enzyme, emulsin – Bredig became a pioneer by performing the first asymmetric C–C bond forming reaction. In 1912, Bredig and Fiske perform the same reaction as Rosenthaler, but in the presence of alkaloids as catalysts, such as the pseudo-enantiomeric quinine **5** and quinidine **6** (Scheme **1.2**). Although these studies were considered groundbreaking, the enantioselectivity of the reaction was less than 10%.[36]



Scheme 1 Erro! Não existe nenhum texto com o estilo especificado no documento..**2** Mandelonitrile synthesis performed by Bredig and Fiske.[36]

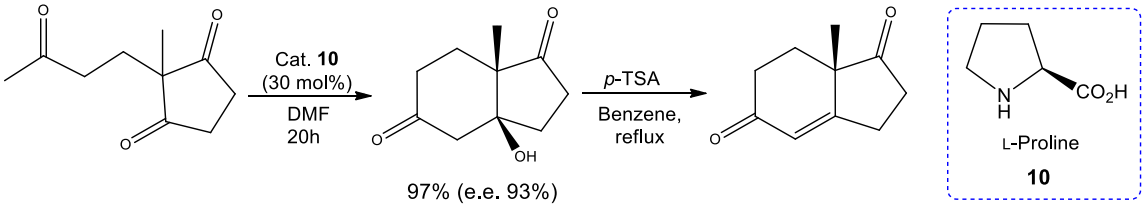
Although catalytic transformations gained increasing importance after the First World War, asymmetric reactions were at the time considered to be an academic curiosity. The reinvestigation of Bredig's asymmetric cyanohydrin synthesis by Prelog during the mid-1950s undoubtedly promoted the concept of asymmetric synthesis, and led the way for more efficient reactions. Only in 1960 synthetically useful levels of enantioselectivity were obtained, when Pracejus demonstrated that methyl phenyl ketene **7** could be converted to (-)-α-phenyl methylpropionate **8** using cinchona alkaloids as catalyst, more specifically *O*-acetylquinine **9** (Scheme **1.3**).[37,38] This quite impressive result inspired the reinvestigation of other possible reaction types for the cinchona catalyst system.



Scheme 1.3 Pracejus's enantioselective ester synthesis from phenyl methyl ketene.[37,38]

In early 1970s, perhaps one of the most famous key events in the history of organocatalytic reactions was reported – the discovery of an efficient L-proline-mediated asymmetric Robinson annulation, through the work developed by two independent research groups led by Zoltan G. Hajos, from Hoffmann-La Roche, and Rudolf Wiechert, from Schering AG. The reaction that became known has the Hajos-Parrish-Eder-Sauer-Wiechert

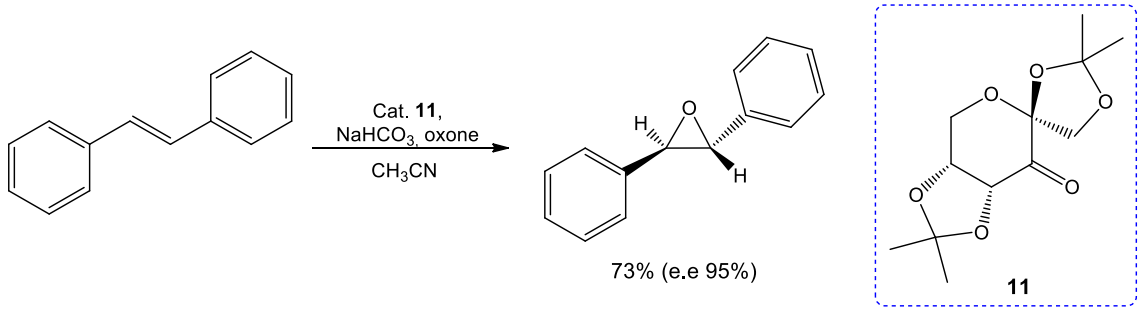
reaction (an intramolecular aldol reaction) (Scheme **1.4**) allowed access to some key intermediates for the synthesis of natural products.[39]



Scheme 1.4 L-proline-mediated Robinson annulation.[39]

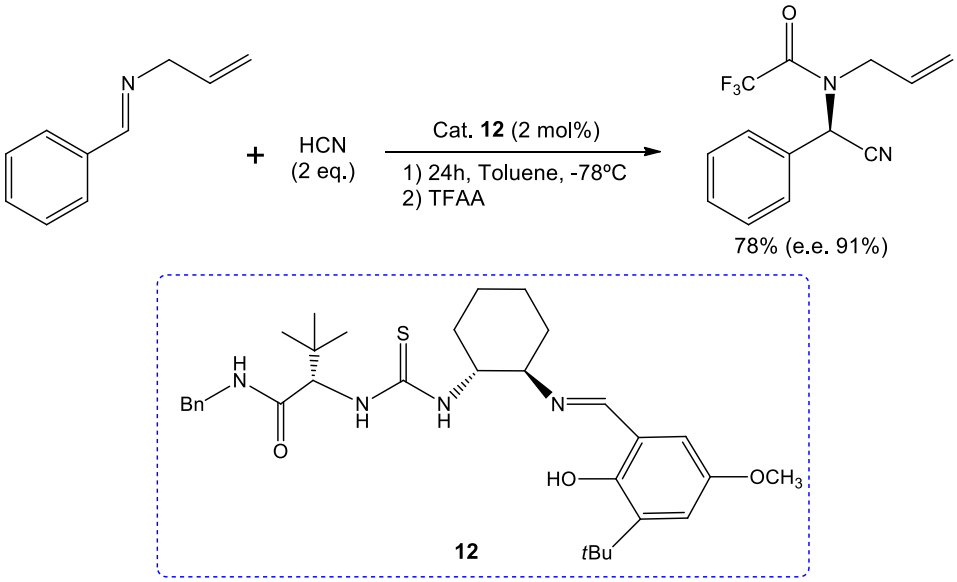
It all started in 1971 when Eder, Sauer and Wiechert reported a Robison annulation (a Michael addition followed by an intramolecular aldol condensation) using a catalytic amount of L-proline **10**, that was enough to obtain the desired product with an 83% yield and 71% enantiomeric excess.[40] Three years later, Hajos and Parrish were able to reproduce a similar reaction at lower temperatures and perform the dehydration step in isolation, obtaining the desired product with an astonishing 93% enantiomeric excess.[39]

Although the L-proline-mediated annulation received a considerable synthetic and mechanistic interest, this field of chemistry remained inexplicably relatively dormant for about 20 years. There were some minor discoveries made during the late 1970s and 1980s, with the discovery of reactions which proceeded via ion-paring mechanisms[41,42] and relatively efficient phase-transfer reactions by Merck.[43,44] Only during the late 1990s, chemists starting turning their attention back to organocatalysis when Dan Yang,[45] Scott Denmark[46] and Yian Shi,[47] with their respective research groups, used enantiomerically pure ketones to catalyze enantioselective epoxidations of simple alkenes, with good yields and up to 95% enantiomeric excess (Scheme **1.5**).



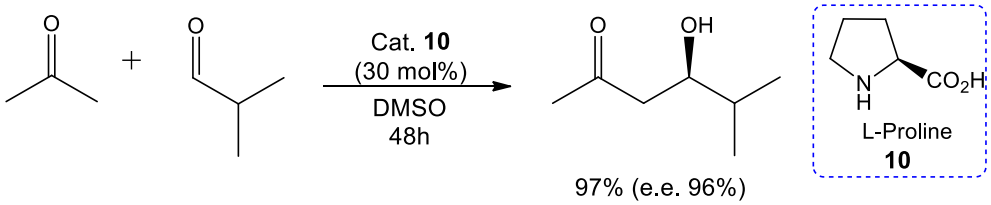
Scheme 1.5 Olefin asymmetric epoxidation catalyzed by chiral ketones.[47]

Sometime later, three independent research groups lead by M. Lipton[48], Elias Corey[49] and Eric Jacobsen[50] reported the first examples of catalysis mediated by hydrogen bonds, namely asymmetrical Strecker reactions (Scheme **1.6**), while Miller[51] and his team introduced the concept of kinetic resolution in alcohols with small peptides.



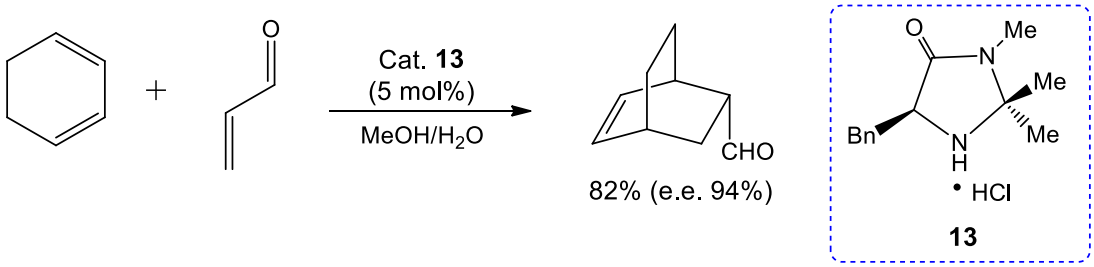
Scheme 1.6 Example of a Strecker reaction performed by Sigman and Jacobsen.[50]

While these studies as a whole didn't consecrate organocatalysis as an effective field of research, these early examples provided inspiration for many of the reactivity principles in common usage today and allowed to understand, for the first time, the role of these small organic molecules in the synthesis of very important chiral compounds.[18] Only after the independent publication of two papers in 2000, as previously mentioned, the potential of organocatalysis was recognized, firmly establishing it as an indispensable branch of contemporary synthetic chemistry. Mirroring the enamine reactivity of type I aldolases, Carlos Barbas III, Richard Lerner and Benjamin List[17] reported that direct asymmetric aldol reactions between acetone and simple aldehydes could by catalyzed by L-proline **10** (Scheme **1.7**). This observation occurred during the reinvestigation of the Hajos-Parrish-Eder-Sauer-Wiechert reaction during the late 1990s – that extended this reaction to several others aldehydes in intermolecular aldol reactions – which also opened an avenue for a number of related transformations such as the enantioselective intramolecular crossed-aldol reaction, as well as Mannich, Michael and Diels-Alder type transformations, and the application of these transformations in multistep (domino) reactions.[5,52,53]



Scheme 1.7 Example of an intermolecular aldol reaction studied by Barbas III.[17]

Simultaneously, Ahrendt, Borths and MacMillan[16] reported the first highly enantioselective organocatalytic Diels-Alder reaction mediated by an imidazolidinone **13** derived from L-phenylanine (Scheme **1.8**). In that same publication MacMillan defined and conceptualized organocatalysis as a new and in expansion branch of asymmetric synthesis. Since then, there has been an almost exponential and unprecedented increase in publications, citations and research groups working in this field.[18]



Scheme 1.8 Example of a Diels-Alder reaction performed by MacMillan.[16]

The very good results obtained along the years motivated scientists to study and develop new classes of organocatalysts from different chemical structures, such as cinchona alkaloids,[54] BINOL,[55] TADDOL,[56] sugars,[57] L-proline,[58] DMAP[59] derivatives, amongst many other examples.[60-61] However scientist didn't just focus their efforts on the synthesis of catalysts, but also their application. Within a relatively short time frame, modern organocatalysis has found application in all branches of synthesis ranging from preparation of biologically important compounds to materials science. All the knowledge obtained about organocatalysts also permitted the development of new reactions such as tandem, cascade, domino and multicomponent reactions,[72] as well as reactions in aqueous medium and the immobilization of catalysts in solid supports.[20,68]

Currently, as mentioned before, there are numerous asymmetric reactions that can be catalyzed by organocatalysts,[18] such as, for example, halogenations, aldol condensations, epoxidations, reductions, Mannich reactions, oxidations, Michael additions, alkylation,

arylation, alylation, acylation, Diels-Alder reactions, 1,3-dipolar cycloadditions, amongst many others.[62]

1.1.3 Conceptualization

To date organocatalysis has definitively been recognized as the third methodology available in asymmetric catalysis, parallel to organometallic catalysis and to biocatalysis (i.e. enzymatic catalysis).[63] Each of these methodologies possess advantages and disadvantages – some of them already mentioned – with some similarities and differences between them. The biggest, and maybe most obvious, similarity is that the catalysts used in all these methodologies can by principle promote chemical transformations. However, this leads us to the main difference between them – the mode of action by which the catalyst promotes the chemical reactions. While an organometallic catalyst possesses a transition metal as catalytic center, an organocatalyst possess a carbon structure with particular heteroatoms endowing it with properties characteristic of a catalytic center. In the case of enzymes it's a little more complicated, because even though they possess hundreds of amino acids in their structure, only a small fraction of them belong to the catalytic center and they have different properties.[64]

In order to establish organocatalysis as the superior methodology of asymmetric synthesis, it is important to know the strengths and weakness of all the methodologies available. Starting with organometallic catalysis, which for many decades dominated the field of asymmetric catalytic synthesis, its main advantage relies on the possibility of using different transition metals, increasing ligand structure and subsequently maximizing yields and enantioselectivity. This can be done using very small amounts of catalysts (usually between 1 to 100 ppm), another significant benefit to this methodology.[65] The significant disadvantages are mostly related to the high cost of the metal, the fact that the majority of metal catalysts are very instable to oxygen and moisture in the atmosphere, and also with some problems associated with purification processes.[66] Another disadvantage is the low amount of metal contamination allowed in pharmaceutical products, which diminishes the potential use of this methodology in the pharmaceutical and biological industrys.[67]

In regards to biocatalysis, enzymes usually exhibit exceedingly high enantioselectivity values due to their complex protein structure. Like in the case of metal catalysts, only a very small amount of enzyme catalyst is used and, unlike metal catalysts, they obviously do not

present any toxicity issues. However, the presence of organic solvents, temperature and/or substrate concentration can inhibit or even denature the enzymes. Besides, it's usually very difficult to synthesize both target enantiomers with these biomolecules, since enzymes can only work within a very limited range of structures, due to their characteristic high specificity.[69]

With the benefits of organocatalysis – previously mention in section 1.1.1 – in mind and everything that was formerly said about the other two available methodologies of asymmetric synthesis, we can clearly see the advantages of organic molecules as catalysts. The weakness of organometallic catalysis and biocatalysis are the strengths of organocatalysis – operational simplicity, generally stable under aerobic conditions (i.e. stable when oxygen and moisture is present in the atmosphere), and are readily available with very low costs.[70] It is noteworthy that organocatalysis presents some similarities with the other two methodologies. Like for organometallic catalysis, in organocatalysis is relatively easy to obtain both enantiomers of a catalytic product.[71] In addition, similarly to enzyme catalysts, there are no toxicity problems with organocatalysts since they do not possess any metal in their structure. Moreover, there is no risk of metal leakage, and no expensive recovery process is required for waste treatment. To date the only disadvantage of organocatalysis is the amount of catalyst needed in the asymmetric reaction (usually between 1-20 mol%).[18]

Table **1.1** summarizes the strengths and weakness of each of the three methodologies available in asymmetric synthesis.[18]

Table 1.1 General summary of the advantages and disadvantages of the three asymmetric catalysis methodologies.[18]

Characteristic properties	**Organometallic catalysis**	**Enzymatic catalysis**	**Organocatalysis**
High catalytic activity	✓	✓	✓
Wide range of substrates	✓	×	✓
Structural simplicity	✓	×	✓ [a]
Obtain both enantiomers	✓	×	✓
Reduced costs	×	×	✓
Absence of toxicity.	×	✓	✓
Oxygen stability	×	✓	✓
Aqueous media stability	×	✓	✓
Thermic stability	✓	×	✓
Organic solvents stability	✓	×	✓
Reduced amounts of catalysts	✓	✓	×

[a] except for some rare exceptions of organocatalysts with complex structures.

Some critics suggest that low turnover numbers (TON), more specifically low turnover frequency (TOF), might limit the potential uses of organocatalysis for industrial applications, however this point of view is simplistic and dogmatic. From another perspective, cost and safety are the most salient considerations for any large-scale catalytic process. Since organocatalysts are often cheaper than transition metal-based catalyst, these catalysts can be used in larger quantities than metal-based ones for the same price and there is no impurities in the final product due to trace metal contamination. Moreover, in manufacturing it is widely recognized that the removal of toxic catalyst-related impurities from the waste stream can often have a larger financial impact than the turnover number of the catalyst. Organocatalysts are more easily removed from waste streams and can be tolerated to a large extend in waste streams.[18]

Organocatalyst were and still are being studied and develop for the use in potential industrial applications. One of the most promising applications is in medicinal chemistry, since chiral organocatalysts meet all the operational requirements for the manufacturing of therapeutic agents enriched in one particular enantiomer. [1]

1.1.4 Classification of Modern Organocatalysis

Perhaps most crucial to the success of organocatalysis during the last decades has been the invention or identification of generic modes of catalysts activation, induction and reactivity. A generic activation mode (or activation mechanism) describes a reactive species that can participate in many reaction types with consistently high enantioselectivity. Such reactive species arise from the interaction of a single chiral catalysts with a basic functional group in a highly organized and predictable manner.[18]

The discovery of these modes of activation for organocatalytic transformations basically allowed authors to create a general and universal classification of catalysts used in organocatalysis. The value of generic activation modes is that, after they have been established, it is relatively straightforward to use them as a platform for designing new enantioselective reactions.[73,74]

In order to better understand the field of organocatalysis, the main activation modes are very briefly summarized below and can crudely be divided into covalent and non-covalent catalysis, accordingly to the substrate activation.

1.1.4.1 Covalent catalysis

The first class of catalysts is the one whose substrate activation occurs trough the formation of a covalent bond between the organocatalyst and the substrate, therefore increasing the interaction between both of them during the reaction. Most of the organocatalytic reactions occurs trough this type of catalysis, which possess two main subcategories – amine catalysis and Lewis base catalysis (or nucleophilic catalysis) (Figure **1.1**).[9,73-75]

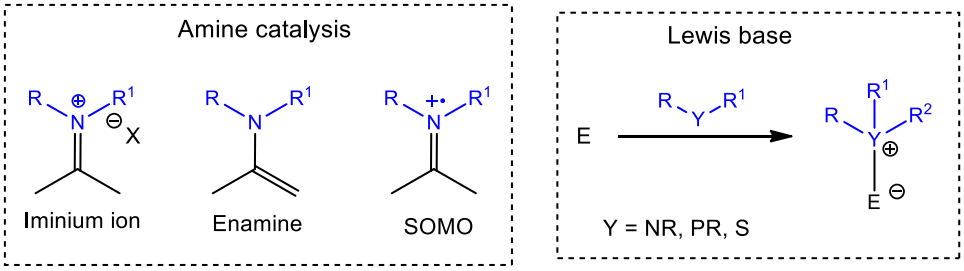


Figure 1.1 General activation mode observed in covalent catalysis and its subcategories (catalyst structure in blue).

Alkaloids, amino acids, peptides and nitrogen-based synthetic molecules are some of the examples of structures that usually belong to this class of organocatalysis, because they establish activation covalent bonds with the substrates.[9,73-75]

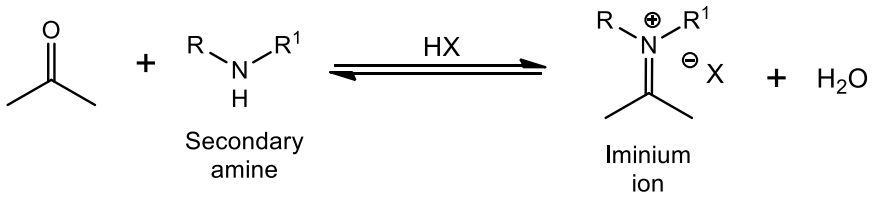
1.1.4.1.1 Amine catalysis

In the last few years, amine catalysis – catalysis mediated by nucleophilic amines – has stood as the center of attentions, being the target of researchers from around the world from a synthetic and mechanistic point of view.[75]

Taking into account all the knowledge obtained on this subject, amine catalysis earned its own particular classification. Initially there were only two known activation modes – enamine catalysis[17] and iminium catalysis[16] – which have become the pillars of organocatalysts activation. These two activation modes were expanded to include an extension of enamine catalysis (dienamine[76] and trienamine[77] catalysis) and a new, more

recent mode of activation – SOMO[78,79] (Singly Occupied Molecular Orbital) catalysis that is characterized by the formation of a cationic enamine radical.

These three modes of activation have distinct reactive intermediaries, however they are mechanistically intertwined, and have the reversible condensation between the amine function (primary or secondary) of the catalysts and the carbonyl of the substrate as a starting point, where an iminium ion is formed (Scheme **1.9**).[80]

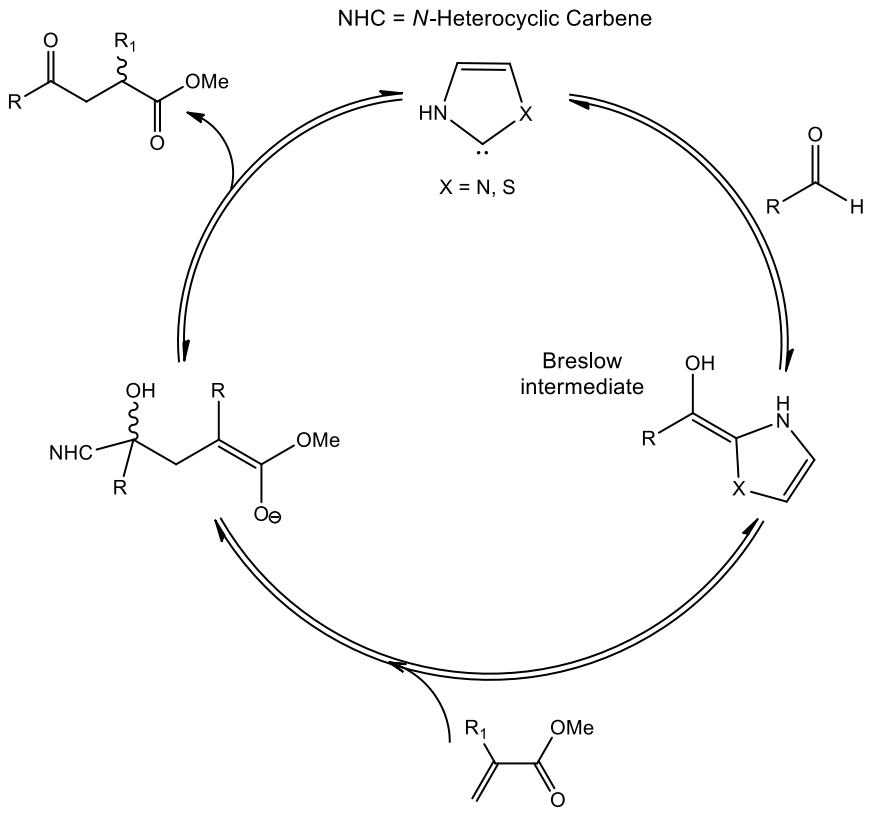


Scheme 1.9 General formation of iminium ion though reversible condensation between a secondary amine and a ketone.

The reaction will occur according to enamine catalysis, iminium catalysis or SOMO activation of the substrate depending on the nature of the carbonyl compound (saturated or unsaturated) and the surrounding reaction system.

1.1.4.1.2 Lewis base catalysis

The other class of organocatalysis that revolves around the formation of a covalent bond for substrate activation is Lewis base catalysis (or nucleophilic catalysis). Generally, the catalysts that are included in this class present the common characteristic of possessing an atom with severe nucleophilic character in their structure, such as nitrogen, phosphorus and sulfur atoms or even a carbon that covalently bonds to the respective substrate.[5] There are several examples of nucleophilic heteroatoms in the literature, but perhaps one of the most interesting is the carbene functionalized organocatalysts, since they are based on enzymatic models. *N*-Heterocyclic carbenes (NHCs) bring an additional level of diversity to nucleophilic organocatalysis on account of their structural resemblance and reactivity similarities to the coenzyme thiamine (vitamin B_1).[151] Reactions mediated by NHCs are characterized by the presence of an acyl anion intermediate equivalent, more commonly known as the Breslow intermediate (Scheme **1.10**).[82]



Scheme 1.10 General organocatalytic cycle of a carbene reagent in nucleophilic catalysis.

There are several reported examples of applications of this type of catalyst[83], from which we highlight the asymmetric Stetter reaction, that can be used to synthesize amino acid derivatives.[84]

1.1.4.2 Non-covalent catalysis

The second class of catalyst are the ones whose activation mode occurs trough non-covalent (weak) bonds between the catalyst and substrate and can by divided into hydrogen bonding catalysis, phase transfer catalysis and Brønsted acids or bases (Figure **1.2**).[9,73,74]

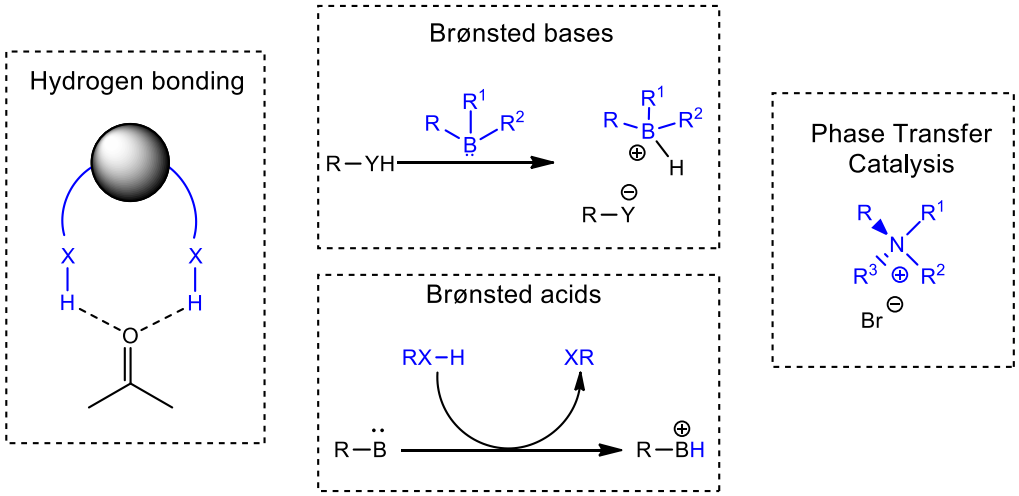


Figure 1.2 General activation mode observed in non-covalent catalysis and its subcategories (catalyst structure in blue).

1.1.4.2.1 Hydrogen bonding catalysis

Hydrogen bonds are responsible for many of the structures that surround us. Besides there key role in several life depending structures, hydrogen bonds play a crucial role in asymmetric catalysis. The activation mode observed in this type of catalysts is based on an electronic density decrease of the electrophiles, due to the interaction between the organocatalysts hydrogen bonds with this species that activates the organocatalysts allowing a nucleophilic attack. In this case, the reaction enantioselectivity is due to the immensely organized and weak non-covalent interactions between the nucleophile, catalyst and electrophile.[85]

This type of organocatalyst is very frequently used, being applied in several catalytic applications, such as for example Pictet-Spengler, Mannich, Strecker and Biginelli asymmetric reactions and asymmetric reductive aminations.[86]

1.1.4.2.2 Brønsted-Lowry acids and bases

Brønsted acids and bases are an exceptionally important group of organocatalysts in the non-covalent catalysis class, due to their many catalytic applications as well as to the exceptional results obtained in asymmetric synthesis.

In the reactions with Brønsted bases, the nucleophile is formed *in situ* by deprotonation of its precursor and the reaction enantioselectivity is due mainly to the ionic interaction between the catalyst and the substrate. The catalysts belonging to this class usually possess nitrogen-containing functional groups, such as tertiary amines, guanidine or imidazole. Cinchona alkaloids are probably some of the most important catalysts belonging to this subclass.[88] In the literature there are numerous examples of applications of this subclass of catalysts, from which we can highlight the (aza)Henry, Mannich and (hetero)Michael reactions as well as kinetic resolution systems[89] and some enantioselective rearrangements such as Komblum-DeLaMare rearrangements.[90]

In this subclass of catalysts we also have Brønsted acids, whose activation, similar to catalysis with Brønsted bases, occurs due to the strong ionic interaction resulting from substrate (of basic character) protonation by the organocatalysts and formation of a tight ion-pair. Once again, this ionic interaction is essential for the enantioselectivity of this organocatalyst subclass.[87]

1.1.4.2.3 Phase transfer catalysis

The last discussed type of non-covalent catalysis is phase transfer catalysis, in which chiral organic salts are used for the enantioselective preparation of organic compounds. Generally speaking, the activation mode of this type of catalysts is based on ionic pair interactions between the nucleophilic anion and the positively charged catalysts, usually a quaternary ammonium salt.[91,92] The general mechanism of phase transfer catalysis (Figure **1.3**) starts with the exchange of the catalyst counter-anion with the nucleophile (cyanide ion in the example below) in the aqueous phase. After this exchange, the nucleophile is transferred to the organic phase, as part of a tight ion-pair with the organocatalyst, which then reacts in the presence of the electrophile.[93]

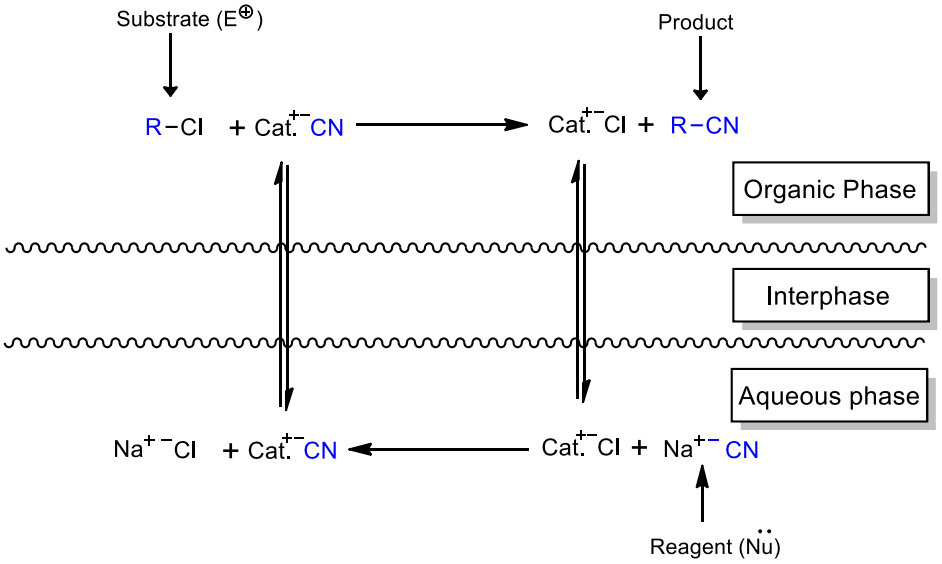


Figure 1.3 Illustration of the general mechanism of a phase transfer catalysis.

In phase transfer catalysis, the product enantioselectivity is the result of a stereochemical control of the chiral catalysts though electrostatic interactions between the catalyst and substrate, hydrogen bonds or in some cases π-π interactions.[93]

The number of phase transfer catalysts has increased exponentially during the last decades, allowing the study and development of several asymmetric catalytic reactions, such as aldol reactions, epoxidations, redox reactions, asymmetric alkylation, Michael, Strecker and Mannich reactions.[93-97]

1.1.5 Privileged Catalysts

Some catalysts may have the extraordinary capacity to mediate efficiently not only one but rather a variety of seemingly unrelated chemical transformations – these are called privileged catalysts. The term “privileged” chiral catalyst was coined in analogy to pharmaceutical compound classes that are active against a number of different biological targets.[98] This adjective was conceived to describe some catalyst classes due to their unique and highly versatile structure that allows them to be used in several asymmetric applications.

To date, there is a steadily growing number of such organic compounds, of natural or synthetic nature, that possess this incredible chemical property. The list of organocatalysts belonging to this category is too extensive to be referenced here in its totality. However,

there are some families of this type of structures that deserve to at least be mentioned here. The most regularly used organocatalysts are derivatives of L-proline **10**, BINOL **14**, TADDOL **15**, carbohydrates **16** and cinchona alkaloids **5** (Figure **1.4**).[9,99] Each family has a different historical past and, most importantly, different chemical properties. However, due to the nature of the work developed in this dissertation, we will only discuss cinchona alkaloids.

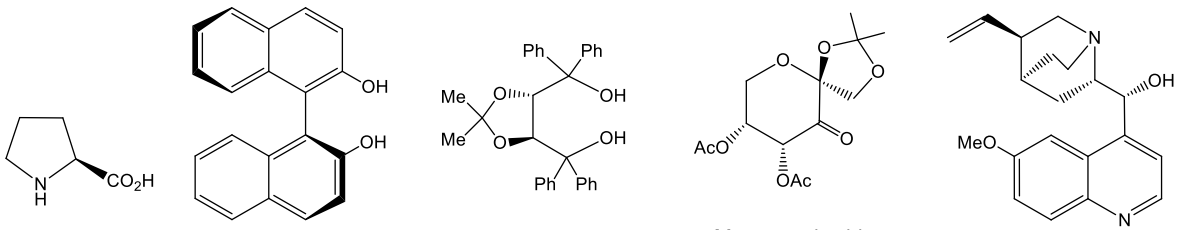


Figure 1.4 Examples of carbonated chiral skeletons with privileged catalysts that are used in asymmetric catalysis.

