Chalcogen Based Organocatalysts in Transesterification

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„Ich bin nicht entmutigt,
denn jeder erkannte Irrtum
ist ein weiterer Schritt nach vorn.“

Thomas Alva Edison

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List of Abbreviations

[α]	specific rotation
AcOH	acetic acid
aq.	aqueous
Asp	aspartic acid
B. subtilis	*Bacillus subtilis*
bp	boiling point
br s	broad singlet
°C	degree Celsius (centigrade)
cat.	catalyst
d	doublet (NMR)
DCC	dicyclohexyl carbodiimide
dd	doublet of doublet
ddd	doublet of doublet of doublets
ddt	doublet of doublet of triplets
DEAD	diethyl azodicarboxylate
DFT	density functional theory
DIAD	diisopropyl azodicarboxylate
DIPEA	*N*,*N*-diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMSO	dimethyl sulfoxide
dt	doublet of triplets
e.g.	*exempli gratia*, (for example)
ee	enantiomeric excess
equiv.	equivalent
ESI-MS	electrospray ionization – mass spectrometry
et al.	*et alia*, (and others)
g	gram
GC-MS	gas chromatography – mass spectrometry
h	hour(s)
His	histidine
HCN	hydrogen cyanide
HPLC	high-performance liquid chromatography
HR ESI-MS	high resolution electrospray mass spectra
i	iso-
i.e.	*id est*, (that is)

J	coupling constant (NMR)
k	rate constant
k_{obs}	observed rate constant
$k_{without}$	rate constant of the uncatalysed reaction
l	liter
lit.	literature
λ	wavelength
M	Molarity
m	milli
m	multiplet (NMR)
*m*CPA	*meta*-chloroperoxybenzoic acid
MeOH	methanol
min	minutes
MMA	methyl methacrylate
mp	melting point
MTBE	methyl *tert*.-butyl ether
M. W.	microwave
µ	micro
N	Normality
n	normal- (no branching in alkyl)
NMR	nuclear magnetic resonance
p-	*para*-
PET	polyethylene terephthalate
*p*NP	*para* nitrophenyl ester
ppm	parts per million
q	quartet (NMR)
R_F	retention factor
rt	room temperature
s	seconds
s	singlet (NMR)
Ser	serine
t	triplet (NMR)
$t_{1/2}$	half-life
TBAF	tetrabutylammonium fluoride
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl

t_R	retention time
UV	ultraviolet
V. fischeri	*Vibrio fischeri (Allivibrio fischeri)*

Chapter 1

Introduction to Asymmetric Organocatalysis

Abstract:

After a short introduction about the definition and benefits of catalysis, three different domains of the asymmetric synthesis are presented in this chapter: metal, bio-, and organocatalysis. Thereby, the attention is focused on organocatalysis as a counterpart of metal and biocatalysis in the stereoselective synthesis. The historical background is shown and different types of organocatalysts are briefly demonstrated.

1.1 Introduction

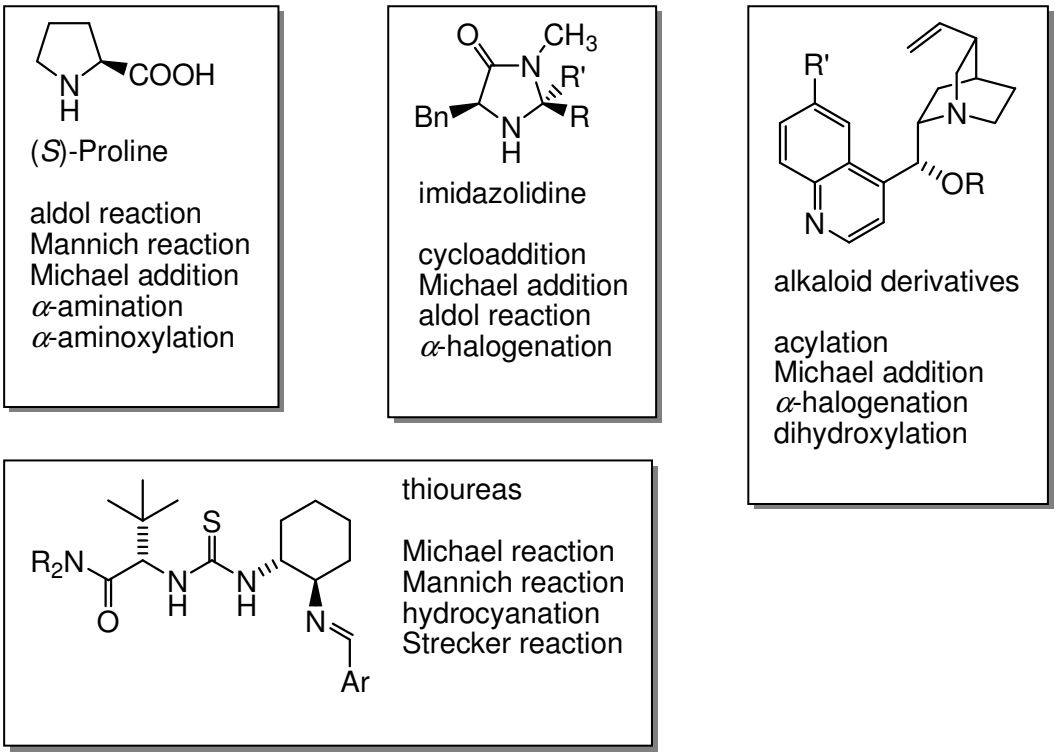
Almost daily we come in contact with catalysts without knowing it. For example, after cutting open an apple or a pear, so they change their color quickly to brown in the air. Thereby, available proteins (enzymes) act in the fruit as biocatalysts which become effective in connection with the atmospheric oxygen and initiate brown coloring. Without special enzymes most biochemical processes can not proceed in living organisms. This includes various metabolic pathways in all biological cells such as digestion or photosynthesis. A further representative application is the use of catalysts for detoxifcation of exhaust emissions of cars.

Catalysts and catalysis are indispensable for a functioning chemical industry. Approximately 80 % of all chemical products are produced with the help of catalytic processes. Catalytic reactions help to reduce excessive consumption of raw materials and energy; but most of all, they reduce reaction times and byproduct formation. For that, catalysis is sometimes referred to as a "foundational pillar" of green chemistry.[1]

The scientific concept of catalysis goes back to the first decades of the 19th century.[2] Scientists, such as Döbereiner, Mitscherlich, Berzelius, and later Liebig observed over and over again that some sluggish reactions become fast after addition of or in contact with certain other substances. In 1836, Jöns Jakob Berzelius coined the phrase "catalysis" (Greek *katálysis*: annulment) based on the observed effect; and the substances which increase the reaction rate, are called "catalysts" since this time. About 1900, Wilhelm Ostwald made fundamental research in the field of the chemical equilibrium and reaction rates. He gave the phrase catalysis the modern definition: *„Katalyse ist die Beschleunigung eines langsam verlaufenden chemischen Vorgangs durch die Gegenwart eines fremden Stoffes."*[3] Later, he specified in a presentation: *„Ein Katalysator ist jeder Stoff, der, ohne im Endprodukt einer chemischen Reaktion zu erscheinen, ihre Geschwindigkeit verändert*."[4] In 1909, Ostwald was awarded the Nobel Prize in Chemistry for his work.

After the pioneering work of Ostwald, the innovation and the success in the field of catalysis went on.[5,6] This is strengthened by the fact that till 2014 about ten further Nobel Prizes have been awarded for prominent achievements in the area of catalysis. So far the research focus has been in the field of metal-catalyzed reactions and particularly in the catalytic asymmetric synthesis based on using chiral transition metal complexes. In 2001, the Nobel Prize in Chemistry was awarded to William R. Knowles and Ryoji Noyori for their work on chiral catalyzed hydrogenation reactions and to K. Barry Sharpless for his work on chiral catalyzed oxidation reactions (Sharpless-oxidation).[7] But also with biocatalysts (usually enzymes) good progress was achieved in the area of catalytic asymmetric synthesis, e.g. because of the

discovery of enzymes from novel organism useful for preparative reactions and the optimization of the enzyme performance by selective mutation or evolutionary methods.[8-11]
In addition to bio- and metal catalysis, asymmetric catalysis has seen expansion in a third area, mostly since the beginning of 2000 – the asymmetric organocatalysis. Since that time, this field developed to an explosively growing and fascinating area in the organic chemistry. Organocatalysis means that a chemical reaction is accelerated by an addition of catalytic amounts of a metal-free organic molecule, i.e. catalysts (mainly) composed of carbon, hydrogen, nitrogen, oxygen, sulphur and phosphorus. In Scheme 1.1, some typical organocatalysts and reactions catalyzed by them are illustrated.



Scheme 1.1: Typical organocatalysts and the reactions catalyzed by them

1.2 Organocatalysis *versus* Bio- and Metal Catalysis

Chemists in academic and industrial research laboratories constantly have to face higher demands in their search for new active substances. Often this requires molecules with one or several asymmetric centres. The development of enantiomerically pure active compounds is very important in the drug industry because individual enantiomers can show different effects and adverse reactions (Figure 1.1). [12-14]

There are different ways to introduce chirality (Greek *cheir*: hand) into a molecule such as the synthesis of racemates with following separation of enantiomers, the preparation from the 'chiral pool' of nature or the isolation from natural products.[15-17] Another elegant way is enantioselective synthesis.[18] There are two approaches in order to induce a chiral transformation: one by using a chiral auxiliary (chiral compound which covalently binds to

(*R*)-Thalidomid (*S*)-Thalidomid

effective against morning sickness teratogenic, causes birth defects

Figure 1.1: Biological active compound which show different effects

the starting material), the auxiliary-directed synthesis; and the other one by using a catalytic amount of a chiral controller (enzymes, metals bearing a chiral ligand or small, chiral organic molecules), the enantioselective catalysis. Enantioselective catalysis has been emerged as the economically most attractive way.[19,20] This method is dominated by three strategies: biocatalysis,[21,22] transition-metal catalysis[23] and organocatalysis.[24-27] Metal catalysis is a very effective method. Because of the high molecular and structural diversity of metal complexes, but principally because of the usually strong interaction of reactants with the metal center, high levels of enantioselectivity can be achieved and a broad substrate scope has been demonstrated. Disadvantages can be high prices, toxicity, pollution, waste treatment and product contamination.

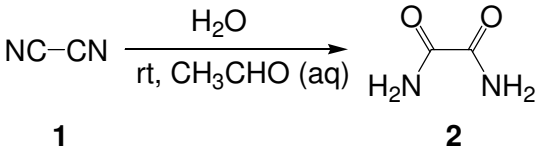
Enzymes possess a high biocompatibility and biodegradability with high turnover and selectivity. In contrast they often suffer from limited substrate scope and require often an expensive production and isolation.

Organocatalysis benefits from the disadvantages of bio- and metal catalysis. Organocatalysts show a high availability because they can be synthesized from many natural occurring compounds. The catalysts are commonly inexpensive and stable. For that, organocatalytic reactions are manageable under aerobic conditions and hydrous solvents. Besides, the products are not contaminated with metals. This point is very important for the synthesis of pharmaceutical compounds. Furthermore, they can build multiple stereogenic centers in cascade reactions and they can be anchored to a solid support, so that an easy recovery is possible. However, organocatalysts have disadvantages, too. Organcatalytic reactions often require high catalyst loadings (20-30 mol%) and quite long reaction times (up to days).

Consequently, organocatalysis can be appreciated as an alternative to metal catalysis and biocatalysis.

1.3 Historical Background

Although the origins of the organocatalysis go back to the early age of synthetic chemistry, their enormous potential in organic synthesis has been realized only in the past decade.[28-31] The first organocatalytic reaction was performed by the German scientist Justus von Liebig in 1860.[32] He reported on the conversion of dicyan **1** into oxamide **2** in the presence of an aqueous solution of acetaldehyde (Scheme 1.2). Later, this efficient reaction formed the basis of the Degussa oxamide synthesis.



1 **2**

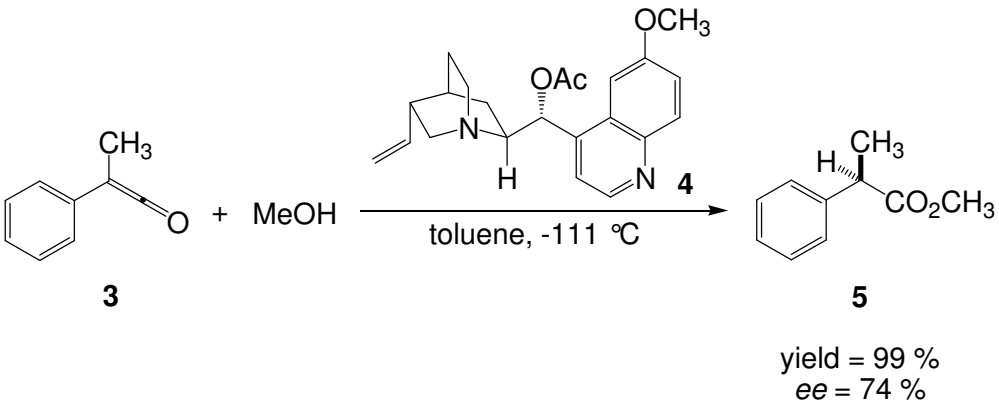
Scheme 1.2: Liebig`s oxamide synthesis

In 1896, Emil Knoevenagel described the aldol condensation of β-ketoesters or malonates with aldehydes or ketones catalyzed by piperidine. With this, he laid the foundation for the development of modern aminocataylsis.[33]

The first asymmetric organocatalytic reaction was presented by Bredig and Fiske in 1912.[34] The addition of HCN to benzaldehyde was accelerated in the presence of certain alkaloids as catalysts, such as quinine or quinidine. Although this reaction showed only low enantioselectivity, the concept of these studies can be considered as groundbreaking in the area of asymmetric catalysis.

Already in 1928, the German chemist Wolfgang Langenbeck published a book in which he described the analogies of the catalytic activities between enzymes and certain organic substances.[35] Four years later, he named these organic substances as organic catalysts ("*Organische Katalysatoren*").[36] Thus, Langenbeck is probably the first chemist who desribed the concept of organocatalysis and established a relationship between organocatalysts and enzymes.[37]

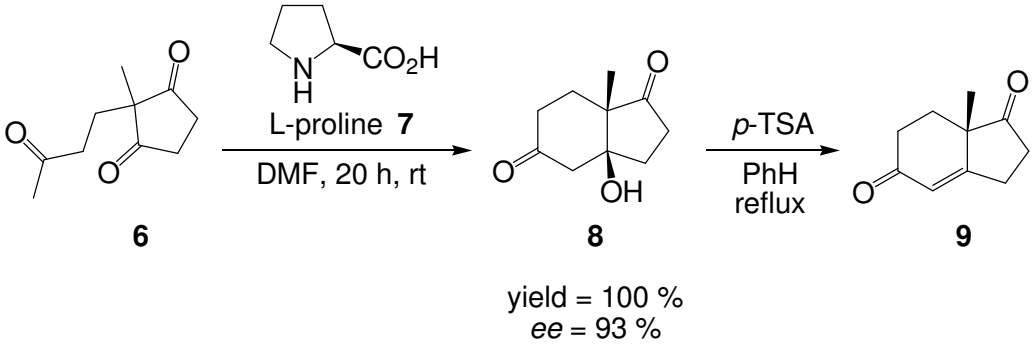
In 1960, Pracejus *et al.* reported the enantioselective addition of MeOH to phenyl ketene **3**, catalyzed by chinchona alkaloid derivatives **4** (Scheme 1.3).[38] He found an enantiomeric excess (*ee*) of 74 %. It should be noted that for the first time such useful levels of *ee* have been achieved.



Scheme 1.3: Pracejus` enantioselective ester synthesis

In the end of the 1960s it was also reported on a non-enantioselective catalytic reaction by Steglich. He used 4-dialkylaminopyridines as catalysts for acyl transfer reactions.[39]

However, the first commercial use of an organocatalytic reaction was described only in the beginning of the 70s. Two industrial research groups – Eder, Sauer and Wiechert from Schering AG and Hajos and Parrish from Hoffmann-La Roche – discovered independently from each other the first proline-catalyzed intramolecular aldol reaction which is used in the synthesis of steroids and several other natural products (Scheme 1.4).[40-43] The so-called Hajos-Parrish-Eder-Sauer-Wiechert reaction is a Robinson type annulation of achiral trione **6** which is transformed to the bicyclic ketol **8** (Wieland-Miescher ketone) in quantitative yield and high *ee* (> 90 %).

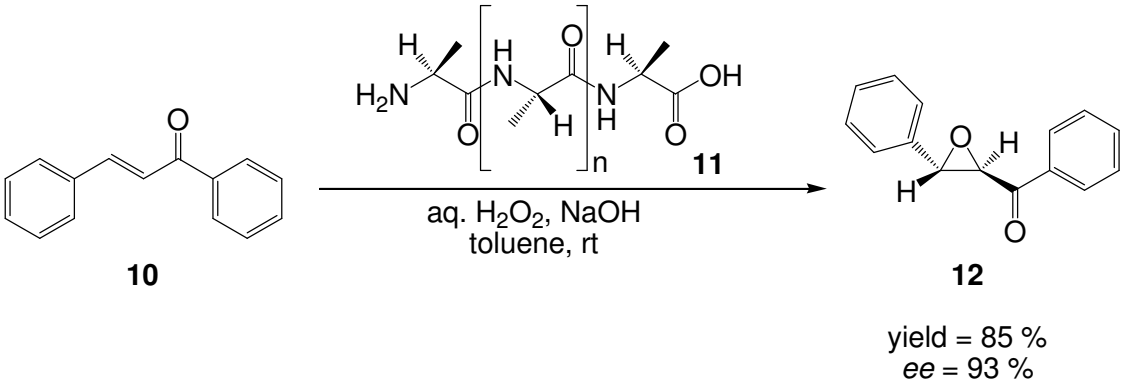


Scheme 1.4: The Hajos-Parrish-Eder-Sauer-Wiechert reaction

Further breakthroughs in enantioselectivities were achieved in the 1980s. Remarkable are the poly-amino acid **11** catalyzed Juliá-Colonna epoxidation of chalcones **10** (Scheme 1.5) and the cyclic dipeptide catalyzed addition of HCN to benzaldehyde (Inoue *et al.*) can serve as examples.[44-47] Another example is the *N*-benzylcinchoninium halides catalyzed asymmetric *α*-methylation of substituted 2-phenyl-1-indanone by researchers of Merck at the end of 1980s.[48]

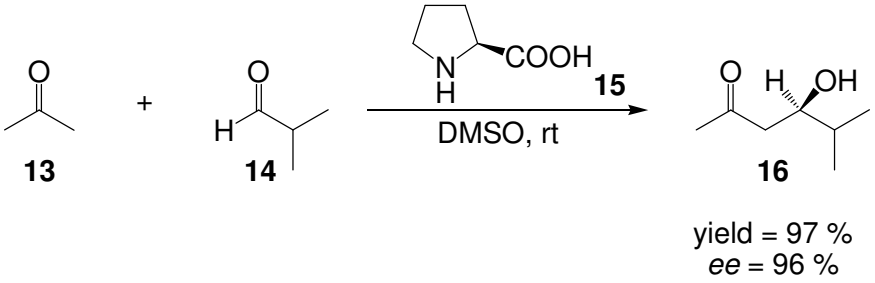
The next wave of efficient organocatalytic reactions was initiated in the late 1990s. Shi *et al.*, Yang *et al.* and Denmark *et al.* described several enantioselective epoxidation reactions of

simple alkenes catalyzed by enantiomerically pure ketones,[49-51] Jacobsen *et al*. and Corey *et al*. reported on hydrogen-bonding catalysis in an asymmetric Strecker reaction,[52, 53] and Miller *et al.* demonstrated the application of tripeptides in the kinetic resolution of alcohols.[54]

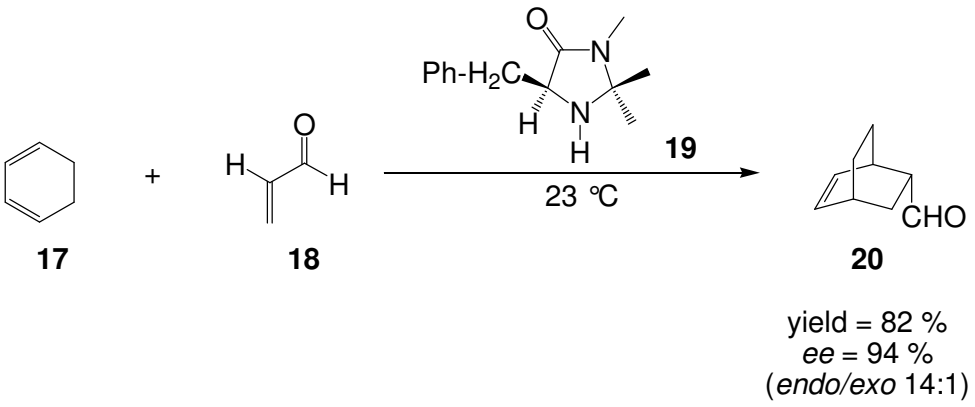


Scheme 1.5: Juliá-Colonna epoxidation of chalcones

The breakthrough of the concept of organocatalysis proceeded with two publications in 2000: one from List, Lerner and Barbas[55] on enamine catalysis in aldol reactions (Scheme 1.6); and the other from MacMillan *et al.*[56] on iminium catalysis in Diels-Alder reactions (Scheme 1.7). Since this date, the interest in catalysis mediated by small organic molecules began to explode.



Scheme 1.6: Proline-catalyzed intermolecular aldol reaction



Scheme 1.7: Secondary amine-catalyzed Diels-Alder reaction

1.4 Different Types of Organocatalysts

Organocatalytic reactions can be classified according to their activation modes of the used organocatalyst. Hence, it can be distinguished between catalysts that form a covalent interaction with the substrate (covalent catalysis) and such that form non-covalent interaction with the substrate (non-covalent catalysis).
The covalent catalysis is initiated by the nucleophilic/ electrophilc addition of the catalyst to the substrate. The resulting complex reacts, and the product as well as the catalyst is then liberated. The catalysts can be characterized as Lewis bases or Lewis acids (Figure 1.2).

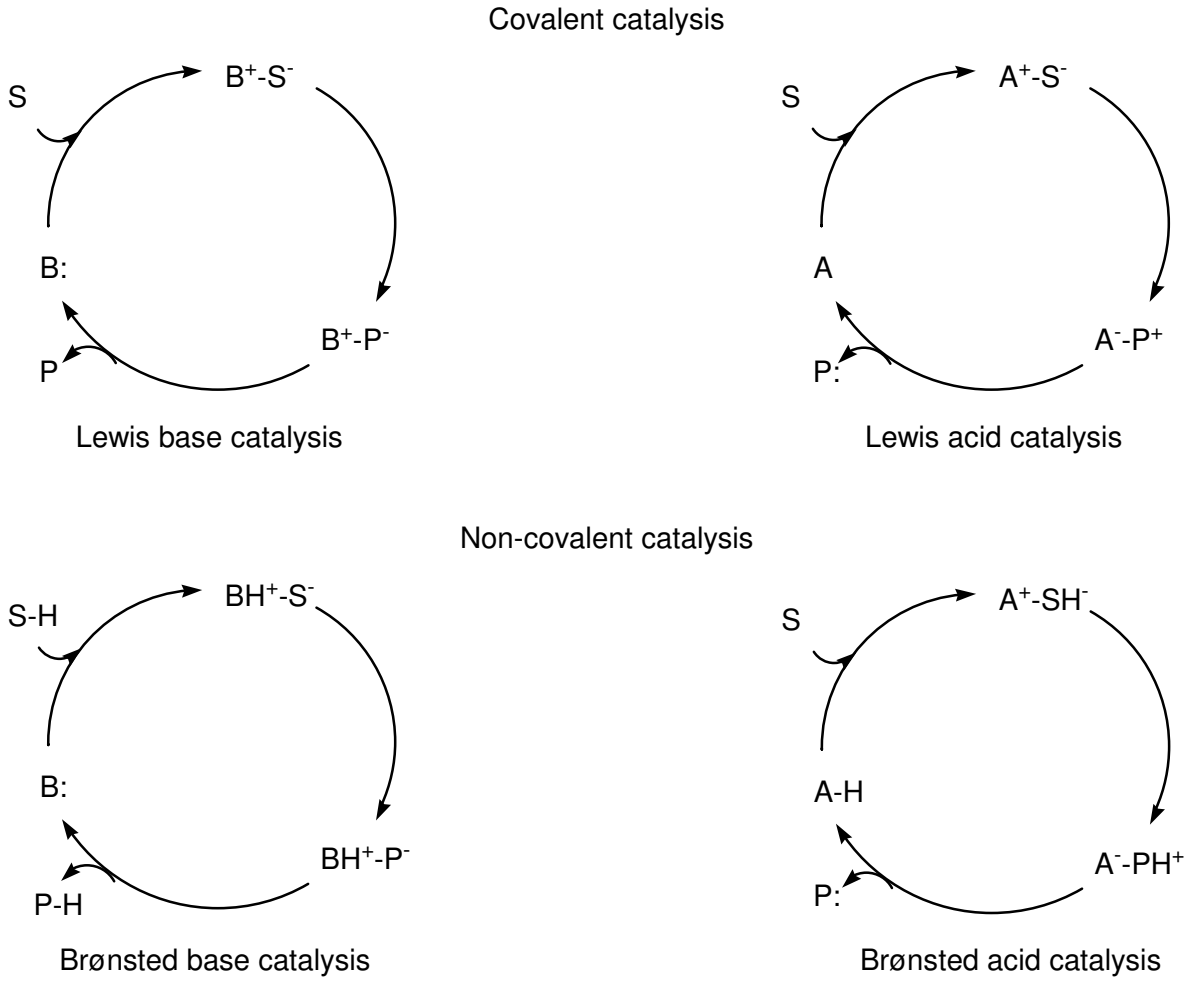


Figure 1.2: Schematic catalytic cycles of organocatalysts; A: acid, B: base, S: substrate, P: product

An example of a Lewis acid is the *D*-fructose derived ketone **21** (Figure 1.3). The ketone introduced by Shi *et al.* catalyzes the asymmetric epoxidation of olefins in presence of persulfate as the oxygen source. Lewis bases are represented by a multitude of catalysts. For example, proline **23** catalyzes aldol and related reactions by iminium or enamine

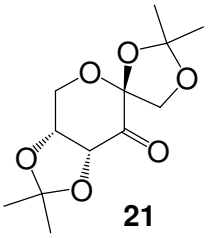
pathways (List *et al.*[57] and MacMillan *et al.*[58]). Chinchona alkaloids **24** are successful employed as chiral bases (Wynberg *et al.*[59]) or as nucleophilic catalysts (Bolm *et al.*[60] and Deng *et al.*[61]). But also DMAP derivatives **25** (Fu *et al.*[62]) or chiral phosphines **26** (Vedejs *et al.*[63]) can act as nucleophilic catalysts, e.g. in acyl transfer reactions. The pentapeptide **27** introduced by Miller *et al.* can be used as an artificial kinase that enables highly enantioselective phosphorylation.[64] Furthermore, sulfides **28** catalyze the epoxidation of aldehydes or aziridination of imines (Aggarwal *et al.*[65]), or the phosphoramides **29** which are used in the intermolecular aldol reaction or allylation of aldehydes (Denmark *et al.*[66]). The carbenes **30** as catalysts for the intramolecular Stetter reaction or benzoin-condensation should be mentioned too (Enders *et al.*).[67]

The non-covalent catalysis relies on the formation of hydrogen-bonding or ion pairs. Non-covalent interactions are formed by Brønsted bases or Brønsted acids. They catalyze the reaction *via* deprotonation or protonation of the substrate (Figure 1.2). Brønsted bases are presented by tertiary amines or guanidines **31** which can be applied in cyanhydrin and Strecker reactions (Corey *et al.*[53]). Brønsted acids are chiral thioureas **32**, chiral diols **33** or polyamino acids **34**. Chiral thioureas introduced by Jacobsen *et al.* have enabled excellent *ee* in e.g. the asymmetric Michael reaction of malonates to nitro olefins or the hydrocyanation of imines.[68] Chiral diols (Huang, McDougal *et al.*) are applied as efficient and enantioselective catalysts in Hetero-Diels-Alder- and Morita-Baylis-Hilmann reactions.[69,70]

Phase-transfer catalysts are an exception. They fall into the category of “non-covalent” catalysis, but most of them can be assigned to Lewis acid catalysts. A typical phase-transfer catalyst is the chinchonidine-derived quartenary ammonium salt **22** (Corey, Lygo, Maruoka *et al.*) which alkylates glycine imines to appropriate *α*-substituted amino acid esters with very high enantioselectivities.[71-73]

In Figure 1.3, some examples of organocatalysts are depicted according to the four groups Lewis base/acid and Brønsted base/acid.

Lewis acids:



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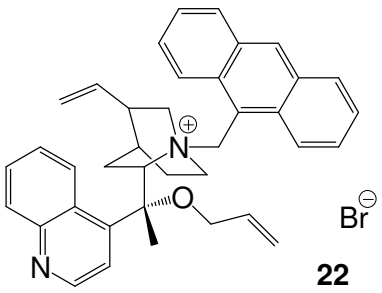

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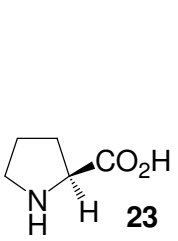
Lewis bases:



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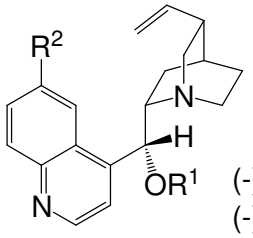
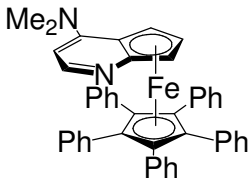


(-)-quinine: R^1 = H, R^2 = OCH_3 **24a**
(-)-cinchonidine: R^1 = R^2 = H **24b**



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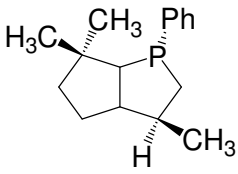

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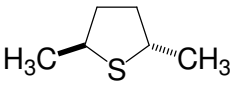

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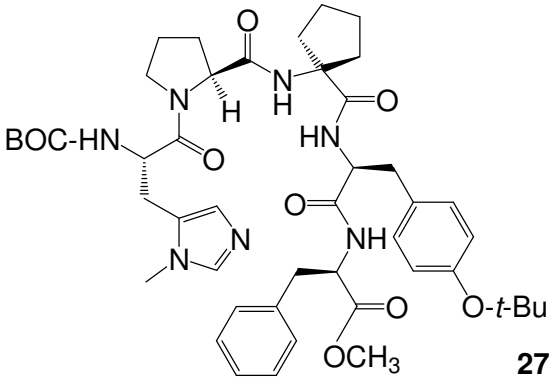

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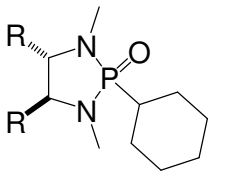

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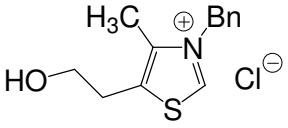

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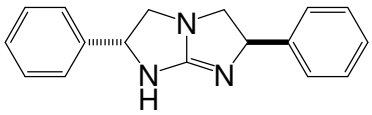
Brønsted base:



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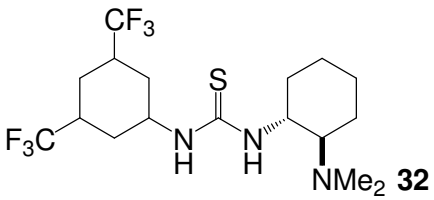
Brønsted acids:



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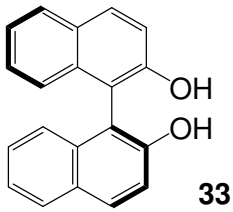

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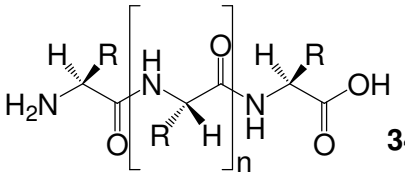

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Figure 1.3: Organocatalysts indexed as Lewis base/acid and Brønsted base/acid.

1.5 Summary and Outline

In this Chapter, organocatalysis was introduced as practical and broadly applicable methodological approach in asymmetric synthesis in addition to bio- and metal catalysis. The historic roots of organocatalysis were briefly shown. Furthermore, different types of organocatalysts were presented. Furthermore, some examples of catalysts and their reactions were given.

This thesis sets its focus on organocatalysts which possess a chalcogen atom like oxygen or sulfur as crucial catalytic site, i.e. the chalcogen atom itself is involved as active site in the catalytic cycle. The chalcogen based organocatalysts, which are used in this thesis, were applied only for transesterification or acylation reactions. To this end, chapter 2 describes the kinetic mechanistic studies on transesterification reactions between active esters and alcohol. In chapter 3, the desymmetrization of various *meso*-anhydrides is discussed. Finally, chapter 4 shows the regioselective acylation of some macrocyclic antibiotics.

1.6 References

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Chapter 2

Kinetic and Mechanistic Studies on Transesterification Reactions Promoted by Chalcogen-Based Organocatalysts

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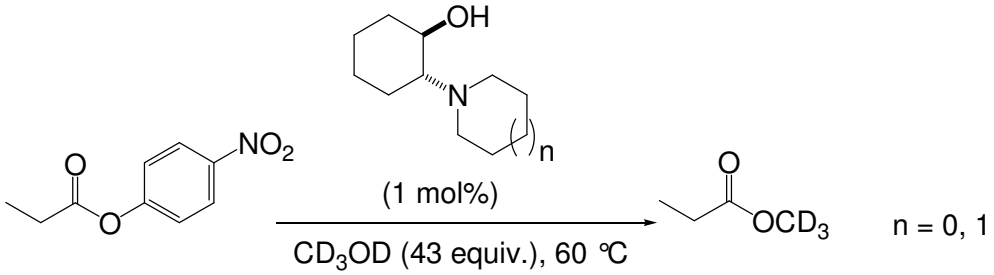
Abstract [*] *:*

Various organocatalysts, such as amino alcohols, sulfoxides, and amino sulfoxides, were studied with respect of their catalytic behavior in the methanolysis of propionic acid *para*-nitrophenyl ester. High catalytic activities could be achieved with cyclohexane-based *β*-amino alcohol catalysts. Their mechanism of action could be determined as *O*-nucleophilic mechanism.



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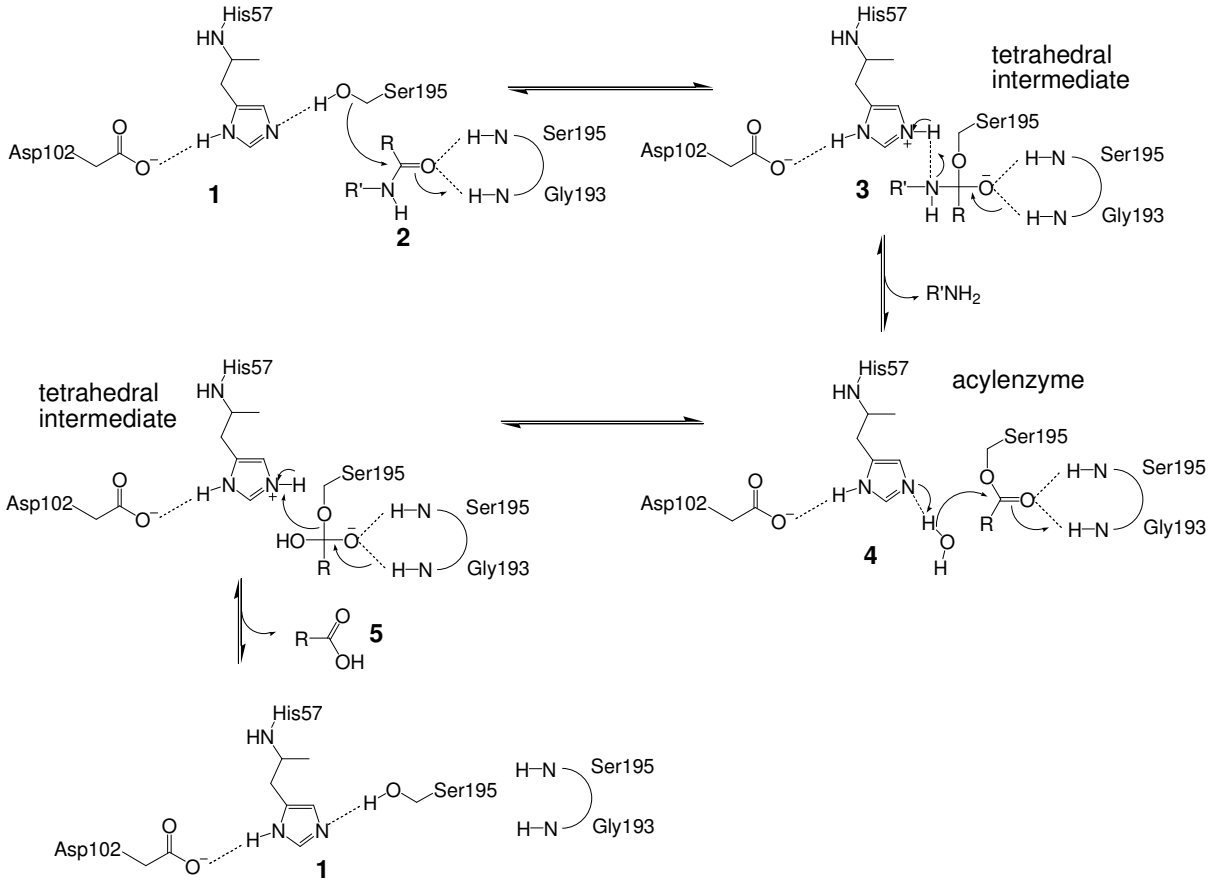
2.1 Introduction

Ester hydrolysis, esterification or acylation, and transesterification reactions play an important role in nature and organic synthesis including the synthesis of natural products.[1-4] The classic synthesis of esters is the Fischer esterification, which uses mineral or sulfonic acids as catalysts in the presence of alcohols and carboxylic acid. But many substrates are unstable under these conditions. For that, a series of alternative esterification reactions were developed including the reaction between an alcohol and carboxylic acid chloride, anhydride, or ester (transesterification). Another possibility is the use of coupling reagents such as dicyclohexyl carbodiimide (DCC, catalyzed by DMAP = Steglich esterification)[5,6] or the Mitsunobu reaction[7], which performs the production of esters under inversion of the alcoholic carbon using triphenylphosphine and diethyl azodicarboxylate (DEAD). Esters may also be produced by oxidation, such as the Baeyer-Villiger oxidation.

Esterification technology is widely used in the chemical industry, for example in the production of polyesters like polyethylene terephthalate (PET) which is employed for the production of food packaging. Another example is the acrylic ester methyl methacrylate (MMA) the polymer of which (PMMA) is used in place of glass and other optical materials. Furthermore, esters are applied in the production of biodiesel fuel (mixture of methyl esters of fatty acids) or in medicine for the treatment of pain, fever and inflammation with e.g. acetylsalicylic acid. Besides, oils and fats (triesters of glycerol and fatty acids), which occur in plants and animal products, are used in margarine, plasticizer, lubricating oils, and as surfactant for soaps and food emulsifier (e.g. lecithin). Esters are also employed as flavoring agents in foodstuff and as fragrances in perfumes and other cosmetics.

In nature, transesterification reactions include for example enzymatic reactions of lipases, esterases, and other hydrolases that mostly rely on the catalytic triade of serine proteases.[8-11] Serine proteases are hydrolases which are responsible for the cleavage of peptide bonds. The name derives from serine which is one of the amino acids in the active site of the enzyme. Representatives of serine proteases are e.g. the digestive enzyme chymotrypsin and the enzyme subtilisin which can be obtained from *Bacillus subtilis* and is principally used in laundry detergents. Chymotrypsin-like proteases are the most abundant proteases in nature. The mechanism of hydrolysis of peptide bonds involves a catalytic triad which is located in the active site of the enzyme chymotrypsin. The catalytic triad **1** consists of three essential amino acids: serine (Ser195), histidine (His57) and aspartic acid (Asp102). Histidine makes serine more nucleophilic (and basic), so that the hydroxyl group of serine can attack the carbonyl of an amide **2**. A tetrahedral intermediate **3** is generated, whose peptide bond is broken proton transfer from the histidine nitrogen. An acyl-enzyme intermediate **4** is formed. This intermediate **4** undergoes histidin base promoted hydrolysis

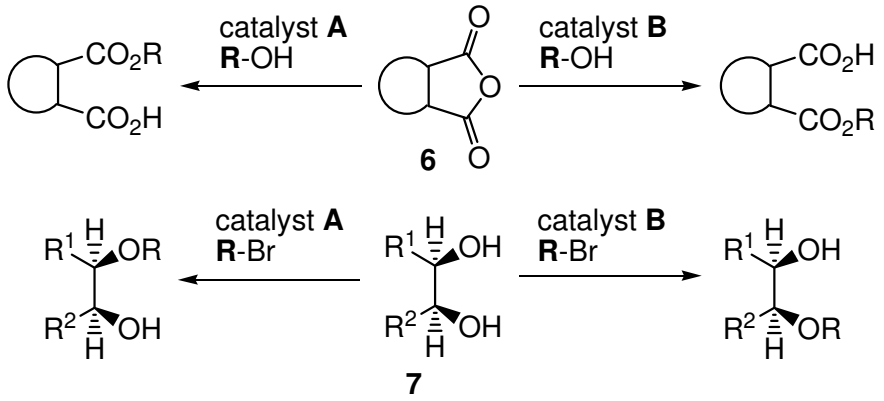
and provides the carboxylic acid **5** (Scheme 2.1).



