Sunil Jagtap

Synthesis and Application of new chiral Peptides, Guanidines and Formamides as Organocatalysts for Asymmetric C-C Bond Formation Reactions

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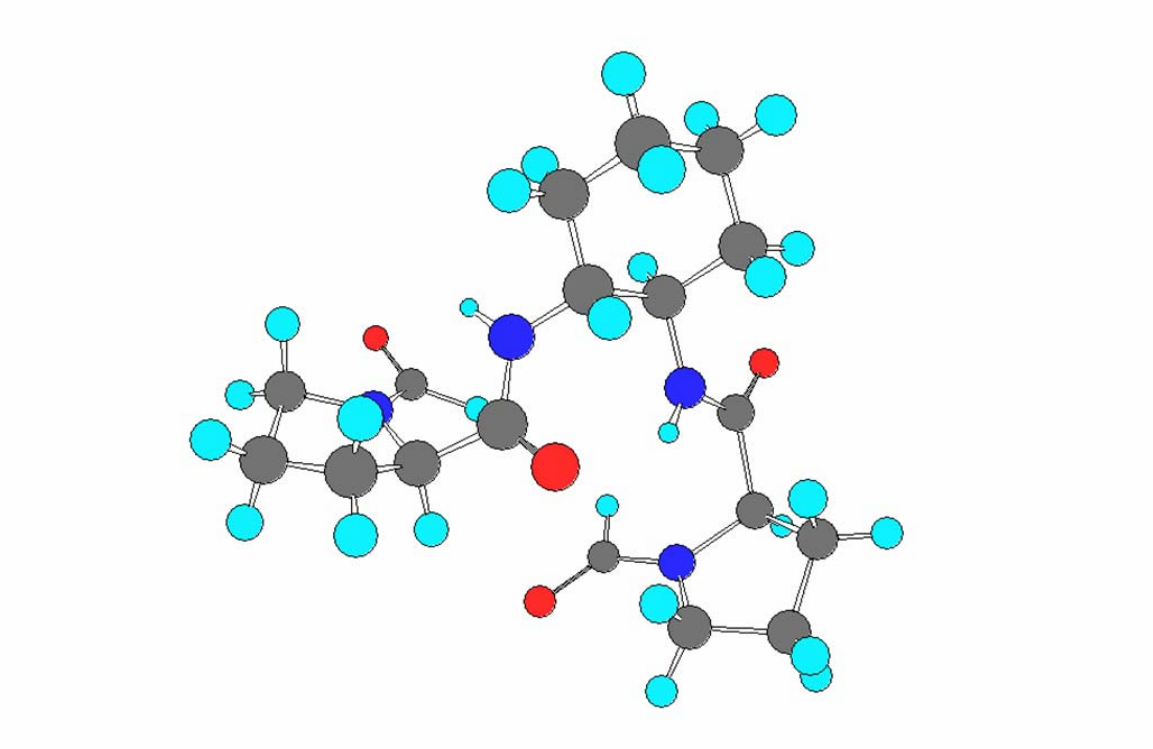

Göttingen 2006

Synthesis and Application of new chiral Peptides, Guanidines and Formamides as Organocatalysts for Asymmetric C-C Bond Formation Reactions

DISSERTATION

zur Erlangung des Doktorgrades
der Mathematisch-Naturwissenschaftlichen Fakultäten
der Georg-August-Universität zu Göttingen

vorgelegt von

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aus
Kothale, Indien

Göttingen 2006

D7

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Die vorliegende Arbeit wurde unter der Leitung von Junior Prof. Dr. Svetlana B. Tsogoeva in der Zeit von Februar 2003 bis Mai 2006 im Institut für Organische und Biomolekulare Chemie der Georg-August-Universität Göttingen angefertigt.

Frau Junior Prof. Svetlana B. Tsogoeva möchte ich an dieser Stelle für die Überlassung des interessanten Themas, ihre hilfreichen Anregungen, ihre Diskussionsbereitschaft und die stete Unterstützung während der Anfertigung dieser Arbeit herzlich danken.

To My Family

Abbreviations

Ac	Acetyl
aq.	Aqueous
Ar	Aryl
Boc	*tert*-butoxycarbonyl
Bn	Benzyl
bs	Broad singlate (^{1}H NMR)
Bu	Butyl
N-BuLi	n-Butyl lithium
Bz	Benzoyl
conv.	Conversion
cat.	Catalyst
Cbz	Benzyloxycarbonyl
$CDCl_3$	Deuterated chloroform
d	doublet (^{1}H NMR)
dd	double of doublets (^{1}H NMR)
DCM	Dichloromethane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
de	Diastereomeric excess
DIBAl	Diisobutylaluminiun Hydride
DIPEA	N,N'-Diisopropylethylamine
DMF	N,N'-Dimethylformamide
DMSO	Dimethylsulfoxide
δ	Chemical shift (NMR)
EDCI	Ethylenediisopropylcarbodiimide
ee	Enantiomeric excess
equiv.	Equivalent
ESI	Electron spray ionization (mass spectroscopy)
Et	Ethyl
EtOAc	Ethylacetate

H	Hours
HMPA	Hexamethylphosphoramide
HPLC	High performance liquid chromatography
Hz	Hertz
i-Pr	*iso*-propyl
LDA	Lithium diisopropylamide
m	multiplate (^{1}H NMR)
Me	Methyl
min.	Minutes
M.S.	Molecular sieves
MW	Molecular weight
m/z	mass/charge
NMR	Nuclear magnetic resonance
Pd/C	Palladium on carbon
Ph	Phenyl
Pr	Propyl
q	Quartet (N MR)
Rt	Room temperature
S_N2	Nucleophilic bimolecular substitution
Stoich.	Stoichiometric
t	triplet (^{1}H NMR)
t-Bu	*tert*-butyl
temp	Temperature
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
Ts	Tosyl
TLC	Thin layer chromatography
X	halogen (Cl, Br, I)

1. Introduction

1.1. Chirality

Chirality is of critical importance in chemistry and unites the traditionally-defined subdisciplines of chemistry. Many biologically active molecules are chiral, including the naturally occurring amino acids (the building blocks of proteins) and vitamins. The concept of chirality was first introduced in 1815 by French chemist Jean Baptiste Biot when he discovered optical activity in nature.[1] One of his students Louis Pasteur achieved the first separation of enantiomers in 1848 when he manually resolved a racemic mixture of tartaric acid salt based on differently shaped crystals.[2] Since then Chirality has become of tremendous importance in our daily life.

A chiral object is one that possesses the property of ´´handedness''. Thus molecule can exist in two forms, which are nonsuperimposable mirror images of each others. A chiral object such as our hand is one that can not be placed on its mirror image so that all parts coincide (figure 1). A chiral molecule and its mirror image are called enantiomers, and possess identical physical properties in an achiral environment. Enantiomers are rotate the plane of polarized light by the same angle, but in opposite directions.

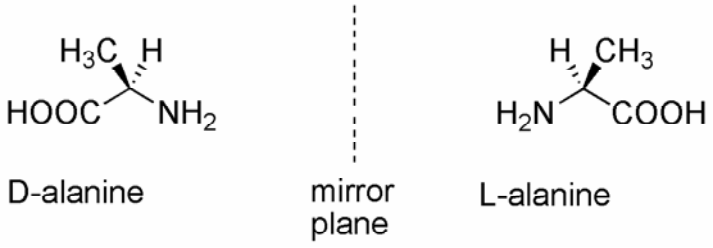


Figure 1. The two enantiomers of the alanine.

The majority of biological systems are composed of chiral molecules; all but one of the twenty amino acids that make up naturally occurring proteins are chiral. This implies that the two enantiomers of a molecule will interact differently with a living organism. Indeed, usually only one enantiomer of a drug provides the desired effect, while the other

enantiomer is, less or not active. Ibuprofen, the drug used for the treatment of orthostatic hypotension has two enantiomers, out of two enantiomers (*S*)-(+)-ibuprofen (dexi ibuprofen) is active while other has no effect. However, in some cases the undesired enantiomer can cause serious side effects or even death. The most well-known and tragic example of one enantiomer causing serious side effects is the drug thalidomide (Figure 2), which was given as a racemic mixture during the 1960s to alleviate the symptom of morning sickness in pregnant woman. It was later discovered that only one of the thalidomide enantiomers has the intended effect, while the other induces abnormalities in human embryos. Unfortunately, the situation is complicated by the racemisation of the desired enantiomer in the body.

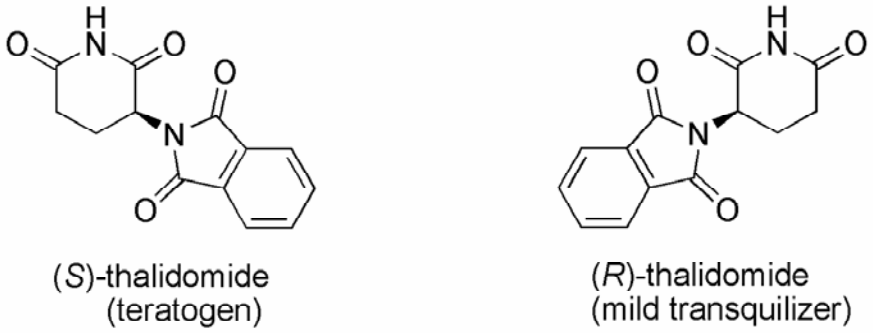


Figure 2. The two enantiomers of thalidomide.

Chiral molecules are not only primordial for the pharmaceutical industry but also for the perfumery and food industry; with our sense of taste and smell also depending on chirality. For example S-carvone is the flavor of caraway, while R-carvone is the flavor of spearmint (Figure 3).

Figure 3. Enantiomers having different smell.

These are just a few reasons why the field of asymmetric synthesis has developed enormously in recent decades. In 2001 this area of chemistry received the ultimate recognition with the Nobel Prize in Chemistry being awarded to K. Barry Sharpless, William S. Knowles, and Ryoji Noyori for their work on catalytic asymmetric methods for oxidation and reduction.

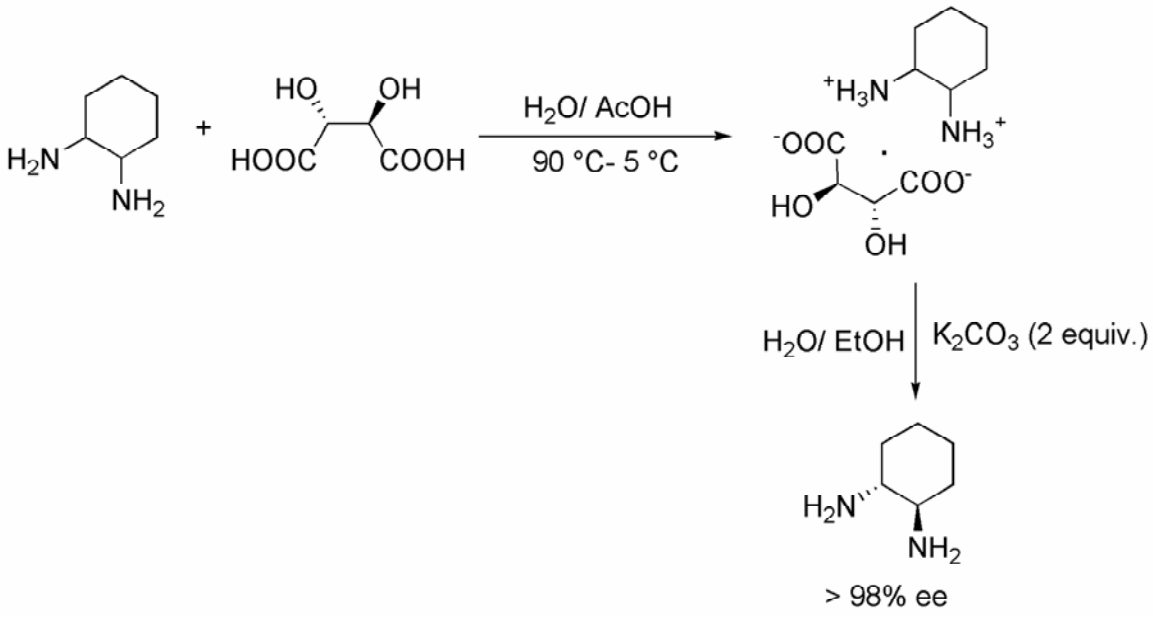
1.2 A search for the single isomer

There are three main ways to synthesis an enantiomerically pure or enriched compound

1) Resolution of racemic mixtures.
2) The "Chiral pool" based on the use of a naturally occurring chiral starting material.
3) Asymmetric synthesis (both through stoichiometric and catalytic processes).

1.2.1 Resolution of racemic mixtures

In industry, enantiomerically pure compounds are traditionally made from enantiomerically pure naturally occurring compounds or by resolution of racemic mixtures. Normally, the resolution is applied at the end of a racemic synthetic sequence, and is performed with the aid of an enantiomerically pure compound. However, because only one optical antipode is useful, half of the synthetic product is often discarded. Even if the unimportant isomer can sometimes be converted to the active form, via racemisation and resolution, extensive work is required. A further drawback of this method is the need to use an equimolar amount of an enantiopure material; which can not always be recycled and reused. Even so, the resolution of racemates is a powerful method that is still widely used in industry. Generally racemmic mixture is treated with a resolving agent (another chiral molecule), so that diastereomeric salts are formed, which can then be separated by crystallization. The resolving agent then removed by acid or base neutralization which gives the desired compound in enantioenriched form. A typical example of resolution by crystallization is illustrated in Scheme 1.[3]



Scheme 1. Classical resolution of trans-1,2-diaminocyclohexane.

1.2.2 The chiral pool or "Chiron" approach

In this case, the synthetic method is based on the transformation of a naturally occurring enantiomerically highly pure starting material.[4] The most common chiral compounds offered by nature are amino acids, carbohydrates, terpenes or alkaloids (Figure 4).

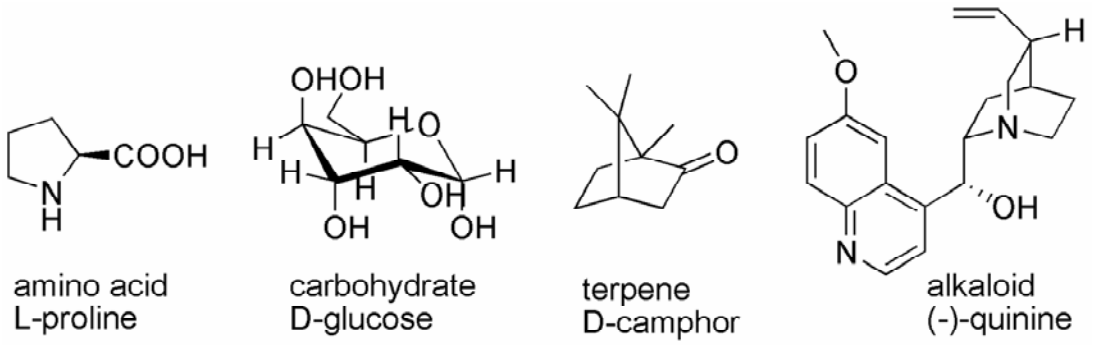
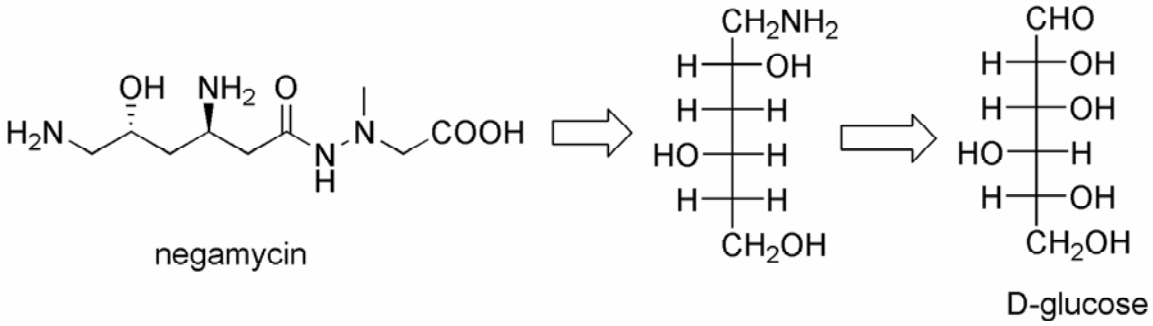


Figure 4. Example of naturally occurring chiral molecules.

A strong limitation of the chiral pool approach is the limited number of starting materials available, which can sometimes be very expensive or difficult to obtain, thus restricting the synthetic applications of this stratergy. Another disadvantage of this method is due to the chiral aspect of nature, which often produces only one of the two possible

enantiomers of a compound, also it requires a specific design concept for every new target compound.

The synthesis of negamycin, a broad-spectrum antibiotic, from glucose is a typical example of the Chiron approach (Scheme 2).



Scheme 2. Synthesis of D-glucose from negamycin.

1.2.3 Asymmetric synthesis

The principle of asymmetric synthesis is the formation of a new stereogenic centre under the influence of a chiral group. Currently this is the most powerful and commonly used method in the preparation of chiral molecules. Asymmetric synthesis can be further divided into four categories, depending of how the stereo-centre is introduced:

1) Substrate-controlled methods.

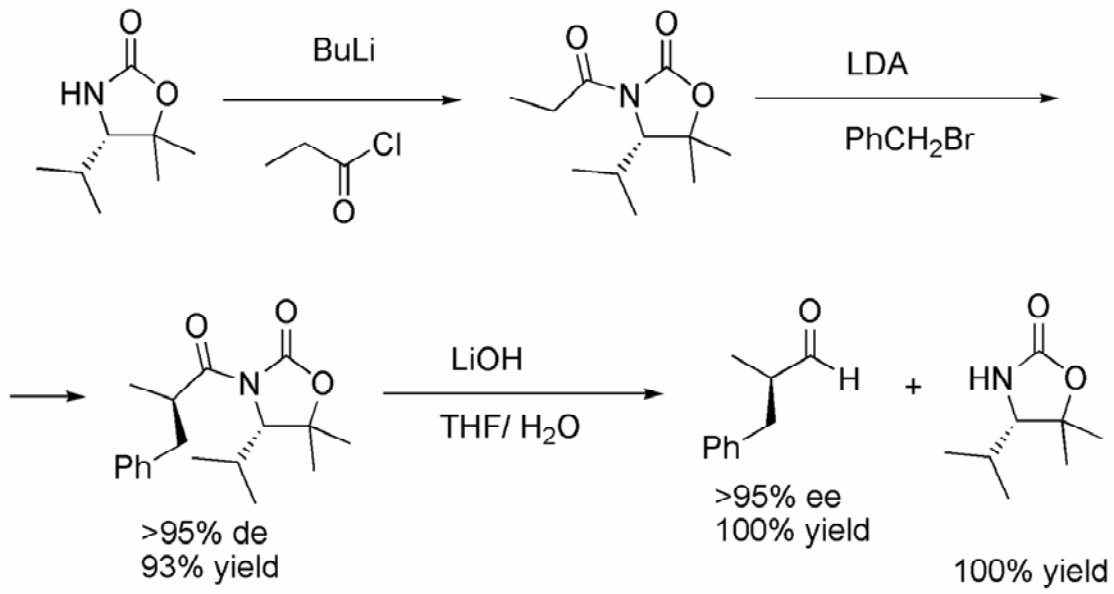
2) Auxiliary-controlled methods.

3) Reagent-controlled methods.

4) Catalyst-controlled methods.

In the case of the substrate-controlled method or "first generation of asymmetric synthesis", the stereogenic unit that already exists within the chiral substrate directing the formation of new chiral centre. The auxiliary-controlled method or "second generation of asymmetric synthesis" is based on the same principle as the first generation method in which the asymmetric control of the reaction is achieved by a chiral group in the substrate. The advantage of this method is that the enantiomerically pure chiral auxiliary is attached to an achiral substrate in order to direct the enantioselective reaction. The chiral auxiliary can be removed once the transformation is performed and often reused.

This method usually offers high levels of selectivity and has proven itself to be very useful. However, this methodology needs two extra steps to attach and remove the chiral auxiliary. Davies *et al*.[5] have developed a typical procedure where they use an "Evans type" chiral oxazolidinone to control the alkylation of an enolate (Scheme 3).



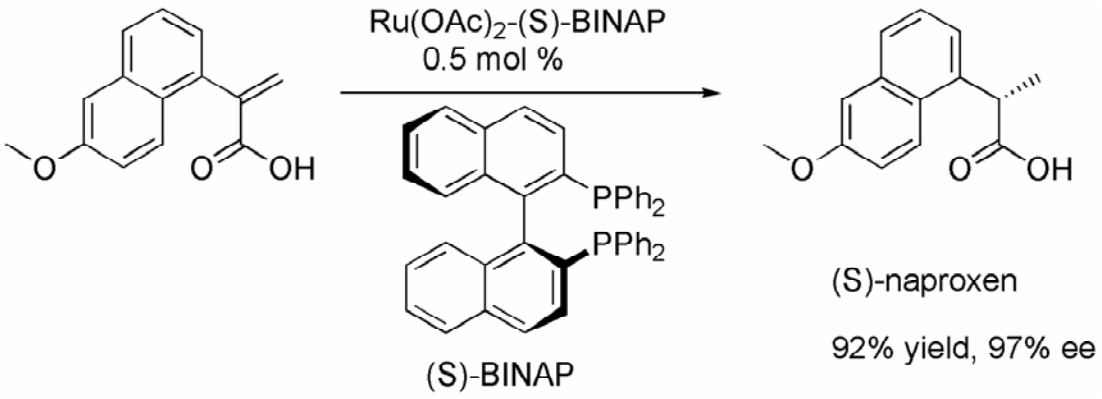
Scheme 3. Enantioselective alkylation directed by a chiral auxiliary.

In the third method, by using an enantiomerically pure chiral reagent an achiral substrate is directly transformed to a chiral product. All three previously described chiral transformations have a common feature, which is the requirement of at least one equivalent of an enantiomerically pure compound. This requirement is not satisfactory from an economical and environmental perspective. Thus, the most significant advance in asymmetric synthesis during the past three decades has been the development and application of chiral catalysts to induce the transformation of an achiral molecule to an enantioenriched chiral product. Due to its importance, this process will be dealt within more details in the following section.

1.3 Asymmetric catalysis

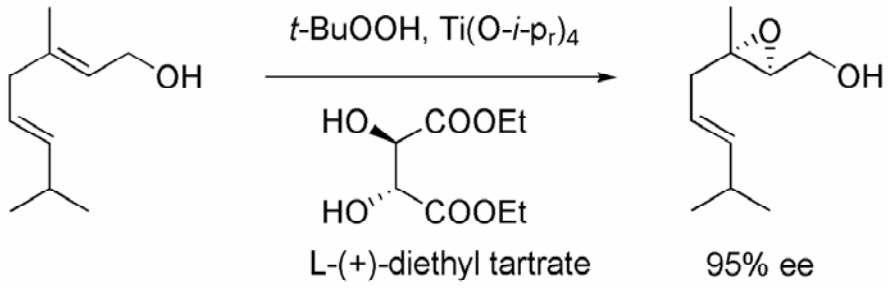
Asymmetric catalysis is a combination of asymmetric synthesis, where a chiral molecule is used to govern an enantioselective transformation, and catalysis. In catalysis an

addition of a small amount of a foreign material called "catalyst" speeds up a chemical process by decreasing the transition state energy, thus increasing the rate of the reaction without being consumed itself during the transformation. This process seems ideal for the preparation of chiral molecules since it only requires a very small amount of chiral catalyst to transform an achiral molecule into an enantioenriched chiral product. Noyori reported pioneering work in the field of catalytic asymmetric transformations in the mid 60s.[6] Although the observed enantioselectivity was poor, it opened up a new field in organic synthesis that became the focus of many research groups during the last decades. The most common asymmetric catalytic methods involve a transition metal, which once bonded to a chiral ligand, become the chiral catalyst. As mentioned earlier, in 2001 the Nobel Prize in Chemistry was awarded to Dr William S. Knowles, Professor Ryoji Noyori, and Professor K. Barry Sharpless for *"their development of catalytic asymmetric synthesis"*. Knowles and Noyori received half the Prize for: *"their work on chirally catalysed hydrogenation reactions"* and Sharpless was rewarded with the other half of the Prize for: ``*his work on chirally catalysed oxidation reactions"*. This was the final recognition for a process which has had a remarkable impact on the chemical industry and especially the pharmaceutical industry where catalytic systems are used to prepare an enantiopure drugs on large-scale. An important example resulting from the work of Noyori,[7, 8] and based on the work of Knowles, is the synthesis of the anti-inflammatory agent naproxen, involving a stereoselective catalytic hydrogenation reaction (Scheme 4).

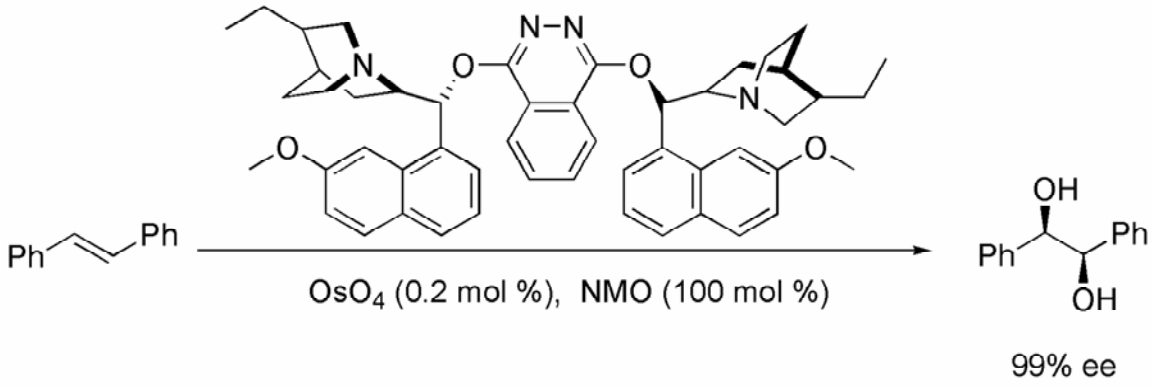


Scheme 4. Asymmetric synthesis of (*S*)-naproxen.

The hydrogenation catalyst in this reaction is an organometallic complex formed from ruthenium and a chiral organic ligand called (*S*)-BINAP. The reaction is truly remarkable because it proceeds with excellent enantiomeric excess (97%) and in high yield (92%). The development of highly enantioselective oxidation reactions by Sharpless has proved to be crucial to organic synthesis. The asymmetric epoxidation of allylic alcohols[9] and the asymmetric dihydroxylation of olefins[10] became widely used tools in the synthesis of complex chiral molecules (Scheme 5 and 6).



Scheme 5. Sharpless epoxidation of allylic alcohol.



Scheme 6. Sharpless dehydroxylation of alkenes.

For decades, it was generally accepted that transition metal complexes and enzymes were the two main classes of very efficient asymmetric catalysts. Indeed, synthetic chemists have scarcely used small organic molecules as catalysts throughout the last century, even though some of the very first asymmetric catalysts were purely organic molecules. Already in 1912, Bredig reported a modestly enantioselective alkaloid-catalysed

cyanohydrin synthesis. Only in recent years has the scientific community begun to appreciate the great potential of organocatalysis as a broadly useful methodology.

Today many methods using simple chiral molecules have been reported to catalyse asymmetric transformations with a very high degree of enantioselectivity. Now a days, organocatalysis is one of the fastest growing areas in organic chemistry.[11]

2. Asymmetric Organocatalysis

2.1. State of the art

The concept of asymmetric catalysis has become synonymous with the use of metals in chiral environments.[12-15] Metal catalysts have some advantages: for example molecular and structural diversity and large reactivity patterns that can easily be tailored by variation of ligands. But there are also some disadvantages such as high price, toxicity, pollution, waste treatment and product contamination.[16]

A large number of asymmetric transformations are based on organic reagents. The chiral organic catalyst can be regenerated and reused for further reactions. The concept will certainly be helpful for development of a number of new catalytic reactions in the near future. On the other hand applications that are typically associated with metals, for example, as Lewis acids/ bases and as redox agents[17, 18] can be emulated fairly well by organic compounds.

There is a dichotomy between organic and organometalic catalysis, particularly with respect to their reactivity and applications. On one hand organocatalytic reactions have evolved essentially from the ligand chemistry of organometalic reactions. Numbers of ligands were developed for metal mediated enantioselective catalytic reactions and are still among the most effective organocatalysts. It is thus not surprising that there are metal catalyzed reactions in which the metal free ligand is known to be active by itself, even in the same enantioselective transformation.[19-21] On the other hand, organocatalytic reactions can be more closely related to enzyme or antibody catalyzed reactions than organometalic processes. Indeed these small organic molecules, which are often known as artificial enzymes[22] show some characteristic features of bioorganic reactions.

Organic molecules catalyze chemical reactions through four different mechanisms:[11b]

1) Activation of a reaction based on the nucleophilic/ electrophilic properties of the catalysts. The chiral catalyst is not consumed in the reaction and does not require parallel regeneration. This type of activation is reminiscent of conventional Lewis acid/ base activation.

2) Organic molecules that form reactive intermediates. The chiral catalyst is consumed in the reaction and requires a parallel catalytic cycle.
3) Phase transfer reactions. The chiral catalyst forms a host-guest complex with the substrate and shuttles between the standard organic solvent and second phase (i.e. the solid, aqueous or fluorous phase in which the reaction takes place).
4) Molecular cavity accelerated asymmetric transformations, in which the catalyst may choose between the competing substrates, depending on size and structure criteria. The rate acceleration of the given reaction is similar to the Lewis acid/ base activation and is a consequence of the simultaneous action of different polar functions.

In metal mediated enantioselective catalytic reactions, the metal plays an organisational role by translating chiral information and activating the reagents. In the absence of metal, the well organised transition state, which is required for the enantioselective transformation, can be formed either by passive or dynamic interactions, as is the case in biological systems. Passive binding refer to ordinary molecular recognition through hydrophobic, Van der walls and electrostatic interaction. Dynamic binding refers to interactions between catalyst and substrates at the reaction centres. Hydrogen bonding plays a crucial role in the determination of stereoselectivity of the reaction. Although this constitutes an energy contribution of only 1-6 Kcal mol^{-1} to the interactions, influence of hydrogen bonding on the conformational preferences by forming rigid three dimensional structures contributes to the affinity and selectivity of molecular recognition. Hydrogen bonding also plays an important role in stabilizing the reactive intermediates and in modulating the reactivity,[23] in a way very similar to enzyme catalysis. More and more evidence is being gathered on the complexity of the enantioselective transformation caused by the formation of aggregates (dimers) between substrates and catalyst with the highest enantioselectivity. These new findings challenge our traditional view, which is based essentially on the consideration of monomers.

The Lewis acid/ base function of organometalic reagents can be emulated by organic systems and applied to enantioselective catalytic processes. A particularity of organocatalysts is the facile equilibrium between the electron rich and electron deficient states (i.e. the acidic and basic forms) of the same centre. It is easy to conceive this equilibrium simply by considering protonation-deprotonation, which on one hand can

activate the reagent and on the other hand can contribute to the kinetic lability of the ligand. As a result of this equilibrium the same centre can act as Lewis acid or as a Lewis base, depending on the reaction conditions. Although in any given reaction one might have a clear idea of the role of the organic catalyst as either an acid or base, the classification based on the electron donating or electron accepting ability of the molecules can be ambiguous. This acid-base dichotomy is well known in biological systems. In many enzymes one of the carboxy groups acts as an acid and the ionized form of another carboxy group acts as a base or as a nucleophile.[24] Moreover, the acid- base classification of the catalyst is hampered by the fact that a number of organocatalysts, for example, amino acids possess both acidic and basic functions and mediate the reaction by a push-pull mechanism.

Not all but some natural products like Cinchona alkaloids and its derivatives act as good catalysts.[25, 26] Also some amino acids like proline and phenylalanine[19] (Figure 5) and their derivatives have been used in enantioselective catalysts for a long time. The peptides derived from these amino acids are also showing good activity.

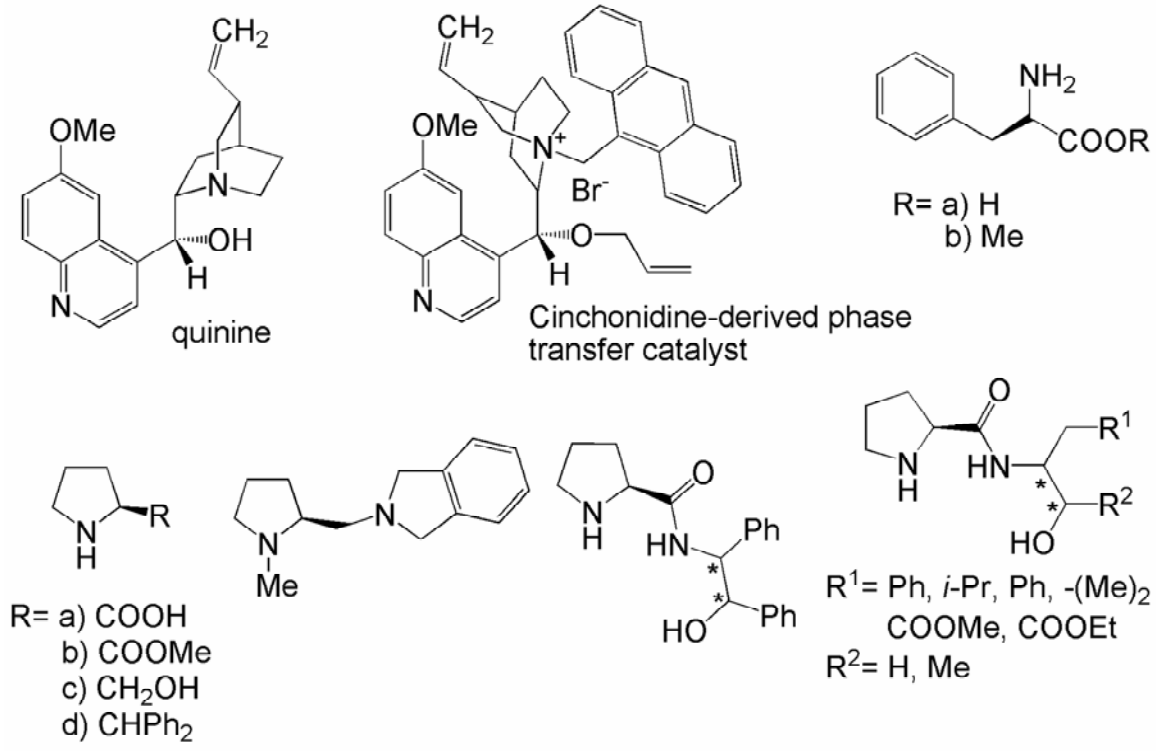
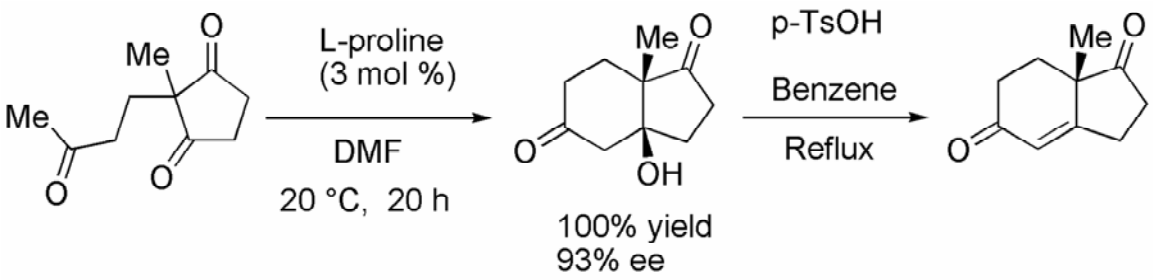


Figure 5. Some examples of organocatalysts derived from cinchona alkaloids and amino acids.

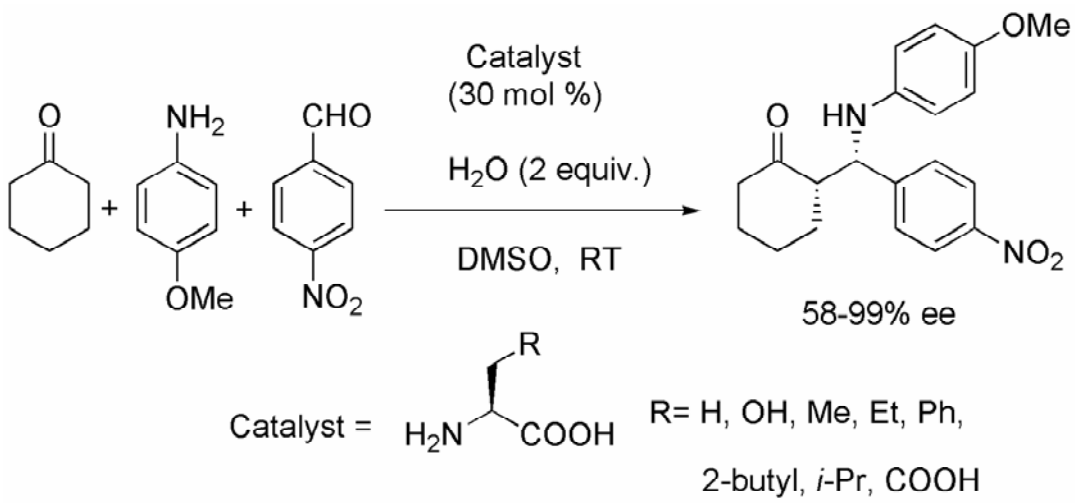
In early 1970 two groups independently reported Robinson annulation of meso triones in the presence of L-proline (3 mol %). Hajos and Parrish isolated ketol[27] while Wiechert and co-workers reported the synthesis of enone.[28]



Scheme 7. Proline catalyzed asymmetric Robinson annulation.

Till early 2000 very few groups were working on this topic and the field was very narrow. In 2000 List and Barbes has reported on use of simple proline in asymmetric aldol reaction[29] and after that, world has witnessed tremendous growth of this field. Simple amino acid like proline and it's derivatives has been used as organocatalysts for the asymmetric aldol reaction,[29-40] the Robinson annulation,[27, 41] Diels-Alder reaction,[42] Michael reaction,[43-50] α-halogenation,[51] epoxidation[52-55] and Mannich reaction.[56-60]

Other amino acids are also useful in asymmetric Mannich reaction. Cordova reported on direct three component Mannich reaction with >99% enantioselectivitie.[61] Simple linear amino acids such as alanine, valine, serine, isoleucine, catalyzed the Mannich reactions with excellent results (Scheme 8).



Scheme 8. Three component Mannich reaction catalyzed by amino acids.

Short peptides are also used as catalysts in several asymmetric transformations. The ability of their primary structure to mediate catalysis suggests that short peptides could also be successful catalysts.

The main advantage of the use of synthetic short peptide catalysts is that both forms of its enantiomers are readily available and the structure can be easily modified. In addition, it is easy to prepare the peptide sequence that can produce opposite enantiomer of the product. This is not often possible with enzymes.

2.2. Aim of the work

1) The studies of peptide-based catalysis till 2003 (when we started this work) appeared to have been focused on two extremes in the spectrum of possible catalysts: either small, conformationally rigid cyclic dipeptides, or large peptides and polyamino acids which, by virtue of their increased size and flexibility, likely adopt a specific tertiary structure in solution.

a) Also peptides, containing one proline unit, whose secondary amine normally functions as a catalytically active centre, were introduced as asymmetric catalysts for C-C bond forming reactions. To the best of our knowledge, short peptides with two to four proline units have never been examined. We were interested to explore whether there is a correlation between the amount of catalytic centers (secondary amine functionalities) and the catalytic activity of the oligo-α-amino acid. Hence we decided to investigate the potential of short peptides with two, three and four proline units as organic catalysts for the Michael reactions, which are regarded to be among the synthetically important carbon-carbon bond forming reactions.

b) Surprisingly, dipeptides, which are not containing L-proline (e. g. Leu-His, His-Leu), have never been investigated as chiral catalysts for the conjugate addition reactions. This was the motivation to develop a new catalytic system, based on dipeptides, for C-C bond formation reactions by example of asymmetric Michael additions.

2) It is known that guanidines could be used for molecular recognition of carboxylate anions because of their ability to form strong zwitterionic hydrogen bonds. Although, tetramethylguanidine (TMG) has been used as a catalyst for carbon-carbon bond formation, and known reactions catalysed by TMG include Michael additions and aldol condensations, guanidines are relatively unexplored type of bond formation catalysts. Only a few examples of guanidine catalysed enantioselective synthesis exist. In order to maintain the structure of the guanidinium group and to enhance its binding abilities, one may incorporate it into a rigid cyclic framework, which should improve the predictability of the host-guest orientation. Hence the synthesis of new chiral cyclic guanidines and their application for conjugate addition reactions was the next aim of this work.

3) While N-acylhydrazones were reported to be reactive for the allylation, it was observed that simple imines were resistant to allyltrichlorosilanes.

The first example of allylation of imines derived from aldehydes and 2-aminophenols with allyltrichlorosilane using DMF as neutral coordinate-organocatalyst (NCO) to afford the corresponding homoallylic amines has been reported in 2003 by Kobayashi and co-workers. However, no enantioselective allylation of these simple imines with allyltrichlorosilane has been attained to date.

Thus we aimed to develop the asymmetric organocatalytic version of this reaction by application of the new proline derived C2-chiral bisformamides.

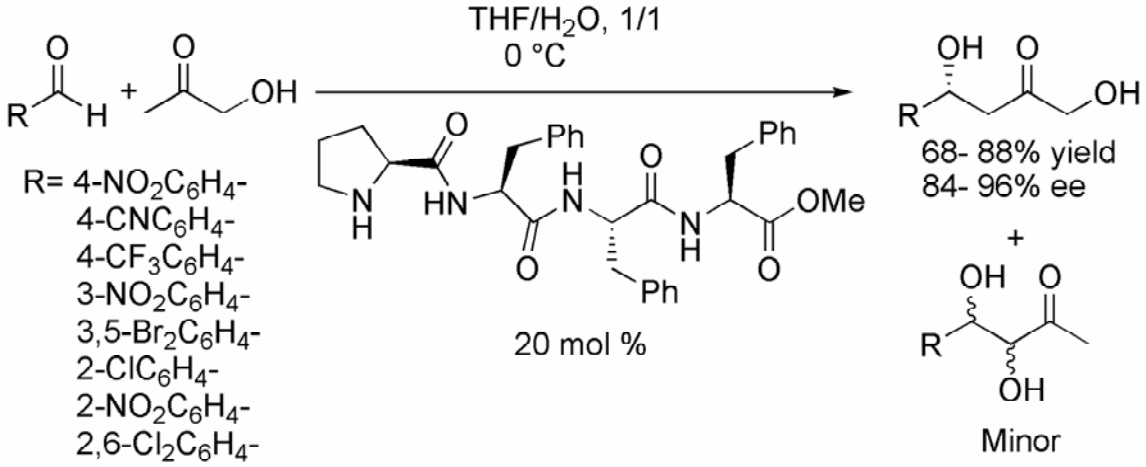
3. Short Peptides as Organic Catalysts in Asymmetric Conjugate Addition Reactions

3.1. State of the art

Short peptides have recently been found to be excellent asymmetric catalysts for a number of organic transformations. Their ability to perform a variety of transformations is complemented by their ready availability, stability and ease of handling. In the majority of examples, both the amine and the acid functionalities in peptides are altered or eliminated.[62]

Inter- and intramolecular aldol reactions are widely studied reactions in asymmetric organicatalysis. These reactions have given good results in different organic solvents, ionic liquids and also water. Mostly polar solvents favour the aldol reactions. Several groups tried to find out the mechanism of proline and other short peptides based organocatalytic aldol reactions with experimental as well as theoretical studies. Agami has proposed non-linear effects in the proline catalyzed aldol reaction,[63-66] but List and Houk reported linear effect in the same reaction[67] and suggested that the reaction goes through enamine intermediate formation.