1.1.5.1 Cinchona alkaloids

Cinchona alkaloids are well-known natural products with a fascinating medicinal history and an intriguing molecular structure that is responsible for their use in chemistry.[98] The readily available and inexpensive cinchona alkaloids are obtained from the bark extract of the *Cinchona* tree, belonging to the *Rubiáces* family which are native to South America. Currently, they are extracted mainly from the bark of *Cinchona ledgeriana* and consist of about 30 alkaloids in total, from which quinine, quinidine, cinchonidine and cinchonine represent 50% of these extracted alkaloids.[100]

About 50 years ago, interest in these alkaloids arose from a catalytic perspective, and consequently these molecules have been historical connected with organic and pharmaceutical chemistry, being very important to the welfare of humanity.[101] Their history goes back to the XVIIth century when the *Cinchona* bark was used for medicinal purposes in Europe – after the discovery of its anti-malaria properties circa 1640. At the time South American natives already used the Cinchona barks to treat fevers demonstrating their antipyretic properties. As a curiosity, the term “cinchona” was implemented in 1742 by the Swedish botanist Linnaeus, after the bark was allegedly used to cure Countess Cinchon, the Spanish vice-king of Peru’s wife, from malaria.[102]

Due to its very important medicinal properties, attentions then turned to the discovery and isolation of the cinchona alkaloids. The first contribution to the isolation of these natural compounds came from the Portuguese naval doctor Bernardino António Gomes in 1811, after he performed a then very sophisticated recrystallization of the aldol extract of *Cinchona* bark. Gomes added water and a small amount of potassium hydroxide to the extract observing the formation of crude organic product crystals, which he called "cinchonine".[102] However, Pelletier and Caventou in 1820 showed that the isolated cinchonine by Gomes was in fact a mixture of two alkaloids, which they later called quinine and cinchonine.[103,104] A few years later the remaining two alkaloids were isolated – Delondre and Henry[105,106] isolated quinidine in 1833 and Winckler[107] isolated cinchonidine (whose name was given by Pasteur in 1851) in 1847.

700 tons of cinchona alkaloids are obtained annually due to their several applications and their industrial importance. For example, 40% of the extracted quinine is used in the pharmaceutical industry, and the remaining 60% is used in the food industry manly as bitter aromatic agents in tonic and other soft drinks.[108] Quinidine is already used in the medicinal industry as an antiarrhythmic drug and cinchonidine is used in the racemic resolution of naproxeno.[109]

Interest in the field of asymmetric catalysis with cinchona alkaloids has increased tremendously in the last two decades as part of the sudden explosion of interest in organocatalysis. Preceding the present interest in cinchona alkaloids, their use in asymmetric synthesis has been extensively reviewed and compiled by several authors, such as Pracejus[110] in 1967, Morrison and Mosher[111] in 1971, Wynberg[112] in 1986, Kacprazak e Gowroński[113] in 2001, Kaufman e Rúveda[102] in 2005, Marcelli and Hiemstra[54] in 2010, Xi and Shi[114] in 2013 and most recently Zheng and Shienebeck[115] in 2014, as well as Song's book[100] in 2009 and many others.[9,116-118] Briefly, the earliest examples of the use of cinchona alkaloids in catalysis are the addition of HCN to benzaldehyde as reported by Bredig and Fiske[36] in 1912 (Scheme **1.2**), the work of Pracejus[37,38] in 1960 on the addition of methanol to phenyl methyl ketene (Scheme **1.3**) and the pioneering work by Wynberg and coworkers[112], who showed that cinchona alkaloids can serve as catalysts for various enantioselective reactions. Until the late 1990s, cinchona alkaloids and its derivatives were mainly applied in phase transfer catalysis.[119-121,154] Succeeding these early studies, numerous reports have appeared concerning organocatalysis with cinchona alkaloids and synthetically prepared derivatives thereof.

So what makes Cinchona alkaloids effective and attractive as catalysts? They fulfill all the requirements usually associated with privileged catalysts – they are commercially available compounds, of low cost due to high production, are stable and recoverable compounds, as well as of robust and versatile structure which allows them to be easily modified for diverse catalytic applications. This makes cinchona alkaloids a target of interests from the scientific community.[113]

In terms of asymmetric catalysis, the cinchona alkaloid family consists of two pairs of diastereomers – cinchonine (**CN**)/ cinchonidine (**CD**) and quinine (**QN**)/ quinidine (**QD**) (Figure **1.5**).[113] Their unusual and rich structure is the key that makes these four alkaloids of extreme importance in several areas, particularly in (organo)catalysis.

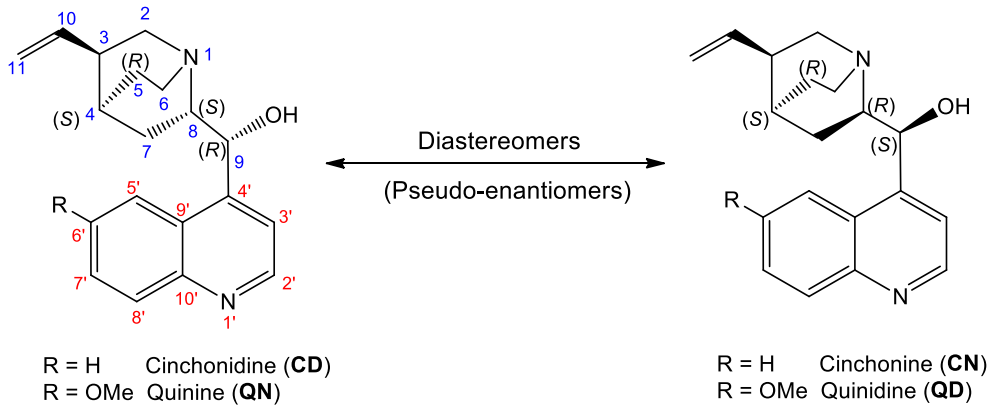


Figure 1.5 Chemical structure of the two diastereomeric pairs of Cinchona alkaloids and their respective chiral center absolute configuration.

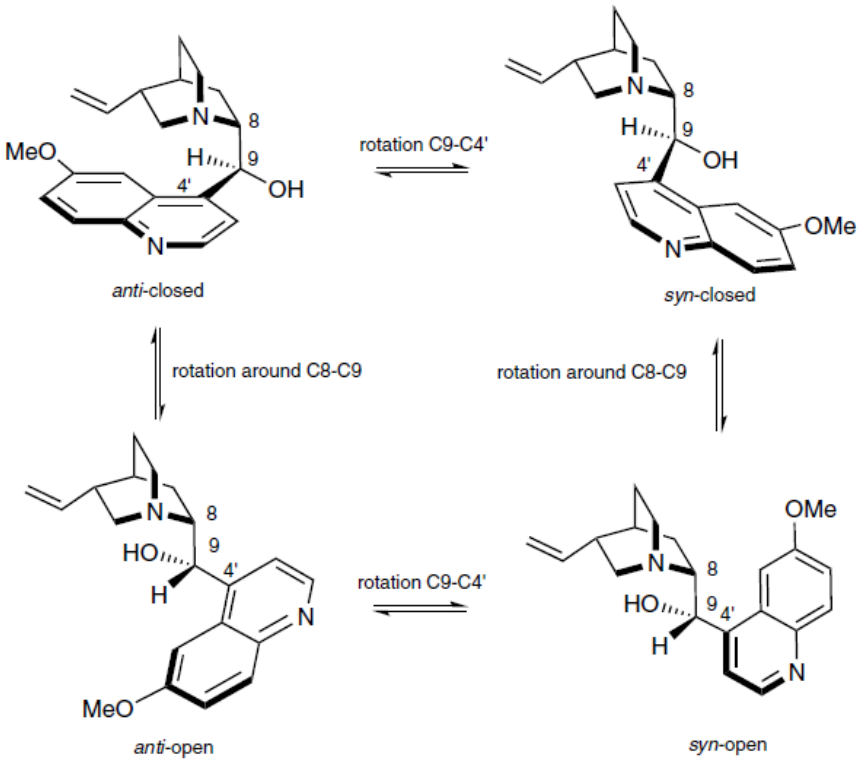
The elucidation of the complete structure of these alkaloids was not an easy one, having taken longer than 50 years to conclude. The atomic numbering that is currently used in cinchona alkaloids was initially proposed by Rabe in 1907 – a German chemists that dedicated more than 40 years of his life to the study of quinine.[122,123] However, only in 1944 did this stereochemical assignment, as it is currently known, was completed by Prelog and Zalan.[124,125]

The natural cinchona alkaloids possess several functional groups that can be divided in four different parts – the quinuclidine moiety (a bicyclic tertiary amine), a quinoline part (aromatic ring), a secondary alcohol (or a β-hydroxylamine subunit) and a vinyl or ethyl group connected to the quinuclidine unit.

Both diastereomeric pairs have five stereogenic centers in their structure, four of them chiral carbons (C3, C4, C8 and C9) and one chiral nitrogen of quinuclidine (N1).[54,98] The absolute configuration in N1, C3 and C4 is the same in all cinchona alkaloids, with the absolute configuration only differing in C8 and C9.[126] When employed in asymmetric catalytic reactions, each pair of these catalysts is responsible for the enantioselective product with the opposite absolute configuration (i.e. quinine and cinchonidine are (-) and thereby induce selectivity for one enantiomer, while quinidine and cinchonidine are (+) and afford the other enantiomer), acting as enantiomeric pairs. Thus despite **CD**/**CN** and **QD**/**QN** being chemically diastereomers (i.e. there not mirror image of each other and not superimposable), they act as enantiomers with asymmetric catalytic power, known as pseudo-enantiomers. In other words, if **CD**/**CN** and **QD**/**QN** didn't possess the vinyl group connected to the quinuclidine unit, they would be enantiomers.[54,98,113,127,128]

Because of the presence of the secondary alcohol (Lewis acid site) and the nitrogen in the quinuclidine unit (Brønsted base site), cinchona alkaloids and their derivatives are bifunctional catalysts. Cinchona alkaloids are mechanistically characterized as Brønsted bases when the nitrogen moiety partially or fully activates a proton, resulting in the chiral intermediate species with facial selectivity in asymmetric catalysis.[129]

Cinchona alkaloids can adopt different conformations due to the rotations about the C4'-C9 and C9-C8 bonds. Through both NMR spectroscopy and computational techniques, four low-energy conformers called *anti*-closed, *syn*-closed, *anti*-open and *syn*-open were identified (Scheme **1.11**). This denomination comes from the fact that in the "open" conformers, the quinuclidine nitrogen is distant from the quinoline, being "exposed", while in "closed" conformers the same nitrogen is aligned with the quinoline, "blocking" it. The *syn* and *anti* is related to the position of the hydroxyl in relation to C6' hydrogen: *syn* when both are on the same side and *anti* when they are on opposite sides.[126, 130-134]



Scheme 1.11 The four principal conformers of quinidine.[126]

According to molecular modeling (MM) calculations, quinine and quinidine preferentially adopt the *syn*-closed conformation in the gas phase. However, in apolar solvents the *anti*-open conformation is preferred, whereas polar solvents favor the two closed conformers, *syn*-closed and *anti*-closed. In addition, protonation of the quinuclidine nitrogen atom is reported to hinder rotation about C4'-C9 and C8-C9 bonds. In the case of cinchonidine, NMR studies and MM calculations showed that *anti*-open conformation is preferred when protonated. This shows that many factors (such as nature of solvent, intermolecular interactions, protonation) can influence the complex conformational behavior of cinchona alkaloids in solution.[135,136]

One should note that substituents at C9 play a key role in determining the conformation of cinchona alkaloids. For example, esters are present in the *anti*-closed form in solution, while C9 methyl ethers prefer *anti*-open conformation.[137]

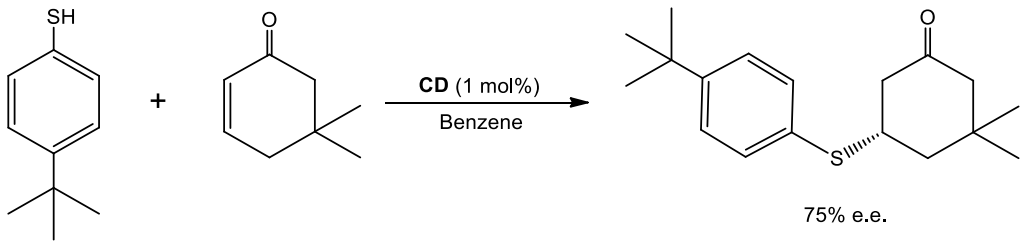
As previously mentioned, cinchona alkaloids have a versatile structure that allows simple and selective derivations in different key places of these molecules. These derivations allow maximization of the catalytic activity for several asymmetric applications.

There is “no limits” to the possible derivations that can be carried out on cinchona alkaloids, however most derivatizations are in the C9 secondary alcohol position, the quinuclidine nitrogen and the quinoline methoxyl (in the case of quinine and quinidine).[113] The most common derivations that can be done with these catalyst are the following. In the case of the secondary alcohol in C9 (which in its native form acts as weak acid as well as hydrogen bond donor), this can be easily derived or substituted by other groups, creating new functional groups such as amides, thioureas, ethers, esters, free or substituted amines, guanidine, amongst many others. Many of these transformations lead to a configuration inversion of C9, forming what it is known as *epi*-alkaloids. The quinuclidine nitrogen also has a very important role because it can be easily alkylated forming quaternary ammonium salts, widely used in phase transfer catalysis. In the case of quinidine and quinine, the methoxyl group present in the quinoline unit can be, for example, substituted by a hydroxyl group or even an amine, which can be further derivatized.[99]

Lastly, but definitely not least, the vinyl group connected to the quinuclidine allows the catalyst to be immobilized on different solid supports. This transformation allows the catalyst’s recovery and recycle after a catalytic reaction, granting economic advantages, especially on an industrial scale.[138]

Due to the work developed during this dissertation, from the several functionalization that can be done in the alkaloids we have special interests in the pyridinecarboxamides derived cinchona alkaloids (i.e. substitution of C9 alcohol by a picolinamide group) and will discuss it in more detail in section 1.1.5.1.1.

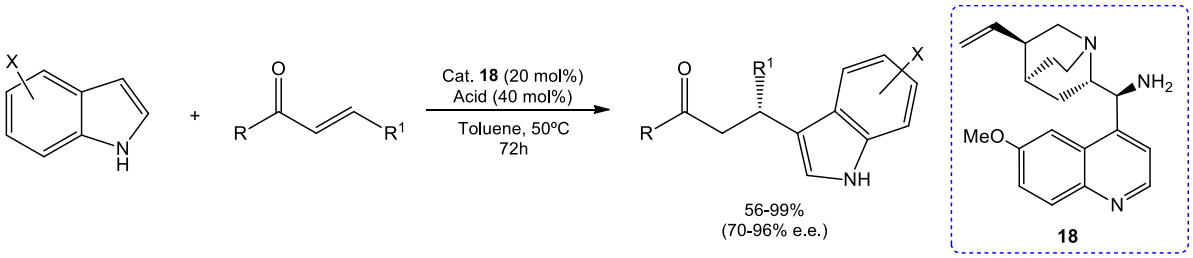
Cinchona alkaloids have successfully and efficiently been employed in a number of chemical and medicinal applications. One of the most important applications is perhaps their use in organocatalytic asymmetric transformations. As previously mentioned, the use of cinchona alkaloids in asymmetric synthesis is not something new (dating back to the 1900s), however, only recently some very good results have been reported. Wynberd and collaborators – who used these natural compounds as nucleophilic catalysts – demonstrated that cinchona alkaloids are very versatile and can be applied in a wide range of reactions. In 1981, Wynberg and Hiemstra[139] reported that cinchonidine (**CD**) is a very good catalyst in the conjugated addition of aromatic thiols to α,β-unsaturated cyclohexanones (Scheme **1.12**), while somewhat lower e.e.’s were obtained with quinine and quinidine.



Scheme 1.12 Asymmetric conjugated addition using cinchonidine as catalyst reported by Wynberg and Hiemstra.[139]

Later, Wynberg reported the synthesis of β-lactones (intermediaries in malic acid synthesis), using quinine as organocatalyst. The reaction between ketenes and chloral afforded the desired products with an impressive enantioselectivity of 98% and with equally good yields.[140]

Another very important development in the use of cinchona alkaloids appeared in 1995 when Brunner[141] reported the synthesis of 9-amino-(9-desoxy)-*epi*-cinchona derivatives. After the turn of the millennium, in 2007, the enantioselective catalytic potential of these molecules were revealed when Cheng and Deng[142] reported their use in Michael additions and when Melchiorre[143] used them in Friedel-Crafts alkylation reactions (Scheme **1.13**), both with very good yields and enantioselectivities.

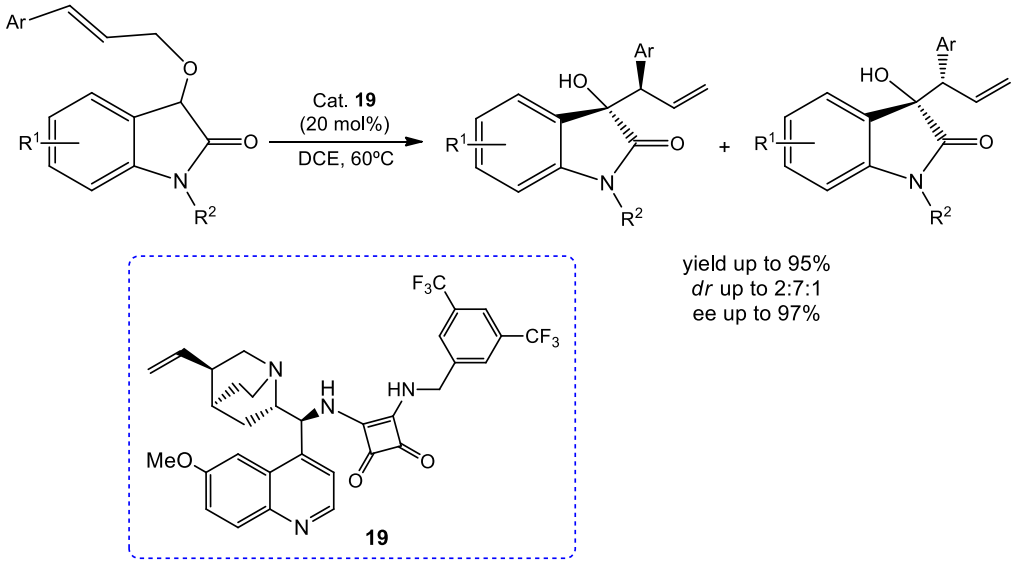


Scheme 1.13 Friedel-Crafts alkylation reported by Melchiorre.[143]

During the next few years the cinchona alkaloid derivatives were used in numerous catalytic reactions, such as rearrangements, epoxidations, Diels-Alder, substitution and aza-Michael reactions.[144-153]

The dawn of the "golden age"[155] of organocatalysis led to the development of this field as a whole and brought with it innovation, creativity and enthusiasm for the study and development of new classes of relatively simple, low cost, effective and versatile cinchona

alkaloids, in order to obtain enantiomerically pure products as well as develop new catalytic reactions (Scheme **1.14**).[157-170]

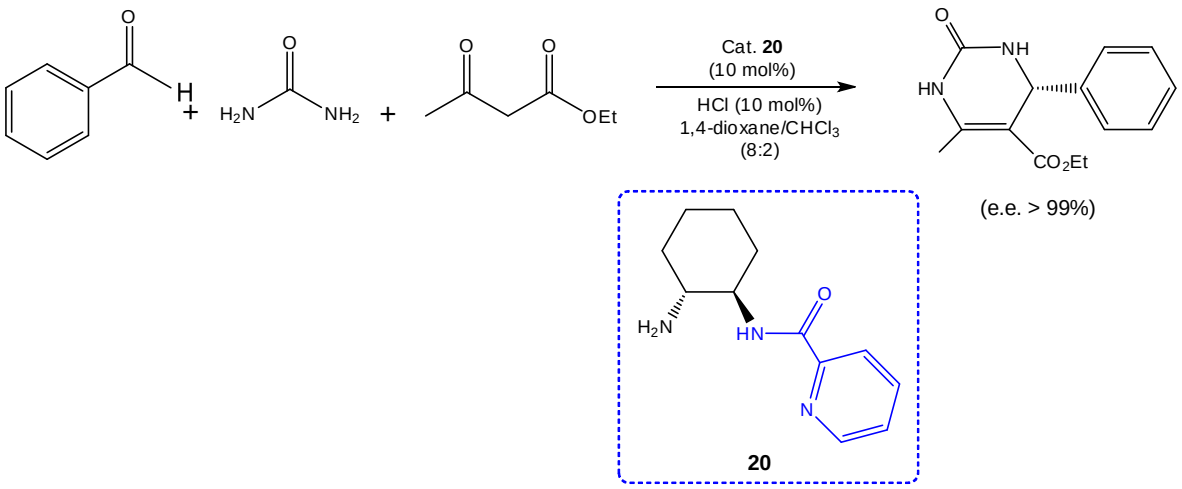


Scheme 1.14 Asymmetric organocatalytic Wittig [2,3]-rearrangement of oxindole catalyzed by a squaramide derived cinchona alkaloid reported by Ošeka[165] in 2016.

Inevitably the industry became interested in organocatalysts (which will be briefly discussed in section 1.1.6).

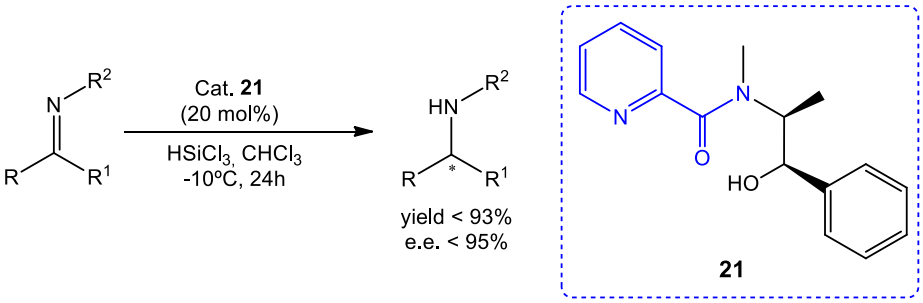
1.1.5.1.1 Pyridinecarboxamides derived cinchona alkaloids

In the past decade, picolinamides – amides derived from commercially available picolinic acid – have been successfully incorporated as functional subunits in several carbon skeletons of organocatalysts. These new type of skeletons have demonstrated some very good and promising results, regarding asymmetric organocatalysis. One example is the work reported by Wang[171] in 2012. They reported an asymmetric Biginelli reaction with good yields and excellent enantioselectivity, using the bifunctional organocatalyst **20** composed of a primary amine and a picolinamide subunit (Scheme **1.15**).



Scheme 1.15 Enantioselective Bignelli reaction catalyzed by an organocatalysts containing a picolinamide subunit (represented in blue) reported by Wang.[171]

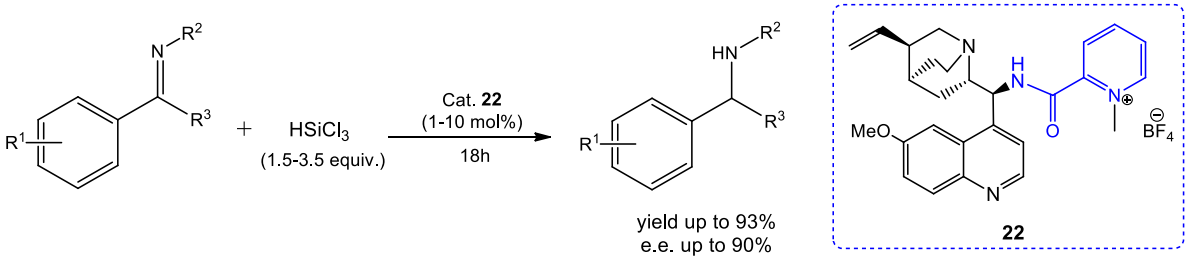
Another example is the work performed by Zhang[172] in 2007 on the development and application of chiral *N*-picolino amino alcohols in ketimine reduction using trichlorosilane as a reducing agent (Scheme **1.16**).



Scheme 1.16 General representation of Zhang's work in the asymmetric reduction of ketimines.[172]

The incorporation of picolinic acid in a chiral compound led, once again, to very good results. There are many other examples in the literature such as that reported by Matsumura[173], Benaglia[174-176] and Jones.[177]

Inspired by these very good results, Barrulas and Burke[178] developed a new class of cinchona alkaloids – cinchona-derived picolinamides[179]. This new class of organocatalysts was then applied in the stereoselective hydrosilylation of imines (Scheme **1.17**), affording very good yields and enantioselectivities.[180]



Scheme 1.17 Enantioselective reduction of ketimines using a cinchona-derived picolinamide as organocatalyst reported by Barrulas.[180]

Motivated by these very good results, we decided to apply these picolinamides derived from cinchona alkaloids in the stereoselective reduction of ketimines, more specifically ketimines intermediates of Rivastigmine and other biologically active compounds (this topic will be discussed in section 1.2). To the best of our knowledge there are no further reports of the use of cinchona-derived picolinamides in any other synthetic applications.

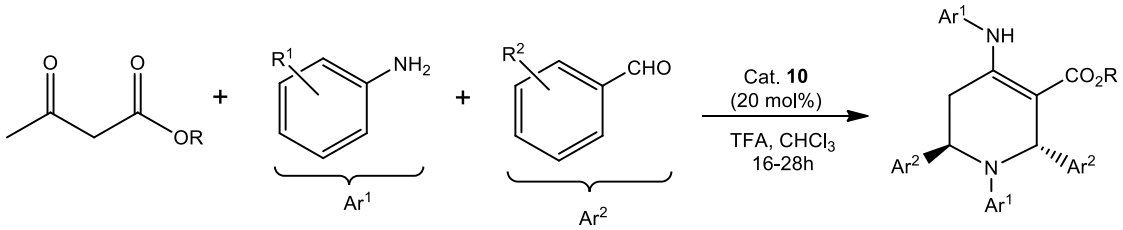
1.1.6 Industrial and Medicinal Chemistry Applications of Organocatalysis

Due to the establishment of organocatalysis as an effective field of research, this area has aroused a lot of attention from the pharmaceutical industry. However, the expansion and development of catalytic process that can be applied at the industrial scale is an arduous one, because industries focus mainly on profit generation.

In the last few years, pharmaceutical interest in organocatalysis has increased mainly due to its, previously referred, benefits over organometallic catalysis and the very expensive biocatalysis. The scale-up of organocatalysis has some inherent problems, such as catalyst loading for the process, product inhibition, substrate range and catalysts efficiency for specify reactions.[65] The chemical and pharmaceutical industry as well as academia has been working on surpassing these obstacles and are currently taking steps towards establishing organocatalysis as an effective alternative to current methodologies on the industrial scale.

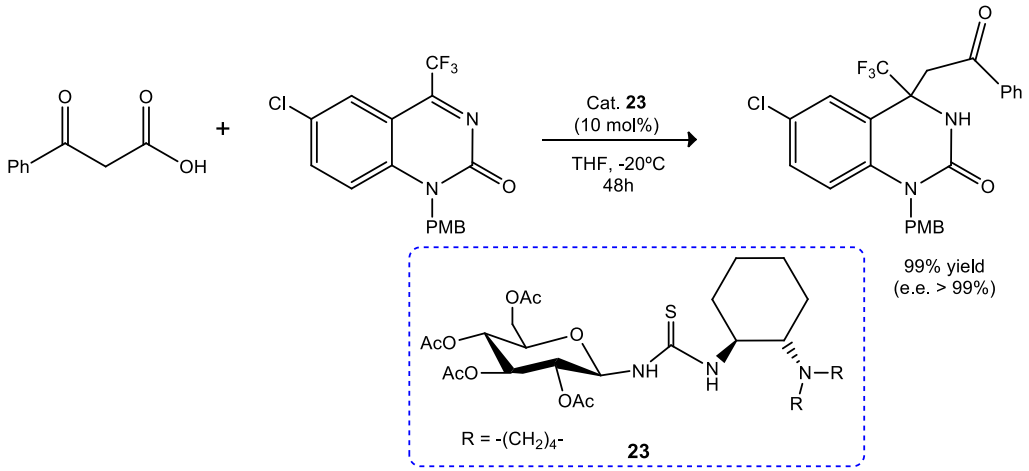
In order to highlight the role of organocatalysis in industrial applications we will present some key examples available in the literature. One example is the use of an organocatalyst in the synthesis of antimalarial agents. Currently, only a small number of safe drugs for the treatment of malaria exists, one of them being tetrahydropyridine (THP). A small library of these TPH was recently synthesized in a one-pot reaction using L-proline/TFA as

organocatalyst and with low cost starting materials (Scheme **1.18**). Preliminary *in vitro* studies showed very promising results for the antimalarial activity of these compounds.[181]



Scheme 1.18 Tetrahydropyridines synthesized and tested as possible antimalarial agents in 2009 by Tripathi and coworkers.[181]

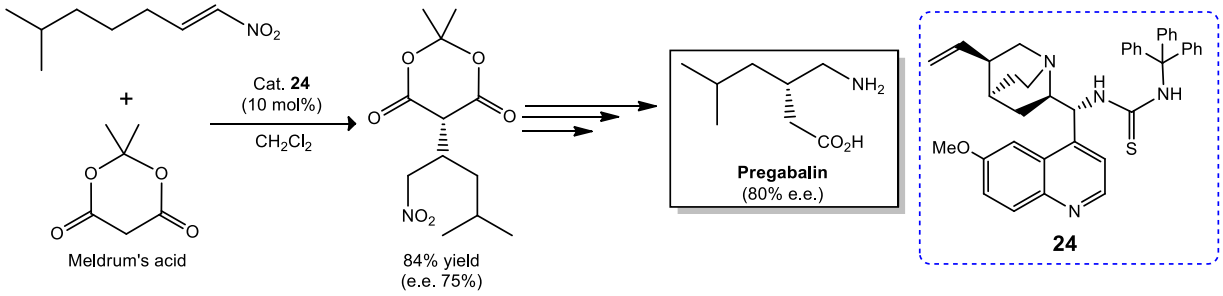
Another example is the synthesis of compounds with anti-HIV activity using organocatalysts. There are several studies on this subject but we would like to point out the one performed by Ma and his team[182] in 2013. They developed a decarboxylative asymmetric Mannich reaction between β-keto acids and ketimines using a monosaccharide-derived amino thiourea **23** as organocatalyst (Scheme **1.19**). There were able to obtain the desired product with an astounding 99% yield and enantioselectivity of 99%. This study revealed to be a new and efficient pathway to asymmetrically synthesize the anti-HIV drug, DPC 083.[182]



Scheme 1.19 Synthesis of intermediates for the preparation of anti-HIV compounds by Ma.[182]

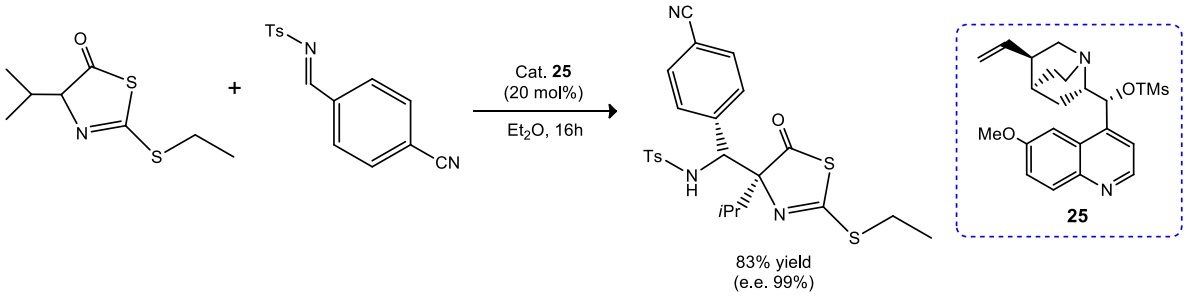
In 2009, Koskinen and his team[183] described a new enantioselective synthesis of an anti-convulsive and anti-epileptic drug – pregabalin, commercially sold by Pfizer as Lyrica® – used for the treatment of epilepsy and neuropathic pain. They used a quinidine derived

thiourea **24** in an asymmetric Michael addition of Meldrum's acid to a nitro-olefin – a key step in the synthesis of this drug – with good yield and an ee of 75 % (Scheme **1.20**).[183]



Scheme 1.20 Enantioselective synthesis of Pregabalin developed by Koskinen and his team.[183]

One last example is the work developed by Wang and collaborators[184] in 2011. Wang reported that cinchona alkaloid derivatives, more specifically derived from quinine, are extremely efficient catalysts when applied to asymmetric aza-Mannich additions of *N*-tosyl imines, with good yields and an e.e. of up to 99% (Scheme **1.21**). The products obtained by this reaction showed anti-cancer activities.[184]



Scheme 1.21 Wang's work developed in 2011 for anti-cancer applications.[184]

In the literature there are many other applications of organocatalysis for (at least in part of) the synthesis of compounds with medicinal interests. The use of organic catalysts in the total synthesis of some well-known drugs have been reported, such as Oseltamivir[185] (commercial sold by Roche as Tamiflu®), Paroxetine[186] (an antidepressant), Maraviroc[187] (an anti-viral), Blacofeno[188] (a muscular relaxant) and Warfarin[189] (an anticoagulant).

The results obtained in this dissertation work can also be considered another example of the application of organocatalysis in medicinal chemistry, since we have applied organocatalysts (more specifically picolinamides derived from cinchona alkaloids) in the

synthesis of Rivastigmine, a drug used for the treatment of Alzheimer's disease (see section 1.2).

1.2 Rivastigmine

1.2.1 General Aspects

Rivastigmine (Figure **1.6**) – (*S*)-*N*-ethyl-3-[1-(dimethyl-amino)ethyl]-*N*-methylphenyl carbamate – is a noncompetitive, reversible acetylcholinesterase (AChE) inhibitor used in the treatment of mild to moderate dementia associated with Alzheimer's disease (AD) and in some cases with Parkinson's disease (PD). It is referred to as a pseudo-irreversible inhibitor because it is considered a long duration reversible inhibitor.[190-192]

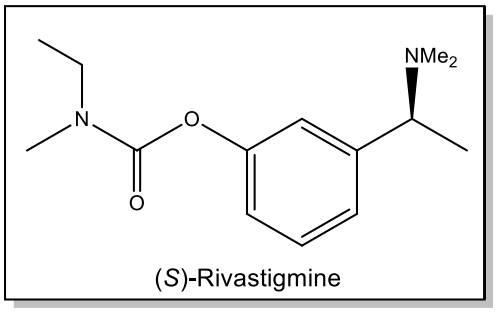


Figure 1.6 Chemical structure of (*S*)-Rivastigmine.

