Stockholm University

# Development of Catalytic Enantioselective Approaches for the Synthesis of Carbocycles and Heterocycles

Luca Deiana

Cover picture: Jan Van der Straet “Distillatio”.

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Verum, sine mendacio
certum et verissimum,
quod est inferius, est sicut quod est superius, et quod est superius, est sicut quod est inferius: ad perpetranda miracula rei unius.
[*Hermes Trismegistus*]

# Abstract

In biological systems, most of the active organic molecules are chiral. Some of the main constituents of living organisms are amino acids and sugars. They exist predominantly in only one enantiomerically pure form. For example, our proteins are built-up by L-amino acids and as a consequence they are enatiomerically pure and will interact in different ways with enantiomers of chiral molecules. Indeed, different enantiomers or diastereomers of a molecule could often have a drastically different biological activity. It is of paramount importance in organic synthesis to develop new routes to control and direct the stereochemical outcome of reactions.

The aim of this thesis is to investigate new protocols for the synthesis of complex chiral molecules using simple, environmentally friendly proline-based organocatalysts.

We have investigated, the aziridination of linear and branched enals, the stereoselective synthesis of $\beta$-amino acids with a carbene co-catalyst, the synthesis of pyrazolidines, the combination of heterogeneous transition metal catalysis and amine catalysis to deliver cyclopentenes bearing an all-carbon quaternary stereocenter and a new heterogeneous dual catalyst system for the carbocyclization of enals. The reactions presented in this thesis afforded the corresponding products with high levels of chemo-, diastero- and enantioselectivity.

# List of Publications

This thesis is based on the following publications, referred to in the text by their Roman numerals I-V.

**I.** **Catalytic Asymmetric Aziridination of α,β-Unsaturated Aldehydes**
Luca Deiana, Pawel Dziedzic, Gui-Ling Zhao, Jan Vesely, Ismail Ibrahem, Ramon Rios, Junliang Sun, Armando Córdova
*Chemistry-A European Journal* **2011***, 17,* 7904-7917.

**II.** **Organocatalytic Enantioselective Aziridination of α-Substituted α,β-Unsaturated Aldehydes: Asymmetric Synthesis of Terminal Aziridines**
Luca Deiana, Gui-Ling Zhao, Shuangzheng Lin, Pawel Dziedzic, Qiong Zhang, Hans Leijonmarck, Armando Córdova
*Advanced Synthesis and Catalysis* **2010***, 352,* 3201-3207.

**III.** **Direct Catalytic Asymmetric Synthesis of Pyrazolidine Derivatives**
Luca Deiana, Gui-Ling Zhao, Hans Leijonmarck, Junliang Sun, Christian W. Lehmann, Armando Córdova
*ChemistryOpen* **2012**, *1*, 134-139.

**IV.** **Highly Enantioselective Cascade Transformations by Merging Heterogeneous Transition Metal Catalysis with Asymmetric Aminocatalysis**
Luca Deiana, Samson Afewerki, Carlos Palo-Nieto, Oscar Verho, Eric V. Johnston, Armando Córdova
*Scientific Report* **2012**, 2:851.

**V.** **Highly Enantioselective Heterogeneous Synergistic Catalysis for Asymmetric Cascade Transformations**
Luca Deiana, Lorenza Ghisu, Oscar Verho, Eric V. Johnston, Niklas Hedin, Zoltan Bacsik, Armando Córdova
*Manuscript submitted*.

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# Abbreviations

| | |
|---|---|
| Ac | acetyl |
| AHCC | amine and heterocyclic carbene catalysis |
| Ar | aryl |
| Anth | anthracenyl |
| Bn | benzyl |
| Boc | *tert*-butoxycarbonyl |
| Cbz | Benzyloxycarbonyl |
| Cat. | catalyst |
| Conv | conversion |
| DFT | density functional theory |
| DMSO | dimethyl sulfoxide |
| DMF | *N,N*-dimethylformamide |
| DNA | deoxyribonucleic acid |
| Dr | diastereomeric ratio |
| DYKAT | dynamic kinetic asymmetric transformation |
| E | electrophile |
| ee | enantiomeric excess |
| Et | ethyl |
| EtOAc | ethyl acetate |
| HOMO | highest occupied molecular orbital |
| HPLC | high performance liquid chromatography |
| $K_a$ | acid dissociation constant |
| Lg | leaving group |
| LUMO | lowest unoccupied molecular orbital |
| MCF | mesocellular foam |
| Me | methyl |
| MeOH | methanol |
| Mts | mesitylene sulphonyl |
| n.d. | not determined |
| NHC | N-heterocyclic carbene |
| Nu | nucleophile |
| Ph | phenyl |
| PBI | pyrrole [1,2-α] benzimiazole |
| p$K_a$ | -$\mathrm{Log}_{10}K_a$ |
| PNB | para-nitro benzyl |

| | |
|---|---|
| T | temperature |
| THF | tetrahydrofuran |
| TMS | trimethylsilyl |
| TES | triethylsilyl |
| TFA | trifluoroacetic acid |
| Ts | tosyl |

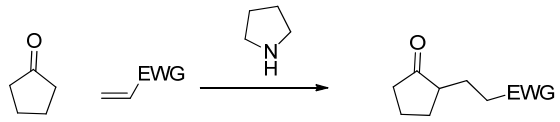
# 1. Introduction

## 1.1 Organocatalysis

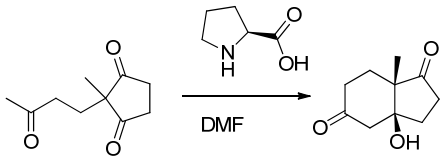
A goal in organic chemistry is to develop new and efficient methods to construct carbon-carbon and carbon-heteroatom bonds with complete control of the stereochemistry of the reaction. Chiral auxiliaries have partially solved this problem, but this approach requires a stoichiometric amount of the auxiliary and additional steps to remove and introduce the chiral unit.[1] The use of catalytic amounts of a catalyst, to construct complex optically active molecules, with one or more stereospecific centers, is of utmost importance in organic synthesis. Organocatalysis fulfills these requirements and is today considered a field of central interest for the synthesis of chiral compounds.[2] New and highly efficient ways of substrate activation have been achieved using simple chiral organic molecules that can now deliver unique, orthogonal and complementary selectivities to metal-catalyzed processes. The use of organocatalysts have several important advantages, since they are easily available, inexpensive, stable and environmentally friendly. The application of amino acids, peptides[3] and alkaloids as catalysts has disclosed new routes for the preparation of important chiral products with the exclusion of any trace of hazardous metals, a condition of fundamental importance in the pharmaceutical and medical industry.[4] Organocatalytic reactions can be performed in wet solvents under air atmosphere, which increase the reproducibility and operational simplicity compared to sensitive metal catalysts which require inert conditions. These methods allow the researcher to devise new multicomponent tandem sequences for the synthesis of useful building blocks and complex natural products.[5]

Usually alkylation or acylation of aldehydes and ketones is carried out in the presence of strong bases to form the corresponding enolates. This strategy is associated with several problems: (1) the possible self-condensation of the substrate, (2) the 1,2-addition of the base to the carbonyl, (3) the polyalkylation of the starting material, (4) reaction of unsymmetrical ketones, with an alkylating agent, predominantly occur at the more substituted carbon. In 1963, Stork understood the necessity of a new selective method for the al-

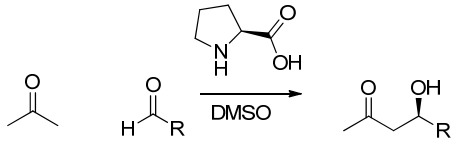
kylation and acylation of carbonyl compounds to avoid all these undesired side-reactions (Scheme 1).[6] The condensation of an amine with a ketone or an aldehyde, generates an enamine without the requirement of using of a base. The enamine is more reactive than the corresponding enolate, because the orbital of the electron pair on the nitrogen atom is higher in energy compared to the orbital of the lone-pair on the oxygen, which increases the energy of the highest occupied molecular orbital (HOMO). The enamine intermediate, formed from an unsymmetrically substituted ketone, can now provide monoalkylation (e.g. with alkyl halides) or monoacylation (e.g. with acid chlorides) exclusively to the less substituted carbon. Hydrolysis mediated by water affords the product with high levels of regio- and chemoselectivity. The first example of an amino acid-catalyzed asymmetric reaction, which disclosed the field of organocatalysis, was reported in 1970 and received its name from the discoverers: Hajos–Parrish.[7] It was closely followed by the work of Eder, Sauer and Wiechert.[8] In the Hajos–Parrish reaction context, proline is the chiral catalyst for an intramolecular aldol reaction (Scheme 2). The starting material is a triketone and only a catalytic amount of the amino acid (3 mol%) was required to obtain the product in a high enantiomeric excess (93% *ee*). Their work showed that a small amino acid could catalyze the formation of carbon-carbon bonds with a mechanism similar that of an enzyme.[9] However, it was not until 2000 that the field of aminocatalysis, which is a subfield of organocatalysis, was effectively launched by the works of Barbas, Lerner, List and MacMillan.[10] For instance, they presented examples of enantioselective intermolecular aldol additions between ketones and aldehydes (Scheme 3) and between two different aldehydes (Scheme 4).



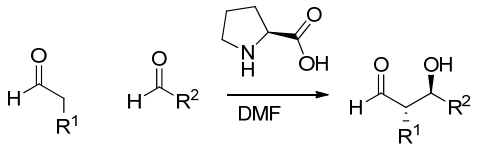

**Scheme 1.** Stork reaction (1963).




**Scheme 2.** Hajos–Parrish reaction (1970).




**Scheme 3.** Asymmetric aldol reaction (List, Lerner, Barbas 2000).




**Scheme 4.** Cross-aldol reaction of aldehydes (MacMillan 2002)

### 1.2 Aminocatalysts

In the past, many scientists firmly believed that a high level of stereoselectivity could only be reached by using well-organized and complex biological molecules, such as enzymes, to catalyze chemical reactions. The amino acids in the active site of the enzyme interact with the substrate *via* hydrogen bonding, electrostatic and steric interactions, positioning the compound in an orientation so that the transition state is stabilized. Chemists thought that an amino acid with a five-membred ring was essential to achieve high reactivity and high levels of diastereo- and enantioselectivity. In 2005, our group showed that acyclic amino acids and peptides were able to catalyze asymmetric intermolecular carbon-carbon bond-forming reactions with high enantioselectivity.[3,11] Ishihara demonstrated that acyclic amino acid peptide derivatives can catalyze the Diels-Alder reaction with good enantioselectivity.[12] Single amino acids or dipeptides activate the substrate and pre-organize the transition state, thus lowering the energy, with covalent bonds (amine moiety), hydrogen bonds (carboxylic proton) and steric interactions (bulky groups). Cyclic secondary amines such as proline, protected prolinol derivatives and MacMillan`s imidazolidinones are able to activate aldehydes and ketones (Figure 1).[13] The condensation of a secondary amine with the carbonyl moiety forms a positively charged iminium intermediate. In the case of saturated aldehydes, the generation of the iminium ion favors the creation of a nucleophilc enamine. In the case of unsaturated aldehydes, this intermediate promotes a nucleophilic attack by the reactant on the *β*-position. The extraordinary reactivity of this class of organocatalysts could be attributed to the nature of the cyclic secondary amine. The rigid ring structure keeps the

substituents away from the nitrogen lone pair, avoiding interferences during the nucleophilic attack on the carbonyl. This structural feature makes pyrrolidine derivatives more nucleophilic in comparison with acyclic amines leading to the formation of more stable enamines. The strained five-membered ring has also a great influence on the geometry of the transition state. In the case of proline, the carboxylic group can coordinate the approach of the electrophile by hydrogen bond formations.[14] For the imidazolidinone and the protected prolinol derivatives it is the selective shielding of the bulky groups that directs the facial discrimination (Figure 1).[15] Several proline derivatives have been synthetized to enhance the solubility and the proton acidity. The bulky aromatic groups of the protected prolinol catalyst can be modified by transforming the proline ester into tertiary alcohols, *via* reaction with Grignard reagents and following protection of the hydroxyl group.[16] It should be mentioned that the free hydroxyl group can form an unreactive hemiaminal species, with the iminium intermediate, leading to poor yields and low stereoselectivities (Scheme 5).[17] Silicon-based protecting groups offer some advantages compared to the carbon–based groups (e.g. Boc and Cbz). The C-Si bond (1.89 Å) is significantly longer than the C-C bond (1.54 Å) increasing the size of the trialkylsilyl group. The low basicity of Si-O linkage promotes inertness and increased stability towards organic acids (e.g. benzoic acid) as compared to the carbamate protecting groups.[18]

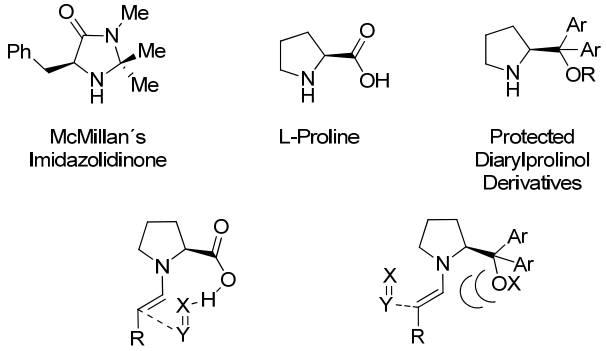
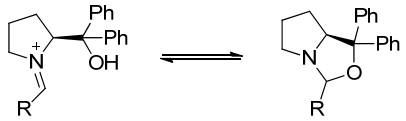
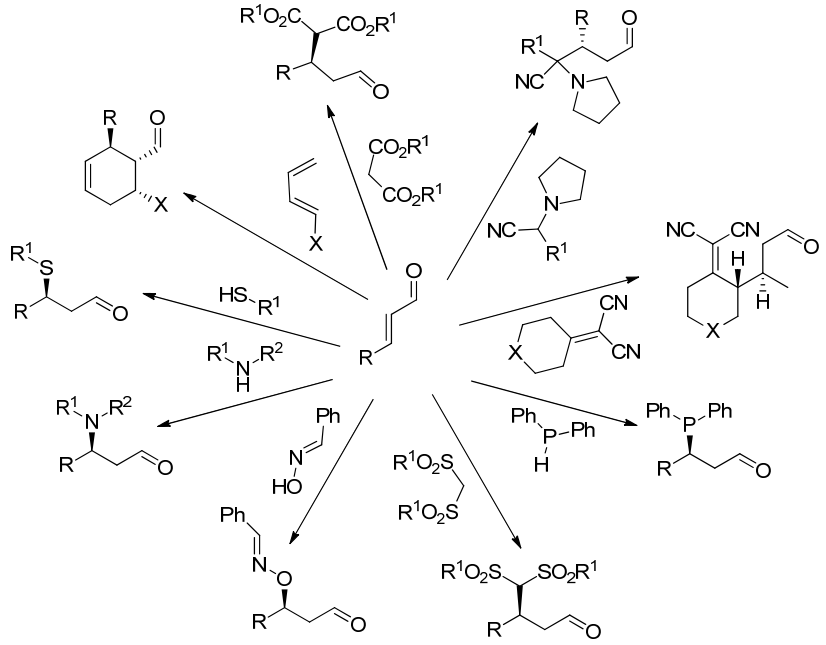



**Figure 1.** Cyclic secondary amine catalysts and enamine activation modes.



**Scheme 5.** Formation of the unreactive hemiaminal species.

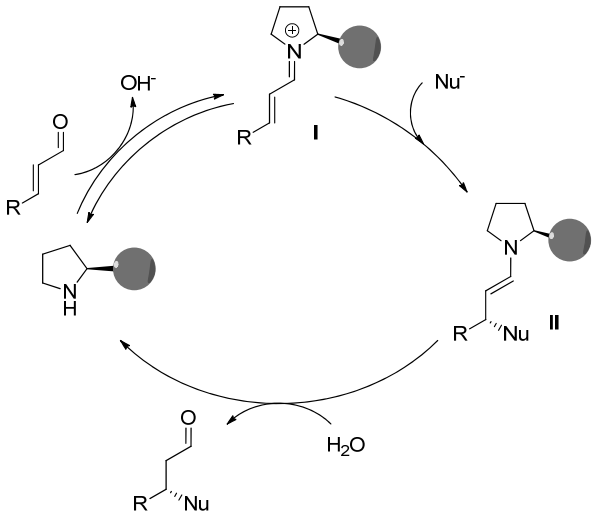
## 1.3 Amine Catalysis Involving Iminium Activation



**Scheme 6.** Reactions involving iminium activation by a chiral amine catalyst.

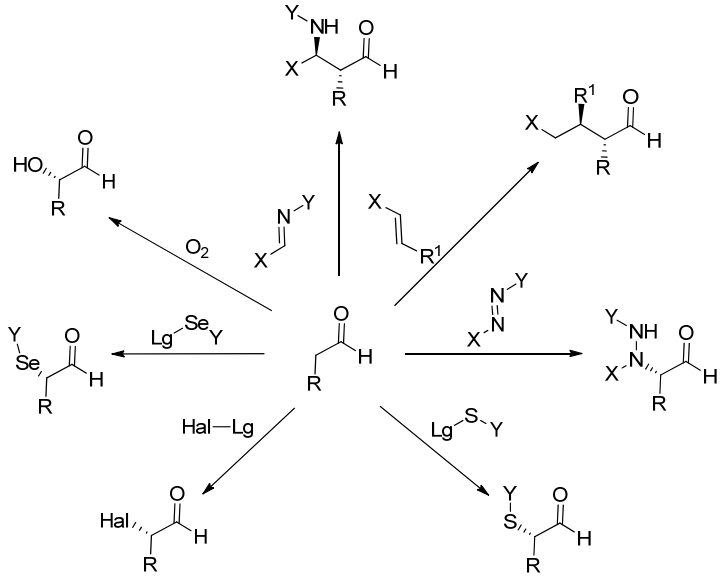
The conjugate addition of a nucleophile to an *α,β*-unsaturated aldehyde is aided by the presence of an amine catalyst. The iminium activation of enals gives direct access to the *β*-position of carbonyl compounds. *β*-Functionalizations of enals are carried out usually by 1,4-additon to the double bond (Scheme 6). Several types of nucleophiles can be used to form carbon-carbon bonds in the *β*-position, such as aminonitriles,[19] dicyanoolefines[20], malonates[21] and arylsulfonyl methanes.[22] *β*-Heterofunctionalizations are reachable with oxa-,[23] aza-,[24] phos-[25] and sulfa-[26] conjugate Michael additions. In his pioneering work, MacMillan showed that after iminium activation simple aldehydes were able to function as dienophiles for Diels-Alder reactions.[10e] The reversible formation of positively charged iminium intermediate (**I**) from the condensation of *α,β*-unsaturated aldehydes and chiral amines emulate the equilibrium dynamics and π-orbital electronics that are inherent to Lewis acid catalysis. The catalytic cycle starts with the condensation of the amine with an *α,β*-unsaturated aldehyde (**I**). The energy of the lowest unoccupied molecular orbital (LUMO) of the system is lowered, making the *α,β*-unsaturated aldehydes more electrophilic. The iminium ion can now react with a nucleophile at the *β*-position forming an enamine in-

termediate (**II**). Hydrolysis of the enamine releases the product and the catalyst for the next catalytic cycle (Scheme 7).



