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SYNTHESIS AND APPLICATIONS OF CHIRAL CATALYSTS BASED ON HETEROCYCLIC UNITS

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List of abbreviations used

AAS = Atom absorption spectroscopy

Acac = Acetyl acetone

Ac_2O = Acetic anhydride

AcOEt = Ethyl acetate

AcOH = acetic acid

AIBN = Azobisisobutyronitrile

[BMIM]NTf_2 = 1-Butyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide

-Bn = Benzyl

$Bu_4N^+I^-$ = Tetrabutylammonium iodide

CBA = Chiral Brønsted Acid

CD = Circular dichroism

Cy_2NMe = *N*,*N*-Dicyclohexylmethylamine

$Cu(OTf)_2$ = Copper triflate

1,2-DCE = 1,2-Dichloroethane

DCM = Dichloromethane

DEA = Diethylamine

DFT = Density functional theory

DIPEA = iPr_2NEt = Diisopropylethylamine

DMEDA = *N*,*N*-Dimethylethylendiamine

DMF = Dimethylformamide

DMSO = Dimethyl sulfoxide

dppf = 1,1'-Bis(diphenylphosphino)ferrocene

EtOH = Ethanol

Hex = Hexane

HMPA = Hexamethylphosphoramide

ICP = Inductively Coupled Plasma

IL = Ionic liquid

IPA = Isopropyl alcohol

LB = Lewis base

LDA = Lithium diisopropylamide

MeCN = Acetonitrile

Me_4NI = Tetramethylammonium iodide

NBS = *N*-Bromosuccinimide

NIS = *N*-Iodosuccinimide

PA = Phosphoric acid

$Pd(OAc)_2$ = Palladium(II) acetate

Py = pyridine

PMP = *Para*-Methoxy Phenyl

p-TSA = *p*-Toluenesulfonic acid

$Rh(cod)_2BF_4$ = Bis(1,5-cyclooctadiene)rhodium(I) tetrafluoroborate

TADDOL = α,α,α',α'-tetraaryl-1,3-dioxolane-4,5-dimethanol

-TBS = *Tert*-Butyldimethylsilyl

TEA = Et_3N = Triethylamine

TFA = Trifluoroacetic acid

THF = Tetrahydrofuran

TMEDA = *N*,*N*,*N*,*N*-Tetramethylethylendiamine

TMHD = 2,2,7,7-tetramethylhepta-2,5-dione

TMS = Trimethylsilyl

Ts = Tosyl

Tol = Toluene

Preface

One of the most important challenges in organic chemistry is the design and the development of a synthetic strategy which, employing as few steps as possible, would permit the preparation of intermediates, precursors or target products of great commodity value. However, the choice of such synthetic strategy is always connected to the availability of the reagents, to the quantity of the desired target molecule and to other considerations of economic type and sustainability.

In this contest, catalysis plays nowadays a fundamental role on the development of new methodologies mostly in the industrial field. In addition, another important challenge for the organic chemist is constituted by the stereoselective synthesis of chiral enantiopure compounds, with a defined stereochemistry.

The preparation of chiral molecules as single enantiomers or diastereoisomers has been of huge increasing importance mostly in pharmaceutical industry,[1] especially from the first years nineties when the FDA (1992) and EU (1994) released important guidelines about the synthesis of new chiral drugs, which impose the development of enantiopure compounds.[2] Indeed, many drugs contain at least a stereogenic centre, being able to exist, therefore, as racemic mixtures.

Many possibilities can occur in terms of pharmacokinetics and pharmacodynamics when the racemate of the chiral drug is dispensed: sometimes it can be possible that each enantiomer is active, or, often, only one of them is the responsible for the therapeutic effect (*eutomer*), while the other one, besides being less active, or completely inactive, could be the cause of even serious side effects (*distomer*). Furthermore, it could be also possible that two enantiomers explicate two different therapeutic effects, as in the case of dextropopoxyphene (analgesic action) and the levopropoxyphene (antitussive action) (Figure 1). In other words, this is a case in which the distomer becomes the eutomer for a different pharmacological activity. Their enantiomeric relationship is also highlighted from their commercial names, DARVON/NOVRAD.

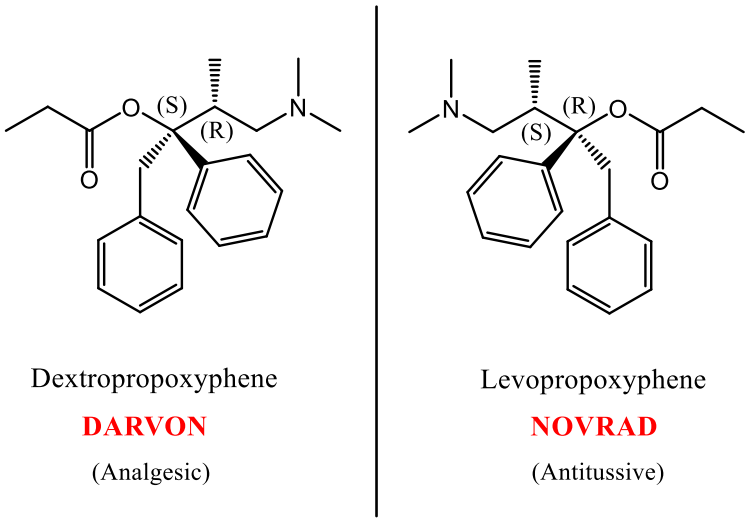


Figure 1

The reasons related to the different behaviour performed by the two enantiomers are connected to the fact that their biological targets are constituted by chiral building blocks such as aminoacids or carbohydrates, so that different specific interactions can be established, responsible for the different biological action.

Many agencies that regulate the marketing of drugs require separate toxicological studies for each impurity present in concentrations greater than 1%, including possible enantiomers or diastereoisomers of the drug. Therefore, the development of simple stereoselective synthesis methods allowing the production of enantiopure molecules is highly necessary.

In order to obtain a single enantiomer, with desired biological activity, two possible pathways are available:

- Synthesis of the racemate followed by its resolution that requires a chiral resolving agent. The limits of this approach are that the yield cannot exceed 50% and the costs of the resolving agent are to take in consideration too;
- asymmetric synthesis.

The latter can be realized through different strategies:

a) *chiral pool synthesis*: a pure enantiomer is used as starting material to obtain the desired chiral enantiopure product;

b) *auxiliary chiral approach*: chiral enantiomerically pure molecules (used in stoichiometric amounts) are covalently linked to a reaction partner in order to control the stereochemical outcome of a reaction and removed once the desired product is obtained.

c) *asymmetric catalysis*: in which a chiral enantiopure catalyst favours preferentially the formation of only one enantiopure species.

The last approach represents the most convenient one for several reasons. Firstly, differently from the other ones, only catalytic amounts of chiral promoter are required; in addition, being catalysts, they are able to accelerate the reaction rates. For these reasons the use of catalysts provides a huge number of benefits in terms of cost reduction, time savings and waste generation.

Furthermore, the enhanced focus on the development of more environmentally friendly and sustainable processes makes catalysis one of the most favoured approaches promoted by the green chemistry.[3] Indeed, compared to non-catalytic transformations, catalysed reactions are able to give increased yields in less time, spending less energy.[1]

The most common chiral catalysts utilised in organic chemistry are: transition metal complexes (given from the *in situ* combination of a transition metal with a chiral ligand), the more environmentally friendly enzymes (used in the field of biocatalysis, in which the intrinsic catalytic features of enzymes are exploited) and organocatalysts (small organic molecules which do not require any metal in their catalysed reactions).

Differently from metalloorganic catalysis, that received a huge emphasis in the past, providing a flexible ground of several asymmetric transformations, organocatalysis has been having a great deal of influence in organic chemistry only in the last few decades, since asymmetric organocatalytic reactions were considered for a long time to be inefficient and limited in scope.[4]

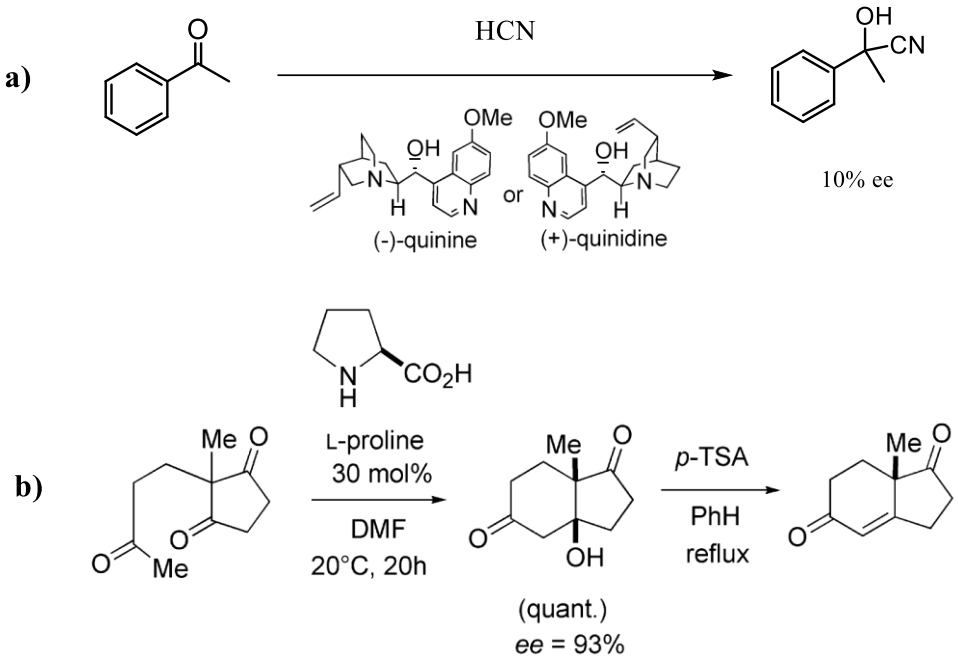
However, organocatalysts display several advantages such as the facile handling, ready availability, low cost, enhanced stability, chemical efficiency and the non-toxicity making organocatalysis a very interesting field of investigation.

The first organocatalytic transformation was reported by Von Liebig in 1860, when cyanogen was converted to oxamide in the presence of aqueous acetaldehyde.[5]

Fifty years later, Bredig and Fiske published the first asymmetric organocatalytic reaction consisting in the cinchona alkaloids catalysed addition of hydrogen cyanide to benzaldehyde, affording cyanohydrins although in poor 10% ee. Despite the low enantioselectivity observed in the reaction, this process was presented as highly groundbreaking (Scheme 1a).[6]

Aminoacids were first employed as organocatalysts at the beginning of 1930,[7] and another significant breakthrough in the history of organocatalytic transformations was the discovery of efficient L-Proline catalysed asymmetric Robinson annulation reported at the early 1970s. This

reaction represents the first successful asymmetric organocatalysed reaction affording some key intermediates for the synthesis of natural products in quantitative yields and excellent enantioselectivities (93% ee, Scheme 1b).[8]



Scheme 1

Interestingly, after this discovery, the employment of organocatalysts remained confined in few rare pubblications until the first years 2000, when MacMillan, reporting the first highly enantioselective organocatalytic Diels Alder reaction,[9] coined the term "organocatalysis" defined as *the acceleration of a chemical transformation through addition of a substoichiometric amount of an organic compound which does not contain a metal atom*.[9] After this contribution, a huge number of stereoselective organocatalysed transformations have been reported, some of them employed for the synthesis of pharmaceutical compounds and developed on a large scale.[1, 10]

In this PhD Thesis a contribution about two classes of chiral organocatalysts is given, namely diphosphinoxides, employed in Lewis-Base catalysed Lewis-Acid mediated transformations, and phosphoric acids, both characterized by a heterocyclic backbone.

Furthermore, always in the field of asymmetric catalysis, a new class of heterocyclic chiral promoters that requires the use of metals, namely phosphoramidites based on 3,3'-bithiophene scaffold, is also developed.

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1. Development of Lewis Bases in organocatalysis

1.1 Introduction

Lewis bases represent one of the most investigated classes of compounds that have found applications in a large number of chemical transformations, thanks to their strong versatility and applicability. The remarkable versatility performed by Lewis Bases in their catalysed reactions is essentially due to the fact that, differently from Lewis Acids, they are capable of enhancing both the electrophilic and nucleophilic character of molecules to which they are bounded.[1] This concept may seem surprising at first glimpse, since both modes of activation rely on the formation of Lewis acid-base adducts. However, the difference becomes clear by recognizing that Lewis acid activation only leads to net transfer of electron density away from the substrate, whereas Lewis base activation leads to net transfer of electron density toward the substrate. This fundamental difference between the modes of activation has important consequences on the way in which electron density is distributed in the adducts.[1] Indeed, in terms of reactivity, it is well known that the transfer of electron density toward the newly formed adduct leads normally to an increase of the electron density, that most of the time corresponds to an increase of the nucleophilicity of the acceptor subunit. The idea of Lewis base catalysis simply as *nucleophilic catalysis* is generally valid, but actually it represents only **a possible effect** of a Lewis base binding. Indeed, a much less intuitive consequence of the binding of a Lewis base is the **capacity to increase the electrophilic nature of the acceptor**. This particular behaviour seems to be in contrast to the commonly affirmed hypothesis about the effects of acid-base interactions on the chemical properties of the adduct. What happens effectively is that Lewis base catalysis is able to promote transformations of nucleophilic, electrophilic, and amphiphilic reagents. Whatever are the features of the Lewis base or acid employed, the acceptor fragment within the adduct shows inevitably increased electron density respect to the corresponding Lewis acid. However, it is the **distribution of this electron density** among the constituent atoms that must be taken in consideration to rationalize the effects of the newly formed adduct on reactivity.

To better understand this concept, it might be helpful to consider the nature of the dative bond that can occur between Lewis Base and Lewis Acid species.

In 1978 Jensen proposed that all Lewis acid-base interactions could be classified in terms of the identities of the interacting orbitals.[2] In this analysis, it was reported that nine types of bonding phenomena are possible through the combination of three kinds of acceptor orbitals with three kinds of donor orbitals (Table 1).

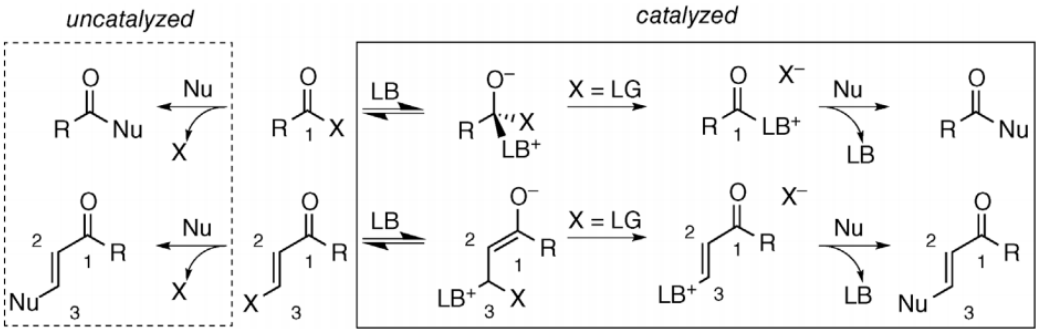
Donor		Acceptor		
		n*	σ*	π*
	n	n–n*	n–σ*	n–π*
	σ	σ–n*	σ–σ*	σ–π*
	π	π–n*	π–σ*	π–π*

Table 1: Jensen's orbital analysis of molecular interactions.

Although every combination may represent a possible productive interaction, in practice, only three of them are relevant in terms of catalysis: 1) interactions between nonbonding electron (n) pairs and antibonding orbitals with π character (n–π* interactions), 2) nonbonding electron pairs and antibonding orbitals with σ character (n–σ* interactions), and finally 3) interactions between nonbonding electron pairs and vacant nonbonding orbitals (n–n* interactions).

1.1.1 Catalysis by Nucleophilic Addition: n–π* Interactions

Lewis base catalysis, generally- although incorrectly- called "nucleophilic catalysis" is characterized by n-π* interactions;[3,4] in particular, the nonbonding electron pair of a Lewis base (LB) interacts with a π* acceptor orbital, such as typical of alkynes, alkenes, carbonyl compounds or other derivatives showing common unsaturated functional groups. These reactivity patterns are very similar to those observed in the nucleophilic 1,2-additions to carbonyl groups (that generate alkoxides) and nucleophilic 1,4-additions to α,β-unsaturated compounds (that generate α-stabilized anions). These two processes are the first clearly identified examples of Lewis base catalysis. In the case of simple carbonyl groups as acceptors, the attack of the Lewis base conducts to the formation of a zwitterionic, tetrahedral intermediate with increased nucleophilic character at the oxygen atom.



Scheme 1. Parallels between the catalysed and uncatalysed reactions of unsaturated functional groups.

If the carbonyl compound has a leaving group, as in the case of an acid chloride and other active carboxylic acid derivatives, this intermediate can transform into a new ionic species showing an enhanced electrophilic character at C1 (Scheme 1).

A similar pattern of reactivity is observed in α,β-unsaturated compounds. In the case of simple α,β-unsaturated carbonyl compounds, conjugate addition of the Lewis base leads to the formation of a zwitterionic enolate with enhanced nucleophilic character at C2, that becomes a position susceptible of a nucleophilic attack. However, if a suitable leaving group is present at C3, as would be the case in a γ-alkoxy-α,β-unsaturated carbonyl compound, this zwitterion can collapse, generating, in this way, a species with enhanced electrophilic character at C3, also in this case susceptible of nucleophilic attack.

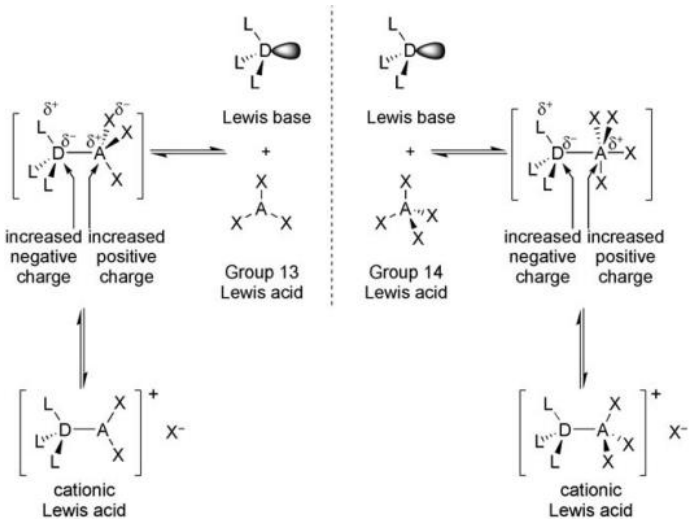
These reactions represent an example of the unique catalytic behaviour of LBs, characterized by the fact that both electrophilic (first intermediate) and nucleophilic (second intermediate) activation can be provided (Scheme 1).

1.1.2 Catalysis by Polarization: n–σ* and n–n* Interactions

The other two types of interactions, namely the n–σ* and n–n* ones, even if less well-known, are the basis of several catalysed reactions. The use of "σ*" to describe the acceptor orbital on the Lewis acidic species is a general term, because these interactions include several organometallic reagents consisting of main-group elements. On the other hand, the "n*" term is representative of a specific group of Lewis acid acceptors such as boranes and other elements belonging to Group 13.

An important requirement for these types of interactions is that the Lewis acidic acceptor could be able to expand its coordination sphere and reach a "hypervalent" state.[4] The changes in the bond order induced by the adduct formation lead to the **simultaneous enhancement of nucleophilic and electrophilic character**, dependent on bond polarizability as seen in the n–π* analysis. The behaviour of hypervalent species that often conducts to novel forms of reactivity was first understood through Gutmann's empirical analysis of acid-base interactions.[5]

Gutmann recognized that the formation of an acid-base adduct conducts to an overall increment in the electron density in the acceptor portion of the adduct, but he noticed that the distribution of this electron density is not equal among the constituent atoms (Scheme 2). As a consequence, this redistribution of electron density has empirically observable repercussions on bond lengths.



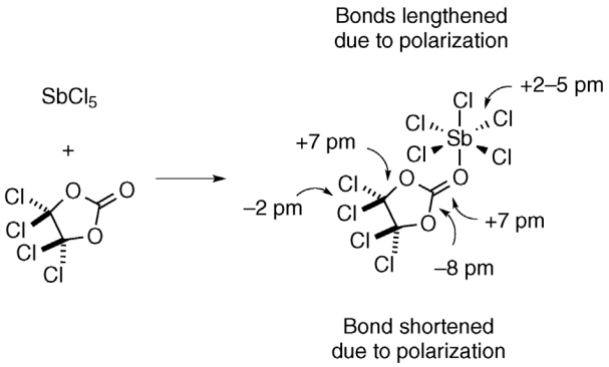
Scheme 2. Electronic redistribution resulting from Lewis acid-base complexation.

These observations give the basis of Gutmann's four rules regarding the molecular adduct formation:[5, 6]

1) the smaller is the intramolecular distance between the donor (D) and the acceptor (A), the greater the induced lengthening of the peripheral bonds (A-X), 2) the longer the bond between D and A, the greater the degree of polarization of electron density across that bond, 3) as the coordination number of an atom increases, so increase the lengths of all the bonds originating from that coordination centre, 4) both the bonds adjacent to D and A will contract or elongate to compensate for the changes in electron density at D and A.

Furthermore, a corollary to Gutmann's fourth rule concerns charge density variations, and states that: *"although a donor–acceptor interaction will result in a net transfer of electron density from the donor species to the acceptor one, it will, in the case of polyatomic species, actually lead to a net increase or "pile-up" of electron density at the donor atom of the donor species and to a net decrease or "spill-over" of electron density at the acceptor atom of the acceptor species. This results from the accompanying changes in the intramolecular charge distribution induced by the primary donor-acceptor interaction. These disperse the net change in electron density among all the atoms and in so doing, overcompensate for the initial changes induced at the donor and acceptor atoms. This result is important as it contradicts then usual assumption of the organic chemist that the net changes in formal charges remain localized on the donor and acceptor atoms."* [5]

These empirical rules regarding the structural and polarization consequences of adduct formation between a Lewis acid and a Lewis base can be better understood by examining specific examples. For instance, the effects of binding of a Lewis base to the Lewis acidic species antimony pentachloride, $SbCl_5$, have been carefully examined by X-ray crystallography (Scheme 3).[5]



Scheme 3. X-ray crystallographic analysis of $SbCl_5$ and its complex carbonate complex.

The binding of tetrachloroethylene carbonate to $SbCl_5$ causes notable changes in bond lengths throughout the complex: some bonds appear lengthened, others contracted. In particular, in the $(RO)_2C=O$-Sb-Cl subunit, the C=O bond is lengthened so that polarizes it toward antimony and leads to a "pile-up" of electron density at the carbonyl oxygen, while a loss of electron density occurs at the carbonyl carbon. These changes in bond lengths are an evident manifestation of both the first and fourth rules.

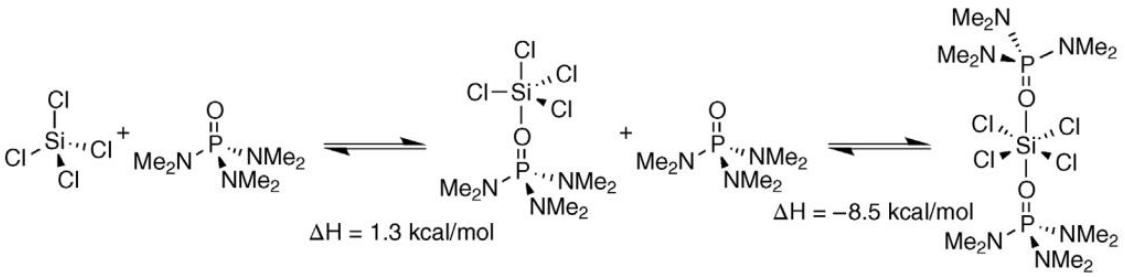
The polarization of the C=O bond is followed by an increased electron donation from the carbonate oxygens, leading to contractions in the distal oxygen-carbonyl carbon bonds. This observation is also in agreement with the predictions of the fourth rule.

But the more interesting and catalytically relevant effect occurs on the Lewis acid's side. Indeed, in response to the interaction with the Lewis base, the coordination number of the antimony increases by one and the bonds around the antimony are lengthened, as enunciated in the third and fourth rules. This corresponds to the "spill-over" effect in which the increased electron density around the antimony is spread to the more electronegative, peripheral atoms. A **crucial consequence** of the spill-over effect is that *the Lewis acidic centre is often made more electrophilic compared to the parent Lewis acid while its ligands are rendered more nucleophilic*.[7] While the structural manifestations of Gutmann's rules can be readily confirmed by X-ray crystallographic analysis of Lewis acid-base complexes, the electronic consequences, that is the real fractional charges residing on an atom, can be discerned through computational analysis already done for similar Lewis acid-base adducts.

Most of the experimental and computational studies on donor-acceptor complexes concerns the Group 13 elements. The "unexpected" trend in Lewis acidity for the various boron halides (BF_3 < BCl_3 < BBr_3) has stimulated a great deal of debate and computational investigations.[8]

For the Group 14 elements, the trends are even more dramatic than the previous ones, since these Lewis acids can expand their valences twice. For example, the series SiF4, $SiCl_5^-$, and $SiCl_6^{2-}$ has Mulliken charges (a computational parameter that provides a means of estimating partial atomic charges) at silicon of +1.19, +1.14, and +2.12 respectively,[9] whereas the series $SiCl_4$, $SiCl_5^-$, and $SiCl_6^{2-}$ has Mulliken charges at silicon of +0.178, +0.279, and +0.539, respectively. These trends are truly remarkable as the binding Lewis base in these cases is charged (F and Cl) rendering the adducts formally negatively charged (and erroneously viewed as negative at silicon), although the acceptor silicon atom increases in its positive character.[10]

A second measure of the Gutmann spill-over effect is seen both experimentally and computationally in studies on the complexation of $SiCl_4$ with HMPA. The role of the stoichiometry on the formation of these complexes was investigated and, $(HMPA)_2$•$SiCl_4$ adducts were observed only even with substoichiometric amounts of HMPA.[11] The logical conclusion is that (HMPA)•SiCl4 is more Lewis acidic than $SiCl_4$, thus outcompeting the nascent Lewis acid for the available Lewis base.[12] Support for this conclusion is found in calculations of the enthalpies of the two complexes (Scheme 4).[13]



Scheme 4. Calculation of complexation enthalpies for $SiCl_4$ and HMPA.

An important example of hypervalent bonding formation is given by the hypervalent silicate intermediates.[14] Differently from carbon, silicon has the capacity to make more than four bonds, necessary to satisfy the octet rule. In the presence of donor molecules, the formation of five-, six- and even seven-coordinated silicon species could be possible; some of which have been also isolated and characterized.[15]

In order to explain this behaviour, two main different theories have been hypothesized: the first considers the employment of the silicon 3d orbitals in the expansion of the coordination sphere both in the five-coordinated species (in which the silicon orbitals would have a sp^3d hybridization, with trigonal-bipyramidal geometry) and in the six-coordinated species (where the hybridization would be sp^3d^2 with octahedral geometry) (Figure 1A).[15] In this case the reduced s-character of the silicon orbitals in the hypercoordinated species would justify their increased Lewis acidity and the corresponding transfer of electron-density to the ligands.

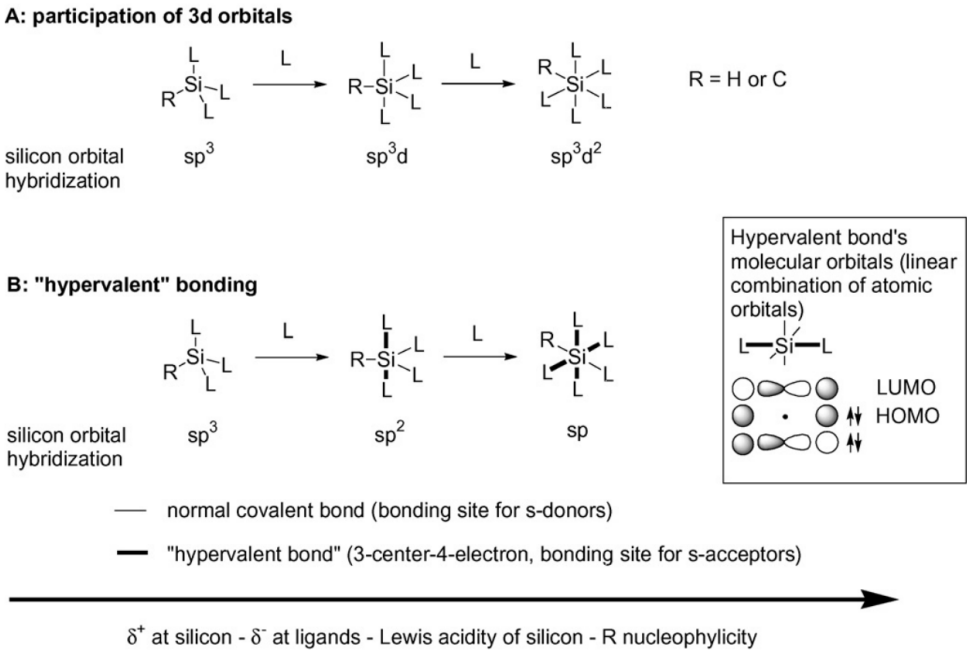


Figure 1

In contrast to this first theory, the second theoretical approach (Figure 1B) excludes the participation of the 3d orbitals in the bonding process and supposes a so-called "hypervalent-bonding": according to this theory, the formation of a penta- or hexa-coordinated silicon species would involve respectively one or two 3-center-4-electron molecular bonds, each of them constituted by a silicon p-orbital and two p-orbitals of electronegative ligands featuring a relative *trans*-disposition. An important effect is the *non-equivalence* of the ligand positions in five- and six-coordinated silicon species: the -acceptor ligands prefer "hypervalent" bonds while the donors form favourably normal covalent bonds with the sp^2 (for penta-coordinated species) or sp (for hexa-coordinated species) silicon orbitals. In addition, the presence of hypervalent bonds imposes some stereochemical constraints (like the *trans*-disposition of the most electronegative ligands), so on the basis of the electronic properties of the ligand it could be possible to formulate predictions about their positions respect to the silicon atom.

Anyway, both theories are able to explain the fundamental properties of hypervalent silicon species, which have a completely different reactivity from that shown by four-coordinated compounds, such as the increased Lewis acidity of the silicon atom and the transfer of electronic density to the ligands, that give two silicon-bound R groups (carbanion or hydride equivalent) important nucleophilic properties. The hypervalent silicon species employed in synthetically useful processes are generally formed *in situ* by reaction between a four-coordinated species and a Lewis base in what is often called the "activation step".[16] The so-formed five- or six-coordinated silicon species is able to promote the desired reaction in a catalytic process if the Lewis-base can dissociate from silicon after the formation of the product.

1.1.3 Lewis Base-Catalysed, Lewis Acid-Mediated Reactions ($n \rightarrow \sigma^*$)[17]

To sum up what described in the previous paragraph, the coordination between a Lewis base (LB) and a Lewis acid leads traditionally to the formation of an acid-base adduct, where, after the formation of a dative bond, both the donor and the acceptor atoms satisfy the octet rule. This coordination is generally thermodynamically favourable and generally brings to a decrement of reactivity of the acid and the base. However, in particular cases, the coordination leads to an increase of either nucleophilic or electrophilic character of the intermediate involved in the reaction mechanism.

An example of this concept is represented by hypercoordinated silicon species, in which the new adduct formed shows both enhanced electrophilic reactivity at the silicon atom and increased nucleophilic reactivity at the silicon ligands that can be modulated according to the features of the Lewis base.

The chemistry of chiral, hypercoordinated silicon species has attracted increasing attention because of the ability of these compounds to catalyse a variety of stereoselective transformations. In particular, over the last 20 years the remarkable reactivity and stereoselection ability shown by species generated from silicon-based Lewis acids and chiral Lewis bases was highlighted.

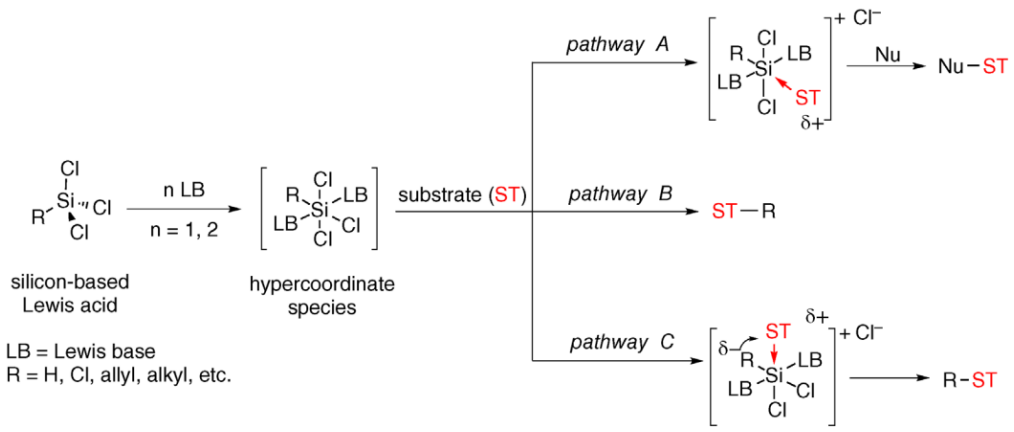
This chapter of the present thesis is focused on the study and the development of Lewis base catalysed reactions characterized by the interaction between the nonbonding electron pairs of the Lewis base donor (n) and the σ-antibonding orbitals of the silicon-based Lewis acid (n→σ*).

When a silicon-based Lewis acid takes part in the formation of an acid-base adduct, the electronic density over the peripheral ligands is subjected to a redistribution. This "redistribution" results in bond elongation when the coordination number of the Lewis acid increases with the expansion of the coordination sphere.

The hypercoordinated silicon species, generated *in situ* by association of a four-coordinate silicon species with one or more molecule of a Lewis base, can follow three different pathways, depending on the other components involved in the chemical transformation (Scheme 5).

The hypercoordinated species (HS) may for example act as a Lewis acid that coordinates and activates the substrate for the attack of an external nucleophile (*pathway A*). A significant example of the first case is the Aldol addition between aldehydes and silyl ketene acetals promoted by $SiCl_4$ and a Lewis base.

According to *pathway B*, the HS could transfer one of its ligands to a substrate that is not coordinated to the silicon atom.

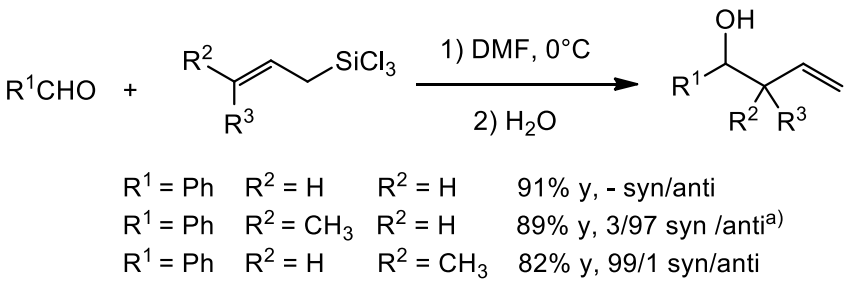


Scheme 5

The reduction with $HSiCl_3$ is representative of this second case.

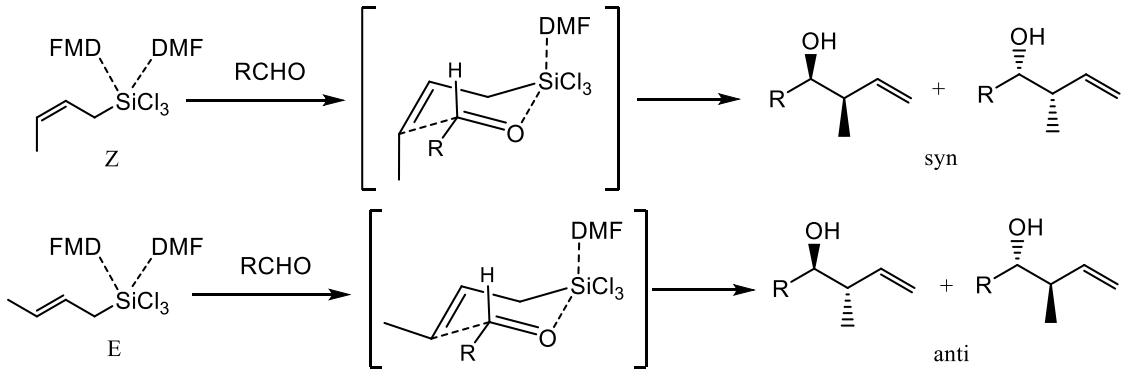
The third pathway (C) is a combination between the first two, where the hypercoordinate species coordinates the substrate while simultaneously transferring one of its ligands. The allylation and aldolization reactions of aldehydes with allyltrichlorosilane or enoxy trichlorosilanes follow this kind of mechanism.

The first example of a Lewis Base-catalysed Lewis Acid-Mediated reaction through a silicon-based intermediate was given by Kobayashi in 1993, describing for the first time a diastereoselective allylation of aldehydes using allyltrichlorosilanes activated by dimethylformamide, the solvent utilised for that transformations.[18] In particular, the substrates employed were generally the pure (*Z*)- and (*E*)-crotyltrichlorosilane and the allyltrichlorosilane with different kind of aldehydes (such as the PhCOH, the $Ph(CH_2)_2COH$) and the PhCH=CHCOH) (Scheme 6).



Scheme 6. Allylation of aldehydes in the Kobayashi conditions with some results. a) starting from a 3/97-*Z*/*E* ratio.

As shown above, high yields and excellent regio- and diastereoselectivities were obtained. Indeed, the new C-C bond formation involves only the γ-positions of allyltrichlorosilanes. Furthermore, *syn* diastereoisomers were obtained from (*Z*)-crotyltichlorosilane, while *anti* diastereoisomers were achieved from (*E*)-crotyltrichlorosilane in almost complete diastereoselectivities. The formation of a six-membered cyclic transition state must be considered in order to justify these results (Scheme 7):



Scheme 7

This hypervalent silicon species exhibit both a Lewis acidic character, deriving from the electron withdrawing chlorine groups, and nucleophilicity, due to electron donation from the hypervalent silicon atom to the allyl π systems (σ-π conjugation), which allow to the reaction to proceed smoothly and diastereoselectively. It must be noted, anyway, that in all the reactions described so far, the products were obtained in very high yields but, obviously, as a racemate. To conduct this reaction stereoselectively in order to obtain enantiopure products, a chiral enantiopure Lewis base must be used.

However, starting from this work, many examples of diastereo- and enantio-selective transformations, involving the use of chiral Lewis bases for the activation of trichlorosilane, allyltrichlorosilane and silicon tetrachloride were developed to carry out different kind of chemical transformation involving C-H or C-C bond formation.[19]

As described in Scheme 5, the coordination of Lewis bases to a tetracoordinated silicon atom conducts to hypervalent silicate species characterized by enhanced Lewis acidity at the silicon centre. When the coordination occurs, the derived extra-coordinated organosilicon compounds become very reactive either toward hydride donors, as in the C-H bond formation reactions, or toward carbon nucleophiles, as in C-C bond transformations.

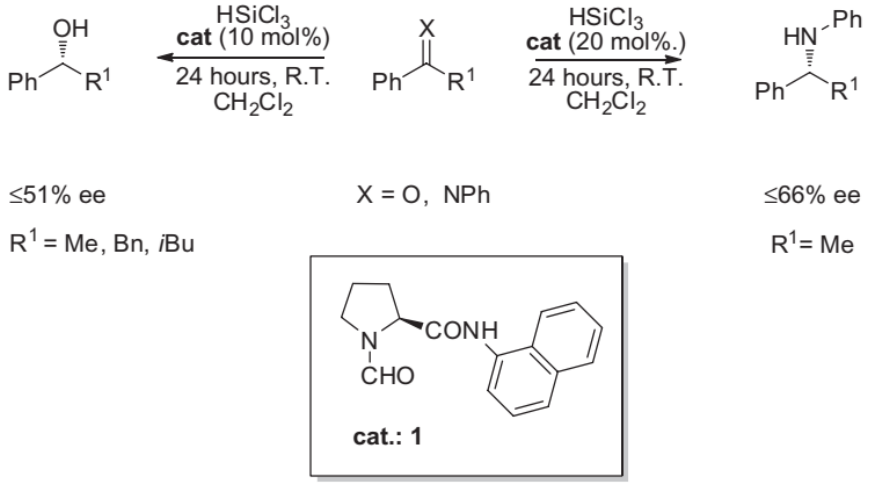
1.1.4 Stereoselective C–H bond formation

In this field, particularly interesting are stereoselective methodologies for the synthesis of chiral amines (important compounds in a large number of fields such as pharmaceutical, agrochemical and fragrances) since they might represent a solution to the problems related to the presence of toxic metals, whose traces could contaminate the final product.[20]

In this sense, the use of trichlorosilane as a reducing agent is particularly attractive since it is a cheap reagent easily prepared by the silicon industry.

Trichlorosilane needs to be activated by coordination with Lewis bases to generate a hexacoordinated hydridosilicate, the real active reducing agent that operates under mild conditions. If the Lewis base employed is a chiral compound there is the possibility to control the absolute stereochemistry of the process and this has been widely explored in the last years, leading to the development of some really efficient catalysts. The catalytic systems may be classified as follows: 1) *N*-formyl derivatives, which may be historically considered the first class of compounds developed as chiral activators of trichlorosilane, 2) chiral picolinamides and 3) other Lewis basic compounds.

The first example of stereoselective catalytic reduction with $HSiCl_3$ was given in 1999: Matsumura and co-workers showed *N*-formyl cyclic amine compounds [basically (*S*)-proline derivatives] to be effective activators to reduce ketones in the presence of trichlorosilane.[21a] A catalytic amount of these Lewis bases was used to achieve enantiomerically enriched secondary alcohols [up to 51% enantiomeric excess (ee) (Scheme 8, left hand side)]. Two years later the same group found that trichlorosilane, activated with the same chiral Lewis basic *N*-formylproline, is an effective reagent for chemo- and stereoselective reduction of imines (Scheme 8, right-hand side). The corresponding amines were isolated in moderate yields with up to 66% ee.[21b]

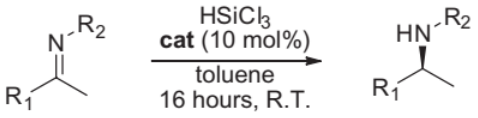


Scheme 8. *N*- formyl proline as chiral promoter of $HSiCl_3$- mediated reactions.

This contribution in designing *N*-formyl pyrrolidine derivatives as $HSiCl_3$ activators can be evaluated as a milestone for the asymmetric reduction of ketones and imines using the trichlorosilane as a reducing agent, and traced the road to the synthesis of other related systems. Since then,

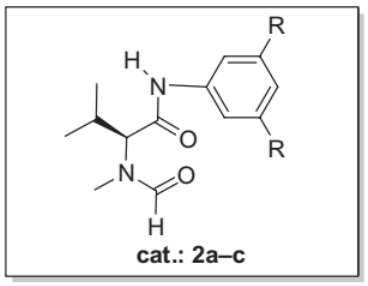
considerable efforts have been given to the development of efficient catalysts for the reduction of carbon-nitrogen double bonds, and remarkable progress has been made.

An important breakthrough in the field was achieved by Malkov et al. in 2004, when the first highly stereoselective Lewis basic catalyst characterized by a *N*-methyl-(*S*)-valine scaffold (**cat. 2**) was developed.[22a] This chiral promoter was so efficient that it became commercially available since 2009 (Scheme 9).



R_1= Ph, 4-$MeOC_6H_4$, 2-naphth, 2-MeC_6H_4, cC_6H_{11}, 4-$CF_3C_6H_4$, *i*Pr, Ph-CH=CH

R_2= Ph, 4-$MeOC_6H_4$, 3,5-*t*$Bu_2C_6H_3$, 3-MeC_6H_4, 3,5-$Me_2C_6H_3$



a; R = Me ≤92% ee
b; R = *i*Pr ≤94% ee
c; R = *t*Bu ≤95% ee (cat. 5 mol%)

Scheme 9

After two years, the same Authors reported a detailed investigation of the *N*-methyl-(*S*)-aminoacid derivatives catalysed reduction of imines with $HSiCl_3$.[22b] A library of chiral *N*-formylated aminoacids was envisaged and synthesized, with structural variations at the carboxyamide group. In particular, the main variation concerns the isopropylic group that was replaced by either aromatic or aliphatic substituents. Furthermore, some derivatives in which the formyl unit was substituted by a trifluoroacetyl and primary anilide groups were investigated.[22b] The reaction was carried out in nonpolar solvents; in particular toluene was chosen for its relatively low environmental impact and different substituted *N*-aryl ketoimines have been tested as substrates (Scheme 9).

After this screening valine was selected as the stereogenic element of choice to perform stereocontrol in the mechanism (Figure 2).

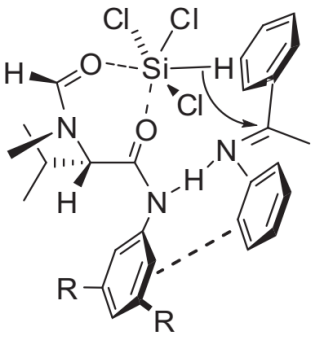
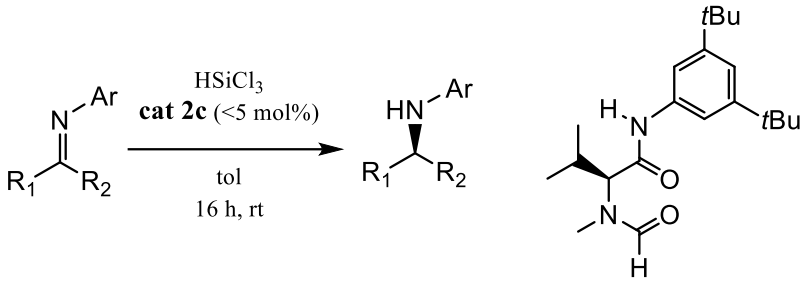


Figure 2. Model of stereoselection for (*S*)-valine-derived organocatalyst.

A model of stereoselection was proposed in order to support these results from which the following conclusions were proposed: (1) the *N*-methyl formamide moiety of the catalyst is fundamental for the enantioselectivity; (2) arene-arene interactions may play an important role in determining the stereoselectivity of the catalyst; (3) the anilide moiety of the catalyst has to be a secondary amide; (4) the silicon atom is activated by coordination with the formamide moieties; (5) the configuration of the resulting product depends on the nature of the aminoacid side chain; and (6) bulkier groups in the 3,5-positions of the aromatic ring (diisopropyl and di -*tert*-butyl) determine an increment of enantioselectivity in the reduction of aromatic and nonaromatic ketoimines.

Furthermore, the hydrogen bonding and coordination among the catalyst, the substrate and the silicon atom were found to play a fundamental role in determining the stereoselectivity of the catalyst. In the proposed TS, an additional element of stereocontrol is the formation of the hydrogen bond between the amide group of the catalyst and the substrate (Figure 2).

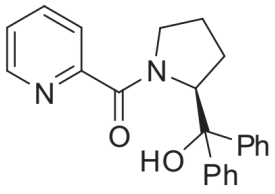
The general applicability of catalyst **2c** (called Sigamide, Scheme 10) was then investigated in the reduction of multifunctionalized ketoimines bearing also heterocyclic and aliphatic substituents.[22c] The reaction exhibited high enantioselectivities with ketoimines derived from aromatic amines and aromatic, heteroaromatic, conjugated, and nonaromatic ketones with an appreciable steric difference between the alkyl groups R_1 and R_2 (from 72% to 95% y; from 91 to 94% ee).



Scheme 10

Moreover, the introduction of a heteroatom into the aromatic system (pyridyl derivatives) afforded the products with almost no enantioselection, probably due to the competition of the substrate pyridine nitrogen with the catalyst in the coordinating of the silicon atom of $HSiCl_3$. A further advantage of this kind of catalysts is the fact that they can be also recovered after the use.

Another class of chiral organocatalysts able to perform stereoselective $HSiCl_3$ mediated reductions was introduced in 2006 by Matsumura.[23] His group showed that *N*-picolinoylpyrrolidine derivatives are able to activate trichlorosilane in the reduction of aromatic imines, demonstrating that the *N*-formyl group is not always essential for the catalytic activity. *N*-Picolinoyl-(2*S*)-(diphenylhydroxymethyl)-pyrrolidine (**cat. 3**, Figure 3) gave the best results, with enantioselectivities up to 80% ee. Concerning the stereoselection mechanism, it was proposed that both the nitrogen atom of the picolinoyl group and the carbonyl oxygen are important in the coordination of the silicon atom, while the hydrogen of the hydroxyl group was supposed to be involved in a hydrogen bond with the nitrogen atom of the imine.

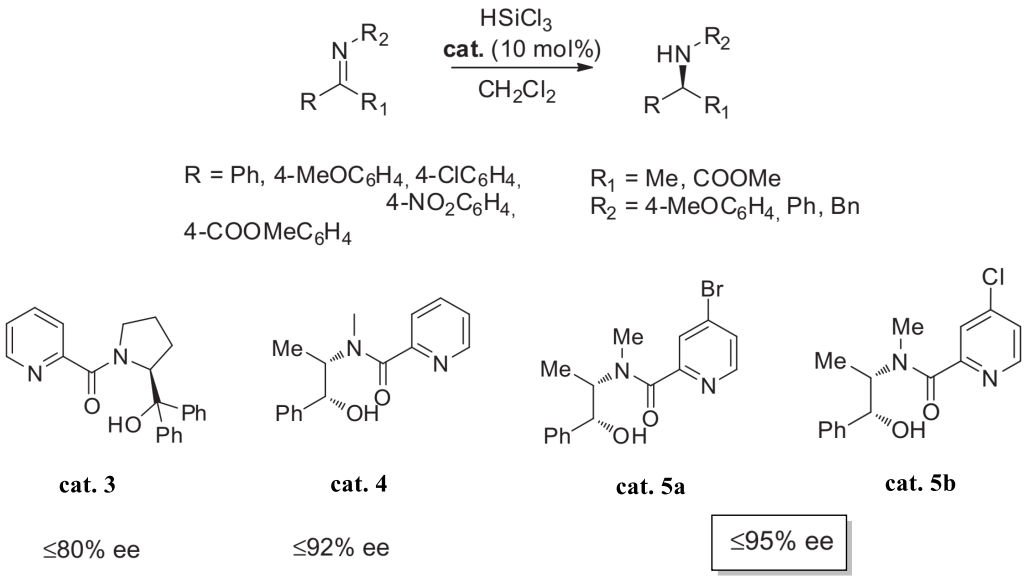


cat. 3

Figure 3. *N*-Picolinoyl-(2*S*)-(diphenylhydroxymethyl)-pyrrolidine

Based on these preliminary works, few years later, a new class of enantioselective Lewis bases, derived from simple condensation of a chiral aminoalcohol with picolinic acid or its derivatives, was developed for the reduction of *N*-aryl and *N*-benzyl ketoimines with trichlorosilane by the Benaglia

group of the University of Milan[24] and Zhang[25] almost simultaneously. The latter reported in a preliminary communication the use of several aminoalcohols and the best results were obtained using (1*S*,2*R*)-ephedrine and pseudoephedrine-derived picolinamides. In particular, using catalyst **4**, easily prepared from 2-picolinic acid and (1*S*,2*R*)-ephedrine, a variety of *N*-aryl ketoimines and *N*-benzyl ketoimines were reduced in high yields (up to 93%) and moderate to excellent ee values (up to 92%) under mild experimental conditions (Scheme 11).



Schema 11. Chiral *N*-picolinoyl derivatives

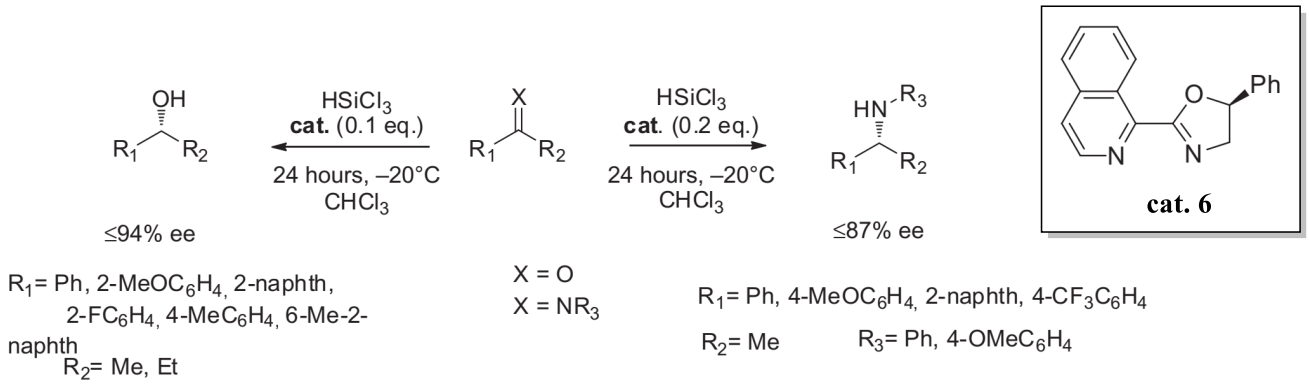
The Benaglia group performed also further investigations on these organocatalysts.[24] Several derivatives were synthesized in a single-step procedure by reaction of picolinic acid and different enantiomerically pure amino alcohols mediated by condensing agents or simply by reaction of picolinoyl chloride and the amino alcohol. It was noticed in that work that the pyridine ring, the free hydroxyl group, and *N*-alkyl substitution in the aminoalcohol portion are key structural elements, necessary to give good stereocontrol. Furthermore, it was shown that the introduction of a proper substituent in the 4-position of the pyridine moiety could improve the catalytic efficiency. Indeed, 4-bromo and 4-chloro picolinic derivatives **5a** and **5b** showed notable catalytic properties: working at 0°C in CH_2Cl_2 with catalyst **5a** the chiral amine was obtained in quantitative yield and 83% ee; enantioselectivity was increased up to 88% by working in chloroform. A better result was obtained by performing the reaction at -20°C when enantioselectivity reached 95% with no loss of the chemical yield, being the reduction product isolated, basically, in quantitative yield. In addition, also

working with a very small amount of catalyst (1 mol%), **cat. 5b** promoted the reduction in 90% yield after only 2 hours.

A model of stereoselection was proposed based on this systematic screening, from which the following important information emerged: 1) the pyridine nitrogen and the C=O amidic group of picolinamide activate trichlorosilane by coordination; 2) the hydroxylic group's hydrogen atom plays a fundamental role in coordinating the imine nitrogen through hydrogen bonding; 3) the presence of two stereogenic centres on the aminoalcohol moiety with the correct relative configuration such as in (1*R*, 2*S*)-(–) ephedrine is necessary to stereodirect the imine attack by trichlorosilane; 4) the methyl groups on the amide nitrogen and on the stereocentre in position 2 of the aminoalcohol chain apparently have the optimum size for maximizing the enantioselection of the process.

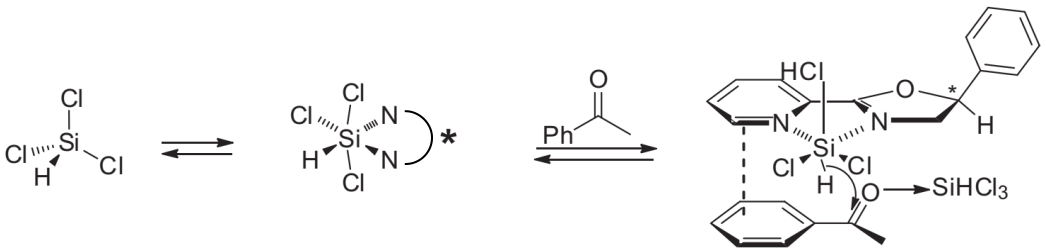
Good results were also achieved in the enantioselective reduction of *N*-alkyl imines,[24b] where quantitative yields and very high ee (up to 91%) were obtained. Among the advantages exhibited by these organocatalysts, must be mentioned the low costs of the commercially available raw materials, and their simple synthesis consisting of a single condensation step. Furthermore, the reduction of the C=N was performed in very mild experimental conditions and highly pure products were obtained after a simple aqueous work up.

In 2006, a novel chiral Lewis base organocatalyst was reported by Malkov[26] based on heterocyclic scaffolds namely a chiral oxazoline functionalised with an isoquinoline fragment. This catalyst was employed in the trichlorosilane-mediated reduction of aromatic ketones and imines affording the products with a good level of enantioselectivity (Scheme 12).



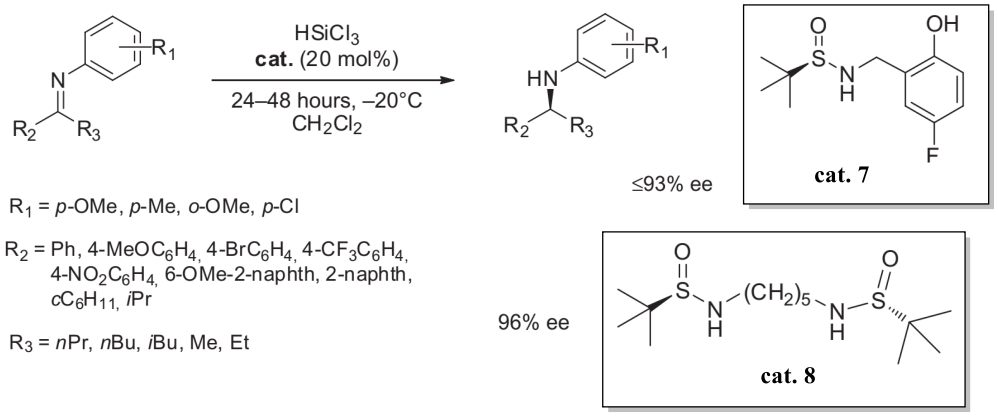
Scheme 12

The maximum level of enantioselectivity reached in the reduction of ketoimines was 87%, while even better results were obtained in the ketones reduction, where 94% enantioselectivity was reached. Also in this case, the Authors hypothesized that coordination of the trichlorosilane by the catalyst would generate a chiral hexacoordinated silicon species that would be the real reducing species (Scheme 13).



Scheme 13. Stereoselective catalytic reduction mechanism promoted by oxazoline-based chiral catalyst.

Almost in the same period, Sun reported a novel class of organocatalysts characterized by a sulfinamide group as stereogenic element.[27] Several compounds were tested differing from the nature of the substituents on the nitrogen atom: the most effective one was **cat. 7** (Scheme 14) that was able to activate $HSiCl_3$ performing the stereoselective reduction of *N*-aryl ketoimines in good yields (from 73 to 98%) and enantioselectivities (from 74 to 93%).



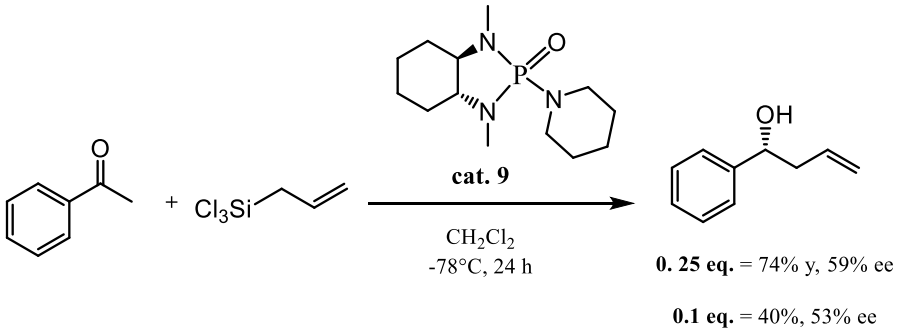
Scheme 14. Chiral sulfinamide as promoter of imine reduction.

Subsequently, based on the assumption that the mechanism would involve two equivalents of Lewis base for the trichlorosilane activation, a novel chiral bis-sulfinamide was then developed. After a screening of different derivatives based on this structure, the compound of choice for the reduction of the model substrate, namely the *N*-phenyl imine of acetophenone, was the bis-sulfinamide (**cat.**

8) bearing a five-methylene linkage that allowed to obtain the desired product in 96% ee (Scheme 14).[28]

1.1.5 Stereoselective C-C bond formation

In 1994, Denmark reported the first enantioselective catalytic addition of allyltrichlorosilane to aldehydes promoted by chiral phosphorotriamides.[29] At the beginning, on the basis of the pioneering studies reported by Kobayashi a year before,[18] he found that the allylation reaction between benzaldehyde and allyltrichlorosilane can occur in quantitative yield also in the presence of stoichiometric amounts of phosphoramide (HMPA) instead of DMF as Lewis base allylation promoter.[29] Then, he demonstrated that the reaction can be also performed in a stereoselective way by using chiral enantiopure phosphoramides, that were successfully employed first in stoichiometric and then also in catalytic amounts. The best results were given by a *trans*-diaminocyclohexane-*N*-piperidine-phosphoramide (**cat. 9**) derivative that allowed to achieve the allylation product in good yield (74%) but modest enantioselectivity (59%) (Scheme 15).



Scheme 15

Moreover, in these preliminary experiments, they noticed that when the catalyst loading is reduced, a decrement in both the reaction rate and the enantioselectivity was observed (Scheme 15). This suggested them the possibility that the reaction could proceed by a transition state involving either two phosphoramides bound to the chlorosilane or a less selective pathway involving only one catalyst molecule coordinated to the silicon species.[30] For this reason, in order to confirm this hypothesis and further elucidate the reaction mechanism, a series of detailed studies using **cat. 9** were performed,[30a] and what emerged was that two different simultaneously operating pathways are effectively involved: the first considers the formation of an octahedral cationic silicon species,

coordinated by two Lewis bases molecules, while the second pathway envisages the presence of only a phosphoramide bound to silicon in order to form a pentacoordinate silicon centre.