Alzheimer's disease is an irreversible, complex, neurodegenerative disorder characterized by progressive cognitive impairment, a variety of neuropsychiatric and behavioral disturbances and restrictions in daily life activities.[193] This is an age related disease and is the most common cause of dementia in the older population. It's very rapidly becoming a worldwide public health concern, affecting up to 10% of the population over the age of 65 and 30% or more of the population over the age of 80. In the developed world, AD is the fourth major cause of death, after cardiovascular disease, cancer and cerebral accidents. With the increase of life expectancy due to the advances of modern medicine, the number of AD patients is anticipated to increase drastically. Worldwide, there are approximately 35 million people suffering from AD, and that number is expected to grow to 107 million by 2050. [194-195] In Portugal is estimated that about 153 000 people suffer from

dementia, 90 000 of them suffering from AD. In other words, about 1% of the Portuguese population has AD.[196]

The etiology of AD is not yet known, however the neuropathological changes typically observed in the brain of AD patients is well documented. The postmortem brain examination of AD patients has shown that the loss of the basal forebrain cholinergic system is one of the most significant aspects of neurodegeneration in the AD suffering brains, and it is thought to play a central role in generating cognitive impairments.[194] Over the years, several therapeutic strategies were studied. Enhancement of cholinergic transmission – increase of cholinergic neurotransmission in relevant parts of the brain by the use of acetyl cholinesterase (AChE) inhibitors to delay the breakdown of acetylcholine (ACh) released into synaptic clefts – has been regarded as one of the most promising methods for treating AD patients. Clinical trials have shown that AChE inhibitors are among the best known therapeutic drugs for AD treatment.[197]

The discovery and development of Rivastigmine (ENA 713) arose from the search for a novel AChE inhibitor with enhanced clinical efficacy and improved pharmacokinetic and pharmacodynamic properties compared with earlier compounds. In 2006, Rivastigmine became the first U.S. FDA and the first worldwide approved drug for the treatment of mild to moderate dementia associated with AD.[198]

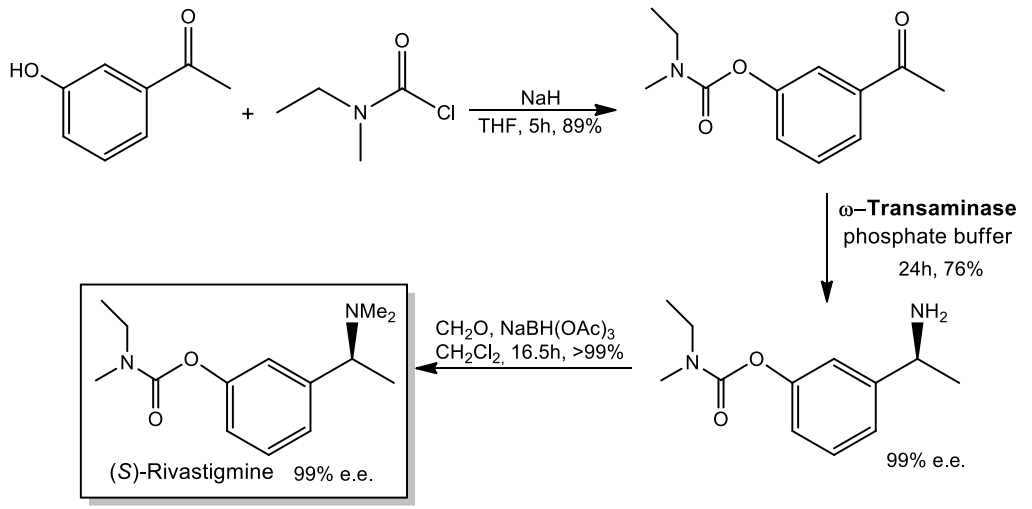
Rivastigmine belongs to the carbamate group of AChE inhibitors and has a distinct chemical structure relative to other AChE inhibitors. It's known as a dual inhibitor because it works by blocking AChE, the enzyme responsible for ACh degradation, and butylrylcholinesterase (BuChE), the enzyme responsible for the hydrolysis of ACh, thereby increasing both the level and duration of the neurotransmitter acetylcholine.[199]

In particular, Rivastigmine appears to have marked effects in patients showing a more aggressive course of the disease, such as those with early onset AD or those experiencing symptoms such as nausea and vomiting. The high potentiality of Rivastigmine against Alzheimer's disease deserves an appropriate position in the "Blockbuster Drug List".[190]

Rivastigmine is commercially sold as Exelon® by Novartis, Switzerland. To the best of our knowledge, the methodology used by Novartis for Exelon® synthesis is not publicly know. However, by a brief overview of the existing literature, we can see that there are a few and well cited synthetic methodologies available for the synthesis of Rivastigmine.[191-200] These methodologies address a wide range of chemical transformations, and to date, several asymmetric methods have been developed for the preparation of enantiopure Rivastigmine (e.g. racemate resolution using chiral acids[201-203], asymmetric addition of

organozinc species onto imines using transition metal catalysis,[204] diastereoselective reductive amination[205] or lipase-catalyzed (dynamic) kinetic resolution of a hydroxy-presursor[206-208]). Generally speaking, the only successful catalytic route to this class of compound is via asymmetric catalytic hydrogenation of ketimines (see 1.2.2.1).

An asymmetric total synthesis of Rivastigmine was recently reported, and it entailed the formation of the chiral amine moiety via enzymatic reductive-amination of the corresponding ketone precursor employing ω-transaminases[209] (Scheme **1.22**). Very good results in terms of yield and enantioselectivity were attained. However, some problems were observed, namely the reaction equilibrium, which was displaced more on the alanine/ketone side.[210] There are other examples of chemeoenzymatic synthesis of Rivastigmine, for example using alcohol dehydrogenase from baker's yeast[211] or ketoreductase[212].



Scheme 1.22 Chemeoenzymatic asymmetric synthesis of (S)-Rivastigmine reported by Fuchs and his team.[209]

The use of organocatalysts in Rivastigmine synthesis hasn't been much explored. To the best of our knowledge, there is only one publication on the use of organocatalysts in the synthesis of this compound, namely Cinchona-derived quaternary ammonium salts for stereoselective imine reductions.[213] Some very good, preliminary and promising results on Rivastigmine synthesis were obtained. This study was performed in collaboration with the Benaglia group, at the Università Degli Studi di Milano, Italy, and our group at Universidade de Évora.

1.2.2 Target Reaction

1.2.2.1 Reduction of ketimines

Chiral amines are an important class of structural motifs found in a vast array of natural products and biologically active compounds, and it is thus imperative to develop synthetic methods for the construction of stereogenic centers bearing nitrogen.[214] The asymmetric reduction of the C=N bond is one of the most straightforward approaches to afford chiral amines. There is a wide range of methods for the reduction of imines and carbonyl compounds to chiral amines or alcohols, from asymmetric hydrogenation to asymmetric hydrosilylation to transfer hydrogenation, using transition metals, enzymes or purely organic catalysts.[215-217]

The asymmetric hydrogenation of unsaturated organic compounds is currently becoming a standard procedure in both academic laboratories and industrial applications. Until recently, all the methods developed for the reduction of organic compounds have been dominated by the use of metal catalysts coordinated with specific stereodiscriminating chiral ligands, however recently this changed due to the discovery that simple small organic molecules are able to catalyze chemeoselective reductions.[218] The enantioselective reduction of imines to obtain chiral amines still represents a challenge. Although many highly enantioselective hydrogenations of ketones and alkenes are known, only less effective reductions of imines are available. The development of efficient catalysts giving high enantioselectivity has proved to be much more difficult in the case of imines, compared with alkenes and ketones.[1]

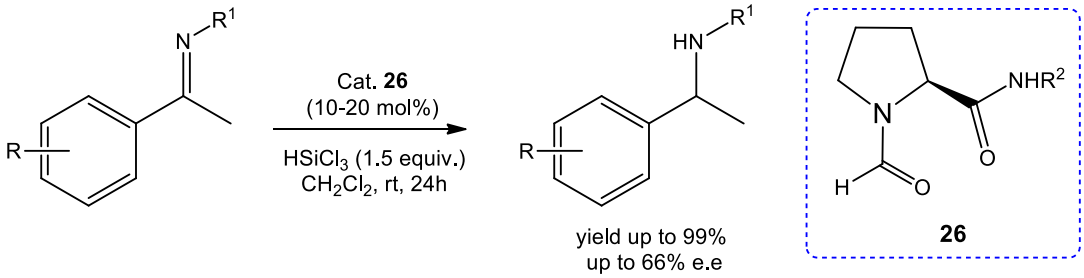
The name hydrosilylation (or hydrosilation) refers to the reaction of addition of organic and inorganic silicon hydrides to π bonds, in particular carbon-carbon and carbon-heteroatom (i.e. carbon-oxygen and carbon-nitrogen) double bonds. The first example of hydrosilylation dates back to 69 years ago, when in 1947 Leo Sommer reported the reaction occurring between trichlorosilane and 1-octene in the presence of acetyl peroxide.[219]

Until a decade ago, while the hydrosilylation of ketones was well established, ketimines were scarcely recognized by researchers, with only a limited portfolio of acceptably efficient protocols reported at the time.[220] In the last few years, the development of new catalysts for the asymmetric catalytic reduction of chiral ketimines became the main objective for researchers all around the world, due to the well-established importance of chiral amines in the pharmaceutical industry.[221]

A variety of reducing reagents have been used for ketimine asymmetric reduction but it is still worthwhile to exploit new methods, which can be carried out using inexpensive reducing reagents under mild conditions. Compared with the chiral Brønsted acid catalyzed asymmetric transfer hydrogenation, in which the electrophile substrate (C=N bond) was activated by Brønsted acid via formation of an ion pair or hydrogen bond, Lewis base catalyzed hydrosilylation of C=N bond proceeds through a coordination of the Lewis base with a silane, which could form a more reactive hypervalent silane complex.[1] Silanes are very attractive reagents since they are relatively cheap, non-toxic and are considered non-metal compounds and thus have received considerable attention from organic chemists.[225]

Trichlorosilane ($HSiCl_3$) is a colorless liquid, readily available material primarily manufactured and used in the organosilicon industry. This reagent accounts for 75% of the world's production of polycrystalline silicon through the Siemens process, in which high purity silicon rods are exposed to trichlorosilane at elevated temperatures, leading to decomposition of the trichlorosilane and additional silicon to be deposited onto the rods.[222] Thrichlorosilane needs to be activated by coordination with a Lewis base to generate hexacordinated hydridosilicate, believed to be the reducing agent that operates under mild conditions. The use of chiral Lewis bases[223] offers the potential to control the absolute stereochemistry of the process, and this has been widely explored in the last decade, leading to the development of some very efficient catalysts, such as chiral tertiary amines, sulfonamides, amino alcohols, imidazole derivatives, picolinamides and *N*-formamides.[224] Trichlorosilane has already been employed on large scales for transforming phosphane oxides into phosphines and *N*-acyliminium ions into *N*-acylamines. Although the methodology may present some problems with regards to, for example, the generation of some quantities of halogen waste, it undeniably deserves consideration as a viable tool for the synthesis of chiral secondary amines.[226]

The organocatalytic reduction of ketimines is a relatively recent field of research. The first reported example of asymmetric reduction of ketimine using a chiral Lewis base and trichlorosilane as the hydride was by Matsumura[227] in 2001. The proline-derived chiral formamide **26** facilitated the reduction of a variety of *N*-phenyl and benzyl protected aryl methyl ketimines with excellent yield and moderate enantioselectivity of up to 66% (Scheme **1.23**). Although only moderate enantioselectivities were obtained for the chiral amine products, this preliminary results opened the door to the chemistry of imine reduction with organic Lewis base catalysts.



Scheme 1.23 Reduction of aryl methyl ketimines using a proline-derived chiral formamide as organocatalyst developed by Matsumura.[227]

Three years later, Malkov and Kocovsky[228] and co-workers developed another type of *N*-formyl-based Lewis base derived from L-valine. These types of catalysts are more flexible since they are open chain, compared with the proline framework of the previously studied catalysts, yet they are highly efficient for the asymmetric reduction and provided up to 92% ee. The authors proposed a transition state for their catalysts (Figure **1.7**), where it coordinates with trichlorosilane to form a hexacoordinated complex, in which hydrogen bonding and π-π staking are possibly involved, according to some experiments they conducted.[228] This study was decisive for the development of new organocatalysts by research groups from all around the world.

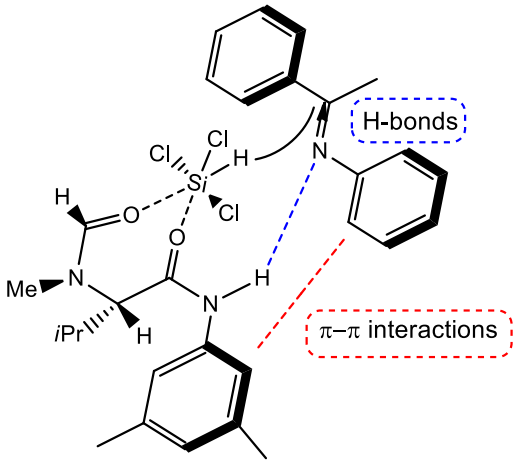
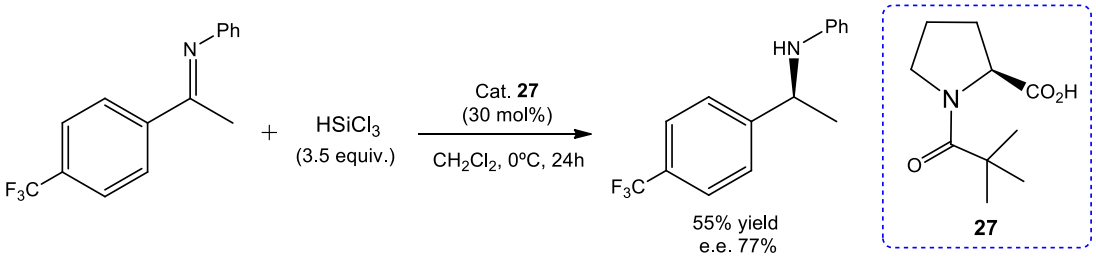


Figure 1.7 Transition state proposed by Malkov[228] for the hydrosilylation of ketimines catalyzed by L-valine derivatives.

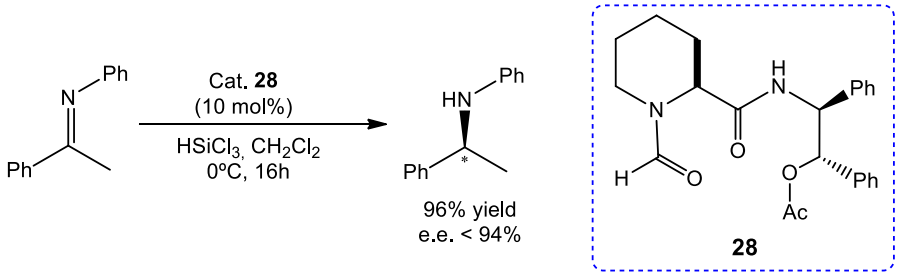
While an *N*-formyl group was essential for previous chiral activators of thrichlorosilane, Kocovsky[229] and Matsuda[230] independently reported a new non-*N*-formyl Lewis base organocatalysts – based on chiral pyridyl-oxazolines and isoquinolyloxazolines – in 2006. In

the following years, there were reported numerous applications in this field.[220,221,225,231-235] In 2013, Benaglia[226] *et al.* reported the enantioselective reduction of ketimines promoted by several proline derivatives, with good yields and a highest enantioselectivity of up to 77% (Scheme **1.24**).



Scheme 1.24 Hydrosilylation of ketimines with new L-proline derivatives developed by Benaglia and his team.[226]

In the same year, Wang[236] *et al.* applied *N*-formamides derived from L-pipecolic acid in the hydrosilylation of ketimines, for which they obtained exceptional results (Scheme **1.25**).



Scheme 1.25 Asymmetric hydrosilylation of ketimines with L-pipecolic acid reported by Wang.[236]

As previously mentioned, last year, Barrulas[180] *et al.* reported the use of cinchona-derived picolinamides – a new type of chiral Lewis base, a cationic species – in the stereoselective imine hydrosilylation of a wide range of aromatic ketimines (Scheme **1.17**). They obtained excellent yields with good to high enantioselectivities (up to 91%) and observed remarkably high turnover frequencies for the hydrosilylation of imines.

The use of organocatalysts in hydrosilylation of ketimines is a new and very promising field that's still in development with new studies being published every year – such is the objective of the work developed during this master's dissertation. However, the main challenge is the moderate TOFs and TONs associated with these organocatalytic processes, particularly when compared to those obtained from metal-based catalysis.

2. Results and Discussion

"*Nothing has such power to broaden the mind as the ability to investigate systematically and truly all that comes under thy observation in life*."
Marcus Aurelius

The main objective of this dissertation project was the synthesis of a pharmaceutically active agent, Rivastigmine, using an organocatalytic method. To accomplish this objective, we designed a general synthetic pathway were the enantioselective reduction of ketimine intermediates (precursors of Rivastigmine), catalyzed by a recently developed family of cinchona alkaloids derivatives, was the key step.

The results acquired during this project as well as their discussion are divided in four distinct sections. First we present the results obtained for the synthesis of the selected organocatalysts (namely cinchona-derived picolinamides). Secondly, we discuss the synthesis of Rivastigmine precursors, which are divided by the precursor type. And this is followed by the application of the synthesized catalysts in the asymmetric reduction of ketimine intermediates. Lastly, we present some preliminary results obtained for the immobilization of this class of organocatalysts.

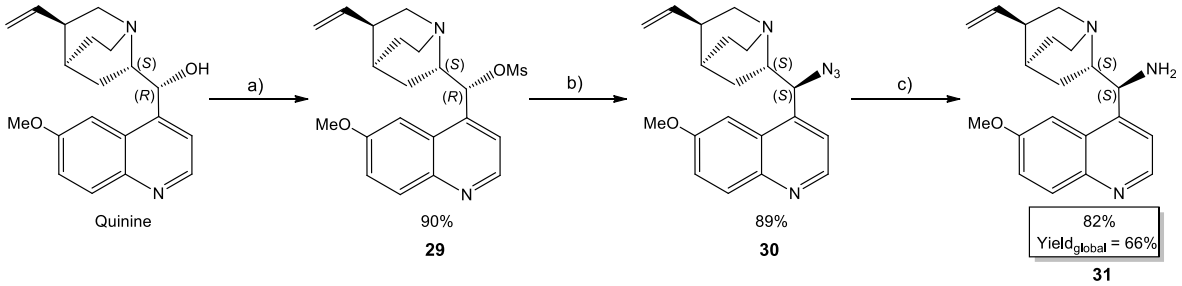
2.1 Synthesis of 9-Picolinamide-Cinchona Alkaloid Organocatalysts

The synthesis of picolinamides derived from cinchona alkaloids was an important goal of this project. These organocatalysts have previously shown high activity and enantioselectivity in the hydrosilylation of ketimines,[180] which led us to using them in the enantioselective reduction of the desired Rivastigmine precursors.

Before the preparation of the organocatalysts, we had to choose which of the four commercially available cinchona alkaloids to start from. Because we wished to obtain only one of the Rivastigmine enantiomers – the (*S*) enantiomer – we choose to work with the (-)-quinine and cinchonidine, which are known to give the desired enantiomer in the asymmetric reduction of ketimines used in this project.[180,213] As already mentioned, the complete synthesis of cinchona-derived picolinamides has been previously established by Barrulas *et al*.[178,179] The synthesis of both the quinine and cinchonidine-derived catalysts was carried out using the same experimental protocol.

Starting from commercially available quinine, first we transformed the hydroxyl present in this compound in a mesylate group (Scheme **2.1**). This is a well-known chemical reaction that comes down to transforming a weak leaving group (hydroxyl) into a very good leaving group (mesylate), which is very useful in many nucleophilic substitutions at C9 position and mesylates usually can be handled more easily. The mesylation of quinine (and cinchonidine) has been previously reported by Hoffmann[237] in 2003. We used the same experimental

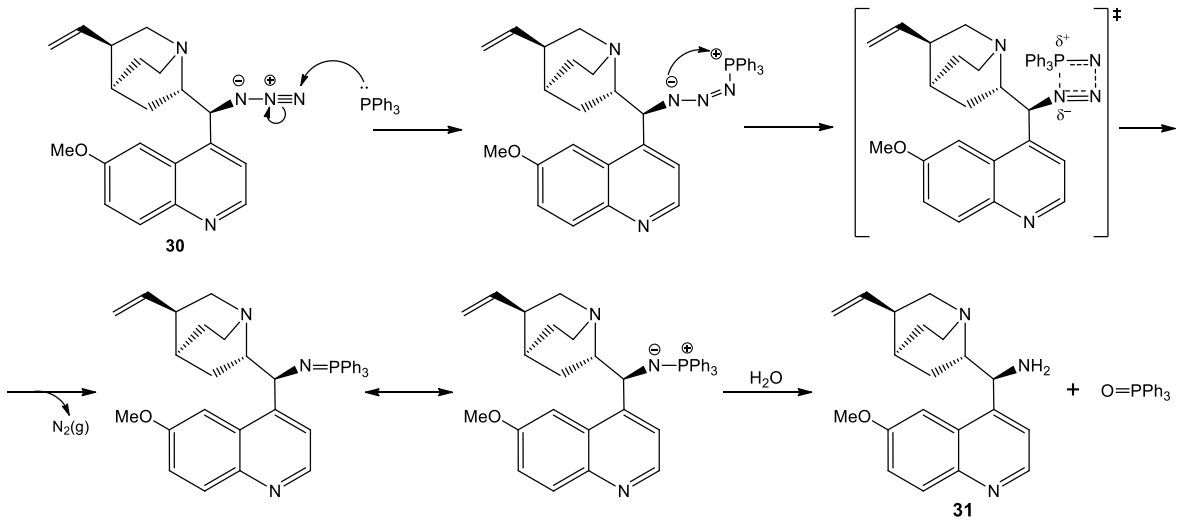
conditions as Hoffmann in the synthesis of quinine-derived mesylate compound **29**, with a yield of 90% (slightly higher than the 82% obtained by Hofmann[238]). The mesylation step proceeded with complete retention of configuration in the C9 position.



Scheme 2.1 Synthetic pathway for 9-amino-(9-deoxi)-*epi*-quinine **31**. Reagents and conditions: a) MsCl, NEt_3, THF, 0ºC; b) NaN_3, DMF, 80-85ºC; c) (1) PPh_3, THF, (2) H_2O.

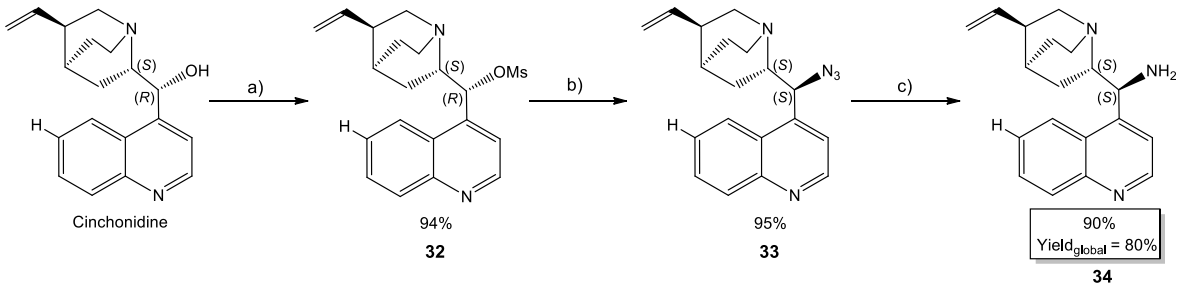
The next step in the synthesis of 9-amino-(9-deoxi)-*epi*-quinine **31**, was the preparation of azide compound **30**. This step is also a classical reaction in organic chemistry, a bimolecular nucleophilic substitution (S_N2). In this case, a nucleophilic substitution with complete inversion of configuration at the electrophilic carbon C9, occurred in the presence of an azide nucleophile (N_3^-). There are several azidation methods described in the literature, which differentiate mainly in the azide anion source such as hydrazoic acid, trimethylsilyl azide, diphenylphosphoryl azide, sodium azide, amongst many others.[239] Due to experimental simplicity and for less exposure to dangerous and toxic reagents, we chose a method already described for cinchona alkaloid derivatives[240], that uses sodium azide as an azide anion source. With this method, we were able to obtain the desired quinine compound **30** with an 89% yield.

Having successfully prepared the azide compound **30**, we set out to obtain the amine **31**. 9-amino-(9-deoxi)-*epi*-quinine and 9-amino-(9-deoxi)-*epi*-cinchonidine are a secondary amine that has been previously synthesized and applied in several organocatalytic asymmetric processes. The first described synthesis of these chiral amines dates back to the mid-1990s, when Brunner[114] reported it in 1995. Based on the work developed by Brunner[114] we choose to do the chemeoselective reduction of the azide using a Staudinger reaction[241] (Scheme **2.2**). With the Staudinger reaction we were able to synthesize 9-amino-(9-deoxi)-*epi*-quinine **31** with a very good yield (82%), having a global reaction yield of 66% after three steps.



Scheme 2.2 Reaction mechanism for the Staudinger reaction performed to obtain amine **31**.

For the synthesis of 9-amino-(9-deoxi)-*epi*-cinchonidine **34** we followed the same synthetic pathway as the one previously described for the quinine derivative (Scheme **2.3**), starting from the commercially available cinchonidine and with a very good global reaction yield of 80%.

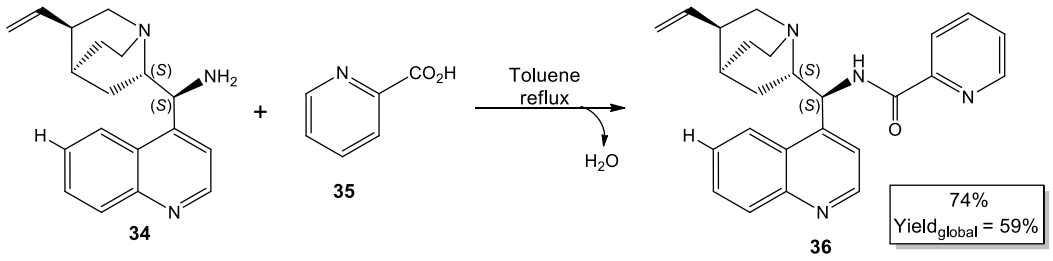


Scheme 2.3 Synthetic pathway for 9-amino-(9-deoxi)-*epi*-cinchonidine **34**. Reagents and conditions: a) MsCl, NEt_3, THF, 0ºC; b) NaN_3, DMF, 80-85ºC; c) (1) PPh_3, THF, (2) H_2O.

After the successful preparation of the amine compounds **31** and **34**, we then focused on the synthesis of the target picolinamide derivatives. To achieve this, we needed to complete the next reaction step that consisted of the formation of an amide bond. There are numerous methods available in the literature to perform this transformation, from a simple direct condensation between a carboxyl and an amide at high temperatures[242] (in which there is the elimination of a water molecule for each amide bond formed), to a catalytic condensation with Lewis acids[242,243] or through coupling reactions after carboxyl activation.[244-247] All the

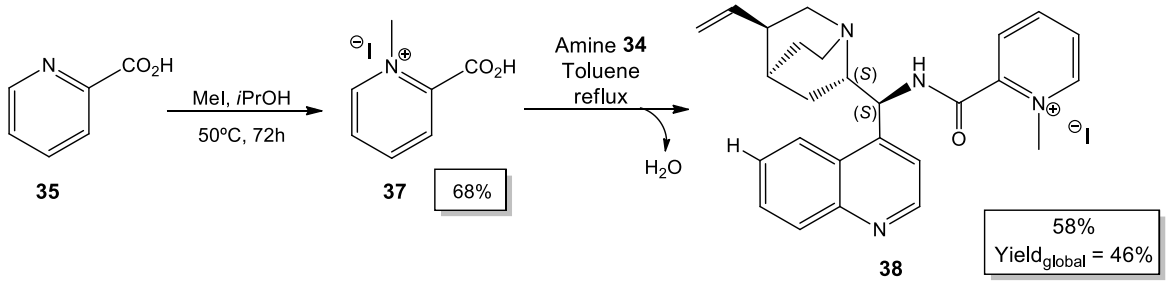
available methods for this transformation, as seen in many other organic chemistry methodologies, have their disadvantages, due to many aspects such as, for example, harsh reaction conditions or byproduct formation.

In regard to compound **36**, we initially performed its synthesis by a direct condensation between the cinchonidine-derived amine **34** and commercially available picolinic acid **35** (Scheme **2.4**). The reaction was carried out in toluene and under reflux, using a Dean-Stark apparatus for the removal of released water during the reaction.[242] After the purification step, we were able to obtain picolinamide-derived catalyst **36** with a yield of 74% and a global reaction yield of 59% (after four reaction steps).



Scheme 2.4 Synthesis of 9-picolinamide-(9-deoxi)-*epi*-cinchonidine **36** through a direct condensation.

We decided to also use the direct condensation method for the synthesis of the *N*-methyl pyridinium salt derived catalyst **38** (Scheme **2.5**). Before performing the direct condensation, we first need to synthesize compound **37** – the *N*-methyl picolinic acid. There are several described methods for the methylation of amines and we decided to use a bimolecular nucleophilic substitution with the method developed by Liebscher.[248] Through a S_N2 reaction between the commercially available picolinic acid and iodomethane in *i*PrOH, we were able to obtain the desired compound with a yield of 68%.



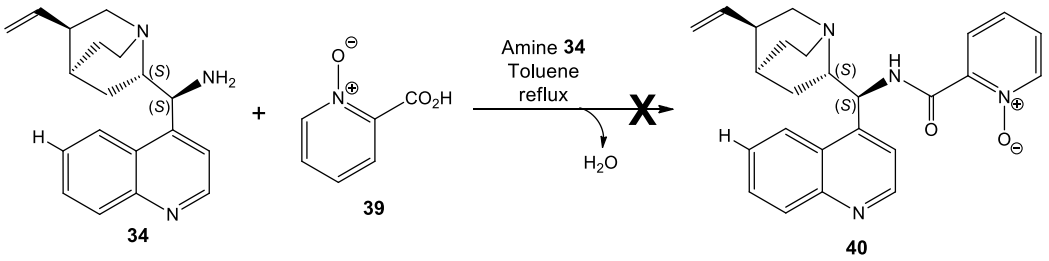
Scheme 2.5 Synthetic pathway used for the synthesis of compound **37** and **38**.

Similar to the synthesis of picolinamide **36**, the final step for the preparation of *N*-methyl pyridinium catalyst **38** was the direct condensation between cinchonidine-derived amine **34** with *N*-methyl picolinic acid **37**, with a yield of 58% and a global reaction yield of 46%. *N*-methyl pyridinium-cinchonidine **38** is a patented compound by Barrulas and Burke (WO 2015/052656).

Using the same synthetic procedure, the synthesis of these two very structurally similar compounds **36** and **38** afforded slightly different yields. One of the possible explanations for this fact can be related to the nature of the picolinic acid when the condensation occurs. In the case of the methylated picolinic acid (used for the synthesis of catalysts **38**), this obviously presents much lower solubility in organic solvents, due to the fact that it is a quaternary ammonium salt. This lower solubility can certainly lead to a reduction of the concentration of these substrates in the reaction medium, consequently lowering the effective collisions of these molecules with the remaining reagents, resulting in a lower reaction yield.

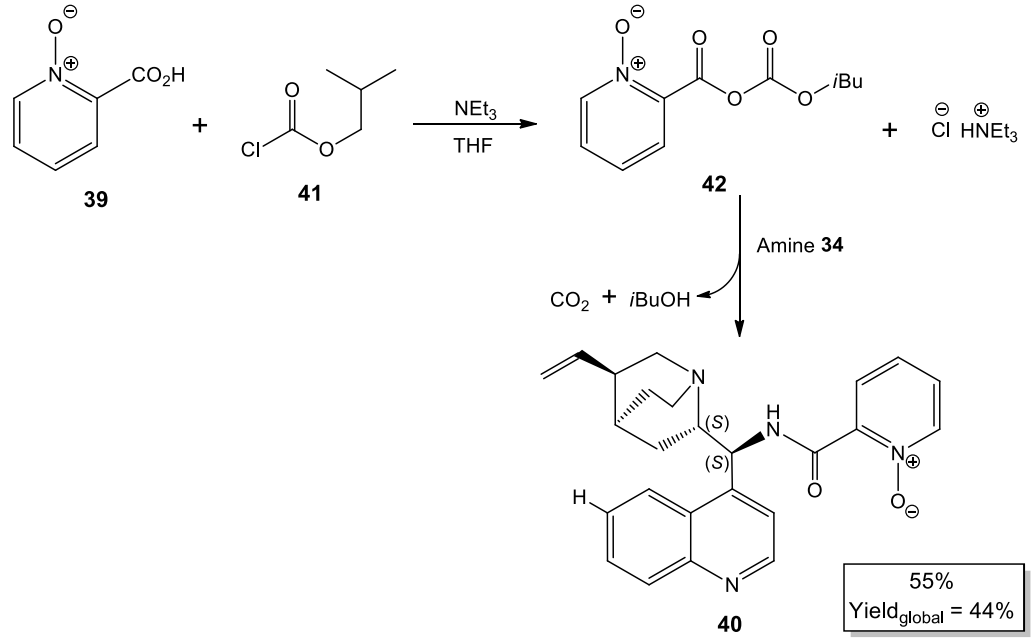
Another objective of this dissertation project was the development of a new *N*-alkylated class of cinchona alkaloid derivatives. The presence of a methyl group in the picolinamide ring, has shown to increase the catalysts activity exponentially. That led us to believe that the presence of other, more robust alkyl groups (such as benzyl), would also increase catalyst activity. And thus, we attempted to synthesize *N*-benzyl picolinic acid, from the commercially available picolinic acid and benzyl bromide with several solvents (acetonitrile, DMF, *i*PrOH, EtOH and AcOEt), at different temperatures (40-85ºC), using different heating techniques (such as microwave systems). Unfortunately, as expected, after many attempts this synthesis was not possible and we decided to not proceed with the preparation of this new class of catalysts.

