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# **CARBON-NITROGEN DOUBLE BOND STEREOSELECTIVE REDUCTION**

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## CHAPTER I

# *Enantioselective Organocatalytic Reductions of C=N Double Bonds*

### 1.1 Introduction

The reduction of C=N bonds represents a powerful and widely used transformation which allows new nitrogen-containing molecules to be generated.

Specifically, the carbon-nitrogen double bond enantioselective reduction is of paramount importance in a variety of bioactive molecules such as alkaloids, natural products, drugs, and medical agents.<sup>[1]</sup>

The employment of a “chiral technology” is, in principle, the most attractive procedure to perform this transformation.<sup>[2]</sup> Catalytic enantioselective reactions provide the most efficient method for the synthesis of chiral compounds, because large quantities of chiral compounds are expected to be prepared using small amounts of chiral sources.<sup>[3]</sup> Recent market analyses have shown that global revenues from chiral technologies soared from \$6.63 billion in 2000 to \$16.03 billion in 2007, growing at a compounded annual rate of 13.4%, and approximately 80% of all products currently in development for the

pharmaceutical industry are based on chiral building blocks.<sup>[4]</sup> In addition, over 90% of chemicals derive from a catalytic process.<sup>[5]</sup>

Over the years, the replacement of metal-based catalysts with equally efficient metal-free counterparts have attracted increasing interest for their low toxicity and for their environmental and economic advantages.<sup>[6]</sup>

Organic catalysis represents now an established possibility of using an organic molecule of relatively low molecular weight, simple structure and low cost to promote a reaction in substoichiometric quantity. Noteworthy, it is also possible to work in the absence of any metal and under non-stringent reaction conditions that are typical of organometallic catalytic process.<sup>[7]</sup>

The organocatalytic approach also satisfies many of the well-known twelve principles of green chemistry.<sup>[8]</sup> Any process based on a catalytic methodology is *green* by definition, because it minimizes waste and increase energy efficiency compared to process that employ stoichiometric reagents. In particular, by employing less hazardous solvents and promoting safer reaction conditions, organocatalysts might represent a solution to the problems related to the presence of toxic metal, whose leaching could contaminate the product and may lead to the design of safer processes and products. In fact, the enantioselective metal-catalyzed hydrogenations suffer from several drawbacks:<sup>[9]</sup> they are generally quite expensive species, typically constituted by an enantiomerically pure ligands (whose synthesis may be costly, long and difficult), and a metal species, in many cases a precious element and there is the possibility of the deactivation or poisoning of catalysts by compounds containing nitrogen and sulfur atoms.

Thus, the replacement of metal-based catalysts with equally efficient metal-free counterparts is very appealing in view of future possible applications in non-toxic, low cost, and more environmentally friendly processes on industrial scale.

Therefore, it's not surprising that in recent years this field of research have attracted the attention of many research groups who are putting extraordinary efforts in studying and developing novel and alternative synthetic organocatalytic stereoselective methodologies.<sup>[10]</sup>

In addition, catalysis in pharmaceutical R&D has been attracting increasing attention due to the competitive pressure to reduce drug development cost and time, the increasing

regulatory requirements that force the companies to develop and study single-enantiomer drugs,<sup>[11]</sup> and environmental protection laws. The picture is completed by the continue discovery of new practical catalysts from both academia and industry, that make new solutions available for production.<sup>[12]</sup>

Catalysis can also be a solution for companies that are exploring ways to address the problem of the increasing complexity of the chemical targets. The average number of manipulations required to synthesize an active pharmaceutical ingredient (API) continues to grow and currently amounts to an average of 12 synthetic steps.

In this context, it is clear how the stereoselective reduction can be considerate a fundamental process and in this chapter the enantioselective reduction of carbon-nitrogen double bond promoted by organocatalysts was briefly discussed.

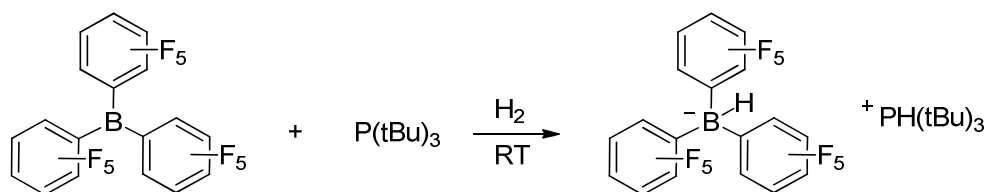
In particular, the FLP (Frustrated Lewis Pair) method and binaphthol-derived phosphoric acids in the presence of a dihydropyridine-based compound were described, while the use of trichlorosilane for CN reduction will be deeply discussed in the next chapter.

## 1.2 Catalytic hydrogenation with Frustrated Lewis Pairs

The use of H<sub>2</sub> as a reducing agent for unsaturated substrates is very well known procedure and it can be considered as perhaps the most important catalytic method in synthetic organic chemistry. Indeed, hydrogenation catalysis is the most common transformation used in the chemical industry and is employed in the preparation of scores of commercial targets, including natural products and commodity and fine chemicals.<sup>[13]</sup> Several studies led to a number of important developments including the transition metal dihydrogen complexes, transition metal systems that effect the heterolytic cleavage of hydrogen and metal-based catalysts for asymmetric hydrogenation; the fundamental importance of these studies has been clearly recognized by the award of the Nobel Prize to Knowles and Noyori.

Recent studies have been directed to the exploitation of non-transition metal systems for the activation of H<sub>2</sub> and the subsequent use in hydrogenation. A novel and promising approach to the utilization of hydrogen in catalysis has emerged from studies related to the use of a proper combination of a Lewis acid and a Lewis base, in which steric

demands preclude classical adduct formation, called “frustrated Lewis pairs” or “FLPs”.<sup>[14]</sup> In these unique Lewis acid–base (LA–LB) adducts, the steric hindrance precludes the formation of stable donor–acceptor complexes on account of which these pairs are kinetically able to promote various unprecedented reactions with organic and inorganic molecules. Their most remarkable reactivity is the heterolytic cleavage of hydrogen at ambient temperature (Eq. 1), a process that was long thought to be the exclusive characteristic of transition metals.



**Equation 1**

Computational studies suggest the generation of a phosphine-borane “encounter complex”, stabilized by H···F interactions.<sup>[15]</sup> In this species the boron and phosphorus centers are close but fail to form P to B dative bond as a result of steric congestion. Interaction of H<sub>2</sub> in the reactive pocket between the donor and acceptor sites (Figure 1) results in heterolytic cleavage of H<sub>2</sub>; according to the proposal FLPs fulfill a similar function as the frontier orbitals on transition metals.

However very recent computational studies<sup>[16]</sup> of the (quasi)linear P···H-H···B activation mechanism of the system cast some doubt on the corresponding transition state. According to these new results, a transition state in a linear arrangement only appears for rather large P···B distances over 4.5 Å. Such values seem to be artificially induced by the quantum chemical method (B3LYP) which is well known to overestimate steric congestion. With properly dispersion-corrected density functional no linear transition state exists and only one minimum with a rather large H–H distance of about 1.67 Å could be found. This points to an alternative bimolecular mechanism in which H<sub>2</sub> access into the *frustrated* P···B bond is the rate-determining step. Further theoretical studies to address this important question are needed in order to fully elucidate the mechanism.



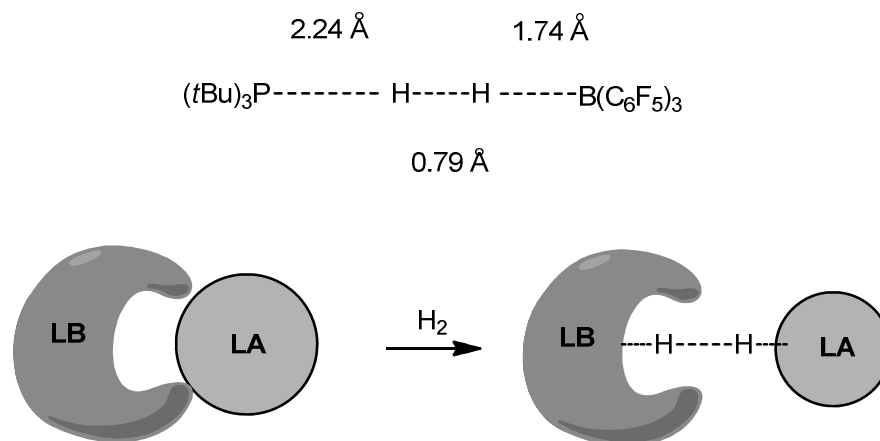


Figure 1

Several inter- and intramolecular combinations of bulky Lewis acid–base pairs were effectively tested for the heterolytic cleavage of hydrogen. Highly active FLPs **2-3** of Figure 2 with a linked design were reported from the groups of Erker, Repo, Rieger and Tamm.<sup>[17]</sup>

Subsequently, this methodology was exploited in metal-free hydrogenation procedures. First, Stephan and co-workers reported a structurally bifunctional phosphine–borane **1** for the metal-free hydrogenation catalysis (Figure 2).<sup>[18]</sup>

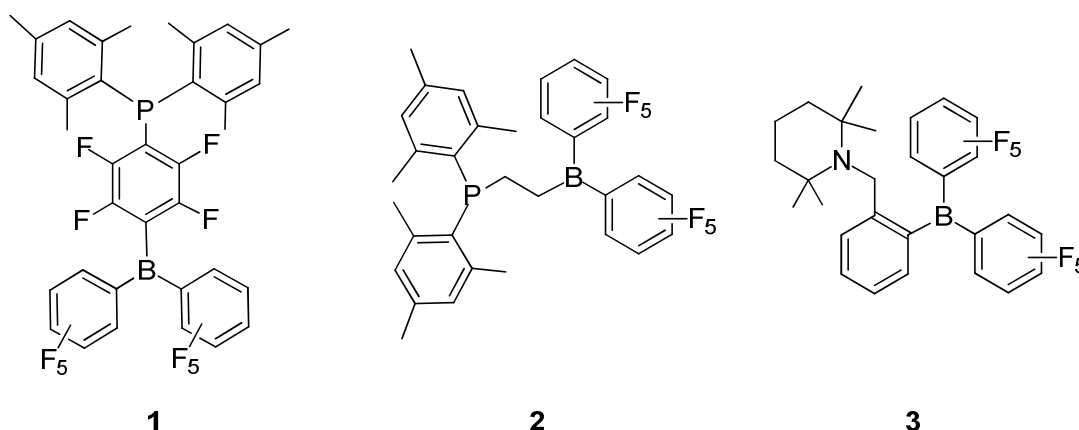
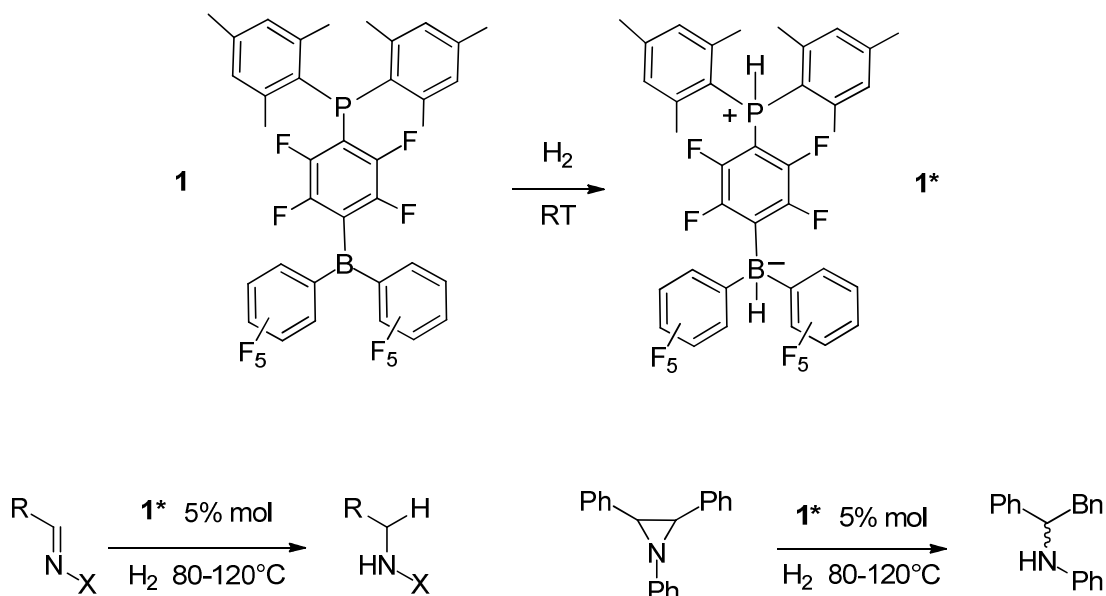


Figure 2

Thus, using a catalytic amount of **1\*** and heating to 80–120 °C under 1–5 atm H<sub>2</sub> resulted in the hydrogenation of a variety of imines in high isolated yields. Similarly, the *N*-aryl

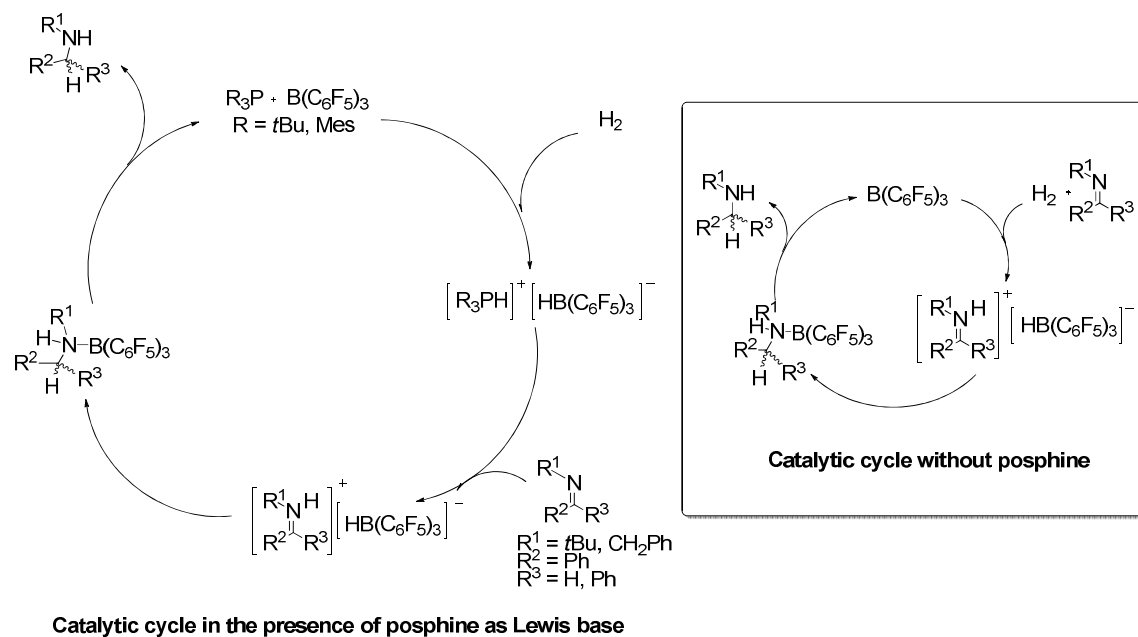
aziridines were catalytically hydrogenated. Mechanistic studies point to the initial protonation of the imine, followed by hydride transfer to the carbon of the iminium salt (Scheme 1).



**Scheme 1**

Then, more focus was placed on the development of intermolecular and easily available FLPs for hydrogen activation and relied on the tris(pentafluorophenyl)borane as the LA component.<sup>[14]</sup> Following these initial studies about metal-free catalytic hydrogenation of imines, the authors thought to use the substrate as the base-partner of an FLP, requiring only a catalytic amount of tris-pentafluorophenyl borane.

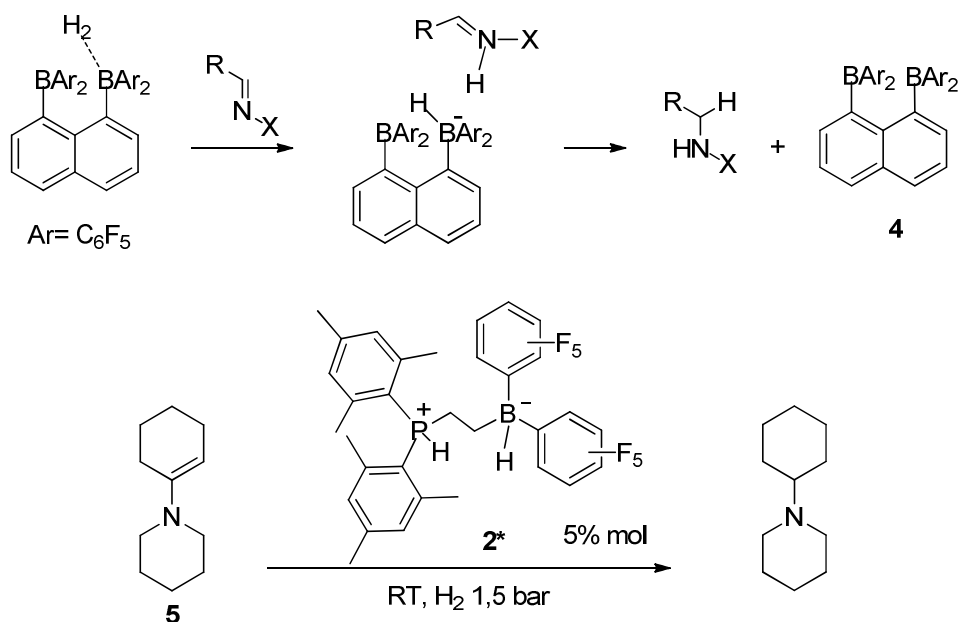
Indeed, a series of differently substituted imines were reduced under hydrogen using just a catalytic amount of B(C<sub>6</sub>F<sub>5</sub>)<sub>3</sub> (Scheme 2).<sup>[19]</sup> In case of poorly basic imines, addition of catalytic amount of sterically encumbered phosphine accelerated the reductions. This presumably results from the greater ease with which phosphine/borane heterolytically cleaves hydrogen.



### Scheme 2

Berke and coworkers described the use of 2,2,6,6-tetramethylpiperidine and 1,8-bis(dipentafluorophenylboryl)naphthalene **4** to activate  $H_2$  and to reduce a variety of imines under mild conditions (Scheme 3).<sup>[20]</sup>

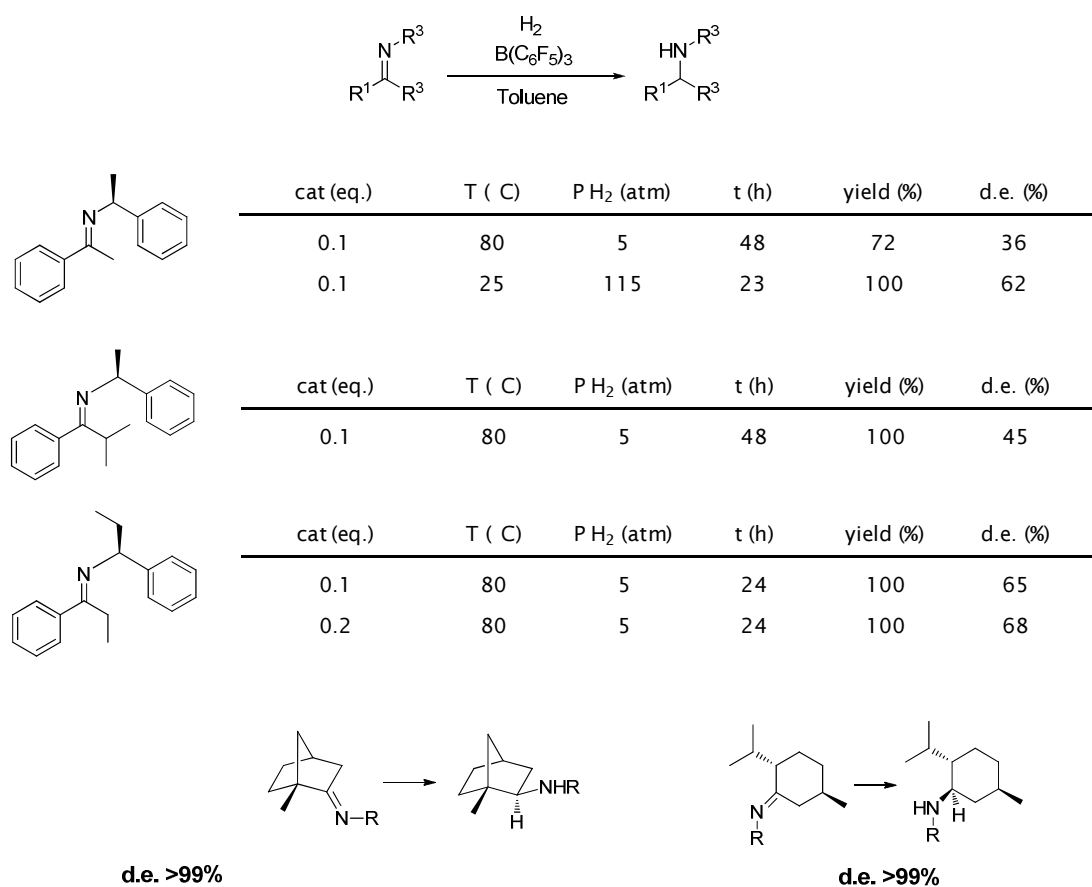
The Erker group has extended the range of these reductions, demonstrating that the species **2\*** acts as a catalyst for the hydrogenation of imines and ketimines under ambient conditions. 1,8-Bis(diphenylphosphino)-naphthalene and  $B(C_6F_5)_3$  promotes also the hydrogenation of enamines **5** and silyl enol ethers at 25°C under 2 bar of hydrogen when used in high concentrations (Scheme 3).<sup>[21]</sup>



Scheme 3

The potential of this system for applications in asymmetric synthesis is highly desirable. Indeed, stereoselective methodologies can be designed considering FLP reductions as a catalytic version of borohydride reductions.

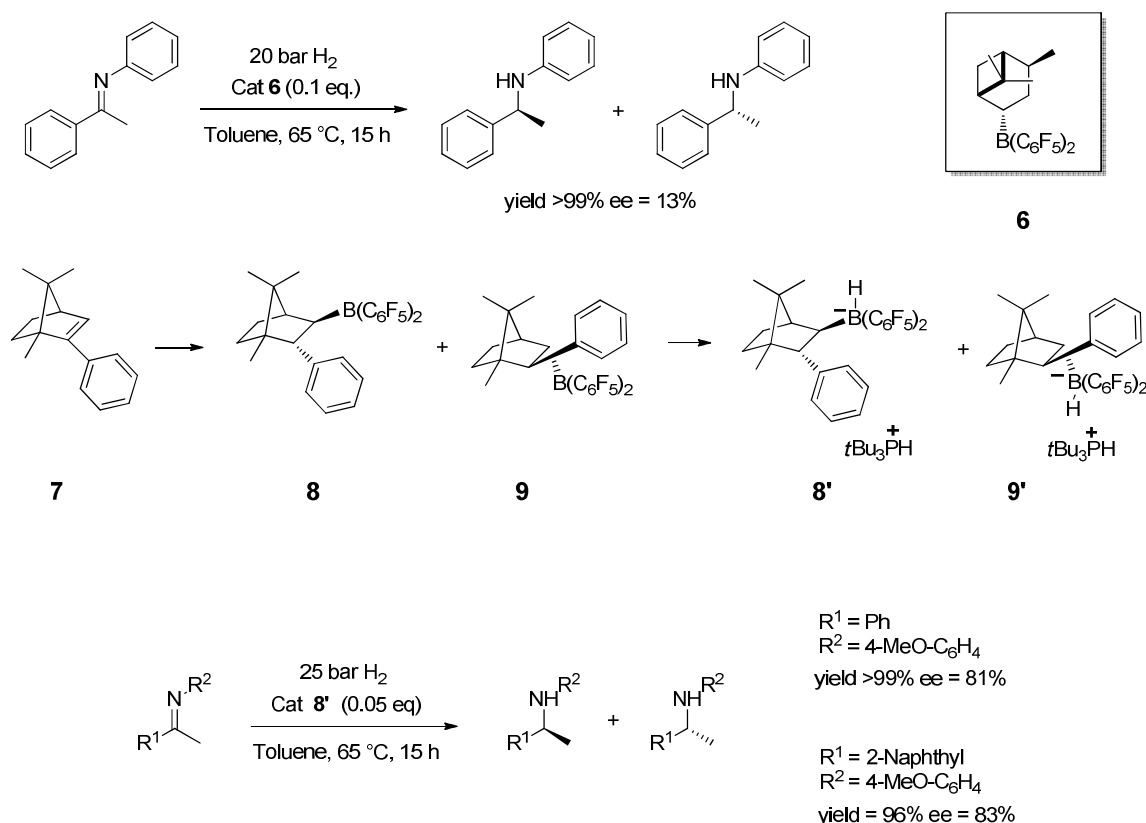
With this in mind, Stephan studied the catalytic hydrogenation of chiral ketimines using tris-pentafluorophenyl borane as a catalyst.<sup>[22]</sup> Using imines derived from camphor and menthone, the reductions proceed with high diastereoselectivity. The reduction of chiral imines with B(C<sub>6</sub>F<sub>5</sub>)<sub>3</sub> resulted in excellent diastereoselectivities when the stereogenic center was close to the unsaturated carbon center, probably due to the larger effect of proximity of the stereocenter on the approach of the sterically bulky [HB(C<sub>6</sub>F<sub>5</sub>)<sub>3</sub>] species. On the other hand, the presence of the stereogenic center close to the unsaturated nitrogen center had a minor impact on the diastereoselectivity of the hydrogenation. (Scheme 4)



Scheme 4

Once again, the imine acts as base partner for  $\text{B}(\text{C}_6\text{F}_5)_3$  to perform the heterolytical  $\text{H}_2$  cleavage. The resulting anion  $[\text{HB}(\text{C}_6\text{F}_5)_3]^-$  then transfers the hydride to the carbon-atom of the iminium cation affording the amine and regenerating the initial borane which is then available for further reduction. By using camphorimines and menthonimines, the hydride-transfer from  $[\text{HB}(\text{C}_6\text{F}_5)_3]^-$  to the corresponding iminium cation proceeds *via* approach of the anion toward one of the two diastereotopic faces of the iminium cations. Finally, an important development has been made by Klankermayer, who developed asymmetric FLP hydrogenation with a sterically crowded chiral borane as Lewis acid (Scheme 5). In preliminary effort to perform an enantioselective catalytic FLP hydrogenation a chiral borane **6** was used to reduce a ketimine. In early experiments employing a pinene-derived chiral catalyst, asymmetric reduction of imines was achieved, although with low enantioselectivity (13% ee).<sup>[23]</sup>

In a very recent work, this group has extended this strategy, developing chiral borane catalysts for the enantioselective imine reduction with enantioselectivities as high as 84%.<sup>[24]</sup>



Scheme 5

The hydroboration of a 2-phenyl bicycloheptene **7** derivative using bis(perfluorophenyl)borane (Scheme 5) in toluene or pentane gave the diastereomeric boranes **8** and **9** in a 20:80 ratio as confirmed by multinuclear NMR spectroscopy. Treatment of an *n*-pentane solution of the borane mixture **8** and **9** with hydrogen at 25°C in the presence of tri-*tert*-butylphosphine resulted in the precipitation of a colorless solid in 53% yield. Multinuclear NMR spectroscopy confirmed the product to be a mixture of the activated FLP salts **8'** and **9'** after the hydrogen splitting isolation of the diastereomerically pure compounds through kinetically controlled product formation. Then, with the chiral compounds **8'** and **9'** in hand, the catalytic hydrogenation of prochiral imines was investigated. In the presence of 5 mol% catalyst (1:1 mixture of the

two diastereoisomers) at 65°C and 25 bar hydrogen, imine *N*-(1-phenylethylidene)aniline was transformed into the corresponding secondary amine with an enantioselectivity of 20% ee. The use of the diastereomerically pure salts as catalysts for the hydrogenation process gave more encouraging results. By using **8'**, full conversion into the *S* product was achieved in 48% ee, while **9'** led to the *R* enantiomer with a higher enantioselectivity of 79% ee.

These results represent only the beginning of a very promising area,<sup>[25]</sup> the investigation and the development of highly stereoselective metal-free catalytic methodologies, based on the general concept of FPL activation of hydrogen and other small organic molecules.

### 1.3 Enantioselective reductions promoted by chiral phosphoric acids

The electrophilic activation of a substrate by means of a Brønsted acid is certainly the most straight forward and common approach used to promote a reaction and hence Brønsted acids have been widely utilized as efficient catalysts for numerous organic transformations. However, the synthetic utility of a Brønsted acid as catalyst for stereoselective reactions has been quite limited until recently (Figure 3). It was generally accepted that the Brønsted acid must have a “proton-like” character to effectively activate a substrate and the conjugate base ( $A^-$ ) has any effect in the stereo- and regioselective formation of products but only influences the catalytic activity.

Thus, in the past decade, research has focused on chiral Brønsted acid catalysis, in which enantioenriched products are obtained using a catalytic amount of a chiral organic molecule bearing an acidic functionality. The key to obtain enantioselective catalysis using a chiral Brønsted acid is the hydrogen bonding interaction between a protonated substrate ( $Sub-H^+$ ) and the chiral conjugate base ( $A^{*-}$ ) (Figure 3). Therefore the organic transformations proceed under a chiral environment created by the chiral conjugated base ( $A^{*-}$ ), which exists in the proximity of the substrate through hydrogen bonding interactions.

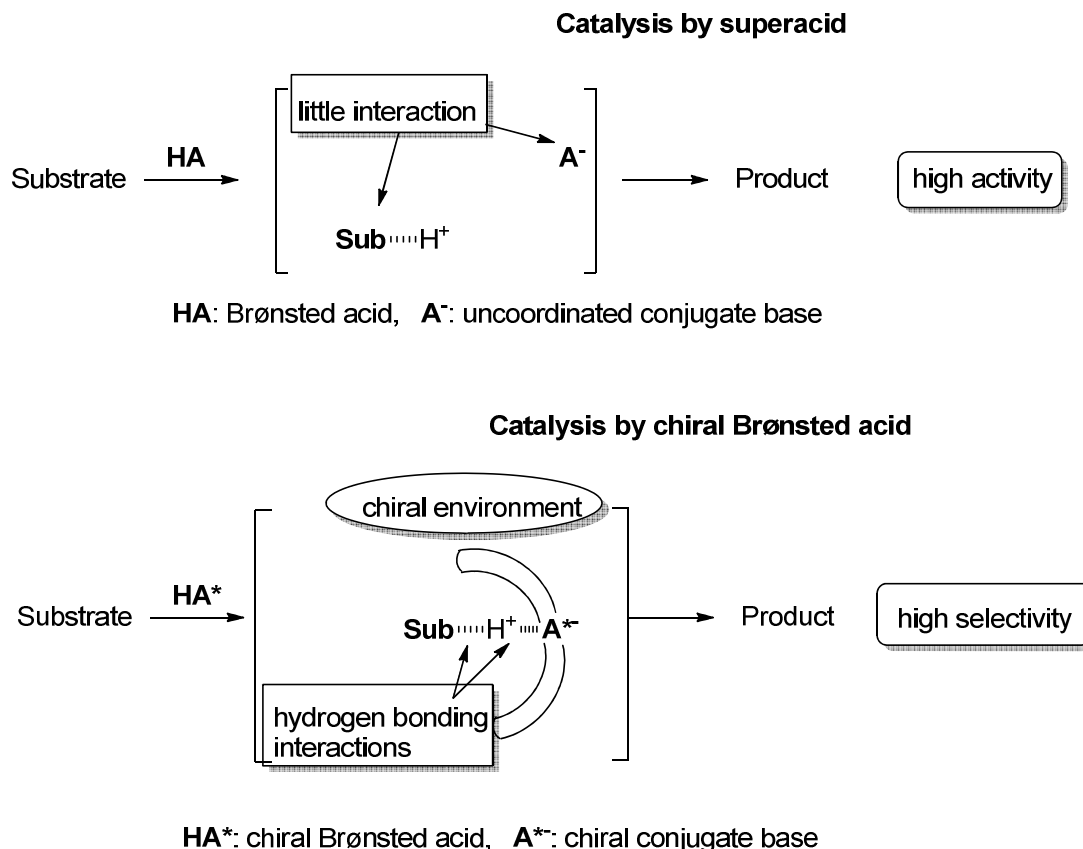


Figure 3

In this context, phosphoric acids attracted much attention because they are expected to capture electrophilic components through hydrogen bonding interactions without the formation of loose ion-pairs thanks to their relatively strong but appropriate acidity (for example  $pK_a$  of  $(EtO)_2P(O)OH$  is 1.39).<sup>[28]</sup>

The phosphoryl oxygen would function as a Brønsted basic site and, in this way, it can be anticipated an acid/base dual function even for monofunctional phosphoric acid catalysts.

The introduction of a ring structure can prevent the free rotation at the  $\alpha$ -position of the phosphorus centre and exert steric hindrance. This characteristic cannot be found in other Brønsted acids such as carboxylic and sulfinic acids.

Substituents (STG) can be introduced on the ring system to provide a chiral environment for enantioselective transformations (Figure 4).

Therefore an efficient substrate recognition site could be constructed around the activation site of the phosphoric acid catalyst, namely the acidic proton, as a result of the acid/base dual function and stereoelectronic influence of the substituents.



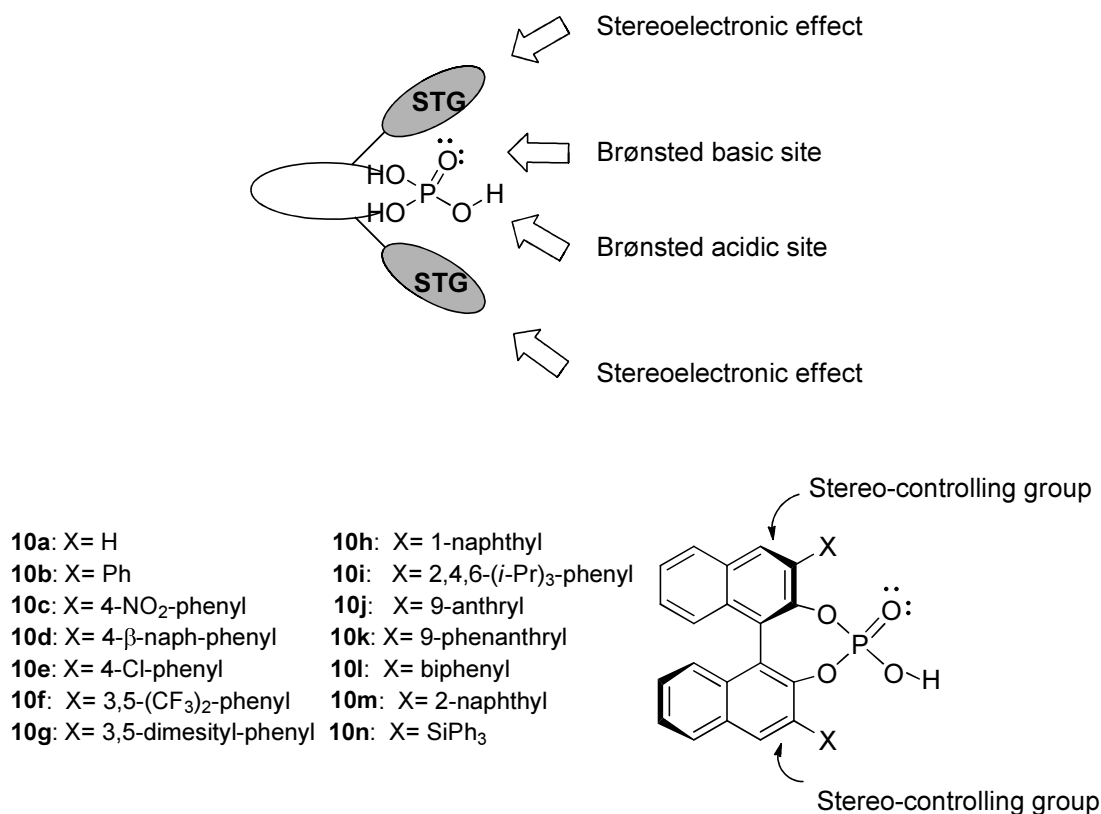
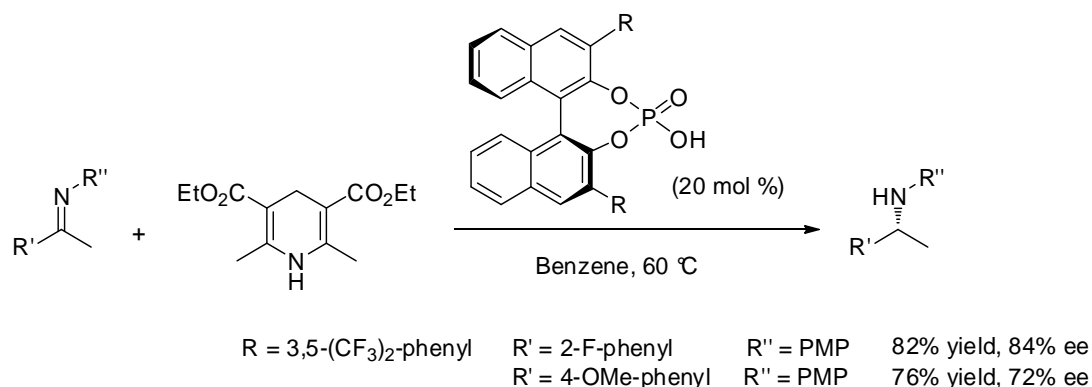


Figure 4

Binaphthol (BINOL) is well known molecule having  $C_2$  symmetry, whose derivatives have been extensively used as chiral ligands for metal catalysis. Thus, the BINOL derivatives were selected as chiral sources to assemble the catalyst with the advantage that both enantiomers are commercially available and numerous protocols for introducing substituents at the 3,3'-position of the binaphthyl backbone are known. A few examples of (*R*)-BINOL-derived phosphoric acids developed in the last few years as catalysts for a great number of reactions are reported in Figure 5.<sup>[29]</sup>

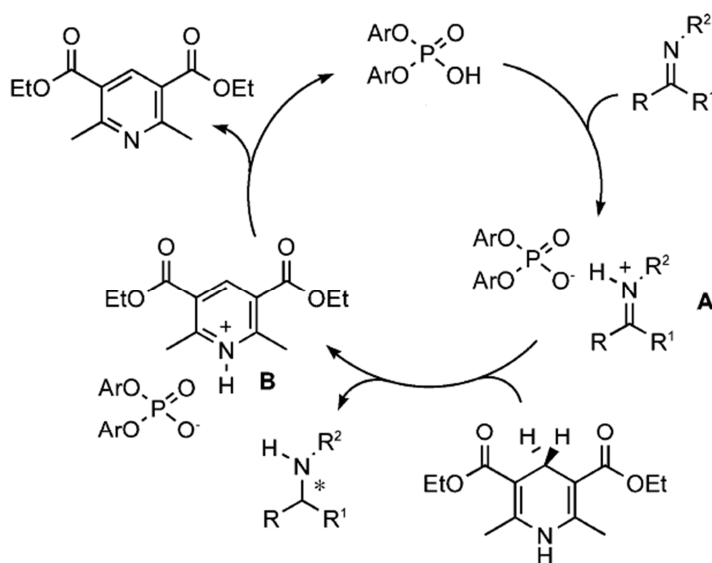
In 2005 Rueping's group reported the first enantioselective Brønsted acid-catalysed reduction of ketimines.<sup>[30]</sup> The authors reported several derivatives bearing acidic protons for catalyse the reduction of imines under hydrogen-transfer conditions with Hantzsch dihydropyridine as hydride source, envisioning a catalytic enantioselective process. Phosphoric acid **10f** was selected as best performing catalyst, showing that steric as well

as electronic effects play a role in this transformation. No reaction was observed in polar protic media while the best yields and selectivities were obtained in benzene (68-84% ee, Scheme 6).



**Scheme 6**

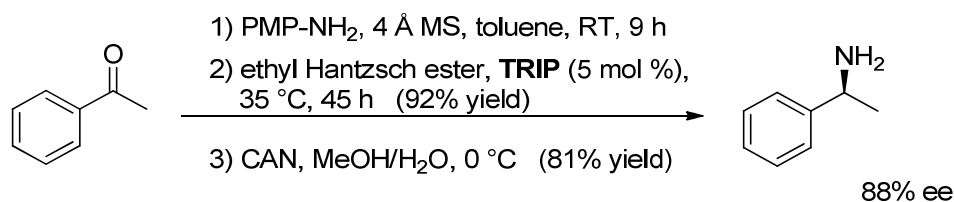
As shown in Figure 5, the ketimine was activated through protonation by the Brønsted acid affording iminium ion **A**. The hydrogen transfer from dihydropyridine yields the chiral amine and pyridinium salt **B**, which undergoes proton transfer to regenerate the phosphoric acid. In the proposed transition state, the ketimine is activated by the Brønsted acid and the mechanism proceeds through nucleophilic addition from the least hindered *Si* face, because aryl group shields the *Re* face.



**Figure 5**

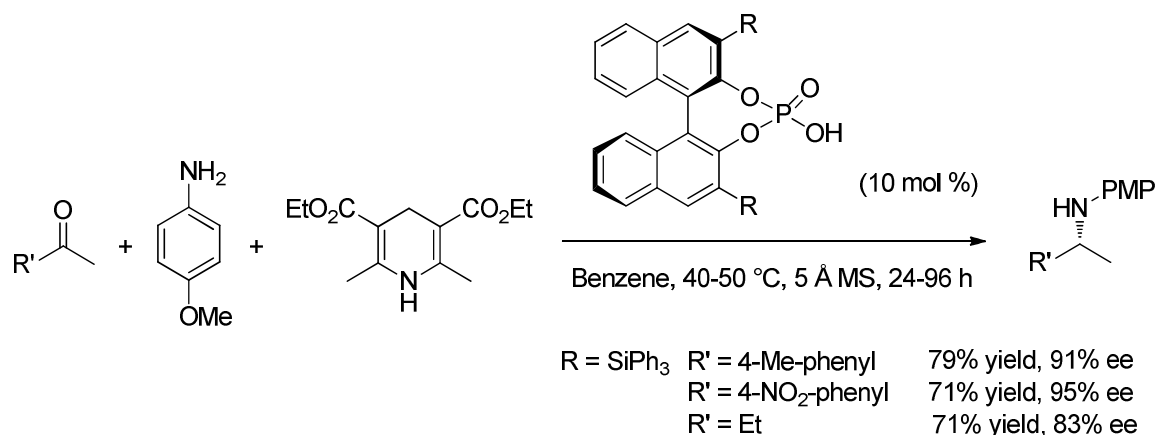
Parallel and independent studies conducted by List resulted in the development of new catalysts.<sup>[31]</sup> Indeed, a differently substituted catalyst (**10i**, (*R*)-3,3'-bis(2,4,6-triisopropylphenyl)-1,1'-binaphthyl-2,2'-diyl hydrogen phosphate (TRIP)), under optimized condition, performed better than the one reported by Rueping in terms of shorter reaction times, higher yields and ee values (80–98% yields, 80–93% ee) and lower catalyst loading. Moreover, this catalyst was also used in the reduction of aliphatic ketimines with high enantioselectivity.

This work also reported the first enantioselective organocatalytic reductive amination. Acetophenone was first treated with 4-OMe-aniline in the presence of molecular sieves, followed by *in situ* reduction catalyzed by TRIP. Finally, oxidative removal of the PMP group with cerium ammonium nitrate afforded the corresponding primary amine in very good yield and enantiomeric excess (Scheme 7).



**Scheme 7**

More recently, MacMillan's group properly explored this organocatalytic reductive amination and reported the use of the *ortho*-triphenylsilyl phosphoric acid **10n**, in the presence of MS 5 Å, to promote the coupling between acetophenone and 4-OMe-aniline in high conversion and with excellent levels of enantiocontrol at 40 °C (87% yield, 94% ee).<sup>[32]</sup> The scope of this reaction is quite wide, as a variety of substituted acetophenone derivatives can be successfully employed, including electron-rich, electron-deficient, as well as *ortho*, *meta* and *para* substituted aryl ketone systems. Moreover, also methyl alkyl ketones proved to be suitable substrates (Scheme 8). It is noteworthy that this last example highlights a key benefit of reductive amination versus imine reduction: in this way also the unstable imines derived from alkanones were reduced.



Scheme 8

The reduction of the pyruvic acid-derived cyclic imino ester was also reported with excellent enantioselectivity. However, when aliphatic ketone was exposed to the same reaction conditions, a dramatic decrease in both yield and enantioselectivity was observed. More specifically, imines that incorporate a methyl group are predicted to undergo selective catalyst association wherein the C=N *Si*-face is exposed to hydride addition. In contrast, the ethyl containing substrate is conformationally required to position the terminal CH<sub>3</sub> of the ethyl group away from the catalyst framework, thereby ensuring that both enantiofacial sites of the iminium  $\pi$ -system are similarly shielded (Figure 6).

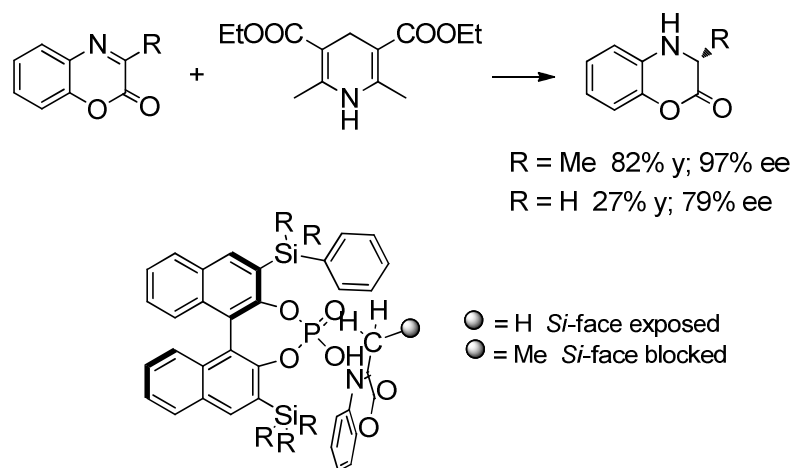
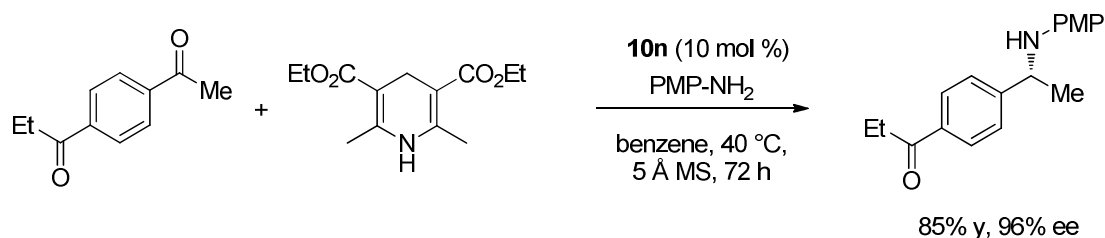


Figure 6

This example suggests that this catalyst is generically selective for the reduction of iminium ions derived from methyl ketones. Similarly, the system was successfully tested in the amination of the *para* substituted aryl diketone reported in Scheme 9: this substrate underwent chemoselective reduction with a 18:1 preference for reaction at the methyl ketone site.



Scheme 9

While it is obvious that aldimines cannot undergo direct enantioselective reduction due to the formation of an achiral product, List's group discovered an interesting variation on this theme with the direct reductive amination of chiral  $\alpha$ -branched aldehydes *via* an efficient dynamic kinetic resolution (DKR).<sup>[33]</sup> Under the reductive amination conditions an  $\alpha$ -branched aldehyde undergoes a fast racemization in the presence of the amine and acid catalyst *via* an imine/enamine tautomerization. The reductive amination of one of the two imine enantiomers would then have to be faster than that of the other, resulting in an enantiomerically enriched product *via* a dynamic kinetic resolution (Figure 7).

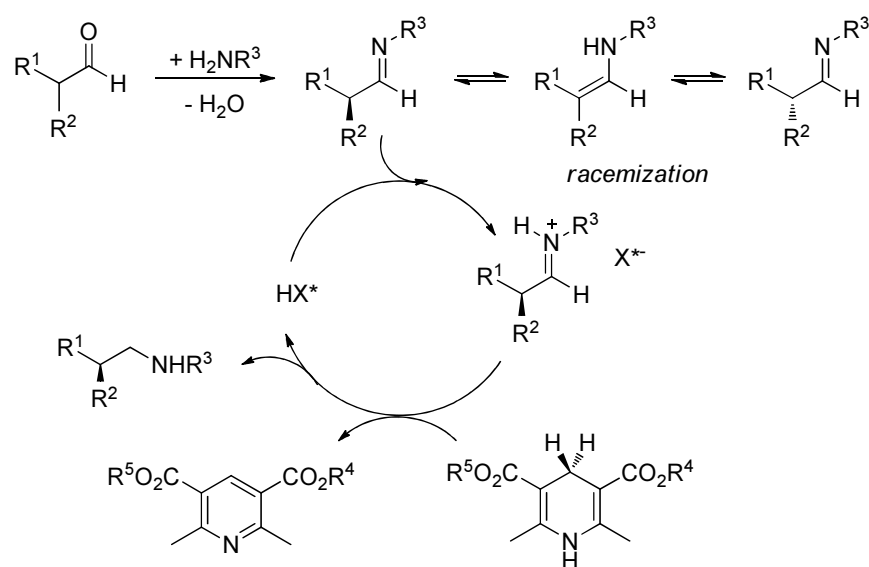
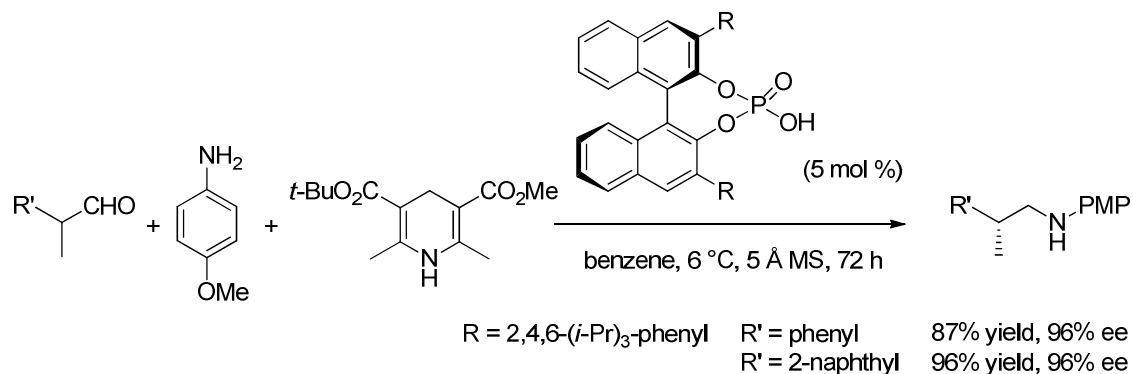


Figure 7

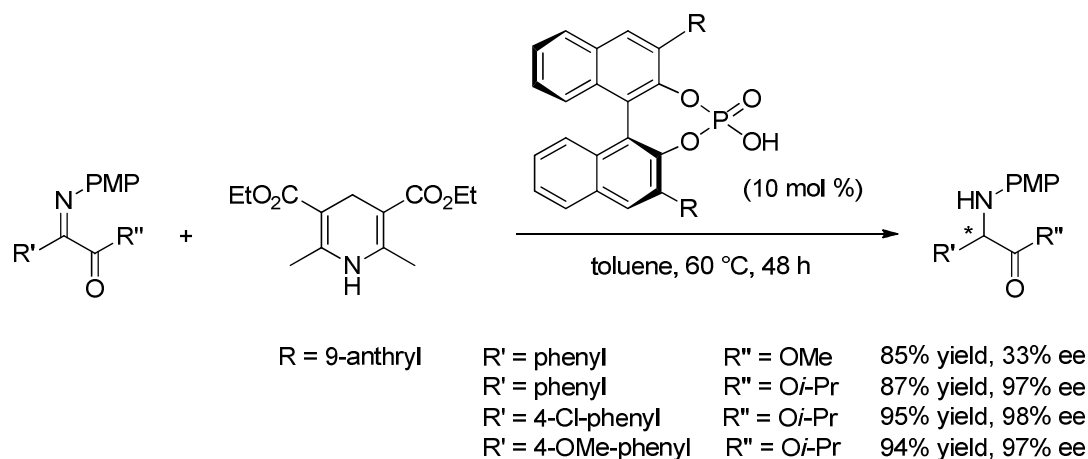
TRIP once again turned out to be the most effective and enantioselective catalyst for this transformation and provided the chiral amine product in 50% yield with enantiomeric ratio equal to 84:16, which could be raised to 87% yield and 96% ee under optimized conditions (Scheme 10).



**Scheme 10**

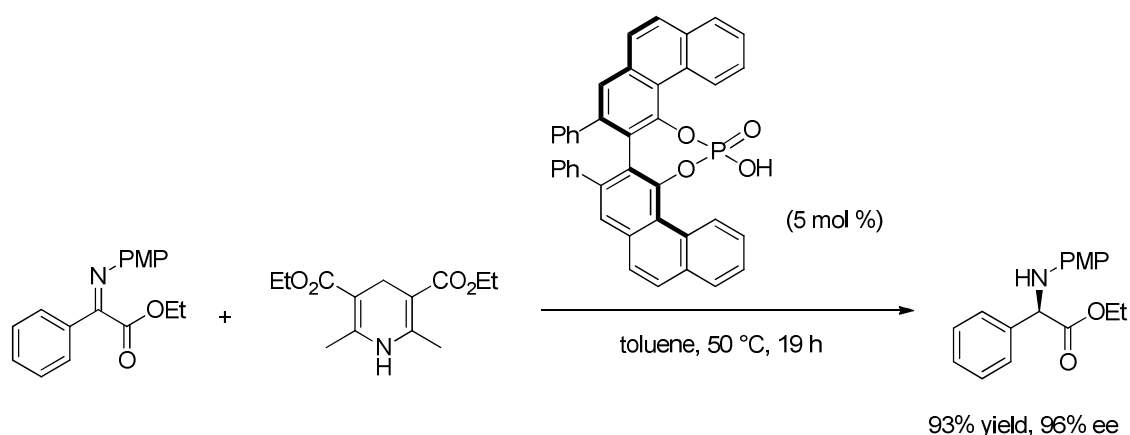
The efficient removal of water formed during the reaction seems to be important as the enantiomeric ratio improved considerably upon using 5 Å molecular sieves; furthermore, oxygen-free conditions are required to avoid the generation of acetophenone and *p*-formyl anisidine.

In 2007, You extended the use of chiral phosphoric acids for the hydrogenation of  $\alpha$ -imino esters and their derivatives, also reporting the synthesis of a gram scale sample *via* this methodology.<sup>[34]</sup> With the best performing catalyst (**10j**) and under optimized conditions, the reaction scope was examined. It was observed that the enantioselectivity was highly dependent on the steric size of the ester group. High ee were obtained with substrates bearing bulky ester groups such as *i*-Pr and *t*-Bu, whereas only 33% ee was given for the methyl ester substrate. In addition, several substituted phenyl isopropyl esters containing either electron-donating or electron-withdrawing groups were tested and all of them led to good yields and excellent ee (Scheme 11). However, a low reactivity towards the alkyl-substituted imino ester was observed.



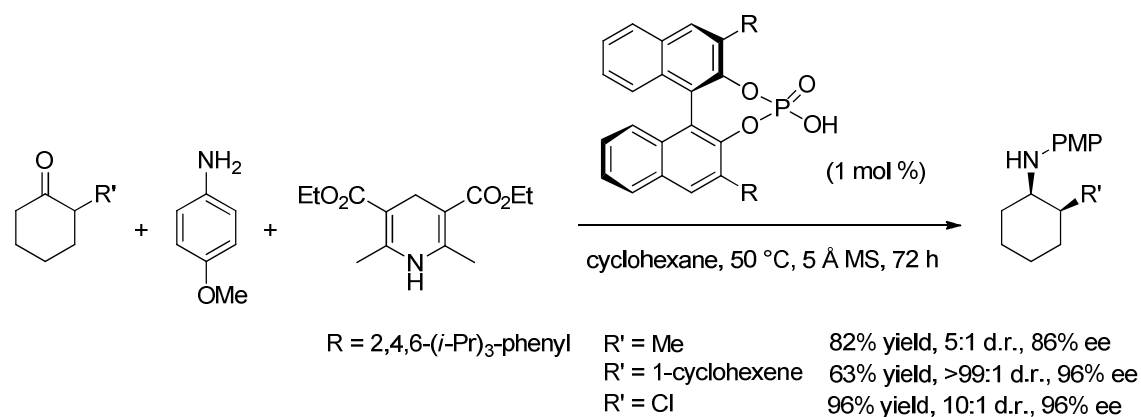
Scheme 11

Later, Antilla and co-workers reported the organocatalytic reduction process in the enantioselective synthesis of protected  $\alpha$ -amino acids.<sup>[35]</sup> Using a VAPOL-derived phosphoric acid, readily available  $\alpha$ -imino esters were efficiently reduced to the corresponding amines with stoichiometric amounts of Hantzsch ester. Notably, the VAPOL derivative gave excellent results, as well as to a small library of alternative chiral phosphoric acid catalysts. The scope of the reaction is quite general: imino esters derived from both aromatic and aliphatic  $\alpha$ -keto esters could be transformed smoothly. However, the analogous reductive amination process involving *in situ* imino ester formation is inefficient and selective only when the starting materials bear aliphatic substituents (Scheme 12).