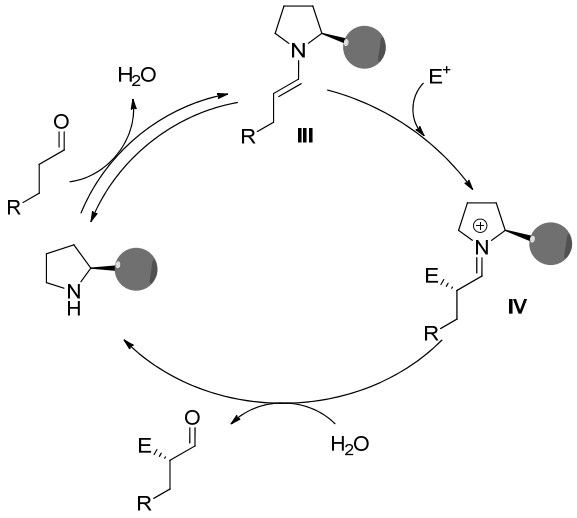

**Scheme 7.** Amine catalysis involving iminium activation.

### 1.4 Amine Catalysis Involving Enamine Activation

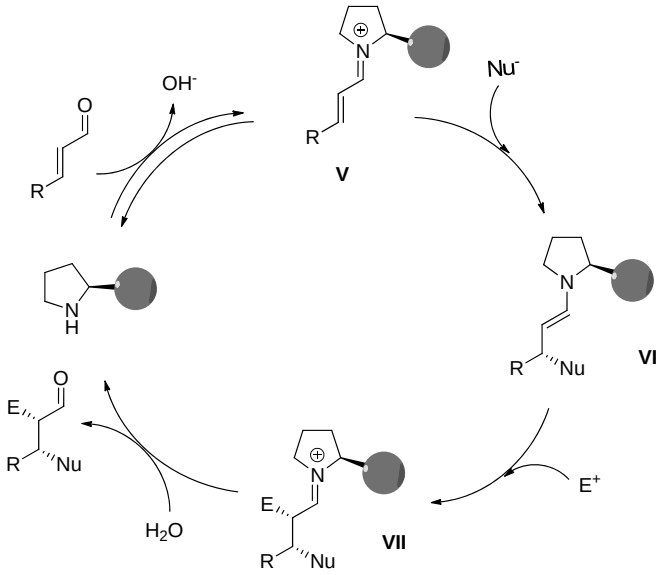



**Scheme 8.** Reactions involving enamine activation by a chiral amine catalyst.

Enamine activation can lead to a large variety of $\alpha$-functionalized aldehydes and ketones (Scheme 8).[27] Many protocols have been developed in the last decade. Carbon-carbon bond formation is easily achieved via Mannich[28] reactions and Michael additions.[29] $\alpha$-Heterofunctionalization can be achieved by $\alpha$-amination,[30] $\alpha$-sulfenylation,[31] $\alpha$-halogenation,[32] $\alpha$-selenylation[33] and $\alpha$-hydroxylation[34] using an appropriate electrophile. In the amine catalysis involving nucleophilic enamine activation, the catalytic cycle starts with the condensation of a secondary amine and a saturated aldehyde. The reversible formation of the correspondent iminium ion induces a fast deprotonation, which leads to the generation of the enamine (**III**) and a subsequent raise in energy of the highest occupied molecular orbital (HOMO). The enolate equivalent formed performs a nucleophilic attack on the electrophile generating an iminium intermediate (**IV**). The final hydrolysis of the iminium intermediate releases the product and the catalyst for the next cycle (Scheme 9).




**Scheme 9**. Amine catalysis involving enamine activation.




**Scheme 10**. Catalytic domino reactions involving iminium ion and enamine intermediates.

Reduction of waste products and time optimization are of primary importance in chemical industry. The development of atom- and step-economic procedures is becoming the predominant goal for many research groups. "One-pot" procedures involving formation of two or more new chemical bonds, without any further addition of reagents or catalysts, are highly desirable.[35] In domino reactions, every step is a consequence of the functionality formed in the previous one. A careful retrosynthetic analysis of the desired product dictates the choice of suitable substrates. Combinations of iminium/enamine activation allows for the creation of efficient "one-pot" protocols. In the LUMO activation, it can be observed that as a consequence of the $\beta$-addition of a nucleophile to the iminum ion an enamine is formed, which is HOMO activated. Next, a nucleophilic attack can be performed to an electrophile. Based on this strategy, it is possible to plan a two-component domino reaction. Michael-Michael,[36] Michael-aldol,[37] Michael/Morita-Baylis-Hillman,[38] Michael-Knoevenagel,[39] Oxa-,[40] Sulfa-,[41] Aza-[42] Michael-heterocyclization and alkylation[43] domino reactions, aziridination, epoxidation[44] and cyclopropanation[45] give access to a wide variety of complex chiral molecules bearing different functionalities. Reactions with three or more substrates were developed in an extremely regio- and chemoselective fashion enabling for the synthesis of products that is often

impossible to prepare with traditional "step by step" procedures.[46] The catalytic cycle starts with the condensation of an $\alpha,\beta$-unsaturated aldehyde with the chiral amine catalyst forming a labile iminium-ion intermediate (**V**). The nucleophile then adds to the activated electrophilic $\beta$-position generating the enamine (**VI**). The resulting enamine can then undergo a second reaction with an electrophile (**VII)** to afford, after hydrolysis, the product with two new stereocentres and the recycled catalyst (Scheme 10).

### 1.6 Carbocycles and Heterocycles

Carbocycles and heterocycles are cyclic organic molecules. The latter can contain different heteroatoms such as nitrogen, oxygen, sulfur etc. The nature of the heteroatom incorporated into the ring can dictate its chemical behaviors and the degree of toxicity. The most common saturated cyclic compounds (Figure 2) can have 3-membered rings (cyclopropane, epoxide, aziridine, thiirane), 4-membered rings (cyclobutane, azetidine, oxetane, thietane), 5-membered rings (cyclopentane, pyrrolidine, tetrahydrofuran, thiolan) and 6-membered rings (cyclohexane, piperidine, oxane, thiane). These compounds can be functionalized with substituents and chiral centers making them useful intermediates in the synthesis of pharmaceuticals, agrochemicals and natural products. Traditionally the synthesis of this class of organic molecules has been a challenging task for chemists. Many protocols were developed during the last decades to control the chemo and stereoselective outcome of the reactions.[47] Most of them require long and tedious syntheses due to the choice of complex starting materials and the preparation and isolation of many intermediates. Organocatalysis integrates with parallel and unexplored routes the asymmetric synthesis of complex cyclic molecules.[48] The aim of this thesis is to provide an easier and more elegant approach to the synthesis of chiral polyfunctionalized carbocycles and heterocycles.

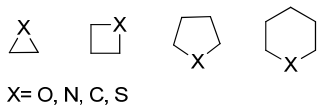



**Figure 2.** Common carbocycles and heterocycles.

# 2. Asymmetric Aziridination (Paper I-II)

## 2.1 Aziridines and Aziridination

Aziridines, also called ethylenimine or azaethylene units, are 3-membered heterocycles containing one nitrogen atom. Aziridines are important building blocks for the synthesis of natural products like $\beta$-lactams, aza-sugars and alkaloids.[49] They have also found applications as chiral ligands and chiral auxiliaries.[50] Many important drugs and natural products contain nitrogen in their structure.[51] Aziridine containing natural products are powerful alkylating agents and they can act as DNA cross-linking agents. Some antitumor and antibiotic drugs presenting this structural motif include: Mitosanes, FR and FK anticancer agents, Azinomycines, PBI (pyrrole [1,2-α] benzimiazole) class of natural products (Figure 2).[52] The ring strain of aziridines (27 kcal $mol^{-1}$), renders this compound susceptible to regio- and stereoselective ring-opening with various nucleophiles.[53] This accentuated reactivity permits for the installation of a wide range of functional groups, including carbon and heteroatoms, in a 1,2-relationship to the nitrogen. Aziridines, bearing an electron-withdrawing group on the nitrogen, show high reactivity toward ring opening particularly favored by the presence of Lewis acids. The hydroxyl group present on the aziridine, after reduction of the aldehyde moiety, can coordinate organometallic reagents, allowing for an intramolecular nucleophilic displacement to occur on the proximal carbon atom. Aziridino esters derivatives, prepared by simple oxidation of the aldehyde moiety, are useful intermediates for the regioselective ring-opening and the synthesis of functionalized amino acids. Therefore, nucleophilic ring-opening, is a practical tool to deliver $\alpha$- or $\beta$-amino acids, di-amines, $\beta$-aminosulfides, 1,2-aminoethers and several others important compounds depending on the nature of the nucleophile. Non-activated aziridines with an alkyl or aryl moiety on the nitrogen are difficult to open unless protonated, coordinated with a Lewis acid or quaternized. On this kind of aziridines it is possible to perform a series of safe transformations at ring atoms or in side chains without undesirable by-products.

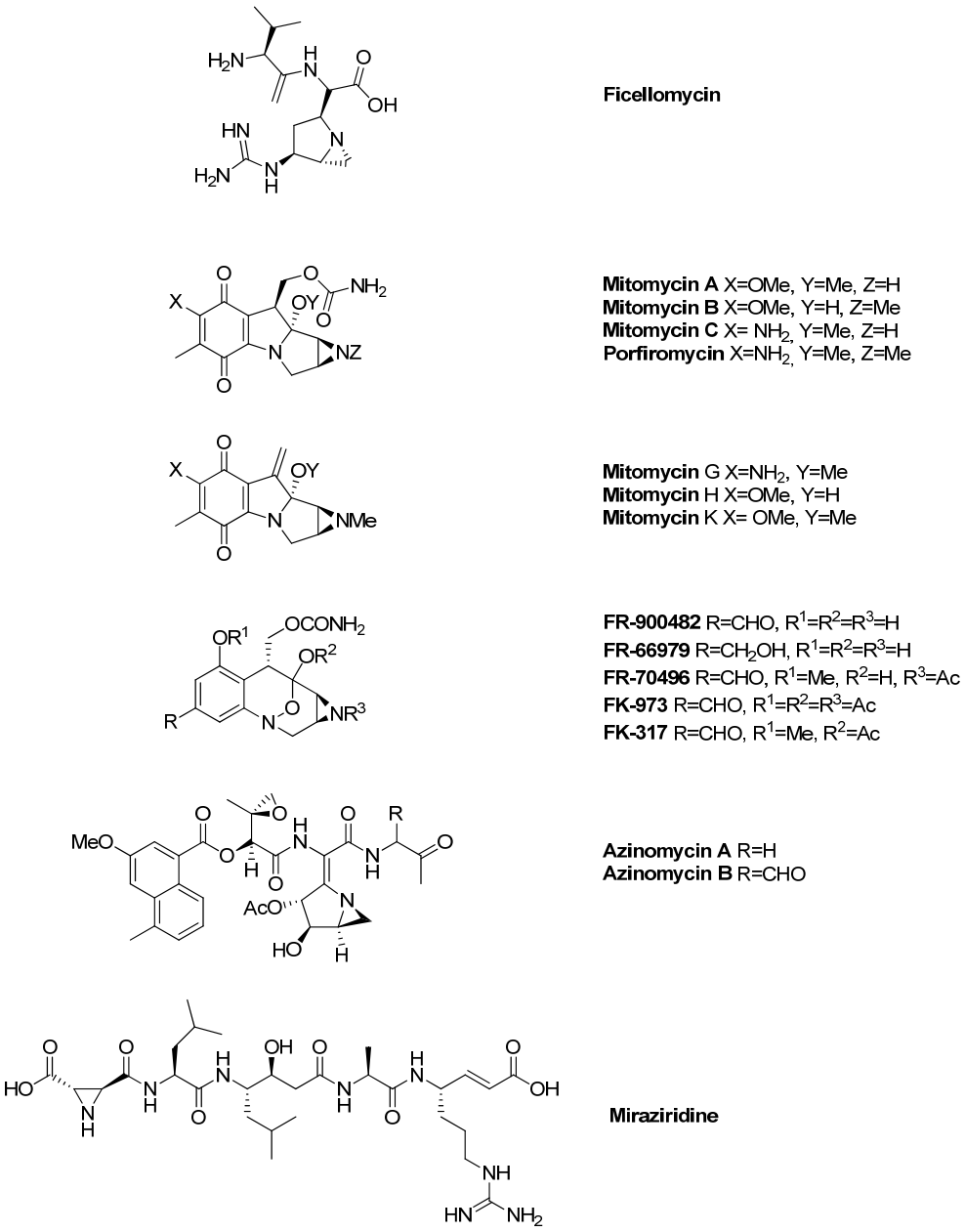
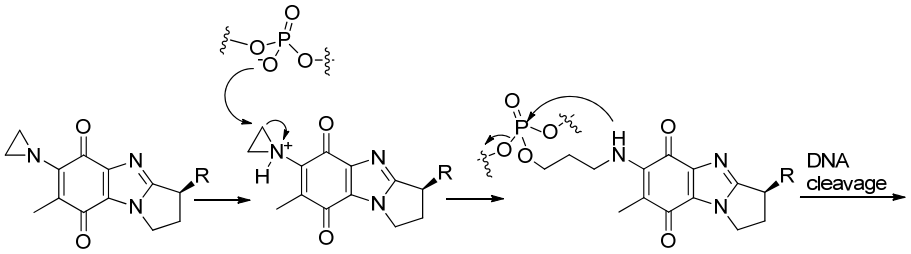


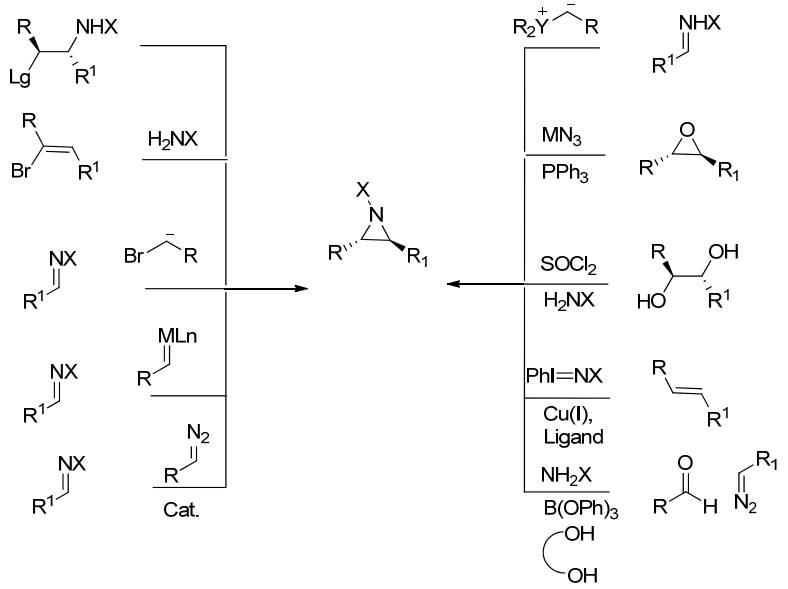

**Figure 3.** Aziridine containing natural products.

As mentioned before, due to the ring-strain, aziridines are good alkylating agents. PBI natural products are able to cleave the DNA upon reductive activation of the quinone ring by DT-diaphorase[54] and alkylation by phosphate of the nucleobases guanine (G) and adenine (A) leaving untouched cytosine (C) and thymine (T) (Scheme 11).[55]




**Scheme 11.** DNA cleavage mediated by a PBI natural product.

The milestone of aziridine synthesis was laid by Gabriel in 1888, where a 2-haloamine was converted to the smallest nitrogen containing heterocycle.[56] In 1935, Wenker prepared aziridines in two steps starting from ethanolamine. Ethanolamine was reacted with sulfuric acid at 250 $^{o}$C to give the sulfonate salt, which in the presence of sodium hydroxide, gave the corresponding aziridine.[57] Rapidly, different new methods were proposed for the synthesis of this important heterocycle (Scheme 12).[58] The $S_N2$-type cyclisation of enantiopure substituted amines is a good way for ring-closure.[59] The ring-opening of an epoxide by an azide and the following reduction with triphenylphosphine, under Staudinger conditions,[60] gives the corresponding aziridine after a thermally-induced cyclisation.[61] Aziridination by direct addition of a nitrene to a 2-haloacrylate, or similar reagent, has been reported by several groups.[62] Tosylimino phenyliodinane is used as the nitrogen source while different metals such as Mn(III), Fe(III), Rh(II), Cu(I), Cu(II) can catalyze the reaction in a stereospecific fashion with appropriate ligands.[63] Reaction of Schiff bases with carbenes or diazo compounds, in the presence of a transition metal catalyst, have also been deeply studied.[64] *N*-sulfonylimines reacts with sulfonium ylides, produced *in situ* from sulfonium salts, to give different functionalized aziridines depending on the nature of the substituents on the substrates.[65] A five-component aziridination reaction was recently published by Wulff where an aldehyde, an amine, ethyl diazoacetate, $B(OPh)_3$ and a biaryl ligand reacted simultaneously.[66] Herein, we propose an alternative synthesis involving an iminium/enamine activated domino reaction between $\alpha,\beta$-unsaturated aldehydes and a proper nitrogen source which is able first to act as a nucleophile and at the later stage as an electrophile.