Scheme 2.1: The general reaction mechanism of chymotrypsin-like serine proteases

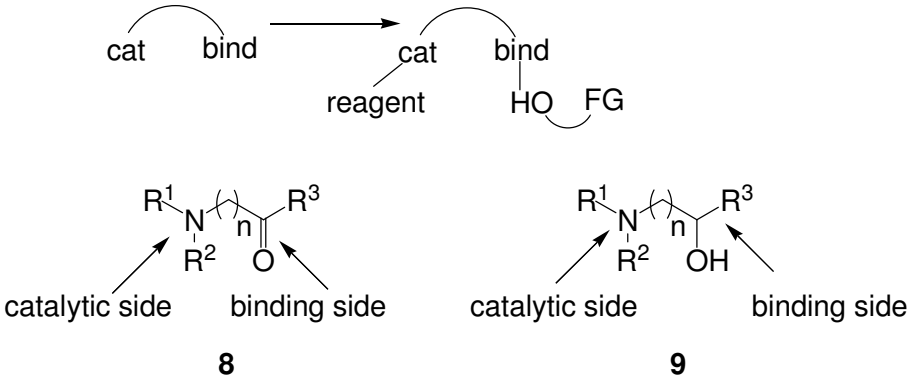
In this thesis, two different types of (trans-)acylation will be discussed: Firstly, the “classical” transesterification between an acyl donor and a nucleophile will be considered in view of its mechanistic aspects (chapter 2). Subsequently, the kinetic resolution or desymmetrization of cyclic anhydrides will be presented (chapter 3).

The kinetic resolution of chiral, racemic esters, anhydrides, or alcohols relies on the faster conversion of only one substrate enantiomer by the chiral catalyst, whereas the other enantiomer ideally remains unchanged. A special case within kinetic resolutions is the desymmetrization of *meso*-anhydrides **6** or *meso*-diols **7** that requires a selective conversion of one of the two enantiotopic functional groups (carbonyl or hydroxyl group) (Scheme 2.2).



Scheme 2.2: Desymmetrization of *meso*-anhydride **6** or *meso*-diol **7**

For acylation reactions, a variety of acyl-transfer catalysts are well-known, such as tertiary amines (e.g. (-)-quinine), *N*-heteroaromatic compounds (e.g. Steglich catalyst DMAP), or phosphines, which act as general base or general nucleophile catalysts.[12-14]Many of these catalysts are bifunctional catalysts, i.e. they possess two functional groups, one being the catalytic side (N-atom) and one as a binding side, e.g. a carbonyl group **8** or hydroxyl group **9** (Scheme 2.3).

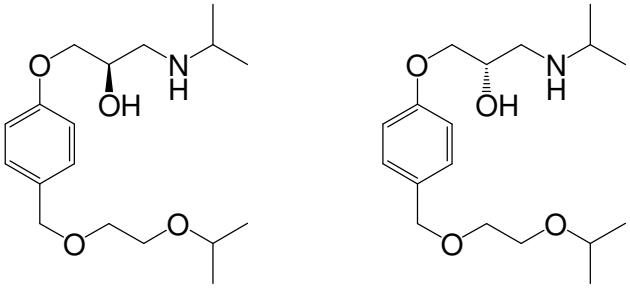


Scheme 2.3: Bifunctional acyl-transfer catalysts **8** and **9**

However, most use group V elements (N, P) as catalytic center, in contrast to nature, that uses chalcogenes (O, S, Se) in its hydrolases. In the following, organocatalysts based on organochalcogenes will be the focus.

2.2 Amino Alcohols as Acyl-Transfer Catalysts

Amino alcohols are an important class of organic substances which can serve as chiral mediator or as ligands for catalysis. A very large number of biologically active compounds (e.g. alkaloids, antibiotics and *β*-blockers) contain the *β*-amino alcohol moiety.[15,16] For example, Bisoprolol **10** (Figure 2.1) is a drug belonging to the group of selective β_1 adrenergic receptor blockers (*β*-blocker) which is applied for the treatment of hypertension, angina pectoris and chronic heart failure. The racemate is used as active agent.

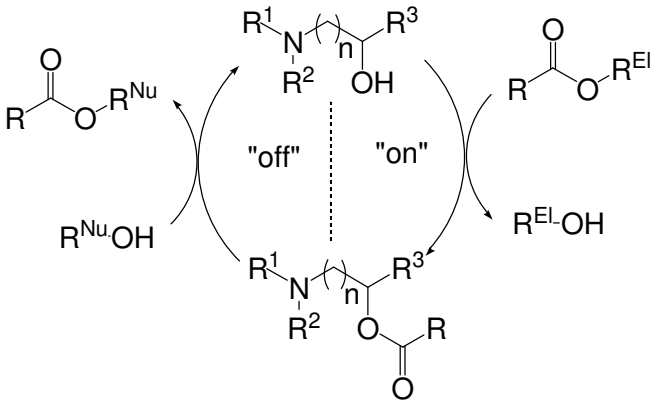


10a **10b**

Figure 2.1: *(R)*-Bisoprolol **10a** and *(S)*-Bisoprolol **10b**

However, amino alcohols can be also applied as organocatalysts. Early studies already describe the application of amino alcohol catalysts as models for the catalytic diad as crucial subelement of the triad found in serine proteases in the transesterification between an active ester (e. g. *p*-nitrophenyl acetates) and a nucleophile like water.[17-27] In recent years, Sammakia *et al*. introduced a series of amino alcohol-derived acyl-transfer catalysts bearing electron-withdrawing groups in close proximity to the hydroxyl group which show similar reaction rates as the well studied DMAP and its derivatives in the methanolysis of *p*-nitrophenyl methoxyacetate.[28-30] Later, similar studies were reported by Funabiki *et al.* with *α*-perfluoroalkylated N-methylprolinols as acyl transfer catalysts in the methanolysis of 4-nitrophenyl 2-methoxyacetate.[31] In 2008, Sakai and coworkers developed biomimetic thiourea-based trifunctional catalysts as a mimic for the active site of serine proteases which also provide high acceleration rates for the acyl transfer reaction with highly active vinyl trifluoroacetate.[32]

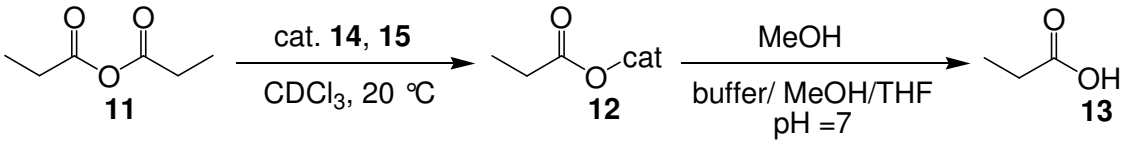
The general catalytic cycle of an amino alcohol in a transacylation reaction can be described as an acylation-deacylation mechanism (Scheme 2.4).[33-35] The amino alcohol operates by a mechanism in which the functional hydroxyl group attacks the carbonyl of an active ester to form the acyl catalyst intermediate in a first step. This is catalyzed by the nitrogen of the catalyst which acts as a general base. Subsequently, the intermediate undergoes hydrolysis or alcoholysis, to provide the acid or ester, respectively, and to regenerate the catalyst. This step is also base catalyzed by the proximal nitrogen of the catalyst.



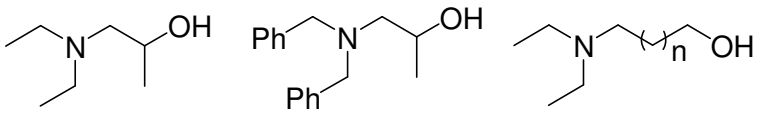
Scheme 2.4: Acylation-deacylation mechanism for amino alcohol catalysts. (R^{El} = residue with better leaving group ability than R^{NU}; “on” = catalyst-on half cycle: attack of the catalyst to the carbonyl of the active ester; “off” = catalyst-off half cycle: regeneration of the catalyst)

In 2008, Wessjohann *et al*. reported the transacylation properties of a series of dialkyl amino alcohols **14** and **15** as catalysts (Scheme 2.5).[36] They described the influence of structural and electronic parameters on the acylation and deacylation rate in independent measurements (catalyst-on half cycle vs. catalyst-off half cycle). Through kinetic ^{1}H-NMR-studies it has been proven that the acylation rate between the dialkyl amino alcohols **14** or **15** and the acyl donor **11** (butyric anhydride) depends on the number of (carbon) spacer atoms, flexibility of the molecule, and the presence and position of further heteroatoms. Besides, it could be detected that the methanolysis (catalyst-off half cycle) of the formed *β*-amino ester intermediate **12** follows a similar trend as the acylation reaction, but appeared to be rate limiting in the setup of this study.[36]

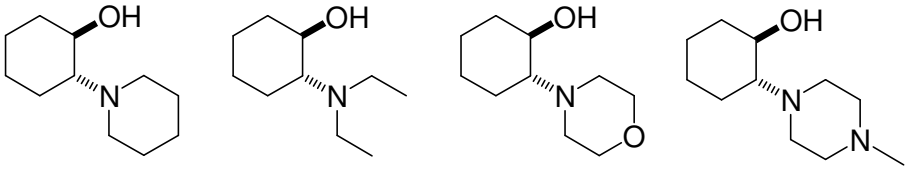
Following up on these results, it was the initial target of this work to study and modify the most active amino alcohols and to apply them in the methanolysis of different active esters. Thereby, the catalytic ability of the amino alcohols was investigated by means of ^{1}H-NMR kinetic measurements. In Figure 2.2, the amino alcohols tested are depicted.



amino alcohol catalysts:

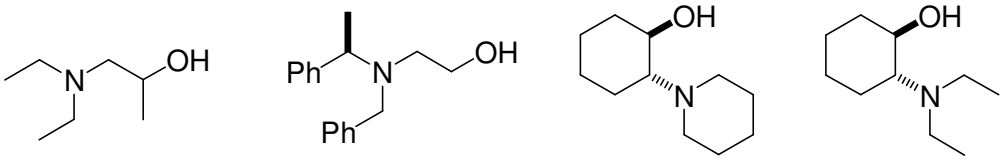


14a **14b** **14c**: n = 1
14d: n = 2
14e: n = 3

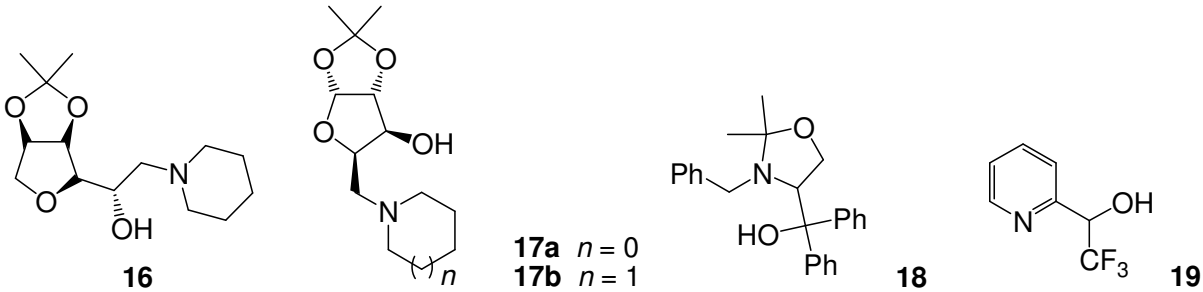


15a **15b** **15c** **15d**

Scheme 2.5: Series of dialkyl amino alcohols **14** and **15**. The catalysts **15a** and **15b** are the most active ones.



14a **14f** **15a** **15b**



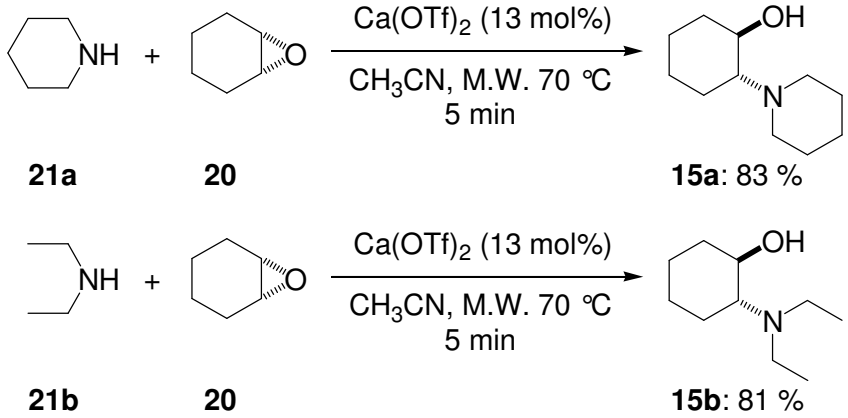
16 **17a** *n* = 0 **17b** *n* = 1 **18** **19**

Figure 2.2: The acyclic **14a**, **14f** and the cyclic *β*-amino alcohol catalysts **15a**, **15b** and **16**-**19**

2.2.1 Synthesis of Catalytic Amino Alcohols

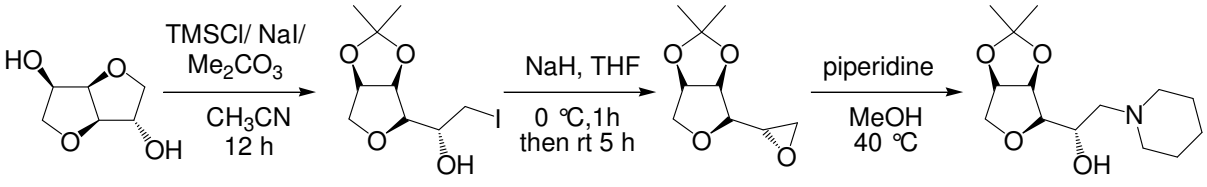
There is a multitude of possibilities to synthesize (enantiomeric) amino alcohols. Beside the reduction and derivatization of naturally available enantiopure amino acids,[37,38] other methods include e.g. the preparation *via* α-hydroxynitriles or the reduction of α-ketoimines.[39] Alternative routes involve the Sharpless´ asymmetric aminohydroxylation,[40] the Pinacol cross-coupling reaction of an aldehyde with an imine,[41] or the stereoselective ring-opening of epoxides,[42] aziridines,[43] sulfates,[44] and carbonates.[45] Further approaches toward the synthesis of β-amino alcohols are Mannich-type reactions[46] and Lewis acid-catalyzed aldol reactions.[47]

The cyclohexane-based β-amino alcohol catalysts **15a** and **15b** were readily prepared from cyclohexene oxide **20** based on a procedure described in literature (Scheme 2.6).[36,48] The calcium(II)-triflate catalysed ring-opening of the epoxide **20** with the appropriate amine **21** was carried out under microwave heating and provides the catalysts **15a** and **15d** in high yields after a reaction time of five minutes.

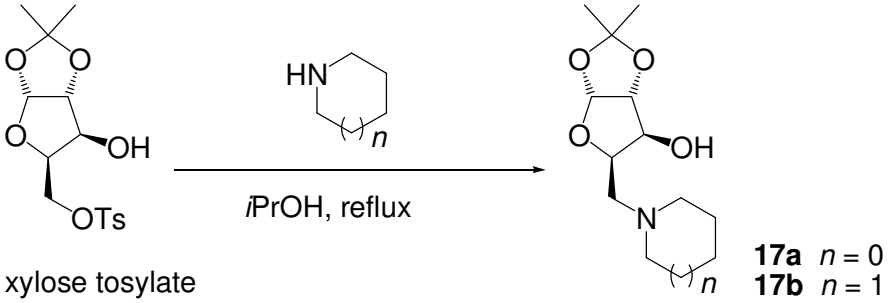


Scheme 2.6: Synthesis of cyclohexane-based β-amino alcohol catalysts **15a** and **15b**

The chiral β-amino alcohol **16** was obtained starting from isosorbide in three steps by the procedure of Saluzzo *et al*. (Scheme 2.7).[49] The synthesis is carried out *via* readily available epoxide **23**, whose oxirane group is opened with piperidine in good yields. The known β-amino alcohols based on the D-xylose scaffold like **17** were synthesized in the research group of D. Lüdtke.[50] The synthesis of catalysts **17** was carried out by reaction of the xylose tosylate as described by Lüdtke *et al*. and Cho *et al*.[51] The tosylate function was displaced with an appropriate secondary amine to provide the chiral catalysts **17** (Scheme 2.8).

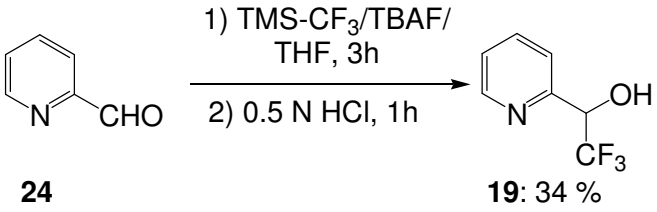


Scheme 2.7: Synthesis of *β*-amino alcohol **16** derived from isosorbide



Scheme 2.8: Synthesis of *β*-amino alcohols **17** derived from D-xylose reported by Lüdtke *et al.*[51b]

The trifluoromethyl-substituted *β*-amino alcohol catalyst **19** was prepared from 2-pyridinecarbaldehyde **24** based on the procedure of Prakash *et al*. (Scheme 2.9).[52] The reaction was accomplished in presence of an excess of trifluoromethyltrimethylsilane (TMS-CF_3) and a catalytic amount of tetrabutylammonium fluoride (TBAF). The amino alcohol **19** was obtained in moderate yields.



Scheme 2.9: Synthesis of trifuoromethyl-substituted *β*-amino alcohol catalyst **19**

The *β*-amino alcohol catalyst **14a** is commercially available, while the acyclic catalyst **14f** and the oxazolidine-based catalyst **18** were synthesized in the research groups of A. L. Braga[53] (**14f**) and P. H. Schneider[54] (**18**).

2.2.2 Kinetic and Mechanistic Studies on *β*-Amino Alcohol Catalyzed Transesterification Reactions

In recent years, many formidable examples of kinetic and mechanistic studies on non-enzymatic acylation reactions have been reported using 4-aminopyridine derivatives,[28,29,55] dihydroimidazole-based catalysts,[56] thiourea-based catalysts[32], *β*-amino alcohol catalysts[30,31,36,57], 1,2,4-triazole anion[58], spiroligozyme (a spirocyclic peptidomimetic catalyst)[59] and tetra-*n*-butylammonium fluoride[60]. Here, the influence of different *β*-amino alcohol catalysts on transesterification reactions is described in view of kinetic and mechanistic aspects.

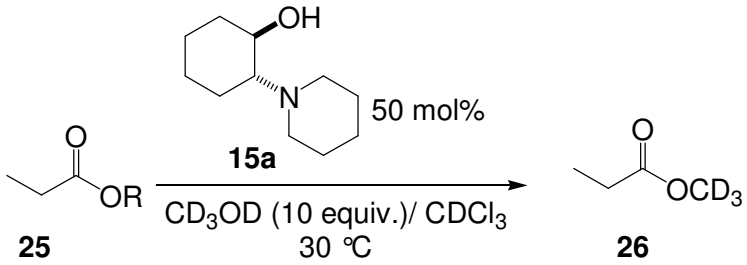
2.2.2.1 Variation of the Alcohol Component of Activated Esters

As mentioned above, the results reported by Wessjohann *et al*. give the reason to analyze the possibility of the most active *β*-amino alcohol catalysts.

At first, five different esters derived from propionic acid **25** were prepared and their methanolysis with 2-piperidine-1-cyclohexanol **15a** as catalyst were measured by following the progress of the reactions (Table 2.1). The reactions were run at 30 °C and at a concentration of 0.1 M ester, 0.05 M catalyst, and 1.0 M methanol-d_4 in $CDCl_3$. The conversion of the transesterification was observed by ^{1}H-NMR. As expected, the *para*-nitrophenyl ester (pNP) **25a** shows the highest reactivity because of its strong electron-withdrawing effect. The trifluormethyl-subsituted propionic acid **25e** performs worst. This can be attributed to the fact that the trifluormethyl moiety is proven to be a worse leaving group in comparison to the substituted phenyl groups.

Because the pNP ester **25a** proves to be the most suitable acylation reagents of this selection, further kinetic studies were carried out with ester **25a**.

Table 2.1: Conversion rates of the methanolysis reaction of propionates **25**



25 **26**

entry	R		time [d]	conversion [%]
1	$PhNO_2$	**25a**	4	64
2	PhCl	**25b**	4	16
3	PhF	**25c**	4	12
4	Ph	**25d**	8	20
5	CH_2CF_3	**25e**	8	0

2.2.2.2 Influence of Amino Alcohol Catalyst Structure on Methanolysis Rates

Considering the conversion rates of methanolysis, it is conspicuous that the reactions proceed very sluggish in spite of high catalytic amounts of *β*-amino alcohol catalysts. Consequently, the reaction conditions of methanolysis must be improved and optimised. For that reason, the methanolysis was now carried out at 60 °C and at a concentration of 1 M ester, 0.01 M catalyst in methanol-d_4 (43 equiv.). At this, methanol-d_4 acts as both solvent and nucleophile. As a consequence of this, a high catalytic activity could be achieved for catalyst **15a**. On the basis of these optimized conditions, further *β*-amino alcohol catalysts were studied for the methanolyis of pNP ester **25a**. Their catalytic activities were also measured by controlling the consumption of ester **25a** as a function of time. The reaction progress was monitored by ^{1}H-NMR. The results are presented in Figure 2.3. The methanolysis, which is accomplished in the presence of the mixture of 2-propanol and triethylamine, serves as control reaction. As depicted in Figure 2.3, the cyclohexane-based *β*-amino alcohols **15** show the best results in the acceleration of the transesterification of pNP ester **25a**, in which the 2-piperidine-1-cyclohexanol **15a** shows an higher conversion rate than its analogue **15b**. Their catalytic activity is similar to with DMAP. The acyclic *β*-amino alcohol **14a** accelerates the methanolysis of pNP ester **25a** slower than the cyclic catalysts **15**. This result confirms the kinetic studies reported by Wessjohann *et al*. that cyclic *β*-amino alcohols are better than acyclic catalysts.[36] However, the acyclic catalyst **14a** exhibits a higher reaction rate than the carbohydrate-based *β*-amino alcohols **16** and **17a**. Because of their carbohydrate moiety, the catalysts **16** and **17a** appear more hindered and

less flexible which likely impinges upon the acceleration rate. The amino alcohols **16** and **17a** have similar catalytic activities.

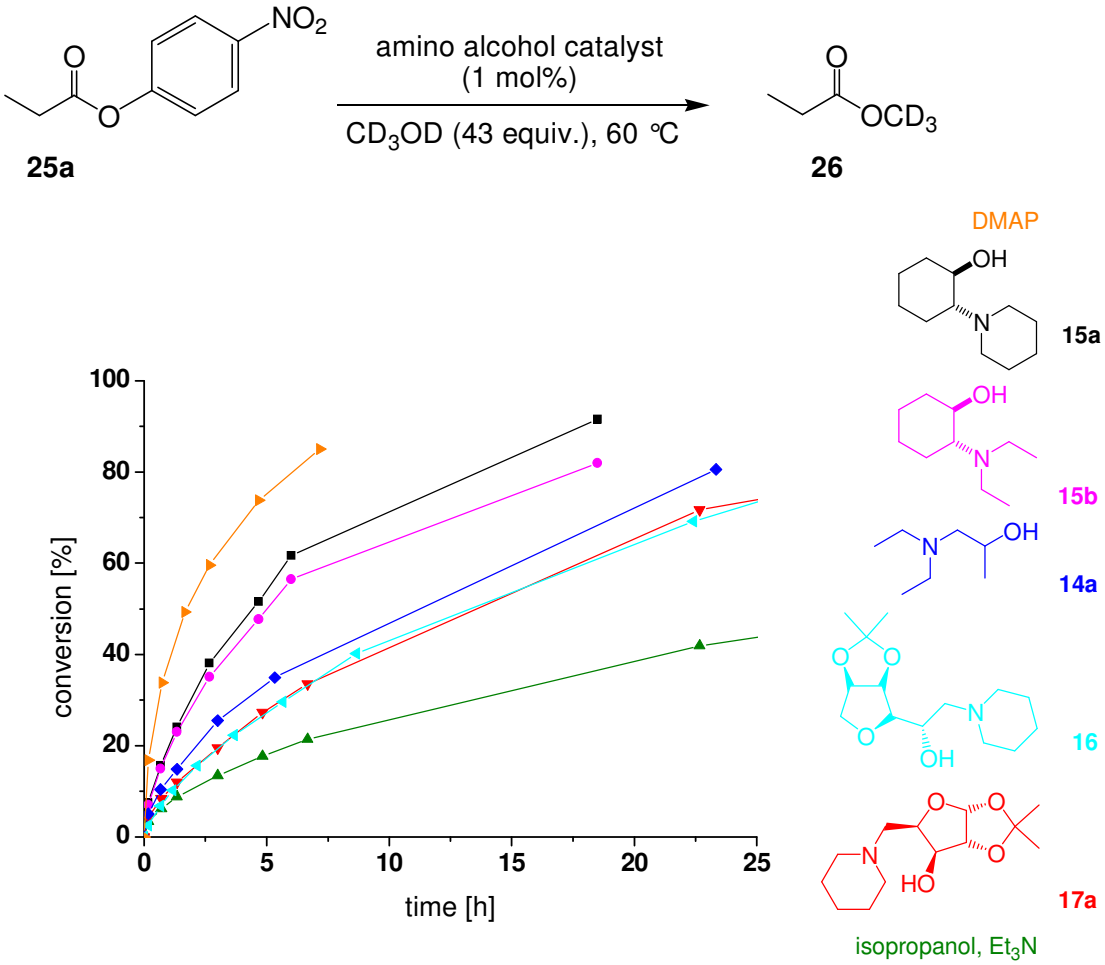
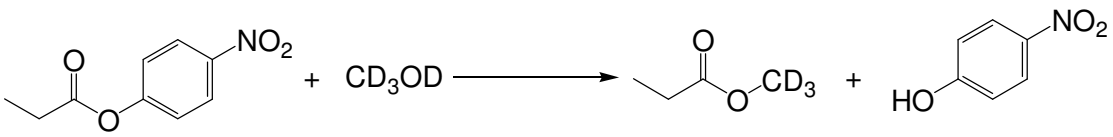


Figure 2.3: Kinetics of methanolysis of pNP ester **25a** by using different amino alcohols as catalysts (1 mol%)

2.2.2.3 Influence of Amino Alcohol Catalyst Structure on Methanolysis Rate Constants

The methanolysis of pNP ester **25a** can be treated as pseudo-first order kinetics, because the concentration of methanol-d_4 is high and can be considered as almost constant. The derivation of the pseudo-first order equation is presented in Scheme 2.10.



25a **26**

$$r = k[pNP][CD_3OD] \quad (1)$$

$$[CD_3OD] \gg [pNP]\ ;\ k_{obs} = k[CD_3OD]_0 \quad (2)$$

$$r = k_{obs}[pNP] \quad (3)$$

$$\frac{d[pNP]}{dt} = -k_{obs}[pNP] \quad (4)$$

$$\frac{d[pNP]}{[pNP]} = -k_{obs}dt \quad (5)$$

$$\int_{[pNP]_0}^{[pNP]} \frac{d[pNP]}{[pNP]} = \int_0^t -k_{obs}dt \quad (6)$$

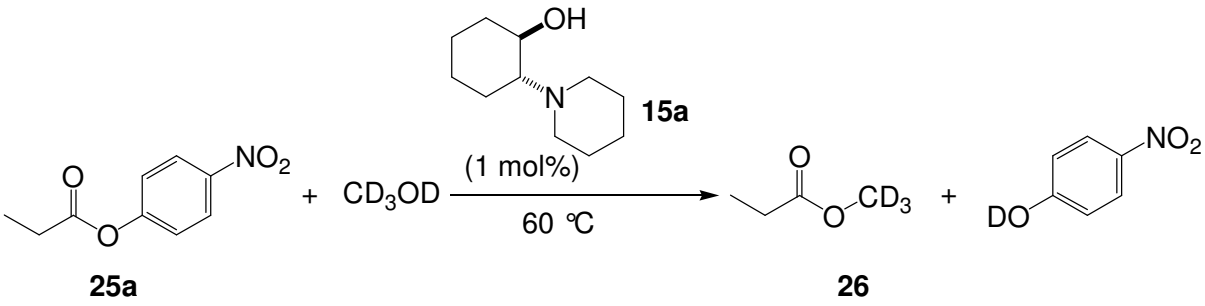
$$\ln\left(\frac{[pNP]}{[pNP]_0}\right) = -k_{obs}t \quad (7)$$

$$\ln[pNP] = -k_{obs}t + \ln[pNP]_0 \text{ or } [pNP] = [pNP]_0 e^{-k_{obs}t} \quad (8)$$

$$\tau_{\frac{1}{2}} = \frac{\ln 2}{k_{obs}} \quad (9)$$

Scheme 2.10: Derivation of the pseudo-first order equation

Figure 2.4 depicts the time versus ln[*pNP*]/[*pNP*]$_0$ plot for the transesterification of pNP ester **25a** catalyzed by 2-piperidine-1-cyclohexanol **15a**. The plot shows a straight line with a negative slope. This is evidence for a pseudo-first order reaction. From such time versus ln[*pNP*]/[*pNP*]$_0$ plots, the rate constant and the half-life can be calculated for each catalyst. In Table 2.2, the rate constants k_{obs} and half-lifes $\tau_{½}$ for the methanolysis of pNP ester **25a** by using various amino alcohol catalysts are listed.



25a **26**

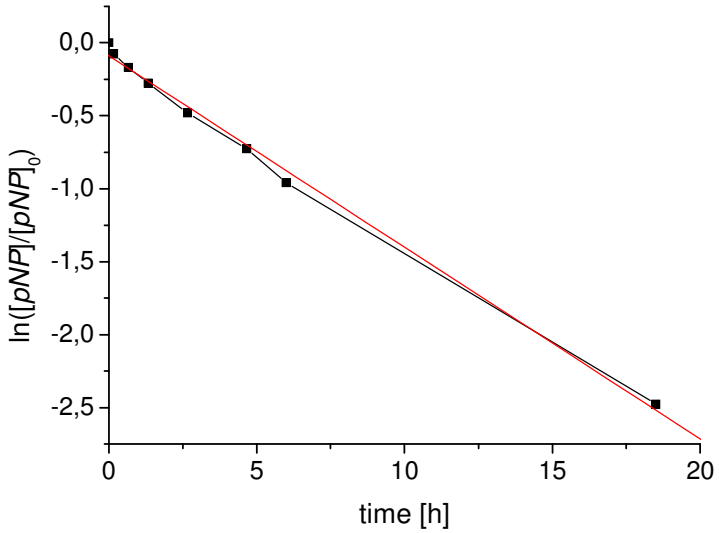
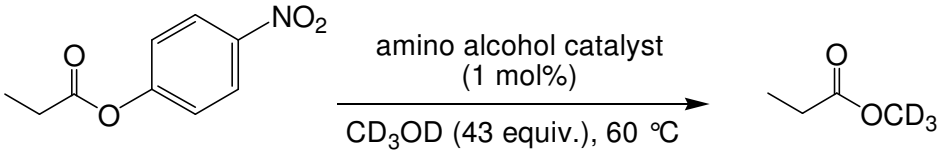
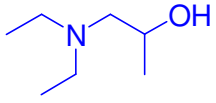
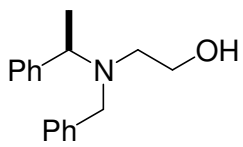


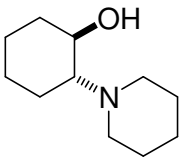
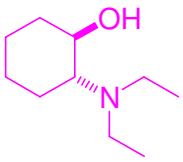
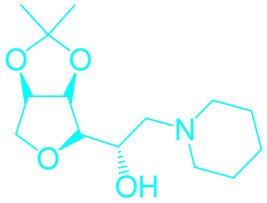
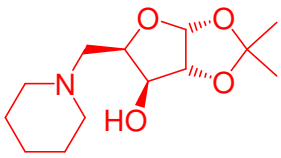
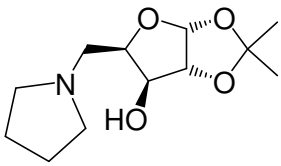
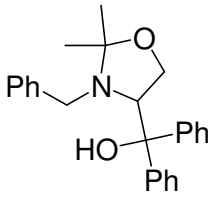
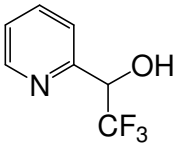
Figure 2.4: Time versus ln[*pNP*]/[*pNP*]$_0$ plot for the transesterification of pNP ester **25a** catalyzed by 2-piperidine-1-cyclohexanol **15a**

Table 2.2: Rate constant k_{obs} and half-life $\tau_{½}$ of the methanolysis of pNP ester **25a** using various amino alcohol catalysts



25a **26**

entry	catalyst	k_{obs} [s^{-1}]	$\tau_{½}$ [h]	$k_{obs}/k_{without}$ [a]
1	 **14a**	5.7 x 10^{-4}	10	5.3
2	 **14f**	1.3 x 10^{-4}	46	1.2

3	 **15a**	1.1×10^{-3}	5	10.1
4	 **15b**	7.5×10^{-4}	8	7.0
5	 **16**	3.9×10^{-4}	15	3.7
6	 **17a**	5.1×10^{-4}	11	4.8
7	 **17b**	4.8×10^{-4}	12	4.4
8	 **18**	9.2×10^{-5}	63	0.9
9	 **19**	6.7×10^{-5}	87	0.6
10	2-propanol/triethylamine (control reaction)	1.5×10^{-4}	38	1.4

[a] The $k_{without}$ value of the methanolysis of pNp **25a** without catalyst is = 1.1×10^{-4} s^{-1} and $\tau_{½}$ = 54 h.

Comparing the rate constants k_{obs} and half-lifes $\tau_{½}$ of the listed catalysts with the ones from the control reagent (2-propanol/triethylamine), it emerged that amino alcohols **14f**, **18**, and **19** are even less effective then simple base catalysis by triethylamine, i.e. no cooperative effect of amine and alcohol is observed, in some cases the reaction is even decelerated vs. an uncatalyzed one, although it remains unclear how such methanolysis inhibition can be explained.

The results are illustrated in Figure 2.5 which presents the rate $k_{obs}/k_{without}$ arranged according

to the acceleration rate of the catalysts studied. The $k_{without}$ value marks the reaction rate of the uncatalyzed background reaction. The methanolysis with the acyclic catalyst **14f** is almost nine times slower than that with piperidine-derived, cyclohexane-based amino alcohol **15a**. This fact can be attributed to the bulky phenyl groups which are sterically more hindered. The oxazolidine-based catalyst **18** has a rigid system which limits the flexibility of the catalyst. Thus, a very low reaction rate is observed. Unfortunately, also the trifluoromethyl-substituted *β*-amino alcohol catalyst **19** shows no acceleration. This can be explained that on the one hand the movement is restricted by the hydroxyl-substituted carbon, and on the other hand the basicity of the pyridine nitrogen is diminished. The reduced basicity can be attributed to the lack of an 4-amino substitutent at the pyridine nucleus which in DMAP renders the pyridine nitrogen more basic and more nucleophilic. This fact has been demonstrated by kinetic studies on the methanolysis of *α*-hydroxy esters reported by Sammakia *et al.*[30]

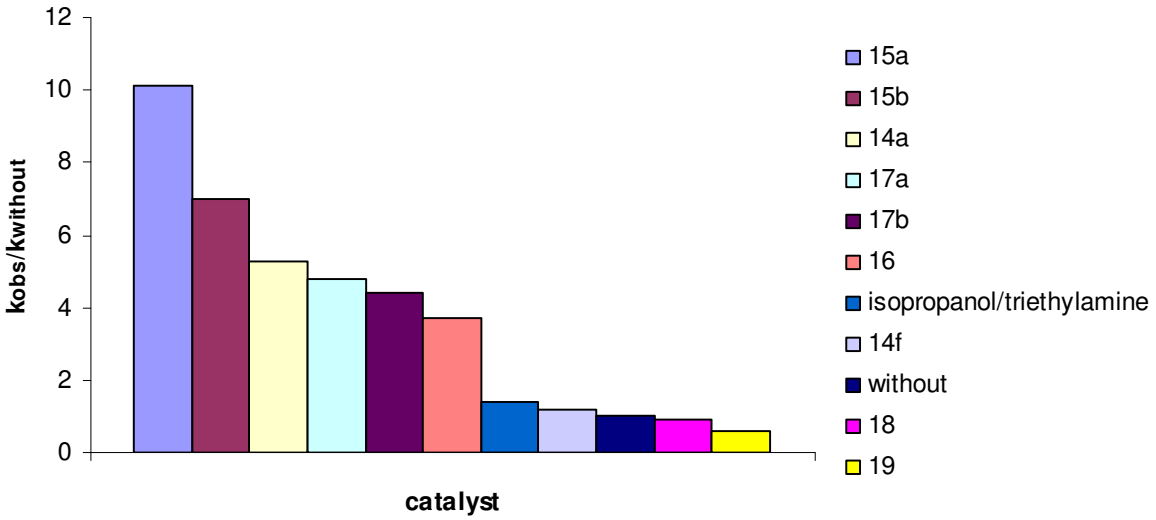
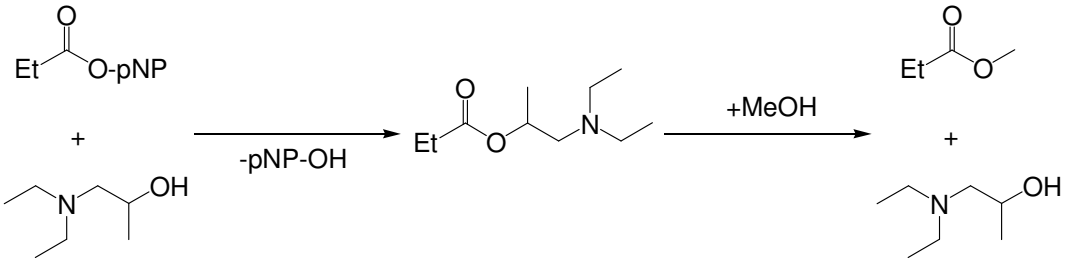
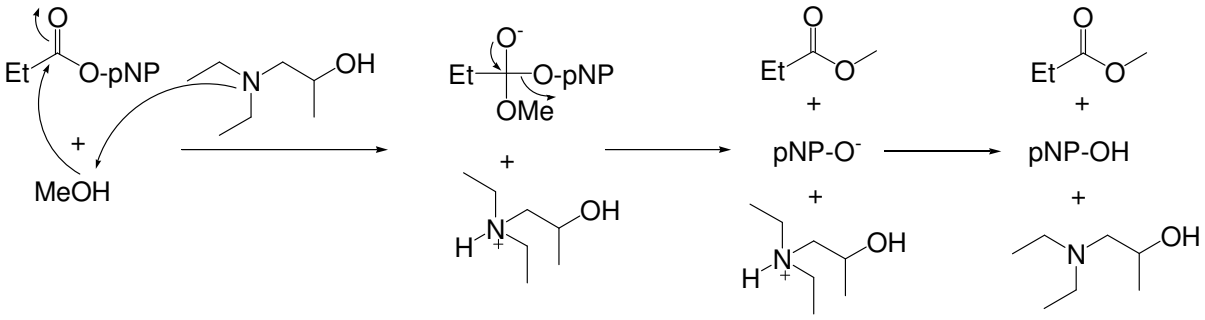


Figure 2.5: Comparison of the rate $k_{obs}/k_{without}$ of the several amino alcohol catalysts (uncatalyzed reaction: $k_{obs}/k_{without} = 1$).

After the determination of the kinetic order, the attention was set on the elucidation of the mechanism of the methanolysis, in order to distinguish between a nucleophilic and a general base catalysis (Scheme 2.11). In case of the nucleophilic mechanism, the hydroxyl group of the *β*-amino alcohol catalyst attacks the carbonyl of the ester; an acylated intermediate is formed which is transformed into the methyl ester by an attack of methanol. The catalyst is regenerated. By a general base catalysis, the ester undergoes an attack by methanol. This attack is supported because the nitrogen atom of the *β*-amino alcohol catalyst acts as base and traps a proton from the hydroxyl group of the methanol.



Nucleophilic catalysis



General base catalysis

Scheme 2.11: Nucleophilic and general base mechanism of a *β*-amino alcohol catalyst

Because the reaction progress is monitored by ^{1}H-NMR, it was possible to identify the acylated intermediate which is formed during the transesterification of pNP ester **25a**. In Figure 2.6, the reaction progress of the methanolysis of pNP ester **25a** catalyzed by the amino alcohol **15a** is depicted. The plot reveals that the transesterification follows a nucleophilic mechanism. The intermediate **27** could be detected, because the acylation is faster than the de-acylation. The substrate and the catalyst are rapidly consumed at the same rate as the intermediate appears. But the formation of the product is rate-limiting, so that the consumption of the intermediate needs more time. The proposed catalytic cycle by Wessjohann *et al*. could be confirmed (Figure 2.7).[36] The amino alcohol **15a** attacks the substrate **25a** by an *O*-nucleophilic mechanism in which the hydroxyl group is activated by forming an hydrogen bond with nitrogen. Then, the originated amino ester **27** undergoes alcoholysis due to a neighboring effect of the amino group, to provide the product **26** and regenerate the catalyst **15a**.

