THESIS ON NATURAL AND EXACT SCIENCES B97

Asymmetric Organocatalytic Michael and Aldol Reactions Mediated by Cyclic Amines

MARJU LAARS

TUT
PRESS

TALLINN UNIVERSITY OF TECHNOLOGY
Faculty of Science
Department of Chemistry

Dissertation was accepted for the defence of the degree of Doctor of Philosophy in Natural and Exact Sciences on October 6th, 2010

Supervisor: Professor Tõnis Kanger, Department of Chemistry,
Tallinn University of Technology, Estonia

Opponents: Professor Andrei Malkov, Department of Chemistry,
Loughborough University, UK

Dr. Asko Uri, Institute of Chemistry, University of Tartu, Estonia

Defence of the thesis: November 25, 2010

Declaration:
Hereby I declare that this doctoral thesis, my original investigation and achievement, submitted for the doctoral degree at Tallinn University of Technology has not been submitted for any academic degree.

Marju Laars

ISSN 1406-4723
ISBN 978-9949-23-038-9

LOODUS- JA TÄPPISTEADUSED B97

Asümmeetriline organokatalüütiline Michaeli ja aldoolreaktsioon tsükliliste amiinide toimel

MARJU LAARS

TTÜ
KIRJASTUS

Contents

List of publications

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

I Kriis, K.; Kanger, T.; Laars, M.; Kailas, T.; Müürisepp, A.-M.; Pehk, T.; Lopp, M. Enantioselective synthesis of Wieland-Miescher ketone trough bimorpholine-catalyzed organocatalytic aldol condensation. *Synlett* **2006**, 1699-1702.

II Sulzer-Mossé, S.; Laars, M.; Kriis, K.; Kanger, T.; Alexakis, A. Synthesis and use of 3,3′-bimorpholine derivatives in asymmetric Michael addition and intramolecular aldol reaction. *Synthesis* **2007**, 1729-1732.

III Kriis, K.; Laars, M.; Lippur, K.; Kanger, T. Bimorpholines as alternative organocatalysts in asymmetric aldol reactions. *Chimia* **2007**, *61*, 232-235.

IV Kanger, T.; Kriis, K.; Laars, M.; Kailas, T.; Müürisepp, A.-M.; Pehk, T.; Lopp, M. Bimorpholine-mediated enantioselective intramolecular and intermolecular aldol condensation. *J. Org. Chem*. **2007**, *72*, 5168-5173.

V Laars, M.; Kriis, K.; Kailas, T.; Müürisepp, A.-M.; Pehk, T.; Kanger, T.; Lopp, M. Structural constraints for C_2-symmetric heterocyclic organocatalysts in asymmetric aldol reactions. *Tetrahedron: Asymmetry* **2008**, *19*, 641-645.

VI Laars, M.; Ausmees, K.; Uudsemaa, M.; Tamm, T.; Kanger, T.; Lopp, M. Enantioselective organocatalytic Michael addition of aldehydes to *β*-nitrostyrenes. *J. Org. Chem.* **2009**, *74*, 3772-3775.

VII Uudsemaa, M.; Laars, M.; Kriis, K.; Tamm, T.; Lopp, M.; Kanger, T. Influence of protonation upon the conformations of bipiperidine, bimorpholine, and their derivatives. *Chem. Phys. Lett.* **2009**, *417*, 92-96.

VIII Laars, M.; Raska, H.; Lopp, M.; Kanger, T. Cyclic amino acid salts as catalysts for the asymmetric Michael reaction. *Tetrahedron: Asymmetry* **2010**, *21*, 562-565.

Author's contribution

Articles **I-IV**: performed a large part of the experiments; played a minor part in writing the manuscript.
Article **VII**: synthesis of investigated compounds.
Articles **V**, **VI** and **VIII**: extensive contribution to the experiments; main person responsible for planning and writing the manuscript.

Abbreviations:

BP	(2*R*, 2'*R*)-bipiperidine
BM	(3*S*, 3'*S)*-bimorpholine
Bn	benzyl
^{13}C	carbon (NMR)
cat	catalyst
d	day(s)
DCM	dichloromethane
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
d.r.	diastereomeric ratio
DSS	4,4-dimethyl-4-silapentane-1-sulfonic acid
ee	enantiomeric excess
GC	gas chromatography
h	hour(s)
^{1}H	proton (NMR)
HOMO	highest occupied molecular orbital
HPLC	high performance liquid chromatography
IR	infrared
LUMO	lowest unoccupied molecular orbital
M	unspecified metal
MCA	(*S*)-morpholine-3-carboxylic acid
MS	mass spectrometry
PE	petroleum ether
R	unspecified substituent
r.r.	regioisomeric ratio
rt	room temperature
SOMO	singly occupied molecular orbital
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMS	trimethylsilyl
TS	transition state
Tf	trifluoromethanesulfonic
TfOH	trifluoromethanesulfonic acid
UV	ultraviolet

Introduction

In synthetic organic chemistry today, the discovery of new methods, new reagents and new catalysts has become increasingly focused on achieving high levels of regioselectivity, chemoselectivity, and possibly most importantly, stereoselectivity. In modern times, the foundations of stereoselectivity lie in asymmetric synthesis. The activity of a biologically significant molecule is commonly linked to only one of the possible stereoisomers present and the development of new highly selective strategies to access enatiomerically enriched, or pure, compounds is at the forefront of synthetic organic chemistry.

Organocatalysis[1,2,3,4,5,6,7,8,9,10], the use of small organic molecules to catalyse organic transformations, is a popular field within the domain of chiral molecule (or enantioselective) synthesis. The term 'organocatalysis' describes the acceleration of chemical reactions through the addition of a substoichiometric quantity of an organic compound.[11] Organocatalysis has become the third main branch in catalytic asymmetric synthesis along with enzymatic and organometallic catalysis.

Although organocatalysis has been known about for several decades[12,13], the approach under that name has mostly taken place within the last decade, fuelling the development of a number of outstanding catalysts and applications. Generic modes of activation commonly used in organocatalysis are enamine and iminium, hydrogen-bonding, SOMO and counterion catalysis.

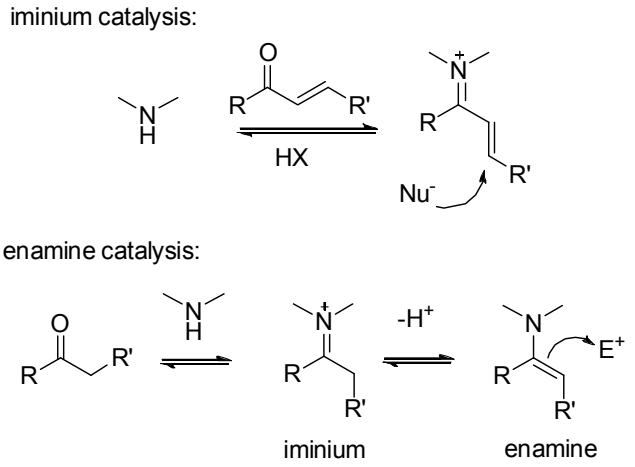
1. Literature overview

1.1. Introduction and background

Organocatalysis is not a new methodology although it has grown explosively only in the last decade: some examples can be found in the literature since the beginning of the last century or even earlier (for example the Knoevenagel reaction[14]). During the 1970s, the proline-catalysed intramolecular aldol process was reported simultaneously by Hajos, Parrish, Wiechert, Eder and Sauer[15,16], but the studies on the use of small organic molecules as catalysts for asymmetric reactions were viewed more as unique chemical reactions than as integral parts of a larger, interconnected field.
In the late 1990s, however, things began to change when Shi[17], Denmark[18] and Yang[19] demonstrated that enantiomerically pure ketones could be used to catalyse the enantioselective epoxidation of simple alkenes.
The field of organocatalysis was effectively launched in 2000 by two publications by Barbas III[20] (on enamine catalysis) and MacMillan[21] (on iminium catalysis) that appeared almost simultaneously, early reports were mainly from those two research groups. Organocatalysis has emerged during the last decade as a concept with a significant number of synthetic applications and it has become the third main branch of catalytic asymmetric synthesis, along with enzymatic and organometallic catalysis. Organocatalytic reactions catalysed by amines, especially secondary amines, are widespread, as secondary amines are capable of both enamine and iminium catalysis.

1.1.1. Mechanistic insights into aminocatalysis

The efficiency and the scope of organocatalysis and, particularly, aminocatalysis[22] have been broadly established. Covalently bonded aminocatalysts operate through two mechanisms, by converting carbonyl substrates either into activated nucleophiles (enamine intermediates) or electrophiles (iminium intermediates) (Scheme 1). In iminium catalysis[23,24], the addition of the amine catalyst to the carbonyl substrate generates an iminium ion as the active species, with lowered LUMO energy, which can react with a nucleophile, whereas in enamine catalysis[25,26,27], the deprotonation of the iminium ion provides the nucleophilic enamine intermediate, with increased HOMO energy, which can attack the electrophile.



Scheme 1. Iminium and enamine catalysis.

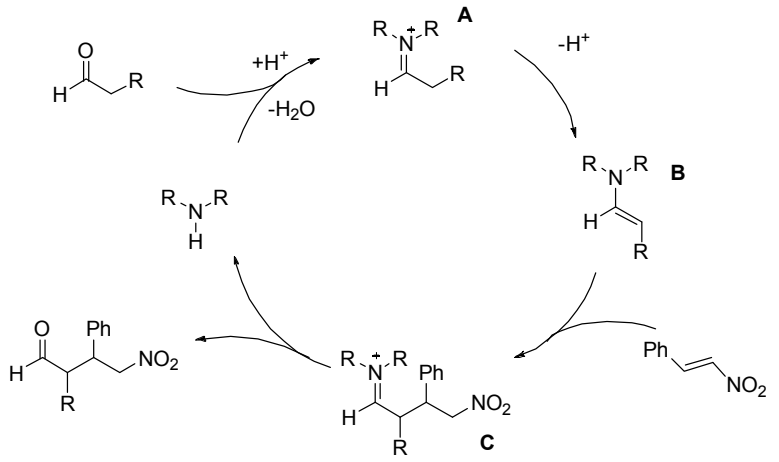
This thesis describes the investigation of organocatalytic Michael and aldol reactions, and therefore this chapter gives an overview of Michael[28] and aldol[29,30,31,32] reactions catalysed by an enamine pathway.

1.2. Organocatalytic Michael reaction

The Michael reaction or Michael addition is the nucleophilic addition of a carbanion or another nucleophile to an α,β-unsaturated carbonyl compound or to a double bond connected with a strongly electron-withdrawing substituent (e. g. nitroolefins).[33] The organocatalytic Michael addition to an α,β-unsaturated carbonyl compound follows an iminium pathway, whereas, in addition to nitroalkenes, a nucleophile is derived from the carbonyl compound via an enamine pathway.

The general mechanistic features of the reaction via the enamine pathway are outlined in Scheme 2. In the first step, an iminium ion **A** is generated by the reversible reaction between a chiral amine catalyst and a carbonyl compound and can be easily deprotonated to form the enamine nucleophilic intermediate **B**, due to the increase of C-H acidity. This enolate equivalent can react with an electron-deficient olefin in order to create a new C-C bond. Subsequent hydrolysis of the α-modified iminium ion **C** affords the Michael adduct and restores the aminocatalyst, which is ready to participate in a new catalytic cycle.

The Michael reaction of nitroolefins represents a convenient access to branched nitroalkanes, which are versatile intermediates in organic synthesis.



Scheme 2. Catalytic cycle of the Michael addition.

1.2.1. Stereodifferentiation in Michael reactions

Running a reaction with a chiral catalyst, stereoselectivity is expected. In general, due to steric hindrance, the *E*-enamine (which is thermodynamically favoured and derives from either an aldehyde or a ketone) would be predominant unless other interactions were to favour the Z-enamine (Figure 1). The α-substituent of the catalyst governs the position of the equilibrium between rotamers, which therefore influences the facial selectivity of the nucleophilic attack on the enamine. The relative sizes of the two sides of the enamine depend on the carbonyl substrate. The smallest group – hydrogen for aldehydes – leads to the formation of the relatively more stable *anti*-rotamer, whereas, in the case of ketones, the less-hindered moiety is the double bond which gives, preferentially, the *syn*-rotamer, as long as other interactions are not involved.

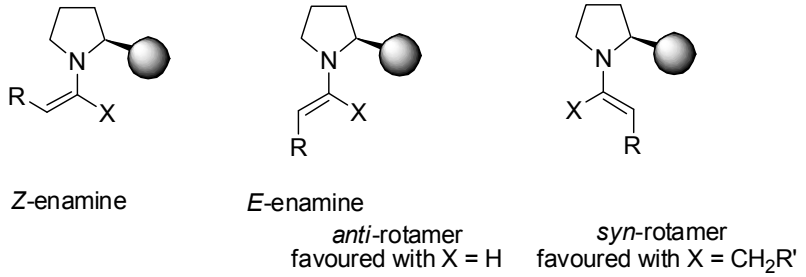


Figure 1. Stereoisomers of enamine.

The stereochemistry of the Michael adduct is generally determined by Seebach's topological rules.[34,35] According to these rules, and as can be seen in the Figure 2a,

the donor (C=C)-bond is in a gauche (synclinal) arrangement between the (C=A)- and the (C-H)-bonds of the acceptor. If the components can exist in (*E*/*Z*) (anti/syn)-isomeric forms, the actual donor and acceptor atoms are situated close to each other. It has also been mentioned that the rules may not hold when very bulky groups and substituents are present or when a protic solvent is used. A bulky group on the catalyst framework could prevent coordinative bonding interactions and force the attack from the opposite side on the chiral substituent. Therefore, the *Si*,*Si* approach is favoured for aldehydes (Figure 3a) and the *Re,Re* approach for ketones (Figure 3b).

In the case of a Michael addition of enamine derived from amine and carbonyl compound to nitroolefin, according to these rules, the enamine double bond is in a gauche arrangement between the C=C and C-H bonds of the nitroolefin (Figure 2b). Additional electrostatic stabilisation between the electron pair of the amino group and nitrogen atom in the nitro group takes place in this conformation. Because the donor and acceptor atoms are situated close to each other, the bigger substituent on enamine is in an anti-periplanar position with respect to the C=A bond, leading to the *Re*,*Re* approach affording *syn* product.

In conclusion, the preferred diastereoselectivity and enantioselectivity of the addition relies on electronic or steric interactions and, obviously, also on the absolute configuration of the chiral aminocatalyst.

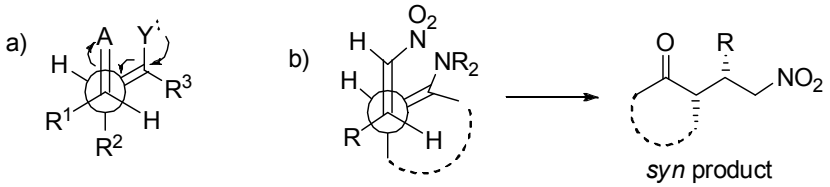


Figure 2. Topological rule for Michael addition of enamine to acceptor.

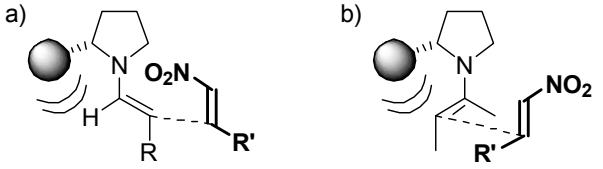


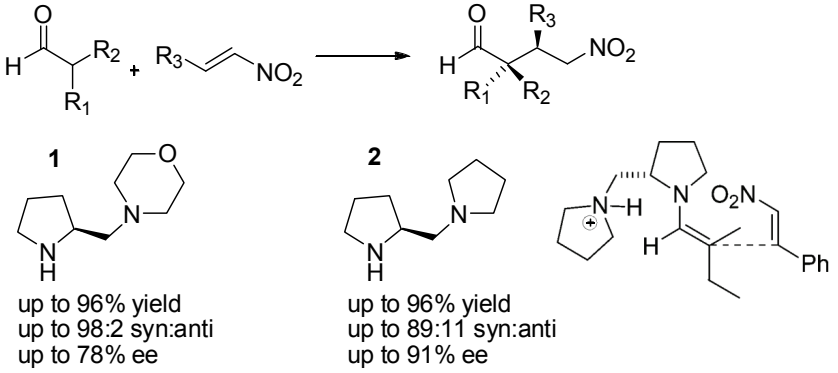
Figure 3. Steric shielding transition state.

1.2.2. Examples of organocatalytic Michael addition

Although many asymmetric variants of the Michael reaction exist, a small selection of the organocatalysts responsible for this selective transformation is presented as follows.

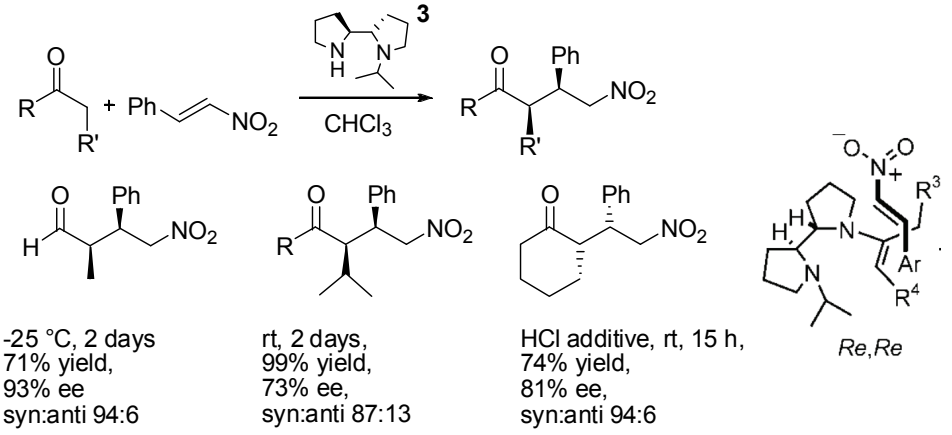
The Barbas group[36,37] reported a highly diastereoselective direct addition of aldehydes to nitro olefins in the presence of (*S*)-2-(morpholinomethyl)pyrrolidine **1**

and (*S*)-1-(2-pyrrolidinylmethyl)pyrrolidine **2** as catalysts (Scheme 3). The reactions proceeded in good to high yields (up to 96%) in a highly *syn* manner (up to 98:2), with up to 91% *ee* values. For (pyrrolidinylmethyl)pyrrolidine, 30 mol% of TFA was used to increase selectivity. The high *syn* selectivity is explained by an acyclic synclinal model, in which there are favourable electrostatic interactions between the partially positive nitrogen of the enamine and the partially negative nitro group in the transition state. An approach of the nitro olefin from the less hindered *Si* face of the enamine would produce the observed stereochemistry.



Scheme 3. Michael addition catalysed by **1** and **2**.

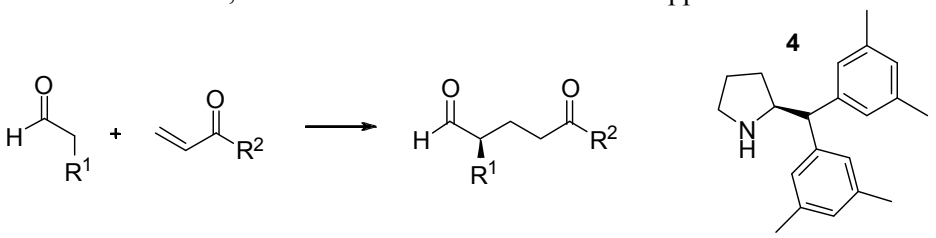
Using this structural analogy, Alexakis et al[38,39] explored the catalytic activity and selectivity of 2,2'-bipyrrolidine derivatives and they found that, in a Michael reaction, the best selectivity was obtained with *N*-iPr-bipyrrolidine **3** as a catalyst (Scheme 4). Linear aldehydes, such as propionaldehyde, provided a higher reaction rate and selectivity (93% *ee*) than such branched aldehydes as isovaleraldehyde



Scheme 4. (*S*,*S*)-iPr-bipyrrolidine catalysed conjugate addition of aldehydes and ketones to nitrostyrene.