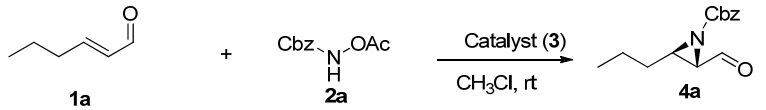

**Scheme 12**. Synthetic routes for the aziridines synthesis.

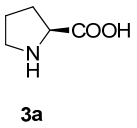
## 2.2 Aziridination of *α,β*-Unsaturated Aldehydes

We planned the reaction with the intent to find a suitable nitrogen source able of working first as a nucleophile and in a second step as electrophile. It is fundamental for the chemoselectivity and yield of the reaction that the nitrogen source preforms only a 1,4-addition to the double bond and not a 1,2-addition to the carbonyl leading to the formation of a racemic iminium intermediate. The p$K_a$ of the proton on the nitrogen needs be tuned to avoid a possible reversible *N*-addition step. It is known in the literature that reaction of an *O*-protected *N*-aryl or *N*-alkyl substituted hydroxylamine, with an *α,β*-unsaturated aldehyde, leads to iminium formation,[67] while reactions with an *N*-carbamate protecting group proceed through aza-conjugate addition.[68] The carbamate electron withdrawing group makes the *β*-amino intermediate non-basic circumventing the reversible elimination of the newly installed nitrogen. After these considerations, we decided to use an acylated hydroxycarbamate as a "nitrene equivalent". We began to screen the reaction conditions with *trans*-2 hexenal **1a** as the enal (0.25 mmol) and benzyl *N*-acetoxycarbamate **2a** (0.3 mmol) as the nitrogen source (Table 1). In our previous work we found that chloroform was the most suitable solvent compared to acetonitrile and dimethylformamide.[69] We tested the aziridination reaction with different amino catalysts **3**. The best results were obtained

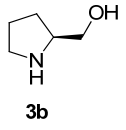
using the TMS-protected diphenylprolinol **3f** and dinaphthylprolinol **3g** (entries 6-7, Table1). Catalyst **3f** delivered the product with high diastero- and enantioselectivity. Therefore, we selected the *O*-TMS-protected diphenylprolinol **3f** as secondary amine for the aziridination of $\alpha,\beta$-unsaturated aldehydes. Based on these results we screened different leaving groups on the *N*-carbobenzyloxy-protected hydroxylamine **(**Table 2). We found that replacing the acetate with a better leaving group such as tosylate, where the negative charge is stabilized by resonance, in the presence of three equivalents of sodium acetate, resulted in an increased reaction rate and diastereoselectivity (entry 6, Table 2). Comparison of the tosyl leaving group vs the mesyl group shows a slight increase in the diastereoselctivity but a decrease in enantioselectivity and conversion (entry 7, Table 2). Substituting the carboxybenzyl (Cbz) protecting group with *tert*-butyloxycarbonyl (Boc) increased the enantioselectivity (entries 18-20, Table 2).

**Table 1.** Catalysts screening.[a]

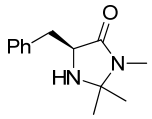


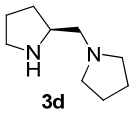

3a



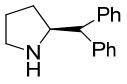

3b



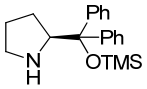

3c



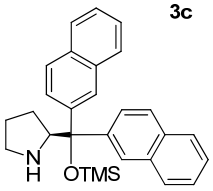

3d



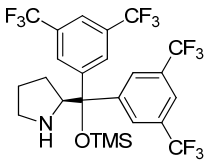

3e




3f




3g

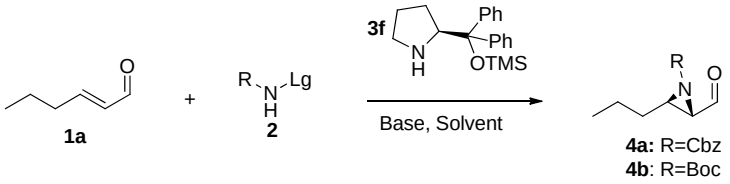



3h

| Entry | Catalyst (**3**) | Time (h) | Conv. (%)[b] | Dr[c] | ee (%)[d] |
|---|---|---|---|---|---|
| 1 | **3a** | 24 | 0 | - | - |
| 2 | **3b** | 16 | 5 | n.d. | n.d. |
| 3 | **3c** | 24 | 0 | - | - |
| 4 | **3d** | 4 | 15 | 1:1 | n.d. |
| 5 | **3e** | 4 | 4 | 1:1 | 57 |
| 6 | **3f** | 3 | 86 | 9:1 | 99 |
| 7 | **3g** | 4 | 76 | 5:1 | 90 |
| 8 | **3h** | 24 | 20 | >19:1 | 98 |
| 9[e] | **3f** | 0.5 | 100 | 5:1 | 96 |

[a] Experimental conditions: A mixture of aldehyde **1a** (0.25 mmol), **2a** (0.30 mmol) and catalyst **3** (20 mol%) in 1.0 mL of $CHCl_3$ was vigorously stirred for the time given in the table. [b] Conversion into product as determined by $^1$H NMR spectroscopic analysis. [c] Determined by $^1$H NMR spectroscopic analysis. [d] Determined by chiral–phase HPLC analysis after reduction to the corresponding alcohol. [e] The reaction was performed at 40 $^o$C. N.d. = not determined.

**Table 2.** Leaving-group and condition screening.[a]

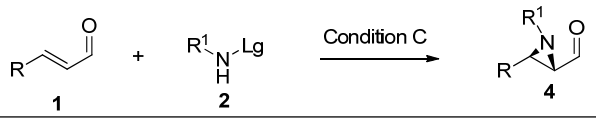


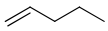
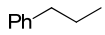
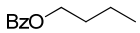
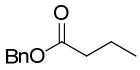
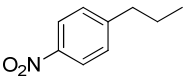
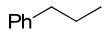

| Entry | R | Lg | Base | Solvent | T ($^{o}$C) | t (h) | Conv.(%)[b] | Dr[c] | ee (%)[d] |
|---|---|---|---|---|---|---|---|---|---|
| 1 | Cbz | OAc | - | $CH_3Cl$ | RT | 3 | 86 | 9:1 | 99 |
| 2 | Cbz | OAc | - | $CH_3Cl$ | 40 | 0.5 | 100 | 5:1 | 96 |
| 3 | Cbz | OTs | - | $CH_3Cl$ | RT | 3 | 11 | 20:1 | n.d. |
| 4 | Cbz | OTs | - | $CH_3Cl$ | 40 | 1.5 | 32 | 20:1 | n.d. |
| 5 | Cbz | OAc | NaOAc | $CH_3Cl$ | RT | 0.5 | 48 | 3:1 | 98 |
| 6 | Cbz | OTs | NaOAc | $CH_3Cl$ | RT | 0.5 | 100(78) | 15:1 | 97 |
| 7 | Cbz | OMs | NaOAc | $CH_3Cl$ | RT | 0.5 | 58 | 20:1 | 95 |
| 8 | Cbz | OTs | NaOAc | toluene | RT | 0.5 | 78 | 7:1 | 97 |
| 9 | Cbz | OTs | NaOAc | $CH_2Cl_2$ | RT | 0.5 | 100 | 8:1 | 94 |
| 10 | Cbz | OTs | $Et_3N$ | $CH_3Cl$ | RT | 0.5 | 40 | 5:1 | 94 |
| 11 | Cbz | OTs | $Na_2CO_3$ | $CH_3Cl$ | RT | 0.5 | 61 | 15:1 | 96 |
| 12 | Cbz | OTs | $K_2CO_3$ | $CH_3Cl$ | RT | 0.5 | 90 | 11:1 | 99 |
| 13[e] | Cbz | OTs | NaOAc | $CH_3Cl$ | RT | 0.5 | 64 | 10:1 | 96 |
| 14[f] | Cbz | OTs | NaOAc | $CH_3Cl$ | RT | 1.6 | 100(67) | 7:1 | 96 |
| 15[g] | Cbz | OTs | NaOAc | $CH_3Cl$ | RT | 5 | 84 (58) | 10:1 | 98 |
| 16[h] | Cbz | OTs | NaOAc | $CH_3Cl$ | RT | 16 | 63 (45) | 10:1 | 97 |
| 17[i] | Cbz | OTs | NaOAc | $CH_3Cl$ | RT | 16 | 60 (41) | 10:1 | 97 |
| 18[j] | Boc | OTs | NaOAc | $CH_3Cl$ | RT | 0.67 | 100(84) | 10:1 | 99 |
| 19[k] | Boc | OTs | NaOAc | $CH_3Cl$ | RT | 5 | 96 (74) | 7:1 | 99 |
| 20[l] | Boc | OTs | NaOAc | $CH_3Cl$ | RT | 8 | 88 (69) | 8:1 | 98 |

[a] Experimental conditions: A mixture of aldehyde **1a** (0.25 mmol), **2** (0.30 mmol), catalyst **3f** (20 mol%) and base (3 equiv.) in 1.0 mL of solvent was vigorously stirred for the time given in the table. [b] Conversion into product as determined by $^{1}$H NMR spectroscopic analysis and the value in parentheses is the isolated yield. [c] Determined by $^{1}$H NMR spectroscopic analysis. [d] Determined by chiral-phase HPLC analysis after reduction to the corresponding alcohol. [e] NaOAc 1 equiv, was used. [f] NaOAc 1.5 equiv. was used. [g] 10 mol% catalyst was used. [h] 5 mol% catalyst was used. [i] 2.5 mol% catalyst was used. [j] Boc-NHOTs was used and the catalyst loading was 20 mol%. [k] Boc-NHOTS was used and the catalyst loading was 10 mol%. [l] Boc-NHOTs was used and the catalyst loading was 5 mol%. Lg= leaving group.

With these results in hand, we were able to investigate the aziridination reaction on different enals using *N*-Cbz and -Boc protected hydroxylamine as nitrene equivalents. Aliphatic and aromatic aldehydes, decorated with different substituent patterns, yielded the corresponding protected aziridines with excellent diastero (up to 19:1) and enantioselectivity (up to 99%) and in good yields. Linear simple aldehydes containing four, six and seven carbon atoms delivered the corresponding *N*-Cbz and -Boc protected aziridines in good yields and *ee´*s (entries 11-13, Table 3). Aliphatic aldehydes functionalized with a double bond, an ethyl ester, benzyl ether and aromatic rings also afforded the desired products with excellent diastero and enantioselectivity (entries 14-16, 19, 21, Table 3) showing the tolerance of the reaction toward several functional groups. The aminocatalytic aziridination was tested also on aromatic aldehydes with different substituents on the aromatic ring (Table 4). The reaction seemed to work better with electron-withdrawing substituents such as the nitro (entries 5, 10, Table 4) and the cyano groups (entry 2, Table 4) as compared to electron-donating substituents such as the methyl (entry 7, Table 4). The elimination product **5** is present preferentially in reactions involving aziridines bearing Cbz as protecting group (entries 4-6, Table 4) and in particularly unstable products generated from aldehydes containing electron-donating groups (entries 7-8, Table 4). It is worth noting that the reactions performed in a 1 mmol scale displayed the same results as the reactions performed on a 0.25 mmol scale (entry 22, Table 3 and entry 12, Table 4).

**Table 3.** Asymmetric aziridination of aliphatic enals.[a]

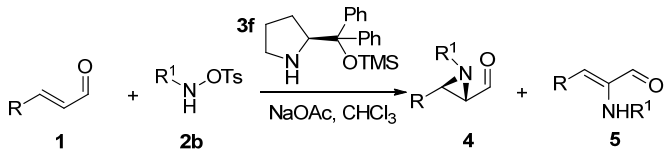


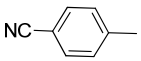
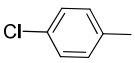
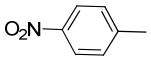
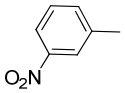
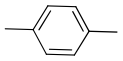
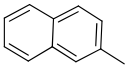
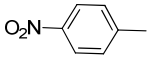
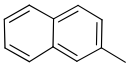

| Entry | R | $R^1$ | Cond. | T (°C) | t (h) | Yield (%)[b] | Dr[c] | ee (%)[d] |
|---|---|---|---|---|---|---|---|---|
| 1 | *n*-Pr | Cbz | C1 | 40 | 0.5 | 78 | 4:1 | 96 |
| 2[e] | *n*-Pr | Cbz | C1 | 40 | 0.5 | 68 | 4:1 | 90 |
| 3 | *n*-Bu | Cbz | C1 | 40 | 0.5 | 70 | 5:1 | 96 |
| 4 |  | Cbz | C1 | 40 | 0.5 | 68 | 6:1 | 96 |
| 5 |  | Boc | C2 | 40 | 0.4 | 68 | 5:1 | 92 |
| 6 | Me | Boc | C2 | 18 | 5 | 54 | 5:1 | 90 |
| 7 |  | Boc | C2 | 40 | 0.4 | 60 | 5:1 | 98 |
| 8 | Et | Cbz | C1 | 40 | 0.6 | 60 | 5:1 | 97 |
| 9 |  | Cbz | C1 | 40 | 0.5 | 62 | 5:1 | 84 |
| 10 |  | Cbz | C1 | 40 | 0.4 | 66 | 7:1 | 92 |
| 11 | *n*-Pr | Cbz | C3 | 18 | 0.5 | 72 | 15:1 | 97 |
| 12 | *n*-Bu | Cbz | C3 | 18 | 1 | 65 | 15:1 | 97 |
| 13 | Me | Cbz | C3 | 18 | 0.5 | 65 | 15:1 | 95 |
| 14 |  | Cbz | C3 | 18 | 0.5 | 84 | 10:1 | 94 |
| 15 | $CO_2Et$ | Cbz | C3 | 18 | 0.67 | 57 | 5:1 | 91 |
| 16 | $CO_2Et$ | Boc | C4 | 18 | 0.67 | 67 | 6:1 | 91 |
| 17 | H | Cbz | C3 | 4 | 0.5 | 77 | - | 91 |
| 18 | *n*-Pr | Boc | C4 | 18 | 0.67 | 84 | 10:1 | 99 |
| 19[e] |  | Boc | C4 | 18 | 5.5 | 73 | 7:1 | 99 |
| 20 | Et | Cbz | C3 | 18 | 0.4 | 74 | 13:1 | 98 |
| 21 |  | Boc | C4 | 18 | 0.4 | 68 | 10:1 | 97 |
| 22[e] | *n*-Pr | Cbz | C3 | 18 | 0.5 | 70 | 19:1 | 97 |

[a] Experimental conditions: C1: A mixture of Cbz-NHOAc (0.30 mmol), aldehyde **1** (0.25 mmol) and catalyst **3f** (20 mol%) in 1.0 mL of $CHCl_3$ was vigorously stirred for the time given in the table. C2: A mixture of Boc-NHOAc (0.30 mmol), aldehyde **1** (0.25 mmol) and catalyst **3f** (20 mol%) in 1.0 mL of $CHCl_3$ was vigorously stirred for the time given in the

table. C3: A mixture of Cbz-NHOTs (0.25 mmol), aldehyde **1** (0.30 mmol), catalyst **3f** (20 mol%) and NaOAc (3 equiv.) in 1.0 mL of $CHCl_3$ was vigorously stirred for the time given in the table. C4: A mixture of Boc-NHOTs (0.25 mmol), aldehyde **1** (0.30 mmol), catalyst **3f** (20 mol%) and NaOAc (3 equiv.) in 1.0 mL of $CHCl_3$ was vigorously stirred for the time given in the table. [b] Isolated yield after silica-gel column chromatography. [c] Determined $^1$H NMR spectroscopic analysis. [d] Determined by chiral-phase HPLC analysis. [e] 10 mol% of catalyst was used. [f] 5 mol% of catalyst was used. [g] Reaction performed at 1 mmol scale of α,β-unsaturated aldehyde. Lg= leaving group.

**Table 4.** Asymmetric aziridination of aromatic enals.[a]




| Entry | R | $R^1$ | t (h) | (**4**:**5**) Ratio[b] | Yield (%)[c] | Dr[d] | ee (%)[e] |
|---|---|---|---|---|---|---|---|
| 1 |  | Cbz | 0.5 | 10:1 | 52 | 19:1 | 99 |
| 2[f] |  | Cbz | 2 | 20:1 | 60 | 18:1 | 99 |
| 3 |  | Cbz | 0.5 | 20:1 | 40 | 19:1 | 97 |
| 4 |  | Cbz | 0.5 | 4:1 | 64 | 15:1 | 95 |
| 5 |  | Cbz | 0.5 | 6:1 | 64 | 15:1 | 99 |
| 6 |  | Cbz | 0.5 | 4:1 | 44 | 10:1 | 99 |
| 7 |  | Cbz | 0.67 | 3:1 | 55 | 12:1 | n.d. |
| 8 |  | Cbz | 0.67 | 4:1 | 25 | 19:1 | 95 |
| 9 |  | Boc | 1 | 25:1 | 63 | 15:1 | 99 |
| 10 |  | Boc | 1 | 20:1 | 72 | 19:1 | 99 |
| 11 |  | Boc | 1.5 | 9:1 | 38 | 19:1 | 99 |
| 12[g] |  | Cbz | 0.5 | 10:1 | 69 | 19:1 | 99 |

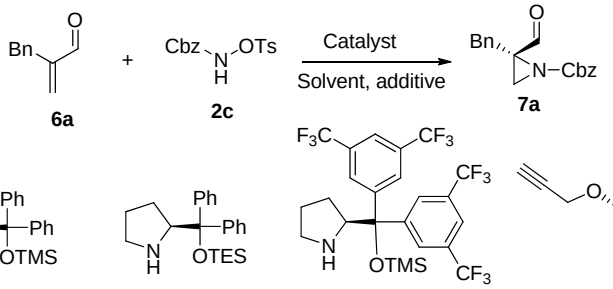
[a] Experimental conditions: A mixture of aldehyde **1** (0.25 mmol), **2b** (0.30 mmol), NaOAc (3 equiv.) and catalyst **3f** (20 mol%) in 1.0 mL of $CHCl_3$ was vigorously stirred for the time given in the table. [b] The ratio was determined by $^1$H NMR spectroscopic analysis. [c] Isolated yield of pure product after silica-gel column chromatography. [d] Determined by $^1$H NMR spectroscopic analysis. [e] Determined by chiral phase HPLC analysis. [f] Reaction performed at 4 $^o$C. [g] Reaction performed at a 1 mmol scale of α,β-unsaturated aldehyde. N.d.= not determined.