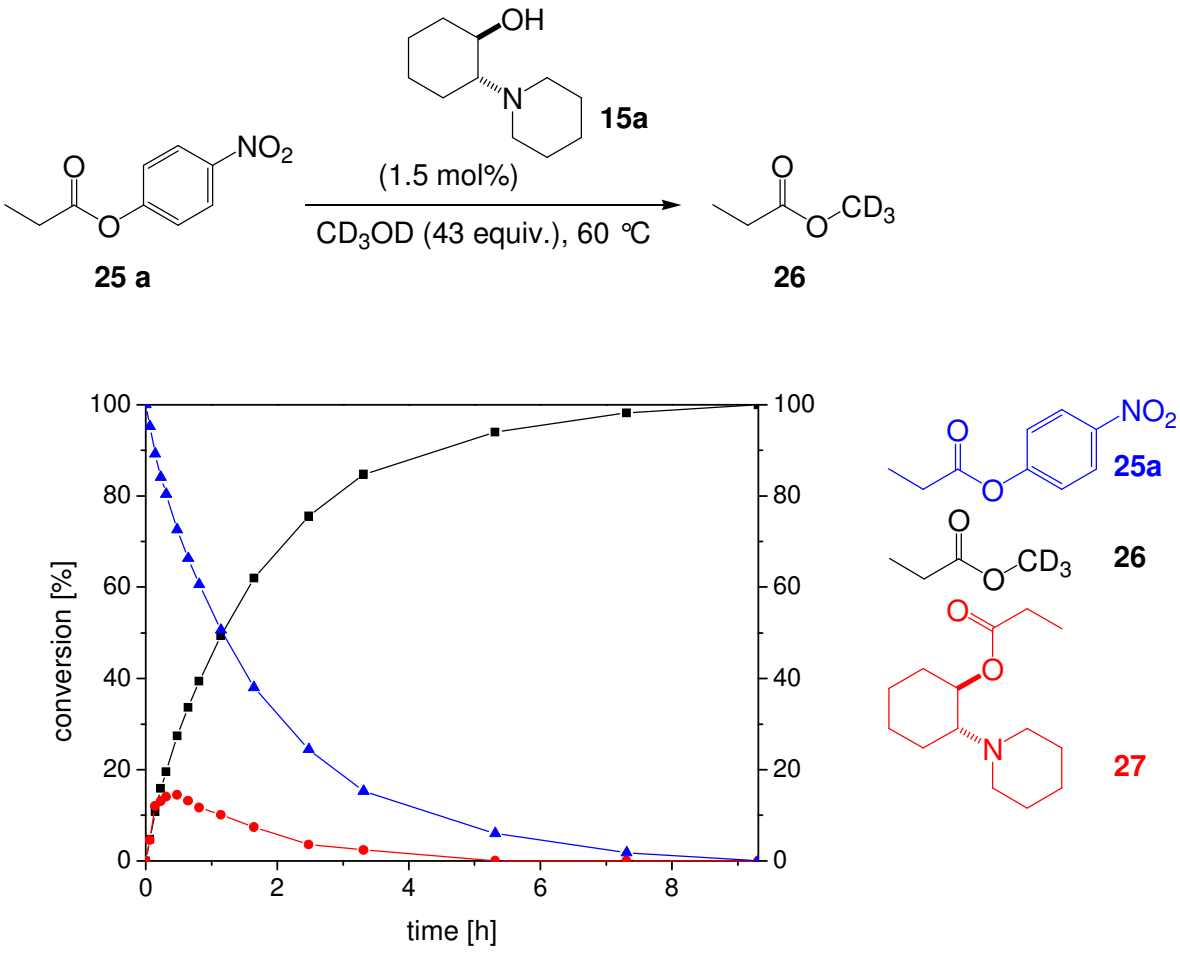


Figure 2.6: Reaction progress of the methanolysis of pNP ester **25a** catalyzed by the 2-piperidine-1-cyclohexanol catalyst **15a**

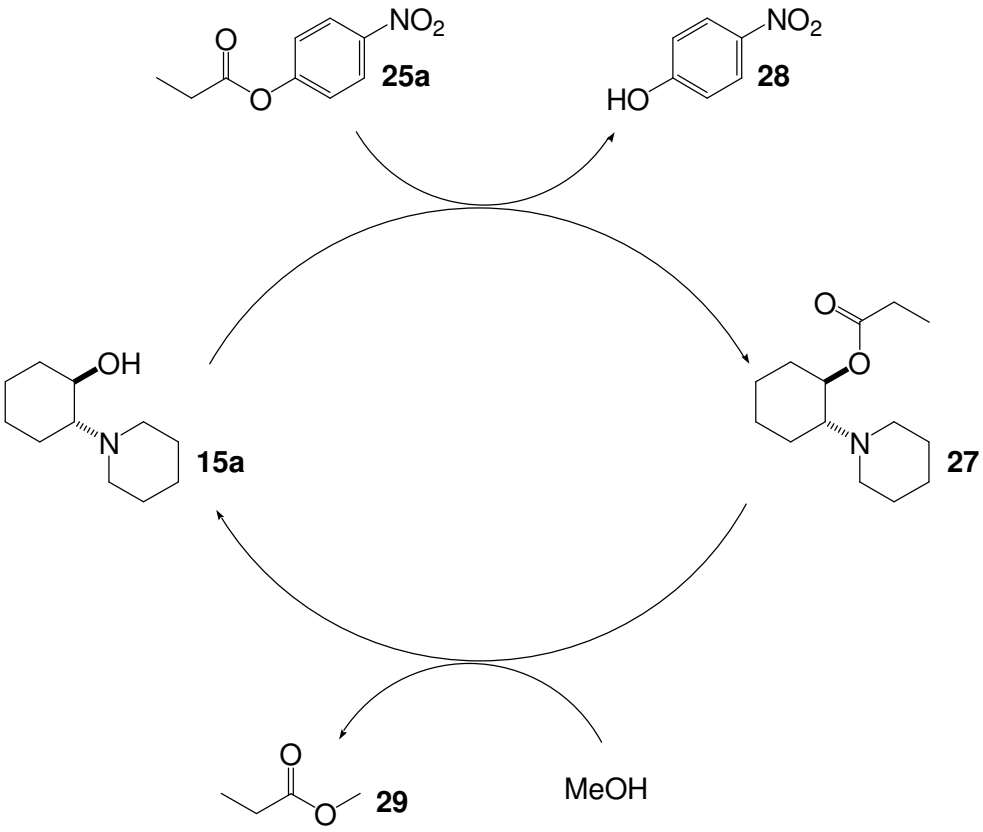


Figure 2.7: Catalytic cycle of pNP-propionate transacylation catalyzed by 2-piperidine-1-cyclohexanol **15a**

In Figure 2.8, the progress of methanolysis is depicted with the help of ^{1}H-NMR spectra. The rate of the reaction was monitored on the one hand through the proton signals of the methyl groups in the pNP ester **25a** and the product **26**, and on the other hand through the proton signals of the phenyl core in the pNP ester **25a** and the originating *p*-nitrophenol. During the reaction, the signals of the pNP ester **25a** (H_a, H_b, H_c, H_d) decrease with an increase of the signals of *p*-nitrophenol and that of ester **26**.

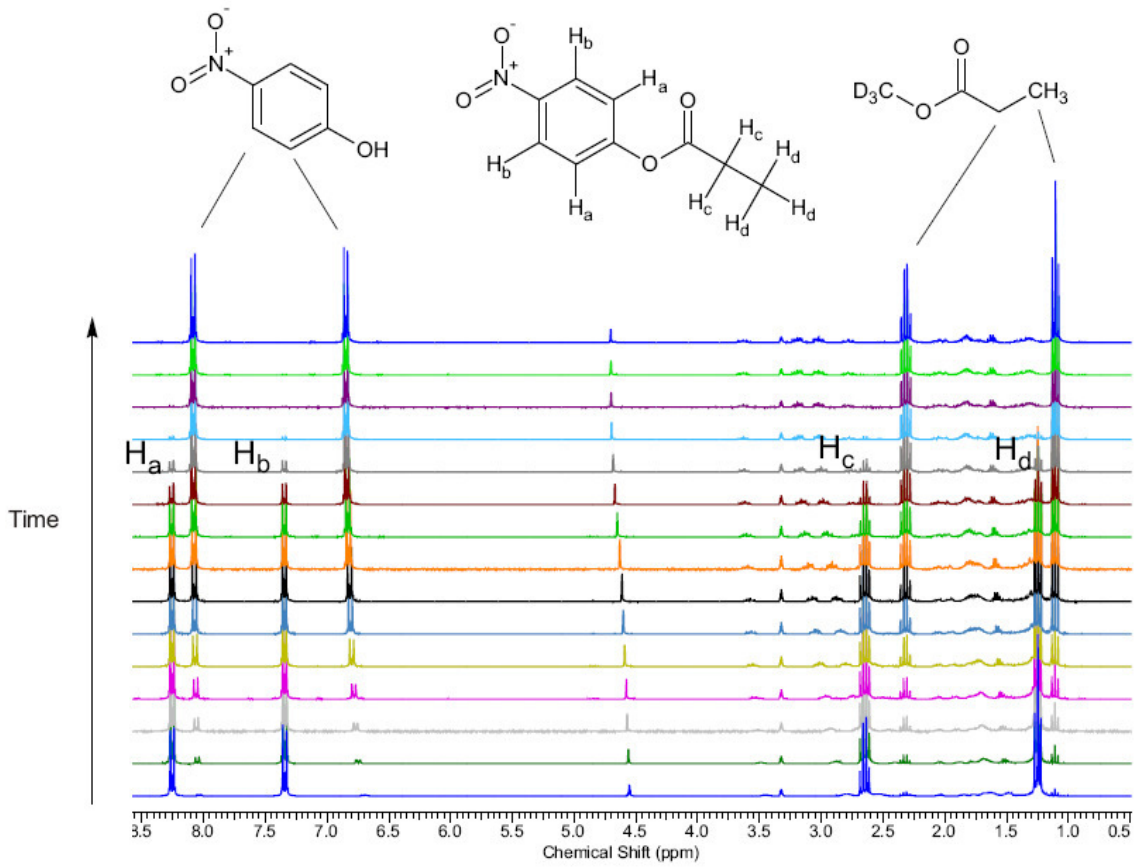


Figure 2.8: ^{1}H-NMR spectra from 8.5 to 0.5 ppm of the reaction depicted in Figure 2.6. The first spectrum was recorded after 3 minutes and 48 seconds. The next spectra were taken in the following intervals: 5, 5, 5, 10, 10, 10, 20, 30, 50, 120, 120, 120, 160 minutes.

Figure 2.9 shows the range from 3.45 to 5.00 ppm which shows that the amino ester intermediate **27** is formed during the reaction and subsequently reacts to the corresponding product **26**. The rate of formation of the amino ester **27** was based on the proton signals of the cyclohexyl group at C-8 in the intermediate **27** and catalyst **15a**.

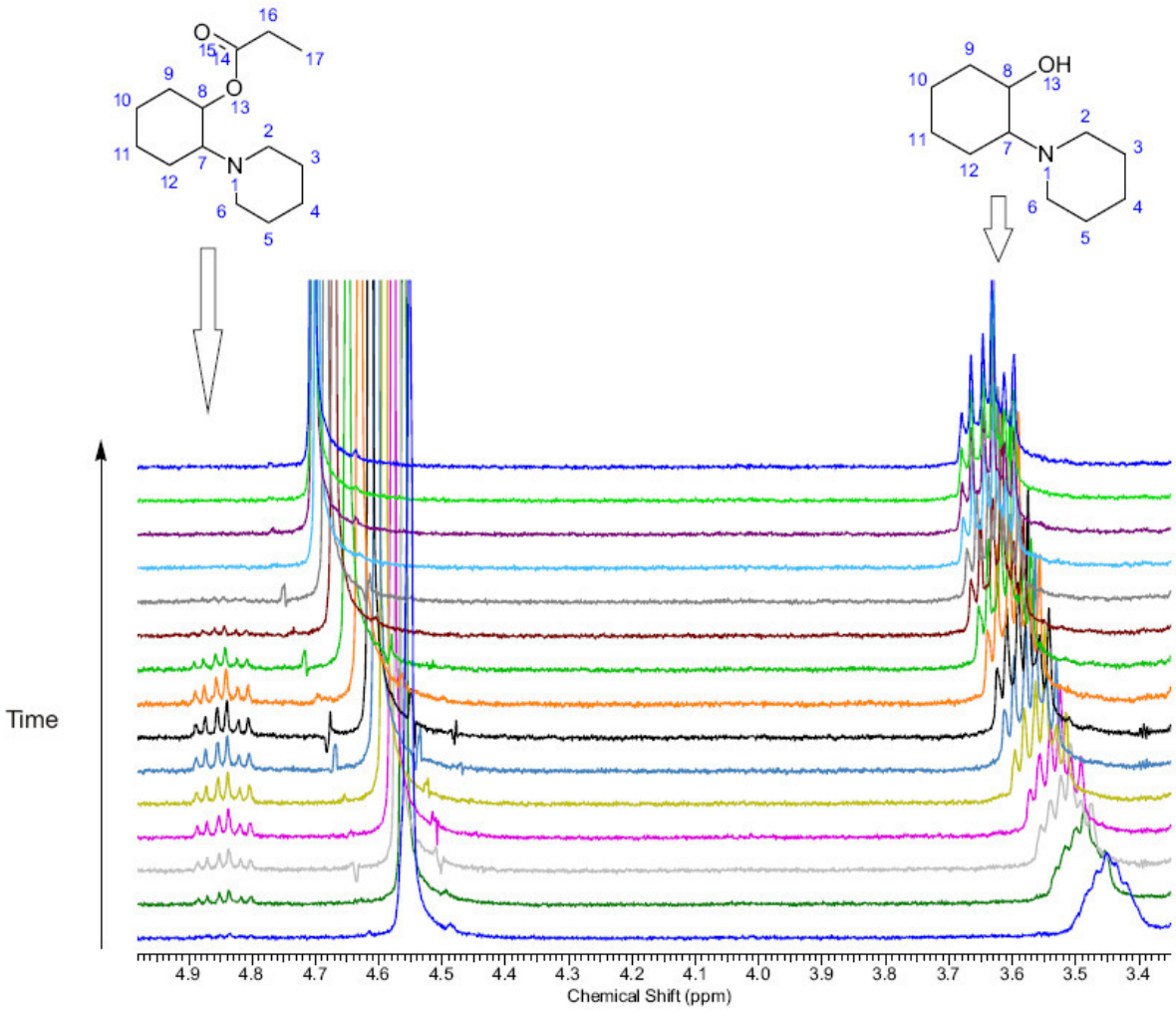
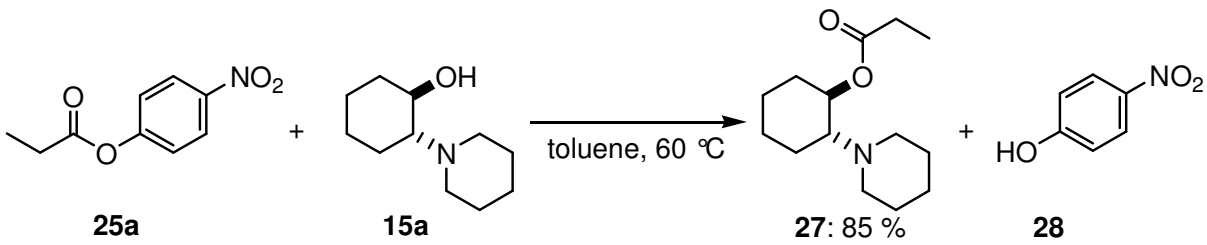


Figure 2.9: ^{1}H-NMR spectra from 5.00 to 3.45 ppm of the reaction depicted in Figure 2.6. The first spectrum was recorded after 3 minutes and 48 seconds. The next spectra were taken in the following intervals: 5, 5, 5, 10, 10, 10, 20, 30, 50, 120, 120, 120, 160 minutes.

In addition to the spectroscopic evidence, intermediate **27** could be isolated from the reaction of pNP ester **25a** with the catalyst in toluene (Scheme 2.12). In Figure 2.10, the ^{1}H-NMR spectrum of the amino ester **27** is shown. Isolation of the highly volatile methyl butyrate **29** from d_4-methanol may be possible by preparative gas chromatography, however the *p*-nitrophenol **28** can be isolated easily from the methanolysis reaction in high yields (Scheme 2.13)



Scheme 2.12: Isolation of 2-(piperidin-1-yl)cyclohexyl propionate **27**

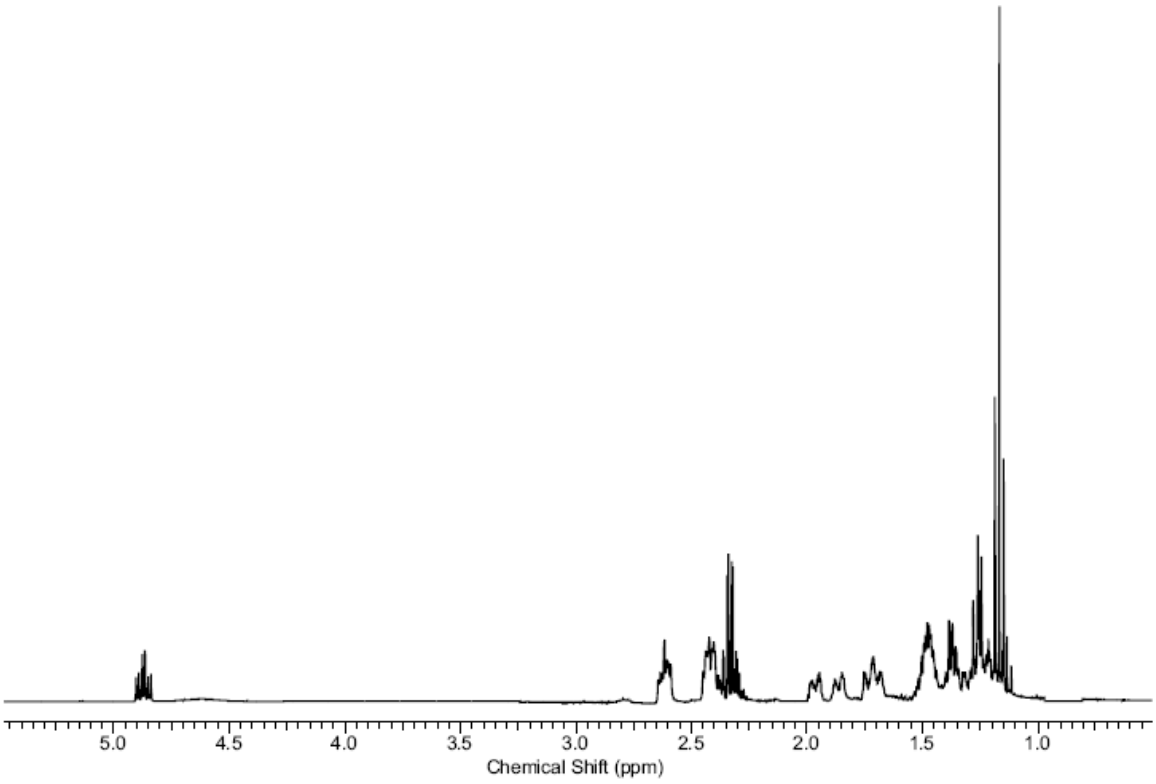
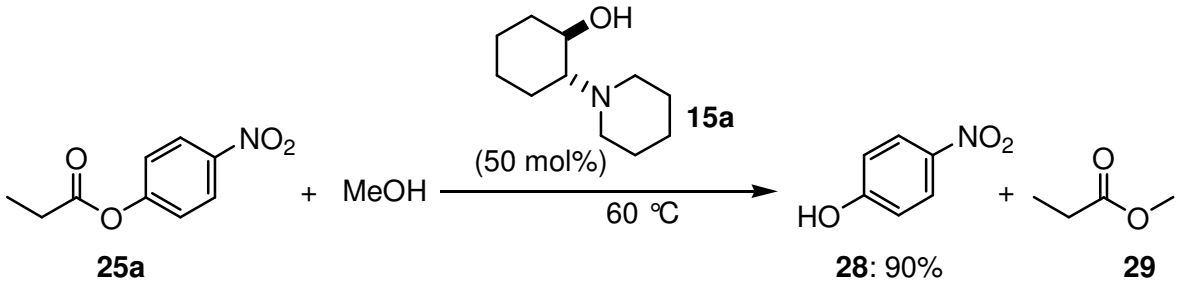


Figure 2.10: ^{1}H-NMR spectrum of the 2-(piperidin-1-yl)cyclohexyl propionate **27**



Scheme 2.13: Isolation of *p*-nitrophenol **28**

2.3 Sulfoxides and Amino Sulfoxides as Potential Acyl-Transfer Catalysts

The most developed acyl-transfer catalysts contain either a nitrogen or a phosphorus(III) atom as active center for the hydroxyl group activation. But the use of acyl-transfer catalysts with a sulfinyl group has not been exploited.[61]

The sulfinyl moiety has been well established as chiral template of chiral auxiliaries and ligands in asymmetric synthesis.[62] Because of the structural property (steric and electronic differences between the substituents of the sulfur atom: a lone pair electron, an oxygen, two carbon ligands), the sulfinyl group possesses a high configurational and optical stability as well as a good accessibility in both enantiomeric forms (Figure 2.11).

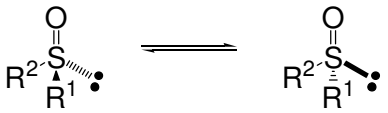
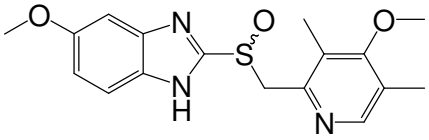


Figure 2.11: Pyramidal structure of the sulfinyl moiety

Therefore, the application of sulfoxides has been intensively investigated in Michael additions,[63] Diels-Alder reactions,[64] and asymmetric allylations.[65] Furthermore, the sulfinyl group is found in many biologically active compounds, e.g. in Omeprazol **30**, a topselling drug used for therapy and prevention of stomach acid-conditioned diseases, such as gastrointestinal ulcer (Figure 2.12).



30

Figure 2.12: Omeprazol **30**

In 1997, Wessjohann *et al*. reported on the application of sulfoxides as hydroxyl transfer catalysts in the conversion of aryl and allylic bromides to alcohols.[66]

Following up on these results, showing that sulfoxides can act as oxygen transfer catalyst, different catalysts with a sulfinyl group were investigated in the transesterification of pNP ester **25a** to probe their catalytic ability (Figure 2.13).

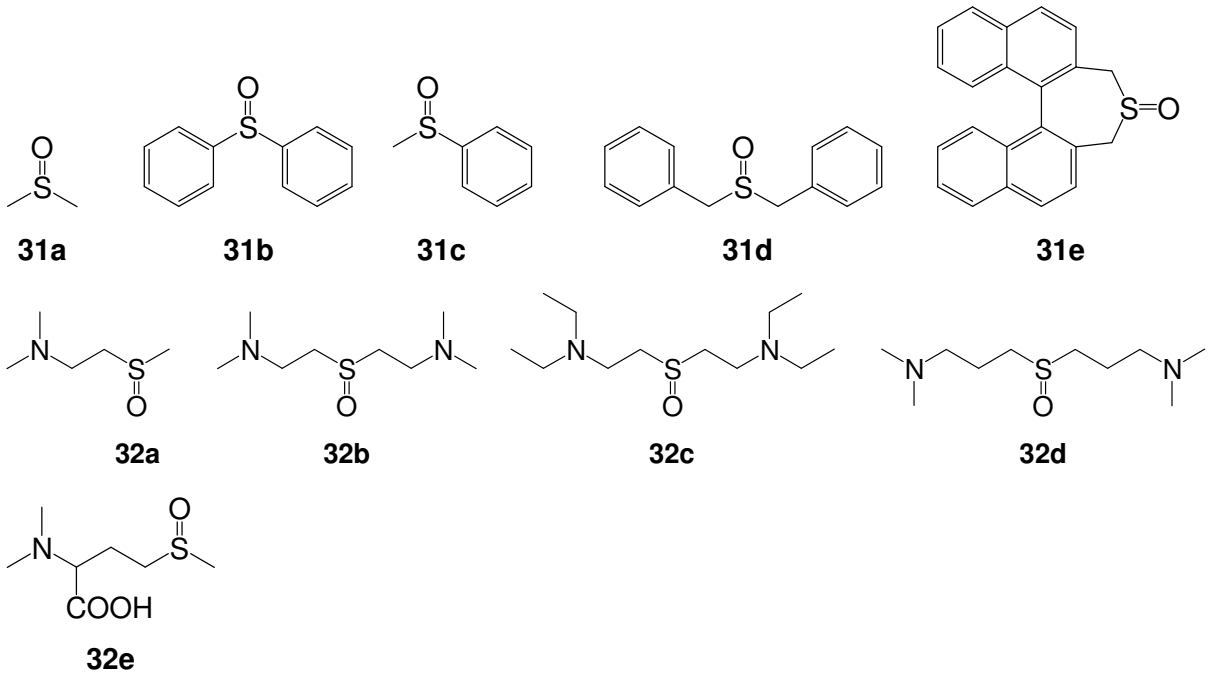


Figure 2.13: The sulfoxide catalysts **31a**-**e** and the amino sulfoxide catalysts **32a**-**e**

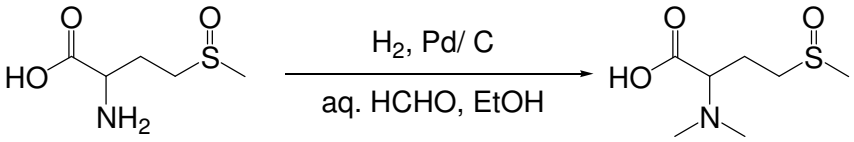
2.3.1 Synthesis of different Sulfoxides

Of the methods presently available to obtain sulfoxides, the classical Andersen method is one of the most relevant examples to produce enantiopure sulfoxides by the addition of a Grignard reagent to an optically active sulfinate ester.[67] Another approach is the Poli method, a palladium-catalyzed arylation of sulfenate anions under biphasic conditions.[68] A further method to obtain non-racemic sulfoxides is the asymmetric oxidation of sulfides which was independently reported by Kagan and Modena using a modified Sharpless reagent [Ti(O*i*-Pr)$_4$/(*R,R*)-DET/*t*-BuOOH].[69] Nowadays, different methods are developed for the selective oxidation of sulfides by using aqueous hydrogen peroxide,[70] peracetic acid,[71] *m*CPA,[72] sodium metaperiodate,[73], nitrogen tetraoxide as oxidants[74] and biocatalytic oxidation.[75]

The sulfoxides **31a**-**d** are commercially available, whereas the asymmetric sulfoxide **31e** and the amino sulfoxides **32a**-**d** were prepared in the work group of Wessjohann.[76] The sulfoxide **31e** can be obtained by the oxidation of the appropriate sulfide with sodium perborate in glacial AcOH.[77] The amino sulfoxides **32a**-**d** can be prepared by the procedure of Lawson *et al.*, an addition of an alcoholic solution of an appropriate amine to the *β*,*β*´-dichloro-alkyl sulfoxides.[78]

The amino sulfoxide **32e** was readily synthesized from methionine sulfoxide **33** based on the procedure described in literature (Scheme 2.14).[79] The methylation of sulfoxide **33** was carried out in presence of aqueous formaldehyde and palladised charcoal under hydrogen

atmosphere. The amino sulfoxide derived from methionine was obtained in moderate yield.



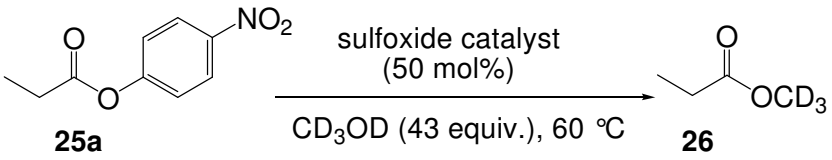
33 **32e**: 65 %

Scheme 2.14: Synthesis of 2-(dimethylamino)-4-(methylsulfinyl)butanoic acid **32e**

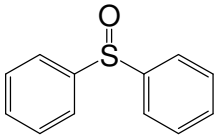
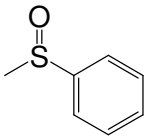
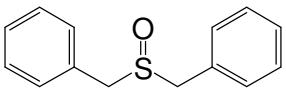
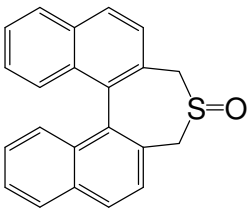
2.3.2 Kinetic Studies on the Methanolysis of the *p*-Nitrophenyl Ester (pNP) by using different Sulfoxide and Amino Sulfoxide Catalysts

The catalytic behavior and the kinetic order of different sulfoxides **31a**-**e** were investigated for the transesterification of pNP ester **25a**. The reactions were monitored by ^{1}H-NMR under the same catalysis conditions as used for the amino alcohols, but at a catalyst loading of 50 mol%. The rate of the reaction was monitored on the one hand through the proton signals of the methyl groups in the pNP ester **25a** and the product **26**, and on the other hand through the proton signals of the phenyl core in the pNP ester **25a** and the originating *p*-nitrophenol. The methanolysis of pNP ester **25a** catalyzed by sulfoxides **31a**-**e** can also be treated as pseudo-first order kinetics. Thus, the rate constant k_{obs} and half-life $\tau_{½}$ of each catalyst can be calculated after the same principle as mentioned in section 2.2.2.3 (Table 2.3).

Table 2.3: Rate constants k_{obs} and half-lifes $\tau_{½}$ of the methanolysis of pNP ester **25a** by using various sulfoxide catalysts



25a **26**

entry	catalyst	k_{obs} [s^{-1}]	$\tau_{½}$ [h]	$k_{obs}/k_{without}$ [a]
1	 **31a**	1.1×10^{-4}	52	1.1
2	 **31b**	1.4×10^{-4}	40	1.4
3	 **31c**	8.1×10^{-5}	72	0.8
4	 **31d**	8.5×10^{-5}	68	0.8
5	 **31e**	4.2×10^{-5}	139	0.4

[a] The $k_{without}$ value of the methanolysis of pNp **25a** without catalyst is = 1.1×10^{-4} s^{-1} and $\tau_{½}$ = 54 h.

In Figure 2.14, the conversion of the methanolysis of pNP ester **25a** with different sulfoxide catalysts is depicted. It is remarkable that the sulfoxides **31a**-**e** show very long reaction rates in comparison to the amino alcohols **14a**/**f**, **15a**/**b**, **16**, and **17a**/**b**. In spite of a higher catalyst loading, the methanolysis with DMSO catalyst **31a** is ten times slower than that with piperidine derived cyclohexane-based amino alcohol **15a**. Interestingly, the phenyl sulfoxide **31b** shows a higher reaction rate than DMSO **31a**. Probably, this can be attributed to a stronger positive electronic than the expected negative steric effect. Only phenyl sulfoxide **31b** and DMSO **31a** provide moderate activity as acyl-transfer catalysts. The other sulfoxides **31c**-**e** exhibit no catalytic activity. The reason likely is that they are sterically more hindered. They exhibit obviously higher half-lifes $\tau_{½}$ and lower rate constants k_{obs} than the uncatalyzed methanolysis. Therefore, the ratio $k_{obs}/k_{without}$ is less than 1.

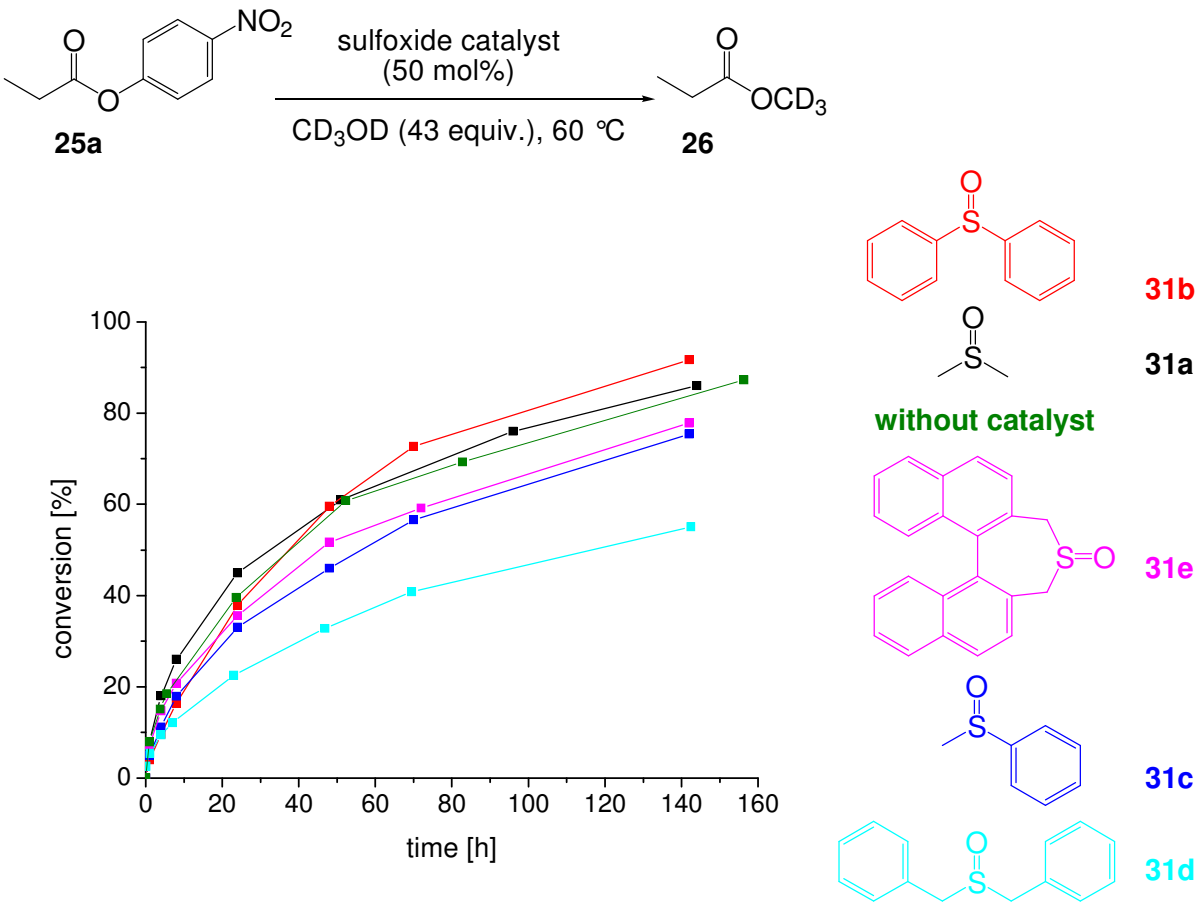


Figure 2.14: Kinetics of methanolysis of pNP ester **25a** by using different sulfoxides (50 mol%)

The sulfoxides **31a** and **31b** proved to be weak acyl-transfer catalysts. In order to improve the catayltic effectivity, the catalytic influence of amino sulfoxides **32a**-**e** on the methanolysis of pNP ester **25a** was studied under the same conditions as for the amino alcohols (60 °C, 1 equiv. ester, 1 mol% catalyst, 43 equiv. methanol-d_4). Their reaction rates were also measured by ^{1}H-NMR. Interestingly, they exhibit a high catalytic activity at a catalyst loading of 1 mol%. As depicted in Figure 2.15, the catalyst **32d** shows the best reaction rate in comparison to the other amino sulfoxides **32a**-**c,e**. This can be due to the increased number of the dialkylamino groups and the longer carbon chain between the sulfur and the nitrogen atom. No acceleration is observed for the methanolysis catalyzed by the amino sulfoxide derived from methionine **32e**. This can be attributed to the limited flexibilty of the molecule and the acid (hermaphrodite ionic structure).

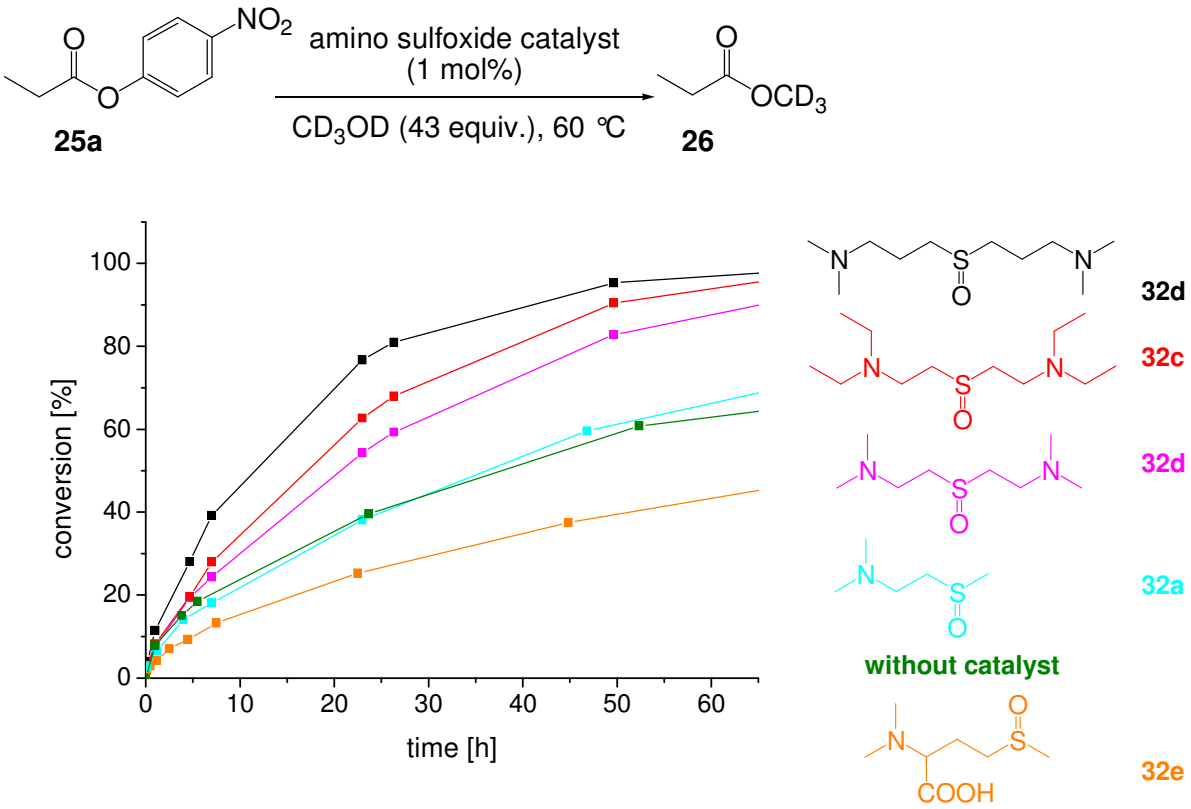
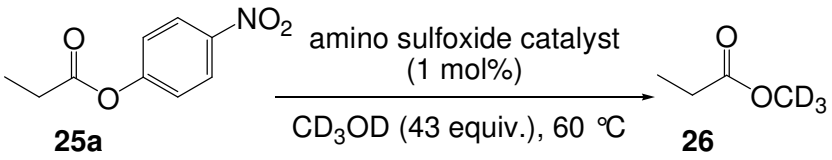


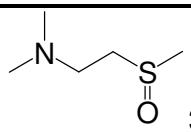
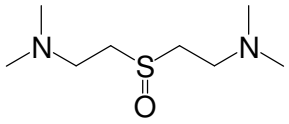
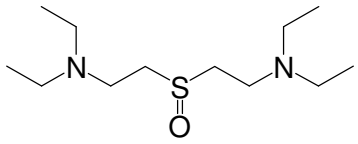
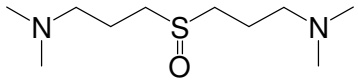
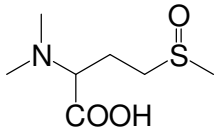
Figure 2.15: Kinetics of methanolysis of pNP ester **25a** by using different amino sulfoxides (1 mol%)

Also amino sulfoxide-catalyzed transesterifications of pNP ester **25a** follow pseudo-first order kinetics. In Table 2.4, the rate constant k_{obs} and half-life $\tau_{½}$ of each catalyst are presented.

Table 2.4: Rate constants k_{obs} and half-lifes $\tau_{½}$ of the methanolysis of pNP ester **25a** by using various amino sulfoxides



25a **26**

entry	catalyst	k_{obs} [s^{-1}]	$\tau_{½}$ [h]	$k_{obs}/k_{without}$ [a]
1	 **32a**	1.5×10^{-4}	40	1.4
2	 **32b**	3.0×10^{-4}	20	2.8
3	 **32c**	4.1×10^{-4}	14	3.8
4	 **32d**	4.9×10^{-4}	12	4.6
5	 **32e**	6.3×10^{-5}	91	0.6

[a] The $k_{without}$ value of the methanolysis of pNp **25a** without catalyst is = 1.1×10^{-4} s^{-1} and $\tau_{½}$ = 54 h.

During the ^{1}H-NMR-monitoring of the progress of the methanolysis, no intermediate was detected. The reason is that the substrate and the catalyst are consumed with the same rate as the product is formed. Therefore, it was of interest to find out where the high catalytic activity of the amino sulfoxide originates. The high catalytic activity of amino sulfoxides can be based on the base-catalytic effect of the amino group or can be caused by an attack of the sulfinyl group. For that reason, the reaction rates of triethylamine **33a** and diamine **33b** are important reference data. They catalyze the pNP ester **25a** by a general base mechanism. In Figure 2.16, a comparison of the kinetics of the amino sulfoxides **32c**/**d**, the sulfoxide **31a**, and the amines **33a**/**b** is shown. It is remarkable that the reaction rates of the catalysts **33a**/**b** and **32d** are very similar. The sulfoxide **31a** affects the transesterification adversely. From this follows that the base-catalytic effect of the amino group seems to be of more important than the attack of the sulfinyl group.