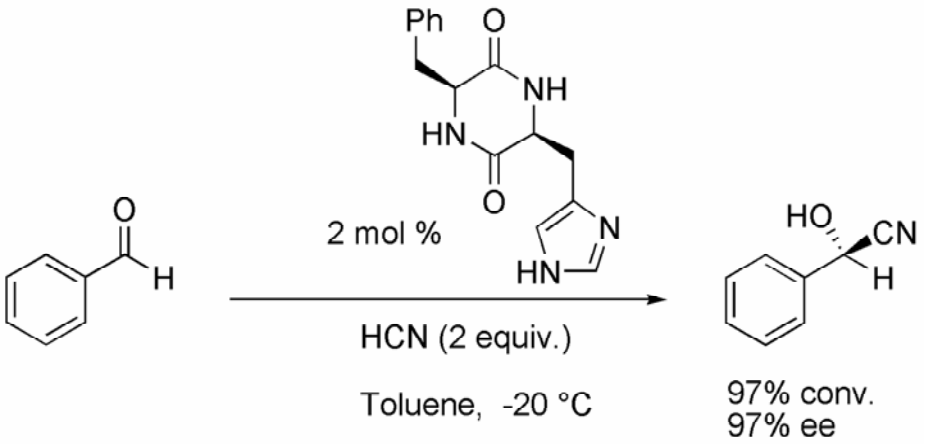
Gong and co-workers reported on aldol reaction with proline based peptid (H-Pro-Phe-Phe-Phe-OMe) with 68- 88% yield and up to 96% enantioselectivities (Scheme 9).[68]



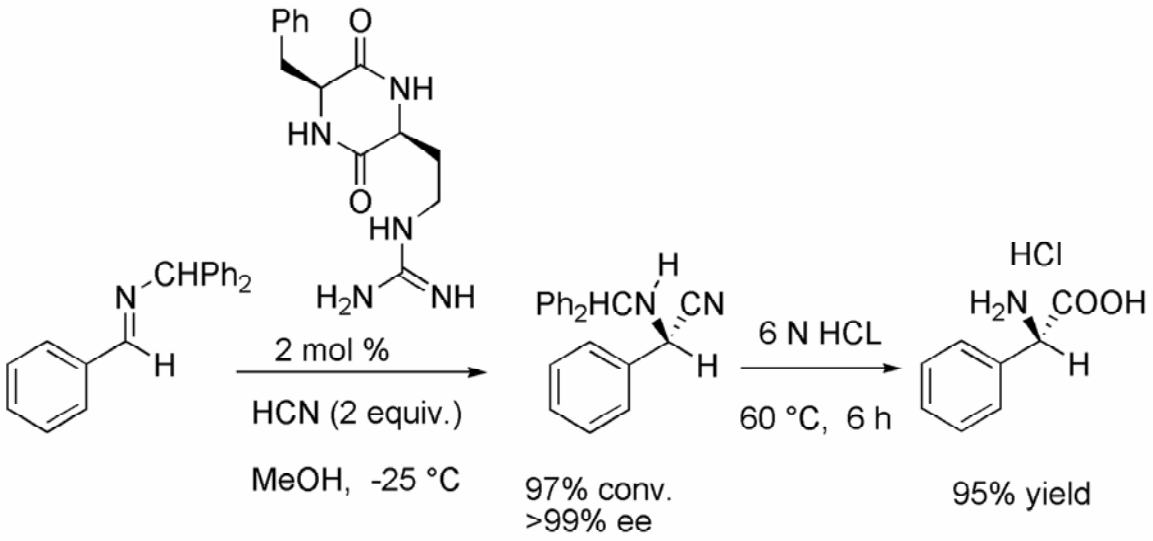
Scheme 9. Asymmetric aldol reaction catalyzed by proline derived peptide catalyst.

Some di- and tri-peptides containing mostly alanine, leucine and histidine functionality were also used for aldol reactions to get higher enantioselectivities.[69, 70]

Another attractive strategy to achieve asymmetric catalysis is an addition of hydrogen cyanide to aldehydes or imines (Strecker synthesis) to obtain enantiopure cyanohydrine and cyanoamine respectively. Inoue and co-workers reported the hydrocyanation of aldehydes (Scheme 10)[71] and Lipton and wo-workers reported the hydrocyanation of imines (Scheme 11),[72, 73] to get enantiopure cyanohydrine and cyanoamine, respectively.



Scheme 10. Inoue's hydrocyanation of benzaldehyde.



Scheme 11. Lipton's asymmetric Strecker synthesis of amino acids.

Schiff base derived from peptides catalyze asymmetric Strecker reaction with higher enantioselectivities. Jacobsen and co-workers used urea and thiourea based Schiff bases (Figure 6) for the Strecker synthesis with high yields and enantioselectivities.[74-76]

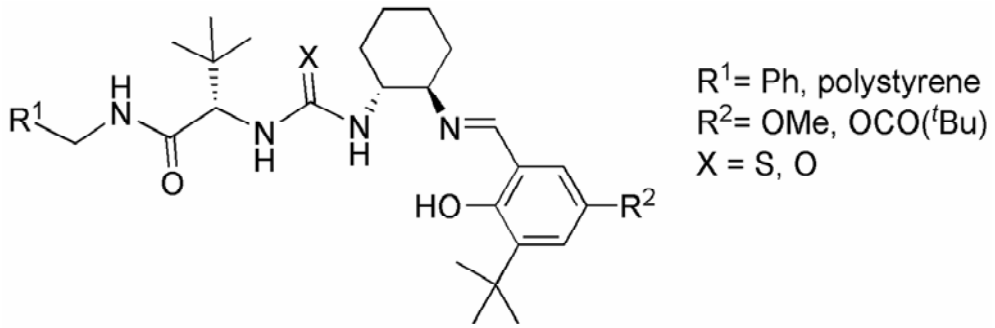
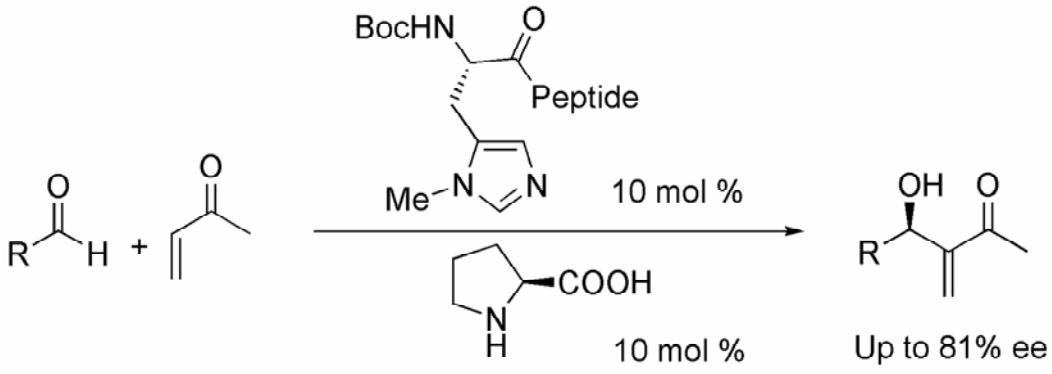


Figure 6. Jacobsen's peptide derived catalyst.

This reaction has very high importance for the synthesis amino acids (Scheme 11). Interestingly in the hydrocyanation of aldehydes, which gives α-hydroxy carboxylic acid upon hydrolysis the autocatalysis is observed. Upon formation of the enantioenriched product, the enantioselectivity and the rate of reaction increase significantly. It is possible to obtain the cyanohydrine product with 82% ee using a catalyst of only 2% ee.[77] Shvo showed that the reaction displays a second order kinetic dependence on catalyst.[78]

Miller and co-workers reported on asymmetric Baylis-Hilman reaction in the presence of peptide catalyst and proline as a co-catalyst. High enantioselectivity and yield are achieved when both peptide catalyst and proline are used together, but independently they are not so effective in case of enantioselectivity and yield. (Scheme 12).[79, 80]



Scheme 12. Baylis-Hilman reaction in the presence of peptide and L-proline.

Short peptides can also be used as catalysts for the asymmetric cycloaddition reactions. Miller reported the asymmetric azidation reaction in the presence of proline based catalyst to achieve higher enantioselectivities.[81]

Along with proline derived peptides which are useful for asymmetric epoxidation, some other peptides containing leucine and alanine residues are also used to achieve higher enantioselectivities.[82-86] In an effort to expand the scope of this reaction to include enolisable ketones and other substrates that are sensitive to aqueous base, Roberts and co-workers developed the two phase system.[87]

MacMillan's catalyst derived from phenyl alanine (Figure 7) has also shown good activity for various reactions.[42, 88-100] Jorgensen has reported similar type of catalyst with some modification and good catalytic activity.[101, 102]

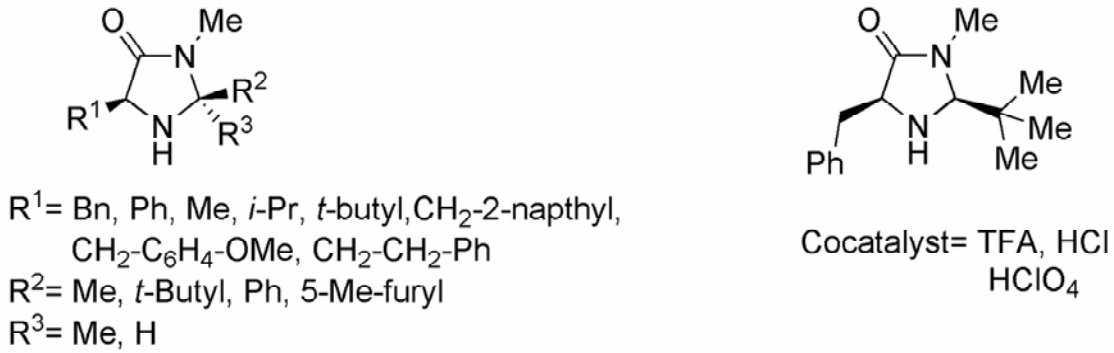
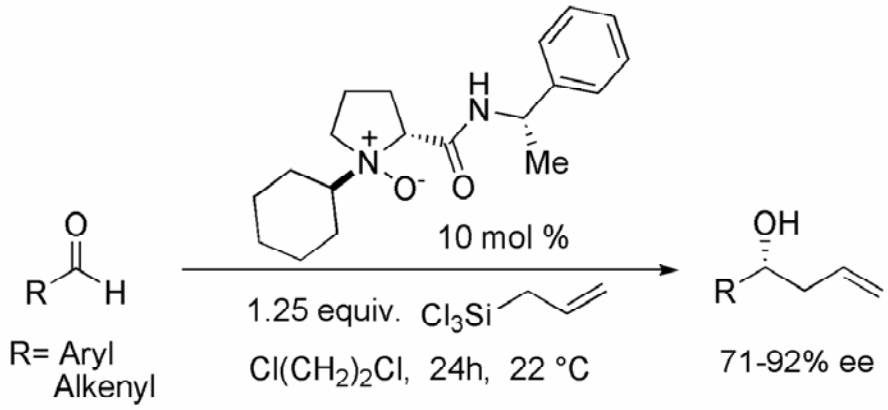


Figure 7. MacMillan's catalyst derived from phenylalanine.

Snapper and co-workers has reported on proline based N-Oxide as catalyst for asymmetric allylation of aldehydes to get enantiopure homoallylic alcohols (Scheme 12).[103]



Scheme 13. Asymmetric allylation of aldehydes by Proline based N-Oxide.

All lengths of linear peptides are currently used as enantioselective catalysts. Miller and co-workers have reported a series of peptides, containing alkylated histidine residues that are capable to effect kinetic resolution of functionalized secondary or tertiary alcohols. Oligopeptides (Figure 8) are useful in the kinetic resolution of mitosane[104] and some other alcohols[105] by acylation or benzylation.[106] Very low catalyst loading (0.3-2.5 mol %) is required. The products are obtained with high enantioselectivities.

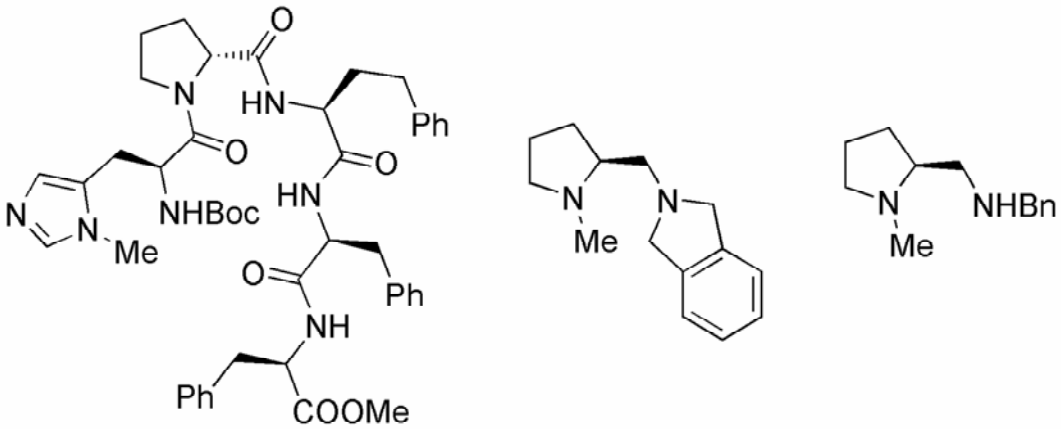


Figure 8. Peptide based catalysts used for kinetic resolution of alcohols.

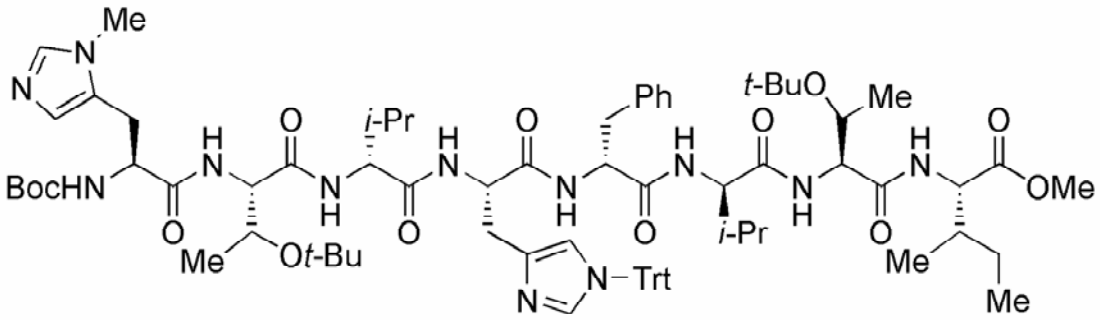
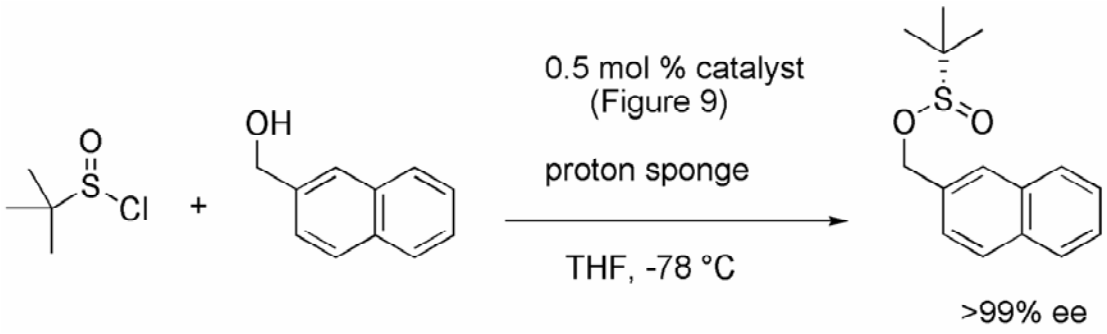


Figure 9. Peptide catalyst used for kinetic resolution of alcolohls by acylation.

Through systematic replacement of each residue in peptide (Figure 9) with alanine of the appropriate stereochemistry, an unambiguous evaluation of the kinetic role of each amino acid side chain in the acylation catalyst was carried out and the bifunctional mechanism of action was confirmed. While a hydrogen bond between the imidazole π-nitrogen and a

backbone -NH group might contribute to secondary structural stabilization, it may also serve to transmit heightened basicity to the corresponding backbone carbonyl oxygen, which could then serve as a general base (secondary nucleophile) within the bifunctional catalyst.[107] In addition, the results of the alanine scan underlined the importance of a combination of both of the two histidine residues to create a highly active and selective peptide catalyst.

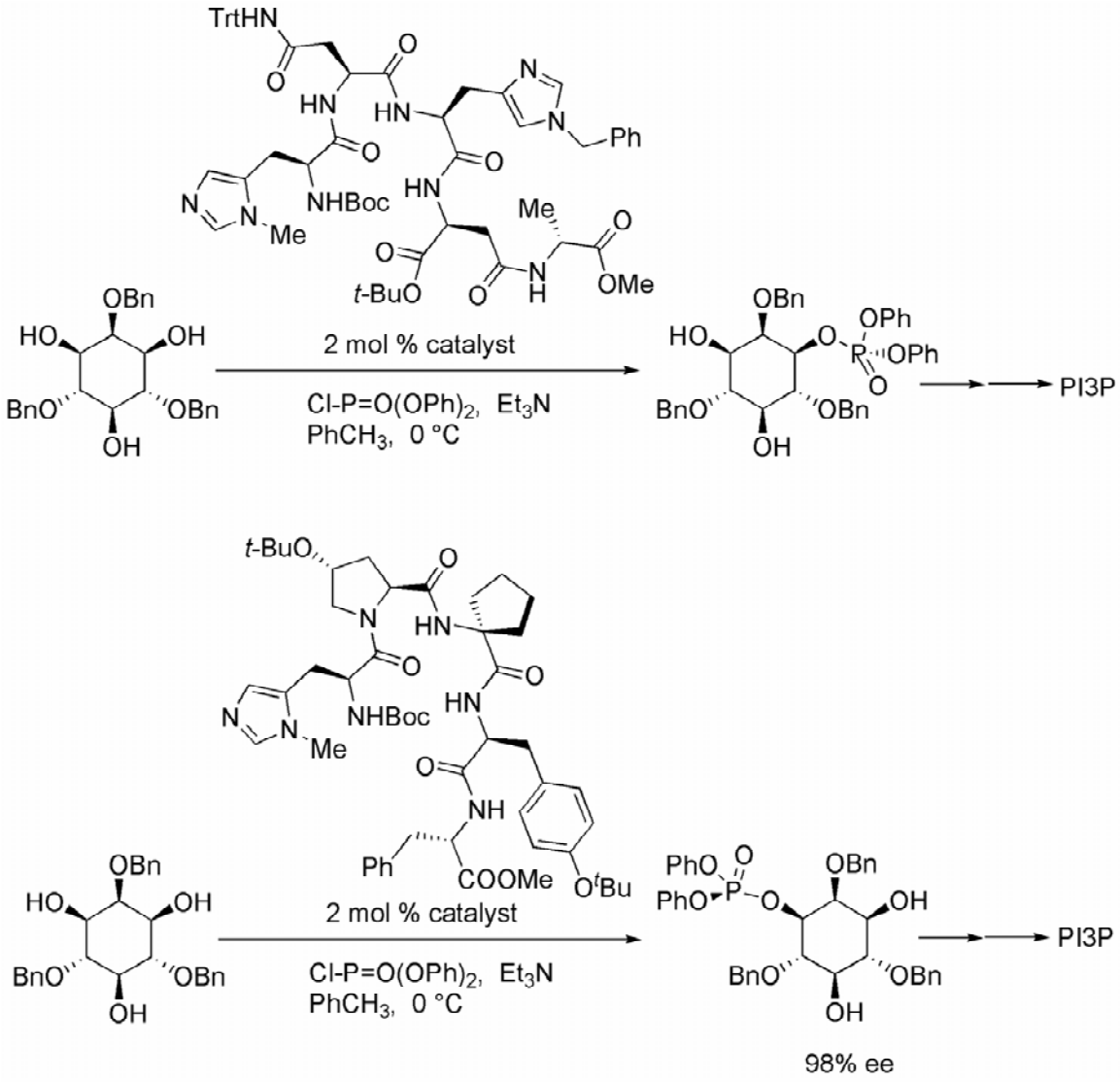
Ellman and Miller have reported the first example of an enantioselective synthesis of sulfinate esters through dynamic resolution of racemic *tert*-butanesulfinyl chloride (scheme 14), catalyzed by the same octapeptide.[108] Under optimal conditions (0.5 mol % of the chiral catalyst) the desired sulfinate ester product (which might serve as a versatile intermediate for the preparation of a variety of optically pure *tert*-butyl sulfoxides and *tert*-butanesulfinamides) was obtained with over 99% ee.



Scheme 14. Catalytic enantioselective sulfinyl transfer.

Not only the first example of the catalytic dynamic resolution of sulfinyl derivatives, but also to date the most enantioselective method for the synthesis of sulfinate esters, has been achieved by this method. In analogy to histidine containing peptide catalysts for asymmetric acyl transfer, enantio- and regioselective phosphorylation has been developed by Miller and coworkers using peptide catalysts (Scheme 14) containing alkyl histidine moieties.[62, 105, 109] The application of the discovered peptide catalysts for the enantioselective total synthesis of phosphatidylinositol-3-phosphates (**PI3P**) with saturated and unsaturated side chains were reported in 2004 by the same group.[110] As the key step toward either enantiomer of **PI3P**, the peptide-catalyzed asymmetric phosphorylations were employed (Scheme 15). This approach seems to be very useful in

the preparation of optically pure **PI3P** analogues of interest and provides an opportunity to deliver improved access to optically pure targets in this family of natural products.



Scheme 15. Enantioselective Phosphorylation of meso triol.

1,4-addition to α,β-unsaturated aldehydes, ketones and cyanides (Michael addition) is another interesting reaction in asymmetric synthesis. It is one of the most fundamental C-C bond forming reactions. Yamaguchi has reported on rubidium prolinate as a catalyst for the conjugate addition of nitroalkanes to enones with optimum enantioselectivities (up to 84%).[19-21] Later Hanessian has reported the same reaction with better ee's (up to 93%) using L-proline as a catalyst and *trans*-2,5-dimethyl piperazine as a co-catalyst.[43] But

Hanessian reported this reaction only with cyclic substrates. Both acidic and basic functionalities play an important role in asymmetric synthesis and that's why proline which is having both functionalities together gave better stereoselectivities than its rubidium salt in which acidic functionality is absent. List used proline derived peptides for the addition of acetone to nitroolefin, but with low enantioselectivities (up to 31% ee).[111] Cordova and co-workers reported direct small peptide-catalyzed enantioselective Michael addition of ketones to nitroolefins. They used simple di- and tripeptides derived from alanine as catalysts for the asymmetric Michael additions with 68: 1 dr and 98% ee.[112] Miller and co-workers achieved higher ee's using proline derived peptide catalyst for conjugate addition of azides to α,β-unsaturated carbonyl compounds.[81, 113]

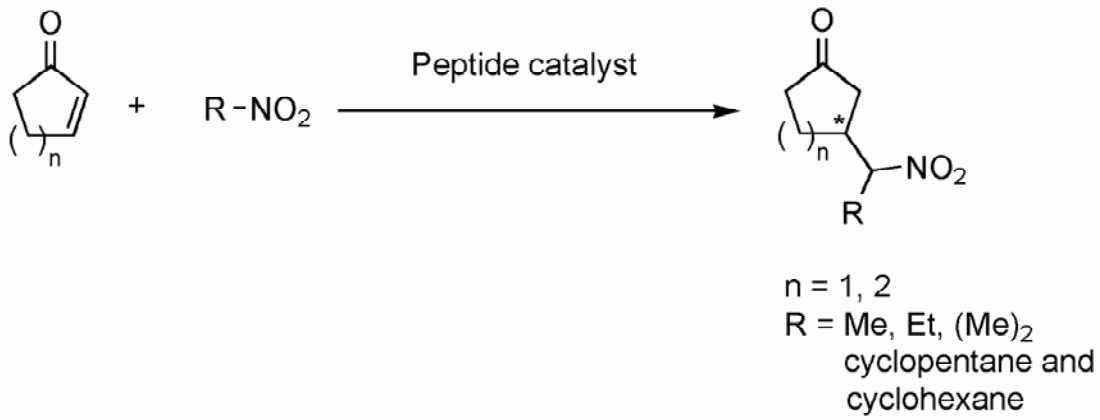
3.2. Objective and goals

The "**oligopeptide approach**", pioneered by Miller and Jacobsen, has attracted our attention, since it offers some practical advantages for catalyst development, *for instance:*

- the efficiency of the catalyst can be improved by varying the nature of the amino acids;
- the simplicity of the oligopeptides in comparison with enzymes facilitates mechanistic investigations.

The structural diversity available even with di- and tripeptide sequences makes this class of molecules thus particularly promising for the development of new chiral organocatalysts. Hence, we decided to use short peptides as catalysts for asymmetric C-C bond formation reactions.

Though very interesting work has been reported so far for asymmetric 1,4-conjugate addition reaction, still there is vast scope for development of this reaction by means of different substrates, nucleophiles, solvents and co-catalysts. Also we were interested to find out the relation between structure and reactivity of different peptide catalysts and their use with different co-catalysts in different proportions for the reaction. For our studies the 1,4-conjugate addition of nitroalkanes to cyclic enones were chosen as the model reactions (Scheme 16).



Scheme 16. 1,4-Conjugate addition of nitroalkanes to cyclic enonen.

The presence of electron withdrawing nitro group makes α-proton of nitroalkane more acidic. Amino group of peptide can form iminium ion with substrate containing carbonyl group. Cyclic enones are better prochiral acceptor than acyclic enones.

Product obtained in this reaction is important because the nitro group can be easily converted to primary amines by reduction. The presence of proton at β-position to electron-withdrawing group allows a base-assisted elimination of nitrous acid with consequent introduction of a double bond in the molecular framework. The nitro group can be converted to carbonyl group, the transformation widely known as Nef reaction.

3.3. Results and Discussion

3.3.1. Proline based Di-, Tri- and Tetrapeptides as Organocatalysts

Simple and inexpensive small amino acid like proline has shown tremendous activity in C-C bond formation reaction. With the single catalytic centre proline gives good enantioselectivities, so we were interested in exploring whether there was any correlation between the amount of catalytic centers (secondary amine functionalities) and the catalytic activity of the oligo-α-amino acid. To gather more information about it we decided to use 4-*trans*-amino-proline based di-, tri- and tetrapeptides **1**, **2** and **3** (Figure

10) respectively in 1,4-conjugate addition reaction. Catalyst **2** is recently described as an ingredient of a poor DNA binding agent.[114]

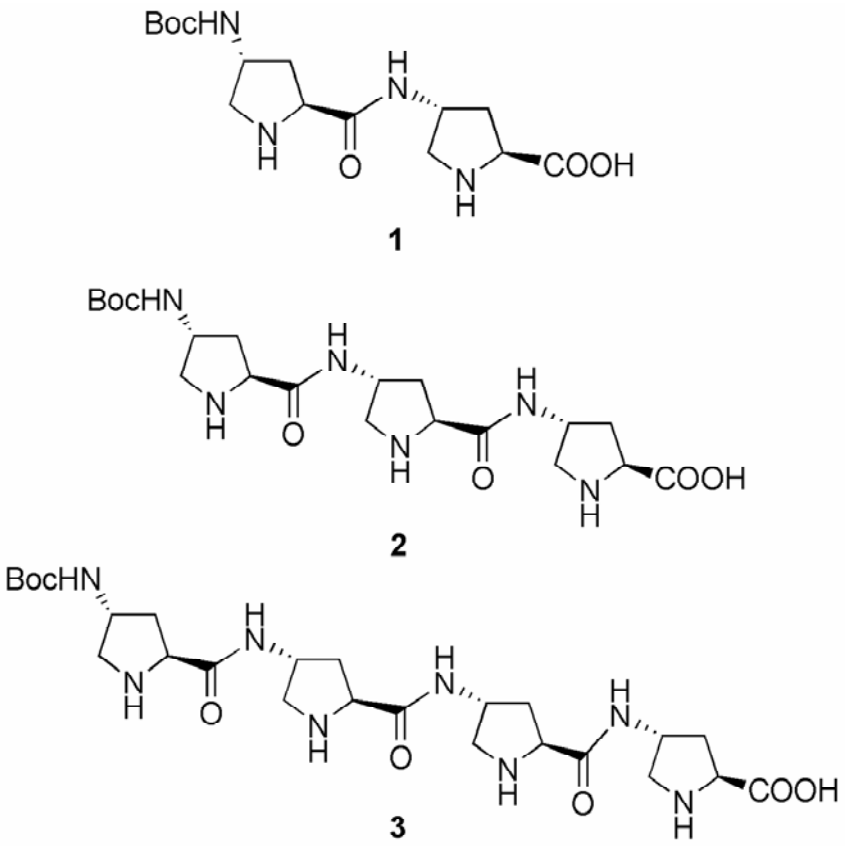
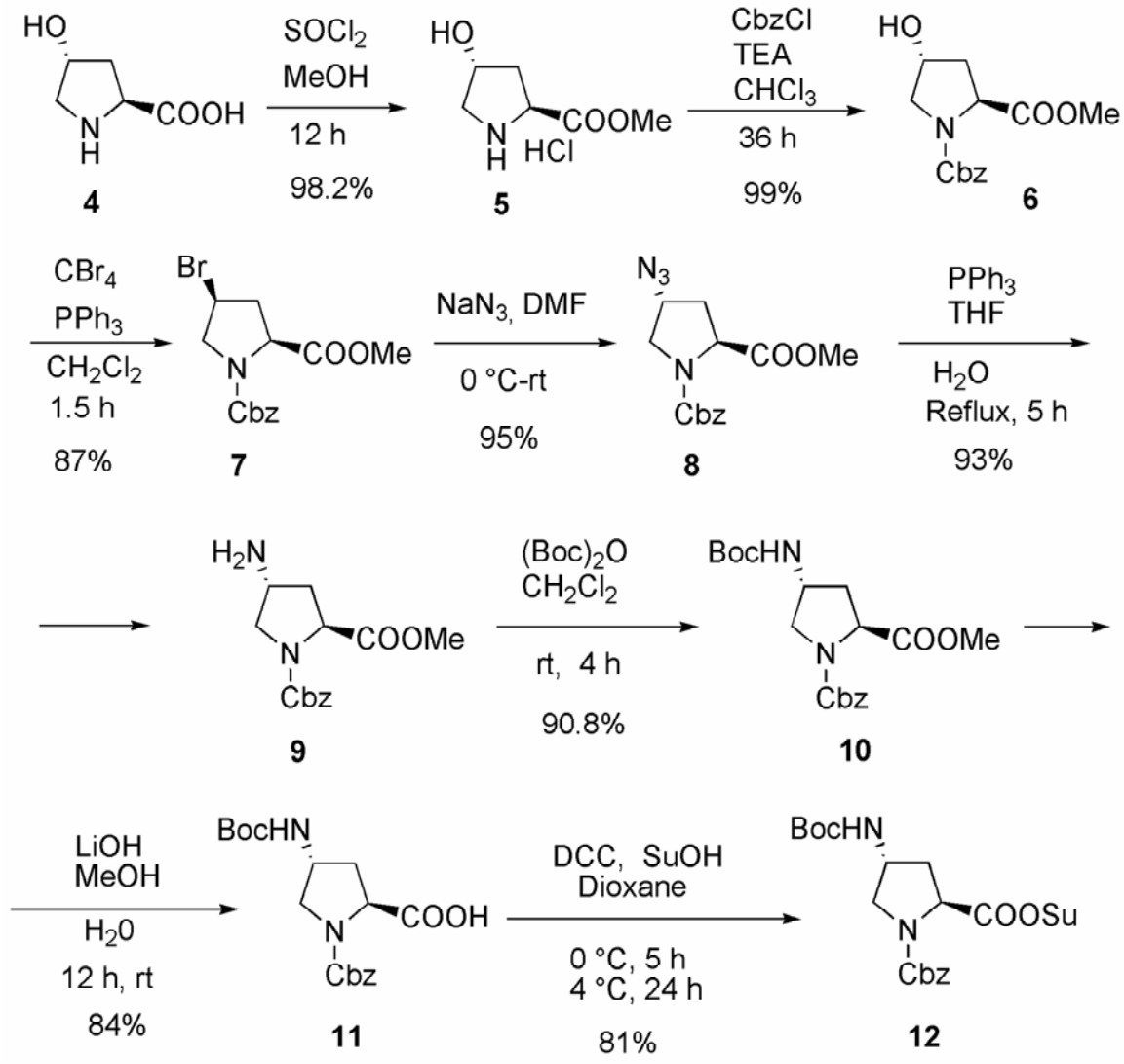


Figure 10. New 4-*trans*-amino-proline based organic catalysts for asymmetric conjugate addition reactions.

Synthesis of 4-*trans*-amino-proline derivative (**12**) was carried out from readily available inexpensive S-(-)-4-*trans*-hydroxy-proline by known literature methods[115] and used as a starting material for the synthesis of catalysts **1, 2,** and **3** (Scheme 17).

Esterification of 4-*trans*-amino-proline was carried out by its reaction with thionyl chloride in methanol. Stirring at room temperature for 12 hours 4-hydroxy-2-methoxycarbonyl-pyrrolidinium chloride (**5**) was obtained in 98.2% yield. Secondary amino group of compound **5** was protected by its treatment with CbzCl and TEA in chloroform. Compound **6** was obtained after 36 hours room temperature stirring in 99% yield. Treatment of tetrabromomethane and triphenylphosphine in dichloromethane gives bromo derivative (**7**) in 87% yield after 1.5 hours. Compound **7** obtained in this reaction is cis configured because of S_N^2 reaction. Compound **7** was treated with sodiumazide in DMF to obtain again *trans* product (azide) in 95% yield. Reduction of the azide group of

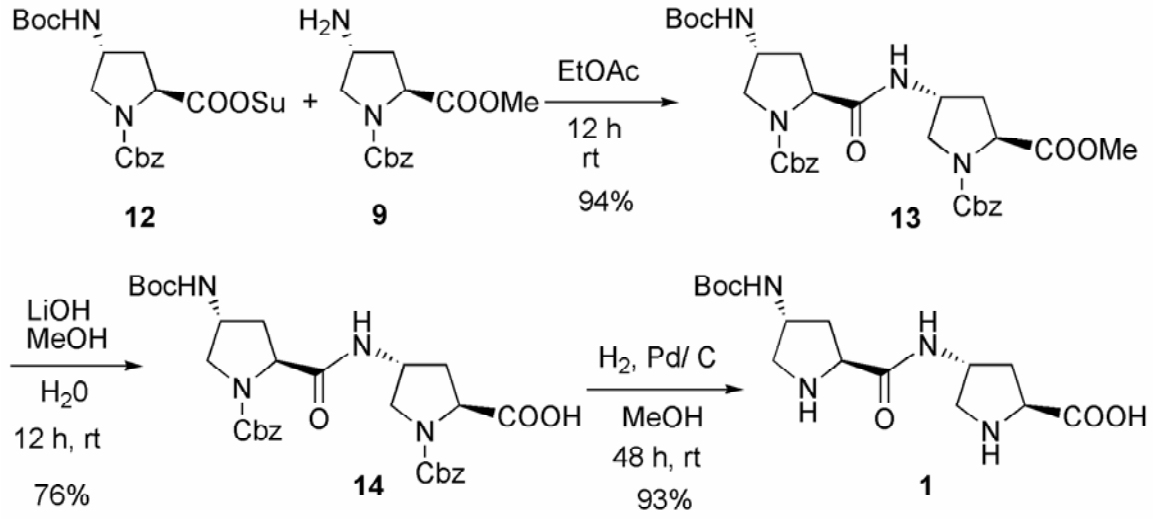
compound **8** to amine was carried out by refluxing it with triphenylphosphine in water and THF for 5 hours. Compound **9** was obtained from this reaction in 93% yield. Amine group of unstable **9** was protected with Boc group. Reaction completed in 4 hours at room temperature and gave **10** in 90.8% yield.



Scheme 17. Synthesis of 4-*trans*-amino-proline derivative.

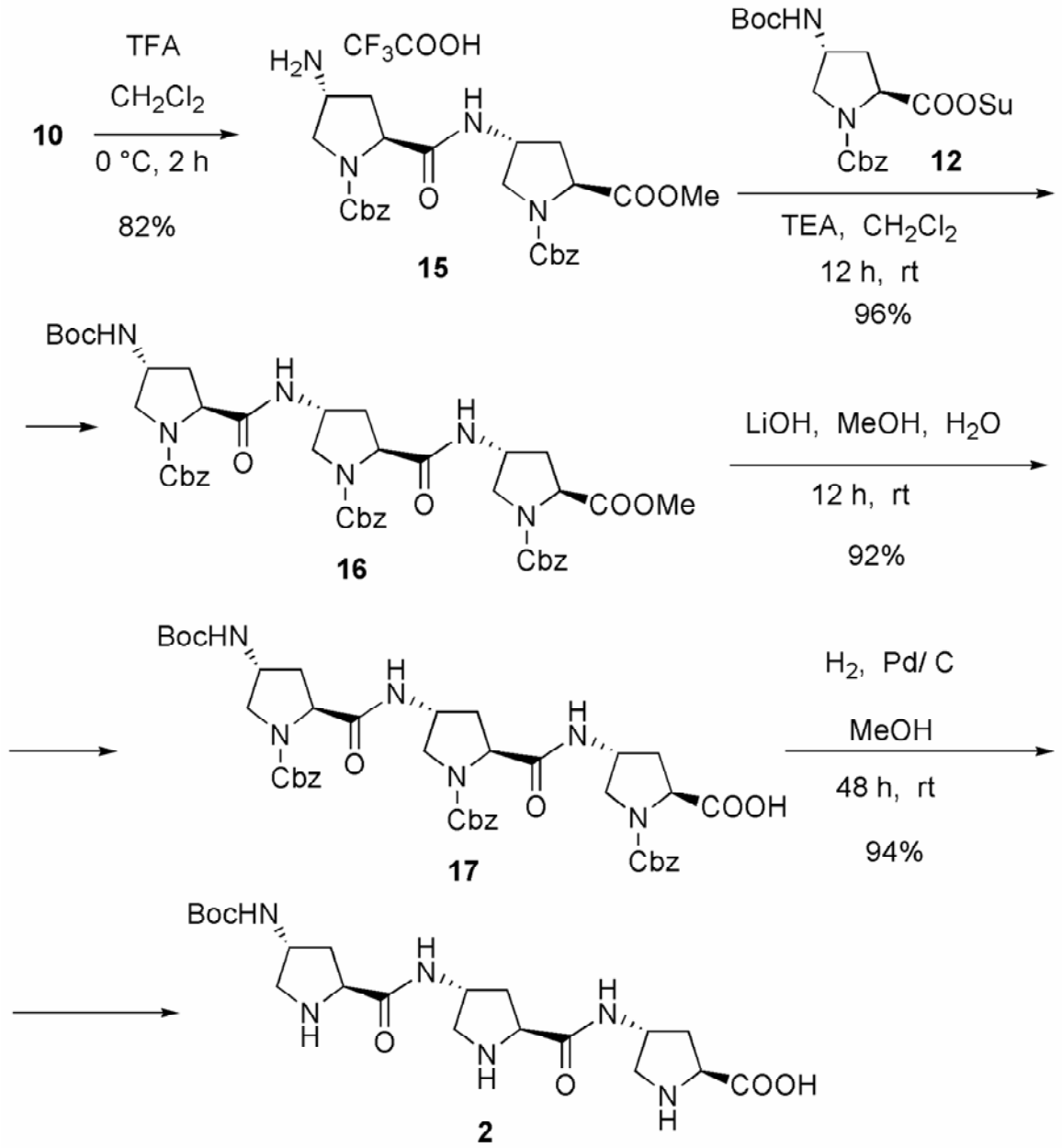
Ester hydrolysis of **10** was carried out by stirring it in LiOH, methanol and water for 12 hours to get **11** in 84% yield. Esterification of **11** was carried out with of N-hydroxysuccinimide and DCC in dioxane to get compound **12** in 81% yield.

Dipeptide **1** was prepared in three steps from compound **12** as shown in Scheme 18. Coupling of activated **12** with **9** in ethyl acetate at room temperature gave dipeptide **13** in 94% yield. Saponification of methyl ester **13** was performed by the same procedure used for saponification of **10**. Free acid **14** obtained in this procedure (76% yield) was hydrogenated subsequently by hydrogen gas in presence of Pd/ C as a catalyst in methanol. Reaction completed after 48 hours stirring at room temperature. Dipeptide **1** was obtained in 93% yield.



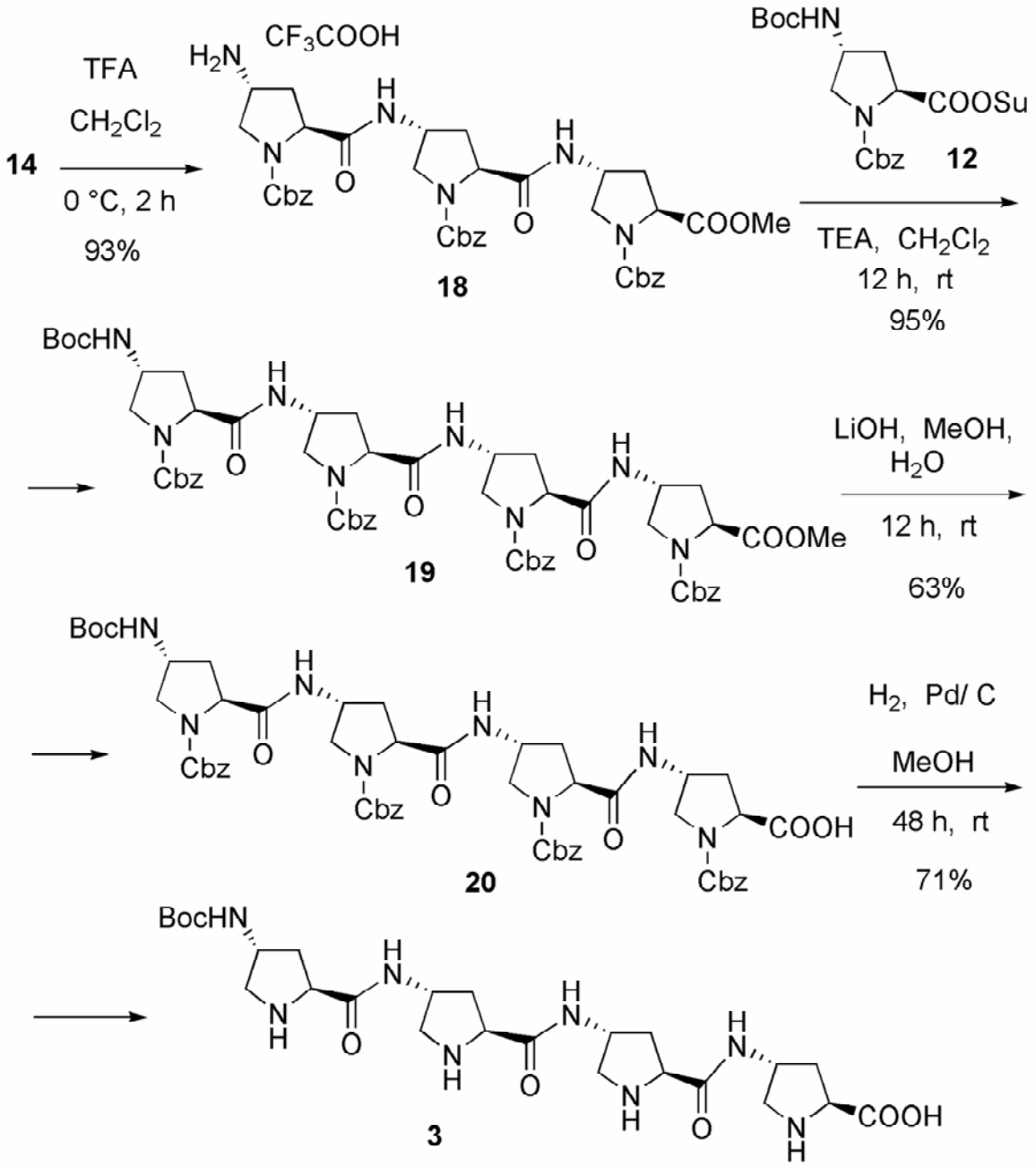
Scheme 18. Synthesis of proline based linear dipeptide **1** for C-C bond formation reaction.

