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EXPLORING NOVEL ORGANOCATALYTIC METHODOLOGIES FOR CARBON-NITROGEN DOUBLE BOND REDUCTION

Tesi di Dottorato di

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To my family and friends

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Introduction

"Creative people see Prometheus
in a mirror, never Pandora."
David Brin, Brightness Reef

"Chemistry is so all pervading in our lives, that it often passes unnoticed", says Jean-Marie Lehn, French Nobel Prize laureate in chemistry in 1987. "A world without chemistry would be a world without synthetic materials and that means no telephones, computers, aspirin, soap, paper or books".[1] However, just like the mythical Janus, chemistry can show two opposite faces: one embodying the extraordinary benefits to humanity, the other the harm caused by pollution.

Therefore it's important for a chemist to be aware that his work is not limited at the development of a new material, but it also has an impact, directly or not, on the environment. For that reason a global picture of the process of production is needed even at laboratory scale, covering not only the application of the products but also its byproducts and wastes.

Consequently, over the last two decades, an ever increasing interest towards a sustainable chemistry has risen, aiming at new chemical processes that are more eco-compatible while remaining profitable. This approach, more precisely defined as "green chemistry", regards the design of chemical products and processes that reduce or eliminate the use and generation of hazardous substances. Green chemistry applies across

the life cycle of a chemical product, including its design, manufacture and use,[2] and it's based on the twelve principles defined by Anastas and Warner in 1998:

1. **Prevention**

   It's better to prevent waste than to treat or clean up waste afterwards

2. **Atom economy**

   Design synthetic methods to maximize the incorporation of all materials used in the process into the final product

3. **Less hazardous chemical syntheses**

   Design synthetic methods to use and generate substances that minimize toxicity to human health and the environment

4. **Designing safer chemicals**

   Design chemical products to effect their desired function while minimizing their toxicity

5. **Safer solvents and auxiliaries**

   The use of auxiliary substances (e.g., solvents, separation agents, etc.) should be kept to a minimum wherever possible and innocuous when used

6. **Design for energy efficiency**

   Minimize the energy requirements of chemical processes and carry out synthetic methods at ambient temperature and pressure if possible

7. **Use of renewable feedstocks**

   A raw material or feedstock should be renewable rather than depleting whenever technically and economically practicable

8. **Reduce derivatives**

   If possible, minimize or avoid unnecessary derivatization (use of blocking groups, protection-deprotection, temporary modification of physical/chemical processes), which requires additional reagents and generate waste

9. **Catalysis**

   Catalytic reagents are superior to stoichiometric reagents

10. **Design for degradation**

    Design chemical products so that they break down into innocuous products that do not persist in the environment

11. **Real-time analysis for pollution prevention**

    Analytical methodologies need to be further developed to allow for real-time, in-process monitoring and control prior to the formation of hazardous substances

12. **Inherently safer chemistry for accident prevention**

    Choose substances and the form of a substance used in a chemical process to minimize the potential for chemical accidents, including releases, explosions and fires

In particular, pharmaceutical R&D has been devoting increasing efforts to the study of green chemistry due to the environmental protection laws and the increasing regulatory requirements that force the companies to develop and study single-enantiomer drugs.[3] Specifically, the enantioselective reductions of carbon-nitrogen double bond are frequently used as the key step in the stereoselective synthesis of a variety of bioactive molecules such as alkaloids, natural products, drugs and medical agents.[4] Also for economical reasons, the ability to direct the synthesis towards only one out of all the possible stereoisomers of a compound is an essential issue in the pharmaceutical industry. However, the stereochemical control of a reaction remain a challenging task and, in principle, the employment of a "chiral technology" is the most attractive procedure to perform this kind of transformations.[5] Recent market analysis showed that global revenues from chiral technology soared from $6.63 billion in 2000 to $16.03 billion in 2007, growing at a compound annual rate of 13.4% during that period. Approximately 80% of all products currently in development for the pharmaceutical industry are based on chiral building blocks.[6]

Chiral organocatalysis provides an elegant way to combine the fulfilling of many of the twelve principles listed above with the necessity to perform the reactions in a highly stereocontrolled fashion.

By definiton, the use of a catalytic methodology is *green*, because it increases energy efficiency and diminishes waste compared to processes that employ stoichiometric reagents. Since a catalyst often allows to run a reaction in milder conditions, this approach offer remarkable advantages from the economic and energetic point of view. At the same time, catalytic enantioselective reactions provide the most efficient method for the synthesis of chiral compounds, because the employment of just small amounts of chiral sources can result into the preparation of large quantities of chiral compounds.[7] Thus, keeping at a minimum the stoichiometric use of chiral auxiliaries, this route provides the best outcome in terms of atom economy. Moreover, the average number of manipulations required to synthesize an active pharmaceutical ingredient continues to grow: catalysis can constitute an attractive solution for companies willing to address the problem of the increasing complexity of the chemical targets.

Due to these significant advantages, paired with the continuous discovery of new catalysts by both academia and industry, enantioselective catalysis has become of fundamental importance not only for pharmaceutical companies, as clearly demonstrate by the fact that over 90% of chemicals derive, to some extent, from a catalytic process.[8] Anyway, amongst the catalytic methodologies, organocatalysis offers further benefits when compared to two other major catalytic techniques: metal-complex-mediated and enzymatic catalysis.[9]

In spite of their established role, there is not a generally accepted definition of what are the features of organic catalysts. One of the first definitions describe the organocatalyst as a purely "organic" molecule, that is composed of (mainly) carbon, hydrogen, nitrogen, oxygen, sulfur and phosphorus. Clearly, this definition is incomplete, because does not consider what these molecules are able to do. So, a more recent one defines an organic catalyst as "an organic compound of relatively low molecular weight and simple structure, capable of promoting a given transformation in substoichiometric quantity".[10] Implicitly, the term "organic" emphasizes the advantages of performing a catalytic reaction under metal-free conditions.

Organocatalysts are usually robust, inexpensive, readily available and non-toxic species. Moreover, demanding reaction conditions such as inert atmospheres, low temperatures and dry solvents in many instances are not required, because organocatalysts are generally inert towards moisture and oxygen.

In particular, the use of toxic transition metals often presents leaching problems, which could result into contamination of the product. Organocatalysts might represent a solution to this problem, making them an attractive alternative for the preparation of compounds the use of which can't tolerate metal contamination, (e.g. pharmaceutical products) or in processes where the purification and the elimination of metals are one of the main expensive steps. Besides, transition metal catalyst are generally quite expensive species, typically constituted by an enantiomerically pure ligand, whose synthesis may be long and difficult, and a metal species, in many cases a precious element. Therefore the possibility of the poisoning of catalysts by compounds containing nitrogen and sulfur atoms constitutes a serious issue in some applications.[11]

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.[12]

At the same time, even if only in some cases they display the remarkable selectivity peculiar of enzymes, organic catalysts are generally more stable and offer a broader scope than bioorganic catalysts.

Finally organocatalysts show advantages also for their immobilization on a support, which is a very appealing feature because it can facilitate catalyst's recovery and recycling. In fact, organic catalysts are more readily amenable to anchoring on a support than both metal-based and biocatalysts. Supporting an enzyme can have a deeper impact on its complex structure (and, hence, on its properties) than on the simpler skeleton of an organic derivative. Moreover, the small size of an organocatalyst allows an easier introduction of several units on a polyvalent support. On the other hand, the recycling of a metal-based catalyst immobilized on a support often requires catalyst regeneration by metal replenishment due to the extensive metal leaching.[10a]

Considering all these advantages, it's not surprising that in recent years this field of research has attracted the attention of many research groups. Extraordinary efforts are currently being devoted to the study and the development of novel and alternative synthetic organocatalytic stereoselective methodologies.[13] Several comprehensive publications, that give a full account of the organocatalysis field, are available.[14]

In this context, it is clear how the catalytic synthesis of chiral amines can be considered a fundamental process. In the following chapters, the enantioselective reduction of carbon-nitrogen double bond promoted by organocatalysts will be briefly discussed, focusing primarily on three methodologies: the Frustrated Lewis Pairs (FLP) method, the use of binaphthol-derived phosphoric acids in the presence of a dihydropyridine-based compound, and the use of activated trichlorosilane.

CHAPTER 1

Catalytic hydrogenation of C=N double bonds with frustrated Lewis pairs systems

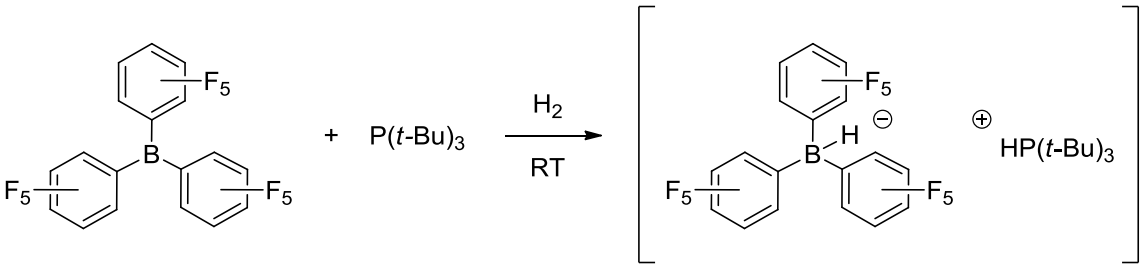
"It is through science that we prove,
but through intuition that we discover."
Henri Poincaré

The use of H_2 as a reducing agent for unsaturated substrates is so widespread it can be considered as perhaps the most important catalytic method in synthetic organic chemistry.[15]

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, commodity, and fine chemicals.[15] 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.

Recently, studies have been directed to the exploitation of non-transition metal systems for the activation of H_2 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. Such systems have been termed ''frustrated Lewis pairs'' or ''FLPs''.[16] 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 (Scheme **1.1**), an accomplishment that was long thought to be the exclusive characteristic of transition metals.



Scheme 1.1 Hydrogen activation promoted by frustrated Lewis pair

Computational studies[17] suggest the generation of a phosphine-borane "encounter complex", stabilized by H···F interactions. 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_2 in the reactive pocket between the donor and acceptor sites (Figure **1.1**) results in heterolytic cleavage of H_2; according to the proposal FLPs fulfill a similar function as the frontier orbitals on transition metals.

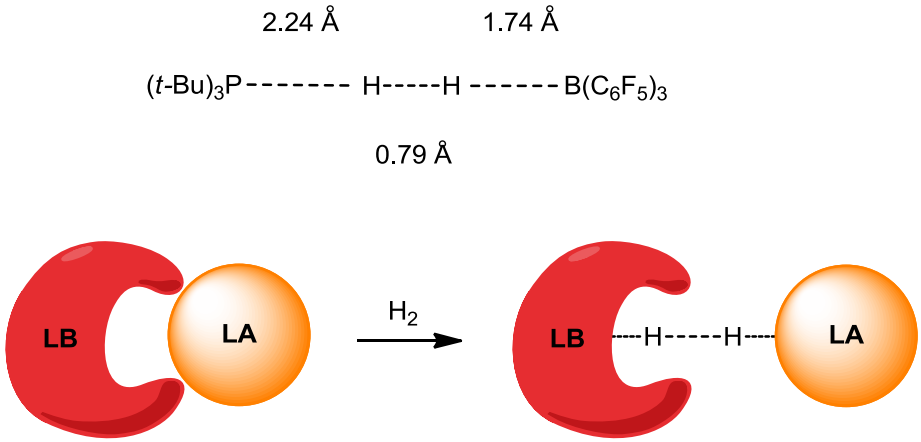


Figure 1.1 Schematic representation of H_2 interaction in the reactive pocket

The mechanism of the H_2 activation is still disputed in the literature, but it can be understood by the interaction of the Lewis base's highest occupied molecular orbital

(HOMO) with the lowest unoccupied molecular orbital (LUMO) of the H_2 (Figure **1.2**, left) diminishing the H–H σ-bond energy. Simultaneously, the Lewis acid interacts with its LUMO with the HOMO of H_2, also weakening the H–H σ-bond (Figure **1.2**, right).[18] Such simultaneous interaction reminds of the binding situation in metal carbonyl complexes and can be described as synergistic activation.[19]

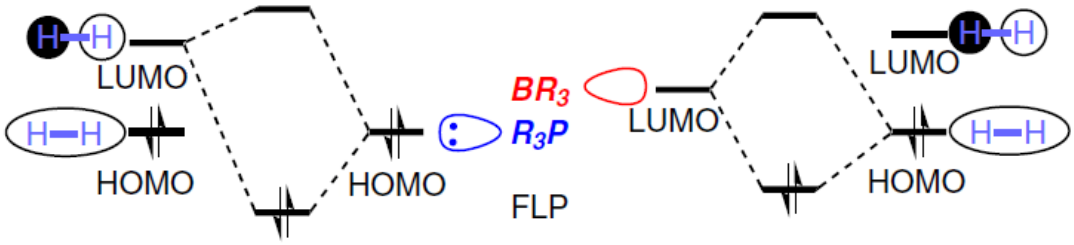


Figure 1.2 Synergistic activation of hydrogen by Lewis acid and Lewis base

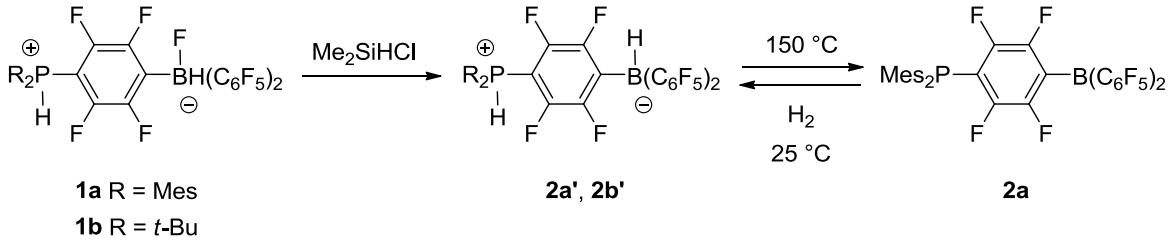
However very recent computational studies[20] of the quasi-linear P···H-H···B activation mechanism cast some doubts on the corresponding transition state. According to these new results, a transition state in a linear arrangement only appears for rather large P···B distances over 4.5 Å. Such values seem 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_2 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.

1.1 Synthesis and reactivity of FLP systems

Over the last years, several both inter- and intramolecular combinations of bulky Lewis acid–base pairs were developed and effectively tested for the heterolytic cleavage of hydrogen.

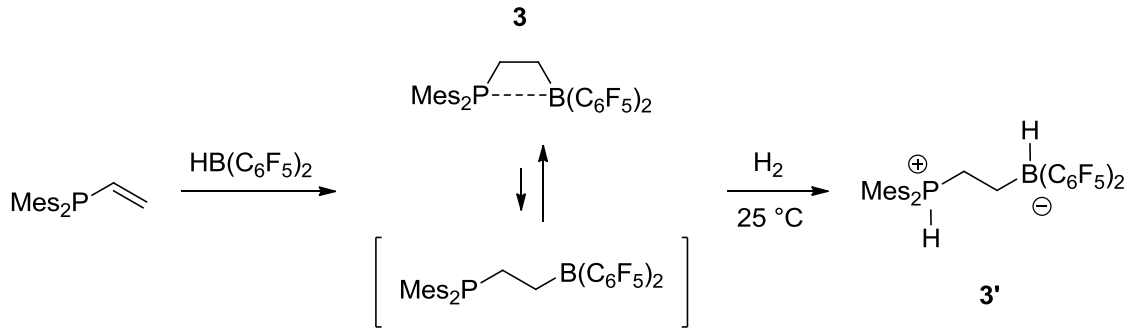
In 2006, the Stephan group reported that the treatment of the zwitterionic salt **1a** with Me_2SiHCl cleanly yielded **2a'** as monomeric species in solution, due to the sterical congestion of the B and P centers that precludes higher aggregation (Scheme **1.1.1**).[21] This species is a rare example of a molecule that contains both protic and hydridic fragments. Indeed, it was anticipated that this species might spontaneously lose H_2.

However, this was not the case: on the contrary, this species was found to be quite robust and air and moisture stable. Nonetheless, heating this species to 150 °C prompted the elimination of H_2 generating the orange-red phosphino-borane **2a**, as confirmed by X-ray crystallographic analysis. It's remarkable that the addition of H_2 at 25 °C to this newly generated phosphino-borane resulted in the rapid and facile regeneration of the zwitterionic salt **2a'**, making it suitable for organocatalytic applications. This significant finding represents the first non-transition-metal system known that both releases and takes up dihydrogen. Another important conclusion was that a combined aggregate of proper Lewis acidity and basicity is required to perform the activation of H_2 by a frustrated Lewis pair. In fact, the related species **2b** (Scheme **1.1.1**) is stable to 150 °C, inferring that the 2,4,6-$Me_3C_6H_2$ derivative **2a** provides the correct balance between the acidity of the phosphonium with the hydricity of the BH fragment that permits the elimination and the uptake of H_2.



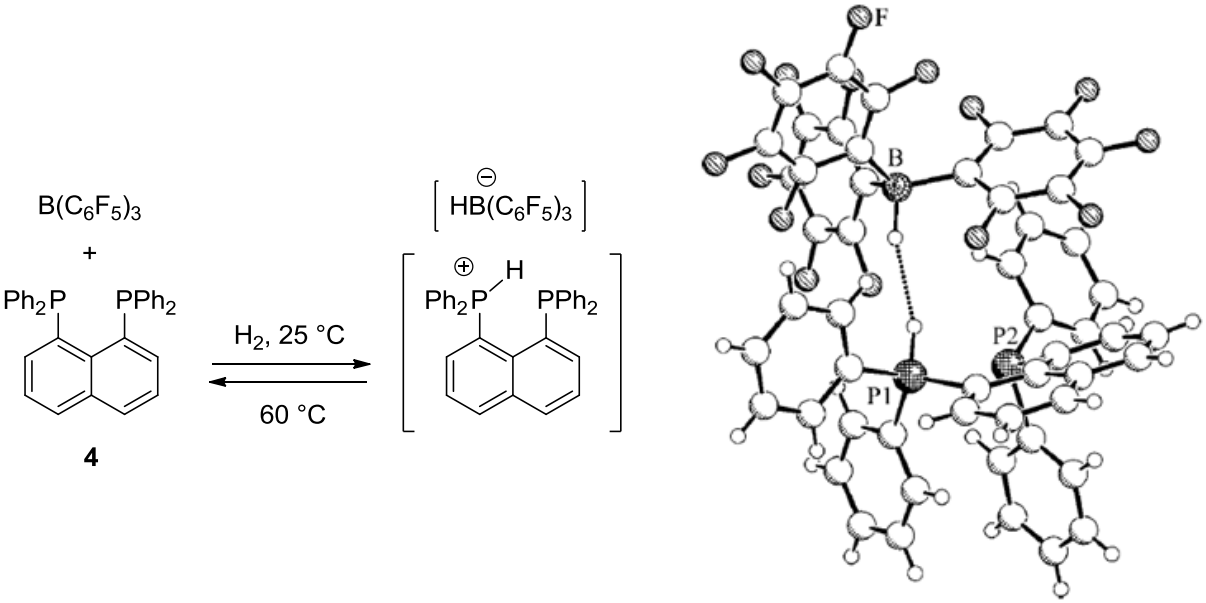
Scheme 1.1.1 Synthesis and reactivity of **2a** and **2b**

Erker and co-workers developed another intramolecular FLP system by reaction of the bulky (dimesityl)vinylphosphine with $HB(C_6F_5)_2$, isolating the hydroboration product **3** (Scheme **1.1.2**).[22] Theoretical analysis revealed that the global minimum for this monomeric bifunctional system features a four-membered heterocyclic structure with a weak P···B interaction,[23] which at higher temperature is in rapid equilibration with the open-chain form. This geometry is in part supported by favorable π–π-stacking interactions[24] between an electron-poor C_6F_5 arene ring on the boron and a parallel electron-rich mesityl substituent at phosphorus. Exposure of a solution of **3** to an atmosphere of H_2 (1.5 bar) at ambient temperature immediately produced the zwitterionic product **3'** (Scheme **1.1.2**) as a white precipitate, the structure of which was confirmed by characteristic NMR spectral features.



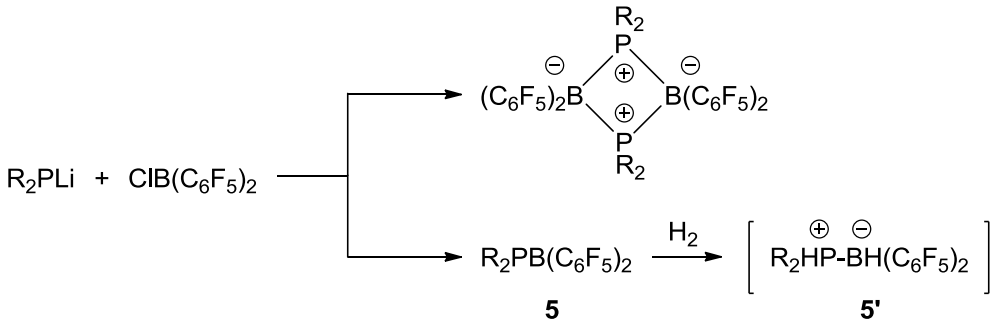
Scheme 1.1.2 Synthesis and reactivity of **3**

One year later, the Erker group also developed a new intermolecular frustrated Lewis pair based on 1,8-bis(diphenylphosphino)-naphthalene **4** capable of heterolytic hydrogen cleavage. The combination of this bidentate phosphine with $B(C_6F_5)_3$ in a 1:1 molar ratio resulted in a non-quenched Lewis pair that activated H_2 under very mild pressure (1.5 bar), yielding the phosphonium hydridoborate salt (Scheme **1.1.3**).[25] As evidenced by crystallographical and ^{31}P NMR spectral data,[26] this compound possesses a non symmetrical structure where a single proton rapidly exchanges between the two phosphine sites, although this exchange process is slow at low temperature. When heated at 60 °C the zwitterion released H_2 regenerating the mixture of biphosphine and borane, thus confirming the capability of this metal-free system to reversibly activate hydrogen.



Scheme 1.1.3 Reversible H_2 activation by **4**/$B(C_6F_5)_3$ and relative X-ray crystal structure

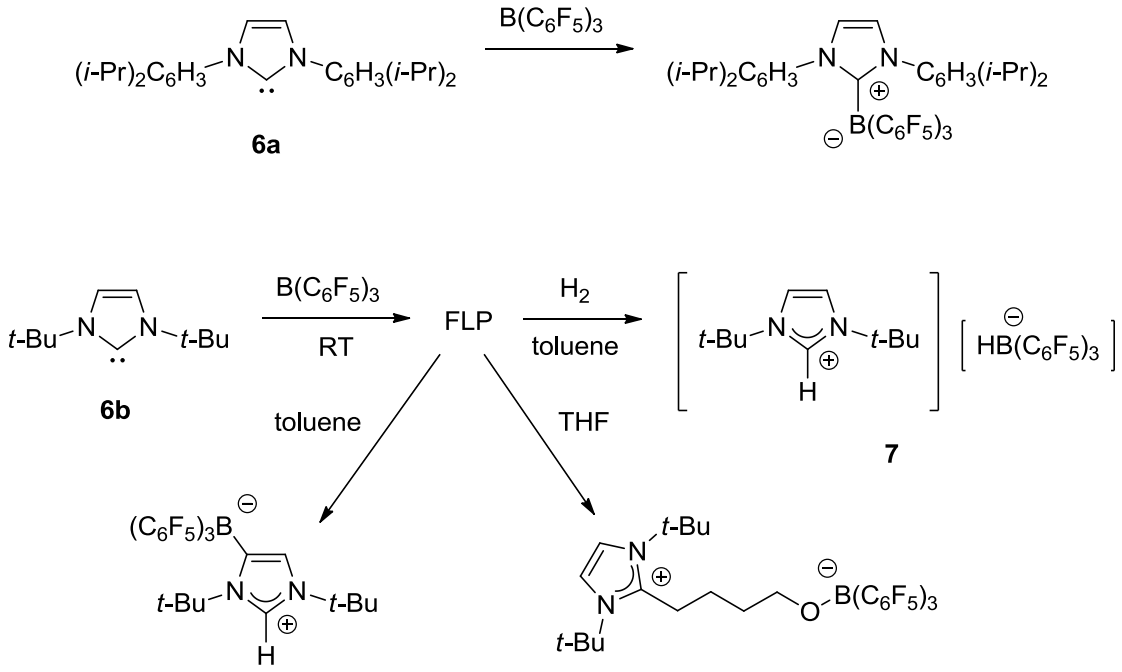
Given that frustrated Lewis pairs are derived from the combination of unquenched donor and acceptor sites, in 2008 Stephan queried the possibility that such fragments could be directly bound to each other. With this in mind, several phosphido-boranes were prepared.[27] While sterically undemanding substituents on phosphorus resulted in the formation of dimeric products, more sterically demanding groups gave the monomeric species which retain the donor and acceptor properties at phosphorus and boron, respectively (Scheme **1.1.4**). Under 4 atm H_2 pressure at 60 °C, these compounds were converted into the corresponding phosphine-borane adducts **5'** over 48 h. It's noteworthy that in the case of **5** the geometries about boron and phosphorus are pseudo-trigonal planar with a very short B···P distance of 1.786(4) Å, while the distance in the activation product (1.966(9) Å) is dramatically longer.[27] DFT studies of this system showed that H_2 initially attacks the Lewis acidic boron center, using the H-H bond as a Lewis base. Subsequently, dihydrogen rotates so that the H-H bond lies parallel to the B-P bond and H_2 can be split with formation of the new P-H bond.



Scheme 1.1.4 Synthesis and reactivity of phosphido-boranes

Apart from phosphines, also other Lewis bases were found to be suitable partners for the formation of frustrated Lewis pairs.

In 2008 Stephan[28] and Tamm[29] simultaneously reported the use of sterically hindered N-heterocyclic carbenes and $B(C_6F_5)_3$ in frustrated Lewis pair chemistry. Carbene **6a**, although considered bulky in transition-metal chemistry, forms a stable classical Lewis acid/base adduct with $B(C_6F_5)_3$ (Scheme **1.1.5**). Instead, the related carbene **6b** is able to form a frustrated Lewis pair in presence of the borane. Even if on prolonged standing these two components react to give $B(C_6F_5)_3$ substitution on the backbone of the carbene, exposure of the freshly generated frustrated Lewis pair mixture to H_2 results in the immediate formation of the imidazolium hydridoborate salt **7** (Scheme **1.1.5**).

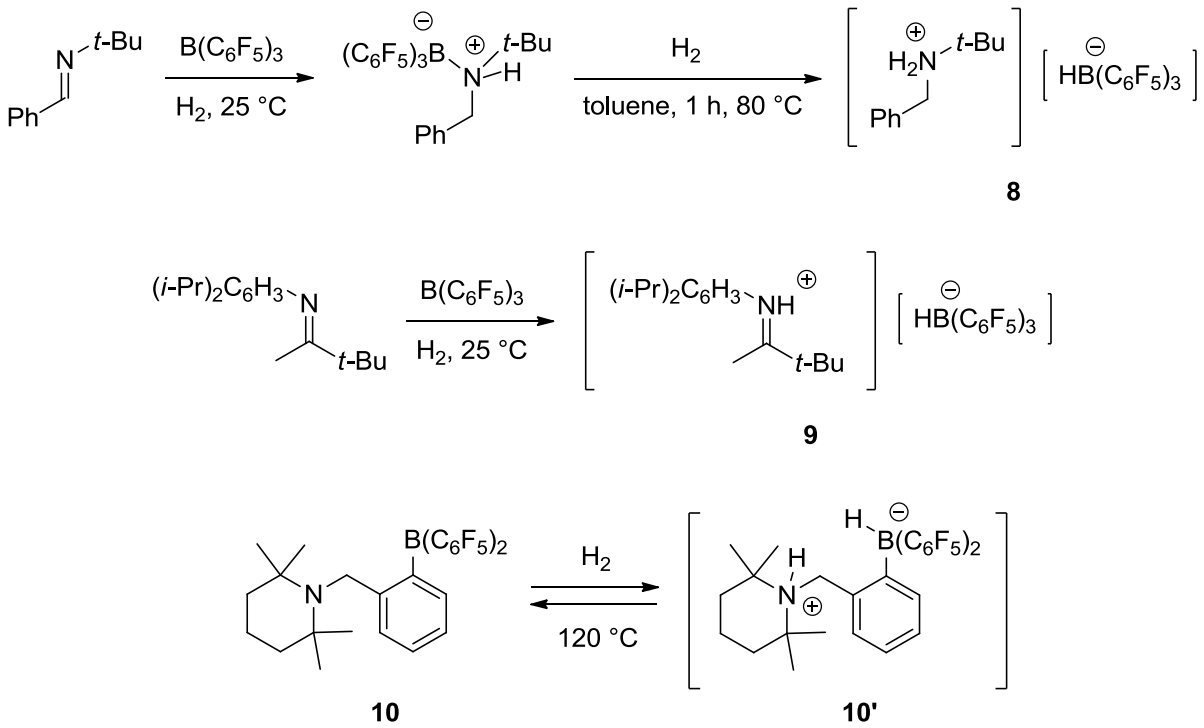


Scheme 1.1.5 Frustrated Lewis pair chemistry of N-heterocyclic carbenes

In the same year, it was reported that also imines and amines can be used for FLP activation of H_2. The stoichiometric reaction between an aldimine and $B(C_6F_5)_3$ in presence of H_2 provides the corresponding amine-borane (Scheme **1.1.6**), inferring the transient formation of an iminium hydridoborate which undergoes hydride transfer to the iminium carbon atom to yield the amine adduct. Further heating of this product at 80 °C for 1 h under H_2 resulted in additional H_2 activation to give salt **8**;[30] its X-ray crystal structure shows a B-H···H-N close contact of 1.87(3) Å, consistent with a nontraditional proton–hydride hydrogen bond.[31]

The analogous reactions of a more sterically encumbered ketimine with $B(C_6F_5)_3$ under H_2 yielded the iminium cation salt **9** (Scheme **1.1.6**). This result suggests that the steric congestion precludes hydride transfer to the iminium carbon.[30]

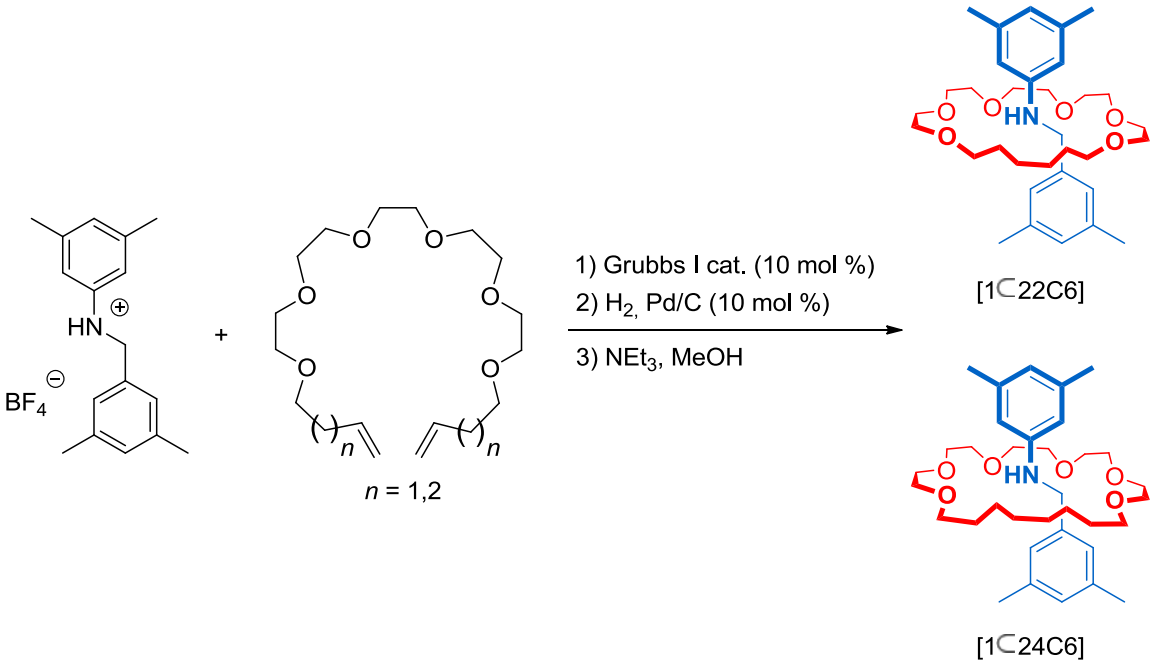
Similarly, exposure of mixtures of amine (such as diisopropylamine or tetramethylpiperidine) and borane to H_2 gave quantitative formation of the corresponding ammonium-borate. In particular, tetramethylpiperidine moiety was recently employed in the construction of the linked amine-borane system **10**/**10'**, which again exhibited the ability to effect reversible H_2 activation.



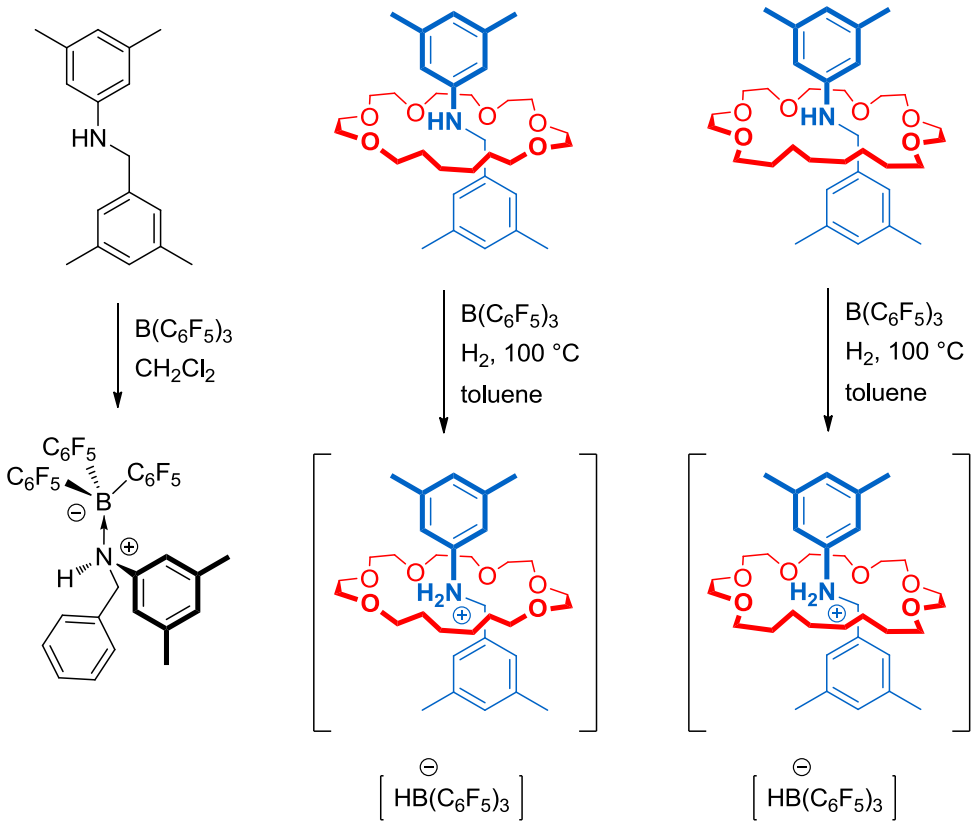
Scheme 1.1.6 Use of imines and amines to activate H_2

Despite these outstanding accomplishments, the requirement that FLP partners contain either bulky alkyl or aryl substituents directly bonded to the heteroatom can be synthetically challenging. Very recently, Stephan envisioned an alternative strategy to sterically encumber Lewis bases without covalent modification.[32] The authors hypothesized that the incorporation of a secondary amine into a mechanically interlocked molecule, such as a [2]rotaxane, could convert a Lewis base that would normally form a classical adduct with $B(C_6F_5)_3$ into one that participates as a partner in an FLP. This [2]rotaxane design utilizes a short axle with only two nonhydrogen atoms (NH and CH_2) between the stoppering xylene groups, so that the macrocyclic wheel can only undergo limited translational motion and cannot simply slide along the axle and expose the reactive nitrogen center. Indeed, ring-closing metathesis and subsequent reduction permitted the synthesis of [2]rotaxanes [1⊂22C6] and [1⊂24C6] (Scheme **1.1.7**). Their X-ray structures show that the macrocycle encircles the central NH–CH_2 unit, with a single NH···O hydrogen bond as the only substantial noncovalent interaction between the two interlocked components. While reaction of the sterically unencumbered N-benzylaniline with one equivalent of $B(C_6F_5)_3$ under H_2 resulted in the formation of the classical stable Lewis acid-base adduct, analogous combination of the [2]rotaxanes led to

FLP activation of H_2, as demonstrated by multinuclear NMR spectroscopy (Scheme **1.1.8**).



Scheme 1.1.7 Synthesis of [2]rotaxanes [1⊂22C6] and [1⊂24C6]



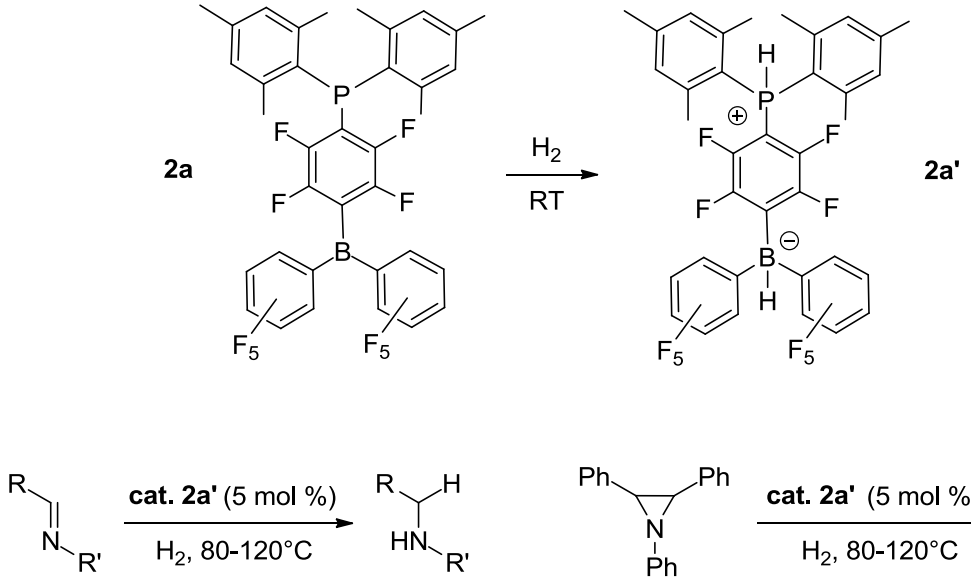
Scheme 1.1.8 Reaction of the bare amine and the [2]rotaxanes with $B(C_6F_5)_3$ and H_2

1.2 Application of FLP systems in catalytic hydrogenations

Subsequently, this significant capacity was exploited in metal-free hydrogenation procedures.

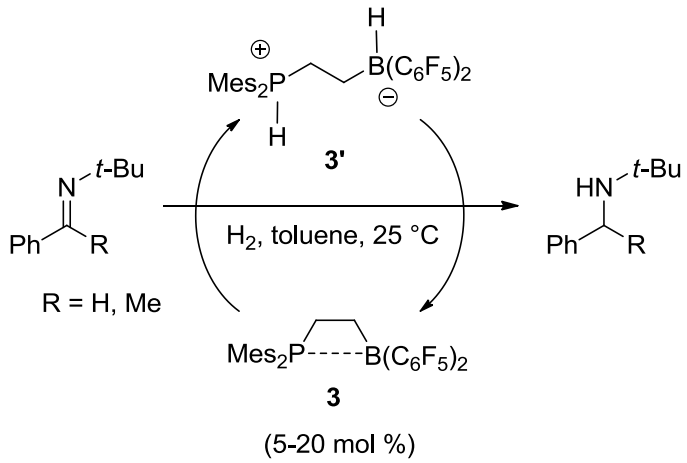
First, Stephan and co-workers reported the use of the structurally bifunctional phosphine–borane **2a** for the metal-free hydrogenation catalysis (Scheme **1.2.1**).[33] Thus, using a catalytic amount of **2a'** and heating the solutions to 80-120 °C under 1-5 atm H_2, the authors were able to perform the hydrogenation of a variety of imines in high isolated yields. In addition, catalytic reductive ring opening of the N-aryl aziridines also proceeded readily under similarly mild conditions. It's noteworthy that compounds with electron-withdrawing substituents on the nitrogen require longer times and/or higher temperatures, suggesting that protonation of the nitrogen atom may be rate determining. Moreover, mechanistic studies suggest that the process is initiated by protonation of the imine, followed by hydride transfer to the carbon of the iminium salt.[33]

Instead, imines with less sterically demanding substituents on the nitrogen atom, such as benzyl, are only stoichiometrically reduced, presumably because the corresponding amines bind more strongly to the boron center. This problem was circumvented using $B(C_6F_5)_3$ as a protecting group. Since $B(C_6F_5)_3$ is a stronger Lewis acid than the boron center in the catalyst, the amine formed does not inhibit the catalyst, but it should be noted that the stoichiometric use of this protecting group is quite expensive.[33]



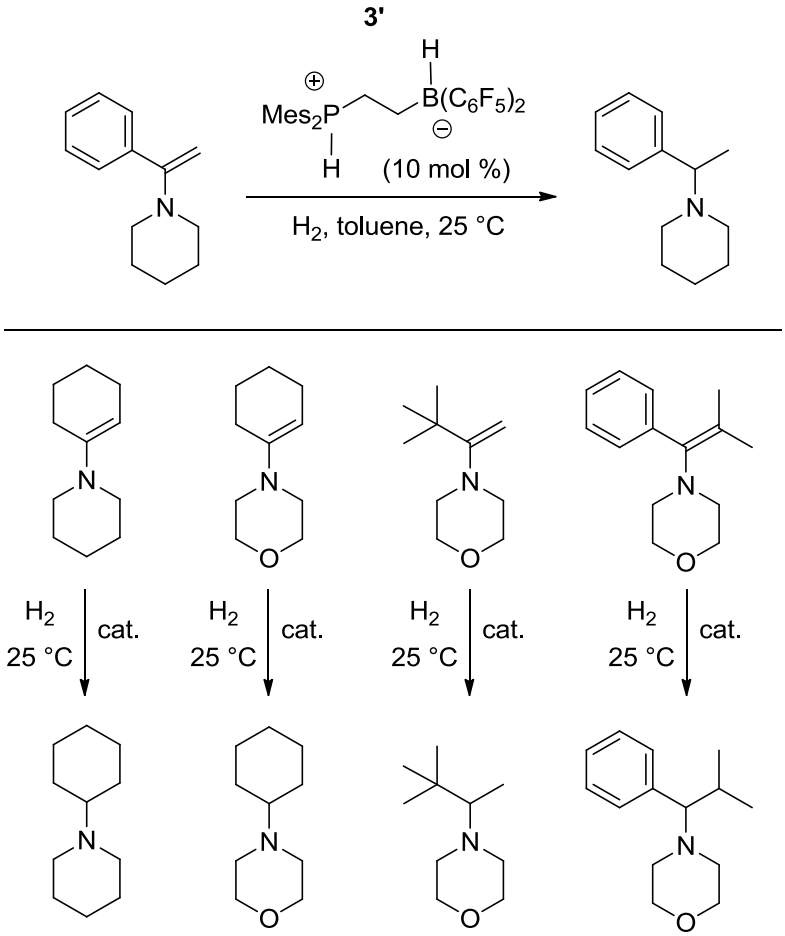
Scheme 1.2.1 Catalytic imines hydrogenation and aziridine opening using **2a**/**2a'** pair

The **3**/**3'** pair is an even more active catalyst for the metal-free hydrogenation of imines as it operates effectively at ambient conditions. Erker and co-workers reported that a 20 mol % loading of **3**/**3'** system catalyzed the hydrogenation of aldimines at 25 °C under 1.5 bar H_2 pressure; surprisingly, catalytic hydrogenation of the related ketimine was much more effective and complete hydrogenation was achieved with only a 5 mol % loading of the catalyst under very mild reaction conditions (Scheme **1.2.2**).[34]



Scheme 1.2.2 Catalytic hydrogenation of imines using **3**/**3'** pair

Since it is conceivable that these reactions proceed by means of the corresponding iminium-ion intermediates, also other substrates amenable to its formation were considered. Indeed, the Erker group observed that the same catalyst **3'** rapidly promoted the reduction of enamines to the corresponding amines at ambient conditions, yielding the desired product with practically quantitative conversion. Notably, a loading of the catalyst as low as 3 mol % was sufficient to achieve near-complete enamine hydrogenation under these mild reaction conditions (Scheme **1.2.3**).[35]



Scheme 1.2.3 Metal free catalytic hydrogenation of enamines

Soon after these achievements, more focus was placed on the development of intermolecular and easily available FLPs for hydrogen activation, relying on the tris(pentafluorophenyl)borane as the LA component.[16] Following these initial studies about metal-free catalytic hydrogenation of imines, the authors hypothesized that the substrate itself could serve as the base-partner of an FLP and thus only a catalytic amount of tris-pentafluorophenyl borane should be required.

Indeed, under conditions similar to those described above, a series of differently substituted imines were reduced under hydrogen using just a catalytic amount of $B(C_6F_5)_3$.[30] In case of poorly basic imines, addition of catalytic amount of sterically encumbered phosphine accelerated the reductions, presumably due to the greater ease with which the phosphine/borane pair heterolytically cleaves hydrogen. The proposed catalytic cycles are shown in Figure **1.2.1**.

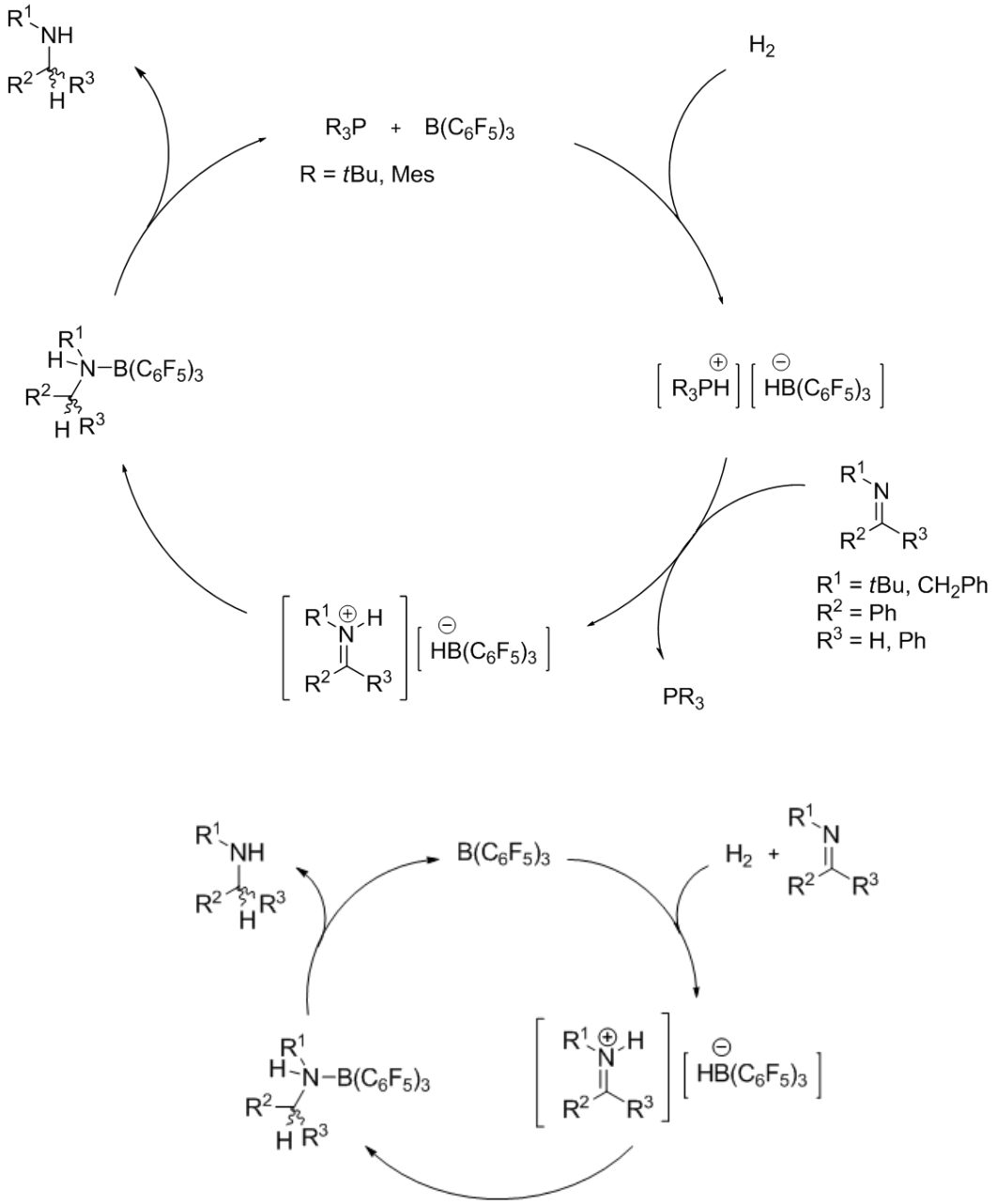
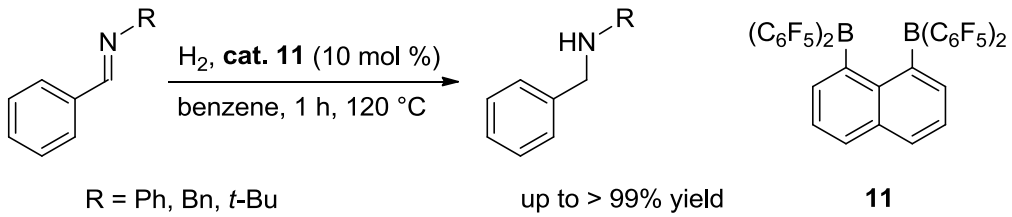


Figure 1.2.1 Catalytic cycles using phosphine and substrate, respectively, as Lewis bases

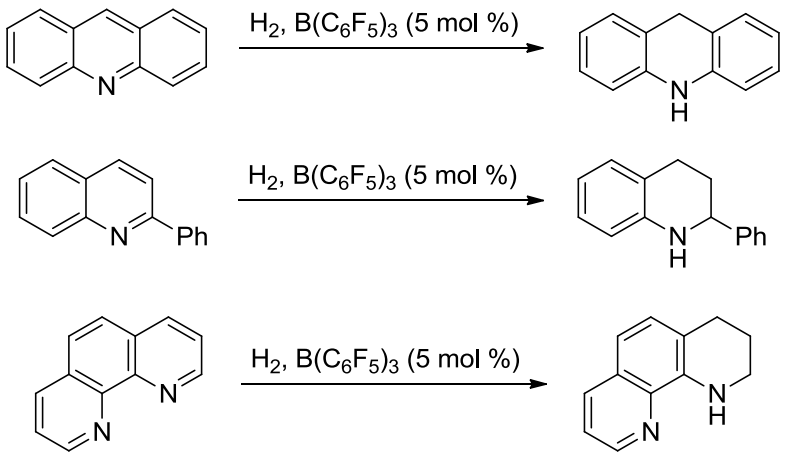
In 2009, Berke and coworkers envisioned the use of a bidentate Lewis acid, bearing both Lewis acidic centers in close vicinity. In their hypothesis, this would enhance the reactivity *via* an increase in Lewis acidity and/or the use of neighboring effects. Indeed, in this work they described the successful use of the novel 1,8-bis(dipentafluorophenylboryl)-naphthalene **11** to activate H_2 and to reduce a variety of aldimines in quantitative yield under 15 bar of H_2 pressure at 120 °C. (Scheme **1.2.4**).[36] The authors suggested that, in this case, the hydrogen activation *via* the ‘‘super Lewis acidic activation pathway’’ involving both B centers has a higher barrier than the

‘‘external’’ access of H_2 to just one boron center; therefore a monodentate hydrogen activation takes place.



Scheme 1.2.4 Catalytic hydrogenation of aldimines promoted by compound **11**

One year later, Stephan further extended the range of suitable substrates communicating the reduction of substituted N-heterocycles such as quinoline, phenanthralene and acridine catalyzed by 5 mol % amount of $B(C_6F_5)_3$. The reaction, performed at ambient conditions, allowed the isolation of the desired products in high chemical yield (Scheme **1.2.5**).[37]



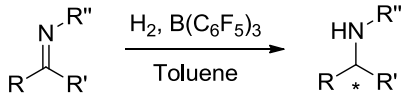
Scheme 1.2.5 Examples of catalytic hydrogenation of N-heterocycles

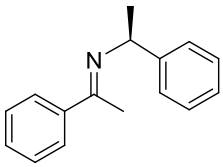
1.3 Development and application of chiral FLPs

The application to asymmetric synthesis is a logical and highly desirable extension of these findings. Indeed, stereoselective methodologies can be designed based on the consideration that FLP reductions can be viewed as a catalytic version of borohydride reductions.

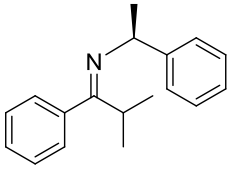
With this in mind, in 2011 Stephan studied the catalytic hydrogenation of chiral ketimines using tris-pentafluorophenyl borane as a catalyst.[37] Using imines derived from

camphor and menthone, the reductions proceed with quantitative yields and high diastereoselectivities (up to 99% *d.e.*). Generally, the reduction of chiral imines with $B(C_6F_5)_3$ resulted in excellent diastereoselectivities when the stereogenic center was close to the unsaturated carbon center, probably due to the proximity of the stereocenter to the approach of the sterically bulky $[HB(C_6F_5)_3]^-$ species. On the other hand, when the stereogenic center was close to the unsaturated nitrogen center, like in the case of imines bearing chiral auxiliaries as protecting groups, it showed a less beneficial effect on the diastereoselectivity of the hydrogenation (*d.e.* up to 68%). (Scheme **1.3.1**)

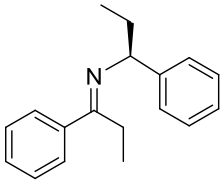




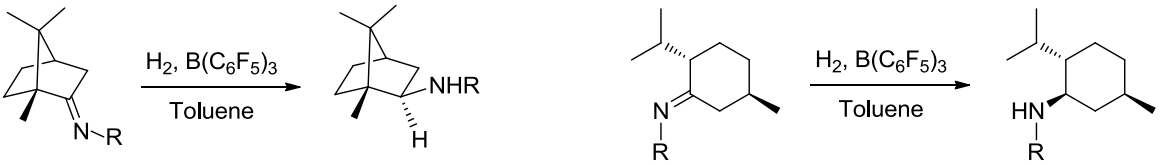
cat. (eq.)	T (°C)	p H_2 (atm)	t (h)	yield (%)	*d.e.* (%)
0.1	80	5	48	*72*	*36*
0.1	25	115	23	100	*62*



cat. (eq.)	T (°C)	p H_2 (atm)	t (h)	yield (%)	*d.e.* (%)
0.1	80	5	48	100	*45*



cat. (eq.)	T (°C)	p H_2 (atm)	t (h)	yield (%)	*d.e.* (%)
0.1	80	5	24	100	*65*
0.2	80	5	24	100	*68*



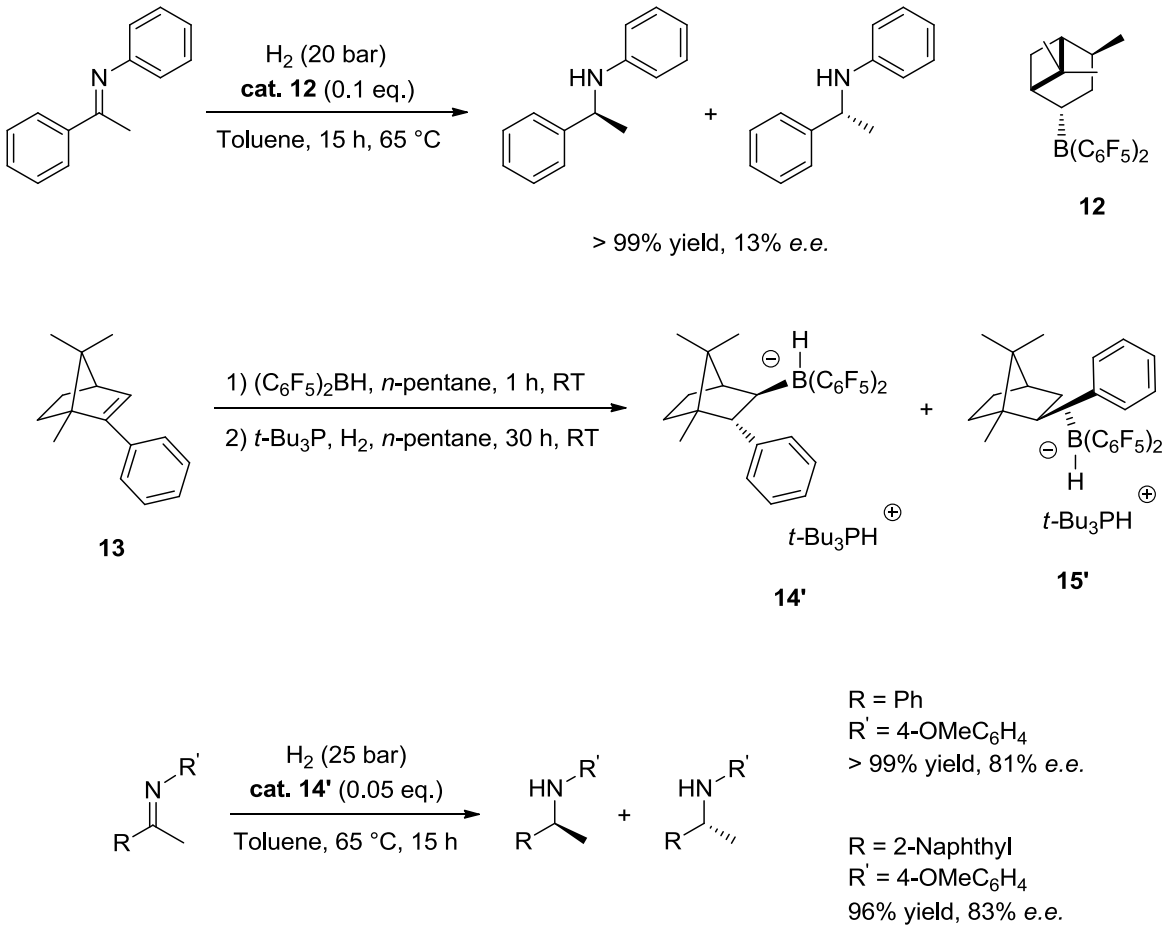
Scheme 1.3.1 Catalytic hydrogenation of chiral imines with $B(C_6F_5)_3$

Once again, the imine acts as base partner for $B(C_6F_5)_3$ to perform the heterolytical H_2 cleavage. The resulting anion $[HB(C_6F_5)_3]^-$ 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 $[HB(C_6F_5)_3]^-$ to the corresponding iminium cation proceeds almost exclusively *via* approach of the anion toward one of the two diastereotopic faces of the iminium cations.

Recently, an important improvement was obtained by Klankermayer's group, who developed asymmetric FLP hydrogenation employing sterically crowded chiral boranes as Lewis acids (Scheme **1.3.2**). In preliminary effort to perform an enantioselective catalytic FLP hydrogenation, the chiral borane **12** was used to reduce a ketimine. In early experiments, the use of this pinene-derived chiral catalyst allowed to achieve the asymmetric reduction of acetophenone derived ketimines, albeit with low enantioselectivity (13% *e.e.*).[38]

In a more recent work this group extended this strategy, developing a chiral borane derived from camphor which allowed to reach high enantiomeric excess (up to 83%) in the enantioselective reduction of imines.[39]

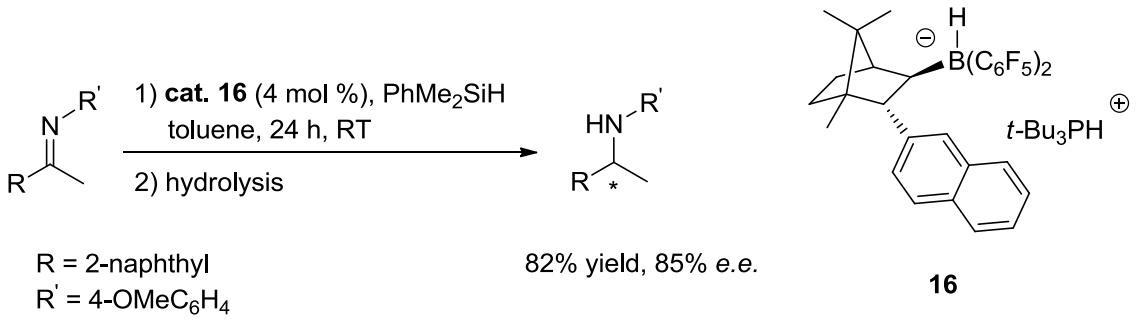


Scheme 1.3.2 Enantioselective hydrogenation of ketimines with chiral boranes

The hydroboration of a 2-phenyl bicycloheptene **13** derivative using bis(perfluorophenyl)borane in toluene or pentane gave the diastereomeric boranes **14** and **15** in a 20:80 ratio as confirmed by multinuclear NMR spectroscopy. Treatment of an *n*-pentane solution of the borane mixture **14** and **15** with hydrogen at 25 °C in the presence of tri-*tert*-butylphosphine resulted in the precipitation of a colorless solid in 53% yield, which multinuclear NMR spectroscopy confirmed to be a mixture of the activated FLP salts **14'** and **15'**.

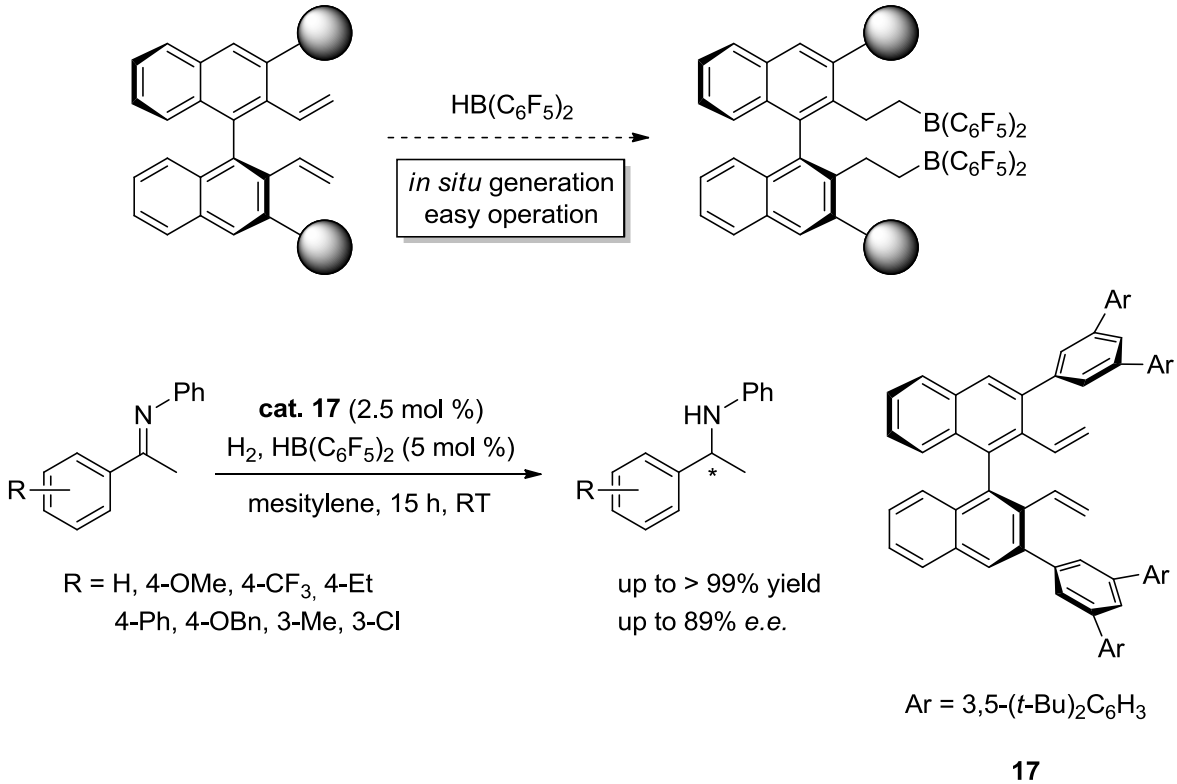
Then, with the chiral compounds **14'** and **15'** in hand, the catalytic hydrogenation of prochiral imines was investigated. In the presence of a 5 mol % amount of the catalyst (1:1 mixture of the two diasteoisomers) at 65°C and 25 bar hydrogen, imine *N*-(1-phenylethylidene)aniline was transformed into the corresponding secondary amine with a 20% *e.e.*. Obviously, the use of the diastereomerically pure salts as catalysts for the hydrogenation process gave more encouraging results. By using **15'**, full conversion into the product was achieved in 48% *e.e.* for the *S* enantiomer, while **14'** led to the *R* enantiomer with higher enantioselectivity (79% *e.e.*). Notably, the presence of a methoxy group in 4-methoxy-N-(1-(naphthalen-2-yl)ethylidene)aniline favored the catalytic hydrogenation, leading to an excellent conversion of 96% and a noticeable enantioselectivity of 83%.

In 2012, the same group reported the enantioselective hydrosilylation of various imines using a slightly modified version of the previous camphor derived catalyst.[40] Hydrosilylation of sterically hindered imine afforded only negligible conversion and the introduction of an electron-withdrawing group in the acetophenone moiety led to relatively low conversion, albeit with high enantioselectivity. However, the presence of a methoxy donor group strongly enhanced the conversion (up to 90%), while retaining high levels of enantioselectivity (up to 85% *e.e.*). Again, the highest enantioselectivity was obtained with the imine derived from naphthalenylethanone, reaching 87% enantiomeric excess (Scheme **1.3.3**).



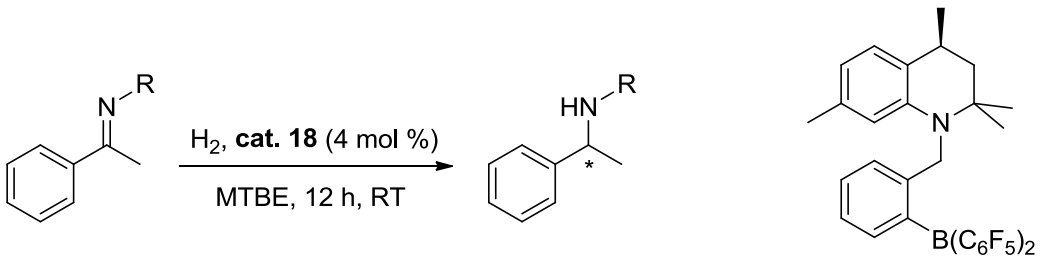
Scheme 1.3.3 Enantioselective hydrosilylation of imines catalyzed by FLP systems

Later, Du envisioned that direct hydroboration of chiral dienes bearing two terminal olefins with $HB(C_6F_5)_2$ could provide simple access to a new class of chiral borane catalysts for the asymmetric hydrogenation of imines.[41] In this strategy, binaphthyl based chiral diene **17** acts like a "ligand" to generate the borane catalyst *in situ* without further isolation, thus ensuring easy operation and rapid evaluation (Scheme **1.3.4**). Moreover, terminal olefins offer the advantage of generating enantiomerically pure boranes by hydroboration, instead of the diastereoisomer mixture which would be obtained in the case of internal olefins. After proper tuning of the reaction conditions and the substituents at the 3,3′-positions of binaphthyl framework, a variety of imines was smoothly hydrogenated in good yields and high enantioselectivities (up to 89% *e.e.*)



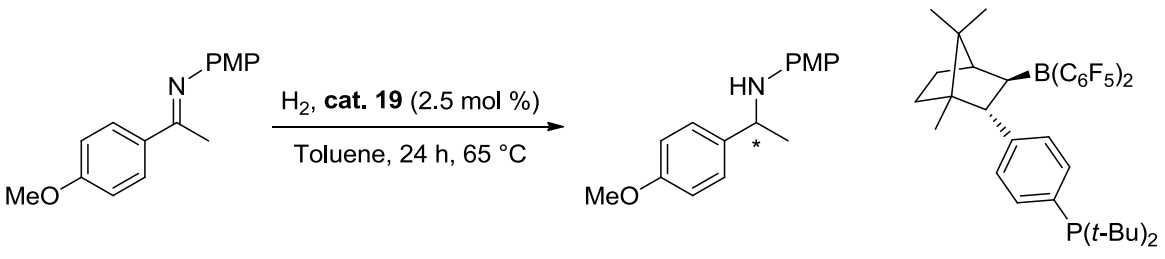
Scheme 1.3.4 Use of chiral dienes in FLP catalyzed asymmetric hydrogenations

However, one of the main issues related to these intermolecular FLP systems is the reduced stability in the presence of air and moisture, thus complicating their effective recycling. Recently, Rieger and Repo described a chiral intramolecular FLP catalyst (cat. **18**, Scheme **1.3.5**) with high air and moisture stability, foreshadowing the extended applicability of these systems.[42] This catalyst was used in the enantioselective hydrogenation of imines with a moderate catalytic loading, leading to an enantiomeric excess up to 37% *e.e.*.



Scheme 1.3.5 Ketimines asymmetric catalytic hydrogenation employing catalyst **18**

More interestingly, Klankermayer and co-workers developed a modified version of the previously described camphor borane featuring a strongly enhanced stability.[43] After the first hydrogenation experiment, which yielded the desired amine with full conversion and 76% enantiomeric excess, the recycled solid catalyst was subsequently retransferred to the autoclave, mixed with toluene and substrate and pressurized with 25 bar hydrogen. Four consecutive runs demonstrated constant levels of conversion and enantioselectivity, confirming the effectiveness and stability of this novel chiral FLP catalyst (Scheme **1.3.6**).



Scheme 1.3.6 Recycling experiments with catalyst **19**

These results represent only the beginning of a very promising area, which revolves around the development of highly stereoselective metal-free catalytic methodologies based on the FLP activation of hydrogen and other small organic molecules.[44]

CHAPTER 2

Enantioselective double bond reductions promoted by chiral phosphoric acids

"Consider your origins: you were not made to live as brutes, but to follow virtue and knowledge."

Dante Alighieri, The Divine Comedy

The electrophilic activation of a substrate by means of a Brønsted acid is, undoubtedly, the most straightforward and common approach used to promote a reaction and hence Brønsted acids have been widely utilized as efficient catalysts for numerous organic transformations. The majority of research looks toward the development of highly active Brønsted acids to generate unstable, and hence highly reactive, protonated intermediates (**Sub**-H^+) (Figure **2.1**). In this context, conjugate bases ($\mathbf{A}^-$) are designed to be uncoordinatable to gain high catalytic activities, avoiding unfavorable interactions such as hydrogen bonding.

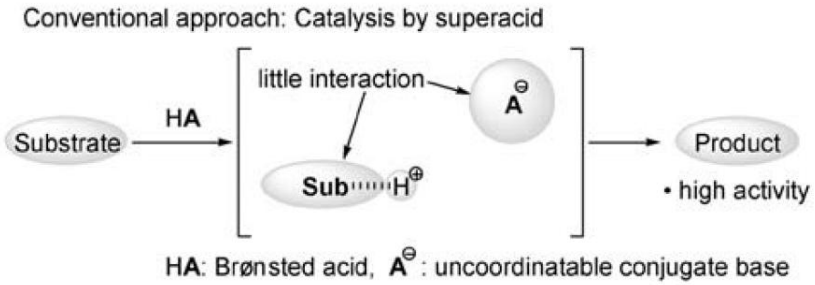


Figure 2.1 Catalysis by superacid

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 realizing enantioselective catalysis using a chiral Brønsted acid is the hydrogen bonding interaction between a protonated substrate (**Sub**-H^+) and the chiral conjugate base (**A***$^-$). Thus 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 **2.2**).

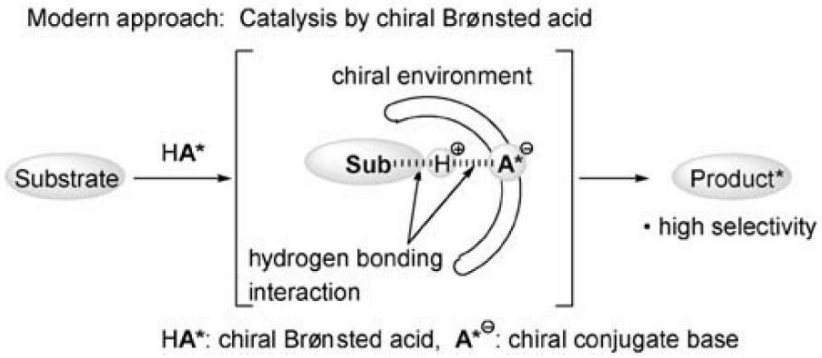


Figure 2.2 Catalysis by chiral Brønsted acid

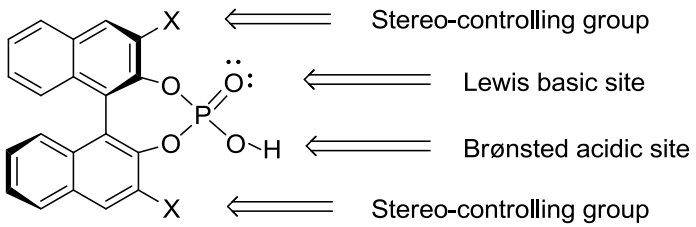
Among the various organic Brønsted acids, phosphoric acids possess several advantages. [45] In fact, even if sulfonic acids are one of the most common acid catalysts, it seems likely that sulfonic acid is too strong to maintain hydrogen bonding interactions between a protonated substrate and the conjugated base. On the other hand, carboxylic acids and sulfinic acids would be good candidates in terms of appropriate acidity; however, the acidic functionality should be introduced to a chiral backbone *via* a single bond, which could pose an issue to enantioselection due to free rotation around the bond. In addition, introduction of substituents is restricted to the α-position of these acids, four atoms away from the proton which functions as the activation site for an electrophilic component.

Instead, phosphoric acids show a series of positive features, as summarized below:

- Strong but appropriate acidity, which should allow hydrogen bonding interactions with the electrophilic components without the formation of loose ion-pairs (pK_a of $(EtO)_2P(O)OH$ is 1.39, similar to HBF_4 (-0.44))
- The phosphoryl oxygen would function as a Brønsted basic site and hence it can be anticipated an acid/base dual function even for monofunctional phosphoric acid catalysts

- Two substituents can be directly introduced at the phosphorous atom, meaning that a chiral environment can be created one atom closer to the activation site compared to carboxylic and sulfinic acids
- When a ring structure is introduced to the phosphoric acid, an acidic functionality is still available. This ring system prevents the free rotation at the α-position of the phosphorus centre
- Substituents can be introduced on the ring system to provide a chiral environment

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. As additional requirement, a C_2 symmetry is crucial in the design of these catalysts because it means that the same catalyst molecule is generated when the acidic proton migrates to the phosphoryl oxygen. Due to their symmetry, the commercial availability of both the enantiomers and the numerous protocols for introducing substituents at the 3,3'-position of the binaphthyl backbone, BINOL derivatives were generally selected as chiral scaffold to construct the ring structure. Some of the most common examples of this class of phosphoric acids are shown in Figure **2.3**.



20a: X= H
20b: X= Ph
20c: X= 4-NO_2-phenyl
20d: X= 4-β-naph-phenyl
20e: X= 4-Cl-phenyl
20f: X= 3,5-$(CF_3)_2$-phenyl
20g: X= 3,5-dimesityl-phenyl
20h: X= 1-naphthyl
20i: X= 2,4,6-(*i*-Pr)$_3$-phenyl
20j: X= 9-anthryl
20k: X= 9-phenanthryl
20l: X= biphenyl
20m: X= 2-naphthyl
20n: X= $SiPh_3$

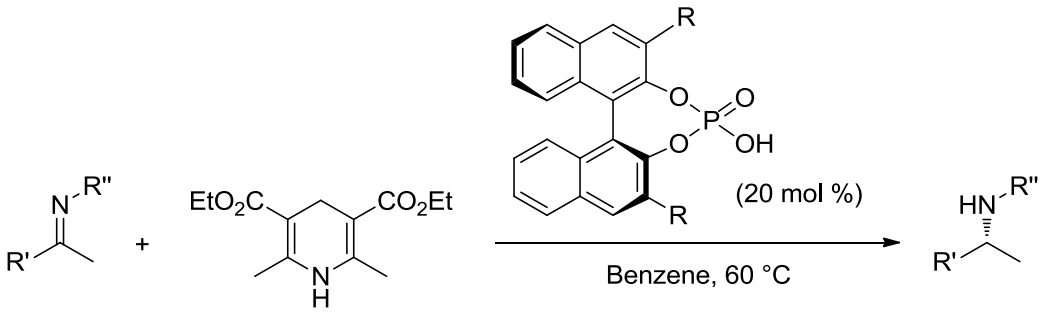
Figure 2.3 BINOL derived chiral phosphoric acids

The appropriate choice of the substituents at the 3,3'-position is crucial for high enantioselectivity. For example, **20a** gave racemic compounds in the Mannich-type reaction of ketene silyl acetal with aldimines; introduction of phenyl groups at the 3,3'-position had a beneficial effect, while the use of phosphoric acid **20c** gave the best result, allowing to obtain the corresponding β-amino ester in 87% *e.e.*

2.1 Reduction of C=N bonds

In 2005 Rueping's group reported the first enantioselective Brønsted acid-catalyzed hydrogenation of ketoimines.[46] Authors found that several proton acids are able to catalyze the reduction of imines under hydrogen-transfer conditions, using Hantzsch dihydropyridine, a synthetic analogue of NADH, as the hydrogen source. Starting from this observation, they envisioned a catalytic enantioselective variant of this process.

A screening of various phosphoric acids selected acid **20f** as best performing catalyst, showing that not only steric but also electronic effects of the 3,3' substituents on binaphthol scaffold play a role in this transformation, while a screening of solvents established that nonpolar solvents are essential. No reaction was observed in polar protic media such as methanol and the best yields and selectivities were obtained in benzene (68-84% *e.e.*, Scheme **2.1.1**).



R = 3,5-$(CF_3)_2$-phenyl R' = 2-F-phenyl R'' = PMP 82% yield, 84% *e.e.*
R' = 4-OMe-phenyl R'' = PMP 76% yield, 72% *e.e.*

Scheme 2.1.1 Enantioselective phosphoric acid catalyzed reduction of ketoimines

Mechanistically Rueping and co-workers assume that activation of ketimine by protonation through Brønsted acid will generate the iminium **A**. Subsequent hydrogen transfer from the dihydropyridine yields the chiral amine and pyridinium salt **B**, which undergoes proton transfer to regenerate the phosphoric acid (Figure **2.1.1**).

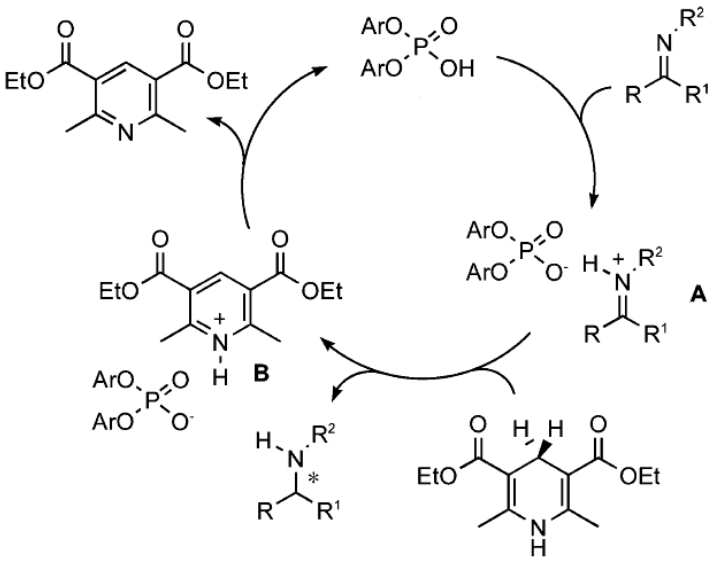


Figure 2.1.1 Proposed catalytic cycle for ketimine hydrogenation

In the proposed transition state, the ketimine is activated by the Brønsted acid, thereby favoring approach of the nucleophile from the less hindered *Si* face, as the *Re* face is shielded by the aryl group of the catalyst (Figure **2.1.2**).

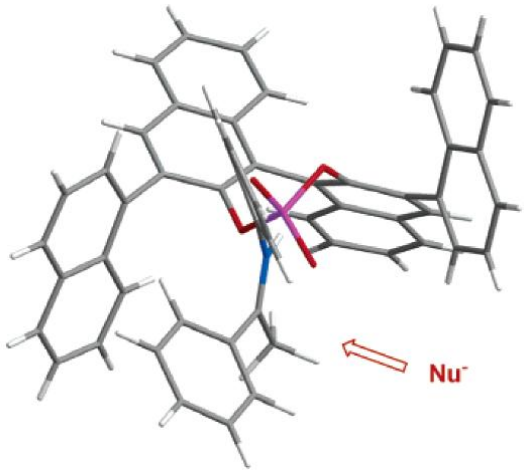
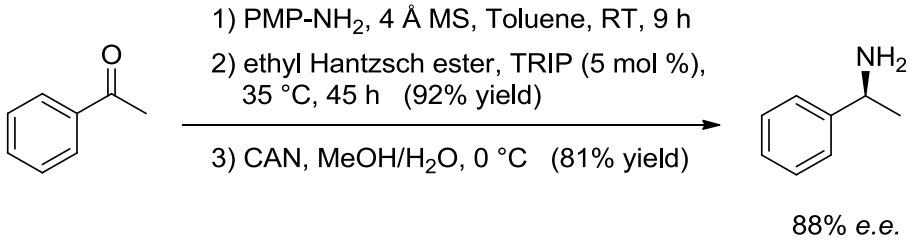


Figure 2.1.2 Model of stereoselection

Some months later List's group reported the same reaction from parallel and independent studies, that resulted in the development of a significantly improved new catalyst.[47] This group observed that a differently substituted catalyst (**20i**, (*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's group

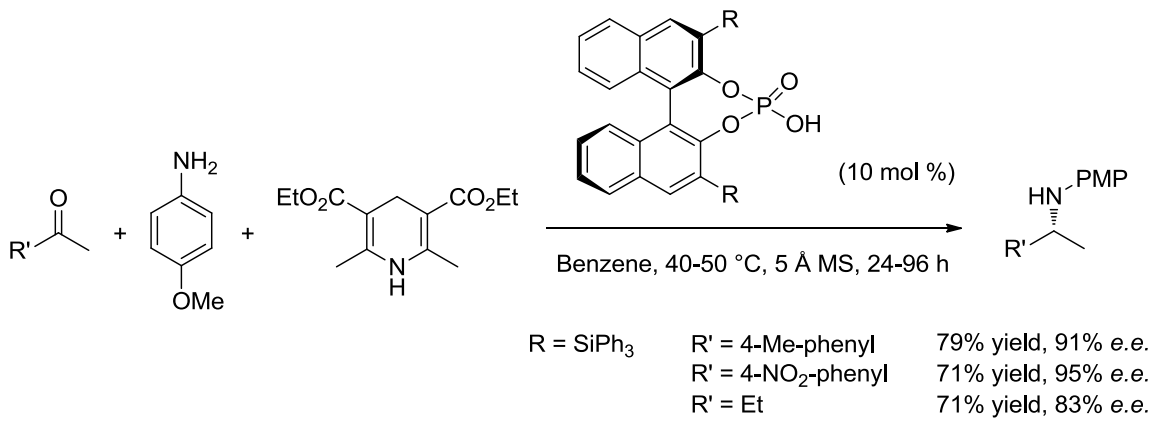
under many aspects, with shorter reaction times, lower temperature, higher yields and *e.e.* values (80–98% yields, 80–93% *e.e.*) and, most notably, much lower catalyst loading.

Moreover, this catalyst was also able to reduce highly enantioselectively aliphatic ketimines. This publication also detailed an example representing the first enantioselective organocatalytic reductive amination reaction. 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 **2.1.2**).



Scheme 2.1.2 First example of enantioselective organocatalytic reductive amination

Soon after, MacMillan's group properly explored this organocatalytic reductive amination,[48] observing that the *ortho*-triphenylsilyl phosphoric acid **20n** in the presence of MS 5 Å facilitates the desired coupling of acetophenone and 4-OMe-aniline in high conversion and with excellent levels of enantiocontrol at 40 °C (87% yield, 94% *e.e.*). The scope of this reaction is quite wide, as a variety of substituted acetophenone derivatives can be successfully coupled, including electron-rich, electron-deficient, as well as *ortho*, *meta*, and *para* substituted aryl ketone systems. Moreover, also methyl alkyl substituted ketones are suitable substrates (Scheme **2.1.3**). It is noteworthy that this last example highlights a key benefit of reductive amination versus imine reduction: imines derived from alkyl-alkyl ketones are unstable to isolation, a fundamental limitation that is bypassed using this route.



Scheme 2.1.3 Enantioselective organocatalytic reductive amination reaction

Authors report also the reduction of the pyruvic acid-derived cyclic imino ester with excellent enantioselectivity. However, implementation of the corresponding ethyl substituted imine resulted in a dramatic decrease in efficiency. Computational studies revealed that this effect arises from the catalyst imposing torsional constraints on substrate conformation: imines that incorporate a methyl group undergo selective catalyst association wherein the C=N *Si*-face is exposed to hydride addition, while the ethyl-containing substrate locates the terminal CH_3 of the ethyl group away from the catalyst framework, thereby shielding both enantiofaces of the iminium system (Figure **2.1.3**).

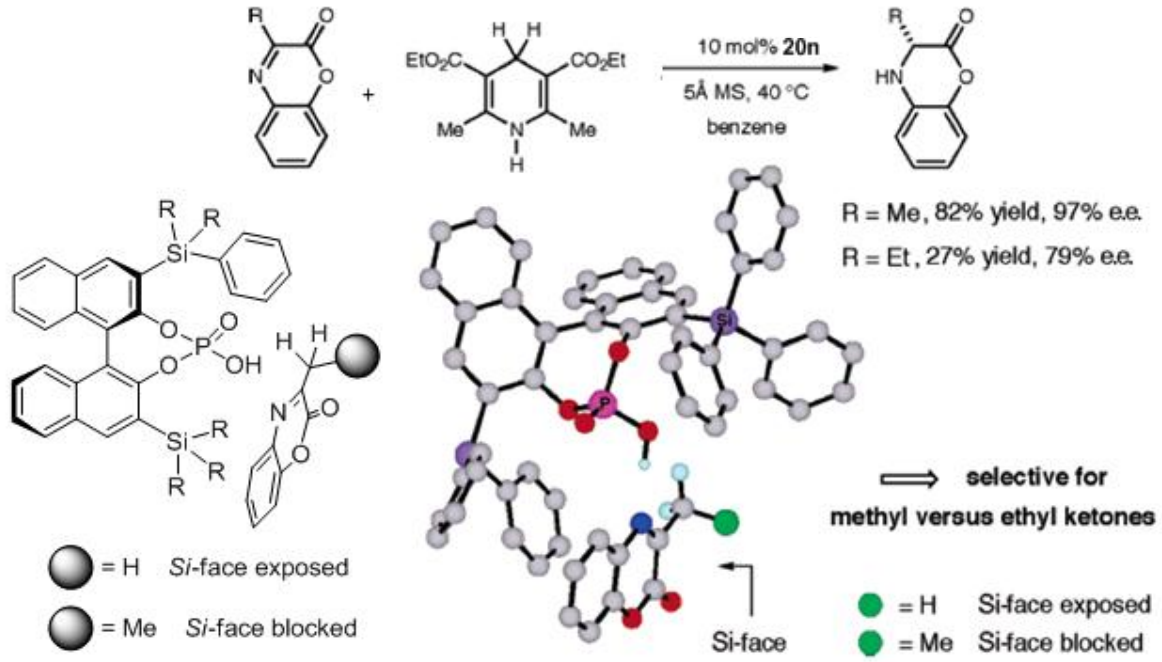
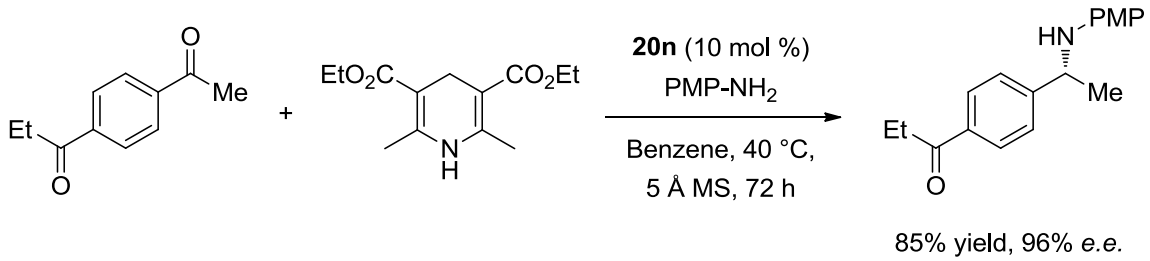


Figure 2.1.3 Proposed model of stereoselection

This example suggests that this catalyst should be generically selective for the reduction of iminium ions derived from methyl ketones, as it was successfully shown by MacMillan's group through the amination of the *para* substituted aryldiketone reported in Scheme **2.1.4**: this substrate underwent chemoselective reduction with a 18:1 preference for coupling at the methyl ketone site.



