



UNIVERSITÀ DEGLI STUDI DELL'INSUBRIA

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# Exploiting Supramolecular Interaction for Asymmetric Catalysis

Ph. D. dissertation of

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Academic Year  
2010-2011



# Exploiting Supramolecular Interaction for Asymmetric Catalysis

Como  
December 22<sup>nd</sup>, 2011

Room S.02  
16.00

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*“Science and opinion.  
The first begets knowledge, the latter ignorance”  
(Hippocrates)*



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# *Chapter 1*

## *Introduction*



## 1.1 General introduction

Molecular chirality is one of the principal elements governing natural processes and its importance is underscored by the fact that in nature it plays a key role in a wide range of biological and physical properties. Life itself depends on chirality, because living systems interact with enantiomers in different ways. A variety of functions occur because receptors, enzymes or binding sites recognize molecules having specific chirality.

The discovery of chirality prompted chemists to develop methods to obtain enantiopure substances but, although many asymmetric reactions have been discovered so far, until the early 1970s resolution of racemates (spontaneous or with the aid of an enantiopure reagent) was the primary way to obtain optically active compounds. Many other methods, involving transformation of readily available natural chiral compounds (such as amino acids, carbohydrates or alkaloids), or forming enantiomerically pure molecules from prochiral substrates by use of enzymes or whole microorganisms, were used in this field. In the last decades synthetic chemists developed a variety of versatile stereoselective reactions that complement biological processes. Asymmetric catalysis is an ideal method to obtain chiral molecules. The chemical approach, which uses a small amount of a man-made chiral catalyst (metal or metal-free), leads to the formation of naturally occurring and non-naturally occurring chiral material in large quantities.

Recently combinatorial chemistry has appeared as an important methodology for the rapid synthesis of huge numbers of chemical compounds and the discovery and application of new catalysts has become an effective tool to overcome the drawbacks that hamper the use of enantioselective catalysis in an industrial environment.

## 1.2 Non-covalent interactions for supramolecular catalytic systems

The term “supramolecular” has been used for many years in the complex field of biological structures and ionic charges, and although the concept existed since the XIX century, an important contribute to rationalize the meaning of the word must be attributed to Jean-Marie Lehn, Nobel in chemistry in 1987, who introduced the definition “chemistry beyond the molecule”. According to this definition, a supramolecule is an organized complex entity created from the association of two or more chemical species held together by intermolecular additive and cooperative forces including hydrogen bonding, coordination, hydrophobic interactions,  $\pi$ - $\pi$  interactions, electrostatic interactions and their properties are different than the sum of the properties of each individual component. To better understand the concept is worth using an analogy from daily life, and the best one is that “a strong team is greater than the sum of its parts”.

Supramolecular chemistry can be split into two big categories which can be arbitrarily named *host-guest chemistry* and *self-assembly chemistry*. The difference between the two classes is peculiar. The first subtends the concept of molecular recognition, a molecule significantly larger than another can wrap around it, and the meaning of host and guest appears quite clear. This family includes many biological systems among which worth mentioning the system enzyme-substrate. Where there is no significant difference in size and no species is acting as a host for another, the non-covalent joining is named *self-assembly*. Specifically, the self-assembly is equilibrium between two or more molecular components to produce an aggregate with a structure dependent only on the characteristic of the chemical building blocks.

Since the aim of this thesis is the use of this second type of interactions for the development of new catalytic systems, in this chapter only the concepts related to self-assembly processes will be analyzed.

### 1.3 Self-assembly

*Self-assembly*, in its most general sense, means the spontaneous association of two or more species to create a larger aggregate through the formation of reversible, and generally supramolecular, interactions. This generic definition has significantly broadened over time to incorporate many aspects of biology, biochemistry and nanotechnology which employ the basic principles of chemical self-assembly, albeit with subtle variations.

Examples of such self-assembly processes are repeatedly found in nature. The DNA double-helix requires two complementary strands to become entwined *via* hydrogen bonds and  $\pi$ - $\pi$  stacking in a self-assembly process. The strands recognize each other and join together to form the most thermodynamically stable assembly product. Protein folding and viral assembly operate in a broadly similar manner.

Synthetic self-assembly systems are based on the ability of the chemists to design molecules containing complementary functionalities. The chemist has no direct control over the assembly process otherwise it would not be termed *self*-assembly, however, it is possible to induce the chemical system to rearrange to the most thermodynamically stable - and desired - product, by a careful and judicious choice of the different parts of the system.

#### **Self-assembly in nature**

Processes that rely upon self-assembly are ubiquitous in nature and life could not exist without them. Vital biological processes are governed by countless weak interactions that cause highly complex architectures to form reliably and spontaneously. It is relatively easy to understand why self-assembly systems play such important biological and biochemical roles. If every biological process required strong chemical bonds to be formed or broken, then biological systems

would consume enormous amounts of energy and the synthesis of biological molecules would be extremely complex and time-consuming.

Pairing of the two DNA helices is without doubt the best known self-assembly in biological systems. The double helix, and in particular the complementarity of the nucleobases, perfectly explains the basic concept of self-assembly.

However, DNA pairing is not the only natural process involving non-covalent interaction. Nature uses self-assembly to build highly structured systems for specific functions. Examples include the folding process of proteins to give rise to secondary, tertiary and quaternary structures, hydrophobic effect in the formation and activity of lipid membranes, RNA interactions in the structure of Virus, functioning of molecular machines such as the system actin-myosin, tubulin assembly to give microtubules, biomineralization processes, and so on.

Nature demonstrates an ability to outperform humans in efficiency of design and strength of materials, thus is therefore reasonable to assert that a better understanding of self-assembly processes in biological systems will lead chemist to develop systems even more efficient and will lead to an exploitation of their advantages.

### **Self-assembly for developing new metal-based stereoselective catalysts**

For many years synthetic chemists involved in catalysis focused on the research and development of new powerful and selective chiral ligands for new high selective metal-catalyzed asymmetric reactions. While bidentate  $C_2$ -ligands were for more than thirty years the preferred structures for asymmetric catalysis, in the last decade a real renaissance of monodentate ligands was observed thanks to the pioneering studies independently performed by several groups including Reetz, Feringa and De Vries.<sup>1</sup> These ligands showed themselves capable of excellent ees,

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<sup>1</sup> (a) M. T. Reetz, T. Sell, A. Meiswinkel, G. Mehler, *Angew. Chem. Int. Ed.* **2003**, *42*, 790. (b) M. T. Reetz, T. Sell, A. Meiswinkel, G. Mehler, DE-A 10247633.0, **2002**. (c) M. T. Reetz, X. Li, *Angew. Chem. Int. Ed.* **2005**, *44*, 2959. (d) M. T. Reetz, G. Mehler, *Tetrahedron Lett.* **2003**, *44*, 4593.

particularly in enantioselective hydrogenations. Later, the same groups discovered that mixing different monodentate ligands often gave rise to comparable and sometimes even better results. Fascinated by these interesting results the groups developed numerous libraries of phosphonites, phosphites and phosphoramidites and investigated their applications in various asymmetric transformations, mainly hydrogenations.<sup>2</sup>

This methodology is relevant whenever two different ligands are coordinated to the same metal center; therefore, the crucial point is the study the coordination process. In the simplest case  $L_a$  and  $L_b$  in the presence of a metal  $M$ , can generate three different species in equilibrium with each other: two homocomplexes  $[ML_aL_a]$  and  $[ML_bL_b]$  and the heterocomplex  $[ML_aL_b]$  (Scheme 1.1). In the absence of limiting agent or additional factors a statistical ratio (1:1:2) will be obtained, although in several cases the thermodynamic stability of the heterocomplex favoured its formation.



**Scheme 1.1**

The number of possible combinations in this approach can be calculated from the equation

$$\frac{n \times (n - 1)}{2}$$

where  $n$  is the number of ligands although in some cases the equilibrium can be shifted towards the heterocomplex by varying the relative ligand ratio.<sup>3</sup>

In this approach, enhancement of the ee can be obtained when the heterocomplex is more active and selective than the corresponding homocomplexes.<sup>1</sup>

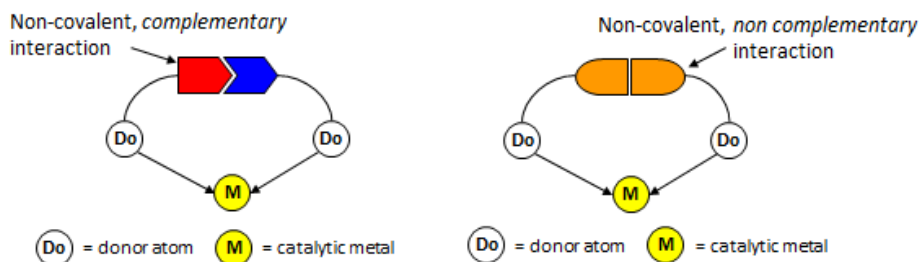
<sup>2</sup> For a review on monodentate ligands in combinatorial approach see M. T. Reetz, *Angew. Chem. Int. Ed.* **2008**, *47*, 2556.

<sup>3</sup> C. Monti, C. Gennari, U. Piarulli, J. G. de Vries, A. H. M. de Vries L. Lefort, *Chem. Eur. J.*, **2005**, *11*, 6701.

More recently, the concept of supramolecular bidentate ligands emerged as a tool for the selective formation of heterocomplexes. This strategy requires that two ligands involved in the coordination process possess additional functionalities capable of interact each other shifting the equilibrium in the direction of the heterocomplex.<sup>4</sup>

The systems thus created have fewer degrees of freedom, while still maintaining appeal for a combinatorial exploitation, compared to the analogues complexes with monodentate ligands; in fact, they combine the most peculiar qualities of monodentate ligands (ease and speed of synthesis) with a conformational behavior similar to the classic bidentate ligands.

Depending on the nature of the non-covalent interaction, complementary or not, the formation of respectively heterocomplexes or homocomplexes will take place (Scheme 1.2).



**Scheme 1.2**

In this section, supramolecular bidentate ligands will be mentioned depending on the type of non-covalent interaction used.

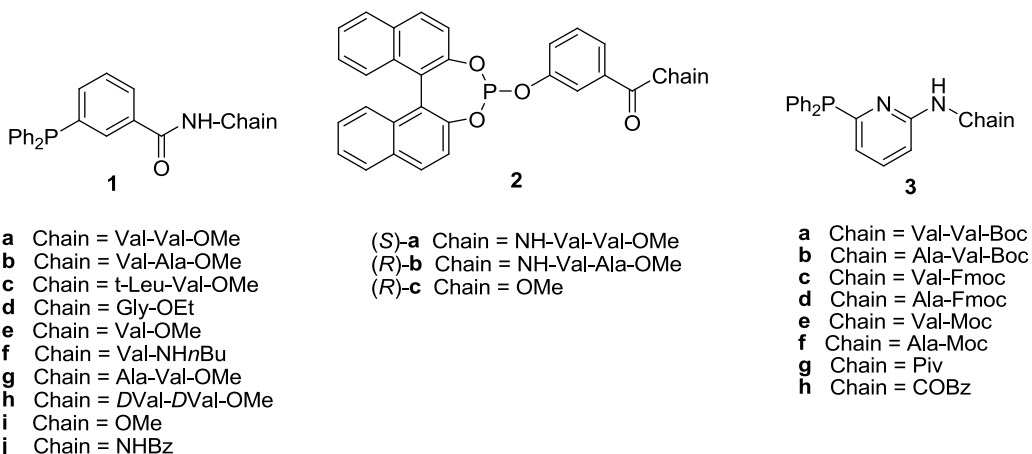
<sup>4</sup> (a) B. Breit, *Angew. Chem. Int. Ed.*, **2005**, *44*, 6816. (b) M. J. Wilkinson, P. W. N. M. van Leeuwen, J. N. H. Reek, *Org. Biomol. Chem.*, **2005**, *3*, 2371. (c) A. J. Sandee, J. N. H. Reek, *Dalton Trans.*, **2006**, 3385; (d) P. E. Goudriaan, P. W. N. M. van Leeuwen, M.-N. Birkholz, J. N. H. Reek, *Eur. J. Inorg. Chem.*, **2008**, 2939; (e) G. Gasparini, M. Dal Molin, L. J. Prins, *Eur. J. Org. Chem.*, **2010**, 2429; (f) J. Meeuwissen, J. N. H. Reek, *Nat. Chem.*, **2010**, *2*, 615.



### 1.3.1 Self-assembly through hydrogen bonding

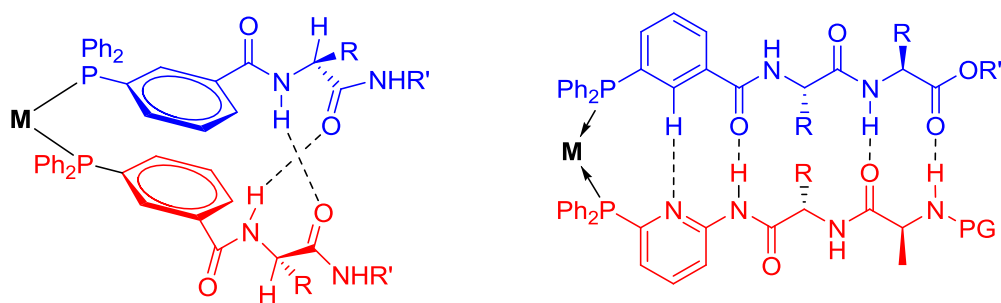
#### Hydrogen bonding by peptides

Peptides are probably the best known functionalities capable of intermolecular interaction by hydrogen bonding and recently this ability has been used by Breit and coworkers in the development of a library of phosphines **1** and phosphites **2** that mimic the well known PhanePhos ligand.<sup>5</sup> *Meta*-carboxypeptidyl-substituted triarylphosphines or phosphites were employed to construct PhanePhos-like structures by means of an inter-ligand helical hydrogen-bonding network (Scheme 1.3). The latter, in turn, induces a planar  $\pi$ -stacking arrangement of the two *meta*-substituted arene rings which resembles the planar stereogenic element present in PhanePhos, as it was demonstrated by X-ray and NMR analysis of Pt- and Rh-complexes. The homocombinations of ligands **1** and **2**, in the presence of  $[\text{Rh}(\text{cod})_2\text{BF}_4]$ , were tested in the enantioselective hydrogenation of methyl 2-acetamido acrylate, methyl (*Z*)-2-acetamido cinnamate and dimethyl itaconate; the best combinations (involving ligands **69**) gave enantioselectivity levels comparable with those of PhanePhos ligands (75–99% e.e.).



<sup>5</sup> (a) P. J. Pye, K. Rossen, R. A. Reamer, N. N. Tsou, R. P. Volante and P. J. Reider, *J. Am. Chem. Soc.*, 1997, **119**, 6207; (b) P. J. Pye, K. Rossen, R. A. Reamer, R. P. Volante and P. J. Reider, *Tetrahedron Lett.*, 1998, **39**, 4441.

The concept of utilising peptide-functionalised *P*-ligands was further developed and expanded to the formation of heterocomplexes.<sup>6</sup> Indeed, when *C*-linked peptides **1** are combined with *N*-linked peptides **3** in the presence of platinum(II) and rhodium(I) salts, a two-stranded, antiparallel  $\beta$ -sheet structure forms (Scheme 1.3), which serves as basis for the generation of a heterobidentate ligand library. The latter was screened in the enantioselective hydroformylation of styrene; remarkably, the stereocentres of the peptide chains can induce a moderate selectivity, although they are remote from the catalytic metal centre.

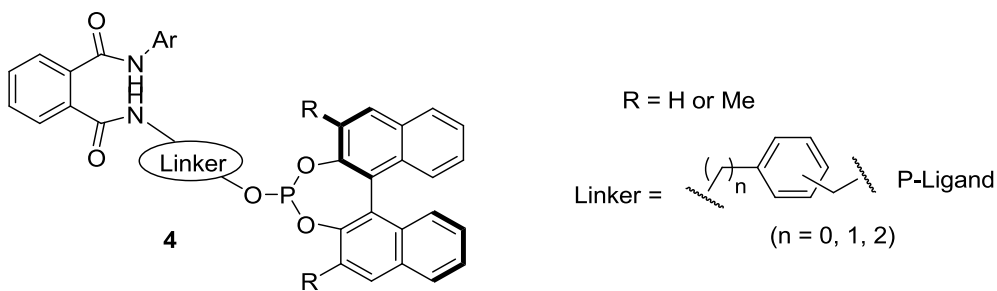


Scheme 1.3

Recently our group and Gennari reported a new class of chiral monodentate phosphite ligands **4**, named PhtalaPhos, which contain a phthalic acid primary diamide moiety.<sup>7</sup> The phthalamidic group displays both donor and acceptor hydrogen-bonding properties that, in principle, can give rise to supramolecular interactions both between the ligands and with the reaction substrate (Scheme 1.4). Ligands were used in the rhodium catalyzed enantioselective hydrogenation of olefins with excellent results and enantioselectivities up to >99%.

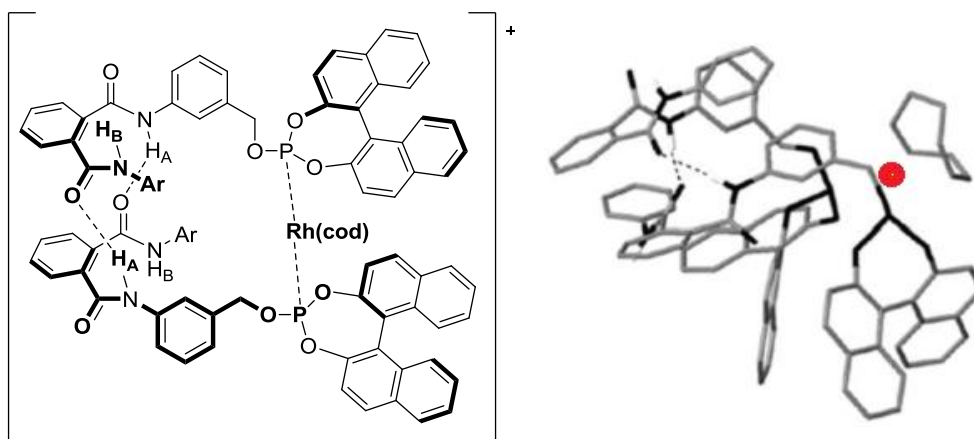
<sup>6</sup> C. Laungani, J. M. Slattery, I. Krossing, B. Breit, *Chem.–Eur. J.*, **2008**, *14*, 4488.

<sup>7</sup> L. Pignataro, S. Carboni, M. Civera, R. Colombo, U. Piarulli, C. Gennari, *Angew. Chem. Int. Ed.* **2010**, *49*, 6633.



**Scheme 1.4**

Computational studies were also made to investigate the real structure of the precatalyst and an effective double hydrogen bond array (Scheme 1.5).



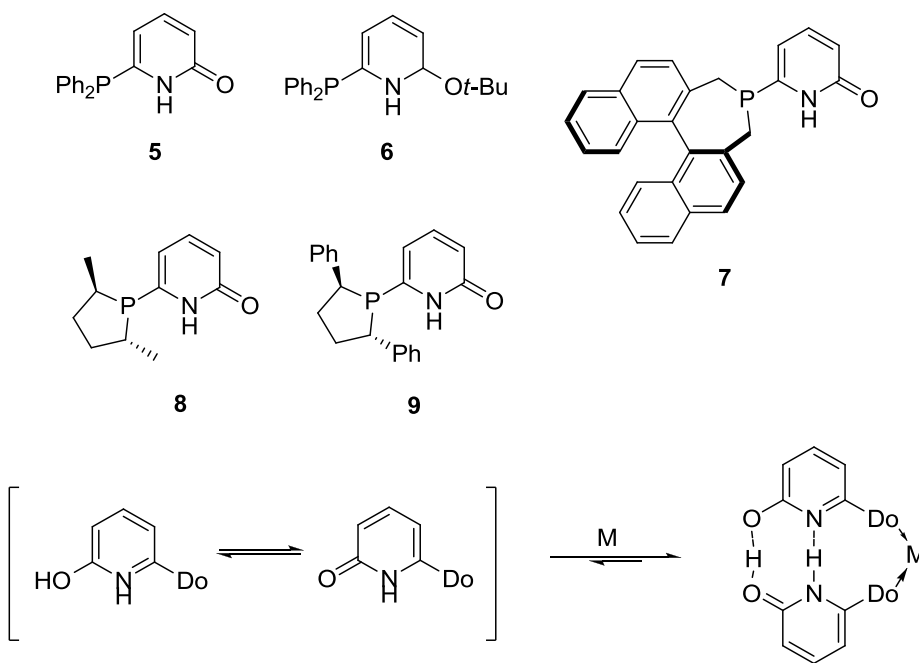
**Scheme 1.5**

### Hydrogen bonding by heterocycles

The first example concerning the synthesis of supramolecular bidentate ligands using hydrogen bonding by heterocycles is attributed to Breit who developed a number of phosphines **5-9** using as hydrogen bond source the already known<sup>8</sup>

<sup>8</sup> (a) K. Mashima, H. Nakano, A. Nakamura, *J. Am. Chem. Soc.* **1993**, *115*, 11632. (b) K. Mashima, M. Tanaka, K. Tani, H. Nakano, A. Nakamura, *Inorg. Chem.* **1996**, *35*, 5244.

equilibrium between the two tautomeric forms of 2-hydroxypyridine derivatives.<sup>9</sup> The general concept is shown in Scheme 1.6.



**Scheme 1.6**

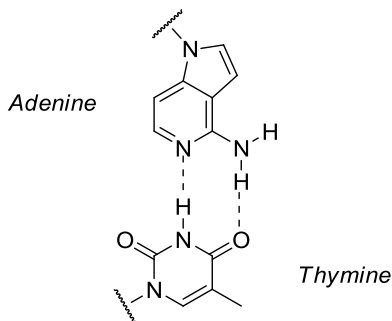
Ligands were used in rhodium-catalyzed hydrogenations of olefins with enantioselections up to 99%. The importance of the tautomeric equilibrium was evidenced by poor result obtained with ligand **6**, unable to self-assemble.

Breit also explored the possibility to exploit “tautomeric interactions” in a combinatorial fashion. To overcome the problem of statistic mixtures, a DNA approach was used, or rather a non-tautomeric system based on Adenine-Thymine interplay (Scheme 1.7).<sup>10</sup> A library of 8 building blocks were synthesized to obtain heterocomplexes which form stable hydrogen bonding even if in protic solvents like methanol.<sup>10</sup> Tautomeric and non-tautomeric systems were then used in a various list

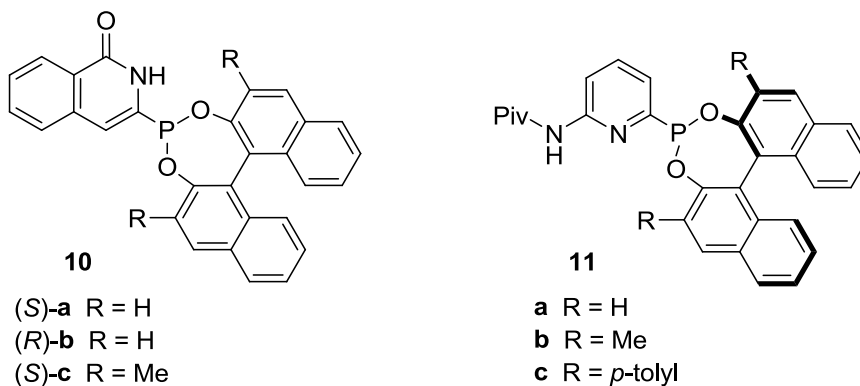
<sup>9</sup> (a) B. Breit, W. Seiche, *J. Am. Chem. Soc.* **2003**, *125*, 6608. (b) W. Seiche, A. Schuschkowski, B. Breit, *Adv. Synth. Catal.* **2005**, *347*, 1488. (c) B. Breit, W. Seiche, *Pure and Appl. Chem.* **2006**, *78*, 249. (d) B. Breit, W. Seiche, *Angew. Chem. Int. Ed.*, **2005**, *44*, 1640.

<sup>10</sup> Waloch, C.; Wieland, J.; Keller, M.; Breit, B. *Angew. Chem. Int. Ed.* **2007**, *46*, 3037

of reactions like hydrogenation,<sup>11,17</sup> *anti*-Markovnikov hydration of terminal alkynes,<sup>12</sup> hydration of nitriles,<sup>13</sup> allylic amination<sup>14</sup> and hydrocyanation of alkenes.<sup>15</sup>



Phosphonites **10** and **11** were then introduced using a BINOL moiety in order to create the chiral ligand donor group and tested in the hydrogenation of olefins.<sup>16</sup>



<sup>11</sup> Birkholz, M.-N.; Dubrovina, N.V.; Jiao, H.; Michalik, D.; Holz, J.; Paciello, R.; Breit, B.; Börner, A. *Chem. Eur. J.*, **2007**, *13*, 5896

<sup>12</sup> Chevallier, F.; Breit, B. *Angew. Chem. Int. Ed.*, **2006**, *45*, 1599

<sup>13</sup> Smejkal, T.; Breit, B. *Organometallics*, **2007**, *26*, 2461

<sup>14</sup> (a) Birkholz, M.-N.; Dubrovina, N.V.; Shuklov, I.A.; Holz, J.; Paciello, R.; Waloch, C.; Breit, B.; Börner, A. *Tetrahedron: Asymmetry*, **2007**, *18*, 2055. (b) Usui, I.; Schmidt, S.; Keller, M.; Breit, B. *Org. Lett.*, **2008**, *10*, 1207.

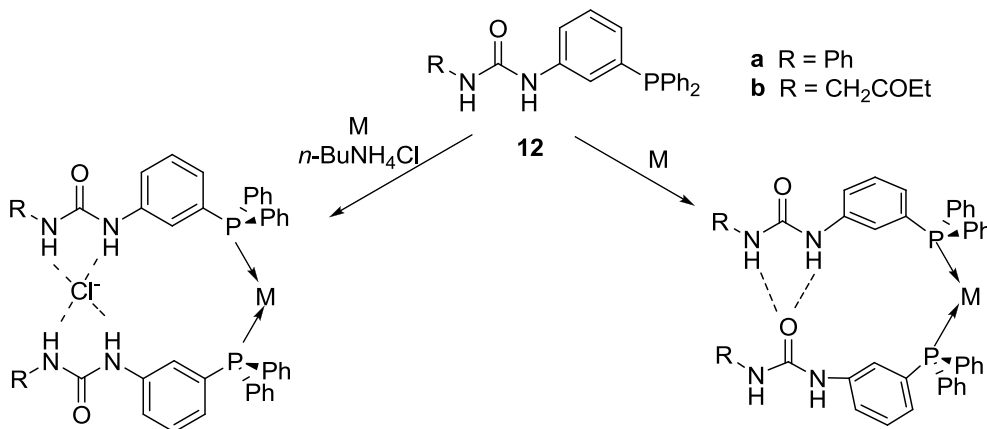
<sup>15</sup> De Greef, M.; Breit, B. *Angew. Chem. Int. Ed.*, **2009**, *48*, 551

<sup>16</sup> M. Weis, C. Waloch, W. Seiche, B. Breit, *J. Am. Chem. Soc.* **2006**, *128*, 4188.

## Hydrogen bonding by Urea functionalities

In this field two principal groups had a key-player role for the development of new efficient urea-based systems. Reek<sup>17</sup> and Love<sup>18</sup>, independently, synthesized ligands **12** and studied the process of self-assembly in presence of a palladium source.

Love observed with **12a** the formation of polymeric species meanwhile Reek with **12b** the formation of *trans* complex. Both of them found completely symmetric specie in presence of Metal source and *n*-butyl ammonium chloride due to the interaction between chlorine and the four NH (Scheme 1.8).

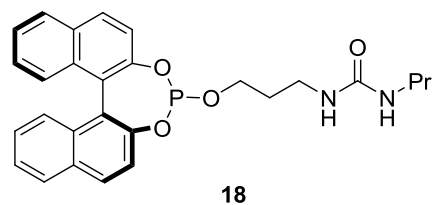
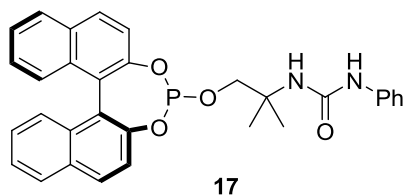
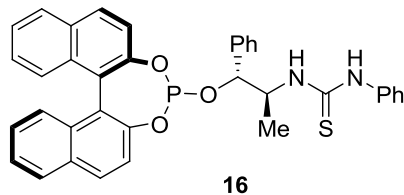
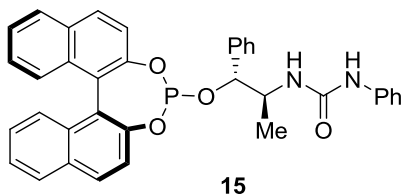
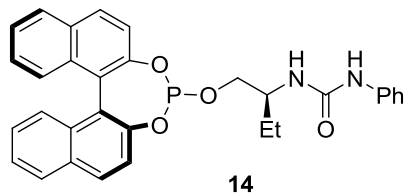
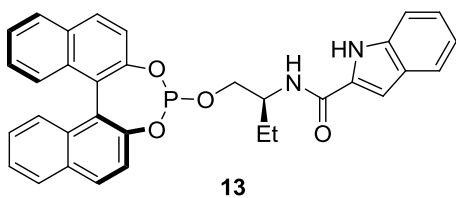


**Scheme 1.8**

Subsequently, Reek developed a library of phosphite derivatives **13-18** called *UREAPhos*, with which were obtained high levels of enantioselection in Rhodium-catalyzed hydrogenation of benchmark substrates.<sup>12b</sup> In addition, the presence of stereocenters in the linker between the phosphate and the urea, seems to be useful to obtain higher selectivity.

<sup>17</sup> (a) L. K. Knight, Z. Freixa, P. W. N. M. van Leeuwen, J. N. H. Reek, *Organometallics* **2006**, *25*, 954. (b) A. J. Sandee, A. M. van der Burg, J. N. H. Reek, *Chem. Commun.* **2007**, 864. (c) J. Meeuwissen, M. Kuil, A. M. Van der Burg, A. J. Sandee, J. N. H. Reek, *Chem. Eur. J* **2009**, *15*, 10272

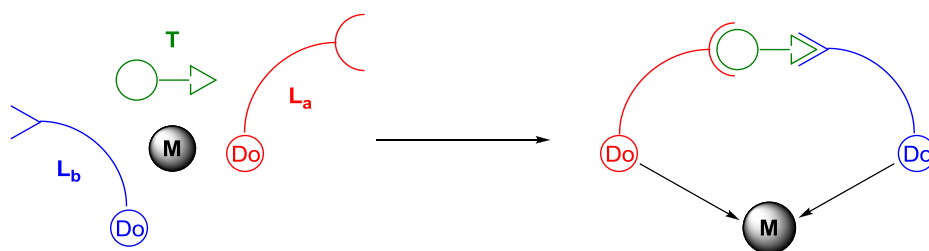
<sup>18</sup> P. A. Duckmanton, A. J. Blake, J. B. Love, *Inorg. Chem.* **2005**, *44*, 7708.



### 1.3.2 Self-assembly through coordinative bonding

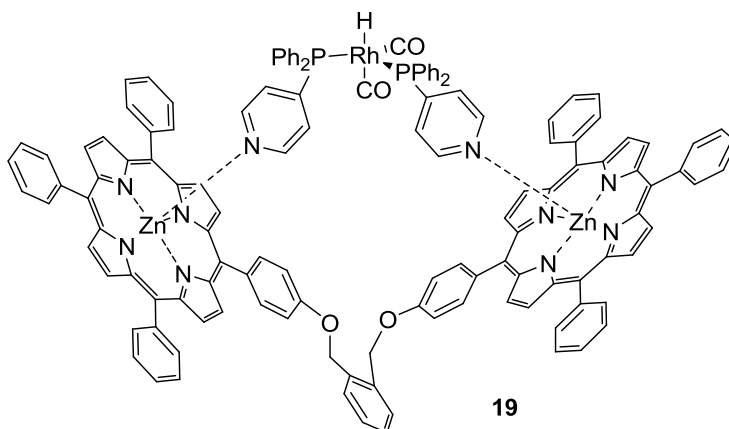
An attractive approach for the achievement of supramolecular bidentate ligands is the use of coordinative forces to direct the assembly.

In general, one template component **T** is able to interact, by coordination, with two ligands **L<sub>a</sub>** and **L<sub>b</sub>** bearing a donor atom **Do** for the coordination to the catalytic metal **M**. (Scheme 1.9). The additional tunable center permits an excellent exploitability for a combinatorial approach, being the number of possible combinations  $n_{L_a} \times n_{L_b} \times n_T$ .

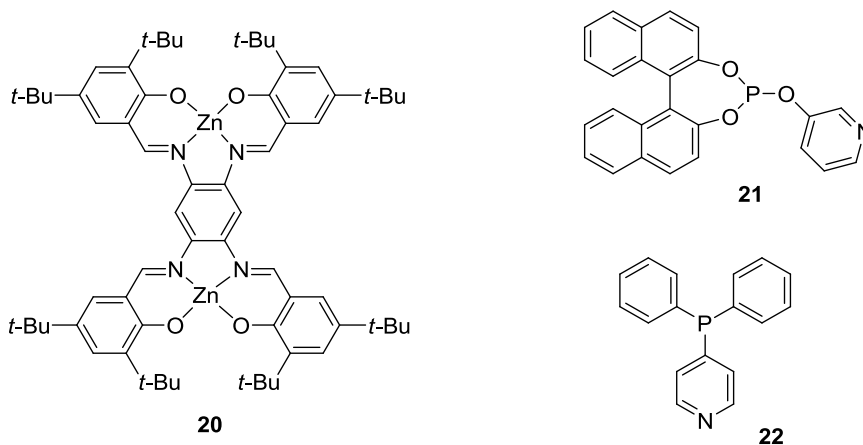


Scheme 1.9

The first system based on this strategy was **19** developed by Reek.<sup>19</sup> The assembly was performed from a zinc(II)porphyrin, two (diphenylphosphino)pyridine ligands and [Rh(acac)(CO)<sub>2</sub>]. The system was used in the hydroformylation of 1-octene and styrene with high selectivity.



Another interesting example of a template-direct bidentate ligand was introduced by Reek in 2006 and involved dimeric Zn(II)salen template **20**. Ligands **21** and **22** were used to obtain the catalytic systems which proved to be more selective in the heterobidentate form.<sup>20</sup>

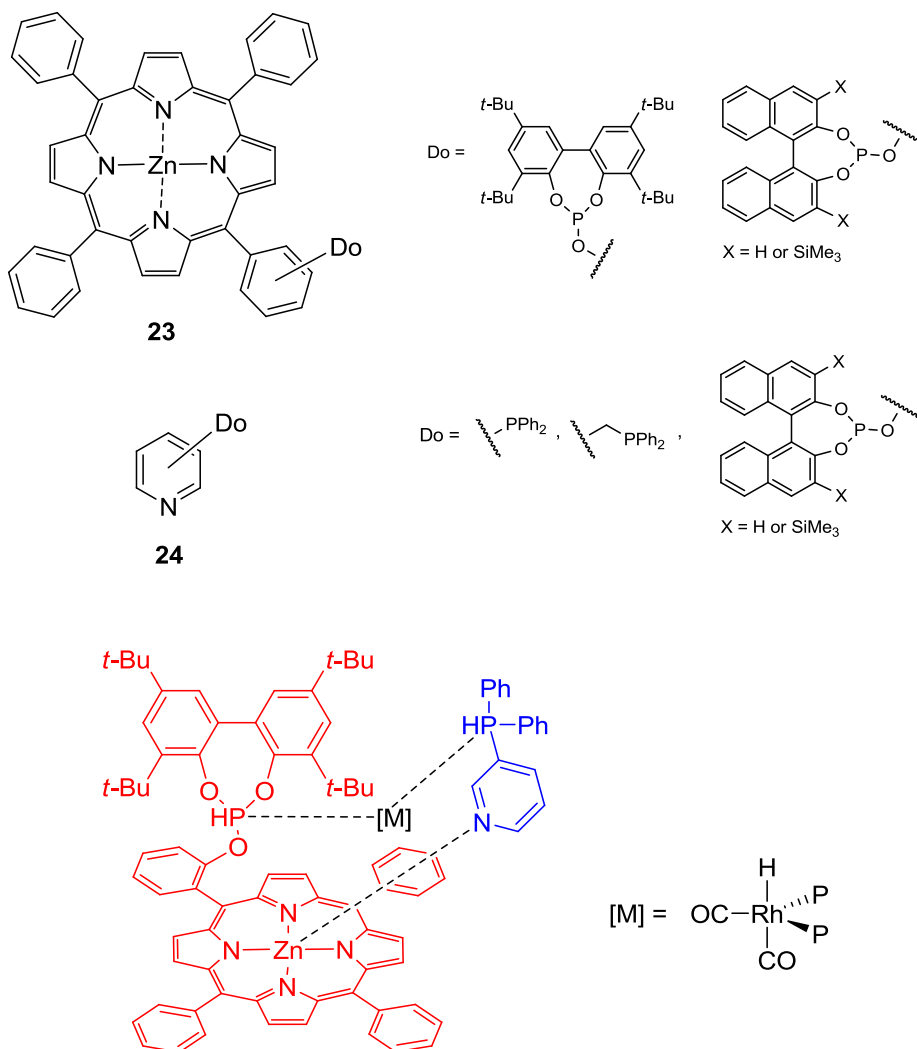


<sup>19</sup> Slagt, V.F.; van Leeuwen, P. W. N. M.; Reek, J. *Chem. Commun.* **2003**, 2474.

<sup>20</sup> (a) Kuil, M.; Goudriaan, P. E.; van Leeuwen, P. W. N. M.; Reek, J. *Chem. Comm.*, **2006**, 4679. (b) Kuil, M.; Goudriaan, P. E.; Kleij, A. W.; Tooke, D. M.; Spek, A. L.; van Leeuwen, P. W. N. M.; Reek, J. *Dalton Trans.*, **2007**, 2311.



Coordinative bonds can be used to promote the formation of supramolecular bidentate ligands also in the absence of a template. This kind of approach was pioneered by Reek who, in 2004, proposed a self-assembly strategy relying on the direct, complementary interaction between a zinc-porphyrin complex bearing a phosphite group **23** and a pyridyl phosphine or phosphite **24** (Scheme 1.10). A library of 48 supramolecular systems, called Supraphos, was prepared from smaller libraries of **23** and **24** and screened in the Pd-catalyzed allylic alkylation of 1,3-diphenylallyl acetate with dimethyl malonate (Scheme 1.11-A).

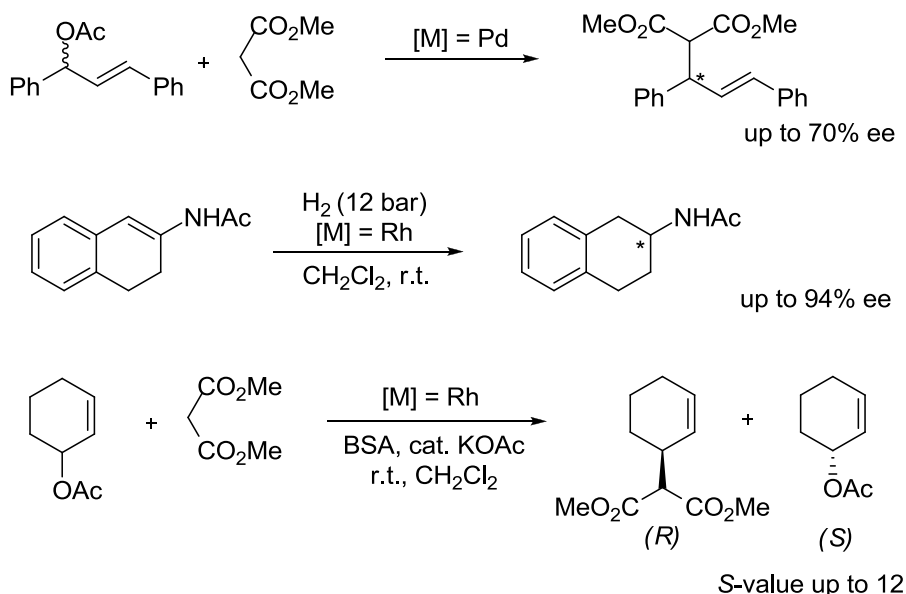


**Scheme 1.10**

The self-assembled systems proved significantly more active than the corresponding monodentate ligands, although their enantioselectivity (up to 70% e.e.) was inferior (a ligand of the series **39** alone gave 97% e.e.).

The phosphite–phosphine heterocomplex was studied by UV–vis spectroscopy and it was demonstrated that the pyridine group of the phosphine selectively coordinates to the zinc(II) porphyrin moiety of the phosphite ligand. <sup>31</sup>P-NMR spectroscopy showed the exclusive formation of the heterocomplex.

The Supraphos systems were later screened in other reactions, such as the Rh-catalysed hydroformylation of styrene, the Rh-catalysed hydrogenation of challenging enamides (Scheme 1.11-B) and the Pd-catalysed kinetic resolution of racemic cyclohexenyl acetate (Scheme 1.11-C).



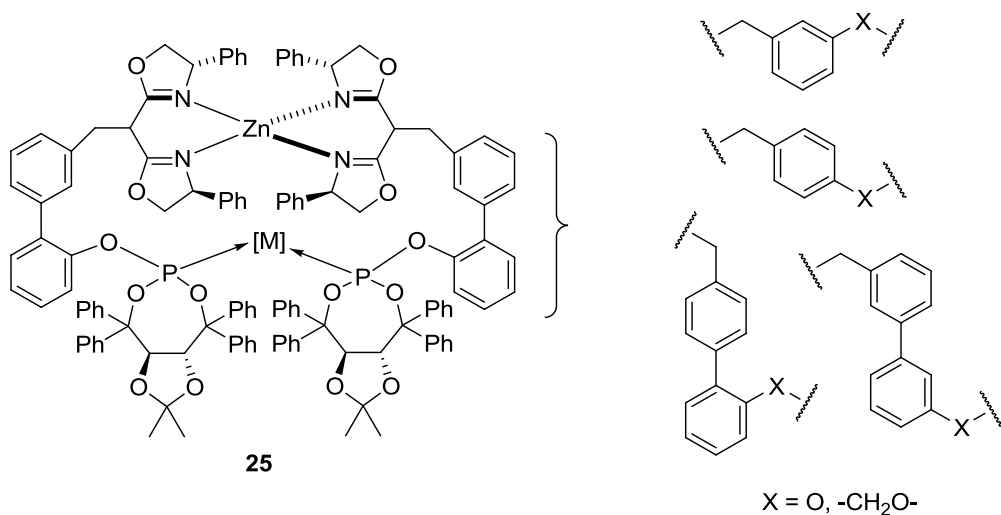
**Scheme 1.11**

Probably the most impressive work in the field of self-assembly by coordination has been published by Takacs in 2004.<sup>21</sup> In this beautiful study the catalytic systems **25**

<sup>21</sup> Takacs, J. M., Reddy, D. S., Moteki, S. A., Wu, D., Palencia, H, *J. Am. Chem. Soc.* **2004**, *126*, 4494.

had two different sets of chiral inducers. The proper template effect is due to the coordination to a Zinc atom by two different bisoxazolinic derivatives; whereas the catalytic metal coordinating group are TADDOL-derived phosphite unites.

The strength of this system is that the heteroleptic Zinc(II)bisoxazoline assembly is thermodynamically more stable (and therefore more selective) than the homoleptic counterpart. In simple terms the two bisoxazolinic systems coordinating the Zinc(II) must have opposite configuration.



#### 1.4 Hydrogen bonding as supramolecular interaction in organocatalysis.

Over the years, the main strategy for asymmetric catalysis of electrophile-nucleophile reactions has been based on the electrophile activation by Lewis acids,<sup>22</sup> in which the rate acceleration is due to the decrease of LUMO orbital's energy and their application is dated back to the 19<sup>th</sup> century by the studies of Friedel and Crafts.<sup>23</sup> The protic catalytic effect in cycloaddition reactions was

<sup>22</sup> a) *Lewis Acids in Organic Synthesis*, (Ed.: H. Yamamoto), Wiley, New York, **2000**; b) M. Santelli, J.-M. Pons, *Lewis Acids and Selectivity in Organic Synthesis*, CRCs, Boca Raton, **1996**.

<sup>23</sup> C. Friedel, J.-M. Crafts, *C. R. Acad. Sci.* **1884**, 449.

already known since early 1940s by the studies of Wassermann;<sup>24</sup> however for many decades the use of Lewis acids had a dominant role in this field. The better sort of Friedel-Craft's approach was certainly not based on the inefficiency of Brønsted acid catalysis, but more probably on the higher variability of steric and electronic environment of catalysts.

Nevertheless, in the last decades the electrophile activation by organic H-bond donors has emerged as powerful strategy for new applications and developments. Due to the aim of this thesis a brief overview of this area will be here below reported.

The relatively strong intermolecular interactions between molecules capable of hydrogen bonding were first observed by Faraday in 1823 even if the real hydrogen bond definition will be introduced by Pauling in 1912 and can be summarized in Scheme 1.12 by a subdivision based on the strength interaction.

	Weak	Moderate	Strong
Bond type	electrostatic	mostly electrostatic	mostly covalent
Length [Å]	2.2-3.2	1.5-2.2	1.2-1.5
Angle (°)	90-150	130-180	175-180
Energy (kcal mol <sup>-1</sup> )	<4	4-15	14-40

### Scheme 1.12

The massive number of works concerning this field has proven chemists understanding of catalysis by proton donors.<sup>25</sup> Two principal mechanisms can accelerate reactions: (i) proton transfer in the transition state on the rate determining step or (ii) a reversible protonation of electrophile in a pre-equilibrium step. A more

<sup>24</sup> a) A. Wassermann, *J. Chem. Soc.* **1942**, 618; b) W. Rubin, H. Steiner, A. Wassermann, *J. Chem. Soc.* **1946**, 3046.

<sup>25</sup> (a) W. P. Jencks, *Acc. Chem. Res.* **1976**, *9*, 425; (b) E. Ciuffarin, A. Loi, M. Isola, A. Lupetti, L. Sagramora, L. Senatore, *J. Org. Chem.* **1983**, *48*, 1047; (c) S. Scheiner, *Acc. Chem. Res.* **1994**, *27*, 402.

profound and effective classification is based on the nature of molecules, focusing the attention on the functional groups capable of H-bond donation.

#### 1.4.1 Catalysis by single hydrogen bond donation.

Highly enantioselective reactions involving molecules capable of only one H-bond donation are not largely employed due to the little chance of having high directionality and strength of bonds and consequently a rigid catalyst-substrate complex. Nevertheless some interesting works have been reported on the use of chiral diols as asymmetric inducers.

Chiral diols and diphenols are commonly used in catalysis but for years only as efficient ligands for enantioselective Lewis acid mediated processes.<sup>26</sup> The application as real catalysts is more recent<sup>27</sup> and has opened a new area of a metal-free catalysis. Initially was commonly accepted that diols might act as double H-bond donors,<sup>28</sup> however more recent studies of enantioselective variants suggest that, at least in certain cases, mechanisms involving single H-bond activation may be operative.

Pioneering studies in the latter field were undertaken by Toda in 1980s on the use of TADDOL derivatives as efficient resolving agents for a wide number of species such as sulfoxides, amines and alcohols.<sup>29</sup> Toda reported X-ray structures clearly showing a single H-bond donation by diols (Scheme 1.13).

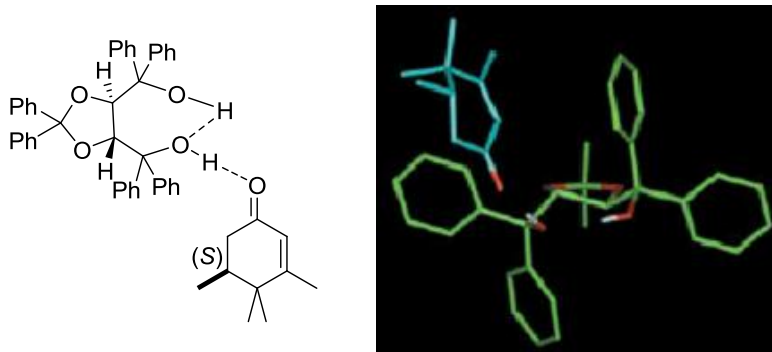
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<sup>26</sup> For useful review: (a) D. Seebach, A. K. Beck, A. Heckel, *Angew. Chem.* **2001**, *113*, 96; (b) J. M. Brunel, *Chem. Rev.* **2005**, *105*, 857.

<sup>27</sup> (a) J. Hine, S.-M. Linden, V. M. Kanagasabapathy, *J. Am. Chem. Soc.* **1985**, *107*, 1082; (b) T. R. Kelly, P. Meghani, V. S. Ekkundi, *Tetrahedron Lett.* **1990**, *31*, 3381.

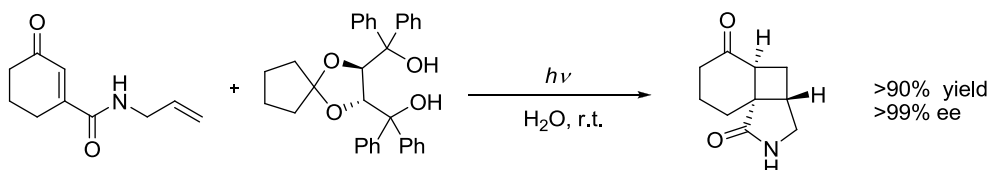
<sup>28</sup> (a) J. Hine, S.-M. Linden, V. M. Kanagasabapathy, *J. Am. Chem. Soc.* **1985**, *107*, 1082; (b) J. Hine, S.-M. Linden, V. M. Kanagasabapathy, *J. Org. Chem.* **1985**, *50*, 5096; (c) T. R. Kelly, P. Meghani, V. S. Ekkundi, *Tetrahedron Lett.* **1990**, *31*, 3381.

<sup>29</sup> (a) F. Toda, K. Tanaka, L. Infantes, C. Foces-Foces, R. M. Claramunt, J. Elguero, *J. Chem. Soc. Chem. Commun.* **1995**, 1453.



**Scheme 1.13**

These results led to an employment in enantioselective reactions among which is worth mentioning the asymmetric cyclization of cocrystal of N-allyl-3-oxocyclohex-1-enecarboxamide and a TADDOL derivative (Scheme 1.14)<sup>30</sup> with excellent results.

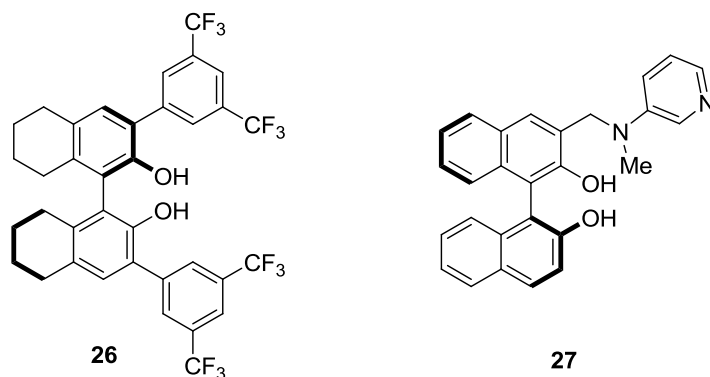


**Scheme 1.14**

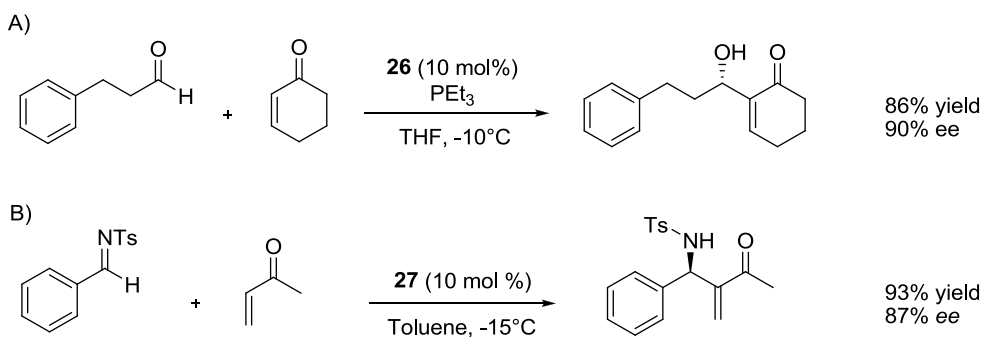
BINOL has been more recently introduced by Schaus as a proficient catalyst in the Morita-Baylis-Hillman reaction. Catalyst **26** promoted the coupling between 3-phenylpropanal and 2-cyclohexenone with appreciable selectivity (Scheme 1.15-A).<sup>31</sup>

<sup>30</sup> K. Tanaka, F. Toda, *J. Chem. Soc. Chem. Commun.* **1983**, 593.

<sup>31</sup> (a) N. T. McDougal, S. E. Schaus, *J. Am. Chem. Soc.* **2003**, *125*, 12094; (b) N. T. McDougal, W. L. Trevellini, S. A. Rodgen, L. T. Kliman, S. E. Schaus, *Adv. Synth. Catal.* **2004**, *346*, 1231.



Product **27** was used by Sasai in the aza-Morita-Baylis-Hillman reaction (Scheme 1.15-B). The author suggests a bifunctional role of the catalyst with electrophile activation by phenols and pyridine as group able to form the enolate.<sup>32</sup>



**Scheme 1.15**

### 1.4.2 Catalysis by double hydrogen bond donation.

The simultaneous donation of two H-bonds has proven to be a powerful strategy for the activation of a wide range of electrophiles including carbonyl compounds, nitro compounds and imine derivatives.