## 2.3 Aziridination of α-Substituted α,β-Unsaturated Aldehydes

Terminal aziridines formed from *α*-substituted *α,β*-unsaturated aldehydes possess a quaternary stereocenter at the *α*-position to the aldehyde. They are useful building blocks due to the ring-opening on the terminal and less hindered carbon to give polysubstituted *α*-amino acids. Nucleophilic ring opening on the α-position give access to $\beta^2$-amino acids. *β*-Peptides generally are not present in nature and they can offer the possibility to develop new drugs able of avoiding the antibiotic bacterial resistance and the hydrolysis by metabolic peptidases. During our studies on the aziridination of *α*-substituted *α,β*-unsaturated aldehydes, two parallel papers where published on epoxidation[70] and cyclopropanation[71] of terminal enals, using diphenylprolinol silyl ether as catalysts. These three publications cover the synthesis of terminal chiral three-membered cyclic molecules. After the previous excellent results, on linear aldehydes we evaluated the possibility to prepare terminal aziridines from *α*-substituted acryl aldehydes.[72] We screened the reaction using 2-phenylacrylaldehyde **6a** (0.25 mmol) and Cbz-protected hydroxylamine **2c** (0.30 mmol) as the nitrogen source (Table 5). First, we tried different bases as additive (entries 1-4, Table 5), using chloroform as solvent, obtaining the highest enantioselectivity with sodium acetate (entry 1, Table 5). We then went on to screen solvents and catalysts. The highest yield and enantiomeric excess was achieved using the diarylprolinol catalyst **3f** and toluene as solvent at 4 $^o$C (entry 13, Table 5). When these conditions were found, we investigated the scope of the reaction using different aldehydes with Boc and Cbz *N*-protected hydroxylamine **2b** as nitrene source (Table 6). 2-Alkyl substituted aziridines **7** were formed from simple enals such as *n*-butyl, *n*-pentyl and *n*-hexyl aldehydes with superlative results (entries 3-6, Table 6). Aldehydes with benzyl, terminal double bond and benzoyl as functional groups gave the corresponding terminal aziridines with excellent yields and *ee´*s (entries 1, 2, 7-10, Table 6). The absolute stereochemistry of terminal aziridines was assigned by means of TD-DFT calculations of the electronic di-

chroism (ECD) spectra of benzyl 2-benzyl-2-formylaziridine-1-carboxylate **7a**. The density functional theory (DFT) calculations of the (*S*)-enantiomer matched with the experimental ECD spectra. Thus, the absolute configuration at C-2 was assigned as *S*.

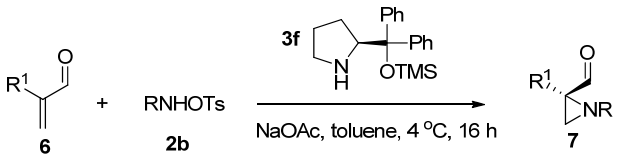
**Table 5.** Screening of reaction condition of asymmetric aziridination of $\alpha$-substituted $\alpha,\beta$-unsaturated aldehydes.[a]

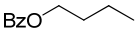
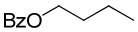



| Entry | Catalyst | Solvent | Additive | t (h) | Conv. (%)[b] | ee (%)[c] |
|---|---|---|---|---|---|---|
| 1 | **3f** | $CHCl_3$ | NaOAc | 17 | 69 | 88 |
| 2 | **3f** | $CHCl_3$ | $K_2CO_3$ | 17 | 69 | 7 |
| 3 | **3f** | $CHCl_3$ | $Et_3N$ | 16 | 66 | 25 |
| 4 | **3f** | $CHCl_3$ | $Na_2CO_3$ | 16 | 46 | 14 |
| 5 | **3f** | toluene | NaOAc | 17 | 100 (49)[d] | 94 |
| 6 | **3f** | $CH_2Cl_2$ | NaOAc | 19 | 54 | 84 |
| 7 | **3f** | EtOH | NaOAc | 17 | 100 | 59 |
| 8[e] | **3f** | toluene | NaOAc | 17 | 100 (68)[d] | 92 |
| 9 | - | toluene | NaOAc | 17 | 0 | - |
| 10 | **3g** | toluene | NaOAc | 16 | 100 | 93 |
| 11 | **3h** | toluene | NaOAc | 16 | 43 | 72 |
| 12[f] | **3i** | toluene | NaOAc | 20 | 100 | 76 |
| 13[e,g] | **3f** | toluene | NaOAc | 16 | 100(88)[d] | 94 |

[a] Experimental conditions: A mixture of aldehyde **6a** (0.25 mmol), **2c** (0.30 mmol), additive (0.75 mmol) and catalyst **3** (20 mol%) in 1.0 mL of solvent was vigorously stirred for the time given in the table. [b] Conversion of determined by $^1$H NMR spectroscopic analysis. [c] Determined by chiral-phase HPLC analysis. [d] Isolated yield in parenthesis. [e] Reaction performed in 0.5 mL solvent. [f] Catalyst **3i** (10 mol%) was used. [g] Reaction performed at 4 $^o$C and 1.5 equiv. of NaOAc were used.

**Table 6.** Asymmetric aziridination of $\alpha$-substituted $\alpha,\beta$-unsaturated aldehydes.[a]




| Entry | $R^1$ | R | Yield (%)[b] | ee (%)[c] |
|---|---|---|---|---|
| 1 | Bn | Cbz | 88 | 94 |
| 2 | Bn | Boc | 89 | 96 |
| 3 | *n*-Bu | Boc | 81 | 96 |
| 4 | *n*-pentyl | Cbz | 64 | 95 |
| 5 | *n*-pentyl | Boc | 67 | 95 |
| 6 | *n*-hexyl | Cbz | 69 | 95 |
| 7 |  | Cbz | 65 | 91 |
| 8 |  | Boc | 73 | 92 |
| 9[d] |  | Cbz | 75 | 92 |
| 10 |  | Boc | 90 | 94 |
| 11 | *n*-pentyl | Ts | 92 | 84 |
| 12[e] | *n*-hexyl | Cbz | 60 | 95 |

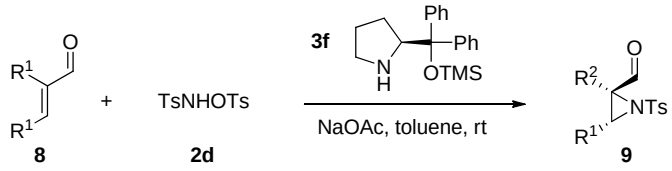
[a] Experimental conditions: A mixture of aldehyde **6** (0.25 mmol), **2b** (0.30 mmol), NaOAc (0.375 mmol) and catalyst **3f** (20 mol%) in 0.5 mL of solvent was stirred at 4 °C for 16 h. [b] Isolated yield of pure product after silica-gel column chromatography. [c] Determined by chiral-phase HPLC analysis. [d] Reaction performed at r.t. [e] Reaction performed at a 1 mmol scale of α,β-unsaturated aldehydes.

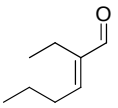
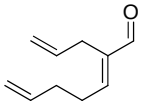
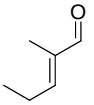
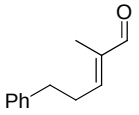
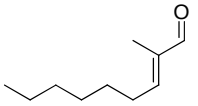
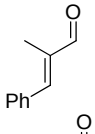
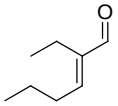
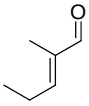
## 2.4 Aziridination of Disubstituted $\alpha,\beta$-Unsaturated Aldehydes

After our previous success, we embarked on the challenging and unprecedented synthesis of aziridines from disubstituted enals **8** (Table 7). We first tested the reaction with Boc-NHOTs as the nitrogen source, which afforded the corresponding product in high yield but with low stereoselectivity (entry 7, Table 7). After further investigations, we discovered that the nitrene equivalent tosyl *N*-protected hydroxylamine **2d** gave the corresponding aziridine in good yield and excellent *ee´s* (entry 1, Table 7). Using this new nitrogen source we prepared different substituted aldehydes to investigate the scope of the reaction (Table 7). To our satisfaction we obtained the corresponding disubstituted aziridines in high yields (up to 84%) and excellent

diastero- and enantioselectivities (25:1 dr, 99% *ee*) showing that our methodology constitutes a useful way for aziridinating mono- and disubstituted aldehydes without any loss of selectivity. The absolute configuration of the disubstituted aziridine products was determined by X-ray analysis of 2-ethyl-3-propyl-1-tosylaziridine-2-carbaldehyde.

**Table 7.** Asymmetric aziridination of *α,β*-disubstituted *α,β*-unsaturated aldehydes.[a]



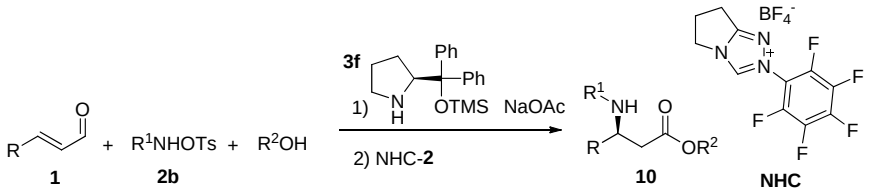

| Entry | Aldehyde | t (h) | Yield (%)[b] | Dr[c] | ee (%)[d] |
|---|---|---|---|---|---|
| 1 |  | 74 | 61 | 8:1 | 99 |
| 2 |  | 68 | 77 | 10:1 | 99 |
| 3 |  | 66 | 84 | >25:1 | 99 |
| 4 |  | 72 | 79 | >25:1 | 99 |
| 5 |  | 66 | 83 | 17:1 | 99 |
| 6 |  | 65 | 55 | >25:1 | 98 |
| 7[e] |  | 70 | 75 | 4:1 | 34 |
| 8[f] |  | 66 | 78 | >25:1 | 99 |

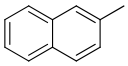
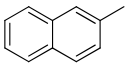
[a] Experimental conditions: A mixture of aldehyde **8** (0.25 mmol), **2d** (0.30 mmol), NaOAc (0.375 mmol) and catalyst **3f** (20 mol%) in 0.5 mL toluene was vigorously stirred at r.t. for the time given in the table. [b] Isolated yield after silica-gel column chromatography. [c] Determined by crude $^1$H NMR spectroscopic analysis. [d] Determined by chiral-phase HPLC analysis. [e] Boc-NHOTs was used as nitrogen source. [f] The reaction was performed at a 1 mmol scale of α,β-unsaturated aldehydes.

## 2.5 Synthesis of *β*-Amino Esters

*β*-Amino acids are the constituent of *β*-peptides. This class of compounds is very important in biological and medical research because they are commonly stable toward proteolytic degradation by enzymes. Several synthetic protocols have been developed in the past years involving chemical reactions and biocatalysis.[73] In 2004, Bode showed that epoxyaldehydes and aziridinylaldehydes can be converted into the corresponding acyclic esters by the use of heterocyclic carbene catalysts.[74] Usually the carbon on the carbonyl group is partially positively charged due to the presence of the more electronegative oxygen. In depth studies of the coenzyme thiamine and the understanding of the activation mechanism of benzaldehyde by cyanide ion, to carry out the benzoin condensation, increased the interest of the scientific community on the possibility of using carbenes not only as ligand for metal catalyst but also as nucleophilic organocatalysts.[75] The role of the carbene is to switch the reactivity of the carbonyl carbon atom with the formation of an intermediate acyl carbanion, thus creating a phenomenon that is called "umpolung". The activated aldehyde can now act as a nucleophile, which allows for the preparation of heteroatoms substituted molecules.[76] In 2007, our group disclosed the first "one-pot" combination of amine and heterocyclic carbene catalysis to synthetize *β*-amino esters starting directly from simple *α*,*β*-unsaturated aldehydes.[77] For the first step the protocol previously refined was used. Once the aziridine was formed, we added the Rovis **NHC** catalyst, the alcohol and the reaction was stirred overnight (Table 8). The reaction on several different enals, aliphatic and aromatic, was tried using Boc and Cbz *N*-protected hydroxylamine as nitrogen source. The results in Table 8 shows that the reaction was highly enantioselective (up to 99% *ee*) and gave the corresponding *β*-amino esters **10** in good yields (up to 77%). The opening can be carried out using different kinds of alcohols such as ethanol and benzyl alcohol reducing the loading to three equivalents (entries 7-11, Table 8).

**Table 8.** Synthesis of protected *β*-amino acid ester derivatives. [a]

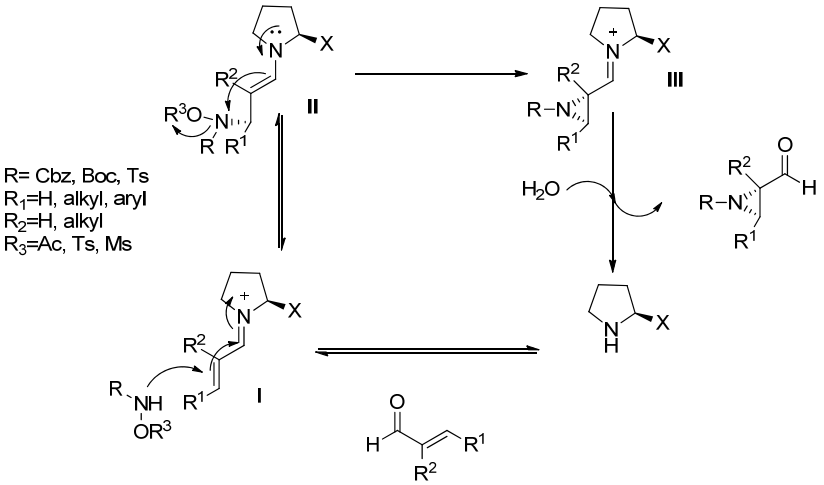



| Entry | R | $R^1$ | $R^2$ | Cat. **3f** (mol%) | t (h) | Yield (%)[b] | ee (%)[c] |
|---|---|---|---|---|---|---|---|
| 1 | *n*-Pr | Cbz | Me | 20 | 0.5 | 62 | 93 |
| 2 | Ph | Cbz | Me | 20 | 0.5 | 54 | 96 |
| 3 | BnO | Boc | Me | 5 | 8 | 73 | 93 |
| 4 | Ph | Boc | Me | 5 | 8 | 80 | 92 |
| 5 |  | Cbz | Me | 20 | 0.7 | 25 | 95 |
| 6 |  | Boc | Me | 20 | 1 | 38 | 99 |
| 7[d] | *n*-Pr | Cbz | Me | 20 | 0.5 | 62 | 95 |
| 8[d] | *n*-Pr | Cbz | Et | 20 | 0.5 | 69 | 94 |
| 9[d] | *n*-Pr | Cbz | Bn | 20 | 0.5 | 62 | 94 |
| 10[d] | Ph | Cbz | Me | 20 | 0.5 | 46 | 94 |
| 11[d] | Ph | Boc | Me | 5 | 8 | 77 | 92 |
| 12[e] | *n*-Pr | Cbz | Me | 20 | 0.5 | 64 | 95 |

[a] Experimental conditions: A mixture of aldehyde **1** (0.25 mmol), **2b** (0.30 mmol), NaOAc (0.75 mmol) and catalyst **3f** (5-20 mol%) in 1.0 mL of $CHCl_3$ was vigorously stirred at r.t. for the time given in the table. Then, methanol (1.0 mL) and **NHC** (3 mol%) was added to the reaction mixture. The reaction was stirred for 16 h at r.t. [b] Isolated yield of pure product after silica-gel column chromatography. [c] Determined by chiral-phase HPLC analysis. [d] 3 equiv. of alcohol were used. [e] The reaction was performed at a 1 mmol scale of α,β-unsaturated aldehydes.