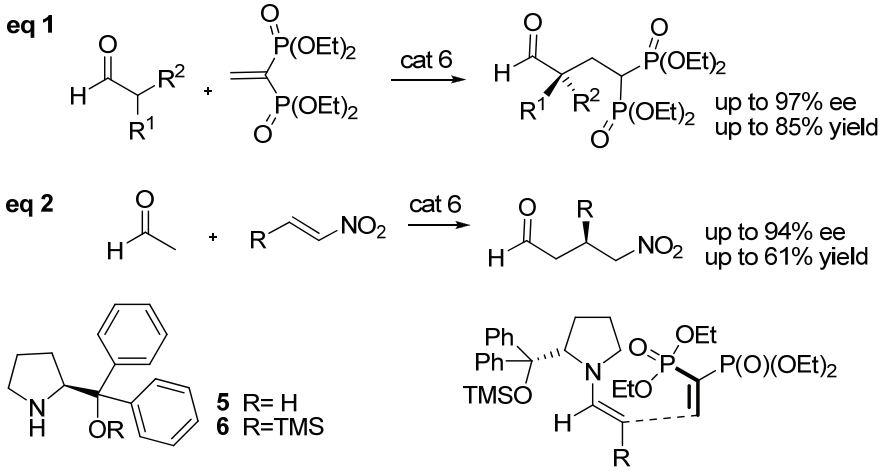
(73% *ee*). Also, the addition of ketones to nitrostyrene was studied using the same catalyst. They found that one equivalent of HCl was needed for the enamine formation, because no reaction occurred without an acid additive. Again, the *syn* selectivity is explained by an acyclic *syn*-clinal model. The isopropyl group blocks the back face against the approach of the nitroolefin, promotes the selective formation of the *E*-enamine and induces the *Re*,*Re* approach (the *Si*,*Si* transition state is certainly less stable on account of the allylic strain present in the transition state).

Melchiorre and Jørgensen[40] developed the first organocatalytic direct enantioselective Michael addition of simple aldehydes to vinyl ketones (Scheme 5). Optically active substituted 5-keto aldehydes formed in moderate to high yields (30-93%) and with good enantioselectivities (50-82%) in the presence of 20 mol% of pyrrolidine **4**. They proposed a transition state based on calculations in which one of the 3,5-dimethylphenyl groups of catalyst **4** shielded the *Re*-face of the enamine intermediate, while the *Si*-face was available for approach.



Scheme 5. (*S*)-2-[bis(3,5-dimethylphenyl)methyl]pyrrolidine **4** catalysed addition of aldehydes to vinyl ketones.

Compared to 2-(diphenylmethyl)-pyrrolidine, diphenyl prolinol [41,42,43,44] **5** was found to be an inefficient catalyst due to the low catalyst turnovers, mainly due to the formation of relatively stable and unreactive hemiaminal species[45]



Scheme 6. Prolinol ether **6** catalysed Michael addition.

that remove a significant amount of catalyst from the catalytic cycle. The simple introduction of a siloxy group into the proline structure, first reported by Hayashi[46], led to increased catalytic activity, thus allowing a decrease in catalyst loading and shorter reaction times. The diaryl prolinol ethers showed a remarkable generality as organocatalysts, as they can catalyse a large number of different types of reactions with excellent stereoselectivity.[47,48,49,50,51,52,53,54] For example, prolinol ether **6** catalysed the enantioselective addition of aldehydes to vinyl phosphonates in 49-85% yield and in 46-97% *ee* as reported by Alexakis et al[55](Scheme 6, eq 1).The bulky aryl and silyl groups promote the selective formation of the *E*-enamine and selectively shield its *Re*-face leading to *Si* attack.
List et al[56] used 20 mol% of catalyst **6** for a Michael addition of acetaldehyde to nitroolefins in up to 94% *ee* and in reasonable yields (Scheme 6, eq 2).
Wennemers et al[57] reported tripeptide **7** catalysed Michael addition of a broad range of aldehydes to nitroolefins and nitroethane (Figure 4). Products formed in an excellent yield (82% - quantitative yield) and selectivity (d.r. 6:1 to 99:1, *ee* 90-99%). They found that only 0.1 mol% of a peptide could be used by reducing the amount of water present in the reaction media. [58]

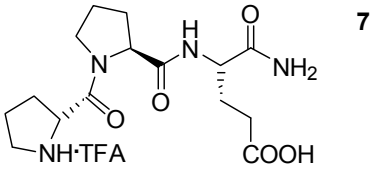
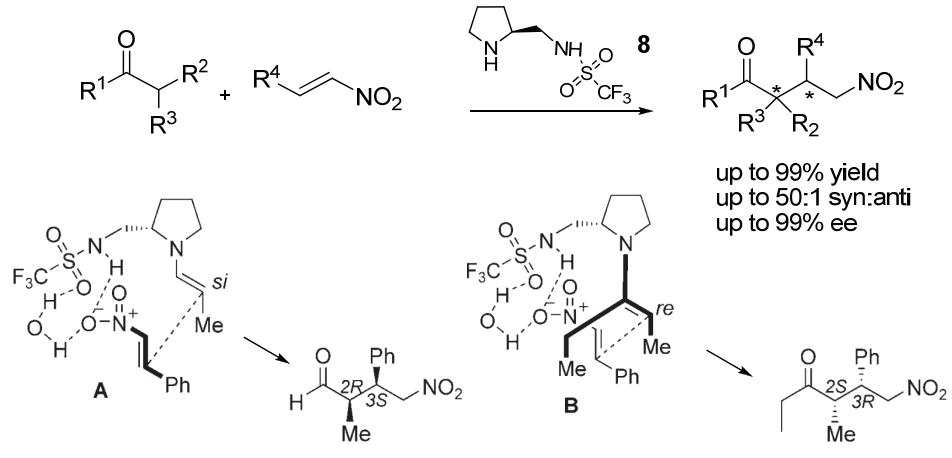


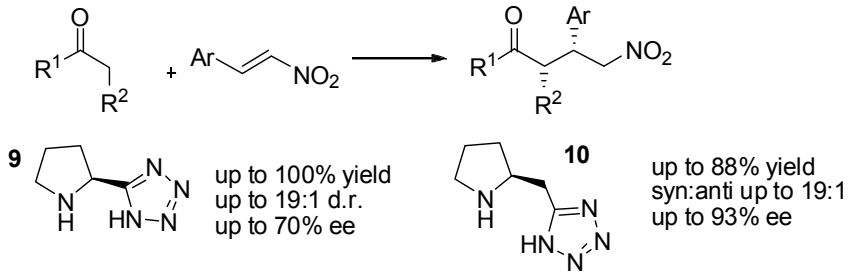
Figure 4. Structure of H-D-Pro-Pro-Glu-NH_2.

Wang et al[59,60] found that (*S*)-pyrrolidine trifluoromethanesulfonamide **8** could be used to promote a highly efficient, asymmetric addition of aldehydes and ketones to nitroolefins (Scheme 7). Reactions took place with excellent diastereo- and enantioselectivity, probably due to the bulkiness of the sulfonamide group and the



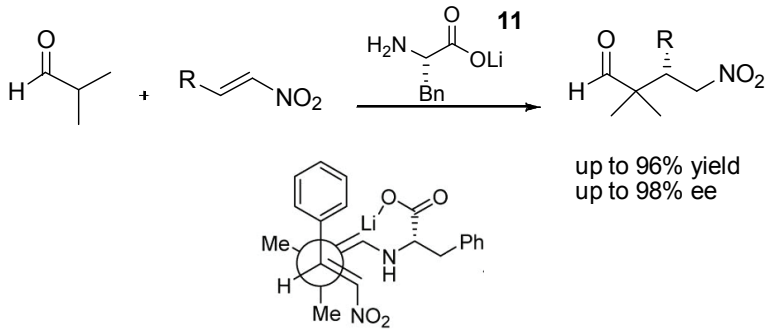
Scheme 7.(*S*)-pyrrolidine trifluoromethanesulfonamide catalysed Michael reaction.

hydrogen bonding between the NH group of pyrrolidine sulfonamide and the nitro group of the olefin, leading to the observed product in a highly selective manner.
The representative transition state models A and B (Scheme 7) for reactions of energetically favoured *anti*-enamines, formed from a catalyst and aldehydes (e.g. propanal) and ketones (e.g. pentanone), are proposed to account for the high enantio- and diastereoselectivity of these Michael addition reactions.
The Ley group[61,62] found that pyrrolidin-2-yltetrazole **9** was a moderately selective catalyst: product formed in up to 70% *ee* (Scheme 8). Later they improved the results by introducing homo-proline tetrazole **10** as a catalyst, and a comparison of those two catalysts under the same conditions revealed an increase of *ee* from 62% to 91%.[63] In general, the addition of a wide range of ketones to nitroolefins was described as giving *ee* up to 93%.



Scheme 8. Proline tetrazole and homo-proline tetrazole catalysed Michael addition.

Yoshida et al[64,65] described the use of primary amino acid salts as catalysts for a Michael addition of aldehydes to nitroalkanes. Although the catalysts contained a metal atom, and by definition were not organocatalysts, they worked via an enamine pathway as organocatalysts. For that reason, and in relation to this thesis, an example of L-phenylalanine Li-salt **11** catalysed reactions is described (Scheme 9). It is noteworthy that the amino acid itself did not catalyse this addition, presumably because of the formation of zwitterion. In the transition state, the benzyl group of the enamine occupies the opposite side of the isobutenyl group to avoid a steric hindrance; therefore, the carboxylate group is fixed on one side of



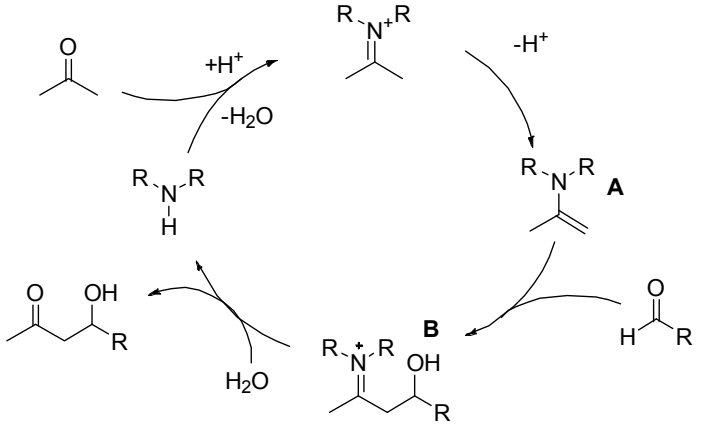
Scheme 9. Phe-OLi **11** catalysed Michael addition.

the enamine and it is thought that the enamine attacks the *Re* face of nitrostyrene. According to the Seebach model for the Michael addition of an enamine to a nitroalkene, there is an electrostatic interaction between the nitrogen atom of enamine and the nitro group, leading to the formation of a (*S*) stereocentre.

Asymmetric organocatalysis represents an elegant and economically attractive way to perform enantioselective Michael reaction due to the versatility of organocatalysts. A wide variety of catalysts are derivatives of pyrrolidine, even subtle changes in the catalysts' structures lead to remarkable improvement in terms of selectivity and reactivity. Secondary amines generate enamines from carbonyl compounds more readily than do primary amines. However, in the case of using sterically hindered carbonyl compounds, such as α-branched aldehydes, primary amines can generate enamines more readily. Undoubtedly, the scope of the catalysts will continue to widen.

1.3. Organocatalytic aldol reaction

The aldol reaction, first discovered by Wurtz in 1872, is one of the most powerful transformations in organic chemistry. The process unites two carbonyl partners to give β-hydroxyketones with up to two stereocentres.
The organocatalytic amine catalysed aldol reaction follows the enamine pathway, the catalytic cycle is presented in Scheme 10. First, enamine **A** is formed from the carbonyl compound and amine. Then the enamine acts as a nucleophile and attacks the electrophilic carbonyl compound affording the iminium intermediate **B**, which will hydrolyse to afford the aldol product and release the amine catalyst. With a chiral catalyst, a stereoselective reaction is expected.

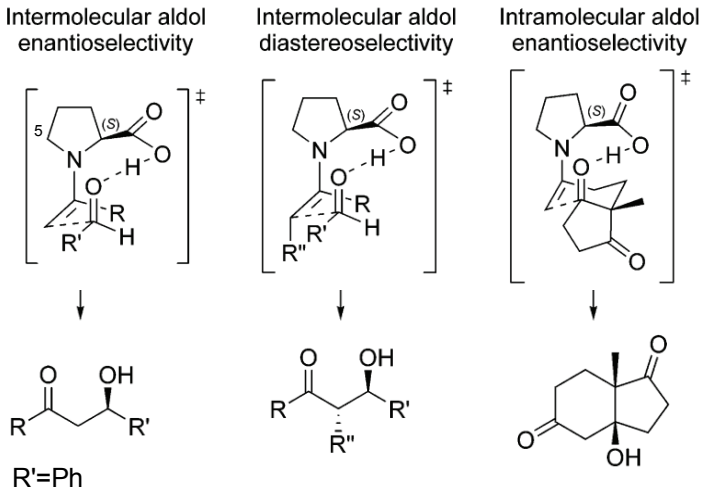


Scheme 10. Mechanism of the amine catalysed aldol reaction.

The aldol reaction has been studied in the presence of various small organic molecules that take advantage of the enamine mechanism, among them L-proline. A short overview and selected examples follow.

1.3.1. Stereoselectivity in the aldol reaction

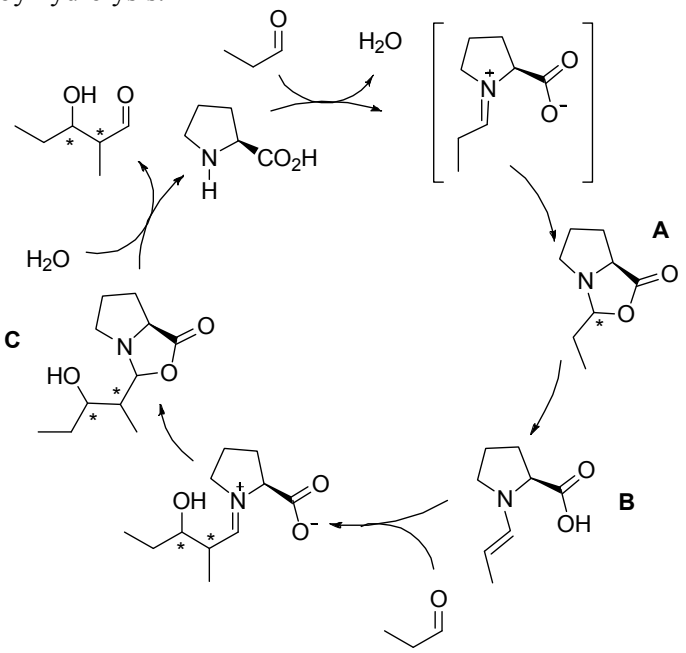
The stereoselectivity of the reactions can be explained by the Houk model [66,67,68] (Scheme 11). According to the model, an *anti*-rotamer is formed from a carbonyl compound and amine. The *anti-Re* transition state has the phenyl group in an ideal equatorial position in the Zimmerman–Traxler transition state. This transition state also includes electrostatic stabilisation due to the N–C5–H···O interaction (hydrogen of the catalyst's C5). The steric hindrance and non-ideal arrangement for proton transfer makes the *syn*-rotamer unfavourable due to the lack of NCH···O electrostatic stabilisation, distortion of the developing iminium double bond to achieve favourable proton transfer from the carboxylic acid, and a partially eclipsed arrangement of the substituents around the forming C-C bond.
In the intramolecular aldol reaction between aldehyde and enamine formed from acetone, one stereogenic centre is formed. Using ketones other than acetone gives rise to a diastereoselectivity, the *anti* aldol adducts are favoured over the *syn* configuration in most cases. In an intermolecular reaction, *cis*-fused bicyclic ketol is formed (Scheme 11).



Scheme 11. Stereoselectivity models for proline-catalysed aldol reactions.

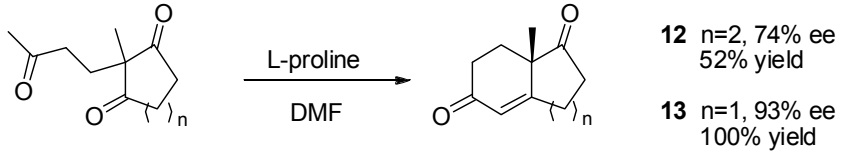
1.3.2. Proline-catalysed aldol reaction

Due to its natural abundance and low cost, L-proline catalysed reactions have been extensively studied and an alternative reaction mechanism was proposed by Seebach et al.[69] and recently slightly modified by Gschwind[70] (Scheme 12). First, oxazolidinone **A** is formed from aldehyde and L-proline, probably via iminium intermediate. Next, the *trans*-rotamer of *E*-enamine **B** is formed from oxazolidinone **A**, which forms a C-C bond with aldehyde. Subsequently, the product oxazolidinone **C** is observed and, in the final step, the catalyst and product are released by hydrolysis.



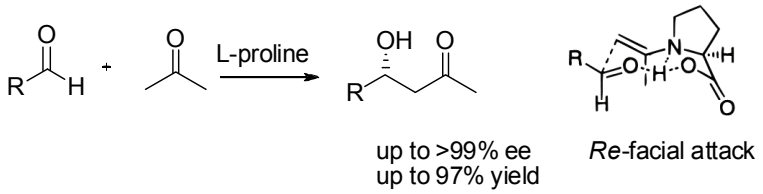
Scheme 12. Alternative oxazolidinone mechanism proposed by Gschwind et al.

The first asymmetric amine-catalysed aldolisation – the proline catalysed intra-molecular aldol reaction – was reported by Hajos, Parrish, Wiechert, Eder and Sauer[15,16]. A six-membered Wieland-Miescher ketone **12** formed with modest yield and selectivity, but the reaction with the five-membered ring substrate **13** proceeded with excellent yield and selectivity to give the cyclised product (Scheme 13). It is noteworthy, that only 3 mol% of L-proline was used. The transition state leading to the observed selectivity is presented in Scheme 11.



Scheme 13. Synthesis of Wieland-Miescher ketone and its nor-analogue.

An intermolecular aldol reaction between acetone and aldehydes catalysed by L-proline was reported by Barbas[20] and Avery[71] (Scheme 14). The highest yield and selectivity were obtained using aryl and branched aliphatic aldehydes, and the desired products were obtained in up to >99% *ee*. Although product formed with high selectivity, a high catalyst loading was required (30-35 mol%).
The stereoselectivity of a proline catalysed aldol reaction is determined with the cyclic transition state, where a hydrogen bonding between the acceptor and carboxylic proton allows the selection between stereotopic faces of the carbonyl groups. In general, *Re*-facial attack is preferable.