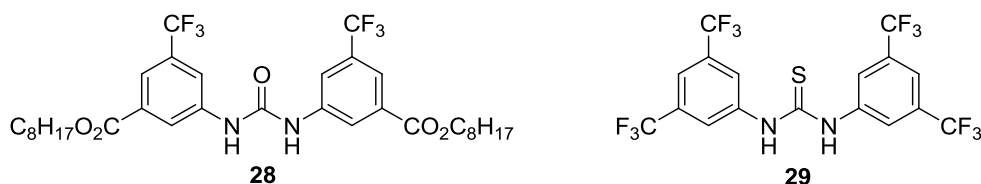
The two principal categories of molecules having this employment are ureas (and thioureas) and guanidium ions.

<sup>32</sup> K. Matsui, S. Takizawa, H. Sasai, *J. Am. Chem. Soc.* **2005**, *127*, 3680.

## Ureas and thioureas

The notion that ureas and thioureas could act as chiral activators of electrophiles through H-bond donation has been known for years, but the massive use of these molecules as real organocatalysts is more recent.

Interesting studies were performed by Jacobsen in late 1990s concerning the use of ureas and thioureas as ligands for Lewis acid metal-catalyzed hydrocyanations of imines.<sup>33</sup> The discovery that higher enantioselectivities were achieved in absence of metal additives was really unexpected. NMR, kinetic and computational studies highlighted the existence of a double H-bond between the acidic NH protons and the imine ion pair serving to activate the electrophile towards attack by cyanide.<sup>34</sup> Initially, achiral ureas and thioureas were synthesized as efficient catalytic systems for organic transformations. In many examples the maximum rate acceleration was observed with aromatic derivatives and consequently these results allowed to hypothesize a relationship between the NH acidity and catalytic ability. Curran and Schreiner developed products **28** and **29** and reported their use as catalyst respectively in Claisen rearrangements<sup>35</sup> and Diels Alder reaction (Scheme 1.16).<sup>36</sup>



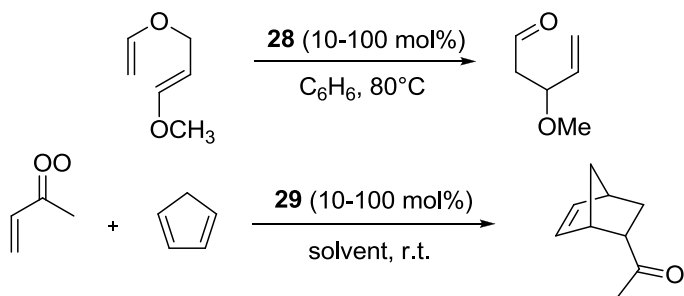
<sup>33</sup> (a) M. S. Sigman, E. N. Jacobsen, *J. Am. Chem. Soc.* **1998**, *120*, 4901; (b) P. Vachal, E. N. Jacobsen, *Org. Lett.* **2000**, *2*, 867; (c) M. S. Sigman, P. Vachal, E. N. Jacobsen, *Angew. Chem.* **2000**, *112*, 1336.

<sup>34</sup> P. Vachal, E. N. Jacobsen, *J. Am. Chem. Soc.* **2002**, *124*, 10012.

<sup>35</sup> (a) D. P. Curran, L. H. Kuo, *J. Org. Chem.* **1994**, *59*, 3259; (b) D. P. Curran, L. H. Kuo, *Tetrahedron Lett.* **1995**, *36*, 6647.

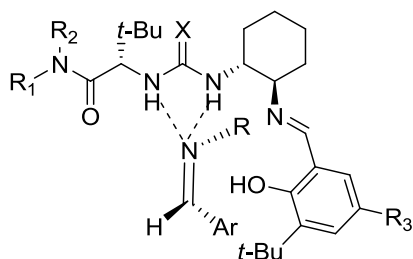
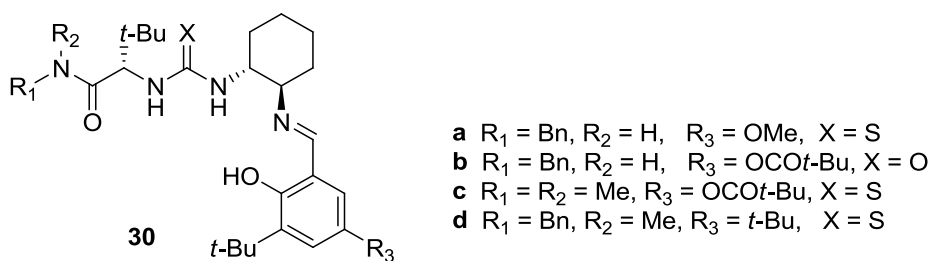
<sup>36</sup> (a) P. R. Schreiner, A. Wittkopp, *Org. Lett.* **2002**, *4*, 217; (b) A. Wittkopp, P. R. Schreiner, *Chem. Eur. J.* **2003**, *9*, 407.





**Scheme 1.16**

Nevertheless, asymmetric induction has been the principal target of these studies, and during the years several catalysts were performed. Jacobsen has been one of the principal players in this field and recently introduced catalysts **30** with which performed numerous asymmetric reaction as allylations of imines, Mannich reactions and aza-Baylis-Hillman reactions<sup>37</sup> whose transition state involve a double hydrogen bond between urea and enamine derivative (Scheme 1.17).



**Scheme 1.17**

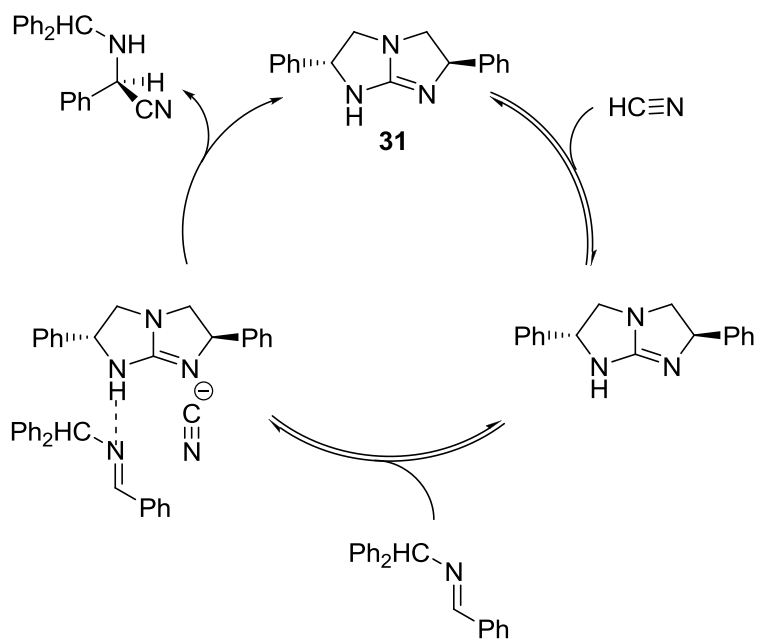
<sup>37</sup> I. T. Raheem, E. N. Jacobsen, *Adv. Synth. Catal.* **2005**, *347*, 1701.

## Chiral guanidinium ions

Guanidinium ions, structural relatives of ureas, are able to participate in H-bond processes as for example arginine in biological systems. The positive charge nature of these groups causes a higher H-bond donating ability than ureas and a related higher catalytic effect.

Pioneering works were carried out by Corey in late 1990s, which performed catalysts based on bicyclic guanidine **31** and relative application in Strecker reaction of aromatic imines.<sup>38</sup>

The mechanism proposed involves the generation of guanidinium cyanide, followed by an attack of the cyanide ion on the imine. H-bond should accelerate this last attack (Scheme 1.18).



**Scheme 1.18**

<sup>38</sup> E. J. Corey, M. J. Grogan, *Org. Lett.* **1999**, *1*, 157.

### 1.4.3 Bifunctional hydrogen-bond catalysts

This is without doubt the most attractive and studied field of H-bond catalysis. During the years many works have been reported on the development of systems capable of simultaneous activation of nucleophiles and electrophiles. Most of the first studies involved Lewis acids equipped with additional Brønsted or Lewis basic functionalities; however more systems proved to be highly exploitable to asymmetric metal-free catalysis.

#### Proline and analogues

$\alpha$ -Amino acids are the simplest bifunctional molecules bearing both an acidic and basic groups and, in particular the 20 naturally occurring, of course are easily available in the enantiopure form.

Despite the function of proline as organocatalyst was known from 1970s due to Hayos and Parrish's research, it is surprising that chemists ignored the catalytic opportunities offered by amino acids, in particular by proline.

In 2000 Lerner, List and Barbas introduced different proline-based systems for the direct asymmetric aldol reactions and since then, hundreds of publications have appeared in related topics.<sup>39</sup>

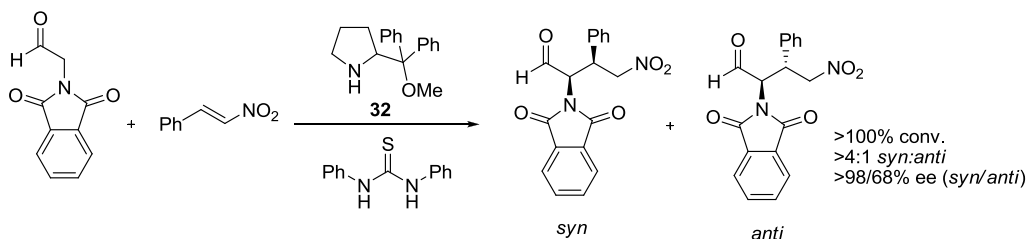
Barbas in 2004 reported the synthesis and application of a number of proline derivatives and their application as catalyst in Michael addition of  $\alpha,\alpha$ -disubstituted aldehydes to nitrostyrene with good results.<sup>40</sup> Some years later he reported the prolinol derivative **32** as efficient catalyst in presence of a thiourea as additive (Scheme 1.19).<sup>41</sup>

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<sup>39</sup> Brindle, C. S.; Trost, B. M. *Chem. Soc. Rev.* **2010**, *39*, 1600.

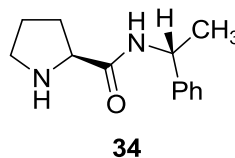
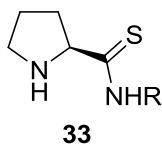
<sup>40</sup> Mase, N.; Thayumanavan, R.; Tanaka, F.; Barbas, C. *Org. Lett.*, **2004**, *6*, 2527

<sup>41</sup> Albertshofer, K.; Thayumanavan, R.; Utsumi, N.; Tanaka, F.; Barbas, C. *Tetrahedron Lett.* **2007**, *48*, 693.



**Scheme 1.19**

In 2005 Gryko and Chimni independently synthesized products **33** and **34** and reported their use in asymmetric aldol reaction between acetone and electron-poor benzaldehydes with different results. These studies proved thioamides as more efficient catalysts with enantiomeric excesses up to >99.9%.<sup>42,43</sup>



- a** R = Ph
- b** R = Bn
- c** R = (*R*)-CH(CH<sub>3</sub>)Ph
- d** R = (*S*)-CH(CH<sub>3</sub>)Ph

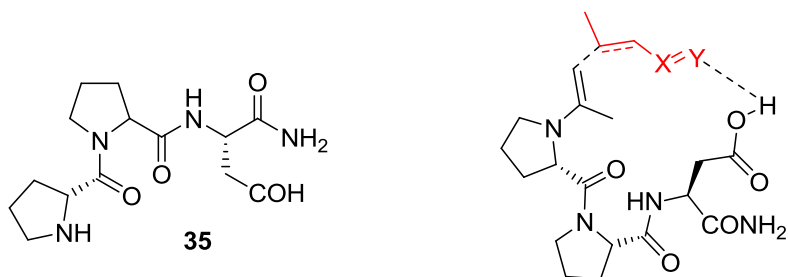
A very interesting work was developed by Wennemers and coworkers who synthesized oligopeptides proline-containing and studied their role as catalyst having an high level of conformational rigidity. The power of these systems were proved by the tripeptide **35** which provided excellent levels of enantioselectivity (up to 98% ee) in a Michael addition of aldehydes to nitrostyrene.<sup>44</sup>

The mechanism proposed involves a synergic contribution of the two different functionalities. Proline act as promoter of enamine catalysis while the carboxylic acid interact with the nitro moiety and makes the attack possible only on one face of enamine (Scheme 1.20).

<sup>42</sup> D. Gryko and R. Lipinski, *Adv. Synth. Catal.*, **2005**, 347, 1948.

<sup>43</sup> S. S. Chimni, D. Mahajan and V. V. S. Babu, *Tetrahedron Lett.*, **2005**, 46, 5617.

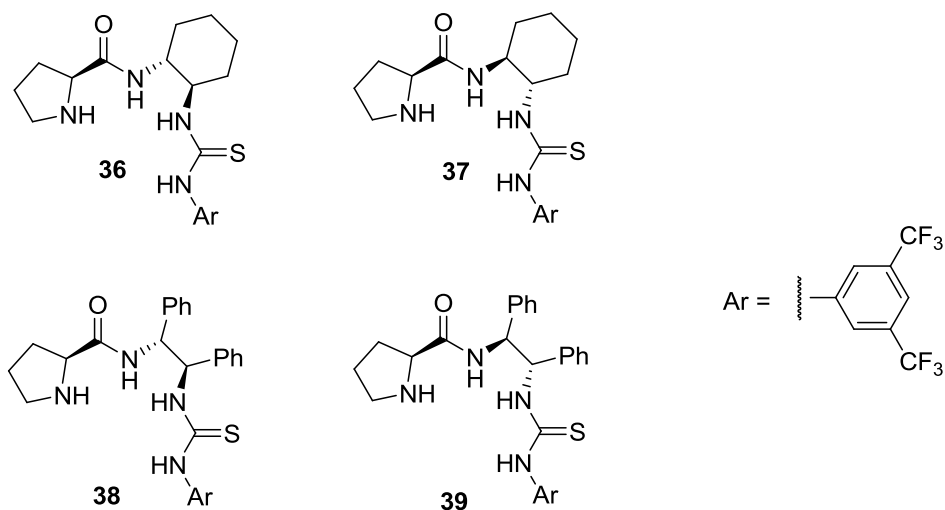
<sup>44</sup> Wiesner, M.; Revell, J. D.; Wennemers, H. *Angew. Chem. Int. Ed.* **2008**, 47, 1871.



**Scheme 1.20**

Similar approach was undertaken by Tsogoeva in 2009 and small dipeptides Pro-Phe were used in the same reaction but with lower selectivity.<sup>45</sup>

Recently, Wang introduced some variations at the strategy with the development of chiral pyrrolidine–thiourea bifunctional catalysts **36-39** having a proline, a thiourea as electrophile activation moiety and non aminoacidic chiral linkers. Catalysts were tested in the benchmark Michael addition of aldehydes to nitroolefins with good levels of enantioselection.<sup>46</sup>



<sup>45</sup> Freund, M.; Schenker, S.; Tsogoeva, S. B. *Org. Biomol. Chem.* **2009**, *7*, 4279.

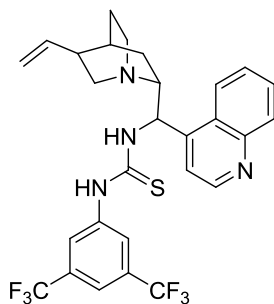
<sup>46</sup> J.-F. Bai, X.Y. Xu, Q.-C. Huang, L. Peng, L.-X. Wang, *Tetrahedron Lett.* **2010**, *51*, 2803

## Cinchona alkaloids and derivatives

Natural products isolated from the bark of trees belonging to *Cinchona* and *Remijia* species have been largely used in asymmetric synthesis as resolving agents.<sup>47</sup> The hypothesis of their use as bifunctional organocatalyst was first suggested by Wynberg<sup>48</sup> due to the observation that these alkaloids possess a free hydroxyl group and consequently can promote conjugate additions with higher rates and enantioselectivity.

This theory was in part denied by Deng who in 2002 reported an highly enantioselective variant of an osmium-catalyzed dihydroxylation of alkenes<sup>49</sup> in which the product were obtained with (DHQD)<sub>2</sub>PYR. The lack of free hydroxyl group suggested that this catalyst may operate by a different mechanism.

Recently, Dixon reported the use of several cinchona derivatives as efficient catalyst for different reactions. In particular, molecule **40** proved to be highly selective in Michael addition, Mannich and Krapcho reactions.<sup>50</sup>



**40**

<sup>47</sup> (a) K. Kacprzak, J. Gawronski, *Synthesis* **2001**, 961; (b) S.-K. Tian, Y. Chen, J. Hang, L. Tang, P. McDaid, L. Deng, *Acc. Chem. Res.* **2004**, *37*, 621.

<sup>48</sup> H. Hiemstra, H. Wynberg, *J. Am. Chem. Soc.* **1981**, *103*, 417.

<sup>49</sup> P. McDaid, Y. Chen, L. Deng, *Angew. Chem.* **2002**, *114*, 348; P. McDaid, Y. Chen, L. Deng, *Angew. Chem. Int. Ed.* **2002**, *41*, 338.

<sup>50</sup> J. Je, D. J. Dixon, P. Hynes, *Chem Comm*, **2005**, 4481; A. L. Tillman, J. Je, D. J. Dixon, *Chem Comm*, **2006**, 1181.

## 1.5 Aim and outline of this thesis

This thesis deals with the design of new catalytic systems involving non covalent interaction, in particular hydrogen-bonding, as basic principle on which they are developed and their application in asymmetric catalysis.

In chapter 2 the preparation of a new class of chiral supramolecular (bis)oxazolines (SupraBox) for metal catalysis is described. The supramolecular system consists in two oxazoline-containing ligands that are linked by hydrogen bonding between urea functionalities. Attention will be focused on the modular strategy for the synthesis of ligands, the formation and characterization of metal-complexes and obviously on the catalytic reaction in which complexes have been tested.

Chapter 3 deals with the development of a new bifunctional organocatalyst based on a diketopiperazinic backbone. The system is centered on a conformationally rigid scaffold functionalized with proline-containing and carboxylic-containing side arms. The synthesis will be reported and particular attention will be dedicated on the conformational studies of the molecules. Hydrogen bond interaction between the system and substrates has proved to be crucial to obtain high selectivity.





# *Chapter 2*

## *Supramolecular chiral bis(oxazolines) for asymmetric metal catalysis*



## 2.1 Oxazolines-containing chiral ligands

Oxazolines are five-membered cyclic aminoesters which were first synthesized at the end of XIX century. These molecules were initially used in organic synthesis as masked carboxylic acids, but their importance has grown over the years in particular from the moment they began to be used as ligands for metal catalysis.

Because of their accessibility and applicability in a wide range of transformations, compounds containing chiral oxazolinic rings have become one of the most versatile, and commonly used classes of ligands for asymmetric catalysis.<sup>1</sup> The majority of these ligands are derived from readily available chiral amino alcohols in a few synthetic steps. The enantiocontrol resides on the stereochemistry of the carbon atom neighboring the coordinating nitrogen atom of the ring and, therefore, in close proximity to the metal active site, thus having a direct influence on the stereochemical outcome of the reaction.

Since the first report by Wimmer in 1986 of the use of chiral oxazolines as ligands in asymmetric catalysis,<sup>2</sup> a wide range of ligands having one, two, or more oxazolines incorporating various heteroatoms, additional chiral motifs, and specific structural features have been used with great success in many asymmetric reactions. Here below will be listed the main, but not all, categories of oxazoline-containing ligands.

Since the main part of the ligands mentioned will be bidentate, some brief on the bite-angle concept should be spent. Bite angle is easily defined as the angle formed by two bonds existing between a metal center and two ligand atoms, so it is strongly dependent on the linker between the two donor groups. Is well known that catalytic activity is depending on the bite angle, therefore bidentate ligands can have a

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<sup>1</sup> (a) Ghosh, A. K.; Mathivanan, P.; Cappiello, J. *Tetrahedron: Asymmetry* **1998**, *9*, 1. (b) Helmchen, G.; Pfaltz, A. *Acc. Chem. Res.* **2000**, *33*, 336. (c) Sutcliffe, O. B.; Bryce, M. R. *Tetrahedron: Asymmetry* **2003**, *14*, 2297.

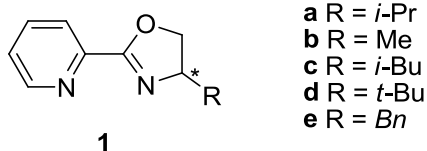
<sup>2</sup> Brunner, H.; Obermann, U.; Wimmer, P. *J. Organomet. Chem.* **1986**, *316*, C1.

preference for a specific geometry and reactivity. Many pioneering studies have been undertaken in order to understand how exactly reactions are affected by this.<sup>3</sup> Since a reaction can be steered by influencing of the initial state, transition state or final state of the metal complex involved, ligands that enforce a well-defined bite angle can be used to induce distortions of certain geometries. Not only this will have impact on activity and selectivity of a catalytic reaction, but even alternative reaction pathways can become accessible. Already in the late 1970s Hoffmann calculated that in the transition state of an insertion reaction of palladium-bis(phosphine) complexes the bite angle P-Pd-P is larger than that in the starting complex.<sup>4</sup>

### 2.1.1 Mono(oxazolines)

#### Mono(oxazolines) N,N-Ligands

The first example of ligand with two nitrogen donor atoms **1** for catalytic applications appeared in 1986 with a success in Rhodium(I)-catalyzed hydrosilylation.<sup>2</sup> Since then, many modifications have been successfully used in a wide range of reactivity.

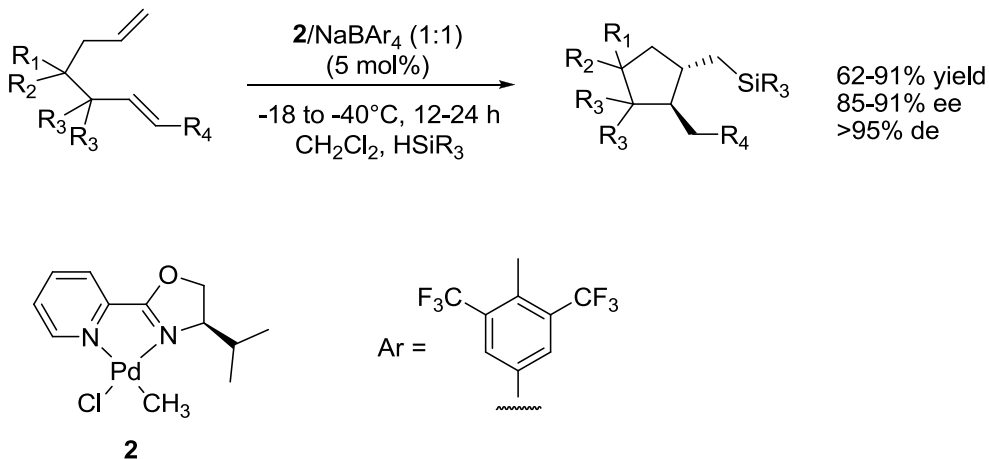


Widenhoefer has reported the first examples of the asymmetric formation of functionalized carbocycles by the cyclization/hydrosilylation of functionalized 1,6-

<sup>3</sup> (a) S. Otsuka, *J. Organomet. Chem.* **1980**, *200*, 191; (b) J. J. Low, W. A. Goddard, *J. Am. Chem. Soc.* **1984**, *106*, 6928; (c) P. Hofmann, H. Heiss, G. Müller, *Z. Naturforsch. B.* **1987**, *42*, 395; (d) P. Dierkes, P. W. N. M. van Leeuwen, *J. Chem. Soc. Dalton Trans.* **1999**, 1519; (e) Z. Freixa, P. W. N. M. van Leeuwen, *Dalton Trans.* **2003**, 1890; (f) R. Fazaeli, A. Ariaifard, S. Jamshidi, E. S. Tabatabaie, K. A. Pishro, *J. Organomet. Chem.* **2007**, *692*, 3984; (g) V. P. Ananikov, D. G. Musaev, K. Morokuma, *Eur. J. Inorg. Chem.* **2007**, 5390.

<sup>4</sup> D. L. Thorn, R. Hoffmann. *J. Am. Chem. Soc.*, **1978**, *100*, 2079.

dienes using palladium complexes of the pyridinyl-oxazoline ligands **1a-d** (Scheme 2.1).<sup>5</sup> It was found that the palladium complex **2** of the ligand **1a** was suitable for a wide range of substrates as diesters, diols and dienes with various trialkylsilanes.



**Scheme 2.1**

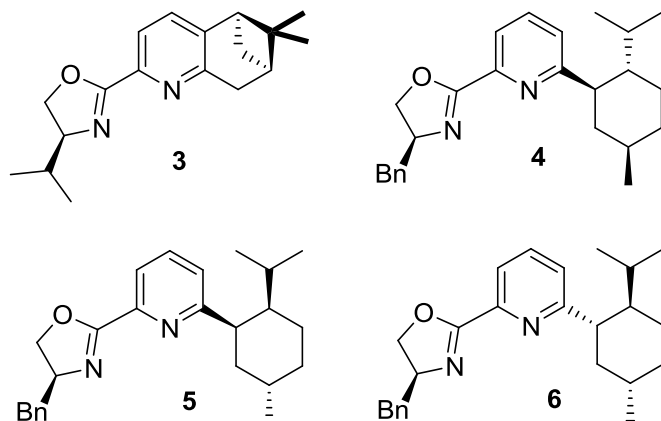
Studies on the nature of the complexes have been done using ruthenium salts and ligands **1**; Davies found that ((mesitylene)RuCl ((*S*)-**1**)[SbF<sub>6</sub>]) exists as single diastereomer and catalyzes Diels-Alder reactions with high selectivity.<sup>6</sup>

Ligands having optically active substituents at the 2- and 6-positions of the pyridinic ring were introduced to study the effect of bulky groups in proximity of the coordination site. Ligands **3-6** were tested in the rhodium-catalyzed hydrosylation of acetophenone with diphenylsilane.<sup>7</sup> Product **3** gave higher selectivity compared to ligand **1a** (80% vs. 63% ee) but the menthyl-substituted ligands **4-6** gave very low levels of selectivity compared to **1e**, which may be a result of the inability of these molecules to coordinate the metal due to the high steric hindrance.

<sup>5</sup> (a) Perch, N. S.; Widenhofer, R. A. *J. Am. Chem. Soc.* **1999**, *121*, 6960. (b) Perch, N. S.; Pei, T.; Widenhofer, R. A. *J. Org. Chem.* **2000**, *65*, 3836. (c) Pei, T.; Widenhofer, R. A. *J. Org. Chem.* **2001**, *66*, 7639.

<sup>6</sup> (a) Davenport, A. J.; Davies, D. L.; Fawcett, J.; Garratt, S. A.; Russell, D. R. *J. Chem. Soc., Dalton Trans.* **2000**, 4432. (b) Davies, D. L.; Fawcett, J.; Garratt, S. A.; Russell, D. R. *Chem. Commun.* **1997**, 1351.

<sup>7</sup> Brunner, H.; Stořrko, R.; Nuber, B. *Tetrahedron: Asymmetry* **1998**, *9*, 407.

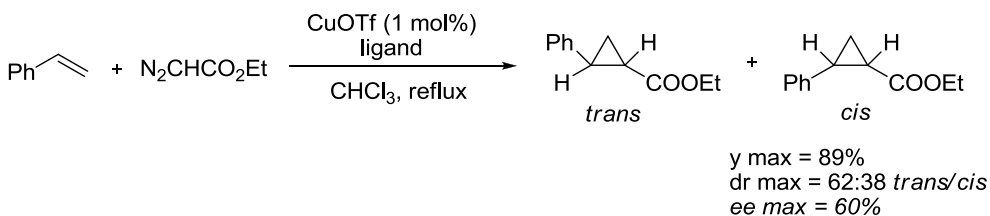
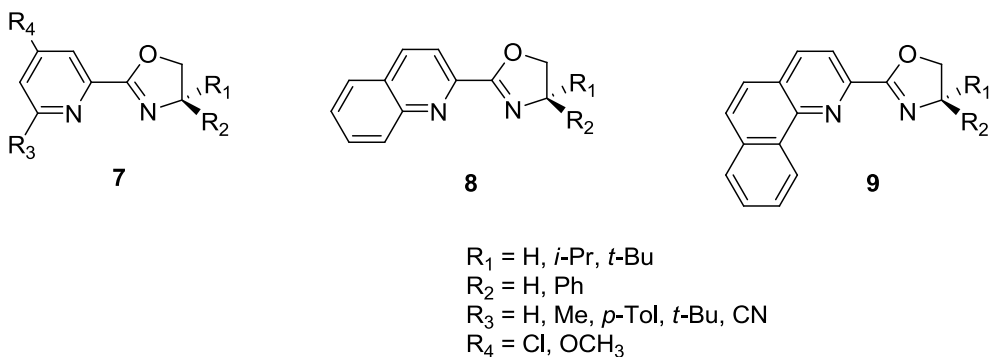


The role of steric and electronic effects on pyridinyl-oxazoline ligand was investigated by the use of a library of ligands **7-9** in the Palladium-catalyzed asymmetric alkylation of 1,3-diphenyl-2-propenyl acetate with dimethyl malonate.<sup>8</sup> The examination of catalytic results revealed that the enantioselectivity increased with increasing size of oxazoline substituent and with the introduction of electron-donating groups at the 4-position of the pyridine. Ligand **7** ( $R_1 = t\text{-Bu}$ ,  $R_3 = \text{Me}$ , and  $R_2, R_4 = \text{H}$ ) proved to be the most selective (92% ee) whereas ligands with an electron-withdrawing chloro group afforded low-rate reaction with selectivity compared to unsubstituted pyridinic rings.

Ligands **7-9** were also screened in the Cu(I)-catalyzed cyclopropanation of styrene with ethyl diazoacetate (Scheme 2.2).<sup>9</sup> The results showed a trend completely comparable with the previous reactivity where enantioselectivity increases with the increase of steric bulk on the oxazoline even if in this case the effect of electro-withdrawing groups seemed to be less important.

<sup>8</sup> Chelucci, G.; Medici, S.; Saba, A. *Tetrahedron: Asymmetry* **1999**, *10*, 543. Chelucci, G.; Deriu, S. P.; Saba, A.; Valenti, R. *Tetrahedron: Asymmetry* **1999**, *10*, 1457.

<sup>9</sup> Chelucci, G.; Sanna, M. G.; Gladiali, S. *Tetrahedron* **2000**, 2889.

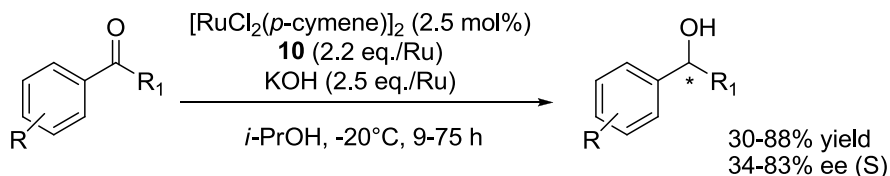
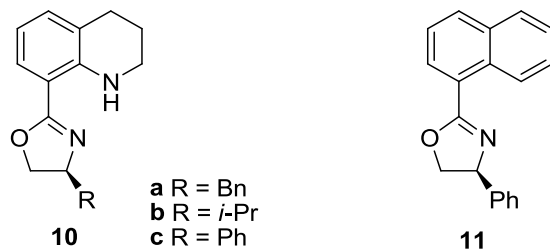


**Scheme 2.2**

In 2002 Zhou reported the synthesis of the tetrahydroquinolinic ligands **10** and their application in ruthenium-catalyzed asymmetric transfer hydrogenation of aromatic ketones.<sup>10</sup> The aim of this study was to combine the selectivity induced by the ligand's framework and the key role of the NH group in the mechanism of transfer hydrogenation (Scheme 2.3).<sup>11</sup> The effect was demonstrated by results of ligand **10c** compared with analogous ligand **11** (73% vs. 25% ee).

<sup>10</sup> Zhou, Y.-B.; Tang, F.-Y.; Xu, H.-D.; Wu, X.-Y.; Ma, J.-A.; Zhou, Q.-L. *Tetrahedron: Asymmetry* **2002**, *13*, 469.

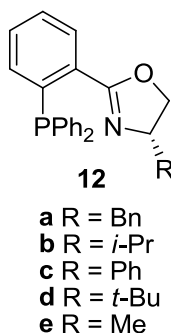
<sup>11</sup> (a) Haack, K.-J.; Hashiguchi, S.; Fujii, A.; Ikariya, T.; Noyori, R. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 285. (b) Alonso, D. A.; Brandt, P.; Nordin, S. J. M.; Andersson, P. G. *J. Am. Chem. Soc.* **1999**, *121*, 9580. (c) Casey, C. P.; Johnson, J. B. *J. Org. Chem.* **2003**, *68*, 1998.



**Scheme 2.3**

### Mono(oxazolines) N,P-Ligands

This class of ligands has been applied over the years with great success in diverse range of asymmetric reactions. The first phosphinooxazoline **12** was introduced by Pfaltz in 1993 as efficient ligand for allylic alkylation<sup>12</sup> but the ease of accessibility of these molecules from readily available starting materials has led to the development of a wide array of phosphinooxazoline ligands similar to **12**.

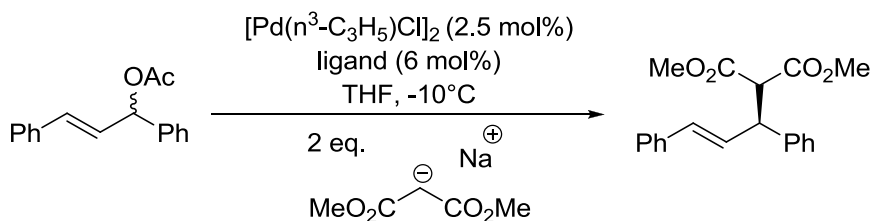
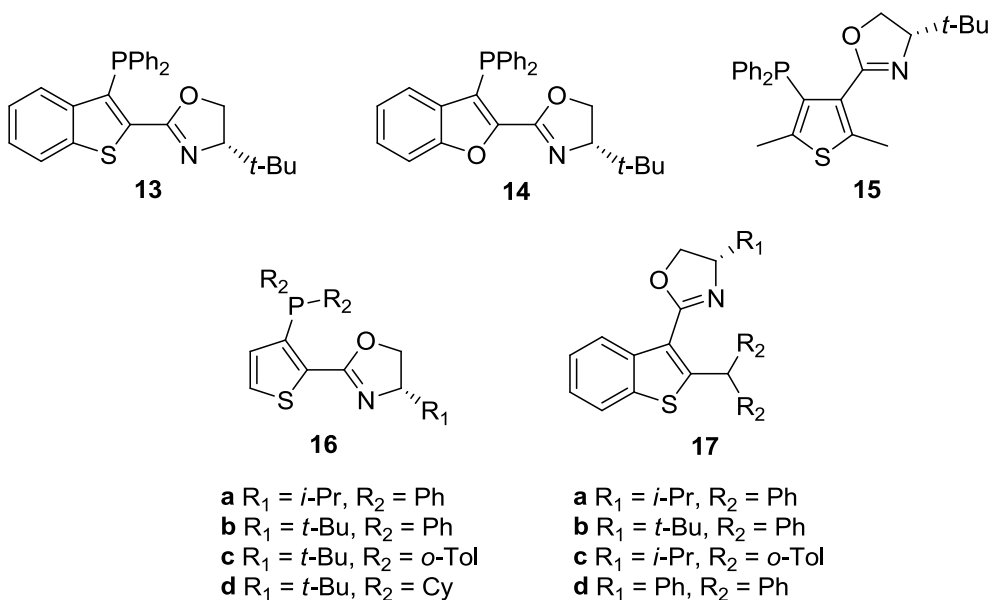


<sup>12</sup> (a) Matt, P.; Pfaltz, A. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 566. (b) Sprinz, J.; Helmchen, G. *Tetrahedron Lett.* **1993**, *34*, 1769. (c) Dawson, G. J.; Frost, C. G.; Williams, S. J. *Tetrahedron Lett.* **1993**, *34*, 3149.



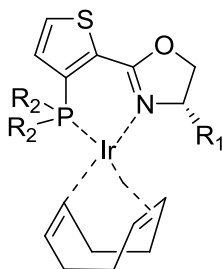
Tietze applied a large library of benzothiophene, thiophene and benzofuran phosphinoxazoline ligands **13-17** in palladium-catalyzed alkylation of 1,3-diphenyl-2-propenyl acetate with sodium dimethyl malonate (Scheme 2.4)<sup>13</sup> with high yields and selectivity.

Thiophene moiety has been used also by Cozzi in the development of ligands **18** and **19** which proved to be highly active in the iridium-catalyzed asymmetric hydrogenation of olefins and imines.<sup>14</sup>



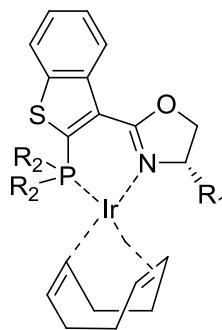
<sup>13</sup> Tietze, L. F.; Lohmann, J. K. *Synlett* **2002**, 2083.

<sup>14</sup> Cozzi, P. G.; Menges, F.; Kaiser, S. *Synlett* **2003**, 833.



**18**

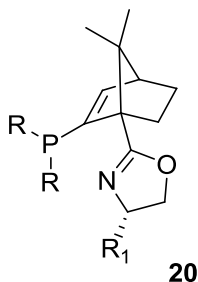
- a R<sub>1</sub> = *i*-Pr, R<sub>2</sub> = Ph
- b R<sub>1</sub> = *t*-Bu, R<sub>2</sub> = Ph
- c R<sub>1</sub> = *t*-Bu, R<sub>2</sub> = *o*-Tol
- d R<sub>1</sub> = *t*-Bu, R<sub>2</sub> = Cy



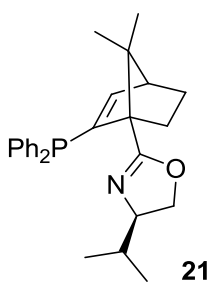
**19**

- a R<sub>1</sub> = *i*-Pr, R<sub>2</sub> = Ph
- b R<sub>1</sub> = *t*-Bu, R<sub>2</sub> = Ph
- c R<sub>1</sub> = *i*-Pr, R<sub>2</sub> = *o*-Tol
- d R<sub>1</sub> = Ph, R<sub>2</sub> = Ph

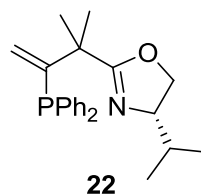
The role of the rigidity of the linker between N and P coordination atoms was investigated by Gilbertson with the development of chiral phosphinoxazolines **20** and **21** based on (1*S*)-(+)-ketopininc acid and their application in the asymmetric palladium-catalyzed Heck reaction<sup>15</sup>. The two diastereomers **20b** and **21** indicated that the asymmetry of the reaction is induced by the chirality of the oxazoline, however, the low enantioselectivity obtained by the corresponding acyclic analogue **22** highlighted the importance of the rigid bicyclic system for high values of enantioselection.



**20**



**21**

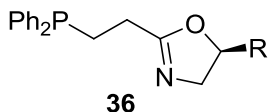


**22**

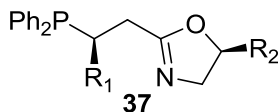
- a R<sub>1</sub> = *t*-Bu, R = Ph
- b R<sub>1</sub> = *i*-Pr, R = Ph
- c R<sub>1</sub> = Ph, R = Ph
- d R<sub>1</sub> = *t*-Bu, R = Cy

<sup>15</sup> Gilbertson, S. R.; Fu, Z. *Org. Lett.* **2001**, 3, 161.

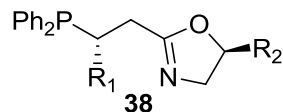
Alkyl chains were also used as linking motif and in 1998 Gilbertson reported the synthesis of ligands **23-25** with both one and two stereocenters and their application in allylic alkylations.<sup>16</sup> In the benchmark palladium-catalyzed alkylation of 1-3-diphenyl-2-propenyl acetate the introduction of a second stereocenter enhanced the asymmetric induction, attesting the effective importance of the linker's rigidity.



- a R = Me
- b R = Bn
- c R = *i*-Pr
- d R = Ph



- a R<sub>1</sub> = Me, R<sub>2</sub> = *i*-Pr
- b R<sub>1</sub> = Ph, R<sub>2</sub> = Bn
- c R<sub>1</sub> = Ph, R<sub>2</sub> = *i*-Pr
- d R<sub>1</sub> = Ph, R<sub>2</sub> = Ph
- e R<sub>1</sub> = Ph, R<sub>2</sub> = *t*-Bu



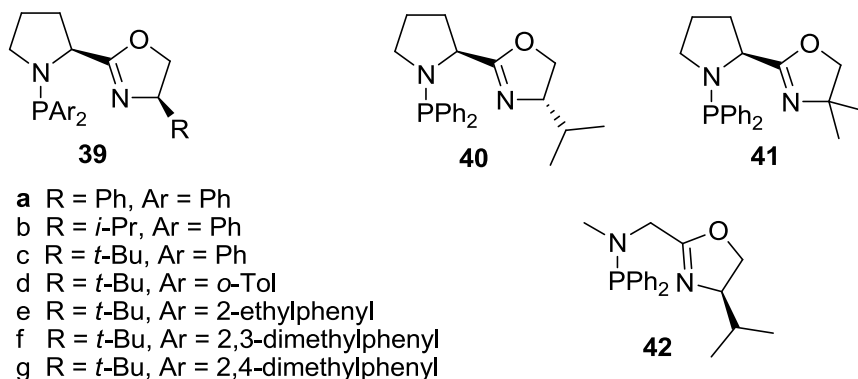
- a R<sub>1</sub> = Me, R<sub>2</sub> = *i*-Pr
- b R<sub>1</sub> = Ph, R<sub>2</sub> = Bn
- c R<sub>1</sub> = Ph, R<sub>2</sub> = *i*-Pr
- d R<sub>1</sub> = Ph, R<sub>2</sub> = Ph
- e R<sub>1</sub> = Ph, R<sub>2</sub> = *t*-Bu

Interesting studies in this field were undertaken by Gilbertson and coworkers who synthesized ligands **39-42** to permit to study both the importance of the stereocenters in the linker and the activity of diarylphosphino groups directly bonded to a nitrogen atom. The ligands were proline-based and tested in palladium-catalyzed asymmetric alkylation and amination<sup>17</sup> and in the iridium-catalyzed enantioselective hydrogenation of aromatic olefins.<sup>18</sup> The influence of the stereogenic proline in the asymmetric induction was demonstrated by the much lower ee achieved with the structurally similar ligand **42** which lacks the rigidity of the pyrrolidine ring.

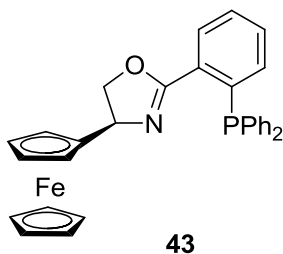
<sup>16</sup> Gilbertson, S. R.; Chang, C.-W. T. *J. Org. Chem.* **1998**, *63*, 8424.

<sup>17</sup> Xu, G.; Gilbertson, S. R. *Tetrahedron Lett.* **2002**, *43*, 2811.

<sup>18</sup> Xu, G.; Gilbertson, S. R. *Tetrahedron Lett.* **2002**, *44*, 953.



A characteristic variant of ligand **1** with a ferrocene substituent at the 4-position of the oxazoline was introduced by Patti. The ligand **43** was applied in the Palladium-catalyzed allylic alkylation with good results<sup>19</sup>. Following this route Moyano reported an alternative synthesis of the enantiomeric ligand (*S*)-**43** and the formation of a palladium-allyl complex  $[(\text{Pd}(\eta^3\text{-C}_3\text{H}_5)\text{-51})\text{PF}_6]$  affording enantioselectivity up to 99.6% although with low catalytic activity.<sup>20</sup>



Binaphthyl moiety is one the most largely used backbone for the synthesis of chiral ligands and over the years it has been used also for the development of new classes of phosphino-oxazolines.

Ligands **70**, with an axial chirality, have been used independently by Hayashi<sup>21</sup> and Ikeda<sup>22</sup> for the palladium-catalyzed alkylation of 1,3-diphenyl-2-propenyl acetate

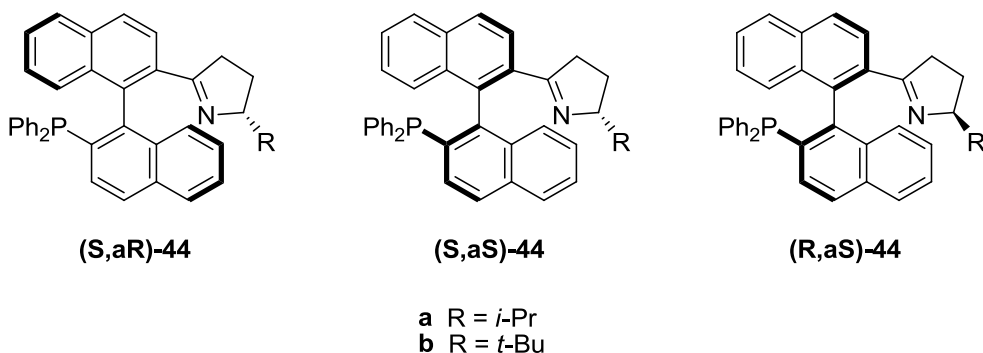
<sup>19</sup> Patti, A.; Lotz, M.; Knochel, P. *Tetrahedron: Asymmetry* **2001**, *12*, 3375.

<sup>20</sup> Moreno, R. M.; Bueno, A.; Moyano, A. *J. Organomet. Chem.* **2002**, *660*, 62.

<sup>21</sup> Ogasawara, M.; Yoshida, K.; Kamei, H.; Kato, K.; Uozumi, Y.; Hayashi, T. *Tetrahedron: Asymmetry* **1998**, *9*, 1779.

<sup>22</sup> Imai, Y.; Zhang, W.; Kida, T.; Nakatsuji, Y.; Ikeda, I. *Tetrahedron Lett.* **1998**, *39*, 4343.

with dimethyl malonate; the best results was achieved by Ikeda using (S,aR)-**44b**. The most important feature of this work is the opposite enantioselectivity obtained by the two diastereomers (S,aR)-**44a** and (S,aS)-**44a** which indicates that the chiral binaphthyl skeleton is the more influential stereogenic unit in the structure.



One of the few examples of a highly enantioselective rhodium-catalyzed allylic alkylation was instead reported by Hayashi, which obtained high enantio- and regioselectivities using ligand **44**.<sup>23</sup>

### Mono(oxazolines) N,O-Ligands

Metal complexes bearing 2-(oxazoliny)phenolato ligands have been used in a wide range of reactivity such as Baeyer-Villiger oxidations,<sup>24</sup> cyclopropanations,<sup>25</sup> allylic functionalizations,<sup>26</sup> and C-C bond formations.<sup>27</sup>

In 2001 Feng reported the synthesis of ligands **45** and their application in titanium-catalyzed oxidation of prochiral sulfides to chiral sulfoxides (Scheme 2.5)<sup>28</sup> with

<sup>23</sup> Hayashi, T.; Okada, A.; Suzuka, T.; Kawatsura, M. *Org. Lett.* **2003**, 5, 1713.

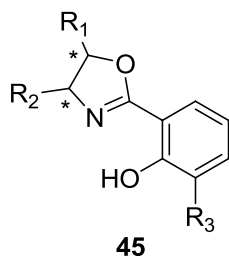
<sup>24</sup> (a) Bolm, C.; Schlingloff, G.; Weickhardt, K. *Angew. Chem., Int. Ed. Engl.* **1994**, 33, 1848. (b) Bolm, C.; Schlingloff, G.; Weickhardt, K. *Tetrahedron Lett.* **1993**, 4, 3405. (c) Bolm, C.; Schlingloff, G. *Chem. Commun.* **1995**, 1247.

<sup>25</sup> Brunner, H.; Berghofer, J. *J. Organomet. Chem.* **1995**, 501, 161.

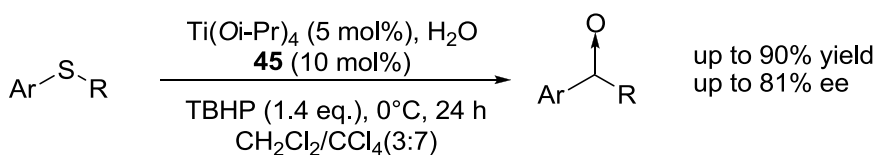
<sup>26</sup> Yang, H.; Khan, M. A.; Nicholas, K. M. *Organometallics* **1993**, 12, 3485.

<sup>27</sup> Cozzi, P. G.; Floriani, C. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2357.

good results. The same ligands were also tested in the copper-catalyzed oxidation of 2-phenylcyclohexenone with lower selectivity.<sup>29</sup>



- (4S,5R)-**a** R<sub>1</sub> = R<sub>2</sub> = Ph, R<sub>3</sub> = *t*-Bu  
 (4S,5S)-**b** R<sub>1</sub> = R<sub>2</sub> = Ph, R<sub>3</sub> = *t*-Bu  
 (4S,5R)-**c** R<sub>1</sub> = R<sub>2</sub> = Ph, R<sub>3</sub> = H  
 (4S,5S)-**d** R<sub>1</sub> = R<sub>2</sub> = Ph, R<sub>3</sub> = H  
 (4S)-**e** R<sub>1</sub> = H, R<sub>2</sub> = Ph, R<sub>3</sub> = *t*-Bu  
 (4S)-**f** R<sub>1</sub> = H, R<sub>2</sub> = PhCH<sub>2</sub>, R<sub>3</sub> = *t*-Bu



**Scheme 2.5**

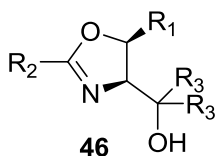
Hydroxymethyl oxazolines **46** and **47** were introduced respectively by Williams<sup>30</sup> and Braga<sup>31</sup> as efficient ligands for the asymmetric addition of diethylzinc to aldehydes. The best results were achieved by Braga in the addition of diethylzinc to substituted benzaldehydes with the less sterically hindered derivative **47a**.

<sup>28</sup> Peng, Y.; Feng, X.; Cui, X.; Jiang, Y.; Chang, A. S. C. *Synth. Commun.* **2001**, *31*, 2287.

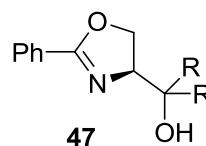
<sup>29</sup> Peng, Y.; Feng, X.; Yu, K.; Li, Z.; Jiang, Y.; Yeung, C.-H. *J. Organomet. Chem.* **2001**, *619*, 204.

<sup>30</sup> (a) Allen, J. V.; Frost, C. G.; Williams, J. M. J. *Tetrahedron: Asymmetry* **1993**, *4*, 649. (b) Allen, J. V.; Williams, J. M. J. *Tetrahedron: Asymmetry* **1994**, *5*, 277.

<sup>31</sup> Braga, A. L.; Rubim, R. M.; Schrekker, H. S.; Wessjohann, L. A.; de Bolster, M. W. G.; Zeni, G.; Sehnem, J. A. *Tetrahedron: Asymmetry* **2003**, *14*, 3291.



- a** R<sub>1</sub> = H, R<sub>2</sub> = Me, R<sub>3</sub> = Me  
**b** R<sub>1</sub> = H, R<sub>2</sub> = Me, R<sub>3</sub> = Ph  
**c** R<sub>1</sub> = Ph, R<sub>2</sub> = Me, R<sub>3</sub> = H  
**d** R<sub>1</sub> = Ph, R<sub>2</sub> = Ph, R<sub>3</sub> = H  
**e** R<sub>1</sub> = Ph, R<sub>2</sub> = thiophene, R<sub>3</sub> = H

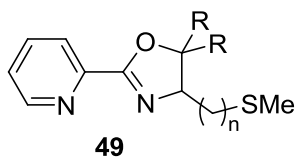
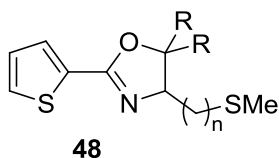


- a** R = H  
**b** R = Me  
**c** R = Et  
**d** R = Ph

### Mono(oxazolines) N,S-Ligands

This family of oxazolines, having an auxiliary sulfur donor atom, was developed first by Williams in 1993 as efficient ligand for a benchmark palladium-catalyzed alkylation of 1,3-diphenyl-2-propenyl acetate with dimethyl malonate with good selectivity.<sup>32</sup>

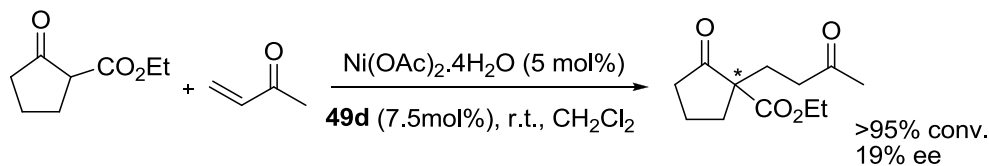
A few years later, Christoffers synthesized tridentate ligands **48** and **49** having heteroaryl and thioether donor groups and screened them in the asymmetric Michael reaction of  $\beta$ -keto ester with methyl vinyl ketone using several metal salts. Best results were achieved with nickel(II) acetate and ligand **49d** (Scheme 2.6).<sup>33</sup>



- a** R = H, n = 1  
**b** R = Ph, n = 1  
**c** R = H, n = 2  
**d** R = Ph, n = 2

<sup>32</sup> (a) Allen, J. V.; Coote, S. J.; Dawson, G. J.; Frost, C. G.; Martin, C. J.; Williams, J. M. J. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2065. (b) Dawson, G. J.; Frost, C. G.; Martin, C. J.; Williams, J. M. J. *Tetrahedron Lett.* **1993**, *34*, 7793. (c) Frost, C. G.; Williams, J. M. J. *Tetrahedron Lett.* **1993**, *34*, 2015.

<sup>33</sup> Christoffers, J.; Mann, A.; Pickardt, J. *Tetrahedron* **1999**, *55*, 5377.