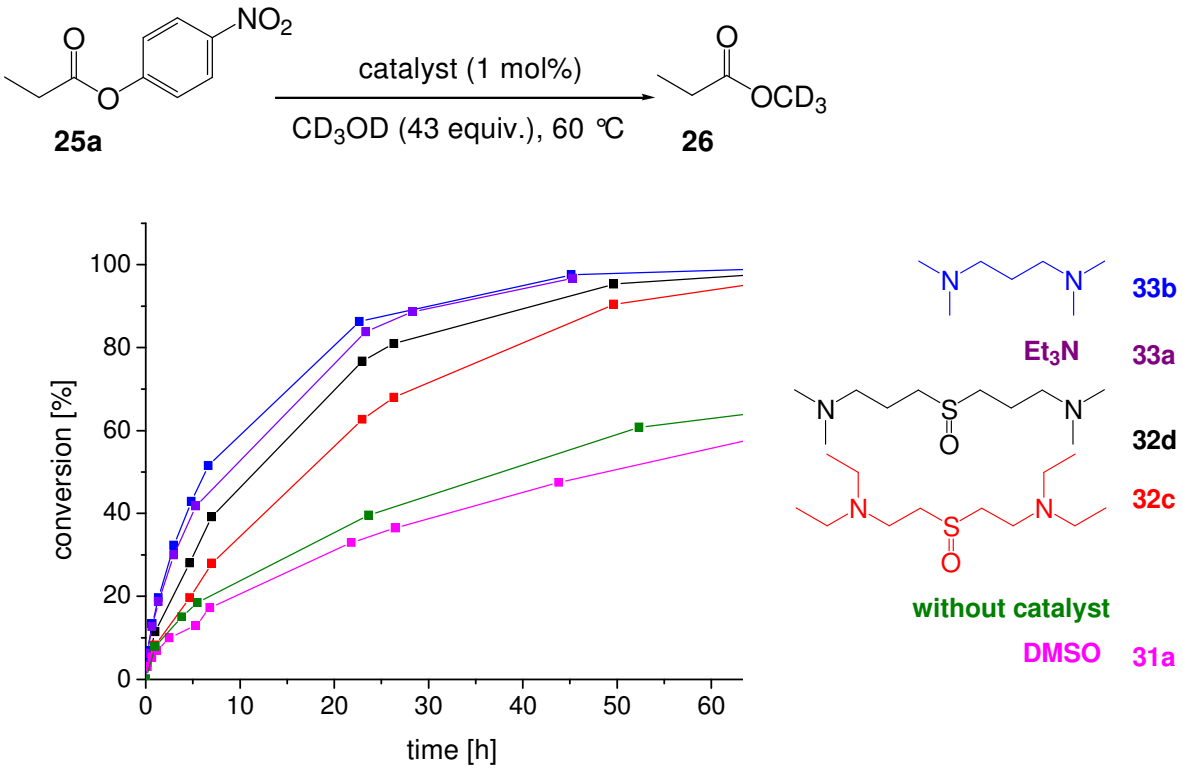
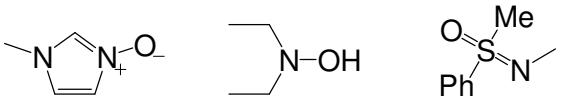


Figure 2.16: Kinetics of methanolysis of pNP ester **25a** by using amino sulfoxide **32c**/**d**, amines **33a**/**b** or DMSO **31a** (1 mol%).

2.4 Several Chalcogen-Based Acyl-Transfer Catalysts

In the preliminary sections, different chalcogen-based acyl-transfer catalysts were discussed regarding their kinetic behavior. On the one hand, several amino alcohols were considered which contain an oxygen atom as active centre. On the other hand, different catalysts with a sulfinyl moiety were tested, such as sulfoxides and amino sulfoxides. Now, acyl-transfer catalysts **34**-**36** will be discussed which bear an oxygen or sulfur atom (Figure 2.17).

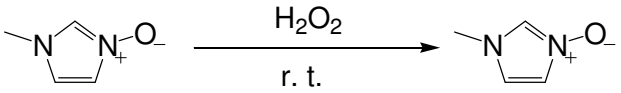


34 **35** **36**

Figure 2.17: Additional structures of potential acyl-transfer catalysts **34**-**36**

2.4.1 Synthesis of different Chalcogen-Based Acyl-Transfer Catalysts

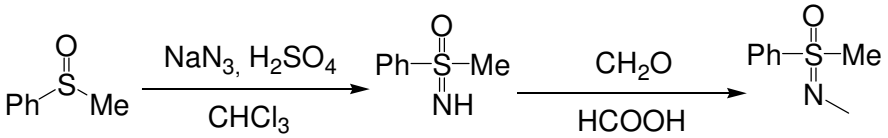
N-Oxides are primarily known as organocatalysts in the hydrocyanation of imines (Strecker reaction)[80] and in the asymmetric allylation of aldehydes.[81] But they are also applied as catalysts for the Morita-Baylis-Hillman reaction of *α,β*-unsaturated ketones.[82] and for the enantioselective ring-opening of *meso*-epoxides.[83] Because *N*-oxides exhibit good nucleophilic and weak basic properties, they can be considered as catalysts for the transesterification of pNP ester **25a**. The 1-methylimidazole 3-*N*-oxide catalyst **34** is synthesized by the oxidation of 1-methylimidazole **37** with hydrogen peroxide in quantitative yield (Scheme 2.15). [84]



38 **34**: 29 %

Scheme 2.15: Synthesis of 1-methylimidazole 3-*N*-oxide **34**

Another class of acyl-transfer catalysts represents hydroxylamines which can serve e.g. as reacting agent in the copper-catalyzed annulative amination of *ortho*-alkynylphenols[85], as oxygen source in the TEMPO-catalyzed oxidation of alcohols,[86] in the enantioselective synthesis of trifluoromethyl-substituted 2-isoxazolines,[87] and as oxidation catalyst for several organic substrates.[88] In early studies, the hydroxylamines are also applied as acylating agent in the acylation of activated esters.[89] For that reason, it is of interest to investigate the commercially available *N*-ethyl-*N*-hydroxyethanamine **35** as acyl-transfer catalyst in the methanolysis of pNP ester **25a**. A further catalyst which will be considered in this context is *N,S*-dimethyl *S*-phenyl sulfoximine **37**. The sulfoximine chemistry began with the discovery of the sulfonimidoyl moiety in 1950.[90] Since this date, sulfoximines are widely applied as chiral auxiliary,[91] chiral ligand,[92] and as building blocks in organic synthesis.[93] The *N,S*-dimethyl *S*-phenyl sulfoximine catalyst **36** was prepared from methyl phenyl sulfoxide **31c** based on the procedure of Johnson *et al*. and Schmidbauer *et al*.[93] The first step is the conversion of the sulfoxide **31c** into the appropriate sulfoximine **39** by the sodium azide method.[92a] The *N*-alkylation of the sulfoximine **39** is carried out under Clarke-Eschweiler conditions which gives the catalyst **36** in moderate yields (Scheme 2.16).[94]

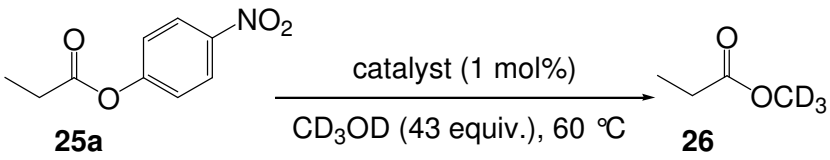


31c **39**: 86 % **36**: 62 %

Scheme 2.16: Synthesis of *N,S*-dimethyl *S*-phenyl sulfoximine catalyst **36**

2.4.2 Kinetic Studies on the Methanolysis of the *p*-Nitrophenyl Ester (pNP) by using different Chalcogen-Based Acyl-Transfer Catalysts

The catalytic activities of the organocatalyts **34**-**36** were investigated by kinetic ^{1}H-NMR studies under the same conditions as mentioned above. The rate of the reaction was monitored on the one hand through the proton signals of the methyl groups in the pNP ester **25a** and the product **26**, and on the other hand through the proton signals of the phenyl core in the pNP ester **25a** and the originating *p*-nitrophenol. Unfortunately, only 1-methylimidazole 3-*N*-oxide **34** accelerated the methanoylsis of pNP ester **25a**, whereas the hydroxyl amine **35** and the sulfoximine **36** show no catalytic activity (Figure 2.18). But the catalyst **34** exhibits only a low acceleration rate. For that reason, it was interesting to study the kinetic behavior of the amino oxide **34** at higher catalyst loading of 3 mol%. Surprisingly, a raise of the reaction rate has been observed (Figure 2.19). Consequently, the kinetics of organocatalysts **32a**/**e** and **34**-**36** were studied. Their conversion rates are depicted in Figure 2.19.



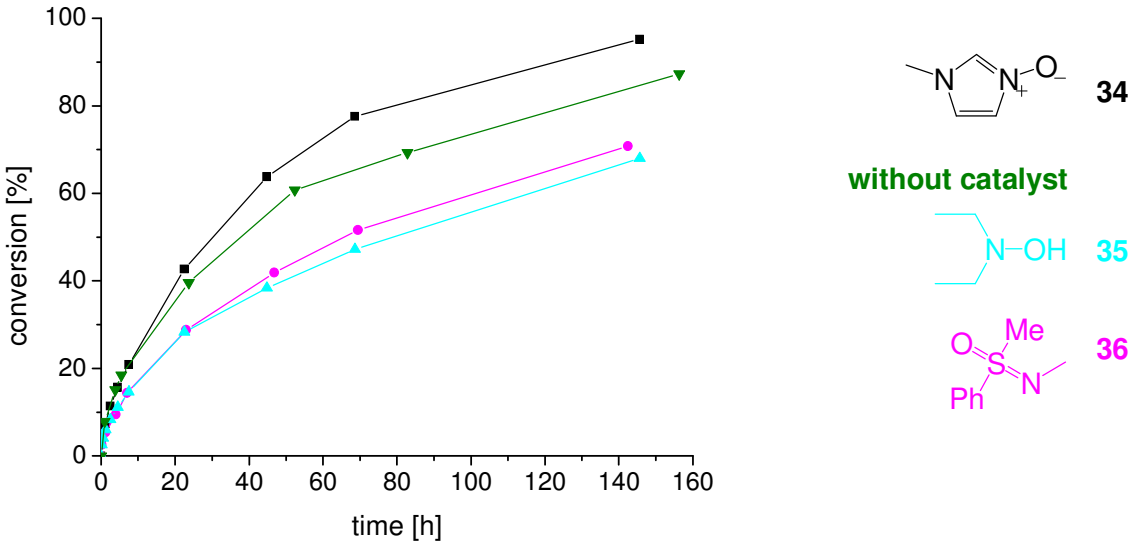


Figure 2.18: Kinetics of methanolysis of pNP ester **25a** by using potential chalcogen-based acyl-transfer catalysts **34**-**36**

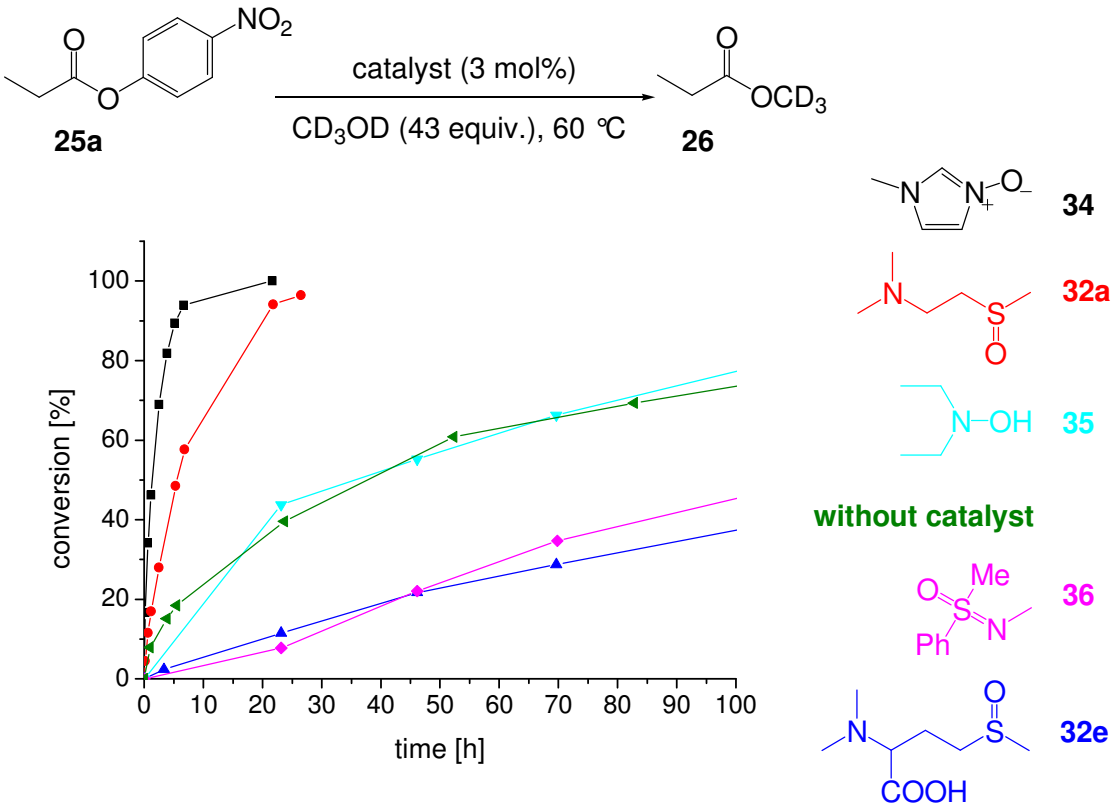
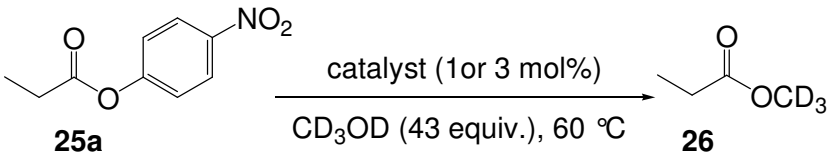


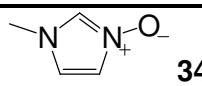
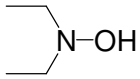
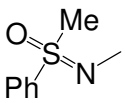
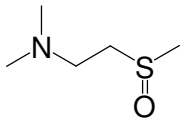
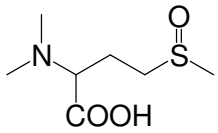
Figure 2.19: Kinetics of methanolysis of pNP ester **25a** by using different chalcogen-based acyl-transfer catalysts (3 mol%) **32a**/**e** and **34**-**36**

Only the amino sulfoxide **32e** proved to be a succesful organocatalyst. The sulfoximine **36** and the amino sulfoxide derived from methionine **32e** affect the transesterification adversely. The reaction rate could not be improved in spite of a higher catalyst loading. In Table 2.5, the rate constants k_{obs} and half-lifes $\tau_{½}$ are presented which were determined after the same principle as described before. Hence, the tested catalysts **32a**/**e** and **34**-**36** also react following pseudo-first order kinetics.

Table 2.5: Rate constants k_{obs} and half-lifes $\tau_{½}$ of the methanolysis of pNP ester **25a** by using various chalcogen-based acyl-transfer catalysts



25a **26**

entry	catalyst	mol%	k_{obs} [s^{-1}]	$\tau_{½}$ [h]	$k_{obs}/k_{without}$ [a]
1	 **34**	1	1.7×10^{-4}	34	1.6
		3	3.4×10^{-3}	2	32.1
2	 **35**	1	6.4×10^{-5}	90	0.6
		3	1.4×10^{-4}	40	1.4
3	 **36**	1	7.1×10^{-5}	81	0.7
		3	5.6×10^{-5}	104	0.5
4	 **32a**	1	1.5×10^{-4}	40	1.4
		3	1.1×10^{-3}	5	9.8
5	 **32e**	1	6.3×10^{-5}	91	0.6
		3	3.9×10^{-5}	146	0.4

[a] The $k_{without}$ value of the methanolysis of pNp **25a** without catalyst is = 1.1×10^{-4} s^{-1} and $\tau_{½}$ = 54 h.

2.5 Conclusion

In conclusion, the catalytic behavior of different classes of acyl-transfer catalysts was investigated in the methanolysis of the para-nitrophenyl ester **25a** derived from propionic acid (Figure 2.20). The highest acceleration rates could be achieved with amino alcohol and some amino sulfoxide catalysts. Although, it was found that the amino alcohols prove to be more successful as reactive chalcogen-based organocatalysts than amino sulfoxides. The best result could be achieved with the cyclohexane-based *β*-amino alcohol catalyst 2-piperidine-1-cyclohexanol **15a**. Besides, it was possible to provide evidence for the catalytic cycle of an

amino alcohol which operates by an *O*-nucleophilic mechanism. Furthermore, it could be determined that the methanolysis of the pNP ester **25a** can be treated as a kinetic of pseudo-first order. Also other oxygen-transfer catalysts like DMSO **31a**, 1-methylimidazole 3-*N*-oxide **34** and hydroxyl amine **35** accelerate the methanoylsis of pNP ester **25a**, but require a higher catalyst loading than 1 mol%.

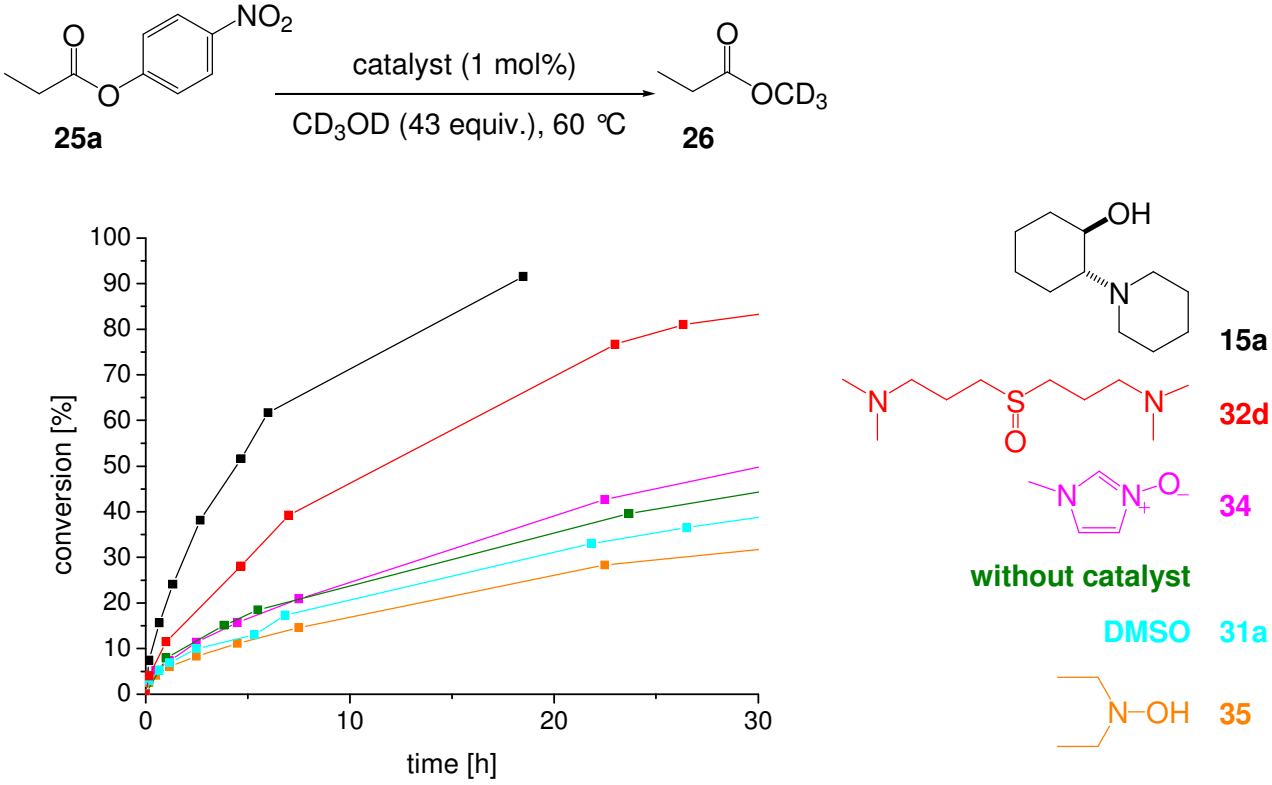


Figure 2.20: Kinetics of methanolysis of pNP ester **25a** by using different organocatalysts

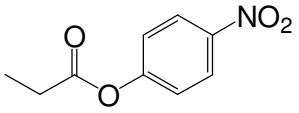
2.6 Experimental

2.6.1 General Information

All commercially available reagents were used without further purification unless stated, and solvents were purified and dried by standard methods. Analytical thin layer chromatography (TLC) was performed on silica gel (Kieselgel 60 F_{254}, 0.040-0.063 mm, Merck KgaA, Darmstadt, Germany) with detection either by UV light or molybdato phosphoric acid. Column chromatography was done using silica gel 60 (0.040-0.063 mm) from Merck KgaA, Darmstadt, Germany as stationary phase. ^{1}H- and ^{13}C-NMR were recorded at room temperature on a Varian Mercury 400 MHz. Chemical shifts were recorded in ppm relative to TMS (δ=0 ppm, ^{1}H-NMR) and to the solvent signal (^{13}C-NMR). Mass spectra were recorded on Applied Biosystems API-150 at 70 eV. Melting points were determined by standard methods on the melting point apparatus Leica DM L52 and were uncorrected. Optical rotations were obtained on JASCO DIP-1000 spectrometer.

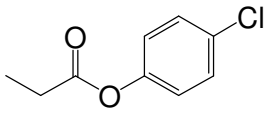
2.6.2 Preparation of Activated Esters

2.6.2.1 4-Nitrophenyl propionate 25a[95]



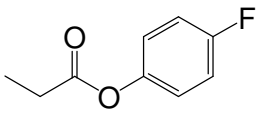
A solution of propionic acid (0.05 mol, 3.73 ml) and 4-nitrophenol (0.05 mol, 6.96 g) in dichloromethane were combined with a catalytic amount of 4-dimethylaminopyridine. The mixture was stirred 15 min at room temperature. Afterwards, dicyclohexylcarbodiimide (0.055 mol, 11.35 g) was added to the solution and stirred overnight. Subsequently, the precipitated urea was filtered and the solvent was removed under reduced pressure in a rotary evaporater. The residue was purified by chromatography on a silica gel column with petroleum ether/ethyl acetate (9:3) as eluent. Finally, the raw product was recrystallized from ethanol/ethyl acetate to obtain ester **25a** as a white solid; yield: 5.86 g (60 %); **mp** 59 °C [lit.[96] mp 59 °C]; $\boldsymbol{R_F}$=0.83 (eluent: petroleum ether/ethyl acetate (9:3)); **^{1}H-NMR** ($CDCl_3$, 400 MHz) δ = 1.30 (t, J=7.32 Hz, 3H), 2.65 (q, J=7.68 Hz, 2 H), 7.25 - 7.31 (m, 2 H), 8.24 - 8.30 (m, 2 H), ppm; **^{13}C-NMR** ($CDCl_3$, 100 MHz) δ = 8.83, 27.70, 122.38 (2 CH), 125.15 (2 CH), 145.20, 155.48, 171.95 ppm; **GC-MS**: *m/z* = 195.0.

2.6.2.2 4-Chlorophenyl propionate 25b[97]



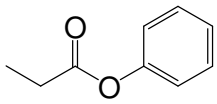
The reaction was performed according to procedure 2.6.2.2: Propionic acid (0.05 mol, 3.73 ml), 4-chlorophenol (0.05 mol, 6.43 g), a catalytic amount of 4-dimethylaminopyridine, and dicyclohexylcarbodiimide (0.055 mol, 11.35 g). Purification by "bulb-to-bulb" distillation (bp 140 °C/25 torr [lit.[98] bp 76-78 °C/2 torr]) gave **25b** as a colorless oil; yield: 6.23 g (68 %); **^{1}H-NMR** ($CDCl_3$, 300 MHz) δ = 1.26 (t, *J*=7.50 Hz, 3 H), 2.59 (q, *J*=7.68 Hz, 2 H), 6.95 - 7.06 (m, 2 H), 7.25 - 7.36 (m, 2 H) ppm; **^{13}C-NMR** ($CDCl_3$, 100 MHz) δ = 9.10, 27.75, 122.82 (2 CH), 129.32 (2 CH), 130.94, 149.04, 172.61 ppm; **GC-MS**: *m/z* = 183.9.

2.6.2.3 4-Fluorophenyl propionate 25c[99]



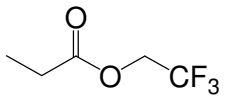
The reaction was performed according to the procedure 2.6.2.2: Propionic acid (0.06 mol, 4.48 ml), 4-fluorophenol (0.06 mol, 6.73 g), a catalytic amount of 4-dimethylaminopyridine and dicyclohexylcarbodiimide (0.066 mol, 13.62 g). Purification by "bulb-to-bulb" distillation (bp 130 °C/45 torr [lit.[99b] bp 55.85 - 57.85 °C/0.5 - 1 torr]) gave **25c** as a colorless oil; yield: 5.82 g (58 %); **^{1}H-NMR** ($CDCl_3$, 300 MHz) δ = 1.26 (t, *J*=7.68 Hz, 3 H), 2.59 (q, *J*=7.32 Hz, 2 H), 6.70 - 6.76 (m, 1 H), 6.87 - 6.94 (m, 1 H), 7.05 (d, *J*=1.10 Hz, 2 H) ppm; **^{13}C-NMR** ($CDCl_3$, 100 MHz) δ = 9.11, 27.75, 122.82 (2 CH), 129.31 (2 CH) 149.03, 154.15, 172.59 ppm; **GC-MS**: *m/z* = 168.0.

2.6.2.4 Phenyl propionate 25d[100]



The reaction was performed according to the procedure 2.6.2.2: Propionic acid (0.05 mol, 3.73 ml), phenol (0.05 mol, 4.71 g), a catalytic amount of 4-dimethylaminopyridine and dicyclohexylcarbodiimide (0.055 mol, 11.35 g). Purification by "bulb-to-bulb" distillation (bp 125 °C/45 torr [lit.[100b] bp 130-142 °C/60-67 torr]) and chromatography on a silica gel column with hexane/ethyl acetate (9:1) as eluent to obtain **25d** as a colorless oil; yield: 4.93 g (66 %); **^{1}H-NMR** ($CDCl_3$, 300 MHz) δ = 1.27 (t, *J*=7.61 Hz, 3 H), 2.60 (q, *J*=7.48 Hz, 2 H), 7.06 - 7.10 (m, 2 H), 7.20 - 7.25 (m, 1 H), 7.34 - 7.41 (m, 2 H) ppm; **^{13}C-NMR** ($CDCl_3$, 100 MHz) δ = 9.20, 27.83, 121.45 (2 CH), 125.60, 129.27 (2 CH), 150.58, 172.82 ppm; **GC-MS**: *m/z* = 149.99.

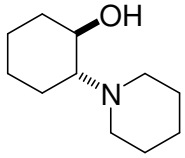
2.6.2.5 2,2,2-Trifluoroethyl propionate 25e[101]



2,2,2-Trifluoroethanol (0.06 mol, 4.4 ml) was slowly added to ice-cooled propionyl chloride (0.08 mol, 7 ml). The mixture was stirred overnight at room temperature. Subsequently, the mixture was heated up to 100 °C and hold at this temperature for 30 min under reflux. After cooling, nitrogen was passed into the mixture in order to remove the hydrogen chloride. The solution was poured into ice-water and was extracted with diethyl ether. The organic layer was washed with sodium hydrogen carbonate solution and water, and afterwards dried over sodium sulfate. Finally, the raw product was purified by "bulb-to-bulb" distillation (bp 94-96 °C [lit. [101] bp 93 °C]) to obtain **25e** as a colorless oil; yield: 2.89 g (31 %); **^{1}H-NMR** ($CDCl_3$, 400 MHz) δ = 1.19 (t, *J*=7.61 Hz, 3 H), 2.45 (q, *J*=7.61 Hz, 2 H), 4.47 (q, *J*=8.59 Hz, 2 H) ppm; **^{13}C-NMR** ($CDCl_3$, 100 MHz) δ = 8.77, 26.971, (59.63, 59.99, 60.36, 60.72) CH2CF3, (118.86, 121.61, 124.37, 127.12) CF3, 172.81 ppm.

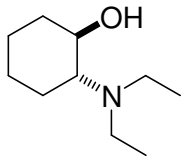
2.6.3 Preparation of Catalysts

2.6.3.1 2-(Piperidin-1-yl)cyclohexanol 15a



To a solution of cyclohexylene oxide (14.2 mmol, 1.44 ml) and piperidine (14.2 mmol, 1.4 ml) in 5 ml of dry acetonitrile calcium (II)-triflate (1.77 mmol, 0.6 g) was added. The solution was stirred for 5 seconds and was irradiated in the microwave (300 Watt, 70 °C) for 300 s. Afterwards, the mixture was cooled to 50 °C by gas-inject cooling. Subsequently, the acetonitrile was removed in vacuo. The residue was extracted with 200 ml of diethyl ether. The organic layer was washed with sat. $NaHCO_3$ (3 x 10 ml), water (3 x 10 ml), and brine (1 x 10 ml), and finally dried over sodium sulfate. The solvent was removed under reduced pressure in a rotary evaporater to obtain catalyst **15a** as a light yellow-brown solid; yield: 2.15 g (83 %); R_F = 0.43 (eluent: petroleum ether/acetone/triethyl amine (2:1:0.01)); **^{1}H-NMR** ($CDCl_3$, 400 MHz) δ = 1.06 - 1.29 (m, 4 H), 1.41 - 1.64 (m, 6 H), 1.66 - 1.80 (m, 3 H), 2.00 - 2.18 (m, 2 H), 2.32 (br. s., 2 H), 2.66 (ddd, *J*=10.89, 7.27, 3.32 Hz, 2 H), 3.31 - 3.38 (m, 1 H), 4.14 (br. s., 1 H) ppm; **^{13}C-NMR** ($CDCl_3$, 100 MHz) δ = 22.07, 24.06, 24.80, 25.57, 26.68, 33.20, 68.46, 70.93 ppm; **ESI-MS**: *m/z* = 184.2 $[M+H]^+$.

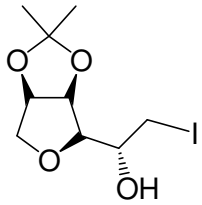
2.6.3.2 2-(Diethylamino)cyclohexanol 15b



The reaction was performed according to the procedure 2.6.3.1: To a solution of cyclohexylene oxide (14.2 mmol, 1.44 ml) and diethylamine (14.2 mmol, 1.48 ml) in 5 ml of dry acetonitrile calcium (II)-triflate (1.77 mmol, 0.6 g) was added. Purification by extraction with 200 ml of diethyl ether, washing with sat. $NaHCO_3$ (3 x 10 ml), water (3 x 10 ml), and brine (1 x 10 ml) gave catalyst **15b** as a colorless oil; yield: 1.96 g (81 %); R_F=0.90 (eluent: petroleum ether/acetone/triethyl amine (2:1:0.01)); **^{1}H-NMR** ($CDCl_3$, 400 MHz) δ = 1.04 (t, *J*=7.13 Hz, 6 H) 1.14 - 1.26 (m, 4 H) 1.69 - 1.78 (m, 3 H) 2.11 - 2.14 (m, 1 H), 2.27 - 2.41 (m, 3 H), 2.63 (dq, *J*=12.96, 7.33 Hz, 2 H), 3.26 - 3.34 (m, 1 H) ppm; **^{13}C-NMR** ($CDCl_3$, 100 MHz) δ = 14.71, 22.79, 24.15, 25.72, 33.17, 43.19, 66.14, 69.00 ppm; **ESI-MS**: *m/z* = 172.0 $[M+H]^+$.

2.6.3.3 3,6-Anhydro-1-(piperidino)-1-deoxy-4,5-*O*-isopropylidene-D-sorbitol 16

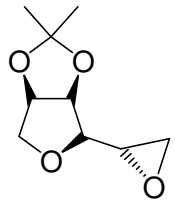
2.6.3.3.1 *O,O*-Isopropylidene-3,6-anhydro-1-deoxy-1-iodo-D-glucitol 22



A mixture of isosorbide (16 mmol, 2.3 g), dry acetone (3 mmol, 2.4 ml) and anhydrous NaI (33 mmol, 4.9 g, previously dried in a "bulb-to-bulb" distillation under reduced pressure at 113 °C in presence of phosphorus pentoxide which is in a receiver flask), was dissolved in 56 ml dry acetonitrile under nitrogen atmosphere. After that, freshly distilled chlorotrimethylsilane (4.2 ml 0.033 mol) was added dropwise to the stirred mixture. The reaction mixture was stirred for 19 h at room temperature under exclusion of light. Subsequently, 32 ml diethyl ether, 9.6 ml aqueous saturated sodium carbonate solution, and 16 ml water were added to the resulting orange-brown mixture. The aqueous phase was separated and extracted twice with 16 ml diethyl ether. The combined organic phases were washed with 6.4 ml aqueous saturated sodium thiosulfate solution and 8 ml brine. After drying over anhydrous sodium sulfate, the solvent was removed in a rotary evaporater, and the yellow residue was recrystallized from petrol ether to give **22** as a white solid; yield: 2.778 g (55 %); **mp** 71 °C; $[\alpha]_D^{24}$ =-57.6 (c=1.0, CH_2Cl_2) [lit.[102] mp 72°C; $[\alpha]_D^{22}$ =-66.6 (c=1.0, CH_2Cl_2)]; R_F=0.5 (eluent: CH_2Cl_2/MeOH (10:0.2)); **^{1}H-NMR** ($CDCl_3$, 400 MHz) δ = 1.33 (s, 3

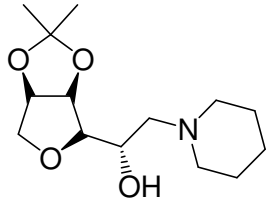
H), 1.54 (s, 3 H), 3.02 (d, *J*=2.74 Hz, 1 H, OH), 3.31 - 3.55 (m, 4 H), 3.86 - 3.92 (m, 1 H), 4.09 (d, *J*=10.9 Hz, 1 H), 4.72 (dd, *J*=6.1, 3.6 Hz, 1 H), 4.82 (dd, *J*=6.2, 3.7 Hz, 1 H) ppm; **^{13}C-NMR** ($CDCl_3$, 100 MHz) δ = 8.9, 24.4, 25.9, 69.6, 72.6, 80.3, 81.4, 84.2, 112.6 ppm; **ESI-MS**: *m/z*=337.4 $[M+Na]^+$.

2.6.3.3.2 *O,O*-Isopropylidene-1,2:3,6-dianhydro-D-glucitol 23



A solution of iodo alcohol **22** (8.3 mmol, 2.6 g) in 12.6 ml dry tetrahydrofuran was added dropwise to a stirred suspension of 8.4 ml tetrahydrofuran and sodium hydride (9.8 mmol, 0.234 g) within 1 h at 0 °C under nitrogen atmosphere. After that, the reaction mixture was stirred 5 h at room temperature and the volume of the mixture was reduced to 8.4 ml under reduced pressure. Subsequently, 12.6 ml diethyl ether was added to the mixture. The solution was cooled to 0 °C and carefully quenched with 2.5 ml aqueous saturated ammonium chloride solution. The aqueous phase was separated and the organic layer was washed with two portions of 2 ml brine. Thereafter, 4.2 ml water was added to the combined aqueous phases, which were extracted twice with 4.2 ml dichloromethane. The combined organic phases were dried over sodium sulfate and concentrated in vacuo. Finally, the crude product was recrystallized in hexane to give pure **23** as a white solid; yield: 1.387 g (90 %); **mp** 78 °C; $[\alpha]_D^{25}$ =-80.3 (c=0.505, CH_3OH) [lit.[103] mp 77 °C; $[\alpha]_D^{26}$ =-80.5 (c=0.505, CH_3OH)]; R_F=0.65 (eluent: CH_2Cl_2/MeOH (10:0.2)); **^{1}H-NMR** ($CDCl_3$, 400 MHz) δ = 1.34 (s, 3 H), 1.53 (s, 3 H), 2.66 (dd, *J*=4.9, 2.7 Hz, 1 H), 2.91 (t, *J*=4.5 Hz, 1 H), 3.03 (dd, *J*=6.9, 3.8 Hz, 1 H), 3.28 (m, 1 H), 3.52 (dd, *J*=10.9, 3.7 Hz, 1 H), 4.11 (d, *J*=10.9 Hz, 1 H), 4.70 (dd, *J*=6.2, 3.8 Hz, 1 H), 4.80 (dd, *J*=6.2, 3.7 Hz, 1 H) ppm; **^{13}C-NMR** ($CDCl_3$, 100 MHz) δ = 24.7, 26.0, 43.7, 49.99, 73.2, 81.1, 81.4, 84.5, 112.6 ppm; **ESI-MS**: *m/z*=209.1 $[M+Na]^+$.

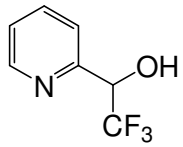
2.6.3.3.3 3,6-Anhydro-1-(piperidino)-1-deoxy-4,5-*O*-isopropylidene-D-sorbitol 16



A mixture of epoxide **23** (7.1 mmol, 1.315 g) and piperidine (14.1 mmol, 1.4 ml) in 36 ml MeOH was heated up to 60 °C and hold at this temperature for 16 h under nitrogen atmosphere. The solvent was removed in a rotary evaporater and the residue was purified by

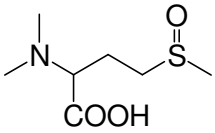
flash chromatography on a silica gel column (CH_2Cl_2/MeOH = 9:1) to give **16** as slightly yellow solid; yield: 1.308 g (85 %); **mp** 62 °C; $[\alpha]_D^{24}$ =-80.7 (c=1.005, CH_2Cl_2); R_F=0.57 (eluent: CH_2Cl_2/MeOH (2:1)); **^{1}H-NMR** ($CDCl_3$, 400 MHz) δ = 1.31 (s, 3 H), 1.40 - 1.48 (m, 5 H), 1.52 - 1.63 (m, 4 H), 2.37 (dd, *J*=12.50, 9.57 Hz, 3 H), 2.59 (dd, *J*=12.1, 3.7 Hz, 3 H), 3.29 (dd, *J*=7.03, 3.5 Hz, 1 H), 3.50 (dd, *J*=10.7, 3.7 Hz, 1 H), 4.03 - 4.09 (m, 2 H), 4.63 (dd, *J*=6.2, 3.6 Hz, 1 H), 4.77 (dd, *J*=6.3, 3.7 Hz, 1 H) ppm; **^{13}C-NMR** ($CDCl_3$, 100 MHz) δ = 24.2, 24.8, 25.97, 26.0, 54.8, 60.4, 66.2, 72.8, 80.5, 81.2, 84.7, 112.2 ppm; **ESI-MS**: *m/z* = 272.5 $[M+H]^+$.

2.6.3.4 2,2,2-Trifluoro-1-(pyridin-2-yl)ethanol 19



A mixture of pyridine-2-carbaldehyde (10 mmol, 0.89 ml) and trifluoromethyltrimethylsilane (TMS-CF_3) (12 mmol, 1.77 ml) in 25 ml THF was cooled down to 0 °C in an ice bath. Subsequently, tetrabutylammonium fluoride (TBAF) (0.076 mmol, 20 mg) was added. Then, the mixture was allowed to warm to room temperature while it was stirred for 3 h. After treated with 0.5 N aq HCl solution, the mixture was stirred for 1 h. The mixture was extracted three times with diethyl ether. The organic layer was dried over sodium sulfate. After removing the solvent under reduced pressure in a rotary evaporater, the residue was purified by flash chromatography on a silica gel column (hexane/ethyl acetate = 9:1) and "bulb-to-bulb" distillation under reduced pressure (bp 140 °C/25 torr [lit.[104] bp 75 °C/12 torr]) to obtain **19** as white solid; yield: 0.595 g (34 %); **mp** 41 °C [lit.[104] mp 46 °C]); **^{1}H-NMR** ($CDCl_3$, 400 MHz) δ = 5.04 (q, *J*=6.70 Hz, 1 H), 7.37 - 7.45 (m, 2 H), 7.80 (td, *J*=7.71, 1.56 Hz, 1 H), 8.64 (dt, *J*=4.88, 1.27 Hz, 1 H) ppm; **^{13}C-NMR** ($CDCl_3$, 100 MHz) δ = 70.13, 70.44, 70.76, 71.08, 122.61, 124.44, 125.43, 137.24, 148.26, 150.93 ppm; **ESI-MS**: *m/z* = 177.8.

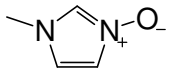
2.6.3.5 2-(Dimethylamino)-4-(methylsulfinyl)butanoic acid 32e



To a solution of methionine (8 mmol, 1.25 g) in 45 ml ethanol aq. formaldehyde solution (37 %) (0.127 mol, 4.61 ml) and palladium on carbon, 10 wt. % loading (1.25 g) were added. The mixture was stirred for 5 h under hydrogen atmosphere at room temperature. Then, the mixture was heated up to the boiling point and filtered several times. After removing the solvent under pressure in a rotary evaporater, the raw product was recrystallized in ethanol-acetone to obtain **32e** as white solid; yield: 0.998 g (65 %); **mp** 216 °C [lit.[105] mp 196-197

°C]); **^{1}H-NMR** (CD_3OD, 400 MHz) δ = 2.13 - 2.39 (m, 2 H), 2.68 (s, 3H), 2.82 - 2.98 (m, 7 H), 3.12 (ddd, *J*=13.28, 11.13, 5.08 Hz, 1 H), 3.59 - 3.67 (m, 1 H) ppm; **^{13}C-NMR** (CD_3OD, 100 MHz) δ = 21.94, 38.12, 41.97, 50.71, 70.59, 171.55 ppm; **ESI-MS**: *m/z* = 180.1 $[M+H]^+$.