Tripeptide **2** was synthesized from the intermediate dipeptide **13** as described in Scheme 18 (Scheme 19). Boc deprotection was carried out at 0 °C using trifuoroacetic acid to obtain trifuoroacetic acid salt of peptide **15** in 82% yield. Compound **15** was treated with **12** in the presence of triethylamine in dichloromethane at room temperature for 12 hours to get **16** in 96% yield. Hydrolysis of ester gives compound **17** in 92% yield. Finally, deprotection of Cbz group of **17** was carried out by hydrogenation to give tripeptide **2** in 94% yield.



Scheme 19. Synthesis of proline based linear tripeptide **2**.

Tetrapeptide **3** (Scheme 20) was prepared by similar way as tripeptide. Boc deprotection of **16** by trifuoroacetic acid gave trifuoroacetic acid salt of peptide **18** in 93% yield. Coupling of **18** with **12** in dichloromethane in presence of triethylamine in 12 hours yielded **19** in 95% yield. Hydrolysis of ester and hydrogenation was carried out by similar way as described in Scheme 18 and 19 to obtain compounds **20** and **3** in 63% and 71% yields, respectively.



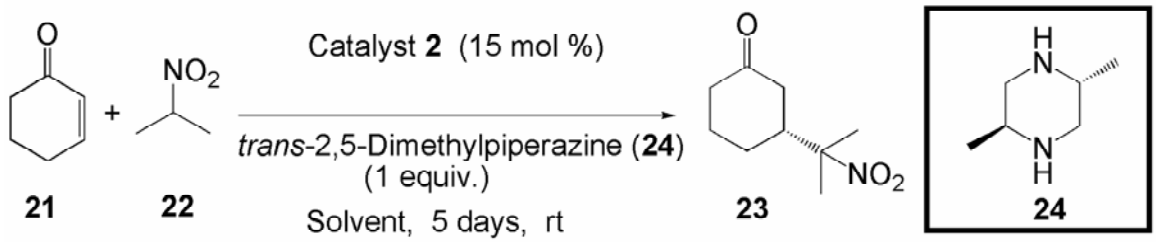
Scheme 20. Synthesis of proline based linear tetrapeptide **3**.

3.3.1.1. Applications of Proline based Di-, Tri- and Tetrapeptides in Asymmetric Michael Addition

We tested first peptide catalyst **2** for conjugate addition of 2-nitro propane to cyclohex-2-ene-1-one (Scheme 21) in different polar and nonpolar solvents like $CHCl_3$, acetone, DMF, DMSO and the ionic liquid [bmim]PF_6 to choose the best solvent for the reaction.

The dipole moment (μ) and dielectric constants (ε) are different for all these solvents and it was our aim to study the influence of these physical properties on reaction by means of yields and enantiomeric excesses.

Additives play an important role in asymmetric synthesis. They enhance the stereoselectivity, yields and rates of reaction.[116] Generally, nitrogen bases are the most common additives, and it became an usual practice to screen nitrogen bases to improve the yield in catalytic asymmetric reactions. Here we have chosen *trans*-2,5-dimethylpiperazine (**24**)[43, 48] as an additive for the reaction.



Scheme 21. Conjugate addition of 2-nitropropane to cyclohex-2-ene-1-one in different solvents catalyzed by tripeptide **2**.

The dipole moments (μ) and dielectric constants (ε) of all solvents used for the reaction are given in Table 1.[117]

Table 1. Dipole moments and dielectric constants of solvents used for the conjugate addition.

Entry	Solvent	Dipole moment (μ)	Dielectric constant (ε)
1	$CHCl_3$	1.15	4.9
2	Acetone	2.69	20.7
3	DMF	3.86	36.7
4	DMSO	4.3	48.7
5	[bmim]PF_6	Ions	Conductors

All reactions were carried out at room temperature with or without peptide **2** and additive *trans*-2,5-dimethylpiperazine (**24**).[43, 48] The results are summarized in Table 2.

Table 2. Conjugate addition of 2-nitropropane to cyclohex-2-ene-1-one.

Entry	Solvent	Tripeptide (2) (mol %)	Additive (24) (equiv.)	Yield (%)[a]	ee (%)[b]
1	$CHCl_3$	15	-	No reaction	-
2	Acetone	15	-	No reaction	-
3	DMF	15	-	No reaction	-
4	DMSO	15	-	No reaction	-
5	[bmim]PF_6	15	-	No reaction	-
6	$CHCl_3$	-	1	No reaction	-
7	Acetone	-	1	No reaction	-
8	DMF	-	1	5	0
9	DMSO	-	1	39.5	0
10	[bmim]PF_6	-	1	25	0
11	$CHCl_3$	15	1	80	77
12	Acetone	15	1	43	80
13	DMF	15	1	>99	63
14	DMSO	15	1	85	7
15	[bmim]PF_6	15	1	>95	51

[a] Isolated yields after column chromatography.
[b] % *ee* measured by ^{13}C-NMR of corresponding ketal with (2*R*,3*R*)-2,3-butanediol.

Catalyst **2** without additive can not catalyze reaction in all solvents either polar or nonpolar (entries 1-5, Table 2). The results clearly indicate necesity of additive for this reaction. Next, reactions were carried out with one equimolar of *trans*-2,5-dimethylpiperazine (pK_a = 9.83) as an additive in the absence of catalyst to study whether the additive itself shows any enantioselective conversion or not. In chloroform and acetone no product formation was observed (entry 6, Table 2). Surprisingly in DMF, DMSO and ionic liquid [bmim]PF_6, 5%, 39.5% and 25% of product, respectively was formed but without any stereoselectivity (entries 6-10, Table 2).

The emerging results illustrate puzzlingly complex behaviour. Combination of peptide **2** with *trans*-2,5-dimethylpiperazine (**24**) in $CHCl_3$ provided product **23** in 80% yield and

77% *ee* (entry 11, Table 2). The observed asymmetric induction in $CHCl_3$ is apparently due to a collaboration between tripeptide and *trans*-2,5-dimethylpiperazine, since neither conversion occurred with the peptide catalyst in the absence of *trans*-2,5-dimethylpiperazine, nor with the additive alone in the absence of the peptide. Similarly to the situation in $CHCl_3$, peptide **2** affords 80% *ee* and 43% yield in acetone (entry12, Table 2). The significant drop in yield (43%) could be due to competition between the two carbonyl compounds (acetone and cyclohex-2-en-1-one) for iminium ion formation.

The results in DMF again resemble those in $CHCl_3$, with the sole exception of the reduced enantiomeric excess (>99% yield and 63% ee; entry 13, Table 2). In the still more polar DMSO, better yield (85%), but lower enantioselectivity (7% *ee*; entry 14, Table 2) was attained in the presence of peptide **2** and *trans*-2,5-dimethylpiperazine (**24**), relative to the results in chloroform. Higher conversion rates in DMSO might be the result of better solvation and stabilization of the nucleophile. In addition, the solvatating power measured by the dipole moments (μ) and/or dielectric constants (ε) of the solvent molecules (Table 1), increases in the same direction. Solvent polarity has an adverse effect on the complexation of substrate with the peptide and consequently on the enantiomeric excess: entropy favours hydrogen bonding in nonpolar solvents while better solvation in polar media lets the solvent molecules get in the way. Polarity helps with the yields while the enantioselectivity drops sharply.

Surprisingly, even the presence of *trans*-2,5-dimethylpiperazine (p*K*a = 9.83) alone results in the product in 5% yield in DMF and in 39.5% yield in DMSO. Apparently, the substrate reacts with the nucleophile without being polarized at all. Alternatively, the protonated *trans*-2,5-dimethylpiperazine lives long enough in the more polar solvent to be able to transfer a proton to the oxo group of the enone, activating the β-position for the attack of the nucleophile. This results in competition between the peptide catalysts and the protonated additive for catalyzing the reaction through direct interaction with the substrate, thereby lowering the enantiomeric excesses of the product by the ratio of the contribution of the achiral additive.

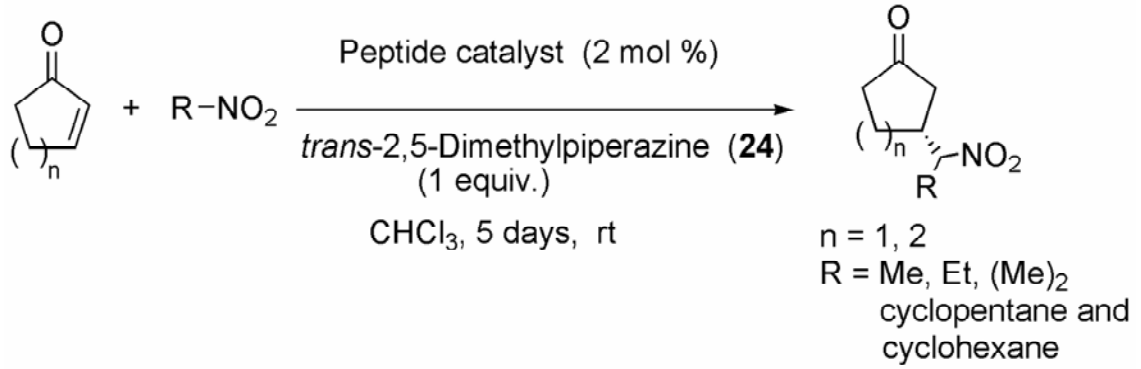
The lower enantioselectivities observed in DMSO with respect to $CHCl_3$ in the presence of a combination of peptide **2** and additive could thus be explained in terms of solvent polarity, while the individual results in DMSO arise from the balance of the competition

and the cooperation effect. The low enantiomeric excess with catalyst **2** in DMSO contradicts the assumption of the enamine mechanism here.

Peptide **2** afforded the product in over 95% yield and with 51% *ee* (entry 15, Table 2) at room temperature ionic liquid [bmim]PF_6. In the highly polar ionic liquid we also encountered an additional phenomenon typical of the presence of ion clouds in solutions: screening. The screened nucleophile, shrouded by the cloud of cations, becomes less active (but more selective) than the nucleophile in the merely polar solvent DMSO. This might explain the stronger enantioselectivity observed with tripeptide **2** in [bmim]PF_6 relative to DMSO and the reduced activity of the additive when acting alone.

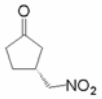
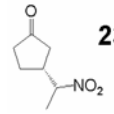
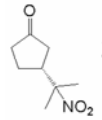
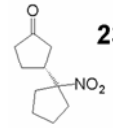
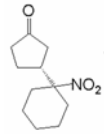
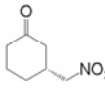
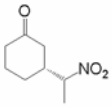
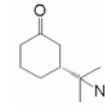
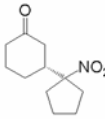
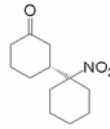
At the outset, in analogy to Hanessian[43] we established that the combination of a peptide catalyst and *trans*-2,5-dimethylpiperazine could provide an asymmetric co-catalysis of Michael reactions. We found that even *trans*-2,5-dimethylpiperazine alone can support the conversion into the product in polar solvents. Although the solvent influence on yields and enantioselectivities is obviously a rather complex phenomenon and has to be carefully analyzed for each individual case, our results showed that solvent polarity is a double-edged sword in the case of the title reaction and the catalysts employed here, while the polarity helps to facilitate the reaction, it could also give rise to reduced enantiomeric excesses. The above experiments demonstrated that a combination of solvents could result in improved yields with roughly the same enantioselectivities.

Encouraging by these results we reduced the mol % of catalyst **2** from 15 mol % to 2 mol % for conjugate addition of 2-nitropropane to cyclohex-2-ene-1-one and surprisingly with only 2 mol % of catalyst enantioselectivity was increased to 81% from 77%. So we decided to use 2 mol % catalysts for the scope of reactions (Scheme 22).



Scheme 22. Peptide catalyzed conjugate addition of nitroalkanes to prochiral acceptors.

Table 3. Peptide catalyzed addition of nitroalkanes to cyclic enones.

Entry	Product	Dipeptide (1)		Tripeptide (2)		Tetrapeptide (3)	
		Yield (%)[a]	ee (%)[b]	Yield (%)[a]	ee (%)[b]	Yield (%)[a]	ee (%)[b]
1	 **23A**	14	47	9	44	18	28
2	 **23B**	65	LP :- 61[c] MP:- 54[d]	22	LP:- 50[c] MP:-42[d]	71	LP :- 47[c] MP:- 48[d]
3	 **23C**	40	76	24	67	50	64
4	 **23D**	64	77	37	70	41	60
5	 **23E**	9	52	24	41	6	44
6	 **23F**	75	57	95	58	75	55
7	 **23G**	100	LP :- 66[c] MP:- 66[d]	83	LP :- 56[c] MP:-65[d]	100	LP :- 58[c] MP:- 59[d]
8	 **23**	46	77	80	81	80	81
9	 **23H**	100	88	71	84	57	82
10	 **23I**	13	80	24	78	24	83

[a] Isolated yields after column chromatography.
[b] % *ee* measured by ^{13}C-NMR of corresponding ketal with (2*R*,3*R*)-2,3-butanediol.
[c] % *ee* of less polar (LP) isomer.
[d] % *ee* of more polar (MP) isomer.

For the scope of reaction of Michael addition we decided to use two enones i.e. cyclohex-2-en-1-one and cyclopent-2-en-1-one as cyclic prochiral acceptor and cyclic and acyclic nitroalkanes such as nitromethane, nitroethane, 2-nitropropane, nitrocyclopentane and nitrocyclohexane as nucleophiles. 2 mol % of all linear peptide catalysts (**1**, **2** and **3**) were used for all reactions. Stiochiometric amount of *trans*-2,5-dimethylpiperazine (**24**) was used as an additive and all reactions were carried out at room temperature for five days in chloroform. The results are summarized in Table 3.

Better yields and enantioselectivities were achieved with least bulkier nucleophile we selected for the reaction i.e. nitromethane for the addition of six membered cyclic enone (75%, 95%, and 75% yields and 57%, 58% and 55% ee's with peptide catalysts **1**, **2** and **3** respectively; entry 6, Table 3) than its five membered counterpart (14%, 9%, and 18% yields and 47%, 44% and 28% ee's for cyclopent-2-en-1-one and with peptide catalysts **1**, **2** and **3** respectively; entry 1, Table 3). Yields and ee's were increased when nitroethane was used in place of nitromethane [65%, 22%, and 71% yields for cyclopent-2-en-1-one (entry 2, Table 3) and 100%, 83% and 100% yields when cyclohex-2-en-1-one (entry 7, Table 3) used as acceptor with peptide catalysts **1**, **2** and **3** respectively]. Similar results were obtained for 2-nitropropane and other nitroalkanes. We found that the bulkiness of nitroalkanes did affect the reactivities and enantioselectivities. When R became larger (Me→Et→*i*-Pr→Cp), the higher enantioselectivity has been obtained. This result can be rationalized by the fact that during the attack of the nucleophile, the enone is forming an iminium ion intermediate with the peptide catalyst, impairing the approach of space consuming nucleophiles. The large nucleophile might react slowly, but more selective, with the activated enone.

Additionally, the ring size of the enones also affected the enantioselectivity. Higher levels of asymmetric induction were observed with cyclohexenone compared to cyclopentenone. With all three peptide catalysts **1**, **2** and **3**, approximately equimolar amounts of diastereomers were formed from the reaction of nitroethane (entries2 and 7, Table 3). Whereas similar results in terms of reaction rates were observed with peptide catalysts **1**, **2** and **3**, slightly higher enantioselectivities were obtained in the presence of dipeptide **1** (88% ee) with respect to tripeptide **2** (84% ee) and tetrapeptide **3** (82% ee), when nitrocyclopentane was used as nucleophile (entry 9, Table 3).

These results demonstrate that in the case of conjugate additions of nitroalkanes to cyclic enones there is no increase in catalytic activity and selectivity with increasing chain length or active catalytic centres in the peptide catalyst. This may be possible because all catalysts are having only one acidic functionality, while 2-4 secondary amine groups. Also this acidic functionality is far from other secondary amine groups.

3.3.2. H-Asp-Phe-Arg-OH and H-Asp-Pro-Arg-OH as Organocatalysts

Although linear peptides were once considered unsuitable for catalysis due to their flexible nature and variable conformation, several recent examples of peptide and peptide-based catalysts for a variety of reactions have been reported. Unmodified peptides have been used as catalysts much less frequently, and so we decided to test the unprotected peptides H-Asp-Phe-Arg-OH (**25**) and H-Asp-Pro-Arg-OH (**26**) (known as active ingredients of anticholesteremic[118] and antiallergic[119] agents (Figure 11) as catalysts for asymmetric Michael addition reactions.

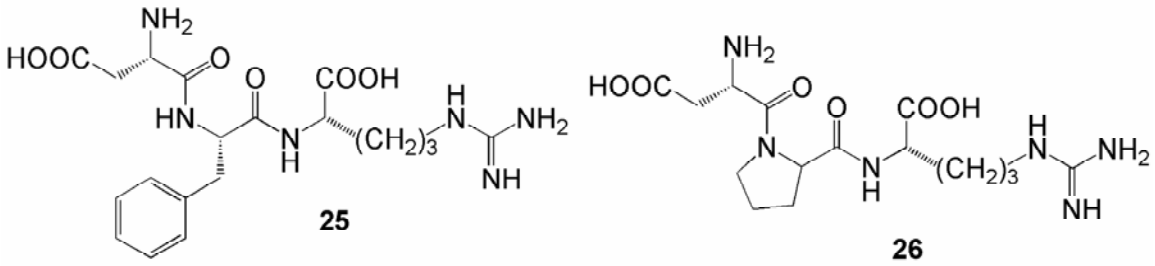
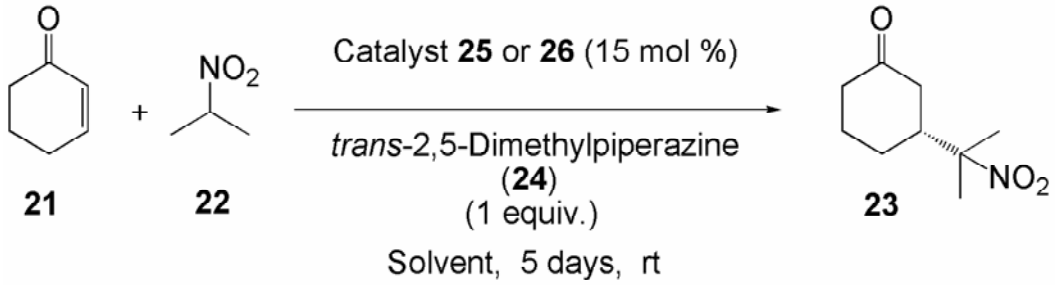


Figure 11. Peptide catalysts H-Asp-Phe-Arg-OH and H-Asp-Pro-Arg-OH.

3.3.2.1. Application of tripeptides H-Asp-Phe-Arg-OH (25) and H-Asp-Pro-Arg- OH (26) in Asymmetric Michael Addition Reactions

Similar to scheme 21, we tested peptide catalysts **25** and **26** for conjugate addition of 2-nitro propane to cyclohex-2-ene-1-one (Scheme 23) in different polar and nonpolar solvents like $CHCl_3$, acetone, DMF, DMSO and the ionic liquid [bmim]PF_6.

Stoichiometric *trans*-2,5-dimethylpiperazine (**24**) was used as additive and all reactions were carried out for five days at room temperature with 15 mol % tripeptide as catalyst.



Scheme 23. Conjugate addition of 2-nitro propane to cyclohex-2-ene-1-one catalyzed by peptide catalyst **25** or **26**.

We observed different trends when reactions were carried out in different solvents having different physical properties. The results are summarized in table 4.

Catalyst **26** gave 66.7% product **23** with 8% enantioselectivity when reaction was carried out in DMSO (entry 14, Table 4) without additive *trans*-2,5-dimethylpiperazine (**24**). No product formation was observed when reactions were carried out with catalysts **25** and **26** in all solvents in the absence of additive (entries 1-5 and 11-15, Table 4).

Combination of *trans*-2,5-dimethylpiperazine with peptides **25**, and **26** in $CHCl_3$ provided **23** in 18%, and 71% *ee*, respectively (entries 6 and 16, Table 4). The observed asymmetric induction in $CHCl_3$ is apparently due to a collaboration between tripeptides and *trans*-2,5-dimethylpiperazine, since neither conversion occurred with the peptide catalysts in the absence of *trans*-2,5-dimethylpiperazine, nor with the additive alone in the absence of the peptides.

In $CHCl_3$, the tripeptides **25** and **26** in the presence of the additive gave the product **23** in similarly low yields (around 10%, while tripeptide **2** produced **23** in 80% yield). This may be explainable in terms of differences in their mechanisms of catalysis, but perhaps also by the low solubility of **25** and **26** in $CHCl_3$. The tripeptides **25** and **26** most probably induce the enantioselectivity in $CHCl_3$ through hydrogen bond formation with the substrate.

Table 4. Michael addition reaction catalyzed by tripeptide catalyst **25** and **26**.

Entry	Solvent	Tripeptide Cat.	Additive (24) (equiv.)	Yield (%)[a]	ee (%)[b]
1	$CHCl_3$	25	-	No reaction	-
2	Acetone	25	-	No reaction	-
3	DMF	25	-	No reaction	-
4	DMSO	25	-	No reaction	-
5	[bmim]PF_6	25	-	No reaction	-
6	$CHCl_3$	25	1	<10	18
7	Acetone	25	1	No reaction	-
8	DMF	25	1	16	28
9	DMSO	25	1	53	29
10	[bmim]PF_6	25	1	44	5
11	$CHCl_3$	26	-	No reaction	-
12	Acetone	26	-	No reaction	-
13	DMF	26	-	No reaction	-
14	DMSO	26	-	66.7	8
15	[bmim]PF_6	26	-	No reaction	-
16	$CHCl_3$	26	1	<10	71
17	Acetone	26	1	No Reaction	-
18	DMF	26	1	<10	17
19	DMSO	26	1	73	23
20	[bmim]PF_6	26	1	35	<5

[a] Isolated yields after column chromatography.
[b] % *ee* measured by ^{13}C-NMR of corresponding ketal with 2*R*,3*R*-2,3-butane diol.

Peptides **25** and **26** are even less soluble in acetone than in $CHCl_3$, which probably explains the absence of any conversion of the substrate (entries 2 and 17, Table 4), and the additive alone is also inactive here. Similar to $CHCl_3$, in DMF tripeptide catalysts **25** and **26** give also low yield in the presence of additive (entries 8 and 18, Table 4). Catalyst **25** gave 16% yield with 28% ee (entry 8, Table 4) and catalyst **26** gave less than 10%

yield with 17% ee (entry 18, Table 4). Both catalysts were having poor solubility in DMF. Catalyst **25** has shown better enantioselectivity in DMF (28% ee) than $CHCl_3$ (18% ee), while it is reverse in case of catalyst **26** which gave better enantioselectivities in $CHCl_3$ (71% ee) than DMF (17% ee). When more polar solvent like DMSO has been used, it gave better yields and enantioselectivities [53% yield and 29% ee by catalyst **25** (entry 9, Table 4) and 73% yield and 23% ee by catalyst **26** (entry 19, Table 4)]. Though enantioselectivity was decreased with catalyst **26** in DMSO with respect to that in $CHCl_3$ (71% ee in $CHCl_3$ while only 23% ee in DMSO), but the yield increased in DMSO (73%) compare to that in $CHCl_3$ (<10%).

Higher conversion rates in DMSO might be the result of better solvation and stabilisation of the nucleophile. Solvent polarity has an adverse effect on the complexation of substrate with the peptide and consequently on the enantiomeric excess. Polarity helps with the yields while the enantioselectivity drops sharply.

No reaction took place in DMSO with peptides **25** in the absence of additive. Intriguingly, peptide **26** gave the product in 67% yield and with 8% *ee* under the same conditions. Since the strongest base (guanidine group of arginine, p*K*a = 13.20 in water) in the system with **25** and **26** is generally deactivated through formation of zwitterions, only the proline residue of peptide catalyst **26** appears to be basic enough to deprotonate the nitroalkane. [Second p*K*a values of the amino acids making up the peptides: proline (p*K*a = 10.64) is a better proton acceptor than phenylalanine (p*K*a = 9.46); here we have employed the p*K*a values of the individual amino acids in water as an approximation. It has been found that acid/base pairs have the same relative p*K*a values in nonaqueous media as they do in water].[120, 121] Generaly, in the presence of the additive yield and enantioselectivity is increasing; only in DMF with catalyst **26** the the yield decreased. Alone catalyst gave 66.7% yield while in presence of additive *trans*-2,5-dimethylpiperazine yield was decreased to 10%. It is still unclear why catalyst **26** gave higher enantioselectivities in DMSO in combination with additive (23% ee) than in the absence of additive (8% ee).

One possible explanation for the cooperative effect might be the formation of a noncovalently bound complex of additive and peptide that interacts with the substrate through hydrogen bonds. The possibility for peptides to form noncovalent interactions

with the additive seems particularly intriguing. The lower enantioselectivities observed in DMSO with respect to $CHCl_3$ in the presence of a combination of peptides **25** and additive could thus be explained in terms of solvent polarity, while the individual results in DMSO arise from the balance of the competition and the cooperation effect (e.g., in case of **26**, the cooperation outweighs the competition, while in the case of **25**, the complex with the substrate might be a more stable one).

We next examined the room-temperature ionic liquid [bmim]PF_6 as an alternative solvent. The enantiomeric excesses of product obtained in the presence both of peptides (**25** or **26**, respectively) and of additive in the ionic liquid [bmim]PF_6 were further reduced to 5%, compared to the reaction in DMSO, accompanied by significant drops in yields (44% and 35%, respectively). Notably, the Michael product is nearly racemic here, indicating the influence of peptides **25** and **26** chirality as minimal in [bmim]PF_6 as solvent. Whereas tripeptide **25** alone gave the product in 37% yield and with 5% *ee*, no reaction took place in [bmim]PF_6 with peptides **25** in the absence of additive. Use of additive alone gave the Michael product in 25% yield.

The enantiomeric excesses in the products formed in the presence of **25** and **26** decreased so dramatically in relation to the results in DMSO (or DMF, $CHCl_3$) could reflect the greater liability and reduced stability of hydrogen bond complexes that may form between Michael acceptor and the peptides and which could influence the outcome of the choice between enantiomeric forms.

3.3.3. H-Leu-His-OH and H-His-Leu-OH as Organocatalysts

Michael additions catalyzed by proline or proline derivatives are known in literature but there was no repot on proline-free peptide catalysts. List has reported on N-terminal prolyl peptides like Pro-His-Ala tripeptide with only 7% enantioselectivity and 70% yield for Michael addition reaction of acetone to nitrostyrene.[111, 122] We reported previously H-Asp-Phe-Arg-OH for conjugate addition of 2-nitro propane to cyclohex-2-ene-1-one.[122] Cordova and co-workers reported high enantioselectivities with di- and tripeptides containing H-Ala-Ala-OH, H-Ala-Ala-Ala-OH, H-Ala-Val-OH, H-Ala-Phe-

OH, H-Ala-Gly-OH, H-Val-Val-OH, H-Val-Phe-OH, H-Ser-Ala-OH.[112] They used 10 equivalents of water in the reaction.

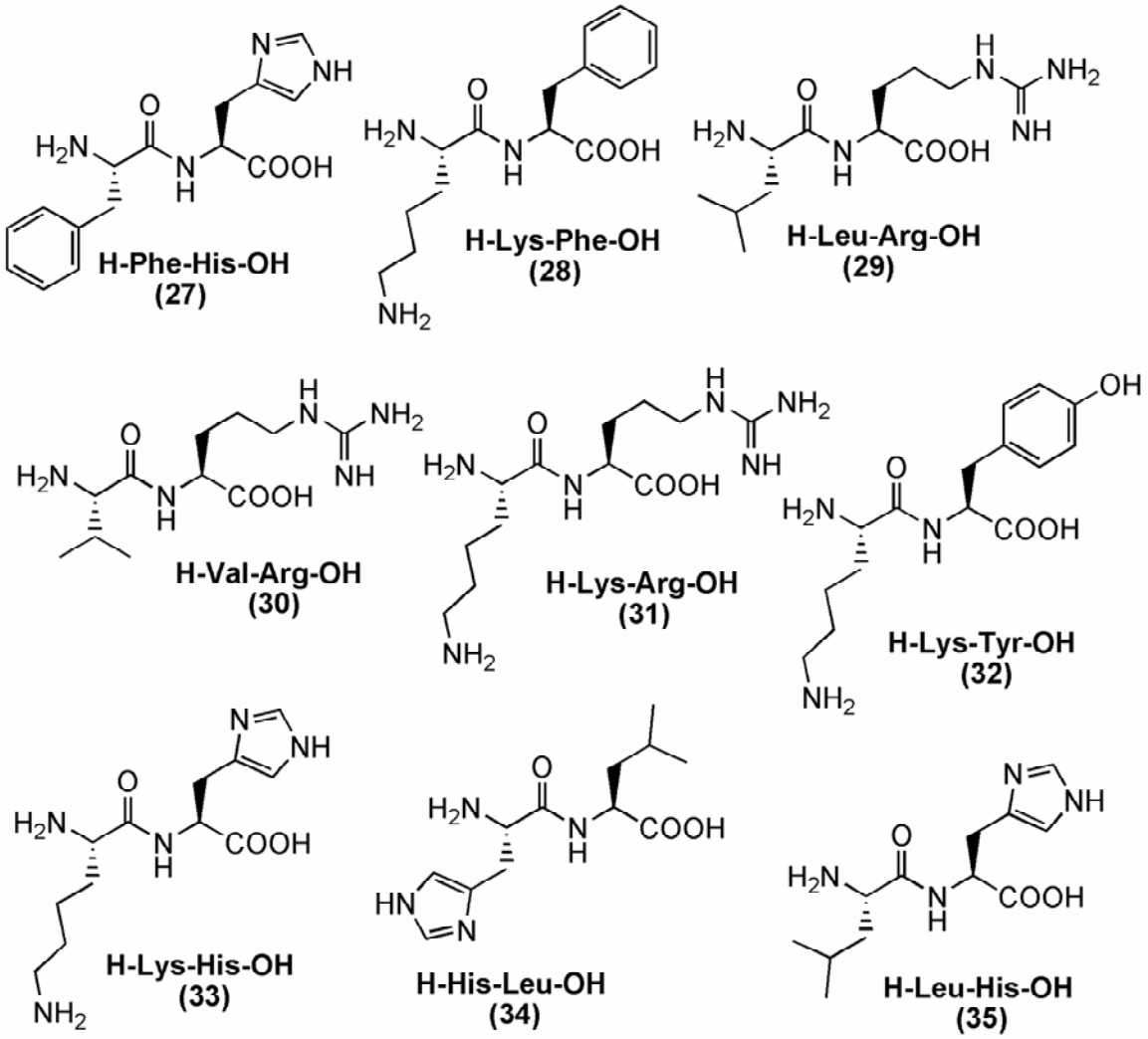
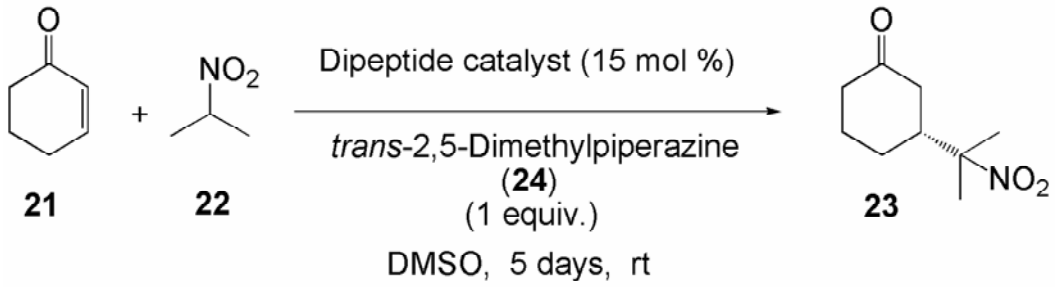


Figure 12. Catalyst screening for Michael addition reaction.

We were interested to use readily available simple dipeptides for asymmetric Michael addition, hence we screened various dipeptides for conjugate addition of 2-nitro propane to cyclohex-2-ene-1-one in the presence of *trans*-2,5-dimethylpiperazine selected as an additive. Reactions were carried out at 15 mol % of peptide catalyst in DMSO for five days at room temperature. DMSO was used as solvent for screening because of better solubility of all catalysts in it (Scheme 24). The results are summarized in Table 5.



Scheme 24. Conjugate addition of 2-nitro propane to cyclohex-2-ene-1-one catalyzed by dipeptide catalysts.

Table 5. Screening of dipeptides for conjugate addition reaction in DMSO.

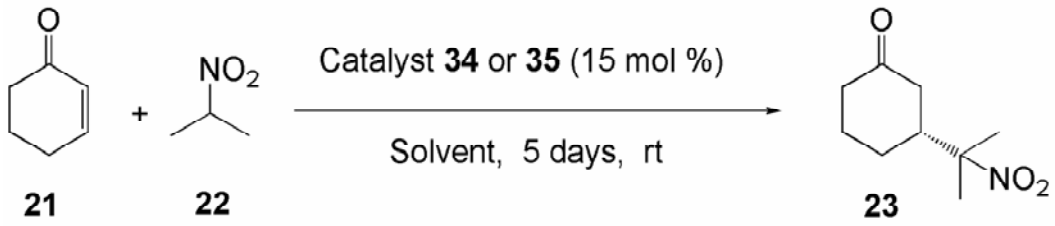
Entry	Peptide	Yield (%)[a]	ee (%)[b]	Configuration
1	H-Phe-His-OH (**27**)	84	5	*R*
2	H-Lys-Phe-OH (**28**)	82	3	*R*
3	H-Leu-Arg-OH (**29**)	86	3	*R*
4	H-Val-Arg-OH (**30**)	64	0	-
5	H-Lys-Arg-OH (**31**)	80	0	-
6	H-Lys-Tyr-OH (**32**)	49	0	-
7	H-Lys-His-OH (**33**)	>99	0	-
8	H-His-Leu-OH (**34**)	95	26	*R*

[a] Isolated yields after column chromatography.
[b] % Enantioselectivities were determined by chiral HPLC analysis (Daicel Chiralpak AS) in comparison with authentic racemic material.

Dipeptide catalysts H-Phe-His-OH (**27**), H-Lys-Phe-OH (**28**) and H-Leu-Arg-OH (**29**) give very good yields but low enantioselectivities (84%, 82% and 86% yields and 5%, 3% and 3% ee respectively, entries 1, 2 and 3, Table 5), while catalysts H-Val-Arg-OH (**30**), H-Lys-Arg-OH (**31**), H-Lys-Tyr-OH (**32**) and H-Lys-His-OH (**33**) give good yields (64%, 80%, 49% and >99% respectively, entries 4, 5, 6 and 7, Table 5) but without having any enantiomeric excess in the product. Good yield and moderate

enantioselectivity (95% yield and 26% ee, entry 8, Table 5) was observed when dipeptide H-His-Leu-OH (**34**) was used as catalyst. Because of better results obtained by dipeptide catalyst H-His-Leu-OH our interest was increased in another dipeptide containing histidine functionality H-Leu-His-OH (**35**) which is having just reversed sequence of amino acids. H-Leu-His-OH also showed similar catalytic activity like H-His-Leu-OH. For the same Michael addition reaction H-Leu-His-OH gave 53% yield and 30% enantiomeric excess.

Next we tested dipeptide catalysts **34** and **35** in different solvents with or without additive *trans*-2,5-dimethylpiperazine (**24**) to choose the best solvent for this reaction. All reactions were carried out with 15 mol % of catalyst. Michael addition reaction was carried out in three different solvents $CHCl_3$, DMF and DMSO (Scheme 25). Results are summarized in Table 6.



Scheme 25. Conjugate addition of 2-nitro propane to cyclohex-2-ene-1-one catalyzed by dipeptide catalysts.

As it was expected, $CHCl_3$ as a solvent was not a suitable solvent because peptide **34** has not good solubility in it while peptide **35** has partial solubility. No product (**23**) formation was observed when reaction was carried out in $CHCl_3$ without additive *trans*-2,5-dimethylpiperazine (entries 2 and 8, Table 6), while with additive, catalyst **35** gave 10% yield and H-His-Leu-OH (**34**) gave <5% yield (entries 1 and 7 respectively, Table 6). Product **23** obtained in the reaction catalyzed by H-Leu-His-OH (**35**) and additive has not shown any enantioselectivity.

Table 6. Screening of solvents with dipeptides **34** and **35** with or without additive *trans*-2,5-dimethylpiperazine.

Entry	Catalyst	Additive (equiv.)	Solvent	Yield (%)[a]	ee (%)[b]	Configuration
1	35	1	$CHCl_3$	10	0	-
2	35	-	$CHCl_3$	No reaction	-	-
3	35	1	DMF	24	30	*R*
4	35	-	DMF	6	21	*R*
5	35	1	DMSO	53	30	*R*
6	35	-	DMSO	13	42	*R*
7	34	1	$CHCl_3$	<5	nd[c]	-
8	34	-	$CHCl_3$	No reaction	-	-
9	34	1	DMF	29	41	*R*
10	34	-	DMF	No reaction	-	*R*
11	34	1	DMSO	95	26	*R*
12	34	-	DMSO	9	48	*R*

[a] Isolated yields after column chromatography.
[b] % Enantioselectivities were determined by chiral HPLC analysis (Daicel Chiralpak AS) in comparison with authentic racemic material.
[c] Not determined.

Still in more polar solvent DMF, catalyst **35** alone gave only 6% yield and 21% enantioselectivity in the absence of additive, while in the presence of additive the yield was increased to 24% and enantioselectivity to 30% (entries 3 and 4, Table 6). With catalyst **34** no product **23** was formed when reaction carried out without additive in DMF, while the combination of additive and catalyst gave the product in 29% yield and 41% enantioselectivity (entry 9, Table 6).

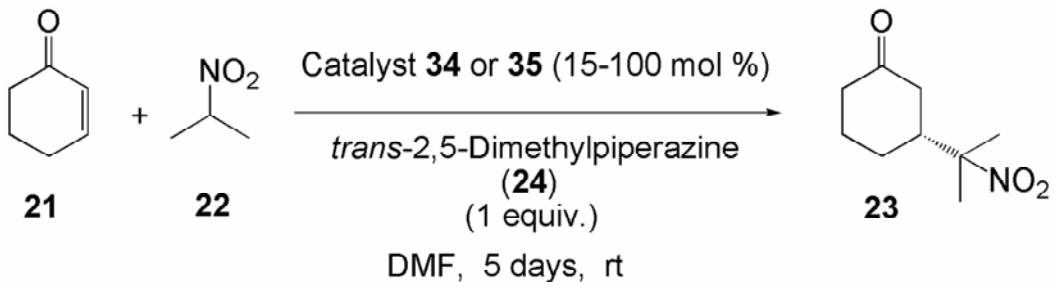
In more polar solvent DMSO with catalyst **35**, the yield enantioselectivity increased (13% yield, 42% ee; entry 6, Table 6) compare to that in DMF (6% yield, 21% in DMF)

in the absence of additive. Different result was obtained in the presence of additive. With catalyst **35** the yield and the enantioselectivities were increased when DMSO was used as a solvent instead of DMF. In the presence of additive the yield was increased to 53% (without additive: 13% yield only) but enantioselectivity has slightly dropped (30% ee, entry 5, Table 6). It means that there should be some different mechanism of reaction with catalyst **35** in both cases i.e. with and without additive.

In DMSO catalyst **34** alone gave 9% yield and 48% ee (entry 12, Table 6), while the yield was increased to 95% with 26% ee (entry 11, Table 6) when catalyst **34** was used combination with an additive.

In all cases product (**23**) obtained has '*R* `configuration. DMF was found as a solvent of choice.

After getting good results with the catalysts **34** and **35** we were interested to continue our studies to increase yields and enantioselectivities by carrying out reactions with different mol % of catalysts and additives (15, 30, 50, and 100 mol %). Therefore, first we carried out conjugate reaction of 2-nitropropane to cyclohex-2-ene-1-one with different mol % of catalysts and one equivalent of *trans*-2,5-dimethylpiperazine (**24**) as an additive (Scheme 26). The results are summarized in Table 7.



Scheme 26. Conjugate addition of 2-nitro propane to cyclohex-2-ene-1-one catalyzed by dipeptide catalysts in DMF.

Table 7. Michael addition reaction with different loading of catalyst and one equivalent of *trans*-2,5-Dimethylpipirazine(**24**) in DMF.

Entry	Catalyst (mol %)	H-Leu-His-OH (35)		H-His-Leu-OH (34)	
		Yield (%)[a]	ee (%)[b]	Yield (%)[a]	ee (%)[b]
1	15	24	30	29	41
2	30	46	31	38	43
3	50	58	37	53	45
4	100	42	44	57	51

[a] Isolated yields after column chromatography.
[b] % Enantioselectivities were determined by chiral HPLC analysis (Daicel Chiralpak AS) in comparison with authentic racemic material.

By increasing the loading of dipeptide catalyst H-His-Leu-OH (**34**) in presence of one equiv. of *trans*-2,5-Dimethylpipirazine in DMF, the yield has increased. 15%, 30%, 50% and 100 mol % of catalyst gave 29%, 38%, 53% and 57% yields respectively. The enantiomeric excess has also increased by increasing the loading of catalyst. The same trends were observed with the catalyst **34** and the product was obtained in 41%, 43%, 45% and 51% ee's, respectively.

Similar results were observed with dipeptide catalyst H-Leu-His-OH (**35**). With catalyst in 15%, 30%, 50% and 100 mol % loading showed 24%, 46%, 58% and 42% yields; and 30%, 31%, 37% and 44% ee's respectively.

Though slight increase in yields and enantiomeric excess was observed by increasing the loading of catalyst, still it was not enough and we were interested to increase it further. In our initial studies, we have shown that even achiral *trans*-2,5-dimethylpiperazine alone resulted in product with 39.5% yield in DMSO and 5% yield in DMF, and therefore, influenced the enantiomeric excesses of the products when peptides were used as the catalysts[122] (although the dominating influence on the enantioselectivities comes from the peptides). Accordingly, we assumed that the use of suitable chiral co-catalysts might improve further the enantiomeric excesses of dipeptide-catalyzed reactions and decided

to perform our further experiments with commercially available chiral mono- and diamines **36**-**40** shown in the Figure 13.

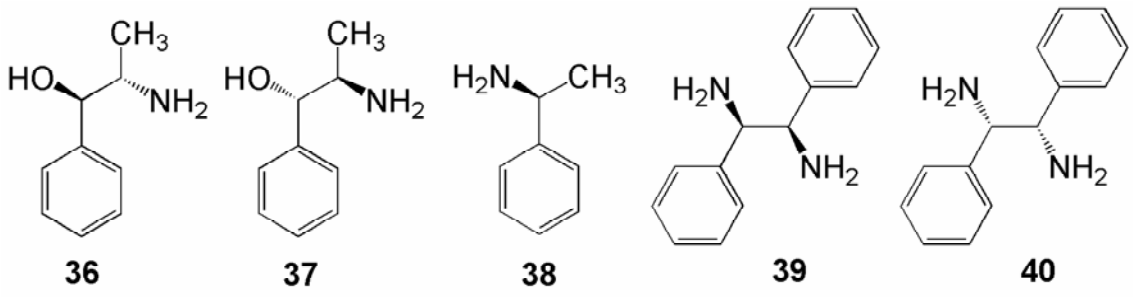
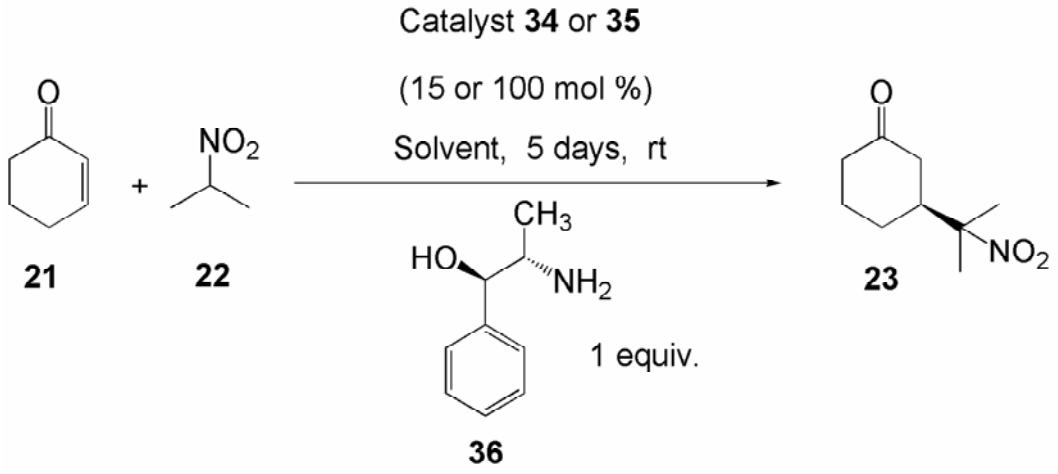


Figure 13. Chiral mono- and diamines used as co-catalysts in Michael addition reaction.