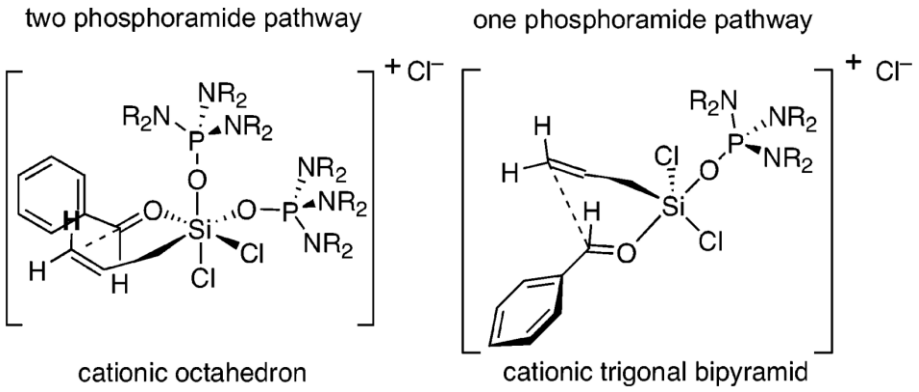


Figure 4

Hypothetical transition structures for both pathways (Figure 4) clearly show how the di-phosphoramide pathway, involving an octahedral hexacoordinate siliconate, would be more enantioselective than the mono-phosphoramide one, due to the formation of a more rigid chiral transition state.

On the basis of these mechanistic considerations, in order to address the reaction mechanism to the formation of the cationic octahedron, Denmark and co-workers envisioned the utilization of bidentate ligands in the test allylation of benzaldehyde.[30c] In designing these bidentate chiral phosphoramides, they thought about two different types of chiral biphosphoramides, namely 1) **Type A**, where two chiral phosphoramide units are separated by an achiral linker, and 2) **Type B**, in which a chiral linkage is used to connect two achiral phosphoramide units (Figure 5).

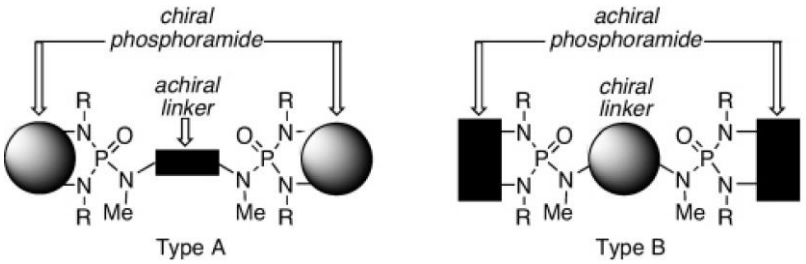
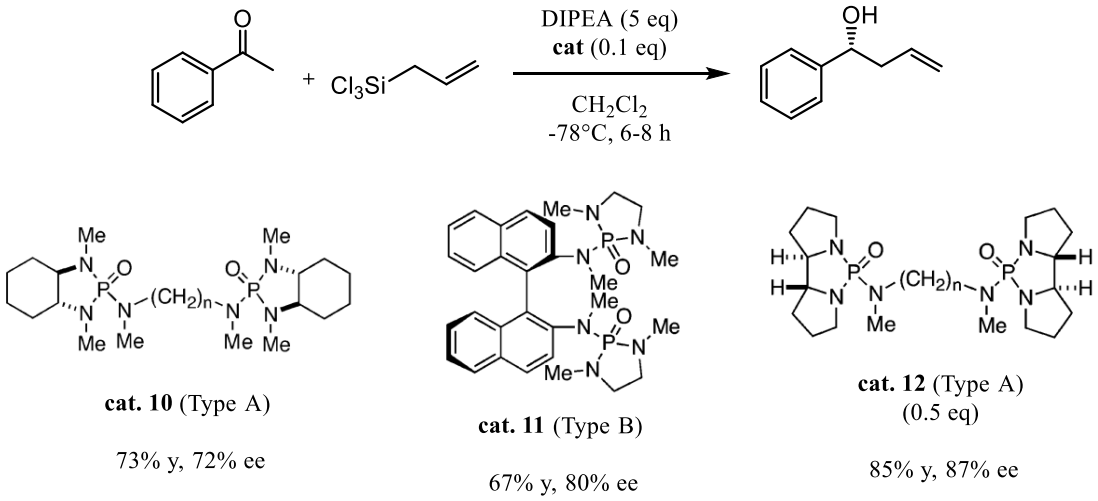


Figure 5

Initially they focused their attention on the design of Type A chiral phosphoramides. In particular, polymethylene chains were utilised as linkages and (1*R*,2*R*)-*N*,*N*-dimethyl-1,2-*trans*-diaminocyclohexane was chosen as the chiral phosphoramide unit, thanks to the promising results

obtained with the corresponding monophosphoramide.[29] These considerations led to the synthesis of phosphoramide **10** (Scheme 16) having a $(-CH_2-)_5$ chain, that was able to catalyse the allylation reaction of benzaldehyde with allyltrichlorosilane in 73% yield and 72% ee (-78°C, 6 h) only using 0.1 eq. of catalyst loading when the reaction was performed in the presence of DIPEA, a precious additive in allylation reactions with allyltrichlorosylane since it was demonstrated by Nakajima that it could enhance the reaction rate without affecting the enantioselectivity.[31]

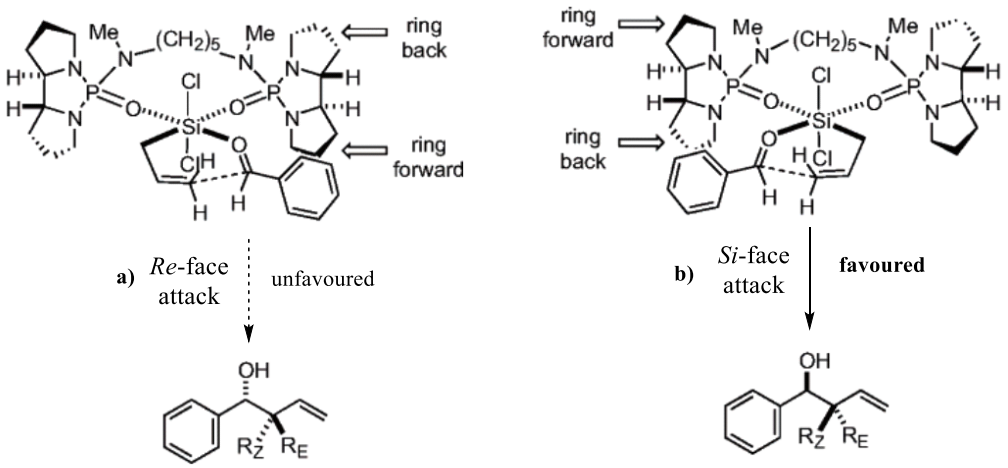
An example of chiral bi-phosphoramide Type B investigated by Denmark was **cat. 11**, in which two achiral subunits are separated by an enantiopure binaphtylic backbone. Performing the reaction with **cat. 11** maintaining the same experimental conditions, the allylation product was achieved in 67% yield and 80% ee. Then, further accurate studies in order to design more selective catalysts for this kind of transformations conducted to the synthesis of the bi-phosphoramide **12** derived from (*R*,*R*)-2,2′-bispyrrolidine, another example of chiral bi-phosphoramide Type A (Scheme 16). Catalyst **12** was found to be a really efficient promoter for the allylation reaction, affording the homoallylic alcohol in 85% yield and 87% ee.



Scheme 16

After having investigated and found the best catalyst and experimental conditions in the test reaction, the scope of the reaction was studied employing various *γ*- substituted allyltrichlorosilanes as starting materials in presence of **cat. 12**, leading to the products in high yields, extremely high diastereoisomeric ratio in all cases (> 99/1), and up to 96% ee.[30c]

A rationalization of the highly diastereo- and enantio-selective behaviour of catalyst **12** was also reported[30c] (Scheme 17): in the proposed transition state a) the aldehyde ring is located in an unfavourable position occupied by a forward-pointing pyrrolidine ring, generating in this case destabilizing steric interactions. On the contrary, in the case of diastereoisomeric transition state b), the aldehyde ring does not have any unfavourable interaction with the reward-pointing pyrrolidine unit, conducing preferentially to the experimentally observed product of *S*-configuration.



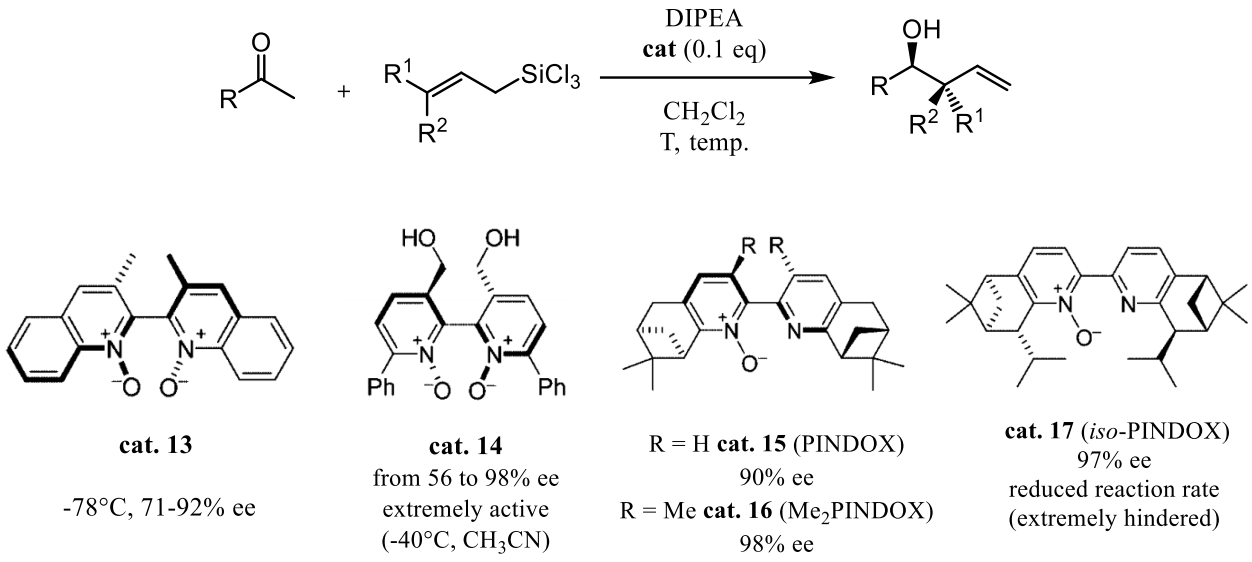
Scheme 17

Another class of Lewis basic catalysts that deserve a particular consideration, especially in the field of the allylation reaction, is that of the chiral *N*-oxides (Scheme 18).[32] In these catalysts, the combination of the high nucleophilicity of the *N*-oxide oxygen and its high affinity for silicon represented an ideal starting point for the development of new synthetic methodology based on nucleophilic activation of organosilicon reagents.

The first example of chiral *N*-oxides catalysed allylation reaction was given in 1998 by Nakajima, introducing an axially chiral biquinoline bis-*N*-oxide **13** (Scheme 18) that was able to promote the reaction in high yields and enantioselectivities (cat. 10 mol%, -78°C, CH_2Cl_2, 71-92% ee).[31] In the first years 2000, Hayashi reported another bis-*N*-oxide based on a bipyridine structure **14** achieving similar level of enantioselectivities (from 56 to 98% ee)[33] (Scheme 18). In particular catalyst **14** is remarkable for the loading required for the reaction to occur: it works well even employing 0.001 eq. (-40°C, CH_3CN) and continues to retain moderate selectivity also at 0.0001 eq. as catalyst loading. For this reason, this organocatalyst can be considered one of the most reactive reported so far.

An important contribution in the field was given by Malkov and Kočovský in the same period.[34] In particular they showed that new terpene-derived bipyridine *N*-monoxides such as PINDOX,

Me_2PINDOX, and *iso*-PINDOX **15**-**17** (cat. 0.1 eq., -78°C, CH_2Cl_2) were even more performing than **cat. 12** in terms of enantioselection ability, although the reaction rate was reduced, especially with the extremely hindered *iso*-PINDOX (**17**) (Scheme 18).



Scheme 18

The most performing catalysts of this series is Me_2PINDOX (**16**), the first *N*-oxide used in asymmetric catalysis that combines the effects of both central and axial chirality, since the rotation round the bond connecting the two pyridine moieties is restricted by the two methyl groups and the N-O group. However, the barrier rotation is rather low, and an inconvenience that can occur with **cat. 16** is that within few weeks it isomerize to a 1:2 mixture of the two atropisomers, which obviously weakens the stereoselection ability.[34b] On the contrary, PINDOX (**15**) and *iso*-PINDOX (**17**) do not have any restriction to the free rotation, so, considering the very interesting results that they were able to provide, a suitable configuration is apparently established on coordination to the silicon in the transition state, and the enantioselectivity is anyway, obviously, provided by the stereocentres.[34]

It must be noted that all the successfully employed *N*-oxides we have talked about until this moment are bidentate ligands. Also for *N*-oxides, as seen for the Denmark diphosphoramides,[30] the formation of an octahedral transition state due to the double coordination among the silicon species and the bidentate chiral Lewis bases was hypothesized (Figure 6, **cat. 13** is chosen as model).[31-34]

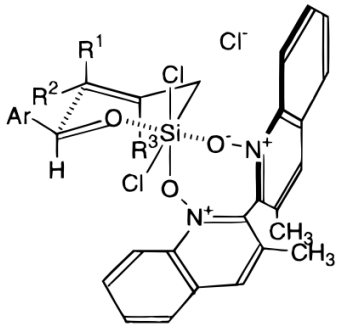
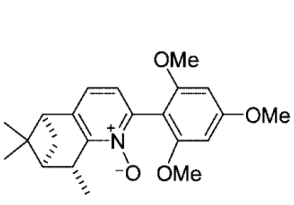


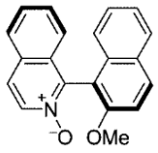
Figure 6

Furthermore, the discovery of METHOX (**18**) (Figure 7) permitted to Malkov and Kočovský to demonstrate that the lack of the second pyridine ring does not lead to a decrease of the enantioselectivity.[35] Indeed **cat. 18** was able to further improve the catalytic activity (≥ 95% y) with the same level of stereoselectivity (96% ee at 1-5 mol% of catalyst loading, -40°C, CH_3CN)[35] suggesting that the substitution of the pyridine nitrogen of **14**-**17** with another Lewis basic group (OCH_3) brings to a maintenance of the catalytic efficiency. in addition, the case of METHOX (**18**) shows clearly that the axial chirality (either predetermined as in the case of **13** and **14**, or induced during the reaction, as for **15** and **17**) is not a necessary condition for achieving high enantioselectivities in the *N*-oxides catalysed allylation reaction.

Another two pyridine-type mono-*N*-oxides, namely QUINOX (**19**)[36] and **20**,[37] have also been reported as successful organocatalysts, then, an *N*,*N*,*N*-trioxide **21**[38] and the chiral-at-nitrogen *N*-oxide **22**,[39] the first aliphatic tertiary *N*-oxide amine reported (Figure 7). Noteworthy, catalysts **18** and **22** retain high enantioselectivity even at room temperature.

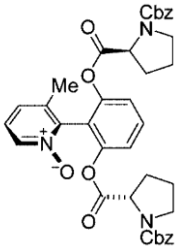


cat. 18 (METHOX)
96% ee
enantioselective even
at rt



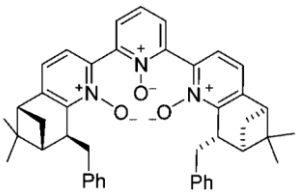
cat. 19

89% ee



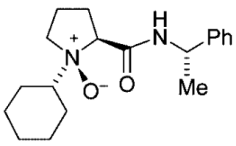
cat. 20

84% ee



cat. 21

86% ee

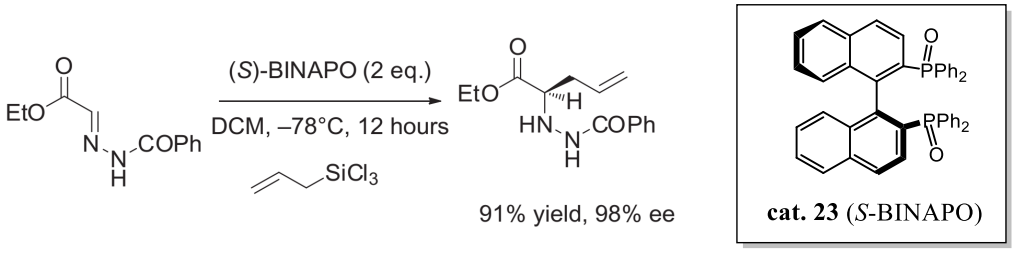


cat. 22
87% ee
enantioselective even
at rt

Figure 7

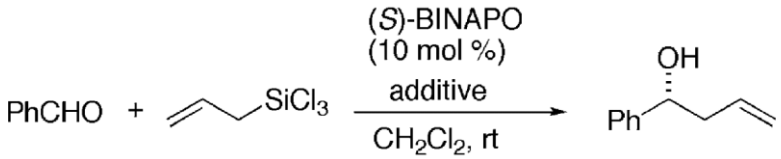
In 2005, for the first time, it was demonstrated by Nakajima that also chiral phosphine oxides, such as (*S*)-BINAPO (**23**), can also act as organocatalysts in the enantioselective addition of

allyltrichlorosilane to aldehydes.[40] The potentialities of **23** as chiral promoter were investigated for the first time by Kobayashi in 2004,[41] when it was employed in the addition of allyltrichlorosilane to *N*-benzoylhydrazones: the catalyst was used in stoichiometric amounts to achieve high yields and very high enantioselectivity levels (Scheme 19). This represents one of the few examples of enantioselective allylation of the C=N double bond mediated by a non-metallic promoter.



Scheme 19

As anticipated, a year later it was reported that (*S*)-BINAPO can also be employed as organocatalyst in the enantioselective addition of allyltrichlorosilane to aldehydes.[40] Initially, the homoallylic alcohol was obtained in CH_2Cl_2 in the presence of 10% mol amount of (*S*)-BINAPO in only 32% y and 36% ee (Table 2). Better results were obtained by using proper additives such as $Bu_4N^+I^-$ and 5 eq. of DIPEA improving the yield to 92% after only 4 hours at room temperature, even if with still modest enantioselectivity (43% ee).

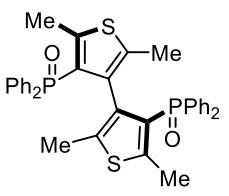


Entry	Additive (equiv)	Time (h)	Yield (%)	Ee (%)
1	None	24	32	36
2	$^iPr_2NEt(5)$	24	79	37
3	$Bu_4N^+I^-(1.2)$	12	54	46
4	$^iPr_2NEt(5) + Bu_4N^+I^-(1.2)$	4	92	43

Table 2

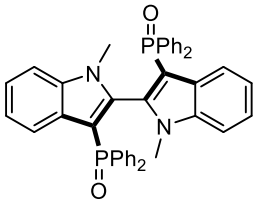
A remarkable improvement in the catalytic efficiency of chiral phosphine oxides was obtained in our group exploring the features of heteroaromatic systems.[42] Biheteroaryldiphosphine oxides offer some advantages respect to carbocyclic aromatic derivatives, such as the easier synthetic accessibility and the possibility of testing a series of catalysts showing different electronic properties, in which the influence of both the electronic availability of the heterocyclic system and of the position of the phosphorous atoms may be investigated.

In particular three biheterocyclic systems were investigated with different electronic availability in comparison with (*S*)-tol-BINAPO and it was noted that (*S*)-BITIANPO, the less electron-rich diphosphinoxide is the less effective catalyst of the series. Indeed (*S*)-TetraMe-BITIOPO (**24**) and (*R*)-*N*-Me-2-BINPO, based on electron-rich heterocyclic systems, promote the addition of allyltrichlorosilane to benzaldehyde at 0°C in higher yields respect to the medium electron-rich diphosphine oxide tol-BINAPO (Table 3). [42]

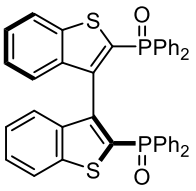


cat. 24

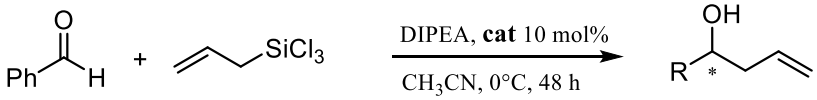
(*S*)-TetraMe-BITIOPO



(*R*)-*N*-Me-2-BINPO



(*S*)-BITIANPO



Entry	*Catalyst*	*T (°C)*	*Solvent*	*Yield (%)*	ee (%)
1	(S)-Tol-BINAPO	0	CH_3CN	55	51
2	(S)-tetraMe-BITIOPO	0	CH_3CN	85	93
3	(S)-*N*-Me-2-BINPO	0	CH_3CN	83	81
4	(S)-BITIAMPO	0	CH_3CN	<5	n.d.

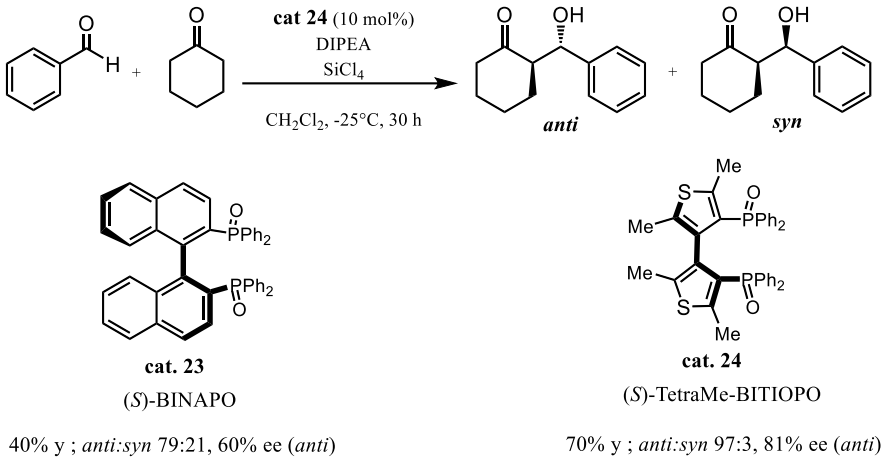
Table 3

The most enantioselective catalyst was the (*S*)-TetraMe-BITIOPO (**24**), which was able to promote the allylation of benzaldehyde using CH_3CN as solvent at 0°C in 85% yield and 93% ee, improving the results both in term of catalytic activity and enatioselection ability. Then, **cat. 24** was employed to promote the addition of allyltrichlorosilane to aromatic aldehydes bearing electron-withdrawing groups as well as electron-donating ones with enantioselectivities constantly higher than 90%.

An exhaustive investigation of the catalytic potentialities of the bithiophene based diphosphinoxide **24** in stereoselective catalysed C-C bond formation reactions is represented by the direct aldol-type reactions of aldehydes with ketones and thioesters. In this case, chiral phosphine oxides are used to activate $SiCl_4$ and generate a trichlorosilyl enol ether *in situ*.[43]

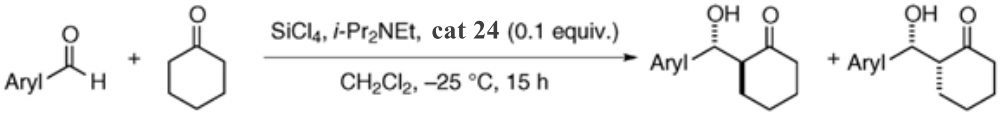
The aldol reaction between cyclohexanone and benzaldehyde catalysed by 10 mol% of (*S*)-BINAPO conducted to the formation of aldol products in 81% yield, 86 : 14 *anti*/*syn* ratio with 77 : 23 er for the *anti*-diastereomer.[44] The reaction was tested also with different substituted aromatic aldehydes and what was observed is that superior diastereo- and enantio-selectivity are obtained with electron-rich aldehydes. For example, when 4-methoxybenzaldehyde was employed, the aldols were obtained in 69% yield, 38 : 1 *anti*/*syn* ratio and 85.5 : 14.5 er for the *anti*-diastereoisomer. What is more, the reaction performed on cinnamaldehyde afforded the products in modest yield and selectivity (53% yield, 6 : 1 *anti*/*syn* ratio and 75.5 : 24.5 er for the *anti*-diastereoisomer), while dihydrocinnamaldehyde is unreactive.[44]

Also in this case, the employment of a more electron-rich diphosphine-oxide such as the precited (*S*)-tetraMe-BITIOPO (**24**) furnished an improved version of the direct aldol reaction between ketones and aldehydes.[43] in Scheme 20, a side-by-side comparison between (*S*)-TetraMe-BITIOPO (**24**) and (*S*)-BINAPO (**23**) is shown, clearly illustrating the greater catalytic activity and stereochemical efficiency of the heteroaromatic based catalyst, highlighting once again the importance of the electronic properties of the chiral phosphine oxide.



Scheme 20

The scope of this reaction was investigated starting from 20 different substrates. The heteroaromatic catalyst promoted the formation of the aldol products often in higher yields and with improved diastereo- and enantioselectivity respect to the (*S*)-BINAPO[44] (Table 4).

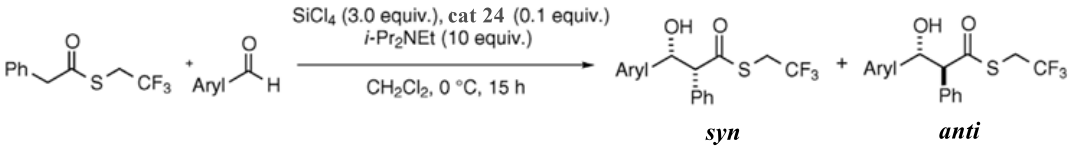


Entry	Aryl	Yield (%)	*anti:syn*	er (*anti*)
1	C_6H_5	70	93:7	90.5:9.5
2	4-NO_2-C_6H_4	71	87:13	96.5:3.5
3	4-Cl-C_6H_4	56	98:2	85.5:14.5
4	3,5-CF_3-C_6H_3	65	94:6	91.5:8.5
5	4-CH_3-C_6H_4	55	98:2	88.5:11.5
6	1-Naphthyl	40	93:7	88.5:11.5
7	$C_6H_5CH{=}CH$	41	90:10	68.5:31.5

Table 4. Direct aldol addition catalysed by (*S*)-TetraMe-BITIOPO.

β-Hydroxy ketones are obtained with high diastereoselectivity, up to 93 : 7 *anti*/*syn* ratio, and enantiomeric ratios often higher than 85 : 15 and up to 96.5 : 3.5.

In addition to ketones and aldehydes, esters can also take part as donors in Lewis base-catalysed aldol additions. The inherent problem of low enolizability of esters can be overcome by the use of more acidic, fluorinated thioesters. The first example of the aldol addition of activated thioesters mediated by $SiCl_4$ and catalysed by phosphine oxides was reported in 2011 by Benaglia and co-workers (Table 5).[45]



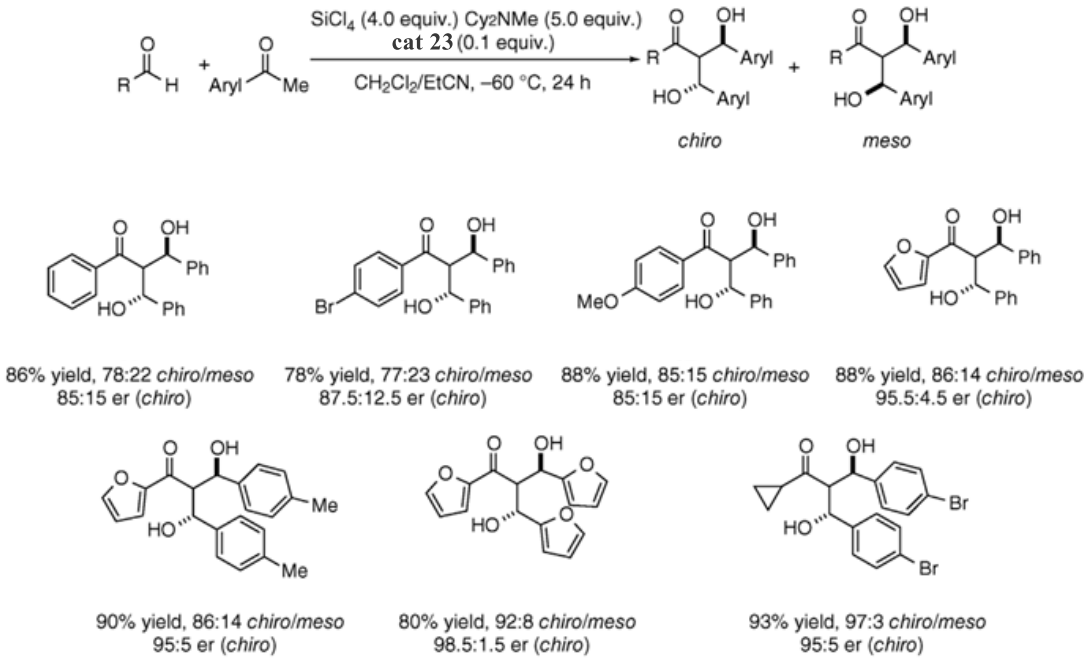
Entry	Aryl	Yield (%)	*syn:anti*	er (*syn*)
1	C_6H_5	80	98:2	94.5:5.5
2	4-ClC_6H_4	40	88:12	90.5:9.5
3	4-$NO_2C_6H_4$	33	80:20	77.5:22.5
4	4-$CH_3OC_6H_4$	51	>98:2	91.5:8.5
5	1-Naphthyl	41	66:34	81.5:18.5
6	2-Furyl	37	>98:2	95.5:4.5
7	2-Thienyl	25	>98:2	96.5:3.5
8	$C_6H_5CH{=}CH$	63	>98:2	91.5:8.5
9	$(CH_3)_2CH$	nr	nd	nd

Table 5. Direct aldol addition of thiol esters catalysed by (*S*)-TetraMe-BITIOPO.

The use of the more acidic S-(2,2,2-trifluoroethyl)-2-phenylethanethioate as activated nucleophilic substrate in the presence of an aromatic aldehyde, $SiCl_4$ and (*S*)-TetraMe-BITIOPO permitted to achieve the corresponding *syn*-β-hydroxy-activated thiol esters from modest to good yields.

Good stereoselectivity levels were obtained with benzaldehyde or aromatic aldehydes bearing electron-donating groups, while aldehydes bearing electron-withdrawing substituents (entries 2 and 3) or the 1-naphthylcarbaldehyde (entry 5) gave lower diastereo- and enantio-selectivities. Cinnamaldehyde achieved the aldol product both in good yields and diastereo- and enantio-selectivity (entry 8), whereas aliphatic aldehydes did not react under these conditions as demonstrated by entry 9. Noteworthy, also in this case (*S*)-BINAPO behaved as a less effective catalyst affording the aldol derived from benzaldehyde in lower yields (35% *vs*. 80%) but with comparable stereoselection levels (97/3 *vs*. 98/2 *syn*/*anti* and 81% *vs*. 89% ee for the *syn* diastereoisomers).[45]

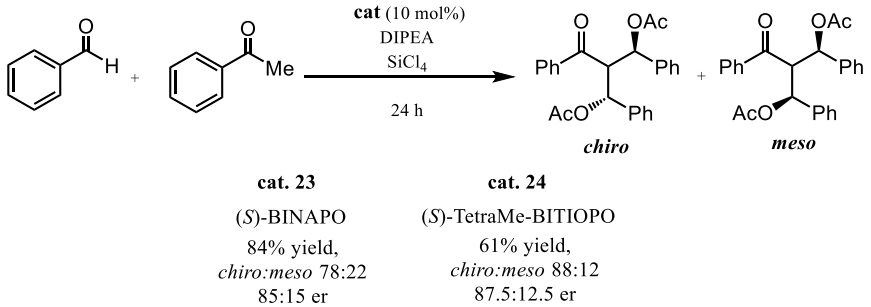
Nakajima introduced the direct aldol reaction between ketones and aldehydes catalysed by BINAPO (Scheme 21)[46] that provided complex molecules from readily available starting compounds.



Scheme 21. Examples of branched, double-aldol addition.

The combination of aromatic or aliphatic ketones with 2 eq. of aromatic aldehydes led to the formation of a mixture of two aldol diastereomers in high yields, with good diastereomeric ratios and, in some cases, also high enantioselectivities (Scheme 21). It must be considered that this reaction gives two diastereoisomers, one of which is chiral (indicated with *chiro*); the achiral one (indicated as *meso*) may actually exist as a couple of diastereoisomers because the α-carbon of the carbonyl group is an achirotopic, stereogenic centre. The best yields and stereoselectivities were obtained with electron-rich aldehydes and aromatic ketones bearing electron-donating groups.

The double-aldol reaction between benzaldehyde and acetophenone was investigated using (*S*)-TetraMe-BITIOPO (**24**) as chiral promoter obtaining comparable results, both in terms of diastereo- and enantio-selection ability (Scheme 22).[47]



Scheme 22. Comparison of double-aldol additions using different phosphine oxides.

Besides the diphosphinoxides previously discussed, a further enlarging of their structural variety was reported in more recent years (Figure 8). In 2009, Ready synthesized the diphosphinoxide **25** characterized by an allene scaffold which was efficiently employed in the asymmetric ring-opening of meso epoxides.[48] One year later, it was reported that SEGPHOSO (**26**) and DIOPO (**27**) are able to promote the stereoselective reductive aldol reaction performed in the presence of trichlorosilane;[49] aryl group-modified DIOP dioxides, such as 2,8-dimethylphenoxaphosphine-DIOPO **28** was found to be effective in promoting the phosphonylation of conjugated aldehydes.[50]

In 2012 the Benaglia group reported that also catalysts **29** and **30**, based on proline backbone can be used in the stereoselective aldol reactions of activated thioesters,[45b] while, one year later, BridgePHOS Oxides (**31**),[51] spyro-type catalyst **32**[52] and conformationally rigid atropisomeric chiral diene phosphine oxide **33** based on (*Z*,*Z*)-2,3-bis[1-(diphenylphosphinyl)ethylidene]tetralin[53] were reported as efficient catalysts in $SiCl_4$ mediated reactions.[54]

Furthermore, more recently, tropos BIPHEPO- ligand **34** and catalysts **35** and **36,** based on bis-(triazolyl) scaffold, have found applications in the enantioselective Abramov type phosphonylation of aldehydes[55] and in the organocatalysed asymmetric double-Aldol-reaction.[56]

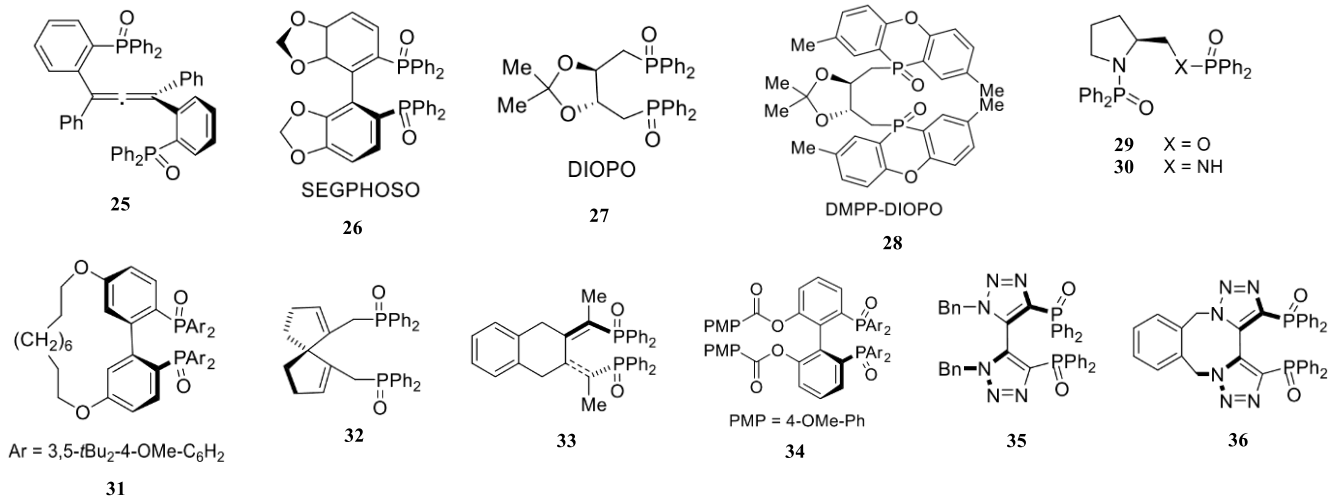


Figure 8

1.2 Results and Discussion

Considering the very interesting results obtained with (*S*)-TetraMe-BITIOPO (**24**) in stereoselective phosphine oxide-catalysed Lewis acid-mediated reactions, in a previous PhD Thesis[57] the synthesis of the new 2,2′,5,5′-tetraphenyl-4,4′-bis-[di-(4-methyl)-phenylphosphino]-3,3′-bithiophene oxide (TetraPh-Tol-BITIOPO **37**, Figure 9) was investigated.

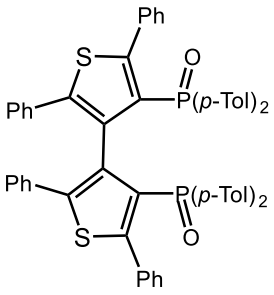


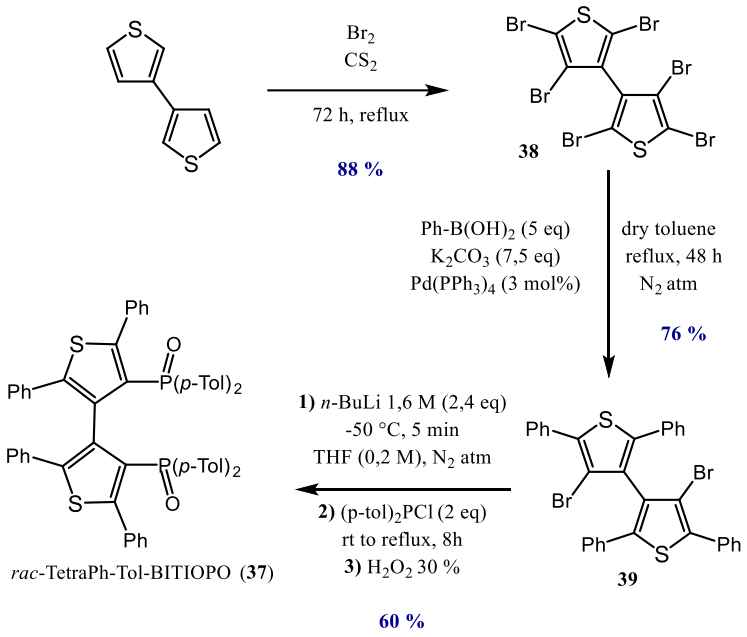
Figure 9. (*rac*)-TetraPh-Tol-BITIOPO **37**.

Differently from the (*S*)-TetraMe-BITIOPO which was achieved in an enantiopure form through classic resolution,[58] the antipodes of TetraPh-Tol-BITIOPO were obtained after the resolution of the racemate by semipreparative HPLC.

The aim of my research project was to synthesize TetraPh-Tol-BITIOPO, and after resolution of the racemate, to test it in a few selected stereoselective organic reactions promoted by the activation of a silicon weak Lewis acidic species in comparison with the similar heteroaromatic enantiopure Tetra-Me-BITIOPO (**24**).

The synthesis of diphosphine-oxide **37** was achieved starting from commercially available 3,3′-bithiophene (Scheme 23), in order to avoid the crucial, encumbrance sensitive, coupling reaction of functionalised thiophene units tested in previous PhD thesis. The bromination of the 3,3′-bithiophene in refluxing CS_2 afforded the corresponding hexabromoderivative **38** in good yields without any further purifications needed. Unluckily, the use of the smelly and toxic CS_2 was found to be essential for the correct development of the reaction, since when the reaction was carried out both in other solvents such as CCl_4, $CHCl_3$ and AcOH, or in the absence of a solvent, only the formation of 2,2′,5,5′-tetrabromothiophene was observed. The tetraphenylderivative **39** was synthesized in good yields through a regioselective Suzuki coupling reaction mediated by a catalytic

amount of Tetrakis(triphenylphosphine)palladium.[59] Finally, the bis-anion of compound **39**, generated with *n*-BuLi at -50°C was treated with 2 eq. of ditolylphosphinic chloride and the crude product was oxidized *in situ* with a 30% hydrogen peroxide solution to give, after column chromatography, the racemate of TetraPh-Tol-BITIOPO **37** in 60% yield.



Scheme 23. Synthesis of *rac*-TetraPh-Tol-BITIOPO (**37**).

The resolution of TetraPh-TolBITIOPO (**37**) was initially investigated through the formation of diastereomeric adducts with enantiopure chiral acids, following a classical strategy successfully applied to the resolution of the racemates of electron-rich diphosphane oxides.[60]

The separation of the two enantiomers of **37** on a multimilligram scale was finally successfully carried out by HPLC on a chiral stationary phase.[61]

Excellent separation of the enantiomers of **37** was obtained by HPLC using a Chiralpak IB column (250 mm × 4.6 mm; 5 µm particle size) in a normal-phase chlorinated elution mode. (*i.e.* mobile phase: *n*-hexane-dichloromethane-2-propanol-diethylamine 70 : 15 : 30 : 0.1 (v/v/v/v)). Typical HPLC UV and CD chromatograms pertinent to the analytical resolution of **37** are shown in Figure 10.

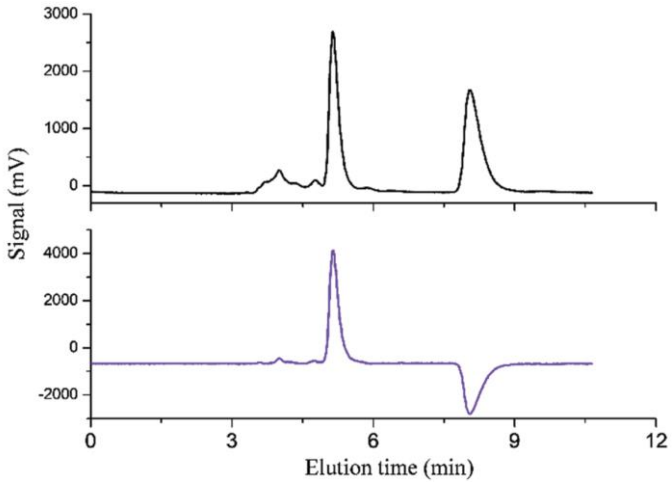


Figure 10. Analytical HPLC resolution of **37**. Column, Chiralpak IB (250 mm × 4.6 mm); mobile phase, *n*-hexane : CH_2Cl_2 : 2-propanol : diethylamine 70 : 15 : 30 : 0.1; flow-rate, 1.0 ml min-1; temperature, 40 °C; detection, UV (black) and CD (purple) at 280 nm.

After a successful analytical separation, this process was easily scaled up to a semipreparative scale using a 250 mm × 10 mm Chiralpak IB column. At a flow-rate of 5.0 ml min-1 and a temperature of 40° C, the chromatographic run was completed within 6 min. Thus, considering that the maximum limit of sample injection onto the 1 cm i.d. Chiralpak IB column was 5 mg (dissolved in 0,5 ml of eluent) and the yields of enantiomeric separations were about 90%, a total of 22.5 mg for each enantiomer per hour could be achieved. Moreover, the enantiomeric excess of each antipode, collected in a multimilligram level, was > 99.0%.

Then, in order to attribute their absolute configuration (AC), Electronic Circular Dichroism (ECD) and Optical Rotation Dispersion (ORD) spectra were recorded. Both spectra were afterwards compared to the related ones simulated by means of Density Functional Theory (DFT) calculations, starting from the (*S*)-TetraPh-Tol-BITIOPO enantiomer (Figure 11).

Thanks to these analyses, it was possible to attribute the (*S*) configuration to the first eluted enantiomer (-)-TetraPh-Tol-BITIOPO (**37**).[61]

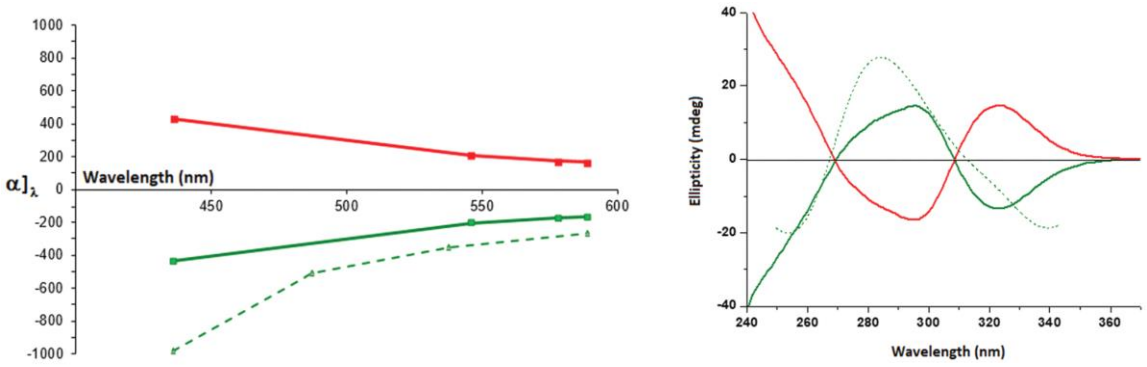
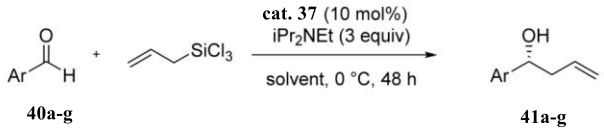


Figure 11. Experimental (full lines) and calculated (dashed lines) ORD and ECD spectra of TetraPh-Tol-BITIOPO enantiomers in chloroform. First eluted (-)-**37** is shown as a green line; (+)-**37** as a red line. Dashed traces refer to calculated ORD or ECD spectra of the (*S*)-TetraPh-Tol-BITIOPO enantiomer.

Optically pure TetraPh-Tol-BITIOPO (**37**) was then tested as chiral promoter in a few stereoselective Lewis base-catalysed Lewis acid-mediated reactions. The first reaction investigated was the stereoselective allylation of aromatic aldehydes: a typical experiment involves the reaction of 1 eq. of aldehyde **40a-g** with 1.2 eq. of allyltrichlorosilane, 0.1 eq. of the catalyst and 3 eq. of DIPEA in CH_3CN for 40 h at 0°C.[42] The isolation yields and the enantiomeric excesses, determined by HPLC on a chiral stationary phase, are reported in Table 6. The absolute configuration of each product was assigned by comparison with literature data.



40a-g **41a-g**

Entry	Aldehyde	Ar	Catalyst	Solvent	Product	Yield (%)	ee[a] (%)
1	**40a**	C_6H_5	(−)-(*S*)-TetraPh-Tol-BITIOPO	CH_3CN	**41a**	87	70(*S*)
2	**40a**	C_6H_5	(+)-(*R*)-TetraPh-Tol-BITIOPO	CH_2Cl_2	**41a**	50	94(*R*)
3	**40b**	4-OCH_3-C_6H_4	(+)-(*R*)-TetraPh-Tol-BITIOPO	CH_3CN : CH_2Cl_2 (1 : 1)	**41b**	49	94(*R*)
4	**40c**	4-Cl-C_6H_4	(+)-(*R*)-TetraPh-Tol-BITIOPO	CH_2Cl_2	**41c**	46	96(*R*)
5	**40d**	4-NO_2-C_6H_4	(−)-(*S*)-TetraPh-Tol-BITIOPO	CH_3CN	**41d**	50	90(*S*)
6	**40e**	Ph–CH=CH–	(−)-(*S*)-TetraPh-Tol-BITIOPO	CH_3CN	**41e**	98	70(*S*)
7[b]	**40e**	Ph–CH=CH–	(+)-(*R*)-TetraPh-Tol-BITIOPO	CH_3CN	**41e**	96	69(*R*)
8	**40f**	2-Thiophenyl	(−)-(*S*)-TetraPh-Tol-BITIOPO	CH_2Cl_2	**41f**	60	76(*S*)
9	**40g**	Ph–CH_2CH_2	(+)-(*R*)-TetraPh-Tol-BITIOPO	CH_2Cl_2	**41g**	43	Rac

[a] Determined using HPLC on a chiral stationary phase; stereogenic center configuration was assigned based on comparison with literature data.
[b] Reaction conducted at −20 °C.

Table 6. Substrate scope of the enantioselective addition of allyltrichorosilane to aldehydes.

Preliminary experiments with benzaldehyde (**40a**) under standard conditions gave homoallyl alcohol (**41a**) in 87% yield and 70% ee (Table 6, entry 1). This outcome is similar to that reported in literature for enantiopure Tetra-Me-BITIOPO.[42] However, due to the scarce TetraPh-Tol-BITIOPO (**37**) solubility in acetonitrile, the use of CH_2Cl_2 was also investigated. In this case, the desired product **41a** was obtained in 94% ee, even if the yield decreased to 50% (entry 2).

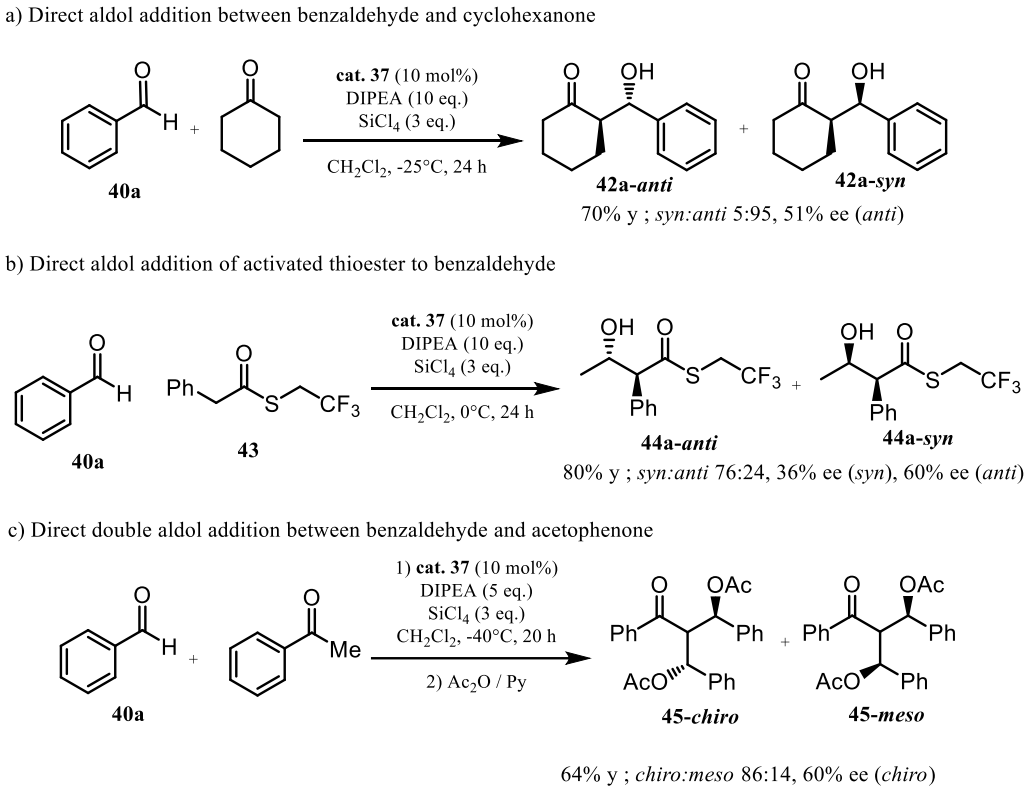
Considering the improved enantioselection ability of catalyst **37** when the reaction was carried out in CH_2Cl_2, the substrate scope was extended performing the reaction starting from differently substituted aldehydes, bearing electron donating as well as electron withdrawing substituents on the aromatic ring (entries 3-5). In all cases, the products were afforded in moderate yields but with high enantioselectivities (up to 96% ee), proving that the catalyst is effectively able to control the stereoselectivity of the process.

Interestingly, catalyst **37** resulted also efficient in the allylation of cinnamaldehyde **40e** allowing the formation of the corresponding alcohol **41e** in almost quantitatively conversion and with 70% ee (entry 6). Enantiopure TetraPh-Tol-BITIOPO showed to be active also at -20°C and the product was obtained in 96% yield and 69% ee (entry 7). In this case, a considerable improvement was observed respect to enantiopure Tetra-Me-BITIOPO that gave the alcohol **41e** in 55% yield and 55% ee.[42]

The allylation of heteroaromatic aldehydes, such as 2-thiophenyl carboxaldehyde **40f**, was also investigated and product **41f** was achieved in 60% yield and 76% ee (entry 8).

Encouraged by these results, the use of catalyst **37** was extended to other Lewis base-catalysed Lewis acid- mediated reactions such as the direct aldol reaction between aromatic aldehydes with both ketones and thioesters (Scheme 24a and b) as well as the direct double aldol reaction between aryl methyl ketones with aromatic aldehydes in the presence of $SiCl_4$ (Scheme 24c).

The reaction between cyclohexanone and benzaldehyde was carried out by using stoichiometric amounts of $SiCl_4$ and a catalytic amount of enantiopure (-)-TetraPh-Tol-BITIOPO (**37**) at -25°C for 36 h.[43] β-Hydroxyketone **42a** was obtained in 70% yield with very high diastereoselectivity in favour of the *anti* diastereoisomers (95 : 5 *anti*/*syn* ratio) and in 51% ee for the (1'*S*,2*R*)-**42a**-*anti* enantiomer.[61]



Scheme 24. Direct (double) aldol reaction of benzaldehyde with activated nucleophiles.

Then, organocatalytic stereoselective direct aldol reaction of trifluoroethyl thioester **43** was investigated according to a literature procedure.[45a] The corresponding β-hydroxy thioester **44a** was obtained in 74% yield with a 76 : 24 *syn*/*anti* ratio, although a decrement in terms of enantioselectivity was observed (see Table 5 entry 1). However, these results are notable if we compare them with what obtained with BINAPO, which is not able to effectively promote this type of transformation (35% yield).[45a]

Finally, the $SiCl_4$-mediated direct double aldol reaction between acetophenone and benzaldehyde was also investigated (Scheme 24c). The double aldol product was purified as a diacetate form in 64% yield and 86 : 14 ratio between the chiral stereoisomer **45**-*chiro* and the achiral **45**-*meso* was observed, with a 60% ee for the chiral one. It must be reported that **45**-*meso* is an achiral molecule that may exist in two diastereoisomers; however, in this case only one form was observed by ^{1}H-NMR). These results are similar to those obtained with optically pure Tetra-Me-BITIOPO (**24**) in terms of yield and diastereomeric ratio,[47] however the stereoselection ability of **37** appears to be slightly lower than both enantiopure Tetra-Me-BITIOPO (**24**) and BINAPO (**23**), that resulted to be the most effective catalyst for this kind of transformation in terms of yield (86%, see Scheme 21).

So, comparing the newly synthesized catalyst TetraPh-TolBITIOPO (**37**) and the previously reported TetraMe-BITIOPO (**24**) in terms of chemical and stereochemical efficiency, we can say that both organocatalysts are able to promote the allylation of aldehydes with good yields and high enantioselectivities. However, a lower level of enantioselection was observed when the direct aldol reaction between benzaldehyde and cyclohexanone was performed in the presence of catalyst **37**. Interestingly, the two catalysts having the same 3,3'-bithiophene chiral scaffold, gave, in all the investigated reactions, enantiomers with an opposite configuration, while maintaining, in the case of the direct aldol reaction, the same diastereoselectivity.

In order to clarify the origin of this behaviour, the direct aldol reaction between benzaldehyde and cyclohexanone catalysed by both TetraMe-BITIOPO (**24**) and TetraPh-Tol-BITIOPO (**37**) was studied by semiempirical calculations (Figure 12).

Initially, a conformational analysis with a Monte Carlo technique was carried out using the OPLS_2005 force field[62] with a Macromodel Schrodinger suite package[63] on a model of the TSs, in order to reach the best geometrical arrangement for the different substituents. Then, the two structures leading to the formation of the two experimentally observed *anti* products were fully optimized to the relative genuine TSs with AM1 methods (both with only one imaginary frequency).[64] The calculations, carried out by using (*S*)-TetraMe-BITIOPO (**24**) as the catalyst, showed that **TS-1**, responsible for the formation of the experimentally observed *anti*-(2*S*,1'*R*)-(**42a**)-diastereoisomer, is more stable by 0.67 kcal mol^{-1} than **TS-2**. The same calculations using (*S*)-TetraPh-Tol-BITIOPO (**37**) revealed instead an opposite trend: **TS-3**, which conducts to the formation of the *anti*-(2*R*,1'*S*)-diastereoisomer, is more stable by only 0.17 kcal mol^{-1} than **TS-4**. Furthermore, as underlined in Figure 12, the energy differences between the TSs determined by computational studies are in good agreement with the experimentally observed lower enantioselectivity achieved with catalyst (*S*)-**37** compared to the (*S*)-TetraMe-BITIOPO derivative (**24**).

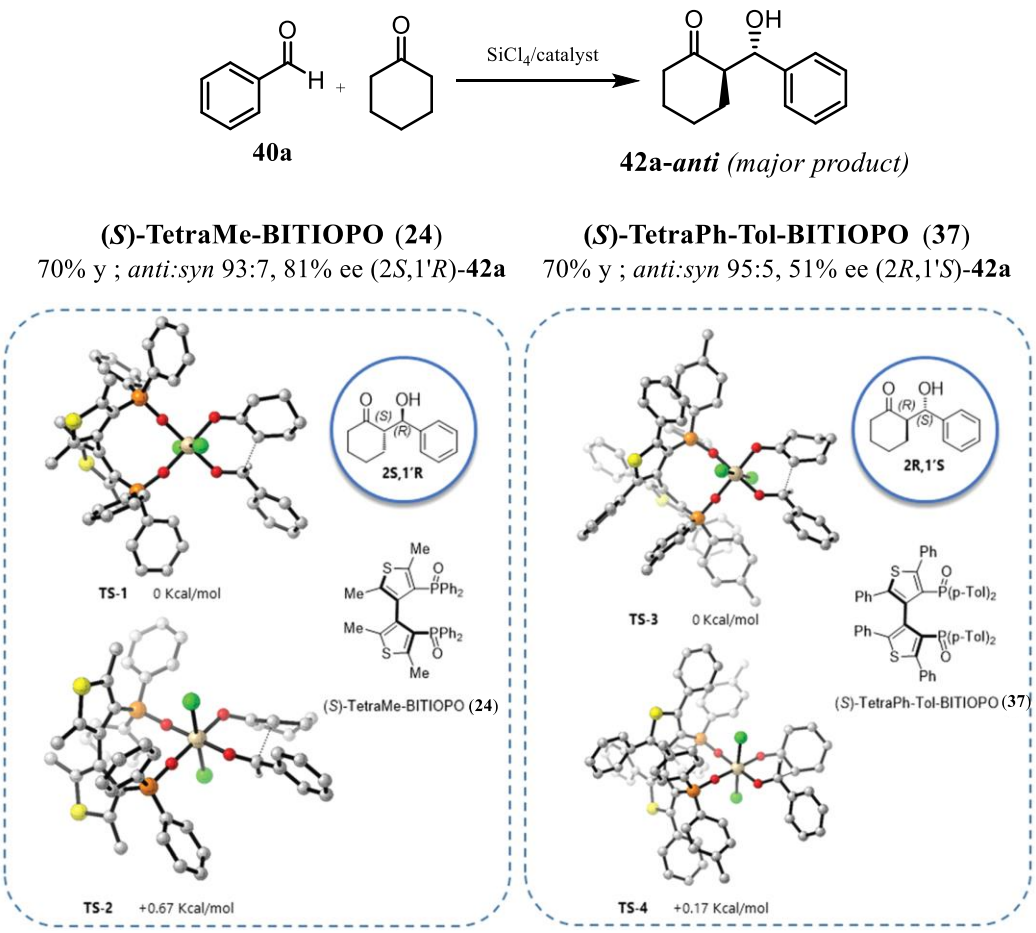


Figure 12. ΔΔG in kcal mol-1 at the AM1 level of theory of TSs related to the aldol addition reaction mediated by $SiCl_4$ and promoted by BITIOPO catalysts (hydrogen was omitted for clarity, cream = silicon, yellow = sulphur, green = chlorine, red = oxygen, orange = phosphorus, grey = carbon).

This unexpected behaviour can be explained by the presence in catalyst **37** of a π–π interaction between a phenyl group of the 3,3'-bithienylic scaffold and a tolyl group connected to the phosphorous atom. Such interaction causes a different local atom rearrangement in the chiral pocket formed between the hypervalent silicon species, the $SiCl_4$, and the catalyst-(**37**), compared to those generated when (*S*)-TetraMe-BITIOPO (**24**) was employed.

1.3 Conclusions

A new chiral 3,3'-bithiophene based diphosphinoxide nicknamed as TetraPh-Tol-BITIOPO (**37**) was successfully employed, after resolution of the racemate through semi-preparative HPLC, as chiral promoter in organocatalysis in some Lewis Base catalysed Lewis Acid mediated C-C bond formation reactions.

The catalytic performances were compared to those obtained with the previously synthesized 3,3'-bithiophene-based catalyst (*S*)-TetraMe-BITIOPO differing from the presence of for methyl groups in the thiophene α positions.

The new catalyst showed a slight decrease of the catalytic activity for what concern the allylation reaction of different substituted aromatic aldehydes (from 46 to 50% yield) respect to enantiopure TetraMe-BITIOPO, maintaining the same excellent levels of enantioselectivities (from 90 to 96% ee).

An improvement in terms of catalytic activity and stereoselection ability was observed in the allylation of cinnamaldehyde performing the reaction both at 0°C (98% yield, 70% ee) and at -20°C (96% yield, 69% ee) respect to the TetraMe-substituted phosphine oxide (55% yield, 55% ee).

The direct aldol reaction of aromatic aldehydes with both ketones and thioesters and the direct double aldol reaction between aryl methyl ketones and aromatic aldehydes, in the presence of $SiCl_4$, were also investigated. Comparable results in terms of yields, diastereoisomeric ratio and enantioselection levels were achieved. However, lower enantiodiscrimation was observed when the direct aldol reaction between benzaldehyde and cyclohexanone was performed in the presence of catalyst **37** (51% ee instead of 81% obtained with enantiopure (*S*)-TetraMe-BITIOPO).

Interestingly, in all the reactions studied, comparing the results with those achieved with enantiopure TetraMe-BITIOPO, maintaining the same catalyst configuration, opposite antipodes of the products were obtained.