Scheme 12

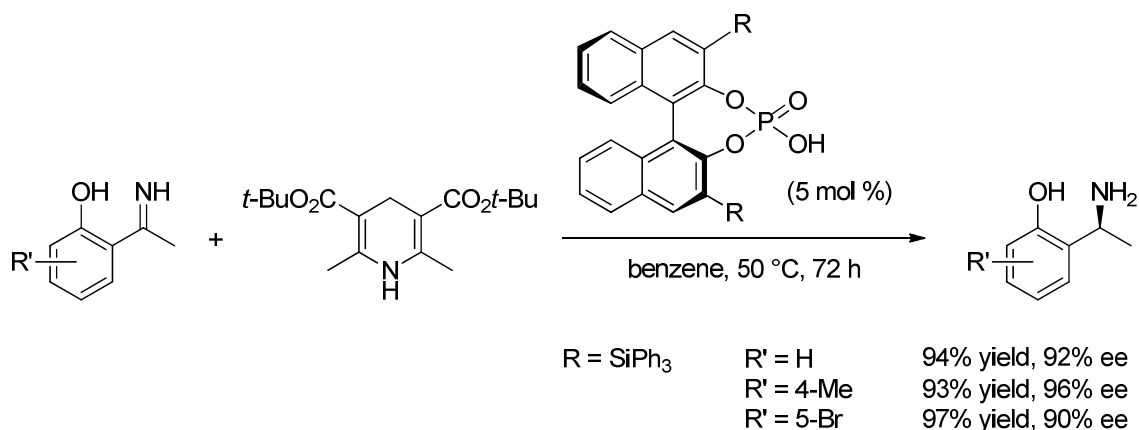
Three years later, List's group reported the first catalytic asymmetric reductive amination of racemic  $\alpha$ -branched ketones using dynamic kinetic resolution (DKR)<sup>[36]</sup>. This methodology was used with a variety of different substituents whilst maintaining excellent enantioselectivity. Simple alkyl-substituted substrates are particularly reactive, requiring low amount of catalyst, while sterically more-demanding substrates, as well as aromatic substrates, requires slightly higher catalyst loadings. Even chlorine is tolerated in the  $\alpha$  position, and, by employing 2.4 equivalents of the Hantzsch ester,  $\alpha,\beta$ -unsaturated,  $\alpha$ -branched ketones can be also converted into the desired product in reasonable yields and excellent selectivity (Scheme 13).



**Scheme 13**

During the same year, Wang and co-workers reported the first examples of enantioselective transfer hydrogenation of unprotected orthohydroxyaryl alkyl N-H ketimines using chiral phosphoric acid as a catalyst and Hantzsch ester as the hydride source<sup>[37]</sup>. The hindered (*S*)-3,3'-bis(triphenylsilyl)-substituted phosphoric acid turned out to be the most effective in terms of stereoselectivity, and benzene was the best reaction medium. Under optimal conditions, authors isolated the unsubstituted amine in 94% yield with 92% ee, while the presence of either an electron-withdrawing or an electron-donating group at C-3, C-4, and C-5 positions of the aromatic ring did not affect significantly the enantioselectivity (Scheme 14). It is remarkable to observe that previously only *N*-Ar imines derived from acetophenone were used as substrates in this highly enantioselective phosphoric acid catalyzed methodology.





Scheme 14

NMR studies showed that phosphoric acid **10n** is able of breaking the intramolecular H-bond between the phenolic O-H and the imine nitrogen and activating the imine *via* the formation of an intermolecular H-bond with the imine nitrogen. Consequently, authors proposed the transition state A shown in Figure 8, wherein the phosphoric acid formed H-bonds with both the hydroxyl and the imine functions of the substrate. The hydride transfer occurs from the *Re* face of the imines and lead to amines with *S* configuration.

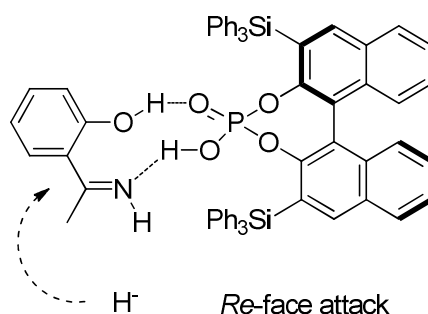
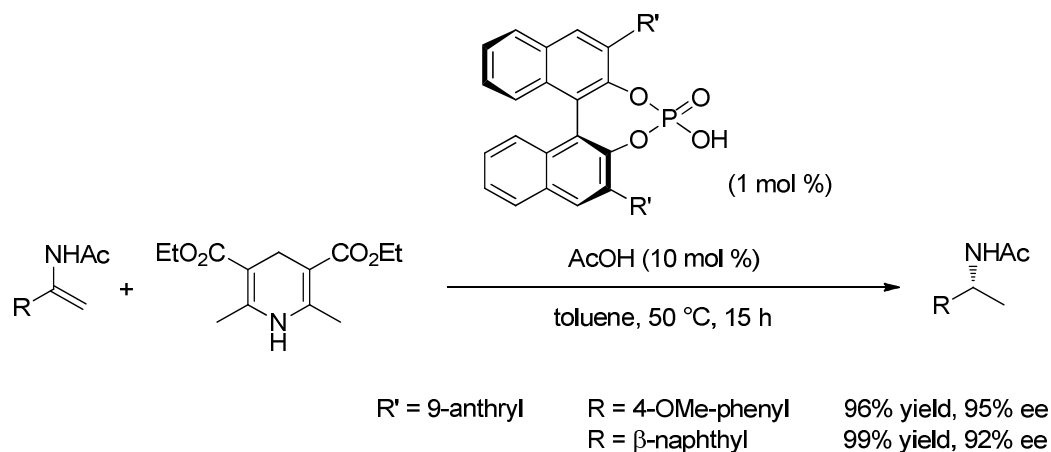


Figure 8

One important breakthrough in the field was achieved by Antilla and Li in 2009<sup>[38]</sup>, who reported the asymmetric hydrogenation of enamides with high enantioselectivity by using chiral phosphoric acid catalysis. Although the reductive amination of ketones and the hydrogenation of ketimines catalysed by chiral Brønsted acids have already been reported with high enantioselectivities, these reactions were limited to aniline and its derivatives. As a result, the deprotection of the amino group is relatively difficult and make these methods less synthetically appealing. On the contrary, considering *N*-acyl enamide

substrates, the acyl group can be easily removed under standard procedures in good yield. The catalytic strategy to couple the phosphoric acid with a suitable achiral weaker acid allowed to facilitate iminium formation, which is inactive in the hydrogenation step, and to achieve a significant increase of yield with no loss in enantioselectivity (Scheme 15).



**Scheme 15**

In the hypothesized catalytic cycle, the enamides tautomerized in the presence of catalyst and acetic acid to the corresponding imine, which is activated by the acid *via* the iminium intermediate. In the following step, only chiral phosphoric acid is active enough to catalyse the hydrogenation of the imine, while the acetic acid maintains an adequate concentration of iminium intermediate (Figure 9).

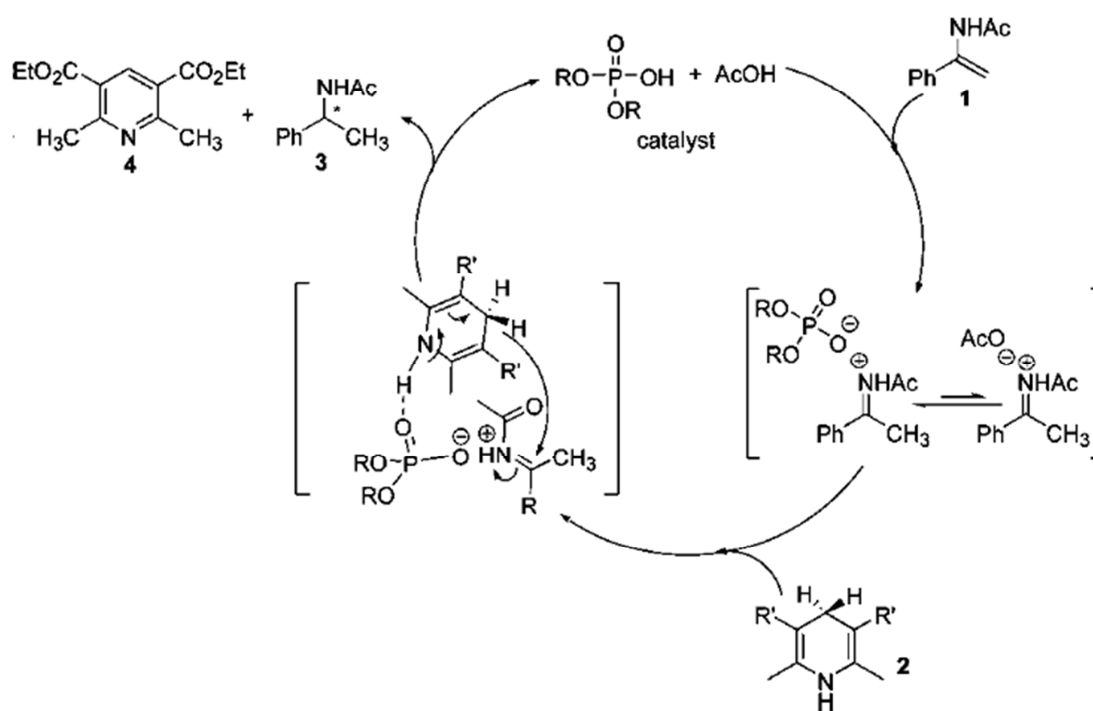


Figure 9



## CHAPTER II

### *Silicate-mediated Stereoselective Reductions Catalyzed by Chiral Lewis Bases*

The chemistry of penta and/or hexavalent silicon compounds has recently attracted much attention because of the possibility to develop organocatalysed enantioselective reactions in the presence of cheap, low toxic and environmental friendly species such as hypervalent silicates.<sup>[39]</sup> Even if the discovery of silicon compounds with a coordination number greater than four dates back to 1809, when the adduct  $\text{SiF}_4 \cdot 2 \text{NH}_3$  was reported by Gay-Lussac,<sup>[40]</sup> only in the last forty years the distinctive reactivity displayed by penta- and hexavalent silicon compounds has been increasingly studied, and organosilicon compounds have become more and more important intermediates in organic synthesis.<sup>[41]</sup> More recently, the possibility to develop organocatalytic silicon-based methodologies has given even new impulse to the studies in this field. The tremendous growth of the interest in what is currently referred to as the "organocatalytic" approach toward enantioselective synthesis, is strongly indicative of the general direction toward which modern stereoselective synthesis is moving.

In the last few years, stereoselective versions of several reactions promoted by silicon-based catalysts have been developed,<sup>[42]</sup> especially promoted by hypervalent silicate

intermediates used as chiral Lewis bases.<sup>[43]</sup> Before entering in the discussion of these different reactions, it is important to summarize the mechanism that is responsible of the formation of silicon hypervalent states.

## 2.1 Hypervalent bonding analysis

The theory of acid–base interactions, pioneered by G. N. Lewis at the beginning of the 20th century, provides the basis for the state of knowledge about hypervalent silicon; indeed, hypervalent compounds are adducts generated by an interaction between a Lewis base and a Lewis acid.

When a Lewis base interacts with a Lewis acid, a new bond is formed, because of the interaction between the two molecules; citing Lewis “*the basic substance furnishes a pair of electrons for a chemical bond; the acid substance accepts such a pair*”.<sup>[44]</sup> Related to Lewis's definition of the acid–base interaction, the octet rule defines that each atom must have eight electrons in its valence shell, giving it the same electronic configuration of a noble gas. Generally, when the formation of an acid–base adduct is favorable, the donor and acceptor atoms reach their octets through the formation of a dative bond that leads to enhanced thermodynamic stability. In this way, a decrease in the reactivity of the acid and the base occurs, by a reaction called neutralization.

However, there are also many exceptions to Lewis assumptions about the octet rule, where stable acid–base adducts show enhanced reactivity, as in the case of hypervalent silicon species. Lewis base, at variance from a Lewis acid, can indeed enhance its chemical reactivity by modifying the nucleophilicity or the electrophilicity of molecules, by modulating their electrochemical properties.<sup>[45]</sup>

In a reaction catalyzed by a Lewis base, the rate of reaction is accelerated by the action of a catalytic amount of an electron-pair donor on an electron-pair acceptor, that could be the substrate or a reagent. The binding of the Lewis base to a Lewis acid generates a transfer of electron density from the base to the acid, and a new adduct is formed. This electron transfer is the principal factor responsible of the chemical reactivity of a Lewis base. The most common effect of this transfer is the enhancement of the nucleophilicity of the acceptor, but in some rare cases, the binding of a Lewis base enhances the

electrophilic character of the Lewis acid. To visualize this concept clearly, it is important to examine the nature of the newly formed dative bond.

In this respect, Jensen has classified all the possible types of interactions on the basis of the involved orbitals, and nine type of bonding phenomena were identified.<sup>[46]</sup> They are shown in Table 1.

Donor	Acceptor		
	$n^*$	$\sigma^*$	$\pi^*$
$n$	$n - n^*$	$n - \sigma^*$	$n - \pi^*$
$\sigma$	$\sigma - n^*$	$\sigma - \sigma^*$	$\sigma - \pi^*$
$\pi$	$\pi - n^*$	$\pi - \sigma^*$	$\pi - \pi^*$

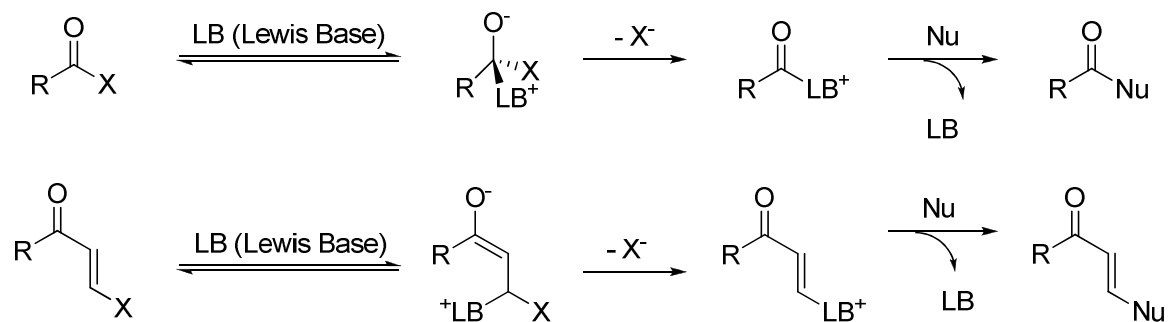
**Table 1**

Although each of these combinations could represent a productive interaction, in practice, only three of these interactions are significant in terms of catalysis.<sup>[47]</sup>

These are the:

- interaction between nonbonding electron pairs and antibonding orbitals with  $\pi$  character ( $n-\pi^*$  interactions),
- interaction between nonbonding electron pairs and antibonding orbitals with  $\sigma$  character ( $n-\sigma^*$  interactions),
- interaction between nonbonding electron pairs and vacant nonbonding orbitals ( $n-n^*$  interactions).

The first one is the most common interaction and represents almost all the examples of Lewis basis catalysis. The nonbonding electron pairs of the donor interact with the antibonding orbitals with  $\pi$  character, contained in alkynes, alkenes, carbonyls, azomethines, or other common unsaturated functional groups. One example of this  $n-\pi^*$  interaction is the 1,4-addition to  $\alpha,\beta$ -unsaturated compounds (Scheme 16).

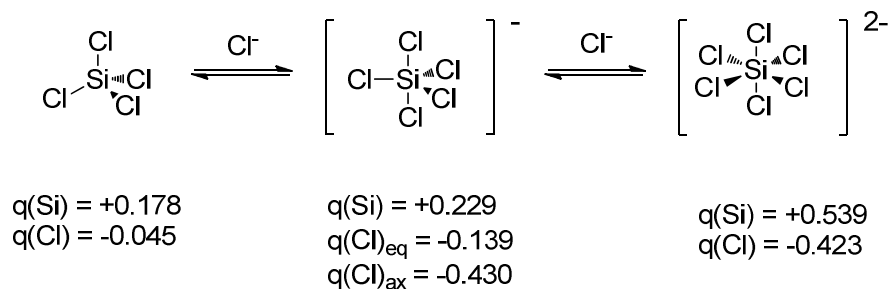


Scheme 16

The second and third interactions,  $n-\sigma^*$  and  $n-n^*$  are less known, but activate the dative bond in the same way. The difference is correlated to the type of acceptor orbital involved in the interaction; in the case of boron and other group 13 elements this is an  $n^*$  orbital, whereas, for group 14 elements, is a  $\sigma^*$  orbital. An important requirement for these types of interactions is that the Lewis acidic acceptor must be able to expand its coordination sphere giving a “hypervalent” state.<sup>[48]</sup> When the dative bond is formed, the preference of nucleophilic or electrophilic character of the new species depends on the polarizability of the new generated bond, as predict by Gutmann empirical analysis.<sup>[49]</sup> When an acid–base adduct is generated, the electron density in the acceptor fragment increases. However, its distribution is not equal among the constituent atoms; so the redistribution of the electron density in the adduct to compensate the electronic changes results in the lengthening of some bonds, and the contraction of other bonds. As a consequence, the coordination number of the Lewis acid increases, and an expansion of the coordination sphere occurs (Figure 10).







Scheme 17

Contrary to carbon (its first row group 14-analogue), silicon displays the ability to form more bonds than the four necessary for fulfilling the octet rule: in the presence of donor molecules or ions it is possible the formation of five-, six- and even seven-coordinated silicon species, some of which have been isolated and/or characterized.<sup>[51]</sup>

In order to explain this behaviour, two main different theories have been formulated: the first invokes the participation of the silicon 3d orbitals in the expansion of the coordination sphere; the second proposes instead a so-called “hypervalent bonding”.

The first theory asserts that in the five-coordinated species the silicon orbitals would have a  $sp^3d$  hybridization (with trigonal-bipyramidal geometry), while in the six-coordinated species the hybridization would be  $sp^3d^2$  (with octahedral geometry).<sup>[52]</sup>

The reduced s-character of the silicon orbitals in the hypercoordinated species would explain their increased Lewis acidity and the transfer of electron density to the ligands.

#### Participation of 3d orbitals

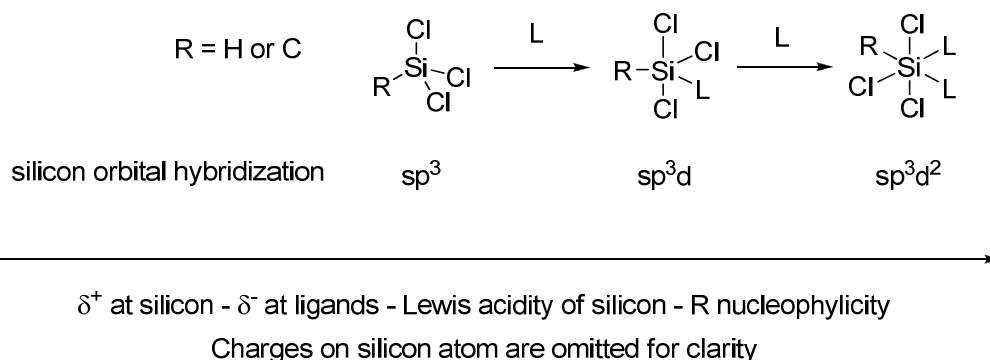
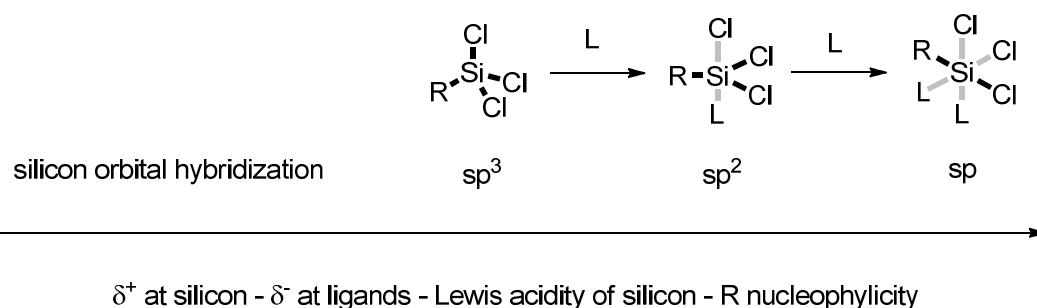


Figure 11

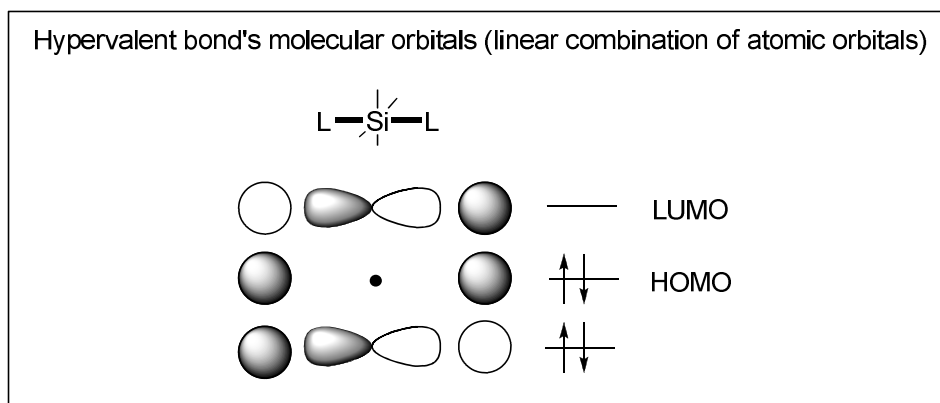
The second theoretical approach in contrast, rules out the participation of the 3d orbitals in the bonding process and hypothesizes instead a so-called “hypervalent bonding” (Figure 12).<sup>[53]</sup>

The ability of main-group elements to form compounds which appear to break the Langmuir–Lewis octet rule was originally explained by invoking an availability of d orbitals (such as 3d for silicon) by using an analogy to transition-metal complexation. However, silicon is not a transition metal, and it is now generally accepted that the 3d orbitals on silicon are too diffuse to engage in meaningful bonding.<sup>[52a]</sup>

### "Hypervalent" bonding



- normal covalent bond (bonding site for  $\sigma$ -donors)
- "hypervalent bond" (3-center-4-electron, bonding site for  $\sigma$ -acceptors)



**Figure 12**

The ability of silicon to expand its coordination sphere (leading to hypervalent bonding) is due to the ability of the silicon 3p orbitals to engage in electron-rich three-center-four-electron bonding. Therefore the formation of a penta- or hexa-coordinated silicon species

would involve respectively one or two 3-center-4-electron molecular bonds, each formed by a silicon p-orbital and two p-orbitals of electronegative ligands featuring a relative *trans*-disposition. An important consequence is the non-equivalence of the ligand positions in five- and six-coordinated silicon species, the  $\sigma$ -acceptor ligands preferring “hypervalent” bonds and the  $\sigma$ -donors forming preferentially normal covalent bonds with the  $sp^2$  (for pentacoordinated compounds) or  $sp$  (for hexacoordinated compounds) silicon orbitals.

The presence of hypervalent bonds imposes some stereochemical constraints (like the *trans*-disposition of the most electronegative ligands) and allows to formulate predictions about the positions of the other ligands on the basis of their electronic properties. Accordingly, the number of possible configurations of the silicon ligands to be considered in the elaboration of a stereoselection model is actually restricted, as shown in a recent paper by Denmark and co-workers.<sup>[54b]</sup>

Both theories are helpful in the interpretation of the fundamental properties of hypervalent silicon species, that clearly distinguish their reactivity from that of four-coordinated compounds, such as the increased Lewis acidity of the silicon atom and the transfer of electronic density to the ligands, which confer to silicon-bound R groups (carbanion or hydride equivalent) marked nucleophilic properties. The hypervalent silicon species involved 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”.<sup>[53,55]</sup> The so-formed five- or six-coordinated silicon species is able to promote the desired reaction in a catalytic process if the base can dissociate from silicon after the product is formed.

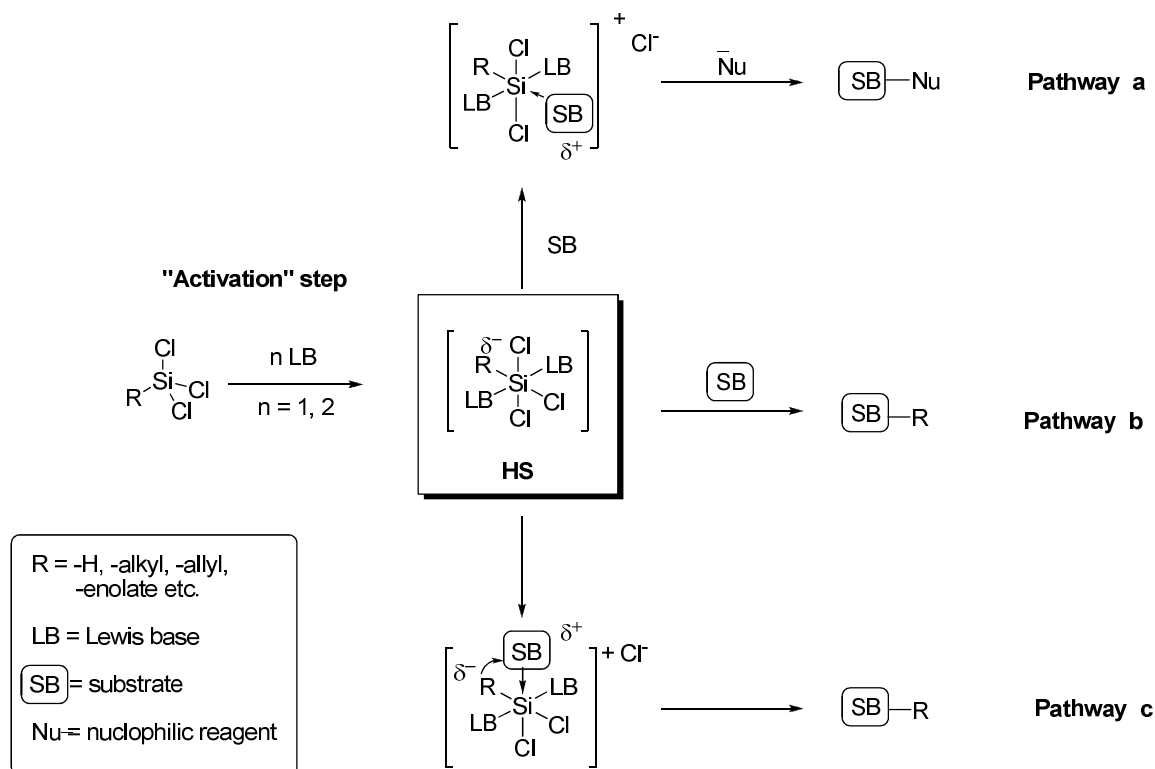


Figure 13

Three general types of reaction mechanism can be envisaged depending on the role of the hypervalent species (Figure 13):

- the hypervalent species (HS) may act as a Lewis acid accepting the lone pair from substrate and thus activating it towards the attack of an external nucleophile (Figure 13, pathway a);
- a nucleophilic silicon ligand is transferred to the substrate which is not coordinated by silicon (Figure 13, pathway b);
- the hypervalent species coordinates the substrate transferring at the same time one of its ligands to it (Figure 13, pathway c).

In the last case both of the peculiar properties of hypervalent silicon species are exploited at the same time. When a mechanism of type *c* is operating, the cyclic transition state allows an efficient control of the relative stereochemistry of the product.

This classification should be helpful for a more immediate comprehension of the mechanistic details that are discussed in the following sections, where the mechanism of several reactions promoted by hypervalent silicon species is reported.

Reductions will be discussed first, followed by carbon-carbon bond formations and opening of epoxides and other miscellaneous reactions. Trimethylsilyl cyanide addition to carbon-nitrogen double bonds will not be discussed, because the mechanism of this reaction is not fully understood.<sup>[47,53]</sup>

## 2.2 Stereoselective C-H bond formation

The use of chiral Lewis bases offers the possibility to control the absolute stereochemistry of the process and it has been widely explored in the last few years, leading to the development of some really efficient catalytic protocols. The catalytic systems able to coordinate trichlorosilane and promote stereoselective reductions may be classified as **amino acid derivatives**, which may be historically considered the first class of compounds developed as chiral activators of trichlorosilane, **amino alcohol derivatives**, a second class, deeply investigated in the very last few years and **other Lewis basic compounds**.

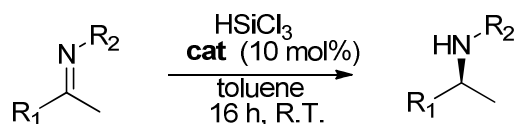
### 2.2.1 Reactions catalyzed by amino acids-derived chiral Lewis bases

In 1999<sup>[56]</sup> and 2001<sup>[57]</sup> Matsumura reported the first examples of stereoselective hydrosilylation with  $\text{HSiCl}_3$  and (*S*)-proline derivatives as effective activators. These works can be considered as a milestones for the asymmetric reduction of ketones and imines using  $\text{HSiCl}_3$  as reducing agent and paved the road to the synthesis of other related systems. Since then, considerable efforts have been devoted to the development of efficient catalysts for the reduction of carbon-nitrogen double bonds, and remarkable progress has been made.

Indeed, Malkov and Kočovský reported one important improvement in the field of asymmetric reduction with  $\text{HSiCl}_3$ , developing the first highly selective catalyst for the reduction of *N*-aryl aromatic ketimine (Scheme 18).<sup>[58]</sup> They identified as organocatalyst of choice the (*S*)-valine-derived type 1, commercially available since 2009. The authors

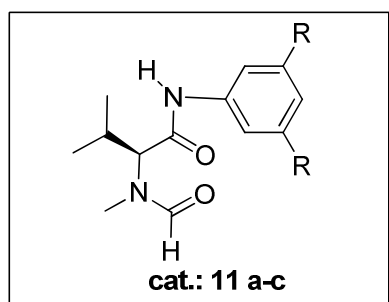
proposed a transition state model in which the silicon atom is coordinated by the two carboxamide groups and a key catalyst-substrate hydrogen bond is responsible for binding of the substrate. The *N*-aryl groups is believed to play an important role in the stereocontrol because it should be involved in  $\pi$ - $\pi$  stacking interaction between catalyst and substrate (see picture reported in Scheme 18).

Over the years, Malkov and Kočovský reported a detailed investigation of the reduction of huge number of imines bearing aryl, heteroaryl and aliphatic substituents, focusing on the use of best catalyst, the Sigamide (**cat. 11c**). In all cases good to excellent levels of enantioselection were achieved, as evident in their 2009 perspective, in which they clearly described their contribution to this field.<sup>[59]</sup> Sigamide has also been shown to be applicable, with high enantioselectivities and good yields, to the reduction of  $\alpha$ -chloro ketimines<sup>[60]</sup> and a variety of  $\beta$ -enamino esters and nitriles.<sup>[61]</sup>

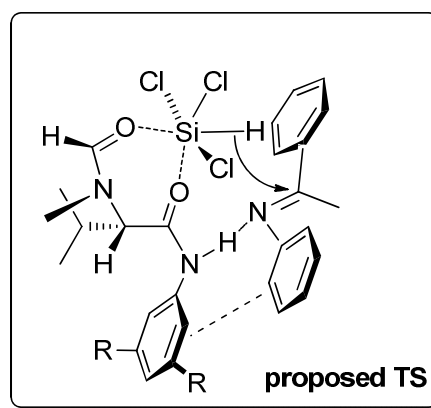


$R_1 = \text{Ph, 4-MeOC}_6\text{H}_4, \text{2-naphth, 2-MeC}_6\text{H}_4, \text{cC}_6\text{H}_{11}, \text{4-CF}_3\text{C}_6\text{H}_4, \textit{iPr}, \text{Ph-CH=CH}$

$R_2 = \text{Ph, 4-MeOC}_6\text{H}_4, \text{3,5-}t\text{Bu}_2\text{C}_6\text{H}_3, \text{3-MeC}_6\text{H}_4, \text{3,5-Me}_2\text{C}_6\text{H}_3$



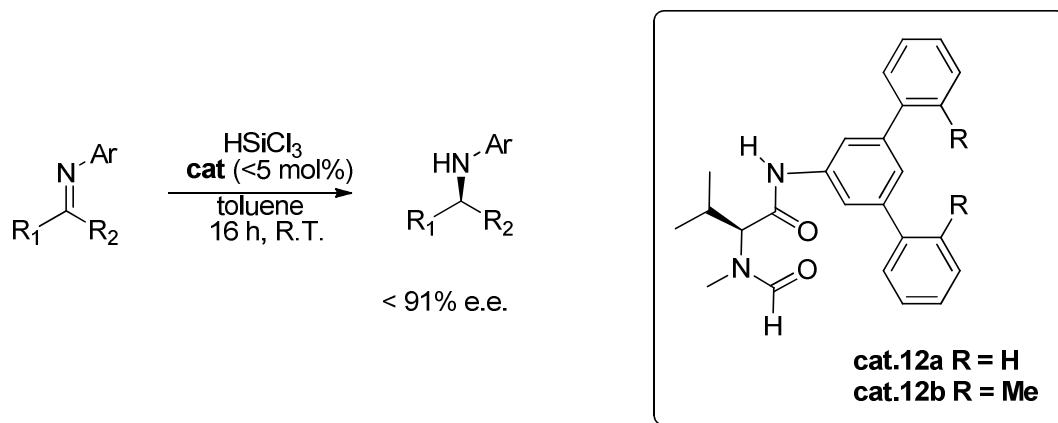
**a:**  $R = \text{Me} \leq 92\% \text{ ee}$   
**b:**  $R = \textit{iPr} \leq 94\% \text{ ee}$   
**c:**  $R = \textit{tBu} \leq 95\% \text{ ee}$



**Scheme 18**

Recently two new (*S*)-valine-derived organocatalysts (Scheme 19) bearing a bulky aromatic substituent at the amidic nitrogen were synthesized.<sup>[62]</sup> The efficiency of the

new compounds was tested in the reduction of acetophenone-derived ketimines, showing a slightly inferior result compared with that of Sigamide.



**Scheme 19**

Eventually, a number of functionalized Sigamide derivatives have been prepared to facilitate the recovery and reuse of catalysts (Figure 14). Recovery strategies that have been employed include attachment of the catalyst to fluorinated tags (enabling recovery by filtration through a pad of fluorous silica),<sup>[63]</sup> traditional polymeric Merrifield, Wang, Tentagel and Marshall resins,<sup>[64]</sup> gold nanoparticles<sup>[65]</sup>, block polymethacrylate polymers,<sup>[66]</sup> and third generation dendrons.<sup>[66]</sup> In all cases, detailed comparisons were made of the results obtained with the recoverable reagents and those with conventional solution-phase reactions.



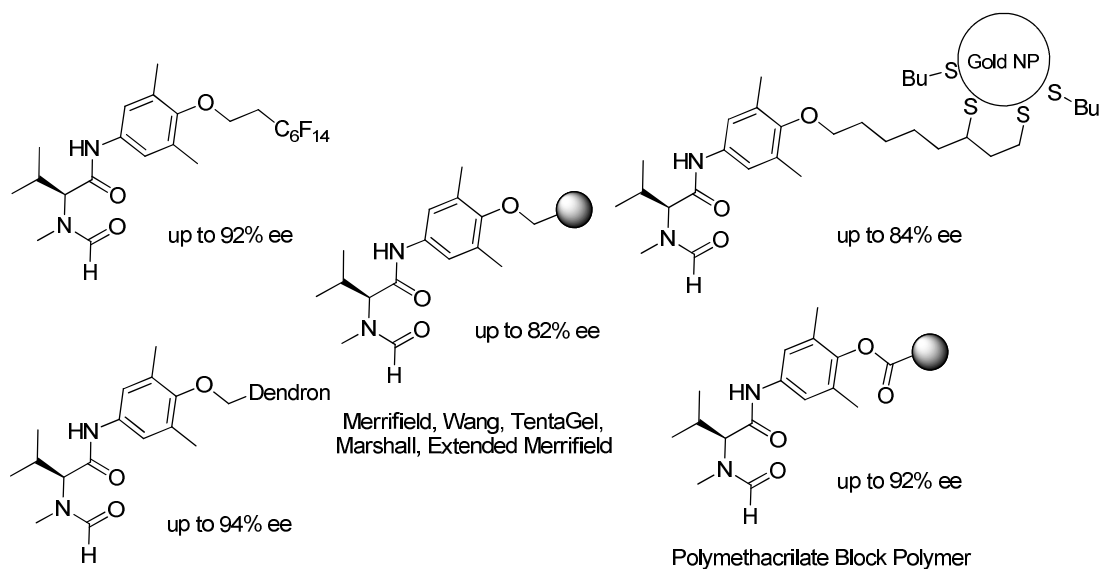
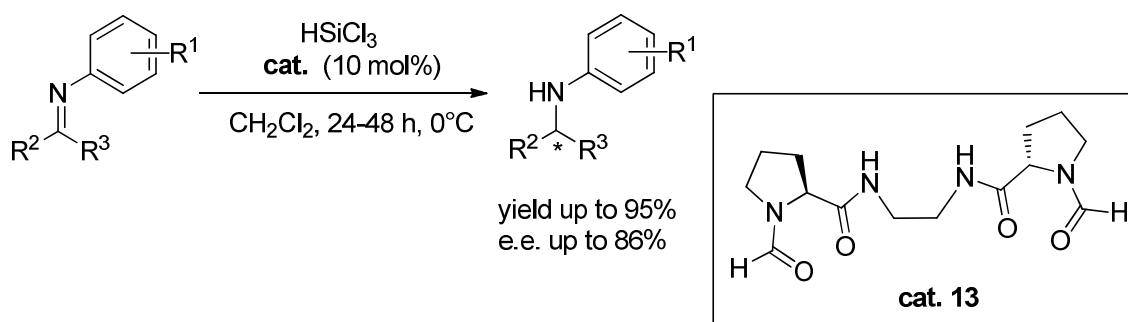
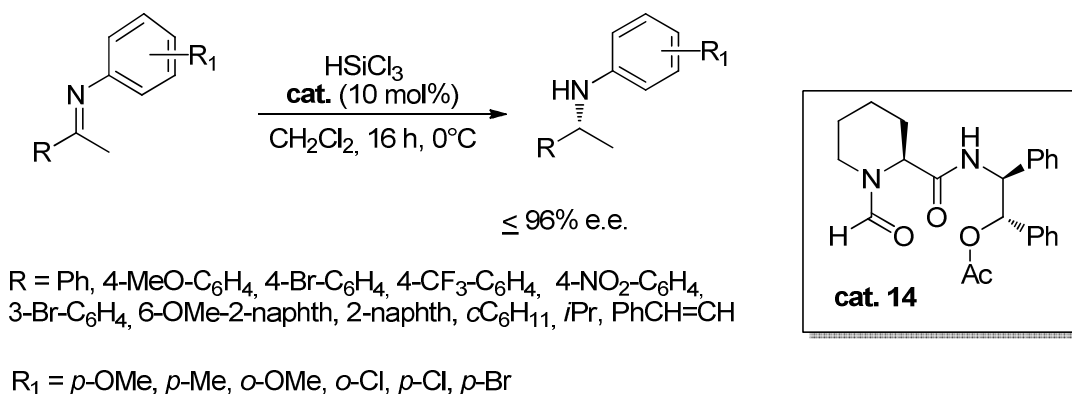


Figure 14

Sun also gave a great contribution to this field, developing novel class of catalysts for the enantioselective hydrosilylation of ketimines. He reported (*S*)-proline-derived catalyst **13** obtaining high yields and moderate to high enantioselectivities.<sup>[67]</sup> Moreover, he developed the first catalyst derived from (*L*)-pipecolic acid (**cat. 14**), able to promote the reaction with high yields and enantioselectivity and, for the first time, the reduction of aliphatic ketimines.<sup>[68]</sup> This work was also the first to demonstrate the independence of the ketimine geometry on the selectivity of the reaction (Scheme 20).

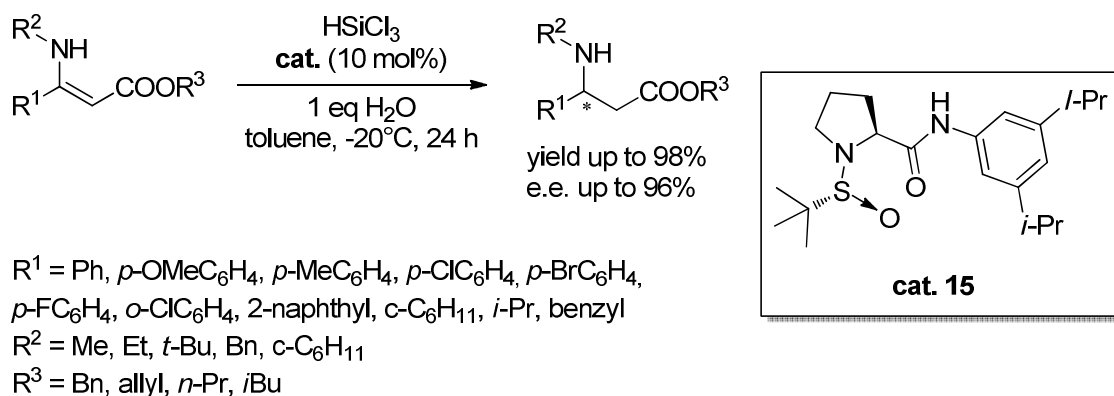


$\text{R}^1 = \text{Ph}, 4\text{-MeO-C}_6\text{H}_4, 4\text{-Br-C}_6\text{H}_4, 4\text{-NO}_2\text{-C}_6\text{H}_4, 4\text{-Br-C}_6\text{H}_4,$   
 $2\text{-naphthyl}, 6\text{-OMe-2-naphthyl}, \text{cC}_6\text{H}_{11}$   
 $\text{R}^2 = \text{Me}, \text{Et}, n\text{-Pr}, n\text{-Bu}, t\text{-Bu}$   
 $\text{R}^3 = \text{Ph}, 4\text{-Cl-C}_6\text{H}_4, 4\text{-MeO-C}_6\text{H}_4$



Scheme 20

Recently, *N*-sulfinyl L-proline amides have been used for the enantioselective reduction of a range of *N*-alkyl  $\beta$ -enamino esters (Scheme 21).<sup>[69]</sup> In this case, the use of water as additive is crucial for high reactivity and enantioselectivity, accelerating enamine-imine tautomerization and increasing the electrophilicity of the imine through protonation of the nitrogen atom.

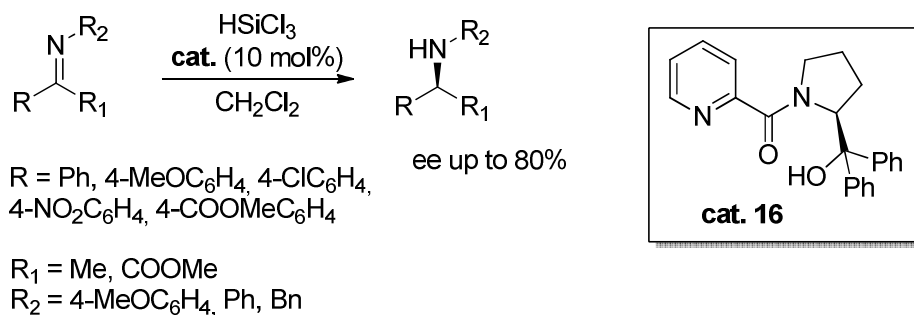


Scheme 21

### 2.2.2 Reactions catalyzed by amino alcohol- derived chiral Lewis bases

A contribution by Matsumura in 2006 paved the way towards the development of a novel class of catalysts for trichlorosilane-mediated reductions, derived from chiral amino alcohols.<sup>[70]</sup>

This group identified a series of *N*-picolinoylpyrrolidine derivatives able to activate trichlorosilane in the reduction of aromatic imines, leading to good enantioselectivity (up to 80%). The authors proposed that both the nitrogen atom of the picolinoyl group and the carbonyl oxygen are involved in the coordination and activation of silicon atom. In addition, it was found that the hydroxyl group is essential for high enantioselectivity. This observation led to hypothesize the presence of hydrogen bonding between the hydroxyl group and the nitrogen atom of the imine (Scheme 22).



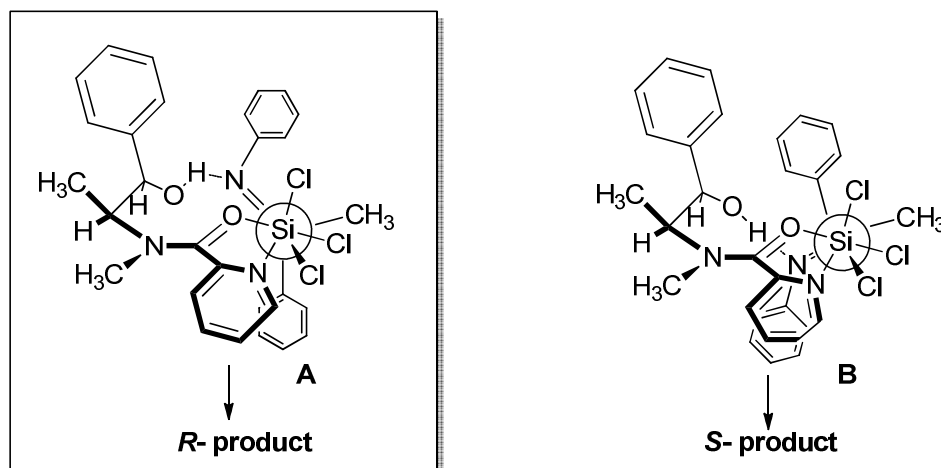
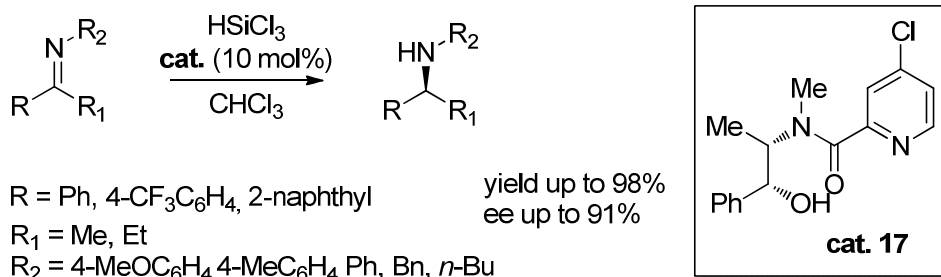
**Scheme 22**

Based on these seminal works, our group has recently focused onto the design and synthesis of a wide class of catalysts prepared by simple condensation of a chiral amino alcohol with picolinic acid or its derivatives. While our investigation led to a patent deposit,<sup>[71]</sup> at the same time Zhang independently reported in a preliminary communication the use of ephedrine and pseudoephedrine-derived picolinamides in the reduction of *N*-aryl and *N*-benzyl ketimines promoted by trichlorosilane.<sup>[72]</sup>

In 2009 our group reported an extensive exploration of this class of organocatalysts, applicable to a large variety of substrates (both *N*-aryl and *N*-alkyl ketimines) with 1 mol% catalyst (Scheme 23).<sup>[73]</sup> A very convenient enantioselective organocatalytic three component methodology was also developed; the reductive amination process, starting simply by a mixture of a ketone and an aryl amine, opens an easy access to chiral amines

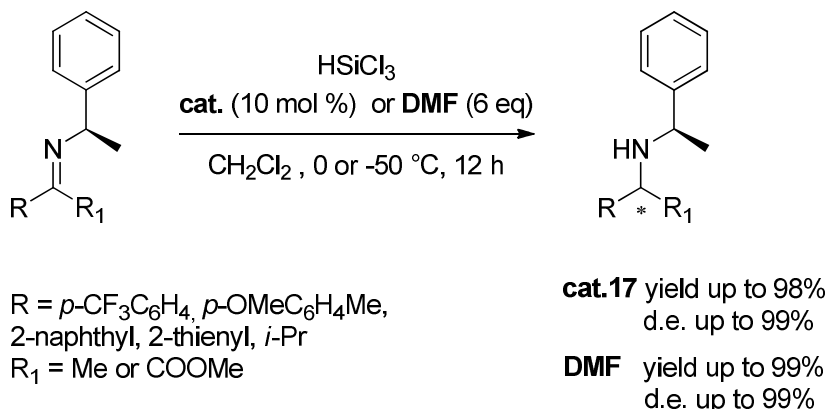
with a straightforward experimental methodology. One of the most important disclosures in this work was the ability to affect the asymmetric reductive amination with unactivated ketones. The screening of different organocatalysts led also to identify the key structural factors for their efficiency:

- the pyridine nitrogen and the CO amidic group coordinated trichlorosilane;
- the hydrogen atom of hydroxyl group plays a fundamental role in coordinating the imine through hydrogen bonding;
- the presence of two stereogenic centers on the amino alcohol moiety with the correct relative configuration such as in (1*R*, 2*S*)-(-)-ephedrine is necessary to stereocontrol the imine attack by trichlorosilane;
- the methyl groups on the amide nitrogen and on the stereocenter in position 2 of the amino alcohol chain apparently have the optimum size for maximizing the enantiodifferentiation of the process (see the picture of the proposed TS in Scheme 11, leading to the experimentally observed preferred formation of the *R* isomer of the product amine).



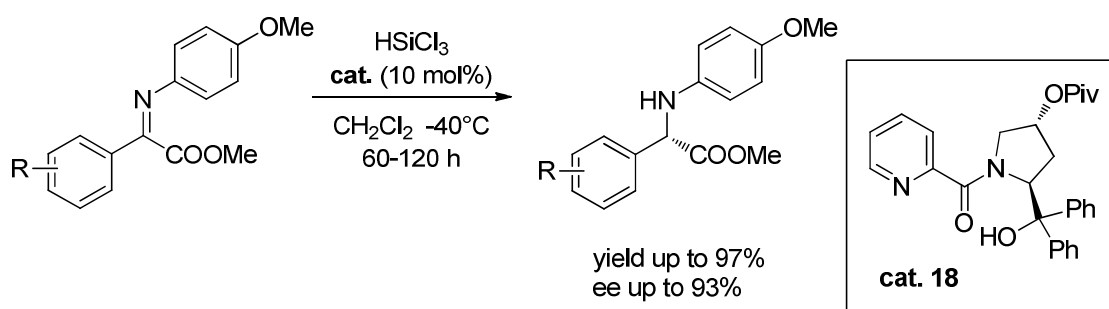
Scheme 23

To further improve the selectivity of the ketimine reduction process, the hydrosilylation of a range of substrates derived from (*R*)-1-phenylethylamine were examined.<sup>[74]</sup> Optimization of the reaction conditions allowed obtaining complete diastereoselective reduction of a wide range of acetophenone-derived ketimines as well as  $\alpha$ -imino esters, demonstrating the cooperative effect of the catalyst and the (*R*)-methyl benzyl residue at the imine nitrogen. In this way, we reported a very convenient, low cost protocol for a highly stereoselective reduction of ketimines bearing a very cheap and removable chiral auxiliary, promoted by an achiral inexpensive Lewis base, such as DMF (Scheme 24).<sup>[75]</sup>



Scheme 24

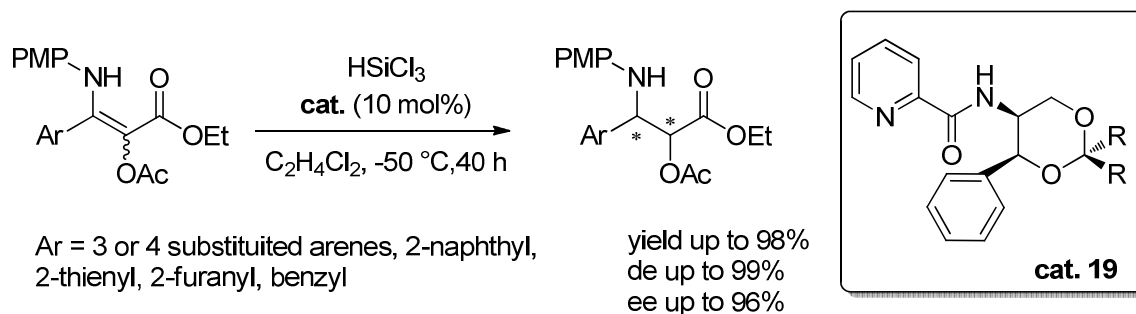
Recently Zhang reported the first highly efficient protocol for the reductive synthesis of  $\alpha$ -amino esters with prolinol-derived catalyst.<sup>[76]</sup> The O-pivaloyl *trans*-4-hydroxy proline derivative (**cat. 18**) gave the best results and was chosen as catalyst of choice. Crucial for the efficiency of the process was the addition of small quantities of pentanoic acid. Through this approach, a broad range of chiral  $\alpha$ -amino esters were synthesized in good yields (up to 97%) and with high levels of enantioselectivity (up to 93%) (Scheme 25).



Scheme 25

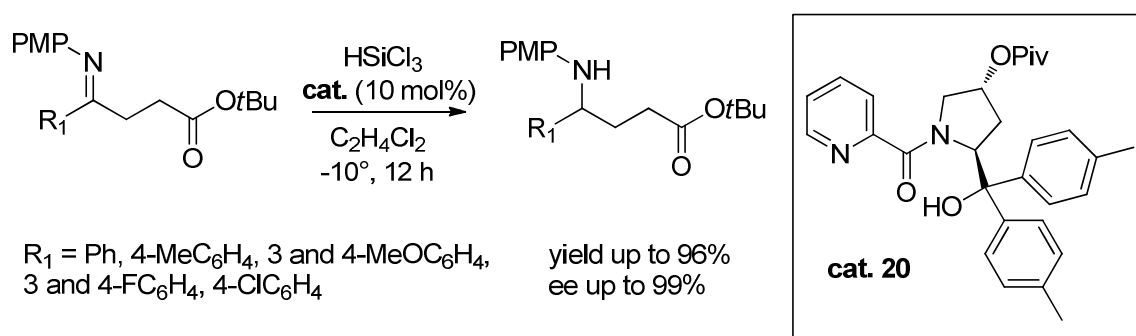
Most recent studies from this group have extended the substrate scope to include  $\alpha$ -acetoxy- $\beta$ -enamino esters.<sup>[77]</sup> In order to perform the reaction on those substrates a novel class of chiral Lewis base catalysts was developed, prepared from readily available chiral source (Scheme 26). A wide variety of *N*-aryl  $\beta$ -aryl and -heteroaryl substrates were reduced in excellent yields (up to 98%) and selectivity (up to 99:1 *syn*: *anti* and 99 % ee).

This methodology was used to perform the reaction under very mild reaction conditions and the removal of water and oxygen from the reaction system was not necessary, suggesting the generation of Bronsted acid that promoted tautomerisation of the enamine. This methodology was additionally applied successfully in the synthesis of the taxol C13 side chain and of an oxazolidinone which is a potent hypocholesterolemic agent.



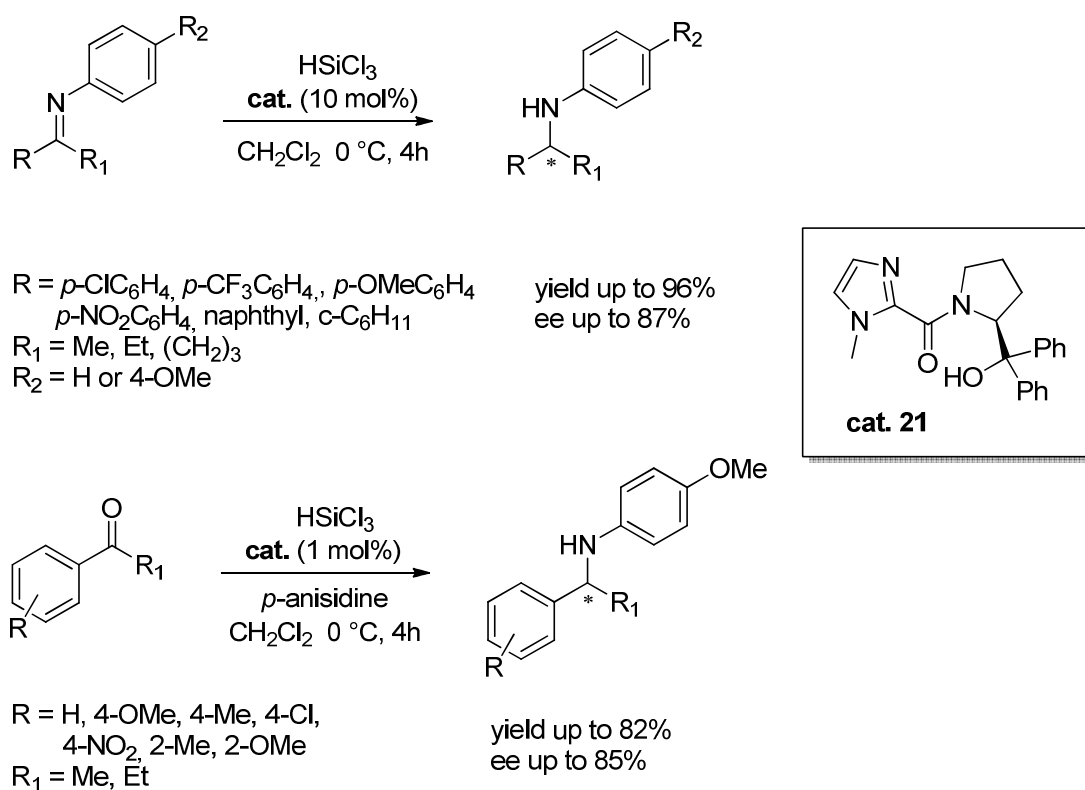
Scheme 26

Very recently Zhang also developed a general, highly enantioselective hydrosilylation of  $\gamma$ -imino esters promoted by chiral Lewis base organocatalysts (Scheme 27).<sup>[78]</sup> However, this transformation always led to the undesired formation of side products, such as cyclized  $\gamma$ -lactam or a  $\alpha$ ,  $\beta$  unsaturated ketimine. The problem was solved by the use of bulkier substrate, obtaining the synthesis of various chiral  $\gamma$ -amino esters in high yield (96%) with excellent enantioselectivities (99 %) They also demonstrated the applicability of this protocol synthesizing two optically active  $\gamma$ -lactams, which are important in the construction of pharmaceutically active agents.