First, we chosen L-(-)-norephedrine (**36**) as co-catalyst for our studies with 15 and 30 mol % of catalyst. Co-catalyst was used in 100 mol % in DMSO or DMF as solvent (Scheme 27). The results are summarized in Table 9.



Scheme 27. Conjugate addition of 2-nitro propane to cyclohex-2-ene-1-one catalyzed by dipeptide catalysts **34** or **35** and L-(-)-norephedrine (**36**).

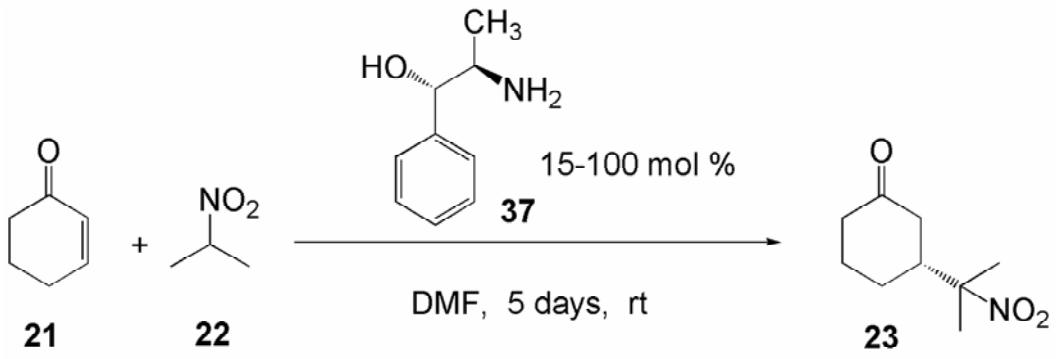
Exchange of additive **24** for L-(-)-norephedrine (**36**) produced in DMSO as well as in DMF the *S*-enantiomer of the Michael product in much better yields (67–99%, but low to moderate enantioselectivities (3-31%), enties 1-6, Table 8). Interestingly, the presence of additive **36** alone results in the *S*-product with 60% yield and 2% ee in DMSO and in 14% yield, 28% ee in DMF (entries 7, 8, Table 8).

Table 8. Michael reaction in presence of one equiv. co-catalyst L-(-)-norephedrine (**36**)

Entry	**Catalyst**	**Catalyst (mol %)**	**Solvent**	**Yield (%)[a]**	**ee (%)[b]**	**Configuration**
1	H-Leu-His-OH (**35**)	15	DMSO	>99	3	*S*
2	H-Leu-His-OH (**35**)	15	DMF	77	31	*S*
3	H-Leu-His-OH (**35**)	30	DMF	67	30	*S*
4	H-His-Leu-OH (**34**)	15	DMSO	93	7	*S*
5	H-His-Leu-OH (**34**)	15	DMF	70	28	*S*
6	H-His-Leu-OH (**34**)	30	DMF	72	30	*S*
7	-	-	DMSO	60	2	*S*
8	-	-	DMF	14	28	*S*

[a] Isolated yields after column chromatography.
[b] % Enantioselectivities were determined by chiral HPLC analysis (Daicel Chiralpak AS) in comparison with authentic racemic material.

For further investigation of the reaction mechanism we tested D-(+)-norephedrine (**37**) as co-catalyst. We carried out all reactions with dipeptide catalyst H-Leu-His-OH (**35**) with 15 or 30 mol % or without catalyst in DMF. The loading of co-catalyst was varied from 15 to 100 mol % (Scheme 28). The results are summarized in Table 9.



Scheme 28. Conjugate addition of 2-nitro propane to cyclohex-2-ene-1-one in presence of D-(+)-norephedrine (**37**) in DMF.

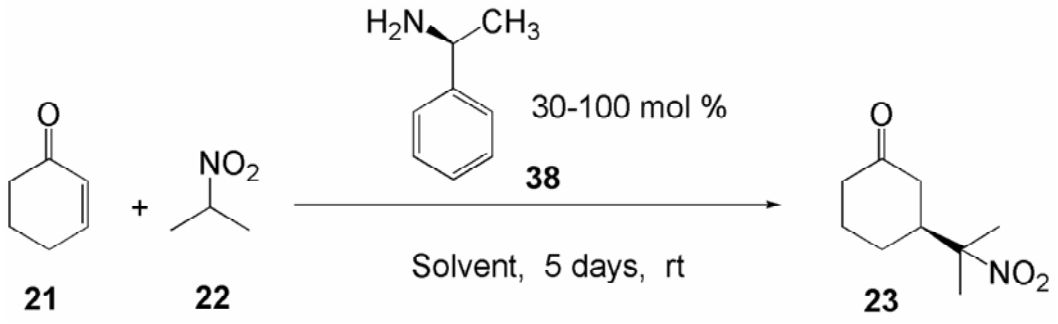
Table 9. Michael addition reaction in presence of co-catalyst D-(+)-norephedrine (**37**).

Entry	Catalyst (mol %)	Co-catalyst (mol %)	Yield (%)[a]	ee (%)[b]	Configuration
1	-	15	6	30	*R*
2	-	30	6	34	*R*
3	-	50	11	30	*R*
4	-	100	21	32	*R*
5	**35** (15)	15	27	30	*R*
6	**35** (15)	30	27	30	*R*
7	**35** (15)	50	49	30	*R*
8	**35** (15)	100	79	32	*R*
9	**35** (30)	15	18	32	*R*
10	**35** (30)	30	22	30	*R*
11	**35** (30)	50	42	32	*R*
12	**35** (30)	100	73	30	*R*

[a] Isolated yields after column chromatography.
[b] % Enantioselectivities were determined by chiral HPLC analysis (Daicel Chiralpak AS) in comparison with authentic racemic material.

D-(+)-norephedrine (**37**) in combination with dipeptide **35** in DMF provides the product with similar yield and enantioselectivity (79%, 32% ee, entry 8, Table 9 vs entry 2, Table 8), but with opposite *R*-configuration, as expected. D-(+)-norephedrine alone gave *R*-product in 21% yield and 32% ee (entry 4). Considering the results shown in entries 1 and 7 (Table 8) in DMSO and also entry 4 (in Table 6), entries 2 and 8 (in Table 8) in DMF one might conclude that even in the presence of dipeptides the dominating influence on the enantioselectivities comes from the norephedrine. The variation of concentration of dipeptide **35** (0, 15, 30 mol %) and D-(+)-norephedrine (15, 30, 50, 100 mol %) and their different combinations did not lead to an increase in selectivity (being constant at around 30% ee). However, the presence of both dipeptide and norephedrine drastically increases the yield of Michael product with respect to independently acting dipeptide or norephedrine and is much higher than the sum of its individual yields (entry 6 in Table 6, entries 1 and 7 in Table 8, in DMSO), which indicates the possibility of synergistic effects.

Next, we evaluated (*R*)-(+)-1-phenylethylamine (**38**) as co-catalyst in DMF and DMSO as solvents (Scheme 29). The results are summarized in Table 10.



Scheme 29 . Conjugate addition of 2-nitro propane to cyclohex-2-ene-1-one in presence of (*R*)-(+)-1-phenylethylamine (**38**).

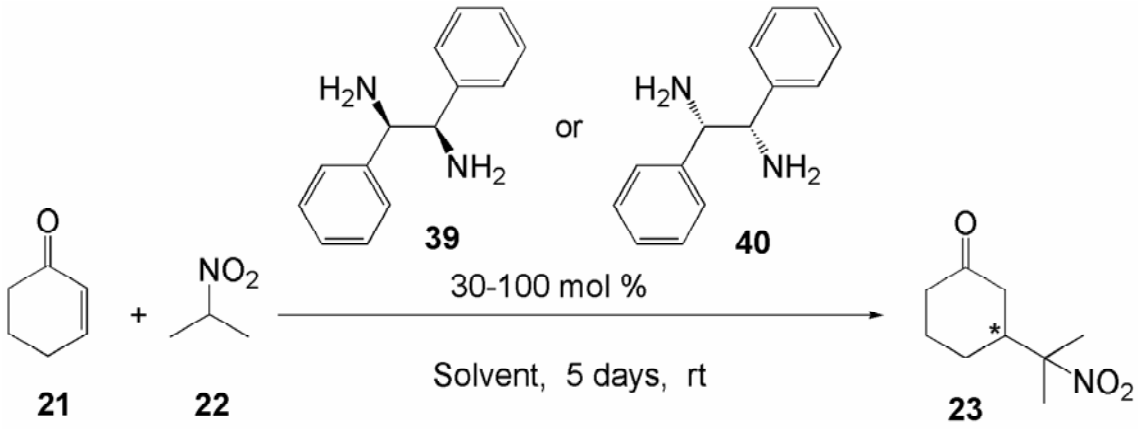
Table 10. Michael addition reaction catalyzed by dipeptides **35** in the presence of (*R*)-(+)-1-phenylethylamine (**38**)

Entry	Catalyst	Catalyst (mol %)	Co-catalyst (mol %)	Solvent	Yield (%)[a]	ee (%)[b]	Configuration
1	-	-	100	DMF	30	30	*S*
2	-	-	100	DMSO	>97	22	*S*
3	H-Leu-His-OH (**35**)	15	100	DMF	74	45	*S*
4	H-Leu-His-OH (**35**)	15	30	DMF	54	47	*S*

[a] Isolated yields after column chromatography.
[b] % Enantioselectivities were determined by chiral HPLC analysis (Daicel Chiralpak AS) in comparison with authentic racemic material.

Combination of **35** and co-catalyst **38** (1 equiv.) gives *S*-product with 74% yield and 45% ee (entry 15, Table 10), whereas by reducing the loading of co-catalyst **38** to 30 mol %, the enantioselectivity remained nearly the same (47% ee; entry 4, Table 10), but yield reduced to 54% in DMF. Co-catalyst (*R*)-(+)-1-phenylethylamine (**38**) alone gives *S*-product with 30% yield and 30% ee in DMF (entry 1, Table 10), while in DMSO it gives much higher yield (>99%) but low ee (entry 2, Table 10).

Next we tested the co-catalyst 1*R*,2*R*-(+)-1,2-diphenylethylenediamine (**39**) and 1S,2S-(-)-1,2-diphenylethylenediamine (**40**) in DMF or DMSO without any dipeptide catalyst (Scheme 30). The resullts are summarized in Table 11.



Scheme 30. Conjugate addition of 2-nitro propane to cyclohex-2-ene-1-one in presence of chiral 1,2-diphenyl ethylenediamine **39** or **40**.

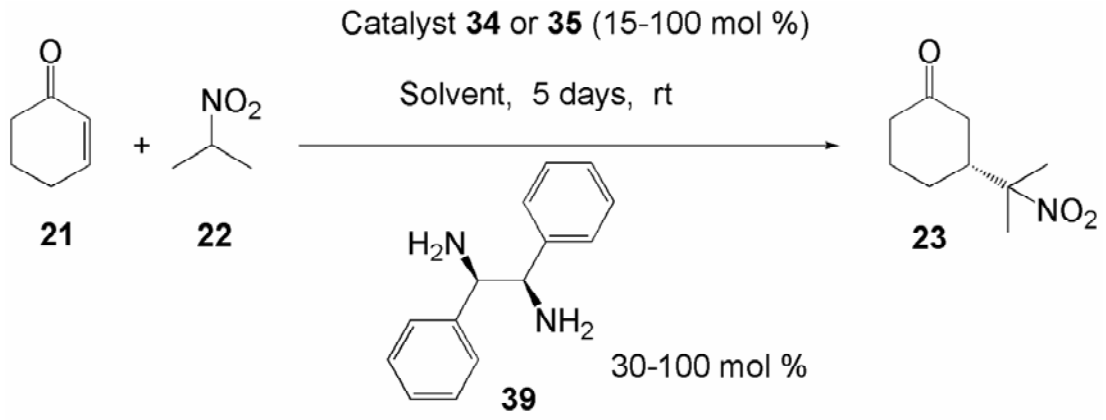
Table 11. Michael addition reaction catalyzed by 1*R*,2*R*-(+)-1,2-diphenyl-ethylenediamine (**39**) and 1*S*,2*S*-(-)-1,2-diphenylethylenediamine (**40**) in DMF and DMSO.

Entry	Co-catalyst	Co-catalyst (mol %)	Solvent	Yield (%)[a]	ee (%)[b]	Configuration
1	**39**	30	DMF	2	nd[c]	-
2	**39**	100	DMF	12	45	*R*
3	**40**	100	DMF	29	33	*S*
4	**39**	30	DMSO	25	17	*R*
5	**39**	100	DMSO	62	17	*R*

[a] Isolated yields after column chromatography.
[b] % Enantioselectivities were determined by chiral HPLC analysis (Daicel Chiralpak AS) in comparison with authentic racemic material.
[c] Not determined.

With 30 mol % of 1*R*,2*R*-(+)-1,2-diphenylethylenediamine (**39**) only 2% of product was obtained in DMF (entry 1, Table 11), while up to 12% yield and 45% ee was achieved when 100 mol % of **39** was used (entry 2, Table 11). When DMSO was used as a solvent, 30 mol % of **39** gave 25% yield and 17% ee (entry 4, Table 11), while 100 mol % **39** produced the product with much better yield and the same ee (62% yield and 17% ee; entry 5, Table 11). 1*S*,2*S*-(-)-1,2-diphenylethylenediamine (**40**) in DMF gives 29% yield and 33% ee (entry 3, Table 11). 1*R*,2*R*-(+)-1,2-diphenylethylenediamine (**39**) provides *R*-product while 1*S*,2*S*-(-)-1,2-diphenylethylenediamine (**40**) gives *S*-product.

For Michael addition co-catalyst **39** gave better enantioselectivity than **40**. Hence we chosen co-catalyst **39** for our further studies with catalysts **34** and **35** by varying the loading of both catalyst and co-catalyst **39** (Scheme 31). The results are summarized in Table 12.



Scheme 31. Conjugate addition of 2-nitro propane to cyclohex-2-ene-1-one in the presence of catalyst **34** or **35** and co-catalyst 1*R*,2*R*-(+)-1,2-diphenyl ethylenediamine(**39**).

Table 12. Michael Addition reaction catalyzed by **34** and/or **35** in the presence of (1*R*,2*R*)-(+)-1,2-diphenyl ethylenediamine (**39**)

Entry	**Catalyst (mol %)**	**Co-catalyst (mol %)**	**Solvent**	**H-His-Leu-OH (34)**		**H-Leu-His-OH (35)**	
				Yield (%)[a]	**ee (%)[b]**	**Yield (%)[a]**	**ee (%)[b]**
1	15	30	DMF	21	43	21	42
2	15	100	DMF	34	49	62	61
3	30	30	DMF	26	39	86	75
4	30	100	DMF	39	49	73	30
5	30	100	DMSO	89	24	86	36
6	50	100	DMF	51	48	41	91
7	100	100	DMF	21	>91	39	91

[a] Isolated yields after column chromatography.
[b] % Enantioselectivities were determined by chiral HPLC analysis (Daicel Chiralpak AS) in comparison with authentic racemic material.

With 15 mol % of catalysts **34** and **35** in DMF in combination with 30 mol % of co-catalyst 1*R*,2*R*-(+)-1,2-diphenylethylenediamine (**39**) we obtained the product in 21%

yields each and 43% and 42% ee's, respectively (entry 1, Table 12). The Michael addition reaction with catalyst and co-catalyst combination gave better yield than the reaction with a co-catalyst alone (entry 1 in Table 12 vs. entry 1 in Table 11).

By using the same amount of catalyst **34** (15 mol %) and 100 mol % of co-catalyst, 34% yield and 49% ee was obtained while the same ratio of catalyst **35** and co-catalyst gave much better yield (62%) and enantioselectivity (61% ee).

When 30 mol % of both catalyst **34** and co-catalyst **39** were used for this reaction, only 26% yield and 39% ee was observed. Interestingly, the same combination of catalyst **35** and co-catalyst **39** (30 mol % each) gave much better yield and ee than **34** (86% yield and 75% ee, entry 3, Table12). Because of this we increased loading of co-catalyst to 100 mol % by keeping loading of catalyst constant at 30 mol %, we observed increased yields and ee's in case of catalyst **34** (39% yield and 49% ee, entry 4, Table 12), but surprisingly, the yield and the ee was decreased in case of catalyst **35** (73% yield and 30% ee, entry 4, Table 12). With the same combination of catalyst (30 mol %) and co-catalyst (100 mol %) in DMSO instead of DMF better yields were observed as expected, but ee was decreased as compared to that in DMF (89% yield and 24% ee with catalyst **34**, while 86% yield and 36% ee with catalyst **35**; entry 5, Table 12). Higher enantioselectivities were achieved (up to 91% ee) but decrease in the yield was observed when the amount of catalyst was increased to 50 and 100 mol % (entries 6 and 7 in Table 12).

These experiments show that the combination of dipeptide **34** and **35** with additive **39** provides a catalytic system that appears to be better than the sum of its parts. A matching pairs of co-catalysts (**34** and **35** with **39**) were thus identified.

In conclusion, we have demonstrated the first example of catalytic asymmetric conjugate addition in the presence of dipeptides H-Leu-His-OH, H-His-Leu-OH and achiral and chiral amines as co-catalysts. By example of conjugate addition of 2-nitropropane to 2-cyclohexen-1-one, we have shown that the combination of H-Leu-His-OH (**35**) and (1*R*,2*R*)-(+)-1,2-diphenylethylenediamine (**39**) as co-catalysts in a suitable ratio can lead to a new catalytic system for the C–C bond formation reactions.

4. Synthesis and Application of New Chiral Guanidine Catalysts for Conjugate addition Reactions

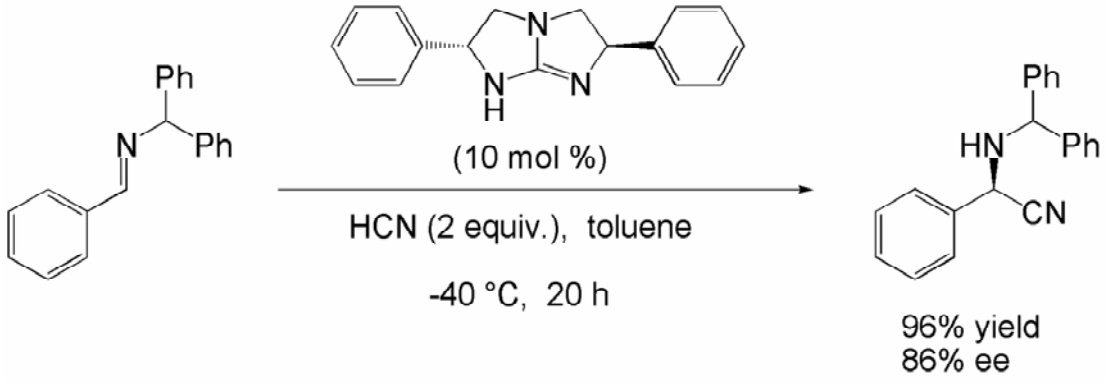
4.1. State of the art

Guanidines can be categorized as organic superbases[123, 124] owing to the resonance stabilization of their conjugated acids[125] and are therefore expected to catalyze various types of base mediated organic reactions. It is a ubiquitous element in natural products and plays a key role in many biological activities. In peptides, guanidine, a residue of arginine, exists in the protonated form as a guanidinium ion, which functions as an efficient recognition moiety of anionic functionalities, such as carboxylate, phosphate, and nitronate, through double hydrogen bonds.[126] In addition to their biological roles, guanidine derivatives are widely utilized in synthetic organic chemistry as strong bases.[125] It is anticipated that the strong basic character of guanidine derivatives coupled with their ability to act as recognition elements will lend them to application as asymmetric base catalysts. Enantiomerically pure guanidines have attracted considerable recent attention as chiral basic catalysts for asymmetric processes. Indeed, chiral guanidine catalysts are attractive targets[127] in organocatalysis, a research topic of increasing interest.[128] However, enantioselective catalysis using chiral guanidine bases has faced limited success. One major and intrinsic problem in the development of guanidine as an efficient chiral catalyst is its planar and hence highly symmetric structure. To overcome this structural drawback, a general approach to constructing chiral guanidine catalysts is to introduce a mono to polycyclic system composed of five and/or six membered rings with central chiralities.[129-132]

Although as early as 1981 Inoue and co-workers disclosed the asymmetric addition of HCN to benzaldehyde catalyzed by diketopiperazine derivative (Scheme 10),[71] the similar reaction, the catalytic asymmetric Strecker reaction, was first reported by Lipton and co-workers 15 years later, using catalyst which is analogous to Inoue's catalyst (Scheme11).[72, 73] The only difference is that Inoue's catalyst bears an imidazole group while Lipton's catalyst has a guanidine. Though Inoue's catalyst is effective for

hydrocyanation of benzaldehyde but it is unable to catalyze reaction when benzaldehyde is replaced by imine. Interestingly replacement of imidazole functionality of catalyst by guanidine changes the results dramatically.

Corey and co-workers found that bicyclic guanidine itself could catalyze Strecker reaction efficiently with high yield and good enantioselectivity.[132] This C2-symmetric catalyst is readily available in a multistep synthesis starting from D-phenylglycine, which represents a cheap and easily accessible chiral starting material. In the presence of 10 mol % of catalyst which has a guanidine functionality embedded in a bicyclic framework, the addition of HCN to *N*-benzhydryl imines has been investigated in detail. The hydrocyanation of the benzaldehyde derived aldimine gave the corresponding (*R*)-amino nitrile in 96% yield, and with an enantioselectivity of 86% (Scheme 32). The reaction can be also carried out at an increased reaction temperature of -20°C, which results in a faster reaction rate (99% yield after 8 h) and comparable 82% ee.



Scheme 32. Guanidine catalyzed asymmetric Strecker synthesis by Corey's catalyst.

This reaction is highly substrate specific, it turns out that the choice of the *N*-substituent is of importance. In contrast to the high enantioselectivities when using an imine bearing a *N*-benzhydryl substituent, remarkably lower asymmetric induction was observed for other types of *N*-substituents. For example, *N*-benzyl or *N*-(9-fluorenyl) substituted imine substrates gave low enantioselectivities of 0-25% ee. Groger reviewed various organocatalysts for asymmetric Strecker synthesis.[133]

Taylor and co-workers reported asymmetric epoxidation of cyclic enons catalyzed by monocyclic, bicyclic as well as acyclic guanidine derivatives (Figure 14).[129, 130, 134] But

with acyclic guanidine catalysts they achieved very low enantioselectivities; while up to 60% enantioselectivity was achieved when greater conformational rigidity was incorporated on bicyclic guanidine catalyst. It was observed that the free alcohol functionality on catalyst improves the enantioselectivity but decreases the yield of the reaction. Also enantioselectivities were improved by introduction of larger aryl group adjacent to chiral centre.

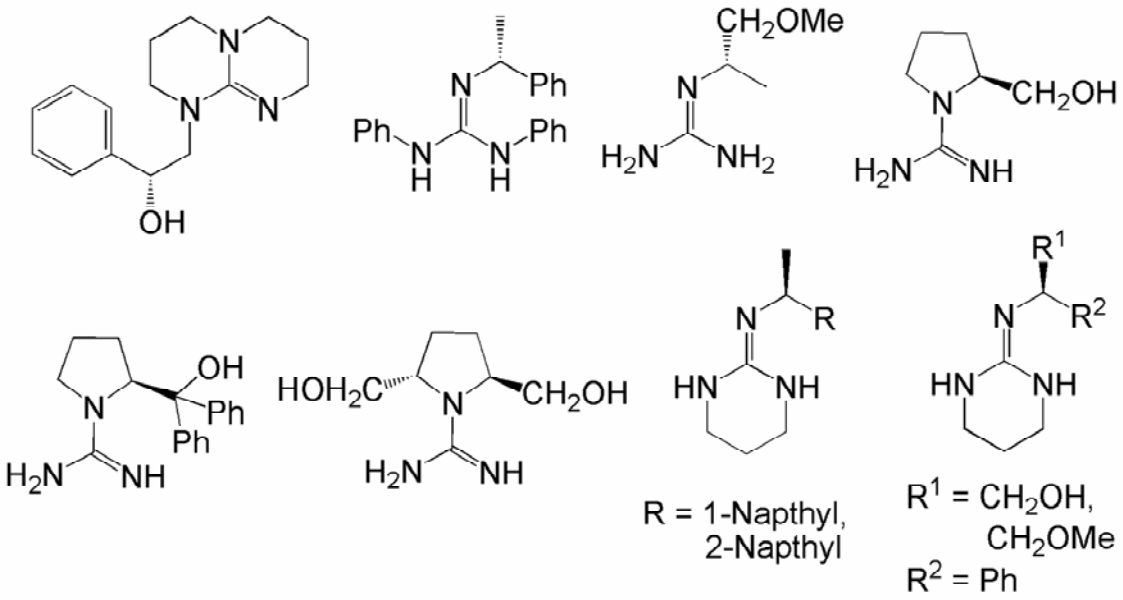


Figure 14. Chiral guanidine derivatives used as catalysts for asymmetric epoxidation reactions.

Ishikawa and co-workers reported Michael addition reaction by modified guanidine catalysts (Figure 15).[127, 135, 136]

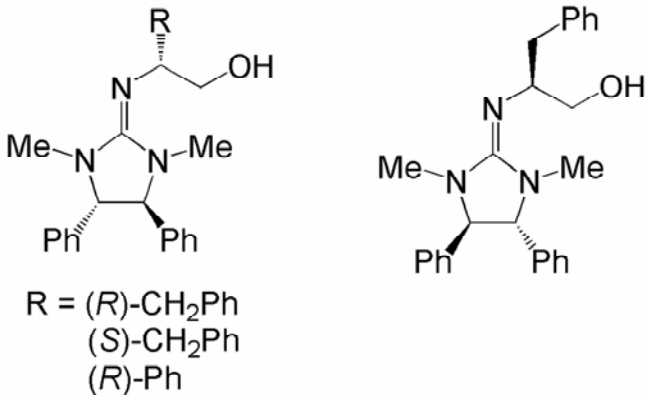
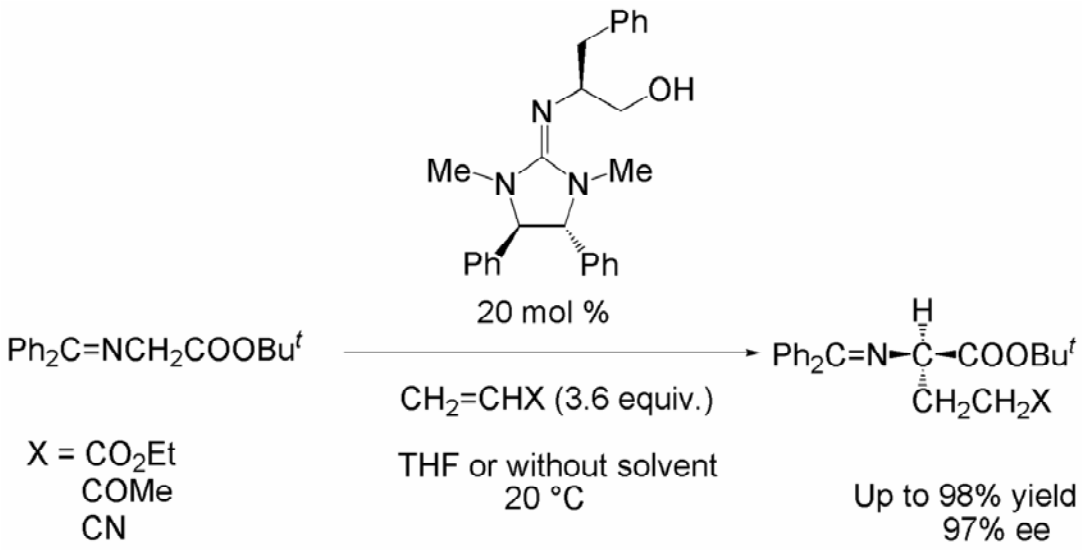


Figure 15. Chiral modifided guanidines used by Ishikawa for asymmetric reactions.

In solvents like chloroform, toluene and ethanol less than 10% yield was obtained while yields were improved when THF was used as a solvent. Interestingly, no change in enantioselectivity and yield was observed when the reaction was carried out in solvent free condition. Also rate of reaction was increased in solvent free conditions (Scheme 33). Similar to Taylor's catalyst Ishikawa and co-workers derived catalysts has also free alcoholic functionality in chiral guanidine catalyst.



Scheme 33. Asymmetric Michael addition reaction catalyzed by modified chiral guanidines.

For similar reaction Ma and co-workers achieved very high yield (up to 99%) but low enantioselectivities (up to 29%) by cyclic and acyclic guanidines.[137]

Tan and co-workers reported addition of nitroalkanes and malonates to acyclic enones in presence of bicyclic guanidine catalyst. They achieved up to 99% yield and 61% enantioselectivity.[138]

Ma and co-workers reported chiral guanidine (Figure 16) catalyzed Henry reaction (Scheme 34).[139]

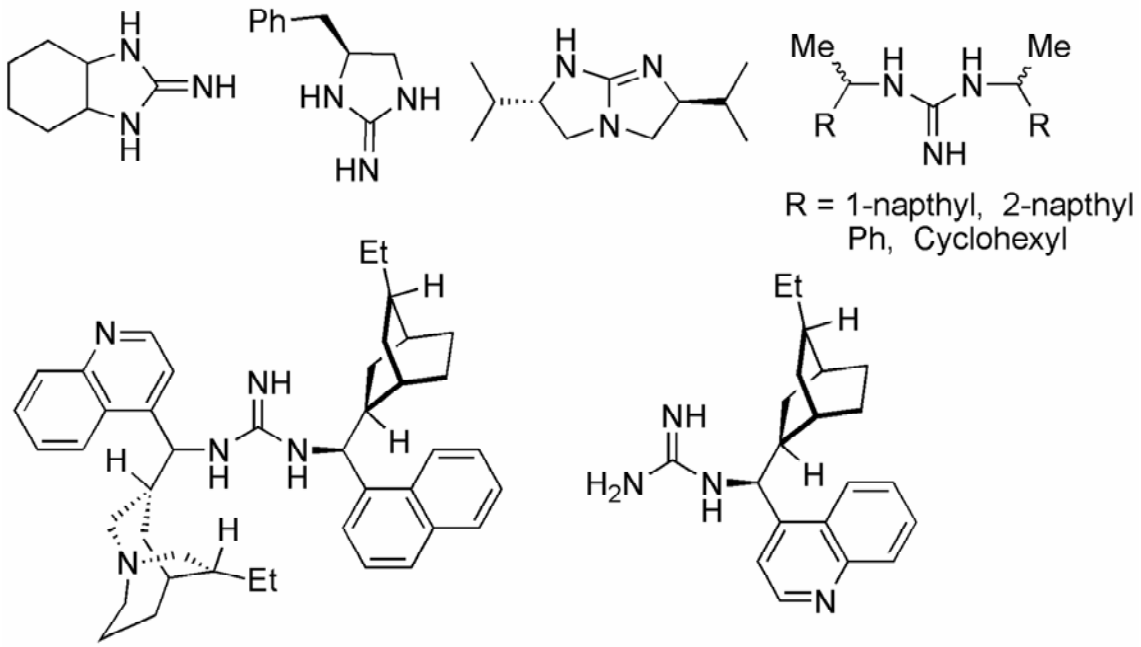
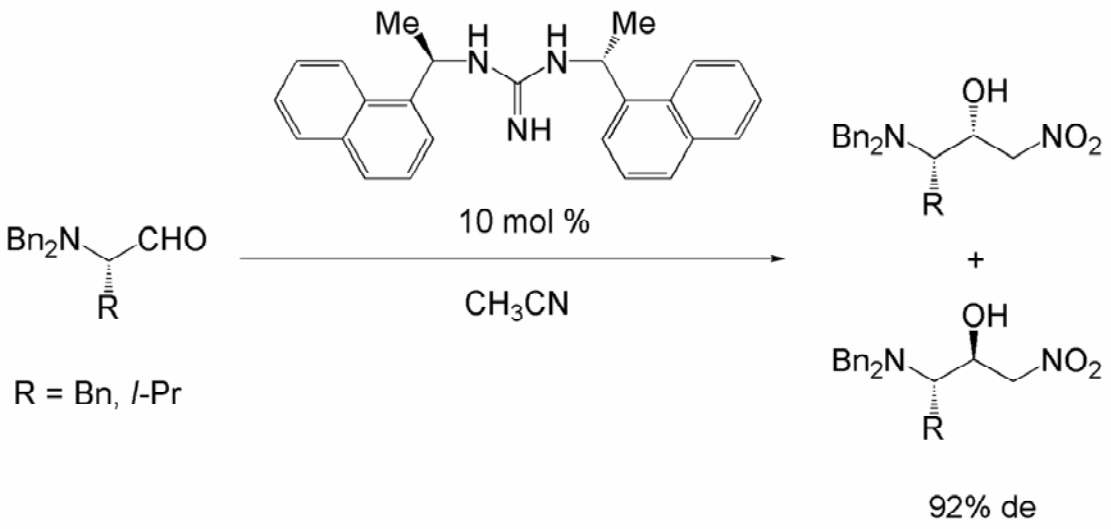


Figure 16. Enantiopure guanidine catalysts used for asymmetric Hennry reaction.



Scheme 34. Henry reaction catalyzed by guanidine derived by ma and co-workers.

The best result (92% de) was obtained when the (*R*)-1-(1-naphthyl) ethylamine derived guanidine was employed as the catalyst for asymmetric Henry reaction.

Nearly all catalysts give good yields (up to 96%). The absolute configurations of the guanidines obviously influenced the diastereoselectivity, because the (*R*,*R*)-guanidine (Scheme 34) showed a higher preference towards than (*S*,*S*)-guanidine. This result also

implied that the chiralities of both catalyst and substrate influenced the asymmetric induction. Diastereoselectivity was still highly dependent on the substrates also. When the L-isoleucine derived aldehyde was used as the substrate, good diastereoselectivity (91%) was observed. Other substrates provided moderate or poor (for the L-proline derived aldehyde) diastereoselectivity. Najera also reported asymmetric Henry reaction with good yields (up to 77%) and moderate enantioselectivities (up to 54%).[140]

Nagasawa and co-workers reported guanidine-thiourea based bifunctional catalysts for Henry reaction with higher yields and enantioselectivities (up to 91% yield and 92% ee).[141] These reactions were performed in the presence of 5 mol % catalysts under biphasic conditions in toluene-aqueous potassium hydroxide at 0 °C. Later, same group reported highly diastereoselective Henry reaction (diastereomer ratio of 84:16 to 99:1) of α-substituted aldehydes with nitromethane was developed using guanidine-thiourea bifunctional catalyst.[127, 142]

C2-symmetric chiral pentacyclic guanidines were used as phase transfer catalysts in asymmetric alkylation of *tert*-butyl glycinate Schiff bases under biphasic condition (Figure 17).[143]

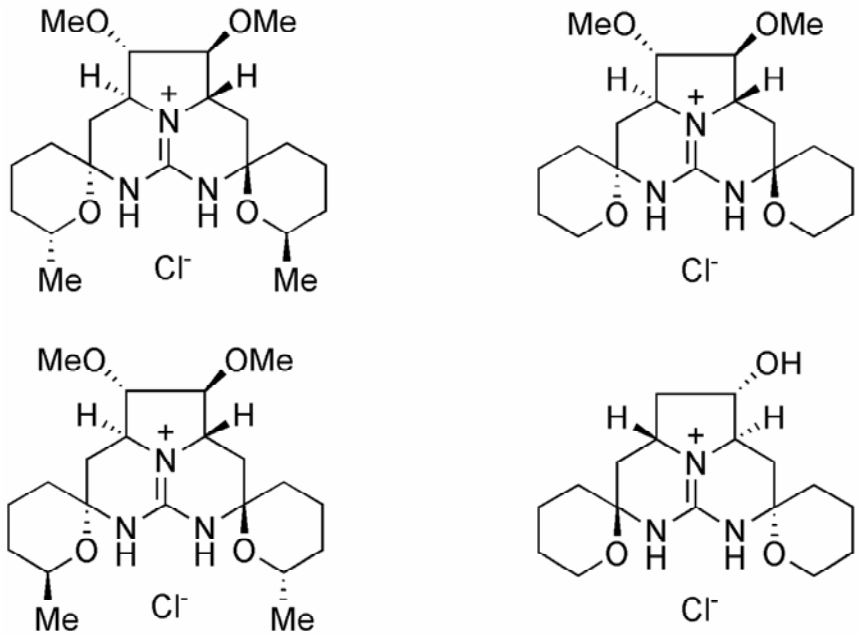


Figure 17. C2-symmetric chiral guanidines are used as phase transfer catalysts in asymmetric alkylation reaction.

CH_2Cl_2-H_2O was used as solvent for this reaction. Higher enantioselectivities (76-90% ee) were obtained by C2-symmetric chiral pentacyclic guanidines. Phase transfer catalyst can be recovered easily in almost quantitative yield by the use of silica gel column chromatography.

Murphy and co-worker used C2-symmetric chiral guanidine catalyst for various reactions with high yield and enantioselectivities.[144] Catalyst used for different model reaction like Henry reaction (isovaleraldehyde with nitromethane gave in 52% yield and in 20% ee), Michael addition of 2-nitropropane to chalcone (70% yield and 23% ee), alkylation (up to >97% conversion and 86% ee) and epoxidation of chalcone (up to 93% ee).

Ishikawa and co-workers reported guanidine catalyzed trimethylsilylcyanation of carbonyl compounds.[145] They obtained higher yields (up to 97%) and moderate enantioselectivities (up to 70%).

4.2. Objective and goals

Corey and co-workers has used above mentioned chiral bisguanidine as a catalyst in asymmetric Strecker synthesis.[132] This bisguanidine gave 50-88% ee. So far several amino acids and their derivatives were used as an effective catalysts but this is an example of having only basic functional group and is effective without acidic functionality. But still the enantioselectivities were not satisfactory. Ishikawa has reported Michael addition reaction with higher yields and enantioselectivities (up to 98% yields and 97% ee).[127, 135, 136]

We designed three new chiral guanidines **41**, **42** and **43** for the asymmetric catalysis (Figure 18). It could be possible to obtain better enantioselectivities by using bulkier bisguanidines. Hence our first aim was to prepare C2-symmetric bisguanidine **41** which should meet the requirements in terms of rigidity, interaction mode, chirality and stability. A branched structure is supposed to have a beneficial effect on the solubility of polar bisguanidine in nonpolar solvents in which hydrogen bonding should favor strong complexation.

To access the homochiral guanidines, several groups have employed amino acids or their derivatives as starting points in multistep syntheses.[126] Hence chiral cyclic guanidine catalysts **42** and **43** were prepared from L-proline and L-prolinol, respectively. It is known that introduction of alcoholic functionality on guanidine catalyst increases enantioselectivities,[129] so the catalyst **43** was designed with an alcoholic group. To compare the effect of hydrogen bonding of –COOH and –OH functionalities on enantioselectivities catalyst **42** was designed with –COOH group.

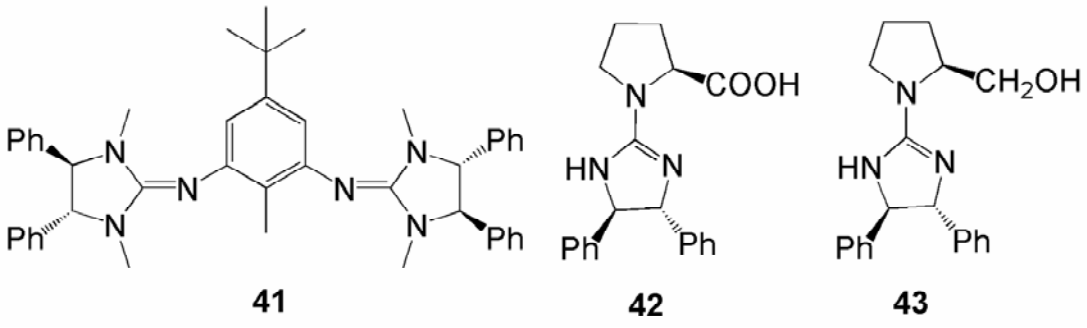


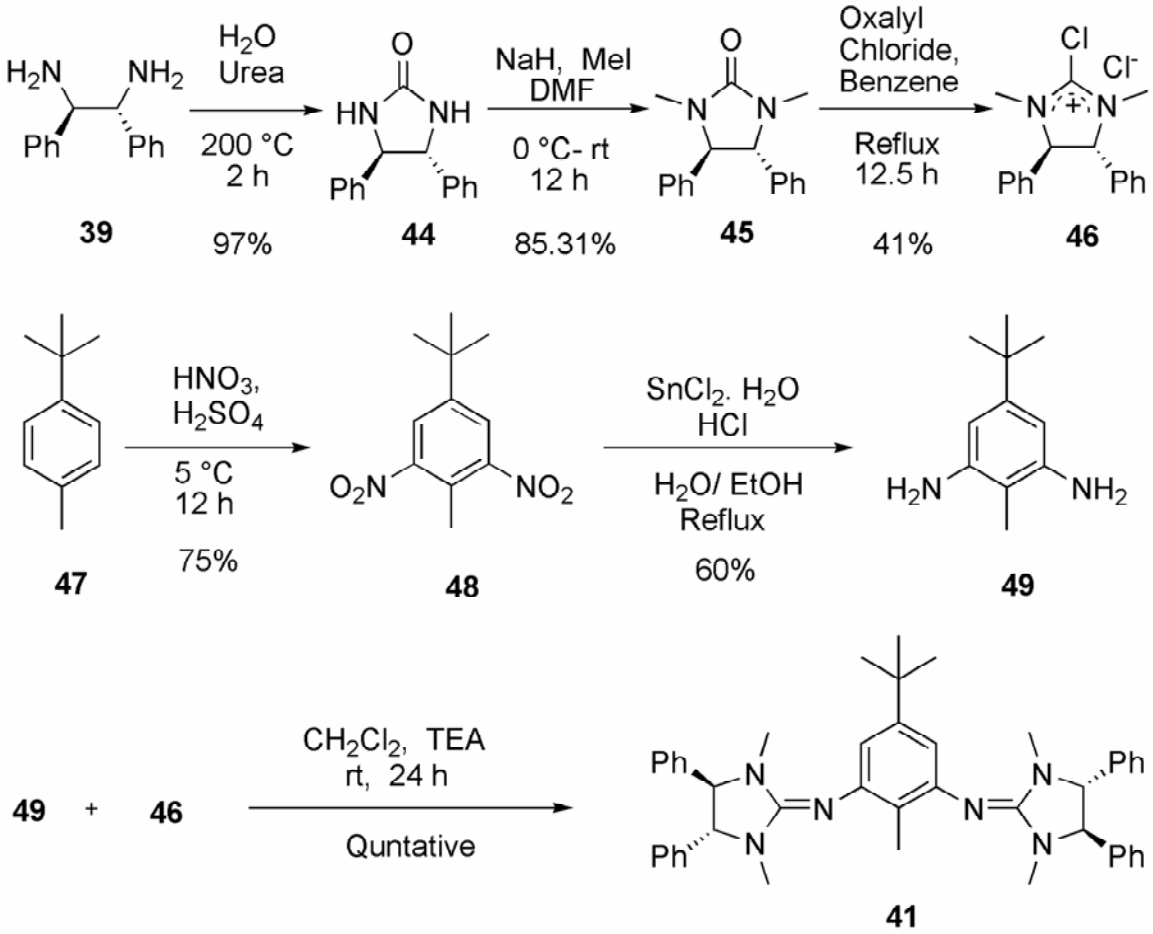
Figure 18. Chiral mono- and bisguanidines designed for asymmetric catalysis.