1.4 Experimental Section

1.4.1 General Information

Methods:

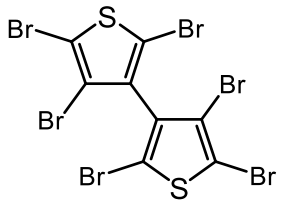
Reactions were monitored by analytical thin-layer chromatography (TLC) using silica gel 60 F_{254} pre-coated glass plates (0.25 mm thickness) and visualized using UV light. Flash chromatography was carried out on silica gel (230-400 mesh). ^{1}H-NMR spectra were recorded on spectrometers operating at 300 MHz (Bruker Fourier Advanced 300); proton chemical shifts are reported in ppm (δ) with the solvent reference relative to tetramethylsilane (TMS) employed as the internal standard ($CDCl_3$ δ = 7.26 ppm) and coupling constants are reported in Hertz (Hz). Splitting patterns are indicate as follows: s = singlet, d = doublet, t = triplet, q = quartet, qn = quintuplet, m = multiplet, bs = broad singlet, dd = double doublet. ^{13}C-NMR spectra were recorded on 300 MHz spectrometers operating at 75 MHz with complete proton decoupling; carbon chemical shifts are reported in ppm (δ) relative to TMS with the respective solvent resonance as the internal standard ($CDCl_3$, δ = 77.0 ppm). ^{31}P-NMR spectra were recorded on 300 MHz spectrometers (Bruker Fourier Advanced 300) at 121.4 MHz and were referenced to phosphoric acid (H_3PO_4) at 0.0 ppm. Mass spectra and accurate mass analysis were carried out on a VG AUTOSPEC- M246 spectrometer (double-focusing magnetic sector instrument with EBE geometry) equipped with EI source or with LCQ Fleet ion trap mass spectrometer, ESI source, with acquisition in positive ionization mode in the mass range of 50-2000 m/z.

The CD spectra of the enantiomers of **37**, dissolved in chloroform (concentration about 0.30 mg mL^{-1}) in 0.1 cm path-length quartz cell at 25 °C, were measured by using a Jasco Model J-700 spectropolarimeter. The spectra are average computed over three instrumental scans and the intensities are presented in terms of ellipticity values (mdeg). Specific rotations were measured by a PerkinElmer polarimeter model 241 equipped with Na/Hg lamps. The volume of the cell was 1 mL and the optical path was 10 cm. The system was set at a temperature of 20 °C. For semipreparative HPLC separations a Perkin-Elmer (Norwalk, CT, USA) 200 LC pump equipped with a Rheodyne (Cotati, CA, USA) injector, a 5000 µL sample loop, a Perkin-Elmer LC 101 oven and a Waters 484 detector (Waters Corporation, Milford, MA, USA) were used.

Melting point determinations were performed by using a Buchi B-540 instrument.

1.4.2 Synthesis of *rac* TetraPh-Tol-BITIOPO (37)

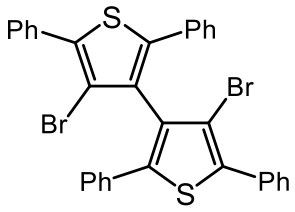
1.4.2.1 Synthesis of hexabromo-3,3'-bithiophene (38)



Bromine (40 ml) was added dropwise to a stirred solution of 3,3'-bithiophene (3.8 g, 23 mmol, 1 eq) in CS_2 (114 ml); the reaction mixture was heated at reflux and stirred for 36 h; then the excess of bromine was reduced by slowly adding a saturated solution of sodium metabisulphite at 10°C until clarification of the mixture. The residue was extracted with toluene (100 ml); the organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. Hexabromo-3,3'-bithiophene[65] (**38**) was obtained without any further purification as a white solid (88% yield).

Mp: 178-181°C.

1.4.2.2 Synthesis of 4,4'-dibromo-2,2',5,5'-tetraphenyl-3,3'-bithiophene (39)

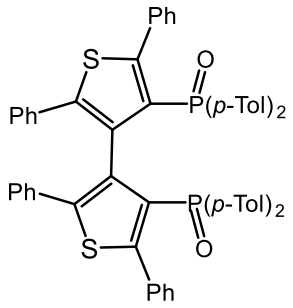


A mixture of hexabromo-3,3'-bithiophene (0.5 g, 0.78 mmol, 1 eq), phenyl boronic acid (0.62 g, 5.1 mmol, 6.5 eq) and K_2CO_3 (0.65 g, 4.7 mmol, 6 eq) in dry toluene (20 ml) was stirred at room temperature for 10 minutes, then palladium tetrakis (0.027 g, 0.023 mmol, 3 mol%) was added and the mixture was heated at reflux for 24 hours. The solvent was removed at reduced pressure, and the crude dissolved in CH_2Cl_2 (20 ml) and washed with water (20 ml); the organic layer was dried and concentrated under reduced pressure.
Flash chromatography (*n*-hexane/CH_2Cl_2 9:1) gave **39**[65] as a white solid (76 % yield).

^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 7.79 (4H, d, *J* 6.0 Hz), 7.48 (2H, t, *J* 6.0 Hz), 7.41 (4H, d, *J* 6.0 Hz), 7.23-7.09 (10H, m).

m/z (EI) 629 (M^+).

1.4.2.3 Synthesis of *rac* TetraPh-Tol-BITIOPO (37)



A 1.6 M *n*-BuLi solution (3.02 ml, 4.83 mmol, 2.4 eq) was added dropwise under stirring into a solution of **39** (1.26 g, 3.97 mmol, 1 eq) in dry THF (10 ml) under a N_2 atmosphere at -50 °C. After 45 min the temperature was allowed to warm up to -40 °C and ditolylphosphinic chloride was added dropwise (1.0 g, 4.02 mmol, 2 eq). The reaction mixture was refluxed for 8 h and the solvent evaporated under reduced pressure. The residue was diluted with CH_2Cl_2 (10 ml) and a 30% H_2O_2 solution (5 ml) was added at room temperature. The reaction mixture was stirred for 1 h, then treated with a 1N HCl solution (20 ml). The organic layer was washed with a saturated $NaHCO_3$ solution (20 ml); the aqueous phase was extracted with CH_2Cl_2 (3 x 20 ml) and the combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by flash column chromatography (CH_2Cl_2 /AcOEt/ Et_3N 7:3:0.1).

The last fractions eluted was combined and evaporated to dryness to give **37** as a white solid (60 % yield).

M.p. 134 °C

^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 7.30-6.90 (14H, m), 6.81 (2H, dd, *J* 2.4 Hz), 6.71 (2H, dd, *J* 2.4 Hz), 2.22 (3H, s), 2.16 (3H, s).

^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 151.15, 150.97, 142.14, 141.97, 140.29, 135.67, 135.50, 134.09, 133.40, 132.31, 132.17, 132.04, 131.90, 131.37, 131.23, 130.67, 129.92, 129.83, 129.36, 128.98, 128.65, 128.54, 128.24, 128.05, 127.86, 127.47, 127.29, 126.95, 21.48, 21.41.

^{31}P NMR (121.4 MHz, $CDCl_3$, δ ppm): 21.82.

MS (EI) = 926 (M^+).

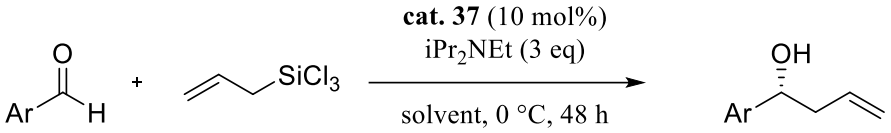
The resolution of racemic **37** was carried out through a semipreparative chiral HPLC using a 250 mm × 10 mm Chiralpak IB column. At a flow-rate of 5.0 ml/min and a temperature of 40° C.

(*S*)-enantiomer: $[\alpha]_D^{25}$ = - 166 (c = 0.249 g/ml, $CHCl_3$)

(*R*)-enantiomer: $[\alpha]_D^{25}$ = + 165 (c = 0.205 g/ml, $CHCl_3$)

1.4.3 Catalytic experiments with enantiopure TetraPh-Tol-BITIOPO (37)

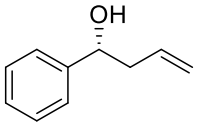
1.4.3.1 General procedure for the enantioselective allylation reaction



40a-g **41a-g**

Allyltrichlorosilane (40.49 mg, 0.214 mmol, 1.2 eq) was added dropwise to a mixture of an antipode of TetraPh-Tol-BITIOPO (**37**) (0.017 mg, 0.018 mmol, 10 mol%), freshly distilled aldehyde (**40**) (0.178 mmol, 1 eq), and diisopropylethylamine (0.093 ml, 0.534 mmol, 3 eq) dissolved in the desired solvent (1.2 ml, 0.15 M) under a N_2 atmosphere at 0 °C. The reaction mixture was stirred at maintained at this temperature for 48 h, then quenched with a saturated $NaHCO_3$ aqueous solution (1 ml). The mixture was allowed to warm up to room temperature, then the layers were separated and the aqueous layer was extracted with AcOEt (2 x 5 mL). The combined organic layer was washed with aqueous sodium chloride, dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel (*n*-hexane/AcOEt 9:1).

1-Phenylbut-3-en-1-ol (41a)

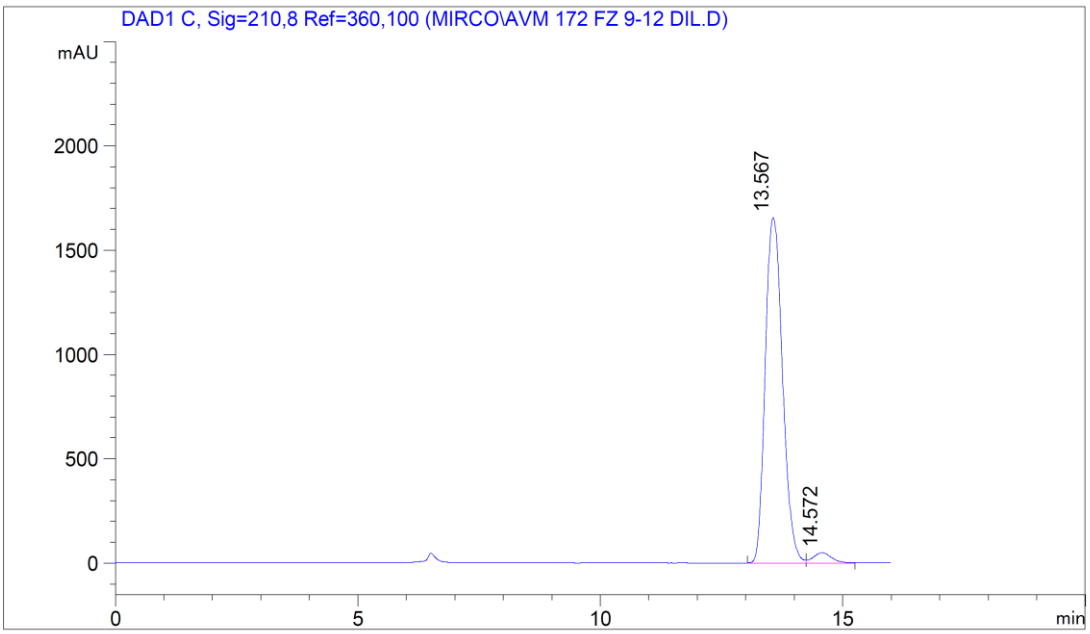


Purification by flash column chromatography (*n*-hexane/AcOEt 95:5).

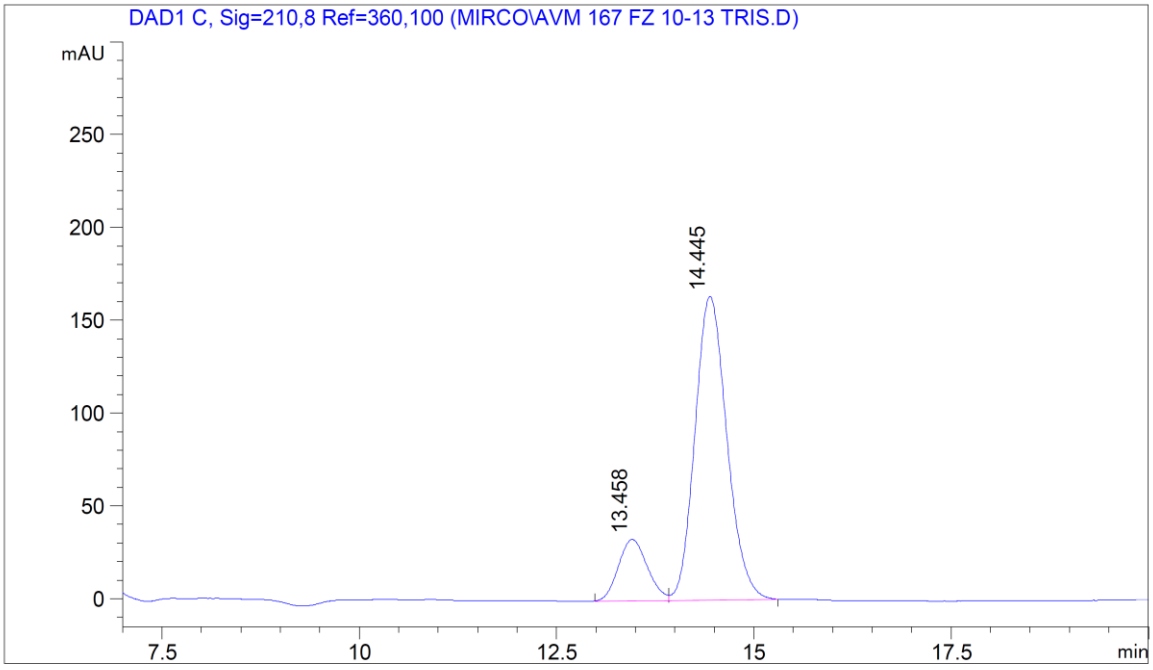
^{1}H-NMR (300 MHz, $CDCl_3$, δ ppm): 7.27-7.04 (5H, m), 5.90-5.76 (1H, m), 5.16-5.15 (2H, m), 4.76 (1H, dd, *J* 7.6 Hz, *J* 5.6 Hz,), 2.61-2.46 (2H, m), 2.05 (1H, bs).[66]

The enantiomeric excess was determined by chiral HPLC with Daicel Chiralpak OD-H column, eluent: 95:5 Hex/IPA; 0.5 ml/min flow rate, detection: 210 nm; t_R 13.5 min ((*R*)-enantiomer), t_R 14.5 ((*S*)-enantiomer).

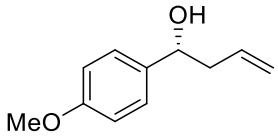
Reaction performed using catalyst (***R***)-(+)-TetraPh-Tol-BITIOPO in CH_2Cl_2 led to the formation of product **41a** in 50 % yield and 94% ee with (*R*)-antipode prevailing.



Reaction performed using catalyst (*S*)-(-)-TetraPh-Tol-BITIOPO in CH_3CN led to the formation of product **6a** in 87 % yield and 70 % ee with (S) antipode prevailing.



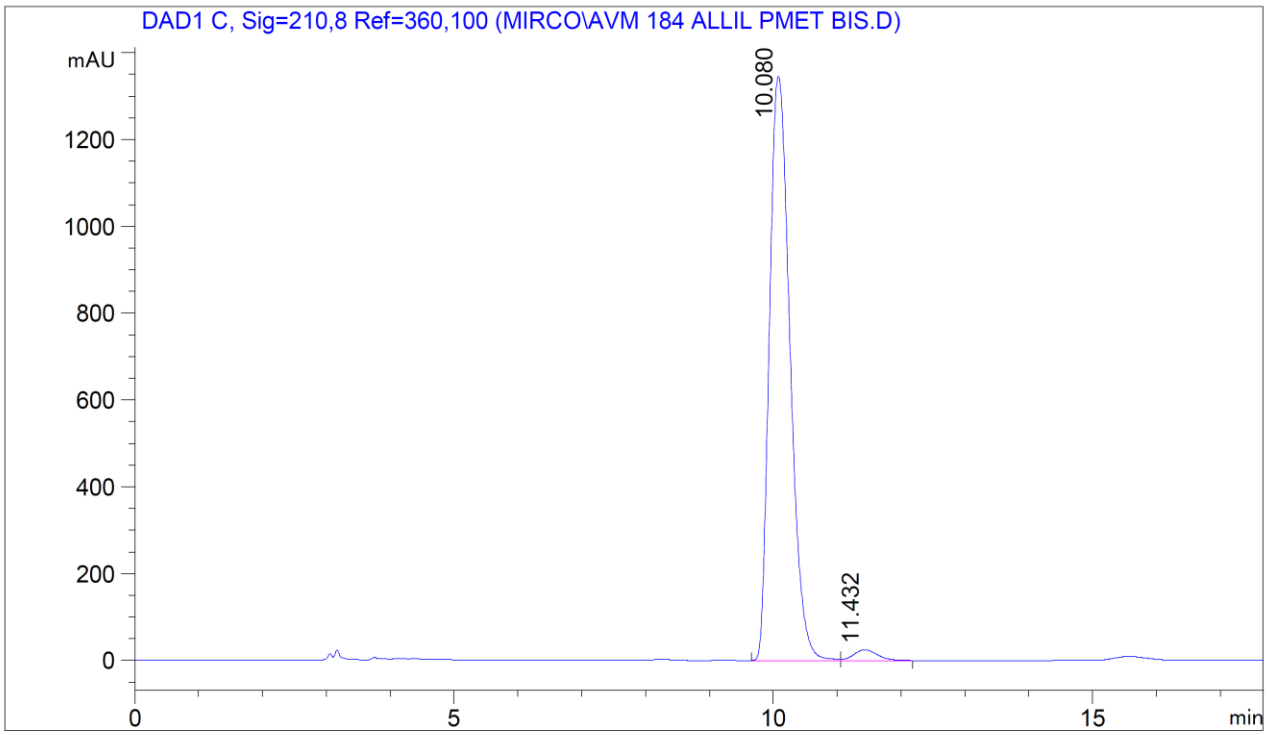
1-(4-Methoxy-phenyl)but-3-en-1-ol (41b):



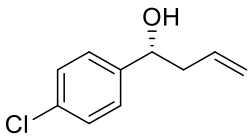
Purification by flash column chromatography (*n*-hexane/ AcOEt 9:1) (49 % yield)

^{1}H-NMR (300 MHz, $CDCl_3$, δ ppm): 7.29 (2H, d, *J* 11.6 Hz), 6.90 (2H, d, *J* 11.6 Hz), 5.89-5.5.75 (1H, m), 5.20-5.13 (2H, m), 4.71 (1H, t, *J* 6.5 Hz), 2.54-2.36 (2H, m), 1.60 (1H, bs), 1.27 (3H, s).[67]

The enantiomeric excess (94 % ee) was determined by chiral HPLC with Daicel Chiralpak OD-H column, eluent: 95:5 Hex/IPA; 1.0 ml/min flow rate, detection: 210 nm; t_R 10.0 min ((*R*)-enantiomer), t_R 11.4 ((*S*)-enantiomer).



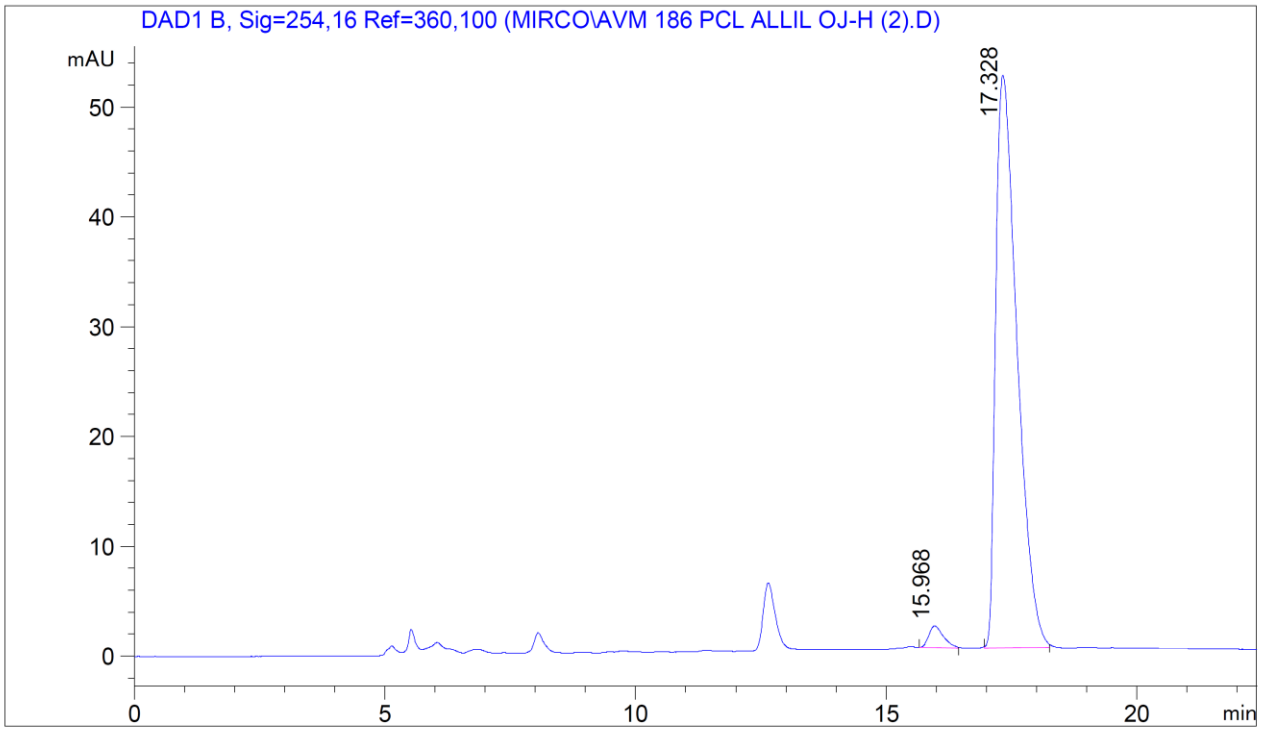
1-(4-Chloro-phenyl)but-3-en-1-ol (41c).



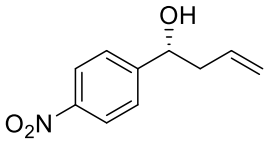
Purification by flash column chromatography (*n*-hexane/AcOEt 9:1) (46 % yield).

^{1}H-NMR (300 MHz, $CDCl_3$, δ ppm): 7.36-7.28 (4H, m), 5.87-5.73 (2H, m), 5.22-5.14 (1H, m), 4.74 (1H, dd, *J* 7.8 Hz, *J* 5.1 Hz), 2.53-2.46 (2H, m), 2.07 (1H, bs).[68]

The enantiomeric excess (96%) was determined by chiral HPLC with Daicel Chiralpak OJ-H column, eluent: 95:5 Hex/IPA; 0.6 ml/min flow rate, detection: 254 nm; t_R 15.9 min ((*S*)-enantiomer), t_R 17.3 ((*R*)-enantiomer).



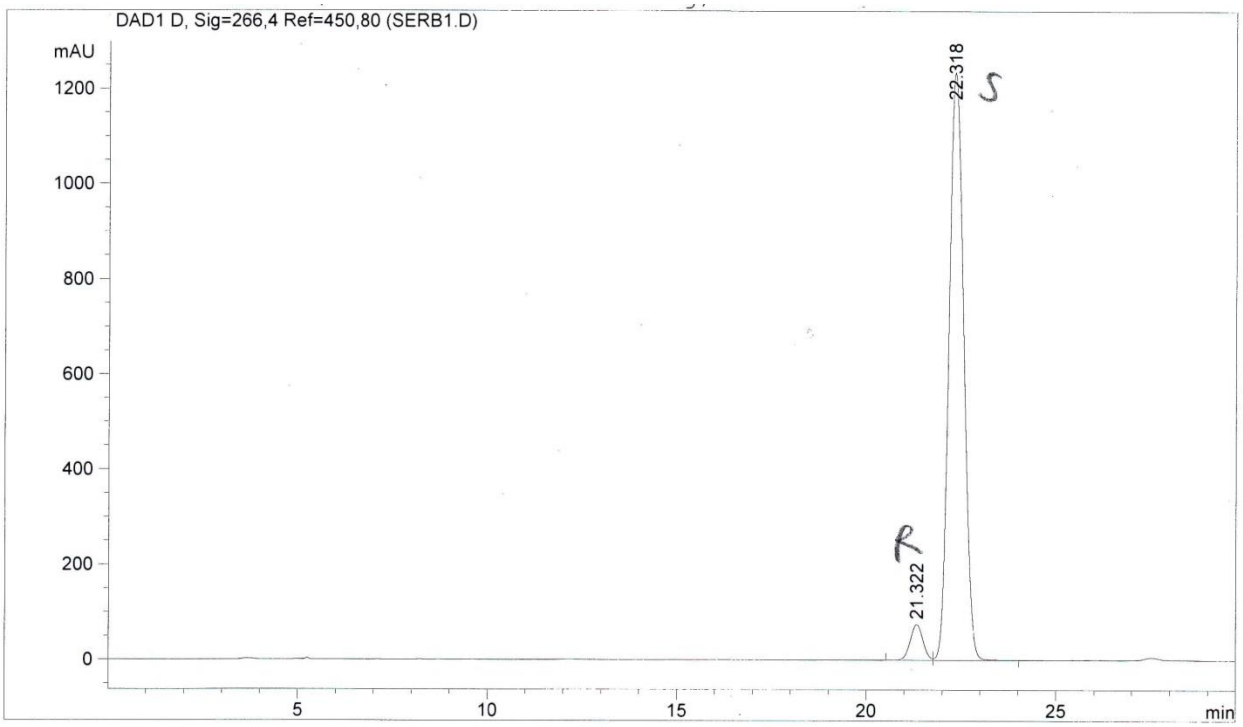
1-(4-Nitro-phenyl)but-3-en-1-ol (41d)



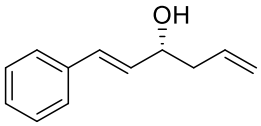
Purification by flash column chromatography (n-hexane/AcOEt 6:4) (50 % yield).

^{1}H-NMR (300 MHz, $CDCl_3$, δ ppm): 8.18 (2H, d, *J* 8.0), 7.52 (2H, d, *J* 8.0), 5.84-5.72 (1H, m), 5.21-5.14 (1H, m), 4.85 (1H, dd, *J* 8.0 Hz, *J* 4.2 Hz), 2.59-2.52 (1H, m), 2.49-2.40 (1H, m), 2.38 (1H, bs).[69]

The enantiomeric excess (90%) was determined by chiral HPLC with Daicel ChiralCel AS-3 column, eluent: 93:7 Hex/IPA; 0.8 ml/min flow rate, detection: 266 nm; t_R 21.0 min ((*R*)-enantiomer), t_R 22.2 ((*S*)-enantiomer).



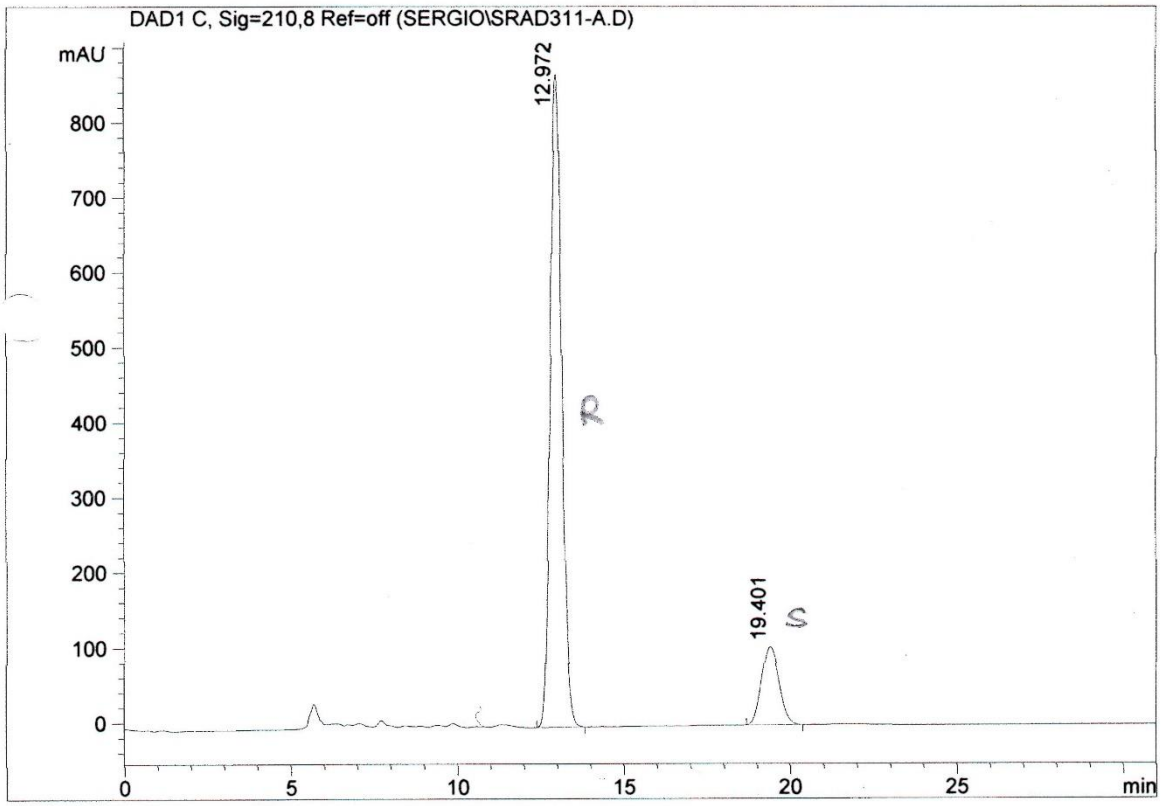
(*E*)-1-Phenylhexa-1,5-dien-3-ol (41e):



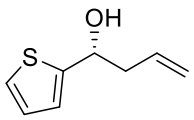
Purification by flash column chromatography (*n*-hexane/AcOEt 9:1) (98 % yield).

^{1}H-NMR (300 MHz, $CDCl_3$, δ ppm): 7.42-7.28 (5H, m), 6.64 (1H, d, *J* 18 Hz), 6.24 (1H, dd, J_1 18 Hz, J_2 6 Hz), 5.90-5.88 (1H, m), 5.24-5.18 (2H, m), 4.39 (1H, q, *J* 6 Hz), 2.51-2.41 (2H, m), 1.67 (1H, bs, OH).[70]

The enantiomeric excess (70 %) was determined by chiral HPLC with Daicel ChiralCel OD-H column, eluent: 9:1 Hex/IPA; 0.8 ml/min flow rate, detection: 210 nm; t_R 12.9 min ((*R*)-enantiomer), t_R 19.4 ((*S*)-enantiomer).



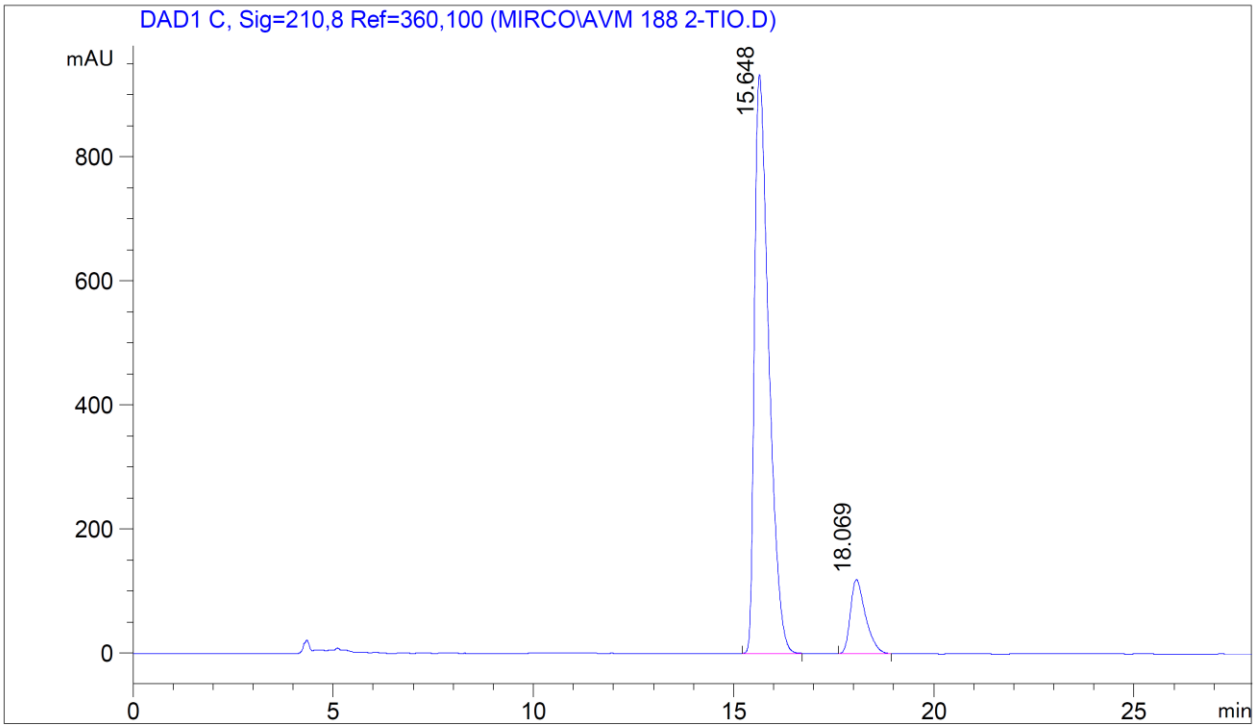
1-(Thiophen-2-yl)-but-3-en-1-ol (41f)



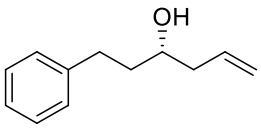
Purification by flash column chromatography (*n*-hexane/AcOEt 9:1) (60 % yield).

^{1}H-NMR (300 MHz, $CDCl_3$, δ ppm) 7.27-7.25 (1H, m), 7.01-6.97 (2H, m), 5.92-5.78 (1H, m), 5.25-5.16 (m, 2H), 5.01 (1H, t, *J* 6.3 Hz), 2.67-2.57 (1H, m).[70]

The enantiomeric excess (76%) was determined by chiral HPLC with Daicel ChiralCel OJ-H column, eluent: 95:5 Hex/IPA; 0.7 ml/min flow rate, detection: 210 nm; t_R 15.6 min ((*S*)-enantiomer), t_R 18.0 ((*R*)-enantiomer).



1-Phenylhex-5-en-1-ol (41g):

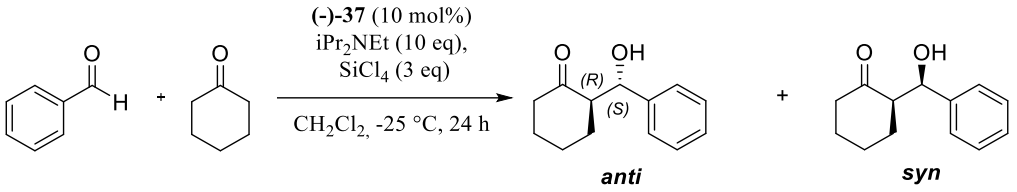


Purification by flash column chromatography (*n*-hexane/AcOEt 8:2).

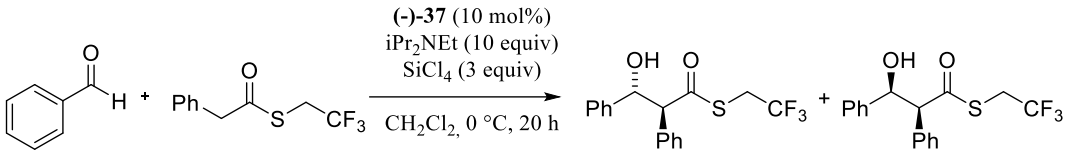
^{1}H-NMR (300 MHz, $CDCl_3$, δ ppm): 8.18 (2H, d, *J* 8.0), 7.52 (2H, d, *J* 8.0), 5.84-5.72 (1H, m), 5.21-5.14 (1H, m), 4.85 (1H, dd, *J* 8.0 Hz, *J* 4.2 Hz), 2.59-2.52 (1H, m), 2.49-2.40 (1H, m), 2.38 (1H, bs).[70]

The enantiomeric excess was evaluated by chiral HPLC with Daicel ChiralCel OD-H column, eluent: 90:1 Hex/IPA; 0.5 ml/min flow rate, detection: 210 nm; t_R 11.3 min ((*S*)-enantiomer), t_R 16.8 ((*R*)-enantiomer). The product was obtained as racemic form.

1.4.3.2 General procedure of enantioselective direct aldol-type reaction



yield = 70% *anti:syn* 95:5, 51% ee (*anti*)



yield = 74%, *anti:syn* 24:76, 60% ee (*anti*), 36% ee (*syn*)

Diisopropylethylamine (0.310 ml, 1.78 mmol, 10 eq) and cyclohexanone (0.035 g, 0.356 mmol, 2 eq) or thioester S-(2,2,2-trifluoroethyl)-2-phenylethanethioate (0.099 g, 0.356 mmol, 2 eq) were added to a stirred solution of enantiopure TetraPh-Tol-BITIOPO **37** (0.017 g, 0.018 mmol, 10 mol%) in CH_2Cl_2 (1.2 ml) under a N_2 atmosphere. The mixture was then cooled at 0 °C and freshly distilled tetrachlorosilane (0.031 ml, 0.267 mmol, 1.5 eq) was added dropwise via syringe. After 15 min, freshly distilled aldehyde (0.018 ml, 0.178 mmol, 1 eq) was added. The mixture was stirred for 5/12 hours (5 h for thioesters, 12 h for ketones), then the same amount of tetrachlorosilane (1.5 eq) was added. After further 12/15 hours (15 h for thioesters, 12 h for ketones), the reaction was quenched by the addition of a saturated $NaHCO_3$ aqueous solution (3 ml). The mixture was allowed to warm up to room temperature and stirred for 30 min, then water (2.5 ml) and ethyl acetate (8 ml) were added. The two-layers mixture was separated and the aqueous layer was extracted with ethyl acetate (8 ml). The combined organic layers were washed with 10% HCl (10 ml), sat. $NaHCO_3$ (10 ml) and brine (10 ml), dried (Na_2SO_4) filtered and concentrated under vacuum at room temperature. The crude product was purified by column chromatography with *n*-hexane/AcOEt 9:1 mixture as eluent to afford the pure aldol adducts (see below).

The *syn/anti* ratio was calculated by ^1H NMR spectroscopy of the crude mixture; the enantiomeric excesses were determined by HPLC. Catalyst **37** was quantitatively recovered by further elution with 10% CH_3OH in CH_2Cl_2 without any loss of optical purity.

2-(Hydroxyphenylmethyl)cyclohexan-1-one (42a):

anti ***syn***

Purification by flash column chromatography (*n*-hexane/AcOEt 9:1 gave a mixture of *anti* and *syn* aldol adducts.[43]

Data for *anti* diastereoisomer:

R_f = 0.21 (*n*-hexane/AcOEt 9:1 stained blue with phosphomolibdic acid)

^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 7.31-7.24 (5H, m), 4.82 (1H, d, *J* 8.4 Hz), 3.96 (1H, bs), 2.75-2.35 (3H, m), 2.12-2.05 (1H, m), 1.71-1.52 (4H, m), 1.31-1.26 (1H, m).

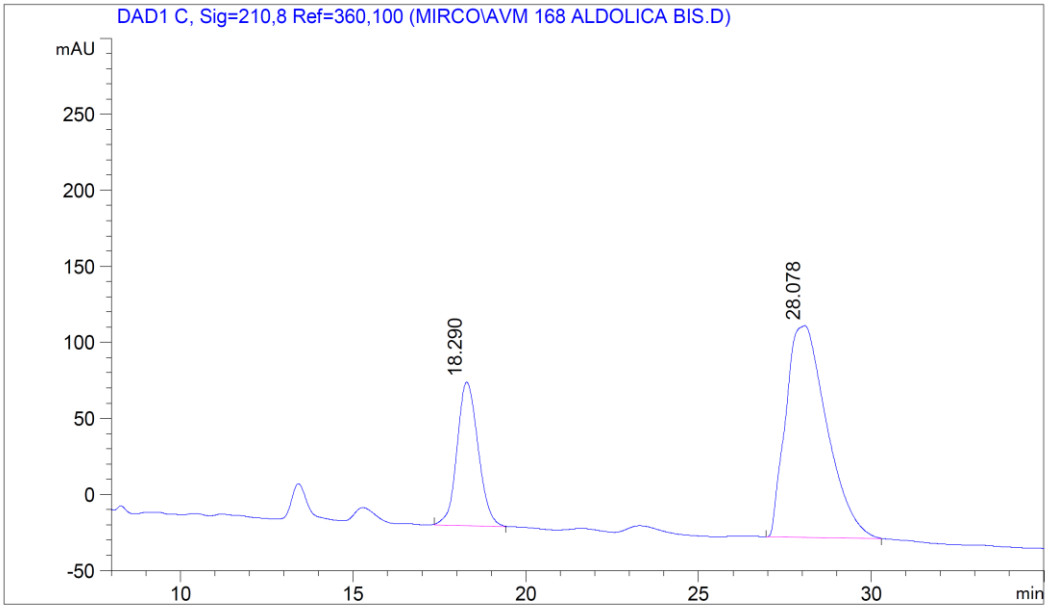
Data for *syn* diastereoisomer:

R_f = 0.32 (*n*-hexane/AcOEt 9:1 stained blue with phosphomolibdic acid)

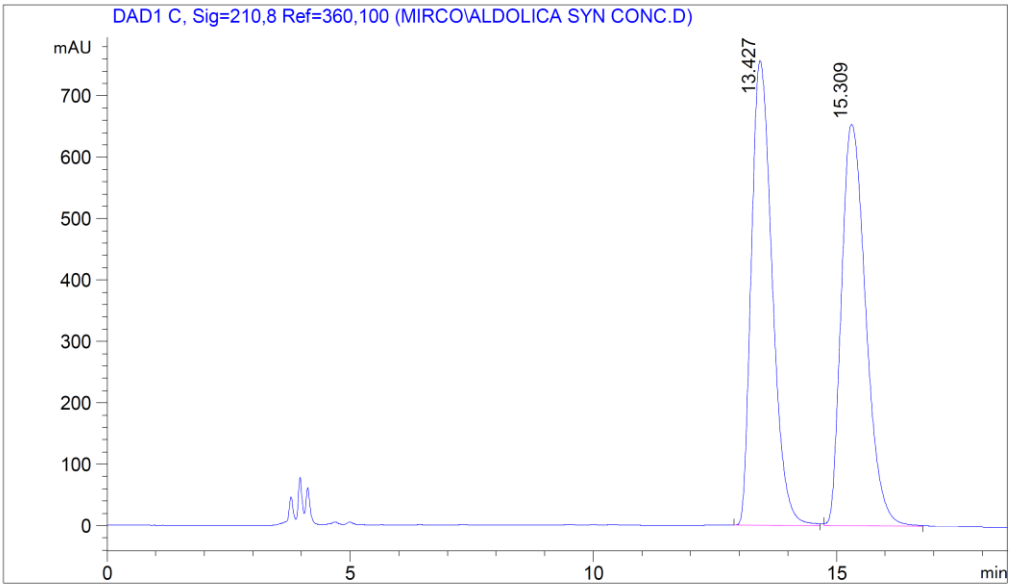
^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 7.38-7.25 (5H, m), 5.39 (1H, d), 2.60 (1H, m), 2.60-2.32 (2H, m), 2.08-2.01 (1H, m), 1.87-1.29 (5H, m).

The enantiomeric excess was determined by chiral HPLC with Daicel Chiralpak OD-H column, eluent: 98:2 Hex/IPA; 0.8 ml/min flow rate, detection: 210 nm; t_R 13.55 min (syn), t_R 15.48 min (syn), t_R 18.2 min ((1'R,2S)-anti-major), t_R 30.63 min ((1'S,2R)-anti-minor)

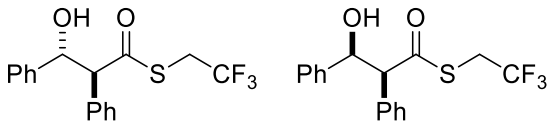
Chiral HLC analysis of *anti* diastereoisomers:



Chiral HLC analysis of *syn* diastereoisomer.



S-2,2,2-Trifluoroethyl 3-hydroxy-2,3-diphenylpropanthioate (44a)



anti **s*yn***

Purification by flash column chromatography (*n*-hexane/AcOEt 8:2). ^{1}H NMR data were in agreement with those reported in the literature.[45a]

Data for the syn diastereoisomer:

R_f = 0.62 (*n*-hexane/AcOEt 8:1 stained blue with phosphomolibdic acid)

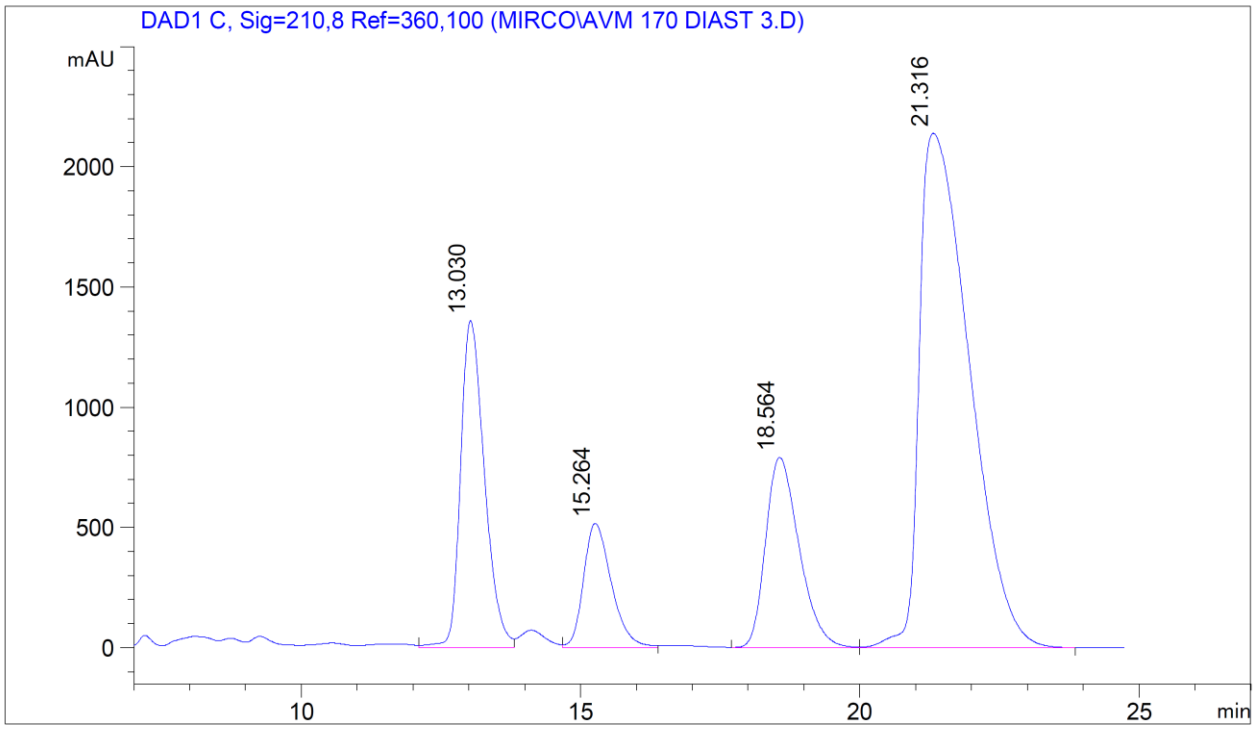
^{1}H-NMR (300 MHz, $CDCl_3$, δ ppm): 7.37 (5H, s), 7.31 (5H, s), 5.41 (1H, d, *J* 7.5 Hz) 4.11 (1H, d, *J* 7.5 Hz), 3.42-3.24 (2H, m), 2.37 (1H, br).

Data for the anti diastereoisomer

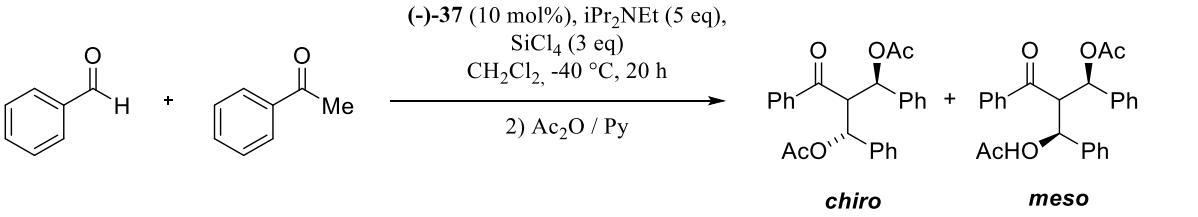
R_f = 0.58 (*n*-hexane/AcOEt 8:2 stained blue with phosphomolibdic acid)

^{1}H-NMR (300 MHz, $CDCl_3$, δ ppm): 7.36 (5H, s), 7.30 (5H, s), 5.34 (1H, d, *J* 9.2 Hz) 4.13 (1H, d, *J* 9.2 Hz), 3.70-3.55 (2H, m), 2.20 (1H, br).

The enantiomeric excess was determined by chiral HPLC with Daicel Chiral pack AD column, eluent: 9:1 Hex/IPA; 0.8 ml/min flow rate, detection: 230 nm; t_R 13.0 min (*syn*-major), t_R: 15.2 min (*syn*-minor), t_R: 18.5 min (*anti*-minor), t_R: 21.3 min (*anti*-major).



1.4.3.3 Enantioselective direct double aldol-type reaction: (3-acetoxy-2-(10-acetoxy(phenyl)methyl)-1,3-diphenylpropan-1-one (45)



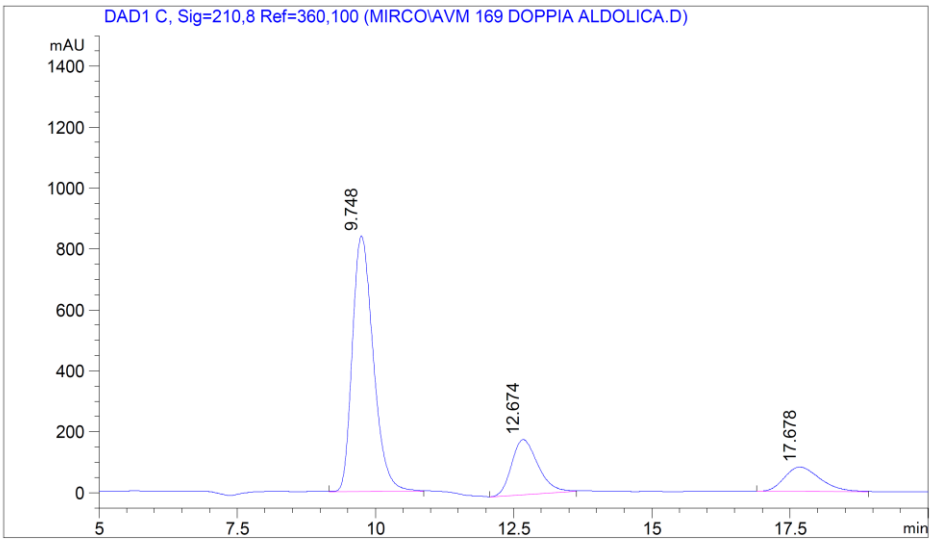
yield = 64%, *chiro*:*meso* 86:14, 60% ee (*chiro*)

Diisopropylethylamine (0.155 ml, 0.89 mmol, 5 eq) and acetophenone (0.021 g, 0.178 mmol, 1 eq) were added to a stirred solution of enantiopure TetraPh-Tol-BITIOPO **37** (0.017 g, 0.018 mmol, 10 mol%) in CH_2Cl_2 (1.2 ml) under a N_2 atmosphere. The mixture was then cooled at -40 °C and freshly distilled tetrachlorosilane (0.081 ml, 0.712 mmol, 4 eq) was added dropwise via syringe. After 15 min, freshly distilled aldehyde (0.044 ml, 0.391 mmol, 2.2 eq) was added. The mixture was stirred for 20 h. Then, the reaction was quenched by the addition of a saturated NH_4Cl aqueous solution (2 ml). The mixture was allowed to warm to room temperature and stirred for 30 min, then CH_2Cl_2 (10 ml) was added. The two-layer mixture was separated and the aqueous layer was extracted with CH_2Cl_2 (15 ml). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated under vacuum at room temperature to give the crude 1,3-diols, as confirmed by 1H-NMR spectroscopy. The crude products were then treated with acetic anhydride (0.185 ml, 1.95 mmol, 11 eq) in pyridine

(2 ml) at room temperature. After stirring for 20 h, the mixture was quenched with H_2O (5 ml) and extracted with CH_2Cl_2 (2 x 8 ml). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum at silica. Purification by flash chromatography (*n*-hexane/AcOEt 8:2) gave a mixture of the two diastereoisomers.[47]

Data for *chiral* diastereoisomer:
R_f = 0.33, (8:2 *n*-hexane/AcOEt)
^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 7.44 (2H, d, *J* 7.3 Hz), 7.31-7.13 (13H, m), 6.36 (1H, d, *J* 7.3 Hz), 6.23 (1H, d, *J* 9.7 Hz), 4.68 (1H, dd, *J* 9.7, 7.3 Hz), 1.96 (3H, s), 1.74 (3H, s).
Data for *meso* diastereoisomer:
R_f = 0.31, (8:2 *n*-hexane/AcOEt)
^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 7.54 (2H, d, *J* 4.6 Hz), 7.35-7.11 (13H, m), 5.99 (2H, d, *J* 7.4 Hz), 4.50 (1H, t, *J* 7.4 Hz,), 1.95 (3H, s), 1.65 (3H, s).

The enantiomeric excess was determined by chiral HPLC with Daicel Chiralpak AD column, eluent: 8:2 Hex/IPA; 0.8 ml/min flow rate, detection: 210 nm, t_R 9.74 min (chiral, major), t_R 12.67 min (chiral, minor), t_R 17.66 min (meso).



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2. Development of Brønsted Acids in Organocatalysis

2.1 Introduction

Catalysis promoted by Acidic Species has the fundamental role to activate C=X bonds (X = O, NR, CR_2) by decreasing the LUMO energy of the activated electrophiles and promoting a nucleophilic attack to C=X bonds.

Initially, metal-centred Lewis-acid catalysts have been developed only for that purpose. Then, in order to perform stereoselectively that kind of transformations, the combination of a Lewis acid and a chiral ligand brought to the *in situ* formation of chiral Lewis-acid catalysts that have been largely investigated affording excellent enantioselectivities.[1]

However, typical Lewis acid roles can be also emulated by organocatalytic systems. Indeed, the proton is arguably the smallest and most common Lewis acid found in Nature. Whereas general Lewis-acid catalysts have been mainly employed as promoters for carbon-carbon bond-forming reactions, Brønsted acids have been used primarily as catalysts for the cleavage and formation of C-O and C-N bonds, as in hydrolysis and formation of esters, acetals, and other functional groups (Figure 1). Then, during the first years 2000, Brønsted acids emerged as an efficient class of catalysts for a wide range of stereoselective transformations involving the formation of C-C bonds.[2]

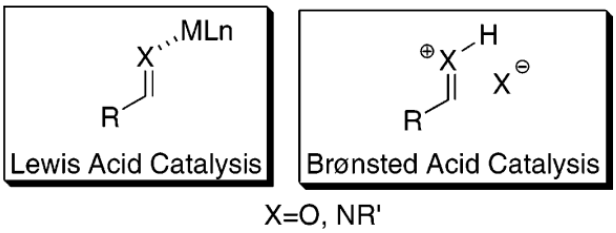


Figure 1. Lewis-acid catalysis and Brønsted-acid catalysis.

Differently from Lewis acids, Brønsted acids present some practical advantages such as the fact that they are easier to handle, generally stable toward oxygen and water and they can be stocked for a long period of time. Furthermore, they are more environmentally friendly and can be applicable to large-scale synthesis. In addition, chiral Lewis-acid catalysts are generally prepared *in situ* from a Lewis acid and a chiral ligand, and used immediately after preparation, while chiral Brønsted acids are employed as they are, being small organic molecules.

Chiral Brønsted acids are classified in two categories:

1) **Neutral** Brønsted acids, such as thiourea[3] and TADDOL (α,α,α',α'-tetraaryl-1,3-dioxolane-4,5-dimethanol)[4] derivatives. These compounds are defined as hydrogen-bonding catalysts since in a catalytic transformation they behave as hydrogen-bonding donor.

2) **Stronger** Brønsted acids, such as BINOL derivatives and phosphoric acids characterized by acidic protons (Figure 2).

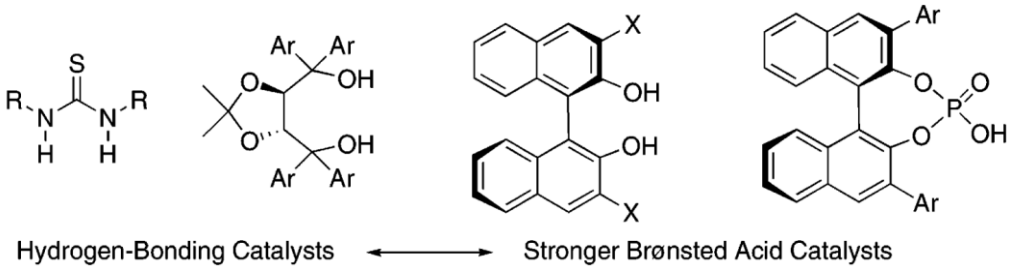


Figure 2. Chiral Brønsted acids.

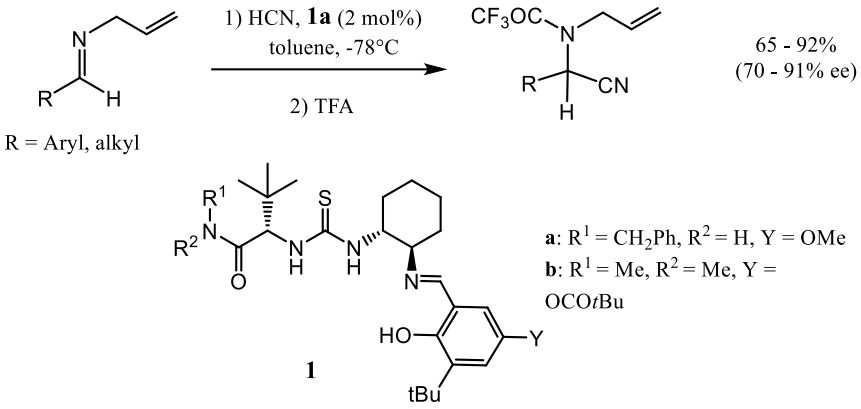
All these compounds have been intensively investigated in the area of molecular recognition due to their strong hydrogen-bonding activity. The presence of one or more hydrogen-bonding donor sites makes them able not only to recognize Lewis basic sites in organic molecules, but also to activate them, more or less strongly, toward the attack of different nucleophile species.

The strength of this activation depends on the pK_a of the investigated Brønsted acids: the more the pK_a is low the more the electrophile is activated so that it can be easily subjected to the attack of even weaker nucleophiles. This is what, in principle, discriminate the use of a Brønsted acid respect to another one in Brønsted acids catalysed reactions in terms of catalytic activity.

Concerning asymmetric transformations catalysed by neutral Brønsted acids based on a thiourea scaffold, the most remarkable improvements were obtained in Jacobsen's research group.[5] They studied the activation of alkyl-acyl-substituted imines and developed and optimized a series of urea- and thiourea- containing Schiff-base catalysts for various kinds of asymmetric transformations.

The first example was reported in 1998, when Jacobsen *et al.* first published the asymmetric Strecker reaction of *N*-allyl aldimines with Shiff-base urea catalyst **1** (Scheme 1).[5a] The three fragments of *L*-*tert*-leucine, (*R*,*R*)-1,2-diaminocychlohexane and 3-*tert*-butyl-5 methoxysalicylaldehyde characterising the structure of **1** are essential for achieving from good to excellent enantioselectivities (70-91% ee).

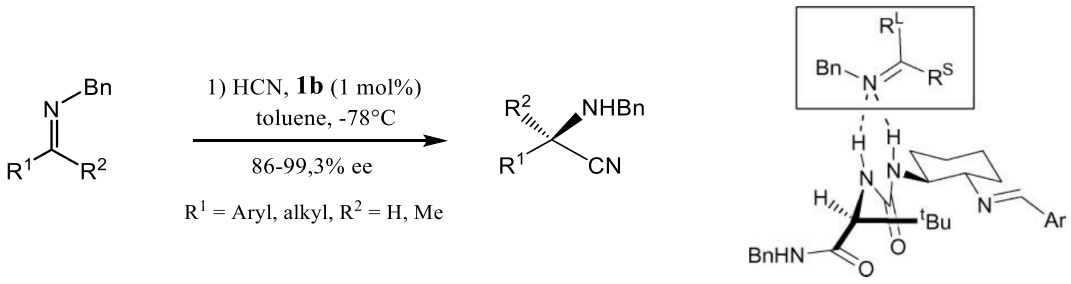
A family of catalysts, having the general formula **1,** where substituents R^1, R^2 and Y were varied, was tested in order to investigate the effects of the substitution on the performances of the Jacobsen's chiral promoters.



Scheme 1. Asymmetric Strecker reaction of *N*-Allyl imines using Jacobsen catalyst **1**.

The most performing Jacobsen catalyst resulted to be compound **1b** that was employed in enantioselective Strecker reaction of *N*-benzyl aromatic and aliphatic imines in very low catalyst loading (1 mol%) obtaining enantiomeric excesses up to 99.3 % (Scheme 2).[5e]

The design of the most active catalysts was performed by investigating the reaction mechanism. In particular, both spectral experiments and high-level calculations suggested that the *Z*-isomer of imines preferentially interacts with both urea hydrogens of the catalyst in a bridging mode (Scheme 2).

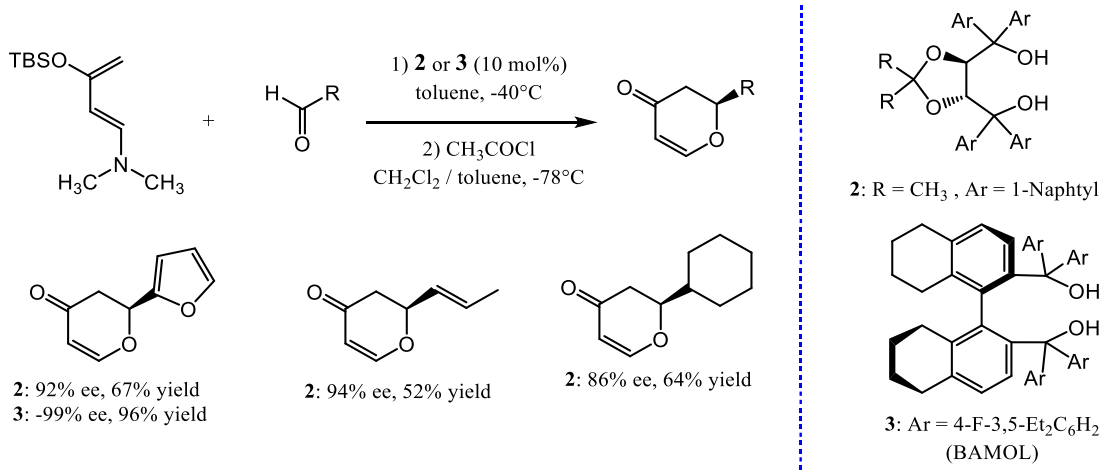


Scheme 2. Most performing Strecker reaction with Jacobsen catalyst. On the right side the proposed mechanism of the Strecker reaction using **1b**.