Scheme 2.1.4. Methyl *vs.* ethyl ketone selectivity

While it is obvious that aldehydes 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 α-branched aldehydes *via* an efficient dynamic kinetic resolution (DKR).[49] Under the reductive amination conditions an α-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 **2.1.4**).

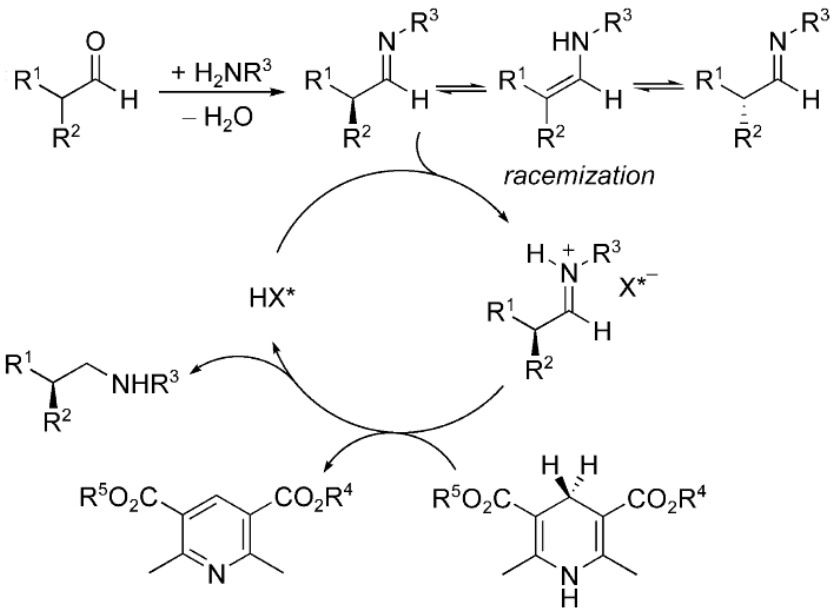
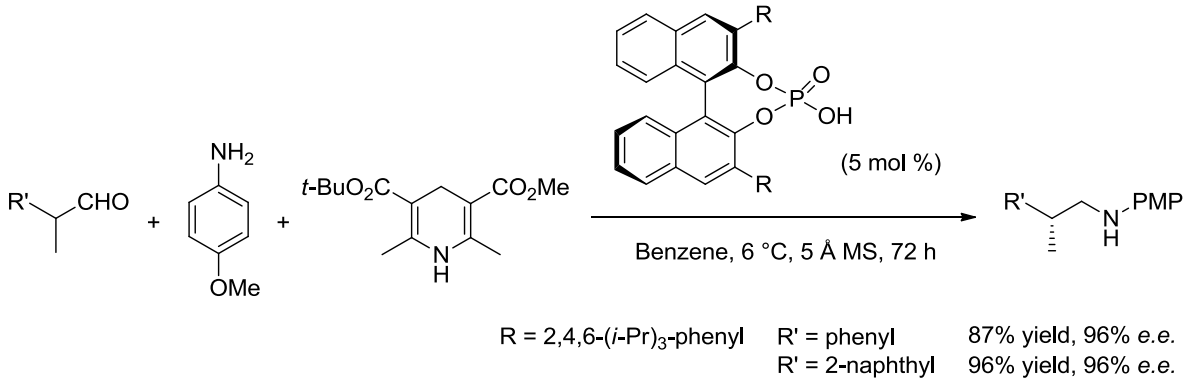


Figure 2.1.4 Proposed cycle for α-branched aldehydes dynamic kinetic resolution

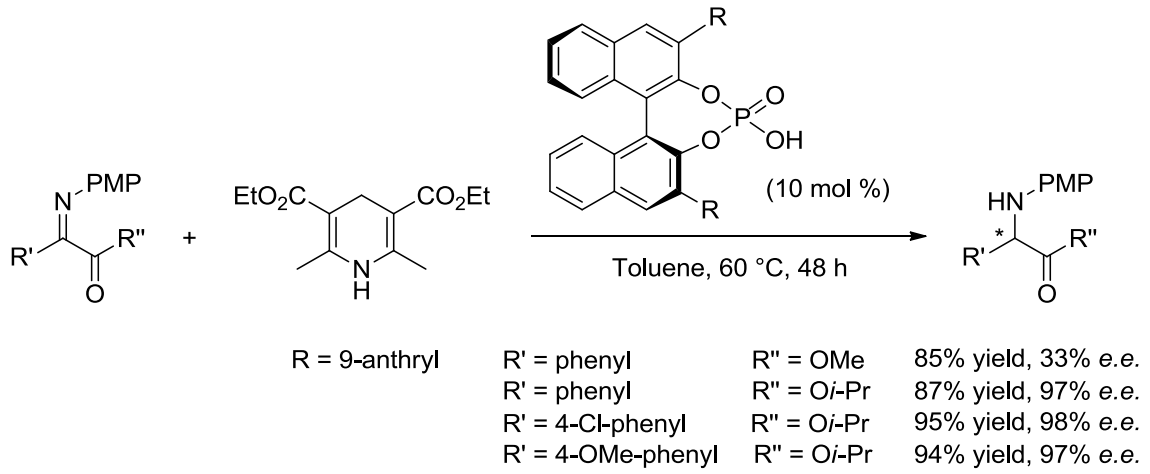
TRIP once again turned out to be the most effective and enantioselective catalyst for this transformation and provided the chiral amine product in 50% yield and an enantiomeric excess of 68%, which could be raised to 87% yield and 96% *e.e.* under optimized conditions (Scheme **2.1.5**).



Scheme 2.1.5 Reductive amination of α-branched aldehydes

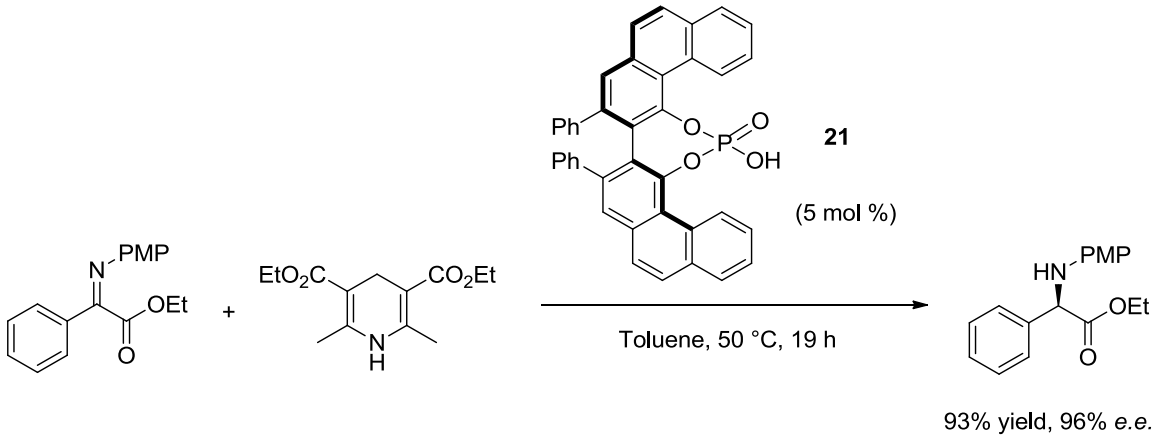
The efficient removal of water formed during the reaction seems to be important as the enantiomeric ratio improved considerably upon using 5 Å molecular sieves; furthermore, oxygen-free conditions are required as substantial acetophenone and *p*-formylanisidine formation was observed in the presence of oxygen, presumably *via* an oxidative cleavage of the hydratopaldehyde enamine intermediate.

In 2007, You extended the use of chiral phosphoric acids for the hydrogenation of α-imino esters and their derivatives, also reporting the synthesis of a gram scale sample *via* this methodology.[50] With the best performing catalyst **20j** and the optimized conditions in hand, the reaction scope was examined. Regarding the effect of different esters, authors observed that the enantioselectivity was highly dependent on the steric size of the ester R" group. High *e.e.* were obtained for the substrates bearing bulky ester groups such as *i*-Pr and *t*-Bu, whereas only 33% *e.e.* was observed for the methyl ester substrate. As for the scope of R', several substituted phenyl isopropyl esters containing either electron-donating or electron-withdrawing groups all led to good yields and excellent *e.e.* (Scheme **2.1.6**). However, a low reactivity was observed in the case of the alkyl-substituted imino ester.



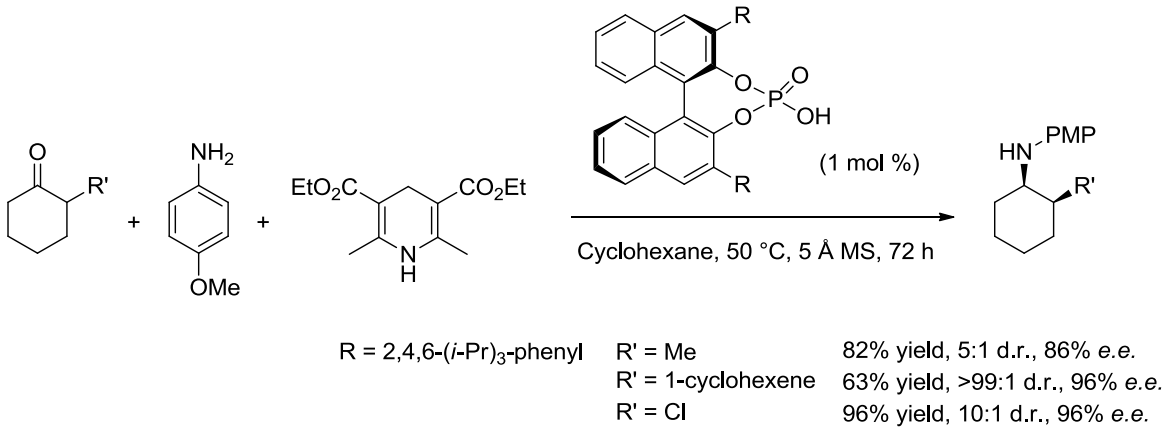
Scheme 2.1.6 Reduction of α-imino esters

Some time later, Antilla and co-workers developed an organocatalytic reduction process for the enantioselective synthesis of protected α-amino acids.[51] Using a VAPOL-derived phosphoric acid, readily available α-imino esters could be efficiently reduced to the corresponding amines with stoichiometric amounts of ethyl Hantzsch ester. It is notable that this VAPOL derivative **21** was found to be superior in this reaction to BINOL derived phosphoric acid, as well as to a small library of alternative chiral phosphoric acid catalysts. The scope of the reaction is quite general: iminoesters derived from both aromatic and aliphatic α-keto esters could smoothly be transformed. However, the analogous reductive amination process involving *in situ* imino ester formation was not efficient and was selective only when starting materials bearing aliphatic substituents were used (Scheme **2.1.7**).



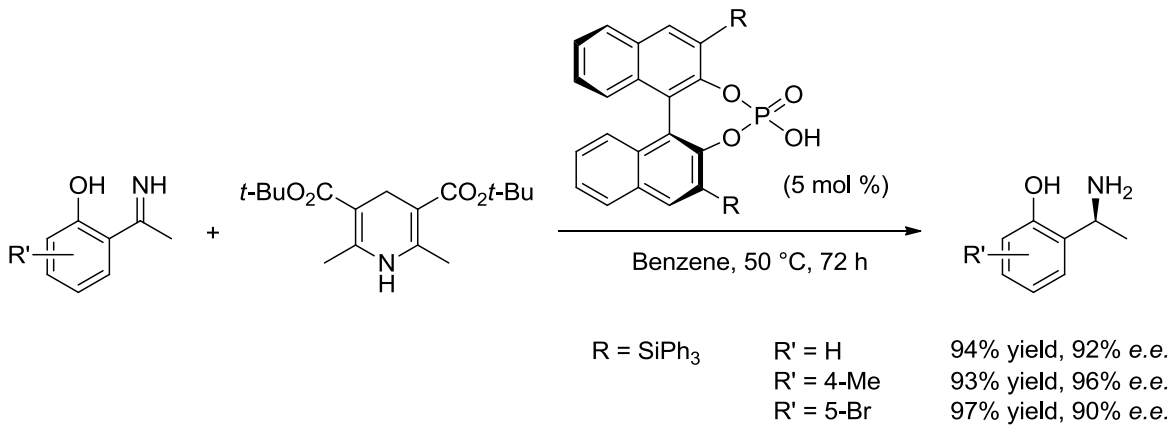
Scheme 2.1.7 VAPOL-derived phosphoric acid as catalyst of reduction of α-imino esters

Three years later, List's group reported the first example of the catalytic asymmetric reductive amination of racemic α-branched ketones using dynamic kinetic resolution (DKR).[52] An important feature of this process is its tolerance of a variety of different substituents whilst maintaining excellent enantioselectivity. Simple alkyl-substituted substrates are particularly reactive, requiring only a very low amount of catalyst, while sterically more-demanding substrates, as well as aromatic substrates, require slightly higher catalyst loadings. Even chlorine is tolerated in the α position, and, by employing 2.4 equivalents of the Hantzsch ester, even α,β-unsaturated, α-branched ketones could be converted into the desired product in reasonable yields and excellent selectivity (Scheme **2.1.8**).



Scheme 2.1.8 Asymmetric reductive amination of α-branched ketones

At the same time, Wang and co-workers reported the first examples of enantioselective transfer hydrogenation of unprotected *ortho*-hydroxyaryl alkyl N-H ketimines using chiral phosphoric acid as a catalyst and Hantzsch ester as the hydrogen source.[53] The hindered (*S*)-3,3'-bis(triphenylsilyl)-substituted phosphoric acid turned out to be the most effective in terms of transfer of the stereochemical information. Benzene was a better reaction medium amongst the solvents screened. Under the optimal conditions, authors managed to isolate the unsubstituted amine in 94% yield with 92% *e.e.*, 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 **2.1.9**). 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 2.1.9 Enantioselective reduction of *ortho*-hydroxyaryl alkyl ketimines

From NMR studies, authors observed that this phosphoric acid **20n** is capable of breaking the intramolecular H-bond between the phenolic O-H and the imine nitrogen and, most probably, activating the imine *via* the formation of an intermolecular H-bond with the imine nitrogen. Consequently, authors proposed transition state **A** (Figure **2.1.5**), wherein the phosphoric acid formed H-bonds with both the hydroxyl and the imine functions of the substrate. The hydride transfer would then occur from the *Re* face of the imines to deliver the amines with the observed (*S*) configuration.

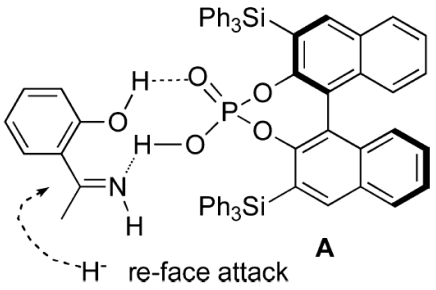
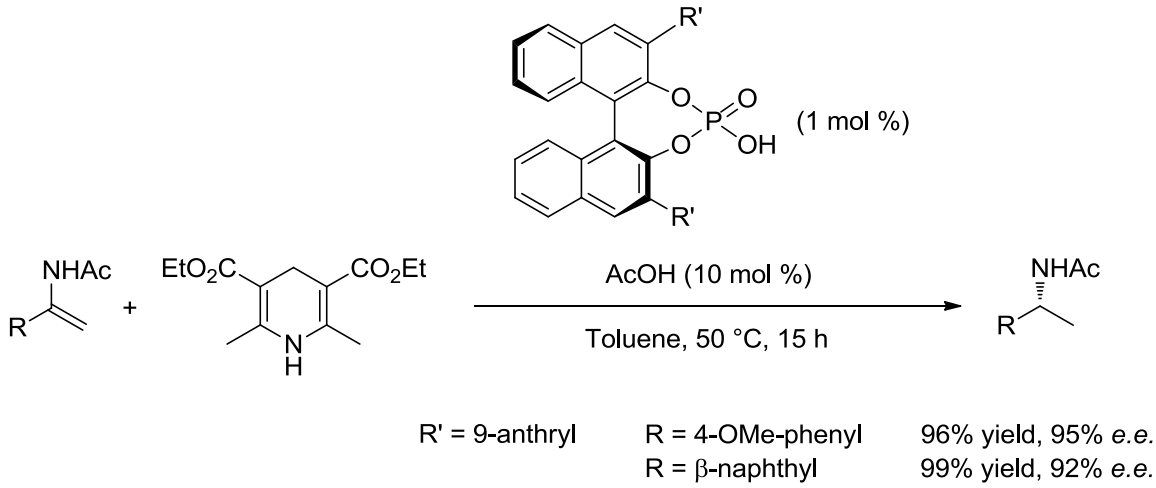


Figure 2.1.5 Model of stereoselection

One important breakthrough in the field was achieved by Antilla and Li in 2009, when they reported the asymmetric hydrogenation of enamides with high enantioselectivity through the employment of chiral phosphoric acid catalysis.[54] Although the reductive amination of ketones and the hydrogenation of ketimines catalyzed by chiral Brønsted acids were already reported with high enantioselectivities, these reactions were limited primarily to reactants derived from aniline and its analogues.

As a result, the deprotection of the aromatic group to release the amino group could be relatively difficult, rendering these methods less synthetically appealing. On the contrary, when considering *N*-acyl enamide substrates, the acyl group of the reduction product can be easily removed under standard procedures in good yield.

Starting from the assumption that a reactive iminium was the intermediate of this reaction, authors followed the catalytic strategy to pair the phosphoric acid with a suitable achiral acid, to facilitate iminium formation while being inactive in the hydrogenation step, reporting a significative increase of isolated yield with no loss of *e.e.* (Scheme **2.1.10**).



Scheme 2.1.10 Asymmetric reduction of enamides

In the hypothesized catalytic cycle, in the presence of catalyst and the cocatalyst acetic acid, the enamide **A** is tautomerized to the corresponding imine, which is activated by the acid *via* an iminium intermediate. In the following step, only chiral phosphoric acid is active enough to catalyze the hydrogenation of the imine, while the acetic acid role is probably only to help keep a sufficient concentration of iminium intermediate present since was used in such small quantities (Figure **2.1.6**).

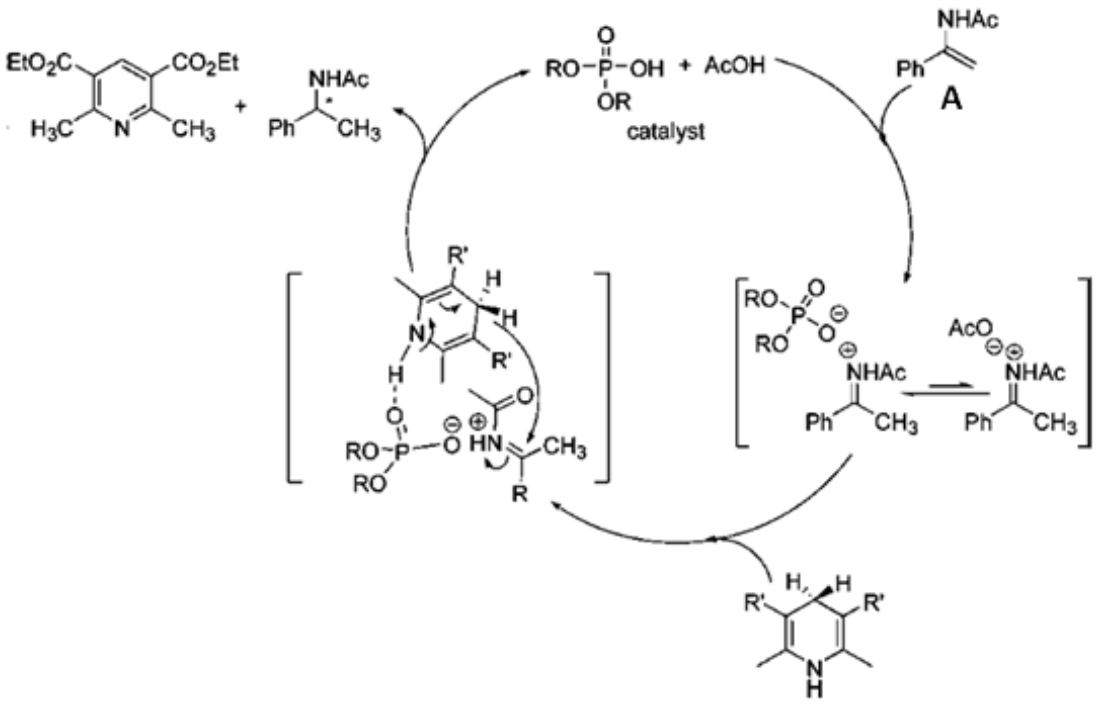
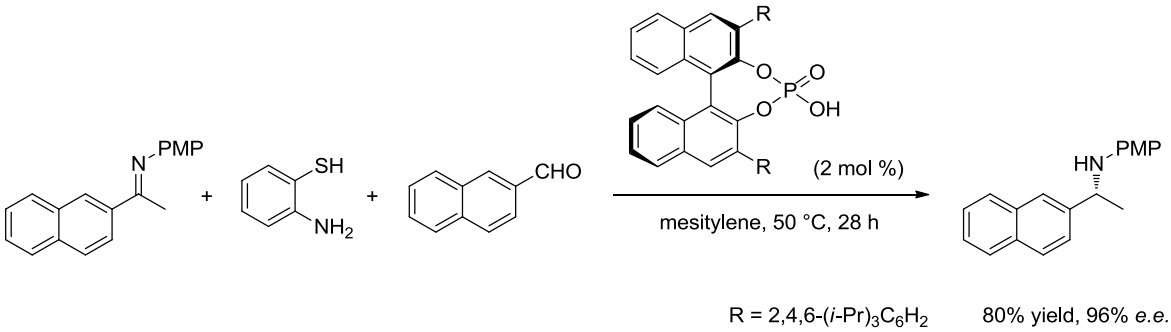


Figure 2.1.6 Proposed catalytic cycle for the enantioselective reduction of enamides

Until recently, the hydrogen sources employed in organocatalytic hydrogenations were limited to Hantzsch esters. In 2009, Akiyama and Zhu introduced benzothiazoline derivatives as a novel hydrogen source, using as driving force of the reaction their conversion into the more stable aromatic benzothiazole after hydride transfer.[55] In this first work, authors explored the reduction of aromatic ketimines: electron-donating and electron-withdrawing substituents on the phenyl ring were well tolerated in this hydrogenation system and even an example of aliphatic ketimine underwent the reduction while maintaining excellent enantioselectivity.

However, the distinct advantage of this protocol is that the reducing agent can be generated *in situ* from 2-naphthalenecarbaldehyde and 2-aminothiophenol. Thus, the three-component reaction between the imine and the *in situ* generated benzothiazoline becomes operative without considerable loss of enantioselectivity and chemical yield (Scheme **2.1.11**).



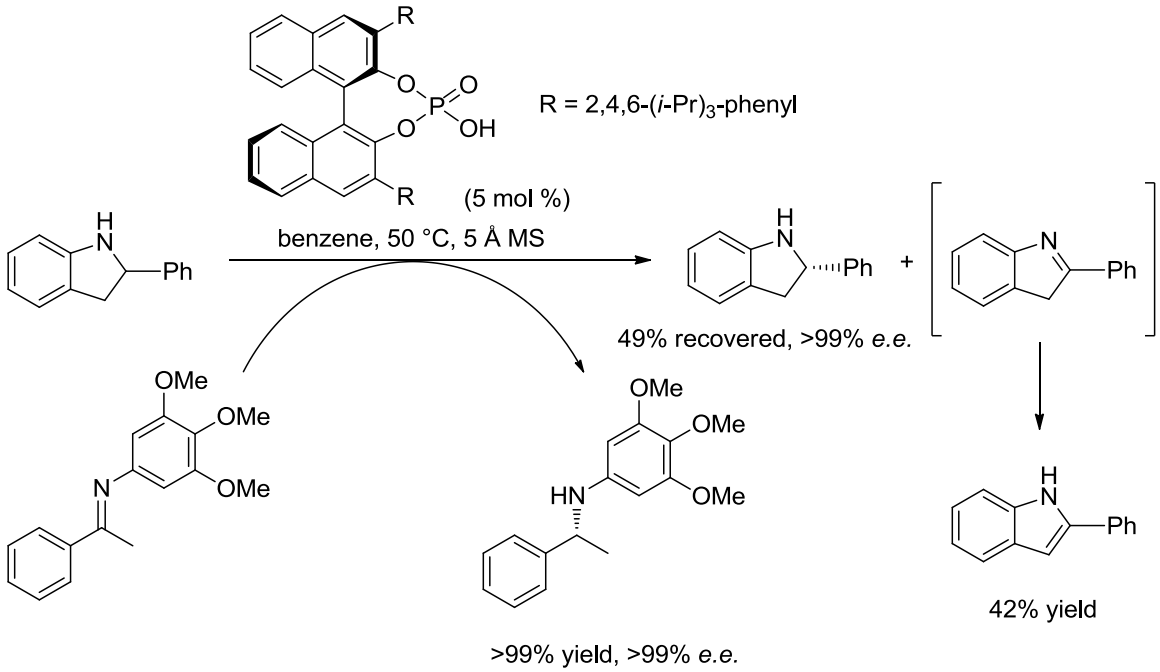
Scheme 2.1.11 Hydrogen transfer reaction by use of benzothiazoline generated *in situ*

Successive reports from the same group described the application of this new class of reducing agents to the reduction of α-imino esters,[56] giving high yields and enantioselectivities over a wide range of substrates, and to the reductive amination of aliphatic ketones.[57] It is noteworthy that the use of this novel hydrogen source generally provides the corresponding products with higher enantioselectivities than those obtained in previous reports where Hantzsch ester was employed, suggesting that benzothiazolines are more effective reagents for these transformations.

One of the disadvantages of the transfer hydrogenation reaction that uses the Hantzsch ester lies in the difficulty of separating the product from the pyridine derivatives generated by dehydrogenation, and these benzothiazolines agents suffer from the same problem. As further development, Akiyama and co-workers introduced a hydroxy group onto the 2-aryl group of the benzothiazoline. The advantage resulting from this modification is three-fold:

- the benzothiazole by-product precipitates and is readily removable by filtration
- additional purification by chromatography is facilitated due to the presence of the polar hydroxy group
- it permits further modification to support the benzothiazoline on a polymer

In 2013, Akiyama's group reported the Brønsted acid-catalyzed asymmetric hydrogen transfer reaction of indolines employing imines as hydrogen acceptors, which represents the first example of an efficient oxidative kinetic resolution of secondary amines.[58] This approach allows the isolation of 2-substituted and 2,3-disubstituted indolines in high yields with excellent enantioselectivities, allowing at the same time the synthesis of chiral amines in a nearly enantiopure form (Scheme **2.1.12**).



Scheme 2.1.12 Catalytic oxidative kinetic resolution of indolines

From a mechanistic point of view, one enantiomer of the indoline would preferentially participate in this hydrogen transfer reaction and be converted into a cyclic imine, which would immediately isomerize to a stable indole. On the basis of the bifunctional nature of the phosphoric acid and preliminary DFT calculations, authors hypothesized a dicoordinated cyclic TS. Whereas the Brønsted acidic proton activates the ketimine, the Lewis basic phosphoryl oxygen coordinates to the indoline N−H. Eight possible TS structures can be obtained from the two absolute configurations of indoline, the two configurations of the imino group and the enantiofacial selection of the ketimine. The most favorable TS resulting from DFT calculations shows the *N*-aryl group of the ketimine and the 2-phenyl group of the indoline to have no unfavorable steric interactions. In contrast, the steric hindrance between the 3,3′-substituents of the chiral phosphoric acid and the two aryl groups of the substrates destabilizes the other possible transitions states (Figure **2.1.7**).

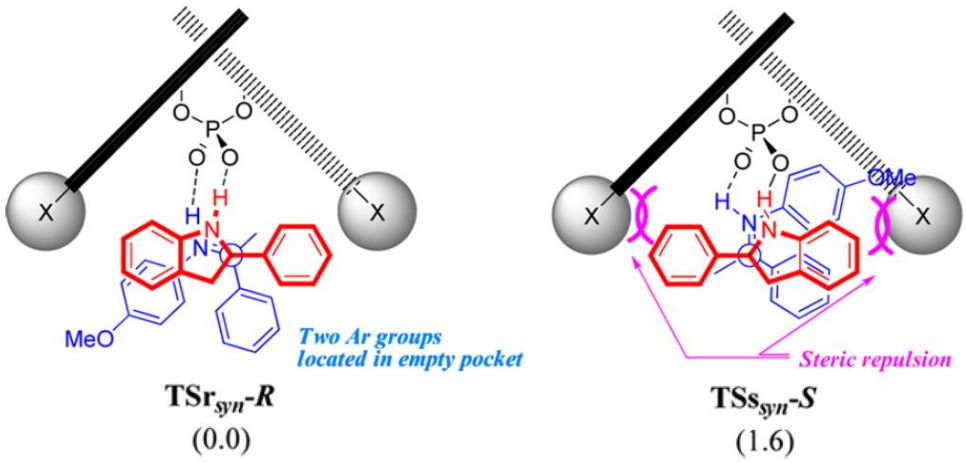
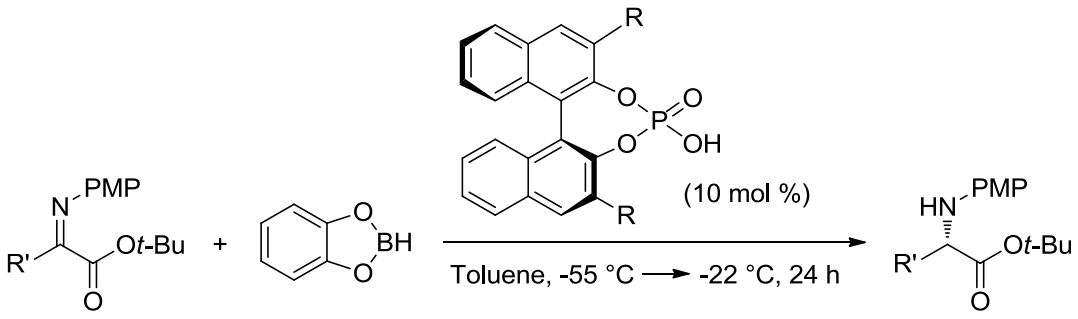


Figure 2.1.7 Representation of the two most favored TS obtained from DFT calculations

At the same time, extending the scope of the work reported by Antilla in 2011 (see the "Reduction of C=O Bonds" section of this chapter), Enders and co-workers described the reduction of ketimines and α-imino esters with catecholborane *via* Brønsted acid catalysis.[59] Under optimized conditions, various electron-rich as well as electron-deficient aromatic α-imino esters with different substitution patterns were reduced, obtaining the corresponding products with very good enantioselectivity and high chemical yield (Scheme **2.1.13**).



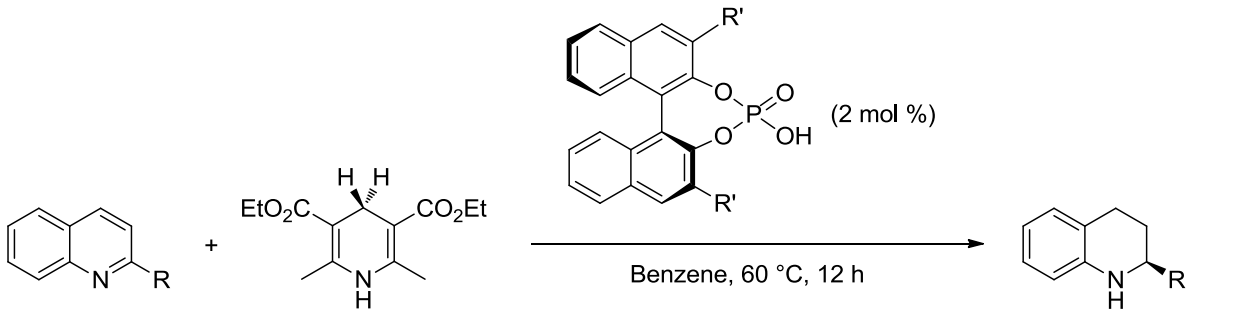
Scheme 2.1.13 Enantioselective reduction of α-imino esters with catecholborane

It's noteworthy that aromatic imino esters substituted in the 2 or 3-position gave superior results compared to the 4-substituted substrates. Authors assumed that the substituent in the 4-position directly points to one of the catalyst's moieties in the

transition state structure, resulting in lower selectivities with increasing steric demand of the substituent.

2.2 Reduction of heterocyclic C=N bonds

Examples of efficient catalysts for the asymmetric hydrogenation of aromatic and heteroaromatic compounds are quite rare, even amongst the chiral Rh, Ru, and Ir complexes. It was therefore an important breakthrough the development by Rueping's group in 2006 of an enantioselective phosphoric acid catalyzed partial reduction of quinoline derivatives,[60] which are of great synthetic importance in the preparation of pharmaceuticals and agrochemicals, as well structural key element of many alkaloids. This represent the first example of a metal-free reduction of heteroaromatic compounds. After screening of a variety of sterically congested phosphoric acid, (*R*)-(−)-9-phenanthryl-1,1′-binaphthyl-2,2′-diyl hydrogenphosphate was selected as catalyst of choice to generate 2-phenyltetrahydroquinoline in 97% *e.e.* (Scheme **2.2.1**).



Scheme 2.2.1 Enantioselective partial reduction of quinoline derivatives

Examining the scope of this reaction, authors found out that this class of catalyst is able to afford several tetrahydroquinolines with aromatic and heteroaromatic residues as well as aliphatic substituents in good yields and high enantioselectivities.

Mechanistically, Rueping's and co-workers assume 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 **2.2.1**). 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 **C**, which will again be subjected 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.

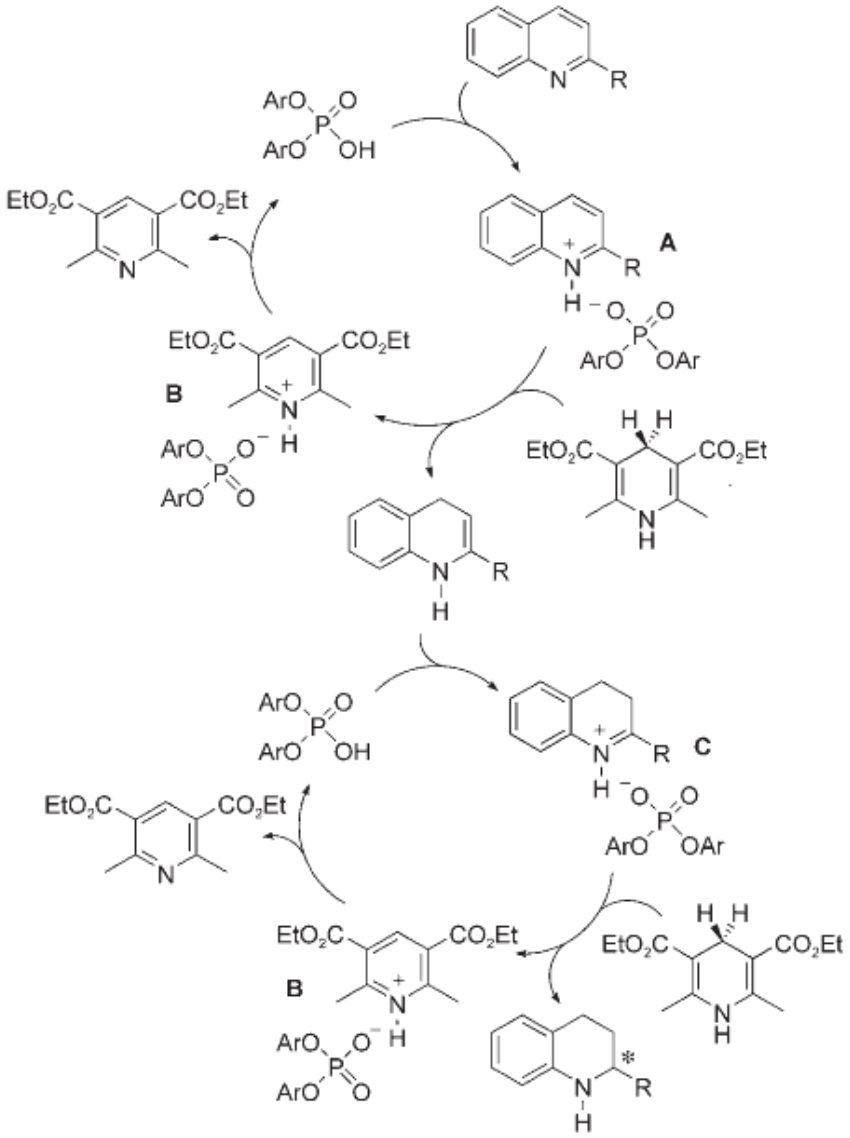
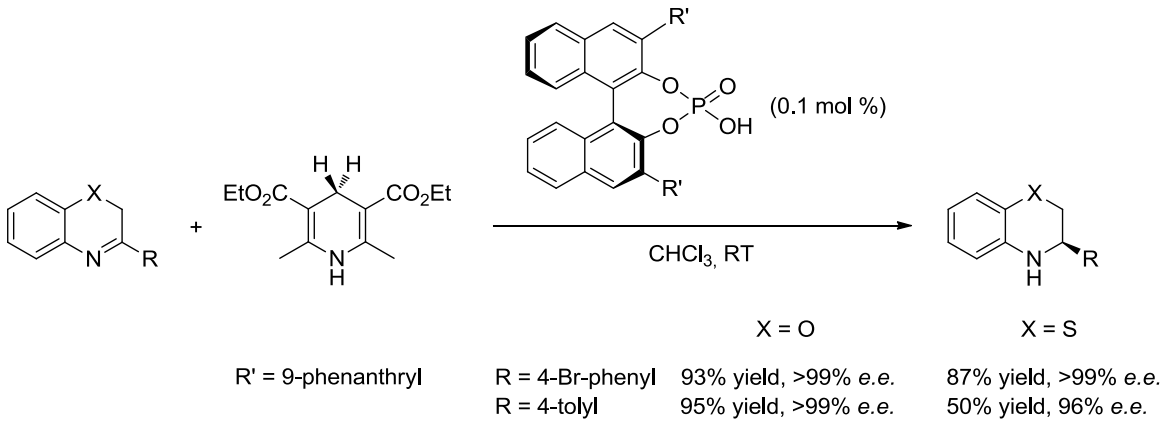


Figure 2.2.1 Catalytic cycle for phosphoric acid catalyzed quinoline hydrogenation

The absolute configuration of the products can be explained by a stereochemical model proposed by the authors. In the transition state 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.

Later in that year, the same group extended this catalytic methodology to the hydrogenation of cyclic imines, such as benzoxazine and benzothiazine.[61] Again, 9-phenanthryl derivative of BINOL phosphoric acid was selected as best performing catalyst. Further studies allowed to decrease the catalyst loading to 0.01 mol % without a considerable loss in reactivity and selectivity, one of the lowest catalyst loading to be reported for an organocatalytic enantioselective transformation at the time. 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 **2.2.2**).



Scheme 2.2.2 Asymmetric partial reduction of benzoxazine and benzothiazine

It is worth mentioning that this is the first enantioselective hydrogenation of benzothiazines, and represents one of the advantage 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 applied this system to the reduction of benzoxazinones, managing to obtain the cyclic aryl glycine derivatives in good yields and enantioselectivities (90–99% *e.e.*), which then were able to be opened to the corresponding linear amino acid amides without racemization.

Authors hypothesized that, similar to several biomimetic transfer hydrogenations, benzoxazines and benzothiazines would be activated by catalytic protonation through Brønsted acid (Figure **2.2.2**). This activation would generate a chiral ion pair, which would subsequently undergo a hydride transfer addition from Hantzsch dihydropyridine to give the desired dihydro-2H-benzoxazine and benzothiazine as well as the regenerated phosphoric acid.

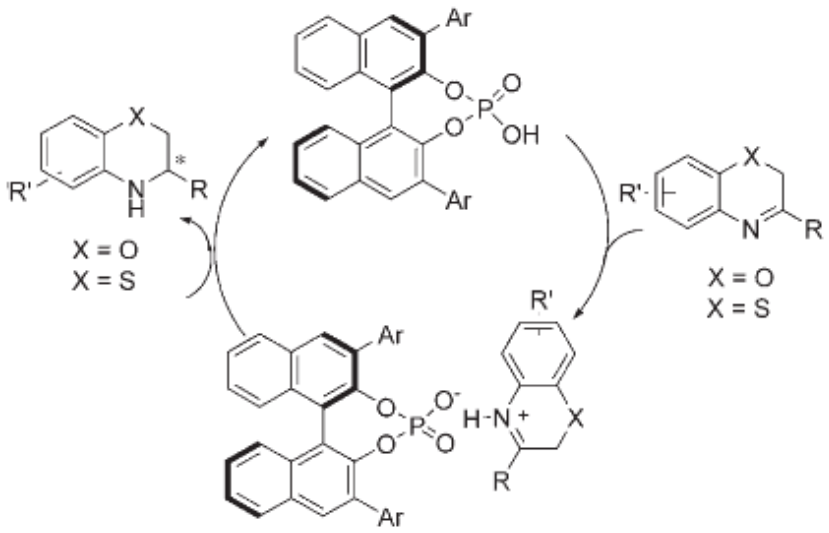


Figure 2.2.2 Proposed catalytic cycle for benzoxazine and benzothiazine hydrogenation

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 **2.2.3**).

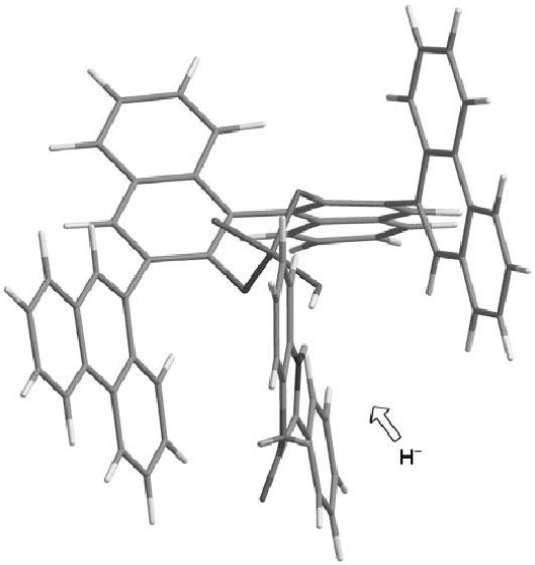


Figure 2.2.3 Model of stereoselection

In 2008 Du and co-workers further improved the asymmetric transfer hydrogenation of quinolines introduced by Rueping by the use of new chiral phosphoric acid catalysts.[62] Since the substitutents 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 no enantioselectivity), Du's group assumed that if the substituents at

the 3,3'-positions of BINOL phosphate **I** possess two stable stereogenic axes, then better performance may be achieved compared to the mono axial catalysts based on the same scaffold. Indeed, the newly proposed catalysts possess three stereogenic axes and have a larger chiral pocket compared with the previously developed phosphoric acid catalysts (Figure **2.2.4**).

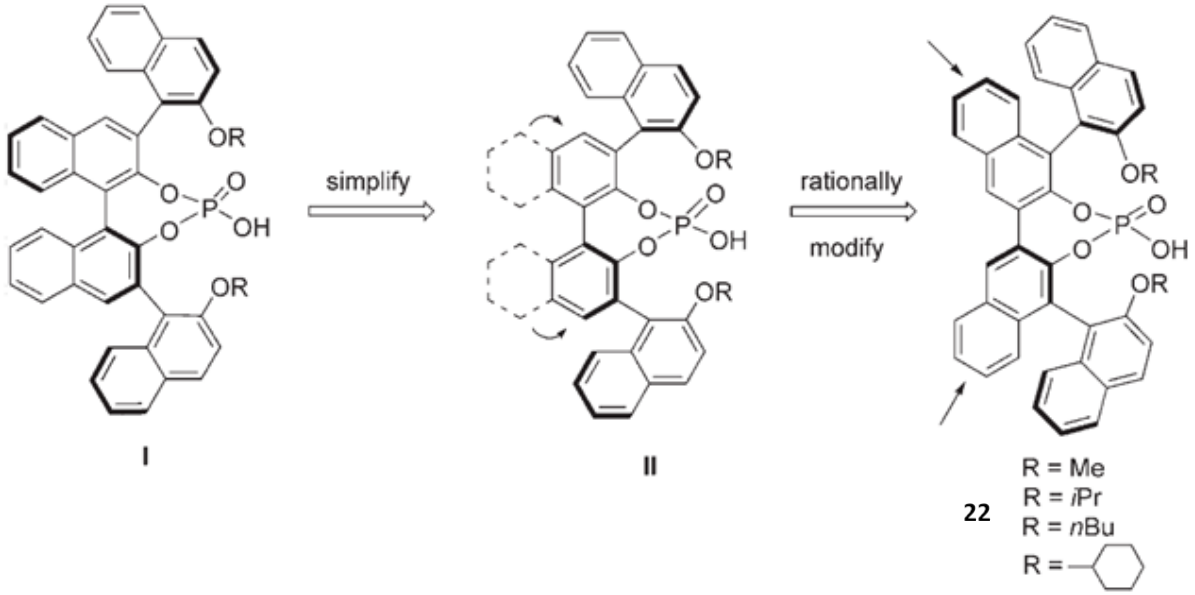
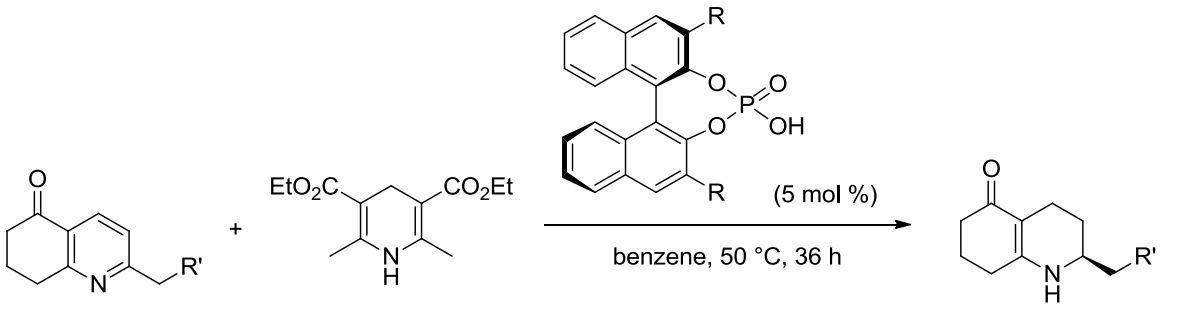


Figure 2.2.4 Development of new chiral phosphoric acid catalysts

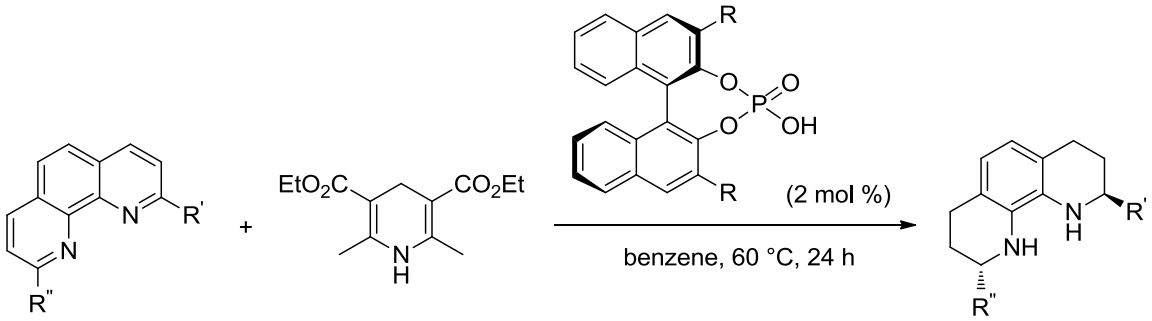
A variety of 2-aryl-substituted tetrahydroquinolines were already synthesized with excellent enantioselectivities under the conditions developed by Rueping's group, but 2-alkyl-substituted tetrahydroquinolines gave lower enantioselectivities (87–91% *e.e.*). With the use of this new phosphoric acid,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

Rueping and Antonchick successively applied the cascade transfer hydrogenation strategy to the enantioselective reduction of pyridine derivatives.[63] Catalyst **20j** functioned efficiently in the hydrogenation of this class of compounds to furnish the corresponding hexahydroquinolinones with high enantioselectivities. The method allows access to enantioenriched nitrogen heterocycles as useful precursors of various natural products. The mechanism proposed by the authors is analogue to the one already described for the partial reduction of quinoline derivatives (Scheme **2.2.3**).



Scheme 2.2.3 Enantioselective reduction of pyridines catalyzed by phosphoric acid

Later, Metallinos et al. reported the enantioselective reduction of 2-substituted and 2,9-disubstituted 1,10-phenanthrolines (Scheme **2.2.4**).[64]

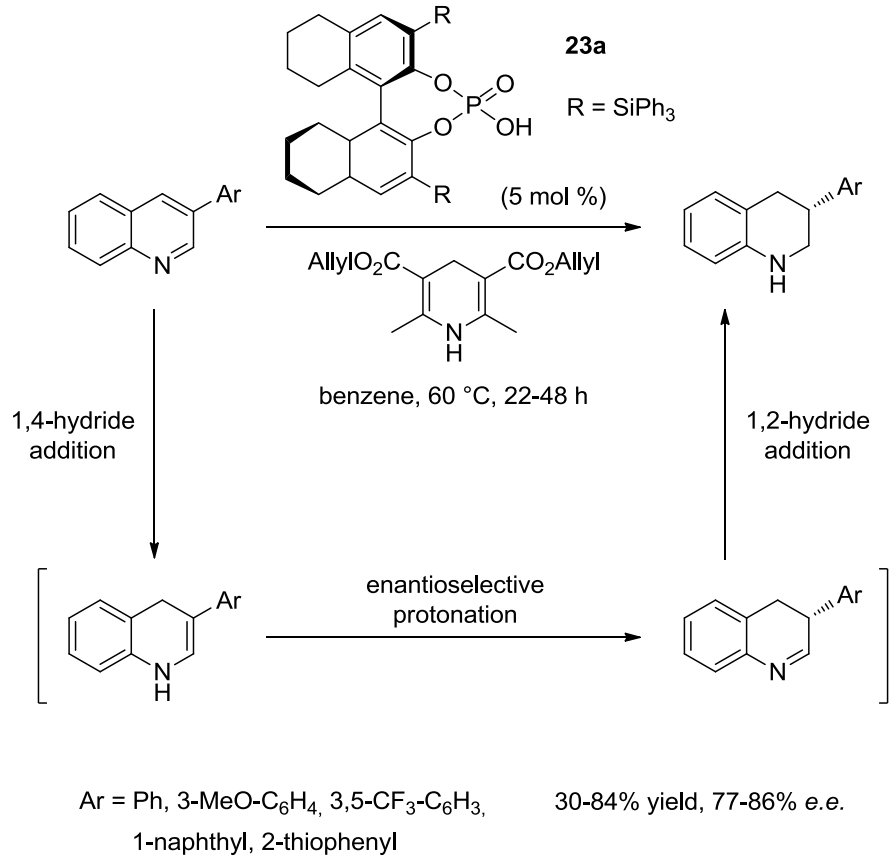


Scheme 2.2.4 Chiral Brønsted acid catalyzed reduction of substituted phenanthrolines

Although the method does not extend easily to substrates with larger substituents (*i*-Pr, Ph), which are plagued by low enantioselectivity and/or low yields, and in spite of the fact that considerable amounts of *meso*-isomers were formed in the hydrogenation of 2,9-disubstituted 1,10-phenanthrolines, the desired octahydrophenanthrolines were generally obtained with good to excellent enantioselectivities.

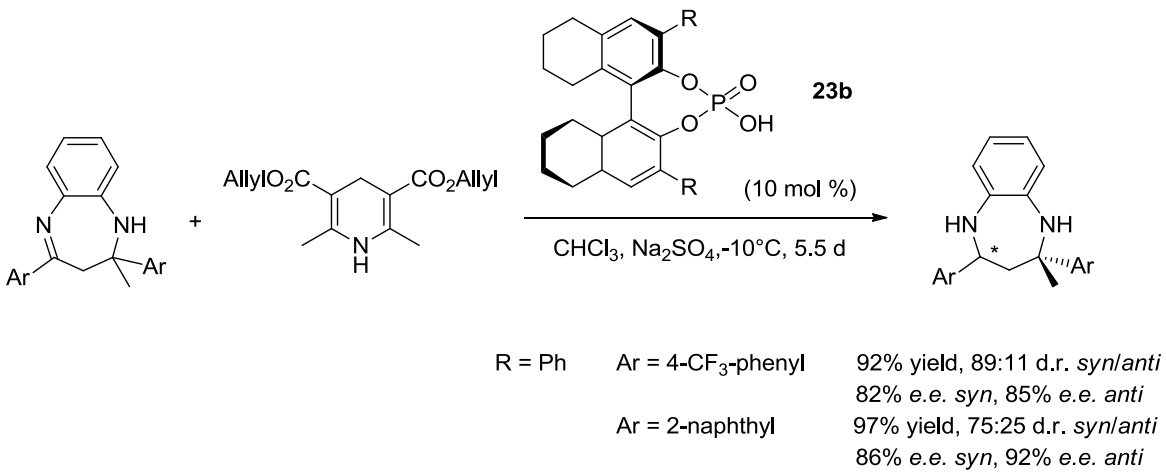
Rueping et al. further extended the method to the hydrogenation of 3-substituted quinolines.[65] The mechanism of the stereodetermining step is entirely different from that of the asymmetric hydrogenation of 2-substituted quinolines, where the 1,2-hydride addition step is the key to determining the stereochemical outcome. Here instead, the key step of the asymmetric transfer hydrogenation of 3-substituted quinolines is the

enantioselective protonation of the intermediary enamine, which, after 1,2-hydride addition, results in the 3-substituted tetrahydroquinoline with good enantioselectivities (Scheme **2.2.5**). Moreover, the authors applied this methodology to the reduction of 2,3-substituted quinolines, which under the optimized reaction conditions allowed to isolate the octahydroacridine in good yield and with excellent diastereo- and enantioselectivities.



Scheme 2.2.5 Transfer hydrogenation of 3-substituted quinolines to tetrahydroquinolines

In 2009 Gong and co-workers reported a facial synthesis of chiral 1,3-diamine derivatives bearing a quaternary stereogenic center *via* the transfer hydrogenation of 2,4-diaryl-2,3-dihydrobenzodiazepines on the basis of dynamic kinetic resolution, isolating the products in high yields with good to high stereoselectivity (Scheme **2.2.6**).[66]



Scheme 2.2.6 Asymmetric reduction of dihydrobenzodiazepines

The presence of electronically poor aryl substituents on the substrate was beneficial to diastereoselectivity. Instead, enantiomeric excess did not relate on the electronic characteristic of the substituents, but it seemed that a *para*-substitution was important to achieve high levels of enantioselectivity.

The transfer hydrogenation of the *S*-enantiomer of the racemic starting material proceeds rapidly under catalysis of the Brønsted acid to afford the (2*S*,4*R*)-*syn* product predominantly, along with minor amounts of (2*S*,4*S*)-*anti*. Meanwhile, the opposite enantiomer undergoes slow transfer hydrogenation; at the same time, the unreacted amount of *R*-enantiomer quickly racemizes *via* the sequential retro-Mannich and Mannich reactions. (Figure **2.2.5**).

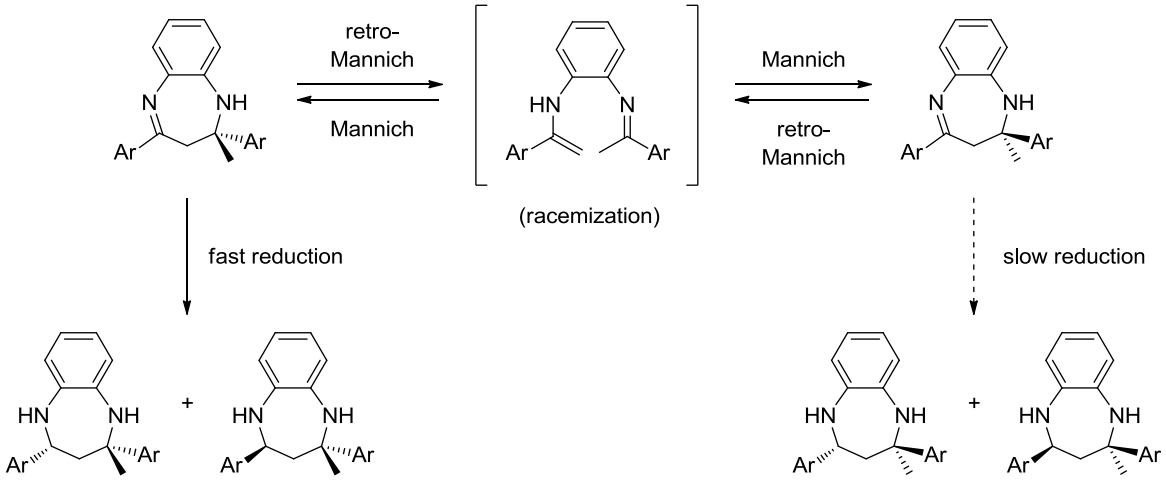
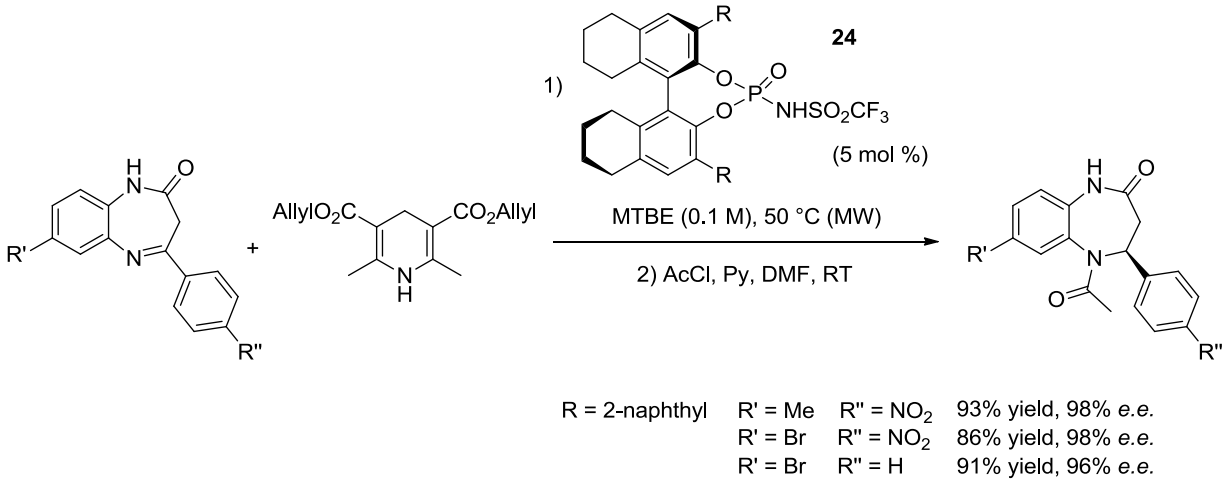


Figure 2.2.5 Mechanism of the dynamic kinetic transfer hydrogenation

One year later, 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 β-amino acids.[67] Due to the basic nature of these benzodiazepinones, the reactions conducted with various chiral phosphoric acid diesters gave only very low conversion, while improved reactivity was obtained when the corresponding *N*-triflyl phosphoramides were employed as catalysts, with 2-naphthyl derivative being the 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 **2.2.7**).



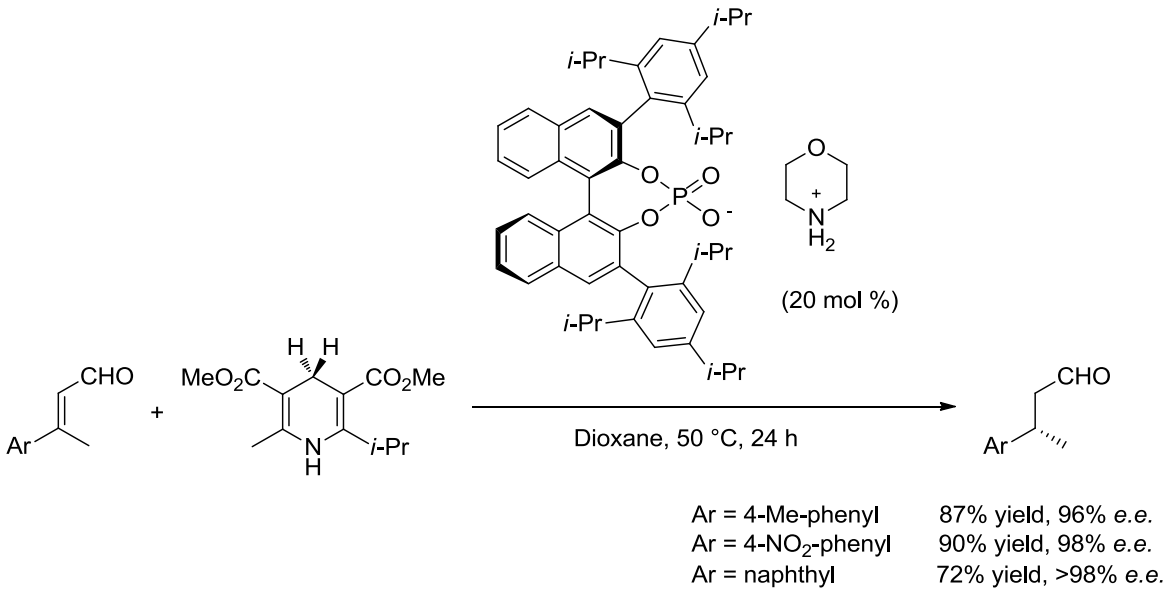
Scheme 2.2.7 Asymmetric reduction of benzodiazepinones

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. While the selectivities were essentially the same, the yield were higher with an electronwithdrawing group substituent on 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.

2.3 Reduction of C=C bonds

In 2006,[68] List and coworkers reported that the organic salt of (*R*) 3,3'-bis(2,4,6-triisopropylphenyl)-1,1'-binaphthyl-2,2'-diyl hydrogen phosphate (TRIP) and morpholine was able to promote the transfer hydrogenation *via* Hantzsch dihydropyridine of α,β-

unsaturated aldehydes with high levels of enantioselectivity, ranging between 96% and >98% *e.e.* (Scheme **2.3.1**).

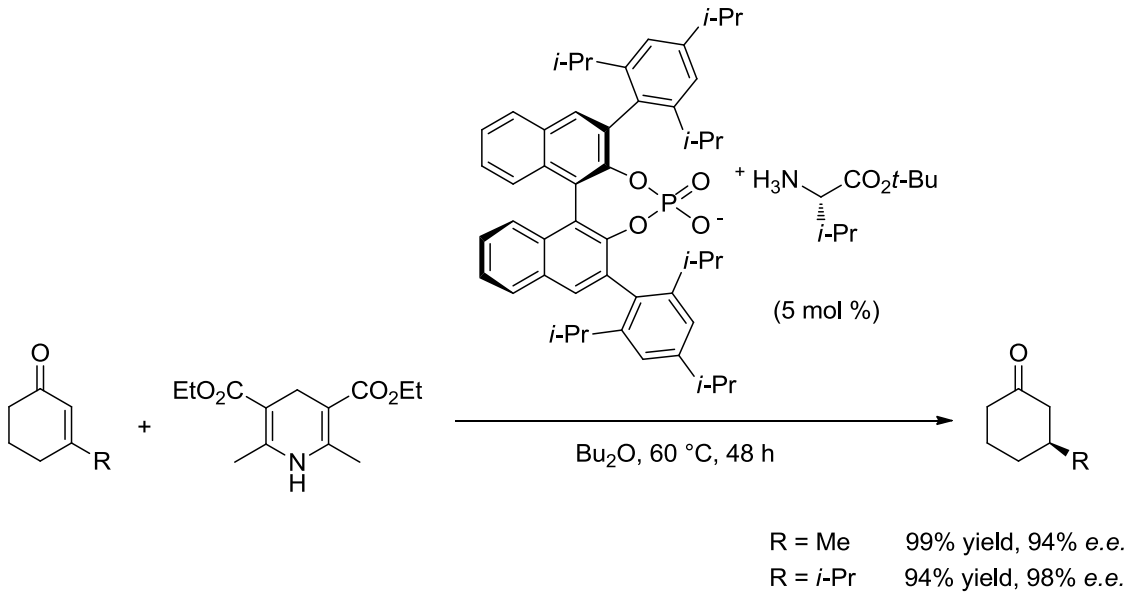


Scheme 2.3.1 Enantioselective reduction of α,β-unsaturated aldehydes

It is noteworthy that this catalyst was successfully used to convert citral into (*R*)-citronellal with an *e.e.* value of 90%, which represents the highest enantioselectivity reported until then for this reaction. The result represented an advancement compared to the previous studies by List and McMillan, where chiral amine-based catalysts were not useful for the reduction of sterically nonhindered aliphatic substrates.[69]

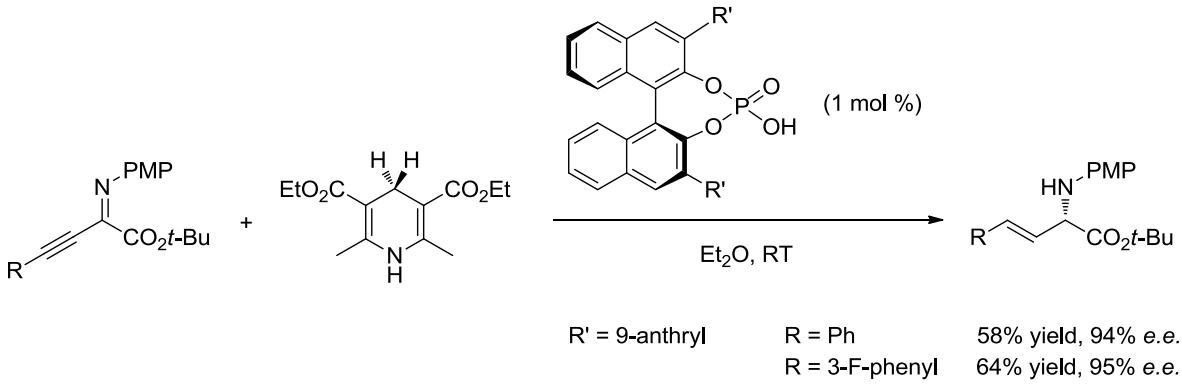
Authors proposed that the reaction proceeds *via* an iminium ion intermediate since salts of tertiary amines are ineffective, and stereoselection presumably occurs in the cationic transition state of the reaction by means of a stereochemical communication with the chiral phosphate counteranion, possibly through CH···O hydrogen-bonding interactions. However, from an historical point of view, it should be mentioned here that List and co-workers reported in 2004 the reduction of β-methyl, α,β-unsaturated aldehyde using a substoichiometric amount of the HCl salt of a chiral imidazolinone to afford the product in 81% yield with 81% *e.e.*, as the first example of an enantioselective metal-free transfer hydrogenation of an olefin.[70] Immediately after List[71] and MacMillan[72] almost concurrently reported that β,β-disubstituted aldehydes could be reduced in good yields and with excellent enantioselectivity. The catalysts used by both groups were based on the same imidazolidinone skeleton and differed only in the ring substituents.

Back to the chiral Brønsted acids-promoted reactions, some months later List successfully extended the use of these catalysts to the more challenging transfer hydrogenation of α,β-unsaturated ketones with Hantzsch esters.[73] Authors started from the assumption that primary amine catalysts, due to their reduced steric requirements, might be suitable for the activation of ketones. After screening of a variety of amino acids, the salt formed by (*R*)-(TRIP) and valine was selected as best performing catalyst (Scheme **2.3.2**). While the effect of the amino acid ester α-substituent on the enantioselectivity was not very pronounced, the chirality present in the amino acid seems to be required as corresponding glycine derived catalyst gave significantly reduced enantioselectivity, as did the reaction promoted by the phosphoric acid alone. Interestingly, when the opposite enantiomeric counteranion ((*S*)-TRIP) was used to form the catalyst, the same enantiomeric product was formed but with much lower enantioselectivity, illustrating a dramatic case of a matched/mismatched catalyst-ion pair combination.



Scheme 2.3.2 Enantioselective reduction of α,β-unsaturated ketones

Two years later, You and co-workers reported the synthesis of β,γ-alkenyl α-amino acids *via* chiral phosphoric acids catalyzed asymmetric transfer hydrogenation,[74] which unprecedentedly reduces both the alkyne and imine moieties. It should be noted that only a *trans*-alkene substituted product was observed during the reduction. This work provides straightforward access to these compounds with high *e.e.* without needing to rely on the chiral auxiliary approach, although isolated yields are modest (Scheme **2.3.3**).



Scheme 2.3.3 Asymmetric reduction of β,γ-Alkynyl α-imino esters

In addition, several β,γ-alkynyl α-imino esters bearing different ester groups were tested for the reaction. The isolated yields of the desired products were highly dependent on the steric size of the ester groups, with methyl ester yielding the desired product in only 15% yield while moderate yields were obtained for the substrates bearing bulky ester groups. No significant influence on the enantioselectivities can instead be noticed by varying the ester group. Finally, electron-withdrawing groups on the phenyl ring are able to give excellent values of enantiomeric excess.

Experiments carried out to elucidate the mechanism of the reaction showed that the reduction of carbon-carbon triple bond is faster than that of carbon-nitrogen double bond and that the desired product can not be further reduced under these reaction conditions.

2.4 Reduction of C=O bonds

In 2011, Antilla reported the first example of highly enantioselective reduction of ketones catalyzed by a chiral phosphoric acid derivative.[75] The reduction of variously substituted acetophenone with catecholborane promoted by a series of BINOL-derived phosphoric acids gave the desired product with only modest enantioselectivity, with the catalyst **20j**, bearing a 9-anthryl group in the 3,3'-position of the scaffold as the best performing one. Quite interestingly, the corresponding *N*-triflyl phosphoramide, which is a stronger Brønsted acid than its phosphoric acid counterpart, provided the product with reverse absolute configuration and low *e.e.* However, authors found out that an increase of the enantiomeric excess could be obtained by lowering the reaction temperature to -20 °C, and it can further be raised to excellent values using 4-(dimethylamino)pyridine (DMAP) as an additive. The addition of this pyridine derivative is likely to form the

corresponding pyridium phosphate salt, a very weak acid (Figure **2.4.1**). Also other amine additives were evaluated, such as pyrrolidine, triethylamine and cinchodine, but in each case lower *e.e.* values were observed.

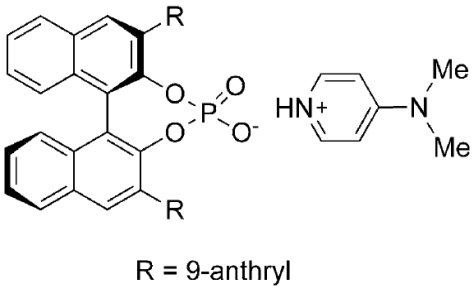
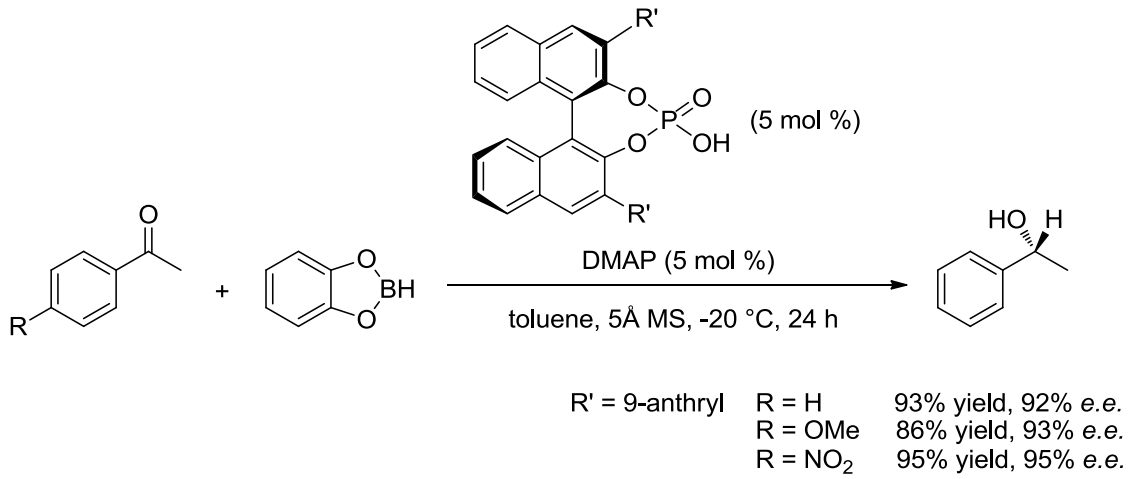


Figure 2.4.1 Proposed active catalytic species

As for the scope of the reaction, the substrates bearing either electron-donating or electron-withdrawing groups on the phenyl ring furnished the resulting chiral alcohols with good selectivity; labile functional groups, such as nitrile, nitro, ester, iodide and bromide, were generally well tolerated (Scheme **2.4.1**).



Scheme 2.4.1 Enantioselective chiral phosphoric acid catalyzed reduction of ketones

The transition state envisioned by the authors is shown in Figure **2.4.2**:

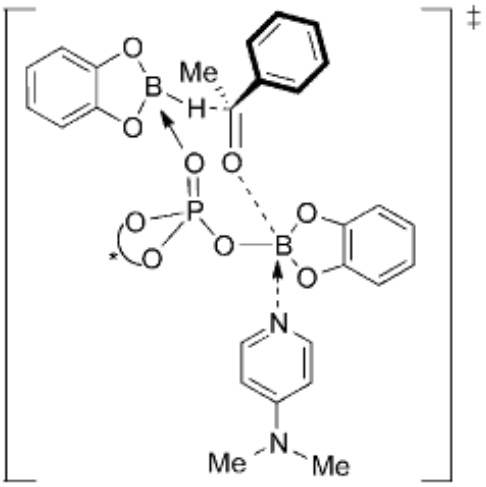


Figure 2.4.2 Proposed transition state

The boron center is believed to act as a Lewis acid to activate the carbonyl, while the P=O moiety can act as a Lewis base to increase the nucleophilicity of catecholborane. Simultaneously, the hydride from unreacted catecholborane is added to the activated carbonyl in a chiral environment to form the enantioenriched hydroboration product and regenerate the catalyst.

CHAPTER 3

Silicate-mediated stereoselective reactions catalyzed by chiral Lewis bases

"If knowledge can create problems, it is not through ignorance that we can solve them."

Isaac Asimov

The chemistry of penta- and/or hexavalent silicon compounds has recently attracted much attention because of the possibility to develop organocatalyzed enantioselective reactions in the presence of cheap, low toxic and environmental friendly species such as hypervalent silicates.[76] Even if the discovery of silicon compounds with a coordination number greater than four dates back to 1809, when the adduct $SiF_4 \bullet 2\ NH_3$ was reported by Gay-Lussac,[77] only in the last forty years the distinctive reactivity displayed by penta- and hexavalent silicon compounds has been extensively studied, and organosilicon compounds have become more and more important intermediates in organic synthesis.[78]

More recently, the possibility to develop organocatalytic silicon-based methodologies has given even new impulse to the studies in this field.[79] 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,[80] especially promoted by hypervalent silicate intermediates used as chiral Lewis bases.[81]

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.

3.1 Hypervalent bonding analysis

The theory of acid–base interactions, pioneered by G. N. Lewis at the beginning of the 20th century, is at the basis of 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*".[82] 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. A Lewis base, at variance with a Lewis acid, can indeed enhance its chemical reactivity by modifying the nucleophilicity or the electrophilicity of molecules modulating their electrochemical properties.[83] 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 change 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 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 identified nine type of bonding phenomena.[84] These are shown in Table **3.1.1**:

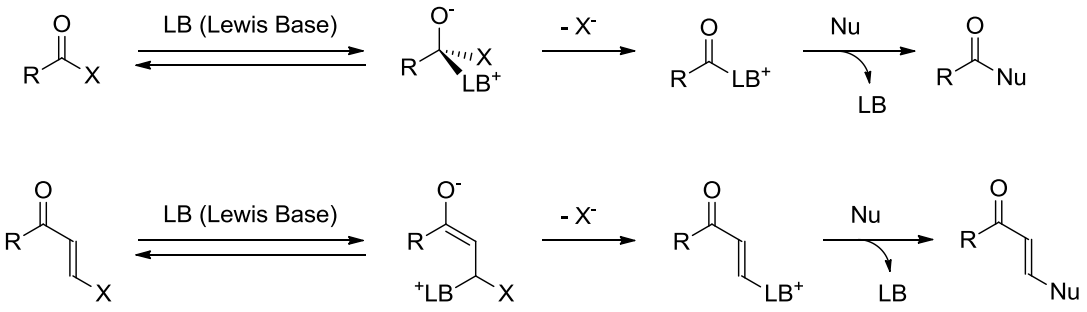
Donor	Acceptor		
	*n**	σ*	π*
n	*n* - *n**	*n* - σ*	*n* - π*
σ	σ - *n**	σ - σ*	σ - π*
π	π - *n**	π - σ*	π - π*

Table 3.1.1 Jensen's orbital analysis of molecular interactions

Although each of these combinations could represent a productive interaction, in practice, only three of these interactions are significant in terms of catalysis.[79c] These are the:

- interaction between nonbonding electron pairs and antibonding orbitals with π character (n–π* interactions)
- interaction between nonbonding electron pairs and antibonding orbitals with σ character (n–σ* 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 π character, contained in alkynes, alkenes, carbonyls, azomethines, or other common unsaturated functional groups. One example of this n–π* interaction is the 1,4-addition to α,β-unsaturated compounds (Scheme **3.1.1**).



Scheme 3.1.1 Example of n–π* interactions

The second and third interaction, n–σ* 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 σ* 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.[85] When the dative bond is formed, the preference of nucleophilic or electrophilic character of the new specie depends on the polarizability of the new generated bond, as predicted by Gutmann empirical analysis.[86] 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 **3.1.1**).

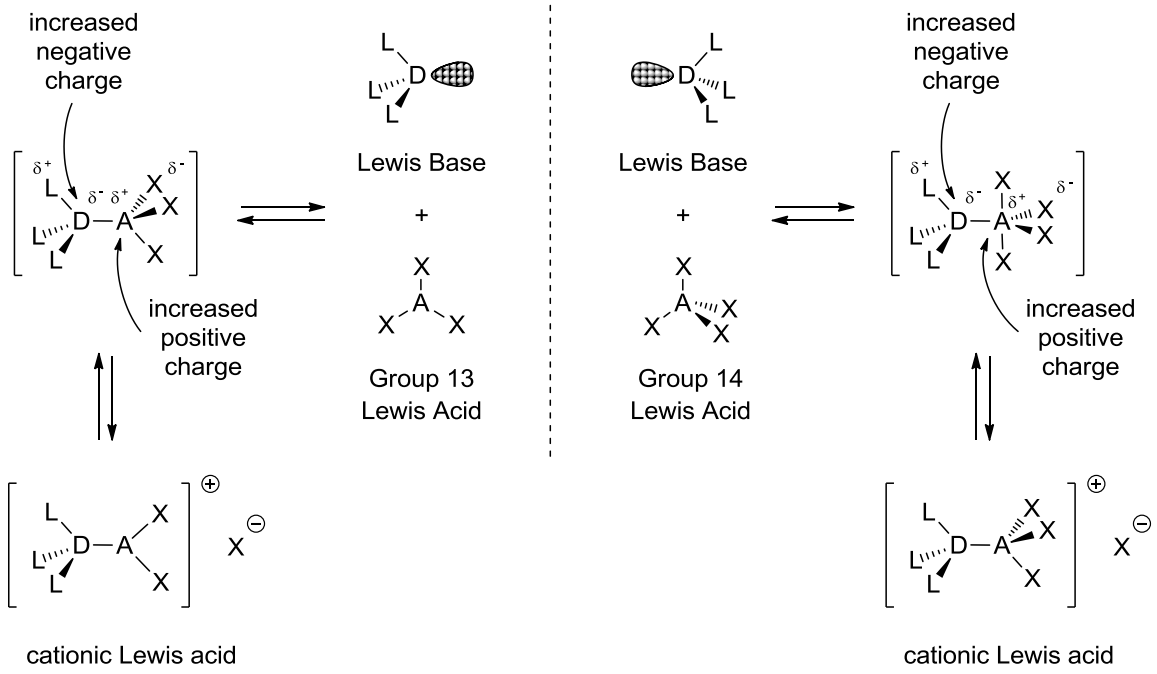


Figure 3.1.1 Electronic redistribution resulting from Lewis acid-base complexation

Support to this conclusion can be derived from calculations performed with relevant Lewis acid-base adducts of silicon tetrachloride (Figure **3.1.2**). Gordon and coworkers have studied the binding of chloride ion to $SiCl_4$ to form penta- and hexacoordinate silicates at the 6-311^{++}G(d,p) level of theory and observed changes in bond lengths and electron densities consistent with the Gutmann analysis.[87] The addition of the first chloride ion is exothermic by 40.8 kcal/mol, but, more interestingly, leads to an increase in the partial positive charge at silicon by +0.051. A corresponding increase in the partial negative charge at the chlorine atoms accompanies this change. A greater degree of the

negative charge accumulates at the axial chlorine atoms when compared to the equatorial chlorine atoms due to their involvement in a hypervalent three-center/four electron bond. Binding of the second chloride ion, although now an endothermic process by 48.3 kcal/mol, further accentuates this polarization, as the partial positive charge at silicon increases by another +0.310 kcal/mol. So, the polarization of the adjacent bonds in the metal fragment of the adduct leads to ionization of one of the other ligands and generation of a cationic metal center.

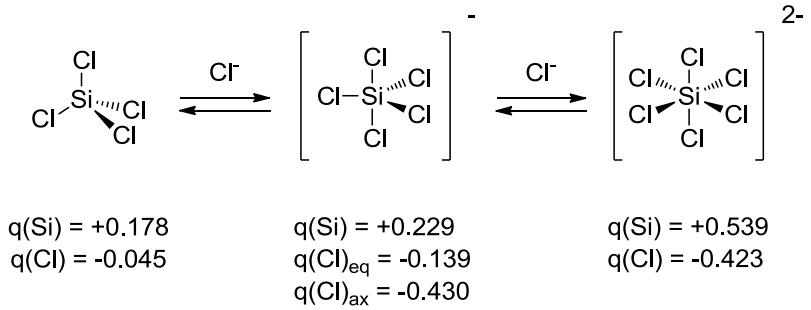


Figure 3.1.2 Gordon analysis of $SiCl_4$

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.[78] 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[80,81] as shown in Figure **3.1.3**; the second proposes instead a so called "hypervalent bonding" (showed in Figure **3.1.4**).

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). 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.

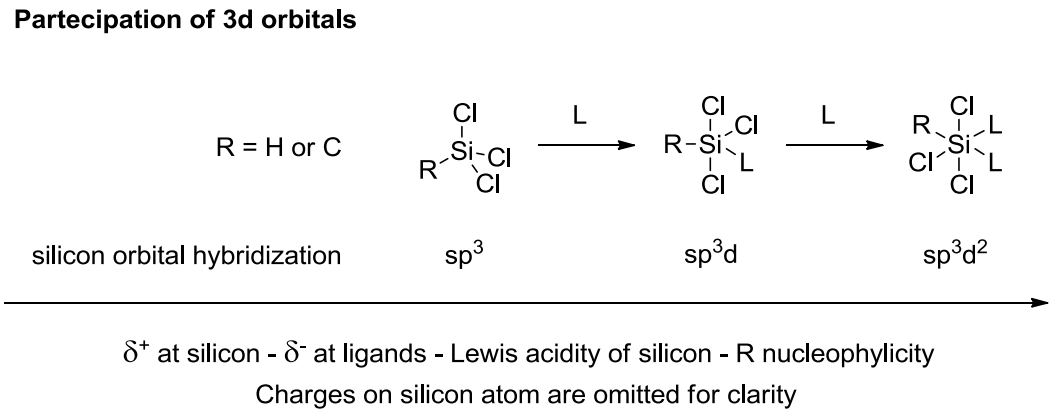
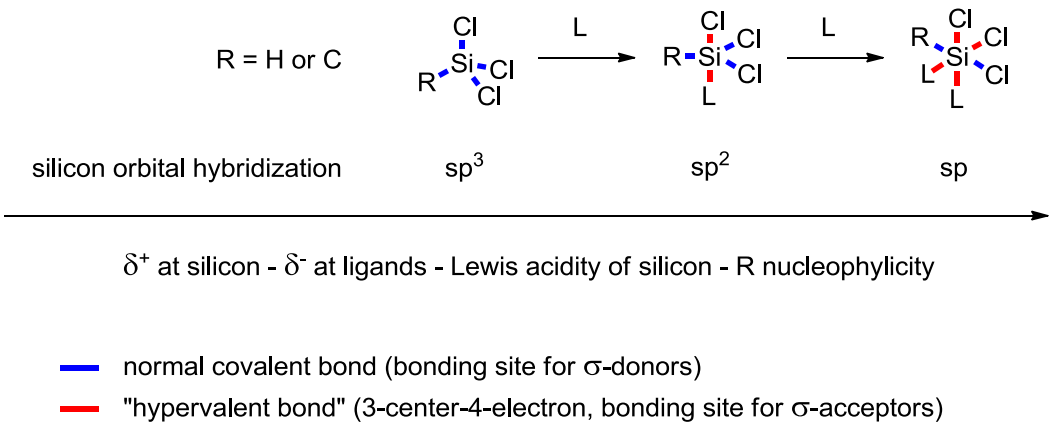


Figure 3.1.3 Expansion of the coordination sphere of silicon atom

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 **3.1.4**).[79d] 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.[88]



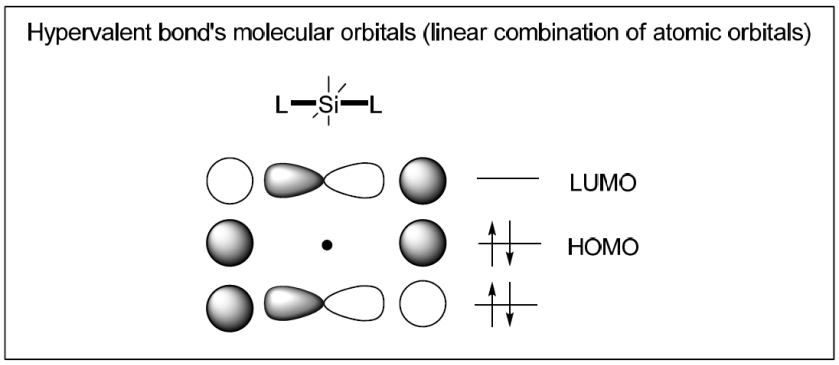


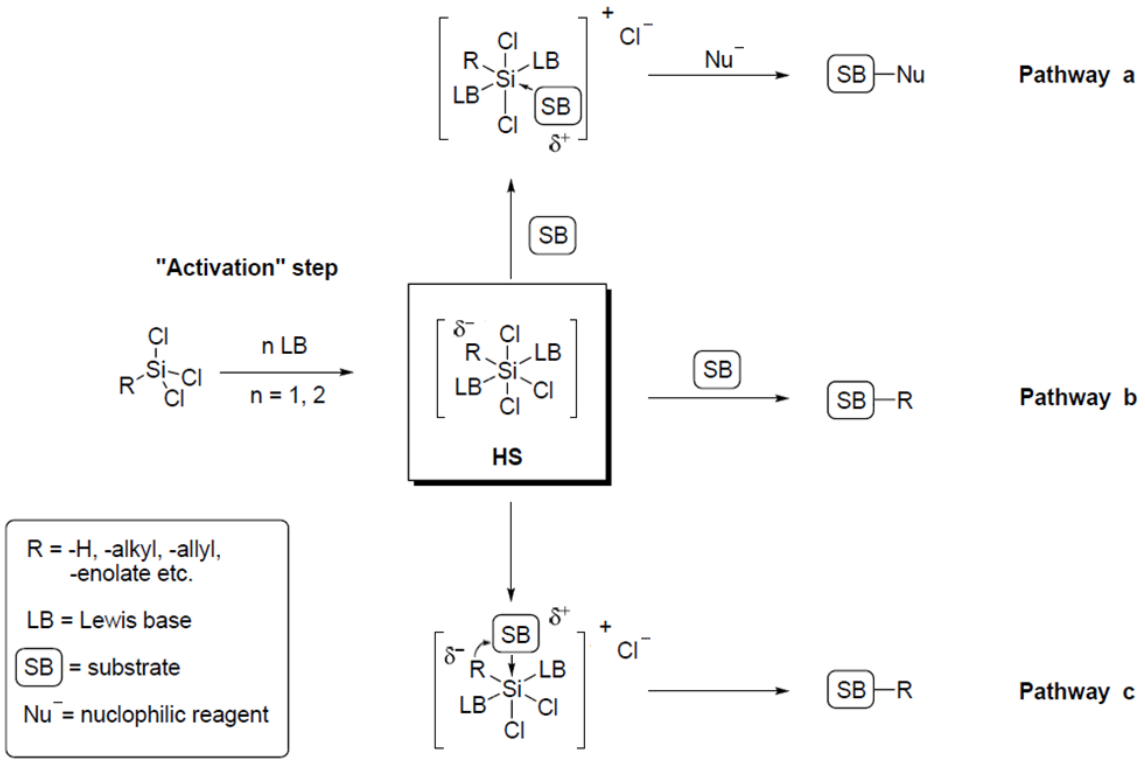
Figure 3.1.4 Hypervalent bonding theory

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 σ-acceptor ligands preferring "hypervalent" bonds and the σ-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.[89]

Both theories are helpful in the interpretation of the fundamental properties of hypervalent silicon species, that clearly distinguish their reactivity from that of fourcoordinated 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".[79d,80] 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.