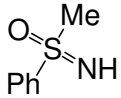
2.6.3.6 1-Methylimidazole-3-*N*-oxide 36



To a solution of 1-methylimidazol (30 mmol, 2.38 ml) in 60 ml THF hydrogen peroxide (30 %) (36 mmol, 4.1 ml) was added. The mixture was stirred for 3 h at room temperature. Then, the mixture was washed with 60 ml water. The water layer was extracted with 90 ml dichloromethane. Subsequently, the organic layer was washed with 60 ml water and 60 ml brine, and finally dried over sodium sulfate. After removing the solvent under reduced pressure in a rotary evaporater, the raw product was purified by flash chromatography on a silica gel column (CH_2Cl_2/ MeOH = 10:0.4) to obtain **36** as brown oil; yield: 0.85 g (29 %); R_F=0.93 (eluent: CH_2Cl_2/MeOH (10:0.4)); **^{1}H-NMR** ($CDCl_3$, 400 MHz) δ = 3.69 (s, 3 H), 6.88 (t, *J*=1.17 Hz, 1 H), 7.05 (s, 1 H) 7.43 (s, 1 H) ppm; **^{13}C-NMR** ($CDCl_3$, 100 MHz) δ = 33.29, 120.06, 129.42, 137.78 ppm.

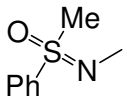
2.6.3.7 (*N*,*S*-Dimethylsulfonimidoyl)benzene 38

2.6.3.7.1 (*S*-Methylsulfonimidoyl)benzene 41



A mixture of methyl phenyl sulfoxide (20 mmol, 2.8 g) and sodium azide (22 mmol, 1.43 g) in 20 ml of chloroform was cooled in an ice bath. Then, concentrated sulfuric acid (94 mmol, 5 ml) was added slowly. The mixture was heated carefully up to 45 °C in a heating mantle for 12 h. After cooling the mixture, 40 ml of ice-cold water was added and stirred until all the salts were dissolved. The water layer was extracted with 12 ml of chloroform. Subsequently the aqueous layer was made slightly alkaline with 20 % sodium hydrogen solution, washed with chloroform (2 x 20 ml), and dried over sodium sulfate. The solvent was removed under reduced pressure in a rotary evaporater to obtain **41** as slightly yellow oil; yield: 2.66 g (86 %); **^{1}H-NMR** ($CDCl_3$, 400 MHz) δ = 3.12 (s, 3 H), 7.54 - 7.59 (m, 2 H), 7.61 - 7.66 (m, 1 H), 8.01 - 8.04 (m, 2 H) ppm; **^{13}C-NMR** ($CDCl_3$, 100 MHz) δ = 46.10, 127.62 (2 x CH), 129.21 (2 x CH), 133.02, 143.40 ppm; **ESI-MS**: *m/z* = 156.2 $[M+H]^+$.

2.6.3.7.2 (*N,S*-Dimethylsulfonimidoyl)benzene 38



To a solution of (*S*-methylsulfonimidoyl)benzene **41** (9.66 mmol, 1.5 g) in 0.9 ml formic acid paraformaldehyde (11.59 mmol, 0.35 g) was added whilst stirring vigorously. Then, concentrated sulfuric acid (94 mmol, 5 ml) was added slowly to the reaction mixture. The mixture was heated up to 100 °C, hold at this temperature for 2 h, and at 130 °C for 1h until the gas evolution was finished. After concentration of the solution, 58 ml of 2 M sulfuric acid was added. The water layer was neutralized with sodium carbonate and washed with dichlrormethane. After drying over sodium sulfate, the solvent was removed. The raw product was purified with column chromatography on a silica gel column (ethyl acetate/MeOH = 9:1) to obtain **38** as brown oil; yield: 1.02 g (62 %); R_F=0.63 (eluent: EtOAc/MeOH (9:1)); **^{1}H-NMR** ($CDCl_3$, 400 MHz) δ = 2.66 (s, 3 H), 3.09 (s, 3H), 7.56 - 7.65 (m, 3 H),7.89 - 7.93 (m, 2 H) ppm; **^{13}C-NMR** ($CDCl_3$, 100 MHz) δ = 29.50, 44.91, 128.73 (2 x CH), 129.23 (2 x CH), 132.89, 138.57 ppm; **ESI-MS**: *m/z* = 170.2 $[M+H]^+$.

2.6.4 Kinetic Measurements

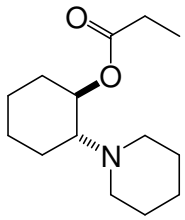
2.6.4.1 Kinetics of Ester Methanolysis

The amino alcohol catalyst 2-piperidine-1-cyclohexanol **15a** (0.11 mmol, 19.2 mg), the ester (0.209 mmol) and methanol-d_4 (2.09 mmol, 85 µl) were dissolved in 0.6 ml of chloroform-*d* in a NMR tube. The sample was shaken in the heating thermo mixer MHR 23 (firm Carl Roth GmbH + Co. KG) at 30 °C and 600 rpm. In a certain time interval (1, 10, 60, 600 min), the consumption of the ester was monitored by ^{1}H-NMR using Varian Mercury 400 MHz. The kinetic data are based on quantification of disappearing the proton signals of the methyl group in the pNP ester **25a** and appearing the proton signals of the methyl group in the product **26** as well as disappearing the proton signals of the phenyl core in the pNP ester **25a** and appearing proton signals of the phenyl core in the originating *p*-nitrophenol.

2.6.4.2 Kinetics of Methanolysis of 4-Nitrophenyl Propionate 25a

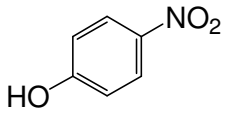
The catalyst (4 µmol) and 4-nitrophenyl propionate **25a** (0.4 mmol, 78.1 mg) were dissolved in 0.7 ml methanol-d_4 in a NMR tube. The sample was shaken in the heating thermo mixer MHR 23 (firm Carl Roth GmbH + Co. KG) at 60 °C and 600 rpm. In a certain time interval (see Fig. 2.3, 2.14-2.16, 2.18, 2.20-2.22), the consumption of the ester was monitored by ^{1}H-NMR using a Varian Mercury 400 MHz spectrometer.

2.6.4.3 Isolation of 2-(piperidin-1-yl)cyclohexyl propionate 27



A solution of 4-nitrophenyl propionate **25a** (0.25 mmol, 49.6 mg) and 2-(piperidin-1-yl)cyclohexanol **15a** (0.23 mmol, 42.2 mg) in toluene was shaken in the heating thermo mixer MHR 23 at 60 °C and 600 rpm overnight. Then, the reaction mixture was diluted in 100 ml diethyl ether. The organic layer was washed with sodium bicarbonate solution (3 x 10 ml), water (1 x 10 ml), and brine (1 x 10 ml). After drying over sodium sulfate, the solvent was removed under reduced pressure in a rotary evaporater. The raw product was purified by column chromatography on a silica gel column (petroleum ether/ethyl acetate/triethylamine = 9:3:0.02) to obtain **27** as a pale yellow oil; yield: 47 mg (85 %); $\boldsymbol{R_F}$=0.75 (eluent: PE/EtOAc/Et_3N (9:3:0.02)); **^{1}H-NMR** ($CDCl_3$, 400 MHz) δ = 1.14 - 1.19 (m, 3 H) 1.20 - 1.54 (m, 10 H) 1.65 - 1.77 (m, 2 H) 1.82 - 1.90 (m, 1 H) 1.92 - 2.01 (m, 1 H) 2.28 - 2.37 (m, 2 H) 2.37 - 2.46 (m, 3 H) 2.59 - 2.63 (m, 2 H) 4.81 - 4.92 (m, 1 H) ppm; **^{13}C-NMR** ($CDCl_3$, 100 MHz) δ = 9.42, 24.39, 24.78, 24.89, 25.10, 26.59, 28.08, 32.00, 50.23, 67.71, 71.72, 173.90 ppm; **ESI-MS**: *m/z* = 240.0 $[M+H]^+$.

2.6.4.4 Isolation of *p*-nitrophenol 28



A solution of 4-nitrophenyl propionate **25a** (0.26 mmol, 50.99 mg) and 2-(piperidin-1-yl)cyclohexanol **15a** (0.13 mmol, 23.8 mg) in 0.45 ml of methanol was shaken in the heating thermo mixer MHR 23 at 60 °C and 600 rpm for 30 h. Then, the solvent was removed under reduced pressure in a rotary evaporater. The raw product was purified by column chromatography on a silica gel column (dichloromethane/ ethyl acetate = 10:1) to obtain **28** as a light yellow solid; yield: 32.5 mg (90 %); $\boldsymbol{R_F}$=0.85 (eluent: CH_2Cl_2/ EtOAc (10:1)); **^{1}H-NMR** ($CDCl_3$, 400 MHz) δ = 6.91 - 6.95 (m, 2 H), 8.16 - 8.22 (m, 2 H) ppm; **^{13}C-NMR** ($CDCl_3$, 100 MHz) δ = 115.67 (2 x CH), 126.27 (2x CH), 140.8, 161.37 ppm; **ESI-MS**: *m/z* = 137.8 $[M-H]^-$.

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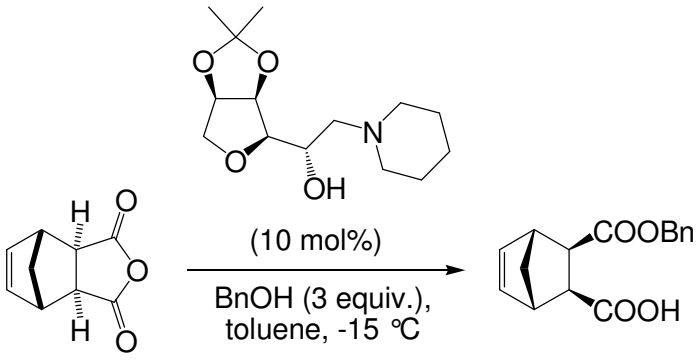
Chapter 3

Enantioselective Desymmetrization of *meso*-Anhydrides

Abstract [*]*:*

Various chiral *β*-amino alcohol derivatives and bifunctional thiourea derivatives were applied as potential chiral organocatalysts for enantioselective desymmetrization of cyclic *meso*-anhydrides. The best catalyst is the *β*-amino alcohol synthesized from isosorbide, a by-product of the starch industry. This new catalyst promotes the enantioselective alcoholysis of various cyclic *meso*-anhydrides in high enantiomeric excess and quantitative yields.



[*] Part of this Chapter will be published: K. Brand, L. A. Wessjohann, A. D. Wouters, D. S. Lüdtke, Enantioselective Desymmetrization of *meso*-Anhydrides: Catalyzed by Carbohydrate-based Organocatalysts, *manuscript in preparation*.

3.1 Introduction

The stereoselective ring opening of cyclic anhydrides gives enantiomerically pure hemiesters containing either single or multiple stereocenters. These optically active hemiesters are used as versatile intermediates in the synthesis of natural products or bioactive compounds.[1] The first metal-free enantioselective anhydride opening was reported by Oda *et al.* and shortly after by Aitken *et al.*[2,3] They introduced natural and modified cinchona alkaloids as catalysts for the asymmetric methanolysis of cyclic *meso*-anhydrides which give good to excellent yields and moderate enantioselectivities. Bolm *et al*. developed an improved procedure which affords excellent enantioselectivities for the desymmetrization of *meso*-anhydrides by using a stoichiometric amount of quinine or quinidine.[4] Later, Deng *et al*. investigated commercially available modified cinchona alkaloid Sharpless ligands $(DHQD)_2AQN$ and its pseudoenantiomer $(DHQ)_2AQN$ as catalysts which also provide high enantioselectivities.[5] In recent years, Connon *et al*. and Song *et al*. reported cinchona-based thiourea bifunctional catalysts which catalyze the methanolysis of cyclic anhydrides at room temperature with high enantioselectivities.[6]

Except numerous alkaloid-based catalysts, a variety of other bifunctional organocatalysts were developed, such as thiourea or sulfonamide catalysts.[7] List *et al*. introduced bifunctional chiral Brønsted acid/base catalysts which promote highly enantioselective desymmetrizations of cyclic *meso*-anhydrides.[8] Furthermore, a multitude of *β*-amino alcohols catalysts was reported for the enantioselective alcoholysis of various anhydrides.[9] For instance, Bolm *et al*. presented low molecular, cyclohexane-based *β*-amino alcohol derivatives which allow the desymmetrization of cyclic *meso*-anhydrides with high enantioselectivities.[10]

Inspired by the work of Bolm`s group we focused our attention on chiral carbohydrate-derived *β*-amino alcohols. A multiplicity of carbohydrates can be found in nature or can be obtained by synthetic paths. But only few are available in sufficient quantities and at cost-effective prices such as isosorbide and D-xylose. D-Xylose can be obtained from plants rich in hemicelluloses, such as strawdust and corn cobs, by hydrolysis with diluted acids. Isosorbide is an important by-product of the starch industry which is generated by dehydration of D-sorbitol. Both D-xylose and isosorbide represent inexpensive and commercially available chiral starting materials which can be applied in asymmetric organic synthesis as chiral pool for the preparation of chiral auxiliaries,[11] ligands,[12] and catalysts.[13] These plant carbohydrates or their derivatives can also be used in medicine, e.g. isosorbide dinitrate as cardiac or vasolidator[14] and D-xylose as agent to test for malabsorption.[15] Furthermore, some substituted xylosides and amino alcohol derivatives from isosorbide show glucosidase inhibitor activity.[16] Besides, isosorbide can be used for the synthesis of biodegradable polymers[17] or as amphiphile.[18]

In this chapter, the application of chiral *β*-amino alcohols derived from isosorbide **1** and D-xylose **2** as organocatalysts for the enantioselective alcoholyses of cyclic *meso*-anydrides is presented (Figure 3.1). Thereby their catalytic activity and enantioselectivity is compared with the cyclohexane-based *β*-amino alcohol catalyst **3** and two thiourea catalysts **4** and **5**.

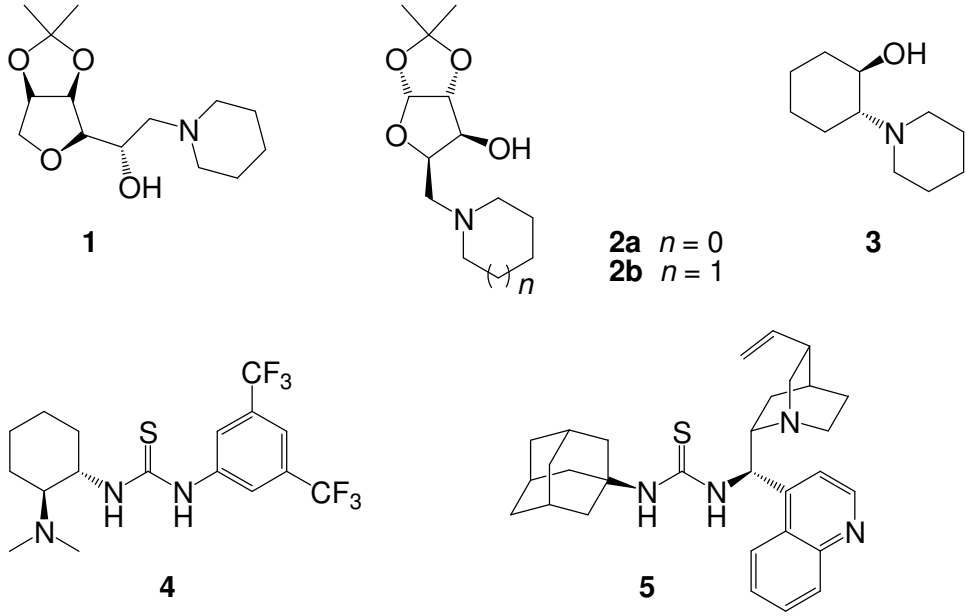
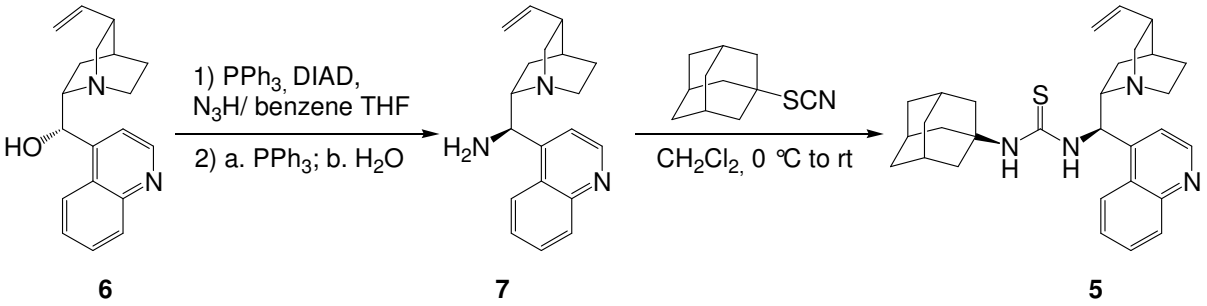


Figure 3.1: Chiral *β*-amino alcohols **1**-**3** and chiral thioureas **4** and **5**

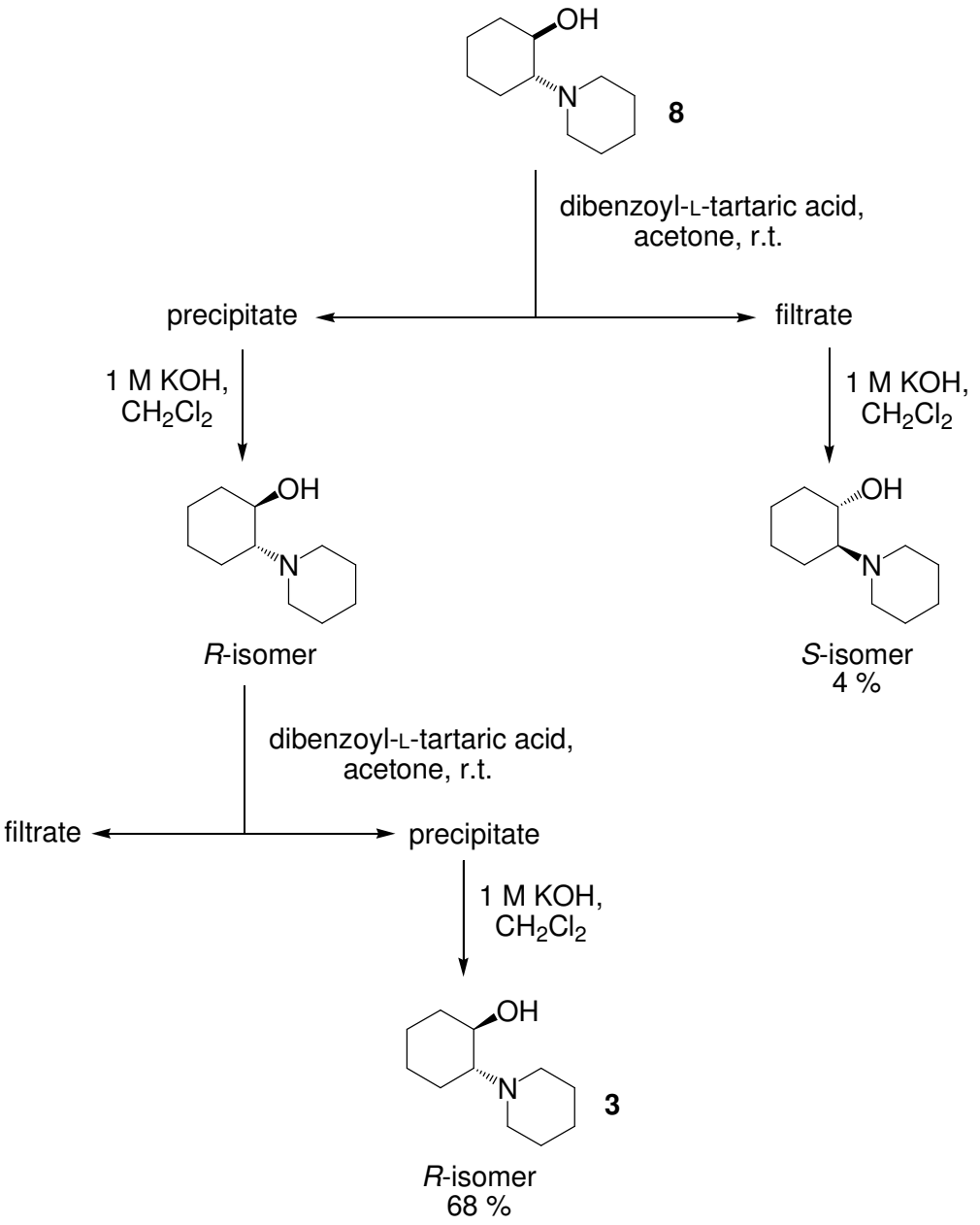
3.2 Results and Discussion

3.2.1 Preparation of the Catalysts

The preparation of the carbohydrate-based *β*-amino alcohols **1** and **2** were described in chapter 2 (section 2.2.1).[12e, 13e-g, 19,20] The known Takemoto thiourea catalyst **4** was obtained from 3,5-bis(trifluoromethyl)phenyl isothiocyanate and (*R,R)-N,N*-dimetyl-*trans*-diaminocyclohexane by a simple procedure described by Takemoto *et al.*[21,22] The cinchonidine derived thiourea catalyst **5** was synthesized in two steps by a modified method of Chen *et al.*[23] At first, cinchonidine **6** was transformed into the corresponding primary amine **7** which subsequently was reacted with 1-adamentyl isothiocyanate to provide catalyst **5** (Scheme 3.1).



Scheme 3.1: Synthesis of cinchonidine derived thiourea catalyst **5**



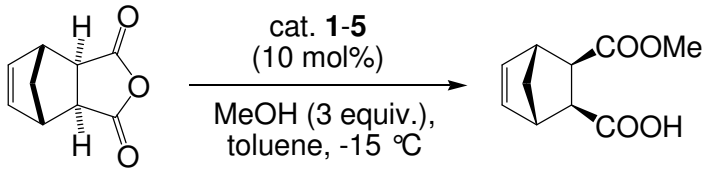
Scheme 3.2: Preparation of the chiral cyclohexane-based *β*-amino alcohol **3** according to procedure of Periasamy *et al.*[24]

The cyclohexane-based *β*-amino alcohol catalyst **3** was prepared in enantiomerically pure form *via* resolution of the racemic *trans*-2-(piperidin-1-yl)cyclohexanol **8** by a method of Periasamy *et al*. (Scheme 3.2).[24] As reagent for the resolution of the racemic *β*-amino alcohol **8** dibenzoyl-L-tartaric acid was used. The *β*-amino alcohol catalyst **3** could be obtained in an enantiomerically pure form from the precipitate in two steps from compound **8**. The overall yield was 68 %.

3.2.2 Catalyst Screening for the Asymmetric Methanolysis of Cyclic *meso*-Anhydrides

With the chiral catalysts in hand, their catalytic activity and enantioselectivity were investigated in the methanolysis of *cis*-5-norbornene-*exo*-2,3-dicarboxylic anhydride **9** as model substrate. The experiments were accomplished in presence of 10 mol% catalyst and 3 equiv. methanol in toluene at -15 °C (Bolm`s protocol).[10a] The screening results are depicted in Table 1. Unfortunately, the piperidine and pyrrolidine derivatives from D-xylose **2a** and **2b** induced no enantioselectivity in the ring-opening of the cyclic *meso*-anhydride **9**. In addition, they provided the hemiester **10a** in moderate yield after 73.5 h. However, the *β*-amino alcohol derived from isosorbide **1** proved to be a very efficient catalyst for the enantioselective ring-opening of anhydride **9**. The hemiester **10a** could be formed in 83 % overall yield with 92 % enantiomeric excess after 72 h. The cyclohexane-based *β*-amino alcohol **3** showed approximately the same results like catalyst **1**. Catalyst **3** desymmetrized anhydride **9** in 83 % overall yield with 89 % enantiomeric excess after 72 h. Bolm *et al*. already applied the chiral *β*-amino alcohol **3** for the enantioselective ring-opening of *cis*-*endo*-bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic anhydride **11** (Scheme 3.3).[25]

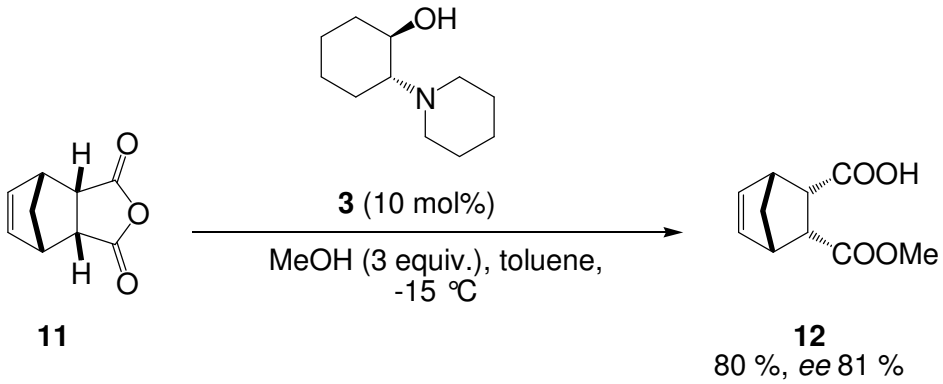
Table 3.1: Catalyst screening for the asymmetric methanolysis of anhydride **9**[a]



9 **10a**

entry	catalyst	time [h]	yield [%][b]	*ee* [%][c]
1	**1**	72	83	92
2	**2a**	73.5	55	51
3	**2b**	73.5	66	56
4	**3**	72	83	89
5	**4**	96	76	33
6	**5**	96	75	84

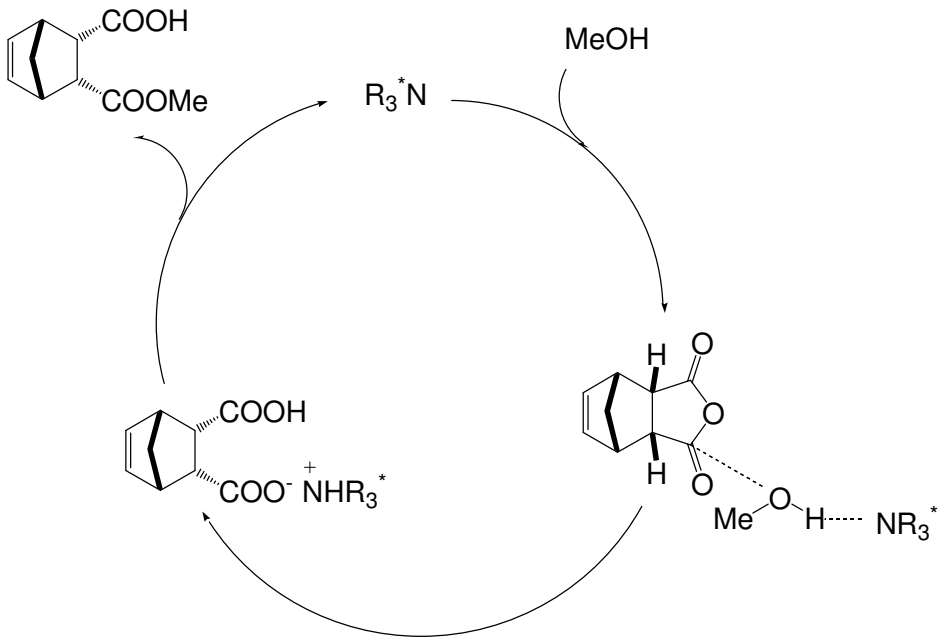
[a] The reactions were carried out using anhydride **9** (1 mmol), 10 mol% catalyst, and 3 equiv. MeOH in toluene (5 ml) at -15 °C. [b] Yield of isolated product after column chromatography. [c] Determined by HPLC analysis of the corresponding methyl-4-bromophenyl diester using a chiral stationary phase.



11 **12**
80 %, *ee* 81 %

Scheme 3.3: Enantioselective methanolysis of anhydride **11** catalyzed by *β*-amino alcohol **3** reported by Bolm *et al.*[25]

The mechanism of methanolysis of cyclic anhydride **11** has been investigated by Aviyente *et al.*[26] For this purpose, the reaction has been calculated using DFT (density functional theory) quantum mechanics investigations. It was determined that the asymmetric ring-opening of anhydride **11** proceeds by a general base catalysis pathway, in which the addition of the methanol to the anhydride is assisted by the chiral catalyst (Scheme 3.4). The nitrogen atom of the catalyst activates methanol by deprotonation and the alcohol moiety stabilizes the oxyanion by H-bonding. The chiral catalyst acts as a general base in the process.



Scheme 3.4: Mechanism of the asymmetric desymmetrization of cyclic *meso*-anhydrides

Aviyente *et al*. calculated that the general base catalysis mechanism is favored energetically by 26.8 kcal mol^{-1} (23.4 kcal mol^{-1} in toluene) over the nucleophilic catalysis (nucleophilic attack of the catalyst on the anhydride to form a chiral acylammonium salt which is transformed to the ester by nucleophilic attack of the alcohol). Furthermore, they determined that the stereoselectivity in base catalysis is dependent on the relative orientation of the catalyst with respect to the anhydride. Deng *et al*. confirmed also the general base catalysis mechanism for the cinchona alkaloid-catalyzed alcoholysis of *meso*-anhydrides. They accomplished kinetic studies on the enantioselective alcoholysis which are consistent with a general base catalysis pathway.[27] Likewise, Song *et al*. computed the general base catalysis pathway for enantioselective alcoholysis of *meso*-anhydrides catalyzed by a bifunctional thiourea-based cinchona alkaloid catalyst.[6a] Computational investigations indicated that the quinuclidine group activates the alcohol as a general base and the thiourea group activates the carbonyl group of the anhydride by H-bonding (Figure 3.2). In addition, it was observed by ^{1}H-NMR dilution experiments that thiourea catalysts can form inactive dimers which reduce the enantioselectivity of the reaction. This fact can be a reason for the low *ee*-value (33 %) for the Takemoto catalyst **4**. Catalyst **5** in contrast exhibits a high enantioselectivity (84 %) which is slightly lower in comparison to the chiral cyclohexane-based *β*-amino alcohol catalyst **3**.

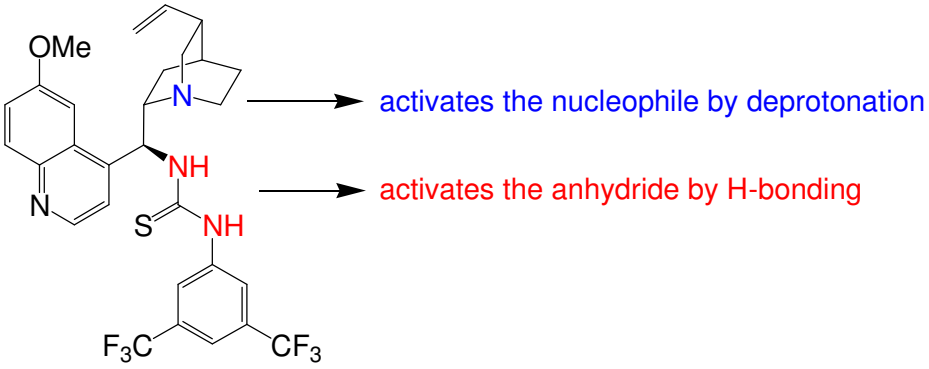
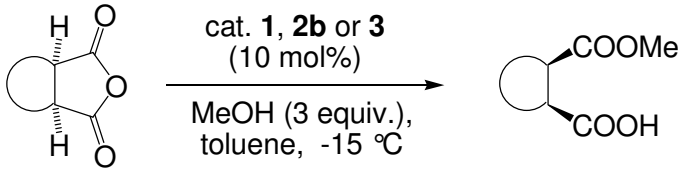


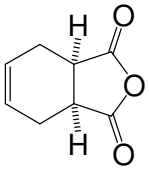
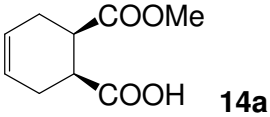
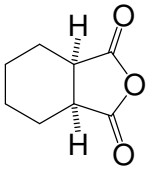
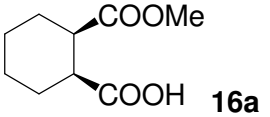
Figure 3.2: Bifunctional thiourea-based cinchona alkaloid catalyst

In summary, the *β*-amino alcohol derived from isosorbide **1** and the *β*-amino alcohol with the cyclohexane scaffold **3** show the best results with respect to their catalytic activity and enantioselectivity. For that reason, a further supplementary study examined the methanolysis of *cis*-cyclohexanedicarboxylic anhydride **15** in presence of chiral *β*-amino alcohol catalyst **1**, **2b** and **3** (Table 3.2). Also in this case, it could be observed similarly good yield and enantioselectivity with catalysts **1** and **3**. The pyrrolidine derivatives from D-xylose **2b** proved to be reactive (80 % yield in 22 h), but not as enantioselective (57 %).
Finally, the *β*-amino alcohol derived from isosorbide **1** was tested in the methanolysis of bicyclic anhydride **13**; good *ee* value (84 %) and yield (82 %) was obtained as well.

Table 3.2: Asymmetric methanolysis of *meso*-anhydrides **13** and **15**[a]



13, **15** **14a**, **16a**

entry	catalyst	anhydride	product	time [h]	yield [%][b]	*ee* [%][c]
1	**1**	 **13**	 **14a**	28	82	84
2	**1**	 **15**	 **16a**	26	84	88
3	**2b**	**15**	**16a**	22	80	57
4	**3**	**15**	**16a**	22	86	87

[a] The reactions were carried out using anhydride **13** and **15** (1 mmol), 10 mol% catalyst, and 3 equiv. MeOH in toluene (5 ml) at -15 °C.

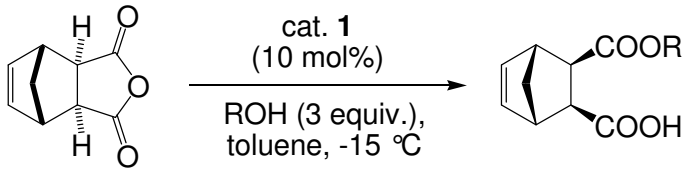
[b] Yield of isolated product after column chromatography.

[c] Determined by HPLC analysis of the corresponding methyl-4-bromophenyl diester using a chiral stationary phase.

3.2.3 Asymmetric Alcoholysis of *meso*-Anhydrides

Having identified the *β*-amino alcohol **1** as the best catalyst of the series, the influence of the nucleophile on the alcoholysis of anhydride **9** was examined (Table 3.3). The asymmetric alcoholysis is almost independent of the steric properties of the alcohols. High enantioselectivities were observed in all cases excepting naphthyl alcohol. Phenolic or other stabilized (acidic) hydroxyl nucleophiles like allyl, naphtyl, and substituted phenyl alcohol expectedly are less reactive with catalyst **1**. Only moderate yields were achieved, whereas the “normal” alcohols methanol and benzyl alcohol show excellent yields.

Table 3.3: Asymmetric alcoholysis of anhydride **9** by using different alcohols[a]



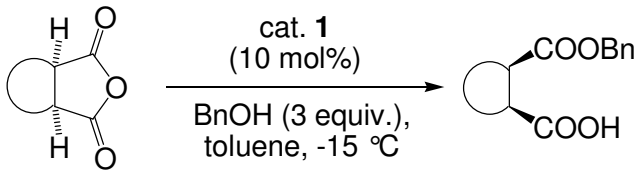
9 **10a-e**

entry	alcohol	hemiester	time [h]	yeld [%][b]	*ee* [%][c]
1	methanol	**10a**	72	83	92
2	benzyl alcohol	**10b**	94	70	93
3	allyl alcohol	**10c**	94	62	91
4	naphthyl alcohol	**10d**	98	46	88
5	(4-bromophenyl)methanol	**10e**	98	41	90

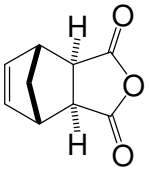
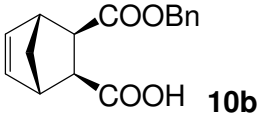
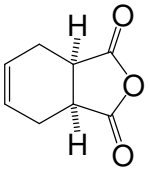
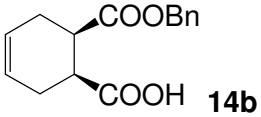
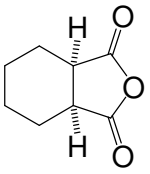
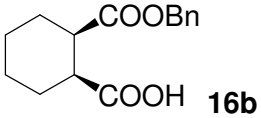
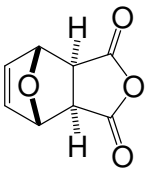
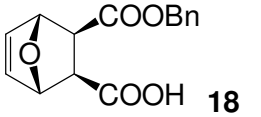
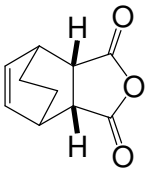
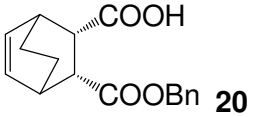
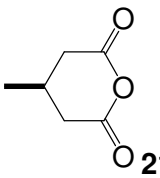
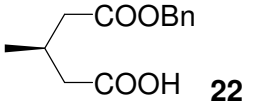
[a] The reactions were carried out using anhydride **9** (1 mmol), 10 mol% catalyst **1**, and 3 equiv. alcohol in toluene (5 ml) at -15 °C. [b] Yield of isolated product after column chromatography. [c] Determined by HPLC analysis on a chiral stationary phase.

The next step was to study the substrate scope with benzyl alcohol as nucleophile. As shown in Table 3.4, a variety of bicyclic and tricyclic anhydrides were converted to the corresponding hemiesters. High enantioselectivities (up to 95 %) and good yields (78 %) were achieved with the bicyclic anhydrides **13** and **15**. In contrast, the tricyclic anhydrides **17** and **19** and the bicyclic glutaric anhydride **21** react more sluggishly. Additionally, anhydrides **19** and **21** show moderate enantioselectivities (up to 66 %), whereas the oxygen-bridged anhydride **17** exhibits a better enantioselectivity (82 % *ee*).

Table 3.4: Enantioselective ring-opening of cyclic *meso*-anhydrides **9**-**21** with benzyl alcohol using catalyst **1**[a]



9-**21** **10**-**22**

entry	anhydride	product	time [h]	yield [%][b]	*ee* [%][c]
1	 **9**	 **10b**	94	70	93
2	 **13**	 **14b**	96	78	90
3	 **15**	 **16b**	96	72	95
4	 **17**	 **18**	167	38	82
5	 **19**	 **20**	92	36	66
6	 **21**	 **22**	167	45	64

[a] The reactions were carried out using anhydride **9**-**21** (1 mmol), 10 mol% catalyst **1**, and 3 equiv. benzyl alcohol in toluene (5 ml) at -15 °C. [b] Yield of isolated product after column chromatography. [c] Determined by HPLC analysis on a chiral stationary phase.

3.3 Conclusions

In conclusion, various chiral *β*-amino alcohols and thiourea catalysts were applied in the methanolytic desymmetrization of cyclic *meso*-anhydrides. The most efficient catalyst was the *β*-amino alcohol derived from isosorbide **1** which provided hemiesters by enantioselective ring-opening of cyclic *meso*-anhydrides with benzyl alcohol in up to 95 % *ee*. Apart from benzyl alcohol and methanol, even phenols can be used in the enantioselective alcoholysis and furnish high enantioselectivities as well.

3.4 Experimental

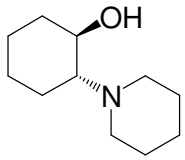
3.4.1 General Information

All commercially available reagents were used without further purification, and solvents were purified and dried by standard methods. Analytical thin layer chromatography (TLC) was performed on silica gel (Kieselgel 60 F_{254}, 0.040-0.063 mm, Merck KgaA, Darmstadt, Germany) with detection either by UV light or molybdato phosphoric acid. Column chromatography was done using silica gel 60 (0.040-0.063 mm) from Merck KgaA, Darmstadt, Germany, as stationary phase. ^{1}H- and ^{13}C-NMR were recorded at room temperature on a Varian Mercury 400 MHz. Chemical shifts were recorded in ppm relative to TMS (δ=0 ppm, ^{1}H-NMR) and to the solvent signal (^{13}C-NMR). Mass spectra were recorded on Applied Biosystems API-150 at 70 eV. Optical rotations were obtained on JASCO DIP-1000 spectrometer. Analytical HPLC was performed on YMC ODS-A (4.6 x 15 mm) column with UV detection at 254 nm.