TADDOL derivatives were first introduced as chiral H-bond donor catalysts in the context of the enantioselective hetero-Diels-Alder reaction of aminosiloxydienes.[4a,6] In the presence of 10 mol% TADDOL **2**, 1-amino-3-siloxybutadiene reacts with a variety of aromatic, aliphatic, and α,β-

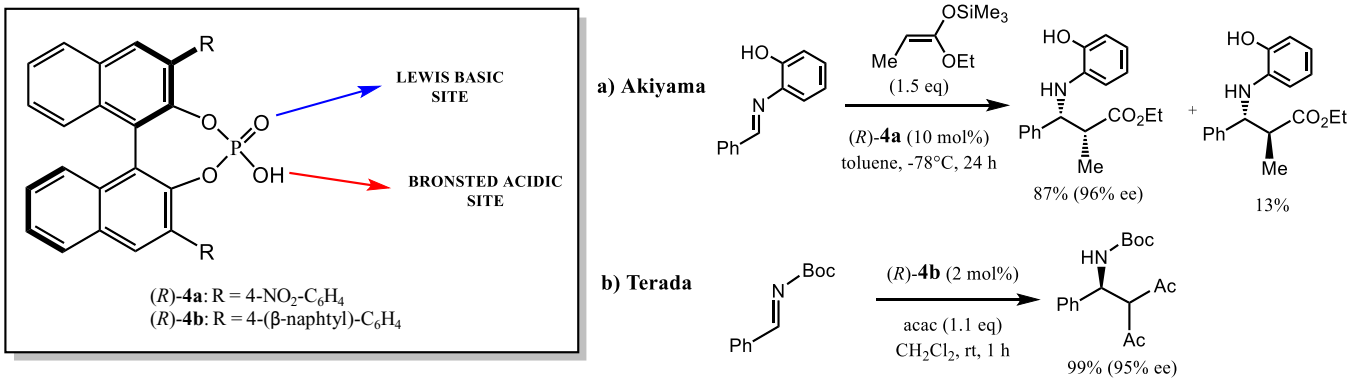
unsaturated aldehydes to achieve, after treatment with acetyl chloride, dihydropyrones in good yields and, also in this case, excellent enantioselection levels (Scheme 3).[4a,b]

Analogous results,[4c] in term of catalytic activity and stereoselection ability, were obtained by using the atropisomeric 1,1'-biaryl-2,2'-dimethanol based catalyst **3**, nicknamed as BAMOL.



Scheme 3. TADDOL-catalysed Enantioselective Hetero-Diels-Alder Reactions.

A significant breakthrough in the field of asymmetric catalysis performed by stronger Brønsted acids was given in 2004, when the research groups of Akiyama[7] and Terada[8] reported independently the development of a new class of chiral phosphoric acids (**4a**, **4b**, Scheme 4) based on the BINOL scaffold.



Scheme 4. Prototype phosphoric acid catalysts for Mannich-type reactions. Boc = *tert*-butoxycarbonyl, acac = acetylacetone.

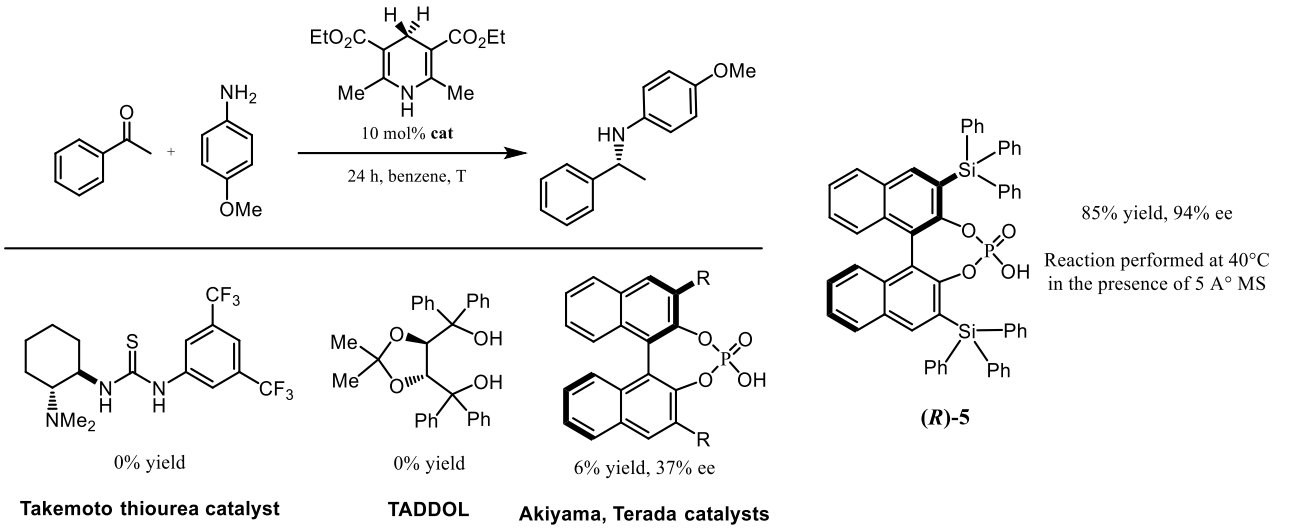
The introduction of the BINOL atropisomeric derivatives in the field of Brønsted acid catalysed reactions allowed to develop a large family of catalysts analogously to what happened for the highly successful thiourea-based catalysts **1**.

This new class of organocatalysts has some peculiar features: they are conformationally rigid and they are characterized by the presence of a single Brønsted acidic site (a proton of considerable acidity)[9]. Furthermore, the contemporary presence of a Lewis basic phosphoryl moiety in the catalyst active site potentially allows bifunctional catalysis, that is the simultaneous activation of both electrophilic and nucleophilic functional groups, as already seen for the Takemoto thiourea based catalysts[10].

BINOL-derived phosphoric acids were efficiently employed in addition reactions to imines, promoting Mannich-type reactions between *N*-aryl- and *N*-Boc-substituted imines with silyl ketene acetals[7] and acetyl acetone,[8] respectively (Scheme 4).

After these seminal studies, it became soon evident that chiral phosphoric acids have great potentialities for application in novel asymmetric processes for which no catalytic strategies (either metal-ion based or organocatalytic) were previously available.

An example was furnished by MacMillan and co-workers that in 2005 reported the first example of organocatalytic asymmetric reductive amination.[11] In particular they proposed that the compresence of ketone and amine coupling partners with a chiral hydrogen bonding catalyst would result in the intermediate formation of an iminium species, that in the presence of a suitable Hantzsch ester would promote enantioselective hydride reduction. Initially, they started the investigation employing acetophenone, *p*-anisidine, ethyl Hantzsch ester and several classes of established hydrogen bonding catalyst (Scheme 5). Takemoto thiourea catalyst and TADDOL did not provide any reductive amination product, only BINOL-derived phosphoric acids, introduced by Terada and Akiyama, were able to achieve the desired amine adduct, even though with moderate conversions and stereoselectivities. Subsequent optimizations of the catalyst structure and reaction conditions (by removing the *in situ* formed H_2O molecules through the use of 5 Å Molecular sieves) permitted to achieve very highly efficient and enantioselective reductive amination employing an unprecedented *ortho*-triphenylsilyl variant of the Terada-Akiyama catalyst (**5**, Scheme 5).[11]



Scheme 5. The first asymmetric organocatalytic reductive amination reported by MacMillan.

During the last 15 years a lot of new chiral Brønsted acids able to promote the formation of C-C, C-O and C-N bonds in a stereoselective way have been developed, and hundreds of Chiral Brønsted acid catalysed reactions have been reported.[12] For example, only in 2013, over one hundred research papers in which chiral BINOL-derived phosphoric acids are used as chiral promoters were published.

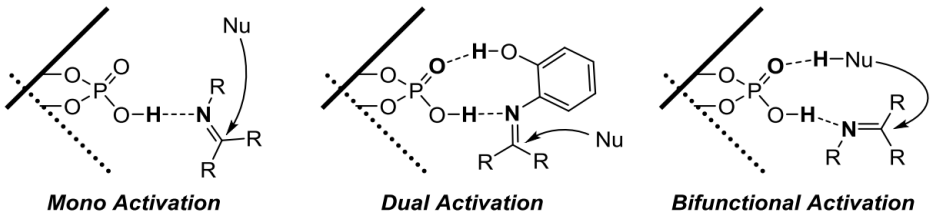
Typical substrates subjected to strong activation by means of acidic catalysis are imines, deriving from both aldehydes and ketones,[13] characterized by a prostereogenic double Carbon-Nitrogen bond, which are suitable substrates for the synthesis of enantio-enriched amines. They are versatile substrates since both their electrophilicity and hydrogen-bond-accepting ability can be modulated by choosing the *N*-protecting group.

Chiral phosphoric acids can activate substrates, and in particular imines, in 3 different ways, namely through a mono, dual or bifunctional activation (Scheme 6).

In the first case, the phosphoric acid simply acts as a proton donor, coordinating the imine through a single H-bond, so that an external nucleophile species attacks the activated imine without being previously coordinated by the catalyst.

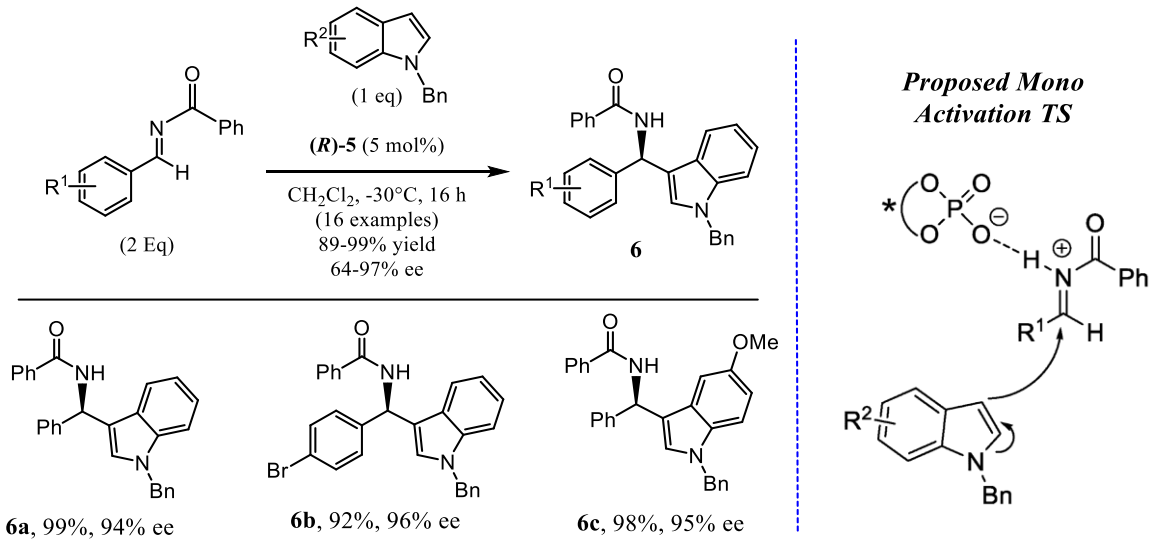
In the second case, the electrophilic substrate is coordinated by more than one H-bond, and is subjected to the attack of the nucleophile, that still behaves as an independent species.

Finally, in the bifunctional activation, the catalyst acts both as an acid (through the POH moiety) and as a base (through the P=O Lewis basic site), activating in this way, by coordination, both the electrophile and the nucleophile (Scheme 6).



Scheme 6

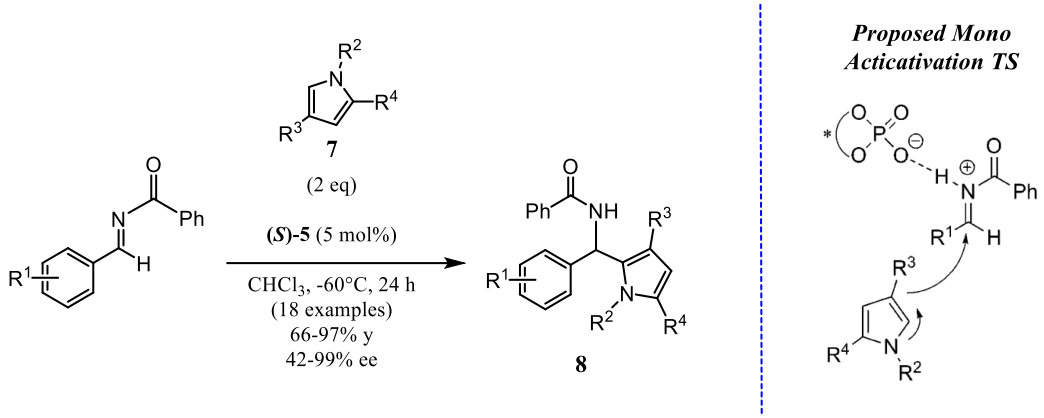
A few examples of each mode of activation are here reported for a better understanding. A typical reaction that can occur through mono-activation of imines is Brønsted acids catalysed Friedel Crafts reaction,[14] that is one of the most common and highly practical methods to form C-C bonds and introduce substitutions to aromatic systems. An example was furnished by Antilla, that in 2007 reported a Friedel Crafts reaction between *N*-Acyl imines and benzyl protected indoles (Scheme 7).[15a]



Scheme 7

The reaction was carried out using 5 mol% of the phosphoric acid **5** and the corresponding products **6** were achieved in excellent yields and stereoselectivities. Electron-donating as well as electron-withdrawing groups were well tolerated both on imines and on the indole backbones. Interestingly, when the reaction was performed using free *N*-H indole, lower yields and enantioselectivities were obtained. For this reason, it was proposed that for the success of the reaction the indole component has no formal interactions with the catalyst active site, in which only the imine component is coordinated and activated. Few months later, the same group published a highly enantioselective

Friedel-Crafts reaction of *N*-Acyl imines with pyrroles **7** to afford alkylated products **8** in high yields and enantioselectivity (Scheme 8).[15b]



Scheme 8

The reactions were performed at lower temperatures (-60°C) in $CHCl_3$ employing 5 mol% of the (*S*) enantiomer of catalyst **5**. Different substituted imines and electron-rich pyrroles were tolerated for the reaction. Also in this case the nature of the group bounded to the nitrogen atom of the pyrrole plays an important role in the catalytic activity of the chiral promoter and in the stereochemical outcome of the reaction. For example, when the reaction was carried out with the unprotected pyrrole, almost no enantioselectivity (14% ee) was observed, while, starting from bulky substituents such as *i*Pr only traces of the product were observed. The best tolerated groups for a good reaction outcome were the Me group and primary alkyl chains in general.[15b] As previously discussed for the unprotected indoles, the results obtained with unprotected pyrrole derivatives suggested that the reaction occurred with a mono activation mechanism.

The first example of dual activation model was given by Akiyama[7], and corresponds to one of the first stereoselective phosphoric acids catalysed reactions shown in Scheme 4:

Akiyama's protocol considers the use of 2-hydroxyphenyl imines with silyl ketene acetals in the presence of 10 mol% of the catalyst **(*R*)-4a** to achieve *syn* diastereoisomer products generally in high yields and enantioselectivities. Although no mechanistic studies had been initially conducted, Akiyama recognized the crucial role of the 2-hydroxy substituent in the reaction mechanism and supposed a mono activation model. But three years later, in 2007, he was able to demonstrate by theoretical calculations that the reaction mechanism is based on a dual activation model:[16] the acidic proton obviously activates the imine by protonation, then there is another interaction between the catalyst Lewis basic site and the phenol proton that permits to achieve a rigid and stronger chiral environment around the substrate (Figure 3).

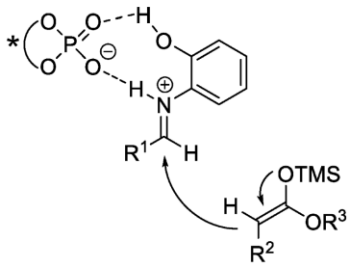
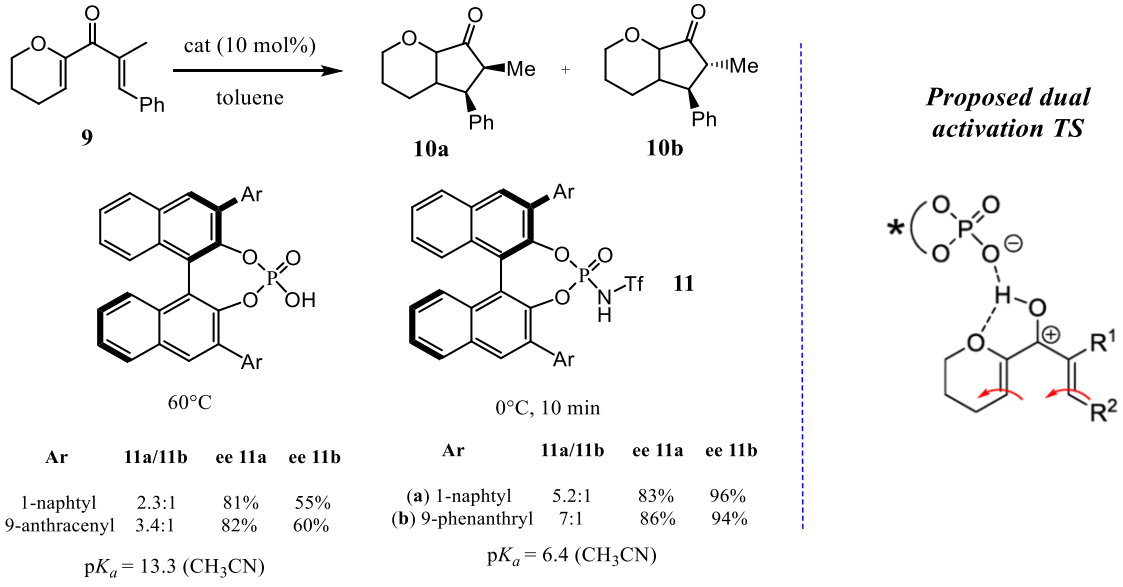


Figure 3. Proposed dual activation TS for the Mannich type reaction by Akyiama (Scheme 4)

However, the dual activation can also involve only the acidic proton of the catalyst through a double interaction with the electrophilic reacting partners.[17] An example of this behaviour was furnished by Rueping that, in 2007, reported the first case of chiral Brønsted acid that catalysed the Nazarov cyclisation affording enantiomerically enriched products starting from α-alkoxy ketones.[18] Initially, they looked for the best experimental conditions by employing different chiral Brønsted acids for the enantioselective elettrocyclization of the dienone **9** (Scheme 9). Using various BINOL-based phosphoric acids in toluene at 60°C, they were able to achieve cyclopentenones **10a** and **10b** in up to 82% ee. However, improved reactivity was achieved by using the corresponding more acidic *N*-triflyl phosphoramides **11** that gave complete conversions after few minutes conducting the reaction at 0°C (pK_a = 6.4 in CH_3CN against 13.3 of the corresponding phosphoric acids) beside an improvement of both diastereoselectivity (*cis*/*trans* ratio up to 7:1) and enantioselectivity (up to 96%) (Scheme 9).



Ar	11a/11b	ee 11a	ee 11b
1-naphtyl	2.3:1	81%	55%
9-anthracenyl	3.4:1	82%	60%

pK_a = 13.3 (CH_3CN)

Ar	11a/11b	ee 11a	ee 11b
(**a**) 1-naphtyl	5.2:1	83%	96%
(**b**) 9-phenanthryl	7:1	86%	94%

pK_a = 6.4 (CH_3CN)

Scheme 9. Brønsted acid catalysed Nazarov cyclisation by Rueping (2007).

Further experiments allowed to state the role of the solvent on the reactivitiy and the enantioselectivity in Brønsted acid catalysed Nazarov cyclisation. Indeed, no reactions were observed in more polar solvents, such as THF and CH_3CN, while reactions proceeded smoothly in aromatic and halogenated solvents. Several substituted dienones were employed as starting materials under the best experimental conditions (2 mol% of **cat 11b**, $CHCl_3$, 0°C) affording the desired cyclopentenones in very good yields and excellent stereoselectivities.[18]

Concerning the reaction mechanism, it was proposed that the acidic proton of the catalyst could be involved in a dual interaction with both the α-alkoxy group and the carbonyl oxygen. The bidentate interaction would be responsible of the carbonyl group activation as demonstrated by the fact that the more acidic *N*-triflyl phosphoramides is more performing than chiral Brønsted acids (Scheme 9). After the activation, cyclisation occurs followed by protonation of the enolate species to give the product and regenerate the catalyst.

The last mode of activation is the bifunctional activation. One of the most significant example of bifunctional activation by phosphoric acids is the previously cited Mannich reaction of acetyl acetone with *N*-Boc imines reported by Terada in 2004 (Scheme 4).[8] As anticipated, at the beginning, mechanistic studies performed in 2007 by Terada suggested a single H-bonding interaction between the imine and the catalyst.[19] However, four years later, Goodman research group showed that actually the catalyst has a bifunctional role and activate both the imine and the nucleophile (acetyl acetone) through the tautomeric enol form (Figure 4).[20] Furthermore, it must be highlighted that protonation is thought to occur on the nitrogen atom of the *N*-Boc imine, even if protonation at the more basic oxygen atom of the Boc-group cannot be fully excluded.

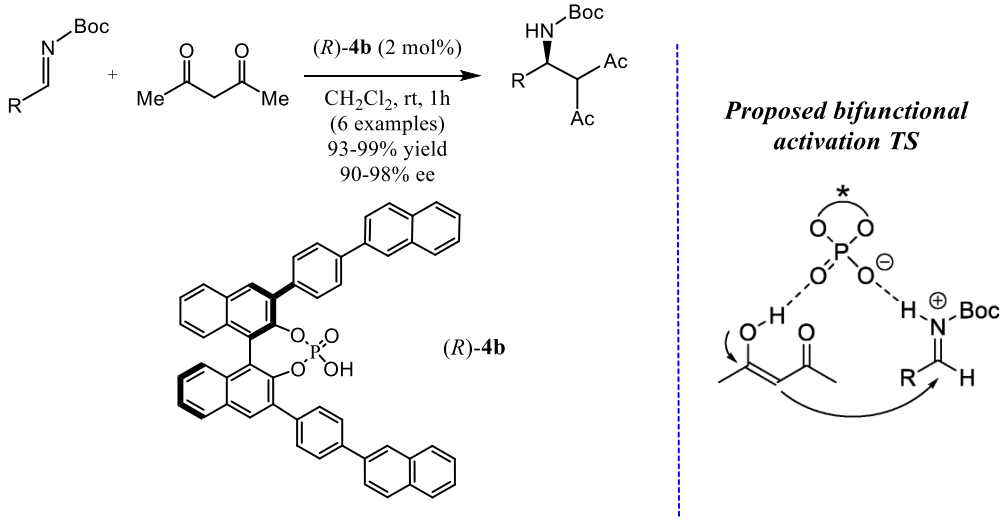
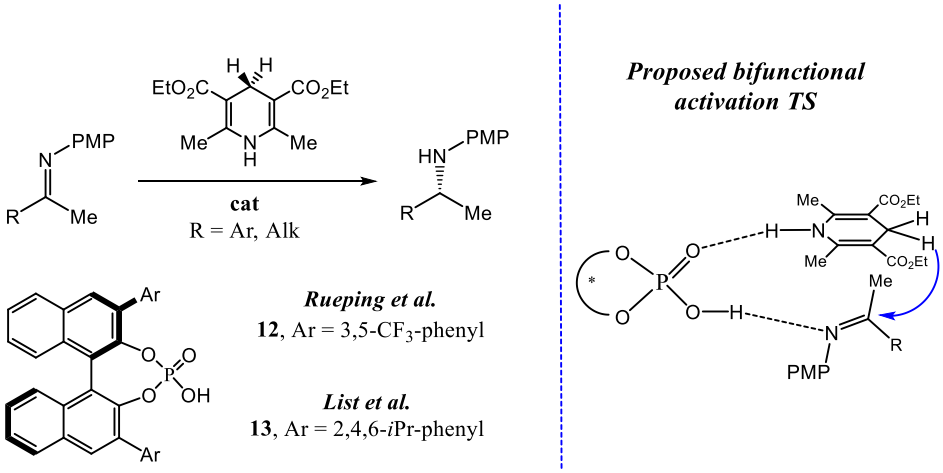


Figure 4. Direct Mannich reaction by Terada (2004).

Another important example of bifunctional activation in Chiral Brønsted acid catalysis is the Hantzsch ester mediated transfer hydrogenation of ketoimines. The first enantioselective Hantzsch ester mediated phosphoric acid catalysed hydride transfer reaction was reported by Rueping in 2005.[21] Almost at the same time List published an identical transformation employing a smaller amount of the more hindered phosphoric acid **13** obtaining better stereoselectivities (Scheme 10).[22] A fundamental contribution to the elucidation of the reaction mechanisms was given by Goodman[23] and Himo[24] groups which realized that a bifunctional mechanism must be active. According to this hypothesis, the imine is activated by coordination with the acidic functional group of the catalyst, while, at the same time, the P=O group coordinates the *N*-H moiety of the Hantzsch ester, giving a rigid transition state responsible for the good stereoselectivities achieved in these reactions (Scheme 10).



Cat (mol%)	**R**	**Solvent**	**T (°C)**	**Y** (%)	**ee** (%)
12 (20)	Ph	benzene	60	76	74
12 (20)	Napht	benzene	60	82	70
12 (20)	2-F-Ph	benzene	60	82	84
13 (1)	Ph	tol	35	96	88
13 (1)	Napht	tol	35	85	84
13 (1)	2-F-Ph	tol	35	95	85

Scheme 10

Better results in terms of enantioselectivities (up to 96% ee) were obtained one year later By MacMillan in the Hantzsch ester mediated one-pot reductive amination starting from aromatic ketones employing the even more hindered catalyst **5** (scheme 5).[11]

Beside chiral Brønsted acids based on the enantiopure BINOL scaffold, another important class of chiral phosphoric acids is the one of the spiro-compounds deriving from SPINOL (Figure 5).[25]

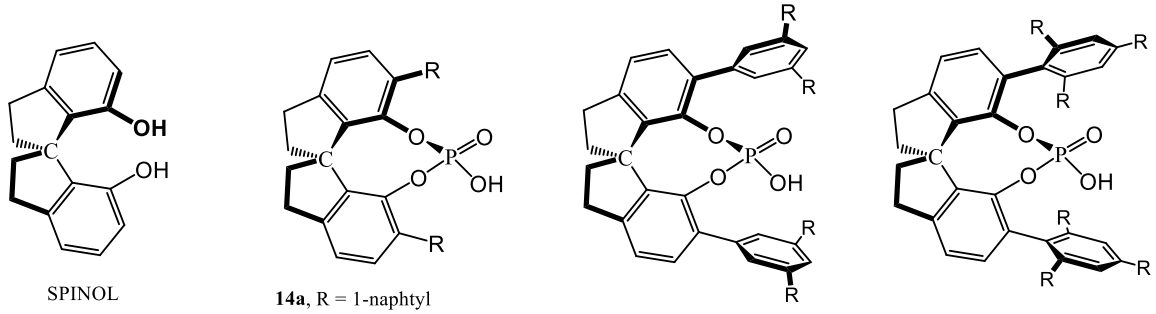
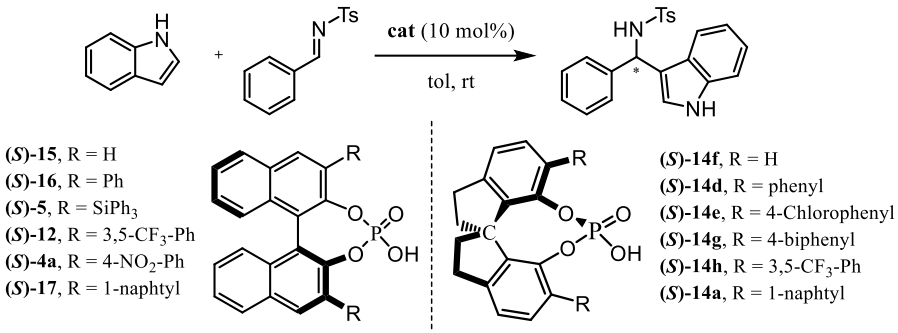


Figure 5

One of the first examples of the application of phosphoric acids based on the SPINOL scaffold in organocatalysis was the enantioselective Friedel-Crafts reaction of indoles with *N*-Tosyl imines, reported in 2010 by Wang, to afford 3-indolyl methanamines.[25c] This reaction was actually chosen as a model reaction since it was already reported in 2007 by You using BINOL-derived phosphoric acids affording excellent results in terms of both yields and stereoselectivities.[26]

A comparison of the results achieved with the two different classes of chiral Brønsted acids is reported in Scheme 11.



Entry	cat	y (%)	ee (%)
1	**(*S*)-15**	85	0
2	**(*S*)-16**	60	73
3	**(*S*)-5**	69	73
4	**(*S*)-12**	80	83
5	**(*S*)-4a**	66	92
6	**(*S*)-17**	78	93
7*	**(*S*)-17**	83	98
8	**(*S*)-14f**	80	11
9	**(*S*)-14d**	89	72
10	**(*S*)-14e**	87	73
11	**(*S*)-14g**	75	72
12	**(*S*)-14h**	100	56
13	**(*S*)-14a**	90	89
14*	**(*S*)-14a**	80	96

Scheme 11. Chiral Brønsted acids catalysed Friedel-Crafts reaction of indoles with *N*-Tosyl imines. *Reaction performed at -60°C.

Differently from what obtained with simple BINOL-phosphoric acid **(*S*)-15**, which gave the desired product in good yields but as a racemate, the unsubstituted catalyst **(*S*)-14f** produced a modest 11% ee. Anyway, for both catalysts it was found that substituents in the *ortho* positions to the phosphoric group played a crucial role for the stereoselective efficiency of the chiral promoters. In particular the most active catalysts were the BINOL-derivatives **(*S*)-4a** and **(*S*)-17**, that allowed to afford the desired product in 66 and 78% yields, respectively, with 92 and 93% of ee, while in the family of SPINOL-derivatives **(*S*)-14a**, was the most performing catalyst, giving the corresponding 3-indolyl methanamine in 90% y and 89% ee. Therefore, the 1-naphtyl group resulted to be the most efficient substituent for both the catalysts (Entry 6 and 13 of scheme 11) and they were then tested at lower temperatures improving the results in terms of stereoselectivity (Entry 7 and 14).

Once found the best experimental conditions (10 mol%, toluene, -60°C), several different substituted 3-indolyl methanamines were obtained using the catalyst **(*S*)-17** and **(*S*)-14** with comparable yields and stereoselective levels >99%.

Concerning the proposed transition state, differently from what observed in the enantioselective Friedel Crafts reactions reported by Antilla,[15] calculations and data published by Simon and Goodman[27] disclosed that transition state in the BINOL-derived phosphoric acid catalysed reaction would involve a bifunctional activation. To the same conclusions went Wang regarding the class of the SPINOL-derived catalysts (Figure 6).

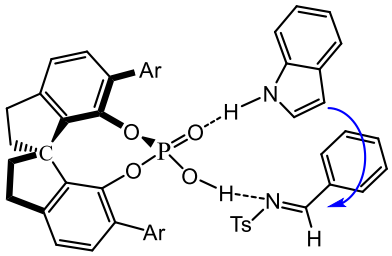


Figure 6. Proposed bifunctional activation transition state for the SPINOL-derived phosphoric acid catalysed enantioselective Friedel-Crafts reaction of indoles with *N*-Tosyl imines.

2.2 Results and Discussion

2.2.1 Synthesis of new Brønsted Acids based on a decahydroquinoxalinic scaffold functionalised with thiophenic units

As already discussed in the introduction, the most popular chiral Brønsted acids (CBA) used in organocatalysis are nowadays BINOL and SPINOL derivatives both characterized by the presence of a stereogenic axis. While BINOL-derivatives present no carbon spacer between the arylic moieties bearing the acidic functional group, SPINOL-derivatives show the presence of one carbon atom as a spacer. These kinds of catalysts are efficient, but in the same time they are very expensive, so that the development of new cheaper and easier-to-synthesize alternative CBA scaffold is a topic of great interest.

In the last few years, a new class of CBA having a two-carbon spacer between the two aryl units was investigated in the Benaglia group of the University of Milan (Figure 7).

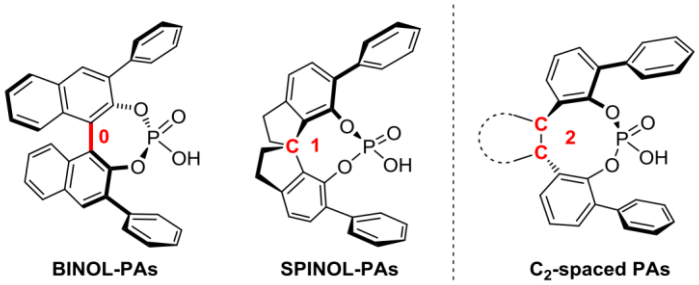


Figure 7

The inspiration for the design of the new scaffold was given by Rhodium monodentate ligands introduced by Ding which appeared to be efficient enantioselective promoters in the hydrogenation of prochiral enamides (Figure 8).[28]

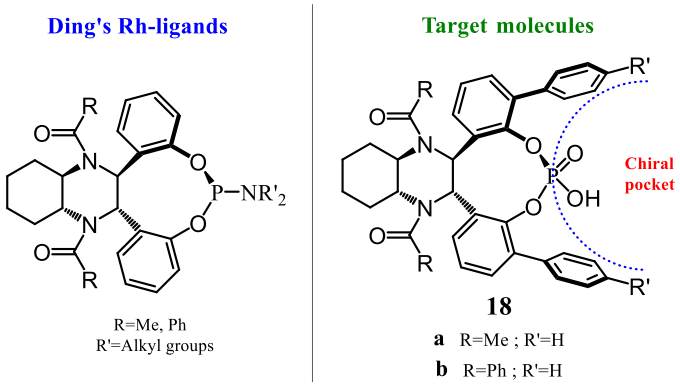
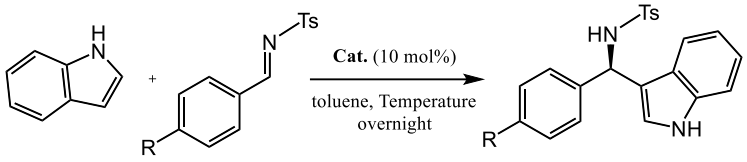


Figure 8

The main difference between the two chiral promoters is the presence of two additional aryl groups on the phosphoric acid scaffold necessary to generate the so-called *chiral pocket* and acting as stereodirecting elements.

The new organocatalysts were simply synthesized starting from commercially available 1,2-*trans*-diaminocyclohexane and aromatic aldehydes bearing an hydroxylic group in ortho position and they were tested as organocatalysts in some typical CBA catalysed reactions investigated in literature, in particular the Friedel-Craft alkylation of indole with *N*-tosyl imines (Scheme 12).[26,25c,29]



Scheme 12

Products were afforded with moderate to good levels of enantioselectivity. The best results were obtained with catalyst **18a** when the reaction was performed with the *N*-tosyl imine of the benzaldehyde; enantiomeric excesses up to 74% ee and excellent yield (99%) was achieved carrying out the reaction at -50°C in toluene.

Furthermore, it seems that also encumbrance on the N atoms could play a role on the stereoselection ability of the new catalysts, since compound **18b**, characterized by an increased steric crush between the benzoyl groups and the facing phenyl rings, afforded lower enantioselectivities than **18a**.

Performing the same reaction with more hindered **18a**-type catalysts functionalised with substituents R' (Figure 8), characterized by different stereo-electronic effects, lower enantiomeric excesses were observed (40-50% ee).

Furthermore, even starting from different substituted benzaldehydes-derived imines (*p*-Cl, *p*-Me, *p*-OMe) and using the most performing catalyst **18a**, a decrease both in catalytic activity and stereoselection ability was observed.[30]

These results suggest that the catalyst's active site is placed in a too hindered portion of space, preventing in this way the achievement of good stereochemical outcomes.

This hypothesis can be confirmed through a comparative analysis performed with semi-empirical method PM6 of BINOL-derived phosphoric acid (PA), SPINOL-derived PA and **18a** (Figure 9, all the hydrogen atoms have been removed for clarity).

Calculations shown in Figure 9 indicate that the chiral pocket's size becomes smaller going from the BINOL-derived PA to the SPINOL-derived one and then to **18a**. Indeed, it seems that the distance between the P atom and the more distant phenyl ring's carbon decreases passing from 5.56 to 5.28 Å for the first two compounds, to 4.71 Å for catalyst **18a**.

In the same way, the C-P-C angle (where C refers to the two farthest carbon atom of the bulky groups), decreases gradually from 151 to 125° for the BINOL and SPINOL derivatives up to 100° for **18a**.

These results suggest that **18a** displays a too hindered active site that could be, most likely, responsible for its moderate stereochemical efficiency.

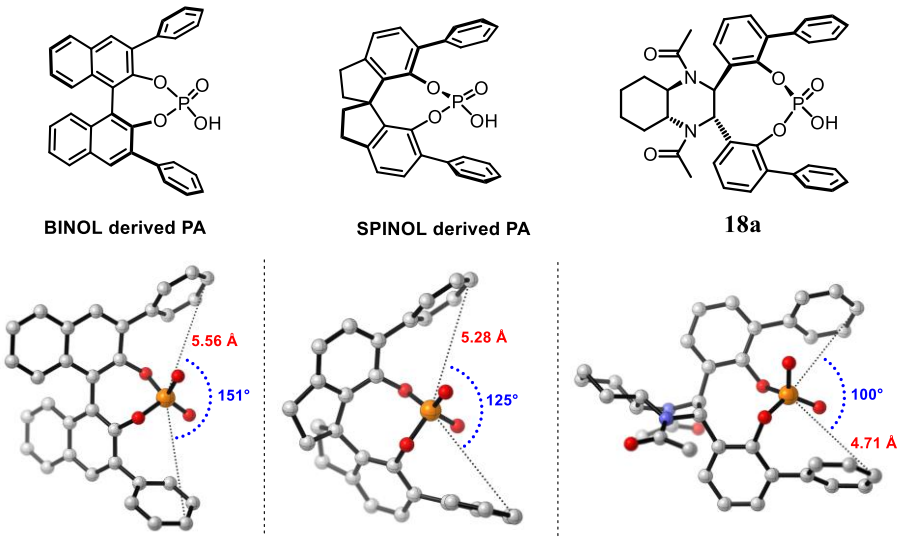


Figure 9

In order to change the chiral pocket size, we designed a new catalyst based on the same scaffold in which the phenyl groups in the position 2 and 3 of the decahydroquinoxalinic ring are substituted by two thiophene units, bearing each one two phenyl groups in the *ortho* positions (Figure 10, compound **19**).

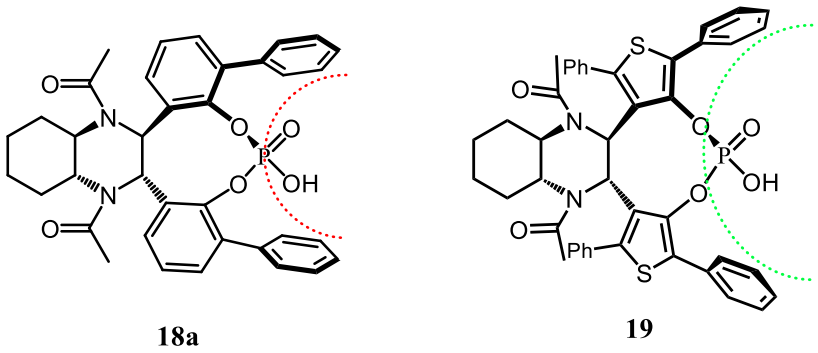
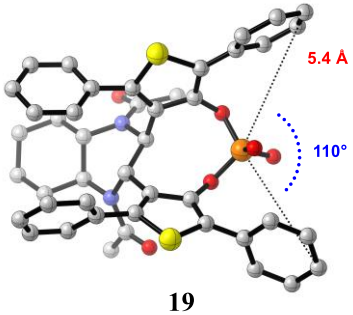


Figure 10

PM6 calculations performed by Dr. Sergio Rossi of the University of Milan supported this idea (Figure 11) since from this investigation resulted that the substitution of the phenyl groups with thienylic units on the decahydroquinoxalinic scaffold produces a substantial difference in the geometry of the chiral pocket. Indeed, the presence of pentatomic heterocyclic rings increases both the distance between the P atom and the farthest C atoms of the two bulky groups which circumscribe the chiral pocket (from 4.71 Å for **18a** to 5,4 Å for **19**) and the previous cited C-P-C angle from a value of 100° of compound **18a** to 110° producing a chiral pocket more similar to that exhibited by the most

efficient catalysts. Furthermore, also the chiral pocket's shape seems to be more suitable to host reagents in the transition state, because it appears more like a funnel rather than a channel, as shown in the case of compound **18a** (Figure 9).

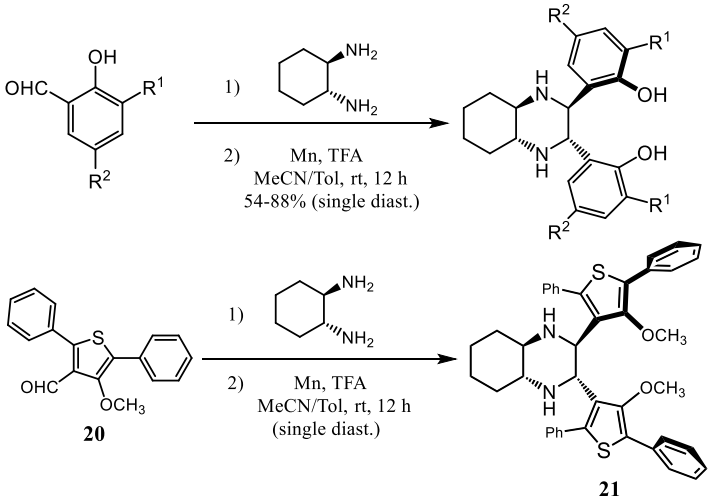


19

Figure 11. PM6 calculations performed on the compound **19**.

Another notable difference between the two catalysts is the presence of two additional phenyl groups facing the amide substituents in compound **19** that could have represented a problem for the stereochemical performances of the catalyst. After all, the functionalization of both the α-positions of the thiophene ring appeared fundamental to design a simple synthetic strategy.

One of the objectives of this PhD Thesis was to investigate the synthesis of this new chiral phosphoric acid and its catalytic behaviour in the same test reactions performed with catalyst **18a**, in order to verify if the new geometry of the chiral pocket could improve the stereochemical outcome of the process.



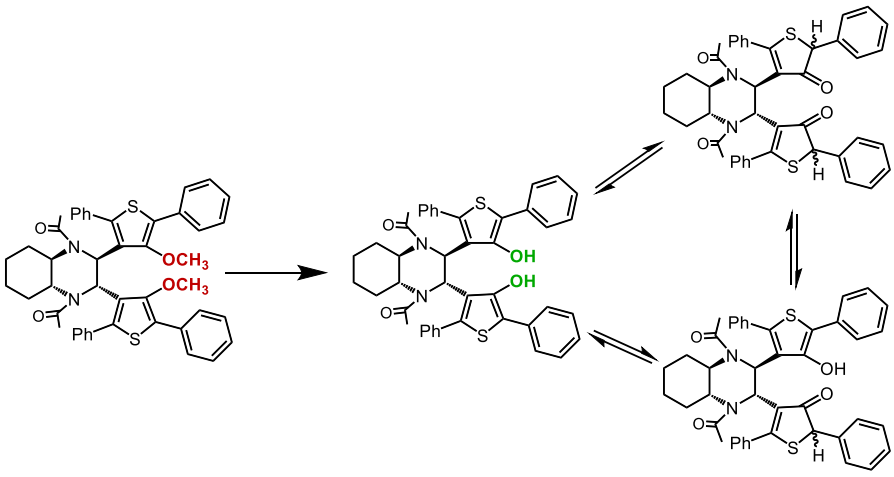
Scheme 13

According to the synthetic strategy developed by Benaglia's group for the synthesis of catalysts **18**, the key step for the achievement of the intermediate diol was the formation of the decahydroquinoxalinic ring which, as reported in Scheme 13, required the condensation reaction between a suitable benzaldehyde derivative and the *trans*-1,2-diaminocyclohexane. The bis-imine intermediate reacted in the presence of manganese and TFA in order to induce the pinacol reaction according to the procedure developed by Sigman *et al.*.[31]

The reaction of formation of the decahydroquinoxalinic scaffold proceeded in moderate to good yields affording a single diastereoisomer being the stereochemical outcome of the reaction dictated from the configuration of the stereocentres of the chiral diamine.

Hence, it appeared easy to adapt this strategy to the synthesis of the corresponding diol of **19** starting from the 2,5-diphenyl-4-hydroxy-3-thiophenecarbaldehyde.

However, since it is well known that hydroxythiophenes are subjected to tautomeric equilibrium in which the ketonic-derivative is thermodynamically favoured, initially it seemed advantageous to perform the reaction of the formation of the decahydroquinoxalynic ring starting from the 4-methoxy-2,5-diphenylthiophene-3-carbaldehyde (**20**), maintaining protected the hydroxylic function as methoxy group until the end of the synthetic path, in order to prevent possible complications due to the presence of potential tautomers, as reported in Scheme 14.

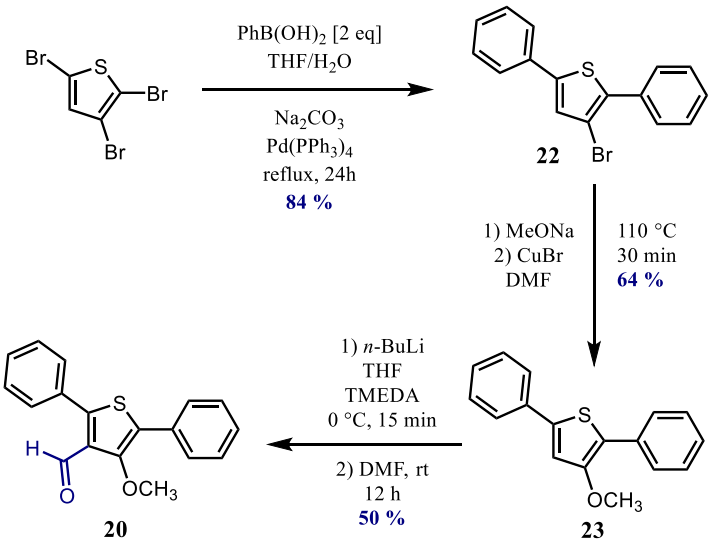


Scheme 14

The synthesis of the aldehyde **20** reported in Scheme 15 required the availability of the methoxy-derivative **23**; its synthesis has been already investigated for other purposes in our laboratory and starts from commercially available tribromothiophene.

The precursor of the methoxyderivative is the 3-bromo-2,5-diphenylthiophene (**22**) that was prepared by exploiting a regioselective Suzuki reaction mediated by palladium(tetrakis) in a biphasic

solution of THF/aq. sol. 20% Na_2CO_3. The reaction was performed for 24 h and the desired diphenyl-derivative **22** was obtained in 60% yield beside the 3,5-dibromo-2-phenylthiophene. The two products were separated by column chromatography and the monophenyl-substituted derivative was then treated in the same experimental conditions to be finally converted into the product **22**, achieving in the end an overall yield of 84%. This procedure, even if a little tedious, gave better results when compared with those obtained by prolonging the reaction time since, in the latter case, a considerable amount of 2,3,5-triphenylthiophene was obtained.



Scheme 15

The 3-methoxy-2,5-diphenylthiophene **23** was achieved in 59% yield through a copper catalysed nucleophilic substitution in the presence of an excess of sodium methoxide, following a protocol described in literature for the synthesis of alkyl-aryl and alkyl-heteroaryl ethers.[32]

The synthesis of the aldehyde **20** resulted to be the first crucial step of the whole synthetic path. Indeed, initially the product **20** was obtained in only 22% yield, despite the presence of a strong electron-donating substituent in the α-position as the methoxy group, when the anion, generated with *n*-BuLi in the presence of TMEDA, was reacted with the DMF at -78°C. Even if the starting material can be recovered and reutilized in a new reaction, these results were too disappointing and a detailed screening of the reaction conditions was conducted. Since the formation of the anion was deeply investigated in a precedent Thesis[33] and the related procedure set up, the low conversion yields must be attributed to a scarce reactivity of the anion toward the electrophile. For this reason, we decided to do several experiments by varying the temperature at which the DMF is added and finally we improved the yields to 40% by performing the addition of DMF at 0 °C, and to 50% when

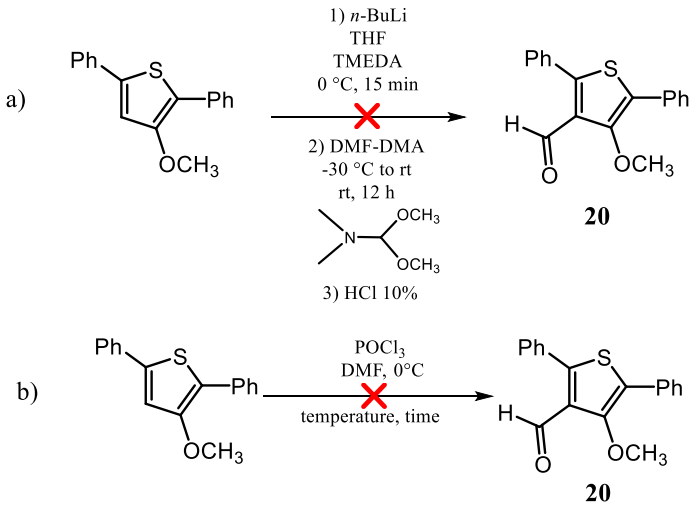
the addition was carried out at rt, and this is still now our best protocol for the synthesis of the aldehyde **20**.

However, even if we considered these results acceptable, we tried also other different approaches in order to improve them (Scheme 16).

According to the same synthetic strategy, we first considered the use of the *N*,*N*-dimethylaminodimethylacetale instead of the DMF as electrophile, but only the unreacted starting material was recovered.

A different approach was based on the Vilsmeier-Haack reaction even if it is generally used to introduce a formyl group in the position 2 of thiophenes.[34] However, in our case, the presence of the methoxy group which activates the adjacent position could produce a favourable reaction outcome.

Also in this case several attempts were performed, carrying out the reaction employing different experimental conditions by varying the reaction temperature from room temperature to 50-70°C and by using DMF both as reagent and solvent. Finally, CH_2Cl_2 was employed to increase the solubility of the substrate but in all the reactions tried we couldn't obtain the desired product not even in traces.

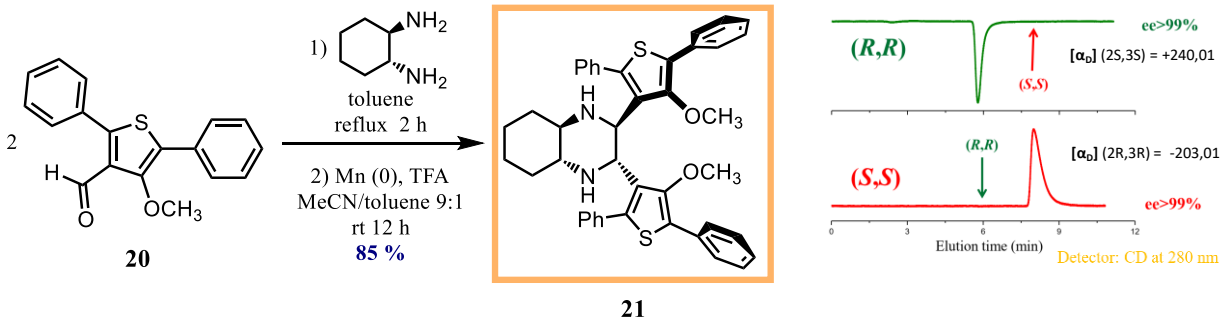


Scheme 16

As anticipated in Scheme 13, the synthesis of the decahydroquinoxalinic scaffold was achieved through a Manganese-Mediated Reductive Cyclization of the intermediate bis-iminederivative obtained by condensation of two molecules of aldehyde with a single enantiomer of the 1,2-*trans*-

diaminocyclohexane. Before proceeding with the second step, the formation of the bis-imine, performed in refluxing toluene, can be checked by protonic NMR spectroscopy following the disappearance of the signal at 10 ppm, attributable to the aldehyde proton, and the appearance of a singlet at 8 ppm.

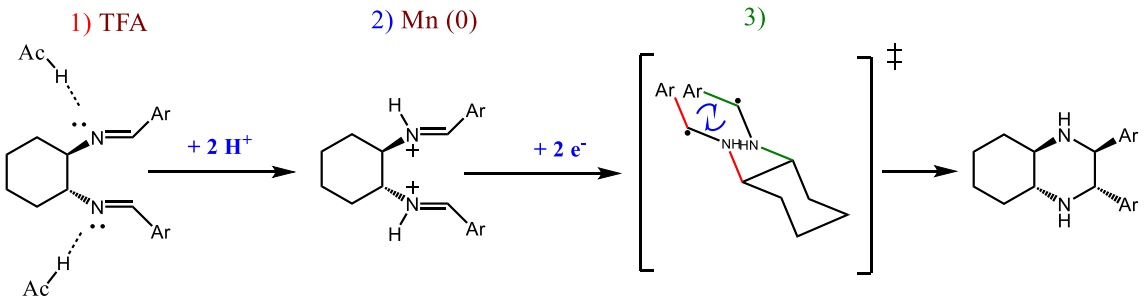
The reaction was performed with both the enantiomers of the chiral amine and the cyclization products obtained in 85% yields as single diastereoisomers as demonstrated by the HPLC chromatograms recorded by Dr. Roberto Cirilli of the *Istituto Superiore di Sanità* in Rome (Scheme 17). Furthermore, the results obtained with a CD detector showed that the compounds derived from the antipodes of the diaminocyclohexane are enantiomers (Scheme 17).



Scheme 17. Synthesis of the compound **21**. Note: the configurations shown in the chromatograms refers to that of the 1,2-*trans*-diaminocyclohexane used as starting material.

The reaction mechanism can be divided into 3 steps[31] (Scheme 22)

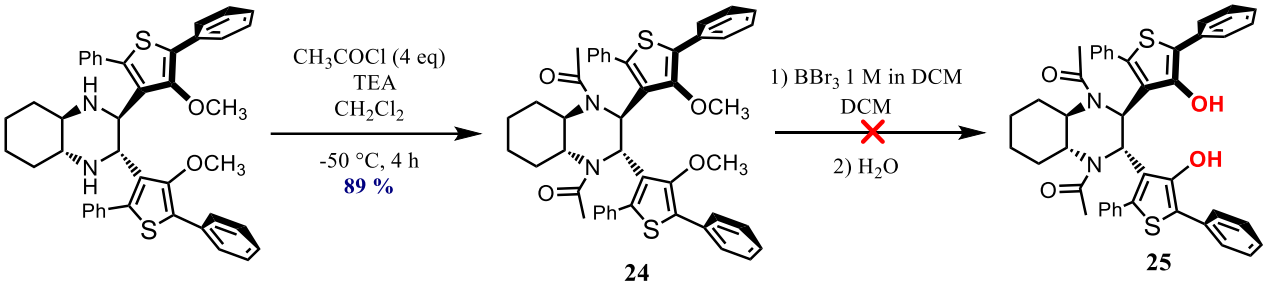
1. The imine's activation by means of the trifluoroacetic acid;
2. the iminium ion's reduction on the surface of manganese powder forming two benzylic radicals;
3. the formation of a new carbon-carbon bond through the coupling of the benzylic radicals.



Scheme 22

The last step is that responsible of the stereochemistry of the final product: the formation of the new ring proceeds so that the two arylic substituents, that in our case are the two thiophene rings, assume the trans-di-equatorial arrangement. Obviously, the configuration of the new stereocentres is determined by that of the 1,2-*trans*-diaminocyclohexane employed.

Once obtained the decahydroquinoxalinic scaffold, the subsequent step was the acetylation reaction of its nitrogen atoms, necessary in order to switch off their basic nature that could complicate both the formation of the phosphoric acid with $POCl_3$ and the outcomes of the phosphoric acid catalysed reactions. The acetylation reaction was carried out by using an excess of acetyl chloride (4 eq) at the temperature of -50°C for 4 h in the presence of TEA, and the compound **24** was obtained in 89% yield (Scheme 23).



Scheme 23

Unfortunately, the last step of the synthetic sequence, that in theory appeared trivial, represented another crucial point of the synthesis.

Indeed, the reaction with BBr_3 performed in CH_2Cl_2, starting from room temperature to refluxing one, was completely ineffective (Scheme 23).

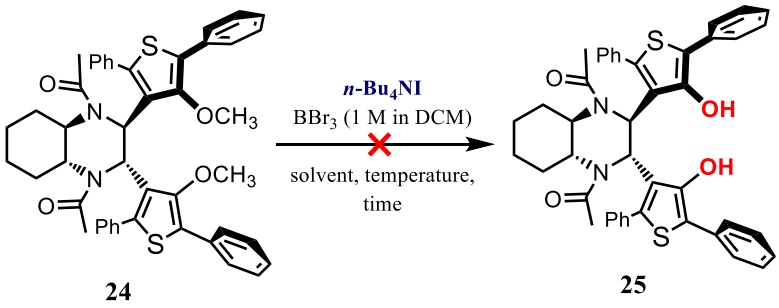
The difficulties met at this step forced us to test stronger experimental conditions. For example, the treatment of the methoxy-derivative **24** with a 48% HBr solution in water and a Phase Transfer Catalyst (Aliquat-336)[35] at 110°C for 16 h allowed us to obtain a product that, on the basis of ^{1}H-NMR spectroscopy and the mass analysis, was identified as the product derived from the demethoxylation and the deacetylation of the substrate. Since the nitrogen atoms must be protected in the final catalyst, we proceeded with the tetracetylation of the product obtained and the following hydrolysis of the O-acetylated derivative to achieve, even if in small amounts, the desired diol **25**.

However, this procedure didn't appear reproducible when carried out on large scale and a new approach was required.

In order to overcome the problems related to the scarce solubility of the substrate in water, the reaction was carried out with a 30% HBr solution in acetic acid starting from the compound **21**. Several experiments were carried out by varying reaction times and temperatures recovering, also for prolonged times, only the unreacted starting material.

So, we decided to come back to the use of BBr_3 as demethylating reagent employing it in combination with the tetra-*n*-butyl-ammonium iodide (*n*-Bu_4NI) following a protocol shown in literature in which is described that by using a Boron Tribromide/Tetra-*n*-Butylammonium iodide combination for the cleavage of primary alkyl aryl ethers. According to the Authors, the role of the salt is that of furnishing the iodide ion that acts both as a stabilizing ligand of boron (favouring the formation of an active oxonium species) and as a more potent nucleophile in the reaction mechanism, giving more easily the nucleophilic substitution on the dibromoalcoxyborane intermediate, releasing the corresponding alkoxide.[36]

The investigation of the reactions carried out with the BBr_3/*n*-Bu_4NI combination is reported in Table 1.



24 25

Entry	BBr_3 (eq.)	*n*-Bu_4NI (eq.)	Solvent	T (°C)	Time	Outcome
1	5	3	DCM	rt/reflux	12	nr
2	10	3	1,2-DCE	85°C	4	?
3	10	3	1,2-DCE	85°C	12	?
4	10	3	1,2-DCE	60°C	4	?
5	10	-	1,2-DCE	60°C	4	?

Table 1

When the reaction was performed in CH_2Cl_2, starting from the room temperature to the refluxing one, no product was observed despite the presence of the ammonium salt.

At that point we decided to proceed investigating stronger experimental conditions, following a procedure reported in literature for another methyl aryl ether,[37] in which, always working with a BBr_3/*n*-Bu_4NI combination, the demethylation product can be obtained only using 10 eq. of BBr_3 in a higher boiling point solvent such as the 1,2-DCE.

Carrying out the reaction in refluxing 1,2-DCE, after 4 h the formation of a new product was observed. This product was isolated, after column chromatography, in 42% yield (Table 1, Entry 2). On the basis of the ^{1}H-NMR spectrum recorded at rt, this compound appeared to be a product of partial demethylation, since it was evident the loss of the C_2 symmetry (Figure 12, b). Following this hypothesis, the reaction was performed both in the same experimental conditions, but for a prolonged time, and at 60°C (Table 1, Entry 3-4), always obtaining the same reaction product.

In addition, the same compound was obtained performing the reaction in the presence of the Me_4NI, easily removable *in vacuo*, in order to reduce the problems related to the presence of *n*-Bu_4NI that complicate the purification of the product.

Then, in order to verify the effective importance of the iodide in the formation of the product, the reaction was repeated without ammonium salts in 1,2-DCE at the temperature of 60 °C recovering, also in this case, the same product (Entry 5). The latter experiment allowed to exclude the presence of an iodide atom into the unknown product's structure.

Another clue on the possible nature of the new compound was given by the boron NMR spectrum that excluded the presence of a boron atom underlining that the new product couldn't be an intermediate still containing the boron atoms.

The compound's structure was finally clarified thanks to the help of Prof. Rita Annunziata of the University of Milan, who performed several NMR experiments on the target compound with different solvents and at different temperatures.

A first important information was given by the protonic spectrum recorded in DMSO at 100 °C reported in Figure 12 (a). In these conditions the molecule exhibited a perfect C_2 symmetry, differently from what observed at rt, where the presence of different conformers (attributable to the prevented rotation of the thiophenic units due to the presence of the amidic functions) was evident. At 100 °C the NMR spectrum becomes simpler thanks to the coalescence of the conformers and some attributions could be done.