Scheme 3.1.2 Three different pathways depending on the role of hypervalent specie

Three general types of reaction mechanism can be envisaged depending on the role played by the hypervalent species (Scheme **3.1.2**):

- the hypervalent species (HS) may act as a Lewis acid coordinating the substrate and activating it towards the attack of an external nucleophile (Pathway **a**)
- a nucleophilic silicon ligand is transferred to the substrate which is not coordinated by silicon (Pathway **b**)
- the hypervalent species coordinates the substrate transferring at the same time one of its ligands to it (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. Trimethylsilyl cyanide addition to carbon-nitrogen double bonds will not be discussed, because the mechanism of this reaction is not fully understood yet.[79c,d]

3.2 Stereoselective C-H bond formation

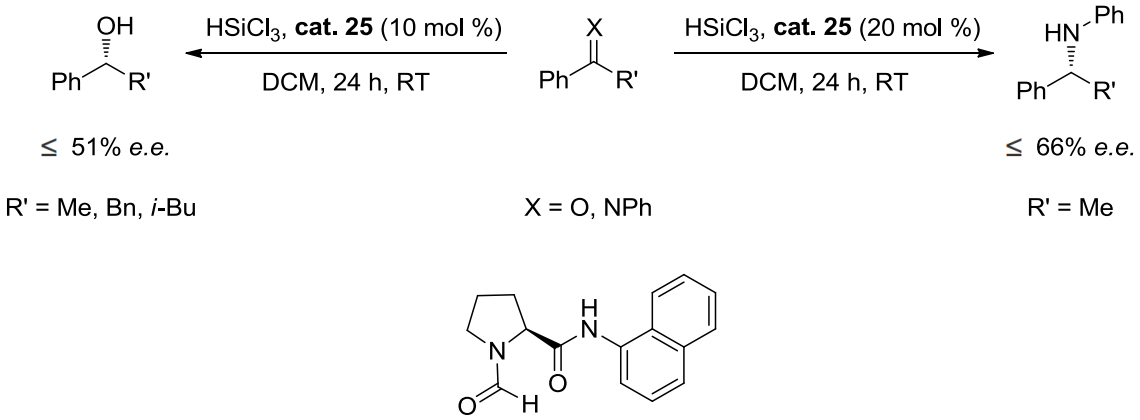
Among the metal-free methodologies recently developed, the use of trichlorosilane as reducing agent is particularly attractive. This cheap reagent is a colorless liquid, easily prepared in the silicon industry, which has already been employed on large scales for transforming phosphine oxides into phosphines and *N*-acyliminium ions into *N*-acylamines. It is a volatile compound and can be removed under reduced pressure; alternatively, after workup with dilute aqueous saturated $NaHCO_3$, $HSiCl_3$ and its byproducts are converted into harmless hydroxysilanes. Although the methodology may present some problems with regard to, for example, the generation of some quantities of halogen waste, it undeniably deserves consideration as a viable tool for the synthesis of chiral secondary amines. As already mentioned, such reagent needs to be activated by coordination with Lewis bases, such as *N*,*N*-dimethylformamide, acetonitrile, or a trialkylamines, to generate hexacoordinated hydridosilicate, the real active reducing agent that operates under mild conditions. In particular, 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 can be classified as **aminoacid derivatives**, which may be historically considered the first class of compounds developed as chiral activators of trichlorosilane, **aminoalcohol derivatives**, a second class deeply investigated in the very last few years, and **other Lewis basic compounds.**

3.2.1 Reactions catalyzed by aminoacid derived chiral Lewis bases

The first example of stereoselective catalytic hydrosilylation with $HSiCl_3$ was reported in 1999 by Matsumura and co-workers. In this work the authors showed that *N*-formyl cyclic amine compounds derived from (*S*)-proline scaffold are able to enantioselectively reduce ketones in the presence of trichlorosilane.[90] Catalytic amounts

of these Lewis bases were used to obtain enantiomerically enriched secondary alcohols in up to 51% *e.e.* (Scheme **3.2.1.1**). Two years later the same group found that trichlorosilane, also activated with *N*-formylproline as a chiral Lewis base, is an effective reagent for the chemo- and stereoselective reduction of imines (Scheme **3.2.1.1**).[91] The corresponding amines were isolated in moderate yields with up to 66% *e.e.*. Matsumura contribution in the design of *N*-formyl pyrrolidine derivatives as $HSiCl_3$ activators can be considered as a milestone for the $HSiCl_3$ mediated asymmetric reduction of ketones and imines and paved the road to the synthesis of 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.



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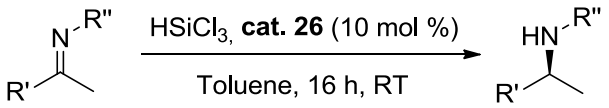
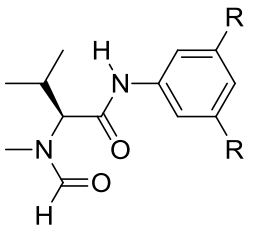
Scheme 3.2.1.1. *N*-Formylproline as a chiral promoter of $HSiCl_3$-mediated reactions

Indeed, in 2004 Malkov and Kočovský achieved one important improvement in the field of asymmetric reduction with $HSiCl_3$, developing the first highly selective catalyst for the reduction of *N*-aryl aromatic ketimine (Scheme **3.2.1.2**).[92] They identified as organocatalyst of choice the *N*-methyl-(*S*)-valine-derived type **26** compounds, commercially available since 2009.



R' = Ph, 4-MeOC$_6$H$_4$, 2-naphthyl, 2-MeC$_6$H$_4$, c-C$_6$H$_{11}$, 4-CF$_3$C$_6$H$_4$, *i*-Pr, Ph-CH=CH
R'' = Ph, 4-MeOC$_6$H$_4$, 3,5-(*t*-Bu)$_2$C$_6$H$_3$, 3-MeC$_6$H$_4$, 3,5-Me$_2$C$_6$H$_3$



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

26a-c

Scheme 3.2.1.2 *N*-formyl derivative of *N*-methyl-(*S*)-valine

Two years later, the same authors reported a detailed investigation on the use of *N*-methyl-(*S*)-amino acid derivatives as activators of trichlorosilane, using differently substituted *N*-aryl ketimines as substrates.[93] Reductions were carried out in non-polar solvents and toluene was chosen for its relatively low environmental impact.

A library of chiral *N*-formylated aminoacids was designed and synthesized, with structural variations at the carboxyamide group provided by either aromatic or aliphatic substituents. The screening of a variety of *N*-methyl-(*S*)-amino acids highlighted valine as chiral element of choice to perform stereocontrol and a few conclusions were proposed:

- the *N*-methyl formamide moiety of the catalyst is fundamental to achieve high levels of enantioselectivity
- arene-arene interactions may play an important role in determining the stereoselectivity of the catalyst
- the anilide moiety of the catalyst has to be a secondary amide (therefore retaining an NH group)
- the silicon atom is activated by coordination with the formamide moiety
- the configuration of the resulting product depends on the nature of the aminoacid side chain
- bulkier groups in the 3,5-positions of the aromatic ring (diisopropyl and ditertbutyl) determine an increase of enantioselectivity in the reduction of aromatic and non-aromatic ketimines

Catalyst-substrate hydrogen bonding and coordination of the silicon atom by the two carboxyamide groups were suggested to play a fundamental role in determining the stereoselectivity of the reaction. In the proposed transition state an additional element of stereocontrol is the formation of a hydrogen-bond between the secondary amide group of the catalyst and the substrate. The *N*-aryl group is believed to play an important role in the stereocontrol because it should be involved in π-π stacking interaction between catalyst and substrate (Figure **3.2.1.1**).

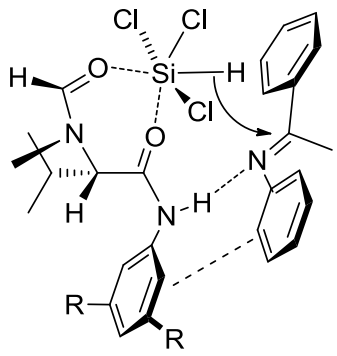
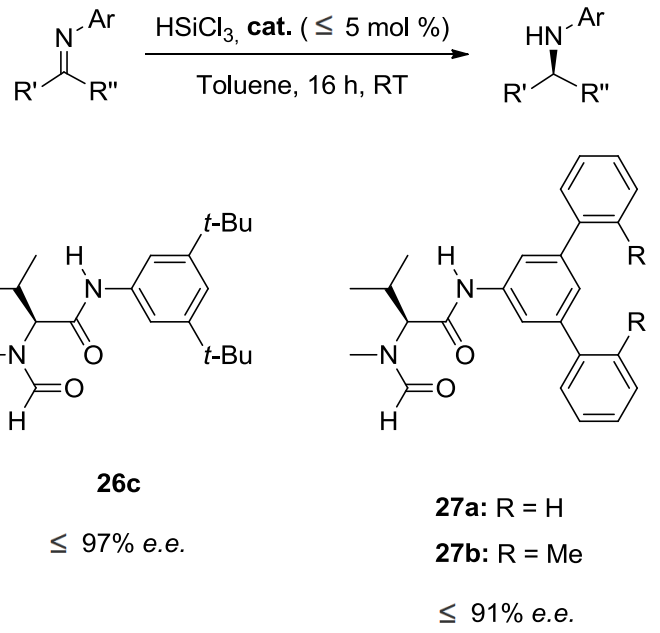


Figure 3.2.1.1 Model of stereoselection for (*S*)-valine-derived organocatalysts

The general applicability of the best performing catalyst **26c**, known as Sigamide, was then investigated in the reduction of multifunctionalized ketimines bearing heterocyclic and aliphatic moieties.[94] The reaction exhibited high enantioselectivities with ketimines derived from aromatic amines and ketones (aromatic, heteroaromatic conjugated and nonaromatic) with an appreciable steric difference between the alkyl groups R' and R". It's noteworthy that the introduction of a heteroatom into the aromatic system (as in pyridyl derivatives) afforded the products with almost no enantioselection, probably due to the competition of the substrate pyridine nitrogen with the catalyst in the coordination of the silicon atom of $HSiCl_3$.

Recently two new (*S*)-valine-derived organocatalysts (**27a**, **27b**, Scheme **3.2.1.3**) bearing a bulky aromatic substituent at the amide nitrogen were synthesized.[95] The efficiency of the new compounds was tested in the model reduction of ketimines derived from aryl methyl ketones, showing a slightly inferior result compared with that of Sigamide.



26c

≤ 97% *e.e.*

27a: R = H

27b: R = Me

≤ 91% *e.e.*

Scheme 3.2.1.3 New (*S*)-valine-derived organocatalysts

The recoverability of this family of catalysts has also been studied. A fluorous-tagged catalyst was shown to operate in solution, with very little difference from the untagged version in terms of catalytic efficiency.[96] The products were separated from the catalyst by filtration though a pad of fluorous silica and the catalyst was easily recovered and recycled. Another study on the development of a polymer-anchored version of the same catalyst was recently reported: different supports such as Merrifield and extended Merrifield, Wang, TentaGel, Marshall resins, were all employed to immobilize the organocatalysts through an ethereal bond.[97] The enantioselective reduction of *N*-aryl ketimines in the presence of trichlorosilane was tipically performed by employing 15-25 mol % amount of the supported catalyst, a higher loading than the one used with the non supported system (typically 5-10 mol % cat). The immobilized catalysts showed a significant dependence on the reaction solvent: while the non-supported organocatalyst works well in toluene, the polymer-anchored species behaves much better in chloroform. By operating under the best experimental condition, with the Merrifield-anchored catalyst, the product was isolated in good yield and in an *e.e.* about 10% lower than the enantioselectivity obtained with the nonsupported catalyst. After filtration of the immobilized organocatalyst, it was possible to reuse it five times maintaining the same level of stereoselectivity; however, a catalyst's reactivation step was required. Other

recovery strategies that have been employed include the use of gold nanoparticles,[98] block polymethacrylate polymers[99] and third generation dendrons.[99]

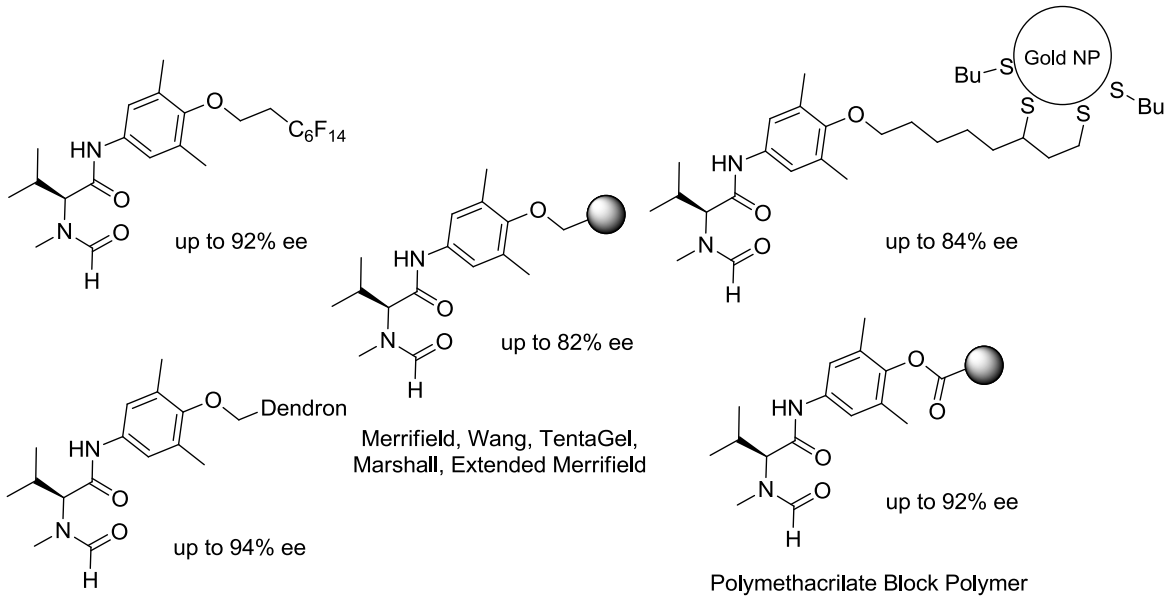
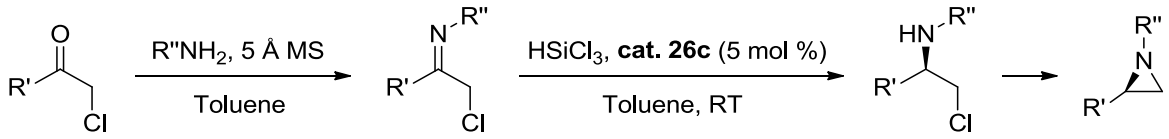


Figure 3.2.1.2 Functionalized Sigamide derivatives developed to enhance recyclability

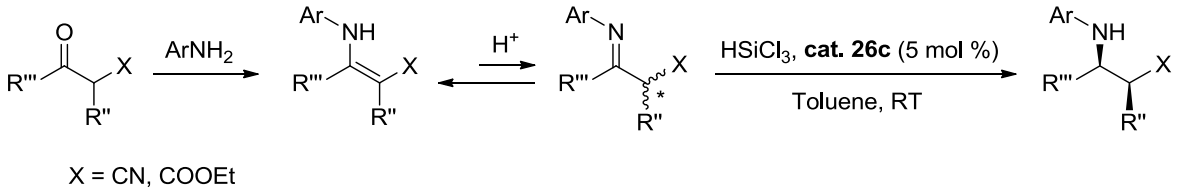
The use of Sigamide was also extended to the reduction of α-chloro-ketimines. These compounds were generated *in situ* from corresponding α-chloroketones and aniline derivatives. Their reduction in the presence of $HSiCl_3$ at room temperature gave the α-chloro-amines with high enantioselectivities (up to 96% *e.e.*), good yields and led, after cyclization, to the corresponding aziridines as final products (Scheme **3.2.1.4**).[100]



Scheme 3.2.1.4 Stereoselective synthesis of aziridine

Very recently, catalyst **26c** proved to be suitable also for the development of a new protocol for the enantioselective synthesis of β-aminoacids derivatives from enamine precursors.[101] Treatment of the β-ketoester or β-ketonitrile with *p*-anisidine afforded enamines, which as such cannot be reduced by $HSiCl_3$. Since the enamine-imine equilibration is facilitated by Brønsted acids, a number of acid additives were examined, among which AcOH (one mol equivalent) emerged as a good compromise between reactivity and selectivity. Enamine was reduced to give the amino ester in high yield and 89 % *e.e.*, and a single crystallization allowed the isolation of the enantiomerically pure

product. Nitriles exhibited the same behavior as the esters in terms of reactivity. The authors then focused on the synthesis of β-amino acids: in this case, since the starting achiral enamines are in fast equilibrium with the corresponding racemic imines, the reaction can be considered as a dynamic kinetic resolution (Scheme **3.2.1.5**). The corresponding amino esters and amino nitriles were prepared in good yields, high enantioselectivities (≤ 90% *e.e.*) and excellent diastereoselectivities (≤ 99 % *d.e.*).



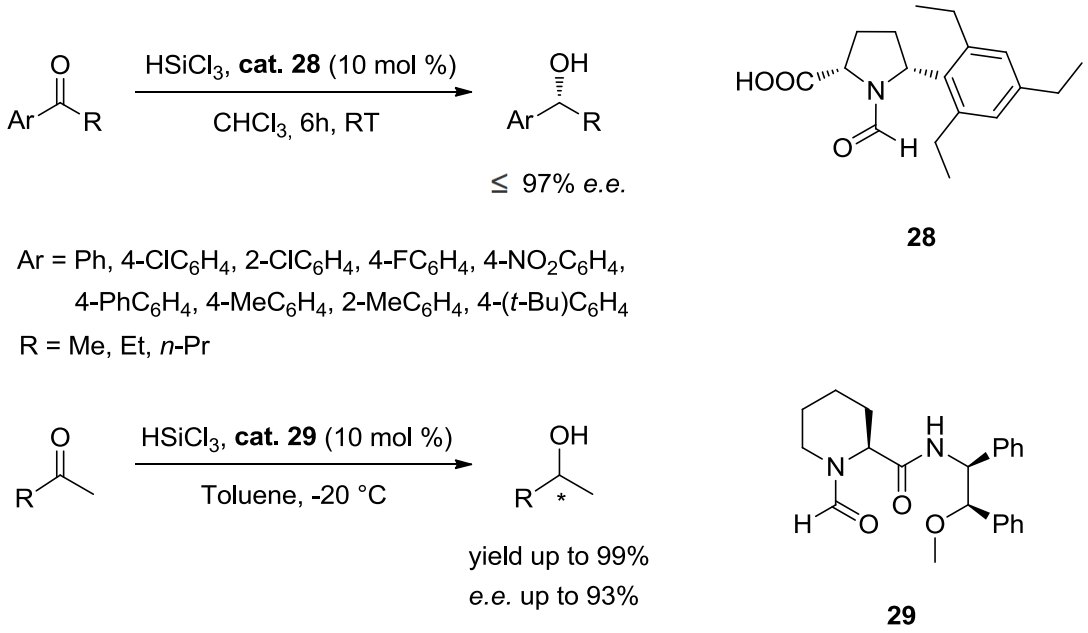
Scheme 3.2.1.5 Stereoselective reduction of enamines

Following his previous studies with prolinamides, in 2006 Matsumura reported the activity of *N*-formyl proline derivatives in the reduction of ketones in the presence of trichlorosilane.[102] Secondary alcohols could be synthesized with high enantioselectivity (up to 97%, Scheme **3.2.1.6**) employing a catalytic amount of *N*-formyl-α'-(2,4,6-triethylphenyl)-(*S*)-proline (catalyst **28**). The selection of the best performing compound was the result of the screening of a series of α'-arylproline derivatives. Both carbonyl group at the α-position and a 2,4,6-triethylphenyl group at the 5 position in the proline ring play an important role to determine the high enantioselectivity.

In a closely related work,[103] our group reported a similar use of chiral amino acids, whose ability to form hydrogen bonds with the substrate provides an easy route to induce enantioselectivity. This approach was applied for the first time to the $HSiCl_3$ mediated reduction of carbon-nitrogen double bonds employing proline-derived Lewis bases as catalysts, leading to high chemical yields and enantiomeric excess up to 75%.

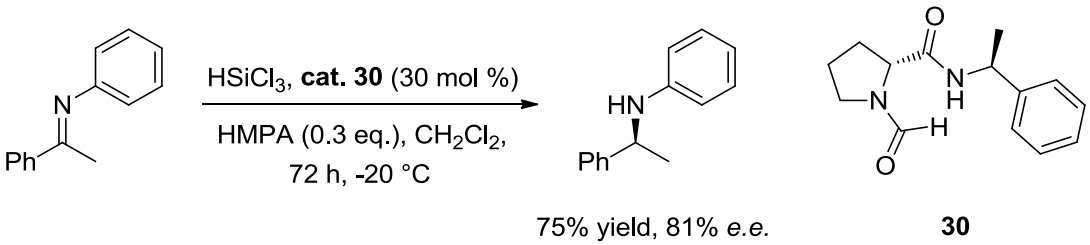
More recently the use of *N*-formyl-*L*-pipecolinic acid derivatives as organocatalysts was also extended to the reduction of aromatic and aliphatic ketones.[104,105] The best catalyst for the reduction of carbonyl compounds was found to be amide **29**, characterized by the presence of the methoxy group on carbon C2' of the chiral aminoalcohol moiety (Scheme **3.2.1.6**), that turned out to be crucial for high enantioselectivity. Indeed the replacement of this moiety with either a larger alkoxy group or a group with a less electron-rich 2'-oxygen led to a decreased reactivity and/or enantioselectivity. According

to the authors catalyst **29** works as a tridentate activator and promotes the hydrosilylation of ketones through a transition structure that features a heptacoordinate silicon species.



Scheme 3.2.1.6 Stereoselective reduction of ketones

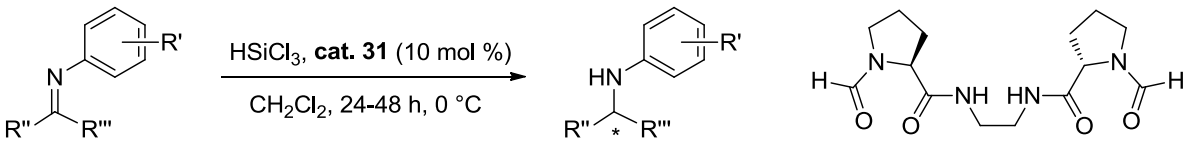
In 2007, Tsogoeva's research group reported the use of new chiral formamides in the reduction of ketimines in presence of trichlorosilane.[106] A second element of stereocontrol, such as a chiral amine, was coupled with the proline moiety. Catalyst **30**, the *N*-formyl prolinamide of (*R*)-α-methyl-benzylamine, activated trichlorosilane in the ketimine reduction, affording the product in 75% yield and 81% *e.e.* in the presence of an additive. HMPA and *p*-nitrobenzoic acid were tested as additives, and, quite surprisingly, the former turned out to be the more effective (Scheme **3.2.1.7**).



Scheme 3.2.1.7 *N*-Formylprolinamides with chiral substitution

In the same year the Sun group gave a great contribution to this field, reporting the (*S*)-proline-derived C_2-symmetric chiral tetraamide **31** (Scheme **3.2.1.8**) as a novel

catalyst in the enantioselective hydrosilylation of ketimines.[107] The choice of catalyst **31** was the result of the screening of a series of C_2-symmetric chiral tetraamide derivatives, in which the linkage of the two proline diamide units proved to have a significant impact on the enantioselectivity. Either a shorter or longer linkage, as well as aromatic linkages, provided products with much lower enantioselectivities. The reaction products were isolated in high yields (up to 95%) and moderate to high enantioselectivities (up to 86% *e.e.*) for a broad range of substrates, including aromatic and aliphatic imines. The two diamide units in the chiral Lewis base work cooperatively, showing a synergistic effect.



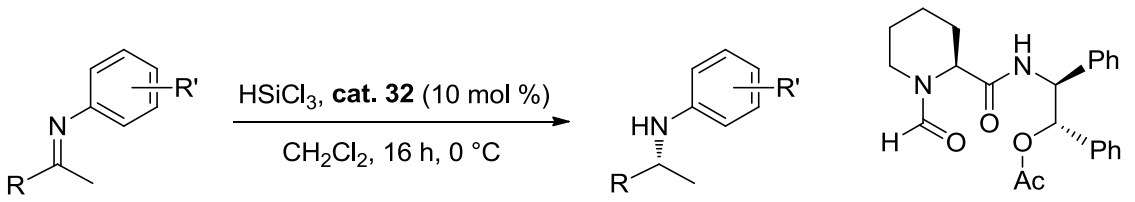
31

R' = Ph, 4-MeOC$_6$H$_4$, 4-BrC$_6$H$_4$, 4-NO$_2$C$_6$H$_4$, 4-BrC$_6$H$_4$, 2-naphthyl, 6-MeO-2-naphthyl, c-C$_6$H$_{11}$
R'' = Me, Et, *n*-Pr, *n*-Bu, *t*-Bu
R''' = Ph, 4-ClC$_6$H$_4$, 4-MeOC$_6$H$_4$

yield up to 95%
e.e. up to 86%

Scheme 3.2.1.8 Chiral bis *N*-formylprolinamides

Moreover, Sun and co-workers developed a catalyst derived from (*L*)-pipecolinic acid (catalyst **32**) able to promote the reduction of *N*-aryl ketimines with trichlorosilane with high yields and good enantioselectivities.[108] They reported that switching from the five-membered ring of proline to a six-membered ring had a beneficial effect on the enantioselectivity. For the first time, the reduction of aliphatic ketimines was accomplished with the use of this catalyst and this work was also the first to demonstrate the independence of the ketimine geometry on the selectivity of the reaction (Scheme **3.2.1.9**).



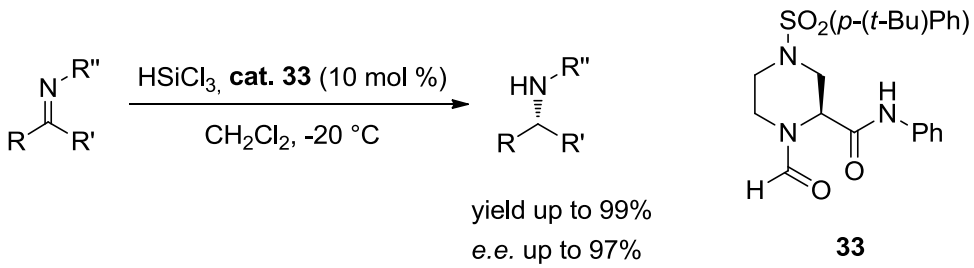
≤ 96% *e.e.*

32

R = Ph, 4-MeOC$_6$H$_4$, 4-BrC$_6$H$_4$, 4-CF$_3$C$_6$H$_4$, 4-NO$_2$C$_6$H$_4$, 3-BrC$_6$H$_4$, 6-MeO-2-naphthyl, 2-naphthyl, *c*-C$_6$H$_{11}$, *i*-Pr, PhCH=CH
R' = 4-MeO, 4-Me, 2-OMe, 2-Cl, 4-Cl, 4-Br

Scheme 3.2.1.9 Chiral pipecolinic acid derived organocatalyst

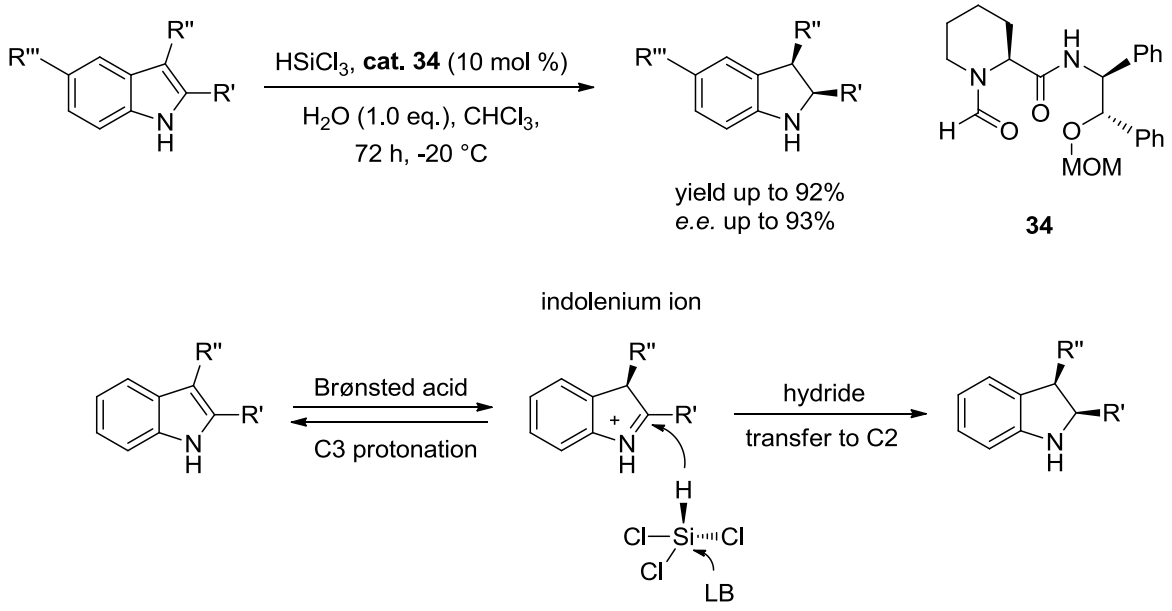
Later, a piperazinyl backbone was employed as building block for the construction of a new catalyst.[109] The arenesulfonyl group on the 4-position was shown to be a key element for obtaining a high level of enantiocontrol (Scheme **3.2.1.10**). Catalyst **33** promoted the reduction of a broad range of imines with good yields and enantioselectivities.



Scheme 3.2.1.10 Chiral piperazinyl derived organocatalyst

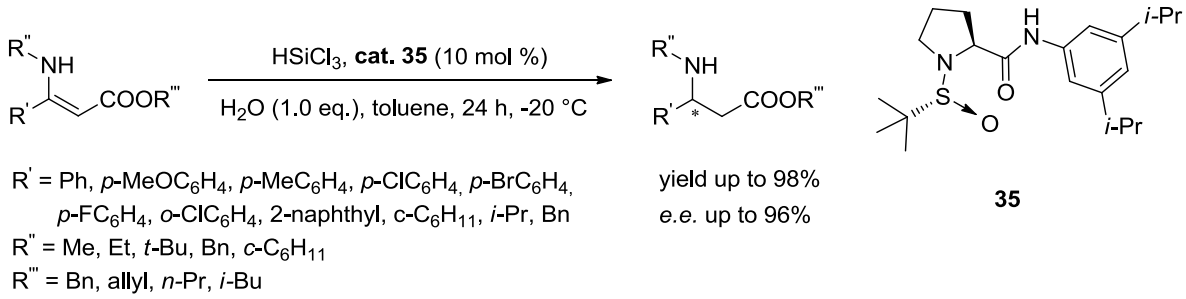
In 2009 Schreiner published a detailed investigation of the influence that non aromatic groups in *N*-formylprolinamide may have on the enantiomeric excesses of ketimine reductions, also employing computational methods in the attempt to get some mechanistic insights in the process.[110] By working with a series of novel chiral organocatalysts derived from proline, valine, and pipecolinic acid, the dominant role of the amino acid scaffold in the enantiodifferentiating step was demonstrated. DFT mechanistic studies seem to confirm that the catalyst not only coordinates to trichlorosilane, but also reacts as a proton donor in the crucial transition structure; indeed, the importance of the presence of acidic NH proton of a secondary amide group, able to bind to the basic nitrogen of the reacting imine, has been demonstrated. Although the authors suggest that the enantiodifferentiating steps for proline, pipecolinic acid, and valine-derived catalysts may be different, from the computational studies they propose a general picture for the catalytic reduction of ketimines with trichlorosilane, that could be described as a formal H^+/H^- transfer to the C=N double bond.

More recently, Sun reported the first direct enantioselective hydrosilylation of prochiral 1H-indoles by combined Brønsted acid/Lewis base activation.[111] The key factor for this methodology is the addition of one equivalent of water to react with $HSiCl_3$ 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 catalyzed enantioselective hydrosilylation with $HSiCl_3$ (Scheme **3.2.1.11**).



Scheme 3.2.1.11 Direct enantioselective hydrosilylation of prochiral 1H-indoles

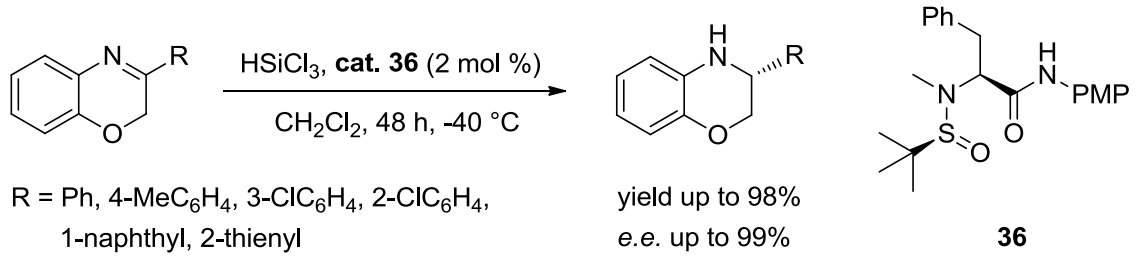
In the same year *N*-sulfinyl L-proline amides have been used for the enantioselective reduction of a range of *N*- alkyl β-enamino esters (Scheme **3.2.1.12**).[112] Also in this case the use of water as an additive is crucial to obtain high levels of reactivity and enantioselectivity, accelerating the enamine-imine tautomerization and increasing the electrophilicity of the imine through protonation of the nitrogen atom.



Scheme 3.2.1.12 Chiral *N*-sulfinyl L-prolinamidic derivatives

In 2013, Sun and co-workers reported the first highly enantioselective trichlorosilane mediated hydrosilylation of 3-aryl-1,4-benzooxazines,[113] thus implementing a more cost-efficient route for the synthesis of this class of compounds compared to the organocatalytic approach that employes chiral phosphoric acids and Hantszch esters (See Chapter 2). Catalyst of choice was found to be a *N*-sulfinyl *L*-phenylalanine derived amide, which allowed to produce a broad range of 3-substituted 3,4-dihydro-2H-1,4-benzooxazines in very good chemical yield and high enantioselectivity, even when a

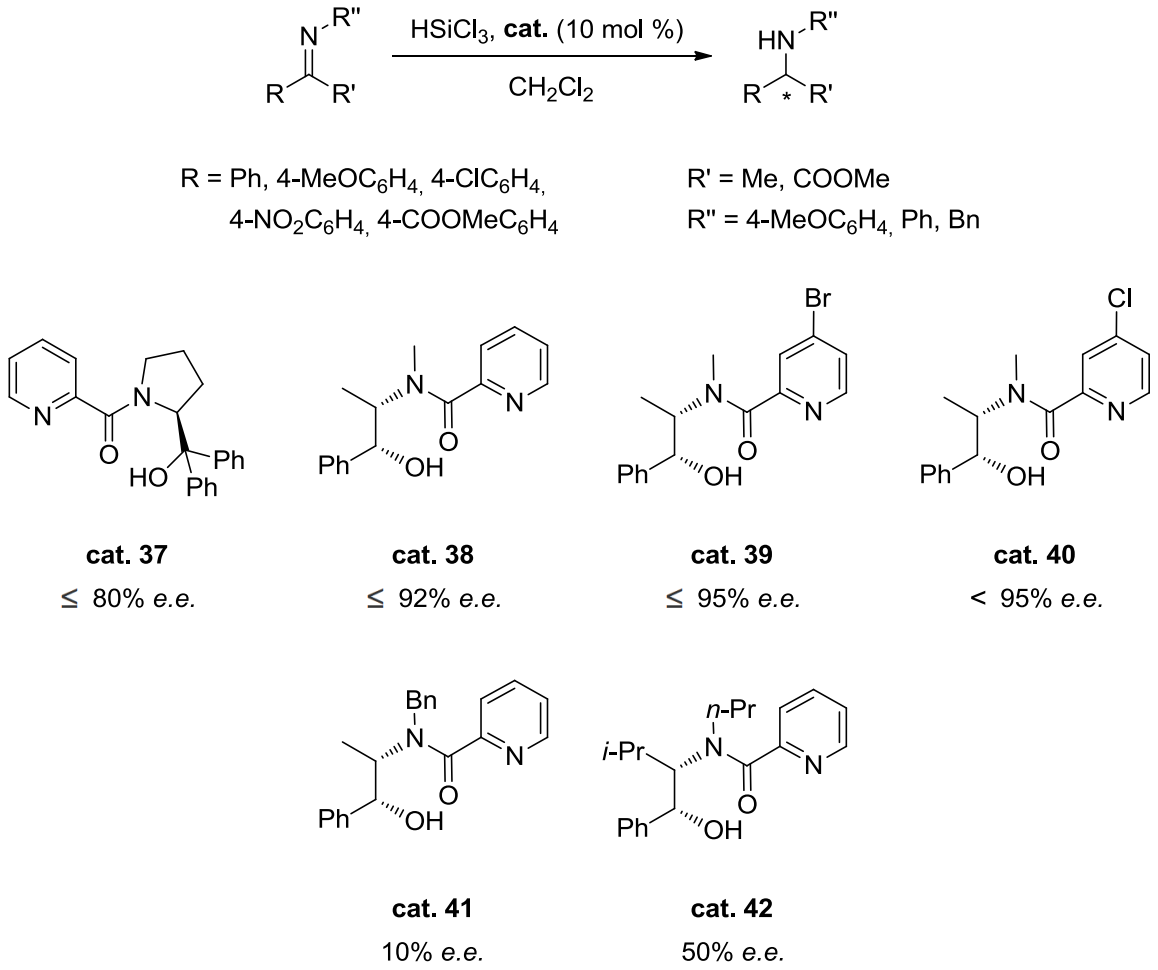
catalyst loading as low as 2 mol % was used (Scheme **3.2.1.13**). It's quite interesting that the catalyst's diastereomer with opposite stereochemistry on the sulfur atom exhibited much lower enantioselectivity, indicating that a stereochemical match between the carbon and the sulfur stereogenic centers is crucial for the enantiocontrol. Authors underlines that the acyclic *L*-phenylalanine backbone, matching well with the cyclic structure of the substrate, plays a fundamental role in determining the efficiency of this catalyst, while a cyclic *L*-proline backbone is apparently much less suitable for the these cyclic substrates.



Scheme 3.2.1.13 Lewis Base catalyzed asymmetric hydrosilylation of 1,4-benzooxazines

3.2.2 Reactions catalyzed by aminoalcohol derived chiral Lewis bases

A contribution by Matsumura in 2006 opened the way towards the development of a novel class of catalysts for trichlorosilane-mediated reductions, derived from chiral amino alcohols.[114] His group reported that *N*-picolinoylpyrrolidine derivatives are able to activate trichlorosilane in the reduction of aromatic imines, showing that the *N*-formyl group is not always essential for catalytic activity. *N*-picolinoyl-(2*S*)-(diphenylhydroxymethyl)-pyrrolidine **37** gave the best results, leading to enantioselectivities up to 80%. The authors proposed that both the nitrogen atom of 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 to obtain high levels of enantioselectivity, leading to hypothesize the presence of hydrogen bonding between the hydroxyl group and the nitrogen atom of the imine (Scheme **3.2.2.1**).



Scheme 3.2.2.1 Chiral *N*-picolinoyl derivatives

Based on these seminal works, our group has recently focused on the design and synthesis of a wide class of catalysts prepared by simple condensation of a chiral aminoalcohol with picolinic acid or its derivatives. While our investigation led to a patent deposit[115], 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.[116] With catalyst **38** easily prepared from 2-picolinic acid and (1*R*,2*S*)-ephedrine, a variety of *N*-aryl ketimines and *N*-benzyl ketimines were reduced with trichlorosilane in high yields (≤ 93%) and moderate to excellent *e.e.* (≤ 92%) under mild conditions (Scheme **3.2.2.1**).

In 2009 our group reported an extensive exploration of this class of organocatalysts.[117] In a single step procedure, several derivatives were synthesized simply either by treatment of picolinic acid with different enantiomerically pure amino alcohols, mediated by condensing agents, or by reaction of picolinoyl chloride with the amino alcohols. The

pyridine ring, the free hydroxyl group and *N*-alkyl substitution in the aminoalcohol portion were identified as key structural elements, necessary to secure good stereocontrol; the effect of different substituents at the nitrogen atom and at the two stereocenters was also studied. By studying several differently substituted derivatives it was shown that *N*-benzyl derivative **41** (Scheme **3.2.2.1**) catalyzed the reduction of *N*-aryl ketimines with only 10% *e.e.*, whereas compound **42**, bearing an isopropyl group, was able to promote the reaction, but in lower enantiomeric excess than compound **38**, confirming ephedrine as the chiral amino alcohol of choice. Lastly, to study the modification of the picolinoyl moiety, a selection of ephedrine derivatives obtained by condensation with picolinic acids bearing different substituents in the 3-, 4-, or 6-positions of the pyridine ring was prepared. It was observed that the introduction of a proper substituent in 4 position of the pyridine moiety could improve catalyst efficiency. Indeed 4-bromo and 4-chloro picolinic derivatives **39** and **40** showed remarkable catalytic properties. Working at 0 °C in dichloromethane with catalyst **40** the chiral amine was obtained in quantitative yield and 83% enantiomeric excess; performing the reaction in chloroform allowed to raise the enantioselectivity up to 88% *e.e.*. A further improvement was observed by performing the reaction at -20 °C: enantioselectivity reached 95% *e.e.* and at the same time no erosion of the chemical yield was observed, with the reduction product isolated in quantitative yield. Even by working with 1% mol amount, catalyst **38** promoted the reduction in 90% yield after only 2 hours.

The screening of systematically modified organocatalysts of this family led to identify the key structural factors that influence their catalytic properties and to propose a tentative model of stereoselection:

- the pyridine nitrogen and the amidic CO group activate trichlorosilane by coordination
- the hydrogen atom of hydroxyl group plays a fundamental role, coordinating the imine through hydrogen bonding
- the presence of two stereogenic centers on the aminoalcohol moiety with the correct relative configuration, as in (1*R*, 2*S*)-(-)-ephedrine, is necessary to efficiently direct the stereochemistry of 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 to maximize the enantiodifferentiation of the process

In the proposed stereoselection model **A** (Figure **3.2.2.1**), leading to the experimentally observed preferred formation of the *R* isomer of the product, the steric interaction between the pyridine ring and *N*-aryl group is much less significant than that observed in adduct **B**, that is therefore disfavored.

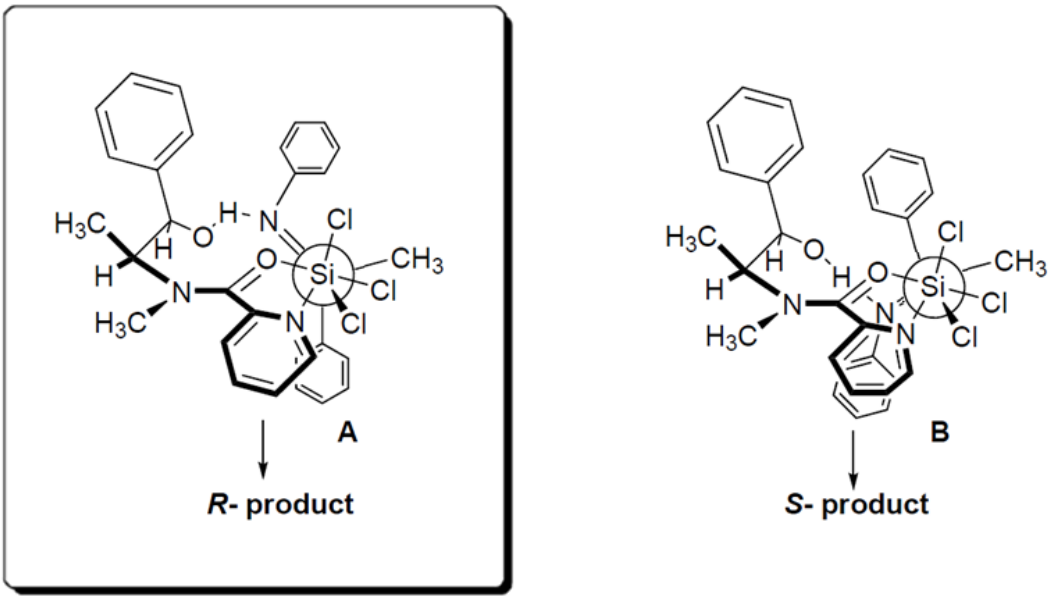
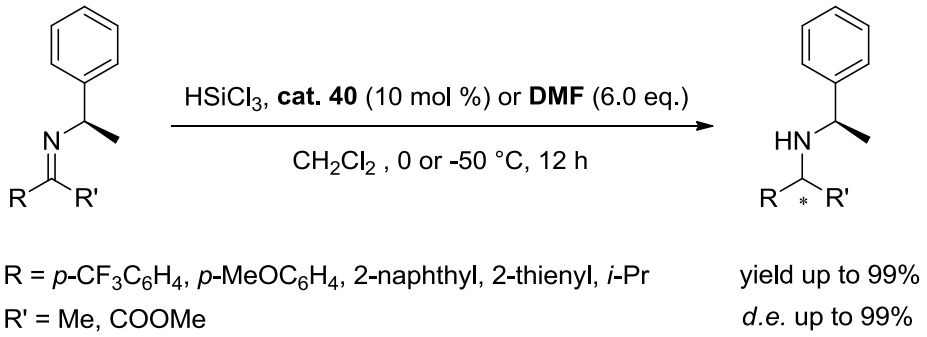


Figure 3.2.2.1 Proposed model of stereoselection for the reduction of *N*-aryl ketimines

Good results were also obtained in the enantioselective reduction of *N*-alkyl imines, [118] a transformation only recently accomplished organocatalytically.[119] Ephedrine-based picolinamides promoted the reaction of *N*-butyl imine of acetophenone in excellent yields and high stereoselectivities: under the best conditions (chloroform, 0 °C, 24 hours), the 4-chloropicolinic derivative **40** promoted the reduction in 98% yield and 91% *e.e.*. These organocatalysts have several convenient features: they are easily prepared, by a single condensation step, between commercially available compounds; they are low cost catalysts, the source of stereocontrol being a very cheap and largely available aminoalcohol such as ephedrine; the reduction of carbon-nitrogen double bond is performed under very mild reaction conditions and with an extremely simple experimental procedure that allows to obtain a highly pure product after an aqueous work up. A very convenient enantioselective organocatalytic three-component methodology was also developed; the reductive amination process, starting simply from 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 un-activated ketones. All these

positive traits make the present catalytic method suitable, in principle, also for large scale applications; its synthetic potentiality was indeed demonstrated by successfully employing the present metal-free catalytic procedure in the preparation of (*S*)-metolachlor, a potent and widely used herbicide.[117]

To improve upon the selectivity of the ketimine reduction process further, the hydrosilylation of a range of substrates derived from (*R*)-1-phenylethylamine were examined.[120] It was found that a catalytic amount of *N*,*N*-dimethyl formamide was able to promote $HSiCl_3$ addition with good stereoselectivity, although in low yield.[121] By optimizing the reaction conditions it was shown that best results were obtained at -50 °C in chlorinated solvents by performing the reduction with six equivalents of DMF. Under these conditions, a wide range of acetophenone-derived ketimines were effectively reduced to the corresponding secondary amines in quantitative yields, with 90-99% diastereoselectivity. In this context, 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 **3.2.2.2**).[121] Moreover, when chiral picolinamide **40** was employed as a catalyst, the control of the stereoselectivity was total, as demonstration of the presence of a cooperative effect between Lewis basic catalyst and the (*R*)-methyl benzyl residue at the imine nitrogen.[120]

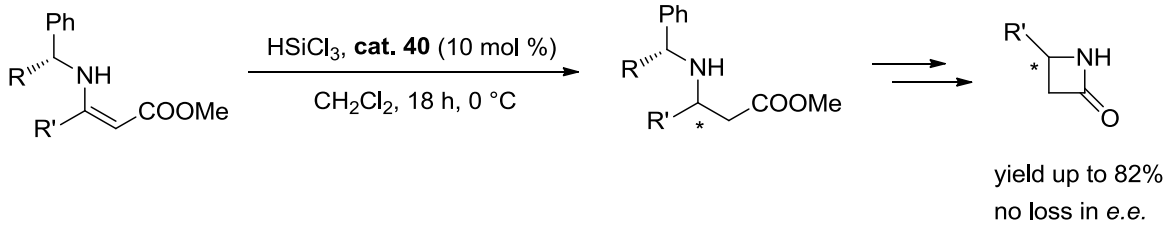


Scheme 3.2.2.2 Stereoselective catalytic reduction of chiral imines

This last approach was extended to the synthesis of several enantiomerically pure secondary amines with C_1 or C_2 symmetry. Also the imine derived from methyl isopropyl ketone was readily reduced in >98% yield in the presence of catalyst **40** to afford an enantiomerically pure direct precursor of (*R*)-isopropyl methyl amine.

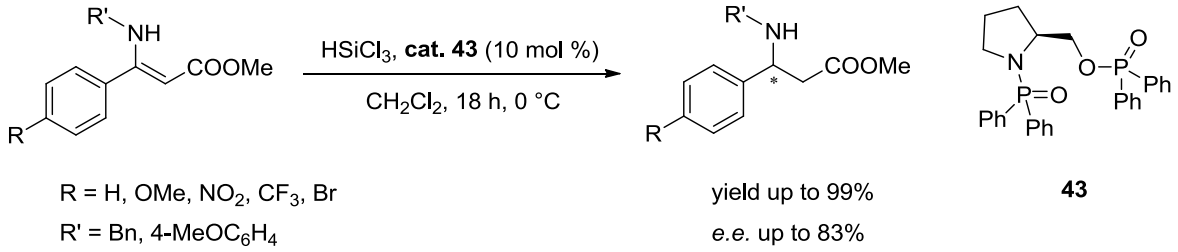
The wide applicability of this method was demonstrated also in the preparation of α-amino esters. Catalyst **40** promoted the reduction of *N*-benzyl iminoester in quantitative yield and up to 71% *e.e.*. Besides, in the reduction of *N*-α-methylbenzyl imine of methyl-phenyl glyoxylate at 0 °C in dichloromethane the same catalyst afforded the corresponding chiral aminoester in 73% yield and 91% diastereoisomeric excess.

In 2011, our group also used this class of catalysts to reduce a series of *N*-benzyl and *N*-α methyl benzyl β-enaminoesters (Scheme **3.2.2.3**).[122] Best results were obtained with catalyst **40** and, once again, an improvement of the enantioselectivity was observed with the use of a chiral auxiliary. Then, hydrogenolysis of the enantiomerically enriched *N*-benzyl β-aminoesters, followed by LDA-promoted ring closure, afforded enantiomerically pure 4-aryl or 4-alkyl substituted β-lactams.



Scheme 3.2.2.3 Stereoselective catalytic reduction of *N*-benzyl β-enaminoesters

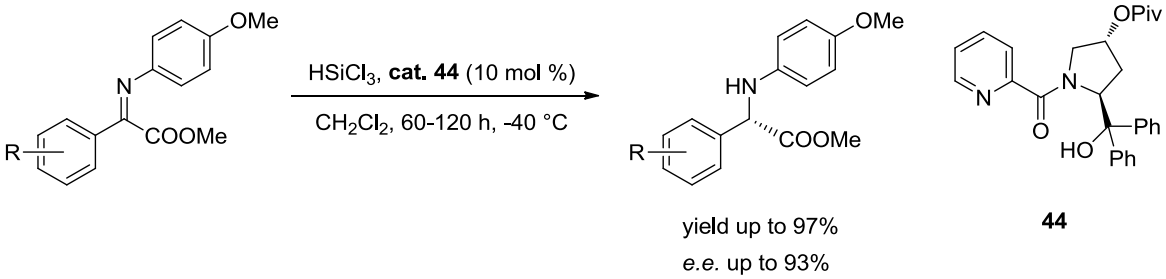
Furthermore, we reported a novel class of chiral prolinol derivatives to promote the hydrosilylation of α-imino and β-imino esters.[123] In nearly all cases, catalyst **43** was the most effective in the reduction of a range of electron rich and electron deficient substrates (Scheme **3.2.2.4**).



Scheme 3.2.2.4 Chiral prolinol derived phosphoroamides as chiral Lewis bases

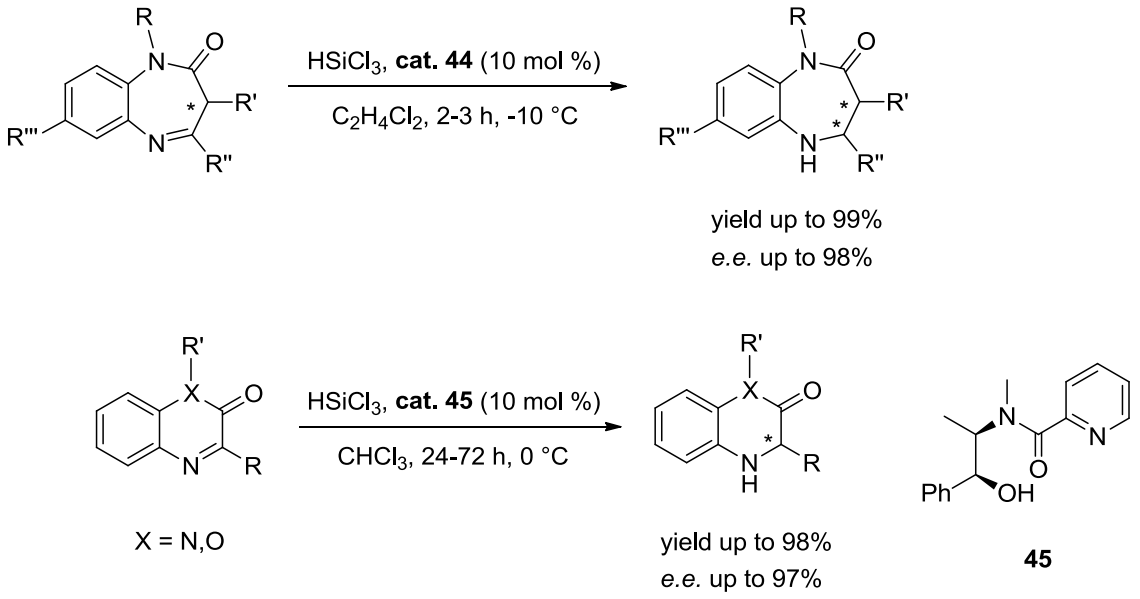
Zhang recently reported the first highly efficient protocol for the organocatalytic synthesis of α-amino esters.[124] A novel class of chiral Lewis base organocatalysts derived from *trans*-4-hydroxy-*L*-proline was developed (Scheme **3.2.2.5**); it's noteworthy that the prolinol-derived catalyst of choice, compound **44**, exhibited only moderate

enantioselectivities in the hydrosilylation of *N*-aryl β-enamino esters, but promoted the reduction of α-imino esters with high enantioselectivities (up to 93% *e.e.*). The introduction of a bulky group at C4 of the pyrrolidine ring was decisive in order to obtain high stereoselectivities. The hydroxy group was functionalized with various bulky groups: while benzyl, trimethylsilyl, and isovaleryl protection of the hydroxy group only caused marginal changes in the enantioselection, an increase in enantioselectivity was observed when *O*-pivaloyl catalyst **44** was employed. Crucial for the efficiency of the process was the addition of small quantities of pentanoic acid. Through this approach, a broad range of chiral α-amino esters were synthesized in good yields (up to 97%) and with high levels of enantioselectivity (up to 93%). In exploring the applicability of the catalyst to imines of differently substituted aryl glyoxylates, it was found that both *para* and *meta* functionalized substrates could be reduced with good enantioselectivity (80-93% *e.e.*), while *ortho* substitution caused a decrease of stereoselection (50-60% *e.e.*).



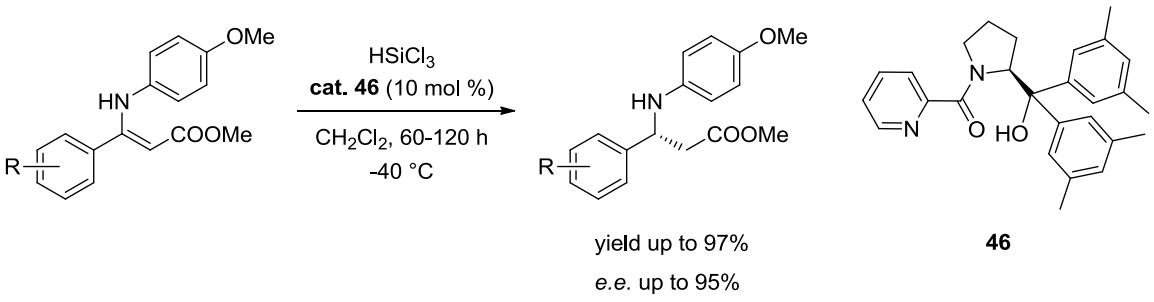
Scheme 3.2.2.5 Catalytic reduction of α-imino esters

The same catalyst (catalyst **44**) has also been used for the stereoselective synthesis of chiral heterocyclic building blocks, such as dihydrobenzodiazepinones.[125] The corresponding products were obtained in excellent yields (up to 99%) and enantioselectivities (up to 98%). Moreover, other heterocycles have been used as substrates in the reduction promoted by an ephedrine derived catalyst in presence of water, obtaining improved yield and selectivity (Scheme **3.2.2.6**).[126]



Scheme 3.2.2.6 Trichlorosilane mediated stereoselective synthesis of chiral heterocycles

Zhang's group also employed picolinamide derivatives of prolinol to realize an efficient enamine reduction.[127] Chiral *N*-picolinoylpyrrolidine and *N*-picolinoylephedrine derivatives were evaluated in hydrosilylation of (*Z*)-methyl-3-phenyl-3-(phenylamino)acrylate, leading to the corresponding reduction product with good enantioselectivities in chloroform at 0 °C. The enantioselectivity improved slightly with the increase of the size of the aryl groups in the catalyst. The best yield and enantioselectivity were obtained with catalyst **46** at -30 °C for 48 h. Under optimized conditions, the scope of the Lewis base organocatalyzed hydrosilylation of β-enamino esters was examined. In the presence of 10 mol % of Lewis base, β-enamino esters were reduced in high yields and enantioselectivities typically ranging from 90% to 95%. It is worth mentioning that *N*-acyl β-enamino esters were totally inactive in the present organocatalytic system. The reaction is supposed to proceed through the imine tautomer rather than its enamine counterpart. In the proposed mechanism the nitrogen atom of the pyridine ring and the carbonyl oxygen atom of the catalyst are coordinated to $HSiCl_3$, while the imine is activated by the hydroxy group of the Lewis base through hydrogen bonding. It has also been hypothesized, although not demonstrated, that a stabilization due to arene-arene interactions between the aromatic systems of the catalyst and the substrate may occur.

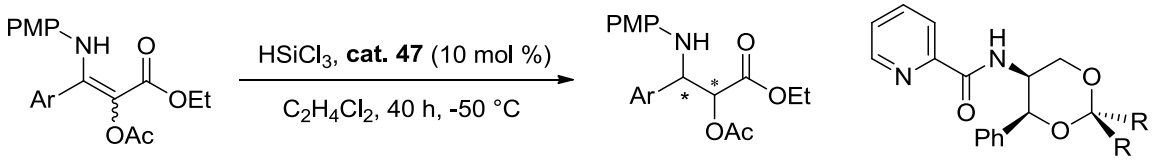


yield up to 97%
e.e. up to 95%

46

Scheme 3.2.2.7 Catalytic reduction of β-enamino esters

More recent studies from this group have extended the substrate scope to include α-acetoxy-β-enamino esters.[128] In order to perform the reaction on those substrates a novel class of chiral Lewis base catalysts, prepared from a readily available chiral source was developed (Scheme **3.2.2.8**). A wide variety of *N*-aryl β-aryl and -heteroaryl substrates were reduced in very good yields (up to 98%) and selectivity (up to 99:1 *syn*/ *anti* and 99 % *e.e.*). 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 a Brønsted acid that promoted tautomerisation of the enamine. This methodology was also applied successfully in the synthesis of both the taxol C13 side chain and a potent hypocholesterolemic agent.



Ar = 3 or 4 substituited arenes, 2-naphthyl, 2-thienyl, 2-furanyl, Bn

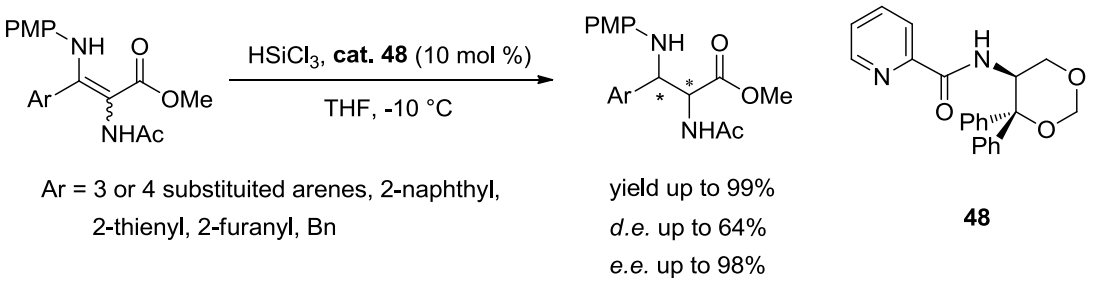
yield up to 98%
d.e. up to 99%
e.e. up to 96%

47

Scheme 3.2.2.8 Catalytic reduction of α-acetoxy-β-enamino esters

In a closely related work,[129] published two years later, Zhang reported the Lewis base-catalyzed asymmetric hydrosilylation of α-acetamido-β-enamino esters, which proceeded smoothly to give the corresponding products with high yields (up to 99%), excellent enantioselectivities (up to 98% *e.e.*) and moderate diastereoselectivities (up to 80:20 d.r.). The lower diastereocontrol observed in this study is ascribed by the authors to the role of the hydrogen of the α-acetamide group. Indeed, the enamine isomerization preferentially forms the *E*-imine; however in this case the *Z*-imine can be stabilized by

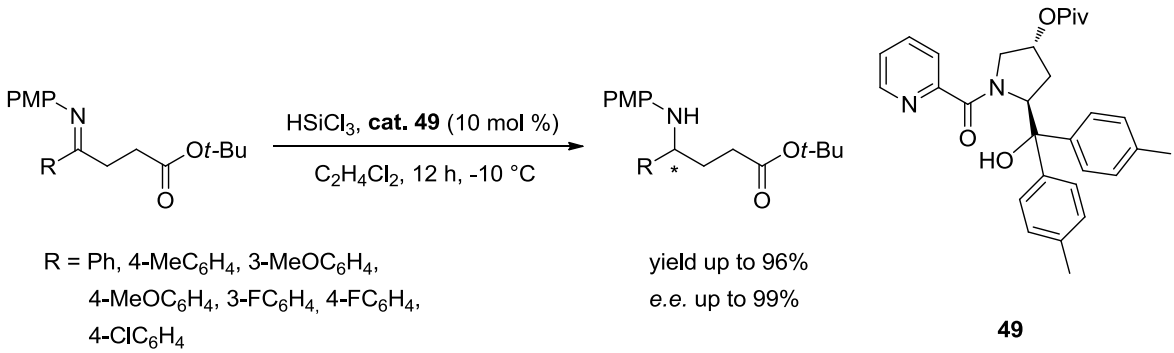
hydrogen bonding between the hydrogen of the α-acetamide group and the nitrogen of the imine. In this way, considerable amounts of *Z*-imine could be generated, resulting in lowers levels of diastereoselectivity.



Scheme 3.2.2.9 Catalytic hydrosilylation of α-acetamido-β-enamino esters

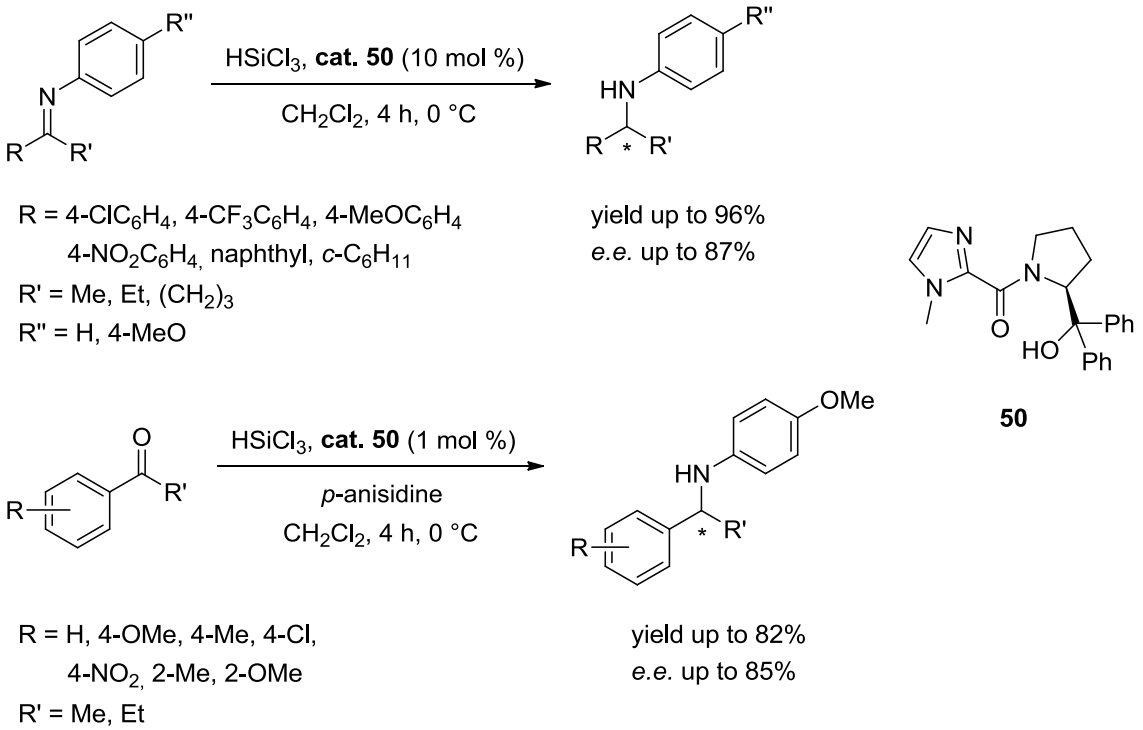
In 2013,[130] the same catalyst **48** was successfully employed to perform the enantioselective hydrosilylation of cyclic β-enamino esters, whose reduction resulted in very poor enantioselectivities in previous reports. The corresponding cyclic β-amino esters were obtained in high yields (up to 98%), excellent diastereoselectivities (>99:1 *syn*/*anti*) and good enantioselectivities (up to 96% *e.e.*).

In 2012 Zhang also developed a general, highly enantioselective hydrosilylation of γ-imino esters promoted by chiral Lewis base organocatalysts (Scheme **3.2.2.10**).[131] However, this transformation always led to the formation of undesired side products, such as cyclized γ-lactam or a α, β-unsatured ketimine. The problem was solved by the authors through the use of bulkier substrate, obtaining the synthesis of various chiral γ-amino esters in high yield (96%) with excellent enantioselectivities (99%). They also demonstrated the applicability of this protocol by synthesizing two optically active γ-lactams, which are important compounds in the construction of pharmaceutically active agents.



Scheme 3.2.2.10 Enantioselective hydrosilylation of γ-imino esters

In the last few years, Jones reported the use of the *N*-methyl imidazole bifunctional catalyst **50** derived from prolinol.[132] 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% *e.e.*. Interesting, the authors noted that the ratio of the ketimine geometric isomers did not seem to have great influence on the outcome of the reaction. The same catalyst was then reported for the high selective reductive amination of a large variety of ketones and aryl or aliphatic amines.[133] Essential for this protocol was the *in situ* formation of the imine using microwave irradiation and the subsequent reduction of carbon-nitrogen double bond with trichlorosilane (Scheme **3.2.2.11**). Very recently, the same group described in their perspective an interesting quantitative comparison between organocatalysts and transition metal mediated process, demonstrating that catalysts offer efficiencies comparable to their metal counterparts.[79b]

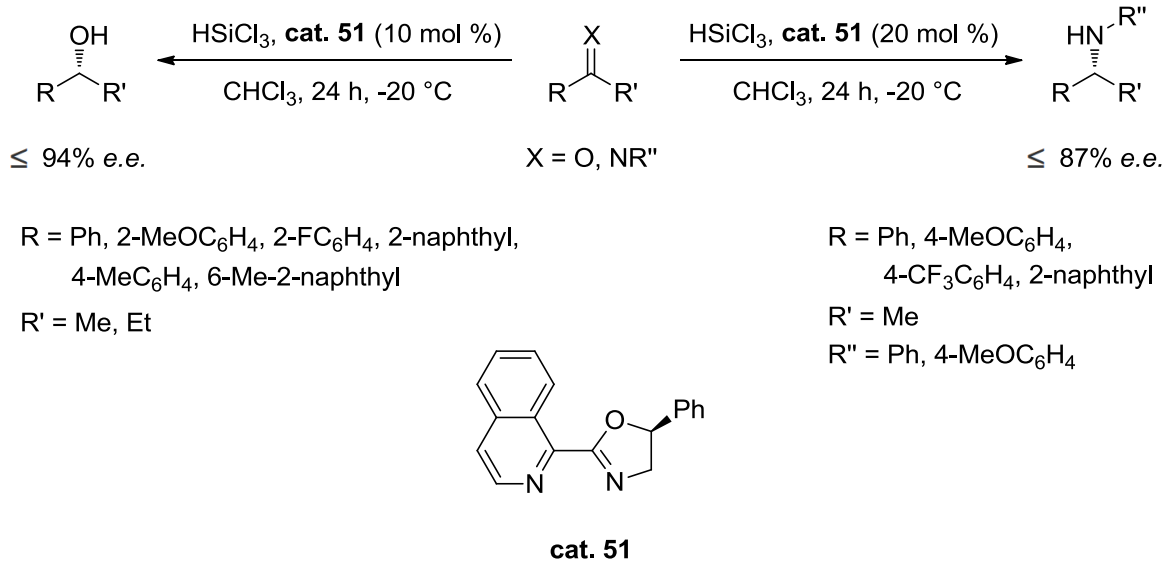


Scheme 3.2.2.11 Stereoselective reduction and reductive amination with catalyst **50**

3.2.3 Reactions catalyzed by other chiral Lewis bases

In 2006 a novel Lewis basic system was reported by Malkov and Kočovský comprising chiral oxazolines containing isoquinoline fragments. Catalyst **51** was

employed in the reduction of aromatic ketones and imines with trichlorosilane, providing the products with a good level of enantioselectivity (Scheme **3.2.3.1**).[134,135]



Scheme 3.2.3.1 Catalytic reductions promoted by an oxazoline-based chiral catalyst

The best enantiomeric excess reached in the reduction of ketones was 87%, while even better results were achieved in the ketimines reduction (92% *e.e.*). The authors hypothesized that coordination of the trichlorosilane by the catalyst would generate a hexacoordinated silicon species that would act as the actual reducing species. When a ketone is the reactive substrate, further activation would be provided by coordination of a molecule of trichlorosilane by the carbonyl oxygen.

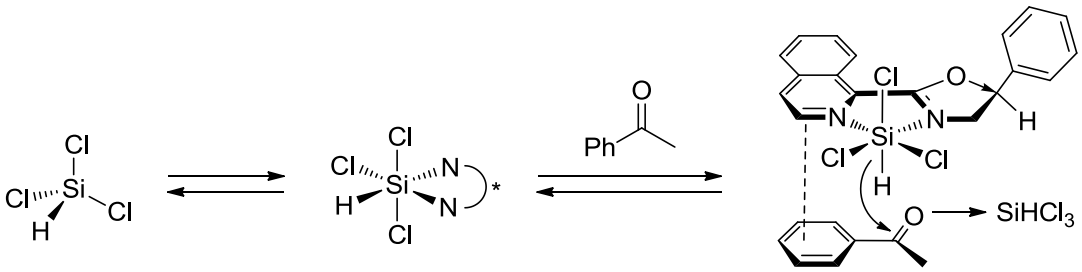
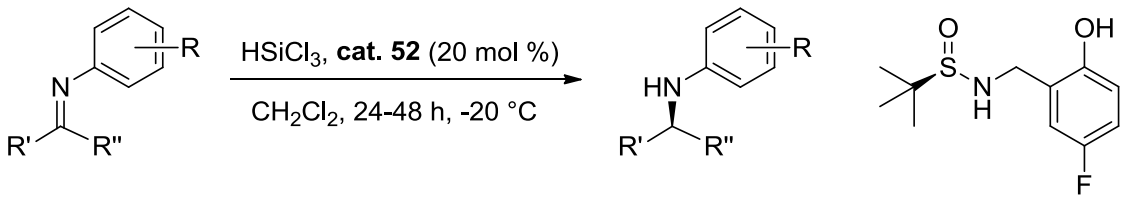


Figure 3.2.3.1 Proposed mechanism for the reductions promoted by catalyst **51**

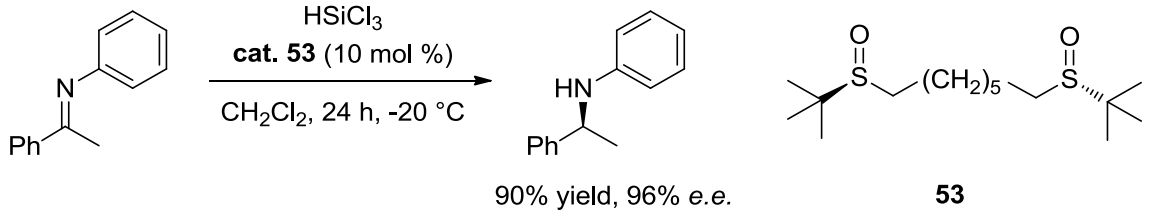
Almost at the same time, Sun published a novel catalyst featuring a sulfinamide group as the stereocontrolling element.[136] This family of organocatalysts was found to be able to activate trichlorosilane for the stereoselective reduction of *N*-aryl ketimines with good yields and enantioselectivities, catalyst **52** being the most successful compound in terms of stereoselection (Scheme **3.2.3.2**).



R = 4-MeO, 4-Me, 2-MeO, 4-Cl,
R' = Ph, 4-$MeOC_6H_4$, 4-BrC_6H_4, 4-$CF_3C_6H_4$, 2-naphthyl, 4-$NO_2C_6H_4$, 6-MeO-2-naphthyl, *c*-C_6H_{11}, *i*-Pr
R'' = *n*-Pr, *n*-Bu, *i*-Bu, Me, Et

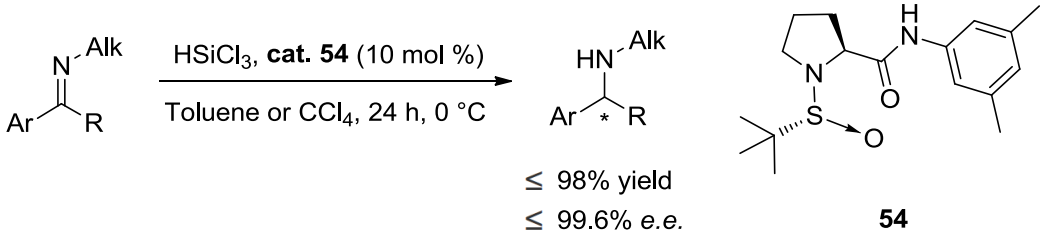
Scheme 3.2.3.2 Use of a chiral sulfinamide as a promoter of imine reductions

Based on the assumption that the mechanism would involve two molecules of Lewis base for the activation of $HSiCl_3$, a novel chiral bis-sulfinamide was then developed. [137] After a screening of different derivatives, the compound of choice was found to be a bis-sulfinamide bearing a five-methylene linkage. Catalyst **53** promoted the reduction of the model substrate, *N*-phenyl imine of acetophenone, with 96% *e.e.* (Scheme **3.2.3.3**).



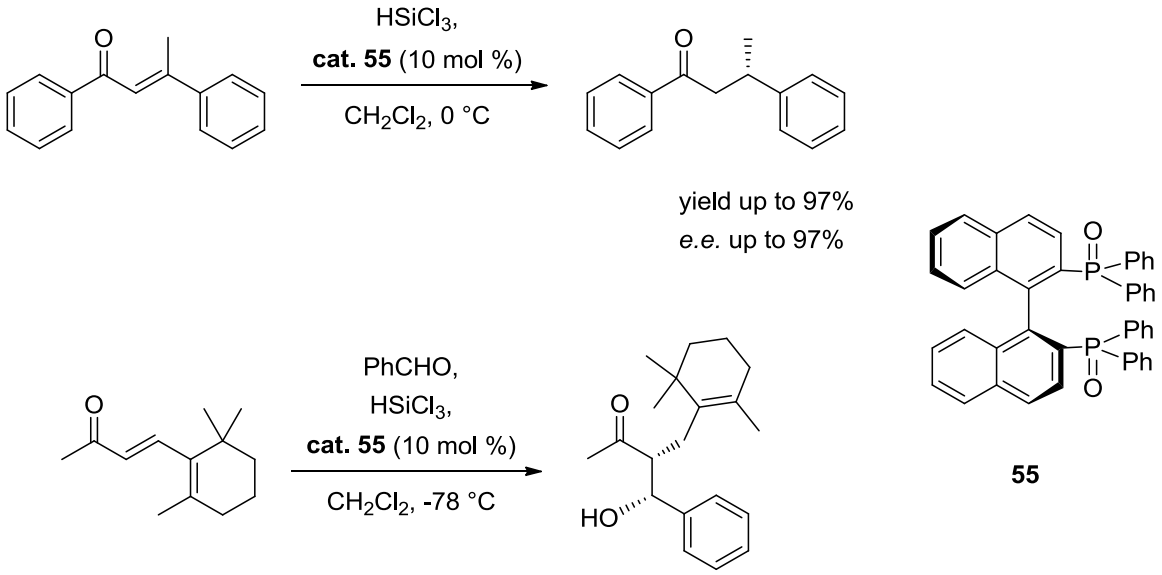
Scheme 3.2.3.3 Novel chiral bis-sulfinamide derivative

Later, Sun's group prepared the new sulfinamidic catalyst **54**.[119] This derivative incorporates two different elements responsible for the stereochemical control of the process: a sulfinamide group with a stereogenic sulfur atom and a *N*-aryl prolinamide. This system was employed to reduce aromatic *N*-alkyl ketimines in presence of trichlorosilane, providing the corresponding amines with good enantioselectivities (up to 99.6% *e.e.*) and high yields.



Scheme 3.2.3.4 Use of a novel sulfinamidic prolinamide as chiral Lewis base

A clearly innovative catalytic system was reported by Nakajima, who introduced chiral phosphine oxides as suitable Lewis bases for activating trichlorosilane in stereoselective transformations. Indeed, trichlorosilane was used in the conjugate reduction of α,β-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 **55** ((*S*)-BINAPO) at 0 °C led to the corresponding saturated compound in 97% yield and a somehow surprising, but very good, 97% *e.e.*.[138] In the same work the authors also described an alternative methodology for organocatalytic conjugate reduction of enones and subsequent reaction with aldehydes, to perform an asymmetric reductive aldol reaction. The idea was to activate the silane with a suitable Lewis base to perform the 1,4-reduction *via* a six-membered transition state; then, with the assistance of the same Lewis base, the generated trichlorosilyl enolate should react with the electrophilic aldehyde. (Scheme **3.2.3.5**).

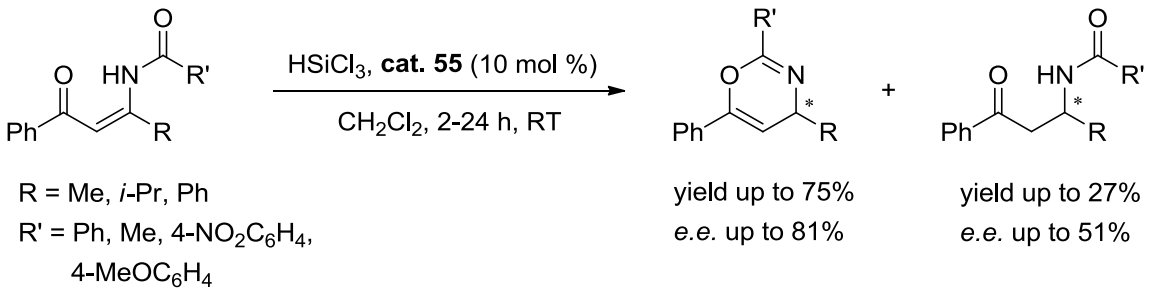


Scheme 3.2.3.5 Asymmetric reduction of unsaturated ketones and reductive aldol reaction

The phosphine dioxide **55** gave even more appealing results in the reductive aldol reduction of β-ionone with benzaldehyde, in which a very high *syn* stereoselectivity was observed along with 96% enantioselectivity for the *syn* isomer.

In a recent report the same group, by studying the stereoselective synthesis of *N*-acylated β-amino ketones, unexpectedly found that optically active 4*H*-1,3-oxazines could be directly obtained *via* reductive cyclization of *N*-acylated β-amino enones using

trichlorosilane and chiral Lewis base catalysts.[139] In the presence of catalytic amounts of (*S*)-BINAPO, the reaction of trichlorosilane with (*Z*)-*N*-benzoyl enone derived from 3-amino-1-phenylbutane-1,3-dione, surprisingly afforded the 4*H*-1,3-oxazine as major product in 68% yield and 74% enantioselectivity. Similar yields and stereoselectivity (up to 81% *e.e.*) were obtained by extending the reaction to other five substrates (Scheme **3.2.3.6**). Among the different chiral phosphine oxides investigated, BINAPO was found to secure the best performances.

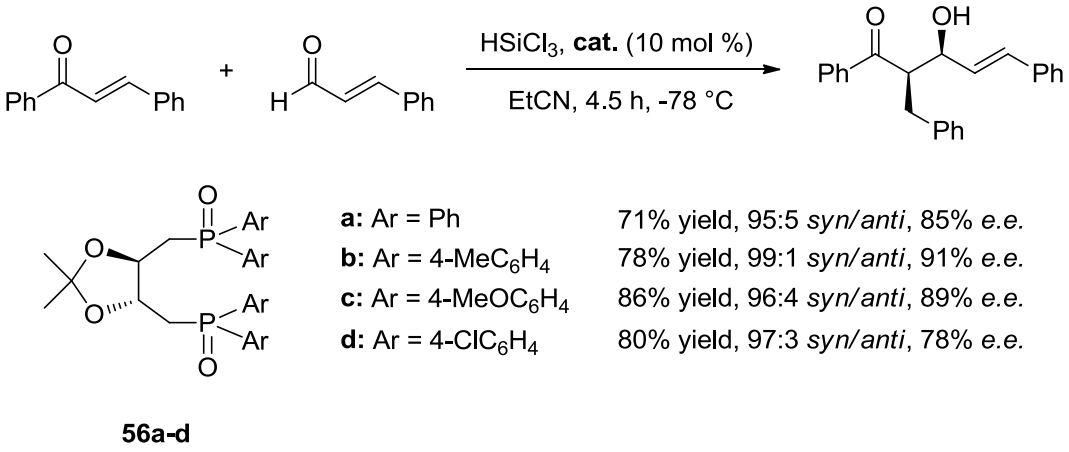


Scheme 3.2.3.6 (*S*)-BINAPO-catalyzed stereoselective synthesis of oxazines

From some preliminary experiments it was observed that trichlorosilane acts not only as a reductant, but also as a dehydrating agent. Different ratios of oxazine and the expected β-keto amide were formed in the reaction, depending on the experimental conditions. Interestingly, it was observed that the two products were obtained with different levels of stereoselection, and sometimes even with different absolute configuration. The result was tentatively explained by assuming that the oxazine was not derived from the ketoamide by simple dehydration. It was proposed that 4*H*-1,3-oxazine is generated through the conjugate reduction of the *N*-acylated β-amino enone, followed by cyclization of the resulting enolate and elimination of $HOSiCl_3$, whereas the ketoamide originates from the 1,2-reduction of the *N*-acyl imine generated *via* equilibration of the enamide.

In 2012, Nakajima and co-workers reported the synthesis and application of a new class of phosphine oxide Lewis base catalysts (Ar-DIOPOs), easily formed by one step reaction between optically pure tartaric acid diiodide and secondary diarylphosphine oxides.[140] These modular catalysts offer the possibility to be readily modified by selecting the proper phosphine oxide used in the preparation. Instead, the modification of catalysts such as BINAPO requires the synthesis of each diphosphine followed by oxidation, which can hinder further optimization. The unsubstituted DIOPO catalyst **56a** gave good results in the $HSiCl_3$ mediated reductive aldol reaction of chalcone and cinnamaldehyde, leading to the desired product in good yield and high stereoselectivity. More electron-donating

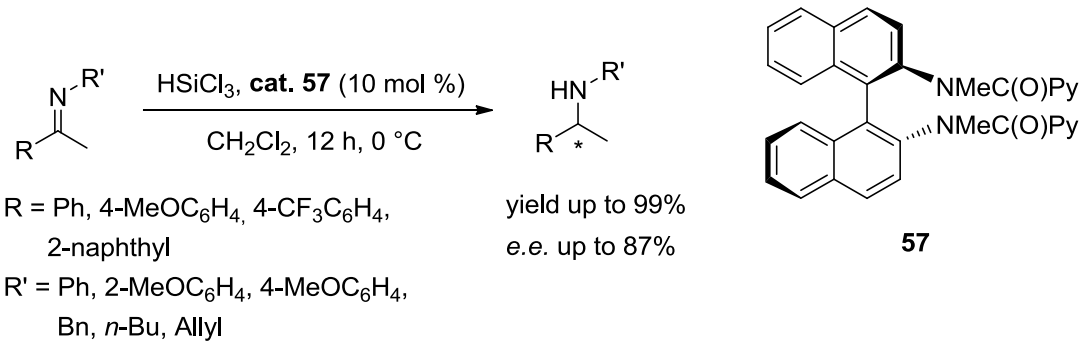
derivatives, like *p*-tolyl and *p*-MeOphenyl-DIOPO (catalyst. **56b** and **56c**), furnished the product in higher yield and enantiomeric excess, while as expected the less electron-rich *p*-Clphenyl-DIOPO **56d** decreased both the diastereo- and enantioselectivities.



56a-d

Scheme 3.2.3.7 Ar-DIOPOs-catalyzed reductive aldol reactions

Our group also reported a class of chiral picolinamides, derived from enantiomerically pure chiral diamines, as efficient chiral organocatalysts for trichlorosilane-mediated reactions.[141] Indeed, a very short route to chiral Lewis bases was envisaged in reactions between pyridine-2-carboxylic acid and commercially available enantiomerically pure binaphthyldiamine derivatives. In particular, the condensation of (*R*)-*N*,*N*'-dimethyl amino binaphthyl diamine with picolinic acid afforded catalyst **57** in 73% yield after chromatographic purification. Notably, binaphthyldiamine-derived bis-picolinamides showed a remarkable activity and both amide-nitrogen atoms were pivotal to obtain high enantioselectivity.[142] Good results were obtained performing the reduction of *N*-aryl (up to 83% *e.e.*), *N*-benzyl (up to 87% *e.e.*) and *N*-alkyl ketimines (up to 87% *e.e.*), working typically at 0 °C.[141] Furthermore, the catalyst **57** was also employed in the reduction of *N*-benzyl imine of ketoesters, although with less success (71% *e.e.*).[142]



57

Scheme 3.2.3.8 Novel chiral Lewis base derived from binaphthyldiamine scaffold

3.3 Stereoselective C-C bond formation

The coordination of a Lewis base to a tetracoordinated silicon atom leads to hypervalent silicate species of increased Lewis acidity at the silicon centre. As a consequence, such extracoordinated organosilicon compounds become very reactive carbon nucleophiles or hydryde donors with a strong electrophilic character at silicon and an enhanced capability to transfer a formally negative charged group to an acceptor (See Figures **3.1.3** and **3.1.4**). When a hypervalent silicon atom is involved as the reactive site in a transformation, carbon-carbon as well as carbon-heteroatom bond formation can occur. On the contrary, when a tetracoordinated silicon atom is exclusively involved in the reaction mechanism, a carbon-silicon as well as heteroatom-silicon bond formation may occur (but not a carbon-carbon formation). Along these lines several asymmetric catalytic systems have been explored in order to develop new stereoselective substoichiometric methodologies for carbon-carbon bond construction. The following sections contain a general overview on the allyltrichlorosilane addition to C=N and C=O bonds and on the aldol condensation in the presence of silyl compounds.