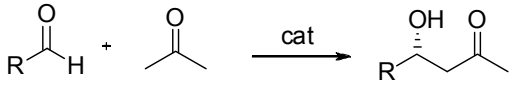


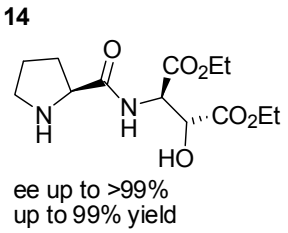
Scheme 14. L-Proline catalysed aldol reaction between acetone and aldehydes.

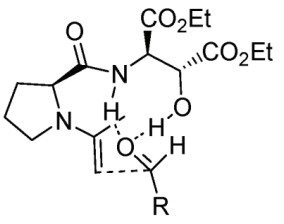
Despite the high efficiency shown in a series of reactions, proline suffers from problems such as poor solubility in organic solvents and high catalyst loading; it is known to react with electron-deficient aromatic aldehydes to form iminium salts that decarboxylate even at room temperature[72]. Therefore, a great deal of effort has been exerted for the development of new catalysts.

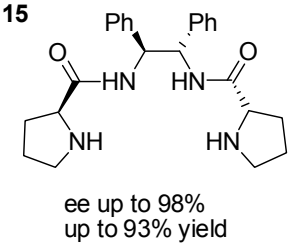
1.3.3. Other organocatalysts in aldol reaction

Gong et al[73,74] found that although proline amide was ineffective in an aldol reaction, proline amides with a terminal hydroxyl group exhibited increased catalytic activity and enantioselectivity, and a strongly electron-withdrawing









Scheme 15. Asymmetric aldol reaction catalysed by **14** and **15**.

substituent on an α- or β-carbon was crucial to the catalytic performance (Scheme 15, catalyst **14**). Aldol products were obtained in up to >99% *ee* and 99% yield using 20 mol% of catalyst **14**. The high catalytic activity was explained through the double hydrogen bond between both the amide and the hydroxyl groups with the aldehyde where they acted as Lewis acids (Scheme 15).

Zhao et al[75] further improved the proline amide-type catalyst by introducing an additional proline amide moiety into the catalyst, this C_2-symmetric bisproline amide **15** having much higher reactivity with only 10 mol% of catalyst loading. The design of the catalyst was based on the hypothesis that the chance of the substrate meeting with the coordinative centre increases when the number of the coordinative centres of the catalyst is increased.

For the same reaction Maruoka et al[76] introduced artificial amino acid based on binaphthalene: up to 96% *ee* was obtained at room temperature using 5 mol% of catalyst **16** and DMF as a solvent (Figure 5). Later they further improved the catalyst by introducing electron-donating methoxy groups with the expectation of an increasing nucleophilicity of the enamine moiety, so that lower catalyst loading would be required.[77] Indeed, the new catalyst **17** was more reactive: even 0.5 mol% was sufficient to get a high yield in a reasonable time without the loss of enantioselectivity. A transition state for the catalyst **16** was proposed[78] for the reaction between cyclohexanone and aldehydes, where the *Re*-face of an aldehyde approached the *Re*-face of the *trans*-rotamer of enamine to form a new C-C bond (Figure 5).

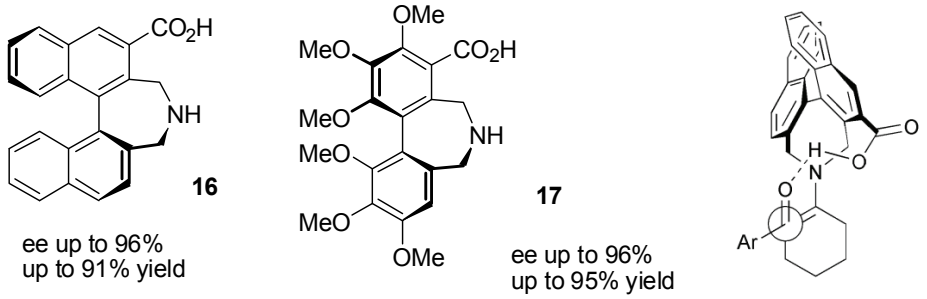
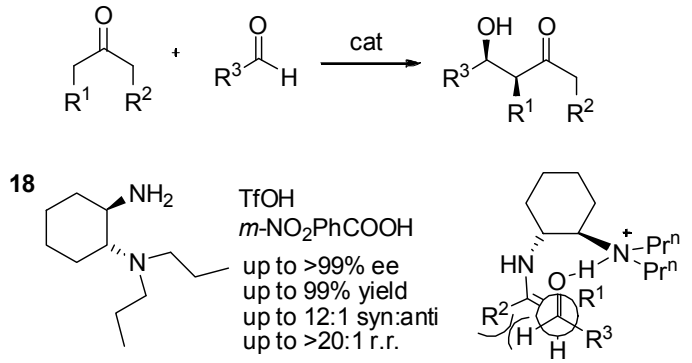


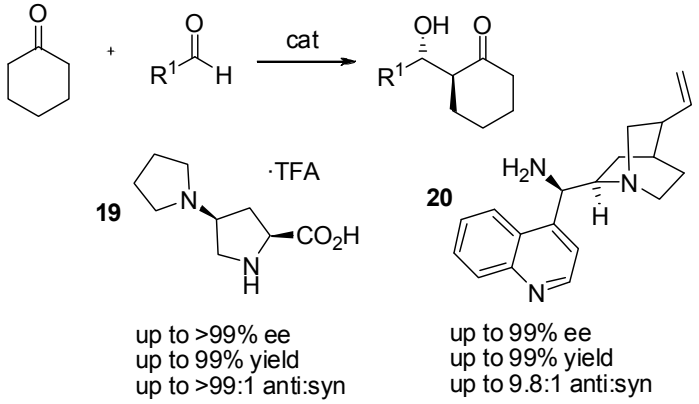
Figure 5. Structures of axially chiral amino acids and TS for aldol reaction.

Luo and Cheng[79] reported the use of 10 mol% of primary amine catalyst **18** with 10 mol% of TfOH and 10 mol% of *m*-NO_2PhCOOH additive in the aldol reaction between linear aliphatic ketones and aldehydes (Scheme 16); products were obtained with excellent enantioselectivities and high diastereo- and regioselectivity. The role of the second acidic additive was probably related to its possible function in facilitating the enamine catalytic cycle. The *syn* diastereoselectivity can be explained by a *Z*-enamine transition state as proposed in Scheme 16, where the protonated tertiary amine serves as a directing hydrogen-bonding donor.



Scheme 16. Catalyst **18** and transition state for asymmetric aldol reaction.

The aldol reaction of aromatic aldehydes with cyclohexanone was studied by Sun et al[80]. 20 mol% of c*is*-4-substituted proline **19** was found to be a highly selective catalyst: products were isolated in up to 99% yield and in excellent selectivity (>99% *ee*) (Scheme 17). The presence of TFA was found to be critical for the high yield and selectivity. Liu et al[81] used cinchona-derived primary amine **20** to catalyse the same reaction (Scheme 17) and, also in this case, an acid additive was needed to achieve better yield and selectivity.



Scheme 17. Asymmetric aldol reaction of aldehydes with cyclohexanone catalysed by **19** and **20**.

Cis-diamine **21** was introduced as a catalyst by Maruoka et al[82] (Figure 6). They studied a direct aldol reaction of various cyclic ketones to aldehydes in the presence of 5 mol% of catalyst and obtained aldol product with excellent selectivity (up to 99% *ee*) and yield. Furthermore, in some cases, they showed that only 1 mol% could be used without loss in selectivity. A possible transition state model has been proposed as shown in Figure 5 to account for the observed configuration of aldol product.

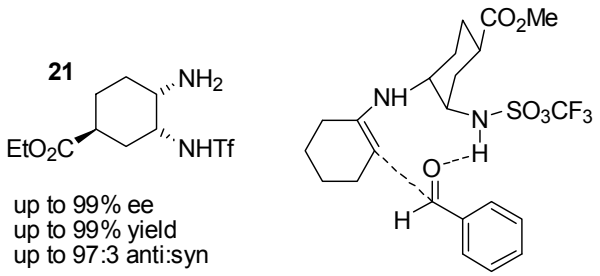


Figure 6. Catalyst **21** and proposed transition state.

L-proline is inexpensive and widely used, but has its shortcomings. So far the best results in terms of stereoselectivity are obtained using bifunctional catalysts because they possess a synergistic effect where simultaneous activation of a nucleophile and an electrophile takes place; in addition to the formation of an enamine, an aldehyde (or ketone) is activated by hydrogen bonding. The properties of the catalyst can be tuned by modifying the side chain of the cyclic amine as a basic core of the catalyst. Changing the pK_a value of the H-donor is most widely used for that purpose. The proline amides and sulfonamides described earlier are only some examples.

1.4. Summary of asymmetric Michael and aldol reactions

A great deal of research has been dedicated to the development of asymmetric organocatalytic Michael and aldol reactions in recent years. Wide varieties of catalysts have been screened for these reactions (Figure 7).
Many catalysts have been developed based on the structure of proline. Some of the common modifications to the proline structure include increasing the hydrophobicity to improve solubility in organic solvents and the modification of the carboxylic acid to a variety of other hydrogen-bonding groups. Secondly, the catalyst design is based on adding steric bulk and stereocentres to enhance the enantioselectivity by making only one face of the catalyst accessible and enabling coordinative bonds between enamine and substrate in a transition state, hence leading to higher selectivity. As can be seen from the many examples described above, often acid additive improves the reactivity and selectivity of the catalyst. A proper combination of the acid that matches the basicity of the amine is responsible for high catalytic efficiency.[83] Acid shifts the equilibrium toward the formation of the key intermediates: the iminium ion and enamine lead to improved yield and selectivity.
A great deal of research effort has been invested in developing more selective and reactive catalysts and intense research will undoubtedly continue in this area in the future.

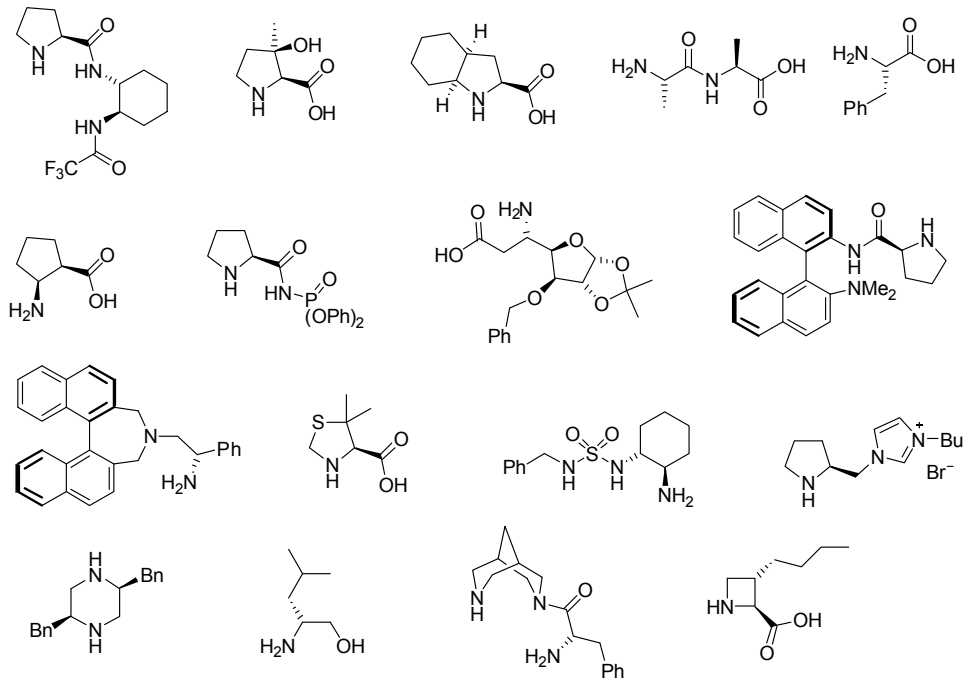


Figure 7. Structures of organocatalysts typically employed for enantioselective Michael and aldol reactions.

1.5. Aims of the present work

In the present work, the aim was to broaden the scope of aminocatalysts for asymmetric organocatalytic Michael and aldol reactions, so far being limited mainly to proline derivatives. In more detail we wanted to:

- investigate structural features that are responsible for the high enantioselectivity of cyclic (di)amines as organocatalysts.

- synthesise enantiomeric 2,2'-bipiperidine, a cheaper analogue of 3,3'-BM, and compare their catalytic ability and selectivity in an asymmetric Michael addition, and in an intra- and intermolecular aldol reaction.

- synthesise morpholine carboxylic acid and determine whether, in a Michael addition, six-membered heterocyclic rings (morpholine, piperidine and piperazine) have any superiority over pyrrolidine ring (known organocatalyst proline) in terms of selectivity.

2. Synthesis of BM derivatives, BP derivatives and morpholine-3-carboxylic acid salts

We were interested in broadening the scope of aminocatalysts with enantiomeric 3,3'-bimorpholine and 2,2'-bipiperidine as organocatalysts for Michael and aldol reactions (Figure 8). Most of the catalysts that have been used for these reactions so far contain pyrrolidine structure. The monosalts of BM and BP have many similarities with well-known organocatalyst proline. Proline and monoprotonated diamines both have a basic nitrogen (Lewis base, highlighted in blue) and an acidic proton (Brønsted acid, highlighted in green) in the same molecule and both of the structures have acidic proton at a distance of four chemical bonds from the nitrogen atom, enabling hydrogen bond and thereby possibly a more stable conformation and a fixed transition state. Both BM and BP have a stereogenic centre at the α-position of the nitrogen atom like in proline. Compared to proline's pyrrolidine cycle, bimorpholine has two additional oxygen atoms (highlighted in red) that are potential coordination centres, but on the other hand, a six-membered ring is more flexible than a five-membered ring. Easy derivatisation with the substituents of different steric bulk and with various acids makes BM and BP highly tunable catalysts. Another advantage over proline is the high solubility of diamines in common organic solvents.

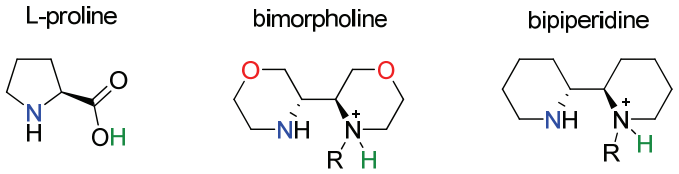


Figure 8. Structures of proline, bimorpholine and bipiperidine.

If we can show an advantage of the morpholine ring over the piperidine ring in terms of selectivity, than this raises a question whether the morpholine-3-carboxylic acid will be a highly selective catalyst and still have enough reactivity

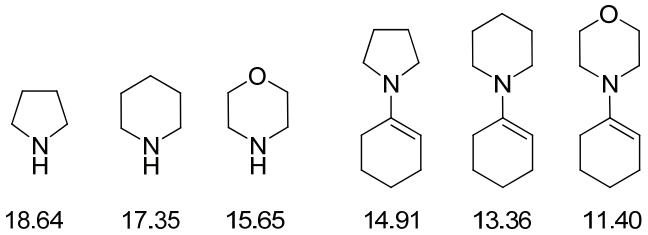
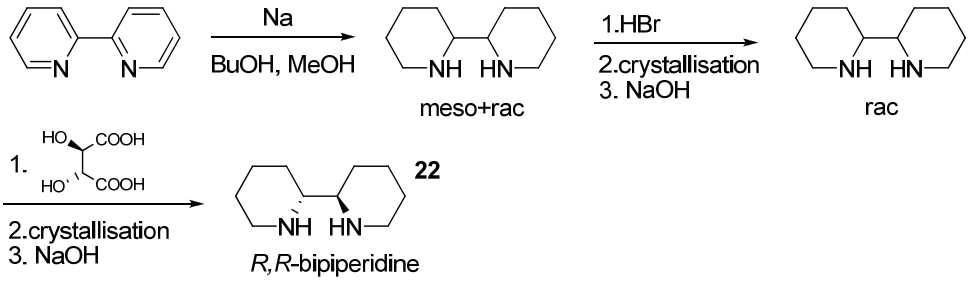


Figure 9. Values of nucleophilicity parameter *N* of amines in acetonitrile and enamines in DCM. [86,84]

because the relative reactivities of different enamines to various electrophiles generally decrease in the order pyrrolidine > piperidine > morpholine (Figure 9). Due to the higher nucleophilicity of piperidine compound compared to morpholine compound, higher reactivity of the BP catalyst was expected. [84,85,86,87]

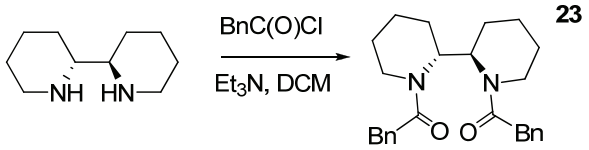
2.1. Synthesis of BM and BP derivatives (Articles II, IV and V)

A synthetic route for BM had been developed by us previously.[88,89] Even though the synthesis was straightforward, the route contained seven steps. Therefore, the simpler synthetic analogue 2,2'-bipiperidene was envisioned: both compounds are six-membered heterocyclic bridged 1,2-diamines.
2,2'-bipiperidine **22** was synthesised from commercially available 2,2'-bipyridyl in just one step[90] (Scheme 18). A reduction with metallic sodium in BuOH/MeOH yielded a 1:1 mixture of meso (*R,S*) and racemic (*R,R* and *S,S*) BP. First, their separation as hydrochloric acid salt[91,92] was attempted but, although this separation is described, we and others failed[93] in this process. Also, it is known from the literature that bipiperidine can be resolved as a hydrobromic acid salt.[93] Indeed, meso-BP crystallised from hot ethanol, leaving a mother liquid rich in racemic form, from which it precipitated after cooling.

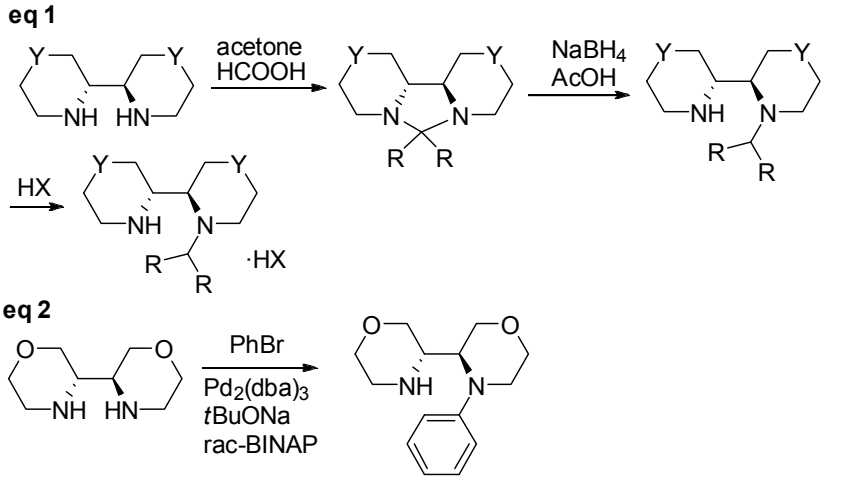


Scheme 18. Synthesis and resolution of 2,2'-bipiperidine.

The enantiomers of the free diamine were then resolved using L-tartaric acid.[94] The treatment of a tartaric acid salt of (*R,R*)-BP with NaOH yielded a new organocatalyst, whose enantiomeric purity was determined by chiral HPLC as a dibenzoyl derivative, and was found to be higher than 99 % (Scheme 19).



Scheme 19. Derivatisation of (*R,R*)-bipiperidine.