Scheme 27

In the last few years, Jones reported the use of the *N*-methyl imidazole bifunctional catalyst **21** derived from prolinol.<sup>[79]</sup> This was employed in the reduction of a wide range of aromatics and aliphatics ketimines, with just 1 mol% of catalyst and a short reaction time, obtaining up to 96% yield and 87% ee. Interesting, the authors noted that the ketimine isomerism did not seem to have great influence on the outcome of the reaction. The same catalyst was then applied to the high selective reductive amination of a large variety of ketones and aryl or aliphatic amines.<sup>[80]</sup> Essential for this protocol was the formation of the imine *in situ* using microwave irradiation and the subsequently reduction of carbon-nitrogen double bond with trichlorosilane (Scheme 28). Very recently, the same group described in their perspective an interesting quantitative comparison between organocatalysts and transition metal mediated process, demonstrating that catalysts offer comparable efficiencies to their metal counterparts.<sup>[81]</sup>

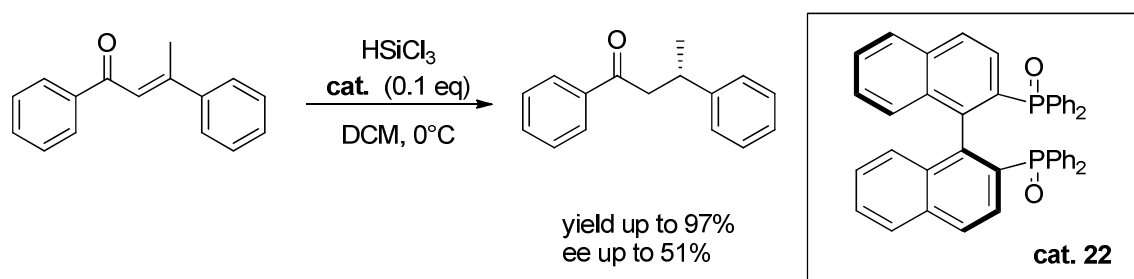


Scheme 28



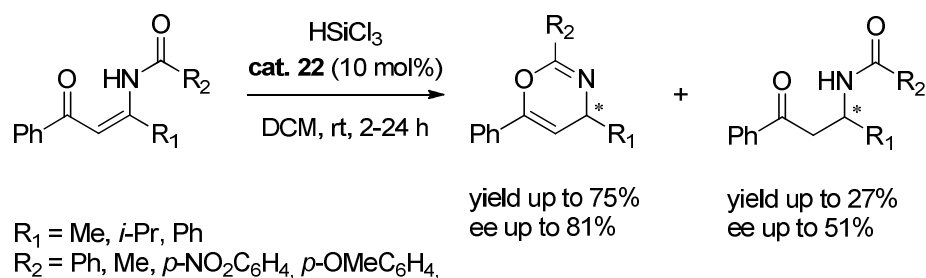
### 2.2.3 Reactions catalyzed by other chiral Lewis bases

An innovative catalytic system was reported by Nakajima, who introduced chiral phosphine oxides as suitable Lewis bases for activating trichlorosilane in stereoselective transformations.<sup>[82]</sup> Indeed trichlorosilane has been used in the conjugate reduction of  $\alpha,\beta$ -unsaturated ketones in the presence of a catalytic amount of a chiral Lewis base. The reduction of 1,3-diphenylbutenone promoted by catalytic amounts of 2,2'-bis(diphenylphosphanyl)-1,1'-binaphthyl dioxide (**cat. 22**, BINAPO) at 0°C was successfully accomplished leading to the corresponding saturated compound in 97% yield and a somehow surprising, but very good, 51% ee (Scheme 29).



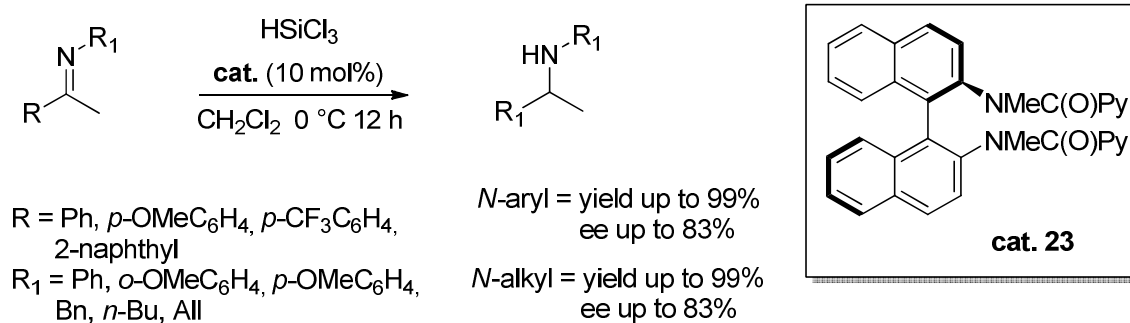
**Scheme 29**

BINAPO was also employed in the synthesis of enantioenriched 4*H*-1,3-oxazines, though enantioselective reductive cyclization of *N*-acylated  $\beta$ -amino enones.<sup>[83]</sup> The product was isolated in 56% yield and 71% ee while the acyclic *N*-acylated  $\beta$ -amino ketone was obtained in up to 13% yield and 4% ee. On the basis of the limited examples reported, it was noted that the absolute configuration of this acyclic product was opposite to those of the oxazine and this suggested the existence of two independent mechanistic pathways. The authors proposed that the conjugate reduction of the *N*-acylated  $\beta$ -amino enone and ensuing cyclisation of the enolate, eliminating  $\text{HOSiCl}_3$ , would afford the observed oxazine. The uncyclised minor product was believed to originate from the 1,2-reduction of the *N*-acyl imine generated via equilibration of the enamide (Scheme 30).



Scheme 30

Our group reported a class of chiral picolinamides, derived from enantiomerically pure chiral diamines for trichlorosilane-mediated reactions.<sup>[84]</sup> Picolinic acid was condensed with (*R*)-*N,N'*-dimethyl amino binaphthyl diamine to afford catalyst 13 in 73% yield after chromatographic purification. Noteworthy binaphthyldiamine-derived bis-picolinamides showed a remarkable activity and both amide-nitrogen atoms was pivotal for high enantioselectivity.<sup>[85]</sup> Good results were obtained performing the reduction of *N*-aryl (up to 83% ee), *N*-benzyl (up to 87% ee) and *N*-alkyl ketimines (up to 87% ee), under mild conditions and with a large variety of substrates (see for a few selected examples Scheme 31).



Scheme 31

## CHAPTER III

### *Proline-based Catalysts for the Reduction of Carbon-Nitrogen Double Bond*

As thoroughly described in Chapter II, in 1999 and 2001 Matsumura reported the first examples of stereoselective hydrosilylation with  $\text{HSiCl}_3$  and (*S*)-proline derivatives as effective activators.<sup>[56,57]</sup> These works can be considered as a milestone for the asymmetric reduction of ketones and imines using  $\text{HSiCl}_3$  as reducing agent and paved the road to the synthesis of other related systems. Since then, considerable efforts have been devoted to the development of efficient catalysts for the  $\text{HSiCl}_3$  reduction of carbon-nitrogen double bonds, and remarkable progress has been made.

In the last few years, our group played a very active role in the development of chiral organic catalysts easily prepared from inexpensive, commercially available, enantiopure material whose manipulation must be kept to minimum. Following this interest, we decided to focus this thesis on the synthesis of very simple proline derivatives for application in trichlorosilane-mediated reduction of C-N double bond.

### 3.1 Reduction of ketimine

Inspired by the work of Arndtsen, we decided to explore the use of one of the simplest amino acids, specifically L-proline, as chiral catalysts with the aim to keep the carboxyl group unaltered.<sup>[86]</sup>

Indeed Arndtsen demonstrated that coupling metal catalysis and the ability of amino acids to hydrogen bond provide an easy route for inducing both enantioselectivity and selectivity. The elevated enantioselectivity is due to the hydrogen bond between the chiral amino acid and the substrate, while high selectivity is achieved by tuning the metal catalyst (Figure 14).

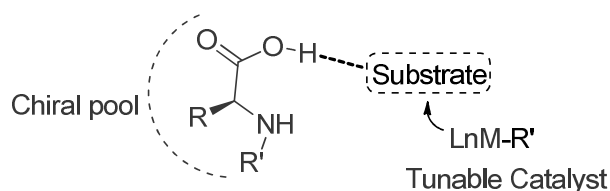


Figure 14

With this in mind, we started to imagine the use of amino acids in trichlorosilane mediated reductions of carbon-nitrogen double bond.

As shown in Figure 15, our idea was to take advantage of the interaction between the hydrogen of the carboxylic OH and the nitrogen of the ketimine during the enantiodifferentiation process. On the other hand, we also satisfied the requirement of activation of the reducing agent by coordination of the silicon atom through the carbonyl groups.

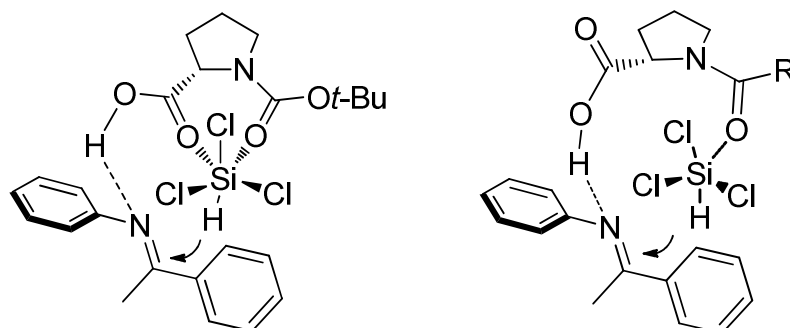
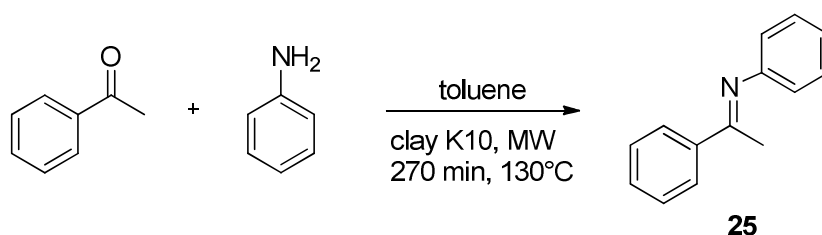


Figure 15

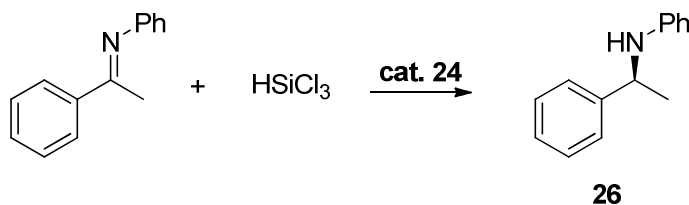
We decided to start our investigation testing the commercially available *N*-Boc-L-proline (**cat. 24**) as catalyst in the reduction of ketimines with trichlorosilane.

The imine **25** was prepared with a microwave-promoted reaction between acetophenone and aniline in toluene in the presence of K10 clay as activator (Scheme 32): a prolonged reaction time was necessary in order to obtain good yield.



Scheme 32

The first screening allowed us to determine the best catalyst loading and the solvent of choice.



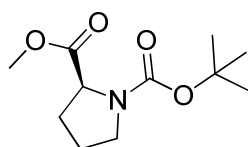
Scheme 33

entry	cat (%)	solvent	t (h)	T (°C)	y (%)	ee (%)
1	10	DCM	8	0	20	49
2	20	DCM	18	0	74	49
3	30	DCM	32	-20	74	73
4	30	CH <sub>3</sub> Cl	18	0	27	73
5	30	Hexane	18	0	25	43
6	30	Toluene	18	0	25	45

Table 2

In terms of chemical activity this system achieved good results; the use of *N*-Boc-L-proline (**cat. 24**) allowed to obtain product **26** in up to 74% yield. These preliminary data showed that the appropriate catalyst loading seemed to be 30 mol % to achieve good yield after 18 hours. Under these conditions the process gave also interesting level of enantioselectivity and by running the reaction in dichloromethane and chloroform we achieved up to 73% ee.

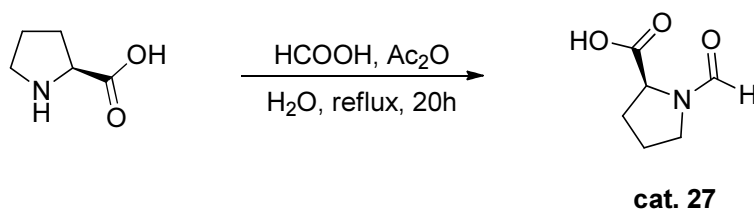
In order to validate our hypothesis, we also tested the *N*-Boc-L-proline methyl ester. After 32 hours at -20°C neither the level of enantioselection nor the yield were satisfactory: the enantiomeric excess was 19% and yield 49%. The outcome of this experiment strongly suggested the importance of hydrogen bond between catalyst and substrate for the enantioselectivity.



49% y, 19% ee

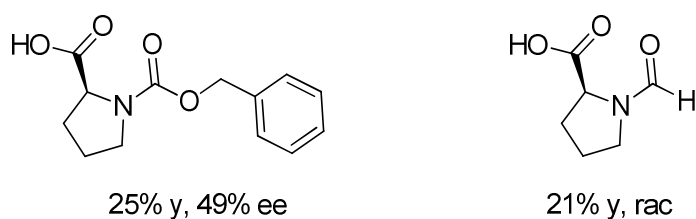
**Figure 16**

We next tested differently *N*-protected L-prolines, such as *N*-formyl and *N*-carbobenzyloxy proline. *N*-Cbz-L-proline is commercially available while *N*-formyl-L-proline (**cat. 27**) was synthesized starting from proline in the presence of acetic anhydride and formic acid (Scheme 34).



**Scheme 34**

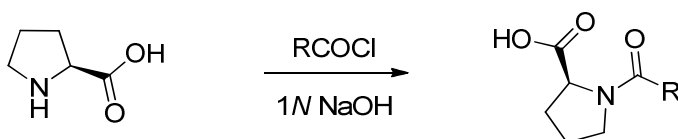
The catalytic efficiency of these catalysts were evaluated in the reduction of ketimine.



**Figure 17**

After 32 hours at  $-20^{\circ}\text{C}$  *N*-Cbz-*L*-proline afforded the amine with 25% yield and 49% ee. The *N*-formyl-*L*-proline (**cat. 27**) led to a racemic product in 21% yield. These results seem to suggest the importance of having a bulky group on the nitrogen atom.

Considering these encouraging results, the second step was to evaluate the effect of structural modifications of the catalyst. To this end, we easily synthesized a series of catalysts with different structural features, in terms of electronic and steric proprieties, at the prolinic nitrogen atom. The easy one-step reaction between *L*-proline and various acyl chloride, in presence of 1*N* NaOH, allowed to obtain the catalysts illustrated in Figure 18. The acyl chlorides, when not commercially available, were prepared starting from the corresponding acid by treatment with thionyl chloride under reflux for 4 hours.



**Scheme 35**

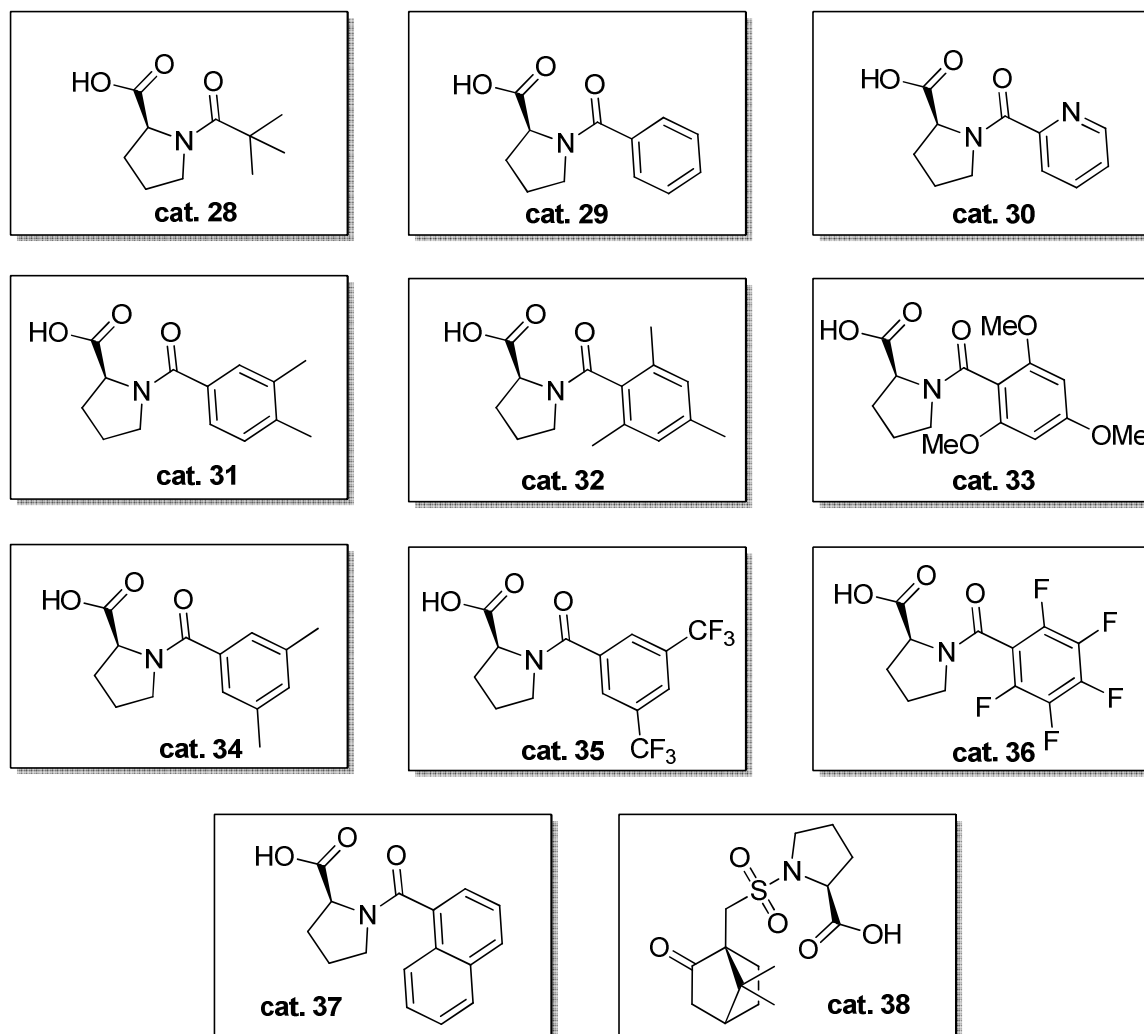
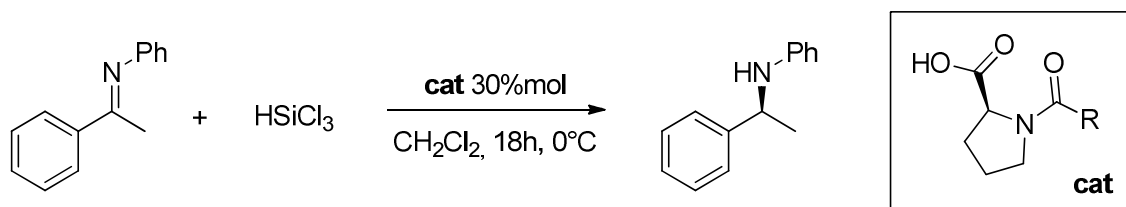


Figure 18

As shown in Figure 18, we obtained a wide range of catalysts and we evaluated their performances in the trichlorosilane-mediated reduction of ketimine.



Scheme 36



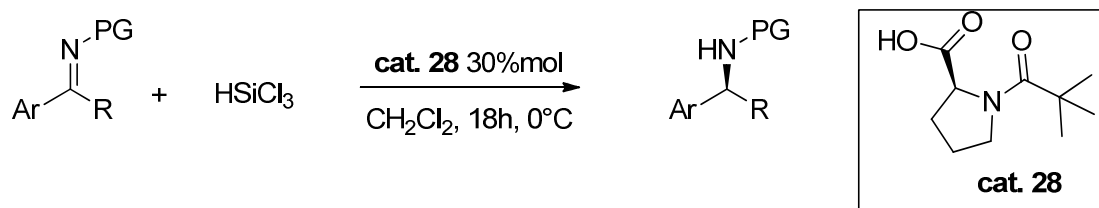
entry	cat	R	y (%)	ee (%)
1	<b>24</b>	<i>O</i> tBu	74	49
2	<b>28</b>	<i>t</i> Bu	36	70
3	<b>29</b>	Ph	63	59
4	<b>30</b>	Py	98	11
5	<b>31</b>	3,4-MePh	56	30
6	<b>32</b>	2,4,6-MePh	54	34
7	<b>33</b>	2,4,6-OMePh	30	27
8	<b>34</b>	3,5-MePh	74	62
9	<b>36</b>	2,3,4,5,6-FPh	10	8 ( <i>R</i> )
10	<b>37</b>	naphtyl	30	32

**Table 3**

After running the reaction in dichloromethane at 0°C for 18 hours, all the catalysts afforded the desired product. Using catalysts **29** and **34** we obtained the amine with good chemical efficiency (63% and 74% yield) and discrete level of enantioselection, 59% and 62% ee, respectively. Increasing the steric hindrance on the aromatic ring, the catalyst showed lower chemical activity and a remarkable drop in the enantioselectivity. Also the pyridine moiety doesn't have a positive effect on the process in terms of stereocontrol (entry 3), probably due to its coordination to the silicon atom.

Noteworthy, catalyst **28**, with the pivaloyl group on the nitrogen atom, afforded the product with 36% yield and 70% of enantiomeric excess. This data demonstrate therefore the good potentiality of these catalysts.

On the basis of these results, compounds **28** and **29** were selected to investigate the substrate scope in the enantioselective reduction of differently substituted imines (Scheme 37). Using catalyst **28** with 30 mol% loading, a broad range of ketimines were reduced with trichlorosilane in CH<sub>2</sub>Cl<sub>2</sub>.



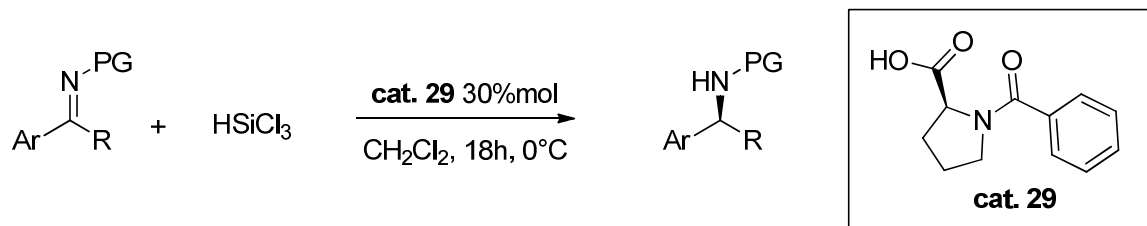
Scheme 37

entry	Ar	R	PG	y (%)	ee (%)
1	Ph	CH <sub>3</sub>	Ph	36	70
2	Ph	CH <sub>3</sub>	PMP	76	68
3	4-CF <sub>3</sub> Ph	CH <sub>3</sub>	Ph	55	74
4	Ph	CH <sub>3</sub>	3,4,5-(OMe) <sub>3</sub> Ph	-	-
5	1-naphthyl	CH <sub>3</sub>	Ph	88	59
6	Ph	CH <sub>2</sub> CH <sub>3</sub>	Ph	79	5

Table 4

Catalyst **28** showed a good chemical activity, promoting the enantioselective reduction in yields up to 88%, except when very bulky protecting group was used (entry 4). The reaction of both *N*-Ph and *N*-PMP imines derived from acetophenone achieved discrete level of enantioselectivity, with 70% and 68% ee, respectively. Analogously, the reduction of imine derived from 4-trifluoromethylacetophenone, led to product in 74% ee. A remarkably drop of enantioselectivity was observed when the imine derived from propiophenone was employed (entry 6).

The same series of experiment was carried out with catalyst **29**, in dichloromethane for 18 hours at 0°C. The results are collected in Table 5.

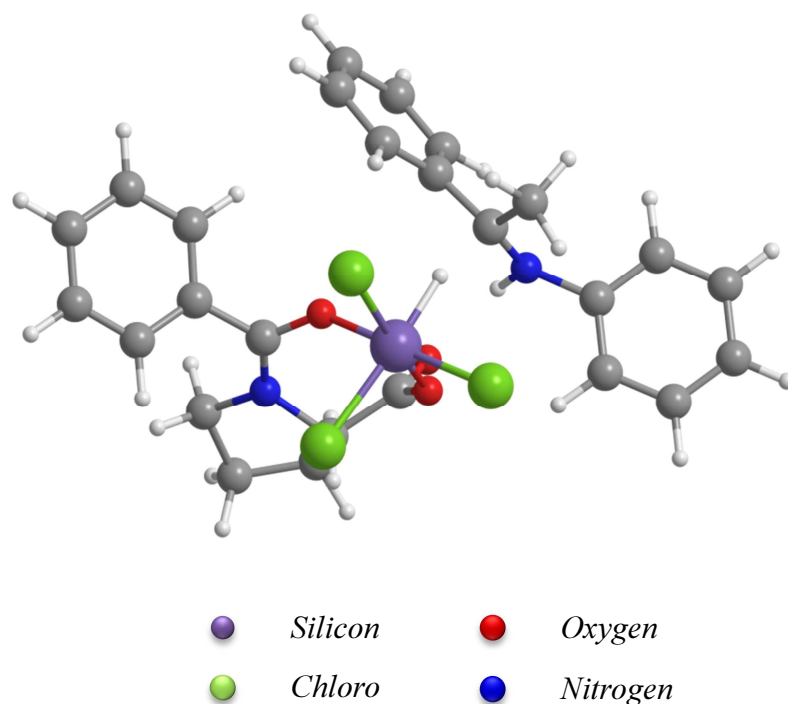


Entry	Ar	R	PG	y (%)	ee (%)
1	Ph	CH <sub>3</sub>	Ph	63	59
2	Ph	CH <sub>3</sub>	PMP	79	55
3	4-CF <sub>3</sub> Ph	CH <sub>3</sub>	Ph	83	49
4	Ph	CH <sub>3</sub>	3,4,5-(OMe) <sub>3</sub> Ph	-	-
5	1-naphthyl	CH <sub>3</sub>	Ph	80	55
6	Ph	CH <sub>2</sub> CH <sub>3</sub>	Ph	85	53

**Table 5**

Basically this series followed the same trend observed using catalyst **28**. The chemical activity was good, but no improvement of the stereochemical efficiency of the catalysts was observed. Indeed the best result was achieved performing the reaction with the *N*-Ph imine derived from acetophenone, with 63% yield and 62% ee.

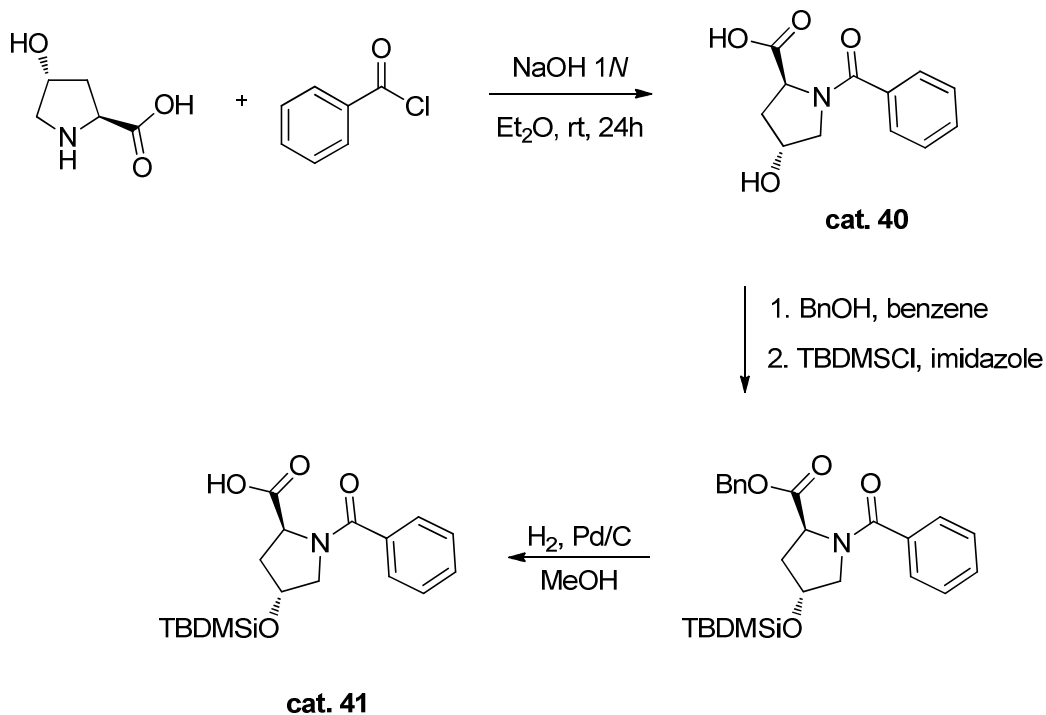
Theoretical studies were also performed in order to elucidate the origin of the stereoselection. Figure 19 shows the structure of the lowest energy TS for the reduction of the imine **25** promoted by catalyst **29**, performed with DFT calculation (B3LYP/6-31G(d,p)). From inspection of the molecular vibrations of the imaginary frequency, it is clear that the reaction is concerted but not synchronous. Indeed, the proton-transfer from the carboxylic group to the imine nitrogen is almost complete while the hydride transfer is still occurring. In this way, the hydrogen bond between the N-H bond just formed and the proline carboxylate guarantees the proximity of all reactants.



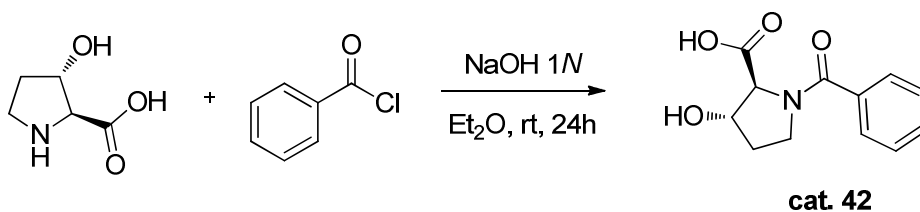
**Figure 19**

We decided to test chiral proline-derivatives as catalysts bearing an additional oxydrilic group on the chiral scaffold, such as *N*-Boc-*trans*-3-Hydroxy-L-proline, *N*-Bz-*trans*-3-Hydroxy-L-proline and *N*-Bz-*trans*-4-Hydroxy-L-proline.

*N*-Boc-*trans*-3-Hydroxy-L-proline (**cat. 39**) is commercially available, while catalysts **40** and **42** were prepared by single-step procedure involving the use of benzoyl chloride in presence of 1*N* NaOH in quantitative and 67% yield, respectively. We also prepared the derivative **41** with the aim to evaluate the role of the hydroxyl group, which might be involved in the coordination of HSiCl<sub>3</sub> by oxygen atom. The introduction of a bulky silyl group could also modify the steric hindrance of the catalyst, thus affecting the stereochemical outcome of the reaction.

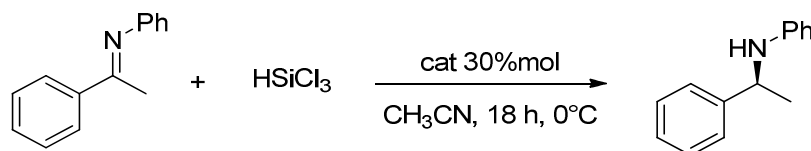


**Scheme 39**



**Scheme 40**

Once again the catalysts (30 mol%) were tested in the reduction of ketimine **25** for 18 hours at 0°C in acetonitrile, because their poor solubility in dichloromethane and chloroform.



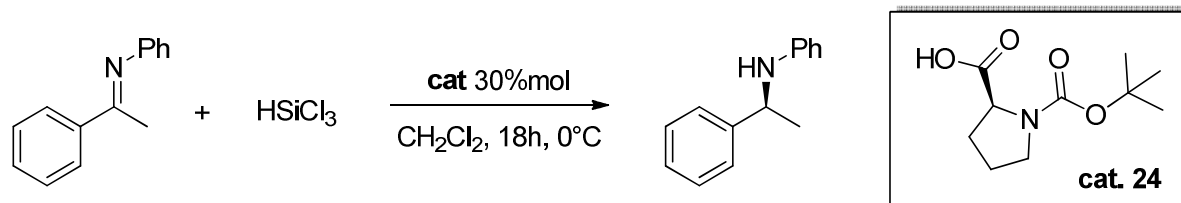
**Scheme 41**

entry	cat	y (%)	ee (%)
1	<b>39</b>	46	rac
2	<b>40</b>	26	rac
3	<b>41</b>	71	66
4	<b>42</b>	36	rac

Table 6

As clearly shown in Table 6, the presence of a hydroxyl group led to a racemic product while the silyl ether derivative promoted the reaction with good enantioselectivity, proving that the OH group is a competitive site of coordination for trichlorosilane.

Driven by this results we decided to focused on more in-depth study of the best system, catalyst **24**, and we tried to add additives to the reaction, with the aim of increasing the chemical activity and especially the stereocontrol. For this purpose, we added stoichiometric amount of different organic bases, such as 1,8-diazabicycloundec-7-ene (DBU), quinine and quinidine. Hopefully, the use of an ionic pair increases the steric hindrance of the catalyst and, as consequence, the stereocontrol.



Scheme 42

entry	additive	y (%)	ee (%)
1	-	74	49
2	DBU	67	42
3	quinine	88	16
4	quinidine	38	38

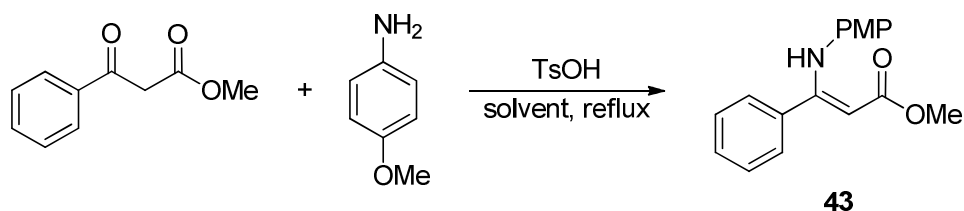
Table 7

The use of an achiral base (DBU) allowed to obtain good results, both in terms of chemical efficiency and stereocontrol, demonstrating how the presence of a base in the reaction does not prevent the formation of hydrogen bond between catalyst and substrate, necessary for the good stereochemical outcome of the process. Conversely, the use of a chiral base, with the goal of adding an additional source of stereochemical information, did not give equally good results in terms of enantiomeric excess. Even employing the quinidine, the catalyst didn't give satisfactory results in stereoselection.

### 3.2 Reduction of $\beta$ -enamino esters and $\alpha$ -imino esters

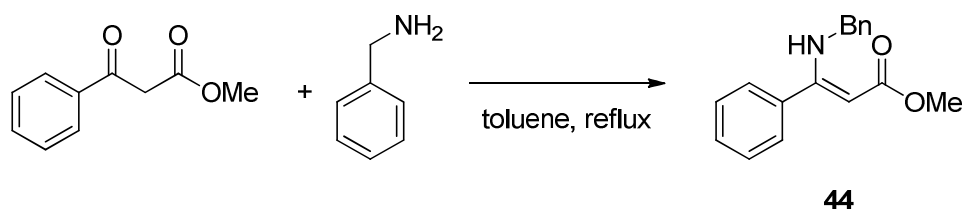
Trichlorosilane has also been used in the reduction of imines derived from  $\alpha$ -keto esters, leading to the synthesis of natural and unnatural  $\alpha$ -amino acids, and in the reduction of  $\beta$ -enamino esters. The use of these substrates lead indeed to the formation of very attractive products, because they are highly functionalized and can be exploited to obtain a wide range of derivatives by subsequent synthetic transformations. For this reason we decided to test the most promising catalysts in the enantioselective reduction of these substrates.

We prepared  $\beta$ -enamino esters **43** and **44**, with two different protecting groups on the nitrogen atom. The reaction of ketoesters with *p*-methoxy aniline gave product **43** in 68% yield (Scheme 43).



**Scheme 43**

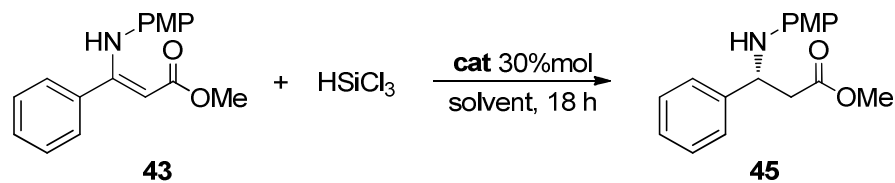
The reaction between the  $\beta$ -ketoester with benzylamine afforded the  $\beta$ -enamino ester **44** in 30% yield (Scheme 44).



**Scheme 44**

In Table 8 are summarized the results obtained in the reduction of  $\beta$ -imino esters, promoted by different catalysts.





Scheme 45

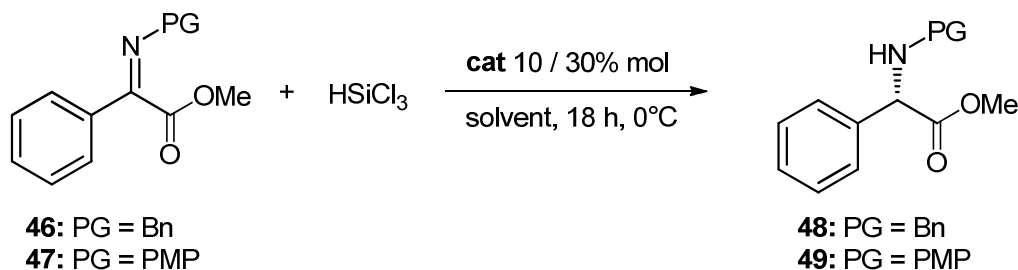
entry	cat	solvent	T (°C)	y (%)	ee (%)
1	<b>24</b>	DCM	0	32	41
2	<b>28</b>	DCM	0	27	36
3	<b>39</b>	DCM	0	>99	rac
4	<b>40</b>	CH <sub>3</sub> CN	0	35	rac
5	<b>41</b>	CH <sub>3</sub> CN	0	55	56
6	<b>41</b>	CH <sub>3</sub> CN	-20	46	24
7	<b>42</b>	CH <sub>3</sub> CN	-20	31	7

Table 8

All experiments gave the desired  $\beta$ -amino ester **45**. The reduction conducted with catalyst **24** and **28**, in DCM at 0°C (entry 1 and 2) led to a low yield and also modest level of enantioselectivity. Catalyst **39** (entry 3) gave the racemic product in quantitative yield. The reactions, carried out in acetonitrile with the catalysts **40** and **42** led to discrete yields but low enantiomeric excesses (entry 4 and 7). The use of catalyst **41** in acetonitrile at 0°C allowed to obtain the product in 55% yield and 56% ee. In order to obtain an increase of stereocontrol, we carried out the reaction at a lower temperature, but observing no improvements.

However, by performing the same experiments in the absence of catalyst, we observed a strong “background reaction” (conversions higher than 50%), probably due to the presence of a carbonyl able of activate the trichlorosilane; this could partly explain the difficulty of our catalysts to exert any appreciable in stereocontrol.

Then we decided to change substrates and tested  $\alpha$ -imino esters (**46** and **47**). In Table 9 are reported the results of the reduction of this compound promoted by catalysts **24**, **28**, **29**, **39**, **40** and **41**.



Scheme 46

entry	PG	cat	solvent	mol (%)	y (%)	ee (%)
1	Bn	<b>24</b>	DCM	30	34	5
2	Bn	<b>28</b>	DCM	30	21	7
3	PMP	<b>28</b>	DCM	10	85	33
4	PMP	<b>29</b>	DCM	10	82	rac
5	PMP	<b>39</b>	DCM	10	>99	21
6	PMP	<b>40</b>	CH <sub>3</sub> CN	10	79	rac
7	PMP	<b>41</b>	CH <sub>3</sub> CN	10	79	rac

Table 9

Due to their remarkable reactivity as highly electrophilic imines, in all case the substrates led to the desired product in high yields even with low catalyst loading. Noteworthy, the reductions of the benzyl derivative are more difficult to obtain due to their instability (entry 1 and 2). However none of these systems showed good level of enantioselectivity. By control experiments, it was discovered that also in this case, a consistent “background reaction” takes place: in the absence of catalyst the product was formed in 98% and 62% yield at 0°C and -20°C, respectively. The competition of such non-catalytic (and non-stereoselective) reaction pattern is clearly responsible of the low overall level of stereoselectivity of the process.

In conclusion, the straight forward synthesis of a series of enantiomerically pure Lewis bases by simple condensation of commercially available enantiopure proline or its derivatives was described. Such compounds together with some commercially available catalysts were shown to promote the enantioselective reaction of ketimines with trichlorosilane in very high chemical yield. In the reduction of the model substrate *N*-phenyl acetophenone imine the organocatalysts lead to the formation of the corresponding amine with good stereoselectivity (up to 73% ee).



## CHAPTER IV

### *Trichlorosilane-mediated Stereoselective Synthesis of $\beta$ -amino Esters*

Following our interest in the development of trichlorosilane-mediated reactions, we developed a highly stereoselective reduction of *N*-benzylenamines, which can be conveniently deprotected by hydrogenolysis to the corresponding  $\beta$ -amino esters and eventually converted to  $\beta$ -lactams.<sup>[87]</sup>

The combination of a low cost, easy to make metal-free catalyst and an inexpensive chiral auxiliary allowed to carry out the reaction on substrates with different structural features. In addition, by performing the stereodetermining crucial reductive step under the best conditions, we were able to obtain almost enantiomerically pure  $\beta$ -lactams.

As profusely described in Chapter II, trichlorosilane-based methodologies have allowed to efficiently performing the reduction not only of *N*-aryl, *N*-benzyl and *N*-alkyl ketimines, but also of imines derived from  $\alpha$ -ketoesters, leading to the synthesis of natural and unnatural  $\alpha$ -amino acids. However, just very recently this metal-free procedure has been employed in the reduction of  $\beta$ -enamino esters, as valid alternative to the metal-catalysed hydrogenations and only few examples are reported in literature. Taking advantage of the fast equilibration between enamine and imine form, Malkov and Kocovsky have successfully accomplished the synthesis of  $\beta$ -amino acids by trichlorosilane mediated enamine reduction catalysed by the (*S*)-valine-derived formamide **50**.<sup>[61]</sup> Analogously Zhang developed an efficient methodology where the catalyst of choice was found to be the chiral picolinamide **51** (Figure 21).<sup>[88]</sup>

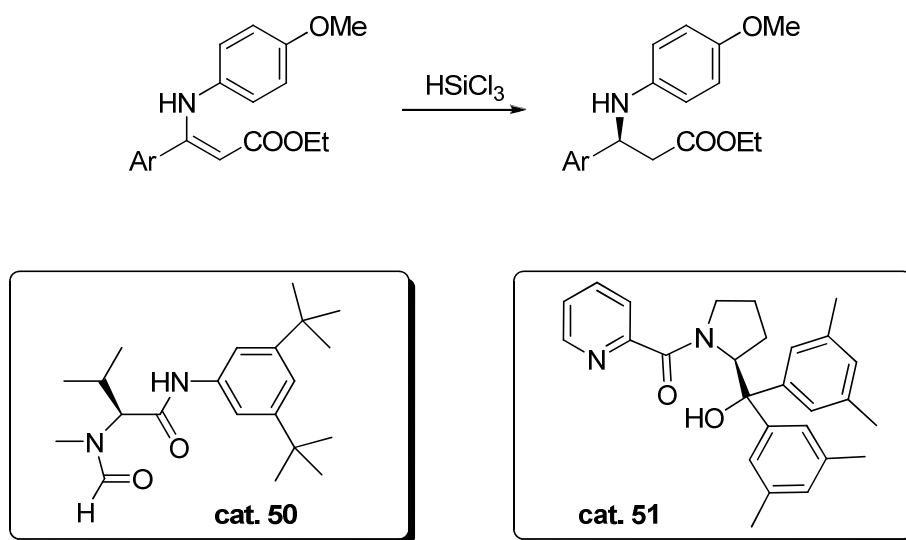


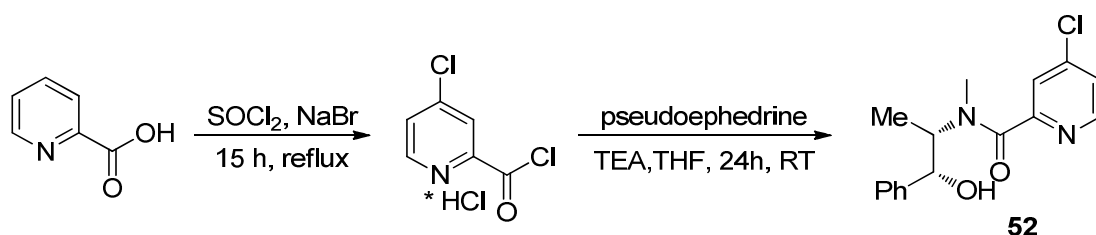
Figure 21

Even if high enantioselectivities were achieved, it must be noted that both methods rely on the use of *N*-aryl enamines, whose conversion to *N*-deprotected amino acids require an oxidative deprotection protocol, with cerium ammonium nitrate (CAN) or trichloroisocyanuric acid (TCCA). Considering this, we started to look for a more convenient deprotection protocol.

For this reason, we decided to focus our attention on the study of the stereoselective reduction of *N*-benzylamines, which led to the corresponding  $\beta$ -amino esters. The use of the *N*-benzyl group is very attractive because the  $\beta$ -amino esters can be conveniently and easily deprotected by hydrogenolysis and finally converted to  $\beta$ -lactams.

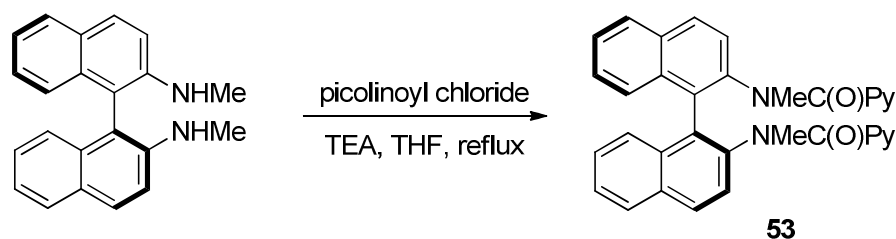
Based on our previous experience, we decided to investigate the catalytic behaviour of the ephedrine-derived 4-chloropicolinamide **52**<sup>[73,74]</sup> and bis-picolinamide derivative of 1,1'-binaphthyl-2,2'-diamine **53**.<sup>[84, 85]</sup>

We first prepared 4-chloro-2-picolinoyl chloride from picolinic acid by treatment with thionyl chloride in presence of sodium bromide. This was condensed with (1*R*,2*S*)-ephedrine to afford the compound **52** in 71% overall yield.



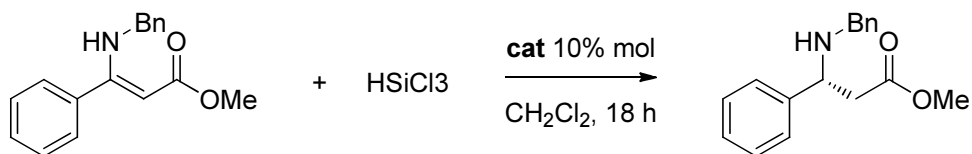
Scheme 47

We synthesized the catalyst **53** by reaction of (*S*)-*N,N'*-dimethyl-[1,1'-binaphthalene]-2,2'-diamine with the picolinoyl chloride in 73% yield after chromatographic purification (Scheme 48).



Scheme 48

We then investigated their performance in the trichlorosilane-mediated reduction of  $\beta$ -enamino esters **48**.



**Scheme 49**

entry	cat	T(°C)	y (%)	ee (%)
1	<b>52</b>	0	73	67
2	<b>53</b>	0	71	61
3	<b>52</b>	-20	70	81
4	<b>53</b>	-20	43	73

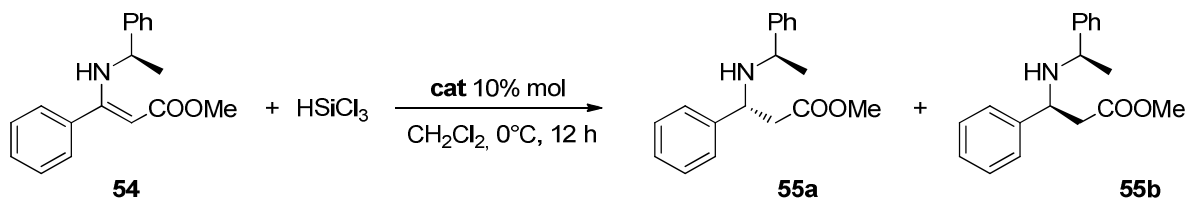
**Table 10**

The reduction of *N*-benzyl enamine of 3-oxo-3-phenyl-propionic acid methyl ester, by employing 10% of chiral Lewis bases **52** and **53** at 0°C in dichloromethane, afforded the product in 73% and 71% yield, respectively, and 67% and 61% ee (Table 10). Lower reaction temperatures allowed to slightly increase the enantioselection up to 81% ee with only a minor effect on the yield (entry 3).

By running the reaction in chloroform at -20°C, catalyst **52** promoted the reaction with an improvement of chemical efficiency, obtaining 98% yield, even though the enantioselectivity decrease to 71%. For this reason we decided to run further experiments only in dichloromethane.

In the attempt of improving the selectivity of the process, we decided to take advantage of the introduction of a chiral auxiliary at the imine nitrogen,<sup>[74]</sup> therefore trichlorosilane mediated reduction of enamine **54** derived from (*R*)-1-phenyl-ethyl amine was studied.

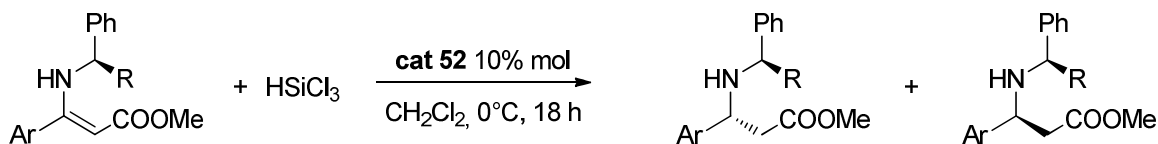




Scheme 50

$\beta$ -Amino ester **55** was obtained after 12 hours in 48% yield with a total control of the stereoselectivity by employing the ephedrine-based catalyst **52**. Also binaphthyl-derived bis-picolinamide **53** catalysed efficiently the reduction of chiral enamines **54**, although with a lower selectivity (81% dr). In this case the matching pair was represented by the catalyst obtained from (*S*)-binaphthyldiamine derivative **53** and enamine prepared from (*R*)-methyl benzylamine.

Having shown the potentiality of the synthetic approach, the methodology was extended to the synthesis of a wide range of enantiomerically pure  $\beta$ -aryl- $\beta$ -amino esters by employing ephedrine-based catalyst **52**.



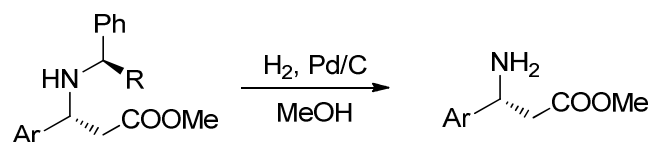
Scheme 51

entry	R	Ar	y (%)	ee (%)
1	H	4-CF <sub>3</sub> Ph	97	78
2	Me	4-CF <sub>3</sub> Ph	75	99
3	H	4-OMePh	80	70
4	Me	4-OMePh	71	99
5	H	1-naphtyl	75	68
6	Me	1-naphtyl	85	99

Table 11

*N*- $\alpha$ -methyl benzyl enamines with different electronic properties were effectively reduced in the presence of catalyst **52** with excellent levels of stereoselectivity. While the reduction of *N*-benzyl enamine derived from 3-oxo-3-(4-trifluoromethyl-phenyl)-propionic acid methyl ester afforded chiral amine with 78% ee (entry 1), the trichlorosilane addition to chiral enamine led to the corresponding amino ester with a diastereoisomeric ratio higher than 99/1 (entry 2). Analogous results were obtained with electron rich aryl-substituted substrates. In both cases, starting from chiral enamines the reduction was successfully accomplished in 71% and 85% yield, respectively and always with complete stereocontrol (entries 4 and 6). Noteworthy the chiral Lewis base amount could be decreased and the reaction was successfully performed in the presence of only 1% of catalyst **52** in 36 hours: the reduction of *N*-benzyl enamine of 3-oxo-3-phenyl-propionic acid methyl ester afforded amine with 65% yield, although with a lower selectivity (91:9 dr).

Obviously the present methodology becomes synthetically appealing only if the benzyl group may be successfully removed, thus demonstrating the feasibility of the approach for the preparation of enantiomerically pure primary amino esters and *N*-unprotected  $\beta$ -lactams. Therefore hydrogenolysis of different chiral  $\beta$ -amino esters was attempted (Scheme 52).



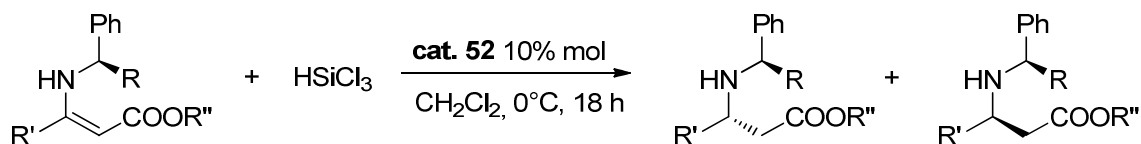
Scheme 52

entry	R	Ar	y (%)	ee (%)
1	H	Ph	>99	79
2	Me	Ph	>99	99
3	H	4-CF <sub>3</sub> Ph	>99	99
4	Me	4-OMePh	>99	99

Table 12

When 3-*N*-benzylamine-3-phenyl propionic acid methyl ester was reacted with hydrogen in the presence of catalytic amount of Pd/C in methanol at 1 atm at 25°C, chiral amino ester was isolated in quantitative yield after 16 hours. Starting from an enantiomerically enriched compound (81% ee), the corresponding product was obtained in 79% ee, thus showing that the reduction occurs with basically no loss of stereochemical integrity (entry 1, Table 12). The removal of the more bulky *N*- $\alpha$ -methyl benzyl group required more drastic conditions and it was successfully performed by hydrogenating the starting material for 16 hours in methanol with Pd/C at 15 atm (entry 2, Table 12). Noteworthy the reaction occurred without any appreciable loss of stereochemical integrity. Similarly, it was demonstrated that *N*- $\alpha$ -methyl benzyl-removal was possible also for substrates bearing both electron rich and poor-substituted aromatic rings: chiral amines gave the corresponding primary amine ester basically in quantitative yield as single stereoisomer (entry 3 and 4, Table 12).

The trichlorosilane mediated reduction was then applied to enamines derived from  $\alpha$ -alkyl- $\beta$ -keto esters by employing the ephedrine-based catalyst **52** (Scheme 53).



Scheme 53

Entry	T (°C)	R	R'	R''	y (%)	ee (%)
1	0	H	Et	Me	63	21
2	0	H	Bn	Me	51	53
3	0	Me	Bn	Me	45	71
4	0	H	<i>i</i> -Pr	Me	55	51
5	-20	H	<i>i</i> -Pr	Me	31	71
6	0	Me	<i>i</i> -Pr	Me	65	75
7	0	H	Ph	<i>t</i> -Bu	98	76

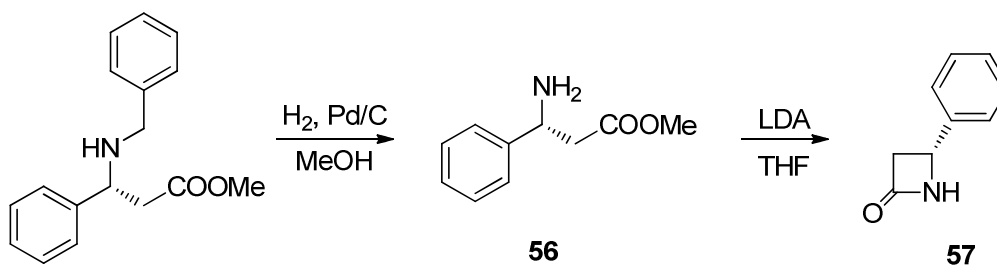
Table 13

When R' is an ethyl group the reduction of enamine afforded the product in low enantioselectivity (entry 1); some more interesting results were obtained when R' is benzyl: in this case the product was isolated in 45% yield and 71% ee (entry 3).

When the reduction was attempted with the enamine carrying an *iso*-propyl group the product was isolated in 55% yield and 51% ee (entry 4). The stereoselection of the process was improved by running the reaction at lower temperatures (71% ee at  $-20^{\circ}\text{C}$ ), although this reduce the yield to 31% (entry 5).

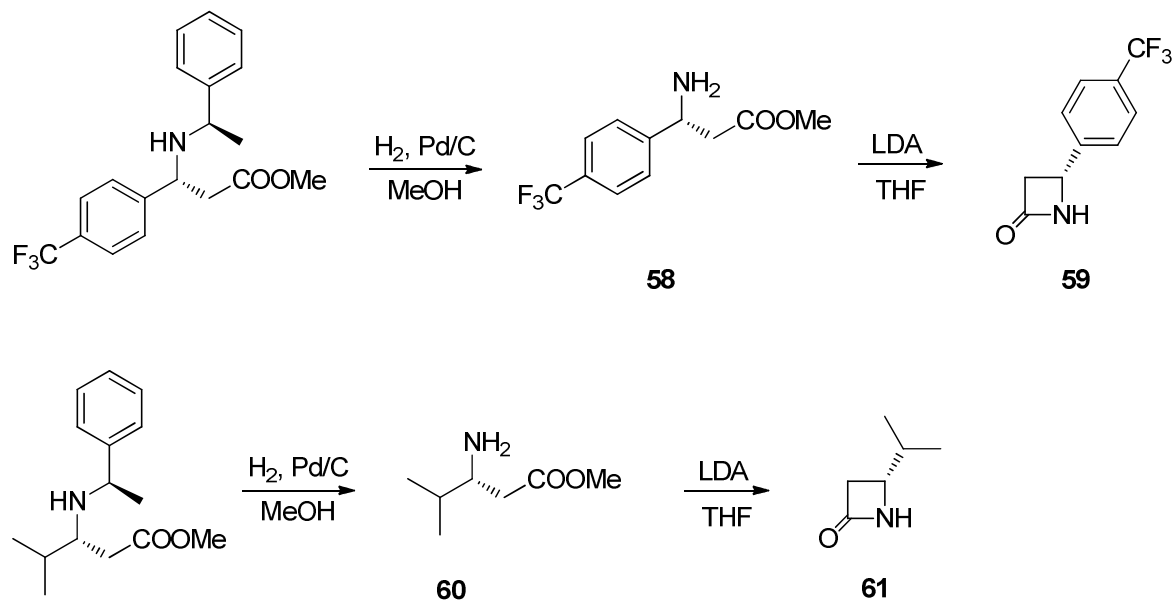
The role of the ester group was also briefly investigated. *N*-benzyl enamine of 3-oxo-3-phenyl-propionic acid *t*-butyl ester was synthesized and reacted with trichlorosilane in the presence of catalyst **52**. The product was obtained at  $0^{\circ}\text{C}$  in 71% yield and slightly higher enantioselectivity than the corresponding methyl ester (75% ee vs. 67% ee, entry 7).