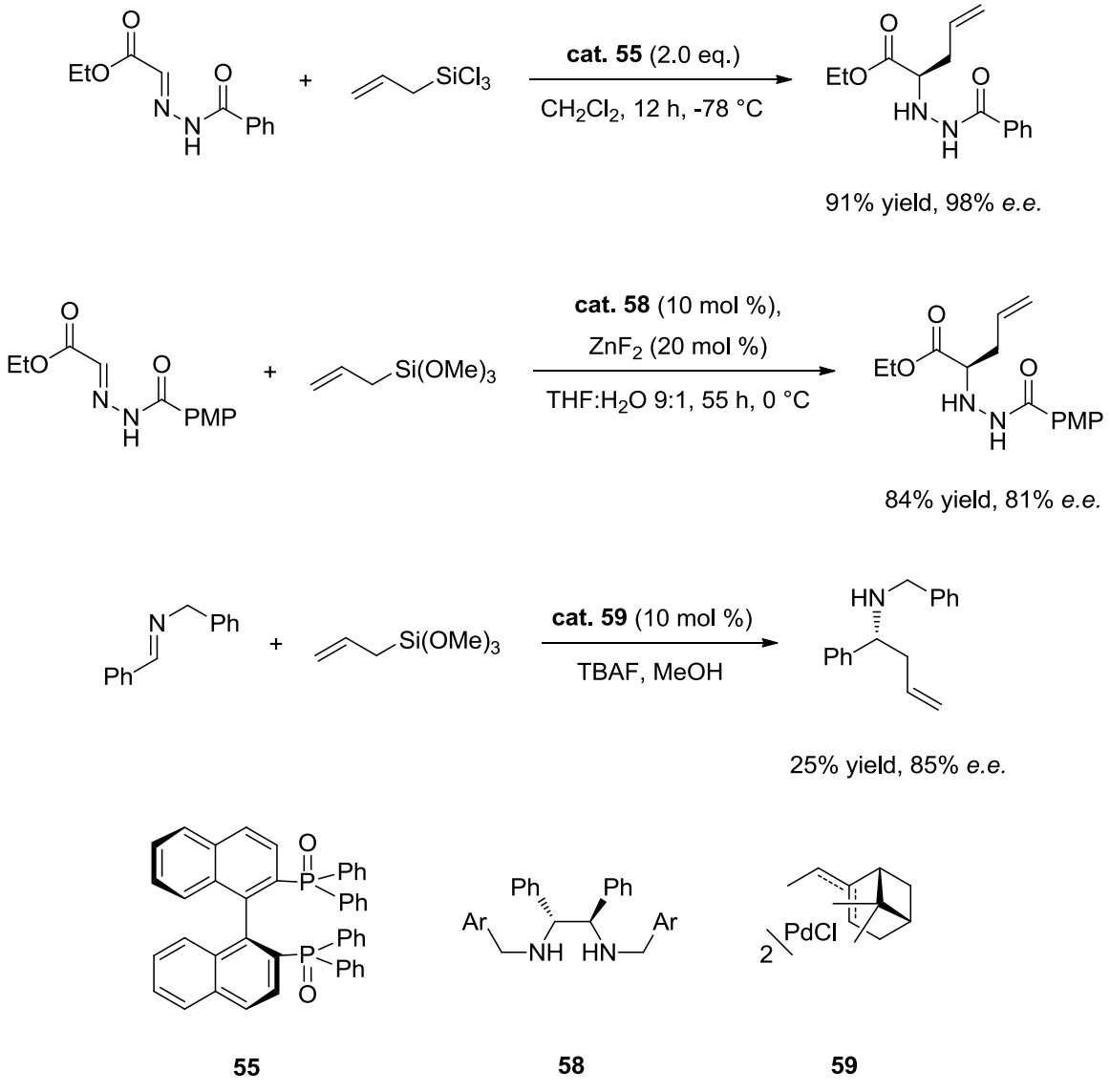
3.3.1 Allylation of C=N group

The synthesis of enantiomerically enriched homoallylic amines is a topic of paramount importance since they represent useful synthetic intermediates that may be converted into different classes of compounds. However, while the catalytic enantioselective allyl addition to carbonyl compounds is well developed, only a few examples of the analogous reaction with imines and imino esters are known, despite their utility in organic synthesis.[143]

In 2004 Kobayashi reported the first example of allyltrichlorosilane addition to *N*-benzoyl hydrazones, a reaction promoted by a chiral phosphine oxide as Lewis base.[144] Phosphine oxide **55** ((*S*)-BINAPO) was employed in the reaction of α-hydrazono esters, (obtained from ethyl glyoxylate and benzhydrazide) with allyltrichlorosilane, affording the product in high yields and enantioselectivities at -78 °C in dichloromethane (Scheme **3.3.1.1**). The reaction is stereospecific, in that (*E*)-crotyltrichlorosilanes afford exclusively the *syn* isomers, and (*Z*)-crotyltrichlorosilanes their *anti* counterparts.

It must be noted that a more than stoichiometric amount of what was called NCO (Neutral Coordinate-Organocatalyst) was necessary in order to achieve high

stereoselectivities, while 0.2 equivalent of BINAPO catalyzed the reaction in only 11% yield and 56% *e.e.*. Another drawback of the methodology is represented by the reductive cleavage of the N-N bond (accomplished by using SmI_2) required in order to obtain synthetically useful compounds. Even if the chiral source could be recovered without loss of stereochemical integrity, it is obvious that the reaction cannot be considered catalytic; however it has some merit, since it represents the first example, and still one of the few cases, of enantioselective allylation of a carbon-nitrogen double bond involving a metal free promoter.[145]



Scheme 3.3.1.1 Stereoselective addition of carbon-nitrogen double bond

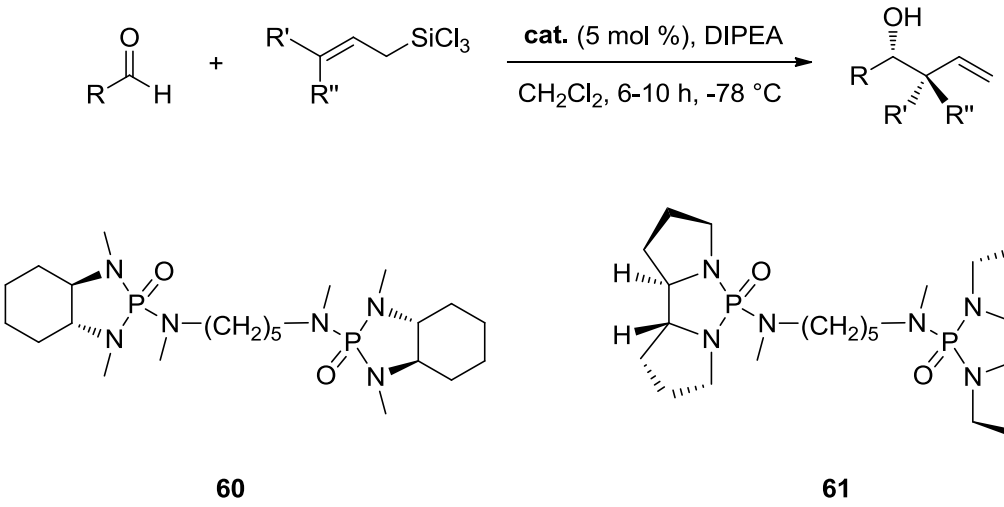
Recently Kobayashi has also developed a zinc fluoride catalyzed addition of allyltrimethoxy silane[146] to acylhydrazono esters, in the presence of a chiral diamine

ligand **58** (Scheme **3.3.1.1**).[147] Water plays a determinant role in affording the product of reaction, that suffers anyway of substrate limitations. Recently Yamamoto and Fernandes have reported the addition of allyltrimethoxysilane to simple imines mediated by a dual activation/promotion process that involves the use of TBAF and the chiral complex of palladium **59**; the product is isolated in 84% *e.e.* but very low yields (Scheme **3.3.1.1**).[148]

3.3.2 Allylation of C=O group

Previously promoted by chiral Lewis acids, this reaction, that may lead to the formation of two new stereocenters, can currently be carried out in the presence of a variety of organic Lewis bases as catalysts. Since a few reviews have recently covered the topic,[79c,d] in the present section only the most important contributions to the field will be discussed as representative examples of different classes of catalysts; in addition, the more recent achievements in the allylation reaction of carbonyl compounds will be included. In 1994 Denmark reported the first enantioselective, non catalytic, addition of allyltrichlorosilane to aldehydes promoted by chiral phosphorotriamides.[149] A series of detailed studies demonstrated that two pathways were possible; one involving an octahedral cationic silicon atom, coordinated by two Lewis bases molecules leading to a good selectivity,[150] and a less selective one, where only one phosphoroamide was bound to a pentacoordinated silicon centre.[151] In view of these mechanistic considerations several chiral bidentate phosphoroamides were prepared and studied in the test allylation of benzaldehyde; a catalyst loading as low as 5 mol % of compound **60** was found to promote the reaction affording the product in high yield and enantioselectivity up to 72% (Scheme **3.3.2.1**).[152]

Based on these results, that clearly indicated the beneficial effect of combining two phosphoramide units through a diamminoalkyl chain, new bidentate catalysts derived from 2,2'-bispyrrolidine and 2,2'-bis piperidine units were investigated. Compound **61** was found to be a really efficient promoter for the allylation reaction of benzaldehyde with allyltrichlorosilane and afforded the homoallylic alcohol in 85% yield and 87% *e.e.*.[150,151] Various γ-substituted allyltrichlorosilanes were employed leading to the products in high yields and up to 96% *e.e.*, showing a good correlation between the configuration of the C=C double bond in the reagent and the *syn/anti* diastereoisomeric ratio of the products.



Scheme 3.3.2.1 Allylation reactions promoted by chiral phosphoroamides

A rationalization of the behaviour of catalyst **61** was also proposed (Figure **3.3.2.1**). In the chairlike, cyclic **TS A** the aldehyde ring is located in an unfavorable position occupied by a forward-pointing pyrrolidine ring, creating destabilizing steric interactions. In the diastereoisomeric chairlike arrangement of **TS B** the aldehyde ring does not have any unfavorable interaction with the backward-pointing pyrrolidine unit, leading to the experimentally observed product of *S* configuration.

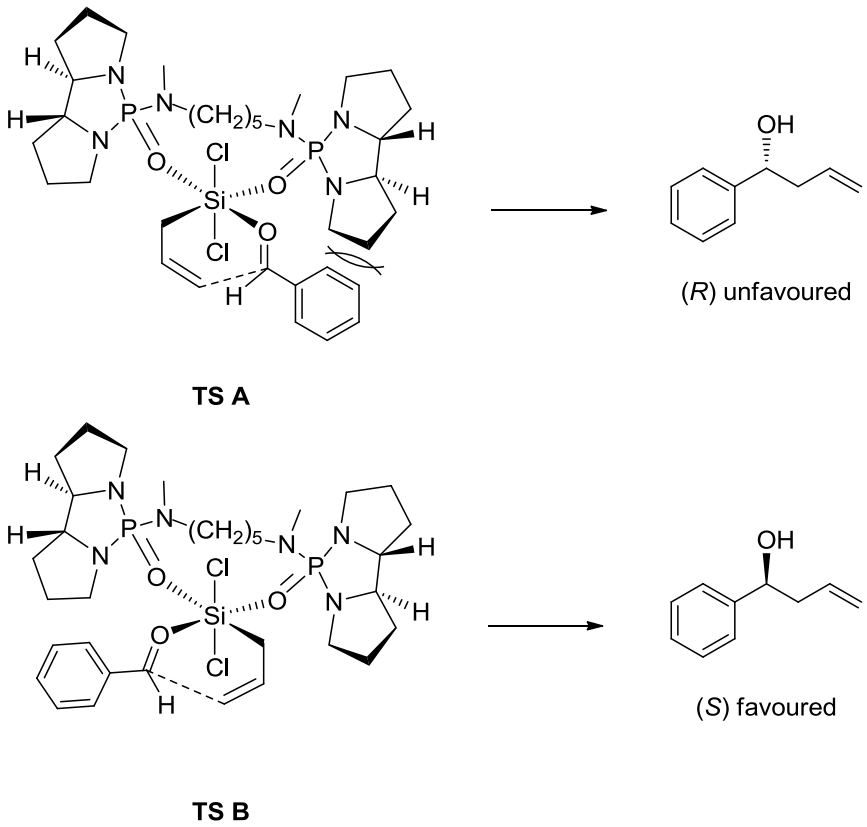


Figure 3.3.2.1 Proposed model of stereoselection for the allylations with catalyst **61**

Among Lewis basic catalysts, another class of compounds that deserve a special attention is represented by amine *N*-oxides.[153] The high nucleophilicity of the oxygen in *N*-oxides, coupled with the high affinity of silicon for oxygen, represents ideal properties for the development of synthetic methodology based on nucleophilic activation of organosilicon reagents. The first asymmetric addition of trichlorosilane to aldehyde catalyzed by bisquinoline *N,N'*-dioxides **62** was reported in 1998 by Nakajima.[154] The reaction was accelerated by the addition of diisopropylethylamine and afforded the products in high yields and enantioselectivities (up to 92%) with aromatic and heteroaromatic aldehydes. Lower yields and stereocontrol were observed with non conjugated aldehydes (Figure **3.3.2.2**).

Later, Hayashi developed another chiral catalyst, **63**, with a stereogenic axis as key element of stereocontrol, leading to comparable enantioselection with catalyst **62** (56-98% *e.e.*).[155] Remarkably, Hayashi's catalyst was found to be effective at 0.1 mol % level (-40 °C, acetonitrile) and retains moderate activity even at 0.01 mol % loading, which makes this organocatalyst the most reactive one reported to date. More recently, a simple synthesis of unsymmetric atropoisomeric bipyridine *N,N'*-dioxides in three steps from commercially available material was reported.[156] The key step of this reaction sequence is the cobalt-catalyzed heterocyclotrimerization of 1-pyridyl-1,7-octadiynes with nitriles to provide unsymmetrical bipyridines, followed by oxidation and resolution into enantiomers. Catalyst **64** promoted the addition of allyltrichlorosilane to aromatic aldehydes in up to 80% *e.e.*. Another class of catalysts was actively studied by Malkov and Kočovský, which have shown that the terpene-derived bipyridine *N*-monoxides Me-2-PINDOX, **65** (cat. 10 mol%, -78 °C, CH_2Cl_2) was extremely enantioselective (up to 98% *e.e.*), although the reaction was sluggish.[157] Such catalyst combines the effects of both stereogenic centers and axis, the rotation around the bond connecting the two pyridine moieties being restricted by the two methyl groups and the N-O residue.

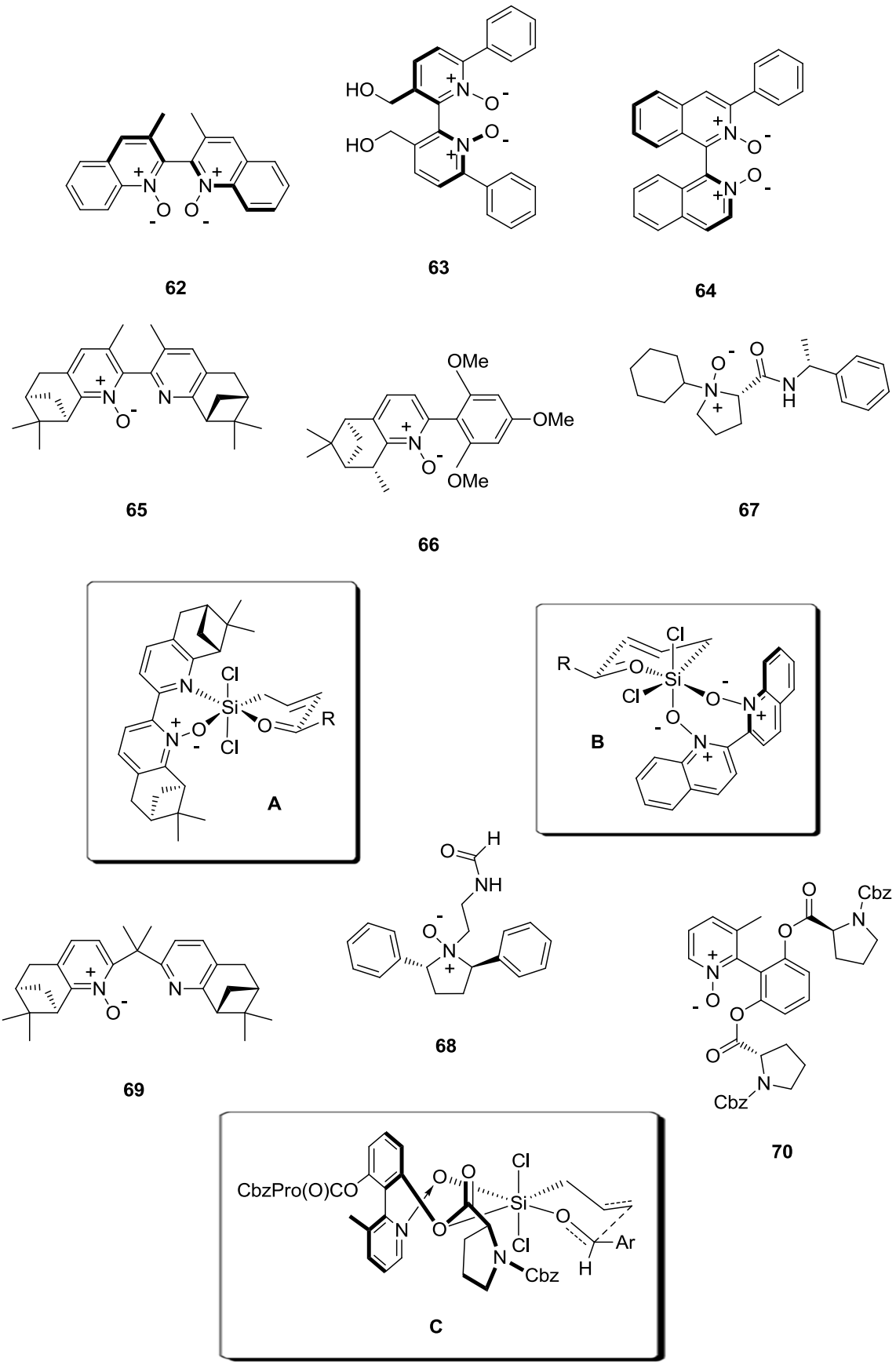


Figure 3.3.2.2 Chiral *N*-oxides as catalysts for allylation of carbonyl compounds

In analogy to the previously proposed model, chelation of the silicon in allyltrochlorosilane by the O and N atoms was also proposed for **65** (Figure **3.3.2.2**).

In another important contribution, Malkov and Kočovský showed that two *N*-oxide groups are not mandatory, but one *N*-oxide and a second coordination element (such as in the new developed catalyst **66**)[158] are enough to guarantee high levels of stereocontrol, The proposed transition structure for the mono-*N*-oxide derivatives **A** is very similar to that proposed for bis-*N*-oxide compounds, **B** (Figure **3.3.2.2**). In catalyst **66** arene-arene interactions between the catalyst and the substrate have been suggested to account for the high reactivity and selectivity. Furthermore, it was shown that the axial stereogenicity, whether predetermined or induced during the reaction, is not a prerequisite for attaining high enantioselectivity in the allylation reaction.[159] As further demonstration of these considerations, Hoveyda developed the *N*-oxide **67**, the only representative of aliphatic tertiary amine *N*-oxides so far reported in this series, that presents a stereogenic center at nitrogen.[160] It is pertinent to note that catalysts **66** and **67** secure high enantioselectivity even at room temperature.

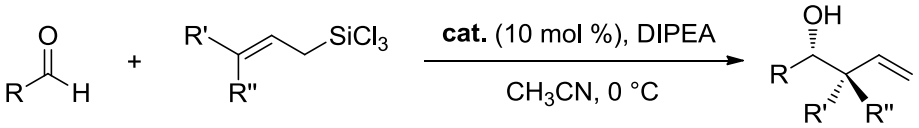
The only other example of chiral non-pyiridinic *N*-oxide used as promoter of the allylation reaction has been recently developed by our group.[161] A new class of amine *N*-oxides derived from *trans*-2,5-diphenylpyrrolidine were synthesized in enantiomerically pure form and tested as catalysts in the reaction of aldehydes with allyltrichlorosilane to afford homoallylic alcohols. The products were obtained in fair to good yields and up to 85% *e.e.*. Noteworthy a catalyst capable of promoting the allylation of aliphatic aldehydes with an almost unprecedent and unusually high enantioselectivity, up to 85%, was identified in **68**.

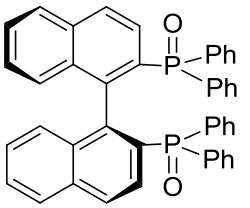
Based on these studies other systems lacking the stereogenic axis were recently developed.[162] For example, new chiral dipyridine *N*-monoxides and *N,N'*-dioxides, which possess an isopropylidene backbone between two pyridine rings, have been prepared from naturally occurring monoterpenes, the more efficiently being compound **69** (Figure **3.3.2.2**).[163] Its efficiency as organocatalyst has been demonstrated in the enantioselective addition of allyltrichlorosilane to aldehydes, where enantioselectivities up to 85% *e.e.* have been obtained.

A series of structurally simple pyridine *N*-oxides have readily been assembled from inexpensive aminoacids and tested as organocatalysts in the allylation of aldehydes with allyltrichlorosilane to afford homoallylic alcohols.[164] (*S*)-Proline based catalyst **70** afforded the products derived from aromatic aldehydes in fair to good yields and up to

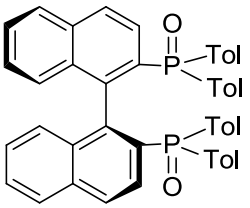
84% *e.e.*. By implementing the results of conformational analysis with those of a few control experiments, transition structure **C** shown in Figure **3.3.2.2** can be proposed to tentatively explain the stereochemical result of the allylation reaction. In this model, the hypervalent silicon atom is coordinated by the pyridine *N*-oxide oxygen and the phenolic oxygen of one side arm. The bulky proline residue effectively blocks one side of the adduct and accomodates the aldehyde better than the sterically more requiring allyl residue as its *cis* substituent.

In 2005 it was demonstrated for the first time that also chiral phosphine oxides, such as BINAPO, can act as organocatalysts in the enantioselective addition of allyltrichlorosilane to aldehydes.[165] In the presence of 10% mol of (*S*)-BINAPO **55** the homoallylic alcohol was obtained in DCM in only 32% yield and 36% *e.e.* (Scheme **3.3.2.2**). By employing a proper additive such as $Bu_4N^+I^-$ and 5 equivalents of DIPEA the yield was improved to 92% after only 4 hours at room temperature, even if with still modest enantioselectivity (43% *e.e.*), definitely lower than that obtained with the best phosphoroamide-derived catalysts. The reduced chemical activity might be ascribed to the different electronic properties of the ligands. However, for this kind of reactions it had been already suggested that the effectiveness of a catalyst is determined not only by the donor properties of the Lewis base but also by the steric hindrance at the oxygen atom. For example, dimethylphosphinic *N*,*N*-dimethylamide is a better promoter for the allylation of benzaldehyde than methylphosphonic di-(*N*,*N*-dimethylamide) that, in its turn, is better than HMPA (hexamethylphosphoric triamide). However if in dimethylphosphinic *N*,*N*-dimethylamide a methyl group is replaced by an isopropyl group, the chemical efficiency of the catalyst dramatically decreases, clearly pointing at the importance of the steric accessibility of the oxygen atom for co-ordination. A marked improvement of the catalytic efficiency of chiral phosphine oxides was obtained by our group exploring the characteristics of heteroaromatic systems.[166] The advantages offered by the biheteroaryldiphosphine oxides, with respect to carbocyclic aromatic derivatives, reside in their greater synthetic accessibility and in the possibility of testing a series of catalysts displaying different electronic properties, where the influence of both the electronic availability of the heterocyclic system and of the position of the phosphorus atoms on the latter may be investigated.

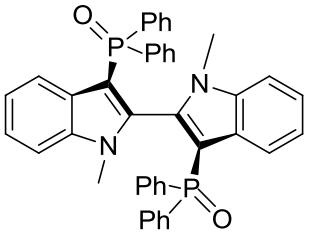




55 (*S*)-BINAPO

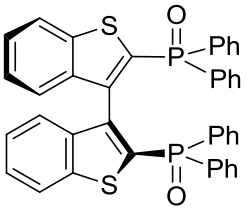


71 (*S*)-Tol-BINAPO

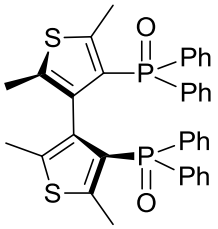


72 (*S*)-*N*-Me-2-BINPO

55-95% yield, 55-71% *e.e.*



73 (*S*)-BITIANPO



74 (*S*)-tetraMe-BITIOPO

55-98% yield, 83-95% *e.e.*

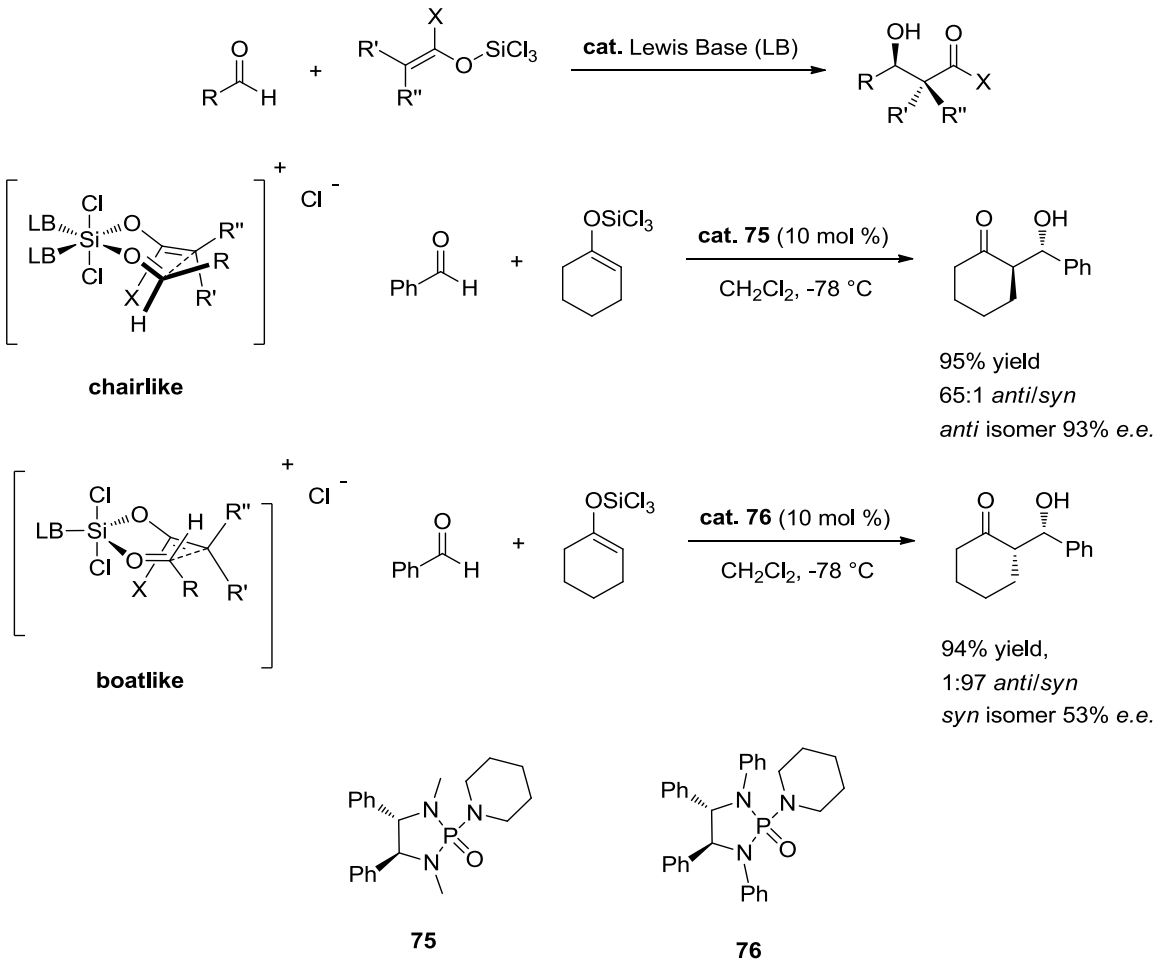
Scheme 3.3.2.2 Phosphine oxide catalyzed addition of allyltrichlorosilane to aldehydes

While the most electron deficient diphosphine oxide BITIANPO did not promote the reaction in appreciable yields, more electron-rich compounds showed a significant catalytic activity, promoting the addition of allyltrichlorosilane to benzaldehyde at 0 °C in higher yield (85%) than medium electron rich diphosphine oxide Tol-BINAPO. Biheteroaromatic diphosphine oxides showed also an extraordinary ability in determining the stereochemical outcome of the reaction, being (*S*)-*N*-Me-2-BINPO able to catalyze the reaction in 81% *e.e.*, clearly a better result than that obtained with Tol-BINAPO (51%). The catalyst of choice was found to be (*S*)-tetramethyl-bithiophene phosphine oxide, (*S*)-TetraMe-BITIOPO, **74**, which promoted the allylation of benzaldehyde in 93% *e.e.*, a very high level of enantioselectivity, comparable to those obtained with the best known organocatalysts. The same catalyst efficiently promoted the addition of allyltrichlorosilane to aromatic aldehydes bearing electron-withdrawing as well as electron-donating groups with enantioselectivities constantly higher than 90%.

3.3.3 Aldol condensation reaction

Since the structure and the reaction mode of allylsilane may recall that of silyl enol ether (C-Si bond cleavage *vs.* O-Si bond cleavage), the addition of trichlorosilyl enol ethers to carbonyl derivatives catalyzed by Lewis bases was studied.[167] However since silyl enol ethers have a higher nucleophilicity compared to the corresponding allylsilanes, the aldol addition of trichlorosilyl enol ethers to aldehydes proceeds readily at room temperature even without a catalyst and exhibits simple first-order kinetics in each component. Nevertheless, the fact that the reaction is substantially accelerated by Lewis bases, sets the scene for the development of an asymmetric variant. Denmark introduced a range of efficient chiral phosphoramides as nucleophilic activators for enantioselective C-C bond aldol formation and also carried out a detailed mechanistic investigation.[168]

In 1996 the first example of aldol condensation of trichlorosilyl enol ethers was reported.[169]

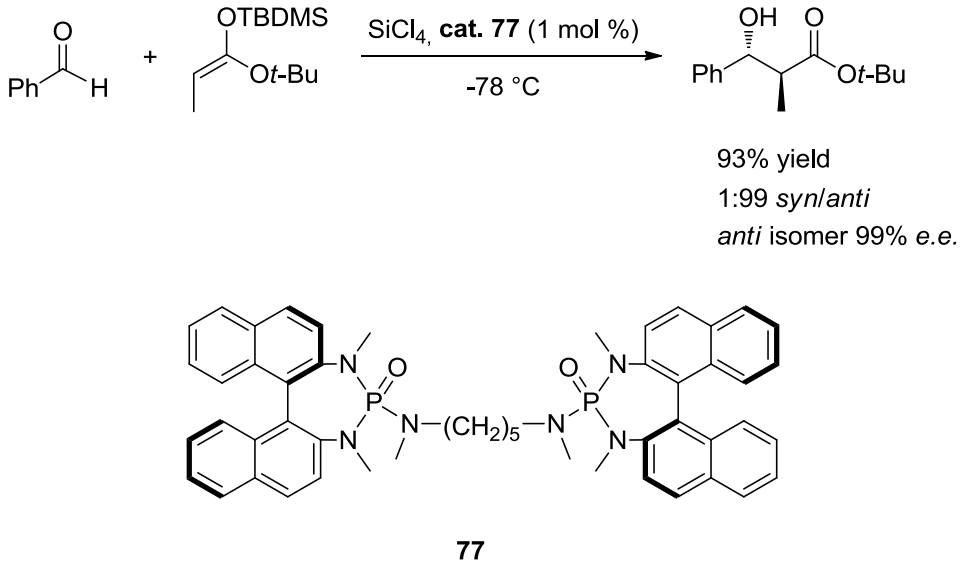


Scheme 3.3.3.1 Aldol condensation promoted by chiral phosphoroamides

Denmark and co-workers successfully employed the chiral phosphoroamide **75** derived from 1,2-diphenyl-ethylendiamine to promote the addition of the trichlorosilyl enol ether of cyclohexanone to benzaldehyde in 95% yield, 65:1 *syn/anti* ratio and 93% *e.e.* (Scheme **3.3.3.1**). However it was demonstrated that the diastereoselectivity was largely dependent on the structure of the chiral catalyst. After carrying out a detailed mechanistic study bidentate and smaller monodentate catalysts were shown to react through a cationic chairlike transition state, similar to that usually proposed for the allylation reaction, involving octahedral extracoordinate silicon. According to this scheme, (*Z*)-enol ethers produced *syn* adducts, whereas (*E*) derivatives provides *anti* diastereoisomers. In the case of a bulky monodentate activator, where coordination of the second catalyst molecule is precluded by steric factors, the diastereoselectivity of the reaction was reversed. Here, the reaction presumably proceeds *via* the cationic boatlike TS, in which the silicon is pentacoordinate. According to this scheme, the cyclohexanone-derived enol ether with a fixed (*E*) configuration of the double bond gave rise to the *syn* product with sterically demanding catalyst **75** and to the *anti* isomer with catalyst **76**.[170]

For a long time, only monophosphoramides have been known; recently, also bis-phosphoramides (where two phosphorous atoms are connected by a nitrogen linker) were developed.[150,151]

In the presence of stoichiometric amount of tetrachlorosilane the use of catalytic amounts of binaphthyldiamino-based phosphoramide **77**, even at 1 mol % loading, was found to be able to promote the addition of silyl ketene acetals and silyl enol ethers to aromatic aldehydes in high enantioselectivities. When an aliphatic aldehyde was employed instead, the reactivity enormously decreased and no product was formed. It is important to highlight that these are not Lewis acid-catalysed reactions; the fact that the aldol products are trichlorosilyl ethers, as demonstrated by NMR analysis, proves that each molecule of tetrachlorosilane partecipating to the catalytic cycle is incorporated into the product. Further studies also demonstrated that the presence of ammonium salts (TBAI) improves the chemical activity, without loss of stereoselection.



Scheme 3.3.3.2 Aldol condensation promoted by chiral bisphosphoroamides

The hypothesized catalytic cycle involves the chiral trichlorosilyl cation **A** that binds the aromatic aldehyde to give adduct **B**, which is reputed to exist in equilibrium with the alkylchloro silyl ether **D**. Intermediate **B** is then attacked by the silyl ketene acetal to afford **C**. This adduct, after dissociation from the catalyst, leads to the product as trichlorosilyl ether (Figure **3.3.3.1**).

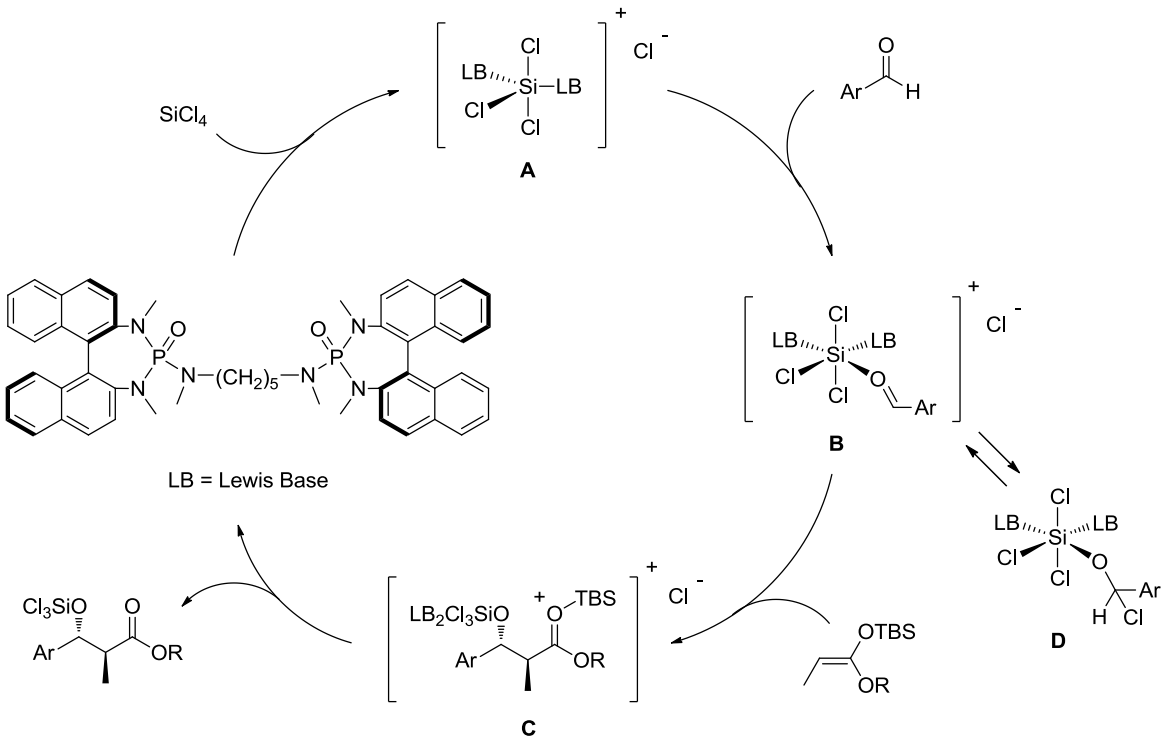
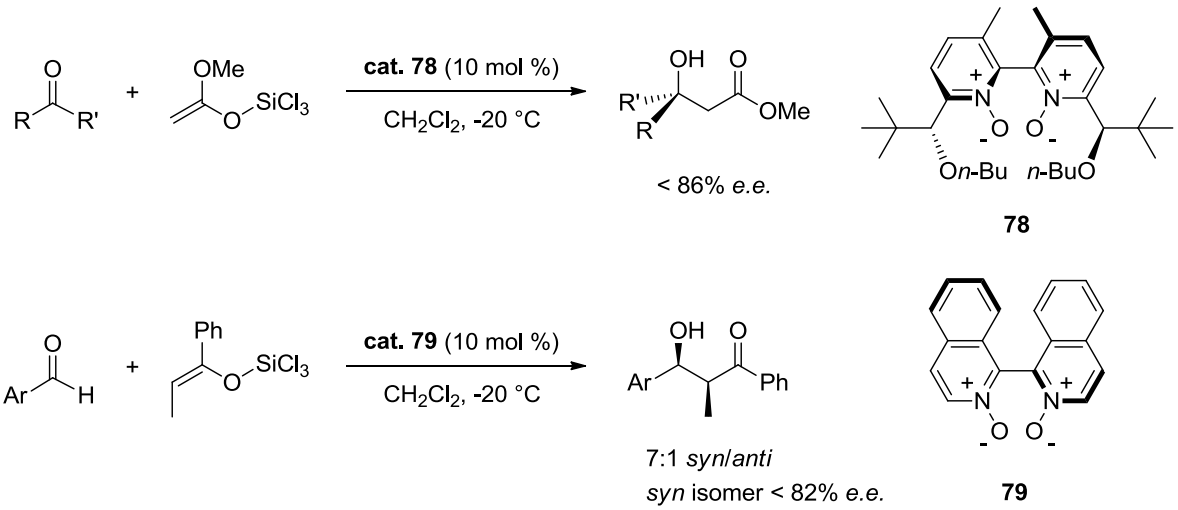


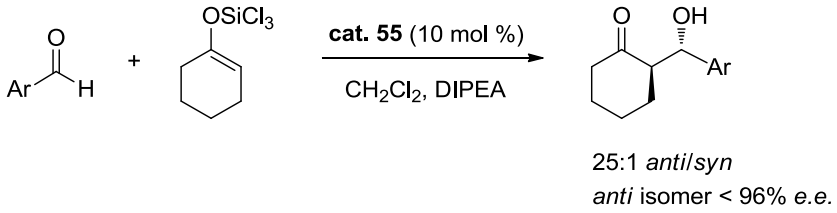
Figure 3.3.3.1 Lewis base-catalyzed Lewis acid-mediated reactions

Notably, the reaction is not only *anti* selective, but also diastereoconvergent, affording the same stereoisomer independently from the geometry of the starting enolate. This behavior was tentatively rationalized by proposing that the decisive factor responsible for the observed trend in diastereoselectivity is the interaction between the α-substituent and the bound silyl cation complex in an open, acyclic transition structure.

Also pyridine *N*-oxides were demonstrated to act as catalysts in the aldol reaction. In the absence of an activator, addition of trichlorosilyl ketene acetal to acetophenone slowly takes place at 0 °C, but it can be accelerated by a Lewis base (Scheme **3.3.3.3**). Bis-*N*-oxide **78** emerged as the most promising in terms of reactivity and enantioselectivity (cat. 10 mol %, -20 °C, CH_2Cl_2), affording the β-hydroxy ester, with a quaternary stereocenter, in 94% yield and 84% *e.e.*.[171] A new procedure for the synthesis of atropoisomeric bis-*N*-oxide has also been developed. An X-ray crystal structure of the complex between the catalyst and silicon tetrachloride has been obtained. Extensive computational analysis were conducted to propose a stereochemical rationale for the observed trends in enantioselectivities. Other chiral *N*-oxides were employed, but with less success; for example, Nakajima reported that catalyst **79** promoted the addition of trichlorosilyl enol ethers to aromatic aldehydes in decent diastereoselectivity and enantioselection up to 82%.[172] (Scheme **3.3.3.3**).

Also phosphine oxide **55** was able to catalyze the addition of cyclohexanone-derived silyl enol ether with activated aromatic aldehydes in high stereoselectivity.[173] The aldol adduct was obtained in moderate yield and diastereoselectivity, with 82% enantioselectivity for the *anti* isomer (Scheme **3.3.3.3**).

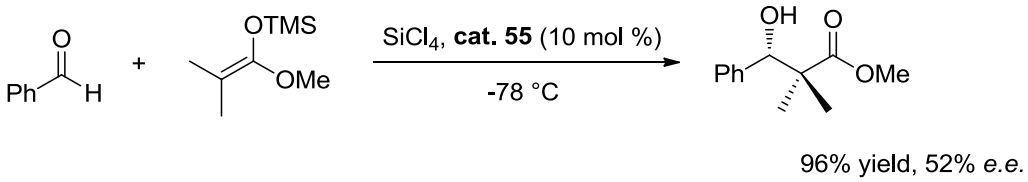




Scheme 3.3.3.3 Aldol reactions catalyzed by chiral *N*-oxides and phosphine-oxides

By the addition of DIPEA both chemical and stereochemical efficiency was increased, the product being isolated (-78 °C, DCM) in 94% yield, 86% of *anti* diastereoselectivity and 87% *e.e.* for the *anti* isomer. It was proposed that the tertiary amine additive may work not only as acid scavenger to neutralize the hydrogen chloride produced by adventitious hydrolysis of trichlorosilyl enolethers, but also accelerating the reaction rate by promoting the dissociation of phosphine oxide from the silicon atom. The Lewis-base promoted condensation afforded *anti* adducts starting from (*E*)-silanes and *syn* adducts from (*Z*)-silanes, confirming the hypothesis that similarly to allylation reaction, a cyclic, six membered transition state is involved.

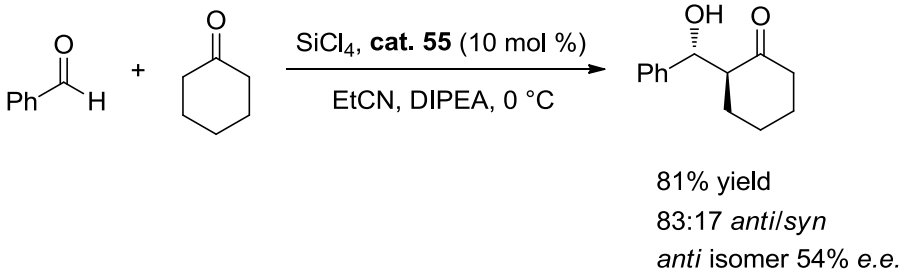
In 2005 it was demonstrated that also chiral phosphine oxides such as (*S*)-BINAPO **55** are able to promote the silyl ketene acetals addition to aromatic aldehydes in the presence of a stoichiometric amount of silicon tetrachloride, smoothly affording the aldol adduct in high yield but only moderate enantioselectivity (52% *e.e.*, Scheme **3.3.3.4**).[165]



Scheme 3.3.3.4 Reaction of aldehydes with trimethylsilyl ketene acetals promoted by **55**

Four years later, the Nakajima's group reported a more interesting work where the *in situ* preparation of trichlorosilyl enol ether was investigated.[174] The aldol reaction of trichlorosilyl enolethers developed by Denmark suffers from the major drawback of requiring the preparation of the trichlorosilyl derivatives according to an environment-unfriendly procedure that involves the use of mercury salts. To improve the efficiency of the methodology, the direct synthesis of the enolethers from the carbonyl compounds with tetrachlorosilane in the presence of phosphine oxides was realized: the resulting trichlorosilyl enol ether was simultaneously activated by phosphine oxide to add to

aldehydes and afford a β-hydroxy ketone in a direct aldol-type reaction, reaching high yields (81%), good diasteroselectivity (17 : 83 *syn/anti*) and moderate enantioselectivity (54% *e.e.* for *anti* isomer).



Scheme 3.3.3.5 Direct aldol-type reaction catalyzed by phosphine oxides

A direct aldol-type reaction between two different aldehydes was also successfully accomplished, taking advantage of the poor reactivity of aliphatic aldehydes as electrophiles: the reaction between benzaldehyde and isobutyraldehyde in the presence of (*S*)-BINAPO **55** led to the expected β-hydroxy aldehyde with 55% *e.e.*.

In recent times, our group has successfully extended the direct aldol condensation between ketones and aromatic aldehydes, using as chiral Lewis basis the TetraMe-BITIOPO already employed in the addition of allyltrichlorosilane to aldehydes.[175] The results confirm the trend already observed and point to the importance of the electronic properties of the chiral phosphine oxide in fine-tuning the catalyst's performance: in fact it was found that BITIOPO constantly performed better than BINAPO, permitting to obtain the desired product with higher yields and better diastereo- and enantioselectivity. Under the best experimental conditions the desired β-hydroxy ketones were obtained with high diasteroselectivity, up to 93:7 *anti/syn* ratio, and enantiomeric excess often higher than 85%. Higher levels of enantioselectivity were achieved in the case of electron deficient aldehydes, reaching up to 93% *e.e.*. The methodology was successfully extended to structurally different ketones, including compounds containing heteroatoms such as nitrogen, oxygen and sulfur. Moreover, this technique was found to be suitable for the cross aldol condensation between aromatic and aliphatic aldehydes.

A chairlike six-membered cyclic transition state was hypothesized to explain the *anti* selectivity generally observed (Figure **3.3.3.2**). The steric hindrance of the diphenyl-phosphinoyl group of the Lewis base with cyclohexanone-derived enolether would be responsible for the favourable attack of the enolether onto the *Re* face of the aldehyde,

resulting in the experimentally observed (2*S*,1'*R*)-*anti* major stereoisomer. The proposed cyclic TS was confirmed from an additional experiment, where the aldol condensation between benzaldehyde and cyclohexanone was performed in the presence of a stoichiometric amount of BF_3, a Lewis acid able to competitively coordinate the aldehyde. In that case the product was isolated in virtually racemic form, clearly underlining the importance of the aldehyde's coordination to the chiral cationic silicon species.

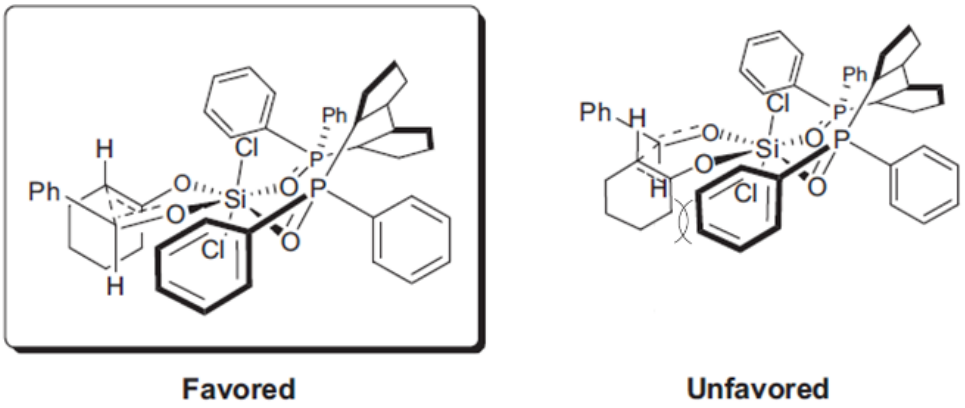
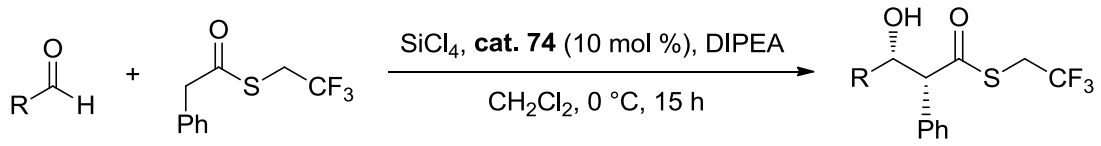


Figure 3.3.3.2 Proposed transition state for $SiCl_4$-mediated direct aldol condensation

Later, we successfully managed to perform the first stereoselective, organocatalytic direct aldol addition of activated thioesters to aldehydes.[176,177] The development of a direct diastereo- and enantioselective, catalytic aldol reaction of esters with carbonyl derivatives remains one of the unsolved challenges in organocatalysis, due to the lower acidity of the α protons of carboxylic esters compared to those of a ketone or an aldehyde. The use of trifluoroethyl thioesters, bearing in the α position an additional activating element such as an aryl residue or an halogen atom, offer a pK_a value low enough to allow the deprotonation by an amine. By reaction of a properly activated trifluoroethyl thioester with aromatic aldehydes β-hydroxy trifluoroethylthioester can be synthesized with moderate to good yields, up to 98:2 *syn/anti* ratio and up to 89% of enantiomeric excess for the *syn* isomer. These good results in terms of chemical and stereochemical efficiency were confirmed when different activated thioesters and aldehydes were employed (Scheme **3.3.3.6**).



Scheme 3.3.3.6 Direct aldol condensation between aldehydes and activated thioesters

In attempting a rationalization of the stereochemical outcome of this reaction, the understanding of the enolization step of the thioester is of crucial importance. On the basis of steric considerations, the adduct formed by coordination of the thioester with the chlorosilane species can be expected to adopt the so-called "pinwheel" conformation **A**[178] (See Figure **3.3.3.3**). In this way the repulsion between the bulky peripheral groups should be to minimized. Deprotonation with a bulky base such as DIPEA should occur as in **B**[179] to afford *O*-silylenolate **C**. From this "*Z*" enolate the formation of *syn* aldol is expected to occur *via* a chair-like transition structure in which the Lewis acidic silicon atom coordinates and activates the aldehyde towards the attack of the nucleophile. Of the two competing transition structures leading to the *syn* aldols, model **D**, affording the experimentally obtained (2*R*,3*R*)-product can tentatively be considered favoured over model **E**, since the latter features a destabilizing steric interaction between a phenyl residue of the catalyst and the bulky trifluoroethylthio group of the thioester.

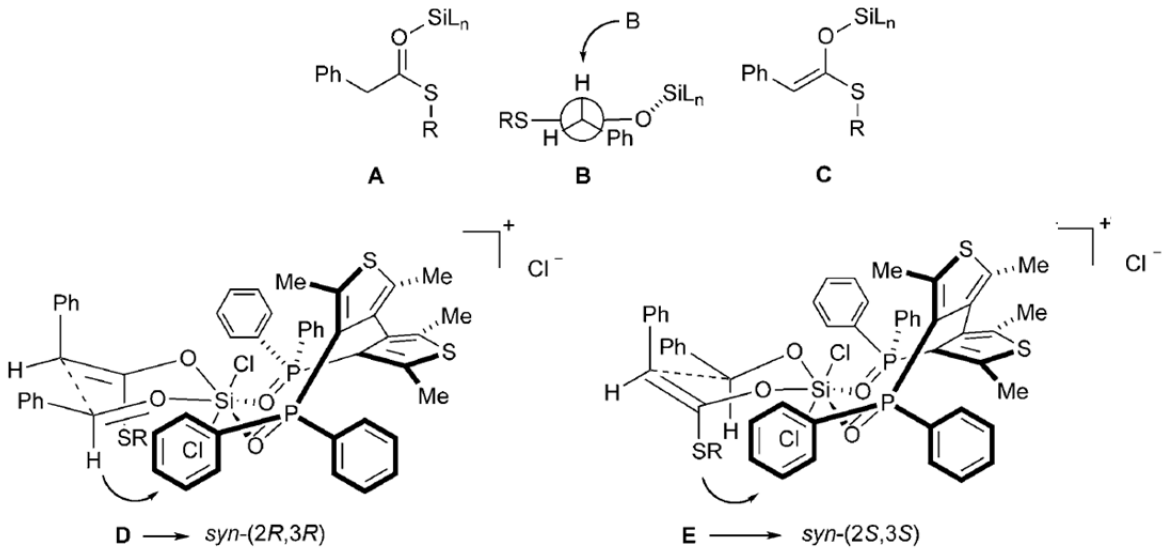


Figure 3.3.3.3 Proposed TS for $SiCl_4$-mediated aldol condensation of activated thioesters

CHAPTER 4

Diastereoselective hydrogenation of ketimines catalyzed by frustrated Lewis pairs

"The scientist is not a person who gives the right answers, he's one who asks the right questions."

Claude Lévi-Strauss

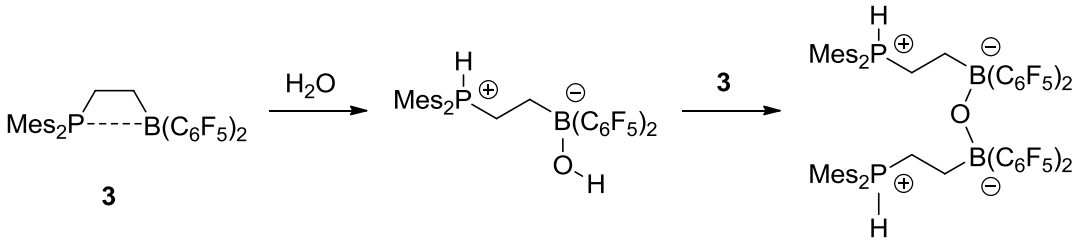
With its impressive growth[180] and very promising results, frustrated Lewis pairs area represents a very interesting novel methodology for the reduction of carbon nitrogen double bonds, whose potential soon attracted our attention. Since at the beginning of our study no highly enantioselective reduction catalyzed by FLPs had been reported yet, our first aim in this field was to develop an asymmetric efficient hydrogenation promoted by these systems. Indeed, until that moment the only known example of a stereoselective frustrated Lewis pairs was the α-pinene derived chiral borane reported by Chen and Klankermeyer, which allowed the synthesis of the product amine in only 13% enantiomeric excess. Even now the developed chiral FLP systems are limited to few examples and this field still remains quite unexplored.

Moreover, in Chapter 1 it was already mentioned that FLP systems often suffer from reduced stability in the presence of air and moisture, which complicates their use and effective recycle.

As frustrated Lewis pairs retain most of the typical reactivity of their Lewis base and Lewis acid components, they undergo reactions that are characteristic for each separate component. However, in addition they add cooperatively to a variety of substrates. This

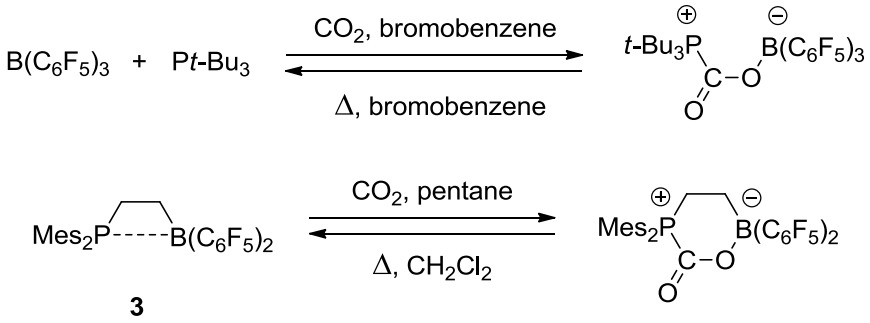
extends the scope of their potential use far beyond their application for metal-free heterolytic H_2 activation and metal-free hydrogenation catalysis, but also exposes the FLP systems to the risk of unwanted side reactions.[16a] Indeed, FLP activation of several small molecules other that dihydrogen has been reported, for example the 1,2-addition to the reactive C=O double bond of isocyanates[181,182] and the addition to alkenes, conjugated dienes and alkynes.[183,184,185] Of particular importance are the reactions of frustrated Lewis pairs with water and CO_2.

Since the boron center in **3** is quite Lewis acidic, it adds to a variety of small donor ligands. Among them a sometimes unwanted reaction partner is the H_2O molecule. Reaction of **3** with water occurs in a well-defined way if insufficient precautions are taken to exclude moisture from reaction mixtures. Addition of H_2O to the $B(C_6F_5)_2$ unit substantially increases the Brønsted acidity of the water molecule.[186] Rapid intramolecular deprotonation by the adjacent Mes_2P base then leads to the formation of the product (Scheme **4.1**). Moreover, because the B-OH unit is still quite acidic, it may react further with **3** if this is present in an excess.[181]



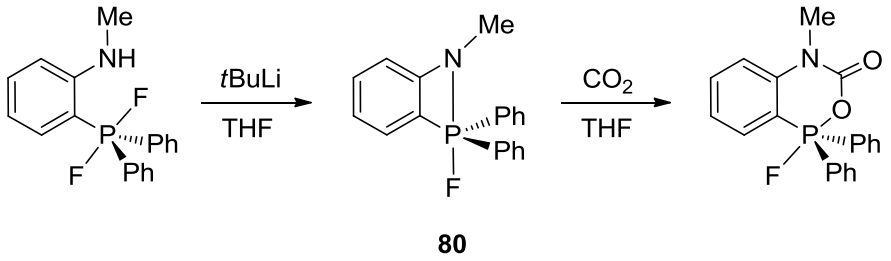
Scheme 4.1 Reaction of the frustrated Lewis pair **3** with water

In a collaborative report, Stephan et al. and Erker et al. found that CO_2 reacts with frustrated Lewis pairs in a straightforward fashion.[187] For example, the components of the *t*-$Bu_3P/B(C_6F_5)_3$ pair add to CO_2 at room temperature in bromobenzene with P-C and O-B bond formation (Scheme **4.2**).[188] Similarly, the intramolecular frustrated Lewis pair **3** also reacts with CO_2 under analogous reaction conditions: pressuring a solution of the FLP in pentane with CO_2 (2 bar) leads to the precipitation of the adduct.[187]



Scheme 4.2 Reactions of frustrated P/B Lewis pairs with CO_2

In these cases, the carboxylation of the frustrated Lewis pair is reversible and liberation of CO_2 occurs upon heating. However this is not always true: the exposure of a THF solution of amidophosphorane **80** to 1 atm of CO_2 at ambient temperature results in the formation of the carbamatofluorophosphorane shown in Scheme **4.3**. The facile insertion of CO_2 into the P-N bond of **80** is thought to relieve strain within the four-membered ring dramatically accelerating the reaction. However the product is thermally robust, as it remains unchanged on heating to 120 °C, leading to irreversible sequestration of CO_2.[189]



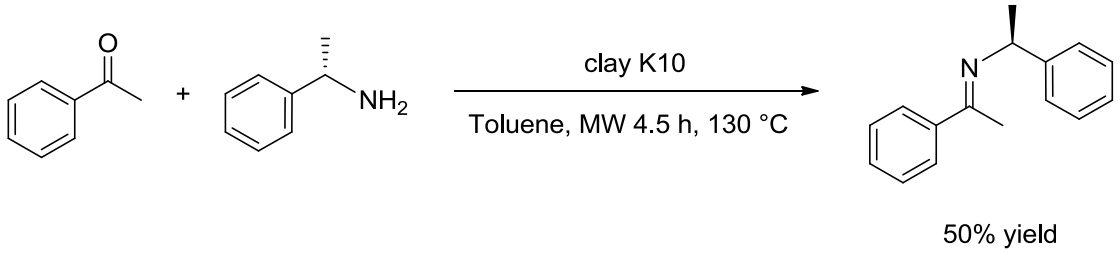
80

Scheme 4.3 Reactions of frustrated P/B Lewis pairs with CO_2

As a consequence of the high sensitivity of many of these systems to air and moisture it's generally indispensable to perform the hydrogenation inside a glovebox and perform three freeze-pump-thaw cycles with liquid nitrogen to remove dissolved gases. However this instrument setup is not so commonly available and the need of a dedicated equipment severely limits the general applicability of this methodology. Therefore our second objective was to find an alternative experimental setup which doesn't involve the use of a glovebox, in order to provide a more user-friendly technique.

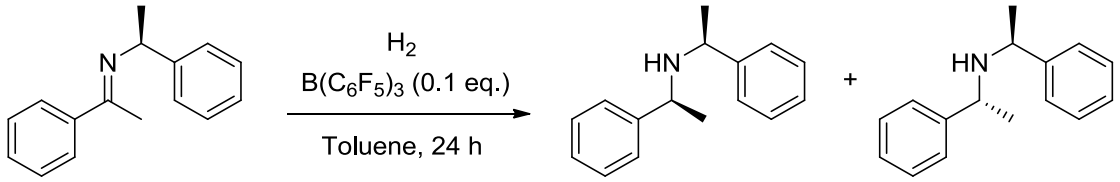
Regarding our first goal, there are two main avenues for the development of a stereoselective reaction: the use of chiral reagents or the employment of a chiral catalyst. We initially focused on the first of these approaches, exploring the reduction of an imine

carrying an inexpensive chiral auxiliary. This substrate was synthesized with a microwave-assisted reaction between acetophenone and (*S*)-1-phenylethylamine in toluene in the presence of K10 clay as activator (Scheme **4.4**):



Scheme 4.4 MW-promoted synthesis of the chiral imine

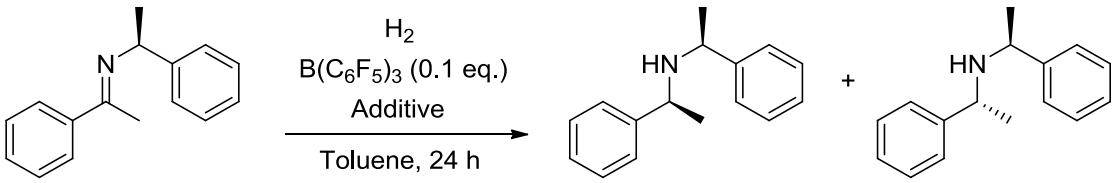
At first the reaction promoted by the borane alone was tested, using the substrate itself as the base-partner of the FLP (Table **4.1**):



entry	T (°C)	p H_2 (bar)	y (%)	d.r. ((*S*,*S*) : (*R*,*S*))
1	100	5	14	72 : 28
2	65	20	18	82 : 18
3	50	50	12	90 : 10

Table 4.1 FLP catalyzed reduction of the chiral ketimine substrate

Interestingly, the corresponding amine was obtained with good stereoselectivity (up to 90 : 10); however in our hands chemical yields were really low. Our experimental setup can be partly accounted for this problem, since it doesn't allow to work under complete exclusion of air and moisture over the entire course of the experiment. In order to overcome this problem, an optimization of the reaction has been necessary: several additives were tested to find a more efficient catalytic pair. Some selected results are reported in Table **4.2**:



entry	additive	T (°C)	p H_2 (bar)	y (%)	d.r. ((*S*,*S*) : (*R*,*S*))
1	DABCO (0.1 eq.)	65	20	12	86 : 14
2	PPh_3 (0.1 eq.)	65	20	15	89 : 11
3	PCy_3 (0.1 eq.)	65	20	14	62 : 38
4	P(*t*-Bu)$_3$ (0.1 eq.)	80	20	67	82 : 18

Table 4.2 Screening of more efficient frustrated Lewis pairs

DABCO, triphenylphospine and tricyclohexylphosphine were unable to increase the yield appreciably, even when temperature and pressure were raised. At last, P(*t*-Bu)$_3$ was employed as Lewis base. Performing the reaction at 80 °C under 20 hydrogen bar pressure was found to be an acceptable compromise, leading to the formation of the desired amine in 67% yield while retaining good diastereoselectivity.

During our studies, Stephan's group published a paper on this very theme reporting the reduction of several variously hindered chiral ketimines (See Chapter 1). While the obtained chemical yields were higher than ours due to the above mentioned reasons, the levels of diastereoselectivity were quite comparable. However, despite this interesting result, the high sensitivity of this methodology dissuaded us from proceeding in the design of a chiral frustrated Lewis pair catalyst.

In conclusion, the FLP catalyzed diastereoselective hydrogenation of the model substrate (*S*)-*N*-(1-phenylethyl)-1-phenylethanimine was accomplished without the necessity to perform the reaction in glovebox. Under optimized conditions (80 °C, 20 bar H_2) desired product was obtained in 67% yield and 82 : 18 diastereoisomeric ratio. These d.r. values are in good agreement with the ones reported in an analogous work published by Stephan and co-workers in 2011.

CHAPTER 5

Chiral phosphoric acids as catalysts in trichlorosilane mediated carbon-nitrogen double bond reductions

"Wisdom is not the counting of all the drops in a waterfall,
but learning why the water seeks the earth."
Mark Rosewater

As thoroughly described in Chapter 2, in 2005 Rueping's group reported the first enantioselective phosphoric acid-catalyzed hydrogenation of ketoimines, using Hantzsch esters as the hydrogenation transfer reagent.[46] This work can be considered as a milestone for the asymmetric reduction of imines promoted by Brønsted acids and paved the road to the synthesis of related systems. Since then, considerable efforts have been devoted to broaden the scope of this organocatalytic system, develop more efficient catalysts and find alternative hydrogen sources, accomplishing remarkable advancements. Taking into account the excellent enantioselectivities obtained in the reduction of C-N double-bonds with phosphoric acid catalysis, we decided to explore the performance of these systems employing $HSiCl_3$ as reducing agent. Compared with the other hydrogen sources utilized until this moment, the use of this compound would present several advantages: it's cheaper, commercially available and easily removable by aqueous workup or under reduced pressure.

Our initial working hypothesis is shown in Figure **5.1**. The combined use of a phosphoric acid (P.A.) and trichlorosilane would take advantage of the bifunctional nature of the catalyst: the Brønsted acidic site would coordinate the substrate, while the

Lewis basic site should provide $HSiCl_3$ activation. Finally, the presence of proper substituents in 3,3' positions of the binaphthyl scaffold shall create a chiral environment for enantioselective reduction.

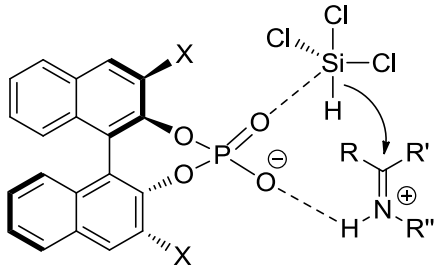
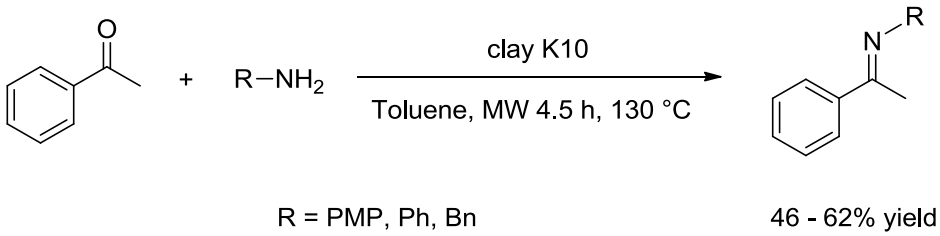


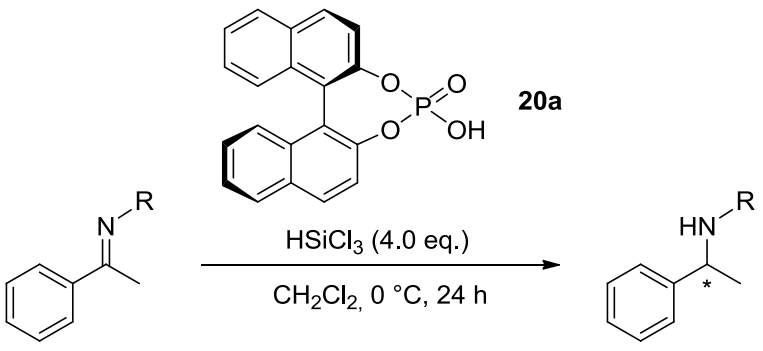
Figure 5.1 Preliminary working hypothesis of the transition state

With this in mind, we decided to start our investigation performing a preliminary screening with several ketiminic substrates. These compounds were prepared with a microwave-promoted reaction between acetophenone and the corresponding amine in toluene in the presence of K10 clay as activator (Scheme **5.1**); a prolonged reaction time was necessary in order to obtain good yields.



Scheme 5.1 MW-assisted synthesis of the imine substrates

Then, we investigated the outcomes of the reduction performed on these compounds with both stoichiometric and sub-stoichiometric amounts of unsubstituted BINOL-derived phosphoric acid (Table **5.1**):



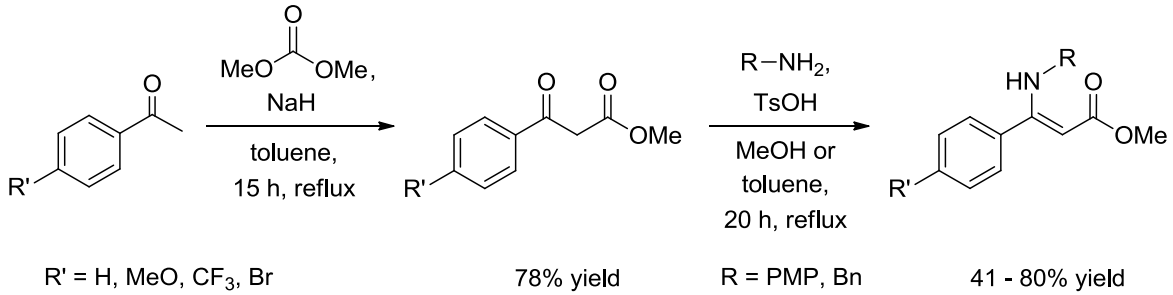
entry	R	phosphoric acid (eq.)	y (%)	*e.e.* (%)
1	PMP	1.0	89	*rac*
2	PMP	0.1	31	*rac*
3	Ph	1.0	23	*rac*
4	Ph	0.1	/	/
5	Bn	1.0	/	/
6	Bn	0.1	/	/

Table 5.1 Phosphoric acid promoted ketimine reduction

While the reduction of the *N*-benzyl and *N*-phenyl protected ketimines showed little or no formation of the corresponding amine, reaction of *N*-4-methoxyphenyl imines exhibited a good chemical activity compared to the uncatalyzed reductions. These interesting results suggest an actual activation of the trichlorosilane by the phosphoric acid. However, all of the products obtained in these preliminary tests were racemic. This outcome could be interpreted in several ways: the interaction between the protonated substrate and the chiral conjugate base could be too loose to effectively influence the stereochemistry of the process; the steric hindrance of this unsubstituted acid may be too small to stereodirect the reduction; the acidic moiety could be unable to properly coordinate the substrate in the present system.

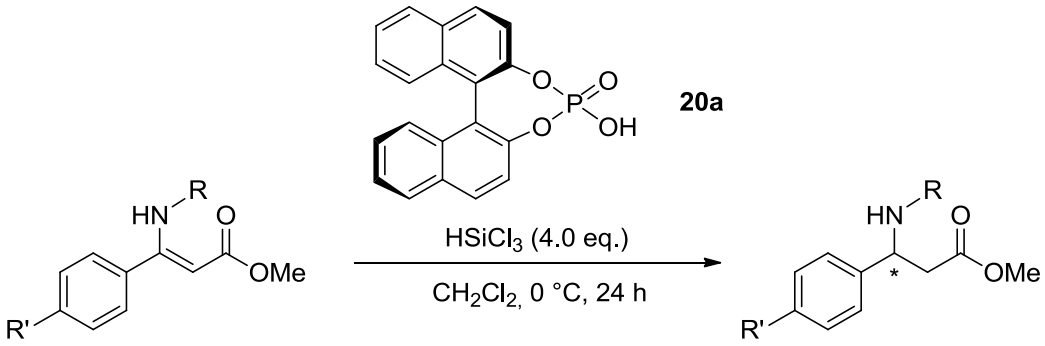
We also explored the use of this methodology in the reduction of β-enamino esters. The use of these substrates leads to the formation of very attractive products, because they are highly functionalized and can be exploited to obtain a wide range of derivatives by subsequent synthetic transformations.

At first, we prepared several β-keto esters bearing both electrowithdrawing and electrodonating substituents. Then, we converted them into the corresponding β-enamino esters by reaction with the proper amine (Scheme **5.2**):



Scheme 5.2 Synthesis of β-enamino esters substrates

Once finished the synthesis of the substrates, we performed their metal-free reduction promoted by catalysts **20a**. Results are summarized in Table **5.2**:



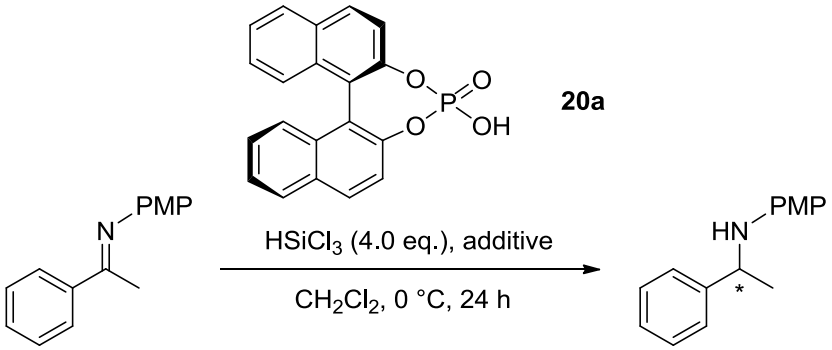
entry	R	R'	phosphoric acid (eq.)	y (%)	*e.e.* (%)
1	PMP	H	1.0	78	*rac*
2	PMP	H	0.1	50	*rac*
3	PMP	MeO	1.0	/	/
4	PMP	CF_3	1.0	45	*rac*
5	PMP	Br	1.0	>99	*rac*
6	Bn	Br	1.0	/	/

Table 5.2 Phosphoric acid promoted β-enamino esters reduction

Similarly to the results obtained in the reduction of ketimines, also β-amino esters were obtained with good chemical yield but no enantiomeric excess. This result was observed with both catalytic and stoichiometric quantities of the phosphoric acid, even if a drop in the yield can be observed when a 10 mol % amount is used. As expected, the electron deficient enamino ester gave better results than the electron rich substrates, due to their increased electrophilic character. Noteworthy, the hydrosilylations of the benzyl derivatives are more difficult to obtain: the reduction of the *N*-benzyl protected compound didn't show any sign of the formation of the product, while the corresponding *N*-PMP substrate afforded the desired β-amino ester in quantitative yield.

Generally, it was observed that passing from stoichiometric to sub-stoichiometric quantities of the phosphoric acid led to a decrement in chemical yield. This could suggest that only part of the catalyst is reprotonated at the end of the catalytic cycle, slowing down the reaction. Therefore, before addressing the stereoselectivity problem, we performed the reductions in presence of a more than stoichiometric amount of

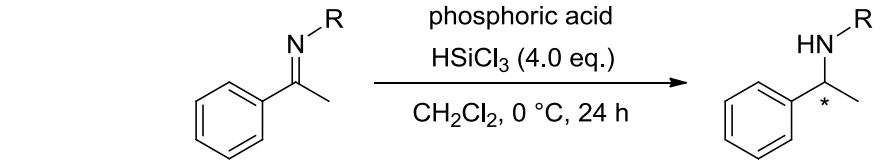
reprotonating agent, to observe if this translate into an increase of chemical activity (Table **5.3**):

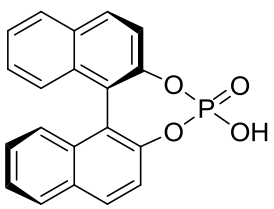


entry	phosphoric acid (eq.)	additive	y (%)
1	1.0	/	89
2	0.3	/	28
3	0.3	TFA (1.8 eq.)	59

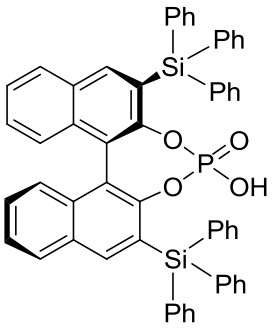
Table 5.3 Imine hydrosilylation performed in presence of a reprotonating agent

While the addition of trifluoroacetic acid doesn't increase the chemical yield up to the values obtained with the stoichiometric quantity of phosphoric acid, it's obvious that it exerts a beneficial effect on the activity of the catalyst. As future development, a fine tuning of the pK_a of the additive could permit to further improve the yield of the reaction.
We then turned our attention to the lack of stereocontrol that plagued this methodology. As already mentioned in Chapter 2, the presence of proper 3,3'-substituents on the binaphthyl backbone often plays a crucial role in attaining high enantioselectivity. Hence, our first approach was to test the performance of the commercially available acids **20n** and **20f** in the reduction of *N*-PMP and *N*-Ph ketimines respectively (Table **5.4**):

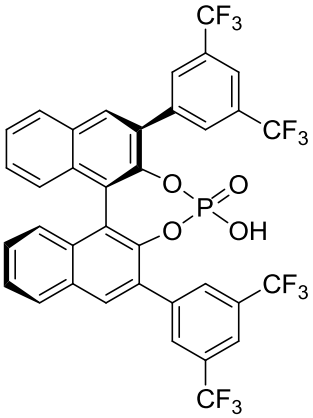




20a



20n



20f

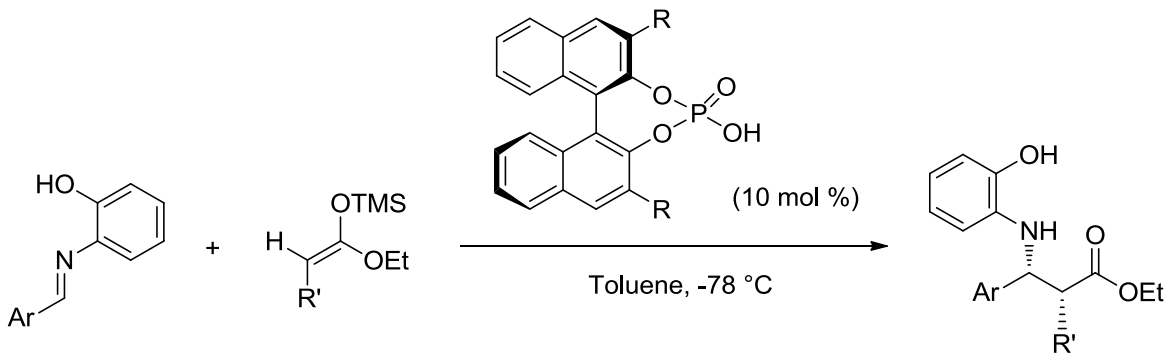
entry	R	phosphoric acid (eq.)	y (%)	*e.e.* (%)
1	Ph	**20a** (1.0 eq.)	23	*rac*
2	Ph	**20n** (1.0 eq.)	/	/
3	PMP	**20a** (1.0 eq.)	89	*rac*
4	PMP	**20f** (1.0 eq.)	56	*rac*

Table 5.4 Use of more sterically hindered phosphoric acids

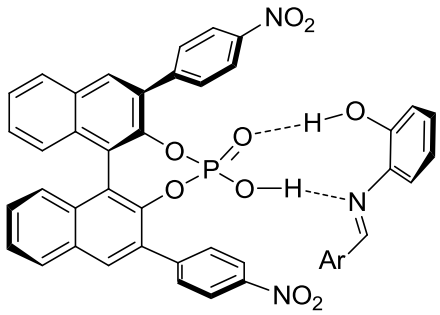
As shown in Table **5.4**, phosphoric acid **20n** didn't promoted the reduction at all. Moreover, even the traces of the weak background reaction are suppressed in presence of this compound. This could be due to the fact that the phosphoric acid moiety is very hindered and shield the coordinated substrate from the attack by trichlorosilane.

Disappointingly, even the use of a stoichiometric amount of (*R*)-3,3'-bis(3,5-bis(trifluoromethyl)-phenyl)-phosphoric acid **20f** was of no avail: the increased steric hindrance caused a decrease in chemical yield but didn't exerted any beneficial effect on the stereoselectivity. This result alone is not sufficient to rule out the possibility that at the root of the enantioselectivity issue there is the necessity of a proper steric hindrance. However, this prompted us to shift our attention to the analysis of the coordination between the phosphoric acid and the substrate.

In 2004 Akiyama and co-workers reported examples of enantioselective Mannich-type reactions promoted by phosphoric acid catalysis.[190] Of particular interest is the observation that the presence of an *o*-hydroxy functionality on the *N*-aryl group is essential to achieve high levels of enantioselectivity. In fact, when the hydroxyaryl substrate was replaced with *N*-benzylideneaniline, the enantiomeric excess of the Mannich adduct was decreased from 96 to 39% (Scheme **5.3**). The authors hypothesized that the reaction takes place *via* a nine-membered transition state, wherein the phosphate hydrogen activates the imine and the phosphoryl oxygen interacts with the hydrogen of the OH group of the aldimine by hydrogen bonding.



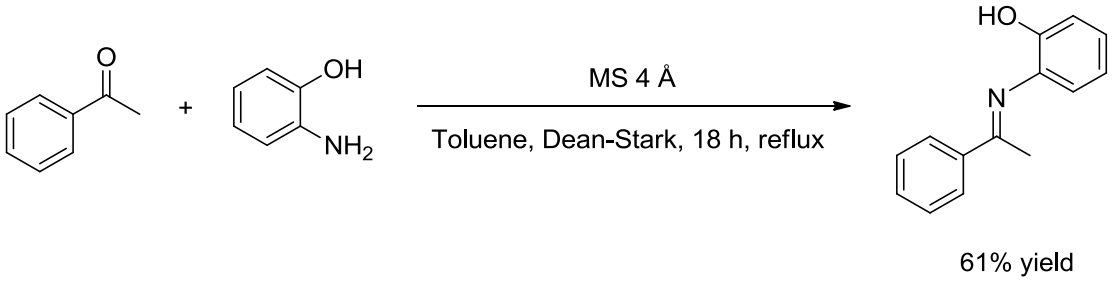
Ar = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-FC_6H_4 R = 4-$NO_2C_6H_4$ up to 96% *e.e.*
R' = Me, Bn



Scheme 5.3 Phosphoric acid catalyzed stereoselective Mannich-type reactions

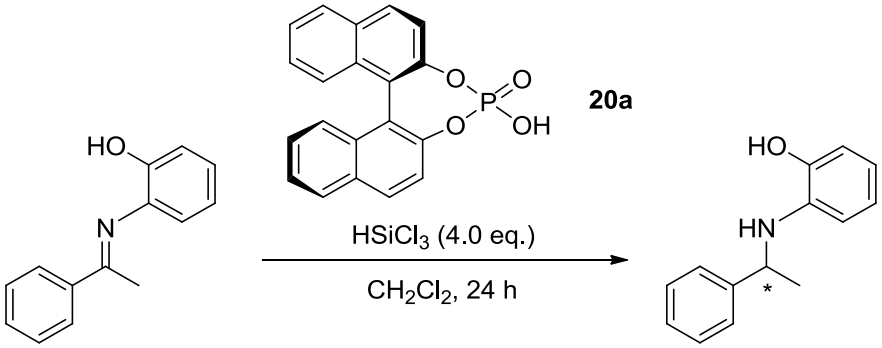
Inspired by this work, we decided to adopt this *o*-hydroxy aryl moiety as protecting group at the nitrogen atom in our imine substrates. Hopefully, the resulting tighter ion pair should be able to direct the stereochemistry of the reduction more efficiently.

Therefore we proceeded to synthesize the ketimine by reaction of acetophenone with *o*-hydroxy aniline in presence of 4 Å molecular sieves, isolating the product in good yield (Scheme **5.4**). Being an highly water sensitive compound, the synthesis necessarily required the use of a Dean-Stark apparatus.



Scheme 5.4 Synthesis of the *N*-(*o*-hydroxy)aryl protected imine

With this substrate in hand we began to study its trichlorosilane mediated reduction in presence of both stoichiometric and sub-stoichiometric amounts of **20a**:



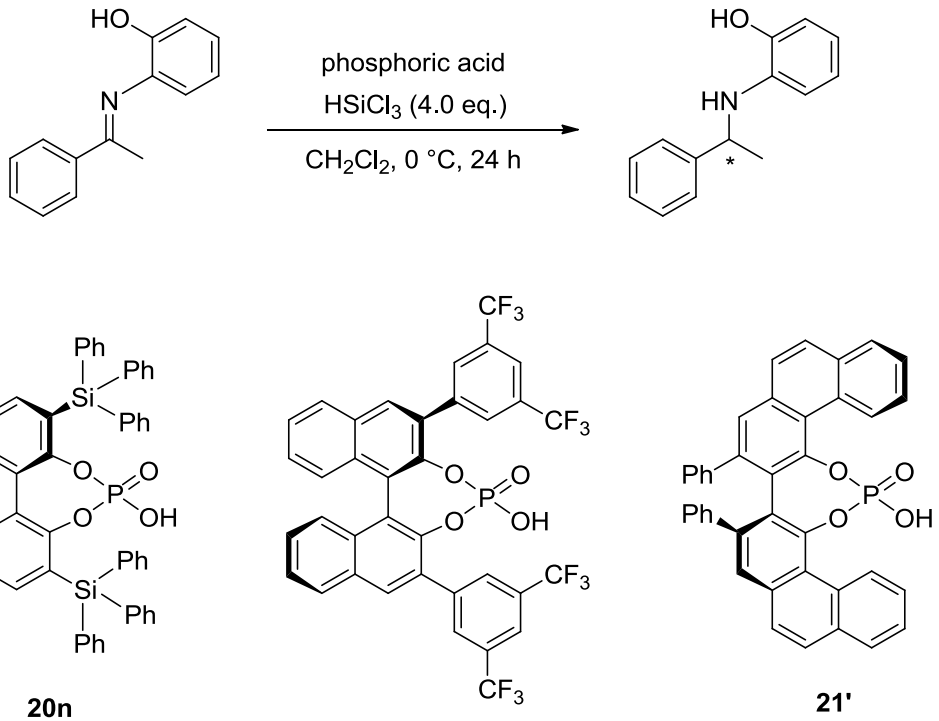
entry	phosphoric acid (eq.)	T (°C)	y (%)	*e.e.* (%)
1	1.0	0	>99	*50* (+)
2	0.1	0	96	*rac*
3	1.0	-40	34	*61* (+)
4	0.1	-40	19	*rac*

Table 5.5 Phosphoric acid promoted reduction of *N*-(*o*-hydroxy)aryl protected imine

The reduction performed at 0 °C led to the corresponding amine in excellent yields. More important, the use of a stoichiometric amount of phosphoric acid yielded the product with 50% enantiomeric excess. However, the process suffers from a strong background reaction, which we initially thought to be the cause of the stereoselectivity drop observed when a catalytic quantity of acid is employed. Most likely, this side reaction is due to an intramolecular activation of the trichlorosilane by the substrate itself. Consequently, we lowered the reaction temperature to -40 °C. Our twofold purpose was to assess if this parasitic reaction could be suppressed at low temperature and at the same

time to verify if a temperature decrease may have a beneficial effect on the enantioselectivity of the reduction. Indeed, even if a predictable decrease of chemical yield was observed, the enantiomeric excess was raised to 61%. Nonetheless, the use of a catalytic amount of **20a** still afforded the amine with no stereoselectivity.