**Scheme 2.6**

### 2.1.2 Bis(oxazolines)

In 1986, Pfaltz and co-workers developed semicorrins **50**,<sup>34</sup> a new class of bidentate ligands having a rigid scaffold defined by the planar  $\pi$  system and the two heterocycles. This feature makes them attractive as ligand for asymmetric metal catalysis.

These complexes showed a very high enantioselectivity in copper-catalyzed asymmetric cyclopropanation of olefins<sup>35</sup> and the cobalt-catalyzed conjugate addition of  $\alpha,\beta$ -unsaturated esters and amides.<sup>36</sup>

The electron-rich vinylogous amidine group imparts an electron donating character to the ligands, reducing the electrophilicity of the metal center. For some reactivity, is preferable to have a weak electron donating character or even a  $\pi$ -acceptor ligand.<sup>37</sup> In order to decrease this effect, neutral analogues of the semicorrins **50**, (bis)oxazolines **51** and other ligands such as bi-oxazolines and aza-semicorrins were independently developed by several groups in the early 90's.<sup>38</sup> These bis(oxazolines), commonly called BOX, were then successfully applied with excellent results to a wide range of reactions including cyclopropanation of olefins and Diels-Alder reactions.

<sup>34</sup> Fritschi, H.; Leutenegger, U.; Pfaltz, A. *Angew. Chem. Int. Ed.* **1986**, *25*, 1005.

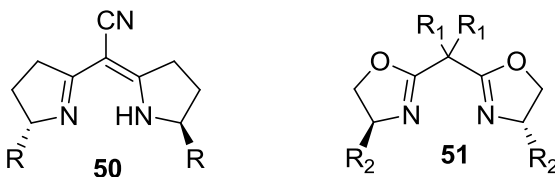
<sup>35</sup> Pfaltz, A. *Acc. Chem. Res.* **1993**, *26*, 339.

<sup>36</sup> (a) Leutenegger, U.; Madin, A.; Pfaltz, A. *Angew. Chem. Int. Ed.* **1989**, *28*, 60. (b) von Matt, P.; Pfaltz, A. *Tetrahedron: Asymmetry* **1991**, *2*, 691.

<sup>37</sup> Leutenegger, U.; Umbricht, G.; Fahrni, C.; von Matt, P.; Pfaltz, A. *Tetrahedron* **1992**, *48*, 2143.

<sup>38</sup> (a) Evans, D. A.; Woerpel, K. A.; Hinman, M. M.; Faul, M.; M. *J. Am. Chem. Soc.* **1991**, *113*, 726. (b) Corey, E. J.; Imai, N.; Zhang, H.-Y. *J. Am. Chem. Soc.* **1991**, *113*, 728.





Since then, the popularity of these ligands rapidly increased due to two factors: the ease of synthesis and the catalytic activity. Ligands **50** are readily obtained by a simple 2-3 step procedure. In this field a variety of options are available, among which, worth mentioning are Corey's<sup>39</sup>, Masamune's<sup>40</sup> and Evans's.<sup>41</sup> Several hundred BOX ligands have been developed so far and used in various reactions such as Diels-Alder, aziridination, cyclopropanation, allylic substitution, Mukayama, Michael, and many others.<sup>42</sup>

### **(Bis)oxazolines with a stereocenter**

(Bis)oxazolines with a carbon spacer between the two oxazolinic rings are the most frequently used, affording high selectivity in a wide range of metal-catalyzed reactions. Modification on the nature, size and flexibility of the linker and substituents on the two oxazolines, have led to the development of numerous chiral ligands.

In 1998 Desimoni developed ligand **53**, having a bulky 2-naphthyl group at 4-position of the oxazolines, in an attempt to increase the selectivity of **52a**. The aim was achieved in the Lewis acid-catalyzed Diels-Alder reaction of cyclopentadiene

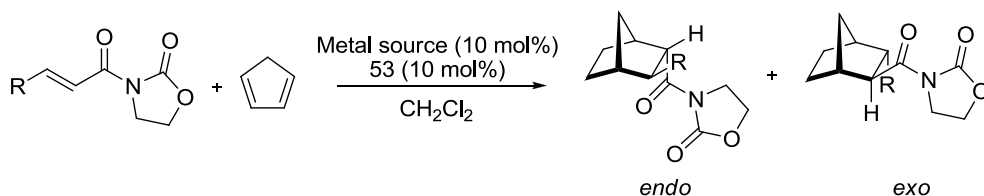
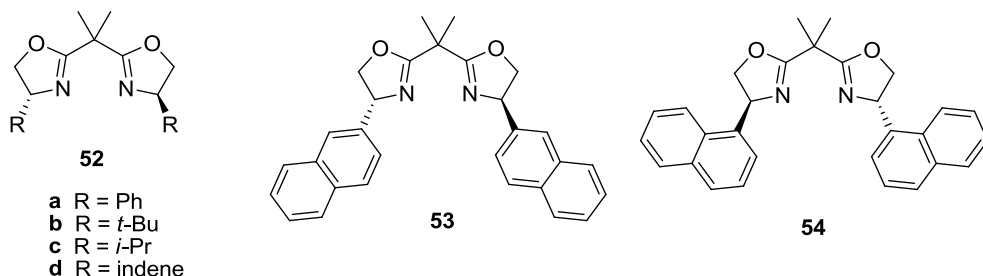
<sup>39</sup> Corey, E. J.; Imai, N.; Zhang, H.-Y. *J. Am. Chem. Soc.* **1991**, *113*, 728.

<sup>40</sup> (a) Lowentahl, R. E.; Abiko, A.; Masamune, S. *Tetrahedron Lett.* **1990**, *31*, 6005. (b) Lowentahl, R.E.; Masamune, S. *Tetrahedron Lett.* **1991**, *32*, 7373. (c) Desimoni, G.; Faita, G.; Mella, M. *Tetrahedron* **1996**, *52*, 13649.

<sup>41</sup> Evans, D. A.; Woerpel, K. A.; Scott, M. J. *Angew. Chem. Int. Ed.* **1992**, *31*, 430.

<sup>42</sup> Desimoni, G.; Faita, G.; Jørgensen, K. A. *Chem. Rev.* **2006**, *106*, 3561.

and N-alkenoyl-oxazolidin-2-ones (Scheme 2.7) using different different metal salts.<sup>43</sup>



**Scheme 2.7**

Product **54** was compared to ligands **52** by Rutjes using Cu(II) complexes in the Mukaiyama aldol reactions and Diels-Alder reactions obtaining enantioselections higher than that obtained with **52a** but significantly lower than those achieved with *tert*-butyl-substituted ligand **52b**.<sup>44</sup>

In 2010 Fu performed the use of **52a** in the nickel(II)-catalyzed asymmetric Kumada reaction of a wide variety of  $\alpha$ -bromoketones<sup>45</sup> with high enantioselectivity and more recently, Lu reported the use of Ligand **52c** as efficient ligand for copper(II)-catalyzed enantioselective Friedel-Crafts reactions of substituted indoles with trifluoethylidene malonates.<sup>46</sup>

<sup>43</sup> Crosignani, S.; Desimoni, G.; Faita, G.; Righetti, P. *Tetrahedron* **1998**, *54*, 15721.

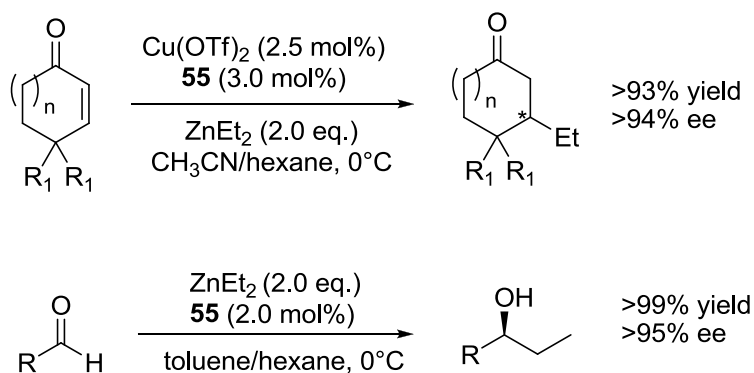
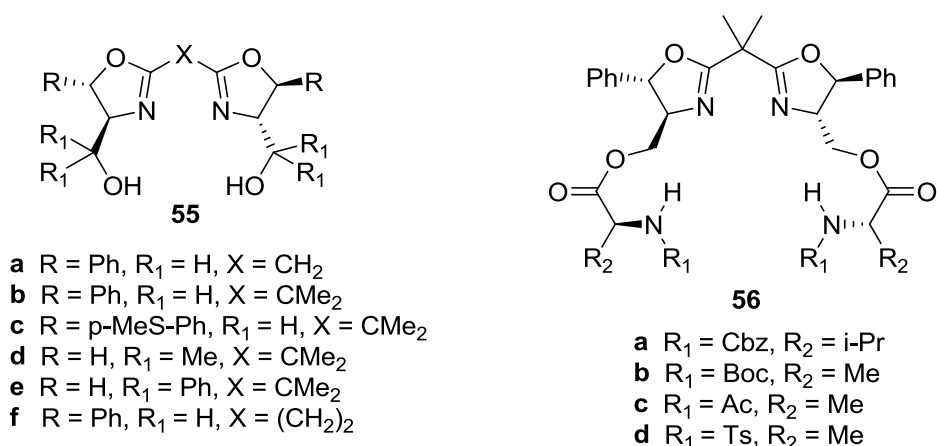
<sup>44</sup> van Lingen, H. L.; van de Mortel, J. K. W.; Hekking, K. F. W.; van Delft, F. L.; Sonke, T.; Rutjes, F. P. J. T. *Eur. J. Org. Chem.* **2003**, 317.

<sup>45</sup> Lou, S.; Fu, G. C. *J. Am. Chem. Soc.* **2010**, *132*, 1264.

<sup>46</sup> Wen, L.; Shen, Q.; Wan, X.; Lu, L. *J. Org. Chem.* **2011**, *76*, 2282.

Ligand **52d** has recently been applied by Kim in the asymmetric Friedel-Crafts alkylations of indoles with  $\alpha$ -phosphoric enones with excellent levels of enantioselectivity (up to 98%).<sup>47</sup>

(Bis)oxazolines ligands which possess hydroxy groups at the stereogenic 4-position of the oxazoline ring were deeply studied by Reiser, which developed ligands **55**, suitable for both Copper and Zinc coordination. Ligands were tested in Copper(II)-catalyzed conjugate addition of diethylzinc to cyclic enones and in Asymmetric addition of diethyl zinc to a range of aldehydes with good results (Scheme 2.8).<sup>48</sup>



**Scheme 2.8**

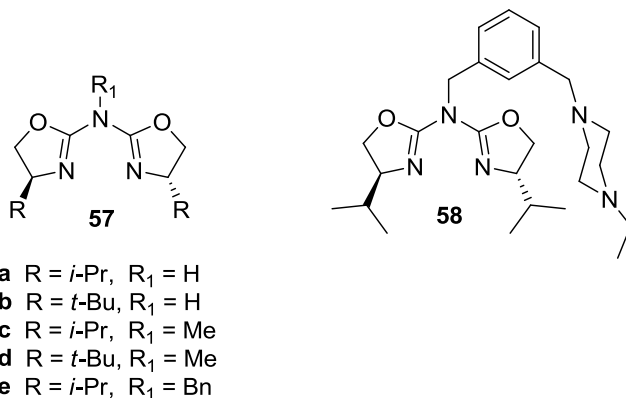
<sup>47</sup> Yang, H. T.; Kim, S. *Org. Lett.* **2007**, *9*, 1983

<sup>48</sup> Schinneri, M.; Seitz, M.; Kaiser, A.; Reiser, O. *Org. Lett.* **2001**, *3*, 4259.

In 2003 Reiser investigated the use of ligands **55** and **56**, which possess secondary binding sites, in the Copper(I)-catalyzed cyclopropanation.<sup>49</sup> In this work, the authors proposed that the hydrogen bond donor groups of the oxazolines 4-substituents are able to form hydrogen bonding with the substrate, controlling the direction of the attack.

An asymmetric version of ligands **52** has been synthesized by Orlandi in 2007. In his approach the two substituted 4-positions on the oxazolines bear different groups,<sup>50</sup> and the ligand was applied to the Cu(II)-catalyzed Mukayama aldol reaction with relatively low levels of selectivity (up to 55% ee).

Reiser reported also an interesting variant of ligands **51** where the central atom, connecting the two oxazolines, was replaced by a nitrogen atom, giving rise at what are called aza-(bis)oxazolines. Ligands **57** were tested in the palladium-catalyzed allylic alkylation and copper catalyzed cyclopropanation with very interesting results.<sup>51</sup>



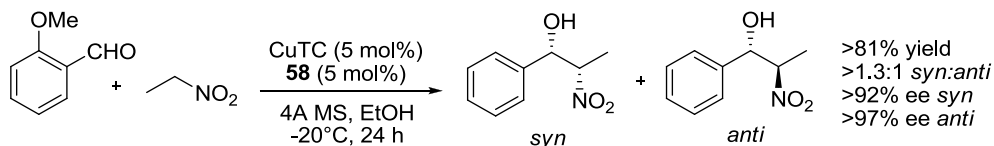
A recent work of Hong has introduced the concept of dual activation in the field of oxazolines. Hong developed a bifunctional aza-(bis)oxazoline **58** in which in addition to the two oxazolinic rings, a 1-benzyl-4-ethylpiperazine group is directly bounded to the nitrogen linker. This additional functionality causes a rate

<sup>49</sup> Schinnerl, M.; Böhmer, C.; Seitz, M.; Reiser, O. *Tetrahedron: Asymmetry* **2003**, *14*, 765.

<sup>50</sup> Orlandi, S.; Benaglia, M.; Dell'Anna, G.; Celentano, G. *J. Organomet. Chem.* **2007**, *692*, 2120.

<sup>51</sup> Glos, M.; Reiser, O. *Org. Lett.* **2000**, *2*, 2045.

acceleration of 2.5 times and an increase of enantioselectivity (compared to the unsubstituted analogue) in the copper-catalyzed Henry reaction (Scheme 2.9).<sup>52</sup>



**Scheme 2.9**

### (Bis)oxazolines with a stereoaxis

Ligands with biphenyl and binaphthyl backbone were the first stereoaxis-containing (bis)oxazolines to be employed in a wide range of asymmetric reactions.<sup>53,54</sup>

Rippert prepared a numerous library of (bis)phenyl analogues **59** and investigated their characteristics in the copper(I)-catalyzed cyclopropanation of styrene with ethyl diazoacetate<sup>55</sup> finding a dependence of the enantioselectivity on the steric hindrance at the 5-position of the oxazoline.

A binaphthyl skeleton was used by Hayashi to prepare ligands **60** and **61** for the application in Palladium(II)-catalyzed Wacker-type cyclizations.<sup>56</sup>

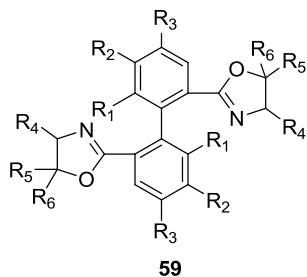
<sup>52</sup> Lang, K.; Park, J.; Hong, S. *J. Org. Chem.* **2010**, *75*, 6424.

<sup>53</sup> (a) Uozumi, Y.; Kyota, H.; Kishi, E.; Kitayama, K.; Hayashi, T. *Tetrahedron: Asymmetry* **1996**, *7*, 1603. (b) Gant, T. G.; Noe, M. C.; Corey, E. J. *Tetrahedron Lett.* **1995**, *36*, 8745. (c) Andrus, M. B.; Asgari, D.; Sclafani, J. A. *J. Org. Chem.* **1997**, *62*, 9365.

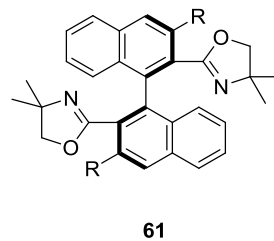
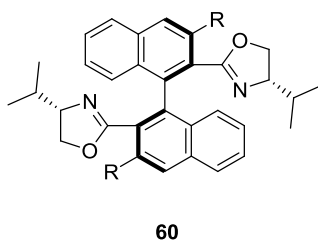
<sup>54</sup> (a) Uozumi, Y.; Kato, K.; Hayashi, T. *J. Am. Chem. Soc.* **1997**, *119*, 5063. (b) Uozumi, Y.; Kato, K.; Hayashi, T. *J. Org. Chem.* **1998**, *63*, 5071.

<sup>55</sup> Rippert, A. *J. Helv. Chim. Acta* **1998**, *81*, 676.

<sup>56</sup> Uozumi, Y.; Kyota, H.; Kato, K.; Ogasawara, M.; Hayashi, T. *J. Org. Chem.* **1999**, *64*, 1620.

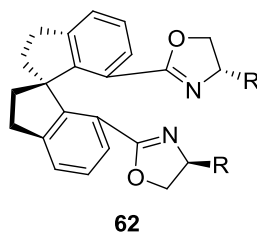


R<sub>1</sub> = Me, OMe, Br  
 R<sub>2</sub> = H, OMe  
 R<sub>3</sub> = H, OMe, Br  
 R<sub>4</sub> = Et, *i*-Pr, Ph, Me, *t*-Bu  
 R<sub>5</sub>, R<sub>6</sub> = H, Ph



**a** R = CO<sub>2</sub>Me  
**b** R = SiMe<sub>3</sub>  
**c** R = CONMe<sub>2</sub>  
**d** R = CHO  
**e** R = I

An interesting class of (bis)oxazolines has been introduced by Sasai in 2004,<sup>57</sup> and later refined by Zhou in the last years. In this area Zhou also reported the synthesis of ligands **62** and their application to the catalytic asymmetric N-H insertion of amines with diazoesters<sup>58</sup> and in the enantioselective insertion of carbenoids into the O-H bonds of phenols.<sup>59</sup> (Scheme 2.10)

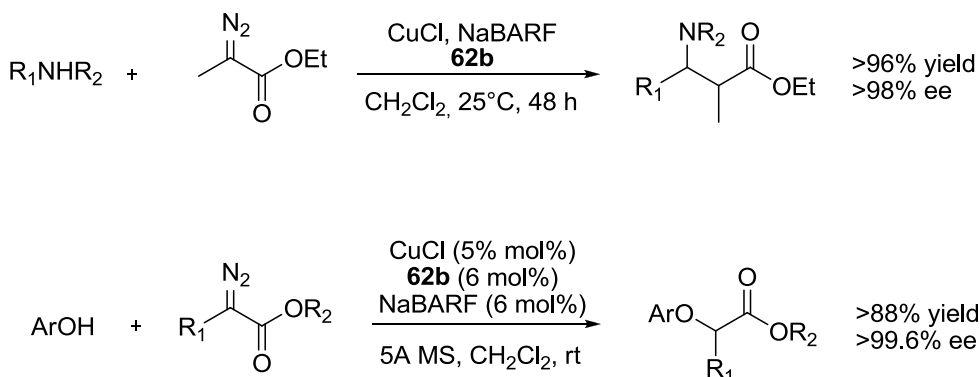


**a** R = *i*-Pr  
**b** R = Ph  
**c** R = Bn  
**d** R = *t*-Bu

<sup>57</sup> Kato, T.; Marubayashi, K.; Takizawa, S.; Sasai, H. *Tetrahedron: Asymmetry* **2004**, *15*, 3693.

<sup>58</sup> (a) Liu, B.; Zhu, S.-F.; Wang, L.-X.; Zhou, Q.-L. *Tetrahedron: Asymmetry* **2006**, *17*, 634. (b) Liu, B.; Zhu, S.-F.; Chen, C.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2007**, *129*, 5834.

<sup>59</sup> Chen, C.; Zhu, S.-F.; Liu, B.; Wang, L.-X.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2007**, *129*, 12616.



**Scheme 2.10**

### Tridentate (bis)oxazolines

The introduction of a donor group into the link between the two oxazolines has led to the development of tridentate (bis)oxazolines ligands. The most important members of this category are ligands having a nitrogen atom in the linker. Other, less important, will not be mentioned here.

“Pybox ligands” **63** are the best-known examples of this class of derivatives, developed first by Nishiyama. They have been used in a wide range of reactivity such as copper(I)-catalyzed oxidation of allylic and benzylic compounds,<sup>60</sup> copper(II)-catalyzed 1,3-dipolar cycloaddition of nitrones,<sup>61</sup> palladium(II)-catalyzed resolution of racemic tosylaziridines,<sup>62</sup> tin(II)- and copper(II)-catalyzed aldol reactions,<sup>63,64</sup> scandium(III)-catalyzed Diels-Alder reaction,<sup>65</sup> scandium(III)-catalyzed and copper(II)-catalyzed Nazarov reaction,<sup>66</sup> and even more.

<sup>60</sup> Schulz, M.; Kluge, R.; Gelalcha, F. G. *Tetrahedron: Asymmetry* **1998**, *9*, 4341.

<sup>61</sup> Jensen, K. B.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **1999**, *64*, 2353.

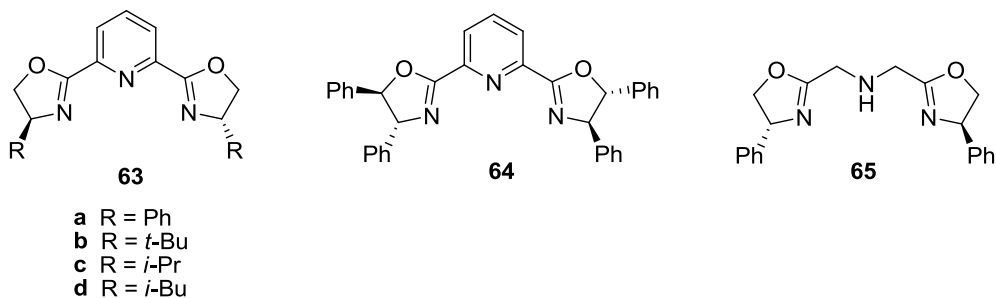
<sup>62</sup> Leung, W.-H.; Mak, W.-L.; Chan, E. Y. Y.; Lam, T. C. H.; Lee, W.-S.; Kwong, H.-L.; Yeung, L.-L. *Synlett* **2002**, 1688.

<sup>63</sup> Evans, D. A.; MacMillan, D. W. C.; Campos, K. R. *J. Am. Chem. Soc.* **1997**, *119*, 10859.

<sup>64</sup> Evans, D. A.; Murry, J. A.; Kozlowski, M. C. *J. Am. Chem. Soc.* **1996**, *118*, 5814.

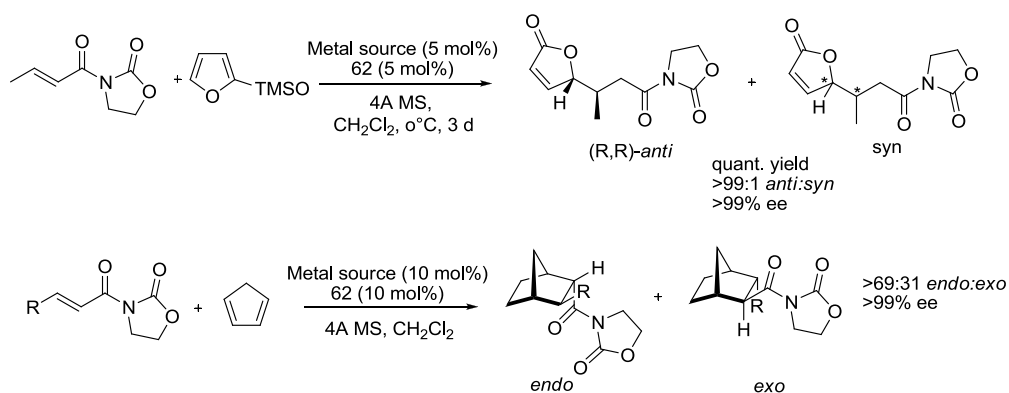
<sup>65</sup> Fukuzawa, S.; Matsuzawa, H.; Metoki, K. *Synlett* **2001**, 709.

<sup>66</sup> Tang, Y., et al. *Angew. Chem. Int. Ed.* **2010**, *49*, 4463.



Tridentate pybox **64** with *trans*-4,5-diphenyl substitution was developed by Desimoni and used in the Mukaiyama-Michael and Diels-Alder reaction.<sup>67,68</sup> In both cases the selectivity proved to be excellent with quantitative yields and enantioselectivity up to 99% (Scheme 2.11).

Zhang applied ligand **65** in the Ru(II)-catalyzed transfer hydrogenation of aromatic ketones<sup>69</sup>, demonstrating the importance of central NH comparing the excellent results of product **65** with the poor selectivity of the N-methylated analogue.



**Scheme 2.11**

<sup>67</sup>Desimoni, G.; Faita, G.; Filipponi, S.; Mella, M.; Zampori, M. G.; Zema, M. *Tetrahedron* **2001**, *57*, 10203.

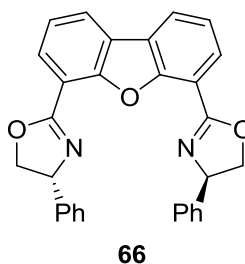
<sup>68</sup>Desimoni, G.; Faita, G.; Guala, M.; Pratelli, C. *Tetrahedron* **2002**, *58*, 2929.

<sup>69</sup>Jiang, Y.; Jiang, Q.; Zhang, X. *J. Am. Chem. Soc.* **1998**, *120*, 3817.



A successful application of **63c** has been performed in the asymmetric nickel-catalyzed Negishi cross-coupling of secondary  $\alpha$ -bromo amides with organozinc reagents<sup>70</sup>, whereas ligand **63a** proved to be suitable by Evans for the use in the Scandium-catalyzed asymmetric Sakurai-Hosomi additions.<sup>71</sup>

Special mention is required for the studies of Willis, who recently reported the development of heterotridentate (bis)oxazoline **66** based on dibenzofuran moiety. The ligand was used in Mannich reaction<sup>72</sup> and in the addition of nitrones to cyclopropanes<sup>73</sup> with excellent enantioselectivity in both cases.



### 2.1.3 Tris(oxazolines)

(Tris)oxazolines play in a marginal area in the world of oxazolines. However some works reported the synthesis of  $C_3$ -symmetric ligands having mentionable results.

Ligands **66** and **67** were developed by Katsuki and their efficiency was used in enantioselective oxidation of cycloalkenes with *tert*-butyl peroxybenzoate<sup>74</sup> and in the copper(II)-catalyzed oxidative desymmetrization of racemic dicyclopentadiene derivatives.<sup>75</sup>

<sup>70</sup> Fischer, C.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 4594.

<sup>71</sup> Evans, D. A.; Aye, Y.; Wu, J. *Org. Lett.* **2006**, *8*, 2071.

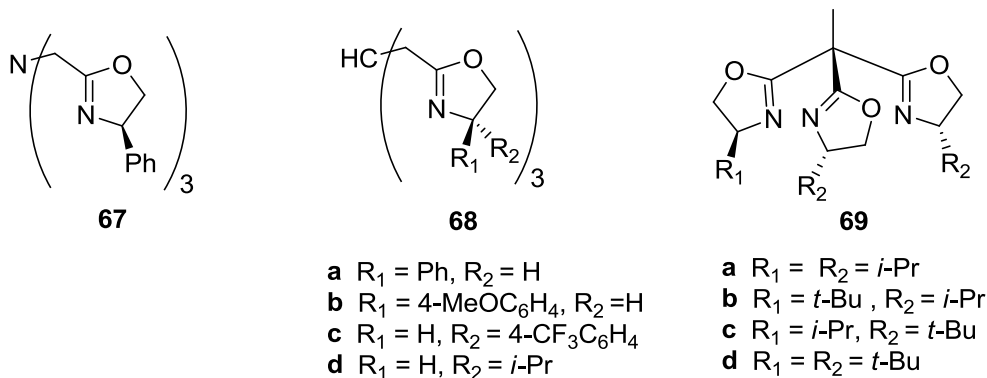
<sup>72</sup> Cutting, G. A.; Stainforth, N. E.; John, M. P.; Kociek-Koehn, G.; Willis, M. C. *J. Am. Chem. Soc.* **2007**, *129*, 10632.

<sup>73</sup> Sibi, M. P.; Ma, Z.; Jasperse, C. P. *J. Am. Chem. Soc.* **2005**, *127*, 16–5764.

<sup>74</sup> Kohmura, Y.; Katsuki, T. *Tetrahedron Lett.* **2000**, *41*, 3941.

<sup>75</sup> Kohmura, Y.; Katsuki, T. *Synlett* **1999**, 1231.

Tripodal (tris)oxazolines **68** have been performed by Gade as ligand suitable for copper(I)-catalyzed asymmetric cyclopropanation of styrene.<sup>76</sup>

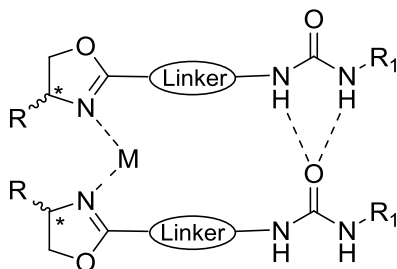


## 2.2 Development and application of the catalytic system

As we discussed in the introduction, the concept of self-assembly of bidentate ligands through hydrogen bonding for combinatorial homogeneous catalysis was recently introduced, and several powerful ligands were described with outstanding reactivity and selectivity. Supramolecular ligands possess, besides the atom(s) coordinating the catalytic metal, additional functionalities capable of non-covalent interactions: mainly hydrogen or coordinative bonds. Hydrogen bond, is arguably the most practical and efficient, among the different kinds of non-covalent interaction that have been used so far. Several efficient and selective catalytic systems based on this strategy have recently been published, though containing exclusively phosphorus based ligands (i.e. phosphines, phosphites, etc).

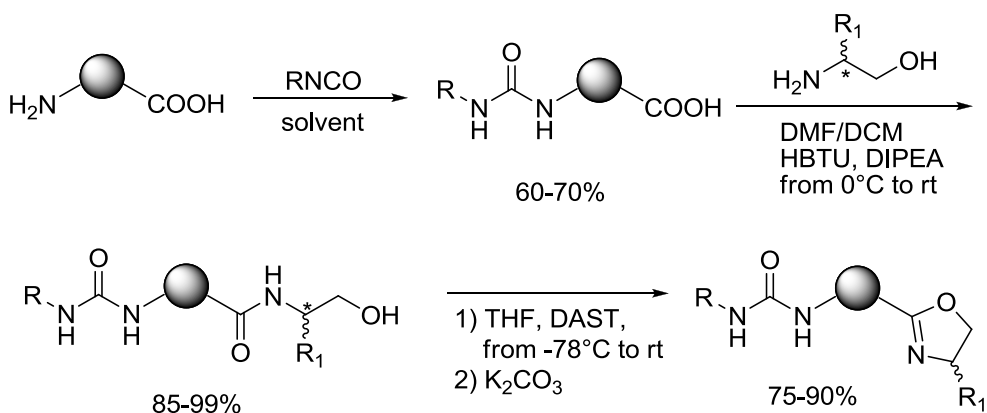
In this chapter we will describe our idea to extend this approach to nitrogen ligands, and in particular to synthesize a new class of supramolecular bis-oxazolines ligands which we called SupraBox. An urea functionality was introduced in the ligand through a linker moiety, to induce the self-assembly of the SupraBox ligands.

<sup>76</sup> Bellemin-Laponnaz, S.; Gade, L. H. *Angew. Chem., Int. Ed. Engl.* **2002**, *41*, 3473.



## 2.2.1 Synthesis of the catalysts

In general terms a class of ligands suitable for a combinatorial exploitation should be accessed in a limited number of steps, through a highly modular synthesis which allows for the creation of a wide diversity from a limited number of building blocks. Our SupraBox ligands possess three possible tunable sites: i) the oxazoline moiety, ii) the linker, iii) the urea substituents which can be coupled in three straightforward synthetic steps involving only two chromatographic purifications (Scheme 2.12).

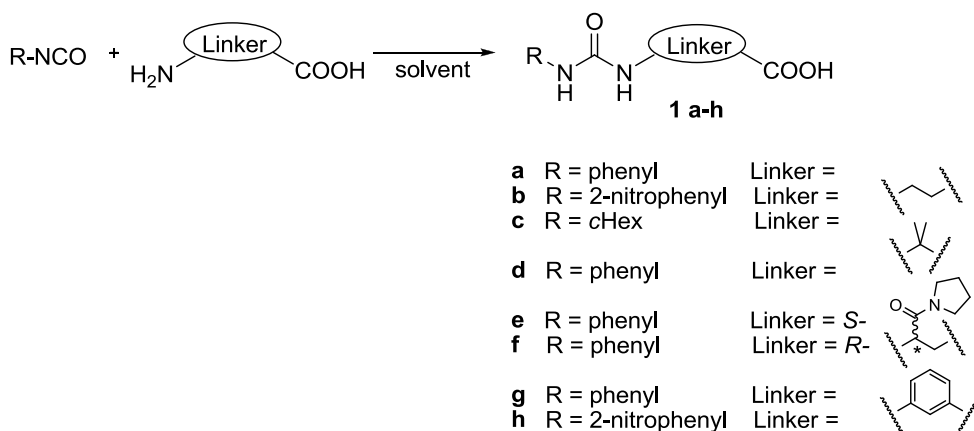


**Scheme 2.12**

Three different isocyanates (phenyl, cyclohexyl and 2-nitrophenyl isocyanate) were included in the screening to vary the H-bond forming properties of the ligands. The formation of the urea is probably the limiting step in terms of total yield of the

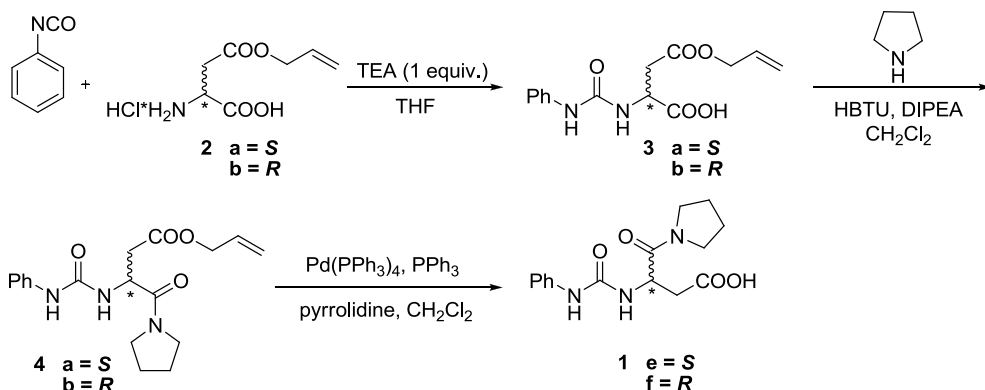
synthesis, the main problem being due to the low solubility of the different amino acids used in the reaction. In general THF proved to be a good solvent even if the solubility of products was not optimal. In one case the almost total insolubility of the 2-amino-isobutyric acid has necessitated the use of a 2M NaOH solution as solvent, anyway leading low yield.

Four different linkers, namely  $\beta$ -alanine, 2-amino-isobutyric acid, L- and D-aspartic acid  $\alpha$ -pyrrolidinamide and 3-aminobenzoic acid, were used to impart different conformational rigidity to the ligands and hence influence the global conformation of the complexes (Scheme 2.13).



**Scheme 2.13**

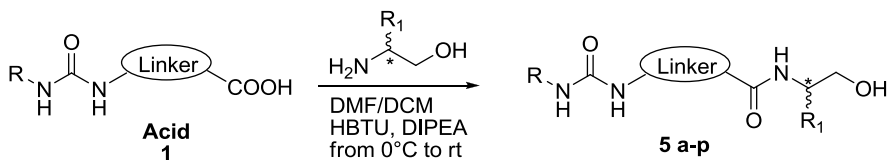
Achiral linkers were readily available commercial products, whereas the chiral linker was synthesized *ad hoc* starting from aspartic acid (Scheme 2.14). In particular, the presence of stereocenters at the  $\alpha$ -position of carboxylic groups (and hence of oxazolines) were deemed dangerous in terms of the stereo-integrity of the final ligand. Oxazolines in fact are known to be susceptible of epimerization during the coupling of the starting carboxylic acid with the amino alcohols and the subsequent cyclization. On the other hand commercial enantiopure  $\beta^3$ -homo amino acids are very expensive and, despite several published synthetic protocols, suffer from difficult availability in multigram quantities.



**Scheme 2.14**

Coupling of the amino alcohols gave no particular problem, using standard procedures. On the other hand, chromatographic purification of the resulting amide was complicated by the use of DIPEA. An acidic work-up would be theoretically sufficient to remove the base, but the tendency of the product to be soluble in aqueous phases made this procedure not recommended.

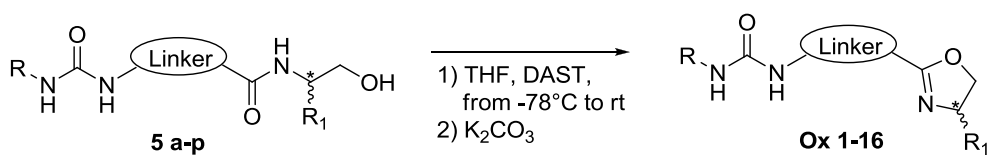
Different substituents on the oxazolinic ring lead obviously to a different chemical environment around the catalyst metal and consequently different levels of steric hindrance can modify the selectivity of the catalyst. Due to the synthetic strategy the stereochemistry and the nature of the substituent is related to the starting amino alcohol (Scheme 2.15).



- |                                                           |                                                           |
|-----------------------------------------------------------|-----------------------------------------------------------|
| <b>a</b> Acid = <b>1a</b> , $R_1 = (R)\text{-Et}$         | <b>i</b> Acid = <b>1e</b> , $R_1 = (S)\text{-}i\text{Pr}$ |
| <b>b</b> Acid = <b>1a</b> , $R_1 = (S)\text{-Bn}$         | <b>j</b> Acid = <b>1f</b> , $R_1 = (S)\text{-}i\text{Pr}$ |
| <b>c</b> Acid = <b>1a</b> , $R_1 = (S)\text{-}i\text{Pr}$ | <b>k</b> Acid = <b>1g</b> , $R_1 = (R)\text{-Et}$         |
| <b>d</b> Acid = <b>1a</b> , $R_1 = (R)\text{-Ph}$         | <b>l</b> Acid = <b>1g</b> , $R_1 = (S)\text{-Bn}$         |
| <b>e</b> Acid = <b>1b</b> , $R_1 = (S)\text{-Bn}$         | <b>m</b> Acid = <b>1g</b> , $R_1 = (S)\text{-}i\text{Pr}$ |
| <b>f</b> Acid = <b>1c</b> , $R_1 = (S)\text{-}i\text{Pr}$ | <b>n</b> Acid = <b>1g</b> , $R_1 = (S)\text{-}t\text{Bu}$ |
| <b>g</b> Acid = <b>1d</b> , $R_1 = (S)\text{-}i\text{Pr}$ | <b>o</b> Acid = <b>1g</b> , $R_1 = (R)\text{-Ph}$         |
| <b>h</b> Acid = <b>1d</b> , $R_1 = (R)\text{-Et}$         | <b>p</b> Acid = <b>1h</b> , $R_1 = (S)\text{-}i\text{Pr}$ |

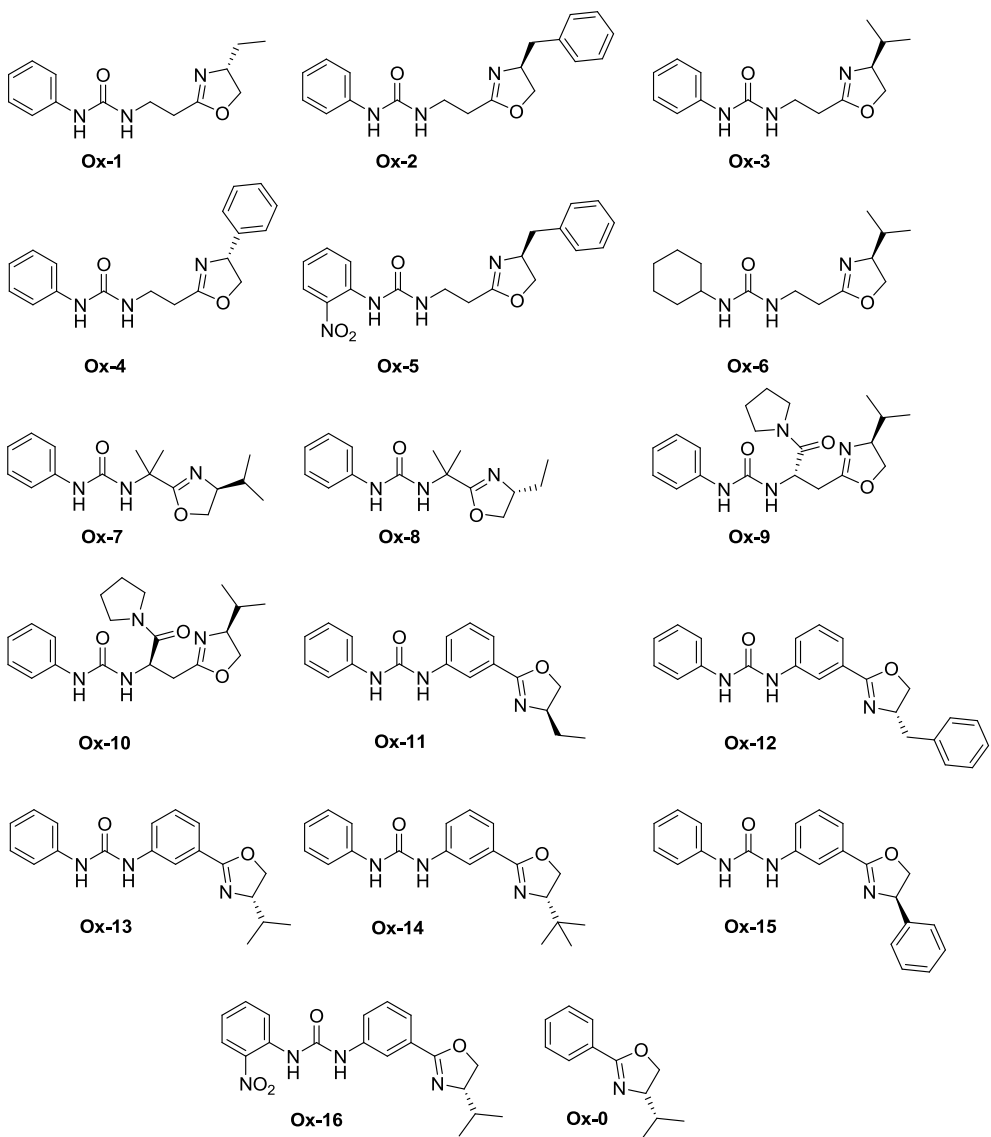
**Scheme 2.15**

Cyclization reactions to give oxazoline ring were carried out using diethylaminosulfur trifluoride (DAST) at  $-78^{\circ}\text{C}$ . Due to the presence in the molecule of other nucleophilic oxygen atoms, an excess of DAST (2.2 equiv.) was necessary to obtain the cyclized product in considerable yields (Scheme 2.16).



**Scheme 2.16**

Due to this variables, a small library of 16 ligands **Ox 1-16** was prepared for testing. In addition, one mono(oxazoline) **Ox-0** devoid of functional group capable of hydrogen bond were added to validate the importance of the supramolecular interaction.



### 2.3.2 Complexation studies

Before screening the library in catalytic applications we decided to investigate the formation of transition metal complexes of our ligands. Bis(oxazolines) have developed into one of the most useful ligand classes also due to their ability to

coordinate to different metals<sup>77</sup> and, also to impart specific coordination geometries to these metal ions. We will focus our attention on copper, which is known to be one of the metals with more coordination geometries, forming tri- tetra- penta- and hexacoordinate complexes.

Tricoordinated complexes are almost exclusively prerogative of Cu(I), and in particular of copper(I)-carbene complexes as intermediates in cyclopropanations of alkenes with diazoacetates.<sup>78</sup>

The two main geometries possible for tetracoordinated bis(oxazoline) complexes are square-planar and tetrahedral. These are indeed widely found for such complexes with varying degrees of distortion. Zinc (II), nickel (II) and iron(II) complexes have proven to form distorted tetrahedral complexes, meanwhile with copper(II) are considerably more distorted towards a square-planar geometry. Quite obviously, the chloride ligands, when present, orient themselves away from the ligand quadrants blocked by the sterically demanding substituent and in general is possible to say that the degree of distortion from the ideal tetrahedral geometry is increasing with the steric bulk of the oxazoline substitution (Scheme 2.17-A).<sup>79</sup> A similar trend is present for square-planar Cu(II)-complexes, which prefer this geometry in presence of hydroxyl- or carbonyl-containing ligands. (Scheme 2.17-B).<sup>80</sup>

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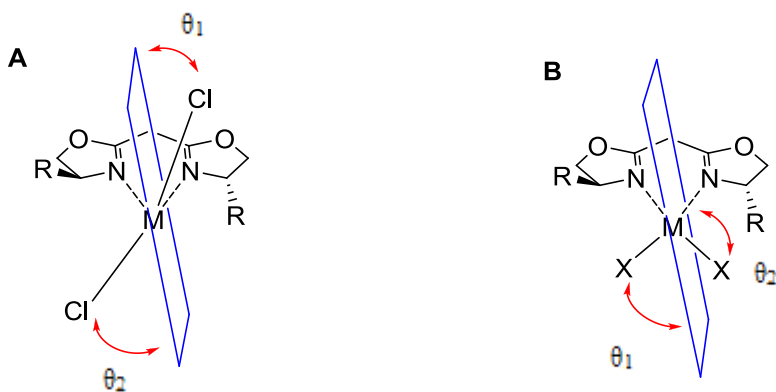
<sup>77</sup> S. Dagorne, S. Bellemin-Laponnaz, A. Maisse-François, *Eur. J. Inorg. Chem.* **2007**, 913.

<sup>78</sup> R. Lowenthal, A. Abiko, S. Masamune, *Tetrahedron Lett.* **1990**, *31*, 6005; R.E. Lowenthal, S. Masamune, *Tetrahedron Lett.* **1991**, *32*, 7373; D.A. Evans, K.A. Woerpel, M.M. Hinman, M.M. Faul, *J. Am. Chem. Soc.* **1991**, *113*, 726.

<sup>79</sup> J. Thorhauge, M. Roberson, R.G. Hazell, K.A. Jørgensen, *Chem. Eur. J.* **2002**, *8*, 1888; D.A. Evans, S.J. Miller, T.v.M.P. Lectka, *J. Am. Chem. Soc.* **1999**, *121*, 7559; R. Rasappan, M. Hager, A. Gissibl, O. Reiser, *Org. Lett.* **2006**, *8*, 6099.

<sup>80</sup> D.A. Evans, G.S. Peterson, J.S. Johnson, D.M. Barnes, K.R. Campos, K.A. Woerpel, *J. Org. Chem.* **1998**, *63*, 4541; D.A. Evans, T. Rovis, J.S. Johnson, *Pure Appl. Chem.* **1999**, *71*, 1407; D.A. Evans, T. Rovis, M.C. Kozlowski, C.W. Downey, J.S. Tedrow, *J. Am. Chem. Soc.* **2000**, *122*, 9134; D.A. Evans, T. Rovis, M.C. Kozlowski, J.S. Tedrow, *J. Am. Chem. Soc.* **1999**, *121*, 1994.





Metal	R	$\theta_1/\theta_2$
Cu	Ph	45/38
Cu	<i>t</i> Bu	45/45
Cu	<i>i</i> Pr	31/25

Metal	R	X	$\theta_1/\theta_2$
Cu	Ph	H <sub>2</sub> O	79/66
Cu	<i>t</i> Bu	H <sub>2</sub> O	52/50
Cu	Ph	PhCH=C(CO <sub>2</sub> Me) <sub>2</sub>	90/85
Cu	<i>t</i> Bu	PhCH=C(CO <sub>2</sub> Me) <sub>2</sub>	79/75

**Scheme 2.17**

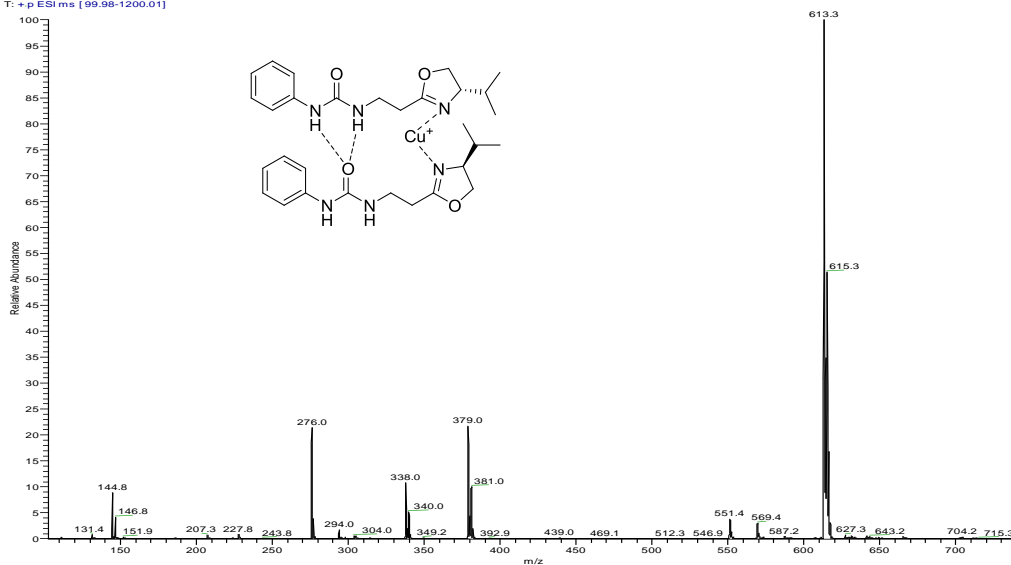
Hexacoordinate complexes are almost absent with bis(oxazolines), meanwhile pentacoordination is more widespread. The main part of examples are reported concerning square-pyramidal complexes (which moreover is the principal geometry recognizable with Py-BOX ligands) however also trigonal-bipyramidal geometry is possible.<sup>81</sup>

The copper (II) complex of ligand **Ox-3** was obtained treating the ligand with CuCl<sub>2</sub> in CH<sub>2</sub>Cl<sub>2</sub>, followed by recrystallization from CH<sub>2</sub>Cl<sub>2</sub>/hexanes. Its molecular composition was assessed by ESI-MS spectroscopy and revealed one principal peak at *m/z* 613.3, corresponding to a copper atom coordinated to two molecules of ligand [CuL<sub>2</sub>]<sup>+</sup> (Scheme 2.18). The reduction of Cu<sup>2+</sup> to Cu<sup>+</sup> has been reported to occur using ESI as ionization source.<sup>82</sup>

<sup>81</sup> S. Hanessian, E. Jnoff, N. Bernstein, M. Simard, *Can. J. Chem.* **2004**, *82*, 306.

<sup>82</sup> Girault H., *J. Am. Soc. Mass. Spectrom.* **2008**, *19*, 560; Hoppiliard Y., *J Am Soc Mass Spectrom* **1998**, *9*, 1217.

dur76259 #1 RT: 0.00 AV: 1 SM: 3B NL: 3.03E6  
T: +p ESI ms [99.98-1200.01]



**Scheme 2.18**

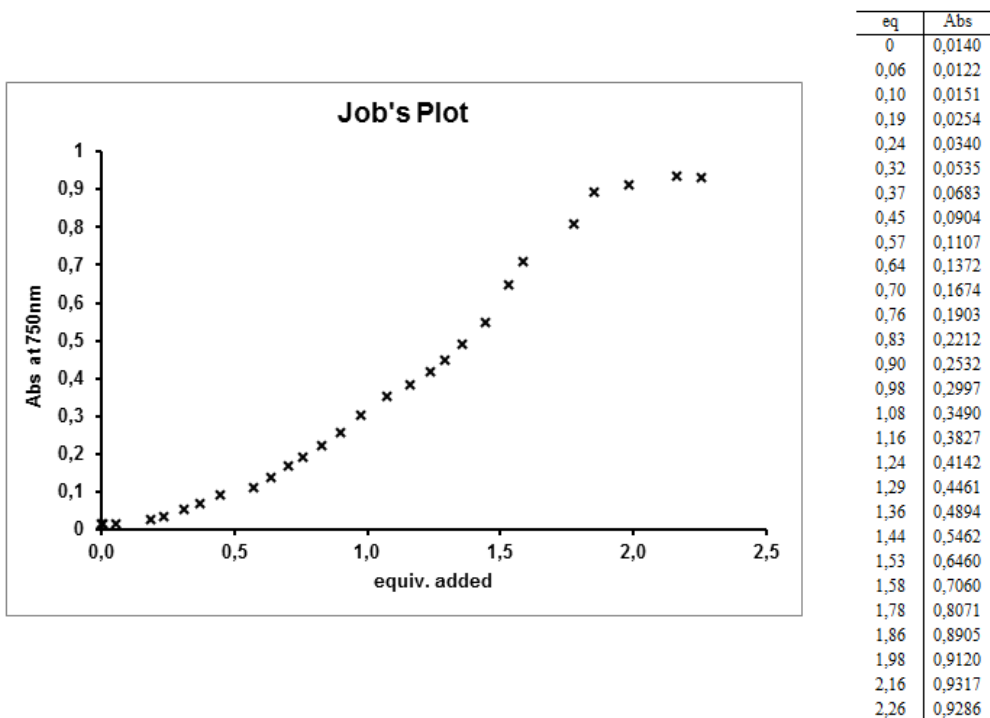
The presence of two ligands of **Ox-3** coordinated to Cu<sup>2+</sup> was further confirmed by a Job's plot analysis of the absorbance of the complex as a function of the ligand stoichiometry (Scheme 2.19). Job's plot technique exploits the correlation between a physical property and the amount of ligand in presence of a metal source, providing interesting information about the coordination processes of ligands to metal centers.<sup>83</sup>

In our case, we measured the absorbance at 750nm as a function of the ligand/metal ratio, and a linear increase up to two equivalents of ligands added was observed, suggesting the presence of only one specie ascribable to one copper coordinated to two molecule of ligands. Some practical observations also suggested and anticipated the results of the experiment. The procedure requires multiple additions, directly in the quartz cuvette used for the analysis, of small amounts of ligand to the metal salt and in our case the solvent used was dichloromethane. Initially the solution was obviously clear and colorless due the insolubility of the salt and as the ligand was added it became greener. The important observation is that once one

<sup>83</sup> Bühlmann, P., Olson, E. J., *J. Org. Chem.* **2011**, 76, 8406.