3.4.2 Preparation of Catalysts

The *β*-amino alcohols based on D-xylose scaffold **2** were prepared in the work group of Lüdtke *et al*. according to the literature procedure.[13e-g] The chiral thiourea catalysts **4** and **5** were synthesized in the work group of Westermann *et al*. according to literature procedure.[22] The *β*-amino alcohol derived from isosorbide **1** was prepared according the procedure described in chapter 2.[12e, 19]

3.4.2.1 (1*R*,2*R*)-2-(Piperidinyl)cyclohexanol 3



Racemic *trans*-2-(piperidinyl)cyclohexanol **8** (1.7 g, 9.21 mmol) and dibenzoyl-L-tartaric acid (3.3 g, 9.21 mmol) in 111 ml acetone and were stirred overnight at room temperature. Subsequently, the precipitate was filtered and suspended in a mixture of CH_2Cl_2 and aqueous 1M KOH solution. The organic extract was separated and washed with brine. After drying over anhydrous sodium sulfate, the solvent was removed under reduced pressure in a rotary evaporator to obtain the *R*-isomer (69 % yield); $[\alpha]_D^{24}$ =-14.4 (c=3.02, $CHCl_3$). The

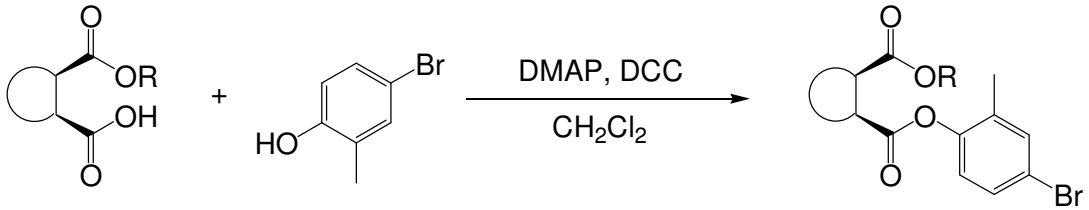
filtrate was concentrated and treated as mentioned before to obtain the *S*-isomer (4 % yield); $[\alpha]_D^{24}$ =+38.0 (c=2.655, $CHCl_3$). The *R*-isomer was further enriched using dibenzoyl-L-tartaric acid (2.3 g, 6.4 mmol). The mixture was stirred in 76.8 ml acetone at room temperature for 6 h. The precipitate was treated as outlined above to obtain the *R*-isomer, which was recrystallized from EtOH/EtOAc to give **3** as a slightly brown oil; yield: 1.145 g (68 %); $[\alpha]_D^{24}$ =-58.55 (c=2.990, $CHCl_3$) [lit.[10a] $[\alpha]_D^{25}$ =-54.50, c=3.000, $CHCl_3$]; R_F=0.86 (eluent: Et_2O/pentane/Et_3N (2:5:0.2)); **^{1}H-NMR** ($CDCl_3$, 400 MHz) δ = 1.09 - 1.29 (m, 4 H), 1.38 - 1.47 (m, 2 H), 1.47 - 1.65 (m, 4 H), 1.66 - 1.73 (m, 1 H), 1.73 - 1.82 (m, 2 H), 2.08 - 2.17 (m, 2 H), 2.31 (br s, 2 H), 2.66 (ddd, *J*=10.9, 7.2, 3.4 Hz, 2 H), 3.32 - 3.38 (m, 1 H), 4.15 (br s, 1 H) ppm; **^{13}C - NMR** ($CDCl_3$, 100 MHz) δ = 22.1, 24.1, 24.8, 25.6, 26.7, 33.2, 49.7, 68.5, 71.0 ppm; **ESI-MS**: *m/z* = 183.9 $[M+H]^+$.

3.4.3 General Procedure for the Enantioselective Alcoholysis of *meso*-Anhydrides

A mixture of anhydride (1 mmol), chiral catalyst (0.1 mmol), and anhydrous toluene was stirred 15 min at room temperature under argon atmosphere. After the mixture was cooled down to -15 °C, the alcohol (3 mmol) was added. Subsequently, the reaction mixture was stirred for 72 - 167 h at -15 °C. The reaction was quenched with 20 ml of 2N HCl solution. Thereafter, the mixture was extracted with ethyl acetate (3 x 20 ml) and dried over sodium sulfate. Evaporation of the solvent provides the crude hemiesters **9**-**21** which were purified by column chromatography with CH_2Cl_2/MeOH as eluent. The enantiomeric excesses for the stereoselective anhydride-opening were determined by HPLC analysis on the chiral column after conversion into the corresponding methyl-4-bromophenyl diesters **23a**-**d** (for **10a**, **10c**, **14a**, and **16a**), or directly from the hemiesters (for **10b**, **10d**, **10e**, **14b**, **16b**, and **18**-**22**). Absolute configuration was determined by comparing the specific rotation of **10a**, **10b**, **14a**, **14b**, **16a**, **16b**, and **18** with that of the literature data. For hemiesters **10c**-**e** and **20,** the configuration was assigned by analogy. The configuration of hemiester **10c** was also correlated in comparison to data from related compounds (2S,3R)-*endo*-3-(allyloxycarbonyl)bicyclo[2.2.1]hept-5-ene-2-carboxylic acid[7e] and (2*R*,3*S*)-3-*endo*-(allyloxycarbonyl)-bicyclo[2.2.1]hept-5-ene-2-*endo*-carboxylic acid[4c]. The configuration of hemiester **20** was tentatively determined by comparing the literature data.[7e]

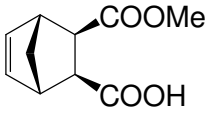
*Enantiomeric ratio determination of hemiesters **10a**, **10c**, **14a**, and **16a***[28]

A solution of hemiester **10a**, **10c**, **14a**, or **16a** (1 equiv.), 4-bromo-2-methylphenol (1 equiv.), 4-dimethylaminopyridine (0.25 equiv.), and dichloromethane were stirred 15 min at room temperature. Then, dicyclohexylcarbodiimide (1.1 equiv.) was added to the solution and stirred overnight. Subsequently, the urea was filtered and the solvent was removed under reduced pressure in a rotary evaporater. The residue was purified by chromatography on a silica gel column with CH_2Cl_2/MeOH (10:0.1) as eluent.



10a, **10c**, **14a**, **16a** → **23a-d**

3.4.3.1 (2*S*,3*R*)-*exo*-3-(Methoxycarbonyl)bicyclo[2.2.1]hept-5-ene-2-carboxylic acid 10a



Tab. 3.1 - entry 1:

Purification by chromatography on a silica gel column (CH_2Cl_2/MeOH = 10:1) gave **10a** as a white solid; yield: 0.164 g (83 %); $[\alpha]_D^{21}$=-0.56 (c=1.625, CH_2Cl_2) [lit.[4b] $[\alpha]_D^{20}$=-5.8, c=1.65, $CHCl_3$, 93 % *ee*]; 92 % *ee*; **HPLC**-analysis of the methyl-4-bromophenyl diester: (Chiralcel AD-H, *n*-Hept:*i*-PrOH 98:2, flow rate 0.5 mL/min, λ=254 nm), t_R=24.52 min (minor), 31.95 min (major); R_F=0.86 (eluent: CH_2Cl_2/MeOH (10:1)); **^{1}H-NMR** ($CDCl_3$, 400 MHz) δ = 1.34 (br d, *J*=8.6 Hz, 1 H), 1.49 (dt, *J*=8.7, 1.9 Hz, 1 H), 3.15 - 3.22 (m, 2 H), 3.26 - 3.39 (m, 2 H), 3.59 (s, 3 H), 6.22 (dd, *J*=5.6, 3.0 Hz, 1 H), 6.33 (dd, *J*=5.5, 3.1 Hz, 1 H) ppm; **^{13}C-NMR** ($CDCl_3$, 100 MHz) δ = 46.04, 46.59, 47.91, 48.22, 48.77, 51.50, 134.25, 135.61, 172.86, 178.09 ppm; **ESI-MS**: *m/z* = 219.2 $[M+Na]^+$.

Tab. 3.1 - entry 2:

Purification by chromatography on a silica gel column (CH_2Cl_2/MeOH = 10:1) gave **10a** as a white solid; yield: 0.108 g (55 %); 51 % *ee*; **HPLC**-analysis of the methyl-4-bromophenyl diester: (Chiralcel AD-H, *n*-Hept:*i*-PrOH 98:2, flow rate 0.5 mL/min, λ=254 nm), t_R=25.03 min, 33.85 min; R_F=0.62 (eluent: CH_2Cl_2/MeOH (10:1)); **^{1}H-NMR** ($CDCl_3$, 400 MHz) δ = 1.34 (br d, *J*=8.6 Hz, 1 H), 1.49 (dt, *J*=8.6, 2.0 Hz, 1 H), 3.18 (d, *J*=13.3 Hz, 2 H), 3.31 (qd, *J*=10.3, 3.1 Hz, 2 H), 3.59 (s, 3 H), 6.21 (dd, *J*=5.7, 3.0 Hz, 1 H), 6.32 (dd, *J*=5.5, 3.1 Hz, 1 H) ppm; **^{13}C-**

NMR ($CDCl_3$, 100 MHz) δ = 45.94, 46.45, 47.94, 48.11, 48.65, 51.40, 134.17, 135.46, 172.79, 178.69 ppm; **ESI-MS**: *m/z* = 219.2 $[M+Na]^+$.

Tab. 3.1 - entry 3:

Purification by chromatography on a silica gel column (CH_2Cl_2/MeOH = 10:1) gave **10a** as a white solid; yield: 0.130 g (66 %); 56 % *ee*; **HPLC**-analysis of the methyl-4-bromophenyl diester: (Chiralcel AD-H, *n*-Hept:*i*-PrOH 98:2, flow rate 0.5 mL/min, λ=254 nm), t_R=25.27 min, 33.96 min; R_F=0.64 (eluent: CH_2Cl_2/MeOH (10:1)); **^{1}H-NMR** ($CDCl_3$, 400 MHz) δ = 1.34 (d, *J*=8.6 Hz, 1 H), 1.49 (dt, *J*=8.7, 1.9 Hz, 1 H), 3.18 (d, *J*=13.3 Hz, 2 H), 3.31 (qd, *J*=10.2, 3.3 Hz, 2 H), 3.59 (s, 3 H), 6.21 (dd, *J*=5.5, 2.7 Hz, 1 H), 6.32 (dd, *J*=5.7, 2.9 Hz, 1 H) ppm; **^{13}C-NMR** ($CDCl_3$, 100 MHz) δ = 45.93, 46.45, 47.94, 48.11, 48.65, 51.40, 134.17, 135.45, 172.80, 178.66 ppm; **ESI-MS**: *m/z* = 219.2 $[M+Na]^+$.

Tab. 3.1 - entry 4:

Purification by chromatography on a silica gel column (CH_2Cl_2/MeOH = 10:1) gave **10a** as a white solid; yield: 0.163 g (83 %); $[\alpha]_D^{22}$=-0.36 (c=1.005, CH_2Cl_2) [lit.[4b] $[\alpha]_D^{20}$=-5.8, c=1.65, $CHCl_3$, 93 % *ee*]; 89 % *ee*; **HPLC**-analysis of the methyl-4-bromophenyl diester: (Chiralcel AD-H, *n*-Hept:*i*-PrOH 98:2, flow rate 0.5 mL/min, λ=254 nm), t_R=24.61 min (minor), 31.96 min (major); R_F=0.71 (eluent: CH_2Cl_2/MeOH (10:1)); **^{1}H-NMR** ($CDCl_3$, 400 MHz) δ = 1.34 (br d, *J*=8.6 Hz, 1 H), 1.49 (dt, *J*=8.8, 1.7 Hz, 1 H), 3.14 - 3.22 (m, 2 H), 3.25 - 3.37 (m, 2 H), 3.59 (s, 3 H), 6.22 (dd, *J*=5.5, 2.7 Hz, 1 H), 6.33 (dd, *J*=5.7, 2.9 Hz, 1 H) ppm; **^{13}C-NMR** ($CDCl_3$, 100 MHz) δ = 46.04, 46.57, 47.92, 48.21, 48.76, 51.50, 134.24, 135.61, 172.85, 178.17 ppm; **ESI-MS**: *m/z* = 219.3 $[M+Na]^+$.

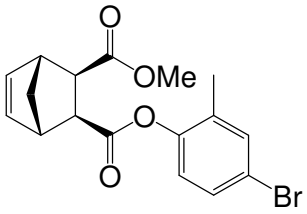
Tab. 3.1 - entry 5:

Purification by chromatography on a silica gel column (CH_2Cl_2/MeOH = 10:0.5) gave **10a** as a white solid; yield: 0.150 g (76 %); $[\alpha]_D^{22}$=-0.242 (c=1.075, CH_2Cl_2) [lit.[4b] $[\alpha]_D^{20}$=-5.8, c=1.65, $CHCl_3$, 93 % *ee*]; 33 % *ee*; **HPLC**-analysis of the methyl-4-bromophenyl diester: (Chiralcel AD-H, *n*-Hept:*i*-PrOH 98:2, flow rate 0.5 mL/min, λ=254 nm), t_R=23.85 min (major), 32.36 min (minor); R_F=0.74 (eluent: CH_2Cl_2/MeOH (10:1)); **^{1}H-NMR** ($CDCl_3$, 400 MHz) δ = 1.34 (br d, *J*=9.0 Hz, 1 H), 1.49 (dt, *J*=8.6, 2.0 Hz, 1 H), 3.18 (d, *J*=12.9 Hz, 2 H), 3.26 - 3.37 (m, 2 H), 3.60 (s, 3 H), 6.22 (dd, *J*=5.5, 2.7 Hz, 1 H), 6.33 (dd, *J*=5.7, 2.9 Hz, 1 H) ppm; **^{13}C-NMR** ($CDCl_3$, 100 MHz) δ = 46.07, 46.58, 47.84, 48.21, 48.77, 51.52, 134.29, 135.58, 172.87, 177.54 ppm; **ESI-MS**: *m/z* = 219.2 $[M+Na]^+$.

Tab. 3.1 - entry 6:

Purification by chromatography on a silica gel column (CH_2Cl_2/MeOH = 10:0.5) gave **10a** as a white solid; yield: 0.147 g (75 %); $[\alpha]_D^{22}$ =-0.868 (c=1.060, CH_2Cl_2) [lit.[4b] $[\alpha]_D^{20}$ =-5.8, c=1.65, $CHCl_3$, 93 % *ee*]; 84 % *ee*; **HPLC**-analysis of the methyl-4-bromophenyl diester: (Chiralcel AD-H, *n*-Hept:*i*-PrOH 98:2, flow rate 0.5 mL/min, λ=254 nm), t_R=24.14 min (minor), 32.19 min (major); R_F=0.74 (eluent: CH_2Cl_2/MeOH (10:1)); **^{1}H-NMR** ($CDCl_3$, 400 MHz) δ = 1.34 (br d, *J*=8.6 Hz, 1 H), 1.49 (dt, *J*=8.6, 1.8 Hz, 1 H), 3.18 (d, *J*=13.7 Hz, 2 H), 3.25 - 3.37 (m, 2 H), 3.59 (s, 3 H), 6.22 (dd, *J*=5.5, 2.7 Hz, 1 H), 6.33 (dd, *J*=5.7, 2.9 Hz, 1 H) ppm; **^{13}C-NMR** ($CDCl_3$, 100 MHz) δ = 46.05, 46.58, 47.91, 48.22, 48.77, 51.50, 134.27, 135.61, 172.86, 178.09 ppm; **ESI-MS**: *m/z* = 219.4 $[M+Na]^+$.

3.4.3.2 (2*S*,3*R*)-*exo*-2-(4-Bromo-2-methylphenyl) 3-methyl bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylate 23a



Tab. 3.1 - entry 1:

Purification by chromatography on a silica gel column (CH_2Cl_2/MeOH = 10:0.1) gave **23a** as a white solid; yield: 0.063 g (30 %); **^{1}H-NMR** ($CDCl_3$, 400 MHz) δ = 1.42 (d, *J*=8.6 Hz, 1 H), 1.54 - 1.58 (m, 1 H), 2.16 (s, 3 H), 3.24 (br s, 1 H), 3.32 (br s, 1 H), 3.43 (dd, *J*=10.2, 3.5 Hz, 1 H), 3.54 (dd, *J*=10.2, 3.5 Hz, 1 H), 3.62 (s, 3 H), 6.29 - 6.34 (m, 2 H), 6.95 (d, *J*=8.6 Hz, 1 H), 7.26 - 7.29 (m, 1 H), 7.33 - 7.34 (m, 1 H) ppm; **^{13}C-NMR** ($CDCl_3$, 100 MHz) δ = 16.08, 46.45, 46.51, 47.93, 48.24, 48.76, 50.20, 51.70, 123.69, 129.74, 132.26, 133.59, 134.73, 135.28, 148.43, 170.47, 172.60 ppm; **ESI-MS**: *m/z* = 386.9 $[M+Na]^+$.

Tab. 3.1 - entry 2:

Purification by chromatography on a silica gel column (CH_2Cl_2/MeOH = 10:0.1) gave **23a** as a white solid; yield: 0.093 g (51 %); **^{1}H-NMR** ($CDCl_3$, 400 MHz) δ = 1.42 (d, *J*=8.6 Hz, 1 H), 1.52 - 1.59 (m, 1 H), 2.15 - 2.18 (m, 3 H), 3.24 (br s, 1 H), 3.32 (br s, 1 H), 3.43 (dd, *J*=10.2, 3.12 Hz, 1 H), 3.54 (dd, *J*=10.2, 3.1 Hz, 1 H), 3.62 (s, 3 H), 6.29 - 6.35 (m, 2 H), 6.95 (d, *J*=8.6 Hz, 1 H), 7.26 - 7.30 (m, 1 H), 7.33 - 7.35 (m, 1 H) ppm; **ESI-MS**: *m/z* = 386.9 $[M+Na]^+$.

Tab. 3.1 - entry 3:

Purification by chromatography on a silica gel column (CH_2Cl_2/MeOH = 10:0.1) gave **23a** as a white solid; yield: 0.080 g (42 %); **^{1}H-NMR** ($CDCl_3$, 400 MHz) δ = 1.42 (d, *J*=9.0 Hz, 1 H),

1.54 - 1.58 (m, 1 H), 2.16 (s, 3 H), 3.24 (br s, 1 H), 3.32 (br s, 1 H), 3.43 (dd, *J*=10.2, 3.5 Hz, 1 H), 3.54 (dd, *J*=10.2, 3.5 Hz, 1 H), 3.62 (s, 3 H), 6.29 - 6.34 (m, 2 H), 6.95 (d, *J*=8.6 Hz, 1 H), 7.26 - 7.29 (m, 1 H), 7.34 (d, *J*=2.3 Hz, 1 H) ppm; **ESI-MS**: *m/z* = 386.9 $[M+Na]^+$.

Tab. 3.1 - entry 4:

Purification by chromatography on a silica gel column (CH_2Cl_2/MeOH = 10:0.1) gave **23a** as a white solid; yield: 0.079 g (32 %); **^{1}H-NMR** ($CDCl_3$, 400 MHz) δ = 1.42 (d, *J*=8.6 Hz, 1 H), 1.54 - 1.58 (m, 1 H), 2.16 (s, 3 H), 3.24 (br s, 1 H), 3.32 (br s, 1 H), 3.43 (dd, *J*=10.2, 3.5 Hz, 1 H), 3.54 (dd, *J*=10.2, 3.5 Hz, 1 H), 3.62 (s, 3 H), 6.30 - 6.34 (m, 2 H), 6.95 (d, *J*=8.6 Hz, 1 H), 7.24 - 7.30 (m, 1 H), 7.33 - 7.34 (m, 1 H) ppm; **^{13}C-NMR** ($CDCl_3$, 100 MHz) δ = 16.08, 46.45, 46.51, 47.92, 48.24, 48.75, 51.70, 123.69, 129.73, 132.26, 133.58, 134.73, 135.27, 148.42, 170.46, 172.60 ppm; **ESI-MS**: *m/z* = 387.2 $[M+Na]^+$.

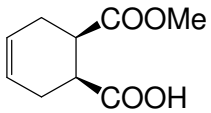
Tab. 3.1 - entry 5:

Purification by chromatography on a silica gel column (CH_2Cl_2/MeOH = 10:0.1) gave **23a** as a white solid; yield: 0.079 g (45 %); **^{1}H-NMR** ($CDCl_3$, 400 MHz) δ = 1.42 (d, *J*=8.6 Hz, 1 H), 1.51 - 1.61 (m, 1 H), 2.16 (s, 3 H), 3.24 (br s, 1 H), 3.32 (br s, 1 H), 3.40 - 3.44 (m, 1 H), 3.51 - 3.56 (m, 1 H), 3.62 (s, 3 H), 6.27 - 6.35 (m, 2 H), 6.96 (dd, *J*=8.6, 4.7 Hz, 1 H), 7.26 - 7.29 (m, 1 H), 7.33 - 7.35 (m, 1 H) ppm; **ESI-MS**: *m/z* = 387.2 $[M+Na]^+$.

Tab. 3.1 - entry 6:

Purification by chromatography on a silica gel column (CH_2Cl_2/MeOH = 10:0.1) gave **23a** as a white solid; yield: 0.013 g (37 %); **^{1}H-NMR** ($CDCl_3$, 400 MHz) δ = 1.42 (d, *J*=8.6 Hz, 1 H), 1.52 - 1.59 (m, 1 H), 2.16 (s, 3 H), 3.24 (br s, 1 H), 3.32 (br s, 1 H), 3.43 (dd, *J*=10.0, 3.3 Hz, 1 H), 3.51 - 3.57 (m, 1 H), 3.62 (s, 3 H), 6.32 (ddt, *J*=9.1, 5.7, 2.9, 2.9 Hz, 2 H), 6.95 (d, *J*=8.6 Hz, 1 H), 7.25 - 7.29 (m, 1 H), 7.33 - 7.35 (m, 1 H) ppm; **ESI-MS**: *m/z* = 387.2 $[M+Na]^+$.

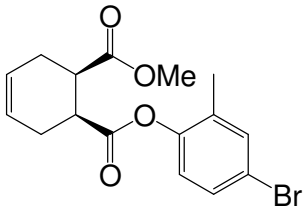
3.4.3.3 (2*S*,3*R*)-*cis*-2-(Methoxycarbonyl)-cyclohex-4-ene-1-carboxylic acid 14a



Purification by chromatography on a silica gel column (CH_2Cl_2/MeOH = 10:1) gave **14a** as a colorless oil; yield: 0.152 g (82 %); $[\alpha]_D^{21}$ =-0.456 (c=0.965, CH_2Cl_2) [lit.[4b] $[\alpha]_D^{20}$ =-10.3, c=1.32, acetone, 93 % *ee*]; 84 % *ee*; **HPLC**-analysis of the methyl-4-bromophenyl diester: (Chiralcel AS-H, *n*-Hept:*i*-PrOH 80:20, flow rate 0.5 mL/min, λ=254 nm), t_R=10.30 min (minor), 13.53 min (major); R_F=0.63 (eluent: CH_2Cl_2/MeOH (10:1)); **^{1}H-NMR** ($CDCl_3$, 400 MHz) δ = 2.33 - 2.42 (m, 2 H), 2.54 - 2.63 (m, 2 H), 3.04 - 3.11 (m, 2 H), 3.70 (s, 3 H), 5.68 (t, *J*=1.6 Hz, 2 H)

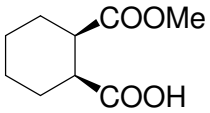
ppm; **^{13}C-NMR** ($CDCl_3$, 100 MHz) δ = 25.52, 25.69, 39.42, 39.54, 51.93, 125.02, 125.15, 173.67, 179.50 ppm; **ESI-MS**: *m/z* = 207.0 $[M+Na]^+$.

3.4.3.4 (1*R*,2*S*)-1-(4-Bromo-2-methylphenyl) 2-methyl cyclohex-4-ene-1,2-dicarboxylate 23b



Purification by chromatography on a silica gel column (CH_2Cl_2/MeOH = 10:0.1) gave **23b** as a colorless oil; yield: 0.104 g (47%); **^{1}H-NMR** ($CDCl_3$, 400 MHz) δ = 2.15 (s, 3 H), 2.41 - 2.55 (m, 2 H), 2.63 - 2.75 (m, 2 H), 3.16 - 3.22 (m, 1 H), 3.29 - 3.34 (m, 1 H), 3.71 (s, 3 H), 5.30 (s, 1 H,) 5.74 (t, *J*=1.6 Hz, 1 H), 6.88 (d, *J*=8.4 Hz, 1 H), 7.30 (dd, *J*=8.6, 2.3 Hz, 1 H), 7.35 - 7.37 (m, 1 H) ppm; **ESI-MS**: *m/z* = 375.1 $[M+Na]^+$.

3.4.3.5 (1*S*,2*R*)-*cis*-2-(Methoxycarbonyl)cyclohexanecarboxylic acid 16a



Tab. 3.2 - entry 2:

Purification by chromatography on a silica gel column (CH_2Cl_2/MeOH = 10:1) gave **16a** as a colorless oil; yield: 0.156 g (84 %); $[\alpha]_D^{21}$=-0.452 (c=1.000, CH_2Cl_2) [lit.[4b] $[\alpha]_D^{20}$=-4.2, c=0.98, $CHCl_3$, 93 % *ee*]; 88 % *ee*; **HPLC**-analysis of the methyl-4-bromophenyl diester: (Chiralcel AS-H, *n*-Hept:*i*-PrOH 80:20, flow rate 0.5 mL/min, λ=254 nm), t_R=12.53 min (minor), 14.18 min (major); R_F=0.78 (eluent: CH_2Cl_2/MeOH (10:1)); **^{1}H-NMR** ($CDCl_3$, 400 MHz) δ = 1.37 - 1.60 (m, 4 H), 1.79 (m, 2 H), 1.98 - 2.07 (m, 2 H), 2.82 - 2.88 (m, 2 H), 3.68 (s, 3 H) ppm; **^{13}C-NMR** ($CDCl_3$, 100 MHz) δ = 23.63, 23.74, 25.98, 26.27, 42.36, 42.46, 51.71, 174.06, 179.43 ppm; **ESI-MS**: *m/z* = 209.1 $[M+Na]^+$.

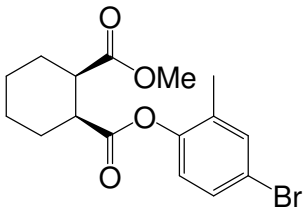
Tab. 3.2 - entry 3:

Purification by chromatography on a silica gel column (CH_2Cl_2/MeOH = 10:1) gave **16a** as a colorless oil; yield: 0.150 g (80 %); 57 % *ee*; **HPLC**-analysis of the methyl-4-bromophenyl diester: (Chiralcel AS-H, *n*-Hept:*i*-PrOH 80:20, flow rate 0.5 mL/min, λ=254 nm), t_R=12.03 min, 13.73 min; R_F=0.73 (eluent: CH_2Cl_2/MeOH (10:1)); **^{1}H-NMR** ($CDCl_3$, 400 MHz) δ = 1.37 - 1.59 (m, 4 H), 1.73 - 1.83 (m, 2 H), 1.97 - 2.07 (m, 2 H), 2.85 (br s, 2 H), 3.69 (s, 3 H) ppm; **^{13}C-NMR** ($CDCl_3$, 100 MHz) δ = 23.62, 23.73, 25.96, 26.24, 42.33, 42.44, 51.72, 174.07, 179.49 ppm; **ESI-MS**: *m/z* = 209.1 $[M+Na]^+$.

Tab. 3.2 - entry 4:

Purification by chromatography on a silica gel column (CH_2Cl_2/MeOH = 10:1) gave **16a** as a colorless oil; yield: 0.1569 g (86 %); $[\alpha]_D^{21}$=-0.291 (c=1.170, CH_2Cl_2) [lit.[4b] $[\alpha]_D^{20}$=-4.2, c=0.98, $CHCl_3$, 93 % *ee*]; 87 % *ee*; **HPLC**-analysis of the methyl-4-bromophenyl diester: (Chiralcel AS-H, *n*-Hept:*i*-PrOH 80:20, flow rate 0.5 mL/min, λ=254 nm), t_R=12.29 min (minor), 13.88 min (major); R_F=0.75 (eluent: CH_2Cl_2/MeOH (10:1)); **^{1}H-NMR** ($CDCl_3$, 400 MHz) δ = 1.37 - 1.60 (m, 4 H), 1.79 (m, 2 H), 1.97 - 2.08 (m, 2 H), 2.85 (br s, 2 H), 3.68 (s, 3 H), 7.27 (s, 3 H) ppm; **^{13}C-NMR** ($CDCl_3$, 100 MHz) δ = 23.62, 23.73, 25.96, 26.24, 42.33, 42.46, 51.73, 174.07, 179.65 ppm; **ESI-MS**: *m/z* = 209.1 $[M+Na]^+$.

3.4.3.6 (1*S*,2*R*)-1-(4-Bromo-2-methylphenyl) 2-methyl cyclohexane-1,2-dicarboxylate 23c



Tab. 3.2 - entry 2:

Purification by chromatography on a silica gel column (CH_2Cl_2/MeOH = 10:0.1) gave **23c** as a colorless oil; yield: 0.130 g (54 %); **^{1}H-NMR** ($CDCl_3$, 400 MHz) δ = 1.24 - 1.35 (m, 2 H), 1.45 - 1.65 (m, 2 H), 1.78 - 1.88 (m, 2 H), 1.90 - 1.96 (m, 2 H), 2.16 (s, 3 H), 2.94 - 3.02 (m, 1 H), 3.05 - 3.09 (m, 1 H), 3.70 (s, 3 H), 6.88 (d, *J*=8.6 Hz, 1 H), 7.28 - 7.32 (m, 1 H), 7.35 - 7.36 (m, 1 H) ppm; **ESI-MS**: *m/z* = 379.5 $[M+Na]^+$.

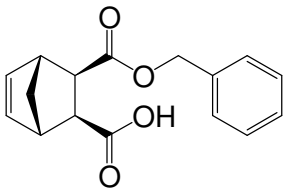
Tab. 3.2 - entry 3:

Purification by chromatography on a silica gel column (CH_2Cl_2/MeOH = 10:0.1) gave **23c** as a colorless oil; yield: 0.103 g (48 %); **^{1}H-NMR** ($CDCl_3$, 400 MHz) δ = 1.23 - 1.37 (m, 2 H), 1.43 - 1.67 (m, 2 H), 1.78 - 1.88 (m, 2 H), 1.89 - 1.98 (m, 2 H), 2.16 (s, 3 H), 2.93 - 3.02 (m, 1 H), 3.03 - 3.12 (m, 1 H), 3.70 (s, 3 H), 6.88 (d, *J*=8.4 Hz, 1 H), 7.28 - 7.32 (m, 1 H), 7.35 - 7.37 (m, 1 H) ppm; **ESI-MS**: *m/z* = 379.5 $[M+Na]^+$.

Tab. 3.2 - entry 4:

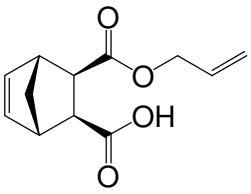
Purification by chromatography on a silica gel column (CH_2Cl_2/MeOH = 10:0.1) gave **23c** as a colorless oil; yield: 0.099 g (43 %); **^{1}H-NMR** ($CDCl_3$, 400 MHz) δ = 1.16 - 1.38 (m, 2 H), 1.43 - 1.67 (m, 2 H), 1.78 - 1.88 (m, 2 H), 1.89 - 2.00 (m, 2 H), 2.16 (s, 3 H), 2.95 - 3.01 (m, 1 H), 3.04 - 3.10 (m, 1 H), 3.70 (s, 3 H), 6.88 (d, *J*=8.6 Hz, 1 H), 7.28 - 7.32 (m, 1 H), 7.35 - 7.38 (m, 1 H) ppm; **ESI-MS**: *m/z* = 379.5 $[M+Na]^+$.

3.4.3.7 (2*S*,3*R*)-*exo*-3-(Benzyloxycarbonyl)bicyclo[2.2.1]hept-5-ene-2-carboxylic acid 10b



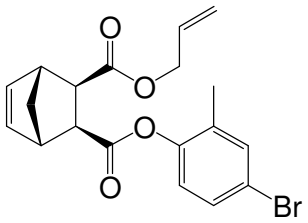
Purification by chromatography on a silica gel column (CH_2Cl_2/MeOH = 10:0.2) gave **10b** as a white solid; yield: 0.192 g (70 %); $[\alpha]_D^{22}$ =+5.6 (c=1.215, CH_2Cl_2) [lit.[4c] $[\alpha]_D^{25}$ =+21.6 (*c*=1.000, $CHCl_3$, 92 % *ee*)]; 93 % *ee*; **HPLC**: (Chiralcel AD-H, *n*-Hept:*i*-PrOH 85:15, flow rate 0.5 mL/min, λ=254 nm), t_R=16.73 min (major), 20.65 min (minor); R_F=0.7 (eluent: CH_2Cl_2/MeOH (10:1)); **^{1}H-NMR** ($CDCl_3$, 400 MHz) δ = 1.33 (d, *J*=8.6 Hz, 1 H), 1.48 (dt, *J*=8.6, 1.8 Hz, 1 H), 3.17 - 3.20 (m, 2 H), 3.32 - 3.33 (m, 2 H), 4.92 (d, *J*=11.7, 1 H), 5.09 (d, *J*=12.1 Hz, 1 H), 6.22 (dd, *J*=5.7, 2.9 Hz, 1 H), 6.29 (dd, *J*=5.5, 3.1 Hz, 1 H), 7.26 - 7.36 (m, 5 H) ppm; **^{13}C-NMR** ($CDCl_3$, 100 MHz) δ = 46.14, 46.59, 48.06, 48.29, 48.73, 66.40, 128.08, 128.30 (2 CH), 128.45 (2 CH), 134.37, 135.32, 172.21, 178.34 ppm; **ESI-MS**: *m/z* = 295.2 $[M+Na]^+$.

3.4.3.8 (2*S**,3*R**)-*exo*-3-(Allyloxycarbonyl)bicyclo[2.2.1]hept-5-ene-2-carboxylic acid 10c



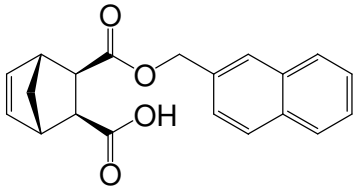
Purification by chromatography on a silica gel column (CH_2Cl_2/MeOH = 10:0.5) gave **10c** as a white solid; yield: 0.139 g (62 %); $[\alpha]_D^{22}$ =-0.8 (c=1.155, CH_2Cl_2); 91 % *ee*; **HPLC**-analysis of the methyl-4-bromophenyl diester: (Chiralcel AD-H, *n*-Hept:*i*-PrOH 98:2, flow rate 0.5 mL/min, λ=254 nm), t_R=24.45 min (minor), 28.53 min (major); R_F=0.79 (eluent: CH_2Cl_2/MeOH (10:1)); **^{1}H-NMR** ($CDCl_3$, 400 MHz) δ = 1.34 (d, *J*=8.6 Hz, 1 H), 1.49 (dt, *J*=8.6, 2 Hz, 1 H), 3.17 - 3.21 (m, 2 H), 3.25 - 3.39 (m, 2 H), 4.48 (ddt, *J*=13.3, 5.9, 1.0 Hz, 1 H), 4.54 (ddt, *J*=13.3, 5.9, 1.0 Hz, 1 H), 5.21 (dq, *J*=10.5, 1.0 Hz, 1 H), 5.29 (dq, *J*=17.3, 1.4 Hz, 1 H), 5.79 - 5.94 (m, 1 H), 6.22 (dd, *J*=5.5, 2.7 Hz, 1 H), 6.32 (dd, *J*=5.7, 2.9 Hz, 1 H) ppm; **^{13}C-NMR** ($CDCl_3$, 100 MHz) δ = 46.10, 46.58, 48.02, 48.30, 48.76, 65.25, 118.28, 132.18, 134.34, 135.53, 172.05, 178.23 ppm; **ESI-MS**: *m/z* = 245.2 $[M+Na]^+$.

3.4.3.9 (2*S**,3*R**)-*exo*-2-Allyl-3-(4-bromo-2-methylphenyl) bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylate 23d



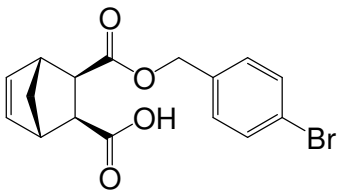
Purification by chromatography on a silica gel column (CH_2Cl_2/MeOH = 10:0.1) gave **23d** as a white solid; yield: 0.049 g (28 %); **^{1}H-NMR** ($CDCl_3$, 400 MHz) δ = 1.42 (d, *J*=8.6 Hz, 1 H), 1.50 - 1.60 (m, 1 H), 2.15 (s, 3 H), 3.26 (br s, 1 H), 3.32 (br s, 1 H), 3.46 (dd, *J*=10.2, 3.5 Hz, 1 H), 3.55 (dd, *J*=10.0, 3.3 Hz, 1 H), 4.43 - 4.60 (m, 2 H), 5.16 - 5.32 (m, 2 H), 5.81 - 5.92 (m, 1 H), 6.26 - 6.36 (m, 2 H), 6.95 (d, *J*=8.6 Hz, 1 H), 7.23 - 7.37 (m, 2 H) ppm; **ESI-MS**: *m/z* = 413.4 $[M+Na]^+$.

3.4.3.10 (2*S**,3*R**)-*exo*-3-(Naphthyloxycarbonyl)bicyclo[2.2.1]hept-5-ene-2-carboxylic acid 10d



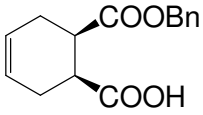
Purification by chromatography on a silica gel column (CH_2Cl_2/MeOH = 10:0.5) gave **10d** as a white solid; yield: 0.147 g (46 %); $[\alpha]_D^{20}$ =-11.6 (c=1.180, CH_2Cl_2); 88 % *ee*; **HPLC**: (Chiralcel AD-H, *n*-Hept:*i*-PrOH 85:15, flow rate 0.5 mL/min, λ=254 nm), t_R=25.86 min (major), 33.03 min (minor); R_F=0.63 (eluent: CH_2Cl_2/MeOH (10:0.5)); **^{1}H-NMR** ($CDCl_3$, 400 MHz) δ = 1.32 (d, *J*=8.5 Hz, 1 H), 1.48 (d, *J*=8.8 Hz, 1 H), 3.17 (d, *J*=8.8 Hz, 2 H), 3.31 (ddd, *J*=22.6, 10.0, 3.5 Hz, 2 H), 5.08 (br d, *J*=12.3 Hz, 1 H), 5.24 (d, *J*=12.6 Hz, 1 H), 6.26 (dq, *J*=24.3, 2.9 Hz, 1 H), 7.36 - 7.49 (m, 5 H), 7.71 - 7.84 (m, 2 H) ppm; **^{13}C-NMR** ($CDCl_3$, 100 MHz) δ = 46.18, 46.54, 48.05, 48.35, 48.74, 66.51, 125.96, 126.11, 126.14, 127.31, 127.64, 127.98, 128.25, 133.01, 133.12, 133.31, 134.42, 135.50, 172.26, 178.37 ppm; **ESI-MS**: *m/z* = 345.1 $[M+Na]^+$.

3.4.3.11 (2*S**,3*R**)-*exo*-3-((4-Bromobenzyloxy)carbonyl)bicyclo[2.2.1]hept-5-ene-2-carboxylic acid 10e



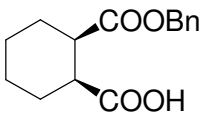
Purification by chromatography on a silica gel column (CH_2Cl_2/MeOH = 10:0.5) gave **10e** as a colorless oil; yield: 0.142 g (41 %); $[\alpha]_D^{20}$ =-3.1 (c=1.185, CH_2Cl_2); 90 % *ee*; **HPLC**: (Chiralcel AD-H, *n*-Hept:*i*-PrOH 90:10, flow rate 0.5 mL/min, λ=254 nm), t_R=26.95 min (major), 32.19 min (minor); R_F=0.5 (eluent: CH_2Cl_2/MeOH (10:0.5)); **^{1}H-NMR** ($CDCl_3$, 400 MHz) δ = 1.34 (d, *J*=8.6 Hz, 1 H), 1.50 (dt, *J*=8.7, 1.9 Hz, 1 H), 3.19 (d, *J*=10.2 Hz, 2 H), 3.36 (s, 2 H) 4.90 (d, *J*=12.1 Hz, 1 H), 5.03 (d, *J*=12.5 Hz, 1 H), 6.21 (dd, *J*=5.7, 2.9 Hz, 1 H), 6.28 (dd, *J*=5.5, 3.1 Hz, 1 H), 7.12 - 7.21 (m, 2 H), 7.44 - 7.48 (m, 2 H) ppm; **^{13}C-NMR** ($CDCl_3$, 100 MHz) δ = 46.18, 46.61, 48.09, 48.26, 48.80, 66.58, 122.15, 130.01 (2 CH), 131.62 (2 CH), 134.44, 134.89, 135.52, 172.14, 178.32 ppm; **ESI-MS**: *m/z* = 351.2 $[M+H]^-$.

3.4.3.12 (1*S*,2*R*)-*cis*-2-Benzyloxycarbonyl-cyclohexane-1-carboxylic acid 14b



Purification by chromatography on a silica gel column (CH_2Cl_2/MeOH = 10:0.1) gave **14b** as a colorless oil; yield: 0.188 g (72 %); $[\alpha]_D^{20}$ =-2.3 (c=0.89, CH_2Cl_2) [lit.[4c] $[\alpha]_D^{25}$ =-2.8 (*c*=1.09, $CHCl_3$, 93 % *ee*)]; 95 % *ee*; **HPLC**: (Chiralcel AD-H, *n*-Hept:*i*-PrOH 90:10, flow rate 0.5 mL/min, λ=254 nm), t_R=16.77 min (major), 25.81 min (minor); R_F=0.84 (eluent: CH_2Cl_2/MeOH (10:0.5)); **^{1}H-NMR** ($CDCl_3$, 400 MHz) δ = 1.33 - 1.61 (m, 4 H), 1.76 - 1.82 (m, 2 H), 2.01 - 2.07 (m, 2 H), 2.86 - 2.90 (m, 2 H), 5.12 (q, *J*=12.5 Hz, 2 H), 7.26 - 7.34 (m, 5 H) ppm; **^{13}C-NMR** ($CDCl_3$, 100 MHz) δ = 23.63, 23.69, 26.01, 26.20, 42.40, 42.45, 66.30, 128.03 (2 CH), 128.06, 128.46 (2 CH), 135.97, 173.37, 179.90 ppm; **ESI-MS**: *m/z* = 285.2 $[M+Na]^+$.