In order to evaluate if the enantioselectivity observed with this substrate could be further improved, more sterically hindered phosphoric acids were tested. The obtained results are reported in Table **5.6**:



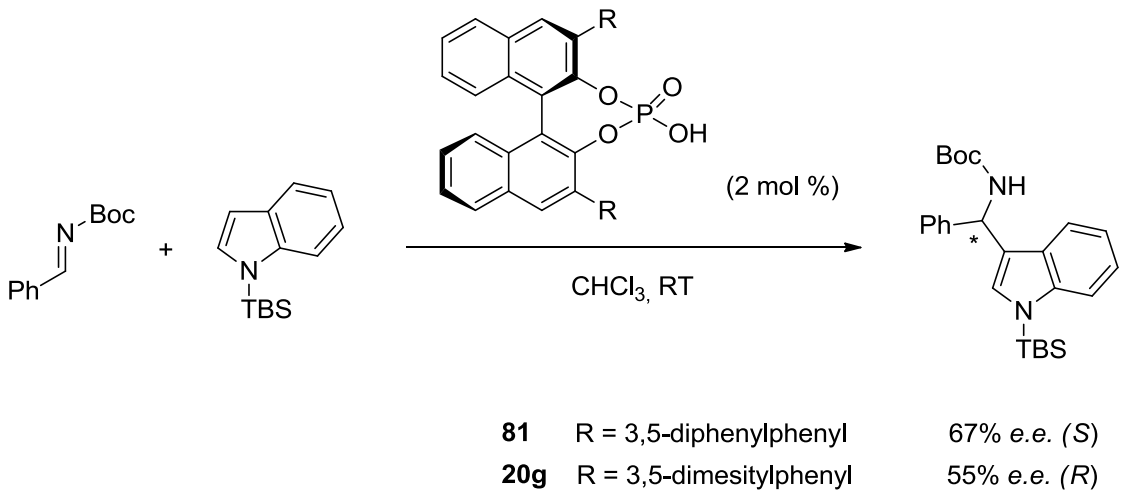
20n **20f** **21'**

entry	phosphoric acid (eq.)	y (%)	*e.e.* (%)
1	**20n** (1.0 eq.)	/	/
2	**20f** (1.0 eq.)	>99	*22* (-)
3	**20f** (0.1 eq.)	97	*rac*
4	**21'** (1.0 eq.)	/	/
5	**21'** (0.1 eq.)	77	*rac*

Table 5.6 Use of more sterically hindered phosphoric acids

Again, the reaction carried out in presence of stoichiometric phosphoric acid **20n** didn't lead to the reduction product. This result seems to confirm that the coordinated

imine is fully shielded by the 3,3'-substituents, completely suppressing even the background reaction. The same result is also observed with (*R*)-VAPOL phosphoric acid **21'**, while the employment of a stoichiometric quantity of **20f** allowed to isolate the product with 22% enantiomeric excess but opposite configuration. This inversion of stereoselectivity is probably caused by the different conformations adopted by phosphoric acids bearing different 3,3'-substituents. Terada reported a similar behaviour for the 1,2-aza-Friedel–Crafts reaction of indoles promoted by Brønsted acids catalysis.[191] In fact, the preliminary screening of several catalyst revealed that phosphoric acids **81** and **20g** led to opposite stereochemical outcomes (Scheme **5.5**).



Scheme 5.5 1,2-Aza-F–C reaction of imine with *N*-TBS indole

In an effort to understand the inversion of configuration observed with catalysts **81** and **20g**, the authors carried out a computational study of the 3D-structures of the catalysts at the B3LYP/6-31G** level of theory (the optimized 3D-structures are shown in Figure **5.2**). They speculated that the observed inversion of the enantioselectivity should be attributed to the accessibility of the reactants to the acidic site of the catalyst. As depicted in Fig. **5.2** (a) and (b), the 3,5-diphenylphenyl substituents of **81** were arranged in a nearly parallel mode on the top and bottom sides of the phosphoric acid moiety, forming a reaction pocket in the region which could be termed as the "front" of the acid group. It is likely that the catalyst (*R*)-**81** provides enough space to allow assembly of the transient structure of the Friedel–Crafts reaction in front of the acidic moiety (Figure **5.2** (a)). In contrast, for the sterically demanding 3,5-dimesitylphenyl substituents of (*R*)-**20g** (Figure **5.2** (c) and (d)), the *ortho* methyl substituents force the mesityl ring to be perpendicular to the phenyl moiety and thus the front side of the acidic

moiety is congested. Hence, formation of the transient structure of the Friedel–Crafts reaction would be prevented on the front side of the phosphoric acid (Figure **5.2** (c)). As a result, Terada and co-workers hypothesized that the catalytic reaction would proceed in such a manner as to avoid the sterically congested front side of the acidic moiety. It's possible that an analogous situation takes place also in our case, even if computational studies are required to confirm this assumption.

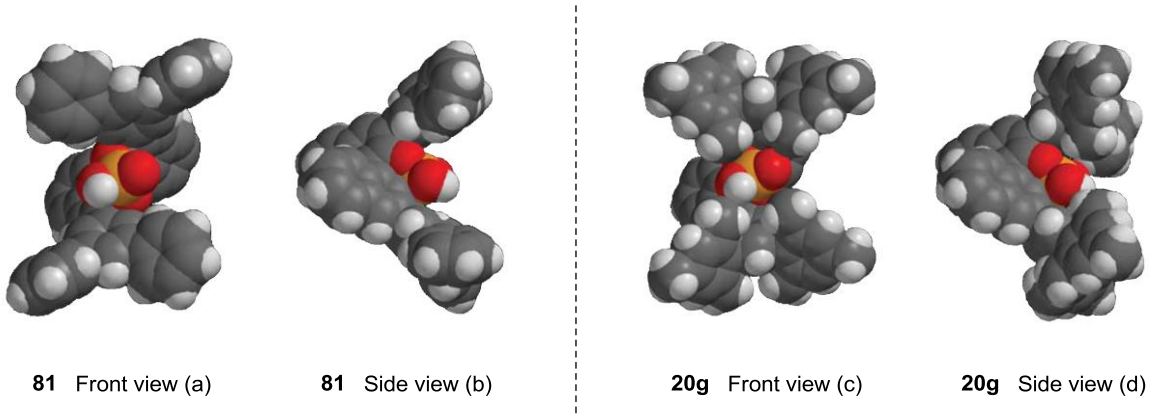
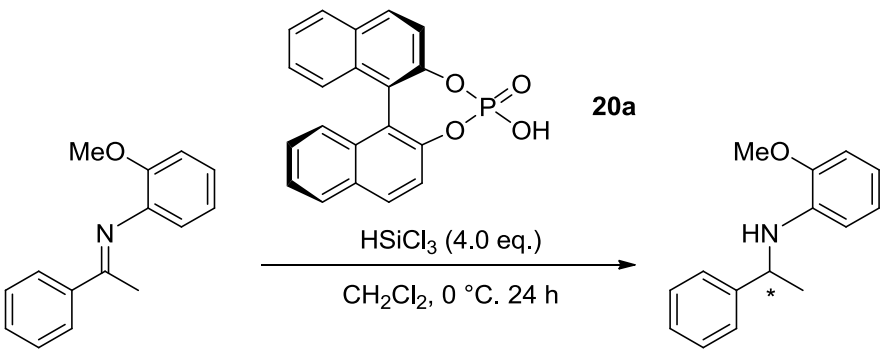


Figure 5.2 3D-structures for the optimized geometries of **81** and **20g** (P tan, O red, C gray, H white)

Encouraged by the results obtained with *N*-(*o*-hydroxy)aryl ketimine, we tried to suppress the unwanted background reaction by performing the reduction of a ketimine having a methoxy group in the *ortho* position of the *N*-aryl group. While still providing a coordinating moiety, the absence of free hydrogen atoms should avoid the activation of the $HSiCl_3$ by the substrate.

The microwave assisted synthesis already used for some of the other substrates allowed the isolation of the desired product in 28% yield. The results of its subsequent reduction are reported in Table **5.7**:

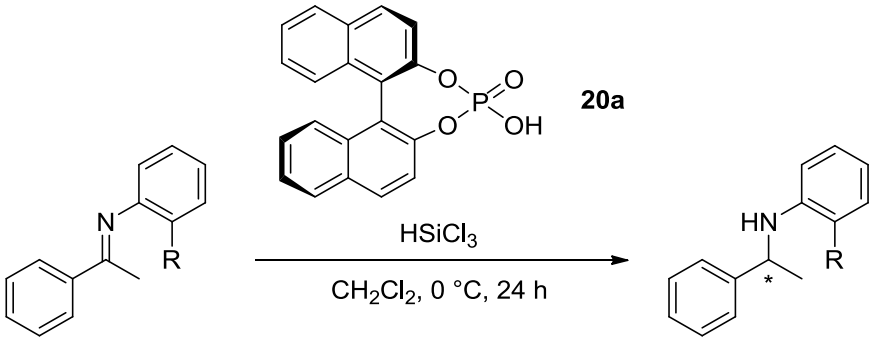


entry	phosphoric acid (eq.)	y (%)	*e.e.* (%)
1	1.0	17	*41* (*R*)
2	0.1	22	*rac*

Table 5.7 Phosphoric acid promoted reduction of *N*-(*o*-methoxy)aryl protected imine

Indeed, using this compound no reaction was observed in absence of the phosphoric acid. Moreover, the use of a stoichiometric amount yielded the desired product with 41% *e.e.*, confirming the coordinating role of the methoxy group. It's really interesting that the reaction run with a catalytic quantity of **20a** gave the amine with no enantioselectivity, even in absence of background reaction. On the downside, all of the reactions performed on this substrate led to the product in a disappointingly low yield.

These observations led us to think that the phosphoric acid : silane ratio, rather than the phosphoric acid : substrate ratio, could be the key factor to determine the stereoselectivity of the process. In order to verify this supposition, we performed the reaction in presence of variable amounts of trichlorosilane and **20a**, as described in Table **5.8**:

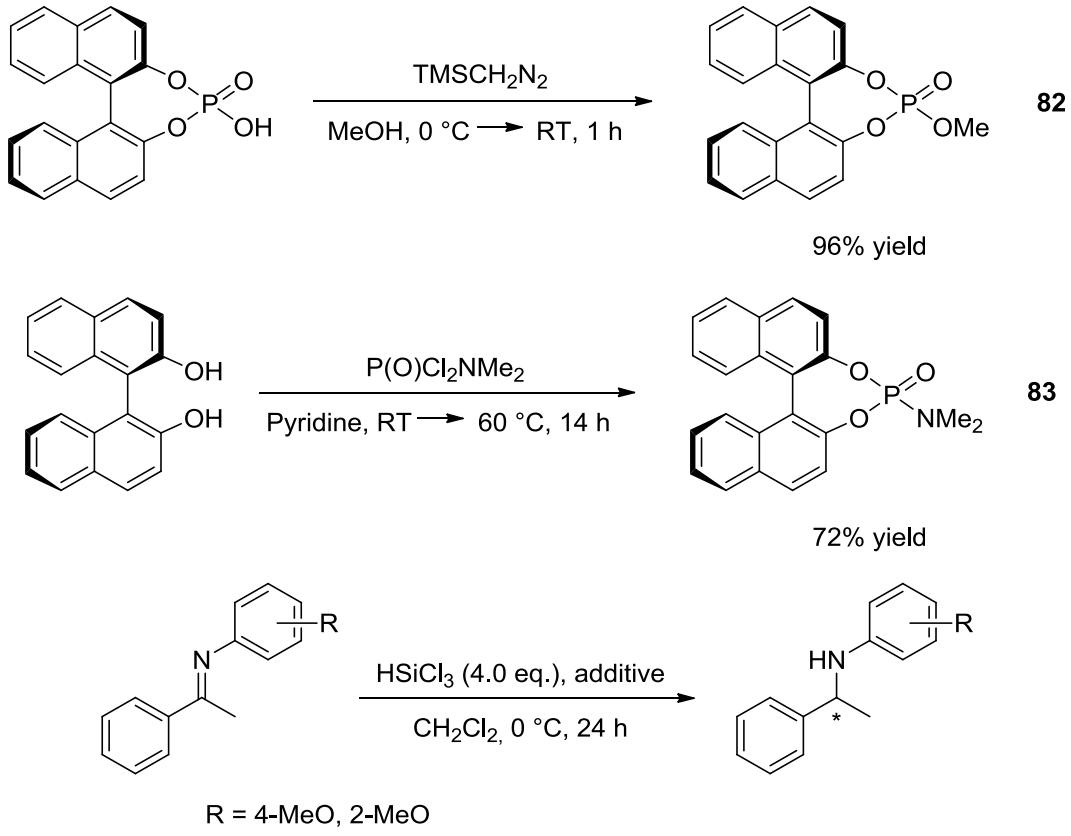


entry	R	phosphoric acid (eq.)	$HSiCl_3$ (eq.)	P.A. : Si ratio	y (%)	*e.e.* (%)
1	MeO	1.0	4.0	1 : 4	17	*41* (*R*)
2	MeO	0.1	4.0	1 : 40	22	*rac*
3	MeO	0.25	1.0	1 : 4	18	*40* (*R*)
4	MeO	0.1	1.0	1 : 10	9	*29* (*R*)
5	MeO	1.0	1.0	1 : 1	27	*60* (*R*)
6	OH	0.25	1.0	1 : 4	>99	*13* (+)

Table 5.8 Variation of the phosphoric acid : trichlorosilane ratios

We were glad to see that this was indeed the case: independently from the phosphoric acid : imine ratio, the use of a 1 : 4 ratio between the acid and the silane (P.A. : Si ratio) produced the same outcome. Upon using a low phosphoric acid : trichlorosilane ratio *e.e.* up to 60% were obtained; instead, the increase of the amount of the silane progressively diminished the enantiomeric excess. Even with the *o*-OH substrate a small *e.e.* was observed.

To gain some insight on the complex mechanism of the present system, some additional experiments were carried out. Derivatives **82** and **83** were prepared and used in the ketimines reduction to verify the actual role of the phosphoric acid in the activation of trichlorosilane. In fact the activation of the silane by coordination with the Lewis basic phosphoryl oxygen isn't the only possible path: by reaction of the acidic group with $HSICl_3$ a new more active silicon species could be formed.



entry	R	additive (eq.)	y (%)
1	4-MeO	**82** (1.0 eq.)	50
2	4-MeO	**83** (1.0 eq.)	64
3	2-MeO	**83** (1.0 eq.)	23

Table 5.9 Ketimines reduction carried out in presence of phosphoric acid **20a** derivatives

The use of a stoichiometric quantity of these compounds afforded the reduction products in acceptable yield, confirming that the reaction proceeds through activation of the trichlorosilane by coordination with the phosphoryl oxygen.

A preliminary ^{31}P NMR analysis was also performed. Upon addition of increasing amounts of $HSiCl_3$ at 0 °C, the position of the signal of the phosphoric acid **20a**, initially located at 7.1 ppm in CD_2Cl_2, significantly shifted (-9.7 ppm). After trichlorosilane removal under reduced pressure, the original position was nearly completely restored. The same behaviour was observed with phosphoric acid **20f**. On the other hand, the ^{31}P NMR spectra of compound **83** remained totally unaltered even after the addition of a large amount of trichlorosilane (Figure **5.3**).

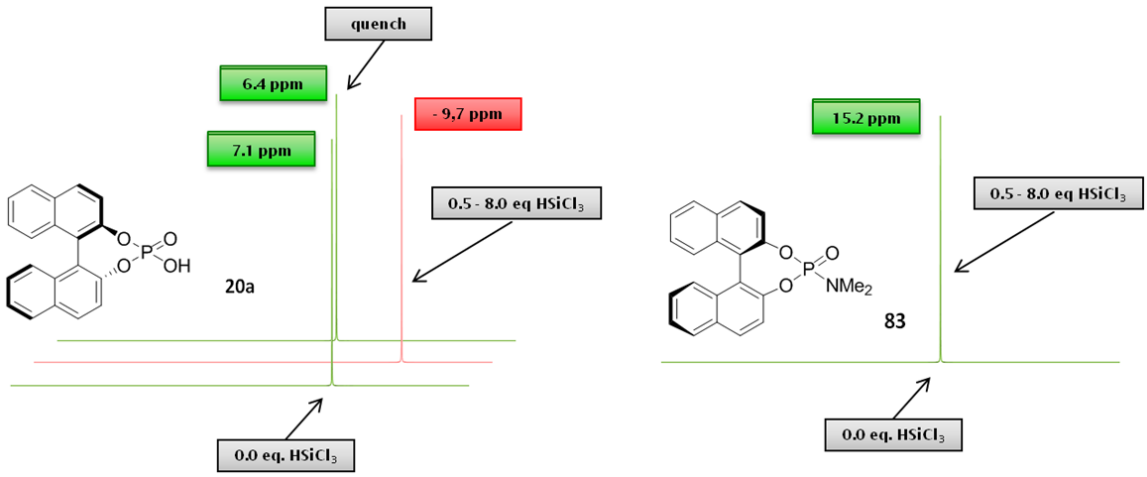


Figure 5.3 ^{31}P NMR analysis

While it wasn't possible to observe the coordination of $HSiCl_3$ by the phosphoryl oxygen of the catalyst, these results suggest that in the present methodology at least part of the phosphoric acid exists as *O*-silylated species.

On the basis of the collected data, we hypothesized the two transition states reported in the Figure **5.4**:

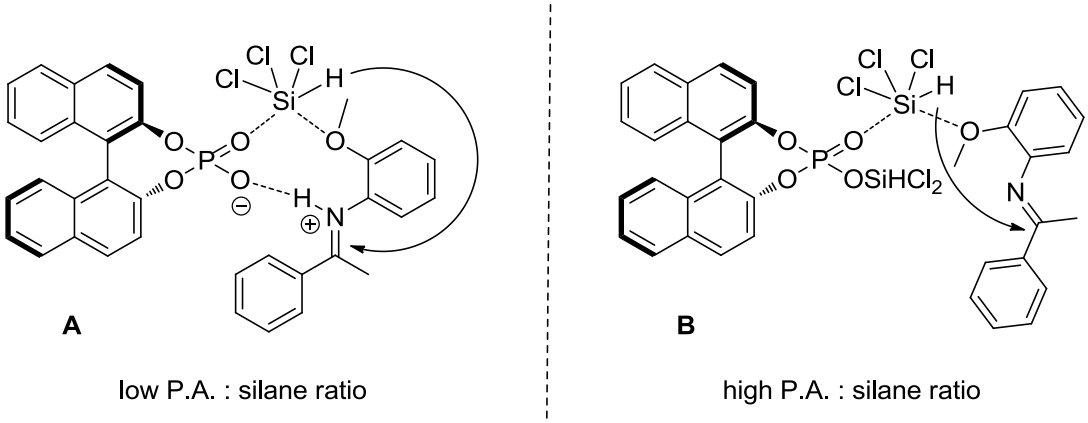


Figure 5.4 Hypothesized mechanism

In both cases the reducing agent is supposed to be activated by coordination with both the phosphoryl oxygen of the catalyst and the methoxy group of the substrate. However, in the presence of a low amount of trichlorosilane most of the catalyst should still possess an acid functionality able to protonate the imine substrate (case **A**). On the other hand, the use of a large excess of $HSiCl_3$ would promote the formation of the *O*-silylated species, which is involved in a much looser transition state (case **B**).

In conclusion, a preliminary investigation of the phosphoric acid catalyzed trichlorosilane mediated reduction of ketoimines was carried out and a possible mechanism was proposed. After an optimization of the stoichiometry of the reaction, we were able to achieve up to 29% *e.e.* using 10 mol % unsubstituted phosphoric acid **20a**. Anyway, a coordinating moiety on the substrate was required to achieve enantioselectivity, but the use of these compounds was affected by undesired background reactions or low chemical yields. Further studies will be required in order to overcome these problems and find a more suitable catalyst and protecting group.

CHAPTER 6

Stereoselective catalytic synthesis of chiral trifluoromethyl aryl and alkyl amines

"There are more things in heaven and earth, Horatio,
than are dreamt of in your philosophy."
William Shakespeare, Hamlet

As the most electronegative element, fluorine has played a key role in recent materials science: it has been employed in heat-transfer agents, liquid crystals, dyes, surfactants, plastics, elastomers, membranes and other materials. Furthermore, many fluorine-containing biologically active agents are finding applications as pharmaceuticals and agrochemicals. Progress in synthetic fluorine chemistry has been critical to the development of these fields and has led to the invention of many novel fluorinated molecules as future drugs and materials. Of particular relevance is the recent appearance of drug candidates featuring fluorine atoms, which often present a favorable therapeutic profile. As a consequence, the introduction of one or more fluorine atoms is now routine in every new drug discovery and development program.[192] The exceptionally high frequency of fluorinated molecules in the pharmaceutical pipeline is truly astonishing considering that only a dozen of fluorinated natural products have been identified on Earth.[193]

The reasons for introducing a trifluoromethyl group into a molecule are several:

- Incorporation of a trifluoromethyl group into organic molecules generally increases their chemical stability, owing to the high bond strength that can induce increased resistance to metabolic decomposition.
- This moiety can act as an isostere of the isopropyl group: the van der Waals molar volume of the trifluoromethyl group was calculated to be 21.3 cm^3/mol, similar to the molar volume of the isopropyl.[194]
- α-trifluoromethyl alcohols and amines are becoming increasingly popular as chiral enantiopure synthons in the design of new drugs since peptides incorporating fluoroalkyl amino acids often display enhanced absorption, higher permeability through biological barriers and retarded proteolytic degradation.
- The trifluoroethylamine moiety $CH(CF_3)NH$ is emerging as a remarkable surrogate of the natural peptide bond C(O)NH in the area of peptide mimics.[195]

Even these few examples clearly show how the incorporation of fluorine or fluorine-containing groups into an organic molecule can drastically perturb the chemical, physical and biological properties of the parent compound (a wider exhibit of fluorine effects is displayed in Figure **6.1**). Taking advantage of this behaviour, it is thought that is possible to exploit the synthesis of fluorinated compounds to produce novel agents and materials endowed with predetermined functions.

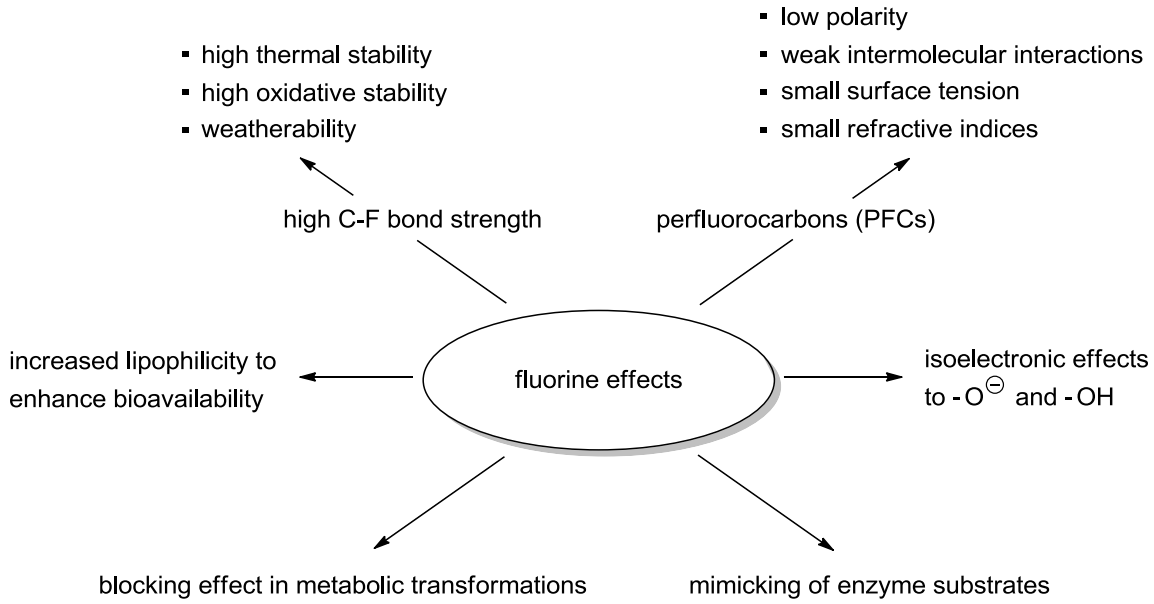


Figure 6.1 Fluorine effects in biologically active agents and materials

Anyway, since naturally occurring organofluorine compounds are rare, target organofluorine compounds are generally accessible only by organic synthesis. However, as a result of inductive and resonance effects caused by fluorine substituents, fluorinated substrates and reagents often exhibit unusual and unique chemical properties which can make them incompatible with established synthetic methods.[196]

For example, fluorine-substituted carbocations are stabilized by the donation of nonbonding electron pairs on the fluorine atom, whereas electrostatic p–n repulsion between an anionic center and the lone electron pairs on the fluorine atom destabilizes a fluorine-substituted anion (Figure **6.2**).

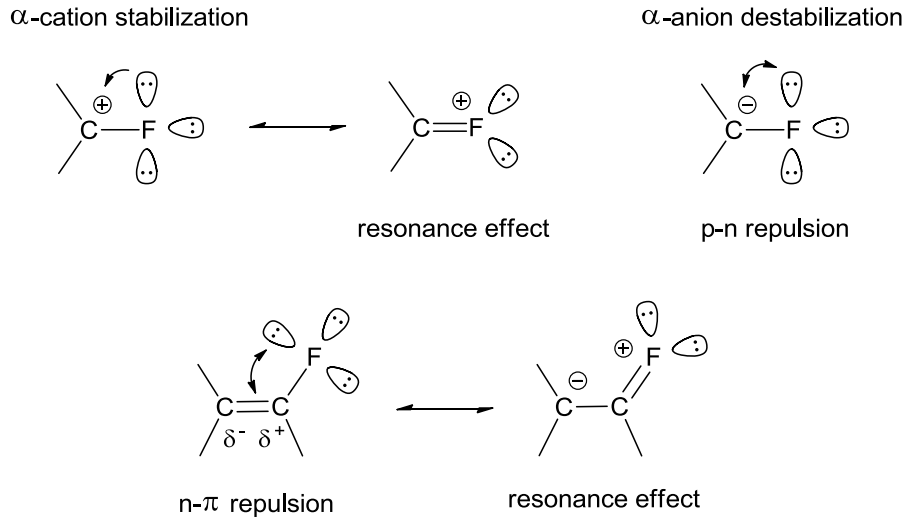


Figure 6.2 α-fluorine effects

Similarly, n–π repulsion between the lone pairs and a π-electron system pushes the π electrons far apart distorting it. Furthermore, a resonance effect operates in which the lone pairs participate in conjugation with the π system.

Instead, like various other fluorine-containing groups, trifluoromethyl groups at sp^2 and sp^3 carbon atoms always withdraw electrons to destabilize cations and to stabilize anions (Figure **6.3**). This anion stabilization can be also understood as a result of negative hyperconjugation, resulting from an overlap of an anionic p orbital with the σ* orbital of a C-F bond.[197]

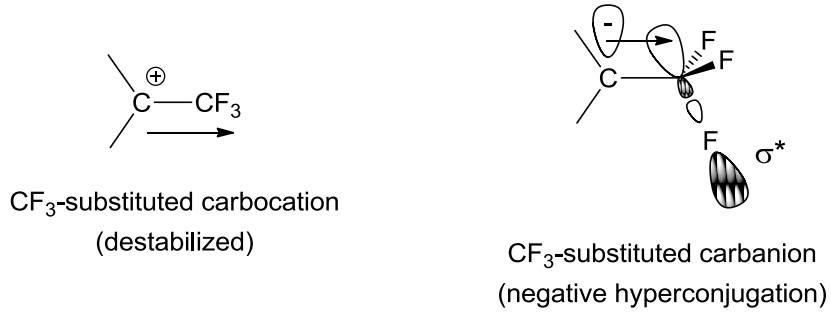


Figure 6.3 α-CF_3 effects on carbocations and carbanions

Trifluoromethyl groups also strongly affect chemical reactivity. For example, nucleophilic substitution at a trifluoromethyl-substituted carbon atom is not an easy process. The difficulty is attributed to the destabilization of the transition state by fluorine and also to electrostatic repulsion between a nucleophile and the lone pairs of electrons on the fluorine atoms.

In view of the unique characteristics of fluorine, it is easy to recognize that conventional synthetic methods are not always applicable to the synthesis of organofluorine compounds. Thus, the problem of how to control the unusual properties of compounds with fluorine substituents has attracted much attention, promoting the design of facile, efficient and environmentally benign methods for the synthesis of valuable organofluorine targets.

In particular, the stereocontrol at carbon center featuring a fluorinated motif (whether it be a single fluorine, a trifluoromethyl group or a polyfluoroalkyl substituent) is a highly challenging task. Two complementary strategies could be applied: the first one consists of the direct introduction of a single fluorine atom or a fluorinated moiety through nucleophilic, electrophilic, or radical reactants;[198] instead the second strategy exploits already fluorinated substrates as building blocks for the construction of chiral fluorinated products. This latter approach is well suited for the valorization of readily available fluorinated building blocks and was the path we adopted in our effort to develop a novel enantioselective procedure for the synthesis of fluorinated amines.

Therefore, in accord to the great importance of this class of compounds, there has been a continuing interest in the development of highly efficient methods for the asymmetric synthesis of organofluorine substances. In this context, enantiopure trifluoromethylated molecules are at the forefront of innovation in modern organofluorine chemistry. They stimulate high interest due to the ever increasing occurrences of this

motif in a wide range of applications, including biologically active compounds, chiral reagents and materials for optoelectronic devices.[199] In particular, among the incredibly large number of fluorinated molecules of interest, trifluoromethylated chiral amines play a fundamental role in medicinal chemistry. In Figure **6.4** a few selected examples of these amines are reported: many of them are well recognized important drugs where the fluorinated amino group typically guarantees improved lipophilicity and metabolic stability over the corresponding methyl amines.

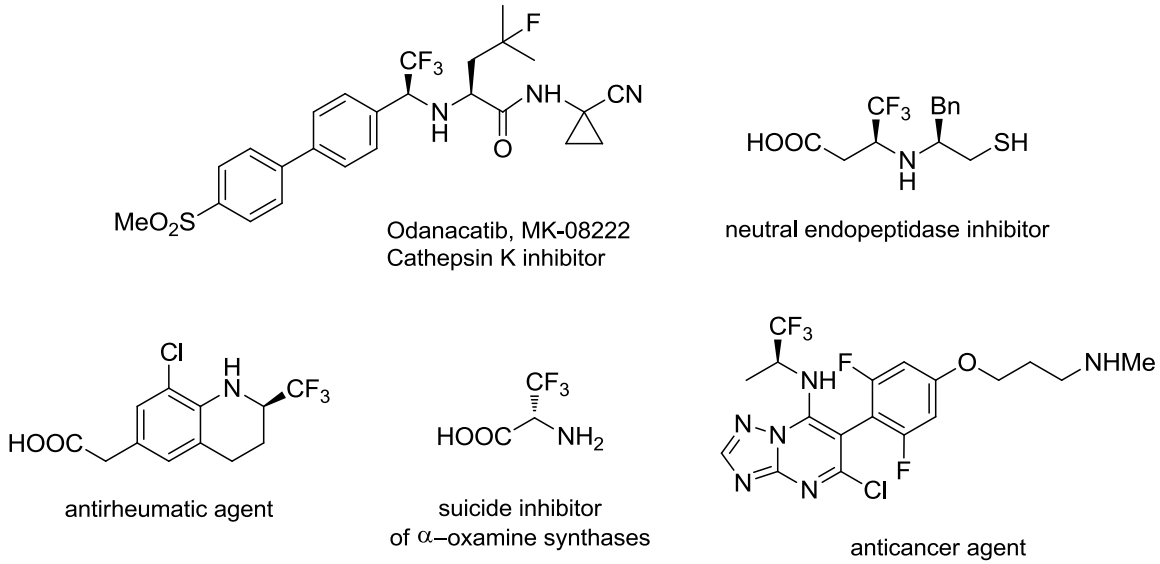


Figure 6.4 Biologically active trifluromethylated chiral amines

Considering that trifluoromethyl ketones are readily accessible, and many of them are even commercially available, the catalytic enantioselective reduction of the corresponding ketimine derivatives offers a viable approach for the synthesis of enantiomerically pure trifluoromethylated amines. Notably, only very few enantioselective hydrogenations have been reported on these substrates.[200] Moreover, in one of these examples the Pd catalyzed reduction is limited to fluorinated iminoesters,[200a] while in the other work, although the enantioselectivities range from good to high, the reaction is afflicted by significant drawbacks such as the use of relatively high pressures of hydrogen and of an expensive and toxic transition-metal catalyst.[200b] Lately a highly enantioselective organocatalyzed procedure has also been developed, but it is limited to trifluoromethyl aryl ketones, involves the use of a consistent amount of a quite expensive sterically hindered phosphoric acid and relies on the use of stoichiometric amounts of benzothiazolines as reducing agents.[201] More recently the stereoselective synthesis of

amines *via* catalytic isomerization of imines, either derived from trifluoromethyl aryl or trifluoromethyl alkyl ketones, has been described.[192a]

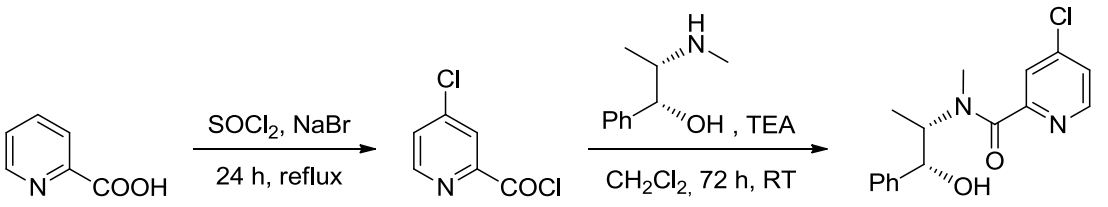
Considering the very limited number of reported methods and despite the undoubted recent successes, the catalytic highly stereoselective synthesis of such compounds remains a challenge, especially relative to the preparation of chiral trifluoromethyl alkyl amines, documented only in two works.[192a,200b]

We have therefore decided to investigate the use of activated trichlorosilane as reducing agent to stereoselectively perform this specific transformation.[202] This methodology, become by now a reliable method to perform the enantioselective reduction of carbon nitrogen double bonds, allows to combine the use of an environmentally friendly technique with the advantage of reducing an already fluorinated substrate, avoiding the problems linked to the stereoselective insertion of a fluorinated group.

We started our investigation by screening different types of chiral activators; some of these catalysts had been developed by our own group during previous works, while the others had been reported by other groups. Chiral picolinamides derived from ephedrine (catalyst **40**),[120] binaphthyl diamine (catalyst **57'**)[142] and prolinol (catalyst **37**)[102] were tested, as well as other Lewis bases like (*S*)-prolinol-derived phosphoroamides (catalyst **43**)[123] and chiral biphosphine oxides, like compound **74**.[176]

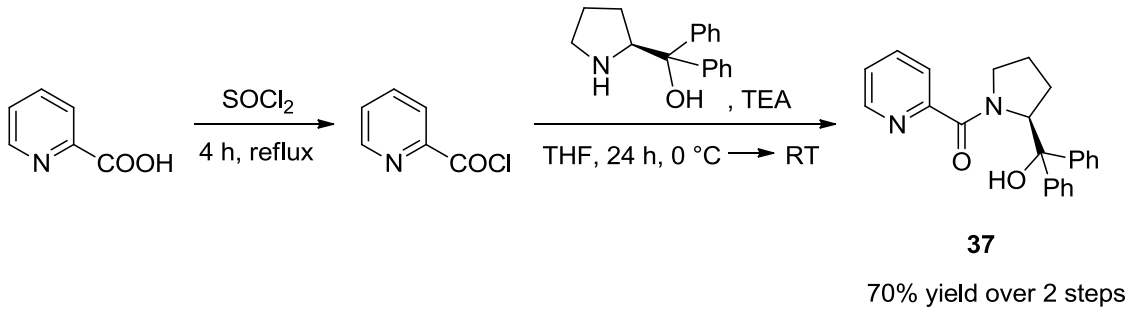
Initially picolinamidic catalyst **40**, **37** and **57'** were prepared according to the reported procedures, while catalyst **43** and **74** were already available in our laboratories.

4-Cl picolinoyl chloride, synthesized by treatment of picolinic acid with thionyl chloride for prolonged time, was reacted with the ephedrine scaffold to yield catalyst **40** in 30% overall yield. Similarly, catalyst **37** was straightforwardly obtained by reaction of diphenylprolinol with picolinoyl chloride, allowing to isolate the desired compound in good yield.



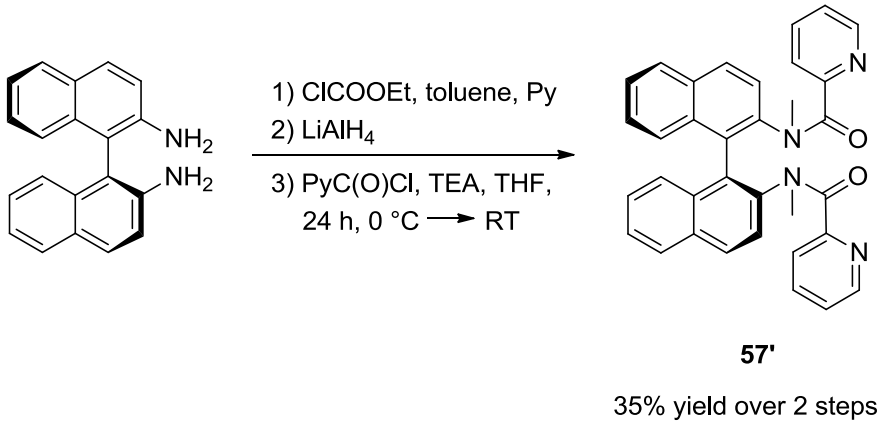
40

30% yield over 2 steps



Scheme 6.1 Synthesis of catalysts **40** and **37**

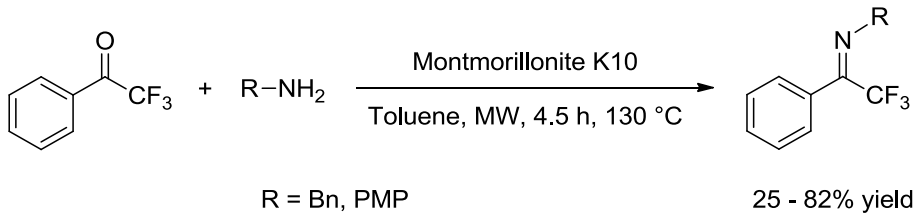
Instead the preparation of catalyst **57'** required a first step of methylation of the amino groups, followed by condensation with the picolinoyl moiety (35% yield over 2 steps).



Scheme 6.2 Synthesis of catalysts **57'**

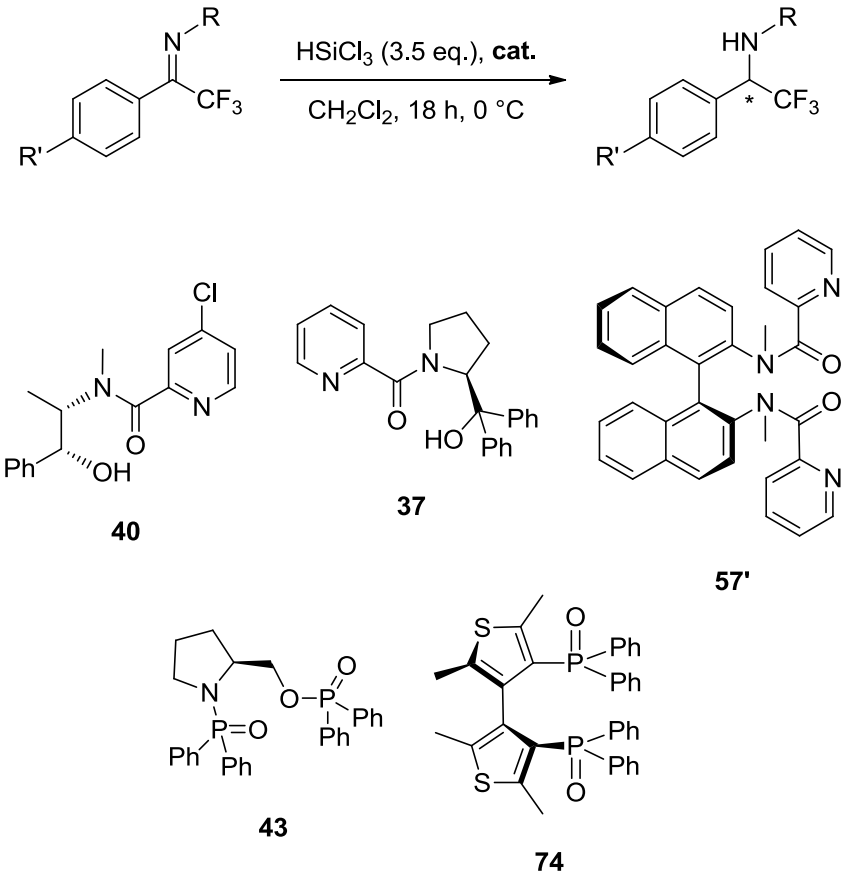
These five catalysts, whose structure are shown in Table **6.1**, were subsequently employed in preliminary studies to identify the catalyst and the experimental conditions of choice.

Ketimines derived from the trifluoromethyl phenyl ketone were selected as model substrates. These compounds were generally prepared in moderate to good yields through the MW assisted synthesis already successfully employed for the non fluorinated substrates.



Scheme 6.3 Synthesis of trifluoroacetophenone derived imines bearing different PGs

Then, their chiral Lewis bases catalyzed reduction was studied. In a typical procedure the reaction was performed at 0 °C in dichloromethane for 18 hours in the presence of 10 mol % amount of catalyst (Table **6.1**).



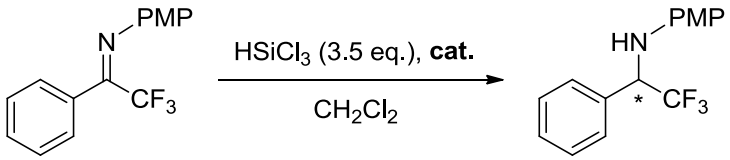
entry	R	R'	cat.	conv. (%) [a]	y (%) [a]	*e.e.* (%)
1	PMP	H	**40** (0.1 eq.)	83	25	*87* (*R*)
2	Bn	H	**40** (0.1 eq.)	15	n.d.	*n.d.*
3	PMP	H	**37** (0.1 eq.)	71	51	*53* (*S*)
4	Bn	H	**37** (0.1 eq.)	67	65	*15* (*S*)
5	PMP	H	**57'** (0.1 eq.)	> 99	77	*73* (*R*)
6	PMP	H	**43** (0.1 eq.)	47	26	*35* (*S*)
7	PMP	H	**74** (0.1 eq.)	/	/	/
8	PMP	Cl	**74** (0.1 eq.)	75	61	*25* (*R*)

[a] yields were determined by NMR on the crude reaction mixture and confirmed on the isolated product after chromatographic purification

Table 6.1 Screening of various catalysts and protecting groups

At the beginning of the investigation both *N*-PMP and *N*-benzyl ketimines were employed in the addition of trichlorosilane mediated by chiral Lewis bases **40** and **37**. It emerged that *N*-aryl protected imines behaved better than *N*-benzyl derived substrates (see Table **6.1**, entries 1-4). It was observed that ephedrine-derived picolinamide **40** was able to promote the reduction of *N*-4-methoxyphenyl imine of 2,2,2-trifluoroacetophenone in 83% yield and 87% *e.e.* after 18 hours at 0 °C in dichloromethane. However the same ligand was almost unable to catalyze the reduction of the *N*-benzyl imine. On the other hand, with prolinol-based catalyst **37** both *N*-PMP and *N*-Bn imines were reduced in good yield. Anyway the products were obtained with different enantioselectivities: a higher *e.e.* was observed with the *N*-PMP protected imine. Therefore, *N*-PMP substituted imines were selected as preferred substrates for further studies. The screening of other catalysts showed that the bispicolinamide catalyst **57'** promoted the reaction in quantitative yield but with lower enantioselectivity (73% *e.e.*), while phosphoroamide and phosphine oxide catalysts **43** and **74** were less efficient, both chemically and stereochemically.

Further studies were then directed to find the best experimental conditions, by evaluating different parameters like temperature, stoichiometry, solvent and reaction work up. Chlorinated solvents afforded the most reliable and interesting results, therefore dichloromethane was selected as preferred reaction medium.



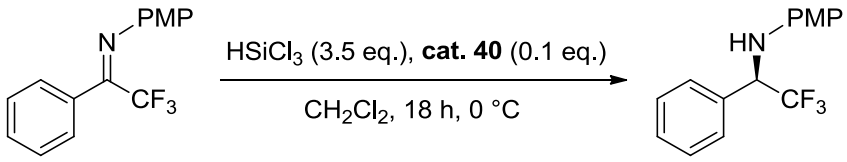
entry	cat.	T (°C)	t (h)	conv. (%) [a]	y (%) [a]	*e.e.* (%)
1	**40** (0.1 eq.)	0	18	83	25	*87* (*R*)
2	**40** (0.1 eq.)	-50	40	61	57	*77* (*R*)
3	**40** (0.1 eq.)	20	18	77	51	*85* (*R*)
4	**37** (0.1 eq.)	0	18	71	51	*53* (*S*)
5	**37** (0.1 eq.)	-50	40	67	55	*45* (*S*)

[a] yields were determined by NMR on the crude reaction mixture and confirmed on the isolated product after chromatographic purification

Table 6.2 Screening of different temperatures for catalyst **40** and **37**

As shown in Table **6.2**, the reduction performed at lower temperature (-50 °C), either with catalyst **40** or **37**, did not lead to any appreciable *e.e.* improvement, while noteworthy ephedrine-based catalyst promoted the reaction with 85% *e.e.* also at 20 °C.

During these initial studies, we often observed a discrepancy between the conversion value determined by NMR analysis and the isolated yield after chromatographic purification. Therefore we decided to attempt different quench and work up procedures (a few selected results are reported in Table **6.3**).



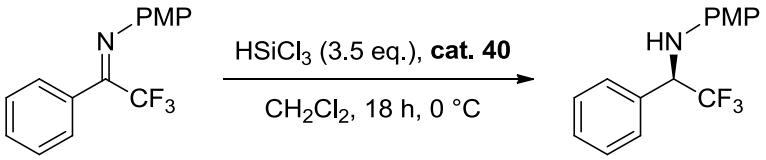
entry	quench	conv. (%) [a]	y (%) [a]	*e.e.* (%)
1	$NaHCO_3$ s.s. (excess)	83	25	*87*
2	$NaHCO_3$ s.s.	93	83	*89*
3	NaOH 10% sol.	>99	91	*91*
4	HCl 10% sol., then NaOH 10% sol.	98	51	*90*

[a] yields were determined by NMR on the crude reaction mixture and confirmed on the isolated product after chromatographic purification

Table 6.3 Optimization of the workup conditions

Those studies highlighted that the use of smaller amounts of aqueous solution during the quench led to increased isolated yields. The methodology that gave the best results involved the quenching of the reaction with a limited and controlled amount of NaOH solution. This procedure allowed to isolate the desired amine in 91% yield (against a quantitative conversion evaluated by NMR on the crude reaction mixture), while maintaining high level of stereoselectivity (91% *e.e.*).

Finally, operating under the best experimental conditions, it was attempted to lower the catalyst loading; we were happy to see that catalyst still worked efficiently at 5 mol %, leading to the product in quantitative yield and 91% *e.e.*; remarkably, also at 1 mol % chiral Lewis base **40** catalyzed the reaction with 89 % *e.e.* albeit in lower yield (Table **6.4**).



entry	cat. (eq.)	conv. (%) [a]	y (%) [a]	*e.e.* (%)
1	0.1	>99	91	*91*
2	0.05	>99	90	*91*
3	0.01	73	53	*89*

[a] yields were determined by NMR on the crude reaction mixture and confirmed on the isolated product after chromatographic purification

Table 6.4 Variation of the catalyst loading

It is worth mentioning that, by performing the reaction with 5 mol % of chiral base, the ACE (Asymmetric Catalyst Efficiency) of catalyst **40** is 15.1. Even better, ACE reaches the value of 43.5 for the reaction performed with 1 mol % of catalyst (values calculated on the basis of data of entries 2-3, Table **6.4**).

The definition of Asymmetric Catalyst Efficiency (ACE) was recently proposed[203] in the attempt to compare and evaluate the efficiency of different catalysts. This classification takes into consideration not only the level of enantioselectivity and the yield guaranteed by the catalyst, but also the loading of the catalyst and the molecular weight of the product and of the catalyst itself.

$$ACE = \frac{MW_B}{MW_{Cat}} \times \frac{1}{mol\ \%} \times \frac{e.e.}{100} \times yield$$

Relative size of catalyst and product — Amount of catalyst needed — Quantity of excess of major enantiomer

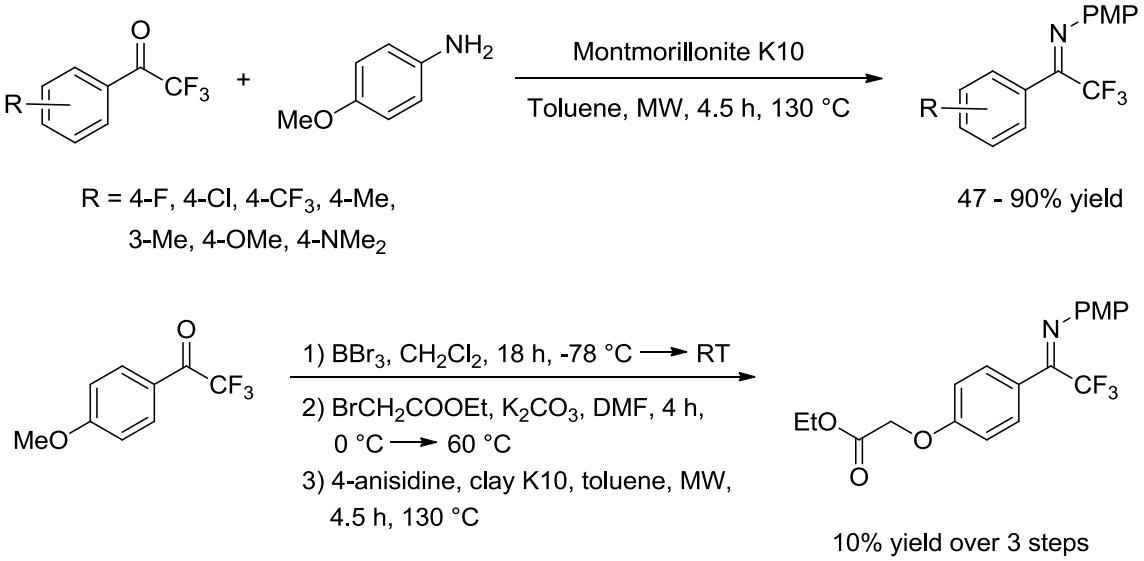
Figure 6.5 Definition of Asymmetric Catalyst Efficiency (ACE)

This formula is straightforward in that the relevant values are almost always known for any given catalytic asymmetric reaction, and yield, *e.e.* and loading are used in their standard forms (i.e. as percentages). Moreover, multiplying ACE value by the quantity of catalyst employed gives the amount of the excess of the major enantiomer produced by a

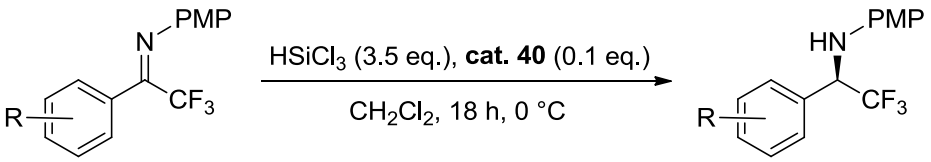
specific reaction: thus ACE parameter permits a simple calculation of the cost of the catalysts for the various transformations.

It's noteworthy that, according to this classification, picolinamide **40** favourably compares both to chiral phosphoric acids (ACE value 4)[201] and even to organometallic catalysts (ACE value 15.7).[200b]

The general applicability of the methodology was then investigated; a series of *N*-PMP imines derived from different trifluoromethyl aryl ketones were prepared and reduced at 0 °C in DCM (Scheme **6.4**, Table **6.5**). In particular, a fluorinated ketimine bearing an ester moiety in 4- position was synthesized through a three step procedure, affording the desired substrate in 10% overall yield.



Scheme 6.4 Synthesis of variously substituted trifluoromethyl aryl imines



entry	R	conv. (%) [a]	y (%) [a]	*e.e.* (%)
1	4-Cl	>99	93	*90*
2	4-F	83	77	*89*
3	4-CF_3	>99	90	*90*
4	3-Me	>99	87	*91*
5	4-Me	80	70	*90*

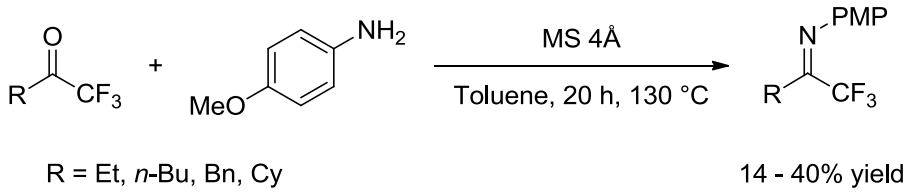
entry	R	conv. (%) [a]	y (%) [a]	*e.e.* (%)
6	4-OMe	> 99	90	*91*
7	4-NMe_2	80	70	*75*
8	4-OCH_2COOEt	> 99	75	*67*

[a] yields were determined by NMR on the crude reaction mixture and confirmed on the isolated product after chromatographic purification

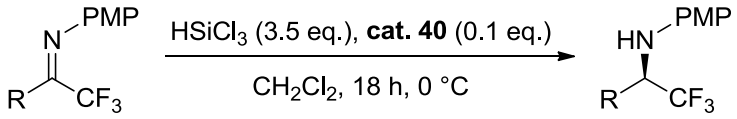
Table 6.5 Reduction of electronrich and electrondeficient trifluoromethyl imines

By operating under the best reaction and work up conditions, high yields and enantioselectivities were generally obtained, indipendently from the electronic nature of the aromatic ring substituents. For example, the reduction of imine derived from trifluoromethyl 4-chlorophenyl ketone was accomplished in quantitative yield and 90% *e.e.*; comparable levels of enantioselectivity were also obtained with substrates bearing either electronwithdrawing groups (F, CF_3) or electrondonating residues (Me, OMe). It's worth mentioning that the reduction of the imine bearing the ester moiety didn't affect the ester itself, thus proving the tolerance of this synthetic methodology to the presence of other reducible groups.

Even more interestingly, the methodology was successfully employed in the reduction of imines derived from trifluoromethyl alkyl ketones. It is important to note that although numerous fluorinated compounds of relevant biological importance are trifluoromethyl *alkyl* amines, their preparation through reduction is much less studied. Therefore we examined the trichlorosilane-mediated reduction of several alkyl imines in the presence of picolinamide **40** and we were pleased to find out that the present catalytic system also works with alkyl derivatives (Table **6.6**, entry 1)



Scheme 6.5 Synthesis of aliphatic fluorinated substrates



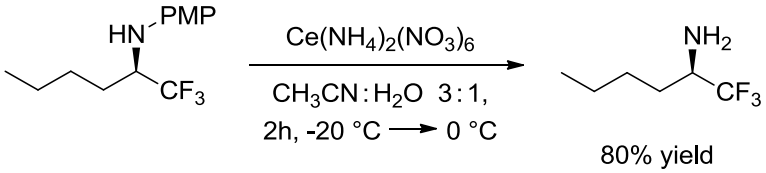
entry	R	conv. (%) [a]	y (%) [a]	*e.e.* (%)
1	Et	98	78	*90*
2	*n*-Bu	> 99	97	*90*
3	Bn	> 99	83	*91*
4	Cy	> 99	93	*98*

[a] yields were determined by NMR on the crude reaction mixture and confirmed on the isolated product after chromatographic purification

Table 6.6 Reduction of imines derived from trifluoromethyl alkyl ketons

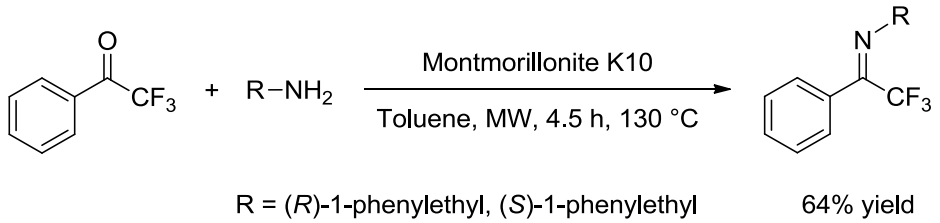
Initially we carried out the trichlorosilane-mediated reduction of 1,1,1-trifluoro-2-butanone-derived imine, isolating the chiral amine in 98% yield (78% isolated yield) and 90% *e.e.*. Similar results were also observed with other linear alkyl trifluoromethyl ketoimines, whose reduction led to the products with enantioselectivities constantly around 90%. A branched alkyl fluorinated ketimine was also considered: the trifluoromethyl cyclohexyl ketone-derived imine was converted into the corresponding amine in quantitative yield with 98% enantiomeric excess.

Release of the primary amine by removing the protecting group is obviously a highly desirable feature, and currently most reports describe oxidative deprotection of the 4-methoxyphenyl group with ceric ammonium nitrate (CAN).[204] However, the application of this method of deprotection to aliphatic fluorinated amines had not been reported yet. Therefore we proceeded to verify the applicability of this oxidative removal performing the reaction with CAN at -20 °C in aqueous acetonitrile, isolating the deprotected amine in 80% yield with no loss of *e.e.*.

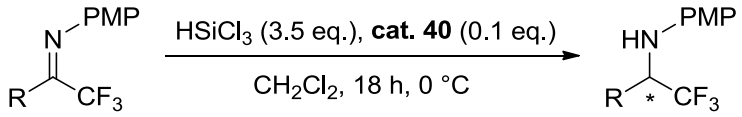


Scheme 6.6 CAN promoted *N*-PMP deprotection of an aliphatic fluorinated amine

A further improvement in the stereoselectivity of the process was obtained by performing the reduction of a fluorinated chiral ketimine in the presence of catalyst **40**. It has been already demonstrated that the combination of an inexpensive chiral, removable group at the imine nitrogen with the proper catalyst often allows to produce the corresponding chiral amine with complete stereoselectivity.[120] The pair of enantiomeric substrates was prepared following the general procedure and subsequently reduced with trichlorosilane (Scheme **6.7**, Table **6.7**).



Scheme 6.7 MW-assisted synthesis of the chiral imine substrates



entry	R	cat.	conv. (%) [a]	y (%) [a]	*e.e.* (%)
1	(*S*)-1-phenylethyl	DMF (0.5 eq.)	73	66	*38* (*S*,*S*)
2	(*S*)-1-phenylethyl	**40** (0.1 eq.)	98	93	*64* (*S*,*S*)
3	(*R*)-1-phenylethyl	**40** (0.1 eq.)	98	95	*96* (*R*,*R*)
4	(*S*)-1-phenylethyl	**37** (0.1 eq.)	96	91	*94* (*S*,*S*)
5	(*R*)-1-phenylethyl	**37** (0.1 eq.)	93	87	*60* (*R*,*R*)

[a] yields were determined by NMR on the crude reaction mixture and confirmed on the isolated product after chromatographic purification

Table 6.7 Reduction of imines derived from trifluoromethyl alkyl ketones

Initially, the reduction of the chiral substrate with trichlorosilane in the presence of DMF was investigated, to evaluate the intrinsic stereoselectivity of this reaction. The reduction led to the product in 73% yield and 69 : 31 diastereosiomeric ratio. Then hydrosilylation of the (*R*)- and (*S*)-1-phenylethyl protected imines with both catalyst **40** and **37** was studied. Ephedrine derived catalyst **40** was able to promote the reduction of (*R*)-1-phenylethyl ketimine affording the corresponding amine in almost quantitative

yield and 98 : 2 diastereoisomeric ratio. Instead, the reduction of the enantiomeric substrate with trichlorosilane in the presence of **40** led to the amine with the opposite absolute configuration in 98% yield and 82 : 18 diastereoisomeric ratio, this showing the existence of a matching and mismatching combination. Notably, by performing the reaction in the presence of catalytic amounts of **37**, which generally promotes the imine reduction with the opposite sense of stereoselectivity of catalyst **40**, the (*S*)-1-phenylethyl ketimine led to product in 97:3 d.r..

In the attempt to rationalize the stereochemical outcome of the reductions promoted by catalyst **40**, the tentative model of stereoselection reported in Figure **6.6** was initially proposed. According to previous studies, the pyridine nitrogen and the amidic CO group of the picolinamide are thought to activate trichlorosilane by coordination.[120] In the proposed stereoselection model **A**, leading to the observed major enantiomer, the steric interaction between the pyridine ring and the aryl group is much less significant than the one observed in adduct **B**, which is thus disfavored (Figure **6.6**).

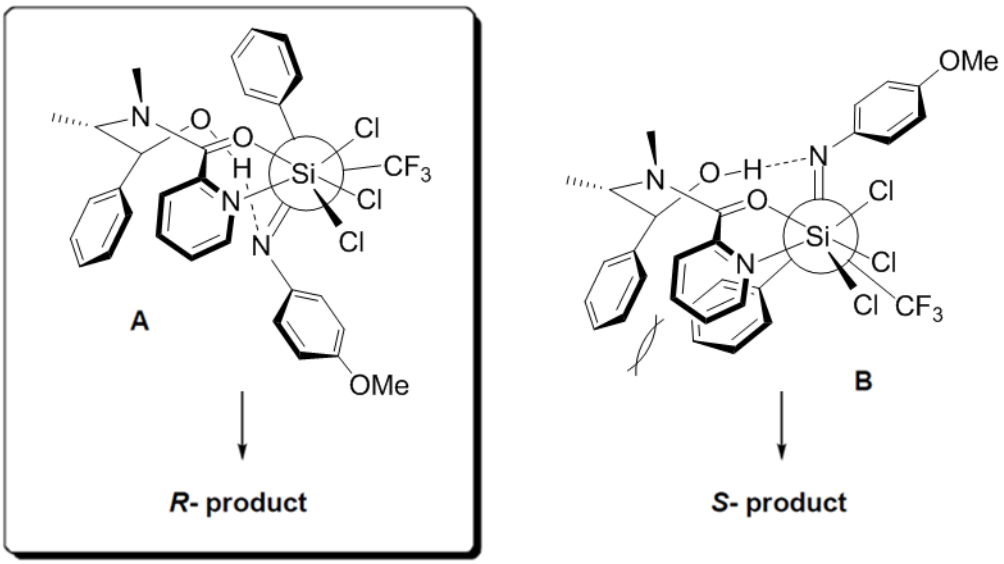


Figure 6.6 Proposed model of stereoselection featuring a *Z* configurated imine

The proposed model involves a *Z* configurated substrate, by analogy with the non fluorinated substrates. The hypothesized *Z* configuration was also supported by comparison of our preliminary NMR data with the ones reported in literature. However, further NMR and crystallographic studies seem to point towards the existence of the fluorinated imines in the *E* configuration. Moreover, also computational studies

performed at the B3LYP-6311+G(d,p) level of theory designate the *E* configuration as the most stable (Figure **6.7**).

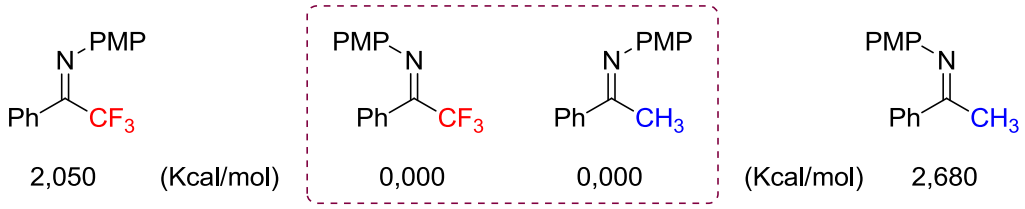


Figure 6.7 B3LYP-6311+G(d,p) studies

On the basis of these results, the new model reported in Figure **6.8** was proposed:

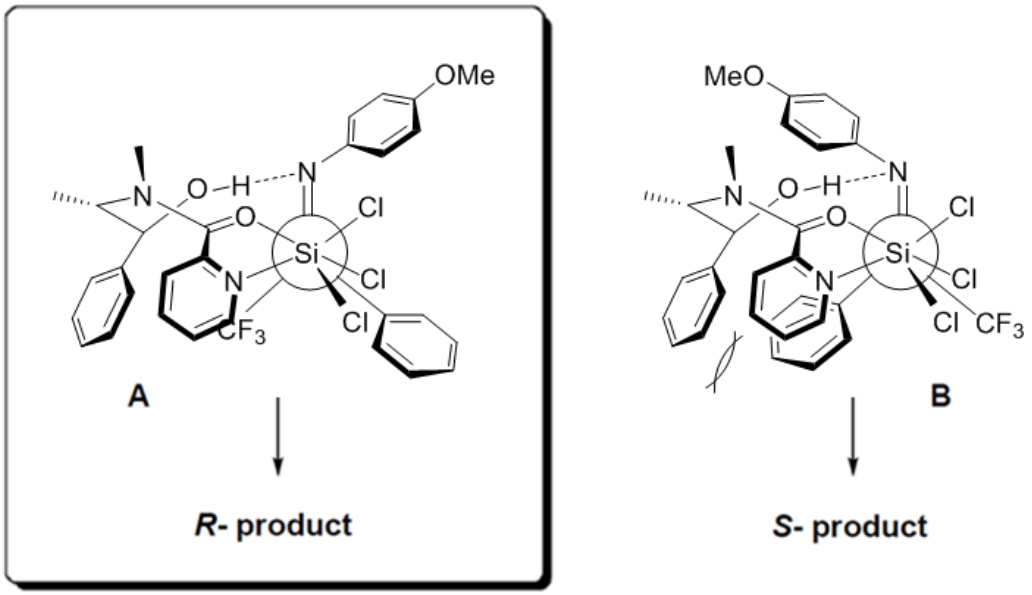


Figure 6.8 Proposed model of stereoselection featuring an *E* configurated imine

Further studies are currently in progress to definitely assess the actual configuration of the starting material.

In conclusion, the enantioselective organocatalytic reduction of fluorinated ketoimines was successfully realized by using trichlorosilane as reducing agent in the presence of catalytic amounts of an inexpensive and readily available picolinamide. The methodology allowed to reduce imines derived both from aryl and alkyl trifluoromethyl ketones in very good yields and high enantioselectivities, typically of 90% *e.e.* and up to 98% *e.e.*. With a ACE value of about 44, picolinamide **40** established itself as one of the most efficient and versatile catalyst for the reduction of a wide range of fluorinated imines. The well documented possibility to easily remove the *N*-PMP residue[200b] or the

benzyl group[205] makes the present method a viable and attractive synthesis also for highly enantiomerically enriched fluorinated primary amines.

CHAPTER 7

Cinchona alkaloids-based catalysts for the reduction of carbon-nitrogen double bonds

"Where Nature ceases to produce its own species,
Mankind begins, using natural things, and with the
aid of this very Nature, creates an infinity of species…"
Leonardo da Vinci

As profusely described in Chapter 3, trichlorosilane-based methodologies have become an established way to efficiently perform the stereoselective reduction not only of *N*-aryl, *N*-benzyl and *N*-alkyl ketimines, but also of imines derived from α-, β- and γ-ketoesters. Over the last years our group has widely explored this field, focusing primarily onto the use of picolinamidic derivatives as chiral Lewis bases. Several members of this class of catalyst are based on natural chiral scaffolds, such as proline and ephedrine. Following our interest in the development of new catalysts for the trichlorosilane-mediated reactions, we decided to took advantage of another group of natural alkaloids, obtained from the bark of the cinchona tree: quinine, quinidine, cinchonidine and cinchonine.

Several reasons concur to make cinchona scaffolds so widely used in asymmetric organocatalysis: the easy availability of these compounds has surely been an important factor, but they possess also other interesting features.[206] Cinchona alkaloids are small yet complex molecules containing five stereogenic centers, a basic and nucleophilic quinuclidine, a quinoline unit, a secondary alcohol, an aryl methyl ether (in the case of quinine and quinidine) and a terminal olefin (Figure **7.1**). This structural richness has been extensively exploited for the facile modification of the naturally occurring alkaloids

to develop synthetic, tailor-made compounds for specific applications. Moreover, the presence of many functional groups on the alkaloid scaffold often renders the immobilization of cinchona-derived organocatalysts on insoluble polymeric supports straightforward.[10b,207]

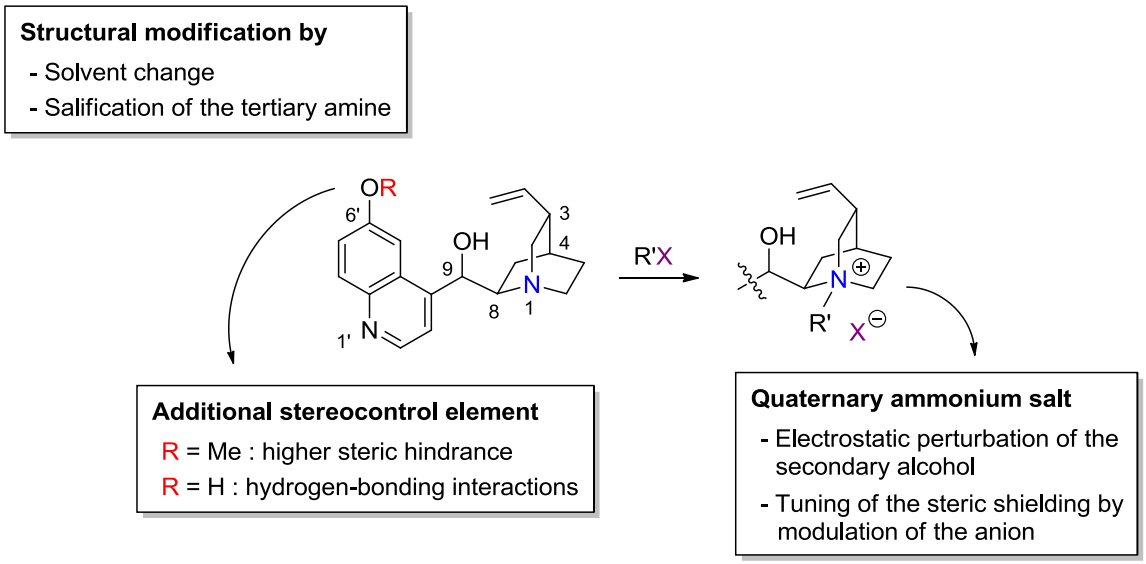


Figure 7.1 Structural features of cinchona alkaloids' scaffold

It's noteworthy that the absolute configurations at N1, C3 and C4 are identical in all cinchona alkaloids; on the other hand, the other stereogenic centers (C8 and C9) have opposite absolute configurations in quinidine and quinine (the same applies to cinchonine *vs.* cinchonidine, Figure **7.2**). Since the C3, C8 and C9 stereocenters are considered responsible for the asymmetric induction in organocatalysis, cinchona alkaloids are usually described as pairs of pseudoenantiomers. As a result, when a quinine derivative is used as a chiral organocatalyst or ligand, the corresponding quinidine derivative usually gives the opposite enantiomer of the same product with comparable selectivity. This feature makes cinchona alkaloids attractive scaffolds for the development of asymmetric catalysts because, unlike other chiral bases such as (-)-sparteine, both pseudoenantiomeric couples of alkaloids are commercially available in bulk amounts at a relatively low price.

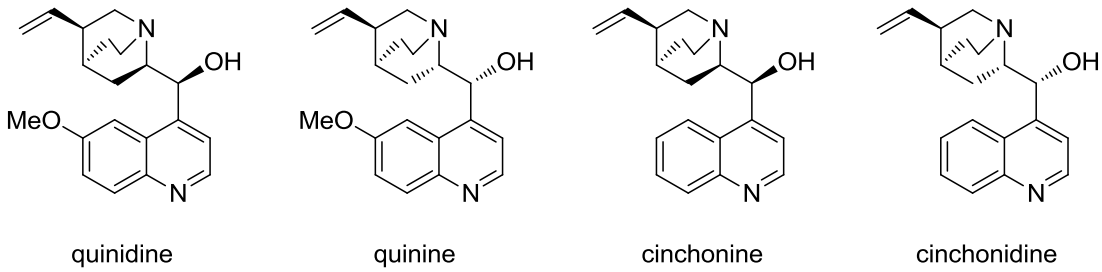


Figure 7.2 Structures of cinchona alkaloids

Another important characteristic is that cinchona alkaloids are flexible molecules and in solution they can adopt several conformations: the four most common ones for quinidine are depicted in Figure **7.3**. Three-dimensional structural modifications can be induced by different chemical stimuli, such as a solvent change[208] or protonation of the *N*-quinuclidine moiety.[209] It has already been shown how modulation of the solvent polarity directly reflects on the ability of a cinchona catalyst to induce a preferred handedness in the product.[210] The degree of flexibility of the cinchona catalysts can also account for their wide tolerance toward substrates having a different steric bias, since slight structural modifications can modulate the three-dimensional catalytic assembly to accommodate a variety of reactants.

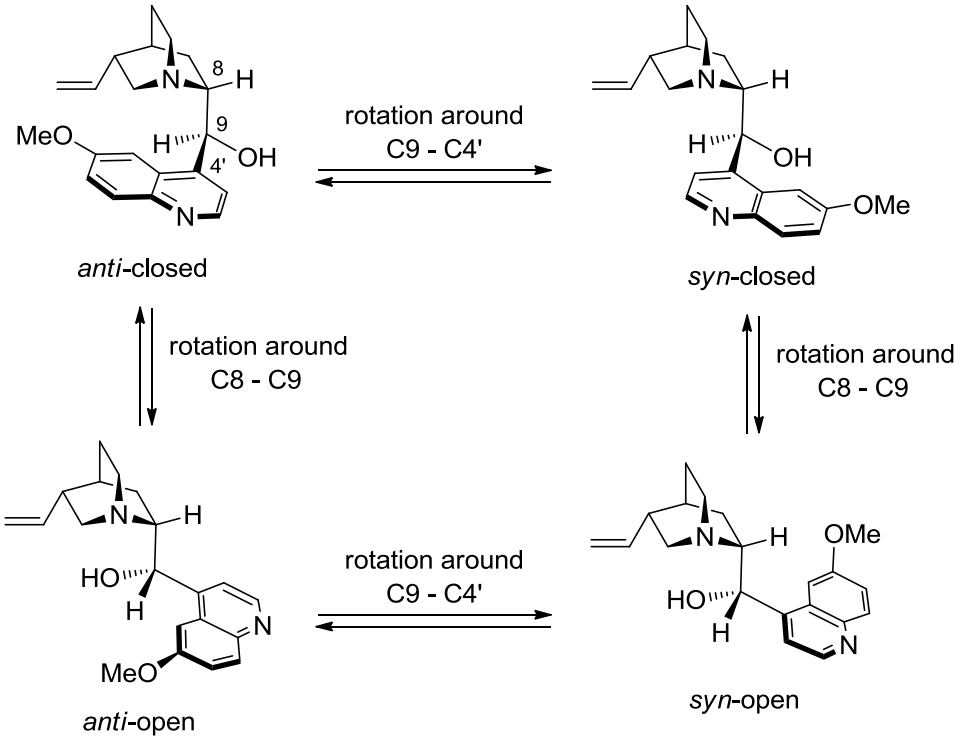


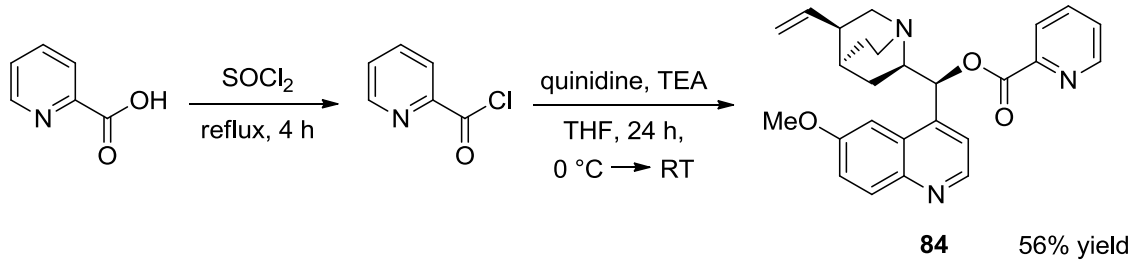
Figure 7.3 Quinidine most common conformers

Their unique molecular recognition abilities render cinchona alkaloids and their derivatives invaluable compounds in nearly every field where asymmetric chemistry is involved: they have been used as surface modifiers, selectors for chromatographic separations, bases for the resolution of racemates, ligands for transition-metal complexes, building blocks for supramolecular architectures and chiral catalysts. In particular, the tasks carried out by cinchona organocatalysts range from the asymmetric promotion of domino reactions to bifunctional catalysis, counteranion directed catalysis and multicomponent reactions.

7.1 Reduction of aromatic and aliphatic ketimines

Prompted by the outstanding results obtained in the field of asymmetric catalysis through the use of these substances, we began to explore the performance of cinchona-derived picolinamides in trichlorosilane-promoted reductions.

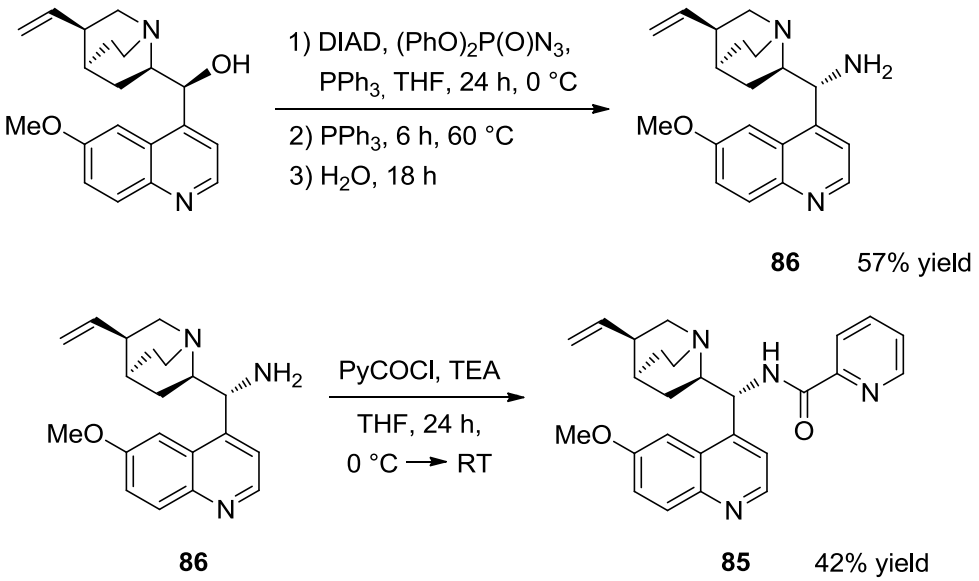
The first structures that we studied were catalysts **84** and **85**. As shown in Scheme **7.1.1**, the straightforward synthesis of the ester compound simply consisted of the reaction of the commercially available chiral alcohol with the picolinoyl chloride.



84 56% yield

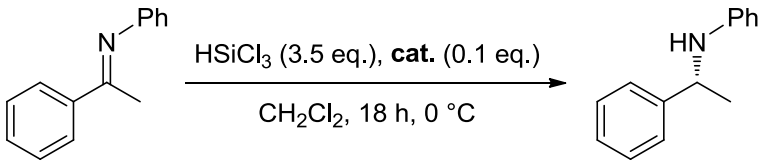
Scheme 7.1.1 Synthesis of the ester **84**

9-amino-*epi*-quinidine, necessary for the synthesis of the other catalyst, was obtained by performing Mitsunobu reaction on the corresponding alcohol; then, the isolated amine was converted into the final product following the same synthetic strategy of **84** (Scheme **7.1.2**).



Scheme 7.1.2 Synthesis of the amide **85**

Then, we studied their behaviour in the hydrosilylation of *N*-phenyl protected ketimine derived from acetophenone (Table **7.1.1**):



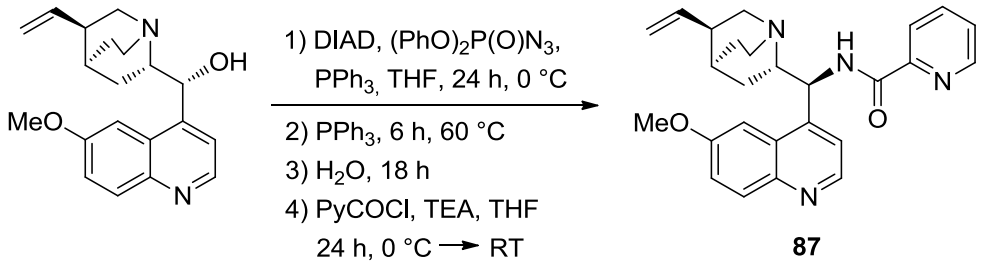
entry	cat.	y (%)	*e.e.* (%)
1	**84**	87	*rac*
2	**85**	98	*80*

Table 7.1.1 Comparison of the performances of ester and amidic catalysts

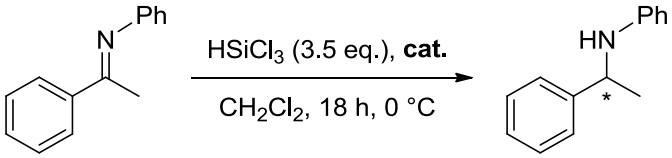
Very interestingly, both catalyst are able to promote the reaction in high to excellent yield. However, they exhibit a really different stereochemical efficiency: while ester derivative **84** leads to the racemic amine, amide **85** permits to produce the desired product in a very promising 80% *e.e.*. This results highlights the superior capability of amides to stereodirect the process, due to their higher rigidity.

Next, we checked if the use of pseudoenantiomeric catalyst **87** would afford the enantiomeric product with comparable enantioselectivity. Following the synthesis

depicted in Scheme **7.1.3**, the picolinamidic compound was prepared in good yield; the results of the reduction promoted by this catalyst are shown in Table **7.1.2**.



Scheme 7.1.3 Synthesis of the pseudoenantiomeric catalyst **87**

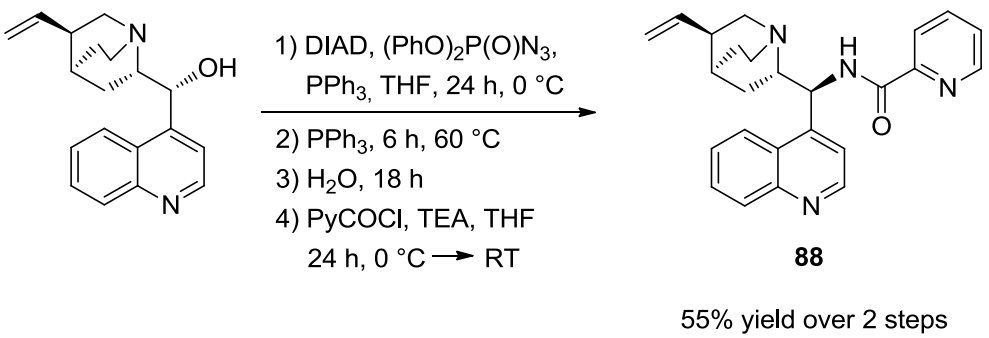


entry	cat.	y (%)	*e.e.* (%)
1	**85** (0.1 eq.)	98	*80* (*R*)
2	**87** (0.1 eq.)	91	*76* (*S*)

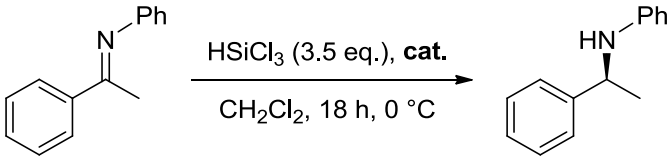
Table 7.1.2 Comparison of the catalytic efficiency of the pseudoenantiomers **85** and **87**

In good accord with the usual behaviour of cinchona alkaloids derived catalysts, employment of compounds **85** and **87** permitted to respectively isolate *R* and *S* enantiomer of the product with equivalent stereoselection.

We looked into the actual role of the methoxy moiety on the quinoline ring by comparing the results obtained with quinine and cinchonidine derived catalysts (Scheme **7.1.4**, Table **7.1.3**):



Scheme 7.1.4 Synthesis of the catalyst derived from cinchonidine

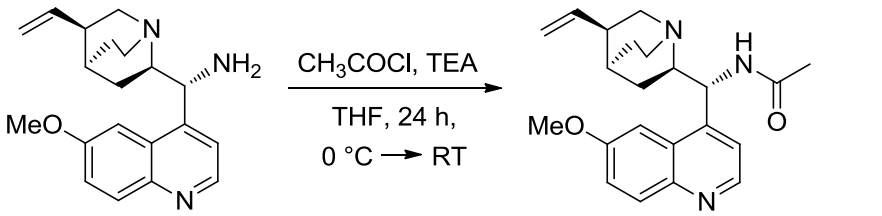


entry	cat.	y (%)	*e.e.* (%)
1	**87** (0.1 eq.)	91	*76*
2	**88** (0.1 eq.)	97	79

Table 7.1.3 Comparison between quinine and cinchonidine picolinamides

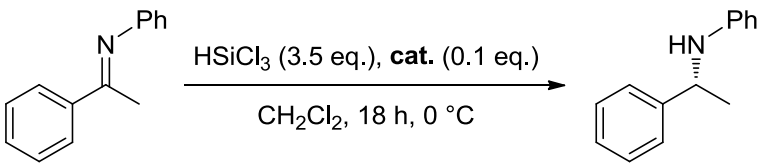
Interestingly, the steric hindrance provided by the methoxy group doesn't seem to have any effect on the enantioselectivity of the reaction. In fact, both of the picolinamidic catalysts allowed to isolate the product with similar levels of enantiomeric excess.

The abundance of Lewis basic sites in these structures also prompted us to verify if the picolinamidic moiety is indeed responsible for the activation of trichlorosilane. Therefore we examined the reduction promoted by the unprotected 9-amino-*epi*-quinidine **86**, as well as the reaction with its acetamidic derivative **89** (Scheme **7.1.5,** Table **7.1.4**).



86 **89** 99% yield

Scheme 7.1.5 Synthesis of the acetamide **89**

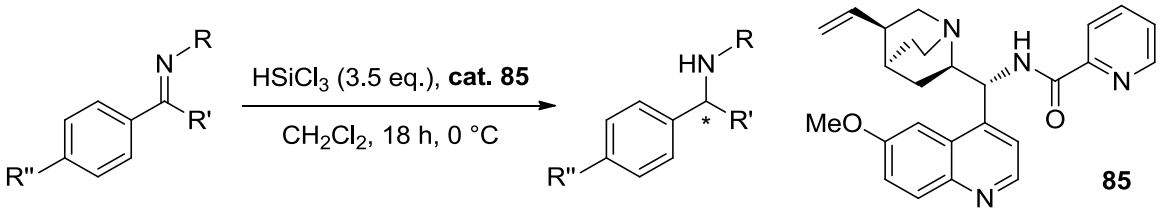


entry	cat.	y (%)	*e.e.* (%)
1	**86**	30	*rac*
2	**89**	30	*rac*

Table 7.1.4 Reduction of *N*-Ph acetophenone imine promoted by **86** and **89**

In the absence of the picolinamidic group the products was obtained with a large decrease of chemical yield and no stereocontrol. Notably, this holds true even when the pyridine ring is the only missing portion of the molecule.

Once defined the basic structure of the catalyst, we proceeded to test it with others imines bearing different protecting groups at the nitrogen atom. Also the reduction of some *N*-PMP trifluoromethyl aryl imines was examined (Table **7.1.5**):

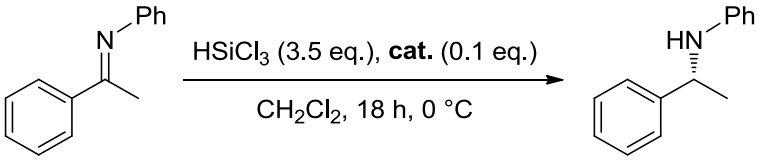


entry	R	R'	R"	y (%)	*e.e.* (%)
1	Ph	CH_3	H	98	*80* (*R*)
2	PMP	CH_3	H	92	*78* (*R*)
3	PMP	CF_3	H	54	*16* (*R*)
4	PMP	CF_3	Cl	55	*18* (*R*)

Table 7.1.5 Reduction of various methyl and trifluoromethyl aryl imines

Generally, the nature of the protecting group didn't have a significant effect on the chemical and stereochemical outcomes of the reaction, and the amines were obtained in quantitative yields and high enantiomeric excesses. Quite surprisingly, while ephedrine derived catalyst **40** was able to reduce both methyl and trifluoromethyl imines with high enantioselectivity, catalyst **85** performed poorly with fluorinated substrates, yielding the corresponding products with only 16 - 18% *e.e.*. If the *E* configuration of these fluorinated compounds were to be confirmed, it could possibly be the reason for this different behaviour.