Scheme 20. Synthesis of BM and BP derivatives.

A derivatisation of BM[95] and BP was conducted using simple methodology – the aminal formation.[38] Due to the C_2-symmetric nature of these bicyclic compounds monosubstituted enantiomeric diamines can be synthesised. Two different substituents of different sizes were introduced.

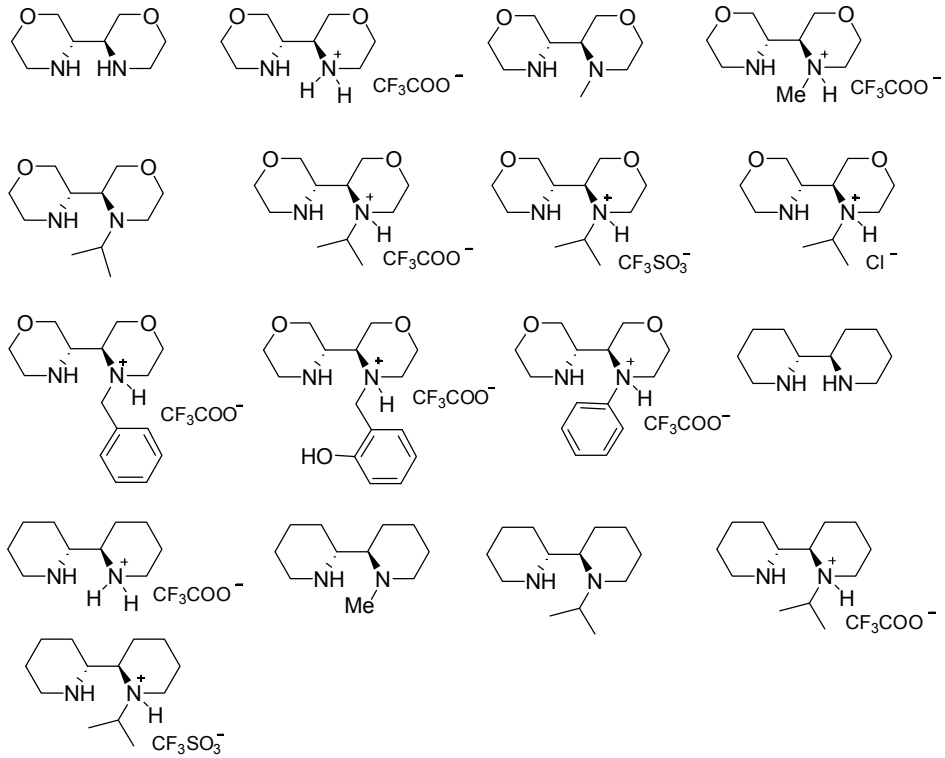


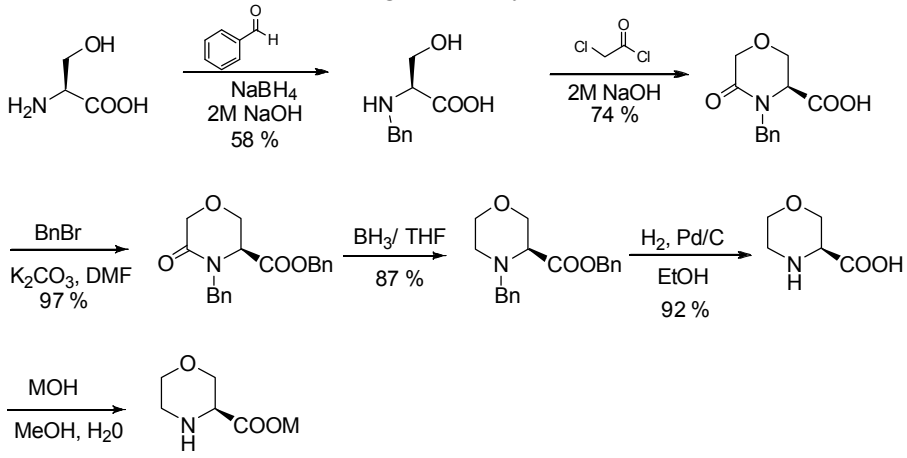
Figure 10. Organocatalysts synthesised by our group.

iPr-substituted diamines were synthesised using acetone and formic acid, the crude aminal was reduced with $NaBH_4$ to afford monosubstituted product in good yield. A smaller methyl group was introduced via a reaction with formaldehyde, and crude aminal was reduced using $NaCNBH_3$, also in good yield (Scheme 20, eq 1). Only the synthesis of phenyl-substituted BM did not follow this pattern, a Pd-catalysed coupling of bromobenzene with BM was employed instead (Scheme 20, eq 2).

It is known that a Brønsted acid additive has a substantial influence on the selectivity of a Michael addition to nitrostyrenes.[96,97,98,99,100] Therefore, hydrochloric, trifluoroacetic and trifluoromethanesulfonic acid monosalts of BP and BM derivatives were synthesised using one equivalent of acid (Figure 10).

2.2. Synthesis of (*S*)-morpholine-3-carboxylic acid and its salts (Article VIII)

The synthesis of (*S*)-MCA started with the protection of the amine functionality of (*S*)-serine using reductive amination, followed by the cyclisation with 2-chloroacetyl chloride to give oxomorpholine-3-carboxylic acid (Scheme 21).[101] After the protection of the acid functionality, a reduction of lactame was attempted with 9-borabicyclo[3.3.1]nonane, and the desired product formed in low yield (41%). Using borane as a reducing agent, the reaction was clean, and protected morpholine carboxylic acid formed in high yield. Simple hydrogenation removed both benzyl groups. The enantiomeric purity of the target compound was determined as dibenzyl derivative using chiral HPLC (*ee* 98%), to show that no racemisation had occurred throughout the synthetic route.



Scheme 21. Synthesis of (*S*)-morpholine-3-carboxylic acid and its salts.

It is known that salts of amino acids have been used as organocatalysts.[64,102,103,104,65] Therefore, Li, Na, K, Cs and NBu_4 salts of MCA were synthesised using one equivalent of the corresponding hydroxide.

In summary, the new organocatalyst (*R,R*)-2,2'-bipiperidene was synthesised in just one step, compared to the seven step synthesis of BM, which is a huge advantage in terms of time and money. BM and BP were derivatised using the same methodology. A wide selection of potential new organocatalysts was obtained.

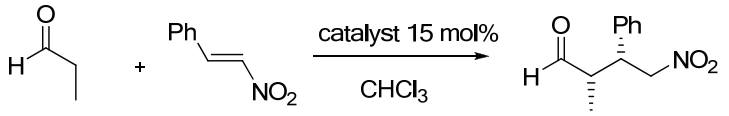
(*S*)-MCA was synthesised over five steps in a 31% overall yield and turned into five different salts.

3. Asymmetric organocatalytic Michael reaction

3.1. Michael reaction catalysed by iPrBM and iPrBP derivatives (Articles II and VI)

The asymmetric Michael reaction is an important transformation to obtain new carbon-carbon bonds, generally with the formation of new stereocentres. We tested our organocatalysts in a Michael addition of propionaldehyde to nitrostyrene, and the results are presented in the table below. The reaction was catalysed according to the enamine mechanism.
Firstly, we investigated the catalytic activity and selectivity of BM derivatives[95] (Table 1, entries 1-3). The influence of the substituent on BM was very significant. The iPr group was revealed to be more selective than the smaller methyl group, affording product in 88% *ee*. The influence of an acid additive was also investigated with a more selective iPrBM catalyst. Although the product formed with slightly higher selectivity, the reaction time increased from three to eight days, making the catalyst inefficient (Table 1, entry 2). Consequently, we focused our attention on the iPrBM catalyst, reaching the best compromise in terms of selectivity and reactivity.

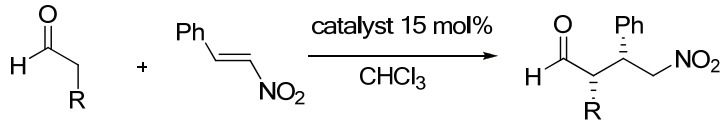
Table 1. Michael addition catalysed by different BM and BP derivatives.



entry	catalyst	conditions	yield %	syn:anti	*ee* %(syn)
1	iPrBM	3 d	85	94:6	88
2	iPrBM·HCl	8 d	68	95:5	91
3	MeBM	8 d	59	93:7	64
4	BP	32 h	45	60:40	70
5	BP·TFA	10 d	15	77:23	54
6	iPrBP	1 h	91	83:17	86
7	iPrBP·TFA	9 d	56	85:15	84
8	MeBP	2 h	94	75:25	-59

Next, we tested BP derivatives in the same reaction. The unsubstituted BP catalysed addition was complete in 32 hours, in a low yield and in 70% *ee* (Table 1, entry 4). The bulky iPr-substituent made the catalyst more selective (*ee* 86%) and, at the same time, increased the rate of the reaction significantly: reaction was complete in one hour (entry 6). A TFA additive made the reaction slower; the product was isolated in a poor yield and 54% *ee* (entry 5). Furthermore, the same trend was observed in the case of iPrBP salt, again, it made the reaction substantially slower without increasing the enantioselectivity, showing that the acid salt was not a suitable catalyst for this transformation (entry 7). A sterically less demanding methyl-group on nitrogen made the reaction faster but did not have a positive effect on selectivity compared to the unsubstituted BP (entry 8). Undoubtedly, iPrBP was the catalyst of choice to proceed with our investigation.

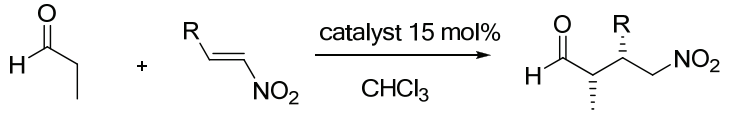
Table 2. Asymmetric conjugate addition of different donors to nitrostyrene catalysed by iPrBM and iPrBP.



entry	R	catalyst	conditions	yield %	syn:anti	*ee* %(syn)
1	CH_3	iPrBM	1 d, rt	90	82:18	74
			3 d, -3°C	86	90:10	80
2	Propyl	iPrBM	1.5 d, rt	88	87:13	89
3	i-Propyl	iPrBM	3 d, rt	85	94:6	88
4	c-Hex	iPrBM	13 d, rt	88	95:5	90
5	CH_3	iPrBP	1 h, rt	91	83:17	86
			2 h, 0°C	85	90:10	93
			23 h, -25°C	82	94:6	96
6	Propyl	iPrBP	8 h, rt	96	89:11	88
7	i-Propyl	iPrBP	8 h, rt	85	96:4	89
8	Ph	iPrBP	3 h, rt	76	62:38	37
9	Me, Me	iPrBP	7 d, rt	14	-	41

Table 2 incorporates the comparative results obtained with iPrBM and iPrBP. The addition of propionaldehyde to nitrostyrene catalysed by iPrBM gave a Michael adduct in 90% yield and 74% *ee* (entry 1). Decreasing the temperature allowed the enantioselectivity to increase to 80%. For more hindered aldehydes, a longer reaction time was required, but this led to an increased selectivity. High selectivity was obtained with valeraldehyde and isovaleraldehyde, in 89% and 88% *ee*, respectively (Table 2, entries 2 and 3). 2-Cylohexylacetaldehyde gave good enantioselectivity, but the reaction was unacceptably slow: an 88% yield was obtained after 13 days (entry 4).
It is clear from Table 2 that iPrBP is a much more reactive catalyst than iPrBM: the addition of propionaldehyde to nitrostyrene was complete after one hour at room temperature (entry 5), while iPrBM gave product in one day. The enamine derived from BP was clearly more nucleophilic and reacted faster. Even at -25 °C, the reaction was relatively fast and product was formed with excellent selectivity: 96% *ee* was observed. Valeraldehyde and isovaleraldehyde yielded products with the same selectivity as in the case of iPrBM (entries 6 and 7). Because the catalyst containing the piperidine ring was significantly more active, the addition of more

Table 3. Asymmetric conjugate addition to different acceptors catalysed by iPrBM and iPrBP



entry	R	catalyst	conditions	yield %	syn:anti	*ee* % (syn)
1	Ph	iPrBM	3 d, -3°C	86	90:10	80
2	*p*-Cl-Ph	iPrBM	3 d, -3°C	84	80:20	75
3	*p*-MeO-Ph	iPrBM	3 d, -3°C	81	84:16	78
4		iPrBM	3 d, -3°C	89	89:11	79
5	c-Hex	iPrBM	13 d, -3°C	23	85:15	85
6	Ph	iPrBP	1 h, rt	91	91:9	86
7	*p*-MeO-Ph	iPrBP	6 h, rt	82	87:13	88
8	*p*-Br-Ph	iPrBP	1 h, rt	99	87:13	90
9	*p*-CF_3O-Ph	iPrBP	1 h, rt	90	84:16	89
			30 h, -20 °C	78	87:13	89

hindered aldehyde (methylpropanal with branching at the α-position) to nitrostyrene was possible, although the yield and *ee* remained low (Table 2, entry 9).
The scope of the Michael addition of aldehydes to nitrostyrenes was briefly explored under optimised reaction conditions (Table 3). Both electron-rich and electron-poor *β*-nitrostyrenes were good Michael acceptors for propionaldehyde. Significantly, the iPrBM catalysed reaction was independent of the nature of substituents on the phenyl ring, and product formed after three days. The reaction time increased dramatically when nonaromatic cyclohexyl nitroethene was employed as the acceptor (entry 5). In the case of BP, a clear dependence on the substituent on the phenyl ring was observed, the electron-donating MeO-group deactivated the substrate towards the Michael addition, and the reaction was complete after six hours (Table 3, entry 7). In all cases, the substituent had a very small influence on enantio- and diastereoselectivity. It was found that lowering the temperature did not have any influence on selectivity.

To explain the stereochemical outcome of this reaction, a conformational analysis of enamine derived from iPrBP and propionaldehyde in chloroform was carried out by DFT calculations. A conformer with both piperidine rings in chair conformation and with equatorial C-C bond relation to both rings had the highest Bolzmann probability (91%) (Figure 11). The dihedral angle of N-C-C-N was close to 180º and the enamine was in *anti* conformation. Therefore, the *Si*-face of the enamine was shielded by an iPr-substituted ring and an attack came preferentially from the *Re*-face of the enamine. Nitrostyrene faced the enamine with the *Re*-face because the nitrogen atom of the piperidine ring interacted with the nitro group, leading to *syn* product.

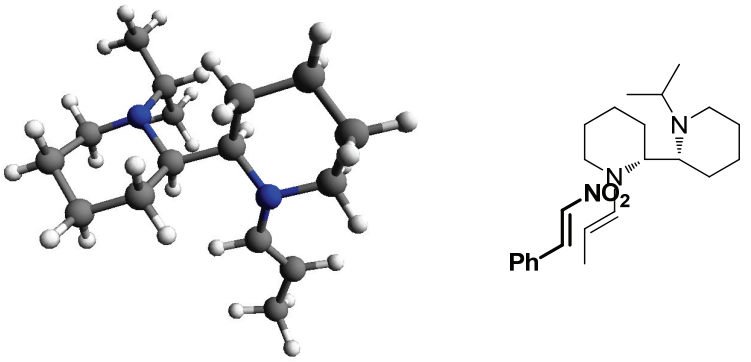
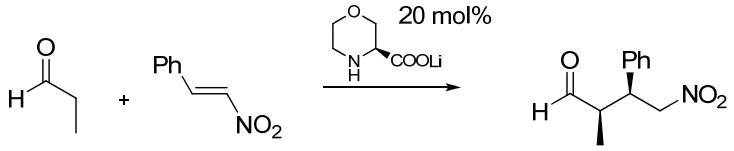


Figure 11. Calculated conformation of iPrBP propionaldehyde enamine and proposed transition state

3.2. (*S*)-morpholine-3-carboxylic acid salts catalysed Michael reaction (Article VIII)

In addition to our bicyclic organocatalysts, the addition of propionaldehyde to nitrostyrene was conducted in chloroform in the presence of MCA. But even after five days no product was detected. Next, an acid lithium salt was examined as a catalyst and, indeed, after 24 hours 83% of product was isolated in 60% *ee*, encouraging us to screen different reaction media. The results are summarised in Table 4. Non-polar and weakly polar aprotic solvents (DCM, toluene and THF) afforded products in moderate enantioselectivities (46-60%); a strongly polar aprotic solvent acetonitrile gave 43% *ee* and DMF, a racemic product. The reaction in protic solvent methanol was extremely fast, the Michael addition was complete in less than five minutes (entry 6). Although the product was racemic, this accelerating effect was exploited: 10 vol% of methanol was added to DCM and, indeed, the reaction was complete in two hours (entry 7) instead of 24 hours. Water was not a suitable medium due to the poor solubility of nitrostyrene. DCM was the solvent of choice for the investigation of the Michael addition catalysed by different MCA salts, because it gave the highest *ee* value.
Knowing the accelerating nature of methanol, an MCA catalysed addition was

Table 4. Screening of solvents

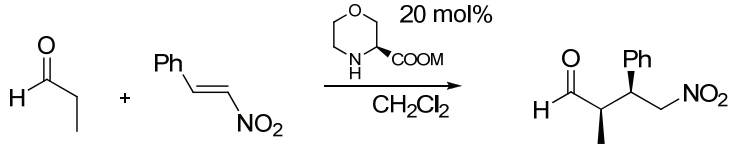


entry	solvent	time, h	yield %	syn:anti	*ee* %(syn)
1	CH_2Cl_2	24	83	89:11	60
2	toluene	24	54	84:16	52
3	THF	24	91	78:22	46
4	MeCN	24	64	86:14	43
5	DMF	24	32	60:40	rac
6	MeOH	5 min	99	85:15	rac
7	CH_2Cl_2:MeOH 9:1	2	100	86:14	51
8	H_2O	24	36	76:24	rac

attempted again in a DCM:methanol 9:1 mixture and, indeed, after eight days at room temperature, 70% of the product was isolated in 42% *ee*, with quite high d.r. (*syn*:*anti* 89:11). Also, the influence of an additive was examined: to a reaction mixture 20 mol% of LiCl or NaCl was added. A clear increase in yield and selectivity was observed with LiCl: after 72 hours, the desired product was isolated in high yield and in 58% *ee*. The addition of NaCl to the reaction mixture did not enhance the rate or selectivity, the only the yield dropped to 49%. In conclusion, MCA Li-salt prepared beforehand was much more reactive and slightly less selective than the MCA catalysed reaction with LiCl additive under the same conditions.

With the optimal solvent system in hand, the influence of the cation was examined and the results obtained with Li, Na, K, Cs and NBu_4 salts of MCA are presented in Table 5. Compared to the lithium salt, the sodium salt showed high reactivity: reaction was complete after two hours with a quantitative yield (entry 2). In addition to being more reactive, sodium salt turned out to be a more selective catalyst in this reaction: *ee* increased from 60% to 72%. A similar result was obtained with potassium salt (entry 4). Caesium and tetrabutylammonium salts both gave the product in low yield and selectivity; interestingly, the latter yielded the opposite enantiomer. The decreased catalyst loading affected only the rate of the reaction, while enantioselectivity remained unchanged (entry 3). The reactivity was in correlation with the metal ion radius. Sodium and potassium ions had the optimal radii for the for the transition state, lithium and caesium made the reaction slow and less selective.