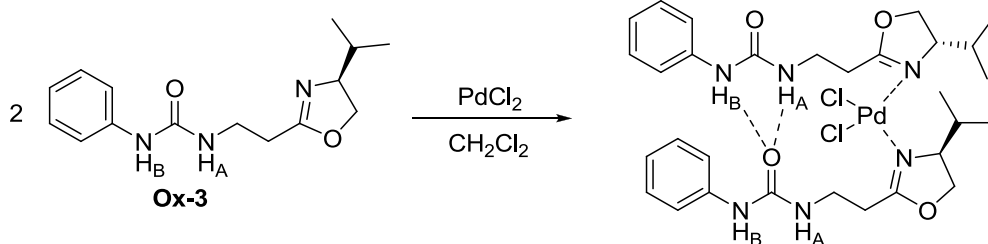
equivalent of ligand was added, some unsolved copper chloride was still present on the bottom of the cuvette and some solid powder remained undissolved until the reaching of two equivalents of ligand globally added.

This fact, in addition to the plot of absorbance values, led us to hypothesize the formation of only the desired product.



**Scheme 2.19**

Due to the paramagnetism of Cu(II), NMR spectroscopy could not be used to characterize the complex; therefore the formation of other complexes in solution was further studied. Palladium chloride was reacted with two equivalents of ligand **Ox-3** in dichloromethane and the complex  $[Pd(\mathbf{Ox-3})_2Cl_2]$  was isolated by precipitation with hexanes and since in this case the complex is diamagnetic, the formation of the supramolecular bidentate specie was studied by  $^1H$ -NMR (Scheme 2.20).

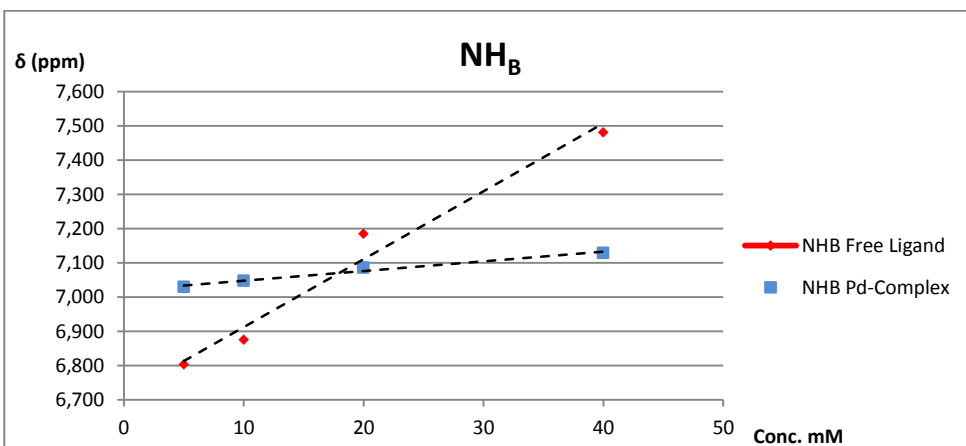
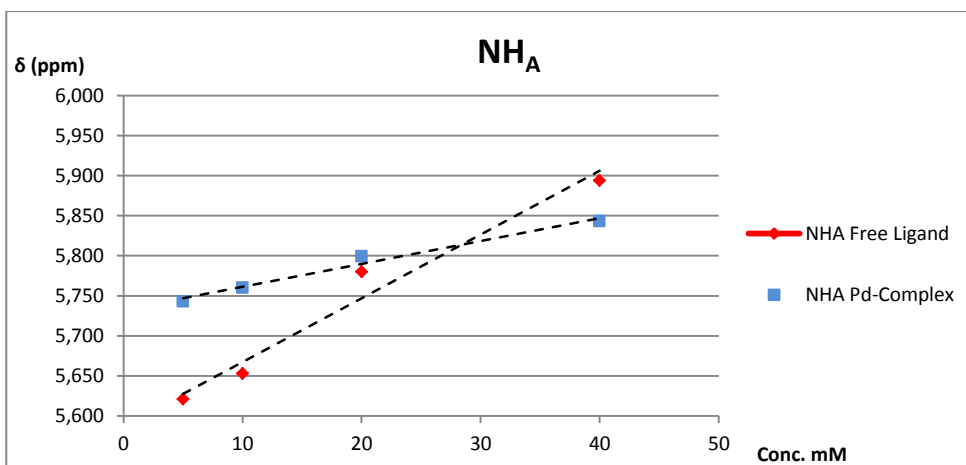


**Scheme 2.20**

Our attention focused on the more representative signals of NH protons. In fact, while the coordination of the oxazoline to the metal ion is almost certain, the coordination of two ligands on the same atom and moreover an interaction between them is far from obvious. A study of the chemical shifts of protons, which should give rise to H-bonding, could therefore provide important information.

The hydrogen bonding status of the NH protons for both the free ligand and the Pd-complex was then studied by  $^1\text{H}$  NMR spectroscopy, and in particular the variation of the chemical shift of the N-H signals upon dilution was considered for both the ligand and the complex.

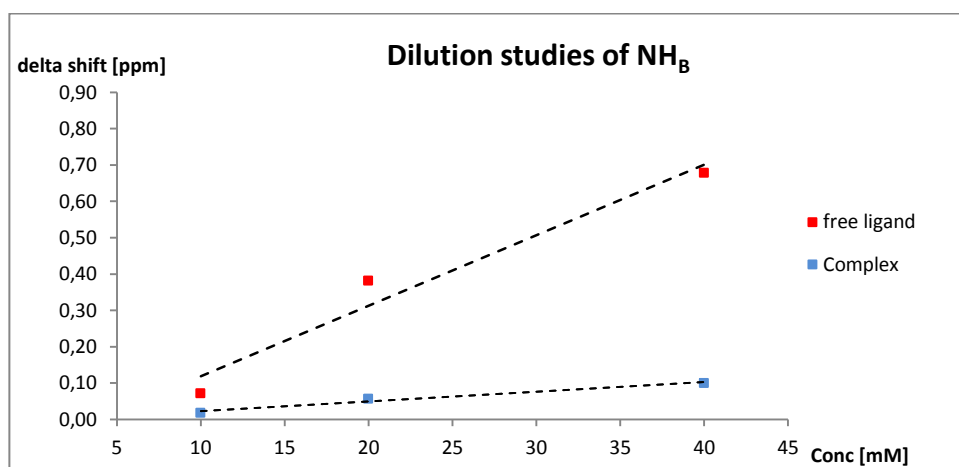
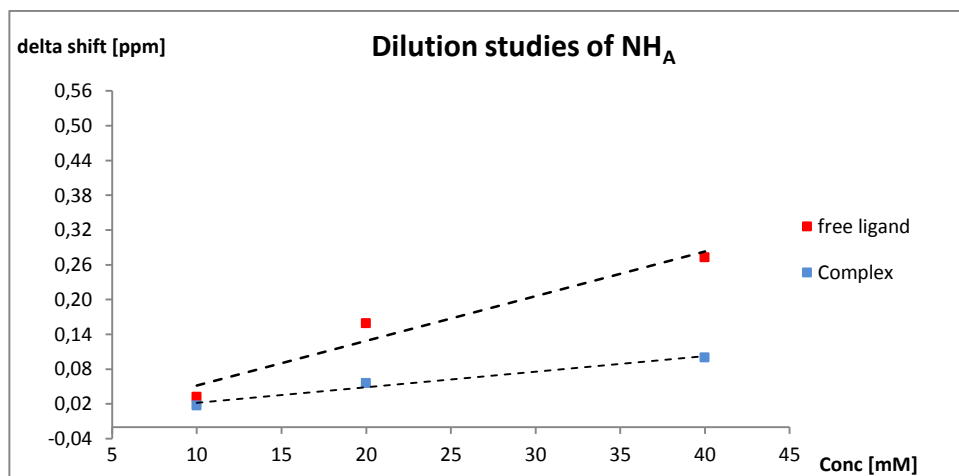
conc (mM)	NH <sub>A</sub>		NH <sub>B</sub>	
	free ligand $\delta$ (ppm)	complex $\delta$ (ppm)	free ligand $\delta$ (ppm)	complex $\delta$ (ppm)
5	5,6210	5,7430	6,803	7,029
10	5,6530	5,7600	6,875	7,047
20	5,7800	5,7990	7,185	7,086
40	5,8940	5,8430	7,481	7,129



Also important is the correlation between the variation of chemical shifts and the variation of the concentration in free ligand and complex. We chose the [5mM]

sample as reference. This trend, if present, is important to show an eventually chemically different behavior of the NH, that in our case would indicate the presence of hydrogen bonding.

conc (mM)	NH <sub>A</sub>		NH <sub>B</sub>	
	free ligand $\Delta\delta / \Delta\text{conc}$	complex $\Delta\delta / \Delta\text{conc}$	free ligand $\Delta\delta / \Delta\text{conc}$	complex $\Delta\delta / \Delta\text{conc}$
5	0,0000	0,0000	0,0000	0,0000
10	0,0320	0,0170	0,0720	0,0180
20	0,1590	0,0560	0,3820	0,0570
40	0,2730	0,1000	0,6780	0,1000



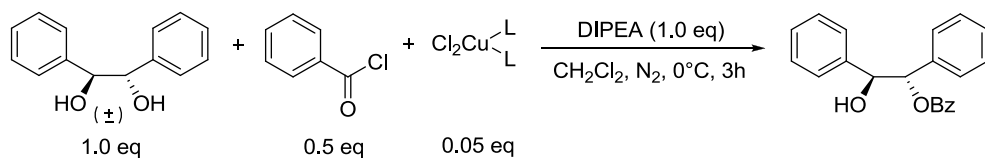
The results clearly show that free ligands and complex have a different behavior. The chemical shifts of both NH in the complex are less influenced by concentration and at the same time more deshielded compared to the free ligand. In particular NH<sub>B</sub> appears fairly independent from the concentration.

What now seems to be curious is the lack of different sets of signals. Since one ligand act as donor the other as acceptor, two different sets of chemical shift should be present. Therefore we decided to investigate the behavior of complex depending on the temperature and we found that at temperature lower than 268K two signals appeared. This experiment, commonly used to differentiate between random-coil peptides and peptides in hydrogen bonded conformations, in addition to the previous observations, indicated that the two ligands coordinated to the metal atom interact intramolecularly via hydrogen bonds.

### 2.3.3 Catalytic applications

Copper bis-oxazoline complexes have been shown to be efficient catalysts in the kinetic resolution of racemic diols and in particular hydrobenzoin. For this reason we decided to screen our small library of ligands in this reaction (Scheme 2.21). The reaction was carried out in dichloromethane using half equivalent of benzoyl chloride and 5 mol% of CuCl<sub>2</sub> and 10 mol% of the chosen ligand.

Isopropyl substitution on the oxazoline ring gives best results in term of enantioselectivity independently of linker and urea used in the ligand. Aromatic linker (entries 12-15) hampers enantioselectivity, probably because of the high rigidity does not allow the rapprochement of the two urea functionalities. Rigidity itself seems to thwart selectivity but probably is not the main cause (entries 7-8). Stereocenters on the linker don't improve ee (entries 10-11 vs. entry 4). The absence of selectivity with the use of **Ox-0** demonstrates the importance of the self-assembled structure.

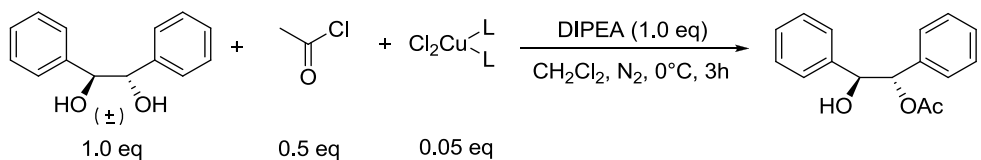


Entry	Ligand	Isolated Yield (%)	er % (R,R:S,S)
1	<b>Ox-0</b>	40	50 : 50
2	<b>Ox-1</b>	45	7 : 93
3	<b>Ox-2</b>	43	85 : 15
4	<b>Ox-3</b>	44	93 : 7
5	<b>Ox-4</b>	47	40 : 60
6	<b>Ox-5</b>	45	51 : 49
7	<b>Ox-6</b>	41	72 : 28
8	<b>Ox-7</b>	44	82 : 18
9	<b>Ox-8</b>	26	22 : 78
10	<b>Ox-9</b>	37	61 : 39
11	<b>Ox-10</b>	35	68 : 32
12	<b>Ox-11</b>	35	50 : 50
13	<b>Ox-12</b>	38	67 : 33
14	<b>Ox-13</b>	17	56 : 44
15	<b>Ox-14</b>	39	57 : 43
16	<b>Ox-15</b>	28	43 : 57
17	<b>Ox-16</b>	34	60 : 40

**Scheme 2.21**

To better investigate the role of the acylating agent the reaction was performed in the same conditions but using acetyl chloride, tosylchloride and pivaloyl chloride. The latter two proved to be not reactive under these conditions. The results with acetyl chloride are reported in Scheme 2.22. Unfortunately, acetyl chloride produced generally only low selectivity except **Ox-8** which gave a moderate 48% ee.

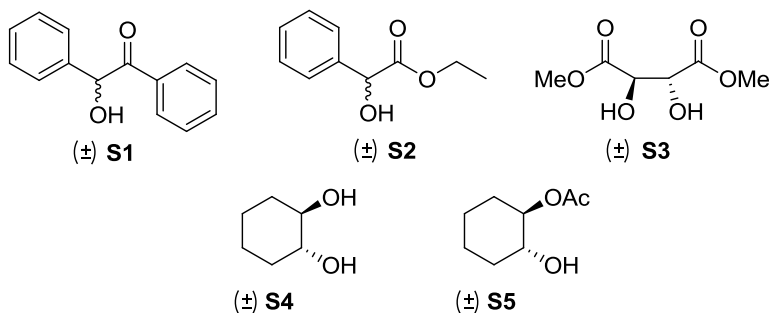




Entry	Ligand	Conversion (%)	er % (sx:dx)
1	<b>Ox-1</b>	30	39 : 61
2	<b>Ox-3</b>	29	56 : 44
3	<b>Ox-7</b>	42	64 : 36
4	<b>Ox-8</b>	43	26 : 74
5	<b>Ox-11</b>	37	46 : 54
6	<b>Ox-12</b>	31	54 : 46
7	<b>Ox-13</b>	32	53 : 47
8	<b>Ox-14</b>	34	53 : 47
9	<b>Ox-16</b>	28	52 : 48

**Scheme 2.22**

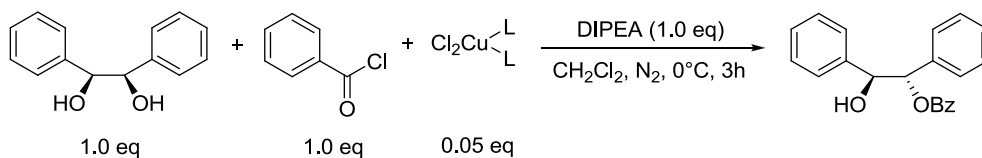
The scope of the reaction was then explored with the commercially available substrates **S1-S5**, which were screened in the selective benzylation. Unfortunately lower ee's were obtained in all cases, and only racemic dimethyl tartrate caused 53% ee Here below (Scheme 2.23) are reported only the best results for each substrate.



Entry	Substrate	Ligand	Yield (%)	er % (sx:dx)
1	<b>S1</b>	<b>Ox-3</b>	5	64 : 36
2	<b>S2</b>	<b>Ox-3</b>	38	54.5 : 45.5
3	<b>S3</b>	<b>Ox-3</b>	39	76.5 : 23.5
4	<b>S4</b>	<b>Ox-7</b>	41	65 : 35
5	<b>S5</b>	<b>Ox-3</b>	traces	n.d.

**Scheme 2.23**

While the kinetic resolution of racemic substrates by acylation has found several solutions using both metal and organo-catalysis, the desymmetrization of *meso*-diols and in particular *meso*-hydrobenzoin, was not reported with copper bis(oxazoline) complexes. Unexpectedly, reactivities were observed with enantioselectivities largely comparable, and in some cases even better, with respect to the racemic substrate (Scheme 2.24). Also in this screening the best result was achieved using ligand **Ox-3** and **Ox-1**, while other ligands caused in general similar or poorer results (e.g. **Ox-2** and **Ox-10**).



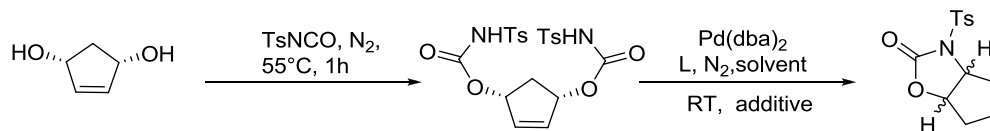
Entry	Ligand	Yield (%)	er % (sx:dx)
1	<b>Ox-0</b>	73	50 : 50
2	<b>Ox-1</b>	97	11 : 89
3	<b>Ox-2</b>	77	52 : 48
4	<b>Ox-3</b>	92	94 : 6
5	<b>Ox-4</b>	70	38 : 62
6	<b>Ox-6</b>	89	69 : 31
7	<b>Ox-7</b>	88	84 : 16
8	<b>Ox-8</b>	99	27 : 63
9	<b>Ox-9</b>	68	70 : 30
10	<b>Ox-10</b>	62	60 : 40
11	<b>Ox-13</b>	68	59 : 41
12	<b>Ox-15</b>	74	48 : 52

**Scheme 2.24**

Pivaloyl chloride and tosyl chloride proved to be unreactive, while concerning other substrates, only dimethyl tartrate was used obtaining the same enantioselectivity of **S3** (54% ee vs. 53%).

To extend the application of our ligands to different metals, we decided to investigate palladium catalyzed reactions. Several reactions were carried out but unfortunately only one gave interesting results. It was the Pd(II)-catalyzed asymmetric desymmetrization of meso-cyclopenten-2-ene-1,4-diol biscarbamate.<sup>84</sup> Different ligands and conditions were tested (Scheme 2.25) and best results were achieved in THF, with **Ox-13**. Triethylamine proved to be necessary to obtain good yield but deleterious for enantioselectivity.

<sup>84</sup> Ruffo, F., Del Litto, R., De Roma, A., D'Errico, A., Magnolia, S., *Tetrahedron: Asymmetry* **2006**, *17*, 2265.

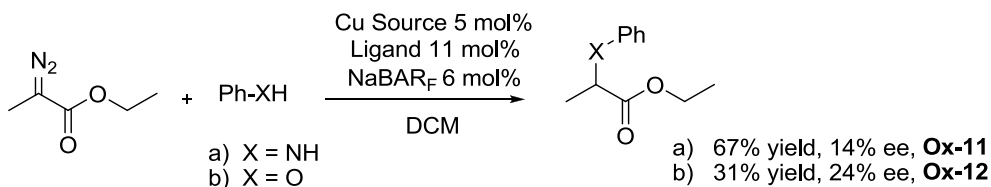


Entry	Ligand	Solvent	Time (h)	Additive	Conv. %	er % (S,R:R,S)
1	none	THF	24	-	-	-
2	Ox0	THF	20	-	-	-
3	Ox1	THF	6	-	<5	40 : 60
4	Ox1	THF	20	-	30	37.5 : 62.5
5	Ox1	THF	20	TEA (1.0 equiv)	87	45 : 55
6	Ox1	THF	48	-	<5	38 : 62
7	Ox1	DCM	20	-	Traces	-
8	Ox1	DCM	20	TEA (1.0 equiv)	18	47.5 : 52.5
9	Ox3	THF	20	-	Traces	61 : 39
10	Ox3	THF	20	TEA (1.0 equiv)	100	52 : 48
11	Ox3	THF	48	-	<5	63 : 37
12	Ox7	THF	20	-	39	-
13	Ox7	THF	48	-	19	-
14	Ox8	THF	48	-	11	46 : 54
15	Ox11	THF	20	-	18	26 : 74
16	Ox11	THF	48	-	23	27.5 : 72.5
17	Ox12	THF	48	-	36	54 : 46
18	Ox13	THF	20	-	10	22.5 : 77.5
19	Ox13	THF	20	TEA (1.0 equiv)	73	-
20	Ox13	THF	48	-	25	75 : 25
21	Ox14	THF	48	-	<5	57.5 : 42.5

### Scheme 2.25

To explore different copper-catalyzed reactivity our attention was focused on the insertion of carbenoids into N-H and O-H bonds. Indeed this reaction is known to take place in dichloromethane and is catalyzed by Cu(I). Moreover Zhou in 2007

reported the use of chiral spiro bis(oxazolines) as efficient ligands for the reaction.<sup>85</sup> Unfortunately the tests gave only poor results (Scheme 2.26).



**Scheme 2.26**

## 2.2.4 Conclusions

In this chapter we have reported the synthesis of a new class of supramolecular bis(oxazolines) named SupraBox using urea moiety as self-assembly inducer.

A library of 16 ligand, with different degree of structural diversity, has been prepared by a 3-step modular synthesis starting from readily available starting materials. Palladium- and Copper-complexes were characterized by NMR spectroscopy, UV spectroscopy and Mass spectrometry to investigate their structures and properties and used as catalysts in kinetic resolutions of racemic diols and in the desymmetrization of *meso* diols.

Catalysts proved to give best results in the asymmetric benzylation of hydrobenzoin and good enantiomeric excesses were achieved with both racemic and *meso* substrate. This unusual property, and the selectivity itself, proved to be correlate to the ligand's structure and in general more flexible ligands gave better results. We hypothesize that the above mentioned flexibility, peculiar of our system but not of classical Box and aza-Box, best fit to the structure of *meso* compounds, thus leading better results.

<sup>85</sup> Zhou, Q. L., *J. Am. Chem. Soc.* **2007**, 5834; Zhou, Q. L., *J. Am. Chem. Soc.* **2007**, 12616.

## 2.2.5 Experimental part

### General Remarks

All reactions were carried out in flame-dried glassware with magnetic stirring under a nitrogen atmosphere, unless otherwise stated. Dry solvents (over molecular sieves in bottles with crown caps) were purchased from Sigma–Aldrich and stored under nitrogen. The reactions were monitored by analytical TLC using silica gel 60 F254 precoated glass plates (0.25 mm thickness). Visualization was accomplished by irradiation with a UV lamp and/or staining with a potassium permanganate alkaline solution. Flash column chromatography was performed using silica gel 60 Å, particle size 40–64 µm, following the procedure reported by Still and coworkers.<sup>86</sup> <sup>1</sup>H NMR spectra were recorded with a spectrometer operating at 400.13 MHz. Chemical shifts are reported in ppm with the solvent reference relative to tetramethylsilane (TMS) employed as the internal standard (CDCl<sub>3</sub> δ = 7.26 ppm). The following abbreviations are used to describe spin multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br. = broad signal, dd = doublet of doublets. <sup>13</sup>C NMR spectra were recorded with a 400 MHz spectrometer operating at 100.56 MHz with complete proton decoupling. Chemical shifts are reported in ppm relative to TMS with the respective solvent resonance as the internal standard (CDCl<sub>3</sub>, δ = 77.23 ppm). Infrared spectra were recorded with a standard FTIR spectrometer. Optical rotation values were measured with an automatic polarimeter with a 1-dm cell at the sodium D line (λ = 589 nm). HPLC was performed with an instrument equipped with a diode array detector using a chiral column. HRMS were measured with a Fourier Transform Ion Cyclotron Resonance (FT-ICR) Mass Spectrometer APEX II & Xmass software (Bruker Daltonics)–4.7 T Magnet (Magnex) equipped with ESI source, available at CIGA (Centro Interdipartimentale Grandi Apparecchiature), c/o Università degli Studi di Milano. MS were acquired either with a Thermo- innigan LCQ Advantage mass spectrometer (ESI ion source) or a VG Autospec M246 spectrometer (FAB ion

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<sup>86</sup> W. C. Still, M. Kahn, A. Mitra, *J. Org. Chem.* **1978**, *43*, 2923.

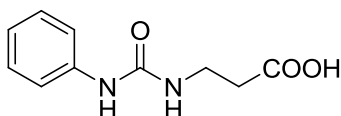
source). Elemental analyses were performed with a Perkin–Elmer Series II CHNS/O Analyzer 2000.

## Materials

Commercially available reagents were used as received. 4-(allyloxy)-2-amino-4-oxobutanoic acid<sup>87</sup> (**2**) and (S)-4-isopropyl-2-phenyl-4,5-dihydrooxazole<sup>88</sup> (**Ox-0**) were prepared according to literature procedures.

## Synthesis and characterization of the ligands

### 3-(3-phenylureido)propanoic acid (**1a**)



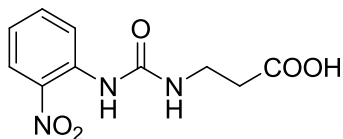
Phenylisocyanate (5.0 mL, 44 mmol, 1.0 equiv.) was dissolved in 220 mL THF and then  $\beta$ -alanine (3.92 g, 44 mmol, 1.0 equiv.) was added and the reaction mixture stirred at room temperature for 3 days. The mixture was treated with cold Et<sub>2</sub>O to provide the precipitation of the product. After filtration the crude product was purified by flash chromatography eluting with 3→10% MeOH in DCM to yield product **1a** as fine white powder (8.33 g, 40 mmol, 91%).

R<sub>f</sub> = 0.24 (DCM/MeOH 95:5) — m.p. 160–161 °C — <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD, 25 °C):  $\delta$  = 2.55 (t, 2H, *J* = 6.3 Hz), 3.47 (t, 2H, *J* = 6.3 Hz), 6.98 (t, 1H, *J* = 6.8 Hz), 7.25 (dd, 2H, *J* = 8.4, 7.4 Hz), 7.33 (m, 2H). — <sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>, 25 °C):  $\delta$  = 34.1, 35.2, 119.0, 122.0, 128.4, 139.5, 156.8, 174.3. — IR:  $\nu$  = 3584, 3329, 2725, 1694, 1638, 1571, 1108. — C<sub>10</sub>H<sub>12</sub>N<sub>2</sub>O<sub>3</sub> (208.21): calcd. C 57.68, H 5.81, N 13.45; found C 57.73, H 5.57, N 13.81.

<sup>87</sup> A. S. M. Ressurreicao, A. Bordessa, M. Civera, L. Belvisi, C. Gennari, U. Piarulli, *J. Org. Chem.* **2008**, *73*, 652

<sup>88</sup> Focken, T., Hargett, A. B., *Org. Lett.* **2006**, *14*, 2985.

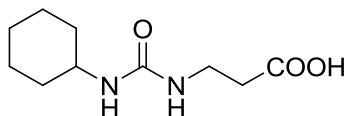
### 3-(3-(2-nitrophenyl)ureido)propanoic acid (**1b**)



2-nitro-phenylisocyanate (1.000 g, 6.09 mmol, 1.0 equiv.) was dissolved in 30 mL THF and then  $\beta$ -alanine (1.085 g, 12.18 mmol, 2.0 equiv.) was added and the reaction mixture stirred at room temperature for 3 days. The mixture was treated with cold Et<sub>2</sub>O to provide the precipitation of the product. After filtration the crude product was purified by flash chromatography eluting with 3→5% MeOH in DCM to yield product **1b** as fine yellow powder (1.077g, 4.25 mmol, 67%).

R<sub>f</sub> = 0.41 (DCM/MeOH 95:5) — m.p. 160-161°C — <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 25°C):  $\delta$  = 2.56 (t, 2H, *J* = 6.6 Hz), 3.48 (t, 2H, *J* = 6.6 Hz), 7.13 (ddd, 1H, *J* = 8.5, 7.2, 1.3), 7.61 (ddd, 1H, *J* = 8.6, 7.2, 1.6), 8.12 (dd, 1H, *J* = 8.5, 1.6 Hz), 8.35 (dd, 1H, *J* = 8.6, 1.3 Hz). — <sup>13</sup>C NMR (100.6 MHz, CD<sub>3</sub>OD, 25°C):  $\delta$  = 33.8, 35.5, 121.4, 122.1, 125.1, 134.6, 135.7, 137.1, 155.4, 174.0. — IR:  $\nu$  = 3583, 3393, 3330, 2753, 2360, 1694, 1611, 1582, 1539, 1342, 1258, 1142, 1085, 798. — C<sub>10</sub>H<sub>11</sub>N<sub>3</sub>O<sub>5</sub> (253.21): calcd. C 47.43; H 4.38; N 16.59; found C 47.62, 4.23, 16.2

### 3-(3-cyclohexylureido)propanoic acid (**1c**)

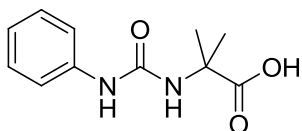


Cyclohexylisocyanate (2.86 mL, 22 mmol, 1.0 equiv.) was dissolved in 150 mL THF and then  $\beta$ -alanine (2.00 g, 22.4 mmol, 1.0 equiv.) was added and the reaction mixture stirred at room temperature for 3 days. The mixture was treated with cold Et<sub>2</sub>O to provide the precipitation of the product. After filtration the crude product was purified by flash chromatography eluting with 5→15% MeOH in DCM to yield product (**1c**) as fine white powder (3.60 g, 16.8 mmol, 76%).



R<sub>f</sub> = 0.23 (DCM/MeOH 95:5) — m.p. 159-160°C — <sup>1</sup>H NMR (400 MHz, DMSO, 25°C): δ = 0.97-1.16 (m, 3H), 1.18-1.30 (m, 2H), 1.50 (m, 1H), 1.61 (m, 1H), 1.70 (m, 1H), 2.31 (t, 2H, J = 6.5 Hz), 3.15 (q, 2H, J = 6.5 Hz), 5.74 (t, 1H, J = 5.8 Hz), 5.83 (d, 1H, 7.9 Hz), 12.17 (s, 1H). — <sup>13</sup>C NMR (100.6 MHz, DMSO, 25°C): δ = 24.9, 25.8, 33.7, 35.5, 35.7, 48.1, 157.7, 173.9. — IR: ν = 3335, 1699, 1626, 1580, 1535, 1307, 1248, 1222, 1080, 921. — C<sub>10</sub>H<sub>18</sub>N<sub>2</sub>O<sub>3</sub> (214.26): calcd. C 56.06; H 8.47; N 13.07; found C 55.87, H 8.62, N 12.72.

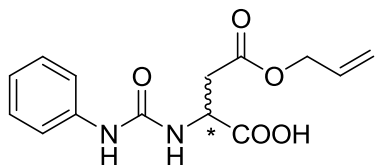
### 2-methyl-2-(3-phenylureido)propanoic acid (**1d**)



2-aminoisobutyric acid (3.0 g, 29 mmol, 1.3 equiv) was suspended in 10 mL of 2M NaOH then phenylisocyanate (2.37 mL, 22 mmol, 1.0equiv) was added and the mixture reaction was stirred for 60 minutes at room temperature. The mixture was filtered and the product was precipitated from solution by slow addition of 1M HCl. The white solid was dissolved in 10 mL of 1M NaOH and the solution washed with DCM. Addition of 1M HCl provides the precipitation of product **1d** as fine white powder (1.73 g, 7.78 mmol, 35%).

R<sub>f</sub> = 0.37 (DCM/MeOH 95:5) — m.p. 157-158°C — <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OH, 25°C): δ = 1.53 (s, 6H), 6.41 (s, 1H), 6.95 (m, 1H), 7.24 (m, 2H), 7.30 (m, 2H), 8.19 (s, 1H). — <sup>13</sup>C NMR (100.6 MHz, CD<sub>3</sub>OD, 25°C): δ = 24.6, 55.3, 118.6, 121.9, 128.3, 139.4, 155.7, 177.3. — IR: ν = 3381, 2724, 1704, 1648, 1544, 1308, 1158, 1069. — C<sub>11</sub>H<sub>14</sub>N<sub>2</sub>O<sub>3</sub> (222.24): calcd. C 59.45; H 6.35; N 12.60; found C 59.55, H 5.55, N 12.61.

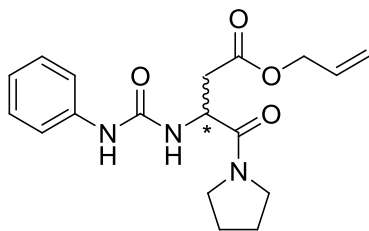
#### 4-(allyloxy)-4-oxo-2-(3-phenylureido)butanoic acid (3a-3b)



4-(allyloxy)-2-amino-4-oxobutanoic acid hydrochloride (1.20 g, 5.72 mmol, 1.0 equiv.) was suspended in 57 mL THF and triethylamine (0.79 mL, 5.72 mmol, 1.0 equiv) added dropwise. The reaction mixture was vigorously stirred for 30 minutes then phenylisocyanate (0.65 mL, 5.72 mmol, 1.0 equiv) added and stirred for 3 days at room temperature. The mixture was treated with acid Et<sub>2</sub>O to provide the precipitation of a white powder. The solid was washed with KHSO<sub>4</sub> 1M to obtain product **3a** and **3b** as fine white powder (*R*-enantiomer: 1.394 g, 4.77 mmol, 83%. *S*-enantiomer: 1.407 g, 4.81 mmol, 84%).

*R<sub>f</sub>* = 0.28 (DCM/MeOH 95:5) — m.p. 186-187°C — <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 25°C): δ = 2.86 (bs, 2H), 4.54 (bs, 2H), 4.78 (bs, 1H), 5.19 (d, 1H, *J* = 10.4 Hz), 5.26 (d, 1H, *J* = 17.1 Hz), 5.84 (m, 1H), 6.8 (bs, 1H), 6.96 (t, 1H, *J* = 6.8 Hz), 7.20 (t, 2H, *J* = 7.1 Hz), 7.39 (d, 2H, *J* = 7.0 Hz), 8.46 (bs, 1H), 11.23 (bs, 1H). — <sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>, 25°C): δ = 36.5, 49.9, 65.6, 118.4, 119.4, 122.6, 128.8, 131.8, 139.1, 156.5, 170.9. — IR: ν = 3311, 2738, 2603, 2531, 2496, 1716, 1702, 1596, 1547, 1397, 1172, 1072, 1036, 851, 807. — C<sub>14</sub>H<sub>16</sub>N<sub>2</sub>O<sub>5</sub> (292.29): calcd. C 57.53; H 5.52; N 9.58; found C 57.89, H 5.87, N 9.34.

#### allyl 4-oxo-3-(3-phenylureido)-4-(pyrrolidin-1-yl)butanoate (4a-4b)

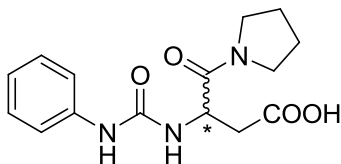


4-(allyloxy)-4-oxo-2-(3-phenylureido)butanoic acid (1.300 g, 4.45 mmol, 1.0 equiv) and N,N-diisopropylethylamine (1.90 mL, 11.1 mmol, 2.5 equiv.) were dissolved in 45 mL DMF and the solution cooled at 0°C. HBTU (1.3equiv) was added and the solution stirred at the same temperature for 30 minutes, then pyrrolidine (0.44 mL, 5.34 mmol, 1.2 equiv.) was added and the reaction mixture stirred at 0°C for 60 minutes and overnight at room temperature.

The solvent was evaporated under reduced pressure and the mixture separated by flash chromatography eluting with MeOH (gradient from 2 to 6%) in DCM to yield the products **4a** and **4b** as pale yellow oil (*R*-enantiomer: 1.122 g, 3.24 mmol, 73%. *S*-enantiomer: 1.199 g, 3.47 mmol, 78%).

*R*<sub>f</sub> = 0.28 (DCM/MeOH 95:5) — <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 25°C): δ = 1.88 (m, 2H), 1.99 (m, 2H), 2.68 (dd, 1H, *J* = 15.8, 6.7 Hz), 2.89 (dd, 1H, *J* = 15.8, 7.4 Hz), 3.42 (m, 2H), 3.67 (m, 1H), 3.78 (m, 1H), 4.59 (t, 1H, *J* = 1.3 Hz), 4.61 (t, 1H, *J* = 1.3 Hz), 5.01 (t, 1H, *J* = 7.0 Hz), 5.20 (ddd, 1H, *J* = 10.5, 2.7, 1.2 Hz), 5.31 (ddd, 1H, *J* = 17.2, 3.0, 1.6 Hz), 5.92 (m, 1H), 6.98 (m, 1H), 7.24 (m, 2H), 7.34 (dd, 2H, *J* = 8.8, 1.0 Hz). — <sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>, 25°C): δ = 23.7, 25.5, 36.6, 46.0, 46.5, 48.2, 65.1, 117.2, 118.8, 122.3, 128.4, 132.1, 139.2, 155.7, 170.2, 170.4. — IR: ν = 2721, 2656, 2512, 2345, 1721, 1678, 1600, 1329, 1178, 1109, 1074, 997, 856. — C<sub>18</sub>H<sub>23</sub>N<sub>3</sub>O<sub>4</sub> (345.39): calcd. C 62.59; H 6.71; N 12.17; found C 62.33, H 6.57, N 11.99.

#### 4-oxo-3-(3-phenylureido)-4-(pyrrolidin-1-yl)butanoic acid (**1e-1f**)

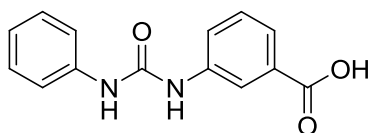


allyl 4-oxo-3-(3-phenylureido)-4-(pyrrolidin-1-yl)butanoate (1.10g, 3.18mmol, 1.0 equiv) was dissolved in 30mL DCM and the solution cooled at 0°C. Pyrrolidine (0.31 mL, 3.82 mmol, 1.2 equiv.), triphenylphosphane (0.149 g, 0.57 mmol, 0.18

equiv.) and tetrakis(triphenylphosphane)palladium(0) (0.147 g, 0.13 mmol, 0.04 equiv.) were added and the reaction mixture stirred for 1 hour at 0°C. The mixture was poured into AcOEt (200mL) and extracted with satd.  $\text{NHCO}_3$  solution (5x 30mL). Organic layers were acidified to pH 2 with 1M  $\text{KHSO}_4$  solution. The acidified aqueous solutions was extracted with DCM (3x 25mL) and the combined organic layers were dried with  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure. The crude product was purified by flash chromatography eluting with 6% MeOH in DCM to yield the product as yellow solid (*R*-enantiomer 0.754 g, 2.47 mmol, 77%. *S*-enantiomer 0.778 g, 2.55 mmol, 80%).

$R_f = 0.30$  (DCM/MeOH 95:5) — m.p. 168-169°C —  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ , 25°C):  $\delta = 1.85$  (m, 2H), 1.96 (m, 2H), 2.73 (dd, 1H,  $J = 15.7, 6.2$  Hz), 2.84, (dd, 1H,  $J = 15.7, 6.1$  Hz), 3.44 (m, 2H), 3.62 (m, 1H), 3.80 (m, 1H), 5.13 (m, 1H), 6.75 (d, 1H,  $J = 8.8$  Hz), 6.97 (t, 1H,  $J = 7.5$  Hz), 7.21 (t, 2H,  $J = 7.5$  Hz), 7.34 (d, 2H,  $J = 7.7$  Hz), 8.08 (s, 1H). —  $^{13}\text{C NMR}$  (100.6 MHz,  $\text{CDCl}_3$ , 25°C):  $\delta = 24.1, 25.9, 37.5, 46.6, 47.1, 48.2, 119.5, 122.7, 128.8, 139.1, 155.4, 170.6, 173.7$ . — **IR**:  $\nu = 3347, 3202, 3145, 1728, 1685, 1615, 1553, 1518, 1481, 1312, 1203, 1119, 1046, 997$ . —  $\text{C}_{15}\text{H}_{19}\text{N}_3\text{O}_4$  (305.33): calcd. C 59.01; H 6.27; N 13.76; found C 59.34, H 5.99, N 13.44.

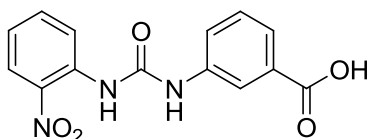
### 3-(3-phenylureido)benzoic acid (1g)



Phenylisocyanate (1.59 mL, 14.5 mmol, 1.0 equiv.) and 3-aminobenzoic acid (2.0 g, 14.5 mmol, 1.0 equiv) were dissolved in 80 mL THF and the reaction mixture stirred at room temperature for 3 days. The mixture was treated with cold  $\text{Et}_2\text{O}$  to provide the precipitation of the product as fine white powder (2.34 g, 9.15 mmol, 63%).

R<sub>f</sub>= 0.35 (DCM/MeOH 95:5) — m.p.152-153°C — <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD, 25°C): δ = 7.03 (m, 1H), 7.30 (m, 2H), 7.37-7.46 (m, 3H), 7.68 (ddd, 1H, *J*= 7.7, 1.5, 1.1 Hz), 7.73 (ddd, 1H, *J*= 8.0, 2.3, 1.1 Hz), 8.08 (t, 1H, *J*= 1.7 Hz). — <sup>13</sup>C NMR (100.6 MHz, CD<sub>3</sub>OD, 25°C): δ = 119.1, 119.9, 122.6, 123.2, 123.5, 128.4, 128.6, 131.2, 139.0, 139.5, 151.1, 168.2. . — IR: ν = 3354, 2724, 1738, 1680, 1649, 1556, 1310, 1156, 1066. — C<sub>14</sub>H<sub>12</sub>N<sub>2</sub>O<sub>3</sub> (256.26): calcd. C 65.62; H 4.72; N 10.93; found C 63.38, 4.44, 10.81.

### 3-(3-(2-nitrophenyl)ureido)benzoic acid (1h)



2-nitrophenyl isocyanate (1.0 g, 6.09 mmol, 1.0 equiv.) and 3-aminobenzoic acid (0.84 g, 6.09 mmol, 1.0 equiv) were dissolved in 60 mL THF and the reaction mixture stirred at room temperature for 3 days. The mixture was treated with cold Et<sub>2</sub>O to provide the precipitation of the product as fine yellow powder (1.36 g, 4.50 mmol, 74%).

R<sub>f</sub>= 0.26 (DCM/MeOH 95:5) — m.p.174-175°C — <sup>1</sup>H NMR (400 MHz, DMSO, 25°C): δ = 7.22 (ddd, 1H, *J*= 8.4, 7.2, 1.2 Hz), 7.42 (t, 1H, *J*= 7.8 Hz), 7.59 (dt, 1H, *J*=7.7, 1.2 Hz), 7.66-7.73 (m, 2H), 8.09 (dd, 1H, *J*= 8.4, 1.6 Hz), 8.15 (t, 1H, *J*= 1.8 Hz), 8.29 (dd, 1H, *J*= 8.5, 1.2 Hz), 9.61 (s, 1H), 10.03 (s, 1H), 12.93 (s, 1H). — <sup>13</sup>C NMR (100.6 MHz, DMSO, 25°C): δ = 119.7, 122.8, 123.0, 123.7, 125.8, 129.6, 131.9, 135.2, 135.4, 138.3, 140.0, 152.3, 167.6. — IR: ν = 3354, 3281, 2724, 1829, 1739, 1652, 1543, 1310, 1155, 1073, 949. — C<sub>14</sub>H<sub>11</sub>N<sub>3</sub>O<sub>5</sub> (301.25): calcd. C 55.82; H 3.68; N 13.95; found C 55.54, H 3.34, N 14.30.

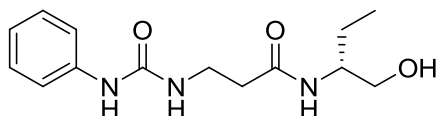
## Synthesis of products (5)

### General procedure

Carboxylic acid (1.1 equiv) and N,N-Diisopropylethylamine (3 equiv) were dissolved in DCM (0.1M solution) and the solution cooled at 0°C. HBTU (1.3equiv) was added and the solution stirred at the same temperature for 30 minutes, then the aminoalcohol (1.0 equiv) was added and the reaction mixture stirred at 0°C for 60 minutes and overnight at room temperature.

The solvent was evaporated under reduced pressure and the mixture separated by flash chromatography eluting with MeOH (gradient from 2 to 10%) in DCM to yield the product.

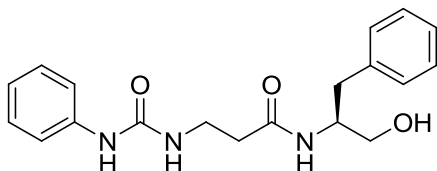
### (R)-N-(1-hydroxybutan-2-yl)-3-(3-phenylureido)propanamide (5a)



According to the general procedure product **5a** was yielded as white solid (0.604 g, 2.16 mmol, 99%) starting from acid **1a** (0.500g, 2.4mmol) and coupled with (R)-2-aminobutan-1-ol..

R<sub>f</sub> = 0.23 (DCM/MeOH 94:6) — m.p. 131-132°C — [α]<sup>20</sup><sub>D</sub> = +32.01(c = 0.1, CHCl<sub>3</sub>) — <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD, 25°C): δ = 0.93 (t, 3H, J = 7.4 Hz), 1.42 (m, 1H), 1.63 (m, 1H), 2.46 (m, 2H), 3.43-3.52 (m, 4H), 3.80 (m, 1H), 6.97 (m, 1H), 7.23 (m, 2H), 7.33 (m, 2H). — <sup>13</sup>C NMR (100.6 MHz, CD<sub>3</sub>OD, 25°C): δ = 18.6, 23.9, 36.5, 37.3, 53.9, 64.8, 119.8, 123.0, 128.9, 138.9, 157.0, 173.3. — IR: ν = 3327, 3265, 2724, 1738, 1647, 1557, 1307, 1154, 1070. — C<sub>14</sub>H<sub>21</sub>N<sub>3</sub>O<sub>3</sub> (279.33): calcd. C 60.20; H 7.58; N 15.04; found C 60.42, H 7.59, N 14.79.

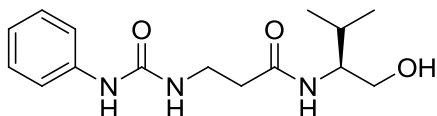
**(S)-N-(1-hydroxy-3-phenylpropan-2-yl)-3-(3-phenylureido)propanamide (5b)**



According to the general procedure product **5b** was yielded as white solid (0.802 g, 2.35 mmol, 98%) starting from acid **1a** (0.500 g, 2.4 mmol) and coupled with (S)-2-amino-3-phenylpropan-1-ol.

R<sub>f</sub> = 0.30 (DCM/MeOH 95:5). — m.p. 131-132°C — [α]<sub>D</sub><sup>20</sup> = -34.68 (c = 0.1, CHCl<sub>3</sub>) — <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD, 25°C): δ = 2.38 (t, 2H, J = 6.4 Hz), 2.71 (dd, 1H, J = 13.8, 8.1), 2.90 (dd, 1H, J = 13.8, 6.2 Hz), 3.38 (m, 2H), 3.53 (m, 2H), 4.12 (m, 1H), 6.97 (m, 1H), 7.15 (m, 1H), 7.21-7.27 (m, 6H), 7.33 (m, 2H). — <sup>13</sup>C NMR (100.6 MHz, CD<sub>3</sub>OD, 25°C): δ = 35.9, 36.1, 36.6, 52.8, 62.9, 118.8, 122.1, 125.9, 126.9, 127.9, 128.4, 128.9, 138.4, 139.5, 156.8, 172.5. — IR: ν = 3320, 2724, 2453, 1829, 1738, 1625, 1545, 1308, 1263, 1156, 1071, 1036. — C<sub>19</sub>H<sub>23</sub>N<sub>3</sub>O<sub>3</sub> (341.40): calcd. C 66.84; H 6.79; N 12.31; found C 67.01, H 6.46, N 12.37.

**(S)-N-(1-hydroxy-3-methylbutan-2-yl)-3-(3-phenylureido)propanamide (5c)**

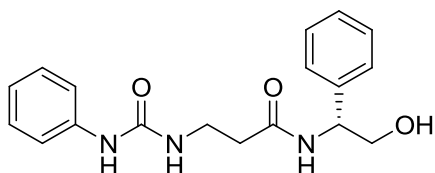


According to the general procedure product **5c** was yielded as white solid solid (0.569 g, 1.94 mmol, 89%) starting from the acid **1a** (0.500 g, 2.4 mmol) and coupled with L-valinol.

R<sub>f</sub> = 0.22 (DCM/MeOH 95:5). — m.p. 121-122°C — [α]<sub>D</sub><sup>20</sup> = -31.01 (c = 0.1, CHCl<sub>3</sub>) — <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 25°C): δ = 0.89 (d, 3H, J = 6.8 Hz), 0.91 (d, 3H, J = 6.8 Hz), 1.83 (m, 1H), 2.57 (m, 2H), 2.90 (bs, 1H), 3.47-3.59 (m, 3H), 3.67 (dd, 1H, J = 11.6, 3.2 Hz), 3.75 (m, 1H), 6.85 (d, 1H, J = 8.5 Hz), 6.98 (m, 1H), 7.21 (m, 2H), 7.28 (m, 1H), 7.44 (m, 1H), 7.55 (m, 1H), 7.86 (bs, 1H). — <sup>13</sup>C NMR

(100.6 MHz, CDCl<sub>3</sub>, 25°C):  $\delta$  = 18.9, 19.4, 29.1, 36.5, 37.2, 57.4, 63.3, 119.8, 123.1, 128.9, 138.7, 156.9, 173.4. — **IR**:  $\nu$  = 3337, 3243, 3087, 2478, 2419, 1670, 1632, 1560, 1503, 1354, 1295, 1260, 1141, 1117, 1063, 1029, 970, 760. — C<sub>15</sub>H<sub>23</sub>N<sub>3</sub>O<sub>3</sub> (293.36): calcd. C 61.41; H 7.90; N 14.32; found C 61.21, H 8.02, N 14.72.

**(R)-N-(2-hydroxy-1-phenylethyl)-3-(3-phenylureido)propanamide (5d)**

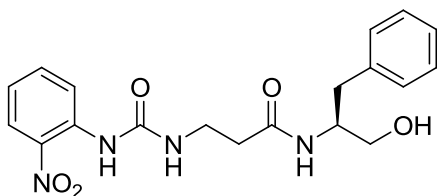


According to the general procedure product **5d** was yielded as white solid (0.505 g, 1.54 mmol, 64%) starting from acid **1a** (0.500 g, 2.4 mmol) and coupled with (R)-2-amino-2-phenylethanol.

R<sub>f</sub> = 0.31 (DCM/MeOH 95:5). — m.p. 119-120°C —  $[\alpha]_D^{20}$  = -37.23 (c = 0.1, CHCl<sub>3</sub>) — **<sup>1</sup>H NMR** (400 MHz, CD<sub>3</sub>OD, 25°C):  $\delta$  = 2.53 (m, 2H), 3.47 (t, 2H, *J* = 6.5 Hz), 3.77 (dd, 1H, *J* = 11.2, 7.7 Hz), 3.75 (dd, 1H, *J* = 11.2, 5.3 Hz), 5.01 (dd, 1H, *J* = 7.7, 5.3 Hz), 6.97 (tt, 1H, *J* = 7.3, 1.2 Hz), 7.20-7.35 (m, 9H). — **<sup>13</sup>C NMR** (100.6 MHz, CD<sub>3</sub>OD, 25°C):  $\delta$  = 35.9, 36.0, 55.6, 64.9, 118.8, 122.0, 126.6, 127.0, 128.1, 128.4, 139.5, 139.9, 156.8, 172.5. — **IR**:  $\nu$  = 3382, 3308, 2462, 2364, 1644, 1598, 1544, 1313, 1243, 1153, 1125, 1078, 1056, 905. — C<sub>18</sub>H<sub>21</sub>N<sub>3</sub>O<sub>3</sub> (327.38): calcd. C 66.04; H 6.47; N 12.84; found C 65.89, H 6.75, N 12.56.



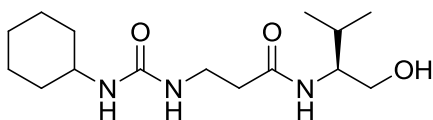
**(S)-N-(1-hydroxy-3-phenylpropan-2-yl)-3-(3-(2-nitrophenyl)ureido)propanamide (5e)**



According to the general procedure product **5e** was yielded as yellow solid (0.211 g, 0.546 mmol, 46%) starting from acid **1c** (0.300 g, 1.18 mmol) and coupled with (S)-2-amino-3-phenylpropan-1-ol.