During our preliminary studies we noticed that different batches of the catalyst sometimes showed some differences in their ability to enantioselectively promote the reaction. Some selected data are reported in Table **7.1.6**:



entry	cat.	y (%)	*e.e.* (%)
1	**85** (batch 1)	98	*80*
2	**85** (batch 2)	64	*79*
3	**85** (batch 3)	50	*56*
4	**85** (batch 3)[a]	70	*68*

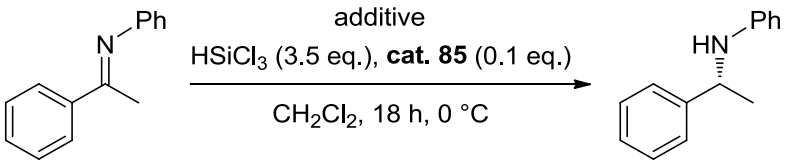
[a] catalyst dried at 60 °C under high vacuum for 24 h

Table 7.1.6 Reproducibility tests

Since these compounds often show an high retention of solvents, we verified if this was the cause of the variations observed in some of the experiments. Actually, improvements in both yield and enantioselectivity were observed by drying the catalyst for a prolonged time (Table **7.1.6**, entries 3 and 4); however, the usual levels of chemical and stereochemical efficiency were not completely restored, suggesting that also other factors play a role in these discrepancies.

In order to overcome this issue, we then performed an optimization of both reaction conditions and catalyst structure.

At first, several acid additives were evaluated in the reduction of the *N*-Ph imine derived from acetophenone, selected as model substrate (Table **7.1.7**):



entry	additive	y (%)	*e.e.* (%)
1	CH_3COOH (0.1 eq.)	96	*77*
2	PhCOOH (0.1 eq.)	95	*64*
3	CF_3COOH (0.1 eq.)	80	*rac*

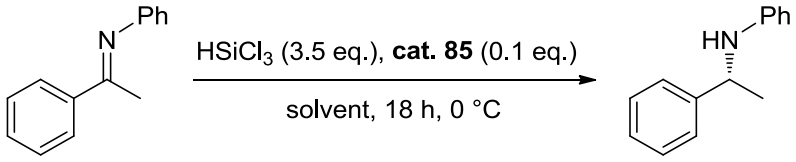
Table 7.1.7 Studies of protonation of the catalyst

It's noteworthy that the addition of a 10 mol % amount of a weak acid such as acetic acid nearly brought back yield and enantiomeric excess to their original values (Table **7.1.6** entry 4 *vs.* Table **7.1.7** entry 1). However the use of a slightly stronger acid such as benzoic acid caused a significant drop in enantioselectivity. This trend was confirmed when trifluoroacetic acid was employed: the reduction, presumably promoted by the catalyst completely in protonated form, resulted in the formation of the racemic product.
This observation led us to think that the use of a base could further raise the enantioselectivity of the process: it is well known in fact that small amounts of HCl are generated by trichlorosilane over the course of the reaction, which may lead to a partial protonation of the catalyst. However, even the use of large excesses of *N*,*N*-diisopropylethylamine or potassium carbonate didn't show any appreciable improvement (Table **7.1.8**):

entry	additive	y (%)	*e.e.* (%)
1	DIPEA (10.0 eq.)	/	/
2	DIPEA (3.5 eq.)	/	/
3	K_2CO_3 (17.5 eq.)	97	*68*

Table 7.1.8 Outcomes of the $HSiCl_3$ mediated ketimine reduction in presence of bases

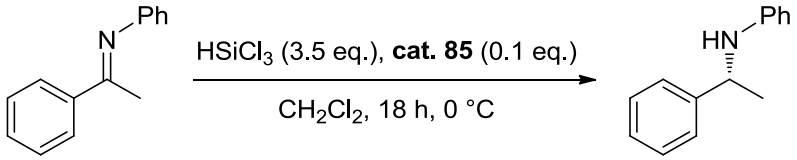
Thereafter, we performed a screening of different solvents whose results are reported in Table **7.1.9**:



entry	solvent	y (%)	*e.e.* (%)
1	CH_2Cl_2	87	*68*
2	CH_3CN	92	*35*
3	Toluene	83	*12*
4	THF	97	*10*

Table 7.1.9 Screening of different solvents

Dichloromethane was confirmed to be the solvent of choice, while the use of other solvents was detrimental for the enantioselectivity of the process. More coordinating solvents like CH_3CN and THF likely disturb the coordination between trichlorosilane and the catalyst; instead, the enantioselectivity drop observed with a non coordinating solvent such as toluene may be attributed to the formation of catalyst aggregates in solution.
As already described in the introduction of this chapter, cinchona alkaloids are rather flexible structures and the concentration of the solution could contribute to determine the adopted conformation. To investigate the effects of the changes in the conformation of the scaffold and of the eventual formation of aggregates, the reaction was carried out at different degrees of dilution (Table **7.1.10**):

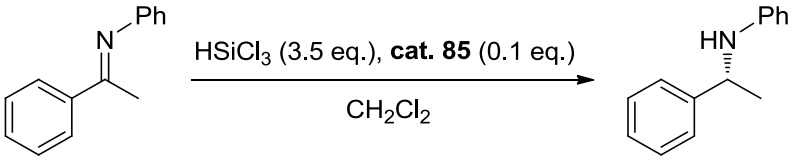


entry	solvent (mL)	y (%)	*e.e.* (%)
1	0.5	96	*46*
2	2.0	87	*68*
3	6.0	90	*75*

Table 7.1.10 Hydrosilylation of imines run at different degrees of dilution

As clearly shown in Table **7.1.10**, the concentration actually plays a significant role in determining the enantioselectivity of the process: a considerable decrease of the enantiomeric excess was observed when the reaction was run with 0.5 mL of solvent, while higher dilution (6.0 mL) led to an appreciable increase.

With the purpose of achieving higher stereocontrol, we also studied the reduction of the substrate at a lower temperatures (Table **7.1.11**):

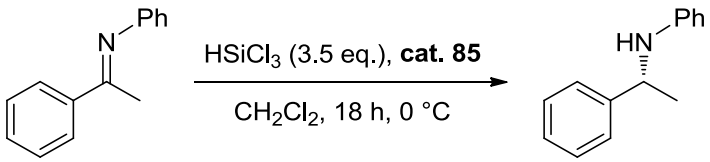


entry	T (°C)	t (h)	y (%)	*e.e.* (%)
1	0	18	96	*76*
2	-20	18	42	*78*
3	-40	18	14	*83*
4	-40	48	14	*82*

Table 7.1.11 Evaluation of the effects of temperature decrease

However, lowering the reaction temperature at -20 °C had virtually no effect on the enantioselectivity of the reaction promoted by catalyst **85**, and even a further decrease to -40 °C had only a marginally positive effect. On the other hand chemical yields suffered a large drop, which convinced us to keep 0 °C as working temperature also for the successive experiments.

Finally we tried to decrease the loading of the catalyst to 5 and 1 mol %. The obtained results are summarized in Table **7.1.12**:



entry	cat. (eq.)	y (%)	*e.e.* (%)
1	0.10	98	*79*
2	0.05	96	*75*
3	0.01	88	*59*
4[a]	0.01	98	*77*

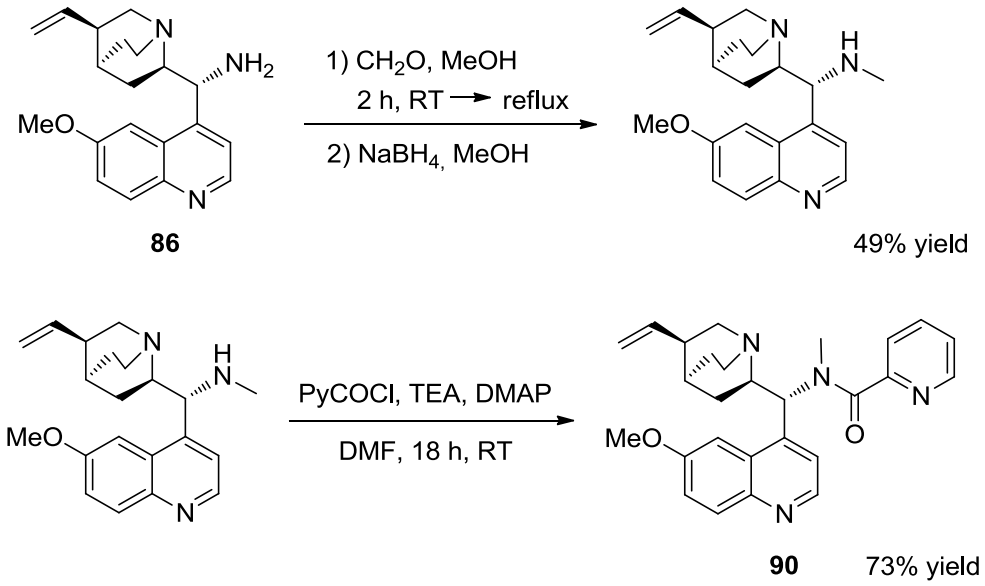
[a] reaction performed at 6 mL dilution

Table 7.1.12 Variation of the catalyst loading

We were very pleased to see that the catalyst still worked efficiently at 5 mol %, leading to the amine in nearly quantitative yield and 79% *e.e.*. Operating under the same

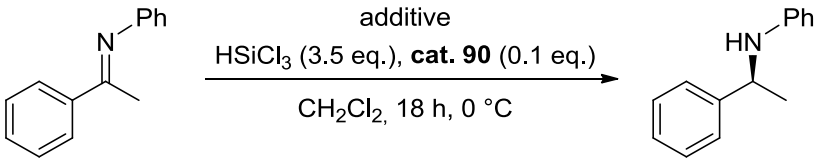
reaction conditions, a 1 mol % amount of the catalyst gave the desired product in good chemical yield but with significantly lower enantioselectivity (59% *e.e.*); however, by performing the reaction at higher dilution the product was obtained with the same yield and enantiomeric excess of the reaction that employed 10 mol % of catalyst (Table **7.1.12**, entries 1 and 4). Notably, this lowering of the catalyst requirements to 5 and 1 mol % translates into ACE values of 6.6 and 34.7 respectively (values calculated on the basis of data of Table **7.1.12**, entries 2 and 4).

At the same time, we attempted to improve both performance and reproducibility by modifying catalyst structure. In the ephedrine derived catalyst **40** a methyl substituent on the picolinamidic moiety was found to fulfill a key role in securing good stereocontrol. Therefore, the first change that we envisioned was the synthesis of the *N*-methyl analogue of **85**. After having explored several synthetic routes, the *N*-methyl-9-amino-*epi*-quinidine was initially obtained through the Eschweiler–Clarke reaction in 34% yield. Better results were later obtained with the synthesis reported in Scheme **7.1.6**, which allowed to obtained catalyst **90** with 36% yield over two steps.



Scheme 7.1.6 Synthesis of the *N*-methyl picolinamidic catalyst **90**

The efficiency of catalyst **90** in the trichlorosilane mediated reduction of the model substrate was examined (Table **7.1.13**):

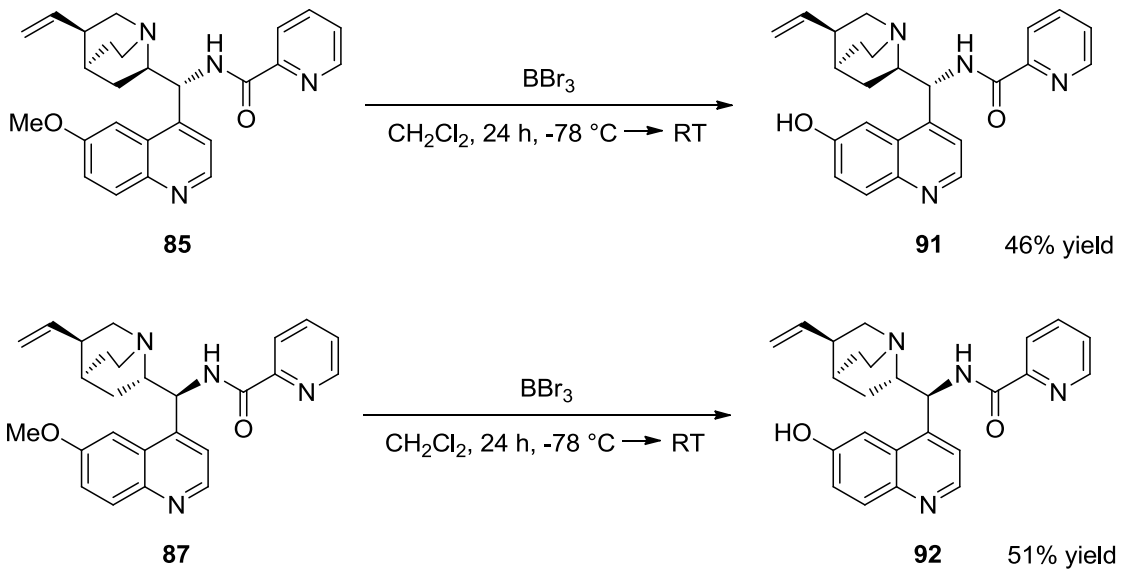


entry	additive	y (%)	*e.e.* (%)
1	/	50	*19*
2	CH_3COOH (0.1 eq.)	17	*rac*
3	2-FC_6H_4COOH (0.1 eq.)	41	*rac*

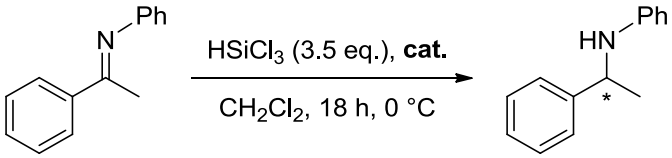
Table 7.1.13 Results of the reduction of *N*-Ph acetophenone imine promoted by **90**

Quite surprisingly, this modification led to a complete inversion of the configuration of the reduction product, which was isolated in 19% *e.e.* for the (*S*) enantiomer. Also the addition of different acid additives didn't produce any beneficial effect, yielding the amine with no enantioselectivity.

Inspired both by the fundamental role that a free hydroxyl group played in the selectivity of the ephedrinic picolinamide and by the good results that have been obtained with the 6'-OH cinchona derived catalysts,[211] we also synthesized catalysts **91** and **92** by straightforward demethylation of **85** and **87** with BBr_3. Subsequently we investigated their performances in the catalytic hydrosilylation of *N*-Ph acetophenone imine (Scheme **7.1.7**, Table **7.1.14**):



Scheme 7.1.7 Synthesis of the catalysts **91** and **92** bearing an hydroxy group

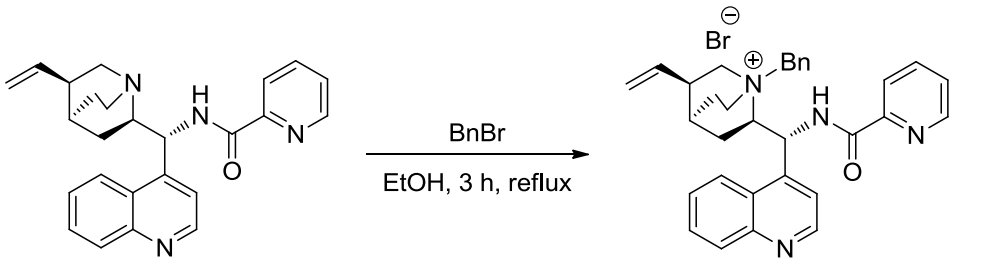


entry	cat.	y (%)	*e.e.* (%)
1	**91** (0.1 eq.)	> 99	*88* (*R*)
2	**92** (0.1 eq.)	82	*80* (*S*)

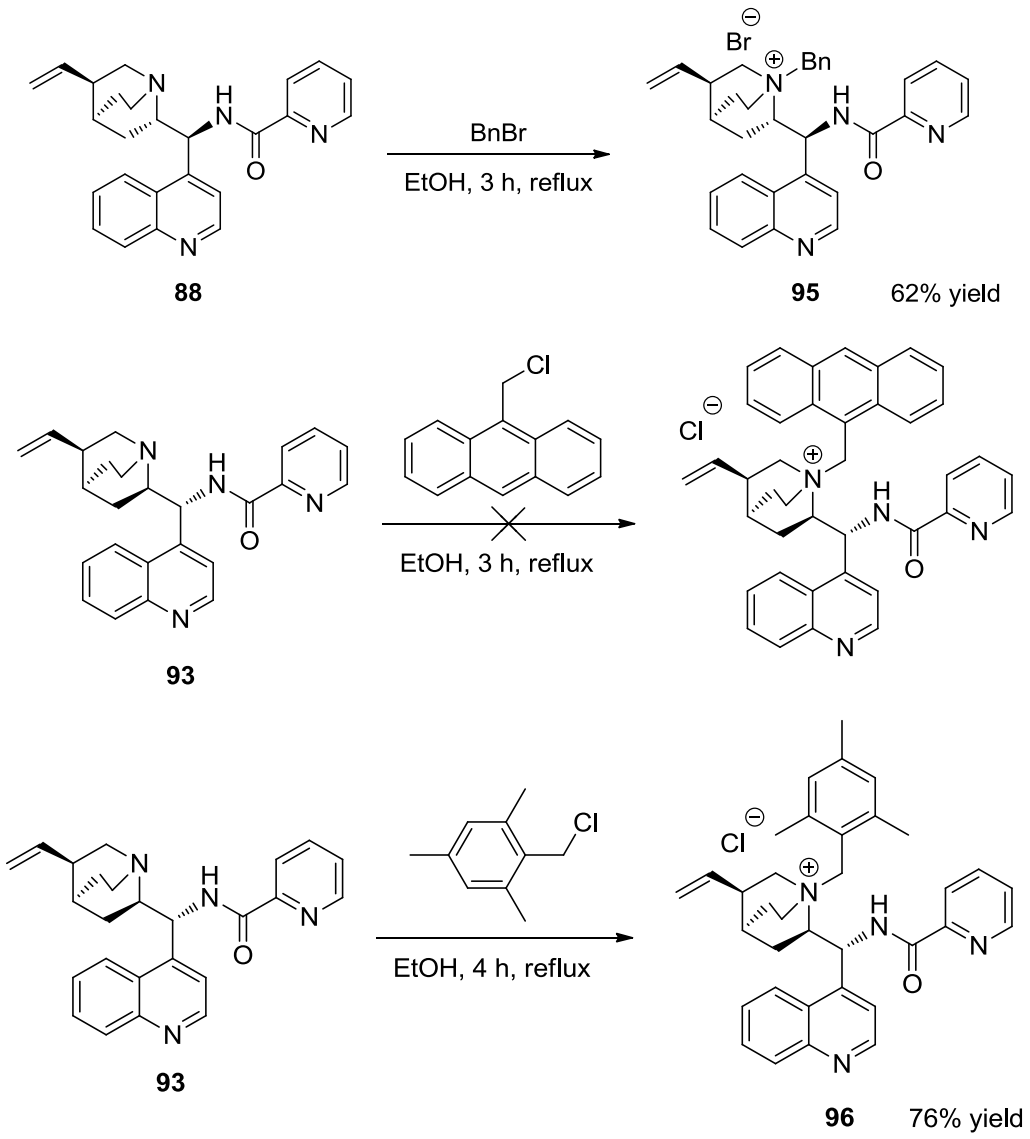
Table 7.1.14 Comparison between the activities of the catalysts **91** and **92**

Again, the two pseudoenantiomers of this structure afforded the product with opposite configuration and comparable levels of enantioselectivity. To our pleasure, catalyst **91** was able to promote the formation of the product in quantitative yield and with a very good 88% enantiomeric excess. Catalyst **92** performed a little worse but both yield and *e.e.* remained quite high.

The last variation we explored was the introduction of a bulky substituent at the quinuclidine nitrogen atom through the synthesis of the corresponding quaternary ammonium salt. Several salts were prepared by treatment of the cinchonine and cinchonidine picolinamides with the required benzyl halide analogue. The reactions generally proceeded smoothly yielding the products in moderate to good yield after three hours; the only exception was the synthesis of the 9-methylanthracenyl salt, where no sign of the formation of the product was observed even after prolonged time (Scheme **7.1.8**).

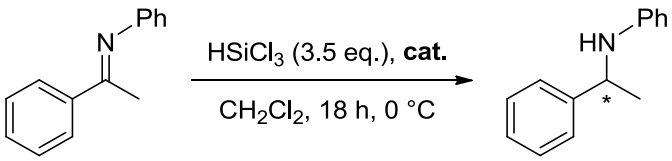


93 **94** 56% yield



Scheme 7.1.8 Synthesis of the ammonium salts **94**, **95** and **96**

Then, we studied the behaviour of these catalysts in the reduction of *N*-phenyl protected acetophenone imine (Table **7.1.15**):



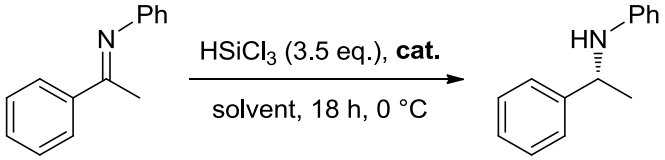
entry	cat.	y (%)	*e.e.* (%)
1	**94** (0.1 eq.)	98	*86* (*R*)
2	**95** (0.1 eq.)	91	*74* (*S*)
3	**96** (0.1 eq.)	66	*67 (R)*

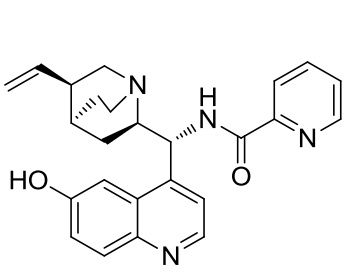
Table 7.1.15 Performances of the ammonium salts **94**, **95** and **96** in ketimine hydrosilylation

Also the benzyl salt **94** showed an improvement compared to the original catalyst, leading to the product with 98% yield and 86% *e.e.* (Table **7.1.1** entry 2 *vs.* Table **7.1.15** entry 1). It's noteworthy that the picolinamide derived from cinchonine (**94**) performed slightly better than the catalyst synthesized from cinchonidine (**95**), confirming the trend already observed with the other catalyst derived respectively from quinidine and quinine. Worse results were instead obtained with compound **96**, which afforded the amine only with 66% yield and 67% enantiomeric excess.

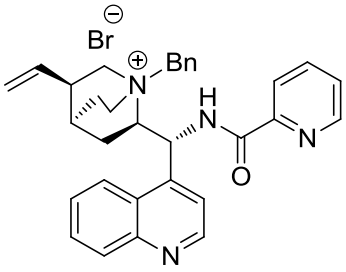
It's important to highlight that working under optimized conditions the variations in the outcomes of the reduction promoted by catalyst **85** were considerably lowered, and no reproducibility issues were observed for the experiments carried out with the hydroxy and ammonium salt catalysts.

Finally, a screening of the reaction conditions, namely by changing the solvent and the temperature, was also run for the best performing catalysts **91** and **94**. Results are reported in Table **7.1.16** and **7.1.17**:





91

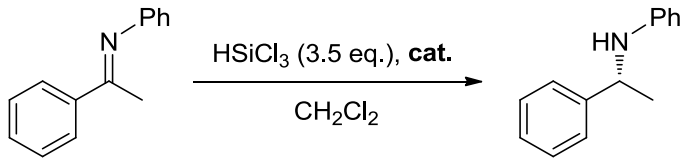


94

entry	cat.	solvent	y (%)	*e.e.* (%)
1	**91** (0.1 eq.)	CH_2Cl_2	> 99	*88*
2	**91** (0.1 eq.)	CH_3CN	98	*52*
3	**91** (0.1 eq.)	THF	> 99	*45*
4	**94** (0.1 eq.)	CH_2Cl_2	98	*86*
5	**94** (0.1 eq.)	CH_3CN	98	*53*
6	**94** (0.1 eq.)	THF	97	*22*

Table 7.1.16 Solvents optimization for the catalysts **91** and **94**

The same trend already observed for catalyst **85** was found again also with compounds **91** and **94**. However it can be noticed that the decrease in enantioselectivity detected upon switching from DCM to THF is definitely smaller for the hydroxy derivative **91** than for **85** and **94**.

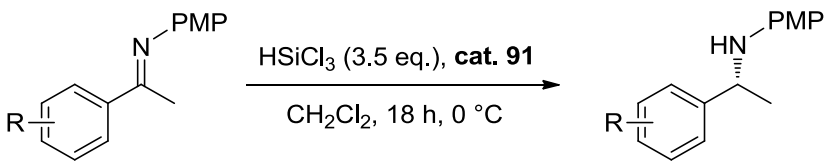


entry	cat.	T (°C)	t (h)	y (%)	*e.e.* (%)
1	**91** (0.1 eq.)	0	18	> 99	*88*
2	**91** (0.1 eq.)	- 20	18	77	*90*
3	**91** (0.1 eq.)	- 40	48	14	*94*
4	**94** (0.1 eq.)	0	18	98	*86*
5	**94** (0.1 eq.)	- 20	18	65	*72*
6	**94** (0.1 eq.)	- 40	48	11	*92*

Table 7.1.17 Temperature optimization for the catalysts **91** and **94**

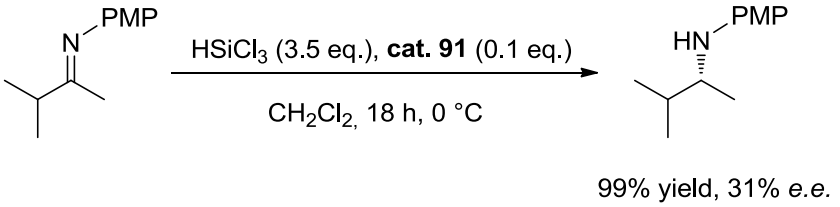
The temperature decrease allowed to achieve very high levels of enantioselectivity with both the catalysts, permitting to isolate the product in 94 and 92% *e.e.* respectively. However, like in the previous screening with catalyst **85**, chemical yields were subjected to a harsh drop when temperature was lowered.

We then proceeded to evaluate the scope of the reduction promoted by the best performing derivative **91**; both electron-rich and electron-deficient aryl ketimines, as well as one example of an aliphatic substrate, were tested (Table **7.1.18**, Scheme **7.1.9**):



entry	R	y (%)	*e.e.* (%)
1	4-Cl	99	*89*
2	4-Br	99	*88*
3	3-Br	67	*88*
4	4-OMe	/	/

Table 7.1.18 Screening of variously substituted ketimines



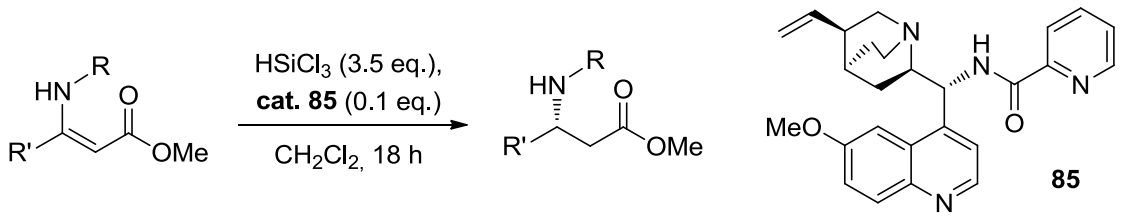
Scheme 7.1.9 Catalytic reduction of an aliphatic ketimine

As expected, aryl ketimines carrying electron withdrawing groups on various positions of the aromatic ring were reduced with very good results. On the other hand, the electronrich 4-OMe substituted aryl imine was completely unreactive. Also the stereoselective reduction of the aliphatic isopropyl methyl imine was unsatisfactory, yielding the product in quantitative yield but with only 31% enantiomeric excess.

7.2 Reduction of β-enaminoesters and α-iminoesters

As widely described in Chapter 3, trichlorosilane has also been used in the reduction of imines derived from α-keto esters, leading to the synthesis of natural and unnatural α-amino acids, and in the reduction of β-enamino esters. As already mentioned, the use of these substrates allows to synthesize some very attractive products, due to their high degree of functionalization. In fact, they can be exploited to gain access to a wide range of derivatives by subsequent synthetic transformations. For this reason we decided to test the efficiency of catalyst **85** also in the enantioselective reduction of these substrates.

β-enaminoesters were prepared in good yields according to the general procedure already described in Chapter 5. Then, their organocatalytic reduction was investigated, leading to the results summarized in Table **7.2.1**:

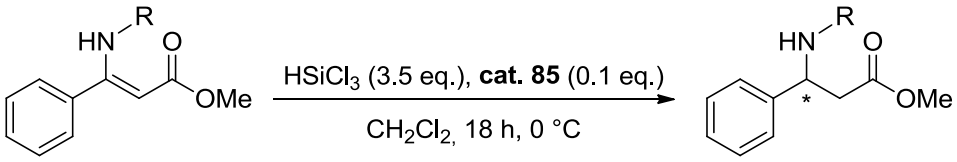


entry	R	R'	T (°C)	y (%)	*e.e.* (%)
1	PMP	Ph	0	86	*81*
2	PMP	4-MeC_6H_4	0	95	*83*
3	PMP	4-BrC_6H_4	0	97	*72*
4	PMP	4-$CF_3C_6H_4$	0	96	*70*
5	PMP	4-BrC_6H_4	-20	98	*81*
6	Ph	Bn	0	97	*rac*
7	Bn	Ph	-20	/	/

Table 7.2.1 Lewis base-catalyzed $HSiCl_3$-mediated reduction of β-enamino esters

All of the *N*-PMP protected products were obtained in yields ranging from high to quantitative, showing at the same time also a good level of enantioselectivity. A good tolerance for different electrowithdrawing and electrodonating substituents on the aryl ringwas observed. Generally it seems that electronrich β-iminoesters behave better than the electrondeficient substrates, yielding the products with higher enantiomeric excesses. Notably, a temperature decrease provided a significant improvement in enantioselectivity. As already observed in Chapter 5, the hydrosilylations of the benzyl derivatives seems to be more challenging: indeed, only traces of the desired product were observed. As expected, the hydrosilylation of the aliphatic substrate (Table **7.2.1**, entry 6) produced the β-aminoester with no stereocontrol. This is due to the very similar chemical environment around the imine moiety which does not allow to differentiate enough the enantiofaces of the substrate.

In the attempt of improving the selectivity of the process, we decided to employ again the approach of introducing a cheap chiral auxiliary at the imine nitrogen.[120] Therefore, the two β-enaminoesters carrying respectively (*R*)- and (*S*)-1-phenylethyl moiety as protecting group were synthesized and their trichlorosilane mediated reduction was subsequently studied (Table **7.2.2**):



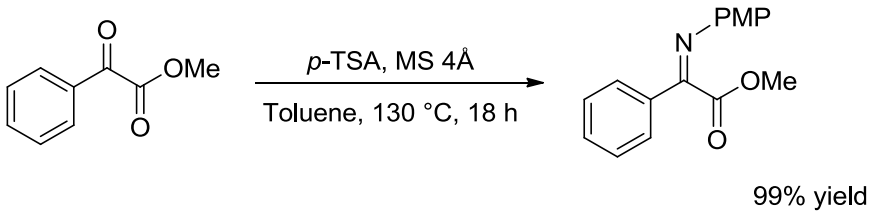
entry	R	y (%)	*e.e.* (%)
1	(*S*)-1-phenylethyl	19	*97* (*S*,*S*)
2	(*R*)-1-phenylethyl	98	*97* (*R*,*R*)

Table 7.2.2 Catalytic hydrosilylation of chiral β-enamino esters

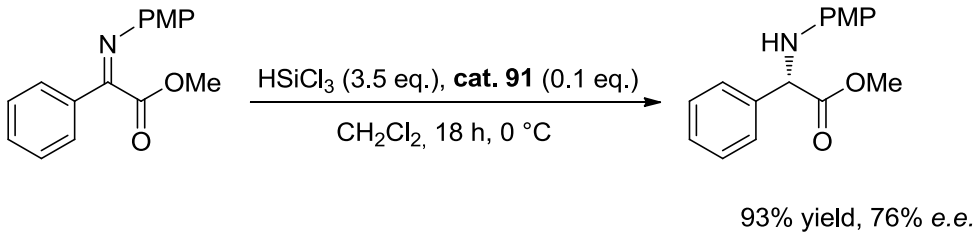
Surprisingly, the outcome of the reactions was rather different: substrate carrying (*R*)-1-phenylethyl group was reduced in quantitative yield and excellent stereoselectivity, while the reduction of β-enaminoester with the (*S*) chiral auxiliary afforded the corresponding aminoester with only 19% yield. This difference in chemical activity could point towards a different activation of the catalyst: in the case of the (*S*) substrate steric constraints could make the $HSiCl_3$ coordination with the picolinamidic site not productive; instead, a less effective activation by the other Lewis basic sites of the catalyst could take place.

Then we decided to test our methodology in the preparation of α-amino acids because very few successful examples are currently reported in literature. In fact, both in case of transition metal-catalyzed hydrogenations and in case of organocatalytic methodologies only a limited number of cyclic and acyclic α–imino esters were studied.

The model substrate was prepared in excellent yield following the synthetic strategy reported in Scheme **7.2.1**; then its reduction with activated trichlorosilane was studied (Scheme **7.2.2**):



Scheme 7.2.1 Synthesis of the *N*-PMP α–iminoester



Scheme 7.2.2 Catalytic reduction of the α–iminoester substrate

After 18 hours at 0 °C in dichloromethane, best performing catalysts **91** managed to promote the reduction of *N*-PMP α–iminoester in nearly quantitative yield with a good level of stereocontrol, achieving 76% enantiomeric excess (Scheme **7.2.2**).

In conclusion, the straightforward synthesis of a novel class of cinchona-based chiral Lewis bases was developed. A series of enantiomerically pure Lewis bases were obtained by performing a Mitsunobu reaction on the commercially available alkaloids followed by simple condensation with picolinic acid. Under the optimized reaction conditions, such compounds were shown to promote the enantioselective reduction of ketimines with trichlorosilane with nearly quantitative chemical yield and high enantioselectivity. Even more interestingly, these high levels of yields and enantioselectivity remained constant when the reaction was carried out with only a 1 mol % catalyst loading. Further modification of these compounds led to the even more efficient catalysts **91** and **94**: indeed, in the reduction of the model substrate *N*-phenyl acetophenone imine these derivatives led to the quantitative formation of the corresponding amine with up to 88% *e.e.*. These catalyst were successfully employed also in the organocatalytic reduction of α-imino and β-enamino esters with trichlorosilane, obtaining the corresponding products with high chemical yield and good enantiomeric excess. Moreover, the combination of low cost, easy to make metal-free catalyst **85** and an inexpensive chiral auxiliary allowed to obtain chiral β–amino esters with nearly total control of the stereoselectivity.

Outlook and Perspectives

"The aim of science is not to open the door to infinite wisdom, but to set a limit to infinite error."
Bertolt Brecht, Life of Galileo

Even if a large number of chiral molecules are currently in pipeline in pharmaceutical, flavor and agrochemical industries, their development and commercialization is not without problems. A key reason is the lack of general solutions to address chirality-related problems. In addition, development is mostly focused upon cost effectiveness, rather than on research and application of state-of-the-art technologies. However, enantioselective catalysis is rapidly becoming more and more popular also at the industrial level: examples come from technologies such as asymmetric hydrogenation. In fact, as chiral techniques develop over time, declining costs enable companies to access public-domain technologies. This is one of the factors that led to the increased activity in terms of academic and industrial investment that stereoselective catalysis lately witnessed. Moreover, the discovery and application in pharmaceutical synthesis of new processes and reactions make industries keen on further growth for the chiral technologies field. Furthermore, also the rising complexity of new chemical entities calls for the evolution of advanced chiral technology. In this general picture the advent of organocatalysis brought in new attractive possibilities, allowing to stereoselectively synthesize complex chiral molecules with metal-free processes. The enantioselective

organocatalytic methodologies described in the present thesis are good examples of the potentialities of metal-free catalytic reductions.

Cinchona-based picolinamides were shown to perform very well in the asymmetric reduction of ketimines with trichlorosilane, affording the desired products with nearly quantitative chemical yield and high enantioselectivity. The use of this new class of catalysts was also successfully extended to the synthesis of α- and β-amino esters, obtaining the corresponding products with high chemical yield and good enantiomeric excess; in addition, nearly total stereocontrol was achieved employing an inexpensive chiral auxiliary. The process in which a Lewis base activates a Lewis acid was found to be feasible also for the enantioselective organocatalytic reduction of fluorinated ketimines, yielding both aryl and alkyl trifluoromethyl amines in very good yields and up to 98% enantiomeric excess. Moreover, even if many problems still need to be tackled, some encouraging results were also obtained in the development of a more user-friendly methodology for the use of frustrated Lewis pairs and in the use of trichlorosilane as reducing agent for phosphoric acid catalyzed reductions.

These examples clearly show that organocatalysis can represent a valid alternative to metal-complex-mediated and enzymatic catalysis, and it is most likely that research in this field can open the way to many other options and possibilities. It is evident that this is only the beginning of the story: even if both pharmaceutical companies and fine chemicals supplier have been continuously investing in chiral technologies over the last years, the chiral market is still steadily growing and always calls for new stereoselective catalytic methodologies for the synthesis of chiral molecules. On the basis of these considerations it is easy to predict that we will see a continuously increasing interest in the field of stereoselective reactions promoted by chiral organocatalysts; hopefully this survey will stimulate further research in a very exciting area, where hypervalent silicate species will play a decisive role in the invention of new, highly chemically and stereochemically efficient catalytic systems of low environmental impact.

CHAPTER 8
Experimental section

"*No amount of experimentation can ever prove me right; a single experiment can prove me wrong.*"
Albert Einstein

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_{254} pre-coated glass plates (0.25 mm thickness) and visualized using UV light, phosphomolybdic acid or ninhydrin. 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 an AMX 300 Bruker, a BrukerAvance 500, aBruker Fourier 300, a Bruker AC 200 or AC 300 spectrometers. ^{1}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 ($CDCl_3$ δ = 7.26 ppm). The following abbreviations are used to describe spin multiplicity: s = singlet, d =

doublet, t = triplet, q = quartet, m = multiplet, br s = broad signal, dd = doublet of doublets. ^{13}C-NMR spectra were recorded on 300 MHz spectrometers (Bruker AMX 300 or Fourier 300) operating at 75 MHz, with complete proton decoupling. Carbon chemical shifts are reported in ppm (δ) relative to TMS with the respective solvent resonance as the internal standard ($CDCl_3$, δ = 77.0 ppm). ^{31}P-NMR spectra were recorded on 300 MHz spectrometers (Bruker AMX 300) operating at 121.4 MHz with complete proton decoupling. Phosphorus chemical shifts are reported in ppm (δ) and were referenced to phosphoric acid (H_3PO_4) at 0.0 ppm. ^{19}F-NMR spectra were recorded on 300 MHz spectrometers (Bruker AMX 300) operating at 282.1 MHz. Fluorine chemical shifts are reported in ppm (δ) and were referenced to trichlorofluoromethane ($CFCl_3$) at 0.0 ppm.

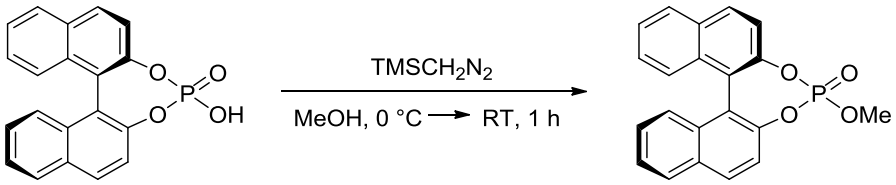
Optical rotations were obtained on a Perkin-Elmer 241 polarimeter at 589 nm using a 5 mL cell, with a length of 1 dm. IR spectra were obtained on a Jasco FT/IR-4100 type A instrument. Mass spectra were registeredon an APEX II &Xmass software (BrukerDaltonics) instrument or on a Thermo Finnigan LCQ Advantage instrument, equipped with an ESI ion source. HPLC analyses for *e.e.* determination were performed on an Agilent Instrument Series 1100 or on an Agilent Instrument Series 1200 on chiral stationary phase, under the conditions reported below. Microwave-accelerated reactions were performed with a CEM Discover class S instrument. Reaction mixtures were centrifuged with MPW-260 laboratory centrifuge at 4500 rpm for 7 minutes. Hydrogenation experiments were performed with a Parr 4871 series multiple reactor system.

Starting materials: (*R*)-1,1′-bis(2-naphthol), 2-picolinic acid, benzyl bromide, 2-(chloromethyl)-1,3,5-trimethylbenzene, 9-(chloromethyl)anthracene, methyl phenylglyoxylate, ketones (3-methyl-2-butanone, acetophenone, 4'-methoxy-acetophenone, 4'-nitro-acetophenone, 4'-trifluoromethyl-acetophenone, 4'-bromo-acetophenone, 3'-bromo-acetophenone, 4'-chloro-acetophenone,2,2,2-trifluoroacetophenone, 3'-methyl-2,2,2-trifluoroacetophenone, 4'-*N*,*N*-dimethylamino-2,2,2-trifluoroacetophenone, 4'-fluoro-2,2,2-trifluoroacetophenone, 4'-methyl-2,2,2-trifluoroacetophenone, 4'-methoxy-2,2,2-trifluoroacetophenone, 4'-chloro-2,2,2-trifluoroacetophenone, 4'-trifluoromethyl-2,2,2-trifluoroacetophenone, 1-cyclohexyl-2,2,2-trifluoro-ethanone, 1,1,1-trifluoro-2-butanone, 1,1,1-trifluoro-2-hexanone, 1,1,1-trifluoro-3-phenyl-2-propanone); amines (aniline, 4-methoxyaniline, benzylamine, 2-

methoxyaniline, 2-aminophenol,(*R*)-1-phenylethylamine, (*S*)-1-phenylethylamine, 1,4-diazabicyclo[2.2.2]octane (DABCO), quinine, quinidine, cinchonidine, cinchonine); aldehydes (benzaldehyde, 4-trifluoromethyl-benzaldehyde, 4-chloro-benzaldehyde, 4-nitro-benzaldehyde, 4-methoxy-benzaldehyde, 4-methyl-benzaldehyde, 1-naphthaldehyde, 2-furaldehyde, 2-thiophenecarbaldehyde, 3,4-dimethoxybenzaldehyde); phosphines (triphenylphosphine, tricyclohexylphosphine, tri-*tert*-butylphosphine) and phosphoric acids ((*R*)-1,1'-binaphthyl-2,2'-diyl hydrogenphosphate, (*R*)-3,3'-bis[3,5-bis(trifluoromethyl)phenyl]-1,1'-binaphthyl-2,2'-diyl hydrogenphosphate, (*R*)-3,3′-bis(triphenylsilyl)-1,1′-binaphthyl-2,2′-diyl hydrogenphosphate, (*R*)-2,2′-diphenyl-3,3′-biphenanthryl-4,4′-diyl phosphate) were obtained commercially. Commercially available $HSiCl_3$ and $SiCl_4$ were freshly distilled before use. Commercially available $B(C_6F_{5)3}$ was sublimated before use.

8.1 Synthesis of catalysts

*Preparation of compound **82**:*



	eq	mmol	MW (g/mol)	mg	d (g/mL)	mL
(*R*)-1,1'-binaphthyl -2,2'-diyl hydrogen phosphate	1.0	0.58	348.29	201.0	/	/
Trimethylsilyldiazo methane 2M in hexane	32.8	19.0				9.5
MeOH (dry)						10.0

To a solution of (*R*)-BINOL-derived phosphoric acid in dry MeOH, trimethylsilyldiazo methane solution was added dropwise at 0 °C (allowing nitrogen venting) until a persistent yellow coloration was reached. Once completed the addition, the reaction mixture was allowed to warm to room temperature and monitored with TLC using 8:2 hexane/ethyl acetate as eluent. The reaction was then quenched by the addition of few drops of glacial acetic acid and the solvent was removed by rotary evaporation. The residue was dissolved in DCM, washed with a saturated solution of $NaHCO_3$, dried over Na_2SO_4 and the solvent was removed by rotary evaporation. The desired product was purified by flash column chromatography on silica gel with a 1:1 hexane/ethyl acetate mixture as eluent. The purification afforded the desired product in 96% yield.

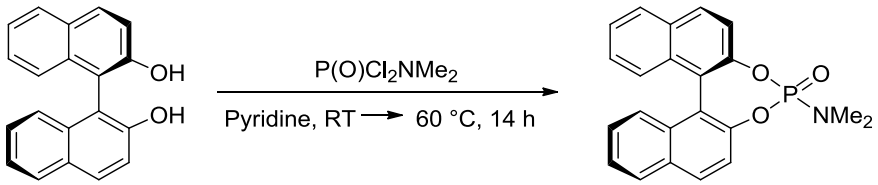
R_f = 0.28 (1:1 hexane/ethyl acetate).

^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.05-8.00 (m, 2H), 7.95-7.92 (m, 2H), 7.63-7.60 (m, 1H), 7.50-7.44 (m, 3H), 7.39-7.25 (m, 4H), 3.98 (d, J = 9 Hz, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ 147.47, 147.32, 146.30, 146.20, 132.26, 131.89, 131.66, 131.54, 131.24, 128.54, 128.47, 127.17, 127.00, 126.88, 126.83, 125.86, 121.40, 121.22, 120.58, 120.09, 55.91.

^{31}P-NMR (121 MHz, $CDCl_3$): δ 5.09.

*Preparation of compound **83**:*



	eq	mmol	MW (g/mol)	mg	d (g/mL)	mL
(*R*)-BINOL	1.0	2.66	286.32	762.8	/	/
N,*N*'-dimethyl phosphoramic dichloride	3.0	7.98	161.95	1292.4	1.362	0.95
Pyridine						6.0

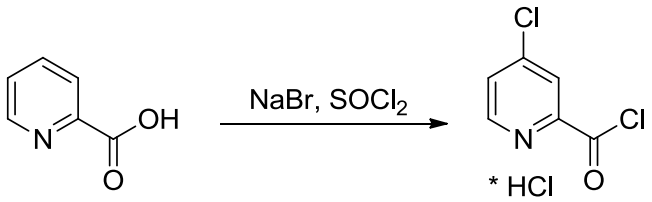
To a solution of (*R*)-BINOL in pyridine, dimethyl phosphoramic dichloride was added dropwise at room temperature; then, the reaction mixture was heated to 60 °C and stirred at this temperature for 12 h. After this period the reaction was quenched by the addition of H_2O (6 mL) and the resulting biphasic system was stirred for 2 h at 50 °C. The reaction mixture was then diluted with CH_2Cl_2,washed with 1N HCl, dried over Na_2SO_4 and the solvent was removed by rotary evaporation. The desired product was purified by flash column chromatography on silica gel with a 98:2 DCM/MeOH mixture as eluent. The purification afforded the desired product in 72% yield.

R_f = 0.73 (9:1 DCM/MeOH).

^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.03-7.91 (m, 4H), 7.63-7.60 (m, 1H), 7.52-7.49 (m, 1H), 7.46-7.41 (m, 3H), 7.33-7.20 (m, 3H), 2.63 (d, J = 12 Hz, 6H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ 148.39, 148.25, 146.89, 146.77, 132.37, 132.30, 131.76, 131.37, 131.27, 130.95, 128.49, 127.19, 126.95, 126.83, 126.63, 125.72, 125.63, 121.37, 121.15, 120.89, 37.49.
^{31}P-NMR (121 MHz, $CDCl_3$): δ 15.47.

*<u>Preparation of catalyst **40**:</u>*

Step 1

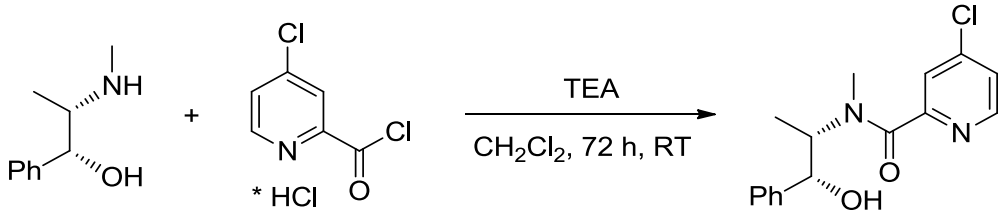


	eq	**mmol**	**MW (g/mol)**	**mg**	**d (g/mL)**	**mL**
picolinic acid	1.0	8.12	123.11	1000.0	/	/
thionyl chloride	13.7	111.52	118.97	13267.8	1.638	8.1
NaBr	2.0	16.24	102.90	1671.1	/	/

A mixture of picolinic acid, NaBr and $SOCl_2$ 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.

^{1}H NMR (300 MHz, *d*6-DMSO) δ: 8.71 (dd, 1H), 8.00 (dd, 1H), 7.82 (dd, 1H).

Step 2



	eq	**mmol**	**MW (g/mol)**	**mg**	**d (g/mL)**	**mL**
(1*R*,2*S*)-ephedrine	1.0	7.06	165.23	1166.5	/	/
4-Cl picolinoyl chloride	1.0	7.06	212.46	1500.0	/	/
TEA (dry)	1.2	8.47	101.19	857.0	0.726	1.2
THF (dry)						20.0

Triethylamine and a solution of 4-Cl picolinoyl chloride hydrochloride in dry CH_2Cl_2 were added to a solution of ephedrine in dry CH_2Cl_2 and the solution was stirred for 72 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 $MgSO_4$, concentrated on a rotary evaporator and purified by silica gel flash chromatography with a 98:2, 95:5 and 9:1 DCM/MeOH mixture as eluent. The purification afforded the desired product in 30% yield.

R_f = 0.59 (9:1 DCM/MeOH).

Data for *rotamer 1*:

^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.32 (m, 1H), 7.25 (m, 3H), 7.23 (m, 1H), 7.08 (d, J = 6 Hz, 2H), 6.48 (s br, 1H), 4.63 (d, J = 4 Hz, 1H), 4.08 (m, 1H), 2.86 (s, 3H), 1.31 (d, J = 7 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 167.9, 155.4, 148.3, 144.9, 141.7, 128, 127.6, 126.1, 124.3, 124.1, 75.2, 58.8, 28.8, 14.2.

Data for *rotamer 2*:

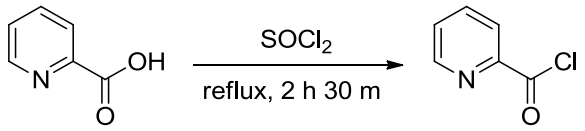
^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.30 (m, 1H), 7.4 (m, 2H), 7.3 (m, 3H), 7.25 (m, 1H), 7.23 (m, 1H), 5.0 (m, 1H), 4.55 (m, 1H), 2.80 (s, 3H), 1.25 (d, J = 7 Hz, 3H).

^{13}C NMR (75 MHz, CDCl3): δ 168.1, 155.8, 149.1, 145, 141.8, 128.0, 127.3, 126.1, 124.3, 123.3, 75.9, 57.6, 34.2, 11.1.

$[\alpha]_D^{25}$ = -36.06 (solvent: DCM; *c* = 0.244 g/100 mL; λ = 589 nm).

HRMS Mass (ESI+): m/z = calc. for $C_{16}H_{17}ClN_2O_2Na^+$ = 327.09, found 327.09 [M + Na].

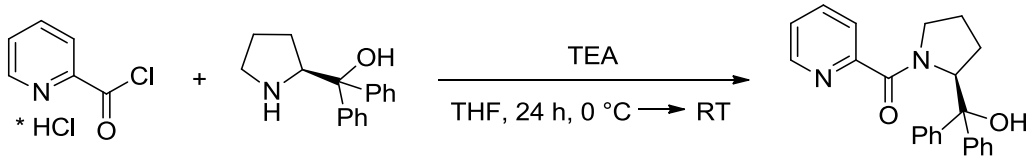
Preparation of picolinoyl chloride:



	eq	**mmol**	**MW (g/mol)**	**mg**	**d (g/mL)**	**mL**
Picolinic acid	1.0	0.89	123.11	110.0	/	/
Thionyl chloride	7.0	6.23	118.97	741.2	1.631	0.45

In a two necked flask equipped with magnetic stirrer the thionyl chloride was added to the picolinic acid; the solution was heated to 79 °C and stirred at that temperature for 2h 30 min. Then the reaction was allowed to cool to room temperature and the residual thionyl chloride was removed under high flux of nitrogen; finally, the resulting solid was dried under vacuum for 2 min. The desired product was obtained in quantitative yield, with sufficient purity for being employed in the subsequent reaction without further purification.

*Preparation of catalyst **37**:*



	eq	**mmol**	**MW (g/mol)**	**mg**	**d (g/mL)**	**mL**
picolinoyl chloride	1.2	4.06	141.56	574.7	/	/
(*S*)-α,α-diphenyl-2-pyrrolidinyl methanol	1.0	3.38	253.34	856.3	/	/
TEA (dry)	1.2	4.06	101.19	410.8	0.726	0.57
THF (dry)						25.0

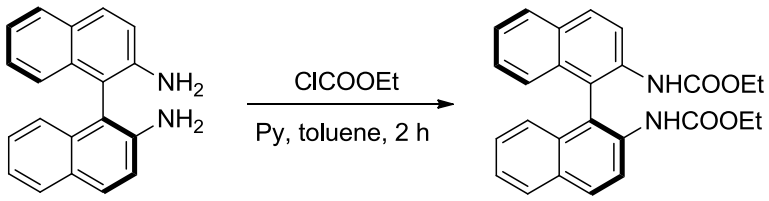
To a solution of substrate and TEA in dry THF a solution of picolinoyl chloride in THF was slowly added dropwise at 0 °C. The mixture was stirred for 24 hours at room temperature and then concentrated in vacuum. The desired product was purified by flash column chromatography on silica gel with a 7:3 hexane/ethyl acetate mixture as eluent. The purification afforded the desired product in 70% yield as a white solid.

R_f = 0.32 (2:8 hexane/ethyl acetate).

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 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 **57'**:*

Step 1



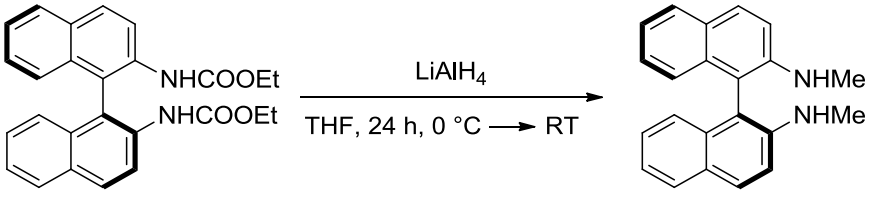
	eq	**mmol**	**MW (g/mol)**	**mg**	**d (g/mL)**	**mL**
(*R*)-1,1'-binaphtyl-2,2'-diamine	1.0	1.76	284.12	500.0	/	/
ethyl chloroformate	2.6	4.61	108.52	500.3	1.135	0.44
pyridine	8.7	15.31	79.10	1211.0	0.981	1.2
toluene						6.0

(*R*)-1,1'-binaphtyl-2,2'-diamine was dissolved in toluene and pyridine and cooled to 0 °C. A solution of ethyl chloroformate in toluene 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 2N 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_2SO_4 and the solvent was removed by rotary evaporation. After drying, a pale pink powder was obtained in quantitative yield, with sufficient purity for being employed in the subsequent reaction.

R_f = 0.76 (7:3 hexane/ethyl acetate).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.57 (d, J = 9 Hz, 2H), 8.08 (d, J = 9 Hz, 2H), 7.94 (d, J = 8 Hz, 2H), 7.46-7.41 (m, 2H), 7.30-7.24 (m, 2H), 6.98 (d, J = 8 Hz, 2H), 6.28 (br s, 2H), 4.1 (q, J = 7 Hz, 4H), 1.18 (t, J = 7 Hz, 6H).

Step 2



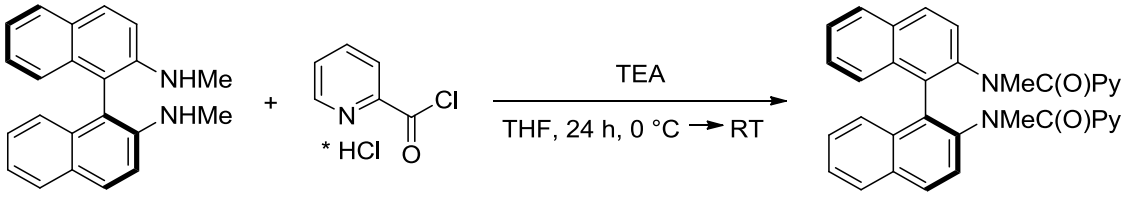
	eq	**mmol**	**MW (g/mol)**	**mg**	**d (g/mL)**	**mL**
(*R*)-binaphthyl diyldicarbamate	1.0	1.75	428.48	749.8	/	/
$LiAlH_4$	6.3	11.03	37.95	418.6	/	/
THF (dry)						10.0

$LiAlH_4$ was suspended in dry THF and cooled to 0 °C. The substrate dissolved in dry THF was then slowly added *via* dropping funnel; subsequently the mixture was warmed and refluxed for 24 h. The reaction was followed by TLC using 8:2 hexane/ethyl acetate as eluent. After cooling to room temperature, excess $LiAlH_4$ 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. The desired product was purified by flash column chromatography on silica gel with a 8:2 hexane/ethyl acetate mixture as eluent. The purification afforded the desired product in 83% yield.

R_f = 0.67 (8:2 hexane/ethyl acetate).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.93 (d, J = 9 Hz, 2H), 7.84-7.79 (m, 2H), 7.27 (d, J = 9 Hz, 2H), 7.23-7.14 (m, 4H), 7.00-6.96 (m, 2H), 2.84 (s, 6H).

Step 3



	eq	mmol	MW (g/mol)	mg	d (g/mL)	mL
(*R*)-*N*,*N*'-dimethyl-1,1'-binaphtyl-2,2'-diamine	1.0	0.56	312.16	174.8	/	/
picolinoyl chloride	4.0	2.24	141.57	317.1	/	/
TEA (dry)	16.0	8.96	101.19	906.7	0.726	1.25
THF (dry)						10.0

To a solution of substrate and TEA in dry THF a solution of picolinoyl chloride in dry THF was slowly added dropwise at 0 °C. The mixture was stirred for 24 hours at RT and then concentrated in vacuum. The desired product was purified by flash column chromatography on silica gel with a 98:2 DCM/MeOH mixture as eluent. The purification afforded the desired product in 42% yield.

R_f = 0.05 (98:2 DCM/methanol).

Data for *rotamer 1*:

^{1}H-NMR (500 MHz, *d*6-DMSO) δ: 8.57 (s, J = 3 Hz, 1H), 7.94 (d, J = 8 Hz, 2H), 7.80 (d, 1H), 7.78 (d, 2H), 7.5 (m, 2H), 7.43 (d, J = 7 Hz, 2H), 7.38 (m, 1H), 7.33 (m, 2H), 7.26 (m, 1H), 7.15 (t, J = 8 Hz, 2H), 7.06 (d, J = 9 Hz, 2H), 6.9 (d, J = 9 Hz, 2H), 2.9 (s, 3H), 2.75 (s, 3H).

^{13}C-NMR (125 MHz, d*6*-DMSO) δ: 169.8, 154.8, 148.4, 143.1, 137.3, 136.5, 134.5, 131.8, 129.6, 128.8, 128.3, 128.1, 127.2, 126.5, 125.0, 123.5, 36.9, 36.5.

Data for *rotamer 2*:

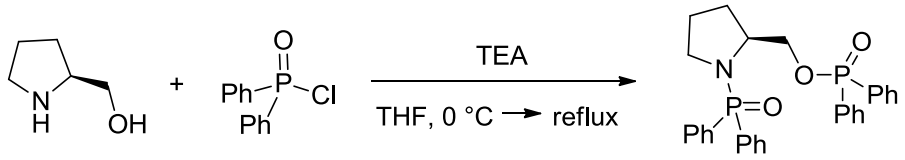
^{1}H-NMR (500 MHz, *d*6-DMSO) δ: 8.2 (d, J = 4 Hz, 1H), 7.94 (d, J = 8 Hz, 2H), 7.78 (d, J = 9 Hz, 1H), 7.73 (d, J = 9 Hz, 2H), 7.5 (m, 2H), 7.43 (d, J = 7 Hz, 2H), 7.33 (m, 2H), 7.26 (m, 2H), 7.15 (t, J = 8 Hz, 2H), 6.95 (d, J = 9 Hz, 2H), 6.85 (d, J = 9 Hz, 2H), 2.9 (s, 3H), 2.75 (s, 3H).

^{13}C NMR (125 MHz, *d*6-DMSO) δ: 169.4, 154.8, 148.6, 142.9, 137.6, 136.5, 134.3, 131.5, 129.5, 128.7, 128.3, 128.1, 127.2, 126.5, 125.0, 123.5, 36.9, 36.5.

$[\alpha]_D^{25}$ = + 413.9 (solvent: DCM; *c* = 0.244 g/100 mL; λ = 589 nm).

HRMS Mass (ESI+): m/z = calc. for $C_{34}H_{26}N_4O_2^+$ = 523.21, found 523.21 [M + H].

*Preparation of catalyst **43**:*



	eq	mmol	MW (g/mol)	mg	d (g/mL)	mL
(*S*)-prolinol	1.0	2.50	101.15	252.9	1.025	0.25
diphenylphosphinyl chloride	3.0	7.50	236.64	1774.8	1.240	1.43
TEA (dry)	3.0	7.50	101.19	758.9	0.726	1.03
THF (dry)						5.0

To a solution of the substrate in dry THF 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 $NaHCO_3$ s.s. was added. The organic layer was separated and the aqueous layer was washed with DCM (3×10 mL). The combined organic solution was dried over Na_2SO_4, filtered and the solvent was evaporated. The desired product was purified by flash column chromatography on silica gel with a 98:2 DCM/MeOH mixture as eluent. The purification afforded the desired product in 60% yield.

^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.92-7.71 (m, 10H), 7.54-7.33 (m, 10H), 4.01-3.80 (m, 1H), 3.78-3.76 (m, 2H), 3.13-3.09 (m, 2H), 2.08-2.05 (m,2H), 1.87-1.85 (m, 2H).

^{13}C-NMR (125 MHz, $CDCl_3$) δ: 132.0, 131.7, 131.5, 131.4, 131.0, 129.0, 127.9, 127.8, 66.0, 58.0, 48.0, 29.0, 25.0.

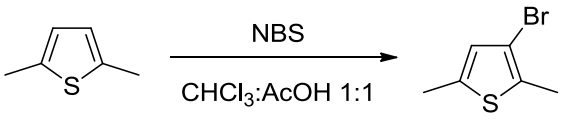
^{31}P-NMR (202 MHz, $CDCl_3$) δ: 31.9, 27.3.

$[\alpha]_D^{25}$ = + 6.3 (solvent: $CHCl_3$; *c* = 0.382 g/100 mL; λ = 589 nm).

HRMS Mass (ESI+): m/z = calc. for $C_{29}H_{29}NO_3P_2Na^+$ = 524.15, found 524.15 [M + Na].

*Preparation of catalyst **74**:*[212]

Step 1



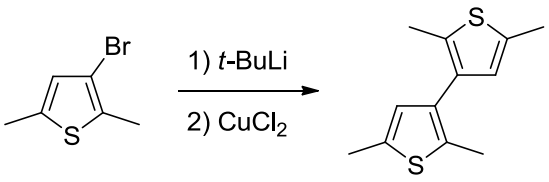
	eq	mmol	MW (g/mol)	mg	d (g/mL)	mL
2,5-dimethyl thiophene	1.0	17.84	112.11	2000.0	0.980	2.03
NBS	1.0	17.84	177.98	3175.1	/	/
hydroquinone	0.002	0.036	110.11	3.9	/	/
$CHCl_3$						17.5
AcOH						17.5

2,5-dimethylthiophene was dissolved in a 1:1 mixture of $CHCl_3$:AcOH and cooled to 0 °C, then hydroquinone and a recent crystallized NBS were added. The mixture was stirred at 0 °C for 1 h, then was warmed to room temperature and stirred for 2 h. The reaction, followed by TLC using 9:1 hexane/ethyl acetate as eluent, was quenched by the addition of H_2O (10 mL) and diluted with DCM (15 mL). The organic layer was separated, and washed with a saturated solution of $NaHCO_3$ (10 mL) and water (10 mL), dried over Na_2SO_4 and the solvent was removed by rotary evaporation. After drying, a brown oil was obtained in 96% yield, that was employed in the next step without further purification.

R_f = 0.65 (9:1 hexane/ethyl acetate).

^{1}H-NMR (200 MHz, $CDCl_3$): δ 6.53 (s, 1H), 2.40 (s, 3H), 2.29 (s, 3H).

Step 2



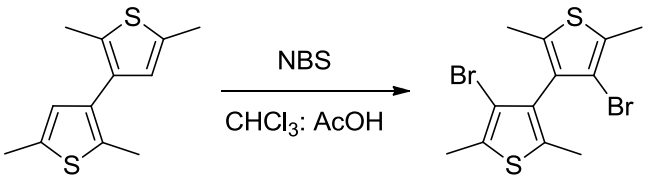
	eq	**mmol**	**MW (g/mol)**	**mg**	**d (g/mL)**	**mL**
2,5-dimethyl-3-Br thiophene	1.0	10.47	191.09	2000.0	/	/
t-BuLi 1.5M	2.1	21.98				14.6
$CuCl_2$	1.0	10.47	134.45	1407.19	/	/
Et_2O (dry)						10.0

A solution of the substrate in dry Et_2O was added dropwise to a solution of *t*-butyl lithium cooled to -30 °C under nitrogen atmosphere. After 30 min, the mixture was cooled to -60 °C and $CuCl_2$ was added. The mixture was stirred for 4 h at -60 °C, then it was allowed to warm to room temperature. After this time, a solution of 5% HCl was added (20 mL). The organic layer was separated and the aqueous layer was extracted with DCM (2 × 15 mL). The organic layers were then washed with H_2O (10 mL), a saturated solution of $NaHCO_3$ (10 mL) and H_2O (10 mL), dried over Na_2SO_4 and the solvent was removed by rotary evaporation. The desired product was purified by flash column chromatography using VersaFlash Station and VersaPak cartridge (40x75 mm, Supelco, eluent: hexane). The purification afforded the desired product in 77% yield.

R_f = 0.73 (hexane).

^{1}H-NMR (200 MHz, $CDCl_3$): δ 6.52 (s, 2H), 2.41 (s, 6H), 2.27 (s, 6H).

Step 3

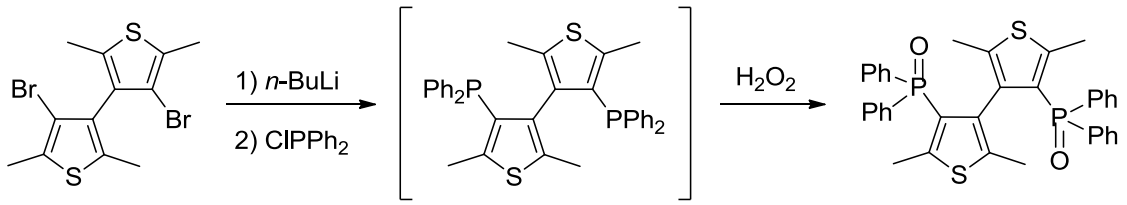


	eq	**mmol**	**MW (g/mol)**	**mg**	**d (g/mL)**	**mL**
tetramethyl bisthiophene	1.0	2.25	222.37	500.0	/	/
NBS	1.0	2.25	177.98	400.2	/	/
hydroquinone	0.002	0.004	110.11	0.5	/	/
$CHCl_3$						10.0
AcOH						10.0

The synthetic procedure is identical to that reported at the step 1.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.40 (s, 6H), 2.15 (s, 6H).

Step 4



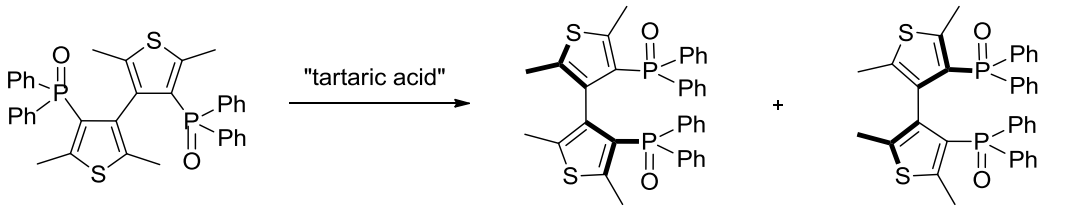
	eq	mmol	MW (g/mol)	mg	d (g/mL)	mL
dibromotetramethyl bisthiophene	1.0	3.03	380.16	1150.0	/	/
n-BuLi 1.6M	2.0	6.05				3.78
Ph_2PCl	2.0	6.05	220.64	1334.9	1.230	1.09
THF (dry)						30.0

A solution of the substrate in dry THF at -60 °C under nitrogen atmosphere was dropped into a solution of *n*-BuLi in dry THF. The mixture was allowed to warm to -30 °C; then, after 20 min of stirring, a solution of diphenylphosphin chloride in THF was added dropwise in 15 min using a syringe pump. After 1 h, the mixture was allowed to warm to room temperature and stirred for an additional of 18 h. After this time, the mixture was concentrated under reduced pressure and the residue was treated with water (20 mL) and extracted with DCM (10 mL). The organic layer was treated with H_2O_2 (10 mL, 35%) at 0 °C. The mixture was stirred for 1 h at 0 °C, for 1 h at RT and finally diluted with water. The organic layer was separated, dried over Na_2SO_4 and the solvent was removed by rotary evaporation. The desired product was purified by flash column chromatography on silica gel with a 7:3:0.1 DCM/ethyl acetate/TEA mixture as eluent. The purification afforded the desired product in 85% yield.

R_f = 0.75 (95:5 ethyl acetate/isopropyl alcohol).

^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.60 (m, 20H), 1.95 (d, 6H), 1.65 (s, 6H).
^{31}P-NMR (121 MHz, $CDCl_3$): δ 21.19.

Step 5



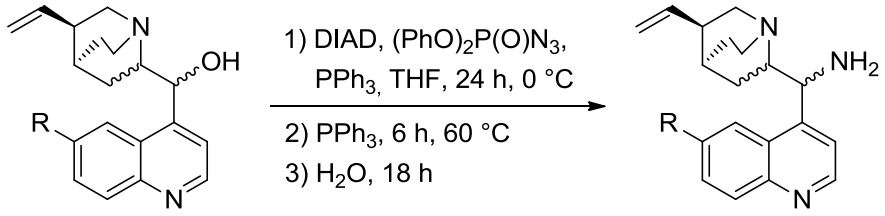
	eq	mmol	MW (g/mol)	mg	d (g/mL)	mL
rac-TetraMe-BITIOPO	1.0	3.21	622.72	2000.0	/	/
2,3-*O*,*O*'-dibenzoyl tartaric acid	1.0	3.37	376.31	1269.0	/	/
THF (dry)						15.0

A racemic mixture of TetraMe-BITIOPO and monohydrate (-)-DBTA was dissolved in THF, refluxed for a few minutes, and allowed to stand at room temperature for 24 h. An adduct between (+)-TetraMe-BITIOPO and (-)-DBTA was collected, and the filtrate was stored for recovery of (-)-TetraMe-BITIOPO. The adduct was dissolved into warm THF (30 mL) and a pure adduct was collected after standing for 10 days. The adduct was treated with NaOH solution, and the mixture was extracted exhaustively with DCM. The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to give a solid that was recrystallized from a hexane/benzene 1:1 mixture to give (+)-TetraMe-BITIOPO. The mother liquors from the first resolution step were concentrated to dryness to give a solid that was treated with a 0.75N NaOH solution and extracted with DCM. The organic layer was washed with water, dried over Na_2SO_4 and concentrated *in vacuo* to give (-)-TetraMe-BITIOPO, which was recrystallized from a mixture of hexane/benzene 1:1.

(+)-TetraMe-BITIOPO: $[\alpha]_D^{25}$ = +62.0 (solvent: benzene; *c* = 0.490 g/100 mL; λ = 589 nm).

(-)-TetraMe-BITIOPO: $[\alpha]_D^{25}$ = -62.0 (solvent: benzene; *c* = 0.490 g/100 mL; λ = 589 nm).

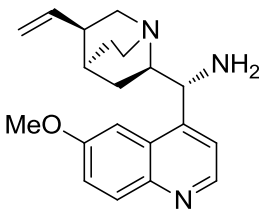
Preparation of 9-amino-epi-cinchona derivatives:



R = OMe, H

General procedure: Cinchona alkaloid (6.2 mmol, 1.0 eq) and triphenylphosphine (7.4 mmol, 1.2 eq) were dissolved in dry THF (43 mL); then the resulting solution was cooled to 0 °C stirred for 10 min. Subsequently the DIAD (7.4 mmol, 1.2 eq) was added dropwise, followed by the slow addition of the solution of $(PhO)_2P(O)N_3$ (7.4 mmol, 1.2 eq, 0.57 M solution in dry THF). Then the mixture was allowed to warm to room temperature and stirred for 24 h. The solution was then heated to 60 °C for 3 h; after this time, triphenylphosphine (7.4 mmol, 1.2 eq) was added as 0.46 M solution in dry THF. Then the reaction was stirred at 50 °C for 3 h, cooled to room temperature and 700 μL of distilled H_2O were added; finally, the reaction mixture was stirred for further 18 h. Then the solvent was removed under reduced pressure and 40 mL of CH_2Cl_2 and 40 mL of HCl 10% were added to the dried crude product. The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 30 mL). The acqueous layer was then basified until pH = 12 with NH_4OH 30-33% and subsequently extracted with CH_2Cl_2 (3 x 30 mL). The combined organic solution was dried over dry Na_2SO_4, filtered and the solvent was removed under reduced pressure. Purification methods for each product are reported below.

9-amino-epi-quinidine:[213,214]



This product was purified by flash column chromatography on silica gel with a 49.5:49.5:1 ethyl acetate/MeOH/NH_4OH 30-33% mixture as eluent. The purification afforded the desired product in 57% yield.

R_f = 0.41 (49.5:49.5:1 ethyl acetate/MeOH/NH_4OH 30-33%).

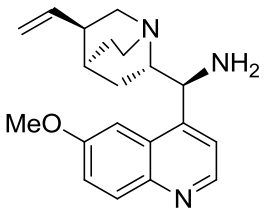
^1H NMR (300 MHz, $CDCl_3$) δ: 8.72 (d, J = 5 Hz, 1H), 8.00 (d, J = 9 Hz, 1H), 7.60 (br s, 1H), 7.50 (br s, 1H), 7.34 (dd, J = 9 Hz, 3 Hz, 1H), 5.86 (ddd, J = 17 Hz, 11 Hz, 6 Hz, 1H), 5.07-5.01 (m, 2H), 4.64 (d, J = 9 Hz, 1H), 3.94 (s, 3H), 3.04-2.88 (m, 5H), 2.24 (br s, 1H), 2.02 (s, 2H), 1.60-1.56 (m, 1H), 1.54-1.48 (m, 2H), 1.11 (dd, J = 13 Hz, 9 Hz, 1H), 0.96-0.88 (m, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 157.6, 147.8, 147.5, 144.7, 140.7, 131.8, 128.7, 121.6, 119.9, 114.4, 101.4, 62.4, 55.4, 51.6, 49.5, 47.4, 39.4, 27.6, 26.7, 25.0.

$[\alpha]_D^{20}$ = +79.6 (solvent: $CHCl_3$; *c* = 1.05 g/100 mL; λ = 589 nm).

HRMS Mass (ESI+): m/z = calc. for $C_{20}H_{26}N_3O^+$ = 324.21, found 324.21 [M + H].

9-amino-epi-quinine:[213,215]



This product was purified by flash column chromatography on silica gel with a 49.5:49.5:1 ethyl acetate/MeOH/NH_4OH 30-33% mixture as eluent. The purification afforded the desired product in 87% yield.

R_f = 0.14 (49.5:49.5:1 ethyl acetate/MeOH/NH_4OH 30-33%).

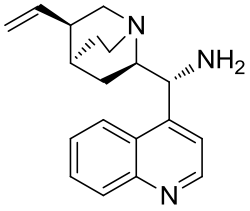
^1H NMR (300 MHz, $CDCl_3$) δ: 8.73 (d, J = 4 Hz, 1H), 8.01 (d, J = 9 Hz, 1H), 7.64 (s, 1H), 7.43 (d, J = 4 Hz, 1H), 7.36 (dd, J = 9 Hz, 3 Hz, 1H), 5.78 (ddd, J = 17 Hz, 10 Hz, 7 Hz, 1H), 5.00-4.93 (m, 2H), 4.57 (d, J = 10 Hz, 1H), 3.94 (s, 3H), 3.26 (dd, J = 14 Hz, 10 Hz, 1H), 3.21-3.15 (m, 1H), 3.11-3.02 (m, 1H), 2.82-2.75 (m, 2H), 2.30-2.23 (m, 1H), 1.94 (br s, 2H), 1.62-1.58 (m, 1H), 1.57-1.50 (m, 2H), 1.45-1.36 (m, 1H), 0.75 (ddt, J = 14 Hz, 8 Hz, 2 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 157.6, 147.8, 147.0, 144.7, 141.7, 131.8, 128.7, 121.2, 119.9, 114.3, 102.0, 61.9, 56.3, 55.5, 52.5, 40.9, 39.8, 28.2, 27.5, 26.0.

$[\alpha]_D^{28}$ = +107.4 (solvent: $CHCl_3$; *c* = 0.220 g/100 mL; λ = 589 nm).

HRMS Mass (ESI+): m/z = calc. for $C_{20}H_{26}N_3O^+$ = 324.21, found: 324.21 [M + H].

9-amino-epi-cinchonine:[215]



This product was purified by flash column chromatography on silica gel with a 49.5:49.5:1 ethyl acetate/MeOH/NH_4OH 30-33% mixture as eluent. The purification afforded the desired product in 77% yield.

R_f = 0.17 (49.5:49.5:1 ethyl acetate/MeOH/NH_4OH 30-33%).

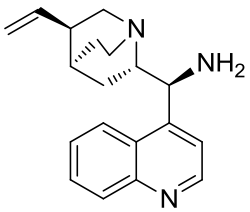
^1H NMR (300 MHz, $CDCl_3$) δ: 8.85 (d, J = 4 Hz, 1H), 8.29 (d, J = 6 Hz, 1H), 8.09 (d, J = 8 Hz, 1H), 7.67 (t, J = 8 Hz, 1H), 7.54 (t, J = 8 Hz, 2H), 5.84-5.76 (m, 1H), 5.06-5.01 (m, 2H), 4.74 (d, J = 7 Hz, 1H), 3.86 (br s, 2H), 3.05-2.90 (m, 5H), 2.25 (dd, J = 16 Hz, 8 Hz, 1H), 1.56-1.49 (m, 3H), 1.10-1.05 (m, 1H), 0.94-0.89 (m, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 150.3, 148.8, 148.5, 140.3, 130.4, 129.1, 127.7, 126.5, 123.3, 119.7, 114.8, 62.3, 49.3, 47.1, 39.4, 27.6, 26.4, 24.9, 22.6.

$[\alpha]_D^{28}$= +74.8 (solvent: $CHCl_3$; *c* = 0.250 g/100 mL; λ = 589 nm).

HRMS Mass (ESI+): m/z = calc. for $C_{19}H_{24}N_3^+$ = 294.19, found 294.19 [M + H].

9-amino-epi-cinchonidine:[213]



This product was purified by flash column chromatography on silica gel with a 49.5:49.5:1 ethyl acetate/MeOH/NH_4OH 30-33% mixture as eluent. The purification afforded the desired product in 86% yield.

R_f = 0.54 (49.5:49.5:1 ethyl acetate/MeOH/NH_4OH 30-33%).

^1H NMR (300 MHz, $CDCl_3$) δ: 8.87 (d, J = 5 Hz, 1H), 8.33 (br s, 1H), 8.11 (dd, J = 9 Hz, 1 Hz, 1H), 7.68 (ddd, J = 8 Hz, 7 Hz, 2 Hz, 1H), 7.56 (ddd, J = 8 Hz, 7 Hz, 1 Hz, 1H), 7.49 (d, J = 4 Hz, 1H), 5.77 (ddd, J = 17 Hz, 10 Hz, 7 Hz, 1H), 4.99-4.91 (m, 2H), 4.67

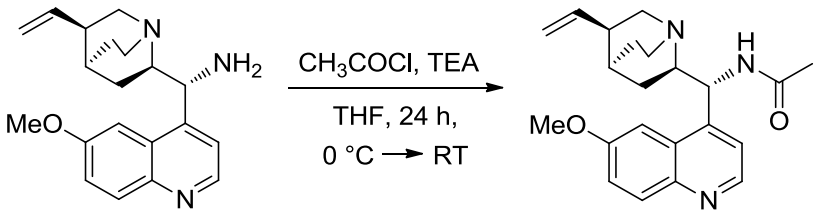
(d, J = 9, 1H), 3.24 (dd, J = 14 Hz, 10 Hz, 1H), 3.20-3.13 (m, 1H), 3.04 (br s, 1H), 2.81-2.73 (m, 2H), 2.27-2.21 (m, 1H), 2.01 (s, 2H), 1.59-1.50 (m, 3H), 1.38 (t, J = 12 Hz, 1H), 0.71 (ddt, J = 14 Hz, 8 Hz, 2 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 150.3, 148.7, 148.6, 141.8, 130.4, 128.9, 127.8, 126.4, 123.3, 119.6, 114.2, 61.9, 56.3, 51.8, 40.9, 39.8, 28.1, 27.5, 26.0.

$[\alpha]_D^{25}$ = +89.6 (solvent: $CHCl_3$; *c* = 0.220 g/100 mL; λ = 589 nm).

HRMS Mass (ESI+): m/z = calc. for $C_{19}H_{24}N_3^+$ = 294.20, found 294.20 [M + H].

*Preparation of catalyst **89**:*



	eq	mmol	MW (g/mol)	mg	d (g/mL)	mL
9-amino-*epi*-quinidine	1.0	0.77	323.43	250.0	/	/
acetyl chloride	1.2	0.93	78.50	73.0	1.104	0.066
TEA (dry)	1.2	0.93	101.19	93.9	0.726	0.130
THF (dry)						10.0

In a two necked flask the acetyl chloride was dissolved in part of the solvent; then the resulting solution was cooled to 0 °C and the triethylamine was added. Subsequenly, the solution of 9-amino-epi-quinidine in dry THF was added dropwise and the reaction was warmed to room temperature and stirred for 24 h. After this time the reaction was quenched with $NaHCO_3$ s.s. (3 mL) and the organic solvent was removed under reduced pressure. Then CH_2Cl_2 (10 mL) was added and the organic layer was separated; next the aqueous layer was extracted with CH_2Cl_2 (5 x 10 mL). The combined organic solution was dried over dry Na_2SO_4, filtered and the solvent was removed under reduced pressure. The desired product was obtained, in quantitative yield, with sufficient purity for being employed without further purification.

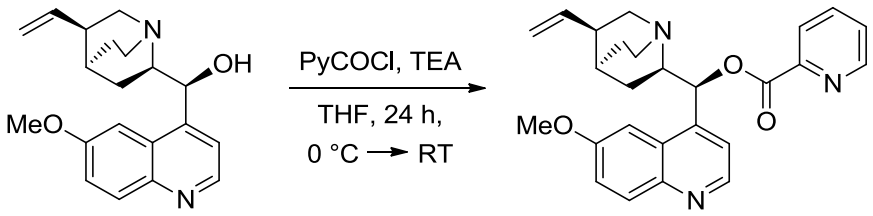
R_f = 0.80 (9:1 DCM/MeOH).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.63 (d, J = 4 Hz, 1H), 7.93 (d, J = 9 Hz, 1H), 7.40 (d, J = 3 Hz, 1H), 7.29 (dd, J = 9 Hz, 3 Hz, 1H), 7.24 (d, J = 4 Hz, 1H), 6.61 (d, J = 6 Hz, 1H), 6.00-5.89 (m, 1H), 5.09-5.01 (m, 2H), 3.90 (s, 3H), 3.27-3.18 (m, 1H), 2.96-2.86 (m, 2H), 2.85-2.76 (m, 1H), 2.73-2.65 (m, 1H), 2.29-2.19 (m, 1H), 2.07 (s, 3H), 1.95-1.86 (m, 1H), 1.77 (br s, 1H), 1.52-1.47 (m, 2H), 1.46-1.34 (m, 1H), 1.25-1.14 (m, 1H).
^{13}C NMR (75 MHz, $CDCl_3$) δ: 169.50, 158.18, 147.18, 144.57, 143.17, 139.49, 131.63, 126.67, 122.17, 118.09, 115.38, 101.22, 72.85, 58.65, 55.94, 49.58, 48.76, 39.04, 27.68, 25.65, 22.41, 21.11.

$[\alpha]_D^{23}$ = +75.2 (solvent: $CHCl_3$; *c* = 0.502 g/100 mL; λ = 589 nm).

HRMS Mass (ESI+): m/z = calc. for $C_{22}H_{28}N_3O_2^+$ = 366.47, found 366.47 [M + H].

*Preparation of catalyst **84**:*



	eq	mmol	MW (g/mol)	mg	d (g/mL)	mL
quinidine	1.0	0.74	324.43	240.6	/	/
picolinoyl chloride	1.2	0.89	141.56	125.9	/	/
TEA (dry)	1.2	0.89	101.19	90.0	0.726	0.124
THF (dry)						10.0

In a two necked flask the picolinoyl chloride was dissolved in part of the solvent; then the resulting solution was cooled to 0 °C and the triethylamine was added. Subsequenly, the solution of quinidine in dry THF was added dropwise and the reaction was warmed to room temperature and stirred for 24 h. After this time the reaction was quenched with $NaHCO_3$ s.s. (3 mL) and the organic solvent was removed under reduced pressure. Then CH_2Cl_2 (10 mL) was added and the organic layer was separated; next the aqueous layer was extracted with CH_2Cl_2 (5 x 10 mL). The combined organic solution was dried over dry Na_2SO_4, filtered and the solvent was removed under reduced pressure.
The desired product was purified by flash column chromatography on silica gel with a 95:5 DCM/MeOH mixture as eluent. The purification afforded the desired product in 56% yield.

R_f = 0.80 (9:1 DCM/MeOH).

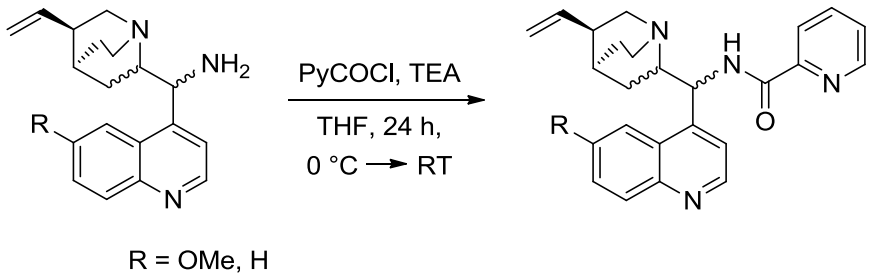
^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.24 (d, J = 4 Hz, 2H), 8.58 (d, J = 8 Hz, 1H), 8.51 (d, J = 9 Hz, 1H) 8.25 (t, J = 8 Hz, 1H), 8.11 (d, J = 2 Hz, 1H), 8.01 (d, J = 4 Hz, 1H), 7.93-7.84 (m, 2H), 7.35 (d, J = 7 Hz, 1H), 6.70-6.58 (m, 1H), 5.61-5.56 (m, 2H), 4.48 (s, 3H), 4.06-3.98 (m, 1H), 3.60-3.53 (m, 1H), 3.45-3.31 (m, 2H), 3.27-3.17 (m, 1H), 2.80-2.72 (m, 1H), 2.57-2.50 (m, 1H), 2.31-2.03 (m, 4H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 164.44, 158.01, 149.96, 147.70, 147.40, 144.70, 143.32, 140.43, 137.30, 136.91, 131.69, 127.12, 125.31, 122.00, 118.90, 114.81, 101.50, 74.80, 59.18, 49.81, 49.14, 39.91, 38.06, 27.99, 26.31, 23.65.

$[\alpha]_D^{23}$ = +2.7 (solvent: $CHCl_3$; *c* = 0.566 g/100 mL; λ = 589 nm).

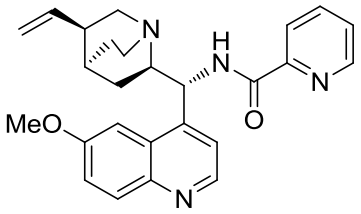
HRMS Mass (ESI+): m/z = calc. for $C_{26}H_{27}N_3O_3Na^+$ = 452.19, found 452.19 [M + Na]; $C_{26}H_{28}N_3O_3^+$ = 430.21, found 430.21 [M + H].

*Preparation of catalysts **85**, **87**, **88** and **93**:*



General procedure: In a two necked flask the picolinoyl chloride (0.89 mmol, 1.2 eq) was dissolved in dry THF (5 mL); then the resulting solution was cooled to 0 °C and the triethylamine (0.89 mmol, 1.2 eq) was added. Subsequenly, the solution of 9-amino-epi-cinchona derivative (0.74 mmol, 1.0 eq, 0.15 M solution in dry THF) was added dropwise and the reaction was warmed to room temperature and stirred for 24 h. After this time the reaction was quenched with $NaHCO_3$ s.s. (3 mL) and the organic solvent was removed under reduced pressure. Then CH_2Cl_2 (10 mL) was added and the organic layer was separated; next the aqueous layer was extracted with CH_2Cl_2 (5 x 10 mL). The combined organic solution was dried over dry Na_2SO_4, filtered and the solvent was removed under reduced pressure. Purification methods for each product are reported below.