Table 5. Michael addition catalysed by different morpholine carboxylic acid salts



entry	metal	time, h	yield %	syn:anti	*ee* %(syn)
1	Li	24	83	89:11	60
2	Na	2	100	86:14	72
3*	Na	5	98	91:9	71
4	K	2.5	88	83:17	69
5	Cs	23	46	74:26	45
6	NBu_4	3	22	67:33	-20

* 5 mol% of catalyst was used

The stereochemical outcome of the reaction can be explained by Seebach's topological rules[105] (Figure 12). In the proposed transition state, electrostatic interactions are allowed between the positively charged *N*-atom of the nitro group and the partially negative *N*-atom of the morpholine ring. This interaction takes place if nitrostyrene is in gauche conformation and enamine is in *E*-configuration. The conformation can be further fixed and a Michael acceptor activated by chelation of the metal with *O*-atoms of morpholine carboxylate and a nitro group of styrene. The *Re*-face of the nitrostyrene is shielded by the aromatic ring. Therefore, the *Si*-face of the enamine approaches the *Si*-face of nitrostyrene, providing *syn*-selectivity and affording product in a (2*R*,3*S*)-configuration. In protic solvents, this rigid conformation is disrupted by competing hydrogen bonding, causing the formation of a racemic product.

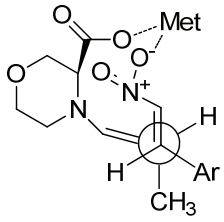


Figure 12. Transition state for Michael addition.

To complete the study, we evaluated the catalytic properties of different cyclic amino acid sodium salts. The Michael addition was investigated in the presence of 20 mol% of proline, pipecolic acid and piperazine carboxylic acid sodium salts (Table 6). All these catalysts were quite reactive, catalysts with a six-membered piperidine and piperazine ring gave low *ee* (44-45%) and yield in a short reaction time (entries 4 and 5). The most selective catalyst turned out to be a sodium salt of proline, affording the product in 88% *ee* but in low d.r.: 71:29 (Table 6, entry 2). As shown previously, a potassium salt of proline behaved quite similarly to the sodium salt, affording an identical *ee* value. We believe that a five-membered ring gives proline higher conformational rigidity, which was responsible for the higher enantioselectivity.

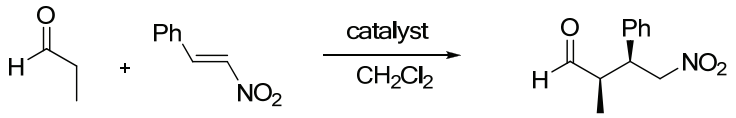
The scope of the carbonyl compounds in this reaction was limited to aldehydes: the reaction with ketones gave only traces of the product.

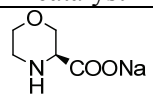
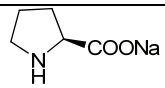
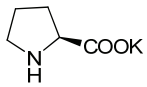
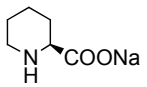
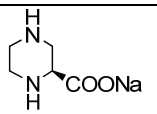
In summary, in the Michael addition of aldehydes to nitroolefins, iPrBP is a highly selective and much more reactive catalyst than iPrBM, affording products in up to 96% *ee* and 96:4 d.r. Furthermore, the BP is easily accessible in a one-step synthesis from commercial and cheap 2,2'-dipyridyl, and C_2-symmetry enables easy derivatisation to afford enantiomeric iPrBP.

MCA itself did not catalyse this reaction, sodium salt, on the other hand, was a reactive catalyst in this transformation and afforded the desired product in quantitative yield and good enantioselectivity (72%). The study of different amino acid sodium salts revealed the superiority of the pyrrolidine ring over the

morpholine ring, the sodium salt of proline catalysed an enantioselective addition in 88% *ee*.

Table 6. Michael addition catalysed by cyclic amino acid salts



entry	catalyst	time, h	yield %	syn:anti	*ee* %(syn)
1		2	100	86:14	72
2		4	68	71:29	88
3		2	70	80:20	88
4		1	46	74:26	45
5		0.5	67	87:13	44

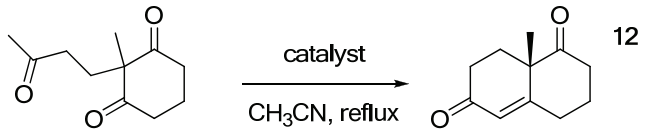
4. BM and BP derivatives catalysed asymmetric organocatalytic aldol reaction

For the investigation of an intramolecular aldol reaction, a synthesis of Wieland-Miescher ketone and its nor-analogue was carried out in the presence of our catalysts. To evaluate organocatalysts in an intermolecular aldol reaction, the addition of acetone to benzaldehydes was used as a model.

4.1. Intramolecular aldol reaction (Articles I, II, III, IV, V and VII)

We examined our BM and BP derivatives as catalysts in an intramolecular aldol reaction and the results are as follows. Firstly, BM derivatives were tested. Free diamines (BM and iPrBM) gave poor results, affording Wieland-Miescher ketone **12** in poor yield, with the latter catalyst giving a racemic product (Table 7, entries 1 and 4). When TFA salts of those catalysts were tested, the outcome of the reaction was drastically changed – products were isolated in high yield and selectivity:

Table 7. Synthesis of Wieland–Miescher Ketone.



entry	catalyst	mol%	time, d	yield %	*ee* %
1	BM	5	4	<10	n.d.
2	BM·TFA	5	2	92	79
3	MeBM·TFA	5	3	73	82
4	iPrBM	5	3	45	rac
5	iPrBM·TFA	5	3	84	91
6	iPrBM·TfOH	5	4	60	95
7	PhBM·TFA	5	5	14	-29
8	BnBM·TFA	5	3	75	88
9	2-OH-BnBM·TFA	5	3	70	74

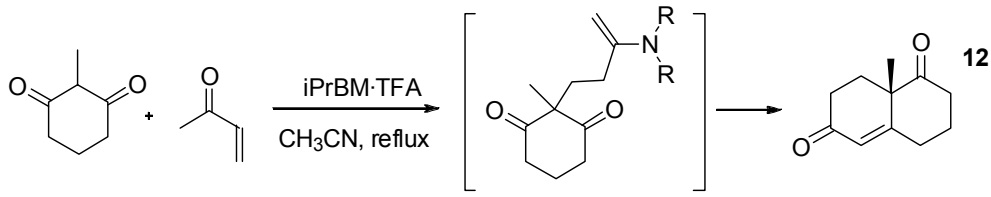
10	iPrBP	10	8	7	43
11	iPrBP·TFA	10	8	38	78
12	iPrBP·TfOH	10	8	55	52
13	MCA*	10	6	30	37

*DMF was used as a solvent

an iPrBM·TFA catalysed reaction yielded product with 91% *ee* after refluxing for three days in acetonitrile (Table 7, entry 5), in contrast to free amine, affording a racemic product. TFA salt with sterically less hindered methyl substituent on a nitrogen atom gave product with lower selectivity (entry 3). It is clear that acid had an enormous influence on the outcome of the reaction. Next, the influence of triflic acid on selectivity and reactivity was tested. Indeed, the acid had a positive influence on selectivity: *ee* increased to 95%, but with loss in yield (Table7, entry 6). TFA was shown to be a more suitable additive for BM derivatives. Benzyl and 2-OH-benzyl substituted BM TFA salts both yielded Wieland-Miescher ketone with good to high selectivity and with good yield (Table 7, entries 8 and 9). However, in the case of a phenyl substituted catalyst (entry 7), secondary amine was protonated because of the higher basicity and thereby the nucleophilicity of the catalyst was lowered and the rate of cyclisation was retarded (entry 7).
Next, bipiperidine derivatives were tested in this transformation. Again, an amine catalyst as a free base afforded product in poor yield and selectivity (Table 7, entry 10). For BP derivatives, a higher catalyst loading and longer reaction times than in the case of BM derivatives were required. The same trend was observed: a TFA additive increased the selectivity, as well as the yield, and product was isolated in 78% *ee*, compared to the 43% obtained with free diamine. A stronger triflic acid additive did not further increase the selectivity: *ee* remained modest (entry 12).
As salts of both diamines showed, an acidic proton was needed for the acceleration of aldol condensation. Substitution at the nitrogen atom allowed us, via electronic or steric effects, to change the enantiopreference of the reaction. On the basis of these considerations, our diamines are finely tunable bifunctional organocatalysts.
Surprisingly, only 30% of aldol product was isolated after six days in 37% *ee* using MCA as a catalyst and DMF as a solvent (Table 7, entry 13), while only traces of Wieland–Miescher ketone formed in an acetonitrile-water mixture, 30 vol% of water was needed because of the low solubility of the catalyst.

We also investigated the tandem process where Wieland-Miescher ketone **12** forms as a result of a sequence of two reactions from diketone and methyl vinyl ketone in CH_3CN, in the presence of 10 mol% of iPrBM·TFA (Scheme 22). The tandem process involved, first, an intermolecular Michael addition to an *α,β*-unsaturated ketone, followed by an intramolecular aldol condensation of the formed enolate. Disappointingly, the reaction was sluggish: desired product formed in only 52%

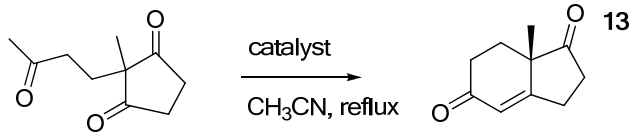
yield after nine days, although the selectivity remained the same (91% *ee*) as when triketone made beforehand was used as the starting material (Table 7, entry 5).



Scheme 22. Tandem process for the synthesis of diketone **12**.

The synthesis of nor-Wieland–Miescher ketone **13** was also examined and similar trends were expected and, indeed, also observed. Only catalysts with acid additive were investigated in this transformation (Table 8). The TFA salt of unsubstituted BM was the less selective catalyst among the BM derivatives (entry 1), the iPr-substituent increased the selectivity to 80%. Even higher enantioselectivity (87%) was observed with a triflic acid salt of iPrBM, but the reaction was very sluggish (nine days at reflux) (entry 3). Again, BP derivatives were very unreactive in this aldol condensation reaction, TFA and triflic acid salts both were unsuitable for this transformation (Table 8, entries 4 and 5). Notably, in the reaction catalysed by iPrBP·TfOH 59% of *β*-hydroxyketone was isolated.

Table 8. Synthesis of nor-Wieland-Miescher ketone.

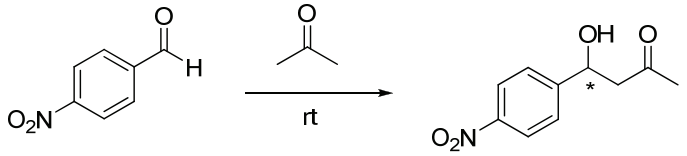


entry	catalyst	mol%	time, h	yield %	*ee* %
1	BM·TFA	5	1	87	58
2	iPrBM·TFA	5	3	83	80
3	iPrBM·TfOH	5	9	68	87
4	iPrBP·TFA	10	8	12	74
5	iPrBP·TfOH	10	7	7	42

4.2. Intermolecular aldol reaction (Articles II, III, IV, V and VII)

The intermolecular aldol reaction was investigated in the same manner. The reaction between *p*-nitrobenzaldehyde and acetone was used as a model reaction to screen our catalysts, and the results are summarised in Table 9. In general, a long reaction time and high catalyst loading (30 mol%) were required for this transformation. Free diamines, both iPrBM and iPrBP gave racemic product after stirring for six to seven days at room temperature (entries 1 and 4). Again, an acid additive made the catalyst highly selective, TFA and TfOH salts of iPrBM catalysed a reaction with 85-88% *ee*. For this reaction, iPrBM·TfOH was the optimal catalyst, giving higher yield and selectivity (entry 3). In terms of reactivity, an even higher difference between salts of iPrBP was revealed. With iPrBP·TFA, only 18% of the desired product was isolated contrast to the 83% yield obtained with triflic acid salt (entry 6). In both cases, products formed in 68-81% *ee*.

Table 9. Intermolecular aldol reaction



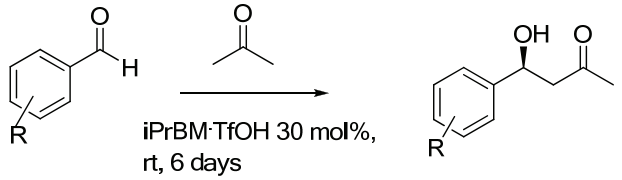
entry	catalyst	Mol%	time, d	yield %	*ee* %
1	iPrBM	30	7	n.d.	rac
2	iPrBM·TFA	30	9	38	85
3	iPrBM·TfOH	30	6	70	88
4	iPrBP	30	6	<10	rac
5	iPrBP·TFA	30	6	18	81
6	iPrBP·TfOH	30	6	83	68
7	MCA	10	6	<10	53
8	MCA*	10	6	38	50
9	MCA·Na	15	3	<10	16
10	MCA·Na*	15	3	30	rac

*DMSO was used as a solvent

MCA and its sodium salt were also tested in an intermolecular aldol reaction between acetone and *p*-nitrobenzaldehyde. In neat acetone, a very poor yield was obtained (Table 9, entries 7 and 9). MCA gave product in 53% *ee*, its sodium salt in 16% *ee*. The poor yield was probably due to the poor solubility of the catalysts. Therefore, DMSO was used as a solvent and, indeed, an increase in the yield was observed but, on the other hand, the reaction was less selective (entries 8 and 10).

The intermolecular aldol reaction was investigated in more detail in the presence of the most efficient organocatalyst, iPrBM·TfOH, and the results are presented in Table 10. Unsubstituted benzaldehyde was unreactive, but product formed in a high *ee* of 85% (entry 1). In general, all non-activated aldehydes (entries 1-3) afforded product in poor yield and activated aldehydes (entries 4-7) in good yield, enantioselectivity was relatively unaffected by the substituent on the phenyl ring: the *ee* ranged from 76% to 94%. The highest selectivity was obtained with a nitro-substituent in *orto*-position (entry 7), but the outcome of this selectivity can not be explained only by steric effect, because a similar *ee* was obtained with a substituent in the *para*-position (88% *ee*).

Table 10. Intermolecular aldol reaction



entry	R	time, d	yield %	*ee* %
1	H	10	18	85
2	4-Cl	10	12	88
3	4-iPr	10	<10	76
4	4-NO_2	6	70	88
5	2,4-di-Cl	6	74	88
6	2-Cl	6	79	89
7	2-NO_2	6	77	94

A computational study of enamine formed from acetone and iPrBP showed that the non-protonated as well as the protonated enamine catalysts were in an axial-axial conformation (Figure 13, left image). The enamine of iPrBM was either in an equatorial-equatorial (Bolzmann probability 49%) or in an axial-axial (51%) conformation, while upon protonation enamine had only an axial-axial conformation (100%) (Figure 13, right image). Both protonated catalysts were fixed by hydrogen bond, 1.92 Å and 1.88 Å, respectively.

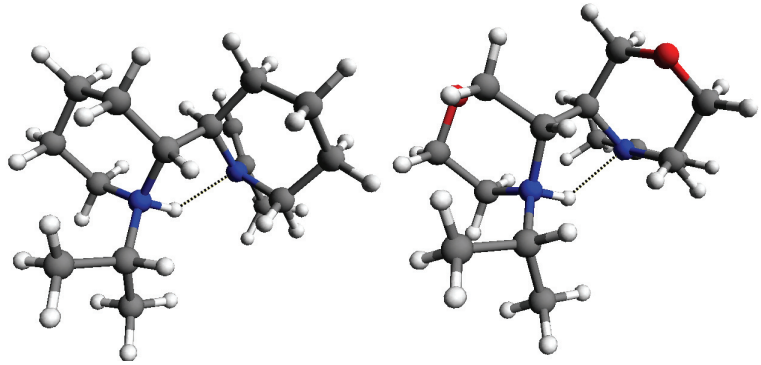


Figure 13. Conformations of enamines derived from protonated iPrBP (left) and iPrBM (right).

In summary, BM derivatives were more suitable catalysts for intramolecular aldol reaction than BP derivatives, the reaction was faster and more selective, and the highest *ee* was observed with an iPrBM·TfOH catalysed reaction, where Wieland-Miescher ketone formed in 60% yield and 95% *ee*. The most selective of the BP derivatives was the TFA salt of iPrBP: Wieland-Miescher ketone formed in 78% *ee* but with low yield. For the intermolecular aldol reaction between acetone and *p*-nitrobenzaldehyde, iPrBM·TfOH was the best catalyst: product was isolated in 70% yield and 88% *ee*. MCA and its sodium salt were not suitable for this transformation.

It has been shown clearly that an acid additive improves the reactivity and selectivity of the catalyst. A proper combination of the acid that matches the basicity of the amine makes the catalyst more reactive and selective. Acid shifts the equilibrium toward the formation of the key intermediates: an iminium ion and enamine leading to improved yield and selectivity. The computational study showed that, upon protonation, a stable conformation is fixed by an intramolecular hydrogen bond.

Conclusions:

- The scope of aminocatalysts was broadened with cyclic diamines – BM and BP – and their derivatives. These new catalysts are bidentate (BP) or ambidentate (BM) bridged compounds with low molecular weight and good solubility in common organic solvents. They possess a C_2-symmetry axis that avoids the problem of regioselectivity in *N*-monoalkylation and opens the possibility of the fine tuning of the catalyst properties. Protonation makes these compounds bifunctional catalysts, having simultaneously Lewis base and Brønsted acid properties.
- A synthetic route to (3*S*,3'*S)*-bimorpholine had been developed by us previously. Bipiperidine was synthesised in just one step, and (2*R*,2*R*)-bipiperidine was obtained after crystallisation. Both catalysts were derivatised similarly.
- New organocatalysts were tested in Michael and aldol reactions. In a Michael addition of aldehydes to nitrostyrenes, iPrBP was the best catalyst, affording Michael adducts in high yield and up to 96% *ee*. The stereoselectivity of the reaction depends on the substituent at the nitrogen atom. The catalyst with the sterically more demanding iPr-group was the most selective. The scope of Michael donors is limited with aldehydes.
- In the aldol reaction, BM derivatives were found to be the most effective and selective catalysts. Again, the outcome of the reaction depended heavily on the substituent on the nitrogen atom, the iPr-group being the most selective of them.
- The influence of the conformational flexibility of six-membered ring on the stereoselectivity of the aldol reaction can be reduced by fixing its conformation with hydrogen bonding via protonation. It has a tremendous impact on the selectivity and reactivity of the catalyst in the aldol reaction.
- A useful synthetic intermediate - Wieland-Miescher ketone - was obtained in a tandem reaction (intermolecular Michael reaction and intramolecular aldol condensation) in high *ee* (91%).
- We have shown that BM derivatives are more suitable catalysts for an aldol reaction, and BP derivatives for a Michael reaction.
- The scope of aminocatalysts was also broadened with MCA and its salts. (*S*)-morpholine-3-carboxylic acid was synthesised in five steps and turned into different salts, sodium salt being the most active of them. MCA was tested in the reactions listed above but showed moderate selectivity. A comparison of different cyclic amino acids revealed the superiority of the five-membered pyrrolidine ring over the six-membered heterocyclic rings.