$R_f = 0.31$  (DCM/MeOH 95:5). — m.p. 146-147°C —  $[\alpha]_D^{20} = -43.40$  ( $c = 0.1$ ,  $\text{CHCl}_3$ ) —  $^1\text{H NMR}$  (400 MHz,  $\text{CD}_3\text{OD}$ , 25°C):  $\delta = 2.40$  (t, 2H,  $J = 6.6$  Hz), 2.72 (dd, 1H,  $J = 13.7, 8.3$ ), 2.90 (dd, 1H,  $J = 13.7, 6.1$  Hz), 3.41 (m, 2H), 3.51 (dd, 1H,  $J = 11.1, 5.6$  Hz), 3.56 (dd, 1H,  $J = 10.6, 5.1$  Hz), 4.14 (m, 1H), 7.13 (m, 2H), 7.23 (m, 4H), 7.61 (ddd, 1H,  $J = 8.7, 7.2, 1.6$ ), 8.13 (dd, 1H,  $J = 8.4, 1.6$  Hz), 8.35 (dd, 1H,  $J = 8.6, 1.2$  Hz). —  $^{13}\text{C NMR}$  (100.6 MHz,  $\text{CD}_3\text{OD}$ , 25°C):  $\delta = 35.9, 36.2, 36.6, 52.8, 62.8, 121.4, 122.1, 125.1, 125.9, 127.8, 128.9, 134.6, 135.7, 137.1, 138.4, 155.4, 172.2$ . — **IR**:  $\nu = 3371, 3329, 3282, 2368, 1676, 1649, 1585, 1556, 1155, 1116, 1082, 960, 840$ . —  $\text{C}_{19}\text{H}_{22}\text{N}_4\text{O}_5$  (355.43): calcd. C 59.06; H 5.74; N 14.50; found C 59.23, H 6.00, 14.76.

**(S)-3-(3-cyclohexylureido)-N-(1-hydroxy-3-methylbutan-2-yl)propanamide (2f)**

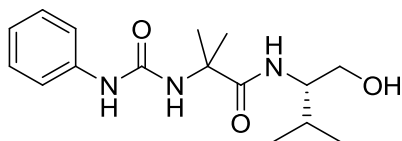


According to the general procedure product **5f** was yielded as white solid (0.688 g, 2.19 mmol, 99%) starting from acid **1c** (0.500 g, 2.3 mmol) and coupled with L-Valinol.

$R_f = 0.44$  (DCM/MeOH 95:5). — m.p. 140-141°C —  $[\alpha]_D^{20} = -30.12$  ( $c = 0.1$ ,  $\text{CHCl}_3$ ) —  $^1\text{H NMR}$  (400 MHz,  $\text{CD}_3\text{OD}$ , 25°C):  $\delta = 0.91$  (d, 3H,  $J = 6.7$  Hz), 0.94

(d, 3H,  $J = 6.7$  Hz), 1.17 (m, 3H), 1.34 (m, 3H), 1.60 (dt, 1H,  $J = 12.6, 3.8$  Hz), 1.72 (dt, 1H,  $J = 13.3, 3.8$  Hz), 1.85 (m, 3H), 2.42 (m, 2H), 3.39 (m, 2H), 3.53 (dd, 1H,  $J = 11.4, 6.6$  Hz), 3.61 (dd, 1H,  $J = 11.3, 4.4$  Hz), 3.71 (m, 1H). —  $^{13}\text{C}$  NMR (100.6 MHz,  $\text{CD}_3\text{OD}$ ,  $25^\circ\text{C}$ ):  $\delta = 17.4, 18.6, 24.6, 25.3, 28.6, 33.3, 36.1, 36.5, 56.6, 61.9, 158.9, 172.9$ . — **IR**:  $\nu = 3312, 3278, 2409, 1623, 1578, 1545, 1345, 1214, 1123, 1076, 965$ . —  $\text{C}_{15}\text{H}_{29}\text{N}_3\text{O}_3$  (299.41): calcd. C 60.17; H 9.76; N 14.03; found C 59.89, H 10.09, N 14.33.

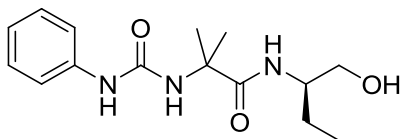
**(S)-N-(1-hydroxy-3-methylbutan-2-yl)-2-methyl-2-(3-phenylureido)propanamide (5g)**



According to the general procedure product **5g** was yielded as white solid (0.630 g, 2.04 mmol, 100%) starting from acid **1d** (0.500 g, 2.25 mmol) and coupled with L-Valinol.

$R_f = 0.25$  (DCM/MeOH 95:5) — m.p.  $135\text{--}136^\circ\text{C}$  —  $[\alpha]_D^{20} = -38.27$  ( $c = 0.1$ ,  $\text{CHCl}_3$ ) —  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ,  $25^\circ\text{C}$ ):  $\delta = 0.86$  (d, 3H,  $J = 6.8$  Hz), 0.89 (d, 3H,  $J = 6.7$  Hz), 1.52 (s, 3H), 1.53 (s, 3H), 1.70 (m, 1H), 3.39 (t, 1H,  $J = 10.2$  Hz), 3.70 (m, 2H), 3.98 (bs, 1H), 6.43 (s, 1H), 6.86 (d, 1H,  $J = 9.8$  Hz), 6.94 (t, 1H,  $J = 7.2$  Hz), 7.15 (t, 2H, 7.6 Hz), 7.28 (d, 2H, 7.7 Hz), 8.09 (s, 1H). —  $^{13}\text{C}$  NMR (100.6 MHz,  $\text{CHCl}_3$ ,  $25^\circ\text{C}$ ):  $\delta = 19.2, 19.7, 24.7, 26.9, 29.1, 56.8, 57.9, 64.2, 120.1, 123.0, 128.7, 138.7, 156.1, 177.4$ . — **IR**:  $\nu = 3358, 2724, 1649, 1578, 1542, 1310, 1150, 1133, 1087, 965$ . —  $\text{C}_{16}\text{H}_{25}\text{N}_3\text{O}_3$  (307.39): calcd. C 62.52; H 8.20; N 13.67; found C 62.22, H 8.06, N 14.01.

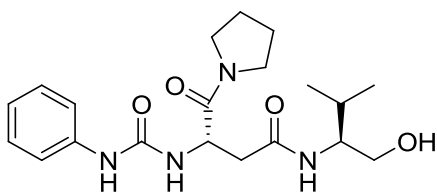
**(R)-N-(1-hydroxybutan-2-yl)-2-methyl-2-(3-phenylureido)propanamide (5h)**



According to the general procedure product **5h** was yielded as white solid (0.630 g, 2.04 mmol, 100%) starting from acid **1d** (0.500 g, 2.25 mmol) and coupled with (R)-2-aminobutan-1-ol.

$R_f = 0.27$  (DCM/MeOH 95:5). — m.p. 137-138°C —  $[\alpha]_D^{20} = +39.99$  ( $c = 0.1$ ,  $\text{CHCl}_3$ ) —  $^1\text{H NMR}$  (400 MHz,  $\text{CD}_3\text{OD}$ , 25°C):  $\delta = 0.94$  (t, 3H,  $J = 7.6$  Hz), 1.46 (m, 1H), 1.50 (s, 6H), 1.62 (m, 1H), 3.52 (d, 2H,  $J = 5.4$  Hz), 3.81 (m, 1H), 6.97 (t, 1H,  $J = 7.3$  Hz), 7.23 (m, 2H), 7.33 (dd, 2H,  $J = 8.5, 1.0$  Hz). —  $^{13}\text{C NMR}$  (100.6 MHz,  $\text{CHCl}_3$ , 25°C):  $\delta = 10.6, 23.4, 24.8, 26.9, 53.9, 56.7, 65.6, 120.0, 123.0, 128.7, 138.7, 156.0, 177.4$ . — **IR**:  $\nu = 3382, 3271, 3133, 2724, 1648, 1598, 1542, 1494, 1312, 1253, 1220, 1168, 1062, 845$ . —  $\text{C}_{15}\text{H}_{23}\text{N}_3\text{O}_3$  (293.36): calcd. C 61.41; H 7.90; N 14.32; found C 61.22, H 8.01, N 13.97.

**(S)-N-((S)-1-hydroxy-3-methylbutan-2-yl)-4-oxo-3-(3-phenylureido)-4-(pyrrolidin-1-yl)butanamide (5i)**

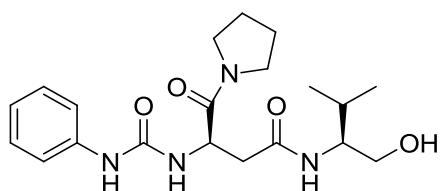


According to the general procedure product **5i** was yielded as yellow pale oil (0.154 g, 0.39 mmol, 60%) starting from the acid **1e** (0.200 g, 0.65 mmol) and coupled with L-valinol.

$R_f = 0.33$  (DCM/MeOH 95:5). —  $[\alpha]_D^{20} = -78.04$  ( $c = 0.1$ ,  $\text{CHCl}_3$ ) —  $^1\text{H NMR}$  (400 MHz,  $\text{CD}_3\text{OD}$ , 25°C):  $\delta = 0.91$  (d, 3H,  $J = 6.8$  Hz), 0.94 (d, 3H, 6.7 Hz), 1.82-1.93 (m, 2H), 2.00 (m, 1H), 2.57 (dd, 1H,  $J = 14.4, 7.4$  Hz), 2.72 (dd, 1H,  $J = 14.4,$

6.7 Hz), 3.38-3.60 (m, 4H), 3.69 (m, 2H), 3.79 (m, 1H), 5.02 (t, 1H,  $J= 7.2$  Hz), 6.98 (m, 1H), 7.24 (m, 2H), 7.33 (m, 2H). —  $^{13}\text{C}$  NMR (100.6 MHz,  $\text{CD}_3\text{OD}$ ,  $25^\circ\text{C}$ ):  $\delta= 17.4, 18.6, 23.7, 25.5, 28.5, 38.4, 45.9, 46.5, 48.8, 56.7, 61.7, 118.8, 122.2, 128.4, 139.2, 155.8, 170.7$ . — IR:  $\nu = 3310, 3259, 2767, 2456, 2412, 1665, 1565, 1508, 1459, 1334, 1300, 1211, 1098, 980, 876$ . —  $\text{C}_{20}\text{H}_{30}\text{N}_4\text{O}_4$  (390.48): calcd. C 61.52; H 7.74; N 14.35; found C 61.66, H 7.60, N 14.53.

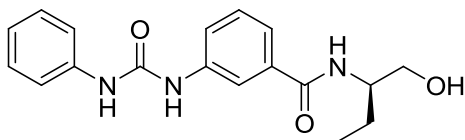
**(R)-N-((S)-1-hydroxy-3-methylbutan-2-yl)-4-oxo-3-(3-phenylureido)-4-(pyrrolidin-1-yl)butanamide (5j)**



According to the general procedure product **5j** was yielded as yellow pale oil (0.144 g, 0.37 mmol, 56%) starting from the acid **1f** (0.200 g, 0.65 mmol) and coupled with L-valinol.

$R_f = 0.33$  (DCM/MeOH 95:5). —  $[\alpha]_D^{20} = -12.35$  ( $c = 0.1, \text{CHCl}_3$ ) —  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ ,  $25^\circ\text{C}$ ):  $\delta = 0.89$  (d, 3H,  $J= 6.8$  Hz), 0.93 (d, 3H,  $J= 6.7$  Hz), 1.80-1.92 (m, 3H), 2.00 (m, 2H), 2.58 (dd, 1H,  $J= 14.3, 6.8$  Hz), 2.73 (dd, 1H,  $J= 14.3, 7.4$  Hz), 3.35-3.63 (m, 4H), 3.70 (m, 2H), 3.82 (m, 1H), 4.99 (t, 1H,  $J= 7.0$  Hz), 6.98 (m, 1H), 7.24 (m, 2H), 7.33 (dd, 2H,  $J= 8.8, 1.2$  Hz). —  $^{13}\text{C}$  NMR (100.6 MHz,  $\text{CD}_3\text{OD}$ ,  $25^\circ\text{C}$ ):  $\delta= 17.3, 18.6, 23.7, 25.5, 28.5, 38.3, 45.9, 46.5, 48.7, 56.7, 61.7, 118.7, 122.2, 128.4, 139.2, 155.8, 170.6, 170.8$ . — IR:  $\nu = 3300, 3256, 2789, 2481, 2426, 1656, 1599, 1548, 1499, 1315, 1224, 1100, 978, 856$ . —  $\text{C}_{20}\text{H}_{30}\text{N}_4\text{O}_4$  (390.48): calcd. C 61.52; H 7.74; N 14.35; found C 61.84, H 7.70, N 14.39.

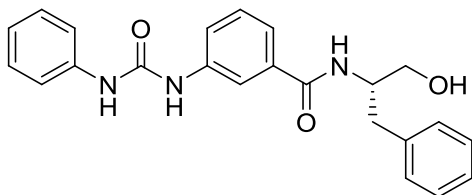
**(R)-N-(1-hydroxybutan-2-yl)-3-(3-phenylureido)benzamide (5k)**



According to the general procedure product **5k** was yielded as white solid (0.565 g, 1.72 mmol, 97%) starting from acid **1g** (0.500 g, 1.95 mmol) and coupled with (R)-2-aminobutan-1-ol.

$R_f = 0.40$  (DCM/MeOH 95:5). — m.p. 146-147°C —  $[\alpha]_D^{20} = +42.58$  ( $c = 0.1$ ,  $\text{CHCl}_3$ ) —  $^1\text{H NMR}$  (400 MHz,  $\text{CD}_3\text{OD}$ , 25°C):  $\delta = 1.00$  (t, 3H,  $J = 7.5$  Hz), 1.56 (m, 1H), 1.76 (m, 1H), 3.63 (dd, 2H,  $J = 5.6, 0.9$  Hz), 4.03 (m, 2H), 7.03 (t, 1H,  $J = 7.3$  Hz), 7.29 (dd, 2H,  $J = 8.5, 7.5$  Hz), 7.36 (t, 1H,  $J = 7.8$  Hz), 7.44 (dd, 2H,  $J = 8.7, 1.2$  Hz), 7.48 (dt, 1H,  $J = 7.7, 1.3$  Hz), 7.58 (ddd, 1H,  $J = 7.9, 2.2, 1.1$  Hz), 7.88 (t, 1H,  $J = 1.8$  Hz), 8.05 (d, 1H,  $J = 8.3$  Hz). —  $^{13}\text{C NMR}$  (100.6 MHz,  $\text{CD}_3\text{OD}$ , 25°C):  $\delta = 9.6, 23.66, 53.7, 63.43, 117.9, 119.1, 121.2, 121.9, 122.6, 128.5, 128.7, 135.6, 138.9, 139.4, 153.9, 169.2$ . — **IR**:  $\nu = 3383, 2724, 1697, 1648, 1542, 1154, 1069$ . —  $\text{C}_{18}\text{H}_{21}\text{N}_3\text{O}_3$  (327.38): calcd. C 66.04; H 6.47; N 12.84; found C 65.93, H 6.70, N 12.58.

**(S)-N-(1-hydroxy-3-phenylpropan-2-yl)-3-(3-phenylureido)benzamide (5l)**

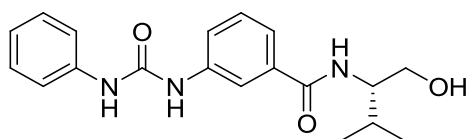


According to the general procedure product **5l** was yielded as white solid (0.689 g, 1.77 mmol, 100%) starting from acid **1g** (0.500 g, 1.95 mmol) and coupled with (S)-2-amino-3-phenylpropan-1-ol.

$R_f = 0.34$  (DCM/MeOH 95:5). — m.p. 157-158°C —  $[\alpha]_D^{20} = -50.29$  ( $c = 0.1$ ,  $\text{CHCl}_3$ ) —  $^1\text{H NMR}$  (400 MHz,  $\text{CD}_3\text{OD}$ , 25°C):  $\delta = 2.87$  (dd, 1H,  $J = 13.7, 8.6$

Hz), 3.03 (dd, 1H,  $J = 13.7, 6.2$  Hz), 3.66 (d, 2H,  $J = 5.5$  Hz), 4.34 (m, 1H), 7.04 (t, 1H,  $J = 7.5$  Hz), 7.17 (m, 1H), 7.29 (m, 6H), 7.37 (m, 2H), 7.45 (dd, 2H,  $J = 8.6, 1.0$  Hz), 7.56 (dt, 1H,  $J = 7.0, 2.2$  Hz), 7.79 (m, 1H). —  $^{13}\text{C NMR}$  (100.6 MHz,  $\text{CD}_3\text{OD}$ ,  $25^\circ\text{C}$ ):  $\delta = 36.6, 53.6, 62.9, 117.8, 119.0, 121.1, 121.8, 122.6, 125.9, 128.0, 128.5, 128.6, 129.0, 134.7, 135.5, 138.5, 139.0, 139.3, 153.9, 168.8$ . — **IR**:  $\nu = 3324, 2724, 1739, 1648, 1543, 1310, 1265, 1155, 1069, 876, 840$ . —  $\text{C}_{23}\text{H}_{23}\text{N}_3\text{O}_3$  (389.45): calcd. C 70.93; H 5.95; N 10.79; found C 70.88, H 6.18, N 7.78.

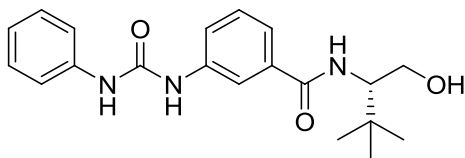
**(S)-N-(1-hydroxy-3-methylbutan-2-yl)-3-(3-phenylureido)benzamide (5m)**



According to the general procedure product **5m** was yielded as white solid (0.578 g, 1.69 mmol, 96%) starting from acid **1g** (0.500 g, 1.95 mmol) and coupled with L-Valinol

$R_f = 0.38$  (DCM/MeOH 95:5). — m.p.  $167\text{-}168^\circ\text{C}$  —  $[\alpha]_D^{20} = -44.37$  ( $c = 0.1$ ,  $\text{CHCl}_3$ ) —  $^1\text{H NMR}$  (400 MHz,  $\text{CD}_3\text{OD}$ ,  $25^\circ\text{C}$ ):  $\delta = 1.00$  (d, 3H,  $J = 6.8$  Hz), 1.03 (d, 3H,  $J = 6.8$  Hz), 2.00 (m, 1H), 3.67-3.76 (m, 2H), 3.91 (m, 1H), 7.03 (t, 1H,  $J = 7.3$  Hz), 7.30 (m, 2H), 7.39 (t, 1H,  $J = 7.9$  Hz), 7.44 (dd, 2H,  $J = 8.7, 1.2$  Hz), 7.48 (dt, 1H,  $J = 7.7, 1.3$  Hz), 7.58 (ddd, 1H,  $J = 8.1, 2.1, 1.0$  Hz), 7.88 (t, 1H,  $J = 1.8$  Hz). —  $^{13}\text{C NMR}$  (100.6 MHz,  $\text{CD}_3\text{OD}$ ,  $25^\circ\text{C}$ ):  $\delta = 17.8, 18.7, 28.9, 57.4, 61.7, 117.9, 119.0, 121.2, 121.8, 122.6, 128.4, 128.6, 135.7, 138.9, 139.4, 153.9, 169.2$ . — **IR**:  $\nu = 3266, 3200, 2722, 1656, 1609, 1565, 1501, 1310, 1221, 1167, 1089, 989, 840$ . —  $\text{C}_{19}\text{H}_{23}\text{N}_3\text{O}_3$  (341.40): calcd. C 66.84; H 6.79; N 12.31; found C 66.62, H 7.14, N 12.14.

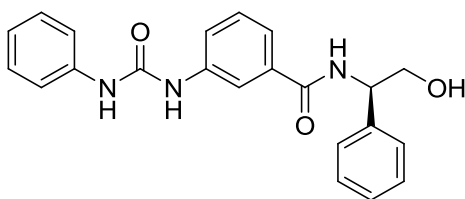
**(S)-N-(1-hydroxy-3,3-dimethylbutan-2-yl)-3-(3-phenylureido)benzamide (5n)**



According to the general procedure product **5n** was yielded as white solid (0.552 g, 1.55 mmol, 88%) starting from acid **1g** (0.500 g, 1.95 mmol) and coupled with (S)-2-amino-3,3-dimethylbutan-1-ol.

$R_f = 0.37$  (DCM/MeOH 95:5). — m.p. 97-98°C —  $[\alpha]_D^{20} = -49.69$  ( $c = 0.1$ ,  $\text{CHCl}_3$ ) —  $^1\text{H NMR}$  (400 MHz,  $\text{CD}_3\text{OD}$ , 25°C):  $\delta = 1.02$  (s, 9H), 3.63 (dd, 1H,  $J = 11.4, 8.8$  Hz), 3.68 (dd, 1H,  $J = 11.4, 3.5$  Hz), 4.04 (dd, 1H,  $J = 8.8, 3.5$  Hz), 7.04 (m, 1H), 7.30 (m, 1H), 7.40 (t, 1H,  $J = 7.7$  Hz), 7.42-7.50 (m, 3H), 7.59 (ddd, 1H,  $J = 7.9, 2.2, 1.1$  Hz) 7.87 (t, 1H,  $J = 1.7$  Hz) —  $^{13}\text{C NMR}$  (100.6 MHz,  $\text{CD}_3\text{OD}$ , 25°C):  $\delta = 26.0, 33.9, 54.4, 60.9, 117.9, 119.1, 121.3, 121.8, 122.6, 128.5, 128.7, 136.0, 138.9, 139.2, 153.9, 169.9$ . — **IR**:  $\nu = 3278, 3204, 2727, 1670, 1625, 1589, 1553, 1500, 1310, 1233, 1134, 1088, 1047, 840$ . —  $\text{C}_{20}\text{H}_{25}\text{N}_3\text{O}_3$  (355.43): calcd. C 67.58; H 7.09; N 11.82; found C 67.44, H 7.16, N 12.11.

**(R)-N-(2-hydroxy-1-phenylethyl)-3-(3-phenylureido)benzamide (5o)**

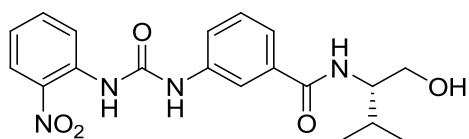


According to the general procedure product **5o** was yielded as white solid (0.420 g, 1.12 mmol, 98%) starting from acid **1g** (0.320 g, 1.25 mmol) and coupled with (R)-2-amino-2-phenylethanol.

$R_f = 0.39$  (DCM/MeOH 95:5). — m.p. 112-113°C —  $[\alpha]_D^{20} = -46.89$  ( $c = 0.1$ ,  $\text{CHCl}_3$ ) —  $^1\text{H NMR}$  (400 MHz,  $\text{CD}_3\text{OD}$ , 25°C):  $\delta = 3.87$  (d, 2H,  $J = 6.6$  Hz), 5.21

(t, 1H,  $J = 6.6$  Hz), 7.02 (t, 1H,  $J = 7.3$  Hz), 7.23-7.45 (m, 10H), 7.51 (d, 1H,  $J = 7.7$  Hz), 7.58 (dd, 1H,  $J = 8.0, 1.1$  Hz), 7.90 (s, 1H). —  $^{13}\text{C}$  NMR (100.6 MHz,  $\text{CD}_3\text{OD}$ ,  $25^\circ\text{C}$ ):  $\delta = 56.4, 64.7, 118.0, 119.1, 121.3, 122.0, 122.6, 126.6, 127.0, 128.1, 128.5, 128.7, 135.3, 138.9, 139.4, 139.9, 153.9, 168.9$ . — IR:  $\nu = 3300, 3205, 2727, 1646, 1621, 1599, 1563, 1348, 1298, 1235, 1175, 1065, 844$ . —  $\text{C}_{22}\text{H}_{21}\text{N}_3\text{O}_3$  (375.42): calcd. C 70.38; H 5.64; N 11.19; found C 70.37, H 5.73, N 12.11.

**(S)-N-(1-hydroxy-3-phenylpropan-2-yl)-3-(3-(2-nitrophenyl)ureido)benzamide  
(5p)**



According to the general procedure product **5p** was yielded as yellow solid (0.568 g, 1.47 mmol, 97%) starting from acid **1h** (0.500 g, 1.66 mmol) and coupled with L-Valinol.

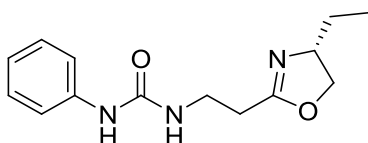
$R_f = 0.36$  (DCM/MeOH 95:5). — m.p.  $140-141^\circ\text{C}$  —  $[\alpha]_D^{20} = -47.64$  ( $c = 0.1$ ,  $\text{CHCl}_3$ ) —  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ ,  $25^\circ\text{C}$ ):  $\delta = 1.00$  (d, 1H,  $J = 6.8$  Hz), 1.03 (d, 1H,  $J = 6.8$  Hz), 2.01 (m, 1H), 3.71 (m, 2H), 3.92 (m, 1H), 7.19 (ddd, 1H,  $J = 8.4, 7.4, 1.3$ ), 7.42 (t, 1H,  $J = 7.8$  Hz), 7.51 (dt, 1H,  $J = 7.8, 1.3$  Hz), 7.67 (m, 2H), 7.97 (t, 1H,  $J = 1.8$  Hz), 8.19 (dd, 1H,  $J = 8.4, 1.4$  Hz), 8.48 (dd, 1H,  $J = 8.6, 1.2$  Hz). —  $^{13}\text{C}$  NMR (100.6 MHz,  $\text{CD}_3\text{OD}$ ,  $25^\circ\text{C}$ ):  $\delta = 17.8, 18.7, 28.9, 57.4, 61.7, 118.2, 121.6, 122.0, 122.3, 125.2, 128.7, 134.7, 135.2, 135.8, 153.2, 169.2$ . — IR:  $\nu = 3296, 3205, 1722, 1697, 1628, 1604, 1565, 1340, 1252, 1194, 1141, 1074, 1028, 846$ . —  $\text{C}_{19}\text{H}_{22}\text{N}_4\text{O}_5$  (355.43): calcd. C 59.06; H 5.74; N 14.50; found C 59.27, H 6.09, N 14.83.



## General procedure for cyclization of products (5) to oxazolines

Peptidic precursor **5** (1.0 equiv) was dissolved in THF (0.1M solution) and cooled at  $-78^{\circ}\text{C}$ ; then DAST (2.2 equiv) was added dropwise and the reaction stirred at the same temperature for 90 minutes. The mixture was filtered and the solvent evaporated under reduced pressure. The product was purified by flash chromatography eluting with MeOH (gradient from 1 to 5%) in DCM.

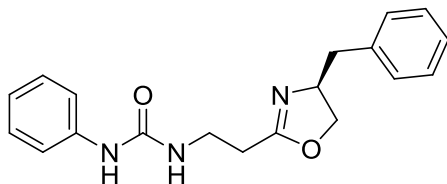
### (R)-1-(2-(4-ethyl-4,5-dihydrooxazol-2-yl)ethyl)-3-phenylurea (Ox-1)



According to the general procedure product **Ox-1** was yielded as pale yellow solid (0.410 g, 1.57 mmol, 77%) starting from precursor **5a** (0.570 g, 2.04 mmol).

$R_f = 0.57$  (DCM/MeOH 95:5). — m.p.  $68-69^{\circ}\text{C}$  —  $[\alpha]_D^{20} = +29.07$  ( $c = 0.1$ ,  $\text{CHCl}_3$ ) —  $^1\text{H NMR}$  (400 MHz,  $\text{CHCl}_3$ ,  $25^{\circ}\text{C}$ ):  $\delta = 0.91$ (t, 3H,  $J = 7.3$  Hz), 1.56 (m, 1H), 1.67 (m, 1H), 2.69 (t, 1H,  $J = 5.6$  Hz), 3.57 (m, 2H), 4.06-4.20 (m, 2H), 4.63 (t, 1H,  $J = 8.8$  Hz), 6.38 (bs, 1H), 7.02 (t, 1H,  $J = 7.7$  Hz), 7.25 (m, 2H), 7.39 (d, 2H,  $J = 7.3$  Hz), 7.75 (bs, 1H). —  $^{13}\text{C NMR}$  (100.6 MHz,  $\text{CDCl}_3$ ,  $25^{\circ}\text{C}$ ):  $\delta = 9.8, 24.0, 36.5, 37.3, 53.6, 64.6, 119.6, 122.8, 128.9, 139.2, 156.8, 173.0$ . — **IR**:  $\nu = 3321, 2725, 1640, 1556, 1309, 1243, 1156, 1070$ . —  $\text{C}_{14}\text{H}_{19}\text{N}_3\text{O}_2$  (261.32): calcd. C 64.35; H 7.33; N 16.08; found C 64.44, H 7.43, N 15.41.

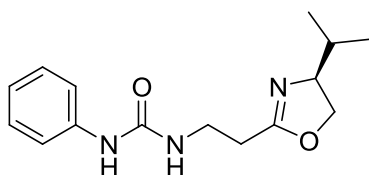
**(S)-1-(2-(4-benzyl-4,5-dihydrooxazol-2-yl)ethyl)-3-phenylurea (Ox-2)**



According to the general procedure product **Ox-2** was yielded as pale yellow solid (0.175g, 0.541mmol, 53%) starting from precursor **5b** (0.350 g, 1.03 mmol).

$R_f = 0.51$  (DCM/MeOH 95:5). — m.p. 130-131°C —  $[\alpha]_D^{20} = -44.65$  ( $c = 0.1$ ,  $\text{CHCl}_3$ ) —  $^1\text{H NMR}$  (400 MHz,  $\text{CHCl}_3$ , 25°C):  $\delta = 2.44$  (t, 2H,  $J = 5.8$  Hz), 2.64 (dd, 1H,  $J = 13.7, 7.8$  Hz), 2.96 (dd, 1H,  $J = 13.7, 5.6$  Hz), 3.43-3.62 (m, 2H), 3.98 (t, 1H,  $J = 7.4$  Hz), 4.20 (t, 1H, 8.4 Hz), 4.29 (m, 1H), 6.06 (bs, 1H), 7.03 (t, 1H,  $J = 7.3$  Hz), 7.13 (m, 2H), 7.16-7.40 (m, 8H), 7.63 (bs, 1H). —  $^{13}\text{C NMR}$  (100.6 MHz,  $\text{CDCl}_3$ , 25°C):  $\delta = 28.8, 36.6, 41.6, 66.7, 71.9, 120.5, 123.3, 126.6, 128.6, 129.1, 129.2, 137.7, 139.0, 156.2, 167.4$ . — **IR**:  $\nu = 3331, 2724, 1679, 1632, 1595, 1565, 1497, 1444, 1349, 1311, 1242, 1191, 1084, 975, 924$ . —  $\text{C}_{19}\text{H}_{21}\text{N}_3\text{O}_2$  (323.39): calcd. C 70.57; H 6.55; N 12.99; found C 70.78, H 6.32, N 13.04.

**(S)-1-(2-(4-isopropyl-4,5-dihydrooxazol-2-yl)ethyl)-3-phenylurea (Ox-3)**

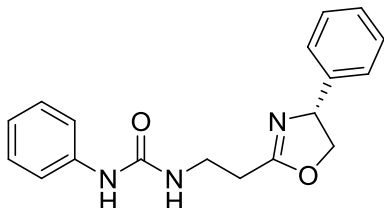


According to the general procedure product **Ox-3** was yielded as white solid (0.519g, 1.88mmol, 99%) starting from precursor **5c** (0.560 g, 1.91 mmol)

$R_f = 0.59$  (DCM/MeOH 95:5). — m.p. 81-81°C —  $[\alpha]_D^{20} = -29.80$  ( $c = 0.1$ ,  $\text{CHCl}_3$ ) —  $^1\text{H NMR}$  (400 MHz,  $\text{CD}_3\text{OD}$ , 25°C):  $\delta = 0.89$  (d, 3H,  $J = 6.8$  Hz), 0.94 (d, 3H,  $J = 6.7$  Hz), 1.74 (m, 1H), 2.52 (m, 2H), 3.49 (m, 2H), 3.91 (m, 1H), 4.07 (t, 1H,  $J = 7.9$  Hz), 4.31 (dd, 1H,  $J = 9.8, 8.7$  Hz), 6.97 (m, 1H), 7.24 (m, 2H), 7.33 (dd, 2H,  $J = 8.7, 1.2$  Hz). —  $^{13}\text{C NMR}$  (100.6 MHz,  $\text{CD}_3\text{OD}$ , 25°C):  $\delta = 17.4, 18.6, 28.6, 36.1$ ,

36.2, 56.6, 61.8, 118.8, 122, 128.4, 139.5, 156.8, 172.8. — **IR**:  $\nu = 3205, 2728, 1694, 1639, 1594, 1527, 1380, 1353, 1168, 1077, 1029, 920, 832$ . —  $C_{15}H_{21}N_3O_2$  (273.35): calcd. C 65.43; H 7.69; N 15.26; found C 65.61, H 7.99, N 14.61.

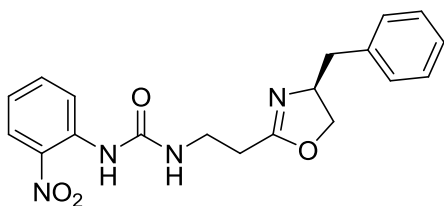
**(R)-1-phenyl-3-(2-(4-phenyl-4,5-dihydrooxazol-2-yl)ethyl)urea (Ox-4)**



According to the general procedure product **Ox-4** was yielded white solid (0.257g, 0.83 mmol, 77%) starting from precursor **5d** (0.500 g, 1.54 mmol).

$R_f = 0.59$  (DCM/MeOH 95:5). — m.p. 122-123°C —  $[\alpha]_D^{20} = +38.08$  ( $c = 0.1$ ,  $CHCl_3$ ) —  $^1H$  NMR (400 MHz,  $CHCl_3$ , 25°C):  $\delta = 2.51$  (t, 2H,  $J = 5.8$  Hz), 3.54 (m, 2H), 4.06 (t, 1H,  $J = 8.3$  Hz), 4.56 (dd, 1H,  $J = 10.1, 8.6$  Hz), 5.09 (t, 1H,  $J = 9.2$  Hz), 6.18 (t, 1H,  $J = 6.0$  Hz), 6.97 (m, 1H), 7.13-7.36 (m, 10H). —  $^{13}C$  NMR (100.6 MHz,  $CDCl_3$ , 25°C):  $\delta = 28.9, 36.6, 67.7, 69.4, 120.1, 122.9, 127.8, 128.8, 129.0, 139.1, 141.8, 156.4, 171.8$  — **IR**:  $\nu = 3310, 2726, 1678, 1620, 1567, 1541, 1310, 1245, 1180, 1076, 978, 845$ . —  $C_{18}H_{19}N_3O_2$  (309.36): calcd. C 69.88; H 6.12; N 13.58; found C 69.58, H 6.34, N 13.89.

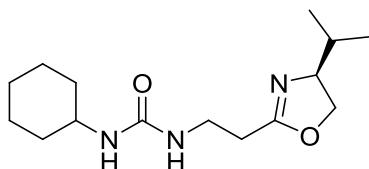
**(S)-1-(2-(4-benzyl-4,5-dihydrooxazol-2-yl)ethyl)-3-(2-nitrophenyl)urea (Ox-5)**



According to the general procedure product **Ox-5** was yielded as yellow solid (0.101 g, 0.274 mmol, 50%) starting from precursor **5e** (0.210 g, 0.543 mmol).

$R_f = 0.34$  (DCM/MeOH 95:5). — m.p. 154-155°C —  $[\alpha]_D^{20} = -42.12$  ( $c = 0.1$ , CHCl<sub>3</sub>) — **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>, 25°C):  $\delta = 2.56$  (t, 2H,  $J = 5.7$  Hz), 2.78 (dd, 1H,  $J = 13.7, 7.9$  Hz), 3.08 (dd, 1H,  $J = 13.7, 5.4$  Hz), 3.61 (m, 2H), 4.10 (dd, 1H,  $J = 8.3, 7.4$  Hz), 4.33 (t, 1H,  $J = 8.9$  Hz), 4.49 (m, 1H), 6.17 (bs, 1H), 7.04 (m, 1H), 7.20-7.35 (m, 5H), 7.58 (ddd, 1H,  $J = 8.7, 7.3, 1.6$  Hz), 8.16 (dd, 1H,  $J = 8.4, 1.5$  Hz), 8.58 (d, 1H,  $J = 8.6$  Hz), 9.72 (s, 1H). — **<sup>13</sup>C NMR** (100.6 MHz, CDCl<sub>3</sub>, 25°C):  $\delta = 28.1, 36.6, 41.5, 66.6, 71.9, 121.3, 121.5, 125.7, 126.7, 128.6, 129.3, 134.7, 135.8, 137.0, 137.4, 153.9, 172.2$ . — **IR**:  $\nu = 3353, 2724, 1651, 1613, 1543, 1309, 1264, 1140, 1104, 794$ . — C<sub>19</sub>H<sub>20</sub>N<sub>4</sub>O<sub>4</sub> (368.38): calcd. C 61.95 ; H 5.47, N 15.21; found C 61.66, H 5.78, N 14.99.

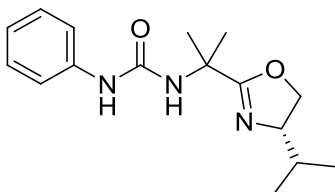
**(S)-1-cyclohexyl-3-(2-(4-isopropyl-4,5-dihydrooxazol-2-yl)ethyl)urea (Ox-6)**



According to the general procedure product Ox-6 was yielded as white solid (0.402 g, 1.42 mmol, 62%) starting from precursor **5f** (0.688 g, 2.30 mmol).

$R_f = 0.54$  (DCM/MeOH 95:5). — m.p. 103-104°C —  $[\alpha]_D^{20} = -39.45$  ( $c = 0.1$ , CHCl<sub>3</sub>) — **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>, 25°C):  $\delta = 0.90$  (d, 3H,  $J = 6.8$  Hz), 0.98 (d, 3H,  $J = 6.8$  Hz), 1.08-1.39 (m, 6H), 1.59 (dt, 1H,  $J = 12.8, 3.8$  Hz), 1.71 (m, 2H), 1.77 (m, 1H), 1.92 (m, 2H), 2.50 (m, 2H), 3.51 (m, 2H), 3.92 (m, 1H), 4.02 (t, 1H,  $J = 8.1$  Hz), 4.32 (dd, 1H,  $J = 9.5, 8.5$  Hz), 4.61 (d, 1H,  $J = 7.5$  Hz), 5.49 (bs, 1H). — **<sup>13</sup>C NMR** (100.6 MHz, CDCl<sub>3</sub>, 25°C):  $\delta = 18.1, 18.7, 24.9, 25.6, 28.6, 32.5, 33.9, 36.6, 49.4, 70.3, 71.3, 157.6, 167.4$ . — **IR**:  $\nu = 3351, 3305, 2350, 1669, 1624, 1579, 1532, 1309, 1251, 1167, 1082, 982, 939, 891, 791$ . — C<sub>15</sub>H<sub>27</sub>N<sub>3</sub>O<sub>2</sub> (281.39): calcd. C 64.02 ; H 9.67, N 14.93; found C 63.89, H 9.90, N 14.79.

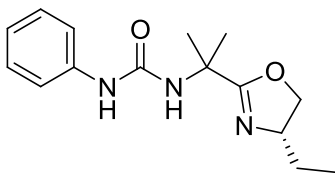
**(S)-1-(2-(4-isopropyl-4,5-dihydrooxazol-2-yl)propan-2-yl)-3-phenylurea (Ox-7)**



According to the general procedure product **Ox-7** was yielded as white solid (0.501 g, 1.73 mmol, 84%) starting from precursor **5g** (0.635 g, 2.06 mmol).

$R_f = 0.50$  (DCM/MeOH 95:5). — m.p. 189-190°C —  $[\alpha]_D^{20} = -43.12$  (c = 0.1, CHCl<sub>3</sub>) — <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD, 25°C):  $\delta = 0.89$  (d, 3H,  $J = 6.7$  Hz), 0.95 (d, 3H,  $J = 6.8$  Hz), 1.56 (s, 3H), 1.59 (s, 3H), 1.82 (m, 1H), 4.00 (ddd, 1H,  $J = 9.8, 7.2, 5.5$  Hz), 4.12 (dd, 1H,  $J = 8.6, 7.2$  Hz), 4.32 (dd, 1H,  $J = 9.8, 8.6$  Hz), 6.96 (m, 1H), 7.23 (dd, 2H,  $J = 8.6, 7.5$  Hz), 7.31 (dd, 2H,  $J = 8.6, 1.2$ ). — <sup>13</sup>C NMR (100.6 MHz, CD<sub>3</sub>OD, 25°C):  $\delta = 16.4, 17.5, 25.5, 25.7, 31.9, 51.5, 70.0, 71.2, 118.6, 121.9, 128.9, 139.4, 155.5, 172.2$ . — IR:  $\nu = 3338, 2725, 1646, 1600, 1557, 1543, 1310, 1264, 1152, 1071, 800$ . — C<sub>16</sub>H<sub>23</sub>N<sub>3</sub>O<sub>2</sub> (289.37): calcd. C 66.41; H 8.01, N 14.52; found C 66.53, H 8.11, 14.77.

**(S)-1-(2-(4-ethyl-4,5-dihydrooxazol-2-yl)propan-2-yl)-3-phenylurea (Ox-8)**

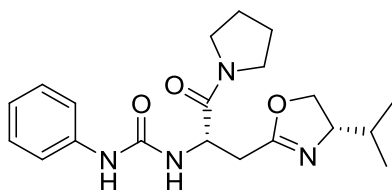


According to the general procedure product **Ox-8** was yielded as white solid (0.441 g, 1.60 mmol, 74%) starting from precursor **5h** (0.636 g, 2.17 mmol).

$R_f = 0.49$  (DCM/MeOH 95:5). — m.p. 122-123°C —  $[\alpha]_D^{20} = +40.82$  (c = 0.1, CHCl<sub>3</sub>) — <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD, 25°C):  $\delta = 0.94$  (t, 3H,  $J = 7.3$  Hz), 1.55 (s, 3H), 1.56 (m, 1H), 1.57 (s, 3H), 1.66 (m, 1H), 4.01 (t, 1H,  $J = 7.6$  Hz), 4.08 (m, 1H), 4.39 (dd, 1H,  $J = 9.0, 7.8$  Hz), 6.96 (t, 1H,  $J = 7.3$  Hz), 7.23 (t, 2H,  $J = 7.9$  Hz), 7.30 (dd, 2H,  $J = 8.8, 1.2$  Hz). — <sup>13</sup>C NMR (100.6 MHz, CD<sub>3</sub>OD, 25°C):  $\delta = 8.3, 25.5,$

25.6, 27.6, 51.3, 66.8, 72.3, 118.6, 122.0, 128.3, 139.3, 155.4, 172.2. — **IR**:  $\nu$  = 3321, 2725, 1661, 1641, 1596, 1587, 1500, 1302, 1250, 1218, 1132, 1082, 1068, 979, 955, 924, 843. —  $C_{15}H_{21}N_3O_2$  (275.35): calcd. C 65.43; H 7.69, N 15.26; found C 65.57, H 7.66, N 15.37.

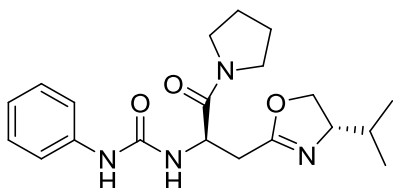
**1-((S)-3-((S)-4-isopropyl-4,5-dihydrooxazol-2-yl)-1-oxo-1-(pyrrolidin-1-yl)propan-2-yl)-3-phenylurea (Ox-9)**



According to the general procedure product **Ox-9** was yielded as yellow solid (0.083 g, 0.22 mmol, 58%) starting from precursor **5i** (0.150 g, 0.38 mmol).

$R_f$  = 0.43 (DCM/MeOH 95:5). — m.p. 122-123°C —  $[\alpha]_D^{20}$  = -71.70 ( $c$  = 0.1,  $CHCl_3$ ) —  **$^1H$  NMR** (400 MHz,  $CDCl_3$ , 25°C):  $\delta$  = 0.84 (d, 3H,  $J$  = 6.7 Hz), 0.92 (d, 3H,  $J$  = 6.7 Hz), 1.66 m, 1H), 1.87 (m, 2H), 1.96 (m, 2H), 2.68 (dd, 1H,  $J$  = 15.2, 6.4 Hz), 2.82 (dd, 1H,  $J$  = 15.2, 8.0 Hz), 3.49 (m, 2H), 3.78-3.92 (m, 4H), 4.20 (dd, 1H,  $J$  = 9.4, 8.2 Hz), 5.20 (m, 1H), 6.88-6.96 (m, 2H), 7.22 (t, 2H,  $J$  = 7.6 Hz), 7.36 (d, 2H,  $J$  = 7.6 Hz), 8.26 (s, 1H). —  **$^{13}C$  NMR** (100.6 MHz,  $CDCl_3$ , 25°C):  $\delta$  = 18.3, 18.7, 24.3, 25.9, 31.8, 32.6, 46.3, 47.1, 48.3, 70.3, 72.2, 118.8, 122.1, 128.7, 139.6, 155.2, 163.7, 170.9. — **IR**:  $\nu$  = 3330, 3223, 2721, 1656, 1623, 1567, 1504, 1398, 1311, 1214, 1200, 1178, 1123, 1083, 1034, 970. —  $C_{20}H_{28}N_4O_3$  (372.46): calcd. C 64.49 ; H 7.58, N 15.04; found C 64.67, H 7.30, N 14.99.

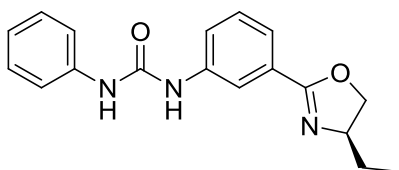
**1-((R)-3-((S)-4-isopropyl-4,5-dihydrooxazol-2-yl)-1-oxo-1-(pyrrolidin-1-yl)propan-2-yl)-3-phenylurea (Ox-10)**



According to the general procedure product **Ox-10** was yielded as yellow solid (0.074 g, 0.20 mmol, 58%) starting from precursor **5j** (0.134 g, 0.34 mmol).

$R_f = 0.43$  (DCM/MeOH 95:5). — m.p. 126-127°C —  $[\alpha]_D^{20} = -13.76$  (c = 0.1, CHCl<sub>3</sub>) —  $^1\text{H NMR}$  (400 MHz, CDCl<sub>3</sub>, 25°C):  $\delta = 0.83$  (d, 3H,  $J = 6.7$  Hz), 0.87 (d, 3H,  $J = 6.7$  Hz), 1.65 (m, 1H), 1.88 (m, 2H), 1.97 (m, 2H), 2.67 (dd, 1H,  $J = 15.6, 6.6$  Hz), 2.81 (dd, 1H,  $J = 15.6, 8.3$  Hz), 3.42-3.55 (m, 2H), 3.83-3.93 (m, 4H), 4.19 (dd, 1H,  $J = 8.7, 7.9$  Hz), 5.23 (m, 1H), 6.89 (d, 1H,  $J = 9.5$  Hz), 6.94 (t, 1H,  $J = 7.3$  Hz), 7.21 (t, 2H,  $J = 7.7$  Hz), 7.35 (d, 2H, 7.8 Hz), 8.35 (s, 1H). —  $^{13}\text{C NMR}$  (100.6 MHz, CDCl<sub>3</sub>, 25°C):  $\delta = 18.2, 18.4, 24.3, 25.9, 31.9, 32.4, 46.3, 47.1, 48.0, 70.2, 72.1, 118.8, 122.0, 128.7, 139.8, 155.1, 163.9, 171.0$ . — **IR**:  $\nu = 3312, 2729, 1678, 1634, 1603, 1593, 1549, 1334, 1212, 1150, 1115, 1084, 1065, 991, 840$ . — C<sub>20</sub>H<sub>28</sub>N<sub>4</sub>O<sub>3</sub> (372.46): calcd. C 64.49 ; H 7.58, N 15.04; found C 64.71, H 7.44, N 14.81.

**(R)-1-(3-(4-ethyl-4,5-dihydrooxazol-2-yl)phenyl)-3-phenylurea (Ox-11)**

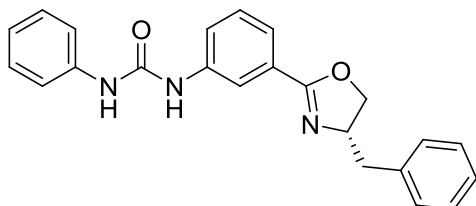


According to the general procedure product **Ox-11** was yielded as white solid (0.370 g, 1.20 mmol, 78%) starting from precursor **5k** (0.500 g, 1.53 mmol).

$R_f = 0.46$  (DCM/MeOH 95:5). — m.p. 147-148°C —  $[\alpha]_D^{20} = +43.30$  (c = 0.1, CHCl<sub>3</sub>) —  $^1\text{H NMR}$  (400 MHz, CD<sub>3</sub>OD, 25°C):  $\delta = 0.99$  (t, 3H,  $J = 7.3$  Hz), 1.63

(m, 1H), 1.74 (m, 1H), 4.14 (t, 1H,  $J = 7.7$  Hz), 4.24 (m, 1H), 4.54 (dd, 1H,  $J = 9.4, 8.2$  Hz), 7.02 (m, 1H), 7.29 (m, 2H), 7.37 (t, 1H,  $J = 8.2$  Hz), 7.43 (dd, 2H,  $J = 8.7, 1.1$  Hz), 7.58 (dt, 1H,  $J = 7.7, 1.3$  Hz), 7.68 (ddd, 1H,  $J = 8.1, 2.3, 1.0$  Hz), 7.96 (t, 1H,  $J = 2.0$  Hz). —  $^{13}\text{C NMR}$  (100.6 MHz,  $\text{CD}_3\text{OD}$ ,  $25^\circ\text{C}$ ):  $\delta = 8.52, 28.0, 67.1, 72.0, 118.4, 119.0, 122.1, 122.6, 127.8, 128.5, 128.7, 138.9, 139.6, 153.8, 164.6$ . — **IR**:  $\nu = 3309, 3281, 1644, 1612, 1592, 1572, 1448, 1311, 1298, 1237, 1168, 1080, 1059, 973, 926$ . —  $\text{C}_{18}\text{H}_{19}\text{N}_3\text{O}_2$  (309.36): calcd. C 69.98; H 6.19, N 13.58; found C 70.01, H 6.15, N 13.54.

**(S)-1-(3-(4-benzyl-4,5-dihydrooxazol-2-yl)phenyl)-3-phenylurea (Ox-12)**

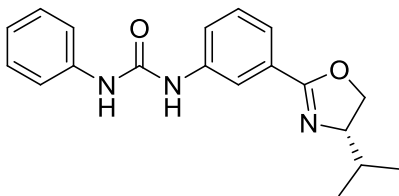


According to the general procedure product **Ox-12** was yielded as white solid (0.518 g, 1.39 mmol, 78%) starting from precursor **5I** (0.693 g, 1.78 mmol).

$R_f = 0.52$  (DCM/MeOH 95:5). — m.p.  $106\text{--}107^\circ\text{C}$  —  $[\alpha]_{\text{D}}^{20} = -37.89$  ( $c = 0.1$ ,  $\text{CHCl}_3$ ) —  $^1\text{H NMR}$  (400 MHz,  $\text{CHCl}_3$ ,  $25^\circ\text{C}$ ):  $\delta = 2.64$  (dd, 1H,  $J = 13.7, 9.0$  Hz), 3.12 (dd, 1H,  $J = 13.7, 5.1$  Hz), 4.02 (t, 1H,  $J = 7.8$  Hz), 4.22 (t, 1H,  $J = 8.8$  Hz), 4.47 (m, 1H), 6.95 (t, 1H,  $J = 7.1$  Hz), 7.11–7.27 (m, 11H), 7.54 (d, 1H,  $J = 7.1$  Hz), 7.94 (d, 2H,  $J = 8.1$  Hz), 8.04 (s, 1H). —  $^{13}\text{C NMR}$  (100.6 MHz,  $\text{CDCl}_3$ ,  $25^\circ\text{C}$ ):  $\delta = 41.8, 67.6, 72.0, 119.8, 120.5, 123.0, 123.1, 123.6, 126.6, 128.1, 128.6, 128.9, 129.0, 129.1, 137.8, 138.2, 138.7, 154.0, 164.4$ . — **IR**:  $\nu = 3353, 2724, 2360, 1649, 1597, 1555, 1310, 1264, 1201, 1154, 1074, 896, 845$ . —  $\text{C}_{23}\text{H}_{21}\text{N}_3\text{O}_2$  (371.43): calcd. C 74.37; H 5.70, N 11.31; found C 77.37, H 5.68, N 10.95.



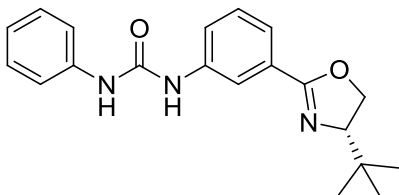
**(S)-1-(3-(4-isopropyl-4,5-dihydrooxazol-2-yl)phenyl)-3-phenylurea (Ox-13)**



According to the general procedure product **Ox-13** was yielded as white solid (0.458 g, 1.42 mmol, 91%) starting from precursor **5m** (0.530 g, 1.55 mmol).

$R_f = 0.49$  (DCM/MeOH 95:5). — m.p. 138-139°C —  $[\alpha]_D^{20} = -35.05$  ( $c = 0.1$ , CHCl<sub>3</sub>) —  $^1\text{H NMR}$  (400 MHz, CD<sub>2</sub>Cl<sub>2</sub>, 25°C):  $\delta = 0.92$  (d, 3H,  $J = 6.8$  Hz), 1.01 (d, 3H,  $J = 6.7$  Hz), 1.84 (m, 1H), 2.15 (bs, 1H), 4.09 (ddd, 1H,  $J = 9.5, 8.2, 6.4$  Hz), 4.16 (t, 1H, 8.2 Hz), 4.43 (dd, 1H,  $J = 9.5, 8.3$  Hz), 7.10 (m, 1H), 7.14 (bs, 1H), 7.25 (bs, 1H), 7.28-7.37 (m, 5H), 7.50 (ddd, 1H,  $J = 8.0, 2.1, 0.9$  Hz), 7.60 (dt, 1H,  $J = 7.7, 1.1$  Hz), 7.95 (t, 1H,  $J = 1.7$  Hz). —  $^{13}\text{C NMR}$  (100.6 MHz, CDCl<sub>3</sub>, 25°C):  $\delta = 17.6, 18.8, 32.4, 70.6, 71.2, 119.4, 120.8, 123.2, 123.6, 123.9, 128.9, 129.1, 129.3, 138.0, 138.8, 139.0, 153.6, 165.0$ . — **IR**:  $\nu = 3319, 2725, 1743, 1646, 1595, 1567, 1309, 1262, 1155, 1069, 801$ . — C<sub>19</sub>H<sub>21</sub>N<sub>3</sub>O<sub>2</sub> (323.39): calcd. C 70.57; H 6.55, N 12.99; found C 70.19, H 6.41, N 12.83.