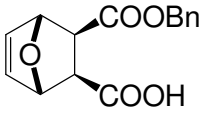
3.4.3.13 (1*S*,2*R*)-*cis*-2-Benzyloxycarbonyl-cyclohex-4-ene-1-carboxylic acid 16b



Purification by chromatography on a silica gel column (CH_2Cl_2/MeOH = 10:0.1) gave **16b** as a colorless oil; yield: 0.203 g (78 %); $[\alpha]_D^{21}$ =-0.5 (c=1.12, CH_2Cl_2) [lit.[4c] $[\alpha]_D^{25}$ =-12.1 (*c*=1.00, MeOH, 95 % *ee*)]; 90 % *ee*; **HPLC**: (Chiralcel AD-H, *n*-Hept:*i*-PrOH 90:10, flow rate 0.5 mL/min, λ=254 nm), t_R=19.83 min (major), 22.61 min (minor); R_F=0.78 (eluent: CH_2Cl_2/MeOH

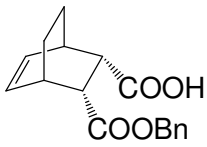
(10:0.5)); **^{1}H-NMR** ($CDCl_3$, 400 MHz) δ = 2.31 - 2.45 (m, 2 H), 2.52 - 2.68 (m, 2 H), 3.06 - 3.14 (m, 2 H), 5.14 (dd, *J*=16.1, 12.6 Hz, 2 H), 5.69 (br s, 2 H), 7.25 - 7.37 (m, 5 H) ppm; **^{13}C-NMR** ($CDCl_3$, 100 MHz) δ = 25.56, 25.69, 39.52, 39.54, 66.53, 125.03, 125.16, 128.00 (2 CH), 128.09, 128.45 (2 CH), 135.77, 172.97, 179.45 ppm; **ESI-MS**: *m/z* = 283.6 $[M+Na]^+$.

3.4.3.14 (2*R*,3*S*)-3-*exo*-Benzyloxycarbonyl-7-oxabicyclo-[2.2.1]hept-5-ene-2-*exo*-carboxylic acid 18



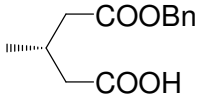
Purification by chromatography on a silica gel column (CH_2Cl_2/MeOH = 10:0.1) gave **18** as a white solid; yield: 0.103 g (38 %); $[\alpha]_D^{21}$ =+10.84 (c=1.105, CH_2Cl_2) [lit.[4c] $[\alpha]_D^{25}$ =+29.8 (*c*=1.00, MeOH, 94 % *ee*)]; 82 % *ee*; **HPLC**: (Chiralcel AD-H, *n*-Hept:*i*-PrOH 70:30, flow rate 0.5 mL/min, λ=254 nm), t_R=15.02 min (major), 18.02 min (minor); R_F=0.73 (eluent: CH_2Cl_2/MeOH (10:1)); **^{1}H-NMR** ($CDCl_3$, 400 MHz) δ = 2.84 (s, 2 H), 5.07 (d, *J*=12.1 Hz, 1 H), 5.17 (d, *J*=12.5 Hz, 1 H), 5.28 (d, *J*=11.7 Hz, 2 H), 6.43 - 6.47 (m, 2 H), 7.30 - 7.38 (m, 5 H) ppm; **^{13}C-NMR** ($CDCl_3$, 100 MHz) δ = 46.86, 47.03, 67.06, 80.25, 80.68, 128.20, 128.36 (2 CH), 128.47 (2 CH), 135.48, 136.44, 136.54, 171.79, 174.18 ppm; **ESI-MS**: *m/z* = 297.0 $[M+Na]^+$.

3.4.3.15 (2*S**,3*R**)-*endo*-3-(Benzyloxycarbonyl)bicyclo[2.2.2]oct-5-ene-2-carboxylic acid 20



Purification by chromatography on a silica gel column (CH_2Cl_2/MeOH = 10:0.2) gave **20** as a white solid; yield: 0.102 g (36 %); $[\alpha]_D^{21}$ =-1.17 (c=0.985, CH_2Cl_2); 66 % *ee*; **HPLC**: (Chiralcel AD-H, *n*-Hept:*i*-PrOH 90:10, flow rate 0.5 mL/min, λ=254 nm), t_R=18.79 min (major), 27.45 min (minor); R_F=0.61 (eluent: CH_2Cl_2/MeOH (10:0.5)); **^{1}H-NMR** ($CDCl_3$, 400 MHz) δ = 1.28 - 1.37 (m, 2 H), 1.49 - 1.60 (m, 2 H), 2.92 (br s, 2 H), 3.03 (s, 2 H), 4.90 (dd, *J*=12.1, 4.3 Hz, 1 H), 5.08 (d, *J*=12.1 Hz, 1 H), 6.28 (ddd, *J*=7.9, 6.5, 1.2 Hz, 1 H), 6.34 (ddd, *J*=8.1, 6.5, 1.4 Hz, 1 H), 7.28 - 7.35 (m, 5 H) ppm; **^{13}C-NMR** ($CDCl_3$, 100 MHz) δ = 24.39, 24.53, 32.20, 32.62, 47.38, 47.45, 66.38, 128.08, 128.27 (2 CH), 128.47 (2 CH), 131.92, 132.75, 135.89, 172.67, 178.65 ppm; **ESI-MS**: *m/z* = 309.3 $[M+Na]^+$.

3.4.3.16 (*R*)-3-Methyl-pentanedioic acid monobenzyl ester 22



Purification by chromatography on a silica gel column (CH_2Cl_2/MeOH = 10:0.1) gave **22** as a colorless oil; yield: 0.105 g (45 %); $[\alpha]_D^{21}$=-2.92 (c=1.22, CH_2Cl_2) [lit.[29] $[\alpha]_D^{23}$=-3.6 (*c*=0.43, $CHCl_3$, 88 % *ee*)]; 64 % *ee*; **HPLC**: (Chiralcel AS-H, *n*-Hept:*i*-PrOH 90:10, flow rate 0.5 mL/min, λ=254 nm), t_R=23.67 min (minor), 26.85 min (major); R_F=0.58 (eluent: CH_2Cl_2/MeOH (10:0.5)); **^{1}H-NMR** ($CDCl_3$, 400 MHz) δ = 1.04 (d, *J*=6.25 Hz, 3 H) 2.13 - 2.36 (m, 2 H) 2.41 - 2.52 (m, 3 H) 5.12 (s, 2 H) 7.30 - 7.38 (m, 5 H) ppm; **^{13}C-NMR** ($CDCl_3$, 100 MHz) δ = 19.80, 27.20, 40.48, 40.68, 66.30, 128.26 (2 CH), 128.27, 128.58 (2 CH), 135.84, 172.17, 178.57 ppm; **ESI-MS**: *m/z* = 259.1 $[M+Na]^+$.

3.5 References

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Chapter 4

Utilizing the Special Reactivity of *β*-Amino Alcohols in Macrocyclic Antibiotics for Regioselective Acylation

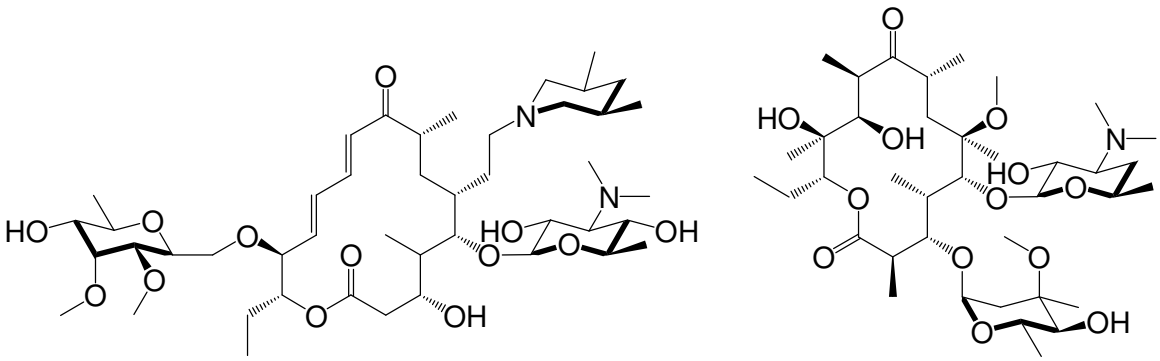
Abstract [*] ***:***

Several ester derivatives of tilmicosin and clarithromycin were synthesized, in which the hydroxyl group adjacent to the nitrogen atom is easily acylated. Some of these derivatives were investigated with respect to their antibacterial activity compared to the parent compounds tilmicosin and clarithromycin.

[*] Part of this Chapter will be published: K. Brand, L. A. Wessjohann, R. Heinke, S. Stark, Utilizing the Special Reactivity of *β*-Amino Alcohols in Macrocyclic Antibiotics for Regioselective Acylation, *manuscript in preparation*.

4.1 Introduction

As already described in the previous chapters, *β*-amino alcohols show a high catalytic ability with respect to the acylation of activated esters or anhydrides. Because the *β*-amino alcohol moiety occurs in many biologically active compounds, their properties can be used for a neighboring group assisted protection/deprotection strategy in organic synthesis. For example, many studies discuss the selective acylation of the macrolide antibiotic erythromycin.[1] In 2008, Wessjohann and Zhu reported on the selective self-autocatalyzed acylation-deacylation of some macrocyclic antibiotics, e.g. desmycosin and erythromycin.[2] Following up on these results, the regioselective acylation of tilmicosin **1** and clarithromycin **2** should be studied (Figure 4.1). Tilmicosin **1** and clarithromycin **2** belong to the antibiotic class of macrolides which are characterized by a macrocyclic lactone ring decorated with sugar side chains. They are applied for the treatment of bacterial infectious diseases. Their mechanism of action is based on the inhibition of protein synthesis by binding to the bacterial ribosomes.[3]



1 **2**

Figure 4.1: The macrocyclic antibiotics tilmicosin **1** and clartithromycin **2**

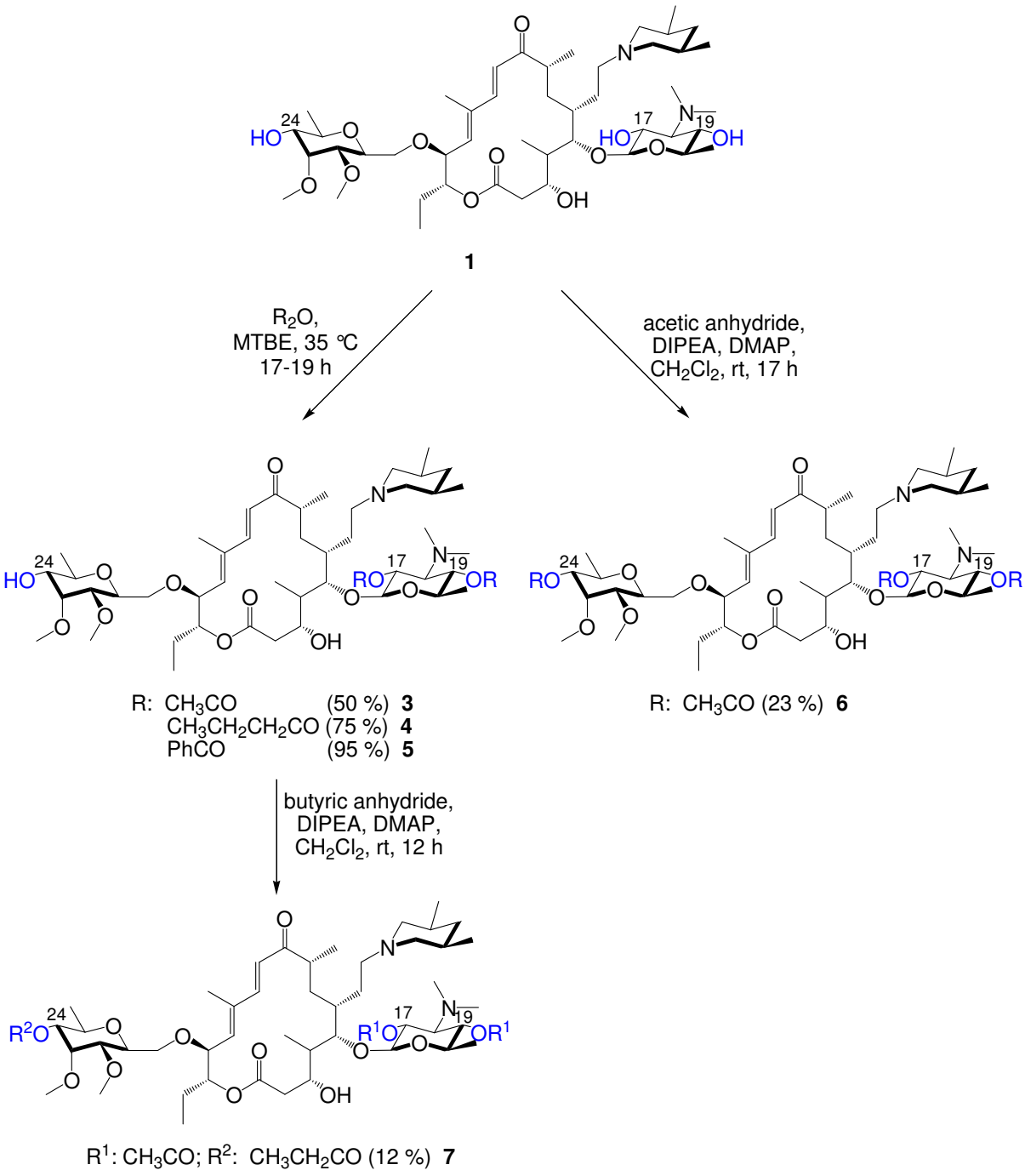
Tilmicosin **1** (20-deoxo-20-(3,5-dimethyl-piperidin-1-yl)desmycosin) is a 16-membered macrolide derived from tylosin which can be prepared from desmycosin *via* reductive amination of the C-20 aldehyde group.[4] It shows a broad spectrum of activity toward Gram-positive bacteria but it is also effective toward some Gram-negative bacteria, such as *Pasteurella* or *Mycoplasma* species.[5] Tilmicosin **1** was developed for veterinary medicine in order to treat and prevent pneumonia in cattle, sheep, and pigs, pasteurellosis in calves and pigs as well as respiratory disease in cattle.[6]

Clarithromycin **2** (6-*O*-methylerythromycin A) is a semi-synthetic analogue of erythromycin A. It is classified the second-generation macrolide like azithromycin.[7] It can be synthesized by regioselective methylation at 6-OH of erythromycin.[8] Clarithromycin **2** was developed to overcome the acid instability of the first-generation macrolide erythromycin which lead to the formation of 6,9-hemiketal and consequential degradation products.[9] For that reason,

clarithromycin **2** exhibits fewer gastrointestinal side effects.[10] Besides, it is effective toward Gram-positive bacteria like *streptococcus* and *staphylococcus*. In comparison to erythromycin it shows an increased activity toward Gram-negative bacteria, such as *legionellosis* and *gonococcus* and *haemophilus influenzae.* Clarithromycin **2** is applied for the treatment of upper and lower respiratory tract infections, chronic bronchitis, pneumonia, pharyngitis, tonsillitis, and sinusitis. Its therapeutic utility is limited by the emergence of widespread bacterial resistance.[11] Therefore, third-generation macrolides, e.g. telithromycin[12] and cethromycin[13] are developed. The search of new classes of antibiotics remains a challenge for medicinal chemistry in order to address the problem of the bacterial resistance.

4.2 Regioselective Acylation of Tilmicosin

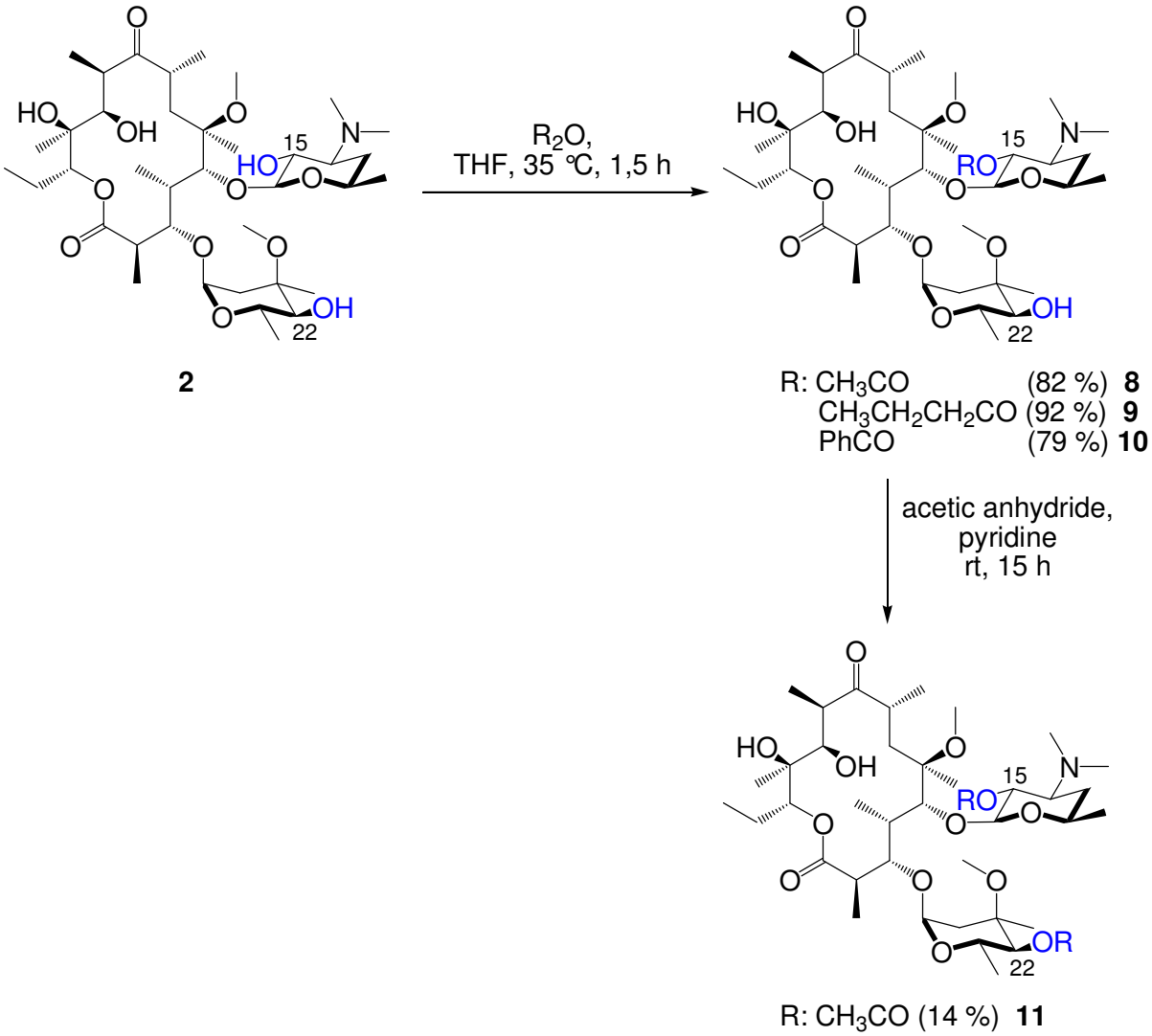
The commercially available tilmicosin **1** has two OH-groups in the mycaminose moiety which are adjacent to a tertiary amine. Thus, the C17- and C19-hydroxyl group should be more favoured for acylation reaction than the other secondary alcohols. Only gentle reaction conditions are needed to form the acetate, butyrate or benzoate derivatives of tilmicosin **3**-**5** (Scheme 4.1). The 17,19-*O*-diacyl tilmicosins (**3**-**5**) are obtained in moderate to good yields (up to 95 %). The subsequent acylation on C24-OH-group proves to be more ambitious. In spite of using catalysts DMAP and DIPEA, only a low yield of the triacylated product **6** could be observed. Also the reaction of diacetyl derivative **3** to 17-*O*,19-*O*-Diacetyl-24-*O*-butyryl tilmicosin **7** in presence of catalysts DMAP and DIPEA are obtained in low yield.



Scheme 4.1: Regioselective acylation of tilmicosin **1**

4.3 Regioselective Acylation of Clarithromycin

The syntheses of several acylated derivatives of clarithromycin already have been discussed in detail.[14] As is known, clarithromycin **2** possesses a C15 hydroxyl group on the desosamine sugar adjacent to the dimethylamino group. This *β*-amino sugar moiety is structurally similar to the *β*-amino alcohol moiety which is responsible for the high reactivity. For that reason, the C15-OH reacts easily with different acid anhydrides under mild reaction conditions (Scheme 4.2). The 15-*O*-acyl clarithromycins **8**-**10** were obtained in high yields. The further acylation on C22-OH with acetic anhydride and pyridine shows a lower reactivity than the acylation on C15-OH. The diacetylated product **11** could only be achieved in low yields (14 %).



Scheme 4.2: Regioselective acylation of clarithromycin **2**

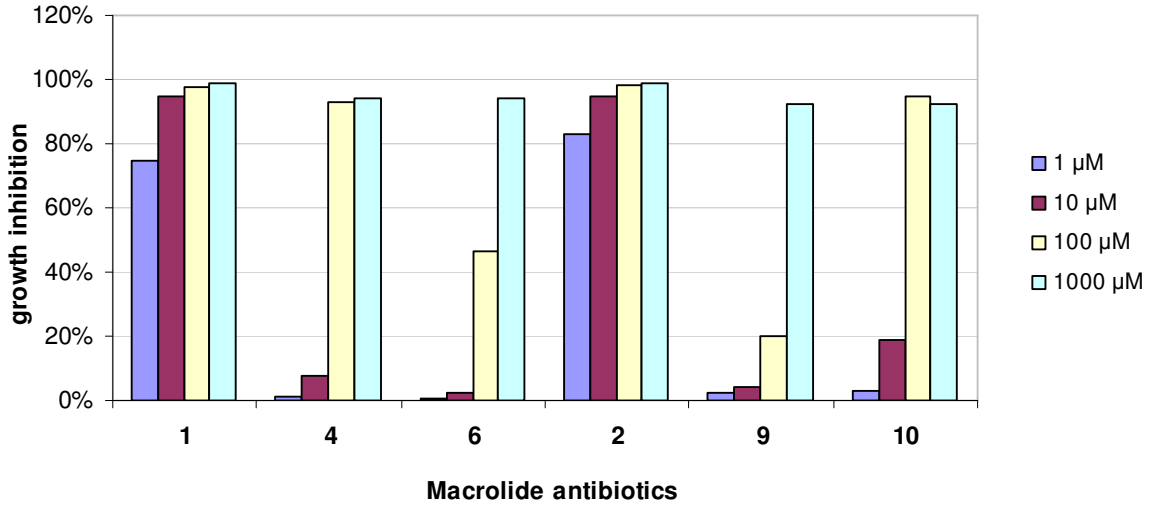
4.4 Antibacterial Activity of Acylated Derivatives of Tilmicosin and Clarithromycin[a]

The antibacterial activity of compounds **4**, **6**, **9**, and **10** as well as the reference compounds tilmicosin **1** and clarithromycin **2** were determined toward V*ibrio fischeri* and against *Bacillus subtilis*. The Gram-negative bacterium *V. fischeri* commonly exists in symbiosis with certain marine animals. Its bioluminescent property is utilized for the evaluation of acute toxicity of different organic chemicals (antibiotics, therapeutics, and herbicides) and for the investigation of water quality. The inhibition or toxicity assay according to ISO 11348 is a world known standardized bioassay which is based on the inhibition of the luminescence emitted by the *V. fischeri*. The bioluminescence from *V. fischeri* is generated by the oxidation of reduced flavin and long-chain aldehyde in presence of the enzyme luciferase.[15]

The Gram-positive bacterium *B. subtilis* is commonly found in soil, but also in dust, water, and air. Because of its sensitivity to antibiotics, it will be applied as screening organism testing for antimicrobially active substances.

The biological activities of compounds **4**, **6**, **9**, and **10** are presented in Scheme 4.3 and Scheme 4.4. In Scheme 4.3, the growth inhibition of *V. fischeri* measured as decrease of bioluminescence intensity is depicted. The *V. fischeri* assay is based on measuring the bioluminescence intensity after an incubation time of 24 hours at 23 °C. Generally, the antibacterial activity of compounds **4**, **6**, **9**, and **10** as well as the reference compounds tilmicosin **1** and clarithromycin **2** increase with rising substrate concentration as would be expected. Besides, it could be detected that tilmicosin **1** shows a better biological activity toward *V. fischeri* as its di-acylated **4** and tri-acylated compound **6**. The growth of *V. fischeri* is already inhibited at a low substrate concentration (1 µM), whereas the acylated compounds **4** and **6** show a growth inhibition only at concentrations >100 µM. However, di-acylated macrolide **4** exhibits a better antibacterial activity toward *V. fischeri* at a concentration of 100 µM than the tri-acylated derivative **6**. Compounds **4** and **6** display IC_{50} values of 53.9 µM and 107.4 µM whereas the IC_{50} values of reference compound **1** are less than 1 µM and can be considered as more active. These results reveal: the greater the number of hydroxyl groups, the higher the antibacterial activity toward *V. fischeri*. The same effect could also be determined for clarithromycin **2** (IC_{50} < 1 µM) and its monoesters **9** and **10**. Interestingly, it should be mentioned that the benzoate derivative **10** shows a better biological activity toward *V. fischeri* than the butyrate derivative of clarithromycin **9**. This result is also reflected in the IC_{50} values. Compound **10** exihibits a higher IC_{50} value of 49.3 µM than compound **9** with IC_{50} values of 509.5 µM.

[a] in cooperation with Ramona Heinke and Sebastian Stark

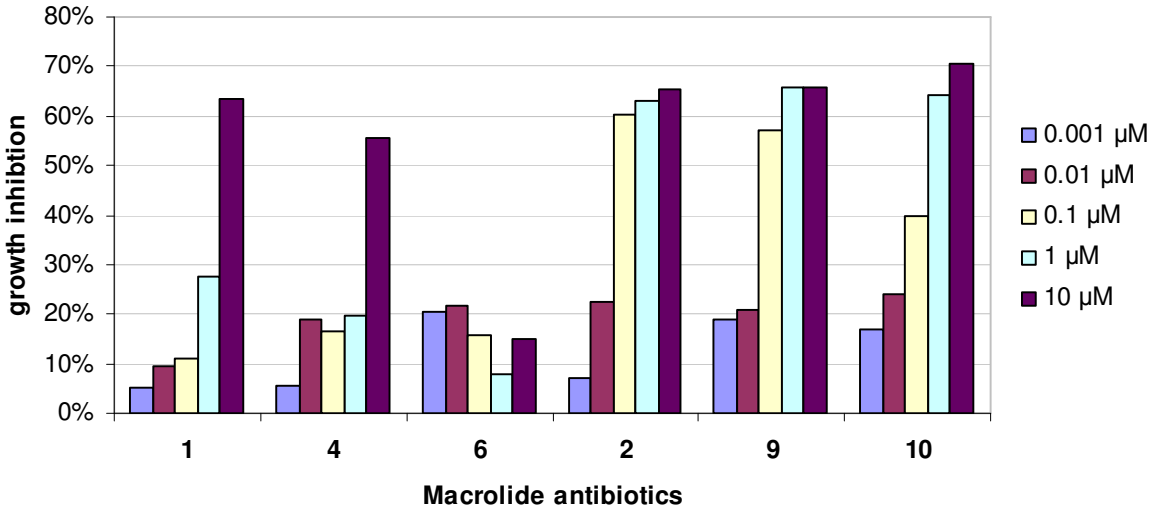


Scheme 4.3: Antibacterial activity of compounds **4**, **6**, **9**, and **10** toward *V. fischeri* in a 24 h assay at 23 °C.

Scheme 4.4 presents the growth inhibition of *B. subtilis* by compounds **4**, **6**, **9**, and **10** as well as the reference compounds tilmisosin **1** and clarithromycin **2**. The antimicrobial test is based on measuring the growth inhibition of *B. subtilis* measured as decrease of bioluminescence intensity in a 15 h assay at 30 °C.

For clarithromycin **2** and its monoesters **9** and **10**, the growth of *B. subtilis* is inhibited only at high substrate concentrations (> 0.1 µM). The compounds **2** and **9** are the most active ones with IC_{50} values of 0.077 µM and 0.082 µM. However, the di-benzoate of clarithromycin **10** with IC_{50} value of 0.61 µM has a moderate biological activity at a substrate concentration of 0.1 µM in comparison to compounds **2** and **9**, but it possesses an improved activity at a concentration of 10 µM. Thus either antibiotic activity is only to a minor extent influenced by acylation, or chemical or biological deacylation processes are fast enough to provide sufficient free clarithromycin.

For tilmicosin **1** and its derivatives **4** and **6**, it is conspicuous that only tilmicosin **1** (IC_{50} value of 7.0 µM) and its di-acylated compound **4** (IC_{50} value of 8.6 µM) show any antibacterial activity against *B. subtilis* at a high substrate concentration of 10 µM, whereas the tri-acylated compound **6** (IC_{50} value of 52.4 µM) has no antibiotic activity within the testing period. In case of tilmicosin and its derivatives **4** and **6**, the hydroxyl groups seem to be essential for the antibacterial activity, and deacylation obviously is not noteworthy in the assay's timeframe.



Scheme 4.4: Antibacterial activity of compounds **4**, **6**, **9**, and **10** against *B. subtilis* in a 15 h assay at 30 °C.

Finally, acylation decreases the antibacterial activity. But acylation can be effective in case of long application due to exposition of parent compound by auto-catalyzed deacylation. This effect can be used in order to investigate the influence of certain OH-groups in the molecule.

4.5 Conclusion

In summary, the alcohol moieties *β*-positions to amino groups of tilmicosin and clarithromycin proved to be highly reactive through their autocatalytic neighbouring group effect, so that the corresponding ester derivatives of tilmicosin and clarithromycin become selectively available. Some ester derivatives were evaluated with respect to their antibacterial behavior toward the Gram-negative bacterium *V. fischeri* and against the Gram-positive bacterium *B. subtilis*. The acylated derivatives demonstrated a good biological activity toward *V. fischeri* and a moderate to low antibacterial efficacy against *B. subtilis*. Generally, the ester derivatives show no decreased antibacterial activity compared with their parent compounds tilmicosin and clarithromycin in the standard assays. It can also not be excluded that the activity observed is due to partial chemical or enzymatic ester hydrolysis, i.e. the acylated derivatives are acting as pro-drugs. This would explain why the more hydrolysis resistant larger acyl groups give lower activities.

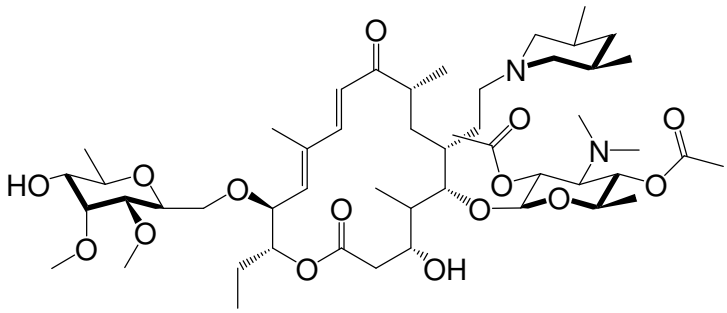
4.6 Experimental

4.6.1 General Information

All commercially available reagents were used without further purification, and solvents were purified and dried by standard methods. Analytical thin layer chromatography (TLC) was performed on silica gel (Kieselgel 60 F_{254}, 0.040-0.063 mm, Merck KgaA, Darmstadt, Germany) with detection either by UV light or molybdato phosphoric acid. Column chromatography was done using silica gel 60 (0.040-0.063 mm) from Merck KgaA, Darmstadt, Germany as stationary phase. ^{1}H- and ^{13}C-NMR were recorded at room temperature on a Varian Mercury 400 MHz. Chemical shifts were recorded in ppm relative to TMS (δ=0 ppm, ^{1}H-NMR) and to the solvent signal (^{13}C-NMR). Mass spectra were recorded on Applied Biosystems API-150 at 70 eV. The high resolution ESI mass spectra were obtained from a Bruker Apex 70e Fourier transform ion cyclotron resonance mass spectrometer equipped with a 7.0 Tesla superconducting magnet and an external electrospray ion source (Agilent, off axis spray).

4.6.2 Preparation of Ester Derivatives of Tilmicosin and Clarithromycin

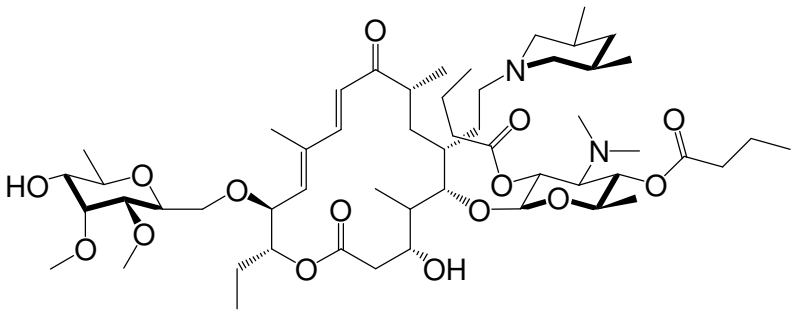
4.6.2.1 17-*O*,19-*O*-Diacetyl tilmicosin 3



A solution of tilmicosin (0.072 mmol, 62.3 mg) and acetic anhydride (0.278 mmol, 27.1 µl) in 3.3 ml of MTBE was stirred 18 h at 35 °C. Then, the solvent was removed under reduced pressure in a rotary evaporater. The residue was purified by chromatography on a silica gel column with petroleum ether/acetone/triethyl amine (10:3:0.1) as eluent to obtain ester derivative **3** as a white solid; yield: 32.7 mg (48 %); $\boldsymbol{R_F}$=0.79 (eluent: petroleum ether/acetone/triethyl amine (6:4:0.1)); **^{1}H-NMR** ($CDCl_3$, 400 MHz) δ = 0.80 - 1.00 (m, 12 H), 1.10 - 1.13 (m, 6 H), 1.19 - 1.28 (m, 10 H), 1.54 - 1.70 (m, 6 H), 1.75 - 1.80 (m, 7 H), 1.82 - 1.95 (m, 2 H), 2.05 (m, 4 H), 2.18 (m, 2 H), 2.35 (m, 6 H), 2.64 (m, 3 H) 2.75 (t, *J*=10.54 Hz, 1 H), 3.00 (dd, *J*=7.81, 2.73 Hz, 2 H), 3.38 (m, 2 H), 3.47 (s, 3 H), 3.52 (dd, *J*=6.25, 2.53 Hz,

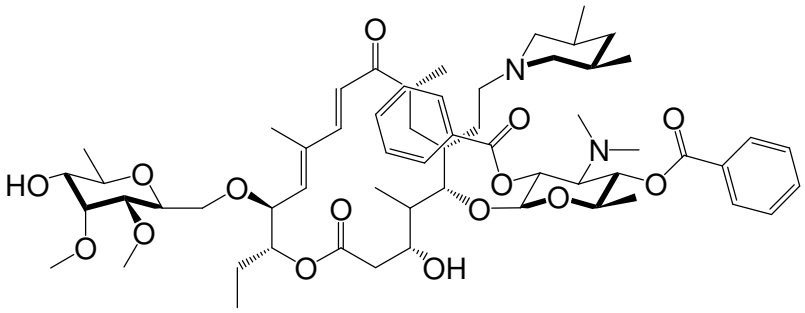
2 H), 3.61 (s, 3 H), 3.73 - 3.75 (m, 2 H), 4.00 - 4.02 (m, 1 H), 4.35 (d, *J*=7.42 Hz, 1 H), 4.56 (d, *J*=7.81 Hz, 1 H), 4.76 (t, *J*=9.76 Hz, 1 H), 4.82 - 4.93 (m, 2 H), 5.82 (d, *J*=10.15 Hz, 1 H), 6.33 (d, *J*=15.62 Hz, 1 H), 7.27 (d, *J*=14.06 Hz, 1 H) ppm; **^{13}C-NMR** ($CDCl_3$, 100 MHz) δ = 8.50, 9.54, 13.09, 17.78, 17.86, 19.53, 19.87, 21.26, 21.39, 25.44, 30.95, 31.28, 31.75, 32.49, 33.49, 39.44, 41.27 (2 x $\underline{C}H_3$), 42.18, 42.43, 45.17, 45.23, 58.63, 59.81(2 x $\underline{C}H_3$), 63.66 (2 x $\underline{C}H_2$), 67.23, 69.36, 70.62, 70.93, 71.53, 72.64, 73.68, 77.44, 79.86 (2 x $\underline{C}H$), 81.89 (2 x $\underline{C}H$), 90.19, 101.16, 102.37, 118.39, 134.58, 142.92, 147.54, 169.37, 169.81, 171.98, 204.25 ppm; **ESI-MS**: *m/z* = 952.1 $[M-H]^-$; **HR ESI-MS**: calculated for $C_{50}H_{84}N_2O_{15}$ $[M+H]^+$: 953.594446; found: 953.595493.

4.6.2.2 17-*O*,19-*O*-Dibutyryl tilmicosin 4



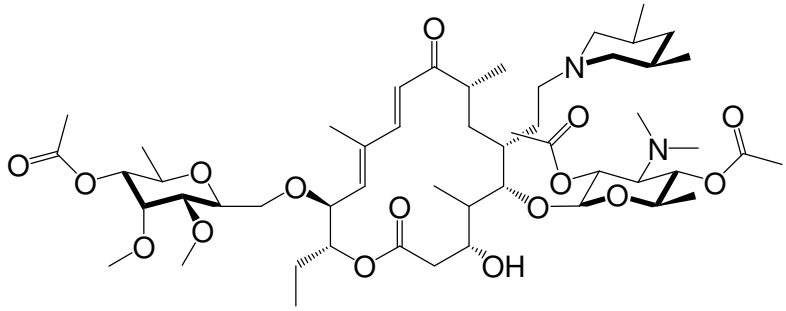
The reaction was performed according to procedure 4.6.2.1: tilmicosin (0.013 mmol, 11 mg), butyric anhydride (0.05 mmol, 8.3 µl) and 0.6 ml MTBE. Purification by chromatography on a silica gel column ($CHCl_3$/MeOH = 10:0.4) gave **4** as a white solid; yield: 9.8 mg (75 %); R_F=0.61 (eluent: petroleum ether/acetone/triethyl amine (6:4:0.1)); **^{1}H-NMR** ($CDCl_3$, 400 MHz) δ = 0.82 - 1.00 (m, 18 H), 1.11 - 1.15 (m, 4 H), 1.18 - 1.29 (m, 8 H), 1.54 - 1.70 (m, 13 H), 1.75 - 1.78 (m, 8 H), 1.82 - 1.94 (m, 2 H), 2.25 - 2.33 (m, 15 H), 2.73 (d, *J*=10.54 Hz, 3 H), 3.01 (d, *J*=2.73 Hz, 1 H), 3.18 (dd, *J*=9.37, 3.12 Hz, 1 H), 3.46 - 3.48 (m, 3 H), 3.52 (dd, *J*=6.25, 3.12 Hz, 2 H), 3.62 (s, 3 H), 3.74 - 3.75 (m, 1 H), 3.92 - 4.07 (m, 1 H), 4.56 (d, *J*=7.81 Hz, 1 H), 4.79 (t, *J*=9.96 Hz, 1 H), 4.85 - 4.97 (m, 2 H), 5.85 (d, *J*=10.15 Hz, 1 H), 6.29 (d, *J*=15.23 Hz, 1 H), 7.26 (d, *J*=15.23 Hz, 1 H) ppm; **^{13}C-NMR** ($CDCl_3$, 100 MHz); δ = 8.79, 9.57, 12.91, 13.01, 13.61, 17.48 (2 x $\underline{C}H_3$), 17.75, 18.26, 18.33, 18.65, 19.17, 25.38, 29.67, 31.91, 36.49, 36.76, 39.25, 39.55, 40.39, 40.8, 41.20 (2 x $\underline{C}H_3$), 41.86, 45.13, 58.36, 59.77 (2 x $\underline{C}H_3$), 61.77 (2 x $\underline{C}H_2$), 65.7, 67.24, 69.24, 70.35, 70.60, 70.96, 71.27, 72.62 (2 x $\underline{C}H$), 74.79, 79.86 (2 x $\underline{C}H$), 80.29, 81.89 (2 x $\underline{C}H$), 101.12, 102.31, 118.36, 134.61, 142.83, 147.64, 171.93, 172.43, 178.05, 204.14 ppm; **ESI-MS**: *m/z* = 1010 $[M+H]^+$; **HR ESI-MS**: calculated for $C_{54}H_{92}N_2O_{15}$ $[M+H]^+$: 1009.657047; found: 1009.657417.