5. Experimental

General

Enantiomeric excess is calculated according to equation, where *R* and *S* are representative fractions of enantiomers in a mixture such that R+S=1.

$$ee = \frac{R - S}{R + S} \cdot 100\%$$

Chemicals were purchased from Aldrich Chemical Co or Alfa Aesar and were used as received. Full assignment of ^{1}H and ^{13}C chemical shifts are based on the 1D and 2D FT NMR spectra on a Bruker Avance III 400 MHz instrument. TMS and DSS were used as chemical shift reference. IR spectra were measured on a Perkin-Elmer Spectrum BX FTIR spectrometer. Elemental analyses were performed on a Perkin-Elmer C, H, N, S–Analyzer 2400. Optical rotations were obtained using Anton Paar GWB Polarimeter MCP 500 or Rudolph Research Analytical Autopol® V. The chiral HPLC was performed using Agilent Technologies 1200 Series chromatograph equipped with Chiralcel OD-H or AS-H (250 x 4.6 mm) column. Precoated silica gel 60 F_{254} plates from Merck were used for TLC, whereas for column chromatography silica gel KSK40-100 μm was used. All reactions sensitive to moisture or oxygen were carried out under Ar atmosphere in oven-dried glassware.

Tandem process for synthesis of Wieland Miescher ketone 12

To a solution of 2-methyl-1,3-cyclohexanedione (63 mg, 0.50 mmol) in CH_3CN (2 mL) iPrBM·TFA (16 mg, 0.050 mmol) and methylvinylketone (220 μL, 2.89 mmol) were added and refluxed for nine days. Solvent was evaporated and crude product purified by column chromatography on silica gel (PE:EtOAc 4:1) yielding 46 mg product in 52 % yield. Enantiomeric excess of the product was determined by chiral HPLC (Chiralcel AS-H column, 254 nm, Hex:iPrOH 94:6, 0.8 mL/min) t_R=19.21 min (major), t_R= 21.57 min (minor).

(2*R*,2'*R*)-*N*,*N*-dibenzoylbipiperidine 23

(2*R*,2'*R*)-bipiperidine (12 mg, 0.0722 mmol) was dissolved in 1 mL of DCM and Et_3N (22 μL, 0.159 mmol) was added. For the addition of benzoyl chloride (18 μL, 0.159 mmol) the reaction mixture was cooled down to 0 °C. The mixture was stirred at room temperature for 4 hours until completion was observed by TLC. Water and DCM were added and phases separated. The aqueous phase was extracted 3 times with DCM, dried over Na_2SO_4, filtered and concentrated. The crude product was purified by column chromatography on silica gel (PE:EtOAc 1:1). Product was obtained in quantitative yield. Enantiomeric excess of the product was determined by chiral HPLC (Chiralcel OD-H column, 210 nm, Hex:iPrOH 94:6, 1 mL/min) t_R=7.92 min (major), t_R= 9.85 min (minor).

Michael addition of propanal to *β*-nitrostyrene with LiCl additive
To a solution of MCA (8.8 mg, 0.067 mmol) in 1 mL of DCM:MeOH 9:1 mixture LiCl (2.8 mg, 0.067 mmol), *β*-nitrostyrene (50 mg, 0.335 mmol) and propanal (50 μL, 0.67 mmol) were added. The reaction was stirred for 3 days at rt. After completion of the reaction, satd aq NaCl was added and organic layer was separated. The aqueous phase was extracted with CH_2Cl_2 (4 x 3 mL), dried over $MgSO_4$, filtered, concentrated and purified by column chromatography on silica gel (PE/EtOAc 11:1) and isolated in 86% yield. The *ee* of the product was determined by HPLC (Chiralcel OD-H column), hexane/iPrOH 8:2, 1 mL/ min,UV 230 nm, 1 mL/min, syn: t_R = 13.71 (major) and t_R = 20.19 (minor). Syn:anti 87:13, *ee* 58%.

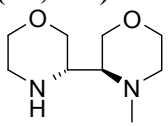
Michael addition of propanal to *β*-nitrostyrene with NaCl additive
To a solution of MCA (8.8 mg, 0.067 mmol) in 1 mL of DCM:MeOH 9:1 mixture NaCl (3.9 mg, 0.067 mmol), *β*-nitrostyrene (50 mg, 0.335 mmol) and propanal (50 μL, 0.67 mmol) were added. The reaction was stirred for 8 days at rt. After completion of the reaction, satd aq NaCl was added and organic layer was separated. The aqueous phase was extracted with CH_2Cl_2 (4 x 3 mL), dried over $MgSO_4$, filtered and concentrated. The *ee* of the crude product was determined by HPLC (Chiralcel OD-H column), hexane/iPrOH 8:2, 1 mL/ min,UV 230 nm, 1 mL/min, syn: t_R = 13.45 (major) and t_R = 20.00 (minor). Syn:anti 84:16, *ee* 39%.

Supporting information pertaining to article IV.

Full assignment of ^{1}H and ^{13}C chemical shifts is based on the 1D and 2D FT NMR spectra on a 500 MHz instrument. Deuterosolvent peaks (C**H**Cl_3 δ=7.27, **C**DCl_3 δ=77.00, C**H**D_2OD δ=3.30, **C**D_3OD δ=49.00) were used as chemical shift references. The mass spectra were obtained in GC/MS mode (EI, 70 eV). IR spectra were recorded on FTIR spectrometer. Optical rotations were measured using an automatic digital polarimeter and are reported as follows: $[\alpha]_\lambda^{T\ deg\ C}$(c = g/100 mL, solvent). Gas chromatography was performed using a DB-5 column (25 m x 0.25 mm). Chiral HPLC analyses were performed using Chiralcel OD-H (250 x 4.6 mm), Chiralpak AD-H (250 x 4.6 mm) and Chiralpak AS-H (250 x 4.6 mm) column. Reactions sensitive to oxygen or moisture were conducted under argon atmosphere in flame-dried glassware. Commercial reagents were generally used as received. Petroleum ether used had bp 40-60 °C.

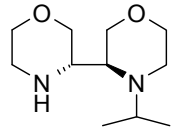
Synthesis of substituted bimorpholines

(3*S*, 3'*S*)-4-Methyl-3,3'-bimorpholine 4a



Title compound was prepared as described earlier.

(3*S*, 3'*S*)-4-Isopropyl-3,3'-bimorpholine 4b



Title compound was prepared as described earlier.

General method for the organocatalytic intermolecular aldol condensation of aromatic aldehydes and acetone

To a solution of the corresponding aromatic aldehyde **9a-i** (0.3 mmol) in acetone (0.6 mL) was added organocatalyst **6b** (0.09 mmol) and the mixture was stirred at room temperature for an appropriate time (6-10 days). The reaction mixture was treated with brine, extracted with EtOAc or Et_2O (4 x 2 mL) and the combined organic layers were dried over anhydrous Na_2SO_4. After filtration and concentration in vacuum, the crude product **10a-i** was purified by chromatography on silica gel.

(4*S*)-Hydroxy -4-(4´-nitrophenyl)-butan-2-one 10a

Yield: 70%; $[\alpha]_D^{22}$ = -55.7 (c = 4.61, $CHCl_3$); *ee* 88%, determined by HPLC (Daicel Chiralpak AD-H, Hex/iPrOH/MeOH 96:4:1), UV 210 nm, flow rate 1.0 mL/min, major: t_R 27.9 min and minor t_R 29.4 min.

(4*S*)-Hydroxy -4-(2´-nitrophenyl)-butan-2-one 10b

Yield: 77%; $[\alpha]_D^{22}$ = +142.8 (c = 1.97, CH_2Cl_2); *ee* 94%, determined by HPLC (Daicel Chiralpak AS-H, Hex/iPrOH 80:20), UV 254 nm, flow rate 0.8 mL/min, major: t_R 13.1 min and minor t_R 19.8 min.

(4*S*)-Hydroxy -4-(4´-triflouromethylphenyl)-butan-2-one 10c

Yield: 48%; $[\alpha]_D^{22}$ = -46.9 (c = 3.55, CH_2Cl_2); *ee* 90%, determined by HPLC (Daicel Chiralpak AD-H, Hex/iPrOH/MeOH 98:2:1), UV 210 nm, flow rate 0.9 mL/min, major: t_R 33.0 min and minor t_R 31.2 min.

(4*S*)-4-(4´-Chlorophenyl)-4-hydroxybutan-2-one 10d

Yield: 12%; $[\alpha]_D^{22}$ = -46.3 (c = 0.92, CH_2Cl_2); *ee* 88%, determined by HPLC (Daicel Chiralpak AS-H, Hex/iPrOH 90:10), UV 206 nm, flow rate 0.8 mL/min, major: t_R 24.0 min and minor t_R 19.3 min.

(4*S*)-4-(2´-Chlorophenyl)-4-hydroxybutan-2-one 10e

Yield: 79%; $[\alpha]_D^{22}$ = -98.5 (c = 1.71, CH_2Cl_2); *ee* 89%, determined by HPLC (Daicel Chiralpak AS-H, Hex/iPrOH 90:10), UV 206 nm, flow rate 0.8 mL/min, major: t_R 12.0 min and minor t_R 16.8 min.

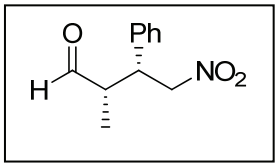
(4*S*)-4-(2´,4´-Dichlorophenyl)-4-hydroxybutan-2-one 10f
Yield: 74%; $[\alpha]_D^{22}$ = -91.4 (c = 1.58, CH_2Cl_2); *ee* 88%, determined by HPLC (Daicel Chiralpak AS-H, Hex/iPrOH 90:10), UV 206 nm, flow rate 0.8 mL/min, major: t_R 10.8 min and minor t_R 13.4 min.

4-(2´-Chloro-6´-fluorophenyl)- 4-hydroxybutan-2-one 10g
Yield: 91%; $[\alpha]_D^{22}$ = +15.3 (c = 3.16, CH_2Cl_2); *ee* 88%, determined by HPLC (Daicel Chiralpak AS-H, Hex/iPrOH 90:10), UV 206 nm, flow rate 0.8 mL/min, major: t_R 14.4 min and minor t_R 17,7 min. IR (KBr): 3442, 3088, 2923, 1714, 1605, 1577, 1455, 1418, 1361, 1243, 1076, 904, 785, 733 cm^{-1}. MS (EI): *m/z* (%) = 198 (7), 181 (80), 159 (100), 139 (13), 123 (17), 121 (18), 95 (18), 58 (61), 43 (62). HRMS exact mass calculated for $(C_{10}H_{10}FO_2)^+$ requires *m/z* 181.0663, found *m/z* 181.0663. Anal. Calcd for $C_{10}H_{10}ClFO_2$ (216.64): C 55.44, H 4.65. Found C 55.11, H 4.56.

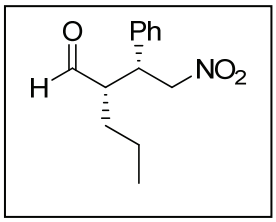
(4*S*)-Hydroxy-4-phenyl-butan-2-one 10h
Yield: 18%; $[\alpha]_D^{22}$ = -52.8 (c = 0.39, CH_2Cl_2); *ee* 85%, determined by HPLC (Daicel Chiralcel OD-H, Hex/iPrOH 93:7), UV 210 nm, flow rate 1.0 mL/min, major: t_R 12.0 min and minor t_R 12.8 min.

4-Hydroxy-4-(4´-isopropylphenyl)-butan-2-one 10i
Yield: <10%; *ee* 76%, determined by HPLC (Daicel Chiralpak AD-H, Hex/iPrOH/MeOH 98:2:1), UV 210 nm, flow rate 1.0 mL/min, major: t_R 33.3 min and minor t_R 29.4 min.
MS (EI): *m/z* (%) = 206 (8), 188 (2), 163 (11), 149 (30), 133 (27), 119 (12), 105 (63), 91 (25), 79 (36), 58 (11), 43 (100).
HRMS exact mass calculated for $(C_{10}H_{11}O_2)^+$ requires *m/z* 163.0757, found *m/z* 163.0757 and for $(C_{13}H_{18}O_2)^+$ requires *m/z* 206.1306, found *m/z* 206.1321.

Supporting information pertaining to article VI.

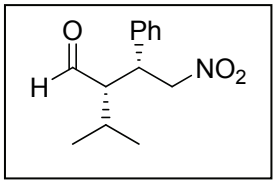


(2*S*,3*R*)-2-methyl-4 nitro-3-phenylbutyraldehyde 7a
From propionaldehyde **5a** and nitrostyrene **6a** at -25 °C according to the general procedure to give a white solid (57 mg, 82%). The enantiomeric excess was determined by HPLC (Chiralcel OD-H), Hex : iPrOH 8:2, UV 254 nm, 1 ml/min, syn: t_R=14.09 (major) and t_R=20.85 (minor). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.72 (d, *J* = 1.7, 1H), 7.38 – 7.26 (m, 3H), 7.18-7.16 (m, 2H), 4.81 (dd, *J* = 5.5, 12.7, 1H), 4.69 (dd, *J* = 9.3, 12.7, 1H), 3.82 (td, *J* = 5.5, 9.2, 1H), 2.84 – 2.72 (m, 1H), 1.01 (d, *J* = 7.3, 3H).



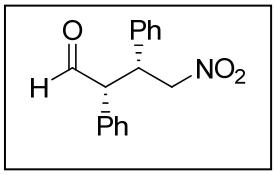
2-(*S*)-(2-nitro-1-(*R*)-phenylethyl)-pentanal 7b

From pentanal **5b** and nitrostyrene **6a** at rt according to the general procedure to give a pale yellow oil (76 mg, 96%). The enantiomeric excess was determined by HPLC (Chiralcel OD-H), Hex : iPrOH 8:2, UV 254 nm, 1 ml/min, syn: t_R=10.50 (major) and t_R=14.34 (minor). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.71 (d, *J* = 2.8, 1H), 7.39 – 7.28 (m, 3H), 7.21 – 7.15 (m, 2H), 4.75-4.61 (m, 2H), 3.78 (td, *J* = 5.3, 9.5, 1H), 2.71 (tt, *J* = 3.2, 9.5, 1H), 1.54 – 1.44 (m, 1H), 1.42-1.26 (m, 2H), 1.24 – 1.10 (m, 1H), 0.81 (t, *J* = 7.1, 3H).



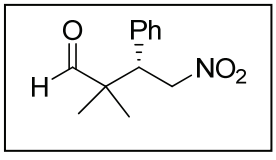
(2*S*,3*R*)-2-(methylethyl)-4-nitro-3-phenylbutyraldehyde 7c

From isovaleraldehyde **5c** and nitrostyrene **6a** at rt according to the general procedure to give pale yellow oil (67 mg, 85%). The enantiomeric excess was determined by HPLC (Chiralcel OD-H), Hex : iPrOH 8:2, UV 254 nm, 1 ml/min, syn: t_R=9.27 (major) and t_R=9.85 (minor). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.91 (d, *J* = 2.4, 1H), 7.35 – 7.24 (m, 3H), 7.19 – 7.14 (m, 2H), 4.65 (dd, *J* = 4.4, 12.5, 1H), 4.55 (dd, *J* = 10.0, 12.5, 1H), 3.88 (td, *J* = 4.4, 10.4, 1H), 2.75 (ddd, *J* = 2.4, 4.1, 10.8, 1H), 1.76 – 1.63 (m, 1H), 1.08 (d, *J* = 7.2, 3H), 0.86 (d, *J* = 7.0, 3H) .



(2R, 3 R)-4-nitro-2,3-diphenylbutyraldehyde 7d

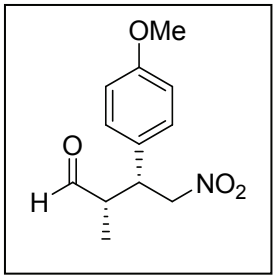
From 2-phenylacetaldehyde **5d** and nitrostyrene **6a** at rt according to the general procedure to give a white solid (67 mg, 74 %). The enantiomeric excess was determined by HPLC (Chiralcel OD-H), Hex : iPrOH 8:2, UV 220 nm, 1 ml/min, syn: t_R= 13.07 (minor) and t_R=14.58 (major). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.50 (d, *J* = 2.1, 1H), 7.42 – 6.88 (m, 10H), 4.44 (dd, *J* = 10.4, 12.7, 1H), 4.34 (dd, *J* = 4.3, 12.7, 1H), 4.30 – 4.18 (m, 1H), 4.03 (dd, *J* = 2.0, 10.5, 1H).



(S)-2,2-dimethyl-4-nitro-3-phenylbutyraldehyde 7e

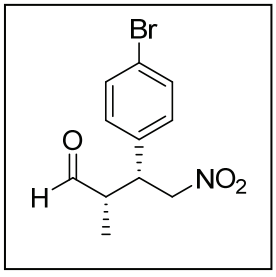
From isoburyraldehyde **5e** and nitrostyrene **6a** at rt according to the general procedure to give a yellowish solid (10 mg, 14 %). The enantiomeric excess was determined by HPLC (Chiralcel OD-H), Hex : iPrOH 8:2, UV 254 nm, 1 ml/min, t_R= 11.58 (minor) and t_R=16.19 (major).

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.54 (s, 1H), 7.38 – 7.28 (m, 3H), 7.23 – 7.18 (m, 2H), 4.86 (dd, *J* = 11.3, 13.0, 1H), 4.70 (dd, *J* = 4.2, 13.1, 1H), 3.79 (dd, *J* = 4.2, 11.2, 1H), 1.15 (s, 3H), 1.02 (s, 3H).



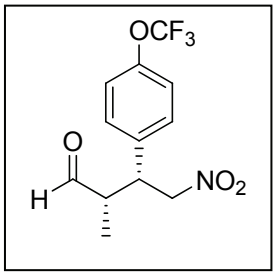
(2S, 3R)-3-(4-methoxyphenyl)-2-methyl-4-nitrobutyraldehyde 9a

From propionaldehyde **5a** and *trans*-4-methoxy-*β*-nitrostyrene **8a** at rt according to the general procedure to give a yellow oil (54 mg, 82 %). The enantiomeric excess was determined by HPLC (Chiralcel AS-H), Hex : iPrOH 7:3, UV 254 nm, 0.9 ml/min, syn: t_R= 16.81 (major) and t_R= 23.39 (minor). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.71 (d, *J* = 1.7, 1H), 7.15 – 7.06 (m, 3H), 6.89 – 6.84 (m, 2H), 4.82 – 4.71 (m, 1H), 4.64 (dd, *J* = 9.4, 12.5, 1H), 3.79 (s, 3H), 2.85 – 2.67 (m, 1H), 1.21 (d, *J* = 7.2, 1H), 1.01 (d, *J* = 7.3, 3H).



(2S, 3R) 3-(4-bromophenyl)-2-methyl-4-nitrobutyraldehyde 9b

From propionaldehyde **5a** and *trans*-4-bromo-*β*-nitrostyrene **8b** at rt according to the general procedure to give a white solid (62 mg, 99 %). The enantiomeric excess was determined by HPLC (Chiralcel OD-H), Hex : iPrOH 9:1, UV 254 nm, 1 ml/min, t_R= 27.54 (major) and t_R= 29.68 (minor). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.70 (d, *J* = 1.5, 1H), 7.52 – 7.45 (m, 2H), 7.13 – 7.03 (m, 2H), 4.80 (dd, *J* = 5.2, 12.8, 1H), 4.65 (dd, *J* = 9.6, 12.8, 1H), 3.91 – 3.67 (m, 1H), 2.93 – 2.62 (m, 1H), 1.01 (d, *J* = 7.3, 3H).