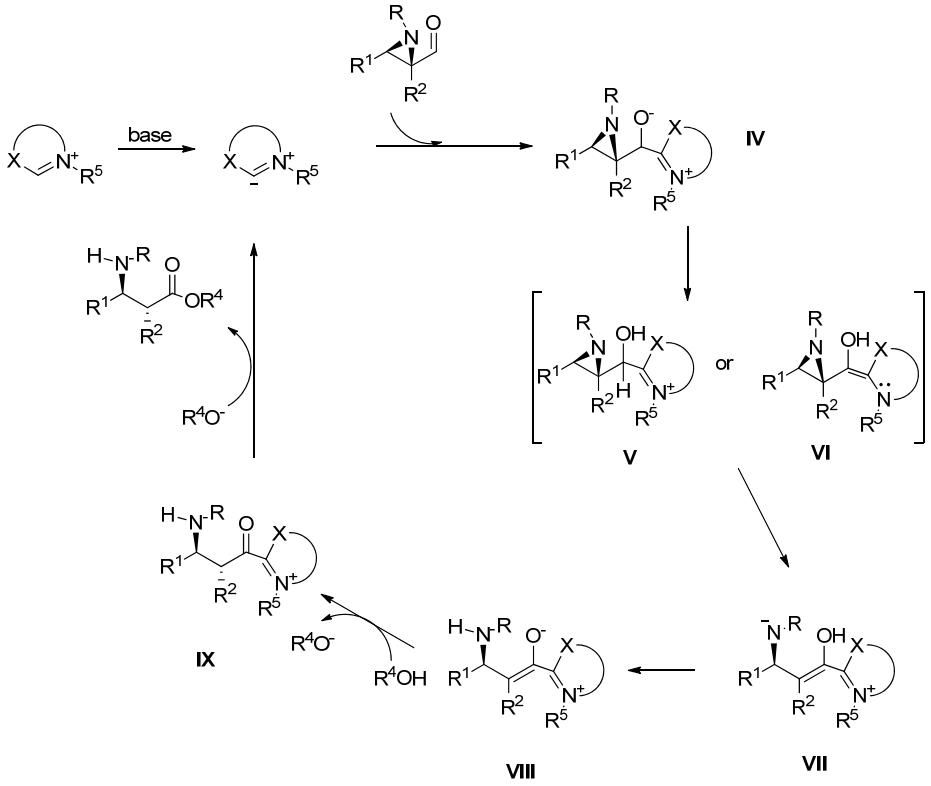
## 2.6 Proposed Mechanistic Cycles

The reversible condensation of the chiral catalyst with an enal generates an iminium intermediate (**I**). The shielding of the chiral intermediate, by the trimethyl silyl group, allows the nucleophilc attack of the amino group on the *β*-carbon of the enal, selectively, from the *Re*-face ($R^1$=alkyl). Next, the new generated enamine intermediate (**II)** undergoes an irreversible 3-*exo*-tet nucleophilic attack on the electrophilic nitrogen. The leaving group is released and hydrolysis of the iminium intermediate (**III)** gives the heterocyclic product and the catalyst for the next catalytic cycle (Scheme 13).




**Scheme 13.** Reaction pathway for the aziridination of enals.

The mechanism proposed for the ring opening of aziridines catalyzed by the *N*-heterocyclic carbene catalyst (AHCC) is shown in Scheme 14. The carbene catalyst is deprotonated *in situ* by the base generating a zwitterionic specie, that performs a nucleophilc attack on the aldehyde moiety of the aziridine, giving an azolium salt adduct (**IV**). The opening of the aziridine occurs *via* a concerted elimination (**V**) or in a stepwise manner *via* a stabilized anion (**VI**) to give (**VII**). Keto-enol tautomerization proceeds through the intermediate (**VIII**) forming the activated carbonyl intermediate (**IX**). The nucleophilic substitution by the alcohol affords the *β*-amino ester product and regenerates the carbene catalyst for the next cycle.




**Scheme 14.** Reaction pathway for the aziridine ring-opening.

## 2.7 Conclusions

We have developed highly chemo- and stereoselective synthetic methods to access linear, terminal and complex polysubstituted aziridines containing tertiary and quaternary stereocenters. We also disclosed a quick and atom economical route to generate *β*-amino acid ester derivatives starting from simple enals.

# 3. Asymmetric Synthesis of Pyrazolidines (Paper III)

### 3.1 Pyrazolidines, Pyrazolines and Pyrazolidones

Pyrazolidines are five-membered heterocycles with two adjacent nitrogen centers. They can be easily converted to pyrazolines after dehydratation under acidic conditions and to pyrazolidinones by oxidation of the hydroxyl group.[78] Pyrazolidines are also the precursors for the synthesis of 1,3-diamines after reductive cleavage of the N-N bond.[79] Their structure is present in many natural products and they are useful intermediates for the synthesis of important drugs with bioactivities such as antidepressant, antiviral, antimicrobial, immunosuppressive, anti-obesity, anti-inflammatory, psycho analeptic, anticonvulsant activities. Some examples of important compounds bearing a pyrazolidine structure are depicted in Figure 4.[80]

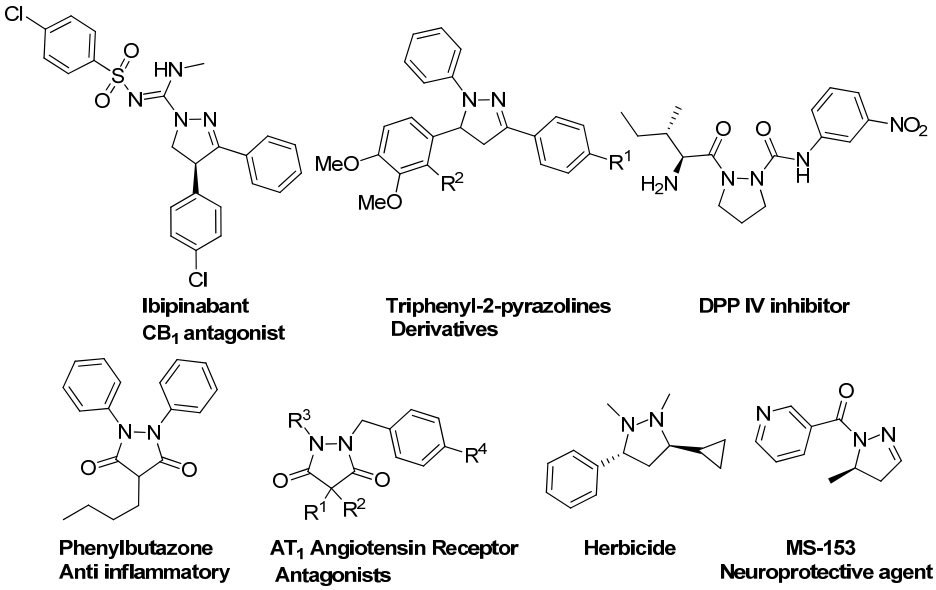
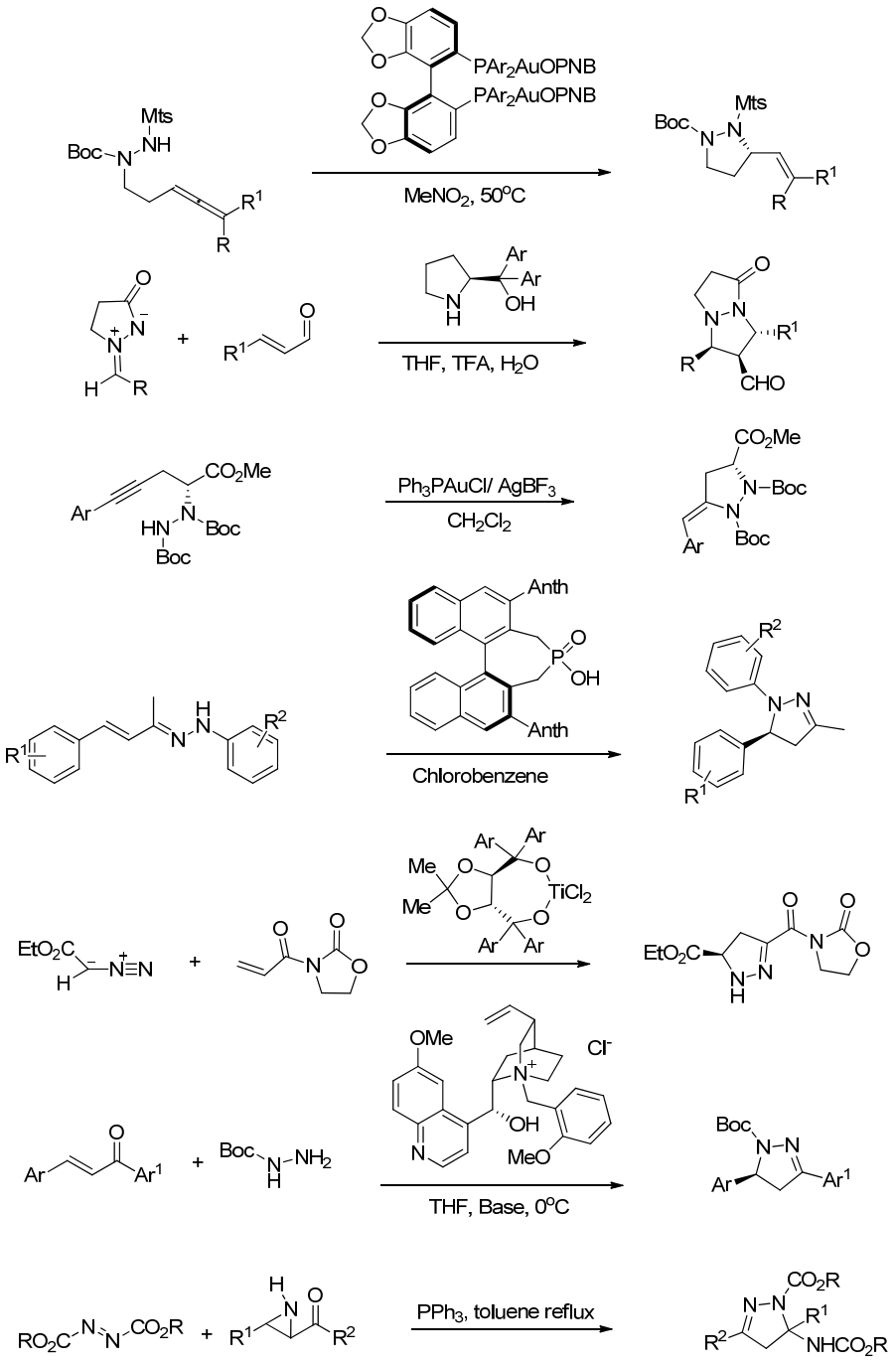



**Figure 4.** Pyrazolidine, pyrazoline and pyrazolidone drugs and natural products.

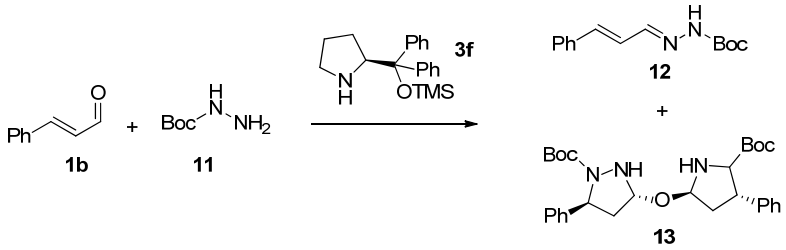
The first synthesis of pyrazolines was described in 1887 by Fisher and Knövenagel using acrolein and phenylhydrazine.[81] After them, many research groups have been involved in the synthesis of these important dinitrogen containing heterocycles. However, only recently the asymmetric synthesis of pyrazolidines was disclosed (Scheme 15). The enantioselective hydroamination of allenes with hydrazines in presence of a chiral biarylphosphinegold (I) complex gives diprotected pyrazolidines with high *ee´s*.[82] The [3+2] cycloaddition of azomethineimines with *α,β*-unsaturated aldehydes catalyzed by diarylprolinol derivatives was reported by Chen.[83] The Au(I) catalyzed ring closure of enantioenriched *α*-hydrazino esters bearing an alkyne group to give 2-4 disubsituted pyrazolidines.[84] 1,3-Dipolar cycloaddition, using titanium-TADDOLate reagent, delivered chiral 2-pyrazolines in good yield.[85] The 6π-electrocyclization of an *α,β*-unsaturated hydrazone catalyzed by a chiral phosphoric acid to give 2-pyrazolines was reported in 2009.[86] A phase transfer domino aza-Michael cyclocondensation reaction between Boc-protected aziridines and *β*-aryl enones catalyzed by quaternary ammonium salt was reported in 2010 by Brière.[87] Wang reported an elegant synthesis where racemic pyrazolines were prepared directly from aziridinylketones and azodicarboxylate.[88] Driven by our precedent studies on the synthesis of 5-hydroxy isoxazolidines[89] and an accurate retrosynthetic analysis, we envisioned that the organocatalytic reaction between enals and *N*-protected hydrazine would be an efficient asymmetric route for the synthesis of 3-hydroxypirazolidines.




**Scheme 15**. Synthetic routes for the synthesis of pyrazolidines and pyrazolines.

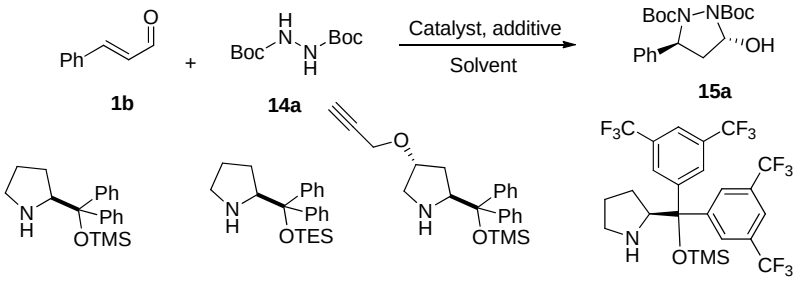
### 3.2 Direct Catalytic Asymmetric Synthesis of Pyrazolidine Derivatives

Our initial attempts to synthetize pyrazolines used a Fisher-type reaction between an enal **1b** and *N*-Boc-hydrazine **11**. The reaction was run for 18 h and after flash chromatography the only products isolated were the corresponding hydrazine **12** and dimer **13** (Scheme 16). Thus, the 1,2-addition of hydrazine to the aldehyde was the predominant pathway. With this experiment we understood the importance of having a di-protected hydrazine to direct the reaction toward a 1,4-addition stereoselective pathway. With these results in our hands we decided to begin our studies testing the reaction between cinnamic aldehyde **1b** and di-1,2-*N*-*tert*-butoxycarbonyl *Boc*-protected hydrazine **14a**. We initially started screening different solvents using the *O*-TMS-protected diphenylprolinol **3f** as the organocatalyst. As shown in the table 9 the reaction worked well in THF, toluene and trifluoromethyl benzene (entries 2, 4, 7, Table 9) delivering the 3-hydroxypyrazolidine **15a** only in the $\alpha$-anomeric form with high enantioselectivity but in moderate yield. We observed that prolonging the reaction time (entry 15, Table 9) and using additives, such as sodium acetate or acetic acid (entries 8, 9, Table 9), did not improve the conversion significantly. Other diarylprolinol derivatives delivered the product with high *ee´s* but in low yields (entries 16-18, Table 9). However, running the reaction at 4 $^{o}$C increased the yield and the enantiomeric excess (entry 14, Table 9). It is worth noting that the reaction was also performed between *N*-Ts-protected hydrazine and hexanal or cinnamic aldehyde, in presence of sodium acetate, without any trace of product after 4 days.[90]




**Scheme 16**. Attempt of Fisher type reaction catalyzed by *O*-TMS-diphenylprolinol.

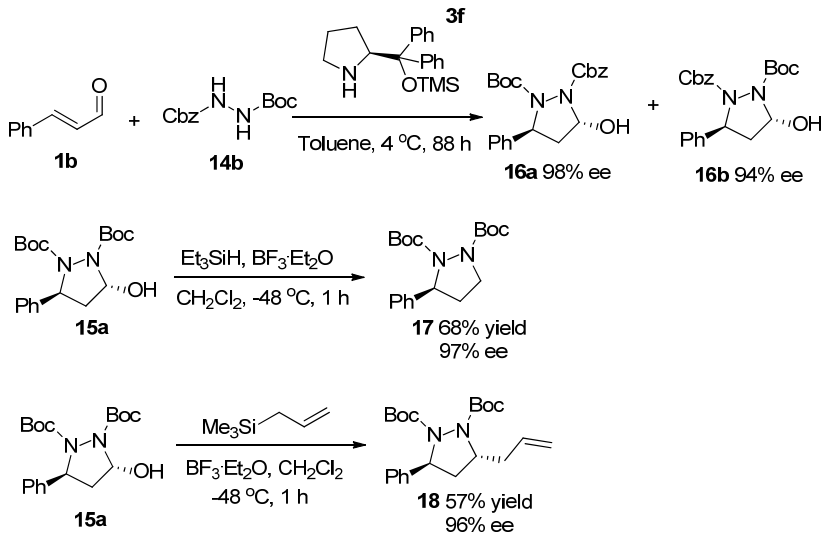
**Table 9.** Condition screening.[a]




| Entry | Catalyst | Solvent | t (h) | T ($^{o}$C) | Yield (%)[b] | ee (%)[c] |
|---|---|---|---|---|---|---|
| 1 | **3f** | $CHCl_3$ | 113 | RT | 33 | 76 |
| 2 | **3f** | THF | 113 | RT | 23 | 99 |
| 3 | **3f** | $CH_3CN$ | 113 | RT | 24 | 63 |
| 4 | **3f** | $PhCF_3$ | 48 | RT | 46 | 95 |
| 5 | **3f** | DMF | 94 | RT | 18 | 83 |
| 6 | **3f** | MeOH | 93 | RT | 33 | 18 |
| 7 | **3f** | toluene | 42 | RT | 54 | 98 |
| 8[d] | **3f** | toluene | 42 | RT | 54 | 98 |
| 9[e] | **3f** | toluene | 42 | RT | 42 | 98 |
| 10[f] | **3f** | toluene | 20 | RT | 43 (53)[g] | 99 |
| 11[f] | **3f** | toluene | 52 | RT | 48 (59)[g] | 98 |
| 12 | **3f** | toluene | 53 | 40 | 27 | 86 |
| 13[f] | **3f** | toluene | 119 | 4 | 56 | 98 |
| 14 | **3f** | toluene | 72 | 4 | 57 (60)[g] | >99 |
| 15 | **3f** | toluene | 144 | 4 | 64 (68)[g] | >99 |
| 16 | **3g** | toluene | 66 | RT | 44 | 98 |
| 17 | **3i** | toluene | 67 | RT | 26 | 99 |
| 18 | **3h** | toluene | 66 | RT | traces | n.d. |

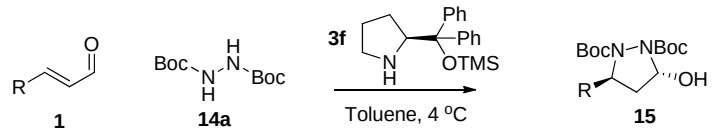
[a] Experimental conditions: a mixture of hydrazine **14a** (0.3 mmol), aldehyde **1b** (0.25 mmol) and catalyst **3** (20 mol%) was stirred for the time and temperature shown in the table in 0.5 mL of solvent. [b] Isolated yield after silica-gel column chromatography. [c] Determined by chiral HPLC analysis. The α:β ratio of **15a** was always >20:1 as determined by $^{1}$H NMR analysis of the crude reaction mixture. [d] 20 mol% AcOH was added. [e] NaOAc (1.1 equiv.) was added. [f] Toluene (0.3 mL). [g] Conversion as determined by $^{1}$H NMR analysis of the crude reaction mixture.