After synthesizing the *N*-methyl pyridinium 9-picolinamide-(9-deoxi)-*epi*-cinchonidine derivative, we decided to prepare a novel pyridinecarboxamide compound – an *N*-oxide picolinamide-derived cinchona alkaloid. Initially, the direct condensation method for the synthesis of compound **40** was attempted (Scheme **2.6**), using the cinchonidine-derived amine **34** and the commercially available picolinic acid *N*-oxide **39**. However, the reaction didn't occur and no desired product formation was observed by ^{1}H NMR.



Scheme 2.6 Attempted synthesis of the *N*-oxide derivative **40** by direct condensation.

After the failed synthesis of catalyst **40** by direct condensation, we turned our attentions back to the available literature and decided to try the synthesis of this compound using a different method – a coupling reaction through the mixed anhydride method.[249] This method requires more reaction steps, than the direct condensation method, and leads to the formation of other secondary products, however the use of milder reaction conditions and reduced reaction times make this a attractive alternative. Through the mixed anhydride method[249] we were able to synthesize compound **40** (Scheme **2.7**).

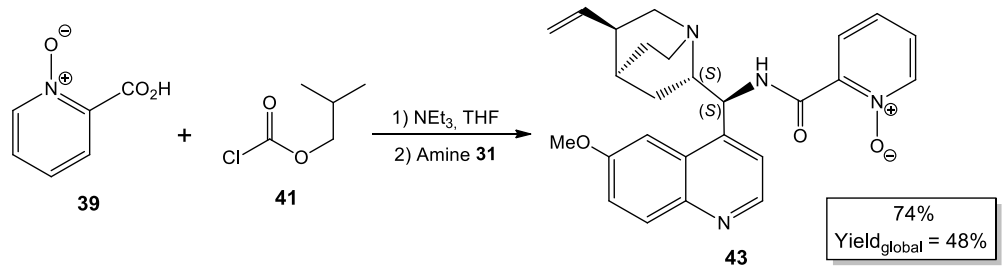


Scheme 2.7 Synthesis of the *N*-oxide derivative **40** by the mixed anhydride method.

In the first step of this reaction, the reactive intermediate **42** was formed, a mixed anhydride, obtained by activation of carboxylic acid **39** with isobutyl chloroformate through an acylic nucleophilic substitution. In the second step, the condensation of cinchonidine-derived amine **34** with the previously formed mixed anhydride occurs, also through an acylic

nucleophilic substitution, with the release of carbon dioxide and isobutanol as secondary products. We were able to obtain the desired catalyst **39** with a yield of 55% and a global reaction yield of 44% (after five reaction steps).

Following the same synthetic pathway as mentioned above and using amine **31**, we were also able to synthesize the quinine-derived *N*-oxide catalyst **43** (Scheme **2.8**), with a yield of 74% and a global reaction yield of 48% (slightly higher than observed for the cinchonidine-derived catalysts).

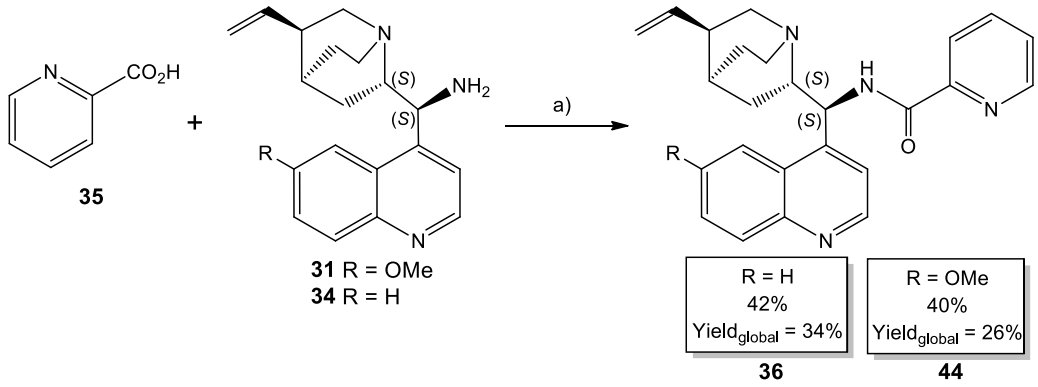


39 41 43

Scheme 2.8 Synthesis of *N*-oxide derivative **43** by the mixed anhydride method.

Inspired by the good results obtained for *N*-oxide organocatalyst synthesis using the mixed anhydride method, we decided to apply this method in the synthesis of cinchonidine-derived compounds **36** and **38**, as well as their quinine-derived counterparts. This was done in order to see if there were any significant differences in terms of reaction yield, using milder reaction conditions and lower reaction times.

Following the same procedure for the mixed anhydride method as described before,[249] we synthesized picolinamide-derived catalysts **36** and **44** (Scheme **2.9**). The cinchonidine-derived compound **36** was obtained with a 42% yield and a global reaction yield of 34%, while the quinine-derived **43** was acquired with a 40% yield and 26% global reaction yield.

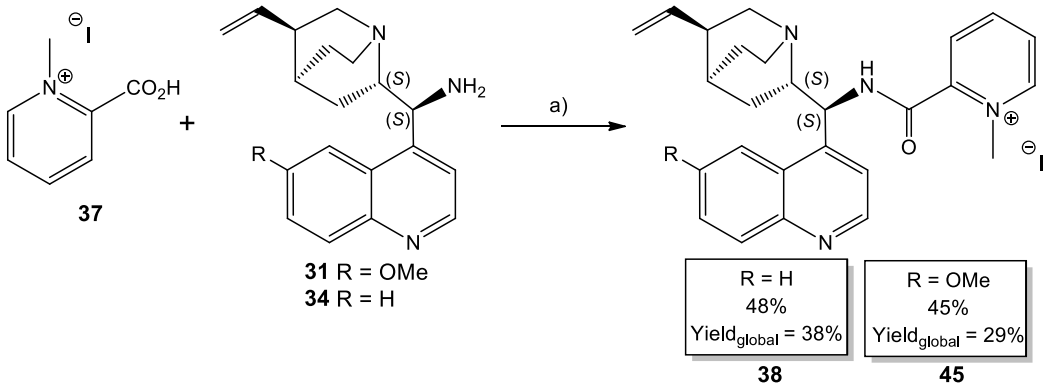


35 36 44

Scheme 2.9 Synthesis of compounds **36** and **44** through the mixed anhydride method. Conditions and reagents: a) NEt_3, isobutyl chloroformate, THF.

In the case of the cinchonidine-derived catalyst **36**, the reaction yield obtained with this method was slightly lower than the one observed in the direct condensation method (74%). However, the global reaction yield is similar, and because the reaction time is decreased from 24 to 4 hours, with milder reaction conditions, we consider this method to be a better option to synthesize these organocatalysts.

We also decided to synthesize the *N*-methyl pyridinium-derived catalysts **38** and **45** using the mixed anhydride method (Scheme **2.10**). In this case, the cinchonidine-derived catalyst **38** was obtained with a yield of 48% and a global reaction yield of 38%, while a yield of 45% and a global reaction yield of 29% was observed for the quinine-derived catalyst **45**.



Scheme 2.10 Synthesis of compounds **38** and **45** through the mixed anhydride method. Conditions and reagents: a) NEt_3, isobutyl chloroformate, THF.

The difference in yield obtained by the direct condensation method and the mixed anhydride method for the synthesis of catalyst **38** was only 10%. Thus, although the mixed anhydride method has two more reaction steps than the direct condensation, the very small difference in yields between them, the experimental simplicity and, once again, the fact that the reaction time is decreased to only four hours, henceforth makes this method the selected synthetic approach used for the synthesis of this class of organocatalysts.

Because some of the catalysts were prepared by two different methods, in order to facilitate the comparison between them, the obtained results are summarized in table **2.1**.

Table 2.1 Summary of the reaction and global yields obtained in the organocatalysts synthesis, with the respective used synthetic method.

Entry	Catalyst	Method	Yield (%)	$Yield_{global}$ (%)
1	**36**	Direct condensation	74	59
2	**36**	Mixed anhydride	42	34
3	**38**	Direct condensation	58	46
4	**38**	Mixed anhydride	48	38
5	**40**	Mixed anhydride	52	44
6	**43**	Mixed anhydride	74	48
7	**44**	Mixed anhydride	40	26
8	**45**	Mixed anhydride	45	29

Having successfully synthesized the desired organocatalysts, the next step was the evaluation of their catalytic activity in the enantioselective reduction of the desired ketimine intermediates (see section 2.3).

2.2 Synthesis of Rivastigmine Precursors

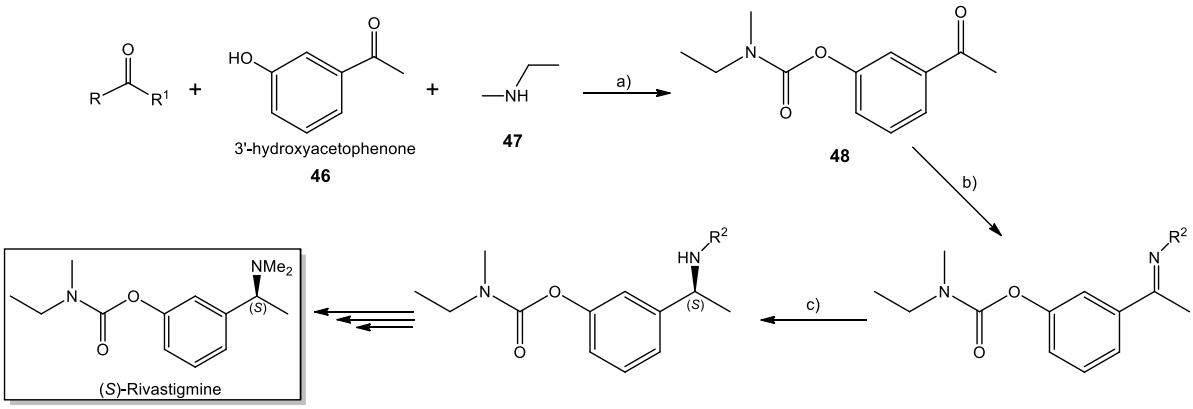
Another objective of this project was the synthesis of Rivastigmine ketimine precursors, for subsequent catalytic hydrosilylation reaction to afford the chiral amine unit catalyzed by our previously prepared picolinamide based organocatalysts. As previously mentioned (see section 1.2.1) there are numerous methods described in the literature for the synthesis of Rivastigmine.[191-212] Based on one of these established methodologies,[250] we devised a general strategy for Rivastigmine synthesis, where obviously our focus was the hydrosilylation step.

We choose 3'-hydroxyacetophenone **46** – a commercially available and inexpensive compound – as the starting material. However, when analyzing the proposed strategy for Rivastigmine synthesis, we observed that two different routes can be taken when starting from compound **46**: (a) we could start with the synthesis of the carbamate intermediate **48**, which would be later transformed into the corresponding ketimine – route **A** (Scheme **2.11**); or (b) we could first synthesize the ketimine directly from compound **46** and, after the hydrosilylation step, synthesize the corresponding carbamate – route **B** (Scheme **2.15**).

Due to these two possible strategic synthetic routes and in order to simplify the analysis of the obtained results, we divided the Rivastigmine precursors into two main types: carbamate intermediates [(3-acetylphenyl)-*N*-ethyl-*N*-methyl carbamate] and ketimines (derived from 3'-hydroxyacetophenone).

2.2.1 Synthesis of (3-acetylphenyl)-*N*-ethyl-*N*-methyl carbamate

As previously mentioned, the proposed synthesis of Rivastigmine can be initiated with the formation of carbamate **48** (Scheme **2.10**), starting from commercially available compounds, namely 3'-hydroxyacetophenone **46** and *N*-ethylmethylamine **47**.

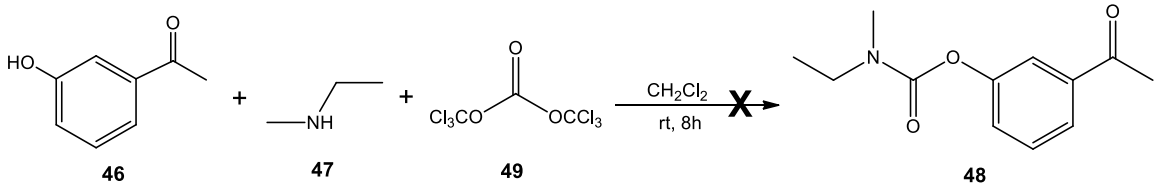


Scheme 2.11 Synthetic route **A** proposed for the synthesis of (S)-Rivastigmine. (a) Carbamate synthesis, (b) Ketimine synthesis, (c) Enantioselective ketimine hydrosilylation.

Organic carbamates, and more specifically *N*-substituted carbamates, represent an important class of compounds showing various interesting properties. They have found wide utility in various areas, such as pharmaceuticals,[251-255] agrochemicals[256-258] (pesticides, herbicides, insecticides, fungicides, etc.), as intermediates in organic synthesis(!),[259-261] for the protection of amino groups in peptide chemistry,[262,263] and as linkers in combinatorial chemistry.[264-266] Organic carbamates have been extensively used as intermediate for the synthesis of structurally diverse synthetic intermediates/molecules of biological significance.[267-270] Therefore, considerable interest has been generated in the recent past in the development of efficient and safe methodologies for carbamate synthesis.

According to the type of carbonyl source ($COCl_2$, CO, CO_2, dimethyl carbonate, ureas, just to name a few), the processes for the synthesis of *N*-substituted carbamates mainly include phosgenation of amines,[271,272] reductive carbonylation of nitro compounds,[273,274] oxidative carbonylation of amines,[275,276] methoxycarbonylation of amines,[277,278] alcoholysis of substituted ureas[279,280] and direct synthesis from CO_2, amines and alcohols.[281-283]

Initially, we tried to synthesize carbamate **48** using the phosgenation process (Scheme **2.12**), the most commonly used method for the synthesis of this type of compound. This process is basically achieved through the reaction of an amine with an alcohol using phosgene or its derivatives as carbonyl source. Phosgene is, however, an extremely toxic compound and so we decided to use a relatively safer alternative, *bis*-(trichloromethyl) carbonate **49** (also known as triphosgene).[284]



Scheme 2.12 Attempted synthesis of carbamate **48** using the phosgenation process.

Carbamate synthesis using phosgene and its derivatives has been extensively studied, with numerous procedures described in the literature.[271,272] For the synthesis of compound **48**, we attempted to use perhaps the simplest described method, that basically consists of combining the reagents in CH_2Cl_2, under anhydrous conditions, at room temperature for 8 hours (Scheme **2.12**).[285] However, under these conditions, the reaction didn't occur. The fact that no product formation was observed left us perplexed. A possible explanation for this fact may be connected to the nature of the involved compounds and so we decided to look more closely at the chemical properties of the starting materials. Although the starting secondary amine **47** is very reactive and easily couples with triphosgene, the same cannot be said about the starting alcohol **46**. Like many other chemical structures, compound **46** has more than one functional group, namely it has a hydroxyl group (alcohol) and a carbonyl group (ketone) attached to the aromatic ring in *meta* position relative to one another. Whilst the hydroxyl group is a good nucleophile (electron donating group), the ketone is an electron withdrawing group that deactivates the aromatic ring by decreasing its electron density. The deactivation of the aromatic ring most likely also partially deactivates the hydroxyl group,

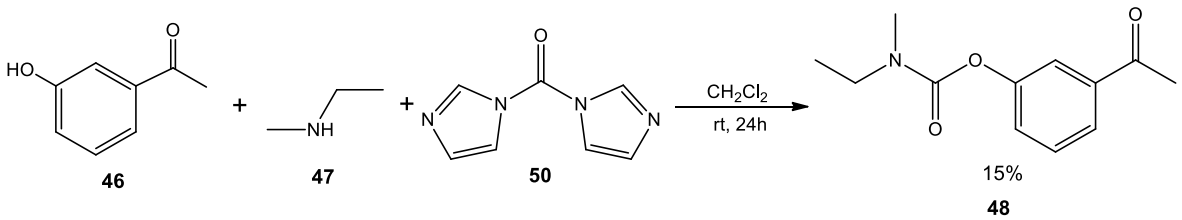
decreasing its reactivity and nucleophilic capacities, and prevents the desired reaction from occurring.

In order to try to increase the nucleophilic strength of the hydroxyl group, we decided to perform the reaction using the same conditions, but this time in the presence of a base, namely sodium bicarbonate.[286] We believed that the deprotonation of the hydroxyl group by this inorganic base, would increase its nucleophilic strength enough for the reaction to occur. However, once again, the reaction didn't proceed proving that the synthesis of carbamate **48** is not as "easy" as initially thought. We also tried other stronger bases, such as potassium hydroxide and sodium hydride, under different conditions, but no product formation was observed.

Because the phosgenation process, which usually involves the use of hazardous compounds and generally produces highly corrosive hydrochloride as a side product, wasn't very successful, we decided to attempt another, more environmentally friendly method for carbamate synthesis – using carbonyl di-imidazole (CDI).

CDI is a safe and versatility acyl transfer agent that is easier to handle when compared with commonly used triphosgene. This reagent is commercially available in large quantities at low costs and it was been successfully applied in the preparation of carbonates, ureas, amides, urethanes, esters,[287-290] or as a coupling agent for peptide synthesis[291-293] in solution. It can be easily adopted for large scale production of several biologically active compounds, since it generates relatively innocuous and easy to remove by-products (imidazole and carbon dioxide).

The use of CDI in carbamate synthesis is well established in the published literature.[294-303] We decided to employ similar conditions to the ones previously applied in the phosgenation method, but using CDI as a carbonyl source and with a longer reaction time (Scheme **2.13**).

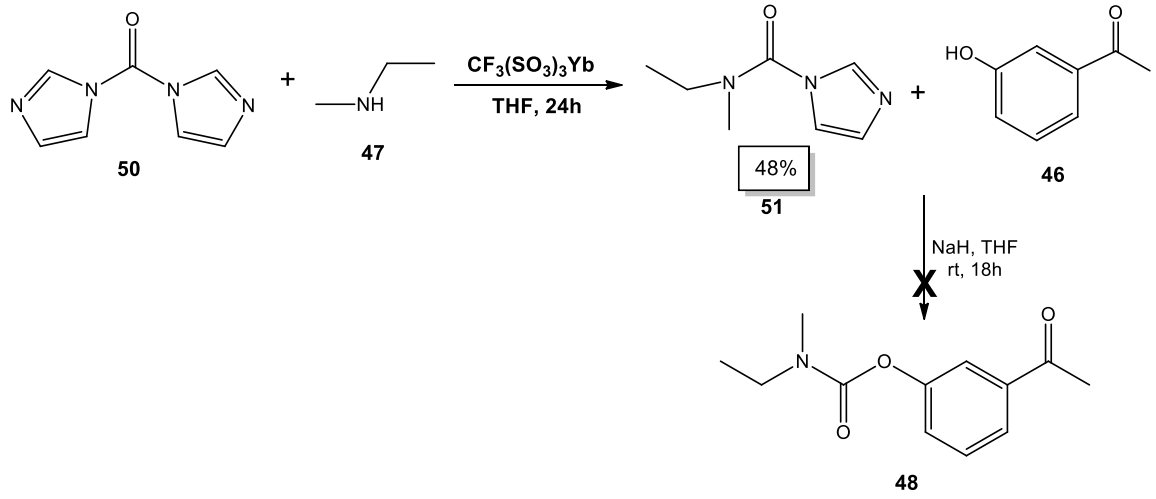


46 **47** **50** **48**

Scheme 2.13 Synthesis of carbamate **48** using CDI as carbonyl source.

In this case, we are able to synthesize the carbamate **48**, however, with a yield of only 15%. We expected that the nature of the starting alcohol would, once again, interfere in the reaction and although it was reassuring that we were able to synthesize the desired compound, this low yield on only the first, of the five required steps to synthesize Rivastigmine, was a matter of concern. At this point, in an attempt to optimize reaction conditions and subsequently increase its yield, we decided to try other methods from the wide range available in the literature. Starting with the use of bases to deprotonate the alcohol, such as sodium bicarbonate,[286] potassium hydroxide,[304] triethylamine and sodium hydride[286], using different solvents (dichloromethane, toluene, THF), with temperatures ranging from 25 to 150ºC, we were incapable of replicating the synthesis of carbamate **48**. We also tried some alternative methods using UV light and microwave irradiation, but were once again unsuccessful.

As a last effort, we applied a reported method using an ytterbium catalyst[305] for the synthesis of carbonate intermediate **51** (Scheme **2.14**). While the synthesis of this intermediate was possible, with a yield of 48%, unfortunately, the next step – the incorporation of the starting alcohol – was unsuccessful!



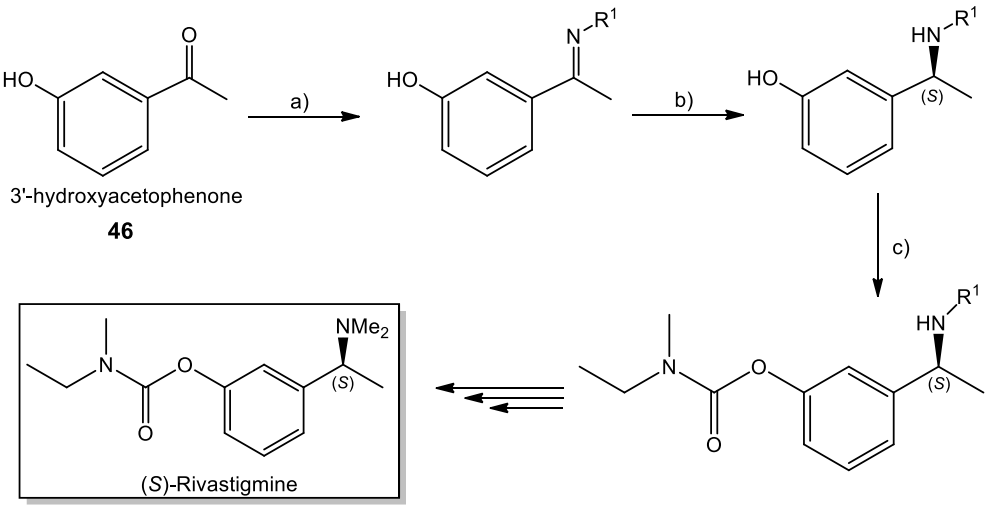
Scheme 2.14 Synthesis of intermediate **51** and attempted synthesis of carbamate **48**.

The attempt to use the ytterbium catalyst for the synthesis of the intermediate starting with CDI and the alcohol **46** (instead of the amine **47**) was also carried out. However, in this case, no product formation was observed.

Disappointed by the results that were obtained in the synthesis of carbamate **48**, we decided to abandon this synthetic pathway for Rivastigmine and focus on the other proposed route **B**.

2.2.2 Synthesis of ketimines derived from 3'-hydroxyacetophenone

Nitrogen and oxygen atoms possesses very similar reactivity (since they have similar electronegativity values), yet a ketone and an amine group obviously have very different chemical characteristics. As previously mentioned, a ketone is an electron withdrawing group that deactivates the aromatic ring, which may be a contributing factor for the difficulties observed in carbamate **48** synthesis. However, an amine is an electron donating group that activate the aromatic ring, adding electron density to the π system making it more nucleophilic. This led us to postulate that the carbamate synthesis would be easier to accomplish with an amine group in the *meta* position relatively to the hydroxyl. And so we turned our attention to the proposed synthetic route **B** (Scheme **2.15**), where the corresponding amine of 3'-hydroxyacetophenone is prepared first, to be posteriorly applied in the carbamate synthesis.



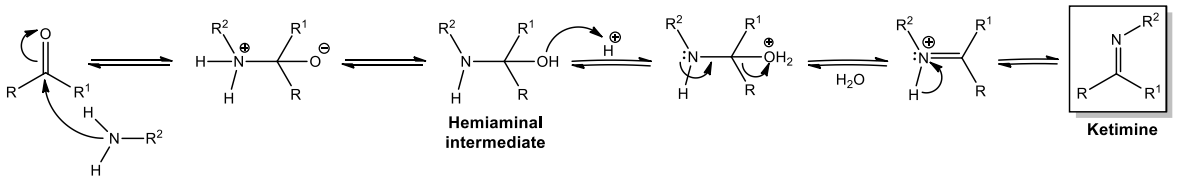
Scheme 2.15 Synthetic route **B** proposed for the synthesis of (S)-Rivastigmine. (a) Ketimine synthesis, (b) Enantioselective ketimine hydrosilylation, (c) Carbamate synthesis.

The asymmetric reduction of the C=N bond is one of the most straightforward approaches to afford chiral amines. Before we could study this asymmetric reduction reaction, we first had to explore the synthesis of a range of imines derived from commercially available 3'-hydroxyacetophenone, i.e. conduct a number of model reactions.

Imines are important intermediates in the synthesis of various biologically active *N*-heterocyclic compounds and in industrial synthetic processes.[306-309] Imines which have a structure analogous to ketones are referred to as ketimines. Ketimines are represented by the general formula R,R^1-C=N-R^2, where R, R^1 and R^2 could be an alkyl or an aryl group (Scheme **2.16**). These compounds can also be called *Schiff bases*,[321] when R^2 is not a hydrogen atom, and its stability is granted by the substituent on the nitrogen.

Information on the synthesis and chemistry of imines can be found scattered throughout the literature.[310-321] Significant progress has been made in recent years in the development of methods for imine synthesis, which include condensation of aldehydes/ketones with amines, addition of aryl halides and liquid ammonia to aldehydes/ketones, hydroamination of alkynes, oxidative coupling of amines to give imines, oxidative coupling of alcohols and amines, dehydrogenation of secondary amines, coupling of aldehydes/ketones with nitro compounds and the reaction between chemical equivalents of aldehydes/ketones and amines.[322]

The synthesis of ketimines if often accomplished by the direct condensation of ketones with primary amines according to the mechanism presented in Scheme **2.15**. The equilibrium of this reaction usually favors the carbonyl molecule and the amine, but it can be forced towards the product by azeotropic distillation of the formed water, using a Dean-Stark trap, or using drying agents or even molecular sieves.



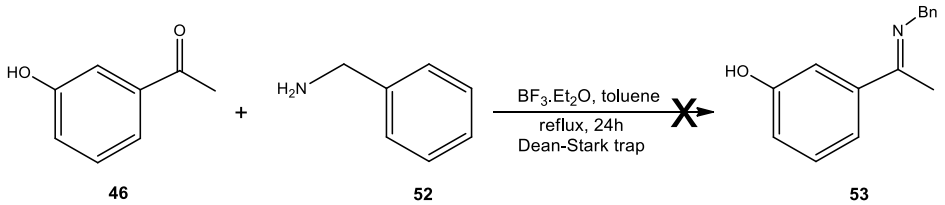
Scheme 2.16 Proposed mechanism for the synthesis of ketimines from ketones and amines.[323]

There are numerous primary amines, with a wide range of structurers, available for ketimine synthesis. However, from a logical synthetic point of view, only primary amines with relatively easy removable activating groups were chosen. This directly eliminates the use of some well-known amines, such as for example tosyl, nosyl, mesyl and BOC derivatives,

which are usually very difficult groups to remove, requiring harsher conditions, and are also more difficult to synthesize with ketones.

To the best of our knowledge, the ketimine **53** obtained from 3'-hydroxyacetophenone and benzylamine has not yet been reported. Due to this fact and that benzyl is a relatively easy removable group, we decided to focus our attention on the development of these *N*-benzyl ketimines.

We first attempted the synthesis of ketimine **53** by using a very well-known literature procedure[324] (Scheme **2.17**) that uses $BF_3.Et_2O$ as a catalyst to initiate the condensation reaction. However, after purification by liquid column chromatography, only the starting materials were detected with no product formation observed.



Scheme 2.17 Attempted synthesis of *N*-benzyl ketimine **53** using $BF_3.Et_2O$ as a catalyst.

We then tried another well-known procedure from the literature.[325] In this case, titanium ethoxide was used as catalyst in THF (under reflux) and in the presence of 4 Å molecular sieves (MS), and, once again, after the purification step, no product formation was detected, having only retrieved the starting materials. Pyridinium *p*-toluenesulfonate was also tested as the catalyst for this reaction, in CH_2Cl_2 (under reflux) and in the presence of 4 Å MS,[326] however the reaction didn't proceed.

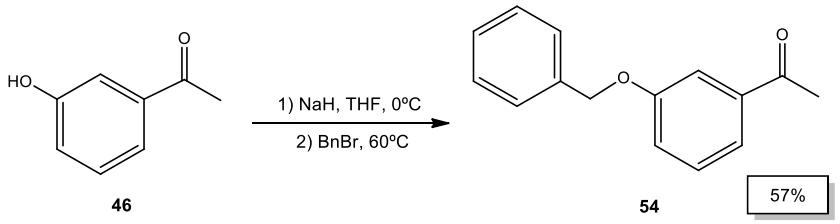
At this point, we started to suspect that two things could be occurring: (1) ketimine **53** synthesis is not, for some reason, possible; or (2) the ketimine **53** when formed is very unstable and hydrolyzes back to the starting ketone and amine. It is well-known that imines, in the presence of an aqueous medium, easily suffer hydrolysis. That's the reason why all the direct condensation methods require a drying agent or a Dean-Stark apparatus.

To try to clarify which, if any, of these two possibilities was occurring, we attempted to perform a ^1H NMR analysis of the obtained crude mixtures. However, no definitive conclusions were possible due to the disarray of signals observed in the spectrum. Nevertheless, we decided to try a few more know procedures for the synthesis of ketimine **53**. Ley[327] developed a simple method for the synthesis of complex ketimines, using sodium

bicarbonate, in toluene and 4 Å MS, under anhydrous conditions at 100ºC. When applied to our desired ketimine this method was unsuccessful and no product formation was observed.

The use of microwave (MW) irradiation in imine synthesis has been studied extensively over the last few decades, and it has already being established as an effective alternative to traditional methods. Typically, the described MW procedures use clay as catalyst and drying agents for this organic reaction. We attempted to synthesize ketimine **53** under MW irradiation using montmorillonite K10, in acetonitrile and toluene[213,328], and, once again, only the starting materials were recuperated.

Frustrated with these poor results, we came to the conclusion, that no matter the reason, we needed to devise a new strategy to synthesize the desired ketimines. We decided to turn to the "oldest trick" in the organic chemist's book – the use of protecting groups. We postulated that the protection of the phenolic group would stabilize the ketimine structure, allowing its synthesis and isolation. Because in order to synthesize Rivastigmine we would need to remove the benzyl group attached to the amine, we decided to protect the hydroxyl with another benzyl group, forming a benzyl ether (Scheme **2.18**). This would allow us to remove the two protecting groups in one single step.



Scheme 2.18 Synthesis 3'-benzyloxy-acetophenone **54**.

O-benzyl protected compound **54** was synthesized using a very well-known literature procedure,[329] with an isolated product yield of 57%.

Having protected the hydroxyl group, we attempted to synthesize the corresponding *N*-benzyl ketimine **55** using the first previously described procedure. However, to our disbelief, with $BF_3.Et_2O$ as catalyst, the reaction didn't occur again. We decided to adapt all the previous described methods for the synthesis of ketimine **53**, in the synthesis of compound **55**. Unfortunately, none of these methods afforded the desired compound.

Despite these discouraging results, we tried two new methods described in the literature. Miyaura[330] reported imine synthesis using $CuSO_4{\cdot}5H_2O$, $MgSO_4$ in CH_2Cl_2 and Ruano and Cid[331] developed a highly efficient method for the synthesis of aldimines in the presence of

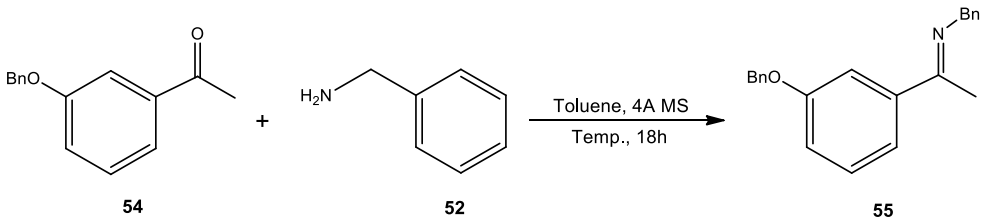
pyrrolidine as catalyst. Only starting material was recovered and no product formation was observed in both cases.

In order to try to understand what was happening, we decided to again perform a ^{1}H NMR analysis of the crude mixtures, in this case, of the one obtained using the method developed by Ley.[327] After careful analysis of the NMR spectrum, we came to the conclusion that ketimine **55** was present in a very small amount. However, after purification by liquid column chromatography on silica gel, only the starting materials were detected. This led us to believe that this ketimine is very unstable under acidic conditions, hydrolyzing to the ketone and amine very easily. The detection of ketimine in the crude mixture gave us hope that product synthesis was possible, but other purification methods needed to be used. We unsuccessfully tried liquid column chromatography with several different conditions. We also tried to purify the desired ketimine by micro distillation, but this was not feasible, due to the very high boiling and melting point of the starting materials and the unknown chemical properties of the product.

At this point, we started to believe that the protection of the phenolic group was enough to stabilize the ketimine structure for its synthesis, but not for its isolation. We decided to focus on ketimine synthesis, leaving its isolation on “standby”.

In a desperate attempt to find a method to synthesize the desired ketimine, we learned that a significant difference in the chemical shift between the starting ketone and ketimine was observed.[213] In compounds with very similar structure to the ketimine **55**, the chemical shift of the methyl group (a singlet) changes from 2.6 (in the ketone) to 2.25-2.35 ppm (in the ketimine). This clear difference can be used to observe the presence of the desired ketimine and subsequently determine the reaction yield by NMR. Henceforth, all the yields for the ketimines synthesis were determined by ^{1}H RMN, using the signal characteristic of the methyl group.

Inspired by this fact, we used a very simple direct condensation method described in the literature.[213] We were finally able to synthesize the *O*-benzyl protected ketimine **55**, with a yield of 50% by just allowing the starting materials to react in toluene at room temperature for 18h in the presence of 4 Å MS and under anhydrous conditions (Scheme **2.19**). To be sure that isolation was not possible, purification by liquid column chromatography and micro distillation were unsuccessfully attempted.