**(S)-1-(3-(4-tert-butyl-4,5-dihydrooxazol-2-yl)phenyl)-3-phenylurea (Ox-14)**

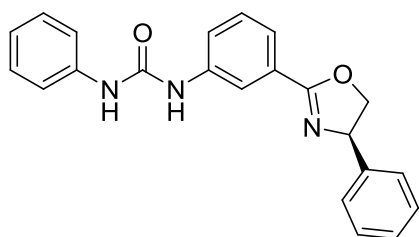


According to the general procedure product **Ox-14** was yielded as white solid (0.436 g, 1.29 mmol, 83%) starting from precursor **5n** (0.552 g, 1.55 mmol).

$R_f = 0.48$  (DCM/MeOH 95:5). — m.p. 170-171°C —  $[\alpha]_D^{20} = -47.13$  ( $c = 0.1$ , CHCl<sub>3</sub>) —  $^1\text{H NMR}$  (400 MHz, CD<sub>3</sub>OD, 25°C):  $\delta = 1.02$  (s, 9H), 3.63 (dd, 1H,  $J = 11.5, 8.9$  Hz), 3.88 (dd, 1H,  $J = 11.5, 3.4$  Hz), 4.04 (dd, 1H,  $J = 8.9, 3.4$  Hz), 7.03 (t,

1H,  $J=7.4$  Hz), 7.30 (dd, 2H,  $J=8.4, 7.4$  Hz), 7.40 (t, 1H,  $J=7.7$  Hz), 7.44 (m, 2H), 7.48 (ddd, 1H,  $J=7.7, 1.7, 1.1$  Hz), 7.59 (ddd, 1H,  $J=8.2, 2.2, 1.1$  Hz), 7.82 (t, 1H,  $J=1.7$  Hz) —  $^{13}\text{C NMR}$  (100.6 MHz,  $\text{CDCl}_3$ , 25°C):  $\delta=25.8, 33.9, 68.8, 75.9, 119.8, 120.6, 123.0, 123.1, 123.6, 128.3, 129.0, 138.1, 138.6, 154.0, 163.7$ . — **IR**:  $\nu=3352, 2724, 2360, 1740, 1647, 1596, 1560, 1309, 1264, 1204, 1154, 1073, 897, 799$ . —  $\text{C}_{20}\text{H}_{23}\text{N}_3\text{O}_2$  (337.42): calcd. C 71.19 ; H 6.87, N 12.45; found C 71.44, H 7.10, N 12.47.

**(R)-1-phenyl-3-(3-(4-phenyl-4,5-dihydrooxazol-2-yl)phenyl)urea (Ox-15)**

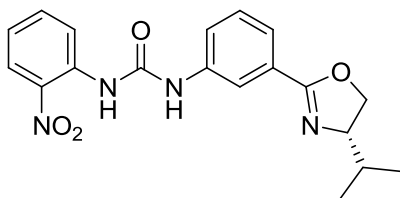


According to the general procedure product **Ox-15** was yielded as white solid (0.103 g, 0.29 mmol, 30%) starting from precursor **5o** (0.400 g, 1.06 mmol).

$R_f = 0.45$  (DCM/MeOH 95:5). — m.p. 134-135°C —  $[\alpha]_D^{20} = -51.78$  ( $c = 0.1$ ,  $\text{CHCl}_3$ ) —  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ , 25°C):  $\delta = 4.25$  (t, 1H,  $J=8.3$  Hz), 4.90 (dd, 1H,  $J=10.1, 8.3$  Hz), 5.45 (dd, 1H,  $J=10.1, 8.3$  Hz), 6.98 (t, 1H  $J=7.3$  Hz), 7.24-7.31 (m, 3H), 7.34-7.41 (m, 5H), 7.55 (dd, 2H,  $J=8.7, 1.1$  Hz), 7.65 (dt, 1H,  $J=7.7, 1.3$  Hz), 7.73 (ddd, 1H,  $J=8.2, 2.3, 1.1$  Hz), 8.23 (t, 1H,  $J=1.9$  Hz), 8.36 (s, 1H), 8.52 (s, 1H). —  $^{13}\text{C NMR}$  (100.6 MHz,  $\text{CDCl}_3$ , 25°C):  $\delta=69.5, 74.9, 118.2, 118.5, 118.6, 121.5, 121.6, 121.9, 122.1, 126.7, 127.3, 128.1, 128.5, 128.7, 128.9, 139.9, 140.4, 142.9, 152.5, 164.3$ . — **IR**:  $\nu=3321, 3278, 2725, 1709, 1656, 1611, 1561, 1311, 1223, 1189, 1063, 970, 840$ . —  $\text{C}_{22}\text{H}_{19}\text{N}_3\text{O}_2$  (357.41): calcd. C 73.93 ; H 5.36, N 11.76; found C 73.57, H 5.63, N 11.46.

**(S)-1-(3-(4-isopropyl-4,5-dihydrooxazol-2-yl)phenyl)-3-(2-nitrophenyl)urea**

**(Ox-16)**



According to the general procedure product **Ox-16** was yielded as yellow solid (0.441 g, 1.20 mmol, 82%) starting from precursor **5p** (0.565 g, 1.46 mmol).

$R_f = 0.38$  (DCM/MeOH 95:5). — m.p. 166-167°C —  $[\alpha]_D^{20} = -49.37$  ( $c = 0.1$ , CHCl<sub>3</sub>) —  $^1\text{H NMR}$  (400 MHz, CD<sub>2</sub>Cl<sub>2</sub>, 25°C):  $\delta =$  (d, 3H,  $J = 6.7$  Hz), 1.05 (d, 3H,  $J = 6.7$  Hz), 1.84 (m, 1H), 4.07-4.18 (m, 2H), 4.45 (dd, 1H,  $J = 9.2, 7.8$  Hz), 7.10 (bs, 1H), 7.15 (ddd, 1H,  $J = 8.4, 7.2, 1.3$  Hz), 7.43 (t, 1H,  $J = 7.7$  Hz), 7.64 (ddd, 1H,  $J = 7.9, 2.1, 1.0$  Hz), 7.68 (ddd, 1H,  $J = 8.7, 7.1, 1.6$  Hz), 7.72 (dt, 1H,  $J = 7.7, 1.2$  Hz), 8.04 (t, 1H,  $J = 2.0$  Hz), 8.22 (dd, 1H,  $J = 8.6, 1.6$  Hz), 8.68 (dd, 1H,  $J = 8.7, 1.1$  Hz), 9.94 (bs, 1H). —  $^{13}\text{C NMR}$  (100.6 MHz, CH<sub>2</sub>Cl<sub>2</sub>, 25°C):  $\delta =$  17.8, 18.6, 32.8, 70.3, 72.5, 119.7, 121.9, 122.1, 122.9, 123.4, 125.5, 128.8, 129.1, 135.4, 136.0, 136.7, 138.4, 151.8, 163.1. — **IR**:  $\nu =$  3339, 3281, 2724, 1650, 1591, 1557, 1309, 1278, 1155, 1066, 823. — C<sub>19</sub>H<sub>20</sub>N<sub>4</sub>O<sub>4</sub> (368.39): calcd. C 61.95 ; H 5.47, N 15.21; found C 61.71, H 5.84, N 13.47.

**General procedure for kinetic resolution of 1,2 diols**

Ligand (0.1 equiv.) was solved in CH<sub>2</sub>Cl<sub>2</sub> (0.15 M solution respect the substrate) and CuCl<sub>2</sub> (0.05 equiv.) added and the mixture stirred until the solution became clear and then cooled at 0°C. Substrate (1.0 equiv.), diisopropylethylamine (1.0 equiv.) and acyl chloride (0.5 equiv.) were added and the reaction stirred for 3 hours at 0°C. The reaction mixture was filtered on silica gel washing with CH<sub>2</sub>Cl<sub>2</sub> and the solvent evaporated under reduced pressure. Monobenzoylated product was purified

by flash chromatography on silica gel eluting with Hexane-Ethyl acetate (variable from 6:1 to 3:1). Spectroscopical datas of products were in agreement with the literature and enantiomeric excesses were determined by HPLC equipped with chiral column Chiracel AS-H.

### **General procedure for selective desymmetrization of *meso*-1,2 diols**

Ligand (0.1 equiv.) was solved in CH<sub>2</sub>Cl<sub>2</sub> (0.15 M solution respect the substrate) and CuCl<sub>2</sub> (0.05 equiv.) added and the mixture stirred until the solution became clear and then cooled at 0°C. Substrate (1.0 equiv.), diisopropylethylamine (1.0 equiv.) and acyl chloride (1.0 equiv.) were added and the reaction stirred for 3 hours at 0°C. The reaction mixture was filtered on silica gel washing with CH<sub>2</sub>Cl<sub>2</sub> and the solvent evaporated under reduced pressure. Monobenzoylated product was purified by flash chromatography on silica gel eluting with Hexane-Ethyl acetate (variable ratios from 6:1 to 3:1). Spectroscopical data of products were in agreement with the literature and enantiomeric excesses were determined by HPLC equipped with chiral column Chiracel AS-H.

### **General procedure for selective desymmetrization of *meso*-1,4-diols**

To a solution of *cis*-2,4-cyclopentenediol (10 mg, 0.099 mmol, 1.0 equiv) in 1.0 mL of dry THF (or DCM) was added tosyl isocyanate (35  $\mu$ L, 0.23 mmol, 2.3 equiv) and the colorless solution was stirred at 55°C for 1 hour and then was allowed to cool a room temperature. Triethylamine was added (if required) and the reaction mixture cooled to 0°C, and then added dropwise to an orange solution of [Pd(dba)<sub>2</sub>] (0.05 equiv) and ligand (0.1 equiv.) in 1.0 mL of dry THF. The orange reaction mixture was stirred at room temperature for 6-48 hours. The solvent was removed under vacuum and column chromatography on silica gel (1:10 ethyl

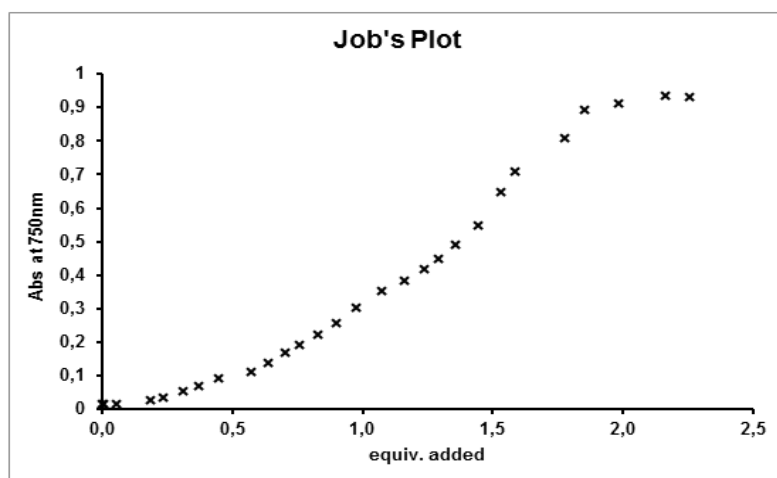
acetate–hexane) gave the desired product as a white solid. The enantiomeric excesses were determined by chiral HPLC equipped with Chiralcel OD-H (hexane:*i*PrOH 10:1, flux 0.5 mL/min., rt (*R,S*)= 23 min, rt (*S,R*)= 31 min). Spectroscopic data were in agreement with literature.

## Characterization of metal complexes

### Job's plot

4.88mg CuCl<sub>2</sub> (0.0363 mmol) were transferred in a quartz cuvette and 3.5mL CH<sub>2</sub>Cl<sub>2</sub> were added. (S)-1-(2-(4-isopropyl-4,5-dihydrooxazol-2-yl)ethyl)-3-phenylurea (**Ox-3**) was then sequentially added in accurately weighed portions of ~1mg (0.00363 mmol) up to 2.3 equivalents of ligand, performing UV absorption spectrum after each addition.

UV absorption value at 750 nm ( $\lambda_{\max}$ ) and the amount of ligand added were plotted in a 2D graph.

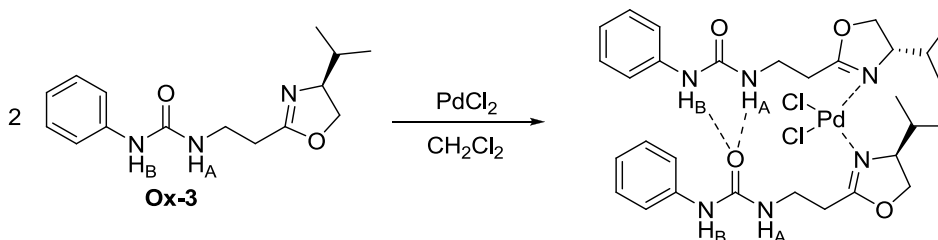


eq	Abs
0	0,0140
0,06	0,0122
0,10	0,0151
0,19	0,0254
0,24	0,0340
0,32	0,0535
0,37	0,0683
0,45	0,0904
0,57	0,1107
0,64	0,1372
0,70	0,1674
0,76	0,1903
0,83	0,2212
0,90	0,2532
0,98	0,2997
1,08	0,3490
1,16	0,3827
1,24	0,4142
1,29	0,4461
1,36	0,4894
1,44	0,5462
1,53	0,6460
1,58	0,7060
1,78	0,8071
1,86	0,8905
1,98	0,9120
2,16	0,9317
2,26	0,9286

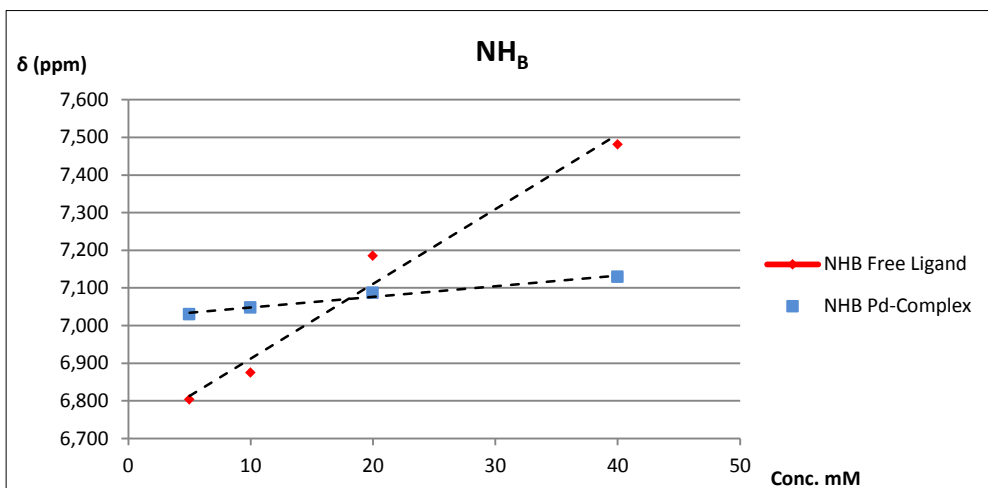
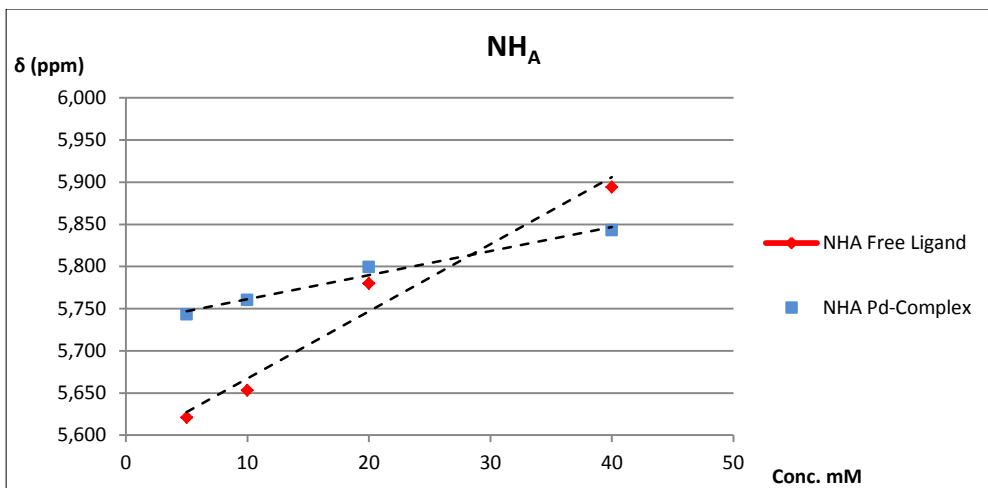
## NMR evaluations

(S)-1-(2-(4-isopropyl-4,5-dihydrooxazol-2-yl)ethyl)-3-phenylurea (**Ox-3**) (100mg, 0.363mmol) and  $\text{PdCl}_2(\text{CH}_3\text{CN})_2$  (47.1mg, 0.181mmol) were dissolved in 5mL DCM and stirred for 1 hour at room temperature. Complex was achieved by precipitation with hexane.

$^1\text{H}$  NMR experiments were carried out focusing on the variation of chemical shift of the NH signals upon different concentrations (5, 10, 20 and 40 mM) both in the complex and in the free ligand.



conc (mM)	$\text{NH}_A$		$\text{NH}_B$	
	free ligand	complex	free ligand	complex
5	5,6210	5,7430	6,803	7,029
10	5,6530	5,7600	6,875	7,047
20	5,7800	5,7990	7,185	7,086
40	5,8940	5,8430	7,481	7,129







# *Chapter 3*

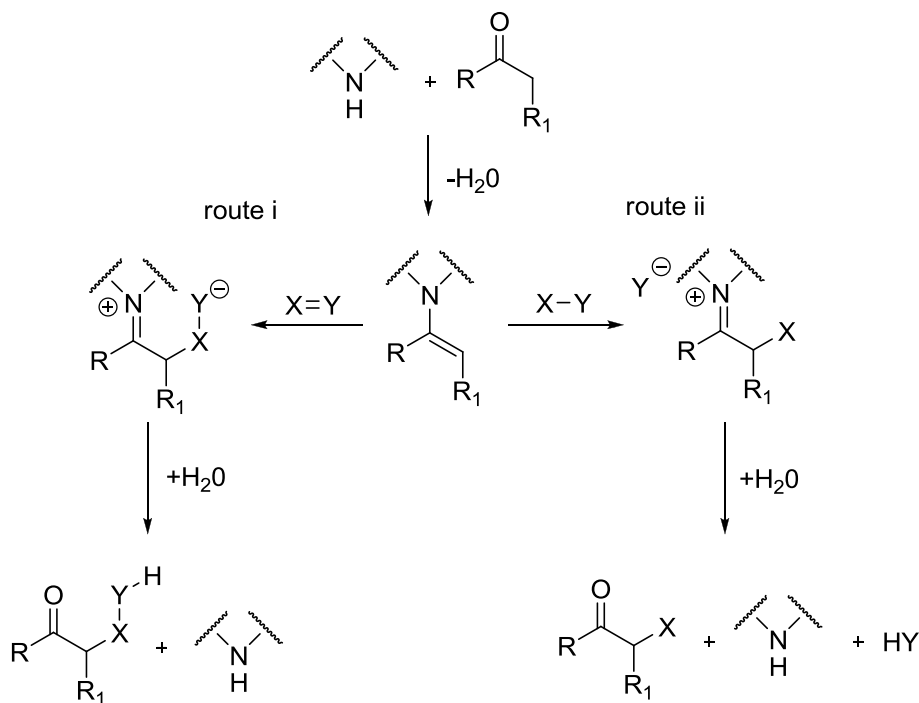
## *Bifunctional organocatalysts for asymmetric conjugate additions*



### 3.1 Enamine catalysis

In the last decade the potential of organocatalysis has successfully been demonstrated. In particular primary and secondary amines have emerged as a broadly applicable class of organocatalysts for many types of reactions. The catalysis of electrophilic substitutions in the  $\alpha$ -position of carbonyl compounds and related reactions via enamine intermediates is called enamine catalysis.<sup>1</sup>

In general an enamine is generated by reaction of a carbonyl compound with an amine under dehydrating conditions. Reaction of the enamine can proceed via an addition (route i) or substitution (route ii) depending on the nature of the reaction partner (electrophile). In either case, iminium ions are usually formed, which are then hydrolyzed to afford the products (Scheme 3.1). During the years many variants have been introduced in enamine chemistry; therefore, a catalytic version of this chemistry was highly desirable.

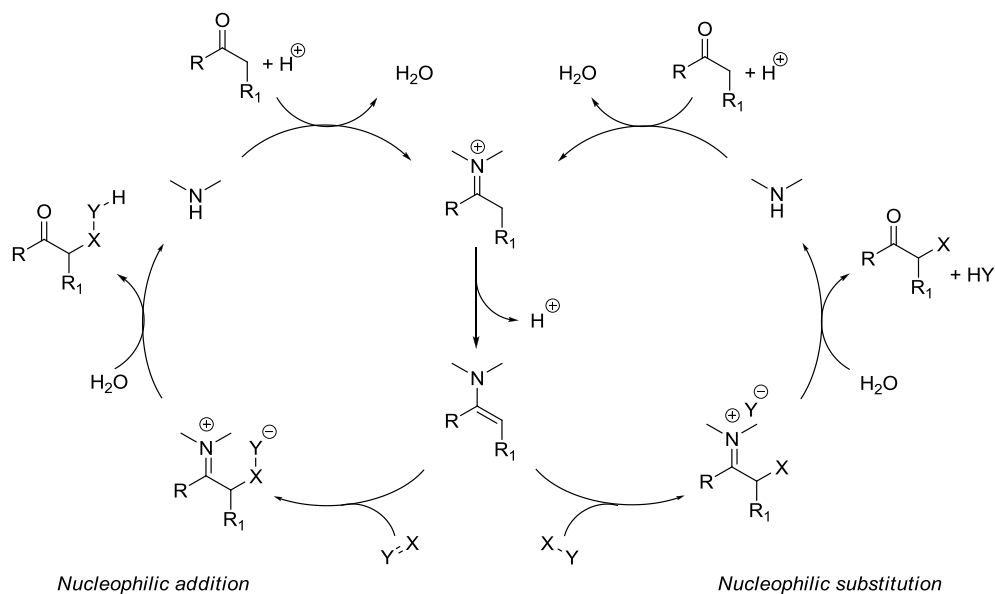


**Scheme 3.1**

<sup>1</sup> List, B. *Synlett* **2001**, 1675; List, B. *Acc. Chem. Res.* **2004**, 37, 548.

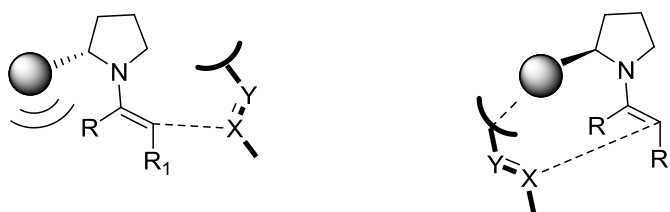
In recent years an exponential growth in the field of enamine catalysis occurred and, particularly, asymmetric enamine catalysis. This happened because, in addition to being almost ideally atom-economic and step-economic, the scope of the catalytic version exceeds those of the stoichiometric approach (Scheme 3.1). The basis of enamine catalysis is the reversible generation of enamines from a catalytic amount of an amine and a carbonyl compound. The key step of the process is the LUMO lowering effect and the resulting increase in C-H acidity upon initial conversion of the carbonyl compound into an iminium ion.

Two different mechanisms can be identified (Scheme 3.2) depending on the nature of electrophiles used. On the one hand, the double bond containing electrophiles such as aldehydes, imines, Michael acceptors, etc. are inserted into the  $\alpha$ -C-H bond of the carbonyl compound via a nucleophilic addition reaction of the enamine intermediate. On the other hand single bond containing electrophiles such as alkyl halides react in a nucleophilic substitution reaction.



**Scheme 3.2**

The asymmetric induction naturally is due to the structure of catalyst and initial carbonyl compound. The selectivity could be simplistically explained with the figures shown in Scheme 3.3 where is clear that, in the transition state, the geometry of enamine and the presence of interaction between catalyst and the electrophile govern the configuration of the product.



**Scheme 3.3**

Summarizing, enamine catalysis has developed into a powerful strategy for asymmetric synthesis and many studies are coming up in amazing pace, in this extremely active area. Here below the principal enamine-catalyzed reactions will be reported, in particular Michael reaction which will be widely used in this chapter.

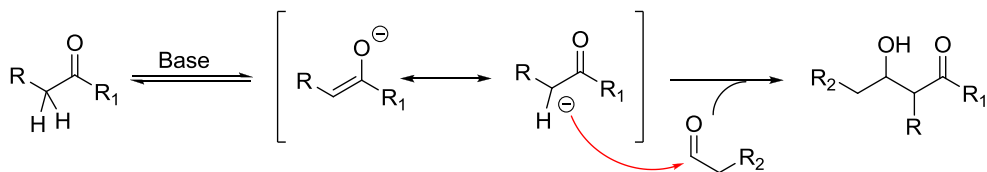
### 3.1.1 Enamine-catalyzed Aldol reaction

The aldol reaction is among the most commonly applied C-C bond forming reactions.<sup>2</sup> The versatility of this reaction stems from its utility in constructing chiral building blocks (via the stereoselective formation of C-C bonds) for the synthesis of structurally complex molecules, namely natural products or non-natural drug molecules. Aldol reactions combine a nucleophilic addition, which is acid-catalyzed, with an enolization, which is catalyzed by both acids and bases.<sup>3</sup> These properties make it possible for the aldolization to be catalyzed by both Lewis and Brønsted acids and bases (Scheme 3.4).

<sup>2</sup> Heathcock, C. H. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Heathcock, C. H., Eds.; Pergamon: Oxford, 1991; Vol. 2, pp 133.

<sup>3</sup> Tanaka, F.; Barbas, C. F., III. In *Enantioselective Organocatalysis*; Dalko, P. I., Ed.; Wiley-VCH: Weinheim, 2007; pp 19.

The direct aldol reaction between two unmodified carbonyl compounds has a great importance, especially for practical reason since it does not require the isolation of the reactive enolates.<sup>4</sup>



**Scheme 3.4**

Chemists became inspired by nature and developed catalysts that mimic the functional concept of aldolases for this purpose. One such approach includes antibody-catalyzed direct asymmetric aldol reactions developed by Barbas<sup>5</sup> and Reymond.<sup>6</sup> Purely chemical direct catalytic asymmetric aldol reactions were achieved by multifunctional heterobimetallic complexes reported by Shibasaki<sup>7</sup> and by dinuclear Zn complexes reported by Trost<sup>8</sup> and Shibasaki.<sup>9</sup> Both aldolases and even more so Knoevenagel-like chemistry may have stimulated chemists to employ amino acids for the catalysis of the aldol reaction. Initial efforts in asymmetric catalysis have concentrated on Proline-catalyzed enantioselective intramolecular aldolizations.

The first example of an asymmetric aldol reaction catalyzed by secondary amines was the intramolecular Proline-catalyzed aldolization of di- and triketones, reported by Hajos-Parrish-Eder-Sauer-Wiechert. Discovered in the early 1970s, this reaction

<sup>4</sup> Alcaide, B.; Almendros, P. *Eur. J. Org. Chem.* **2002**, 1595; Alcaide, B.; Almendros, P. *Angew. Chem., Int. Ed.* **2003**, *42*, 858.

<sup>5</sup> Tanaka, F.; Barbas, C. F., III In *Modern Aldol Reactions*; Mahrwald, R., Ed.; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, 004; Vol. 1, pp 273.

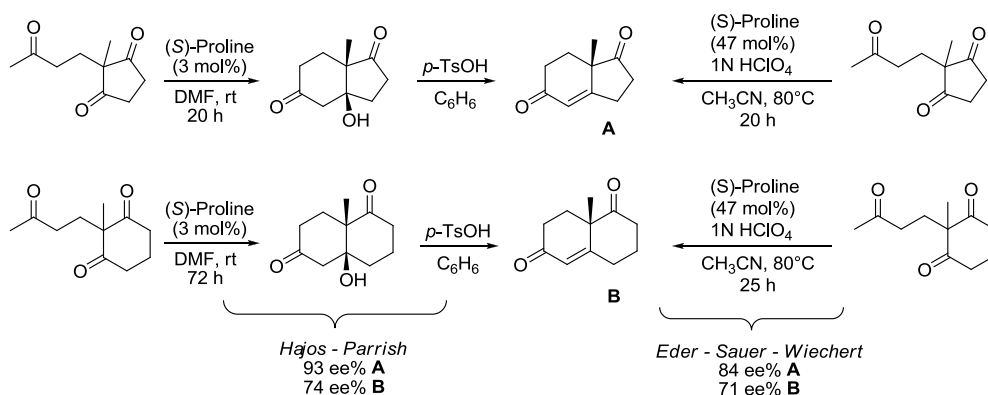
<sup>6</sup> Reymond, J.-L.; Chen, Y. *J. Org. Chem.* **1995**, *60*, 6970.

<sup>7</sup> Yamada, Y. M. A.; Yoshikawa, N.; Sasai, H.; Shibasaki, M. *Angew. Chem., Int. Ed.* **1997**, *36*, 1871; Yoshikawa, N.; Yamada, Y. M. A.; Das, J.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1999**, *121*, 4168; Kumagai, N.; Matsunaga, S.; Yoshikawa, N.; Ohshima, T.; Shibasaki, M. *Org. Lett.* **2001**, *3*, 1539; Yoshikawa, N.; Kumagai, N.; Matsunaga, S.; Moll, G.; Ohshima, T.; Suzuki, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 2466; Shibasaki, M.; Matsunaga, S.; Kumagai, N. In *Modern Aldol Reactions*; Mahrwald, R., Ed.; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, 2004; Vol. 2, pp 197.

<sup>8</sup> Trost, B. M.; Ito, H. *J. Am. Chem. Soc.* **2000**, *122*, 12003; Trost, B. M.; Silcoff, E. R.; Ito, H. *Org. Lett.* **2001**, *3*, 2497.

<sup>9</sup> Kumagai, N.; Matsunaga, S.; Kinoshita, T.; Harada, S.; Okada, S.; Sakamoto, S.; Yamaguchi, K.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 2169.

was the first example of a highly enantioselective organocatalytic process, although at that time neither its mechanism was well understood nor its potential for other reactions was realized. The Hajos-Parrish-Eder-Sauer-Wiechert reaction is a 6-enol-endo aldolization. Hajos and Parrish discovered that Proline is an effective catalyst for the intramolecular aldol reaction of triketones, furnishing aldols in good yields and in one case with high enantioselectivity (Scheme 3.5). Acid-catalyzed dehydration of the aldol addition products gave condensation products.<sup>10</sup> Independently in the same year, Eder, Sauer, and Wiechert directly isolated the aldol condensation products when the same cyclizations were conducted in the presence of Proline and an acid cocatalyst.<sup>11</sup>



**Scheme 3.5**

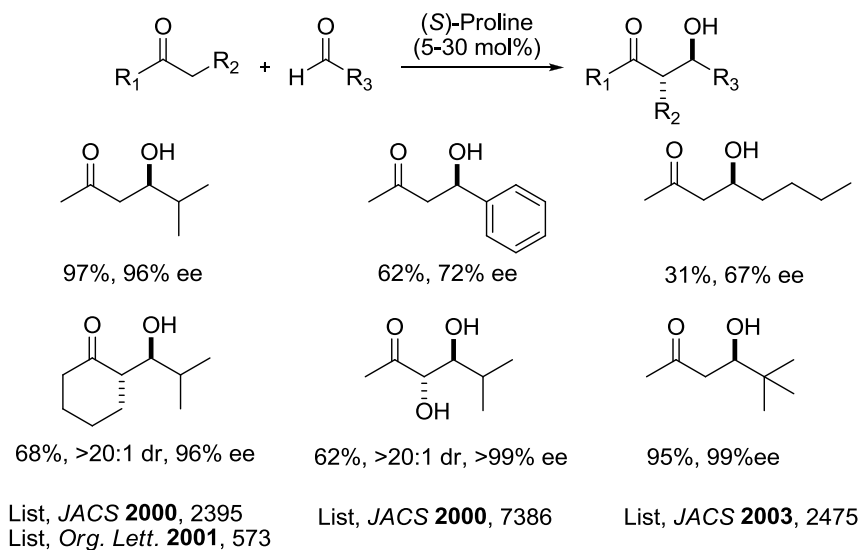
Despite its enormous potential, this methodology remained almost neglected for more than two decades and it was only towards the end of the millennium that a real burgeoning of this approach was observed with hundreds of examples being reported in very few years.<sup>12</sup> List's group, over the years, proved to be one of the most active in the field of proline catalysis and in the last decade reported numerous

<sup>10</sup> Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615.

<sup>11</sup> Eder, U.; Sauer, G. R.; Wiechart, R. German Patent DE 2014757, 1971.

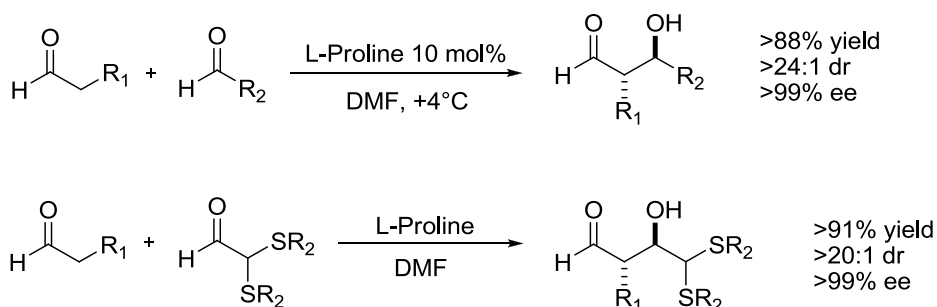
<sup>12</sup> Trost, B. M., Brindle, C. S. *Chem. Soc. Rev.* **2010**, *39*, 1600.

works. Several versions of the reaction were performed to obtain different adducts and a small selection of these are reported in Scheme 3.6.<sup>13</sup>



**Scheme 3.6**

MacMillan also reported very interesting works on aldol, in particular concerning the first enantioselective cross-aldol reaction of aldehydes<sup>14</sup> and  $\alpha$ -thioacetal aldehydes (Scheme 3.7).<sup>15</sup>



**Scheme 3.7**

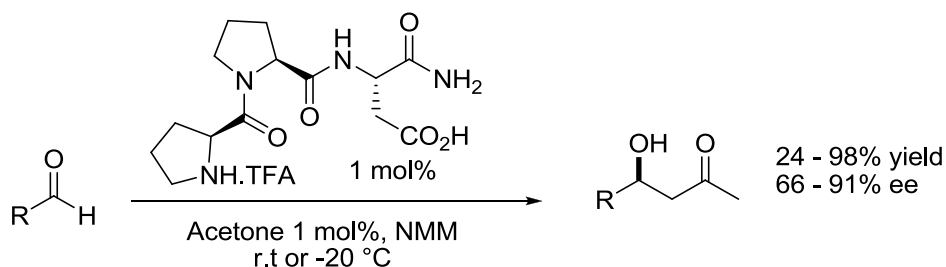
<sup>13</sup> List, B., Lerner, R. A., Barbas III C., F., *J. Am. Chem. Soc.*, **2000**, 122, 2395; Notz, W., List, B., *J. Am. Chem. Soc.*, **2000**, 122, 7386; List, B., Pojarliev, P., Castello, C., *Org. Lett.* **2001**, 4, 573; Bahmanyar, P., Biller, W. T., Martin, H., J., List, B., *J. Am. Chem. Soc.* **2003**, 9, 2475.

<sup>14</sup> Northrup, A. B., MacMillan, D. W. C., *J. Am. Chem. Soc.* **2002**, 124, 6798.

<sup>15</sup> Storer, I., R., MacMillan D. W. C., *Tetrahedron* **2004**, 60, 7705.



Wennemers in 2003 reported the exploitation of oligopeptides as efficient organocatalysts for asymmetric aldol reactions (Scheme 3.8).<sup>16</sup> Oligopeptides proved highly suitable for a rapid modification of the catalyst's structure and, more important, conformation, the latter proving the importance of the nature and arrangement of the functional groups for a simultaneous activation of the nucleophile and of the electrophile. The tripeptide Pro-Pro-Asp-NH<sub>2</sub> emerged as best asymmetric catalyst, for aldol reaction, from a library of 3375 tripeptides generated by the split-mix methodology and screened by "catalyst-substrate coimmobilization".<sup>17</sup>



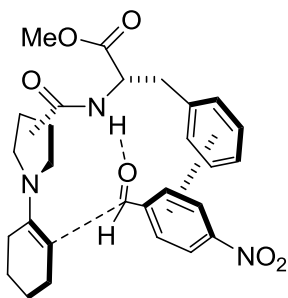
**Scheme 3.8**

In 2010 Juaristi reported the use of the dipeptide Pro-Phe as efficient organocatalyst for aldol reaction between cyclic ketones and electron-poor aromatic aldehydes in solvent-free conditions with good results (ees up to 95%).<sup>18</sup> The peculiarity of this work is the transition state proposed in which the dipeptide acts as bifunctional-like catalyst interacting with the aldehyde by  $\pi$ - $\pi$  interaction (Scheme 3.9).

<sup>16</sup> Revell, J. D., Wennemers, H., *Adv. Synth. Catal.* **2008**, 350, 1046 and references therein.

<sup>17</sup>(a) P. Krattiger, C. McCarthy, A. Pfaltz, H. Wennemers, *Angew. Chem. Int. Ed.* **2003**, 42, 1722;( b) J. D. Revell, H. Wennemers, *Adv. Synth. Catal.* **2008**, 350, 1046; (c) M. Messerer, H. Wennemers, *Synlett* **2011**, 499.

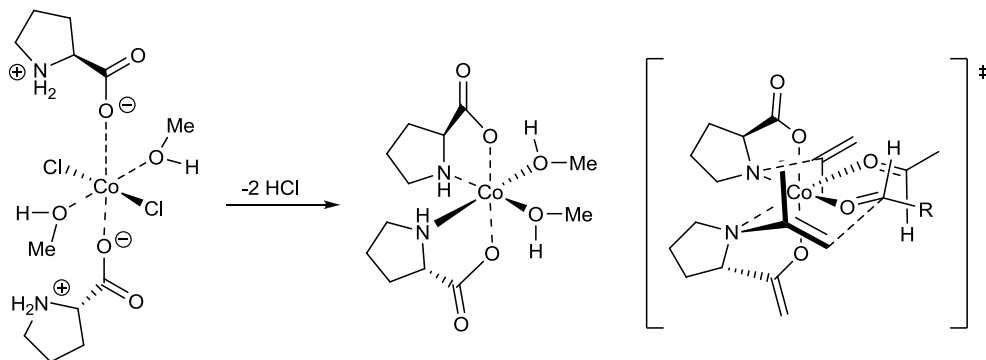
<sup>18</sup> Hernandez, J. G., Juaristi, E., *J. Org. Chem.* **2011**, 76, 1464.



**Scheme 3.9**

Reiser has recently reported a novel kind of proline catalyzed aldol reaction.<sup>19</sup> While proline itself is able to act as asymmetric catalyst, an improvement of efficiency was observed in presence of cobalt chloride as co-catalyst.

The system was tested with a wide range of ketones and aldehydes with excellent results in terms of diastereo- (up to 45:1 *anti/syn*) and enantioselectivity (up to >99%). The mechanism proposed involves two prolines coordinated to the cobalt ion to form a  $C_2$ -symmetric complex. Due to the symmetry, both prolines give rise to the same enamines and consequently the same aldol product (Scheme 3.10).



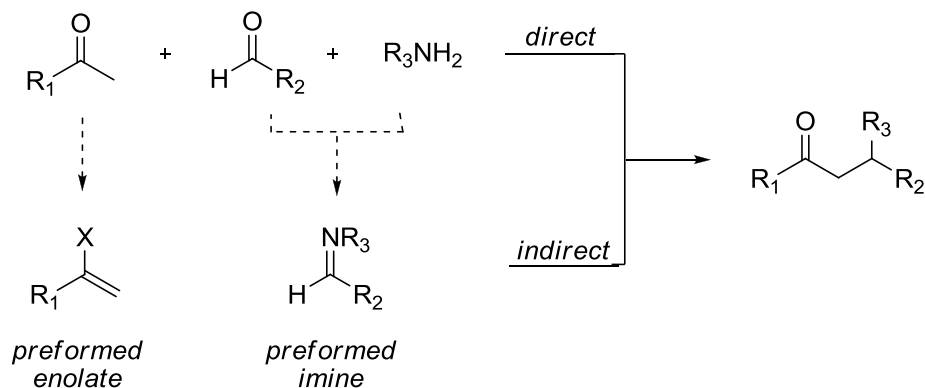
**Scheme 3.10**

<sup>19</sup> Karmakar, A., Maji, T., Wittmann, S., reiser, O., *Chem. Eur. J.* **2011**, *17*, 11024.

### 3.1.2 Enamine-catalyzed Mannich reaction

The Mannich reaction, developed by Carl Mannich more or less 100 years ago, is a highly useful transformation for the construction of nitrogenous molecules.<sup>20</sup> In this transformation three components, two carbonyl compounds and an amine, react to form a  $\beta$ -amino-carbonyl compound. The key element in Mannich reactions is an iminium intermediate, which is susceptible to nucleophilic attack by a variety of nucleophiles such as enolized ketones or equivalents thereof, resulting in carbon-carbon bond formation adjacent to the nitrogen atom.

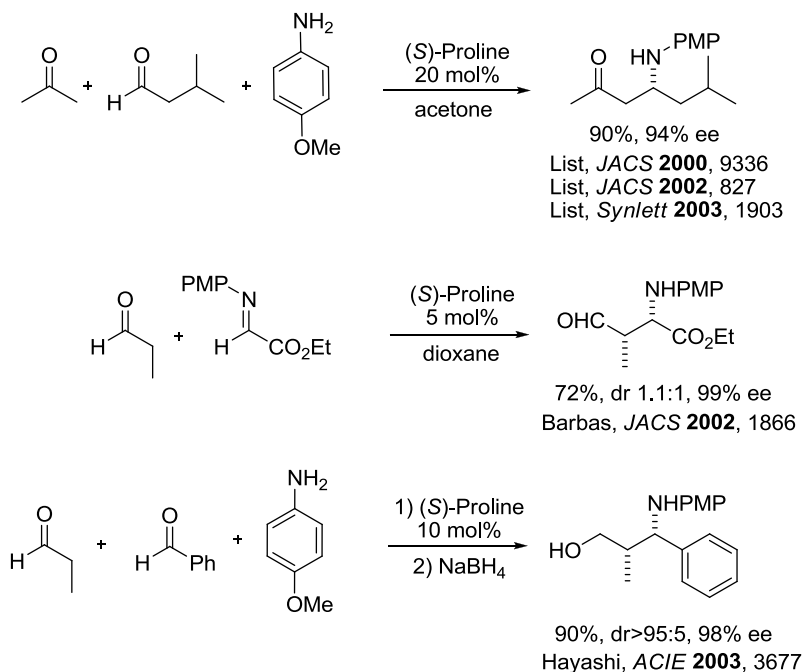
The increasing popularity of the Mannich reaction has been fueled by the ubiquitous nature of nitrogen in drugs and natural products as well as by the potential of this multicomponent reaction to generate diversity. Both direct variants with unmodified ketone donors and indirect variants utilizing preformed enolate equivalents have been described. In addition, the imine intermediate may be preformed or its amine and aldehyde precursors may be used directly (Scheme 3.11).



Scheme 3.11

<sup>20</sup> Mannich, C.; Krosche, W. *Arch. Pharm.* **1912**, 250, 647.

Enantioselective variants are especially attractive and over the years many groups have been involved in the development of asymmetric version of Mannich reaction<sup>21</sup> and some of the most interesting works are reported in Scheme 3.12 even if many others could worth mention.



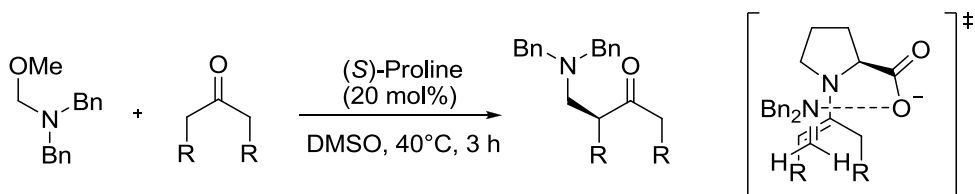
**Scheme 3.12**

.Based on important contributions by Gellman,<sup>22</sup> Cordova and co-workers reported the asymmetric R-aminomethylation of cyclohexanone with dibenzyl aminomethyl ether using (*S*)-proline as catalyst.<sup>23</sup> The results proved that (*S*)-proline gives the corresponding R-aminomethylated ketones in generally modest yields (32-75%) with high enantioselectivities (75-99% ee). A possible transition state was also suggested (Scheme 3.13).

<sup>21</sup> Rutjes, F. P. J. T. *Chem. Soc. Rev.*, **2008**, 37, 29.

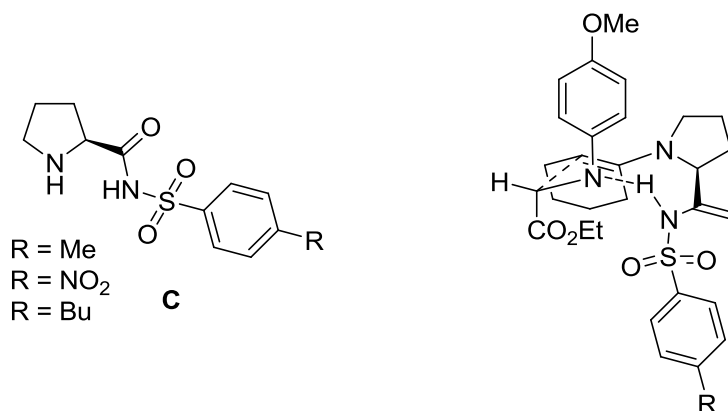
<sup>22</sup> Chi, Y.; Gellman, S. H. *J. Am. Chem. Soc.* **2006**, 128, 6804.

<sup>23</sup> Ibrahim, I.; Dziedzic, P.; Cordova, A. *Synthesis* **2006**, 23, 4060.



**Scheme 3.13**

More recently Toma reported that Proline-derived N-sulfonylcarboxamides **C** efficiently catalyze the asymmetric Mannich reaction of cyclic ketones with N-(p-methoxyphenyl)-protected iminoglyoxylate. The reaction proceeded with high enantioselectivity (99% ee).<sup>24</sup> Enamine intermediates were investigated by DFT calculations and a transition state was hypothesized (Scheme 3.14).



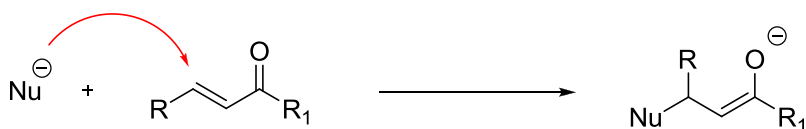
**Scheme 3.14**

### 3.1.3 Enamine-catalyzed Michael reaction

The Michael reaction, developed by Arthur Michael in the late 19<sup>th</sup> century, is one of the most common C-C bond forming reactions used in organic synthesis. In broad terms, the Michael reaction may be most readily summarized as a “1,4

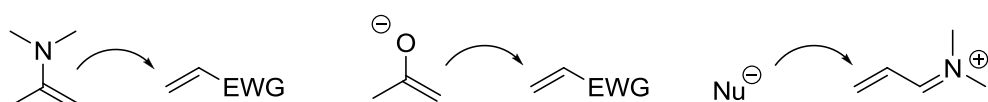
<sup>24</sup> Veverková, E., Štrasserová, J., Šebesta, R., Toma, Š., *Tetrahedron: Asymmetry*, **2010**, 21, 58.

addition”, or “conjugate addition”, of a nucleophile to the  $\beta$ -position of an  $\alpha,\beta$ -unsaturated carbonyl compound (Scheme 3.15).



**Scheme 3.15**

The increasing demand for optically active compounds has aroused considerable interest, since stereogenic centers can be created in the course of the Michael reaction. Thus, much effort has been made to develop efficient catalytic stereoselective methods. Since chemical transformations that avoid additional reagents, waste, and working time are highly desirable, a more promising and atom-economic strategy would involve direct addition of unmodified carbonyl compounds to Michael acceptors. Consequently, aminocatalysis has gained considerable attention. The Michael donor can be catalytically activated either through enamine or enolate formation for the addition to a Michael acceptor. Complementarily, carbonyl-derived Michael acceptors can be activated via formation of an iminium species (Scheme 3.16).

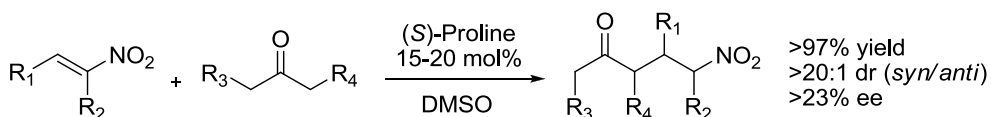


**Scheme 3.16**

Although the properly called “Michael Reaction” involves the  $\beta$ -position of an  $\alpha,\beta$ -unsaturated carbonyl compounds, the term Michael is commonly use to indicate the site of attack in a simple addition to  $\alpha,\beta$ -unsaturated compounds, whereby a classification based on the nature of the electrophile is useful.

## Nitroolefins as Michael acceptors

The enamine-catalyzed Michael addition of carbon nucleophiles to nitroalkenes is a useful synthetic method for the preparation of  $\gamma$ -nitrocarbonyl compounds. Owing to the various possible transformations 1,4-addition adducts are important precursors in organic synthesis.<sup>25</sup> In organocatalysis, a number of different Michael acceptors have already been used. Among them, nitroalkenes are the most prominent ones because of their high acceptor reactivity and the possible conversion into other useful functionalities.<sup>26</sup> The first enamine-catalyzed asymmetric intermolecular Michael reaction was developed by List in 2001.<sup>27</sup> The addition of unactivated symmetric ketones to nitroolefins was found to proceed in the presence of catalytic amounts of (*S*)-Proline to furnish the desired  $\gamma$ -nitro ketones in generally high yields and good diastereoselectivities (*syn*) but only low enantioselectivities (up to 23% ee) (Scheme 3.17).



**Scheme 3.17**

In general, Proline-catalyzed Michael reactions seem to be highly *syn* diastereoselective but less enantioselective than Mannich or aldol reactions, which might be due to less efficient hydrogen bonding between the catalyst and the Michael acceptor.

To explain the *syn* diastereoselectivity and the absolute configuration observed, Enders proposed an acyclic synclinal transition state based on Seebach's model.<sup>28</sup> Following this model, all bonds around the newly formed bond are staggered, with a *gauche* relationship of the donor and the acceptor  $\pi$ -systems. Additionally, the

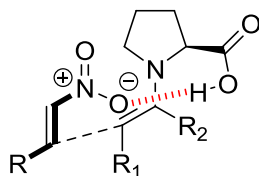
<sup>25</sup> Ono, N. *The Nitro Group in Organic Synthesis*; Wiley-VCH: Weinheim, 2005.

<sup>26</sup> Berner, O. M.; Tedeschi, L.; Enders, D. *Eur. J. Org. Chem.* **2002**, 1877.

<sup>27</sup> List, B.; Pojarliev, P.; Martin, H. J. *Org. Lett.* **2001**, 3, 2423.

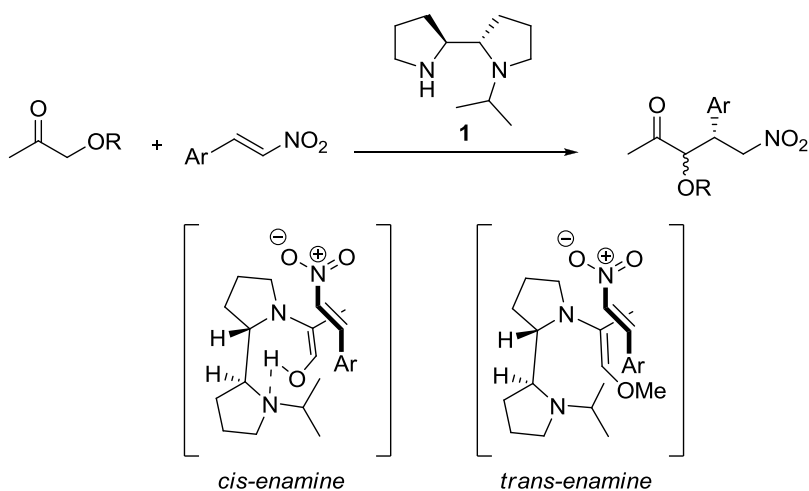
<sup>28</sup> Enders, D.; Seki, A. *Synlett* **2002**, 26; Seebach, D.; Golinski, J. *Helv. Chim. Acta* **1981**, 64, 1413; Blarer, S. J.; Seebach, D. *Chem. Ber.* **1983**, 116, 2250.

partially positive nitrogen of the enamine and the partially negative nitro group should be situated close to each other, due to favorable electrostatic interactions. A hydrogen bond between the carboxylic acid moiety and the nitro group was postulated to further fix the conformation (Scheme 3.18).