(2S,3R)-2-methyl-4-nitro-3-[4-(trifluoromethoxy)-phenyl]-butyraldehyde 9c

From propionaldehyde **5a** and *trans*-4-(trifluoromethoxy)-*β*-nitrostyrene **8c** at rt according to the general procedure to give a colourless oil (56 mg, 90 %). The enantiomeric excess was determined by HPLC (Chiralcel AD-H), Hex : iPrOH 95:5, UV 230 nm, 1 ml/min, t_R= 12.09 (minor) and t_R=15.95 (major). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.72 (d, *J* = 1.5, 1H), 7.30 – 7.19 (m, 6H), 4.83 (dd, *J* = 5.2, 12.9, 1H), 4.69 (dd, *J* = 9.6, 12.9, 1H), 3.93 – 3.82 (m, 1H), 2.90 – 2.73 (m, 1H), 1.03 (d, *J* = 7.3, 3H).

Computational aspects

Calculations of the energetic parameters were performed at the BP86/TZVPP level.[1] In this study the resolution of identity (RI)[2] approximation was used to

[1] (a) Perdew, J. P. *Phys. Rev. B* **1986**, *33*, 8822−8824. (b) Becke, A. D. *Phys. Rev. A* **1988**, *38*, 3098−3100. (c) Schäfer, A.; Huber, C.; Ahlrichs, R. *J. Chem. Phys.* **1994**, *100*, 5829−5835.

speed up the geometry optimisations of the systems. The auxiliary basis functions provided with the Turbomole 5.10 package were used.[3]
Continuum solvent effects were modeled using the COSMO model as implemented in the Turbomole 5.10 package.[4] The dielectric constant of chloroform (4.8) was used. For the cavity construction in the COSMO calculations, the default atomic radii of the Turbomole package were used.
For the BP86 calculations the zero-point vibrational energies (ZPE) were calculated from vibrational analysis and the energies were added to the calculated energies of all systems for getting the total energy of the system. Minima were confirmed by the vibrational analysis at the TZVPP level, with the geometry re-optimised in gas phase. One conformer (5_3_cis) had a minor (15.55i cm^{-1}) imaginary frequency, others had none.

[2] Eichkorn, K.; Weigend, F.; Treutler, O.; Ahlrichs, R. *Theor. Chim. Acta,* **1997**, *97*, 119−124
[3] Ahlrichs, R.; Bär, M.; Häser, M.; Horn, H.; Kölmel, C. *Chem. Phys. Lett.* **1989**, *162*, 165−169, for current version: see http://www.turbomole.de
[4] Klamt, A.; Schüürmann, G. *J. Chem. Soc., Perkin Trans. 2.* **1993**, pp 799−805.

Acknowledgements

This work was conducted in the Department of Chemistry at the Tallinn University of Technology. This work was financially supported by the Estonian Ministry of Education and Research ((Grant No. 0142725s06), the Estonian Science Foundation (Grant No. 8289), and the EU European Regional Development Fund (3.2.0101.08-0017). This work has been partially supported by graduate school ‘New production technologies and processes’ and ‘Functional materials and processes’ receiving funding from the European Social Fund under project 1.2.0401.09-0079 in Estonia.

It is a pleasure to thank those who made this thesis possible.

In particular, I would like to thank Professor Tõnis Kanger for all his guidance, support and help throughout the course of this work and for giving me the opportunity to become a long-serving membered of his group.
A huge thank you must go to the members of the Kanger group especially to Kadri, Kristin, Kerti, Kärt, Artur and Henri, and to the Lopp group for making the lab fun and enjoyable. Also, many thanks to Professor Toomas Tamm and to Merle Uudsemaa for computational study.

I am indebted to some of the staff for the provision of services: many thanks to Professor Tõnis Pehk, Marina and Kalle for NMR analysis, to Tiiu for IR analysis and to Mati for MS analysis.

I am very grateful to Professor Alexakis for giving me the opportunity to work in his group and to Sarah Sulzer-Mossé for her help throughout this collaboration.

“Suur tänu” to Professor Snieckus - it was an honour for me to work in his group at Queen’s University - and to Jignesh Patel for all his guidance and friendship.

I would like to express my gratitude to Professor Clayden for allowing me to be a member of his group and to Paul MacLellan for sharing thiocarbamate chemistry with me.

I would like to say a big thank you to my family for their unconditional support.

Abstract

This thesis describes the investigation of organocatalytic Michael and aldol reactions in the presence of (2*R*,2'*R*)-bipiperidine (BP) derivatives, (3*S*,3'*S*)-bimorpholine (BM) derivatives and (*S*)-morpholine-3-carboxylic acid (MCA) salts.

Chapter 1 illustrates previous work in the area of organocatalysis by other research groups, and presents the aims of the project.
Chapter 2 describes the synthesis of bimorpholine and bipiperidine derivatives and morpholine carboxylic acid salts. Bipiperidine was synthesised in just one step: (2*R*,2'*R*)-BP was obtained after crystallisation. The derivatisation of BM and BP was conducted using the same methodology. (*S*)-Morpholine-3-carboxylic acid was synthesised in five steps and turned into different salts.
Chapter 3 narrates the diastereoselective Michael reaction catalysed by iPrBM, iPrBP, MCA salts and other amino acid salts. The reaction with iPrBM yielded products in up to 90% *ee*; the iPrBP catalysed reaction gave products in up to 96% *ee*. The morpholine carboxylic acid sodium salt gave products in 72% *ee*. The iPrBP and morpholine carboxylic acid salts were quite reactive: reactions were complete within hours, the Michael addition with iPrBM took several days to complete.
Chapter 4 describes the iPrBM and iPrBP catalysed aldol reaction. The important synthetic intermediate Wieland–Miescher ketone was synthesised in up to 95% *ee* and the nor-analogue in 87% *ee*, using iPrBM triflic acid salt. The iPrBP TFA gave Wieland-Miescher ketone in up to 78% *ee* and its nor analogue in 74 % *ee*, but with low yield.
The intermolecular aldol reaction was investigated in the presence of iPrBM and iPrBP derivatives. Although reactions were sluggish and took days to complete, the aldol product was obtained with good selectivity, in up to 88% *ee* and 81% *ee*, respectively. The morpholine carboxylic acid and its sodium salt were not suitable catalysts for this reaction.
It was found that BM derivatives are more suitable for aldol reaction, and BP derivatives for the Michael reaction.
Chapter 5 contains the experimental methods and data pertaining to Chapters 2-4.

Kokkuvõte

Antud töös uuriti asümmeetrilist organokatalüütilist Michaeli ja aldoolreaktsiooni (2*R*,2'*R*)-bipiperidiini (BP) ja (3*S*,3'*S*)-bimorfoliini (BM) derivaatide ning (*S*)-morfoliin-3-karboksüülhappe (MCA) soolade toimel.

Esimeses peatükis tuuakse kirjandusülevaade organokatalüütilistest Michaeli ja aldoolreaktsioonidest. Samuti on esitatud töö eesmärgid.

Teises peatükis kirjeldatakse bimorfoliini ja bipiperidiini derivaatide ning morfoliinkarboksüülhappe soolade sünteesi. Bipiperidiin sünteesiti ühes etapis, (2*R*,2'*R*)-BP saadi kristallimise tulemusena, BM ja BP derivatiseerimiseks kasutati sama meetodit. (*S*)-morfoliin-3-karboksüülhape sünteesiti 5 etapiga ning seejärel valmistati happest erinevad soolad.

Peatükis 3 vaadeldakse iPrBM, iPrBP, MCA soolade ja teiste aminohappe soolade katalüüsitud diastereoselektiivset Michaeli reaktsiooni. iPrBM katalüüsil saadi produktid enantiomeerse puhtusega kuni 90%, iPrBP katalüüsil *ee*-ga kuni 96% ja MCA naatriumi soolaga produktid *ee*-ga kuni 72%. iPrBP ja MCA soolad olid reaktiivsed, Michaeli reaktioonid kestsid tunde, seevastu iPrBM katalüüsitud reaktsioonid kestsid päevi.

Peatükis 4 uuritakse iPrBM ja iPrBP katalüüsitud aldoolreaktsiooni. Oluline intermediaat Wieland–Miescher ketoon saadi enantiomeerse puhtusega kuni 95% ja tema nor-analoog kuni 87% enantiomeerse puhtusega, kasutades katalüsaatorina iPrBM trifluorometaansulfohappe soola. iPrBP trifluoroetaanhappe soolaga saadi produkt *ee*-ga 78% ja tema nor-analoog 74% *ee*-ga, kuid saagised jäid madalaks.
Uuriti ka molekulidevahelist aldoolreaktsiooni, kasutades katalüsaatoritena iPrBM ja iPrBP derivaate. Kuigi reaktsioonid olid aeglased ning kestsid päevi, saadi aldoolprodukt kõrge enantiomeerse puhtusega, vastavalt 88% ja 81%. MCA ega tema naatriumisool ei ole selle reaktsiooni jaoks sobivad katalüsaatorid.
Leiti, et BM derivaadid on sobivad katalüsaatorid aldoolreaktsiooni jaoks, BP derivaadid aga Michaeli reaktsiooni jaoks.

Peatükk 5 sisaldab eksperimentaalosa peatükis 2-4 toodud reaktsioonide kohta.

References

[1] Berkessel, A.; Gröger, H.; *Asymmetric Organocatalysis*; Wiley-VCH: Weinheim, 2005.
[2] Movassaghi, M.; Jacobsen, E. N. *Science* **2002**, *298*, 1904.
[3] List, B. *Tetrahedron* **2002**, *58*, 5573.
[4] Seayad, J.; List, B. *Org. Biomol. Chem*. **2005**, *3*, 719.
[5] List, B. *Chem. Rev*. **2007**, *107*, 5413.
[6] Gaunt, M. J.; Johansson, C. C. C.; McNally, A.; Vo, N. T. *Drug Discovery Today* **2007**, *12*, 8.
[7] Enders, D.; Grondal, C.; Hüttl, M. R. M. *Angew. Chem., Int. Ed*. **2007**, *46*, 1570.
[8] Dondani, A.; Massi, A. *Angew. Chem., Int. Ed*. **2008**, *47*, 4638.
[9] Yu, X.; Wang, W. *Org. Biomol. Chem*. **2008**, *6*, 2037.
[10] Grondal, C.; Jeanty, M.; Enders, D. *Nature Chemistry* **2010**, *2*, 167.
[11] Dalko, P. I.; Moisan L. *Angew. Chem. Int. Ed*. **2004**, *43*, 5138.
[12] List, B. *Angew. Chem. Int. Ed*. **2010**, *49*, 1730.
[13] MacMillan, D. W. C. *Nature* **2008**, *455*, 304.
[14] Knoevenagel, E. *Ber. Dtsch. Chem. Ges*. **1896**, *29*, 172.
[15] Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem., Int. Ed*. **1971**, *10*, 496.
[16] Hajos, Z. G.; Parrish, D. R. *J. Org. Chem* **1974**, *39*, 1615.
[17] Tu, Y., Wang, Z. & Shi, Y. *J. Am. Chem. Soc.* **1996**. *118*, 9806.
[18] Denmark, S. E., Wu, Z., Crudden, C.: Matsuhashi, H. *J. Org. Chem.* **1997**, *62*, 8288.
[19] Yang, D.; Yip, Y-C.; Tang, M-W.; Wong, M-K.; Zheng, J-H.; Cheung, K-K. *J. Am. Chem. Soc.* **1996,** *118,* 491.
[20] List, B.; Lerner, R.A.; Barbas III, C.F. *J. Am. Chem. Soc*. **2000**, *122*, 2395.
[21] Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000,** *122,* 4243.
[22] Melchiorre, P.; Marigo, M.; Carlone, A.; Bartoli, G. *Angew. Chem., Int. Ed*. **2008**, 47, 6138.
[23] Lelais, G.; MacMillan, D. W. C. *Aldrichimica Acta* **2006**, *39*, 79.
[24] Erkkilä, A.; Majander, I.; Pihko, P. M. *Chem. Rev*. **2007**, *107*, 5416.
[25] Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev*. **2007**, *107*, 5471.
[26] Notz, W.; Tanaka, F.; Barbas III, C.F. *Acc. Chem. Res*. **2004**, *37*, 580.
[27] List, B. *Acc. Chem. Res*. **2004**, *37*, 548.
[28] Tsogoeva, S. B. *Eur. J. Org. Chem*. **2007**, 1701.
[29] Allemann, C.; Gordillo, R.; Clemente, F. R.; Cheong, P. H-Y.; Houk, K. N. *Acc. Chem. Res*. **2004**, *37*, 558.
[30] Saito, S.; Yamamoto, H. *Acc. Chem. Res*. **2004**, *37*, 570.
[31] Guillena, G.; Nájera, C.; Ramón, D. J. *Tetrahedron: Asymmetry* **2007**, *18*, 2249.
[32] Trost, B. M.; Brindle, C. S. *Chem. Soc. Rev*. **2010**, *39*, 1600.
[33] Córdova, A. *Catalytic Asymmetric Conjugate Reactions*, Wiley-VCH: Weinheim, 2010, p. 191-195.
[34] Seebach, D.; Golinski, J. *Helv. Chim. Acta* **1981**, *64*, 1413.
[35] Seebach, D.; Beck, A. K.; Golinski, J.; Hay, J. N.; Laube, T. *Helv. Chim. Acta* **1985**, *68*, 162.
[36] Betancort, J. M.; Barbas III, C.F. *Org. Lett*. **2001**, *3,* 3737.
[37] Mase, N.; Thayumanavan, R.; Tanaka, F.; Barbas III, C.F. *Org. Lett*. **2004**, 6, 2527.

[38] Andrey, O.; Alexakis, A.; Tomassini, A.; Bernardinelli, G. *Adv. Synth. Catal*. **2004**, *346*, 1147.
[39] Sulzer- Mossé, S.; Alexakis, A. *Chem. Commun*. **2007**, 3123.
[40] Melchiorre, P.; Jørgensen, K. A. *J. Org. Chem* **2003**, *68*, 4151.
[41] Marigo, M.; Fielenbach, D.; Braunton, A.; Kjærsgaard, A.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 3703.
[42] Halland, N,; Braunton, A.; Bachmann, S.; Marigo, M.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 4790.
[43] Marigo, M.; Wabnitz, T. C.; Fielenbach, D.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 794.
[44] Juhl, K.; Jørgensen, K.A. *Angew. Chem., Int. Ed.* **2003**, *42*, 1498.
[45] Okuyama, Y.; Nakano, H.; Hongo, H. *Tetrahedron: Asymmetry* **2000**, *11*, 1193.
[46] Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M.; *Angew. Chem., Int. Ed*. **2005**, *44*, 4212.
[47] Franzén, J.; Marigo, M.; Fielenbach, D.; Wabnitz, T. C.; Kjærsgaard, A.; Jørgensen, K.A. *J. Am. Chem. Soc.* **2005**, *127*, 18296.
[48] Enders, D.; Hüttl, M. R. M.; Grondal, C.; Raabe, G. *Nature* **2006**, *441*, 861.
[49] Vesely, J.; Ibrahem, I.; Zhao, G.-L.; Rios, R.; Cordova, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 778.
[50] Hayashi, Y.; Okano, T.; Aratake, S.; Hazelard, D. *Angew. Chem., Int. Ed.* **2007**, *46*, 4922.
[51] Xie, H.; Zu, L.; Li, H.; Wang, J.; Wang, W. *J. Am. Chem. Soc.* **2007**, *129*, 10886.
[52] Enders, D.; Narine, A. A.; Benninghaus, T. R.; Raabe, G. *Synlett* **2007**, 1667.
[53] Gotoh, H.; Okamura, D.; Ishikawa, H.; Hayashi, Y. *Org. Lett*. **2009**, *11*, 4056.
[54] For a review, see: Palomo, C.; Mielgo, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 7876.
[55] Sulzer- Mossé, S.; Tissot, M.; Alexakis, A. *Org. Lett*. **2007**, *9*, 3749.
[56] García-García, P.; Ladépêche, A.; Halder, R.; List, B. *Angew. Chem. Int. Ed.* **2008**, *47*, 4719.
[57] Wiesner, M.; Wennemes, H. *Synthesis* **2010**, 1568.
[58] Wiesner, M.; Upert, G.; Angelici, G.; Wennemes, H. *J. Am. Chem. Soc.* **2010**, *132*, 6.
[59] Wang, W.; Wang, J.; Li, H. *Angew. Chem., Int. Ed*. **2005**, *44*, 1369.
[60] Wang, J.; Lou, B.; Zu, L.; Guo, H.; Wang, W. *Chem. Eur. J*. **2006**, *12*, 4321.
[61] Cobb, A. J. A.; Longbottom, D. A.; Shaw, D. A.; Ley, S. V. *Chem. Commun*. **2004**, 1808.
[62] Cobb, A. J. A.; Shaw, D. M.; Longbottom, D. A.; Gold, J. B.; Ley, S. V. *Org. Biomol. Chem*. **2005**, *3*, 84.
[63] Mitchell, E. T.; Cobb, A. J. A.; Ley, S. V. *Synlett* **2005**, 611.
[64] Sato, A.; Yoshida, M:, Hara, S. *Chem Commun*. **2008**, 6242.
[65] Yoshida, M:, Sato, A.;Hara, S. *Org. Biomol. Chem*. **2010**, *8*, 3031.
[66] Allemann, C.; Gordillo, R.; Clemente, F.R.; Cheong, P.H.-Y.; Houk, K.N. *Acc. Chem. Res.* **2004**, *37*, 558.
[67] Clemente, F.R.; Houk, K.N. *Angew. Chem. Int. Ed*. **2004**, *43,* 5766.
[68] Allemann, C.; Um, J. M.; Houk, K.N. *J. Mol. Cat. A*, **2010**, *324*, 31.
[69] Seebach, D.; Beck, A. K.; Badine, D.M.; Limbach, M.; Eschenmoser, A.; Treasurywala A. M.; Hobi, R. *Helv. Chim. Acta* **2007**, *90*, 425.
[70] Schmid, M.B.; Zeitler, K.; Gschwind, R.M. *Angew. Chem. Int. Ed.* **2010**, *49*, 4997.
[71] Zheng, Y.; Avery, M.A. *Tetrahedron* **2004**, *60*, 2091.
[72] Orsini, F.; Pelizzoni, F.; Forte, M.; Destro, R.; Gariboldi, P. *Tetrahedron* **1988**, *44*, 519.
[73] Tang, Z.; Jiang, F.; Yu, L-T.; Cui, X.; Gong, L-Z.; Mi, A-Q.; Jiang, Y-Z.; Wu, Y-D. *J. Am. Chem. Soc*., **2003**, *125*, 5262.