4.6.2.3 17-*O*,19-*O*-Dibenzoyl tilmicosin 5



The reaction was performed according to procedure 4.6.2.1: tilmicosin (0.012 mmol, 10 mg), benzoic acid anhydride (0.046 mmol, 10.4 mg) and 0.53 ml MTBE. Purification by chromatography on a silica gel column (CH_2Cl_2/MeOH = 10:0.4) gave **5** as a white solid; yield: 11.8 mg (95 %); R_F = 0.66 (eluent: CH_2Cl_2/MeOH (10:1)); **^{1}H-NMR** ($CDCl_3$, 400 MHz) δ = 0.71 – 1.00 (m, 9 H), 1.02 - 1.23 (m, 13 H), 1.54 - 1.70 (m, 4 H), 1.72 - 1.80 (m, 9 H), 2.16 – 2.36 (m, 14 H), 2.54 - 2.68 (m, 1 H), 2.75 - 2.88 (m, 2 H), 2.94 (dd, *J*=7.81, 3.12 Hz, 2 H), 3.11 (dd, *J*=9.37, 3.51 Hz, 2 H), 3.35 - 3.46 (m, 6 H), 3.52 - 3.56 (m, 3 H), 3.61 (d, *J*=10.15 Hz, 1 H), 3.67 (t, *J*=3.12 Hz, 1 H), 3.89 (m, 1 H), 4.47 (d, *J*=7.81 Hz, 2 H), 4.84 (m, 1 H), 4.91 - 5.17 (m, 2 H), 5.78 (d, *J*=10.15 Hz, 1 H), 6.16 (d, *J*=15.62 Hz, 1 H), 7.26 (d, *J*=15.23 Hz, 1 H), 7.40 - 7.47 (m, 4 H), 7.45 - 7.53 (m, 2 H), 8.02 - 8.12 (m, 4 H) ppm; **^{13}C-NMR** ($CDCl_3$, 100 MHz) δ = 9.58 (2 x $\underline{C}H_3$), 12.91, 17.73 (2 x $\underline{C}H_3$) 18.86, 18.95, 28.52, 29.34, 29.68, 31.93, 32.58, 35.02, 40.67, 40.80, 41.10 (2 x $\underline{C}H_3$), 41.80, 44.97, 45.37, 58.49, 59.71(2 x $\underline{C}H_3$), 61.79 (2 x $\underline{C}H_2$), 63.92, 67.16, 69.43, 70.57 (2 x $\underline{C}H$), 70.97, 71.80, 72.61, 74.08, 76.47, 79.79 (2 x $\underline{C}H$), 81.82 (2 x $\underline{C}H$), 101.07, 102.25, 115.70, 128.26, 128.31 (2 x $\underline{C}H$), 128.36, 129.79, 130.09 (2 x $\underline{C}H$), 130.45, 133.14 (2 x $\underline{C}H$), 134.80, 142.82, 148.26, 160.27, 165.10, 171.53, 204.23 ppm; **ESI-MS**: *m/z* = 1078.2 $[M+H]^+$; **HR ESI-MS**: calculated for $C_{60}H_{88}N_2O_{15}$ $[M+H]^+$: 1077.635747; found: 1077.62495.

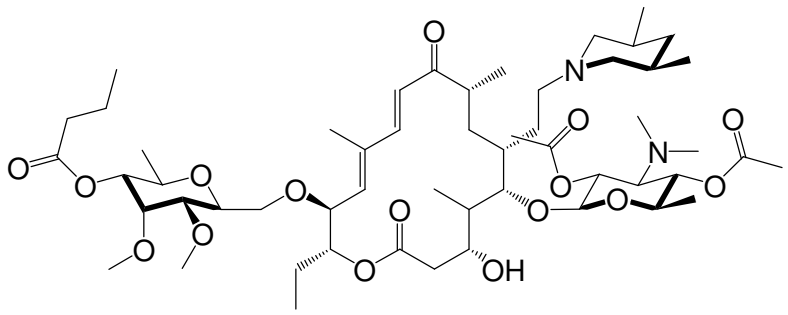
4.6.2.4 17-*O*,19-*O*,24-*O*-Triacetyl tilmicosin 6



A solution of tilmicosin (0.011 mmol, 9.1 mg), acetic anhydride (0.046 mmol, 4.4 µl), DIPEA (0.046 mmol, 0.05 µl) and DMAP (0.001 mmol, 0.2 mg) in 0.17 ml of dichloromethane was stirred 17 h at room temperature. Afterwards, the solvent was removed under reduced pressure in a rotary evaporater and the residue was purified by chromatography on a silica

gel column with CH_2Cl_2/MeOH (10:1) as eluent to obtain ester derivative **6** as a white solid; yield: 2.4 mg (23 %); R_F=0.67 (eluent: CH_2Cl_2/MeOH (10:1)); **^{1}H-NMR** ($CDCl_3$, 400 MHz) δ = 0.79 - 1.05 (m, 12 H), 1.08 - 1.33 (m, 16 H), 1.56 - 1.60 (m, 6 H), 1.75 - 1.80 (m, 7 H), 1.83 (d, *J*=2.34 Hz, 2 H), 1.94 (br. s., 1 H), 1.99 - 2.12 (m, 12 H), 2.34 (s, 7 H), 2.40 (s, 1 H), 2.64 (m, 1 H), 3.03 (dd, *J*=7.81, 2.73 Hz, 2 H), 3.44 - 3.49 (m, 3 H), 3.53 (s, 4 H), 3.62 (s, 1 H), 3.88 - 3.95 (m, 2 H), 4.44 (dd, *J*=9.76, 2.73 Hz, 1 H), 4.63 (d, *J*=7.81 Hz, 1 H), 4.75 (s, 1 H), 4.90 (m, 2 H), 5.82 (m, 1 H), 6.33 (d, *J*=15.62 Hz, 1 H), 7.27 (d, *J*=14.06 Hz, 1 H) ppm; **^{13}C-NMR** ($CDCl_3$, 100 MHz) δ = 8.50, 9.54, 13.07, 17.37, 17.86, 19.03, 20.99, 21.26, 21.39, 21.60 25.44, 29.35, 29.69 (2 x $\underline{C}H_3$), 30.91, 31.91, 41.27 (2 x $\underline{C}H_3$), 42.32, 42.46, 45.23, 48.54, 59.61(2 x $\underline{C}H_3$), 61.58 (2 x $\underline{C}H_2$), 67.32, 69.46, 70.55, 70.92, 71.46, 72.64, 73.68, 74.70, 77.20 (2 x $\underline{C}H$), 80.54 (2 x $\underline{C}H$), 101.08, 102.33, 118.40, 134.68, 142.82, 148.16, 169.61, 169.85, 170.15 (2 x C), 204.25 ppm; **ESI-MS**: *m/z* = 995.8 $[M+H]^+$; **HR ESI-MS**: calculated for $C_{52}H_{86}N_2O_{16}$ $[M+H]^+$: 995.605011; found: 995.604755.

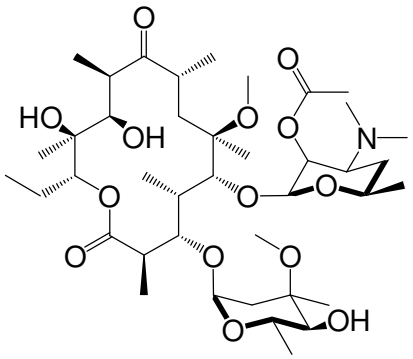
4.6.2.5 17-*O*,19-*O*-Diacetyl-24-*O*-butyryl tilmicosin 7



A solution of 17-*O*,19-*O*-diacetyl tilmicosin (0.011 mmol, 10.9 mg), butyric anhydride (0.114 mmol, 18.6 µl), DIPEA (0.114 mmol, 19.9 µl) and DMAP (0.02 mmol, 2.4 mg) in 0.7 ml of dichloromethane was stirred 12 h at room temperature. Subsequently, 0.7 ml ethanol was added to consume the unreacted butyric anhydride. The mixture was stirred for 10 min. Afterwards, the mixture was diluted in 10 ml ethyl acetate. The resulting organic layer was washed with sat. aq. $NaHCO_3$ solution (1 x 3 ml), water (1 x 3 ml), and brine (1 x 3 ml) and dried over Na_2SO_4. The solvent was removed under reduced pressure in a rotary evaporater and the residue was purified by chromatography on a silica gel column with CH_2Cl_2/MeOH (10:1) as eluent to obtain ester derivative **7** as a white solid; yield: 7.6 mg (69 %); R_F=0.58 (eluent: CH_2Cl_2/MeOH (10:1)); **^{1}H-NMR** ($CDCl_3$, 400 MHz) δ =0.78 - 1.02 (m, 15 H), 1.07 - 1.30 (m, 16 H), 1.53 - 1.62 (m, 4 H), 1.64 - 1.74 (m, 3 H), 1.74 - 1.80 (m, 5 H), 1.88 - 1.97 (m, 2 H), 2.06 (d, *J*=5.08 Hz, 6 H,) 2.30 - 2.37 (m, 9 H), 2.66 (d, *J*=4.69 Hz, 2 H), 2.69 - 2.78 (m, 2 H), 3.03 (dd, *J*=8.20, 2.73 Hz, 2 H), 3.39 (d, *J*=3.12 Hz, 2 H), 3.43 - 3.48 (m, 3 H), 3.49 - 3.55 (m, 5 H), 3.71 (d, *J*=9.76 Hz, 1 H), 3.87 - 3.95 (m, 2 H), 4.01 (dd, *J*=9.18, 3.71 Hz, 1 H), 4.34 (d, *J*=7.42 Hz, 1 H), 4.45 (dd, *J*=9.76, 2.34 Hz, 1 H), 4.63 (d, *J*=8.20 Hz, 1 H), 4.76 (t, *J*=9.76 Hz, 1 H), 4.85 - 4.93 (m, 2 H), 5.82 (d, *J*=10.54 Hz, 1 H), 6.31 (d, *J*=15.23 Hz, 1 H),

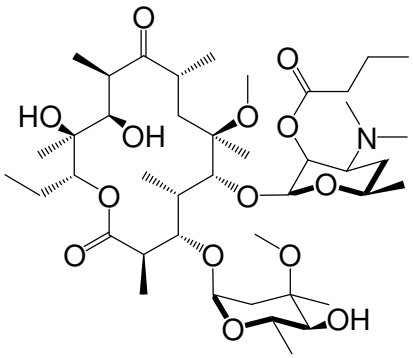
7.23 (m, 1 H) ppm; **^{13}C-NMR** ($CDCl_3$, 100 MHz) δ = 8.49, 9.52, 13.08, 13.64, 17.39, 17.86, 18.42, 19.51, 19.84, 21.26, 21.37, 25.42, 29.68, 29.82, 30.94, 31.28, 36.21, 41.25 (2 x $\underline{C}H_3$), 42.14, 45.23, 58.62, 59.62, 61.58 (2 x $\underline{C}H_3$), 63.58 (2 x $\underline{C}H_2$), 66.20, 67.22, 69.36, 69.49, 70.56, 70.92, 71.51, 73.75, 74.43, 76.48, 77.21, 77.88, 79.84, 80.59 (2 x $\underline{C}H$), 95.97, 101.11, 102.36, 124.22, 134.60, 142.76, 147.51, 169.39, 169.83, 172.01, 172.79, 204.19 ppm; **ESI-MS**: *m/z* = 1023.8 $[M+H]^+$; **HR ESI-MS**: calculated for $C_{54}H_{90}N_2O_{16}$ $[M+H]^+$: 1023.636311; found: 1023.6384670.

4.6.2.6 15-*O*-Acetyl clarithromycin 8[14d-e,16]



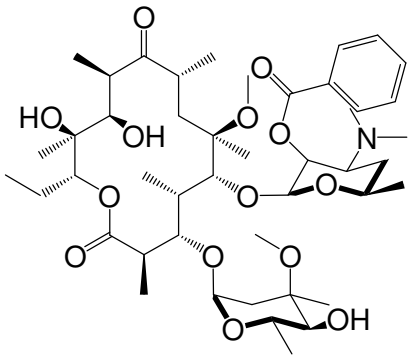
A solution of clarithromycin (0.11 mmol, 82.3 mg) and acetic anhydride (0.33 mmol, 31.2 µl) in 2.75 ml of THF was stirred 1.5 h at 35 °C. Afterwards, the reaction mixture was diluted in 100 ml ethyl acetate. The resulting organic layer was washed with sat. aq. $NaHCO_3$ solution (1 x 8 ml), water (1 x 8 ml), and brine (1 x 8 ml) and dried over Na_2SO_4. The solvent was removed under reduced pressure in a rotary evaporater and the residue was purified by chromatography on a silica gel column with CH_2Cl_2/MeOH (10:1) as eluent to obtain ester derivative **8** as a white solid; yield: 70.8 mg (82 %); R_F=0.36 (eluent: petroleum ether/acetone (2:3)); **^{1}H-NMR** ($CDCl_3$, 400 MHz) δ = 0.84 (t, *J*=7.42 Hz, 3 H), 0.93 (d, *J*=7.81 Hz, 3 H), 1.09 - 1.16 (m, 6 H), 1.19 - 1.34 (m, 12 H), 1.37 - 1.51 (m, 4 H), 1.53 - 1.75 (m, 4 H), 1.81 - 1.97 (m, 3 H), 2.05 (s, 3 H), 2.60 (m, 6 H), 2.36 (d, *J*=15.23 Hz, 2 H), 2.53 - 2.64 (m, 2 H), 2.85 (dd, *J*=9.37, 7.42 Hz, 1 H), 2.96 - 3.07 (m, 6 H), 3.21 (s, 1 H), 3.33 - 3.39 (m, 2 H), 3.48 (dd, *J*=5.27, 3.71 Hz, 1 H), 3.61 (d, *J*=6.64 Hz, 1 H), 3.73 - 3.78 (m, 2 H), 3.95 - 4.02 (m, 2 H), 4.57 (d, *J*=7.42 Hz, 1 H), 4.74 (dd, *J*=10.54, 7.42 Hz, 1 H), 4.93 (d, *J*=4.30 Hz, 1 H), 5.06 (dd, *J*=11.13, 2.15 Hz, 1 H) ppm; **^{13}C-NMR** ($CDCl_3$, 100 MHz) δ = 8.93, 10.53, 12.24, 15.91, 16.01, 17.84, 18.61, 19.79, 20.97, 21.24, 21.44, 21.46, 30.35, 34.81, 37.16, 38.67, 38.84, 40.65, 44.96, 45.12, 49.32, 50.39, 63.42, 65.78, 68.10, 69.02, 71.68, 72.71, 74.11, 76.52, 77.79, 77.90, 77.95, 78.25, 80.37, 95.76, 100.42, 169.92, 175.58, 221.10 ppm; **ESI-MS**: *m/z* = 790.7 $[M+H]^-$; **HR ESI-MS**: calculated for $C_{40}H_{71}NO_{14}$ $[M+H]^+$: 790.4947324; found: 790.4943960.

4.6.2.7 15-*O*-Butyryl clarithromycin 9



The reaction was performed according to procedure 4.6.2.6: clarithromycin (0.06 mmol, 44.9 mg), butyric anhydride (0.18 mmol, 29.4 µl) and 1.5 ml THF. Purification by chromatography on a silica gel column (CH_2Cl_2/MeOH = 20:1) gave **9** as a white solid; yield: 45.2 mg (92 %); R_F=0.65 (eluent: petroleum ether/acetone (2:3)); **^{1}H-NMR** ($CDCl_3$, 400 MHz) δ = 0.84 (t, *J*=6.83 Hz, 3 H), 0.89 - 1.00 (m, 6 H), 1.05 - 1.17 (m, 6 H), 1.18 - 1.39 (m, 12 H), 1.46 (br. s., 1 H), 1.57 - 1.75 (m, 7 H), 1.83 - 1.95 (m, 2 H), 2.21 - 2.39 (m, 11 H), 2.59 (d, *J*=14.45 Hz, 2 H), 2.83 - 2.88 (m, 1 H), 2.95 - 3.06 (m, 6 H), 3.21 (br. s., 1 H), 3.37 (d, *J*=1.56 Hz, 3 H), 3.48 (br. s., 1 H), 3.61 (d, *J*=6.25 Hz, 1 H), 3.72 - 3.77 (m, 3 H), 3.99 (br. s., 2 H), 4.57 (d, *J*=7.03 Hz, 1 H), 4.73 - 4.79 (m, 1 H), 4.93 (d, *J*=4.69 Hz, 1 H), 5.06 (d, *J*=10.93 Hz, 1 H) ppm; **^{13}C-NMR** ($CDCl_3$, 100 MHz) δ = 9.00, 10.54, 12.24, 13.68, 13.51, 15.92, 15.98, 17.87, 18.41 18.64, 19.80, 20.98, 21.24, 21.45, 30.89, 34.84, 36.43, 37.16, 38.74, 38.85, 40.15, 44.97, 45.11, 49.34, 50.45, 63.08, 65.81, 68.01, 69.04, 71.22, 72.73, 74.14, 76.53, 77.79, 77.95, 78.27, 80.29, 95.79, 100.34, 172.49, 175.61, 221.12 ppm; **ESI-MS**: *m/z* = 818.8 $[M+H]^-$; **HR ESI-MS**: calculated for $C_{42}H_{75}NO_{14}$ $[M+H]^+$: 818.5260326; found: 818.5264440.

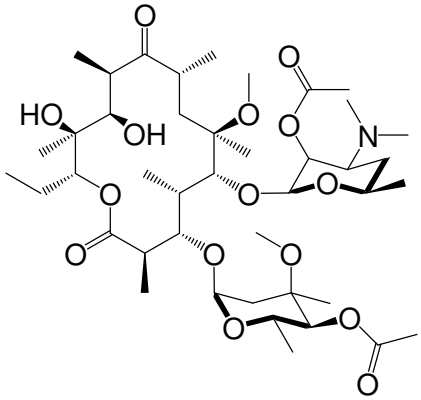
4.6.2.8 15-*O*-Benzoyl clarithromycin 10



The reaction was performed according to procedure 4.6.2.6: clarithromycin (0.06 mmol, 44.9 mg), benzoic anhydride (0.18 mmol, 40.7 mg) and 1.5 ml THF. Purification by chromatography on a silica gel column (CH_2Cl_2/MeOH = 10:1) gave **10** as a white solid; yield: 40.1 mg (79 %); R_F= 0.54 (eluent: petroleum ether/acetone (2:3)); **^{1}H-NMR** ($CDCl_3$, 400 MHz) δ = 0.61 (d, *J*=7.42 Hz, 3 H), 0.78 (t, *J*=7.42 Hz, 3 H), 1.01 (s, 3 H), 1.11 (dd, *J*=18.94, 6.83

Hz, 9 H), 1.22 (s, 3 H), 1.32 (dd, *J*=6.25, 1.56 Hz, 6 H), 1.40 (s, 3 H), 1.50 (d, *J*=10.93 Hz, 1 H) 1.57 - 1.60 (m, 4 H) 1.67 (d, *J*=7.42 Hz, 1 H) 1.80 - 1.91 (m, 1 H) 2.02 - 2.10 (m, 1 H) 2.33 (d, *J*=14.84 Hz, 1 H), 2.57 (s, 6 H), 2.66 (dd, *J*=8.98, 7.42 Hz, 1 H) 2.87 - 2.95 (m, 2 H), 3.00 (s, 3 H), 3.06 (d, *J*=8.98 Hz, 1 H), 3.46 - 3.48 (m, 4 H), 3.64 - 3.68 (m, 2 H), 3.71 (d, *J*=9.37 Hz, 1 H), 3.73 - 3.79 (m, 1 H), 4.01 (dd, *J*=9.37, 6.25 Hz, 1 H), 4.81 (d, *J*=7.42 Hz, 1 H), 4.89 (d, *J*=4.30 Hz, 1 H), 4.98 - 5.01 (m, 1 H), 5.22 (dd, *J*=10.74, 7.22 Hz, 1 H), 7.22 - 7.24 (m, 1 H), 7.34 - 7.40 (m, 1 H), 7.47 - 7.51 (m, 1 H), 7.89 - 7.92 (m, 1 H), 7.97 - 8.00 (m, 1 H) ppm; **^{13}C-NMR** ($CDCl_3$, 100 MHz) δ = 9.48, 10.49, 12.20, 15.80, 15.98, 17.79, 18.72, 19.93, 20.92, 21.23, 21.38, 31.04, 34.89, 37.20, 38.54, 38.92, 39.42, 44.89, 45.05, 49.48, 50.34, 50.63, 62.00, 65.93, 67.55, 69.01, 71.20, 72.75, 74.08, 76.46, 77.75, 77.76, 78.18, 80.27, 95.69, 100.13, 128.00, 128.03, 129.71, 129.85, 132.30, 132.72, 165.52, 175.69, 221.14 ppm; **ESI-MS**: *m/z* = 852.2 $[M+H]^-$; **HR ESI-MS**: calculated for $C_{45}H_{73}NO_{14}$ $[M+H]^+$: 852.5103825; found: 852.5089310.

4.6.2.9 15-*O*,22-*O*-Diacetyl clarithromycin 11[17]



A solution of 15-*O*-acetyl clarithromycin **8** (0.0599 mmol, 47.3 mg) and acetic anhydride (0.31 mmol, 28.8 µl) in 0.31 ml of pyridine was stirred 15 h at room temperature. Afterwards, the reaction mixture was diluted in 70 ml ethyl acetate. The resulting organic layer was washed with 10 % aq. $NaHSO_4$ solution (3 x 7 ml), water (1 x 7 ml), and brine (1 x 7 ml) and dried over Na_2SO_4. The solvent was removed under reduced pressure in a rotary evaporater and the residue was purified by chromatography on a silica gel column with petroleum ether/acetone (2:1) as eluent to obtain ester derivative **11** as a white solid; yield: 6.9 mg (14 %); R_F=0.54 (eluent: petroleum ether/acetone (1:1)); **^{1}H-NMR** ($CDCl_3$, 400 MHz) δ = 0.80 - 1.04 (m, 6 H), 1.10 - 1.37 (m, 24 H), 1.48 (d, *J*=10.93 Hz, 2 H), 1.53 - 1.77 (m, 7 H), 1.80 - 1.97 (m, 3 H), 2.06 (s, 3 H), 2.11 (s, 3 H), 2.30 (s, 6 H), 2.41 (d, *J*=15.23 Hz, 1 H), 2.49 - 2.61 (m, 1 H), 2.69 - 2.80 (m, 1 H), 2.83 - 2.92 (m, 1 H), 2.96 - 3.02 (m, 4 H), 3.20 (s, 1 H), 3.35 (s, 3 H), 3.60 (d, *J*=6.64 Hz, 1 H), 3.71 - 3.78 (m, 3 H), 3.99 (s, 1 H), 4.30 (dd, *J*=9.76, 5.86 Hz, 1 H), 4.66 - 4.71 (m, 2 H), 4.76 (d, *J*=10.54 Hz, 1 H), 4.99 (d, *J*=5.08 Hz, 1 H), 5.07 (dd, *J*=10.93, 2.34 Hz, 1 H) ppm; **^{13}C-NMR** ($CDCl_3$, 100 MHz) δ = 9.03, 10.56, 12.35, 15.96,

16.08, 17.93, 18.34, 19.73, 20.91, 21.04, 21.11, 21.55, 21.59, 29.68, 31.14, 35.31, 37.20, 38.54, 38.61, 40.71, 44.83, 45.26, 49.32, 50.51, 63.09, 67.19, 69.10, 71.89, 72.68, 74.18, 76.58, 77.64, 77.91, 78.22, 78.55, 80.17, 95.74, 99.89, 170.02, 170.45, 175.51, 221.16 ppm; **ESI-MS**: *m/z* = 832.8 $[M+H]^-$; **HR ESI-MS**: calculated for $C_{42}H_{73}NO_{15}$ $[M+H]^+$: 832.5052971; found: 832.5065090.

4.6.3 Procedure of Biological Assays

4.6.3.1 Growth Inhibition Assay with *V. fischeri*[18]

The assay with Gram-negative bacteria *Vibrio fischeri* is based on the measurement of inhibition of bioluminescence against negative control. *V. fischeri* (NRRL-B-11177) bacteria were cultivated in a saline "BOSS"[b] medium (3 % NaCl w/w) whereby at a certain population density, bacterial luminescence will start. The bacterial suspension was diluted, added into 96-well microtiter plates and the respective macrolide were applied as a concentration series (given in scheme 4.3) as solutions in 98 % "BOSS" medium and 2 % DMSO and mixed. The luminescence of bacteria treated with the respective macrolide were measured after 24 h incubation at 23 °C in the GENios Pro microtiter plate reader (firm Tecan), in relation to controls of untreated bacteria.

4.6.3.2 Growth Inhibition Assay with *B. subtilis*[19]

The assay with *Bacillus subtilis* is carried out with a fluorescence-based measurement of the antibacterial activity. A genetically modified strain of Gram-positive bacteria *B. subtilis* 168 was used as test organism which was provided by Prof. O. Kuipers (University of Groningen, Netherlands).[20] *B. subtilis* 168 (P_{AbrB}-IYFP) was cultivated in Trypton-yeast (TY)[c] extract. The medium was autoclaved. After cooling, a steril filtrated Chloramphenicol solution (Chloramphenicol with 5 µg/ml in TY medium) was added to the medium for selection of mutants. TY-CHL-Agar-plates were used as plates for the cultivation of *Bacillus subtilis* 168 P_{AbrB} encoding yellow fluorescent protein IYFP. A 24 h preparatory culture was used as inoculum. For it, approximately 50 ml TY-medium was inoculated. After incubation time of 24 h at 30 °C the cell count of bacteria was determined via Neubauer counting chamber and diluted with TY-medium to a cell count of 1.6×10^5 cells/ml.

The tests were carried in 96-well microtiter plates. In each well were added the macrolide in

[b] Composition of "BOSS" medium: NaCl (30 g), Glycerol (1 g), Bacto-Peptone (10 g), Beef extract (3 g), 15 g Agar Agar to obtain solid medium, distilled water (1000 ml)

[c] Composition of Trypton-yeast (TY) extract medium: Bacto Tryptone (9 g), Bacto Yeast Extract (4.5 g), NaCl (9 g), Agar Agar (13.5 g) to obtain solid medium

amounts (given in scheme 4.4), 240 µl TY-medium and 240 µl bacteria solution (inoculum 1 x 10^4 cells/ml). After inoculation of the microtiter plates the luminescence of bacteria treated with the respective macrolide were measured in the GENios Pro microtiter plate reader (firm Tecan), in relation to controls of untreated bacteria. After 15 h incubation at 23 °C, the luminescence was measured again. The growth inhibition is calculated in relation to controls of untreated bacteria.

$$inhibition = \left(1 - \frac{\bar{X}_{arithm}(sample[t_{15} - t_0])}{\bar{X}_{arithm}(control[t_{15} - t_0])} \right) \cdot 100\%$$

4.7 References

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Summary

Acylation or transesterification is a powerful method for the synthesis of natural products and for the production of bulk chemicals. In nature, transesterifications are catalysed by enzymes such as lipases, esterases, and other hydrolases which are based on the catalytic triade of serine proteases. Since the last decade, the creation of easily accessible, small organic catalysts, the so-called organocatalysts, is an important and exciting subject.
The aim of this research project was to study chalcogen based organocatalysts in respect of their kinetic and enantioselective behavior in acylation reactions (Figure 1).

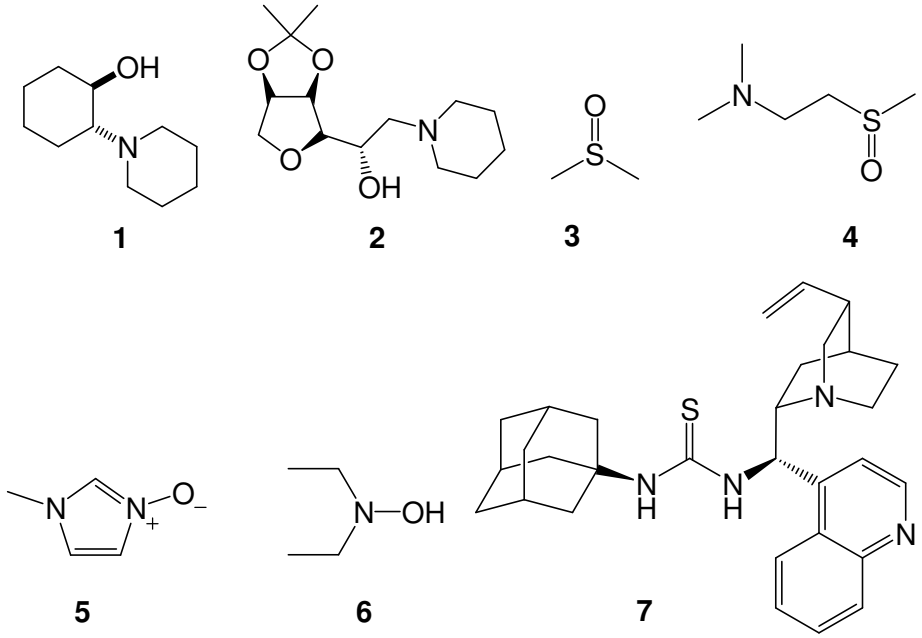
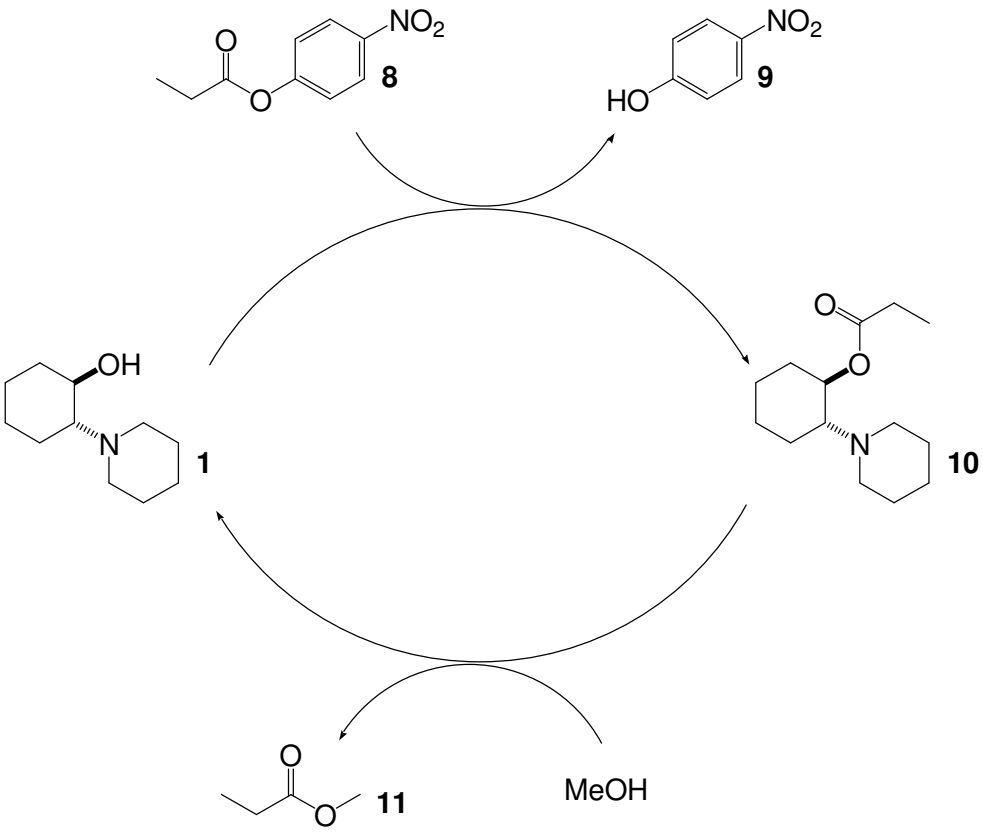


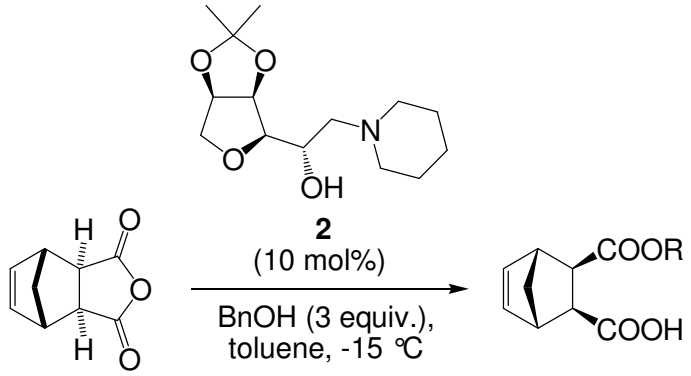
Figure 1: Different organocatalysts which contain a chalcogen atom as reactive center

Chapter 1 introduces organocatalysis as further practical and broadly applicable methodological approach in asymmetric synthesis adjacent to bio- and metal catalysis.
Chapter 2 describes the kinetic mechanistic studies on transesterification reactions between active esters and alcohols. Different nucleophilic oxygen species such as amino alcohols, sulfoxides and amino sulfoxides have been investigated how neighboring groups, steric and electronic effects influence the methanolysis of para-nitrophenyl ester of propionic acid **8**. It was found that the amino alcohols prove to be more successful as reactive acyl-transfer organocatalysts than amino sulfoxides and sulfoxides. The highest catalytic activity could be achieved with cyclohexane-based *β*-amino alcohol catalyst 2-piperidine-1-cyclohexanol **1**.
Through kinetic ^{1}H-NMR-studies it was possible to provide evidence for the catalytic cycle of an amino alcohol which operates by an *O*-nucleophilic mechanism (Scheme 1).



Scheme 1: The catalytic cycle of an amino alcohol catalyst

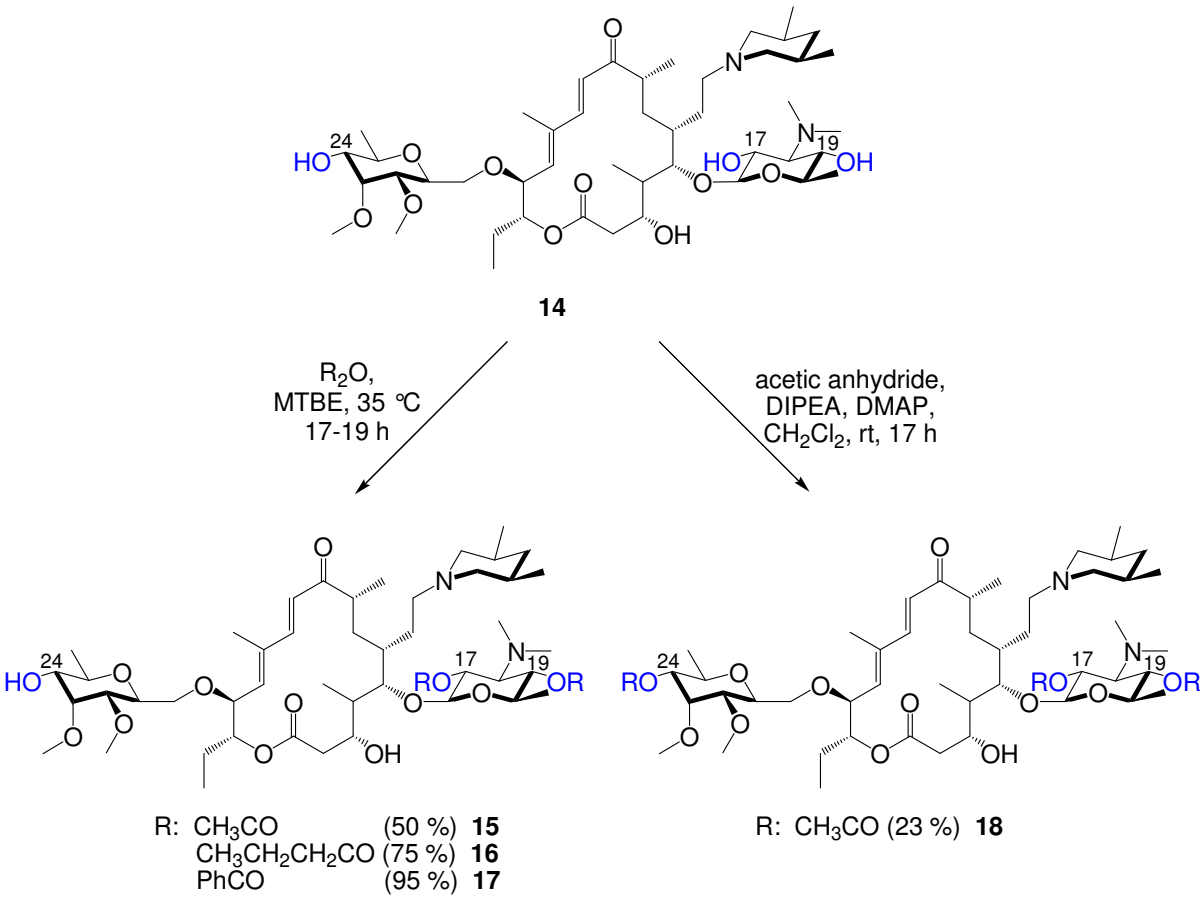
The screening or rather the kinetic study of various organocatalysts affords the basis for the optimization of the structure of the best catalysts, in order to use this one for the enantioselective anhydride-opening of cylic *meso*-anhydrides which is discussed in chapter 3. Various chiral *β*-amino alcohols and thiourea catalysts were investigated in respect of their enantioselective behavior. The most efficient catalyst is the *β*-amino alcohol catalyst derived from isosorbide **1**, a by-product from the starch industry. In addition to its good catalytic activity, this new catalyst **1** promotes the enantioselective alcoholysis of various cyclic *meso*-anhydrides in high enantiomeric excess and quantitative yields. It provided hemiesters in enantioselective ring-opening of cyclic *meso*-anhydrides with benzyl alcohol in up to 95 % ee (Scheme 2).



12 **13**
70 % yield,
93 % *ee*

Scheme 2: Enantioselective ring-opening of cyclic *meso*-anhydride **12** with benzyl alcohol using catalyst **2**

Chapter 4 shows an application of the catalytic activity of amino alcohols in regioselective synthesis of acylated derivatives of tilmicosin **14** and clarithromycin. As described in the previous chapters, the *β*-amino alcohols present itself as highly reactive moiety. Due to the assistance of *β*-amino alcohol moiety, the C17- and C19-OH groups of tilmicosin can be easily acylated without any catalysts (Scheme 3). Also selective acylation could be observed at the hydrogen atom of clarithromycin which is adjacent to the dimethylamino group. Some ester derivatives were evaluated in respect of their antibacterial behavior towards the Gram-negative bacterium *V. fischeri* and against the Gram-positive bacterium *B. subtilis*. The biotests of these acylated derivatives demonstrated a good biological activity towards *V. fischeri* and a moderate antibacterial efficacy against *B. subtilis*.



Scheme 3: Regioselective acylation of tilmicosin **14**

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List of Publications

- L. A. Wessjohann, M. C. Nin Brauer, K. Brand **2011**. *Chalcogen-Based Organocatalysis*. In: R. Mahrwald (ed.), *Enantioselective Organocatalyzed Reactions I: Enantioselective Oxidation, Reduction, Functionalization and Desymmetrization*, 1st edition Springer, Berlin, pp. 209-314.
- K. Brand, L. A. Wessjohann, A. D. Wouters, D. S. Lüdtke, Enantioselective Desymmetrization of *meso*-Anhydrides: Catalyzed by Carbohydrate-based Organocatalysts, *manuscript in preparation*.
- K. Brand, L. A. Wessjohann, R. Heinke, S. Stark, Utilizing the Special Reactivity of *β*-Amino Alcohols in Macrocyclic Antibiotics for Regioselective Acylation, *manuscript in preparation*.

Recent presentations

- *Chalcogen Based Organocatalysis*
  Poster presentation, DFG Research Centres Organocatalysis meeting, November 06-07 2007, Berlin, Germany

- Poster presentation, Orchem 2008, 14. Vortragstagung der Liebig-Vereinigung für Organische Chemie, September 01-09 2008, Weimar, Germany

- Poster presentation, 3rd EuCheMS (the European Association for Chemical and Molecular Sciences) Chemistry Congress, August 29 – September 02 2010, Nürnberg, Germany

Curriculum Vitae

PERSÖNLICHE DATEN

Geboren am 30.10.1982 in Suhl, ledig, 1 Kind

BERUF

seit 05/2011	**Projektmanagerin** bei Lobbe Industrieservice GmbH & Co KG in Spreewitz und Spremberg

STUDIUM

11/2006 – 12/2010	**Wissenschaftliche Mitarbeiterin** (Diplomchemikerin) im Rahmen der Dissertation am Leibniz-Institut für Pflanzenbiochemie und Martin-Luther-Universität Halle (Saale) Dissertationsthema: *Chalcogen Based Organocatalysts in Transesterification*
10/2001 – 10/2006	**Studium Chemie** an der Martin-Luther-Universität Halle (Saale) Studienschwerpunkt: • Biophysikalische Chemie • Organische Chemie Thema Diplomarbeit: • *Kristalline Mesophasen mit polaren Eigenschaften – Synthese und Untersuchung neuer bent-core Mesogene*

SCHULE

1993 - 2001	Abitur am Gymnasium in Suhl

PRAKTIKA

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Aufgaben:

- Erstellen und Präsentation einer Marktanalyse bezogen auf die Einsatzbereiche der Faser Kermel
- Besuch verschiedener Kunden von Kermel in Italien und der Schweiz zur Analyse der Anforderung an das Produkt und möglicher Produktveränderungen

08/2005 Praktikum bei **ML Lubrication GmbH** in Schweinfurt

Aufgaben:

- Optimierung von Messreihen für verschiedene Metallbearbeitungsflüssigkeiten für den Wareneingang, Endkontrolle und Anlagenüberwachung an einem Titrationsautomaten mit anschließender Dokumentation der Ergebnisse
- Mitarbeit in der Entwicklung am Rohstoff-Screening für Schmieröle und in der Qualitätskontrolle

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Aufgabe:

- Betreuung von Studenten bei verschiedenen Tätigkeiten in einem physikalisch-chemischen Labor

12/2004 Tätigkeit als Tutor am Lehrstuhl für Ingenieurwissenschaften an der Martin-Luther-Universität Halle (Saale)

Aufgabe:

- Durchführen von Seminaren in den Grundlagen der anorganischen Chemie

Eidesstaatliche Erklärung

Hiermit erkläre ich, dass ich die vorliegende Arbeit selbstständig und nur mit den angegebenen Hilfsmitteln angefertigt habe. Die den benutzten Werken wörtlich oder inhaltlich entnommene Stellen habe ich gekennzeichnet.

Diese Arbeit wurde nur der Naturwissenschaftlichen Fakultät II (Fachbereich Chemie) der Martin-Luther-Universität Halle-Wittenberg vorgelegt. Ich habe mich zu keinem früheren Zeitpunkt um den Doktorgrad beworben.

Ich bin mir bewusst, dass eine falsche Erklärung rechtliche Folgen haben kann.

Spremberg, den
Kristin Brand