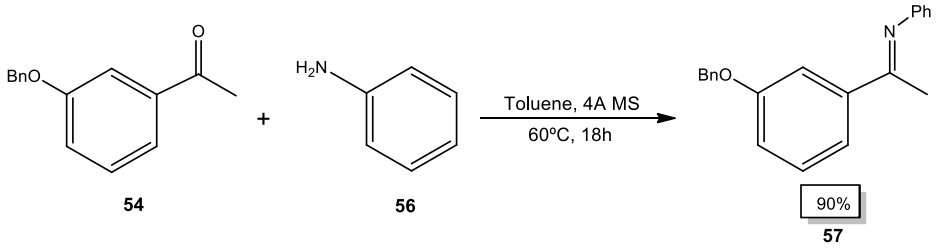


Scheme 2.19 Synthesis of *N*-benzyl ketimine **55** from the corresponding *O*-benzyl protected ketone.

At this point, under the assumption that product purification was not achievable, we decided that no compound obtained with a yield lower than 90% would be used in the study of the organocatalysts in the hydrosilylation of ketimines – the subsequent step of Rivastigmine synthesis. Thus, we needed to increase the yield obtained in the synthesis of ketimine **55**. There were a number of parameters that can be screened in this reaction, such as solvent, temperature and reaction time. We started with a temperature screening and, fortunately, found that a yield of 91% could be achieved at 60ºC.

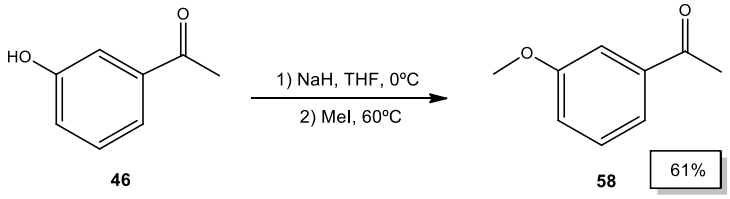
Enthusiastic about these results, we decided to synthesize other ketimines with similar structures. A very short list of primary amines with relatively easy removable groups are available for imine synthesis, being most of which benzyl derived structures. We decided to use phenyl derived amines, namely aniline, for the ketimine synthesis. Although phenyl groups are harder to remove than benzyl groups, their de-protection can be considered relatively easy when compared with tosyl and nosyl groups.[329]

Using the same conditions as previously described, we synthesized *N*-phenyl ketimine **57**, obtained from the *O*-benzyl protected ketone **54** and commercially available aniline **56**, with a yield of 90% (Scheme **2.20**).



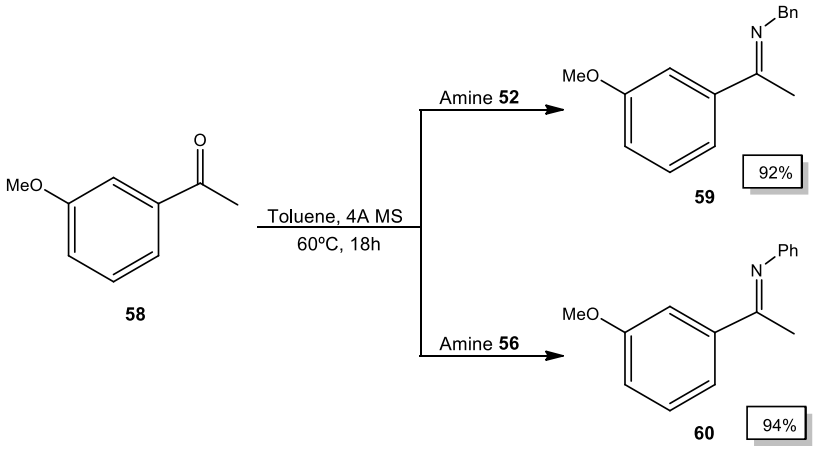
Scheme 2.20 Synthesis of *N*-phenyl ketimine **57** from the corresponding *O*-benzyl protected ketone.

In the case of compound **57**, the removal of the protecting groups cannot be done in one single step, since they are orthogonal and require different de-protection conditions, thus adding an extra step to Rivastigmine synthesis. This opened the precedent for the use of other groups for hydroxyl protection. Thus, in order to have a wider range of ketimines, we decided to use a methyl group to protect the phenolic group. *O*-Methyl protected ketone **58** was synthesized by the same method used for the benzyl protection (Scheme **2.21**),[329] with an isolated product yield of 61%.



Scheme 2.21 Synthesis of 3'-methyloxy-acetophenone **58**.

Having successfully prepared *O*-methyl protected ketone **58**, the aniline and benzylamine derived ketimines were synthesized with the same previously established conditions (Scheme **2.22**). The *N*-benzyl ketimine **59** was obtained with a yield of 92% and a yield of 94% was obtained in the preparation of the *N*-phenyl ketimine **60**.



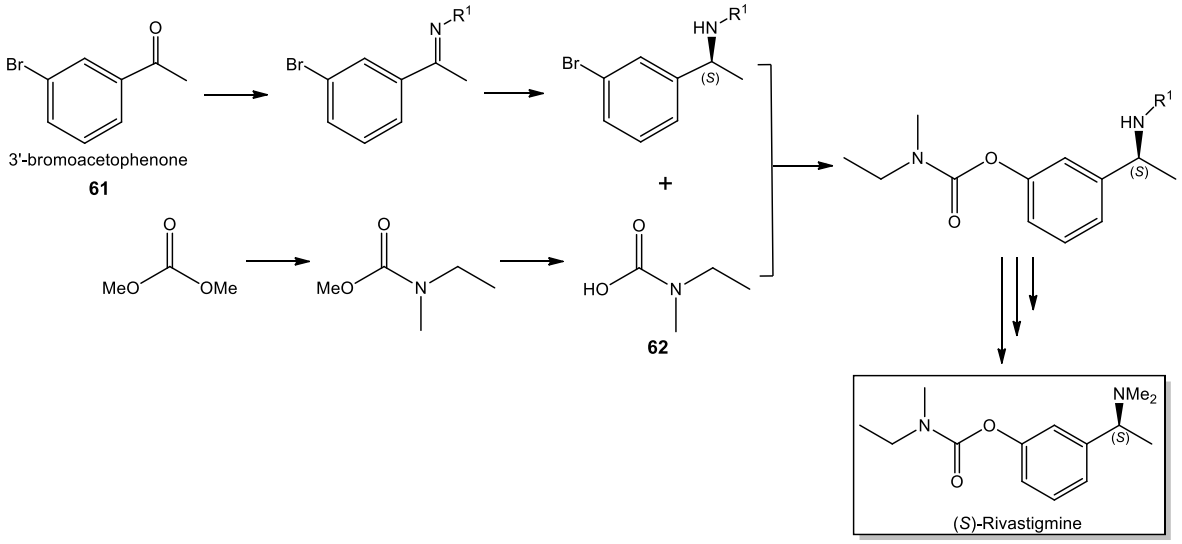
Scheme 2.22 Synthesis of *N*-benzyl ketimine **59** and *N*-phenyl ketimine **60**.

Despite the fact that the yields obtained for the ketimine synthesis were very close to the self-imposed limit of 90%, the increase of reaction temperature to just 80ºC was found to decrease the reaction yield by more than 10%, and thus 60ºC was established as the optimal

reaction temperature. We synthesized four *O*-protected ketimines with yields between 90 and 94%, and its enantioselective reduction using the previously prepared organocatalysts is discussed is section 2.3.

2.2.3 Synthesis of ketimines derived from 3'-bromoacetophenone

Inspired by a carbamate synthesis method reported in the literature,[305] we conceived a third synthetic pathway to Rivastigmine – route **C** (Scheme **2.23**). This pathway differs from the two previously presented routes not just in its starting material (3'-bromoacetophenone) but also in the carbamate synthesis method, which in this case is a metal catalyzed (usually palladium) C-O coupling.[356-362]

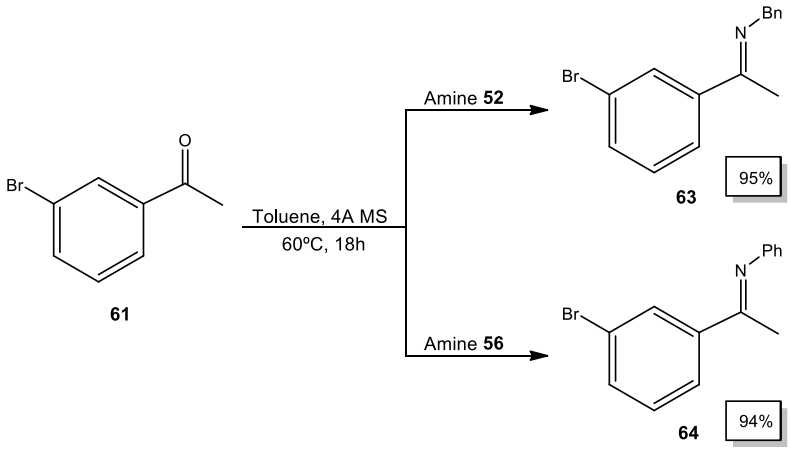


Scheme 2.23 Synthetic route **C** proposed for the synthesis of (*S*)-rivastigmine.

In order to obtain the target compound by this synthetic pathway, the separate synthesis of the chiral amine (derived from 3'-bromoacetophenone) and the carbamate intermediate **62** needed to occur first. Due to the interest of this study, we only focused our initial attention on the synthesis of the chiral amines derived from 3'-bromoacetophenone and consequently its corresponding ketimines.

Analogous to the previous synthetized ketimines, we decided to prepare *N*-benzyl and *N*-phenyl ketimines from the corresponding 3'-bromoacetophenone **61**. An initial attempt to

synthesize these ketimines using the previously described method,[324] in which $BF_3.Et_2O$ acts as a catalyst, was made. However, no product was observed for both ketimines. Thus, we decided to synthesize these compounds with the same procedure previously used for the preparation of the *O*-protected ketimines (Scheme **2.24**).[213] The same rule of a required yield superior to 90% was imposed.



Scheme 2.24 Synthesis of *N*-benzyl protected ketimine **63** and *N*-phenyl protected ketimine **64**.

The *N*-benzyl ketimine **63** was synthesized with an astonishing yield of 95% and an equally impressive yield of 94% was obtained in the preparation of the *N*-phenyl ketimine **63**. The enantioselective reduction of these two synthesized 3'-bromoacetophenone derived ketimines was studied.

2.3 Asymmetric Hydrosilylation of Ketimines

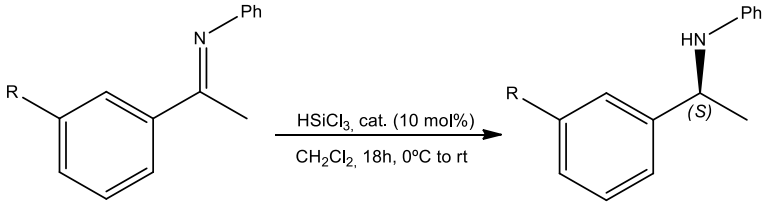
At this point, having successfully synthesized the 9-picolinamide-cinchona alkaloid derivative catalysts (see section 2.1) and the ketimines intermediates of Rivastigmine (see section 2.2), we could now proceed with the main objective of this dissertation project – study the role of the prepared organocatalysts in the enantioselective reduction of these ketimines.

With the hydrosilylation of the ketimine intermediates in mind, and based on existing literature,[180,213,222,224,225,228] we decided to perform a screening of the different organocatalysts using 3.5 equivalents of trichlorosilane in the presence of 10 mol% of the

catalyst, in anhydrous dicloromethane at room temperature for 18 hours. The results are divided into the *N*-phenyl and *N*-benzyl ketimine reduction and can be seen in table **2.2** and **2.3**, respectively.

Chiral amines **66**,[363,364] **67**,[365-369] **69**[370] and **70**[371-373] have been previously reported in the literature and, thus, the stereochemistry of these four compounds was identified by comparison with the available published results. Amines **65** e **68** have never been described in the literature, but, through comparison with similar chemical structures (such as the mentioned above four chiral amines), we identified the stereochemistry of these amines.

Table 2.2 Asymmetric reduction of *N*-phenyl ketimines with picolinamide-derived cinchona alkaloid organocatalysts.



R = OBn **57**
R = OMe **60**
R = Br **64**

R = OBn **65**
R = OMe **66**
R = Br **67**

Entry	R	Catalyst	Yield (%)[a]	e.e (%)[b]
1	OBn	**36**	97	79
2	OBn	**38**	99	85
3	OBn	**40**	77	<10
4	OBn	**43**	86	<10
5	OBn	**44**	91	71
6	OBn	**45**	99	77
7	OMe	**36**	98	77
8	OMe	**38**	94	80
9	OMe	**40**	71	<10
10	OMe	**43**	67	<10
11	OMe	**44**	99	68
12	OMe	**45**	99	70
13	Br	**36**	97	81
14	Br	**38**	96	78
15	Br	**40**	75	<10
16	Br	**43**	83	<10
17	Br	**44**	99	79
18	Br	**45**	99	68

[a] Yields of isolated products.
[b] Determined by HPLC on a chiral stationary phase.

Analysis of the results obtained in the reduction of the *N*-phenyl ketimines (table **2.2**) allowed us to make some simple but important initial observations. First, it is important to underline that all the organocatalysts were effective in the reduction of ketimines with $HSiCl_3$, however only four of them (compounds **36**, **38**, **44** and **45**) exhibited enantioselective properties in the synthesis of chiral amines. The desired enantiomer (*S*) was obtained with these four catalysts, with excellent yields (91-99%) and moderate to good enantiomeric excess (68-85%). Although these four structures are derived from both cinchona alkaloids used in this project, no significant discrepancies, in terms of yield and enantioselectivity, were observed between them. Thus, with differences of only up to 10% in enantiomeric excess and yield, we can claim that catalysts derived from quinine and cinchonidine have very similar catalytic properties when applied on the enantioselective reduction of these ketimines.

Based on models previously reported in the literature, Barrulas *et al.*[180] proposed a hypothetical transition state for the hydrosilylation of ketimines with organocatalysts **36** (Figure **2.1**). They postulated that, in the case of the non-methylated catalysts, at first, it is expected that $HSiCl_3$ activation occurs through the coordination of the silane and two of the three Lewis bases existing in the picolinamide, which will result in the release of a hydride. Simultaneously, a prochiral ketimine molecule can interact with this intermediate, either through π-π interactions between its phenyl groups and the aromatic systems of the picolinamide, or by hydrogen bonds between the nitrogen of the ketimine and the acidic hydrogen of the picolinamide. Thus, it is more likely that an accentuated exposure of the *Si*-face of the ketimine to the "inside" of this intermediate occurs, allowing an enantioselective attack of the release hydride, which would explain the preferred (*S*) enantiomer obtained with this type of catalyst.[178]

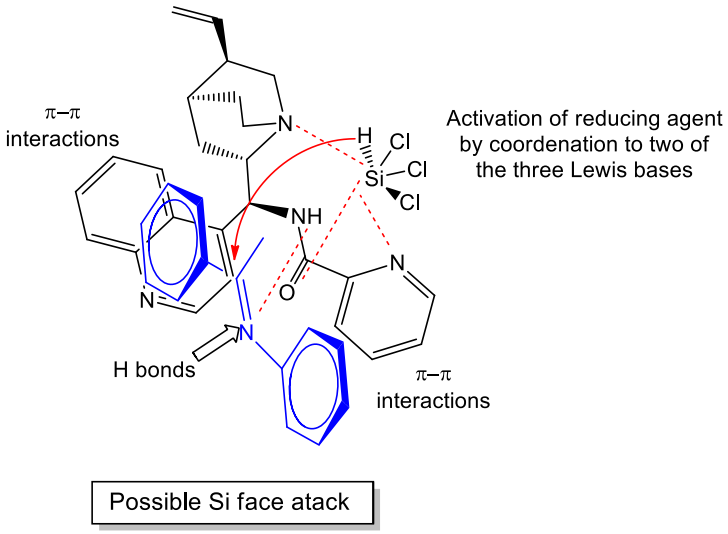


Figure 2.1 Barrulas[178] proposed transition state involving picolinamide **36**, a prochiral ketimine and $HSiCl_3$.

In the case of the *N*-oxide catalysts **40** and **43**, amines were obtained in their racemic form – which was somewhat expected. There have been some recent reports of $HSiCl_3$ deactivation by *N*-oxide structures,[221,222,224,228] but, at the time, we believed that the diverse and robust structure of the catalysts would still allow enantioselectivity, even with reduced enantioselective properties. It was originally conceived that the *N*-oxide oxygen would coordinate with $HSiCl_3$, however, due to the extra bond (N-O), it is likely that the transition state becomes less compact, or less rigid with greater conformational flexibility leading to the enantioselectivity loss.

Although the results obtained for catalysts **36**, **38**, **44** and **45**, in terms of enantioselectivity, are very similar, we can observe a slight improvement in the *N*-methylated class of these compounds. Indeed, generally speaking, compound **38**, the *N*-methylated cinchonidine-derived catalyst, gave the best results, with the overall highest obtained enantiomeric excess of 85% and an excellent yield of 99%.

To try to understand the reason why these catalysts, that possess an *N*-methylated picolinamide in their structure, afford better enantiomeric excess and, in some cases, better yields, we need to look back at the proposed transition state.[178] This minor difference observed in the enantioselectivity might be due to a slight steric hindrance generated by the methyl group, which may, somehow, “reinforce” the proper orientation of either the substrate or the activated silane during the proposed enantioselective transition state (Figure **2.2**). Due to the charge on the pyridine ring, which should be delocalized around the ring, the π-

π interaction (which will be more a π-cation interaction) may be stronger than of the previous π-π interaction obtained in the case of the non-methylated catalysts. However, further theoretical studies (such as DFT calculations) are required to better understand the reaction mechanism associated with these types of structures.

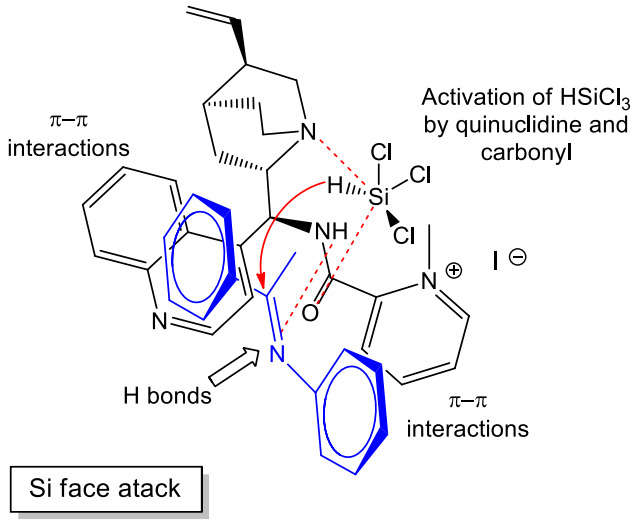
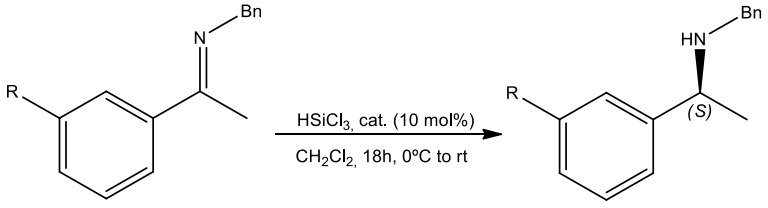


Figure 2.2 Barrulas[178] proposed transition state involving compound **38**, a prochiral ketimine and $HSiCl_3$.

Interestingly the *meta* substituent of the aromatic ring of the ketimines, didn't seem to have much effect on the obtained results. Indeed, the hydrosilylation of *O*-protected ketimines gave very similar results to the reduction of the bromine *meta*-substituted ketimines.

Thrilled with these results, we performed the reduction of the *N*-benzyl ketimines with our six prepared organocatalysts (Table **2.3**).

Table 2.3 Asymmetric reduction of *N*-benzyl ketimines with picolinamide-derived cinchona alkaloid organocatalysts.



R = OBn **55**
R = OMe **59**
R = Br **63**

R = OBn **68**
R = OMe **69**
R = Br **70**

Entry	R	Catalyst	Yield (%)[a]	e.e (%)[b]
1	OBn	**36**	57	29
2	OBn	**38**	49	33
3	OBn	**40**	14	<10
4	OBn	**43**	51	<10
5	OBn	**44**	71	28
6	OBn	**45**	67	45
7	OMe	**36**	52	31
8	OMe	**38**	45	41
9	OMe	**40**	63	<10
10	OMe	**43**	30	<10
11	OMe	**44**	60	32
12	OMe	**45**	69	42
13	Br	**36**	56	14
14	Br	**38**	59	30
15	Br	**40**	76	13
16	Br	**43**	15	<10
17	Br	**44**	52	30
18	Br	**45**	66	38

[a] Yields of isolated products.
[b] Determined by HPLC on a chiral stationary phase.

Unlike what was previously observed for the *N*-phenyl ketimines, slightly disappointing results were obtained for the reduction of the *N*-benzyl ketimines. Although, once again, all the organocatalysts were effective in the reduction of ketimines with $HSiCl_3$, lower yields (14-79%) and enantiomeric excess (13-45%) were observed. The same organocatalysts afforded results with differences ranging from 30-60% between the reduction of the *N*-phenyl and *N*-benzyl ketimines.

Once again, no significant differences on catalyst activity were observed between the three different ketimines structures. Likewise, only very small changes were observed between the quinine and cinchonidine derived catalysts, corroborating our previous statement, that quinine and cinchonidine derived catalysts possess very similar catalytic properties on the hydrosilylation of ketimines.

The *N*-oxide catalysts **40** and **43**, once more, gave the amine products in their racemic form and the *N*-methylated catalysts **38** and **45** afforded some of the best yields (45-69%) and the best enantioselectivity (45%). These results led us to conclude that *N*-oxide picolinamide-derived cinchona alkaloids are not efficient catalysts for the enantioselective reduction of ketimines. They also allow us to claim that the *N*-methylated class are the best and most promising catalysts in the enantioselective hydrosilylation of ketimines.

Unfortunately, (despite our best efforts) we do not know for sure the reason why there's such a significant difference between the hydrosilylation of the *N*-phenyl and *N*-benzyl ketimines with the same organocatalysts. The instability of the ketimine structure may be a possible explanation. Another possibility is that the *N*-phenyl ketimines must give a more compact transition state structure, inductive of better enantiofacial selectivity. However, due to the fact that the transition state of the enantioselective reduction of ketimines with this class of organocatalysts has not yet been completely established, there are consequently many questions regarding the influence of the ketimine structure on the reaction efficacy.

It is worth nothing that these six synthesized organocatalysts are just some representatives of a wide class of multifunctional chiral Lewis bases, as chiral catalysts for stereoselective reductions, characterized by multiple modes of action.[213] Indeed, compounds **36** and **44** feature the picolinamide group as coordinating unit to $HSiCl_3$, and the basic quinuclidine ring that can also play a role in the activation of the reducing agent, while catalysts **38** and **45** might still behave as a bifunctional catalyst, presenting a different coordination mode, with the carboxyamide group and the quinuclidine nitrogen group. The cinchona scaffold is very versatile but, at some levels, is still a mystery. Further studies are required to establish the exact mode of action of each of these catalysts, in order to better understand the mechanisms of the reactions in which they are involved, such as in the enantioselective reduction of ketimines.

2.4 Immobilization of Organocatalysts

Even though the enantioselective reduction of ketimine intermediates of Rivastigmine wasn't as successful as we wished, the great versatility and excellent levels of enantioselectivity previously showed by 9-picolinamide-Cinchona alkaloids in this organocatalyzed reaction,[180,213] make the immobilization of this class of catalysts extremely attractive from a possible industrial application point of view.

Homogeneous asymmetric catalysis possesses some disadvantages that limit their application in industrial processes, such as the high cost of the chiral catalysts and its low versatility, since many of the very selective catalysts have only been developed for reactions with selected model substrates. In addition, for many of the developed catalysts little information is available on catalysts selectivity, activity and productivity. Also, due to difficulties in catalyst handling, separation and recycling, the majority of homogenous catalysts are not available for commercial applications on an industrial scale.[332]

Heterogenization of homogenous organocatalysts represents a logical approach to overcome these problems. The heterogenized catalysts can potentially provide easily recyclable and reusable solid catalysts that have uniform and precisely engineered active sites similar to those of their homogeneous counterparts, and therefore combine the advantages of both homogeneous (high stability, high enantioselectivity and good reproducibility) and heterogeneous (easy separation, stability and reuse) systems.[333] Considering this, there's a growing interests in the immobilization of organocatalysts to solid supports.[334-340] Over the past few decades, many immobilization approaches have been explored, including the attachment of the chiral catalyst to organic polymers, dendrimers, membrane supports and porous inorganic oxides and via biphasic systems.[341]

To date, as far as we know, the immobilization of picolinamide-derived cinchona alkaloids has not been reported in the literature. And so, motivated by the advantages of heterogeneous catalysis, we decided to perform some studies on the immobilization of 9-picolinamide-Cinchona alkaloid derivatives (Figure **2.3**).

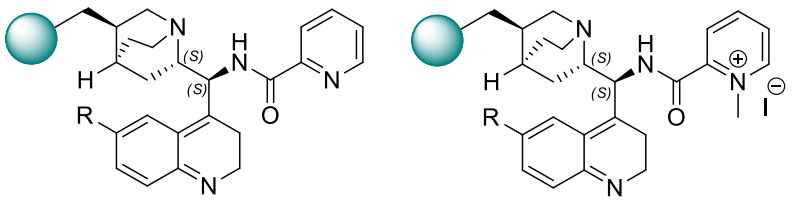


Figure 2.3 General schematic representation of heterogenized 9-picolinamide-Cinchona alkaloid derivatives.

The choice of the solid support is very important, since it is decisive in determining the experimental set-up for performing the reaction and also dictates the recovery and the recycle techniques. Additionally the morphology of the material plays a key role in the selection of a suitable field of application of the immobilized catalytic species. There is another crucial point that needs to be mentioned: the synthesis of the supported catalyst should exploit a starting material comparable in cost and synthetic complexity to that of the compound used for the synthesis of non-supported catalysts. Several different types of supports have been used for the immobilization of chiral catalysts, the most popular being inorganic materials (like silica, zeolites or alumina), soluble organic polymers (PEG, polymethylhydrosiloxan, polyacrylic acid, polyamidoamines, just to name a few) and insoluble polymeric resins.[333]

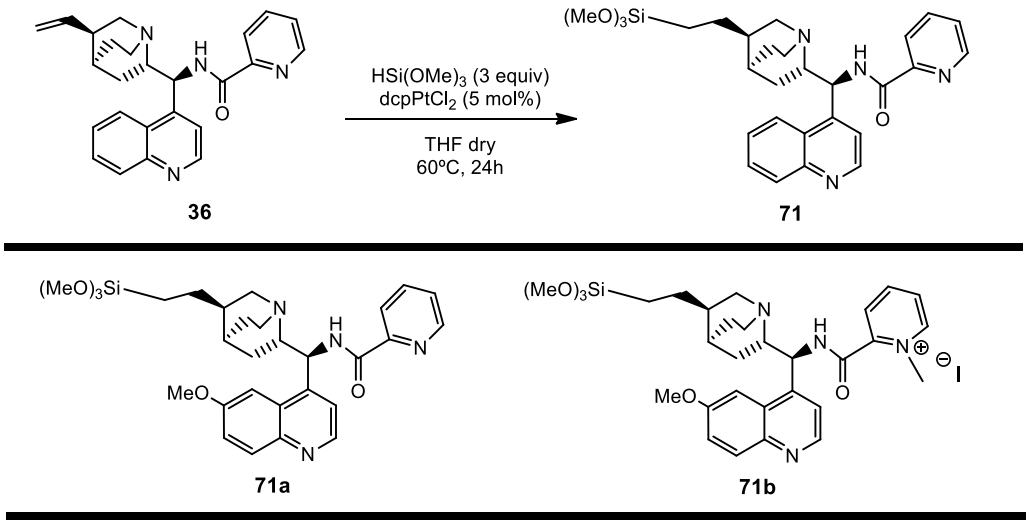
Based on the work developed by Benaglia *et al.*[342] on the immobilization of 9-amino-cinchona alkaloid derivatives, we decided to proceed with the immobilization of our 9-picolinamide-cinchona alkaloid derivatives on two different types of solid supports – a silica and a polymer. Although preliminary studies performed by the Benaglia group[333,342-345] in trichlorosilane-mediated reductions, using catalysts with different structures, showed that silica-supported catalysts are usually less efficient than the polystyrene-supported systems, we decided to study both materials because it is of interest to compare these two in the immobilization of the picolinamide-derived catalysts.

Due to organocatalysts availability issues, we only studied the immobilization of some selected picolinamide-derived catalysts, namely catalysts **36**, **44** and **45** (for silica) and catalyst **44** (for the polymer).

For the synthesis of the silica-supported catalysts we opted for a postgrafting functionalization of an already synthesized material with a chiral trialkoxysilane tether according to previously established procedures from the literature.[343] Commercially

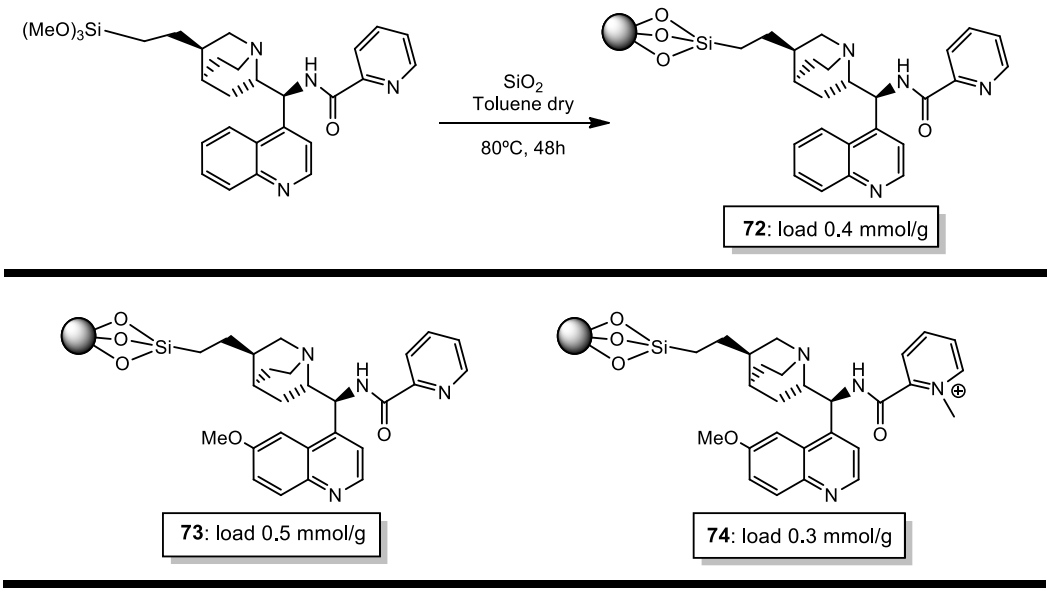
available mesoporous silica nanoparticles were used as a solid support (i.e. the silica matrix) for all three catalysts.

The immobilization of the three catalysts in the commercial silica started with a platinum catalyzed hydrosilylation with trimethoxysilane (Scheme **2.25**). The insertion of a silane group, in the vinyl group attached to the quinuclidine ring, previous to the grafting, is a required step for a more efficient immobilization on the silica. The formation of the enantiopure trialkoxysilane **71** was confirmed by ^{1}H NMR with the disappearance of the multiplets at 4.95-4.05 and 5.74-5.80 ppm (of the double bond of the vinyl group) and the appearance of a singlet at 3.55 ppm (of the methoxyl groups). Likewise, using the same methodology, two analogues of **36** were tethered to a trimethoxysilane group, to give the products **71a** and **71b**, respectively.



Scheme 2.25 Hydrosilylation reaction for the insertion of a silane group in the desired compound.

Having successfully performed the hydrosilylation reaction, we grafted the trialkoxysilanes **71**, **71a** and **71b** to mesoporous silica in toluene at 80ºC for 48h to afford the desired silica-supported catalysts (Scheme **2.26**). The catalysts were isolated by filtration, washed with a mixture of organic solvents and dried under high vacuum to remove any trace of remaining solvent.



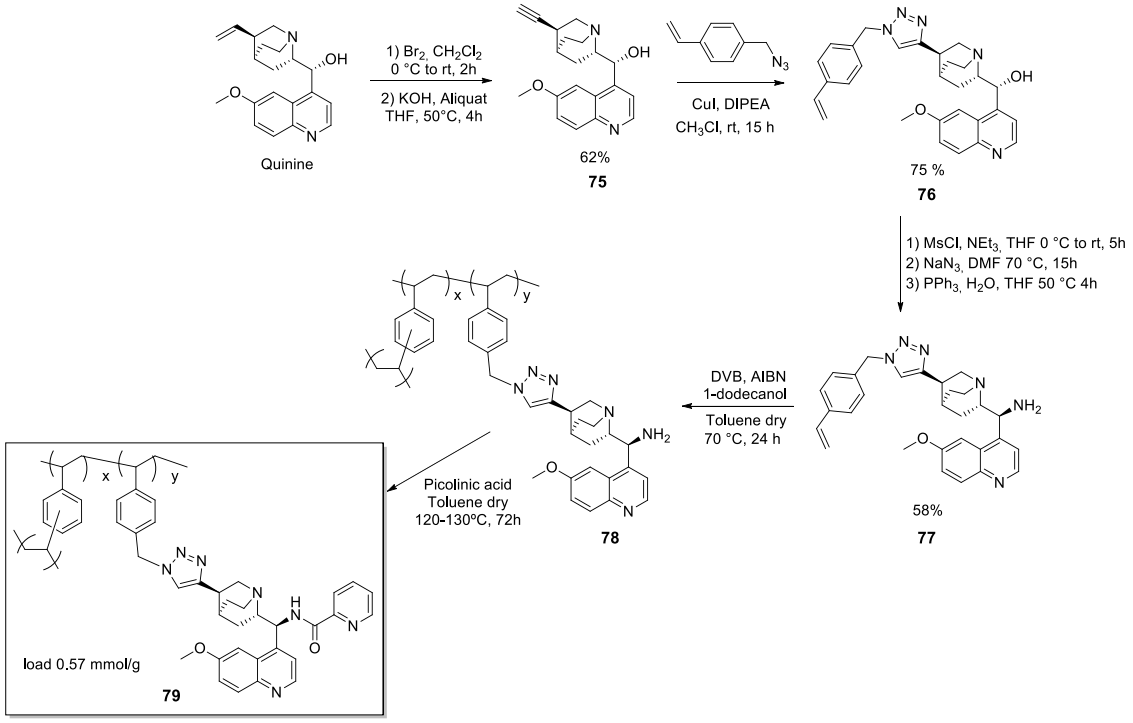
Scheme 2.26 Synthesis of the silica-supported 9-picolinamide-cinchona alkaloid derivatives.