[74] Tang, Z.; Yang, Z-H.; Chen, X-H; Cun, L-F.; Mi, A-Q; Jiang, Y-Z.; Gong, L-Z. *J. Am. Chem. Soc*., **2005**, *127*, 9285.
[75] Samanta, S.; Liu, J.; Dodda, R.; Zhao C. G. *Org. Lett*., **2005**, *7*, 5321.
[76] Kano, T.; Takai, J.; Tokuda O.; Maruoka, K. *Angew. Chem., Int. Ed*., **2005**, *44*, 3055.
[77] Kano, T.; Tokuda, O.; Maruoka, K. *Tetrahedron Lett*., **2006**, *47*, 7423.
[78] Kano, T.; Maruoka, K. *Chem. Commun*. **2008**, 5465.
[79] Luo, S. Xu, H.; Li, J.; Zhang, L.; Cheng, J. P. *J. Am. Chem. Soc*., **2007**, *129*, 3074.
[80] Wang, Y.; Wei, S.; Sun, J. *Synlett* **2006**, 3319.
[81] Zheng, B.-L.; Liu, Q.-Z.; Guo, C.-S.; Wang, X.-L.; He, L. *Org. Biomol. Chem*. **2007**, *5*, 2913.
[82] Nakayama, K.; Maruoka, K.; *J. Am. Chem. Soc.* **2008**, *130*, 17666.
[83] Gryko, D.; Zimnicka, M.; Lipiński, R. *J. Org. Chem*. **2007**, *72*, 964.
[84] Kempf, B; Hampel, N.; Ofial, A. R.; Mayr, H. *Chem. Eur. J.* **2003**, *9*, 2209.
[85] Mayr, H.; Ofial, A. R. *J. Phys. Org. Chem.* **2008**, *21*, 584.
[86] Kanzian, T.; Nigst, T. A.; Maier, A.; Pichl, S.; Mayr H. *Eur. J. Org. Chem*. **2009**, 6379.
[87] Brotzel, F.; Chu, Y. C.; and Mayr, H. *J. Org. Chem. ,* **2007***, 72*, 3679.
[88] Kanger, T.; Kriis, K.; Pehk, T.; Müürisepp, A.-M.; Lopp, M. *Tetrahedron: Asymmetry* **2002**, *13*, 857.
[89] Kanger, T.; Laars, M.; Kriis, K.; Kailas, T.; Müürisepp, A.-M.; Pehk, T.; Lopp, M. *Synthesis* **2006**, *11*, 1853.
[90] Krumholz, P. *J. Am. Chem. Soc.* **1953**, *75*, 2163.
[91] Forostyan, Y. N.; Efimova, E. I.; Soroka, I. I. Zh. Org. Khim. **1971**, *7*, 2198.
[92] Sato, M.; Sato, Y.; Yano, S.;Yoshikawa, S. *J. Chem. Soc., Dalton Trans*. **1985**, 895.
[93] Herrmann, W. A.; Baskakov, D.; Herdtweck, E.; Hoffmann, S. D.; Bunlaksananusorn, T.; Rampf, F.; Rodefeld, L. Organometallics **2006**, *25*, 2449.
[94] Denmark, S. E.; Fu, J.; Lawler, M. J. *J. Org. Chem*. **2006**, *71*, 1523.
[95] Mossé, S.; Laars, M.; Kanger, T.; Kriis, K.; Alexakis, A. *Org. Lett.* **2006**, *8*, 2559-2562.
[96] Mase, N.; Watanabe, K.; Yoda, H.; Takabe, K.; Tanaka, F.; III *J. Am. Chem. Soc.* **2006**, *128*, 4966.
[97] Pansare, S. V.; Pandya, K. *J. Am. Chem. Soc*. **2006**, *128*, 9624.
[98] Ishii, T.; Fujioka, S.; Sekiguchi, Y.; Kotsuki, H. *J. Am. Chem. Soc*. **2004**, *126*, 9558.
[99] Bolm, C.; Rantanen, T.; Schiffers, I.; Zani, L. *Angew. Chem., Int. Ed*. **2005**, *44*, 1758.
[100] Alexakis, A.; Andrey, O. *Org. Lett.* **2002**, *4*, 3611.
[101] Brown, G. R.; Foubister, A. J.; Wright, B. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2577.
[102] Yamaguchi, M.; Shiraishi, T.; Hirama, M. *J. Org. Chem*. **1996**, *61*, 3520.
[103] Li, P.; Yamamoto, H. Chem. Commun. **2009**, 5412.
[104] Yamaguchi, M.; Yokota, N.; Minami, T. *J. Chem. Soc., Chem. Commun*. **1991**, 1088.
[105] Seebach, D.; Golinski, J. *Helv. Chim. Acta* **1981**, *64*, 1413.

Curriculum Vitae

Personal data

Name	Marju Laars
Date and place of birth	13.06.1978, Tallinn
Citizenship	Estonian

Contact information

Address	Akadeemia tee 15-427, Tallinn Estonia
Phone	+3726204367
E-mail	marju.laars@ttu.ee

Education

TUT 2006-2010 doctoral studies
TUT 2006, Chemistry and Materials Science, M.Sc.
TUT 2004, Chemical and Environmental Technology, B.Sc.

Professional Employment

Since 2006	Researcher at TUT, Chair of Organic Chemistry
02/2010-06/2010	Prof. Clayden's group, University of Manchester, UK
02/2008-06/2008	Prof. Snieckus's group, Queen's University, Kingston, Canada
10/2007-11/2007	ProSyntest Ltd
09/2005-11/2005	Prof. Alexakis's group, University of Geneva, Switzerland
09/2002-08/2006	TUT, Chair of Organic Chemistry

Defended theses

Master's thesis 'Asymmetric Synthesis of (3*S*,3′*S*)-Bimorpholine and Application of its Derivatives in Organocatalytic Michael Addition' 2006.
Bachelor's thesis 'Asymmetric Synthesis of (3*S*,3'*S*)-Bimorpholine' 2004.

List of publications

1. Laars, M.; Raska, H.; Lopp, M.; Kanger, T. *Tetrahedron: Asymmetry* **2010**, *21*, 562-565.
2. Laars, M.; Ausmees, K.; Uudsemaa, M.; Tamm, T.; Kanger, T.; Lopp, M. *J. Org. Chem.* **2009**, *74*, 3772-3775.
3. Uudsemaa, M.; Laars, M.; Kriis, K.; Tamm, T.; Lopp, M.; Kanger, T. *Chem. Phys. Lett.* **2009**, *417*, 92-96.
4. Laars, M.; Kriis, K.; Kailas, T.; Müürisepp, A.-M.; Pehk, T.; Kanger, T.; Lopp, M. *Tetrahedron: Asymmetry* **2008**, 19, 641-645.
5. Kriis, K.; Laars, M.; Lippur, K.; Kanger, T. *Chimia* **2007**, *61*, 232-235.

6. Kanger, T.; Kriis, K.; Laars, M.; Kailas, T.; Müürisepp, A.-M.; Pehk, T.; Lopp, M. *J. Org. Chem*. **2007**, *72*, 5168-5173.
7. Sulzer-Mossé, S.; Laars, M.; Kriis, K.; Kanger, T.; Alexakis, A. *Synthesis* **2007**, 1729-1732.
8. Kriis, K.; Kanger, T.; Laars, M.; Kailas, T.; Müürisepp, A.-M.; Pehk, T.; Lopp, M. *Synlett* **2006**, 1699-1702.
9. Kanger, T.; Laars, M.; Kriis, K.; Kailas, T.; Müürisepp, A.-M.; Pehk, T.; Lopp, M. *Synthesis* **2006**, 1853-1857.
10. Mossé, S.; Laars, M.; Kanger, T.; Kriis, K.; Alexakis, A. *Org. Lett.* **2006**, *8*, 2559-2562.

Elulookirjeldus

Isikuandmed

Ees- ja perekonnanimi	Marju Laars
Sünniaeg ja -koht	13.06.1978, Tallinn
Kodakondsus	Eesti

Kontaktandmed

Aadress	Akadeemia tee 15-427, Tallinn Eesti
Telefon	+3726204367
e-mail	marju.laars@ttu.ee

Hariduskäik

Tallinna Tehnikaülikool 2006-2010, doktorant
Tallinna Tehnikaülikool 2006, keemia- ja materjalitehnoloogia, M.Sc.
Tallinna Tehnikaülikool 2004, keemia- ja keskkonnakaitsetehnoloogia, B.Sc.

Teenistuskäik

alates 2006	Tallinna Tehnikaülikooli orgaanilise keemia õppetool, teadur
02/2010-06/2010	Manchesteri Ülikool, Suurbritannia, prof Claydeni grupp
02/2008-06/2008	Queen'si Ülikool, Kingston, Kanada, prof Snieckuse grupp
10/2007-11/2007	AS ProSyntest
09/2005-11/2005	Genfi Ülikool, Šveits, prof Alexakise grupp
09/2002-08/2006	Tallinna Tehnikaülikooli orgaanilise keemia õppetool

Kaitstud lõputööd

Magistritöö "(3*S*,3′*S*)-bimorfoliini asümmeetriline süntees ja tema derivaatide kasutamine organokatalüütilisel Michaeli liitumisel", 2006.
Bakalaureusetöö "(3*S*,3'*S*)-bimorfoliini asümmeetriline süntees" 2004.

DISSERTATIONS DEFENDED AT TALLINN UNIVERSITY OF TECHNOLOGY ON *NATURAL AND EXACT SCIENCES*

1. **Olav Kongas**. Nonlinear dynamics in modeling cardiac arrhytmias. 1998.

2. **Kalju Vanatalu**. Optimization of processes of microbial biosynthesis of isotopically labeled biomolecules and their complexes. 1999.

3. **Ahto Buldas**. An algebraic approach to the structure of graphs. 1999.

4. **Monika Drews**. A metabolic study of insect cells in batch and continuous culture: application of chemostat and turbidostat to the production of recombinant proteins. 1999.

5. **Eola Valdre**. Endothelial-specific regulation of vessel formation: role of receptor tyrosine kinases. 2000.

6. **Kalju Lott**. Doping and defect thermodynamic equilibrium in ZnS. 2000.

7. **Reet Koljak**. Novel fatty acid dioxygenases from the corals *Plexaura homomalla* and *Gersemia fruticosa.* 2001.

8. **Anne Paju**. Asymmetric oxidation of prochiral and racemic ketones by using sharpless catalyst. 2001.

9. **Marko Vendelin**. Cardiac mechanoenergetics *in silico*. 2001.

10. **Pearu Peterson**. Multi-soliton interactions and the inverse problem of wave crest. 2001.

11. **Anne Menert**. Microcalorimetry of anaerobic digestion. 2001.

12. **Toomas Tiivel**. The role of the mitochondrial outer membrane in *in vivo* regulation of respiration in normal heart and skeletal muscle cell. 2002.

13. **Olle Hints**. Ordovician scolecodonts of Estonia and neighbouring areas: taxonomy, distribution, palaeoecology, and application. 2002.

14. **Jaak Nõlvak**. Chitinozoan biostratigrapy in the Ordovician of Baltoscandia. 2002.

15. **Liivi Kluge**. On algebraic structure of pre-operad. 2002.

16. **Jaanus Lass**. Biosignal interpretation: Study of cardiac arrhytmias and electromagnetic field effects on human nervous system. 2002.

17. **Janek Peterson**. Synthesis, structural characterization and modification of PAMAM dendrimers. 2002.

18. **Merike Vaher**. Room temperature ionic liquids as background electrolyte additives in capillary electrophoresis. 2002.

19. **Valdek Mikli**. Electron microscopy and image analysis study of powdered hardmetal materials and optoelectronic thin films. 2003.

20. **Mart Viljus**. The microstructure and properties of fine-grained cermets. 2003.

21. **Signe Kask**. Identification and characterization of dairy-related *Lactobacillus*. 2003.

22. **Tiiu-Mai Laht**. Influence of microstructure of the curd on enzymatic and microbiological processes in Swiss-type cheese. 2003.

23. **Anne Kuusksalu**. 2–5A synthetase in the marine sponge *Geodia cydonium*. 2003.

24. **Sergei Bereznev**. Solar cells based on polycristalline copper-indium chalcogenides and conductive polymers. 2003.

25. **Kadri Kriis**. Asymmetric synthesis of C_2-symmetric bimorpholines and their application as chiral ligands in the transfer hydrogenation of aromatic ketones. 2004.

26. **Jekaterina Reut**. Polypyrrole coatings on conducting and insulating substracts. 2004.

27. **Sven Nõmm**. Realization and identification of discrete-time nonlinear systems. 2004.

28. **Olga Kijatkina**. Deposition of copper indium disulphide films by chemical spray pyrolysis. 2004.

29. **Gert Tamberg**. On sampling operators defined by Rogosinski, Hann and Blackman windows. 2004.

30. **Monika Übner**. Interaction of humic substances with metal cations. 2004.

31. **Kaarel Adamberg**. Growth characteristics of non-starter lactic acid bacteria from cheese. 2004.

32. **Imre Vallikivi**. Lipase-catalysed reactions of prostaglandins. 2004.

33. **Merike Peld**. Substituted apatites as sorbents for heavy metals. 2005.

34. **Vitali Syritski**. Study of synthesis and redox switching of polypyrrole and poly(3,4-ethylenedioxythiophene) by using *in-situ* techniques. 2004.

35. **Lee Põllumaa**. Evaluation of ecotoxicological effects related to oil shale industry. 2004.

36. **Riina Aav**. Synthesis of 9,11-secosterols intermediates. 2005.

37. **Andres Braunbrück**. Wave interaction in weakly inhomogeneous materials. 2005.

38. **Robert Kitt**. Generalised scale-invariance in financial time series. 2005.

39. **Juss Pavelson**. Mesoscale physical processes and the related impact on the summer nutrient fields and phytoplankton blooms in the western Gulf of Finland. 2005.

40. **Olari Ilison**. Solitons and solitary waves in media with higher order dispersive and nonlinear effects. 2005.

41. **Maksim Säkki**. Intermittency and long-range structurization of heart rate. 2005.

42. **Enli Kiipli**. Modelling seawater chemistry of the East Baltic Basin in the late Ordovician–Early Silurian. 2005.

43. **Igor Golovtsov**. Modification of conductive properties and processability of polyparaphenylene, polypyrrole and polyaniline. 2005.

44. **Katrin Laos**. Interaction between furcellaran and the globular proteins (bovine serum albumin β-lactoglobulin). 2005.

45. **Arvo Mere**. Structural and electrical properties of spray deposited copper indium disulphide films for solar cells. 2006.

46. **Sille Ehala**. Development and application of various on- and off-line analytical methods for the analysis of bioactive compounds. 2006.

47. **Maria Kulp**. Capillary electrophoretic monitoring of biochemical reaction kinetics. 2006.

48. **Anu Aaspõllu.** Proteinases from *Vipera lebetina* snake venom affecting hemostasis. 2006.

49. **Lyudmila Chekulayeva**. Photosensitized inactivation of tumor cells by porphyrins and chlorins. 2006.

50. **Merle Uudsemaa**. Quantum-chemical modeling of solvated first row transition metal ions. 2006.

51. **Tagli Pitsi**. Nutrition situation of pre-school children in Estonia from 1995 to 2004. 2006.

52. **Angela Ivask**. Luminescent recombinant sensor bacteria for the analysis of bioavailable heavy metals. 2006.

53. **Tiina Lõugas**. Study on physico-chemical properties and some bioactive compounds of sea buckthorn (*Hippophae rhamnoides* L.). 2006.

54. **Kaja Kasemets**. Effect of changing environmental conditions on the fermentative growth of Saccharomyces cerevisae S288C: auxo-accelerostat study. 2006.

55. **Ildar Nisamedtinov**. Application of ^{13}C and fluorescence labeling in metabolic studies of Saccharomyces spp. 2006.

56. **Alar Leibak**. On additive generalisation of Voronoï's theory of perfect forms over algebraic number fields. 2006.

57. **Andri Jagomägi**. Photoluminescence of chalcopyrite tellurides. 2006.

58. **Tõnu Martma**. Application of carbon isotopes to the study of the Ordovician and Silurian of the Baltic. 2006.

59. **Marit Kauk**. Chemical composition of $CuInSe_2$ monograin powders for solar cell application. 2006.

60. **Julia Kois**. Electrochemical deposition of $CuInSe_2$ thin films for photovoltaic applications. 2006.

61. **Ilona Oja Açik**. Sol-gel deposition of titanium dioxide films. 2007.

62. **Tiia Anmann**. Integrated and organized cellular bioenergetic systems in heart and brain. 2007.

63. **Katrin Trummal**. Purification, characterization and specificity studies of metalloproteinases from *Vipera lebetina* snake venom. 2007.

64. **Gennadi Lessin**. Biochemical definition of coastal zone using numerical modeling and measurement data. 2007.

65. **Enno Pais**. Inverse problems to determine non-homogeneous degenerate memory kernels in heat flow. 2007.

66. **Maria Borissova**. Capillary electrophoresis on alkylimidazolium salts. 2007.

67. **Karin Valmsen**. Prostaglandin synthesis in the coral *Plexaura homomalla*: control of prostaglandin stereochemistry at carbon 15 by cyclooxygenases. 2007.

68. **Kristjan Piirimäe**. Long-term changes of nutrient fluxes in the drainage basin of the gulf of Finland – application of the PolFlow model. 2007.

69. **Tatjana Dedova**. Chemical spray pyrolysis deposition of zinc sulfide thin films and zinc oxide nanostructured layers. 2007.

70. **Katrin Tomson**. Production of labelled recombinant proteins in fed-batch systems in *Escherichia coli*. 2007.

71. **Cecilia Sarmiento**. Suppressors of RNA silencing in plants. 2008.

72. **Vilja Mardla**. Inhibition of platelet aggregation with combination of antiplatelet agents. 2008.

73. **Maie Bachmann**. Effect of Modulated microwave radiation on human resting electroencephalographic signal. 2008.

74. **Dan Hüvonen**. Terahertz spectroscopy of low-dimensional spin systems. 2008.

75. **Ly Villo**. Stereoselective chemoenzymatic synthesis of deoxy sugar esters involving *Candida antarctica* lipase B. 2008.

76. **Johan Anton**. Technology of integrated photoelasticity for residual stress measurement in glass articles of axisymmetric shape. 2008.

77. **Olga Volobujeva**. SEM study of selenization of different thin metallic films. 2008.

78. **Artur Jõgi**. Synthesis of 4'-substituted 2,3'-dideoxynucleoside analogues. 2008.

79. **Mario Kadastik**. Doubly charged Higgs boson decays and implications on neutrino physics. 2008.

80. **Fernando Pérez-Caballero**. Carbon aerogels from 5-methylresorcinol-formaldehyde gels. 2008.

81. **Sirje Vaask**. The comparability, reproducibility and validity of Estonian food consumption surveys. 2008.

82. **Anna Menaker**. Electrosynthesized conducting polymers, polypyrrole and poly(3,4-ethylenedioxythiophene), for molecular imprinting. 2009.

83. **Lauri Ilison**. Solitons and solitary waves in hierarchical Korteweg-de Vries type systems. 2009.

84. **Kaia Ernits**. Study of In_2S_3 and ZnS thin films deposited by ultrasonic spray pyrolysis and chemical deposition. 2009.

85. **Veljo Sinivee**. Portable spectrometer for ionizing radiation "Gammamapper". 2009.

86. **Jüri Virkepu**. On Lagrange formalism for Lie theory and operadic harmonic oscillator in low dimensions. 2009.

87. **Marko Piirsoo**. Deciphering molecular basis of Schwann cell development. 2009.

88. **Kati Helmja**. Determination of phenolic compounds and their antioxidative capability in plant extracts. 2010.

89. **Merike Sõmera**. Sobemoviruses: genomic organization, potential for recombination and necessity of P1 in systemic infection. 2010.

90. **Kristjan Laes**. Preparation and impedance spectroscopy of hybrid structures based on $CuIn_3Se_5$ photoabsorber. 2010.

91. **Kristin Lippur**. Asymmetric synthesis of 2,2'-bimorpholine and its 5,5'-substituted derivatives. 2010.

92. **Merike Luman**. Dialysis dose and nutrition assessment by an optical method. 2010.

93. **Mihhail Berezovski**. Numerical simulation of wave propagation in heterogeneous and microstructured materials. 2010.

94. **Tamara Aid-Pavlidis**. Structure and regulation of BDNF gene. 2010.

95. **Olga Bragina**. The role of Sonic Hedgehog pathway in neuro- and tumorigenesis. 2010.

96. **Merle Randrüüt**. Wave propagation in microstructured solids: solitary and periodic waves. 2010.