*Catalyst **85**:*



This product was purified by flash column chromatography on silica gel with a 95:5 DCM:MeOH mixture as eluent. The purification afforded the desired product in 42% yield.

R_f = 0.32 (9:1 DCM:MeOH).

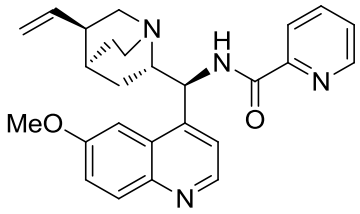
^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.96 (br s, 1H), 8.73 (d, J = 4 Hz, 1H), 8.55 (d, J = 4 Hz, 1H), 8.04-7.98 (m, 2H), 7.75-7.70 (m, 2H), 7.43 (d, J = 5 Hz, 1H), 7.35-7.32 (m, 2H), 5.97-5.86 (m, 1H), 5.60 (br s, 1H), 5.14-5.07 (m, 2H), 3.96 (s, 3H), 3.31-3.21 (m, 1H), 3.13-2.90 (m, 4H), 2.32-2.24 (m, 1H), 1.70-1.62 (m, 1H), 1.59-1.45 (m, 2H), 1.36-1.24 (m, 1H), 1.13-1.03 (m, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 163.89, 157.53, 149.38, 149.23, 147.79, 147.09, 144.41, 139.93, 136.73, 131.32, 127.85, 125.69, 121.84, 121.69, 118.91, 114.93, 100.90, 59.43, 55.09, 49.01, 46.63, 38.52, 30.39, 26.92, 26.13, 25.37.

$[\alpha]_D^{23}$ = +168.5 (solvent: $CHCl_3$; *c* = 0.162 g/100 mL; λ = 589 nm).

HRMS Mass (ESI+): m/z = calc. for $C_{26}H_{28}N_4O_2Na^+$ = 451.21, found 451.21 [M + Na]; $C_{26}H_{29}N_4O_2^+$ = 429.22, found 429.22 [M + H].

*Catalyst **87**:*



This product was purified by flash column chromatography on silica gel with a 95:5 DCM:MeOH mixture as eluent. The purification afforded the desired product in 53% yield.

R_f = 0.25 (9:1 DCM:MeOH).

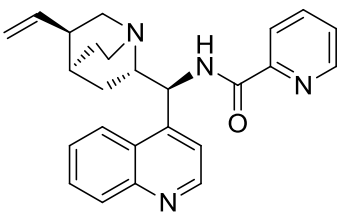
^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.88 (br s, 1H), 8.70 (d, J = 4 Hz, 1H), 8.46 (d, J = 4 Hz, 1H), 8.03-7.96 (m, 2H), 7.75 (d, J = 3 Hz, 1H), 7.71-7.66 (m, 1H), 7.42 (d, J = 4 Hz, 1H), 7.34-7.26 (m, 2H), 5.80-5.69 (m, 1H), 5.62 (br s, 1H), 5.01-4.91 (m, 2H), 3.94 (s, 3H), 3.44-3.36 (m, 1H), 3.33-3.23 (m, 2H), 2.81-2.68 (m, 2H), 2.27 (br, 1H), 1.66-1.48 (m, 4H), 0.96-0.88 (m, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 164.12, 157.96, 149.77, 148.22, 147.57, 144.87, 144.75, 141.41, 137.19, 131.78, 128.40, 126.14, 122.26, 121.84, 119.64, 114.52, 101.83, 59.53, 56.11, 55.64, 51.94 41.16, 39.49, 27.91, 27.50, 26.59.

$[\alpha]_D^{23}$ = -81.1 (solvent: $CHCl_3$; *c* = 0.370 g/100 mL; λ = 589 nm).

HRMS Mass (ESI+): m/z = calc. for $C_{26}H_{29}N_4O_2^+$= 429.22, found 429.22 [M + H].

*Catalyst **88**:*



This product was purified by flash column chromatography on silica gel with a 95:5 DCM:MeOH mixture as eluent. The purification afforded the desired product in 63% yield.

R_f = 0.37 (95:5 DCM:MeOH).

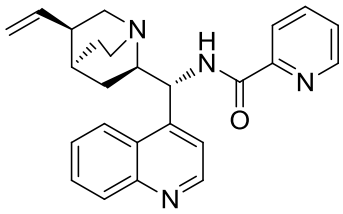
^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.98 (br s, 1H), 8.89 (d, J = 4 Hz, 1H), 8.48-8.43 (m, 2H), 8.13 (d, J = 7 Hz, 1H), 8.03 (d, J = 2 Hz, 1H), 7.75-7.69 (m, 1H), 7.65-7.60 (m, 1H), 7.50-7.49 (d, J = 4 Hz, 1H), 7.37 (dd, J = 2 Hz, 5 Hz, 1H), 5.80-5.69 (m, 1H), 5.64 (br s, 1H), 5.03-4.94 (m, 2H), 3.42-3.18 (m, 3H), 2.88-2.73 (m, 2H), 2.31 (br s, 1H), 1.71-1.53 (m, 3H), 1.50-1.42 (m, 1H), 0.99-0.92 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 162.68, 150.68, 149.64, 148.66, 148.16, 145.16, 140.35, 136.64, 130.04, 128.76, 126.74, 126.50, 125.77, 122.74, 122.43, 119.00, 114.37, 59.38, 55.31, 40.56, 38.70, 29.14, 27.00, 26.86, 25.55.

$[\alpha]_D^{25}$ = -40.4 (solvent: $CHCl_3$; *c* = 0.312 g/100 mL; λ = 589 nm).

HRMS Mass (ESI+): m/z = calc. for $C_{25}H_{27}N_4O^+$ = 399.2, found 399.4 [M + H].

*Catalyst **93**:*



This product was purified by flash column chromatography on silica gel with a 95:5 DCM:MeOH mixture as eluent. The purification afforded the desired product in 63% yield.

R_f = 0.37 (95:5 DCM:MeOH).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.04-8.93 (m, 1H), 8.85 (d, J = 4 Hz, 1H), 8.56 (d, J = 5 Hz, 1H), 8.46-8.40 (m, 1H), 8.11 (d, J = 8 Hz, 1H), 8.02-7.99 (m, 1H), 7.76-7.68 (m, 2H), 7.62-7.57 (m, 1H), 7.50-7.46 (m, 1H), 7.37-7.33 (m, 1H), 5.95-5.84 (m, 1H), 5.60 (br s, 1H), 5.15-5.07 (m, 2H), 3.28-3.19 (m, 1H), 3.11-2.91 (m, 4H), 2.33-2.22 (m, 1H), 1.67-1.61 (m, 1H), 1.57-1.45 (m, 2H), 1.35-1.24 (m, 1H), 1.04-0.93 (m, 1H).

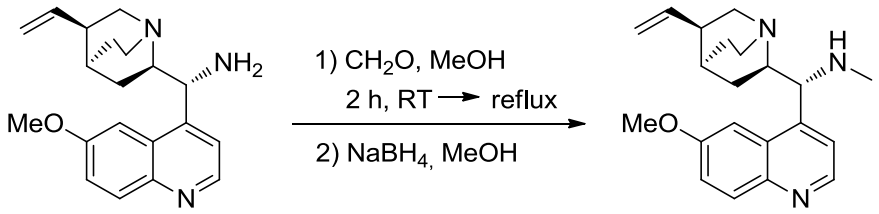
^{13}C NMR (75 MHz, $CDCl_3$) δ: 164.33, 150.03, 149.81, 149.18, 148.56, 148.27, 140.35, 137.20, 130.37, 129.18, 127.35, 126.78, 126.28, 126.14, 123.40, 122.25, 119.31, 114.87, 60.11, 49.40, 47.18, 39.24, 27.43, 26.68, 25.57.

$[\alpha]_D^{25}$ = +134.3 (solvent: $CHCl_3$; *c* = 0.140 g/100 mL; λ = 589 nm).

HRMS Mass (ESI+): m/z = calc. for $C_{25}H_{27}N_4O^+$ = 399.2, found 399.4 [M+H].

*Preparation of catalyst **90**:*

Step 1



	eq	mmol	MW (g/mol)	mg	d (g/mL)	mL
9-amino-*epi*-quinidine	1.0	0.93	323.42	300.0	/	/
formaldehyde (40% in MeOH)	1.4	1.30	30.03	98.3	1.083	0.091
$NaBH_4$	1.2	1.12	37.83	42.1	/	/
MeOH (dry)						5.0

The 9-amino-*epi*-quinidine was dissolved in dry MeOH in a two necked flask. The formaldehyde solution was then added; subsequently the reaction mixture was stirred overnight at room temperature and then refluxed for 2 h. After this time the solution was cooled to room temperature, the $NaBH_4$ was added and the reaction was allowed to proceed overnight at room temperature. Then the reaction was quenched with distilled H_2O (5 mL) and ethyl acetate was added (5 mL). The organic layer was separated and washed with distilled H_2O (10 mL) and NaCl s.s. (5 mL). The organic layer was dried over dry Na_2SO_4, filtered and the solvent was removed under reduced pressure. The desired product was purified by flash column chromatography on silica gel with a 49.5:49.5:1 ethyl acetate/MeOH/NH_4OH 30-33% mixture as eluent. The purification afforded the desired product in 49% yield.

R_f = 0.33 (49.5:49.5:1 ethyl acetate/MeOH/NH_4OH 30-33%).

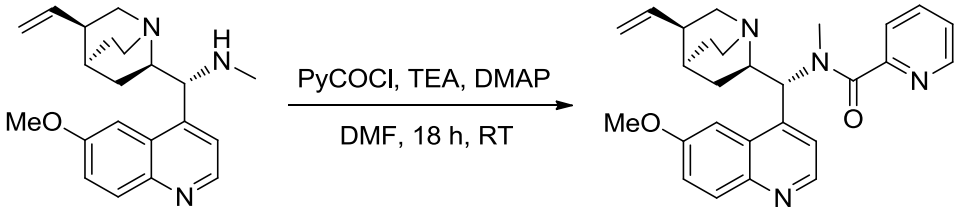
^1H NMR (300 MHz, $CDCl_3$) δ: 8.73 (br s, 1H), 8.03 (d, J = 9 Hz, 1H), 7.65 (d, J = 5 Hz, 1H), 7.85 (dd, J = 9 Hz, 3 Hz, 2H), 5.98-5.86 (m, 1H), 5.12-5.06 (m, 2H), 3.97 (s, 3H), 3.25-3.13 (m, 1H), 3.05-2.86 (m, 5H), 2.20 (s, 3H), 1.64-1.43 (m, 4H), 1.34-1.16 (m, 2H), 0.95-0.72 (m, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 147.88, 147.49, 140.70, 131.68, 121.42, 118.72, 114.44, 100.80, 68.08, 59.82, 55.42, 50.18, 49.39, 47.57, 39.53, 36.12, 34.32, 29.63, 27.51, 26.62, 24.62.

$[\alpha]_D^{23}$ = +70.5 (solvent: CH_2Cl_2; *c* = 0.252 g/100 mL; λ = 589 nm).

HRMS Mass (ESI+): m/z = calc. for $C_{21}H_{28}N_3O^+$ = 338.2, found 338.4 [M + H].

Step 2



	eq	**mmol**	**MW (g/mol)**	**mg**	**d (g/mL)**	**mL**
N-methyl-9-amino-*epi*-quinidine	1.0	0.45	337.46	152.0	/	/
picolinoyl chloride	1.2	0.54	141.56	77.4	/	/
TEA (dry)	3.0	1.35	101.19	136.6	0.726	0.189
DMAP	0.1	0.045	122.17	6.0	/	/
DMF (dry)						4.0

In a two necked flask the *N*-methyl-9-amino-*epi*-quinidine and the DMAP were dissolved in dry DMF (2 mL); subsequently dry TEA was added. Meanwhile the picolinoyl chloride was dissolved in dry DMF (2 mL) and this solution was added dropwise to the the reaction mixture. The reaction was then stirred overnight at room temperature. After this time, the reaction was quenched by addition of few drops of distilled H_2O and the solvent was removed under reduced pressure. Then the crude product was dissolved in DCM and the solution was dried over dry Na_2SO_4, filtered and the solvent was removed under reduced pressure. The desired product was purified by flash column chromatography on silica gel with a 9:1 DCM:MeOH mixture as eluent. The purification afforded the desired product in 73% yield.

R_f = 0.33 (9:1 DCM:MeOH).

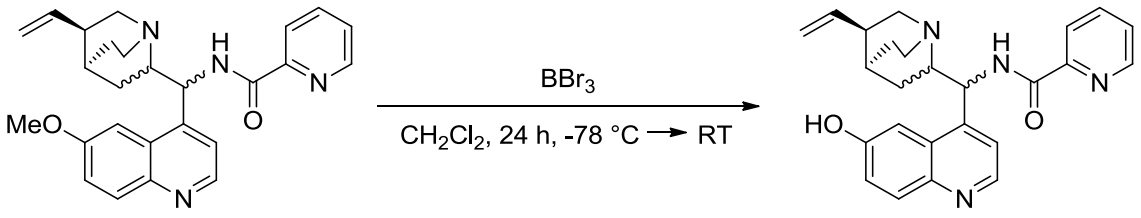
^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.72 (br s, 1H), 8.46 (s, 1H), 8.01-7.95 (m, 2H), 7.68 (t, J = 8 Hz, 1H), 7.46 (d, J = 9 Hz, 1H), 7.34 (d, J = 9 Hz, 1H), 7.28 (br s, 1H), 7.26-7.19 (m, 1H), 6.64 (d, J = 11 Hz, 1H), 5.89-5.62 (m, 1H), 5.20 (d, J = 17 Hz, 1H), 5.02 (d, J = 10 Hz, 1H), 3.94 (s, 3H), 3.70-3.56 (m, 1H), 3.52-3.43 (m, 1H), 3.08-2.91 (m, 2H) 2.65 (s, 3H), 2.26 (br s, 1H), 1.70-1.63 (m, 3H), 1.59-1.45 (m, 1H),1.23-1.08 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 158.52, 148.41, 146.63, 140.50, 140.36, 136.86, 131.49, 131.35, 123.96, 123.14, 122.84, 122.75, 120.24, 114.64, 102.57, 102.42, 56.15, 56.02, 55.90, 53.67, 53.24, 50.07, 47.30, 39.25, 27.63, 27.23, 26.98.

$[\alpha]_D^{23}$ = -9.0 (solvent: $CHCl_3$; *c* = 0.200 g/100 mL; λ = 589 nm).

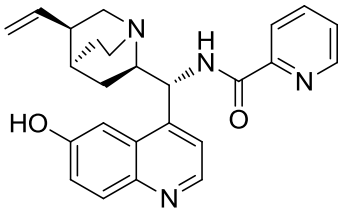
HRMS Mass (ESI+): m/z = calc. for $C_{27}H_{31}N_4O_2^+$ = 443.6, found 443.3 [M + H].

*Preparation of catalysts **91** and **92**:*



General procedure: In a two necked flask the picolinamidic derivative (0.43 mmol, 1.0 eq) was dissolved in dry CH_2Cl_2 (1.5 mL). The solution then was cooled to -78 °C and after 10 min BBr_3 (4.30 mmol, 10.0 eq, 1.0 M solution in dry CH_2Cl_2) was added dropwise. The reaction was then allowed to warm up to room temperature and stirred for 24 h. After this time, the solution was cooled to 0 °C, quenched by addition of NaOH 10% (13 mL) and extracted with CH_2Cl_2 (2 x 10 mL). The aqueous layer was then treated with HCl 37% (8 mL) and subsequently basified till pH = 10 with NH_4OH 30-33%. Finally the acqueous layer was extracted with *n*-BuOH (3 x 10 mL) and the combined organic solution was dried over dry Na_2SO_4, filtered and the solvent was removed under reduced pressure. Purification methods for each product are reported below.

*Catalyst **91**:*



This product was purified by flash column chromatography on silica gel with a 95:5 to 8:2 DCM:MeOH mixture as eluent. The purification afforded the desired product in 46% yield.

R_f = 0.28 (9:1 DCM:MeOH).

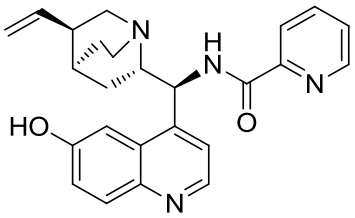
^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.99 (br s, 1H), 8.73 (d, J = 4 Hz, 1H), 8.22 (d, J = 4 Hz, 1H), 7.99 (d, J = 8 Hz, 1H), 7.90 (d, J = 9 Hz, 1H), 7.76-7.72 (m, 1H), 7.66-7.60 (m, 1H), 7.54 (d, J = 5 Hz, 1H), 7.21-7.15 (m, 2H), 5.89-5.78 (m, 1H), 5.73 (br s, 1H), 5.07-4.86 (m, 2H), 3.69-3.57 (m, 1H), 3.20-2.92 (m, 4H), 2.32-2.25 (m, 1H), 1.68 (s, 1H), 1.61-1.55 (m, 2H), 1.39-1.14 (m, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 155.35, 150.47, 148.95, 148.22, 147.38, 146.18, 145.03, 143.45, 139.27, 136.57, 130.97, 125.57, 122.38, 121.78, 121.61, 114.69, 104.55, 59.10, 48.72, 46.74, 38.76, 29.14, 26.98, 25.86, 25.26.

$[\alpha]_D^{25}$ = +75.0 (solvent: $CHCl_3$; *c* = 0.192 g/100 mL; λ = 589 nm).

HRMS Mass (ESI+): m/z = calc. for $C_{25}H_{27}N_4O_2^+$ = 415.2, found 415.4 [M + H].

*Catalyst **92**:*



This product was purified by flash column chromatography on silica gel with a 95:5 to 8:2 DCM:MeOH mixture as eluent. The purification afforded the desired product in 51% yield.

R_f = 0.42 (95:5 DCM:MeOH).

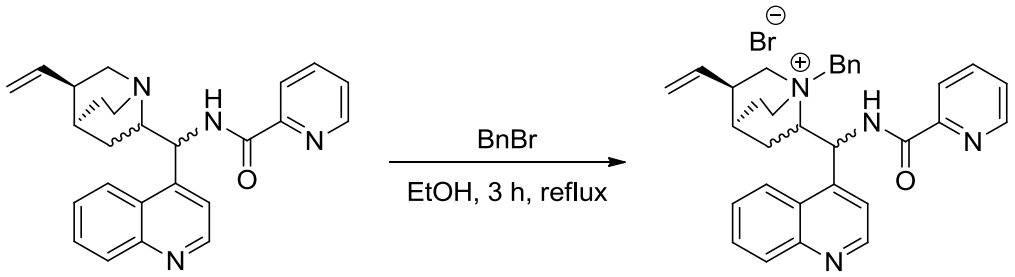
^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.99 (br s, 1H), 8.73 (d, J = 4 Hz, 1H), 8.28 (d, J = 4 Hz, 1H), 8.10 (d, J = 8 Hz, 1H), 7.92 (d, J = 9 Hz, 1H), 7.83 (br s, 1H), 7.67-7.61 (m, 1H), 7.52 (d, J = 5 Hz, 1H), 7.24-7.16 (m, 2H), 5.84-5.73 (m, 2H), 5.00-4.94 (m, 2H), 3.68-3.53 (m, 1H), 3.41-3.22 (m, 2H), 2.87-2.71 (m, 2H), 2.27 (br s, 1H), 1.62-1.39 (m, 4H), 1.27 (s, 1H), 1.03-0.86 (m, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 164.39, 156.33, 149.42, 147.97, 146.43, 144.21, 143.61, 141.09, 137.13, 131.15, 128.71, 126.13, 122.45, 122.30,119.06, 114.72, 105.08, 59.61, 55.69, 53.41, 41.09, 39.25, 29.66, 27.39, 26.26.

$[\alpha]_D^{25}$ = +37.5 (solvent: $CHCl_3$; *c* = 0.240 g/100 mL; λ = 589 nm).

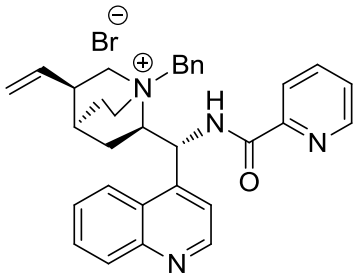
HRMS Mass (ESI+): m/z = calc. for $C_{25}H_{27}N_4O_2^+$ = 415.2, found 415.4 [M + H].

*Preparation of catalysts **94** and **95**:*



General procedure: In a two necked flask the picolinamidic derivative (0.43 mmol, 1.0 eq) was dissolved in EtOH (3.5 mL). The benzyl bromide (1.28 mmol, 3.0 eq) was then added and the reaction mixture was heated to reflux (85°C) and stirred at this temperature for 3 h. After this time the reaction was cooled to room temperature and Et_2O (2.5 mL) was added. The precipitate was then filtered over B*üchner* and washed with Et_2O (5 x 5 mL). The desired products were obtained with sufficient purity for being employed in the subsequent reaction without further purification.

*Catalyst **94**:*



The desired product was obtained in 56% yield.

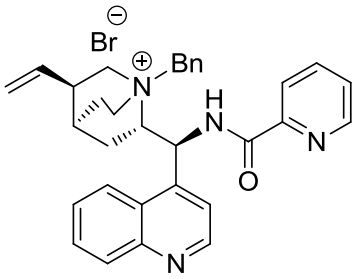
^{1}H NMR (300 MHz, CD_3OD) δ: 9.74 (d, J = 6 Hz, 1H), 9.41 (d, J = 5 Hz, 1H), 8.98-8.64 (m, 3H), 8.82 (d, J = 8 Hz, 2H), 8.32-8.13 (m, 3H), 7.80 (br s, 1H), 7.55-7.41 (m, 3H), 6.70-6.63 (m, 1H), 6.46-6.40 (m, 1H), 6.08-5.96 (m, 1H), 5.50-5.32 (m, 2H), 5.17-5.05 (m, 1H), 4.88 (s, 3H), 3.96-3.84 (m, 2H), 3.76-3.58 (m, 2H), 2.99 (br s, 1H), 2.35-1.92 (m, 4H), 1.55-1.44 (m, 1H).

^{13}C NMR (75 MHz, CD_3OD) δ: 164.17, 153.65, 153.18, 149.11, 146.64, 144.41, 139.37, 137.74, 136.33, 135.35, 134.74, 133.11, 132.24, 130.47, 130.38, 128.77, 128.66, 127.29, 127.06, 125.59, 124.34, 121.47, 121.22, 120.98, 115.95, 60.74, 58.48, 48.85, 35.79, 25.95, 23.28, 21.99.

$[\alpha]_D^{25}$ = +20.8 (solvent: MeOH; *c* = 0.486 g/100 mL; λ = 589 nm).

HRMS Mass (ESI+): m/z = calc. for $C_{32}H_{33}N_4O^+$= 489.26, found 489.26 [M + H].

*Catalyst **95**:*



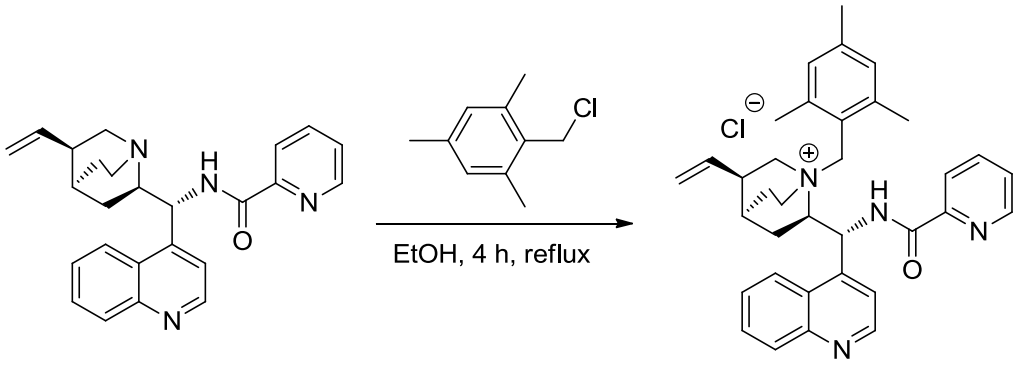
The desired product was obtained in 62% yield.

^{1}H NMR (300 MHz, CD_3OD) δ: 9.74 (d, J = 3 Hz, 1H), 9.41 (d, J = 4 Hz, 1H), 9.13 (d, J = 8 Hz, 1H), 8.99-8.92 (m, 2H), 8.84-8.78 (m, 1H), 8.73-8.68 (m, 2H), 8.40 (d, J = 8 Hz, 1H), 8.29 (br s, 1H), 8.17 (br s, 2H), 7.75-7.73 (m, 3H), 6.74-6.61 (m, 1H), 6.46-6.40 (m, 1H), 6.18-6.05 (m, 1H), 5.40 (d, J = 17 Hz, 1H), 5.25 (d, J = 10 Hz, 1H),4.14 (br s, 1H), 3.91-3.69 (m, 2H), 3.64-3.52 (m, 2H), 3.32 (s, 1H), 2.99 (br s, 1H), 2.27-2.01 (m, 4H), 1.41 (br s, 1H), 1.22-1.16 (m, 1H).

^{13}C NMR (75 MHz, CD_3OD) δ: 160.71, 153.04, 149.07, 144.34, 143.84, 142.92, 138.11, 137.63, 137.08, 135.42, 134.88, 133.20, 132.29, 130.83, 130.56, 128.79, 127.52, 127.17, 126.69, 126.41, 125.15, 120.75, 119.57, 116.14, 60.83, 58.20, 53.16, 42.00, 36.31, 26.13, 23.62, 22.98.

HRMS Mass (ESI+): m/z = calc. for $C_{32}H_{33}N_4O^+$= 489.26, found 489.26 [M + H].

*Preparation of catalyst **96**:*



	eq	mmol	MW (g/mol)	mg	d (g/mL)	mL
catalyst **93**	1.0	0.38	398.50	150.0	/	/
2-(chloromethyl)-1,3,5-trimethyl benzene	3.0	1.13	171.05	190.3	/	/
EtOH						3.0

In a two necked flask the picolinamidic derivative was dissolved in EtOH. The 2-(chloromethyl)-1,3,5-trimethyl benzene was then added and the reaction mixture was heated to reflux (85°C) and stirred at this temperature for 3 h. After this time the reaction was cooled to room temperature and Et_2O (2.5 mL) was added. The precipitate was then filtered over B*üchner* and washed with Et_2O (5 x 5 mL). The desired product were obtained with sufficient purity for being employed in the subsequent reaction without further purification. The desired product was obtained in 76% yield.

^{1}H NMR (300 MHz, CD_3OD) δ: 9.38 (br s, 1H), 8.93-8.68 (m, 4H), 8.64-8.51 (m, 2H), 8.47-8.37 (m, 1H), 8.32-8.00 (m, 4H), 7.11-6.77 (m, 1H), 6.66-6.64 (m, 1H), 6.60-6.26 (m, 1H), 5.98-5.93 (m, 1H), 5.45-5.30 (m, 2H), 4.00-3.46 (m, 6H), 3.03-2.83 (m, 1H), 2.42-2.14 (m, 6H), 2.13-1.74 (m, 4H), 1.56-1.35 (m, 1H), 1.26-1.09 (m, 2H).

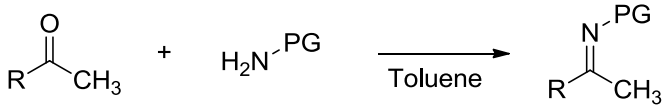
^{13}C NMR (75 MHz, CD_3OD) δ: 161.91, 153.57, 149.78, 149.28, 144.80, 144.07, 141.03, 139.77, 138.08, 136.84, 136.13, 135.28, 131.03, 129.95, 128.96, 128.43, 127.93, 127.16, 126.14, 124.90, 123.45, 123.23, 121.92, 121.45, 119.59, 116.47, 66.25, 58.92, 55.14, 36.31, 26.52, 23.66, 22.46, 20.01, 18.45.

$[\alpha]_D^{23}$ = -9.8 (solvent: MeOH; *c* = 0.164 g/100 mL; λ = 589 nm).

HRMS Mass (ESI+): m/z = calc. for $C_{35}H_{39}N_4O^+$ = 531.6, found 531.6 [M + H].

8.2 Synthesis of substrates

8.2.1 Preparation of imines:

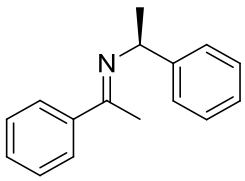


R = Ar, Alk
PG = Ph, PMP, Bn, 1-phenylethyl,
2-MeOPh, 2-OHPh

General procedure A: Toluene (6 mL), montmorillonite K10 clay (150 mg per 0.3 mmol), amine (0.3 mmol, 1 eq.) and ketone (0.3 mmol, 1 eq.) were introduced in a 25 mL vial without inert atmosphere. The stirred mixture was subjected to 200 W microwave irradiation and heated to 130 °C for 4 h 30 min. Constant microwave irradiation as well as simultaneous air-cooling (2 bar) were used during the entire reaction time. After cooling to room temperature, montmorillonite was removed by settling; finally the solvent was removed under reduced pressure. Purification methods for each product are reported below.

General procedure B: Toluene (15 mL), 4 Å molecular sieves (1 g per 0.3 mmol), amine (0.3 mmol, 1 eq.) and ketone (0.3 mmol, 1 eq.) were introduced in a two neck 25 mL round-bottomed flask provided with a condenser and a Dean-Stark apparatus. The reaction mixture was heated to 130 °C and stirred at this temperature for 18 h. After cooling to room temperature, molecular sieves were removed by settling; finally the solvent was removed under reduced pressure. Purification methods for each product are reported below.

N-(1'-phenylethyl)-ethan-1-phenyl-1-imine:

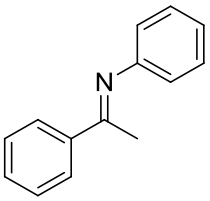


The desired product was prepared according to general procedure A. The residual starting materials were removed by fractional distillation at P = 3 x 10^{-2} mbar at 150 °C with

Glass Oven *B-585 Kugelrohr (only terminal round flask inserted)*. The purification afforded the desired product in 45% yield.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.90-7.87 (m, 2H), 7.52-7.26 (m, 8H), 4.88 (q, J = 6 Hz, 1H), 2.30 (s, 3H), 1.58 (d, J = 6 Hz, 3H).

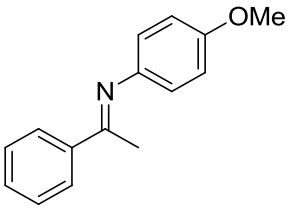
N-phenyl-ethan-1-phenyl-1-imine:



The desired product was prepared according to general procedure A. The residual starting materials were removed by fractional distillation at P = 3 x 10^{-2} mbar at 150 °C with Glass Oven *B-585 Kugelrohr (only terminal round flask inserted)*. The purification afforded the desired product in 70% yield.

^{1}H-NMR (300 MHz, $CDCl_3$) 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).

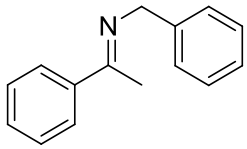
N-(4'-methoxyphenyl)-ethan-1-phenyl-1-imine:



The desired product was prepared according to general procedure B. The residual *p*-anisidine was removed by flash column chromatography on silica gel with a 8:2 hexane/ethyl acetate mixture as eluent. The residual acetophenone was then removed by fractional distillation at P = 3 x 10^{-2} mbar at 150 °C with Glass Oven *B-585 Kugelrohr (only terminal round flask inserted)*. The purification afforded the desired product in 28% yield.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.99-7.98 (m, 2H), 7.47-7.45 (m, 3H), 6.97-6.90 (m, 2H), 6.81-6.74 (m, 2H), 3.85 (s, 3H), 2.28 (s, 3H).

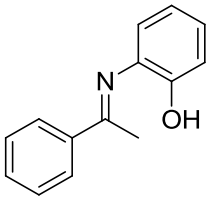
N-benzyl-ethan-1-phenyl-1-imine:



The desired product was prepared according to general procedure A. The residual starting materials were removed by fractional distillation at P = 3 x 10^{-2} mbar at 150 °C with Glass Oven *B-585 Kugelrohr (only terminal round flask inserted)*. The purification afforded the desired product in 60% yield.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.00-7.95 (m, 2H), 7.56-7.34 (m, 8H), 4.82 (s, 2H), 2.39 (s, 3H).

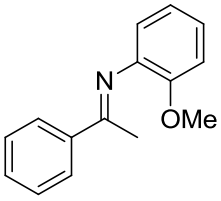
N-(2'-hydroxyphenyl)-ethan-1-phenyl-1-imine:



The desired product was prepared according to general procedure B. The solvent and the residual starting materials were removed by fractional distillation at P = 10 mbar. The purification afforded the desired product in 50% yield.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.04-7.94 (m, 2H), 7.68-6.76 (m, 8H), 2.45 (s, 3H).

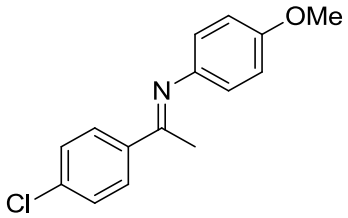
N-(2'-methoxyphenyl)-ethan-1-phenyl-1-imine:



The desired product was prepared according to general procedure A. The product was purified by fractional distillation at P = 3 x 10^{-2} mbar with Glass Oven *B-585 Kugelrohr*; the starting material distilled at about 150 °C, the desired product at about 200 °C. The purification afforded the desired product in 28% yield.

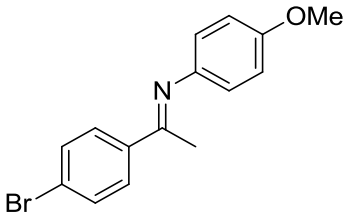
^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.04-8.00 (m, 2H), 7.47-7.42 (m, 3H), 7.27-6.76 (m, 4H), 3.78 (s, 3H), 2.18 (s, 3H).

N-(4'-methoxyphenyl)-ethan-1-(4''-chlorophenyl)-1-imine:



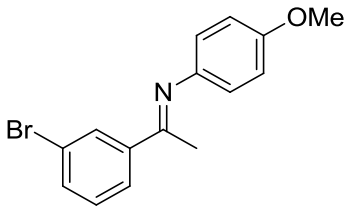
The desired product was prepared according to general procedure A. The residual starting matierials were then removed by fractional distillation at P = 3 x 10^{-2} mbar at 150 °C with Glass Oven *B-585 Kugelrohr (only terminal round flask inserted)*. The purification afforded the desired product in 35% yield.
^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.91 (d, J = 9 Hz, 2H), 7.41 (d, J = 9 Hz, 2H), 6.92 (d, J = 8 Hz, 2H), 6.75 (d, J = 8 Hz, 2H), 3.82 (s, 3H), 2.24 (s, 3H).

N-(4'-methoxyphenyl)-ethan-1-(4''-bromophenyl)-1-imine:



The desired product was prepared according to general procedure B. The residual starting materials were then removed by fractional distillation at P = 3 x 10^{-2} mbar at 150 °C with Glass Oven *B-585 Kugelrohr (only terminal round flask inserted)*. The purification afforded the desired product in 90% yield.
^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.85-7.80 (m, 2H), 7.57-7.34 (m, 2H), 6.92-6.89 (m, 2H), 6.76-6.72 (m, 2H), 3.81 (s, 3H), 2.22 (s, 3H).

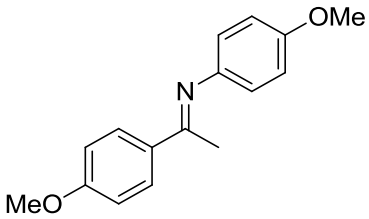
N-(4'-methoxyphenyl)-ethan-1-(3''-bromophenyl)-1-imine:



The desired product was prepared according to general procedure B. The residual starting materials were then removed by fractional distillation at P = 3 x 10^{-2} mbar at 150 °C with Glass Oven *B-585 Kugelrohr (terminal round flask and central ball tube inserted)*. The purification afforded the desired product in 80% yield.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.14-8.13 (m, 1H), 7.85-7.82 (m, 1H), 7.57-7.55 (m, 1H), 7.31-7.28 (m, 1H), 6.92-6.89 (m, 2H), 6.76-6.73 (m, 2H), 3.81 (s, 3H), 2.22 (s, 3H).

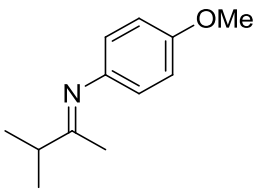
N-(4'-methoxyphenyl)-ethan-1-(4''-methoxyphenyl)-1-imine:



The desired product was prepared according to general procedure A. The residual starting materials were removed by flash column chromatography on silica gel with a 9:1 hexane/ethyl acetate mixture as eluent. The purification afforded the desired product in 12% yield.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.93 (d, J = 9 Hz, 2H), 6.95 (d, J = 9 Hz, 2H), 6.90 (d, J = 9 Hz, 2H), 6.73 (d, J = 9 Hz, 2H), 3.87 (s, 3H), 3.82 (s, 3H), 2.22 (s, 3H).

N-(4'-methoxyphenyl)-isoamyl-2-imine:



The desired product was prepared according to general procedure B. The residual starting materials were then removed by fractional distillation at P = 3 x 10^{-2} mbar at 150 °C with Glass Oven *B-585 Kugelrohr (terminal round flask and central ball tube inserted)*. The purification afforded the desired product in 51% yield as 85:15 *E*/*Z* mixture.

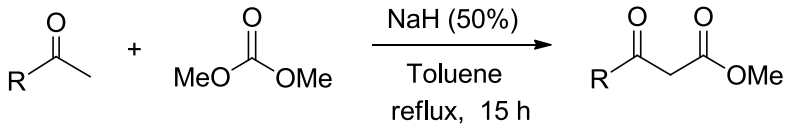
Data for *major*:

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 6.88-6.85 (m, 1H),6.78-6.76 (m, 1H),6.75-6.63 (m, 2H), 3.76 (s, 3H), 2.64 (hept, J = 7 Hz,1H), 1.77 (s, 3H), 1.21 (d, J = 7 Hz, 6H).

Data for *minor*:

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 6.88-6.85 (m, 1H), 6.78-6.76 (m, 1H), 6.75-6.63 (m, 2H), 3.75 (s, 3H), 2.80 (hept, J = 7 Hz, 1H), 2.08 (s, 3H), 1.04 (d, J = 7 Hz, 6H).

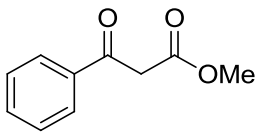
8.2.2 Preparation of ketoesters:



R = Ar, Alk

General procedure: NaH 50% (56.0 mmol, 2.8 eq.), dimethyl carbonate (40.0 mmol, 2 eq.) and toluene (20 mL) were introduced in a dried three-necked flask equipped with a dropping funnel, a condenser and a magnetic stirrer. The mixture was heated to reflux; then, a solution of ketone (20.0 mmol, 1 eq.) in toluene (10 mL) was added dropwise from the dropping funnel over 1 h. After the addition, the mixture was stirred at this temperature until the evolution of hydrogen ceased (15-20 min). Subsequently, the reaction was cooled to room temperature and 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 organic solution was washed with water (10 mL) and brine (10 mL), then dried over Na_2SO_4. Purification methods for each product are reported below.

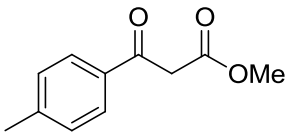
Methyl-3-oxo-3-phenylpropanoate:[216]



This product was purified by flash column chromatography on silica gel with a 98:2 hexane/ethyl acetate mixture as eluent. The purification afforded the desired product in 98% yield.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.92 (d, J = 8 Hz, 2H), 7.59 (dd, J = 8 Hz, J = 7 Hz, 1H), 7.45 (m, 2H), 4.00 (s, 2H), 3.74 (s, 3H).

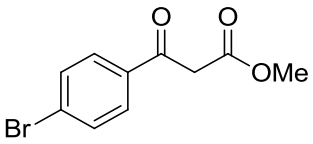
Methyl-3-oxo-3-(4'-methylphenyl)propanoate:[217]



This product was purified by flash column chromatography on silica gel with a 9:1 hexane/ethyl acetate mixture as eluent. The purification afforded the desired product in 82% yield.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.77 (d, J = 8 Hz, 2H), 7.21 (d, J = 8 Hz, 2H), 3.92 (s, 2H), 3.68 (s, 3H), 2.35 (s, 3H).

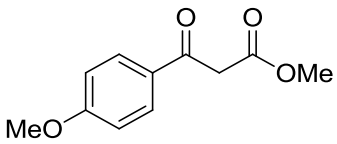
Methyl-3-oxo-3-(4'-bromophenyl)propanoate:[218]



This product was purified by flash column chromatography on silica gel with a 85:15 hexane/ethyl acetate mixture as eluent. The purification afforded the desired product in 93% yield.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.80-7.77 (m, 2H), 7.62-7.58 (m, 2H), 3.98 (s, 2H), 3.73 (s, 3H).

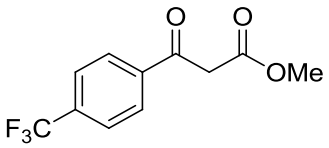
Methyl-3-oxo-3-(4'-methoxyphenyl)propanoate:[218]



This product was purified by flash column chromatography on silica gel with a 85:15 hexane/ethyl acetate mixture as eluent. The purification afforded the desired product in 92% yield.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.95-7.91 (m, 2H), 6.97-6.91 (m, 2H), 3.97 (s, 2H), 3.88 (s, 3H), 3.75 (s, 3H).

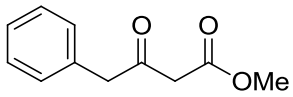
Methyl-3-oxo-3-(4'-trifluoromethylphenyl)propanoate:



This product was purified by flash column chromatography on silica gel with a 98:2 hexane/ethyl acetate mixture as eluent. The purification afforded the desired product in 18% yield.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.55-7.46 (m, 2H), 6.66-6.64 (m, 2H), 3.76 (s, 2H), 3.72 (s, 3H).

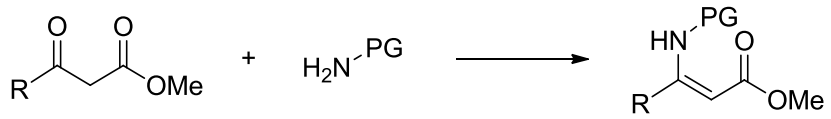
Methyl-3-oxo-4-phenylbutanoate:[219]



This product was purified by flash column chromatography on silica gel with a 98:2 hexane/ethyl acetate mixture as eluent. The purification afforded the desired product in 80% yield.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.37-7.18 (m, 5H), 3.80 (s, 2H), 3.69 (s, 3H), 3.45 (s, 2H).

8.2.3 Preparation of imino and enaminoesters:

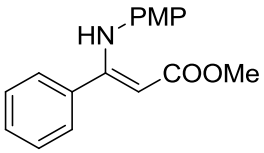


R = Ar, Alk
PG = PMP, Bn, 1-phenylethyl,

General procedure A: A mixture of β-keto ester (9.2 mmol, 1 eq.), amine (9.2 mmol, 1 eq.) and TsOH (1.9 mmol, 0.2 eq.) was dissolved in methanol (10 mL) and refluxed in the presence of 4 Å molecular sieves. After the reaction mixture was cooled to room temperature, the solvent was removed under reduced pressure. Purification methods for each product are reported below.

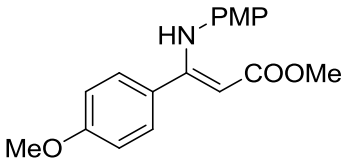
General procedure B: A mixture of β-keto ester (9.2 mmol, 1 eq.) and amine (27.6 mmol, 3 eq.) was dissolved in toluene (10 mL) and refluxed overnight with a Dean Stark apparatus in the presence of 4 Å molecular sieves. After the reaction mixture was cooled to room temperature, the solvent was removed under reduced pressure. Purification methods for each product are reported below.

(Z)-N-(4'-methoxyphenyl)-methyl-3-amino-3-phenylacrylate:



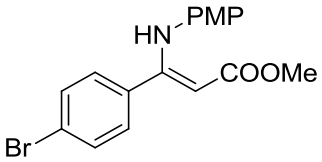
The desired product was prepared according to general procedure A. This product was purified by flash column chromatography on silica gel with a 95:5 hexane/ethyl acetate mixture as eluent. The purification afforded the desired product in 80% yield.
^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.29-7.24 (m, 5H), 6.65-6.58 (m, 4H), 4.95 (s, 1H), 3.75 (s, 3H), 3.70 (s, 3H).

(Z)-N-(4'-methoxyphenyl)-methyl-3-amino-3-(4''-methoxyphenyl)acrylate:



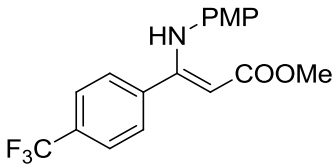
The desired product was prepared according to general procedure A. This product was purified by flash column chromatography on silica gel with a 95:5 hexane/ethyl acetate mixture as eluent. The purification afforded the desired product in 80% yield.
^{1}H-NMR (200 MHz, $CDCl_3$) δ: 7.25-7.23 (m, 2H), 6.76-6.74 (m, 2H), 6.66-6.61 (m, 4H), 4.90 (s, 1H), 3.77 (s, 3H), 3.72 (s, 3H), 3.70 (s, 3H).

(Z)-N-(4'-methoxyphenyl)-methyl-3-amino-3-(4''-bromophenyl)acrylate:



The desired product was prepared according to general procedure A. This product was purified by flash column chromatography on silica gel with a 95:5 hexane/ethyl acetate mixture as eluent. The purification afforded the desired product in 54% yield.
^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.39-7.37 (m, 2H), 7.16-7.14 (m, 2H), 6.65-6.56 (m, 4H), 4.91 (s, 1H), 3.73 (s, 3H), 3.71 (s, 3H).

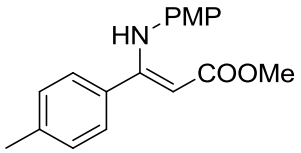
(Z)-N-(4'-methoxyphenyl)-methyl-3-amino-3-(4''-trifluoromethylphenyl)acrylate:



The desired product was prepared according to general procedure A. This product was purified by flash column chromatography on silica gel with a 95:5 hexane/ethyl acetate mixture as eluent. The purification afforded the desired product in 41% yield.
^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.29-7.25 (m, 4H), 6.65-6.59 (m, 4H), 4.95 (s, 1H), 3.75 (s, 3H), 3.70 (s, 3H).

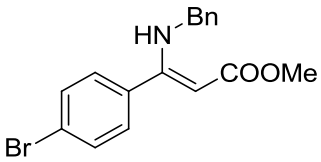
^{13}C NMR (75 MHz, $CDCl_3$) δ: 170.3, 158.2, 156.1, 140.0, 132.8, 128.8, 125.3, 124.6, 114.0, 90.0, 55.2, 50.7.

(Z)-N-(4'-methoxyphenyl)-methyl-3-amino-3-(4''-methylphenyl)acrylate:



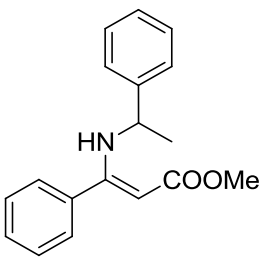
The desired product was prepared according to general procedure A. This product was purified by flash column chromatography on silica gel with a 95:5 hexane/ethyl acetate mixture as eluent. The purification afforded the desired product in 50% yield.
^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.26-7.18 (m, 2H), 7.08-7.05 (m, 2H), 6.66-6.64 (m, 4H), 4.92 (s, 1H), 3.73 (s, 3H), 3.71 (s, 3H), 2.32 (s, 3H).

(Z)-N-benzyl-methyl-3-amino-3-(4'-bromophenyl)acrylate:



The desired product was prepared according to general procedure B. This product was purified by flash column chromatography on silica gel with a 9:1 hexane/ethyl acetate mixture as eluent. The purification afforded the desired product in 40% yield.
^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.38-7.15 (m, 9H), 4.69 (s, 1H), 4.27 (d, 2H), 3.69 (s, 3H).

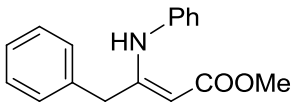
(Z)-N-(1'-phenylethyl)-methyl-3-phenyl-3-aminoacrylate:



The desired product was prepared according to general procedure B. This product was purified by flash column chromatography on silica gel with a 98:2 hexane/ethyl acetate mixture as eluent. The purification afforded the desired product in 46% yield.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.34-7.08 (m, 10H), 4.64 (s, 1H), 4.50 (q, 1H), 3.72 (s, 3H), 1.51 (d, 3H).

(Z)-N-phenyl-methyl-3-amino-3-benzylacrylate:

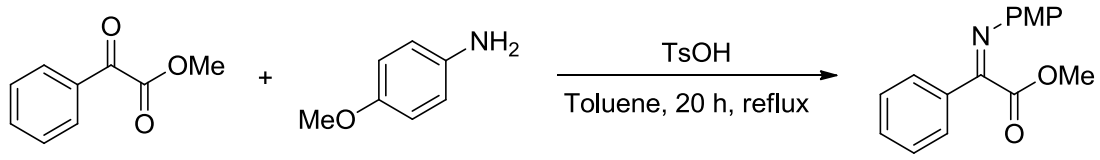


The desired product was prepared according to general procedure B. The product was obtained in 43% yield.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 10.39 (br s, 1H), 7.38-7.19 (m, 6H), 7.17-7.05 (m, 4H), 4.71 (s, 1H), 3.73 (s, 3H), 3.65 (s, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 170.88, 161.66, 138.99, 136.85, 129.04, 128.88, 128.46, 126.68, 125.66, 86.77, 50.37, 38.64.

(Z)-N-(4'-methoxyphenyl)-methyl-2-imino-2-phenylacetate:



	eq	**mmol**	**MW (g/mol)**	**mg**	**d (g/mL)**	**mL**
phenyl methyl glyoxylate	1.0	10.0	164.17	1641.7	1.163	1.4
p-anisidine	1.0	10.0	123.07	1230.7	/	/
p-toluensulfonic acid	0.1	1.0	170.2	170.2	/	/
toluene						8.0

A mixture of α-keto ester, *p*-anisidine and TsOH was dissolved in toluene (8 mL) and refluxed in the presence of 4 Å molecular sieves for 18 h. After the reaction mixture was cooled to room temperature, the solvent was removed under reduced pressure. The desired product was purified by flash column chromatography on silica gel with a 9:1 hexane/ethyl acetate mixture as eluent. The purification afforded the desired product in 55% yield.

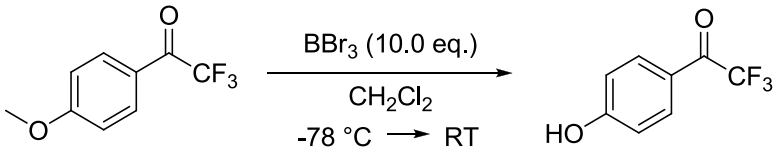
R_f = 0.34 (7:3 hexane/ethyl acetate).

^{1}H-NMR (200 MHz, $CDCl_3$) δ: 7.84-7.80 (m, 2H), 7.46-7.43 (m, 3H), 6.93-6.89 (m, 4H), 3.81 (s, 3H), 3.69 (s, 3H).

8.2.4 Preparation of fluorinated ketones:

Preparation of ethan-2,2,2-trifluoro-1-(4'-ethylphenoxyacetate)-1-ketone:

Step 1[220]



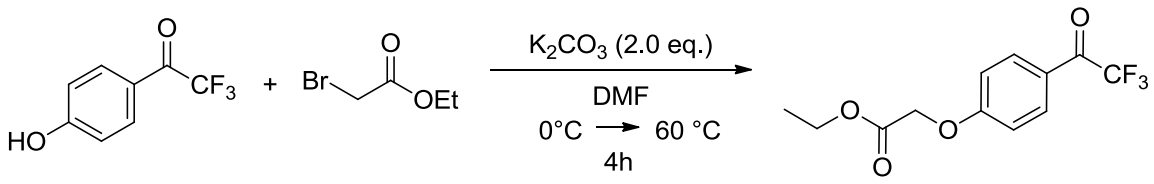
	eq	mmol	MW (g/mol)	mg	d (g/mL)	mL
4'-OMe-trifluoro acetophenone	1.0	1.47	204.15	300.1	1.265	0.237
BBr_3 (1M in CH_2Cl_2)	10.0	14.7				14.7
CH_2Cl_2 (dry)						2.7

BBr_3 was slowly added at -78 °C to a solution of the substrate in dry CH_2Cl_2. The mixture was allowed to reach room temperature and stirred overnight. Then the reaction mixture was cooled to 0°C and quenched by addition of NaOH 10% aq. (20 mL). The aqueous phase was separated, extracted with CH_2Cl_2 and acidified with HCl 37% aq. up to pH = 2. Then NH_4OH was added to the solution until a basic pH was reached. The aqueous phase was extracted again with *n*-butanol. The collected organic phases were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The desired product was purified by flash column chromatography on silica gel with a 95:5 hexane/ethyl acetate mixture as eluent. The purification afforded the desired product in 88% yield.

R_f= 0.16 (9:1 hexane/ethyl acetate).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.00 (d, J = 9 Hz, 2H), 6.96 (d, J = 9 Hz, 2H).
^{13}C NMR (75 MHz, $CDCl_3$) δ: 179.35 (q, J = 34 Hz), 162.44, 133.25, 122.77, 116.89 (q, J = 289 Hz), 116.14.
^{19} F NMR (300 MHz, $CDCl_3$) δ: -71.45.

Step 2[221]



	eq	**mmol**	**MW (g/mol)**	**mg**	**d (g/mL)**	**mL**
4'-OH-trifluoro acetophenone	1.0	0.56	190.12	106.5	/	/
K_2CO_3	2.0	1.10	138.21	153.0	/	/
ethyl bromoacetate	1.1	0.63	167.00	105.2	1.506	0.070
DMF (dry)						0.5

K_2CO_3 and ethyl bromoacetate were added to an ice-cold solution of the ketone in DMF under N_2 atmosphere. The reaction mixture was then heated to 60 °C and stirred at this temperature for 4 h. The reaction mixture was washed with ice-cold water and extracted with ethyl acetate. The collected organic phases were dried over Na_2SO_4 and the solvent was removed under reduced pressure.

The desired product was purified by flash column chromatography on silica gel with a 9:1 hexane/ethyl acetate mixture as eluent. The purification afforded the desired product in 33% yield.

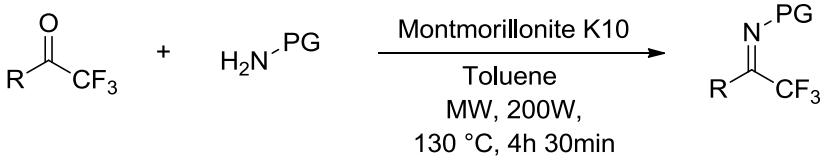
R_f= 0.22 (9:1 hexane/ethyl acetate).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.04 (d, J = 9 Hz, 2H), 7.00 (d, J = 9 Hz, 2H), 4.7 (s, 2H), 4.27 (q, J = 7 Hz, 2H), 1.29 (t, J = 7 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 178.38 (q, J = 35 Hz), 167.20, 162.92, 130.16, 123.17, 116.29 (q, J = 289 Hz), 114.46, 64.65, 61.19, 13.52.

^{19} F NMR (300 MHz, $CDCl_3$) δ: -72.21.

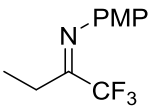
8.2.5 Preparation of fluorinated imines:



R = Ar, Alk
PG = Bn, PMP, 1-phenylethyl

General procedure: Toluene (6 mL), montmorillonite K10 clay (150 mg per 0.3 mmol), amine (0.3 mmol, 1 eq.) and ketone (0.3 mmol, 1 eq.) were introduced in a 25 mL vial without inert atmosphere. The stirred mixture was subjected to 200 W microwave irradiation and heated to 130 °C for 4 h 30 min. Constant microwave irradiation as well as simultaneous air-cooling (2 bar) were used during the entire reaction time. After cooling to room temperature, montmorillonite was removed by settling and subsequent centrifuge; finally the solvent was removed under reduced pressure. Purification methods for each product are reported below.

N-(4'-methoxyphenyl)-butan-1,1,1-trifluoro-2-imine:



This product was purified by flash column chromatography on silica gel with a 9:1 hexane/ethyl acetate mixture as eluent. The purification afforded the desired product in 40% yield.

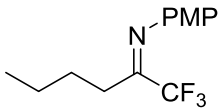
R_f= 0.37 (9:1 hexane/ethyl acetate).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.94 (d, J = 9 Hz, 2H), 6.76 (d, J = 9 Hz, 2H), 3.82 (s, 3H), 2.46 (q, J = 8 Hz, 2H), 1.14 (t, J = 8 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 162.00 (q, J = 31 Hz), 157.16, 154.59, 120.09, 120.05 (q, J = 278 Hz), 114.38, 55.40, 21.80, 11.23.

^{19} F NMR (300 MHz, $CDCl_3$) δ: -76.11.

N-(4'-methoxyphenyl)-hexan-1,1,1-trifluoro-2-imine:[222]



This product was purified by flash column chromatography on silica gel with a 9:1 hexane/ethyl acetate mixture as eluent. The purification afforded the desired product in 47% yield.

R_f = 0.50 (9:1 hexane/ethyl acetate).

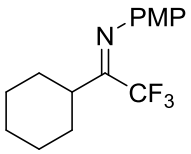
^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.90 (d, J = 9 Hz, 2H), 6.74 (d, J = 9 Hz, 2H), 3.82 (s, 3H), 2.41 (t, J = 8 Hz, 2H), 1.51 (m, 2H), 1.23 (m, 2H), 0.81 (t, J = 7 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 161.4, 157.3, 140.9, 131.4, 121.6, 114.8, 55.6, 28.8, 28.4, 22.9, 13.6.

^{19} F NMR (300 MHz, $CDCl_3$) δ: -71.7.

HRMS Mass (ESI+): m/z = calc. for $C_{13}H_{16}NOF_3Na^+$ = 282.11, found 282.11 [M + Na].

N-(4'-methoxyphenyl)-ethan-1,1,1-trifluoro-2-cyclohexyl-2-imine:

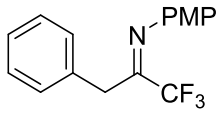


This product was purified by flash column chromatography on silica gel with a 9:1 hexane/ethyl acetate mixture as eluent. The purification afforded the desired product in 7% yield.

R_f = 0.49 (9:1 hexane/ethyl acetate).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.92 (d, J = 9 Hz, 2H), 6.71 (d, J = 9 Hz, 2H), 3.84 (s, 3H), 2.76-2.69 (m, 1H), 1.77-1.58 (m, 6H), 1.27-1.04 (m, 4H).

N-(4'-methoxyphenyl)-3-phenylpropan-1,1,1-trifluoro-2-imine:[223]



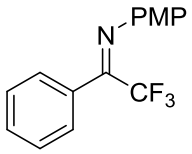
This product was purified by flash column chromatography on silica gel with a 9:1 hexane/ethyl acetate mixture as eluent. The purification afforded the desired product in 14% yield.

R_f= 0.44 (9:1 hexane/ethyl acetate).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.30-7.23 (m, 3H), 7.08-7.05 (m, 2H), 6.91 (d, J = 9 Hz, 2H), 6.82 (d, J = 9 Hz, 2H), 3.88 (s, 2H), 3.80 (s, 3H).

^{19} F NMR (300 MHz, $CDCl_3$) δ: -70.78.

N-(4'-methoxyphenyl)-ethan-2,2,2-trifluoro-1-phenyl-1-imine:[201]



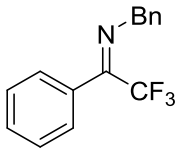
This product was purified by flash column chromatography on silica gel with a 95:5 hexane/ethyl acetate mixture as eluent. The purification afforded the desired product in 49% yield.

R_f = 0.43 (8:2 hexane/ethyl acetate).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.40-7.31 (m, 3H), 7.26-7.23 (m, 2H), 6.77-6.71 (m, 4H), 3.73 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 157.8, 155.4 (q, J = 34 Hz), 139.7, 130.7, 130.1, 128.7, 128.6, 123.3, 120.1 (q, J = 279 Hz), 114.0, 55.2.

N-benzyl-ethan-2,2,2-trifluoro-1-phenyl-1-imine:[224]



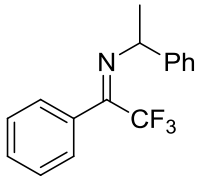
The product was purified by fractional distillation at P = 3 x 10^{-2} mbar: the desired product distilled at about 150 °C. The purification afforded the desired product in 25% yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.07 (m, 1H), 7.36 (m, 4H), 7.26 (m, 5H), 4.60 (s, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 138.2, 130.4, 129.1, 128.9, 128.8, 127.8, 127.8, 127.4, 57.0.

^{19} F NMR (300 MHz, $CDCl_3$) δ: -71.3.

N-(1'-phenylethyl)-ethan-2,2,2 -trifluoro-1-phenyl-1-imine:



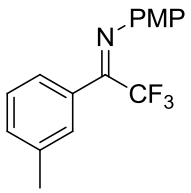
This product was purified by distillation at P = 3 x 10^{-2} mbar: the desired product distilled at about 130 °C. The purification afforded the desired product in 30% yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.54-7.52 (m, 3H), 7.39-7.29 (m, 5H), 7.24-7.22 (m, 2H), 4.58 (q, J = 7Hz, 1H), 1.46 (d, J = 7Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 156.65 (q, J = 33 Hz), 143.84, 130.61, 130.08, 128.82, 128.67, 127.64, 127.30, 126.51, 119.87 (q, J = 278 Hz), 61.44, 24.58.

^{19} F NMR (300 MHz, $CDCl_3$) δ: -71.46.

N-(4'-methoxyphenyl)-ethan-2,2,2 -trifluoro-1-(3''-methylphenyl)-1-imine:



This product was purified by flash column chromatography on silica gel with a 95:5 hexane/ethyl acetate mixture as eluent. The purification afforded the desired product in 60% yield.

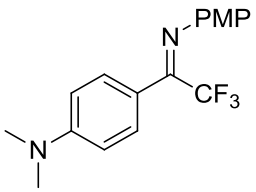
R_f= 0.23 (95:5 hexane/ethyl acetate).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.25-7.21 (m, 2H), 7.12-7.04 (m, 2H), 6.82-6.73 (m, 4H), 3.74 (s, 3H), 2.32 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 157.86, 155.49 (q, J = 34 Hz), 139.77, 138.64, 130.74, 130.29, 128.85, 128.62, 125.71, 123.43, 120.19 (q, J = 276 Hz), 113.96, 55.14, 21.24.

^{19} F NMR (300 MHz, $CDCl_3$) δ: -70.28.

N-(4'-methoxyphenyl)-ethan-2,2,2-trifluoro-1-(4''-(N',N'-dimethylammino)-phenyl)-1-imine:



This product was purified by flash column chromatography on silica gel with a 8:2 hexane/ethyl acetate mixture as eluent to remove the unreacted *4*-methoxyaniline, followed by distillation at P = 3 x 10^{-2} mbar and T = 270 °C to remove the unreacted ketone. The purification afforded the desired product in 71% yield.

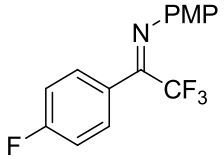
R_f= 0.15 (8:2 hexane/ethyl acetate).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.16 (d, J = 9 Hz, 2H), 6.81-6.74 (m, 4H), 6.56 (d, J = 9 Hz, 2H), 3.78 (s, 3H), 2.98 (s, 6H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 157.06, 155.40 (q, J = 33 Hz), 151.04, 141.19, 130.41, 122.56, 116.73 (q, J = 278 Hz), 116.63, 114.13, 111.14, 55.30, 39.88.

^{19} F NMR (300 MHz, $CDCl_3$) δ: -69.21.

N-(4'-methoxyphenyl)-ethan-2,2,2-trifluoro-1-(4''-fluorophenyl)-1-imine:



This product was purified by flash column chromatography on silica gel with a 95:5 hexane/ethyl acetate mixture as eluent. The purification afforded the desired product in 47% yield.

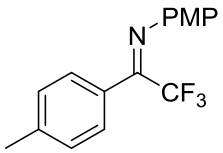
R_f= 0.29 (95:5 hexane/ethyl acetate).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.16-7.12 (m, 2H), 6.96-6.90 (m, 2H), 6.64-6.62 (m, 4H), 3.65 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 163.39 (d, J = 250 Hz), 157.90, 154.31 (q, J = 34 Hz), 139.54, 130.96, 130.84, 126.61, 123.16, 119.94 (q, J = 277 Hz), 116.21, 115.92, 114.12, 55.28.

^{19} F NMR (300 MHz, $CDCl_3$) δ: -70.37, -109.28.

N-(4'-methoxyphenyl)-ethan-2,2,2-trifluoro-1-(4''-methylphenyl)-1-imine:[201]



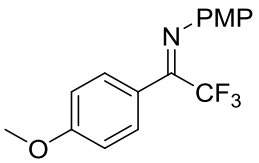
This product was purified by flash column chromatography on silica gel with a 95:5 hexane/ethyl acetate mixture as eluent. The purification afforded the desired product in 68% yield.

R_f = 0.53 (8:2 hexane/ethyl acetate).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.17-7.12 (m, 4H), 6.76-6.71 (m, 4H) 3.74 (s, 3H), 2.33 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 157.6, 155.6 (q, J = 33 Hz), 140.4, 139.9, 129.4, 128.5, 127.5,123.2, 120.1 (q, J = 279 Hz), 114.0, 55.3, 21.4.

N-(4'-methoxyphenyl)-ethan-2,2,2-trifluoro-1-(4''-methoxyphenyl)-1-imine:[201]



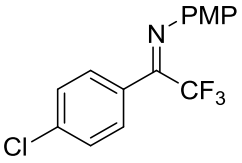
This product was purified by flash column chromatography on silica gel with a 95:5 hexane/ethyl acetate mixture as eluent. The purification afforded the desired product in 83% yield.

R_f = 0.10 (95:5 hexane/ethyl acetate).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.18-7.13 (m, 2H), 6.84-6.80 (m, 2H), 6.74-6.71(m, 4H), 3.79 (s,3H), 3.75 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 160.8, 157.5, 154.9 (q, J = 33 Hz), 140.1, 130.4, 123.0, 122.4, 120.2 (q, J = 279 Hz), 114.1, 114.0, 55.3, 55.2.

N-(4'-methoxyphenyl)-ethan-2,2,2-trifluoro-1-(4''-chlorophenyl)-1-imine:[201]



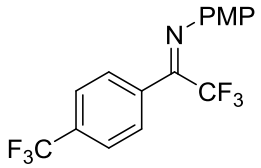
This product was purified by flash column chromatography on silica gel with a 95:5 hexane/ethyl acetate mixture as eluent. The purification afforded the desired product in 55% yield.

R_f = 0.44 (95:5 hexane/ethyl acetate).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.33-7.30 (m, 2H), 7.18 (m, 2H), 6.76-6.70 (m, 4H) 3.75 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 157.9, 154.1 (q, J = 34 Hz), 139.3, 136.4, 130.0, 129.1, 128.9, 123.2, 119.7 (q, J = 279 Hz), 114.1, 55.3.

N-(4'-methoxyphenyl)-ethan-2,2,2-trifluoro-1-(4''-trifluoromethylphenyl)-1-imine:[201]



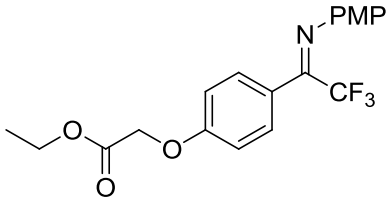
This product was purified by flash column chromatography on silica gel with a 95:5 hexane/ethyl acetate mixture as eluent. The purification afforded the desired product in 33% yield.

R_f = 0.36 (8:2 hexane/ethyl acetate).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.61 (d, J = 8 Hz, 2H), 7.36 (d, J = 8 Hz, 2H), 6.76-6.70 (m, 4H) 3.75 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 158.1, 153.7 (q, J = 34 Hz), 139.0, 134.3, 132.0 (q, J = 33 Hz), 129.1,125.8, 123.7, (q, J = 273 Hz), 123.3, 119.7 (q, J = 278 Hz), 114.2, 55.3.

N-(4'-methoxyphenyl)-ethan-2,2,2-trifluoro-1-(4''-ethylphenoxyacetate)-1-imine:



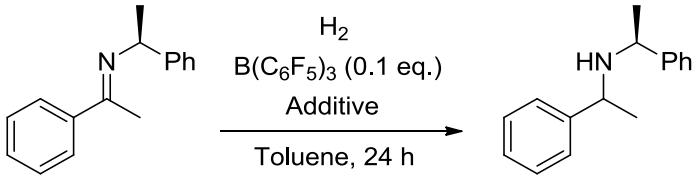
This product was purified by flash column chromatography on silica gel with a 85:15 hexane/ethyl acetate mixture as eluent. The purification afforded the desired product in 31% yield.

R_f= 0.25 (9:1 hexane/ethyl acetate).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.18 (d, J = 9 Hz, 2H), 6.83 (d, J = 9 Hz, 2H), 6.74-6.72 (m, 4H), 4.59 (s, 2H), 4.25 (q, J = 7 Hz, 2H), 3.75 (s, 3H), 1.28 (t, J = 7 Hz, 3H).

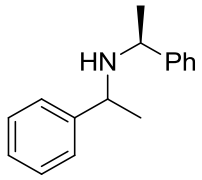
^{19} F NMR (300 MHz, $CDCl_3$) δ: -70.11.

8.3 Frustrated Lewis pairs catalyzed hydrogenations



General procedure: The oven-dried glass vessel was also first heated at 150 °C under vacuum at P = 3 x 10^{-2} mbar and then cooled in the same conditions. The borane (0.02 mmol, 0.1 eq.) was then introduced in the vessel and subjected to three H_2-vacuum cycles. Then, a solution of imine (0.25 mmol, 1.0 eq.) and additive (0.02 mmol, 0.1 eq.) in degassed toluene (4 mL) was added to the vessel *via* syringe; the reaction mixture was further diluted with degassed toluene (4 mL) and the system was subjected to other three H_2-vacuum cycles. The reaction mixture was stirred for 24 h at 300 rps under the reported temperature and hydrogen pressure conditions (see tables). After this period, the reaction was cooled to room temperature, the solvent was removed under reduced pressure and the desired amines were purified by flash column chromatography on silica gel.
Diastereoisomeric ratio and absolute configuration were determined by comparison of the NMR data of the product with literature data.

N-(1'-phenylethyl)-ethan-1-phenyl-1-amine:



This product was purified by flash column chromatography on silica gel with a 8:2 hexane/ethyl acetate mixture as eluent.
Data for *major*:
^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.38-7.21 (m, 10H), 3.55 (q, J = 6 Hz, 2H), 1.31 (d, J = 6 Hz, 6H).
^{13}C NMR (75 MHz, $CDCl_3$) δ: 145.81, 128.30, 126.67, 126.62, 55.01, 24.93.

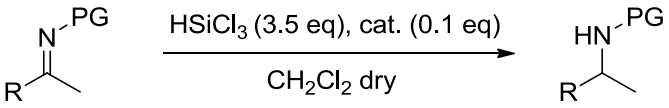
Data for *minor*:

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.38-7.21 (m, 10H), 3.81 (q, J = 6 Hz, 2H), 1.39 (d, J = 6 Hz, 6H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 145.91, 128.33, 126.73, 126.50, 54.82, 23.14.

8.4 Trichlorosilane mediated C=N reductions

8.4.1 Imines reduction:

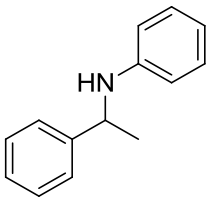


R = Ar, Alk
PG = Ph, PMP, Bn, 2-MeOPh, 2-OHPh

General procedure: The catalyst (0.02 mmol, 0.1 eq.) and a solution 0.9 M of the imine in dry CH_2Cl_2 (0.2 mmol, 1 eq.) were introduced in a 10 mL vial under N_2 atmosphere and further diluted in 2 mL of dry CH_2Cl_2. The mixture was cooled to the desired temperature (see tables) and stirred for 15 min, after which a solution 1.6 M in CH_2Cl_2 of $HSiCl_3$ (0.7 mmol, 3.5 eq.) was added. The reaction mixture was stirred for the reported time (see tables). The reaction mixture was quenched with NaOH 10% aq. until a basic pH was reached. The mixture was stirred at room temperature for 30 min, filtered over celite pad and washed with CH_2Cl_2 and ethyl acetate. The solvent was removed under reduced pressure and the desired amines were purified by flash column chromatography on silica gel.

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

N-phenyl-ethan-1-phenyl-1-amine:



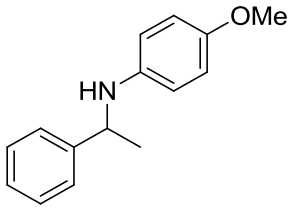
This product was purified by flash column chromatography on silica gel with a 98:2 hexane/ethyl acetate mixture as eluent.

R_f = 0.48 (8:2 hexane/ethyl acetate).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.23-7.19 (m, 7H), 6.61-6.49 (m, 3H), 4.48 (q, 1H), 1.53 (d, 3H).

The enantiomeric excess was determined by chiral HPLC with Daicel Chiralcel OD-H column, eluent: 99:1 Hex/IPA; 0.8 mL/min flow rate, detection: 210 nm, t_R 15.07 min, t_R 18.38 min.

N-(4'-methoxyphenyl)-ethan-1-phenyl-1-amine:



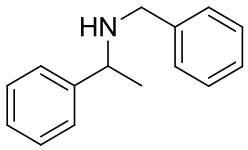
This product was purified by flash column chromatography on silica gel with a 95:5 hexane/ethyl acetate mixture as eluent.

R_f = 0.31 (8:2 hexane/ethyl acetate).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 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).

The enantiomeric excess was determined by chiral HPLC with Daicel Chiralcel OD-H column, eluent: 99:1 Hex/IPA; 0.8 mL/min flow rate, detection: 230 nm, t_R 22.25 min, t_R 25.10 min.

N-benzyl-ethan-1-phenyl-1-amine:



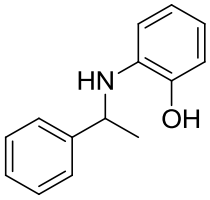
This product was purified by flash column chromatography on silica gel with a 8:2 hexane/ethyl acetate mixture as eluent.

R_f = 0.19 (8:2 hexane/ethyl acetate).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.38-7.24 (m, 10H), 3.82 (q, 1H), 3.67 (d, 1H), 3.60 (d, 1H), 1.37 (d, 3H).

The enantiomeric excess was determined by chiral HPLC with Daicel Chiralcel IB column, eluent: 99:1 Hex/IPA; 0.8 mL/min flow rate, detection: 210 nm, t_R 8.80 min, t_R 9.45 min.

N-(2'-hydroxyphenyl)-ethan-1-phenyl-1-amine:



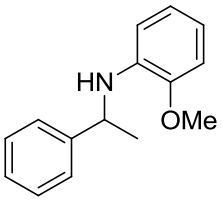
This product was purified by flash column chromatography on silica gel with a 95:5 hexane/ethyl acetate mixture as eluent.

R_f = 0.22 (8:2 hexane/ethyl acetate).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.39-7.23 (m, 5H), 6.71-6.49 (m, 4H), 4.50-4.46 (m, 1H), 1.55 (d, 3H).

The enantiomeric excess was determined by chiral HPLC with Daicel Chiralcel OD-H column, eluent: 95:5 Hex/IPA; 0.8 mL/min flow rate, detection: 242 nm, t_R 16.59 min, t_R 18.49 min.

N-(2'-methoxyphenyl)-ethan-1-phenyl-1-amine:



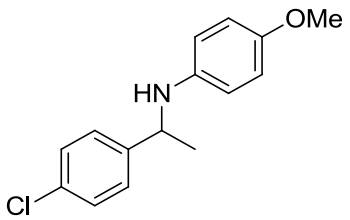
This product was purified by flash column chromatography on silica gel with a 9:1 hexane/ethyl acetate mixture as eluent.

R_f = 0.53 (9:1 hexane/ethyl acetate).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.38-7.21 (m, 6H), 6.77-6.60 (m, 2H), 6.35-6.33 (m, 1H), 4.47 (q, 1H), 3.89 (s, 3H), 1.55 (d, 3H).

The enantiomeric excess was determined by chiral HPLC with Daicel Chiralcel OD-H column, eluent: 99.5:0.5 Hex/IPA; 0.8 mL/min flow rate, detection: 254 nm, t_R 13.04 min, t_R 19.46 min.

N-(4'-methoxyphenyl)-ethan-1-(4''-chlorophenyl)-1-amine:



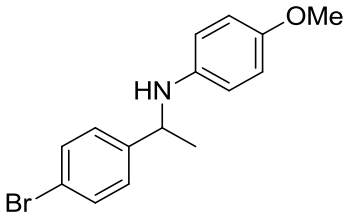
This product was purified by flash column chromatography on silica gel with a 95:5 hexane/ethyl acetate mixture as eluent.

R_f = 0.27 (9:1 hexane/ethyl acetate).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.31-7.25 (m, 5H), 6.70-6.67 (m, 2H), 6.44-6.42 (m, 2H), 4.37 (q, J = 6 Hz, 1H), 3.69 (s, 3H), 1.49 (d, J = 6 Hz,3H).

The enantiomeric excess was determined by chiral HPLC with Daicel Chiralcel OD-H column, eluent: 98:2 Hex/IPA; 0.5 mL/min flow rate, detection: 254 nm, t_R 31.84 min, t_R 38.62 min.

N-(4'-methoxyphenyl)-ethan-1-(4''-bromophenyl)-1-amine:



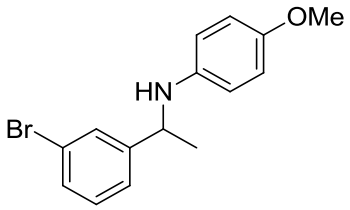
This product was purified by flash column chromatography on silica gel with a 95:5 hexane/ethyl acetate mixture as eluent.

R_f = 0.30 (8:2 hexane/ethyl acetate).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.46 (d, 2H), 7.27 (d, 2H), 6.73 (d, 2H), 6.46 (d, 2H), 4.39 (q, 1H), 3.73 (s, 3H), 1.50 (d, 3H).

The enantiomeric excess was determined by chiral HPLC with Daicel Chiralcel OD-H column, eluent: 98:2 Hex/IPA; 1.0 mL/min flow rate, detection: 230 nm, t_R 16.01 min, t_R 20.05 min.

N-(4'-methoxyphenyl)-ethan-1-(3''-bromophenyl)-1-amine:



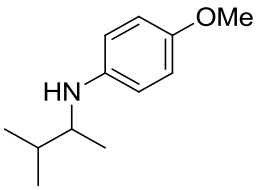
This product was purified by flash column chromatography on silica gel with a 95:5 hexane/ethyl acetate mixture as eluent.

R_f = 0.23 (9:1 hexane/ethyl acetate).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.52-7.50 (m, 1H), 7.36-7.25 (m, 2H), 7.20-7.15 (m, 1H), 6.71-6.67 (d, 2H), 6.47-6.42 (d, 2H), 4.36 (q, 1H), 3.69 (s, 3H), 1.48 (d, 3H).

The enantiomeric excess was determined by chiral HPLC with Daicel Chiralcel OD-H column, eluent: 98:2 Hex/IPA; 0.8 mL/min flow rate, detection: 230 nm, t_R 22.75 min, t_R 28.29 min.

N-(4'-methoxyphenyl)-isoamyl-2-amine:



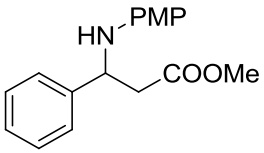
This product was purified by flash column chromatography on silica gel with a 9:1 hexane/ethyl acetate mixture as eluent.

R_f = 0.48 (8:2 hexane/ethyl acetate).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.82-6.78 (d, 2H), 6.61-6.57 (d, 2H), 3.77 (s, 3H), 3.30-3.26 (m, 1H), 1.89-1.86 (m, 1H), 1.12-1.09 (d, 3H), 1.01-0.98 (d, 3H), 0.94-0.92 (d, 3H).

The enantiomeric excess was determined by chiral HPLC with Daicel Chiralcel IB column, eluent: 99:1 Hex/IPA; 0.5 mL/min flow rate, detection: 230 nm, t_R 11.23 min, t_R 12.25 min.

N-(4'-methoxyphenyl)-methyl-3-amino-3-phenylpropanoate:



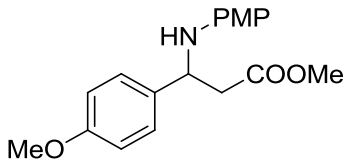
This product was purified by flash column chromatography on silica gel with a 95:5 hexane/ethyl acetate mixture as eluent.

R_f = 0.20 (8:2 hexane/ethyl acetate).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.32-7.20 (m, 5H), 6.70 (d, 2H), 6.50 (d, 2H), 4.78 (m, 1H), 3.70 (s, 3H), 3.60 (s, 3H), 2.75 (d, 2H).

The enantiomeric excess was determined by chiral HPLC with Daicel Chiralcel AD column, eluent: 7:3 Hex/IPA; 0.8 mL/min flow rate, detection: 230 nm, t_R 8.53 min, t_R 9.12 min.

N-(4'-methoxyphenyl)-methyl-3-amino-3-(4''-methoxyphenyl)propanoate:

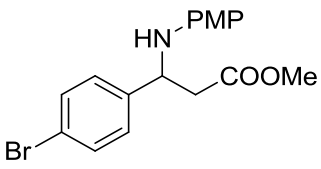


This product was purified by flash column chromatography on silica gel with a 97:3 hexane/ethyl acetate mixture as eluent.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.30 (d, 2H), 6.85 (d, 2H), 6.70 (d, 2H), 6.55 (d, 2H), 4.70 (t, 1H), 3.79 (s, 3H), 3.70 (s, 3H), 3.60 (s, 3H), 2.75 (d, 2H).

The enantiomeric excess was determined by chiral HPLC with Daicel Chiralcel AD column, eluent: 9:1 Hex/IPA; 0.8 mL/min flow rate, detection: 225 nm, t_R 20.79 min, t_R 21.87 min.

N-(4'-methoxyphenyl)-methyl-3-amino-3-(4''-bromophenyl)propanoate:



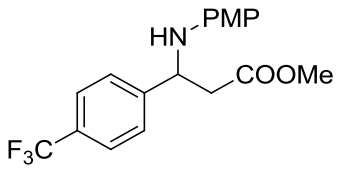
This product was purified by flash column chromatography on silica gel with a 9:1 hexane/ethyl acetate mixture as eluent.

R_f = 0.46 (1:1 hexane/ethyl acetate).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.43 (d, 2H), 7.25 (d, 2H), 6.69 (d, 2H), 6.50 (d, 2H), 4.70 (t, 1H), 3.70 (s, 3H), 3.65 (s, 3H), 2.77 (d, 2H).

The enantiomeric excess was determined by chiral HPLC with Daicel Chiralcel OD-H column, eluent: 9:1 Hex/IPA; 0.8 mL/min flow rate, detection: 210 nm, t_R 17.03 min, t_R 18.48 min.

N-(4'-methoxyphenyl)-methyl-3-amino-3-(4''-trifluoromethylphenyl)propanoate:



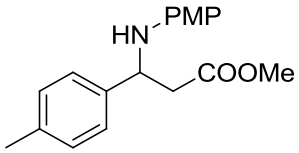
This product was purified by flash column chromatography on silica gel with a 9:1 hexane/ethyl acetate mixture as eluent.

R_f = 0.16 (8:2 hexane/ethyl acetate).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.61 (d, 2H), 7.52 (d, 2H), 6.74 (d, 2H), 6.53 (d, 2H), 4.84 (t, 1H), 3.72 (s, 3H), 3.69 (s, 3H), 2.82 (d, 2H).

The enantiomeric excess was determined by chiral HPLC with Daicel Chiralcel OD column, eluent: 9:1 Hex/IPA; 0.8 mL/min flow rate, detection: 254 nm, t_R14.48 min, t_R 16.54 min.

N-(4'-methoxyphenyl)-methyl-3-amino-3-(4''-methylphenyl)propanoate:



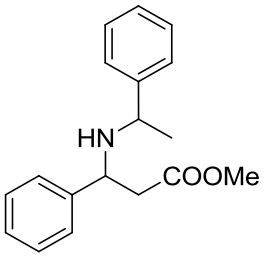
This product was purified by flash column chromatography on silica gel with a 99:1 to 9:1 hexane/ethyl acetate mixture as eluent.

R_f = 0.20 (8:2 hexane/ethyl acetate).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.28 (d, 2H), 7.15 (d, 2H), 6.73 (d, 2H), 6.57 (d, 2H), 4.75 (t, 1H), 3.72 (s, 3H), 3.67 (s, 3H), 2.81 (d, 2H), 2.34 (s, 3H).

The enantiomeric excess was determined by chiral HPLC with Daicel Chiralcel OD-H column, eluent: 9:1 Hex/IPA; 0.8 mL/min flow rate, detection: 230 nm, t_R 12.45 min, t_R 13.96 min.

N-(1'-phenylethyl)-methyl-3-phenyl-3-aminopropanoate:

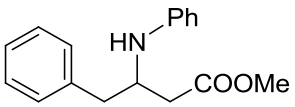


This product was purified by flash column chromatography on silica gel with a 9:1 to 8:2 hexane/ethyl acetate mixture as eluent.

R_f = 0.26 (8:2 hexane/ethyl acetate).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.39-7.19 (m, 10H), 3.81 (dd, 1H), 3.65 (s, 3H), 3.50 (q, 1H), 2.68 (dd, 1H), 2.59 (dd, 1H), 1.28 (d, 3H).

N-phenyl-methyl-4-phenyl-3-aminobutanoate:



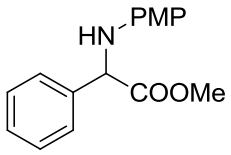
This product was purified by flash column chromatography on silica gel with a 98:2 hexane/ethyl acetate mixture as eluent.

R_f = 0.42 (8:2 hexane/ethyl acetate).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.35-7.21 (m, 7H), 6.79-6.67 (m, 3H), 4.20-4.14 (m, 1H), 3.69 (s, 3H), 2.99 (dd, 1H), 2.93 (dd, 1H), 2.60-2.52 (m, 2H).

The enantiomeric excess was determined by chiral HPLC with Daicel Chiralcel AD column, eluent: 9:1 Hex/IPA; 0.8 mL/min flow rate, detection: 230 nm, t_R 7.84 min, t_R 8.24 min.

N-(4'-methoxyphenyl)-methyl-2-amino-2-phenylacetate:



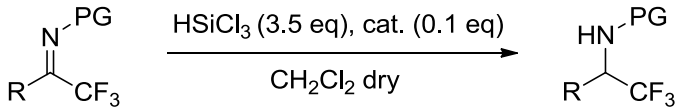
This product was purified by flash column chromatography on silica gel with a 8:2 hexane/ethyl acetate mixture as eluent.

R_f = 0.41 (7:3 hexane/ethyl acetate).

^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.53-7.51 (m, 2H), 7.39-7.36 (m, 3H), 6.75 (d, 2H), 6.56 (d, 2H), 5.03 (s, 1H), 4.70 (br s, 1H), 3.73 (s, 3H), 3.71 (s, 3H).

The enantiomeric excess was determined by chiral HPLC with Daicel Chiralcel OJ-H column, eluent: 7:3 Hex/IPA; 0.8 mL/min flow rate, detection: 210 nm, t_R 50.34 min, t_R 54.18 min.

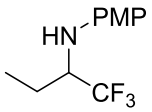
8.4.2 Fluorinated imines reduction:



R = Ar, Alk
PG = Bn, PMP, 1-phenylethyl

General procedure: the catalyst (0.02 mmol, 0.1 eq.) and a solution 0.7 M of the imine in dry CH_2Cl_2 (0.2 mmol, 1 eq.) were introduced in a 10 mL vial under N_2 atmosphere and further diluted in 1 mL of dry CH_2Cl_2. The mixture was cooled to the desired temperature (see tables) and stirred for 15 min, after which a solution 1.6 M in CH_2Cl_2 of $HSiCl_3$ (0.7 mmol, 3.5 eq.) was added. The reaction mixture was stirred for the reported time (see tables). The reaction mixture was quenched with NaOH 10% aq. until a basic pH was reached. The mixture was stirred at room temperature for 30 min, filtered over celite pad and washed with CH_2Cl_2. The solvent was removed under reduced pressure and the desired amines were purified by flash column chromatography on silica gel.
Absolute configuration was determined by comparison of the sign of the optical rotation of the product with literature data.