It is worth mentioning that the presented loading of the supported catalysts is an estimated value roughly determined by the amount of trialkoxysilane recuperated from the organic washing solvents. Further analysis (such as elemental analysis, solid-state NMR, SEM, TGA, just to name a few) of the synthesized materials is required to precisely determine not just the loading of these supported catalysts but also its morphologic characteristics.

The synthesis of the polymer-supported catalysts turn out to be more complex and difficult than their silica-supported counterpart. The general strategy to prepare polystyrene supported 9-picolinamide-cinchona derivatives involves the introduction of a linker on the quinuclidine ring suitable for radical polymerization. However, upon analyzing the synthetic pathway for polymer-supported 9-amino-cinhona alkaloid derivatives developed by Benaglia *et al.*,[342] we observed that three slightly different routes could be taken to synthesize the polymer-supported catalysts. The catalyst loading (mmol/g) for the polymer-supported catalysts were determined by the stoichiometry of the reagents in the polymerization mixture.

In route **1** the picolinamide group is inserted in the catalyst after the polymerization step (Scheme **2.27**). The synthesis starts with the conversion of the double bond of commercially available quinine into a triple bond to afford compound **75** with a yield of 62%. Compound **75** was subjected to a CuAAC click reaction with a previously synthetized azide, in order to establish a styrene moiety ready for polymerization. Alcohol **76** was then converted into

amine **77**, by the same methodology as previously described for the non-supported catalysts[178] (see section 2.1), isolated in 58% overall yield after only one chromatographic purification. Afterwards this amine was employed in a radical co-polymerization under Fréchet-type conditions, with divinylbenzene in the presence of azobis(isobutyronitile) (AIBN) as radical initiator and toluene and 1-dodecanol as porogenic solvents. Lastly, using the direct condensation method previously described,[242] a picolinamide group was added to compound **78**, affording the polymer-supported catalyst **79** with a loading of 0.57 mmol/g. In this case, the polymerization of 9-amino-quinine was performed by Riccardo Porta and we only performed the last modification step (the adition of the picolinamide group).



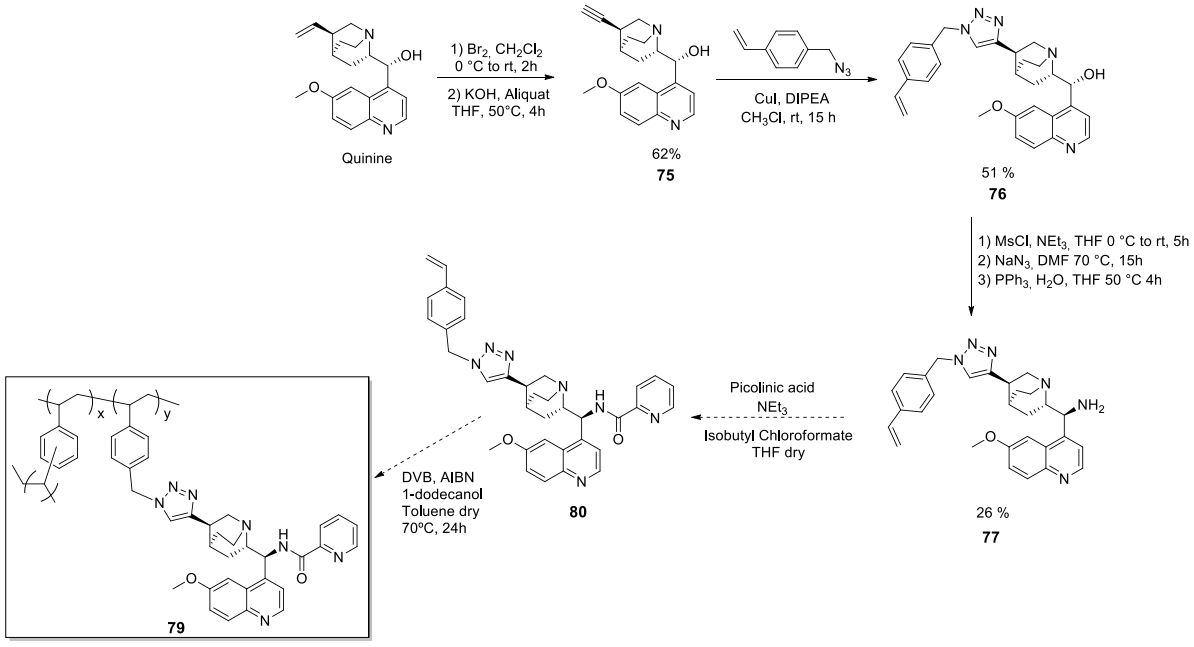
Scheme 2.27 Synthesis of polymer-supported catalyst **79** via route **1**.

The uncertainty associated with the actual structure of the catalyst is a considerable disadvantage of this proposed synthetic pathway. There is a substantial risk that not all the amine catalyst **78** was transformed into picolinamide catalyst **79**, which will obviously affect and undermine the desired reaction efficacy. Performing a simple catalytic test reaction, such as the reduction of ketimines, can be an alternative to the more expensive and arduous analysis techniques. For that reason, we performed the hydrosilylation of a very simple ketimine with catalyst **78** and the supposedly prepared catalyst **79**. Compound **78** afforded the corresponding amine of the *N*-PMP imine of acetophenone as a racemic mixture, while

with **79** an enantiomeric excess of 23% was obtained. Although there is a significant difference between the two tested compounds, the enantioselectivity demonstrated by catalyst **79** is much lower than its non-supported counterpart (80% e.e.).[180]

Two assumptions can be taken from these results: 1) the supported catalyst is much less efficient than the non-supported catalysts, possibly due to chemical effects of the surface material; or 2) it not just catalyst **79** but also a large quantity of remaining untransformed catalyst **78**, which are competing with one another. The later possibility is the more plausible explanation. By altering the structure of an already polymerized catalysts, we need further structural analysis (mainly solid-state NMR) to know the exact changes that happened. Without a thorough analysis and characterization of the immobilized catalyst, no correct conclusions can be made about the synthesized catalyst, which makes this route inadequate for the synthesis of these polymer-supported picolinamide catalyst.

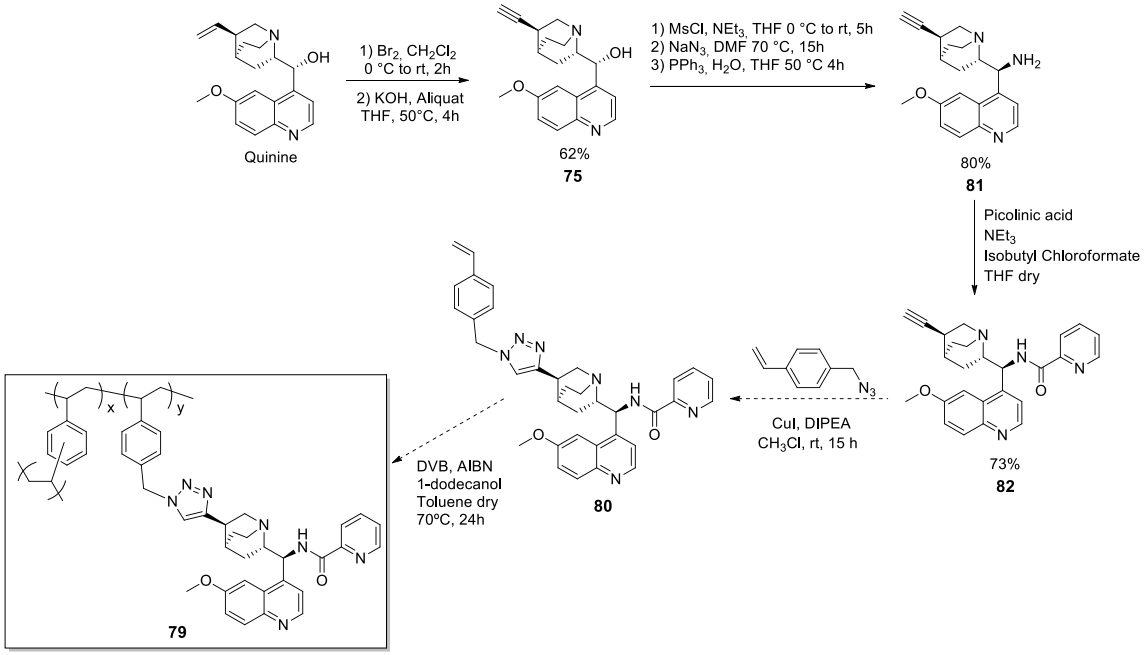
Proposed synthetic route **2** solves the problems of route **1**, since the desired monomer (with the picolinamide structure in the catalyst) is prepared before the polymerization step (Scheme **2.28**). In this synthetic route we performed the synthesis of amine **77** as previously described for route **1**. We then attempted to transform this amine into its corresponding picolinamide, using the mixed anhydride method previously described.[249] However, due to lack of experience of working with this unstable intermediates, the isolation of picolinamide **80** was unsuccessful.



Scheme 2.28 Attempted synthesis of polymer-supported catalyst **79** via route **2**.

^{1}H NMR analysis of the crude mixture **80** allowed the observation of the desired product, however, after purification by liquid column chromatography on silica gel, no product was detected. For some reason (unknown to us), the product possibly degraded during the purification step. Despite this setback, we believe that this synthetic pathway can be very efficient for the preparation of polymer-supported 9-picolinamide-cinchona alkaloid derivatives.

The last proposed synthetic route is very similar to route **2**. The main difference between these two synthetic pathways resides in the step where the styrene moiety is inserted. In route **3** (Scheme **2.29**), after the commercially available quinine is converted into triple bond containing compound **75**, the alcohol was first converted into amine **81** with an overall yield of 80% (instead of the click reaction to insert the styrene moiety). The amine was then transformed into its corresponding picolinamide **82** in a yield of 73%. The picolinamide was then ready to be subjected to the click reaction, in order to establish a styrene moiety ready for polymerization. However, some problems arose during this step. The reaction didn't proceed when using catalytic amounts (0.05 equiv.) of copper iodide. Copper, the catalyst used in the click reaction, has strong affinity for amines and, in their presence, the amine coordination to the metal is preferable. In this case, we believe that by complexing with the 9-picolinamide group, copper was removed from the reaction medium, remaining in a "pocket" near the amine.



Scheme 2.29 Attempted synthesis of polymer-supported catalyst **79** via route **3**.

The click reaction can also occur by thermal induction, but, in this case, there is no stereochemical control, which is undesired. Interestingly we postulated that by using stoichiometric amounts of copper the reaction could be forced to work, because, although a large percentage of the used copper would be complexed with the amine, there would still be a catalytic amount left for the desired reaction. Indeed, when using 1.2 equivalents of copper iodide the formation of crude product **80** was observed by ^{1}H NMR. However, like the situation observed in route **2**, product isolation was not possible. Although the detection of compound **80**, even in small amounts, gives us hope for the synthesis of polymer-supported catalyst **79**, we believe that synthetic route **3** is not the most adequate pathway, since stoichiometric amounts of copper need to be used.

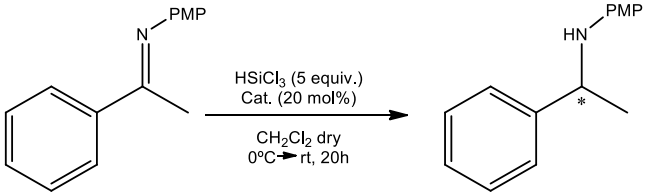
Unfortunately, the efficient synthesis of polymer-supported 9-picolinamide-cinchona alkaloid derivatives was not possible during the time frame of this dissertation project. Yet we believe that proposed synthetic route **2** is the most efficient pathway to prepare these supported catalysts.

The applications of supported 9-picolinamide-cinchona alkaloid derived catalysts in continuous flow systems was one of the objectives that we had in mind when we first started to work on the immobilization of these catalysts. The use of chiral supported organocatalysts under continuous flow conditions offers a great opportunity to combine a powerful methodology, like organocatalysis, with other enabling technologies,[346] opening new avenues towards the automated synthesis of complex molecules.[347-351]

Although we weren't able to adequately prepare the polymer-supported catalyst, three silica-supported catalysts were synthesized. Before we could apply the immobilized catalysts in continuous flow systems, a preliminary assessment of catalysts activity needed to be performed under batch conditions. For this effect, the reduction of *N*-PMP imine of acetophenone with $HSiCl_3$ and the prepared silica-supported catalysts **72**, **73** and **74** was studied and the obtained results are presented in table **2.4**.

The *N*-PMP imine of acetophenone was already available to be used in the hydrosilylation reaction, having been previously prepared by another member of the Benaglia group, using well-known literature procedures.[213]

Table 2.4 Asymmetric reduction of *N*-PMP imine of acetophenone with silica-supported 9-picolinamide-cinchona alkaloid derivatives.



Entry	Catalyst	Yield (%)[a]	e.e (%)[b]
1	**72**	64	30
2	**73**	>99	62
3	**74**	55	27

[a] Yields determined by ^{1}H NMR.
[b] Determined by HPLC on a chiral stationary phase.

The enantioselective reduction catalyzed by the three silica-supported catalysts afforded lower results than expected. Good to excellent yields (55-99%) were observed, while only low to modest enantioselectivities (27-62%) were obtained. Catalysts **73** afforded the best results in terms of both yield (>99%) and enantioselectivity (62%). Unfortunately, with only a best enantiomeric excess of 62%, none of these silica-supported catalysts were adequate to be applied in continuous flow systems. Early studies on supported catalyst recycling were performed, however, they also showed inherent inadequacies.

Despite the lack of very good results, these are very good indicators for what can be expected for the polymer-supported 9-picolinamide-cinchona alkaloid derivatives, since generally polystyrene-supported systems are more efficient than the silica-supported catalysts.[333,342-345]

3. Conclusions and Future Perspectives

"*If you would be a real seeker after truth, it is necessary that at least once in your life you doubt, as far as possible, all things*."
Rene Descartes

The main objective of this master's dissertation was the synthesis of the biologically active compound used for the treatment of Alzheimer's disease, Rivastigmine, by a novel organocatalytic synthetic pathway. Generally speaking, the key step of the proposed synthetic pathway was the enantioselective reduction of ketimine intermediates (precursors of Rivastigmine) using a recently developed family of cinchona alkaloid derivatives as catalysts.

We synthesized four previously described 9-picolinamide-cinchona alkaloid derivatives and two new catalysts also belonging to this class. After the complete characterization of these structures, we can conclude that the synthesis of the desired organocatalysts was very successful, considering the good to very good yields that were obtained (of up to 65%).

Although the synthesis of the carbamate intermediate of Rivastigmine [(3-acetylphenyl)-*N*-ethyl-*N*-methyl carbamate] was more difficult than initially expected, we were able to synthesize three different *N*-benzyl ketimine intermediates and three *N*-phenyl ketimines, derived from both 3'-hydroxyacetophenone and 3'-bromoacetophenone, with excellent yields (90-95%).

When applied in the enantioselective reduction of the prepared ketimine intermediates, the six studied organocatalysts revealed very different catalytic properties that also depended on the ketimine structure. Indeed, there was a large discrepancy in the results of the hydrosilylation of the *N*-phenyl and *N*-benzyl ketimines, with values of both yield and enantioselectivity being much higher (30-60%) in the *N*-phenyl ketimines. Regarding the catalysts itself, while the *N*-methylated class of 9-picolinamide-cinchona alkaloids revealed to be the most efficient for the enantioselective reduction of ketimines, the *N*-oxide derivatives only afforded the amines in their racemic form. We can conclude that the *N*-methylated cinchonidine-derived catalyst **38** (for the *N*-phenyl ketimine) and quinine-derived catalyst **45** (for the *N*-benzyl ketimine) were the best catalysts in the enantioselective reduction of ketimines, regarding enantioselectivity.

Preliminary studies for the immobilization of 9-picolinamide-cinchona alkaloid derivatives were also performed, with the aim of applying the supported catalysts in continuous flow systems. Three silica-supported catalysts were prepared and, a preliminary assessment of catalyst activity, revealed that (when compared with the homogenous version) there is a loss of catalyst efficacy, in the enantioselective reduction of ketimines, when these type of materials are used. Immobilization onto a polymer support was more complex and was not satisfactorily achieved during the time frame of this project. However, the results obtained

for the silica-supported catalysts were very good indicators for what can be expected for the polymer-supported 9-picolinamide-cinchona alkaloid derivatives.

Although we weren't able to conclude the total synthesis of Rivastigmine within the time frame of this project, we believe that the novel proposed synthetic pathway is a very efficient route to obtain enantiomerically pure (*S*)-Rivastigmine. The next step of this project, would be the de-protection of the phenolic and the amine groups of the isolated *N*-phenyl and *N*-benzyl amines, in order to perform the carbamate synthesis.

The elaboration of this master's dissertation, as well as its rich set of results, opens the door for future studies regarding this novel organocatalytic synthetic pathway to Rivastigmine. From the organocatalysts used to the structure of the ketimines intermediates, there are endless possibilities that can be studied.

As a continuation of this work, in the near future, it might be interesting to study the effect of altering the structure of the picolinamide group, present in the catalyst, and to evaluate their activity. Namely, the effect of the counter anion in the *N*-methylated class of these catalysts, which was previously shown to have an influence on catalyst activity.[180] Another possibility may be the development of a new *N*-alkylated class of 9-picolinamide-cinchona alkaloid catalyst, in order to better understand the influence of an alkyl group (such as benzyl), connected to nitrogen of the picolinamide ring, in the transition state.

The preparation of other ketimines structures, using different primary amines as starting materials, is another new objective. The preparation of ketimines with phenyl and benzyl derivatives (i.e. with different substituents in the aromatic ring) may lead to a better understanding of the influence of ketimine structure on the catalyst activity, allowing us to know why there are such discrepancies in their enantioselective reduction results.

Taking into consideration the benefits of heterogeneous catalysis previously mentioned, we are still focused on the preparation of immobilized picolinamide-derived catalysts, specifically on the polymer-supported catalysts. The application of polymer-supported 9-picolinamide-cinchona alkaloid derivatives in continuous flow systems may open new avenues towards the automated synthesis of biologically active molecules, such as Rivastigmine, which would increase the application of these very efficient class of catalysts on an industrial scale.

4. Experimental Section

"*Anybody who has been seriously engaged in scientific work of any kind realizes that over the entrance to the gates of the temple of science are written the words: 'Ye must have faith*"
Max Planck

4.1 General Remarks

Cinchonidine, quinine, picolinic acid, 3'-hydroxyacetophenone, 3'-bromoacetophenone and all remaining reagents used in this work were purchased from Sigma-Aldrich, Fluka, Acros and Alfa Aeser and used as received. All the solvents used in this work were used as received, unless otherwise stated. The anhydrous solvents were purified and dried under an inert atmosphere using common laboratory techniques.[352]

Thin layer chromatography (TLC) was carried out on silica gel 60 F_{254} pre-coated glass plates (0.25 mm thickness) during the immobilization of the catalysts and on aluminium backed Kieselgel 60 F_{254} plates (Merck) for the remaining of the work. TLC plates were eluted with the appropriate solvents described in each experimental procedure. Plates were visualized by UV light (254 and 366 nm) and/or with phosphomolybdic acid in ethanol after heating with a hot air gun.

Column chromatography was carried out on silica gel (SDS, 70-200 μm) and silica gel flash (SDS, 40-63 μm) eluted with the corresponding mobile phase.

NMR spectra were recorded on a Brucker Avance III instrument (^{1}H: 400 MHz; ^{13}C: 100 MHz), using $CDCl_3$ and DMSO-d_6 as solvents and the signal from the residual non-deuterated solvent was used as an internal standard. All ^{1}H and ^{13}C NMR chemical shifts were reported in ppm (δ). All coupling constants are expressed in Hz.

Melting points were determined on a Barnstead/Electrothermal 9100 capillary apparatus.

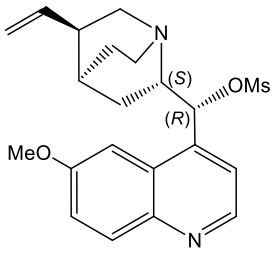
Enantiomeric excess determinations were performed by High Performance Liquid Chromatography (HPLC) in a Hitachi Primaide instrument, equipped with a 1410 series UV detector, using Chiracel OD-H as chiral column.

Unless otherwise stated, all reactions were performed without inert atmosphere (nitrogen).

4.2 General Procedures

4.2.1 Synthesis of Catalysts

4.2.1.1 Synthesis of (8*S*,9*R*)-9-*O*-mesylquinine (**29**)



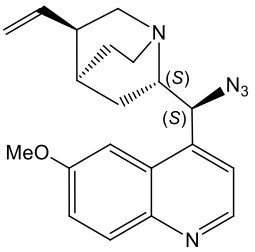
According to the method performed by Hoffmann,[237] 4.015 g of commercial quinine (12.33 mmol) were dissolved in 50 mL of anhydrous THF, to which then there was added 5.41 mL of triethylamine (38.84 mmol). The reaction mixture was cooled to 0ºC in an ice bath and 2.41 mL of methanesulfonyl chloride (24.66 mmol) was slowly added dropwise. After the addition was completed, the mixture was stirred for 2 h at room temperature. 40 mL of a saturated solution of sodium bicarbonate was added to the crude mixture and extracted with CH_2Cl_2 (2 x 20 mL). The organic phase was dried with anhydrous $MgSO_4$, filtered and the solvent was evaporated under reduced pressure in a rotary evaporator. The crude product was purified by silica gel column chromatography (eluted with AcOEt), affording the desired product **29** as a yellowish oily solid (3.86 g, 90%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 8.73 (d, 1H, *J*=4 Hz, H2'), 7.83 (d, 1H, *J*=8 Hz, H8'), 7.60 (t, 1H, *J*=8 Hz, H7'), 7.51 (t, 1H, *J*=8 Hz, H6'), 7.42 (bs, 1H, H3'), 7.31 (d, 1H, *J*=8 Hz, H5'), 6.05 (bs, 1H, H9), 5.79-5.75 (m, 1H, H10), 4.99-4.93 (m, 2H, H11), 3.93 (s, 3H, CH_3), 3.30-3.21 (m, 2H, H6, H8), 3.14 (bs, 1H, H2), 2.79-2.75 (m, 5H, H6, H2, CH_3), 2.28 (bs, 1H, H3), 1.60-1.53 (m, 5H, H7, H5, H4).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 157.03 (C6'), 148.64 (C2'), 144.83 (C10'), 143.01 (C4'), 139.44 (C10), 131.58 (C9'), 130.76 (C8'), 123.07 (C3'), 120.35 (C7'), 114.39 (C11), 103.57 (C5'), 59.35 (C9), 56.15 (C8), 56.06 (C-O), 55.70 (C2), 46.67 (C6), 39.49 (C3, C-mesylate), 28.10 (C7), 27.43 (C4), 25.99 (C5).

The structure was confirmed by comparison with existing results from the literature.[237]

4.2.1.2 Synthesis of (8*S*,9*S*)-9-azido(9-deoxi)-*epi*-quinine (**30**)

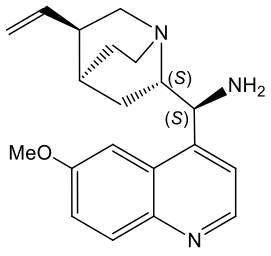


In a round-bottom flask, 3.86 g of compound **29** (11.10 mmol) was dissolved in 20 mL of anhydrous DMF at room temperature and 2 equivalents of NaN_3 (1.6 g, 24.66 mmol) were added. The mixture was stirred for 24 h at 80-85ºC.[240] The reaction was monitored by TLC and, after the complete consumption of the substrate, the solvent was removed by distillation. H_2O (15 mL) was added to the crude mixture and the organic phase was extracted with CH_2Cl_2 (3 x 20 mL), dried with anhydrous $MgSO_4$ and filtered. The solvent was evaporated under reduced pressure on a rotary evaporator and the crude product purified by silica gel column chromatography, eluted with AcOEt. The desired product **30** was obtained as a thick orange oil (4.09 g, 89%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 8.85 (d, 1H, *J*=4 Hz, H2'), 8.03 (d, 1H, *J*=8 Hz, H5'), 7.91 (d, 1H, *J*=8 Hz, H8'), 7.69 (t, 1H, *J*=8 Hz, H7'), 7.50 (t, 1H, *J*=8 Hz, H6'), 7.39 (bs, 1H, H3'), 5.75-5.73 (m, 1H, H10), 5.31 (d, 1H, *J*=10 Hz, H9), 4.98-4.93 (m, 2H, H11), 3.89 (s, 3H, CH_3), 3.32-3.22 (m, 3H, H2, H6, H8), 2.76-2.68 (m, 2H, H6, H2), 2.29 (bs, 1H, H3), 1.65-1.55 (m, 4H, H7, H5, H4), 0.98-0.85 (m, 1H, H7).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 155.98 (C6'), 150.01 (C2'), 145.97 (C10'), 142.57 (C4'), 139.98 (C10), 130.89 (C8'), 124.02 (C3'), 121.53 (C7'), 120.89 (C9'), 113.82 (C11), 108.97 (C5'), 58.98 (C9), 56.42 (C-O) 54.92 (C8), 53.01 (C2), 43.42 (C6), 39.72 (C3), 28.05 (C7), 27.23 (C4), 25.89 (C5).

4.2.1.3 Synthesis of (8*S*,9*S*)-9-amino(9-deoxi)-*epi*-quinine (**31**)



In a round-bottom flask, 4.09 g of organic azide **30** (9.89 mmol) was dissolved in 75 mL of anhydrous THF and 6.68 g of triphenylphosphine (25.47 mmol) was slowly added at room temperature. The mixture was stirred for 4-6 h at 48-52ºC. After the complete consumption of the organic azide, which was monitored by TLC, the reaction mixture was allowed to reach room temperature and 1.5 mL of distilled H_2O was added, in order to hydrolyze the formed intermediate, and left stirring overnight.[114] After the hydrolysis step, the excess H_2O was removed by adding anhydrous $MgSO_4$ to the organic phase. After filtration and solvent

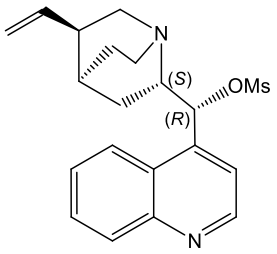
evaporated under reduced pressure on a rotary evaporator, the crude product was purified by silica gel column chromatography, initially eluted with AcOEt followed by a mixture of AcOEt/MeOH/NEt_3 (100:2:3). The amine **31** was obtained was a thick yellowish oil (2.62 g, 82%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 8.83 (d, 1H, *J*=4 Hz, H2'), 8.21 (d, 1H, *J*=8 Hz, H5'), 8.01 (d, 1H, *J*=8 Hz, H8'), 7.65 (t, 1H, *J*=8 Hz, H7'), 7.54 (t, 1H, *J*=8 Hz, H6'), 7.38 (bs, 1H, H3'), 5.79-5.68 (m, 1H, H10), 5.10-4.99 (m, 2H, H11), 4.78 (bs, 1H, H9), 3.93 (s, 3H, CH_3), 3.13 (bs, 1H, H8), 2.81-2.73 (m, 2H, H2, H6), 2.26 (s, 2H, NH_2), 2.09 (bs, 1H, H3), 1.67-1.53 (m, 3H, H7, H5, H4), 1.41-1.35 (m 1H, H5), 0.89-0.71 (m, 1H, H7).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 158.01 (C6'), 150.27 (C2'), 147.88 (C10'), 141.78 (C4'), 140.03 (C10), 130.97 (C8'), 125.11 (C3'), 122.23 (C7'), 119.67 (C9'), 112.97 (C11), 109.87 (C5'), 60.10 (C9), 56.04 (C-O), 55.89 (C8), 52.13 (C2), 42.96 (C6), 40.01 (C3), 28.13 (C7), 26.98 (C4), 25.91 (C5).

The structure was confirmed by comparison with existing results from the literature.[144]

4.2.1.4 Synthesis of (8*S*,9*R*)-9-*O*-mesylcinchonidine (**32**)



Applying the same procedure as previously described (see 4.2.1.1) using 5.011 g of commercial cinchonidine (16.98 mmol), trimethylamine (7.46 mL, 53.49 mmol) and methanesulfonyl chloride (2.63 mL, 33.96 mmol), the crude product was purified by silica gel column chromatography (eluted with AcOEt), affording the desired product **32** as a white solid (5.07 g, 94%).

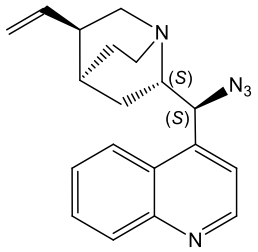
m.p.: 107-108ºC

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 8.89 (d, 1H, *J*=4 Hz, H2'), 8.22 (d, 1H, *J*=8 Hz, H5'), 8.10 (d, 1H, *J*=8 Hz, H8'), 7.80 (t, 1H, *J*=8 Hz, H7'), 7.63 (t, 1H, *J*=8 Hz, H6'), 7.49 (bs, 1H, H3'), 6.62 (bs, 1H, H9), 5.75-5.71 (m, 1H, H10), 5.10-4.99 (m, 2H, H11), 3.51-3.39 (m, 2H, H6, H8), 3.15 (bs, 1H, H2), 2.78-2.75 (m, 5H, H6, H2, CH_3), 2.34 (bs, 1H, H3), 2.01-1.72 (m, 5H, H7, H5, H4).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 150.91 (C2'), 148.64 (C10'), 143.02 (C10), 140.45 (C4'), 131.56 (C8'), 130.3 (C7'), 127.85 (C6', C5'), 123.02 (C3'), 116.52 (C11), 59.38 (C9), 56.42 (C8, C2), 41.02 (C6), 39.25 (C3, C-mesylate), 27.98 (C7), 27.43 (C4), 26.78 (C5).

The structure was confirmed by comparison with existing results from the literature.[237]

4.2.1.5 Synthesis of (8*S*,9*S*)-9-azido(9-deoxi)-*epi*-cinchonidine (**33**)

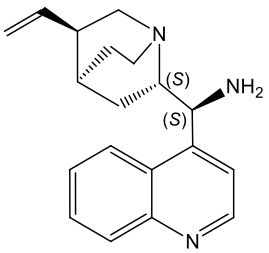


Applying the same procedure as previously described (see 4.2.1.2) using 5.07 g of compound **32** (15.96 mmol), the crude product was purified by silica gel column chromatography (eluted with AcOEt), affording the desired product **33** as a thick orange oil (4.84 g, 95%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 8.92 (d, 1H, *J*=4 Hz, H2'), 8.32 (d, 1H, *J*=8 Hz, H5'), 8.21 (d, 1H, *J*=8 Hz, H8'), 7.82 (t, 1H, *J*=8 Hz, H7'), 7.59 (t, 1H, *J*=8 Hz, H6'), 7.37 (d, 1H, J=8 Hz, H3'), 5.77-5.75 (m, 1H, H10), 5.20 (d, 1H, *J*=10 Hz, H9), 5.00-4.95 (m, 2H, H11), 3.34-3.21 (m, 3H, H2, H6, H8), 2.95-2.85 (m, 2H, H6, H2), 2.31 (bs, 1H, H3), 1.75-1.60 (m, 4H, H7, H5, H4), 0.74-0.71 (m, 1H, H7).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 150.21 (C2'), 149.01 (C10'), 142.57 (C10), 141.51 (C4'), 130.87 (C8'), 126.97 (C6'), 126.13 (C9'), 123.09 (C5'), 120.29 (C3'), 114.28 (C11), 59.81 (C9), 54.99 (C8), 53.48 (C2), 40.87 (C6), 39.43 (C3), 28.01 (C7), 27.19 (C4), 25.91 (C5).

4.2.1.6 Synthesis of (8*S*,9*S*)-9-amino(9-deoxi)-*epi*-cinchonidine (**34**)



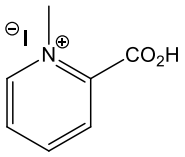
Applying the same procedure as previously described (see 4.2.1.1) using 4.84 g of organic azide **33** (15.16 mmol), the crude product was purified by silica gel column chromatography, initially eluted with AcOEt followed by a mixture of AcOEt/MeOH/NEt_3 (100:2:3), affording the desired product **34** as yellowish oil (4 g, 90%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 8.93 (d, 1H, *J*=4 Hz, H2'), 8.34 (bs 1H, H5'), 8.20 (d, 1H, *J*=8 Hz, H8'), 7.67 (t, 1H, *J*=8 Hz, H7'), 7.59 (t, 1H, *J*=8 Hz, H6'), 7.48 (bs, 1H, H3'), 5.83-5.79 (m, 1H, H10), 5.05-4.77 (m, 2H, H11), 4.76 (bs, 1H, H9), 3.08 (bs, 1H, H8), 2.86-2.81 (m, 2H, H2, H6), 2.44 (s, 2H, NH_2), 2.32 (bs, 1H, H3), 1.65-1.57 (m, 3H, H7, H5, H4), 1.44-1.41 (m 1H, H5), 0.78-0.72 (m, 1H, H7).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 151.02 (C2'), 149.04 (C10'), 141.87 (C10, C4'), 130.57 (C8'), 129.13 (C7'), 127.88 (C6'), 126.64 (C9'), 123.76 (C5'), 120.03 (C3'), 114.53 (C11), 61.94 (C9), 56.28 (C8), 40.86 (C6), 40.02 (C2), 31.03 (C3), 28.18 (C7), 27.54 (C4), 25.99 (C5).