Having demonstrated the generality of the approach, a few substrates were finally converted to  $\beta$ -lactams. Starting from a sample of *N*-benzyl amino ester with 80% ee hydrogenolysis, followed by reaction with LDA in THF, afforded the chiral 4-(*R*)-phenyl azetid-2-one **57** in 82% overall yield and 77% ee (Scheme 54).



**Scheme 54**

Similarly when  $\beta$ -amino ester was reduced by hydrogenation and converted to the corresponding chiral 4-(4-trifluoromethyl phenyl)-substituted  $\beta$ -lactam, product **59** was isolated as single stereoisomer in 80% yield after chromatographic purification (Scheme 55). Finally, by following the same synthetic procedure 4-methyl-2-amino-methyl pentanoate **61**, precursor of 4-isopropyl azetid-2-one, was obtained in 90% yield through hydrogenolysis of **60**.



Scheme 55

In conclusion, the organocatalytic reduction of *N*-benzyl enamines with trichlorosilane was successfully accomplished; the combination of low cost, easy to make metal-free catalyst and an inexpensive chiral auxiliary allowed to obtain chiral  $\beta$ -amino esters often with total control of the stereoselectivity. Finally hydrogenolysis of *N*-benzyl amino esters followed by LDA-promoted ring closure afforded enantiomerically pure 4-aryl or 4-alkyl substituted  $\beta$ -lactams.



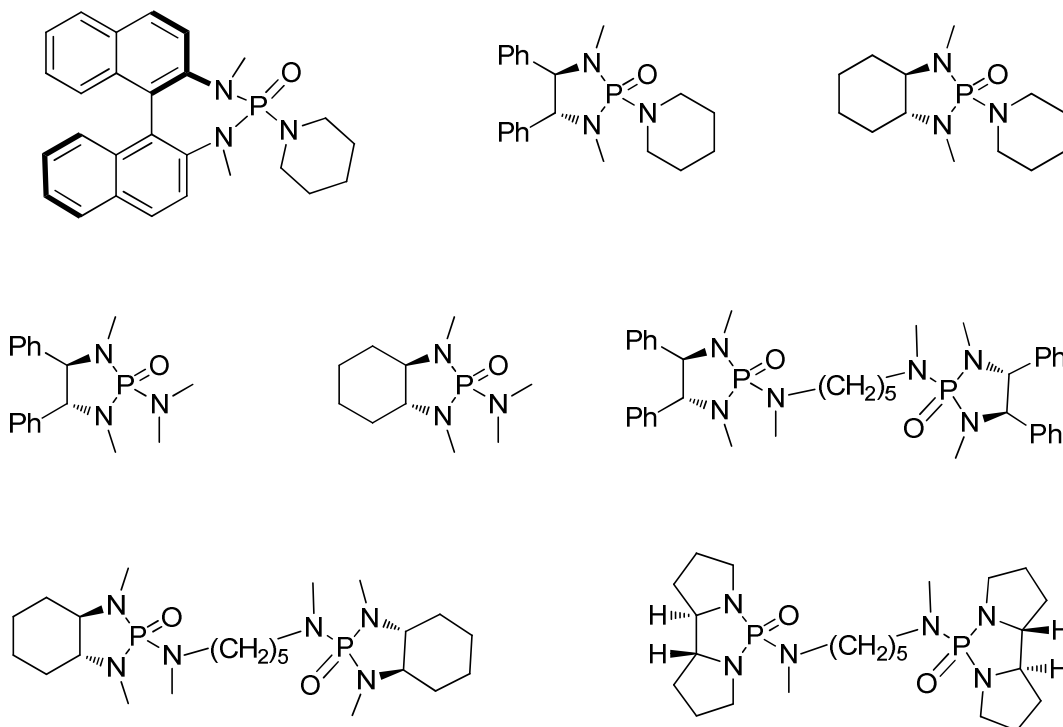
## CHAPTER V

### *New Chiral Organocatalysts for the Reduction of Carbon-Nitrogen Double Bond*

In the attempt to further enlarge the number and types of chiral coordinating Lewis bases suitable for  $\text{HSiCl}_3$ -promoted reductions we explored and developed the use of novel enantiomerically pure phosphoramides.<sup>[89]</sup>

Phosphoramides have found extensive applications in organic chemistry.<sup>[90]</sup> Their Lewis basicity and their strong donor properties make them very important ligands in organometallic chemistry, for their ability to modulate the reactivity at the metal center.<sup>[91]</sup> Phosphoramides have a very strong and polarized P-O double bond, with the phosphorous atom connected to one or more nitrogen subunit.

Recently, the use of chiral phosphoramides became very attractive because of their ability to promote stereoselective reactions as organocatalysts. The most important examples of phosphoroamides as chiral organocatalysts are due to Denmark, who reported the use of monodentate and bidentate phosphoroamides obtained from chiral diamines. A few examples of Denmark's mono- and bis-phosphoramides are collected in Figure 22.



**Figure 22**

These compounds were successfully employed as organic catalysts to promote two types of organic reactions: Mukaiyama aldol addition of silyl enol ethers to carbonyl compounds;<sup>[92]</sup> and allylation of aldehydes with allyltrichlorosilanes.<sup>[93]</sup>

Inspired by these contributions, we designed and used new phosphoramides as Lewis Base in the trichlorosilane-mediated enantioselective reduction of C-N double bond with the idea that simple coordination of the PO groups to  $\text{HSiCl}_3$  allows to generate a the active catalytic species (Figure 23).



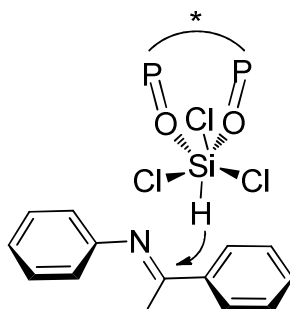
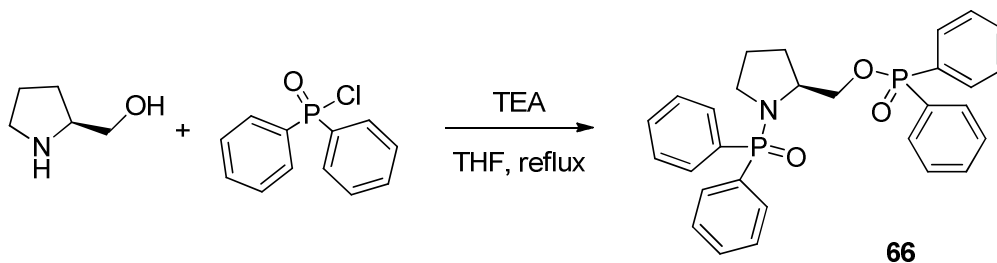


Figure 23

With this goal in mind, we synthesized derivatives in a single step procedure, using different enantiomerically pure scaffold, typically derived from (*S*)-prolinol or similar compounds. These are collected in Figure 24.

More specifically, the general synthesis involved the reaction between the chiral scaffold and diphenyl phosphinoyl chloride in presence of triethylamine under reflux. After chromatography purification, the reaction led to catalysts with yields between 21 and 75%. In Figure 56 it is reported the synthesis of catalyst **66**, as an example.



Scheme 56

Using similar chemistry, we easily prepared various chiral phosphinoamides, which can be distinguished as monodentate, with one site for the coordination to the silicon atom, and bidentate, which allows the bis-coordination.

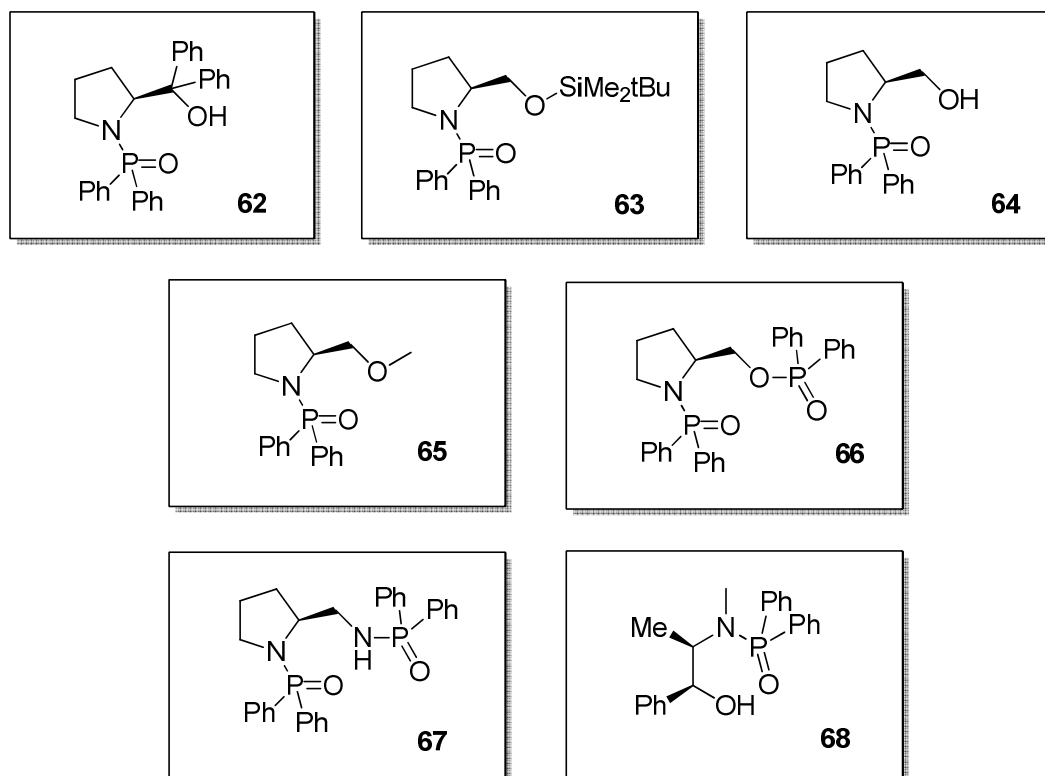
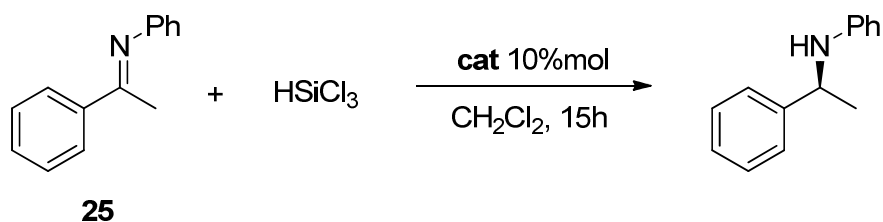


Figure 24

The reactivity of these derivatives were therefore examined in the enantioselective reduction of C-N double bond. First of all we conducted few preliminary experiments of reduction of ketimine **25** in dichloromethane at 0°C and -40°C.



Scheme 57

The most significant results obtained are collected in Table 14.

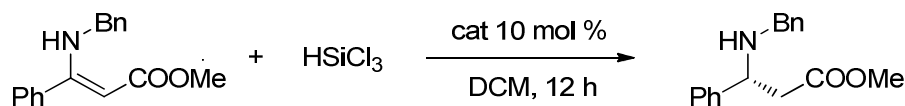
entry	cat	T (°C)	y (%)	ee (%)
1	<b>62</b>	0	47	32
2	<b>64</b>	0	-	-
3	<b>65</b>	0	83	rac
4	<b>66</b>	0	72	40
5	<b>66</b>	-40	64	64
6	<b>67</b>	0	93	rac
7	<b>68</b>	0	20	-

Table 14

From this first screening, we observed that the reduction with trichlorosilane proceeded smoothly to furnish the corresponding amine with good yield (up to 93%). Unfortunately, the enantioselectivity value was not significant using these systems, only catalyst **66** achieved discrete enantiomeric excess at low temperature (64%).

Considering these unsatisfactory results, we evaluated the possibility to apply the catalytic system to other interesting substrates. Indeed, less frequently trichlorosilane has been used in the reduction of  $\beta$ -enamino esters, as valid alternative to the metal-catalyzed hydrogenations.

Attracted to this possibility, we prepared and reduced the *N*-benzyl enamine of 3-oxo-3-phenyl-propionic acid methyl ester. In a typical procedure, the reaction was performed at 0°C in dichloromethane for 12 hours in the presence of 10% mol amount of chiral Lewis base (Scheme 58).



Scheme 58

The most significant results obtained are collected in Table 15.

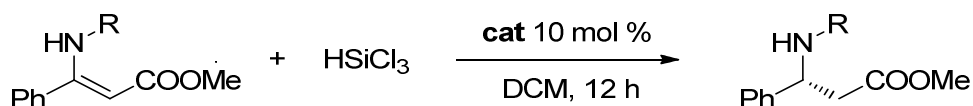
entry	cat	T (°C)	y (%)	ee (%)
1	<b>62</b>	0	41	21
2	<b>63</b>	0	70	7
3	<b>64</b>	0	98	5
4	<b>65</b>	0	47	7
5	<b>66</b>	0	99	35
6	<b>67</b>	0	98	31
7	<b>68</b>	0	47	11
8	<b>66</b>	-40	53	75
9	<b>67</b>	-40	50	85

Table 15

These experiments showed that all catalysts were able to promote the trichlorosilane addition, often in good yield. As predictable, monodentate organocatalysts **62-65** and **68** showed less efficiency and afforded the product generally in lower yield than bis-coordinating systems.

At 0°C only modest enantioselectivities were observed, while at lower temperature they were improved: as in the case of catalysts **66** and **67**, they afforded the product in 75% ee and 85% ee, respectively.

After this initial screening, we focused our attention on the most promising systems, catalysts **66** and **67**, and the following step was to evaluate the effect of most common protecting group on the nitrogen atom.



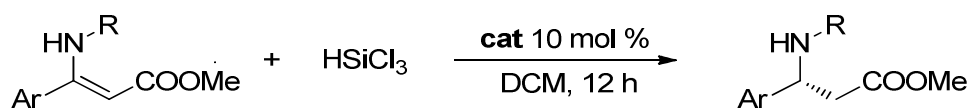
Scheme 59

entry	cat (%)	R	T (°C)	y (%)	ee (%)
1	<b>66</b>	Bn	-40	53	75
2	<b>67</b>	Bn	-40	50	85
3	<b>66</b>	PMP	-40	73	21
4	<b>66</b>	Ph	0	83	65
5	<b>67</b>	Ph	0	81	45

Table 16

The organocatalytic reduction of *N*-benzyl and *N*-PMP imines of  $\beta$ -ketoesters was investigated. The corresponding  $\beta$ -amino esters were obtained in discrete to good chemical yield, as shown in Table 16. Anyway, the best protecting group in this reaction condition remaining the benzyl group.

In order to further investigate the synthetic potentiality of our methodology and to verify the general applicability of the catalytic system, we performed a range of experiments with various substrate. We evaluated the effect of diverse electronic proprieties on the aromatic ring with different protecting group on the nitrogen atom.



Scheme 60

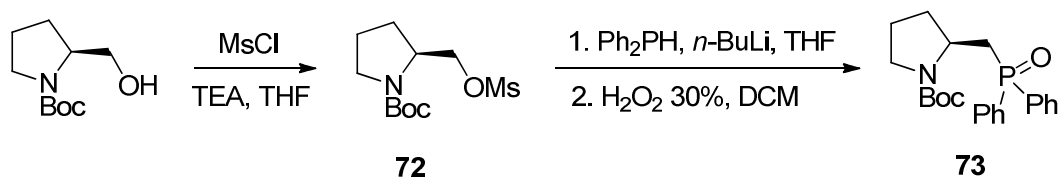
entry	cat	Ar	R	T (°C)	y (%)	ee (%)
1	<b>66</b>	4-OMePh	Bn	0	87	43
2	<b>66</b>	4-OMePh	PMP	0	99	50
3	<b>66</b>	4-OMePh	PMP	-40	71	70
4	<b>67</b>	4-OMePh	PMP	-40	70	21
5	<b>66</b>	4-CF <sub>3</sub> Ph	Bn	-40	73	60
6	<b>66</b>	4-CF <sub>3</sub> Ph	PMP	-40	55	63
7	<b>66</b>	4-BrPh	PMP	0	99	70
8	<b>66</b>	4-BrPh	PMP	-40	77	75
9	<b>66</b>	4-NO <sub>2</sub> Ph	Bn	0	99	80
10	<b>66</b>	4-NO <sub>2</sub> Ph	Bn	-40	75	78
11	<b>67</b>	4-NO <sub>2</sub> Ph	Bn	0	90	40
12	<b>66</b>	4-NO <sub>2</sub> Ph	PMP	0	99	70
13	<b>66</b>	4-NO <sub>2</sub> Ph	PMP	-40	85	83

Table 17

It is worth noting that best performing protection at the imine nitrogen changed from substrate to substrate. *N*-benzyl enamine was reduced with values of enantioselectivity lower than *N*-PMP derivatives when Ar is 4-OMePh (entries 1-2, Table 17) and with comparable results with the other substrates. It must be noticed that catalyst **67** did not confirm the excellent result shown before (entry 2, Table 17) and behaved quite unpredictably in several attempted reactions. Therefore (*S*)-prolinol-derivative **66** was preferably employed with other substrates. Generally PMP-substituted compounds were reduced in a slightly higher enantioselectivities than *N*-benzyl derivatives, always affording  $\beta$ -amino esters with enantiomeric excess higher than 70% and up to 83% ee in the best case (entry 13).

On the basis of those results, we evaluated the effect of various structural modifications of the catalyst, with the aim to understand the key factors that determine the performance of the catalyst and to allow a further improvement of its properties.

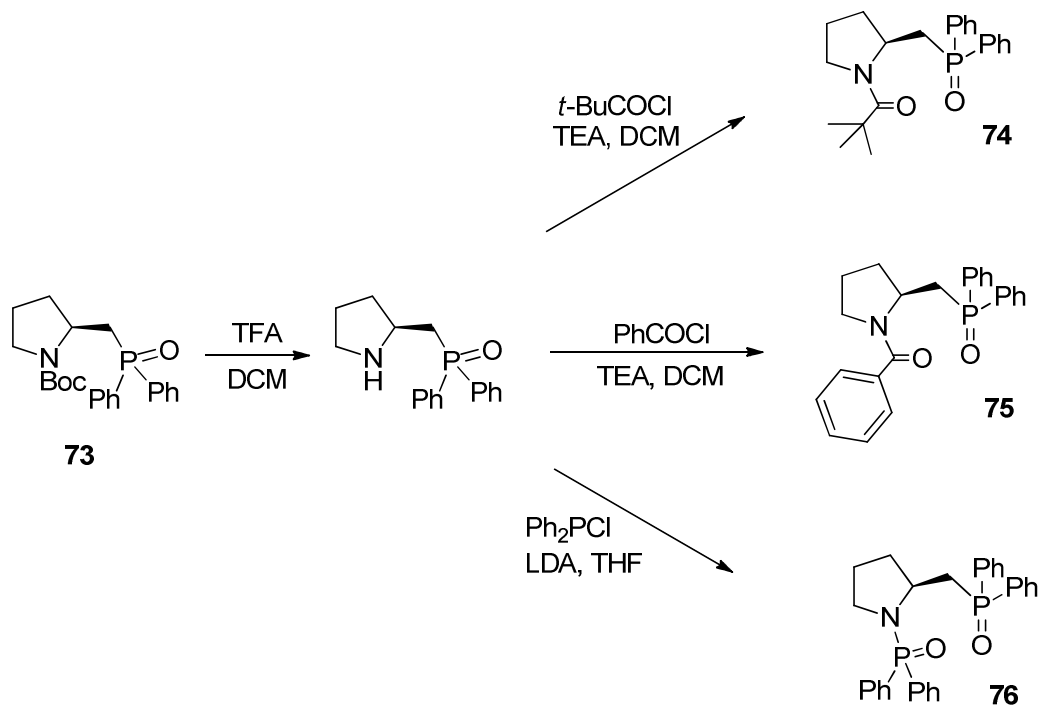
Following our philosophy according to which catalysts must be of simple preparation, we started the synthesis from commercially available *N*-Boc-L-prolinol and we easily obtained in three step catalyst **73**.



**Scheme 61**

The first step involved the preparation of compound **72** by treatment of *N*-Boc-(*S*)-prolinol with mesyl chloride in the presence of triethylamine for 4 hours at room temperature in THF. The diphenylphosphinic group was introduced for simple nucleophilic substitution in 43% yield. Even though the phosphorus atom usually is oxidized spontaneously in air, the oxidation did not take place completely. In order to obtain a complete conversion to phosphinoyl, necessary for the coordination to the silicon atom, the substrate was quantitatively oxidized with hydrogen peroxide.

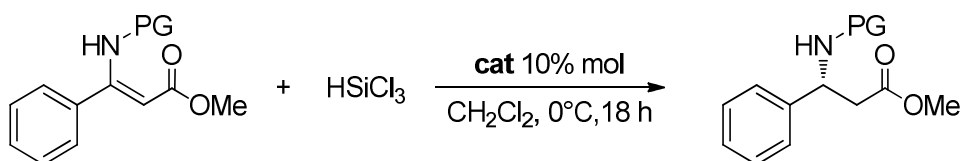
Starting from catalyst **73**, we synthesized three different bis-dentate catalysts. Treatment of catalyst **73** with trifluoroacetic acid allowed to remove the *tert*-butyloxycarbonyl group and the subsequent reaction with pivaloyl chloride in presence of TEA gave the catalyst **74** in 43% yield. Catalyst **75**, in a similar way, was prepared in 35% yield by reaction of **73** with benzoyl chloride. To perform the synthesis of catalyst **76** was necessary to use stronger conditions: substrate **73** reacted with chlorodiphenylphosphine in presence of LDA to obtain the desired product with 84% yield (Scheme 62).



Scheme 62

These organocatalysts were examined in the reduction of  $\beta$ -enamino esters with trichlorosilane (Scheme 63 , Table 19).

The reaction was carried out in dichloromethane as solvent for a time of 18 hours at 0°C, using a 10% catalyst loading.



Scheme 63

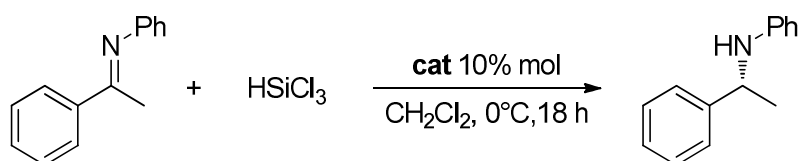
entry	cat	PG	y (%)	ee (%)
1	<b>73</b>	PMP	81	rac
2	<b>74</b>	PMP	49	rac
3	<b>75</b>	PMP	76	rac
4	<b>76</b>	Bn	64	rac



**Table 18**

As shown in Table 18, the reduction of  $\beta$ -enamino esters proceed in all case with very good chemical yields but total absence of stereocontrol.

We then decided to test these catalysts in the reduction of ketimines (Scheme 64). The results are collected in Table 19.

**Scheme 64**

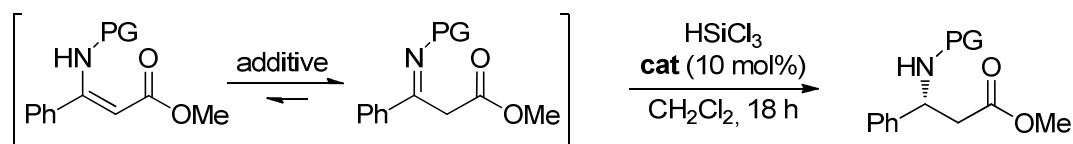
entry	cat	y (%)	ee (%)
1	<b>74</b>	70	rac
2	<b>75</b>	92	rac
3	<b>76</b>	68	rac

**Table 19**

Once again, the results were less satisfactory than those observed with catalysts **66** and **67**: the reactions proceed very well in terms of chemical efficiency but with no stereocontrol.

Discouraged by these results, we decided to change strategy and test the use of additives in the reaction. Recently Sun demonstrated how the addition of special additives increases the rate of reaction as well as the stereocontrol.<sup>[98]</sup> It is based on the understanding that the  $\beta$ -enamino esters themselves could not be reduced by trichlorosilane and that the reduction proceeds through their imine tautomers. The addition of different Bronsted acidic additives enhanced the rate of reduction by accelerating the enamine–imine tautomerization and, in addition, increase the electrophilicity of the imine through protonation of the nitrogen atom.

With this in mind, we added stoichiometric amount of various additives, such as H<sub>2</sub>O, *i*-propanol and trifluoroethanol, with the goal to increase the stereocontrol in the reduction of  $\beta$ -imino esters.



Scheme 65

entry	cat	PG	T (°C)	additive	y (%)	ee (%)
1	<b>73</b>	PMP	0	-	81	Rac
2	<b>73</b>	PMP	0	<i>i</i> PrOH	62	Rac
3	<b>73</b>	PMP	0	CF <sub>3</sub> CH <sub>2</sub> OH	67	Rac
4	<b>66</b>	PMP	0	<i>i</i> PrOH	72	rac
5	<b>66</b>	Bn	0	CF <sub>3</sub> CH <sub>2</sub> OH	55	rac
6	<b>66</b>	Bn	-40	-	53	75
7	<b>66</b>	Bn	-40	H <sub>2</sub> O	>99	50

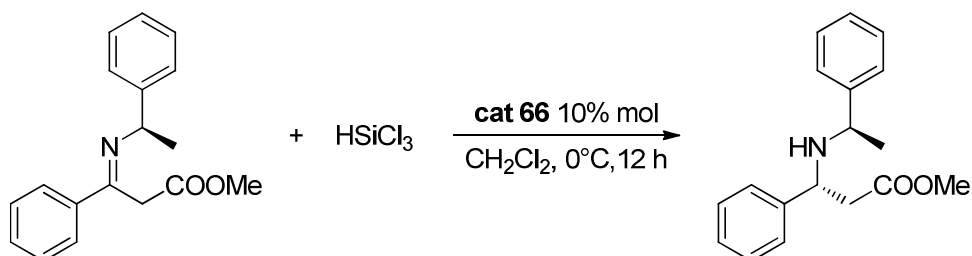
Table 20

From the data shown in Table 20, it was possible to conclude that even this strategy did not lead to the expected results. Indeed, the reduction promoted by catalyst **73** led to products with yields slightly lower than those obtained without additives and, more important, with no effect on the stereocontrol (entry 1-5).

Also catalyst **66** did not improve their performance in the presence of additives: the use of water allowed to isolate the reduction product in quantitative yield even though with 50% ee, lower to the value obtained in the absence of additive (entry 6 and 7).

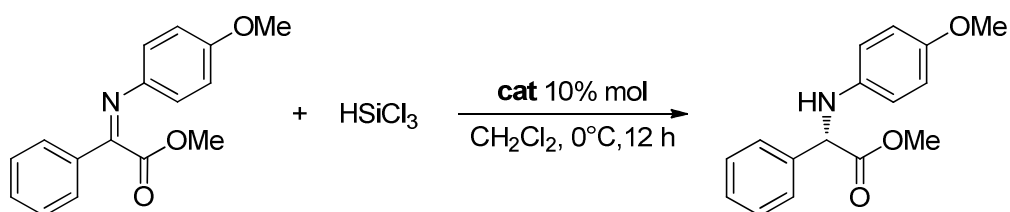
In the attempt of improving the selectivity of the process, we decided to take advantage of the presence of a removable chiral auxiliary at the imine nitrogen;<sup>[74]</sup> therefore trichlorosilane mediated reduction of enamine derived from (*R*)-1-phenyl-ethyl amine

was studied. By running the reaction at 0°C with catalyst **66**, the chiral  $\beta$ -amino ester was obtained after 12 hours in 98% yield with a total control of the stereoselectivity, affording the product as a single stereoisomer, as determined by NMR analysis.



Scheme 66

Then we decided to test our methodology in the preparation of  $\alpha$ -amino acids because very few successful example are currently reported in literature, both in case of transition metal-catalyzed hydrogenations and in case of organocatalytic methodologies with limited number of cyclic and uncyclic  $\alpha$ -imino esters studied.



Scheme 67

entry	C\cat	y (%)	ee (%)
1	66	>99	81
2	67	>99	70

Table 21

After 12 hours at 0°C in dichloromethane, both catalysts **66** and **67** promoted the reduction of *N*-4-methoxyphenyl  $\alpha$ -imino ester in quantitative yield at with good level of stereocontrol, and with 81% and 70% enantiomeric excess, respectively (Table 21).

In conclusion, the straightforward synthesis of a series of novel, inexpensive, easy to make, metal-free chiral catalysts by simple condensation of commercially available enantiopure amino alcohols was described. Such compounds were shown to promote the enantioselective reaction of ketimines,  $\alpha$ -imino and  $\beta$ -imino esters with trichlorosilane in high chemical yield and good enantiomeric excess. Imines bearing an inexpensive and removable chiral auxiliary, were reduced with complete control of the absolute stereochemistry.

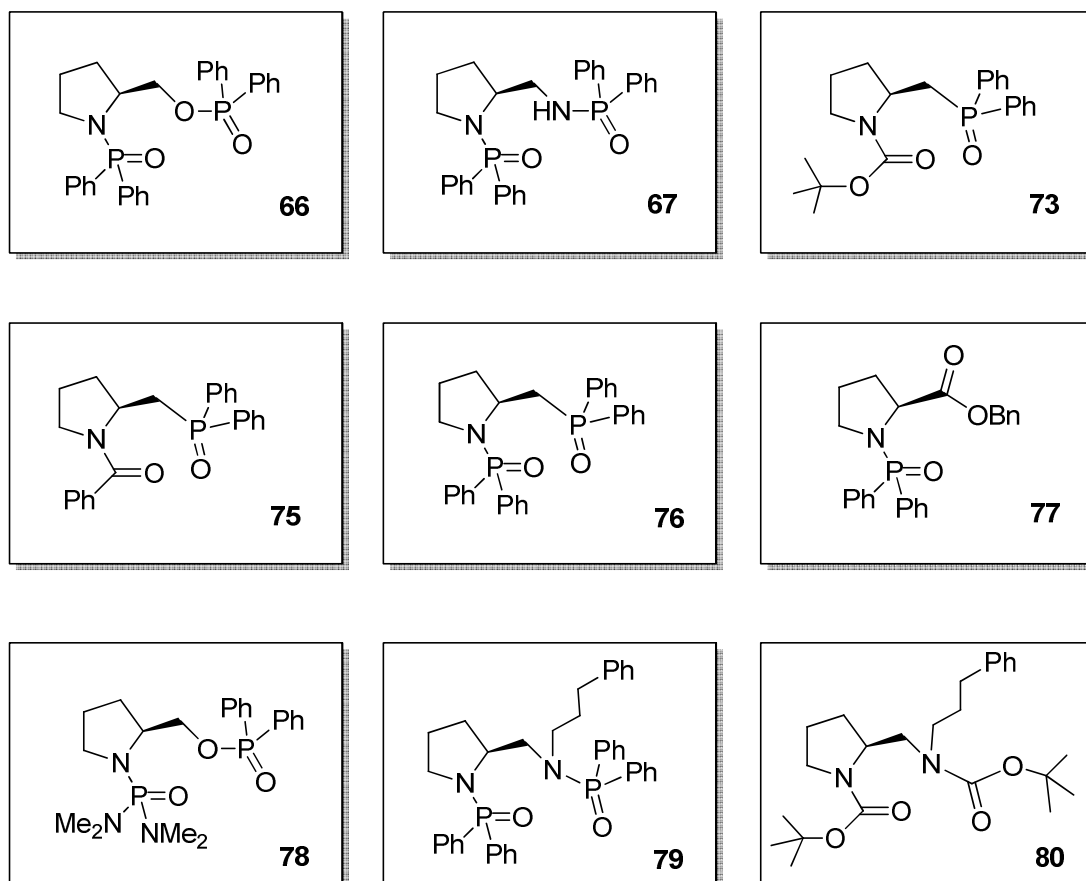
## CHAPTER VI

### *(S)*-Proline-derived Organocatalysts for the Lewis Acid-mediated Lewis Base-catalyzed Stereoselective Aldol Reactions of Activated Thioesters

In the course of our studies about P=O containing compounds and in an attempt to further improve the versatility and both chemical and stereochemical efficiency of these systems, we decided not only to expand the number and types of chiral coordinating Lewis bases for stereoselective reactions, but also to investigate their performance in different enantioselective reactions.

In this way, the newly synthesized P=O containing derivatives were employed as organocatalysts in the Lewis acid-mediated Lewis base-promoted direct stereoselective aldol reactions of activated thioesters with aromatic aldehydes, carried out in the presence of tetrachlorosilane and a tertiary amine.<sup>[94]</sup>

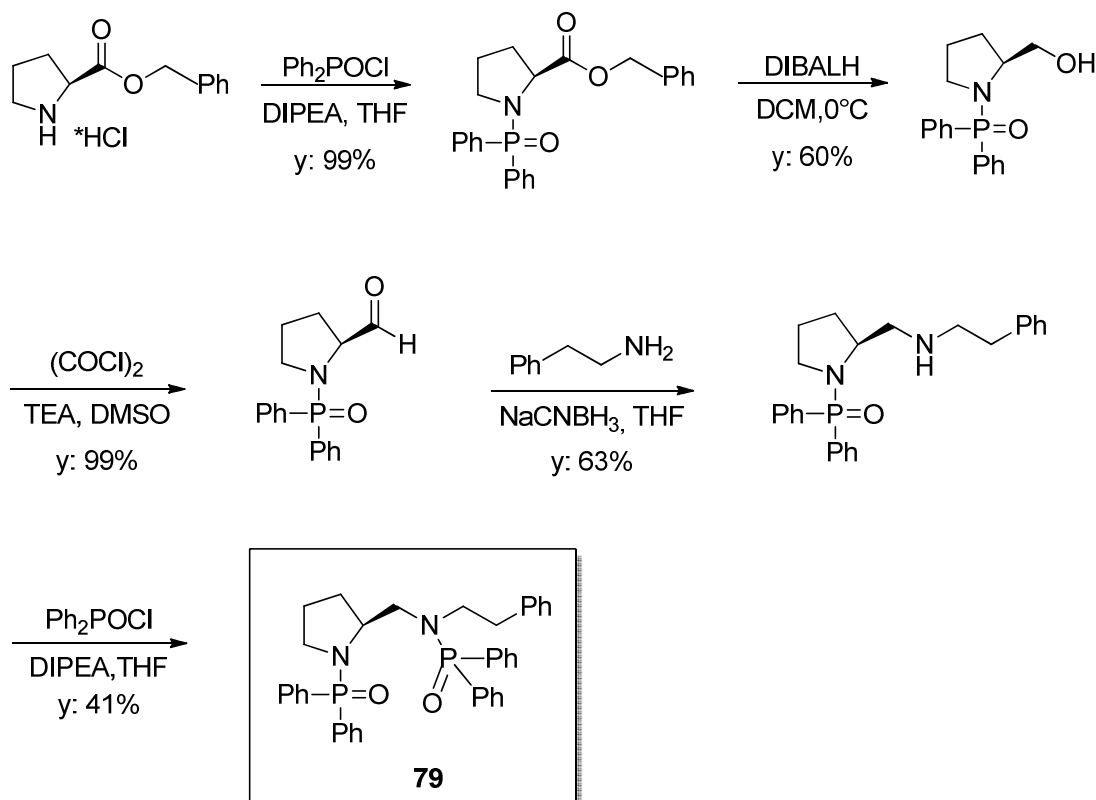
As described above, proline, with its rigid structure and vicinal functionalities, was identified as an inexpensive and readily modified scaffold for the synthesis of a set of enantiomerically pure Lewis bases containing different diphenyl phosphinyl oxide groups, collected in Figure 25.



**Figure 25**

Some of these compounds were synthesized in one step simply by reaction of enantiomerically pure and commercially available (*S*)-proline derivatives with the necessary phosphinoyl chloride. On the other hand, the synthesis of compound **78** required a stepwise procedure starting from proline benzyl ester and involving phosphoroamide formation, ester reduction to the primary alcohol, and reaction of the latter with diphenyl phosphinoyl chloride in 42% of overall yield.

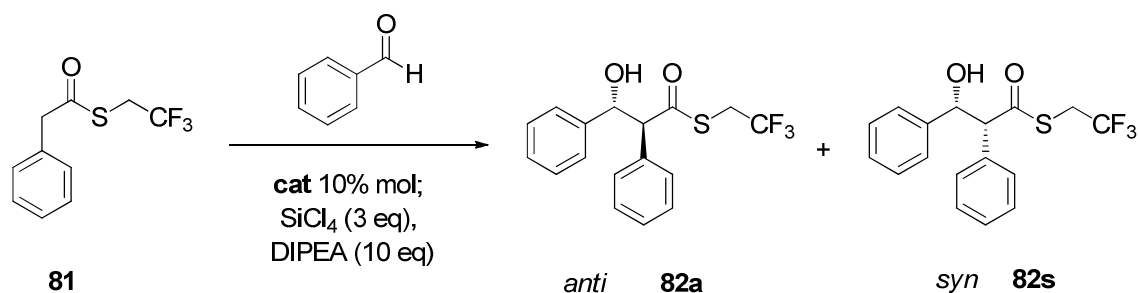
The synthesis of compound **79** also required a few steps (Scheme 68).



Scheme 68

Reduction of ester with excess of DIBALH followed by Swern oxidation led to the corresponding aldehyde in 86% yield. This was subjected to reductive amination with 2-phenyl ethylamine in the presence of sodium cyanoborohydride, and finally to reaction with diphenyl phosphinoyl chloride to afford the expected adduct **79** in 25% overall yield. It is worth mentioning that the present synthetic scheme offers the possibility to introduce two different P=O groups containing different residues at the two nitrogen atoms and thus to tune the properties of the two basic sites of the catalyst. Compound **80** was also prepared as a non-P=O containing analogue of **79** following a similar route starting from *N*-Boc proline benzyl ester (30% overall yield).

The chiral Lewis bases were then employed as catalysts in tetrachlorosilane-mediated aldol-type reactions. In particular, our studies were focused on the challenging aldol-type reaction between activated thioesters and aldehydes, a single example of which had been reported so far in the literature (Scheme 69).<sup>[95]</sup>



**Scheme 69**

The direct condensation of 2 mol equiv of trifluoroethyl phenylthioacetate **81** with 1 mol equiv of benzaldehyde was performed in presence of 3 mol equiv of silicon tetrachloride, 10 mol equiv of DIPEA, and 10 mol % of a chiral Lewis base at 0°C, for 24 h in dichloromethane and led to the results summarized in Table 22.

entry	cat	y (%)	<i>syn/anti</i> ratio	ee <i>syn</i> (%)
1	<b>77</b>	35	98:2	35
2	<b>78</b>	60	96:4	37
3	<b>66</b>	51	97:3	51
4	<b>67</b>	40	94:6	47
5	<b>79</b>	90	98:2	51
6	<b>80</b>	31	98:2	15
7	<b>76</b>	35	92:8	15
8	<b>75</b>	45	97:3	21
9	<b>73</b>	55	96:4	19

**Table 22**

As can be seen from these data, all catalysts were able to promote the aldol reactions, although with widely different efficiency. Satisfactory yields of strongly unbalanced mixtures of *syn* and *anti* β-hydroxythioesters **82s** and **82a** were obtained with catalysts **78**, **66** and especially **79** (up to 90%). The chemical efficiency of the catalysts seemed to



be only in part related to the presence of two highly coordinating P=O Lewis basic sites, as can be seen comparing the yields obtained with adducts **67** and **79** both featuring two phosphoroamidic residues (entries 4 and 5). When the P=O groups were replaced by carbonyl residues, the catalyst led to a particularly slow reaction ( **cat 80**, entry 6), proving that the presence of the P=O basic sites is important.

These experiments also demonstrate that the *syn* diastereoisomer was constantly obtained as the major product, independently from the catalysts employed (*syn/anti* ratio >92:8). The enantiomeric excess of these *syn* isomers ranged from modest to fair. A maximum of 51% ee was obtained with catalysts **66** and **79**. Noteworthy, catalysts featuring both a phosphinamide and a phosphine oxide group were also tested for the first time, (entries 7-9) but with disappointing results.

On the basis of these data, catalysts **78**, **66**, **67** and **79** were selected for further optimization experiments performed by changing the reaction conditions. The results are collected in Table 23.

entry	cat	t (h)	T (°C)	y (%)	<i>syn/anti</i> ratio	ee <i>syn</i> (%)
1	<b>78</b>	40	-40	35	97:3	45
2	<b>66</b>	24	0	60	>98:2	51
3	<b>66</b>	40	-40	51	97:3	37
4	<b>67</b>	40	-40	40	98:2	53
5	<b>79</b>	40	-40	90	98:2	33
6	<b>79</b>	40	-40	31	90:10	22
7	Denmark's Catalyst	24	0	21	85:15	23
8	Tetramethyl BITIOPO	15	0	80	>98:2	89
9	Tetramethyl BITIOPO	15	-40	55	88:12	83

**Table 23**

Lowering the reaction temperature had only a marginally positive effect on the enantioselectivity of the reaction carried out in the presence of catalysts **78** and **67**, no

effect in the case of catalyst **66**, and was clearly negative in the case of catalyst **79**. Compound **79** remained, however, the best performing catalyst in terms of chemical efficiency. By working at low temperature the preferential formation of the *syn* adduct was confirmed, and in some instances slightly improved, for all the studied catalysts.

To assess the value of this new class of proline-based chiral Lewis bases as catalysts, we compare their performance with that of the well-established tetramethyl-BITIOPO<sup>[96]</sup> and binaphthyl derived bisphosphoroamide, the Denmark's catalyst.<sup>[97]</sup>

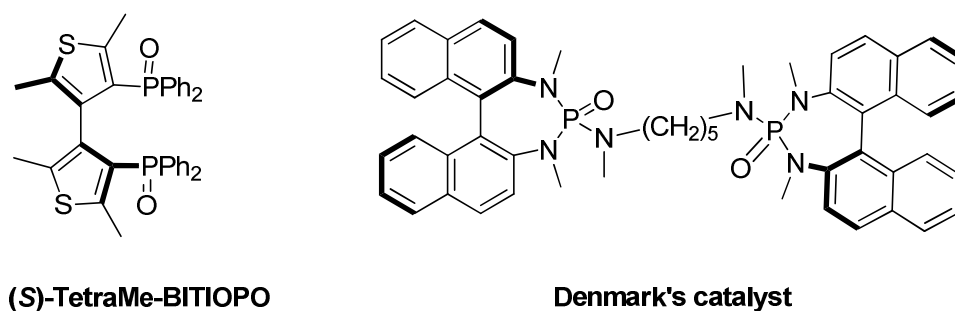
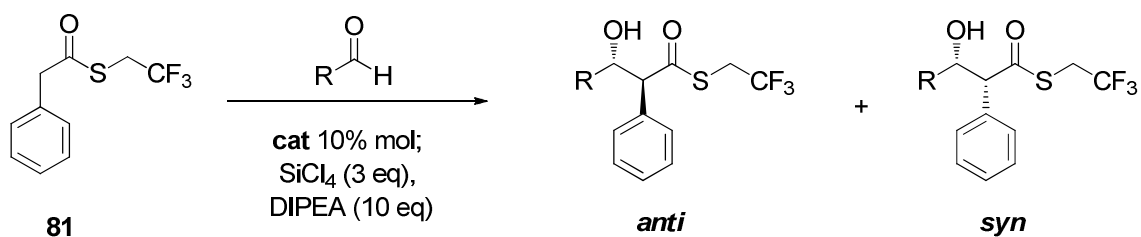


Figure 26

In our hands and under the experimental conditions of Scheme 68, Denmark's catalyst promoted the direct aldol reaction of thioester **81** with benzaldehyde to afford an 85:15 *syn/anti* mixture of  $\beta$ -hydroxythioesters **82**, in only 21% yield and 23% ee for the major *syn* isomer. The result demonstrated that in the present methodology not only the Lewis basicity of the coordinating sites at silicon, but also the steric environment and the interaction of the Lewis bases with the sterically demanding silicon tetrachloride, play a key role in the process. For clearness of comparison, in Table 24 the results obtained with tetramethyl BITIOPO were reported; at 0°C this chiral phosphine oxide promoted the direct aldol reaction in 80% yield and 89% ee.

To determine the effect of a change in the electronic nature of the aromatic residue of the aldehyde on the efficiency of the reaction, thioester **81** was also reacted with 4-methoxy- and 4-trifluoromethyl-benzaldehyde to afford aldol adducts **83s,a** and **84s,a**, respectively. The results are collected in Table 24.



Scheme 70

entry	cat	T (°C)	R	y (%)	<i>syn/anti</i> ratio	ee <i>syn</i> (%)
1	<b>66</b>	0	Ph	51	98:2	51
2	<b>66</b>	0	4-MeOPh	25	96:4	47
3	<b>66</b>	0	4-CF <sub>3</sub> Ph	35	70:30	37
4	<b>67</b>	0	Ph	40	94:6	47
5	<b>67</b>	0	4-MeOPh	41	90:10	33
6	<b>67</b>	0	4-CF <sub>3</sub> Ph	35	70:30	29
7	<b>79</b>	0	Ph	90	98:2	51
8	<b>79</b>	0	4-MeOPh	35	96:4	50
9	<b>79</b>	0	4-CF <sub>3</sub> Ph	48	91:9	31
10	<b>Tetramethyl BITIOPO</b>	0	Ph	80	>98:2	89
11	<b>Tetramethyl BITIOPO</b>	0	4-MeOPh	51	>98:2	83

Table 24

When trifluoroethylthioester was reacted at 0°C with 4-methoxybenzaldehyde in the presence of a catalytic amount of compound **66**, the product was isolated in low yield (25%), high diastereoselectivity (*syn/anti* 96:4) and in 47% ee (entry 2).

The reaction with 4-trifluoromethylbenzaldehyde led to slightly higher yield (35%) but disappointingly low diastereoselectivity (*syn/anti* 70:30), and ee (37%) (entry 3). The use of the 4-methoxy- and 4-trifluoromethyl-benzaldehyde in the reaction carried out with catalyst **67** led to similar results (entries 4-6). On the other hand, the chemical efficiency shown by catalyst **79** in promoting the reaction of thioester with benzaldehyde was not

reproduced with either 4-methoxy- or 4-trifluoromethyl-benzaldehyde (entries 6-8). Once again it is worth mentioning that with tetramethyl-BITIOPO constantly excellent levels of enantioselectivity, higher than 80%, were maintained with different aromatic aldehydes (entries 10 and 11 ).

In an attempt to rationalize the steric course of these reactions and possibly gain some insight into the origin of stereoselectivity that can be useful for a future optimization of the catalyst structure, the transition structures for the aldol addition of the enolate of thioester **81** with benzaldehyde in the presence of catalyst **66** were initially located at the semiempirical PM6 level. Catalyst **66** was studied instead of catalyst **79** because, being structurally more simple, it was more amenable to calculations. It must be remembered that the two catalysts, although of different chemical efficiency, showed similar level of stereocontrol. On the basis of our recent experience in related reactions and of literature data, the formation of a chiral cationic hypervalent hexacoordinated silicon species was postulated, with the two chlorine atoms in the apical positions; both enolate and aldehyde are coordinated to the silicon atom. Thus, cyclic, chair-like transition structures can be easily located, accounting for the formation of all the possible diastereoisomers. They were characterized as true transition structures for the reaction *via* a complete vibrational analysis. The two structures of the lowest energy TS leading to the formation of the *syn* isomers, major (*S,S*)-**82** (structure **A**) and (*R,R*)-**82** (structure **B**), are shown in Figure 28. The parallel-offset orientation of the phenyl rings of the aldehyde and of the enolate, and the T-shaped arrangement of the phenyls of the enolate and of the phosphoroamide, both stabilizing interactions present in **A** but not in **B**, seem to play the major role in determining the stereoselection. However, PM6 data indicate only a moderate selectivity in favor of (*S,S*)-**82**, in qualitative agreement with the experimental data; work is in progress to complete the theoretical analysis of this reaction and to enhance the level of theory, in order to get a deeper insight into the origin of the stereoselection.



In conclusion, we synthesized a novel class of proline-based chiral Lewis bases employed as organocatalysts in Lewis acid-mediated Lewis base-promoted direct stereoselective aldol reactions of activated thioesters with aromatic aldehydes. In the presence of tetrachlorosilane, very high *syn* diastereoselectivities were generally obtained for the direct aldol reaction of thioesters with aromatic aldehydes; although modest to fair enantioselectivities for the major isomer were observed, the results opened the way towards the use of a new class of catalysts in SiCl<sub>4</sub> mediated stereoselective reactions.

## CHAPTER VII

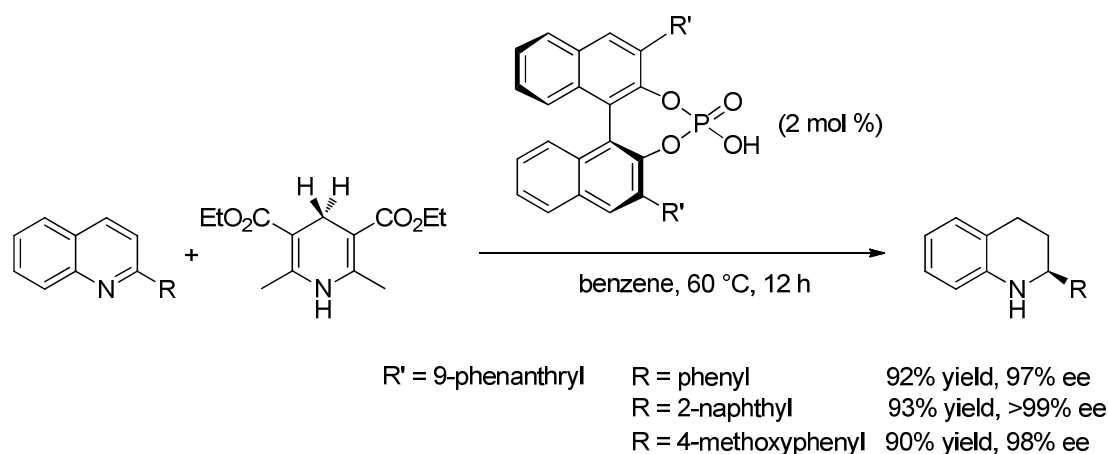
### *Stereoselective Reduction of Heteroaromatic Compounds*

*N*-containing heteroaromatic compounds, particularly those having an indole or quinoline substructure, are important (sub)structures present in numerous natural or synthetic alkaloids. They are known for their high biological activity, and find numerous applications in pharmaceuticals, agrochemicals and cosmetics.<sup>[99]</sup> Various synthetic methodologies have been reported to access these backbones. The most common procedures involve catalytic hydrogenation of unsaturated compounds with transition metal catalysts. However, asymmetric hydrogenation of aromatics or heteroaromatics compounds requires strong reaction conditions, elevated pressures and temperatures.

The possibility to work under mild conditions with metal-free procedures suggests the use of organocatalytic systems. Relatively few examples of organocatalytic systems are known for the stereoselective reduction of a carbon-nitrogen double bond of heterocyclic compounds. They involve the use of Hantzsch esters or trichlorosilane as hydride source, as briefly described below.

## 7.1 Hantzsch esters

The first example of a metal-free reduction of heteroaromatic compounds was reported by Rueping's group in 2006. They developed an enantioselective phosphoric acid catalyst able to catalyse the partial reduction of quinoline derivatives<sup>[100]</sup>, which are of great synthetic importance in the preparation of pharmaceuticals and agrochemicals, as well as structural key element of many alkaloids. After screening variety of sterically congested phosphoric acid, (*R*)-(-)-9-phenanthryl-1,1'-binaphthyl-2,2'-diyl hydrogen phosphate was selected as derivative of choice to perform stereocontrol, which provided 2-phenyltetrahydroquinoline in 97% ee (Scheme 71).

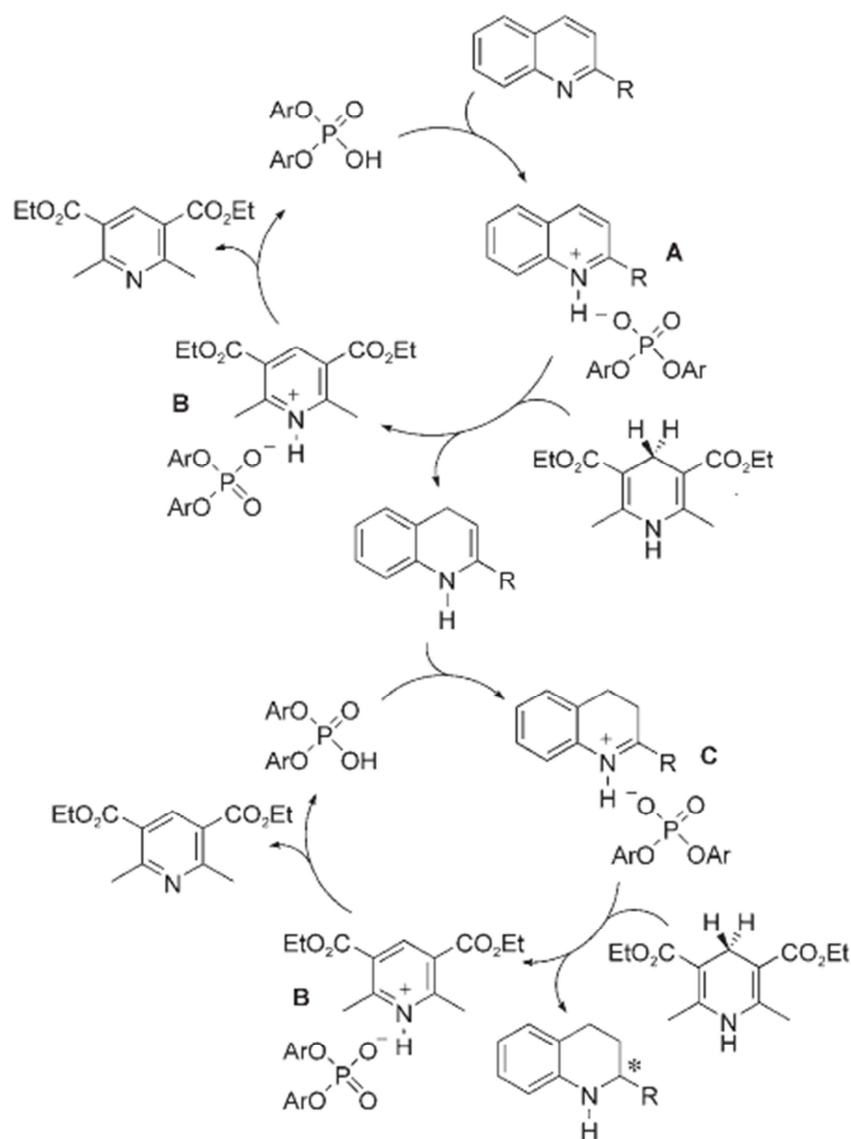


**Scheme 71**

Examining the scope of this reaction, authors found out that this class of catalyst is able to afford in good yields and high enantioselectivities several tetrahydroquinolines with aromatic, heteroaromatic residues and aliphatic substituents. Mechanistically, Rueping and co-workers conjectured that the first step in the enantioselective cascade hydrogenation is the protonation of the quinoline through the Brønsted acid catalyst to generate the iminium ion **A** (Figure 28). Subsequent transfer of the first hydride from the dihydropyridine generates the enamine and pyridinium salt **B**, which undergoes proton transfer to regenerate the Brønsted acid and Hantzsch pyridine. Then the enamine reacts in a second cycle with Brønsted acid to produce iminium ion **C**, which will again be subject to hydride transfer to give the desired tetrahydroquinoline. Subsequent proton



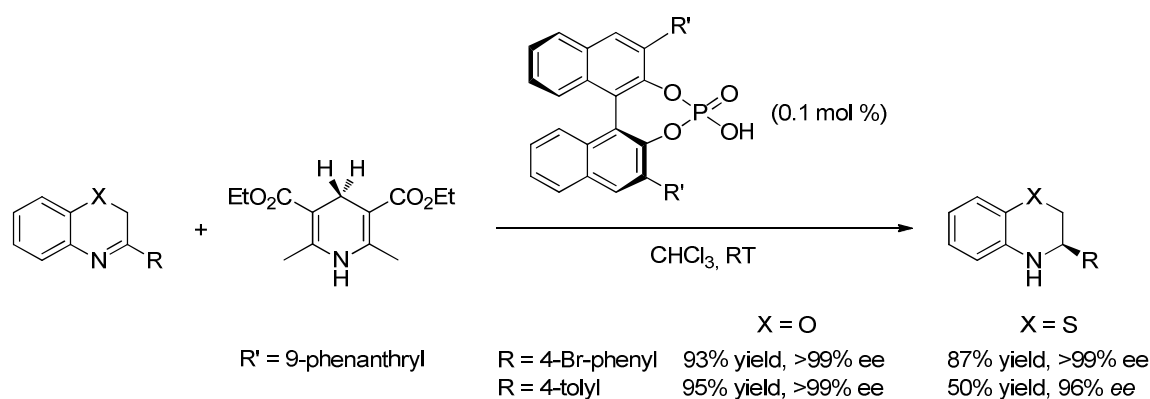
transfer will then recycle the Brønsted acid and generate a second equivalent of the Hantzsch pyridine. The stereochemical outcome of the reaction can be explained by a stereochemical model proposed by a transition state model in which the quinoline is activated by protonation of the chiral Brønsted acid, thereby favoring approach of the hydride nucleophile from the less hindered *Si* face since the *Re* face is shielded by the large phenanthryl group of the catalyst.



**Figure 28**

Later, the same group extended this catalytic methodology to the hydrogenation of cyclic imines, such as benzoxazine and benzothiazine<sup>[101]</sup>.

Once again, 9-phenanthryl derivative of BINOL phosphoric acid turned out to be the best performing catalyst, and further studies allowed to decrease the catalyst loading to 0.01 mol% without a considerable loss in reactivity and selectivity: this is the lowest catalyst loading to be reported for an organocatalytic enantioselective transformation up. In general, differently substituted benzoxazines and benzothiazine (bearing either electron-withdrawing or electron-donating groups) were obtained in good yields and with excellent enantioselectivities (Scheme 72).



Scheme 72

It is worth mentioning that this is the first enantioselective hydrogenation of benzothiazines and represents one of the advantages of this organocatalytic hydrogenation over the application of most metal catalysts, which are known to be poisoned by sulfur-containing substrates. As further development, Rueping successfully reported the reduction of benzoxazinones, obtain in the cyclic aryl glycine derivatives in good yields and enantioselectivities (90–99% ee), which then were opened to the corresponding linear amino acid amides without racemization. The authors hypothesized that, similar to several biomimetic transfer hydrogenations, benzoxazines and benzothiazines would be activated by catalytic protonation through Brønsted acid (Figure 29). Analogously to the previous reduction of quinolines, formation of the chiral ion pair is thought to favor the approach of the hydride from the less hindered *Si* face as the *Re* face is effectively shielded by the large phenanthryl group of Brønsted acid.