Taylor and co-workers reported that introduction of larger aryl group adjacent to chiral centre increases the enantioselectivities in asymmetric epoxidation reactions,[129] hence we synthesized our all guanidine catalysts with phenyl rings on chiral centre. 1*R*,2*R*-(+)-1,2-diphenylethylenediamine was our choice as a starting material for the synthesis of guanidine catalysts.

4.3. Results and Discussion

C2-symmetric chiral bisguanidine **41** was prepared in quantitative yield by condensation[146, 147] of compound **46** and **49**. Reaction was carried out in dichloromethane in the presence of TEA and completed after 24 hours stirring at room temperature (Scheme 35). Compound **46** was prepared by heating of 1*R*,2*R*-(+)-1,2-diphenylethylenediamine (**39**) with urea at 200 °C in a little quantity of water with 97% yield[148] followed by its methylation by Iodomethane (85.31% yield) and chlorination by

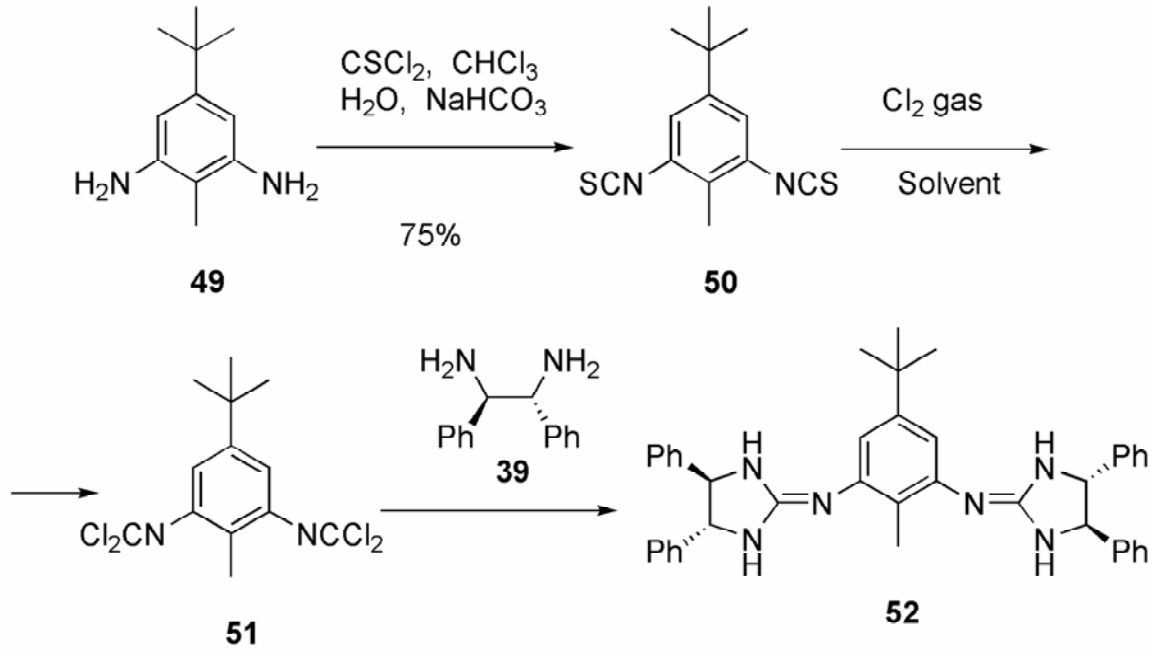
oxalyl chloride (41% yield).[147] Nitration of 4-*tert*-butyltoluene (**47**) was carried out by stirring it at 5 °C for 12 hours with as nitrating mixture (HNO_3, H_2SO_4) to get nitro derivative (**48**) in 75% yield.[149, 150] Reduction of nitro derivative (**48**) was carried by refluxing it in ethanol, water and HCl in the presence of $SnCl_2$. 2,6-Diamino-4-*tert*-butyltoluene (**49)** was obtained in 60% yield.



Scheme 35. Synthesis of C2-symmetric chiral bisguanidine **41**.

All stages gave good yields except the chlorination reaction. The low yield in chlorination reaction affects overall yield of the synthesis. Hence we decided to synthesize the bisguanidine by another way. The only difference in the structure of the target bisguanidine is that, absence of N-methyl groups (**52**). Conversion of 2,6-diamino-4-*tert*-butyltoluene (**49)** into its diisothiocyanate derivative followed by chlorination and condensation of it with 1*R*,2*R*-(+)-1,2-diphenylethylenediamine was another option for

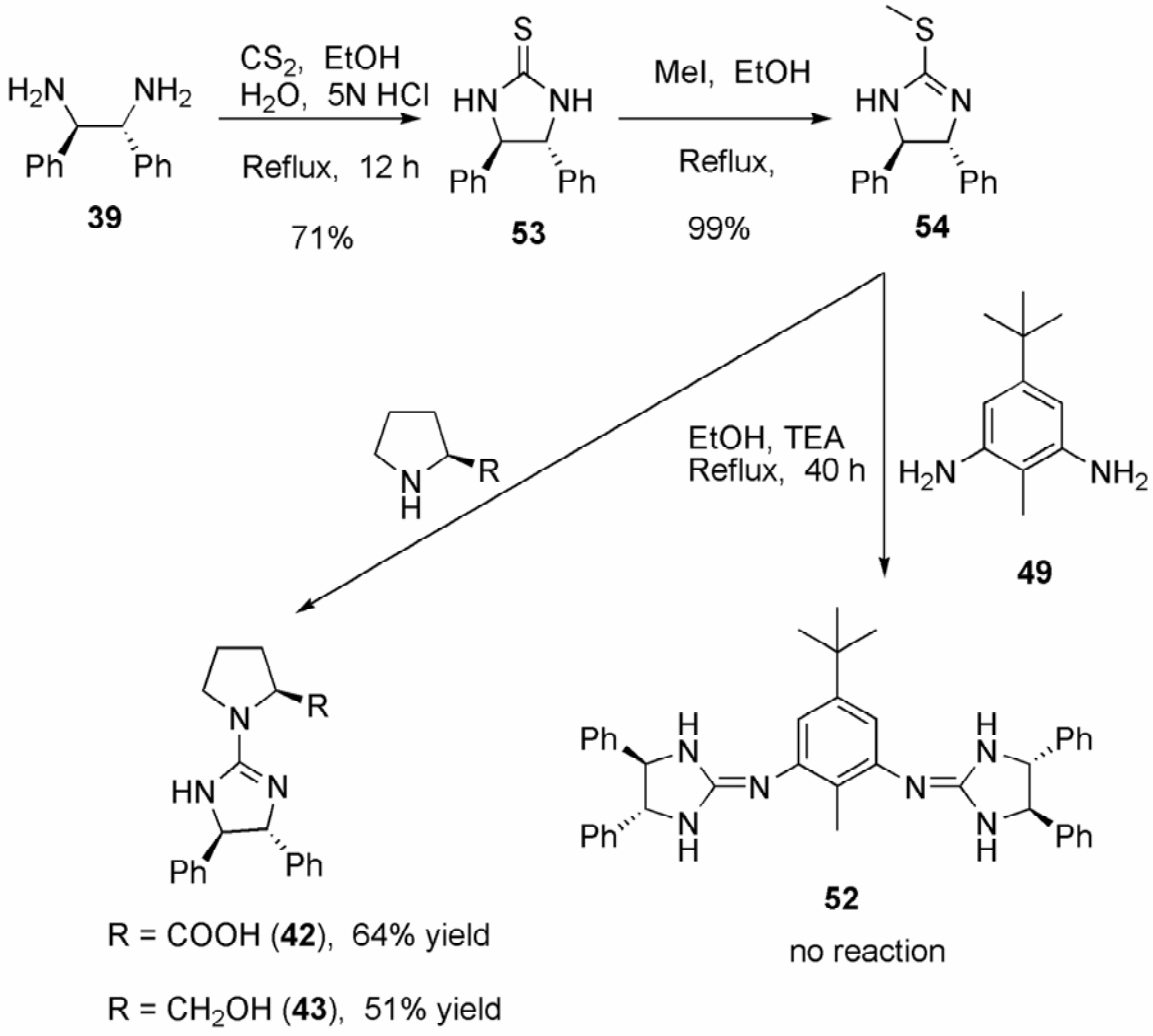
bisguanidine synthesis (Scheme 27). Diisothiocyanate (**50**) was obtained in 75% yield from reaction of $CSCl_2$ with 2,6-diamino-4-*tert*-butyltoluene (**49**). But during chlorination reaction, even after variation of conditions like different of solvents, temperature, flow rate and flow time of chlorine gas, we could not succeed in the preparation of desired chloro product.



Scheme 36. Synthesis of C2-symmetric chiral bisguanidine **52**.

Then we used another synthetic root for guanidine synthesis (Scheme 37). Treatment of 1*R*,2*R*-(+)-1,2-diphenylethylenediamine (**39**) with carbon disulphide in water and ethanol gives trans-(4*R*,5*R*)–diphenylimidazolidine-2-thione (**53)** in 71% yield.[151, 152] We tried several ways to couple **53** with 2,6-diamino-4-*tert*-butyltoluene (**49**), L-proline and L-prolinol to get guanidines **52**, **42** and **43**, respectively. The methods used including the application of Mercury promoted desulfurisation followed by nucleophilic attack on carbodiimide intermidiate,[130, 153, 154] condensation with DICDI (diisopropyl carbodiimide) in dichloroethane[155, 156] and by using quaternary ammonium permanganates under dry as well as under aqueous conditions.[157] But with all these methods we could not get success.

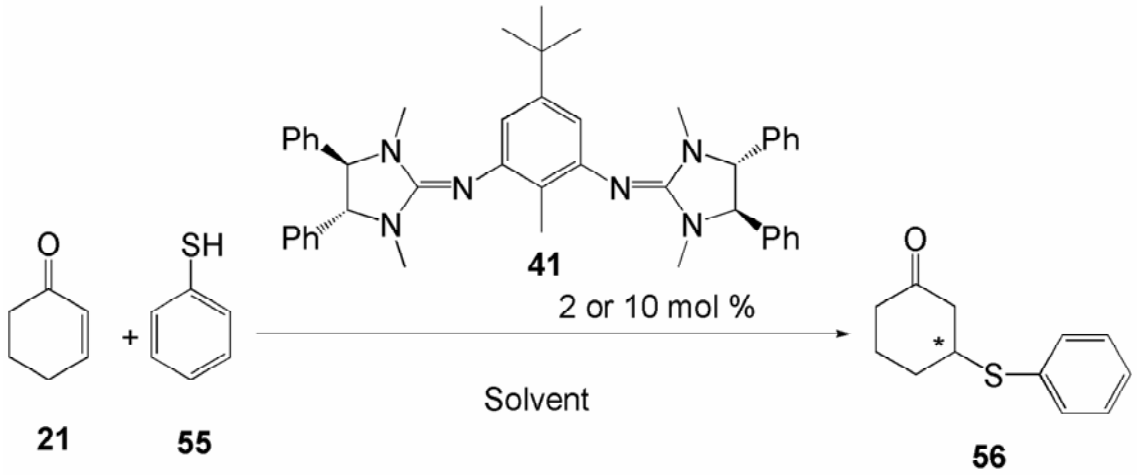
Then we activated **53** by methylation[158] to **54**. Refluxing **54** with L-proline, L-prolinol and 2,6-diamino-4-*tert*-butyltoluene (**49**) allowed us to prepare guanidines, **42** and **43**, respectively. In case of guanidine **42** and **43** we got desirable products in 64% and 51% yield, respectively, but for bisguanidine **52** we could not observe the product formation (Scheme 37).



Scheme 37. Synthesis of chiral guanidines for asymmetric catalysis.

4.4. Application of Chiral Guanidines in Asymmetric Michael Reactions

Catalysts **41, 42,** and **43** were used for various asymmetric reactions. First we carried out conjugate addition of thiophenol to cyclohex-2-en-1-one in the presence of bisguanidine **41** in CH_2Cl_2 and toluene at various temperatures (Scheme 38).



Scheme 38. **C2**-symmetric chiral bisguanidine 41 catalyzed conjugate addition of thiophenol to cyclohex-2-en-1-one.

The results of conjugate addition of thiophenol to cyclohex-2-en-1-one in the presence of bisguanidine **41** are summarized in Table 13.

Table 13. Conjugate addition of thiophenol to cyclohex-2-en-1-one catalyzed by C2-symmetric chiral bisguanidine **41**.

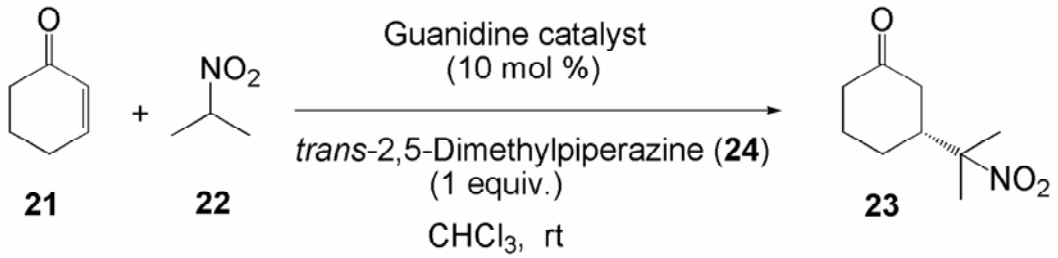
Entry	Catalyst (41) (mol %)	Solvent	Time (h)	Temp. (°C)	Yield (%)[a]	ee (%)[b]
1	10	CH_2Cl_2	3	RT	100	15
2	10	CH_2Cl_2	3	-31	100	16
3	2	Toluene	48	-31	96	16

[a] Isolated yields after column chromatography.
[b] % Enantioselectivities were determined by chiral HPLC analysis (Daicel Chiralpak AD) in comparison with authentic racemic material (n- Hexane: IPA (9: 1), 1 mL/ min).

With 10 mol % catalyst **41** in CH_2Cl_2, reaction was completed in three hours at room temperature and yielded 100% product with 15% enantioselectivity (entry 1, Table 13).

To reduce the rate of reaction and increase the enantioselectivity, the reaction was carried out at -31 °C, but no difference in the enantioselectivities was observed. The reaction completed in 3 hours and gave nearly the same ee (16% ee) with 100% yield (entry 2, Table 13). When toluene was used as a solvent and catalyst was used in 2 mol % instead of 10 mol %, no change in enantioselectivities was observed, but the rate of the reaction decreased and the reaction completed in two days with 96% yield and 16% ee (entry 3, Table 13).

Michael addition reaction of cyclohex-2-en-1-one and 2-nitropropane, as shown in Scheme 39, gave 16% ee with 6% yield when reaction was carried out in $CHCl_3$ with 10 mol % of catalyst and stoichiometric amount of *trans*-2,5-dimethyl piperazine as additive at room temperature for 9 days (entry 1, Table 14). There was no improvement observed by varying solvent, temperature and mol % of catalyst with bisguanidine **41**. The results are summarized in Table 14.



Scheme 39. Conjugate addition of 2-nitropropane to cyclohex-2-en-1-one catalyzed by chiral guanidine catalysts.

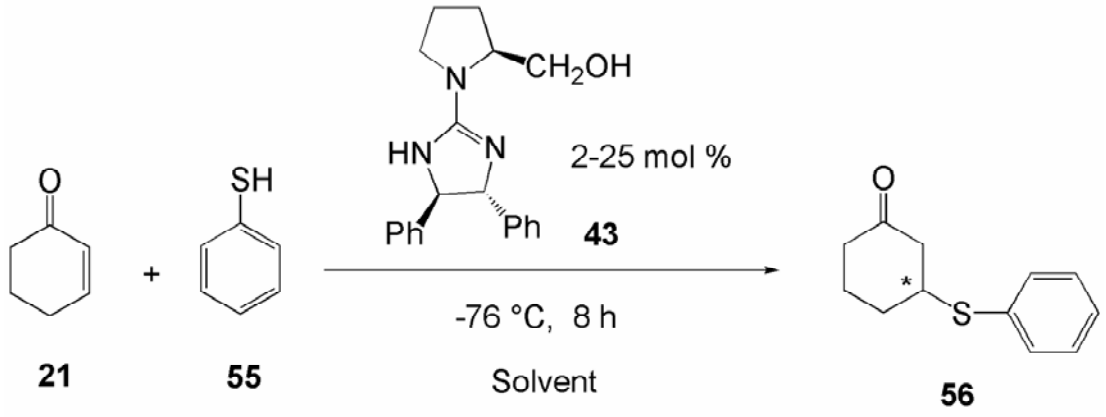
Table 14. Conjugate addition of 2-nitropropane to cyclohex-2-en-1-one catalyzed by chiral guanidines **41**, **42** and **43**.

Entry	Catalyst	Time (Days)	Yield (%)[a]	ee (%)[b]
1	**41**	9	6	16
2	**42**	11	No reaction	-
3	**43**	11	7	0

[a] Isolated yields after column chromatography.
[b] % Enantioselectivities were determined by chiral HPLC analysis (Daicel Chiralpak AS) in comparison with authentic racemic material.

When the same reaction (Scheme 39) was carried out in the presence of monoguanidines **42** and **43** for 11 days at room temperature, with catalyst **42** no product **23** was obtained (entry 2, Table 14). While with catalyst **43**, 7% yield was obtained, but the product did not show any enantioselectivity (entry 3, Table 14).

Next we studied the conjugate addition of thiophenol to cyclohex-2-en-1-one in the presence of guanidine catalyst **43** by varying reaction conditions like solvent and loading of catalyst. All reactions were carried out for 8 hours at -76 °C (Scheme 40). The results are summarized in Table 15.



Scheme 40. Guanidine **43** catalyzed conjugate addition of thiophenol to cyclohex-2-en-1-one.

Table 15. Conjugate addition of thiophenol to cyclohex-2-en-1-one catalyzed by chiral guanidine **43**.

Entry	Catalyst (43) (mol %)	Solvent	Yield (%)[a]	ee (%)[b]
1	2	CH_2Cl_2	<10	5
2	10	CH_2Cl_2	93.4	4
3	25	CH_2Cl_2	70	0
4	2	toluene	54	15
5	2	toluene	<10	6[c]

[a] Isolated yields after column chromatography.
[b] % Enantioselectivities were determined by chiral HPLC analysis (Daicel Chiralpak AD) in comparison with authentic racemic material (n- Hexane: IPA (9: 1), 1 mL/ min.).
[c] Addition of thiophenol to 2-cyclohexene-1-one and catalyst solution instead of addition of 2-cyclohexene-1-one to thiophenol.

In CH_2Cl_2 and at -76 °C 2 mol % of catalyst **43** gave less than 10% yield with only 5% enantioselectivity in 8 hours (entry 1, table 15). While under the same reaction conditions but with 10 mol % catalyst, higher yield was obtained, but enantioselectivity remained low (93.4% yield and 4% ee; entry 2, Table 15). To increase the enantioselectivity the loading of catalyst was increased at the same temperature. However the yield decreased to 70% and the racemic product was obtained (entry 3, Table 15).

When solvent was changed to toluene, with only 2 mol % catalyst at -76 °C in 8 hours, 54% product was yielded, while enantioselectivity also increased to 15% ee (entry 4, Table 15).

With the same reaction conditions we changed the mode of addition of substrate and nucleophile. To increase the selectivity, we added thiophenol to a solution of cyclohex-2-en-1-one and catalyst in toluene at -76 °C but less than 10% yield was obtained and enantioselectivity also decreased to 6% (entry 5, Table 15).

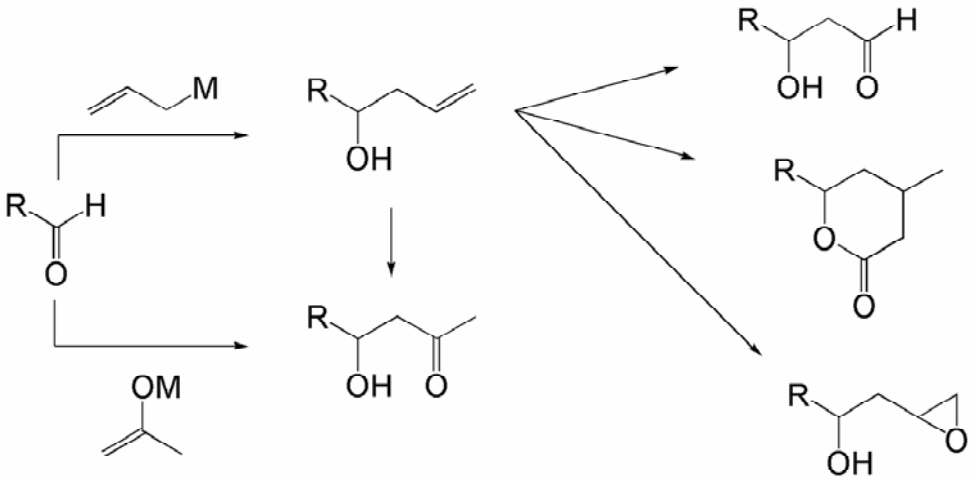
Thus, with new chiral guanidines we achieved high yields (up to 100%), but low enantioselectivities (up to 16% ee) in conjugate addition of thiophenol to cyclohex-2-en-1-one. Further studies, using different chiral as well as achiral additives, might pave the way to more effective guanidine based catalytic systems for this enantioselective C-C bond forming reaction and different other important transformations.

5. Synthesis and Application of New Chiral Bis-formamide in Asymmetric Allylation of aldimines

5.1. State of the art

The reactions of allylmetals with aldehydes and imines are among the most useful carbon-carbon bond forming processes, providing efficient ways to synthetically valuable homoallylic alcohols and homoallylic amines, respectively.

The reaction of allylic organometallic reagents with aldehydes is synthetically analogous to the aldol addition of metal enolates, since the resulting homoallyl alcohol can be easily converted to the aldol (Scheme 41).[159] Further, allylmetal additions have significant advantages over aldol condensations since the alkenes may be readily transformed into aldehydes, may undergo a facile one carbon homologation to 6-lactones via hydroformylation, or may be selectively epoxidized to introduce a third chiral center. Accordingly, the allylic organometallic reaction has attracted the attention of a wide range of organic chemists, and the allylic method has become one of the most useful procedures for controlling the stereochemistry in acyclic systems.[160]

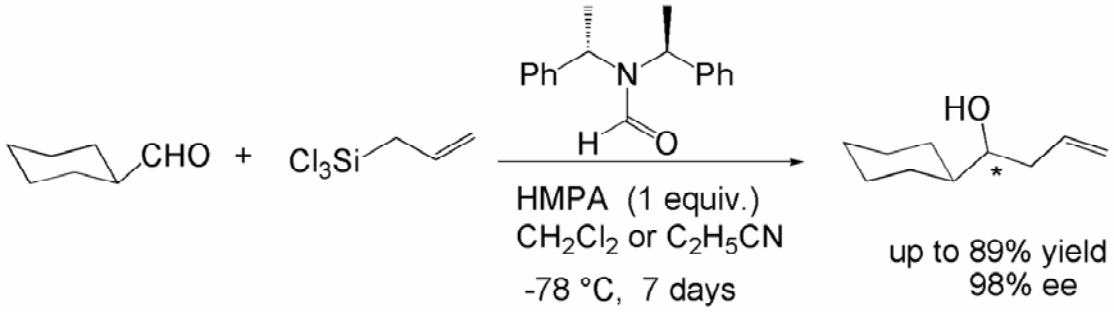


Scheme 41. Allyl metal aldehyde condensation and aldol reaction.

Chiral nitrogen containing compounds are widely distributed in nature and include many biologically important molecules. In these compounds, the nitrogen containing functional

groups are known to play important roles for their bioactivities. For the synthesis of these chiral nitrogen containing building blocks, use of imines as electrophiles is the most promising and convenient route. Similar to homoallylic alcohols homoallylic amines are also useful intermediates for the synthesis of versatile nitrogen containing compounds which are biologically important.[161]

It has been reported that chlorosilanes which are weak Lewis acids served as effective enantioselective Lewis acid catalysts in the presence of chiral Lewis bases. Allyltrichlorosilane is generally preferred over other allylmetals because of its low toxicity. Several weak Lewis bases (or neutral coordinate organocatalysts; NCOs) are reported as a catalyst in asymmetric allylation. For asymmetric allylation Lewis bases like chiral formamides[162], phosphoramides[163-165] and pyridine N-oxides[103, 166-170] have been developed.



Scheme 42. Kobayashi's chiral formamide used for asymmetric allylation of aldehydes.

Kobayashi has reported the asymmetric allylation of aldehyde by chiral formamide to achieve very high yields and enantioselectivities (up to 89% yield and 98% ee).[162]

Denmark and co-workers reported chiral phosphoramide catalysts for the asymmetric allylation of aldehydes (Figure 19). These catalysts promote reaction in catalytic amount in very short time (6 hours) while Kobayashi derived formamides (Scheme 42) takes longer time (7 days) to complete allylation even after using stoichiometric amount of catalyst. These phosphoramide catalysts gave higher yields (up to 94%) and enantioselectivities (up to 94%).

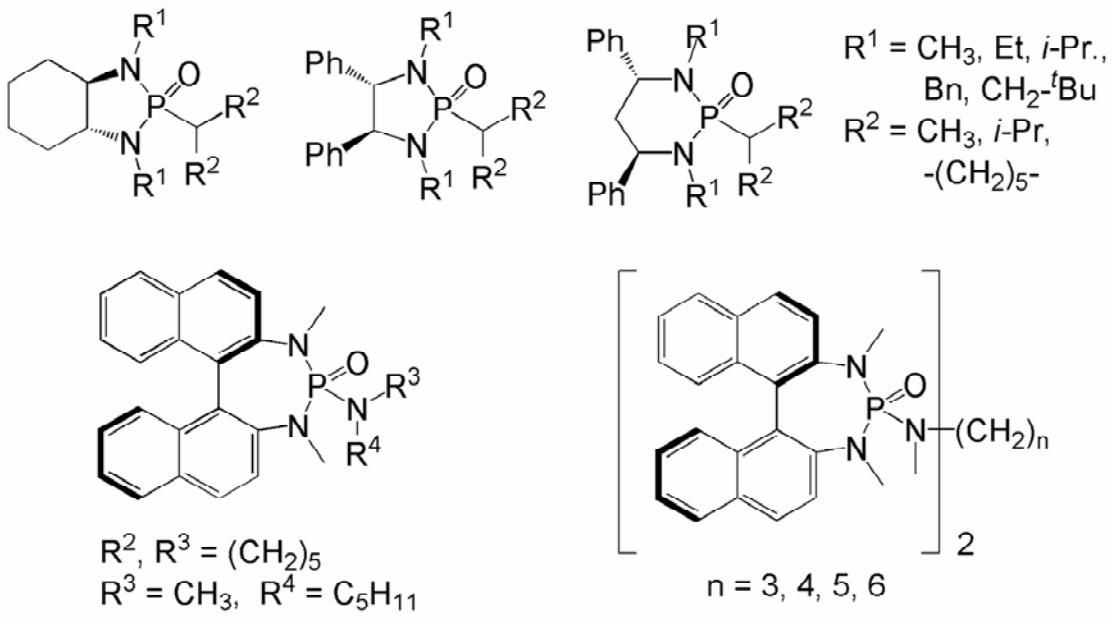


Figure 19. Denmark's phosphoramide catalysts for asymmetric allylation of aldehydes.

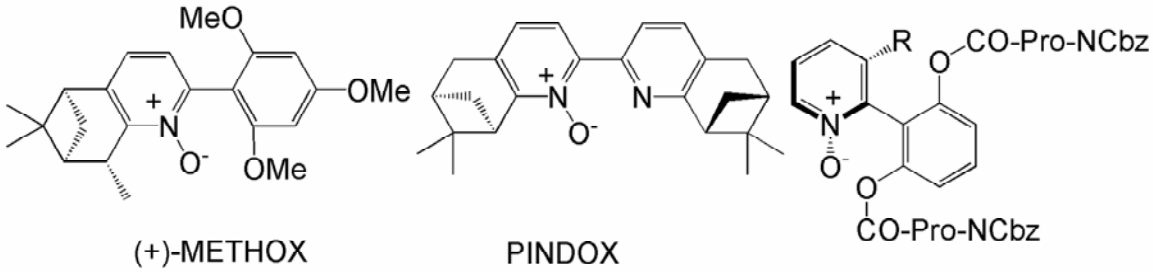
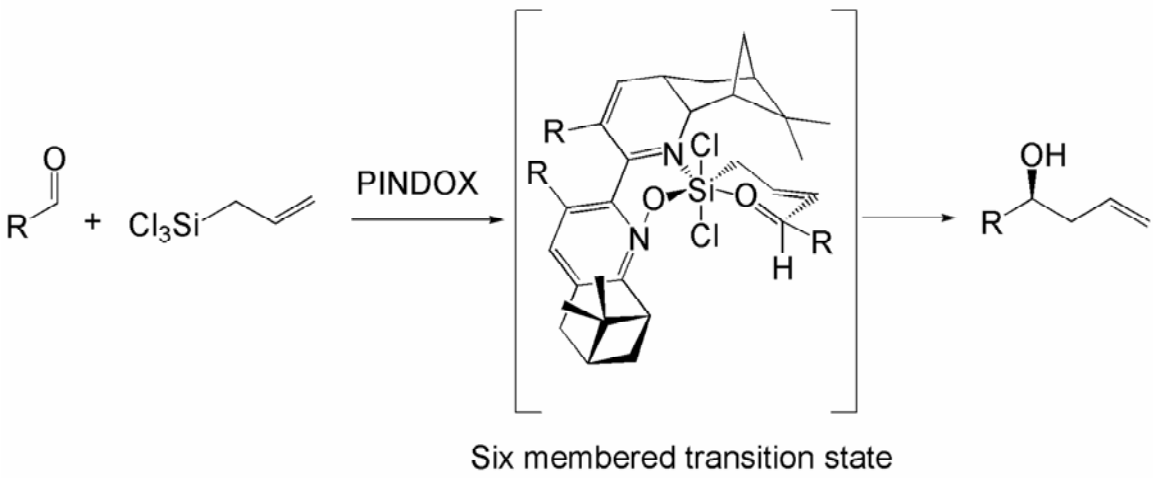


Figure 20. Chiral N-oxides used in asymmetric allylation of aldehydes.

Malkov and co-workers used pyridine derived N-oxides to synthesize highly enantiopure (98% ee) homoallylic alcohols with good yields (up to 78%).[170] The same group reported on PINDOX and (+)-METHOX (Figure 20) as catalysts for asymmetric allylation of aldehydes to achieve higher yields and ee's (up to 85% and 95% yields and 98% ee and 96% ee, respectively).[166, 167] Apart from Snappers report (Scheme 12),[103] Hayashi and co-workers reported chiral bipyridine N,N'-dioxides (in to 99% yields and 94% ee) for asymmetric allylation of aldehydes.[169]

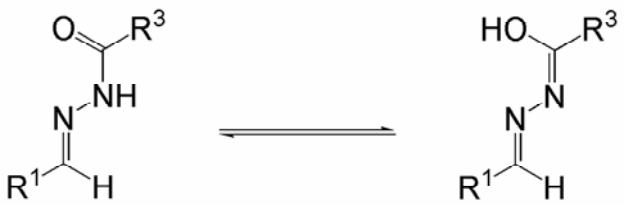


Scheme 43. Proposed transition state for PINDOX catalyzed asymmetric allylation of aldehydes.

Molkov and Kocovsky proposed six membered transition states for the asymmetric allylation of aldehydes with allyltrichlorosilane (Scheme 43). Silicon is co-ordinates with N-oxide and Nitrogen atom of pyridine.

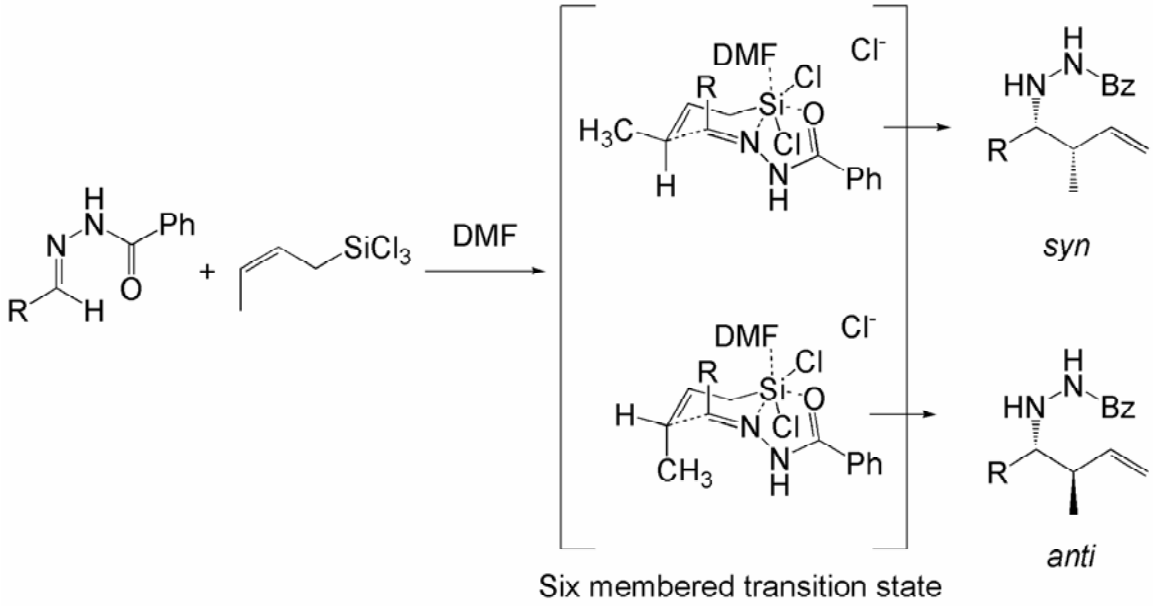
Kobayashi and co-workers have found that N-acylhydrazones in achiral Lewis bases like DMF, HMPA without the use of any catalyst undergo smooth diastereoselective allylation with allyltrichlorosilane.[171-173] While N-acylhydrazones were found to be reactive for the allylation, it was observed that simple imines were resistant to allyltrichlorosilanes under the same reaction conditions.[174]

N-acylhydrazones having a –NHCOR group lay in a tautomerization between amide form and imidic acid form under the reaction conditions, and that the latter might be responsible for the high reactivity toward allyltrichlorosilanes (*N*-benzoylhydrazone having an *N*-methyl group did not undergo allylation with allyltrichlorosilane because of restriction of tautomerization.).[174]



Scheme 44. Tautomerization between amide form and imidic acid of N-acylhydrazone.

Also it is still unclear whether the hydroxyl group of imine forms a covalent bond with allyltrichlorosilanes or simply coordinates to the silicon atom.



Scheme 45. Proposed transitation state for allylation of *N*-benzoylhydrazone with allyltrichlorosilane in DMF**.**

In the proposed transition state the bond between Silicon and Oxygen of hydrazone plays an important role in it. Coordination of a Lewis base to the silicon atom would enhance the nucleophilicity of allyltrichlorosilane, while the Lewis acidic silicon activates the hydrazone. Both factors would be essential for the reaction to take place. Accordingly, coordination of the benzoyl carbonyl group to the silicon atom must be essential, because benzoylhydrazones reacted with allyltrichlorosilane even in noncoordinating solvents like CH_2Cl_2 where external coordination is absent. The coordination is also likely to serve for stabilization of the transition structures.

So far only chiral sulfoxide derivatives[175] and BINAP derivative of phosphine oxide [176] are reported for asymmetric allylation of N-acylhydrazones to get highly enantiopure amines (up to 95% yields, 98% ee and to 91% yields, 98% ee, respectively).

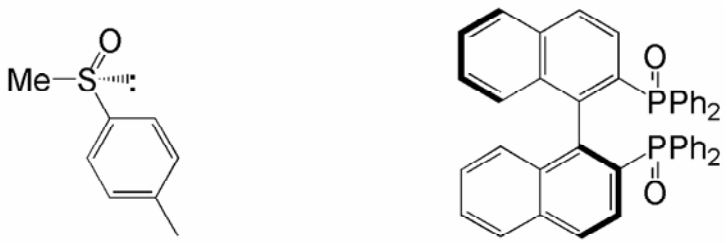
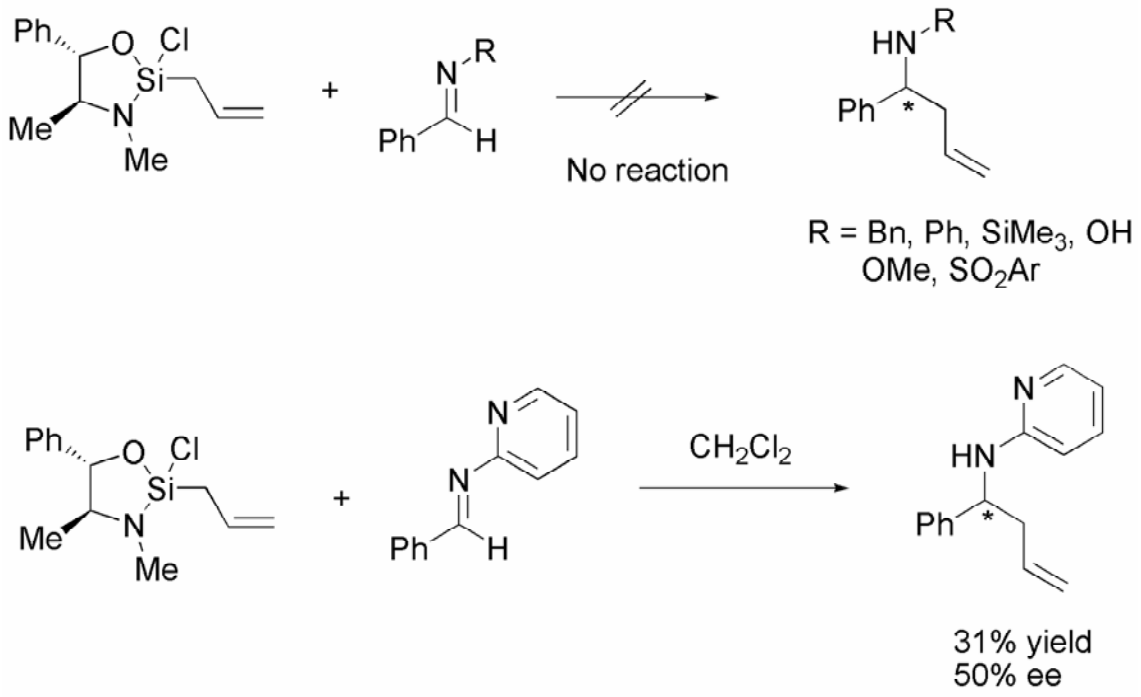


Figure 21. Chiral sulfoxide and phosphine oxide catalysts for asymmetric allylation of N-acylhydrazone.

Some drawbacks of these NCOs are; they used in stoichiometric amounts (2-3 equiv.) and the reactions are substrate specific. Also asymmetric allylation of simple imines is not reported so far.



Scheme 46. Allylation of aldimines with pseudoephedrine derived strained silacycle as a reagent used by Leighton and co-workers.

Leighton and co-workers have reported on the use of pseudoephedrine derived strained silacycle as a reagent for allylation of aldimines (Scheme 46). They achieved up to 80% yield and 98% ee when used N-acylhydrazone was used as substrate. But they could not succeed in product isolation when Nitrogen of aldimine was protected by Bn, Ph, $SiMe_3$, OH, OMe and SO_2Ar. Interestingly, when the aldimine was protected with pyridine

moiety (Lewis basic group) homoallylic amine was obtained in 31% yield and 50% ee.[177]

5.2. Objective and goals

While much progress has been made recently in catalytic enantioselective reactions of aldehydes and ketones such as aldol reaction, allylation, Diels-Alder, cyanation reactions, reduction, etc., progress in catalytic enantioselective reactions of imines is rather slow. There are some difficulties in performing catalytic enantioselective reactions of imines. Imines often exist as mixtures of geometrical isomers ascribed to the C-N double bonds or under rapid equilibrium states. Therefore, plural transition states exist when Lewis acids coordinate imines, which often decrease selectivity. In addition, most Lewis acids are trapped by the basic nitrogen atoms of the starting materials (imines and/or products), and therefore, catalytic reactions using imines as electrophiles and catalysts are difficult to perform.

The first example of allylation of imines derived from aldehydes and 2-aminophenols with allyltrichlorosilane using DMF as neutral coordinate-organocatalyst (NCO) to afford the corresponding homoallylic amines has been reported in 2003 by Kobayashi and co-workers.[174] However, no enantioselective allylation of these simple imines with allyltrichlorosilane has been attained to date.

With an interest in developing an asymmetric organocatalytic version of this reaction we have designed new proline derived C2-chiral bisformamides with a chiral 1,2-diaminocyclohexane as a linker (Figure 22).