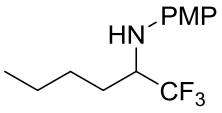
N-(4'-methoxyphenyl)-butan-1,1,1-trifluoro-2-amine:



This product was purified by flash column chromatography on silica gel with a 95:5 hexane/ethyl acetate mixture as eluent.
R_f = 0.45 (8:2 hexane/ethyl acetate).
^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.78 (d, J = 9 Hz, 2H), 6.64 (d, J = 9 Hz, 2H), 3.75 (s, 3H), 3.71-3.59 (m, 1H), 3.27 (brs, 1H), 2.00-1.86 (m, 1H), 1.64-1.49 (m, 1H), 1.05 (t, J = 8 Hz, 3H).
^{13}C NMR (75 MHz, $CDCl_3$) δ: 144.56, 135.41, 128.69, 128.58, 128.18, 126.67, 126.04 (q, J = 281 Hz), 61.66 (q, J = 28 Hz), 56.03, 23.53, 14.07.
^{19}F NMR (300 MHz, $CDCl_3$) δ: -76.30.
HRMS Mass (ESI+): m/z = calc. for $C_{11}H_{15}NOF_3^+$ = 234.11, found 234.11 [M + H].

The enantiomeric excess was determined by chiral HPLC with Daicel Chiralcel OD-H column, eluent: 99:1 Hex/IPA; 0.8 mL/min flow rate, detection: 242 nm, t_R 10.05 min (major), t_R 12.14 min (minor).

N-(4'-methoxyphenyl)-hexan-1,1,1-trifluoro-2-amine:[222]



This product was purified by flash column chromatography on silica gel with a 99:1 hexane/ethyl acetate mixture as eluent.

R_f = 0.46 (9:1 hexane/ethyl acetate).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.78 (d, J = 9 Hz, 2H), 6.62 (d, J = 9 Hz, 2H), 3.77 (s, 3H), 3.74-3.72 (m, 1H), 3.27-3.21 (m, 1H), 1.89-1.82 (m, 1H), 1.56-1.51 (m, 2H), 1.40-1.33 (m, 2H), 0.91 (t, J = 7.1 Hz, 3H).

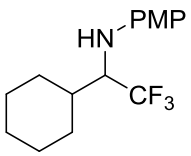
^{13}C NMR (75 MHz, $CDCl_3$) δ: 153.0, 141.1, 126.6 (q, J = 282 Hz), 115.1, 115.0, 57.1 (q, J = 29 Hz), 55.9, 29.6, 27.8, 22.6, 14.0.

^{19}F NMR (300 MHz, $CDCl_3$) δ: -76.0.

HRMS Mass (ESI+): m/z = calc. for $C_{13}H_{17}NOF_3^+$ = 260.13, found 260.12 [M + H].

The enantiomeric excess was determined by chiral HPLC with Daicel Chiralcel OD-H column, eluent: 99:1 Hex/IPA; 0.8 mL/min flow rate, detection: 230 nm, t_R 7.81 min (major), t_R 9.21 min (minor).

N-(4'-methoxyphenyl)-ethan-1,1,1-trifluoro-2-cyclohexyl-2-amine:



This product was purified by flash column chromatography on silica gel with a 99:1 hexane/ethyl acetate mixture as eluent.

R_f = 0.42 (9:1 hexane/ethyl acetate).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.83-6.79 (m, 2H), 6.68-6.64 (m, 2H), 3.78 (s, 3H), 3.71-3.58 (m, 1H), 3.57-3.42 (m, 1H), 1.99-1.64 (m, 6H), 1.45-1.08 (m, 5H).

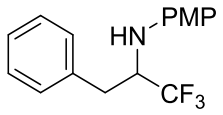
^{13}C NMR (75 MHz, $CDCl_3$) δ: 152.79, 141.40, 126.47 (q, J = 284 Hz), 114.92, 61.50 (q, J = 27 Hz), 55.70, 38.62, 30.38, 27.34, 26.16, 25.96.

^{19}F NMR (300 MHz, CDCl3) δ: -72.74.

$[\alpha]_D^{22}$ = -3.6 (solvent: $CHCl_3$; *c* = 0.356 g/100 mL; λ = 589 nm).

The enantiomeric excess was determined by chiral HPLC with Daicel Chiralcel OD-H column, eluent: 99:1 Hex/IPA; 0.8 mL/min flow rate, detection: 230 nm, t_R 7.79 min (major), t_R 9.35 min (minor).

N-(4'-methoxyphenyl)-3-phenylpropan-1,1,1-trifluoro-2-amine:[225]



This product was purified by flash column chromatography on silica gel with a 99:1 hexane/ethyl acetate mixture as eluent.

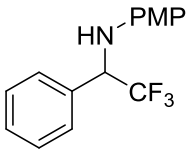
R_f = 0.36 (9:1 hexane/ethyl acetate).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.32-7.26 (m, 5H), 6.74 (d, 2H, J = 9 Hz), 6.53 (d, 2H, J = 9 Hz), 4.08-4.04 (m, 1H), 3.74 (s, 3H), 3.41 (m, 1H), 3.24 (m, 1H), 2.87 (m, 1H).

^{19}F NMR (300 MHz, CDCl3) δ: -75.69.

The enantiomeric excess was determined by chiral HPLC with Daicel Chiralcel OD-H column, eluent: 99:1 Hex/IPA; 0.8 mL/min flow rate, detection: 230 nm, t_R 18.00 min (minor), t_R 20.24 min (major).

N-(4'-methoxyphenyl)-ethan-2,2,2-trifluoro-1-phenyl-1-amine:[201]



This product was purified by flash column chromatography on silica gel with a 95:5 hexane/ethyl acetate mixture as eluent.

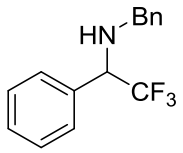
R_f = 0.36 (8:2 hexane/ethyl acetate).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.46-7.44 (m, 2H), 7.42-7.36 (m, 3H), 6.76-6.72 (m, 2H), 6.63-6.59 (m, 2H), 4.81 (q, J = 7 Hz, 1H), 3.72 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 153.3, 139.4, 134.3, 129.0, 128.9, 127.9, 125.1 (q, J = 282 Hz), 115.7, 114.8, 61.7 (q, J = 30 Hz), 55.6.

The enantiomeric excess was determined by chiral HPLC with Daicel Chiralcel AD column, eluent: 95:5 Hex/IPA; 0.8 mL/min flow rate, detection: 230 nm, t_R 13.16 min (minor), t_R 20.74 min (major).

N-benzyl-ethan-2,2,2-trifluoro-1-phenyl-1-amine:[226]



This product was purified by flash column chromatography on silica gel with a 95:5 hexane/ethyl acetate mixture as eluent.

R_f = 0.72 (9:1 hexane/ethyl acetate).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.44-7.39 (m, 5H), 7.36-7.28 (m, 5H), 4.14 (q, J = 7 Hz, 1H), 3.83 (d, J = 13 Hz, 1H), 3.67 (d, J = 13 Hz, 1H).

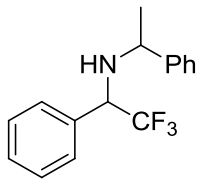
^{13}C NMR (75 MHz, $CDCl_3$) δ: 139.0, 134.2, 129.0, 128.7, 128.6, 128.5, 128.2, 127.4, 125.4 (q, J = 281 Hz), 63.4 (q, J = 29 Hz), 51.0.

^{19} F NMR (300 MHz, $CDCl_3$) δ: -73.9.

HRMS Mass (ESI+): m/z = calc. for $C_{15}H_{14}NF_3^+$ = 265.10, found 265.10 [M + H].

The enantiomeric excess was determined by chiral HPLC with Daicel Chiralcel AD column, eluent: 9:1 Hex/IPA; 0.8 mL/min flow rate, detection: 210 nm, t_R 4.91 min (major), t_R 5.33 min (minor).

N-(1'-phenylethyl)-ethan-2,2,2-trifluoro-1-phenyl-1-amine:



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

R_f= 0.54 (8:2 hexane/ethyl acetate).

Data for *major*:

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.45-7.27 (m, 10H), 4.11 (q, J = 7 Hz, 1H), 4.04 (q, J = 7 Hz, 1H), 1.97 (brs, 1H), 1.43 (d, J = 7 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 144.08, 134.93, 128.23, 128.11, 127.71, 126.86, 126.21, 125.57 (q, J = 280 Hz), 61.21 (q, J = 28 Hz), 55.57, 23.02.

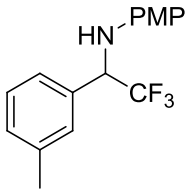
^{19}F NMR (300 MHz, CDCl3) δ: -73.42.

Data for *minor*:

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.45-7.27 (m, 10H), 3.91 (q, J = 7 Hz, 1H), 3.62 (q, J = 7 Hz, 1H), 1.97 (brs, 1H), 1.39 (d, J = 7 Hz, 3H).

HRMS Mass (ESI+): m/z = calc for $C_{16}H_{17}NF_3^+$ = 280.13, found 280.13 [M + H].

N-(4'-methoxyphenyl)-ethan-2,2,2-trifluoro-1-(3''-methylphenyl)-1-amine:



This product was purified by flash column chromatography on silica gel with a 95:5 hexane/ethyl acetate mixture as eluent.

R_f = 0.41 (8:2 hexane/ethyl acetate).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.27-7.16 (m, 4H), 6.75 (d, J = 9 Hz, 2H), 6.62 (d, J = 9 Hz, 2H), 4.76 (q, J = 7 Hz, 1H), 3.72 (s, 3H), 2.36 (s, 3H).

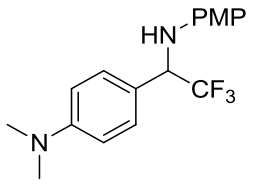
^{13}C NMR (75 MHz, $CDCl_3$) δ: 152.86, 139.20, 138.15, 133.84, 129.36, 128.27, 128.09, 124.74 (q, J = 280 Hz), 124.49, 115.23, 114.40, 61.70 (q, J = 30 Hz), 55.18, 20.94.

^{19} F NMR (300 MHz, $CDCl_3$) δ: -74.40.

HRMS Mass (ESI+): m/z = calc. for $C_{16}H_{17}NOF_3^+$ = 296.12, found 296.12 [M + H].

The enantiomeric excess was determined by chiral HPLC with Daicel Chiralcel OD-H column, eluent: 98:2 Hex/IPA; 0.8 mL/min flow rate, detection: 230 nm, t_R 14.89 min (minor), t_R 15.82 min (major).

N-(4'-methoxyphenyl)-ethan-2,2,2-trifluoro-1-(4''-(N',N'-dimethylammino)-phenyl)-1-amine:



This product was purified by flash column chromatography on silica gel with a 99:1 hexane/ethyl acetate mixture as eluent.

R_f = 0.33 (8:2 hexane/ethyl acetate).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.29 (d, J = 9 Hz, 2H), 6.78-6.72 (m, 4H), 6.63 (d, J = 9 Hz, 2H), 4.72 (q, J = 7 Hz, 1H), 4.01 (brs, 1H), 3.74 (s, 3H), 2.97 (s, 6H).

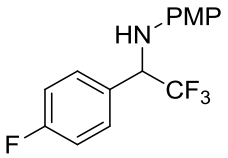
^{13}C NMR (75 MHz, $CDCl_3$) δ: 152.70, 139.47, 128.18, 125 (q, J = 280 Hz), 115.23, 114.36, 112.09, 60.80 (q, J = 29 Hz), 55.26, 55.12, 39.98.

^{19} F NMR (300 MHz, $CDCl_3$) δ: -74.78.

HRMS Mass (ESI+): m/z = calc for $C_{17}H_{20}N_2OF_3^+$ = 325.15, found 325.15 [M + H].

The enantiomeric excess was determined by chiral HPLC with Daicel Chiralpack AD column, eluent: 9:1 Hex/IPA; 0.8 mL/min flow rate, detection: 230 nm, t_R 8.87 min (minor), t_R 22.79 min (major).

N-(4'-methoxyphenyl)-ethan-2,2,2-trifluoro-1-(4''-fluorophenyl)-1-amine:



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

R_f = 0.40 (8:2 hexane/ethyl acetate).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.45-7.40 (m, 2H), 7.10-7.04 (m, 2H), 6.74 (d, J = 9 Hz, 2H), 6.58 (d, J = 9 Hz, 2H), 4.79 (q, J = 7 Hz, 1H), 4.11 (brs, 1H), 3.71 (s, 3H).

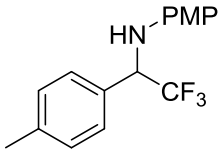
^{13}C NMR (75 MHz, $CDCl_3$) δ: 163.07 (d, J = 246 Hz), 153.43, 139.17, 130.03, 129.78, 129.67, 124.95 (q, J = 280 Hz), 116.07, 115.76, 114.86, 61.07 (q, J = 29 Hz), 55.63.

^{19} F NMR (300 MHz, $CDCl_3$) δ: -74.72, - 112.98.

HRMS Mass (ESI+): m/z = calc. for $C_{15}H_{14}NOF_4^+$ = 300.10, found 300.10 [M + H].

The enantiomeric excess was determined by chiral HPLC with Daicel Chiralpack AD column, eluent: 9:1 Hex/IPA; 0.8 mL/min flow rate, detection: 230 nm, t_R 12.01 min (minor), t_R 17.98 min (major).

N-(4'-methoxyphenyl)-ethan-2,2,2-trifluoro-1-(4''-methylphenyl)-1-amine:[201]



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

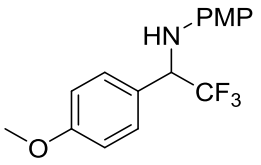
R_f = 0.42 (8:2 hexane/ethyl acetate).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.33 (d, J = 8 Hz, 2H), 7.19 (d, J = 8 Hz, 2H), 6.76-6.72 (m, 2H), 6.63-6.59 (m, 2H), 4.77 (q, J = 7 Hz, 1H), 3.72 (s, 3H), 2.35 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 153.2, 139.5, 138.9, 131.2, 129.6, 127.8, 125.2 (q, J = 282 Hz), 115.6, 114.7, 61.4 (q, J = 30 Hz), 55.6, 21.1.

The enantiomeric excess was determined by chiral HPLC with Daicel Chiralcel AD column, eluent: 9:1 Hex/IPA; 0.8 mL/min flow rate, detection: 230 nm, t_R 10.63 min (minor), t_R 15.24 min (major).

N-(4'-methoxyphenyl)-ethan-2,2,2-trifluoro-1-(4''-methoxyphenyl)-1-amine:[201]



This product was purified by flash column chromatography on silica gel with a 95:5 hexane/ethyl acetate mixture as eluent.

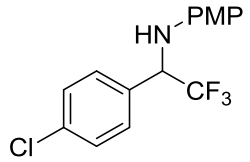
R_f = 0.32 (8:2 hexane/ethyl acetate).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.36-7.31 (m, 2H), 6.93-6.89 (m, 2H), 6.76-6.72 (m, 2H), 6.62-6.58 (m, 2H), 4.75 (q, J = 7 Hz, 1H), 3.80 (s,3H), 3.72 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 160.0, 153.2, 139.5, 129.1, 126.2, 125.2 (q, J = 282 Hz), 115.7, 114.8, 114.2, 61.1 (q, J = 30 Hz), 55.6, 55.3.

The enantiomeric excess was determined by chiral HPLC with Daicel Chiralcel OD-H column, eluent: 99:1 Hex/IPA; 0.8 mL/min flow rate, detection: 230 nm, t_R 44.33 min (major), t_R 52.54 min (minor).

N-(4'-methoxyphenyl)-ethan-2,2,2-trifluoro-1-(4''-chlorophenyl)-1-amine:[201]



This product was purified by flash column chromatography on silica gel with a 95:5 hexane/ethyl acetate mixture as eluent.

R_f = 0.39 (8:2 hexane/ethyl acetate).

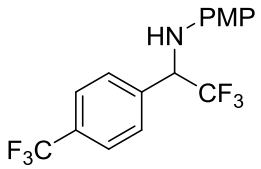
^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.40-7.35 (m, 4H), 6.75-6.71 (m, 2H), 6.58-6.55 (m, 2H), 4.79 (q, J = 7 Hz, 1H), 3.71 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 153.4, 139.0, 135.1, 132.7, 129.3, 129.1, 124.8 (q, J = 282 Hz), 115.7, 114.8,61.1 (q, J = 30 Hz), 55.6.

HRMS Mass (ESI+): m/z = calc. for $C_{15}H_{13}ClNOF_3^+$ = 315.06, found 315.06 [M + H].

The enantiomeric excess was determined by chiral HPLC with Daicel Chiralcel AD column, eluent: 9:1 Hex/IPA; 0.8 mL/min flow rate, detection: 230 nm, t_R 13.37 min (minor), t_R 17.85 min (major).

N-(4'-methoxyphenyl)-ethan-2,2,2-trifluoro-1-(4''-trifluoromethylphenyl)-1-amine:[201]



This product was purified by flash column chromatography on silica gel with a 95:5 hexane/ethyl acetate mixture as eluent.

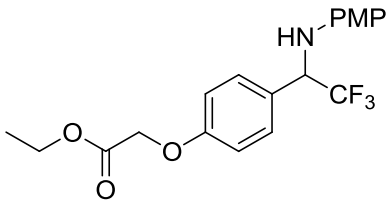
R_f = 0.18 (95:5 hexane/ethyl acetate).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.64 (d, J = 8 Hz, 2H), 7.58 (d, J = 8 Hz, 2H), 6.76-6.72 (m, 2H), 6.58-6.54 (m, 2H), 4.88 (q, J = 7 Hz, 1H), 3.70 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 153.5, 138.8, 138.2, 131.3 (q, J = 33 Hz), 128.4, 125.8, 124.7 (q, J = 282 Hz), 123.8 (q, J = 272 Hz), 115.7, 114.9, 61.4 (q, J = 30 Hz), 55.6.

The enantiomeric excess was determined by chiral HPLC with Daicel Chiralcel OD-H column, eluent: 95:5 Hex/IPA; 0.5 mL/min flow rate, detection: 254 nm, t_R 26.70 min (minor), t_R 32.82 min (major).

N-(4'-methoxyphenyl)-ethan-2,2,2-trifluoro-1-(4''-ethylphenoxyacetate)-1-amine:



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

R_f = 0.22 (8:2 hexane/ethyl acetate).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.36 (d, J = 9 Hz, 2H), 6.90 (d, J = 9 Hz, 2H), 6.72 (d, J = 9 Hz, 2H), 6.58 (d, J = 9 Hz, 2H), 4.74 (q, J = 7 Hz, 1H), 4.60 (s, 2H), 4.26 (q, J = 7 Hz, 2H), 3.71 (s, 3H), 1.28 (t, J = 7 Hz, 3H).

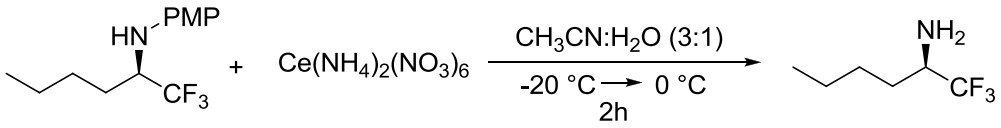
^{13}C NMR (75 MHz, $CDCl_3$) δ: 168.66, 158.36, 153.33, 139.48, 129.21, 127.42, 125.13 (q, J = 279 Hz), 115.04, 115.03, 114.84, 65.43, 61.43, 61.12 (q, J = 37 Hz), 55.64, 14.12.

^{19} F NMR (300 MHz, $CDCl_3$) δ: -74.72.

The enantiomeric excess was determined by chiral HPLC with Daicel Chiralcel OD-H column, eluent: 99:1Hex/IPA; 0.8 mL/min flow rate, detection: 280 nm, t_R 27.24 min (major), t_R 32.56 min (minor).

8.5 Deprotection protocol

Synthesis of (R)-hexan-1,1,1-trifluoro-2-amine:[227]



	eq	mmol	MW (g/mol)	mg	d (g/mL)	mL
N-PMP trifluoro hexanamine	1.0	0.36	261.28	94.1	/	/
CAN	5.0	1.80	548.26	986.9	/	/
H_2O						2.0
CH_3CN						6.0

A solution of ammonium cerium (IV) nitrate in H_2O was added dropwise to a solution of the amine (0.36 mmol, 1.0 eq.) in CH_3CN at -20 °C. The temperature was allowed to rise till 0 °C and the reaction mixture was stirred at this temperature for 2 h. The solution was extracted with ethyl acetate, the collected organic phases were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The desired product was obtained in 80% yield on the crude product.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.04 (brs, 2H), 3.97-3.79 (m, 1H), 2.02-1.87 (m, 2H), 1.64-1.31 (m, 4H), 0.96-0.91 (m, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 124.60 (q, J = 281 Hz), 53.82 (q, J = 31 Hz), 27.19, 22.67, 13.95.

^{19} F NMR (300 MHz, $CDCl_3$) δ: -75.17.

APPENDIX

Highly stereoselective direct double aldol reactions catalyzed by bisthiophene diphosphine oxide

"*If we knew what it was we were doing,*
it would not be called research, would it?"
Albert Einstein

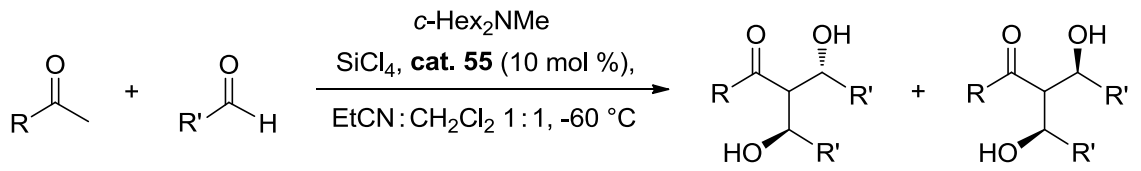
As widely described in Chapter 3, over the last decade phosphoramides and phosphine oxides have found application in the innovative class of reactions that could be termed as "Lewis base-catalyzed Lewis acid-mediated reactions".

A significant breakthrough in the field was accomplished by Denmark who explored the possibility to develop chiral hypervalent silicates to be used as Lewis acids, according to the mode of activation described in Chapter 3 and proposed in Scheme **3.3.3.3**.[88] The authors reported that a weakly acidic species, such as silicon tetrachloride, can be activated by coordination of a strongly Lewis basic chiral compound and subsequent ionization of a chloride ligand, leading to *in situ* formation of a chiral Lewis acid. This species was proven to be an efficient catalyst for the aldol addition of acetate-, propionate-, and isobutyrate-derived silyl ketene acetals to conjugated and nonconjugated aldehydes. In the proposed mechanism the coordination of a Lewis base to a Lewis acid makes it more electrophilic; since a cationic species is generated, the result is a significantly increased Lewis acidity of the new adduct. In this aspect the combination of a chiral Lewis base and silicon tetrachoride to generate a strong Lewis acid is different from most of the other chiral Lewis acid-promoted reactions. Lewis base coordination to

$SiCl_4$ activates the Lewis acid, while complexation of a basic chiral ligand to a Lewis acid precursor normally decreases the reactivity of the chiral complex. Indeed, only after coordination of phosphoramide $SiCl_4$ is sufficiently Lewis acidic to promote addition of silyl ketene acetals to aldehydes with good yield.

By exploiting the same concept, Nakajima and co-workers recently reported[228] that the binaphthyl-based phosphine oxide BINAPO is able to stereoselectively catalyze the sequential double aldol condensation of acetophenone with benzaldehyde. Sequential reactions have gained importance in recent years because they provide attractive approaches to the synthesis of molecules with complex architectures in a single operational step.[229] In particular, the development of sequential enantioselective direct aldol reactions would be of great importance for the preparation of complex structures in the field of organic synthesis. In fact, one of the current challenges in organic chemistry is to develop tandem reactions that provide complex molecules from readily available starting compounds.

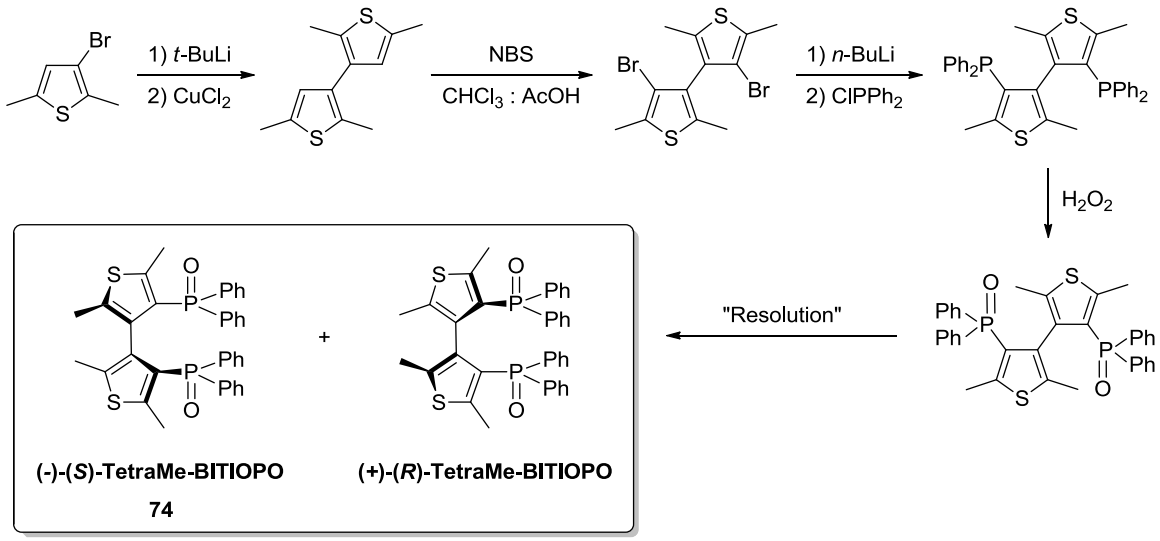
In this work the authors described that the condensation promoted by a 10 mol % amount of (*S*)-BINAPO led to the formation of the corresponding products as a mixture of two diastereoisomers and 60% *e.e.* for the major isomer. While searching for the best experimental conditions it was found that a mixture of DCM and propionitrile as reaction solvent in combination with the use of dicyclohexylmethylamine allowed an increase in the stereoselectivity up to 70% enantiomeric excess; only with 2-furyl and 2-cyclopropyl methyl ketones 90% of enantioselectivity was reached.



Scheme 8.1 Double aldol reaction catalyzed by (*S*)-BINAPO

Quite recently our attention has been devoted to the study of (*S*)-TetraMe-BITIOPO, a C_2-symmetric chiral diphoshine oxide that has already been successfully employed in direct aldol condensation and allylation reactions showing an overall superior

performance compared to BINAPO. This compound is simply obtained by oxidation of 2,2',5,5'-tetramethyl-4,4'-bis(diphenylphosphino)-3,3'-bisthiophene (TetraMe-BITIOP), a chelating ligand for transition metals. The complexes of this electronrich diphosphine with Ru(II) and Rh(I) are very useful catalysts for some enantioselective homogeneous hydrogenation reactions. The synthesis of TetraMe-BITIOPO, reported in Scheme **8.2**, starts from inexpensive materials and consists of only five steps including resolution. The very good synthetic accessibility makes this compound very interesting from the industrial point of view, and TetraMe-BITIOPO is now commercially available in both enantiomeric forms from Chemi S.p.A.[230]

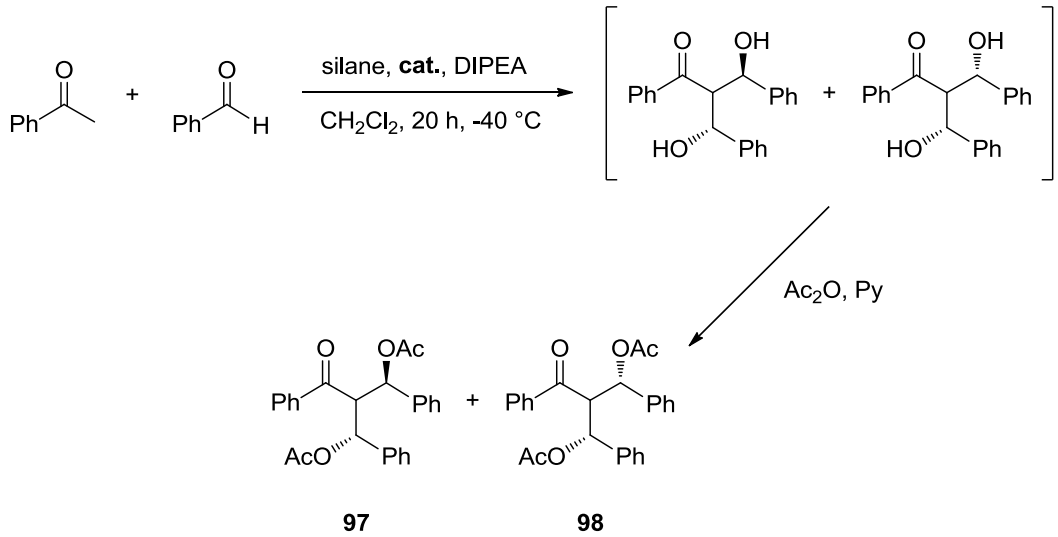


Scheme 8.2 Synthetic scheme of TetraMe-BITIOPO

By analyzing the structure from an electronic point of view, it's possible to observe that the two diphenylphosphino groups are located in the electronrichest position (the β-position) of an inherently electronrich heterocyclic ring. To guarantee configurational stability to the ligand through consistent hindrance to rotation around the interanular bond, four methyl group were introduced in α- and δ-position of the two thiophene rings. While the methyl group adjacent to the biaryl bond directly contributes to the stability of the system, the other one develops a consistent buttressing effect on the phosphine group. The steric hindrance around the biaryl bond makes the bistiophene scaffold similar to a biphenyl backbone, but with lower interplanar angle. It's noteworthy that this structure exist in two enantiomeric forms that can be separated using chiral dibenzoyltartaric acid.
Since in our previous studies it was observed that the use of biheteroaromatic diphosphine oxides, more electronrich than the commonly used binaphthyl diphosphine derivatives,

often led to the formation of the desired products with higher enantioselectivities,[231] we decided to investigate the behavior of (*S*)-TetraMe-BITIOPO in the direct double aldol reaction between aryl methyl ketones and aromatic aldehydes.[232]

The reaction between 1 mol/eq. of acetophenone and 2.2 mol/eq. of benzaldehyde was first investigated in the presence of stoichiometric amounts of $SiCl_4$ and a catalytic amount of enantiomerically pure (*S*)-Tetra-Me-BITIOPO (0.1 mol/eq.). By quenching and working up the reaction with a saturated solution of $NaHCO_3$ allowed to obtain the product as mixture of diastereoisomers, as clearly indicated by ^1H NMR of the crude reaction mixture. However, any attempt to purify the 1,3 diol bisaldol product led to decomposition and low isolation yields and only minor amounts (< 10%) of the mono-aldol product were typically detected. Therefore the crude products were treated with acetic anhydride to afford the corresponding diacetate derivatives, which were isolated as pure compounds and properly analysed and characterized (Table **8.1**).[232]



97 **98**

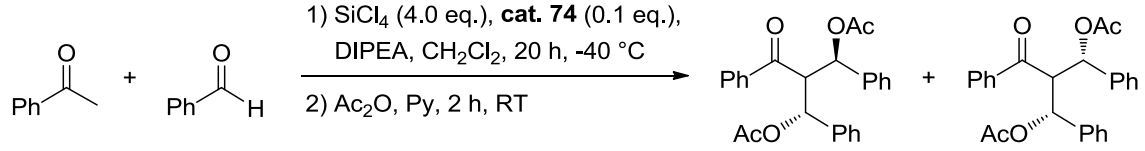
entry	silane	cat.	y (%)	d.r.	*e.e.* (%) (major isomer)
1	$SiCl_4$	**55** (0.1 eq.)	65	84 : 16	*53*
2	$SiCl_4$	**74** (0.1 eq.)	35	86 : 14	*61*
3	Cl_3SiOTf	**55** (0.1 eq.)	31	79 : 21	*31*

Table 8.1 (*S*)-BITIOPO catalyzed condensation of acetophenone with benzaldehyde

After 20 hours at -40 °C the reaction was found to proceed in 35% yield, 86 : 14 ratio between the chiral isomer **97** and the achiral species **98** and 61% *e.e.* for the major

isomer. It must be noted that **98** is an achiral molecule that may exist as two diastereoisomers (carbon in α to carbonyl group is an achirotopic stereogenic centre); however only one set of signals was observed by NMR analysis of this product. Similarly, also HPLC analysis allowed to detect only one peak in spite of the many attempted conditions. For sake of comparison the reaction was performed under the same experimental conditions with (*S*)-BINAPO as chiral catalyst: the product was obtained in higher yields and comparable diastereoselectivity, but with slightly lower enantiomeric excess. The use of trichlorosilyl triflate did not bring any improvement to the process.

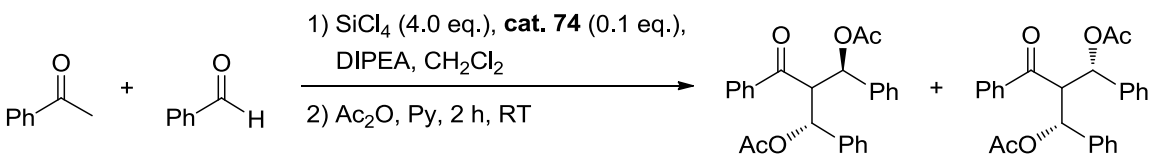
However it was observed that the choice of the base for the reaction work up strongly influenced the chemical yield and the level of the enantioselectivity of the isolated products. It was found that quenching with ammonium chloride allowed to obtain the 1,3 diacetate **97** as major product in good yield, 88 : 12 diastereoisomeric ratio and enantioselectivities up to 75% *e.e.* (Table **8.2**, entry 2).



entry	quench	y (%)	d.r.	*e.e.* (%) (major isomer)
1	$NaHCO_3$ s.s.	35	86 : 14	*61*
2	NH_4Cl s.s.	61	88 : 12	*75*

Table 8.2 Optimization of the workup conditions

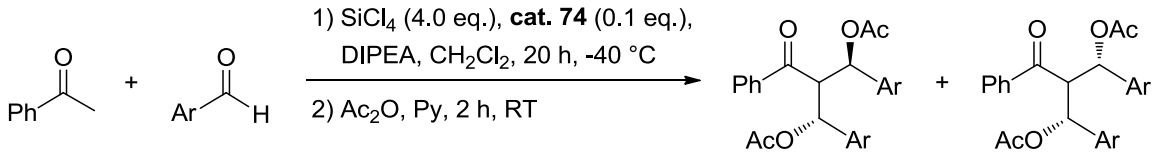
Subsequently, in the attempt to improve the stereoselectivity of the reaction, the reaction temperature was further lowered to -78 °C (Table **8.3**):



entry	T (°C)	t (h)	y (%)	d.r.	*e.e.* (%) (major isomer)
1	-40	20	61	88:12	*75*
2	-78	20	/	/	/
3	-78	72	35	75:25	*69*

Table 8.3 Screening of different temperatures

As expected, the condensation proceeded in lower chemical yields and without appreciable increase of the enantioselectivity, even with prolonged reaction times.
With the optimized experimental conditions in our hands, it was decided to further explore the general scope of the methodology. At first the reaction of acetophenone with differently substituted aromatic aldehydes was investigated: the obtained results are reported in Table **8.4**:



entry	Ar	y (%)	d.r.	*e.e.* (%) (major isomer)
1	Ph	61	88:12	*75*
2	4-$CF_3C_6H_4$	63	90:10	*41*
3	4-ClC_6H_4	65	80:20	*70*
4	4-$NO_2C_6H_4$	51	70:30	*26*
5	4-$OMeC_6H_4$	40	73:27	*91*
6	4-MeC_6H_4	43	89:11	*80*
7	1-naphthyl	55	89:11	*41*
8	2-furyl	45	92:8	*71*
9	2-thienyl	25	90:10	*90*

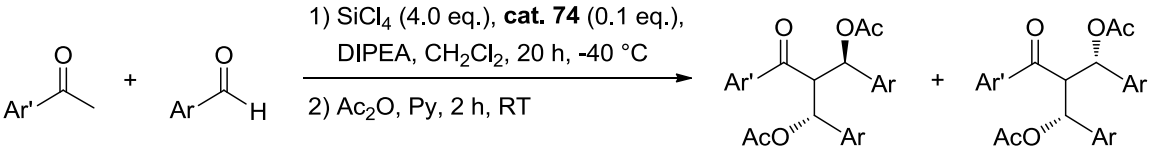
Table 8.4 Screening of differently substituted aldehydes

Generally, aldehydes bearing electron withdrawing groups reacted with acetophenone in higher yields than benzaldehyde, while electronrich aldehydes were less reactive;

however the opposite trend was observed for the enantioselectivity. Indeed, while the diastereoselectivity seems not to be influenced by electronic characteristics of the substrates, enantioselectivities ranging from 80 to 91% were obtained for the reaction of 4-tolualdehyde, 4-anisaldehyde and 2-thiophene caboxyaldehyde.

4-Chlorobenzaldehyde afforded the 1,3-diacetate in good yield and enantioselectivity comparable to that observed with benzaldehyde; reaction with 4-trifluoromethyl benzaldehyde gave the product even in higher enantioselectivity, up to 81% *e.e.*. Instead the analogous 4-nitro derivative was isolated with only 26% *e.e.*, probably due to the interference in the reaction mechanism of the nitro group, able to coordinate tetrachlorosilane.

The behavior of electronically different aryl methyl ketones was then studied: 4-methoxyphenyl and 4-nitrophenyl methyl ketones were reacted with two equivalents of different aromatic aldehydes (Table **8.5**).



entry	Ar'	Ar	y (%)	d.r.	*e.e.* (%) (major isomer)
1	4-$OMeC_6H_4$	Ph	45	85:15	*43*
2	4-$OMeC_6H_4$	4-$CF_3C_6H_4$	71	85:15	*25*
3	4-$OMeC_6H_4$	4-$OMeC_6H_4$	51	86:14	*27*
4	4-$OMeC_6H_4$	3,4-$(OMe)_2C_6H_4$	70	95:5	*15*
5	4-$OMeC_6H_4$	2-furyl	71	84:16	*11*
6	4-$OMeC_6H_4$	2-thienyl	45	77:23	*51*
7	4-$NO_2C_6H_4$	Ph	30	70:30	*83*
8	4-$NO_2C_6H_4$	4-$CF_3C_6H_4$	35	88:12	*55*
9	4-$NO_2C_6H_4$	4-$OMeC_6H_4$	25	55:45	*80*
10	4-$NO_2C_6H_4$	2-furyl	40	83:17	*90*
11	4-$NO_2C_6H_4$	2-thienyl	35	61:39	*90*

Table 8.5 Reaction of aryl methyl ketones with differently substituted aldehydes

The reaction generally afforded the double aldol condensation products in good yields with aldehydes functionalized both with electrowithdrawing or electrondonating groups; diastereoselectivities vary from 61:39 up to 95:5. Unfortunately the reaction with the aryl ketone substituted with an electrondonating group such as the methoxy group generally gave the products with lower enantioselectivities than those obtained with acetophenone. With benzaldehyde and 2-thiophencarboxyaldehyde 43% and 51% *e.e.* for the major isomer were obtained, respectively.

On the other hand, as expected, 4-nitrophenyl methyl ketone showed to be less reactive than acetophenone and with the poorly reactive electronrich aldehydes afforded the desired products in low yields; however, the reaction with 4-anisaldehyde led to the formation of the desired product in 80% *e.e.*, although in low yields and diastereoselectivity. It must be mentioned that the heteroaromatic substrates like 2-furyl carboxyaldehyde and 2-thienyl carboxyaldehyde showed a good reactivity and afforded the corresponding 1,3-diacetate in modest yields but with 90% of enantioselectivity.

In conclusion, the double aldol reaction of aryl methyl ketones with aromatic aldehydes was studied in the presence of catalytic amounts of diheteroromatic diphosphine oxide as chiral Lewis base. The reaction products were isolated as 1,3-diacetate derivatives in yields depending on the electronic characteristics of the reactive substrates: from the chemical activity point of view, best results were obtained by employing an electronrich aryl methyl ketone and electronpoor aromatic aldehydes. However, while the diastereoisomeric ratio seems to be quite independent from the substrate variation, ranging typically from 70 : 30 to 90 : 10, highest enantioselectivities were observed in the reaction with aldehydes bearing electrondonating groups and heteroaromatic aldehydes. In those cases *e.e.* up to 91% were obtained, showing that (*S*)-BITIOPO favorably compares with the BINAP-derived ligand, leading often to the products in higher enantioselectivities. Further studies are needed in order to better address the diastereoselectivity of the process and the chemical activation of the less reactive substrates.

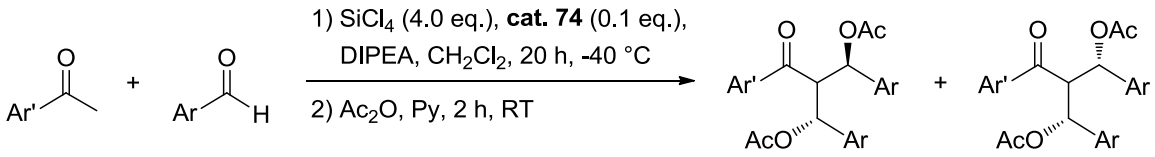
APPENDIX

Experimental section

"Numquam ponenda est pluralitas sine necessitate.
It is pointless to do with more what can be done with fewer."
Ockham's Razor

In this section the synthetic procedures of all products shown in the previous one have been reported. For the general information, see Chapter 8.

Double aldol reaction:



Ar' = Ph, 4-$OMeC_6H_4$, 4-$NO_2C_6H_4$
Ar = Ph, 4-$CF_3C_6H_4$, 4-$OMeC_6H_4$, 3,4-$(OMe)_2C_6H_4$
4-MeC_6H_4, 4-$NO_2C_6H_4$, 4-ClC_6H_4, 2-furyl, 2-thienyl, 1-naphthyl

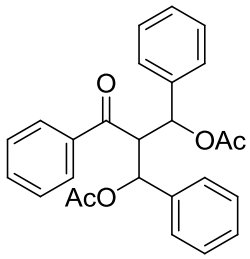
General procedure: To a stirred solution of (*S*)-tetra-Me-BITIOPO (0.016 mmol, 0.1 equiv) in CH_2Cl_2 (2 mL), diisopropylethylamine (0.8 mmol, 5.0 equiv) and the ketone (0.16 mmol, 1.0 equiv) were added. The mixture was cooled to -40 °C, then freshly distilled tetrachlorosilane (0.64 mmol, 4.0 equiv) was added dropwise *via* syringe. After 15 min, aldehyde (0.352 mmol, 2.2 equiv) was added. The mixture was stirred for 20 h. After this time, the reaction was quenched by the addition of a saturated aqueous solution

of NH_4Cl (2 mL). The mixture was allowed to warm up to room temperature and stirred for 30 min, then CH_2Cl_2 (15 mL) was added. The two-layers mixture was separated and the aqueous layer was extracted with CH_2Cl_2 (15 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under *vacuum* at room temperature to give the crude 1,3-diols, as confirmed by ^{1}H-NMR.

The crude products were then treated with acetic anhydride (1.76 mmol, 11.0 equiv) in 2 mL of pyridine at RT. After stirring for 20 h, the mixture was quenched with H_2O (10 mL) and extracted with CH_2Cl_2 (2 x 15 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under *vacuum* at room temperature.

The diastereoisomeric ratio was calculated by ^{1}H-NMR spettroscopy. Yields were determined after chromatographic purification on silica gel with different hexane/ethyl acetate mixture as eluent (see below). The enantiomeric excess was determined by HPLC on a chiral stationary phase. Attributions were performed using racemic mixtures as references. (*S*)-tetra-Me-BITIOPO was quantitatively recovered by further elution with 10% MeOH in CH_2Cl_2 without any loss of optical purity.

3-acetoxy-2-(1'-acetoxy(phenyl)methyl)-1,3-diphenylpropan-1-one:



This product was purified by flash column chromatography on silica gel with a 8:2 hexane/ethyl acetate mixture as eluent. The purification afforded a mixture of *chiral* and *meso* adducts.

R_f = 0.24 (8:2 hexane/ethyl acetate).

Data for *chiral*:

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.99 (d, J = 9 Hz, 2H), 7.44 (d, J = 6 Hz, 2H), 7.35-7.11 (m, 11H), 6.37 (d, J = 6 Hz, 1H), 6.22 (d, J = 9 Hz, 1H), 4.55 (dd, J = 9 Hz, J = 6 Hz, 1H), 2.03 (s, 3H), 2.01 (s, 3H).

^{13}C NMR (300 MHz, $CDCl_3$) δ: 198.59, 169.47, 169.38, 138.47, 138.22, 137.64, 132.60, 128.50, 128.23, 128.08, 127.78, 127.65, 127.2, 74.90, 74.05, 55.91, 20.83, 20.65.

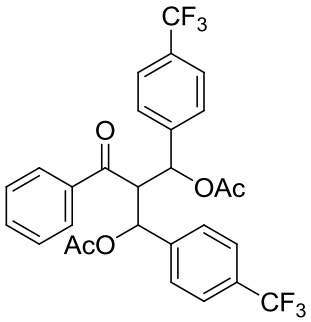
HRMS Mass (ESI+): m/z= calc for $C_{26}H_{24}O_5Na^+$= 439.46, found 439.15 [M + Na].

Data for *meso*:

^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.10 (d, J = 9 Hz, 2H), 7.68 (d, J = 9 Hz, 2H), 7.35-7.11 (m, 11H), 5.95 (d, J = 6 Hz, 2H), 4.40 (t, J = 6 Hz, 1H), 1.78 (s, 6H).

The enantiomeric excess was determined by chiral HPLC with Daicel Chiralcell AD column, eluent: 8:2 Hex/IPA; 0.8 mL/min flow rate, detection: 254 nm,t_R 9.44 min (*chiral*, minor), t_R 12.51min (*chiral*, major), t_R 17.63 min (*meso*)

3-acetoxy-2-(1'-acetoxy-1'-(4-trifluoromethylphenyl)methyl)-1-phenyl-3-(4-trifluoro methylphenyl)-propan-1-one:



This product was purified by flash column chromatography on silica gel with a 85:15 hexane/ethyl acetate mixture as eluent. The purification afforded a mixture of *chiral* and *meso* adducts.

R_f = 0.27 (8:2 hexane/ethyl acetate).

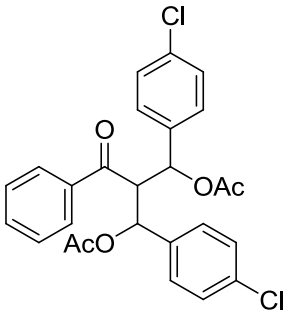
Data for a *chiral*/*meso* mixture:

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.51-7.31 (m, 11H *chiral* + 11H *meso*), 7.28-7.19 (m, 2H *chiral* + 2H *meso*), 6.40 (d, J = 6 Hz, 1H, *chiral*), 6.24 (d, J = 9 Hz, 1H, *chiral*), 6.02 (d, J = 9 Hz, 2H, *meso*), 4.59 (dd, J = 9 Hz, J = 6 Hz, 1H, *chiral*), 4.53 (t, J = 9 Hz, 1H, *meso*), 1.98 (s, 3H, *chiral*), 1.88 (s, 6H, *meso*), 1.78 (s, 3H, *chiral*).

^{13}C NMR (300 MHz, $CDCl_3$) δ: 197.16, 168.82, 168.73, 141.49, 141.01, 137.36, 132.76, 128.06, 127.88, 127.11, 127.43, 127.27, 127.04, 124.93, 73.37, 72.61, 55.26, 20.22, 20.01.

The enantiomeric excess was determined by chiral HPLC with Daicel Chiralcell OD-H column, eluent: 97:3 Hex/IPA; 1.0 mL/min flow rate, detection: 210 nm,t_R 7.71 min (*chiral*, major), t_R 10.14 min (*chiral*, minor), t_R 13.42 min (*meso*).

3-acetoxy-2-(1'-acetoxy-1'-(4-chlorophenyl)methyl)-1-phenyl-3-(4-chlorophenyl)-propan-1-one:



This product was purified by flash column chromatography on silica gel with a 9:1 hexane/ethyl acetate mixture as eluent. The purification afforded a mixture of *chiral* and *meso* adducts.

R_f = 0.25 (8:2 hexane/ethyl acetate).

Data for a *chiral*/*meso* mixture:

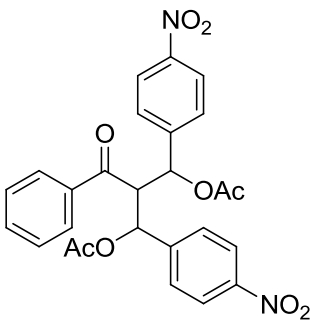
^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.67 (d, J = 9 Hz, 2H, *meso*), 7.48 (d, J = 6 Hz, 2H, *chiral*), 7.45-7.06 (m, 11H*chiral* + 11H *meso*), 6.27 (d, J = 9 Hz, 1H, *chiral*), 6.14 (d, J = 9 Hz, 1H, *chiral*), 5.92 (d, J = 9 Hz, 2H, *meso*), 4.56 (dd, J = 9 Hz, J = 6 Hz, 1H, *chiral*), 4.42 (t, J = 9 Hz, 1H, *meso*), 1.93 (s, 3H, *chiral*), 1.80 (s, 6H, *meso*), 1.76 (s, 3H, *chiral*).

^{13}C NMR (300 MHz, $CDCl_3$) δ: 198.59, 169.68, 138.47, 136.95, 136.43, 134.71, 133.48, 129.41, 129.02, 128.92, 128.75, 128.22, 74.0, 74.41, 73.66, 55.95, 21.14, 21.00.

HRMS Mass (ESI+): m/z = calc for $C_{26}H_{22}Cl_2O_5Na^+$ = 507.07, found 507.20 [M + Na].

The enantiomeric excess was determined by chiral HPLC with Daicel Chiralcell AD column, eluent: 8:2 Hex/IPA; 0.8 mL/min flow rate, detection: 242 nm, t_R 10.52 min (*chiral*, minor), t_R 14.81 min (*chiral*, major), t_R 26.10 min (*meso*).

3-acetoxy-2-(1'-acetoxy-1'-(4-nitrohenyl)methyl)-1-phenyl-3-(4-nitrophenyl)-propan-1-one:



This product was purified by flash column chromatography on silica gel with a 8:2 hexane/ethyl acetate mixture as eluent. The purification afforded a mixture of *chiral* and *meso* adducts.

R_f = 0.12 (8:2 hexane/ethyl acetate).

Data for a *chiral*/*meso* mixture:

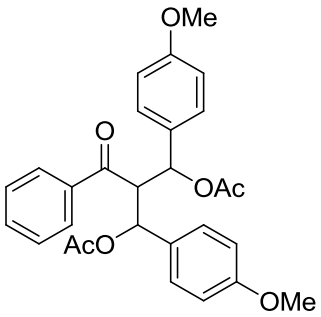
^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.09-8.01 (m, 4H *chiral* + 4H *meso*), 7.64-7.17 (m, 9H *chiral* + 9H *meso*), 6.44 (d, J = 6 Hz, 1H, *chiral*), 6.30 (d, J = 9 Hz, 1H,*chiral*), 6.01 (d, J = 6 Hz, 2H, *meso*), 4.58 (dd, J = 9 Hz, J = 6 Hz, 1H, *chiral*), 4.46 (t, J = 9 Hz, 1H, *meso*), 2.06 (s, 3H, *chiral*), 1.97 (s, 6H, *meso*), 1.89 (s, 3H, *chiral*).

^{13}C NMR (300 MHz, $CDCl_3$) δ: 195.44, 169.98, 144.84, 140.30, 139.26, 136.96, 134.27, 133.39, 129.82, 129.59, 128.73, 127.09, 123.93, 123.70, 73.02, 71.64, 55.43, 20.74.

HRMS Mass (ESI+): m/z = calc for $C_{26}H_{22}N_2O_9Na^+$ = 529.12, found 529.3 [M + Na].

The enantiomeric excess was determined by chiral HPLC with Daicel Chiralcell OD-H column, eluent: 8:2 Hex/IPA; 0.8 mL/min flow rate, detection: 254 nm, t_R 12.73 min (*chiral*, major), t_R 13.97 min (*chiral*, minor), t_R 15.9 min (*meso*).

3-acetoxy-2-(1'-acetoxy-1'-(4-methoxyphenyl)methyl)-1-phenyl-3-(4-methoxyphenyl)-propan-1-one:



This product was purified by flash column chromatography on silica gel with a 8:2 hexane/ethyl acetate mixture as eluent. The purification afforded a mixture of *chiral* and *meso* adducts.

R_f = 0.13 (8:2 hexane/ethyl acetate).

Data for a *chiral*/*meso*mixture:

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.72 (d, J = 9 Hz, 2H, *meso*), 7.59 (d, J = 6 Hz, 2H, *chiral*), 7.53-7.28 (m, 5H *chiral* + 5H *meso*), 7.18-1.10 (m, 2H *chiral* + 2H *meso*), 6.85-6.68 (m, 4H *chiral* + 4H *meso*) 6.26 (d, J = 6 Hz, 1H,*chiral*), 6.16 (d, J = 9 Hz, 1H, *chiral*), 5.96 (d, J = 9 Hz, 2H, *meso*), 4.69 (dd, J = 9 Hz, 10 Hz, 1H, *chiral*) 4.49 (t, J = 9

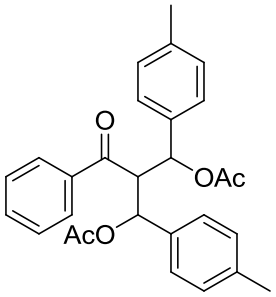
Hz, 1H, *meso*), 3.79 (s, 3H, *chiral*), 3.76 (s, 6H, *meso*), 3.71 (s, 3H, *chiral*), 1.92 (s, 3H, *chiral*), 1.73 (s, 3H, *chiral*), 1.66 (s, 6H, *meso*).

^{13}C NMR (300 MHz, $CDCl_3$) δ: 195.84, 169.53, 159.55, 138.62, 132.63, 130.22, 129.56, 129.06, 128.76, 128.30, 128.17, 128.11, 127.87, 113.86, 113.59, 74.82, 73.86, 56.33, 55.29, 55.13, 20.89.

HRMS Mass (ESI+): m/z = calc for $C_{28}H_{28}O_7Na^+$ = 499.17, found 499.3 [M + Na].

The enantiomeric excess was determined by chiral HPLC with Daicel Chiralcell AD column, eluent: 8:2 Hex/IPA; 0.8 mL/min flow rate, detection: 225 nm, t_R 13.86 min (*chiral*, minor), t_R 20.59 min (*chiral*, major), t_R 30.22 min (*meso*).

3-acetoxy-2-(1'-acetoxy-1'-(4-methylphenyl)methyl)-1-phenyl-3-(4-methylphenyl)-propan-1-one:



This product was purified by flash column chromatography on silica gel with a 9:1 hexane/ethyl acetate mixture as eluent. The purification afforded a mixture of *chiral* and *meso* adducts.

R_f = 0.4 (8:2 hexane/ethyl acetate).

Data for a *chiral*/*meso* mixture:

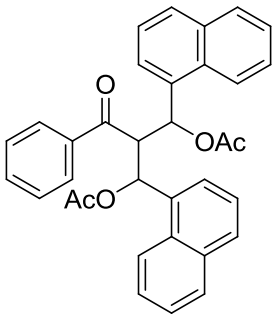
^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.63 (d, J = 6 Hz, 2H, *meso*), 7.51 (d, J = 9 Hz, 2H, *chiral*), 7.46-7.21 (m, 5H *chiral* + 5H *meso*), 7.11-6.92 (m, 6H, *chiral* + 6H *meso*), 6.24 (d, J = 9 Hz, 1H, *chiral*), 6.14 (d, J = 9 Hz, 1H, *chiral*), 5.92 (d, J = 6 Hz, 2H, *meso*) 4.65 (dd, J = 10 Hz, J = 9 Hz, 1H, *chiral*), 4.44 (t, J = 6 Hz, 1H, *meso*), 2.26 (s, 3H, *chiral*), 2.25 (s, 6H, *meso*), 2.18 (s, 3H, *chiral*), 1.90 (s, 3H, *chiral*), 1.69 (s, 3H, *chiral*), 1.26 (s, 6H, *meso*).

^{13}C NMR (300 MHz, $CDCl_3$)δ: 198.70, 169.48, 169.37, 138.63, 138.08, 135.15, 134.53, 132.51, 129.07, 128.88, 128.08, 127.90, 127.65, 127.31, 126.83, 74.97, 74.02, 55.65, 21.05, 20.89.

HRMS Mass (ESI+): m/z = calc for $C_{28}H_{28}O_5Na^+$ = 467.18, found 467.18 [M + Na].

The enantiomeric excess was determined by chiral HPLC with Daicel Chiralcell AD column, eluent: 95:5 Hex/IPA; 0.8 mL/min flow rate, detection: 225 nm, t_R 18.62 min (*chiral*, minor), t_R 44.06 min (*chiral*, major), t_R 50.69 min (*meso*).

3-acetoxy-2-(1'-acetoxy-1'-(1-naphthyl)methyl)-1-phenyl-3-(1-naphthyl)-propan-1-one:



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

R_f = 0.4 (8:2 hexane/ethyl acetate).

Data for *chiral* product:

^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.50 (d, J = 6 Hz, 1H), 8.40 (d, J = 6 Hz, 1H), 7.83 (d, J = 9 Hz, 1H), 7.74-7.68 (m, 2H), 7.67-7.45 (m, 6H), 7.40-7.20 (m, 4H), 7.18-7.12 (m, 2H), 6.99 (d, J = 6 Hz, 2H), 6.87 (d, J = 6 Hz, 2H), 5.27 (dd, J = 9 Hz, J = 3 Hz, 1H), 2.15 (s, 3H), 1.76 (s, 3H).

^{13}C NMR (300 MHz, $CDCl_3$)δ: 197.53, 168.51, 138.40, 133.85, 133.10, 132.48, 130.24, 129.09, 127.90, 127.52, 126.41, 125.69, 125.25, 124.89, 122.90, 53.32, 20.90.

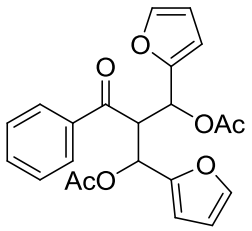
HRMS Mass (ESI+): m/z = calc for $C_{28}H_{28}O_5Na^+$ = 467.18, found 467.18 [M + Na].

The enantiomeric excess was determined by chiral HPLC with Daicel Chiralcell AD column, eluent: 9:1 Hex/IPA; 0.8 mL/min flow rate, detection: 225.8 nm, t_R 12.71 min (*chiral*, minor), t_R 54.14 min (*chiral*, major).

Data for *meso* product:

7.82 (d, J = 6 Hz, 2H), 7.66 (d, J = 6 Hz, 2H), 7.51-7.18 (m, 13H), 7.04 (t, J = 9 Hz, 2H), 6.61 (d, J = 6 Hz, 2H), 5.11 (br, 1H), 2.00 (s, 6H).

3-acetoxy-2-(1'-acetoxy-1'-(furan-2-yl)methyl)-1-phenyl-3-(furan-2-yl)-propan-1-one:



This product was purified by flash column chromatography on silica gel with a 8:2 hexane/ethyl acetate mixture as eluent. The purification afforded a mixture of *chiral* and *meso* adducts.

R_f = 0.10 (8:2 hexane/ethyl acetate).

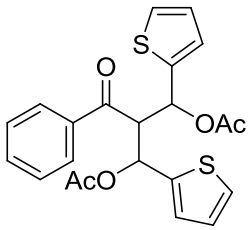
Data for a *chiral*/*meso* mixture:

^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.00 (d, J = 6 Hz, 2H, *meso*), 7.84 (d, J = 9 Hz, 2H, *chiral*), 7.59-7.23 (m, 5H *chiral* +5H *meso*), 6.39-6.15 (m, 6H *chiral* + 6H *meso*), 5.10-5.02 (m, 1H *chiral* + 1H *meso*), 1.90 (s, 3H *chiral*), 1.84 (s, 3H *chiral*), 1.59 (s, 6H *meso*).

^{13}C NMR (300 MHz, $CDCl_3$) δ: 197.42, 169.46, 169.18, 150.07, 149.57, 142.72, 142.60, 137.58, 132.99, 128.33, 128.16, 110.46, 110.41, 110.18, 109.69, 67.66, 66.93, 50.04, 20.67, 20.60.

The enantiomeric excess was determined by chiral HPLC with Daicel Chiralcell AD column, eluent: 8:2 Hex/IPA; 1 mL/min flow rate, detection: 210 nm, t_R 9.86 min (*chiral*, minor), t_R 14.45 min (*chiral*, major), t_R 22.69 min (*meso*).

3-acetoxy-2-(1'-acetoxy-1'-(thiophen-2-yl)methyl)-1-phenyl-3-(thiophen-2-yl)-propan-1-one:



This product was purified by flash column chromatography on silica gel with a 9:1 hexane/ethyl acetate mixture as eluent. The purification afforded a mixture of *chiral* and *meso* adducts.

R_f = 0.27 (8:2 hexane/ethyl acetate).

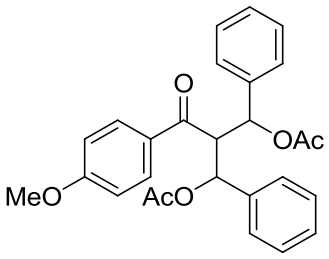
Data for a *chiral*/*meso* mixture:

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.79 (d, J = 9 Hz, 2H, *meso*), 7.68 (d, J = 9 Hz, 2H, *chiral*), 7.46 (t, J = 9 Hz, 1H, *chiral*), 7.41-7.38 (m, 3H, *meso*), 7.33 (t, J = 6 Hz, 2H, *chiral*), 7.21 (d, J = 6 Hz, 1H, *chiral*), 7.17 (d, J = 3 Hz, 3H, *meso*), 7.10 (d, J = 3 Hz, 1H, *chiral),* 7.06 (d, J = 3 Hz, 1H, *chiral*), 6.92-6.76 (m, 3H *chiral*+ 3H*meso*), 6.57 (d, J = 6 Hz, 1H, *chiral*), 6.52 (d, J = 9 Hz, 1H, *chiral*), 6.36 (d, J = 6 Hz, 2H, *meso*), 4.72 (dd, J = 9 Hz, J = 6 Hz, 1H, *chiral*), 4.56 (t, J = 6 Hz, 1H, *meso*) 1.91 (s, 3H *chiral*), 1.79 (s, 3H *chiral*).

^{13}C NMR (300 MHz, $CDCl_3$) δ: 197.79, 169.38, 169.16, 140.70, 139.76, 138.24, 132.94, 128.30, 128.03, 127.67, 126.96, 126.67, 126.50, 125.91, 70.22, 69.78, 56.16, 20.75, 20.63.

The enantiomeric excess was determined by chiral HPLC with Daicel Chiralcell AD column, eluent: 8:2 Hex/IPA; 0.8 mL/min flow rate, detection: 254.16 nm; t_R 9.93 min (*chiral*-minor), t_R 14.11 min (*chiral*-major), t_R 21.89 min (*meso*).

3-acetoxy-2-(1'-acetoxy-1'-(phenyl)methyl)-1-(4-metoxyphenyl)-3-(phenyl)-propan-1-one:



This product was purified by flash column chromatography on silica gel with a 85:15 hexane/ethyl acetate mixture as eluent. The purification afforded a mixture of *chiral* and *meso* adducts.

R_f = 0.17 (8:2 hexane/ethyl acetate).

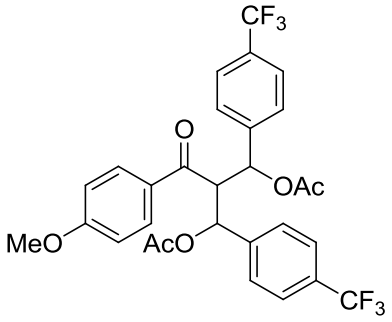
Data for a *chiral*/*meso* mixture:

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.64 (d, J = 9 Hz, 2H, *meso*), 7.51 (d, J = 9 Hz, 2H, *chiral*), 7.43-7.40 (m, 2H *chiral* +2H *meso*), 7.31-7.08 (m, 8H *chiral* +8H *meso*), 6.78 (d, J =9 Hz, 2H, *meso*), 6.70 (d, J = 6 Hz, 2H, *chiral*), 6.35 (d, J = 6 Hz, 1H, *chiral*), 6.26 (d, J = 9 Hz, 1H, *chiral*), 5.98 (d, J = 9 Hz, 2H, *meso*), 4.60 (dd, J = 9 Hz, J = 6 Hz, 1H, *chiral*), 4.43 (t, J = 9 Hz, 1H, *meso*), 3.84 (s, 3H, *meso*), 3.79 (s, 3H, *chiral*), 1.95 (s, 3H, *chiral*), 1.93, (s, 6H, *meso*), 1.75 (s, 3H, *chiral*).

^{13}C NMR (300 MHz, $CDCl_3$) δ: 196.50, 169.47, 163.15, 138.42, 137.85, 131.44, 130.23, 128.41, 128.22, 127.67, 127.22, 126.93, 113.29, 74.97, 74.18, 55.40, 20.89, 20.73.

The enantiomeric excess was determined by chiral HPLC with Daicel Chiralcell AD column, eluent: 8:2 Hex/IPA; 1 mL/min flow rate, detection: 210 nm, t_R 9.96 min (*chiral*, minor), t_R 16.75 min (*chiral*, major), t_R 32.79 min (*meso*).

3-acetoxy-2-(1'-acetoxy-1'-(4-trifluoromethanphenyl)methyl)-1-(4-metoxyphenyl)-3-(4-trifluoromethanphenyl)-propan-1-one:



This product was purified by flash column chromatography on silica gel with a 8:2 hexane/ethyl acetate mixture as eluent.

R_f = 0.31 (8:2 hexane/ethyl acetate).

Data for *chiral* product:

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.56-7.33 (m, 10H), 6.70 (d, J = 6 Hz, 2H), 6.41 (d, J = 3 Hz, 1H), 6.27 (d, J = 9 Hz, 1H), 4.50 (dd, J = 12 Hz, J = 9 Hz, 1H), 3.79 (s, 3H), 2.01 (s, 3H), 1.83 (s, 3H).

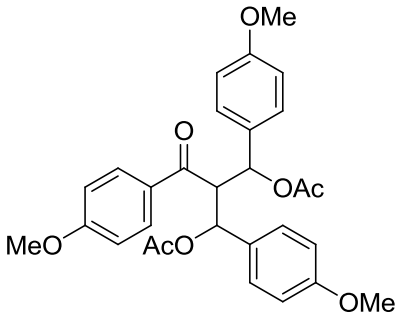
^{13}C NMR (300 MHz, $CDCl_3$) δ: 194.99, 168.88, 168.75, 1633.22, 141.71, 141.24, 130.29, 129.76, 127.42, 127.02, 124.89, 113.09, 73.39, 72.75, 54.93, 20.29, 20.09.

The enantiomeric excess was determined by chiral HPLC with Daicel Chiralcell AD column, eluent: 9:1 Hex/IPA; 0.8 mL/min flow rate, detection: 210 nm; t_R 13.82 min (*chiral*-minor), t_R 18.82 min (*chiral*-major).

Data for *meso* product:

7.72 (d, J = 9 Hz, 2H), 7.54-7.26 (m, 8H), 6.84 (d, J = 9 Hz, 2H), 6.02 (d, J = 9 Hz, 2H), 4.45 (t, J = 9 Hz, 1H), 3.85 (s, 3H), 1.91 (s, 6H).

3-acetoxy-2-(1'-acetoxy-1'-(4-methoxyphenyl)methyl)-1,3-(4-metoxyphenyl)-propan-1-one:



This product was purified by flash column chromatography on silica gel with a 85:15 hexane/ethyl acetate mixture as eluent. The purification afforded a mixture of *chiral* and *meso* adducts.

R_f = 0.10 (8:2 hexane/ethyl acetate).

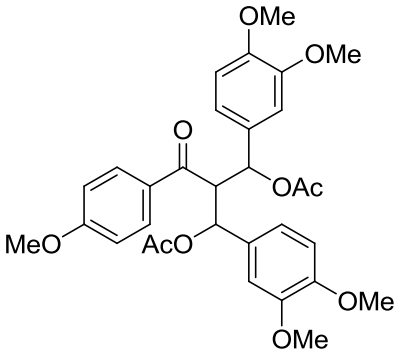
Data for a *chiral*/*meso* mixture:

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.74-7.79 (m, 2H, *meso*), 7.60 (d, J = 9 Hz, 2H, *chiral*), 7.39-6.94 (m, 4H *chiral* + 4H *meso*), 6.84-6.62 (m, 6H *chiral* + 6H *meso*), 6.24 (d, J = 9 Hz, 1H, *chiral*), 6.14 (d, J = 9 Hz, 1H, *chiral*), 5.93 (d, J = 6 Hz, 2H, *meso*), 4.64-4.58 (m, 1H *chiral* + 1 H *meso*), 3.86 (s, 3H, *meso*), 3.82 (s, 3H, *chiral*),3.77 (s, 3H, *chiral*) 3.73 (s, 3H, *meso*), 3.70 (s, 3H, *chiral*) 3.68 (s, 3H, *meso*), 2.01 (s, 6H, *meso*), 1.90 (s, 3H, *chiral*), 1.73 (s, 3H, *chiral*).

^{13}C NMR (300 MHz, $CDCl_3$) δ: 196.74, 196.49, 169.37, 163.17, 159.49, 159.32, 131.59, 130.28, 128.99, 128.71, 126.85, 126.32, 113.78, 113.51, 113.35, 74.83, 74.41, 73.94, 55.3, 55.23, 54.99, 20.84, 20.74.

The enantiomeric excess was determined by chiral HPLC with Daicel Chiralcell AD column, eluent: 6:4 Hex/IPA; 1 mL/min flow rate, detection: 210 nm, t_R 9.57 min (*chiral*, minor), t_R 16.72 min (*chiral*, major), t_R 24.56 min (*meso*).

3-acetoxy-2-(1'-acetoxy-1'-(3,4-dimethoxyphenyl)methyl)-1-(4-methoxyphenyl)-3-(3,4-dimethoxyphenyl)-propan-1-one:



This product was purified by flash column chromatography on silica gel with a 8:2 hexane/ethyl acetate mixture as eluent. The purification afforded a mixture of *chiral* and *meso* adducts.

R_f = 0.10 (8:2 hexane/ethyl acetate).

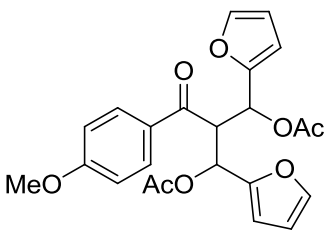
Data for a *chiral*/*meso* mixture:

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.68 (d, J = 9 Hz, 2H, *meso*), 7.56 (d, J = 6 Hz, 2H, *chiral*), 7.00-6.63 (m, 8H *chiral* + 8H *meso*), 6.24 (d, J = 6 Hz, 1H, *chiral*), 6.16 (d, J = 9 Hz, 1H, *chiral*), 5.93 (d, J = 6 Hz, 2H, *meso*), 4.55 (dd, J = 9 Hz, J = 6 Hz, 1H, *chiral*), 4.32 (t, J = 9 Hz, 1H, *meso*), 3.82-3.74 (m, 15H *chiral* + 15H *meso*), 1.97 (s, 3H, *chiral*), 1.92 (s, 6H, *meso*), 1.80 (s, 3H, *chiral*).

^{13}C NMR (300 MHz, $CDCl_3$) δ: 196.61, 169.61, 169.56, 163.29, 149.00, 148.85, 148.43, 131.54, 130.76, 130.52, 130.20, 130.09, 120.41, 119.85, 119.65, 113.42, 111.22, 111.06, 110.73, 74.64, 74.48, 74.03, 55.94, 55.80, 55.73, 55.38, 54.86, 20.94, 20.89.

The enantiomeric excess was determined by chiral HPLC with Daicel Chiralcell AD column, eluent: 8:2 Hex/IPA; 1 mL/min flow rate, detection: 210 nm, t_R 20.49 min (*chiral*, minor), t_R 37.00 min (*chiral*, major).

3-acetoxy-2-(1'-acetoxy-1'-(furan-2-yl)methyl)-1-(4-methoxyphenyl)-3-(furan-2-yl)-propan-1-one:



This product was purified by flash column chromatography on silica gel with a 8:2 hexane/ethyl acetate mixture as eluent. The purification afforded a mixture of *chiral* and *meso* adducts.

R_f = 0.47 (8:2 hexane/ethyl acetate).

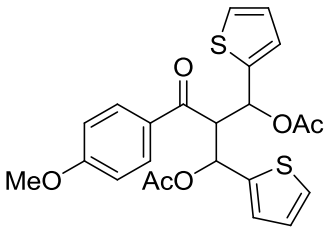
Data for a *chiral*/*meso* mixture:

^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.02 (d, J = 9 Hz, 2H, *meso*), 7.84 (d, J = 9 Hz, 2H, *chiral*), 7.25 (d, J = 6 Hz, 1H, *meso*), 7.14 (s, 1H, *chiral*), 6.94, (d, J = 9 Hz, 2H, *meso*), 6.84 (d, J = 9 Hz, 2H, *chiral*), 6.35-6.12 (m, 7H *chiral* + 7H *meso*), 5.04-4.96 (m, 1H *chiral* + 1H *meso*), 3.87 (s, 3H, *meso*), 3.83 (s, 3H, *chiral*), 2.15 (s, 6H, *meso*), 1.85 (s, 3H, *chiral*), 1.81 (s, 3H, *chiral*).

^{13}C NMR (300 MHz, $CDCl_3$)δ: 195.51, 169.49, 169.21, 163.51, 150.29, 149.74, 142.69, 142.53, 130.61, 113.53, 110.47, 110.38, 110.06, 109.60, 69.79, 67.10, 55.43, 49.61, 20.71, 20.63.

The enantiomeric excess was determined by chiral HPLC with Daicel Chiralcell AD column, eluent: 8:2 Hex/IPA; 1 mL/min flow rate, detection: 210 nm, t_R 14.71 min (*chiral*, minor), t_R 24.89 min (*chiral*, major), t_R 44.77 min (*meso*).

3-acetoxy-2-(1'-acetoxy-1'-(thiophen-2-yl)methyl)-1-(4-methoxyphenyl)-3-(thiophen-2-yl)-propan-1-one:



This product was purified by flash column chromatography on silica gel with a 8:2 hexane/ethyl acetate mixture as eluent. The purification afforded a mixture of *chiral* and *meso* adducts.

R_f = 0.52 (8:2 hexane/ethyl acetate).

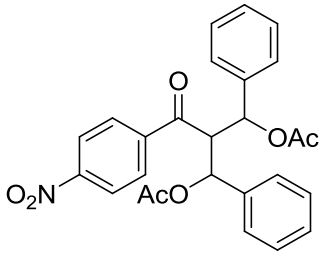
Data for a *chiral*/*meso* mixture:

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.82 (d, J = 9 Hz, 2H, *meso*), 7.72 (d, J = 9 Hz, 2H, *chiral*), 7.28-7.08 (m, 2H *chiral* + 2H *meso*), 6.96-9.77 (m, 6H *chiral* + 6H *meso*), 6.59 (d, J = 6 Hz, 1H, *chiral*), 6.55 (d, J = 9 Hz, 1H, *chiral*), 6.37 (d, J = 9 Hz, 2H, *meso*), 4.68 (dd, J= 9 Hz, J= 6 Hz, 1H, *chiral*), 4.52 (t, J = 9 Hz, 1H, *meso*), 3.87 (s, 3H, *meso*), 3.84 (s, 3H, *chiral*),1.93(s, 3H, *chiral*), 1.91 (s, 6H, *meso*), 1.83 (s, 3H, *chiral*).

^{13}C NMR (300 MHz, $CDCl_3$)δ: 195.68, 169.42, 169.22, 163.45, 140.91, 140.02, 131.21, 130.48, 172.60, 126.85, 126.64, 126.45, 125.79, 113.50, 70.29, 69.86, 55.72, 55.40, 20.77, 20.71.

The enantiomeric excess was determined by chiral HPLC with Daicel Chiralcell AD column, eluent: 8:2 Hex/IPA; 1 mL/min flow rate, detection: 210 nm, t_R 13.25 min (*chiral*, minor), t_R 22.40 min (*chiral*, major), t_R 46.70 min (*meso*).

3-acetoxy-2-(1'-acetoxy-1'-(phenylmethyl)-1-(4-nitrophenyl)-3-phenyl-propan-1-one:



This product was purified by flash column chromatography on silica gel with a 8:2 hexane/ethyl acetate mixture as eluent. The purification afforded a mixture of *chiral* and *meso* adducts.

R_f = 0.18 (8:2 hexane/ethyl acetate).

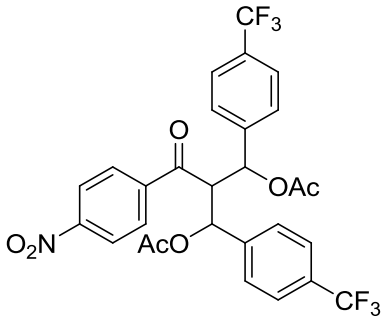
Data for a *chiral*/*meso* mixture:

^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.10 (d, J = 9 Hz, 2H, *meso*), 7.99 (d, J = 9 Hz, 2H, *chiral*), 7.68 (d, J = 9 Hz, 2H, *meso*), 7.44 (d, J = 9 Hz, 2H, *chiral*), 7.35-7.12 (m, 10H *chiral* + 10H *meso*), 6.37 (d, J = 6 Hz, 1H, *chiral*), 6.22 (d, J = 9 Hz, 1H, *chiral*), 5.95 (d, J = 6 Hz, 2H, *meso*), 4.56 (dd, J= 9 Hz, J= 6 Hz, 1H, *chiral*), 4.40 (t, J = 6 Hz, 1H, *meso*), 2.01 (s, 3H, *chiral*), 1.96 (s, 6H, *meso*), 1.78 (s, 3H, *chiral*).

^{13}C NMR (300 MHz, $CDCl_3$) δ: 197.15, 168.95, 168.83, 149.25, 142.29, 137.39, 137.03, 128.30, 127.07, 126.35, 126.16, 122.94, 122.79, 73.73, 73.09, 56.96, 20.38, 20.35.

The enantiomeric excess was determined by chiral HPLC with Daicel Chiralcell AD column, eluent: 8:2 Hex/IPA; 1 mL/min flow rate, detection: 250 nm, t_R 10.97 min (*chiral*, minor), t_R 17.15 min (*chiral*, major), t_R 25.75 min (*meso*).

3-acetoxy-2-(1'-acetoxy-1'-(4-trifluoromethanphenyl)methyl)-1-(4-nitrophenyl)-3-(4-trifluoromethanphenyl)-propan-1-one:



This product was purified by flash column chromatography on silica gel with a 8:2 hexane/ethyl acetate mixture as eluent. The purification afforded a mixture of *chiral* and *meso* adducts.

R_f = 0.52 (8:2 hexane/ethyl acetate).

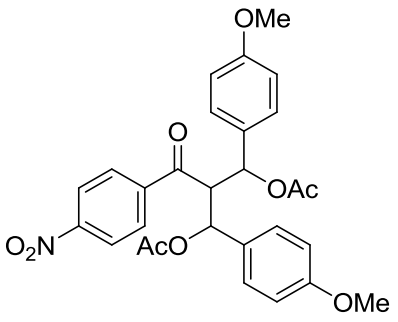
Data for a *chiral*/*meso* mixture:

^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.22 (d, J = 9 Hz, 2H, *meso*), 8.09 (d, J = 6 Hz, 2H, *chiral*), 7.70-7.17 (m, 10H *chiral* + 10H *meso*), 6.41 (d, J = 6 Hz, 1H, *chiral*), 6.24 (d, J = 9 Hz, 1H, *chiral*), 6.00 (d, J = 9 Hz, 2H, *meso*), 4.56 (dd, J = 9 Hz, J = 6 Hz, 1H, *chiral*), 4.51 (t, J = 9 Hz, 1H, *meso*), 2.01 (s, 3H, *chiral*), 1.91 (s, 6H, *meso*), 1.80 (s, 3H, *chiral*).

^{13}C NMR (300 MHz, $CDCl_3$) δ: 195.13, 168.77, 149.98, 140.44, 139.91, 136.92, 132.34, 129.56, 128.64, 127.06, 125.07, 123.27, 75.45, 55.96, 20.30, 20.14.

The enantiomeric excess was determined by chiral HPLC with Phenomenex Lux cellulose 2, eluent: 9:1 Hex/IPA; 0.8 mL/min flow rate, detection: 210 nm; t_R 14.68 min (*chiral*-minor), t_R 15.51 min (*meso*), t_R 17.14 min (*chiral*-major).

3-acetoxy-2-(1'-acetoxy-1'-(4-metoxyphenyl)methyl)-1-(4-nitrophenyl)-3-(4-metoxyphenyl)-propan-1-one:



This product was purified by flash column chromatography on silica gel with a 8:2 hexane/ethyl acetate mixture as eluent. The purification afforded a mixture of *chiral* and *meso* adducts.

R_f = 0.10 (8:2 hexane/ethyl acetate).

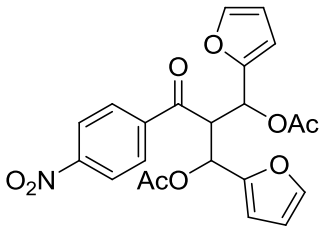
Data for a *chiral*/*meso* mixture:

^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.14 (d, J = 9 Hz, 2H, *meso*), 8.06 (d, J = 9 Hz, 2H, *chiral*), 7.78 (d, J = 9 Hz, 2H, *meso*), 7.58 (d, J = 9 Hz, 2H, *chiral*), 7.28 (d, J = 9 Hz, 2H, *chiral*), 7.16 (d, J = 6Hz, 2H, *chiral*), 7.10 (d, J = 9 Hz, 4H, *meso*), 6.81 (d, J = 6 Hz, 2H, *chiral*), 6.74 (d, J = 9 Hz, 4H, *meso*), 6.69 (d, J = 9 Hz, 2H, *chiral*), 6.29 (d, J = 6 Hz, 1H, *chiral*), 6.16 (d, J = 9 Hz, 1H, *chiral*), 5.92 (d, J = 9 Hz, 2H, *meso*), 4.62 (dd, J = 9 Hz, J = 6 Hz, 1H, *chiral*), 4.40 (t, J = 9 Hz, 1H, *meso*), 3.78 (s, 3H, *chiral*), 3.73 (s, 6H, *meso*), 3.67 (s, 3H, *chiral*), 2.01 (s, 3H, *chiral*), 1.92 (s, 6H, *meso*), 1.75 (s, 3H, *chiral*).

^{13}C NMR (300 MHz, $CDCl_3$) δ: 197.50, 169.34, 169.02, 159.73, 149.73, 143.19, 130.09, 129.41, 128.93, 128.60, 128.37, 128.05, 123.47, 114.08, 74.14, 57.38, 55.24, 20.87.

The enantiomeric excess was determined by chiral HPLC with Daicel Chiralcell AD column, eluent: 8:2 Hex/IPA; 1 mL/min flow rate, detection: 210 nm, t_R 23.14 min (*chiral*, minor), t_R 27.42min (*chiral*, major), t_R 52.76 min (*meso*).

3-acetoxy-2-(1'-acetoxy-1'-(2-furan-2-yl)methyl)-1-(4-nitrophenyl)-3-(furan-2-yl)-propan-1-one:



This product was purified by flash column chromatography on silica gel with a 8:2 hexane/ethyl acetate mixture as eluent. The purification afforded a mixture of *chiral* and *meso* adducts.

R_f = 0.14 (8:2 hexane/ethyl acetate).

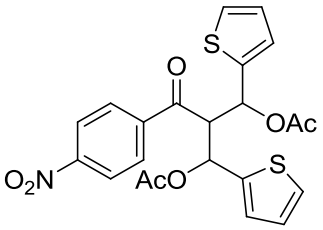
Data for a *chiral*/*meso* mixture:

^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.34 (d, J = 9 Hz, 2H, *meso*), 8.24 (d, J = 9 Hz, 2H, *chiral*), 8.11 (d, J = 9 Hz, 2H, *meso*), 7.93 (d, J = 6 Hz, 2H, *chiral*), 7.33-7.15 (m, 2H *chiral* + 2H *meso*), 6.40-6.12 (m, 6H *chiral* + 6H *meso*), 5.12-5.06 (m, 1H *chiral* + 1H *meso*), 1.96 (s, 3H *chiral*), 1.89 (s, 3H, *chiral*), 1.60 (s, 6H, *meso*).

^{13}C NMR (300 MHz, $CDCl_3$)δ: 196.31, 169.37, 169.07, 150.08, 149.56, 149.26, 142.76, 141.84, 128.99, 123.53, 110.66, 109.82, 67.27, 66.35, 50.92, 20.66, 20.61.

The enantiomeric excess was determined by chiral HPLC with Daicel Chiralcell AD column, eluent: 8:2 Hex/IPA; 1 mL/min flow rate, detection: 210 nm, t_R 12.81 min (*chiral*, minor), t_R 24.75 min (*chiral*, major), t_R 30.64 min (*meso*).

3-acetoxy-2-(1'-acetoxy-1'-(2-thiophen-2-yl)methyl)-1-(4-nitrophenyl)-3-(thiophen-2-yl)-propan-1-one:



This product was purified by flash column chromatography on silica gel with a 8:2 hexane/ethyl acetate mixture as eluent. The purification afforded a mixture of *chiral* and *meso* adducts.

R_f = 0.14 (8:2 hexane/ethyl acetate).

Data for a *chiral*/*meso* mixture:

^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.22 (d, J = 9 Hz, 2H, *meso*), 8.16 (d, J = 9 Hz, 2H, *chiral*), 7.88 (d, J = 9 Hz, 2H, *meso*), 7.74 (d, J = 9 Hz, 2H, *chiral*), 7.28-7.07 (m, 3H *chiral* + 3H *meso*), 6.96-6.80 (m, 3H *chiral* + 3H *meso*), 6.64 (d, J = 9 Hz, 1H, *chiral*), 6.58 (d, J = 9 Hz, 1H, *chiral*), 6.36 (d, J = 9 Hz, 2H, *meso*), 4.67 (dd, J = 9 Hz, J = 6 Hz, 1H, *chiral*), 4.51 (t, J = 6 Hz, 1H, *meso*), 2.01 (s, 3H *chiral*), 1.96 (s, 6H, *meso*), 1.89 (s, 6H, *chiral*).

^{13}C NMR (300 MHz, $CDCl_3$) δ: 196.77, 168.85, 149.97, 142.42, 140.29, 139.66, 128.97, 128.77, 126.98, 126.75, 126.07, 123.45, 69.96, 57.59, 20.73.

The enantiomeric excess was determined by chiral HPLC with Daicel Chiralcell AD column, eluent: 8:2 Hex/IPA; 1 mL/min flow rate, detection: 210 nm, t_R 14.53 min (*chiral*, minor), t_R 22.00 min (*chiral*, major), t_R 46.14 min (*meso*).

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LIST OF COMMON ABBREVIATIONS

Ac	Acetyl
acac	Acetylacetonate
Ac_2O	Acetic anhydride
AcOEt	Ethyl acetate
AcOH	Acetic acid
aq.	Aqueous
Ar	Aromatic
BINAM	1,1’-binaphthyl-2,2'-diamine
BINAP	2,2’-bis(diphenylphosphanyl)-1,1’-binaphthyl
BINAPO	2,2’-bis(diphenylphosphanyl)-1,1’-binaphthyl *P*-dioxide
BINOL	1,1’-bi-2,2’-naphthol
cat.	Catalyst
°C	Temperature in degrees Centigrade
d	Day (days)
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicycloundec-7-ene
DCM	Dichloromethane
DEA	Diethylamine
DIPA	*N*,*N*-diisopropyldiamine
DIPEA	*N*,*N*-diisopropylethyldiamine
DMAP	4-dimethylaminopyridine
DME	Dimethoxyethane
DMSO	Dimethylsulfoxide
DMF	*N*,*N*-dimethylformamide
EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
e.e.	Enantiomeric excess
Et	Ethyl
eq.	Equivalent (equivalents)

EVE	Ethyl vinyl ether
FLP	Frustrated Lewis Pair
h	Hour (hours)
HMPA	Hexamethylphosphorictriamide
HOBt	Hydroxybenzotriazole
IPA	Isopropanol alcohol
LDA	Lithium diisopropylamide
m-CPBA	*meta*-chloroperbenzoic acid
Me_2-BINAM	*N*,*N*-dimethyl-1,1'-binaphthyl-2,2'-diamine
NBS	*N*-bromosuccinimide
NIS	*N*-iodosuccinimide
NMM	*N*-methylmorpholine
P.A.	Phosphoric acid
PMP	*para*-methoxy-phenyl
Py	Pyridine
rac	Racemic
RT	Room temperature
TBAF	Tetra-*n*-butylammonium fluoride
TBAI	Tetra-*n*-butylammonium iodide
TEA	Triethylamine
TetraMe-BITIOP	2,2',5,5'-tetramethyl-4,4'-bis(diphenylphosphino)-3,3'-bithiophene
TetraMe-BITIOPO	2,2',5,5'-tetramethyl-4,4'-bis(diphenylphosphino)-3,3'-bithiophene *P*-dioxide
THF	Tetrahydrofurane
TS	Transition state
TFA	Trifluoroacetic acid