**Scheme 3.18**

Further studies to investigate the possibility of an *anti* diastereoselectivity were performed by Alexakis who decided to evaluate nonsymmetrical ketones, in particular  $\alpha$ -hydroxy and  $\alpha$ -alkoxycarbonyl compounds using the pyrrolidine-derivative **1** as catalyst. Interestingly the expected *syn*-isomer was only obtained using  $\alpha$ -methoxyacetone, whereas  $\alpha$ -hydroxyacetone yielded mainly the unexpected *anti*-isomer.<sup>29</sup> This was explained by an additional hydrogen bond between the OH group of the substrate and the tertiary amine of the catalyst which led to the *cis*- instead of the *trans*-enamine (Scheme 3.19)



**Scheme 3.19**

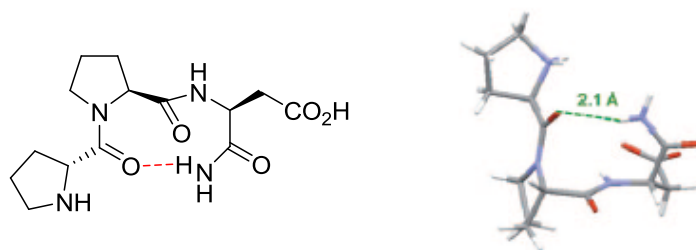
<sup>29</sup> Andrey, O.; Alexakis, A.; Bernardinelli, G. *Org. Lett.* **2003**, 5, 2559.



Concerning steric effects, many studies, done by several groups,<sup>30</sup> have identified the bulk of the catalyst as determinant to have high levels of selectivity. For aldehydes, higher enantioselectivities were observed with increasing substituent bulk in order Me < Bu < *i*-Pr but no reaction took place with the sterically more congested 3,3-dimethylbutyraldehyde, so steric factors play an important role.

The same is true for the nitroolefins. Aromatic aldehydes are the most commonly used nitro-derivative Michael acceptor, however also aliphatic olefins provide the corresponding Michael adducts, although bulky substituents render the reaction impossible.

As already hinted in chapter 1, Wennemers and coworkers have been recently reported one of the most efficient examples of enamine-based catalysts with nitroolefins as acceptor. The tripeptide Pro-Pro-Asp-NH<sub>2</sub> was again found (see above) as the best catalyst for this reaction. The reason of the high activity and selectivity was deeply investigated using as catalyst a number of derivatives D-Pro-Pro-AA-NH<sub>2</sub> in the conjugate addition of various aldehydes to nitrostyrene. Wennemers found that the D-Pro-Pro motif is the major contributor to the high stereoselectivities. The C-terminal amide and the spacer to the carboxylic acid in the side-chain of the C-terminal amino acid are responsible for the fine-tuning of the stereoselectivity.<sup>31</sup>



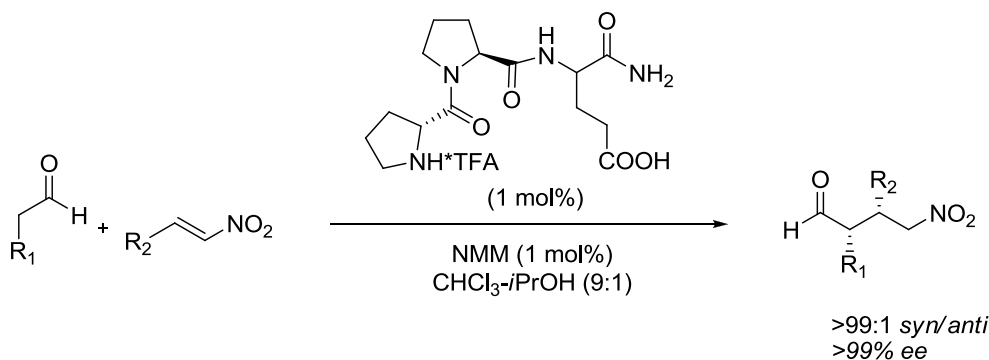
**Scheme 3.20**

<sup>30</sup> Hagiwara, H.; Okabe, T.; Hakoda, K.; Hoshi, T.; Ono, H.; Kamat, V. P.; Suzuki, T.; Ando, M. *Tetrahedron Lett.* **2001**, *42*, 2705; Hagiwara, H.; Komatsubara, N.; Ono, H.; Okabe, T. *J. Chem. Soc., Perkin Trans. 1* **2001**, 316; Betancort, J. M.; Barbas, C. F. *Org. Lett.* **2001**, *3*, 3737.

<sup>31</sup> M. Wiesner, M., Neuburger, H., Wennemers, Chem. Eur. J., **2009**, *15*, 10103.

The crystal structure of the tripeptide D-Pro-Pro-Asp-NH<sub>2</sub> (Scheme 3.20) clearly shows as the global conformation of the molecule is almost independent from the nature of the C-terminal amino acid.

Later a massive study on the exploiting of the tripeptide D-Pro-Pro-Glu-NH<sub>2</sub> in the conjugate addition of aldehydes to nitroolefins was undertaken obtaining excellent results in terms of both stereo- (up to 99:1 *syn/anti*) and enantioselectivity (up to 99%) (Scheme 3.21).<sup>32</sup>



**Scheme 3.21**

$\alpha,\alpha$ -disubstituted aldehydes gave rise to sluggish reactions, while aromatic aldehydes proved to be more reactive. Among these aldehydes with bulky substituents in the  $\beta$ -position, as well as electron-rich aromatic nitroolefins, are slightly less reactive compared to the other substrates.

In addition, no side products, such as homo-aldol condensation products, formed in the course of the reaction. Concerning the acceptors, no big differences were observed changing the nature of the nitroolefins and the results obtained with nitroethylene in terms of *ee*, were comparable with those obtained with nitrostyrene. The reaction proceeds readily in a range of solvents even if highest reactivities are observed in alcohols such as isopropanol, whereas the highest stereoselectivities are obtained in chloroform. Often, a mixture of these two solvents is an ideal

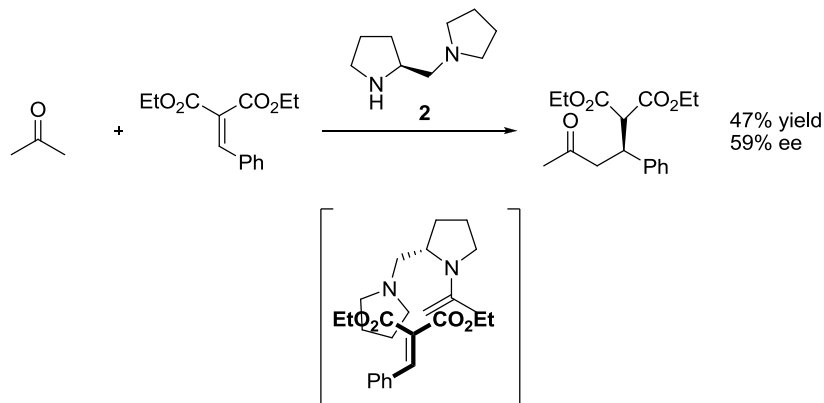
<sup>32</sup> M. Wiesner, H., Wennemers, *Synthesis*, **2010**, 9, 1568.

compromise for obtaining both high reactivity and stereoselectivity. In addition, this solvent mixture allows good solubility of all the reaction components.<sup>33</sup>

### $\alpha,\beta$ -unsaturated carbonyl compounds as Michael acceptors

In most organocatalytic Michael additions, either highly activated nucleophiles or electrophiles have been used. The addition of unactivated carbonyl compounds to nitroalkenes, for instance, is well established (section 3.3.1.), whereas fewer examples are known dealing with the addition to simple enone acceptors.

One of the first asymmetric applications was performed by Barbas in the Michael addition of acetone to diethyl benzylidene malonate using catalyst **2** with moderate yields.<sup>34</sup> The observed stereochemistry was rationalized with a transition state where the alkylidene malonate approaches the enamine from the less hindered *re*-face (Scheme 3.22).



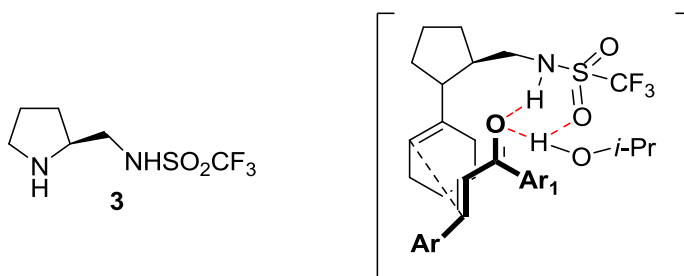
**Scheme 3.22**

As in the case of nitroolefins, the existence of bifunctional catalysts capable of interaction with the Michael acceptor can amplify the enantioselection due to the steric hindrance of substituents.

<sup>33</sup> Wiesner, M.; Revell, J. D.; Wennemers, H. *Angew. Chem.Int. Ed.* **2008**, *47*, 1871.

<sup>34</sup> Betancort, J. M.; Sakthivel, K.; Thayummanavan, R.; Barbas, C. F. *Tetrahedron Lett.* **2001**, *42*, 4441.

Recently Wang developed a highly enantioselective organocatalytic Michael addition of cyclic ketones with  $\alpha,\beta$ -unsaturated ketones.<sup>35</sup> The process was catalyzed by sulfonamide **3** which led good selectivities and yields. The system resulted to be powerful with a wide range of aliphatic and aromatic cyclic ketones. The mechanism reported hypothesizes a bridged H-bond interaction involving sulfonamide, carbonyl group and the protic solvent (Scheme 3.23).

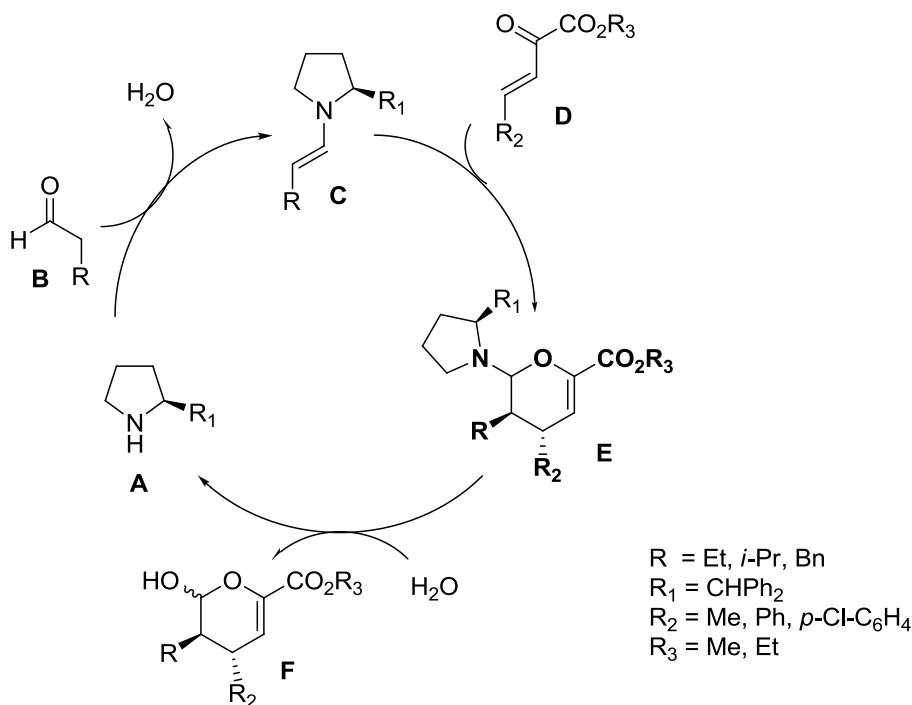


**Scheme 3.23**

An interesting, though definitely different, study involving  $\alpha,\beta$ -unsaturated ketones that is worth mentioning concerns the enamine-catalyzed asymmetric inverse-electron-demand hetero-Diels-Alder (HDA) reaction developed by Juhl and Jørgensen,<sup>36</sup> and a plausible catalytic cycle is represented in Scheme 3.24. The enamine **C**, which is generated from the amine catalyst **A** and the aldehyde **B**, acts as an electron-rich dienophile for the reaction with electron-deficient “diene” **D** to produce the iminal **E**. Hydrolysis of **E** gives hemiacetal **F** and regenerates the catalyst.

<sup>35</sup> Wang, J.; Li, H.; Zu, L.; Wang, W. *Adv. Synth. Catal.* **2006**, *348*, 425.

<sup>36</sup> Juhl, K.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 1498.



**Scheme 3.24**

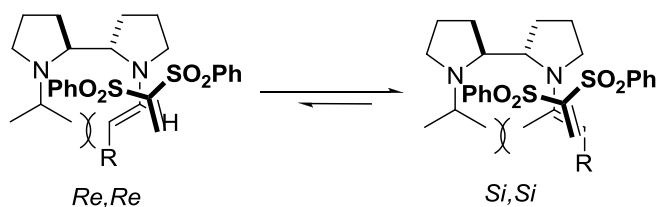
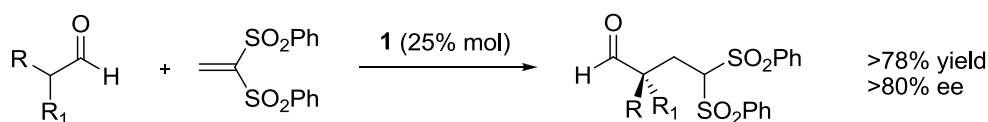
### Vinyl sulfones as Michael acceptor

The reaction of preformed enamines with vinyl sulfones has been known for some time.<sup>37</sup> Although advancement has been made using chiral auxiliaries to develop asymmetric conjugate additions to vinyl sulfones,<sup>38</sup> the direct asymmetric catalytic conjugate addition of carbonyl compounds to vinyl sulfones would be desirable. Since sulfones are widely useful intermediates of unique synthetic versatility in organic synthesis, the desired 1,4-Michael adducts could further react as nucleophilic reagents or be involved in reductive alkylations and Julia-type reactions, among others.

<sup>37</sup> Simpkins, N. S. *Tetrahedron* **1990**, *46*, 6951.

<sup>38</sup> Pinheiro, S.; Guingant, A.; Desmaële, D.; d'Angelo, J. *Tetrahedron: Asymmetry* **1992**, *3*, 1003; d'Angelo, J.; Reviel, G. *Tetrahedron: Asymmetry* **1991**, *2*, 199; Enders, D.; Muller, S. F.; Raabe, G.; Runsink, J. *Eur. J. Org. Chem.* **2000**, 879; Sanki, A. K.; Suresh, C. G.; Falgune, U. D.; Pathak, T. *Org. Lett.* **2003**, *5*, 1285.

The first direct catalytic asymmetric Michael addition of aldehydes to vinyl sulfones was reported in 2005 by Alexakis using 1,1-bis(benzenesulfonyl)-ethylene as Michael acceptor.<sup>39</sup> As nucleophile, various aldehydes were used and the pyrrolidine derivative **1** as catalyst. The results proved to be directly correlated to the bulk of aldehydes even if  $\alpha,\alpha$ -disubstituted aldehydes gave rise to low selectivity. The transition state proposed (Scheme 3.25) shows that the steric hindrance of the pyrrolidine catalyst is absolutely determinant to the formation of the more thermodynamically stable enamine.



**Scheme 3.25**

### 3.2 Development of the catalytic system

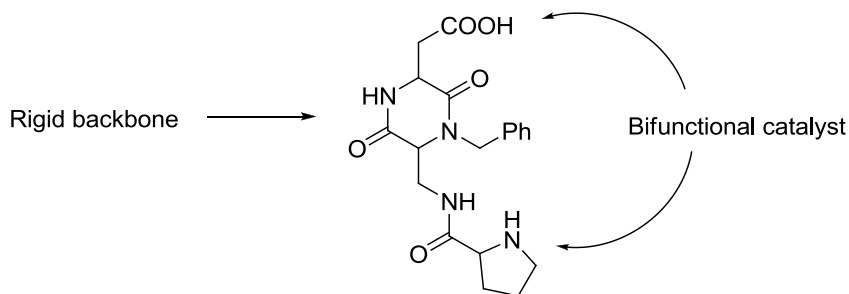
As we showed above in the introductory section, a well-defined structure and conformation of the catalyst is mostly important to develop an efficient catalytic system (chapter 1).

Two different strategies can be used for this purpose: the first aims to develop (or modify) the structure of a catalytic system to improve its performance. The second

<sup>39</sup> Mosse', S.; Alexakis, A. *Org. Lett.* **2005**, 7, 4361.

is based on the use of a backbone having a well-defined conformation, and its derivatization with functional groups capable of catalytic activities.

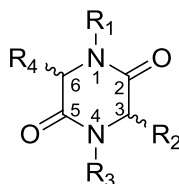
In our approach we focused on the latter route, using as a platform the expertise of our group in the field of diketopiperazines. The idea was to develop a bifunctional system having a diketopiperazinic scaffold connected with a proline and a carboxylic acid as catalytic centers (Scheme 3.26).



**Scheme 3.26**

## 2,5-Diketopiperazines as rigid scaffold

2,5-Diketopiperazines are the smallest cyclic peptides composed by two  $\alpha$ -amino acids and their structure, known since 1938,<sup>40</sup> is contained in many biologically active compounds as antibiotics,<sup>41</sup> vaccines and anticancer agents.<sup>42</sup>



**Scheme 3.27**

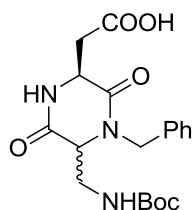
<sup>40</sup> R. B. Corey, *J. Am. Chem. Soc.* **1938**, *60*, 1598.

<sup>41</sup> Y. Funabashi, T. Horiguchi, S. Iinuma, S. Tanida, S. Harada, *J. Antibiot.* **1994**, *47*, 1202; F. Fdhila, V. Vazquez, J. L. Sanchez, R. Riguera, *J. Nat. Prod.* **2003**, *66*, 1299.

<sup>42</sup> W. A. Loughlin, R. L. Marshall, A. Carreiro, K. E. Elson, *Bioorg. Med. Chem. Lett.* **2000**, *10*, 91; B. Nicholson, G. K. Lloyd, B. R. Miller, M. A. Palladino, Y. Kiso, Y. Hayashi, S. T. C. Neuteboom, *Anti-Cancer Drugs* **2006**, *17*, 25.

From a structural and synthetic point of view, 2,5-diketopiperazines are simple heterocyclic scaffolds in which diversity can be introduced at up to four different positions, and stereochemically controlled at two (Scheme 3.27). Their preparation is also feasible from readily available  $\alpha$ -amino acids with conventional procedures,<sup>43</sup> solid state,<sup>44</sup> and microwave-assisted synthesis.<sup>45</sup>

Our group has recently investigated the conformational properties of diketopiperazines with interesting results. In particular, attention has been focused on bifunctional diketopiperazines scaffolds **4**, formally derived from (S)-aspartic acid and either (S)- or (R)-2,3-diaminopropionic acid.



**4a** = 3S    **DKP-1**  
**4b** = 4S    **DKP-2**

These molecules have proven to be useful as  $\beta$ -hairpin inducers<sup>46</sup> and efficient scaffolds for cyclic peptidomimetics.<sup>47</sup> In particular product **4a** derived from L-aspartic acid and (S)-2,3-diaminopropionic acid, bears the amino and carboxylic acid functionalities in a *cis* relationship and, as such, can be seen as a  $\beta$ -turn mimic and promoter of antiparallel  $\beta$ -sheet when introduced in peptidic chains.

<sup>43</sup> I. L. Rodionov, L. N. Rodionova, L. K. Baidakova, A. M. Romashko, T. A. Balashova, V. T. Ivanov, *Tetrahedron* **2002**, *58*, 8515; For a review on synthetic approaches to all three DKP isomers (2,3-, 2,5-, and 2,6-), see: C. J. Dinsmore, D. C. Beshore, *Tetrahedron* **2002**, *58*, 3297, and references therein.

<sup>44</sup> W.-R. Li, J. H. Yang, *J. Comb. Chem.* **2002**, *4*, 106; P. M. Fischer, *J. Pept. Sci.* **2003**, *9*, 9.

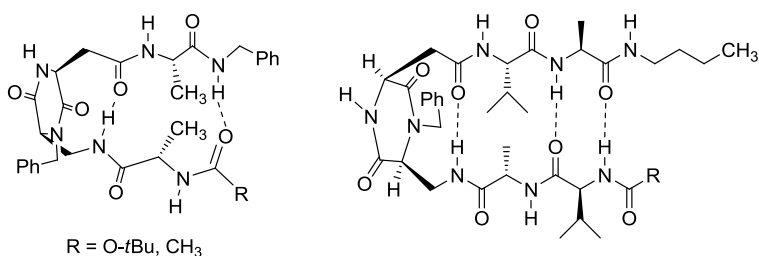
<sup>45</sup> A. Lopez-Cobenas, P. Cledera, J. D. Sanchez, P. Lopez-Alvarado, M. T. Ramos, C. Avendano, J. C. Menendez, *Synthesis* **2005**, *19*, 3412; J. C. O'Neill, H. E. Blackwell, *Comb. Chem. High Throughput Screening* **2007**, *10*, 857.

<sup>46</sup> A. S. M. Ressurreicao, A. Bordessa, M. Civera, L. Belvisi, C. Gennari, U. Piarulli, *J. Org. Chem.* **2008**, *73*, 652;

<sup>47</sup> A. S. M. Ressurreicao, A. Vidu, M. Civera, L. Belvisi, D. Potenza, L. Manzoni, S. Ongeri, C. Gennari, U. Piarulli, *Chem. Eur. J.* **2009**, *15*, 12184; A. S. M. Ressurreicao, R. Delatouche, C. Gennari, U. Piarulli, *Eur. J. Org. Chem.* **2011**, 217–228.

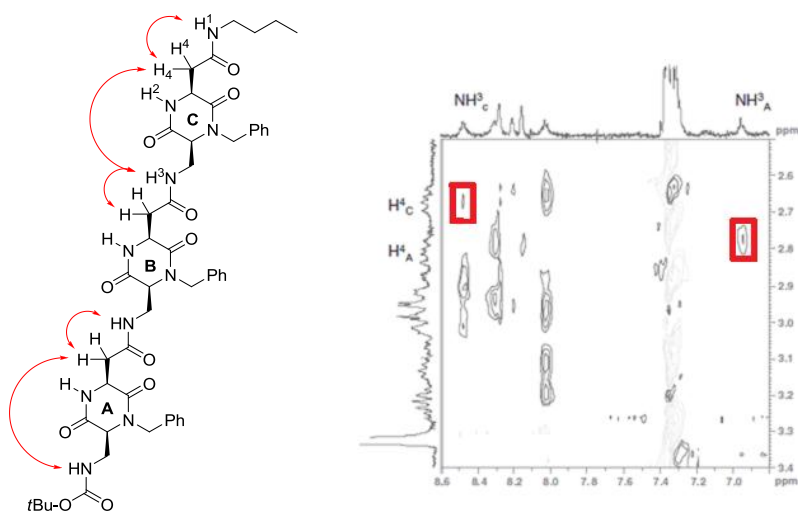


The synthesis of several peptidomimetics was thus performed by solution phase peptide synthesis (Boc strategy). Conformational analysis of these derivatives was carried out by a combination of  $^1\text{H-NMR}$  spectroscopy (chemical shift and NOE studies), IR spectroscopy, CD spectroscopy and molecular modeling, and revealed the formation of  $\beta$ -hairpin mimics involving 10- and 18-membered H-bonded rings and a reverse turn of the growing peptide chain. The  $\beta$ -hairpin conformation of the longer derivative was detected also in competitive, dipolar and even protic solvents such as dimethylsulfoxide and methanol (Scheme 3.28).



**Scheme 3.28**

This attitude was further confirmed in the conformational analysis of two oligomers by  $^1\text{H NMR}$ , CD spectroscopy and molecular modeling.<sup>48</sup>

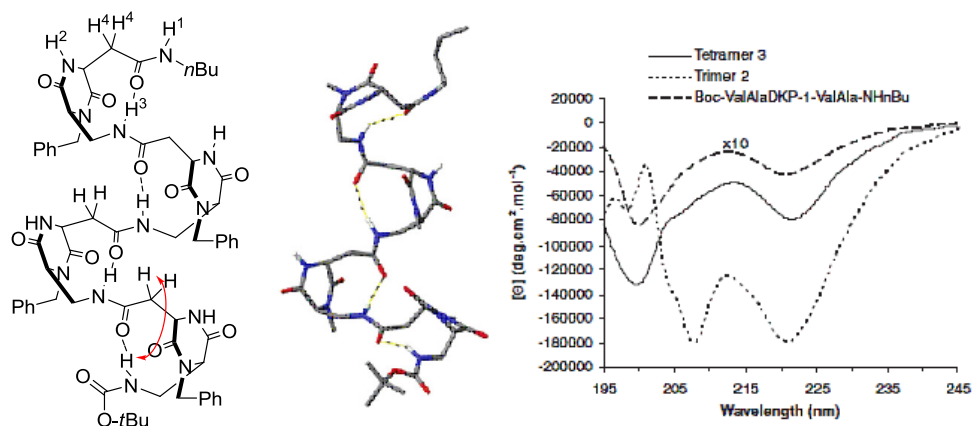


**Scheme 3.29**

<sup>48</sup> R. Delatouche, M. Durini, M. Civera, L. Belvisi, U. Piarulli, *Tetrahedron Lett.* **2010**, *51*, 4278.

In the case of the trimeric structure (Scheme 3.29) the presence of a ribbon was proved by NMR which highlighted NOE contacts between distant protons.

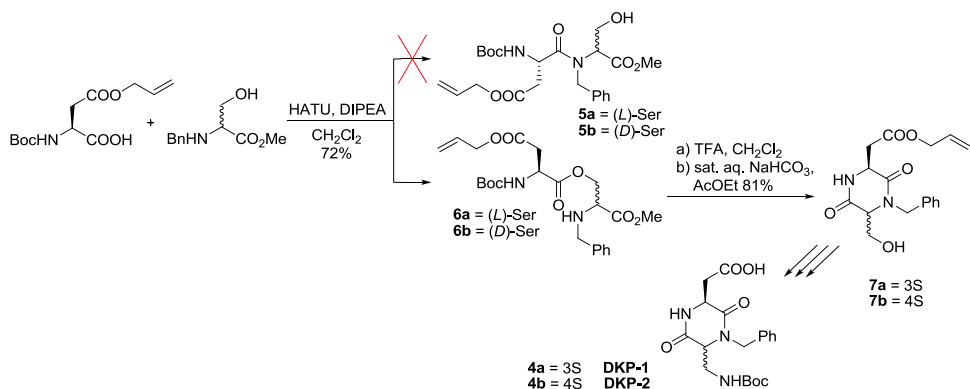
The tetrameric structure was investigated and the predicted conformation obtained by molecular modeling was proved by NMR and CD spectroscopy (Scheme 3.30).



**Scheme 3.30**

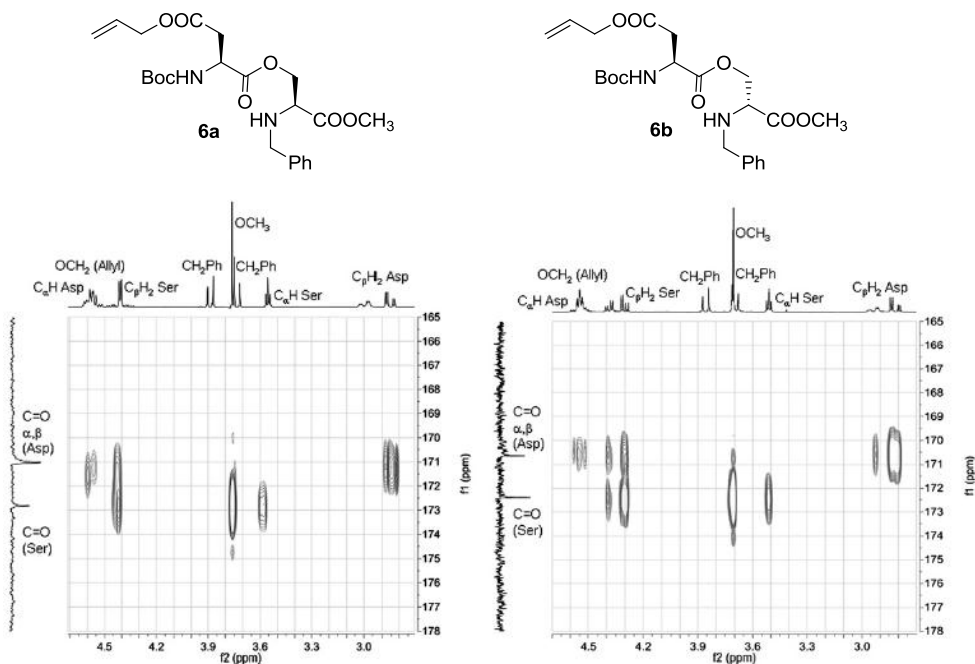
### 3.2.1 Synthesis of catalysts

The synthesis of the diketopiperazine scaffolds **4a** and **4b** was obtained starting from suitably protected *N*-(tert-butoxycarbonyl)-(2*S*)-aspartic acid  $\beta$ -allylester and either (*S*) or (*R*)-*N*-benzylserine methyl ester with a direct coupling using HATU. A closer inspection of the spectroscopic properties revealed that the formation of the isopeptide had occurred via the selective acylation of the unprotected  $\beta$ -hydroxy group of either (*S*)- or (*R*)-*N*-benzyl serine. (Scheme 3.31).



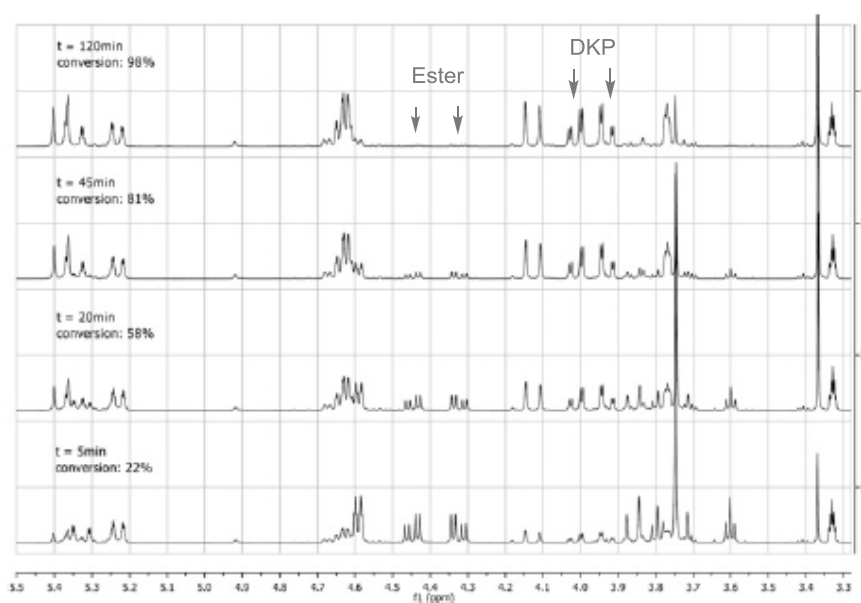
**Scheme 3.31**

This rather uncommon pathway was studied by NMR spectroscopy and two set of signals proved to be diagnostic: i) in the  $^1\text{H}$  NMR spectrum, the O- $\text{CH}_2$  protons of serine were rather deshielded; ii) in the HMBC spectrum of both compounds, a long range coupling (through three bonds) was clearly evident between the O- $\text{CH}_2$  protons of serine and the  $\alpha$ -carbonyl carbon of aspartic acid (Scheme 3.32).



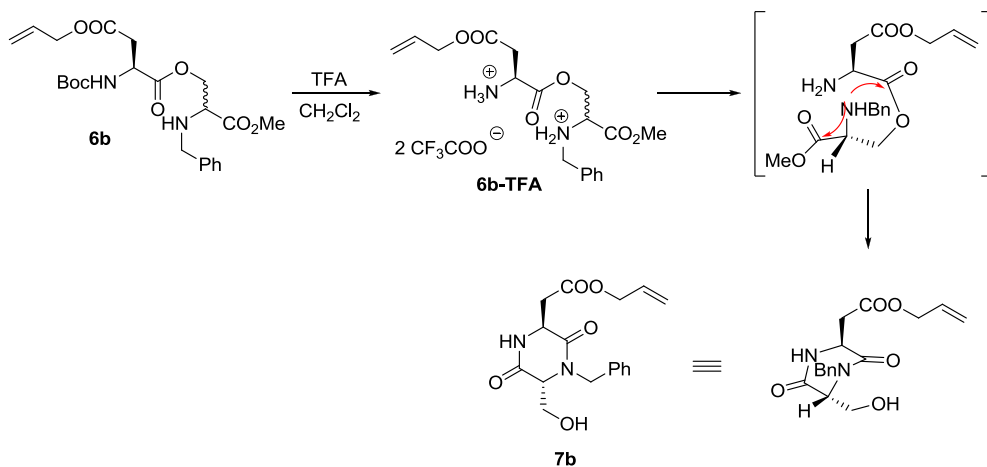
**Scheme 3.32**

The cyclization step was also investigated and product **6b** was used for the study. Since a *O,N*-acyl transfer should occur to give product **7b** upon nitrogen deprotection, the Boc group was cleaved by reaction with TFA to obtain a bis-TFA salt. 4 equiv. of base were added to provide a complete cyclization and the reaction monitored by  $^1\text{H}$  NMR (Scheme 3.33) which clearly showed a decreasing of signals belonging to serine (two dd at  $\delta$  4.32 and  $\delta$  4.45) and concurrent increase of signals belonging to diketopiperazines (two dd at  $\delta$  3.93 and  $\delta$  4.02).



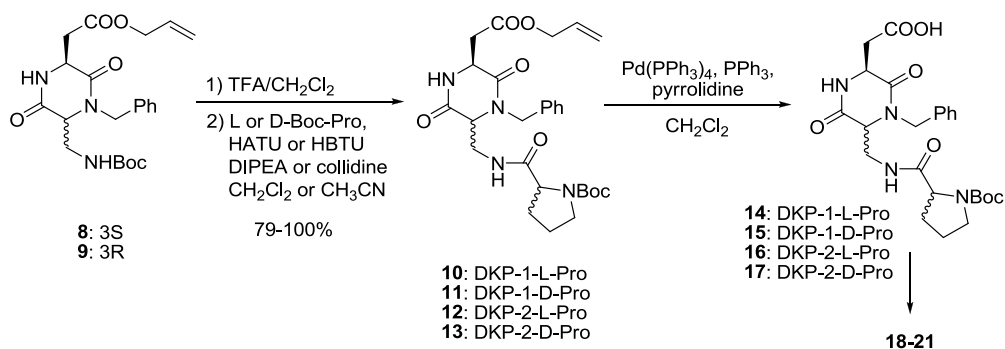
**Scheme 3.33**

Based on these experimental observations, a reasonable mechanistic explanation (Scheme 3.34) involves a rate limiting *O,N*-acyl transfer with immediate ring closure to give rise to diketopiperazines with no peptidic intermediate.

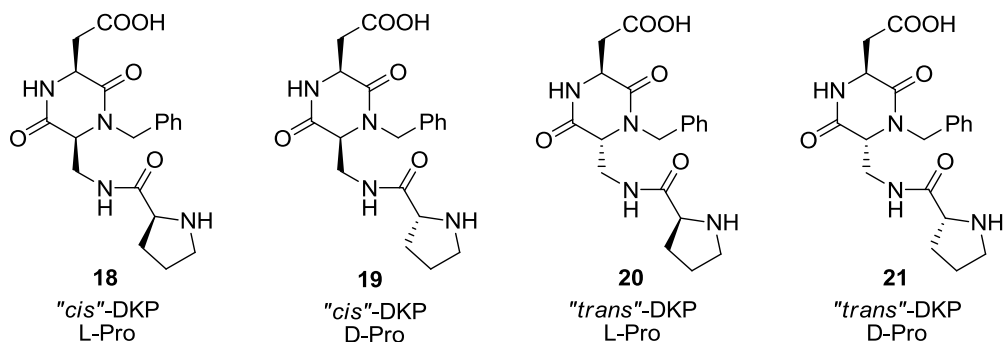


**Scheme 3.34**

Products **8** and **9**, prepared according to the literature,<sup>8</sup> were Boc deprotected and coupled to either L-Boc-Pro or D-Boc-Pro to give in good yields allylesters **10-13**. These precursors have been subject to a deallylation reaction to furnish products **14-17** and Boc deprotection to give catalysts **18-21** which have been stored as trifluoroacetate salts (Scheme 3.35).

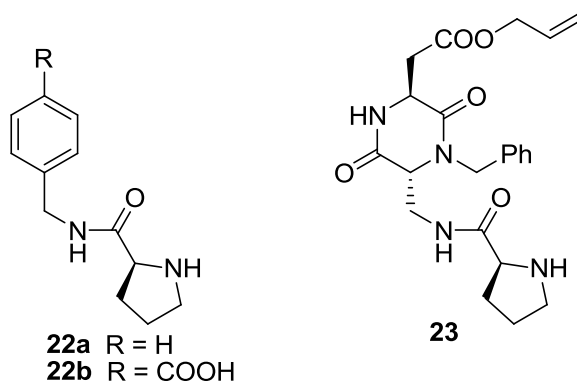


**Scheme 3.35**



Our idea is based on the fact that the high rigidity of the catalysts would lead the two functional groups responsible for the catalytic activity to be in well-defined regions of space.

To bear out this hypothesis, we also synthesized catalysts **22** and **23** to demonstrate respectively that steric hindrance of proline and the structure of diketopiperazine backbone are singularly not sufficient to achieve high enantioselectivity. **22a** and **22b** should reveal the importance of the presence of a carboxylic functionality on the catalyst.



Product **23** was synthesized from precursor **12** by direct Boc deprotection whereas **22a** was prepared by simple coupling between commercially available Boc-Proline and benzylamine with subsequent Boc deprotection.

### 3.2.2 Catalytic applications and results

Conjugate addition of aldehydes to nitroolefines is among the most widely studied reactions concerning proline-based organocatalysts<sup>49</sup> as well as amine catalysis,<sup>50</sup> therefore we chose this reaction to prove the efficiency of our system.

The enantioselective conjugate addition of *n*-butanal to  $\beta$ -nitrostyrene was chosen as benchmark reaction to screen catalysts and conditions (Scheme 3.36). The reactions were performed at 20°C in a different solvents, including CH<sub>2</sub>Cl<sub>2</sub>, CHCl<sub>3</sub>, THF and *i*PrOH, but best results were achieved using a mixture of CHCl<sub>3</sub> and *i*PrOH 9:1 and 5 mol-% of catalyst.

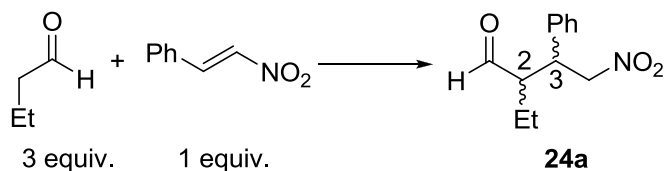
Since catalysts were stored as the corresponding trifluoroacetate salts, one equivalent of N-methylmorpholine (with respect to the amount of catalyst) was added to free the amino group.

Good to excellent results were obtained with the catalysts; in particular **18** and **20** provided quantitative yields as well as excellent diastereoisomeric ratios and enantiomeric excesses (Scheme 3.36). The absolute configuration of the product is dictated by the configuration of the proline moiety (L or D), whereas the rigid diketopiperazinic backbone tunes the degree of selectivity.

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<sup>49</sup> a) C. Palomo, S. Vera, A. Mielgo, E. Gomez-Bengoa, *Angew. Chem. Int. Ed.* **2006**, *45*, 5984; b) M. L. Clarke, J. A. Fuentes, *Angew. Chem. Int. Ed.* **2007**, *46*, 930; c) X. H. Liu, L. L. Lin, X. M. Feng, *Chem. Commun.* **2009**, 6145; d) M. Freund, S. Schenker, S. B. Tsogoeva, *Org. Biomol. Chem.* **2009**, *7*, 4279; e) J. F. Bai, X. Y. Xu, Q. C. Huang, L. Peng, L.X. Wang, *Tetrahedron Lett.* **2010**, *51*, 2803; f) J. Xiao, F.-X. Xu, Y.-P. Lu, Y.-L. Liu, T.-P. Loh, *Synthesis* **2011**, 1912.

<sup>50</sup> a) R. Husmann, M. Jorres, G. Raabe, C. Bolm, *Chem. Eur. J.* **2010**, *16*, 12549; b) Y. Wang, S. Zhu, D. Ma, *Org. Lett.* **2011**, *13*, 1602; c) C. Luo, D.- M. Du, *Synthesis* **2011**, 1968; d) R. Rasappan, O. Reiser, *Eur. J. Org. Chem.* **2009**, 1305; e) H. Uehara, R. Imashiro, G. Hernandez-Torres, C. F. Barbas, *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 20672; f) A. Lu, T. Liu, R. Wu, Y. Wang, G. Wu, Z. Zhou, J. Fang, C. Tang, *J. Org. Chem.* **2011**, *76*, 3872.



Entry	Cat.	Yield [%]	<i>syn:anti</i>	<i>ee</i> [%] ( <i>syn</i> isomer)	Abs. Conf.
1	<b>18</b>	99	40:1	99	(2 <i>R</i> , 3 <i>S</i> )
2	<b>19</b>	99	33:1	76	(2 <i>S</i> , 3 <i>R</i> )
3	<b>20</b>	96	50:1	92	(2 <i>R</i> , 3 <i>S</i> )
4	<b>21</b>	95	33:1	80	(2 <i>S</i> , 3 <i>R</i> )
5	L-Pro	85	8:1	39	(2 <i>R</i> , 3 <i>S</i> )
6	<b>22a</b>	27	5:1	53	(2 <i>R</i> , 3 <i>S</i> )
7	<b>22b</b>	33	4:1	52	(2 <i>R</i> , 3 <i>S</i> )
8	<b>23</b>	76	16:1	82	(2 <i>R</i> , 3 <i>S</i> )

### Scheme 3.36

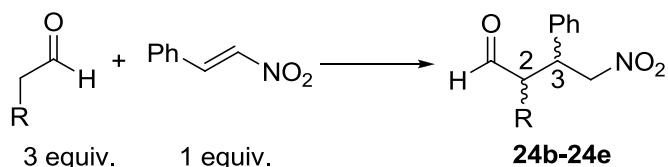
Beyond the results provided by the catalysts, some important considerations have to be done comparing their result with those obtained from reference molecules **22**, **23** and proline.

Proline itself, which has been widely used as an organocatalyst, afforded only moderate reactivity and low diastereo- and enantioselectivity (Scheme 3.36, entry 5). Prolinamides **22** (**22a** reacted in presence of a equimolar amount of benzoic acid) gave rise to low yields and modest selectivities (Scheme 3.36, entries 6 and 7). Ester **23** highlighted the key role of the carboxylic acid in the activation of the nitroolefin: despite the same global structure, it provided poorer results in terms of both diastereo- and enantioselectivity.

The substrate scope of catalysts was then investigated using several aliphatic aldehydes with  $\beta$ -nitrostyrene under the same reaction conditions (Scheme 3.37). In most cases catalyst **20** was the best performing catalyst in terms of



enantioselectivity, whereas better diastereoselectivity was usually obtained with catalyst **18**.

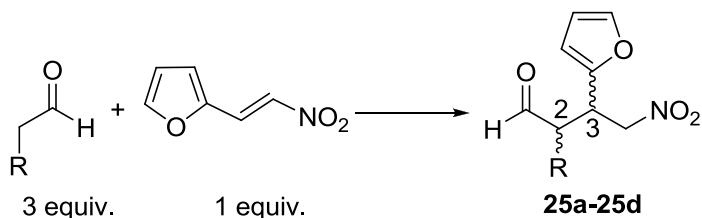


Entry	R	Cat.	Yield [%]	<i>syn:anti</i>	<i>ee</i> [%] ( <i>syn</i> isomer)	Abs. Conf.
1	<i>n</i> -C <sub>3</sub> H <sub>7</sub>	<b>18</b>	99	11:1	83	(2 <i>R</i> , 3 <i>S</i> )
2	<i>n</i> -C <sub>3</sub> H <sub>7</sub>	<b>19</b>	98	13:1	66	(2 <i>S</i> , 3 <i>R</i> )
3	<i>n</i> -C <sub>3</sub> H <sub>7</sub>	<b>20</b>	99	20:1	94	(2 <i>R</i> , 3 <i>S</i> )
4	<i>n</i> -C <sub>3</sub> H <sub>7</sub>	<b>21</b>	99	25:1	82	(2 <i>S</i> , 3 <i>R</i> )
5	<i>i</i> -C <sub>3</sub> H <sub>7</sub>	<b>18</b>	81	99:1	88	(2 <i>R</i> , 3 <i>S</i> )
6	<i>i</i> -C <sub>3</sub> H <sub>7</sub>	<b>19</b>	77	50:1	78	(2 <i>S</i> , 3 <i>R</i> )
7	<i>i</i> -C <sub>3</sub> H <sub>7</sub>	<b>20</b>	40	99:1	92	(2 <i>R</i> , 3 <i>S</i> )
8	<i>i</i> -C <sub>3</sub> H <sub>7</sub>	<b>21</b>	40	99:1	80	(2 <i>S</i> , 3 <i>R</i> )
9	<i>n</i> -C <sub>5</sub> H <sub>11</sub>	<b>18</b>	99	20:1	97	(2 <i>R</i> , 3 <i>S</i> )
10	<i>n</i> -C <sub>5</sub> H <sub>11</sub>	<b>19</b>	98	20:1	91	(2 <i>S</i> , 3 <i>R</i> )
11	<i>n</i> -C <sub>5</sub> H <sub>11</sub>	<b>20</b>	99	8:1	98	(2 <i>R</i> , 3 <i>S</i> )
12	<i>n</i> -C <sub>5</sub> H <sub>11</sub>	<b>21</b>	95	13:1	95	(2 <i>S</i> , 3 <i>R</i> )
13	CH <sub>2</sub> Ph	<b>18</b>	99	33:1	92	(2 <i>R</i> , 3 <i>S</i> )
14	CH <sub>2</sub> Ph	<b>19</b>	97	20:1	83	(2 <i>S</i> , 3 <i>R</i> )
15	CH <sub>2</sub> Ph	<b>20</b>	94	7:1	98	(2 <i>R</i> , 3 <i>S</i> )
16	CH <sub>2</sub> Ph	<b>21</b>	94	10:1	85	(2 <i>S</i> , 3 <i>R</i> )

**Scheme 3.37**

Catalysts **19** and **21**, derived from D-proline, gave the enantiomeric products (2*S*,3*R*)-**24**. Remarkably, **19** and **21** parallel the behavior of **18** and **20** in terms of performance: catalyst **21** gave better *ee* values than **19** and, conversely, **19** was often more diastereoselective than **21**.

Catalysts **20** and **21** have been also tested in the conjugate addition of various aldehydes to (*E*)-2-(furan-2-yl)nitroethene (Scheme 3.38). Good to excellent enantio- and diastereoselectivities were obtained, albeit with moderate conversions, which can be attributed to the lower reactivity of the electron-rich substrate.



Entry	R	Cat.	Yield [%]	<i>syn:anti</i>	<i>ee</i> [%] ( <i>syn</i> isomer)
1	<i>n</i> -C <sub>2</sub> H <sub>5</sub>	<b>20</b>	66	9:1	93
2	<i>n</i> -C <sub>2</sub> H <sub>5</sub>	<b>21</b>	87	16:1	85
3	<i>n</i> -C <sub>3</sub> H <sub>7</sub>	<b>20</b>	61	13:1	94
4	<i>n</i> -C <sub>3</sub> H <sub>7</sub>	<b>21</b>	64	33:1	78
5	<i>i</i> -C <sub>3</sub> H <sub>7</sub>	<b>20</b>	42	99:1	92
6	<i>i</i> -C <sub>3</sub> H <sub>7</sub>	<b>21</b>	31	99:1	80
7	CH <sub>2</sub> Ph	<b>20</b>	97	12:1	95
8	CH <sub>2</sub> Ph	<b>21</b>	81	10:1	77

**Scheme 3.38**

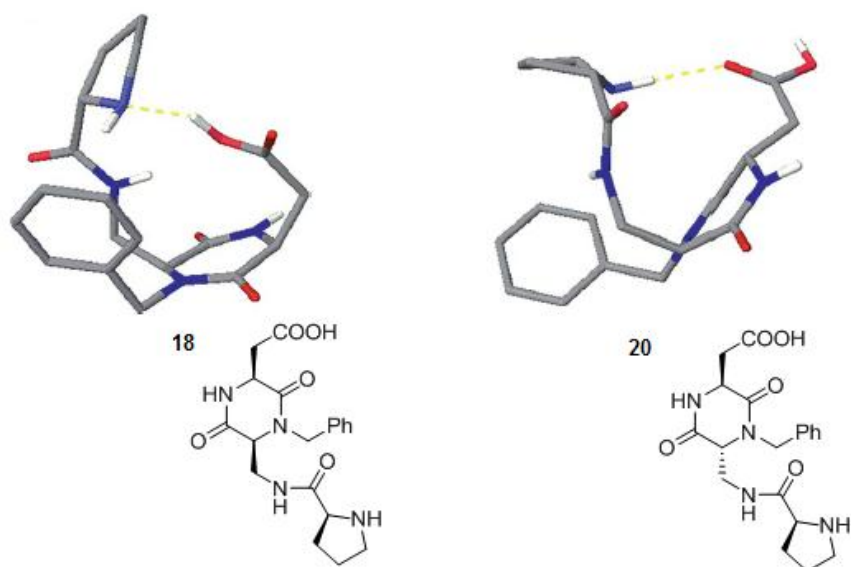
Making a careful overview of the results, the behavior of products **18** and **20** appear quite puzzling. In fact these catalysts, having different stereostructures, yield the conjugate addition products with the same absolute configuration and similar enantioselectivity. As already published in previous works,<sup>51</sup> the absolute configuration of final product is determined by the configuration of terminal proline, however the achievement of the same selectivities is absolutely counterintuitive because the relative stereochemistry of the diketopiperazinic unit

<sup>51</sup> M. Wiesner, J. D. Revell, H. Wennemers, *Angew. Chem. Int. Ed.* **2008**, *47*, 1871

**DKP-1** and **DKP-2** should confer different spatial properties<sup>52</sup> and consequently different relative positions of proline and carboxylic functionality.

To shed light on the activity of catalysts, we decided to undertake a conformational analysis of structures of **18** and **20** by means of computational studies. The molecules were subject to an extensive, unconstrained Monte Carlo/Energy Minimization conformational search<sup>53</sup> by molecular mechanics methods using the OPLSA-AA force field<sup>54</sup> and the implicit CHCl<sub>3</sub> GB/SA solvent model.<sup>55</sup>

Comparing the two minimizations (Scheme 3.39), it is possible to observe a similar folding of the proline in the direction of carboxylic functionality due to an interaction between the proline N-H and the C=O of the acid.



**Scheme 3.39**

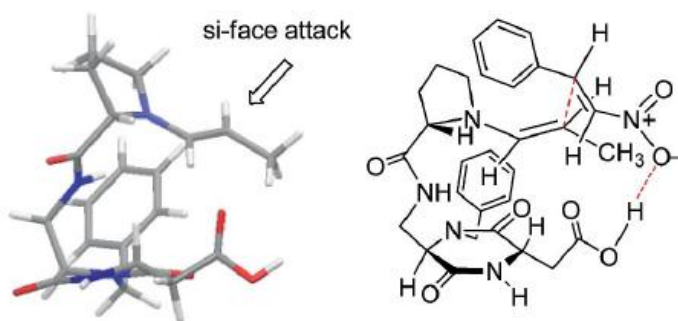
<sup>52</sup> a) A. S. M. Ressurreicao, A. Bordessa, M. Civera, L. Belvisi, C. Gennari, U. Piarulli, *J. Org. Chem.* **2008**, *73*, 652; b) A. S. M. Ressurreicao, A. Vidu, M. Civera, L. Belvisi, D. Potenza, L. Manzoni, S. Ongerì, C. Gennari, U. Piarulli, *Chem. Eur. J.* **2009**, *15*, 12184.

<sup>53</sup> G. Chang, W. C. Guida, W. C. Still, *J. Am. Chem. Soc.* **1989**, *111*, 4379–4386.

<sup>54</sup> G. A. Kaminski, R. A. Friesner, J. Tirado-Rives, W. L. Jorgensen, *J. Phys. Chem. B* **2001**, *105*, 6474.

<sup>55</sup> W. C. Still, A. Tempczyk, R. C. Hawley, T. J. Hendrickson, *J. Am. Chem. Soc.* **1990**, *112*, 6127.

This evidence could be considered as a simple speculation since H-bonds are less important once the enamine is formed. For this reason we performed an Energy Minimization conformational search also on the enamine intermediate of **20**. As we expected the conformational equilibrium in the enamine is more complicated and features either folded and unfolded geometries. However a low-energy structure that superimposes well to the kinked, global minimum of the catalyst gives interesting information (Scheme 3.40). In this conformation the *re*-face of the enamine is shielded by the diketopiperazines and benzyl group, leaving the *si*-face exposed to the attack of nucleophilic nitroolefine. The carboxylic group is likely to act as H-bond donor, activating the acceptor and directing its approach from the less hindered face.