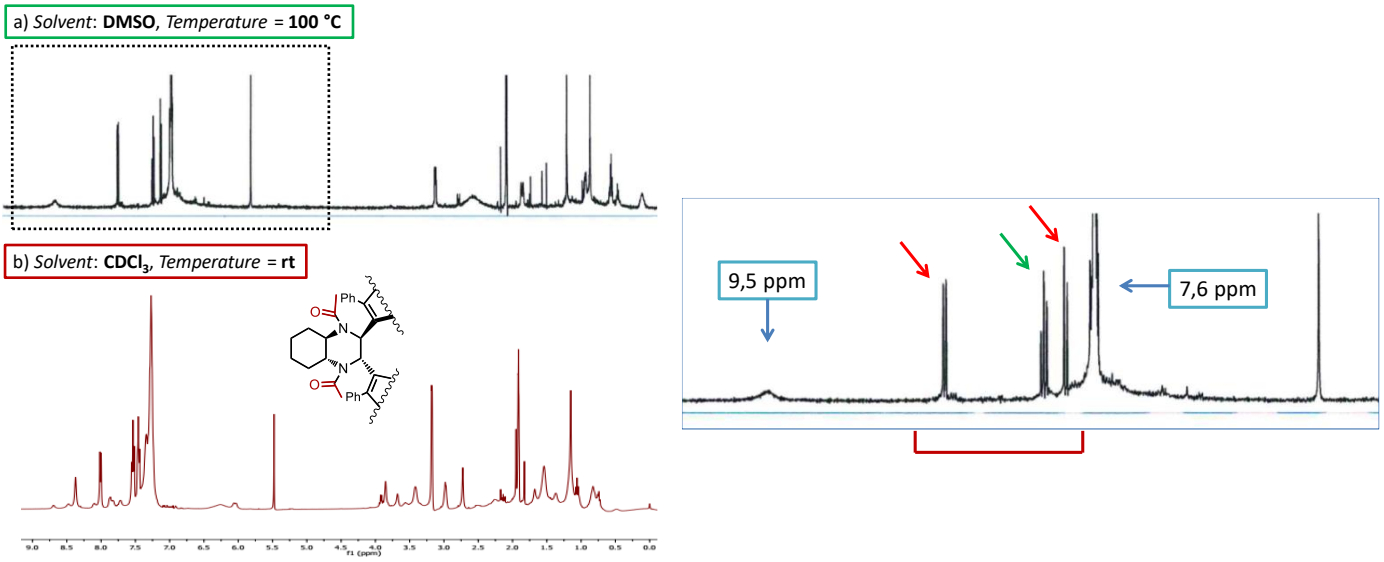


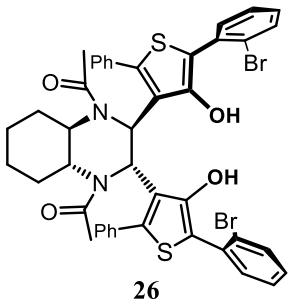
Figure 12. ^{1}H-NMR experiments performed on the unknown product of the demethylation reaction under strong experimental conditions. In the right hand-side an enlargement of the aromatic region of the spectrum a) is shown.

The well evident singlet at about 9,5 ppm was attributable to the presence of an arylic OH group demonstrating that a demethylation reaction has occurred. Furthermore, the presence of an electron-withdrawing substituent bounded to one of the phenyl groups is demonstrated by the shift to low fields of the related signals.

Moreover, the signals' pattern suggested that this substituent should be in the *ortho* position; indeed, two doublets and one triplet are well evident, while the missing second triplet is hidden by the multiplet at about 7.6 ppm, which corresponds to 6 protons (Figure 12, right hand-side).

To confirm the molecular structure, further experiments were performed. Concerning the ^{13}C-NMR spectrum the singlet at 148 ppm confirmed the presence of hydroxylic groups while a broad signal at 123 ppm is compatible with the presence of an aromatic carbon bearing a bromine atom as substituent (=**C**-Br).

On the basis of all these considerations, the possible chemical structure of the unknown compound, further confirmed by mass spectroscopy, is shown in Figure 13.



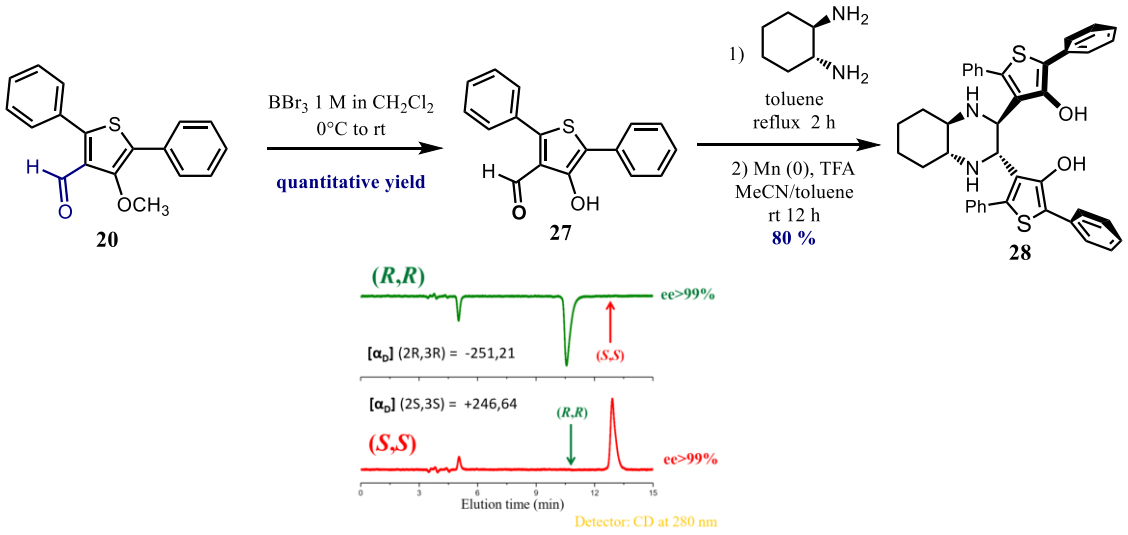
26

Figure 13

In the meanwhile, due to the evident difficulties met in the final step of the previous synthetic strategy, we decided to change the synthetic approach for the synthesis of the diol **25**, overcoming our doubt about the tautomerization process of the thienol derivatives (shown in Scheme 14) and anticipating the demethylation reaction at the level of the aldehyde **20**, namely immediately before the formation of the decahydroquinoxalinic scaffold, following the scheme described for the analogous carbocyclic derivatives synthesized by the Benaglia's group.

The demethylation reaction of **20** proceeded smoothly, in quantitative yield, without further purifications. Furthermore, surprisingly, the ^{1}H-NMR spectrum of the compound **27** suggested us that the keto-enolic tautomerization process was completely absent.

The subsequent step was carried out following the same experimental conditions previously employed with the protected aldehyde **20**. Also in this case the reaction was performed with both the (*R*,*R*) and the (*S*,*S*) enantiomers of the *trans*-1,2-diaminocyclohexane affording the compound **28** (when the *R*,*R* amine was employed) in 80% yield as a single diastereoisomer, as demonstrated by the HPLC analysis (Scheme 24).



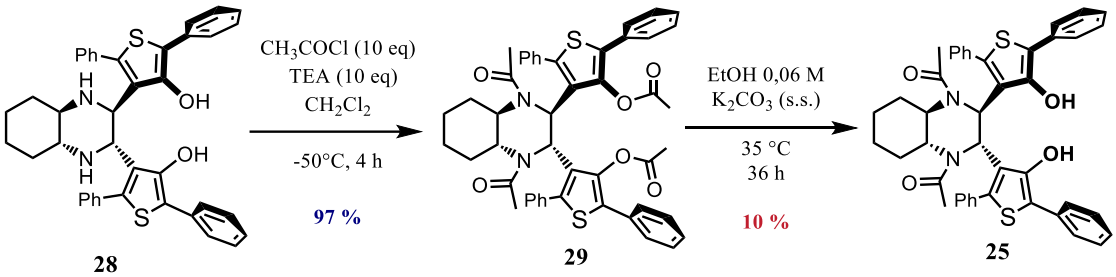
Scheme 24

^{1}H-NMR and the ^{13}C-NMR spectra highlighted that the tautomerization process is completely absent also when the decahydroquinoxalinic scaffold formed. These results are the evidence that all our fears about the tautomerization process in that kind of molecule, which forced us to persist with the first strategy for a long time, were completely misleading.

The acetyl groups were also in this case easily introduced by reaction with acetyl chloride in CH_2Cl_2 in the presence of TEA. Obviously, more equivalents of acetyl chloride and TEA were needed here, due to the presence of the hydroxylic functions that are also subjected to the acetylation reaction.

The first procedure we have tried to convert compound **29** into the target diol **25** was a basic hydrolysis employing a mixture composed by ethanol and a saturated solution of K_2CO_3 in water as suggested by the protocol followed to synthesize the carbocyclic catalysts used as our models.[30] Unfortunately, this step represented a further obstacle for the synthesis of the diol: several attempts were made but only a 10% yield was achieved by modifying the quantity of the base employed and by increasing the temperature up to 35°C for 36 h (Scheme 25).

A basic hydrolysis was performed also in stronger experimental conditions, namely by using 10 eq. of K_2CO_3 in EtOH at the refluxing temperature for 15 h a complete degradation of the product was observed (Scheme 25).



Scheme 25

Considering that the NH groups are more nucleophilic than the OH ones, we tried to reach directly our target product by exploiting a regioselective acetylation employing a stoichiometric amount of acetyl chloride. The reaction permitted us to obtain the product in good yields when carried out on a small scale (50 mg of substrate), but unfortunately, the regioselectivity of the reaction felt down when we performed it on a large scale and a mixture of the substrate, tri-acetylated and tetra-acetylated compounds was obtained.

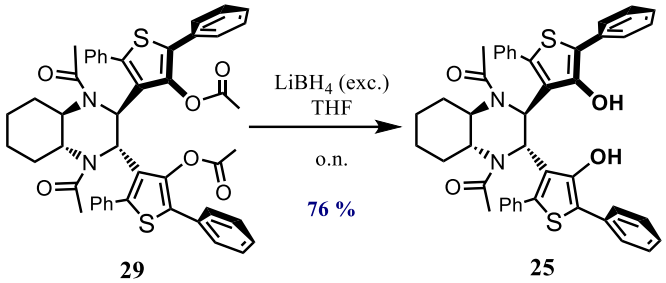
Finally, we followed the Ding's procedure[28] that consists in performing an acetylation reaction using acetic anhydride (6 eq.) followed by a basic hydrolysis with K_2CO_3 in refluxing DMF. In these

conditions the formation of a tetra-acetylated derivative should occur, then the acetoxy groups are subjected to a nucleophilic acylic substitution by the potassium acetate that forms in the reaction, followed by the formation of acetic anhydride and the alcoholate of the diol.

However, following this approach on our substrate we were able to obtain the desired product only in poor yields (20%).

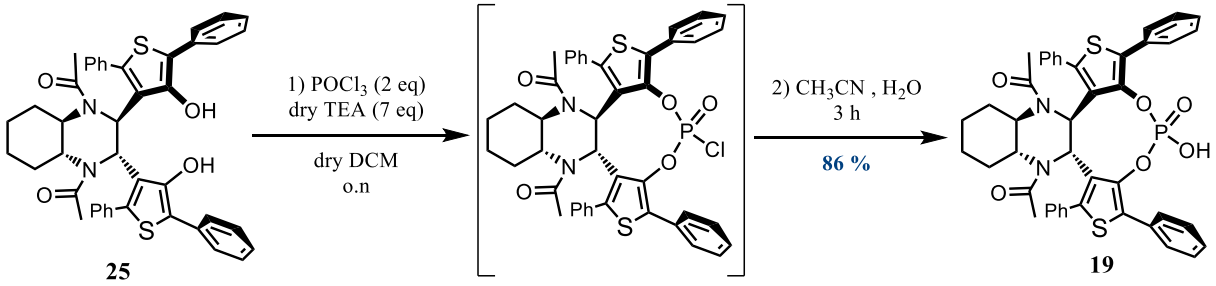
The last attempt of hydrolysis was carried out in acidic conditions using *p*-toluensulfonic acid in refluxing methanol but the starting material was recovered unreacted.

We consider a different approach and we tried a reduction of the ester groups in order to obtain the corresponding alcohol. Finally, the reaction was carried out overnight with an excess of $LiBH_4$ in THF and we were able to achieve the desired diol **25** in good yield (76%) (Scheme 26).



Scheme 26

The synthesis of the phosphoric acid **19** was finally achieved by reaction of diol **25** with $POCl_3$ in the presence of TEA following a one-pot-two-steps procedure. The intermediate phosphoric acid chloride was then hydrolysed giving the corresponding acid **19** in 86% yield (Scheme 27).



Scheme 27

The new chiral Brønsted acid (**19**) was then tested in two organocatalytic reactions in order to compare its activity with catalyst **18a**, and verify if all our expectations regarding the different chiral pocket shape, and also all our efforts for synthesizing it, would be satisfied.

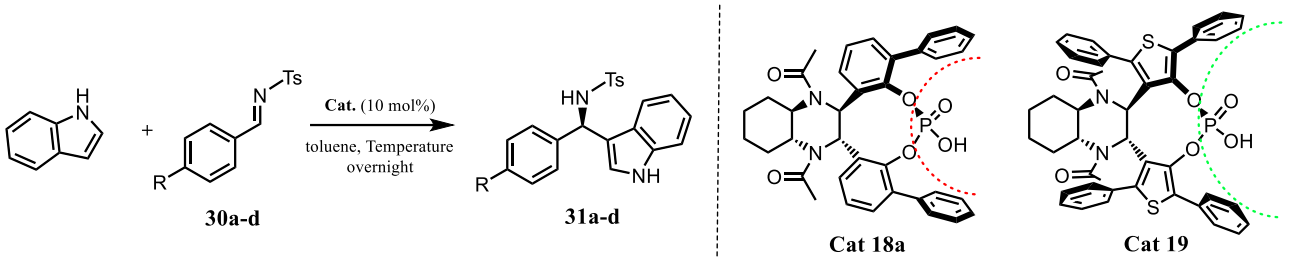
The first investigated reaction was the stereoselective Friedel-Craft alkylation of indole with *N*-tosyl imines (**30a-d**)[26,25c,29] (synthesized according to general procedures, see experimental section)

where, disappointingly, the catalyst **19** didn't give the expected results in terms of stereoselection ability.

Actually, there was a decrease of the enantiomeric excess to 53% from 74% (best result displayed by **18a** for the unsubstituted *N*-tosyl imine) carrying out the reaction in the same experimental conditions (Table 2, Entry 1) and to 60% when CH_2Cl_2 was employed as solvent (Entry 9).

In addition, lower enantiomeric excesses were observed starting from other different substituted substrates changing the temperature (-50°C, -70°C) and the solvent (toluene, CH_2Cl_2).

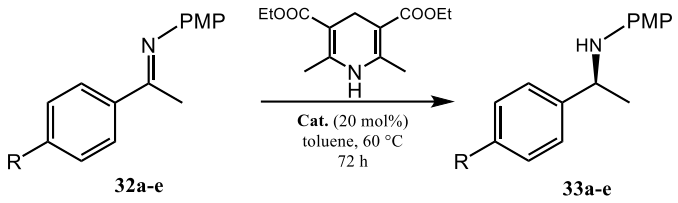
The only improvement given by **cat 19** was its catalytic activity in the reaction with the methyl substituted *N*-tosylimine (Table 2, Entry 4), where the product (**31d**) was isolated in 86% yield, while **cat 18a** was able to produce **31d** only in 37% yields by performing the reaction at -20°C.[30]



Entry	R	Solvent	T	Yield (%)		ee (%)	
				Cat 18a	Cat 19	Cat 18a	Cat 19
1	H (**a**)	tol	-50	99	96	74	53
2	Cl (**b**)	tol	-50	96	38	48	rac
3	OCH_3 (**c**)	tol	-50	96	84	63	23
4	CH_3 (**d**)	tol	-50	nr	86	nr	43
5	H	tol	-70		45		18
6	Cl	tol	-70		41		14
7	OCH_3	tol	-70		nr		nr
8	CH_3	tol	-70		42		20
9	H	DCM	-50		84		60
10	Cl	DCM	-50		81		20
11	OCH_3	DCM	-50		64		22
12	CH_3	DCM	-50		83		40

Table 2

The second reaction in which our catalyst has been tested is the transfer hydrogenation of ketoimines with Hantzsch esters (Table 3).[21,22] This transformation showed an increment of the catalytic activity respect to **cat 18a** (Table 3, Entry 1), but also in this case a further decrement of the stereoselection ability with all the substrates investigated.



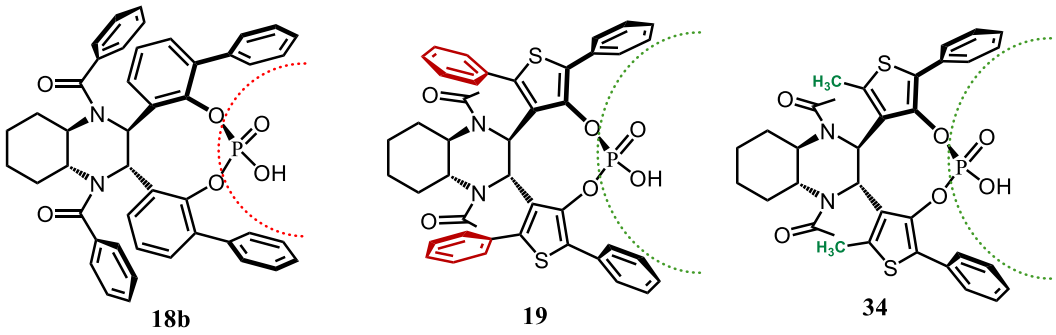
32a-e 33a-e

Entry	R	Yield (%)		ee (%)	
		Cat 18a	Cat 19	Cat 18a	Cat 19
1	H (**a**)	50	91	35	28
2	NO_2 (**b**)		71		10
3	Cl (**c**)		78		20
4	CF_3 (**d**)		60		21
5	F (**e**)		89		20

Table 3

In conclusion, we can say that the new catalyst (**19**) exhibited a good catalytic activity but, despite the favourable chiral pocket shape due to the presence of the two thiophene units, low stereoselection ability. This behaviour could be attributed to the steric encumbrance between the acetyl groups and the phenyl rings, absent in **cat 18a,** confirming the results obtained in the Friedel-Crafts alkylation of indole with *N*-tosyl imines using **cat 18b,** functionalised at the nitrogen atoms with benzoyl groups instead of methyl ones.

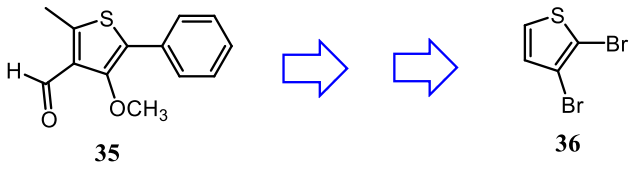
To overcome these problems, a new catalyst (**34**) in which the phenyl rings facing the acetyl groups were substituted by methyl groups was designed in order to reduce the steric hindrance in that molecular region (Figure 14).



18b 19 34

Figure 14

The key intermediate for the synthesis of catalyst **34** is the aldehyde **35** that is a complex objective, since every position of the thiophene ring must be in this case functionalised with different substitutions employing different reactions. (Scheme 28).



Scheme 28

The 2,3-dibromothiophene (**36**) was chosen as the best starting material for the following reasons:

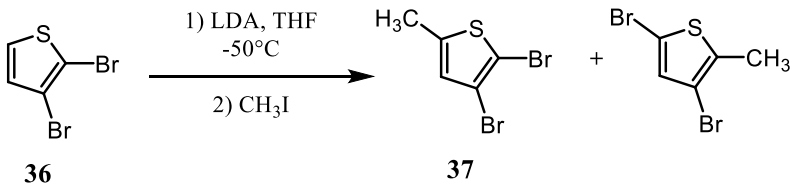
1. The hydrogen in the position 5 is an acidic proton, so it could be utilised for generating an anion by reaction with LDA which, after treatment with CH_3I, would bring to the introduction of the methyl group;
2. It is known that bromine atoms in the *ortho* position to the sulphur atom in thiophene rings are more reactive in the Suzuki couplings, so this regioselectivities would be exploited for selectively introducing a phenyl group in the position 2.

Then, once functionalized the positions 5 and 2 of the thiophene ring, the bromine atom in the position 3 would be utilised for introducing a methoxy group exploiting the CuBr catalysed reaction with NaOMe in DMF already discussed for the synthesis of the methoxy derivative **23**.

Finally, the methoxy group in the position 3 could have contributed to make the hydrogen in position 4 sufficiently acid to be removed by *n*-BuLi, in order to generate the anion necessary to introduce the formyl group.

Following this strategy, the methyl group in position adjacent to the sulphur atom was introduced by quenching the generated anion with LDA in THF with CH_3I. The formation of the anion was carried out through a reverse addition, namely dropping the substrate **36** in a solution of LDA in order to minimize the formation of possible regioisomers due to the phenomenon called "halogen dance" described in literature for analogous compounds.[38]

The reaction was performed at -50°C and the ^{1}H-NMR showed the presence of two compounds difficult to separate, that are supposed to be the desired product **37** and the regioisomer 3,5-dibromo-2-methylthiophene derived from the concomitant "halogen dance" of the bromine atom in position 2 (Scheme 29).

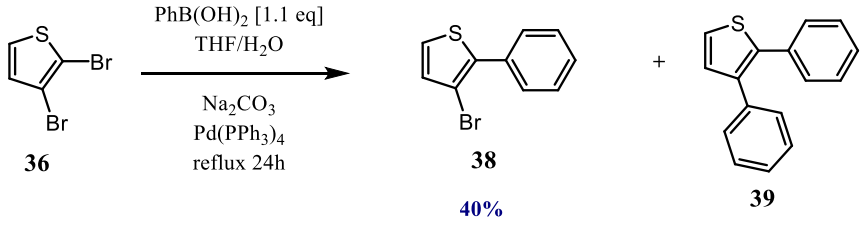


Scheme 29

In order to avoid this process, the bromine atom in position 2 of the thiophene ring was substituted at the beginning of the synthetic sequence with the phenyl group, but we weren't able to find the experimental conditions suitable to obtain the product **37** in good yields.

The 2,3-dibromothiophene (**36**) was subjected to a Suzuki reaction employing the same experimental conditions seen for the synthesis of compound **22** starting from the tribromothiophene, using 1.1 eq of the boronic acid (Scheme 30). However in this case the reaction was moderately regioselective. Indeed, performing the reaction for short times (4 h), only the formation of the desired mono-substituted product **38** was observed, but the starting material was still well visible in the TLC plate. By increasing the reaction time up to 12 h, the reaction progressed, but remarkable amounts of the 2,3-diphenylthiophene (**39**) were also obtained.

By performing the reaction for an intermediate time, the 3-bromo-2-phenylthiophene (**38**) was achieved in 40% yields, after purification by column chromatography, beside the starting material and the disubstituted derivative **39** (Scheme 30).



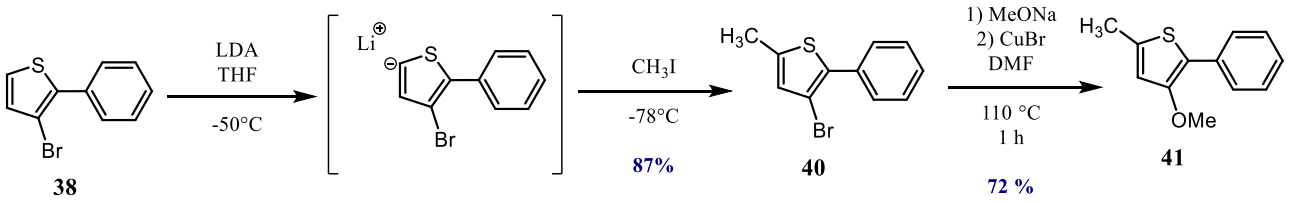
Scheme 30

Finally, the reaction was performed in 1,4-dioxane, which was complete in 4 h and a 1:1 mixture of compounds **38** and **39** was obtained.

We decided to be satisfied by this result and to proceed with the synthesis of the aldehyde knowing that this step must be improved if the following steps would have given a positive result.

The 3-bromo-2-phenylthiophene (**38**) was reacted with LDA in THF at -50°C performing a reverse addition procedure and, after the addition of an excess of CH_3I at -78°C, the 3-bromo-2-phenyl-5-methylthiophene (**40**) was isolated in 87% yield as a single regioisomer.

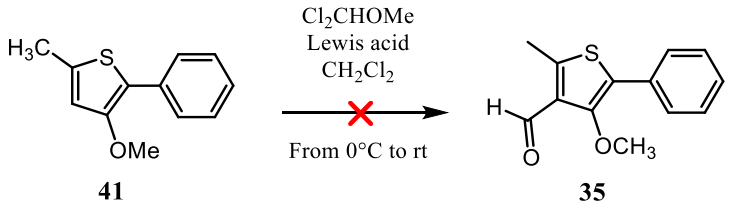
The methoxy group was introduced in position 3 in good yields following the usual reaction procedure (Scheme 31).



Scheme 31

Unfortunately, the introduction of a formyl group in the position 4 represented a crucial step. Indeed, the lithiation reaction, performed with *n*-BuLi in the presence of TMEDA at different reaction temperatures, proceeded with an anomalous trend since the predictable chromatic changes of the reaction mixture (from yellow to blue), typical of an anion formation was observed but no transformation of the substrate was found neither in the presence of DMF nor by quenching the anion with deuterium oxide. This result suggested that the blue intermediate could be a stable radical-anion, so other different strategies for the introduction of the aldehydic substituent were investigated.

Another approach for introducing the aldehydic group was a Rieche formylation following a procedure reported in literature for the synthesis of aromatic aldehydes having in the α-position a methoxy group.[39] This protocol requires the employment of dichloromethyl-methylether (Cl_2CHOMe) in CH_2Cl_2 in the presence of a Lewis acid (Scheme 32). The reaction was performed using different Lewis acids such as the $TiCl_4$ and the $AlCl_3$ initially at 0°C and then at room temperature. Unfortunately, in all cases only the unreacted starting material was recovered.

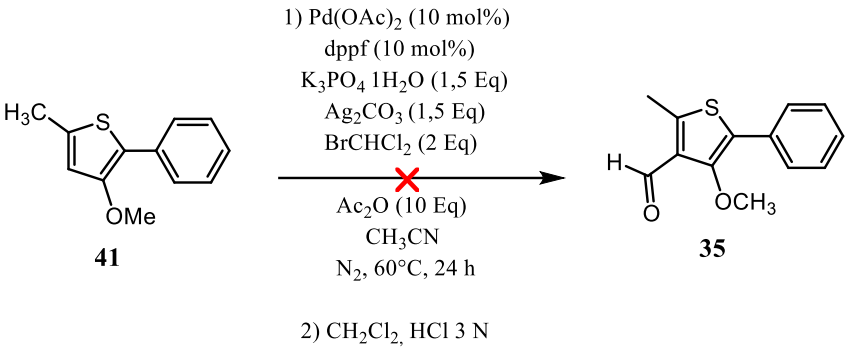


Scheme 32

Furthermore, the reaction was carried out by reverse addition, namely forming previously *in situ* the electrophile species by reaction at 0°C of Cl_2CHOMe with $AlCl_3$ and then dropping after 1h a solution of **41** in CH_2Cl_2 and leaving reacting at room temperature overnight. However, also in this case the reaction did not give a successful result.

The last approach investigated relies on a recently reported palladium catalysed radical type reaction in which the formyl group is generated starting from $BrCHCl_2$.[40] This reaction works both with carbocyclic systems as well as with electron-rich heterocyclic derivatives, such as indoles and thiophenes, even though, in the latter case, no examples related to a formylation reaction in the β-position respect to the sulphur atom is reported. Unfortunately, a complex reaction mixture was obtained where the desired product was not present (Scheme 33).

The difficulties met in the synthesis of the aldehyde **35** forced us to give up with this project.

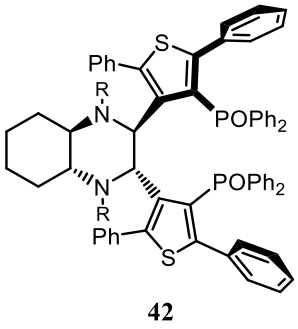


Scheme 33

2.2.2 Synthesis of a new diphosphinoxide based on a decahydroquinoxalinic scaffold functionalised with thiophenic units

Although the catalyst **19** did not give the hoped results in both the two preliminary chiral Brønsted acid catalysed reactions investigated, we decided to exploit our experience in Lewis-base catalysed Lewis-acid mediated reactions and to use the decahydroquinoxalinic backbone to design the new heterocyclic-based diphosphinoxide **42**, since diphosphinoxides catalysed reactions are different from a mechanistic point of view and different kind of transition states are involved.

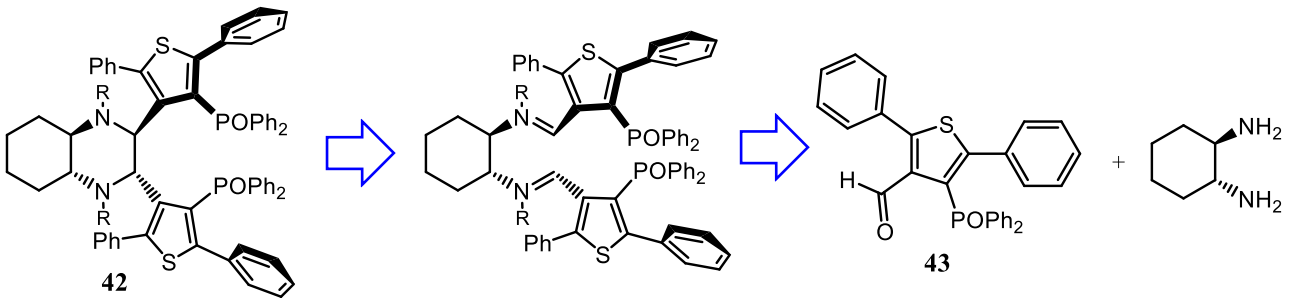
Thus, another aim of this PhD Thesis work was to investigate the synthesis of diphosphinoxide **42** (Figure 15).



42

Figure 15

Following the experience acquired in the previous synthesis of catalyst **19**, the formation of the decahydroquinoxalinic backbone involves the reaction between a suitable functionalized aldehyde and one of the two enantiomers of the 1,2-*trans*-cyclohexanediamine. The retrosynthetic approach is shown in Scheme 34 and it is based on the achievement of the aldehyde **43**.



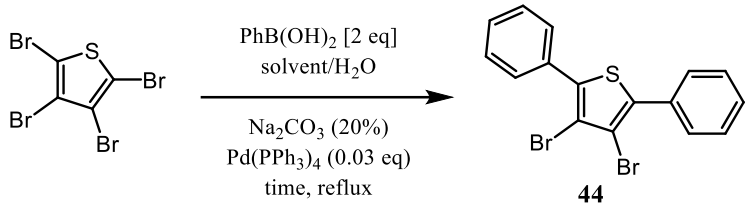
Scheme 34

In this case the tetrabromothiophene appeared to be a versatile key intermediate. The regioselective Pd(tetrakis)-catalysed Suzuki coupling was utilised to functionalised the 2 and 5 positions with the phenyl groups (Scheme 35). A 20% aqueous solution of Na_2CO_3 was employed as a base and the reaction conditions were optimized by varying the solvent and the reaction times.

Differently from what observed for the synthesis of compound **38**, the dioxane did not appear to be a proper solvent, since the formation of the desired product (**44**) was not observed when the reaction was performed in refluxing dioxane for 22 h.

Then, employing THF at the refluxing temperature for 24 h, it was possible to isolate the *ortho*-diphenyl product **44** in 27% beside the 2-phenyl-3,4,5-tribromothiophene.

Finally, prolonging the reaction time up to 48 h the yield was increased up to 85%.

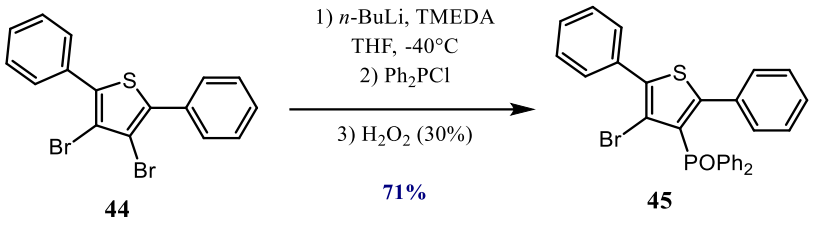


Scheme 35

The functionalisation of the thiophene ring with the diphenylphosphinic group was carried out by exploiting the formation of the anion through a transmetallation reaction with *n*-BuLi; then the reaction with chlorodiphenyldiphosphine and the *in situ* oxidation of the intermediate diphenylphosphine derivative with a of 30% H_2O_2 solution gave the diphenylphosphinoxide.

On the basis of the experience consolidated in our group on this topic, the above described two steps procedure give better results respect the use of the diphenylphosphinoyl chloride that is a less strong electrophile.

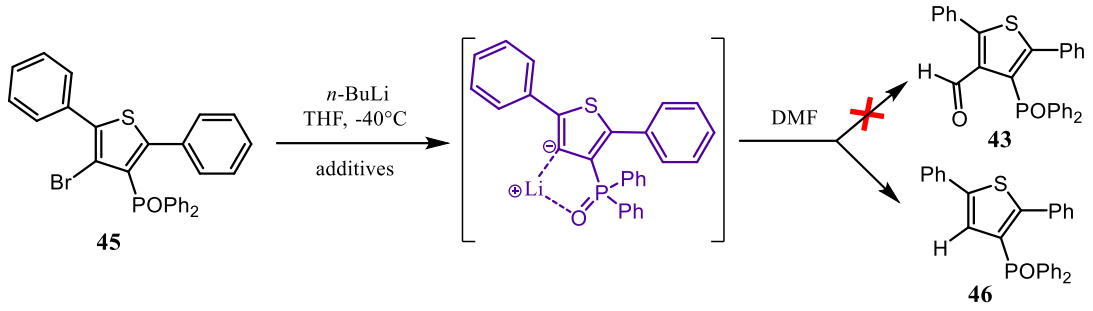
The lithiation reaction was carried out at -40°C in THF using a 20% excess of *n*-BuLi, then the chlorodiphenyldiphosphine was added and the reaction left at room temperature for 2 h. Then the oxidizing agent was added and the reaction left overnight at room temperature (Scheme 36). The product **45** was obtained in 60% yields, after purification through column chromatography. A further improvement of the yield up to 71% was obtained performing the reaction in the presence of 1.5 eq. of TMEDA.



Scheme 36

The synthetic strategy planned for the introduction of the formyl group considered to exploit again a lithiation reaction that was performed in THF at -40°C. The addition of *n*-BuLi produced a very deep violet colour, differently from what usually observed for other thiophene derivatives that assumed green/yellow colours. Unfortunately, the addition of an excess of DMF did not allow the formation of the aldehyde **43** not even in traces and the starting material and the compound **46** deriving from the anion quenching were found in the reaction crude (Scheme 37).

The reaction was repeated several times, prolonging the reaction time related to the anion formation, which maintained unchanged its colour even for hours. It was, therefore, hypothesized that the scarce reactivity of the anion toward the electrophile could be due to a possible stabilization in a new 5-membered structure promoted by an interaction between the oxygen atom of the P=O group and the Lithium one that would shield very strictly the anion, as shown in Scheme 37.

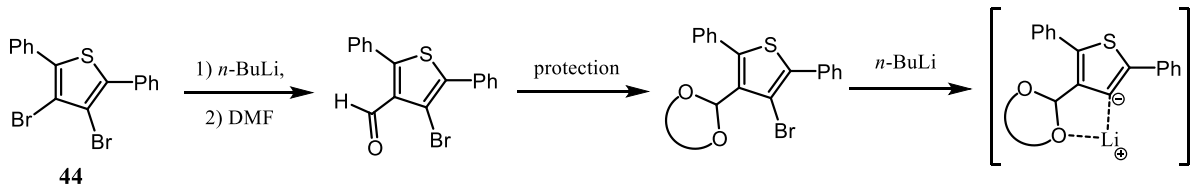


Scheme 37

Also the employment of lithium sequestering agents, such as TMEDA and the benzo-15-crown-ether, did not permit to obtain the desired aldehyde **43**.

In the case of the crown ether, the reaction was performed by adding the sequestering agent both before and after the dropping of *n*-BuLi, without observing any change in the reaction mixture.

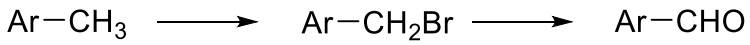
At this point, it was necessary to vary the synthetic approach. An obvious alternative strategy could have been that of introducing the formyl group before the phosphinoyl one. This approach should have implicated the protection of the aldehydic group through the formation of an acetal derivative before the introduction of the phosphinoyl group requiring the use of *n*-BuLi. However, also in this case, a stabilisation of the anion could have occurred through an interaction between the lithium atom and the acetal O-groups (Scheme 38).



Scheme 38

In order to avoid these possible complications, a different synthetic scheme for the introduction of the formyl group was investigated that considered first the introduction of a methyl group that can

be transformed into an aldehydic one through a CH_2Br intermediate,[41] following the reaction scheme reported below (Scheme 39).



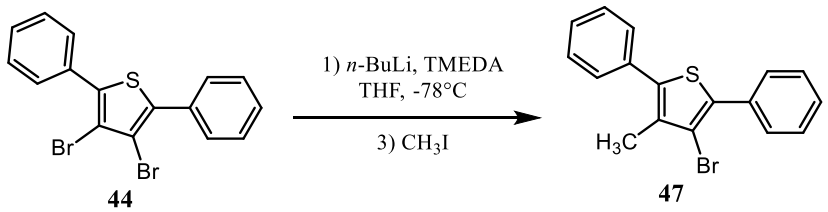
Scheme 39

Thus, starting from compound **44**, the new strategy considered first its functionalization in position 3 with a methyl group, followed by the introduction of the phosphinoyl group and then the conversion of the methyl substituent into the formyl one through a CH_2Br intermediate.

The methyl group was introduced by reaction with *n*-BuLi in THF in the presence of TMEDA, followed by the addition of an excess of CH_3I and, also in this case, the experimental conditions have been tuned.

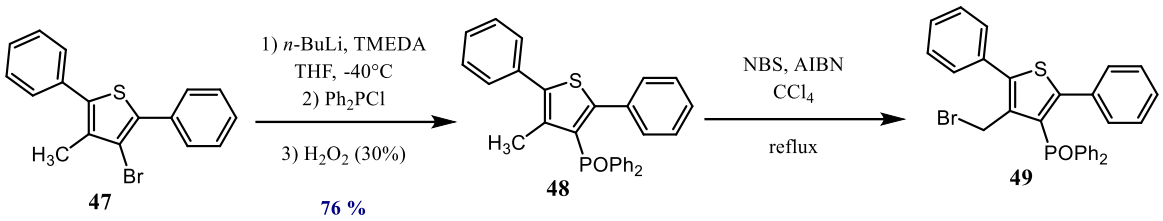
The best results were obtained performing the lithiation at -78°C using 1.2 eq. of *n*-BuLi in the presence of 1.5 eq. of TMEDA. The anion was then treated with 5 eq. of CH_3I and the reaction left at the same temperature for 1 h and subsequently at room temperature for another hour (Scheme 40). The product **47** was obtained in 94% yields after a purification through column chromatography on silica gel.

Yields fell down to 34% and 56% when the lithiation was carried out at -40°C and at -50°C, respectively, and the alkylating reagent added at -78°C.



Scheme 40

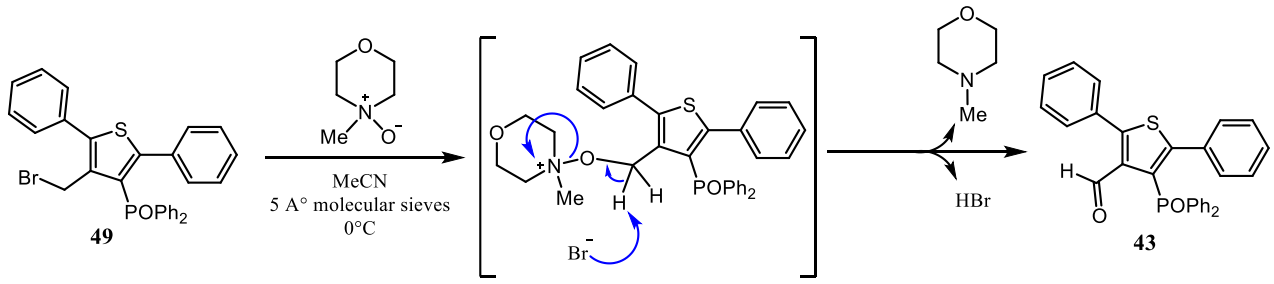
The subsequent transmetallation reaction with *n*-BuLi was performed at -40°C, always in the presence of TMEDA. After 5 min the chlorodiphenyldiphosphine was dropped and after further 2 h, then a 30% H_2O_2 solution was dropped into the reaction mixture to perform the oxidation reaction that was completed in 2 h (Scheme 41) affording phosphinoxide **48** in 76% yield.



Scheme 41

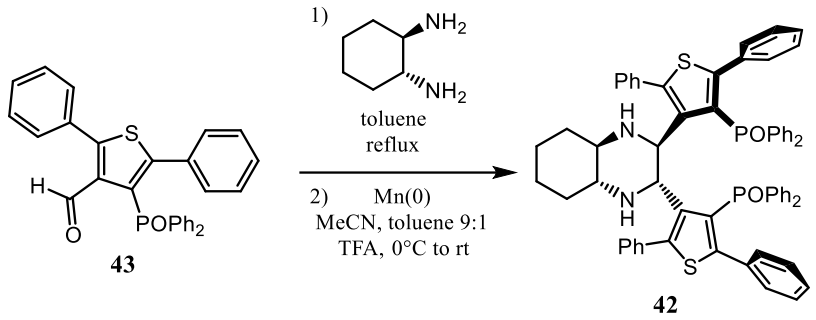
The allylic bromination was performed in CCl_4 using AIBN as radical initiator (Scheme 41); the reaction mixture was heated at the refluxing temperature for 4 hours and the reaction crude utilised without any purification, being the allylic bromide too reactive and lachrymatory. The presence in the ^{1}H-NMR spectrum of a singlet at 5 ppm that integrates 2 hydrogens, related to the methylene group of **49**, and the disappearance of the singlet at 2.24 ppm, related to the substrate methyl group, were taken as evidence of the complete conversion of **48** in **49**.

The transformation of the bromomethyl group in the aldehydic one was carried out by exploiting a nucleophilic substitution with the *N*-oxide of the *N*-methylmorpholine:[41] the intermediate substitution product evolved to the aldehyde **43** in 46% yields, through the elimination of HBr and *N*-methylmorpholine. (Scheme 42).



Scheme 42

Despite the reaction conditions required a further tuning in order to improve the modest yields, we proceeded with the synthesis of the diphosphinoxide **42**, just to verify if the approach utilised for the synthesis of the decahydroquinoxalinic scaffold in the phosphoric acid **19** and the corresponding carbocyclic derivative (**18**), can be feasible also for aldehyde **43** (see Scheme 22 for the reaction mechanism). The reaction of formation of the bis imine intermediate was performed starting from the (*R*,*R*) enantiomer of the 1,2-cyclohexandiamine using toluene as solvent at the refluxing temperature (Scheme 43).



Scheme 43

The reaction was controlled after 6 h by ^{1}H-NMR and the decrease of the aldehydic signal at 9.7 ppm was noticed beside the appearance of a broad singlet at 8.8 attributable to the new formed bis imine. Even though the bis imine formation was not complete, we proceeded with the second step in order to verify the possibility to reach the decahydroquinoxalinic backbone. So the reaction was cooled at the room temperature and then acetonitrile (in 9:1 ratio with toluene), Mn(0) powder were added, followed by the addition of trifluoroacetic acid (TFA) at 0°C (Scheme 43).

The analysis of the reaction crude by mass spectroscopy, demonstrated the formation of the diphosphinoxide **42**, even if in modest yields, and a complete characterisation of the product must be accomplished.

2.3 Conclusions

The synthesis of a new chiral phosphoric acid (**19**) based on a decahydroquinoxalinic scaffold bearing two thiophene units in 2 and 3 positions (in place of phenyl ones, as in the **cat 18** already tested in the Benaglia Group)[30] was envisaged and, after a significant number of efforts, finally developed. However, despite the favourable chiral pocket shape observed by theoretical calculations, due to the presence of the two pentatomic heterocyclic units instead of the hexatomic carbocyclic ones, it didn't give the hoped results when employed in two preliminary stereoselective organocatalytic reactions.

In order to reduce the steric hindrance in the catalyst's overall structure, a new catalyst (**34**) in which the phenyl rings facing the acetyl groups were substituted by methyl groups was designed, but unfortunately still not obtained.

Although the catalyst **19** appeared disappointing, in order to exploit the experience acquired in the synthesis of decahydroquinoxalinic derivatives, we designed a new heterocyclic-based diphosphinoxide **42**, since diphosphinoxides catalysed reactions are different from a mechanistic point of view and different kind of transition states are involved.

Diphosphinoxide **42** was obtained, as confirmed by mass spectroscopy, even if in very low yields, requiring an optimization both of the synthetic process and of its purification.

2.4 Experimental Section

2.4.1 General Information

Methods:

Reactions were monitored by analytical thin-layer chromatography (TLC) using silica gel 60 F_{254} pre-coated glass plates (0.25 mm thickness) and visualized using UV light. Flash chromatography was carried out on silica gel (230-400 mesh). ^{1}H-NMR spectra were recorded on spectrometers operating at 300 MHz (Bruker Fourier Advanced 300), 400 MHz (Bruker AVANCE 400 spectrometer), 500 MHz (Bruker AVANCE 500) or 600 MHz (Bruker AVANCE 600); proton chemical shifts are reported in ppm (δ) with the solvent reference relative to tetramethylsilane (TMS) employed as the internal standard ($CDCl_3$ δ = 7.26 ppm) and coupling constants are reported in Hertz (Hz). Splitting patterns are indicate as follows: s = singlet, d = doublet, t = triplet, q = quartet, qn = quintuplet, m = multiplet, bs = broad singlet, dd = double doublet. ^{13}C-NMR spectra were recorded on 300 MHz, 400 MHz, 500 MHz and 600 MHz spectrometers depending on the analysed compound, operating respectively at 75 MHz, 100 MHz, 125 MHz and 150 MHz with complete proton decoupling; carbon chemical shifts are reported in ppm (δ) relative to TMS with the respective solvent resonance as the internal standard ($CDCl_3$, δ = 77.0 ppm). ^{31}P-NMR spectra were recorded on 300 MHz spectrometers (Bruker Fourier Advanced 300) at 121.4 MHz and were referenced to phosphoric acid (H_3PO_4) at 0.0 ppm. Mass spectra and accurate mass analysis were carried out on a VG AUTOSPEC- M246 spectrometer (double-focusing magnetic sector instrument with EBE geometry) equipped with EI source or with LCQ Fleet ion trap mass spectrometer, ESI source, with acquisition in positive ionization mode in the mass range of 50-2000 m/z.

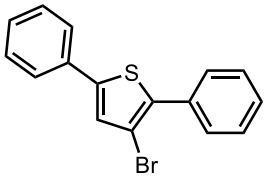
The CD spectra of analysed compound were measured by using a Jasco Model J-700 spectropolarimeter. Enantiomeric excess determinations were performed with Chiral Stationary Phase HPLC analysis on an Agilent 1200 series HPLC instrument. Specific rotations were measured by a PerkinElmer polarimeter model 241 equipped with Na/Hg lamps. The volume of the cell was 1 ml and the optical path was 10 cm. The system was set at a temperature of 20°C.

Melting point were determined on a Stuart Melting Point SMP30 instrument.

2.4.2 Synthesis of the phosphoric acid 19

2.4.2.1 ***First synthetic strategy***

Synthesis of 3-bromo-2,5-diphenylthiophene (22)



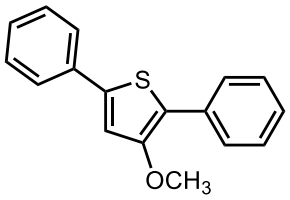
The 2,3,5-tribromothiophene (7.5 g, 23.36 mmol, 1 eq) was added under a N_2 atmosphere to a biphasic system constituted by anhydrous THF (100 ml) and a 20 % w/v sodium carbonate solution (100 ml). Phenylboronic acid (5.701 g, 46.73 mmol, 2 eq) and palladium tetrakis triphenylphosphine (0.809 mg, 0.701 mmol, 0.03 eq) were subsequently added and the biphasic system was refluxed under stirring for 24 h. Then the THF was removed under reduced pressure and the residue was extracted with CH_2Cl_2 (3 x 100 ml). The organic layers were collected, washed with brine (200 ml) and then dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was column chromatographed (*n*-hexane). The first fractions, collected and evaporated to dryness, gave the 3,5-dibromo-2-phenylthiophene (2.775 g, 37%) that was reacted under the same experimental conditions to give other product (84% as total yield after the two reactions).

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 7.71 (2H, d, *J* 7.2 Hz), 7.59 (2H, d, *J* 7.6 Hz), 7.43 (5H, m), 7.34 (1H, q, *J* 7.2 Hz), 7.27 (1H, s).[42]

The following fractions eluted gave the 3-bromo-2,5-diphenylthiophene (**22**) (4.365 g, 59 %) as a light- yellow liquid.

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 7.48 (2H, d, *J* 7.6 Hz), 7.39 (2H, t, *J* 7.6 Hz), 7.34 (1H, d, *J* 7.2 Hz), 7.10 (1H, s).[43]

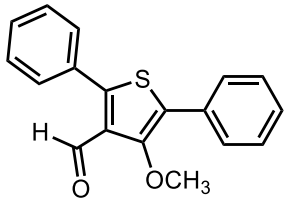
Synthesis of 3-methoxy-2,5-diphenylthiophene (23)



Sodium methoxide was prepared by dissolving metallic sodium (0.7 g, 27 mmol, 5 eq) in dry methanol (6 mL), under N_2 atmosphere, at room temperature; the solvent was partially removed at reduced pressure and the sodium methoxide was dissolved in DMF (3 ml). Then 2,5-diphenyl-3-bromothiophene (**22**) (1.7 g, 5.4 mmol, 1 eq) and copper(I) bromide (0.15 g, 2.2 mmol, 20 mol%) were added and the reaction was warmed at 110°C; after 30 minutes the reaction crude was filtered on a celite pad with *n*-hexane (40 ml). Then the filtered was washed with water (40 ml), and the aqueous phase was extracted with *n*-hexane (2 x 40 ml); the organic layer was dried and concentrated in vacuo.
Gravimetric column chromatography (*n*-hexane/CH_2Cl_2 8:2) led to compound **23**[44] as a yellow solid (62%).

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 7,81 (2H, d, *J* 8 Hz); 7,65 (2H, d, *J* 8 Hz); 7,42 (4H, m); 7,33 (1H, t, *J* 7.2 Hz); 7,26 (1H, t, *J* 8 Hz); 7,20 (1H, s); 4,00 (3H, s).

Synthesis of 4-methoxy-2,5-diphenylthiophene-3-carbaldehyde (20)



The 3-methoxy-2,5-diphenylthiophene (**23**) (3.43 g, 12.89 mmol, 1 eq) was added to a solution of anhydrous THF (200 ml) and TMEDA (3.86 g, 25.78 mmol, 2 eq), then a 2.5 M *n*-BuLi solution (7.21 ml, 18.043 mmol, 1.4 eq) was dropped at 0°C under N_2 atmosphere. The mixture was left under stirring for 15 min and then warmed to room temperature. DMF (2.414 ml, 15.47 mmol, 1.2 eq) was added dropwise and the reaction mixture was left under stirring for 12 h. A saturated solution of

NH_4Cl (150 ml) was added to quench the reaction. Then the THF was removed under vacuum and the residue was extracted with CH_2Cl_2 (3 x 150 ml). The organic phases were collected, dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (*n*-hexane/CH_2Cl_2 6:4) gave 4-methoxy-2,5-diphenylthiophene-3-carbaldehyde (**20**) (1.9 g, 50%) as a yellow solid.

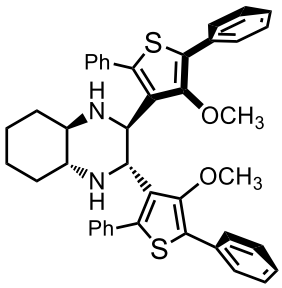
M.p.: 75-83°C.

^{1}H-NMR (400 MHz, CDCl3, δ ppm): 9.91 (1H, s), 7.76 (2H, d, *J* 7.6), 7.57-7.50 (2H, m), 7.50-7.46 (3H, m), 7.44 (2H, t, *J* 7.6), 7.34 (1H, t, *J* 7.2), 3.86 (3H, s).

^{13}C-NMR (100,16 MHz, CDCl3, δ ppm): 184.49 (COH), 151.84 (C), 151.51 (C), 130.87 (C), 130.54 (C), 129.01 (C), 128.82 (CH), 128.57 (CH), 128.53 (CH), 128.00 (CH); 127.93 (CH), 127.89 (CH), 127.85 (CH), 127.79 (CH), 126.89 (CH), 126.65 (C), 126.49 (CH), 60.84 (CH_3).

m/z (ESI) 295.20 (100%) (MH^+).

Synthesis of (2*S*,3*S*,4a*R*,8a*R*)-2,3-bis(4-methoxy-2,5-diphenylthiophen-3-yl)-decahydroquinoxaline (21)



The (*R*,*R*)-trans-diaminocyclohexane (41.8 mg, 0.367 mmol, 1 eq) was added to a solution of 4-methoxy-2,5-diphenylthiophene-3-carbaldehyde (**20**) (221 mg, 0.753 mmol, 2.05 eq) in toluene (0.5 ml). The reaction mixture was refluxed for 2 h and then cooled at room temperature. The almost complete conversion of the substrate to the imine intermediate was checked through ^{1}H-NMR. Anhydrous CH_3CN (4.5 ml) was added to the reaction mixture to achieve a mixture with a CH_3CN/Toluene 9:1 ratio. Manganese powder (51 mg, 0.918 mmol, 2.5 eq) was added, then the reaction mixture cooled at 0°C and TFA (0.141 ml, 1.836 mmol, 5 eq) was added. The reaction mixture was then allowed to reach rt and left under stirring for 24 h. Water (5 ml) was added, CH_3CN was removed under vacuum and the organic phase was extracted with CH_2Cl_2 (3 x 10 ml). The

organic layers were collected, and then dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (CH_2Cl_2/CH_3OH 9:1) gave (2*S*,3*S*,4a*R*,8a*R*)-2,3-bis(4-methoxy-2,5-diphenylthiophen-3-yl)-decahydroquinoxaline (**21**) (0.213 g, 85%) as a yellow solid.

M.p.= 215-216°C.

$[\alpha]_D$= -203.01° (1.1 mg/ml in CH_3Cl) starting from the (*R*,*R*)-*trans*-diaminocyclohexane.

^{1}H-NMR (400 MHz, CD_2Cl_2, δ ppm): 7.40-7.23 (4H, m), 7.23-7.05 (6H, m), 5.23 (1H, s), 4.32 (1H, s), 2.95 (3H, s), 2.23 (1H, bs), 1.84 (1H, bs), 1.72 (3H, s), 1.33 (1H, t, *J* 9.6 Hz), 1.14 (1H, m).

^{13}C-NMR (150.97 MHz, DMSO, 370 K, δ ppm): 152 (C-OCH_3), 137.5 (C), 134.8 (C), 133 (C), 131 (C), 129.4 (CH), 128.2 (CH), 128.3 (CH), 123.8 (C), 62 (CH), 59.1 (OCH_3), 58.3 (CH), 32.6 (CH_2), 25.7 (CH_2).

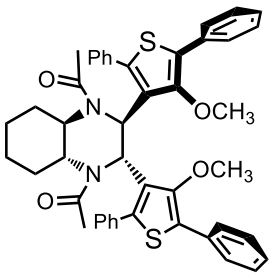
m/z (EI) 668 (30%) (M), 292 (100%).

The procedure reported above was repeated starting from the (*S,S*)-1,2-*trans*-diaminocyclohexane affording the (2*R*,3*R*,4a*S*,8a*S*)-2,3-bis(4-methoxy-2,5-diphenylthiophen-3 yl)decahydroquinoxaline (**21**) in the same yields.

$[\alpha]_D$= +240.01° (1.0 mg/ml in CH_3Cl).

The diastereoisomeric purity of both the diastereoisomers was checked by chiral HPLC analysis in the following experimental conditions: column: IB 250 mm x 4.6 mm; mobile phase: *n*-hexane-IPA-DCM-DEA 100/2/2/0.1; temperature: 25°C; flow rate: 1 ml/min; detector: CD at 280 nm.

Synthesis of the diacetyl-derivative 24



TEA (0.25 ml, 1.79 mmol, 4 eq) was added to a 0.1 M solution of (2*S*,3*S*,4a*R*,8a*R*)-**21** (304 mg, 0.449 mmol, 1 eq) in dry CH_2Cl_2, then the reaction mixture cooled at -50°C and the acetyl chloride (0.1 ml,

1.79 mmol, 4 eq) was dropped. The reaction mixture was stirred for 2 h, maintaining the same temperature. The mixture was warmed to room temperature and a saturated $NaHCO_3$ solution (5 ml) was added. The two phases were separated and the organic phase was extracted with CH_2Cl_2 (2 x 5 ml). The organic phases were collected and washed with a 5 % HCl solution to remove the TEA, and then dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by gravimetric column chromatography (*n*-hexane/ethyl acetate 6:4) gave (2*S*,3*S*,4a*R*,8a*R*)-**24** (400.1 mg, 89%) as a light yellow solid.

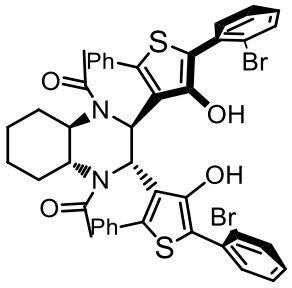
M.p.: 133-140°C.

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 7.65 (2H, d, *J* 8.6 Hz), 7.43-7.28 (8H, m), 5.95 (1H, bs), 3.54 (4H, s), 1.71 (3H, bs), 1.53 (2H, bs), 1.15 (2H, bs).

^{13}C-NMR (150.97 MHz, DMSO, 370 K, δ ppm): 171.5 (N**C**OCH_3), 152 (C-OCH_3), 137 (C), 134 (C), 132.5 (C), 130.3 (C), 129.4 (C), 128.6 (C), 128.4 (C), 128 (C), 127.9 (C), 125.8 (C), 61.6 (OCH_3), 58.3 (CH), 56.9 (CH), 32 (CH_2), 25 (CH_2), 22.5 (NCO**C**H_3).

m/z (EI) 752 (85%) (M), 667 (45%) (M), 292 (100%).

Synthesis of compound 26



The (2*S*,3*S*,4a*R*,8a*R*)-**24** (150 mg, 0.200 mmol, 1 eq) and *n*-Bu_4NI (222 mg, 0.601 mmol, 3 eq) were added under a N_2 atmosphere to anhydrous 1,2-DCE (12 ml). The mixture was cooled at 0°C, then a of 1 M BBr_3 solution in DCM (2 ml, 2 mmol, 10 eq) was added. The reaction mixture was refluxed for 4 h, then cooled at rt and a cold 10% HCl solution was added. The mixture was left under stirring for 30 min. The two phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 5 ml) and then dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (*n*-hexane/ethyl acetate 2:8) gave **26** (74 mg, 42%) as a brown solid.

M.p.= 278-288°C.

^{1}H-NMR (600 MHz, DMSO, 370K, δ ppm): 9.22 (1H, s), 8.19 (1H, d, *J* 12 Hz), 7.68 (1H, t, *J* 6 Hz), 7.56 (1H, d, *J* 12 Hz), 7.4 (6H, m), 6.26 (1H, s), 3.55 (1H, d), 2.31 and 0.54 (2H, d and b m, diastereotopic CH_2), 1.65 (3H, s), 1.36 and 0.9 (2H, d and b m, diastereotopic CH_2).

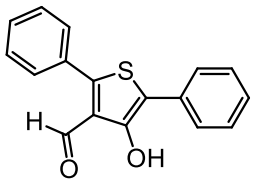
^{13}C-NMR (150.97 MHz, DMSO 370K, δ ppm): 171.7 (C=O), 148.7 (C), 138.6 (C), 137.5 (C), 134.5 (C, CH), 133.5 (CH), 130.5 (CH), 129 (CH), 128,6 (CH), 128 (C), 126.6 (CH), 123 (C, bs), 121.9 (CH), 119 (C), 57.85 (CH), 56,6 (C), 30,8 (CH_2), 25,15 (CH_2), 22.40 (CH_3).

m/z (EI) 881.64 (40%) (M^-), 827.90 (100%), 814.02 (45%).

The procedure reported above was repeated using Me_4NI (3 eq) and also without *n*-Bu_4NI giving the same product.

2.4.2.2 ***Second synthetic strategy***

Synthesis of 4-hydroxy-2,5-diphenylthiophene-3-carbaldehyde (27)



A 1 M BBr_3 solution in DCM (2.652 ml, 2.652 mmol, 1.2 eq) was dropped into a solution of 4-methoxy-2,5-diphenylthiophene-3-carbaldehyde (**20**) (650 mg, 2.21 mmol, 1 eq) in dry CH_2Cl_2 (10 ml). at 0 °C under a N_2 atmosphere. The mixture was left under stirring at rt for 4 h; then water (10 ml) was added and the biphasic mixture was stirred for 30 min. The two phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 10 ml). The organic phases were collected, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The 4-hydroxy-2,5-diphenylthiophene-3-carbaldehyde (**27**) was obtained in quantitative yield (618 mg) as an orange solid and was used in the following step without any purification.

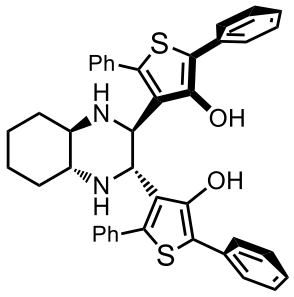
M.p.: 125-126°C.