The structure was confirmed by comparison with existing results from the literature.[144]

4.2.1.7 Synthesis of 2-(*N*-methyl)pyridinium iodide (**37**)



Based on the Liebscher procedure,[248] 4,01 g of picolinic acid (32.49 mmol) were dissolved in 40 mL of *i*PrOH, followed by the addition of 2 equivalents of iodomethane (4.04 mL, 64.98 mmol). The mixture was stirred for 3 days at 50-55ºC. After that time, the reaction mixture was allowed to reach room temperature and the yellow solid that was formed was collected by vacuum filtration and washed with cold *i*PrOH. The desired compound **37** was obtained as an amorphous yellow solid (5.86 g, 68%).

m.p.: 168.9-170.1ºC

^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) = 9.01 (d, 1H, *J*=4 Hz, Ar), 8.61 (t, 1H, *J*=8 Hz, Ar), 8.31 (d, 1H, *J*=8 Hz, Ar), 8.13 (t, 1H, *J*=8 Hz, Ar), 4.42 (s, 3H, CH_3).

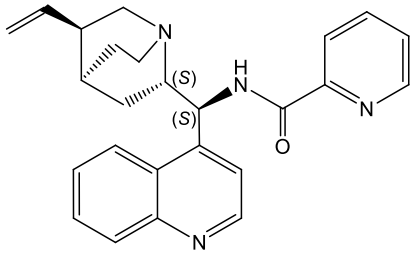
^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) = 161.25 (C=O), 149.12 (Ar), 146.31 (Ar), 138.04 (Ar), 127.26 (Ar), 124.79 (Ar), 47.89 (CH_3).

4.2.1.8 Procedure for the synthesis of picolinamides-cinchona alkaloids derivatives

4.2.1.8.1 Direct condensation method[242]

Taking the synthesis of compound **36** as an example, in a round-bottom flask, equipped with a Dean-Stark apparatus to collect the water formed during the reaction, 0.75 g of amine **34** (2.56 mmol) was dissolved in 30 mL of anhydrous toluene and then 0.315 g of commercial picolinic acid (2.6 mmol) was added, which, at room temperature, formed a white suspension. The reaction was stirred at 120-130ºC for 19 h. After this time, the reaction was allowed to reach room temperature and the solvent was removed under reduced pressure on a rotary evaporator, in order to concentrate the crude organic material as a "spongy" orange solid. The crude product was purified by silica gel column chromatography, eluted with a mixture of AcOEt/MeOH (4:1), giving the desired product as a "spongy" white solid (0.755g, 68%).

4.2.1.8.1.1 Synthesis of (8*S*,9*S*)-9-picolinamide(9-deoxi)-*epi*-cinchonidine (**36**)



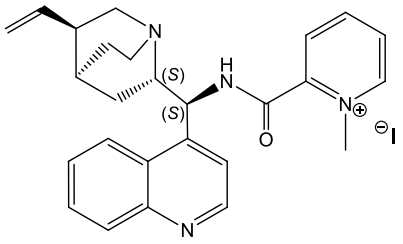
m.p.: 85.5-87.1 ºC

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 9.18 (bs, 1H, NH), 8.92 (d, 1H, *J*=4 Hz, H2'), 8.58 (d, 1H, CH pyridine), 8.48 (d, 1H, CH pyridine), 8.14 (d, 1H, *J*=8 Hz, H5'), 8.04 (d, 1H, *J*=8 Hz, H8'), 7.77-7.74 (m, 2H, H7', CH pyridine), 7.66 (t, 1H, *J*=8 Hz, H6'), 7.53 (d, 1H, *J*=4 Hz, H3'), 5.80-5.71 (m, 2H, H10, H9), 5.06-4.97 (m, 2H, H11), 3.41-3.31 (m, 2H, H6, H2), 3.20 (bs, 1H, H8), 2.95-2.79 (m, 2H, H6, H2), 2.22 (bs, 1H, H3), 1.64-1.58 (m, 3H, H4, H5, H7), 1.30-1.25 (m, 1H, H5), 0.89-0.86 (m, 1H, H7).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 164.47 (C=O), 150.30 (pyridine), 149.83 (C2'), 148.73 (C10'), 148.41 (pyridine), 146.25 (C4'), 140.96 (pyridine), 137.33 (C10), 130.58 (C8'), 129.40 (C7'), 127.46 (C6'), 127.16 (C9'), 126.32 (pyridine), 123.49 (pyridine), 122.47 (C5'), 119.69 (C3'), 115.02 (C11), 60.52 (C9), 59.86 (C8), 55.72 (C2), 41.08 (C6), 39.28 (C3), 27.58 (C7), 27.35 (C4), 26.12 (C5).

The structure was confirmed by comparison with existing results from the literature.[180]

4.2.1.8.1.2 Synthesis of (8*S*,9*S*)-9-[2-(*N*-methyl)pyridinium]-(9-deoxi)-*epi*-cinchonidine iodide (**38**)



Applying the direct condensation method described above (see 4.2.1.8.1), compound **38** was synthesized from 0.512 g of amine **34** (1.74 mmol) and 1.5 equivalents of 2-(*N*-methyl)pyridinium iodide **37** (0.663 g, 2.5 mmol). The crude product was purified by silica gel column chromatography, eluted with a mixture of AcOEt/MeOH (4:1), giving the desired product as an orange "oily" solid (0.545 g, 58%).

^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) = 9.21 (bs, 1H, NH), 8.86 (d, 1H, *J*=4 Hz, H2'), 8.67 (d, 1H, CH pyridine), 8.48 (d, 1H, CH pyridine), 8.02 (d, 1H, *J*=8 Hz, H5'), 7.93 (d, 1H, *J*=8 Hz, H8'), 7.78 (d, 1H, *J*=8 Hz, H7'), 7.69 (t, 1H, *J*=8 Hz, H6'), 7.61-7.58 (m, 2H, H3', CH pyridine), 7.48-7.42 (m, 1H, CH pyridine), 5.83-5.75 (m, 2H, H10, H9), 5.04-4.93 (m, 2H, H11), 3.32 (m, 6H, H8, H6, H2, N-CH_3), 2.87-2.81 (m, 2H, H6, H2), 2.27 (bs, 1H, H3), 1.57 (bs, 3H, H4, H5, H7), 1.40 (bs, 1H, H5), 0.90 (bs, 1H, H7).

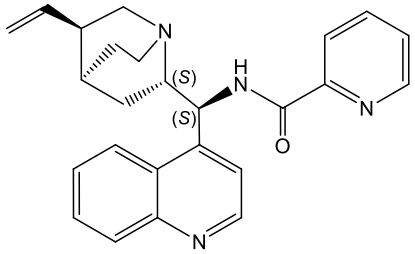
^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) = 163.14 (C=O), [149.52, 148.56, 142.03, 137.90, 135.23, 129.77, 129.11, 128.79, 128.38, 126.73, 126.66, 124.64, 121.83, 114.35 (14C aromatics, 2C vinylics)], [57.89, 55.04, 49.13, 39.62, 27.08, 25.64 (C aliphatic)].

The structure was confirmed by comparison with existing results from the literature.[180]

4.2.1.8.2 Coupling method by the formation of a mixed anhydride intermediate[249]

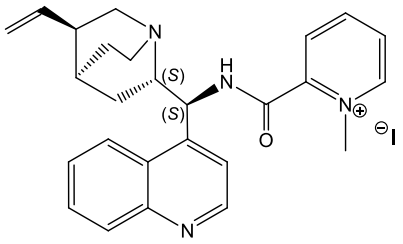
Taking the synthesis of compound **36** as an example, in a round-bottom flask, 0.142 g of commercial picolinic acid was dissolved in 20 mL of anhydrous THF and 0.199 mL of triethylamine (1.43 mmol) was added. The reaction was stirred for 10-15 minutes at room temperature. In a separate two neck round-bottom flask, 0.132 mL of isobutyl chloroformate (1.02 mmol) was dissolved in 10 mL of anhydrous THF, under inert atmosphere, and the reaction mixture was cooled in an ice bath. The picolinic acid and triethylamine mixture was then slowly added to the isobutyl chloroformate, during which the formation of a white precipitate (triethylammonium chloride) was observed. After completing the addition, the reaction was stirred at room temperature for 2 hours. Then 0.3 g of amine **34** (1.02 mmol), previously diluted in 5 ml of THF was added, and the reaction was stirred for another hour. After the consumption of the formed intermediate (mixed anhydride) by TLC, the reaction was quenched with the addition of 10 mL of H_2O and extracted with CH_2Cl_2 (3 x 10 mL). The collected organic phase was dried with anhydrous $MgSO_4$, filtered and the solvent was evaporated under reduced pressure on a rotary evaporator. The crude product purified by silica gel column chromatography, initially eluted with AcOEt followed by a mixture of AcOEt/MeOH (95:5), giving the desired compound as a “spongy” white solid (0.171g, 42%).

4.2.1.8.2.1 Synthesis of (8*S*,9*S*)-9-picolinamide(9-deoxi)-*epi*-cinchonidine (**36**)



The structure was confirmed by comparison with existing results from the literature.[180]

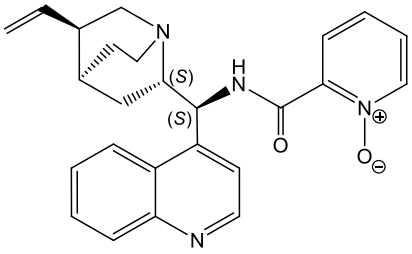
4.2.1.8.2.2 Synthesis of (8*S*,9*S*)-9-[2-(*N*-methyl)pyridinium]-(9-deoxi)-*epi*-cinchonidine iodide (**38**)



Applying the mixed anhydride method described above (see 4.2.1.8.2), compound **38** was synthesized from 0.300 g of amine **34** (1.02 mmol), 2-(*N*-methyl)pyridinium iodide **37** (0.270 g, 1.02 mmol), NEt_3 (0.199 mL, 1.43 mmol) and isobutyl chloroformate (0.132 mL, 1.02 mmol) in THF. The crude product was purified by silica gel column chromatography, initially eluted with AcOEt followed by a mixture of AcOEt/MeOH (95:5), giving the desired product as an orange "oily" solid (0.265g, 48%).

The structure was confirmed by comparison with existing results from the literature.[180]

4.2.1.8.2.3 Synthesis of (8*S*,9*S*)-9-[2-(*N*-oxide)picolinamide]-(9-deoxi)-*epi*-cinchonidine (**40**)



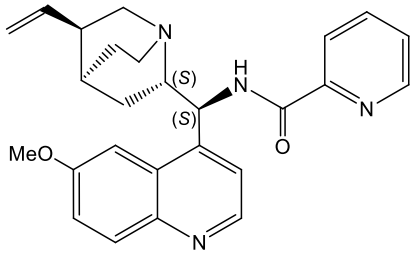
Applying the mixed anhydride method described above (see 4.2.1.8.2), compound **40** was synthesized from 0.300 g of amine **34** (1.02 mmol), picolinic acid *N*-oxide (0.142 g, 1.02 mmol), NEt_3 (0.199 mL, 1.43 mmol) and isobutyl chloroformate (0.132 mL, 1.02 mmol) in THF. The crude product was purified by silica gel column chromatography, eluted with a

mixture of AcOEt/MeOH (95:5), giving the desired product as an yellowish “oily” solid (0.233 g, 55%).

^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) = 8.88 (d, 1H, *J*=4 Hz, H2’), 8.46 (d, 1H, CH pyridine), 8.13 (d, 1H, CH pyridine), 8.03 (d, 1H, *J*=8 Hz, H5’), 7.86 (d, 1H, *J*=8 Hz, H8’), 7.76 (d, 1H, *J*=8 Hz, H7’), 7.68 (t, 1H, *J*=8 Hz, H6’), 6.96-6.93 (m, 2H, H3’, CH pyridine), 6.79-6.42 (m, 1H, CH pyridine), 5.82-5.76 (m, 1H, H10), 5.01-4.91 (m, 2H, H11), 4.27-4.24 (m, 1H, H9), 3.86-3.84 (m, 2H, H6, H2), 3.64 (bs, 1H, H8), 3.19-3.11 (m, 2H, H6, H2), 2.32 (bs, 1H, H3), 1.75-1.73 (m, 3H, H4, H5, H7), 1.50 (bs, 1H, H5), 0.93-0.81 (m, 1H, H7).

^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) = 163.23 (C=O), [154.75, 150.26, 147.89, 146.84, 142.09, 139.08, 138.56, 129.75, 129.09, 126.65, 123.85, 116.92, 114.16, 110.42 (14C aromatics, 2C vinylics)], [73.16, 67.15, 64.76, 55.20, 27.28, 18.84 (C aliphatic)].

4.2.1.8.2.4 Synthesis of (8*S*,9*S*)-9-picolinamide(9-deoxi)-*epi*-quinine (**44**)



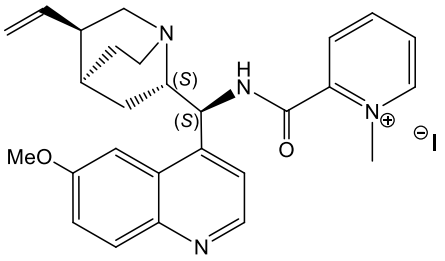
Applying the mixed anhydride method described above (see 4.2.1.8.2), compound **44** was synthesized from 0.300 g of amine **31** (0.928 mmol), commercial picolinic acid (0.129 g, 0.928 mmol), NEt_3 (0.181 mL, 1.30 mmol) and isobutyl chloroformate (0.120 mL, 0.928 mmol) in THF. The crude product was purified by silica gel column chromatography, initial eluted with AcOEt followed by a mixture of AcOEt/MeOH (95:5), giving the desired product as a white “oily” solid (0.159 g, 40%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 8.98 (bs, 1H, NH), 8.76 (d, 1H, *J*=4 Hz, H2’), 8.54 (d, 1H, CH pyridine), 8.48 (d, 1H, CH pyridine), 8.09 (d, 1H, *J*=8 Hz, H5’), 8.02 (d, 1H, *J*=8 Hz, H8’), 7.78-7.74 (m, 2H, H7’, CH pyridine), 7.45 (d, 1H, *J*=4 Hz, CH pyridine), 7.38 (d, 1H, *J*=4 Hz, H3’), 5.84-5.76 (m, 2H, H10, H9), 5.34 (bs, 1H, H11), 5.10-5.05 (m, 2H, H11), 4.00 (s, 3H, CH_3), 3.49-3.38 (m, 2H, H6, H2), 3.23 (bs, 1H, H8), 2.81-2.69 (m, 2H, H6, H2), 2.31 (bs, 1H, H3), 1.63-1.58 (m, 3H, H4, H5, H7), 1.38-1.25 (m, 1H, H5), 0.89-0.86 (m, 1H, H7).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 164.12 (C=O), 157.96 (pyridine), 149.77 (C2'), 148.30 (C10'), 147.60 (pyridine), 144.87 (C4'), 141.41 (pyridine), 137.22 (C10), 131.87 (C8'), 130.03 (C7'), 126.31 (C6'), 122.41 (C9'), 122.10 (pyridine), 121.84 (pyridine), 119.64 (C5'), 114.52 (C3'), 101.66 (C11), 60.41 (C9), 56.11 (C8), 55.64 (C2), 51.14 (C-O), 41.29 (C6), 39.28 (C3), 27.37 (C7), 27.23 (C4), 26.59 (C5).

The structure was confirmed by comparison with existing results from the literature.[180]

4.2.1.8.2.5 Synthesis of (8*S*,9*S*)-9-[2-(*N*-methyl)pyridinium]-(9-deoxi)-*epi*-quinine iodide (**45**)



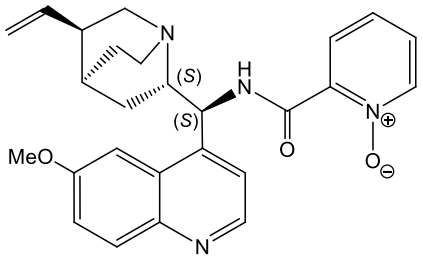
Applying the mixed anhydride method described above (see 4.2.1.8.2), compound **45** was synthesized from 0.300 g of amine **31** (0.928 mmol), 2-(*N*-methyl)pyridinium iodide **37** (0.246 g, 0.928 mmol), NEt_3 (0.181 mL, 1.30 mmol) and isobutyl chloroformate (0.120 mL, 0.928 mmol) in THF. The crude product was purified by silica gel column chromatography, eluted with a mixture of AcOEt/MeOH (95:5), giving the desired product as an yellowish "oily" solid (0.238 g, 45%).

^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) = 9.22 (bs, 1H, NH), 8.72 (d, 1H, *J*=6 Hz, H2'), 8.62 (d, 1H, CH pyridine), 8.45 (d, 1H, CH pyridine), 8.05 (d, 1H, *J*=8 Hz, H5'), 7.95 (d, 1H, *J*=8 Hz, H8'), 7.82 (d, 1H, *J*=8 Hz, H7'), 7.60-7.58 (m, 2H, H3', CH pyridine), 7.43-7.41 (m, 1H, CH pyridine), 5.94-5.74 (m, 2H, H10, H9), 5.10-5.00 (m, 2H, H11), 3.93 (s, 3H, CH_3), 3.43 (m, 6H, H8, H6, H2, N-CH_3), 2.85-2.80 (m, 2H, H6, H2), 2.24 (bs, 1H, H3), 1.58 (bs, 3H, H4, H5, H7), 1.26 (bs, 1H, H5), 0.86 (bs, 1H, H7).

^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) = 157.43 (C=O), [149.52, 148.53, 147.73, 144.12, 142.13, 137.97, 131.39, 129.47, 128.11, 126.83, 124.98, 122.09, 121.36, 115.11 (14C aromatics, 2C vinylics)], [58.15, 55.67, 49.91, 30.76, 26.93, 26.53 (C aliphatic)].

The structure was confirmed by comparison with existing results from the literature.[180]

4.2.1.8.2.6 Synthesis of (8*S*,9*S*)-9-[2-(*N*-oxide)picolinamide]-(9-deoxi)-*epi*-quinine (**43**)



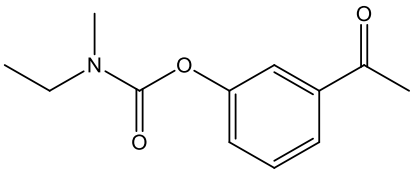
Applying the mixed anhydride method described above (see 4.2.1.8.2), compound **43** was synthesized from 0.300 g of amine **31** (0.928 mmol), picolinic acid *N*-oxide (0.129 g, 0.928 mmol), NEt_3 (0.181 mL, 1.30 mmol) and isobutyl chloroformate (0.120 mL, 0.928 mmol) in THF. The crude product was purified by silica gel column chromatography, eluted with a mixture of AcOEt/MeOH (95:5), giving the desired product as an orange "oily" solid (0.305 g, 74%).

^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) = 8.71 (d, 1H, *J*=4 Hz, H2'), 7.94 (d, 1H, CH pyridine), 7.70 (d, 1H, CH pyridine), 7.49 (d, 1H, *J*=8 Hz, H5'), 7.43 (d, 2H, *J*=8 Hz, H8', H3'), 7.34 (d, 1H, *J*=8 Hz, H7'), 6.31 (d, 1H, CH pyridine), 6.14 (d, 1H, CH pyridine), 5.90-5.86 (m, 2H, H9, H10), 5.27 (m, 1H, H11), 5.03-4.95 (m, 1H, H11), 3.92 (s, 3H, CH_3), 3.67-3.64 (m, 2H, H6, H2), 3.35 (bs, 1H, H8), 2.69-2.62 (m, 2H, H6, H2), 2.24 (bs, 1H, H3), 1.76-1.61 (m, 3H, H4, H5, H7), 1.23-1.15 (m, 1H, H5), 0.85-0.83 (m, 1H, H7).

^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) = 162.24 (C=O), [157.15, 155.85, 147.48, 146.02, 143.85, 142.03, 140.82, 135.32, 131.12, 121.10, 119.87, 11468, 104.69, 102.09 (14C aromatics, 2C vinylics)], [69.68, 55.39, 55.14, 27.47, 26.10, 18.69 (C aliphatic)].

4.2.2 Synthesis of Rivastigmine Precursors

4.2.2.1 Synthesis of (3-acetylphenyl)-*N*-ethyl-*N*-methyl carbamate (**48**)

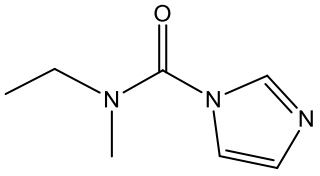


Based on existing methods in the literature,[353,354] 500 mg of carbonyl di-imidazole (3.1 mmol) and 422 mg of 3'-hydroxyacetophenone (3.1 mmol) were dissolved in 10 mL of anhydrous dicloromethane. The reaction was stirred for 1 h at room temperature and, after that time, 291 µL of ethylmethylamine (3.4 mmol) was added to the mixture. The reaction was stirred for another 24 hours at room temperature, under nitrogen atmosphere. The solvent was evaporated under reduced pressure on a rotary evaporator and the crude product purified by silica gel column chromatography eluted with CH_2Cl_2. The desired product **48** was obtained as a colorless oil (103 mg, 15%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 7.41 (m, 1H, Ar), 7.26 (m, 1H, Ar), 7.03 (m, 1H, Ar), 6.87 (m, 1H, Ar), 3.01 (bs, 2H, CH_2), 2.63 (bs, 3H, CH_3), 2.15 (s, 3H, CH_3), 0.85 (bs, 3H, CH_3)

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 198.03 (C=O), 154.56 (C=O), 151.92 (Ar), 137.98 (Ar), 129.67 (Ar), 127.08 (Ar), 125.24 (Ar), 121.67 (Ar), 44.41 (CH_2), 33.97 (CH_3), 26.85 (CH_3), 12.97 (CH_3).

4.2.2.2 Synthesis of *N*-ethyl-*N*-methyl-imidazole-1-carboxamide (**51**)

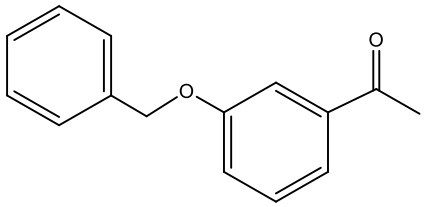


In a round-bottom flask, 0.145 mL ethylmethylamine (1.7 mmol), 1.30 g of carbonyl di-imidazole (8.5 mmol), 52.7 mg of $CF_3(SO_3)_3Yb$ (0.085 mmol) and 10 mL of anhydrous THF were added. The reaction was stirred for 24h at 40ºC and, after that time, the reaction was allowed to reach room temperature.[305] CH_2Cl_2 (2 mL) was added to make precipitate the catalyst, which was then filtered under vacuum. The filtrate was diluted with CH_2Cl_2 (20 mL), washed twice with a 2% solution of citric acid, dried over anhydrous $MgSO_4$, filtered and evaporated under reduced pressure in a rotary evaporator, giving the desired product as a colorless oil (125 mg, 48%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 7.81 (bs, 1H, Ar), 7.17 (bs, 1H, Ar), 7.01 (bs, 1H, Ar), 3.38-3.33 (q, 2H, J=12 Hz, CH_2), 2.96 (s, 3H, CH_3), 1.16 (t, 3H, J=9.4 Hz, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 151.83 (C=O), 136.93 (Ar), 129.26 (Ar), 118.08 (Ar), 45.13 (CH_2), 35.42 (CH_3), 12.30 (CH_3).

4.2.2.3 Synthesis of 3'-benzyloxyacetophenone (**54**)

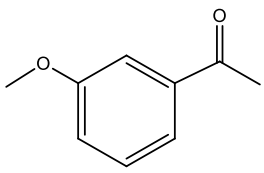


In a two-necked round-bottom flask, 2 g of 3'-hydroxyacetophenone (14.69 mmol) was dissolved in 20 mL of anhydrous THF. The reaction mixture was cooled to 0ºC in an ice bath and 0.388 g of NaH was slowly added. After stirring for a few minutes, the reaction changed aspect acquiring a brownish coloration and 1.92 mL of benzyl bromide was added. The reaction was stirred at 60ºC for 18 h. H_2O (20 mL) was added to the crude mixture and the organic phase was extracted with CH_2Cl_2 (3 x 20 mL), dried with anhydrous $MgSO_4$ and filtered. The solvent was evaporated under reduced pressure on a rotary evaporator and the crude product purified by silica gel column chromatography, initially eluted with hexane and then with a mixture of Hex/AcOEt (95/5). The desired product **54** was obtained as an orange oil (1.88 g, 57%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 7.60 (bs, 1H, Ar), 7.56 (d, 1H, *J*=8 Hz, Ar), 7.46 (d, 1H, *J*=8 Hz, Ar), 7.43-7.35 (m, 4H, Ar), 7.19 (d, 1H, *J*=8 Hz, Ar), 5.11 (s, 2H, CH_2), 2.59 (s, 3H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 197.88 (C=O), 159.02 (C-O), 138.56 (C_q), 136.58 (C_q), 129.68 (Ar), 128.69 (2 Ar), 128.18 (Ar), 127.61 (2 Ar), 121.37 (Ar), 120.30 (Ar), 113.64 (Ar), 70.20 (CH_2), 26.75 (CH_3).

4.2.2.4 Synthesis of 3'-methyloxyacetophenone (**58**)



Applying the same procedure as previously described (see 4.2.2.3) using 2 g of 3'-hydroxyacetophenone (14.69 mmol), NaH (388 mg, 16.16 mmol) and iodomethane (1 mL, 16.16 mmol), the crude product was purified by silica gel column chromatography, initially eluted with hexane followed by a mixture of Hex/AcOEt (95/5), affording the desired product **58** as orange oil (1.35 g, 61%).

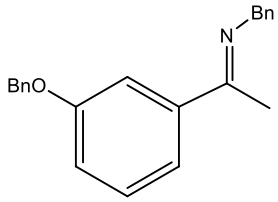
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 7.46 (d, 1H, *J*=8 Hz, Ar), 7.41 (bs, 1H, Ar), 7.29 (t, 1H, *J*=8 Hz, Ar), 7.04 (d, 1H, *J*=8 Hz, Ar), 3.77 (s, 3H, CH_3), 2.52 (s, 3H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 197.71 (C=O), 159.65 (C-O), 138.31 (C_q), 129.43 (Ar), 120.94 (Ar), 119.35 (Ar), 112.25 (Ar), 55.19 (CH_3), 26.51 (CH_3).

4.2.2.5 General procedure for the synthesis of prochiral ketimines[213]

4.42 mmol of ketone, 8.84 mmol of amine, anhydrous toluene (10 mL) and 4 Å molecular sieves were introduced in a two-necked round-bottom flask under nitrogen atmosphere. The reaction mixture was stirred for 18 h at 60ºC. After cooling to room temperature, the crude reaction was filtered and washed with CH_2Cl_2 (previously treated with sodium bicarbonate). The solvent was evaporated under reduced pressure on a rotary evaporator and the crude product used without further purification.

4.2.2.5.1 Synthesis of *N*-(1-(3-(benzyloxy)phenyl)ethylidene)benzylamine (**55**)



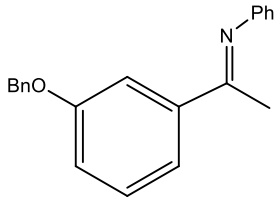
Applying the procedure described above (see 4.2.2.5), ketimine **55** was synthetized starting from 1 g of compound **54** (4.42 mmol) and 0.965 mL of benzylamine (8.84 mmol), as a yellow oil (1.29 g, 91%)

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 7.64 (bs, 1H, Ar), 7.50-7.46 (m, 2H, Ar), 7.44-7.30 (m, 10H, Ar), 7.06 (bs, 1H, Ar), 5.15 (s, 2H, CH_2), 4.79 (s, 2H, CH_2), 2.35 (s, 3H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 165.74 (C=N), 158.84 (C-O), 142.61 (C_q), 140.57 (C_q), 137.04 (C_q), 129.25 (Ar), 128.63 (2 Ar), 128.44 (2 Ar), 128.02 (Ar), 127.74 (2 Ar), 127.64

(2 Ar), 126.61 (Ar), 119.64 (Ar), 116.30 (Ar), 113.13 (Ar), 70.08 (CH_2), 55.70 (CH_2), 15.98 (CH_3).

4.2.2.5.2 Synthesis of *N*-(1-(3-(benzyloxy)phenyl)ethylidene)aniline (**57**)

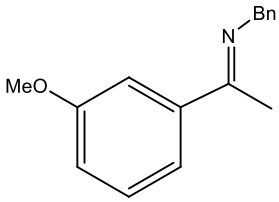


Applying the procedure described above (see 4.2.2.5), ketimine **57** was synthetized starting from 1 g of compound **54** (4.42 mmol) and 0.806 mL of aniline (8.84 mmol), as a yellowish oil (1.21 g, 90%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 7.73 (bs, 1H, Ar), 7.57 (d, 1H, *J*=8 Hz, Ar), 7.51-7.47 (m, 2H, Ar), 7.45-7.37 (m, 7H, Ar), 6.84 (d, 2H, *J*=8 Hz, Ar), 6.71 (d, 1H, *J*=8 Hz, Ar), 5.16 (s, 2H, CH_2), 2.25 (s, 3H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 165.39 (C=N), 159.05 (C-O), 151.69 (C_q), 141.02 (C_q), 135.96 (C_q), 129.46 (Ar), 129.07 (2 Ar), 128.69 (2 Ar), 128.11 (Ar), 127.69 (2 Ar), 123.38 (Ar), 120.38 (Ar), 119.46 (2 Ar), 117.95 (Ar), 133.16 (Ar), 70.25 (CH_2), 17.61 (CH_3).

4.2.2.5.3 Synthesis of *N*-(1-(3-methoxyphenyl)ethylidene)benzylamine (**59**)

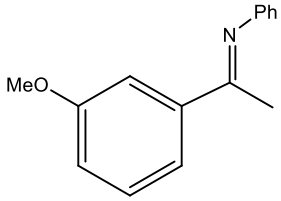


Applying the procedure described above (see 4.2.2.5), ketimine **59** was synthetized starting from 1 g of compound **58** (6.66 mmol) and 1.45 mL of benzylamine (13.32 mmol), as a dark yellow oil (1.48 g, 92%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 7.56-7.49 (m, 4H, Ar), 7.44-7.31 (m, 4H, Ar), 7.01 (bs, 1H, Ar), 4.80 (s, 2H, CH_2), 3.88 (s, 3H, CH_3), 2.35 (s, 3H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 169.48 (C=N), 159.58 (C-O), 142.54 (C_q), 140.52 (C_q), 129.15 (Ar), 128.37 (2 Ar), 127.63 (2 Ar), 126.53 (Ar), 119.33 (Ar), 115.41 (Ar), 112.01 (Ar), 55.27 (CH_2), 15.92 (CH_3).

4.2.2.5.4 Synthesis of *N*-(1-(3-methoxyphenyl)ethylidene)aniline (**60**)

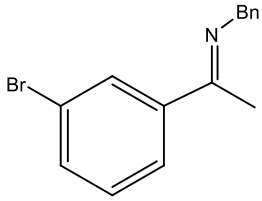


Applying the procedure described above (see 4.2.2.5), ketimine **60** was synthetized starting from 1 g of compound **58** (6.66 mmol) and 1.21 mL of aniline (13.32 mmol), as an orange oil (1.42 g, 94%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 7.64 (bs, 1H, Ar), 7.55 (d, 1H, *J*=8 Hz, Ar), 7.39 (t, 3H, *J*=8 Hz, Ar), 7.06 (d, 1H, *J*=8 Hz, Ar), 6.84 (d, 2H, *J*=8 Hz, Ar), 6.70 (d, 1H, *J*=8 Hz, Ar), 3.80 (s, 3H, CH_3), 2.25 (s, 3H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 165.36 (C=N), 159.75 (C-O), 151.68 (C_q), 140.97 (C_q), 129.37 (Ar), 129.04 (2 Ar), 133.32 (Ar), 119.91 (Ar), 119.68 (2 Ar), 116.89 (Ar), 111.87 (Ar), 55.46 (CH_3), 17.57 (CH_3).

4.2.2.5.5 Synthesis of *N*-(1-(3-bromophenyl)ethylidene)benzylamine (**63**)

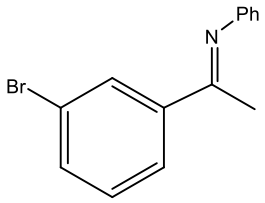


Applying the procedure described above (see 4.2.2.5), ketimine **63** was synthetized starting from 332 µL of 3'-bromoacetophenone (2.51 mmol) and 548 µL of benzylamine (5.02 mmol), as a colorless oil (0.688 g, 95%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 8.09 (bs, 1H, Ar), 7.82 (d, 1H, *J*=8 Hz, Ar), 7.55 (d, 1H, *J*=8 Hz, Ar), 7.48 (bs, 2H, Ar), 7.43-7.39 (t, 2H, *J*=8 Hz, Ar), 7.33-7.28 (m, 2H, Ar), 4.76 (s, 2H, CH_2), 2.32 (s, 3H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 164.43 (C=N), 142.93 (C_q), 140.20 (C_q), 132.50 (Ar), 129.84 (Ar), 129.75 (Ar), 128.46 (Ar), 127.71 (2 Ar), 126.70 (Ar), 125.37 (Ar), 122.61 (C-Br), 55.81 (CH_2), 15.78 (CH_3).

4.2.2.5.6 Synthesis of *N*-(1-(3-bromophenyl)ethylidene)aniline (**64**)

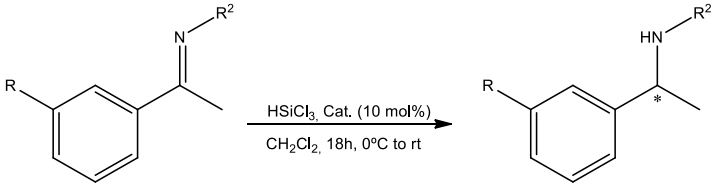


Applying the procedure described above (see 4.2.2.5), ketimine **64** was synthetized starting from 664 µL of 3'-bromoacetophenone (5.02 mmol) and 916 µL of aniline (10.05 mmol), as a colorless oil (1.3 g, 94%).