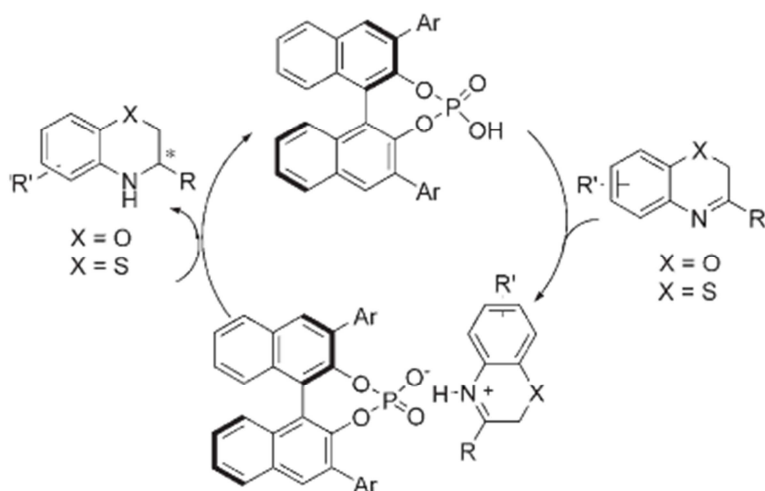


Figure 29

In 2008 Du and co-workers further improved the asymmetric transfer hydrogenation of quinolines introduced by Rueping through the employment of new chiral phosphoric acid catalysts<sup>[102]</sup>. The authors observed that substituents at the 3,3'-positions of BINOL are very important for achieving high selectivity. The use of 3,3'-nonsubstituted BINOL phosphate as a catalyst always gave low or even no enantioselectivity. Therefore, Du's group assumed that the presence of substituents at the 3,3'-positions of binol phosphate results in a better performance in organocatalysis. The newly proposed catalysts have chiral pocket larger than those of previously developed phosphoric acid catalysts (Figure 30).

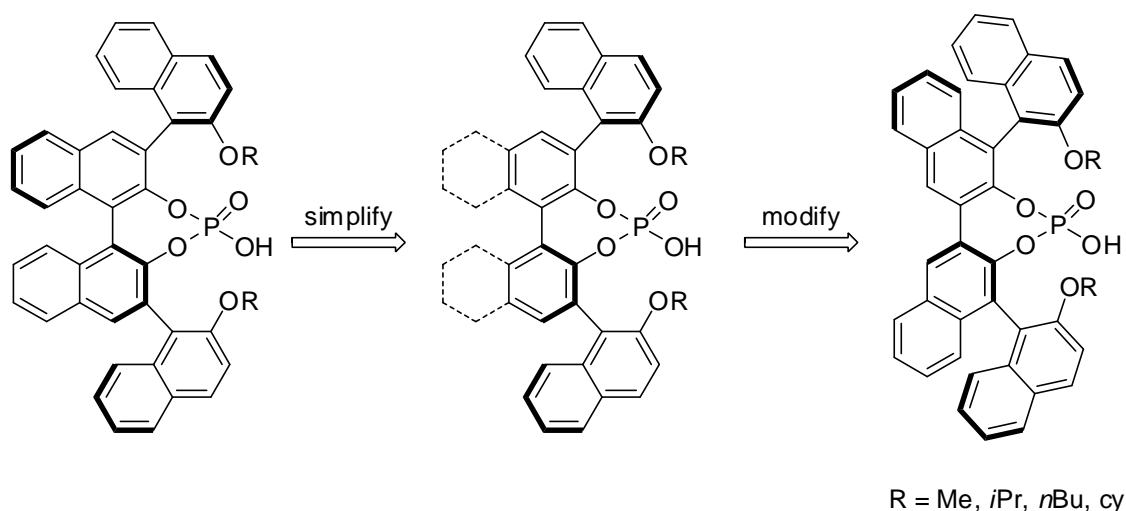
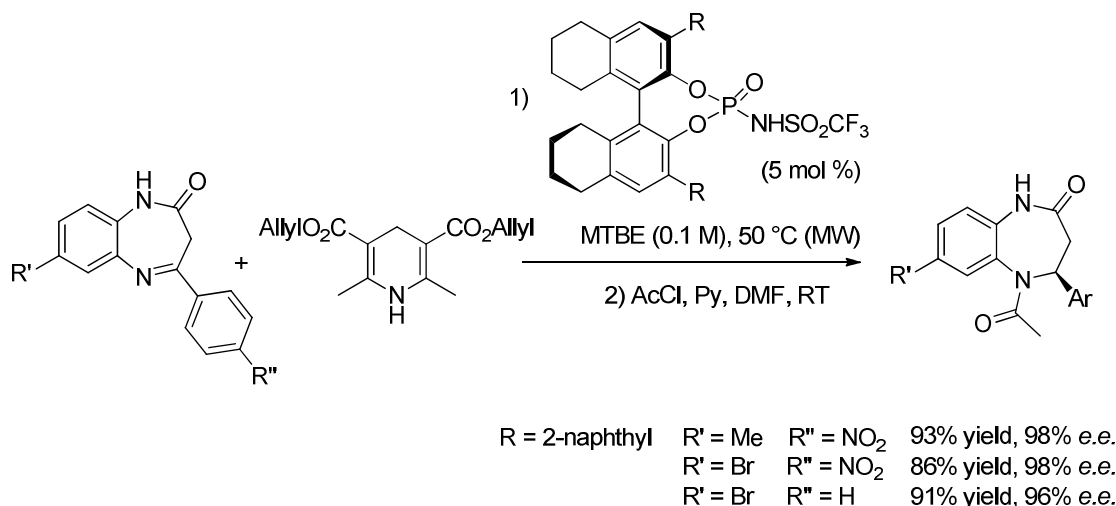


Figure 30

A variety of 2-aryl-substituted tetrahydroquinolines were already synthesized with excellent enantioselectivities under the conditions developed by Rueping's group, but 2-alkyl-substituted tetrahydroquinolines showed lower enantioselectivities (87–91% ee). With this new phosphoric acid, a low catalyst loading (0.2 mol%) is sufficient to obtain excellent enantioselectivities, up to 98% ee for 2-aryl- and 2-alkyl-substituted quinolines. Best results were obtained with *i*-Pr and cyclohexyl derivatives, most likely due to increased steric effects.

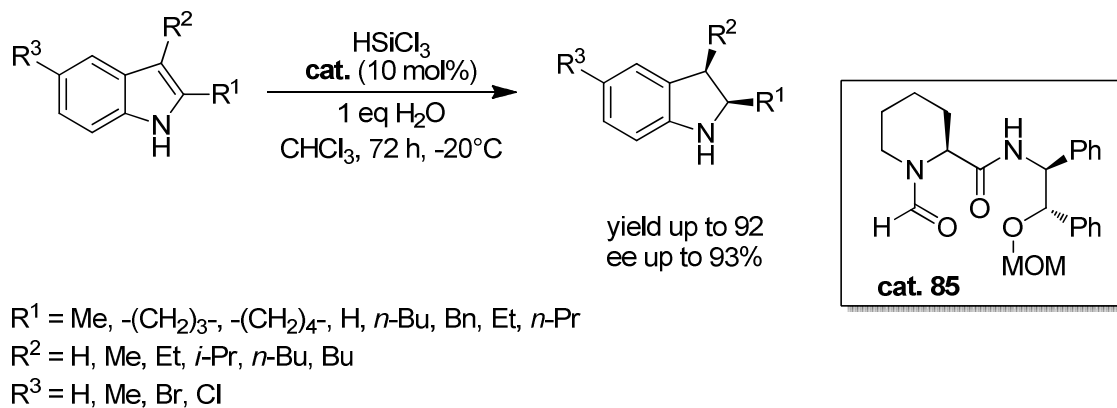
In 2010, Rueping's group reported the first enantioselective approach towards the synthesis of 4-substituted-4,5-dihydro-1H-[1,5]benzodiazepin-2(3H)-ones, which resemble cyclic  $\beta$ -amino acids.<sup>[103]</sup> Due to the basic nature of these benzodiazepinones, the reactions conducted with various chiral phosphoric acid diesters gave only very low conversion because of catalyst inactivation, while improved reactivity was obtained when the corresponding *N*-triflylphosphoramides was employed as catalysts, with 2-naphthyl derivative selected as best performing one. Microwave irradiation proved to be beneficial to further improve the yields, and the reduction, followed by subsequent acylation, allowed to isolate products in very high yields and enantiomeric excess (Scheme 73). The reaction is quite general with respect to the substitution pattern of the benzene ring and phenyl substituent, while electronic effects of the phenyl substituent play a role in the case of 7,8-disubstituted substrates. Whereas the selectivities were essentially the same, the yields were higher with an electron withdrawing group substituent of the phenyl ring. It is noteworthy that, in contrast to most transition metal-catalyzed reactions, this metal-free transfer hydrogenation not only tolerates halogen substituents but also nitro functionalities.



Scheme 73

## 7.2 Trichlorosilane

Very recently, Sun reported the first direct enantioselective hydrosilylation of prochiral 1H-indoles by combined Brønsted acid/Lewis base activation.<sup>[104]</sup> The key factor for this methodology is the addition of one equivalent of water to react with HSiCl<sub>3</sub> to generate a strong Brønsted acid, HCl. In this way the reaction proceeds through the generation of electrophilic indolenium ions by C3 protonation with the *in situ* formed HCl, and subsequent chiral Lewis base mediated enantioselective hydrosilylation with HSiCl<sub>3</sub> (Figure 31). A variety of chiral Lewis bases were tested and L-pipecolinamide derivative bearing MOM ether moiety (**cat. 85**) exhibited high catalytic activity and enantioselectivity with a wide range of substrates (Scheme 74).



Scheme 74

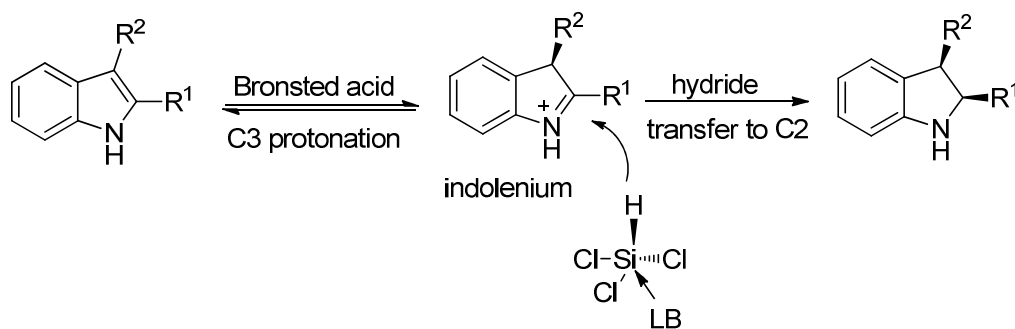
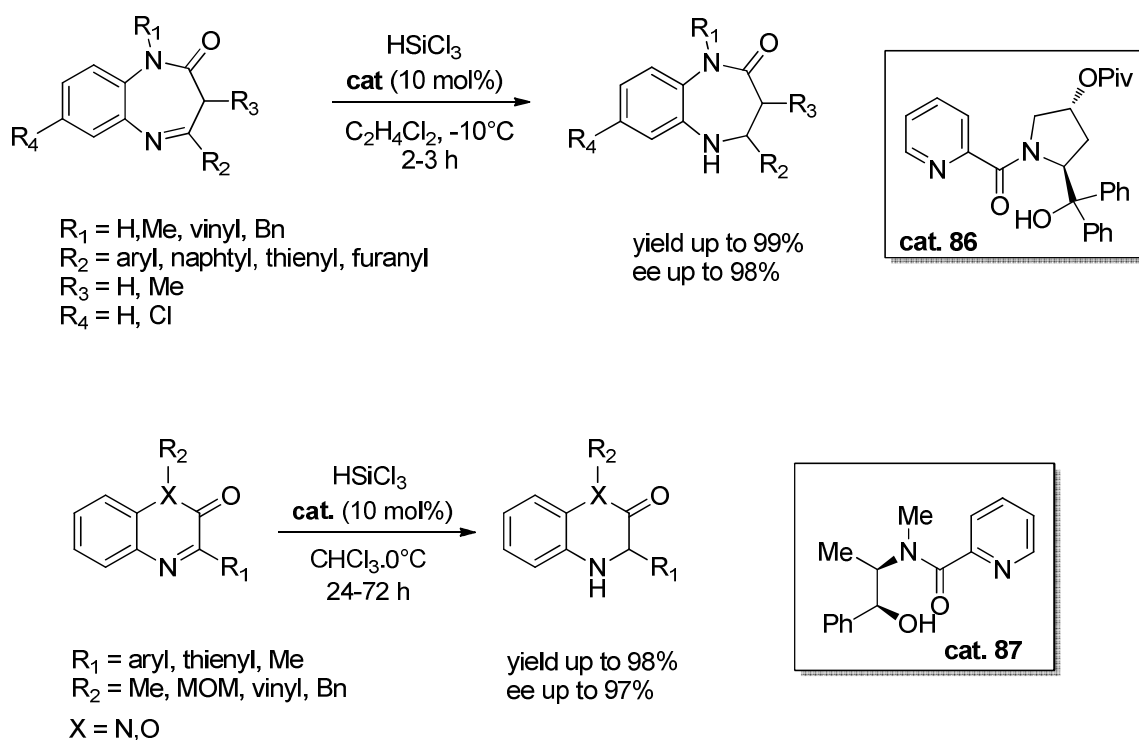


Figure 31

The trichlorosilane-mediated reduction has also been used for the stereoselective synthesis of chiral heterocyclic building blocks, such as dihydrobenzodiazepinones.<sup>[105]</sup> The corresponding products were obtained in excellent yields (up to 99%) and enantioselectivities (up to 98%) with catalyst **86**. Other heterocycles have been used as substrates with catalyst **87** and water to increase the yield and the selectivity (Scheme 75).<sup>[106]</sup>

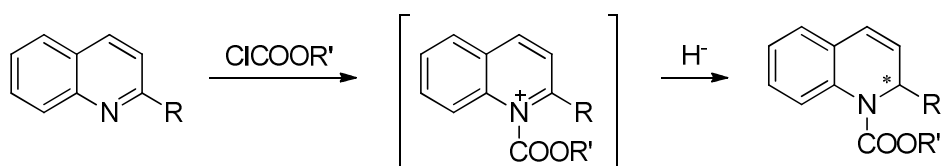


Scheme 75

Following our interest in the development of trichlorosilane-mediated reactions, we decided to apply this reductive methodology also to the synthesis of enantioenriched heterocycles, such as quinolines.

First, we performed the direct reduction of both quinoline and *iso*-quinoline with 3.5 mol equiv of  $\text{HSiCl}_3$  in the presence of a stoichiometric amount of achiral Lewis Base, such as DMF.

Under these conditions, the substrates do not undergo any transformation, probably due to their high stability. For this reason, we decided to improve the reactivity of the substrates with an activating reagent. Thus, asymmetric hydrogenation of quinolines and *iso*-quinolines activated by chloroformates provides a convenient route to synthesize optically active dihydro-heterocycles, because the aromaticity is partially destroyed by the formation of quinolinium and isoquinolinium salts (Scheme 76).<sup>[107]</sup>



**Scheme 76**

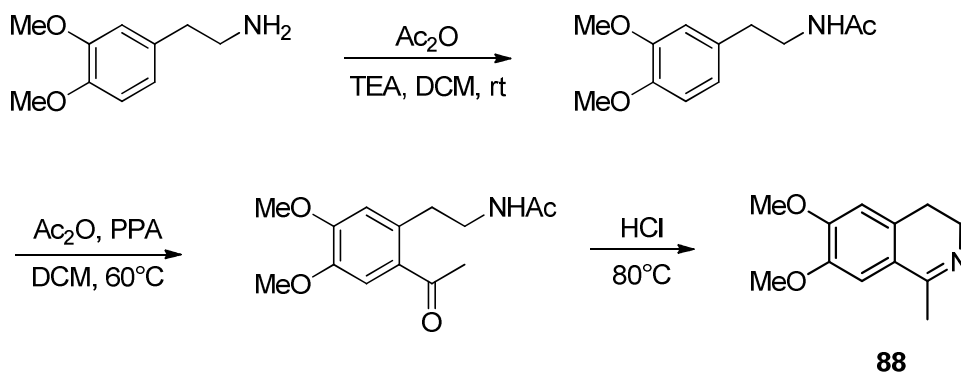
Preliminary experiments were conducted with stoichiometric amount of dimethylformamide as achiral Lewis base, in order to evaluate only the chemical efficiency, in the presence of 1.2 mol equiv of chloroformate.



**Scheme 77**

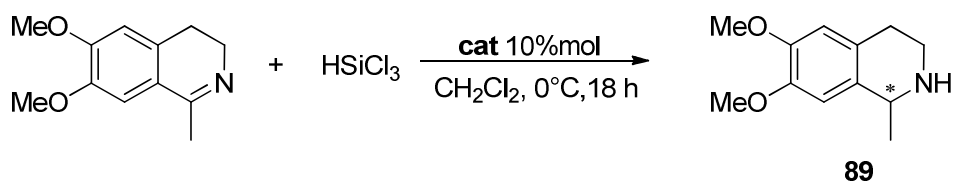
Unfortunately, the reactions carried out with ethyl chloroformate as well as benzyl chloroformate did not lead to the reduction product.

Hence, we decided to change the substrate and study the most reactive 3,4-dihydroisoquinoline. Di-hydro-*iso*-quinoline **88** was obtained starting from dopamine: the three-step synthesis involves first the *N*-functionalization of the primary amino group with acetic anhydride, followed by Friedel-Craft acylation catalyzed by polyphosphoric acid and then cyclization with concentrated HCl.



Scheme 78

Di-hydro-*iso*-quinoline **88** was subsequently tested in the reduction with 3.5 mol equiv of trichlorosilane in the presence of chiral Lewis bases. The first set of experiments were conducted with catalysts used successfully in the reduction of acyclic imines as described in the previous chapters.



Scheme 79



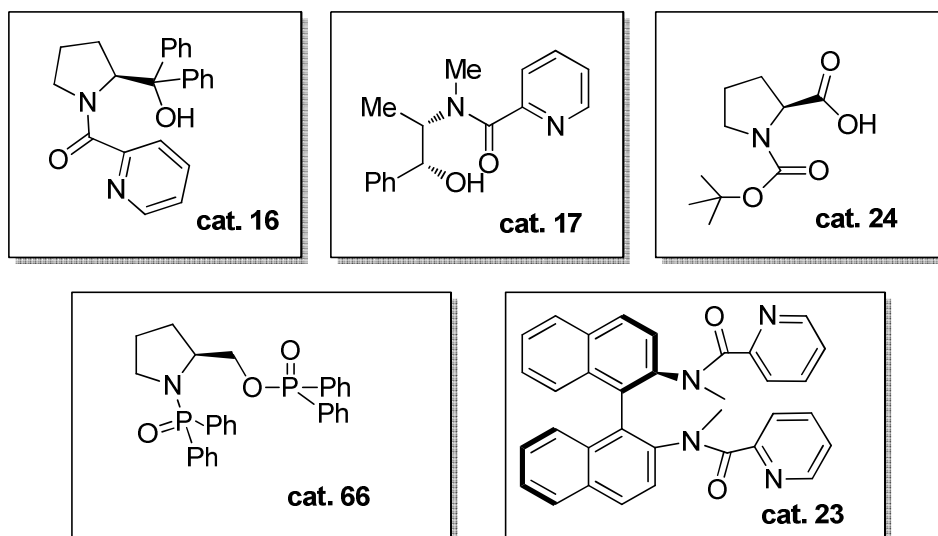


Figure 32

The experiments did not afford the desired results: in the best case we obtained the product in 17% yield and 10% ee with catalyst **16**, while employing catalysts **66** and **23** the reaction didn't take place. The use of additive, such as chloroformates, improved satisfactorily the yield (up to 82%) but the enantioselection remained low.

Considering these unsatisfactory results, we decided to examine a synthetic approach still unexplored for the stereoselective synthesis of heterocycles: the **reductive amination**.

We thought to apply this methodology for the preparation of 1,2,3,4-tetrahydroquinolines. Our idea was to prepare a single precursor, as starting material of different possible intermediates leading eventually to the same reduction product; the approach would have allowed to explore different synthetic pathways and to develop versatile strategies for the synthesis of chiral heterocycles.

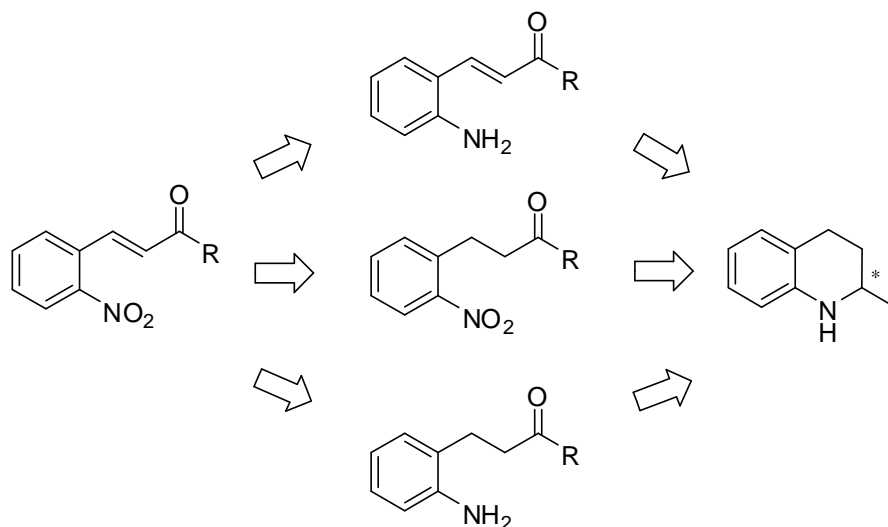
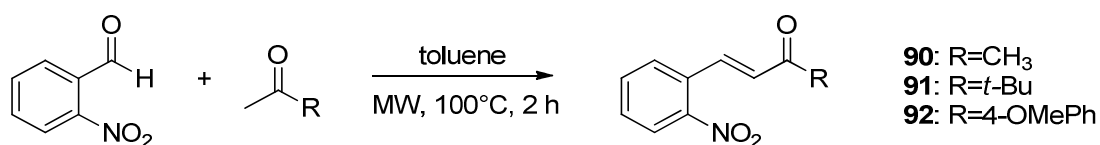


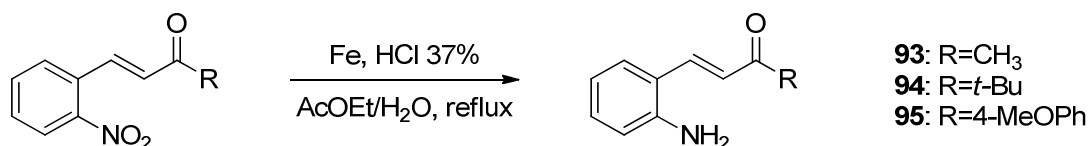
Figure 33

The precursors were prepared with a microwave-promoted reaction between 2-NO<sub>2</sub>-benzaldehyde and the ketone of choice in toluene for 2 hours (Scheme 80).



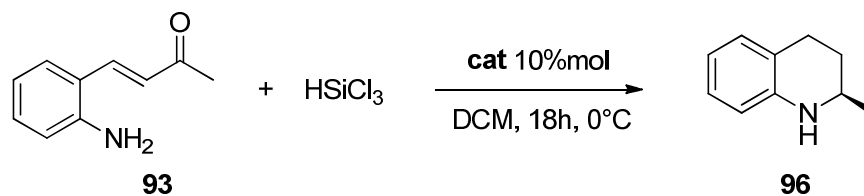
Scheme 80

Substrates **93**, **94** and **95** were subsequently obtained by simple reduction of the nitro group with Fe and catalytic amounts of 37% HCl.



Scheme 81

We then performed few experiments of reductive amination with product **93** in the presence of different chiral Lewis bases, at 0°C for 18h. (Scheme 82)



Scheme 82

The results are collected in Table 25.

Entry	cat	conv. <sup>a</sup> (%)	ee (%)
1	<b>16</b>	74	60 ( <i>S</i> )
2	<b>17</b>	58	75 ( <i>R</i> )
3	<b>23</b>	55	15 ( <i>R</i> )
4	<b>66</b>	50	8 ( <i>R</i> )
5	<b>87</b>	64	71 ( <i>R</i> )

<sup>a</sup> determined by NMR

Table 25

We achieved the first encouraging results: the desired reduced product was obtained with good conversions and good stereocontrol, as determined by NMR spectroscopy. Unfortunately, the purification of the crude mixture was problematic and allowed to isolate the product with very low yields (10-15%). Catalysts **17** and **87** gave good enantioselections, (75% and 71% enantiomeric excess, respectively) and discrete chemical efficiency (58% and 64% of conversion, respectively). Also catalyst **16** showed good ee (60 %), while catalysts **23** and **66** gave fair conversions but very poor enantioselection.

The reductive amination reactions were then carried out under various reaction conditions, namely by changing the solvent and temperature, with the most promising catalysts (**16** and **17**).

entry	cat	solvent	T (°C)	conv. <sup>a</sup> (%)	ee (%)
1	<b>17</b>	DCM	0	58	75 ( <i>R</i> )
2	<b>17</b>	CH <sub>3</sub> Cl	0	51	60 ( <i>R</i> )
3	<b>17</b>	Toluene	0	71	61 ( <i>R</i> )
4	<b>17</b>	DCM	-15	no reaction	-
5	<b>16</b>	DCM	0	74	60 ( <i>S</i> )
6	<b>16</b>	Toluene	0	86	50 ( <i>S</i> )

<sup>a</sup> determined by NMR**Table 26**

Ephedrine-based catalyst **17** showed good efficiency in all solvents, even though the best performance was obtained by running the reaction in DCM. Lowering the temperature, the formation of the product was not observed. Catalyst **16** showed also the best level of enantioselection in DCM, obtaining 60 % of ee.

We performed experiments also with substrates **94** and **95**. The reaction with compound **94** didn't take place, while the reaction with substrate **95** in the presence of different chiral catalysts gave the results illustrated in Figure 35.

**Scheme 83**

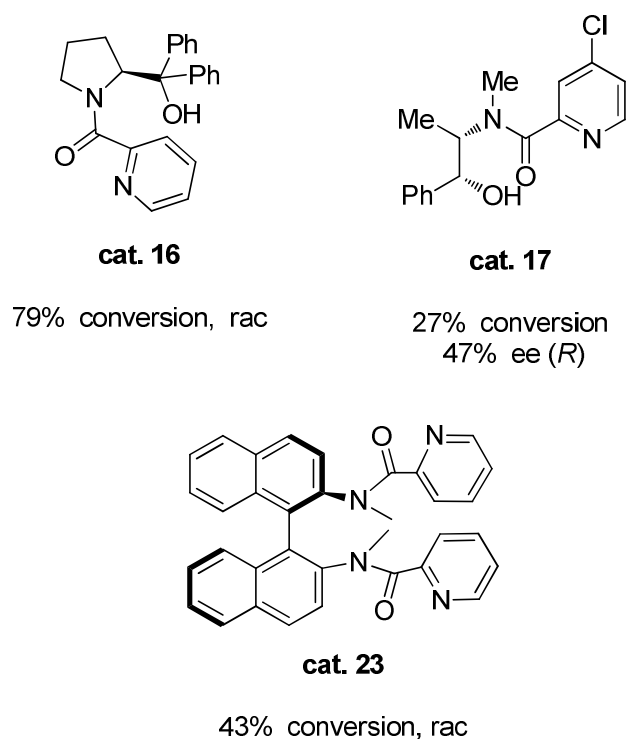
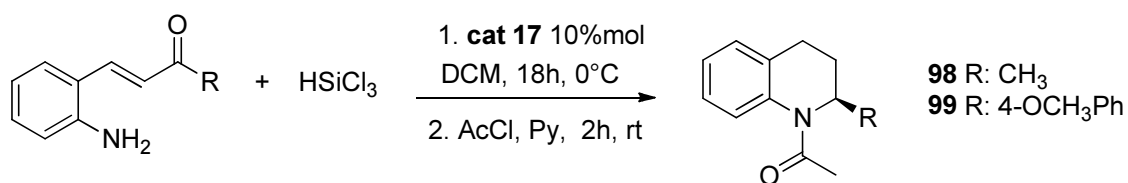


Figure 35

In this case, only the ephedrine-based catalyst **17** was able to lead to an enantiomerically enriched product (47% ee). Catalysts **16** and **23** showed better chemical efficiency, with 79% and 43% of conversion, respectively, but with no effect on the enantioselection.

In order to improve the yields and facilitate the purification step, the reductive amination was followed by *in situ* *N*-acylation of the product, by treatment with acetyl chloride and pyridine for 2 hours (Scheme 84).



Scheme 84

In this way, product **98** and **99** were isolated with 41% and 83% yield, respectively, with no influence on the stereochemical outcome of the reaction.

We also synthesized the Matzomura-derived catalysts illustrated in Figure 36, with the goal of improving the selectivity of the process.

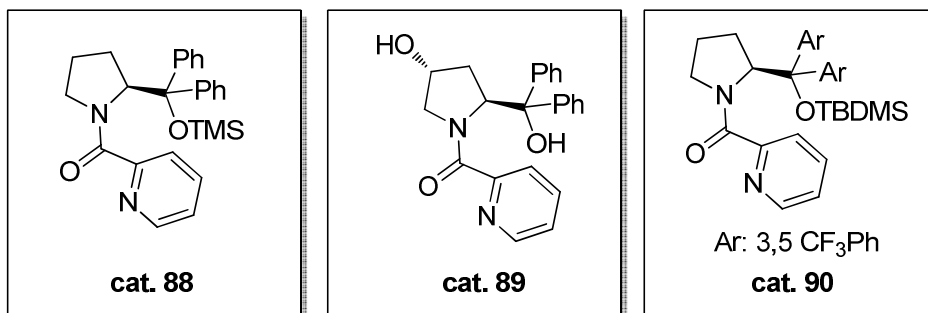
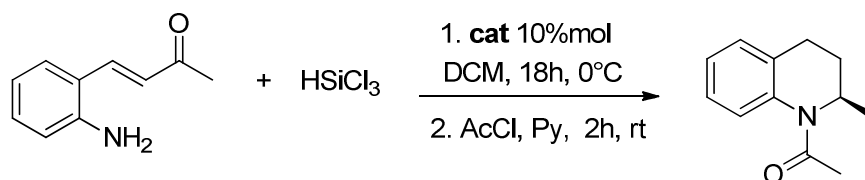


Figure 36



Scheme 85

entry	cat	y (%)	ee (%)
1	<b>88</b>	64	68 ( <i>S</i> )
2	<b>89</b>	41	75 ( <i>S</i> )
3	<b>90</b>	53	14 ( <i>R</i> )

Table 27

When tested in the reductive amination, catalysts **88** and **89** promoted the reaction with good yield and better enantiomeric excess than catalyst **16**, while catalyst **90** showed a remarkable drop in enantioselectivity.

In conclusion, these preliminary experiments allowed to obtain for the first time 1,2,3,4-tetrahydroquinolines *via* reductive amination with good levels of enantioselection, paving the way for further improvements.





## CHAPTER VIII

### *Experimental Section*

In this chapter the synthetic procedures of all products shown in the previous chapters have been reported.

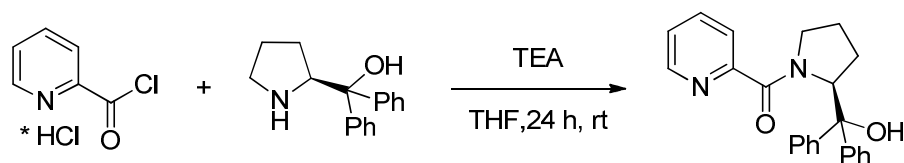
All reactions were carried out in oven-dried glassware with magnetic stirring under nitrogen atmosphere, unless otherwise stated. Dry solvents were purchased by Fluka and stored under nitrogen over molecular sieves (bottles with crown cap). Reactions were monitored by analytical thin-layer chromatography (TLC) using silica gel 60 F<sub>254</sub> pre-coated glass plates (0.25 mm thickness) and visualized using UV light or phosphomolibdic acid. Purification of the products was performed by column chromatography on silica gel (230-400 mesh ASTM, Merck), unless otherwise stated.

NMR spectra were recorded on a AMX 300 Bruker, a Bruker Avance 500, a Bruker AC 200 or AC 300 spectrometers. <sup>1</sup>H-NMR were recorded at 200, 300 or 500 MHz and chemical shifts are reported in ppm (δ), with the solvent reference relative to tetramethylsilane (TMS), employed as the internal standard (CDCl<sub>3</sub> δ = 7.26 ppm). The following abbreviations are used to describe spin multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad signal, dd = doublet of doublets. <sup>13</sup>C-NMR spectra were recorded at 75 and 125 MHz respectively, with complete proton

decoupling. Carbon chemical shifts are reported in ppm ( $\delta$ ) relative to TMS with the respective solvent resonance as the internal standard ( $\text{CDCl}_3$ ,  $\delta = 77.0$  ppm).  $^{31}\text{P}$ -NMR spectra were recorded at 121.4 or 202.4 MHz with complete proton decoupling. Phosphorus chemical shifts are reported in ppm ( $\delta$ ) and were referenced to phosphoric acid ( $\text{H}_3\text{PO}_4$ ) at 0.0 ppm.

Optical rotations were obtained on a Perkin-Elmer 241 polarimeter at 589 nm using a 5 mL cell, with a length of 1 dm. IR spectra were obtained on a Jasco FT/IR-4100 type A instrument. Mass spectra were registered on a Thermo Finnigan LCQ Advantage instrument equipped with an ESI ion source. HPLC analysis for ee determination was performed on a Agilent Instrument Series 1100 on chiral stationary phase, under the conditions reported below. Microwave-accelerated reactions were performed with a CEM Discover class S instrument.

## 8.1 Synthesis of catalysts

Preparation of catalyst 16

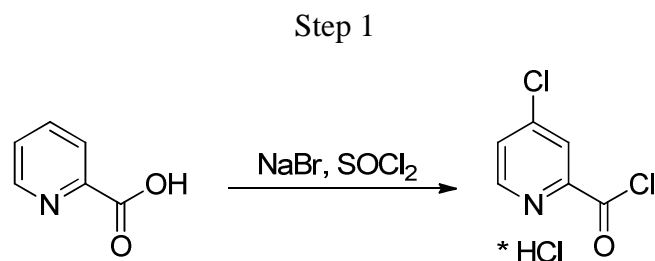
	MW	Eq	mmol	g	mL	d (g/mL)
picolinoyl chloride	141.56	1.2	4.06	575		
(S)- $\alpha,\alpha$ -diphenyl-2-pyrrolidinyl methanol	253.34	1	3.38	856		
TEA	101.19	1.2	4.06	411	0.57	0.726
THF	72.11				25	0.889

Picolinoyl chloride was formed in situ by reaction of picolinic acid and an excess of thionyl chloride (1.5 mL) at reflux for 2 hours.

To a solution of substrate and TEA in dry THF a solution of picolinoyl chloride in THF was slowly added dropwise. The mixture was stirred for 20 hours at room temperature and then concentrated in vacuum. The obtained residue was purified by silica gel flash chromatography.

Flash chromatography (diameter: 4 cm, h: 15 cm): a purification through silica gel (eluent 7:3 hexane/AcOEt) allowed to obtain the product in 70% yield as a white solid.

$^1\text{H-NMR}$  (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.52 (br, 1H), 8.26 (br, 1H), 7.74-7.69 (m, 1H), 7.51-7.26 (m, 11H), 6.67 (s, 1H), 5.45 (m, 1H), 3.60 (m, 1H), 3.20 (m, 1H), 2.19-2.02 (m, 2H), 1.62-1.55 (m, 1H), 1.27-1.15 (m, 1H).

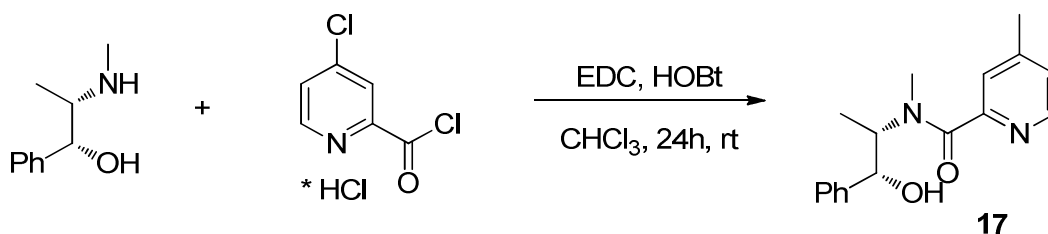
Preparation of catalyst 17

	MW	eq	mmol	g	mL	d (g/mL)
Picolinic acid	123.11	1	8.12	1		
NaBr	102.90	2	16.24	1.67		
H <sub>2</sub> O	18.02				5	

A mixture of picolinic acid, NaBr and SOCl<sub>2</sub> was refluxed for 24 hours. Thionyl chloride was removed by rotary evaporation and gentle heating. The resulting residue was dissolved with ethylene chloride (25 mL) and filtered through celite to remove the insoluble material. Product was obtained in quantitative yield as a solid.

<sup>1</sup>H NMR ( 300 MHz, *d*<sub>6</sub>-DMSO): δ 8.7 (dd, 1H), 8.00 (dd, 1H), 7.8 (dd, 1H).

## Step 2



	MW	Eq	mmol	g	mL	d (g/mL)
(1R,2S)-ephedrine	165	1	7.06	1.17		
4-Cl picolinoyl chloride	212.46	1	7.06	1.5		
TEA	101.19	1.2	8.47	0.86	0.726	1.18
EDC•HCL	155.24	3	10.6	1.56		
HOBt	120.50	3	10.6	1.28		
CH <sub>3</sub> Cl					50	

In a dry 25-mL two-neck round-bottom flask equipped with a magnetic stirring bar ephedrine was dissolved in CH<sub>3</sub>Cl and EDC•HCL and HOBT were added. After stirring 15 min, 4-Cl picolinoyl chloride hydrochloride and triethylamine were added and the solution was stirred for 24 h at room temperature. A solution of 1N HCl was added until pH became slightly acidic. Then the solution was extracted with DCM and the organic layers were combined, dried over anhydrous MgSO<sub>4</sub>, concentrated on a rotary evaporator and purified by silica gel flash chromatography.

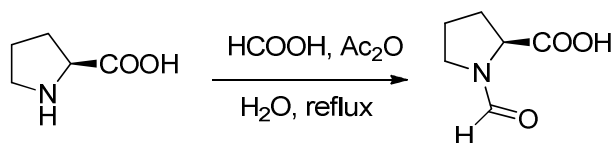
Flash chromatography (diameter: 4 cm, h: 17 cm): a purification through silica gel with 98:2 DCM/MeOH as eluent allowed to obtain the product in 71% yield.

Rotamer 1:

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 8.32 (m, 1H), 7.25 (m, 3H), 7.23 (m, 1H), .08 (d, *J* = 6.1 Hz, 2H), 6.48 (s br, 1H), 4.63 (d, *J* = 4.0 Hz, 1H), 4.08 (m, 1H), 2.86 (s, 3H), 1.31 (d, *J* = 6.7 Hz, 3H).

Rotamer 2:

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): $\delta$  8.30 (m, 1H, 4), 7.4 (m, 2H, 9, 9'), 7.3 (m, 3H, 7, 10, 10'), 7.25 (m, 1H, 5), 7.23 (m, 1H, 11), 5.0 (m, 1H, 2), 4.55 (m, 1H, 1), 2.80 (s, 3H, 3), 1.25 (d, J = 7 Hz, 3H, 8).

Preparation of catalyst 27

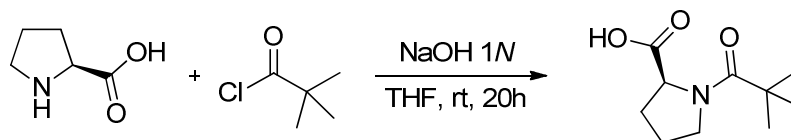
	MW	eq	mmol	g	mL	d (g/mL)
L-proline	115.13	1	17.37	2		
AcOAc	102.09	7.3	127.2	13	12	1.082
HCOOH (95%)	46.02	52.8	917.6	44.5	38	1.270
H <sub>2</sub> O	18.02			5.5	5.5	1.000

L-proline was dissolved in HCOOH (95%) and the mixture was cooled to 0°C. Acetic anhydride was added and the solution was allowed to warm to room temperature. The mixture was stirred for 2 hours at room temperature and then it was diluted with cooled (2-4°C) water (14 mL). The solvents were removed by rotary evaporation. The product was again dissolved in *i*-PrOH (10 mL) and poured in a becker containing 100 mL of Et<sub>2</sub>O. The volatiles were evaporated and the product was dried under high vacuum and obtained with 95% yield.

Two rotamers:

<sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 8.28 (s, 1H), 8.26\* (s, 1H), 4.45 (m, 1H), 3.64 (m, 2H), 3.53\* (t, 2H), 2.22 (m, 2H), 2.00 (m, 2H).

[α]<sub>D</sub><sup>25</sup> = -50.0 (solvent: CH<sub>3</sub>OH; *c* = 5.03 g/100 mL; λ = 589 nm).

Preparation of catalyst 28

	MW	eq	mmol	mg	mL	d (g/mL)
L-proline	115.13	1	2.7	302		
pivaloyl chloride	120.5	1.1	3	362	0.37	0.979
NaOH (1 N)					7.5	
THF					4.5	

*General procedure.* L-Proline was dissolved in 5 mL of 1 N NaOH, cooled to 0 °C in an ice-water bath and stirred magnetically. Trimethylacetyl chloride in THF and 2.5 mL of 1N NaOH were added contemporaneously over the course of 15 min so as to maintain the temperature at 5-10 °C, through dropping funnel. The pH was checked periodically to insure that the solution remained strongly alkaline. After the addition was complete, the reaction mixture was allowed to warm to room temperature and stirred vigorously overnight. To the basic solution was added 1N HCl until pH became slightly acidic. Then the solution was extracted with DCM and the organic layers which were combined, dried over anhydrous MgSO<sub>4</sub>, concentrated on a rotary evaporator and purified by silica gel flash chromatography.

Flash chromatography (diameter: 3.5 cm, h: 8 cm): a purification through silica gel with 8:2 hexane/AcOEt as eluent allowed to obtain the product in 29% yield as a white crystalline solid.

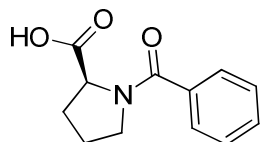
<sup>1</sup>H-NMR (300MHz, CDCl<sub>3</sub>): δ 4.42 (m, 1H), δ 3.53 (m, 1H), δ 1.98 (m, 2H), δ 1.81 (m, 2H), δ 1.22 (s, 9H).

<sup>13</sup>C-NMR (75MHz, CDCl<sub>3</sub>): δ 178.41 (1C), δ 175.62 (1C), δ 129.63 (1C), δ 61.54 (1C), δ 48.41 (1C), δ 38.91 (1C), δ 27.22 (3C), δ 26.82 (1C).

α<sub>D</sub> = - 150.24 (c = 0,286 g/100mL, CHCl<sub>3</sub>).

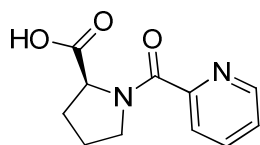
MS (ESI) m/z (%): calc. for C<sub>10</sub>H<sub>17</sub>NO<sub>3</sub> = 119.2; found = 199.0



Catalyst 29

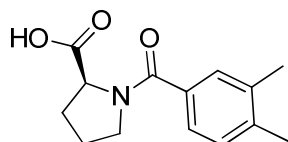
This product was purified by flash column chromatography on silica gel with a 95:5 DCM/MeOH mixture as eluent. Yield quantitative.

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>): δ 2,00 (m, 4H); δ 3,53 (m, 2H); δ 4,65 (dd, 1H); δ 7,32 (m, 5H).

Catalyst 30

This product was purified by flash column chromatography on silica gel with a 95:5 DCM/MeOH mixture as eluent. Yield 58%

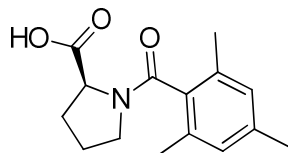
<sup>1</sup>H-NMR (200MHz, CH<sub>3</sub>OD): major: δ 1.71-2.24 (4H, m), δ 3.52-3.78 (2H, m), δ 4.69 (1H), δ 7.27-7.60 (1H, m), δ 7.61-7.87 (2H, m), δ 8.42-8.50 (1H, m); minor: δ 1.71-2.24 (4H, m), δ 3.52-3.78 (2H, m), δ 4.41 (1H, dd), δ 7.27-7.60 (1H, m), 7.61-7.87 (2H, m), 8.42-8.50 (1H, m).

Catalyst 31

This product was purified by flash column chromatography on silica gel with a 98:2 DCM/MeOH mixture as eluent. Yield 85%.

$^1\text{H-NMR}$  (200 MHz,  $\text{CDCl}_3$ ):  $\delta$  1,75 (m, 2H);  $\delta$  1,85 (m, 2H);  $\delta$  2,05 (s, 3H);  $\delta$  2,10 (s, 3H);  $\delta$  3,40 (m, 2H);  $\delta$  4,56 (m, 1H);  $\delta$  7,09 (m, 3H).

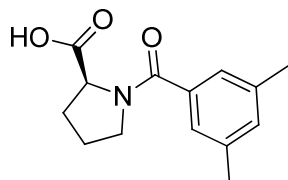
Catalyst 32



This product was purified by flash column chromatography on silica gel with a 98:2 DCM/MeOH mixture as eluent. Yield 25%.

$^1\text{H-NMR}$  (200 MHz,  $\text{CDCl}_3$ ):  $\delta$  1,95 (m, 2H);  $\delta$  2,15 (s, 3H);  $\delta$  2,25 (m, 8H);  $\delta$  3,20 (m, 2H);  $\delta$  4,70 (br, 1H);  $\delta$  6.84 (br, 2H).

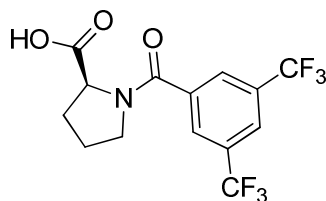
Catalyst 34



This product was purified by flash column chromatography on silica gel with a 98:2 DCM/MeOH mixture as eluent. Yield 86%.

$^1\text{H-NMR}$  (200MHz,  $\text{CDCl}_3$ ):  $\delta$  1,75 (m, 2H);  $\delta$  1,85 (m, 2H);  $\delta$  2,05 (s, 3H);  $\delta$  2,10 (s, 3H);  $\delta$  3,40 (m, 2H);  $\delta$  4,56 (m, 1H);  $\delta$  7,09 (m, 3H).

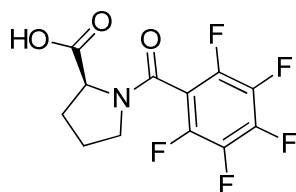
Catalyst 35



This product was purified by flash column chromatography on silica gel with a 98:2 DCM/MeOH mixture as eluent. Yield 75%.

$^1\text{H-NMR}$  (200MHz,  $\text{CDCl}_3$ ):  $\delta$  2,15 (m, 4H);  $\delta$  3,55 (m, 2H);  $\delta$  4,78 (dd, 1H);  $\delta$  7,96 (s, 1H);  $\delta$  8,04 (s, 2H).

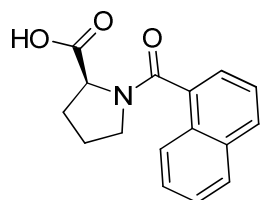
### Catalyst 36



This product was purified by flash column chromatography on silica gel with a 98:2 DCM/MeOH mixture as eluent. Yield 75%.

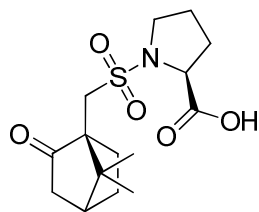
$^1\text{H-NMR}$  (200MHz,  $\text{CDCl}_3$ ):  $\delta$  2,05 (m, 2H);  $\delta$  2,24 (m, 1H);  $\delta$  2,36 (m, 1H);  $\delta$  3,47 (m, 2H);  $\delta$  4,68 (dd, 1H).

### Catalyst 37



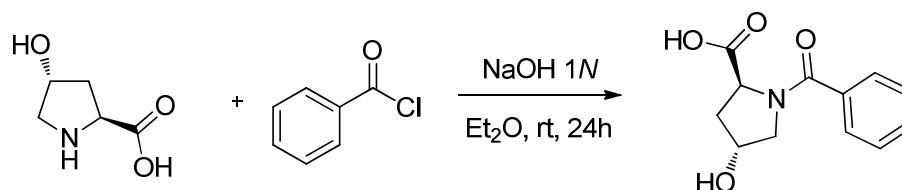
This product was purified by flash column chromatography on silica gel with a 98:2 DCM/MeOH mixture as eluent. Yield 27%.

$^1\text{H-NMR}$  (200MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  1,90 (m, 2H);  $\delta$  2,10 (m, 2H);  $\delta$  2,42 (m, 1H);  $\delta$  3,23 (m, 1H);  $\delta$  4,71 (m, 1H);  $\delta$  7,56 (m, 4H);  $\delta$  7,92 (m, 2H);  $\delta$  8,12 (m, 1H).

Catalyst 38

This product was purified by flash column chromatography on silica gel with a 98:2 DCM/MeOH mixture as eluent. Yield 22%.

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>): δ 0,84 (s, 3H); δ 1,06 (s, 3H); δ 1,24 (m, 1H); δ 1,40 (m, 1H); δ 1,64 (m, 1H); δ 1,93 (d, 1H); δ 2,05 (m, 4H); δ 2,39 (m, 3H); δ 3,08 (d, 1H); δ 3,56 (m, 3H); δ 4,52 (dd, 1H).

Preparation of catalyst 40

	MW	eq	mmol	mg	mL	d (g/mL)
<i>trans</i> -4-hydroxy-L-proline	131.13	1	2.6	302		
benzyl chloride	140.5	1.2	3.1	436.8	0.373	1.17
NaOH (1 N)					4	
Et <sub>2</sub> O					4	

*Trans*-4-hydroxy-L-proline was dissolved in 1N NaOH, cooled to 0 °C in an ice-water bath and stirred magnetically. Benzyl chloride in Et<sub>2</sub>O was slowly added over the course of 15 min through dropping funnel. The pH was checked periodically to insure that the solution remained strongly alkaline. After the addition was complete, the reaction mixture was allowed to warm to room temperature and stirred vigorously overnight. To the basic solution was added 1N HCl until pH became slightly acidic. Then the solution was extracted with DCM and the organic layers which were combined, dried over anhydrous MgSO<sub>4</sub>, concentrated on a rotary evaporator and purified by silica gel flash chromatography.

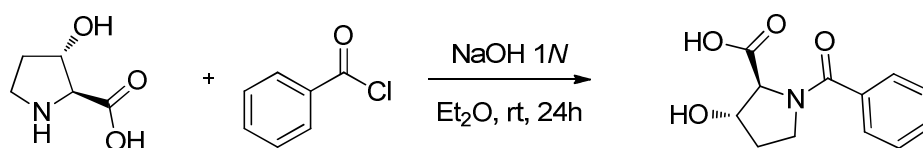
Flash chromatography (diameter: 3.5 cm, h: 8 cm): a purification through silica gel with 8:2 DCM/MeOH as eluent allowed to obtain the product in quantitative yield as a white crystalline solid.

<sup>1</sup>H-NMR (300MHz, MeOD): δ 7.50 (m, 5H), δ 4.88 (s, 2H), δ 4.72 (t, 1H), δ 4.40 (s, 1H), δ 3.82 (d, 1H), δ 3.45 (d, 1H), δ 2.43 (m, 1H), δ 2.20 (m, 1H).

<sup>13</sup>C-NMR (75MHz, MeOD): δ 175.50 (1C), δ 171.01 (1C), δ 135.80 (1C), δ 132.08-126.80 (5C), δ 69.70 (1C), δ 58.80 (1C), δ 58.02 (1C), δ 37.50 (1C).

$\alpha_D = -111.2$  (c = 0,258 g/100mL, MeOH).

MS (ESI) m/z (%): calc. for C<sub>12</sub>H<sub>13</sub>NO<sub>4</sub> = 235.24; found = 235.0

Preparation of catalyst 42

	MW	eq	mmol	mg	mL	d (g/mL)
<i>trans</i> -3-hydroxy-L-proline	131.13	1	0.76	100		
benzyl chloride	140.5	1.3	1	141	0.3120	1.17
NaOH (1 N)					2	
Et <sub>2</sub> O					2	

The synthetic procedure is identical to that described for the previous catalyst, obtaining the product with 67% yield.

<sup>1</sup>H-NMR (300MHz, MeOD): δ 8.01 (d, 2H), δ 7.43 (m, 3H), δ 4.47 (m, 1H), δ 3.82 (m, 1H), δ 3.56 (m, 1H), δ 2.17 (m, 1H), δ 1.80 (m, 1H).

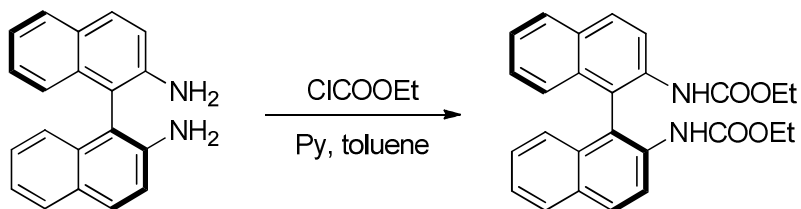
<sup>13</sup>C-NMR (75MHz, MeOD): δ 175.43 (1C), δ 170.55 (1C), δ 131.83 (1C), δ 139.42-126.63 (5C), δ 74.98 (1C), δ 73.53 (1C), δ 44.45 (1C), δ 32.71 (1C).

$\alpha_D = -12.1$  (c = 0,274 g/100mL, MeOH).

MS (ESI) m/z (%): calc. for C<sub>12</sub>H<sub>13</sub>NO<sub>4</sub> = 235.24; found = 235.1

Preparation of catalyst 53

## Step 1

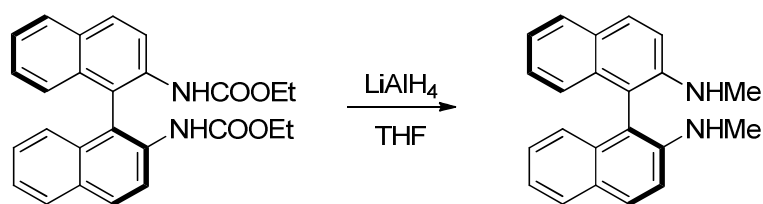


	MW	eq	mmol	g	mL	d (g/mL)
(R)-1,1'-binaphthyl-2,2'-diamine	284.12	1	1.76	0.50		
ethyl chloroformate	108.52	2.6	4.61	0.50	0.44	1.135
pyridine	79.10	8.7	15.31	1.21	1.2	0.981
toluene					6	

(R)-1,1'-binaphthyl-2,2'-diamine was dissolved in toluene and pyridine and cooled to 0 °C. A solution of ethyl chloroformate in toluene (1 mL) was then added dropwise in 15 min. The mixture was subsequently warmed to room temperature and stirred for 2 h. The reaction, followed by TLC using 8:2 hexane/ethyl acetate as eluent, was then quenched by the addition of 2 N KOH (10 mL); the organic layer was separated, and the aqueous layer was extracted with AcOEt (3 × 20 mL). The organic layers were dried with Na<sub>2</sub>SO<sub>4</sub> and the solvent was removed by rotary evaporation. After drying, a pale pink powder was obtained, with sufficient purity for being employed in the subsequent reaction (yield quantitative).

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 8.57 (d, *J* = 9.1 Hz, 2H), 8.08 (d, *J* = 9.1 Hz, 2H), 7.94 (d, *J* = 8.1 Hz, 2H), 7.46-7.41 (m, 2H), 7.30-7.24 (m, 2H), 6.98 (d, *J* = 8.5 Hz, 2H), 6.28 (br., 2H), 4.1 (q, *J* = 7.1 Hz, 4H), 1.18 (t, *J* = 7.1 Hz, 6H).

## Step 2



	MW	eq	mmol	mg	mL	d (g/mL)
substrate	428.48	1	1.75	750		
LiAlH <sub>4</sub>	37.95	6.3	11.03	418		
THF					10	

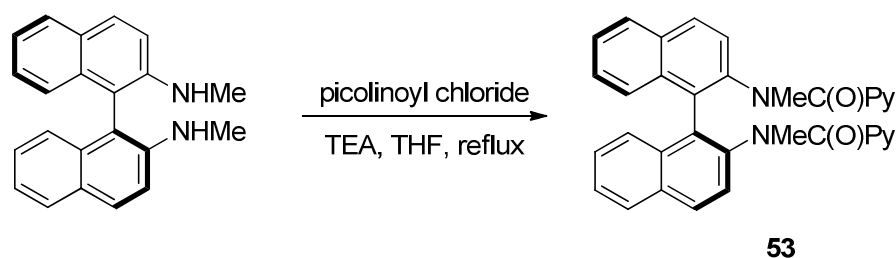
LiAlH<sub>4</sub> was suspended in dry THF and cooled to 0°C. The substrate was dissolved in dry THF (3 mL) was then slowly added via dropping funnel, and the mixture was warmed and then refluxed for 24 h. The reaction was followed by TLC using 8:2 hexane/ethyl acetate as eluent. After cooling to room temperature, excess LiAlH<sub>4</sub> was quenched with MeOH (1 mL), NaOH 15% (0.5 mL) and finally water (0.5 mL). The resultant gray precipitate was filtered off through celite and washed with diethyl ether.

Flash chromatography (diameter: 2.5 cm, h: 18 cm): a purification through silica gel (eluent: 400 mL of 8:2 hexane/AcOEt) allowed to obtain the derivative 246b in 72% yield.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.93 (d, J = 8.9 Hz, 2H), 7.84-7.79 (m, 2H), 7.27 (d, J = 8.9 Hz, 2H), 7.23-7.14 (m, 4H), 7.00-6.96 (m, 2H), 2.84 (s, 6H).