^{1}H-NMR (400 MHz, acetone d_6, δ ppm): 9.99 (1H, s), 9.81 (1H, s), 7.71 (2H, d, *J* 7.7 Hz), 7.59 (2H, m), 7.47 (3H, m), 7.31 (2H, t, *J* 7.8 Hz), 7.16 (1H , t, *J* 7.4 Hz).

^{13}C-NMR (100,16 MHz, $CDCl_3$, δ ppm): 188.7 (COH), 152.6 (C), 150.7 (C), 131.0 (C), 130.2 (C), 128.9 (CH), 128.5 (CH), 128.2 (CH), 128.0 (CH), 127.7 (CH), 127.5 (CH), 127.4 (CH), 126.7 (CH), 125.9 (CH), 125.4 (CH), 124.0 (C), 115.5 (C).

m/z (EI) 280 (100 %) M^+.

Synthesis of 4,4'-((2*S*,3*S*,4a*R*,8a*R*)-decahydroquinoxaline-2,3-diyl)-bis(2,5-diphenylthiophen-3-ol) (28)



The (*R*,*R*)-*trans*-diaminocyclohexane (120 mg, 1.151 mmol, 1 eq) was added to a solution of 4-hydroxy-2,5-diphenylthiophene-3-carbaldehyde (**27**) (608 mg, 2.154 mmol, 2.05 eq) in toluene (4.5 ml) and the reaction mixture was refluxed for 2 h. The almost complete conversion of the substrate to the imine intermediate was checked through ^{1}H-NMR spectroscopy. Dry CH_3CN (20 ml) was added to the reaction mixture to achieve a solution with a CH_3CN/Toluene 9:1 ratio, then Manganese powder (144 mg, 2.626 mmol, 2.5 eq) was added; the temperature cooled at 0 °C and TFA (0.4 ml, 5.253 mmol, 5 eq) dropped into the reaction mixture. Then the reaction mixture was warmed to rt andstirred for 24 h. Water (20 ml) was added and CH_3CN removed under vacuum; the organic product was extracted with CH_2Cl_2 (3 x 25 ml). The organic phases were collected, dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (CH_2Cl_2/CH_3OH 9:1) gave (2*S*,3*S*,4a*R*,8a*R*)-**28** (554 mg, 87%) as a yellow solid.

M.p.= 246-250°C.

$[\alpha]_D$= -251.01° (1.2 mg/ml in CH_3Cl).

^{1}H-NMR (400 MHz, acetone d_6, δ ppm): 10.80 (1H, s), 7.42 (2H, d, *J* 8 Hz), 7.17 (2H, t, *J* 7,6 Hz), 7.01 (3H, m), 6.91 (2H, t, *J* 7,6 Hz), 6.76 (1H, t, *J* 7,2 Hz), 4.52 (1H, s), 3.36 (1H, s), 2.51 (1H, m), 1.78 (1H, m), 1.66 (1H, m), 1.31 (2H, m).

^{13}C-NMR (150.97 MHz, $CDCl_3$, δ ppm): 150.8 (C), 136.7 (C), 133 (C), 132.5 (C), 128.7 (CH), 128.3 (2 CH, 1 C), 128 (CH), 126.4 (CH), 125.9 (CH), 125,8 (C), 59.2 (CH), 56.5 (CH), 56.5 (CH), 31 (CH_2), 24 (CH_2).

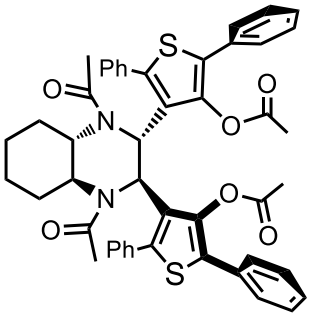
m/z (ESI) 639.69 (100%) (M^-), 1278.95 (40%) (2M).

The procedure reported above was used starting from the (*S*,*S*)-1,2-diaminocyclohexane giving the enantiomer (2*R*,3*R*,4a*S*,8a*S*)-**28**.

$[\alpha]_D$= +246.64° (1.0 mg/ml in $CHCl_3$).

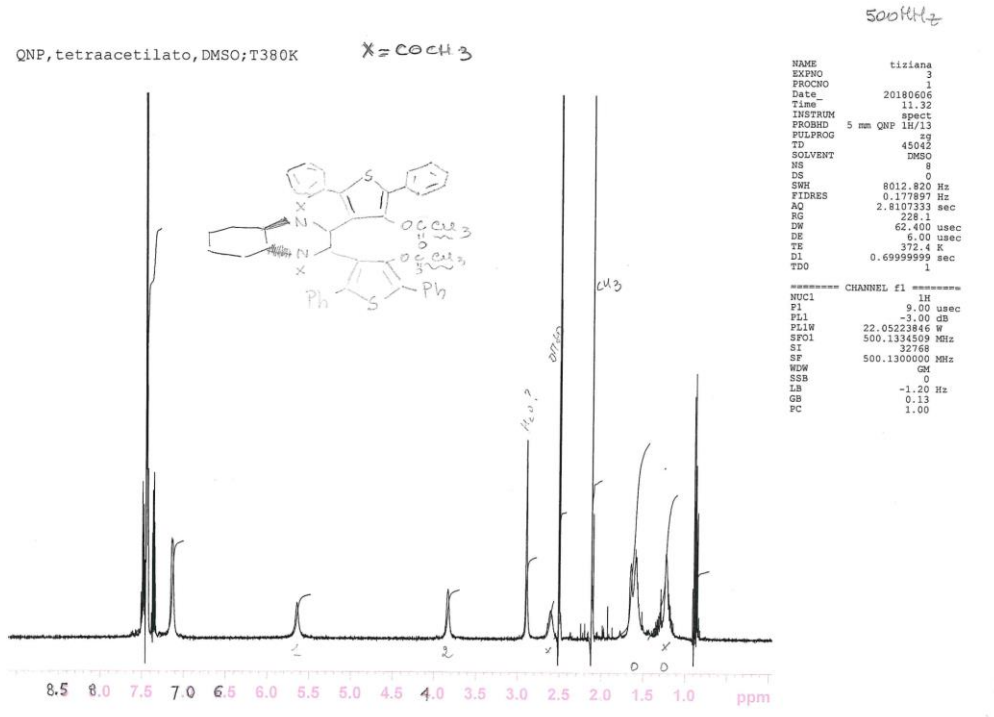
The diastereoisomeric purity of both the diastereoisomers was checked by chiral HPLC analysis in the following experimental conditions: column: IB-3 250 mm x 4.6 mm; mobile phase: *n*-hexane-EtOH-DEA 100/10/0.1; temperature: 40°C; flow rate: 1 ml/min; detector: CD at 280 nm.

Synthesis of the tetra-acetyl derivative 29



TEA (0.48 ml, 3.494 mmol, 7 eq) was added to a 0.1 M solution of (2*R*,3*R*,4a*S*,8a*S*)-(**28**) (320 mg, 0.499 mmol, 1 eq) in anhydrous CH_2Cl_2. The solution was cooled at -50°C and the acetyl chloride (0.25 ml, 3.494 mmol, 7 eq) was dropped, then the reaction was stirred at this temperature for 4 h. The mixture was warmed to room temperature, then a saturated $NaHCO_3$solution (5 ml) was added. The two phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 5 ml). The organic phases were collected and washed with a 5 % HCl solution to remove TEA, and then dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by gravimetric column chromatography (*n*-hexane/ethyl acetate 6:4) gave (2*R*,3*R*,4a*S*,8a*S*)-**29** (403 mg, 99%) as a pale yellow solid.

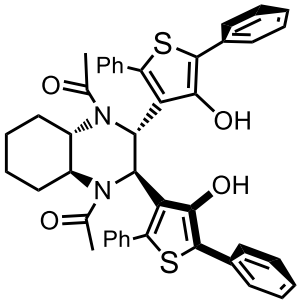
M.p.= 148-156°C.



The ^{1}H-NMR spectrum recorded in DMSO at 380 K using a 500 MHz spectrometer is reported: the presence of the acetyl groups on the position 3 of the thiophene rings is not well evident, however the ESI spectrum reported below confirmed their presence in the product.

m/z (ESI) 831.74 (MNa^+, 100%).

Synthesis of *N*,*N*'-diacetyl-(2*R*,3*R*,4a*S*,8a*S*)-2,3-bis(4-hydroxy-2,5-diphenylthiophen-3-yl) 1,4-deca-hydro-quinoxaline (25)



$LiBH_4$ (216 mg, 9.93 mmol, 15 eq) was slowly added to a solution of (2*R*,3*R*,4a*S*,8a*S*)-**29** (535 mg, 0.662 mmol, 1 eq) in THF (7 ml). The mixture was left under stirring for 16 h. The reaction mixture was then treated with of CH_2Cl_2 (20 ml) and washed with 1 M HCl solution (20 ml). The aqueous phase was then extracted with CH_2Cl_2 (3 x 20 ml). The organic phases were collected and then dried

($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (*n*-hexane/ethyl acetate 6:4) gave (2*R*,3*R*,4a*S*,8a*S*)-**25** (408 mg, 76%) as a white solid.

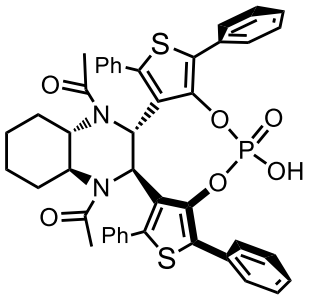
M.p.= 136-140°C.

^{1}H-NMR (300 MHz, $CDCl_3$, δ ppm): 7.78 (1H, bs), 7.734 (2H, d, *J* 8.4 Hz), 7.420 (2H, t, *J* 7.5 Hz), 7.35-7.25 (4H, m), 7.128 (2H, bs), 5.650 (1H, bs), 3.996 (1H, bs), 2.562 (1H, bs), 1.670 (1H, bs), 1.565 (3H, s), 1.265 (2H, s).

^{13}C-NMR (75,48 MHz, $CDCl_3$, δ ppm): 174.40, 146.86, 135.89, 133.94, 132.94, 130.18, 128.82, 128.73, 128.56, 127.39, 127.04, 126.71, 118.90, 59.67, 56.80, 32.64, 25.19, 22.16.

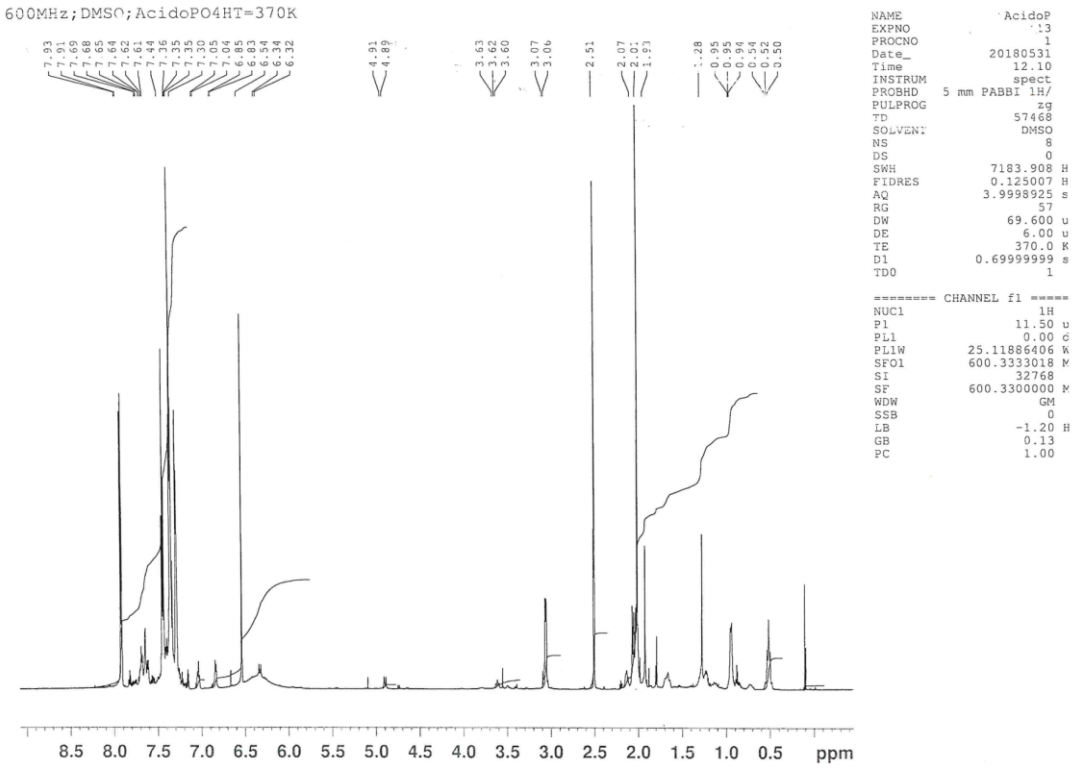
m/z (ESI) 723.99 (M^-, 100 %).

Synthesis of phosphoric acid (2*R*,3*R*,4a*S*,8a*S*)-19



A solution of $POCl_3$ (0.414 ml of a 0.99 M solution; 0.410 mmol of $POCl_3$, 2 eq) in dry CH_2Cl_2 (2 ml) was added dropwise at 0 °C to a solution of (2*R*,3*R*,4a*S*,8a*S*)-**25** (149 mg, 0.205 mmol, 1 eq) and dry TEA (0.199 ml, 1.435 mmol, 7 eq) in dry CH_2Cl_2 (2 ml), then the reaction mixture was stirred overnight at room temperature . CH_3CN (2 ml) and water (1 ml) were added and the reaction mixture was stirred for 4 h. Then $CH_2Cl_2$was added and the reaction mixture was washed with a 1 M HCl solution (20 ml). The aqueous phase was extracted with CH_2Cl_2 (2 x 20 ml). The organic phases were collected and then dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by flash column chromatography (CH_2Cl_2/MeOH 95:5) gave 1,1'-(9b*R*,10a*S*,14a*S*,15a*R*)-**19** (140 mg, 86%) as a pale yellow solid.

M.p.: 154-155°C.



The ^{1}H-NMR recorded in DMSO at 370 K using a 600 MHz spectrometer is reported.

^{13}C-NMR (600 MHz, DMSO, 370 K, δ ppm): 173.6 (CH), 142.8 (C), 136.4 (C), 134 (C), 132.1 (C), 131.3 (CH), 130.5 (C), 129.2 (CH), 128.8 (CH), 128.6 (CH), 128 (CH), 127.8 (CH), 126.8 (C), 58.4 (CH), 55.5 (CH), 27.5 (CH_2), 24.3 (CH_2), 23.7 (CH_3).

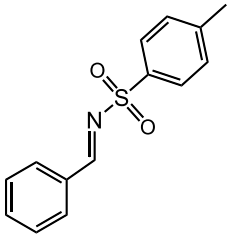
^{31}P-NMR (121.49 MHz, CDCl3, δ ppm): 63.697.

m/z (ESI) 786.07 (M^-, 100%).

2.4.3 Catalytic experiments with phosphoric acid 19

Synthesis of aryl *N*-tosyl imines (30a-d)

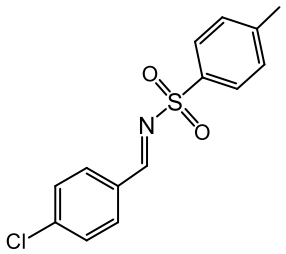
Synthesis of 30a



Benzaldehyde (1.02 ml, 10 mmol, 1 eq) was added to a solution of p-toluensulfonamide (1.7 g, 10 mmol, 1 eq) and sodium p-toluensulfinate (2 g, 11 mmol, 1.1 eq) in formic acid and water 1:1 (18 ml). The mixture was stirred at room temperature for 6 d, filtered and washed with water and *n*-hexane. The crude product was dissolved in CH_2Cl_2 and a $NaHCO_3$ saturated aqueous solution was added. The biphasic solution was stirred at room temperature for 2 h. The organic layer was separated, dried with Na_2SO_4 and the solvent was removed under reduced pressure, affording the pure imine **30a** in 72% yield (1.88 g).

^{1}H-NMR (300 MHz, $CDCl_3$, δ ppm): 9.02 (1H, s), 7.95-7.85 (3H, m), 7.60 (1H, t), 7.47 (2H, t), 7.33 (2H, d), 2.43 (3H, s).[45]

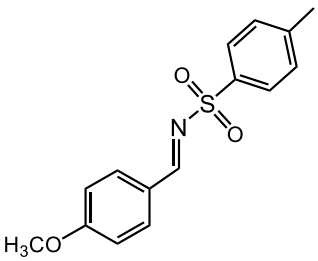
Synthesis of 30b



N-tosyl imine **30b** was synthesized as described for **30a** using p-toluensulfonamide (2.4 g, 14.2 mmol, 1 eq) and sodium p-toluensulfinate (2.8 g, 15.6 mmol, 1.1 eq) in formic acid and water 1:1 (47 ml). The product was obtained in 17% (690 mg).

^{1}H-NMR (300 MHz, $CDCl_3$, δ ppm): 9.01 (1H, s), 7.92-7.85 (3H, m), 7.48 (2H, d), 7.37 (2H, d), 2.45 (3H, s).[45]

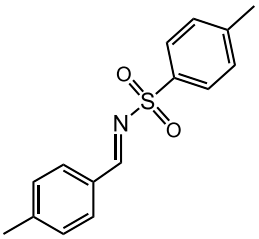
Synthesis of 30c



4-Methoxybenzaldehyde (2g, 14.7 mmol, 1 eq) was added to a solution of *p*-toluensulfonamide (2.5 g, 14.7 mmol, 1 eq) and *p*-toluensulfonic acid (0.029 g, 0.15 mmol, 0.01 eq) in toluene (30 ml). The resulting mixture was heated for 48 h with a Dean-Stark apparatus and then the solvent was evaporated under reduced pressure. The crude product was then dissolved in a minimum quantity of CH_2Cl_2 and recrystallized in Et_2O affording giving after filtration *N*-tosyl imine **30c** (63%, 2.7 g).

^{1}H-NMR (300 MHz, $CDCl_3$, δ ppm): 8.96 (1H, s), 7.93-7.85 (4H, m), 7.34 (2H, d), 6.98 (2H, d), 3.89 (3H, s), 2.43 (3H, s).[45]

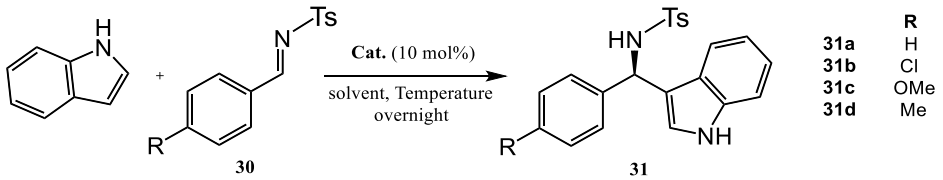
Synthesis of 30d



N-tosyl imine **30d** was synthesized as described for **30c** using 4-tolualdehyde (2 g, 16.6 mmol, 1.2 eq), *p*-toluensulfonamide (2.4 g, 13.9 mmol, 1 eq) and *p*-toluensulfonic acid (0.027 g, 0.139 mmol, 0.01 eq) in toluene (33 ml). The product was obtained in 31% yield (1.18 g).

^{1}H-NMR (300 MHz, $CDCl_3$, δ ppm): 9.01 (1H, s), 7.90 (2H, d), 7.84 (2H, d), 7.36 (2H, d), 7.30 (2H, d), 2.455 (3H, s), 2.451 (3H, s).[46]

Stereoselective Friedel-Crafts Alkylation



General procedure. The indole (0.5 mmol) and the phosphoric acid **19** (0.01 mmol) were dissolved in toluene (1 ml) under N_2 at the desired temperature (generally -50°C). The imine (**30**) (0.1 mmol)

was then added in one portion and the mixture was stirred overnight. A saturated $NaHCO_3$ solution (1 ml) was added to quench the reaction, and the organic phase was extracted with CH_2Cl_2 (5 ml). The organic layer was separated and dried (Na_2SO_4), the solvents were removed under reduced pressure and the residue was purified by flash chromatography (*n*-hexane/AcOEt 8:2) to afford the product (**31**). The phosphoric acid was recovered changing the eluent in CH_2Cl_2/MeOH 9:1. The conversion was evaluated by ^{1}H-NMR spectroscopy on the crude product and the stereoselectivity by CSP-HPLC analysis on the purified product.

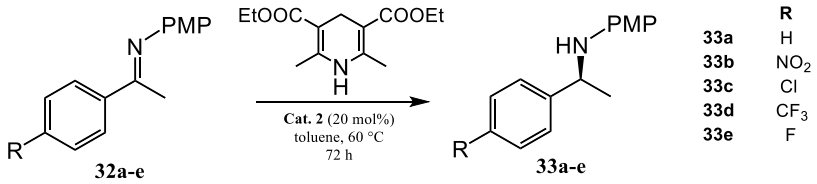
Sulfonamide 31a:[47] 96% yield, 53% ee [Daicel Chiralcel OD-H, Hex/IPA 7:3, 0.6 ml/min, λ = 254 nm, t (minor) = 12.313 min, t (major) = 21.975 min].
^{1}H-NMR (300 MHz, $CDCl_3$, δ ppm): 8.02 (1H, bs), 7.53 (2H, d, *J* 8.4 Hz), 7.11-7.27 (8H, m), 7.06 (2H, d, *J* 7.8 Hz), 6.97 (1H, t, *J* 7.8 Hz), 6.61 (1H, d, *J* 2.4 Hz), 5.82 (1H, d, *J* 6.9 Hz), 5.24 (1H, d, *J* 7.2 Hz), 2.34 (3H, s).

Sulfonamide 31b:[47] 38% yield, rac [Daicel Chiralcel OD-H, Hex/IPA 8:2, 0.8 ml/min, λ = 254 nm, t_1 = 11.84, t_2 = 21.63 min].
^{1}H-NMR (300 MHz, $CDCl_3$, δ ppm): 8.02 (1H, bs), 7.56 (2H, d, *J* 8.1 Hz), 7.31 (1H, d, *J* 8.4 Hz), 7.12-7.21 (8H, m), 7.01 (1H, t, *J* 7.2 Hz), 6.64 (1H, s), 5.82 (1H, d, *J* 6.6 Hz), 5.07 (1H, d, *J* 5.7 Hz), 2.39 (3H, s).

Sulfonamide 31c:[47] 94% yield, 24% ee [Daicel Chiralcel OD-H, Hex/IPA 6:4, 0.75 mL/min, λ 254 nm, t (minor) = 10.34 min, t (major) = 18.66 min].
^{1}H-NMR (300 MHz, $CDCl_3$, δ ppm): 8.01 (1H, br s), 7.57 (2H, d, *J* 8.3 Hz), 7.30 (1H, d, *J* 8.2 Hz), 7.16-7.21 (1H, m), 7.147.12 (5H, m), 6.99 (1H, td, J_1 0.9 Hz, J_2 8.0 Hz), 6.75-6.71 (3H, m), 5.79 (1H, d, *J* 6.7 Hz), 5.01 (1H, d, *J* 6.7 Hz), 3.77 (3H, s), 2.38 (3H, s).

Sulfonamide 31d:[47] 86% yield, 43% ee [Daicel Chiralcel OD-H, Hex/IPA 7:3, 0.8 ml/min, λ = 254 nm, t (minor) = 8.64 min, t (major) = 15.41 min,].
^{1}H-NMR (300 MHz, $CDCl_3$, δ ppm): 8.03 (1H, bs), 7.50 (2H, dd, J_1 1.8 Hz, J_2 8.1 Hz), 7.22 (2H, d, *J* 8.1 Hz), 7.12 (1H, d, *J* 7.2 Hz), 7.02-7.10 (4H, m), 6.92-6.96 (3H, m), 6.61 (1H, m), 5.76 (1H, d, *J* 7.2 Hz), 5.27 (1H, m), 2.33 (3H, s), 2.26 (3H, s).

Stereoselective Transfer Hydrogenation with Hantzsch Esters



General procedure: Imine (**32**) (0.1 mmol), the phosphoric acid **19** (20 mol%), the Hantzsch ester (0.2 mmol) and toluene (1.1 ml) were added to a screw-capped vial and the mixture was exposed to a N_2 atmosphere. The resulting solution was stirred at 60 °C for 3 days in the sealed vial. The solvent was evaporated in vacuo, and the residue was purified by column chromatography on silica gel (*n*-hexane/CH_2Cl_2 2:8) to afford the amine (**33**).

Amine 33a:[48] 91% yield, 28% ee [Daicel Chiralcel OD-H, Hex/IPA 98:2, 0.6 ml/min, λ = 210 nm, t (major) = 14.540 min, t (minor) = 15.843 min].
^{1}H-NMR (300 MHz, $CDCl_3$, δ ppm): 7.41-7.20 (5H, m), 6.72 (2H, d, *J* 9 Hz), 6.50 (2H, d, *J* 9 Hz), 4.44 (1H, q, *J* 6.6 Hz), 3.721 (3H, s), 1.53 (3H, d, *J* 6.6 Hz).

Amine 33b:[48] 71% yield, 10% ee [Daicel Chiralcel OD-H, Hex/IPA 98:2, 0.8 ml/min, λ = 254 nm, t (major) = 16.258 min, t (minor) = 17.669 min].
^{1}H-NMR (300 MHz, $CDCl_3$, δ ppm): 8.19 (2H, d, *J* 8.7 Hz), 7.56 (2H, d, *J* 8.7 Hz), 6.71 (2H, d, *J* 8.7 Hz), 6.42 (2H, d, *J* 8.7 Hz), 4.52 (1H, q, *J* 6.6 Hz), 3.71 (3H, s), 1.54 (3H, d, *J* 6.6 Hz).

Amine 33c:[48] 78% yield, 20% ee [Daicel Chiralcel OD-H, Hex/IPA 98:2, 0.5 ml/min, λ = 254 nm, t (major) = 22.954 min, t (minor) = 27.192 min].
^{1}H-NMR (300 MHz, $CDCl_3$, δ ppm): 7.32-7.25 (4H, m), 6.71 (2H, d, *J* 9 Hz), 6.46 (2H, d, *J* 9 Hz), 4.40 (1H, q, *J* 6.6 Hz), 3.72 (3H, s), 1.49 (3H, d, *J* 6.6 Hz).

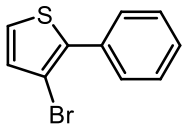
Amine 33d:[48] 60% yield, 21% ee [Daicel Chiralcel OD-H, Hex/IPA 98:2, 1 ml/min, λ = 254 nm, t (major) = 12.976 min, t (minor) = 16.320 min].
^{1}H-NMR (300 MHz, $CDCl_3$, δ ppm): 7.15 (2H, d, *J* 8.7 Hz), 7.06 (2H, d, *J* 8.7 Hz), 6.27 (2H, dd, J_1 9 Hz J_2 1.8 Hz), 6.01 (2H, dd, J_1 9 Hz J_2 1.8 Hz), 4.04 (1H, q, *J* 6.6 Hz), 3.35 (1H, s), 3.28 (3H, d, *J* 1.8 Hz), 1.09 (3H, dd, J_1 6.6 Hz J_2 1.8 Hz).

Amine 33e:[48] 89% yield, 20% ee [Daicel Chiralcel OD-H, Hex/IPA 98:2, 1 ml/min, λ = 254 nm, t (major) = 10.505 min, t (minor) = 11.982 min].

^{1}H-NMR (300 MHz, $CDCl_3$, δ ppm): 7.34 (2H, q, J_1 8.7 Hz J_2 5.7 Hz), 7.01 (2H, t, *J* 8.7 Hz), 6.71 (2H, d, *J* 9 Hz), 6.47 (2H, d, *J* 9 Hz), 4.41 (1H, q, *J* 6.6 Hz), 3.72 (3H, s), 1.50 (3H, d, *J* 6.6 Hz).

2.4.4 Synthesis of phosphoric acid 34

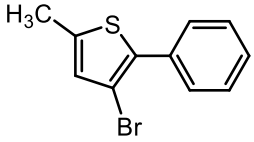
Synthesis of 3-bromo-2-phenylthiophene (38)



A suspension of 2,3-dibromothiophene (2 g, 8.26 mmol, 1 eq) in dry 1,4-dioxane (100 ml) and palladium tetrakis triphenylphosphine (0.9 g, 0.7 mmol, 0.10 eq.) was stirred for ten minutes under a N_2 atmosphere then phenylboronic acid (1.1 g, 9.08 mmol, 1.1 eq) and an aqueous 2 M $NaCO_3$ solution (17 ml) were added. The reaction was heated for 4 hours at 90°C. The reaction was cooled at room temperature and the 1,4-dioxane was removed under reduced pressure. The residue was extracted with CH_2Cl_2 (3 x 100 ml). The organic phases were collected, dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by gravimetric column chromatography (*n*-hexane) gave the 3-bromo-2-phenylthiophene[49] (**38**) (0.98 g, 50%) as a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 7.66 (2H, d, *J* 8 Hz), 7.41 (3H, m), 7.285 (1H, d, *J* 4 Hz), 7.065 (1H, d, *J* 4 Hz).

Synthesis of 3-bromo-5-methyl-2-phenylthiophene (40)

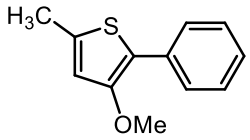


A solution of 3-bromo-2-phenylthiophene (**38**) (2.42 g, 9.9 mmol, 1 eq) in anhydrous THF (11 ml) was dropped slowly at -50°C under a N_2 atmosphere into a 2 M LDA solution (5.44 ml, 0.011 mmol,

1 eq.) and the mixture was left under stirring at the same temperature for 10 minutes. After the change of colour from yellow to deep green/blue, the temperature was cooled at -78°C, CH_3I (2.5 ml, 5 eq) was added. and the reaction mixture was stirred for 1 h. THF was removed under reduced pressure and the residue was extracted with CH_2Cl_2 (3 x 15 ml) and the organic phases were collected, washed with a 2% HCl solution, dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by gravimetric column chromatography (*n*-hexane) gave the 3-bromo-5-methyl-2-phenylthiophene (**40**) (1.5 g, 60%).

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 7.62 (2H, d, *J* 8 Hz), 7.37 (3H, m), 6.73 (1H, s), 2.48 (3H, s).[50]

Synthesis of 5-methyl-3-methoxy-2-phenylthiophene (41)



5-Methyl-3-methoxy-2-phenylthiophene (**41**) was synthesized as described for 3-methoxy-2,5-diphenylthiophene (**23**) starting from 3-bromo-5-methyl-2-phenylthiophene (**40**) (1.5 g, 5.92 mmol, 1 eq), NaOMe (prepared with 0.5 g of Na in 10 ml of dry CH_3OH), CuI (0.17 g, 1.16 mmol, 0.19 eq) in refluxing dry DMF (6 ml) for 1 h. DMF was removed under vacuo and the reaction residue was dissolved in CH_2Cl_2 (20 ml), filtered on celite and then washed with water (20 ml). The organic phase was separated, dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by gravimetric column chromatography (*n*-hexane : CH_2Cl_2 8/2) gave 5-methyl-3-methoxy-2 phenylthiophene (**41**) (0.87 g, 72%) as a brown oil.

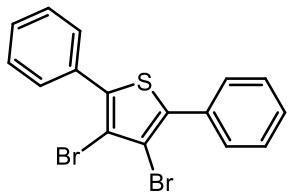
^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 7.60 (2H, d, *J* 8 Hz), 7.25 (2H, t, *J* 8 Hz), 7.09 (1H, t, *J* 8 Hz), 6.56 (1H, s); 3.79 (3H, s), 2.38 (3H, s).[51]

^{13}C-NMR (101 MHz, $CDCl_3$, δ ppm): 153.02 (C), 136.55 (C), 133.93 (C), 128.58 (CH), 126.62 (CH), 125.92 (CH), 117.62 (C), 116.31 (CH), 58.70 (OCH_3), 16.19 (CH_3).

2.4.5 Synthesis of diphosphinoxide 42

2.4.5.1 *First synthetic strategy*

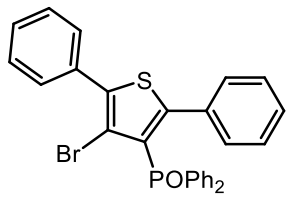
Synthesis of 3,4-bromo-2,5-diphenylthiophene (44)



3,4-Bromo-2,5-diphenylthiophene (**44**) was synthesized as described for 3-bromo-2,5-diphenylthiophene (**22**) starting from tetrabromothiophene (6 g, 15 mmol, 1 eq) with phenylboronic acid (3.66 g, 30 mmol, 2 eq), 20% Na_2CO_3 aqueous solution, palladium tetrakis triphenylphosphine (0.52 g, 0.45 mmol, 0.035 e.) in THF (60 ml). Then the THF was removed under reduced pressure and the residue was extracted with CH_2Cl_2 (3 x 100 ml). The organic phases were collected, washed with brine (200 ml) and then dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by gravimetric column chromatography (*n*-hexane) gave 3,4-bromo-2,5-diphenylthiophene[52] (**44**) (5 g, 85%) as a white solid.

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 7.59 (2H, d, *J* 7.2 Hz), 7.44-7.31 (3H, m).

Synthesis of 3-bromo-4-phosphinoyl-2,5-diphenylthiophene (45)



A 1.6 M *n*-BuLi solution (0.79 ml, 1.52 mmol, 1.2 eq) was dropped into a solution of 3,4-bromo-2,5 diphenylthiophene (**44**) (0.5 g, 1.27 mmol, 1 eq) under N_2 atmosphere at -40°C in the presence of TMEDA (0.28 ml, 1.90 mmol, 1.5 eq) in dry THF (5 ml). After 15 minutes, the chlorodiphenylphosphine (0.28 ml, 1.52 mmol, 1.2 eq.) was added slowly. The reaction mixture was left under stirring at 0°C for 16 h and then a 30% H_2O_2solution (3 ml) was added. After 2 h, the THF was removed under reduced pressure and the residue was extracted with CH_2Cl_2 (3 x 20 ml). The

organic phases were collected, dried ($MgSO_4$), filtered and concentrated reduced pressure. Purification by gravimetric column chromatography (CH_2Cl_2 : AcOEt 7/3) gave the 3-bromo-4-phosphinoyl-2,5-diphenylthiophene (**45**) (0.46 g, 71%).

M.p. = 182-184°C.

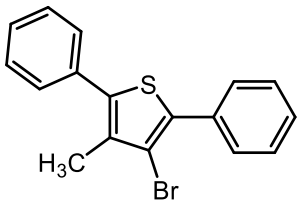
^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 7.53 (6H, m), 7.33 (3H, m), 7.27 (2H, m), 7.17 (4H, m), 7.05 (2H, d, *J* 8 Hz), 6.97 (1H, m), 6.89 (2H, m).

^{13}C-NMR (101 MHz, CDCl3, δ ppm): 153.81 (C), 153.69 (C), 139.90 (C), 139.79 (C), 133.82 (C), 132.74 (C), 132.46 (C), 132.44 (C), 132.12 (CH), 131.82 (CH), 131.72 (CH), 131.41 (CH), 131.38 (CH), 130.01 (CH), 129.74 (CH), 128.78 (CH), 128.56 (CH), 128.49 (CH), 128.28 (CH), 128.16 (CH), 127.70 (CH), 111.56 (C), 111.44 (C).

m/z (ESI) 515 (M^+, 100%).

2.4.5.2 *Second synthetic strategy*

Synthesis of 3-bromo-2,5-diphenyl-4-methylthiophene (47)



A 1.6 M solution of *n*-BuLi (2.56 ml, 4.1 mmol, 1.2 eq) was added dropwise into a solution of 3,4-bromo-2,5-diphenylthiophene (**45**) (1.36 g, 3.4 mmol, 1.2 eq) in dry THF (14 ml) under a N_2 atmosphere at -78°C. After 10 minutes CH_3I (1.06 ml, 17 mmol, 5 eq) was added dropwise and the reaction was left under stirring for 1 h maintaining the temperature at -78°C, and then at room temperature for 12 h. Then water was added, THF was removed under reduced pressure and the residue was extracted with CH_2Cl_2 (3 x 20 ml). The organic phases were collected, dried ($MgSO_4$), filtered and concentrated reduced pressure. The reaction crude was dissolved in *n*-hexane and filtered through a pad of silica giving pure 3-bromo-2,5-diphenyl-4-methylthiophene (**47**) (1.07 g, 94%).

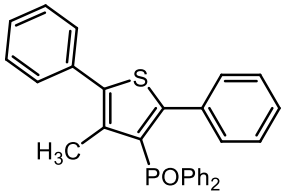
M.p. = 103.5 -103.6 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 7.60 (2H, d, *J* 7.6 Hz), 7.42-7.32 (6H, m), 7.33-7.24 (2H, m), 2.26 (3H, s).

^{13}C-NMR (101 MHz, $CDCl_3$, δ ppm): 137.31 (C), 136.63 (C), 134.26 (C), 133.66 (C), 133.42 (C), 129.21 (C), 129.15 (CH), 129.08 (CH), 128.90 (CH), 128.70 (CH), 128.58 (CH), 128.52 (CH), 128.32 (CH), 128.19 (CH), 127.90 (CH), 127.44 (CH), 125.54 (CH), 11.93 (C).

m/z (ESI) 328 (M^+, 100%).

Synthesis of 2,5-diphenyl-4-methyl-3-phosphinoylthiophene (48)

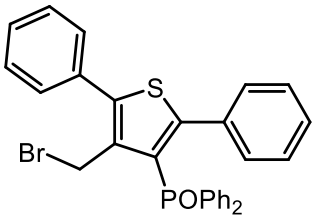


A 1.6 M solution of *n*-BuLi (0.302 ml, 1.7 mmol, 1.2 eq) was added dropwise into a solution of 3-bromo-2,5-diphenyl-4-methylthiophene (**47**) (0.472 g, 1.4 mmol, 1 eq.) in dry THF (4.72 ml) under a N_2 atmosphere at -40°C. After 5 minutes chlorodiphenylphosphine (0.312 ml, 1.7 mmol, 1.2 eq.) was added dropwise and the reaction was warmed to room temperature and stirred for 2 h. Then, a 30% H_2O_2 solution (2.8 ml) was added and the reaction mixture left under stirring for further 2 h. The THF was removed under reduced pressure and the residue was extracted with CH_2Cl_2 (3 x 20 ml). The organic phases were collected, dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by gravimetric column chromatography (CH_3Cl : AcOEt 7/3) gave the 2,5-diphenyl-4-methyl-3-phosphinoylthiophene (**48**) (0.48 g, 76%).

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 7.53-7.48 (4H, m), 7.35-7.26 (4H, m), 7.24-7.19 (3H, m), 7.17-7.15 (4H, m), 7.00-6.99 (2H, m), 6.93-6.91 (1H, m), 6.85-6.82 (2H, m), 2.09 (3H, s).

m/z (ESI) 450 (M^+, 100%).

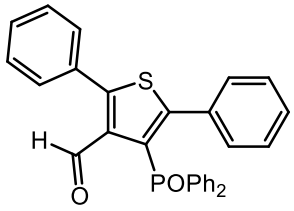
Synthesis of 4-bromomethyl-2,5-diphenyl-3-phosphinoylthiophene (49)



A mixture of 2,5-diphenyl-4-methyl-3-phosphinoylthiophene (**48**) (1.24 g, 2.7 mmol, 1.0 eq), NBS (0.53 g, 2.97 mmol, 1.1 eq) and AIBN (3.4 mg, 0.021 mmol, 0.008 eq.) in CCl_4 (62 ml) was refluxed for 4 h. The reaction mixture was then washed with a 10% NaOH solution, the aqueous phase was then extracted with CH_2Cl_2 (2 x 50 ml). The organic phases were collected, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude reaction (1.37 g) was utilised without further purification for the next reaction.

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 7.67 (2H, d, *J* 7.2 Hz), 7.62-7.53 (4H, m), 7.53-7.38 (6H, m), 7.35-7.29 (3H, m), 7.06 (1H, t, *J* 6.8 Hz), 7.00-6.88 (4H, m), 5.00 (2H, s).

Synthesis of 2,5-diphenyl-4-formyl-3-phosphinoylthiophene (43)



A solution of 4-bromomethyl-2,5-diphenyl-3-phosphinoylthiophene (**49**) (1.36 g, ≈2.6 mmol, 1 eq) in dry CH_3CN (40 ml) was added dropwise into a solution of *N*-methyl-morpholine-*N*-oxide (0.95 g, 8.1 mmol, 3.1 eq) in anhydrous CH_3CN (130 ml) at 0°C under N_2 atmosphere in the presence of 5 A° molecular sieves (50 g). The reaction was warmed at room temperature and kept under slow stirring for 16 h. CH_3CN was removed under residue pressure and the residue was extracted with AcOEt (3 x 50 ml). The organic phases were collected, dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by gravimetric column chromatography ($CHCl_3$: AcOEt 8.5/1.5) gave 2,5-diphenyl-4-formyl-3-phosphinoylthiophene as a white solid (**43**) (0.55 g, 46%).

M.p. = 171-173°C.

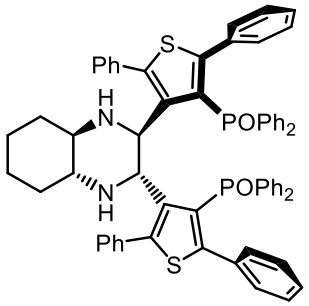
^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 9.75 (s, 1H), 7.60-7.45 (m, 4H), 7.42-7.35 (m, 2H), 7.25-7.05 (8H, m), 6.98 (1H, t, *J* 7.6 Hz), 6.89 (1H, t, *J* 7.2 Hz).

^{13}C-NMR (101 MHz, CDCl3, δ ppm): 185.45 (COH), 154.50 (C, d, *J* 11 Hz), 154.43 (C, d, *J* 11 Hz), 139.15 (C, d, *J* 12 Hz), 134.46 (C), 134.38 (C), 131.95 (C, d, *J* 2.6 Hz), 131.42 (CH), 131.36 (CH), 131.32 (CH),

131.05 (C), 130.16 (CH), 130,13 (CH), 129.62 (CH), 129.15 (C), 128.82 (CH), 128.68 (CH), 128.29 (CH), 128.17 (CH), 127.92 (CH).

m/z (ESI) 464 (M^+, 100%).

Synthesis of diphosphinoxyde 42



The (*R*,*R*)-*trans*-diaminocyclohexane (29.6 mg, 0.26 mmol, 1 eq) was added to a solution of 2,5-diphenyl-4-formyl-3-phosphinoylthiophene (**43**) (250 mg, 0.54 mmol, 2.05 eq) in toluene (1.6 ml) and the solution was refluxed for 4 h and then warmed to room temperature. The conversion of the substrate to the imine intermediate was checked through ^{1}H-NMR spectroscopy. Anhydrous CH_3CN (15 ml) was added to the reaction mixture to achieve a solution with a CH_3CN/toluene 9:1 ratio. Manganese powder (36 mg, 0.65 mmol, 2.5 eq) was added, then the temperature was cooled at 0 °C and TFA (0.1 ml, 1.3 mmol, 5 eq). was added dropwise. The reaction mixture was stirred at room temperature for 24 h and quenched with water (15 ml). CH_3CN was removed under reduced pressure and the residue was extracted with CH_2Cl_2 (3 x 20 ml). The organic phases were collected, dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by flash column chromatography (first CH_2Cl_2/EtOAc 3:7 in order to remove the unreacted aldehyde (**43**), then CH_2Cl_2/CH_3OH 95:5) gave a crude (170 mg) in which the presence of diphosphinoxide **42** was confirmed by mass spectroscopy [*m/z* (ESI) 1009 (M^+)].

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3. Development of chiral phosphoramidites in catalysis

3.1 Introduction

Another class of chiral promoters interesting for this research project is that of phosphoramidites, which require the employment of transition metals when applied in catalysis, differently from the previously discussed Lewis bases and Brønsted acids.

Phosphoramidites belong to the family of the amides of trivalent phosphorus acid H_3PO_3. In particular they contain one P-N and two P-O bonds. Both the phosphorous and the nitrogen atoms have an unshared pair of electrons which are potential metal-binding sites. X-ray analysis[1] revealed two important general features about phosphoramidites structure: the phosphorous atom displays a psudotetrahedral geometry whereas the nitrogen atom is usually trigonal planar, indicating a sp^2 hybridisation.

The electronic properties of phosphorous ligands can be distinguished in terms of their π-accepting and σ-donating features. Generally, it has been observed that the property of phosphorous compounds to act as a π-acceptors increases according to the electronegativity of the substituents on the phosphorous atom. Hence, phosphoramidites stay between the weaker π-acceptors (such as phosphines) and the stronger ones (for example phosphites, having three P-O bonds).

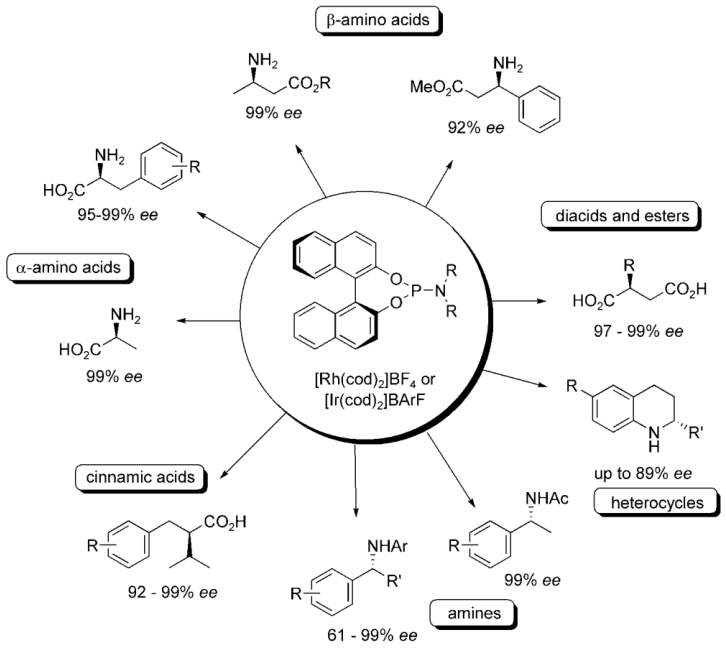
As anticipated, asymmetric catalysis promoted by chiral transition metal complexes is an alternative way for performing a wide range of successful stereoselective transformations.

In the last few decades, a huge number of stereoselective catalysed transformations have been investigated, most of all using bidentate chiral promoters.[2] The reason of their success in asymmetric catalysis resides in the fact that they are able to strongly reduce the conformational freedom in the metal (M)-ligand (L) complexes giving excellent enantioselectivities in hydrogenation reactions.

In particular, the synthesis and the application of the bidentate chiral phosphine DIOP introduced by Kagan and Dang in 1971,[3] which represent the first chiral diphosphine employed in asymmetric catalysis, opened the way to a vast use of bidentate ligands in the field. Furthermore, the application of DiPAMP for the enantioselective synthesis of L-DOPA,[4] which even allowed Knowles to win the Nobel prize for chemistry in 2001, confirmed the supremacy of bidentate phosphorous ligands in asymmetric catalysis.

However, despite the success of bidentate chiral promoters, some applications of chiral monodentate ligands were also reported,[2d, 5] until a significant breakthrough was given in 1994 by Feringa,[6] who introduced and developed chiral phosphoramidites. More specifically, their remarkable potentialities as chiral promoters were discovered two years later, when the same Author reported the enantioselective copper-catalysed conjugate addition of dialkyl zinc reagents to enones using BINOL-based phosphoramidites.[7] Hence, after the excellent enantioselectivities achieved with a simple monodentate ligand in this important enantioselective C-C formation reaction, the number of stereoselective chiral monodentate ligands catalysed reactions increased more and more, questioning for the first time the diffused dogma that high flexibility in the M-L complexes is a disadvantageous property for obtaining high stereocontrol.

Then, in 2000, Feringa and de Vries demonstrated that phosphoramidites are also very efficient chiral promoters for asymmetric hydrogenations,[8] obtaining very high enantioselectivities, comparable with those observed with the most selective bidentate diphosphines in rhodium-catalysed hydrogenation. In addition, several other successful hydrogenation reactions were reported proving that phosphoramidite ligands are particularly versatile in asymmetric hydrogenations, and the transformations summarized in Scheme 1[9] are explicative of the broad scope (α- and β-amino acids, diacids and esters, cinnamic acids, amines, and various heterocyclic compounds) and excellent enantioselectivities achieved with these monodentate ligands.[10]

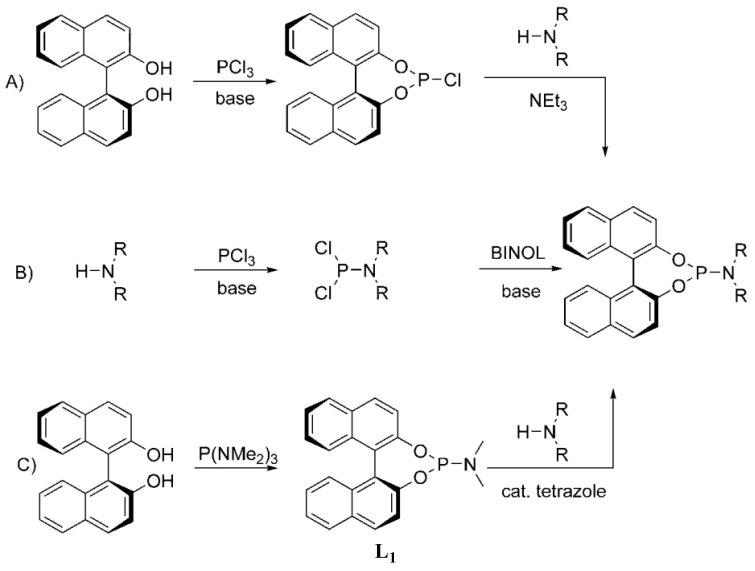


Scheme 1

Furthermore, the contribution given in 2000 by the research groups of Reetz[11] and Pringle[12] independently, for the use of another class of new chiral phosphorous monodentate ligands for asymmetric hydrogenation, the phosphonites, and by Reetz and Mehler[13] for what concern phosphites, represented a further revenge by monodentate ligands in the field of asymmetric catalysis, since they exhibited outstanding catalytic activity and enantioselection ability as rhodium ligands in enantioselective hydrogenation reactions.

In the field of monodentate phosphorous based ligands, phosphoramidites have been widely employed in asymmetric catalysis since they are generally air stable and easy to handle. In addition, their design is very versatile since both the diolic and the amminic portion can be modified allowing a fine-tuning of the stereo-electronic features of the ligand (and consequently the electronic properties at the metal centre) according to the specific catalytic application.

Indeed, three different synthetic strategies have been developed reported in Scheme 2,[9] as an example, for the synthesis of BINOL-derived phosphoramidites.



Scheme 2

The most used approach contemplates the synthesis of a chlorophosphite as intermediate starting from an appropriate diol reacting with $POCl_3$ (Pathway A, Scheme 2), followed by reaction with the desired amine in basic conditions.

If the phosphoramidite is characterized by a more sterically hindered amine, the synthesis involves the formation of a dichloroaminophosphine as intermediate and the subsequent reaction with the diol (Pathway B, Scheme 2).

The third approach consists in the reaction between the diol with the hexametylphosphorous triamide (HMPT) to achieve the dimethylamine-derived phosphoramidite known as MonoPhos (**L_1**).[6] The new formed phosphoramidite can be either used itself as a chiral promoter in asymmetric catalysis or it can be subjected to an amine exchange under basic conditions to afford different chiral ligands (Pathway C, Scheme 2).[14]

A large library of phosphoramidites was easily prepared as low-priced chiral ligands (Figure 1) due to the availability of high yielding synthetic strategies starting from easily obtained substrates.

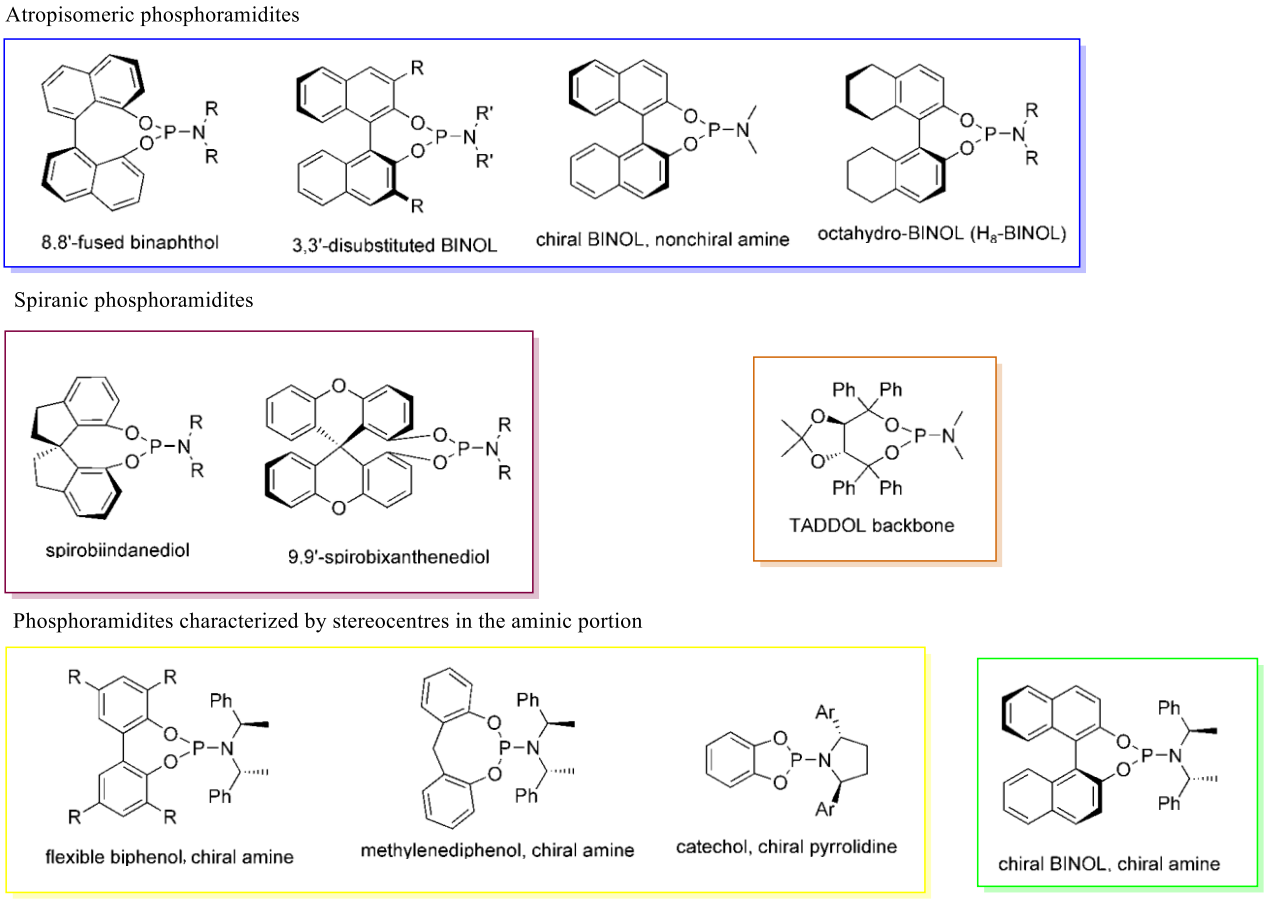
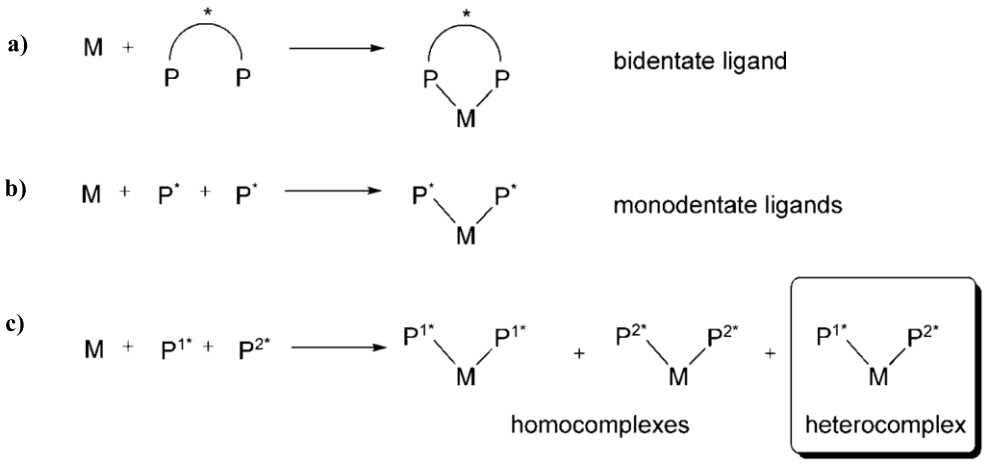


Figure 1

An outstanding feature of phosphoramidite ligands is that the stereodiscrimination can be related to one or more stereogenic elements that can be located both on the diolic and the amminic portion. Concerning the diolic portion, generally the stereogenic element is a stereogenic axis belonging to either an atropisomeric (Figure 1, blue box) or a spiranic structure (violet box). TADDOL based phosphoramidite represents an exception being characterized by the presence of two stereocentres on the diolic framework (orange box). When the diolic portion is flexible (such as in biphenol or methylenediphenol derivatives) or anyway lacking of stereogenic elements, the synthesis of an enatiopure phosphoramidite requires a chiral amine (yellow box).

Finally, phosphoramidites can be also synthesized starting from an atropisomeric diol and a chiral amine (green box).

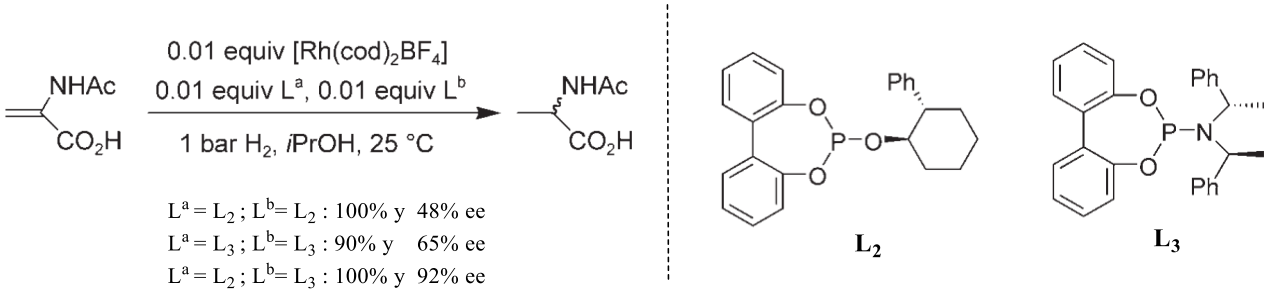
The supremacy in asymmetric catalysis of diphosphines and related bidentate ligands (bisoxazolines, diols, phoshine-oxazolines, etc.) was due to the formation of a very low-flexible and efficient Metal-ligand complex (Scheme 3a).[9]



Scheme 3

Phosphoramidites, as well as monodentate ligands in general, can generate two different kind of complexes as reported in Scheme 3. Indeed, beside the formation of homocomplexes, where two identical units of chiral promoter bond to the metal (Scheme 3b), also the formation of heterocomplexes is possible in which two different monodentate ligands can be accommodated on a single metal centre (Scheme 3c). It was demonstrated that more efficient catalysts can be achieved using a combination of chiral promoters.[15a-c, e]

For example, better enantioselectivities were achieved working with heterochiral complexes in the Rh-catalysed hydrogenation reaction of 2-acetamidoacrylate using a combination of a tropos chiral phosphite with a tropos chiral phosphoramidite (Scheme 4).[16]

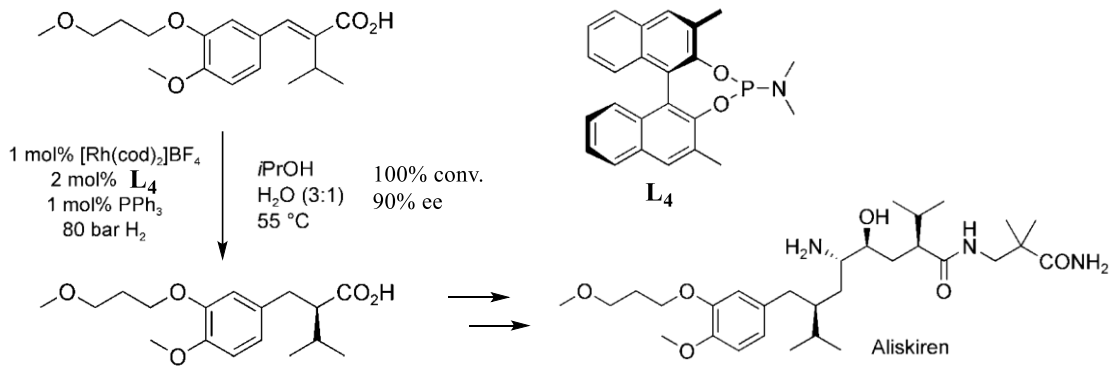


Scheme 4

In particular it was found that using only the chiral phosphite **L_2** or only the phosphoramidite **L_3**, lower yields and enantioselectivities were obtained respect those achieved by employing both chiral promoters in a 1:1 mixture (Scheme 4).

An important extension of this behaviour is also the use of mixtures of chiral monodentate phosphoramidites and achiral ligands, as demonstrated by Feringa and co-workers in several hydrogenation reactions.[17]

One of the most important examples is the asymmetric hydrogenation of the cinnamic acid shown in Scheme 5, to afford a useful intermediate for the synthesis of Aliskiren.[15f] In this case, while the employment of homochiral phosphoramidite ligands gave low enantioselectivities (<16% ee), the combination of chiral **L_4** with achiral PPh_3 allowed to obtain the desired intermediate with complete conversion and very high enantioselection levels (90% ee, Scheme 5).