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 8.22, (bs, 1H, Ar), 7.90 (d, 1H, *J*=8 Hz, Ar), 7.61 (d, 1H, *J*=8 Hz, Ar), 7.40 (t, 2H, *J*=8 Hz, Ar), 7.33 (t, 1H, *J*=8 Hz, Ar), 7.20-7.13 (m, 1H, Ar), 6.83 (t, 2H, J=6 Hz, Ar), 2.23 (s, 3H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 164.02 (C=N), 151.16 (C_q), 141.37 (C_q), 133.29 (Ar), 130.25 (Ar), 129.88 (Ar), 129.02 (2 Ar), 125.80 (Ar), 123.52 (Ar), 119.25 (2 Ar), 115.04 (C-Br), 17.29 (CH_3).

4.3 Hydrosilylation of Ketimines



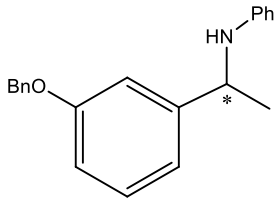
Enantioselective reduction of ketimines with organocatalysts:[175]

In a 10 mL round-bottom flask, the ketimine (0.32 mmol) and 10 mol% of organocatalyst was dissolved in 2 mL of anhydrous CH_2Cl_2, under nitrogen atmosphere. The mixture was cooled to 0ºC and stirred for 15 min, after which 3.5 equivalents of $HSiCl_3$ (1.11 mmol) was added. The reaction mixture was allowed to reach room temperature and stirred for 18 h, after which the mixture was quenched with a solution of NaOH 10% until a basic pH was reached. The organic phase was extracted with CH_2Cl_2 (3 x 10 mL), dried with anhydrous $MgSO_4$ and filtered. The solvent was evaporated under reduced pressure on a rotary evaporator and the crude product purified by silica gel column chromatography, eluted with a mixture of Hex/AcOEt (95:5), giving the desired amine.

Procedure for racemic chiral amines:

In a 10 mL round-bottom flask, the ketimine (0.32 mmol) and 5 equivalents of DMF (1.65 mmol) was dissolved in 2 mL of anhydrous CH_2Cl_2, under nitrogen atmosphere. The mixture was cooled to 0ºC and stirred for 15 min, after which 3.5 equivalents of $HSiCl_3$ (1.11 mmol) was added. The reaction mixture was allowed to reach room temperature and stirred for 18 h, after which the mixture was quenched with a solution of NaOH 10% until a basic pH was reached. The organic phase was extracted with CH_2Cl_2 (3 x 10 mL), dried with anhydrous $MgSO_4$ and filtered. The solvent was evaporated under reduced pressure on a rotary evaporator and the crude product purified by silica gel column chromatography, eluted with a mixture of Hex/AcOEt (95:5), giving the desired amine.

4.3.1 Synthesis of *N*-(1-(3-(benzyloxy)phenyl)ethyl)aniline (**65**)



The desired product was obtained as a yellowish oil.

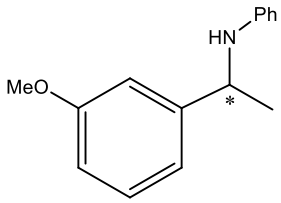
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 7.49 (d, 2H, *J*=8 Hz, Ar), 7.44 (t, 2H, *J*=8 Hz, Ar), 7.39 (d, 2H, *J*=8 Hz, Ar), 7.31 (t, 2H, *J*=4 Hz, Ar), 7.17 (t, 2H, *J*=8 Hz, Ar), 7.10 (bs, 1H, Ar),

7.04 (d, 1H, *J*=4 Hz, Ar), 6.91 (d, 1H, *J*=8 Hz, Ar), 6.73 (t, 1H, *J*=8 Hz, Ar), 6.69 (d, 1H, *J*=8 Hz, Ar), 5.09 (s, 2H, CH_2), 4.41 (q, 1H, *J*=8 Hz, CH), 1.57 (d, 3H, *J*=8 Hz, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 159.26 (C-O), 147.27 (C_q), 137.0 (C_q), 129.79 (Ar), 129.19 (2 Ar), 128.65 (2 Ar), 128.04 (2 Ar), 127.72 (2 Ar), 118.61 (Ar), 117.45 (Ar), 113.47 (Ar), 113.02 (Ar), 112.71 (Ar), 70.06 (CH_2), 53.66 (CH), 25.04 (CH_3).

HPLC: Chiracel OD-H column, hexane/2-propanol (98:2), flow rate: 0.8 mL/min, wavelength detector at 254 nm, t_R= 14.38 min (*S*), t_R= 18.82 (*R*).

4.3.2 Synthesis of *N*-(1-(3-methoxyphenyl)ethyl)aniline (**66**)



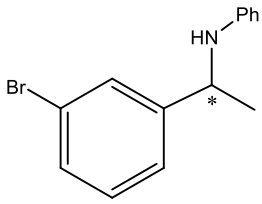
The desired product was obtained as a pale orange oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 7.31 (t, 1H, *J*=8 Hz, Ar), 7.17 (t, 1H, *J*=8 Hz, Ar), 7.05 (bs, 1H, Ar), 7.02 (bs, 1H, Ar), 6.34 (d, 1H, *J*=8 Hz, Ar), 6.73 (t, 1H, *J*=8 Hz, Ar), 6.59 (d, 2H, *J*=8 Hz, Ar), 4.51 (q, 1H, *J*=8 Hz, CH), 3.83 (s, 3H, CH_3), 1.57 (d, 3H, *J*=8 Hz, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 159.95 (C-O), 147.30 (C_q), 147.20 (C_q), 129.70 (Ar), 129.12 (Ar), 118.24 (Ar), 117.31 (Ar), 113.37 (2 Ar), 111.99 (Ar), 111.72 (Ar), 55.14 (CH_3), 53.56 (CH_2), 25.00 (CH_3).

HPLC: Chiracel OD-H column, hexane/2-propanol (98:2), flow rate: 0.8 mL/min, wavelength detector at 254 nm, t_R= 15.44 min (*S*), t_R= 17.91 min (*R*).

4.3.3 Synthesis of *N*-(1-(3-bromophenyl)ethyl)aniline (**67**)



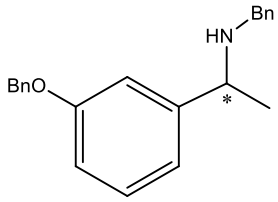
The desired product was obtained as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 7.57 (bs, 1H, Ar), 7.39 (d, 1H, *J*=8 Hz, Ar), 7.33 (d, 1H, *J*=4 Hz, Ar), 7.21 (t, 1H, *J*=8 Hz, Ar), 7.15 (t, 2H, *J*=8 Hz, Ar), 6.72 (t, 1H, *J*=8 Hz, Ar), 6.53 (d, 2H, *J*=8 Hz, Ar), 4.45 (q, 1H, *J*=8 Hz, CH), 1.52 (d, 3H, *J*=8 Hz, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 147.96 (C_q), 146.93 (C_q), 130.37 (Ar), 130.10 (Ar), 129.23 (2 Ar), 129.03 (Ar), 124.57 (Ar), 122.89 (C-Br) 117.67 (Ar), 113.40 (2 Ar), 53.30 (CH), 25.13 (CH_3).

HPLC: Chiracel OD-H column, hexane/2-propanol (90:10), flow rate: 0.8 mL/min, wavelength detector at 254 nm, t_R= 17.07 min (*S*), t_R= 21.97 min (*R*).

4.3.4 Synthesis of *N*-(1-(3-(benzyloxy)phenyl)ethyl)benzylamine (**68**)



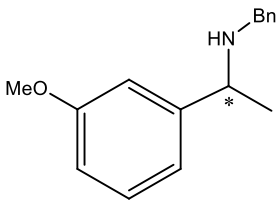
The desired product was obtained as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 7.97 (d, 2H, J=8 Hz, Ar), 7.49 (t, 2H, J=8 Hz, Ar), 7.45-7.35 (m, 7H, Ar), 7.17 (bs, 1H, Ar), 7.08 (d, 1H, J=8 Hz, Ar), 7.00 (d, 1H, J=8 Hz, Ar), 5.18 (s, 2H, CH_2), 3.91 (q, 1H, J=8 Hz, CH), 3.80-3.69 (m, 2H, CH_2), 1.48 (d, 3H, J=8 Hz, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 159.13 (C_q), 147.50 (C_q), 140.69 (C_q) 137.15 (C_q), 129.51 (Ar), 128.58 (2 Ar), 128.42 (2 Ar), 128.39 (2 Ar), 128.17 (Ar), 127.96 (2 Ar), 126.87 (Ar), 119.43 (Ar), 113.23 (Ar), 113.13 (Ar), 69.62 (CH_2), 57.53 (CH), 51.70 (CH_2), 24.58 (CH_3).

HPLC: Chiracel OD-H column, hexane/2-propanol (99:1), flow rate: 0.8 mL/min, wavelength detector at 254 nm, t_R= 15.52 min (*R*), t_R= 23.23 min (*S*).

4.3.5 Synthesis of *N*-(1-(3-methoxyphenyl)ethyl)benzylamine (**69**)



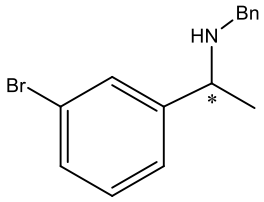
The desired product was obtained as a yellowish oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 7.39-7.29 (m, 6H, Ar), 7.00 (d, 2H, *J*=8 Hz, Ar), 6.86 (d, 1H, *J*=8 Hz, Ar), 4.29 (q, 1H, *J*=8 Hz, CH), 3.86 (s, 3H, CH_3), 3.70 (q, 2H, *J*=8 Hz, CH_2), 1.42 (d, 3H, *J*=8 Hz, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 159.89 (C_q), 147.38 (C_q), 140.62 (C_q), 129.47 (Ar), 128.41 (2 Ar), 128.38 (2 Ar), 126.88 (Ar), 119.12 (Ar), 112.27 (Ar), 112.22 (Ar), 57.55 (CH), 56.12 (CH_3), 51.68 (CH_2), 24.53 (CH_3).

HPLC: Chiracel OD-H column, hexane/2-propanol (98:2), flow rate: 0.8 mL/min, wavelength detector at 254 nm, t_R= 8.79 min (*R*), t_R= 10.51 min (*S*).

4.3.6 Synthesis of *N*-(1-(3-bromophenyl)ethyl)benzylamine (**70**)



The desired product was obtained as a pale white oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 7.66 (bs, 1H, Ar), 7.49 (d, 1H, *J*=8 Hz, Ar), 7.45-7.35 (m, 6H, Ar), 7.30 (t, 1H, *J*=8 Hz, Ar), 3.88 (q, 1H, *J*=8 Hz, CH), 3.73 (q, 2H, *J*=8 Hz, CH_2), 1.45 (d, 3H, *J*=8 Hz, CH_3).

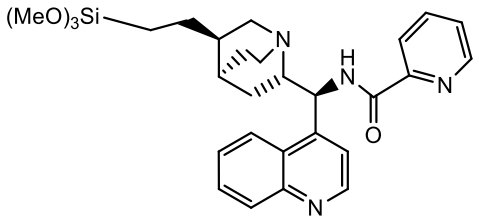
^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 148.22 (C_q), 140.39 (C_q), 130.11 (Ar), 130.06 (Ar), 129.85 (Ar), 128.43 (2 Ar), 128.11 (2 Ar), 126.48 (Ar), 125.42 (Ar), 122.72 (C-Br), 57.19 (CH), 51.70 (CH_2), 22.78 (CH_3).

HPLC: Chiracel OD-H column, hexane/2-propanol (99:1), flow rate: 0.8 mL/min, wavelength detector at 254 nm, t_R= 7.93 (*R*), t_R= 9.01 min (*S*).

4.4 Immobilization of Homogenous Catalysts

4.4.1 Synthesis of silica-supported catalysts

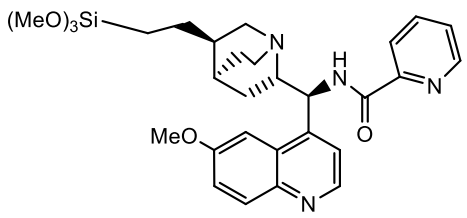
4.4.1.1 Synthesis of (8*S*,9*S*)-(2-trimethoxysilyl)-9-picolinamide(9-deoxi)-*epi*-cinchonidine (**71**)



In a two-necked round-bottom flask, 196 mg of compound **36** (0.492 mmol) was dissolved in anhydrous THF and 0.187 mL of trimethoxysilane (1.476 mmol) and 10 mg of $dcpPtCl_2$ (0.0246 mmol) were added in this order.[343] The mixture was refluxed, under nitrogen atmosphere, for 24 h. The solvent was evaporated under reduced pressure on a rotary evaporator and the crude product **71** was obtained in quantitative yield as a dark oily solid and used without further purification.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 9.28 (bs, 1H, NH), 8.92 (d, 1H, *J*=3 Hz, H2'), 8.59 (d, 1H, CH pyridine), 8.49 (d, 1H, CH pyridine), 8.13 (d, 1H, *J*=6 Hz, H5'), 8.05 (d, 1H, *J*=6 Hz, H8'), 7.76-7.73 (m, 2H, H7', CH pyridine), 7.65 (t, 1H, *J*=6 Hz, H6'), 7.37 (d, 1H, *J*=3 Hz, H3'), 5.89 (bs, 1H, H9), 3.74-3.71 (m, 2H, H6, H2), 3.60-3.52 (m, 3H, H8, H6, H2), 3.47 (s, 9H, CH_3), 2.35 (bs, 1H, H3), 1.86-1.79 (m, 3H, H4, H5, H7), 1.30-1.25 (m, 2H, H5, H10), 0.87-0.83 (m, 2H, H7, H11).

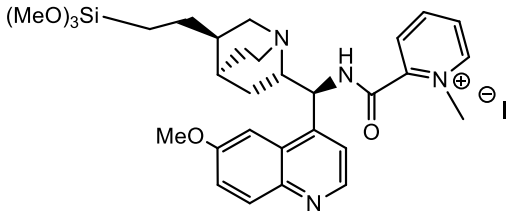
4.4.1.2 Synthesis of (8*S*,9*S*)-(2-trimethoxysilyl)-9-picolinamide(9-deoxi)-*epi*-quinine (**71a**)



Applying the same procedure as described above (see 4.4.1.1) using compound **44** (523 mg, 1.22 mmol), trimethoxysilane (0.465 mL, 3.66 mmol) and $dcpPtCl_2$ (24 mg, 0.061 mmol), the crude product **71a** was obtained in quantitative yield as a dark oily solid and used without further purification.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.94 (bs, 1H, NH), 8.72 (d, 1H, *J*=3 Hz, H2'), 8.52 (d, 1H, CH pyridine), 8.49 (d, 1H, CH pyridine), 8.05-8.01 (m, 1H, H8', H5'), 7.74-7.68 (m, 2H, H7', CH pyridine), 7.43 (t, 1H, *J*=6 Hz, H6'), 7.28 (d, 1H, *J*=3 Hz, H3'), 5.61 (bs, 1H, H9), 3.96 (s, 3H, CH_3), 3.81-3.69 (m, 2H, H6, H2), 3.59-3.51 (m, 3H, H8, H6, H2), 3.33 (s, 9H,CH_3), 2.25 (bs, 1H, H3), 1.86-1.80 (m, 3H, H4, H5, H7), 1.40-1.24 (m, 2H, H5, H10), 0.99-0.82 (m, 2H, H7, H11).

4.4.1.3 Synthesis of (8*S*,9*S*)-(2-trimethoxysilyl)-9-[2-(*N*-methyl)pyridinium]-(9-deoxi)-*epi*-quinine iodide (**71b**)

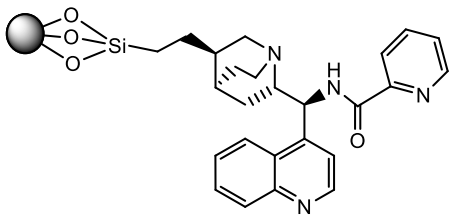


Applying the same procedure as described above (see 4.4.1.1) using compound **45** (338 mg, 0.592 mmol), trimethoxysilane (0.226 mL, 1.777 mmol) and $dcpPtCl_2$ (12 mg, 0.0296 mmol), the crude product **71b** was obtained in quantitative yield as a dark oily solid and used without further purification.

4.4.1.4 Grafting reaction – General procedure[343]

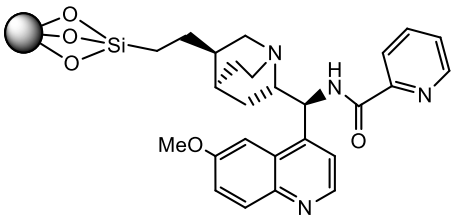
Commercially available mesoporous silica nanoparticles (1 g) and the properly modified organotrimethoxysilane (0.7 mmol) were suspended in anhydrous toluene (15 mL) and stirred at reflux for 48 h, under nitrogen atmosphere. The immobilized catalysts were isolated by filtration, washed with a mixture of organic solvents (AcOEt, CH_2Cl_2 and MeOH) and dried under vacuum to remove any trace of remaining solvent.

4.4.1.4.1 Synthesis of silica-supported (8*S*,9*S*)-9-picolinamide(9-deoxi)-*epi*-cinchonidine (**72**)



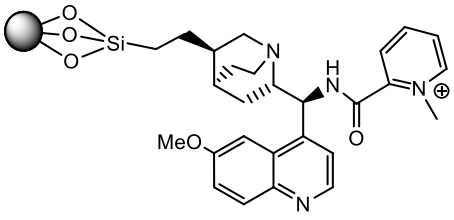
Applying the same procedure as described above (see 4.4.1.4) catalyst **37** was immobilized onto silica as a white solid, with a loading of 0.4 mmol/g.

4.4.1.4.2 Synthesis of silica-supported (8*S*,9*S*)-9-picolinamide(9-deoxi)-*epi*-quinine (**73**)



Applying the same procedure as described above (see 4.4.1.4) catalyst **44** was immobilized onto silica as a white solid, with a loading of 0.5 mmol/g.

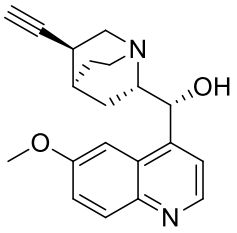
4.4.1.4.3 Synthesis of silica-supported (8*S*,9*S*)-9-[2-(*N*-methyl)pyridinium]-(9-deoxi)-*epi*-quinine iodide (**74**)



Applying the same procedure as described above (see 4.4.1.4) catalyst **45** was immobilized onto silica as a pale yellow solid, with a loading of 0.3 mmol/g.

4.4.2 Synthesis of polymer-supported catalysts

4.4.2.1 Synthesis of ((2S,4S,5S)-5-ethylnyl-2-quinuclidinyl)(6-methoxy-4-quinolinyl) methanol (**75**)



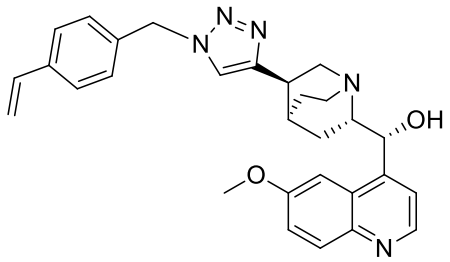
In a two-necked round-bottom flask, was prepared a solution of quinine (2 g, 6.2 mmol) in anhydrous CH_2Cl_2, under nitrogen atmosphere. After cooling to 0ºC in an ice bath, a 6M bromide solution (12.4 mmol) in anhydrous CH_2Cl_2 was added dropwise over a period of 15 minutes. The resulting yellow suspension was vigorously stirred for 1 h at 0ºC and then 1 h at room temperature. After this time, 120 mL of petroleum ether was slowly added in order to precipitate the 10,11-dibromo derivative. The suspension was stirred for 10 minutes and the crude product was collected by filtration and washed with petroleum ether (40 mL). The resultant yellowish solid was dried under high vacuum and then used in the next step without further purification. The crude product was transferred to a single necked round-bottom flask and dissolved in 50 mL of THF. Aliquat (0.6 mmol) was added and, after 5 minutes of stirring, powdered potassium hydroxide (6 mmol) was added in one portion. The mixture was stirred at 45ºC for 1 hour, then freshly powdered potassium hydroxide (6 mmol) was added again and the mixture was stirred for another hour at 45ºC, then for 15 hours at room temperature.[355] The solids were removed by filtration and washed repeatedly with THF (50 mL). The filtrates were concentrated under vacuum giving a brownish solid which was partially purified by flash column chromatography, eluted with AcOEt/MeOH (10:1). The yellowish crude solid obtained was suspended in 80 mL of a mixture of ETP/AcOEt (4:1) and vigorously stirred for 24 h at room temperature. The resultant precipitate was filtered, washed with a mixture of ETP/AcOEt (10:1, 100 mL) and pure petroleum ether (100 mL), and dried under vacuum to give the desired compound **75** as an off-white solid (1.26 g, 3.91 mmol, 63%).

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.70 (d, 1H, *J*=3 Hz, H2'), 7.96 (d, 1H, *J*=6 Hz, H8'), 7.54 (d, 1H, *J*=6 Hz, H7'), 7.33-7.29 (dd, 1H, *J*=6 Hz, H3'), 7.23 (d, 1H, *J*=6 Hz, H5'), 5.72

(bs, 1H, H9), 3.89 (s, 3H, CH_3), 3.61 (bs, 1H, H6), 3.42 (m, 1H, H8), 3.24 (m, 1H, H2), 2.98 (bd, 1H, H6), 2.72 (m, 1H, H2), 2.60 (m, 1H, H3), 1.97 (d, 1H, J=6 Hz, H11), 1.85 (m, 1H, H7), 1.50 (m, 1H, H5), 1.28-1.33 (m, 1H, H4).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 158.1, 148.0, 144.7, 131.9, 127.1, 122.0, 118.9, 101.8, 88.1, 72.4, 69.1, 59.9, 58.3, 56.1, 43.1, 28.0, 27.5, 26.5, 22.8.

4.4.2.2 Synthesis of (8*S*,9*R*)-(2-(4-vinylbenzyl)-triazole)-quinine (**76**)



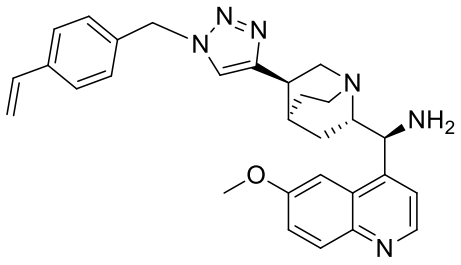
In a two-necked round-bottom flask, 300 mg of compound **75** (0.935 mmol) was dissolved in anhydrous $CHCl_3$ (12 mL), under nitrogen atmosphere, and then 8.9 mg of copper iodide (0.047 mmol) and 1.55 mL of diisopropylethylamine (9.35 mmol) were added. The mixture was stirred for 15 minutes at room temperature, then a solution of 4-azidomethylstyrene (193 mg, 1.22 mmol) in anhydrous $CHCl_3$ (2 mL) was slowly added. The mixture was stirred for 24 hours at room temperature. After this time, 5 mL of a solution of ammonium hydroxide 33% w/t was added and the mixture was stirred for 10 minutes. The collected organic phase was washed with hydrochloric acid 10% w/t (3 x 5 mL), then the aqueous phase was collected and washed with a solution of sodium bicarbonate. The organic phase was extracted with CH_2Cl_2 (3 x 10 mL), dried with anhydrous Na_2SO_4 and filtered. The solvent was evaporated under reduced pressure on a rotary evaporator and the crude product purified by flash column chromatography, eluted with a mixture of CH_2Cl_2/MeOH (9:1) to (7:3), affording desired compound **76** as a white-off solid (230 mg, 51%).

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.66 (d, 1H, *J*=4.3 Hz, H2'), 7.95 (d, 1H, H8'), 7.53 (d, 1H, H3'), 7.33 (d, 2H, *J*=7.8 Hz, CH styrene), 7.30 (dd, 1H, *J*=9.1 Hz, H7'), 7.23 (d, 1H, *J*=0.89 Hz, H5'), 7.11 (d, 2H, CH styrene), 7.09 (d, 1H, H11), 6.70 (dd, 1H, CH styrene), 5.79 (d, 1H, *J*=17.6 Hz, CH styrene), 5.73 (b, 1H, H3), 5.37 (s, 2H, CH_2 styrene), 5.32 (d, 1H, *J*=10.9 Hz, CH styrene), 3.87 (s, 3H, CH_3), 3.68 (m, 1H, H6), 3.39 (m, 2H, H8), 3.06 (m,

1H, H3), 2.79 (m, 1H, H6), 2.11 (bs, 1H, H4), 1.89 (m, 1H, H5), 1.79 (m, 1H, H7), 1.66 (m, 1H, H5), 1.39 (m, 1H, H7).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 157.9 (C6'), 150.4 (C10), 147.4 (C2'), 146.7 (C4'), 144.2 (C9'), 138.1 (C styrene), 135.9 (C styrene), 133.9 (C styrene), 131.5 (C8'), 128.2 (C styrene), 126.8 (C styrene), 126.5 (C10'), 121.7 (C7'), 120.3 (C11), 118.5 (C3'), 114.9 (C styrene), 101.2 (C5'), 70.8 (C9), 59.71 (C8), 55.9 (C2, CH_3), 53.8 (C styrene), 43.4 (C6), 32.9 (C3), 27.8 (C4), 26.8 (C5), 21.5 (C7).

4.4.2.3 Synthesis of (8*S*,9*S*)-(2-(4-vinylbenzyl)-triazole)-9-amino(9-deoxi)-*epi*-quinine (**77**)



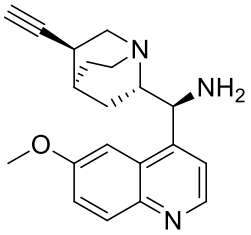
Following the procedure used for the synthesis of (8*S*,9*S*)-9-amino(9-deoxi)-*epi*-quinine **31** (see 4.2.1.3), 227 mg of compound **76** (0.47 mmol) was dissolved in anhydrous THF (8 mL), under nitrogen atmosphere, and 0.208 mL of triethylamine (1.49 mmol) was added. The reaction mixture was cooled to 0ºC in an ice bath and, after 10 minutes of stirring, 0.073 mL of methanesulfonyl chloride (0.946 mmol) was added dropwise. The mixture as allowed to reach room temperature and it was stirred for 5h. After consumption of substrate, monitored by TLC, a saturated solution of $NaHCO_3$ (5 mL) was added. The organic phase was extracted with CH_2Cl_2 (3 x 10 mL), dried with anhydrous Na_2SO_4 and filtered. The solvent was evaporated under reduced pressure on a rotary evaporator and crude product used without further purification. The pale yellow solid obtained was dissolved in 8 mL DMF and then 61.5 mg of sodium azide (0.946 mmol) was added. The mixture was stirred at 80-85ºC for 18 h. After consumption of substrate, monitored by TLC, the solvent was evaporated under reduced pressure in a rotary evaporator. The crude product was dissolved in CH_2Cl_2 and 8 mL of water was added. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic phases were dried with anhydrous Na_2SO_4, filtered and concentrated under vacuum affording a brownish solid

that was used without further purification. This crude product was dissolved in anhydrous THF (5 mL), in a two-necked round-bottom flask, under nitrogen atmosphere. The mixture was heated to 50ºC and a solution of triphenylphosphine (186 mg, 0.71 mmol) in anhydrous THF (3 mL) was slowly added. The reaction mixture was stirred at 50ºC for 5 hours. After this time, the mixture was allowed to reach room temperature and 0.6 mL of distilled water was added. The reaction was stirred for another 15 hours at room temperature. After this time, the solvent was evaporated under reduced pressure on a rotary evaporator, the crude product was diluted in 10 mL CH_2Cl_2 and a solution of HCl 10% w/t was added up to pH 2. The organic layer was washed with CH_2Cl_2 (2 x 5 mL) and then a solution of NH_4OH 33% w/t was added up to pH 8. The organic phase was extracted with CH_2Cl_2 (3 x 10 mL), dried with anhydrous Na_2SO_4 and filtered. The solvent was evaporated under reduced pressure on a rotary evaporator and crude product was purified by flash column chromatography, eluted with CH_2Cl_2/MeOH/NEt_3 (98:2:1), affording desired compound **77** as an off-white solid (59 mg, 26%).

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.71 (d, 1H, *J*=4.6 Hz, H2'), 8.02 (d, 1H, H8'), 7.64 (b, 1H, H5'), 7.41 (d, 1H, H3'), 7.40 (d, 2H, CH styrene), 7.38 (d, 1H, *J*=9.2 Hz, H7'), 7.18 (d, 2H, *J*=8.6 Hz, CH styrene), 7.17 (s, 1H, H11), 6.72 (dd, 1H, CH styrene), 5.82 (d, 1H, *J*=17.6 Hz, CH styrene), 5.46 (s, 2H, CH styrene), 5.33 (d, 1H, *J*=11.4 Hz, CH styrene), 4.62 (bs, 1H, H9), 3.99 (s, 3H, CH_3), 3.54 (dd, 1H, H2), 3.49 (dd, 1H, H2), 3.32 (m, 1H, H6), 3.08 (m, 1H, H3), 2.93 (m, 1H, H6), 1.92 (bs, 1H, H4), 1.67 (m, 2H, H5), 1.32 (m, 1H, H7), 0.76 (m, 1H, H7).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 157.7 (C6'), 151.3 (C10), 147.9 (C2'), 146.8 (C4'), 144.7 (C9'), 138.1 (C styrene), 135.9 (C styrene), 134.1 (C styrene), 131.8 (C8'), 128.8 (10'), 128.2 (C styrene), 126.8 (C styrene), 121.2 (C7'), 120.2 (C11), 119.9 (C3'), 115.0 (C styrene), 102.0 (C5'), 61.6 (C8), 55.8 (CH_3), 55.6 (C2), 53.8 (C9), 41.1 (C6), 33.2 (C3), 27.9 (C4), 27.7 (C5), 26.0 (C7).

4.4.2.4 Synthesis of (8*S*,9*S*)-(2-ethynyl)-9-amino(9-deoxi)-*epi*-quinine (**81**)

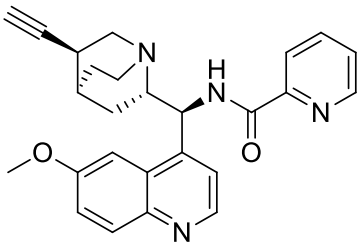


Applying the procedure described above (see 4.4.2.3), starting from 400 mg of compound **75** (1.246 mmol), after only one purification by flash column chromatography eluted with CH_2Cl_2/MeOH (98/2), compound **81** was obtained as a yellowish solid (320 mg, 80%).

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.70 (d, 1H, *J*=3 Hz, H2'), 7.96 (d, 1H, *J*=6 Hz, H8'), 7.54 (d, 1H, *J*=6 Hz, H7'), 7.33-7.29 (dd, 1H, *J*=6 Hz, H3'), 7.23 (d, 1H, *J*=6 Hz, H5'), 5.72 (bs, 1H, H9), 3.89 (s, 3H, CH_3), 3.61 (bs, 1H, H6), 3.42 (m, 1H, H8), 3.24 (m, 1H, H2), 2.98 (bd, 1H, H6), 2.72 (m, 1H, H2), 2.60 (m, 1H, H3), 1.97 (d, 1H, *J*=6 Hz, H11), 1.85 (m, 1H, H7), 1.50 (m, 1H, H5), 1.28-1.33 (m, 1H, H4).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 158.1, 148.0, 144.7, 131.9, 127.1, 122.0, 118.9, 101.8, 88.1, 72.4, 69.1, 59.9, 58.3, 43.1, 28.0, 27.5, 26.5, 22.8.

4.4.2.5 Synthesis of (8*S*,9*S*)-(2-ethynyl)-9-picolinamide(9-deoxi)-*epi*-quinine (**82**)



Applying the previously described mixed anhydride method (see 4.2.1.8.2), compound **82** was synthesized from 200 mg of amine **81** (0.622 mmol), picolinic acid (87 mg, 0.622 mmol), NEt_3 (121 µL, 0.871 mmol) and isobutyl chloroformate (81 µL, 0.928 mmol) in anhydrous THF. The crude product was purified by silica gel column chromatography, eluted with a mixture of CH_2Cl_2/MeOH (95:5), giving the desired product as an off-white solid (194 mg, 73%).

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.78 (d, 1H, *J*=3 Hz, H2'), 8.67 (d, 1H, CH pyridine), 8.10 (d, 1H, CH pyridine), 7.96 (d, 1H, *J*=6 Hz, H8'), 7.79 (d, 2H, *J*=6 Hz, H7', CH pyridine), 7.48 (d, 1H, *J*=3 Hz, CH pyridine), 7.33-7.29 (dd, 1H, *J*=6 Hz, H3'), 7.23 (d, 1H, *J*=6 Hz, H5'), 5.72 (bs, 1H, H9), 3.89 (s, 3H, CH_3), 3.49-3.38 (m, 2H, H6, H2), 3.23 (bs, 1H, H8), 2.81-2.69 (m, 2H, H6, H2), 2.31 (bs, 1H, H3), 1.63-1.58 (m, 3H, H4, H5, H7), 1.38-1.25 (m, 1H, H5), 0.89-0.86 (m, 1H, H7).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 164.25, 158.1, 157.5, 148.0, 147.3, 144.7, 141.4, 131.9, 127.1, 122.4, 122.0, 121.9, 118.9, 101.8, 88.1, 72.4, 69.1, 59.9, 58.3, 43.1, 28.0, 27.5, 26.5, 22.8.

5. References

"*The important thing is not to stop questioning. Curiosity has its own reason for existing"*
Albert Einstein

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