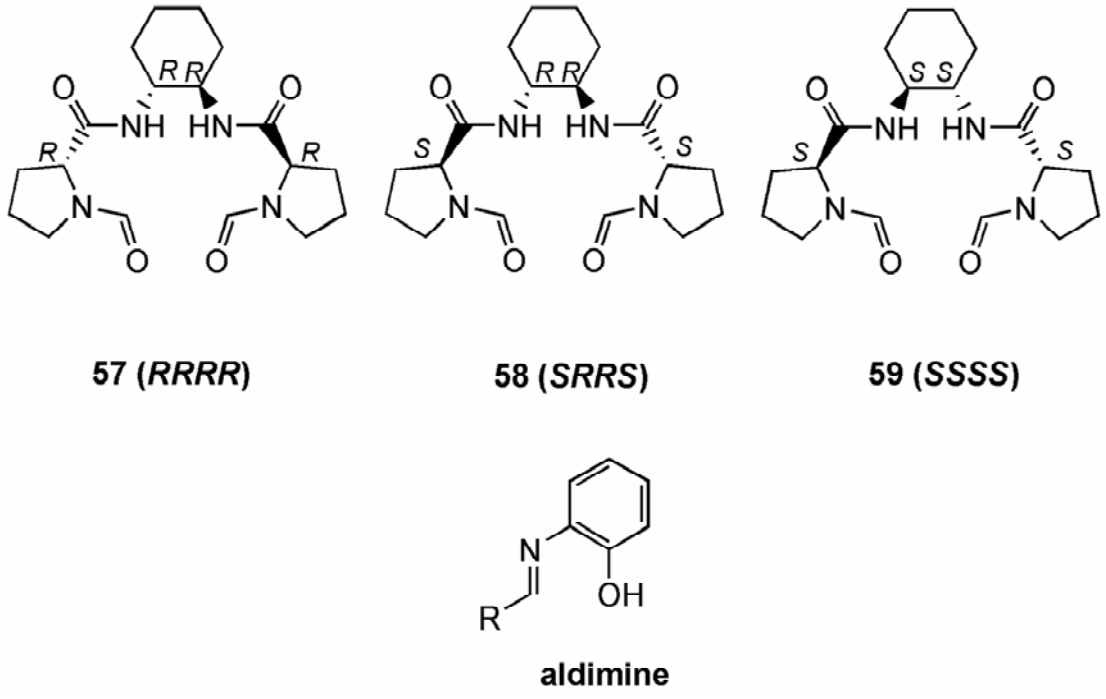


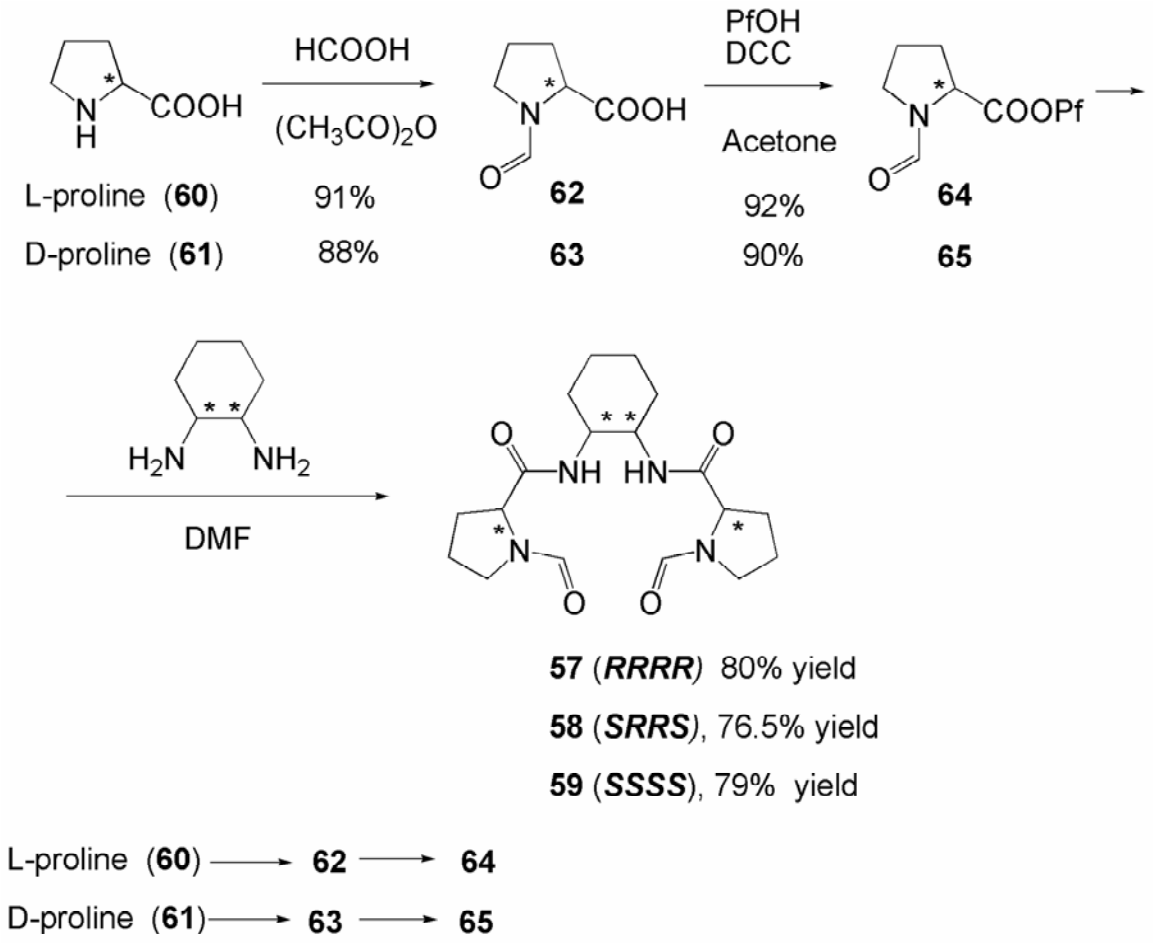
Figure 22. Proline derived new C2-symmetric chiral bisformamides for asymmetric allylation of aldimine.

It is generally accepted that an aldimine is less reactive toward nucleophilic addition than its corresponding aldehyde owing to the difference in electronegativity between Oxygen and Nitrogen, and the steric hindrance present in the aldimine. The product formed after allylation of aldimines i.e. homoallylic amines are useful intermediates for the synthesis of versatile nitrogen containing compounds which are biologically important.[161] Hence we decided to use the C2-chiral bisformamides as NCOs (Neutral Coordinate Organocatalysts) for asymmetric allylation of aldimines (Figure 22).

5.3. Results and Discussion

New C2-chiral bisformamides **57**, **58** and **59** were synthesized from readily available proline as shown in Scheme 47. N-formyl proline **62** and **63** were synthesized in 91% yield from L-proline (**60**) and D-proline (**61**), respectively by known literature method,[178] i.e. by treatment of proline with an excess of formic acid and acetic anhydride. Treatment of **62** and **63** with pentafluorophenol and DCC in acetone gave

compound **64** and **65** in 92% yield, respectively. Coupling of **64** or **65** with chiral 1,2-diaminocyclohexane obtains bisformamide catalysts.



Scheme 47. Synthesis of proline derived C2-symmetric chiral bisformamdie **57**, **58** and **59**.

Proton of aldehyde group in **57**, **58** and **59** give three singlets (δ 8.006, 8.066 and 8.169 ppm, respectively) at room temperature when ^{1}H NMR of bisformamide was measured in DMSO (Figure 23). At 100 °C it shows two broad singlets at δ 8.006 and 8.192 ppm (Figure 24). While at 150 °C only one sharp peak at δ 8.154 ppm has been observed (Figure 25).

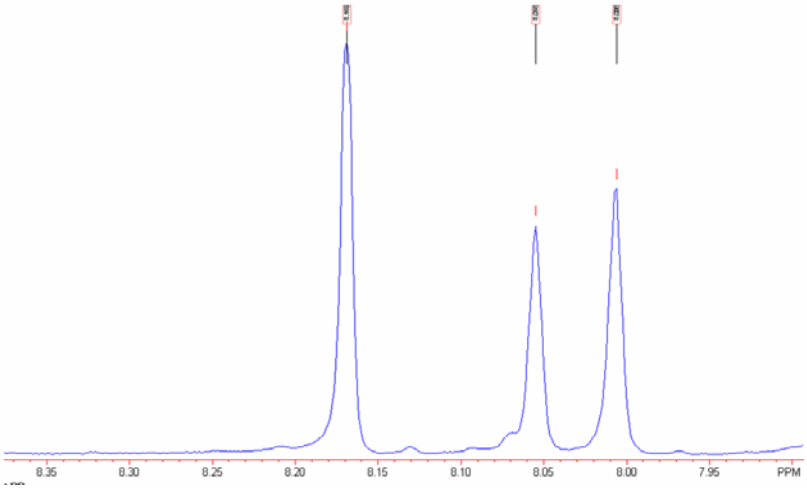


Figure 23. ^{1}H NMR signals of aldehydic proton of bisformamide **57** at room temp. in DMSO.

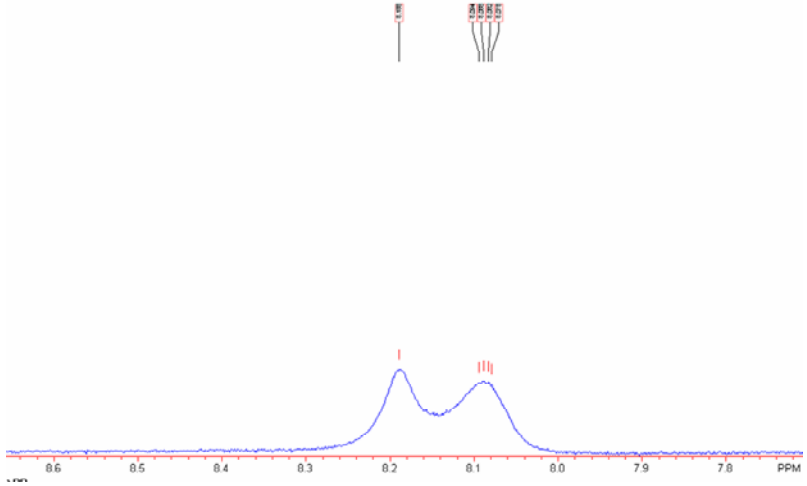


Figure 24. ^{1}H NMR signals of aldehydic proton of bisformamide **57** at 100 °C in DMSO.

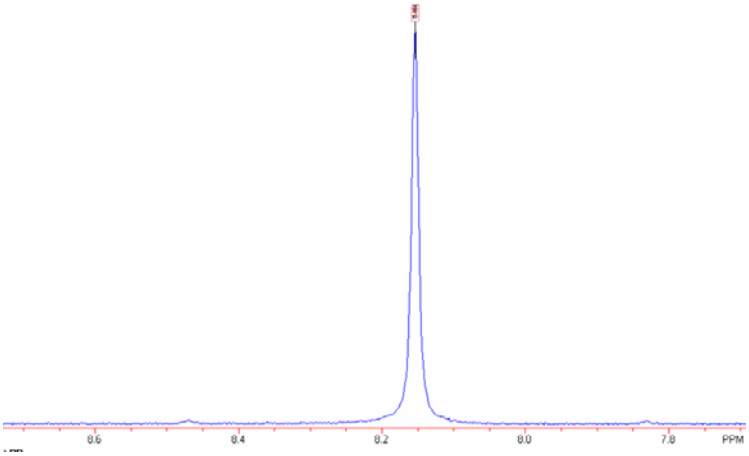
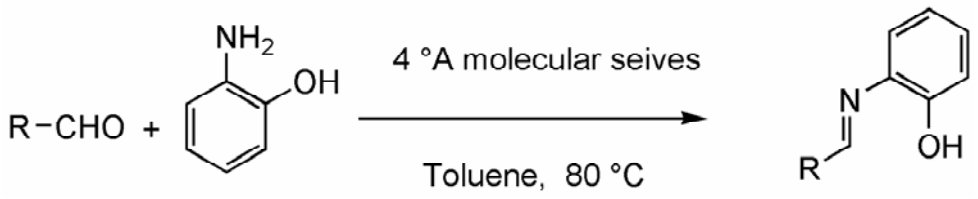


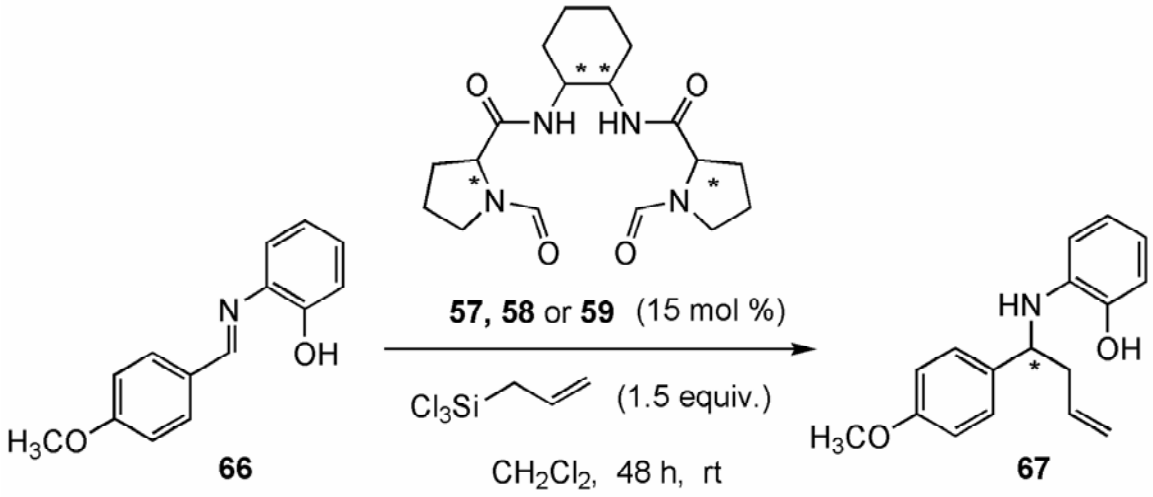
Figure 25. ^{1}H NMR signal of aldehydic proton of bisformamide **57** at 150 °C in DMSO.

Aldimines were prepared by heating aldehydes with *ortho-hydroxy* aniline in toluene at 80 °C as described in literature (Scheme 48).[179]



Scheme 48. Synthesis of aldimines for asymmetric allylation reaction.

We used *4-methoxy*-benzaldehyde derived aldimine for optimization of reaction. Less toxic allyltrichlorosilane was used as a nucleophile (1.5 equiv.). Reactions were carried out at room temperature in the presence of 2 equivalents of new C2-symmetric chiral bisformamdies **57**, **58** and **59** in CH_2Cl_2 (Scheme 49). The results are summarized in Table 16.



Scheme 49. Screening of chiral bisformamides for asymmetric allylation of aldimine **66**.

Table 16. Screening of chiral bisformamide catalysts in asymmetric allylation of aldimines.

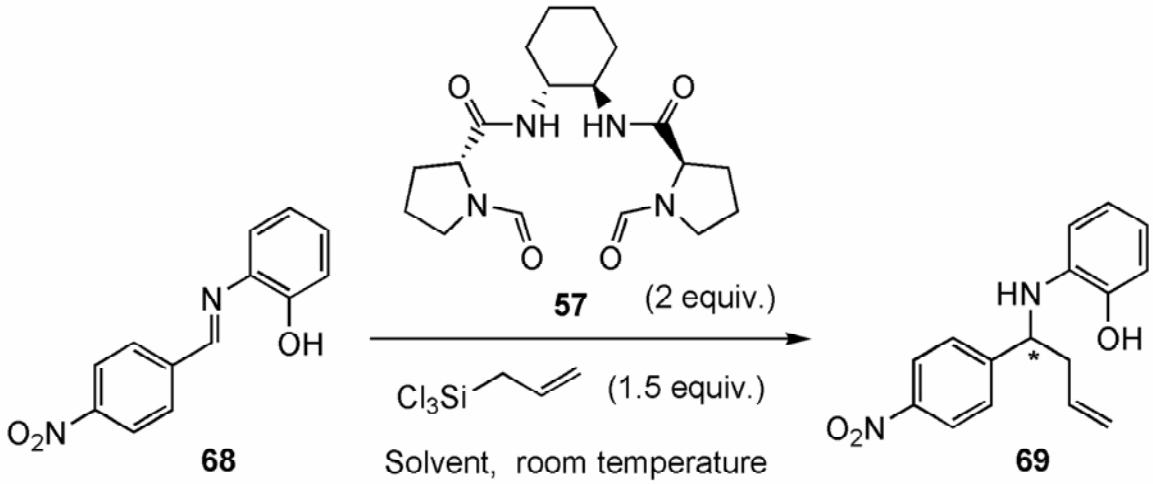
Entry	Catalyst	Conversion (%)[a]	ee (%)[b]
1	**57**	<10	78
2	**58**	<10	58
3	**59**	<10	65

[a] Determined by ^{1}H NMR spectroscopy.
[b]Enantioselectivities were determined by chiral HPLC analysis in comparison with authentic racemic material

In all cases we obtained low conversions (<10%) but the enantioselectivities were moderate to good (58-78% ee). Catalyst **57** gave 78% ee, while with catalyst **58** and **59** we achieved low enantioselectivities as compared to that of catalyst **57** (58% ee and 65% ee, respectively). In case of catalyst **57** and **58** the same enantiomer is obtained as major product while catalyst **59** gives opposite enantiomer in excess. These results reveal that only stereochemistry of proline moiety in the catalyst is responsible for the stereoselectivity of product and not that of cyclohexanediamine linker. In the case of catalysts **58** and **59** the stereochemistry on cyclohexane ring is the same, but they gave the product with different absolute configurations.

The bisformamide **57** was found to be the most promising regarding enantioselectivity. Therefore, we carried out further studies with catalyst **57** and also we changed our substrate from *4-methoxy*-benzaldehyde derived aldimine **66** to *4-nitro*-benzaldehyde derived aldimine **68**.

First we carried out reactions in different solvents. The results of solvents screening are summarized in Table 17.



Scheme 50. Allylation of aldimine in the presence of bisformamide **57** in different solvents.

Table 17. Optimization of reaction conditions of allylation reaction in different solvents.

Entry	Solvent	Time (days)	Conversion (%)[a]	ee (%)[b]
1	CH_3CN	4	Traces	nd[c]
2	Toluene	4	Traces	nd[c]
3	$CHCl_3$	4	54	43
4	CH_2Cl_2	2	93	54

[a] Determined by ^1H NMR spectroscopy.
[b]Enantioselectivities were determined by chiral HPLC analysis in comparison with authentic racemic material.
[c] Not determined.

Acetonitrile and toluene as solvents were not found suitable for allylation of aldimine. After four days only some traces of product were observed (entries 1 and 2, Table 17). In chloroform 54% conversion and 43% enantioselectivity was observed after four days (entry 3, Table 17). To our delight, the use of CH_2Cl_2 as a solvent significantly improved the reaction yield (93%) as well as slightly improving the enantioselectivities (54%) relative to that with $CHCl_3$. The fact that suitable additives and co-catalysts can enhance the yield and in many cases also the enantioselectivity, discussed by the excellent review by Shibasaki and co-authors,[116] has motivated us for the further study.

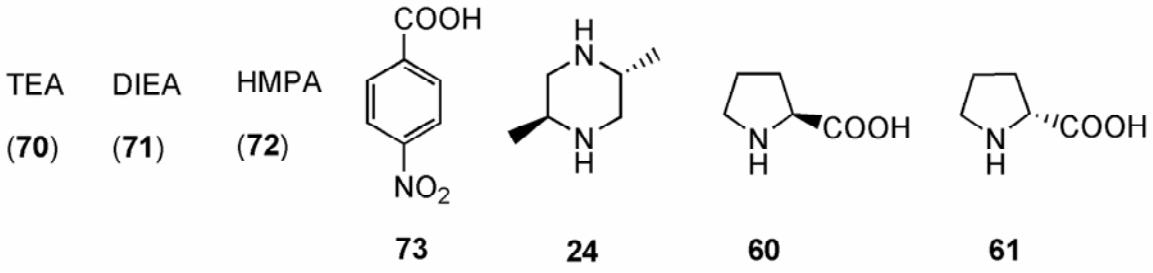
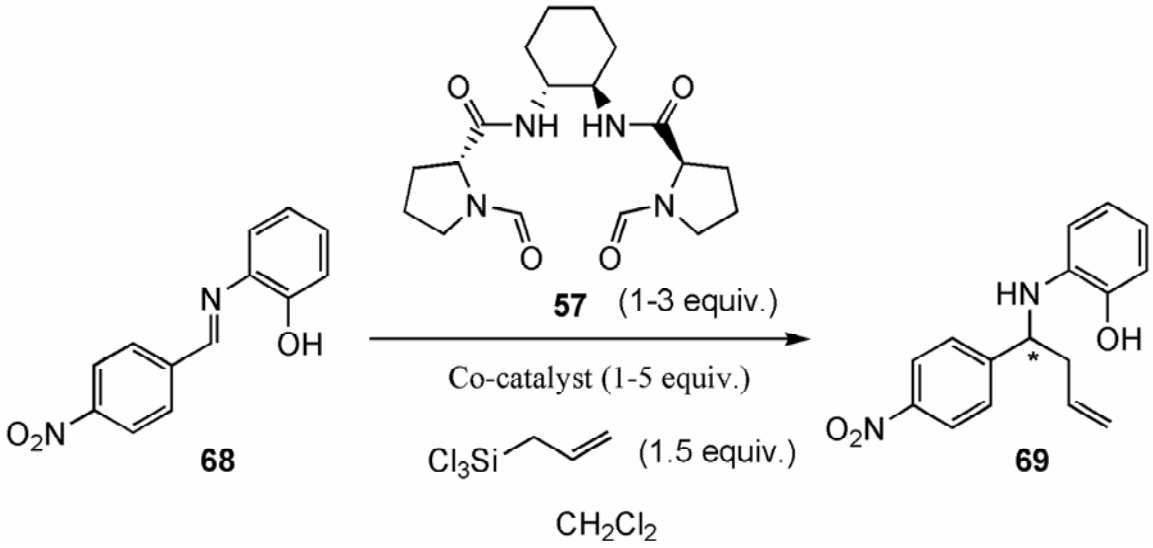


Figure 26. Co-catalysts used for allylation of aldimine.

Bases like triethylamine (TEA), diisopropylethylamine (DIEA), *trans*-2,5-dimethyl-piperazine and Lewis acid hexamethyl phosphoramides (HMPA) etc. were used either with or without bisformamide catalyst **57** (Scheme 51). The results are summarized in Table 18.



Scheme 51. Allylation of aldimine catalyzed by bisformamide catalyst **57** and co-catalysts.

Table 18. Allylation of aldimine **68** using different co-catalysts in CH_2Cl_2

Entry	Catalyst (equiv.)	Additive (equiv.)	Time, (h)	Temp. (°C)	Conversion (%)[a]	ee (%)[b] (±)[c]
1	2	70 (1)	48	RT	83	61 (-)
2	2	71 (1)	48	RT	78	56 (-)
3	2	72 (1)	48	RT	98	38 (-)
4	2	72 (1)	96	0	94	46 (-)
5	2	72(1)	96	-78	72	41 (-)
6	2	72 (0.2)	120	0	100	48 (-)
7	2	73 (1)	48	RT	92	71 (-)
8	2	73(5)	48	RT	82	62 (-)
9	2	24 (1)	48	RT	94	72 (-)
10	2	24 (1)	96	0	39	68 (-)
11	2	24 (5)	48	RT	2	15 (-)
12	1	24 (5)	48	RT	3	51 (-)
13	2	24 (0.5)	48	RT	86	69 (-)
14	3	24 (5)	48	RT	3	65 (-)
15	2	61 (5)	0.5	RT	98	20 (-)
16	2	60 (5)	0.5	RT	>99	82 (-)
17	-	61 (5)	96	RT	No reaction	-
18	-	60 (5)	96	RT	2	Nd[d]
19	2	60 (5)	96	0	No reaction	-
20	3	60 (5)	0.5	RT	98	82 (-)
21	3	60 (2)	4	RT	92	84 (-)
22	2	60 (2)	4	RT	97 (94)[e]	83 (-)
23	1	60 (2)	12	RT	92	84 (-)

[a] Determined by ^{1}H NMR spectroscopy.
[b] Enantioselectivities were determined by chiral HPLC analysis in comparison with authentic racemic material.
[c] The sign of the optical rotation of product.
[d] Not determined.
[e] The value in parenthes shows isolated yield after column chromatography.

Enantioselectivities of homoallylic amine **69** was increased when bases like TEA (**70**) and DIEA (**71**) were used as co-catalysts (one equiv. each) for allylation in the dichloromethane in the presence of 2 equivalents of catalyst **57** at room temperature after 48 hours. With TEA 83% conversion and 61% ee was observed (entry 1, Table 18) while with DIEA homoallylic amine in 78% conversion and 56% ee was obtained (entry 2, Table 18). TEA proved to be better co-catalyst than DIEA. With TEA both conversion and enantioselectivity was increased but when DIEA was used instead of TEA the conversion was dropped to 78% (while bisformamide derivative **57** alone gave 93% conversion).

Next we used hexamethyl phosphoramides (**72**) as a co-catalyst under the same reaction conditions. As expected, conversion increased to 98% but the enantioselectivity decreased to 38% (entry 3, Table 18). The low ee observed is an indication that hexamethyl phosphoramides (**72**) catalyze itself the reaction and is responsible for racemisation of compound. To avoid this it is possible to reduce the rate of reaction by carrying out reaction at low temperature, -0 °C. As expected the reaction has competed only in 96 hours at 0 °C instead of 48 hours at room temperature, and the conversion was almost the same (94%) and the ee was increased to 46% (entry 4, Table 18). Further lowering temperature to (-78 °C) leads to a decrease of both conversion and ee (72% conversion and 41% ee; entry 5, Table 18). Then we decreased the amount of co-catalyst **72** to 20 mol % and the reaction was carried out for a longer time (120 hours). Interestingly, conversion was better at 0 °C than -78 °C (entries 4 vs. 5, Table 18). We achieved 100% conversion at 0 °C but enantioselectivity was almost the same i.e. 48% (entry 6, Table 18).

Next we decided to use *para*-nitrobenzoic acid (**73**) as a co-catalyst for allylation of aldimine **68**. The idea was that acid would protonate the Nitrogen of aldimine and facile the nucleophilic attack on it. With one equivalent of co-catalyst **73** and 2 equivalents bisformamide **57** after 48 hours at room temperature 92% conversion of product **69** was observed and the enantioselectivity was also increased to 71% (entry 7, Table 18). Our attempt to improve the enantioselectivity by increasing the amount of co-catalyst **73** to 5 equivalents failed and we got only 82% conversion and 62% ee (entry 8, Table 18).

Next we tested the achiral *trans*-2,5-dimethylpiperazine (**24**) as a co-catalyst. We achieved higher conversion (94%) and ee (72%) when 1 equivalent of *trans*-2,5-dimethylpiperazine (**24**) was used with 2 equivalents of new chiral bisformamide **57** after 48 hours at room temperature (entry 9, Table 18). Conversion (39%) and enantioselectivity (68% ee) was decreased when reaction was carried out at 0 °C (entry 10, Table 18). Also the reaction takes longer time (96 hours). Interestingly, with 2 equivalent bisformamide **57** and 5 equivalent *trans*-2,5-dimethyl piperazine (**24**) conversion and ee was dropped (2% conversion and 15% ee) after 48 hours at room temperature (entry 11, Table 18). When loading of bisformamide **57** was decreased to 1 equivalent no improvement was observed in conversion (3%) but the enantioselectivity was increased to 51% (entry 12, Table 18).

Next we decreased the amount of *trans*-2,5-dimethyl piperazine (**24**) to 0.5 equivalents (with 2 equiv. bisformamide **57**) and got 86% conversion and 69% ee after 48 hours at room temperature (entry 13, Table 18). Though both conversion and ee were good, when 0.5 equiv. of co-catalyst **24** was used (entry 13, Table 17) in reaction but our former results with 1 equiv. co-catalyst (entry 9, Table 18) was better than this results.

Best results of allylation of **68** to **69** were obtained when 2 equivalent bisformamide **57** was used with stoichiometric amount of *para-nitro* benzoic acid **73** (92% conversion and 71% ee; entry 7, Table 18) and t*rans*-2,5-dimethyl piperazine (**24**) (94% conversion and 72% ee; entry 9, Table 18) at room temperature. But still there was scope to increase the enantioselectivities. Also in both cases (entries 7 and 9, Table18) reaction time was more (48 hours). It was our aim to increase ee's in short period of reaction time. From co-catalyst **73** and **24** it was proved that both acidic and basic residues are better co-catalysts, hence we decided to use chiral amino acids like L-proline (**60**) and D-proline (**61**) as co-catalysts. Both **60** and **61** are having acidic as well as basic functionalities together and they are chiral too. When 5 equivalents of **60** and **61** were used along with 2 equivalents bisformamide **57**, surprisingly both reactions were completed in 30 minutes. Conversion and ee's were increased when L-proline was used as a co-catalyst (>99% conversion, 82% ee; entry 16, Table 18) but interestingly ee was dropped with D-proline as a co-catalyst (98% conversion, 20% ee; entry 15, Table 18). It is clear that bisformamide **57** and D-proline (**61**) are having negative effect on enantioselectivity and

they represent a mismatching pair of co-catalysts. Interestingly, without bisformamide both L-proline (**60)** and D-proline (**61)** are unable to catalyze reaction. Reaction has not shown any progress even after 96 hours when 5 equivalents of D-proline (**61**) alone was used (entry 18, Table 18). After the same reaction time L-proline (**60**) alone gave only 2% conversion (entry 18, Table 17). Notably, co-catalysts **60** and **61** are not soluble in CH_2Cl_2 and the system remains heterogenous till the addition of bisformamide catalyst **57** to the reaction mixture: co-catalysts **60** and **61** in combination with bisformamide became soluble and the reaction mixture is homogenous. Most probably, a covalent bond between basic nitrogen of L-proline and Si-atom of allyltrichlorosilane forms in the reaction mixture, providing a chiral allylating reagent. This suggestion was supported by ^{1}H NMR spectroscopic experiments: upon addition of L-proline to a solution of allyltrichlorosilane in $CDCl_3$, the chemical shift of two allylic protons at δ 5.145-5.213 ppm (m, 2H) were shifted to δ 5.123-5.185 ppm.

The complex formation is also confirmed by mass spectroscopy (ESI-MS: m/z 230.8 [M + Na]$^+$, EI-MS: m/z 218.0 [M],.

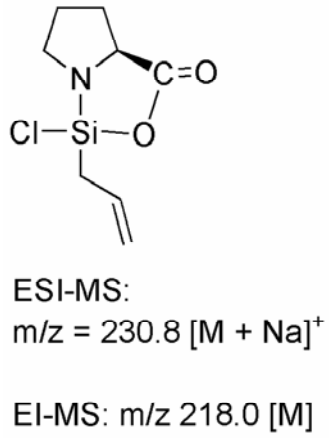


Figure 27. New reagent formed by the reaction of L-proline and allyl trichlorosilane.

These results clearly indicate that the main effect of catalyst is coming from bisformamide **57**. Our further attempts to increase enantioselectivity by reducing temperature of the reaction mixture failed and no product formation was observed even after 96 hours at 0 °C in the presence of both bisformamide **57** and L-proline (**60**) in CH_2Cl_2 (entry 19, Table 18). L-proline remains insoluble at 0 °C. Increasing the amount of bisformamide **57** to 3 equivalents also not shown any change in conversion and ee and

the reaction was completed in 30 minutes with 98% conversion and 82% ee (entry 20, Table 18). Then we tried to reduce the amount of co-catalyst from 5 equiv. to 2 equiv. and we achieved 92% conversion and 84 % ee, but the reaction time increased to 4 hours (entry 21, Table 18). With 2 equivalents of each bisformamide **57** and L-proline (**60**) 97% conversion (94% isolated yield) and 83% ee was observed (entry 22, Table 18). When we reduced the loading of bisformamide to 1 equivalent no change in conversion and ee was observed, but the reaction took longer time to complete (12 hours, 91.7% conversion, 84% ee; entry 23, Table 18).

From these results, we propose plausible transition-state model, which reasonably explain the absolute configuration of the allylation adduct.

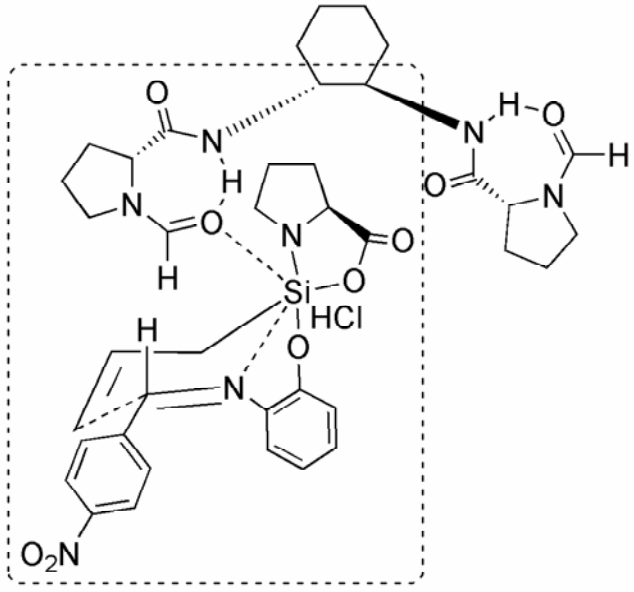
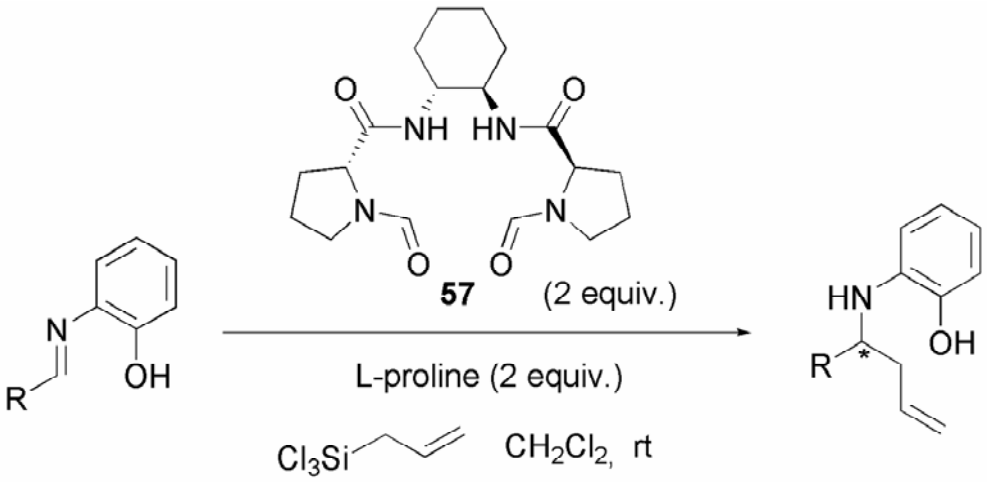


Figure 28. Plausible transition-state model of allylation reaction.

With optimal co-catalysts and reaction conditions established (Scheme 52), a variety of aldimines were then evaluated as substrates. We carried out all reactions in the presence of 2 equivalents of each bisformamide **57** and L-proline (**60**) in CH_2Cl_2 at room temperature. The results are summarized in Table 19.



Scheme 52. Asymmetric allylation of aldimines in the presence of bisformamide **57** and L-proline (**60**).

Table 19. Scope of allylation of aldimines under optimized condition.

Entry	R (Aldimine)	Time (h)	Yield (%)[a]	ee (%)[b] (±)[c]
1	3-NO_2-C_6H_4- (**74**)	4	93	69 (+)
2	4-CF_3-C_6H_4- (**75**)	4	91	81 (-)
3	3-CF_3-C_6H_4- (**76**)	4	95	72 (+)
4	4-Br-C_6H_4- (**77**)	4	84	79 (-)
5	4-Cl-C_6H_4- (**78**)	4	89	85 (-)
6	4-MeO-C_6H_4- (**66**)	4	94	68 (-)
7	2-napthyl (**79**)	4	91	71 (-)
8	Cinnamyl (**80**)	4	88	51 (-)
9	1-furyl (**81**)	4	73	47 (-)
10	2-pyridine (**82**)	2	83	0

[d] Isolated yield after column chromatography.
[b] Enantioselectivities were determined by chiral HPLC analysis in comparison with authentic racemic material.
[c] The sign of the optical rotation of product.

Imine **68** having *para*-nitro substituent in phenyl ring gave under optimized reaction conditions 83% ee, but when imine **74** with *meta*-nitro substituent was used as a substrate

enantioselectivity was decreased to 69% and 93% yield (entry 1, Table 19). The same trend was observed when another substrate having electron withdrawing group - CF_3 was used. With *para-trifluoromethyl* derivative **75**, 90.62% yield and 81% ee was obtained (entry 2, Table 19) while *meta-trifluoromethyl* substituted derivative **76** gave 95% yield and 72% ee (entry 3, Table 19). With *para-bromo* derivative **77** 84% yield and 79% ee was obtained (entry 4, Table 19), while in case of *para-chloro* derivative **78** higher yield (89% yield) and enantioselectivity (85% ee) was obtained as compare to the *para-bromo* derivative **77** (entry 5, Table 19). Electron donating substituent such as *para-methoxy* on aldimine **66** gave higher yield and moderate enantioselectivity (94% yield, 68% ee; entry 6, Table 19).

When we used 2-napthyl derivative **79** as an aldimine the yield was better but the enantioselectivity was moderate (91% yield, 71% ee; entry 7, Table 19). When aldimine derived from cinnamaldehyde **80** was used as a substrate for allylation reaction 88% yield and only 51% ee was obtained (entry 8, Table 19). The flexibility in structure of the substrate might be responsible for low enantioselectivity. Next we carried out allylation of aldimines derived from hetrocyclic rings such as 1-furyl **81** and 2-pyridine **82**. Interestingly with aldimine **81** we achieved 73% yield and 47% ee (entry 9, Table 19). Surprisingly allylation reaction of pyridine-based aldimine **82** was very fast and the reaction completed already in 2 hours. The product was obtained in 83% yield but with 0% ee (entry 10, Table 19). The pyridine functionality of the prochiral substrate might be involved in the activation of allyltrichlorosilane via co-ordination with Si atom resulting in racemic product.

The introduction of electron-withdrawing or electron-donating groups on the aromatic ring of the aldimine did not affect the yields significantly. In all cases by using formamide and L-proline as co-catalysts for asymmetric allylation reactions we achieved good to high yields. However, better enantioselectivities were obtained when aldimines with electron withdrawing groups were used.

In conclusion, we presented for the first time the asymmetric allylation of simple imines derived from aldehydes and 2-aminophenols catalyzed by new catalytic system: chiral bisformamide **57** and L-proline. Co-catalyst L-proline is not only increasing yields and enantioselectivities but also the reaction time. Good to high yields (up to 95%) and ee's

(up to 85% ee) were observed for the allylation reaction of aldimines in the presence of bisformamide **57** and L-proline. This is the first example of asymmetric allylation reaction of simple imines derived from aldehydes and 2-aminophenols with allyltrichlorosilane. The drawback of this reaction, however, is the use of two equivalents of bisformamide catalyst.

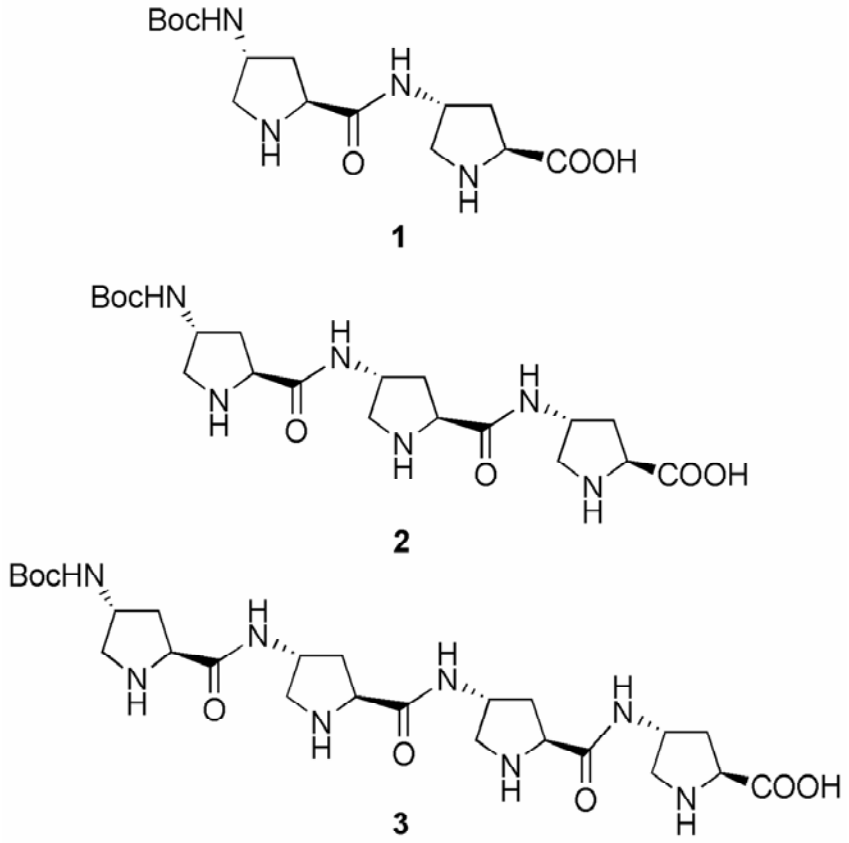
6. Summary of the Work

Asymmetric catalysis represents still one of the major challenges in modern organic chemistry. However, when scientists realized the importance of developing stereoselective organic transformations most attention was brought to the development of transition metal-catalyzed and enzyme mediated selective reactions. Besides the well established asymmetric metal-complex-catalyzed syntheses, organocatalysis has experienced a renaissance and emerged as a rapidly growing field in advanced organic chemistry. Early investigations in the beginning of last century demonstrated that metal-free organic molecules were able to mediate chemical reactions via mechanism that were similar to the ones of enzymes. Organocatalysis is gaining more importance in asymmetric synthesis, complementing bio- and metal-catalysis.

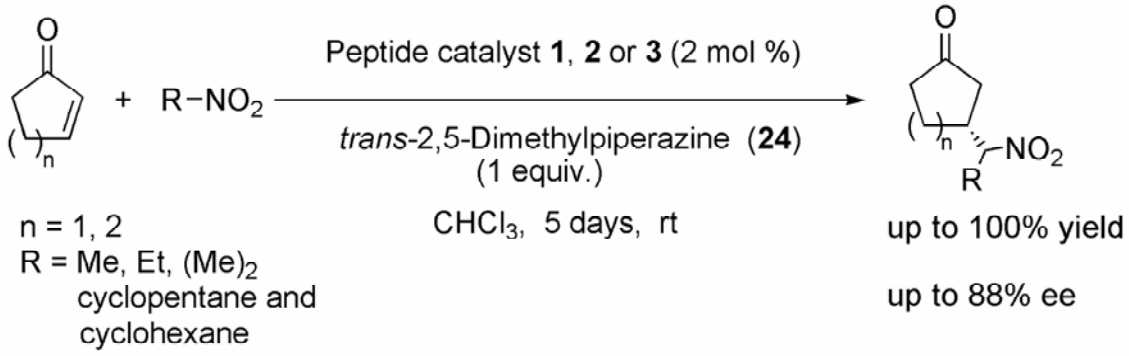
The biocatalysts like enzymes are pure chiral compounds and are responsible for various reactions in nature. Amino acids and short peptides are also found to be useful as catalysts to get highly enantioenriched product. The studies of peptide-based catalysis till 2003 (when we started this work) appeared to have been focused on two extremes in the spectrum of possible catalysts: either small, conformationally rigid cyclic dipeptides, or large peptides and polyamino acids which, by virtue of their increased size and flexibility, likely adopt a specific tertiary structure in solution.

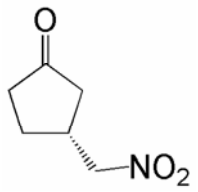
Also peptides, containing one proline unit, whose secondary amine normally functions as a catalytically active centre, were introduced as asymmetric catalysts for C-C bond forming reactions. To the best of our knowledge, short peptides with two to four proline units have never been examined. We were interested to explore whether there is a correlation between the amount of catalytic centers (secondary amine functionalities) and the catalytic activity of the oligo-α-amino acid. Hence we decided to investigate the potential of short peptides with two, three and four proline units as organic catalysts for the Michael reactions, which are regarded to be among the synthetically important carbon-carbon bond forming reactions.

Thus, 4-*trans*-amino-proline based di-, tri- and tetrapeptides **1-3** have successfully been synthesized and applied as chiral catalysts in the enantioselective conjugate addition of nitroalkanes to cyclic enones.

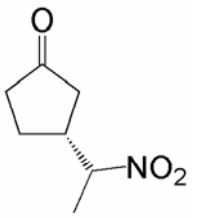


Two 4-*trans*-amino-proline residues were shown to be sufficient to catalyze the conjugate addition of nitroalkanes to cyclic enones with up to 88% ee and up to 100% yield.