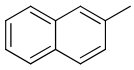
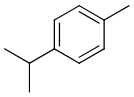
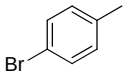
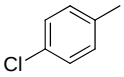
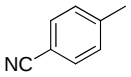
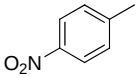
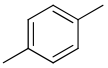
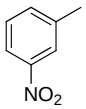
Based on these results, we decided to investigate the 1,3-diaminations of different *α,β*-unsaturated aldehydes **1** (0.25 mmol) with 1,2-*N*-Boc protected hydrazine **14a** as amine donor (0.3 mmol), *O*-TMS-protected diphenylprolinol **3f** as catalyst (20 mol%) and toluene as solvent (0.5 mL) at 4 °C (Table 10). We found that the substituents on the aromatic ring influenced the reactivity giving the desired products in moderate yields for the aldehydes bearing electron-withdrawing groups (entries 4-7, Table 10) and in modest yields for enals bearing electron donating groups (entries 2, 3, 8, Table 10). To our delight, all products were obtained with excellent levels of enantioselectivity (99% *ee*) and as *α*-anomer as the most stable single conformer. Next, we investigated the effect of the protecting groups on the hydrazine. We performed the reaction between cinnamic aldehyde and di-1-*N*-Boc 2-*N*-Cbz protected hydrazine **14b**. The pyrazolidine product was obtained as a mixture of compounds in a 42:58 (**16a**: **16b**) ratio with 98% and 94% of *ee´s* respectively (scheme 16). As mentioned previously, 3-hydroxypyrazolidines are useful building blocks and valuable precursors for the synthesis of other pyrazolidines. We performed the highly diastereoselective boron trifluoride mediated allylation of hemiaminal with allyltrimethylsilane and the dehydroxylation with triethylsilane to give the corresponding pyrazolidine derivatives **17** and **18** in moderate yields and high enantioselectivities (scheme 17). The absolute configuration of the 3-hydroxypyrazoline derivatives was determined by X-ray analysis of (3*R*, 5*S*)-di-tert-butyl 3-hydroxy-5-(3-nitrophenyl) pyrazolidine-1,2-dicarboxylate.




**Scheme 17**. Functionalization of pyrazolidines.

**Table 10.** Asymmetric synthesis of aromatic pyrazolidines.[a]

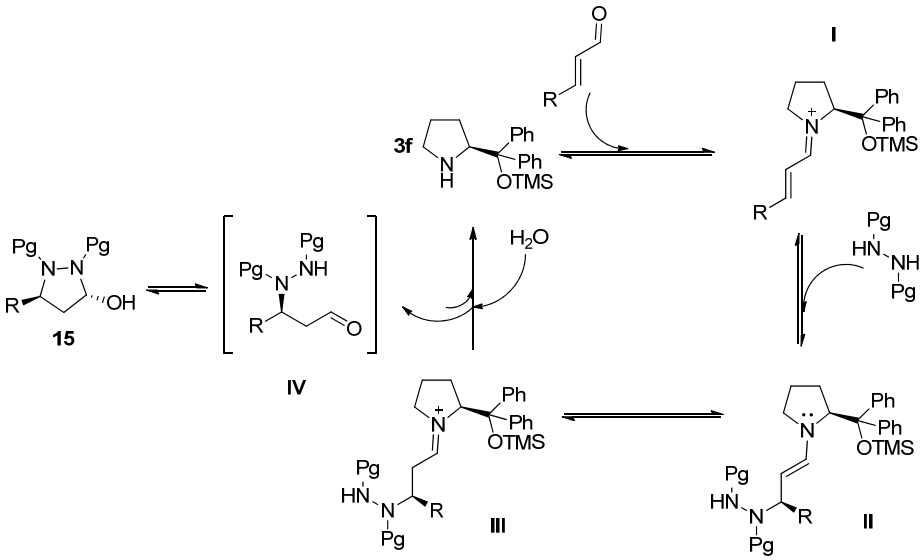



| Entry | R | Yield (%)[b] | ee (%)[c] |
|---|---|---|---|
| 1 |  | 64 | 99 |
| 2 |  | 48 | 98 |
| 3 |  | 47 | 99 |
| 4 |  | 62 | 99 |
| 5 |  | 59 | 99 |
| 6 |  | 68 | 99 |
| 7 |  | 77 | 99 |
| 8 |  | 45 | 99 |
| 9[d] |  | 68 | 99 |

[a] Experimental condtions: a mixture of hydrazine **14a** (0.3 mmol), aldehyde **1** (0.25 mmol), catalyst **3f** (20 mol%) in toluene (0.5 mL) was stirred at 4 °C for 144 h. [b] Isolated yield after silica-gel column chromatography. [c] Determined by chiral HPLC analysis. The α:β ratio of **15** was always >20:1 as determined by $^1$H NMR analysis of the crude reaction mixture. [d] Reaction time was 92 h.

### 3.3 Proposed Reaction Mechanism

The proposed catalytic cycle starts with the formation of an activated iminium ion (**I**) by the condensation of a *α,β*-unsaturated aldehyde and the organocatalyst. Next, a nucleophilic aza-Michael attack performed by hydrazine on the *Si*-face of the iminium intermediate gives an enamine intermediate (**II**). The hydrolysis on the iminium ion (**III**) regenerates the catalyst to afford the Michael-aldehyde adduct (**IV**), that after an intramolecular 5-exo-trig cyclization, forms the corresponding *α*-anomer of the 3-hydroxypyrazolidine product (Scheme 18).



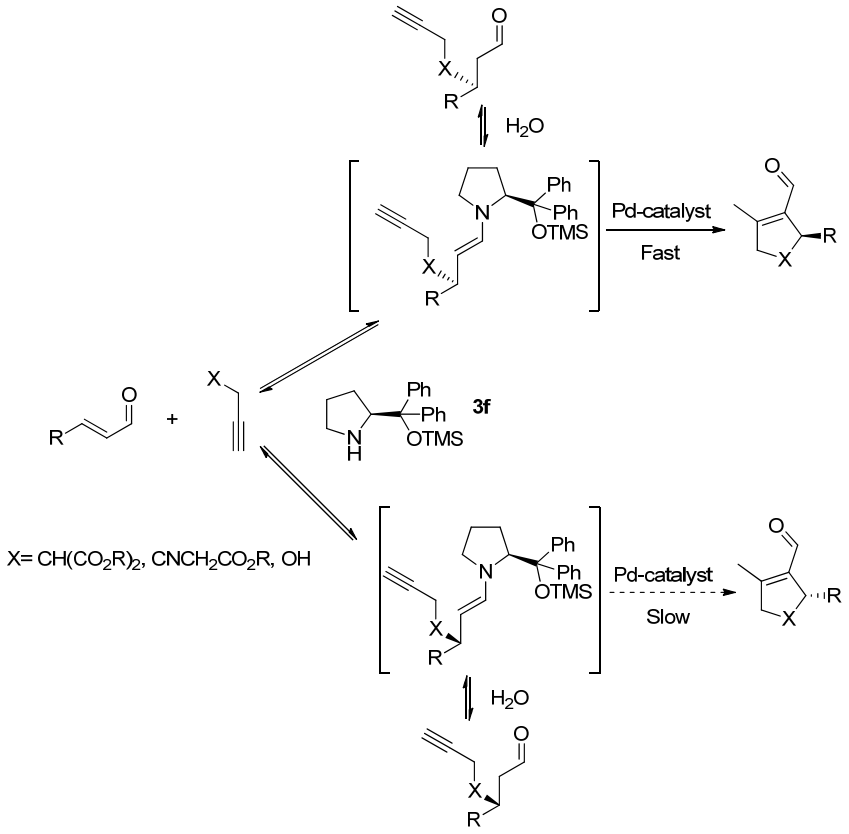

**Scheme 18.** Reaction pathway for the 1,3-diamination of enals.

### 3.4 Conclusions

We have presented a highly enantioselective chiral amine catalyzed Michael/hemiaminal cascade reaction between diprotected hydrazine and aromatic *α,β*-unsaturated aldehydes to give the corresponding 3-hydroxypyrazolidines with high enantioselectivity and exclusively in the most stable *α*-anomeric form.

# 4. Heterogeneous Catalysis (Paper IV)

Synthesis of carbon-carbon, carbon-oxygen and carbon-nitrogen bonds is one of the main goals in organic chemistry. Many pharmaceutical and natural products contain heteroatoms in their structure. Tertiary and quaternary carbon stereocenters are a leitmotif in many drugs. Cascade reactions are one of the most useful strategies to obtain complex molecules in few steps and in an atom economical fashion, thus avoiding the isolation of unstable intermediates. Transition metals have always dominated the bond formation in organic synthesis. Organocatalysis is a new powerful tool to create multiple bonds in one-pot processes. The combination of these two main fields of organic synthesis raises a number of issues. Two (or more) catalysts have to be compatibles with substrates, intermediates and between themselves to have an appropriate chemo- and stereoselectivity. The general problem in the employment of an organocatalyst (Lewis base) and a transition metal (Lewis acid) is due to an acid-base self-quenching with the resulting inactivation of the catalytic system. [91] Our group disclosed in 2006 the possibility to combine transition metal catalysis and amino catalysis in a dual activation system for the α-allylation of ketones and aldehydes.[92] This led to an increased interest in this area as exemplified by the work of Dixon[93] and Kirsch[94] where they performed a non-asymmetric addition of aldehydes to alkynes. In 2010, based on this research we disclosed the first example of one-pot stereoselective dynamic kinetic asymmetric transformations (DYKATs) between enals and propargylated nucleophiles to give functionalized chiral cyclopentenes.[95] Later, Jørgensen and coworkers developed a similar process using Cu(I) as the metal catalyst.[96] The DYKAT proceeds through the reversible 1,4-addition of the propargylated carbon acids to the iminium intermediate resulting in the formation of two Michael adducts roughly racemic after hydrolysis. Next the enamine species perform a nucleophilic attack on the activated alkyne moiety. The irreversible Pd-catalyzed intramolecular cyclization proceeds with extremely different reaction rates for the two Michael enamine intermediates, affording the product with high level of diastero- and enantioselectivity (Scheme 19).

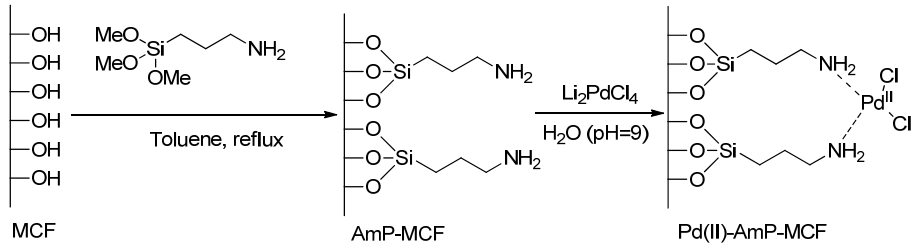



**Scheme 19.** Combined Pd-Amine catalyzed DYKAT.

Complete removal of metal catalysts and corresponding ligands from a reaction mixture and the isolation of pure products could be extremely expensive in an industrial context, reducing the potential of the synthesis merely to the academic research. The concept of using easily made and available solid supports, to which catalysts are bound, is exponentially becoming a hot topic in scientific research.[97] There are many economical and environmental advantages with heterogeneous catalysis. The possibility to recycle the catalyst simplifying the workup protocols and the use of excess of reagents to drive the reaction to completion. The stability conferred by the solid support to the metal creates a protection from moisture, allowing the reaction to be run in air atmosphere avoiding the use of expensive sealed reactors. The transportation and storage of heavy metals is facilitated by the use of carriers, which decreases the probabilities of loss and the formation of toxic salts. The total removal of possible dangerous polluting species, by filtration, decantation, extraction or centrifugation of the heterogeneous catalyst, is of paramount

importance in the pharmaceutical industry. Sometime even upon deactivation, the catalyst can be regenerated for new catalytic cycles decreasing drastically the costs. Silica, alumina, zeolites, polymers, resins, clays and nanotubes have been tested as solid supports during the last century.[98] Silica shows excellent thermal stability and a good inertness toward reagents and solvents.[99] Mesoporous silica materials have a vast surface area and a well-defined pore morphology bearing a high concentration of silanol groups on which it is possible to anchor organic linkers.[100] Palladium is maybe one of the most studied metals for catalytic transformations. Its low toxicity, moderate price and the tolerance to solvents, moisture and many functional groups makes it a good candidate for catalysis. In the past decades coupling reactions, hydrogenations and even oxidations were performed with this precious transition metal.[101] Palladium with oxidation state +2 is a π-electrophilic Lewis acid able to coordinate multiple bonds of alkenes, alkynes and allenes.[102] Once this complex is formed, the attack of a nucleophile on the electron-deficient carbon is facilitated. In heterogeneous catalysis the nature of the ligand-linker plays an important role on the reactivity because electronic and steric effect could dramatically influence the efficiency of the metal. In this study we will show an harmonic and remunerative marriage between heterogeneous metal catalysis and amino catalysis for a highly stereoselctive carbocyclization of aldehydes with alkyne moieties.

### 4.1 Synthesis of the Pd(II)-AmP-MCF Catalyst[100a]




**Scheme 20**. Synthesis of Pd(II)-AmP-MCF Catalyst .

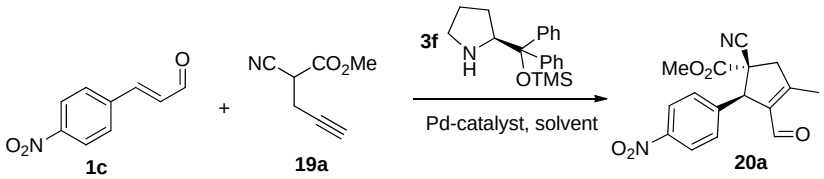
To a suspension in toluene of MCF solid support was slowly added a solution of 3-aminopropyltrimethoxysilane. The reaction was stirred at 110 $^{o}$C for 24 hours under nitrogen. Next, the solid was filtered and washed with toluene, acetone, $CH_2Cl_2$ and dried under reduced pressure. The amino-functionalized MCF was suspended in pH= 9 deionized water solution.

$Li_2PdCl_4$ was solubilized in a pH adjusted deionized water solution and added to the AmP-MCF suspension. The reaction was stirred for 20 h. Next the heterogeneous catalyst was transferred in a centrifuge vial and washed three times with $H_2O$ and three times with acetone. After being dried overnight under vacuum the Pd(II)-AmP-MCF appears as a brown powder. The amount of Pd loaded on the AmP-MCF was determined by Inductively Couple Plasma-Optical Emission Spectrometry (ICP-OES) indicating 8.25 wt% Pd loading (Scheme 20).

### 4.2 Heterogeneous Asymmetric Michael/Carbocyclization Reaction

For an initial screen we used 3-(4-nitrophenyl) acrylaldehyde **1c** (0.2 mmol) as *α,β*-unsaturated aldehyde, propargyl cyanomalonate **19a** (0.24 mmol) as propargylated carbon acid and *O*-TMS-protected diphenylprolinol **3f** (20 mol%) as amine catalyst (Table 11). We found that performing the reaction in $CH_2Cl_2$ and toluene, in the presence of Pd(II)-AmP-MCF (3.0 mol%) the corresponding cyclopentene **20a** could be isolated in good yields with high enantioselectivities (entries 3, 5, Table 11). Decreasing the amount of Pd(II) catalyst to 1.5 mol% decreased also the yield (entry1, Table 11). Shortening the reaction time to 3.5 h is a benefit for the enantioselectivity but the diastereoselectivity slightly decreased (entry 4, Table 11). We also tested the reaction using the Pd(0)-AmP-MCF nanocatalyst[100a] in various solvents (entries 9-13, Table 11) obtaining the best results in toluene (entry 11, Table 11). Next we compared the homogeneous system, using $PdCl_2$ and $Pd(PPh_3)_4$, with the heterogeneous system. To our delight in the heterogeneous system we had an increase in the stereoselectivity, especially in the case of the reaction catalyzed by Pd(0)-AmP-MCF catalyst.

**Table 11.** Condition Screening.[a]



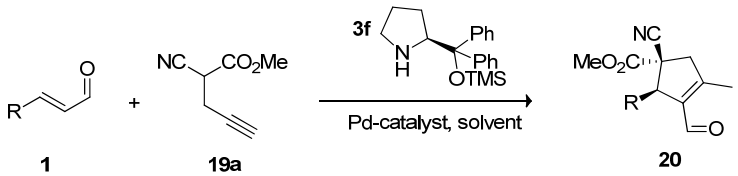

| Entry | t(h) | Solvent | Metal Cat | Yield (%)[b] | Dr[c] | ee (%)[d] |
|---|---|---|---|---|---|---|
| 1[e] | 22 | $CH_3CN$ | Pd(II)-AmP-MCF particles | 37 | 16:1 | 90 |
| 2 | 24 | $CH_3CN$ | Pd(II)-AmP-MCF particles | 68 | 21:1 | 86 |
| 3 | 21 | $CH_2Cl_2$ | Pd(II)-AmP-MCF particles | 80 | 16:1 | 94 |
| 4 | 3.5 | $CH_2Cl_2$ | Pd(II)-AmP-MCF particles | 73 | 10:1 | 96 |
| 5 | 18 | toluene | Pd(II)-AmP-MCF particles | 67 | 10:1 | 94 |
| 6 | 2 | $CH_2Cl_2$ | $PdCl_2$ | 48 | 13:1 | 96 |
| 7 | 4 | $CH_2Cl_2$ | $PdCl_2$ | 81 | 18:1 | 94 |
| 8 | 23 | toluene | $PdCl_2$ | 76 | 9:1 | 94 |
| 9 | 42 | $CH_3CN$ | Pd(0)-AmP-MCF particles | 67 | 17:1 | 86 |
| 10 | 18 | $CH_2Cl_2$ | Pd(0)-AmP-MCF particles | 70 | 16:1 | 91 |
| 11 | 18 | toluene | Pd(0)-AmP-MCF particles | 75 | 15:1 | 95 |
| 12 | 18 | xylene | Pd(0)-AmP-MCF particles | 72 | 15:1 | 92 |
| 13 | 70 | $CH_3CN$ | Pd(0)-AmP-MCF particles | 70 | 8:1 | 83 |
| 14 | 41 | $CH_3CN$ | $Pd(PPh_3)_4$ | 76 | 12:1 | 86 |
| 15 | 18 | toluene | $Pd(PPh_3)_4$ | 77 | 11:1 | 93 |
| 16[f] | 23 | $CH_2Cl_2$ | Pd(II)-AmP-MCF particles | 0 | - | - |
| 17 | 23 | $CH_2Cl_2$ | - | 0 | - | - |

[a] Experimental conditions: A mixture of **19a** (0.24 mmol) and Pd (3mol%) in solvent (0.5 mL) was stirred for 5 min. Next, aldehyde **1c** (0.2 mmol) and amine catalyst **3f** (20 mol%) were added and the reaction was stirred at r.t. for the time shown in the table. [b] Isolated yield after silica-gel column chromatography. [c] Determined by crude $^1$H NMR spectroscopic analysis. [d] Determined by chiral-phase HPLC analysis. [e] The reaction was performed with 1.5 mol% of Pd. [f] No chiral amine was added.