## Step 3



	MW	eq	mmol	g	mL	d (g/mL)
substrate	312.16	1	0.56	0.17		
picolinoyl chloride	141.57	4	2.24	0.32		
TEA	101.19	16	8.96	0.91	1.25	0.726
THF					10	

Picolinoyl chloride was formed in situ by reaction of picolinic acid and an excess of thionyl chloride (1.5 mL) at reflux for 2 hours.

To a solution of substrate and TEA in dry THF a solution of picolinoyl chloride in THF was slowly added dropwise. The mixture was stirred for 20 hours at reflux and then concentrated in vacuum. The obtained residue was purified by silica gel flash chromatography.

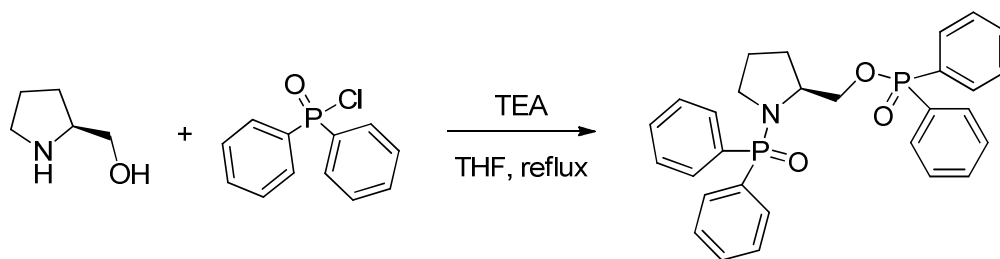
Flash chromatography (diameter: 2 cm, h: 15 cm): a purification through silica gel (eluent: 400 mL of 98:2 CH<sub>2</sub>Cl<sub>2</sub>/MeOH) allowed to obtain the product in 73% yield.

Rotamer 1:

<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>): δ 8.57 (d, J = 2.7 Hz, 2H), 8.05 (d, J = 8.8 Hz, 2H), 7.95 (d, J = 8 Hz, 2H), 7.87 (d, J = 9, 2 Hz), 7.72 (d, J = 7.8 Hz, 2H), 7.7 (t, 2H), 7.48 (t, J = 8.1 Hz, 2H), 7.29 (t, J = 6.8 Hz, 2H), 7.25 (t, 2H), 7.2 (d, 2H), 2.98 (s, 6H).

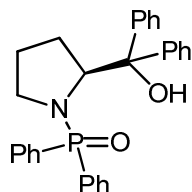
Rotamer 2:

<sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 8.28 (d, J = 4.4 Hz, 2H), 7.83 (d, J = 8.8 Hz, 2H), 7.72 (d, J = 7.8 Hz, 2H), 7.60 (d, J = 8.7 Hz, 2H), 7.59 (t, 2H), 7.45 (t, J = 7.5 Hz, 2H), 7.29 (t, J = 6.8 Hz, 2H), 7.1 (t, 4H), 6.93 (d, J = 8.8 Hz, 2H), 2.64 (s, 6H).

Preparation of catalysts 62-68

	MW	eq	mmol	mg	mL	d (g/mL)
(S)-prolinol	101.15	1	2.5	253	0.25	1.025
diphenylphosphinyl chloride	236.64	3	7.5	1775	1.43	1.24
TEA	101.19	3	7.5	759	1.03	0.726
THF					5	

*General procedure:* to a solution of substrate in solvent was added diphenylphosphinic chloride and TEA at 0°C. After the additions, the mixture was heated to reflux overnight. The reaction was cooled to room temperature and NaHCO<sub>3</sub> ss was added. The DCM layer was separated and the water layer was washed with DCM (3×10 mL). The combined organic solution was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and the solvent was evaporated. The crude product was purified on silica flash.

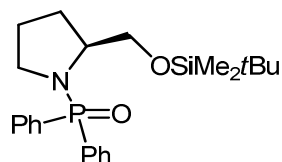
Catalyst 62

The product was purified with a 95:5 DCM/CH<sub>3</sub>OH mixture as eluent. Yield: 27%

<sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 1.1 (m, 1H); δ 1.4 (m, 1H); δ 2.05 (m, 2H); δ 2.4 (m, 1H); δ 2.9 (m, 1H); δ 4.8 (m, 1H); δ 7.2-7.3 (m, 12H); δ 7.3-7.4 (m, 8H); δ 7.5-7.7 (m, 16H); δ 7.8 (m, 4H).

$^{31}\text{P-NMR}$  (121 MHz,  $\text{CDCl}_3$ ):  $\delta$  34.2.

**Catalyst 63**

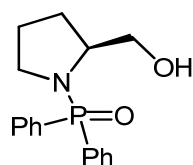


The product was purified with a 95:5 DCM/ $\text{CH}_3\text{OH}$  mixture as eluent. Yield: 63%

$^1\text{H-NMR}$  (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.8–2.0 (m, 4H);  $\square$  3.1–3.2 (m, 2H);  $\delta$  3.35 (m, 2H);  $\delta$  3.7 (m, 1H);  $\delta$  7.4–7.5 (m, 6H);  $\delta$  7.8–7.9 (m, 4H).

$^{31}\text{P-NMR}$  (121 MHz,  $\text{CDCl}_3$ ):  $\delta$  26.9.

**Catalyst 64**

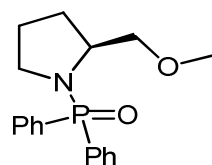


The product was purified with a 95:5 DCM/ $\text{CH}_3\text{OH}$  mixture as eluent. Yield: 53%

$^1\text{H-NMR}$  (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.60–1.80 (m, 3H);  $\delta$  2.05 (m, 1H);  $\delta$  3.10 (m, 2H);  $\delta$  3.45 (m, 2H);  $\delta$  3.7 (m, 1H);  $\delta$  5.0 (m, 1H);  $\delta$  7.3–7.5 (m, 6H);  $\delta$  7.7–7.9 (m, 4H).

$^{31}\text{P-NMR}$  (121MHz,  $\text{CDCl}_3$ ):  $\delta$  28.1.

**Catalyst 65**

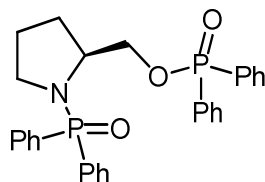


The product was purified with a 95:5 DCM/ $\text{CH}_3\text{OH}$  mixture as eluent. Yield: 61%

<sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 1.8–2.0 (m, 4H); δ 3.1 (s, 3H); δ 3.10–3.2 (m, 4H); δ 3.7 (m, 1H); δ 7.4–7.5 (m, 6H); δ 7.8–7.9 (m, 4H).

<sup>31</sup>P-NMR (121 MHz, CDCl<sub>3</sub>): δ 26.9.

### Catalyst 66



The product was purified with a 98:2 DCM/CH<sub>3</sub>OH mixture as eluent. Yield: 60%.

<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>): δ 1.85 (m, 2H); δ 2.05 (m, 2H); δ 3.10 (m, 2H); δ 3.8 (m, 2H); δ 4.0 (m, 1H); δ 7.3–7.5 (m, 10H); δ 7.7–7.9 (m, 10H).

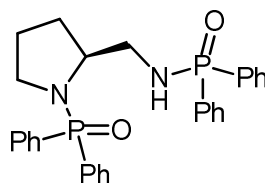
<sup>13</sup>C-NMR (125 MHz, CDCl<sub>3</sub>): δ 25 (1C); δ 29 (1C); δ 48 (1C); δ 58 (1C); δ 66 (1C); δ 127.8 (1C); δ 127.9 (4C); δ 129 (4C); δ 131 (1C); δ 131.4 (3C); δ 131.5 (3C); δ 131.7 (4C); δ 132 (4C).

<sup>31</sup>P-NMR (202 MHz, CDCl<sub>3</sub>): δ 27.3; δ 31.9.

HMRS Mass (ESI +): m/z = calc for C<sub>29</sub>H<sub>29</sub>NO<sub>3</sub>P<sub>2</sub>Na<sup>+</sup> 524.15149, found 524.15190.

[α]<sub>D</sub><sup>25</sup> = + 6.28 (c = 0.382 g/100 mL, CHCl<sub>3</sub>, T = 16°C, λ = 589 nm).

### Catalyst 67



The product was purified with a 98:2 DCM/CH<sub>3</sub>OH mixture as eluent. Yield: 65%.

<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>): δ 1.77 (m, 2H); δ 2.05–1.85 (m, 2H); δ 3.0–2.88 (m, 2H); δ 3.12 (m, 2H); δ 3.4 (m, 1H); δ 7.3–7.4 (m, 10H); δ 7.7–7.8 (m, 10H).

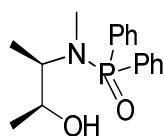
$^{13}\text{C}$ -NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  25.1 (1C);  $\delta$  30.5 (1C);  $\delta$  44.5 (1C);  $\delta$  48 (1C);  $\delta$  60.4 (1C);  $\delta$  128.2 (3C);  $\delta$  128.4 (3C);  $\delta$  128.6 (3C);  $\delta$  131.4 (3C);  $\delta$  131.7 (3C);  $\delta$  131.8 (3C);  $\delta$  132.0 (2C);  $\delta$  132.1 (2C);  $\delta$  132.5 (2C).

$^{31}\text{P}$ -NMR (202 MHz,  $\text{CDCl}_3$ ):  $\delta$  24.4;  $\delta$  26.6.

HMRS Mass (ESI +):  $m/z = \text{calc for } \text{C}_{29}\text{H}_{30}\text{N}_2\text{O}_2\text{P}_2\text{Na}^+ 523.16747$ , found 523.16733.

$[\alpha]_D^{25} = +8.82$  ( $c = 0.306$  g/100 mL,  $\text{CHCl}_3$ ,  $T = 16^\circ\text{C}$ ,  $\lambda = 589$  nm).

### Catalyst 68



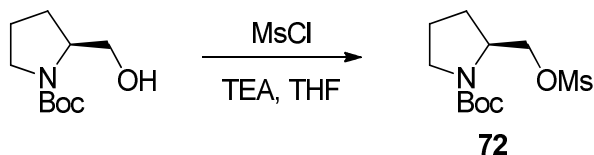
The product was purified with a 95:5 DCM/ $\text{CH}_3\text{OH}$  mixture as eluent. Yield: 21%

$^1\text{H}$ -NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.3 (d, 3H);  $\delta$  2.45 (d, 3H);  $\delta$  3.7 (m, 1H);  $\delta$  4.8 (d 1H);  $\delta$  7.2-7.3 (m, 5H);  $\delta$  7.35-7.5 (m, 5H);  $\delta$  7.6-7.8 (m, 5H).

$^{31}\text{P}$ -NMR (121 MHz,  $\text{CDCl}_3$ ):  $\delta$  34.3.

Preparation of catalysts 73

Step 1



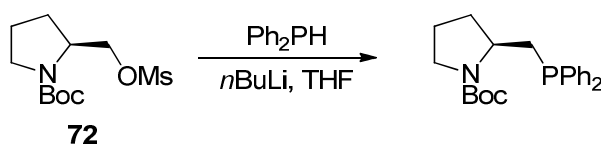
	MW	eq	mmol	g	mL	d (g/mL)
N-Boc-L-prolinol	201.27	1	5	1		
mesyl chloride	114.55	1.1	5.5	0.6	0.423	1.48
TEA	101.19	1.1	5.5	0.55	0.726	0.726
THF					15	

To a solution of *N*-Boc-L-prolinol in THF, triethylamine was added, the mixture was cooled to  $-15^{\circ}\text{C}$  and then mesyl chloride was slowly added. The mixture was allowed to warm up to room temperature and stirred for 4 hours. After this time, 1*N* HCl was added until pH was slightly acidic. The aqueous layer was extracted with DCM, separated and the combined organic layers were dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under vacuum. The crude product was purified on silica flash.

Flash chromatography (diameter: 2.5 cm, h: 17 cm): a purification through silica gel with 8:2 hexane/AcOEt as eluent allowed to obtain the product in quantitative yield.

$^1\text{H-NMR}$  (200MHz,  $\text{CDCl}_3$ ):  $\delta$  4.20 (d, 2H),  $\delta$  3.96 (m, 1H),  $\delta$  3.33 (m, 2H),  $\delta$  2.96 (s, 3H),  $\delta$  1.95 (m, 2H),  $\delta$  1.82 (m, 2H),  $\delta$  1.39 (s, 9H).

## Step 2



	MW	eq	mmol	g	mL	d (g/mL)
Substrate <b>72</b>	279.4	1	3.6	1		
diphenylphosphine	186.19	2.5	8.9	1.6	0.423	1.48
<i>n</i> -BuLi (1.4M)	64.09	2.5	8.9		8.6	
THF					24	

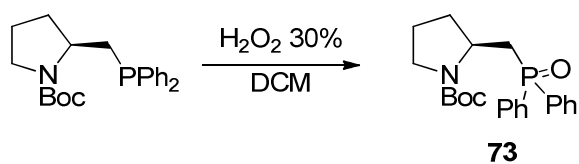
A solution of diphenylphosphine in 14 mL of THF was cooled to 0°C and 1.4M *n*-BuLi was added dropwise. Immediately the solution became red and the substrate, dissolved in 10 mL of THF, was added. The solution was allowed to warm up to room temperature and stirred until it became yellow and cloudy (about 1 hour). The precipitate was then filtered and the cake washed twice with THF. The crude product was purified on silica flash.

Flash chromatography (diameter: 2.5 cm, h: 16 cm): a purification through silica gel with 95:5 hexane/AcOEt as eluent allowed to obtain the product in 43% yield

<sup>1</sup>H-NMR (300MHz, CDCl<sub>3</sub>): δ 7.76-7.43 (m, 10 H), δ 3.68 (d, 2H), δ 3.28 (m, 1H), δ 3.0 (m, 2H), δ 1.95 (m, 2H), δ 1.82 (m, 2H), δ 1.41 (s, 9H).

<sup>31</sup>P-NMR (121MHz, CDCl<sub>3</sub>): δ -21.5.

## Step 3



	MW	Eq	mmol	mg	mL	d (g/mL)
Substrate	369.19	1	0.22	80		
H <sub>2</sub> O <sub>2</sub> 30%	34.01				2	
DCM					2	

To a solution of substrate in DCM the hydrogen peroxide solution was added. After 40 minutes the layers were separated and the aqueous one was extracted three times with 5 mL of DCM. The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under vacuum to afford the product as crystalline solid in quantitative yield.

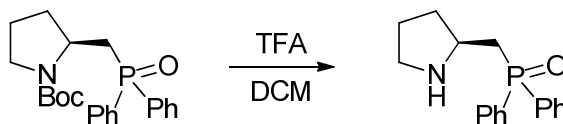
<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>): δ 7.76-7.43 (m, 10 H), δ 3.81 (d, 2H), δ 3.28 (m, 1H), δ 3.0 (m, 2H), δ 1.95 (m, 2H), δ 1.82 (m, 2H), δ 1.41 (s, 9H).

<sup>31</sup>P-NMR (121MHz, CDCl<sub>3</sub>): δ 31.4.



Preparation of catalysts 74

## Step 1

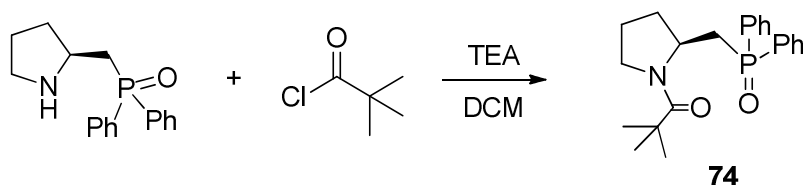


	MW	eq	mmol	Mg	mL	d (g/mL)
<b>cat. 73</b>	385.44	1	0.78	300		
TFA	114.02	10	7.8	1776	1.2	1.489
DCM					2	

To a solution of substrate in DCM TFA was added and the mixture was stirred overnight at room temperature. Then the solvent was evaporated and the crude product was redissolved in DCM. A solution of 1*N* NaOH was added until the pH was basic. The organic layer was separated and the aqueous one extracted with DCM. The combined organic layers were dried with Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated under vacuum to afford the product in quantitative yield.

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>): δ 7.61-7.25 (m, 10 H), δ 3.48 (d, 2H), δ 3.29 (m, 1H), δ 3.06 (m, 2H), δ 1.90 (m, 2H), δ 1.71 (m, 2H).

## Step 2



	MW	eq	mmol	mg	mL	d (g/mL)
substrate	285.32	1	0.35	100		
pivaloyl chloride	120.58	1.1	0.39	46.5	0.05	0.979
TEA	101.19	1.1	0.39	39.5	0.05	0.726
DCM					4	

The substrate was dissolved in 3 mL of DCM and triethylamine was slowly added. Then the mixture was cooled to 0°C and a solution of pivaloyl chloride in 1 mL of DCM was added. The solution was allowed to warm up to room temperature and stirred until TLC showed complete consumption of starting material. Then, 1N HCl was added until pH was slightly acidic. The organic layer was separated and the aqueous one extracted with DCM. The combined organic layers were dried with Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The crude product was purified on silica flash.

Flash chromatography (diameter: 2.5 cm, h: 16 cm): a purification through silica gel with 9:1 DCM/MeOH as eluent allowed to obtain the product in 40% yield.

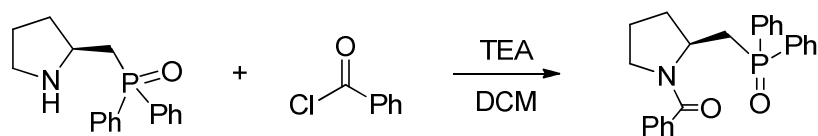
<sup>1</sup>H-NMR(200MHz, CDCl<sub>3</sub>): δ 8.16-7.56 (m, 10 H), δ 3.98 (d, 2H), δ 3.52 (m, 1H), δ 3.33 (m, 2H), δ 1.91 (m, 2H), δ 1.81 (m, 2H), δ 1.22 (s, 9H).

<sup>13</sup>C-NMR(75MHz, CDCl<sub>3</sub>): δ 176.7 (1C), δ 131-128 (12C), δ 77.0 (1C), δ 55.4 (1C), δ 47.9 (1C), δ 33.1 (1C), δ 32.2 (1C), δ 29.7 (1C), δ 29.2 (1C), δ 27.5 (1C), δ 25.4 (1C).

<sup>31</sup>P-NMR(121MHz, CDCl<sub>3</sub>): δ 31.2.

α<sub>D</sub> = + 4,43 (c = 0,158 g/100mL, CHCl<sub>3</sub>).

MS (ESI) m/z (%): calc. for C<sub>22</sub>H<sub>28</sub>NO<sub>2</sub>P = 369.2; found = 370.2

Preparation of catalysts 75

	MW	eq	mmol	mg	mL	d (g/mL)
substrate	285.32	1	0.51	145		
benzoyl chloride	140.57	1.1	0.56	78.4	0.07	1.21
TEA	101.19	1.1	0.56	56.7	0.08	0.726
DCM					4	

The substrate was dissolved in 3 mL of DCM and triethylamine was slowly added. Then the mixture was cooled to 0°C and a solution of pivaloyl chloride in 1 mL of DCM was added. The solution was allowed to warm up to room temperature and stirred until TLC showed complete consumption of starting material. Then, 1N HCl was added until pH was slightly acidic. The organic layer was separated and the aqueous one extracted with DCM. The combined organic layers were dried with Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The crude product was purified on silica flash.

Flash chromatography (diameter: 2.5 cm, h: 16 cm): a purification through silica gel with 9:1 DCM/MeOH as eluent allowed to obtain the product in 35% yield.

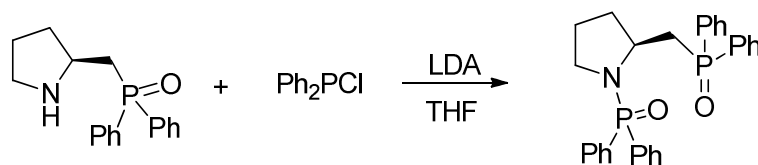
<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>): δ 8.11-7.45 (m, 15H), δ 4.51 (m, 1H), δ 3.69 (m, 2H), δ 3.58 (m, 2H), δ 2.39 (m, 2H), δ 1.84 (m, 2H).

<sup>13</sup>C-NMR (75MHz, CDCl<sub>3</sub>): δ 170.3 (1C), δ 132-126 (18C), δ 77.6 (1C), δ 54.8 (1C), δ 49.9 (1C), δ 32.6 (1C), δ 25.0 (1C).

<sup>31</sup>P-NMR (121MHz, CDCl<sub>3</sub>): δ 31.3.

$\alpha_D = -85,4$  (c = 0,212 g/100mL, CHCl<sub>3</sub>).

MS (ESI) m/z (%): calc. for C<sub>24</sub>H<sub>24</sub>NO<sub>2</sub>P = 389.2; found = 390.2

Preparation of catalysts 76

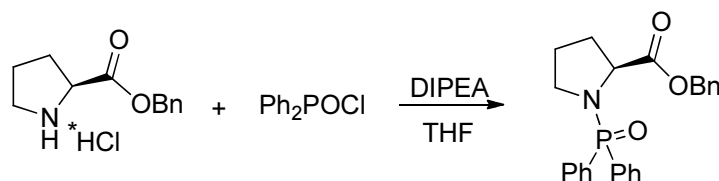
	MW	eq	mmol	mg	mL	d (g/mL)
substrate	285.32	1	0.35	100		
chlorodiphenylphosphine	220.63	1	0.35	77.4	0.06	1.194
DIPA	101.19	1.1	0.39	38.9	0.05	0.722
<i>n</i> -BuLi (1.4M in hexane)	64.09	1.1	0.39		0.03	
THF					7	

A solution of *n*-BuLi was slowly added to a solution of diisopropylamine in dry THF (5 mL) at 0°C under nitrogen atmosphere and, 15 min later, a solution of substrate in 2 mL of THF. Finally chlorodiphenylphosphine was added. The mixture was allowed to warm up to room temperature and stirred overnight. A Solution of 1N HCl was added until pH was slightly acidic and the organic layer was separated. The aqueous layer was extracted with DCM and the combined organic layers were dried with Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated to dryness and the residue was purified on silica flash.

Flash chromatography (diameter: 2.5 cm, h: 16 cm): a purification through silica gel with 98:8 DCM/MeOH as eluent allowed to obtain the product in 84% yield.

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>): δ 7.85-7.25 (m, 20H), δ 3.91 (m, 1H), δ 3.07 (m, 2H), δ 2.41 (m, 2H), δ 1.99 (m, 2H), δ 1.93 (m, 2H).

<sup>31</sup>P-NMR (121MHz, CDCl<sub>3</sub>): δ 29.4.

Preparation of catalysts 77

	MW	eq	mmol	g	mL	d (g/mL)
L-proline benzyester*HCl	241.72	1	5	1.2		
Ph <sub>2</sub> POCl	236.63	1.1	5.5	1.3	1.1	1.24
DIPEA	129.25	2	10	1.3	1.7	0.742
THF					25	

To a solution of L-Proline benzyl ester hydrochloride in dry THF was added 1 eq of DIPEA and it was stirred for 30 min; then DIPEA (1 eq) and diphenylphosphinic chloride were added and the mixture was stirred for 72h. After this time, NaHCO<sub>3</sub>s.s. (10 mL) was added and the mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3×15 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and the solvent was evaporated. The crude product was purified on silica flash.

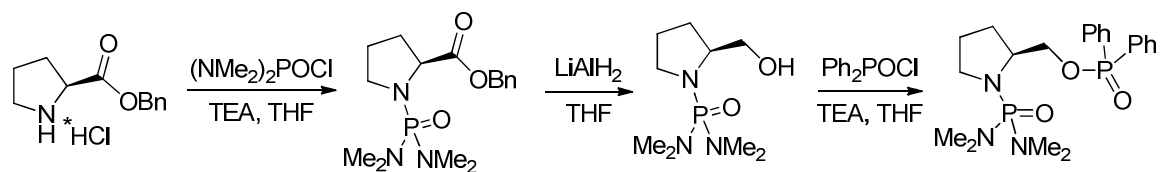
Flash chromatography (diameter: 2.5 cm, h: 16 cm): a purification through silica gel with 98:2 DCM/MeOH as eluent allowed to obtain the product in quantitative yield.

<sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 8.20-7.92 (m, 2 H), 7.81-7.70 (m, 5 H), 7.52-7.15 (m, 8 H), 5.02 (m, 2H), 4.23 (m, 1H), 3.40 (m, 1H), 3.31 (m, 1H), 2.21 (m, 1H), 1.94 (m, 3H).

<sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>): δ 135.3-124.8, 77.2, 65.9, 60.3, 47.3, 32.7, 25.0.

<sup>31</sup>P-NMR (202 MHz, CDCl<sub>3</sub>): δ 28.7.

[α]<sub>D</sub><sup>25</sup> = -5.7 (solvent: CHCl<sub>3</sub>, c = 0.211 g/100mL, T = 25 °C, λ = 589 nm).

Preparation of catalysts 78

To a solution of L-Proline benzyl ester hydrochloride (1 eq, 2.1 mmol) in dry THF (10 mL) were added dry TEA (2.1 eq, 4.4 mmol) and  $(\text{NMe}_2)_2\text{POCl}$  (1.2 eq, 2.5 mmol) at 0 °C. After the additions, the reaction mixture was allowed to warm up to room temperature for 1 h, then it was heated to reflux overnight. The reaction was cooled to room temperature and HCl 5% (7 mL) was added, then it was diluted with water and extracted with AcOEt (3x15 mL). The combined organic solution was dried over  $\text{Na}_2\text{SO}_4$ , filtered and the solvent was evaporated. The product was purified by column chromatography with a 98:2  $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$  mixture as eluent.

A solution of purified product (1 eq, 1.5 mmol) in dry THF (8 mL) was added dropwise at 0 °C to a suspension of  $\text{LiAlH}_4$  (3 eq, 4.5 mmol) in dry THF (8 mL), previously stirred at 0 °C for 10 min. After the addition, the mixture was stirred at this temperature for 5h, then it was quenched by addition of  $\text{H}_2\text{O}$  (1 mL), NaOH 2.7% (1 mL),  $\text{H}_2\text{O}$  (1 mL) and NaOH 2.7% (1 mL), while maintaining temperature at 0 °C. The reaction mixture was then filtered through a celite layer, diluted with water and extracted with  $\text{CH}_2\text{Cl}_2$  (3x40 mL). The combined organic solution was dried over  $\text{Na}_2\text{SO}_4$ , filtered and the solvent was evaporated.

To a solution of isolated product (1 eq, 0.16 mmol) in dry THF (1 mL) was added diphenylphosphinic chloride (1.2 eq, 0.19 mmol) and dry TEA (1.2 eq, 0.19 mmol) at 0 °C. After the additions, the reaction mixture was allowed to warm up to room temperature for 1 h, then it was heated to reflux overnight. The reaction was cooled to room temperature and HCl 5% (3 mL) was added, then it was diluted with water and extracted with  $\text{CH}_2\text{Cl}_2$  (3x15 mL). The combined organic solution was dried over  $\text{Na}_2\text{SO}_4$ , filtered and the solvent was evaporated. The product was purified by column chromatography with a 95:5  $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$  mixture as eluent (28 % yield, yellow waxy solid).

<sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 7.82-7.76 (m, 5 H); 7.47-7.42 (m, 5 H); 4.05-3.85 (m, 3H); 3.18-3.07 (m, 2 H); 2.62 (s, 3 H); 2.58 (s, 6 H); 2.53 (s, 3 H); 2.05-1.80 (m, 4 H).

<sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>): δ 132.0; 131.7; 131.5; 131.4; 129.9; 128.6; 128.4; 127.6; 127.5; 66.9; 58.3; 46.9; 36.7; 28.7; 24.8.

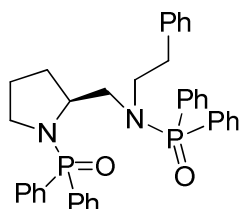
<sup>31</sup>P-NMR (202 MHz, CDCl<sub>3</sub>): δ 32.9; 22.4.

$[\alpha]_D^{25} = + 80.1$  (solvent: CH<sub>2</sub>Cl<sub>2</sub>,  $c = 0.398$  g/100mL, T = 25 °C,  $\lambda = 589$  nm)

HMRS Mass (ESI+):  $m/z = \text{calc for } C_{21}H_{31}N_3O_3P_2Na^+ 458.16, \text{ found } 458.30.$

Preparation of catalysts 79-80

*General procedure.* To a stirred solution of *N*-(*tert*-butoxycarbonyl)-L-proline (1 eq, 7.4 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> HOBt (1.5 eq, 11.1 mmol) and DCC (1 eq, 7.4 mmol) were added and the mixture was stirred for 30 min. Then, 2-phenylethanamine (3 eq, 22.2 mmol) was added and the mixture was stirred overnight at room temperature. The reaction mixture was washed with NaHCO<sub>3</sub> s.s. (10 mL) and HCl 5% (2x10 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuum at room temperature to afford the crude product, that was purified by column chromatography with a 7:3 ETP/AcOEt mixture as eluent. TFA (43 eq, 325 mmol) was added to a solution of product in CH<sub>2</sub>Cl<sub>2</sub> (25 mL) and the mixture was stirred for 2 h. Then the solvent was evaporated, crude product was dissolved in CH<sub>2</sub>Cl<sub>2</sub> and washed with water (3x10 mL). An aqueous solution of NaOH 1*N* was added to the water layer until a slightly basic pH was achieved and product was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2x50 mL). The combined organic solution was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and the solvent was evaporated. A solution of the isolated product (1 eq, 2.76 mmol) in dry THF was added to a stirred suspension of LiAlH<sub>4</sub> (3 eq, 8.28 mmol) in dry THF maintaining temperature at 0 °C. After the addition, the mixture was heated to reflux for 5 h. Then the reaction is quenched by addition of HCl/H<sub>2</sub>O/NaOH at 0 °C and filtered through a celite layer. Finally an aqueous solution of NaOH was added and product was extracted with AcOEt (3x20 mL). The combined organic solution was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and the solvent was evaporated. The crude product was purified by column chromatography with a 8:2 ETP/AcOEt mixture as eluent.

Catalysts 79

It was obtained by preparing the intermediate following general procedure, which was dissolved (1 eq, 0.98 mmol) in dry THF (7 mL) and treated with diphenylphosphinic



chloride (2.2 eq, 2.16 mmol) and dry TEA (2.4eq, 2.35 mmol) at 0°C. After the additions, the reaction mixture was allowed to warm up to room temperature for 45 min, then it was heated to reflux for 4 h. Then the reaction was cooled to room temperature and HCl 5% (3 mL) was added, then it was diluted with water and extracted with AcOEt (3x15 mL). The combined organic solution was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and the solvent was evaporated. The product was purified by column chromatography with a 9:1 CH<sub>2</sub>Cl<sub>2</sub>/CH<sub>3</sub>OH mixture as eluent (5 % yield).

<sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 7.90-7.69 (m, 8H), 7.56-7.34 (m, 10H), 7.29-6.98 (m, 6H), 6.61-6.47 (m, 1H), 4.04 (m, 1H), 3.86 (m, 1H), 3.27-2.49 (m, 5H), 2.32-2.24 (m, 2H), 1.81-1.62 (m, 4H).

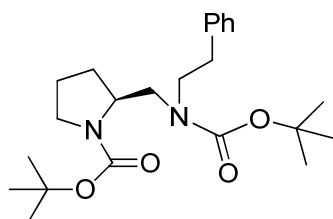
<sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>): δ 133.0-126.1, 57.2, 49.6, 48.3, 47.0, 34.8, 29.5.

<sup>31</sup>P-NMR (202 MHz, CDCl<sub>3</sub>): δ 31.9; 27.2.

[α]<sub>D</sub><sup>25</sup> = -6.9 (solvent: CHCl<sub>3</sub>, c = 0.164 g/100mL, T = 25 °C, λ = 589 nm).

HMRS Mass (ESI +): m/z = calc for C<sub>37</sub>H<sub>38</sub>N<sub>2</sub>O<sub>2</sub>P<sub>2</sub>Na<sup>+</sup> 627.23, found 627.23.

### Catalysts 80



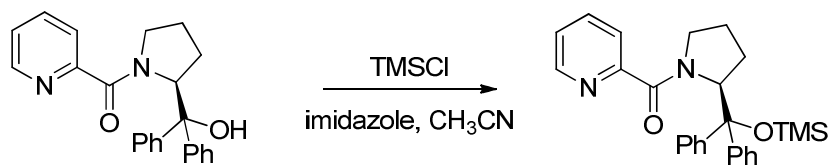
It was obtained by preparing the intermediate following general procedure, which was then dissolved (1 eq, 0.39 mmol) in CH<sub>2</sub>Cl<sub>2</sub> and treated with Boc<sub>2</sub>O (2 eq, 0.78 mmol) and thiourea (0.2 eq, 0.078 mmol). After the additions, the mixture was stirred for 120 h. The product was purified by column chromatography with a 9:1 CH<sub>2</sub>Cl<sub>2</sub>/CH<sub>3</sub>OH mixture as eluent (13 % yield, yellow waxy solid).

<sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 7.25 (m, 5H), 3.80 (s, 1H), 3.40 (m, 2H), 3.21 (brs, 2H), 2.84 (brs, 2H), 2.37-1.05 (m, 24H).

<sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>): δ 128.1, 84.9, 77.0, 56.4, 49.2, 45.7, 35.2, 29.3-26.0.

[α]<sub>D</sub><sup>25</sup> = -9.8 (solvent: CHCl<sub>3</sub>, c = 0.265 g/100mL, T = 25 °C, λ = 589 nm).

HMRS Mass (ESI +): m/z = calc for C<sub>23</sub>H<sub>36</sub>N<sub>2</sub>O<sub>4</sub>Na<sup>+</sup> 427.26, found 427.20.

Preparation of catalyst 88

	MW	eq	mmol	mg	mL	d (g/mL)
substrate (cat 16)	358.43	1	0.20	72		
TMSCl	108.64	4	0.8	64	101	0.856
imidazole	68.08	5	1	68		
CH <sub>3</sub> CN					3	

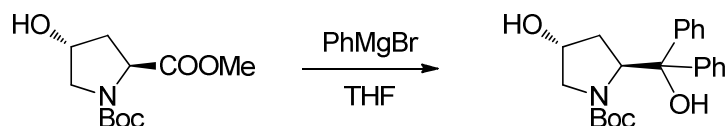
Substrate was dissolved in CH<sub>3</sub>CN and imidazole was added. The solution was cooled to 0 °C and TMSCl was added. The mixture was stirred for 48 hours at room temperature, then the precipitate was filtered off and the solution was concentrated. The obtained residue was purified by silica gel flash chromatography.

Flash chromatography (diameter: 4 cm, h: 15 cm): ): a purification through silica gel (eluent 1:1 hexane/AcOEt) allowed to obtain the product in 39% yield as a white solid.

<sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>) two rotamers : δ 8.60 (d, 1H), 8.44 (d, 1H), 7.62 (m, 1H), 7.52-7.49 (m, 5H), 7.35-7.27 (m, 15H), 7.24-7.07 (m, 3H), 6.55 (d, 1H), 5.76 (t, 1H), 3.99 (m, 1H), 3.27 (m, 1H), 3.15-3.08 (m, 2H), 3.41 (m, 1H), 2.24-2.06 (m, 3H), 1.86-1.76 (m, 2H), 1.66-1.60 (m, 1H), 1.52-1.48 (m, 1H), -0.09 (s, 9H), -0.26 (s, 9H).

Preparation of catalyst 89

## Step 1



	MW	Eq	mmol	mg	mL	d (g/mL)
Substrate	245.27	1	1.63	400		
PhMgBr 3M in Et <sub>2</sub> O	181.31	3.5	5.7		1.9	
THF					9	

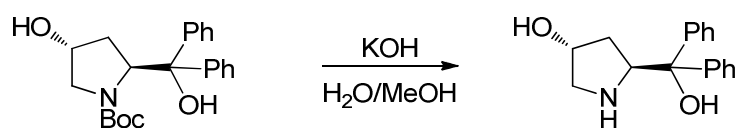
To a stirred solution of PhMgBr 3M in Et<sub>2</sub>O in 4 mL of THF a solution of substrate in 5 mL of THF was slowly added *via* addition funnel. The solution was stirred for 4 h at room temperature and then cooled to -78 °C. After addition of 10 mL of H<sub>2</sub>O, the solution was slowly warmed to room temperature. Decantation and washing precipitated salt with diethyl ether gave a solution that was washed with brine, dried and evaporated.

The obtained residue was purified by silica gel flash chromatography.

Flash chromatography (diameter: 4 cm, h: 15 cm): a purification through silica gel (eluent 8:2 hexane/AcOEt) allowed to obtain the product in 84% yield as a white solid.

<sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 7.41-7.25 (m, 10H), 5.01 (dd, 1H), 3.81 (br, 1H), 3.44 (d, 1H), 2.90 (dd, 1H), 2.09-1.99 (m, 2H), 1.36 (s, 9H).

## Step 2

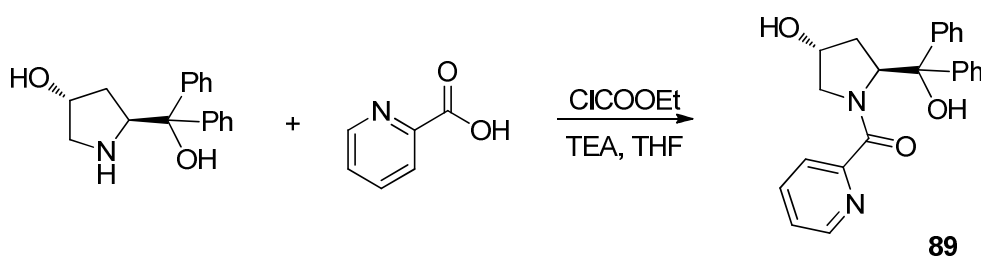


	MW	eq	mmol	mg	mL	d (g/mL)
Substrate	369.45	1	0.95	350		
KOH	56.11	10	9.50	532		
H <sub>2</sub> O/MeOH					3:7	

To a solution of substrate in MeOH, KOH in H<sub>2</sub>O was added. The mixture was stirred at reflux for 24. Then MeOH was evaporated and 5 mL of H<sub>2</sub>O were added. The mixture was extracted with AcOEt, dried and evaporated to give the product in 80% yield .

<sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 7.60 (d, 2H), 7.49 (d, 2H), 7.35-7.18 (m, 8H), 4.68 (dd, 1H), 4.41 (br, 1H), 3.20 (dd, 1H), 3.01 (d, 1H), 1.89-1.83 (m, 2H), 1.53-1.48 (m, 2H).

## Step 3

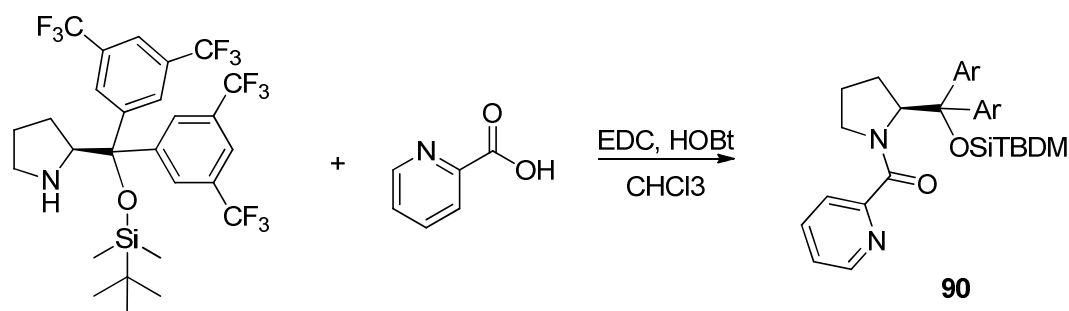


	MW	Eq	mmol	mg	mL	d (g/mL)
Substrate	269.34	1	0.76	200		
picolinic acid	123.11	1	0.76	94		
ClCOOEt	108.5	1	0.76	82.5	0.72	1.14
TEA	101.19	1	0.76	76.9	0.106	0.725
THF					30	

Picolinic acid and TEA were dissolved in THF and cooled to 0°C. To this solution was added ethyl chloroformate dropwise over 15 minutes and stirred for additional 60 minutes. Then substrate in THF was added over 15 minutes. The reaction mixture was stirred at 0°C for 1 hour, then was allowed to reach room temperature and stirred for 16 hours. The mixture was then diluted with water and extracted with ethyl acetate (3 x 30 mL). The organic layers were combined, dried over anhydrous MgSO<sub>4</sub>, concentrated on a rotary evaporator and purified by silica gel flash chromatography.

Flash chromatography (diameter: 3.5 cm, h: 8 cm): a purification through silica gel with 98:2 DCM/MeOH as eluent allowed to obtain the product in 42% yield as a white crystalline solid.

<sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 8.52 (d, 1H), 8.15 (m, 4H), 7.94 (s, 1H), 7.89 (s, 1H), 7.75-7.66 (m, 2H), 7.32-7.29 (m, 1H), 5.88 (br, 1H), 3.26 (m, 1H), 3.10 (m, 1H), 3.27-3.18 (m, 2H), 1.57-1.53 (m, 1H), 1.12 (m, 1H), 0.97 (s, 9H), -0.26 (s, 3H), -0.43 (s, 3H).

Preparation of catalyst 90

	MW	eq	mmol	mg	mL	d (g/mL)
Substrate	639.59	1	0.16	100		
picolinic acid	123.11	1	0.16	20		
EDC•HCL	191.7	1.2	0.19	37		
HOBT	135.13	1.2	0.19	26		
CHCl <sub>3</sub>					5	

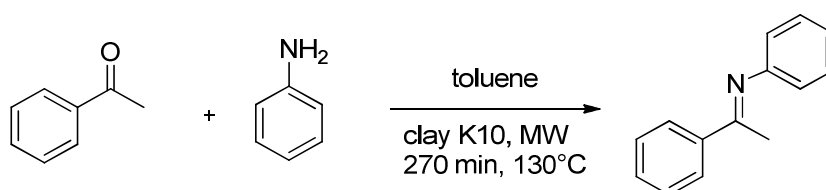
In a dry 25-mL two-neck round-bottom flask equipped with a magnetic stirring bar picolinic acid was dissolved in CH<sub>3</sub>Cl and EDC•HCL and HOBT were added. After stirring 15 min, substrate was added and the solution was stirred for 24 h at room temperature. Then a saturated solution of NaHCO<sub>3</sub> was added and the solution was extracted with DCM; the organic layers were combined, dried over anhydrous MgSO<sub>4</sub>, concentrated on a rotary evaporator and purified by silica gel flash chromatography.

Flash chromatography (diameter: 4 cm, h: 17 cm): a purification through silica gel with DCM as eluent allowed to obtain the product in 73% yield.

<sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 8.48 (s, 1H), 7.75 (m, 1H), 7.49 (d, 2H), 7.59-7.51 (m, 3H), 7.37-7.26 (m, 9H), 6.57 (br, 1H), 5.64 (br, 1H), 4.03 (d, 1H), 3.66 (br, 1H), 3.04-2.70 (m, 2H), 2.21 (br, 2H).

## 8.2 Synthesis of substrates

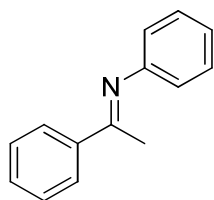
### Preparation of imines



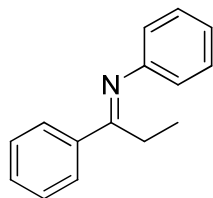
	MW	eq	mmol	mg	mL	d (g/mL)
acetophenone	120.15	1	12.5	1499	1.45	1.026
aniline	93.13	1	12.5	1160	1.4	1.021
clay K10				210		
toluene					7	

*General procedure:* amine (1 eq) was reacted in toluene with ketone (1 eq) in the presence of montmorillonite (250 mg for 5 mmol of reagent) in a microwave reactor (PW = 200 W; T = 130°C; time: 4h and 30min). The product was purified by fractional distillation at P = 1 mbar: the starting material distilled at about 120 °C, the desired product at about 160 °C.

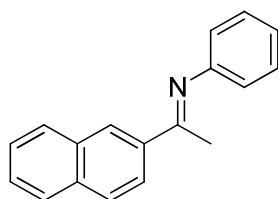
### N-phenyl-(1-phenylethylidene) amine (25)



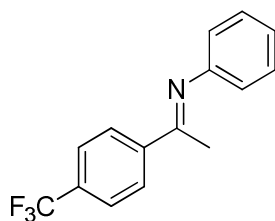
Yield: 70%. <sup>1</sup>H-NMR(300 MHz, CDCl<sub>3</sub>): δ 8.00-7.95 (m, 2H), 7.49-7.41 (m, 3H), 7.39-7.32 (m, 2H), 7.12 -7.06 (m, 1H), 6.83-6.77 (m, 2 H), 2.24 (s, 3H).

*N-Phenyl-(1-phenylpropylidene)amine*

Yield: 76%.  $^1\text{H-NMR}$ (300 MHz,  $\text{CDCl}_3$ ): major isomer:  $\delta$  7.95-7.91 (m, 2H), 7.48-7.43 (m, 3H), 7.37-7.31 (m, 2H), 7.11-7.04 (m, 1 H), 6.81-6.77 (m, 2H), 2.66 (q, 2H), 1.08 (t, 3H); minor isomer: 2.80 (q, 2H), 1.23 (t, 3H).

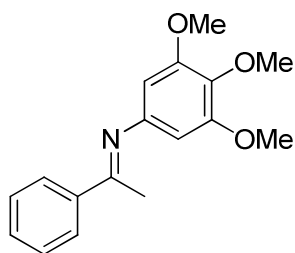
*N-Phenyl-[1-(2-naphthyl)ethylidene]amine*

Yield: 80%.  $^1\text{H-NMR}$ (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.35 (s, 1H), 8.23 (m, 1H), 7.96 -7.86 (m, 3H), 7.58-7.50 (m, 2H), 7.41-7.35 (m, 2H), 7.11 (m, 1H), 6.85 (m, 2H), 2.36 (s, 3H).

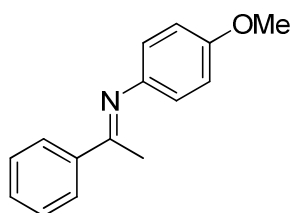
*N-(1-(4-(trifluoromethyl)phenyl)ethylidene)aniline*

Purification: crystallization from hexane. Yield: 40%.  $^1\text{H-NMR}$ (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.06 (d, 2H), 7.70 (d, 2H), 7.4-7.1 (m, 3H), 6.8 (d, 2H), 2.26 (s, 3H).

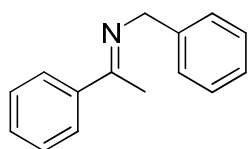


3,4,5-trimethoxy-N-(1-phenylethylidene)aniline

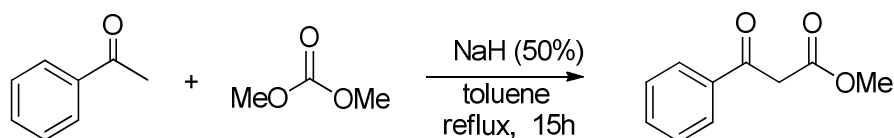
Yield: 34%.  $^1\text{H-NMR}$  (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.95 (m, 2H), 7.44 (m, 3H), 6.02 (s, 2H), 3.81-3.83 (m, 9H), 2.26 (s, 3H).

4-methoxy-N-(1-phenylethylidene)aniline

Yield: 80%.  $^1\text{H-NMR}$  (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.96 (m, 2H), 7.45 (m, 3H), 6.92 (d, 2H), 6.74 (d, 2H), 3.81 (s, 3H), 2.25 (s, 3H).

N-benzyl-(1-phenylethylidene)amine

Yield: 60%.  $^1\text{H-NMR}$ (300 MHz,  $\text{CDCl}_3$ ): major isomer:  $\delta$  7.90-7.88 (m, 2H), 7.46-7.27 (m, 8H), 4.46 (s, 2H), 2.35 (s, 3H); minor isomer: 4.44 (s, 2H), 2.40 (s, 3H).

Preparation of methyl 3-oxo-3-phenylpropanoate

	MW	eq	mmol	mg	mL	d (g/mL)
acetophenone	120.15	1	20	2403	2.34	1.026
dimethylcarbonate	90.08	2	40	3603	3.37	1.069
NaH (50%)	24	2.8	56	3400		
toluene					30	

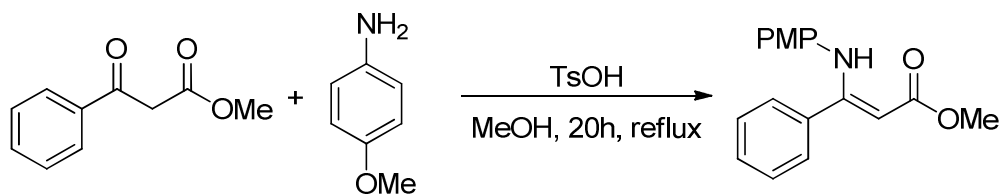
To a dried three-necked flask equipped with a dropping funnel, a condenser, and a magnetic stirrer was added NaH 50%, dimethyl carbonate and toluene (20 mL).

The mixture was heated to reflux. A solution of ketone in 10 mL of toluene was added dropwise from the dropping funnel over 1 h. After the addition, the mixture was heated to reflux until the evolution of hydrogen ceased (15-20 min). When the reaction was cooled to room temperature, glacial acetic acid (3 mL) was added dropwise and a heavy, pasty solid appeared.

Ice-water was added until the solid was dissolved completely. The toluene layer was separated, and the water layer was washed with toluene (3×10 mL). The combined toluene solution was washed with water (10 mL) and brine (10 mL), then dried over Na<sub>2</sub>SO<sub>4</sub>. After evaporation of the solvent, the mixture was purified by silica gel flash chromatography to give the product.

Flash chromatography (diameter: 3 cm, h: 18 cm): a purification through silica gel with 98:2 hexane/AcOEt as eluent allowed to obtain the product in 78% yield.

<sup>1</sup>H-NMR (300MHz, CDCl<sub>3</sub>): δ 12.49 (s, 1H enol), δ 7.95-7.26 (m, 5H + 5H enol), δ 5.67 (s, 1H enol), δ 3.99 (s, 2H), δ 3.80 (s, 3H enol), δ 3.75 (s, 3H).

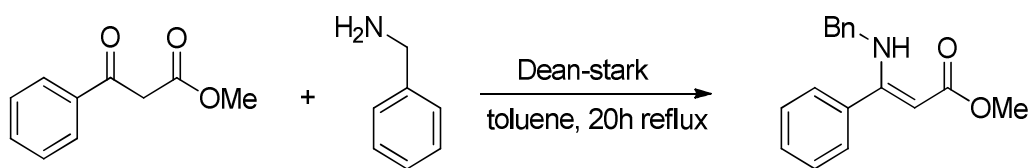
Preparation of (Z)-methyl 3-((4-methoxyphenyl)amino)-3-phenylacrylate (43)

	MW	eq	mmol	Mg	mL	d (g/mL)
methyl 3-phenyl-3-oxopropanoate	178.23	1	9.2	1640		
<i>p</i> -anisidine	123.07	1	9.2	1130		
<i>p</i> -toluensulfonic acid	170.2	0.2	1.9	340		
MeOH					8.5	

*General procedure.* A mixture of  $\beta$ -keto ester, *p*-anisidine and TsOH was dissolved in 10 mL of methanol and refluxed in the presence of molecular sieves (3 Å). After the reaction mixture was cooled to room temperature, the solvent was removed under reduced pressure. The crude was purified by silica gel flash chromatography to give the product.

Yield: 80% This product was purified with a 95:5 hexane/ethyl acetate mixture as eluent.

<sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  3.70 (s, 3H);  $\delta$  3.75 (s, 3H);  $\delta$  4.95 (s, 1H);  $\delta$  6.65 (s, 4H);  $\delta$  7.29 (s, 4H).

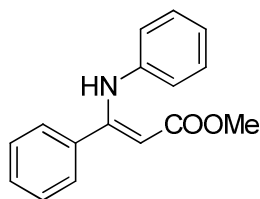
Preparation of (Z)-methyl 3-(benzylamino)-3-phenylacrylate (44)

	MW	Eq	mmol	mg	mL	d (g/mL)
methyl 3-phenyl-3 oxo propanoate	178.23	1	9.2	1640		
benzylamine	107.16	3	27.6	2911	2.97	0.981
toluene					11	

*General procedure.* A mixture of  $\beta$ -keto ester and benzylamine was dissolved in 10 mL of toluene and refluxed overnight with a Dean Stark apparatus in the presence of molecular sieves (3 Å). After the reaction mixture was cooled to room temperature, the solvent was removed under reduced pressure. The crude product was purified on silica flash.

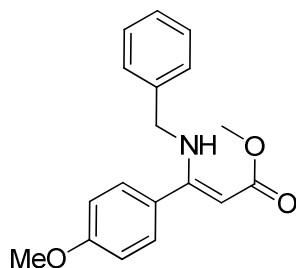
Yield: 40% This product was purified with a 9:1 hexane/ethyl acetate mixture as eluent.

$^1\text{H-NMR}$  (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  3.69 (s, 3H);  $\delta$  4.27 (d, 2H);  $\delta$  4.69 (s, 1H);  $\delta$  7.15-7.38 (m, 10H);  $\delta$  8.91 (br, 1H).

(Z)-methyl 3-(phenylamino)-3-phenylacrylate

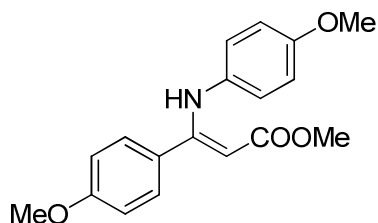
Yield: 40% This product was purified with a 98:2 hexane/ethyl acetate mixture as eluent.

<sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 3.75 (s, 3H); δ 4.98 (s, 1H); δ 6.68 (m, 1H); δ 6.91 (m, 1H); δ 7.09 (m, 3H); δ 7.32 (m, 5H); 10.28 (b, 1H).

(Z)-methyl 3-(benzylimino)-3-(4-methoxyphenyl)propanoate

Yield: 35% This product was purified with a 95:5 hexane/ethyl acetate mixture as eluent.

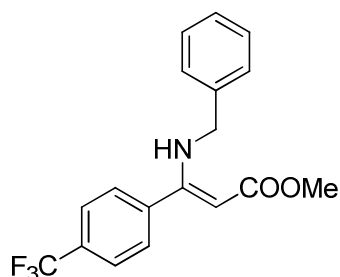
<sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 3.68 (s, 3H); δ 3.82 (s, 3H); δ 4.31 (d, 2H); δ 4.68 (s, 1H); δ 6.82 (d, 2H); δ 7.21-7.31 (m, 7H).

(Z)-methyl 3-(4-methoxyphenylamino)-3-(4-methoxyphenyl)propanoate

Yield: 80%. This product was purified with a 95:5 hexane/ethyl acetate mixture as eluent.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>): δ 3.70 (s, 3H); δ 3.72 (s, 3H); δ 3.77 (s, 3H); δ 4.90 (s, 1H); δ 6.66 (s, 4H); δ 6.76 (d, 2H); δ 7.23 (d, 2H).

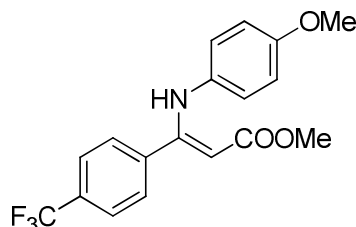
(Z)-methyl 3-(benzylamino)-3-(4-(trifluoromethyl)phenyl)acrylate



Yield: 81% This product was purified with a 95:5 hexane/ethyl acetate mixture as eluent.

<sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 3.70 (s, 3H); δ 4.23 (d, 2H); δ 4.69 (s, 1H); δ 7.15 (d, 2H); δ 7.21-7.32 (m, 3H); δ 7.44 (d, 2H); δ 7.64 (d, 2H); δ 8.90 (br, 1H).

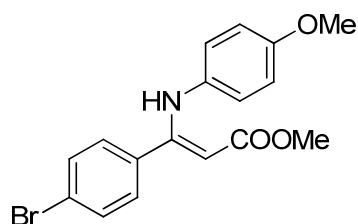
(Z)-methyl 3-(4-methoxyphenylamino)-3-(4-(trifluoromethyl)phenyl)acrylate



Yield: 41% This product was purified with a 95:5 hexane/ethyl acetate mixture as eluent.

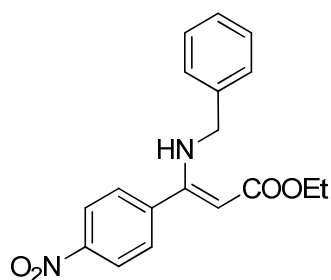
<sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 3.70 (s, 3H); δ 3.75 (s, 3H); δ 4.95 (s, 1H); δ 6.65 (s, 4H); δ 7.29 (s, 4H).

<sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>): δ 50.67 (1C); 55.22 (1C); 90.00 (1C); 114.00 (4C); 124.55 (2C); 125.28 (1C); 128.77 (2C); 132.76 (1C); 139.98 (1C); 156.15 (1C); 158.25 (1C); 170.30 (1C).

(Z)-methyl 3-(4-methoxyphenylamino)-3-(4-bromophenyl)propanoate

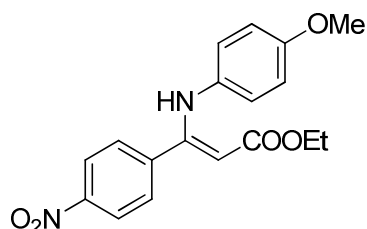
Yield: 54%. This product was purified with a 95:5 hexane/ethyl acetate mixture as eluent.

<sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 3.71 (s, 3H); δ 3.73 (s, 3H); δ 4.91 (s, 1H); δ 6.65 (s, 4H); δ 7.16 (d, 2H); δ 7.39 (d, 2H).

(Z)-ethyl 3-(benzylimino)-3-(4-nitrophenyl)propanoate

Yield: 37%. This product was purified with a 95:5 hexane/ethyl acetate mixture as eluent.

<sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 1.26 (t, 3H); δ 4.15 (m, 2H); δ 4.19 (m, 2H); δ 4.22 (d, 2H); δ 7.12 (d, 2H); δ 7.27 (m, 3H); δ 7.48 (d, 2H); δ 8.23 (d, 2H).

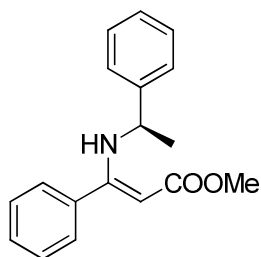
(Z)-ethyl 3-(4-methoxyphenylamino)-3-(4-nitrophenyl)propanoate

Yield: 64% This product was purified with a 95:5 hexane/ethyl acetate mixture as eluent.