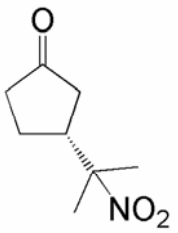




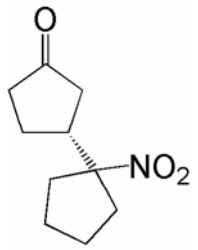
Cat. 1 = 14% yield, 47% ee
2 = 9% yield, 44% ee
3 = 18% yield, 28% ee



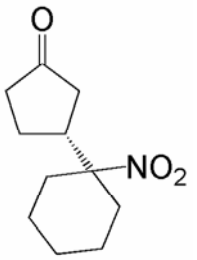
1 = 65% yield, LP: 61% ee
MP: 54% ee
2 =22% yield, LP: 50% ee
MP: 42% ee
3 =71 % yield, LP: 47% ee
MP: 48% ee



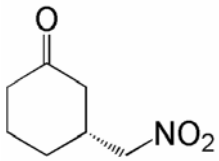
1 = 40% yield, 76% ee
2 = 24% yield, 67% ee
3 = 50% yield, 64% ee



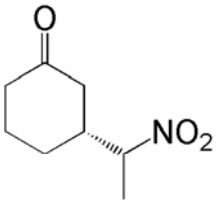
1 = 64% yield, 77% ee
2 = 37% yield, 70% ee
3 = 41% yield, 60% ee



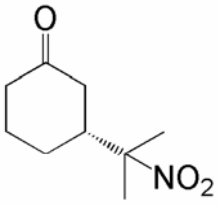
1 = 9% yield, 52% ee
2 = 24% yield, 41% ee
3 = 6% yield, 44% ee



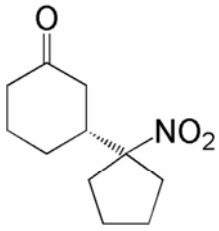
1 = 75% yield, 57% ee
2 = 95% yield, 58% ee
3 = 75% yield, 55% ee



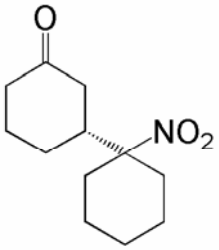
1 = 100% yield, LP: 66% ee
MP: 66 % ee
2 = 83% yield, LP: 56% ee
MP: 65% ee
3 = 100% yield, LP: 58% ee
MP: 59% ee



1 = 46% yield, 77% ee
2 = 80% yield, 81% ee
3 = 80% yield, 81% ee



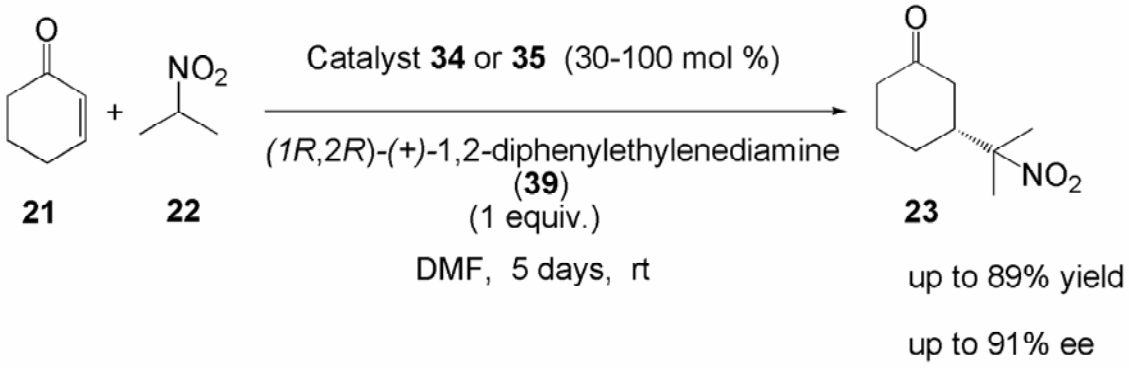
1 = 100% yield, 88% ee
2 = 71% yield, 84% ee
3 = 57% yield, 82% ee



1 = 13% yield, 80% ee
2 = 24% yield, 78% ee
3 = 24% yield, 83% ee

Surprisingly, dipeptides, which are not containing L-proline (e. g. Leu-His, His-Leu), have never been investigated as chiral catalysts for the conjugate addition reactions. This was the motivation to develop a new catalytic system, based on Leu-His and His-Leu dipeptides, for C-C bond formation reactions by example of asymmetric Michael additions.

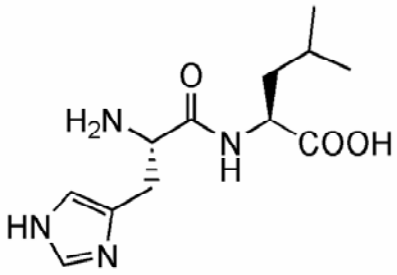
In this work we have demonstrated the first example of catalytic asymmetric conjugate addition in the presence of various dipeptides (H-Phe-His-OH, H-His-Phe-OH, H-Lys-Phe-OH, H-Leu-Arg-OH, H-Val-Arg-OH, H-Lys-Arg-OH, H-Lys-Tyr-OH, H-Lys-His-OH, H-His-Leu-OH, H-Leu-His-OH) and achiral and chiral amines as co-catalysts. The dipeptides H-His-Leu-OH (**34**) and H-Leu-His-OH (**35**) in combination with co-catalyst (1*R*,2*R*)-(+)-1,2-diphenylethylenediamine (**39**) were found to be the most promising dipeptide catalysts regarding enantioselectivities and yields.



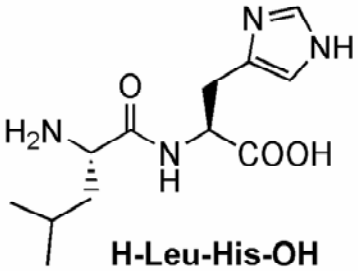
As a result, matching pair of co-catalysts (**35**/**39**) was identified and several ratios of **35** and **39** have been tested.

By example of conjugate addition of 2-nitropropane to 2-cyclohexen-1-one, we have shown that the combination of H-Leu-His-OH (**35**) and (1R,2R)-(+)-1,2-diphenylethylenediamine (**39**) as co-catalysts in a suitable ratio can lead to a new catalytic system for the C-C bond formation reactions.

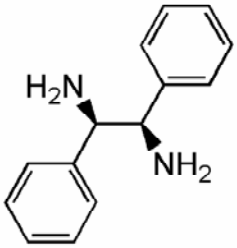
We have shown that the combination of dipeptide **35** with additive **39** provides a catalytic system that appears to be better than the sum of its parts: although neither co-catalyst was sufficiently effective independently in terms of yield or enantioselectivity, their combination resulted in a drastic increase in yields (up to 86%) and absolute selectivities (up to 91% *ee*).



H-His-Leu-OH
(34)



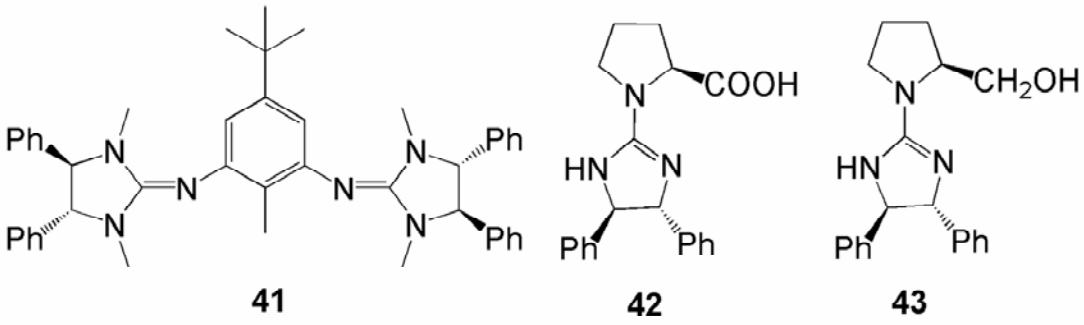
H-Leu-His-OH
(35)



39

Further studies, might pave the way to more effective peptide-based catalysts for this enantioselective C-C bond forming reaction and different other important transformations. In conclusion, the ever expanding contributions in the field of asymmetric synthesis with short-chain peptides as organocatalysts and enzyme mimics undoubtedly confirm that this field of research is very interesting for chemists from academia as well as from industry and that further exciting discoveries of new unpredicted and unprecedented industrially attractive peptide catalysts are to be expected in the near future.

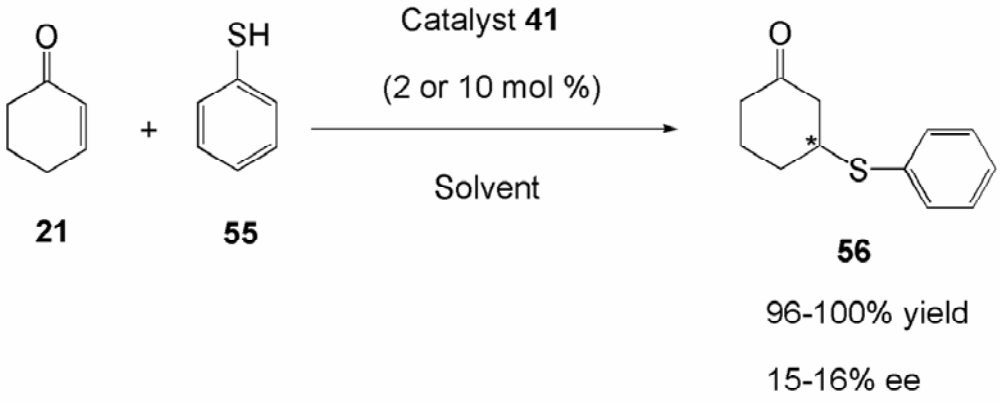
The second part of the thesis deals with the synthesis and applications of new chiral guanidines. It is known that guanidines could be used for molecular recognition of carboxylate anions because of their ability to form strong zwitterionic hydrogen bonds. Although, tetramethylguanidine (TMG) has been used as a catalyst for carbon-carbon bond formation, and known reactions catalyzed by TMG include Michael additions and aldol condensations, guanidines are relatively unexplored type of bond formation catalysts. Only a few examples of guanidine catalyzed enantioselective synthesis exist. In order to maintain the structure of the guanidinium group and to enhance its binding abilities, one may incorporate it into a rigid cyclic framework, which should improve the predictability of the host-guest orientation. Hence the synthesis of new chiral cyclic guanidines **41-43** and their application for conjugate addition reactions was the next aim of this work.

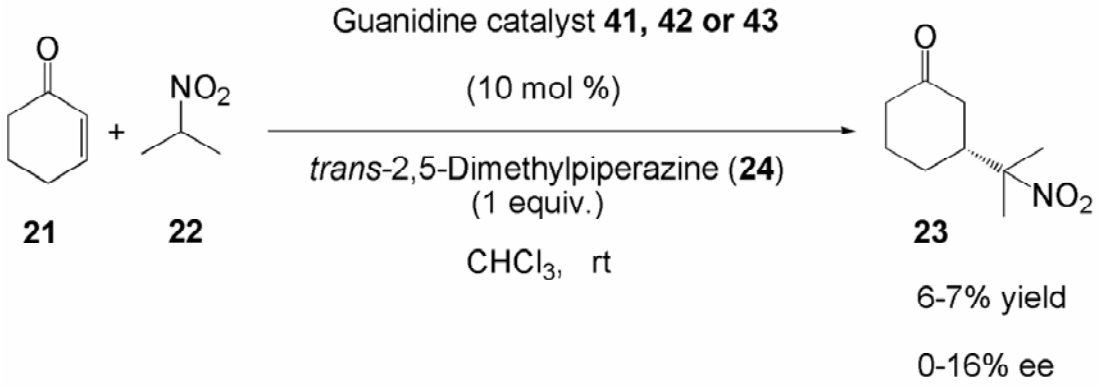


41 **42** **43**

These chiral guanidines were used in asymmetric conjugate addition of thiophenol and 2-nitropropane to cyclohex-2-en-1-one.

To evaluate the catalytic efficiency of the chiral guanidines the conjugate addition reactions of thiophenol and 2-nitropropane to cyclohex-2-en-1-one were performed in different solvents (CH_2Cl_2, toluene) in the presence of each of these catalysts.



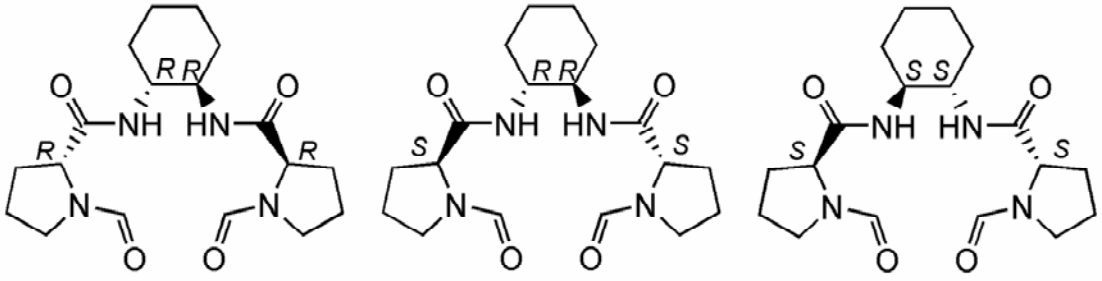


Whereas monoguanidine **43** gave the products **23** and **56** in 7% and 93% yields, respectively, and in low enantioselectivities (up to 15% ee), the bisguanidine **41** produced the Michael products **23** and **56** in high yields (93% and 100%, respectivly), but with low enantioselectivities as well (up to 16% ee).

Third part of this thesis is devoted to the development of the asymmetric organocatalytic version of allylation of simple imines by application of the new proline derived C2-chiral bisformamides.

While N-acylhydrazones were reported to be reactive for the allylation, it was observed that simple imines were resistant to allyltrichlorosilanes.

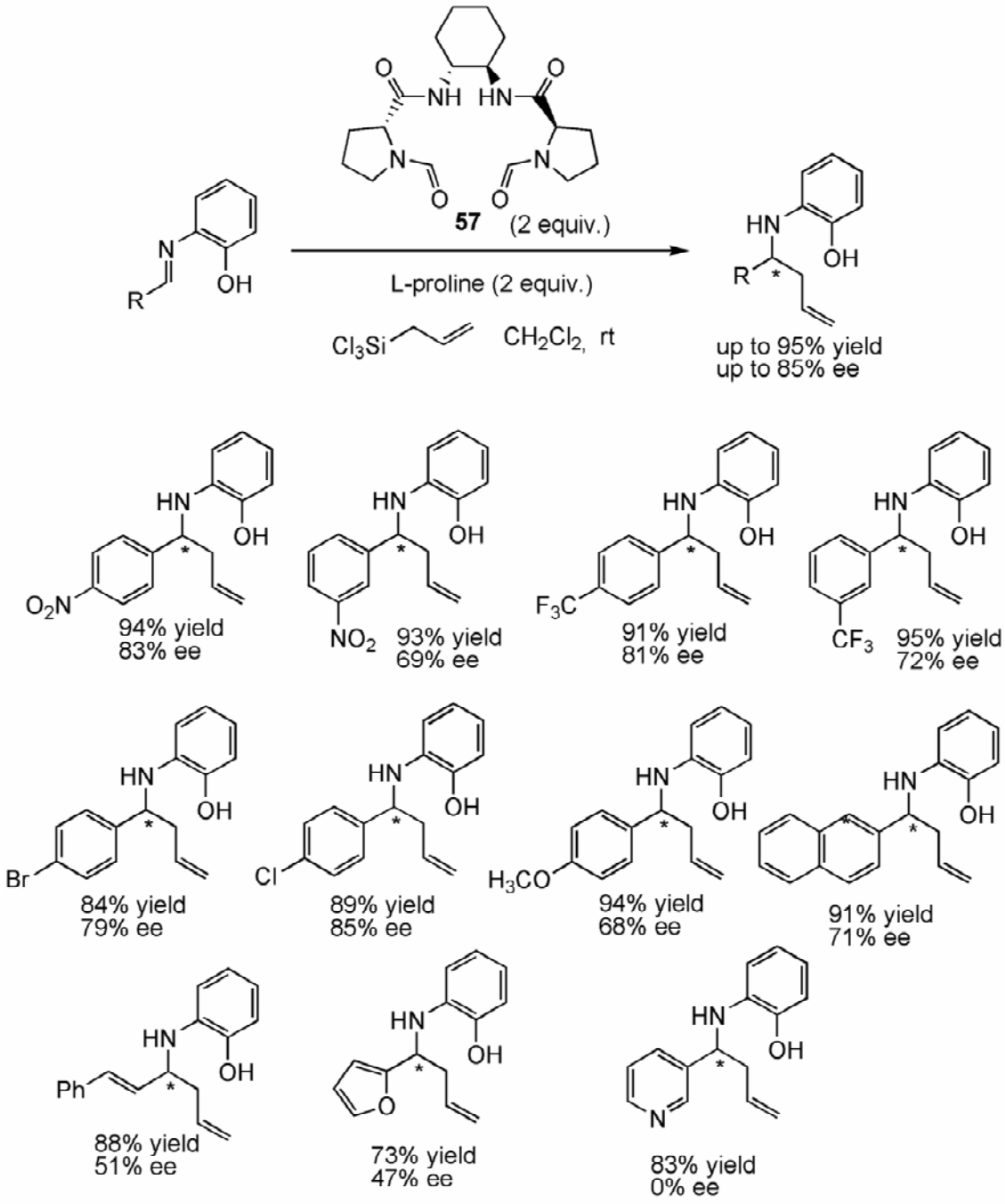
The first example of allylation of imines derived from aldehydes and 2-aminophenols with allyltrichlorosilane using DMF as neutral coordinate-organocatalyst (NCO) to afford the corresponding homoallylic amines has been reported in 2003 by Kobayashi and co-workers. However, no enantioselective allylation of these simple imines with allyltrichlorosilane has been attained to date.



57 (*RRRR*) **58 (*SRRS*)** **59 (*SSSS*)**

Hence we synthesized new C2-chiral bisformamides **57**, **58** and **59** and employed them as organocatalysts for asymmetric allylation of simple aldimines derived from aldehydes and 2-aminophenols.

The presence of both bisformamide and L-proline drastically increases the yield of allylation product with respect to independently acting bisformamide or L-proline and is much higher than the sum of its individual yields, which indicates the possibility of synergistic effects.

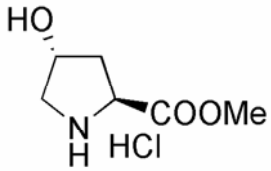


Thus, we have demonstarted for the first time that C2-chiral bisamidine organocatalyts in combination with L-proline as a co-catalyst can catalyze the asymmetric allylation reaction giving high yields (up to 95%) and enantioselectivities (up to 85%) for a wide range of aromatic aldimines.

7. Experimental Section

All solvents were purified by standard procedures and were distilled prior to use. Reagents obtained from commercial sources were used without further purification. TLC chromatography was performed on precoated aluminium silica gel SIL G/UV254 plates (Macherey-Nagel & Co.) or silica gel 60-F254 precoated glass plates (Merck). ^{1}H NMR spectra were recorded with Varian Unity 300 and Varian Inova 600 instruments. ESI mass spectra were measured with an LCQ Finnigan spectrometer. High-resolution mass spectra were recorded with a Bruker APEX IV 7T FTICR instrument. A Perkin-Elmer 241 polarimeter was used for optical rotation measurements.

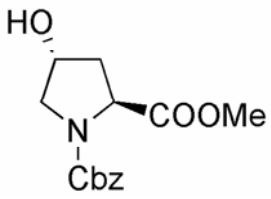
7.1. *trans*-4-Hydroxy-L-proline-methyl ester hydrochloride (5).



$SOCl_2$ (95 mL, 1.309 mol) was added drop wise to the stirred MeOH (385 mL) and cooled to -20 ^{o}C.; to this solution L-Hydroxyproline **4** (50 g, 0.38 mol) was added in one portion. The reaction was stirred for further two hours at -20 °C and then overnight at room temperature. The solvent was removed in vacuum and the residue was diluted with diethyl ether (600 mL). The white crystalline product was filtered and washed with diethyl ether (3 × 100 mL) and dried under reduced pressure. 68 g (98.2%) of compound **5** was obtained.

^{1}H NMR: (300 MHz, CD_3OD); δ = 2.15-2.24 (m, 1H), 2.37-2.45 (m, 1H), 3.28-3.32 (m, 1H), 3.44 (dd, 1H), 3.85 (s, 3H, $COOCH_3$), 4.57- 4.63 (m, 2H).

7.2. N-Benzyloxycarbonyl-*trans*-4-hydroxy-L-proline-methyl ester (6).

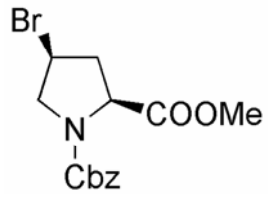


To the vigorously stirred solution of **5** (67 g, 0.368 mol) and TEA (113 mL, 0.812 mol) in $CHCl_3$ (380 ml), the solution of CbzCl (45%, 151 mL, 0.406 mol) in $CHCl_3$ (70 mL) was added at 0 ^oC. Reaction mixture was stirred at room temperature for 40 h. The mixture was washed with H_2O (100 mL), 2N H_2SO_4 (40 mL), 5% $NaHCO_3$ (60 mL), H_2O (100 mL) and dried over Na_2SO_4. Filtration and concentration of organic solution under reduced pressure gave light-yellow oil (102 g, 99%).

^1H NMR: (300 MHz, $CDCl_3$); δ = 1.99-2.12 (m, 1H), 2.22-2.35 (m, 2H), 3.49-3.76 (m, 5H), 4.44- 4.54 (m, 2H), 4.95-5, 22 (m, 2H, $PhCH_2$), 7.28-7.36(m, 5H).

$[\alpha]^{25}_D$= -62.5 (c = 1.00, $CHCl_3$).

7.3. N-Benzyloxycarbonyl-*trans*-4-brom-L-proline-methyl ester (7).

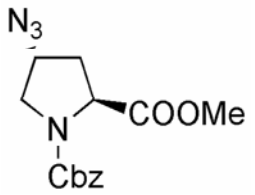


To a stirred solution of Ph_3P (159.2 g, 0.606 mol) and CBr_4 (201 g, 0.606 mol) in CH_2Cl_2 (791 mL) was added solution of **6** (113 g, 0.040 mol) by several portions at 0 °C. The reaction mixture was stirred at inert atmosphere, at room temperature for 1.5 h. Precipitate was filtered off and washed with CH_2Cl_2 (2 × 300 mL). Filtrate was concentrated in vacuum to give oily residue, which was purified by column chromatography (hexane-ethyl acetate 6:1). Colourless oil **7** was obtained. Yield 120.5 g (87%).

^{1}H NMR: (200 MHz, $CDCl_3$); δ = 2.42-2.54 (m, 1H), 2.77-2.90 (m, 1H), 3.62-3-86 (m, 4H), 4.08- 4.20 (m, 1H), 4.26-4.39 (m, 1H), 4.39-4.52 (m, 1H), 5.05-5, 24 (m, 2H, $PhCH_2$), 7.30- 7.41 (m, 5H)

$[\alpha]^{25}_D$= -27.4 (c =1.00, $CHCl_3$).

7.4. N-Benzyloxycarbonyl-*trans*-4-azido-L-proline-methyl ester (8).

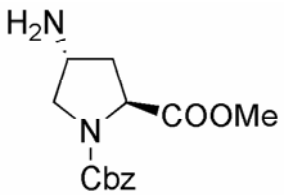


Sodium azide (17.2 g, 0.264 mol) was added to solution of **7** (13 g, 0.038 mol) in DMF (90 mL) at 0 °C. The mixture was stirred at room temperature for 48 h, diluted with water (100 mL) and extracted with ethyl acetate (3 × 120 mL). Combined organic layers were washed with brine, dried over Na_2SO_4, solvent was evaporated in vacuum to give flaxen oil. Yield 11 g (95%).

^{1}H NMR: (300 MHz, $CDCl_3$); δ = 2.16-2.25 (m, 1H), 2.30-2.41 (m, 1H), 3.54-3.80 (m, 5H), 4.19-4.26 (m, 1H), 4.41-4.51 (m, 1H), 5.01-5.23 (m, 2H, $PhCH_2$), 7.27-7.40 (m, 5H).

DCI-MS: Calculated mass for C_{14} H_{16} N_4O_4 = 304.3; found 626.2 $[2M+NH_4]^+$, 322.2 $[M+NH_4]^+$, 305.1 $[M+H]^+$.

7.5. N-Benzyloxycarbonyl-*trans*-4-amino-L-proline-methyl ester (9).



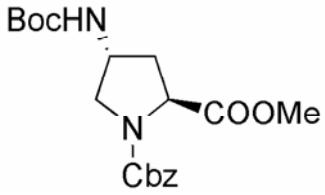
The solution of azide **8** (2 g, 6.57 mmol), Ph_3P (3.45 g, 13.15 mmol) and H_2O (0.236 mL, 13.11 mmol) in THF (30 mL) was refluxed for 5 h. Evaporation of solvent in vacuum

gave oily residue, which was dissolved in diethyl ether (100 mL) and extracted with 1N HCl (50 mL). The aqueous layer was macerated with diethyl ether (2 × 50 mL), neutralized with $NaHCO_3$ (5%) and extracted with CH_2Cl_2. Combined organic layers were washed with brine, dried over Na_2SO_4, solvent was removed under reduced pressure to give yellow oil. Yield 1.7 g (93%).

^{1}H NMR: (300 MHz, $CDCl_3$); δ = 1.45 (s, 2H, NH_2), 1.95-2.09 (m, 1H), 2.11-2.21 (m, 1H), 3.44 (dq, 1H), 3.56-3.82 (m, 5H), 4.44-4.52 (m, 1H), 5.01-5.23 (m, 2H, $PhCH_2$), 7.27-7.37 (m, 5H).

$[\alpha]^{20}_D$= -50.0 (c 0.45, $CHCl_3$).

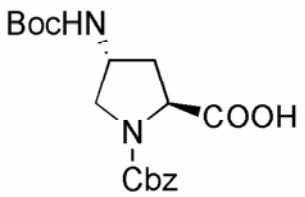
7.6. N-Benzyloxycarbonyl-*trans*-4-tertbutoxycarbonylamino-L-proline-methyl ester (10).



To a solution of **9** (6 g, 21.55 mmol) in CH_2Cl_2 (130 mL) was added $(Boc)_2O$ (5.176 g, 23.71 mmol) and the mixture was stirred at room temperature for 4 h. The solvent was evaporated in vacuum to give **10** as a oil. Yield 7.406 g (90.77%).

^{1}H NMR: (300 MHz, $CDCl_3$); δ = 1.42 (s, 9H, $C(CH_3)_3$), 2.14-2.29 (m, 1H), 3.29-3.44 (m, 2H), 3.65 (d, 3H, $COOCH_3$), 3.74-3.89 (m, 1H), 4.26-4.46 (m, 2H), 4.58-4.63 (m,1H), 4.98-5.21 (m, 2H, $PhCH_2$), 7.30-7.36 (m, 5H).

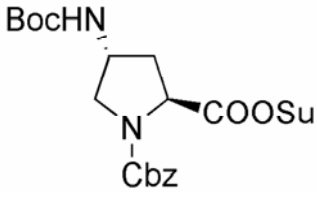
7.7. N-Benzyloxycarbonyl-trans-4-tertbutoxycarbonylamino-L-proline (11).



To a solution of **10** (2.44 g, 6.455 mmol) in MeOH (45 mL) and H_2O (8 mL), was added the solution of LiOH (326 mg, 7.77 mmol) in MeOH (27 mL) and H_2O (9 mL). The reaction mixture was stirred at room temperature overnight, concentrated under reduced pressure to one half of its volume, diluted with H_2O (100 mL) and extracted with EtOAc (3 × 40 mL). Aqueous layer was acidified with 2 N H_2SO_4 to pH=1 and extracted with CH_2Cl_2 (3 × 50 mL). Combined organic layers were washed with H_2O, brine and dried over Na_2SO_4. Solvent evaporated under vacuum. The product **11** was obtained as white foam. Yield 1.98 g (84%).

^{1}H NMR: (300 MHz, $CDCl_3$); δ = 1.44 (s, 9H, $C(CH_3)_3$), 2.08-2.25 (m, 1H), 3.32-3.43 (m, 1H), 3.12-3.39 (m, 1H), 3.80-3.86 (m, 1H), 4.32 (bs, 1H), 4.39-4.48 (m, 1H), 4.71-4.80 (m,1H), 5.12-5.17 (m, 2H, $PhCH_2$), 7.30-7.35 (m, 5H), 7.50-8.20 (bs, 1H).

7.8. 4 N-Benzyloxycarbonyl-trans-4-tertbutoxycarbonylamino-L-proline-(2,5-dioxo-pyrrolidin-1-yl) ester (12).

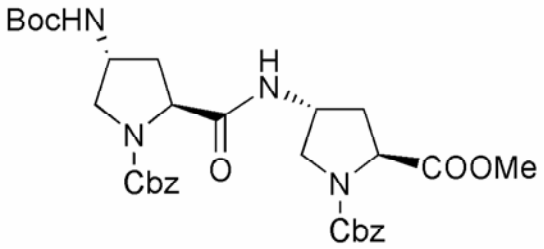


The cooled solution of N,N-dicyclohexylcarbodiimide (DCC) (1.222 g, 5.923 mmol) in dioxane was added dropwise to the stirred solution of **11** (1.96 g, 5.38 mmol) and N-hydroxysucciniimid (HOSu) (0.681 g, 5.923 mmol) at 0 ^oC. The reaction mixture was stirred at 0 ^oC for 5 h and then at 4 ^oC for 24 h. The precipitate formed was filtered off and washed with the mixture of dioxane-diethyl ether (1:3, 20 mL). Combined filtrates

were evaporated in vacuum to afford oily residue which was dissolved in dioxane-diethyl ether (1:3, 50 mL) and stirred at 4°C for 3 h. The precipitate was filtered off and washed with dioxane-diethyl ether mixture. The target compounds with satisfactory purity, was obtained which was used in the next stage without further purification. Yield 2.00 g (81%).

^{1}H NMR: (300 MHz, $CDCl_3$); δ = 1.43 (s, 9H, $C(CH_3)_3$), 2.43-2.53 (m, 2H), 2.79-2.83 (m, 4H), 3.38-3.52 (m, 1H), 3.78-3.88 (m, 1H), 4.25-4.40 (m, 1H), 4.65-4.78 (m,2H), 5.04-5.30 (m, 2H, $PhCH_2$), 7.28-7.39 (m, 5H).

7.9. 4-[(1-Benzyloxycarbonyl-4-*tert*-butoxycarbonylamino-pyrrolidine-2-carbonyl)-amino]- pyrrolidine-1,2-dicarboxylic acid 1-benzyl ester 2-methyl ester (13).



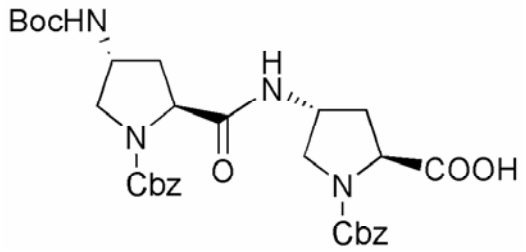
To a stirred solution of amine **9** (1.19 g, 4.3 mmol) in ethyl acetate (20 mL) was added the solution of **12** (1.8 g, 3.9 mmol) in ethyl acetate (35 mL). The reaction mixture was stirred at room temperature for 12 h.; washed with 2N H_2SO_4 (2 × 30 mL), H_2O, 5% $NaHCO_3$ (2 × 30 mL), H_2O, brine and dried over Na_2SO_4. The solvent was removed under reduced pressure to give oily residue, which was precipitated from diethyl ether (75 mL). Filtration of precipitate gave **13** as a white solid. Yield: 2.3 g (94%).

^{1}H NMR: (300 MHz, $CDCl_3$); δ = 1.43 (s, 9H, $C(CH_3)_3$), 1.80-2.00 (m, 1H), 2.05-2.30 (m, 2H), 2.50-2.64 (m, 1H), 3.10-3.52 (m, 2H), 3.56-3.95 (m, 6H), 4.16-4.62 (m, 5H), 5.00-5.21 (m, 4H, 2 × $PhCH_2$), 7.26-7.46 (m, 10H).

ESI-MS: Calculated mass 624.686, observed 647.3 $[M+Na]^+$

Elemental analysis: Calculated for $C_{32}H_{40}N_4O_9$ = C, 61.53, H, 6.45; found C, 61.35, H, 6.52.

7.10. 4-[(4-*tert*-Butoxycarbonylamino-pyrrolidine-2-carbonyl)-amino]-pyrrolidine-2-carboxylic acid (14).

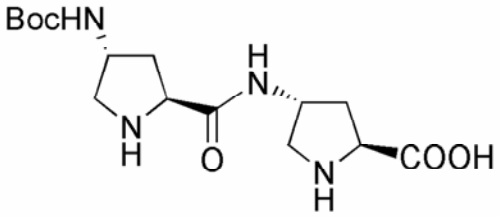


Saponification of the methyl ester **13** (1 g, 1.6 mmol) was performed by the same procedure as described above for **11**, to give **14** as a white foam in 76% yield (0.745 g) of acid was obtained as white foam.

^{1}H NMR: (300 MHz, $CDCl_3$); δ = 1.35 (s, 9H, $C(CH_3)_3$), 1.78-1.95 (m, 1H), 1.97-2.54 (m, 4H), 3.18-3.40 (m, 2H), 3.56-3.82 (m, 2H), 4.06-4.50 (m, 5H), 4.62-4.76 (m, 1H), 4.95-5.10 (m, 4H, 2 × $PhCH_2$), 5.50-6.25 (bs, 1H), 7.13-7.32 (m, 10H).

ESI-MS: Calculated mass for $C_{31}H_{38}N_4O_9$ = 610.659; found 1243.2 $[2M+Na]^+$, 1219.6 $[2M-H]^-$, 633.4 $[M+Na]^+$, 609.7 $[M-H]^-$.

7.11. 4-[(4-*tert*-Butoxycarbonylamino-pyrrolidine-2-carbonyl)-amino]-pyrrolidine-2-carboxylic acid (1).



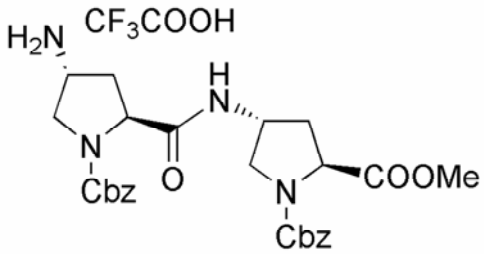
To a solution of **14** (670 mg, 1.1 mmol) in MeOH (40 mL), Pd/C (10%, 40 mg) was added and the resulting mixture was stirred under H_2 at room temperature for 48 h. The catalyst was filtered off with celite and the filtrate was concentrated in vacuum to give semi-solid substance, which was precipitated from MeOH (1 mL) with diethyl ether (30 mL). Yield 349.3 mg (93%).

^{1}H NMR: (300 MHz, CD_3OD); δ = 1.43 (s, 9H, $C(CH_3)_3$), 1.96-2.12 (m, 2H), 2.29-2.34 (m, 2H), 2.83 (dd, 1H), 3.09-3.23 (m, 2H), 3.49-3.55 (m, 1H), 3.82 (t, 1H), 4.00 (quintet, 1H), 4.14 (t, 1H), 4.36 (quintet, 1H).

ESI-MS (positive ion): *m/z* = 343.1 $[M + H]^+$, 684.9 $[2M + H]^+$.

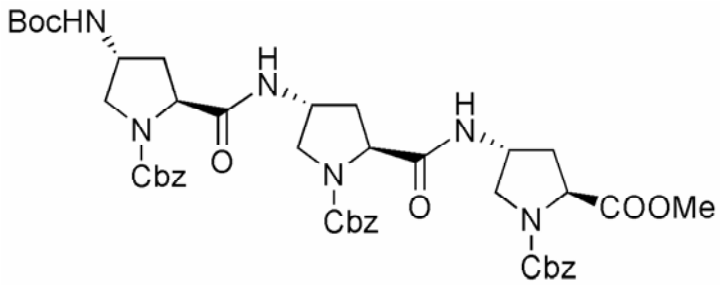
HRMS (ESI): Calculated for $C_{15}H_{26}N_4O_5$ = 343.19760 $[M + H]^+$; found 343.19760.

7.12. 1-Benzyloxycarbonyl-5-(1-benzyloxycarbonyl-5-methoxycarbonyl-pyrrolidin-3-lcarbamoyl)-pyrrolidin-3-yl-ammonium trifluoroacetate (15).



To a stirred solution of **13** (1 g, 1.6 mmol) in CH_2Cl_2 (20 mL), TFA (10 mL) was added in one portion at 0 ^oC. The stirring was continued for 2 h. The solvent was removed under vacuum, diluted with benzene (20 mL) and the rest of solvent was thoroughly evaporated in order to remove traces of trifluoroacetic acid. The oily residue was precipitated with dry diethyl ether (50 mL), filtered and dried in vacuum. Crude product was used to the next reaction without further purification.

7.13. 4-({1-Benzyloxycarbonyl-4-[(1-benzyloxycarbonyl-4-*tert*-butoxycarbonylamino -pyrrolidine-2-carbonyl)-amino]-pyrrolidine-2-carbonyl}-amino)-pyrrolidine-1,2-dicarboxylic acid 1-benzyl ester 2-methyl ester (16).



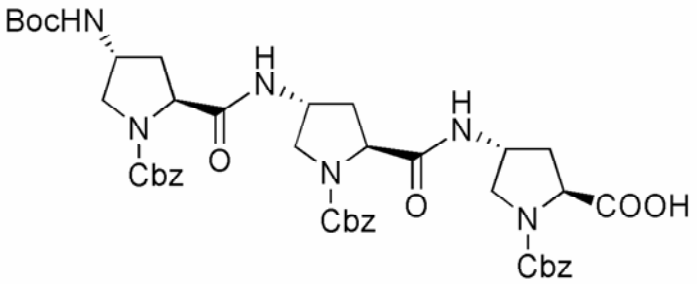
To a stirred solution of **15** (843 mg, 1.32 mmol) and **12** (670 mg, 1.452 mmol) in CH_2Cl_2 (20 mL) was added TEA (0.206 mL, 1.452 mmol) and the reaction mixture was stirred overnight. The reaction mixture washed with 2N H_2SO_4 (2 × 30 mL), H_2O, 5% $NaHCO_3$ (2 × 30 mL), H_2O, brine and dried over Na_2SO_4. The solvent was removed under reduced pressure to give white foam. Yield 1.104 g (96%).

^{1}H NMR: (600 MHz, CD_3OD); δ = 7.36-7.24 (m, 15 H), 5.15-.89 (m, 6 H, 3 × $PhCH_2$), 4.42-4.16 (m, 6 H), 3.83 and 3.64 (m, 3 H), 3.78 and 3.58 (s, 3 H, CH_3O), 3.48-3.05 (m, 3 H), 2.24- 2.02 (m, 6 H), 1.41 [s, 9 H, $C(CH_3)_3$].

ESI-MS (positive ion): *m*/*z* = 893.5 $[M + Na]^+$, 1763.1 $[2M + Na]^-$.

HRMS (ESI): Calculated for $C_{45}H_{54}N_6O_{12}$ = 871.38725 $[M +H]^+$; found 871.38735.

7.14. 4-({1-Benzyloxycarbonyl-4-[(1-benzyloxycarbonyl-4-*tert*-butoxycarbonylamino -pyrrolidine-2-carbonyl)-amino]-pyrrolidine-2-carbonyl}-amino)-pyrrolidine-1,2-dicarboxylic acid 1-benzyl ester (17).



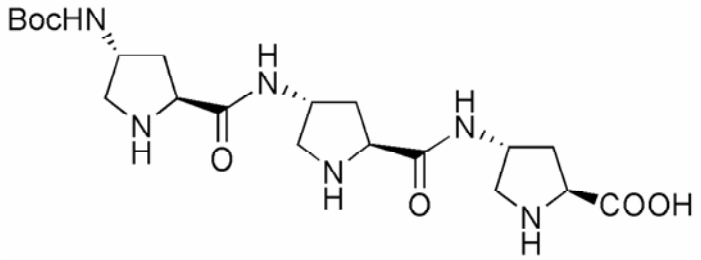
The hydrolysis of **16** (2.120 g, 2.43 mmol) was carried out by the same method as described above for **11**. Desirable acid **17** was obtained as white foam 1.916 g (92%).

^{1}H NMR (600 MHz, CD_3OD); δ = 7.36-7.24 (m, 15 H), 5.13-5.05 (m, 6 H, 3 × $PhCH_2$), 4.43-4.17 (m, 6 H), 3.83-3.75 (m, 3 H), 3.48-3.03 (m, 3 H), 2.30-2.09 (m, 6 H), 1.41 [s, 9 H, $C(CH_3)_3$].

ESI-MS (positive ion): *m*/*z* = 879.6 $[M + Na]^+$, 1735.3 $[2M + Na]^+$. ESI-MS (negative ion): *m*/*z* = 855.5 $[M - H]^-$, 1711.5 $[2 M - H]^-$.

HRMS (ESI): Calculated for $C_{44}H_{52}N_6O_{12}$ = 857.37160 $[M + H]^+$; found 857.37180.

7.15. 4-({4-[(4-*tert*-Butoxycarbonylamino-pyrrolidine-2-carbonyl)-amino]-pyrrolidine -2-carbonyl}-amino)-pyrrolidine-2-carboxylic acid (2).



The hydrogenation (for deprotection of -Cbz group) of **17** (200 mg, 0.23 mmol) was carried out by the same method as used to prepare **1** to give 99.5 mg (94%) of product **2** as a white solid.

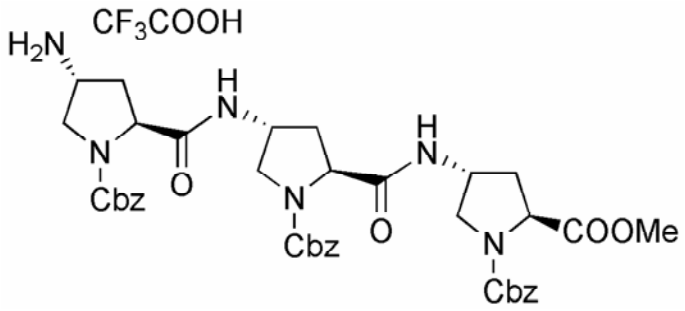
^{1}H NMR (300 MHz, CD_3OD); δ = 4.37 (m, 1 H), 4.27 (m, 1 H), 4.17 (m, 1 H), 4.05 (m, 1 H), 3.95 (m, 2 H), 3.60 (m, 1 H), 3.28-3.20 (m, 3 H), 2.99-2.91 (m, 2 H), 2.39-2.32 (m, 2 H), 2.2-1.95 (m, 4 H), 1.43 [s, 9 H, $C(CH_3)_3$]

ESI-MS (positive ion): m/z = 455.2 $[M + H]^+$, 909.1 $[2 M + H]^+$. ESI-MS (negative ion): m/z = 453.5 $[M - H]^-$.

HRMS (ESI): Calculated for $C_{20}H_{34}N_6O_6$ = 455.26126 $[M + H]^+$; found 455.26144.

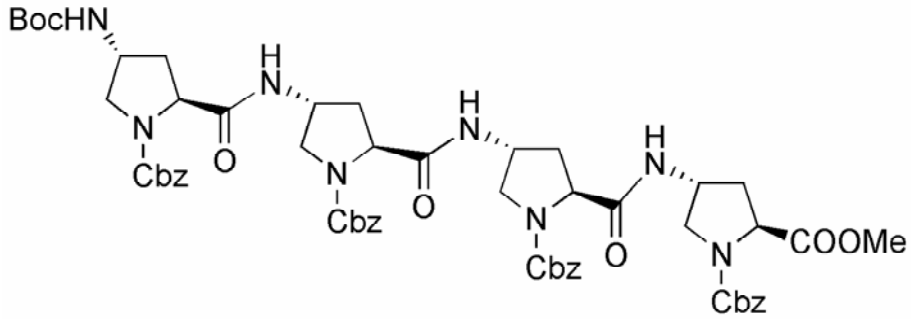
$[\alpha]^{20}_D$ = -7.8 (c = 0.32, MeOH).

7.16. {1-Benzyloxycarbonyl-5-[1-benzyloxycarbonyl-5-(1-benzyloxycarbonyl-5-methoxycarbonyl-pyrrolidin-3-ylcarbamoyl)-pyrrolidin-3-ylcarbamoyl]-pyrrolidin-3-yl}-trimethyl-ammonium trifluoroacetate (18).



The deprotection of Boc- group from **16** (2.47 g, 2.84 mmol) was carried out by the same method as used to prepare trifluoroacetate **15**. Yield: 2.345 g (93%). Crude product was used in the next step without further purification.

7.17. 4-{[1-Benzyloxycarbonyl-4-({1-benzyloxycarbonyl-4-[(1-benzyloxycarbonyl-4-*tert*-butoxycarbonylamino-pyrrolidine-2-carbonyl)-amino]-pyrrolidine-2-carbonyl}-amino)-pyrrolidine-2-carbonyl]-amino}-pyrrolidine-1,2-dicarboxylic acid 1-benzyl ester 2-methyl ester (19).