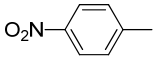
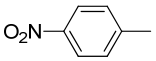
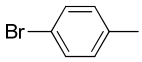
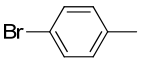
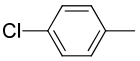
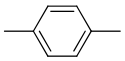
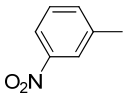
A variety of substrates were examined in our study using $CH_2Cl_2$ as solvent and Pd(II)-Amp-MCF as heterogeneous metal catalyst (Table 12). Aromatic aldehydes with electron-withdrawing, electron-donating and heteroaromatic substituents were tolerated by our system, supplying the corresponding

product **20** with high degrees of diastereo- and enantioselectivity (Table 12). Even for difficult substrates such as aliphatic aldehydes the reaction offered the product with good stereoselectivity (entry 11, Table 12).
Using propargylic alcohol[103] and propargylic ammine Ts-protected[104] as nucleophiles we obtained the corresponding dihydrofurans and dihydro-pyrroles **21** in good yields and high *ee's* (Table 13). To prove the potentiality of our system we performed the reaction nine times utilizing the catalyst recycled from the previous cycle. Table 14 shows that the activity of the catalyst was maintained after nine cycles, affording the product in high yields and excellent stereoselectivity.

**Table 12.** Enantioselective heterogeneous cycloisomerization of enals.[a]

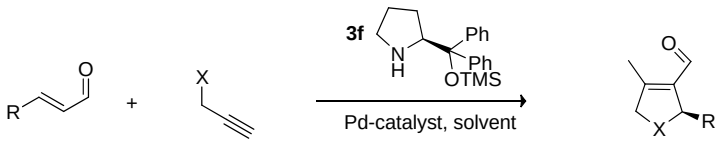



**1** **19a** **20**

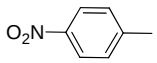
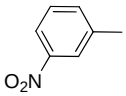
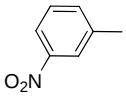
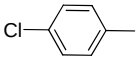
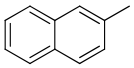
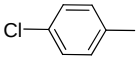
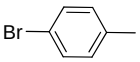
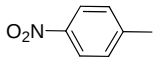
| Entry | R | t (h) | Yield (%)[b] | Dr[c] | ee (%)[d] |
|---|---|---|---|---|---|
| 1[e] |  | 18 | 75 | 15:1 | 95 |
| 2[f] |  | 20 | 80 | 16:1 | 94 |
| 3[f] |  | 16 | 83 | 18:1 | 96 |
| 4[e] |  | 18 | 83 | 18:1 | 96 |
| 5[f] |  | 16 | 78 | 19:1 | 99 |
| 6[f] |  | 16 | 84 | 12:1 | 96 |
| 7[e] |  | 18 | 70 | 15:1 | 91 |
| 8[f] |  | 16 | 86 | 24:1 | 96 |
| 9[f] |  | 5 | 74 | 21:1 | 91 |
| 10[f] |  | 18 | 81 | 12:1 | 91 |
| 11[e] | *n*-Pr | 23 | 67 | 5:1 | 96 |

[a] Experimental conditions: A mixture of **19a** (0.24 mmol) and Pd(II)-AmP-MCF (3 mol%) in solvent (0.5 mL) was stirred for 5 min. Next aldehyde **1** (0.2 mmol) and amine catalyst **3f** (20 mol%) were added and the reaction was stirred at r.t. for the time shown in the table. [b] Isolated yield after silica-gel column chromatography. [c] Determined by crude $^1$H NMR spectroscopic analysis. [d] Determined by chiral-phase HPLC analysis. [e] The reaction was performed with Pd(0)-AmP-MCF in toluene. [f] The reaction was performed with Pd(II)-AmP-MCF in $CH_2Cl_2$.

**Table 13**. Enantioselective heterogeneous synthesis of dihydrofurans and dihydropyrroles.

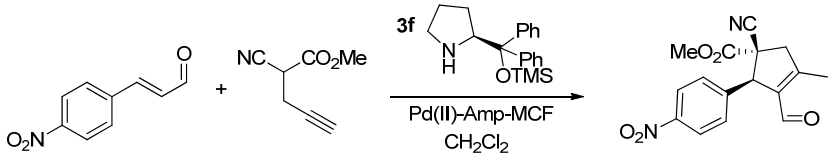



**1** **19** **21**

| Entry | R | Alkyne (X) | t (h) | Yield (%)[b] | ee (%)[c] |
|---|---|---|---|---|---|
| 1[a] |  | OH | 17 | 82 | 92 |
| 2[a] |  | OH | 17 | 69 | 89 |
| 3[d] |  | OH | 40 | 85 | 93 |
| 4[e] |  | OH | 22 | 59 | 94 |
| 5[e] |  | OH | 25 | 59 | 98 |
| 6[f] |  | NHTs | 22 | 53 | 92 |
| 7[f] |  | NHTs | 20 | 59 | 94 |
| 8[f] |  | NHTs | 22 | 53 | 96 |
| 9[f] |  | NHTs | 20 | 67 | 94 |
| 10[f] | Me | NHTs | 23 | 84 | 77 |

[a] Experimental conditions: A mixture of propargyl alcohol (0.375 mmol) and Pd(II)-AmP-MCF (3 mol%) in $CHCl_3$ (0.5 mL) was vigorously stirred for 5 minutes. Next aldehyde **1** (0.25 mmol), amine catalyst **3f** (20 mol%) and benzoic acid (20 mol%) were added and the reaction was stirred at 4 $^oC$ for the time shown in the table. [b] Isolated yield after silica-gel column chromatography. [c] Determined by chiral-phase HPLC analysis. [d] The reaction was performed with Pd(0)-AmP-MCF (5 mol%) in toluene at r.t. [e] The reaction was performed in THF (0.25 mL) and propargyl alcohol (0.75 mmol). [f] Experimental conditions: A mixture of propargyl amine (0.30 mmol) and Pd(II)-AmP-MCF (5 mol%) in toluene (1.0 mL) was stirred for 5 minutes. Next aldehyde **1** (0.20 mmol), amine catalyst **3f** (20 mol%), sodium acetate (2.5 equiv) and $H_2O$ (1 equiv.) were added and the reaction was stirred at room temperature for the time shown in the table.

**Table 14**. Recycling experiments of the heterogeneous Pd(II)-AmP-MCF.[a]



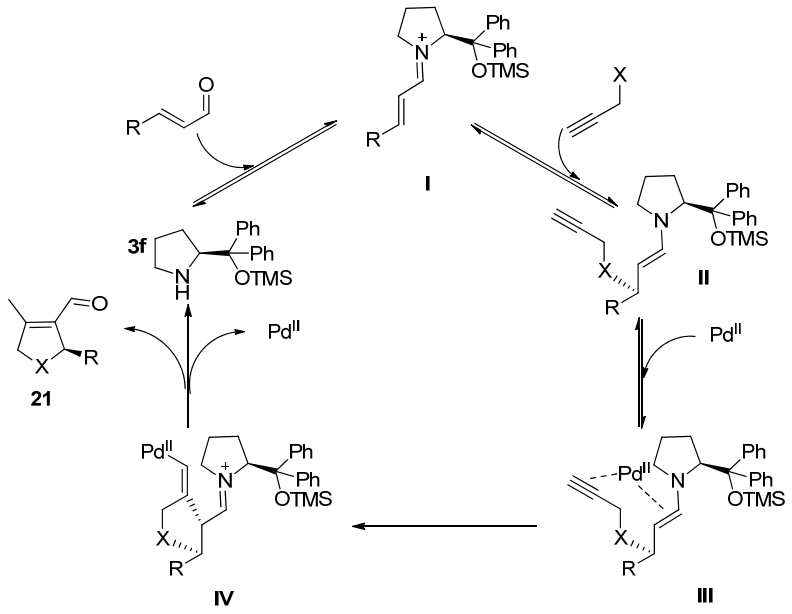

**1c** **19a** **20a**

| Cycles | t (h) | Yield (%)[b] | Dr[c] | ee (%)[d] |
|---|---|---|---|---|
| 1 | 20 | 73 | 13:1 | 92 |
| 2 | 17 | 73 | 19:1 | 93 |
| 3 | 17 | 78 | 23:1 | 92 |
| 4 | 16 | 82 | 21:1 | 93 |
| 5 | 19 | 82 | 23:1 | 93 |
| 6 | 17 | 78 | 30:1 | 94 |
| 7 | 16 | 92 | 18:1 | 94 |
| 8 | 16 | 81 | 16:1 | 94 |
| 9 | 16 | 89 | 17:1 | 94 |

[a] Experimental conditions: A mixture of propargyl cyanomalonate **19a** (0.72 mmol) and Pd(II)-AmP-MCF (3 mol%) in $CH_2Cl_2$ (1.5 mL) was stirred for 5 min. Next, aldehyde **1b** (0.6 mmol) and amine catalyst **3f** (20 mol%) were added and the reaction was stirred at r.t. for the time shown in the table. Next, the reaction mixture was transferred to a centrifuge vial and $CH_2Cl_2$ (5 mL) was added. After centrifugation, the supernatant was removed and the Pd(II)-AmP-MCF catalyst was washed 3 times with $CH_2Cl_2$. The liquid phases were combined together, the solvent removed and the crude reaction mixture was directly loaded on and purified by silica-gel chromatography. [b] Isolated yield after silica-gel column chromatography. [c] Determined by crude $^1$H NMR spectroscopic analysis. [d] Determined by chiral-phase HPLC analysis.

To determine the presence of free Pd-species in solution we performed a hot filtration of the reactions. Pd(0)-AmP-MCF and Pd(II)-AmP-MCF were filtered off after 20% conversion and the solid-free filtrate was allowed to continue to stir. $^1$H-NMR analysis showed that no further conversion to the product occurred. Elemental analysis of the filtrate showed the presence of 80 ppm of homogeneous Pd(II) in solution and no leaching of Pd(0). To ensure that the reaction proceed through a heterogeneous pathway we performed the reaction using 80 ppm of $PdCl_2$. After 4 hours only traces of product were formed while the same reaction with heterogeneous Pd(II) was completed within this time. These results indicate that the reaction operates solely through a heterogeneous pathway, confirming the extremely interesting potentiality of this new approach in asymmetric synthesis.

## 4.3 Proposed General Reaction Mechanism for Homogeneous Catalysis




**Scheme 21.** Reaction pathway for the carbocyclization of enals by combination of amine catalysis and metal catalysis.

The proposed catalytic cycle starts with the generation of the iminium intermediate (**I)** after the condensation of a α,β-unsaturated aldehyde and the secondary amine. This imine undergoes a reversible 1,4-addition to the propargyl nucleophile to form two chiral enamine intermediates (**II)**. Next, activation of the alkyne moiety (**III**) by Pd(II) promotes an intramolecular cycloisomerization (**IV)** where the stereochemical outcome of the reaction is driven by the different rates of cyclization for the two Michael adducts (Scheme 21).

## 4.4 Conclusions

In this work we disclosed a pioneering combination of heterogeneous transition metal catalysis and aminocatalysis. All the cyclization reactions were performed with excellent results. The possibility to recycle the catalyst without any loss of reactivity offers a great and stimulating contribution to organocatalysis, maybe paving the way to new interdisciplinary research fields.

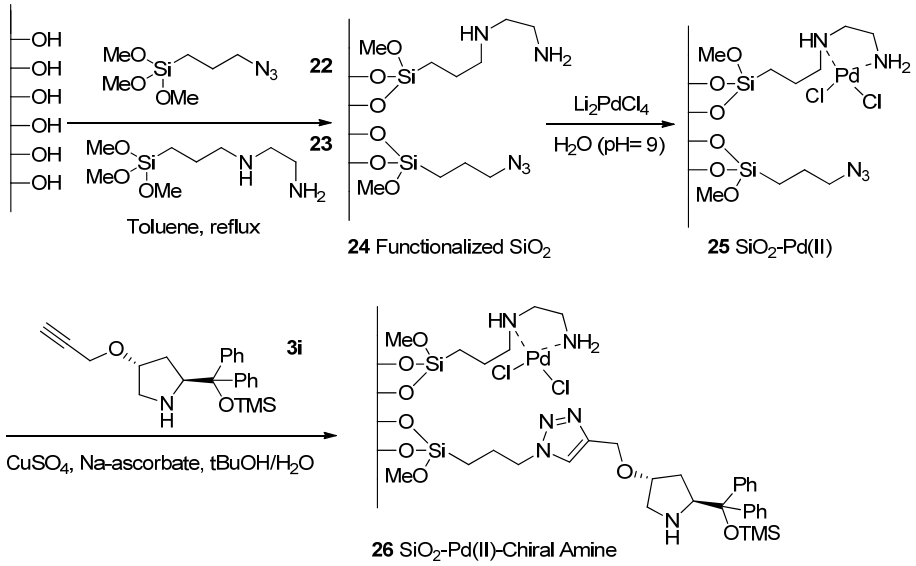
# 5. Heterogeneous Dual Catalysis (Paper V)

Reduction of industrial waste and development of green processes is a prerogative in an industrialized and polluted world. The possibility to own new atom economic protocols, where the reactants are completely converted into products without the requirement of hazardous material disposal, is now the main target of the scientific research. Large scale industrial reactions are usually catalyzed by one or more catalysts that are bound on appropriate carriers. In Nature concurrent activation of substrates, in a synergistic process, is typical of enzymes where different catalytic moieties cooperate to afford specific transformations. The compartmentalization of distinct catalytic sites will avoid compatibility problems and side reactions, with the maximization of the synthetic performances. The use of two or more heterogeneous catalysts in a relay reaction can generate different disadvantages. If the catalyst is linked inside the pores of a solid support, the diffusion of a second heterogeneous catalyst in the cavities results physically impossible. If the catalysts are bound on the support surface, the probabilities of contacts are limited and the rate of the reaction will be lower, compared to a homogeneous pathway. To circumvent these apparently insurmountable problems, we envisioned a heterogeneous system, where two catalysts are bound close to each other on the same solid material.[105] Taking advantages of our previous experience and basing on the scientific background in the linkage of organocatalysts[106] and transition metal catalysts on solid-phase supports, we embarked on this stimulating challenge. The reaction we decided to test envisages a concerted mechanism, where the two catalysts work in a synergistic cooperation, to construct complex chiral structures.[107] The rigidity of the system imposed the use of relatively long linkers to avoid steric constrain limitations and to ensure a better conformational flexibility and simultaneous activation of the substrates in the transition state. Hereunder, we propose the first example of an asymmetric Michael/carbocyclization reaction catalyzed by an heterogeneous dual system composed of a *O*-TMS-protected diphenylprolinol and Pd(II).

### 5.1 Synthesis of the Heterogeneous Dual Catalyst

To a suspension in toluene of chromatographic silica media (LC60A, 60-200 μm) was slowly added an equimolar solution of 3-azidopropyltrimethoxysilane **22** and *N*-[3-(trimethoxysilyl) propyl] ethylenediamine **23** in toluene. The reaction was stirred at 110 $^{o}$C for 24 h under inert atmosphere. Next, the functionalized solid support **24** was filtered and washed with toluene, acetone and $CH_2Cl_2$ and dried under reduced pressure. The functionalized silica **24** was suspended in a basic deionized water solution (pH= 9). $Li_2PdCl_4$ was solubilized in a basic deionized water solution (pH= 9) and slowly added to the suspension. The reaction was stirred for 20 h. Next, the $SiO_2$-Pd(II) catalyst **25** was transferred in a centrifuge vial, washed three times with $H_2O$, three times with acetone and dried under vacuum. The (2*S*,4*R*)-2-(diphenyl((trimethylsilyl)oxy)methyl)-4-(prop-2-yn-1-yloxy) pyrrolidine organocatalyst[108] **3i** was clicked to the to the azide moiety, on the palladium functionalized silica support, by a Cu(I)-catalyzed [1,3] dipolar cycloaddition reaction.[109] The suspension was stirred 20 h at room temperature, transferred to a centrifuge vial, washed three times with $H_2O$, three times with acetone and three times with $CH_2Cl_2$. After being dried overnight under reduced pressure, the $SiO_2$-Pd(II)-Chiral amine heterogeneous catalyst **26** appears as a brown powder (Scheme 22). Solid-state $^{13}C\{^{1}H\}$ Nuclear Magnetic Resonance (NMR) spectra of the functionalized silica **24** showed chemical shifts at 10.4, 23, 40-60 ppm, respectively assigned to the α-$CH_2$, β-$CH_2$ and γ-$CH_2$ (starting from the silicon atom) of the propylethylenediamine and propyl azide linkers, demonstrated the effective functionalization of the silica support. Solid-state $^{13}C\{^{1}H\}$ NMR spectra of the $SiO_2$-Pd(II)-chiral amine **26** showed the presence of peaks for the secondary carbon nuclei of the phenyl rings (128 ppm) and for the methyl groups on the TMS (2.0 ppm), belonging to the organocatalyst, reflecting the real presence of the aminocatalyst linked on the silica solid support (see Appendix B). Infrared spectroscopy (IR) showed three important changes between the spectra of the functionalized silica **24** and the spectra of the $SiO_2$-Pd(II)-chiral amine **26** (see Appendix C). The decreased intensity of 95% for the band at 2101 $cm^{-1}$, assigned to the azide moiety, valuated by using the Si-O-Si overtone bands as internal reference, clearly showed the almost quantitative formation of the triazole as consequence of the click reaction between the organocatalyst **3i** and the functionalized solid support **24**.The appearance of bands for the phenyl groups on the aminocatalyst at 3063 (C=C-H stretching), 1491 and 1445 $cm^{-1}$ (aromatic ring modes). Primary amine groups of the functionalized silica **24** showed bands at 3372, 3290 (NH stretching) and

1607 $cm^{-1}$ ($NH_2$ scissoring). The IR spectra for $SiO_2$-Pd(II)-Chiral amine heterogeneous catalyst **26** showed a shift to lower frequencies for the NH stretching at 3228 $cm^{-1}$ due to the complex formation with $PdCl_2$ resulting in a weakening of the NH bond. Elemental analysis showed content in carbon of 17 wt%, palladium 6 wt%, chlorine 4 wt % and in nitrogen of 3 wt%. It is worth noting that using an inverse procedure, therefore binding first the aminocatalyst and subsequently the palladium to the linkers of the functionalized silica support, the metal will be coordinated not only by the diamine but also by the nitrogen on the protected diphenylprolinol. This will lead to the inactivation of the heterogeneous dual catalyst.