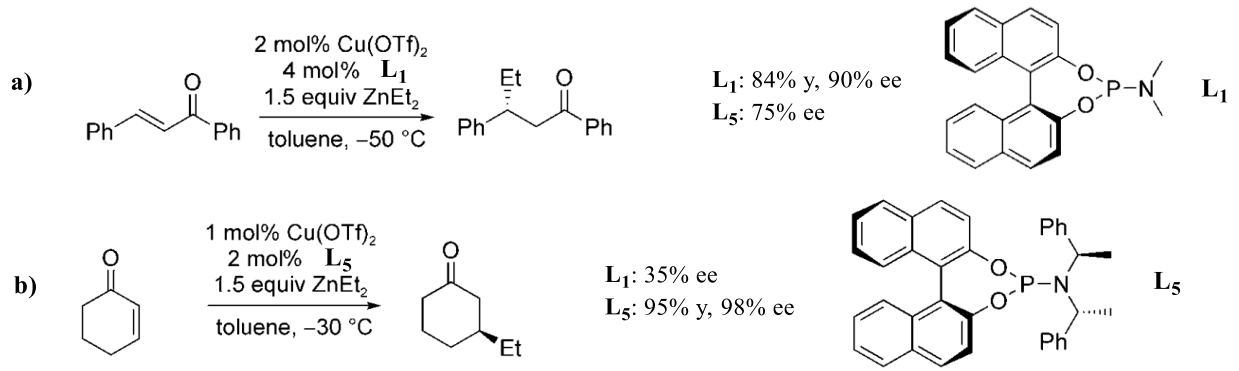


Scheme 5

As mentioned before, another important stereoselective transformation promoted by phosphoramidites, that was reported for the first time in 1996, is the copper-catalysed conjugate addition of dialkyl zinc reagents to Michael acceptors. Initially, high yields and very good enantioselectivities (up to 90%) were obtained in the addition of diethylzinc to calchone employing a BINOL-derived phosphoramidite ligand (MonoPhos, **L_1**, Scheme 6a) in the presence of a Cu(II) salt.[7a] The process was improved in subsequent studies by lowering the catalyst loading (from 4 mol% to 2 mol%) and by employing and optimise metal/ligand ratios (1:2).[7b]

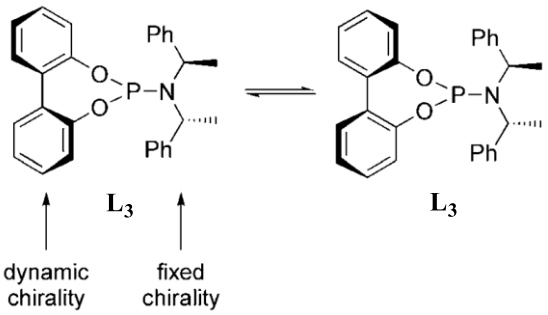
A great increase in the enantioselectivity of the 1,4-addition reactions was observed when an amminic portion characterized by the presence of stereocentres was incorporated in the BINOL-derived phosphoramidites. Indeed, excellent yields (up to 95%) and >98% ee were obtained when the 2-cyclohexenone was reacted with Et_2Zn in the presence of $Cu(OTf)_2$ and of the bis(1-

phenylethyl)amine-derived **L_5** (Scheme 6b).[7b] It must be noted that when **L_5** was employed for the 1,4-addition of Et_2Zn to calchone, a moderate 75% ee was observed (Scheme 6a) respect to a 90% ee displayed by the simpler MonoPhos (**L_1**), proving that not always the presence of more than one stereogenic element is beneficial in order to reach best reaction outcomes, because of matched/mismatched effects.



Scheme 6

Furthermore, at the beginning of the years 2000, it was also demonstrated that the presence of a stereogenic axis in the diolic portion is not necessary to achieve remarkable results in the asymmetric 1,4-addition reactions.[18] A new chiral tropos phosphoramidite with a configurationally flexible biphenylic diolic portion was developed (Scheme 7).



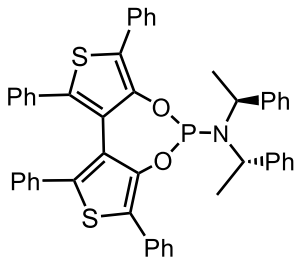
Scheme 7

This new chiral promoter was deeply applied in several experiments of enantioselective 1,4-additions to different kind of Michael acceptors varying the solvent and the Cu(II) source, achieving, quantitative yields (in almost all cases) and up to 96% ee of enantioselectivity.[18b]

3.2 Results and Discussion

On the basis of the excellent results given by **L_3**, our group synthesized in recent years the first chiral heterocyclic *tropos* phosphoramidite based on the 3,3'-bithiophenic scaffold thanks to the experience acquired in the synthesis of analogue chiral promoters.[19]

In particular, in a previous PhD Thesis,[20] the synthesis of phosphoramidite **L_6** (Figure 2) was successfully investigated and set up.



L_6

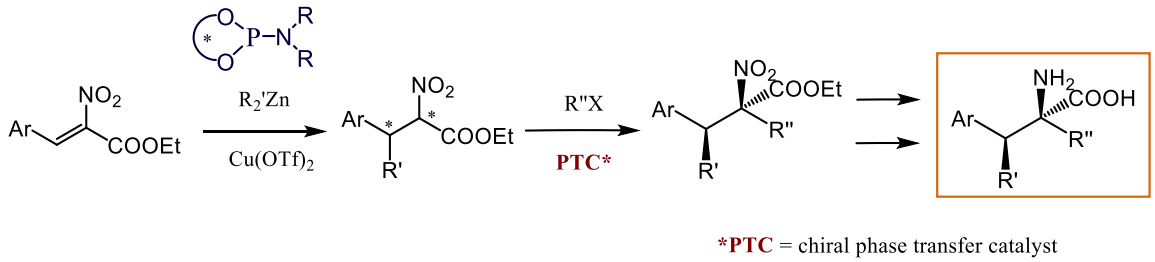
Figure 2

One of the objectives of my research project was to resynthesize **L_6** in order to check its potential role in some preliminary catalytic stereoselective transformations such as the Cu(II)-catalysed 1,4-additions of Et_2Zn to cyclic enones and ethyl 3-aryl-2-nitropropenoates.[21]

In particular, the last transformation is an interesting application since the reaction products could be useful intermediates for the synthesis of non-proteogenic α,α-disubstituted-α-amino acids Scheme 8), compounds displaying several interesting properties. Indeed, they exhibit increased configurational stability respect to the conventional amino acids due to the presence of a quaternary stereocentre.

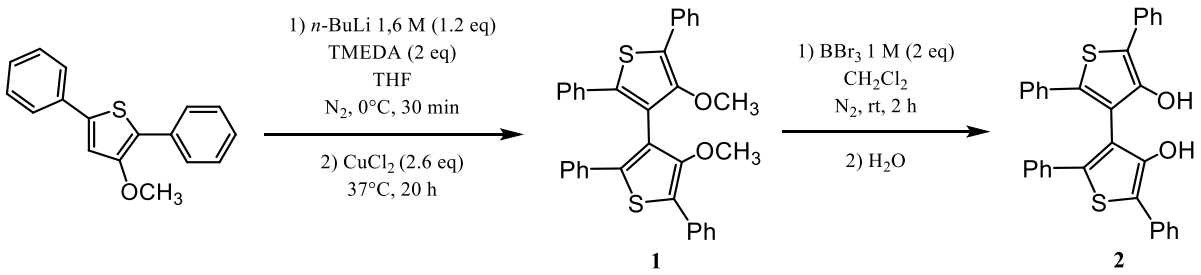
In addition, they can be employed in the design of new peptides or incorporated in peptides already existing producing peptide chains endowed with new features, and also they can play a role as enzymatic inhibitors.

Finally, they represent new building blocks for the synthesis of biologically active compounds, probably with higher half-life respect to the natural agonists.



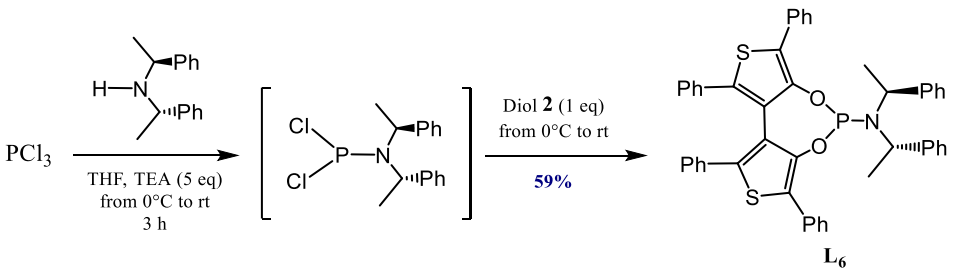
Scheme 8

The synthesis of **L6** starts from the already described (Chapter 2) 3-methoxy-2,5-diphenylthiophene (Scheme 9). The coupling promoted by Cu(II) of the related anions, generated by reaction with *n*-BuLi and TMEDA, afforded the 2,2',5,5'-tetraphenyl-4,4'-dimethoxy-3,3'-bithiophene (**1**) in 32% yield. The dimethoxyderivative **1** was demethylated under standard experimental conditions by using a 1.0 M solution of BBr_3 in CH_2Cl_2, obtaining 2,2',5,5'-tetraphenyl-4,4'-dihydroxy-3,3'-bithiophene (**2**) in 56% yield (Scheme 9).



Scheme 9

Phosphoramidite **L6** was synthesized in a one-pot two steps process: the formation of the chiral dichloroaminophosphine, by reaction of (*S*,*S*)-bis-(1-phenylethyl)amine with PCl_3, followed by slow addition of the diol **2** (Scheme 10). This procedure is in agreement with the previously described one,[20] however the formation of the phosphorous intermediate was performed in milder experimental conditions (from 0°C to rt for 3 h instead of 70°C for 6 h) improving the yield from 36 to 59%.



Scheme 10

^{31}P-NMR, ^{1}H-NMR experiments besides HPLC analysis performed at different temperatures demonstrated that **L_6** is constituted by a configurationally flexible diolic portion at room temperature, showing the presence of two diastereoisomers in 6:1 ratio (Figure 3).[20]

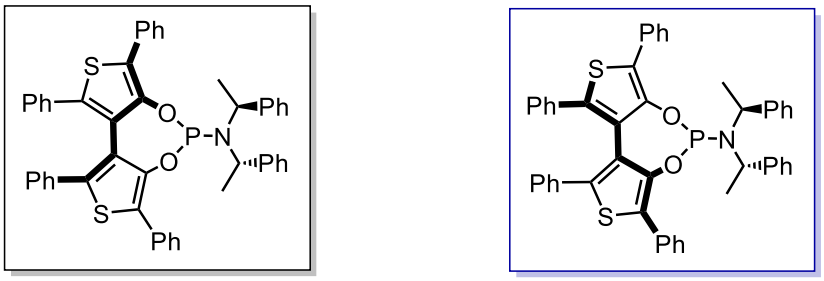
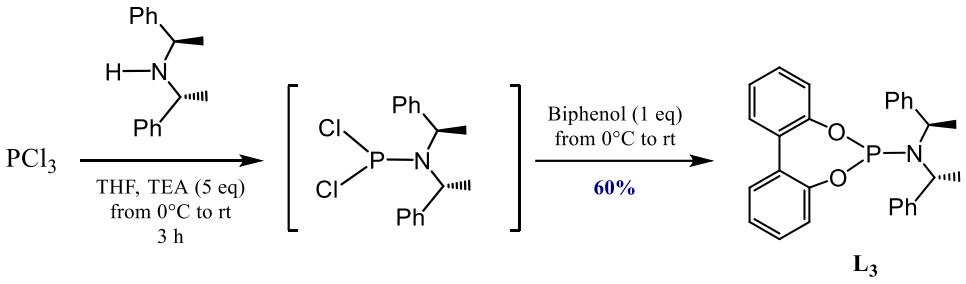


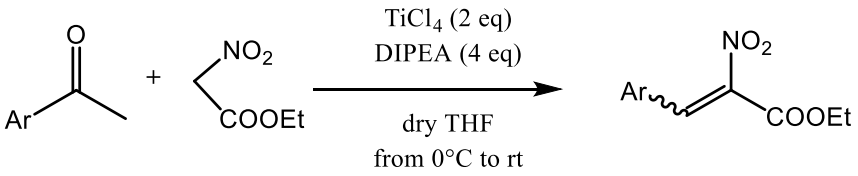
Figure 3

In order to compare chiral *tropos* heterocyclic **L_6** to a similar phosphoramidite reported in literature, **L_3** was synthesized following the same synthetic protocol employing the (*R*,*R*)-bis-(1-phenylethyl)amine (Scheme 11).



Scheme 11

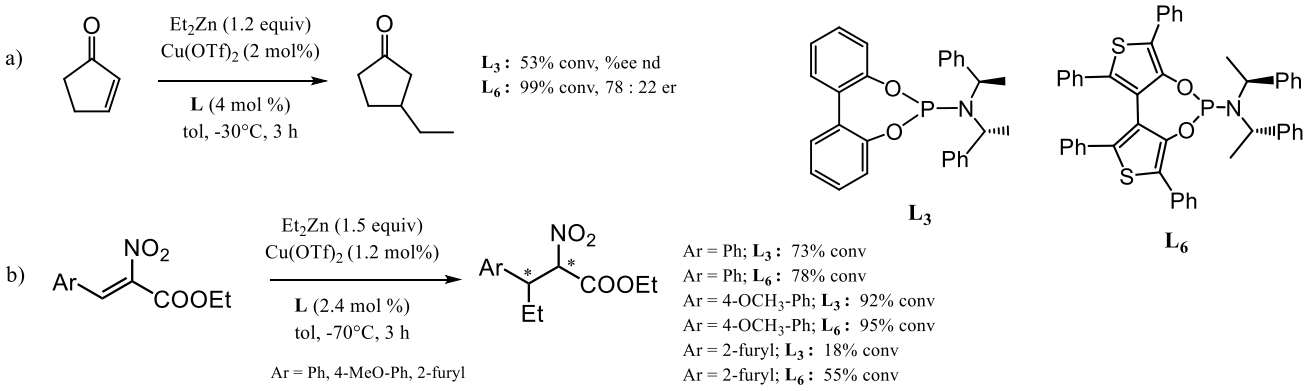
Different ethyl 3-aryl-2-nitropropenoates were prepared by exploiting a Knoevenagel condensation between an aromatic (or heteroaromatic) aldehyde and the ethyl nitroacetate in the presence of $TiCl_4$ as Lewis acid and the DIPEA as base (Scheme 12). Following this procedure, five aryl-nitroalkenes were synthesized with moderate to good yields in similar diastereoisomeric ratio.



Ar	Yield (%)	Z/E
Ph-	37	2
4-OCH_3-Ph-	76	1.4
4-NO_2-Ph-	30	3.5
4-Cl-Ph-	33	2
2-furyl-	65	2

Scheme 12

Then, preliminary experiments of stereoselective catalysed 1,4-additions of diethyl zinc to 2-cyclopenthenone and three different substituted nitroalkenes were carried out (Scheme 13).



Scheme 13

Our chiral promoter **L_6** showed very good catalytic activity resulting to be in some cases more active than **L_3**. However, a moderate conversion (55%) was obtained when the reaction was carried out on the 2-furyl-nitroalkene, where unfortunately, starting from pure *Z*-diastereoisomer the formation of the *E* one was observed.

Concerning the stereoselection ability, a moderate 78 : 22 er was determined by HPLC on a chiral stationary phase for the product related to the 1,4-addition of Et_2Zn to 2-cyclopentenone.

The ability of **L_6** as chiral promoter in the addition reactions to nitroalkenes is still under investigation and more experiments must be carried out in order to clarify the stereochemical outcome of these transformations not exhaustively described in literature.[21]

3.3 Conclusions

A new heterocyclic 3,3'-bithiophene based phosphoramidite was for the first time employed in some preliminary experiments of stereoselective catalysed 1,4-additions of diethyl zinc performed both on enones and trisubstituted nitroalkenes.

The new heteroaromatic ligand showed good catalytic activity while its stereoselection ability is still under investigation.

3.4 Experimental Section

3.4.1 General information

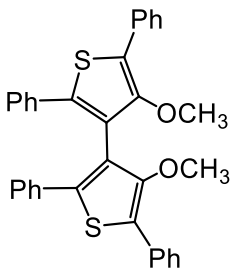
Reactions were monitored by analytical thin-layer chromatography (TLC) using silica gel 60 F_{254} pre-coated glass plates (0.25 mm thickness) and visualized using UV light. Flash chromatography was carried out on silica gel (230-400 mesh).

^{1}H-NMR spectra were recorded on spectrometers operating at 300 MHz (Bruker Fourier Advanced 300), 400 and MHz (Bruker AVANCE 400 spectrometer); proton chemical shifts are reported in ppm (δ) with the solvent reference relative to tetramethylsilane (TMS) employed as the internal standard ($CDCl_3$ δ = 7.26 ppm) and coupling constants are reported in Hertz (Hz). Splitting patterns are indicate as follows: s = singlet, d = doublet, t = triplet, q = quartet, qn = quintuplet, m = multiplet, bs = broad singlet, dd = double doublet. ^{31}P-NMR spectra were recorded on 300 MHz spectrometers (Bruker Fourier Advanced 300) at 121.4 MHz and were referenced to phosphoric acid (H_3PO_4) at 0.0 ppm.

Melting point determinations were performed by using a Buchi B-540 instrument.

3.4.2 Synthesis of the phosphoramidites L_6 and L_3

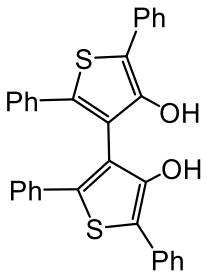
Synthesis of 2,2',5,5'-tetraphenyl-4,4'-dimethoxy-3,3'-bithiophene (1)



A 1.6 M *n*-BuLi solution in hexane (2.81 ml, 1.2 eq.) was added dropwise to a mixture of 2,5-diphenyl-3-methoxythiophene (1 g, 3.75 mmol, 1 eq.) and TMEDA (1.124 ml, 7.5 mmol, 2 eq.) in dry THF (10 ml), at 0°C and under N_2 atmosphere; after 30 minutes, dry $CuCl_2$ (1.31 g, 9.75 mmol, 2.6 eq.), contained in another flask connected to the reaction system through a tube, was rapidly added at 10°C and the reaction mixture was warmed at 37°C for 20 hours. The solvent was removed *in vacuo* and the crude was diluted with CH_2Cl_2 (15 ml) and extracted with a 5% HCl solution (15 ml), a saturated $NaHCO_3$ solution (15 ml) and water (15 ml); the organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography (*n*-hexane/CH_2Cl_2 8:2) gave 2,2',5,5'-tetraphenyl-4,4'-dimethoxy-3,3'-bithiophene in 32% yield.

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 7.81 (2H, d, *J* 7.2 Hz), 7.42 (2H, t, *J* 7.5 Hz), 7.32-7.12 (6H, m), 3.52 (3H, s).[20]

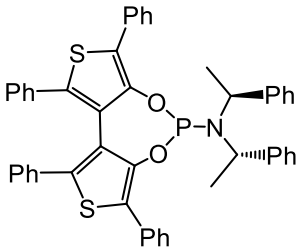
Synthesis of 2,2',5,5'-tetraphenyl-4,4'-dihydroxy-3,3'-bithiophene (2)



BBr_3 (1.0 M solution in CH_2Cl_2, 1.202 ml, 2 eq.) was added to a stirred solution of 2,2',5,5'-tetraphenyl-4,4'-dimethoxy-3,3'-bithiophene (0.319 g, 0.601 mmol, 2 eq.) in dry CH_2Cl_2 (4 ml), under N_2 atmosphere; after 2 hours water (6 ml) was added and the reaction mixture was stirred for further 30 minutes. The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. Flash chromatography (*n*-hexane/CH_2Cl_2 1:1) afforded the 2,2',5,5'-tetraphenyl-4,4'-dihydroxy-3,3'-bithiophene in 56% yield.

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 7.77 (2H, d, *J* 7.2 Hz), 7.42 (2H, t, *J* 7.5 Hz), 7.37-7.21 (6H, m).[20]

Synthesis of the phosphoramidite L_6[20]

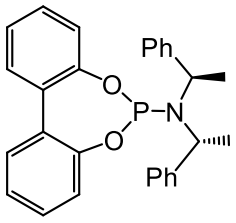


A solution of (*S*,*S*)-bis-(1-phenylethyl)amine (0.77 ml, 0.338 mmol, 1 eq.) in THF (0.4 ml) was added to a stirred mixture of TEA (0.234 ml, 1.69 mmol, 5 eq.) and PCl_3 (0.029 ml, 0.338 mmol, 1 eq.) in anhydrous THF (0.5 ml) at 0°C, and the reaction mixture was stirred for 3 h at room temperature. A solution of 2,2',5,5'-tetraphenyl-4,4'-dihydroxy-3,3'-bithiophene (0.170 g, 0.338 mmol, 1 eq.), in anhydrous THF (1 ml) was added dropwise to the reaction mixture at 0°C and then the suspension was stirred at room temperature overnight. The suspension was diluted with toluene (3 ml) and filtered on neutral alumina. The solution was concentrated and purified by flash chromatography on neutral alumina (dry toluene) to give a white solid that was crystallized with *n*-hexane, washed with diisopropylether and collected to give pure phosphoramidite **L_6** (152 mg, 59% yield).

^{1}H-NMR (400 MHz, CD_2Cl_2, δ ppm) *minor diastereoisomer*: 7.95 (2H, d, *J* 7.62 Hz), 7.81-7.78 (2H, m), 7.54-7.49 (4H, m), 7.38-7.28 (4H, m), 7.13-6.92 (18H, m), 4.68-4.64 (m, 2H), 1.76 (d, 6H, *J* 7.05 Hz); *major diastereoisomer*: 8.07 (2H, d, *J* 7.44 Hz), 7.71-7.68 (2H, m), 7.54-7.49 (4H, m), 7.38-7.28 (4H, m), 7.13-6.92 (18H, m), 4.78-4.68 (2H, m), 1.49 (6H, d, *J* 7.02 Hz).

^{31}P-NMR (300 MHz, CD_2Cl_2, δ ppm): 137.48 (s, *major diastereomer*), 142.71 (s, *minor diastereomer*).

Synthesis of the phosphoramidite L_3[2]



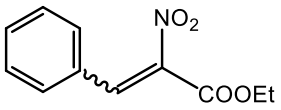
A solution of (*R*,*R*)-bis-(1-phenylethyl)amine (0.914 ml, 4 mmol, 1 eq.) in THF (4.5 ml) was added to a stirred mixture of TEA (2.78 ml, 20 mmol, 5 eq.) and PCl_3 (0.348 ml, 4 mmol, 1 eq.) in anhydrous THF (4.5 ml) at 0°C, and the reaction mixture was stirred for 3 h at room temperature. Biphenol (0.680 g, 4 mmol, 1 eq.), dissolved in a solution of anhydrous THF (4.5 ml) was added dropwise to

the reaction mixture at 0°C and then the suspension was stirred at room temperature overnight. The suspension was diluted in toluene (10 ml) and filtered on neutral alumina. The solution was concentrated and purified by flash chromatography on neutral alumina (dry toluene) to give pure phosphoramidite **L_3** (1.06 g, 60% yield) as a white solid.

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 7.77-7.71 (2H, m), 7.63-7.39 (16H, m), 4.95 (1H, q, *J* 7 Hz), 4.91 (1H, q, *J* 7 Hz), 2.04 (6H, d, *J* 7 Hz).

3.4.3 Synthesis of aromatic nitroalkenes

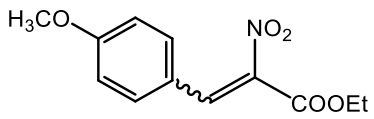
Synthesis of ethyl 2-nitro-3-phenylacrylate[3,4]



A solution of $TiCl_4$ (1 M in CH_2Cl_2) (9.422 ml, 9.422 mmol, 2 eq.) in a mixture of dry THF (20 ml) and CCl_4 (5 ml) was added under a N_2 atmosphere and at 0°C to a mixture of benzaldehyde (0.5 g, 4.711 mmol, 1 eq.) and ethyl nitroacetate (0.56 ml, 4.711 mmol, 1 eq.) in dry THF (2 ml). Then, maintaining the same temperature, a solution of dry DIPEA (3.282 ml, 18.844 mmol, 4 eq.) in THF (4 ml) was added dropwise. The reaction mixture was left warming at the room temperature for 19 h. Then the THF and CCl_4 were removed under vacuum and the crude reaction was extracted using CH_2Cl_2 (3 x 20 ml) and water (3 x 20 ml). The organic phases were collected, then dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by gravimetric column chromatography (*n*-hexane : AcOEt 95:5) gave ethyl 2-nitro-3-phenylacrylate (0.383 g, 37%) as a light-yellow liquid in (*Z*/*E* in 2 : 1 ratio each other).

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): *Z diastereoisomer* (major): 7.56-7.42 (5H, m), 7.47 (1H, s), 4.41 (2H, q, *J* 7 Hz), 1.39 (3H, t, *J* 7 Hz). *E diastereoisomer* (minor): 8.10 (1H, s), 7.56-7.42 (5H, m), 4.49 (2H, q, *J* 7 Hz), 1.38 (3H, t, *J* 7 Hz).[23, 24]

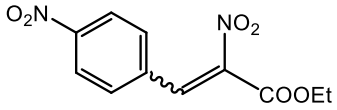
Synthesis of ethyl 3-(4-methoxyphenyl)-2-nitroacrylate



Ethyl 3-(4-methoxyphenyl)-2-nitroacrylate was synthesized as described for ethyl 2-nitro-3-phenylacrylate starting from the *p*-methoxybenzaldehyde (0.500 g, 3.33 mmol, 1 eq.), ethyl nitroacetate (0.395 ml, 3.33 mmol, 1 eq.), $TiCl_4$ (1 M in CH_2Cl_2) (6.66 ml, 6.66 mmol, 2 eq.) and DIPEA (2.320 ml, 13.32 mmol, 4 eq.) using the same THF and CCl_4 amounts described above. Purification by flash column chromatography (*n*-hexane/ethyl acetate, 95:5) gave ethyl 3-(4-methoxyphenyl)-2-nitroacrylate (640 mg, 76 %) as a yellow oil (*Z*/*E* = 1.4).

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): *Z diastereoisomer* (major): 7.47 (1H, s), 7.40 (2H, d, *J* 9 Hz), 6.93 (2H, d, *J* 9 Hz), 4.38 (2H, q, *J* 7 Hz), 3.86 (3H, s), 1.37 (3H, t, *J* 7 Hz). *E diastereoisomer* (minor): 8.05 (1H, s), 7.50 (2H, d, *J* 9 Hz), 6.97 (2H, d, *J* 9 Hz), 4.47 (2H, q, *J* 7 Hz), 3.88 (3H, s), 1.39 (3H, t, *J* 7 Hz).[23, 24]

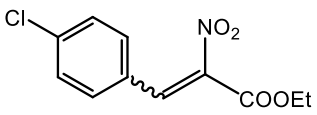
Synthesis of ethyl 2-nitro-3-(4-nitrophenyl)acrylate



Ethyl 2-nitro-3-(4-nitrophenyl)acrylate (7) was synthesized as described for ethyl 2-nitro-3-phenylacrylate (**5**) starting from the *p*-nitrobenzaldehyde (0.500 g, 3.03 mmol, 1 eq.), ethyl nitroacetate (0.361 ml, 3.03 mmol, 1 eq.), $TiCl_4$ (1 M in CH_2Cl_2) (6.055 ml, 6.06 mmol, 2 eq.) and DIPEA (2.11 ml, 12.11 mmol, 4 eq.) using the same THF and CCl_4 amounts reported above. Purification by flash column chromatography (*n*-hexane/ethyl acetate, 95:5) gave *Z*-ethyl 2-nitro-3-(4-nitrophenyl)acrylate (246 mg, 30%) (crude = *Z*/*E* ≈ 3.5).

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): *Z diastereoisomer* (purified product): 8.29 (2H, d, *J* 8.7 Hz), 7.62 (1H, s), 7.61 (2H, d, *J* 8.7 Hz), 4.44 (2H, q, *J* 7 Hz), 1.40 (3H, t, *J* 7 Hz). *E diastereoisomer* (minor): 8.32 (2H, d, *J* 9 Hz), 8.10 (1H, s), 7.71 (2H, d, *J* 9 Hz), 4.52 (2H, q, *J* 7 Hz), 1.45 (3H, t, *J* 7 Hz).[23, 25]

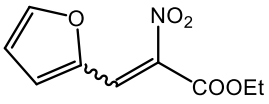
Synthesis of ethyl 3-(4-chlorophenyl)-2-nitroacrylate



Ethyl 3-(4-chlorophenyl)-2-nitroacrylate was synthesized as described for ethyl 2-nitro-3-phenylacrylate starting from the *p*-chlorobenzaldehyde (0.600 g, 4.24 mmol, 1 eq.), ethyl nitroacetate (0.473 ml, 4.24 mmol, 1 eq.), $TiCl_4$ (1 M in CH_2Cl_2) (8.48 ml, 8.48 mmol, 2 eq.) and DIPEA (2.95 ml, 16.96 mmol, 4 eq.) using the same THF and CCl_4 amounts described above. Then the THF and CCl_4 were removed under vacuum and the crude reaction was extracted using Et_2O (3 x 30 ml) and water (3 x 30 ml). The organic phases were collected, washed with a brine solution, then separated and dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by gravimetric column chromatography (*n*-hexane : AcOEt 95:5) gave ethyl 3-(4-chlorophenyl)-2-nitroacrylate (0.545 g, 33%) (*Z*/*E* = 2).

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): *Z diastereoisomer* (major): 7.51 (1H, s), 7.43 (2H, d, *J* 8.7 Hz), 7.37 (2H, d, *J* 8.7 Hz), 4.41 (2H, q, *J* 7 Hz), 1.39 (3H, t, *J* 7 Hz). *E diastereoisomer* (minor): 8.03 (1H, s), 7.46 (4H, d, *J* 3.3 Hz), 4.45 (2H, q, *J* 7 Hz), 1.37 (3H, t, *J* 7 Hz).[23, 24]

Synthesis of ethyl 3-(furan-2-yl)-2-nitroacrylate

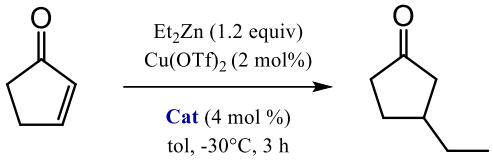


Ethyl 3-(furan-2-yl)-2-nitroacrylate was synthesized as described for ethyl 2-nitro-3-phenylacrylate starting from the 2-furaldehyde (0.5 ml, 6.24 mmol, 1 eq.), ethyl nitroacetate (0.697 ml, 6.24 mmol, 1 eq.), $TiCl_4$ (1 M in CH_2Cl_2) (12.48 ml, 12.48 mmol, 2 eq.) and DIPEA (4.347 ml, 24.96 mmol, 4 eq.) using the same THF and CCl_4 amounts described above. The crude is constituted by a *Z* : *E* ratio of 2. Purification by flash column chromatography (*n*-hexane/ethyl acetate, 95:5) gave ethyl 3-(furan-2-yl)-2-nitroacrylate. The first fraction eluted evaporated to dryness gave the *Z*-diastereoisomer (24 %, 315 mg), while the following fractions gave a mixture of both the diastereoisomers (540 mg, 65 % global isolation yield of the diastereoisomers).

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): *Z diastereoisomer* (major): 7.64 (1H, s), 7.37 (1H, s), 6.94 (1H, d, *J* 3 Hz), 6.58 (1H, dd, *J* 1.6 Hz), 4.38 (2H, q, *J* 7 Hz), 1.37 (3H, t, *J* 7 Hz). *E diastereoisomer* (minor): 7.87 (1H, s), 7.67 (1H, s), 7.08 (2H, d, *J* 3 Hz), 6.64 (1H, dd, *J* 1.6 Hz), 4.50 (2H, q, *J* 7 Hz), 1.43 (3H, t, *J* 7 Hz).[23, 26]

3.4.4 Catalytic 1,4-addition reactions

Synthesis of 3-ethylcyclopentanone



The catalyst (0.04 mmol, 2 eq) was added under N_2 at room temperature to a solution of $Cu(OTf)_2$ (0.02 mmol) in dry toluene (1.5 ml). The solution was stirred at 25°C for 30 min and then cooled to -40°C. Diethyl zinc (1.2 mmol, 1.09 ml of 1.1 M sol. in toluene) was added dropwise at such a rate as the temperature did not rise above -30°C. The solution was stirred for 5 min at -30°C. The substrate (1 mmol) was then added dropwise in 1 min. The reaction mixture was stirred at -30°C for 3 h before being quenched by aqueous NH_4Cl saturated solution. Conversion was determined by ^{1}H-NMR.

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 2.45-2.30 (2H, m), 2.25-2.03 (3H, m), 1.90-1.75 (1H, m), 1.52-1.32 (3H, m), 0.99 (3H, t, *J* 7 Hz).[18b]

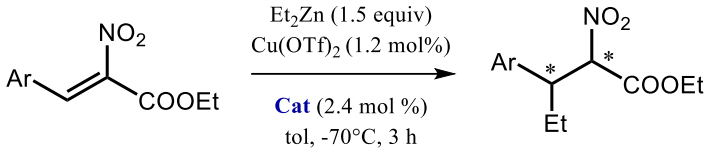
Reaction with **cat. 3**: conv. 99%.

Reaction with **cat. 4**: conv. 56%.

The enantiomeric excess was determined using a Chiralpak IA column (250 mm x 4.6 mm I.D.) in the following experimental conditions:

eluent: *n*-hexane-IPA 100:1; flow rate: 1 ml/min; Temperature: 25°C; Detector: UV at 240 nm.

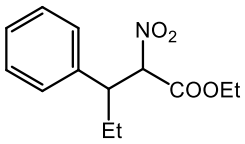
General procedure of catalytic 1,4-addition to trisubstituted nitroalkenes[27, 21]



Ar = Ph, 4-MeO-Ph, 2-furyl

A solution of $Cu(OTf)_2$ (0.012 eq) and catalyst (0.024 eq) in dry toluene (0.5 ml) was stirred for 1 h under N_2 atmosphere. The solution was cooled to -70°C and 1.1 M diethyl zinc solution in toluene (1.5 eq. of) and a solution of the nitroalkene (1.0 eq) in dry toluene (1 ml) were added consecutively. The reaction mixture was stirred for 3 h at -70°C and was subsequently quenched by addition of a aqueous saturated NH_4Cl solution (1.5 ml). The organic layer was separated after warming to room temperature, the aqueous layer was extracted twice, and the organic layers were collected, dried ($MgSO_4$) and concentrated *in vacuo*. Conversion was determined by ^{1}H-NMR.

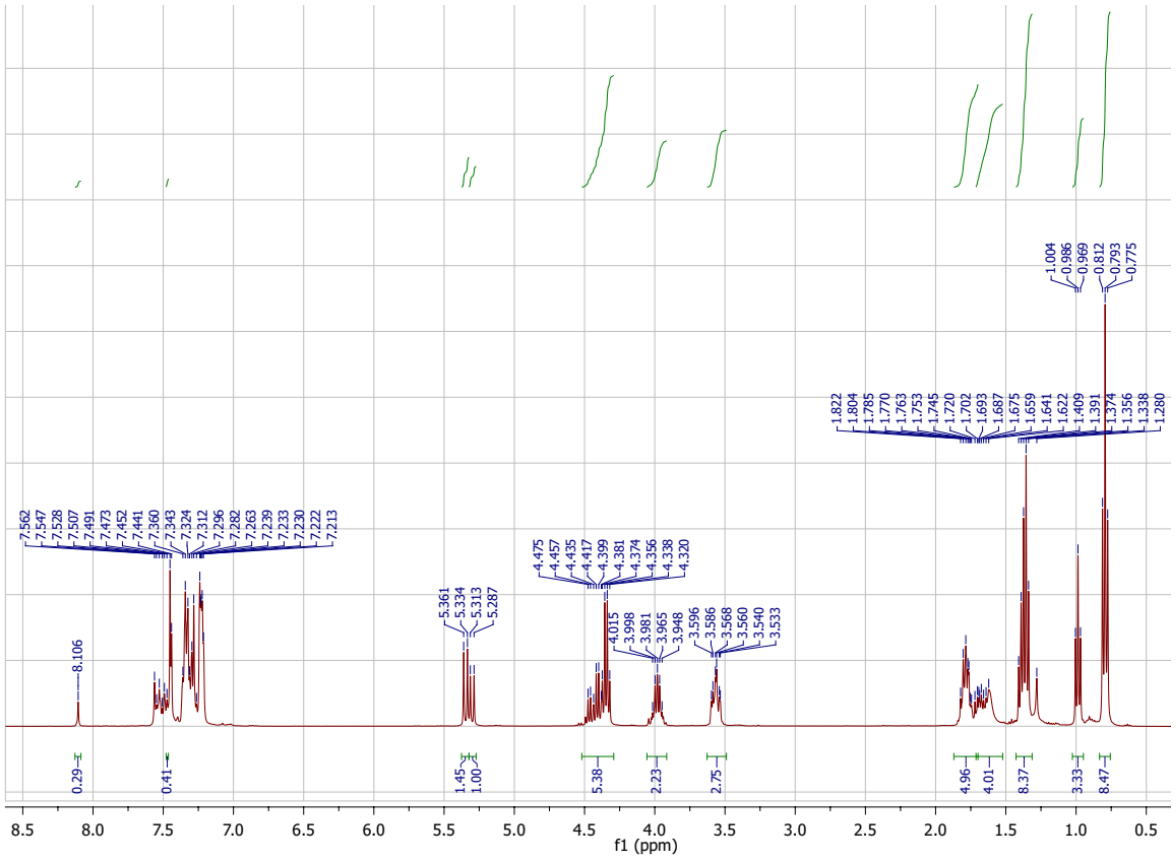
Ethyl 2-nitro-3-phenylpentanoate



The crude reaction was chromatographed (*n*-hexane : AcOEt 95:5) in order to remove the catalyst. Below is reported the ^{1}H NMR where both the substrate (1H, s at 8.10 and 7.47 ppm) and the product diastereoisomers were present (1H, d at 5.35 and 5.30 ppm).

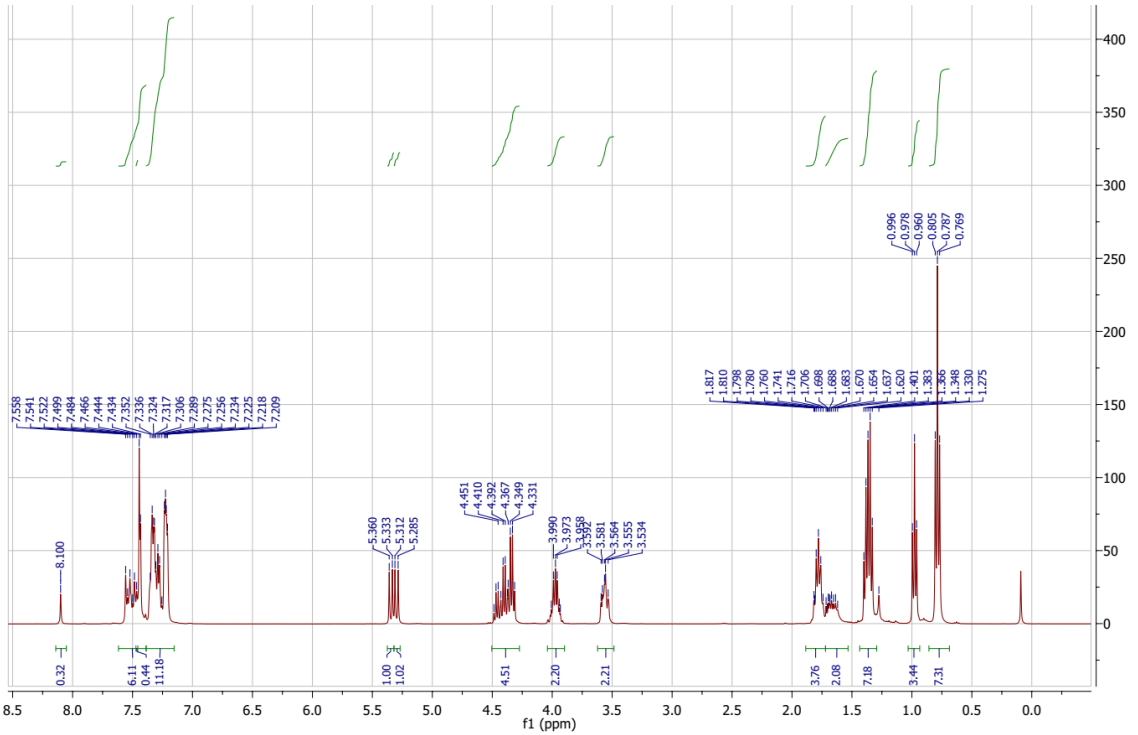
Reaction with **cat. L_6**: conv. 78%.

Starting from *Z*/*E* 2 : 1 ratio of substrate, a 1.5 : 1 diasteroisomeric ratio of the product was obtained.

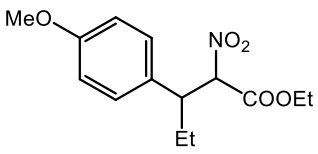


Reaction with **cat. L_3**: conv. 73%.

Starting from *Z*/*E* 2 : 1 ratio of substrate, a 1 : 1 diasteroisomeric ratio of the product was obtained.



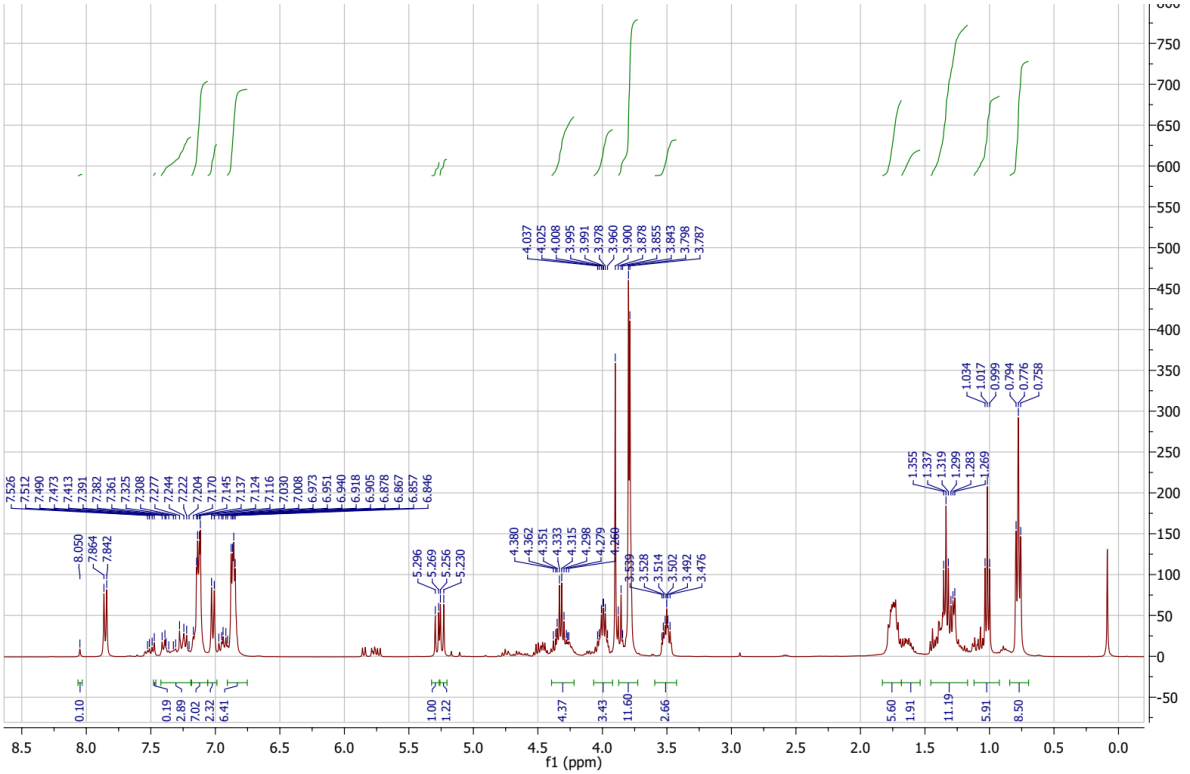
Ethyl 2-nitro-3-*p*-methoxy-phenylpentanoate



The crude reaction was chromatographed (*n*-hexane:AcOEt 95:5) in order to remove the catalyst. Below is reported the ^{1}H NMR where both the substrate (1H, s at 8.05 and 7.47 ppm) and the product diastereoisomers were present (1H, d at 5.27 and 5.24 ppm).

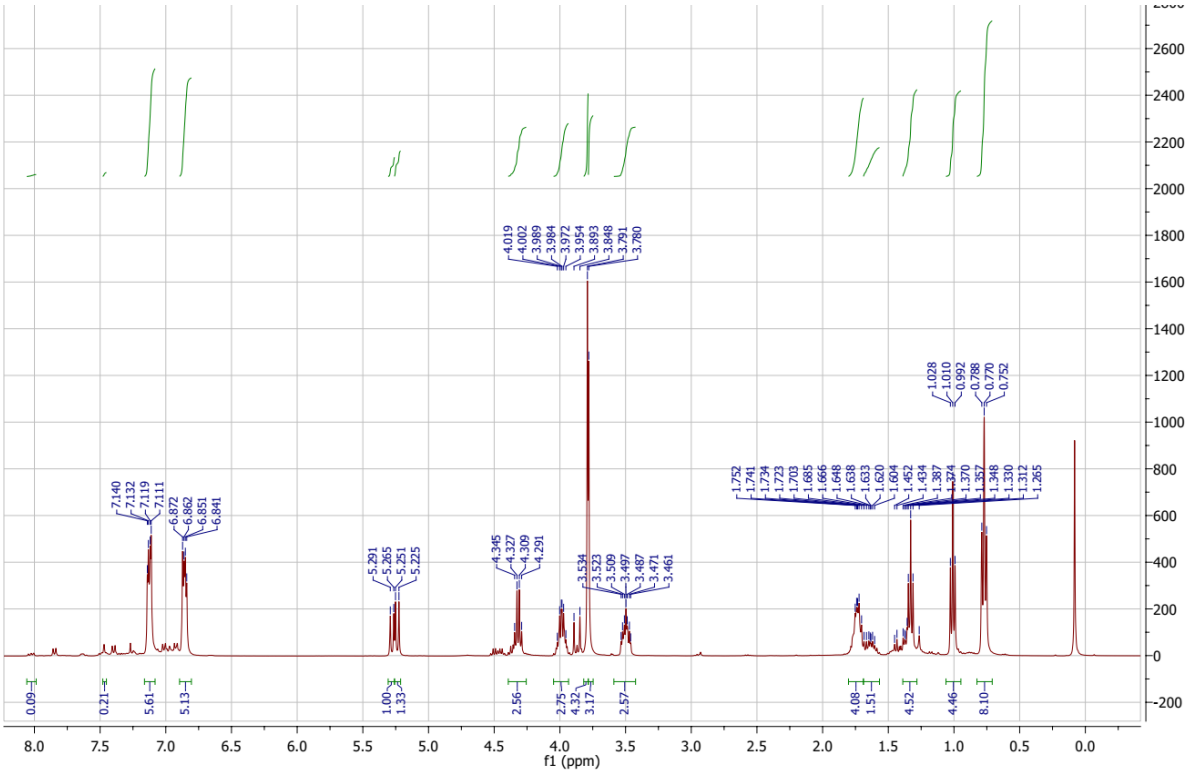
Reaction with **cat. L_6**: conv. 95%.

Starting from a *Z*/*E* = 1,4 ratio of substrates, a 1.2 : 1 diasteroisomeric ratio of the product was obtained.

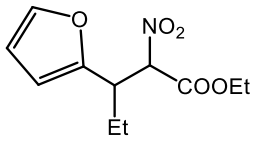


Reaction with **cat. L_3**: conv. 92%.

Starting from a *Z*/*E* = 1,4 ratio of substrates, a 1.3 : 1 diasteroisomeric ratio of the product was obtained.



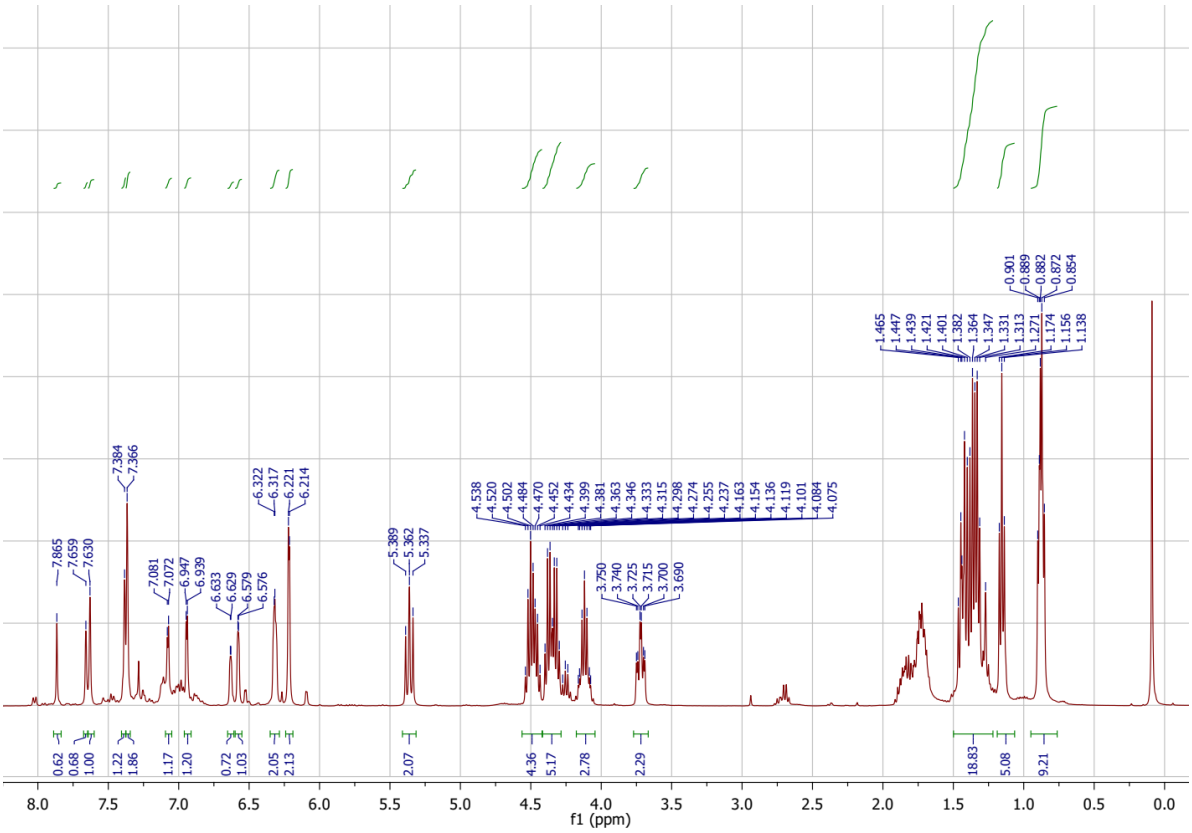
Ethyl 3-(2-furyl)- 2-nitropentanoate (14)



The crude reaction was chromatographed (*n*-hexane : AcOEt 95:5) in order to remove the catalyst. The ^{1}H NMR spectrum reported below suggested that starting from pure *Z*-diastereoisomer the *E* one forms during the reaction is reported the ^{1}H NMR where both the substrate (1H, s at 7.76 and 7.63 ppm) and the product diastereoisomers were present (1H, d at 5.37 and 5.34 ppm).

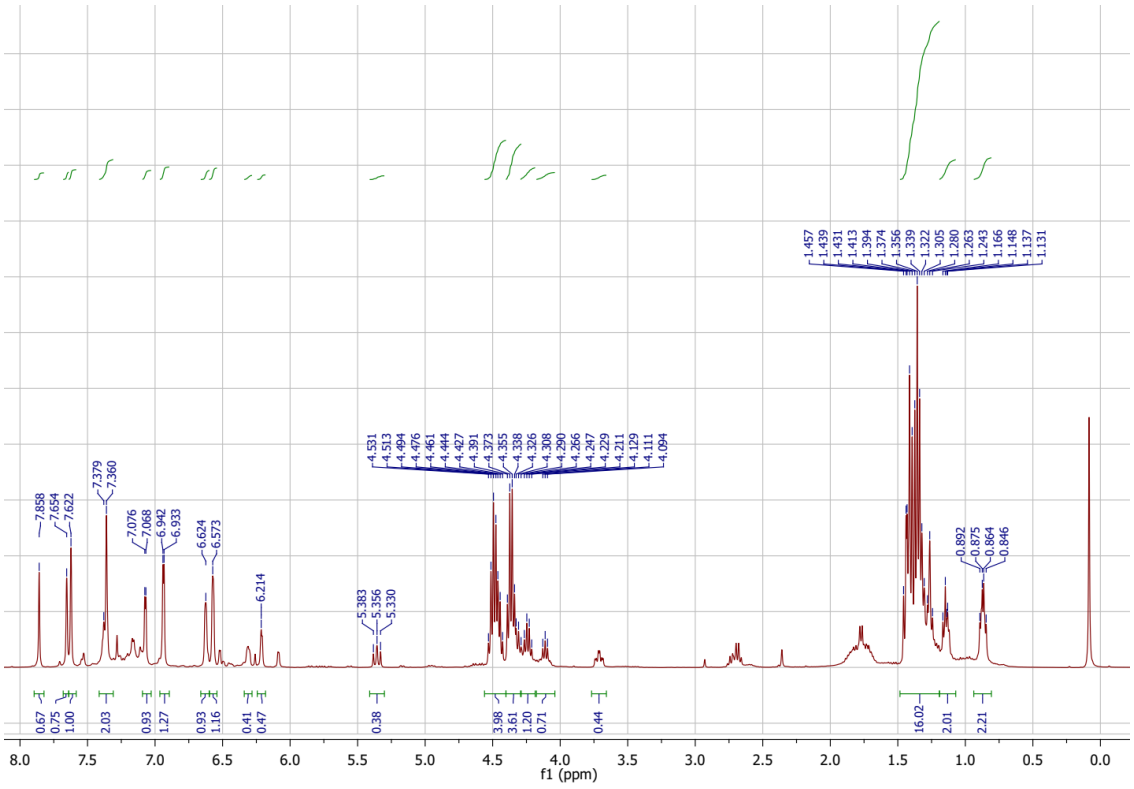
Reaction with **L$_6$**: conv. 55%

Starting from pure *Z* diastereoisomer a 1:1 diasteroisomeric ratio of the products was obtained.



Reaction with **L_3**: conv. 18%.

Also in this case, starting from pure *Z* diastereoisomer a 1:1 diasteroisomeric ratio of the products was obtained beside the formation of the *E*-diastereoisomer.



3.5 *References*

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Appendix- Tandem Iron/Copper Catalysis: One-pot Multistep Synthesis of Benzoxazoles

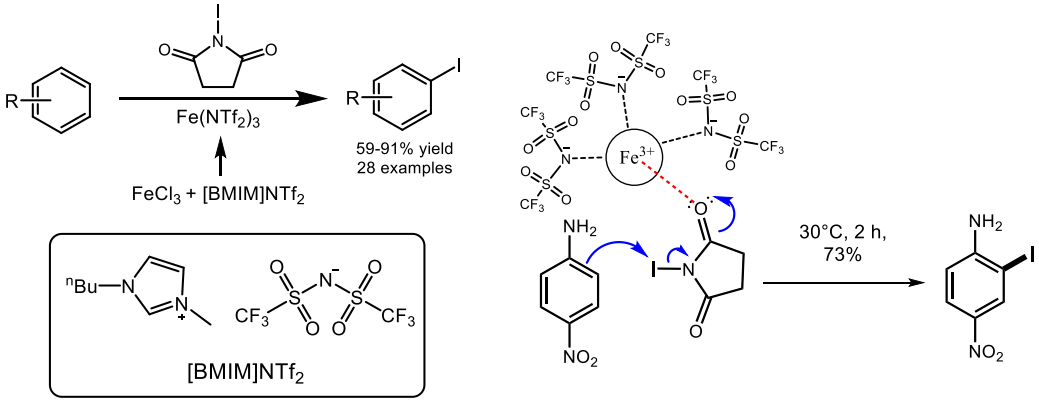
The development of one-pot multistep processes has, in modern times, had a great deal of influence both in academic and in industrial synthetic chemistry. The possibility to put two or more reactions in a single reaction flask gives the chemists advantages in terms of atom economy, time and labour employed, in terms of resource management and consequently waste generation, contributing, therefore, in a positive way, to both the science and art of total synthesis. This brings not only improved practical efficiency, but also enhanced aesthetic appeal to the synthetic planning.[1a] Indeed such processes avoid the need for isolation and handling of intermediates and quite often generate the target compound more efficiently. While significant advances have been made in this area, key strategic objectives remain.[1] Another challenge for organic synthesis is the discovery of alternative catalysts than the highly expensive precious metals such as palladium and ruthenium currently used. In particular, in recent years, the use of environmentally friendly, low cost metals such as iron has been investigated.[2] There are two important reasons why iron should be considered as a catalyst:

- Iron is the most abundant metal in the Earth's crust after aluminium and therefore it is much cheaper than the precious rare transition metals often applied;

- Iron is more compatible with biological systems since various iron compounds are found in cells. So, the low toxicity of many iron species could be a very important feature to take in consideration for many applications in fields such as the pharmaceutical industry, the food industry and cosmetics.[2b]

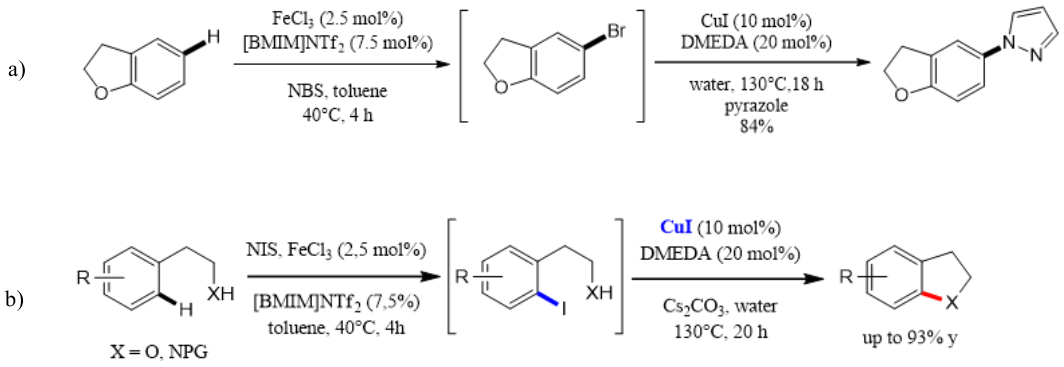
Concerning the application of iron in recent years, the Sutherland group, in which I spent my six months placement at the University of Glasgow, showed that iron(III) can be used catalytically for the Lewis acid activation of *N*-iodosuccinimide (NIS) and the subsequent iodination of substituted arenes.[3] In particular they showed that by using a triflimide-based ionic liquid (IL), in 1 : 3 ratio Fe/IL, they were able to generate a super Lewis acidic species, $Fe(NTf_2)_3$, that can accelerate the iodination reaction performed on arenes bearing also strong deactivated groups.

For example in Scheme 1 is reported the iodination of a *para*-substituted electron-deficient aniline: Fe(III) interacts with three bistriflimide anions and this increases its Lewis acid character and allows coordination with the NIS oxygen atom, making the iodide atom more electrophilic favouring the regioselective formation of the *ortho*-iodinated product in 73% yield after only 2 h.[3]



Scheme 1. Iron catalysed halogenation of arenes through the ionic liquid [BMIM]NTf_2.

The same group reported that this type of process could be tuned using softer Lewis acids such as silver(I), which allowed the efficient halogenation of highly activated arenes such as phenols.[4]
This methodology was also combined with a copper(I)-catalysed amination for the one-pot conversion of aryl C-H bonds to C-N ones[5] (Scheme 2a) as well as the intramolecular C-N and C-O bond formation for the general synthesis of indolines and dihydrobenzofurans[6] (Scheme 2b). Also in this case using copper catalysis for the second step.

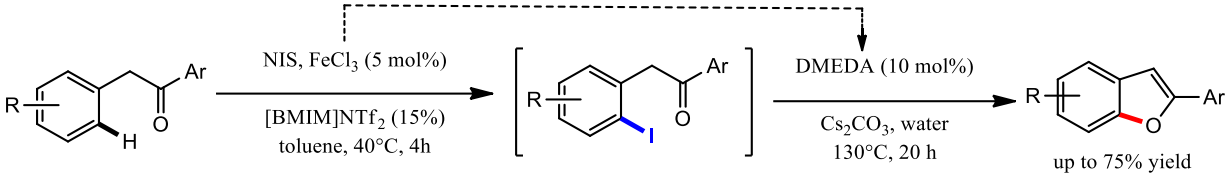


Scheme 2

The process can also be exploited for the synthesis of six and seven membered analogues and has been used for the total synthesis of the neolignan natural product (+)-obtusafuran,[6] demonstrating

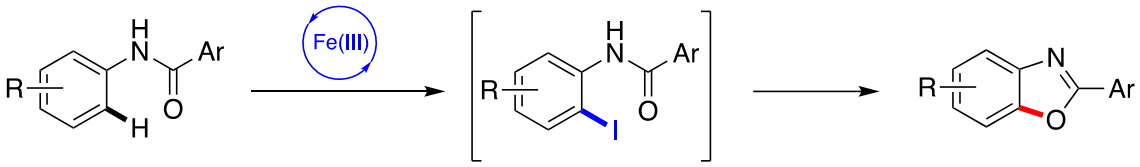
that this new approach can be useful also for the synthesis of important building blocks and targets for medicinal chemistry.

More recently, a similar methodology of iodination and subsequent intramolecular C-O bond formation, for the synthesis of different substituted benzofurans was developed. In this case both steps were catalysed by the same aliquot of $FeCl_3$ (Scheme 3).[7]



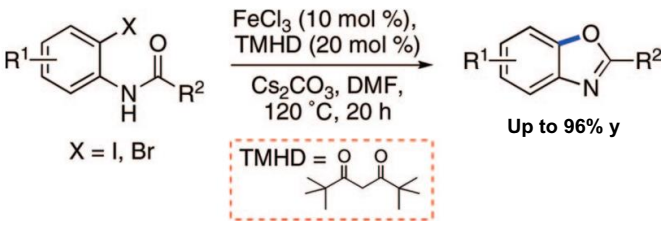
Scheme 3. Iron(III)-catalysed one-pot synthesis of benzofurans starting from substituted aryl-benzylic ketones.

The objective of my research project was to investigate if this kind of approach could be also feasible for the one-pot multistep synthesis of benzoxazoles through tandem iron catalysis starting from suitable substituted acyl anilides (Scheme 4).