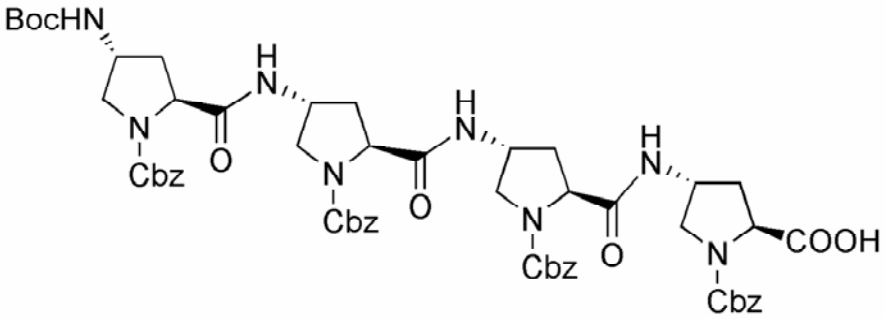


To a stirred solution of **18** (2.345 g, 2.65 mmol) and **12** (1.345 g, 2.91 mmol) in CH_2Cl_2 (40 mL) was added TEA (0.412 mL, 2.91 mmol) and the reaction mixture was stirred overnight, then washed with 2N H_2SO_4 (2 × 30 mL), H_2O, 5% $NaHCO_3$ (2 × 30 mL), H_2O, brine and dried over Na_2SO_4, solvent was removed under reduced pressure to give white foam. Yield 2.83 g (95%).

^{1}H NMR: (300 MHz, $CDCl_3$); δ = 1.42 (s, 9H, $C(CH_3)_3$), 1.65-2.00 (m, 6H), 2.20-2.70 (m, 5H), 3.05-3.43 (m, 4H), 3.56-3.90 (m, 7H), 4.08-4.56 (m, 8H), 4.62-4.74 (m, 1H), 5.05-5.20 (m, 8H, 4 × $PhCH_2$), 7.20-7.34 (m, 20H).

ESI-MS: Calculated mass = 1117.214; found 1139.7 $[M+Na]^+$.

7.18. 4-{[1-Benzyloxycarbonyl-4-({1-benzyloxycarbonyl-4-[(1-benzyloxycarbonyl-4-*tert*-butoxycarbonylamino-pyrrolidine-2-carbonyl)-amino]-pyrrolidine-2-carbonyl}-amino)-pyrrolidine-2-carbonyl]-amino}-pyrrolidine-1,2-dicarboxylic acid 1-benzyl ester (20).

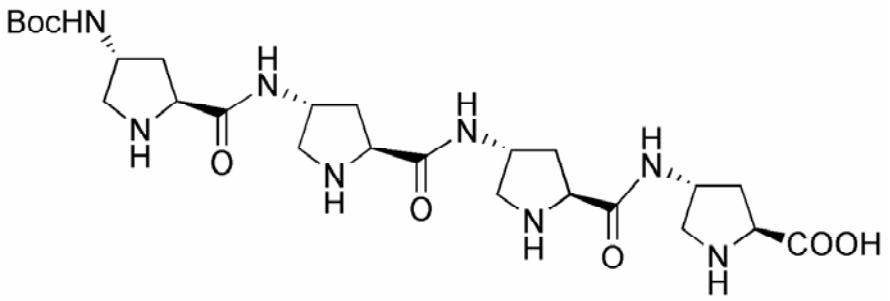


The hydrolysis of **19** (2.8 g, 2.5 mmol) was carried out by the same method as used to prepare **14**. As a result, desirable acid **20** was obtained as white foam. Yield 1.75 g (63%).

^{1}H NMR: (300 MHz, CD_3OD); δ = 1.43 (s, 9H, $C(CH_3)_3$), 1.98-2.28 (m, 10H), 3.04-3.06 (m, 1H), 3.18-3.25 (m, 1H), 3.32-3.52 (m, 2H), 3.61-3.86 (m, 5H), 4.12-4.52 (m, 10H), 4.95-5.20 (m, 8H, 8 × $PhCH_2$), 7.06-7.41 (m, 20H).

ESI-MS: Calculated mass 1103.187; found 1125.7 $[M+Na]^+$, 1101.9 $[M-H]^-$.

7.19. 4-{[4-({4-[(4-*tert*-Butoxycarbonylamino-pyrrolidine-2-carbonyl)-amino]-pyrrolidine-2-carbonyl}-amino)-pyrrolidine-2-carbonyl]-amino}-pyrrolidine-2-carboxylic acid (3).



The hydrogenation (for deprotection of -Cbz group) of **20** (50 mg, 0.045 mmol) was carried out by the same method as used to prepare **1**. Yield: 18 mg (71%).

^{1}H NMR: (300 MHz, CD_3OD); δ = 1.42 (s, 9H, C(CH_3)$_3$), 1.95-2.55 (m, 10H), 2.85-2.98 (m, 3H), 3.12-3.70 (m, 5H), 3.80-4.55 (m, 10H).

ESI-MS (positive ion): *m/z* = 567.7 $[M + H]^+$.

HRMS (ESI): Calculated for $C_{25}H_{42}N_8O_7$ = 567.32492 $[M + H]^+$; found 567.32477.

General procedure for the *Michael* reaction

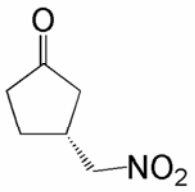
7.20. 3-(2-Nitropropane-2-yl) cyclohexanone (23). 2-Nitropropane (0.63 mmol) was added to a stirred solution of 2-cyclohexen-1-one (0.5 mmol), additive (0.5 mmol) and peptide catalyst in pre-dried solvent (4 mL), and the reaction mixture was stirred at room temperature for 5 days. The reaction mixture was worked up as described in the literature.[43] The residues were purified by chromatography on SiO_2-column (hexane/ethyl acetate) to afford the desired product **23**. The enantiomeric excess of the product was measured by chiral HPLC analysis (Daicel Chiralpak AS) in comparison with authentic racemic material or ^{13}C NMR of corresponding ketal with (2R,3R)-2,3-butane diol.[43]

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.48-2.34 (m, 3H), 2.31-2.21 (m, 1 H), 2.19-2.08 (m, 2 H), 1.85-1.76 (m, 1 H), 1.71-1.53 (m, 1 H), 1.58 (s, 3 H), 1.57 (s, 3 H), 1.48-1.34 (m, 1 H).

^{13}C NMR (150.8 MHz, $CDCl_3$) δ 208.9 (C=O), 90.6 ($C_{quat.}$), 46.5 (CH), 42.6 (CH_2), 40.7 (CH_2), 25.9 (CH_2), 24.3 (CH_2), 23.3 (CH_3), 22.5 (CH_3).

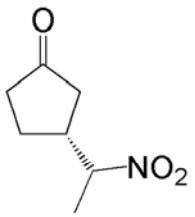
ESI-MS (positive ion): *m/z* 208.1 $[M+Na]^+$.

7.21. 3-(Nitromethyl)-cyclopentanone (23A).



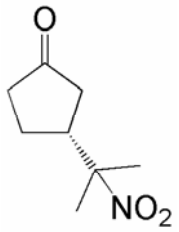
^{1}H NMR: (300 MHz, $CDCl_3$); δ = 1.67-1.75 (m, 1H), 1.96-2.05 (m, 1H), 2.25-2.34 (m, 2H), 2.38-2.48 (m, 1H), 2.51-2.60 (m, 1H), 2.87-3.08 (m, 1H), 4.44-4.52 (m, 2H).

7.22. 3-(2-Nitroethyl)-cyclopentanone (23B).



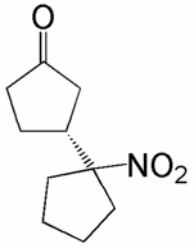
^{1}H NMR: (300 MHz, $CDCl_3$); δ = 1.49-1.75 (m, 3H), 1.87-1.99 (m, 1H), 2.22-2.38 (m, 2H), 2.38-2.45 (m, 2H), 2.65-2.77 (m, 1H), 4.47-4.53 (m, 1H).

7.23. 3-(2-Nitropropane)-cyclopentanone (23C).



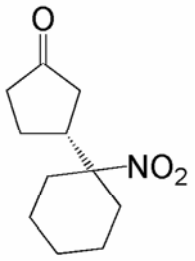
^{1}H NMR: (300 MHz, $CDCl_3$); δ = 1.51-1.73 (m, 8H), 2.06-2.14 (m, 2H), 2.28-2.37 (m, 3H), 2.78-2.88 (m, 1H).

7.24. 3-(Nitrocyclopentyl)- cyclopentanone (23D).



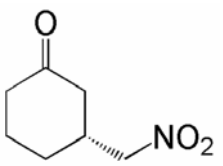
^{1}H NMR: (300 MHz, $CDCl_3$); δ = 1.55-1.85 (m, 8H), 1.99-2.30 (m, 3H), 2.32-3.41 (m, 2H), 2.59-2.69 (m, 2H), 2.89-2.98 (m, 1H).

7.25. 3-(Nitrocyclohexylyl)-cyclopentanone (23E).



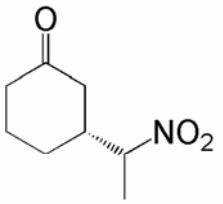
^{1}H NMR: (300 MHz, $CDCl_3$); δ = 1.10-1.38 (m, 1H), 1.50-1.76 (m, 2H), 2.03.2.25 (m, 1H), 2.31-2.40 (m, 1H), 2.51-2.61 (m, 1H).

7.26. 3-(Nitromethyl)-cyclohexanone (23F).



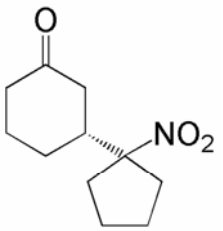
^{1}H NMR: (300 MHz, $CDCl_3$); δ = 1.4-1.6 (m, 1H), 1.67-1.78 (m, 1H), 1.91-2.02 (m, 1H) 2.19-2.28 (m, 2H), 2.25-2.35 (m, 1H), 2.41.2.52 (m, 2H), 2.10-2.20 (m, 1H), 4.31-4.42 (m, 2H).

7.27. 3-(Nitroethyl)-cyclohexanone (23G).



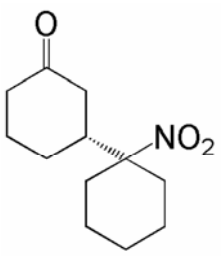
^{1}H NMR: (300 MHz, $CDCl_3$); δ = 1.39-1.48 (m, 1H), 1.49-1.58 (m, 3H), 1.12-1.21 (m, 1H), 2.06-2.15 (m, 2H), 2.20-2.35 (m, 2H), .2.39-2.48-(m, 2H), 4.45-4.53 (m, 1H).

7.28. 3-(Nitrocyclopentyl)-cyclohexanone (23H).



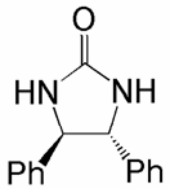
^{1}H NMR: (300 MHz, $CDCl_3$); δ = 1.32-1.86 (m, 8H), 1.88-198 (m, 1H), 2.32-2-60 (m, 4H), 2.34-2.51 (m, 2H), 2.59-2.75 (m, 2H).

7.29. 3-(Nitrocyclohexylyl)-cyclohexanone (23I).



^{1}H NMR: (300 MHz, $CDCl_3$); δ = 1.22-1.31 (m, 4H), 1.49-1.51 (m, 4H), 1.25-1.34 (m, 3H), 1.89-1.97 (m, 1H), 2.05-2.15 (m, 3H), 2.20-2.28 (m, 1H), 2.35-2.43 (m, 1H),2.48-2.56 (m, 3H).

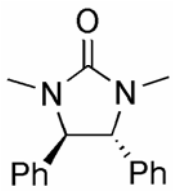
7.30. (4*R*,5*R*)-4,5-diphenyl-2-imidazolidinone (44) .



(1R,2R)-1,2-diphenylethylenediamine (**39**) (200 mg, 0.943 mmol), Urea (57 mg , 0.949 mmol) and water (8 drops) were refluxed at 200 °C for two hrs. Purification by flash column chromatography (petrolium ether: ethyl acetate 4:6) gave 217 mg (97 %) compound (**44**) as a white powder.

^{1}H NMR: (300 MHz, $CDCl_3$); δ = 4.59 (s, 2H), 5 (bs, 2H), 7.25-7.32 (m, 4H), 7.33-7.4 (m, 6H).

7.31. (4*R*,5*R*)-1,3-dimethyl-4,5-diphenylimidazolidinone-2-one (45).

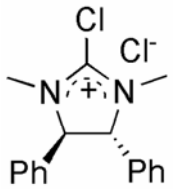


To a ice cold suspension of 80 % NaH (88 mg, 2.933 mmol) in DMF (3.15 mL), under a nitrogen atmosphere, was added portion wise (4*R*,5*R*)-4,5-diphenyl-2-imidazolidinone (**44**) and the mixture was stirred at this temperature for 40 min. After addition of Iodomethane (186 µL, 2.919 mmol) the mixture was stirred at room temperature for overnight. Poured the reaction mixture in 5% HCl and then extracted with dichloromethane. The combined organic layers were washed with water, dried (MgSO4) and evaporated to dryness under reduced pressure. Purification of residue by flash column chromatography (Ethyl acetate: Hexane 4:6) gave 300 mg (85.31 %) pure white compound **45.**

^{1}H NMR: (300 MHz, $CDCl_3$); δ = 1.38 (s, 9H, *tert*-butyl), 2.46 (s, 3H, Me), 7.98 (s, 2H-Aromatic).

$[\alpha]^{20}_{D}$ = - 41.2 (CHCl3).

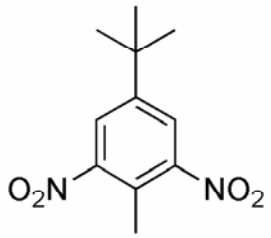
7. 32. (4*R*,5*R*)-2-chloro-1,3-dimethyl-4,5-diphenyl-2-imidazolinium chloride (46) .



A solution of (4*R*,5*R*)-1,3-dimethyl-4,5-diphenylimidazolidinone-2-one (**45)** (180 mg, 0.676 mmol) and Oxalyl Chloride (71 µL, 0.813 mmol) in anhydrous benzene (4.3 mL) were refluxed for 12.5 hrs. After cooling the precipitate was filtered, washed with anhydrous benzene in nitrogen atmosphere and dried under reduced pressure to give (**46)** as a hygroscopic colourless compound (89.3 mg, 41%).

^{1}H NMR: (300 MHz, $CDCl_3$); δ = 1.22 (s, 9H, *tert*-butyl), 1.95 (s, 3H, Me), 3.45 (bs, 4H, $2NH_2$) 6.24 (s, 2H, Aromatic).

7.33. 2, 6-Dinitro-4-*tert*-butyltoluene (48).

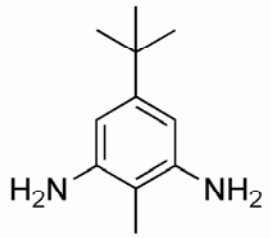


To the mixture of conc. Sulphuric acid (70 mL) and conc. Nitric acid (54 mL) was added drop wise 4-*tert*-butyl toluene (**47**) (34.8 mL, 0.2 mol) over the period of two hours bellow 5 °C. Reaction mixture was stirred further bellow 5 °C for 12 hours.

Poured the reaction mixture in to the ice and dichloromethane was added. Separated layers and aqueous layer extracted with dichloromethane. Combined organic layers were washed with saturated $NaHCO_3$ solution and then with water. Organic layer were dried over Na_2SO_4 and solvent was evaporated at atmospheric pressure. Traces of solvent were removed at reduced pressure. Crystallization by Hexane gave 35.8 g (75%) yellow compound **48.**

^{1}H NMR: (300 MHz, $CDCl_3$); δ = 1.38 (s, 9H, *tert*-butyl), 2.46 (s, 3H, Me), 7.98 (s, 2H, Aromatic).

7.34. 2,6-Diamino-4-*tert*-butyltoluene (49).

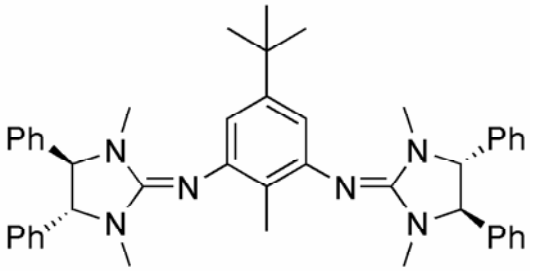


To a boiling solution of 2,6-dinitro-4-*tert*-butyl toluene (**48**) (15 g, 63 mmol) in ethanol (145 mL) was added a solution of Stannous Chloride dihydrate (117.8 g, 522 mmol) in

conc. HCl. The reaction mixture was refluxed for two hours and the solvent was evaporated. The residue was made strongly alkaline by conc. NaOH and the product was extracted by dichloromethane. The organic layer was dried over Na_2SO_4 and the solvent was evaporated. Crystallization by Hexane gave red product **49** in 60 % yield (6.74 g).

^{1}H NMR: (300 MHz, $CDCl_3$); δ = 1.24 (s, 9H), 1.962 (s, 3H), 3.4-3.6 (bs, 4H), 6.249 (s, 2H).

7.35. 5-*tert*-Butyl-N, N-bis(1, 3 dimethyl-4*R*, 5*R*-diphenyl imidazolidin-2-ylidene)-2-methyl-benzene-1, 3-diamine (41).



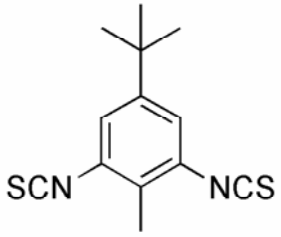
To a stirred solution of 2,6-Diamino-4-*tert*-butyl toluene (**49**)(12 mg, 0.0674 mmol) and Et_3N (38 μL, 0.273 mmol) in CH_2Cl_2 (700 μL) was added drop wise solution of (4*R*,5*R*)-2-chloro-1,3-dimethyl-4,5-diphenyl-2-imidazolinium chloride (**46**) in CH_2Cl_2 (700 μL) at inert atmosphere and the reaction mixture was stirred at room temperature for 24 hrs. Reaction was quenched by dil. HCl. Organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. Solvent was evaporated and residue made basic by 3% NaOH solution and extracted with toluene. The organic layer was dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The compound was purified by preparative TLC.

^{1}H NMR: (300 MHz, $CDCl_3$); δ = 1.29 (s, 9H, *tert*-butyl), 2.28 (s, 3H, Me), 4.01 (s, 2H), 6.71 (s, 2H), 7.16-7.33 (m, 10H)

HRMS calculated for ($C_{45}H_{51}N_6$) $[M + H]^+$ = 675.417; found 675.416.

$[\alpha]^{20}_D$ = -129.2°

7.36. 4-*tert*-Butyl-2,5-diisothiocyanato-toluene (50).



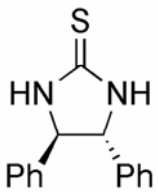
To the stirred solution of 4-*tert*-Butyl-2,6-diamino toluene (**41**) (2.82 g, 15.842 mmol) in Chloroform (1070 mL) and $NaHCO_3$ solution (3.1 g in 400 mL water) was added Thiophosgene (3.4 mL, 44.61 mmol) at 0 °C. Reaction mixture was stirred at 0 °C for 15 minutes and then at room temperature for two and half hours.

Separated layers and aqueous layer was extracted by chloroform (2 × 100 mL). Combined organic layers were washed with water and dried over Na_2SO_4. Evaporation of the solvent gave the brown residue which was purified by flash column chromatography to provide product **50** in 75.3% yield (3.182 g) as yellow crystals.

^{1}H NMR: (300 MHz, $CDCl_3$); δ = 1.27 (s, 9H), 2.36 (s, 3H), 7.13 (s, 2H).

(EI) mass calculated for $C_{13}H_{14}N_2S_2$ = 262.06; found 262.2

7.37. (4*R*,5*R*)-*trans*-diphenylimidazolidine-2-thione (53).



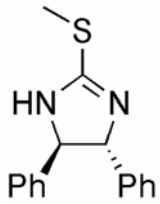
(1*R*,2*R*)-*trans*-diphenyl-1,2-diaminoethane (200 mg, 0.943 mmol), water (470 µL) and ethanol (470 µL) were refluxed with CS_2 (66 µL, 1.094mmol) for one hour. Then reaction mixture was acidified by 5M HCl (9.4 µL) and refluxing was continued for 12 hrs. On cooling yellow solid was formed which was filtered and washed with little amount of cold ethanol. After drying under vacuum, compound **53** was obtained in 71% yield (170 mg).

^{1}H NMR: (300 MHz, $CDCl_3$); δ = 4.81 (s, 2H, CH), 6.42 (bs, 2H, NH), 7.24-7.28 (s, 5H, aromatic), 7.36-7.43 (s, 5H, Ph)

(EI) mass calculated for $C_{15}H_{14}N_2S$ = 254.09; found 254.

$[\alpha]^{20}_D$ = -34.2°

7.38. 2-Methylsulfanyl-(4*R*,5*R*)-diphenyl-4,5-dihydro-1H-imidazole (54).



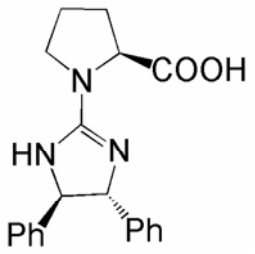
To a stirred solution of (4*R*,5*R*)-diphenyl-imidazolidine-2-thione (405 mg, 1.59 mmol) in ethanol (8 mL) was added Iodomethane (300 μL, 4.81 mmol) and the reaction mixture was refluxed for four hours at inert atmosphere. The solvent was evaporated completely and solid was dissolved in chloroform. The organic solution was washed with 5% $NaHCO_3$ solution and aqueous layer was extracted twice by chloroform. The combined organic layers were dried over Na_2SO_4. The solvent was evaporated and the compound was dried under reduced pressure to obtain 422 mg (98.71%) yellowish white product.

^{1}H NMR: (300 MHz, $CDCl_3$); δ = 2.62 (s, 3H), 4.77 (s, 2H), 7.21-7.36 (m, 10H).

(EI) mass calculated for $C_{16}H_{16}N_2S$ = 268; found 268.

$[\alpha]^{20}_D$ = -75°

7.39. [1,(4*R*,5*R*-Diphenyl-4,5-dihydro-1H-imidazole-2-yl) pyrrolidine-2-yl]-carboxylic acid (42).



To a stirred solution of L-proline (29.2 mg, 0.25 mmol) in ethanol (1.36 mL) and 77.6 μL (0.55 mmol), was added **54** (68 mg, 0.25 mmol) and the reaction mixture was refluxed for 40 hrs. Solvent was evaporated completely and the residue was acidified with 5 N HCl. The aqueous layer was extracted by CH_2Cl_2 (3 × 1.4 mL) and the organic layer was made basic with 3% NaOH solution. Separated layers and aqueous layer was extracted by CH_2Cl_2 (3 × 1.4 mL). Combined organic layers were dried over Na_2SO_4. The solvent was evaporated to get hygroscopic compound **42** in 64% yield.

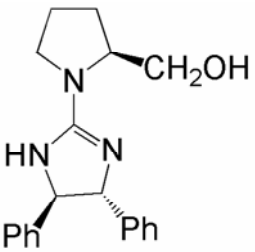
^{1}H NMR: (300 MHz, $CDCl_3$); δ = 2-2.05 (m, 4H), 2.3-2.45 (m, 2H), 3.55-3.8(m, 2H) 4.7 (d, 1H), 4.9 (s, 2H), 7.25-7.55 (m, 10H).

^{13}C NMR: (300 MHz, CD_3OD); δ = 9.2 (CH_2), 24.5 (CH_2), 31.6 (CH_2), 62.4 (CH), 69.9 (CH), 70.1 (CH), 127.6-140 (aromatic), 158 (guanidine), 173.5 (COOH).

HRMS calculated for ($C_{20}H_{22}N_3O_2$) $[M + H]^+$ = 336.171; found 336.170.

$[\alpha]^{20}_D$ = -58.7°

7.40. [1,(4*R*,5*R*-diphenyl-4,5-dihydro-1H-imidazole-2-yl) pyrrolidine-2-yl]-methanol (43).



Guanidine **43** was synthesized by the same procedure as described for **42**.

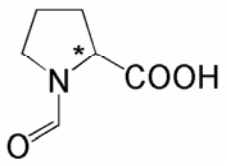
^{1}H NMR: (300 MHz, $CDCl_3$); δ = 1.98-2.05 (m, 4H), 3.47-3.49 (m, 4H), 4.03 (s, 1H), 4.84 (s, 2H), 5.04 (s, 1H), 7.35-7.45 (m, 10H), 8.87 (s, 1H).

^{13}C NMR: (300 MHz, $CDCl_3$); δ = 15.1 (CH_2), 23.4 (CH_2), 27.9 (CH_2), 62.8 (CH_2), 65.7 (CH), 67.9 (CH), 68.3 (CH), 126.6- 137 (aromatic), 157 (guanidine).

HRMS calculated for ($C_{20}H_{24}N_3O$) $[M + H]^+$ = 322.191; found 322.191.

$[\alpha]^{20}_D$ = -44.5° ($CHCl_3$).

7. 41. N-formyl-proline (62 or 63).



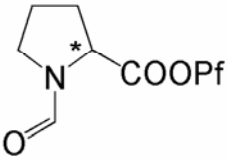
L-Proline (3 g, 26.05 mmol) was dissolved in 85% formic acid (55 mL) and cooled to 0 °C. Acetic anhydride (18 mL) was added and the mixture was stirred at room temperature for 2 h. Ice cold water (21 mL) was then added and the solvent was removed under reduced pressure. The residual pale yellow oil was dissolved in methanol and the solvent was removed under reduced pressure to give the product **62** as a white powder. Yield 3.4 g (91%).

Compound **63** was synthesized in 88% yield by the same procedure as described for **62**.

^{1}H NMR: (300 MHz, $CDCl_3$); δ = 1.97-2.28 (m, 4H), 3.49-3.69 (m, 2H), 4.39-4.48 (m, 1H), 8.23-8.28 (s, 1H), 10.73 (s, 1H).

(ESI) mass calculated for $C_6H_9NO_3$ = 143.06; found 166 $[M + Na]^+$

7.42. Pentaflurophenyl-1-formylpyrolidine-2-carboxylate (64 or 65).



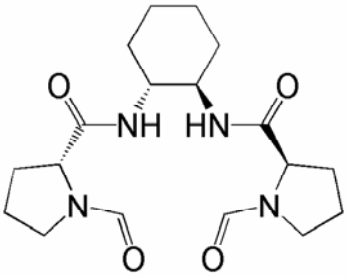
The cooled solution of N,N-dicyclohexylcarbodiimide (DCC) (4.76 g, 23.06 mmol) in acetone (15 mL) was added dropwise to the stirred solution of N-formyl proline **62** (3 g,

20.96 mmol) and pentafurrophenol (PfOH) (4.25 g, 23.09 mmol) in acetone (25 mL) at 0 ^{o}C. The reaction mixture was stirred at 0 ^{o}C for 5 h. The precipitate formed was filtered off and washed with acetone (15 mL). Solvent was evaporated from filtrates in vacuum to afford oily residue which was dissolved in acetone (15 mL) and cooled to 0 °C. Precipitated urea was filtered to get the oily product which on drying and cooling forms white product **64** in 92% yield (5.96 g).

Compound **65** was synthesized in 90% yield by the same procedure as described for **64**.

^{1}H NMR: (300 MHz, $CDCl_3$); δ = 1.98-2.48 (m, 4 H), 3.58-3.74 (m, 2 H), 4.73-4.79 (m, 1 H), 8.32-8.34 (s, 1H).

7. 43. *N,N'*-Bis(*R*-N-formyl-prolyl)-*R,R*-1,2-cyclohexanediamine (57).



To a stirred solution of (1*R*,2*R*)- cyclohexanediamine (490 mg, 4.29 mmol) in DMF (10 mL) was added the solution of **63** (3.051 g, 9.86 mmol) in DMF (15 mL). The reaction mixture was stirred at room temperature for 12 h. The white precipitated product was filtered and washed with cold ethyl acetate. The compound was dried under vacuum to get white powder (**57**). Yield 1.253 g (80%).

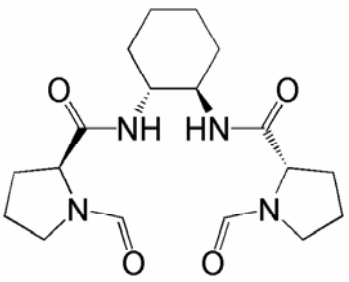
^{1}H NMR: (300 MHz, $CDCl_3$); δ = 1.63-1.65 (s, 4H), 1.70-1.96 (m, 12H), 3.44-3.61 (m, 2H), 4.14-4.30 (m, 2H), 7.56-7.86 (m, 2H), 8.00-8.16 (m, 2H).

HRMS calculated for $C_{18}H_{28}N_4O_4$, 364.44; found 364.21.

Elemental analysis: Calculated C, 59.32; H, 7.74; N, 15.37; O, 17.56; found C, 59.01; H, 7.95; N, 15.21.

$[\alpha]^{20}_{D}$ = +245.6° ($CHCl_3$).

7.44. *N,N'*-Bis(*S*-N-formyl-prolyl)-*R,R*-1,2-cyclohexanediamine (58).



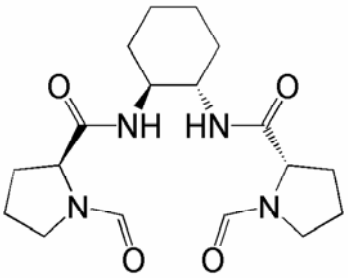
Bis-formamide **58** synthesized by similar way as described for the synthesis of **57** i.e. by coupling of **64** with (1*R*,2*R*)- cyclohexanediamine. Yield 76.5%.

HRMS calculated $C_{18}H_{28}N_4O_4$, 364.44; found 364.21.

Elemental analysis: Calculated C, 59.32; H, 7.74; N, 15.37; O, 17.56; found C, 59.01; H, 7.89; N, 15.15

$[\alpha]^{20}{}_D$ = -108° ($CHCl_3$)

7.45. *N,N'*-Bis(*S*-N-formyl-prolyl)-*S,S*-1,2-cyclohexanediamine (59).



Bisformamide **59**synthesized by similar way as described for the synthesis of **57** and **58** i.e. by coupling of **64** with (1*S*,2*S*)- cyclohexanediamine. Yield 79%.

HRMS calculated $C_{18}H_{28}N_4O_4$, 364.44; found 364.21.

Elemental ananlysis: Calculated C, 59.32; H, 7.74; N, 15.37; O, 17.56; found C, 58.67 H, 7.93; N, 14.83.

$[\alpha]^{20}{}_D$ = + 237° ($CHCl_3$).

7.46. General procedure for synthesis of aldimines.

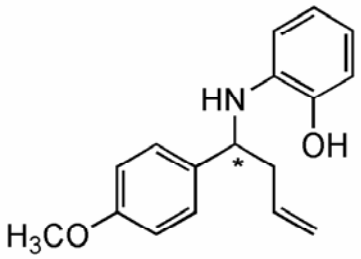
Ortho-aminophenol (5 g, 45.81 mmol) and para-methoxy benzaldehyde (5.017 mL, 41.234 mmol) were heated at 80 °C in toluene with 4 Å molecular sieves for 12 hrs. Reaction mixture was filtered through celite and solvent was evaporated. The compound was crystallized by hexane to get yellow needles of aldimine **66**.

^{1}H NMR: (300 MHz, $CDCl_3$); δ = 3.868 (s, 3H), 6.877-6.881 (t, 1H), 6.964-7.006 (m, 2H), 7.131-7.156 (t, 1H), 7.245-7.273 (d, 1H), 7.855-7.883 (d, 2H), 8.598 (s, 1H).

General procedure for allylation

To a solution of imine (0.0825 mmol), bisformamide **57** (0.165 mmol, 2 equiv.) and L-proline (0.165 mmol, 2 equiv.) in CH_2Cl_2 (0.165 mL) was added allyltrichlorosilane (0.124 mmol, 1.5 equiv). After stirring vigorously at room temperature, triethylamine (0.06 mL) in methanol (0.3 mL) was added to quench the reaction. The mixture was diluted with diethyl ether (11 mL) and water (5 mL). The organic layer was separated, washed twice with water (5 mL), dried over anhydrous Na_2SO_4, filtered, and purified by column chromatography (hexane/ethyl acetate) to give product.

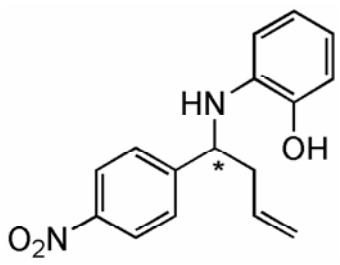
7.47. 2[1-(4-methoxy-phenyl)-but-3-enylamino]-phenol (67).



^{1}H NMR: (300 MHz, $CDCl_3$); δ = 2.56-2.58 (m, 2H), 3.77 (s, 3H), 4.3-4.4 (broad singlate, 1H), 4.75-4.85 (broad singlate, 1H), 5.10-5.30 (m, 2H), 5.75-5.74 (m, 1H), 6.38-6.67 (m, 4H), 6.83-6.86 (m, 2H), 7.24-7.26 (m, 2H).

ESI-MS (negative ion): m/z = 268.1 $[M - H]^-$.

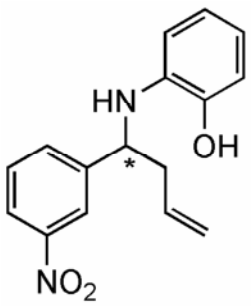
7.48. 2[1-(4-nitro-phenyl)-but-3-enylamino]-phenol (69).



^{1}H NMR: (300 MHz, $CDCl_3$); δ = 2.56-2.69 (m, 2H), 4.30-4.35 (broad singlate, 1H), 4.75 (broad singlate, 1H), 5.13-5.21 (m, 2H), 6.13-6.16 (m, 1H), 6.53-6.66 (m, 4H), 7.51-7.54 (m, 2H), 8.14-8.17 (m, 2H).

ESI-MS (negative ion): *m*/*z* = 283.0 $[M - H]^-$.

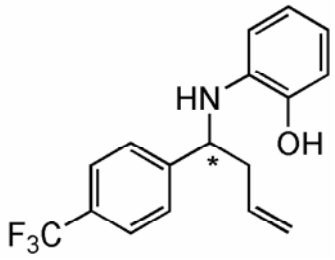
7.49. 2[1-(3-nitro-phenyl)-but-3-enylamino]-phenol.



^{1}H NMR: (300 MHz, $CDCl_3$); δ = 2.51-2.66 (m, 2H), 4.44-4.48 (broad singlate, 1H), 4.81-4.86 (broad singlate, 1H), 5.15-5.22 (m, 2H), 5.66-5.81 (m, 1H), 6.23-6.71 (m, 4H), 7.44-8.24 (m, 4H).

ESI-MS (negative ion): *m*/*z* = 283.0 $[M - H]^-$.

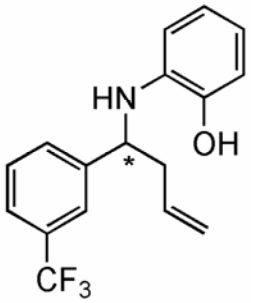
7.50. 2[1-(4-trifluoromethyl-phenyl)-but-3-enylamino]-phenol.



^{1}H NMR: (300 MHz, $CDCl_3$); δ = 2.51-2.61 (m, 2H), 4.12 (broad singlate, 1H), 5.13-5.28 (broad singlate, 1H), 5.21-5.28 (m, 2H), 5.67-5.79 (m, 1H), 6.25-6.70 (m, 4H), 7.45-7.56 (m, 4H).

ESI-MS (negative ion): *m*/*z* = 306.1 $[M - H]^-$.

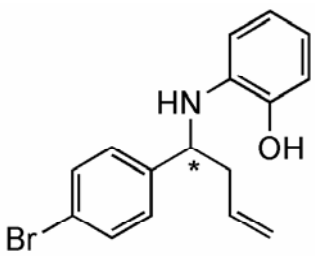
7.51. 2[1-(3-trifluoromethyl-phenyl)-but-3-enylamino]-phenol.



^{1}H NMR: (300 MHz, $CDCl_3$); δ = 2.48-2.64 (m, 2H), 4.36-4.42 (broad singlate, 1H), 4.67-4.76 (broad singlate, 1H), 5.13-5.21 (m, 2H), 5.68-5.82 (m, 1H), 6.28-6.70 (m, 4H), 7.24-7.69 (m, 4H).

ESI-MS (negative ion): *m*/*z* = 306.1 $[M - H]^-$.

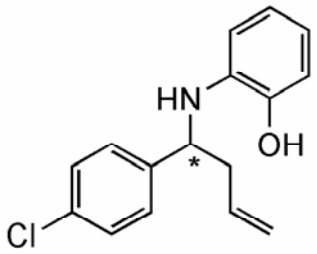
7.52. 2[1-(4-bromo-phenyl)-but-3-enylamino]-phenol.



^{1}H NMR: (300 MHz, $CDCl_3$); δ = 2.50-2.59 (m, 2H), 4.33 (broad singlate, 1H), 4.62-4.86 (broad singlate, 1H), 5.13-5.20 (m, 2H), 5.71-5.81 (m, 1H), 6.31-6.69 (m, 4H), 7.23-7.45 (m, 4H).

ESI-MS (negative ion): *m*/*z* = 316.0 $[M - H]^{2-}$.

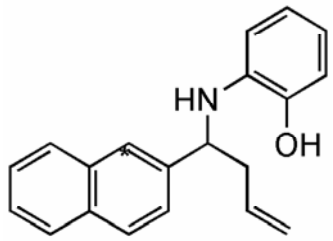
7.53. 2[1-(4-chloro-phenyl)-but-3-enylamino]-phenol.



^{1}H NMR: (300 MHz, $CDCl_3$); δ = 2.50-2.55 (m, 2H), 4.32 (broad singlate, 1H), 4.60-4.83 (broad singlate, 1H), 5.11-5.20 (m, 2H), 5.73-5.75 (m, 1H), 6.29-6.66 (m, 4H), 7.24-7.30 (m, 4H).

ESI-MS (negative ion): *m*/*z* = 272.0 $[M - H]^-$.

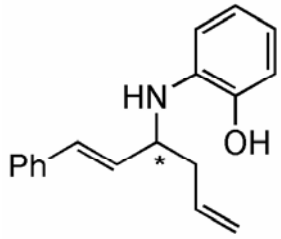
7.54. 2[1-(2-napthyl)-but-3-enylamino]-phenol.



^{1}H NMR: (300 MHz, $CDCl_3$); δ = 2.58-2.70 (m, 2H), 4.52 (broad singlate, 1H), 4.82-4.86 (broad singlate, 1H), 5.12-5.24 (m, 2H), 5.74-5.88 (m, 1H), 6.41-6.68 (m, 4H), 7.23-7.52 (m, 3H), 7.77-7.82 (m, 4H).

ESI-MS (negative ion): *m*/*z* = 288.1 $[M - H]^-$.

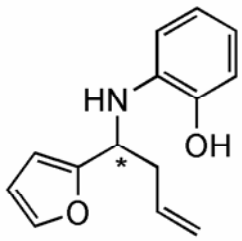
7.55. 2[1-(cinnamyl)-but-3-enylamino]-phenol.



^{1}H NMR: (300 MHz, $CDCl_3$); δ = 2.43-2.51 (m, 2H), 3.96-4.14 (broad singlate, 1H), 4.30-4.85 (broad singlate, 1H), 5.13-5.22 (m, 2H), 5.80-5.94 (m, 1H), 6.15-6.23 (m, 1H), 6.54-6.79 (m, 4H), 7.17-7.53 (m, 5H).

ESI-MS (negative ion): *m*/*z* = 264.0 $[M - H]^-$.

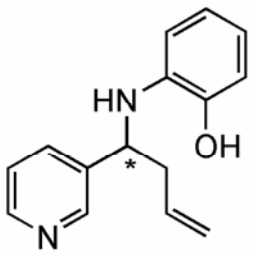
7.56. 2[1-(1-furyl)-but-3-enylamino]-phenol.



^{1}H NMR: (300 MHz, $CDCl_3$); δ = 2.64-2.68 (m, 2H), 4.08-4.15 (m, 1H), 4.41-4.45 (triplate, 1H), 4.60-4.85 (broad singlate, 1H), 5.09-5.19 (m, 2H), 5.70-5.84 (m, 1H), 6.12-6.14 (s, 1H), 6.25-6.27 (s, 1H), 6.60-6.78 (m, 4H), 7.33-7.34 (s, 1H).

ESI-MS (negative ion): *m*/*z* = 228.0 $[M - H]^-$.

7.57. 2[1-(2-pyridine)-but-3-enylamino]-phenol.



^{1}H NMR: (300 MHz, $CDCl_3$); δ = 2.57-2.76 (m, 2H), 4.53-4.58 (m, 1H), 5.04-5.13 (m, triplate, 2H), 5.66-5.82 (m, 1H), 6.40-6.76 (m, 4H), 7.16-7.36 (m, 4H), 8.58-8.59 (broad singlate, 1H).

ESI-MS (negative ion): *m*/*z* = 239.1 $[M - H]^-$.

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9. List of Publications

1) Trends in Asymmetric Michael Reactions Catalysed by Tripeptides in Combination with Achiral Additive in Different Solvents. Svetlana B.Tsogoeva, Sunil B. Jagtap, Zoya A. Ardemasova and Victor N. Kalikhevich. *Eur. J. Org. Chem*. **2004**, 4014.

2) Dual Catalyst Control in the Chiral Diamine-Dipeptide-Catalyzed Asymmetric Michael Addition. Svetlana B.Tsogoeva, Sunil B. Jagtap, *Synlett*. **2004**, 14, 2624.

3) 4-trans-Amino-proline based Di- and Tetrapeptides as Organic Catalysts for Asymmetric C-C Bond Formation Reactions. Svetlana B.Tsogoeva, Sunil B. Jagtap, Zoya A. Ardemasova. *Tetrahedron: Asymmetry*. **2006**, 17, 989.

4) First enantioselective organocatalytic allylation of simple aldimines with allyltrichlorosilane. ***Chem. Commun.*** **2006**, 45, 4747.

10. Lebenslauf

Ich wurde am 19. November 1975 als 4. Kind von Chabubai und Baburao Jagtap in Kothale, Maharashtra, Indien geboren.

Von Juni 1981 bis Mai 1988 besuchte ich die "*Jeevan Sikshan Vidya Mandir*" in Kothale, wechselte dann im Juli 1988 zur "*Mathama Gandhi Vidhyalay*" in Uruli Kanchan, in der ich bis Juli 1991 verblieb.

Von August 1991 bis May 1993 besuchte ich das "*Waghire College, Saswad*" in Maharashtra, in der ich mein I. Sc. (Intermediate in Science) machte.

Von 1995 bis 1998 studierte ich an der "*Waghire College, Saswad, Pune University*" in Maharashtra im Fachgebiet Chemie.

Am April 1998 wurde mir der akademische Grad "First class *B. Sc.* (Bachelor of science)." zugesprochen.

Zum Sommersemester 1998/2000 nahm ich das Studium der Chemie an der "*P.V.P College, Pravaranagar, University of Pune*" auf. Am May 2000 wurde mir der akademische Grad "*M. Sc.* (Master of science)" zuerkannt.

Von 2001 bis Jan. 2003 habe ich in der Pharma industrie für "*WOCKHARDT Pharmaceuticals*" und "*Dr. Reddys Research Laboratories*" gearbeitet.

Seit Feb. 2003 arbeite ich im Arbeitskreis von Junior Prof. Dr. Svetlana B. Tsogoeva an meiner Doktorarbeit mit dem Titel " *Synthesis and Application of new chiral Peptides, Guanidines and Formamides as Organocatalysts for Asymmetric C-C Bond Formation Reactions.*"

Sunil Jagtap