$^1\text{H-NMR}$  (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.32 (t, 3H);  $\delta$  3.71 (s, 3H);  $\delta$  4.20 (q, 2H);  $\delta$  4.99 (s, 1H);  $\delta$  6.64 (s, 4H);  $\delta$  7.48 (d, 2H);  $\delta$  8.10 (d, 2H).

$^{13}\text{C-NMR}$  (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  14.49 (1C); 55.34 (1C); 59.55 (1C); 91.33 (1C); 114.21 (2C); 123.56 (2C); 124.75 (2C); 129.32 (3C); 133.26 (1C); 142.71 (1C); 156.43 (1C); 157.19 (1C); 169.81 (1C).

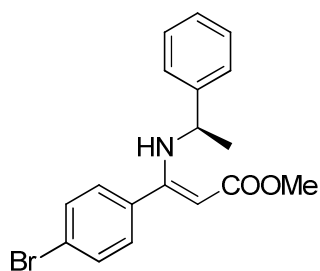
*(R,Z)-methyl 3-phenyl-3-(1-phenylethylamino)acrylate*



Yield: 46% This product was purified with a 98:2 hexane/ethyl acetate mixture as eluent.

$^1\text{H-NMR}$  (300MHz,  $\text{CDCl}_3$ ):  $\delta$  1.51 (d, 3H);  $\delta$  3.72 (s, 3H);  $\delta$  4.50 (m, 1H);  $\delta$  4.64 (s, 1H);  $\delta$  7.08-7.34 (m, 10H);  $\delta$  8.95 (b, 1H).

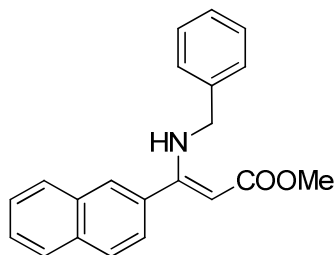
*(R,Z)-methyl 3-(4-bromophenyl)-3-(1-phenylethylamino)propanoate*



Yield: 64% This product was purified with a 98:2 hexane/ethyl acetate mixture as eluent.

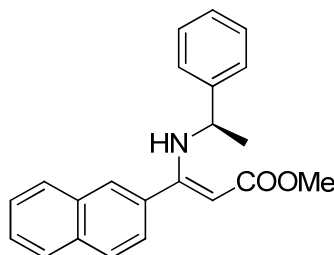
$^1\text{H-NMR}$  (300MHz,  $\text{CDCl}_3$ ):  $\delta$  1.45 (d, 3H);  $\delta$  3.74 (s, 3H);  $\delta$  4.45 (m, 1H);  $\delta$  4.61 (s, 1H);  $\delta$  7.05-7.48 (m, 10H);  $\delta$  8.90 (b, 1H).



(Z)-methyl 3-(benzylimino)-3-(naphthalen-2-yl)propanoate

Yield: 45% This product was purified with a 9:1 hexane/ethyl acetate mixture as eluent.

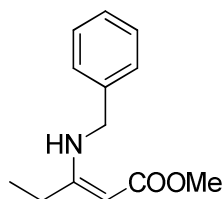
<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>): δ 3.7 (s, 3H); δ 4.32 (d, 2H); δ 4.72 (s, 1H); δ 7.2-7.3 (m, 5H); δ 7.45-7.55 (m, 3H); δ 7.8-7.9 (m, 4H); δ 9.00 (br, 1H).

(R,Z)-methyl 3-(naphthalen-1-yl)-3-(1-phenylethylamino)acrylate

Yield: 45% This product was purified with a 95:5 hexane/ethyl acetate mixture as eluent.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>): **E**: δ 1.40 (d, 3H); δ 3.74 (s, 3H); δ 4.00 (q, 1H); δ 4.68 (s, 1H); δ 6.83-8.15 (m, 12H); δ 9.24 (br, 1H).

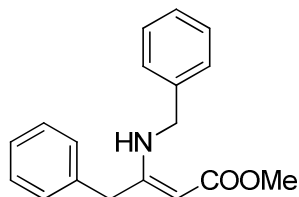
**Z**: δ 1.49 (d, 3H); δ 3.75 (s, 3H); δ 4.50 (q, 1H); δ 4.76 (s, 1H); δ 6.83-8.15 (m, 12H); δ 9 (br, 1H).

(Z)-methyl 3-(benzylamino)pent-2-enoate

Yield: 80% This product was purified with a 95:5 hexane/ethyl acetate mixture as eluent.

$^1\text{H-NMR}$  (200 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.11 (t, 3H);  $\delta$  2.22 (q, 2H);  $\delta$  3.61 (s, 3H);  $\delta$  4.43 (d, 2H);  $\delta$  4.57 (s, 1H);  $\delta$  7.24-7.35 (m, 5H);  $\delta$  8.96 (br, 1H).

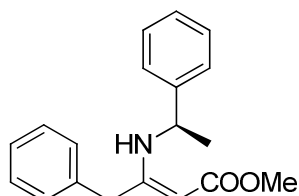
(Z)-methyl 3-(benzylimino)-4-phenylbutanoate



Yield: 80% This product was purified with a 95:5 hexane/ethyl acetate mixture as eluent.

$^1\text{H-NMR}$  (200 MHz,  $\text{CDCl}_3$ ):  $\delta$  3.53 (s, 2H);  $\delta$  3.66 (s, 3H);  $\delta$  4.29 (d, 2H);  $\delta$  4.56 (s, 1H);  $\delta$  7.19-7.33 (m, 10H);  $\delta$  9.0 (br, 1H).

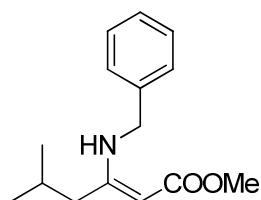
(R,Z)-methyl 4-phenyl-3-(1-phenylethylimino)butanoate



Yield: 70% This product was purified with a 99:1 hexane/ethyl acetate mixture as eluent.

$^1\text{H-NMR}$  (200 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.40 (d, 3H);  $\delta$  3.38 (q, 2H);  $\delta$  3.68 (s, 3H);  $\delta$  4.48 (m, 2H);  $\delta$  7.17-7.40 (m, 10H);  $\delta$  9.0 (br, 1H).

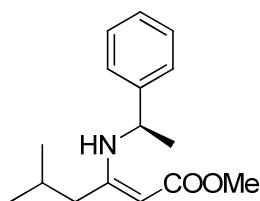
(Z)-methyl 3-(benzylamino)-4-methylpent-2-enoate



Yield: 71% The product was purified by fractional distillation at P = 1 mbar the desired product at about 100 °C.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>): δ 1.11 (d, 6H); δ 2.66 (m, 1H); δ 3.63 (s, 3H); δ 4.45 (d, 2H); δ 4.61 (s, 1H); δ 7.26-7.38 (m, 5H); δ 9.05 (br, 1H).

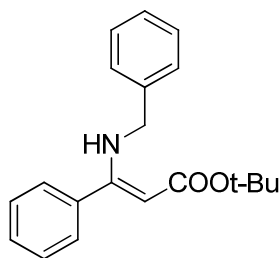
(R,Z)-methyl 4-methyl-3-(1-phenylethylamino)pent-2-enoate



Yield: 80% The product was purified by fractional distillation at P = 1 mbar the desired product at about 100 °C.

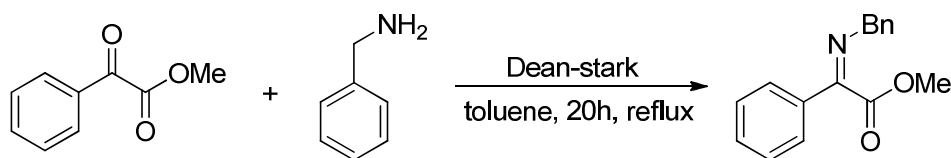
<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>): δ 0.80 (d, 3H); δ 1.12 (d, 3H); δ 1.52 (d, 3H); δ 2.55 (m, 1H); δ 3.66 (s, 3H); δ 4.56 (s, 1H); δ 4.72 (q, 1H); δ 7.23-7.36 (m, 5H); δ 9.15 (br, 1H).

(Z)-tert-butyl 3-(benzylamino)-3-phenylacrylate



Yield: 30% This product was purified with a 95:5 hexane/ethyl acetate mixture as eluent.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>): δ 1.55 (s, 9H); δ 4.30 (d, 2H); δ 4.60 (s, 1H); δ 7.15-7.40 (m, 10H); δ 8.80 (br, 1H).

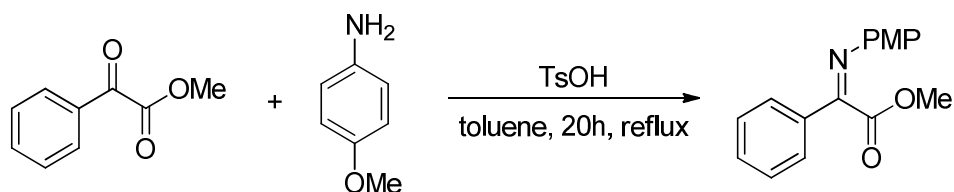
Preparation of (Z)-methyl 2-(benzylimino)-2-phenylacetate (46)

	MW	eq	mmol	g	mL	d (g/mL)
phenyl methyl glyoxylate	164.17	1	10	1.6	1.4	1.163
benzylamine	107.16	1	10	1.1	1.09	0.981
toluene					7	

A mixture of  $\alpha$ -keto ester and benzylamine was dissolved in 7 mL of toluene and refluxed overnight with a Dean Stark apparatus in the presence of molecular sieves (3 Å). After the reaction mixture was cooled to room temperature, the solvent was removed under reduced pressure. The crude product was purified by flash chromatography.

Flash chromatography (diameter: 2.5 cm, h: 17 cm): a purification through *aluminum oxide chromatography* with 98:2 hexane/AcOEt as eluent allowed to obtain the product in 16% yield.

$^1\text{H-NMR}$  (200MHz,  $\text{CDCl}_3$ ):  $\delta$  7.24-7.78 (m, 10H),  $\delta$  4.78 (s, 2H),  $\delta$  3.98 (s, 3H).

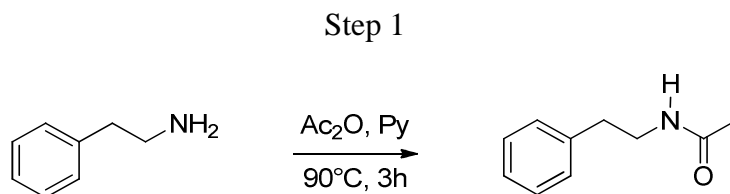
Preparation of (Z)-methyl 2-((4-methoxyphenyl)imino)-2-phenylacetate (47)

	MW	eq	mmol	mg	mL	d (g/mL)
phenyl methyl glyoxylate	164.17	1	10	1640	1.4	1.163
p-anisidine	123.07	1	10	1236		
p-toluensulfonic acid	170.2	0.1	0.1	172		
toluene					8	

A mixture of  $\alpha$ -keto ester, p-anisidine and TsOH was dissolved in 8 mL of toluene and refluxed in the presence of molecular sieves (3 Å). After the reaction mixture was cooled to room temperature, the solvent was removed under reduced pressure. The crude was purified by flash chromatography to give the product.

Flash chromatography (diameter: 2.5 cm, h: 17 cm): a purification through aluminum oxide chromatography with 95:5 hexane/AcOEt as eluent allowed to obtain the product in 55% yield.

$^1\text{H-NMR}$  (200MHz,  $\text{CDCl}_3$ ):  $\delta$  3.69 (s, 3H),  $\delta$  3.81 (s, 3H),  $\delta$  6.93 (m, 4H),  $\delta$  7.46 (m, 3H),  $\delta$  7.84 (d, 2H).

Preparation of compound 88

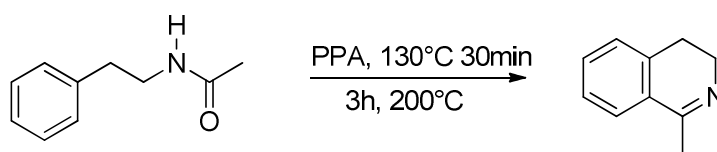
	MW	eq	mmol	g	mL	d (g/mL)
2-phenylethanamine	121.18	1	24.756	3.00	3.10	0.965
pyridine	79.10	1.1	27.232	2.15	2.20	0.978
Ac <sub>2</sub> O	102.09	1.26	31.193	3.18	2.95	1.08

Phenyl ethylamine was dissolved in pyridine, and acetic anhydride was added dropwise to the solution, which was heated at 90°C for 2 h. After cooling to room temperature, the volatiles were removed *in vacuo*. The residue was partitioned between ethyl acetate and 4 M HCl. The organic layer was washed with 1 M NaOH and brine, then it was dried over MgSO<sub>4</sub>. MgSO<sub>4</sub> was filtered off and the organic solvent was evaporated *in vacuo*. Crude *N*-phenethylacetamide was obtained as a light yellow solid, which was used for the next step without further purification. Yield: 88%.

<sup>1</sup>H-NMR(300 MHz, CDCl<sub>3</sub>): δ 7.31-7.17 (m, 5H), 5.5 (s br, 1H), 3.5 (q, 2H), 2.8 (t, 2H), 1.9 (s, 3H).

Mass (ESI<sup>+</sup>): *m/z* = 164.18.

## Step 2



	MW	eq	mmol	g	mL	d (g/mL)
Substrate	163.18	1	21.6	3.5		
PPA				18		

PPA was added to substrate and the obtained syrup was heated at 130°C for 30 min, then at 200°C for 3 h. The reaction was cooled to 40°C and water (90 mL) was added. The solution was taken to pH = 9 with NH<sub>3</sub> (28% aqueous solution) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 100 mL). The organic phase was washed with brine (3 × 50 mL) and dried over MgSO<sub>4</sub>. After filtration and evaporation of the solvent, a black oil was obtained.

Flash chromatography (diameter: 4 cm, h: 15 cm): purification through silica gel (eluent: 600 mL of 98:2CH<sub>2</sub>Cl<sub>2</sub>/MeOH) gave product in 98% yield.

<sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 7.45-7.11 (m, 4H), 3.63 (m, 2H), 2.66 (m, 2H), 2.35 (s, 3H).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ 162.7, 135.8, 129.0, 128.0, 125.9, 125.3, 123.7, 45.4, 24.5, 21.8.

Mass (ESI+): *m/z* = 146.2.

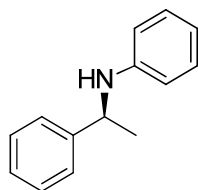
### 8.3 Trichlorosilane-mediated C-N double bond reductions

*General procedure:* To a stirred solution of catalyst (0.1-0.3% mol/eq mmol) in the chosen solvent (2 mL), the imine (1 mmol/eq) was added. The mixture was then cooled to the chosen temperature and trichlorosilane (3.5 mmol/eq) was added dropwise by means of a syringe. After stirring at the proper temperature, the reaction was quenched by the addition of a saturated aqueous solution of NaHCO<sub>3</sub> (1 mL). The mixture was allowed to warm up to room temperature and water (2 mL) and dichloromethane (5 mL) were added. The organic phase was separated and the combined organic phases were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under vacuum at room temperature to afford the crude product.

The amine was purified by flash chromatography.

Absolute configuration was determined by comparison of the sign of the optical rotation of the product with literature data.

#### *N*-(phenyl)-1-phenyl-ethanamine (26)

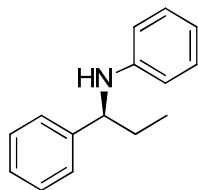


This product was purified by flash column chromatography on silica gel with a 98:2 hexane/ethyl acetate mixture as eluent

<sup>1</sup>H-NMR(300MHz, CDCl<sub>3</sub>): δ 7.23 (m, 7H), δ 6.61 (m, 3H), δ 4.48 (q, 1H), δ 1.53 (d, 3H).

HPLC: Chiralcel OD-H; *n*-Hex/*i*-PrOH 99:1; 0.8 mL/min; t = 15.07 min; 18.38 min.

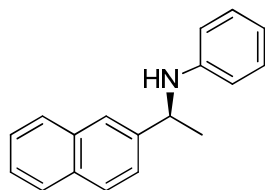


*N*-(1-phenylpropyl)aniline

This product was purified with a 98:2 hexane/ethyl acetate mixture as eluent.

<sup>1</sup>H-NMR(300 MHz, CDCl<sub>3</sub>): δ 7.31 (m, 4H), 7.21 (m, 1H), 7.07 (t, 2H), 6.62 (t, 1H), 6.50 (d, 2H), 4.21 (t, 1H), 4.05 (br s, 1H), 1.81 (m, 2H), 0.94 (t, 3H).

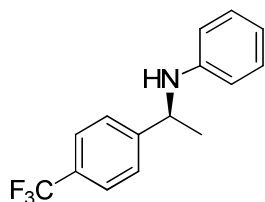
HPLC: Chiralcel IB; *n*-Hex/*i*-PrOH 99:1; 0.8 mL/min;  $t_s = 7.9$  min,  $t_R = 8.5$  min.  $t = 15.07$  min; 18.38 min.

*N*-(1-(naphthalen-2-yl)ethyl)aniline

This product was purified with a hexane:ethyl acetate 98:2 mixture as eluent

<sup>1</sup>H-NMR(300 MHz, CDCl<sub>3</sub>): δ 7.89 (m, 4H), 7.5 (m, 3H), 7.1 (t, 2H), 6.7 (m, 3H), 4.6 (q, 1H), 3.97 (br s, 1H), 1.6 (d, 3H).

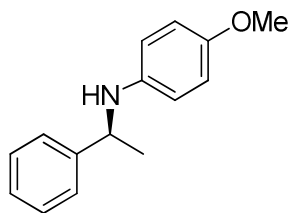
HPLC: Chiralcel OD; *n*-Hex/*i*-PrOH 98:2; 0.8 mL/min;  $t_s = 12.9$  min,  $t_R = 13.8$  min.

*N*-(1-(4-(trifluoromethyl)phenyl)ethyl)aniline

This product was purified with a 98:2 hexane/ethyl acetate mixture as eluent.

$^1\text{H-NMR}$  (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.51 (d, 2H), 7.41 (d, 2H), 7.02 (t, 2H), 6.59 (t, 1H), 6.38 (d, 2H), 4.46 (q, 1H), 3.97 (br s, 1H), 1.46 (d, 3H).

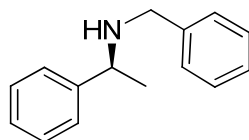
HPLC: Chiralcel OD; *n*-Hex/*i*-PrOH 9:1; 0.8 mL/min;  $t_s = 8.9$  min,  $t_R = 10.5$  min.

*4*-methoxy-*N*-(1-phenylethyl)aniline

This product was purified with a 98:2 hexane/ethyl acetate mixture as eluent.

$^1\text{H-NMR}$  (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.43-7.26 (m, 5H), 6.73 (d, 2H), 6.58 (d, 2H), 4.46 (q, 1H), 3.74 (s, 3H), 1.58 (d, 3H).

HPLC: Chiralcel IB; *n*-Hex/*i*-PrOH 99:1; 0.8 mL/min;  $t_s = 7.4$  min,  $t_R = 9.3$  min.

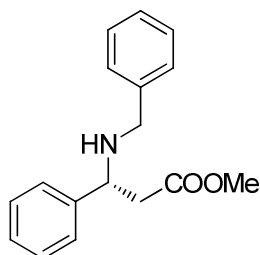
*N*-benzyl-1-phenylethanamine

This product was purified with a 8:2 hexane/ethyl acetate mixture as eluent.

$^1\text{H-NMR}$  (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.38-7.24 (m, 10H), 3.82 (q, 1H), 3.67, 3.60 (AB, 2H), 1.57 (bs, 1H), 1.37 (d, 3H).

HPLC: Chiralcel IB; *n*-Hex/*i*-PrOH 99:1; 0.8 mL/min;  $t_R$  = 8.8 min,  $t_S$  = 9.4 min.

*(R)*-methyl 3-(benzylamino)-3-phenylpropanoate

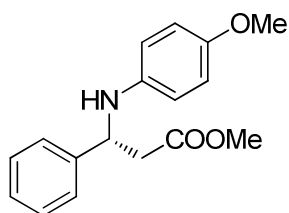


This product was purified with a 95:5 hexane/ethyl acetate mixture as eluent.

$^1\text{H-NMR}$  (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  2.65 (dd, 1H);  $\delta$  2.80 (dd, 1H);  $\delta$  3.53 (d, 1H);  $\delta$  3.62 (s, 3H);  $\delta$  3.69 (d, 2H);  $\delta$  4.12 (m, 1H);  $\delta$  7.25-7.36 (m, 10H).

The enantiomeric excess was determined by HPLC on a Chiralcel OD (96:4 hexane/*i*-PrOH ; flow rate: 0.8 mL/min;  $\lambda$  = 210 nm):  $t_R$  =13.99 min,  $t_S$  =25.18 min.

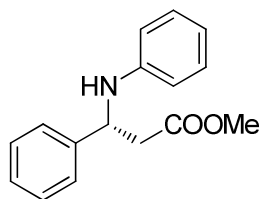
*(R)*-methyl 3-(4-methoxyphenylamino)-3-phenylpropanoate



This product was purified with a 95:5 hexane/ethyl acetate mixture as eluent.

$^1\text{H-NMR}$  (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  2.65 (d, 1H);  $\delta$  3.60 (s, 3H);  $\delta$  3.70 (s, 3H);  $\delta$  4.78 (m, 1H);  $\delta$  6.50 (d, 2H);  $\delta$  6.70 (d, 2H);  $\delta$  7.32 (m, 5H).

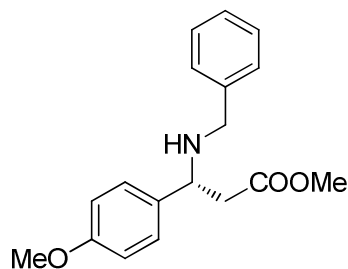
The enantiomeric excess was determined by HPLC on a Chiralpak AD (70:30) hexane/*i*-PrOH ; flow rate: 0.8 mL/min;  $\lambda$  = 210 nm):  $t_R$  =9.8 min,  $t_S$  =14.8 min.

(R)-methyl 3-(phenylamino)-3-phenylpropanoate

This product was purified with a 95:5 hexane/ethyl acetate mixture as eluent.

<sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 2.80 (d, 1H); δ 3.62 (s, 3H); δ 4.82 (m, 1H); δ 6.50 (d, 2H); δ 6.70 (d, 1H); δ 7.10 (m, 2H); δ 7.20-7.40 (m, 5H).

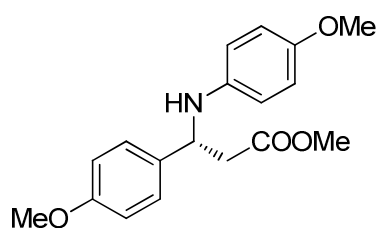
The enantiomeric excess was determined by HPLC on a Chiralpak AD (97:3) hexane/*i*-PrOH ; flow rate: 0.8 mL/min; λ = 210 nm): t<sub>R</sub> = 14.08 min, t<sub>S</sub> = 15.66 min.

(R)-methyl 3-(benzylamino)-3-(4-methoxyphenyl)propanoate

This product was purified with a 97:3 hexane/ethyl acetate mixture as eluent.

<sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 1.28 (d, 3H); δ 2.06 (br, 1H); δ 2.51 (dd, 1H); δ 2.64 (dd, 1H); δ 3.43-3.63 (q, 2H); δ 3.62 (s, 3H); δ 3.85 (s, 3H); δ 4.01 (m, 1H); δ 6.90 (d, 2H); δ 7.26-7.35 (m, 5H).

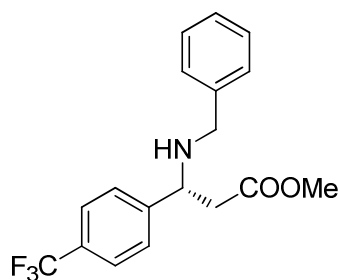
The enantiomeric excess was determined by HPLC on a Chiralpak AD (9:1 hexane/*i*-PrOH ; flow rate: 0.8 mL/min; λ = 225 nm): t<sub>R</sub> = 8.30 min, t<sub>S</sub> = 8.75 min.

(R)-methyl 3-(methoxyphenylamino)-3-(4-methoxyphenyl)propanoate

This product was purified with a 97:3 hexane/ethyl acetate mixture as eluent.

<sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 2.75 (d, 2H); δ 3.60 (s, 3H); δ 3.70 (s, 3H); δ 3.79 (s, 3H); δ 4.70 (t, 1H); δ 6.55 (d, 2H); δ 6.70 (d, 2H); δ 6.85 (d, 2H); δ 7.30 (d, 2H).

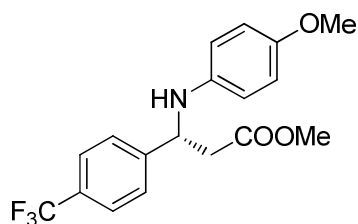
The enantiomeric excess was determined by HPLC on a Chiralpak AD (9:1 hexane/*i*-PrOH ; flow rate: 0.8 mL/min; λ = 225 nm): t<sub>R</sub> = 20.79 min, t<sub>S</sub> = 21.87 min.

(R)-methyl 3-(benzylamino)-3-(4-(trifluoromethyl)phenyl)propanoate

This product was purified with a 95:5 hexane/ethyl acetate mixture as eluent.

<sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 2.10 (br, 1H); δ 2.61 (dd, 1H); δ 2.72 (dd, 1H); δ 3.53 (d, 1H); δ 3.64 (s, 3H); δ 3.64 (d, 1H); δ 4.19 (m, 1H); δ 7.22-7.33 (m, 5H); δ 7.50 (d, 2H); δ 7.62 (d, 2H).

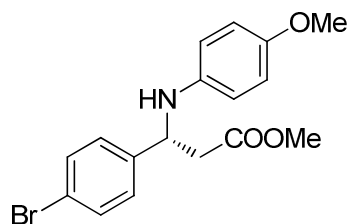
The enantiomeric excess was determined by HPLC on a Chiralcel OD-H (9:1 hexane/*i*-PrOH ; flow rate: 0.5 mL/min; λ = 220 nm): t<sub>R</sub> = 12.11 min, t<sub>S</sub> = 13.46 min.

(R)-methyl 3-(methoxyphenylamino)-3-(4-(trifluoromethyl)phenyl)propanoate

This product was purified with a 95:5 hexane/ethyl acetate mixture as eluent.

<sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 2.81 (d, 2H); δ 3.66 (s, 3H); δ 3.70 (s, 3H); δ 4.80 (m, 1H); δ 6.50 (d, 2H); δ 7.72 (d, 2H); δ 7.47–7.61 (m, 4H).

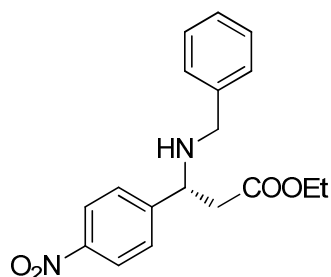
The enantiomeric excess was determined by HPLC on a Chiralcel OD-H (9:1 hexane/*i*-PrOH ; flow rate: 0.8 mL/min; λ = 270 nm): t<sub>R</sub> = 23.73 min, t<sub>S</sub> = 28.33 min.

(R)-methyl 3-(methoxyphenylamino)-3-(4-bromophenyl)propanoate

This product was purified with a 97:3 hexane/ethyl acetate mixture as eluent.

<sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 2.77 (d, 2H); δ 3.65 (s, 3H); δ 3.70 (s, 3H); δ 4.70 (t, 1H); δ 6.50 (d, 2H); δ 6.69 (d, 2H); δ 7.25 (d, 2H); δ 7.43 (d, 2H).

The enantiomeric excess was determined by HPLC on a Chiralpak AD (9:1 hexane/*i*-PrOH ; flow rate: 0.8 mL/min; λ = 210 nm): t<sub>R</sub> = 17.03 min, t<sub>S</sub> = 18.48 min.

(R)-ethyl 3-(benzylamino)-3-(4-nitrophenyl)propanoate

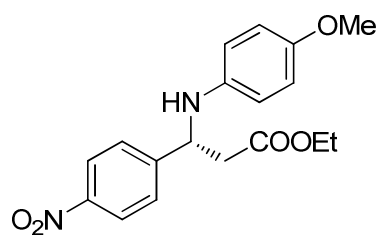
This product was purified with a 97:3 hexane/ethyl acetate mixture as eluent.

<sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 1.19 (t, 3H); δ 2.06 (br, 1H); δ 2.65 (m, 2H); δ 3.57 (q, 2H); δ 4.10 (q, 2H); δ 4.22 (m, 1H); δ 7.25 (m, 5H). δ 7.57 (d, 2H); δ 8.21 (d, 2H).

<sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>): δ 14.13 (1C); 42.53 (1C); 51.45 (1C); 58.34 (1C); 60.81 (1C) 123.89 (2C); 127.25 (1C); 128.11 (2C); 128.23 (2C); 128.50 (2C); 139.38 (1C); 147.55 (1C); 150.14 (1C); 170.95 (1C).

The enantiomeric excess was determined by HPLC on a Chiralpak OD-H (9:1 hexane/*i*-PrOH ; flow rate: 0.8 mL/min; λ = 210 nm): t<sub>R</sub> = 13.03, t<sub>S</sub> = 16.19 min.

[α]<sub>D</sub><sup>25</sup> = +12.2 (c = 0.11g/100 mL, CHCl<sub>3</sub>, λ = 589 nm)

(R)-ethyl 3-(methoxyphenylamino)-3-(4-nitrophenyl)propanoate

This product was purified with a 97:3 hexane/ethyl acetate mixture as eluent.

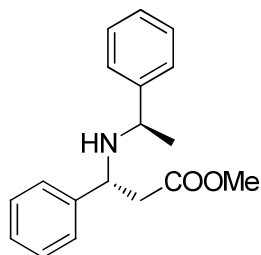
<sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 1.22 (t, 3H); δ 2.79 (d, 2H); δ 3.69 (s, 3H); δ 4.11 (q, 2H); δ 4.85 (t, 1H); δ 6.46 (d, 2H); δ 6.69 (d, 2H); δ 7.56 (d, 2H); δ 8.18 (d, 2H).

<sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>): δ 14.08 (1C); 42.21 (1C); 55.58 (2C); 61.05 (1C); 114.82 (2C); 115.32 (2C); 123.99 (2C); 127.38 (2C); 139.90 (1C); 147.33 (1C); 150.01 (1C); 152.84 (1C); 176.48 (1C).

The enantiomeric excess was determined by HPLC on a Chiralpak AD (9:1 hexane/*i*-PrOH ; flow rate: 0.8 mL/min;  $\lambda = 225$  nm):  $t_R = 42.66$ ,  $t_S = 46.69$  min.

$[\alpha]_D^{25} = + 5.76$  ( $c = 0.30$ g/100 mL, CH<sub>3</sub>Cl,  $\lambda = 589$  nm)

*(R)*-methyl 3-phenyl-3-((*R*)-1-phenylethylamino)propanoate



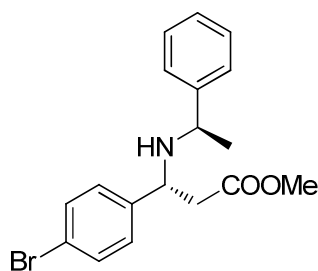
This product was purified with a 95:5 hexane/ethyl acetate mixture as eluent.

<sup>1</sup>H-NMR (300MHz, CDCl<sub>3</sub>): (*R,R*):  $\delta$  1.31 (d, 3H);  $\delta$  2.00 (b, 1H);  $\delta$  2.53-2.80 (m, 2H);  $\delta$  3.50 (q, 1H);  $\delta$  3.61 (s, 3H);  $\delta$  3.84 (dd, 1H);  $\delta$  7.18-7.37 (m, 10H).

The enantiomeric excess was determined by HPLC on a Chiralpak AD (9:1 hexane/*i*-PrOH ; flow rate: 0.8 mL/min;  $\lambda = 225$  nm):  $t_R = 42.66$ ,  $t_S = 46.69$  min.

$[\alpha]_D^{25} = + 61.4$  ( $c = 0.32$ g/100 mL, DCM,  $\lambda = 589$  nm).

*(R)*-methyl 3-(4-bromophenyl)-3-((*R*)-1-phenylethylamino)propanoate



This product was purified with a 95:5 hexane/ethyl acetate mixture as eluent

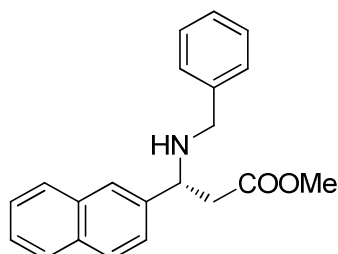
<sup>1</sup>H-NMR (300MHz, CDCl<sub>3</sub>): (*R,R*):  $\delta$  1.29 (d, 3H);  $\delta$  2.00 (b, 1H);  $\delta$  2.53-2.71 (m, 2H);  $\delta$  3.40(q, 1H);  $\delta$  3.62 (s, 3H);  $\delta$  3.80 (dd, 1H);  $\delta$  7.08-7.47 (m, 9H).

The enantiomeric excess was determined by HPLC on a Chiralpak AD (9:1 hexane/*i*-PrOH ; flow rate: 0.8 mL/min;  $\lambda = 225$  nm):  $t_R = 42.71$ ,  $t_S = 51.69$  min.



$[\alpha]_D^{25} = +98.7$  ( $c = 0.20\text{g}/100\text{ mL}$ ,  $\text{CH}_3\text{Cl}$ ,  $\lambda = 589\text{ nm}$ )

*(R)*-methyl 3-(benzylamino)-3-(naphthalen-2-yl)propanoate



This product was purified with a 9:1 hexane/ethyl acetate mixture as eluent.

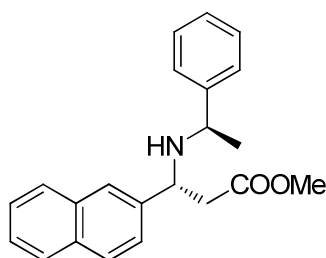
$^1\text{H-NMR}$  (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  2.0 (br, 1H);  $\delta$  2.62 (dd, 1H);  $\delta$  2.75 (dd, 1H);  $\delta$  3.62 (q, 2H);  $\delta$  3.62 (s, 3H);  $\delta$  4.3 (m, 1H);  $\delta$  7.2 (m, 5H);  $\delta$  7.5 (m, 3H);  $\delta$  7.84 (m, 4H).

The enantiomeric excess was determined by HPLC on a Chiralpak AD (9:1 hexane/isopropanol; flow rate: 0.8 mL/min;  $\lambda = 230\text{ nm}$ ):  $t_s = 9\text{ min}$ ,  $t_R = 9.8\text{ min}$ .

$^{13}\text{C NMR}$  (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  42.8 (1C); 51.3 (1C); 51.6 (1C); 60.7 (1C); 126.1 (1C); 126.3 (1C); 126.9 (1C); 127.7 (2C); 127.9 (1C); 128.2 (1C); 128.4 (1C); 128.5 (2C); 129.7 (2C); 133.1 (1C); 133.5 (1C); 139.8 (1C); 140.2 (1C); 172.2 (1C).

$[\alpha]_D^{25} = +30.69$  ( $c = 0.216\text{ g}/100\text{ mL}$ ,  $\text{EtOH}$ ,  $\lambda = 589\text{ nm}$ ).

*(R)*-methyl 3-(naphthalen-2-yl)-3-((*R*)-1-phenylethylamino)propanoate



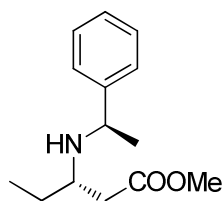
This product was purified with a 85:15 hexane/ethyl acetate mixture as eluent.

$^1\text{H-NMR}$  (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.29 (d, 3H);  $\delta$  2.10 (br, 1H);  $\delta$  2.62 (dd, 1H);  $\delta$  2.75 (dd, 1H);  $\delta$  3.50 (q, 1H);  $\delta$  3.62 (s, 3H);  $\delta$  4.00 (m, 1H);  $\delta$  7.18-7.70 (m, 9H);  $\delta$  7.79-7.85 (m, 3H).

$^{13}\text{C}$  NMR(75 MHz,  $\text{CDCl}_3$ ):  $\delta$  24,6 (1C); 42.4 (1C); 51.6 (1C); 55.1 (1C); 56.7 (1C); 125.9 (1C); 126.1 (1C); 126.5 (1C); 126.9 (1C); 127.2 (1C); 127.4 (1C); 127.8 (1C); 128.1 (2C); 128.2 (2C); 128.5 (1C); 133.0 (1C); 133.3 (1C); 138.8 (1C); 144 (1C); 171.9 (1C).

$[\alpha]_{\text{D}}^{25} = +99.9$  ( $c = 0.228\text{g}/100\text{ mL}$ , DCM,  $\lambda = 589\text{ nm}$ ).

*(S)*-methyl 3-((*R*)-1-phenylethylamino)pentanoate



This product was purified with a 95: 5 hexane/ethyl acetate mixture as eluent.

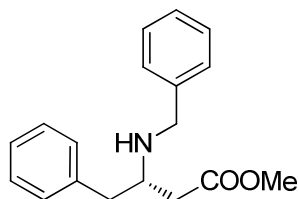
$^1\text{H}$ -NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  0.95 (t, 3H);  $\delta$  1.40-1.59 (m, 2H);  $\delta$  1.64 (br, 1H);  $\delta$  2.45 (d, 2H);  $\delta$  2.99 (q, 1H);  $\delta$  3.68 (s, 3H);  $\delta$  3.78 (s, 2H);  $\delta$  7.21-7.33 (m, 5H).

$^{13}\text{C}$  NMR(75 MHz,  $\text{CDCl}_3$ ):  $\delta$  9.91 (1C); 26.76 (1C); 38.62 (1C); 50.92 (1C); 51.5 (1C); 55.49 (1C); 126.9 (1C); 127.33 (1C); 128.81 (2C); 129.05 (1C); 140.44 (1C); 173.07 (1C).

The enantiomeric excess was determined by HPLC on a Chiralcel OD (99:1 hexane/isopropanol; flow rate: 0.5 mL/min;  $\lambda = 210\text{ nm}$ ):  $t_{\text{S}} = 12.53\text{ min}$ ,  $t_{\text{R}} = 16.16\text{ min}$ .

$[\alpha]_{\text{D}}^{25} = +3.69$  ( $c = 0.116\text{g}/100\text{ mL}$ , DCM,  $\lambda = 589\text{ nm}$ ).

*(S)*-methyl 3-(benzylamino)-4-phenylbutanoate

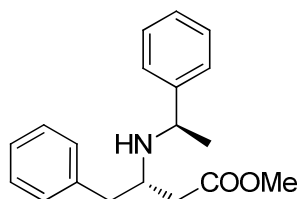


This product was purified with a 95: 5 hexane/ethyl acetate mixture as eluent.

<sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 2.45 (d, 2H); δ 2.75 (dd, 1H); δ 2.9 (dd, 1H); δ 3.35 (m, 1H); δ 3.65 (s, 3H); δ 3.88 (s, 2H); δ 7.10-7.33 (m, 10H).

The enantiomeric excess was determined by HPLC on a Chiralpak AD (99:1 hexane/isopropanol; flow rate: 0.8 mL/min; λ = 210 nm): t<sub>S</sub> = 13.90 min, t<sub>R</sub> = 15.47 min.

*(S)*-methyl 4-phenyl-3-((*R*)-1-phenylethylamino)butanoate



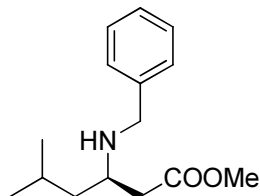
This product was purified with a 95: 5 hexane/ethyl acetate mixture as eluent.

<sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): (*R,S*): δ 1.27 (d, 3H); δ 2.00 (br, 1H); δ 2.23-2.28 (m, 2H); 2.68 (m, 1H); 2.92 (m, 2H); δ 3.59 (s, 3H); δ 4 (q, 1H); δ 7.04-7.33 (m, 10H).

(*R,R*): δ 1.32 (d, 3H); δ 2.23-2.28 (m, 2H); δ 2.68 (m, 1H); δ 2.92 (m, 2H); δ 3.66 (s, 3H); δ 3.85 (q, 1H); δ 7.04-7.33 (m, 10H).

<sup>13</sup>C NMR(75 MHz, CDCl<sub>3</sub>): δ 24.57 (1C); 38.84 (1C); 39.16 (1C); 51.40 (1C); 53.33 (1C); 55.18 (1C); 126.32 (1C); 126.44 (1C); 126.81 (2C); 128.75 (3C); 129.36 (3C); 138.20 (1C); 144.64 (1C); 172.69 (1C).

*(R)*-methyl 3-(benzylamino)-4-methylpentanoate



This product was purified with a 95: 5 hexane/ethyl acetate mixture as eluent.

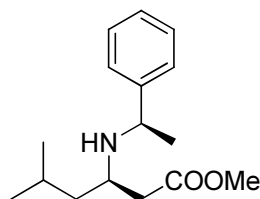
<sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 0.95 (t, 6H); δ 1.56 (br, 1H); δ 1.93 (m, 1H); δ 2.39 (dd, 1H); δ 2.49 (dd, 1H); δ 2.94 (m, 1H); δ 3.70 (s, 3H); δ 3.82 (s, 2H); δ 7.26-7.36 (m, 5H).

$^{13}\text{C}$  NMR(75 MHz,  $\text{CDCl}_3$ ):  $\delta$  17.6 (1C); 18.8 (1C); 26.76 (1C); 29.7 (1C); 36 (1C); 51.5 (2C); 59.6 (1C); 125 (1C); 128.3 (2C); 129.0 (2C); 140.1 (1C); 173.6 (1C).

The enantiomeric excess was determined by HPLC on a Chiralcel OD (99:1 hexane/isopropanol; flow rate: 0.8 mL/min;  $\lambda = 210$  nm):  $t_R=9.13$  min,  $t_S=9.72$  min.

$[\alpha]_D^{25} = +9.2$  ( $c = 0.45$ g/100 mL, DCM,  $\lambda = 589$  nm).

*(R)*-methyl 4-methyl-3-((*R*)-1-phenylethylamino)pentanoate



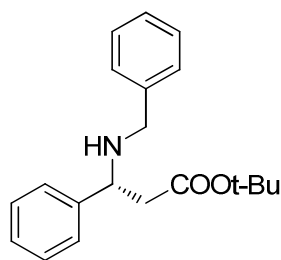
This product was purified with a 95: 5 hexane/ethyl acetate mixture as eluent.

$^1\text{H-NMR}$  (300 MHz,  $\text{CDCl}_3$ ): (***R,R***):  $\delta$  0.81 (d, 3H);  $\delta$  1.28 (d, 3H);  $\delta$  1.92 (m, 1H);  $\delta$  2.17 (dd, 1H);  $\delta$  2.30 (dd, 1H);  $\delta$  2.74 (q, 1H);  $\delta$  3.60 (s, 3H);  $\delta$  3.85 (m, 1H);  $\delta$  7.21-7.32 (m, 5H). (***R,S***):  $\delta$  0.81 (d, 3H);  $\delta$  1.28 (dd, 6H);  $\delta$  1.66 (m, 1H);  $\delta$  2.35 (dd, 1H);  $\delta$  2.45 (dd, 1H);  $\delta$  2.65 (q, 1H);  $\delta$  3.68 (s, 3H);  $\delta$  3.85 (m, 1H);  $\delta$  7.21-7.32 (m, 5H)

$^{13}\text{C}$  NMR(75 MHz,  $\text{CDCl}_3$ ):  $\delta$  16.39 (1C); 18.98 (1C); 24.86 (1C); 29.01 (1C); 29.39 (1C); 35.76 (1C); 54.89 (1C); 56.72 (1C); 126.71 (1C); 126.80 (2C); 129.0 (2C); 145.8 (1C); 173.6 (1C).

$[\alpha]_D^{25} = +26.1$  ( $c = 0.322$  g/100 mL, DCM,  $\lambda = 589$  nm).

*(R)*-tert-butyl 3-(benzylamino)-3-phenylpropanoate

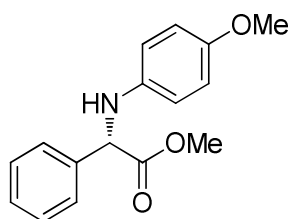


This product was purified with a 95: 5 hexane/ethyl acetate mixture as eluent.

<sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>): δ 1.35 (s, 9H); δ 2.60 (m, 2H); δ 3.55 (dd, 2H); δ 4.10 (m, 1H); δ 7.27 (m, 10H).

The enantiomeric excess was determined by HPLC on a Chiralcel OD-H (96:4 hexane/isopropanol; flow rate: 0.8 mL/min; λ = 220 nm): t<sub>R</sub>=6.69 min, t<sub>S</sub>=7.5 min.

(S)-methyl 2-((4-methoxyphenyl)amino)-2-phenylacetate

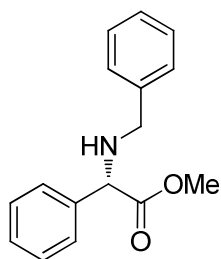


This product was purified with a 98:2 hexane/ethyl acetate mixture as eluent

<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>): δ 3.71 (s, 3H), δ 3.73 (s, 3H), δ 4.19 (b, 1H), δ 5.03 (s, 1H), δ 6.63 (dd, 4H), δ 7.39 (m, 5H).

The enantiomeric excess was determined by HPLC on a Chiralcel OJ-H (7:3 hexane/*i*-PrOH ; flow rate: 0.8 mL/min; λ = 210 nm): t<sub>R</sub>=39.85, t<sub>S</sub>=44.96 min

(S)-ethyl 2-(benzylamino)-2-phenylacetate



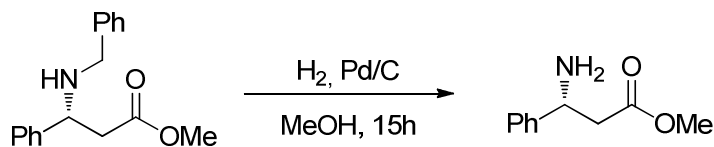
This product was purified by flash column chromatography on silica gel with a 9:1 hexane/ethyl acetate mixture as eluent.

<sup>1</sup>H-NMR (300MHz, CDCl<sub>3</sub>): δ 7.24-7.48 (m, 10H), δ 4.45 (s, 1H), δ 3.70 (s, 2H), δ 3.65 (s, 3H).

HPLC: Chiralcel OD-H; *n*-Hex/*i*-PrOH 95:5; 0,5 mL/min; t = 14.65 min; 16.45 min

## 8.4 Deprotection protocols

### Synthesis of (R)-methyl 3-amino-3-phenylpropanoate



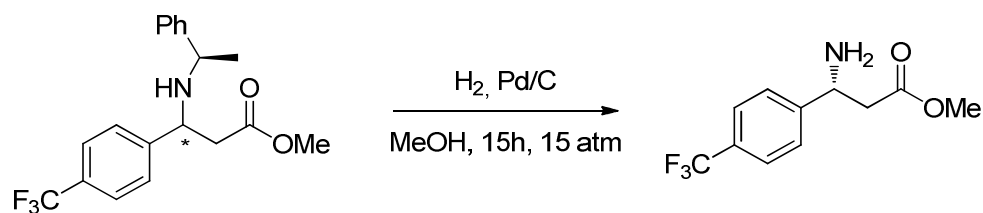
A suspension of (R)-methyl 3-(benzylamino)-3-phenylpropanoate (0.58 mmol) and Pd/C (10%, 36 mg) in methanol (3.5 mL) were stirred in under hydrogen atmosphere at room temperature for 16 h. The catalyst was removed by filtration through a pad of celite, and the filtrate was concentrated and purified by column chromatography (5:5 hexane/ethyl acetate 100 mL, 4:6 hexane/ethyl acetate 100 mL, 3:7 hexane/ethyl acetate 100 mL mixture as eluent).

Yield = 98%

<sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 2.31 (br, 2H); δ 2.67 (d, 2H); δ 3.66 (s, 3H); δ 4.42 (t, 1H); δ 7.21-7.38 (m, 5H).

The enantiomeric excess was determined by HPLC on a Chiralcel OD-H (98:2 hexane/isopropanol; flow rate: 0.8 mL/min; λ = 210 nm): t<sub>R</sub>=26.04 min, t<sub>S</sub>=32.44 min

[α]<sub>D</sub><sup>25</sup> = + 10.5 (c = 0.258 g/100 mL, DCM, λ = 589 nm).

Synthesis of (R)-methyl 3-amino-3-(4-(trifluoromethyl)phenyl)propanoate

The deprotection of *N*- $\alpha$ -methyl benzyl amine required more drastic conditions and it was successfully performed by hydrogenating the starting material for 16 hours in methanol with Pd/C at 15 atm.

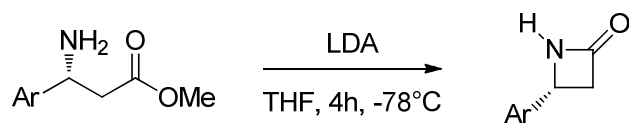
Yield = 98%

<sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  2.43 (br, 2H);  $\delta$  2.72 (d, 2H);  $\delta$  3.68 (s, 3H);  $\delta$  4.52 (t, 1H);  $\delta$  7.51 (d, 2H);  $\delta$  7.60 (d, 2H).

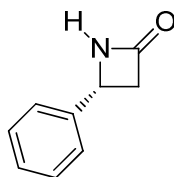
The enantiomeric excess was determined by HPLC on a Chiralpak AD (9:1 hexane/isopropanol; flow rate: 0.8 mL/min;  $\lambda$  = 210 nm):  $t_s$ =9.7 min,  $t_r$ =10.5 min

Deprotection of *N*-PMP group

*General procedure:* A solution of ammonium cerium nitrate (4 eq) in water was added slowly to a stirred solution of substrate (1 eq) in acetonitrile at 0°C. After 2 hours, a solution of NaHCO<sub>3</sub> was added until pH 6. The mixture was extracted. The organic layer was separated and the water layer was washed with ethyl acetate. The combined organic solution was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and the solvent was evaporated.

8.5 Synthesis of  $\beta$ -lactam

*General procedure.* To a solution of LDA (0.676 mmol) in THF (3 mL) at  $-78^{\circ}\text{C}$  was added a THF (1 mL) solution of substrate. Stirring was continued at  $-78^{\circ}\text{C}$  for 16 h after which the reaction was quenched with  $\text{NaHCO}_3$  aq, and then extracted with ethyl acetate. The combined organic layers were washed with brine, dried over  $\text{Na}_2\text{SO}_4$  and concentrated. The residue was purified by column chromatography (7:3 hexane/ethyl acetate 100 mL, 5:5 hexane/ethyl acetate 100 mL mixture as eluent).

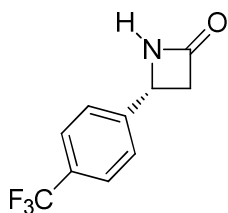
(R)-4-phenylazetidin-2-one

Yield = 84%

$[\alpha]_{\text{D}}^{25} = +106$  ( $c = 0.02$  g/100 mL, EtOH,  $\lambda = 589$  nm).

$^1\text{H-NMR}$  (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  2.87 (dd, 1H);  $\delta$  3.44 (dd, 1H);  $\delta$  4.71 (dd, 1H);  $\delta$  6.30 (br, 1H);  $\delta$  7.30-7.43 (m, 5H).

GLC ( $\beta$ -cyclodextrin column, Isotherm  $150^{\circ}\text{C}$ ):  $t_{\text{R}} = 66.0$  min,  $t_{\text{S}} = 74.0$  min

(R)-4-(4-(trifluoromethyl)phenyl)azetidin-2-one



Yield = 80%

<sup>1</sup>H-NMR(500 MHz, CDCl<sub>3</sub>): δ 2.87 (dd, 1H); δ 3.44 (dd, 1H); δ 4.81 (dd, 1H); δ 6.50 (br, 1H); δ 7.5 (d, 1H); δ 7.55 (d, 1H).

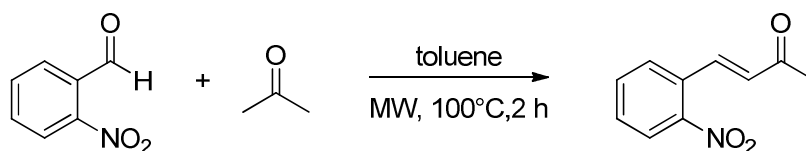
<sup>13</sup>C NMR(125 MHz, CDCl<sub>3</sub>):δ 47.46 (1C); 49.91 (1C); 125.00 (q, 1C); 126.00 (2C); 126.55 (2C); 130.44 (q, 1C); 144.27 (1C); 167.62 (1C).

<sup>19</sup>F-NMR (75 MHz, CDCl<sub>3</sub>): δ -63.46 (1 F).

The enantiomeric excess was determined by HPLC on a Chiralpak IB (9:1 hexane/isopropanol; flow rate: 0.8 mL/min; λ = 225 nm): t<sub>R</sub>=16.13 min, t<sub>S</sub>=20.8.

[α]<sub>D</sub><sup>25</sup> = + 61 (c = 0.2 g/100 mL, DCM, λ = 589 nm).

## 8.6 Synthesis of substrates for reductive amination

Preparation of compound 90

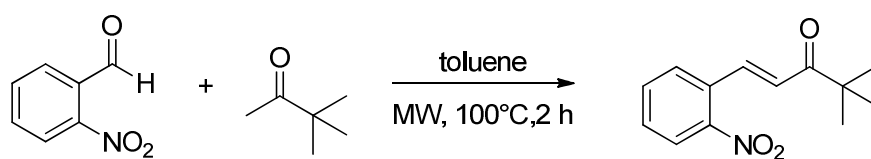
	MW	eq	mmol	g	mL	d (g/mL)
2-NO <sub>2</sub> -benzaldehyde	151.12	1	8.2	1.2		
acetone	58.08	5	41	2.4	3	0.791
toluene					5	

2-NO<sub>2</sub>-benzaldehyde was reacted in toluene with acetone in a microwave reactor (PW = 200 W; T = 10°C; time: 2h). The mixture was concentrated and the crude product was purified on silica flash.

Flash chromatography (diameter: 2.5 cm, h: 17 cm): a purification through silica gel with 8:2 hexane/AcOEt as eluent allowed to obtain the product in 43% yield.

<sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 8.08 (d, 1H), δ 7.99 (d, 1H, J = 15 Hz), δ 7.67-7.65 (m, 2H), δ 7.59-7.55 (m, 1H), δ 6.57 (d, 1H, J = 15 Hz), δ 2.43 (s, 3H).

<sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>): δ 198.0 (1C), δ 148.3 (1C), δ 138.9 (1C), δ 133.7 (1C), δ 131.9 (1C), δ 130.8 (1C), δ 130.4 (1C), δ 129.1 (1C), δ 125.1 (1C), δ 27.0 (1C).

Preparation of compound 91

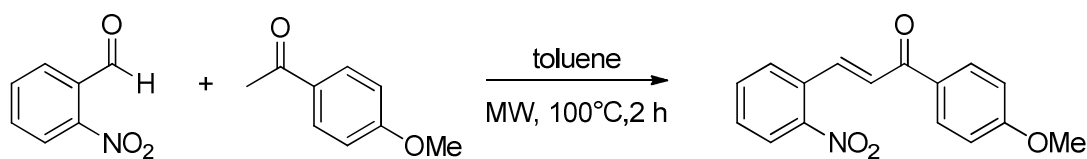
	MW	eq	mmol	g	mL	d (g/mL)
2-NO <sub>2</sub> -benzaldehyde	151.12	1	8.2	1.2		
methyl <i>t</i> -butyl ketone	100.16	5	41	4.1	5.1	0.801
toluene					5	

2-NO<sub>2</sub>-benzaldehyde was reacted in toluene with methyl *t*-butyl ketone in a microwave reactor (PW = 200 W; T = 10°C; time: 2h). The mixture was concentrated and the crude product was purified on silica flash.

Flash chromatography (diameter: 2.5 cm, h: 17 cm): a purification through silica gel with 8:2 hexane/AcOEt as eluent allowed to obtain the product in 36% yield.

<sup>1</sup>H-NMR (300 MHz; CDCl<sub>3</sub>): δ 8.02 (d, 1H, J = 15 Hz), 7.97 (d, 1H), δ 7.68-7.64 (m, 2H), δ 7.54-7.52 (m, 1H), δ 7.03 (d, 1H, J = 15 Hz), 1.21 (s, 9H).

<sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>): δ 203.2 (1C), δ 148.7 (1C), δ 138.0 (1C), δ 133.5 (1C), δ 131.2 (1C), δ 130.2 (1C), δ 129.2 (1C), δ 125.5 (1C), δ 124.8 (1C), δ 43.3 (1C), δ 26.1 (3C).

Preparation of compound 92

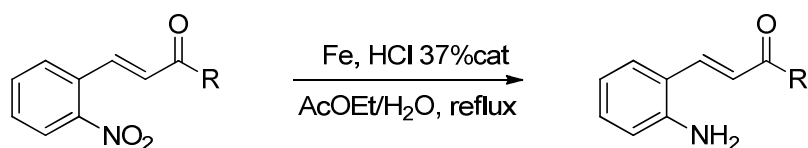
	MW	eq	mmol	g	mL	d (g/mL)
2-NO <sub>2</sub> -benzaldehyde	151.12	1	8.2	1.2		
acetanisole	150.17	5	41	6.1	5.6	1.094
Toluene					5	

2-NO<sub>2</sub>-benzaldehyde was reacted in toluene with acetanisole in a microwave reactor (PW = 200 W; T = 10°C; time: 2h). The mixture was concentrated and the crude product was purified on silica flash.

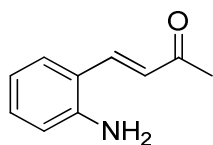
Flash chromatography (diameter: 2.5 cm, h: 17 cm): a purification through silica gel with 8:2 hexane/AcOEt as eluent allowed to obtain the product in quantitative yield.

<sup>1</sup>H-NMR (300MHz, CDCl<sub>3</sub>): δ 8.10 (d, 1H, J = 15 Hz), δ 8.04-8.00 (m, 3H), δ 7.73 (d, 1H), δ 7.75-7.72 (m, 2H), δ 7.54 (t, 1H), δ 7.35 (d, 1H, J = 15 Hz), δ 6.97 (d, 2H), δ 3.88 (s, 3H).