Scheme 4

This idea was supported by the results obtained by the Bolm group in 2008 in the synthesis of benzoxazoles through iron-catalysed intramolecular cyclisation of pre-functionalised 2-haloaryl anilides.[8] The reactions were carried out using different ligands: in particular 2,2,7,7-tetramethylhepta-2,5-dione (TMHD) was reported as the best ligand providing the desired products in up to 96% yield (Scheme 5).[8]



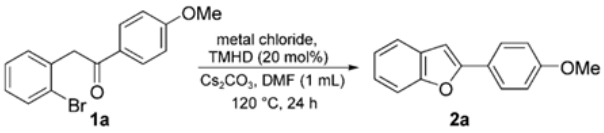
Scheme 5

The role of metal contaminants in reactions catalysed by metal salts, in particular $FeCl_3$, emerged as a problem in the recent years. In particular, Bolm published in 2009[9] that many reactions that were supposed to be catalysed by iron, actually were catalysed by the traces of copper contained in the $FeCl_3$ used. As a consequence of this, all the reactions performed using $FeCl_3$ (in different purity grades from different suppliers) as reagent must be investigated thoroughly in order to better realise which is the real catalyst.

The already discussed benzoxazole synthesis[8], was reported in this paper as a possible example of cyclisation by the presence of copper contaminants.

An exhaustive investigation regarding the role of iron and copper salts in the one-step synthesis of benzo[*b*]furans starting from aryl 2-bromobenzyl ketones was reported by the same authors in 2010.[10] Initially the reaction was performed starting from 2-(2-bromophenyl)-1-(4-methoxyphenyl)-ethanone using 10 mol% of $FeCl_3$ (98% from Merck) in combination with 20 mol% of TMHD and an excess of Cs_2CO_3 (2 equiv.) in DMF at 120°C for 24 h. In these conditions, the corresponding 2-arylbenzo[*b*]furan was afforded in 79% yield.

In order to better realise the main responsible of this transformation, an analysis of the purity of $FeCl_3$ employed was performed through atom absorption spectroscopy (AAS). A sample of $FeCl_3$ (98% from Merck) showed the presence of palladium (13.2 ppm), nickel (190 ppm), manganese (1720 ppm) and copper (344 ppm). Consequently, all of them were tested separately in the same amount contained in 10 mol% of $FeCl_3$ (98% from Merck) to verify the importance of each one in the reaction mechanism. Considering that they were present in a sample of $FeCl_3$ (an oxidant and chlorinating agent) the corresponding chloride salts in oxidation state 2+ were utilised ($PdCl_2$, $NiCl_2{\cdot}6H_2O$, $MnCl_2{\cdot}4H_2O$ and $CuCl_2$) (Table 1). Only $CuCl_2$ was found to be active, and noteworthy, even with only 344 ppm of salt (corresponding to 0,0088 mol%), the product was achieved in 60% yield. These results showed that apparently the copper played an important role in the intramolecular C-O bond formation.



Entry	Metal	ppm	Mol%	Yield [%]
1	$FeCl_3$ (98%)		10	79
2	–	–	–	8
3	$CuCl_2$	344	0.0088	60
4	$MnCl_2 \cdot 4H_2O$	1720	0.0510	8
5	$PdCl_2$	13.2	0.0002	8
6	$NiCl_2 \cdot 6H_2O$	190	0.0053	8

Table 1. Effects of metal dichlorides in cyclisations of **1a**.

Then, in order to further elucidate its effective role in the reaction, the effects of mixtures of high pure $FeCl_3$ and $CuCl_2$ (both from Aldrich with purities of 99.995%) on the same cyclisation reaction were tested.

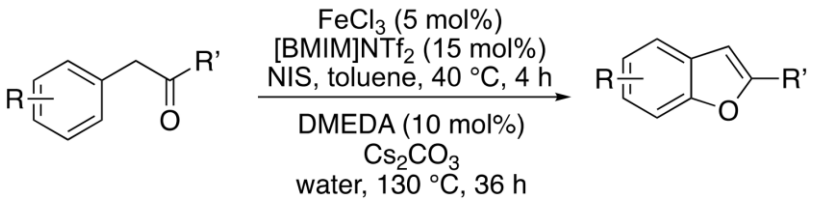
Different experiments were performed which showed that the copper salt has a predominant effect (60% yield starting from only 0.0088 mol% of $CuCl_2$, up to 79% yield using 0.05 mol%) respect to the pure $FeCl_3$, that gave 8% yield when used in 0.0088 mol%. An increase of the yield up to 79% when $FeCl_3$ was employed in 10 mol% without any copper salts, clearly indicating that, actually, there is a catalytical activity when iron was used at high catalyst loading.[10]

On the basis of these considerations, also the previous cited one-pot multistep synthesis of benzofurans starting from different substituted aryl-benzylic ketones carried out in the Sutherland group[7] (see Scheme 3) was deeply investigated. In this case the iron is added as $FeCl_3$ during the first step: while in the second step, the copper impurities present in the $FeCl_3$ catalyst are responsible for the cyclisation. Indeed, the $FeCl_3$ employed in the process was analysed by ICP (Inductively Coupled Plasma) showing that only 44 ppm of copper were present. This was enough to catalyse the cyclisation and this result confirms what the Bolm research group published concerning the one-step synthesis of benzofurans.

The one-pot multistep synthesis of benzoxazoles required the availability of suitable substituted acyl anilides, prepared in excellent yields by the coupling of carboxylic acid derivatives with amines starting either from an aromatic acyl chloride or forming it *in situ* starting from the corresponding carboxylic acid and an excess of $SOCl_2$ at the refluxing temperature (see experimental session).

So, after a first period of exclusive use of $FeCl_3$ for both the steps, having shown that copper impurities are the main responsible for the catalysis of the second step, the one-pot multistep

synthesis of benzoxazoles starting from acyl-anilides herein reported was conducted using $FeCl_3$ for the first step and adding CuI for the second step following the conditions reported in Scheme 6.



Scheme 6

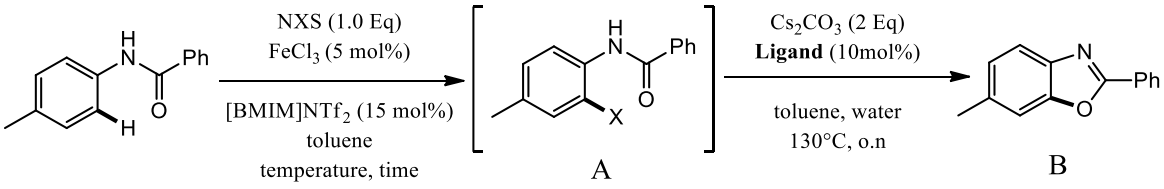
In order to better investigate the reaction conditions for the halogenation reaction, at the beginning, the first step was performed separately. The first substrate investigated was the benzoyl-*p*-toluidine (Table 2) that was submitted to the iodination reaction, since it is well-known that iodinated compounds are more reactive than bromides for cross-coupling reactions.

However, the iodination reaction, that should be regioselective for the *ortho*-position to the nitrogen atom, which is a stronger *ortho*-orienting substituent respect to the methyl group, didn't provide the desired product in good yields (17%).

The bromination reaction seemed to be more suitable for this kind of substrate, probably for steric reasons, with an acceptable yield of 65% when it was carried out at 40°C overnight (Table 2, Entry 2). In order to reach a higher conversion in a shorter time, several attempts were performed at 70°C, but, unfortunately, a slight decrease of the yield was observed.

We considered the above described reaction conditions satisfactory and the bromo-derivative was employed in a one-pot multistep process exploiting the usual experimental conditions utilised for cyclisations in the research group, [6] namely 2 Equiv. of Cs_2CO_3, water to better dissolve the base and DMEDA as ligand.

The desired product was achieved in only 21% yield in agreement with the data reported by Bolm paper[8], concerning the synthesis of 2-phenylbenzoxazole obtained in 25% yield using DMEDA as ligand.



X	Temperature	Time	Ligand	A (y%)	B (y%)
I	70°C	16 h	/	17%	/
Br	40°C	16 h	/	65%	/
Br	70°C	16 h	/	54%	/
Br	40°C	16 h	L1	63%*	21%
Br	40°C	16 h	L2	60%*	/
Br	40°C	16 h	L3	61%*	/

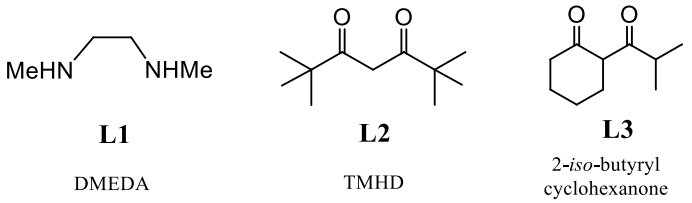
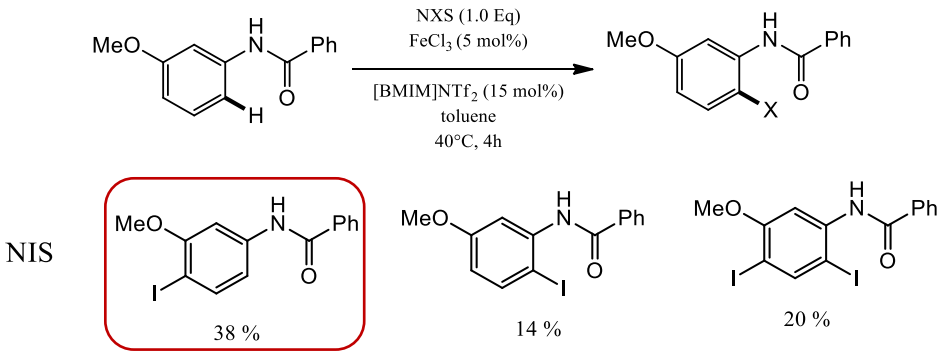
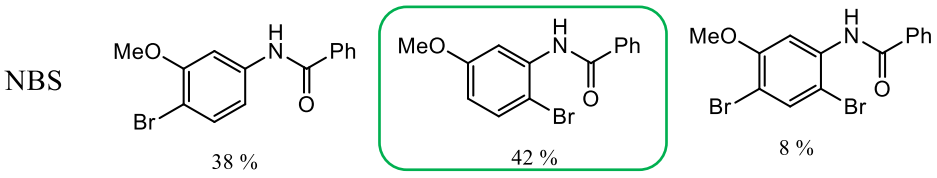


Table 2. Investigation of the one-pot multistep process starting from the benzoyl-*p*-toluidine. * = NMR conversions.

Unexpectedly no product was observed when the one-pot process was performed in the presence of 2,2,7,7-tetramethylhepta-2,5-dione (TMHD, **L2**), the favoured ligand suggested from the literature for this kind of transformation, and 2-*iso*-butyrylcyclohexanone (**L3**), also performing the reactions at different temperatures (from 130°C to 150°C). In order to improve the halogenation step, the reaction was performed on the benzoyl *m*-anisidine (Scheme 7), since $FeNTf_2$-catalysed activation of similar scaffolds gave the *para*-iodinated isomers as the sole product. Furthermore, DFT calculations using Fukui function[11] were performed in order to explore electronic effects of the outcome of this reaction, providing a molecular orbital rationale for the highly regioselective arene iodination process.[6]





Scheme 7

Firstly, the iodination reaction was investigated, but unfortunately, a mixture of products was obtained beside the starting material, in which unexpectedly the main one was the benzoyl-*p*-iodo-*m*-anisidine (Scheme 7) prevailing the *p*-orienting effect of the anilido group respect to the *ortho* one.

Therefore, in order to increase the regioselectivity of the halogenation, the bromination reaction was also investigated improving the selectivity obtaining the desired product with a conversion of only 42%.

In this case, the regioselectivity of the halogenation reaction is complicated by the presence of the anilide nitrogen, which is another, even though less effective, electron donating group.

The 3,4,5-trimethoxybenzoyl aniline (Figure 1) was envisaged as a suitable substrate for carrying out the halogenation step in a regioselective way and in high yields due to its symmetry. In addition, the strong electron-rich nature of the aromatic ring, due to the presence of three methoxy groups, should increase the conversion of the halogenation reaction as well as that of the cyclisation process being only one free position in the intermediate.

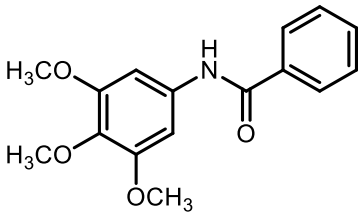
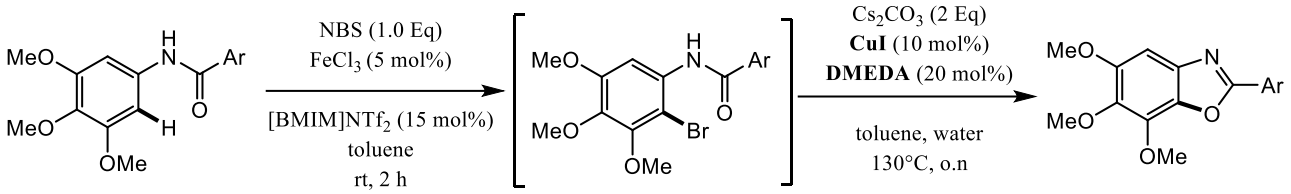


Figure 1

As done for the benzoyl anilides investigated before, firstly the iodination reaction was performed under the stardard experimental conditions (1 eq of NIS, 5 mol% of $FeCl_3$ (99,9% by Sigma Aldrich, 15 mol% of [BMIM]NTf_2 in toluene at 40°C for 4 h) but a complex mixture of products was obtained. Similar results were obtained when the reaction was performed at rt as well as at 0°C, in order to control the rate of that transformation.

The bromination reaction appeared to be better (Scheme 8), and after having achieved a conversion of 80%, the cyclisation reaction was carried out by the addition of Cs_2CO_3 (2 Equiv.), CuI (10 mol%) as catalyst and using DMEDA (20 mol%) as ligand, increasing the temperature to 130°C. The desired product was obtained in only 35% y beside the starting material.



Scheme 8

The product was obtained in 26% yield using, as ligand, the *trans-N,N'*-dimethylcyclohexanone-1,2-diamine, while performing the second step using TMHD in the same conditions, the product was isolated only in traces, even though no dehalogenation of the intermediate was observed, indicating that probably more reaction time could be necessary to complete the reaction.

Therefore, in order to increase the yield, in line with literature data for the synthesis of benzoxazoles, the reaction was carried out at 150 °C for three days. However, also in these experimental conditions, the product was isolated in 21% yield.

In the end we decided to study the substrate scope starting from substrates functionalised on the phenyl ring with electron-donating, as well as electron-withdrawing groups by performing the one-pot multistep process using the conditions shown in Scheme 8 (Figure 2).

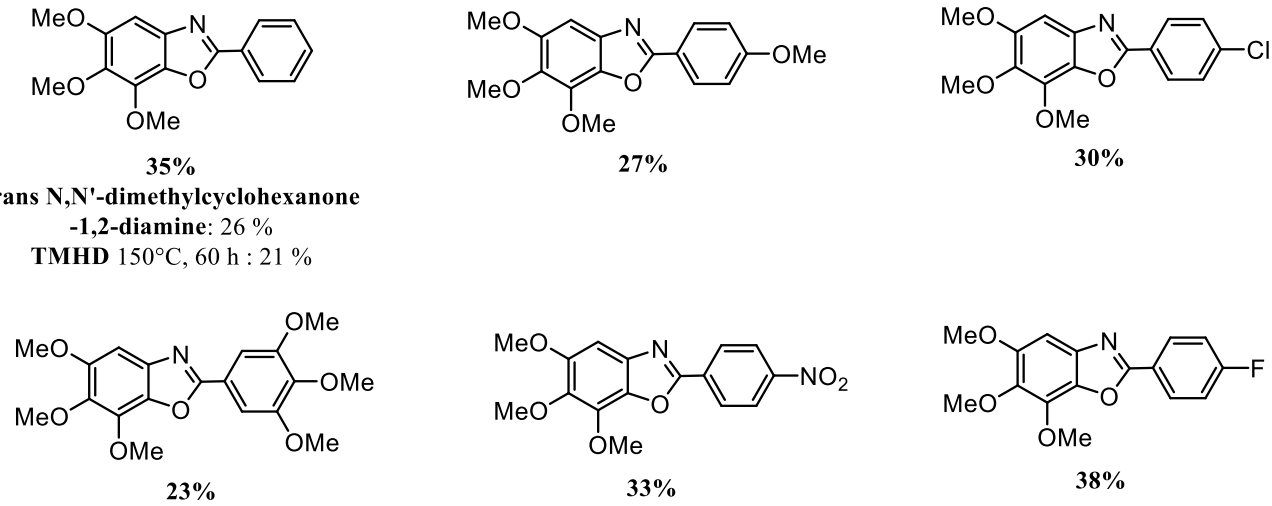


Figure 2

The process seemed to be reproducible since each investigated *N*-aryl anilide transformed into the desired product (initially a mixture of toluene and CH_3CN or THF were employed in order to increase the substrate solubility, see experimental), but unfortunately the yields achieved were modest.

Finally, the *N*-(3,4-dimethoxyphenyl)benzamide, the *N*-*p*-methoxy and *N*-*p*-chloro benzoyl derivatives (Figure 3) were synthesized and reacted in the same experimental conditions above described.

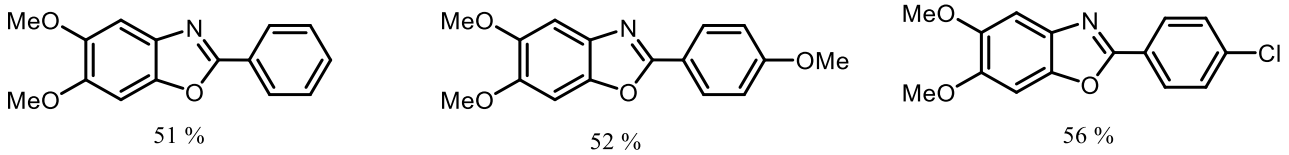


Figure 3

The new substrates investigated, afforded the desired product in good yields (from 51 to 56%) beside the de-halogenated benzoylanilide, suggesting that the one-pot multistep process for the synthesis of benzoxazoles starting from *N*-aryl-anilides could be an applicable process. So, in the final stage of my project, my optimisation studies have led to a successful one-pot process where three target molecules were prepared in good yield over the two steps, on substituents with neutral, electron-rich and electron-deficient side-chains.

In conclusion, as we can see from the results obtained, the electronic nature of the anilide ring plays an important role both in the halogenation and in the cyclisation step, that must be better clarified by studying other derivatives.

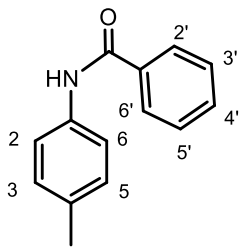
Experimental section

General Information

Methods:

Reactions were monitored by analytical thin-layer chromatography (TLC) using silica gel 60 F_{254} pre-coated glass plates (0.25 mm thickness) and visualized using UV light. Flash chromatography was carried out on silica gel (230-400 mesh). ^{1}H-NMR spectra were recorded on spectrometers operating at 400 MHz (Bruker AVANCE 400 spectrometer) and 500 MHz (Bruker AVANCE 500); proton chemical shifts are reported in ppm (δ) with the solvent reference relative to tetramethylsilane (TMS) employed as the internal standard ($CDCl_3$ δ = 7.26 ppm) and coupling constants are reported in Hertz (Hz). Splitting patterns are indicate as follows: s = singlet, d = doublet, t = triplet, q = quartet, qn = quintuplet, m = multiplet, bs = broad singlet, dd = double doublet. ^{13}C-NMR spectra were recorded on 400 MHz spectrometers operating at 100 MHz with complete proton decoupling; carbon chemical shifts are reported in ppm (δ) relative to TMS with the respective solvent resonance as the internal standard ($CDCl_3$, δ = 77.0 ppm).
Mass spectra and accurate mass analysis were carried out on a VG AUTOSPEC- M246 spectrometer (double-focusing magnetic sector instrument with EBE geometry) equipped with EI source or with LCQ Fleet ion trap mass spectrometer, ESI source, with acquisition in positive ionization mode in the mass range of 50-2000 m/z.
Melting point determinations were performed by using a Buchi B-540 instrument.
IR spectra were recorded on FT-IR Thermo Scientific Nicolet iS10 Smart iTR equipped with a Smart OMNI Transmission instrument, interfaced with Omnic 9.2.98 software; spectra were measured in ATR.

_N_-(_p_-Tolyl)benzamide

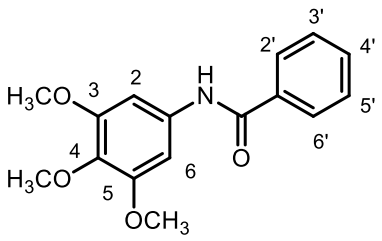


The *p*-toluidine (400 mg, 3.714 mmol) was dissolved in CH_2Cl_2 (8 ml). TEA (0.619 ml, 4.456 mmol, 1.2 eq) was added under stirring and the solution was cooled at 0 °C. Then the benzoyl chloride (0.517

ml, 4.456 mmol, 1.2 eq) was added dropwise and the mixture was left under stirring at 0 °C. After 0.5 h the reaction was warmed to room temperature and left stirring overnight. The reaction was quenched with a $NaHCO_3$satured solution (8 ml) and left under stirring for 0.5 h. The aqueous phase was separated and washed twice with CH_2Cl_2 (10 ml), then the organic phases were collected and washed with a 1 M HCl solution (30 ml) to remove the TEA. The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (hexane/ethyl acetate, 9:1) gave *N*-(*p*-tolyl)benzamide (784 mg, 99,9%) as a white solid.
Spectroscopic data were consistent with the literature.[12]

Mp 154-156 °C (lit., 155-156 °C).
^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 2.339 (3H, s, CH_3), 7.168 (2H, d, *J* 8 Hz, 3-H and 5-H), 7.471 (2H, t, *J* 7.6 Hz, 2'-H and 6'-H), 7.50-7.59 (3H, m, 3'-H, 5'-H and 4'-H), 7.797 (1H, br s, NH), 7.858 (2H, d, *J* 8 Hz, 2-H and 6-H);
^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm): 20.9, 120.5, 127.1, 128.6, 129.5, 131.6, 134.1, 135.1, 135.4, 165.9;
m/z (ESI) 234.0911 (MNa^+. 100%)

_N_-(3,4,5-Trimethoxyphenyl)benzamide



N-(3,4,5-trimethoxyphenyl)benzamide was synthesized as described for *N*-(*p*-tolyl)benzamide using 3,4,5-trimethoxyaniline (1 g, 5.46 mmol), benzoyl chloride (0.826 ml, 6.552 mmol, 1.2 eq) and TEA (0.911 ml, 6.552 mmol, 1.2 eq). Purification by flash column chromatography (*n*-hexane/ethyl acetate, 7:3) gave *N*-(3,4,5-trimethoxyphenyl)benzamide (1.454 g, 93%) as a light yellow solid. Spectroscopic data were consistent with the literature.[13]

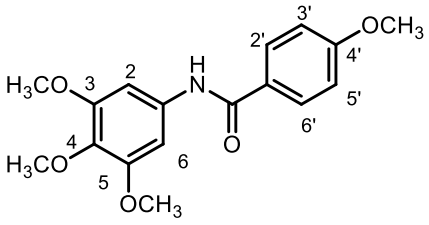
Mp 140-141 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 3.793 (6H, s, 3-OCH_3 and 5-OCH_3), 3.813 (3H, s, 4-OCH_3), 6.973 (2H, s, 2-H and 6-H), 7.440 (2H, t, *J* 7.2 Hz, 3'-H and 5'-H), 7.526 (1H, t, *J* 7.2 Hz, 4'-H), 7.871 (2H, d, *J* 7.2 Hz, 2'-H and 6'-H), 8.142 (1H, br s, NH).

^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm): 56.0, 60.9, 98.1, 127.0, 128.7, 131.8, 134.2, 134.8, 153.3, 165.9.

m/z (ESI) 310.1063 (MNa^+), 597.2237 ($2MNa^+$).

4-Methoxy-*N*-(3,4,5-trimethoxyphenyl)benzamide)



The anisic acid (324.4 mg, 2.132 mmol, 1.3 eq) was dissolved in $SOCl_2$ (3.096 ml, 26 eq) and the solution refluxed under stirring for 1h. Then the $SOCl_2$ was evaporated *in vacuo*. The crude was dissolved in CH_2Cl_2 (10 ml), the solution cooled at 0 °C and the 3,4,5-trimethoxyaniline (300 mg, 1.64 mmol, 1 eq) was added slowly. Then the TEA (0.506 ml, 2.132 mmol, 1.3 eq) was added dropwise. After 0.5 h the reaction was warmed to room temperature and stirred overnight. The reaction was quenched with a satured $NaHCO_3$ solution (10 ml) and left under stirring for 0.5 h. The aqueous phase was separated and exteracted twice with CH_2Cl_2 (10 ml), then the organic phases were collected and washed with a 1 M HCl solution (30 ml) to remove the TEA. The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (*n*-hexane/ethyl acetate, 7:3) gave 4-methoxy-*N*-(3,4,5-trimethoxyphenyl)benzamide (509 mg, 98%) as a light yellow solid. Spectroscopic data were consistent with the literature.[13]

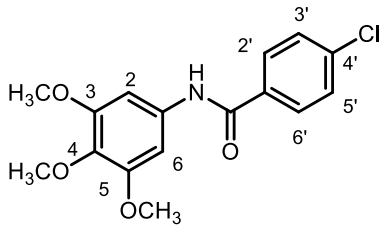
Mp 159-160 °C (lit 159-160 °C).

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 3.828 (3H, s, 4-OCH_3), 3.852 (6H, s, 3-OCH_3 and 5-OCH_3), 3.869 (3H, s, 4'-OCH_3), 6.954 (2H, s, 2-H, 6-H), 6.959 (2H, d, *J* 8.8 Hz, 3'-H and 5'-H), 7.806 (1H, br s, NH), 7.841 (2H, d, *J* 8.8 Hz, 2'-H and 6'-H).

^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm): 55.5, 56.1, 60.9, 97.9, 114.0, 127.0, 128.8, 134.3, 134.8, 153.4, 162.6, 165.2.

m/z (ESI) 318.1343 (MH^+), 340.1170 (MNa^+), 657.2455 ($2MNa^+$).

4-Chloro-*N*-(3,4,5-trimethoxyphenyl)benzamide



4-Chloro-*N*-(3,4,5-trimethoxyphenyl)benzamide (XX) was synthesized as described for 4-methoxy-*N*-(3,4,5-trimethoxyphenyl)benzamide starting from the *p*-chlorobenzoic acid (333.8 mg, 2.132 mmol, 1.3 eq), $SOCl_2$ (3.093 ml, 26 eq), 3,4,5-trimethoxyaniline (300 mg, 1.64 mmol), and TEA (0.296 ml, 2.132 mmol, 1.3 eq). Recrystallization of the product from the crude gave 4-chloro-*N*-(3,4,5-trimethoxyphenyl)benzamide (473.9 mg, 90%) as a pale yellow solid.

Mp 176-178 °C.

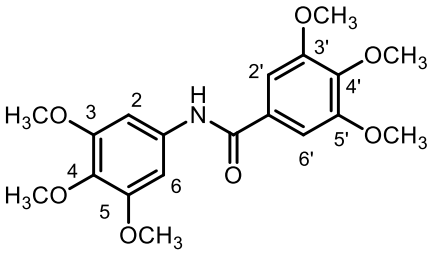
ν_{max}/cm^{-1} (neat) 3385 (NH), 2970 (ArH), 2936, 1674 (C=O), 1595 (C=C), 1535, 1506, 1449, 1408.

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm)3.833 (3H, s, 4-OCH_3), 3.857 (6H, s, 3-OCH_3 and 5-OCH_3), 6.939 (2H, s, 2-H and 6-H), 7.452 (2H, d, *J* 8.4 Hz, 3'-H and 5'-H), 7.775-7.825 (3H, m, 2'-H, 6'-H and NH).

^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm): 56.2, 61.0, 98.1, 128.4, 129.1, 133.3, 133.8, 135.2, 138.2, 153.5, 164.6.

m/z (ESI) 344.0653 (MNa^+. 100%).

3,4,5-Trimethoxy-*N*-(3,4,5-trimethoxyphenyl)benzamide



3,4,5-Trimethoxy-*N*-(3,4,5-trimethoxyphenyl)benzamide was synthesized as described for 4-methoxy-*N*-(3,4,5-trimethoxyphenyl)benzamide starting from the 3,4,5-trimethoxybenzoic acid (317.5 mg, 1.4196 mmol, 1.3 eq), $SOCl_2$ (2.06 ml, 26 Eq), 3,4,5-trimethoxyaniline (200 mg, 1.092

mmol), and TEA (0.197 ml, 1.4196 mmol, 1.3 eq). Purification by flash column chromatography (*n*-hexane/ethyl acetate, 7:3) gave 3,4,5-trimethoxy-N-(3,4,5-trimethoxyphenyl)benzamide (395,3 mg, 96%) as a white solid. Spectroscopic data were consistent with the literature.[14]

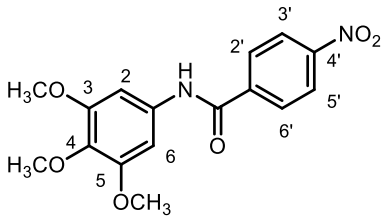
Mp 212-213 °C (lit 212-213 °C).

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 3.839 (3H, s, 4-OCH_3), 3.871 (6H, s, 3-OCH_3 and 5-OCH_3), 3.909 (3H, s, 4'-OCH_3), 3.925 (6H, s, 3'-H and 5'-H), 6.955 (2H, s, 2-H and 6-H), 7.078 (2H, s, 2'-H and 6'-H), 7.753 (1H, br s, NH).

^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm): 56.2, 56.5, 60.9, 61.0, 98.0, 104.5, 130.3, 133.9, 135.0, 141.4, 153.4, 153.4, 165.5.

m/z (ESI) 378.1532 (MH^+), 400.1356 (MNa^+), 777.2803 ($2MNa^+$).

4-Nitro-*N*-(3,4,5-trimethoxyphenyl)benzamide



4-Nitro-*N*-(3,4,5-trimethoxyphenyl)benzamide was synthesized as described for *N*-(*p*-tolyl)benzamide using 3,4,5-trimethoxyaniline (200 mg, 1.092 mmol), 4-nitrobenzoyl chloride (243.15 mg, 1.310 mmol, 1.2 eq) and TEA (0.182 ml, 1.310 mmol, 1.2 eq). A yellow solid precipitate that was collected by filtration and washed with a 2 N HCl solution and MeOH to give 4-nitro-*N*-(3,4,5-trimethoxyphenyl)benzamide (252.8 mg, 70%) as a deep yellow solid. Spectroscopic data were consistent with the literature.[15]

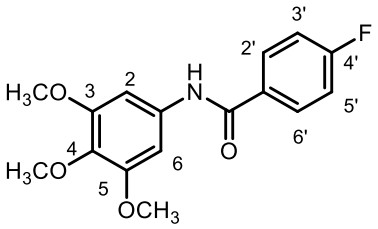
Mp 220-222 °C (lit 220-224 °C).

^{1}H-NMR (400 MHz, DMSO+$CDCl_3$, δ ppm)3.785 (3H, s, 4-OCH_3), 3.867 (6H, s, 3-OCH_3 and 5-OCH_3), 7.203 (2H, s, 2-H and 6-H), 8.209 (2H, d, *J* 8.4 Hz, 3'-H and 5'-H), 8.320 (2H, d, *J* 8.4 Hz, 2'-H and 6'-H), 10.208 (1H, br s, NH).

^{13}C-NMR (100 MHz, DMSO + $CDCl_3$, δ ppm): 55.4, 60.7, 98.0, 122.7, 128.5, 134.0, 134.2, 140.3, 148.8, 152.3, 163.3.

m/z (ESI) 355.0880 (MNa^+), 687.1942 ($2MNa^+$).

4-Fluoro-*N*-(3,4,5-trimethoxyphenyl)benzamide



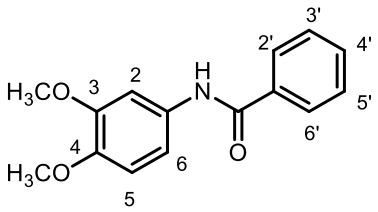
4-Fuoro-*N*-(3,4,5-trimethoxyphenyl)benzamide was synthesized as described for 4-methoxy-*N*-(3,4,5-trimethoxyphenyl)benzamide starting from the *p*-fluorobenzoic acid (229.5 mg, 1.638 mmol, 1.2 eq), $SOCl_2$ (2.58 ml, 26 eq), 3,4,5-trimethoxyaniline (250 mg, 1.365 mmol), and TEA (0.227 ml, 1.638 mmol, 1.2 eq). Purification by flash column chromatography (*n*-hexane/ethyl acetate, 1:1) gave 4-fluoro-*N*-(3,4,5-trimethoxyphenyl)benzamide (370 mg, 88%) as a white solid. Spectroscopic data were consistent with the literature.[13]

Mp 159-160 °C.

^{1}H-NMR (300 MHz, $CDCl_3$, δ ppm): 3.833 (3H, s, 4-OCH_3), 3.857 (6H, s, 3-OCH_3 and 5-OCH_3), 6.938 (2H, s, 2-H and 6-H), 7.157 (2H, t, *J* 8.4 Hz, 3'-H and 5'-H), 7.784 (1H, br s, NH), 7.883 (2H, m, 2'-H and 6'-H); ^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm): 56.2, 61.0, 98.1, 115.921 (d), 129.35 (d), 131.071 (d), 135.1, 153.4, 164.7, 164.965 (d).

m/z (ESI) 328.0966 (MNa^+. 100%).

***N*-(3,4-Dimethoxyphenyl)benzamide**



N-(3,4-Dimethoxyphenyl)benzamide was synthesized as described for *N*-(*p*-tolyl)benzamide using 3,4-dimethoxyaniline (300 mg, 1.958 mmol), benzoyl chloride (0.272 ml, 2.349 mmol, 1.2 eq) and TEA (0.326 ml, 2.349 mmol, 1.2 eq). Purification by flash column chromatography (*n*-hexane/ethyl acetate, 7:3) gave *N*-(3,4-dimethoxyphenyl)benzamide (380 mg, 75%) as a brownish solid. Spectroscopic data were consistent with the literature.[16]

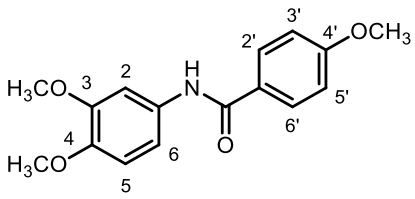
Mp 180-181 °C (lit., 179-181 °C),

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 3.860 (3H, s, 4-OCH_3), 3.864 (3H, s, 3-OCH_3), 6.822 (1H, d, *J* 8.8 Hz, 5-H), 7.011 (1H, dd, J_o 8.4 Hz, J_m 2.4 Hz, 6-H), 7.410-7.485 (3H, m, 2-H, 3'-H and 5'-H), 7. 524 (1H, t, *J* 7.2 Hz, 4'-H), 7.859 (2H, d, *J* 7.2 Hz, 2'-H and 6'-H), 7.965 (1H, br s, NH).

^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm): 55.9, 56.1, 105.3, 111.4, 112.3, 126.9, 128.7, 131.6, 131.7, 134.9, 146.1, 149.1, 165.7.

m/z (ESI) 280.0894 (MNa^+. 100%).

_N_-(3,4-Dimethoxyphenyl)-4-methoxybenzamide



N-(3,4-Dimethoxyphenyl)-4-methoxybenzamide was synthesized as described for 4-methoxy-*N*-(3,4,5-trimethoxyphenyl)benzamide starting from the 4-methoxybenzoic acid (322.8 mg, 2.1216 mmol, 1.3 eq), $SOCl_2$ (3.08 ml, 26 eq), 3,4-dimethoxyaniline (250 mg, 1.632 mmol), and TEA (0.295 ml, 2.1216 mmol, 1.3 Eq). Purification by flash column chromatography (*n*-hexane/ethyl acetate, 7:3) gave *N*-(3,4-dimethoxyphenyl)-4-methoxybenzamide (442.3 mg, 94%) as a brownish solid.

Mp 132-134 °C.

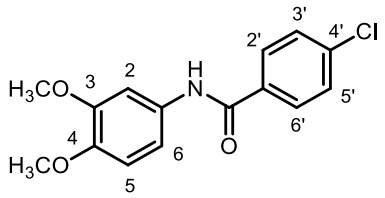
ν_{max}/cm^{-1} (neat) 3284 (NH), 1636 (CO), 1601 (C=C), 1518, 1404.

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 3.860 (3H, s, 4-OCH_3), 3.864 (3H, s, 3-OCH_3), 3.878 (3H, s, 4'-OCH_3), 6.823 (1H, d, *J* 8.4 Hz, 5-H), 6.944 (2H, d, *J* 8.8 Hz, 3'-H and 5'-H), 6.979 (1H, dd, J_o 8.8 Hz, J_m 2.4 Hz, 6-H), 7. 475 (1H, d, J_m 2.4 Hz, 2-H), 7.833 (3H, d, *J* 8.8 Hz, 2'-H ,6'-H and NH).

^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm): 55.5, 55.9, 56.1, 105.3, 111.4, 112.2, 113.9, 127.2, 128.8, 131.8, 145.9, 149.1, 162.4, 165.2.

m/z (ESI) 310.1035 (MNa^+. 100%).

4-Chloro-*N*-(3,4-dimethoxyphenyl)benzamide



4-Chloro-*N*-(3,4-dimethoxyphenyl)benzamide was synthesized as described for 4-methoxy-*N*-(3,4,5-trimethoxyphenyl)benzamide starting from the 4-chlorobenzoic acid (332.1 mg, 2.1216 mmol, 1.3 eq), $SOCl_2$ (3.08 ml, 26 eq), 3,4-dimethoxyaniline (250 mg, 1.632 mmol), and TEA (0.295 ml, 2.1216 mmol, 1.3 eq). Purification by flash column chromatography (*n*-hexane/ethyl acetate, 7:3) gave 4-chloro-*N*-(3,4-dimethoxyphenyl)benzamide (205 mg, 43%) as a white solid. Spectroscopic data were consistent with the literature.[17]

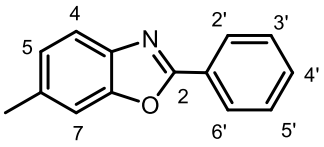
Mp 148-150 °C.

^{1}H-NMR (300 MHz, $CDCl_3$, δ ppm): 3.869 (3H, s, 4-OCH_3), 3.871 (3H, s, 3-OCH_3), 6.827 (1H, d, *J* 8.4 Hz, 5-H), 6.996 (1H, dd, J_o 8.4 Hz, J_m 2.4 Hz, 6-H), 7.401-7.447 (3H, m, 3'-H, 5'-H and 2-H), 7.795 (2H, d, *J* 8.4 Hz, 2'-H ,6'-H), 7.905 (1H, br s, NH).

^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm): 55.9, 56.1, 105.3, 111.3, 112.4, 128.4, 128.9, 131.3, 133.3, 138.0, 146.2, 149.1, 164.6.

m/z (ESI) 314.0524 (MNa^+. 100%).

6-Methyl-2-phenylbenzo[d]oxazole



Iron(III) chloride (2.02 mg, 0.0125 mmol) was dissolved in 1-butyl-3-methylimidazolium bis(trifluoromethanesulfonyl)imide (11 µL, 0.0375 mmol) and stirred for 0.5 h at room temperature. Then the mixture was added to a suspension of *N*-bromosuccinimide (44,5 mg, 0.25 mmol, 1.0 eq) in toluene (0.5 ml). N-(p-tolyl)benzamide (52.81 mg, 0.25 mmol) was added and the mixture was

stirred at 40 °C for 12 h. Upon having checked the conversion to the brominated compound by ^{1}H NMR spectroscopy (65 %), the reaction mixture was cooled to room temperature and cesium carbonate (162.91 mg, 0.5 mmol, 2 eq), copper(I) iodide (4.76 mg, 0.025 mmol, 0.1 eq), toluene (0.5 ml), water (0.4 ml), and DMEDA (5.38 µL, 0.05 mmol, 0.2 eq) were added. The reaction mixture was degassed under argon for 0.1 h and then heated to 130 °C for 16 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate (10 ml), washed with a 1 M aqueous sodium thiosulfate solution (10 mL). The aqueous layer was extracted with ethyl acetate (3 × 10 ml). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (*n*-hexane/ethyl acetate, 9:1) gave 6-methyl-2-phenylbenzo[d]oxazole (12.6 mg, 17%) as a light yellow solid. Spectroscopic data were consistent with the literature.[18]

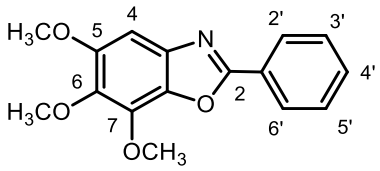
Mp 90-92 °C (lit. 90-92 °C).

^{1}H-NMR (300 MHz, $CDCl_3$, δ ppm): 2.502 (3H, s, CH_3), 7.163 (1H, d, *J* 8 Hz, 5-H), 7.379 (1H, s, 7-H), 7.50-7.54 (3H, m, 3'-H, 5'-H and 4'-H), 7.637 (1H, d, *J* 8 Hz, 4-H), 8.20-8.26 (2H, m, 2'-H and 6'-H).

^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm): 21.8, 110.8, 119.3, 125.8, 127.4, 127.5, 128.9, 131.3, 135.6, 139.9, 151.1, 162.6.

m/z (ESI) 210.0915 (MH^+. 100%).

5,6,7-Trimethoxy-2-phenylbenzo[d]oxazole



5,6,7-Trimethoxy-2-phenylbenzo[d]oxazole was synthesised as described for 6-methyl-2-phenylbenzo[d]oxazole starting from *N*-(3,4,5-trimethoxyphenyl)benzamide (71.82 mg, 0.25 mmol). The bromination step was carried out at rt for 4 h (conv. 74%) and the cyclisation step at 130 °C for 16 h. Purification by flash column chromatography (*n*-hexane/ethyl acetate, 7:3) gave 5,6,7-trimethoxy-2-phenylbenzo[d]oxazole (25 mg, 35%) as a brown solid.

Mp 56-57 °C.

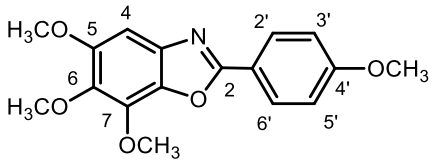
ν_{max}/cm^{-1} (neat) 2947 (ArH), 1601 (C=N), 1487 (C=C), 1458, 1421.

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 3.919 (3H, s, 5-OCH_3), 3.923 (3H, s, 6-OCH_3), 4.306 (3H, s, 7-OCH_3), 6.982 (1H, s, 4-H), 7.515 (3H, m, 3'-H, 4'-H and 5'-H), 8.199 (2H, m, 2'-H and 6'-H).

^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm): 56.5, 60.5, 61.6, 95.9, 127.1, 127.3, 128.9, 131.3, 136.2, 138.5, 138.7, 138.718, 152.0, 162.9;

m/z (ESI) 308.0886 (MNa^+. 100%).

5,6,7-Trimethoxy-2-(4-methoxyphenyl)benzo[d]oxazole



5,6,7-Trimethoxy-2-(4-methoxyphenyl)benzo[d]oxazole was synthesized as described for 6-methyl-2-phenylbenzo[d]oxazole starting from *4*-methoxy-N-(3,4,5-trimethoxyphenyl)benzamide (79.33 mg, 0.25 mmol). The bromination step was carried out at rt for 4 h in a mixture of toluene (0.7 ml) and CH_3CN (100 µL) (conv. 78%) while the cyclisation step at 130 °C for 16 h. Purification by flash column chromatography (*n*-hexane/ethyl acetate, 7:3) gave 5,6,7-trimethoxy-2-(4-methoxy-phenyl)benzo[d]oxazole (21 mg, 27%) as a brown solid.

Mp 99-100 °C.

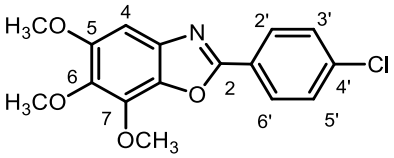
ν_{max}/cm^{-1} (neat) 2918 (ArH), 1605 (C=N), 1501 (C=C), 1487, 1449, 1415.

^{1}H-NMR (300 MHz, $CDCl_3$, δ ppm): 3.887 (3H, s, 4'-OCH_3), 3.910 (3H, s, 5-OCH_3), 3.913 (3H, s, 6-OCH_3), 4.290 (3H, s, 7-OCH_3), 6.949 (1H, s, 4-H), 7.015 (2H, d, *J* 8.8 Hz, 3'-H, and 5'-H), 8.134 (2H, d, *J* 8.8 Hz, 2'-H and 6'-H).

^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm): 55.5, 56.5, 60.5, 61.6, 95.9, 114.4, 119.7, 129.1, 136.1, 138.342, 138.378, 138.9, 151.9, 162.2, 163.1.

m/z (ESI) 338.0990 (MNa^+. 100%).

2-(4-Chlorophenyl)-5,6,7-trimethoxybenzo[d]oxazole



2-(4-Chlorophenyl)-5,6,7-trimethoxybenzo[d]oxazole was synthesized as described for 6-methyl-2-phenylbenzo[d]oxazole starting from 4-chloro-*N*-(3,4,5-trimethoxyphenyl)benzamide (80.44 mg, 0.25 mmol). The bromination step was carried out at rt for 4 h in toluene (0.5 ml) (conv. 78%) and the cyclisation step at 130 °C for 16 h. Purification by flash column chromatography (*n*-hexane/ethyl acetate, 7:3) gave 2-(4-chlorophenyl)-5,6,7-trimethoxybenzo[d]oxazole (24 mg, 30%) as a pale green solid.

Mp 112-114 °C.

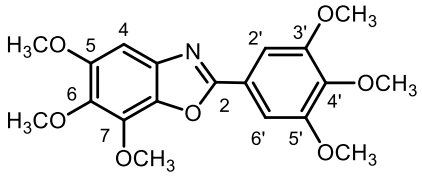
ν_{max}/cm^{-1} (neat) 2936 (ArH), 1597 (C=N), 1460 (C=C), 1425, 1402, 1340.

^{1}H-NMR (300 MHz, $CDCl_3$, δ ppm): 3.917 (3H, s, 5-OCH_3), 3.920 (3H, s, 6-OCH_3), 4.284 (3H, s, 7-OCH_3), 6.966 (1H, s, 4-H), 7.486 (2H, d, *J* 8.8 Hz, 3'-H, and 5'-H), 8.126 (2H, d, *J* 8.8 Hz, 2'-H and 6'-H).

^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm): 56.5, 60.5, 61.6, 96.1, 125.6, 128.5, 129.3, 136.4, 137.5, 138.5, 138.6, 139.0, 152.2, 161.9.

m/z (ESI) 342.0491 (MNa^+. 100%).

5,6,7-Trimethoxy-2-(3,4,5-trimethoxyphenyl)benzo[d]oxazole



5,6,7-Trimethoxy-2-(3,4,5-trimethoxyphenyl)benzo[d]oxazole was synthesized as described for 6-methyl-2-phenylbenzo[d]oxazole starting from 3,4,5-trimethoxy-N-(3,4,5-trimethoxy-phenyl)benzamide (94.35 mg, 0.25 mmol). The bromination step was carried out at rt for 4 h in a mixture of toluene (0.6 ml) and CH_3CN (50 µL). The cyclisation step at 130 °C for 16 h. Purification

by flash column chromatography (*n*-hexane/ethyl acetate, 8:2) gave 5,6,7-trimethoxy-2-(3,4,5-trimethoxyphenyl)benzo[d]oxazole (21.6 mg, 23%) as a white solid.

Mp 131-132 °C.

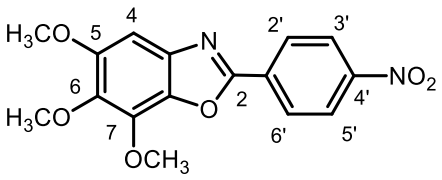
ν_{max}/cm^{-1} (neat) 2951 (ArH), 1591 (C=N), 1558 (C=C), 1498, 1489, 1452, 1414.

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 3.924 (6H, s, 3'-OCH_3 and 5'-OCH_3), 3.936 (3H, s, 4'-OCH_3), 3.984 (3H, s, 5-OCH_3 and 6-OCH_3), 4.281 (3H, s, 7-OCH_3), 6.985 (1H, s, 4-H), 7.438 (2H, s, 2'-H and 6'-H).

^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm): 56.4, 56.5, 60.7, 61.0, 61.6, 96.1, 104.7, 122.3, 136.5, 138.4, 138.6, 138.9, 141.1, 152.1, 153.6, 162.9.

m/z (ESI) 398.1206 (MNa^+. 100%).

5,6,7-Trimethoxy-2-(3,4,5-trimethoxyphenyl)benzo[d]oxazole



5,6,7-Trimethoxy-2-(4-nitrophenyl)benzo[d]oxazole was synthesized as described for 6-methyl-2-phenylbenzo[d]oxazole starting from 4-nitro-N-(3,4,5-trimethoxyphenyl)benzamide (83.08 mg, 0.25 mmol). The bromination step was carried out at rt for 4 h in a mixture of toluene (0.5 ml) and CH_3CN (50 µL) (conv. 76%). The cyclisation step at 130 °C for 16 h. Purification by flash column chromatography (*n*-hexane/ethyl acetate, 7:3) gave 5,6,7-trimethoxy-2-(4-nitrophenyl)benzo[d]oxazole (28 mg, 33%) as a deep yellow solid.

Mp 198-199 °C.

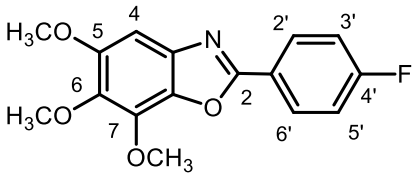
ν_{max}/cm^{-1} (neat) 2924 (ArH), 1614 (C=N), 1556 (C=C), 1520, 1492, 1464, 1429.

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 3.938 (3H, s, 5-OCH_3), 3.940 (3H, s, 6-OCH_3), 4.298 (3H, s, 7-OCH_3), 7.005 (1H, s, 4-H), 8.364 (4H, s, 2'-H, 3'-H, 5'-H and 6'-H).

^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm): 56.5, 60.7, 61.7, 96.3, 124.2, 128.0, 132.6, 136.9, 138.51, 138.54, 139.9, 149.2, 152.6, 160.5.

m/z (ESI) 353.0736 (MNa^+. 100%).

2-(4-Fluorophenyl)-5,6,7-trimethoxybenzo[d]oxazole



2-(4-Fluorophenyl)-5,6,7-trimethoxybenzo[d]oxazole was synthesized as described for 6-methyl-2-phenylbenzo[d]oxazole starting from 4-fluoro-N-(3,4,5-trimethoxyphenyl)benzamide (76.3 mg, 0.25 mmol). The bromination step was carried out at rt for 4 h in a mixture of toluene (0.7 ml) and THF (100 µL) (conv. 76%). The cyclisation step at 130 °C for 16 h. Purification by flash column chromatography (*n*-hexane/ethyl acetate, 7:3) gave 2-(4-fluorophenyl)-5,6,7-trimethoxybenzo[d]oxazole (29.1 mg, 38%) as a white solid.

Mp 89-90 °C.

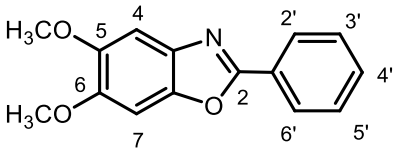
ν_{max}/cm^{-1} (neat) 2927 (ArH), 1601 (C=N), 1498 (C=C), 1489, 1462, 1423.

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 3.918 (3H, s, 5-OCH_3), 3.920 (3H, s, 6-OCH_3), 4.286 (3H, s, 7-OCH_3), 6.964 (1H, s, 4-H), 7.199 (2H, t, *J* 8.8 Hz, 3'-H, and 5'-H), 8.193 (2H, m, 2'-H and 6'-H).

^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm): 56.5, 60.5, 61.6, 96.0, 116.19 (d), 123.46 (d), 129.51 (d), 136.3, 138.5, 138.6, 138.8, 152.1, 162.1, 163.674 (d).

m/z (ESI) 326.0793 (MNa^+. 100%).

5,6-Dimethoxy-2-phenylbenzo[d]oxazole



5,6-Dimethoxy-2-phenylbenzo[d]oxazole was synthesised as described for 6-methyl-2-phenylbenzo[d]oxazole starting from *N*-(3,4-dimethoxyphenyl)benzamide (64.32 mg, 0.25 mmol). The bromination step was carried out at rt for 2 h in a mixture of toluene (0.7 ml) and THF (100 µL) (conv. 82%). The cyclisation step at 130 °C for 16 h. Purification by flash column chromatography (*n*-

hexane/ethyl acetate, 7:3) gave 5,6-dimethoxy-2-phenylbenzo[d]oxazole (32.8 mg, 51%) as a palet yellow solid. Spectroscopic data were consistent with the literature.[19]

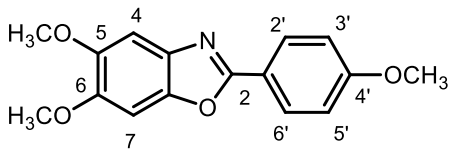
Mp 115-117 °C (lit., 114-115 °C).

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 3.947 (3H, s, 5-OCH_3), 3.957 (3H, s, 6-OCH_3), 7.130 (1H, s, 4-H), 7.253 (1H, s, 7-H), 7.47-7.52 (3H, m, 3'-H, 4'-H and 5'-H), 8.15-8.20 (2H, m, 2'-H and 6'-H).

^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm): 56.452, 56.515, 94.4, 101.8, 126.9, 127.5, 128.9, 130.8, 134.9, 145.2, 147.8, 148.4, 162.3.

m/z (ESI) 278.0783 (MNa^+. 100%).

5,6-Dimethoxy-2-(4-methoxyphenyl)benzo[d]oxazole



5,6-Dimethoxy-2-(4-methoxyphenyl)benzo[d]oxazole was synthesised as described for 6-methyl-2-phenylbenzo[d]oxazole starting from *N*-(3,4-dimethoxyphenyl)-4-methoxybenzamide (71.82 mg, 0.25 mmol). The bromination step was carried out at rt for 2 h in a mixture of toluene (0.7 ml) and THF (100 µL) (conv. 70%). The cyclisation step at 130 °C for 16 h. Purification by flash column chromatography (*n*-hexane/ethyl acetate, 8:2) gave 5,6-dimethoxy-2-(4-methoxy-phenyl)benzo[d]oxazole (36.8 mg, 52%) as a light yellow solid.

Mp 119-120 °C.

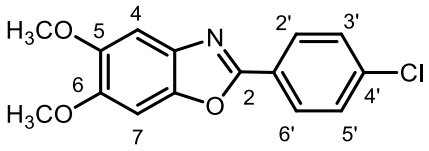
ν_{max}/cm^{-1} (neat) 2928 (ArH), 1604 (C=N), 1501 (C=C), 1481, 1450, 1440, 1421.

^{1}H-NMR (300 MHz, $CDCl_3$, δ ppm): 3.871 (3H, s, 4'-OCH_3), 3.940 (3H, s, 5-OCH_3), 3.947 (3H, s, 6-OCH_3), 7.000 (2H, d, *J* 8.8 Hz, 3'-H and 5'-H), 7.108 (1H, s, 4-H), 7.224 (1H, s, 7-H), 8.106 (2H, d, *J* 8.8 Hz, 2'-H and 6'-H).

^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm): 55.4, 56.45, 56.52, 94.4, 101.7, 114.3, 120.2, 128.7, 135.1, 144.9, 147.6, 147.9, 161.8, 162.5.

m/z (ESI) 308.0883 (MNa^+. 100%).

2-(4-Chlorophenyl)-5,6-dimethoxybenzo[d]oxazole



2-(4-Chlorophenyl)-5,6-dimethoxybenzo[d]oxazole was synthesised as described for 6-methyl-2-phenylbenzo[d]oxazole starting from 4-chloro-*N*-(3,4-dimethoxyphenyl)benzamide (72.93 mg, 0.25 mmol). The bromination step was carried out at rt for 2 h in a mixture of toluene (0.7 ml) and THF (100 µL) (conv. 74%). The cyclisation step at 130 °C for 16 h. Purification by flash column chromatography (*n*-hexane/ethyl acetate, 7:3) gave 2-(4-chlorophenyl)-5,6-dimethoxybenzo[d]oxazole (40.6 mg, 56%) as a pale yellow solid.

Mp 160-161 °C.

ν_{max}/cm^{-1} (neat) 2927 (ArH), 1614 (C=N), 1481 (C=C), 1437, 1402.

^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 3.948 (3H, s, 5-OCH_3), 3.959 (3H, s, 6-OCH_3), 7.110 (1H, s, 4-H), 7.229 (1H, s, 7-H), 7.463 (2H, d, *J* 8.4 Hz, 3'-H and 5'-H), 8.089 (2H, d, *J* 8.4 Hz, 2'-H and 6'-H).

^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm): 56.4, 56.5, 94.2, 101.7, 125.9, 128.2, 129.2, 134.8, 136.9, 145.2, 147.9, 148.6, 161.2.

m/z (ESI) 312.0391 (MNa^+).

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4. Conclusions and Outlook

The present PhD Thesis research was mainly focused on the synthesis and the applications of chiral catalysts based on heterocyclic units, in particular the thiophenic one.

As an appendix of the manuscript, the work concerning my abroad period spent at the University of Glasgow is reported, whose research topic was the synthesis of benzoxazoles through a one-pot two-step procedure involving the use of first iron(III) and copper(I) catalysis for the second step. Even though in this case the research was not addressed to the synthesis of chiral promoters, however the desired products are, as for the rest of the whole manuscript, heterocyclic compounds.

The fields of catalysis investigated are the Lewis Base catalysis and the Brønsted acid catalysis, whose chiral promoters belong to the class of organocatalysis, and finally the catalysis promoted by phosphoramidites that differently from the others, requires the use of metals. Obviously, as suggested from the title of the manuscript, the objective is the stereoselective synthesis.

As a contribution in the catalysis promoted by chiral Lewis Bases and in particular phosphineoxides, the synthesis of TetraPh-Tol-BITIOPO (Chapter 1, **37**) was carried out, which can be considered a further investigation of the huge potentialities of the 3,3'-bithiophenic scaffold in Lewis-base catalysed Lewis-acid mediated reactions, underlined for the first time by enantiopure TetraMe-BITIOPO (Chapter 1, **24**). The molecule was obtained in enantiomerically pure form after chiral semi-preparative HPLC, and then tested as organocatalyst in some stereoselective C-C bond formation reactions. Very good results in terms of catalytic activity were obtained in all the reactions investigated, remarkable ones were achieved also in terms of the stereoselection ability, expecially in the allylation of aromatic aldehydes, in line with what observed using the parent less hindered TetraMe-BITIOPO. Interestingly, comparing the products with those achieved with the latter, in all the investigated reactions, maintaining the same axial configuration, opposite antipodes were obtained. The origin of this interesting behaviour was studied though semiempirical calculations and there are evidences of being a consequence of π-π interactions in the TSs, due to the presence of the phenyl groups in the ortho position of the thiophenes present in the new synthesized TetraPh-Tol-BITIOPO.

For what concern Brønsted acid catalysis, a new chiral phosphoric acid based on a decahydroquinoxalinic scaffold bearing in the position 2 and 3 two thienylic units (Chapter 2, **19**)

was synthesized and tested in two preliminary stereoselective organocatalytic transformations, in order to improve the results in terms of enantioselectivities furnished by the previously synthesized analogue in the Benaglia Group, bearing two phenyl units instead of the thiophenic ones. However, despite the predicted change of the geometry of the chiral pocket size passing from hexatomic carbocyclic rings to pentatomic heterocyclic ones, and all the efforts spent to synthesize cat. **19**, the results obtained were not satisfactory. In order to reduce the steric hindrance in the catalyst's overall structure, the synthesis of a new catalyst (Chapter 2, **34**) in which the phenyl rings facing the acetyl groups were substituted by methyl groups was investigated. Another interesting analogue to get as a target in the future as a further investigation in the field could be the one bearing two fluorine atoms in that molecular region (Figure 1).

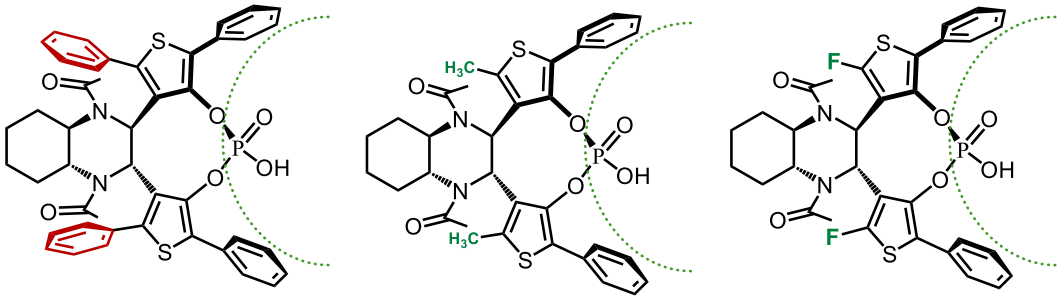

Figure 1

Based on the same decahydroquinoxalinic backbone, we decided to design a new heterocyclic-based diphosphinoxide (Chapter 2, **42**), that was finally achieved, as confirmed by mass spectroscopy, however the process needs to be tuned due to poor yield obtained and the difficulties in the purification of the product.

Leaving the field of organocatalysis, a new heterocyclic phosphoramidite based on a 3,3'-bithiophenic scaffold was synthesized and employed in combination with a copper salt in some catalytic stereoselective 1,4-additions of diethyl zinc to enones and trisubstituted nitroalkenes. The new heteroaromatic ligand showed good catalytic activity while further investigations are needed to evaluate its stereoselection ability.

Concerning the research project under the supervision of Dr. Andrew Sutherland at the University of Glasgow, following an extension of a previous project in the group, the aim was the investigation of a one-pot multistep transformation of *N*-aryl anilides into benzoxazoles through a tandem iron/copper catalysis. After a period of tuning of the suitable substrates and the experimental

conditions, the project resulted to be successful and allowed to the synthesis of nine new benzoxazoles, opening the door to the obtainment of further similar compounds and the investigation of the synthesis of benzothiazoles.

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