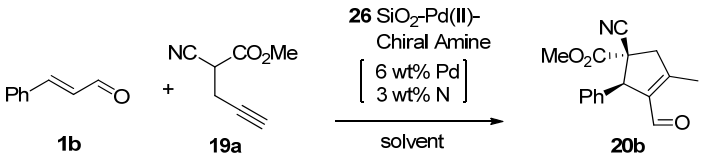

**Scheme 22.** Synthesis of the Heterogeneous Dual Catalyst.

## 5.2 Heterogeneous Synthesis of Cyclopentane Derivatives

We started our investigation of the Michael/Carbocyclization reaction using cinnamic aldehyde **1b** (0.1 mmol) and propargyl cyanomalonate **19a** (0.12 mmol) in presence of the dual heterogeneous catalyst **26** (Table 15). The reaction gave the best results in $CH_2Cl_2$, toluene and $CHCl_3$ (entries 2, 4-5, Table 15). Decreasing the amount of catalyst decreased also the conversion (entry1, Table 15) and increasing the temperature to 40 $^oC$ dropped down the enantioselectivity without any benefit on the yield (entry 7, Table 15). The reaction was tested with the functionalized silica support containing only the

organocatalyst, to exclude the possibility of a parallel reaction pathway catalyzed by possible traces of Cu(II) coming from the click reaction. To our delight, only the presence of the Michael products was detected by $^1$H-NMR analysis (entry 8, Table 15). After this short screening, we decided to extend the scope of the reaction to different enals (Table 16). Aromatic aldehydes with electron donating and electron withdrawing substituents gave the corresponding cyclopentanes derivates **20** in moderate yields with good diastereoselectivity and high enantiomeric excesses. 2-Hexenal gave poor yield and low diastero- and enantioselectivity probably due to the long aliphatic chain that clashes with the sterical encumbered catalyst (entry 5, Table 16).

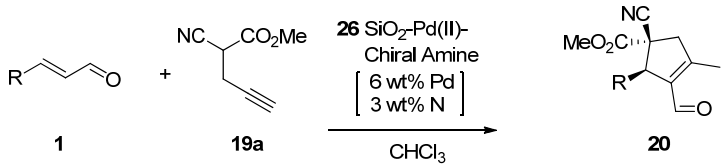
**Table 15.** Condition screening.[a]



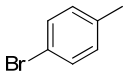
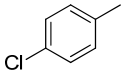
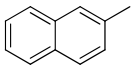
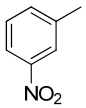

| Entry | Solvent | Cat. (mg) | t (h) | Yield (%)[b] | Dr[c] | ee (%)[d] |
|---|---|---|---|---|---|---|
| 1 | $CH_2Cl_2$ | 17 | 45 | 33 | 82:18 | 95 |
| 2 | $CH_2Cl_2$ | 51 | 46 | 73 | 87:13 | 90 |
| 3 | $CH_3CN$ | 51 | 97 | 22 | 88:12 | 85 |
| 4 | toluene | 51 | 73 | 59 | 85:5 | 95 |
| 5 | $CHCl_3$ | 51 | 46 | 62 | 88:12 | 94 |
| 6[e] | $CH_2Cl_2$ | 51 | 46 | 48 | 87:13 | 94 |
| 7[f] | $CHCl_3$ | 51 | 45 | 55 | 87:13 | 86 |
| 8[g] | toluene | 18 | 90 | - | - | - |

[a] Experimental conditions: A mixture of **1b** (0.1 mmol), catalyst **26** and **19a** (0.12 mmol) in solvent (0.25 mL) was stirred at r.t. for the time shown in the table. [b] Isolated yield after silica.gel column chromatography. [c] Determined by crude $^1$H NMR spectroscopic analysis. [d] Determined by chiral-phase HPLC analysis. [e] 0.5 mL of solvent was used. [f] Reaction preformed at 40 $^o$C. [g] Reaction performed with only the organocatalyst on silica.

**Table 16.** Enantioselective heterogeneous cycloisomerization of enals. [a]




1 19a 20

| Entry | R | t (h) | Yield (%)[b] | Dr[c] | ee (%)[d] |
|---|---|---|---|---|---|
| 1 |  | 45 | 62 | 88:12 | 94 |
| 2 |  | 71 | 69 | 84:16 | 95 |
| 3 |  | 24 | 65 | 87:13 | 94 |
| 4 |  | 76 | 58 | 88:12 | 95 |
| 5 | *n*-Pr | 165 | 47 | 54:46 | 85 (81)[e] |
| 6 |  | 94 | 50 | 88:12 | 92 |
| 7 |  | 48 | 67 | 84:16 | 90 |

[a] Experimental conditions: A mixture of **1** (0.1 mmol), catalyst **26** (51 mg) and **19a** (0.12 mmol) in $CHCl_3$ (0.25 mL) was stirred at r.t. for the time shown in the table. [b] Isolated yield after silica gel column chromatography. [c] Determined by crude $^1H$ NMR spectroscopic analysis. [d] Determined by chiral-phase HPLC analysis. [e] ee of the minor diastereomer.

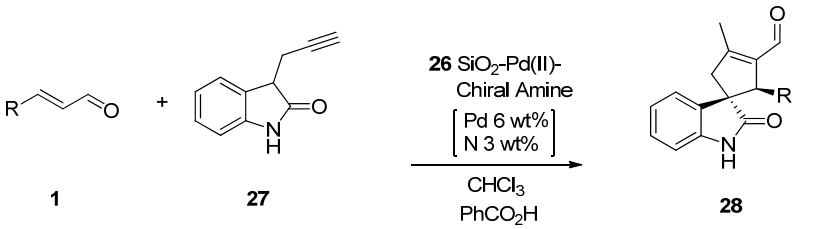
### 5.3 Heterogeneous Synthesis of Spirocyclic Oxindole Derivatives

Spirocyclic scaffolds are present in many relevant drugs and natural products. Pyrrolidine-3,3-oxindole unit is a leitmotif in alkaloids such as Notoamide B, Citrinalin, Paraherquamide, Marcfortine and Cyclopamine. Synthesis of spiro compounds, containing different chiral centers and a quaternary-substituted carbon, embedded within a spiro heterocyclic system, is usually carried out by [3+2] cycloaddition processes and intramolecular Heck reactions.[110] In the field of organocatalysis, Melchiorre exposed an unprecedented reaction where the chiral information was propagated till the $\delta$-position of $\alpha,\beta,\gamma,\delta$-unsaturated dienones exploiting its intrinsic vinylogous

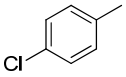
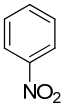
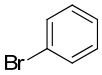
reactivity.[111] Gong presented a formal [4+2] cycloaddition catalyzed by Takemoto type catalysts.[112] Chen proposed a [2+2+2] annulation employing *O*-TMS-protected diarylprolinol.[113] In 2012, Wang studied an iminium/enamine-palladium synergistic reaction for the synthesis of spirocyclic oxindoles derivatives using our asymmetric DYKAT strategy.[114] Herein, we synthetized spirocyclic oxindoles, starting from $\alpha,\beta$-unsaturated aldehydes and 3-substituted oxindole, using our new dual Pd(II)/amine heterogeneous catalyst.

We screened the spirocyclization on different enals **1** using as propargylated substrate 3-(prop-2-yn-1-yl) indolin-2-one **27** (Table 17). The reaction was performed in $CHCl_3$ in the presence of a catalytic amount of benzoic acid and our dual catalyst **26**. Aromatic aldehydes with electron-withdrawing substituents (entry 2-4, Table 17) and cinnamic aldehyde (entry 1, Table 17) could participate to the reaction delivering the product with moderate diastereoselectivities and high enantioselectivities. Aliphatic aldehydes such as 2-hexenal gave the corresponding product with excellent stereoselectivity and in good yield (entry 5, Table 17). With these results in the hand we demonstrated the efficiency and utility of our heterogeneous dual catalyst even on bulky and steric demanding substrates such as polycyclic oxindole derivatives **28**.

**Table 17.** Enantioselective heterogeneous synthesis of spirocyclopentene oxindoles.[a]




1 27 28

| Entry | R | t (h) | Yield (%)[b] | Dr[c] | ee (%)[d] |
|---|---|---|---|---|---|
| 1 |  | 96 | 66 | 78:22 | 99 |
| 2 |  | 70 | 88 | 74:26 | 99 (99)[e] |
| 3 |  | 56 | 77 | 64:36 | 95 (96)[e] |
| 4 |  | 72 | 71 | 74:26 | 99 (99)[e] |
| 5 | *n*-Pr | 120 | 67 | 20:1 | 98 |

[a] Experimental conditions: A mixture of **1** (0.1 mmol), catalyst **26** (51 mg), benzoic acid (20 mol%) and **27** (0.2 mmol) in $CHCl_3$ (0.6 mL) was stirred at r.t. for the time shown in the table. [b] Isolated yield after silica gel column chromatography. [c] Determined by crude $^1H$ NMR spectroscopic analysis. [d] Determined by chiral-phase HPLC analysis. [e] ee of the minor diastereomer.

## 5.4 Conclusions

In this work we have demonstrated a heterogeneous dual catalyst system on which are anchored, on the same solid surface, an organocatalyst and a palladium transition metal catalyst. The asymmetric synthesis of cyclopentanes and spirocyclopentene oxindoles delivered the corresponding products in high yields and excellent stereoselectivities. Further studies on heterogeneous catalysis, employing different Lewis acidic transition metals, will be performed in our laboratory. The optimization of solid supports and the streamlining of different linkers will be carefully taken in consideration. Only the imitation of the natural perfection can lead to the synthesis of com-

plex molecules, in a single reaction event, mimicking the biosynthetic pathways.

# Appendix A- Contribution to publications I-V

I. Performed half part of the experimental work, prepared most of the racemic and chiral aziridines, contributed to the synthesis of the starting materials. Wrote the supporting information and contributed in the writing of the article.

II. Performed the major part of the experimental work. Found the reaction conditions and screened most of the substrates. Wrote the supporting information and contributed in the writing of the article.

III. Performed the major part of the experimental work. Found the reaction conditions and screened most of the substrates. Crystallized the pyrazolidine for the X-ray analysis. Wrote the supporting information and contributed in the writing of the article.

IV. Performed the major part of the experimental work. Found the reaction conditions and screened most of the substrates. Wrote the supporting information and contributed in the writing of the article.

V. Performed the major part of the experimental work. Prepared the heterogeneous dual catalyst. Found the reaction conditions and screened most of the substrates. Prepared the samples for elemental analysis, solid state NMR and IR. Interpreted the data. Supervised the work of the diploma worker Lorenza Ghisu. Wrote the supporting information and contributed in the writing of the manuscript.

# Appendix B- Solid-state $^{13}C\{^{1}H\}$ NMR spectra

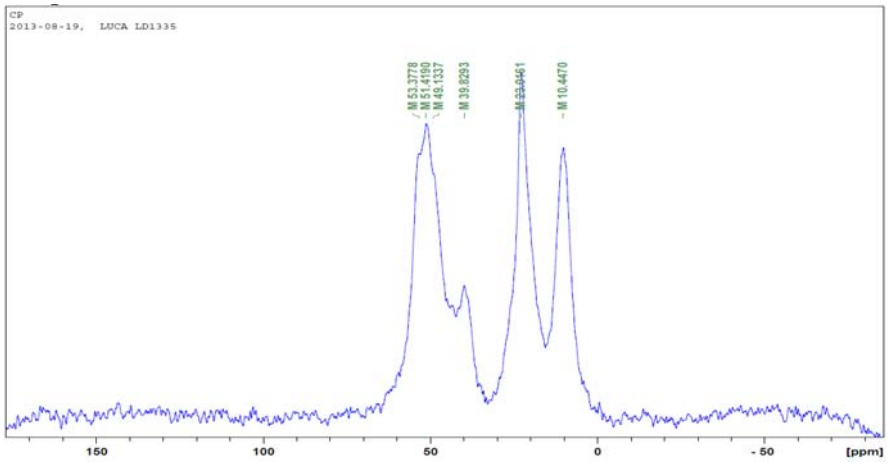



**Figure 5.** Solid-state $^{13}C\{^{1}H\}$ Nuclear Magnetic Resonance (NMR) of the functionalized silica **24**.

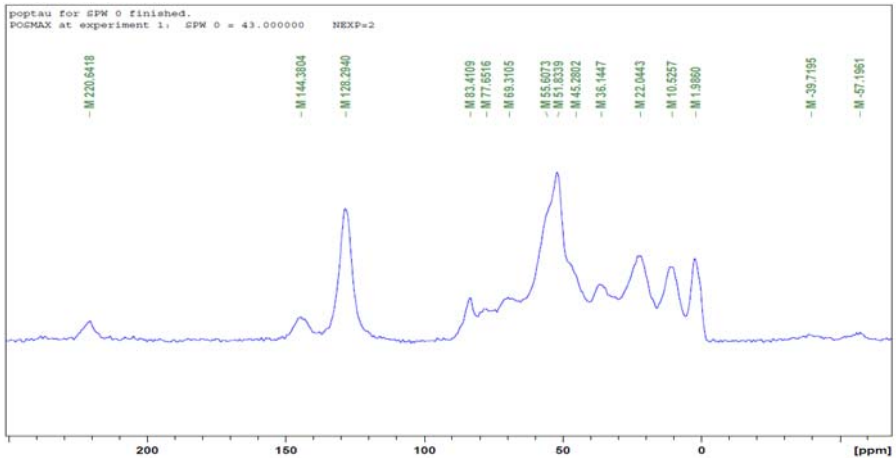



**Figure 6.** Solid-state $^{13}C\{^{1}H\}$ Nuclear Magnetic Resonance (NMR) of the $SiO_2$-Pd(II)-chiral amine catalyst **26**.

# Appendix C- Infrared (IR) spectra

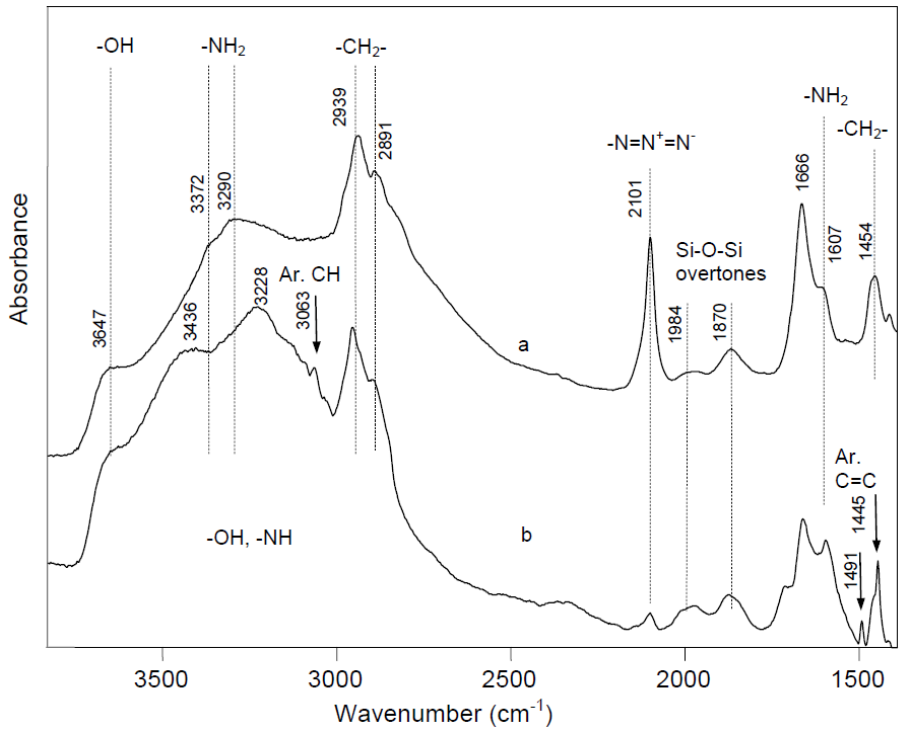



**Figure 7.** Infrared spectra of the (a) functionalized silica support **24** and (b) the $SiO_2$-Pd(II)-chiral amine catalyst **26**.

# Acknowledgments

I would like to thank:

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