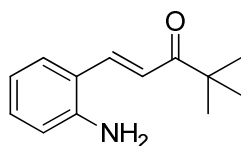
<sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>): δ 188.5 (1C), δ 163.7 (1C), δ 148.6 (1C), δ 139.1 (1C), δ 133.5 (1C), δ 131.4 (1C), δ 131.1 (2C), δ 130.3 (1C), δ 130.2 (1C), δ 129.2 (1C), δ 127.2 (1C), δ 124.9 (1C), δ 114.0 (2C), δ 55.5 (1C).

Preparation of compound 93-95

*General procedure:* to a stirred solution of substrate (1 eq) in AcOEt/H<sub>2</sub>O 4:1 Fe powder (5 eq) and catalytic amount of HCl 37% were added. The mixture was warmed to reflux and stirred vigorously for 4 hours. Then it was allowed to cooled to room temperature, Fe was filtrate through a celite pad and the solution concentrated. The crude product was purified on silica flash.

Compound 93

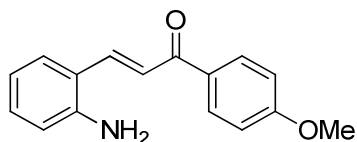
Yield quantitative. This product was purified with a 8:2 hexane/AcOEt mixture as eluent. <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 7.67 (d, 1H, J = 15 Hz), δ 7.38 (d, 1H), δ 7.19 (t, 1H), δ 6.79-6.71 (m, 2H), δ 6.65 (d, 1H, J = 15 Hz), δ 3.97 (br, 2H), δ 2.35 (s, 3H).

Compound 94

Yield 52%. This product was purified with a 8:2 hexane/AcOEt mixture as eluent. <sup>1</sup>H-NMR (300 MHz; CDCl<sub>3</sub>): δ 7.85(d, 1H, J = 15 Hz), δ 7.45 (d, 1H), δ 7.18 (t, 1H), δ 7.07 (d, 1H, J = 15 Hz), δ 6.78 (t, 1H), δ 6.71 (d, 1H), δ 3.99 (br, 2H), δ 1.25 (s, 9H).

$^{13}\text{C}$ -NMR (75 MHz;  $\text{CDCl}_3$ ):  $\delta$  204.4 (1C),  $\delta$  146.1 (1C),  $\delta$  138.2 (1C),  $\delta$  131.3 (1C),  $\delta$  127.9 (1C),  $\delta$  120.9 (1C),  $\delta$  120.3 (1C),  $\delta$  118.8 (1C),  $\delta$  116.7 (1C),  $\delta$  43.2 (1C),  $\delta$  26.4 (3C).

Compound 95

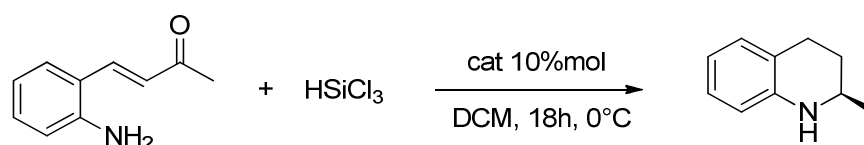


Yield 45%. This product was purified with a 8:2 hexane/AcOEt mixture as eluent.

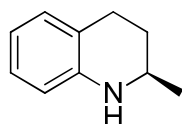
$^1\text{H}$ -NMR (300 MHz;  $\text{CDCl}_3$ ):  $\delta$  8.06 (d, 2H),  $\delta$  7.98 (d, 1H,  $J = 15\text{Hz}$ ),  $\delta$  7.56-7.49 (m, 2H),  $\delta$  7.22 (t, 1H),  $\delta$  7.01 (d, 2H),  $\delta$  6.82 (t, 1H),  $\delta$  6.75 (d, 1H),  $\delta$  4.15 (br, 2H),  $\delta$  3.91 (s, 3H).

$^{13}\text{C}$ -NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  188.0 (1C),  $\delta$  162.9 (1C),  $\delta$  138.0 (1C),  $\delta$  133.5 (1C),  $\delta$  131.2 (1C),  $\delta$  130.2 (1C),  $\delta$  129.2 (1C),  $\delta$  125.5 (1C),  $\delta$  124.8 (1C),  $\delta$  43.3 (1C),  $\delta$  26.1 (3C).

## 8.7 Reductive aminations



*General procedure:* To a stirred solution of catalyst in the chosen solvent (1M), the substrate added. The mixture was then cooled to the chosen temperature and trichlorosilane was added dropwise by means of a syringe (in solution 1M of the chosen solvent). After stirring at the proper temperature, the reaction was quenched by the addition of a saturated aqueous solution of NaHCO<sub>3</sub> (1 mL). The mixture was allowed to warm up to room temperature and water (2 mL) and dichloromethane (5 mL) were added. The organic phase was separated and the combined organic phases were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under vacuum at room temperature to afford the crude product, purified on silica gel.

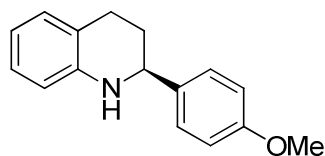
Compound 96

This product was purified with a 9:1 hexane/AcOEt mixture as eluent.

<sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 6.99-6.96 (m, 2H), δ 6.63 (t, 1H), δ 6.50 (d, 1H), δ 3.71 (br, 1H), δ 3.44-3.40 (m, 1H), δ 2.87-2.76 (m, 2H), δ 1.99-1.92 (m, 1H), δ 1.70-1.61 (m, 1H), δ 1.28 (d, 3H)

HPLC (Chiralcel OJ-H; *n*-esano/*i*-PrOH= 97:3; 0.8 mL min<sup>-1</sup>): t<sub>R</sub>= 20.4 min (*S*); 23.4 min (*R*).

Compound 97

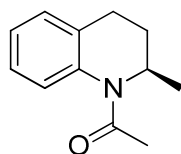


This product was purified with a 9:1 hexane/AcOEt mixture as eluent

$^1\text{H-NMR}$ : (300 MHz,  $\text{CDCl}_3$ )  $\delta$ (ppm) 1.93–2.13 (m, 2H), 2.75 (m, 1H), 2.90–2.98 (m, 1H), 3.83 (s, 3H), 4.00 (br, 1H), 4.39 (dd, 1H), 6.53 (dd,  $J = 8.0, 1.2$  Hz, 1H), 6.66 (m, 1H), 6.89–6.92 (m, 2H), 7.00–7.04 (m, 2H), 7.31–7.34 (m, 2H).

HPLC (Chiralcel OD-H; *n*-esano/*i*-PrOH= 97:3;  $0.8 \text{ mL min}^{-1}$ ):  $t_{\text{R}} = 9.2 \text{ min (S)}$ ;  $14.5 \text{ min (R)}$ .

### Compound 98



This product was purified with a 9:1 hexane/AcOEt mixture as eluent.

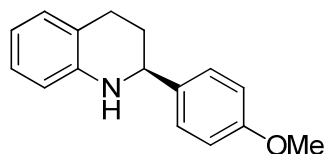
$^1\text{H-NMR}$  (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.18 (m, 4H),  $\delta$  4.84 (br, 1H),  $\delta$  2.65-2.52 (m, 3H),  $\delta$  2.42-2.32 (m, 1H),  $\delta$  2.16 (s, 3H),  $\delta$  1.14 (d, 3H)

$^{13}\text{C-NMR}$  (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  169.7 (1C),  $\delta$  162.9 (1C),  $\delta$  137.8 (1C),  $\delta$  127.4 (1C),  $\delta$  127.0 (1C),  $\delta$  126.3 (1C),  $\delta$  126.0 (1C),  $\delta$  125.6 (1C),  $\delta$  48.5 (1C),  $\delta$  32.8 (1C),  $\delta$  26.3 (1C),  $\delta$  23.1 (1C),  $\delta$  20.4 (1C).

MS (ESI)  $m/z$  (%): calc. for  $\text{C}_{12}\text{H}_{15}\text{NONa}^+ = 212.10459$ ; found = 212.10444.

HPLC (Chiralcel OJ; *n*-esano/*i*-PrOH= 7:3;  $0.8 \text{ mL min}^{-1}$ ):  $t_1 = 12.9 \text{ min}$ ;  $t_2 = 15.5 \text{ min}$ .

### Compound 99





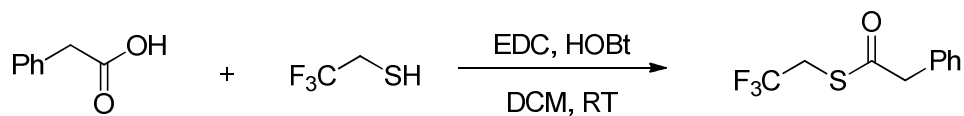
This product was purified with a 9:1 hexane/AcOEt mixture as eluent

<sup>1</sup>H-NMR: (300 MHz, CDCl<sub>3</sub>) δ(ppm) ): δ 7.28-7.18 (m, 4H), δ 7.12 (d, 2H), δ 6.80 (d, 2H), δ 5.66 (br, 1H), δ 3.77 (s, 3H), δ 2.64 (m, 4H), δ 2.17 (s, 3H).

<sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>): δ 170.1 (1C), δ 158.4 (1C), δ 138.7 (1C), δ 135.5 (1C), δ 134.2 (1C), δ 127.5 (2C), δ 127.4 (1C), δ 126.6 (1C), δ 125.9 (1C), δ 125.5 (1C), δ 113.8 (2C), δ 56.4 (1C), δ 55.2 (1C), δ 34.8 (1C), δ 26.8 (1C), δ 23.2 (1C).

HPLC (Chiralcel OD-H; *n*-esano/*i*-PrOH= 9:1; 0.8 mL min<sup>-1</sup>): t<sub>1</sub>= 12.7 min; t<sub>2</sub>=14.2 min.

## 8.8 Synthesis of thioesters

Preparation of compound 81

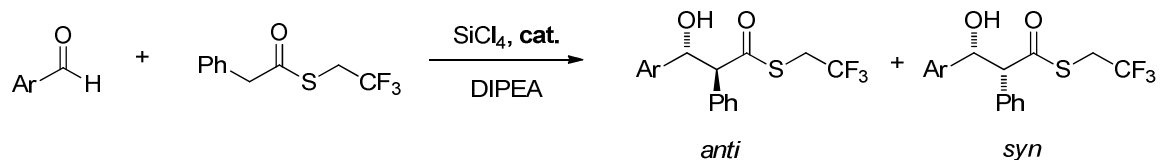
	MW	eq	mmol	mg	mL	d (g/mL)
2-phenylacetic acid	136.15	1	5	676	0.625	1.081
2,2,2-trifluoroethanethiol	116.11	1	5	580	0.445	1.305
HOBT	153.13	1.05	5.25	804		
EDC·HCl	191.70	1.05	5.25	431		
DCM					25	

To a solution of carboxylic acid in DCM was added HOBT at 0°C, and the resulting solution was stirred for 10 min at the same temperature. EDC·HCl was added and the mixture was stirred for 30 min at that temperature. Finally, 2,2,2-trifluoroethanethiol was added at 0°C, and the mixture was allowed to warm to room temperature. After being stirred overnight, the reaction mixture was diluted with DCM(10 mL) and water was added (10 mL). Aqueous layer was extracted with DCM, and the extract was washed with water and brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated in vacuum at room temperature to afford the crude product, that was purified by column chromatography to give the crude product. It was purified by flash column chromatography on silica gel with a 9:1 hexane/ethyl acetate mixture as eluent. Yield: 80%.

<sup>1</sup>H-NMR(300 MHz, CDCl<sub>3</sub>): δ 7.45-7.25 (m, 5H), 3.90 (s, 1H), 3.45 (q, *J* = 19.5 Hz, *J* = 9.9 Hz, 2H).

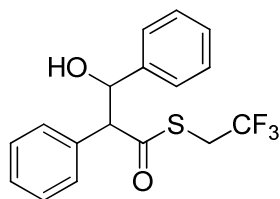
<sup>13</sup>C-NMR(75 MHz, CDCl<sub>3</sub>): δ 193.7, 132.4, 129.6, 128.8, 127.8, 124.6 (t, *J* = 275.8 Hz), 50.0, 30.8 (q, *J* = 34.1 Hz).

## 8.9 Aldol condensation of thioesters with aldehydes



*General procedure.* To a stirred solution of phosphine oxide (0.1 eq, 0.03 mmol) in the chosen solvent (2 mL), the thioester (2 eq, 0.60 mmol) and DIPEA (10 eq, 3 mmol) were added. The mixture was then cooled to the chosen temperature and freshly distilled tetrachlorosilane (1.5 eq, 0.45 mmol) was added dropwise *via* syringe. After 15 min, freshly distilled aldehyde (1 eq, 0.30 mmol) was added. The mixture was stirred for 5 h (if the operating temperature is 0°C) or 12 h (if the operating temperature is -25°C), then the same amount of tetrachlorosilane (1.5 eq, 0.45 mmol) was added. After a proper time (see tables of previous chapters) the reaction was quenched by the addition of a saturated aqueous solution of NaHCO<sub>3</sub> (3 mL). The mixture was allowed to warm up to room temperature and stirred for 30 min, then water (5 mL) and ethyl acetate (15 mL) were added. The two-layers mixture was separated and the aqueous layer was extracted with ethyl acetate (15 mL). The combined organic layers were washed with saturated NH<sub>4</sub>Cl (20 mL) and brine (20 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under vacuum at room temperature. The crude product was purified by column chromatography with different hexane:ethyl acetate mixtures as eluent to afford the pure aldol adducts.

Yield and ee for each reaction are indicated in the tables of previous chapters. The *syn:anti* ratio was calculated by <sup>1</sup>H-NMR spectroscopy. Phosphine oxides were quantitatively recovered by further elution with 10% MeOH in DCM without any loss of optical purity.

S-2,2,2-trifluoroethyl 3-hydroxy-2,3-diphenylpropanthioate (82)

This product was purified by flash column chromatography on silica gel with a 8:2 hexane/ethyl acetate mixture as eluent.

*major diastereoisomer*

$^1\text{H-NMR}$ (200 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.37 (s, 5H), 7.31 (s, 5H), 5.35 (d,  $J = 9.0$  Hz, 1H), 4.10 (d,  $J = 7.5$  Hz, 1H), 3.42-2.24 (m, 2H), 2.37 (br, 1H).

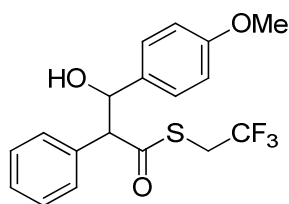
$^{13}\text{C-NMR}$ (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  195.42 (1C), 140.27 (1C), 133.58 (1C), 129.43 (2C), 128.89 (2C), 128.52 (2C), 128.39 (2C), 126.64 (2C), 126.23 (t,  $J = 281.2$  Hz, 1C), 75.01 (1C), 68.21 (1C), 30.50 (q,  $J = 33.75$ , 1C).

HRMS Mass (ESI+):  $m/z = \text{calc for } \text{C}_{17}\text{H}_{15}\text{F}_3\text{O}_2\text{S } 363.06425$ , found 363.0632 [ $\text{M} + \text{Na}$ ].

*minor diastereoisomer*

$^1\text{H-NMR}$ (200 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.36 (s, 5H), 7.30 (s, 5H), 5.20 (d,  $J = 10.0$  Hz, 1H), 4.15-3.90 (m, 2H), 3.6 (d,  $J = 4.8$  Hz, 1H), 1.73 (br, 1H).

The enantiomeric excess was determined by chiral HPLC with Daicel Chiralcel AD column [eluent: 9:1 hex/*i*-PrOH; 0.8mL/min flow rate, detection: 230 nm;  $t_{\text{R}}$ : 13.8 min (major-diast major),  $t_{\text{R}}$ : 15.1 min (minor-diast minor),  $t_{\text{R}}$ : 18.9 min (minor-diast major),  $t_{\text{R}}$ : 23.5 min (major-diast minor)].

*S*-2,2,2-trifluoroethyl 3-hydroxy-3-(4-methoxyphenyl)-2-phenylpropanthioate (83)

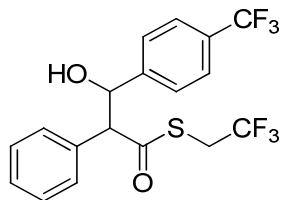
This product was purified by flash column chromatography on silica gel with a 9:1 hexane/ethyl acetate mixture as eluent afforded a mixture of *anti* and *syn* aldol adducts.

*syn:anti*mixture

<sup>1</sup>H-NMR(300 MHz, CDCl<sub>3</sub>): δ 7.45 (s, 5H), 7.25-7.15 (m, 3H), 6.90-6.80 (m, 2H), 5.33 (dd, *J* = 14.6 Hz, *J* = 8.1 Hz, 1H, *minor*), 5.14 (dd, *J* = 6.2 Hz, *J* = 3.3 Hz, 1H, *major*), 4.10-4.00 (m, 2H), 3.80 (s, 3H), 3.45-3.25 (m, 2H).

The enantiomeric excess was determined by chiral HPLC with Daicel Chiralcel AD column [eluent: 9:1 hex/ *i*-PrOH; 0.8mL/min flow rate, detection: 230 nm; *t*<sub>R</sub>: 23.2 min (major-dia<sup>st</sup> major), *t*<sub>R</sub>: 28.7 min(minor-dia<sup>st</sup> major), *t*<sub>R</sub>: 32.6 min (minor-dia<sup>st</sup> minor), *t*<sub>R</sub>: 39.1 min (major-dia<sup>st</sup> minor)].

*S*-2,2,2-trifluoroethyl 3-hydroxy-2-phenyl-3-(4 (trifluoromethyl)phenyl)propanethioate  
(84)



This product was purified by flash column chromatography on silica gel with a 9:1 hexane/ethyl acetate mixture as eluent afforded a mixture of *anti* and *syn* aldol adducts.

*syn:anti* mixture:

<sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ 7.56 (d, *J* = 8.2 Hz, 2H), 7.44-7.20 (m, 7H), 5.44 (d, *J* = 9.0 Hz, 1H, **major**), 5.37 (d, *J* = 10.8, 1H, **minor**), 4.02 (d, *J* = 7.0 Hz, 1H), 3.60-3.31 (m, 2H), 2.48 (s, 1H).

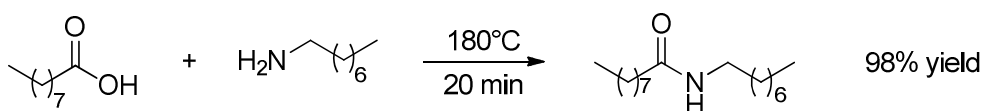
<sup>13</sup>C-NMR (125 MHz, CDCl<sub>3</sub>): δ 195.06, 144.04, 132.28, 128.93, 128.44, 128.22, 126.45, 124.72, 121.94, 76.56, 73.70, 67.25, 29.94.

HRMS Mass (ESI<sup>+</sup>): *m/z* = calc for C<sub>18</sub>H<sub>14</sub>F<sub>6</sub>O<sub>2</sub>SNa<sup>+</sup> 431.05, found 431.05.

The enantiomeric excess was determined by chiral HPLC with Daicel Chiralcel AD column [eluent:9:1 hex/*i*-PrOH; 0.8 mL/min flow rate, detection: 230 nm; *t<sub>R</sub>*: 37.2 min (minor-diast major), *t<sub>R</sub>*: 46.9 min (major-diast minor), *t<sub>R</sub>*: 51.2 min (major-diast major), *t<sub>R</sub>*: 64.9 min (minor-diast minor)].

**APPENDIX*****Cyclopropanone***

The broad importance of carboxylic acid derivatives, particularly amides in peptide bonds, has resulted in significant research efforts directed towards their synthesis. While the direct dehydrative coupling of a free carboxylic acid and nucleophile is one of the most attractive strategies towards this class of compounds, the poor leaving group ability of the hydroxide ion can require high temperatures for the direct coupling to proceed (Figure I). For the process to occur under milder conditions, carboxylic acids are generally activated by forming a more reactive species prone to nucleophilic acyl substitution. The simplest form of activation is protonation with a strong acid, however these reactions are often limited by requiring a large excess of the nucleophile as in the Fischer esterification, or are challenging due to the basicity of the nucleophile as in the case of amines.

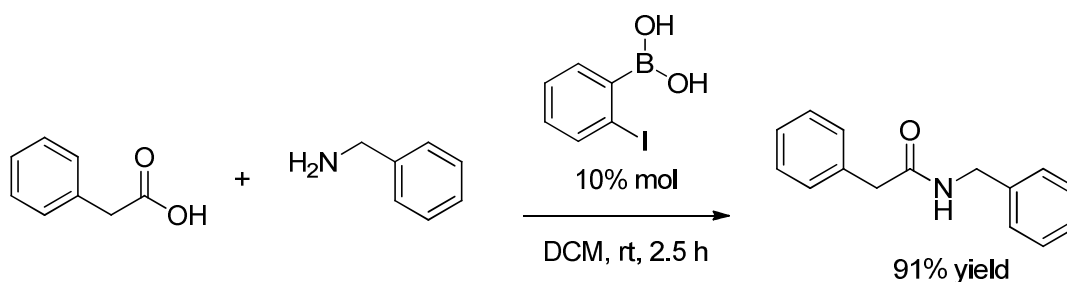
**Figure I**

A large number of stoichiometric coupling reagents have been developed to overcome this challenge and facilitate the direct coupling of carboxylic acids and nucleophiles. One of the earliest reported reagents for this goal was *N,N*-dicyclohexylcarbodiimide (DCC) which was first used in a peptide coupling by Sheehan in 1955.<sup>[108]</sup>

Since that disclosure, new reagents based on several different functionalities have been developed and often have tailored properties such as water solubility, low racemization, or are designed to be particularly effective for solid-phase synthesis. Most of these compounds however suffer from drawbacks in that they are relatively expensive and have poor atom economy, producing chemical by-products that can in some cases be challenging to remove.

Recent progress has been made towards the development of catalysts for direct acyl substitution that overcome the limitations of stoichiometric coupling reagents.<sup>[109]</sup>

Particularly noteworthy, Hall and coworkers have developed boronic acid catalysts, specifically *ortho*-iodophenylboronic acid, to facilitate the direct condensation of an amine and carboxylic acid at ambient temperature (Figure II).<sup>[110]</sup> These catalysts have not yet been successfully applied for mild peptide couplings, a severe limitation of the method.

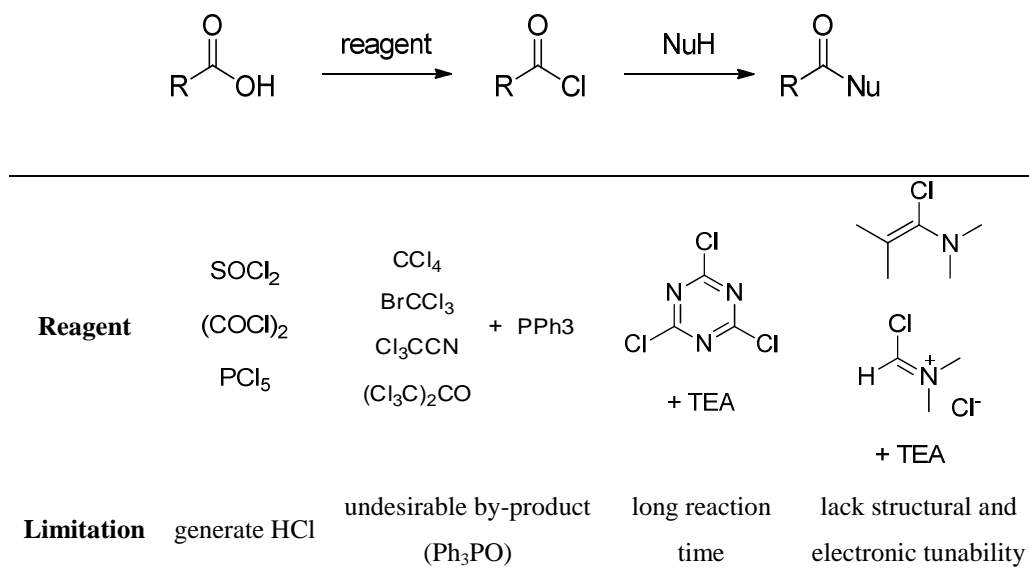


**Figure II**

One of the oldest and most common strategies for achieving nucleophilic acyl substitution is conversion of a carboxylic acid to an acid halide. The high reactivity and the ease with which they can be transformed to almost all other carboxylic acid derivatives has given acyl halides a prominent place in organic chemistry. Many dehydrative conditions for



forming acid chlorides, such as the use of thionyl chloride, oxalyl chloride, and phosphorous chloride, are classic reactions found in introductory textbooks (Figure III).<sup>[111]</sup> The majority of these traditional methods however suffer from the generation of an equivalent of hydrochloric acid, making them incompatible with acid sensitive functionalities.



**Figure III**

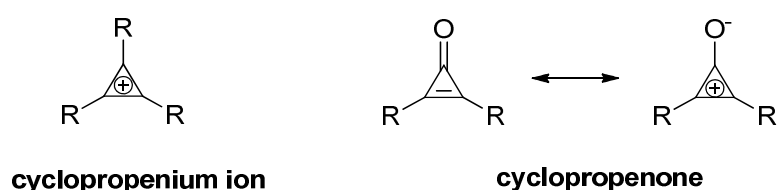
Several methods have been developed to allow the formation of acid chlorides under neutral conditions, but many have significant limitations. One common strategy relies on the formation of adducts with triphenylphosphine,<sup>[112-115]</sup> however the triphenylphosphine oxide by-product of these reactions is notoriously difficult to remove.

Other methods, such as the combination of cyanuric chloride and trialkylamine bases, suffer from long reaction times. High reactivity for forming acid chlorides under mild conditions has seldom been achieved, with exceptions being the use of tetramethyl- $\alpha$ -halogenoamines<sup>[116]</sup> or an immonium chloride with amine base.<sup>[117]</sup> These methods however both rely on reagents that lack easily modifiable structural and electronic properties, useful features for the development of synthetic methods.

A new method that improves on these deficiencies for forming acyl chlorides would be of great utility to the synthetic community. Also, new reagents that produce traceless or

recyclable by-products would be a significant benefit compared to many of the coupling reagents currently used for forming carboxylic acids derivatives.

The Lambert group recently initiated a research program utilizing aromatic ions for the development of new synthetic methods.<sup>[118-123]</sup> These compounds are interesting molecules that satisfy Hückel's rule for possessing aromatic stabilization and have an ionic charge. Within this program my research has focused on aromatic cations, primarily cyclopropenium ions and related cyclopropenones (Figure IV).



**Figure IV**

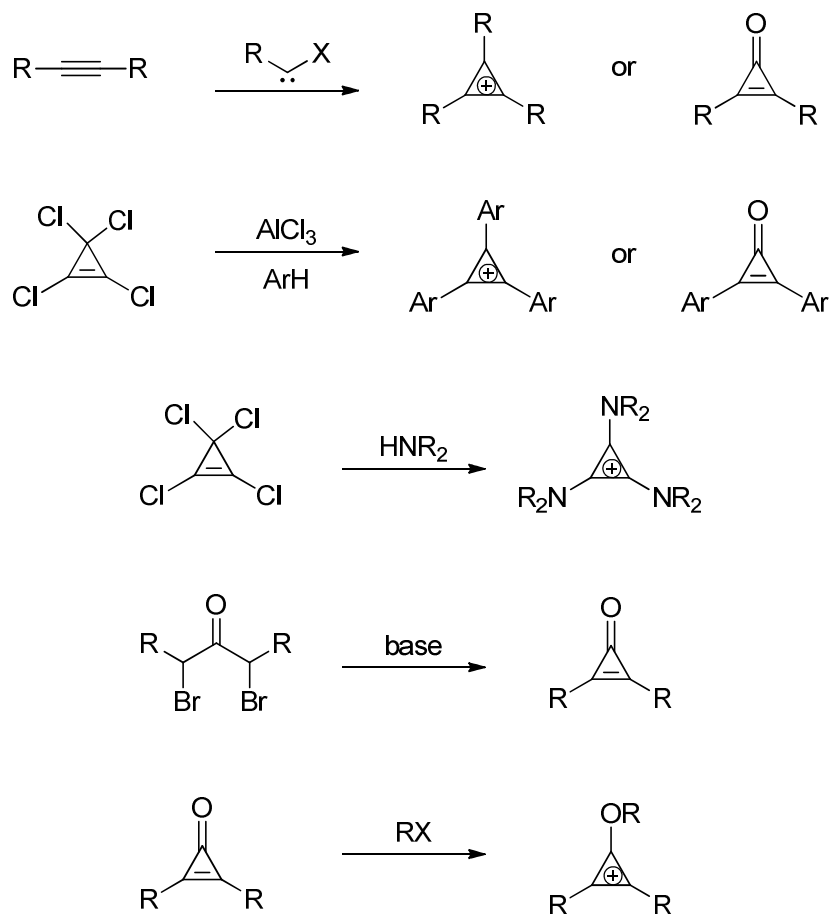
Cyclopropenium cations, the smallest aromatic ion, and cyclopropenones have been well studied since Breslow first synthesized the triphenylcyclopropenium ion in 1957.<sup>[124,125]</sup> A number of different methods have been developed to construct these compounds and permit a wide range of substitution (Figure V). Carbene addition to alkynes, the first approach to these structures, can be used to make both symmetric and unsymmetric cyclopropenium cations and cyclopropenones.

These compounds can also be created from tetrachlorocyclopropane, a versatile commercially available starting material that already incorporates the three-membered ring.<sup>[126]</sup> Treatment of this compound with aluminum trichloride generates an electrophilic trichlorocyclopropenium species that undergoes Friedel-Crafts arylations. Secondary amines can also be incorporated as they undergo substitution reactions with chlorocyclopropanes.<sup>[127]</sup>

One method that has been particularly useful for the large-scale syntheses of cyclopropenones is a Favorskii-type reaction of  $\alpha,\alpha'$ -dibromoketones.<sup>[128]</sup>

Cyclopropenones can also be converted to cyclopropenium ions through O-alkylation of the carbonyl to furnish cyclopropenium ethers.<sup>[129]</sup>

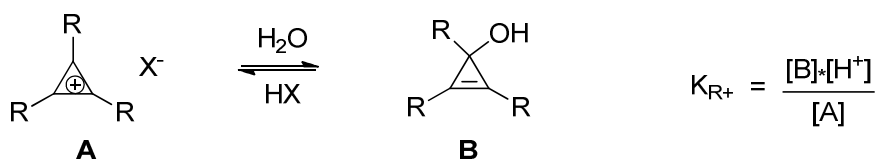
The flexibility provided through these multiple synthetic routes has facilitated detailed studies of the properties of these compounds.



**Figure V**

A particularly interesting feature of cyclopropenium cations is an equilibrium in which they shuttle between neutral and charged states through association with electron lone pairs or anions (Figure VI). The electronics governing this equilibrium can be evaluated through a cation's  $pK_{R^+}$  value, a measure that corresponds to the pH of an aqueous solution where the aromatic charge is half neutralized.<sup>[130]</sup> The  $pK_{R^+}$  value can also be interpreted as a measure of cation stability. While the parent unsubstituted cyclopropenyl cation is relatively unstable with a  $pK_{R^+}$  of  $-7.4$ ,<sup>[131]</sup>  $pK_{R^+}$  values range to greater than  $+10$  in the case of trisaminocyclopropenium ions, which are even stable in hot water.<sup>[132]</sup>

The tunability with regard to electronic and steric properties achievable by adjusting the ring substituents, in combination with the existing equilibrium process, makes these compounds attractive as potential reagents for organic synthesis.



**Figure VI**

In researching the application of aromatic ions as synthetic reagents, the Lambert group has initially focused on dehydrative reactions (Figure VII). Towards this goal, alcohols were found to rapidly react with cyclopropenes bearing geminal leaving groups to form cyclopropenium ethers. These cationic species effectively activate the alcohol towards nucleophilic substitution and this strategy has been employed to develop mild methods for the rapid chlorination of alcohols and the cyclization of diols.<sup>[119,123]</sup>

Cyclopropenium activation has also been extended to dehydrative molecular rearrangements in the form of the Beckmann rearrangement, rapidly converting oximes to amides.<sup>[121]</sup> As the derivatization of carboxylic acids is a dehydrative process with great importance in organic synthesis, we were interested in exploring the application of this strategy to nucleophilic acyl substitution.

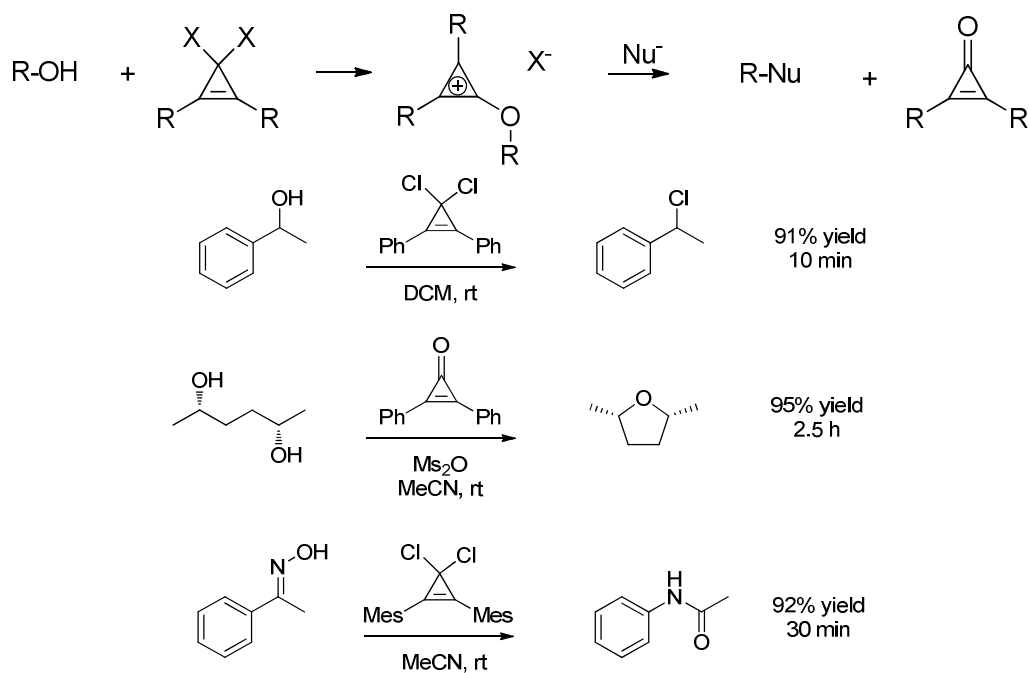


Figure VII

Analogous to the activation of alcohols, they envisioned that a cyclopropene bearing geminal leaving groups, formed from the corresponding cyclopropanone, would exist in equilibrium with its ionized form (Figure VII). Reaction with a carboxylic acid would furnish a cyclopropenium carboxylate intermediate. This species was then expected to be prone to nucleophilic acyl substitution, generating a cyclopropanone and the desired carboxylic acid derivative. While this strategy had been successful for the activation of alcohols, it was not clear if it would function for mechanistically distinct acyl substitution. The previous use of dichlorocyclopropene reagents prompted us to examine the formation of acid chlorides as a starting point for the study of this new reaction scheme.

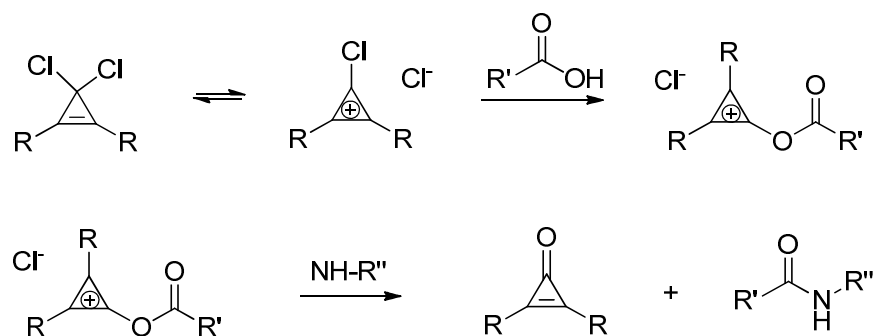


Figure VIII

The group have also demonstrated aromatic cation activation as an effective strategy for nucleophilic acyl substitution.<sup>[118]</sup> Using tunable and recyclable carbon-based reagents that are compatible with amine bases, they developed a rapid and mild method for forming acid chlorides that is compatible with a range of acid-sensitive functional groups.

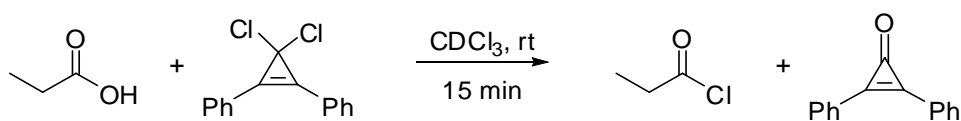


Figure IX

They recently proved that treatment of propionic acid with 1.2 equivalents of 3,3-dichloro-1,2-diphenylcyclopropene in CDCl<sub>3</sub> at room temperature gave quantitative conversion to propionyl chloride and 2,3-diphenylcyclopropanone within 15 minutes, as observed by <sup>1</sup>H NMR (Figure IX).

They hypothesized that treatment of a carboxylic acid with a cyclopropene bearing geminal leaving groups (X) would produce a cyclopropenium carboxylate intermediate. Nucleophilic acyl substitution of this intermediate would then produce a carboxylic acid derivative and cyclopropanone (Figure X).

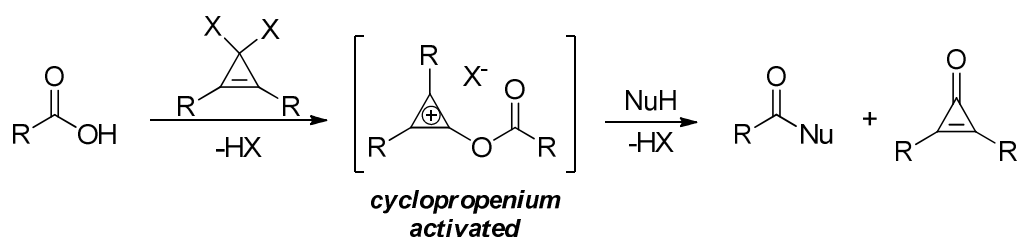
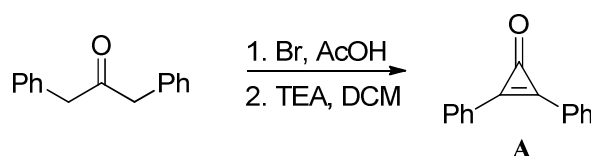


Figure X

The dichlorocyclopropane reagents were quantitatively formed *in situ* at room temperature within 10 min through the action of oxalyl chloride on a solution of the corresponding cyclopropenone.

In this contest, my work was focused on the research of new and mild activating agent for cyclopropenone, which allows the formation of cyclopropenium carboxylate intermediate, the effectively reactive species in the nucleophilic acyl substitution.

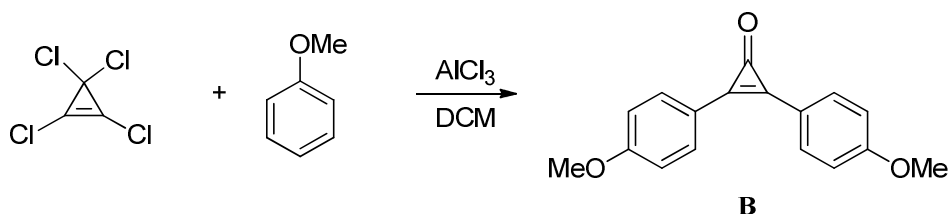
First of all, different cyclopropenones were prepared.



**Figure XI**

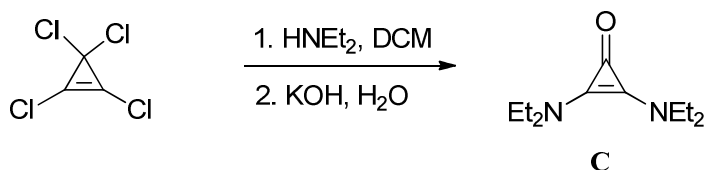
The reaction between 1,3-diphenyl acetone and bromine in glacial acetic acid affords the intermediate 1,3-dibromo-1,3-diphenylpropan-2-one as a white solid, which was then converted in diphenyl cyclopropenone **A** by treatment with triethylamine in 48% overall yield (Figure XI).

2,3-Di(4-methoxyphenyl)cyclopropenone (**B**) was synthesized starting from tetrachlorocyclopropane by reaction with anisole in presence of anhydrous aluminum chloride in 76% yield (Figure XII).

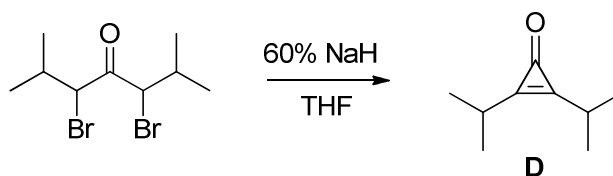


**Figure XII**

The same starting compound was employed for preparing compound **C** by reaction with an excess of diethylamine, followed by basic hydrolysis in the presence of KOH (Figure XIII).

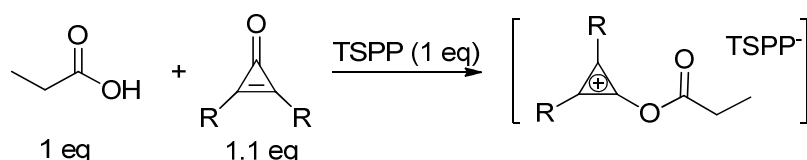
**Figure XIII**

Then the 3,5-dibromo-2,6-dimethylheptan-4-one was converted in the desired diisopropylcyclopropane **D** by simple treatment with NaH in tetrahydrofuran in 28% yield.

**Figure XIV**

The first idea was to explore the use of commercially available tetra sodium pyrophosphate (TSPP) as activating agent, for the reason that, thanks to its cheapness and very low toxicity, would open the way for many applications in pharmaceutical chemistry.

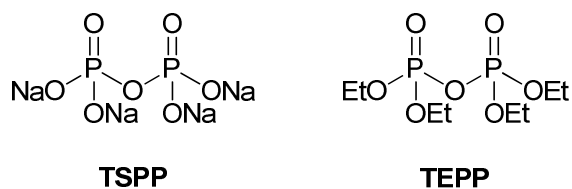
We tested this compound in the amidation protocol, developed in this laboratory: a stoichiometric amount of sodium pyrophosphate was added to a solution of cyclopropenone.<sup>[118]</sup> After 15 min a solution of carboxylic acid and then triethylamine and benzylamine were added and the mixture was stirred overnight (Figure XV).



By running the reaction with all cyclopropenones synthesized (**A-C**) in different solvents, this procedure unfortunately did not afford the desired product, allowing only the



recovery of the unreacted starting compounds. Also changing the carboxylic acid or the amines the result didn't change: in all cases the starting materials were recovered.

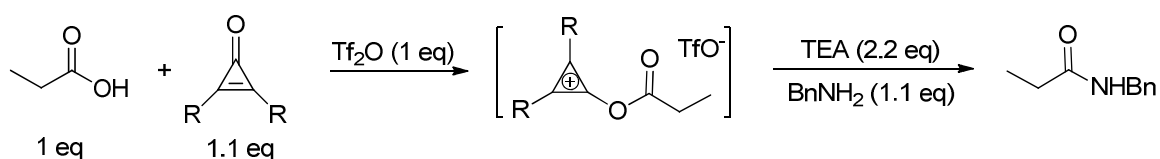


**Figure XVI**

Therefore, in order to overcome the problem associated to the low solubility of sodium pyrophosphate in organic solvents, we prepared tetraethyl pyrophosphate (TEPP), by copper bromide catalysed aerobic oxidative coupling of phosphonic acid diethyl ester in presence of TMEDA, leading to the pyrophosphate in 84% yield.

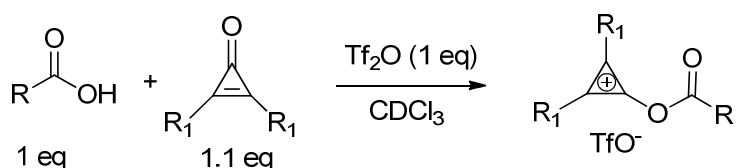
We subsequently performed the same set of experiment using TEPP, but once again the amidation reaction didn't take place.

Looking for a different strategy, we decided to explore the use of trifluoromethansulfonic anhydride as activating agent in the amidation protocol. To a solution of cyclopropanone and triflic anhydride propionic acid, TEA and benzylamine were added in this order with the goal of obtaining *N*-benzylpropionamide (Figure XVII).



**Figure XVII**

Also in this case we did not observe the desired product. For this reason we decided to take a step backwards and carried out some analysis by using NMR spectroscopy to identify the problematic step.

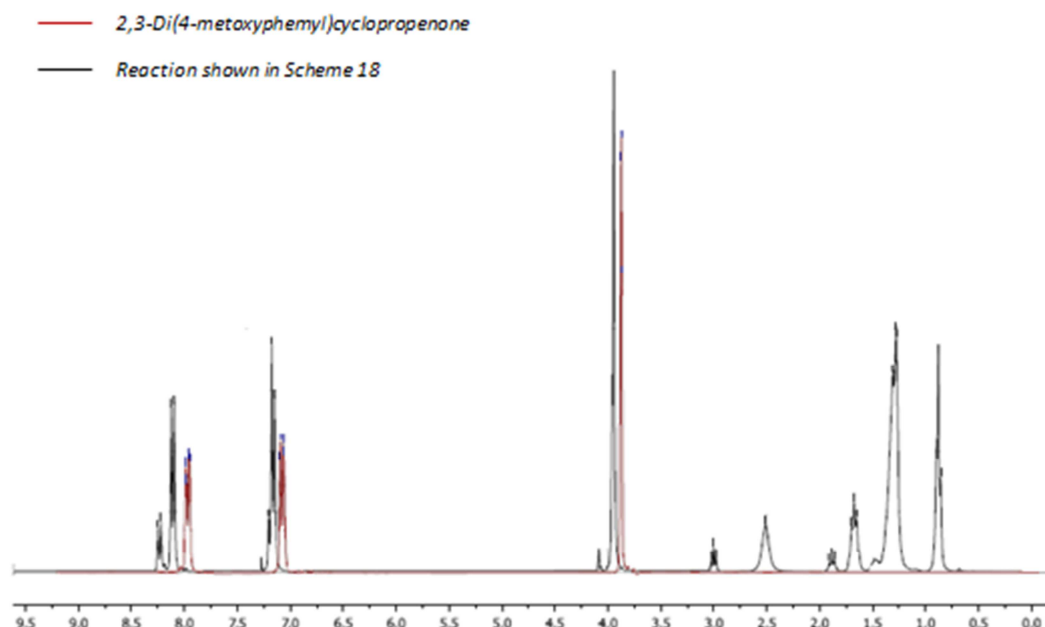


**Figure XVIII**

By running the experiment shown in Figure XVIII with various substrates, instead of the expecting activated cyclopropemium, we observed the formation of two different species, as confirmed by both  $^1\text{H}$  and  $^{13}\text{C}$  NMR, both showing a limited stability.

The ratio between these two species was different in each experiment, even if they were conducted under the same reaction conditions. We were therefore unable to determine the structures of the adducts but, in any case, the subsequent addition of the amine did not lead to the formation of the desired product.

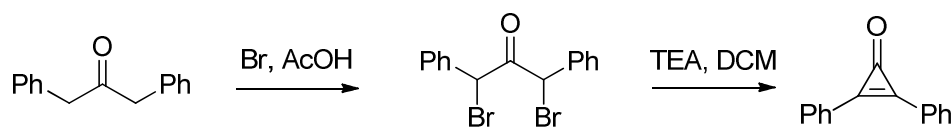
The reaction between 2,3-di(4-methoxyphenyl)cyclopropenone and octanoic acid in presence of triflic anhydride in  $\text{CDCl}_3$  led to the  $^1\text{H}$  NMR spectrum shown in Figure XIX.

**Figure XIX**

As Figure XIV clearly shown, all the proton signals related to the cyclopropenone species were affected by a downfield shift. It is also possible observe the presence of a second set of signals related to a second species.

## Experimental Section

### 2,3-Diphenylcyclopropenone



	MW	eq	mmol	g	mL	d (g/mL)
1,3-diphenyl acetone	210.27	1	8.3	1.7	1.6	1.069
bromine	79.9	2.1	17.4	2.7		3.103
acetic acid					18	
TEA	101.19	2.1	17.4			0.726

*Step 1.* 1,3-diphenyl acetone was added to a 100-mL round-bottomed flask, followed by glacial acetic acid (6 mL). A dropping funnel containing bromine in glacial acetic acid (12 mL) was fitted to the flask. The solution was added over a period of 15 min at 23 °C. After addition was complete, the mixture was stirred for an additional 15 min. The mixture was then poured into water (25 mL). Solid Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> was added to the mixture until the initial yellow color disappeared and the mixture was allowed to stand for 1 h. The light yellow solid was filtered and air-dried. The yellow solid was recrystallized from petroleum ether (with a few drops of benzene), and dried under vacuum to afford the intermediate di-bromide as a white solid with 79% yield.

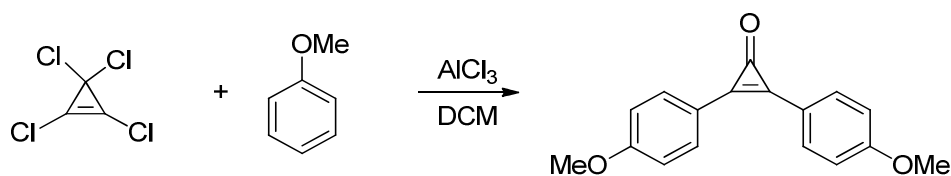
*Step 2.* To a 100-mL round-bottomed flask containing CH<sub>2</sub>Cl<sub>2</sub> (5 mL), was added triethylamine (24.0 mL, 172 mmol). The flask was fitted with a dropping funnel containing the intermediate di-bromide (24.0 g, 65.2 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (110 mL). This solution was added over 1 h. After addition was complete, the solution was stirred for an additional 30 min. The red mixture was then washed with 3 N HCl (3 x 40 mL). The organic layer was transferred to a 500- mL Erlenmeyer flask and cooled to 0 °C in an ice bath. To this stirring solution was slowly added a cold solution of sulfuric acid (12.5 mL)

in water (6 mL). Upon addition, a pink precipitate formed, which was collected on a fritted funnel and washed with CH<sub>2</sub>Cl<sub>2</sub>. The solid was returned to the flask and diluted with CH<sub>2</sub>Cl<sub>2</sub> (60 mL) and water (125 mL). After neutralization by addition of Na<sub>2</sub>CO<sub>3</sub> (1.1 g) in small portions, the layers were separated and the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 60 mL). The combined organics were washed with brine (100 mL), dried (MgSO<sub>4</sub>) and concentrated under vacuum to afford a pink solid. The crude pink solid was purified by silica gel chromatography (50%-100% EtOAc:hexanes) to provide the title compound as a white solid.

Flash chromatography (diameter: 2.5 cm, h: 17 cm): a purification through silica gel chromatography with 8:2 hexane/AcOEt as eluent allowed to obtain the product in 60% yield.

<sup>1</sup>H-NMR (400MHz, CDCl<sub>3</sub>): δ 7.97-7.94 (m, 4H), 7.57-7.55 (m, 6H).

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 155.7, 148.3, 132.6, 131.4, 129.3, 124.0. δ 7.24-7.78 (m, 10H), δ 4.78 (s, 2H), δ 3.98 (s, 3H).

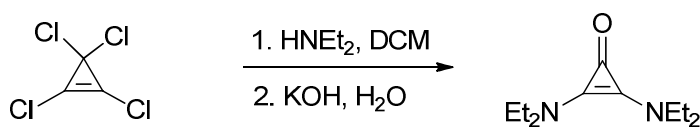
2,3-Di(4-methoxyphenyl)cyclopropanone

	MW	eq	mmol	mg	mL	d (g/mL)
terachlorocyclopropane	177.84	1	2.6	500		
Anisole	108.14	2	5.3	572	575	0.995
AlCl <sub>3</sub>	133.24	1.1	2.8	370		
DCM					6	

A solution of anisole in 1 mL of dichloromethane was added dropwise to a stirred suspension of tetrachlorocyclopropane and anhydrous aluminum chloride in 5 mL of dichloromethane at -78°C. The mixture was stirred for 2 h and cooling bath was removed. Reaction mixture was stirred at room temperature until TLC showed complete consumption of the aromatic compound. The reaction mixture was poured into 10 mL of water, organic layer was separated, aqueous layer was extracted with two 10 mL portions of dichloromethane, combined organic layers were washed with 15 mL of brine, and dried with anhydrous sodium sulfate. Solvent was removed in vacuum, crude cyclopropanone recrystallized from hexanes-dichloromethane mixture. Yield 76%.

<sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>): δ 3.91 (s, 3H), 7.05 (d, *J*=8.8, Hz, 2H), 7.92 (d, *J*=8.8 Hz, 2H).

<sup>13</sup>C NMR (100MHz, CDCl<sub>3</sub>): δ 55.7, 114.1, 114.9, 117.3, 133.7, 144.3, 155.5, 162.9.

2,3-Bis-diethylaminocyclopropanone

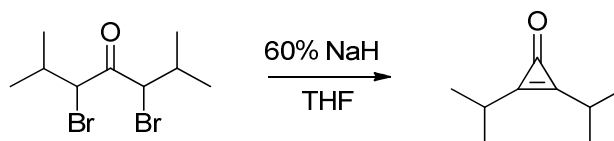
	MW	eq	mmol	mg	mL	d (g/mL)
tetrachlorocyclopropene	177.84	1	2.6	500		
diethylamine	73.14	5	13	949	1.3	0.707
DCM					6	

*Step 1.* Excess diethylamine was added to tetrachlorocyclopropene in dichloromethane at 0°C and stirred at this temperature for 5 hours, then at room temperature overnight and then refluxed for 3 hours. After cooling to room temperature, 70% perchloric acid was added to the solution followed by further stirring for several minutes. The organic layer was separated and dried over sodium sulfate. After removal of the solvent, trisdimethylaminocyclopropenyl perchlorate was quantitatively obtained.

<sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>) δ 1.30 (t, 3H, J = 6.5 Hz), 3.36 (q, 2H, J = 6.5 Hz)].

*Step 2.* Hydrolysis of this salt in 15% aqueous KOH at 65 °C for 2 hour provided, after evaporative distillation (130°C, 0.3 mm), the bis-diethylaminocyclopropanone in 81% yield.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.2 (t, 3 H, J= 7 Hz), 3.25 (q, 2H, J=7 Hz).

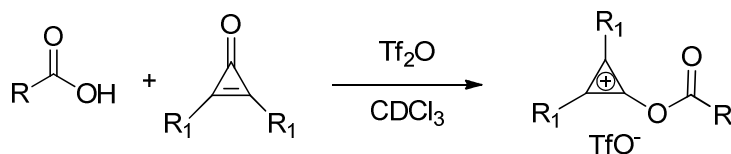
2,3-Diisopropylcyclopropenone

	MW	eq	mmol	g	mL	d (g/mL)
3,5-dibromo-2,6-dimethylheptan-4-one	300.03	1	5.7	1.7		
60% NaH	23.99	2	11.4	0.164		
THF					12	

At  $-80^{\circ}\text{C}$ , NaH (60% suspension in oil ) was added to 3,5-dibromo-2,6-dimethylheptan-4-one in tetrahydrofuran over a period of three hours. The resulting mixture was stirred overnight at ambient temperature. The mixture was then cooled at  $-78^{\circ}\text{C}$  and 2 mL of 10% HCl was added dropwise. The solution was allowed to warm to ambient temperature and the precipitated salts were filtered off and washed with tetrahydrofuran. The washings and filtrate were combined, and the tetrahydrofuran was removed in vacuo. The resulting yellow oil was redissolved in petroleum ether and any residual NaBr filtered off. The cyclopropenone was extracted with portions of water (2 x 10 mL) and then extracted from the water with  $\text{CH}_2\text{Cl}_2$  (2 x 10 mL). The solvent was removed in vacuo to leave a pale yellow oil. Yield 28%.

$^1\text{H-NMR}$  (400 MHz  $\text{CDCl}_3$ ):  $\delta$  2.76 (septet,  $J = 7$  Hz, 2H ), 1.09 (d,  $J = 7$  Hz, 12H).

$^{13}\text{C-NMR}$  (100 MHz  $\text{CDCl}_3$ ):  $\delta$  163.4, 159.3, 27.1, 20.2.

NMR Experiment General Procedure

Carboxylic acid (7.5  $\mu\text{L}$ , 0.10 mmol) was added to cyclopropanone (31.3 mg, 0.12 mmol) in  $\text{CDCl}_3$  (1 mL). The reaction was transferred to an NMR tube under Ar and monitored by  $^1\text{H}$  NMR.

Amidation General Procedure

Activating agent (1 equiv) was added to a solution of diisopropylcyclopropanone (1.1 equiv) in chosen solvent (0.2 M) at room temperature. After 15 min, a solution of carboxylic acid (1 equiv) and triethylamine (2.2 equiv) in solvent (0.2 M) was added in one portion. After stirring for 5 min, the amine (1.1 equiv) was added in one portion. The reaction was diluted with  $\text{CH}_2\text{Cl}_2$  to 3 times the reaction volume and washed with saturated  $\text{NaHCO}_3$  and brine. The organic phase was dried with  $\text{Na}_2\text{SO}_4$  and concentrated. The crude residue was analyzed by NMR spectroscopy.



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## **LIST OF COMMON ABBREVIATIONS**

Ac	acetyl
AcOEt	ethyl acetate
DBU	1,8-diazaabicycloundec-7-ene
DCM	dichloromethane
DIPA	<i>N,N</i> -diisopropylamine
DIPEA	<i>N,N</i> -diisopropylethylamine
DMF	<i>N,N</i> -dimethylformamide
DMSO	dimethylsulfoxide
EDC	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide chlorohydrate
ee	enantiomeric excess
Et	ethyl
eq	equivalent



HOBT	1-hydroxybenzotriazole hydrate
<i>i</i> -PrOH	<i>iso</i> -propanol
LDA	lithium diisopropylamide
MeOH	methanol
<i>n</i> -Hex	<i>normal</i> -hexane
PMP	<i>p</i> -methoxy-phenyl
PPA	polyphosphoric acid
Py	pyridine
rac	racemic
rt	room temperature
TEA	triethylamine
THF	tetrahydrofuran
TFA	trifluoroacetic acid