**Scheme 3.40**

### 3.2.3 Conclusion

In this chapter we have reported the preparation of a new class of peptidomimetic organocatalysts starting from two bifunctional diketopiperazines formally derived from the head-to-tail cyclization of L-aspartic acid and either (*R*)- or (*S*)-2,3-diaminopropionic acid. The terminal amino group in the DKP scaffold was coupled to a L- or D-proline residue giving rise to the four different organocatalysts. These were tested in the conjugate addition reaction of several aldehydes to  $\beta$ -nitrostyrene

and (*E*)-2-(furan-2-yl)nitroethene with good to excellent diastereo- and enantioselectivities. To rationalize the stereoselectivity of these catalysts, a Monte Carlo/Energy Minimization (MC/EM) conformational search by molecular mechanics methods was undertaken on the four catalysts and their enamine derivatives with propanal. The catalysts showed a folded arrangement with the COOH pointing towards the proline nitrogen while the enamine derivatives revealed conformations where one face of the enamine moiety is shielded by the diketopiperazine ring and the carboxylic acid is likely to act as a hydrogen-bond donor, activating the nitroolefin acceptor (-NO<sub>2</sub>) and directing its approach from the less hindered enamine face.

### 3.2.4 Experimental Part

#### General Remarks

All reactions were carried out in flame-dried glassware with magnetic stirring under a nitrogen atmosphere, unless otherwise stated. Dry solvents (over molecular sieves in bottles with crown caps) were purchased from Sigma–Aldrich and stored under nitrogen. The reactions were monitored by analytical TLC using silica gel 60 F254 precoated glass plates (0.25 mm thickness). Visualization was accomplished by irradiation with a UV lamp and/or staining with a potassium permanganate alkaline solution. Flash column chromatography was performed using silica gel 60 Å, particle size 40–64 μm, following the procedure reported by Still and coworkers.<sup>56</sup> <sup>1</sup>H NMR spectra were recorded with a spectrometer operating at 400.13 MHz. Chemical shifts are reported in ppm with the solvent reference relative to tetramethylsilane (TMS) employed as the internal standard (CDCl<sub>3</sub> δ = 7.26 ppm). The following abbreviations are used to describe spin multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br. = broad signal, dd = doublet of doublets. <sup>13</sup>C NMR spectra were recorded with a 400 MHz spectrometer operating

<sup>56</sup> W. C. Still, M. Kahn, A. Mitra, *J. Org. Chem.* **1978**, *43*, 2923.

at 100.56 MHz with complete proton decoupling. Chemical shifts are reported in ppm relative to TMS with the respective solvent resonance as the internal standard (CDCl<sub>3</sub>,  $\delta = 77.23$  ppm). Infrared spectra were recorded with a standard FTIR spectrometer. Optical rotation values were measured with an automatic polarimeter with a 1-dm cell at the sodium D line ( $\lambda = 589$  nm). HPLC was performed with an instrument equipped with a diode array detector using a chiral column. HRMS were measured with a Fourier Transform Ion Cyclotron Resonance (FT-ICR) Mass Spectrometer APEX II & Xmass software (Bruker Daltonics)–4.7 T Magnet (Magnex) equipped with ESI source, available at CIGA (Centro Interdipartimentale Grandi Apparecchiature), c/o Università degli Studi di Milano. MS were acquired either with a Thermo- innigan LCQ Advantage mass spectrometer (ESI ion source) or a VG Autospec M246 spectrometer (FAB ion source). Elemental analyses were performed with a Perkin–Elmer Series II CHNS/O Analyzer 2000.

## Materials

Commercially available reagents were used as received. Allyl [(3*S*,6*S*)-4-benzyl-3-(*tert*-butoxycarbonylaminomethyl)-2,5-dioxopiperazin-5-yl]acetate<sup>57</sup> (**8**), allyl [(3*R*,6*S*)-4-benzyl-3-(*tert*-butoxycarbonylaminomethyl)-2,5-dioxopiperazin-5-yl]acetate<sup>18</sup> (**9**), and (*S*)-benzylprolinamide<sup>58</sup> (**22a**) were prepared according to literature procedures. Spectroscopic and analytical data for the following products were determined in agreement with those described in the literature: 2-ethyl-4-nitro-3-phenylbutanal<sup>59</sup> (**24a**), 4-nitro-3-phenyl-2-propylbutanal<sup>59</sup> (**24b**), 4-nitro-2-pentyl-3-phenylbutanal<sup>59</sup> (**24c**), 2-isopropyl-4-nitro-3-phenylbutanal<sup>59</sup> (**24d**), 2-benzyl-4-

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<sup>57</sup> a) A. S. M. Ressurreicao, A. Bordessa, M. Civera, L. Belvisi, C. Gennari, U. Piarulli, *J. Org. Chem.* **2008**, *73*, 652; b) A. S. M. Ressurreicao, A. Vidu, M. Civera, L. Belvisi, D. Potenza, L. Manzoni, S. Ogeri, C. Gennari, U. Piarulli, *Chem. Eur. J.* **2009**, *15*, 12184.

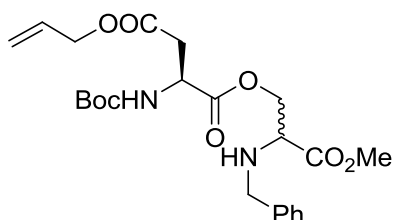
<sup>58</sup> D. Gryko, R. Lipinski, *Adv. Synth. Catal.* **2005**, *347*, 1948.

<sup>59</sup> M. Wiesner, M. Neuburger, H. Wennemers, *Chem. Eur. J.* **2009**, *15*, 10103.

nitro-3-phenylbutanal<sup>59</sup> (**24e**), 2-ethyl-3-(furan-2-yl)-4-nitrobutanal<sup>60</sup> (**25a**), and 3-(furan-2-yl)-4-nitro-2-propylbutanal<sup>61</sup> (**25b**).

## Synthesis and characterization of catalysts

### 4-Allyl 1-[(2R)-2-(benzylamino)-3-methoxy-3-oxopropyl] N-(tert-butoxycarbonyl)-L-aspartate (**6b**).



To a solution of  $\beta$ -allyl (2S)-N-(tert-butoxycarbonyl) aspartate ester (2.24 g, 8.2 mmol, 1.1 equiv) in DMF (70 mL), under a nitrogen atmosphere and at 0°C, HATU (3.39 g, 8.94 mmol, 1.2 equiv), HOAt (1.21 g, 8.94 mmol, 1.2 equiv) and DIPEA (5.1 mL, 29.8 mmol, 4 equiv) were added successively. After 30 min, a solution of (R)-N-benzylserine methyl ester (1.56 g, 7.45 mmol, 1 equiv) in DMF (10 mL) was added. The reaction mixture was then stirred at 0°C for 1 h and at rt for 24 h. The mixture was then diluted with EtOAc (200 mL) and the organic phase was washed with 1 M KHSO<sub>4</sub> (2x 70 mL), aqueous NaHCO<sub>3</sub> (2x 70 mL), and brine (2x 50 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and volatiles were removed under reduced pressure. The residue was purified by flash chromatography on silica gel (Petroleum ether/EtOAc, 3:1) to afford the desired product (**6b**) as a transparent oil (2.73 g, 72% yield).

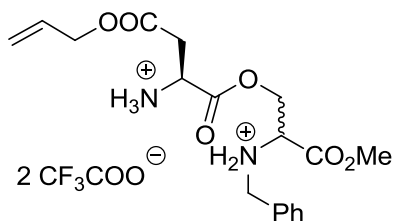
R<sub>f</sub> = 0.30 (hexane/EtOAc 6:4); [ $\alpha$ ]<sub>D</sub><sup>20</sup> +11.0 (CHCl<sub>3</sub>, c = 1.00); <sup>1</sup>H NMR (400 MHz, CD<sub>2</sub>Cl<sub>2</sub>)  $\delta$  = 1.42 (s, 9H), 2.82 (dd, 1H, J = 17.0, 4.8 Hz), 2.94 (dd, 1H, J = 17.2, 4.68 Hz), 3.51 (t, 1H, J = 4.74 Hz), 3.70 (d, 1H, J = 13.1 Hz), 3.71 (s, 3H), 3.86 (d, 1H, J = 13.1), 4.30 (dd, 1H, J = 10.9, 4.8 Hz), 4.39 (dd, 1H, J = 10.9, 4.6 Hz), 4.61–4.48 (m,

<sup>60</sup> Z. Zheng, B. L. Perkins, B. Ni, *J. Am. Chem. Soc.* **2010**, 132, 50.

<sup>61</sup> D. F. Lu, Y. F. Gong, W. Z. Wang, *Adv. Synth. Catal.* **2010**, 352, 644;

3H), 5.34-5.18 (m, 2H), 5.41 (d, 1H, J= 7.8 Hz), 5.95-5.82 (m, 1H), 7.37-7.20 (m, 5H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$ = 28.0, 36.7, 50.0, 51.8, 52.0, 59.1, 65.6, 65.9, 118.1, 127.1, 128.2, 128.3, 131.9, 139.7, 170.6, 172.4; IR (film):  $\nu_{\text{max}}$  3362, 2978, 1740, 1500, 1455, 1368, 1167, 1053; HRMS (ESI)  $m/z$  calcd for  $[\text{C}_{23}\text{H}_{33}\text{N}_2\text{O}_8]^+$ : 465.22314  $[\text{M}+\text{H}]^+$ ; found: 465.22267.

**(2S)-4-(Allyloxy)-1-[[[(2R)-2-(benzylammonio)-3-methoxy-3-oxopropyl]oxy]-1,4-dioxobutan-2-aminium bis(trifluoroacetate) (6B-TFA).**

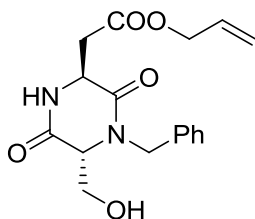


To a solution of **6b** (845 mg, 1.82 mmol) in  $\text{CH}_2\text{Cl}_2$  (14.4 mL) was added trifluoroacetic acid (7.2 mL, 4 mL/mmol). The reaction mixture was stirred for 3 h at rt and then concentrated at reduced pressure. The excess TFA was azeotropically removed from the residue with toluene. Diethyl ether was added to the residue and the resulting suspension was evaporated under reduced pressure to give the isopeptide bis-TFA salt (**6b-TFA**) as a white foamy solid in quantitative yield.

$R_f$ = 0.37 (DCM/MeOH 95:5);  $[\alpha]_{\text{D}}^{32}$  -8.7 ( $\text{CHCl}_3$ ,  $c$ = 1.5);  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$ = 3.10 (dd, 1H, J= 18.5, 6.1 Hz), 3.17 (dd, 1H J= 18.3, 3.9 Hz), 3.89-3.81 (s, 3H), 4.08-4.01 (br, 1H), 4.29 (d, 1H, J= 13.0 Hz), 4.48-4.37 (m, 2H), 4.78-4.59 (m, 4H), 5.41-5.25 (m, 2H), 6.01-5.86 (m, 1H), 7.59-7.37 (m, 5H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$ = 33.4, 49.4, 50.6, 52.9, 53.2, 53.4, 53.7, 53.9, 56.1, 62.7, 66.5, 118.9, 129.3, 130.0, 130.5, 131.2, 166.3, 165.9, 170.1; IR (film):  $\nu_{\text{max}}$  2921, 2850, 1759, 1681, 1539, 1456, 1392, 1202, 1137; HRMS (ESI)  $m/z$  calcd for  $[\text{C}_{18}\text{H}_{25}\text{N}_2\text{O}_6]^+$ : 365.17071  $[\text{M}+\text{H}]^+$ ; found: 365.17033.



**Allyl [(2S,5R)-4-benzyl-5-(hydroxymethyl)-3,6-dioxopiperazin-2-yl]acetate (5b).**

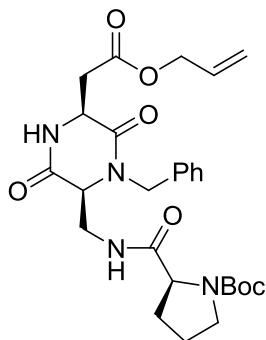


The bis-trifluoro acetate salt **6b-TFA** (1.08 g, 1.82 mmol, 1 equiv) was dissolved in iPrOH (20 mL) and DIPEA (0.9 mL, 5.6 mmol, 4 equiv) was added at rt. The reaction was stirred

for 40 h at rt, monitoring the formation of DKP by TLC (EtOAc/hexane 8:2). The solution was then concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel (Petroleum ether/EtOAc, 3:1) to afford the desired product (**5b**) as a white foam (514.1 mg, 85% yield).

R<sub>f</sub>= 0.10 (AcOEt/hexane 8:2); [α]<sub>D</sub><sup>20</sup> -35.3 (CHCl<sub>3</sub>, c = 1.00); <sup>1</sup>H NMR (400 MHz, CD<sub>2</sub>Cl<sub>2</sub>) δ= 2.86 (dd, 1H, J= 17.4, 8.0 Hz), 3.21 (dd, 1H, J= 17.4, 3.9 Hz), 3.81 (br, 1H), 3.90 (dd, 1H, J= 11.8, 3.0 Hz), 4.01 (dd, 1H, J= 11.8, 1.90 Hz), 4.12 (d, 1H, J= 15.2 Hz), 4.70-4.55 (m, 3H), 5.39-5.20 (m, 3H), 6.02-5.83 (m, 1H), 7.20 (bs, 1H), 7.43-7.25 (m, 5H); <sup>13</sup>C NMR (100 MHz, CD<sub>2</sub>Cl<sub>2</sub>) δ= 37.1, 47.3, 51.1, 61.6, 61.9, 65.7, 117.9, 118.3, 127.8, 127.9, 128.8, 131.8, 135.9, 166.6, 168.2, 170.8; IR (film): ν<sub>max</sub> 3364, 3032, 2942, 1738, 1651, 1452, 1383, 1329, 1273, 1183, 1129; HRMS (ESI)m/z calcd for [C<sub>17</sub>H<sub>20</sub>N<sub>2</sub>NaO<sub>5</sub>]<sup>+</sup>: 355.12644 [M+Na]<sup>+</sup>; found: 355.12590.

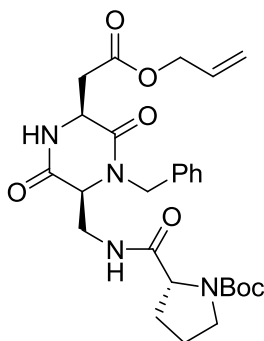
***tert*-Butyl(2*S*)-2-[(*3S,6S*)-6-{2-(Allyloxy)-2-oxoethyl}-4-benzyl-2,5-dioxopiperazin-3-yl)methylcarbamoyl]pyrrolidine-1-carboxylate (10)**



TFA (5 mL) was added dropwise at 0°C to a solution of **7** (170 mg, 0.394 mmol, 1.0 equiv.) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) and the reaction mixture was stirred at the same temperature for 3 h. Volatiles were evaporated under reduced pressure and the residue was treated with Et<sub>2</sub>O to cause the precipitation of the TFA salt, which was isolated by decantation. 1-Boc-Proline (93 mg, 0.432 mmol, 1.1 equiv.) was dissolved in acetonitrile (4 mL), and HATU (194 mg, 0.510 mmol, 1.3 equiv.) and DIPEA (169 μL, 0.985 mmol, 2.5 equiv.) were added at 0 °C under N<sub>2</sub>. The solution was stirred for 30 min before the TFA salt was added, and the mixture was stirred for 1 h at 0°C, and overnight at room temperature. The reaction mixture was poured into EtOAc (40 mL) and washed with 1M KHSO<sub>4</sub> solution (2x 5 mL), satd. NaHCO<sub>3</sub> solution (2x 5 mL), and brine (1x 5 mL). The organic layer was dried with Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography using 2% MeOH in CH<sub>2</sub>Cl<sub>2</sub> to yield **9** as a white solid (164 mg, 0.311 mmol, 79%). *R*<sub>f</sub> = 0.28 (ethyl acetate); m.p. 61–62 °C. [ $\alpha$ ]<sub>D</sub><sup>20</sup> = +6.6 (*c* = 0.1, CHCl<sub>3</sub>). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 25 °C):  $\delta$  = 1.45 (s, 9 H), 1.63 (br., 4 H), 1.87 (br. s, 2 H), 2.82 (m, 1 H), 3.43 (br., 1 H), 3.58 (m, 1 H), 3.79–3.96 (br., 2 H), 4.17 (d, *J* = 15.0 Hz, 1 H), 4.25 (br. s, 1 H), 4.47 (m, *J* = 10.4, 2.6 Hz, 1 H), 4.66 (m, 2 H), 5.29 (dd, *J* = 10.3, 1.2 Hz, 1 H), 5.35 (dd, *J* = 17.2, 1.2 Hz, 1 H), 5.46 (d, *J* = 15.0 Hz, 1 H), 5.91 (m, 1 H), 6.61 (br., 1 H), 7.31 (m, 5 H) ppm. <sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>, 25 °C):  $\delta$  = 24.5, 28.3, 39.5, 40.1, 43.8, 47.1, 52.0,

55.8, 57.8, 66.1, 80.6, 119.2, 128.1, 128.6, 129.0, 131.3, 135.2, 164.4 ppm. IR:  $\nu = 1734, 1662, 1307, 1162, 1124, 970, 842, 723 \text{ cm}^{-1}$ .  $\text{C}_{27}\text{H}_{36}\text{N}_4\text{O}_7$  (528.60): calcd. C 61.35, H 6.86, N 10.60; found C 61.03, H 7.18, N 10.22.

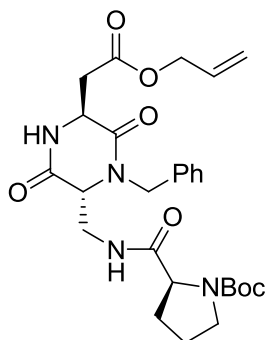
***tert*-Butyl(2*R*)-2-[(*S,S*)-6-{2-(Allyloxy)-2-oxoethyl}-4-benzyl-2,5-dioxopiperazin-3-yl)methylcarbamoyl]pyrrolidine-1-carboxylate (**11**)**



TFA (5 mL) was added dropwise at 0°C to a solution of **7** (170 mg, 0.394 mmol, 1.0 equiv.) in  $\text{CH}_2\text{Cl}_2$  (5 mL). The resulting solution was stirred at the same temperature for 3 h. Volatiles were removed under reduced pressure and the residue was treated with  $\text{Et}_2\text{O}$  to cause the precipitation of the TFA salt, which was isolated by decantation. D-Boc-Proline (93 mg, 0.432 mmol, 1.1 equiv.) was dissolved in  $\text{CH}_2\text{Cl}_2$  (4 mL), and HATU (194 mg, 0.510 mmol, 1.3 equiv.) and DIPEA (169  $\mu\text{L}$ , 0.985 mmol, 2.5 equiv.) were added at 0°C under  $\text{N}_2$ . The solution was stirred for 30 min before the TFA salt was added, and the mixture was stirred for 1 h at 0°C and overnight at room temperature. The reaction mixture was poured into EtOAc (40 mL) and washed with 1M  $\text{KHSO}_4$  solution (2x 5 mL), satd.  $\text{NaHCO}_3$  solution (2x 5 mL), and brine (1x 5 mL). The organic layer was dried with  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography using 2% MeOH in  $\text{CH}_2\text{Cl}_2$  to yield **10** as a white solid (183 mg, 0.346 mmol, 88%).  $R_f = 0.28$  (ethyl acetate); m.p. 63–64 °C.  $[\alpha]_{20\text{D}} = +29.90$  ( $c = 0.1$ ,  $\text{CHCl}_3$ ).  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ , 25°C):  $\delta = 1.44$  (s, 9 H), 1.62–1.99 (br., 4

H), 3.21–3.67 (br., 4 H), 3.84 (br., 1 H), 3.92 (br., 1 H), 4.13 (d,  $J = 14.5$  Hz, 1 H), 4.28 (br., 1 H), 4.48 (d,  $J = 10.7$  Hz, 1 H), 4.58–4.70 (m, 2 H), 5.27 (d,  $J = 10.5$  Hz, 1 H), 5.34 (dd,  $J = 17.2, 1.3$  Hz, 1 H), 5.53 (br. 1 H), 5.91 (m, 1 H), 6.79 (br. s, 1 H), 7.28–7.34 (m, 5 H) ppm.  $^{13}\text{C}$  NMR (100.6 MHz,  $\text{CDCl}_3$ , 25 °C):  $\delta = 24.5, 28.3, 29.6, 39.4, 43.6, 46.8, 47.2, 52.0, 55.7, 60.1, 66.0, 80.6, 119.1, 128.1, 128.6, 129.0, 131.4, 135.1, 164.5, 165.5, 171.2, 173.0$  ppm. IR:  $\nu = 1740, 1667, 1533, 1251, 1164, 1127, 970, 849, 723$   $\text{cm}^{-1}$ .  $\text{C}_{27}\text{H}_{36}\text{N}_4\text{O}_7$  (528.60): calcd. C 61.35, H 6.86, N 10.60; found C 61.21, H 7.14, N 10.25.

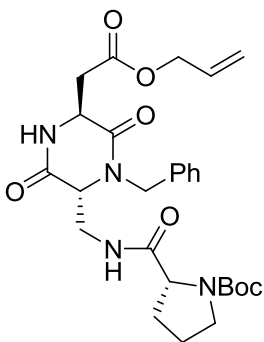
***tert*-Butyl(2*S*)-2-[(*3R,6S*)-6-{2-(Allyloxy)-2-oxoethyl}-4-benzyl-2,5-dioxopiperazin-3-yl)methylcarbamoyl]pyrrolidine-1-carboxylate (12)**



To a solution of **8** (650 mg, 1.50 mmol, 1.0 equiv.) in  $\text{CH}_2\text{Cl}_2$  (19.2 mL) was added TFA (19.2 mL) dropwise at 0 °C, and the resulting solution was stirred at the same temperature for 2 h. Volatiles were evaporated under reduced pressure and the residue was treated with  $\text{Et}_2\text{O}$  to cause the precipitation of the TFA salt, which was isolated by decantation. 1-Boc-Proline (355 mg, 1.65 mmol, 1.1 equiv.) was dissolved in acetonitrile (15 mL), and HBTU (740 mg, 1.95 mmol, 1.3 equiv.) and collidine (0.60 mL, 4.50 mmol, 3.0 equiv.) were added at 0 °C under  $\text{N}_2$ . The solution was stirred for 30 min before the TFA salt was added and the mixture was stirred for 1 h at 0 °C and at room temperature overnight. The reaction mixture was poured into EtOAc (150 mL) and washed with 1M  $\text{KHSO}_4$  solution (2x 20 mL),

satd. NaHCO<sub>3</sub> solution (2x 20 mL), and brine (1x 20 mL). The organic layer was dried with Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography using 2% MeOH in CH<sub>2</sub>Cl<sub>2</sub> to yield **11** as a pale yellow solid (793 mg, 1.50 mmol, 100 %). *R*<sub>f</sub> = 0.26 (ethyl acetate); m.p. 57–58 °C. [ $\alpha$ ]<sub>20 D</sub> = -3.7 (*c* = 0.1, CHCl<sub>3</sub>). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 25 °C):  $\delta$  = 1.47 (s, 9 H), 1.88 (br., 2 H), 2.08 (br., 1 H), 2.81 (br., 2 H), 3.22 (dd, *J* = 17.57, 3.12 Hz, 1 H), 3.33 (br., 1 H), 3.41 (br., 1 H), 3.58 (br., 1 H), 3.88 (br., 1 H), 3.95 (br., 1 H), 4.21 (d, *J* = 15.17 Hz, 1 H), 4.30 (br., 1 H), 4.55–4.63 (m, 3 H), 5.28 (ddd, *J* = 30.17, 17.20, 1.16 Hz, 2 H), 5.43 (d, *J* = 15.16 Hz, 1 H), 5.89 (m, 1 H), 6.97 (br, 1 H), 7.27–7.35 (m, 5 H), 7.51 (br. m, 1 H) ppm. <sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>, 25 °C):  $\delta$  = 24.5, 28.4, 28.6, 37.5, 39.2, 47.0, 47.4, 50.6, 59.0, 59.8, 65.8, 80.6, 118.9, 127.9, 128.4, 128.9, 131.4, 135.6, 164.8, 167.0, 170.6, 173.85 ppm. IR:  $\nu$  = 2360, 1736, 1686, 1532, 1166, 843, 723 cm<sup>-1</sup>. C<sub>27</sub>H<sub>36</sub>N<sub>4</sub>O<sub>7</sub> (528.60): calcd. C 61.35, H 6.86, N 10.60; found C 60.99, H 6.93, N 10.40.

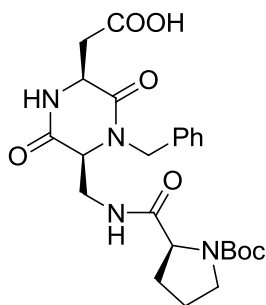
***tert*-Butyl(2*R*)-2-[(*3R,6S*)-6-{2-(Allyloxy)-2-oxoethyl}-4-benzyl-2,5-dioxopiperazin-3-yl)methylcarbamoyl]pyrrolidine-1-carboxylate (**13**)**



Compound **8** (600 mg, 1.39 mmol, 1.0 equiv.) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (18 mL), and TFA (18 mL) was added dropwise at 0°C. The reaction mixture was stirred at the same temperature for 2 h. The solution was evaporated under reduced pressure and the residue was treated with Et<sub>2</sub>O to cause precipitation of the TFA salt, which

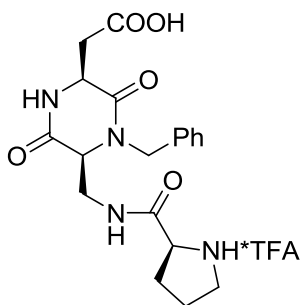
was isolated by decantation. d-Boc-Proline (329 mg, 1.53 mmol, 1.1 equiv.) was dissolved in acetonitrile (14 mL), and HBTU (685 mg, 1.80 mmol, 1.3 equiv.) and collidine (0.55 mL, 4.17 mmol, 3.0 equiv.) were added at 0°C under N<sub>2</sub>. The solution was stirred for 30 min before the TFA salt was added and the mixture was stirred for 1 h at 0 °C and overnight at room temperature. The reaction mixture was poured into EtOAc (150 mL) and washed with 1M KHSO<sub>4</sub> solution (2x 20 mL), 5% NaHCO<sub>3</sub> solution (2x 20 mL), and brine (1x 20 mL). The organic layer was dried with Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography using 2% MeOH in CH<sub>2</sub>Cl<sub>2</sub> to yield **12** as a pale yellow solid (734 mg, 1.39 mmol, 100%). *R*<sub>f</sub> = 0.26 (ethyl acetate); m.p. 59–60 °C. [ $\alpha$ ]<sub>20 D</sub> = +18.20 (*c* = 0.1, CHCl<sub>3</sub>). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 25 °C):  $\delta$  = 1.46 (s, 9 H), 1.86 (br., 2 H), 2.34 (br., 1 H), 2.60 (s, 1 H), 2.79 (m, 1 H) 3.26 (dd, *J* = 17.52, 1.52 Hz, 1 H), 3.31–3.52 (br., 3 H), 3.86 (br., 1 H), 4.05–4.75 (br., 3 H), 4.61–4.80 (m, 3 H), 5.28 (m, 2 H), 5.50 (m, 1 H), 5.89 (m, 1 H), 6.72 (br., 1 H), 7.18 (br., 1 H), 7.25–7.41 (m, 5 H) ppm. <sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>, 25°C):  $\delta$  = 24.5, 28.4, 28.5, 37.7, 38.6, 39.2, 47.0, 47.3, 50.8, 58.6, 60.3, 65.8, 80.6, 119.0, 128.0, 128.3, 128.6, 131.4, 135.4, 165.0, 166.6, 170.7, 173.1 ppm. IR:  $\nu$  = 1733, 1668, 1164, 1126, 723 cm<sup>-1</sup>. C<sub>27</sub>H<sub>36</sub>N<sub>4</sub>O<sub>7</sub> (528.60): calcd. C 61.35, H 6.86, N 10.60; found C 61.24, H 7.10, N 10.74.

**6-[(3*S*,6*S*)-4-Benzyl-3-((2*S*)-1-(*tert*-butoxycarbonyl)pyrrolidine-2-carboxamido)methyl]-2,5-dioxopiperazin-6-yl]acetic Acid (**14**)**



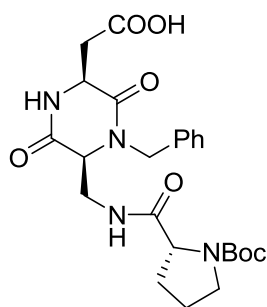
To a solution of **9** (75 mg, 0.142 mmol, 1.0 equiv.) in CH<sub>2</sub>Cl<sub>2</sub> (1.2 mL) at 0 °C were added pyrrolidine (15 μL, 0.170 mmol, 1.2 equiv.), triphenylphosphane (6.7 mg, 0.025 mmol, 0.18 equiv.), and tetrakis- (triphenylphosphane)palladium(0) (6.6 mg, 0.0057 mmol, 0.04 equiv.). The mixture was stirred for 15 min at 0°C and 2 h at room temperature, then poured into EtOAc (20 mL) and extracted into satd. NaHCO<sub>3</sub> solution (3x 3 mL). The organic layers were discarded and the combined aqueous phases were acidified to pH 2 with 1M KHSO<sub>4</sub> solution. The acidified aqueous solution was extracted into CH<sub>2</sub>Cl<sub>2</sub> (3x 5 mL), and the combined organic layers were dried with Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography eluting with 10% MeOH in CH<sub>2</sub>Cl<sub>2</sub> to yield the product as a white solid (56 mg, 0.115 mmol, 81 %). *R*<sub>f</sub> = 0.30 (CH<sub>2</sub>Cl<sub>2</sub>/MeOH 9:1); m.p. 128–129 °C. [ $\alpha$ ]<sub>20 D</sub> = +57.40 (*c* = 0.2, CHCl<sub>3</sub>). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 25°C):  $\delta$  = 1.41–1.48 (br., 9 H), 1.83, 2.34 (br., 4 H), 2.93–3.01 (br., 1 H), 3.10–3.20 (br., 1 H), 3.32–3.63 (br., 4 H), 3.81–3.99 (br., 2 H), 4.24–4.50 (br., 2 H), 5.51 (m, 1 H), 7.28–7.37 (br., 5 H), 7.50 (br., 1 H) ppm. <sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>, 25°C):  $\delta$  = 24.4, 28.4, 29.9, 39.8, 40.5, 46.8, 47.2, 52.1, 57.6, 59.8, 128.1, 128.5, 129.0, 135.0, 155.1, 164.8, 173.3 ppm. IR:  $\nu$  = 2725, 2676, 1738, 1666, 1252, 1162, 1126, 969, 849, 724 cm<sup>-1</sup>. C<sub>24</sub>H<sub>33</sub>N<sub>4</sub>O<sub>7</sub> (489.55): calcd. C 59.00, H 6.60, N 11.47; found C 58.97, H 6.55, N 11.64.

**6-[(3*S*,6*S*)-4-Benzyl-3-((2*S*)-1-pyrrolidine-2-carboxamido)methyl]-2,5-dioxopiperazin-6-yl]acetic Acid, Trifluoroacetate Salt (18·TFA)**



The Boc derivative from the previous reaction was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (1.5 mL), TFA (1.5 mL) was added dropwise at 0°C, and the mixture stirred at the same temperature for 2 h. The solution was evaporated under reduced pressure and the residue was treated with Et<sub>2</sub>O to cause the precipitation of the TFA salt, which was isolated by decantation.

**6-[(3*S*,6*S*)-4-Benzyl-3-((2*R*)-1-(*tert*-butoxycarbonyl)pyrrolidine-2-carboxamido)methyl]-2,5-dioxopiperazin-6-yl]acetic Acid (**15**)**

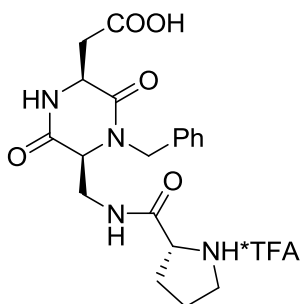


To a solution of **10** (75 mg, 0.142 mmol, 1.0 equiv.) in CH<sub>2</sub>Cl<sub>2</sub> (3 mL) at 0°C were added pyrrolidine (15 μL, 0.170 mmol, 1.2 equiv.), triphenylphosphane (6.7 mg, 0.025 mmol, 0.18 equiv.), and tetrakis-(triphenylphosphane)palladium(0) (6.6 mg, 0.0057 mmol, 0.04 equiv.). The mixture was stirred for 15 min at 0°C and 2 h at room temperature, poured into EtOAc (20 mL), and extracted into satd. NaHCO<sub>3</sub> solution (3x 3 mL). The organic layers were discarded and the combined aqueous phases were acidified to pH 2 with 1M KHSO<sub>4</sub> solution. The acidified aqueous solution was extracted into CH<sub>2</sub>Cl<sub>2</sub> (3x 5 mL) and the combined organic layers were dried with Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography eluting with 10% MeOH in CH<sub>2</sub>Cl<sub>2</sub> to yield the product as a white solid (59.0 mg, 0.120 mmol, 85%). *R*<sub>f</sub> = 0.30 (CH<sub>2</sub>Cl<sub>2</sub>/MeOH 9:1); m.p. 131–132 °C. [α]<sub>20 D</sub> = +107.60 (*c* = 0.2, CHCl<sub>3</sub>). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 25 °C): δ = 1.44 (s, 9 H), 1.70 (br., 1 H), 1.86 (br., 1 H), 2.06 (br., 2 H), 2.90 (dd, *J* = 17.7, 3.2 Hz, 1 H), 3.27 (dd, *J* = 17.7, 4.1 Hz, 1 H)



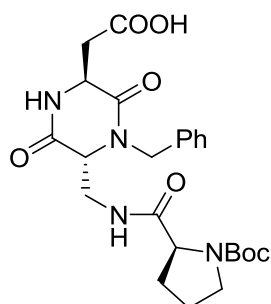
3.33–3.57 (br., 4 H), 3.76–3.86 (m, 2 H), 4.30–4.40 (m, 3 H), 5.66 (d,  $J = 15.3$  Hz, 1 H), 7.18 (d,  $J = 8.7$  Hz, 1 H), 7.28–7.38 (m, 5 H), 8.95 (s, 1 H) ppm.  $^{13}\text{C}$  NMR (100.6 MHz,  $\text{CDCl}_3$ , 25 °C):  $\delta = 24.5, 28.4, 30.3, 35.3, 38.2, 45.6, 47.4, 51.2, 56.4, 60.1, 81.2, 128.2, 128.6, 129.0, 134.6, 154.9, 165.0, 167.3, 173.0, 173.1$  ppm. IR:  $\nu = 2726, 1656, 1165, 1123, 723$   $\text{cm}^{-1}$ .  $\text{C}_{24}\text{H}_{33}\text{N}_4\text{O}_7$  (489.55): calcd. C 59.00, H 6.60, N 11.47; found C 55.91, H 6.54, N 11.58.

**6-[(3*S*,6*S*)-4-Benzyl-3-((2*R*)-1-pyrrolidine-2-carboxamido)methyl)-2,5-dioxopiperazin-6-yl]acetic Acid, Trifluoroacetate Salt (19·TFA)**



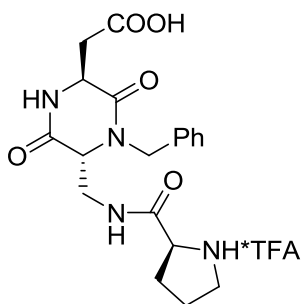
The Boc derivative from the previous reaction was dissolved in  $\text{CH}_2\text{Cl}_2$  (1.6 mL), TFA (1.6 mL) was added dropwise at 0°C, and the mixture stirred at the same temperature for 2 h. The solution was evaporated under reduced pressure and the residue was treated with  $\text{Et}_2\text{O}$  to cause the precipitation of the TFA salt, which was isolated by decantation.

**6-[(3*R*,6*S*)-4-Benzyl-3-({(2*S*)-1-(*tert*-butoxycarbonyl)pyrrolidine-2-carboxamido)methyl]-2,5-dioxopiperazin-6-yl]acetic Acid (**16**)**



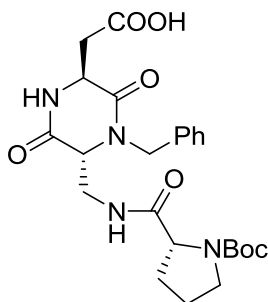
To a solution of **11** (793 mg, 1.50 mmol, 1.0 equiv.) in CH<sub>2</sub>Cl<sub>2</sub> (15 mL) at 0 °C were added pyrrolidine (0.149 mL, 1.80 mmol, 1.2 equiv.), triphenylphosphane (77 mg, 0.3 mmol, 0.2 equiv.), and tetrakis(triphenylphosphane) palladium(0) (87 mg, 0.075 mmol, 0.05 equiv.). The mixture was stirred for 15 min at 0°C and 2 h at room temperature, poured into EtOAc (60 mL), and extracted into satd. NaHCO<sub>3</sub> solution (3x 10 mL). The organic layers were discarded and the combined aqueous phases were acidified to pH 2 with 1M KHSO<sub>4</sub> solution. The acidified aqueous solution was extracted into CH<sub>2</sub>Cl<sub>2</sub> (3x 15 mL) and the combined organic layers were dried with Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography eluting with 10% MeOH in CH<sub>2</sub>Cl<sub>2</sub> to yield the product as a white solid (687 mg, 1.40 mg, 94%). *R*<sub>f</sub> = 0.31 (CH<sub>2</sub>Cl<sub>2</sub>/MeOH 9:1); m.p. 117– 118 °C. [ $\alpha$ ]<sub>20 D</sub> = -50.16 (*c* = 0.2, CHCl<sub>3</sub>). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 25 °C):  $\delta$  = 1.33–1.45 (br., 9 H), 1.75–2.40 (br., 4 H), 2.67 (dd, *J* = 18.0, 10.4 Hz, 1 H), 3.27–3.96 (br., 6 H), 4.16–4.70 (br., 3 H), 4.33–4.60 (br., 1 H), 7.23– 7.34 (br., 5 H) ppm. <sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>, 25 °C):  $\delta$  = 24.4, 28.4, 29.1, 31.2, 38.0, 39.3, 47.3, 50.9, 59.1, 59.9, 80.9, 135.6, 155.8, 164.9, 165.3, 168.3, 168.7, 173.9 ppm. IR:  $\nu$  = 1737, 1652, 1159, 1072, 723 cm<sup>-1</sup>. C<sub>24</sub>H<sub>33</sub>N<sub>4</sub>O<sub>7</sub> (489.55): calcd. C 59.00, H 6.60, N 11.47; found C 59.21, H 6.70, N 11.80.

**6-[(3*R*,6*S*)-4-Benzyl-3-((2*S*)-1-pyrrolidine-2-carboxamido)methyl)-2,5-dioxopiperazin-6-yl]acetic Acid, Trifluoroacetate Salt (20·TFA)**



**(5·TFA):** The Boc derivative from the previous reaction was dissolved in  $\text{CH}_2\text{Cl}_2$  (18.2 mL), TFA (18.2 mL) was added dropwise at  $0^\circ\text{C}$ , and the mixture stirred at the same temperature for 2 h. The solution was evaporated under reduced pressure and the residue was treated with  $\text{Et}_2\text{O}$  to cause the precipitation of the TFA salt, which was isolated by decantation.

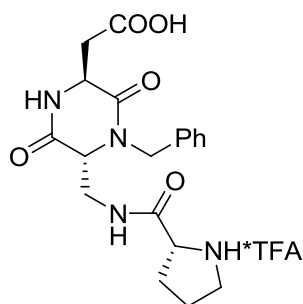
**6-[(3*R*,6*S*)-4-Benzyl-3-((2*R*)-1-(*tert*-butoxycarbonyl)pyrrolidine-2-carboxamido)methyl)-2,5-dioxopiperazin-6-yl]acetic Acid (17)**



Compound **12** (734 mg, 1.39 mmol, 1.0 equiv.) was dissolved in  $\text{CH}_2\text{Cl}_2$  (14 mL), and the solution was cooled to  $0^\circ\text{C}$ . Pyrrolidine (0.138 mL, 1.67 mmol, 1.2 equiv.), triphenylphosphane (73 mg, 0.278 mmol, 0.2 equiv.), and tetrakis(triphenylphosphane)palladium(0) (80 mg, 0.0685 mmol, 0.05 equiv.) were added, the mixture was stirred for 15 min at  $0^\circ\text{C}$  and 2 h at room temperature, poured into  $\text{EtOAc}$  (60 mL), and extracted into satd.  $\text{NaHCO}_3$  solution (3x 10 mL).

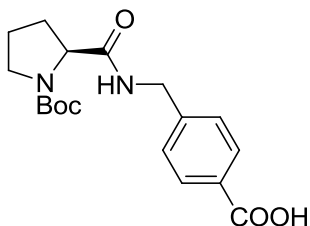
The organic layers were discarded and the combined aqueous phases were acidified to pH 2 with 1M KHSO<sub>4</sub> solution. The acidified aqueous solution was extracted into CH<sub>2</sub>Cl<sub>2</sub> (3x 15 mL) and the combined organic layers were dried with Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography eluting with 10% MeOH in CH<sub>2</sub>Cl<sub>2</sub> to yield the product as a white solid (620 mg, 1.27 mg, 91%). *R*<sub>f</sub> = 0.31 (CH<sub>2</sub>Cl<sub>2</sub>/MeOH 9:1); m.p. 111–112 °C. [ $\alpha$ ]<sub>20 D</sub> = +5.50 (*c* = 0.2, CHCl<sub>3</sub>). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 25°C):  $\delta$  = 1.44 (s, 9 H), 1.75–2.15 (br., 4 H), 2.70 (m, 1 H), 3.35–3.55 (br., 3 H), 3.67 (br., 1 H), 3.82 (br., 1 H), 3.90 (br. s, 1 H), 4.07 (d, *J* = 14.4 Hz, 1 H), 4.35 (br, 1 H), 4.53 (d, *J* = 9.7 Hz, 1 H), 5.48 (d, *J* = 14.4 Hz, 1 H), 7.25–7.45 (m, 5 H), 7.57 (br, 1 H), 8.30 (s, 1H) ppm. <sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>, 25 °C):  $\delta$  = 24.7, 28.4, 29.3, 37.6, 40.0, 47.1, 47.2, 50.9, 58.4, 59.8, 81.2, 128.1, 128.4, 128.9, 135.3, 155.7, 165.3, 168.6, 173.7, 174.3 ppm. IR:  $\nu$  = 1734, 1675, 1163, 1124, 723 cm<sup>-1</sup>. C<sub>24</sub>H<sub>33</sub>N<sub>4</sub>O<sub>7</sub> (489.55): calcd. C 59.00, H 6.60, N 11.47; found C 59.13, H 6.75, N 11.61.

**6-[(3*R*,6*S*)-4-Benzyl-3-((2*R*)-1-pyrrolidine-2-carboxamido)methyl]-2,5-dioxopiperazin-6-yl]acetic Acid, Trifluoroacetate Salt (21·TFA)**



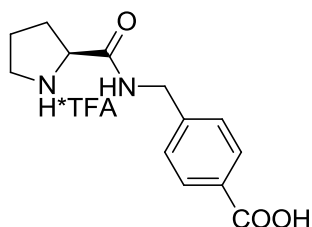
The Boc-protected derivative from the previous reaction was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (16.5 mL), TFA (16.5 mL) was added dropwise at 0°C, and the mixture stirred at the same temperature for 2 h. The solution was evaporated under reduced pressure and the residue was treated with Et<sub>2</sub>O to provide the precipitation of the TFA salt, which was isolated by decantation.

**4-[(2*S*)-1-(*tert*-Butoxycarbonyl)pyrrolidine-2-carboxamido]-methyl]benzoic Acid (22b)**



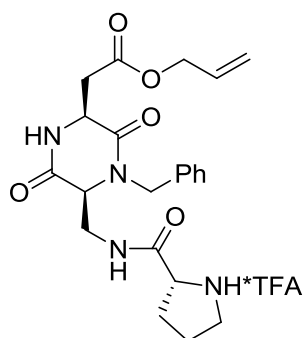
Boc-L-Proline (50 mg, 0.23 mmol, 1.0 equiv.) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (2.5 mL), and HATU (88 mg, 0.23 mmol, 1.0 equiv.) and collidine (73 μL, 0.55 mmol, 2.5 equiv.) were added at 0°C under N<sub>2</sub>. The solution was stirred for 30 min before 4-(aminomethyl)benzoic acid (35 mg, 0.23 mmol, 1.0 equiv.) was added, and the mixture stirred for 1 h at 0°C and overnight at room temperature. The reaction mixture was poured into EtOAc (25 mL) and washed with 1M KHSO<sub>4</sub> solution (3x 15 mL) and brine (1x 20 mL). The organic layer was dried with Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography using 8% MeOH in CH<sub>2</sub>Cl<sub>2</sub> to yield the product as a white-yellow solid (52 mg, 0.15 mmol, 65%). *R*<sub>f</sub> = 0.33 (CH<sub>2</sub>Cl<sub>2</sub>/MeOH 9:1); m.p. 177–178 °C. [α]<sub>20 D</sub> = -73.43 (*c* = 0.1, CHCl<sub>3</sub>). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 25 °C): δ = 1.43 (s, 9 H), 1.82–2.42 (br., 4 H), 3.30–3.55 (br., 2 H), 4.32–4.74 (br., 3 H), 7.30–7.34 (br., 2 H), 7.88–7.93 (br., 2 H) ppm. <sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>, 25 °C): δ = 23.7, 24.7, 28.4, 43.1, 47.2, 60.0, 80.8, 127.3, 128.7, 130.3, 143.9, 155.9, 169.8, 172.5 ppm. IR: ν = 1716, 1649, 1562, 1259, 1162, 1022, 923 cm<sup>-1</sup>. C<sub>18</sub>H<sub>24</sub>N<sub>2</sub>O<sub>5</sub> (348.40): calcd. C 62.05, H 6.94, N 8.04; found C 61.97, H 6.71, N 7.99.

**4-[(2*S*)-Pyrrolidine-2-carboxamido]methyl}benzoic Acid, Trifluoroacetate Salt (22b·TFA)**



The compound from the previous reaction was dissolved in  $\text{CH}_2\text{Cl}_2$  (1.9 mL), TFA (1.9 mL) was added dropwise at  $0^\circ\text{C}$ , and the mixture stirred at the same temperature for 2 h. The solution was evaporated under reduced pressure and the residue was treated with  $\text{Et}_2\text{O}$  to cause the precipitation of the TFA salt, which was isolated by decantation.

**(2*S*)-2-[(*3R,6S*)-6-{2-(Allyloxy)-2-oxoethyl}-4-benzyl-2,5-dioxopiperazin-3-yl)methylcarbamoyl]pyrrolidine, Trifluoroacetate Salt (23·TFA)**



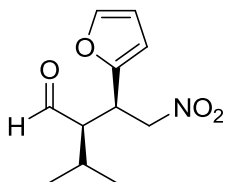
To a solution of **11** (30 mg, 0.06 mmol, 1.0 equiv.) in  $\text{CH}_2\text{Cl}_2$  (0.5 mL) was added TFA (0.5 mL) dropwise at  $0^\circ\text{C}$ , and the resulting solution was stirred at the same temperature for 2 h. Volatiles were evaporated under reduced pressure and the residue was treated with  $\text{Et}_2\text{O}$  to cause the precipitation of the TFA salt, which was isolated by decantation.

## General Procedure for 1,4-Addition Reactions

To a solution of the catalyst (5.6 mg, 0.011 mmol, 0.05 equiv.) in solvent (500  $\mu$ L,  $\text{CHCl}_3/i\text{PrOH}$ , 9:1) was added NMM (1.23  $\mu$ L, 0.011 mmol, 0.05 equiv.), and the solution was stirred for 10 min. The nitroolefin (1 equiv.) and the aldehyde (3 equiv.) were added and the mixture was stirred for 24 h at 20°C. The reaction mixture was purified by flash chromatography on silica gel eluting with a mixture of *n*-hexane and EtOAc.

## Characterization of 1,4-addition reaction products

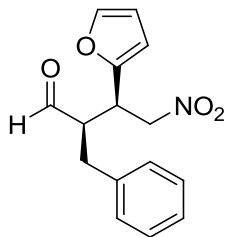
### 3-(Furan-2-yl)-2-isopropyl-4-nitrobutanal (25c)



Synthesized from 2-(2-nitrovinyl)furan and isobutanal according to the general procedure.

The product was purified by flash chromatography (hexane/EtOAc, 9:1).  $R_f = 0.31$  (hexane/EtOAc, 6:1).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ , 25 °C):  $\delta = 0.89$  (d,  $J = 6.9$  Hz, 3 H), 1.16 (d,  $J = 7.2$  Hz, 3 H), 1.75 (m, 1 H), 2.86 (ddd,  $J = 9.9, 4.8, 1.8$  Hz, 1 H), 4.05 (m, 1 H), 4.58–4.68 (m, 2 H), 6.22 (dd,  $J = 3.2, 0.5$  Hz, 1 H), 6.31 (dd,  $J = 3.2, 1.9$  Hz, 1 H), 7.37 (dd,  $J = 1.9, 0.5$  Hz, 1 H) ppm.  $^{13}\text{C}$  NMR (100.6 MHz,  $\text{CDCl}_3$ , 25 °C):  $\delta = 17.8, 21.2, 28.0, 35.9, 57.3, 76.6, 109.0, 110.4, 142.6, 150.3, 203.4$  ppm. IR:  $\nu = 2725, 1715, 1557, 1151, 1015, 731$   $\text{cm}^{-1}$ . HRMS (ESI<sup>+</sup>): calcd. For  $\text{C}_{11}\text{H}_{15}\text{NO}_4\text{Na}$  [ $\text{M} + \text{Na}$ ]<sup>+</sup> 248.08958; found 248.08933. The enantiomeric excess was determined by HPLC using a Chiracel AD-H column (*n*-hexane/*i*PrOH, 99:1, 25 °C) at 0.6 mL/min, UV detection at 212 nm:  $t_{R1}$  (*syn*) = 27.5 min,  $t_{R2}$  (*syn*) = 32.0 min.

## 2-Benzyl-3-(furan-2-yl)-4-nitrobutanal (25d)



Synthesized from 2-(2-nitrovinyl)furan and hydrocinnamaldehyde according to the general procedure. The product was purified by flash chromatography (hexane/EtOAc, 9:1).  $R_f = 0.25$  (hexane/EtOAc, 6:1).  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ , 25 °C):  $\delta = 2.76$  (dd,  $J = 14.4, 5.6$  Hz, 1 H), 2.90 (dd,  $J = 14.4, 8.8$  Hz, 1 H), 3.18 (dddd,  $J = 8.8, 7.2, 5.6, 1.6$  Hz, 1 H), 4.08 (ddd,  $J = 8.8, 7.2, 5.2$  Hz, 1 H), 4.63, (dd,  $J = 12.8, 5.2$  Hz, 1 H), 4.70 (dd,  $J = 12.8, 8.8$  Hz, 1 H), 6.23 (m, 1 H), 6.35, (dd,  $J = 3.2, 2.0$  Hz, 1 H), 7.12 (m, 2 H), 7.24–7.34 (m, 3 H), 7.41 (dd,  $J = 2.0, 0.8$  Hz), 9.73 (d,  $J = 1.6$  Hz, 1 H) ppm.  $^{13}\text{C NMR}$  (100.6 MHz,  $\text{CDCl}_3$ , 25°C):  $\delta = 33.4, 37.2, 53.8, 75.8, 109.1, 110.6, 127.0, 128.4, 128.9, 137.3, 142.8, 149.9, 202.0$  ppm. IR:  $\nu = 2728, 1725, 1554, 1496, 1144, 1074, 1017, 969, 918, 738, 701$   $\text{cm}^{-1}$ . HRMS (ESI<sup>+</sup>): calcd. for  $\text{C}_{15}\text{H}_{15}\text{NO}_4\text{Na}$   $[\text{M} + \text{Na}]^+$  296.08988; found 296.08933. The enantiomeric excess was determined by HPLC using a Chiracel AD-H column (*n*-hexane/*i*PrOH, 99:1, 25°C) at 0.6 mL/min, UV detection at 212 nm:  $t_{R1}$  (*syn*) = 42.1 min,  $t_{R2}$  (*syn*) = 46.7.

### 3.4.3 Computational Studies

All calculations were run using the Schrödinger suite of programs (<http://www.schrodinger.com>) through the Maestro graphical interface. Monte Carlo conformational searches of **3–6** and relative enamine derivatives (MCMC),<sup>62</sup>

<sup>62</sup> G. Chang, W. C. Guida, W. C. Still, *J. Am. Chem. Soc.* **1989**, *111*, 4379–4386.



OPLSA\_2005 force field,<sup>63</sup> implicit CHCl<sub>3</sub> GB/SA solvent model)<sup>64</sup> were performed as implemented in the framework of MacroModel version 9.8.<sup>65</sup> For each search, at least 1000 starting structures for each variable torsion angle were generated and minimized until the gradient was less than 0.05 kJ/Åmol using the truncated Newton–Raphson algorithm.<sup>66</sup> Duplicate conformations of ligands and those with an energy greater than 6 kcal/mol above the global minimum were discarded.

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<sup>63</sup> G. A. Kaminski, R. A. Friesner, J. Tirado-Rives, W. L. Jorgensen, *J. Phys. Chem. B* **2001**, *105*, 6474–6487.

<sup>64</sup> W. C. Still, A. Tempczyk, R. C. Hawley, T. J. Hendrickson, *J. Am. Chem. Soc.* **1990**, *112*, 6127–6129.

<sup>65</sup> *MacroModel*, version 9.8, Schrödinger, LLC, New York, NY, **2010**.

<sup>66</sup> J. W. Ponder, F. M. Richards, *J. Comput. Chem.* **1987**, *8*, 1016–1024.

## *Acknowledgments*

I would like to thank my Ph.D. tutors, prof. Umberto Piarulli and prof. Oliver Reiser for their support, suggestions, interesting scientific discussions and particularly for giving me the opportunity to perform my Ph.D. in their research groups.

Moreover I would like to thank all the people who contributed with their expertise and/or friendship to my experience during these years.